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3rd RUSSIAN CONFERENCE
ON MEDICINAL CHEMISTRY
SEPTEMBER 28 - OCTOBER 03, 2017

ABSTRACT BOOK

ХИМЭКСПЕРТ

Kazan Federal UNIVERSITY

3rd Russian Conference on Medicinal Chemistry

Kazan, September 28 – October 03, 2017

Abstract Book

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The book contains abstracts of all the scientific sessions of the 3rd Russian Conference on Medicinal Chemistry (Kazan, September 28 – October 03, 2017), including plenary lectures, keynote presentations, oral and poster presentations,round-table talks, and correspondent presentations. It also includes the information from industrial partners of the conference, and the author index.

The 3rd Russian Conference on Medicinal Chemistry is held under the auspices of the European Federation for Medicinal Chemistry.

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- Russian Academy of Sciences
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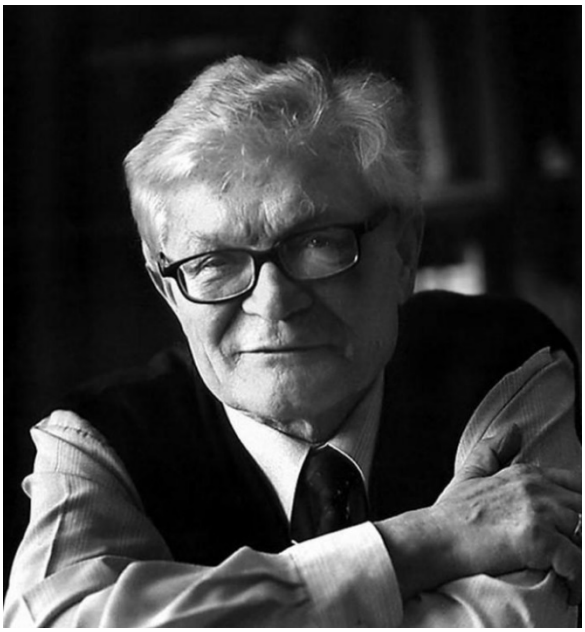
The 3rd Russian Conference on Medicinal Chemistry is dedicated to the memory of Academician Nikolay Serafimovich Zefirov (1935-2017)



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PLENARY LECTURES

Advanced Anti-infective Agents Against Emerging Diseases

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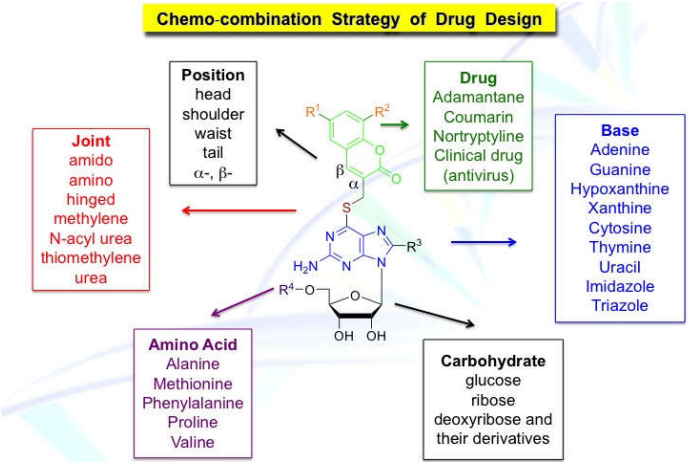
Our laboratory has successfully established 12 compound libraries after five years of research on the SILVER project of the 7th Framework Program funded by European Commission. More than 800 new conjugated compounds containing nucleoside, heterocycle, coumarin, and sulfonate moieties were designed and synthesized, of which the antiviral activities were explored by our SILVER Consortium partners. Results from Leuven University (Belgium), University of Milano (Italy), and Leiden University Medical Center (Leiden) indicate that more than 15 compounds possessed significant potency and identified as leads against chikungunya virus and norovirus. It is the aim of the SILVER project to develop new drugs for emerging and the relatively neglected diseases caused by RNA viruses.



Surmarin, its derivatives, bis(benzofuran–thiazolidinone)s, and bis(benzofuran–thiazinanone)s have also been designed and synthesized. These compounds constitute new types of drug leads for anti-chikungunya virus and norovirus [1-3].

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Modulation of the tumor microenvironment with organometallic compounds

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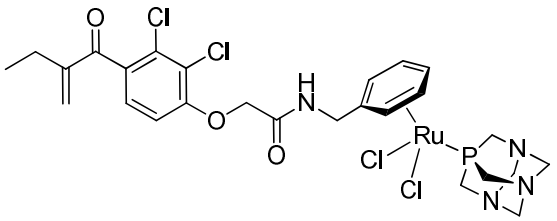
This presentation is concerned with the role of metal compounds in the treatment of cancers [1]. The seminar will focus on our own research on ruthenium-based organometallic compounds that are active against chemoresistant and invasive tumors [2]. We show that lead compounds strongly influence the tumor microenvironment and, when used in combination with other drugs, are effective against chemoresistant tumors. These same compounds also show selectivity towards invasive tumors and metastasis. The mechanisms by which these ruthenium-based organometallic compounds exert their pharmacological effects will also be discussed and drug design strategies highlighted [3].



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Novel synthetic approaches in medicinal chemistry

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In the plenary lecture, the novel synthetic approaches to the design of physiologically active compounds are discussed which are being developed in I.Y. Postovsky Institute of Organic Synthesis and B.N. Eltsyn Ural Federal University (Ekaterinburg, Russia). The Ural academic school is known for its prominent achievements in organic and medicinal chemistry, and design of physiologically active compounds including original innovative drugs recently launched into market.

Specific inhibitors of myosin ATPase and β-secretase – new prospects for drug development

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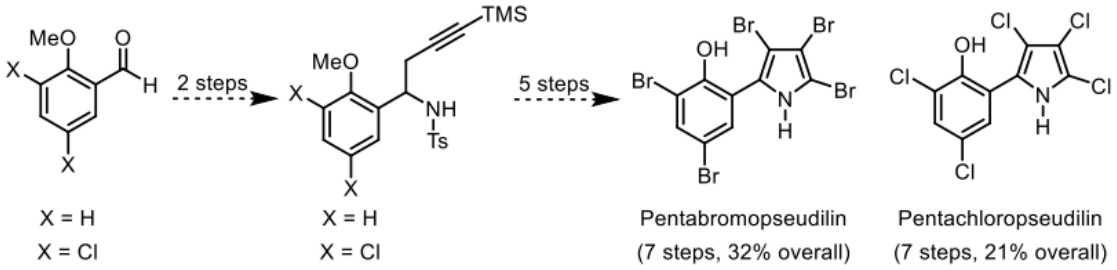
We developed a silver(I)-catalyzed cyclization of homopropargylamines to pyrroles which has been applied to the total synthesis of the alkaloids pentabromopseudilin and pentachloropseudilin.[1,2] The pentahalogenatedpseudilins represent a novel class of inhibitors for myosin ATPase. The fact that pentachloropseudilin is specific for the inhibition of class-1 myosins whereas pentabromopseudilin is specific for the inhibition of class-5 myosins has been exploited in cell biology.[3,4]



Alzheimer's disease (AD) is a neurodegenerative disorder leading to progressive loss of memory and cognitive abilities. In a cooperative project, we have designed potential drugs against AD. A hallmark of AD is the formation of extracellular aggregates of β-amyloid peptides, known as amyloid plaques. These plaques are generated from the membrane-bound amyloid precursor protein (APP) by sequential cleavage of APP involving firstly β-secretase and then γ-secretase. Thus, highly efficient inhibition of the β-secretase enzyme (BACE1) should lead to a potential therapy for AD. Cleavage of APP takes place only when APP and BACE1 are co-internalized into the cell via endocytosis. Based on these findings, we have designed and synthesized a modified lipophilic inhibitor of BACE1 consisting of a tripartite structure, in which each unit exhibits a welldefined function.[5–8]

Inhibitor Spacer Membrane Anchor Linking of a known BACE1 inhibitor to a membrane anchor via a spacer of defined length leads to a tripartite structure which is transported into the cell by endocytosis and delivered to the site of action where BACE1 is active. Compared to non-lipophilic modified inhibitors, our tripartite structures are more effective by several orders of magnitude – in cell culture as well as in living organisms. In a mouse model, simulating AD, our novel inhibitor reduced the formation of β- amyloid peptides by 50% in only four hours, whereas the known inhibitor showed no effect.

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Young scientists' symposium «Innovative developments of young scientists in the field of drug design»

KEYNOTE LECTURE

Phosphonate Congeners of Oseltamivir, Zanamivir and Peramivir as Effective Anti-Influenza Drugs

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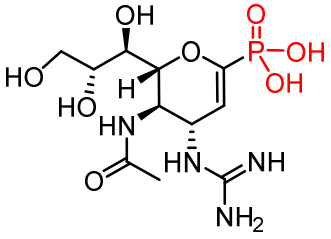
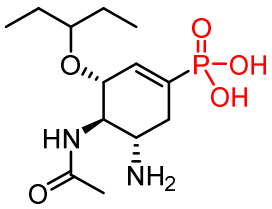
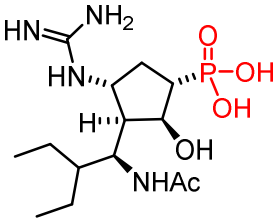
Vaccination and drugs are effective for prevention and treatment of seasonal flu.However, drugs are especially needed in pandemic influenza before new vaccines can be produced. Influenza A is the most infectious type of influenza viruses. There are 18 subtypes of hemagglutinin (HA) and 11 subtypes ofneuraminidase (NA). Avian influenza viral HA recognizes the 2,3-linked sialic acid receptor on the host cell surface, whereas human influenza viral HA recognizes the 2,6-linked sialo-glycoprotein receptors. NA isreponsibleforbreakingtheconnectionbetween viral HA andthe host cell, so thattheprogenyvirusparticlecanbereleasedtoinfectthesurroundingcells. Pandemic influenza infection may occur due to the genetic reassortment of HA and NA.Inhibition of NA is thus a useful strategy in development of anti-influenza drugs.



Phosphono-Zanamivir



Phosphono-Oseltamivir



Phosophono-Peramivir

Zanamivir (Relenza™), oseltamivir (Tamiflu™) and peramivir (Repiacta™) are the NA inhibitors used for treatment of influenza. However, the on-market anti-influenza drugs still have shortcomings, such as the emergence of oseltamivir-resistance viruses, and non-oral availability of zanamivir and peramivir. In this presentation, we shall show the use of phosphonic acid as a bioisostere of carboxylic acid for developing more effective anti-influenza agents that inhibit the drug-resistant viruses.

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The influence of functional groups on the cytotoxicity of amino-derivatives of 7-chloro-3-phenyl-quinoxaline-2-carbonitrile di-*N*-oxide

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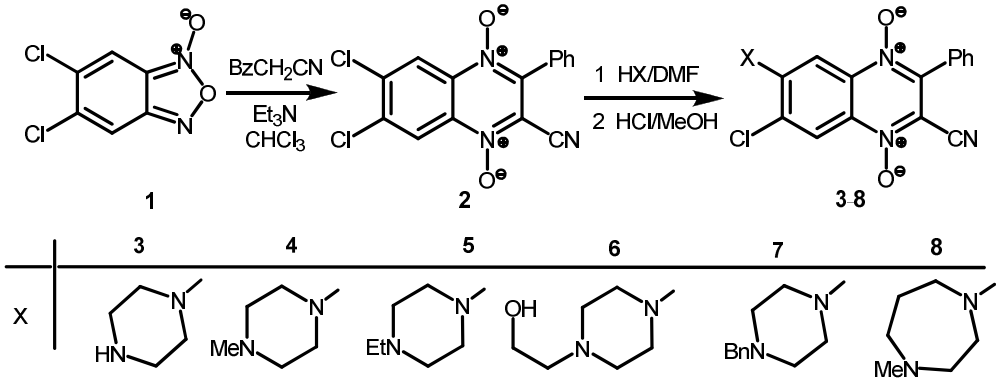
Derivatives of quinoxaline-2-carbonitrile 1,4-di-*N*-oxide are able to selectively inhibit growth of the tumor cells in hypoxic conditions [1]. In order to determine the influence of substituents on the antiproliferating properties the new series of 6-aminoderivatives of 7-chloro-3-phenyl-quinoxaline-2-carbonitrile 1,4-dioxide was synthesized.

The starting compound **2** obtained by the condensation of 5,6-dichlorobenzofuroxane (**1**) with benzoylacetonitrile in the presence of the base [2]. Subsequent replacement of chlorine atom by cyclic diamines afforded the series of 6-aminoderivatives **3**-**8** with distal amino group, the salts of which have a good solubility in aqueous media.



Biological evaluation of the final compounds **3**-**8** revealed that the inhibitory concentration (IC_{50}) are similar or lower than that for the reference drug doxorubicin, cisplatin and tirapazamine for manycompounds. The most interesting were the derivatives of piperazine **3**-**6** where the introduction of substituents in the terminal amino group result in decrease of cytotoxic activity. Distinguishing feature of these derivatives are selective cytotoxicity under hypoxic condition as well as its high activity against resistant cell lines.

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Synthesis of tissue-specific ligands for the targeted drug delivery to hepatic cells

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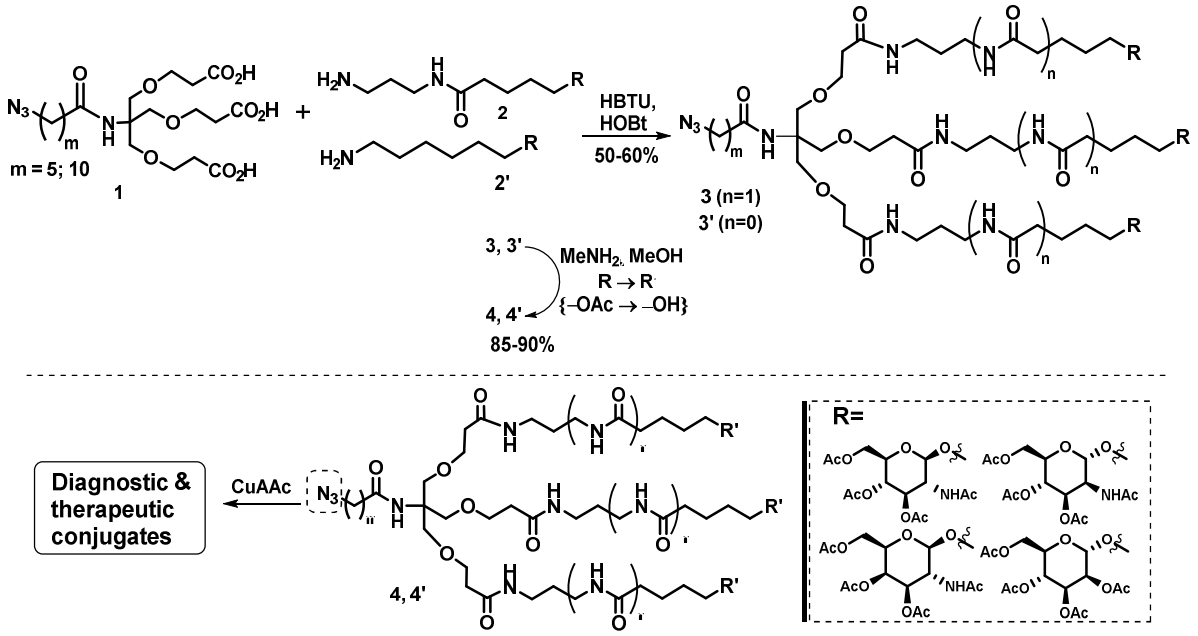
Targeted drug delivery into hepatic cells is a promising approach, since it allows to essentially reduce a single dose of the drug and its toxicity. The two major types of liver cells are hepatocytes and liver macrophages (Kupffer cells) that are known to be involved in the liver's response to various stresses [1]. To facilitate drug delivery into these types of liver cells, asialoglycoprotein receptor (ASGPr) and mannose receptor might be considered as suitable targets.

These two lectins are known to occur on the cell surface as oligomers, consisting of several subunits, so the best binding with the receptors could be attained for branched ligands containing several sugar moieties [2].



This work is devoted to the synthesis of aforementioned ligands and their conjugates with biologically active compounds. For the conjugates obtained biological studies were carried out.

The work is supported by the Russian Scientific Foundation, grant №17-14-01316.

