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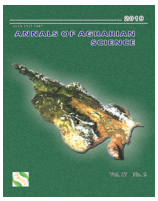

Synthesis and biological activity of 2,3,4,6-tetra-o-acetyl-1-O-(2-hloro-3-phenyl thio propyl)-β-D-Glucopyranose

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A B S T R A C T

Carbohydrate derivatives are distinguished with wide range of biological activity which is proven by successful usage of preparations made of Carbohydrate based in different branches of pharmaceutical chemistry. As a result of research of Carbohydrate compounde, the relationship between unique structure and its chemical and biological properties has been studied. Input of bulk liphophilic adamantane moiety in the proved medications or biologically active molecule in most cases is improved molecule's biological characteristic, drug's lipopilycity and prolonged actin is enhanced, and at the same time toxicity and side negative effects is reduced.We studied the reactions of acetylaryl glycosides with phenylsulfonyl chloride in the presence of a benzoyl peroxide catalyst. A new sulfur-containing glucoside was synthesized: 2,3,4,6-tetra-o-acetyl-1-O-(2-chloro-3-*phenyl thio propyl*)-β-D-Glucopyranose. The bactericidal properties of β-O-(2-chloro-3-*phenyl thio propyl*)-D-glucopyranose (4) of the obtained product after deacetylation were studied. With the help of the computer program PASS (Prediction of Activity Spectra for Substance) onlaines were able to predict the range of activity of substances. The obtained result established correlations on bactericidal properties between biological activity and the intended biological activity. The structure of the synthesized compounds was determined by physico-chemical research methods.

Keywords: Alliglycosides, Thioglycoside, Benzoyl peroxide, Phenylsulfonyl chloride, Bactericidal properties, Biological activity.

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Introduction

Thioglycosides are able to hydrolyze with acids to form mercaptans and the corresponding monosaccharides. However, these compounds are much more resistant to acid hydrolysis than their oxygen counterparts. They are easily broken down by specific enzymes. Thioglycosides have a sharp or burning taste and irritate the mucous membranes and skin, have a strong antimicrobial effect, in small doses stimulate appetite. Due to this property, some plants containing thioglycosides are used in medicine as local irritating and distracting agents for inflammatory processes and rheumatism.

Important compounds of carbohydrate origin are thioglycosides. Recent studies have shown that these compounds are characterized by very significant biological activity and are included in the composition of vitamins, enzymes and coenzymes. All organisms need sulfur [1-2], which it absorbs, in the form of any need. Sulfur-containing compounds are used as an antispasmodic effect, as well as an extension of the capillaries.

For the synthesis of sulfur-containing glucose, the reaction of the addition of monosaccharides (glucose) with phenylsulfonyl chloride was first studied.The starting compounds are synthesized by known methods. [3-4].

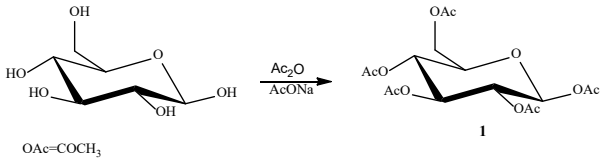
Experimental Part

With acetylation of glucose with acetic anhydride in the presence of sodium acetate on the obtained β-acetylated product (1) by the action of allyl alcohol and $BF_3[O(C_2H_5)_2]$ was syntheside 1-O-ally-2,3,4,6-tetra-o-acetyl-β-D-glucopyranose (2). A new compound 2,3,4,6-tetra-o-acetyl-1-O-(2-chloro-3-*phenyl thio propyl*)-β-D-Glucopyranose

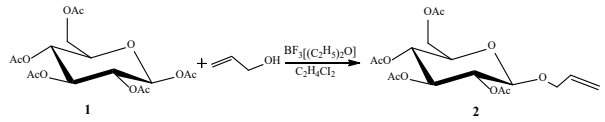
(3) was synthesized at room temperature in chloroform, in the nitrogen region, with mixing and adding phenylsulfonyl chloride solution (in CCI_4).

