DESCRIPTION OF INVENTION

ANTIBACTERIAL AGENT FOR TREATING INFECTIOUS DISEASES OF BACTERIAL ORIGIN

Pertinent art

The invention relates to medicine, namely pharmaceutics, and may be used for treating diseases of bacterial origin, especially in treating diseases caused by drug-resistant strains of microbes, and bacterial and viral (mixed) infections.

Prior knowledge

Main methods and means to damage pathogenic bacteria in the present are antibiotics which combine all medications that suppress activity of infectious agents such as bacteria, fungi, and protozoa.

However, due to increased drug resistance of infectious agents to the known groups of antibiotics, the problem of development of new antimicrobial drugs has not lost its relevance.

Thus, for example, worldwide there is an increase in tuberculosis incidence rate and increase in mortality observed, caused by drug-resistant pathogens. Resistance to antituberculosis drugs was found in all 35 surveyed countries and regions, indicating that the problem is global.

Polyresistance to antituberculosis drugs is the most difficult form of drug-resistance, known at present. According to WHO, since the early 90-ies in different regions of the planet several outbreaks of multidrug-resistant tuberculosis have been reported.

It is known that molecular iodine can easily pass through bi-lipid cell membranes of microorganisms and penetrate into a cell. Antimicrobial action of iodine compound is due to the ability of iodine (elemental iodine, hypoiodine acid, iodine cation) to interact with NH_2-groups of amino acids (lysine, histidine, arginine, etc.), as well as nucleotides (adenine, cytosine, guanine) forming N-iodine derivatives. In addition, there is an oxidation of SH-groups of cysteine

In all of the above known patents, authors did not set the task of synthesizing complex compounds with a given structure and properties, or excreting complex compounds from solutions and determining their composition and physical-chemical properties, which makes it hard to use complex iodine compounds with carbohydrates and proteins with biocidal properties as medicinal products. Moreover, the development of appropriate dosage forms, without a specific set of properties and qualities of complex iodine compounds - antibacterial agents, characterized by physical and chemical properties and composition, is hindered.

In recent years, some works devoted to exploration of the structure of complex compounds of carbohydrates with salts of magnesium, calcium and other complexing agents have appeared in scientific literature (*O.Nimz, K.Geßler, I.Uson, W.Saenger // Carbohydrate Research 2001. V. 336. P.141–153.; M.Noltemeyer, W. Saenger // JACS 1980.V.102:8.9.P.2710.; M.Noltemeyer, W. Saenger // Nature.1976.V.259. 26.P.629).*

Crystalline structure of a whole number of enzymes with having in its composition ions of magnesium, potassium, calcium, lithium, in their composition, i.e., metal salts, has been established. (*Y.Goldgur, F.Dyda, A.B.Hickman, T.M.Jenkins, R.Craigie, D.R.Davies // Proc.Natl.Acid.Sci USA 1998. V.95. №16. P.9150-9154.; F.Dyda, A.B.Hickman, T.M.Jenkins, A. Engelman, R.Craigie, D.R.Davies // Science. 1994. V.266. P.1981-1986*).

At the same time there are no works involving a purposeful synthesis of iodine coordination compounds with a tailored nanoscale structure and, accordingly, tailored biocidal properties, suitable for implementation of a mechanism of action of these compounds.

Thus, the object of this invention is to create antibacterial agent (hereinafter ABA) for the treatment of diseases of bacterial origin, including hospital acquired diseases and drug resistant tuberculosis (hereinafter TB).

Additional objectives of this invention are to develop a method for preparation of antibacterial agent and ABA-based drug to treat infectious diseases

of bacterial origin.

Technical result of the invention is the increase ABA efficiency *in vivo* through activation of immunocompetent cells.

Essence of invention

The technical result is accomplished through the developed ABA, which represents an ionic nanostrutured complex (INSC), formed by proteins and/or carbohydrates, metal salts and iodine intercalated into them, while to obtain an ordered structure of antimicrobial agent and the necessary immunotropic action, the complexation reaction is conducted in four stages – first is interaction of carbohydrates and proteins with metal salts; second step is intercalation of 5-95% of the required amount of iodine into a complex formed during the first stage of complexation reaction at a certain ionic strength; third stage is introduction in the complexing reaction of proteins containing at least one chain-terminal amino acid with electron-donating functional groups and a specific site, accounting for a required immune response, and the fourth stage is intercalation of the remaining amount of iodine in antibacterial agent.