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Development of new, less toxic drugs active against both HIV and other coinfections

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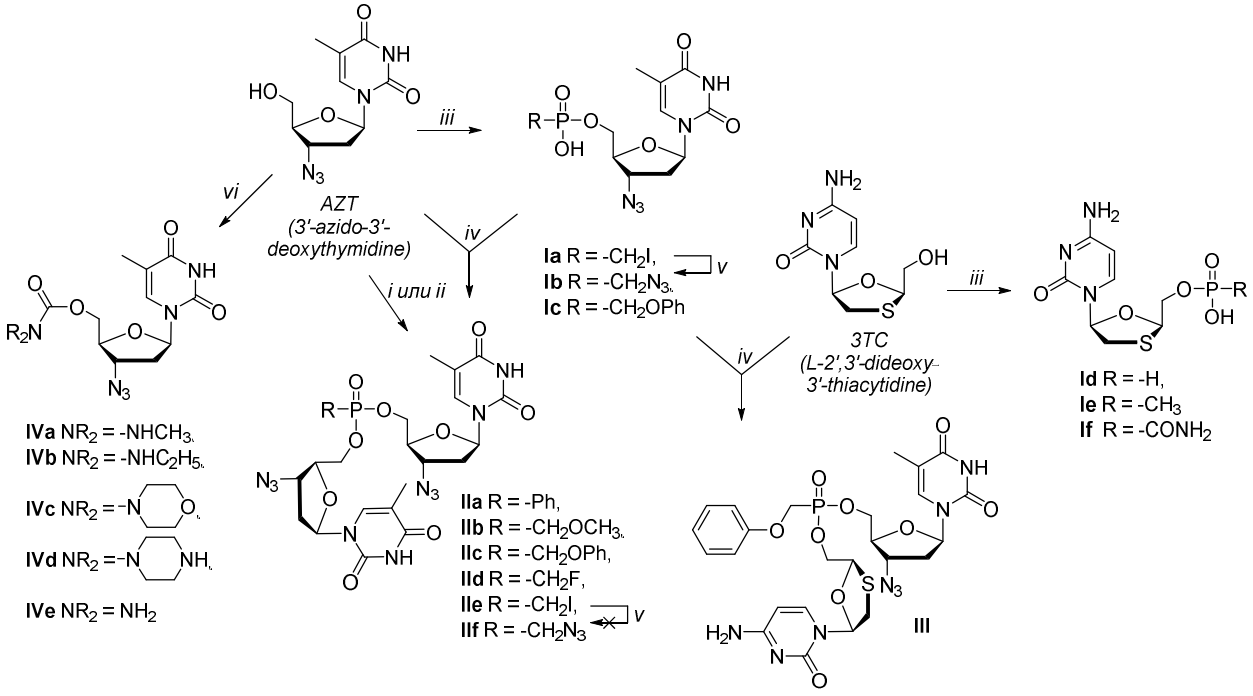
Since the approval of the first-in-class anti-HIV drug 3'-azido-3'-deoxythymidine (AZT), nucleoside and nucleotide analogues have gained much attention, even now, with new classes of antivirals found. This conservative therapy is the most affordable; currently used drugs offer such pharmaceutical benefits as good water solubility, inexpensive synthesis, thoroughly studied mechanisms of action and resistance. Nevertheless, 30 years on, the topic remains: to make nucleosides and nucleotides less toxic in the long-term treatment.

We have synthesized two types of prodrugs based on phosphonate and carbamate derivatives that allowed us to lower the toxicity of 3'-azido-3'-deoxythymidine (AZT) and L-2',3'-dideoxy-3'-thiacytidine (3TC), have tested them in cell cultures and evaluated their pharmacokinetics in animal models (*Scheme 1*). 5'-*O*-AZT morpholinocarbamate, 5'-*O*,*O*'-bis-AZT fluoromethylphosphonate and 5'-*O*-3TC H-phosphonate are most potent prodrugs of these series, exceeding the starting or control drugs in activity / toxicity ratio.



Scheme 1. Conditions: i - $RP(O)Cl_2$, $PO(OEt)_3$, 5°C, 18 h; ii - $RP(O)(OH)_2$, TPS-Cl, Py, 18 ч; iii - $RP(O)(OH)_2$, DCC, Py, 10 ч; iv - 3TC or AZT, TPS-Cl, Py, 18 h; v - NaN_3, DMF, 12 h; vi - CDI, DMF, then NHR_2, 18 h.

Another class, acyclic nucleoside phosphonate analogues bearing unsaturated fragments in the chain have also been designed and obtained.

Synthesis and biological activity studies effects were supported by the Russian Scientific Foundation (project №13-04-00742); evaluation of compounds stability and physicochemical analysis were supported by the Russian Foundation for Basic Research (project № 17-04-00536).

Synthesis of new derivatives of 6-(2,6-dihalobenzyl)pyrimidine-4(3H)-one and evaluation of their biological activity

Novakov I.A.[1], Babuskin A.S.[1], Yablokov A.S.[1], Nawrozkij M.B.[1], Sheikin D.S.[1], Mai A.[2], Rotili D.[2], Maga G.[3], Este J.A.[4]

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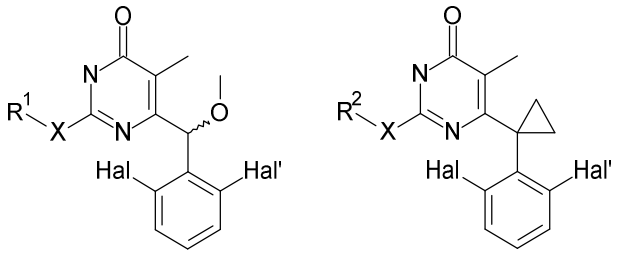
During the course of the current research work two novel series of *NH*-, *N*,*N*- and *S*-DABO analogues were prepared and tested for their antiviral activity and cytotoxicity *in vitro*:



1 **2**

where: Hal = Hal' = F, Cl; X = S, NH, NCH_3;R^1 = C_3H_7, $(CH_3)_2CH$, $C_2H_5(CH_3)CH$, *c*-C_5H_9;R^1 = C_3H_7, $(CH_3)_2CH$, *n*-C_4H_9, $C_2H_5(CH_3)CH$, $(CH_3)CHCH_2$, *c*-C_5H_9, CH_2CH_2SMe.

All the title compounds, belonging to *NH*-DABO and *N*,*N*-DABO series were synthesized by aminolysis of the corresponding N^2-nitroisocytosines in refluxing n-butanol. Novel *S*-DABOs were obtained by direct *S*-alkylation of different 6-substituted 2-thiothymines in anhydrous DMF in the presence of solid K_2CO_3.

The main structured features of the new DABO-analogues, differing them from previously described antivirals of these series, are methoxymethylene and 1,1-cyclopropylidene linkers between pyrimidine and benzene nucleus. The main aim of introduction 2,6-dihalogen-α-methoxybenzyl-substituted into position 6 of the pyrimidine ring was to figure out an influence of hydrophilic-lipophilic balance change upon the scope and intensity of antiviral properties of the title compounds. At the same time, synthesis of 6-[1-(2,6-dihalophenyl)cyclopropyl]-5-methylpyrimidin-4(3*H*)-ones targeted the ability of elimination of benzylic chiral centre in the structure of MC-1046 [1] analogues.

All the compounds showed pronounced anti-HIV-1 activity against a wild type HIV-1 strain, accompanied by low cytotoxicity. On the other hand, none of them appeared to be more promising, then an experimental preparation MC-1501 [2,3] described earlier by our team.

This work was supported by grant of Russian Foundation for Basic Research (No 16-33-6003 мол_а_дк) and Council for Grants under the President of the Russian Federation (SP-496.2016.4).

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Synthesis of new pyridoxine derivatives by the reactions of acetyl ester group with various nucleophiles

M.S. Dzyurkevich, A.A. Palenova, K.O. Filippova, R.M. Khaziyev, N.V. Shtyrlin, R.S. Pavelyev,Yu.G. Shtyrlin

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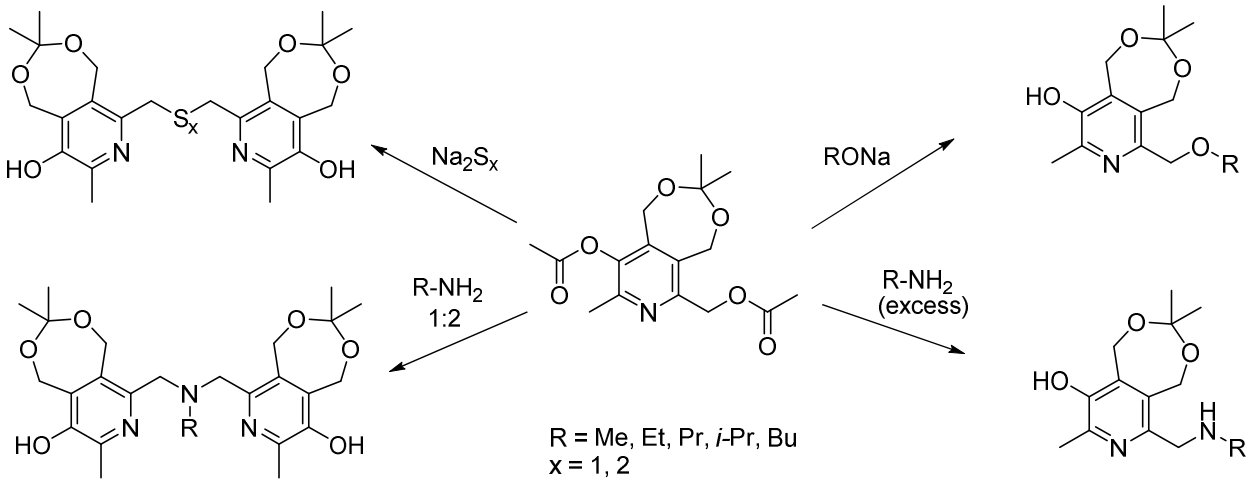
We report a novel approach to the functionalization of 6-position of pyridoxine ring by the use of nucleophilic reagents. It was found that diacetic ester (9-acetoxy-3,3,8-trimethyl-1,5-dihydro-[1,3]dioxepino[5,6-c]pyridin-6-yl)methyl acetate rapidly reacts with N, S and O- nucleophiles with the formation of pyridoxine derivatives (see scheme). The best yields were obtained in alcohol media or water-alcohol mixtures. We suggest that this reaction took place via quinon methide intermediate and solvolysis or aminolysis of phenolic acetoxy group with the release of phenolic OH is necessary step for thequinon methide formation. The starting reagent can be easily obtained with quantitative yield by the acylation of 6-(hydroxymethyl)-3,3,8-trimethyl-1,5-dihydro-[1,3]dioxepino[5,6-c]pyridin-9-ol which synthesis is described before [1].



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Design and stereoselective synthesis of novel phosphodiesterase 4B inhibitors

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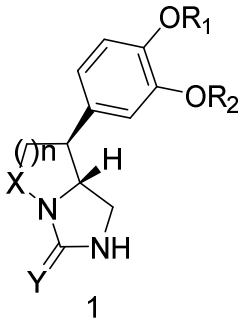
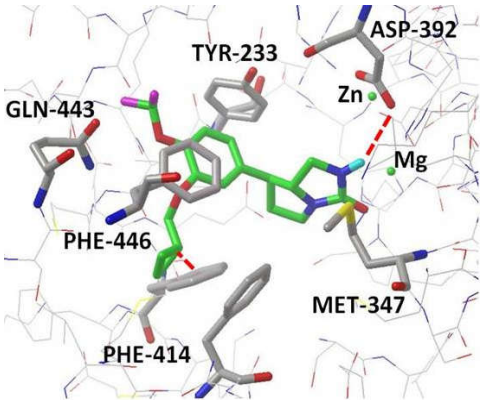
Inhibitors of phosphodiesterase 4B (the enzyme that catalyzes hydrolysis of cyclic adenosine monophosphate and controls its concentration in cells) are used as highly potent pharmaceutical drugs for the therapy of respiratory diseases (e.g. chronic obstructive pulmonary disease and asthma) [1, 2]. The efficiency of PDE 4B inhibitors was proved by *in vitro* and *in vivo* studies [3], but the activity of currently used medicines is still insufficiently high and a lot of them have side effects.

The goal of this project is the development of novel phosphodiesterase 4B inhibitors by means of molecular docking method, followed by their stereoselective chemical synthesis and *in vitro* studies. The molecular structure of target inhibitors is based on a rigid scaffold of bicyclic imidazolidinone **1**. The aromatic (or heteroaromatic) substituent of it can bind effectively with the so-called rolipram site of phosphodiesterase 4B.



1

R_1 – CH_3, AlkF
R_2 – cycloalkyl, Ar
X – CH_2, $CAlk_2$, O
Y – O, S
n = 1,2



As a result of our work, several potentially highly active PDE 4B inhibitors were predicted and the approach to their racemic and asymmetric synthesis was developed.

The research was supported by RFBF (grants # 16-33-01063, 17-03-01079 and 17-33-80172).

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Synthesis and antitumor activity of pyridoxine-based stilbene mimetics

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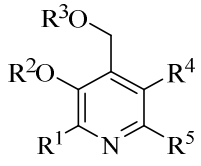
Synthesis of novel biologically active substances with high efficiency and safety is one of the most important tasks solving in medicinal chemistry. It is well known that some stilbene derivatives (tamoxifen, raloxifen and others) are bioisosteric analogues of endogenous ligands of estrogen receptors and are used in clinical practice as hormonal antitumor drugs [1]. Stilbene derivatives of pyridoxine were previously obtained in our group. They have shown high antitumor activity in the human breast cancer cells (MCF-7) and low toxicity in normal human cells (HEK-293) [2-4].

As a continuation of this research we obtained more than 30 new pyridoxine derivatives of stilbene structure by use of Wittig reaction between quaternary phosphonium salts and aromatic aldehydes. *In vitro* study of cytotoxicity of obtained substances revealed that some of them have high antitumor activity and low toxicity. However these compounds have lower activity than analoguesobtainedpreviously.



R¹ = CH_3, C_6H_5-CH=CH, 3,4-$(CH_3O)_2C_6H_3$-CH=CH, 3-(CH_3O)-4-$(OH)C_6H_3$-CH=CH; **R²** = H, $CH_3C(O)$; **R³** = H; **R⁴** = CH_3, CH_2OH, C_6H_5-CH=CH, 3,4-$(CH_3O)_2C_6H_3$-CH=CH, 3-(CH_3O)-4-$(OH)C_6H_3$-CH=CH; **R⁵** = H, CH_2OH, C_6H_5-CH=CH, 4-$(OH)C_6H_4$-CH=CH, 4-(F)C_6H_4-CH=CH, 4-(NC)C_6H_4-CH=CH, 3,4-$(CH_3O)_2C_6H_3$-CH=CH, 2,4-$(CH_3O)_2C_6H_3$-CH=CH, 3-(CH_3O)-4-$(OH)C_6H_3$-CH=CH, 3-(OH)-4-$(CH_3O)C_6H_3$-CH=CH, 2-(OH)-4-$(CH_3O)C_6H_3$-CH=CH, *m*-Pyr-CH=CH, *p*-Pyr-CH=CH, *o*-Pyr-CH=CH; **R²+R³** = $C(CH_3)_2$; **R³+R⁴** = $C(CH_3)_2OCH_2$

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Oxindole derivatives with antiglaucoma activity

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Glaucoma (a group of eye diseases characterized by a constant or periodic increase in intraocular pressure (IOP)) is one of the most dangerous and common causes of blindness in people aged 50 years and above [1]. Existing drugs used to reduce IOP require multiple (3 times) daily use, that is, the duration and absolute magnitude of the biological effect do not satisfy the needs of patients. Therefore, the creation of new generation drugs that have strong and prolonged action is an urgent task.

To create drugs with a given activity, molecular modeling methods were used [2], the search for the most active molecules was carried out using docking based on the oxindole core. A number of patterns of structure-activity were revealed, showing a promising direction for the synthesis of substances with high affinity for the MT3 subtype of melatonin receptors (quinone reductase 2, NQO2) [3]. NQO2 is a promising target therapy of increased IOP-associated diseases; antioxidant and neuroprotective properties of melatonin are also associated with exposure to this target.

A general approach to the synthesis of oxindole derivatives was developed on the basis of simple reactions (Knoevenagel condensation, heterogeneous catalytic reduction, acylation, protecting groups usage) and available reagents (isatin, malonic acid derivatives, common acylating agents – anhydrides, acid chlorides) [3].

The results of the work were the calculation of the binding energy of ligands with NQO2, the determination of the compounds-hits; the development of a suitable synthesis method and, in fact, the synthesis of compounds with a given activity; determination of the biological activity of the resulting compounds *in vivo*.

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In vitro and *in vivo* biological activity of a pyridine derivative TH-14

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As an alternative to the somatic mutation theory, emerging evidence suggests that cancer is primarily a mitochondrial metabolic disease [1]. We suggest that the main hypothesis of metabolic reprogramming of tumor cells is the gradual switching from aerobic glycolysis to oxidative phosphorylation by the use of redox catalyst TH-14 and developing new homeostasis like in normal cells.

In this work, biological effects of the metabolic modulator TH-14 *in vitro* and *in vivo* were evaluated. MCF-7 breast adenocarcinoma cells were grown in α-MEM containing 10% fetal bovine serum, 50 μg/ml penicillin, 50 μg/ml streptomycin, 2 mM L-glutamine and 10 μg/ml (IC_{25}) of the test compound TH-14 at 37°C in CO_2 incubator. Incubation with TH-14 was performed 24 hours and continuously. It was shown that in both variants TH-14 significantly decreased the level of ROS and increased colony formation of MCF-7 cells. In this case, extensive changes in cells are observed only with continuous incubation. TH-14 leads to increased mitochondrial density and mitochondrial potential, promotes a general shift from glycolytic metabolism to oxidative phosphorylation by activating the tricarboxylic acid cycle, as well as activation of the mitochondrial respiratory chain (MRC), promotes increasing sensitivity of MCF-7 cells to antitumor agent Doxorubicin. During incubation for 49 days, there is a gradual decrease in expression for breast cancer markers and overexpression of MRC's proteins, as well as overexpression of transcription factors oct4, sox2, nanog, c-myc. At the same time, the cells do not acquire the cancer stem cells (CSCs) and do not have invasive properties. TH-14 doesn't influent on expression of CSCs markers CD44, CD24 and ALDH1A1.

