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Synthesis and biological activity of Hepta-O-acetyl-1-O-(2-chloro-3-phenyl thio propyl)-β-D-maltose

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ABSTRACT

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 adamantine 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: Hepta-O-acetyl-1-O-*(2-chloro-3-phenyl thio propyl)*-β-D-maltose. The bactericidal properties of β-O-(*2-chloro-3-phenyl thio propyl)*-D-maltose *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: Thioglycosides, maltose, Benzoyl peroxide, Phenylsulfonyl chloride, Biological activity

Introduction

Analysis of the scientific literature in recent years shows that the interest of chemical researchers in the synthesis of products containing bromides, thio sugars, disaccharides containing 1,2-O-glycoside bond has increased dramatically [1]. Studies in this area are expected to lead to the development of new, less toxic, biologically and physiologically active drugs. Due to the urgency of the topic, it is important to conduct scientific research in this

area. The development of methods for the synthesis of Carbohydrate derivatives is one of the important tasks of bioorganic chemistry and has direct interdisciplinary application in the production of biology, medicine, agricultural biotechnology, food industry, pharmaceuticals.

In recent years, the introduction of thio sugars into the structure of physiologically active substances and pesticides to "improve" them, which is one of the most progressive ways to protect a living cell [2-4]. In medical practice, the use of sulfur is based on its ability, when interacting with organic substances of the body, to form sulfides and pentathionic acid, on the presence of which keratolytic, antimicrobial and antiparasitic effects depend. As a result of research of glycoside compounds, the relationship between unique structure and its chemical and biological properties has been studied [5-7].

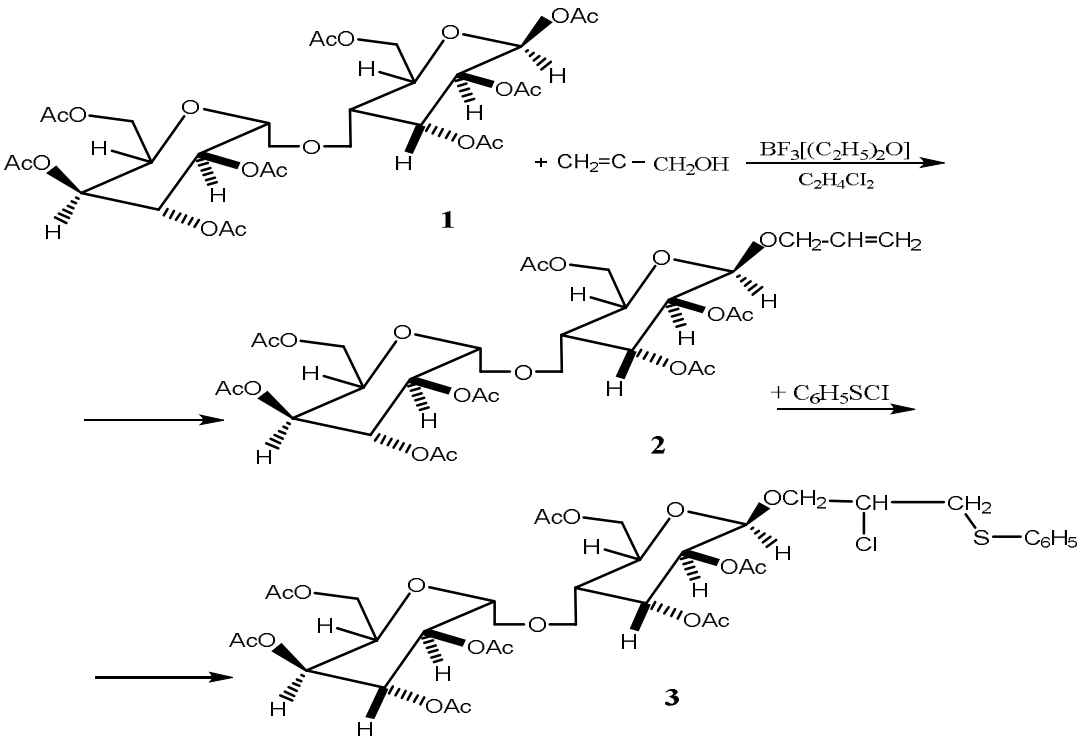
Important compounds of carbohydrate origin are thioglycosides. Recent studies have shown that these compounds are characterized by very significant biological activity and are included in the composition of vitamins, enzymes and coenzymes. Sulfur-containing compounds are used as an antispasmodic effect, as well as an extension of the capillaries [8-9]. For the synthesis of sulfur-containing maltose, the reaction of the addition of Disaccharides (maltose) with phenylsulfonyl chloride was first studied. The starting compounds are synthesized by known methods [10].

