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СИНТЕЗ ГАЛЛИЕВЫХ КОМПЛЕКСОВ *ТРЕТ*-БУТИЛЗАМЕЩЕННЫХ АЦИКЛИЧЕСКИХ И ЦИКЛИЧЕСКИХ СОЕДИНЕНИЙ НА ОСНОВЕ 3,5-ДИАМИНО-1,2,4-ТРИАЗОЛА

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Разработанные к настоящему времени методы синтеза позволяют получать макрогетероциклы с различным строением внутренней координационной полости; включать в состав макросистемы гетероциклические фрагменты, которые входят в состав многих природных биологически активных и синтетических лекарственных веществ, таких как гуаназол. В данной работе обсуждается синтез и состав галлиевых комплексов циклических и ациклических соединений на основе 3,5-диамино-1Н-1,2,4-триазола (гуаназола), который сам по себе широко используется в медицинской практике и, что особенно важно, для лечения онкологических заболеваний, в частности, рака груди («Анастрозол», «Летрозол»). Интерес к соединениям галлия связан с открытием высокой тропности этого элемента к ДНК опухолевых клеток, а также клеткам ретикулоэндотелиальной системы (макрофаги и лимфоциты). Поэтому синтез новых потенциальных препаратов с солями галлия для химиотерапии опухолей является актуальной задачей. Галлиевый комплекс макрогетероциклического соединения симметричного строения на основе гуаназола был получен через стадию образования трехзвенного продукта - 3,5-бис-(5(6)-трет-бутил-3-иминоизоиндолин-1-илиденамино)-1,2,4-триазола и его комплекса, с последующей циклизацией соответствующим диамином - 3,5-диамино-1Н-1,2,4-триазолом в феноле в эквимолярном соотношении. Строение полученных соединений доказано с помощью современных физико-химических методов исследования (ЭСП, ИК, ЯМР-спектроскопии, масс-спектрометрии, элементного анализа). В масс-спектрах полученных соединений присутствуют пики молекулярных ионов целевых продуктов и продуктов их фрагментации. Совпадение значений массового числа m/z с массой молекулярных ионов, а также характеристичных распределений молекулярных ионов с расчетными значениями является подтверждением состава синтезированных галлиевых комплексов.

Ключевые слова: 3,5-диамино-1Н-1,2,4-триазол (гуаназол), соли галлия, металлокомплекс, макрогетероциклическое соединение, трехзвенный продукт

SYNTHESIS OF GALLIUM COMPLEXES OF *TERT*-BUTYLSUBSTITUTED ACYCLIC AND CYCLIC COMPOUNDS BASED ON 3,5-DIAMINO-1,2,4-TRIAZOLE

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Synthetic methods of organic chemistry which are currently available in scientific literature allow obtaining a large number macroheterocycles with structurally different internal coordination cavities. They also provide a number of convenient ways to attach to a macrocyclic platform various biologically active heterocyclic fragments such as guanazol. This paper discusses the synthesis and composition of gallium complexes of cyclic and acyclic compounds based on

3,5-diamino-1H-1,2,4-triazol (guanazol), which is itself widely used in medical practice and, most importantly, for the treatment of cancer, in particular, breast cancer ("Anastrozole", "Letrozole"). Interest in gallium compounds is associated with the discovery of a high tropicity of this element to the DNA of tumor cells, as well as cells of the reticuloendothelial system (macrophages and lymphocytes). Therefore, the synthesis of new potential drugs with gallium salts for tumor chemotherapy is an urgent task. The gallium complex of a macroheterocyclic compound of symmetrical structure based on guanazole was obtained through the formation of a three-unit product - 3,5-bis - (5 (6)-tert-butyl-3-iminoisoindoline-1-ilidenamino)-1,2,4-triazole and its complex, followed by cyclization of 3,5-diamino-1H-1,2,4-triazole in phenol. The structure of the obtained compounds was proved using modern physicochemical research methods (UV, IR, NMR spectroscopy, mass spectrometry, and elemental analysis). In the mass spectra of the obtained compounds there are peaks of molecular ions of the target products and their fragmentation products. The coincidence of the m/z values with the mass of molecular ions, as well as the characteristic distributions of molecular ions with the calculated values, confirms the composition of the synthesized gallium complexes.