In addition, according to the invention, an ABA was proposed, which, despite the fact that it has a weak anti-tumor activity, a weak radioprotective effect, however, in conjunction with the unique ability to recover hematopoietic function of bone marrow, could be of great practical importance for the prevention of possible adverse effects of chemo- and radiotherapy in **accompanying** complex drug therapy of tumors.

Another technical result is accomplished by the fact that proteins and/or polypeptides that are part of the ABA, have immunogenic activity and contain at least one terminal amino acid with electron-donating functional groups, which -

when ABA is administered into body, anchor in the area of stimulating and costimulating receptors of immunocompetent cell through chain-terminal amino acids possessing hydrophobic and electron-donor functional groups, and specific sites of these proteins activate immunocompetent cells of the first and the second lines of defense - monocytes-macrophages and cytotoxic T-lymphocytes.

Further, the invention includes a pharmaceutical form of the claimed ABA

Depending on the specific proposed application, the pharmaceutical composition according to the present invention can be prepared in the form of a solution, suspension, parenteral composition, ointment, cream, aerosol, powder, tablets, capsules, or other acceptable dosage form, which are administered in certain doses, applied or mixed appropriately. Pharmaceutical formulations may include:

a) potential formulations - filler, in particular, pyrogen-free water, buffer or normal saline solution;

b) ointments, creams, aerosols - media, in particular vegetable or synthetic oil, lanolin, petrolatum, or high-molecular alcohols;

c) tablets or capsules - thinners, in particular lactose, binders, lubricating substances (e.g., stearic acid), as well as decomposition products (e.g., corn starch).

All pharmaceutical formulations under the present invention can be combined with antibacterial (e.g., antibiotics), antiviral, antitumor, immunomodulatory and other agents if, when combined, they provide a synergistic effect with the claimed pharmaceutical compositions, or are indifferent toward them, but in combination they expand a therapeutic spectrum.

Moreover, according to this invention, ABA can be used as a non-medicated agent (BAA, food additive, feed additive, personal care product component such as lotions, toothpaste, chewing gum, etc.) subject to observance of certain conditions. Such conditions include, for example, the use in compositions of those components only and only in the concentrations specified in the Codex Alimentarius.

Non-medicinal preparations based on a complex compound of the present

invention have immunomodulatory effects and may be used for the prevention of infectious diseases, such as seasonal influenza, ARVI, iodine deficiency, as well as an adaptogen.

This invention is based on a surprising fact that in solutions of salts of alkali and alkaline earth metals, at a certain ionic strength in the presence of carbohydrate and / or protein, the complex is released into a solid phase in the process of iodine intercalation.

Another surprising fact, laid in the basis of this invention is that, as is established by experimental data, the present invention enables to introduce proteins in the antimicrobial agent composition that contain sites with specific immunological function.

LIST of Figures of Drawings

A claimed invention is illustrated by the following figures of the drawings.

Fig. 1-4 represent micrographs of different crystal structures for the preparation FS-1.

Fig. 5 shows the dependence of the yield for calcium complex of triiodide-ion with carbohydrate on the ionic strength.

Fig. 6 shows the dependence of the yield for the magnesium complex of triiodide ion with carbohydrates on the ionic strength.

Fig. 7 shows the formation of stable coordination compounds in the system carbohydrate-protein-salts LiCl, $MgCl_2$.

Fig. 8 shows the structures illustrating the interaction of molecular iodine with lithium halides, carbohydrates, and side amino acid residues of the protein.

Fig. 9 represents a diagram of the ABA subunit formation.

Fig. 10 a-i represents micrographs of the compounds by examples 1-9.

Fig. 11 represents a micrograph of the compound by Example 5 (FS-1).

Fig. 12 demonstrates the dynamics of survival of rats in the control and experimental groups during 30 days after irradiation: 1) at irradiation dose of 800 R; 2) at irradiation dose of 800 R against the HRP oral administration (1.0 ml) 30

minutes before irradiation.

Data, supporting the possibility of realization of the invention

Proceeding from the above, in accordance with the invention, a method for preparation, in order to ensure the preservation of properties of immunogenic proteins in the antibacterial agent composition, is supplemented with the third and fourth stages of complex formation.

In the context of the present invention, the components, their interrelationship, and the ionic strength interval are essential features in the ABA synthesis.

