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СИНТЕЗ И СВОЙСТВА ТРИАЗОЛСОДЕРЖАЩИХ ТРЕХЗВЕННЫХ ПРОДУКТОВ С 4-ЦИКЛОГЕКСИЛФЕНОКСИГРУППАМИ

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В ходе исследования разработан метод получения нециклического трехзвенного продукта (ТЗП) с 4-циклогексилфеноксигруппами и его металлокомплексов с галлием, медью и цинком, исходными соединениями для синтеза которых являются 3,5-диамино-1,2,4-триазол (гуаназол) и 4,5-ди(4-циклогексилфенокси)фталонитрил. Выбор прекурсоров объясняется тем, что гуаназол и его производные используются в качестве лекарственных препаратов и перспективны для химической модификации, а введение объемных групп придает триазолсодержащим соединениям растворимость в широком спектре органических растворителей, способность формировать мезофазы в растворе или при нагревании, а также каталитические, сенсорные, флуоресцентные свойства и фотодинамическую активность. Таким образом, структурные особенности этих прекурсоров позволяют создавать функциональные материалы с практически полезными свойствами. Синтез циклогексилфеноксизамещенного трехзвенного продукта осуществляли добавлением 4,5-ди-(4-циклогексилфенокси)фталонитрила к раствору метилата натрия, после чего в реакционную массу вносили хлорид аммония и гуаназол. Синтез металлокомплексов проводили реакцией вышеуказанного ТЗП с ацетатами Ga, Cu, Zn в 2-этоксиэтаноле. Строение полученных соединений доказано с помощью современных физико-химических методов исследования. Показана возможность их дальнейшего практического применения. Выполнен in silico прогноз, показавший высокую вероятность проявления биологических, антибактериальных и противогрибковых свойств, а значит целесообразность синтеза выбранных молекул. Согласно прогнозу для исследуемых соединений выявлена высокая вероятность проявления биологических, антибактериальных и противогрибковых свойств, что говорит о целесообразности синтеза выбранных молекул. Антибактериальные свойства синтезированных продуктов исследованы дискодиффузионным методом (ДДМ) на нескольких тестовых культурах: наиболее эффективным составом, обеспечивающим максимальную зону ингибирования роста бактерий, стал трехзвенный продукт с галлием, что делает его интересным в качестве потенциального антибактериального лекарственного препарата к грамотрицательным штаммам.

Ключевые слова: 4-циклогексилфенол, 4,5-ди(4-циклогексилфенокси)фталонитрил, синтез, прогноз биологической активности, антимикробные свойства

SYNTHESIS AND PROPERTIES OF TRIAZOLE-CONTAINING THREE-UNIT PRODUCTS WITH 4-CYCLOHEXYLPHENOXY GROUPS

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In the course of this study, a method was developed for obtaining a non-cyclic three-unit product (TUP) with 4-cyclohexylphenoxy groups and its metal complexes with gallium, copper and zinc the parent compounds for the synthesis of which are 3,5-diamino-1,2,4-triazole (guanazole) and 4,5-di(4-cyclohexylphenoxy)phthalonitrile. The choice of precursors is explained by the fact that guanazole and its derivatives are used as drugs and are promising for chemical modification, and the introduction of bulky groups imparts to triazole-containing compounds solubility in a wide range of organic solvents, the ability to form mesophases in solution or upon heating, as well as catalytic, sensory, fluorescent properties and photodynamic activity. Thus, the properties of these precursors make it possible to create functional materials with practically useful properties. The synthesis of cyclohexylphenoxy-substituted three-member product was carried out by adding 4,5-di-(4-cyclohexylphenoxy)phthalonitrile to a sodium methylate solution, after which ammonium chloride and guanazole were added to the reaction mass. The synthesis of metal complexes was carried out by the reaction of the above-mentioned TUP with Ga, Cu, Zn acetates in 2-ethoxyethanol medium. The obtained compounds structure was confirmed using modern physicochemical research methods. The possibility of their further practical application was shown. An in silico prediction was performed, which showed a high probability of biological, antibacterial and antifungal properties exhibit, and therefore the feasibility of the selected molecules synthesis. The antibacterial properties of the synthesized products were studied by the disk diffusion method (DDM) on several test cultures. The most effective composition, providing the maximum zone of bacterial growth inhibition, was a three-link product with gallium, which makes it interesting as a potential antibacterial drug for gram-negative strains.