Experimental Part

1-O-allyl-hepta-O-acetyl-maltose was synthesized from an acetylated disaccharide in the presence of a BF_3 $[(C_2H_5)_2O]$ catalyst. By dissolving the allylated disaccharide in chloroform at room temperature, in a nitrogen atmosphere with constant stirring, adding dropwise a solution of phenylsulfonyl chloride (dissolved in CCI_4), a new compound was synthesized: Hepta-O-acetyl-1-O- *(2-chloro-3-phenyl thio propyl)*-β-D-maltose with a yield of 56%.

The synthesized compounds are white, very soluble in chloroform. The composition of the derivative was determined by physico-chemical research methods [11].

Composition of compounds, physical and chemical characteristics will be determined by instrumental research methods (elemental, polarimetric, chromatographic analyzes, the so-called BMR 13C and BMR 1H spectroscopy. The definition of optical rotation using elemental analysis, IR and ^{13}C Spectroscopy. The purity of thesubstance as checked using thinlayer chromatography using "silufol" plate in the following solvent system by volume: chloroform-ethanol 1:1. Optical rotation was measured on a SU-3 universal saccharimeter at 20 ^0C. 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:



Characteristics **Hepta-O-acetyl-1-O-*(2-chloro-3-phenyl thio propyl)*-β-D-maltose (3)**

tab. 1

Compound	Brutal-formule	Melting point t °C	Rf	Molecular mass	$[\alpha]^t_D$ $CHCl_3$	Outcome	
						G	%
3	$C_{35}H_{45}O_{18}SCl$	92-96	0.63	820.5	$-15^0(t=20^0)$	0.68	56

^{13}C NMR Spectroscopic analysis Compound 3

tab. 2

168,7-175,8	7RO-CO-CH_3
20,6-20,7	7RO-CO-CH_3'
60.980	R-O-CH_2
100.8; 92.0	C-1; C-1'
61.8; 61.4	C-6; C-6'
77.5; 76.65; 71.05; 70.8; 67.8; 66.8	C_2-6; C_2-5'
29.725-19.386	-CH_2
127.1-137.086	C_6H_5

IR Spectroscopic analysis Compound 3

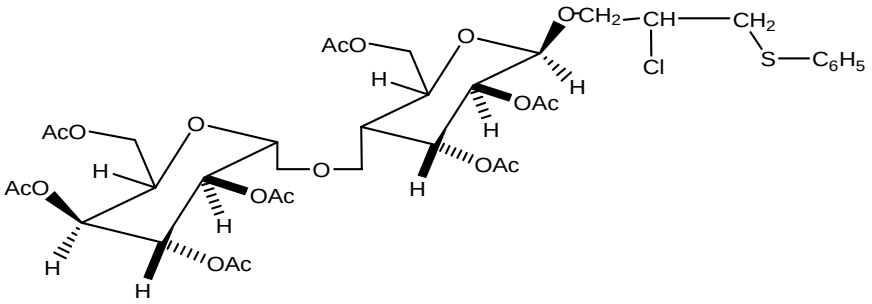
tab. 3

C-O-C	C-S	C-Cl	C-H_{arom}	CH_2	CH_3
1061.1147	453.600	690.739	3070	2924	2850

This substance has a wide range of predicted biological activities. Prediction of the biological activity of the synthesized carbohydrate product: Hepta-O-acetyl-1-O-*(2-chloro-3-phenyl thio propyl)*-β-D-maltose and free hydroxyl-containing hepta-O-1-O-*(2-chloro-3-phenyl thio propyl)*-β-D-maltose was performed using the PASS (Prediction of Activity Spectra for Substance) ONLAINE computer program [12].

