REPUBLIC OF AZERBAIJAN

On the rights of the manuscript

ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

THE SYNTHESIS OF AZAFAGOMINE DERIVATIVES BY ENANTIOSELECTIVE METHOD

Specialty: 2306.01 – Organic chemistry

Field of science: Chemistry

Applicant: **Fidan Nureddin Akhundova**

Baku – 2022

The work was performed at the scientific laboratory of «Thin Organic Chemistry» on the base of Organic Chemistry department at Baku State University.

Scientific supervisors: doctor of chemical sciences, professor
Malahat Musrat Gurbanova;
professor
Maria Jose Alves.

Official opponents: doctor of chemical sciences, professor
Eldar Huseyngulu Mammadbayli;
doctor of chemical sciences, professor
Raya Ali Najafova;
doctor of philosophy in chemistry,
Nazar Mohubbat Nazarov.

Dissertation council ED 1.16 of Supreme Attestation Commision under the President of the Republic of Azerbaijan operating at the Institute of Petrochemical Processes named after acad. Y.H. Mammadaliyev of the Ministry of Science and Education of the Republic of Azerbaijan

Chairman of the Dissertation council:
doctor of chemical sciences, academician
Vagif Majid Farzaliyev

Scientific secretary of the Dissertation council:
doctor of philosophy in chemistry,
associate professor
Lala Mahammad Afandiyeva

Chairman of the scientific seminar:
doctor of chemical sciences, professor
Elmira Teymur Suleymanova

GENERAL DESCRIPTION OF WORK

Actuality and analizing the subject. It is already known that the chemistry of carbohydrates has recently become a topical issue for glucobiologists and pharmacists. Because iminosugars and their derivatives have a biologically active property as a glucosidase inhibitor.

Thus, the biological activity of more than 600 sugars has been proven by scientists. Azasugars or iminosugars are nitrogen-containing sugar analogues where the endocyclic oxygen atom is replaced by a nitrogen atom. This apparently simple substitution raises many synthetic challenges and opens the way to remarkable biological properties. As such, iminosugars undoubtedly form the most attractive class of carbohydrate mimics reported so far. Azasugars demonstrate such activities as antiviral, antibacterial, antiprotozoal, antiparasitarial, antipsoriatic, antifungal, nematicidal, insecticidal, anti-inflammatory, and antitumor.[1]

Among the derivatives of iminosugars that found their application in medicine we can mention miglitol (for type 2 diabetes), N-nonyl-DNJ (Hepatitis B virus agent), miglustat (for Gaucher diseases), castanospermine (anticancer agent), swainsonine (antiviral agent) and so on.[2] In addition to this, it was found that iminosugars inhibit several enzymes of medicinal interest such as glycosyltransferases, glycogen phosphorylases, nucleoside-processing enzymes, a sugar nucleotide mutase, and metalloproteinases.

1-azafagomine and some of its derivatives demonstrated to be very good α-glucosidase inhibitors, and potentially interesting compounds in cancer treatment. Configured restrict iminosugar's structures, mimicking the transition state hydrolysis are generally more

---

[1]Salgueiro D.A. Diels-Alder cycloaddition in the synthesis of 1-azafaqomine, analogs, and derivatives as glycosidase inhibitors / D.A.Salgueiro, C.E.Sousa, M.J.Alves [et al.] // Mini-Reviews in Medicinal Chemistry, – 2012. v. 12, № 14, – p. 1465.

[2] Sastry, G.M. Protein and ligand preparation: parameters, protocols, and influence on virtual screening enrichments / G.M.Sastry, M.Adzhigirey, T.Day [et al.] // Jour-nal of Computer-Aided Molecular Design, – 2013, v. 27, № 3, – p. 221-234.

promising in terms of selectivity.[3] In view of all this, the enantioselective synthesis of new types of 1-azafagomine analogues and the study of their biological activity was raised as a topical issue.

Purpose and object of research. Synthesis and conversion of optically active azfagomine derivatives based on enantioselective Diels-Alder reaction in the presence of chiral organic catalyst (S) - BINOL(1,1'-Bi-2-naphthol). The biological activity and antimicrobial properties of the synthesized optical mono- and bicyclic azafagomine derivatives were studied by molecular docking method.

Goals and objectives of the study. The main purpose of the dissertation was the synthesis of new optically active azafagomine analogues based on the enantioselective Diels-Alder reaction, and some transformations, as well as the determination of the specific rotation and biological and pharmacological properties of synthesized optically active azafagomine derivatives.

a) Synthesis of optically active mono- and bicyclic azafagomine derivatives,

b) Determination of the specific rotation of the synthesized optical azafagomine analogues in the Autopol III polarimeter,

c) Study of the applications of synthesized azafagomines

Investigation methods. Our research was carried out in the scientific laboratory of «Thin Organic Chemistry». The ^{1}H and ^{13}C NMR spectra were recorded at BRUKER-400 (400 MHz ^{1}H and 100.6 MHz ^{13}C) spectrometer. Infrared spectra were recorded on a Bomem MB 104. Samples were run as oils as thin films. Samples were recorded at room temperature in the 4000-400 cm^{-1} infrared field. Solvents were distilled under anhydrous conditions. All reagents were purchased and used without further purification. Glassware was dried prior to use. Compounds were purified by dry flash chromatography using silica 60, <0063 mm and water pump vacuum or by flash-chromatography using silica 60 Å 230–400 mesh as stationary phases. TLC plates (silica gel 60 F254) were visualized either at a UV lamp or in iodine. Melting points are uncorrected. Specific rotation was determined by AUTOPOL III polarimeter.

The main provisions of the defense.

[3] Martin, O.R. Iminosugars: recent insights into their bioactivity and potential as therapeutic agents / O.R.Martin, P.Compain // Current Topics in Medicinal Chemistry, – Hilversum: – 2003. v. 3, № 5, – p. 471-591.

• Synthesis of (S)-diethyl-3-(hydroxymethyl)-3,6-dihydropy ridazine-1,2-dicarboxylate, which plays main role in the production of new optically active mono- and bicyclic azafagomine derivatives based on the ennatioselective Diels-Alder reaction.

• Obtaining new mono- and bicyclic azafagomines based on optically active (S)-diethyl-3-(hydroxymethyl)-3,6-dihydropyri dazine-1,2-dicarboxylate and carrying out some transformations.

• Obtaining N-carboxyamides by adding various isocyanates to the N1 nucleophilic centers in azafagomine derivatives.

• Study of antimicrobial properties of synthesized azafagomine derivatives and determination of pharmacological properties based on comparative calculations with the method of molecular docking.

The novelty of the work. For the first time, using DEAD (diethyl azodicarboxylate) instead of 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) based on the enantioselective Diels-Alder reaction in the presence of (S)-BINOL, Bols' method was modified to obtain high (S)-diethyl-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate. The use of (S)-BINOL (1,1'-Bi-2-naphthol) as a chiral catalyst during the enantioselective Diels-Alder reaction played an important role in the creation of the chiral center and caused the optical activity of the obtained compounds. The used catalyst was purified by dry flash chromatography after use and was continuously used without losing its activity, which increased the importance of the method from the economic and environmental point of view.

As a result of the conversion reactions of (S)-diethyl-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate, new mono- and bicyclic optically active azafagomin derivatives were obtained. Diethyl-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicar boxylate was synthesized using a modified Bols method based on the Dils-Alder reaction, and mono azafagomin derivatives were obtained after a series of conversion reactions. New N-carboxyamide derivatives were obtained by affecting the N1 nucleophilic center in the synthesized azafagomin derivatives with various isocyanates, and their biological properties were studied. The antimicrobial properties of synthesized optically active azafagomin derivatives were studied, and it was determined that they show more effective antimicrobial

properties compared to several medicinal preparations. The biological activity of the synthesized optically active bicyclic azafagomin derivatives was determined based on comparative calculations using the molecular docking method. It was determined by the molecular docking method that the structural properties of optically active bicyclic azafagomin derivatives allow them to be used as antidiabetic drugs in the future.

Theoretical and practical importance of the research. Based on the enantioselective Diels-Alder reaction in the presence of a chiral organic catalyst, optically active azafagomine derivatives with a wide range of applications in medicine were synthesized and some transformations were performed.

Optically active (S)-diethyl-3-(hydroxydimethyl)-3,6-hydropyridazine was synthesized using a combination of non-linear programming methods Powell's, Rosenbrock's, and McCormick's, as well as Kutta-Merson's algorithm for solving a system of differential equations. A mathematical model of the synthesis process of-dicarboxylate was established.

Some of the synthesized compounds have been tested as antimicrobial agents against S. aureus and E. coli bacteria, which may lead to their use in medicine in the future as effective antibacterial drugs. It was also determined that, some azafagomine derivatives synthesized based on comparative calculations with the molecular docking method have the properties of antidiabetic drugs.

Personal addition of author. The applicant was directly involved in the implementation and compilation of the dissertation. She summarized the world literature of recent times on the synthesis of azafagomine compounds and their transformations and showed her author's approach in the literary review. The applicant took an active part in the implementation of laboratory experiments: in the synthesis and purification of compounds (colon and dry-flash chromatography) in the study of the structure of each using physical and chemical research methods (NMR, mass, IR).