Keywords: 4-cyclohexylphenol, 4,5-di(4-cyclohexylphenoxy)phthalonitrile, synthesis, biological activity prediction, antimicrobial properties

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Recently, the creation of functional materials with specified properties is based on the principles of "green chemistry", which offer a completely rational management of chemical processes: energy saving, substance saving, waste prevention, rejection of initial toxic substances, reduction of the number of intermediate stages, energy saving, product life cycle assessment, etc [1-4]. Macrocyclic compounds are interesting objects for obtaining materials with useful properties. Aromatic macroheterocycles (Mc) are analogs of porphyrins, but represent a compounds special structural group [5], fundamentally different in their physicochemical characteristics and reactivity [6]. As a result of further functionalization, these compounds can be given a useful properties wide range (solubility in water, intense luminescence, receptor and catalytic properties, etc.) [7]. Chemical modification of the macrosystem is carried out by introducing pharmacophoric fragments [6, 7] or substituents at the periphery [8], as well as various biogenic metals [9, 10].

It is known that 3,5-diamino-1,2,4-triazole (guanazole) and its derivatives are used in medicine as drugs [11]. The introduction of cyclohexyl groups can impart to triazole-containing compounds [12] solubility in chloroform, the ability to form mesophases in solution or upon heating [13], as well as catalytic [14], sensory [15], fluorescent [16] properties and photodynamic activity [17]. Taking into account the properties of these precursors, it is possible to create functional materials with practically useful properties.

Therefore, the aim of this work was to synthesize triazole-containing three-unit products with 4-cyclohexylphenoxy groups as promising functional materials.

EXPERIMENTAL-METHODICAL PART

The study was carried out using the resources of the Center for Collective Use of Scientific Equipment of the ISUCT.

IR spectra were recorded on an AVATAR 360 FT-IR spectrometer. Samples in the tablets form were prepared by thoroughly grinding the test compound in KBr and pressing, or dissolving in an organic solvent and applying the solution to the RS with subsequent evaporation of the solvent.

MALDI-TOF mass spectra were obtained on a Shimadzu Biotech Axima Confidence mass spectrometer in positive ion mode using DHB (2,5-dihydroxybenzoic acid), CHCA (α-cyano-4-hydroxycinnamic acid) as a matrix. Samples were prepared by dissolving the test compound in chloroform (C = 10^{-4} – 10^{-5} mol/l).

Thin-layer chromatography (TLC) was performed on aluminum plates coated with a layer of silica gel 60 F254 (E. Merck). Silica gel grade Silica 60 0.05-0.20 mm (Macherey-Nagel) was used for column chromatography.

The prediction of the synthesized compounds biological activity spectrum was carried out in the PASS, CLC-Pred and Anti-Bac-Pred programs [18, 19].

For a comprehensive assessment of the drug-like compounds characteristics, the freely available WAY2DRUG web portal [18, 19] was used, which includes bioinformatics' methods for data processing and drug design on a single platform.

The antibacterial activity of the synthesized products was assessed using the disk diffusion method (DDM) at the M.B. Stoyunin Regional Anti-Tuberculosis Dispensary on three bacterial strains: *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus Epidermidis.* These bacterial species were chosen as they are widely used in microbiological studies [20].

Synthesis of the parent compounds. 4,5-Bis(4-cyclohexylphenoxy)phthalonitrile **1** [12], guanazole **2** [21] were obtained according to a known methods.

Synthesis of N3,N5- bis[(1Z)- 5,6- bis(4- cyclohexylphenoxy)- 3- imino- 2,3- dihydro- 1H- isoindole- 1- ilidene] - 1H- 1,2,4- triazole- 3,5- diamine (3)

4,5-Bis(4-cyclohexylphenoxy)phthalonitrile **1** (0.86 g, 2 mmol) was added to a sodium methoxide solution prepared by dissolving 0.16 g (6,8 mmol) of metallic sodium in 20 ml of methanol at 20-25 °C and stirred at this temperature for 2 h. After holding, ammonium chloride and 0.4 g (1 mmol) of guanazole **2** were added to the reaction mixture and the temperature was raised to 40 °C. The reaction mass was mixed for 8 h. After holding, the mixture was cooled and poured into water. The formed precipitate was filtered and washed with water, ether and dried in air.