The synthesized compounds are white colored crystals, very soluble in chloroform. The composition of the derivative was determined by physico-chemical research methods.

In particular, the definition of optical rotation, using elemental analysis, IR and ^{13}C Spectroscopy. The purity of the substance was checked using thin-layer chromatography using "Silufol" plate in the following solvent system by volume: chloroform-ethanol 2:1. Optical rotation was measured on a SU-3 universal saccharimeter at 20^0 C. IR spectra of the samples were taken on a UR-20 spectrometer in KBr tablets. ^{13}C NMR was recorded on a Bruker AM-300, 75.5 MHz spectrometer in deuterochloroforme:



Allyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose (2) was obtained in the interaction of penta-O-acetyl-β-D-glucose (1) with dichloroethane and with alilic alcohol with catalyst $BF_3[(C_2H_5)_2O]$:



By dissolving Allylated monosaccharides at room temperature in chloroform in the nitrogen region, in constant movements with the addition of a solution of phenylsulfonyl chloride (CCI4), a new compound was synthesized -2,3,4,6-tetra-o-acetyl-1-O-(2-chloro-3-*phenyl thio propyl*)-β-D-Glucopyranose (3) 51.8% with output, from which de-acetylations were obtained 1-O-(2-chloro-3-phenylethiopropyle)-β-D-Glucopyranose (4).

In the infrared spectrum of the synthesized products, the absorption band characteristic for the Allyl group is 1643-1700 cm^{-1}, and the following absorption bands are formed: 539, 596 cm^{-1} (C-S); 3070 cm^{-1} (C-H arom.); 690, 739 cm^{-1} (C-CI); 2824 cm^{-1} CH_2; 2850 cm^{-1} CH_3 (for the 3rd substance).

^{13}C NMR (δ, ppm,); $CDCI_3$; 19,38-30,084(RO-CO-$\underline{C}H_3$); 31,970-37,447(-CH_2); 77,740. 77,101. 76,468. 62,8(C_{2-5}); (C-6); 127, 160-137,031 (C_6H_5); 177,5(RO-CO-CH_3) (for the 3rd substance).

The bactericidal properties of compounds were tested against the following microorganisms ─ Bacilus subtilis, Streptomyces albogriseolus, Pseudomonas Fluorescens, Pseudomonas tumelaciens [5,6]. Streptomyces albogriseolus was cultured in Krasilnicovs medium containing (KNO_3-1g, starch – 20g, agar – 20g). Bactericidal properties were assessed by a well method in terms of the zones of sterility around each well. Control consisted of solvent (ethanol-chloroform, 1:1). Substances were loaded into wells at concentrations of 0,001-0,1g/liter. Test substances were found to inhibit the growth of the study microorganisms. It should be noted that compound gave more active inhibition of the growth and development of study microorganisms, apparently because of the presence of a β-D-glucopyranose residue in the molecule.

Table 2. *Glucozides sulfur (3) the impact Growth of microorganismes*

Test-organisms	Concentration of substances%		
	0,1	0,01	0,001
	inhibition zone mm		
Bacilus subtilis	2,0	0	0
Streptomyces albogriseolus	2,0	0	0
Pseudomonas Fluorescens	3,0	1,0	1,0
Pseudomonas tumelaciens	5,0	3,0	1,0

With the help of computer program PASS Online [7-9]. PASS (Prediction of Activity Spectra for Substances) Online predicts over 4000 kinds

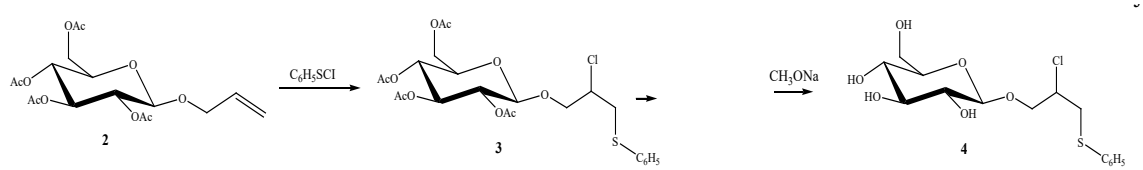


Table 1. *Characteristics 2,3,4,6-tetra-o-acetyl-1-O-(2-chloro-3-phenyl thio propyl)-β-D-Glucopyranose*