Approbation and publication. 14 scientific works were published, including 8 articles and 6 theses on the dissertation. The results of the dissertation were reported and discussed at the following international

and national scientific conferences.

- XIV Republican Scientific Conference on Actual Problems of Chemistry (Baku 2021).
- The Fifth International Scientific Conference "Advances in Synthesis and Complexing" (Moscow 2019).
- III International Scientific Conference of Young Researchers Proceedings (Baku 2019).
- International Chemical Congress, Istanbul (2019).

The total volume of the dissertation with a sign, indicating the volume of the structural units of the dissertation separately. Dissertation work consists of Introduction, 3 chapters, Conclusion and Reference list, it covers 164 pages written in A4 format. The main part of the work (excluding figures, tables, graphs, and bibliog-raphy) is 181210 (including Introduction – 8615, Chapter I – 52000, Chapter II – 82350, Chapter III – 36550, Conclusion – 1695). The list of used literature includes 173 named sources cited in the disserta-tion.

The first chapter dedicated to the analysis of literature review. The presented dissertation reflects the synthesis of azasugar and iminosugar derivatives by different methods and some interesting transformations based on them and the latest scientific research in this field. At the same time, in addition to the synthesis of azafagomine derivatives, their biological activity was also reported.

In the second chapter the synthesis of azafagomine derivatives based on the Diels-Alder reaction and the various transformations are described. Based on the study of antimicrobial properties of the synthesized compounds as physiologically active compounds and comparative calculations with the molecular docking method, it was determined that some azafagomine derivatives synthesized have antidiabetic properties. Further, the study of the application of new methods in the synthesis of azafagomine and its derivatives is given as well.

In the third chapter in the experimental part of the study the physicochemical parameters of the synthesized compounds (^{1}H NMR, ^{13}C NMR, mass spectrometry, IR spectroscopy) are noted.

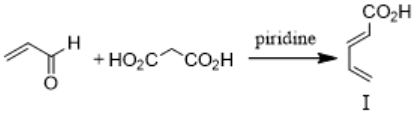
MAIN CONTENT OF THE WORK

It is well known that sugars are sugar analogs of an anomeric carbon atom consisting of a monosaccharide structure containing synthetic nitrogen replaced by a nitrogen atom. Various studies have shown that, azasugars have antiviral, antibacterial, antiparasitic, anti-protozoal, anti-cancer, anti-psoriasis, anti-fungal, nematicidal, anti-insect, anti-inflammatory, glucosidase inhibition and so on. biological activities. In addition, based on sugar derivatives synthesized in various drugs used in medicine for the treatment of diseases (castanospermin-anti-cancer, miglitol-diabetes, swainsonin-antiviral). Given the importance of these compounds, the dissertation is devoted to the enantioselective synthesis of mono- and bicyclic analogues of new species of azafagomine (azafagomine derivatives). Further considering that, the broad-spectrum biological activity of azafagomine derivatives, the antimicrobial properties of synthesized drugs and their activity as a glucosidase inhibitor were studied and positive results were obtained in this direction. First, I would like to note that, the purpose of choosing the enantioselective method during synthesis is to study the difference in the biological activity of enantiotic compounds (individual enantiomers) compared with racemate. The most suitable method for the synthesis of pure enantiotic compounds is asymmetric catalysis. Based on asymmetric catalysis, optically pure compounds are synthesized using a small amount of chiral catalyst. The chiral catalyst increases the output of one enantiomer and decreases the output of the other, as it creates a low-energy transition state with one of the intermediate enantiomers and a high-energy transition state with the other during the reaction. 1,1-Bi-2-naphthol ((S) -BINOL), α, α, α ', α'-tetraaryl-2,2-substituted-1, 3-dioxolan-4,5-dimethanol (TADDOL), BINAP (2,2'-bis (diphenylphosphino) -1,1-binaftil), BOX (bis (oxazoline) ligands have recently been widely used as chiral organic catalysts in asymmetric synthesis. Examples of asymmetric reactions in one stage are Dils-Alder, Sharples, Biginelli, Hans and others. Among these reactions, the Dils-Alder reaction is widely used in the synthesis of drugs. Considering the above, the synthesis of 1-azafagomine and their derivatives was carried out

based on the Dils-Alder reaction by the enatioselective method.

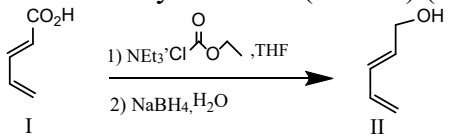
1. Synthesis of optically active diethyl-3-(hydroxymethyl) -3,6-dihydropyridazine-1,2-dicarboxylate by enantioselective method.

As we know that, the synthesis of azafagomine and their derivatives is based on a method developed by Bols and his co-workers. According to this method, cycloadduct, which plays the role of a starting material in the synthesis of 1-azafagomines, based on the Dils-Alder reaction, 4-phenyl-1,2,4-triazole-3,5-dion (PTAD) and diene (2,4-pentadiene carboxylic acid, methyl 2,4-pentadiene and 2,4-pentadienol) are synthesized using this protocol. Thus, using only the mentioned compound as a diene leads to synthesize cycloadduct in a high yield, which plays important role of the starting material in the synthesis of 1-azafagomines. (2E)-Penta-2,4-diene-1-ol alcohol was synthesized by us from (E)-penta-2,4-diencarboxylate according to the method described in the literature. Thus, the method described in the literature was synthesized in the form of a yellow crystal (E) -penta-2,4-diencarboxylic acid (I) based on the Konevenagel reaction in the presence of malonic acid and acrolein (scheme 1).



Scheme 1. (E) -penta-2,4-diencarboxylic acid (I) synthesis

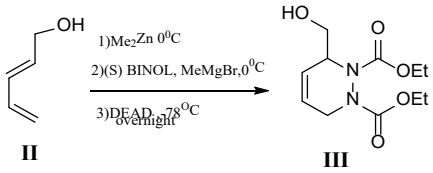
According to the literature, the highest yield of (2E)-Penta-2,4-diene-1-ol alcohol is possible with the second method proposed by Schneider. For this purpose, acid anhydride is obtained from the reaction of (E) -penta-2,4-diene (I) acid with ethyl chloroformate in the main medium (in the presence of triethylamine). It is then possible to synthesize (2E)-Penta-2,4-diene-1-ol (II) alcohol by reacting the acid anhydride with sodium tetrahydroborate ($NaBH_4$) (scheme 2).



Scheme 2. Synthesis of (2E) -Penta-2,4-dien-1-ol (II) alcohol

The next step of synthesis is the synthesis of diethyl-3- (hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate by the Dils-Alder reaction, which plays a starting role in the production of 1-azafagomines. Obtaining the cycloadduct mentioned in the literature by the Bols method, from the reaction of (2E)-Penta-2,4-diene-1-ol (II) alcohol with 4-phenyl-1,2,4-triazole-3,5-dion (PTAD) possible. The synthesis of homochiral (-)-1-azafagomine was accomplished by Bols and coworkers through a synthetic sequence based on the Diels-Alder cycloaddition to 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) to achiral dienes: 2,4-pentadienoic acid, methyl 2,4-pentadienoate and 2,4-pentadienol. The racemic cycloadduct obtained from 2,4-pentadienol and PTAD. The racemic cycloadduct obtained from 2,4-pentadienol and PTAD then was resolved by lipase-mediated transesterification. 1-Azafagomine was then isolated in 37% overall yield from this intermediate. For the first time, we used a cheaper diethylazodiccarboxylate (DEAD) as an alternative to 4-phenyl-1,2,4-triazole-3,5-dion (PTAD) in the above-mentioned reaction and the cycloadduct was successfully synthesized by the Dils-Alder reaction. Hence, we discovered that, instead of using PTAD it is better use DEAD due to its lower price and yield for cycloadduct was obtained 73%.

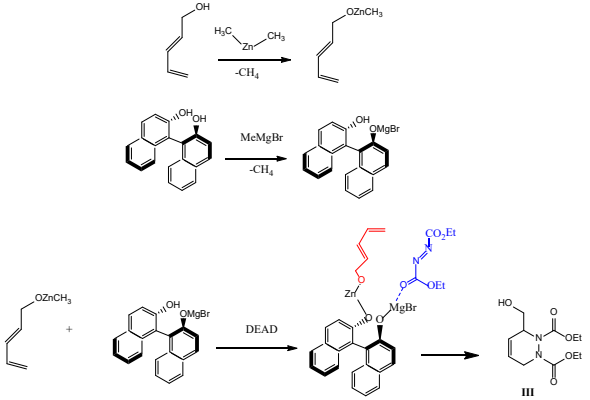
We would like to note that, asymmetric synthesis of cycloadduct (S)-BINOL was carried out and enantioselective cycloaddukt (III) (diethyl-(S)-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarbox ylate) was obtained (scheme 3).