Yield: 1.0 g (95%). IR spectrum, δ, cm^{-1}: 3420 (NH_{val}), 3379 ($NH_{triazol}$), 1590-1530 (NH_{def}), 1500-1450 (C=C), 1275-1040 (C-O-C). MALDI-TOF (CHCA) m/z: 1052 $[M+H]^+$. ^1H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.38 s (8H, c-hex H4); 1.82 m (8H, c-hex, H2.6); 2.41 m (8H, c-hex, H3.5); 2.98 m (4H, c-hex, H1); 4.34 s (2H, =NH); 7.08 d (8H, OPh, H3.5, J = 8.3 Hz); 7.14 s (8H, Pc, H3.6); 7.31 d (8H, OPh, H2.6, J = 8.1 Hz); 7.65 m (8H, OPh, H2.6).

Synthesis of substituted triazoles metal complexes (4a-c).

General procedure: a mixture of 0.31 g (0.5 mmol) of TUP **3** and 0,5 mmol of Ga, Cu, Zn acetates in 15 ml of 2-ethoxyethanol was kept at 80 °C for 90 min. Then mixture was the poured into water, the precipitate was filtered, washed with water, methanol and dried.

Synthesis of (2Z,21Z)- 6,7,17,18- tetrakis(4- cyclohexylphenoxy)- 10,14- diimino- 2,11,13,22,24,25,26- heptaaza- 12- cuprahexacyclo[21.2.1.0^{3,11}.0^{4,9}.0^{13,21}.0^{15,20}] hexacoza- 1(26),2,4,6,8,15,17,19,21,23- decaen- 12- yl acetate (4a).

The compound was obtained from **3** and 0.08 g of copper acetate $Cu(CH_3COO)_2 \cdot H_2O$. Yield: 0.18 (53%). MALDI-TOF (DHB), m/z: 1173 $[M+2H]^+$. ^1H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.29 s (8H, c-hex H4); 1.89 m (16H, c-hex, H2.6); 2.43 m (16H, c-hex, H3,5); 2.58 m (4H, c-hex, H1); 4.63 s (2H, =NH); 7.04 d (8H, OPh, H3.5, J = 8.0 Hz, 1H); 7.14 s (8H, Pc, H3.6); 7.31 d (8H, OPh, H2.6, J = 7.9 Hz).

Synthesis of (2Z,21Z)- 6,7,17,18- tetrakis(4- cyclohexylphenoxy)- 10,14- diimino- 2,11,13,22,24,25,26- heptaaza- 12- zinchexacyclo[21.2.1.0^{3,11}.0^{4,9}.0^{13,21}.0^{15,20}] hexacoza- 1(26),2,4,6,8,15,17,19,21,23- decaen- 12- yl acetate (4b).

The compound was obtained from **3** 0.08 g of zink acetate $Zn(CH_3COO)_2 \cdot 2H_2O$. Yield: 0.19 (56%). MALDI-TOF (DHB), m/z: 1159.08 $[M+H]^+$. ^1H ЯМР (500 MHz, $CDCl_3$), δ, м.д.: 1.29 s (8H, c-hex H4); 1.89 m (16H, c-hex, H2.6); 2.43 m (16H, c-hex, H3.5); 2.58 m (4H, c-hex, H1); 4.95 s (2H, =NH); 7.08 d (8H, OPh, H3.5, J = 8.2 Hz, 1H); 7.14 s (8H, Pc, H3.6); 7.31 d (8H, OPh, H2.6, J = 8.3 Hz).

Synthesis of (2Z,21Z)-6,7,17,18-tetrakis(4-cyclohexylphenoxy)-10,14-diimino-2,11,13,22,24,25,26-heptaaza-12-gallahexacyclo-[21.2.1.0^{3,11}.0^{4,9}.0^{13,21}.0^{15,20}] hexacoza-1(26),2,4,6,8,15,17,19,21,23-decaen-12-yl (4c).

The compound was obtained from **3** and 0.08 g of gallium acetate $Ga(CH_3COO)_2 \cdot H_2O$. Yield: 0.23 (68%). IR spectrum, δ, cm^{-1}: 3292 (NH_{val}), 1590-1530 (NH_{def}), 1500-1450 (C=C), 1275 (C-O-C). MALDI-TOF (DHB), m/z: 1176 $[M^+]$. ^1H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.45 s (8H, c-hex H4); 1.84 m (8H, c-hex, H2.6); 2.41 m (8H, c-hex, H3.5); 2.58 m (4H, c-hex, H1); 6.99 s (8H, Pc, H3.6); 7.05 d (8H, OPh, H3,5, J = 8.0 Hz); 7.14 s (8H, Pc, H3,6); 7.31 d (8H, OPh, H2,6, J = 8.1 Hz).