We tested the efficacy of TH-14 in a MCF-7 xenograft nude mouse model. Our data show that TH-14 in 3, 6 and 9 mg/kg reduced the mass of proliferating tumor tissue 2-5 times, but did not inhibit its growth. A significant decrease in the rate of tumor growth was evaluated at a dose of 6 mg/kg: by 68% during the 40-day therapy, and 80% during the 30-day post-observation. A 100% survival rate of all experimental mice was observed compared to the control group of animals (60%).

Thus, our studies propose a fundamentally new approach to the intracellular metabolic shift of tumor cells to the normal state by regulating the mitochondrial activity of tumor cells. And it is of interest for developments in the field of chemotherapy.

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Pt and Ru complexes with biologically active ligands

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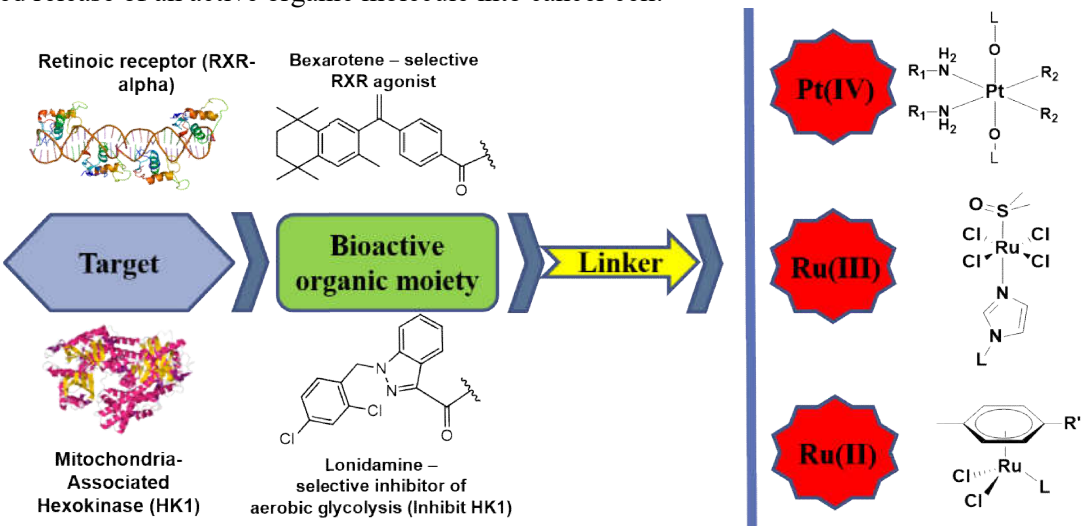
Drug combination is widely applied in cancer chemotherapy and twin-drug approach is one of the lead technic in the modern drug discovery. Such design allows one to control activity and selectivity. Pt(IV) and Ru(III) complexes or Ru(II) organometallic compounds may be considered as a good scaffold for introduction of targeting ligand.

The synthetic advantage of Pt(IV) complexes is the suitability for chemical modifications of axial positions. Ru(III) and Ru(II) compounds could be modified by coordination of bioactive ligands. Conjugation with such ligands can increase the activity or selectivity of new compounds and lead to controlled release of an active organic molecule into cancer cell.



In this work three series of compounds with Pt(IV), Ru(III) and Ru(II) center with modified ligands were prepared. Glycolysis inhibitor lonidamine or retinoid X receptor agonist bexarotene were used as the bioactive organic moiety. Pt(IV) and Ru(II) compounds were characterized by 1D and 2D NMR (^{1}H, ^{13}C, ^{195}Pt, ^{15}N) spectroscopy. Structure and purity were proved by ESI-MS and elemental analysis.

The antiproliferative activity of the all compounds was investigated against cancer cell lines (A549, SW480, MCF7). Several Pt(IV) complexes showed low micromolar *in vitro* activity (IC_{50} 0.07÷11 μM) and notably more active than lonidamine, bexarotene and cisplatin. Highest potential showed Pt(IV) complexes with lonidamine (IC_{50} 0.07÷2 μM) with tendency to nanomolar activity. Ru(III) complexes and Ru(II) compounds are more active than lonidamine and bexarotene, and less toxic than cisplatin and corresponding platinum compounds. For Ru(III) compounds with lonidamine-modified ligands increase of *in vitro* activity with linker lengthening was found (up to IC_{50} 2÷10 μM). All the Ru(II) derivatives have relatively similar activity (IC_{50} 23÷74 μM) which is not influenced by linker length.

This work was supported by Russian Science Foundation (14-13-00483).

Directed *in silico* and *in vitro* search of novel α-glucosidase inhibitors

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Type 2 diabetes mellitus is one of the most fast-spreading socially-important diseases of our days, so researches worldwide are focused on antidiabetic drug discovery. One of the approaches to hyperglycemia pharmacocorrection is inhibition of α-glucosidase, carrying out the hydrolysis of polysaccharides to mono- and disaccharides, which then absorbed into the blood and cause a state of hyperglycemia due to the insulin resistance of the organism. In this regard, the target of the present study is computer-aided search for novel α-glucosidase inhibitors via method of structure similarity with tested substances.

The prediction was carried out using the database containing the information about structure and α-glucosidase inhibition activity of 183 newly tested substances. The data about their maximum inhibiting activity (Δ%) at 1 mM concentration were subjected to clusterization by k-means method, and 3 classes of activity were defined: high (19 subst.), moderate (40), low (74).*In silico* activity prediction for 695 new compounds was performed with TestSim 17.01.28 from IT Microcosm software complex [1]. This utility employs the method of similarity with standards, based on calculation of *QL*-modified Tanimoto similarity index *T* [2]. For each substance *T* values were calculated for all tested substances from database. The maximum value T_{max} was determined, with the indication of code and activity level of the most structurally similar tested substance. A total of 15 compounds with predicted high value and T_{max}>0,6 were tested *in vitro* with method [3] at 1 mM concentration. The reference drug was acarbose.

According to the experimental results, out of 15 promising predicted substances 10 have been found to possess high α-glucosidase inhibition activity. Five compounds were more active than reference drug and another five have the same activity as acarbose. So, the prediction accuracy of the α-glucosidase inhibitory properties by structure similarity with tested substances was defined as 66,7%.

Then, for these 10 substances, a study was performed to determine the IC_{50} values in the concentration range from 10 μM to 1 mM, which showed that tested substances were highly active, with equal or less than 20 times concentrations of the enzyme half-inhibition coefficient as compared to the reference drug (568 μM). Thus, the extended study confirmed the high activity of the compounds, the adequacy and accuracy of the prediction.For these 10 substances the amount of intraperitoneal mouse toxicity by method of structure similarity in the Microcosm ADMET program was predicted, which showed that they belonged to the 4 toxicity class (low toxicity), with predicted LD_{50} values from 76 to 500 mg/kg.

As a result, we can conclude, that this method can be used for *in silico* prediction of new α-glucosidase inhibitors per their structural similarity with the earlier tested substances. The accuracy was 66,7%, and ten newly identified active compounds that showed a high inhibitory α-glucosidase activity were selected for the further detailed pharmacological evaluation. Predicting the toxicity of these compounds suggested that they belong to the 4th toxicity class (low toxicity), which means the perceptivity of further pharmacological study of these compounds.

The work is funded by the Russian Science Foundation, project 14-25-00139.

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Tubuloclustin, its derivatives and analogues: structure – activity relationships

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Natural anticancer agents taxol, colchicine, vinblastine, 2-methoxyestradiol, podophyllotoxin, combretastatin A-4 et al. interact with the cell protein tubulin and either promote or inhibit its polymerization to microtubules. In 2011 we obtained a colchicine – adamantane conjugate (*tubuloclustin*, **I**), which possessed high cytotoxicity *in vitro* and an ability to cause not only depolymerization of microtubules of cancer cells A549, but the formation of unusual tubulin clusters [1].

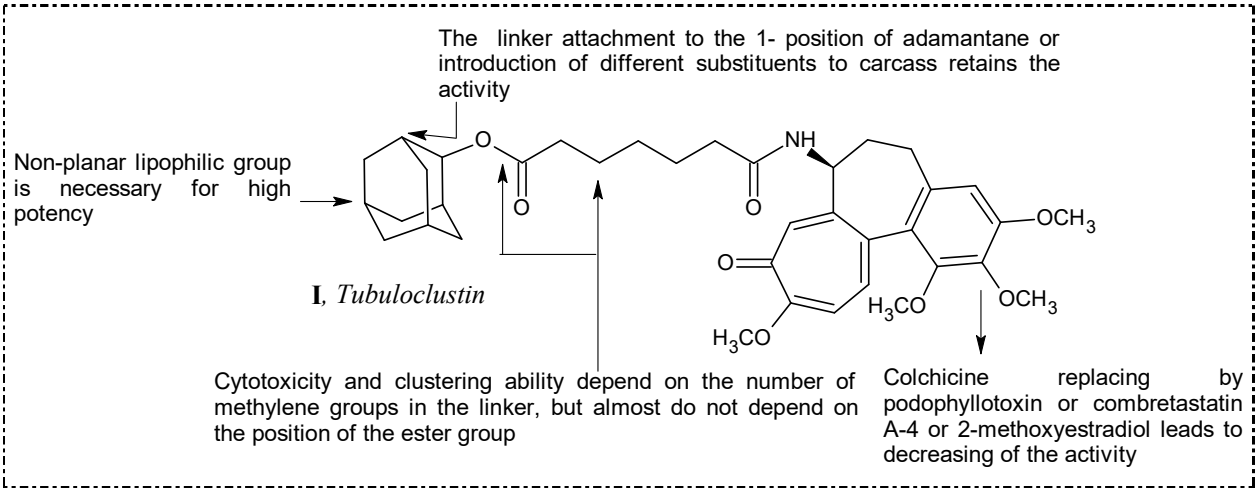

Figure 1. Themainstructure– activity correlationsfor analogues and derivatives of tubuloclustin(**I**).

In the report we present the results of the recent works on the extensive studies of *structure – antiproliferative activity – clustering ability* correlations for numerous derivatives and analogues of tubuloclustin (Figure 1).

The works are supported by grants of Russian Foundation for Basic Research (15-03-04894) and Russian Academy of Sciences.

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Synthesis and biological activity of pyridoxine-based quaternary ammonium salts

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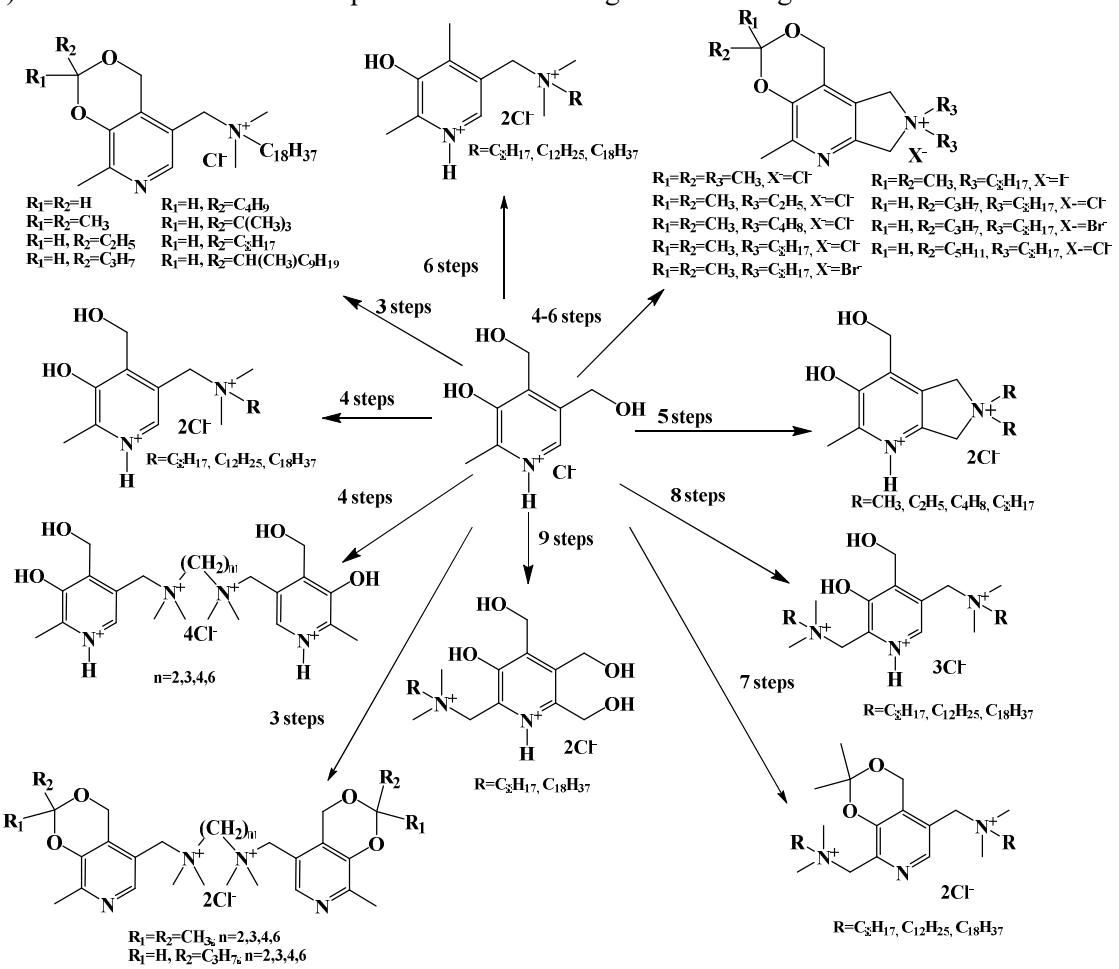
Using selective protection of hydroxyl groups of pyridoxine a wide series of quaternary ammonium salts in 3-9 stages was synthesized [1-3]. Lead compounds with high antibacterial activity *in vitro* (MIC 0.5-4 μg/ml) for clinical strains of Gram-positive and Gram-negative microorganisms have been found.



One of the lead compounds showed high *in vitro* activity against clinical strains of fungi (MIC = 2-12 μg/ml). It should be noted that the MIC value doesn't change with increasing exposure time, which indicates no development of resistance in fungi under its influence. In comparison the MIC value of terbinafine and fluconazole increased significantly with increasing exposure time (4-100 times, depending on the strain). Important advantage of the lead compounds is high safety. Studies of their acute toxicity in rats with oral administration have shown that the LD_{50}> 2000 mg/kg, which is significantly higher than of the widely used antiseptics myramistin (LD_{50} = 900 mg/kg) and benzalkonium chloride (LD_{50} = 240 mg/kg). Sub-acute and chronic toxicity studies of lead compounds using rat models showed no side effects on blood counts, internal organs and animal tissues. The obtained results demonstrate a new low-toxic class of quaternary ammonium compounds with high antimicrobial activity.

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Synthesis and antiviral activity of novel purine and 2-aminopurine conjugates with chiral heterocyclic amines

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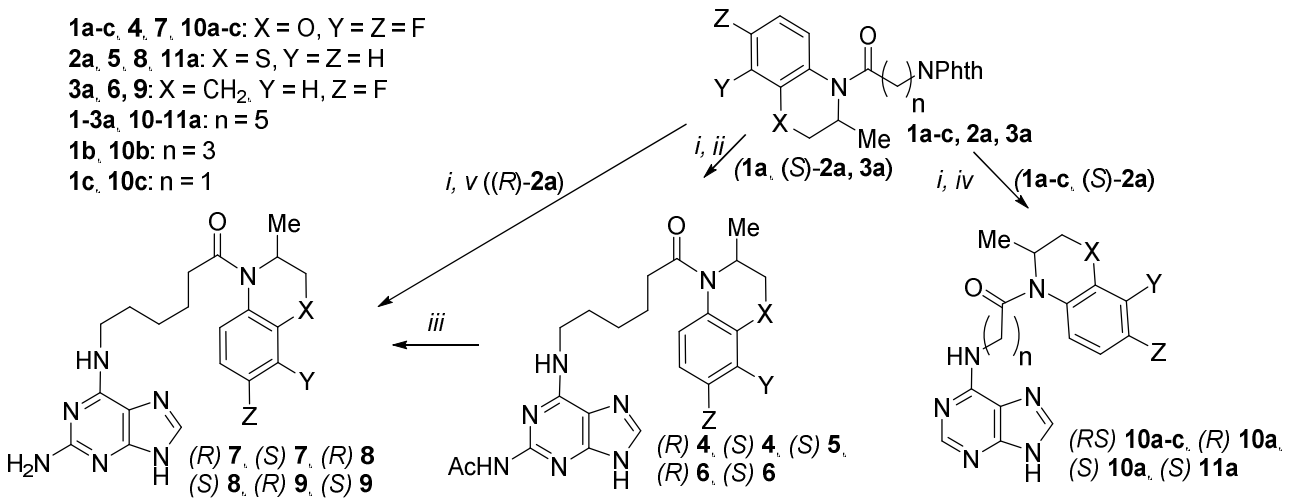
Infections caused by the herpes simplex virus (HSV) are the most widespread in the world. The first-line chemotherapy drugs most effective for the treatment of infections caused by the HSV of both types 1 and 2 are a modified nucleoside acyclovir and its structural analogs. Development of acyclovir resistance in the HSV limits the application of this group of drugs, so the search for new antiviral agents with another mechanism of anti-herpesvirus action is highly topical. From literature it is known about biological activity of purin-6-yl derivatives and compounds containing a fragment of *N*-heterocycle, such as quinoline, benzoxazine and its fluorine-containing analogs. The purpose of our work was to obtain novel purine and 2-aminopurine conjugates of chiral heterocyclic amines and to study their activity against HSV-1.