Scheme 3. Synthesis of diethyl- (S) -3- (hydroxymethyl) -3,6-dihydropyridazine-1,2-dicarboxylate

(2E)-Penta-2,4-dien-1-ol (II) the cycloaddition reaction of alcohol and DEAD in the presence of the chiral catalyst (S)-BINOL occurs when the diene attacks the surface. This process has been demon-

strated during the oxidation and hydration of 5-epi-1-azafagomine in the presence of osminium tetraoxide. The specific rotation for this compound is + 23.4 ° (t = 20^0C, in chloroform, c = 1.25%) calculated by AUTOPOL-III polyarimeter. The presence of (S)-BINOL (1,1'-bi-2-naftol) as a chiral catalyst plays an important role synthesis of asymmetric cycloadduct. In the end of the reaction purification of (S)-BINOL by dry-flash chromatography give a chance to use catalyst constantly without losing activity. Recycling method of catalyst brings economical and ecological benefits. The probable mechanism of the reaction is mentioned below.



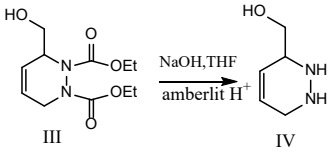
Scheme 4. The probable mechanism of synthesis of optically active (III) cycloadduct

The structure of optically active diethyl (S)-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate was proved by IR, ^{1}H NMR, ^{13}C NMR and HRMS (ESI).

2. Synthesis of a new iminosugar analogue based on (S)-Diethyl-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate.

Continuing our research, we applied optically pure cycloadduct (S)-diethyl-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxy late (III) diethyl carboxylate by applying acid resin (Amberlit) after boiling for 3 hours in NaOH solution. ($COOC_2H_5$) groups are broken down, resulting in the synthesis of a new type of sugar (S)-(1,2,3,6-tetrahydropyridazine-3-yl) methanol (IV) with a yield of 91%. The course of the reaction and the purity of the obtained compound were

monitored by thin-layer chromatography (TLC) (scheme 5).



Scheme 5. Synthesis of substance IV based on (S) -diethyl-3- (hydroxymethyl) -3,6-dihydropyridazine-1,2-dicarboxylate (III)

The structure of the synthesized compound (IV) by mass, IR, ^{1}H and ^{13}C NMR spectroscopy methods were approved. Hence, CH_2N and CHN groups were observed at 3.24-3.35 and 3.54-3.58 m.h. in the spectrum of ^{1}H NMR (400MHz, D_2O) for (S)-(1,2,3,6-trethidropyridazine-3-yl) methanol (IV) as duplets and multiplets. In hydroxymethyl ($HOCH_2$) group at 3.57-3.65 m.h. are observed in the range.

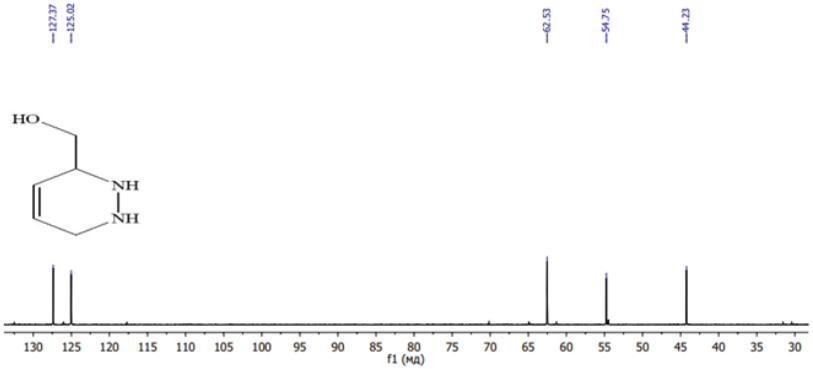


Figure 1. ^{1}H NMR spectra (S) - (1,2,3,6-tetrahydropyridazine-3-yl) methanol (IV) in D_2O solution

In the ^{13}C NMR spectrum (100 MHz, D_2O) of (S) - (1,2,3,6-trethidropyridazine-3-yl) methanol (IV) CH_2N and CHN groups at 44.23 and 54.75 m.h, hydroxymethyl ($HOCH_2$) group at 62.53 m.h, 2CH = groups at 125.02 and 127.37 m.h. are observed in the range.

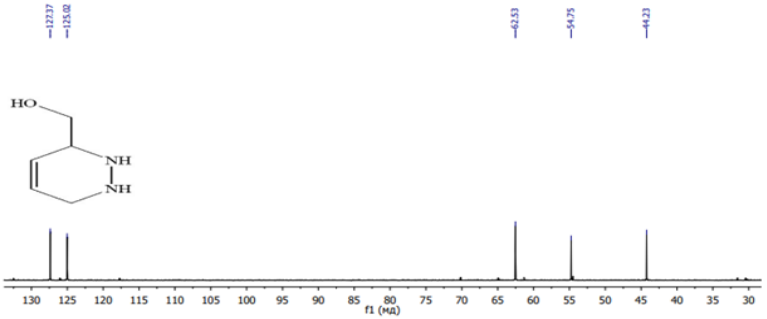
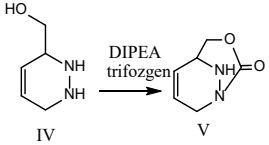


Figure 2. ^{13}C NMR spectra spectra (S) - (1,2,3,6-tetrahydropyridazine-3-yl) methanol (IV) in D_2O solution

The specific rotation -20º (t = 20^0C, ethanol, c = 0.3%) for the synthesized optically active IV compound was calculated by AUTOPOL-III polyarometer.

3. Synthesis of new bicyclic 1-azafagomine analogues based on (S)-diethyl-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate

Continuing the research, the next step of synthesis is the synthesis of a new bicyclic 1-azafagomine analogue based on optically active (S)-(1,2,3,6-tetrahydropyridazin-3-yl)methanol (IV). For this purpose, the optically active compound IV (in the presence of diisopropyl ethylamine (DIPEA)) was reacted with triphosphene ($C_3Cl_6O_3$) by stirring for 5 minutes at room temperature in a magnetic stirrer. The mixture was purified and a yellow oil (5S)-3-oxa-1,9-diazabycyclo [3.3.1] non-6-en-2-on (V) bicyclic compound was synthesized (scheme 6).



Scheme 6. (5S) -3-oxo-1.9 diazabycyclo [3.3.1] non-6-en-2-on (V) synthesis

The structure of the synthesized compound (IV) by mass, IR, ^1H and ^{13}C NMR spectroscopy methods were approved. The structure of the synthesized compound (IV) by mass, IR, ^1H and ^{13}C NMR spectroscopy methods were approved. CH_2N and CHN groups at 3.81-4.05 m.h., OCH_2 group at 4.45 m.h., the NH (amine) group at 4.60 m.h. are observed as duplets and multiplets in ^1H NMR (400 MHz,

$CDCl_3$) spectrum for (5S) -3-oxo-1.9 diazabycyclo [3.3.1] non-6-en-2-on (V).

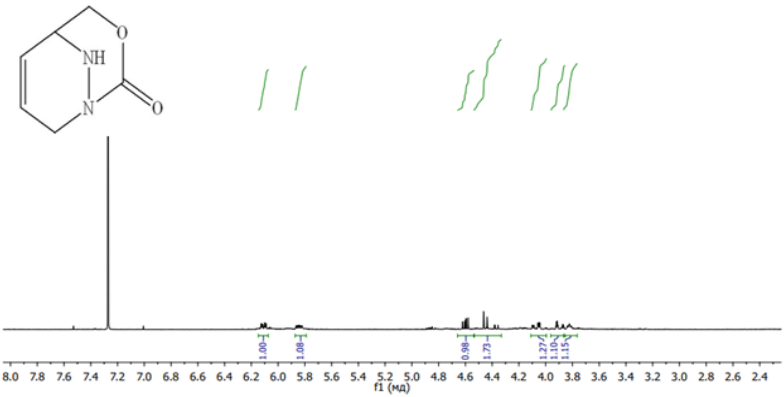


Figure 3. (5S) -3-oxa-1,9-diazabitsiklo [3.3.1] non-6-en-2-onun (V) ^1H NMR spectrum in $CDCl_3$ solution

When it comes to, ^{13}C NMR spectrum for (5S) -3-oxo-1.9 diazabycyclo [3.3.1] non-6-en-2-on (V) carbon atoms of CH_2N and CHN at 48.46 and 52.42 m.h., while the CH_2O group at 74.29 m.h. CH groups which located near the double link at 125.31 and 130.24 m.h., and (COO) group at 162.08 m.h, were recorded.

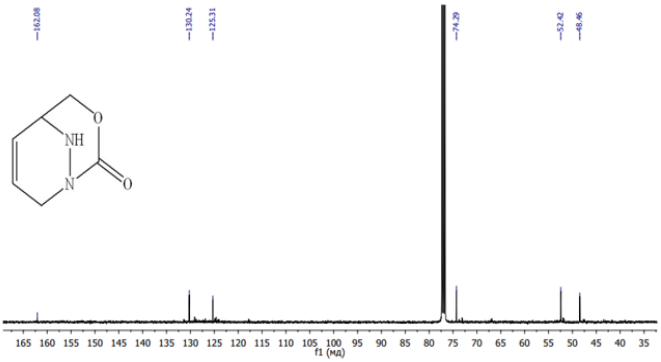
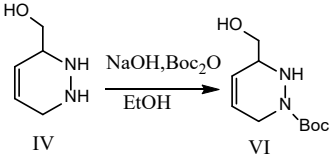


Figure 4. (5S) -3-oxa-1,9-diazabitsiklo [3.3.1] non-6-en-2-onun (V) ^{13}C NMR spectrum in $CDCl_3$ solution

To keep N-1 position as the only nucleophilic center in the molecule for further cyclization in reaction with triphosgene, N-2 position was protected by reaction with Boc (di-tert-butyl dicarbonate) anhydride giving N-Boc-1-azafagomine in 93% yield (scheme 7).