Brutal-formule	melting point t ^{0}C	Rf	Molecular mass	$[\alpha]^t{}_D$ $CHCI_3$	Outcome	
					Gr	%
$C_{23}H_{29}O_{10}SCI$	76 ^{0}C	0,51	532,5	$+8^0(t=20^0)$	1,4	51.8%

of biological activity, including pharmacological effects, mechanisms of action, toxic and adverse effects, interaction with metabolic enzymes and transporters, influence on gene expression, etc.

Computer program Evaluated Estimated Biological Activity 2,3,4,6-tetra-o-acetyl-1-O-(2-chloro-3-*phenyl thio propyl*)-β-D-Glucopyranose (3) (Table 3.) and his deacetylated product-1-O-(2-chloro-3-*phenyl thio propyl*)-β-D-glucopyranose (4)

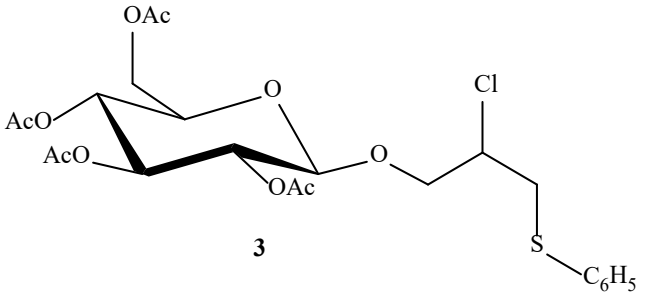


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Table 3. *2,3,4,6-tetra-o-acetyl-1-O-(2-chloro-3-phenyl thio propyl)-β-D-Glucopyranose*

Activity	Pa*	Pi**
Benzoate-CoA ligase inhibitor	0,901	0,005
Cholesterol antagonist	0,851	0,004
Antineoplastic	0,847	0,007
Antileukemic	0,796	0,004
CDP-glycerol glycerophosphotransferase inhibitor	0,812	0,027
Membrane permeability inhibitor	0,753	0,020
Antineoplastic (breast cancer)	0,731	0,005
Antineoplastic (cervical cancer)	0,709	0,004
Mannotetraose 2-alpha-N acetylglucosaminyltransferase inhibitor	0,699	0,027
Immunosuppressant	0,679	0,019
Antifungal	0,639	0,014
Prostate cancer treatment	0,618	0,005
IgA-specific metalloendopeptidase inhibitor	0,609	0,014
Alkenylglycerophosphocholine hydrolase inhibitor	0,632	0,041
Antibacterial	0,566	0,011
Mycothiol-S-conjugate amidase inhibitor	0,565	0,013
Beta glucuronidase inhibitor	0,571	0,020
Nicotinic alpha4beta4 receptor agonist	0,594	0,043
Angiogenesis stimulant	0,550	0,008
Hypolipemic	0,554	0,029
Anaphylatoxin receptor antagonist	0,557	0,049
CYP2H substrate	0,576	0,079
Sugar-phosphatase inhibitor	0,534	0,073

**Pa (probability "to be active") estimates the chance that the studied compound is belonging to the sub-class of active compounds.*

***Pi (probability "to be inactive") estimates the chance that the studied compound is belonging to the sub-class of inactive compounds.*

