Nature and properties of carbohydrate derivatives of piperidin-4-one

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ABSTRACT

In the modern world, drug resistance of pathogens responsible for various diseases has become a deadly threat to mankind, and requires the search for new biologically active substances. One of the approaches is the introduction of carbohydrates with unprotected hydroxyl groups into the structure of medical drugs, which can reduce their toxicity, increase their water solubility and increase the selectivity of action. The aim of the study was to develop a scientific basis for the synthesis of biologically active substances by condensation of glycosylvinylnitrosourea with various γ-piperidone derivatives and to study their properties. The choice of γ-piperidone derivatives was justified by their strong antiviral and antibacterial activity. Despite their low water solubility, these compounds have potential for the development of new effective drugs. Experiments were carried out using various aglycones and carbohydrate components. A variety of methods including analytical, comparative, computer modelling and experimental methods were employed in this work to achieve the results. The results showed potentials in the proposed synthesis methods for the development of new drug compounds. The introduction of unprotected hydroxyl groups into the structure of the medicinal compounds by forming glycosyl carbamide bond improved the toxicological characteristics, solubility, and selectivity. It has been shown experimentally that the interaction of nitroso derivatives of glycosylurea with basic amines is relatively easy. This study opens prospects for the development of new drugs with improved properties and biological activity. The results of this study may lead to the development of effective therapeutic agents in the fight against drug resistance and infectious diseases.

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INTRODUCTION

Carbohydrate derivatives of piperidin-4-one represent a unique class of chemical compounds that are attracting increasing attention in modern medical and pharmaceutical science. These compounds, formed by modification of piperidin-4-ones, include carbohydrate groups and may have a variety of biological activities. Piperidin-4-one, as a chemical structure, is a cyclic amide...
with an amino group at position 4 (Ezeibe et al., 2011; Nyandoro et al., 2014). The molecule has the structural flexibility to introduce various substituents and functional groups, which opens the way for the synthesis of a variety of derivatives with desired properties. Carbohydrate derivatives of piperidin-4-one are highly reactive due to the peculiarities of their molecular structure, which makes them suitable for a variety of chemical transformations and further modifications (Sarymzakova et al., 2021).

There are various approaches for the synthesis of piperidin-4-one derivatives. For example, the method of condensation of glycosylvinylnitrosourea with various 𝛾-piperidone derivatives allows obtaining a variety of molecules with modified molecular structure. Mane et al. (2008) demonstrated that reducing the C5-aldehyde, followed by hydrolysis of the 1,2-acetonide group and reductive aminocyclisation of the C1-aldehyde, leads to the formation of 𝛾-hydroxyalkyl substituted piperidiniminosugars from D-glucose. Also, Maram and Mannich (2019) observed that sugar derivatives can undergo Mannich reactions with ketones, leading to the formation of polyoxy-substituted piperidine derivatives bearing ketone groups. This method of synthesis extends the range of functionality of the molecule. Based on these studies, the potential for condensation of glycosylvinylnitrosourea with various 𝛾-piperidone derivatives can be observed.

Some carbohydrate derivatives of piperidin-4-one exhibit antimicrobial activity, making them potentially valuable in the fight against infectious diseases. In the article by A.S. Girgis et al. (2022) indicated that, piperidin-4-carboxamide analogues exhibit high selectivity in inhibiting cytomegalovirus. This indicates potential applications of these compounds in the control of a particular virus, as reported by Abdelshaheed et al. (2021). In addition, Abu-Zaied et al. (2021) investigated the synthesis of novel pyrimidine thioglycosides which were evaluated for antiviral activity against SARS-COV-2 and avian influenza H5N1 viruses. The results indicate the efficacy of these compounds against infectious diseases caused by the above viruses. Carbohydrate derivatives of piperidin-4-one also have the potential to affect various biological processes in the body, which may be key in the development of new drugs.