IV VI

Scheme 7. Tret-butyl-(S)-3-(hydroxymethyl)-3,6-dihydropyridazine-1 (2H) - carboxylate (VI) synthesis

The structure of the tret-butyl-(S)-3-(hydroxymethyl)-3,6-dihydropyridazine-1(2H)-carboxylate (VI) compound was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis methods. Methyl protons of the t-butyl group (C $(CH_3)_3$) was recorded at 1.50 m.h., range as singlet form. CH2N and CHN groups at 3.56-3.68 m.h. as duplets and multiplets and CH groups in the form of multiplets at 5.90-5.96 m.h. are observed in the range for proton ^{1}H NMR (400 MHz, D_2O) spectrum of tret-butyl-(S)-3-(hydroxymethyl)-3,6-dihydropyridazine-1 (2H)-carboxylate (VI) compound.

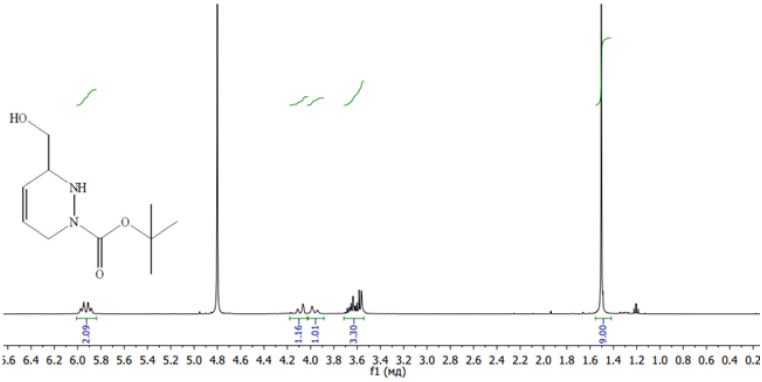


Figure 5. Boc-1-azafagomine (VI) ^{1}H NMR spectrum in D2O solution

Karbon atoms t-Butyl group ($C(CH_3)_3$) at 27.56 m.h., CH_2N, CHN, and hydroxymethyl ($HOCH_2$) groups at 55.87, 61.79, and 61.89 m.h., the CH=CH groups at 125.03 and 125.10 m.h. and ether group were observed at 156.80 m.h. range for ^{13}C NMR spectrum (100 MHz, D_2O) of tret-butyl-(S)-3-(hydroxymethyl)-3,6-dihydro pyridazine-

1(2H)-carboxylate (VI) compound.

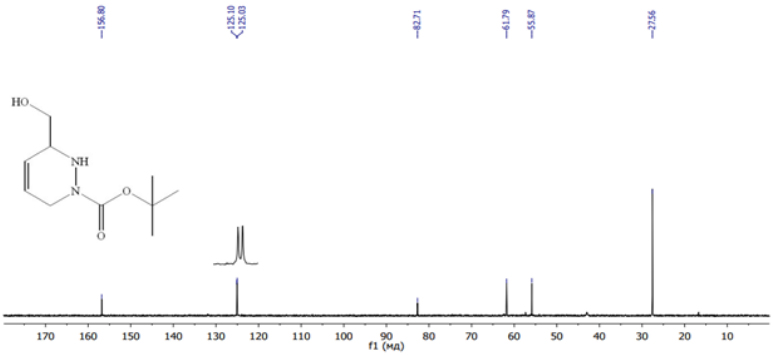
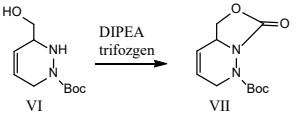


Figure 6. Boc-1-azafagomine (VI) ^{13}C NMR spectrum in D_2O solution

The specific rotation for this compound was found to be equal to [α] D_2O+ 67º (t = 20^0C, dichloromethane, c = 0.78%) in the AUTOPOL III polarimeter.

Obtaining the compound tret-butyl-(S)-3-(hydroxymethyl)-3,6-dihydropyridazine-1 (2H) -carboxylate (VI) resulting in blockade of the N-2position. continue with the synthesis. To do this, the boc-1-azafagomine (VI) compound was reacted in the main medium (in the presence of diisopropyl ethylamine (DIPEA)) with triphosphene ($C_3Cl_6O_3$) at room temperature for 5 min in a magnetic stirrer. The synthesis of the component tetra-butyl-(S)-7-oxo-4a, 5-dihydro-7H-oxazolo [3,4-b] pyridazine-1 (2H)-carboxylate (VII) was possible (scheme 8).



VI VII

Scheme 8. Synthesis of tetra-butyl- (S) -7-oxo-4a, 5-dihydro-7H-oxazolo [3,4-b] pyridazine-1 (2H) -carboxylate (VII)

The structure of the obtained new compound was confirmed by ^1H, ^{13}C NMR and IR spectroscopy methods. Hydrogen protons of CH_2N and CHN groups was recorded at 3.62-3.84 m.h., as duplets and multiplets forms, the tret-butyl ($(CH_3)_3C$) group at 1.38 m.h., OCH_2 group at 4.25-4.64 m.h., and CH groups of the double bond were observed at 5.59- 5.97 m.h. range as multiplet form for proton spectrum ^1H NMR (400 MHz, DMSO) of the tret-butyl- (S) -7-oxy-4a, 5-

dihydro-7H-oxazolo [3,4-b] pyridazine-1 (2H) -carboxylate (VII) compound.

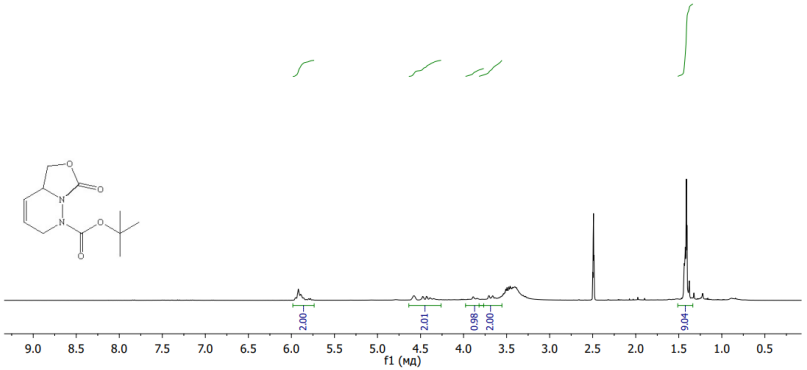


Figure 7. tret-butyl (S)-7-oxo-4a, 5-dihydro-7H-oxazolo [3,4-b] pyridazine-1 (2H) -carboxylate (VII) compound ^{1}H NMR spectrum in DMSO solution

Carbon atoms of tret-butyl ($(CH_3)_3C$) group was recorded at 27.74 m.h., but CH_2N, CHN and OCH_2 groups at 56.21, 58.00 and 61.14 m.h., in the ^{13}C NMR (100 MHz, DMSO) spectrum of the tret-butyl-(S)-7-oxy-4a,5-dihydro-7H-oxazolo [3,4-b] pyridazine-1 (2H) -carboxylate (VII) compound. The signal of the carbon atoms of the CH groups near the double bond at 123.81 and 124.58 m.h., and the ester groups are observed at 152.64 and 153.66 m.h., respectively.

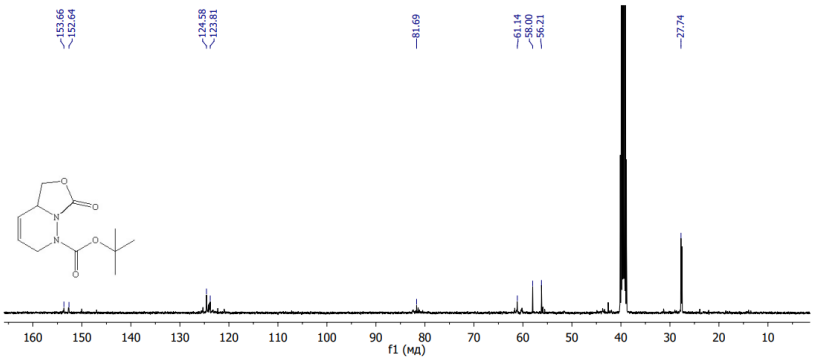
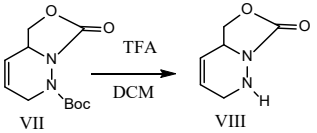


Figure 8. tret-butyl (S)-7-oxo-4a, 5-dihydro-7H-oxazolo [3,4-b] pyridazine-1 (2H) -carboxylate (VII) compound ^{13}C NMR spectrum in DMSO solution

The specific rotation for this compound was found to be equal to [α]

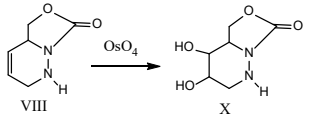
D_2O + 30º (t = 20^0C, dichloromethane, c=0.4%) in the AUTOPOL III polarimeter. In the next stage of synthesis, the deprotection of Boc_2O group leads to formation of (S)-1,2,4a, 5-tetrahydro-7H-oxazolo [3,4-b] pyridazine-7-on (VIII) (scheme 9).