Every attribute that determines the ABA composition and structure, are necessary and sufficient to achieve the formulated goal. None of them can be excluded or replaced by another one, otherwise the technical result will not be obtained. Selection of both the qualitative composition of substances that form ABA, and quantitative ratios of components, and the ionic strength interval, was based on regularities of complex formation and numerous experimental data on the determination of ABA antibacterial activity, depending on the composition of its constituent components.

The qualitative composition of substances was chosen on the basis of their biological significance and chemical properties that provide an antibacterial effect.

Carbohydrates, selected by the authors of the present invention as ligands, are an extremely important class of natural compounds. In biology and medicine, the value of carbohydrates consists in the dominant role assigned to them in animal organisms, and the complexity of their functions. Carbohydrates are involved in most biochemical processes in the form of high-molecular particles, although many bilogic fluids contain mono- and oligosaccharides (Compressive Organic Chemistry / Edited by E. Haslam. V. 5. Biological Compounds Pergamon Press, 19).

The main feature of the ABA, which represents a complex compound of iodine

with carbohydrates and/or proteins and metal salts is the presence of proteins with a specific set of electron-donating functional groups in terminal amino acids and sites.

Proteins play a key role in almost all biological processes; determine the course of biological reactions in cells and are involved in a variety of other functions - such as transport of substances and their accumulation.

The present invention also includes low-molecular peptides and their constituent monomers.

Transport role of proteins is extremely important, because a diffusing molecule bound with protein, in case of passing through the membrane, is not chemically modified and does not link with other types of molecules. Mediated, or simplified, membrane transport processes are characterized by saturation kinetics (i.e. the transport system can be saturated by the transported solute) and specificity to transported substance.

The possibility of mediated transport is due to proteins that can reversibly bind specific substrates, including iodine molecule. These transporting protein molecules have different names: transport systems, transporters, carriers, or translocases.

Table 1 shows the ABA compositions, synthesized from carbohydrates, proteins, and iodine at different ionic strengths of the solution created by the salts of alkali and alkaline earth metals. The crystalline structure of some compounds (antibacterial agent), depending on the ratio of carbohydrate: protein (polypeptide), is shown on optical and electronic photographs, fig. 1-4.

As can be seen in the photographs, ABA can form nanocrystals (Fig. 1: 1A with 400x enlargement, 1B with 40000x enlargement), microcrystals (Fig. 2: 2A with 5000x enlargement, 2B with 12000x enlargement) that are rather large (0.1 mm), monocrystals (Fig. 3), or crystals of various sizes (Fig. 4).

The size of crystals decreases with increasing content of carbohydrate relative to protein (polypeptide), all other things being equal (ionic strength of the solution), as well as with increasing the ratio of iodine: carbohydrate, and/or

$$n_6 Ca^{2+} + n_7 I_3^- + L_1 + L_2 + L_3 \Leftrightarrow Ca_{n_6}[I_3]_{n_7} L_1 L_2 L_3 \qquad K_{10} = \frac{[Ca_{n_4}[I_3]_{n_7} L_1 L_2 L_3]}{[Ca^{2+}]^{n_6} \cdot [I_3^-]^{n_7} \cdot [L_1 L_2 L_3]} \quad (6)$$

ABA output:

$$[Mg^{2+}_{n_4} I^-_{3\,n_5} L_1 L_2 L_3] = \frac{K_5 [L_1 L_2 L_3 Mg^{2+}_{n_1}] \cdot [KI_3]^{4n_3}}{[K]^{5n_4}} \quad (7)$$

$$[Ca^{2+}_{n_4} I^-_{3\,n_7} L_1 L_2 L_3] = \frac{K_6 [L_1 L_2 L_3 Ca_{n_5}] \cdot [KI_3]^{5n_4}}{[K]^{6n_5}} \quad (8)$$

The final product output depends on physico-chemical parameters of the reaction (Table 2, 3).

The unexpected fact was that at a certain ionic strength of the reaction medium, the ABA output approaches 100%.

According to results of calculation of assumed equilibrium, the ABA output changes (increases) with the increase in ionic strength (Fig. 5, 6). There is an especially significant effect of ionic strength observed for the complex containing magnesium ions (Fig.6), which may be due to characteristics of this ion as a harder acid according to Pearson [Pearson R.G., Journal ACS, 1963, 85, cl. 3533. Pearson R.G. Journal Chemical Education, 1968, 45, cl. 643. Pearson R.G., Chemical Communication, 1968, cl. 65, Gehlen H.Z., Physical chemistry, 1954, 203, 125. Finston H.Z., Rychtman A.C., A new view of current acid-base series. N.Y., Wile, 1982].