Carbohydrate derivatives of piperidin-4-one can be obtained by various synthesis methods, which makes this class of compounds an interesting and promising object for research. Despite the available data on the biological activity of these derivatives, the specific mechanisms of their effects on human and other organisms remain unclear at this stage of research (Nyandoro, 2017; Mayaka et al., 2019). Different approaches offer prospects for the development of compounds with improved properties and diverse biological activities, which makes them important subjects for pharmaceutical and medical research. The aim was this work is to investigate different options for the synthesis of carbohydrate derivatives by condensation of glycosylvinylnitrosourea with various 𝛾-piperidone derivatives and to study their biological activities.

MATERIALS AND METHODS

The article used a variety of methods to study the synthesis routes and properties of carbohydrate derivatives of piperidin-4-one. Among them: method of analysis, experiment, comparison, and computer modelling. Collection and analysis of literature allowed collecting and systematizing data on this topic. The techniques for synthesizing the desired substances were based on existing procedures and were modified during the experiment.

The Prediction of Activity Spectra for Substances (PASS) system was used to screen the chemical compounds (Parasuraman, 2011). The PASS system is a tool that is used to predict the biological activity spectrum of chemical compounds based on their structural formulae. In the process, the PASS system analyses the chemical structure of a substance and compares it with a database containing information on the biological activity of many chemical compounds. On the basis of this
comparison, the system makes predictions as to what types of biological activity may be characteristic of a given compound. The main indicators for calculating the spectrum of biological activity are Pa (activity) and Pi (inactivity). The higher the value of Pa and lower the value of Pi, the higher the probability of detecting this activity in the synthesized compounds. The activity types with the highest probability of detection in the compound were selected in the computer prediction analysis. The probability values for each activity type (Pa) and the probability of its absence (Pi) ranged from zero to one. Using computer prediction calculations (Pa)/(Pi), it is possible to select basic structures for the development of new drugs with desired biological properties from the available synthesized compounds. Diagrams of dependence of the manifestation of biological activity on the structure of amyl carbohydrate derivatives in pharmaceuticals were made to compare the calculation results. The results obtained show the promising use of carbohydrate derivatives in pharmaceuticals and the need for further studies.

Synthesis of N-(β-D-glucopyranosyl-carbamoyl)-2.6-diphenyl-3-amylpiperidin-4-one

In 1.8 g of D-glucose, 0.14 g of 4-aminobenzoic acid, 0.3 mL of concentrated hydrochloric acid and 15 mL of absolute alcohol were added in a 200 mL round bottom three-neck flask equipped with a stirrer, thermometer and reflux condenser. The resulting mixture was heated in a water bath at 80°C for 1 hour. After that, a solution of 0.86 g of vinylurea in 10 mL of ethanol was added to the reaction mixture. The reaction mixture was heated in a water bath for another two hours under constant stirring. The mixture was then cooled to 0°C, a cooled solution of 0.69 g sodium nitrite in 1.5 mL of water was added and acidified with 4 mL of cooled glacial acetic acid. Thereafter, a chilled solution of 3.21 g of 2.6-diphenyl-3-amylpiperidin-4-one in 120 mL ethyl alcohol was gradually added over a period of two hours to ensure complete and consistent mixing under controlled conditions. The reaction mixture was left for 16 hours to complete the reaction. The white crystalline precipitate was filtered off under vacuum over a Buechner funnel, washed with ethyl alcohol and dried.

Yield: 3.5 g (52.2%) \( \text{N-(β-D-glucopyranosyl-carbamoyl)-2.6-diphenyl-3-amylpiperidin-4-one.} \) \( T_{\text{pl}}\ ) 168-169°C; \( Rf=0.79 \) in the benzene-dioxane solvent system (60:1); IR – spectrum (\( \text{cm}^{-1} \)): 3416 (\( \text{N–H} \)); 1719, 1650 (\( \text{C=O} \)); 1249 (\( \text{C–O–C} \)); 3430 (\( \text{OH} \)); 1210, 1155, 1090 (\( \text{C–N} \)); 1039, 1003 (\( \text{C–OH} \)).