Scheme 9. Synthesis of (S) -1,2,4a, 5-tetrahydro-7H-oxazolo [3,4-b] pyridazine-7-on (VIII)

The structure of the synthesized optically active compound was confirmed by ^{1}H, ^{13}C NMR and IR spectroscopy.

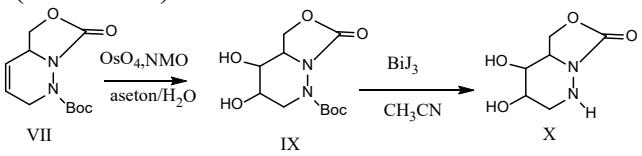
Continuing the research, cis-dihydroxylation of (S)-1,2,4a,5-tetrahydro-7H-oxazolo [3,4-b] pyridazine-7-on (VIII) in the presence of OsO4 and (S)-hexahydro-7H-oxazolo [3,4-b] pyridazine-7-on (X) compound was synthesized (scheme 10).



Scheme 10. Synthesis of (S) -hexahydro-7H-oxazolo [3,4-b] pyridazine-7-on (X) compound

However, the (S)-hexahydro-7H-oxazolo[3,4-b] pyridazine-7-on(X) compound obtained during the reaction was obtained with very low yield (3%). The synthesis was performed in a different direction to obtain the X compound with high yield. To do this, first tret-butyl-(S)-7-oxo-4a, 5-dihydro-7H-oxazolo [3,4-b] pyridazine-1 (2H) -carboxylate (VII) compound osminium tetroxide (OsO_4) cis-dihydroxylation in the presence of N-methylmorpholine N-oxide ($C_5H_{11}NO_2$) and tert-butyl-(S)-7-oxotetrahydro-7H-oxazolo [3,4-b] pyridazine-1 (2H) -carboxylate (IX) diole was synthesized with high yield. N-Boc deprotection was also done in the presence of HCl, H_2SO_4, H_3PO_4, $BF_3{\cdot}OEt_2$, TMSI, TMSOTf, $TiCl_4$, $SnCl_4$, $AlCl_3$, Sn $(OTf)_2$, $K_3PO_4{\cdot}H_2O$ (under microwave conditions), iodine and ZnBr2. However, all these procedures were ineffective. This failure prompted us to find new catalyst for N-Boc deprotection of azasugars. According to the literature data, BiI_3 is a mild ecofriendly Lewis acid, which acidity less than TFA. In addition to this, it was found

that it catalyzes deprotection of acetals in water. Considering success in deprotection of acetals using BiI_3, we decided to use this catalyst for N-Boc deprotection of azasugars. Reflux of compound IX in water in the presence of BiI_3 for 16h led to the final novel compound in 55% yield (scheme 11).



Scheme 11. Synthesis of (S)-hexahydro-7H-oxozolo[3,4-b]pyridazin-7-one (X) compound based on tert-Butyl-(S)-7-oxotetrahydro-7H-oxozolo [3,4-b]pyridazine-1 (2H)-carboxylate (IX)

The structures of the synthesized compounds were confirmed by mass, IR, ^1H and ^{13}C NMR spectroscopy methods. In the proton 1H NMR spectrum (400 MHz, $CDCl_3$) of the (S)-hexahydro-7H-oxazolo [3,4-b] pyridazine-7-on (X) the CH2N and CHN groups at 3.34 and 3.46 m.h., range as duplets and multiplets forms , the methyl groups in the tret-butyl ($(CH_3)_3C$) group at 1.50 m.h., and the OCH_2 group at 3.81 m.h. hydroxyl groups at 3.6 m.h., and CH groups attached to the hydroxyl group at 3.91 and 4.34 m.h. are observed as multiple form.

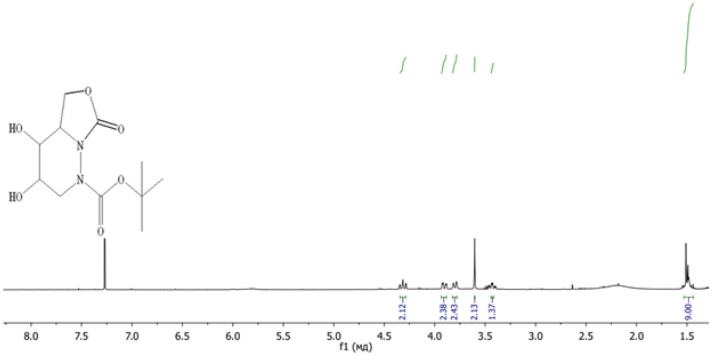


Figure 9. tret-butyl- (S) -7-oxotrethidro-7H-oxazolo [3,4-b] pyridazine-1 (2H) -carboxylate (IX) ^{1}HNMR spectrum in $CDCl_3$ solution

When it comes to, carbon spectrum ^{13}C NMR (100 MHz, $CDCl_3$), carbon signals of the methyl groups at 28.07 m.h, CH_2N and CHN groups at 29.68 and 36.53 m.h, respectively, and CH groups combined with OCH_2 and hydroxyl groups were appeared at 65.16, 66.44

and 68.83 m.h. The quaternary carbon atom attached to the oxygen in the tret-butyl group was featured at 82.60 mH, while the ester groups are observed at 155.96 and 162.62 mH, respectively.

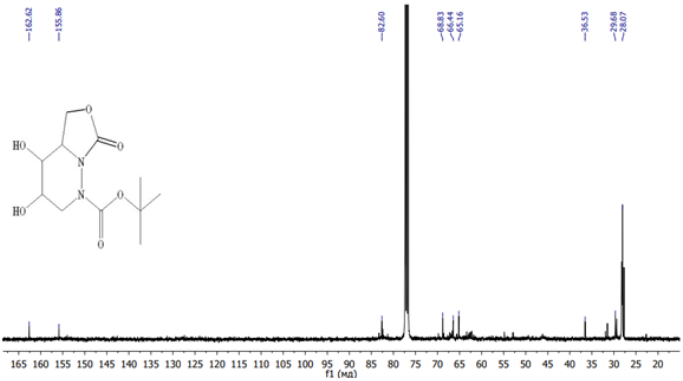


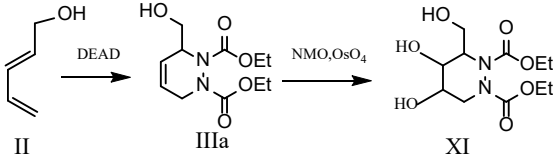
Figure 10. tret-butyl- (S) -7-oxotrethidro-7H-oxazolo [3,4-b] pyridazine-1 (2H) -carboxylate (IX) ^{13}C NMR spectrum in CDCl3 solution

It is already known that the main purpose of our research is synthesis optically active diethyl (S)-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate (III) and the synthesis of new azafagomine derivatives based on optically active adduct. Thus, based on successive transformations, the research results were continued with the synthesis of bicyclic azasugars based on tret-butyl-(S)-3-(hydroxymethyl)-3,6-dihydropyridazine-1(2H)-carboxy late (VI)compound. Then the cleavage of Boc protected group from tret-butyl- (S) -7-oxotrethidro-7H-oxozolo [3,4-b] pyridazine-1 (2H) -carboxylate (IX) leads synthesis of (S)-hexahydro-7H-oxozolo [3,4-b] pyridazine-7-on (X) compound.

4. Transformations of racemic diethyl-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate synthesized based on Dils-Alder reaction.

As already mentioned, we synthesized optically active (S) -diethyl-3-(hydroxymethyl)-3,6-dihydropyridezin-1,2-dicarboxylate (III) accor ding to the Bols protocol, modified by the enantioselective method in the presence of a chiral catalyst. Continuing our research, dihydroxylation of compound III synthesized in the next stage was carried out in the presence of 4-methylmorpholine-N-oxide (NMO) and osmium

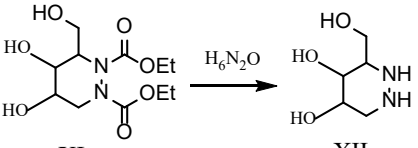
tetraoxide and high-yield diethyl (3R, 4R, 5S)-4,5-dihydroxy-3-(hydroxymethyl) tetrahydropyridazine-1,2-dicarboxy late was synthesized. Continuing our research, dihydroxylation of compound III synthesized in the next stage was carried out in the presence of 4-methylmorpholine-N-oxide (NMO) and osmium tetraoxide and high-yield diethyl (3R,4R,5S)-4,5-dihydroxy-3-(hydroxymethyl) tetrahydropyridazine-1,2-dicarboxylate was synthesized (XI) (scheme 12).



II IIIa XI

Scheme 12. Synthesis of diethyl-3- (hydroxymethyl) -3,6-dihydropyridazine-1,2-dicarboxylate (III) and triol (XI)

The next step is the synthesis of the diamino triol by cleavage of ester groups. Studies have shown that, triol (diethyl (3S, 4S, 5R)-3-(hydroxymethyl)-4,5-dimethyltetrahydropyridazine-1,2-dicarboxyla te) (XI) hydrazine is dissolved in hydrate by heating at 100^0C for 18 hours leads to the cleavage of groups and the synthesis of diamino triol-5-epi-1-azafagomine (3S,4S,5R)-4,5-dimethylhexahydro pyri dazine-3-yl) methanol (XII). The NMR spectra of the XII association overlap with the literature data (Scheme 13).