Even more surprising was the fact of ABA crystals formation, which represents an ionic polymer complex, in the process of extraction using the method of centrifugal chromatography and / or drying; at that the composition of monocrystals is well-defined and constant, which indicates the formation of an individual ABA compound. The ABA structure and sequence of actions for this structure formation, according to method for antibacterial agent preparation claimed after this invention, can be represented as follows (Fig. 7). In this figure, blue balls are carbon atoms, dark blue - nitrogen atoms, yellow - chlorine atoms, red - oxygen atoms, black - magnesium atoms, brown - lithium atoms. For the

$$\Delta E = E_1\cdot(compl.) - (E_2 + E_3), \qquad (9)$$

where E_1 is total complex energy, E_2 – is total $LiClOHC_2H_5$ energy;

E_3 – total energy of I_2 complex with amino-acid residue.

As can be seen from Table 4, the most stable complex is formed with participation of arginine (structure VII), in this case I-I bond breaks; in such a complex the properties of molecular iodine are not preserved. Comparison of the stabilization energies for complexes of molecular iodine with arginine (-18.17 kJ/mol), and with adenosine (-10.93 kcal/mol) and guanine (-11, 50kJ/mol), suggests that if arginine is included in the ABA composition, I_2 molecule remains in the structure of the formulation and will not form a complex with DNA nucleotides.

In I-III complexes I-I bond does not break, but is weakened only. After arginine the most stable complexes are obtained with participation of carbonyl group of protein amide fragment. Amide fragment is a part of polypeptide skeleton and is a part of amino-acid residue of asparagine and glutamine.

The output of final product depends on physico-chemical parameters of the reaction – K_{rev}, stoichiometric coefficient *n*, and concentration of reagents.

Based on the data of UV, Fourier transform IR spectroscopy, electron and optical microscopy, quantum-chemical calculations, the structure of ABA and sequence of acts in formation of this structure, according to the method for ABA preparation claimed in the present invention, schematically can be represented as follows (Fig. 9).

Formation of ABA subunit (molecule) occurs after the influence of ionic strength in the range from 0,015 and up to 10.2, corresponding to the pressure of 286 - 2860 kg/cm^2. After the influence of such pressure (ionic strength), carbohydrate and protein macromolecules are packed in such a way that terminal amino acid triplets not involved in complexation are oriented outwards from the core protein and/or polypeptide skeletal chain, and perform anchoring of antibacterial agent on the cell membrane through chain-terminal amino acids,

The study of ABA cytogenetic activity was performed by taking account of chromosome aberrations in bone marrow leukocytes of mammals *in vivo* in mice.

The study of ABA cytogenetic activity was performed using micronucleus test in polychromatic and orthochromatic erythrocytes of mice's bone marrow cells *in vivo.*

The study of dominant lethal mutations in spermatozoa in mammals when administered FS-1 was performed *in vivo* in mice.

Most of the examples given in the invention description that illustrate the ABA effectiveness against pathogenic microorganisms, including museum and clinical isolates of multidrug-resistant (MDR) Mycobacterium tuberculosis belong to the ABA-based drug after Example 5 (FS-1), without being limited to them.

Experiments for studying radioprotective properties of the drug ABA FS-1 were conducted in white rats weighing 190-200g and white mice weighing 22-25g. In irradiation experiments the animals were exposed to single uniform radiation in RUM-17 therapeutic x-ray apparatus (180kV, 10mA, filters 0.5 mm Cu + 1.0 Al, focal distance - 40 cm, radiation dose rate - 178 R/min) in doses of 800 R (radiation doses close to LD50).

Induction of myelosuppression with ABA FS-1 was performed by the method of [Galoyan A.A., Korochkin L.I., Rybalkina E.J., Pavlova G.V., Saburina I.N., Zaraiski E.I., Galoyan N.A., Davtyan T.K., Bezirganyan K.B., Revishchin A.V. Hypothalamic proline-rich polypeptide enhances bone marrow colony-forming cell proliferation and stromal progenitor cell differentiation // Cell Transplantation. – 2008. – Vol. 17. – P. 1061-1066].