Synthesis of N-(β-D-xylopyranosyl-carbamoyl)-2.6-diphenyl-3-amylpiperidin-4-one

In a round bottom flask with reflux condenser, 0.75 g xylose, 0.68 g 4-aminobenzoic acid, 10 mL ethyl alcohol, 0.18 mL concentrated hydrochloric acid, 0.3 mL glacial acetic acid were mixed. The reaction mixture was heated in a water bath for one hour at 70-75°C. After one hour, 0.43 g of vinylurea dissolved in 10 mL of ethyl alcohol was added to the mixture. Stirring was continued for one hour and twenty minutes. Then the reaction mixture was cooled to 0°C in an ice bath and 0.34 g of sodium nitrite solution was added for twenty minutes under constant stirring, after which 2 mL of glacial acetic acid was added. The progress of the reaction was monitored by thin layer chromatography. Then a cooled solution of 3.21 g of 2.6-diphenyl-3-amylpiperidin-4-one in 120 mL ethyl alcohol was gradually added over a period of two hours to ensure complete and consistent mixing under controlled conditions. The reaction mixture was left for 16 hours for complete completion of the reaction. The precipitate was filtered off and recrystallized from ethanol.

Yield: 1.8 g (55%) \( \text{N-(β-D-xylopyranosyl-carbamoyl)-2.6-diphenyl-3-amylpiperidin-4-one (white crystalline precipitate).} \) \( T_{\text{pl}}\ ) 168-169°C; \( Rf=0.79 \) in benzene-dioxane (60:1) solvent system; IR spectrum (\( \text{cm}^{-1} \)): 3416 (\( \text{N–H} \)); 1242 (\( \text{C–O–C} \)); 3540 (\( \text{OH} \)); 1210, 1147, 1090 (\( \text{C–N} \)); 1210, 1147, 1090 (\( \text{C–O–C} \)).
Synthesis of N-(lactosyl-carmamoyl)-2,6-diphenyl-3-isopropylpiperidin-4-one

In a 200 mL round bottom flask were placed 1.71 g lactose, 0.137 g paraaminobenzoic acid (PABA), 0.43 mg vinylurea, 30 mL ethyl alcohol and 0.4 mol hydrochloric acid. A flask fitted with a reflux condenser was placed in a water bath. The mixture was heated at 75°C until complete dissolution (about two hours). After that, the flask with the obtained mixture was placed in an ice bath, reducing the temperature to -5-10°C by adding glacial acetic acid. 0.69 mg of sodium nitrite in 1 mL of water was added to the flask. In a separate flask, 1.605 mg of 2,6-diphenyl 3-isopropyl pipyridin-4-one was dissolved in 45 mL of ethyl alcohol and added to the reaction mixture. The resulting solution was left until precipitation was complete. The precipitate was filtered off and recrystallized from ethanol.

Yield: 1.1728 g (28%) N-(lactosyl-carmamoyl)-2,6-diphenyl-3-isopropylpiperidin-4-one, white crystals. Rf=0.6 (in benzene-dioxane system 40:1). Tp=176°C. IR – spectrum (cm\(^{-1}\)): 1035 cm\(^{-1}\) (C–O–C); 3433 cm\(^{-1}\) (OH); 1306 cm\(^{-1}\) (C-N-C); 755 cm\(^{-1}\) (C–H\(_{\text{arom}}\)); 1589 cm\(^{-1}\) (Ar ring).

Synthesis of N-(α-D-arabinopyranosyl-carmamoyl)-2,6-diphenyl-3-isopropylpiperidin-4-one

1.5 g of α-arabinose, 0.4 g of paraaminobenzoic acid, 0.86 g of vinylurea, 30 mL of ethyl alcohol and 0.3 mL of concentrated hydrochloric acid were placed in a round bottom flask with a reflux condenser installed. The mixture was heated at 75-76°C in a water bath until the initial products were completely dissolved for 2 hours. After the solution was cooled to -5-10°C, 1.25 mL of acetic acid was added to the reaction mixture and 1.38 g of sodium nitrite was gradually added. The reaction mixture was stirred for 1 hour. 2.93 g of 2,6-diphenyl-3-isopropylpiperidin-4-one dissolved in 50 mL of ethyl alcohol was added batchwise to the cooled reaction mixture over 1 hour. The solution was left to precipitate. The precipitate was filtered off and recrystallized.