N-Phthalimidohexanoyl derivatives of chiral heterocyclic amines **1-3** were used as the starting compounds. Removal of phthaloyl followed by interaction with 6-chloropurine, 2-amino-6-chloropurine or 2-acetamido-6-chloropurine led to the target compounds **10,11a**, (*R*)-**8** and derivatives **4**, (*S*)-**5**, **6**. Removal of acetyl group led to the target products **7**, (*S*)-**8**, **9**.



i: NH_2NH_2, EtOH, Δ; *ii*: 2-acetamido-6-chloropurine, TEA, DMA, 100 °C (62-86%); *iii*: 1N NaOH, rt; *iv*: 6-chloropurine, TEA, *n*-BuOH, 90 °C (28-46%); *v*: 2-amino-6-chloropurine, TEA, *n*-BuOH, 100 °C (92%)

It has been shown that compounds (*R*)-**10a**, (*S*)-**10a**, (*RS*)-**10a**, (*S*)-**8**, (*R*)-**9**, (*S*)-**9** exhibit aninhibitory activityagainst HSV-1 and acyclovir-resistant HSV-1 strains; compounds (*S*)-**10a** and (*RS*)-**10a** were the most active. Compounds (*RS*)-**10b** and (*RS*)-**10c**, homologues of compound (*RS*)-**10a** turned to be inactive against HSV-1 strains.

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N^6-Substituted adenosine derivatives as selective inhibitors of human Enterovirus 71 replication

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N^6-Substituted adenosines are a unique group of natural compounds with wide spectrum of biological activities [1]. Recently, we showed that naturally occurring plant cytokinin nucleosides, namely N^6-benzylaminopurine riboside (BAPR) and N^6-isopentenyladenosine proved potent antiviral effect on human enterovirus EV71, but were cytotoxic [2,3]. Thus, we selected BAPR as a promising compound for further optimization. We demonstrated that a number of BAPR analogues with different structure of the linker between the amino group of adenine heterocycle and the phenyl ring exhibited a pronounced antienteroviral activity [3]. The SAR study clearly showed that the activity is greatly dependent on the size of the linker and that a linker with a length of 2-3 carbon atoms provides the most potent antiviral activity. Furthermore, the compounds with double and triple bonds in the linker structure have better selectivity [3].

Modification of phenyl ring in BAPR structure is another perspective approach for optimization. Therefore, a series of BAPR analogues with different substituents at phenyl ring has been obtained [4]. Our SAR study clearly shows that the presence of small substituents at phenyl ring of BAPR significantly increases antiviral effect. Monofluorination of phenyl ring leads to the high cell toxicity. Interestingly, the incorporation of a second fluorine atom resulted in a significant improvement of selectivity. Moreover, N^6-trifluoromethylbenzyladenosines exhibited also high antiviral activity with low cytotoxicity [4].

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Synthesis and antiadrenergic properties of β-substituted alcohols based on 6-hydroxymethylpyridoxine

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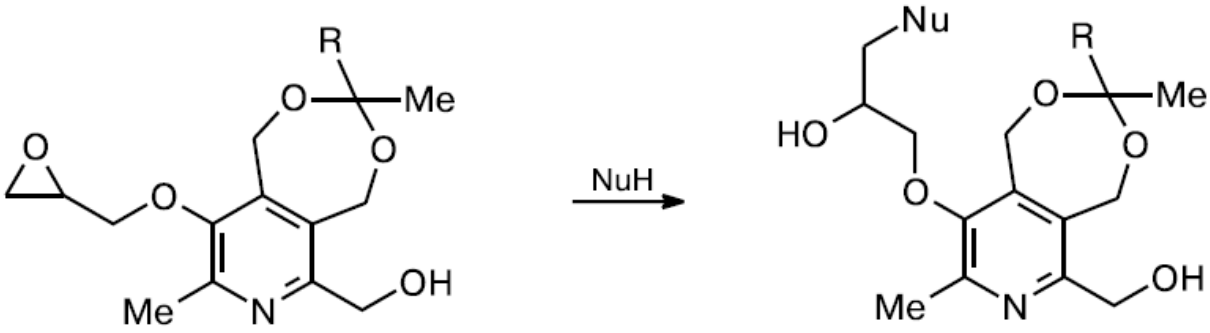
An approach to the synthesis of epoxides based on 6-hydroxymethylpyridoxine acetals was developed. The epoxides obtained were involved in the ring opening reactions by nitrogen-, oxygen-, and sulfur-containing nucleophiles [1]. Atrial myocardial contractile activity of one of the nontoxic compounds (R=Me, Nu=i-PrNH, compound X) was studied *in situ* on the atrium myocardium bands of inbred rats. In the concentrations 10 and 100 μM, metoprolol causes reliable decrease in the contractile activity to 89±4% and 95±2%, respectively, whereas compound X did this to 93±3% and 96±2%, respectively. Thus, compound X has a negative inotropic effect on the activity of the rat atrial myocardium comparable with that of metoprolol. For the most safe compounds the studies of cardiodepressive action were carried out *in vivo*, which was assessed by the decrease in the heart rate of white outbred mice after intragastric administration of compounds. The screening revealed lead compounds, which are comparable with the beta blocker metoprolol in both the onset of the maximal cardiodepressive effect and in its duration. It should be especially noted that the antiadrenergic activity was found not only in β-aminoalcohols, but also in β-alkoxy and β-aryloxyalcohols. We believe that this opens additional possibilities for researches in the development of new adrenoblockers.



R = H, Me; Nu = nitrogen-, oxygen-, and sulfur-containing nucleophiles.

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Prospects for the use of sulfonates in medicinal chemistry

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The physicochemical properties and biological activity of drug molecules directly depend on functional groups within their structure. The sulfo group is not very often used as a substituent in medicinal chemistry, and its applications are usually related to an improvement in drug solubility [1, 2]. What other opportunities are offered when this functional group is introduced into the molecule structure?Toanswerthisquestion we have prepared a review of sulfonates described in the literature, among them were drugs, preclinical/clinical development compounds, as well as more than a hundred experimental inhibitors. In some cases sulfo-substituted derivatives can exhibit increased inhibitory activity, improved solubility, reduced toxicity. The negativelychargedsulfogroup, being a good structural mimetic of carboxyl and phosphategroups [3, 4], isimportantforthedesignofcompetitiveinhibitorsofvarioustherapeutictargets, and the esterified sulfo group may be used in the development of prodrugs. We examined more than a hundred complexes of natural and synthetic sulfonates with proteins, deposited in the Protein Data Bank, and analyzed the binding sites of the sulfo group and its interactions with amino acid residues, metal ions, and water molecules.The retrieved structural data and geometric characteristics of hydrogen bonds of the sulfo group may be used in the design of sulfonate-based drug candidates.

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Special session dedicated to the memory of Acad. Nikolay Zefirov

Examples of design of physiologically active compounds using bridged and caged moieties

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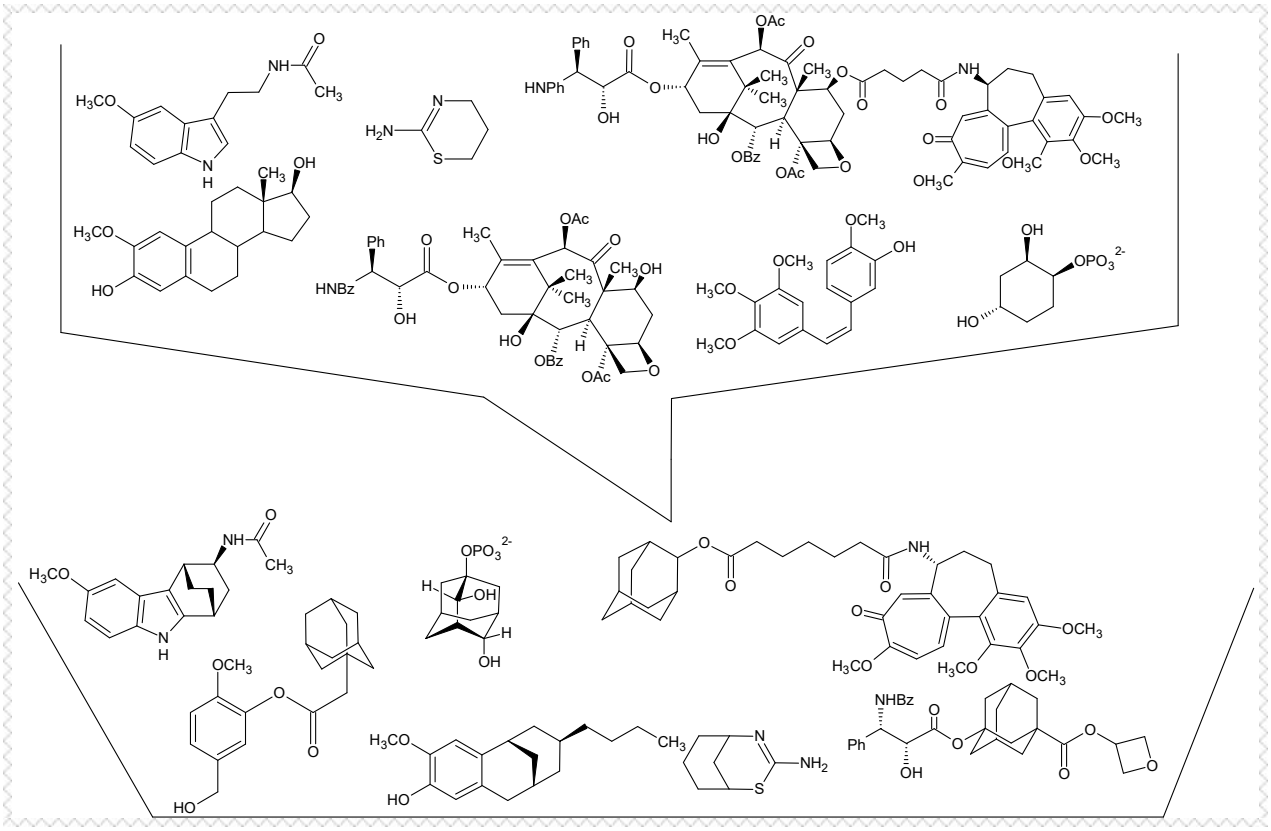
OneofthetrendsoftheinvestigationscarriedoutattheChemistryDepartmentof Moscow State University in the field of medicinal chemistry is an application of bridged and caged fragments for the design of physiologically active compounds.



Inthereportwepresenttheexamplesoftheseworks, whichallowedobtainingnew ligands of colchicine domain of cell protein tubulin, inhibitors of nitric oxide synthase, ligands of melatonin receptors and other compounds with interesting biological properties.

The works were supported by Russian Fund of the Fundamental Research (the current project 15-03-04894) and by Russian Academy of Sciences (program N9).

Development of multitarget agents for the treatment of Alzheimer's disease and related disorders of CNS

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(Dedicated to the memory of academic N.S. Zefirov)

During past 15 years any new agent that was investigated in clinical trials on Alzheimer's disease (AD) patients have not been approved for the market. One of the main problem in successful development of the agents for CNS neurodegenerative disorders treatment related to multifactorial nature of such diseases. In this relation, focused design of multitarget drugs that simultaneously act on several biotargets connected to pathogenesis of the neurodegenerative diseases accepted as a promising approach for developing new generation of neuroprotective CNS agents [1]. In the frame of long-term collaboration between IPAC RAS and cathedra chaired by academic N.Zefirov from Chemical Faculty of M.V. Lomonosov Moscow State University several approaches have been developed for focused design and synthesis of multitarget CNS agents. Novel application (repositioning) of known medicine Dimebon – as a neuroprotector – was proposed and successfully approved in phase 2 clinical trials in AD patients in Russia [2]. The original chemical compounds that combine in one structure the properties of NMDA-receptors blockers and AMPA-receptors positive modulators (both receptors are subtypes of glutamate receptors family that play important role in memory consolidation as well as in neurodegeneration processes) have been developed [3]. Another line of research was connected with the design and synthesis of "polypharmacophore" agents superposing in single molecule several structural fragments of ligands to different biotargets. In particular, synthesis and study of conjugates of phenothiazine (methylene blue) and gamma-carboline (dimebon) derivatives, as well as conjugates of adamantine (memantine) and carbazole derivatives was performed [4,5]. Currently several lead-compounds successfully passed preclinical trials and ready to be moved on further clinical study.

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Inorganic medicinal chemistry - current trends and future directions

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Metal-based drugs represent a relevant sector of the pharmaceutical market with potential development in the treatment of incurable deseases. The aim of this review is to show that there is enormous scope for the design of novel therapeutic and diagnostic metal compounds.

Our study is focused on a novel approach to design hybrid metal-based physiollogically active compounds with opposed modes of action – prooxidant metal center and antioxidant 2,6-dialkylphenol group. The synthesis and anti/prooxidant activity and cytotoxicity studies of novel organometallic/coordination compounds (ferrocenes, complexes with di-(2-picolyl)amine ligand, porphyrins, pyridines, thiols, carboxylates) based on either biogenic metals (Fe, Mn, Co, Cu, Zn, Ni) or exogenic metals (Sn, Au) are presented and discussed.

The multifactor antiprolifirative and antioxidative activities assay of novel compounds has been performed by using DPPH, CUPRAC-tests, and enzymatic methods (*lipoxygenase, gluthathione reductase, thioredoxine reductase, tubulin*); the model reactions of fatty acids peroxidation; *ex vivo* lipid peroxidation in mitochondria isolated from Wistar rat brain and liver, *in vitro* lipid peroxidation in rat liver homogenates. The *in vivo* study was performed for the hit compounds.

This work was supported by RSF (14-13-00483), RFBR (15-03-030557).

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Molecular modelling and conformational analysis in drug design

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Molecular modelling and molecular dynamics simulation are critically important in the analysis of drug-target interactions on the molecular level and in the design of new molecules which bind in the most optimal way to a particular target (usually to either enzyme or receptor). This kind of studies is very popular nowadays and their results are quite fruitful: practically all newly developed drugs passed this stage of studies. However, the interactions of small molecules with so "big" targets as proteins usually cannot be treated on the quantum chemistry level while molecular mechanics used in this case has intrinsic restrictions. The combined QM/MM approaches also do not always help. It is shown that the inclusion of additional parameters into the force fields taking into account the non-classical nature of interactions (which play the main role in "conformational effects", halogen bonding, etc.) significantly improves the situation. Special attention in this presentation is paid to the use of "unusual" conformational behavior (conformational effects) in the design of molecules (drug candidates) pre-organized for optimal binding with particular targets.

The molecular modelling and molecular dynamics simulation of the receptors of glutamatergic and GABAergic systems and their ligands are discussed. The designed ligands have demonstrated a high potency in experimental *in vitro* and *in vivo* studies.

Novel synthetic approach to isoxazole derivatives – promising compounds for biological evaluation

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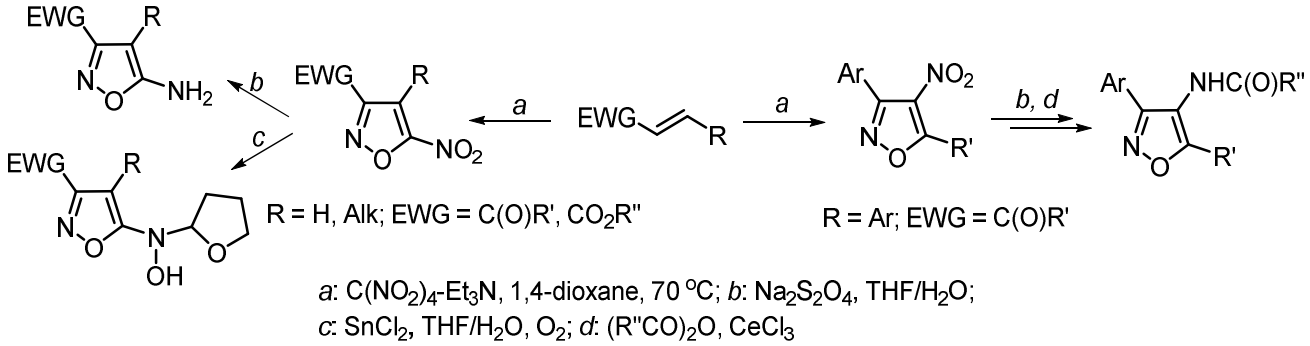
Recently we elaborated novel synthetic approaches to functionalized 5-nitroisoxazoles basing on the heterocyclization of electrophilic alkenes under the treatment with tetranitromethane in the presence of triethylamine [1]. Further we have unexpectedly found that heterocyclization of aryl substituted unsaturated ketones under the same conditions results in 4-nitroisoxazole. Employing synthetically available α,β-unsaturated esters the necessary frameworks were introduced in the target heterocycles to provide certain types of bioactivities. Moreover, we elaborated the chemoselective methods of nitro group reduction affording to obtain amino- and hydroxylaminoisoxazoles [2]. The versatility of our synthetic methodology allowed to prepare a library of compounds varying the substituents in the 3- 4- and 5-position of isoxazole core and opened the opportunity to construct the compounds with desired biological activities.