RESULTS AND DISCUSSION

In the synthesis of cyclohexylphenoxy-substituted three-unit product **3** (three-unit product -TUP **3**) (Scheme 1), 4,5-di(4-cyclohexylphenoxy)phthalonitrile **1** was added to a sodium methylate solution in methanol at 20-25 °C, stirred for 2 hours, then ammonium chloride and guanazole **2** were added, heated to 40 °C, mixed for 8 h, then cooled and poured into water. The resulting precipitate was filtered, washed with water, ether and dried in air.

The synthesis of metal complexes of TUP **4a-c** with copper, zinc and gallium was carried out by heating a mixture consisting of TUP **3** and Ga, Cu, Zn acetates in 15 ml of 2-ethoxyethanol (Scheme 2). The product was isolated by pouring the reaction mass into water, after which the precipitate was filtered, washed with water, methanol, acetone, chloroform and dried.

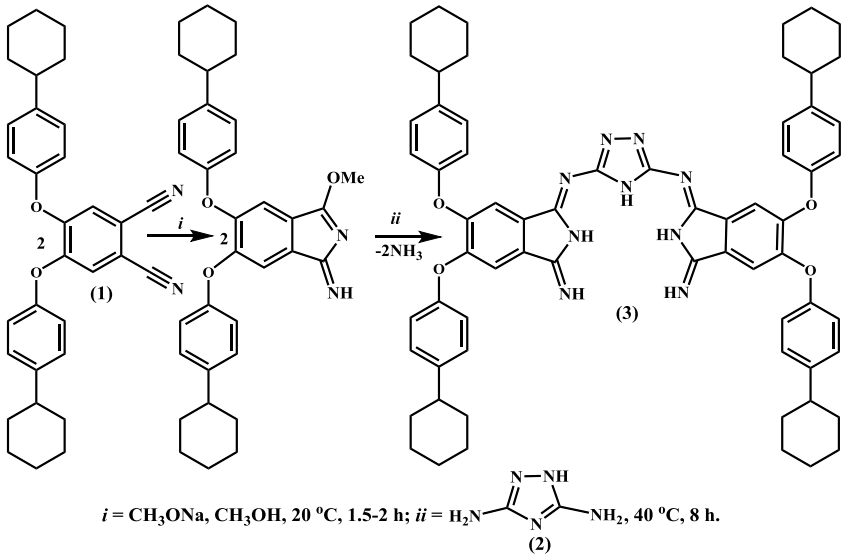

Схема 1
Scheme 1

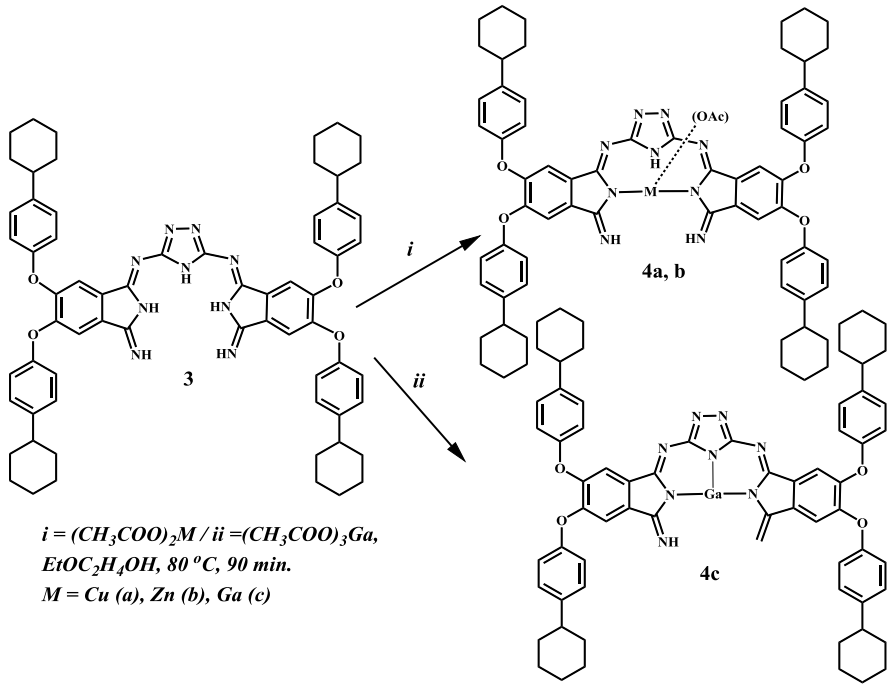

Схема 2
Scheme 2

All the obtained compounds were characterized by physicochemical methods of analysis.