Sampling of peripheral blood and bone marrow of animals was carried out by the method of [Bezirganyan KB, Davtyan TK, Galoyan AA Hypothalamic proline rich polypeptide regulates hematopoiesis / / Neurochem. Res. - 2010. - Vol. 35. - CL. 917-924. Gershanovich M.L., Paikin M.D. Symptomatic treatment of malignancies. 2nd ed. - Moscow: Medicine, 1986. – 285p.].

Assessment of myelosuppression was performed by counting the absolute and relative content of leukocytes, lymphocytes and monocytes in peripheral blood

The resulting solution is transferred to the reactor after the required Product A temperature specified above is reached. The mixture is stirred for 20 minutes (Product B), and after that the temperature in reaction zone is reduced to 25°C.

74.5 g of I_2 and 110.0 g of potassium iodide are dissolved in 500 ml of water. The resulting solution is poured in portions in the complex compound solution (Product B). Intercalation of iodine is carried out in two stages, during 4 hours at 25°C.

The resulting ionic nanostructured ABA complex is extracted from the reaction medium using a suitable method, and dried (Fig. 10(g)).

Ionic strength of the solution is 56.3.

Analysis results:

	Carbohydrate	Albumin	PVA	LiCl	NaCl	$MgCl_2$	$CaCl_2$	I_2	KI
Mole fractures, %	**0.04**	**0.002**	**0.01**	**0.96**	**0.87**	**0.9**	**0.18**	**29.8**	**67.31**

$$[25L_1 \cdot L_2 \cdot 19575I_2] \cdot 7L_3$$

In biological activity testing it was established that ABA FS-1 is active *in vitro* both against clinical isolates, and control strains of MRSA and MSSA. MIC of antimicrobial agent was varied from 0.938 mg/ml to 0.234 mg/ml.

Tests for synergy with oxacillin have shown a decrease in MIC of both drugs. The decline was from 256 to 64 μg/ml for oxacillin, and from 0.234 to 0.117 μg/ml for ALA FS-1. FIC index for this test was 0.75, which can be regarded as a partial synergy between the tested drugs.

Test for synergy with cefamandole has shown a decrease in MIC of both drugs. The reduction ranged from 64 to 8 μg/ml for cefamandole, and from 0.469 μg/ml to 0.234 μg/ml for ABA FS-1. FIC index for this test was 0.62, which determines the interaction of these antibiotics as a partial synergy.

Patent Claims

1. Antibacterial agent for treating bacterial infectious diseases including hospital infections and drug resistant tuberculosis (TB), which comprises an ionic nanostructured complex formed by proteins and/or polypeptides, carbohydrates, salts of alkali and alkaline-earth metals and iodine intercalated into them, characterized in that the proteins and/or polypeptides of the ionic nanostructured complex contain at least one free chain-terminal amino acid with electron-donor functional groups.
2. Antibacterial agent according to claim 1, characterized in that interleukins are used as proteins, and chain-terminal amino acids are Phe, Ala, Val, Ala, Leu, Ile, etc.
3. Antibacterial agent according to claim 1 or claim 2, characterized in that the antimicrobial agent increases bacterial susceptibility to antibiotics, including antibiotic-resistant bacteria.
4. Antibacterial agent according to any one of claims 1 to 3, characterized in that it increases the efficiency of antibiotic treatment for bacterial infectious diseases, including hospital infections and drug-resistant tuberculosis (TB).
5. Antibacterial agent according to any one of claims 1 to 4, characterized in that it has antiviral action.
6. Antibacterial agent according to any one of the preceding claims, characterized in that it has immunogenic activity, increasing the activity of monocyte-macrophages and cytotoxic T-lymphocytes.
7. Antibacterial agent according to any one of claims 1 to 5, characterized in that it stimulates the hematopoietic function of bone marrow.
8. Antibacterial agent according to any one of claims 1 to 5, characterized in that it possesses antineoplastic action.

9. Antibacterial agent according to any one of claims 1 to 5, characterized in that it has radioprotective properties.
10. Antibacterial agent according to any one of claims 1 to 6, characterized in that the ionic nanostructured complex (INSC) has the following formula: $[\{(L_n\,(MeI_3)^+)_y\,[Me\,(L_m)I]^+_x\}\,(Cl^-)_{y+x+k}]$ with M = 30-300 kDa.
11. Antibacterial agent according to any one of claims 1 to 5, characterized in that it is presented in a pharmaceutical form suitable for parenteral, oral, external or other application.
12. Antibacterial agent according to any one of claims 1 to 5, characterized in that in certain acceptable concentrations of components it is a non-medicinal agent.
13. Method of producing the antibacterial agent according to claim 1, comprising complexation reaction of carbohydrates and proteins with metal salts, and intercalation of iodine into complex at ionic strength from $5 \cdot 10^{-4}$ to 15 mol/L, characterized in that introduction of immunotropic proteins is carried out as an individual stage after iodine intercalation of 5 - 95%.