We carried out the computer modeling and partially experimental investigations of antiviral, antimitotic, neuroprotective activities and antioxidant properties for isoxazole derivatives and found the perspective series of compounds for further investigations.

This work was supported by RNF, project 17-15-01455 (computations and biological evaluations) and Presidium of RAS, Program N 8 (synthesis).

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Scientific session

«Target-directed design of novel drugs»

Small Molecular Weight Compounds for Regulation of Gene Transcription

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Gene transcription is a key mechanism of vital processes in all organisms. We analyze the opportunities provided by medicinal chemistry instruments to modulate gene transcription in tumor cells. Three situations are addressed: first, a precise, stimulus- and gene context specific transcriptional activation of a subset of stress response genes. This mechanism involves a Mediator multiprotein complex in which cyclin dependent kinase CDK8 phosphorylates RNA polymerase II for elongation of the transcript. Senexin B, a first-in-class small molecular weight inhibitor of CDK8 and its paralog CDK19 has entered clinical trials [1]. Second, a broader set of genes is likely to be regulated by dual specificity tyrosine-phosphorylation-regulated kinase (DYRK family). These enzymes modulate gene expression at the level of mRNA splicing, thereby perturbing translation and causing cell death. DYRKs can be selectively targeted with new pyridoquinazoline derivatives [2]. Although these strategies presume rather accurate interference with transcription, they may be insufficient as therapeutic tools in intractable cancers when a bigger number of genes need to be deregulated. The third approach is the use of genome-wide transcriptional inhibitors as an alternative. Olivomycin A, an antibiotic of the aureolic acid family, interacts with the DNA minor groove. This compound and its therapeutically promising derivative inhibit gene transcription by RNA polymerases I and II (but not III) resulting in rapid (within hours) down-regulation of dozens of genes. However, up-regulation of some genes is also detectable in response to olivomycin A indicating a complex mode whereby this compound interferes with the transcriptional machinery [3]. In each of the above situations one can identify the lead compounds potent for tumor cells whereas non-malignant counterparts are spared. Thus, small molecular weight chemicals are an efficient instrument for dissection of transcriptional mechanisms. Emergence of medicinal chemistry of transcriptional modulators provides an opportunity to design antitumor agents relevant to the specific transcriptional contexts.

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Protein kinases as valuable therapeutic targets

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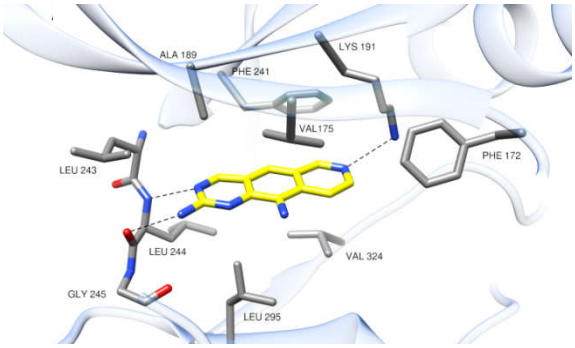
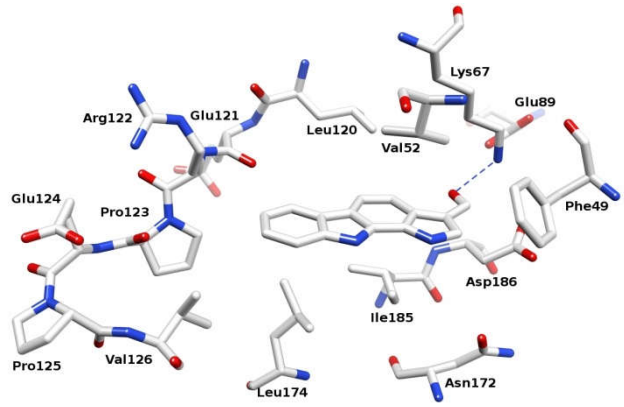
The design and synthesis of novel potent and selective protein kinase inhibitors appears as a major concern due to the essential biological role of kinases in pathologies such as cancer and neurodegenerative diseases. Thus, we are particularly interested in the identification of new heteroaromatic scaffolds showing potent inhibitory potencies toward selected kinases, more particularly Pim and Dyrk/Clk kinase families [1-5]. Here, will be presented our latest findings about the synthesis and biological activities of selected compounds.





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The mitochondrial DNA overproliferation and deletion in the context of the neurodegeneration offeras new multitarget inhibitors for Alzheimer disease and other dementia: recent challenge

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Free radical-induced oxidative damage, mitochondrial alterations, energy/metabolic failure and vascular hypoperfusion are syndromes found to have implications in the pathogenesis of Alzheimer disease (AD). Notably, a decay in mitochondrial function appears to be one key target to the aging cell, as well as for the development and maturation of the AD phenotype. However, the ultrastructural characteristics of the concurrent mitochondrial and vascular lesions associated in these processes, especially the degree and cytological pattern of the mitochondrial lesions and morphometric determination of mitochondrial viability, including increased mitochondrial DNA proliferation and/or deletion, remain unclear. It is widely accepted that during neuronal energy crisis, cerebral hypometabolism and vascular hypoperfusion are major and potentially treatable contributors to the loss of function in patients with stroke as well as AD. The increasing evidence shows that alcohol-related dementia (ARD) is a heterogeneous long-term cognitive problem that can develop in the course of alcoholism. Current understanding of ARD remains limited. The chronic alcoholism appears to be linked to oxidative damage and aging. However, the precise connection between chronic alcoholism and oxidative damage is unclear. Our recent gene expression analysis revealed that genes related to oxidative phosphorylation and longevity were down-regulated in the ethanol-fed monkeys, suggesting that alcohol may accelerate aging in monkeys by damaging their mitochondria.

The development of novel compounds that are able to modify the pathogenesis of neurodegenerative diseases appears to be as a promising approach among different drug discovery strategies in this emerging area. Taking into account the multifactorial nature of neurodegenerative diseases, focusing on the design of multitarget drugs that are capable to act simultaneously on different main biotargets, which are involved in the disease pathogenesis, seems to be very attractive and promising. During the past decade, previous studies have indicated that the progression of AD, amyotrophic lateral sclerosis (ALS) and some other neuropathological disorders is closely connected to dysfunctions in cholinergic and glutamatergic neuronal systems In addition, AD is a multifactorial pathology and the development of new multitarget neuroprotective drugs is promising and attractive. We synthesized a group of original compounds, which combine in one molecule γ-carboline fragment of dimebon and phenothiazine core of methylene blue (MB) linked by 1-oxo- and 2-hydroxypropylene spacers. Inhibitory activity of the conjugates toward acetylcholinesterase (AChE), butyrylcholinesterase (BChE) and structurally close to them carboxylesterase (CaE), as well their binding to NMDA-receptors were evaluated in vitro and in silico. These newly synthesized compounds showed significantly higher inhibitory activity toward BChE with IC_{50} values in submicromolar and micromolar range and exhibited selective inhibitory action against BChE over AChE and CaE. Kinetic studies for the 9 most active compounds indicated that majority of them were mixed-type BChE inhibitors (Figure 2). The main specific protein-ligand interaction is π-π stacking of phenothiazine ring with indole group of Trp82. These compounds emerge as promising safe multitarget ligands for the further development of a therapeutic approach against aging-related neurodegenerative disorders such as Alzheimer and/or other relevant pathological conditions. We theorize that future studies comparing the spectrum of mitochondrial pathophysiology and dependence of these abnormalities on oxidative stress-induced hypoperfusion affects cellular compartments during aging or, more importantly, during the development of AD pathology, which can be used as new and more effective multitarget treatment strategies.

Directed synthesis and biological activity of AChE inhibitors based on uracil derivatives with alkyl substituents

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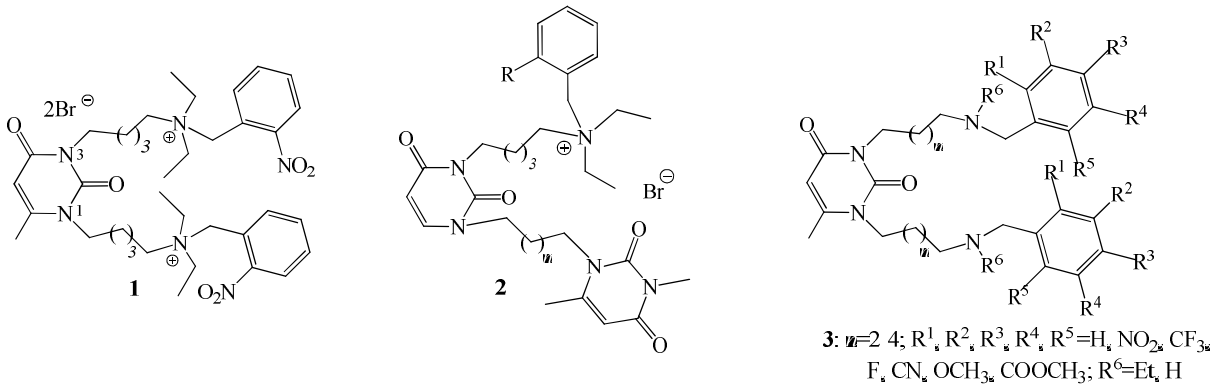
Cholinesterase inhibitors, in particular acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitors with heterocyclic moieties are widely used in medicine for pharmacological correction of cholinergic neurotransmission pathologies, in particular muscle miastenia, Alzheimer's desease.



1 **2**

3: n=2–4; R^1, R^2, R^3, R^4, R^5=H, NO_2, CF_3, F, CN, OCH_3, $COOCH_3$; R^6=Et, H

The compounds **1-3** with ionic and nonionic structure were synthesized starting from 3-mono- and 1,3-bis(ω-bromoalkyl)uracils. These compounds exhibit high activity and selectivity towards AChE and low activity towards BuChE. Their IC_{50} against AChE are 0.5-50nM and ratio IC_{50}(BuChE)/IC_{50}(AChE) is up to 400000. The modeling of the binding of the compounds **1-3** with AChE and BuChE by computational methods made it possible to specify the mechanism of enzyme inhibition and to identify the key moieties of the inhibitor molecules which provide their selectivity against AChE. The report discusses the "structure-activity" relationship of the compounds synthesized towards AChE and BuChE and their high efficiency in the therapy of experimental Alzheimer's disease and myasthenia gravis. Uracil derivatives **1-3** can be used in the development of drugs for the therapy of neurodegenerative diseases, in particular Alzheimer's disease, as well as for the therapy of pathological muscle weakness.

The financial support of RSF (project #14-50-00014) is acknowledged.

Substituted PRO-GLY dipeptide Noopept as a low-molecular regulator of HIF-1-dependent processes

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Fundamental and applied studies of approaches to increase the resistance to hypoxic conditions and ischemia are extremely relevant. This may be due to the fact that these processes to some extent initiate the development of many diseases and accompany their progress (ischemic cardiovascular disorders, pulmonary hypertension, inflammatory and immune responses, oncogenesis, metastasis, neurodegenerative diseases); and they also develop as a result of exposure to various harmful factors [1]. The leading role in the mechanisms of cell adaptation to hypoxia and ischemia is played by the HIF1 protein (hypoxia-inducible factor) that regulates the expression of genes involved in angiogenesis, proliferation, erythropoiesis, glucose metabolism, pH maintenance, apoptosis and migration [2].

Of a particular interest as neuroprotective agents are linear and cyclic proline-containing peptides, and some of them are used in clinical practice (Noopept, *N*-phenylacetyl-*L*-prolyl-glycine ethyl ester, LS 015770). Recently it has been shown that Noopept - substituted Pro-Gly dipeptide with nootropic and neuroprotective properties has the ability to increase both the basal and induced by hypoxia mimetic DNA-binding activity of HIF1 [3]. Investigation of the molecular mechanisms of HIF1-positive effect of Noopept showed that Noopept (100 μM, 24 h) under hypoxic conditions in SH-SY5Y cells in vitro (CoCl2, 50 μM, 6 h) promotes an increase of HIF1α protein by 30% vs control. The level of mRNA gene encoding HIF1α also increases by 20%. The obtained data show the ability of Noopept to stabilize HIF1 due to its impact on the levels of HIF1α protein and its coding gene.

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Novel potent pyridoxine-based inhibitors of AChE and BChE

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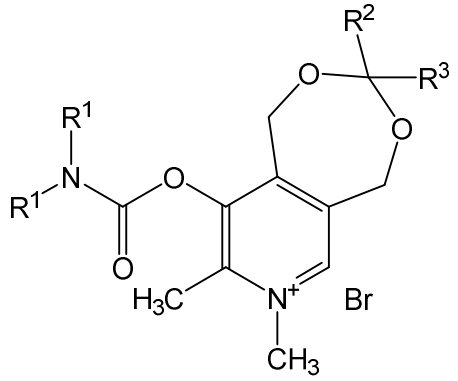
We report a novel class of carbamate-type ChE inhibitors, structural analogs of pyridostigmine [1]. A small library of congeneric pyridoxine-based compounds was designed, synthesized and evaluated for AChE and BChE enzymes inhibition *in vitro*. The most active compounds demonstrated potent enzyme inhibiting activity with IC_{50} values in the range of 0.46-2.1 μM (for AChE) and 0.59-8.1 μM (for BChE), with moderate selectivity for AChE comparable with that of pyridostigmine and neostigmine. Acute toxicity studies using mice models (i.p. administration) demonstrated excellent safety profile of the obtained compounds with LD_{50} in the range of 22-326 mg/kg, while pyridostigmine and neostigmine are much more toxic (LD_{50} 3.3 and 0.51 mg/kg, respectively). The influence of substituents on the binding mode in the enzyme active site was studied using molecular docking calculations. The obtained results pave the way to design of novel potent and safe cholinesterase inhibitors for symptomatic treatment of neurologic disorders.



R^1 = Me, Et, Ph; R^2,R^3 = H, Me, Et, Pr, *i*-Pr, *t*-Bu, *n*-C_7H_{15}, *n*-C_8H_{17}, $CH(CH_3)C_9H_{19}$

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Selective inhibitors of carboxylesterases for increasing the efficacy and rational use of ester-containing drugs

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Carboxylesterases (EC 3.1.1.1, CaE) are enzymes of first-pass metabolism that can hydrolyze a variety of ester-containing drugs and prodrugs, largely determining their pharmacokinetics, bioavailability, efficacy and possible toxic effects [1]. The most common drug substrates of CaE are ester prodrugs specifically designed to enhance bioavailability of the active drug. When the prodrug is orally administered, the CaE of the small intestine or liver hydrolyses it to release the active drug. CaE are one of the most important enzymes involved in ester and amide prodrugs activation. CaE also hydrolyze active drugs containing ester or amide groups, transforming them into inactive metabolites. Selective inhibitors of CaE can be used as co-drugs that increase a half-life of an active drug and reduce its effective dose. CaE inhibitors also determine the conversion rate of prodrug to active drug and thus regulate its bioavailability and modulate toxicity. Several factors influence CaE activity, either directly or at the level of enzyme regulation and thus determine the variability in the therapeutic response to CaE-substrate drugs. The use of CaE inhibitors as co-drugs can implement a fine regulation of CaE activity and rationalize the application of clinically used medicines, improve their therapeutic efficacy and bioavailability, as well as reduce toxicity and side effects [2]. We found that 2-arylhydrazinylidene-3-polyfluoroalkyl-3-oxoesters are effective and selective CaE inhibitors that inhibit the enzyme in the nanomolar range (IC_{50} = 5–13 nM) [3,4]. The high efficiency and low toxicity of the leading compounds allows us to consider them as promising co-drugs for modulation of the metabolism of ester-containing pharmacological agents. Supported by RFBR project №16-03-00417.

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Prospects for creating new drugs that affect P2 receptors

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Extracellular adenosine triphosphate (ATP), along with certain other purine and pyrimidine compounds is capable to regulate many intracellular processes by affecting specific receptors — P2 receptors. These receptors are widely distributed in the organs and tissues of humans and animals. It has been shown that P2-receptors are involved in the vascular tone maintenance, nerve transmission modulation, hemostasis regulation and functions of many internal organs. P2 receptors wide variety and broad representation makes them very attractive as potential targets for new drugs with the original mechanism of action. About 20 years ago in the Kazan State Medical University a laboratory was created and research group on studying the fundamental and applied aspects of the P2 receptors was established. In this presentation, an overview of research carried out in the laboratory over the past two decades to study the physiological and pathophysiological role of P2 receptors in humans and animals, as well as the evaluation of these receptors as potential targets for action of new drugs, is given. In particular, it describes the work to identify new and effective P2 receptors antagonists, the role and characteristics of ecto-ATPase activity in different tissues are described, an overview of studies to assess the unique hypersensitivity of P2 receptors at low temperatures is given. Also studies on assessing the presence and functional role of P2 receptors in the pregnant human uterus, inflamed fallopian tubes, various blood vessels are presented. Obviously, due to the growing interest of many pharmaceutical companies to this area, in the near future we can expect new drugs, which are P2 receptors agonists or antagonists and are effective in treatment of various human diseases.