The mass spectra of the synthesized compounds contain peaks of the target products, as well as fragmentation products. The coincidence of the m/z values with the molecular ion mass, as well as the molecular ions characteristic distributions with the calcu

lated values, confirms the structure of compounds **3, 4a-c**.

Figure shows the MALDI-TOF mass spectrum of TUP **3**, recorded using α-cyano-4-hydroxycinnamic acid (CHCA) as a matrix, in which there is a single signal of the molecular ion with m/z = 1052.60 Da, i.e. corresponding to the molecular mass [M+H] of TUP 3.

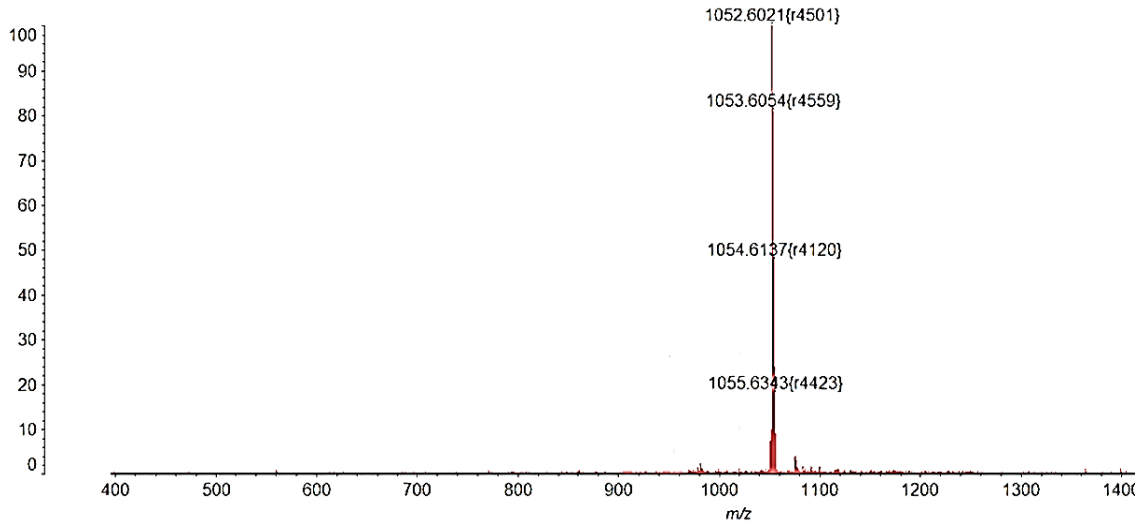

Рис. MALDI-TOF масс-спектр **3** (CHCA)
Fig. MALDI-TOF mass-spectrum of **3** (CHCA)

The IR spectrum of compound **3** contains absorption bands in the region of 3420-3292 cm^{-1} and 1590-1530 cm^{-1}, caused by stretching and deformation vibrations of N-H bond of imino groups, in the region of 1500-1450 cm^{-1}, corresponding to stretching vibrations of C=C bonds of aromatic systems. In addition, there are absorption bands related to stretching vibrations of the C-O-C bonds (1275-1040 cm^{-1}).

As a result of complex formation, the spectral pattern changes significantly. The band in the region of 3200-3500 cm^{-1}, caused by stretching and deformation vibrations of the N-H bond of imino groups, disappears during complex formation. It is also interesting that during the formation of gallium complex **4c**, the band at 3379 cm^{-1}, which refers to the NH bond of the triazole ring, also disappears, since gallium is a trivalent metal, unlike copper and zinc, and is coordinated with the nitrogen atom of the triazole ring.

The ^{1}H NMR spectra of the synthesized compounds - three-unit product **3** and its metal complexes **4a-c** - were studied. The signals were assigned by comparing the experimentally obtained and theoretically calculated ^{1}H NMR spectra in the ChemDraw program.