Yield: 2.4 g (33%) N-(α-D-arabinopyranosyl)-carmamoyl-2,6-diphenyl-3-isopropylpiperidin-4-one, brown crystals. Rf=0.69 (in benzene-dioxane system 40:1) Tp=169°C. IR spectrum (cm\(^{-1}\)): 3433 cm\(^{-1}\) (N-H), at 2968 cm\(^{-1}\) (vasCH\(_3\)), at 1723 cm\(^{-1}\) (C=O), at 1589 cm\(^{-1}\) (Ar ring), at 1306 cm\(^{-1}\) (C-N-C) and at 1035 cm\(^{-1}\) (C-O-N).

RESULTS

Synthesis of carbohydrate derivatives of piperidine carried out for a specific purpose is an important area of research work. Obtaining the final desired products was done through a series of intermediate steps. The multistep synthesis using xylene as starting material is shown in Figure 1.

The first step involves an efficient interaction between xylene and paraaminobenzoic acid, resulting in the formation of N-(β-D-xylopyranosyl)-p-aminobenzoic acid. This step proceeds relatively easily and rapidly, the reaction product being a compound that is an important intermediate in the synthesis process. The next step is transglycosylation, in this case a reaction between the N-glycoside and vinylurea. This reaction results in the formation of a new N-glycosidic bond, in which the vinylurea replaces the aglycone. Transglycosylation allows the introduction of a vinyl radical into the glycoside molecule, which is important for the subsequent reactions and the final properties of the compound. Here, arylamine plays a key role as a nucleophilic catalyst, facilitating the coupling of the monosaccharide to urea derivatives. Importantly, arylamine is utilized in catalytic amounts, which contributes to the efficiency of the reaction and ensures its controllability. This step of the process is of great importance as it determines the structure and properties of the final product.

During the exchange of aglycones under acid catalysis conditions, the acid-induced protonation of oxygen in the pyranose ring of the aglycone occurs at the beginning of the reaction. This leads to ring rupture and formation of the open form of the aglycone. In the next step, the attacking amine attaches to
the open form of the aglycone. This reaction results in the formation of N-acetal. This compound contains an amine group attached to the aglycone. At this point, the initial N-acetal in the reaction captures an excess proton from the incoming aglycone. This is an important step that helps to stabilize the resulting compound. As a result, N-((β-D-xylopyranosyl)-N’-vinylurea is formed. Importantly, unlike the N-glycosides of arylamines, the N-glycosidic bond in glycosylureas is highly resistant to hydrolysis. The N-glycosidic bond is formed by condensation of an aglycone (sugar residue) with the amino group of an amino acid or amine backbone of an arylamine. In the case of glycosylureas, the amine backbone is urea. This bond is highly stable due to the fact that the nitrogen of the amine base of urea is a good nucleophile and can form a strong chemical bond with the carbohydrate. This stability makes fragments containing N-glycosylamide bonds attractive for use as linkers between sugars and bioactive compounds in the development of carbohydrate-containing drugs. In the next step, N-((β-D-xylopyranosyl)-N’-vinyl-N’-nitrosourea is obtained from the overamidation reaction.

N-nitroso derivatives of N-glycosylureas are known to be compounds in which nitroso groups are attached to the urea backbone. These nitroso groups have high chemical reactivity, which attracts the attention of researchers. In the case of N-nitroso derivatives of N-glycosylurea, this can involve various types of reactions such as additions, elimination, oxidative and reductive processes, and more. They provide the opportunity for the synthesis of a variety of N-derivatives of carbohydrates, including those that are difficult to obtain by methods of direct interaction of nucleophilic agents with the glycosidic centre due to the limited reactivity of the attacking amino group. An example of such a synthesis is the preparation of the final compound N-((β-D-xylopyranosylcarbamoyl)-2,6-diphenyl-3-amylpiperidin-4-one.

The PASS system was used to screen the chemical compounds. As a result of the prediction analysis, activity types with high probability of detection in the compound were identified. These probabilities range from zero to one. Using (Pa)/(Pi) calculations, it is also possible to select basic structures for the development of new drugs with desired biological properties from the available compounds. The data of computer calculation of biological activity of the synthesized molecules is given in Table 1.