Key words: 3,5-diamino-1H-1,2,4-triazole (guanazole), gallium salts, metal complex, macroheterocyclic compound, three-unit product

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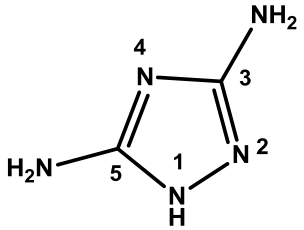
INTRODUCTION

The search for effective methods of combating socially significant diseases, such as tumors of various etiologies, is one of the most important national priorities of the Russian Federation (Decree of the President of the Russian Federation of May 7, 2018 No. 204 «On National Goals and Strategic Tasks of the Development of the Russian Federation for the period until 2024 of the year»). Nitrogen-containing heterocycles are most widely used in practice and, especially, medicine. A number of derivatives of guanazole **1** (3,5-diamino-1,2,4-triazole) are used in medical practice as medicines for the treatment of fungal infections, diseases of the cardiovascular system and, most importantly, oncological diseases, in particular cancer breast [1-3].



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Reaction centers of guanazol **1** can be used to introduce additional groups (substituents or metal ions) into their structure, which opens the prospect of increasing bioavailability, selectivity of accumulation and increasing the effectiveness of chemotherapy.

Moreover, for the synthesis of metal complexes with guanazol, information is limited to the synthesis of zinc, palladium, silver, ruthenium and copper complexes [4-8], although the use of metal complexes of guanazoles with aluminum, manganese and, especially, gallium ions can allow us to reach a qualitatively new level of anti-tumoral activity.

Gallium was chosen by us not by chance, since Ga^{3+} along with other rare earth elements are able to bind and transport as part of transferrin to target cells, and the receipt of such complexes in cells has at least two pathogenic consequences: these metals trigger free radical generation reactions, which leads to DNA damage and complexes of these metals are non-degradable, so [9, 10]. Interest in Ga^{3+} is associated with the discovery of a high tropicity of this element to the DNA of tumor cells, as well as cells of the reticuloendothelial system (macrophages and lymphocytes) [11]. The authors [12] showed that gallium (III) salts have a pronounced toxicity against a

number of tumor cells. For gallium chloride and nitrate [13, 14], the first and second stages of clinical studies were conducted, where they inhibited the growth of tumors of the bladder, liver and lymphatic tissue to some extent. Studies have shown that the effectiveness of drugs is not high enough due to the loss of toxicity due to hydrolysis and difficulties in transmembrane transport into tumor cells due to high hydrophilicity [15]. It is obvious that the solution of the above problems can significantly increase the antitumor activity of gallium salts, which should have a good clinical perspective. Therefore, the search for new effective drugs for tumor chemotherapy is extremely relevant and is currently being conducted in different directions [16-22].

Previously, we have obtained a complex compound with gallium tetrachlorophenol 3,5-diamino-1,2,4-triazole the [23]. The resulting compound is currently undergoing biological research.

Literature analysis has shown that macromolecules of various compositions (chlorins, porphyrins) are used and can be used as sensitizers for photodynamic therapy of cancer [16-19]. Structural analogues of porphyrin are macroheterocyclic compounds (Mc). Small cycles (azoles) are the building blocks for the synthesis of Mc – functional materials with specified properties. Earlier studies [24] for *tert*-butylsubstituted Mc, which include 1-phenyl-and 1,2,4-triazole fragments and their complexes with copper, showed not only moderate antimicrobial activity, but also showed moderate antitumor activity on the model of lymphoid leukemia L-1210 (nickel complex of Mc and 3,5-diamino-1H-1,2,4-triazole), which gives grounds for directed synthesis and search for more active compounds among their analogues [24].

Thus, the analysis of the literature predetermined the necessity and expediency of research in the chosen direction.

EXPERIMENTAL PART

The electronic absorption spectra (UV-vis) in the visible and UV regions were recorded on a HITACHI U-2001 spectrophotometer at room temperature, in quartz rectangular cuvettes 1-10 mm thick.

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

The molecular weights of organic molecules were determined on a time-of-flight mass spectrometer with matrix-associated laser desorption AXIMA Confidence. MALDI-TOF mass spectra were obtained on a Shimadzu Biotech Axima Confidence mass spectrometer in the 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).

The content of carbon, hydrogen, and nitrogen in the samples of synthesized compounds was determined using a FlashEA 1112 CHNS – O Analyzer at Ivanovo State University of Chemistry and Technology.

Qualitative and quantitative analysis of the starting compounds in the mode of fast chromatography-mass spectrometry was performed on a gas chromatography-mass spectrometer GCMS-QP2010Ultra complete in various dried organic solvents (chloroform, dichloromethane).

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

The synthesis of guanazole **1** was carried out according to the known method [23, 25] by the cyclization reaction of dicyandiamide and hydrazine hydrate. 4-tert-Butylphthalonitrile **2** was obtained in accordance with the literature method [24].