Indole- and Furane-Derived Allocolchicinoids: Synthesis and Biological Evaluation

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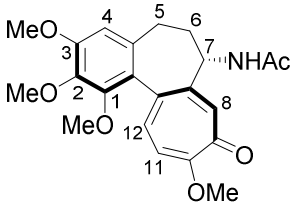
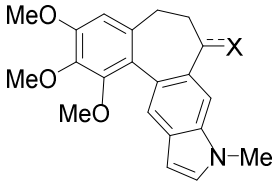
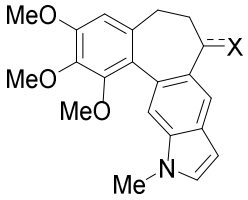
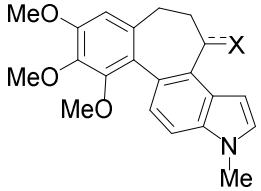
A series of conformationally flexible indole- and furan-derived allocolchicinoids was prepared. Synthesized compounds indicated pronounced cytotoxic activity (proliferation inhibition and apoptosis induction). The major effect of these compounds was the induction of cell cycle arrest in the G2/M phase as a direct consequence of effective tubulin binding. *In vivo* testing of the most potent compounds indicated significant inhibition of the tumor growth. No weight loss, neurological symptoms or change in the behavior of mice were registered.

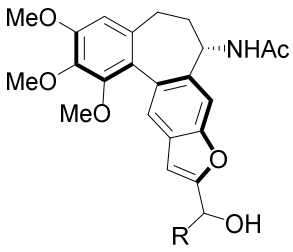


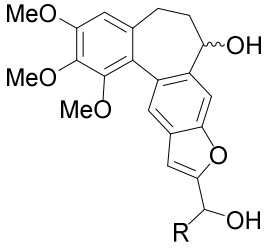
(-)-(a*R*, 7*S*) colchicine

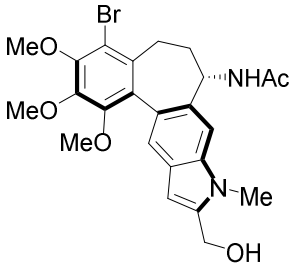












X = N_3, NH_2, OH, O, NHAc; R=H, Me

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Scientific session

«Novel synthetic and technological approaches in medicinal chemistry»

Azoloazines as promising structures for treatment of tick-borne encephalitis

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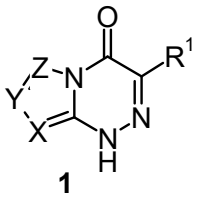
Tick-borne encephalitis (TBE) occupies an important place among the natural focal viral infections by its epidemiological significance for most regions of Russia, the severity of infection and mortality. Over the past 10 years, from 5000 to 10000 cases of disease have been registered annually.Specific prophylaxis of TBE, based on vaccination of high-risk groups, is one of the important remedy for protection against this disease.However,it's important to search for an effective drug against TBE due to the need for multiple vaccinations, the presence of a tendency to uncontrolled expansion of risk groups, the possibility of allergic reactions and post-vaccination complications.

A new original class of non-nucleoside antiviral etiotropic substances, azolo[5,1-*c*]-1,2,4-triazine-7(4*H*)-ones **1** and corresponding azolo[1,5-*a*]pyrimidine-7(4*H*)-ones**2**, structural analogues of purine bases of DNA and RNA, was found during the research work in the Urals Federal University, the Institute of Organic Synthesis of the Ural Branch of the Russian Academy of Sciences, and a number of biological research organizations.



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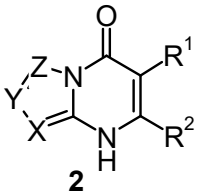

2

R^1 = F, Cl, Br, I, NO_2, CN, COOEt, Ar, Het;
R_2 = H, Alk, Ar; X,Y,Z = N, CH, CR^3

Compounds **1, 2** effectively protect against infections caused by influenza viruses, ARVI, various hemorrhagic fevers.The first drug, created on the basis of this class of compounds - Triazavirin, is included in the register of medicines of the Russian Federation.

It was found that compounds of this class have antiviral activity against TBE *in vitro* and *in vivo* experiments.Thus, the sodium salt of 2-methylthio-6-nitro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazine-7-one dihydrate protected white mice against TBE for 50-55% by oral administration with prophylaxis, emergency prophylaxis, and therapeutic schemes.At the same time, it was note a significant increase in the average life spanindicator of the animals in the experimental groups (from 4 to 5 days), as well as a statistically significant decrease in the accumulation level of virus in the target organ, the brain.

Chemistry of pyridoxine in drug design

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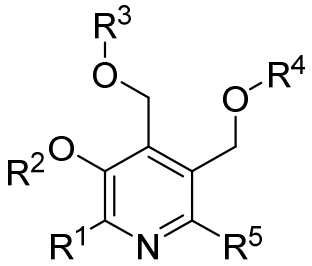
The pyridoxine (vitamin B6) molecule is not only a unique natural object with an extremely wide spectrum of biological activity, but also a molecular scaffold with very rich possibilities of structural modification from the medicinal chemistry point of view. Active synthetic studies being conducted since the 1950s and up to the present have led to discovery of a wide range of physiologically active compounds, some of which have entered clinical practice, and dozens of compounds at various stages of clinical and preclinical trials. The report demonstrates and discusses the most significant examples from the actual practice of the researchers of the Kazan Federal University relating to promising drug candidates based on pyridoxine derivatives [1-5].



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Synthesis and antimycobacterial activity of purine conjugates with amino acids and peptides

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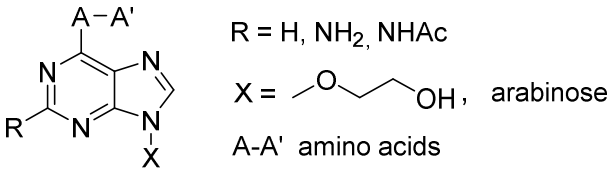
Tuberculosis (TB) is the most common infectious disease in the world. Every year TB kills about 2 million people and up to 10 million new TB cases are registered. One of the reasons that hinder TB treatment is the emergence of multidrug resistance (MDR). Purine and its derivatives play an important role in the metabolism of living organisms. Purine fragments are part of the most important biomolecules: DNA, RNA, ATP, NAD, etc. Therefore, the synthesis and study of purine derivatives are of great interest for designing efficient pharmaceuticals on their basis.

The purpose of this study was to synthesize new purin-6-yl derivatives of amino acids and dipeptides, including containing substituents at positions 2 and 9, and to study their activity against various strains of mycobacteria, including MDR-TB strains. The starting compounds for the preparation of these substances were various derivatives of 6-chloropurine, which were subjected to nucleophilic substitution of chlorine with an amino acid residue followed by the introduction of a second amino acid with subsequent deprotection to afford the target compounds. The methods for monitoring the optical purity of target compounds have been developed. As a result, we obtained a large series of new compounds of the general formula:



In vitro antimycobacterial activity of the obtained compounds was studied. It has been shown that among the synthesized compounds there are substances with high antimycobacterial activity against strains of *Mycobacterium tuberculosis* H37Rv, *M. avium*, *M. terrae* and MDR-TB strains isolated from the tissues of patients in the Ural region [1].

The work was financially supported by the Russian Science Foundation (project 14-13-01077).

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Capillary electrophoresis in the pharmaceutical industry

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Therapeutic proteins make up a rapidly growing segment of global pharmaceutical production. These complex molecules require accurate characterization of product purity, heterogeneity and identity. Analysts handling therapeutic proteins need automated, qualitative and quantitative analysis; simplified functionality and maximum operational efficiency; robust, validated applications that can be transferred globally. The PA 800 plus Pharmaceutical Analysis System addresses these needs by providing robust analytical tools for the development and quality control of therapeutic proteins.

Quantitative Protein Purity Analysis with SDS-Gel Capillary Electrophoresis. The CE SDS-gel application has become the gold standard for protein purity analysis in biopharmaceutical laboratories. Denatured proteins can be reduced or left intact for separation and subsequent analysis. Beckman Coulter's patented replaceable SDS-gel consists of a polymer matrix that allows for quantitative and automated separation of proteins from 10-225kD; sensitivity equivalent to silver-stained gels when using laser-induced fluorescence detection; high-resolution separation capability. IgG Purity and Heterogeneity Assay methodology involves heat denaturation of IgG in the presence of SDS, followed by size separation using high-resolution capillary gel electrophoresis technology with detection of impurities below 0.1% and repeatability of IgG mobility <1% RSD.

Quantitative Protein Charge Heterogeneity. Accurate determination of a protein's charge heterogeneity helps establish identity and stability. Capillary Isoelectric Focusing (cIEF) is a powerful technique that allows quantitative analysis of proteins separated by isoelectric point (pI). The PA 800 plus automates advanced cIEF technology to achieve high precision and quantitative separations. Use of optimized methods and synthetic pI markers attains the highest levels of precision in pI estimation and direct isoform quantitation. An important indicator of the necessary robustness is intermediate precision. Performing advanced cIEF on the PA 800 plus system provides: intermediate precision for calculated pI at <0.1% RSD, Intermediate precision for major isoform quantitation at <3% RSD.

Fast Glycan Labeling and Analysis. There is a growing demand in the biopharmaceutical industry for high throughput, large scale N-glycosylation profiling of therapeutic antibodies in all phases of biologics development. SCIEX has developed a Fast Glycan Labeling and Analysis Kit for high-speed sample preparation and N-linked carbohydrate analysis of glycoproteins. This assay utilizes a high-resolution gel buffer (HR-NCHO) to ensure excellent separation performance of target molecules. Glycan release, fluorophore labeling and clean-up were all optimized resulting in an as fast as 60 min sample preparation time using our novel magnetic bead mediated process that ensures excellent yield and high reproducibility. High resolution N-glycan separation for each sample was obtained in approximately 5 minutes. Our novel triple-internal standard based Glucose Unit (GU) value calculation feature, included in the software package, enables automated and instant GU value based peak assignment and structural interpretation.

Strategies for positioning new chemotypes in medicinal chemistry

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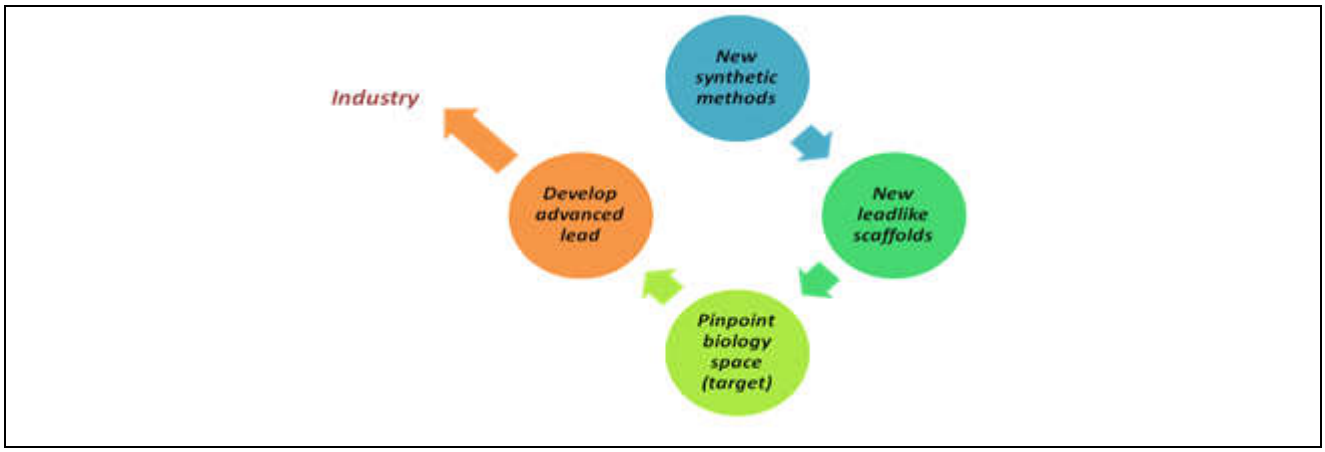
Our laboratory is involved in the development of novel scaffold- and lead-oriented synthetic strategies. In order to unveil the medicinal chemistry potential of our findings for drug discovery we actively position our chemotypes in various therapeutic areas including oncology, infectious disease, metabolic disorders and ophthalmology. The initial success of these, often intuitive, efforts defines the fate of our long-term collaborative projects and draws the attention from industry partners. Tthus, it is awfully important to 'get it right the first time around'. Inthistalk, Iwouldliketopresentsomeexamples of effective medicinal chemistry positioning of new chemistries from our group published in 2014-2017.[1-7]



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Toward pyrazole analogues of midostaurin: synthesis and biological activities

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Staurosporine, a metabolite isolated from *Streptomyces staurosporeus*, is a potent non-selective protein kinase inhibitor (Fig. 1). Staurosporine and its analogues, such as midostaurin, are ATP-competitive protein kinase inhibitors that establish important binding interactions within the ATP-binding pocket of target enzymes. In the case of staurosporine or midaostaurin, the lactam ring is involved in two conserved hydrogen bonds with the hinge region, that mimic those formed between the hinge and the adenine of ATP. The selectivity profile of staurosporine analogues can be affected by structural changes in the lactam ring. In our group, we recently focused on the synthesis of novel protein kinase inhibitors possessing an indazole moiety. Particularly, we synthesized analogues of the aglycon K252c in which the lactam ring was replaced by pyrazole or pyrazolone nucleus (Fig. 1) [1].

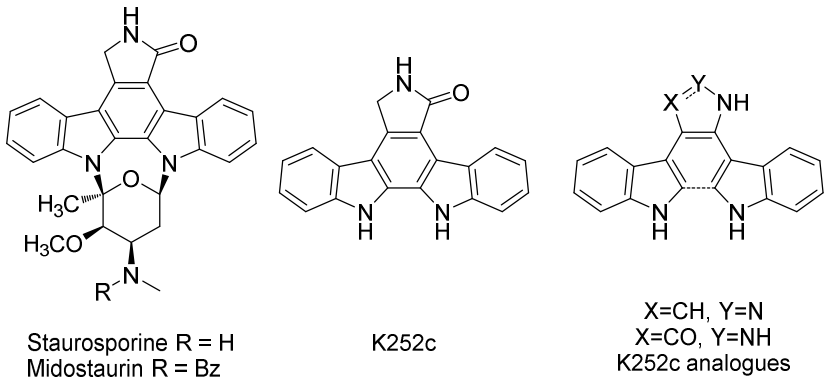

Figure 1. *Structures of staurosporine, midostaurin, aglycon K252c and synthesized analogues.*

The synthesis of the new compounds, as well as their biological activity toward cancer cells, protein kinases, topoisomerase I and DNA will be described.

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Discovery and preclinical evaluation of multitargeted antitumor Anthrafuran

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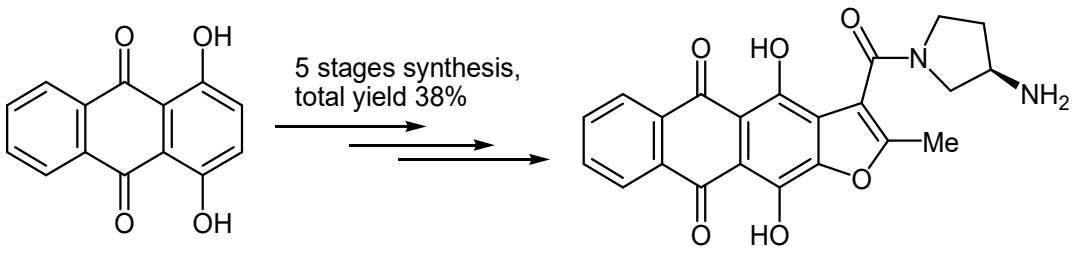
Anthraquinones and their analogues are prospective scaffolds for the searching of new compounds with improved anticancer properties. By using a 'scaffold hopping' approach we have designed and prepared anthra[2,3-*b*]furan-3-carboxamides which possessed pronounced antitumor characteristics [1]. At the initial step, an efficient scheme of synthesis of 4,11-dihydroxy-2-methyl-5,10-dioxoanthra[2,3-*b*]furan-3-carboxamides from the starting quinizarine (**1**) was developed.



LCTA-2034

Among series anthra[2,3-*b*]furan-3-carboxamides the majority of derivatives demonstrated a high antiproliferative potency against a panel of wild type and drug resistant tumor cell lines. At sub-micromolar concentrations the selected derivative of (*S*)-3-aminopyrrolidine – Anthrafuran(**LCTA-2034**)caused an apoptotic cell death preceded by an arrest in the G2/M phase.