Analysing the data in the table, it is worth noting that the synthesized molecules have significant biological activity, which provides prospects for their application in the treatment of various diseases. However, the process of developing new drugs involves more detailed screening of numerous newly synthesized compounds. Those that pass this screening are analysed in greater depth to assess their efficacy and safety. From this array, those compounds are selected that have efficacy for their intended purpose and have minimal harmful effects on the body. However, most of the new compounds are not suitable for pharmacological use due to several reasons, such as high toxicity, low aqueous solubility, mutagenicity and hazardous degradation products. In order to develop safe and effective drugs, it is necessary to make a rigorous selection of compounds undergoing biomedical testing and conduct more in-depth studies and evaluation of their toxicity, pharmacokinetics, pharmacodynamics and other parameters. This approach helps to create medicines that are as effective as possible while minimizing side effects on the body. It is important to realize that despite the potential properties of synthesized substances, they require further investigation before possible application in practice. The use of the PASS resource to predict biological activity represents a useful tool in the development of new drugs. This resource provides predictions for more than 4 thousand biological activities with an average accuracy of 95%. In this study, the selection of aglycones is based on their biological activity, and the piperidine cycle
underlying the structure of alkaloids has specific effects on the human body, and piperidine derivatives have a wide range of pharmacological activities. Therefore, the directed synthesis of piperidine derivatives represents a relevant area of research. However, the prediction provided by the PASS programme does not guarantee that a particular substance will become a drug. It depends on many factors, including biomedical research results, clinical trials and pharmaceutical regulation. Prediction can help to determine what types of biological activity the compound being analysed should be tested for, and which substances are most likely to exhibit the desired activities.

To compare the results of the computer prediction calculation, Figure 2 shows the dependence of the manifestation of biological activity on the structure of the amyl radical and the influence of monosaccharides. The diagram shows that the choice of carbohydrate component can significantly affect the biological activity of the compound. When xylose is introduced, antitumor activity increases, while antiexemic properties, on the contrary, decrease. A similar dependence was observed in the works where xylose was used as a carbohydrate component. This effect is due to the influence of the chemical structure of xylose and its interaction with other components in the reaction. Since different carbohydrate components interact with biological systems and cells of the organism in different ways, which leads to variation of biological effects.

Figure 3 illustrates important aspects of the biological activity of glycosylated gamma-piperidone derivatives, especially in the context of the influence of the carbohydrate component. Firstly, comparison of a disaccharide (lactose) with a monosaccharide (arabinose) reveals differences in biological activity. The introduction of arabinose into the structure of a heterocyclic compound results in enhanced antitumor activity. This important observation indicates the potential of arabinose as a valuable component in the design of bioactive compounds. Furthermore, it should be pointed out that dermatological activity is not influenced by either the structure of the radical or the structure of the carbohydrate component. This means that in the context of dermatological activity, other parameters may play a more significant role.

This information emphasizes the importance of careful choice of carbohydrate component in the synthesis of new compounds with biological activity. They also emphasize the complex interaction of different structural elements in the formation of biological properties of the compound. Such analyses are essential for the design of novel bioactive compounds with targeted effects on the body. The results of the PASS analysis provide valuable predictive data on the potential biological activity of carbohydrate derivatives of piperidin-4-one. However, it is important to emphasize that the prediction itself does not provide a guarantee that a particular substance will become a drug. This process depends on multiple factors, including the results of biomedical research, the completion of clinical trials and compliance with pharmaceutical regulation. Chart analysis also highlights the significance of carbohydrate component selection in compound design. The introduction of different carbohydrates can significantly influence their biological activity, in particular affecting antitumor and dermatological activity. The introduction of arabinose and xylose into the structure of a heterocyclic compound leads to an increase in antitumor activity, while, in the case of xylose, a decrease in anti-eczema activity. The result has important implications for the development of new drugs for antitumor therapy.
Figure 1: General scheme for the synthesis of γ-piperidone derivatives using xylose as an example.

Table 1: Computer prediction of the biological activity of synthesized compounds.