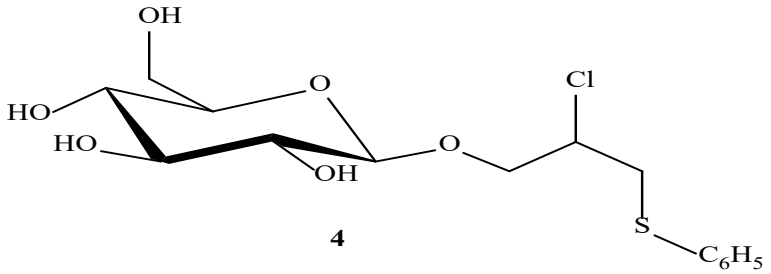

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Table 4. *1-O-(2-chloro-3-phenyl thio propyl)-β-D-glucopyranose*
Predicted activity spectrum

Activity	Pa	Pi
Benzoate-CoA ligase inhibitor	0,956	0,002
Alkenylglycerophosphocholine hydrolase inhibitor	0,956	0,002
IgA-specific metalloendopeptidase inhibitor	0,949	0,001
Sugar-phosphatase inhibitor	0,927	0,003
Cholesterol antagonist	0,923	0,002
Anthranilate-CoA ligase inhibitor	0,914	0,002
CDP-glycerol glycerophosphotransferase inhibitor	0,909	0,008
Fucosterol-epoxide lyase inhibitor	0,881	0,004
Licheninase inhibitor	0,877	0,001
Mycothiol-S-conjugate amidase inhibitor	0,834	0,002
Antileukemic	0,793	0,004
Antitoxic	0,770	0,004
Protein-tyrosine sulfotransferase inhibitor	0,766	0,003
Antineoplastic	0,771	0,015
Membrane permeability inhibitor	0,753	0,020
Vasoprotector	0,746	0,008
Angiogenesis stimulant	0,722	0,003
Sweetener	0,717	0,002
Cytostatic	0,714	0,009
Antineoplastic (cervical cancer)	0,708	0,004
Membrane permeability inhibitor	0,718	0,032
Antithrombotic	0,679	0,009
Lipotropic	0,659	0,005
Hepatoprotectant	0,641	0,010
Antineoplastic (breast cancer)	0,632	0,008
Beta glucuronidase inhibitor	0,612	0,012
Antifungal	0,602	0,018
Chitosanase inhibitor	0,591	0,007
Prostate cancer treatment	0,579	0,005
Antiinfective	0,574	0,015
Antibacterial	0,532	0,014
Antimetastatic	0,532	0,014
Immunostimulant	0,545	0,030
Antidiabetic	0,525	0,020
Hypolipemic	0,501	0,037

The estimation of pharmacological potential of compounds showed, that 1-O-(2-chloro-3-*phenyl thio propyl*)-β-D-glucopyranose (4) has a wider range of biological activity than 2,3,4,6-tetra-o-acetyl-1-O-(2-chloro-3-*phenyl thio propyl*)-β-D-Glucopyranose (3).

A comparison of the PASS predictions data showed, that similar biological activities: *Cholesterol antagonist, Sugar-phosphatase inhibitor, Mycothiol-S-conjugate amidase inhibitor, Beta glucuronidase inhibitor,* compound (4) has with higher Pa value than substance (3) and biological activity: *Antifungal, Prostate cancer treatment* is relatively low Pa.

Based on a generalization of a vast literary material, biologically active compounds are characterized by a certain specificity of composition and structure. Structural modification of compounds by introducing various molecules or atomic groups in a molecule can determine the effect of molecular separation of fragments on bioactivity.

Structural modification may change the toxicity of the drug, change the type of biological action or its prolongation.For example, compounds containing methyl-, ethyl-, phenyl- groups contain high antibacterial activity against gram-positive bacteria and yeast, however, this activity is reduced to fungi [10].

At the same time, it is known that phenolic compounds have a slight antibacterial activity. Compared to non-phenolic compounds. The authors [11] studied the effect of various paints of the Streptomycines genus of microorganisms; it turned out that the effectiveness of these compounds is due to the presence of aromatic rings in their structure.An increase in the hydrocarbon chain in a complex organic compound leads to an increase in physiological activity, the introduction of the group increases the effect of the substance in the respiratory center, the introduction of carbohydrate fragments into the molecule increases the synthesis of the compound, changes in the biological membrane, reduces toxicity, and so on.