The specified computer program evaluated the biological activity of Hepta-O-acetyl-1-O-(*2-chloro-3-phenyl thio propyl*)-β-D-maltose (3) (tab. 4) and his deacetylated product Hepta-O-1-O-*(2-chloro-3-Phenylthiopropyl)*-β-D-maltose (4) (tab. 5).

Biological activity of Hepta-O-acetyl-1-O-
(*2-chloro-3-phenyl thio propyl)*-β-D-maltose (3)



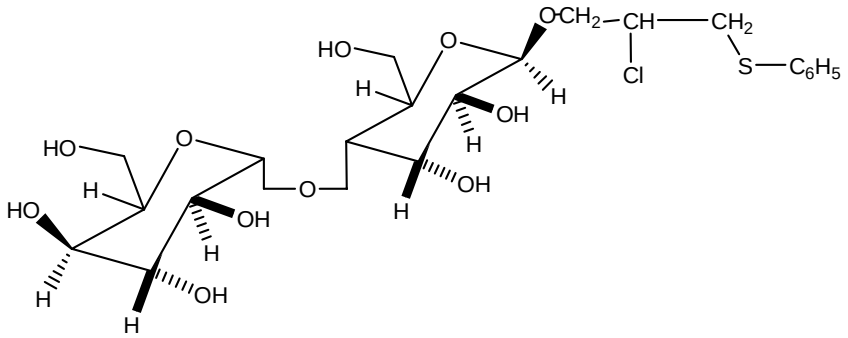
tab.4

All | Pa*>Pi** | Pa>0,3 | Pa>0,7

0,858	0,010	Benzoate-CoA ligase inhibitor
0,810	0,010	Antineoplastic
0,709	0,005	Antileukemic
0,692	0,009	Cholesterol antagonist
0,627	0,007	Antibacterial
0,587	0,004	Antineoplastic (cervical cancer)
0,596	0,030	Immunosuppressant
0,568	0,022	Antifungal
0,543	0,008	Angiogenesis stimulant
0,525	0,033	Hypolipemic
0,451	0,009	Protein synthesis inhibitor
0,542	0,122	Membrane permeability inhibitor
0,389	0,006	Antimycoplasmal
0,318	0,047	DNA synthesis inhibitor
0,296	0,080	Immunostimulant
0,248	0,037	Antioxidant
0,254	0,068	Antiprotozoal

0,245	0,097	Cytostatic
0,220	0,093	Lactose synthase inhibitor
0,242	0,115	Antimetastatic
0,248	0,131	Antiviral (Herpes)
0,168	0,051	Sucrose-phosphate synthase inhibitor
0,255	0,139	Antithrombotic
0,220	0,119	Macrophage stimulant
0,104	0,010	1,3-Beta-glucan synthase inhibitor
0,143	0,060	Antihemorrhagic
0,137	0,103	Alpha-amylase inhibitor
0,041	0,010	Beta glucosidase inhibitor
0,255	0,227	Sugar-phosphatase inhibitor
0,167	0,140	Antiviral (Hepatitis B)
0,181	0,161	Antitoxic
0,146	0,132	Antiparasitic
0,200	0,197	Antiprotozoal (Leishmania)
0,046	0,046	Beta galactosidase inhibitor

Biological activity of deacetylated product Hepta-O-1-O-(*2-chloro-3-Phenylthiopropyl*)-β-D-maltose (4)



tab.5.

All Pa*>Pi** Pa>0,3 Pa>0,7

0,934	0,003	Benzoate-CoA ligase inhibitor
0,859	0,004	Cholesterol antagonist
0,791	0,018	Sugar-phosphatase inhibitor
0,737	0,005	Lactase inhibitor
0,722	0,022	Antineoplastic
0,689	0,004	Angiogenesis stimulant
0,644	0,007	Antileukemic
0,597	0,009	Antibacterial
0,592	0,004	Antineoplastic (cervical cancer)
0,581	0,018	Antithrombotic
0,559	0,028	Immunostimulant
0,549	0,019	Cytostatic
0,542	0,021	Radioprotector
0,531	0,026	Antifungal
0,520	0,016	Antimetastatic
0,501	0,005	Alpha-amylase inhibitor
0,497	0,006	Lactose synthase inhibitor
0,490	0,024	Bilirubin oxidase inhibitor
0,489	0,045	Immunosuppressant
0,449	0,017	Protein-tyrosine sulfotransferase inhibitor
0,472	0,042	Hypolipemic
0,429	0,011	Protein synthesis inhibitor