<table>
<thead>
<tr>
<th>Type of biological activity</th>
<th>No. 1 ( P_a/P_i )</th>
<th>No. 2 ( P_a/P_i )</th>
<th>No. 3 ( P_a/P_i )</th>
<th>No. 4 ( P_a/P_i )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antitumor activity</td>
<td>0.495</td>
<td>0.461</td>
<td>0.661</td>
<td>0.462</td>
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<tr>
<td></td>
<td>0.038</td>
<td>0.005</td>
<td>0.033</td>
<td>0.005</td>
</tr>
<tr>
<td>Anti-eczema properties</td>
<td>0.786</td>
<td>0.583</td>
<td>0.801</td>
<td>0.645</td>
</tr>
<tr>
<td></td>
<td>0.004</td>
<td>0.034</td>
<td>0.018</td>
<td>0.066</td>
</tr>
<tr>
<td>Vasoprotective properties</td>
<td>0.629</td>
<td>0.388</td>
<td>0.692</td>
<td>0.434</td>
</tr>
<tr>
<td></td>
<td>0.045</td>
<td>0.083</td>
<td>0.011</td>
<td>0.062</td>
</tr>
<tr>
<td>Antiviral properties</td>
<td>0.518</td>
<td>0.281</td>
<td>0.511</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>0.02</td>
<td>0.105</td>
<td>0.021</td>
<td>0.233</td>
</tr>
<tr>
<td>Antidiabetic properties</td>
<td>0.358</td>
<td>0.343</td>
<td>0.593</td>
<td>0.323</td>
</tr>
<tr>
<td></td>
<td>0.018</td>
<td>0.022</td>
<td>0.013</td>
<td>0.028</td>
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<tr>
<td>Dermatological properties</td>
<td>0.305</td>
<td>0.269</td>
<td>0.466</td>
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<td></td>
<td>0.085</td>
<td>0.106</td>
<td>0.039</td>
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<tr>
<td>Treatment of Restenosis</td>
<td>0.692</td>
<td>0.581</td>
<td>0.702</td>
<td>0.521</td>
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<td></td>
<td>0.004</td>
<td>0.005</td>
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<tr>
<td>Properties</td>
<td>No. 1 (β-D-glucopyranosyl-carbamoyl)-2.6-diphenyl-3-amylpiperidin-4-one</td>
<td>No. 2 (β-D-xylopyranosyl-carbamoyl)-2.6-diphenyl-3-amylpiperidin-4-one</td>
<td>No. 3 (lactosyl-carbamoyl)-2.6-diphenyl-3-isopropylpiperidin-4-one</td>
<td>No. 4 (α-D-arabinopyranosyl-carbamoyl)-2.6-diphenyl-3-isopropylpiperidin-4-one</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Immunostimulatory properties</td>
<td>0.513</td>
<td>0.363</td>
<td>0.701</td>
<td>0.389</td>
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<td>Antibacterial properties</td>
<td>0.035</td>
<td>0.06</td>
<td>0.014</td>
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<tr>
<td>Antipruritic properties</td>
<td>0.411</td>
<td>0.24</td>
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<td>0.213</td>
<td>0.142</td>
<td>0.034</td>
<td>0.105</td>
</tr>
</tbody>
</table>

Note: No. 1 – N-(β-D-glucopyranosyl-carbamoyl)-2.6-diphenyl-3-amylpiperidin-4-one; No. 2 – N-(β-D-xylopyranosyl-carbamoyl)-2.6-diphenyl-3-amylpiperidin-4-one; No. 3 – N-(lactosyl-carbamoyl)-2.6-diphenyl-3-isopropylpiperidin-4-one; No. 4 – N-(α-D-arabinopyranosyl-carbamoyl)-2.6-diphenyl-3-isopropylpiperidin-4-one.

**Figure 2:** Calculation of computer prediction of biological activity based on the amyl radical.
Figure 3: Calculation of computer prediction of biological activity based on the isopropyl radical.