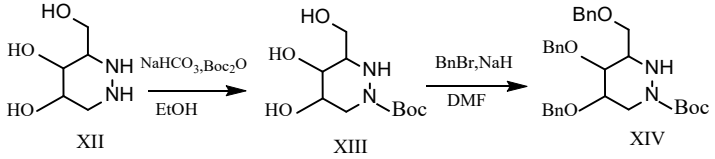


XI XII

Scheme 13. (3S, 4S, 5R) -4,5-dimethylhexahydropyridazine-3-yl) methanol (XII) synthesis

To keep N1 position only one nucleophile center firstly N2 position was protected by Boc_2o protecter group at the end XIII (tert-butoxy-methanone((3S,4S,5R))-1,4,5-trimethylhexa hydropyri dazine-3-year) methanol (N-Boc-5-epi-1-azafagomine) is obtained. The next step is the protecting of hydroxyl groups. For this purpose, ((3S, 4S, 5R) -1,4,5-trimethylhexahydropyridazine-3-year) methanol) (XIII) was reacted with benzyl bromide in the presence of NaH and the protection of the hydroxyl groups leads to synthesize of (tret-

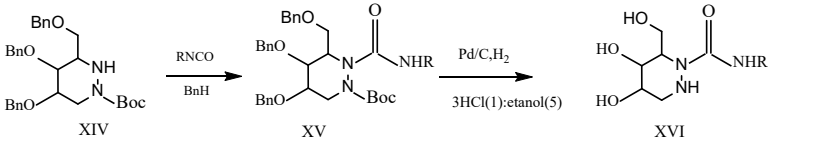
butoxy-methanon (3S,4S,5R)-3-((benzyloxy)methyl)-1,4,5-trimethyl hexahydropyridazine benzyl oxide) (XIV) compound (scheme 14).



XII XIII XIV

Scheme 14. Synthesis of tert-butoxy-methanone(3S,4S,5R)-3-((benzyloxy)methyl)-1,4,5-trimethyl hexahydropyridazine benzyloxidand (XIV)

The progress of the reactions and the purity of the obtained compounds were controlled by the thin layer chromatography (TLC) method. The structure of the synthesized compounds was verified by IR, NMR spectroscopy methods.



XIV XV XVI

R=p-NO$_2$C$_6$H$_4$(XVa),C$_4$H$_9$(XVb), **R=p-NO$_2$C$_6$H$_4$(XVIa),C$_4$H$_9$(XVIb)**

Scheme 14. Synthesis of N-carboxamide derivatives of azafagomine.

Continuing the research, 5-epi-1-azafagomine (N-Boc-tri-O-benzyl-5-epi-1-azafagomine-N-p-nitrophenylcarboxomide) (XVa-b) derivatives were synthesized with a high yield by affecting the N-1 position with various isocyanates. Hydrogenation was carried out by heating in the presence of Pd/C to deprotect of protecter groups. Thus, as a result of research studies, N-carboxyamide derivatives with biological activity were synthesized by acting on the N1 nucleophilic center of azafagomin derivatives with various isocyanates.

5. Antimicrobial and inhibitory properties of some synthesized compounds.

As we know, azafagomine and its various derivatives are known to science as glucosidase inhibitors. Many glucosidase inhibitors have anti-diabetic, anti-viral, anti-fungal and anti-bacterial, anti-tumor, and anti-heart effects. In addition, immunosuppressants have shown positive results in the treatment of antiproliferative, antihypertensive, anti-AIDS and malaria. 1-Azafagomine and their analogues

show such biological activity, which makes it necessary to synthesize new species. The antimicrobial properties of the substances and antibiotics studied (cefotaxime and ceftriaxone) were first studied against two different gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli bacteria*. During the research, it was determined that the studied compounds IV-XI and XI-XVI(a,b) have antimicrobial activity against these bacteria (Table 1), (Table 2).

Table 1.

Antimicrobial activity of the studied substances against *S. aureus* bacteria

Maddələr və saf antibiotiklər	Sefotaksim	Seftriakson	Maddə IV	Maddə V	Maddə VI	Maddə VII	Maddə VIII	Maddə IX	Maddə X	Maddə XI	Maddə XII	Maddə XIII	Maddə XVa	Maddə XVb	Maddə XVIa	Maddə XVIb
Minimum inhibiləşmə konsentrasiya (μg/mL)	4	4	4	1	7	6	6	1	0.5	2	2	3	2	1	4	7

Table 2.

Antimicrobial activity of the studied substances against *E. coli bacteria*

Substances and pure antibiotics	Cefotaxime	Ceftriaxone	Compound IV	Compound V	Compound VI	Compound VII	Compound VIII	Compound IX	Compound X	Compound XI	Compound XII	Compound XIII	Compound XIV	Compound XVa	Compound XVb	Compound XVIa
Minimum inhibitory concentration (μg/mL)	4	4	4	9	10	9	7	0.5	0.25	4	4	4	4	4	7	4

The next stage of the research is to study the activity of the synthesized compounds against gram-negative *K. pneumoniae* bacteria. For this, the minimum antimicrobial activity of substances was determined using the microwashing method. (Table 3.).

Table 3.

Antimicrobial activity of the studied substances against *Klebsiella pneumoniae* bacteria

Substances and pure antibiotics	Cefotaxime	Ceftriaxone	Compound IV	Compound V	Compound VI	Compound VII	Compound VIII	Compound IX	Compound X	Compound XVb	Compound XVIa
Minimum inhibitory concentration (μg/mL)	3	3	3	1	6	5	5	1	0.5	3	6

Given the broad-spectrum activity of imino sugars, the antifungal activity of the above substances has been studied. Thus, studies on diploid fungus Candida albicans, the causative agent of candidiasis,

were conducted and positive results were obtained (Table 4.).

Table 4.

Antimicrobial activity of the studied substances against *C. albicans* bacteria

Researched compounds	Microorganism	Concentration µg/ml	Inhibition zone Φ,%		
			Disco-diffusion method, %	Zonal diffusion method,%	
				0.1 ml	0.2 ml
VI	*Candida albicans*	15	58	61,8	66,7
VII			75	84,2	87,1
VIII			89	92	94
IX			65	72	80
X			72	78	85
XIV			58	61,8	66,7
XVa			75	84,2	87,1
XVb			51	61,7	65,8

Given the importance of the synthesis of new drugs against this bacterium, the antibacterial activity of the compounds we synthesized against the bacterium *Acinetobacter baumannii* was also studied (Table 5).

Table 5.

Antimicrobial activity of the studied substances against *A. baumannii* bacteria

Researched compounds	Microorganism	Concentration, µg/ml	İnhibiləşmə zonası Φ,%		
			Disco-diffusion method , %	Zonal diffusion method , %	
				0.1 ml	0.2 ml
IV	*Acinetobacter baumannii*	15	78,9	77,8	82,7
V			90	90	98
VI			65	70,8	79
VII			85	78	90
VIII			70	75	79,9
IX			62	64,7	70
XVb			77	76,8	80,7
XVIa			75	84,2	87,1
XVIb			89	92	94

Gram-negative *Acinetobacter baumannii*, which is the main cause of respiratory infections and is widespread and high risk, as well as highly resistant to many antibiotics, is one of the main bacteria causing various diseases, including meningitis, pneumonia, wound inflammation, and urological diseases. Given the importance of the synthesis of new drugs against this bacterium, the antibacterial activity of the compounds we synthesized against the bacterium Acinetobacter baumannii was also studied. It is known from the literature that immunosuppressants play an effective role in the treatment of many diseases by inhibiting various enzymes. Thus, compounds

that inhibit glucosidase enzymes can be used in the treatment of diabetes. In this regard, the effect of the following compounds on the activity of the enzyme glucosidase was studied (Table 6).

Table 6.

Measurement of α-glucosidase and β-glucosidase inhibition

Compound	α -Glucosidase (bakers yeast)	β-Glucosidase (almonds)
(±)-IV	>1000[a]	137[a]
(±)-VIII	12.7[b] μM	14.0[b] μM
(±)-X	91.6[b] μM	9.0[b] μM
(a) pH 6.8, (b) pH 7.0		

We can mention that (S)-hexahydro-7H-oxozolo[3,4-b]pyridazin-7-one (X), (S)-1,2,4a,5-tetrahydro-7H-oxozolo[3, Compounds 4-b]pyridazin-7-one (VIII) and (S)-(1,2,3,6-tetrahydropyridazin-3-yl) methanol (IV) showed glucosidase inhibitory properties.

6. Biological activity and molecular docking analysis of some synthesized bicyclic azafagomine derivatives.

Theoretical chemistry is progressing and improving day by day. Without conducting an experimental process with the theoretical calculations, a lot of information is obtained about the biological activities of molecules and their effects on human metabolism. In this study, the biological activities of some bicyclic molecules against enzyme were compared. With these calculations, molecules with the high activity are expected to be used as drugs for human metabolism in the future. Many studies have shown that it is not possible to use every molecule synthesized as a drug of human metabolism, for this, some bicyclic molecules have been ADME/T analysis. With this analysis, the biological effects of molecules on human metabolism were theoretically examined. To prove that the above-mentioned features will be successfully used in future anti-diabetic drugs, synthetic bicyclic azafagomine analogues have been used by molecular docking analysis (Figure 11), (Figure 12), (Figure 13).