1. Synthesis of 3,5-bis-(5(6)-tert-butyl-3-iminoisoindolin-1-ylidenamino)-1,2,4-triazole (4)

Compound **4** was prepared according to the known method [26] by the interaction of 0.21 g (0.004 mol) of guanazole **1** and 0.9 g (0.005 mol) of 4-*tert*-butylphthalonitrile **2** in the presence of sodium methylate. Yield: 1.0 g (60%). The product does not melt when heated to 250 °C. IR spectrum (KBr) $\bar{\nu}$, $см^{-1}$: 3211, 2963, 1638, 1540, 1456, 1406, 1365, 1326, 1262, 1141. 1083, 880, 841, 767. $C_{26}H_{28}N_9$ Calculated, %: C 67.06, H 6.88, N 26.07; Found, %: C 67.02, H 6.80, N 26.02. MM 483.61. MALDI-TOF (DHB) m/z: 483.65 $[M]^+$.

2. Synthesis of nitrate [3,5-bis-(5(6)-tert-butyl-3-iminoisoindolin-1-ylidenamino)-1,2,4-triazole] gallium (III) (5)

A mixture consisting of 2.5 g (5.2 mmol) of the corresponding three-unit product **4** and 2.1 g (5.2 mmol) of gallium nitrate $Ga(NO_3)_3 \cdot 8H_2O$ in 15 ml of

2-ethoxyethanol was kept at a temperature of 80 °C for 90 min. Then the reaction mass was poured into water, the precipitate was filtered off, washed with water, methanol and dried. Yield: 2.21 (72%). Found, %: C 52.25, H 4.53, N 23.41, O 8.02. $C_{26}H_{27}GaN_{10}O_3$. Calculated, %: C 52.28, H 4.56, N 23.45, O 8.05. MM 596.15. MALDI-TOF (DHB), m/z: 603.83 $[M + Li]^+$.

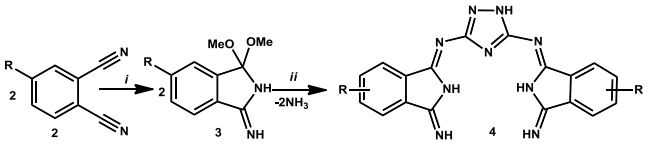
3. Synthesis of the gallium complex of the tert-butylsubstituted macroheterocyclic compound ABAB type with fragments of 3,5-diamino-1H-1,2,4-triazole (6)

A mixture consisting of 3.7 mmol of the gallium complex with substituted 3,5-bis(1-imino-3-isoindolinylideneamino)-1,2,4-triazole **5**, 3.7 mmol of guanazole **1** and 3 g of phenol was stirred for 10 h at a temperature of 140 °C, and then the temperature was raised to 160 °C and held for another 2 h. At the end of the exposure, the reaction mass was poured into water, the precipitate formed was filtered off and washed with a large amount of water, acetone. Additional purification of the complex was carried out by column chromatography on silica gel (the target product was eluted with a mixture of chloroform:methanol = 10:1). The solvent was removed, the product was dried under vacuum. Yield: 65%. T_{melt} > 250 °C. Found, %: C 49.98, H 3.70, N 28.05, O 7.37. $C_{27}H_{24}GaN_{13}O_3$ Calculated, %: C 50.02, H 3.73, N 28.09, O 7.40. *MM* 648.29. MALDI-TOF (DHB), m/z: 650.36 $[M\text{-}CH_2]^+$.

RESULTS AND DISCUSSION

Analyzing the data of a previously synthesized complex compound - 3,5-diamino-1,2,4-triazolium tetrachlorogallate [23], the work was aimed at obtaining gallium metal complexes of macroheterocycles, which can be promising as antitumor preparations.

The synthesis methods developed to date allow one to obtain Mc with a different structure of the internal coordination cavity; include heterocyclic fragments that are part of many natural biologically active and synthetic drugs; carry out structural modification on the periphery. All this serves as the basis for a systematic search for Mc with practically valuable properties, in particular, biological. Three-unit product (bis (1-imino-3-isoindolinylideneamino) arylene) and their metal complexes are important intermediate products in the synthesis of macroheterocyclic compounds of symmetric and asymmetric structure [24, 26]. These compounds can be prepared by reacting 1,3-diimino or 1,1-dialkoxy-3-iminoisoindolines with aromatic diamine in a 2:1 ratio at low temperatures. In addition, three-unit products are capable of reacting with an equimolar amount of the same diamine or 1,3-diminoisoindoline with increasing temperature, forming Ms ABAB or ABBB types. The three-unit product of 3,5-bis-(5(6)-*tert*-butyl-3-iminoisoindolin-1-ylidelamino)-1,2,4-triazole **4** was obtained according to Scheme 1.