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Additional techniques disclosed herein may develop a method for preparation of antibacterial agent and ABA-based drug to treat infectious diseases

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The technical result of the disclosure is the increase ABA efficiency *in vivo* through activation of immunocompetent cells.

Summary

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disclosure have immunomodulatory effects and may be used for the prevention of infectious diseases, such as seasonal influenza, ARVI, iodine deficiency, as well as an adaptogen.

This disclosure is based on a surprising fact that in solutions of salts of alkali and alkaline earth metals, at a certain ionic strength in the presence of carbohydrate and / or protein, the complex is released into a solid phase in the process of iodine intercalation.

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LIST of Drawing Figures

The invention is described, by way of example only, and illustrated by the following drawing figures.

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Transport role of proteins is extremely important, because a diffusing molecule bound with protein, in case of passing through the membrane, is not chemically modified and does not link with other types of molecules. Mediated, or simplified, membrane transport processes are characterized by saturation kinetics (i.e. the transport system may be saturated by the transported solute) and specificity to transported substance.

The possibility of mediated transport is due to proteins that may reversibly bind specific substrates, including iodine molecule. These transporting protein molecules have different names: transport systems, transporters, carriers, or translocases.

Table 1 shows the ABA compositions, synthesized from carbohydrates, proteins, and iodine at different ionic strengths of the solution created by the salts of alkali and alkaline earth metals. The crystalline structure of some compounds (antibacterial agent), depending on the ratio of carbohydrate: protein (polypeptide), is shown on optical and electronic photographs, fig. 1-4.

As can be seen in the photographs, ABA may form nanocrystals (Fig. 1: 1A with 400x enlargement, 1B with 40000x enlargement), microcrystals (Fig. 2: 2A with 5000x enlargement, 2B with 12000x enlargement) that are rather large (0.1 mm), monocrystals (Fig. 3), or crystals of various sizes (Fig. 4).

The size of crystals decreases with increasing content of carbohydrate relative to protein (polypeptide), all other things being equal (ionic strength of the solution), as well as with increasing the ratio of iodine: carbohydrate, and/or

$$n_6 Ca^{2+} + n_7 I_3^- + L_1 + L_2 + L_3 \Leftrightarrow Ca_{n_6}[I_3]_{n_7} L_1 L_2 L_3 \qquad K_{10} = \frac{[Ca_{n_4}[I_3]_{n_7} L_1 L_2 L_3]}{[Ca^{2+}]^{n_6} \cdot [I_3^-]^{n_7} \cdot [L_1 L_2 L_3]} \qquad (6)$$

ABA output:

$$[Mg^{2+}_{n_4} I^-_{3\,n_5} L_1 L_2 L_3] = \frac{K_5 [L_1 L_2 L_3 Mg^{2+}_{n_1}] \cdot [KI_3]^{4n_3}}{[K]^{5n_4}} \qquad (7)$$

$$[Ca^{2+}_{n_4} I^-_{3\,n_7} L_1 L_2 L_3] = \frac{K_6 [L_1 L_2 L_3 Ca_{n_5}] \cdot [KI_3]^{5n_4}}{[K]^{6n_5}} \qquad (8)$$

The final product output depends on physico-chemical parameters of the reaction (Table 2, 3).

The unexpected fact was that at a certain ionic strength of the reaction medium, the ABA output approaches 100%.

According to results of calculation of assumed equilibrium, the ABA output changes (increases) with the increase in ionic strength (Fig. 5, 6). There is an especially significant effect of ionic strength observed for the complex containing magnesium ions (Fig.6), which may be due to characteristics of this ion as a harder acid according to Pearson [Pearson R.G., Journal ACS, 1963, 85, cl. 3533. Pearson R.G. Journal Chemical Education, 1968, 45, cl. 643. Pearson R.G., Chemical Communication, 1968, cl. 65, Gehlen H.Z., Physical chemistry, 1954, 203, 125. Finston H.Z., Rychtman A.C., A new view of current acid-base series. N.Y., Wile, 1982].