**DISCUSSION**

In this work, carbohydrate derivatives of piperidin-4-one obtained by condensation of glycosylvinylnitrosourea with various γ-piperidone derivatives were investigated. This method of synthesis shows efficiency in obtaining a variety of molecules with modified molecular structure. These compounds represent a unique class of chemical compounds combining elements of glycoside and piperidine frameworks with potential biological activity. One of the most important aspects of this study was to analyse the effect of aglycone on the biological activity of the synthesized compounds. The choice of aglycone is based on their ability to exhibit high chemical reactivity. Piperidin-4-one, as a starting material, provides many opportunities for the synthesis of various derivatives. Piperidine derivatives have long attracted the attention of pharmacologists due to their diverse properties and potential therapeutic applications. The piperidine framework is present in alkaloids with specific effects on the human body. The condensation process of glycosylvinylnitrosourea with γ-piperidone derivatives is discussed in detail. An important step is the formation of N-acetal, which leads to the formation of N-(β-D-xylopyranosyl)-N'-vinylurea. This reaction mechanism plays a key role in the synthesis of these compounds.
role in the formation of the target compounds. The resistance of N-glycosidic bond in glycosylureas to hydrolysis indicates the promising potential of these compounds as binders in carbohydrate-containing drugs. The choice of carbohydrate component has a significant influence on the biological activity of the compounds. The introduction of xylose, for example, increases the antitumor activity, while the anti-eczema properties decrease. These observations are of interest for further studies in medicine and pharmacology.

It is also important to note that the application of the PASS programme in the screening of chemical compounds has allowed the prediction of the spectrum of biological activity, which can significantly reduce the amount of laboratory research. The compounds obtained exhibit a variety of biological activities including anti-tumour, anti-eczema and dermatological activity. It is important to note that this activity increases with the introduction of various sugars, however, possibilities to enhance the biological properties should be considered. Analogues of piperidone have been synthesized and studied for a variety of biological applications, including as anticancer agents. In a study by Smith et al. (2023), a library of bis-chalcones structurally similar to EF-24, a bis-chalcone molecule known for its anticancer properties, was synthesized in order to study their therapeutic properties. This report details the synthesis of ten new analogues and their anticancer properties.

Also, Ghatpande et al. (2020) state that spiro[chroman-2,4'-piperidine]-4(3H)-one represents an important pharmacophore that accounts for many drug compounds, potential drugs, and biochemical reagents. It is important to emphasize that the first prototype spirochromanone was synthesized via the reaction of 2-hydroxyacetophenone with cyclic ketoamide using the Kabbe condensation method. This base-catalysed tandem process combines condensation and cyclization to give exclusively spirocyclic compounds. Studies in this field have shown different aspects of the structure, reactions, mechanisms, applications and potential utility of such compounds.

Drawing an analogy with this work, it is worth noting that both piperidone derivatives are obtained by condensation and possess significant pharmacological properties.

Extensive studies by Monisha et al. (2018) confirm that all the tested compounds belonging to the classes of chalcones and piperidines exhibit varying degrees of antioxidant and free radical scavenging activity. The antioxidant activity was found to be directly related to the percentage of purification capacity and inversely proportional to the IC50 value. The piperidine core plays an important role in the inhibitory activity of these compounds. This indicates a significant influence of this element on the biological activity as compared to chalcones. Based on these data, it can also be observed that the available biological properties are directly related to the chemical properties of the piperidine nucleus, which is a karskas in the investigated molecules.

In their work, Cheng et al. (2011) presented the results of enzymatic and cellular characteristics of the compound 1-benzyl-3.5-bis(3-bromo-4-hydroxybenzylidene)piperidine-4-one and its analogues. The compounds showed high and selective activity in inhibiting Coactivator-associated arginine methyltransferase 1, while having low or no activity against other protein arginine methyltransferases or human histone methyltransferases. Coactivator-associated arginine methyltransferase 1 represents a significant target for hormone-dependent tumours such as prostate and breast cancer. These results also highlight the importance of further studies of piperidin-4-one in pharmacology, based on the good biological properties of these compounds.

T.A. Dar et al. (2022) prepared variously substituted 2.6-diphenylpiperidin-4-one 4-fluorobenzhydrazides by direct condensation of the corresponding 2.6-diphenylpiperidin-4-one with 4-fluorobenzhydrazide. All the obtained compounds were characterized using infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy. Also, all the compounds were evaluated for antioxidant and antibacterial
activity and against different free radicals and different bacterial strains respectively. The present study showed good results, indicating the possibility of these compounds to be the basis for future developments for more effective antioxidant and antibacterial agents. Analysing the results of the available studies, the high biological properties of the carbohydrate derivatives of piperidin-4-one should be highlighted, but further improvement and optimization are required for their practical applications.