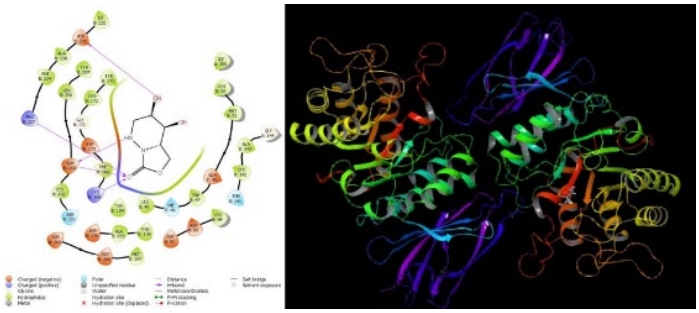


Figure 11. Interaction of X molecule with α-glucosidase enzyme.

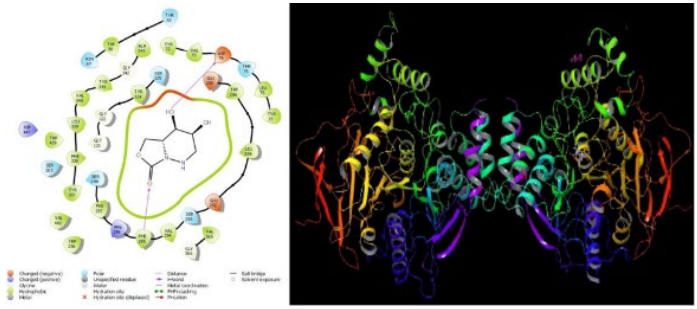


Figure 12. Interaction of X molecule with acetylcholinesterase (AKE) enzyme.

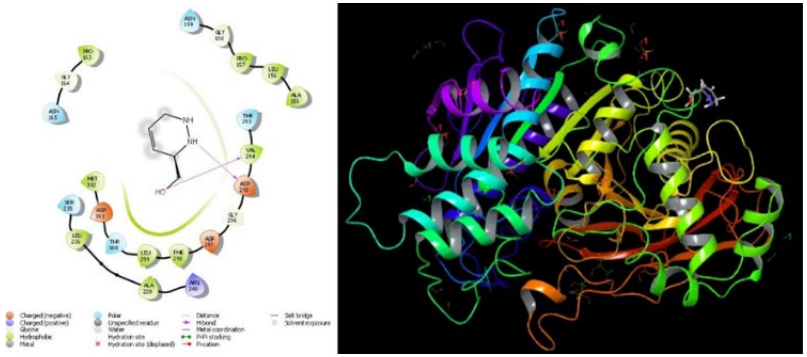


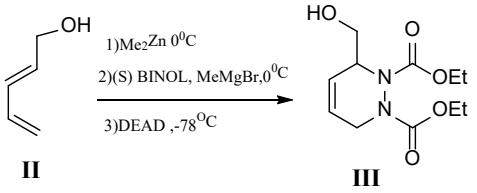
Figure 13. Interaction of IV molecule with butyrylcholinesterase (BKE) enzyme.

Molecular dockingcalculations of some of the bicyclic molecules were made and the biological activities of the molecules were

compared because of the calculations. As a result of these calculations, many parameters were obtained from the interaction of some of the bicyclic molecules with enzymes The most important parameter among the parameters obtained to compare the biological activities of some of the bicyclic molecules is docking scooter. After comparing the biological activities of some of the bicyclic molecules, it is necessary to investigate whether these molecules can be used as drugs in the future. For this examination, ADME/T analysis of molecules should be done. It was found that vicinal nitrogens in iminosugars structure demonstrate different reactivity, which allowed an efficient regio-control in the synthesis. In addition to this removing of the protective group was performed using newly found ecofriendly catalyst for N-Boc deprotection. The parameters obtained from molecular docking calculations of some of the bicyclic molecules and ADME/T analysis results showed that there is no theoretical problem in the future use of these molecules as drugs. These compounds recorded as anti-cholinesterase, are chemicals that prevent the breakdown of the neurotransmitter ACh or BCh. Additionally, the compounds were investigated for BChE, AChE, α-glycosidase enzymes inhibition effects. As we explained above, novel complexes IV and X may be good candidate drugs, the same as AChE, BChE, α-glycosidase inhibitors, respectively.

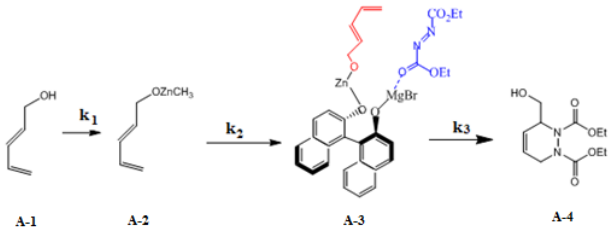
7. Mathematical modelling of the synthesis process of optically active (S)-diethyl-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate

The modified Bols method was used to create optically active (S)-diethyl-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate (III).



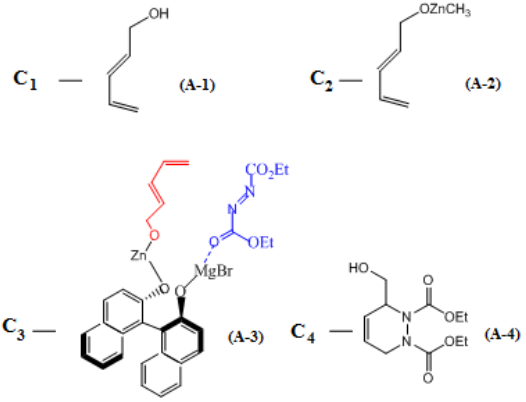
II **III**

To build a mathematical model of the process, the following probable mechanism was mainly adopted for the analysis of the kinetic experiments conducted and the research of literature sources:



(2.1)

As can be seen from the general formula of the reactions, various intermediates are obtained during the production of azafagomin and their derivatives. To simplify the writing of kinetic equations, the following notation is adopted:



Considering the notations shown above, the material balance equations for the components can be written as follows for this mechanism.

$$\begin{aligned}
\frac{dc_1}{d\tau} &= -k_1 c_1^{\alpha_1} c_2^{\alpha_2} \\
\frac{dc_2}{d\tau} &= -k_1 c_1^{\alpha_1} c_2^{\alpha_2} - k_2 c_3^{\alpha_4} c_2^{\alpha_3} \\
\frac{dc_3}{d\tau} &= k_1 c_1^{\alpha_1} c_2^{\alpha_2} - k_2 c_3^{\alpha_4} c_2^{\alpha_3} - k_3 c_3^{\alpha_5} c_4^{\alpha_6} \\
\frac{dc_4}{d\tau} &= k_2 c_2^{\alpha_3} c_3^{\alpha_4} - k_3 c_4^{\alpha_6} c_3^{\alpha_5} \\
\frac{dc_5}{d\tau} &= k_3 c_3^{a_5} c_4^{a_6}
\end{aligned} \qquad (2.2)$$

α_i -compositions of the reaction according to its components; k_j - the reaction rate constants.

The kinetic model (2.2) uses a combination of Powell's, Rosenbrock's, and McCormick's algorithms, which are non-linear programming methods, to find the parameters of the kinetic model, and Kutta-Merson's algorithm is used to solve the system of differential equations (2.2). The comparison of the values calculated by the model with the experimental values showed that the kinetic model based on the above mechanism represents the process more accurately. The observed values of the indicators are given in table 7.

Table 7.

Values of kinetic model indicators (2.4) at different temperatures

t, °C	k_1	k_2	k_3	α_1	α_2	α_3	α_4	α_5	α_6
20	0.4589	0.4078	0.3727	0.5	0.6	1	0.6	1	1
30	0.5502	0.4568	0.4623	0.5	0.6	1	0.6	1	1
50	0.7646	0.5611	0.6833	0.5	0.6	1	0.6	1	1

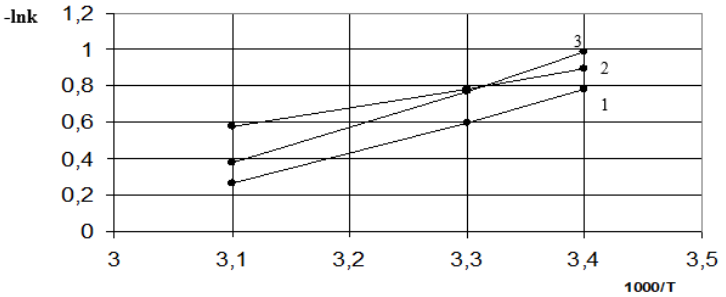


Figure 14. Dependence of logarithms of reaction rate constants on 1/T
1-lnk1; 2-lnk2; 3-lnk3

It is clear from Figure 14 that the inclination angle of 1/T is smaller than the others, that is, the activation energy of the second reaction is smaller than the 1st and 3rd reactions. It is known that the dependence of the rate constant of a chemical reaction on temperature is expressed by the Arrhenius equation. Using the values of the rate constants of the reaction at different temperatures (table 7), their Arrhenius indices were found with the help of the least squares method. The values of these indicators are given in table 8.