Even more surprising was the fact of ABA crystals formation, which represents an ionic polymer complex, in the process of extraction using the method of centrifugal chromatography and / or drying; at that the composition of monocrystals is well-defined and constant, which indicates the formation of an individual ABA compound. The ABA structure and sequence of actions for this structure formation, according to the method for antibacterial agent preparation, can be represented as follows (Fig. 7). In this figure, blue balls are carbon atoms, dark blue - nitrogen atoms, yellow - chlorine atoms, red - oxygen atoms, black - magnesium atoms, brown - lithium atoms. For the

$$\Delta E = E_1(\text{compl.}) - (E_2 + E_3), \qquad (9)$$

where, E_1 is total complex energy, E_2 - total $LiClOHC_2H_5$ energy;

E_3 – total energy of I_2 complex with amino-acid residue.

As can be seen from Table 4, the most stable complex is formed with participation of arginine (structure VII), in this case I-I bond breaks; in such a complex the properties of molecular iodine are not preserved. Comparison of the stabilization energies for complexes of molecular iodine with arginine (-18.17 kJ/mol), and with adenosine (-10.93 kcal/mol) and guanine (-11, 50kJ/mol), suggests that if arginine is included in the ABA composition, I_2 molecule remains in the structure of the formulation and will not form a complex with DNA-nucleotides.

In I-III complexes I-I bond does not break, but is weakened only. After arginine the most stable complexes are obtained with participation of carbonyl group of protein amide fragment. Amide fragment is a part of polypeptide skeleton and is a part of amino-acid residue of asparagine and glutamine.

The output of final product depends on physico-chemical parameters of the reaction – K_{rev}, stoichiometric coefficient *n*, and concentration of reagents.

Based on the data of UV, Fourier transform IR spectroscopy, electron and optical microscopy, quantum-chemical calculations, the structure of ABA and sequence of acts in formation of this structure, according to the method for ABA preparation, schematically can be represented as follows (Fig. 9).

Formation of ABA subunit (molecule) occurs after the influence of ionic strength in the range from 0,015 and up to 10.2, corresponding to the pressure of 286 - 2860 kg/cm^2. After the influence of such pressure (ionic strength), carbohydrate and protein macromolecules are packed in such a way that terminal amino acid triplets not involved in complexation are oriented outwards from the core protein and/or polypeptide skeletal chain, and perform anchoring of antibacterial agent on the cell membrane through chain-terminal amino acids,

The study of ABA cytogenetic activity was performed by taking account of chromosome aberrations in bone marrow leukocytes of mammals *in vivo* in mice.

The study of ABA cytogenetic activity was performed using micronucleus test in polychromatic and orthochromatic erythrocytes of mice's bone marrow cells *in vivo.*

The study of dominant lethal mutations in spermatozoa in mammals, when administered FS-1, was performed *in vivo* in mice.

Most of the examples given in the description illustrate the ABA effectiveness against pathogenic microorganisms, including museum and clinical isolates of multidrug-resistant (MDR) Mycobacterium tuberculosis belong to the ABA -based drug after Example 5 (FS-1), without being limited to them.

Experiments for studying radioprotective properties of the drug ABA FS-1 were conducted in white rats weighing 190-200g and white mice weighing 22-25g. In irradiation experiments the animals were exposed to single uniform radiation in RUM-17 therapeutic x-ray apparatus (180kV, 10mA, filters 0.5 mm Cu + 1.0 Al, focal distance - 40 cm, radiation dose rate - 178 R/min) in doses of 800 R (radiation doses close to LD50).

Induction of myelosuppression with ABA FS-1 was performed by the method of [Galoyan A.A., Korochkin L.I., Rybalkina E.J., Pavlova G.V., Saburina I.N., Zaraiski E.I., Galoyan N.A., Davtyan T.K., Bezirganyan K.B., Revishchin A.V. Hypothalamic proline-rich polypeptide enhances bone marrow colony-forming cell proliferation and stromal progenitor cell differentiation // Cell Transplantation. – 2008. – Vol. 17. – P. 1061-1066].

Sampling of peripheral blood and bone marrow of animals was carried out by the method of [Bezirganyan KB, Davtyan TK, Galoyan AA Hypothalamic proline rich polypeptide regulates hematopoiesis / / Neurochem. Res. - 2010. - Vol. 35. - CL. 917-924. Gershanovich M.L., Paikin M.D. Symptomatic treatment of malignancies. 2nd ed. - Moscow: Medicine, 1986. – 285 p.].