In our case, the biological activity in compound 4 determines the acetylated groups, which may be the result of spatial exposure. Additional information about the biological spectrum will be further confirmed.Using the PASS onlainis computer program, the toxic effects of the synthesized substances were determined (3,4).

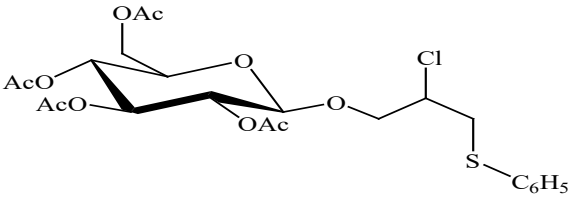

Table 5. *Possible adverse & toxic effects for compound 3 (prediction is based on clinical manifestation, which are sometimes observed in a few or even in a single patient)*

Possible adverse & toxic effects	Pa	Pi
Weakness	0,892	0,008
Diarrhea	0,889	0,012
Muscle weakness	0,859	0,009
Neurotoxic	0,840	0,013
Toxic	0,837	0,021
Drowsiness	0,815	0,019
Sleep disturbance	0,747	0,032
Conjunctivitis	0,725	0,032
Hematotoxic	0,710	0,040
Toxic, gastrointestinal	0,703	0,044

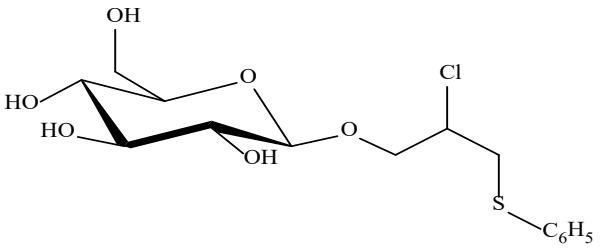

Table 6. *Possible adverse & toxic effects for compound 4 (prediction is based on clinical manifestations, which are sometimes observed in a few or even in a single patient)*

Possible adverse & toxic effects	Pa	Pi
Diarrhea	0,907	0,010
Neurotoxic	0,885	0,007
Dyspnea	0,860	0,009
Toxic, gastrointestinal	0,817	0,023
Fatty liver	0,797	0,004
Drowsiness	0,809	0,020
Hematotoxic	0,803	0,026
Behavioral disturbance	0,791	0,025
Toxic	0,791	0,029
Weakness	0,782	0,021
Sleep disturbance	0,777	0,027
Hyperglycemic	0,743	0,019
Coma	0,733	0,016
Anemia	0,724	0,023
Nausea	0,731	0,035
Embryotoxic	0,708	0,021

The results show that 1-O-(2-chloro-3-*phenyl thio propyl*)-β-D-glucopyranose (4) has a wider range of Toxic effect then 2,3,4,6-tetra-o-acetyl-1-O-(2-chloro-3-*phenyl thio propyl*)-β-D-Glucopyranose (3). Comparison of obtained datasimilar Toxic effect of substance (4) and substance (3): Diarrhea,

Neurotoxic, Toxic gastrointestinal, Drowsiness, Hematotoxic, Toxic, Weakness, Sleep disturbance. At the same time, substance 4 was diagnosed with Diarrhea, Neurotoxic, Toxic gastrointestinal, Hematotoxic, Toxic, Weakness, Sleep disturbance, the higher Pa values of toxic effects than substance 3. While the toxic effect of drowsiness is relatively low Pa.

Conclusion

From a theoretical and practical point of view, it is especially interesting to establish some correlation between structure and biological activity, which serves to search for the biological properties of new compounds with preliminary predictions. Identify the biologically active groups in the substance, determine which fragment is the biological activity of the compound. Our goal is to serve this goal.

By assessment of structure-activity relationships biological activity spectrum of synthesized glycosides have been revealed. The results of the study will enable us providing selection of the most prospective compounds from the set of synthesized samples.

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