Studies of intracellular targets showed thatAnthrafuranformed stable intercalative complexes with the duplex DNA and attenuated topoisomerase 1 and 2 mediated unwinding of the supercoiled DNA. Furthermore, Anthrafuran decreased the activity of human protein kinases Aurora and PIM families *in vitro*, indicating multiple targeting by the new chemotype. Finally, anthra[2,3-*b*]furan-3-carboxamide**LCTA-2034** demonstrated an antitumor activity in a model of murine intraperitoneally transplanted P388 leukemia, achieving the increase of animals' life span up to 262% at tolerable doses. Altogether, the 'scaffold hopping' demonstrated its productivity for obtaining new perspective candidates for multitargeted antitumor drug. The report presents the results of in-depth preclinical studies of the antitumor agent Antrafuran.

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Scientific session

«Scientific and methodological aspects of development of novel drugs»

Overview of translational research at Valdman Institute of Pharmacology

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Increasing Research and Development costs versus decline in numbers of new drug approvals and overall clinical success rate ("low output syndrome) in parallel with the progress of holistic ways of looking at complex system (the "omics revolution", big data analysis) catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of diseases.

Translational medicine is formally dated back to 2005 when E. Zerhouni published his seminal article "Translational and Clinical Science — Time for a New Vision" in the New England Journal of Medicine. At present academic centers, foundations, industry, disease-related organizations, and individual hospitals and health systems have also established translational research programs and special journals are devoted to the topic. The mission of translational research is to reorganize the research process so that new treatments and cures for disease can be delivered to patients faster. By now, four phases of translation (T1-T4) are identified on the way from bench to bedside and to community.

This presentation gives an overview of translational studies at Valdman Institute of Pharmacology, St. Petersburg First Pavlov State Medical University and characterizes research projects directed to different targets (opioid receptors, ligand- and voltage-gated ion channels, $(\alpha4)_2(\beta2)_3$, $(\alpha7)_5$, $(\alpha3)_2(\beta4)_3$ subtypes ofnAChRs, mGluRs , NMDARs, 5HTRs, D_3Rs), phases of translation (T1-T4) completed, and end-points which has been reached. Behavioral markers were primarily used for the assessment of the pharmacological effect in two research domains – pharmacology of pain and addiction.

Target- or effect-oriented search for biologically active substances. Who is right?

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The scientific and technical process of recent years radically changed the strategies and methodology for searching for biologically active substances. Until the beginning of the XX century, for many centuries, isolated facts about the signs of the disease and their treatment with herbal, animal and mineral medicines were based on their effects. Discoveries of the last 150 years have created a new basis for the development of medicines. The possibilities of targeted search for biologically active substances have been expanded, reducing a part of in vivo studies and increasing the prospects for targeted screening, including high-performance preclinical research technologies. The established interaction of the substance with a specific target (receptor, channel, enzyme protein, etc.) does not yet determine the prospect of its clinical application. It is necessary to reveal the expected effect in vivo. Further, these effects must be compared with the reference drugs that are used in clinical practice, if this drug is the first in its class, then its action must be compared with other groups that are used to treat a particular disease. It is necessary to register other (pleiotropic) effects, which can be favorable and unfavorable, and thereby influence the therapeutic potential of the drug being developed. It is necessary to proceed from the fact that there is a unique opportunity with a certain target. It should also be taken into account that each target is heterogeneous and, as a rule, has several subtypes localized in various organs and systems, and this explains that virtually all the funds are available for today. All this emphasizes that the need for effect-oriented research has not disappeared. In the report on the example of 3 developments of medicines performed in recent years, we will consider the evolution process, it will always be equal to these are interrelated technologies. Target-oriented search for biologically active substances improves the effectiveness and predictability of screening for new income, and also as a study of drug safety, gives the final answer about the prospect of developing a drug based on it.

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Are there alternative ways to search and design innovative drugs?

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Current technologies of drug design implements two approaches – development of original and generic drugs. The first approach is costly, time consuming and risky, since only 1-2% of compounds, which proved to be effective in preclinical evaluation, reach commercial success according to pharma companies' statistics. Production of generic drugs is attractive owing to shorter development cycle, expected positive clinical trial results (100% commercialization), and cost effectiveness. These factors explain the attractiveness of generics for small and middle scale pharma companies, in Russia especially.

However, another way to create innovative drugs exists out there – pharmaceutical alternative. It allows to modify structure or formulation of commercially successful drugs and get it patented while investments remain insignificant, since shorter preclinical and clinical studies are sufficient.

One of pharmaceutical alternative approaches considers isolation of pure isomers out of clinically approved racemic mixtures, synthesis of novel salts, ethers, esters or complexes, or varying dosage or strength of existing drugs. Particular interest is focused on different morphology of substances (allotropic modifications), which could be protected with patent in case it proves to be superior in clinical evaluation.

The present report is aiming to summarize literature published and our own experience regarding pharmaceutical alternative techniques that could be employed to design novel drugs.

Expert evaluation of medicinal products

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Expert Evaluation of Medicinal Products in Russia carried out by the Federal State-Funded Institution «Scientific Centre for Expert Evaluation of Medicinal Products» under the Ministry of Health of the Russian Federation (SCEEMP). The SCEEMP's activities are regulated by law [1, 2, 3]. In addition to the basic expert work, the SCEEMP conducts examination for interchangeability, is engaged in information and analytical support of the State register, analyze adverse drugs reactions.

Functions of the SCEEMP:

1. Expert evaluation of preclinical studies results and documents for conducting clinical trials in Russia (including IMCTs).

2. Examination of drug authorisation documentation and post-authorisation changes (quality, efficacy & safety).

3. Documentary and laboratory expert evaluation of drug quality during authorisation.

4. Evaluation of interchangeability (“Russian “Orange Book”).

5. Maintenance of the Drug Register in Russia.

6. Scientific activities: research, development of monographs and other texts for the Russian Pharmacopoeia, publication of three scientific journals.

The staff of the SCEEMP is determined by government decree and is 900 people. 30% of employees have academic degrees: academician of the Russian Academy of Sciences, professors, associate professors, doctors and candidates of Sciences.

The SCEEMP has 21 laboratories certified by WHO and EDQM.

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Neurotrophine tyrosinkinase receptor as a target for novel antidepressants development

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BDNF/TrkB signaling is considered today as a key link in depression pathogenesis [1]. BDNF involvement is due to its important role in regulation of hippocampal neuroplasticity and neurogenesis. Disturbance of this regulation is a major etio-pathogenetic factor of depression. Thereby BDNF can be considered as an object for antidepressants development with the novel mechanism of action. Main biological effects of BDNF are mediated by two post-receptor paths of transduction: MAPK/ERK and PI3K/AKT. Both of them are involved in neurogenesis and neuroplasticity [2]. These data are supported by our researches revealing the antidepressant activity of BDNF mimetics with different patterns of post-receptor paths activation of TrkB [3]. We found that BDNF mimetics selectively activating either PI3K/AKT or MAPK/ERK failed to provoke the antidepressant activity. This indicates the need for simultaneous activation of the two main postreceptor signaling pathways for manifistation of the antidepressant activity. Low-molecular-weight BDNF mimetic GSB-106 (substituted dimeric dipeptide bis(N-monosuccinyl-L-seryl-L-lysine)hexamethylenediamide) was designed and synthesized in the VV Zakusov Institute of pharmacology [4]. Western-Blot analysis revealed GSB-106 ability to activate the specific for BDNF TrkB receptors and their MAPK/ERK and PI3K/AKT signaling pathways [3]. In the conditions of sub-chronic administration GSB-106 completely prevents the stress-induced disturbances of neurogenesis in hippocampal dentate gyrus of mice GSB-106 reveals the pronounced antidepressant activity in the set of validated pharmacological tests in rodents in case of both intraperitoneal and peroral routes of administrations in the dosage interval of 0.05-5.0 mg/kg [5]. Tablet form of GSB-106 is created. The pharmacokinetic study demonstrate that GSB-106 penetrates through BBB ; it may be detected in body within 4 h. At present, GSB-106 is at the final stage of preclinical research It is a potential antidepressant, the first in class with TrkB- activating mechanism of action

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Bivalence of drugs` action. Myth or reality?

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The modern view of the creation of polymodal drugs shifts from the serendipitous discovery of multiple-action to the directed construction of multiple ligands [1]. Today the term "polymodal pharmacology" suggests that more effective drugs can be created through the specific modulation of several targets by one molecule. Investigations for compounds of a multimodal or, at least, bivalent action are being conducted in various areas of medicine.

Dozens of combinations of targets are described, with respect to which ligands are constructed and their activity is investigated [2]. The novel targets are investigated in the treatment of type 2 diabetes mellitus, such as inhibition of the sodium-dependent glucose transporter, the creation of long-acting incretinomimetics, inhibitors of glycogen-syntase kinase 3β, protein tyrosine phosphatase 1B inhibitors [3, 4].

The main strategy of development of the novel antiarrhythmic drugs (AAD) was the principle of blockade of transmembrane ionic currents, which was the basis for the classification proposed by V.Williams. The search of AAD in the period 70-80s of the previous century was aimed at creating selective blockers of a particular transmembrane current, however, during the use of such drugs, the frequency of proarrhythmic effects increased. Nowadays in the development of new antiarrhythmic and cardioprotective agents either bivalent or multimodal substances affecting several pathogenetic targets are searched. In 1991, the solutions of the "Sicilian Gambit" (working group on arrhythmias of the European community of cardiologists) were based on this concept, and further, the superiority of multimodal antiarrhythmics was demonstrated (Amiodarone blocking Na +, K +, Ca ++ channels and alpha- beta-adrenergic blocker) above selectively acting compounds (Ibutilide - selective blocker of K + channels).

In our studies, when searching for new AAD, a Rhythmidazole compound was detected. In silico studies, when docking a new antiarrhythmic substance in presumed activity targets, its ability to interact with several ion channels was established.

It was experimentally proved that Rhythmidazole had a multimodal effect on a number of key targets for antiarrhythmic action. The drug blocked sodium, potassium and calcium channels, and demonstrated the properties of the cholinoblocker, which was proved in various experimental models of arrhythmias.

The efficacy of Rhythmidazole in paroxysmal tachyarrhythmias has been shown in 3 phases of clinical trials, incl. patients with the syndrome of pre-excitation (WPW).

Thus the new generation of antiarrhythmics was developed that blocking incoming fast sodium and slow calcium, outward potassium currents, increasing the duration of the action potential in the His-Purkinje system and myocardial contractility, reduces the automaticity of sinus node, reduces antegrade conduction of the AV-node, increases the effective refractory period of AV-node and atria, increases the duration of the QT interval, and superior in efficiency in supraventricular tachyarrhythmias the reference antiarrhythmic drug Amiodarone.

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Blood Brain Barrier: BDNF delivered to the brain using polylactide nanoparticles improves neurological and cognitive outcome in mice with traumatic brain injury

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Currently, traumatic brain injury (TBI) is the leading cause of death or disabilities in young individuals worldwide. The multi-complexity of its pathogenesis as well as impermeability of the blood-brain barrier (BBB) makes the drug choice and delivery very challenging. The brain-derived neurotrophic factor (BDNF) regulates neuronal plasticity, neuronal cell growth, proliferation, cell survival and long-term memory. However, its short half-life and low BBB permeability are the main hurdles to be an effective therapeutic for TBI. Poly (lactic-co-glycolic acid) (PLGA) nanoparticles coated by surfactant can enable the delivery of a variety of molecules across the BBB by receptor-mediated transcytosis. This study examines the ability of PLGA nanoparticles coated with poloxamer 188 (PX) to deliver BDNF into the brain and neuroprotective effects of BNDF in mice with TBI. C57bl/6 mice were subjected to weight-drop closed head injuries under anesthesia. Using enzyme-linked immunosorbent assay, we demonstrated that the intravenous (IV) injection of nanoparticle-bound BDNF coated by PX (NP-BDNF-PX) significantly increased BDNF levels in the brain of sham-operated mice ($p < 0.001$) and in both ipsi- ($p < 0.001$) and contralateral ($p < 0.001$) parts of brain in TBI mice compared to controls. This study also showed using the passive avoidance (PA) test, that IV injection of NP-BDNF-PX 3 h post-injury prolonged the latent time in mice with TBI thereby reversing cognitive deficits caused by brain trauma. Finally, neurological severity score test demonstrated that our compound efficiently reduced the scores at day 7 after the injury indicating the improvement of neurological deficit in animals with TBI. This study shows that PLGA nanoparticles coated with PX effectively delivered BDNF into the brain, and improved neurological and cognitive deficits in TBI mice, thereby providing a neuroprotective effect.

Evidence-Based Medicine Principles and research synthesis in Pharmacology

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Evidence-Based Medicine (EBM) has become a globally recognized concept over the last 20 years with Cochrane systematic reviews at its heart as the gold standard of research synthesis for informed decisions in health care and better health for all. However, practical implementation of the new knowledge has not yet been achieved on one hand, and excessive repetitive research both in basic and clinical pharmacology calls for adopting EBM principles and methodology.

We aimed to pilot EBM principles and methodology in basic and clinical pharmacology teaching and research.

We used standard Cochrane training materials and the World Health Organization (WHO) Guide to Good Prescribing [1] for delivering teaching sessions to medical and pharmacy students and to practicing physicians. We applied Cochrane research synthesis methodology to basic research in pharmacology.

We present results of this work in progress, success stories, discuss challenges and barriers on its way and set future plans and objectives.

We conclude that EBM principles and methodology can be successfully applied to basic research in pharmacology. Practical implementation of the WHO Guide to Good Prescribing combined with the new knowledge from Cochrane systematic reviews improves prescribing practice.

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Scientific session «Bioinorganic medicinal chemistry»

Implementation of HPLC/MS-based methods and solutions for the metabolomic study in new drug discovery

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The development of a new drug is a long process, requiring major investments and involving many steps before the resulting product is clinically viable.

One of the most important phases of this drug development process is the pre-clinical studies stage, which involves a comprehensive research of its pharmacokinetics in animals. The study of the pharmacokinetic properties of drugs on the pre-clinical level can determine the optimal manner of drug administration that subsequently contributes to the selection of a viable dosage for use in medical practice. Data on the pharmacokinetic properties of drugs allow us to refine the indications and contraindications to their use.

Modern drug development is practically impossible without the use of innovative physicochemical methods of investigation such as high-performance liquid chromatography and mass spectrometry. Using these techniques helps solve the challenges that arise during pharmacokinetic studies such as the analysis of the metabolism of the innovative drug, the determination of the chemical structure of the major metabolites, and the evaluation of their pharmacotherapeutic input to the total activity of the drug. A range of modern LC-MS methods and software solutions for data processing contributes to the formation of a gradual and effective scheme for the metabolic study.

Well-established workflow for assessing the potential of the drug creates a basis for the rational search for new drugs with the desired patterns of distribution in the body. In some cases, it also leads to higher activity and a wider range of actions, such as the detection of metabolites that present advantages over the starting material for the specific activity or safety.

The knowledge developed at the stage of pre-clinical studies, including analytical methods for the quantitative determination of the unchanged drug and its metabolites in biological objects, allows for the use of these techniques in the study of the pharmacokinetics of the drug in clinical practice as well as during pharmaceutical research.

Design of nitrosyl non-heme biomimetics as nitric oxide donors for thetherapy of social diseases: progress and prospect

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The essential role of nitric oxide (NO) in various biological functions such as angiogenesis, apoptosis, immune response, neurotransmission and cardiovascular homeostasis has been identified after the discovery of NO as a signal molecule in the cardiovascular system in the 1980s.These versatile functionalities have brought a rapid increase in researches focused on developing NO-releasing compounds and materials as therapeutic (anty-restenosis, wound healing, anticancer and antibacterial) agents [1]. Much attention has been paid towards the study of nitrosyl transition metal complexes, particularly, biomimetic complexes of iron and copper [2]. Nitrosyl iron complexes being intermediates in the decomposition of proteins and formation of S-nitrosothiols are reservoirs and transporters of NO *in vivo*.

Fundamental researches of the structures and properties (including pharmacologicalactivity and application)of mono- and binuclear nitrosyl iron-sulfur complexes in the solid phaseand in the solutionshave been performed and presented in this work. Being biomimetics of active centers of nitrosyl non-heme proteins, they have been of interest as the basis for developing innovative NO donating medicines possessing of antihypertensive and antiarrhythmic properties of materials – suppressors for bacterial biofilms formation; effective and nontoxic agents, inducers of apoptosis in tumors of various origins [3].