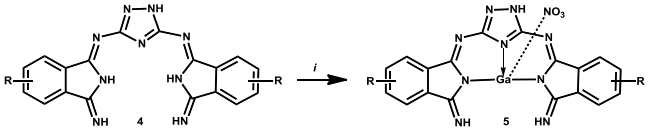
R = tBu, i = MeONa, MeOH, 20 °C, 1.5-2 ч; ii = 3, 40 °C, 8 h.

Схема 1

Scheme 1

At the end of the exposure, the reaction mass was poured into water, the precipitate formed was filtered off, washed with water, methanol and dried. The mass spectrum of MALDI-TOF (DHB) for compound **4** is shown in the experimental part. In the mass spectrum there is a peak with m/z: 603.83 $[M + Li]^+$, which corresponds to the target three-unit product.

Then the mixture consisting of a three-unit product and gallium nitrate in 2-ethoxyethanol was kept at a temperature of 80 °C for 90 min (Scheme 2).



R = tBu, i = Ga $(NO_3)_3 \cdot 8H_2O$*, $EtOC_2H_4OH$, 80 °C, 90 min*

Scheme 2

Схема 2

The mass spectrum of MALDI-TOF (DHB) for compound **5** is shown in Figure. The mass spectrum of compound **5** (Fig. 1) contains peaks of molecular ions $[M + Li]^+$ and $[M + Li + K]^+$. The coincidence of the m/z values with the mass of the molecular ion, as well as the characteristic distributions of molecular ions with the calculated values, confirms the composition of the new complex of the *tert*-butyl substituted three-unit product.

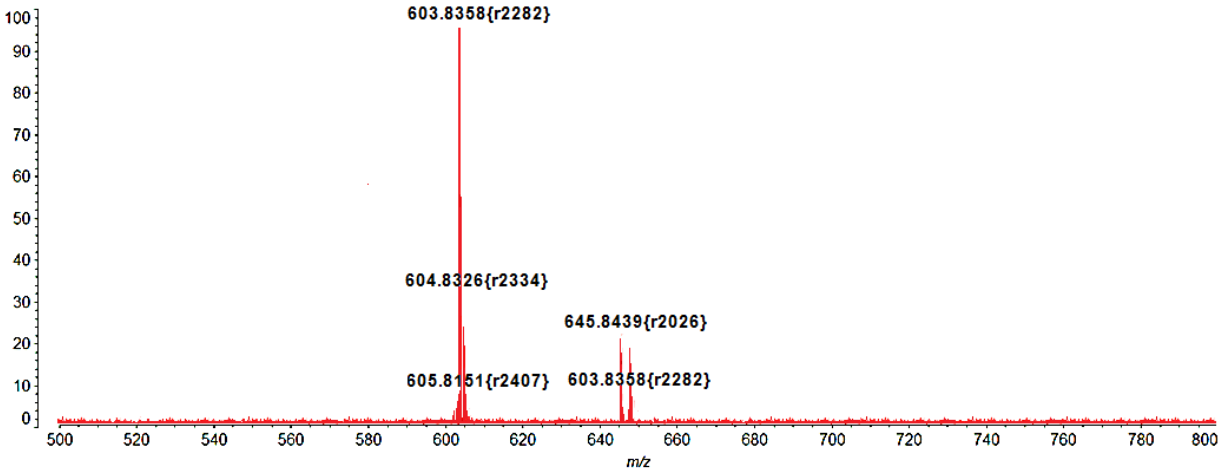
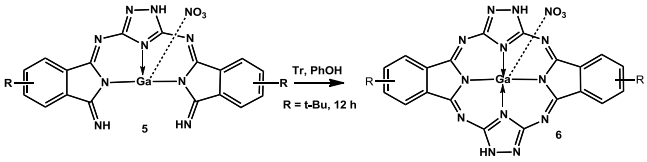


Fig. Mass spectrum of MALDI-TOF (DHB) for the compound **5**
Рис. Масс-спектр MALDI-TOF(DHB) для соединения **5**

Further, by cyclization of the gallium complex of the three-link product **5** with 3,5-diamino-1,2,4-triazole 1 in phenol, a complex of the *tert*-butyl substituted macroheterocyclic compound ABAB-type with gallium was obtained **6** (Scheme 3).



Scheme 3
Схема 3

The peaks of molecular ions m/z = 650 $[M-CH_2]^+$ and fragmentation products are present in the mass spectrum of compound **6**. The coincidence of the m/z values with the mass of the molecular ion, as well as the characteristic distributions of molecular ions with the calculated values, confirms the composition of the new complex of *tert*-butyl substituted macroheterocycle.

CONCLUSIONS

Thus, we obtained gallium complexes of acyclic and cyclic compounds based on guanazole. The compounds obtained are of practical interest and are potential research targets for the photodynamic therapy of cancer. The structure of the obtained compounds is proved using modern physicochemical research methods.

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