A comparison of the PASS predictions data showed, that similar biological activities: Cholesterol antagonist, Angiogenesis stimulant, Immunostimulant, Cytostatic, Lactose synthase inhibitor, Antimetastatic, Antithrombotic, Sugar-phosphatase inhibitor, Protein synthesis inhibitor - compound-4 has with higher Pa value than substance-3 and biological activity: Antifungal, Antineoplastic, Antibacterial is relatively low Pa. And, substance-3 has Antitoxic, Antiprotozoal (Leishmania), Beta galactosidase inhibitor, Beta glucosidase inhibitor, Antihemorrhagic, Membrane permeability inhibitor, Antimycoplasmal, DNA synthesis inhibitor, properties that substance 4 does not.

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.

*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.

Conclusion

From a theoretical and practical point of view, 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.

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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ჰეპტა-O-აცეტილ-1-O-(2-ქლორო-3-ფენილ თიოპროპილ)-β-D-მალტოზასსინთეზი და ბიოლოგიური აქტივობა

ლალი ტაბატაძე, ნელი სიდამონიძე, დარეჯან გულბანი, დარეჯან ირემაშვილი

ანოტაცია

ნახშირწყლების წარმოებულები გამოირჩევიან ბიოლოგიური აქტივობის ფართო სპექტრით, რაც დასტურდება ნახშირწყლების ბაზაზე დამზადებული პრეპარატების ფართო გამოყენებით ფარმაცევტული ქიმიის სფეროში. ნახშირწყლების ნაერთის კვლევის შედეგად შესწავლილია კავშირი უნიკალურ სტრუქტურასა და მის ქიმიურ და ბიოლოგიურ თვისებებს შორის. ლიპოფილური ადამანტინის ნაწილის შეყვანა დადასტურებულ მედიკამენტებში ან ბიოლოგიურად აქტიურ მოლეკულაში უმეტეს შემთხვევაში აუმჯობესებს მოლეკულის ბიოლოგიურ მახასიათებლებს. იზრდება ლიპოფილური თვისებები და ამავდროულად მცირდება ტოქსიკურობა და გვერდითი არასასურველი ეფექტები. ჩვენ მიერ შესწავლილ იქნა აცეტილირებული გლიკოზიდების რეაქციები ფენილსულფონილქლორიდთან ბენზოილის პეროქსიდის კატალიზატორის თანდასწრებით. სინთეზირებულია ახალი გოგირდის შემცველი გლუკოზიდი: ჰეპტა-O-აცეტილ-1-O-(2-ქლორო-3-ფენილ თიოპროპილ)-β-D-მალტოზა. შესწავლილი იქნა დეზაცეტილირების შედეგად მიღებული პროდუქტის β-O-(2-ქლორო-3-ფენილ თიოპროპილ)-D-მალტოზის ბაქტერიციდული თვისებები კომპიუტერული პროგრამის PASS onlaines -ის დახმარებით (Prediction of Activity Spectra for Substance) შესაძლებელი გახდა ნივთიერებების აქტივობის დიაპაზონის პროგნოზირება. მიღებულმა შედეგებმა აჩვენა კორელაცია ბაქტერიციდულ თვისებებთან და PASS-ის დახმარებით ჩატარებულ ბიოლოგიურ აქტივობას შორის. სინთეზირებული ნაერთების სტრუქტურის განსაზღვრა მოხდა ფიზიკურ-ქიმიური კვლევის მეთოდებით.

საკვანძო სიტყვები: თიოგლიკოზიდები, მალტოზა, ბენზოილის პეროქსიდი, ფენილსულფონილქლორიდი, ბიოლოგიური აქტივობა