One of the strategies to enhance the bioactivity of the material is its impregnation with bioactive substances. Ma and Tang (2014) in their article describe this approach to create bioactive PEEK-based composites, which may well be applicable to gamma-piperidin-4-one carbohydrate derivatives. Also, optimizing bioavailability is an important strategy to improve the bioactivity of a compound. This can be achieved by creating complexes or self-associations of the compound with proteins or other bioactive polymers. In the work of Tiwari et al. (2020) piperine has shown the ability to act as a bioenhancer by enhancing the bioavailability of drugs with poor absorption-distribution-metabolism-excretion toxicity properties. Modification of a compound can also be used to improve its bioactivity. For example, modification of polyetheretherketone (PEEK) can increase its bioactivity, osteogenic activity and antimicrobial properties. Another method is predictive modelling, which can be used to improve the bioactivity of a compound by creating predicted bioactive profiles. As described by Norinder et al. (2020), this approach can help to identify compounds with potential bioactivity and optimize their properties. Monosaccharides and their derivatives can be used as a basis for the synthesis of primarily bioactive compounds, and this approach can be successfully applied to the synthesis of carbohydrate derivatives of gamma-piperidin-4-one with improved bioactivity. The results obtained from other studies provide valuable data that can be scrutinized and applied to further improve the bioactivity of the compounds under investigation.

Comparing the results of the current study with previous works, it is possible to identify the main trends in the choice of methods for the synthesis of carbohydrate derivatives of piperidin-4-one by condensation. It is important to note that the resulting compounds exhibited high biological properties, including antioxidant and antibacterial activity. Biological properties strongly depend on the structure and substituents in the molecule, which is of interest for further research and development of these compounds in order to improve their pharmacological properties. These results indicate the promise of the studied compounds in the context of their possible use in the pharmaceutical and medical industries. Research has shown the important potential of carbohydrate derivatives of gamma-piperidin-4-one as biologically active substances with diverse properties. Moving forward in the development of drugs using these compounds requires the use of different strategies. In particular, impregnation of bioactive materials, optimization of bioavailability, compound modification, predictive modelling, and use of monosaccharides as scaffolds are promising approaches to improve their bioactivity. These strategies will help further research and develop effective medical solutions, especially in the fight against cancer, dermatological problems and other pathological conditions.

Conclusion
This study significantly advances drug development by successfully synthesizing biologically active compounds via the condensation of glycosylvinylnitrosourea with γ-piperidone derivatives, using aglycones such as 2,6-diphenyl-3-isopropylpiperidin-4-one and 2,6-diphenyl-3-amylpiperidin-4-one. The carbohydrates used—xylose, glucose, arabinose, and lactose—contributed to forming stable N-glycosidic bonds, leading to compounds with enhanced properties and varied biological activities. These include anti-tumor, anti-eczema, and dermatological effects, with biological activity increasing in the order of xylose>glucose>arabinose>lactose.
Interestingly, changes in the aglycone structure minimally affected the biological activity, suggesting that the choice of carbohydrate significantly impacts activity manifestation. For instance, xylose increased anti-tumor activity while reducing anti-eczema effects. This study also explored methods to enhance these biological activities by modifying the aglycone or carbohydrate structures, such as adding functional groups or altering molecular configurations.

Further research could optimize synthesis conditions and discover more efficient catalysts to increase the yield of bioactive compounds. The potential of these carbohydrate derivatives of piperidin-4-one in treating cancer, skin diseases, and other conditions highlights their importance to the pharmaceutical industry. Future studies might focus on modifying chemical structures, improving synthesis methods, and understanding the action mechanisms of these compounds, aiming to develop effective treatments for various diseases.

COMPETING INTERESTS
The authors declare that they have no competing interests.

AUTHORS’ CONTRIBUTIONS
RS conceived the study and designed the experiments. AI performed the experiments and analyzed the data. BS contributed reagents, materials, and analysis tools. LK cowrote the manuscript. SS reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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