Table 8.

Found values of Arrhenius indicators

Arrhenius indicators	k_1	k_2	k_3
$\ln k_{0j}$	4.7176	2.5384	5.5401
$E_I, \frac{kkal}{mol}$	3.2	2.0	3.8

Considering the found values of the Arrhenius indices of the reactions shown in Table 8 and the composition of the reactions according to the components shown in Table 7 in the kinetic model (2.2), the kinetic equation of the process is obtained as follows:

$$\frac{dc_1}{d\tau} = -111.9e^{-\frac{3200}{RT}} c_1^{0.5} c_2^{0.6}$$
$$\frac{dc_2}{d\tau} = -111.9e^{-\frac{3200}{RT}} c_1^{0.5} c_2^{0.6} - 12.66e^{-\frac{2000}{RT}} c_2^{0.6} c_3$$
$$\frac{dc_3}{d\tau} = 111.9e^{-\frac{3200}{RT}} c_1^{0.5} c_2^{0.6} - 12.66e^{-\frac{2000}{RT}} c_2^{0.6} c_3 - 254.7e^{-\frac{3800}{RT}} c_3 c_4 \quad (2.3)$$
$$\frac{dc_4}{d\tau} = 12.66e^{-\frac{2000}{RT}} c_2^{0.6} c_3 - 254.7e^{-\frac{3800}{RT}} c_3 c_4$$
$$\frac{dc_5}{d\tau} = 254.7e^{-\frac{3800}{RT}} c_3 c_4$$

Here, R is the universal gas constant; $R = 1.987 \frac{kal}{mol.^0 K}$

(2.3) by comparing the results of kinetic experiments with the solution of the system of differential equations, it is determined that the calculated indicators are very close to each other. According to the results obtained from the kinetic experiments (2.3), the average relative error for the conversion of A-1 is 3.1%, for A-2 is 1.6%, for A-3 is 1.9%, and for A-4 is 3.4 is %. The values of the errors and their irregular distribution allow us to say that the established kinetic model (2.3) is adequate for the process. Based on this model, it is possible to optimize the process of obtaining an optically active cycloadduct based on 1-azafagomine.

CONCLUSIONS

1. For the first time, an optical active based on the enantioselective Diels–Alder reaction in the presence of (S)-BINOL was synthesized using DEAD (diethyl azodicarboxylate) instead of 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) by modifying the Bols method The synthesis of (S)-diethyl-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate, which acts as a synthon in the formation of mono- and bicyclic azafagomin analogs, was completed with high yield. [3,7].
2. A new optically active (S)-(1,2,3,6-tetrahydropyridazin-3-yl)methanol was synthesized based on (S)-diethyl-3-(hydroxymethyl)-3,6 dihydropyridazine-1,2-dicarboxylate by a new method. [2,4,6]
3. New optically active bicyclic azafagomin analogs were synthesized based on (S)-(1,2,3,6-tetrahydropyridazin-3-yl)methanol, their structures were confirmed by IR, NMR spectroscopy methods, and the specific rotation was determined in an AUTOPOL-III polarimeter. [11,14]
4. Rasemic diethyl-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate was synthesized using a modified Bols method based on the Dils-Alder reaction, and mono azafagomin derivatives were obtained after a series of conversion reactions. [8]
5. New N-carboxyamide derivatives were obtained by affecting the N1 nucleophilic center in the synthesized azafagomin derivatives with various isocyanates, and their biological properties were studied. [1, 5]
6. The antimicrobial properties of synthesized azafagomin derivatives were studied, and it was determined that they show more effective antimicrobial properties compared to several drugs. [9, 10]
7. The biological activity of the synthesized mono- and bicyclic azafagomin derivatives was determined based on comparative calculations using the molecular docking method. It was deter-

mined that some azafagomin derivatives synthesized by the molecular docking method have the properties of antidiabetic drugs. [12, 13]

Published scientific papers on dissertation materials:

1. Akhundova, F.N. Synthesis of 5-epi-1-Azafagomin derivatives and measurement of their activity as α-, β-glucosidase inhibitors / F.N. Akhundova, M.J. Alves, A.M. Maharramov, M.M. Gurbanova // News of Baku University. Natural sciences series, - Baku: - 2018. No. 1, - p. 12.
2. Axundova, F.N. Synthesis of bicyclic 1-azafagomine analogue obtained from (S)-(1, 2, 3, 6-tetrahydropyridazin-3-yl) methanol / F.N.Axundova, M.M.Qurbanova, M.J.Alves // Journal of Low Dimensional Systems, – Bakı: – 2019. v. 3, № 1, – s. 24-27.
3. Axundova, F.N., Alves, M.J., Qurbanova, M.M. The synthesıs of diethyl (R)-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate in the presence of (R)-binol catalyst // Kimyanın aktual problemləri adlı XIII respublika elmi konfransı, – Bakı: – 15 – 16 may, – 2019, – 42 s.
4. Axundova, F.N., Alves, M.J., Qurbanova, M.M. 1-Azafaqomin analoqu (s)-(1, 2, 3, 6-tetrahidropiridazin-3-il) methanolun sintezi // Kimyanın aktual problemləri adlı XIII respublika elmi konfransı, – Bakı: – 15 – 16 may, – 2019, – 43 s.
5. Axundova, F.N, Kurbanova M.M, Huseynzada A.E, Alves M.J. Synthesis of new analogues of azasugars on the basis of optically active diethyl (S)-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate // The Fifth International Scientific Conference “Advances in Synthesis and Complexing”, – Moscow: – 22 – 26 April, – 2019, – p. 102.
6. Akhundova, F.N., Alves, M.J., Gurbanova, M.M. (S)-(1,2,3,6-tetrahydropyridazin-3-yl)methanol synthesis of a new bicyclic 1-azafagomine analogue // III International Scientific conference of Young Researchers Proceedings, – Baku: – April 29 – 30, – 2019, – s. 160.
7. Akhundova, F.N., Kurbanova, M.M., Huseynzada A.E, Alves M.J, Acar, T. New Bicyclic Analogues of Optically Active

Diethyl-(S)-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate-Based Azasugars Synthesis // 31. National Chemistry Congress, - Istanbul: - September 10 - 13, - 2019, - p. 382.
8. Akhundova. F.N. Synthesis of new derivatives of iminosaccharides based on (S)-(1,2,3,6-tetrahydropyridazin-3-yl) methanol / F.N. Akhundova, M.M. Kurbanova, A.E. Huseynzade, M. J. Alves. // Journal of organic chemistry, – 2019. т. 55, No. 12, - c. 1942-1946.
9. Axundova, F.N. Synthesis of new of bicyclic analogues of azasugars and investigation of their biological activity // – Bakı: Journal of Baku Engineering University, – 2019. v. 3, № 1, – p. 59-63.
10. Akhundova. F.N. Synthesis of new derivatives of iminosaccharides and the study of their antibacterial activity // – Baku: Young Research Journal, – 2019. t. 5, No. 2, – p. 57.
11. Axundova, F.N. Synthesis and bioactivity of new analogue of bicyclic 1-Azafagomine / F.N.Axundova, M.M.Kurbanova, A.E.Huseynzada, A.R. Sucayev. // Chemistry Select, – 2019. v. 4, – p. 13384-13387.
12. Parham, T. Biological activity and molecular docking study of some bicyclic structures: antidiabetic and anticholinergic potentials / T.Parham, F.N.Axundova, M.M.Kurbanova V.M.Farzaliyev, F.Türkan, B.Tuzun, A.M.Məhərrəmov, A.R. Sucayev, N.Sadeghian, I.Gülçin. // Polycyclic Aromatic Compounds, – 2021. – p. 1-14.
13. Akhundova, F.N., Gurbanova, M.M., Maharramov, A.M., Farzaliyev, V.M., Gulchin, I., Taslimi, F., Sucayev, A.R., Turkan, F., Tuzun, B., Alvasel, S. Molecular docking analysis of synthesized optically active 1-azafagomin analogues // XIV republican scientific conference entitled Current problems of chemistry, - Baku: - May 25-26, - 2021, - p. 25-27.
14. Akhundova, F.N. Synthesis of new optically active bicyclic analogues of azasugars / F.N. Akhundova, M.M. Kurbanova, M.J. Alves, A.M. Maharramov. // Journal of scientific works, - Baku: - 2021. - p. 154-159.

The defense will be held on 27th October 2022 at 14^{00} at the meeting of the Dissertation council ED 1.16 of Supreme Attestation Commision under the President of the Rebublic of Azerbaijan operating at the Institute of Petrochemical Processes named after acad. Y.H. Mammadaliyev of the Ministry of Science and Education of the Republic of Azerbaijan

Address: AZ 1025, Baku, Khojaly ave., 30

Dissertation is accessible at the library of the Institute of Petrochemical Processes named after acad. Y.H. Mammadaliyev of the Ministry of Science and Education of the Republic of Azerbaijan

Electronic versions of dissertation and its abstract are available on the official website of the www.nkpi.az

Abstract was sent to the required addresses on 22th September 2022

Signed for print: 22.09.2022
Paper format: 60×90 1/16
Volume: 38 798 characters
Number of hard copies: 20