Assessment of myelosuppression was performed by counting the absolute and relative content of leukocytes, lymphocytes and monocytes in peripheral blood

The resulting solution is transferred to the reactor after the required Product A temperature specified above is reached. The mixture is stirred for 20 minutes (Product B), and after that the temperature in reaction zone is reduced to 25°C.

74.5 g of I_2 and 110.0 g of potassium iodide are dissolved in 500 ml of water. The resulting solution is poured in portions in the complex compound solution (Product B). Intercalation of iodine is carried out in two stages, during 4 hours at 25°C.

The resulting ionic nanostructured ABA complex is extracted from the reaction medium using a suitable method, and dried (Fig. 10(g)).

Ionic strength of the solution is 0.71 mol/L.

Analysis results:

	Carbohydrate	Albumin	PVA	LiCl	NaCl	$MgCl_2$	$CaCl_2$	I_2	KI
Mole fractures, %	**0.04**	**0.002**	**0.01**	**0.96**	**0.87**	**0.9**	**0.18**	**29.8**	**67.31**

$$[25L_1 \cdot L_2 \cdot 19575I_2] \cdot 7L_3$$

In biological activity testing it was established that ABA FS-1 is active *in vitro* both against clinical isolates, and control strains of MRSA and MSSA. MIC of antimicrobial agent was varied from 0.938 mg/ml to 0.234 mg/ml.

Tests for synergy with oxacillin have shown a decrease in MIC of both drugs. The decline was from 256 to 64 μg/ml for oxacillin, and from 0.234 to 0.117 μg/ml for ABA FS-1. FIC index for this test was 0.75, which may be regarded as a partial synergy between the tested drugs.

Test for synergy with cefamandole has shown a decrease in MIC of both drugs. The reduction ranged from 64 to 8 μg/ml for cefamandole, and from 0.469 μg/ml to 0.234 μg/ml for ABA FS-1. FIC index for this test was 0.62, which determines the interaction of these antibiotics as a partial synergy.

Patent Claims

1. Antibacterial agent for treating bacterial infectious diseases including hospital infections and drug resistant tuberculosis (TB), which comprises an ionic nanostructured complex formed by proteins and/or polypeptides, carbohydrates, salts of alkali and alkaline-earth metals and iodine intercalated into them, characterized in that the proteins and/or polypeptides of the ionic nanostructured complex contain at least one chain-terminal amino acid with electron-donor functional groups.

2. Antibacterial agent according to claim 1, characterized in that interleukins are used as proteins, and chain-terminal amino acids are Phe, Ala, Val, Leu, Ile.

3. Antibacterial agent according to claim 1 or claim 2, for use for increasing bacterial susceptibility to antibiotics, including antibiotic-resistant bacteria.

4. Antibacterial agent according to any one of claims 1 to 3, for use for increasing the efficiency of antibiotic treatment for bacterial infectious diseases, including hospital infections and drug-resistant tuberculosis (TB).

5. Antibacterial agent according to any one of claims 1 to 4, for use in antiviral treatment.

6. Antibacterial agent according to any one of the preceding claims, for use for increasing the activity of monocyte-macrophages and cytotoxic T-lymphocytes.

7. Antibacterial agent according to any one of claims 1 to 5, for use for stimulating the hematopoietic function of bone marrow.

8. Antibacterial agent according to any one of claims 1 to 5, for use in antineoplastic treatment.

9. Antibacterial agent according to any one of claims 1 to 5, for use for radioprotective treatment.

10. Antibacterial agent according to any one of claims 1 to 6, characterized in that the ionic nanostructured complex (INSC) has the following formula: [{ $(L_n(MeI_3)^+)_y$ [Me $(L_m)I]^+_x$} $(Cl^-)_{y+x+k}$] with M = 30-300 kDa.

11. Antibacterial agent according to any one of claims I to 5, characterized in that it is presented in a pharmaceutical form suitable for parenteral, oral, external or other application.

12. Antibacterial agent according to any one of claims 1 to 5, characterized in that in certain acceptable concentrations of components it is a non-- medicinal agent.

13. Method of producing the antibacterial agent according to claim 1, comprising complexation reaction of carbohydrates and proteins with metal salts, and intercalation of iodine into complex at ionic strength from 5.10^{-4} to 15 mol/L, characterized in that proteins comprise interleukins and the introduction of interleukins is carried out as an individual stage after iodine intercalation of 5 - 95%.