The signals in the weak field region at 7.3-6.9 ppm correspond to protons of phenol fragments. In the strong field region (2.91-1.23 ppm) 4 intense poorly resolved signals of protons of cyclohexyl substituents are observed.

In the spectrum of compound **3** in the region of 4.0-4.5 ppm there is a broadened signal corresponding to the protons of the acyclic imino groups of isoindole fragments, also observed in the spectra of metal complexes (**4a-c**). The signals related to the protons of the 4-cyclohexylphenoxy groups are observed both in the spectrum of TUP **3** and metal complexes **4a-c** and their location remains virtually unchanged.

One of the most important tasks of pharmaceutical chemistry is the search for and development of safe drugs [18, 22]. The design of new drugs is a laborious and long process. In order to reduce the time spent on searching for a molecule with given properties and the least toxic effect, programs have been developed that allow one to evaluate biological activity based on the structural formulas of organic compounds [23].

Prediction of the biological activity spectrum using the PASS program allowed to conclude which enzymes would be most likely to be affected by the structures studied (Table 1).

Calculations showed that the complex of cyclohexylphenoxysubstituted TUP with gallium **4c** can exhibit activity against non-Hodgkin's lymphoma with a probability of 90,8-91%.

In addition, complex **4c** is potentially capable of inhibiting platelet-derived growth factor receptor kinases (Pa = 0.687; Pi = 0.007), i.e. regulating proliferation, differentiation, and cell growth, as such hindering the development of oncological diseases.

Using the Anti-Bac-Pred program, we determined the possibility of using the synthesized compounds in medicine. It was found that compound **4c** can be active against gram-positive cocci bacteria with a probability of 12% (Table 2), i.e. it is possible to include this molecule in the composition of a drug that can potentially be used to treat various purulent-inflammatory diseases.

Table 1

Prediction of the biological activity spectrum of 4c using the PASS program

***Таблица 1*. Прогноз спектра биологической активности 4c, выполненный программой PASS**

Pa	Pi	Activity
0.908	0.001	Antineoplastic (non-Hodgkon's lymphoma)
0.882	0.002	Macular degeneration treatment
0.873	0.002	Antineoplastic (multiple myeloma)
0.850	0.003	Antineoplastic enhancer
0.841	0.005	Apoptosis agonist
0.801	0.004	Antineoplastic (solid tumor)
0.769	0.004	Restenosis treatment
0.739	0.003	Antineoplastic (brain cancer)
0.644	0.006	Atherosclerosis treatment
0.603	0.005	Antineoplastic (non-small cell lung cancer)

Note: *Pa - "to be active", Pi - "to be inactive"

Примечание: *Па - быть активным, Пи - быть неактивным

Table 2

The prediction antibacterial activity spectrum of 4c

***Таблица 2*. Прогноз спектра антибактериальной активности соединения 4c**

№	Name	Confidence
1	Staphylococcus	0.1189
2	Stable Stenotropomonas maltophilia	0.0631
3	Porphyromonas gingivalis	0.0582
4	Salmonella enterica subspecies enterica	0.0447
5	Listeria monocytogenes	0.0284
6	Prevotella intermedia	0.0008

The assessment of the correctness of the antibacterial activity spectra prediction was carried out at the M.B. Stoyunin Regional Anti-Tuberculosis Dispensary on three bacterial strains: *Escherichia coli, Staphylococcus aureus, Staphylococcus Epidermidis.*

The results of the disk diffusion method (DDM) study showed that gallium complex **4c** exhibits antibacterial activity against the indicated strains, since it is when using **4c** that the maximum inhibition zone (11 mm) is observed, i.e. microorganisms are destroyed or their growth is slowed down [19].

Thus, as a result of the present work, a new triazole-containing three- unit product containing 4-cyclohexylphenoxy groups on the periphery, as well as its metal complexes with gallium, zinc, copper ions, which will allow in the future to obtain macroheterocycles of various structures, were synthesized. The possibility of using *in silico* assessments for the experimental development of a pharma composition based on an acyclic product with gallium as a potential antibacterial drug for gram-negative strains was shown. The antibacterial activity of the three- unit product with gallium **4c**, which provides the maximum zone of inhibition of bacterial growth, was found.

The study was carried out using the resources of the Center for Collective Use of Scientific Equipment of ISUCT and with the financial support of the state assignment of the Ministry of Education and Science of the Russian Federation, topic No. FZZW-2023-0009.

The authors declare the absence of a conflict of interest warranting disclosure in this article.

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