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Organophosphorus compounds as a basis for the design of organic molecules

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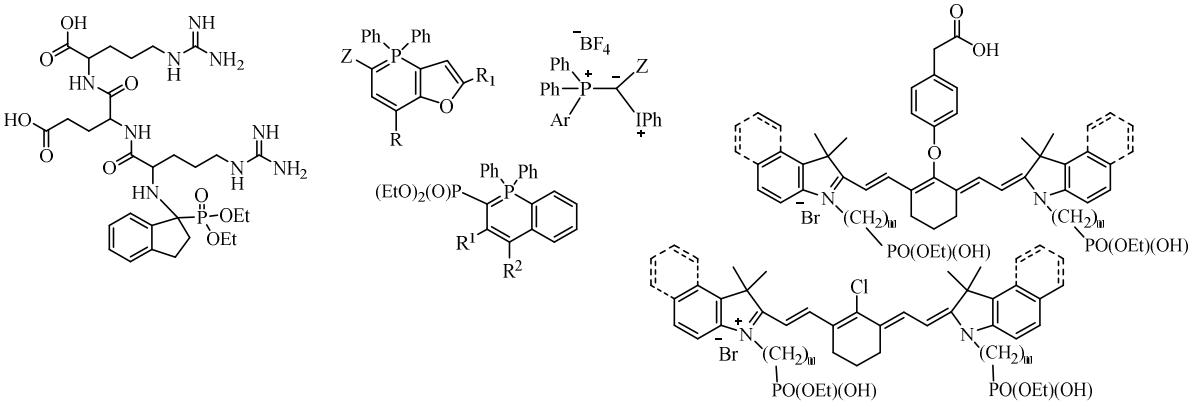
The organophosphorus compounds are of greatimportance for modern organic synthesis.Even the simplest of these compounds are the convenient synthons for creation a variety of new classes of organic molecules. Under the scientific supervision of academician RAS Zefirov N.S. over the past 20 years we carried out systematic studies in some fundamental problems of organic chemistry using organophosphorus compounds.A new catalytic variant of the Kabachnik-Fields and Pudovik reactions was developed using phthalocyanines as homogeneous and heterogeneous catalysts, and a wide range of aminophosphonates, including those based on amino acids and peptides [1-2]. A systematic study of mixed phosphonium-iodonium ylides was carried out, and two heterocyclization reactions with their participation, leading to new phosphorus-containing heterocyclic systems, were discovered. [3-5]. Recently we turned to the problem of creating biomarkers with specified photophysical properties and developed approaches to tricarbocyanines containing hydrophilic phosphonate groups.



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The role of 5-, 6- and 7-membered exocycles in the chemical transformations of natural chlorins

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The presence of additional cyclic structures in natural chlorines makes a notable contribution to their properties and gives wide opportunities for chemical transformations. Numerous reactions of the cyclopentanone ring in chlorophyll *a*derivatives are known, with the formation of conjugates with amino acids and peptides, carbohydrates, fullerenes, boron clusters, etc. A special place is occupied by the conversion of cyclopentanone to six-membered anhydride and imide cycles. We synthesized a large group of similar N-substituted cycloimides, among which promising sensitizers for PDT and BNCT of cancer were found.

Another group of cyclic structures can be obtained by closing the residue of propionic acid either to the adjacent 18-position of the macrocycle or to the 13^2-carbon atom of cyclopentanone. In the first case, as we have shown, a 6-membered lactone is formed at the pyrrole D, the treatment of which with amines made it possible to obtain previously unknown 18-hydroxychlorins.

The seven-membered rings formed when a residue of propionic acid is closed at the cyclopentanone ring were found in a number of marine animals, in which they apparently perform protective functions when exposed to singlet oxygen and other active radicals resulting from extensive sunlight.

Synthesis of a known photosensitizer Talaporfin from chlorin e_6, known to have three carboxyl groups, proceeds strictly regiospecifically only at one of them(position 15^2) also due to the formation of an intermediate seven-membered anhydride ring of two carboxyl groups at the positions 13 and 15 of the macrocycle under the effect of DCC.

The examples considered show that five-, six- and seven-membered exocycles in natural chlorins are important and apparently far from exhaustion sources of obtaining compounds for various purposes.

The work is supported by the grant of RSF № 16-13-10092.

New approaches for the development of physicochemical screening of substances capable of exhibiting bioeffects in the low-concentration range

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In recent decades, the phenomenon of bioeffects in the range of low and ultralow calculated concentrations ($1.0 \cdot 10^{-20}$ - $1.0 \cdot 10^{-6}$ M) of biologically active substances (BAS) is of great interest, but its use is constrained by the absence of an explanation of its physical and chemical nature, as well as the extraordinary complexity associated with the nonmonotonic form of the "concentration-bioeffect" dependence, the presence of "zones of silence", the change of the sign of the bioeffect, etc. The listed signs of dependencies of bioeffects complicate the biological screening of substances that are active in low concentrations. The search for a physicochemical method for selecting such BASs, which simplifies and improves the quality of biological research, is an interesting scientific and important practical task. Recently, for the first time it has been experimentally established that highly dilute aqueous solutions of many BASs are self-organized nanoheterogeneous systems that with dilution and a change of temperature in a range from 25 ºC to 60 ºC undergo a reorganization of the dispersed phase of a domain-nanoassociate type (100-400 nm, ζ-potential from -1 to -20 mV), accompanied by a change in the physicochemical and biological properties of the system [1-3]. It was established that there are three requirements for the nanoassociates to form: a specific structure of the BAS, a special procedure of the solution preparation and the presence of external electromagnetic fields. Through the example of a large number of BAS, the relationship between the formation and rearrangement of nanoassociates, which leads to a change in their parameters, the nonmonotonic dependence of the properties and bioeffects of the systems, is shown. The established behavior is the basis for the development of physicochemical screening of BAS and the method for predicting the bioeffect in the range of low calculated concentrations [4].

This work was supported by the RFBR (project No. 16-03-00076) and the Presidium of the RAS (program 22 (1)).

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Sulfur-containing aurophilic derivatives of natural chlorophylls and their biological properties

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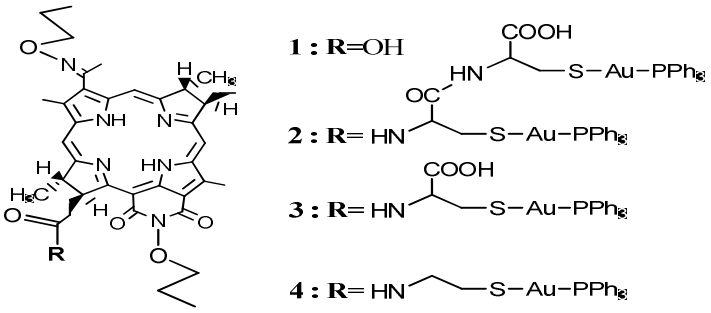
Reduction of the cell resistance to free radicals and oxidative stress may enhance the effectiveness of photodynamic therapy (PDT), where its basic cytotoxic agent is a singlet oxygen. Damage of the main antioxidant enzymes, protecting nucleus and organelles from the free radicals influence, leads to cell death.

In the gold thiolate complexes, cytotoxic properties carrier is the atom of gold, in the composition with phosphinaurate complex, can inhibit glutathione reductase by decreasing cell reduction potential.

This research comprehends the development of high-performance PS, based on dipropoxybacteriopurpurinimide (dipropoxy-BPI) with thiolate gold complexes (I), for combined photodynamic therapy and chemotherapy in oncology. Introduction of triphenylphosphinaurate (TPPA) into the periphery of thiol PS occurred to be impossible due to their rapid oxidation and formation of disulfides. Other approach included complexes (TPPA) synthesis with cysteamine and cysteine for subsequent joining them to dipropoxy-BPI.



Joining TPPA with cysteine to dipropoxy-BPI **1** in the presence of a condensing agent EEDQ led to the obtaining of the PS **2** with the two cysteine-TPPA residues. Remarkable, that the change in the molar ratio of the starting reactants does not affect the product structure, which was proved by ^{1}H NMR and mass spectra. Synthesis of conjugate **3** with a single cysteine-TPPA residue has become possible due to changes in amidation conditions. Preliminary biological studies have shown dark toxicity of conjugates **2** and **4** on the cell line of colon cancer HCT116, and irradiation with light have shown the promotion of their photo-induced cytotoxicity.

According to these results, the possibility of the proposed bacteriochlorine series PS application in combined chemotherapy and photodynamic therapy for the tumors treatment can be presumed.

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Small molecule models of active centers of Cu-containing enzymes as a novel class of antitumor drugs

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Study of antitumor activity of coordination compounds of transition metals is a key task of modern medical chemistry and oncology. The share of metal-containing drugs (primarily platinum compounds) in clinical oncology is 15%. Despite a number of side effects (nephrotoxicity, etc.) for some types of tumors, the use of platinum is the necessary option.

Among other metals, copper is an important trace element, which plays a central role in biochemistry and physiology of every living organism. Copper is one of the most important metals present in the body in trace amounts. Copper is necessary for normal cellular activity as a cofactor in many enzymes. Due to the fact that copper is an endogenous metal, it is expected that the Cu-containing complexes will be less toxic. It was shown that the properties of copper coordination compounds strongly depend on the nature of the ligands and types of donor atoms that coordinate the metal ion. To this end, copper complexes with cytotoxic activity are actively studied *in vitro* and *in vivo*.

In this work, we have obtained for the first time a new class of copper (II, I) coordination compounds containing derivatives of 2-thiogidantoin, 2-selenohydantoin and 2-aminoimidazolinone. Biological study of coordination compounds was carried out: the cytotoxicity was determined on the panel of cell lines, the structure-activity relationship was established, attempts were made to find the target for the action of coordination compounds. The mechanisms of penetration of coordination compounds into cells were also studied. The report will present data on antitumor effect *in vivo* on allogeneic and xenograft models of breast carcinoma. The results of preclinical studies of coordination compounds are presented.

The work was supported by RFBR 16-33-60166, Federal Target Program 14.579.21.0018.

Synthesis, Spectral Characterization and Antimicrobial Activity of2-(5-Cl/NO_2-1*H*-benzimidazol-2-yl)-4-Br/NO_2-phenols and Their SomeTransitionMetalComplexes

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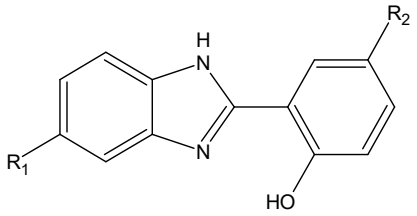
It is known that some metal ions play key roles in the structural organization and activation of certain enzymes, which are involved in the transfer of genetic information from DNA, leading to the synthesis of specific proteins. Transition metal complexes have attracted attentions of inorganic, metallo-organic as well as bio-inorganic chemists because of their extensive applications in wide ranging areas from material to biological sciences [1-3].



HL_1: R_1=Cl, R_2=Br; **HL_2**: R_1=Cl, R_2=NO_2;
HL_3: R_1=NO_2, R_2=Br

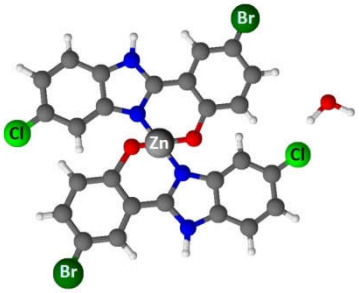


Fig. 1 Chemical structure of the ligands (left) and the Zn(II) complex of HL_1 (right)

In this study, three benzimidazolyl-phenols, 2-(5-R_1-1*H*-benzimidazol-2-yl)-4-R_2-phenols (Fig. 1) and their some transition metal complexes were synthesized and characterized. The compounds were screened for *in vitro* antimicrobial activities against *S. aureus*, *S. epidermidis*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *P. mirabilis* and for antifungal activity against *C. albicans*. It is observed that most of the complexes show considerable activity on *S. aureus*. It was found that HL_3 is the most effective one among the ligands toward *S. aureus* (MIC = 2.4 µg/mL). It was observed that the Zn(II) complex of HL_1 (Fig. 1), $[Zn(L_1)_2]\cdot H_2O$, is highly effective against *S. Aureus* and *S. epidermidis* whereas HL_1 itself is impotent.

Acknowledgement: This work was supported by the Scientific Research Projects Coordination Unit of Istanbul University.

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Ferrocene-modified bioactive compounds for medicinal applications

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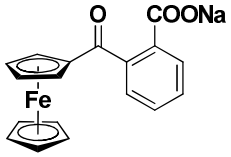
Ferroceron (**1**) is the first and single ferrocene-containing drug on the pharmaceutical market. Along with that, intensive scientific researches allowed to appearance the novel antimalarial drugs (**2**), hormones for specific receptors by ferrocene-modifications of known drugs or by synthesis of original compounds. Antiproliferative investigations are the more developed. It was found that ferrocene-based compounds (**3**) not only significantly inhibit the cancer cells growth but are able to give the regress of the human tumors. Acute toxicities of such ferrocenes are low and therefore in future it will help to improve the life quality of patient`s life.



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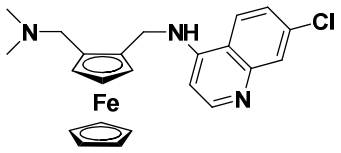

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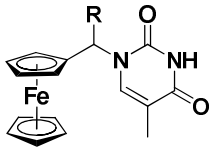

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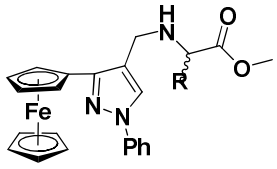

4

It should be noted an appearance of the research studding ferrocene-modified amino acids (**4**) and their bioelectrical brain activity in the animals [3]. An intensification of the enantiomeric-enriched ferrocene compounds studies takes place too [4].

In general, modern organometallic chemistry and particularly ferrocene chemistry significantly connected with biological and medicinal aspects.

This work was financially supported by the Russian Foundation for Basic Research, Grant RFBR No.16-03-00881.

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Stereochemistry of metal complexes of chiral thiophosphorylated thioureas. Structure and bioactivity and magnetic properties

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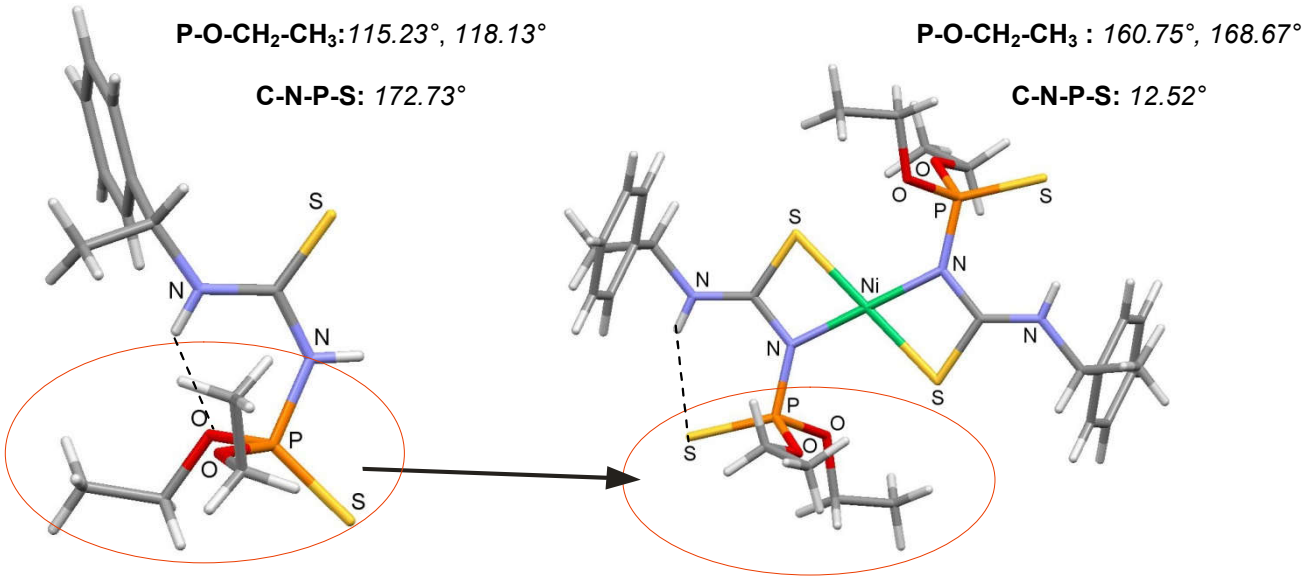
A series of new chiral thiophosphorylated thioureas were synthesized in racemic and enantiopure forms, their structure and coordination properties towards transition metals were studied by X-ray single crystal diffraction. Special attention was paid to self-assembly and molecular recognition of enantiopure and racemic compounds, as well as to stereochemical aspects of metal coordination.



Magnetic properties were studied for racemic and enantiopure metal complexes. Biological activity was evaluated for racemic compounds and both individual enantiomers in respect to *Staphilococcus aureus* and *Bacillus cereus*.

This work was supported by the Russian Foundation for Basic Research, grant 15-43-02486.

X-ray studies were supported by the Russian Science Foundation, grant 17-13-01209.

Medical application of cobalamins and cobinamides

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Vitamin B_{12} (cobalamins, Cbls) cofactors catalyse important biological transformations and are indispensable for humans and most other forms of life [1, 2].Detailed studies have been reported for the inorganic chemistry of Cbls as well as their analogues - cobinamides, Cbis, lacking 5,6-dimethylbenzimidazole nucleotide, with different ligands. Cbls and especially Cbis are highly reactive to cyanide making them the convenient antidotes and chemosensors [3]. Cbls and Cbis have also the perspectives of application as the antidotes for hydrogen sulfide [4]. Herein, we report on the chemistry of Cbls and Cbi complexes with cyanide, sulfur and selenium compounds as well as antidote's and chemosensor's properties of vitamin B_{12} and its analogues.

The other important field of medical application of vitamin B_{12} is cancer therapy. In contrast to healthy body cells, the demand for vitamin B_{12} is elevated at places of enhance proliferation, its high need makes vitamin B_{12} very attractive as an agent to target cancer cells or bacterial infections [5]. It shows additional features suitable for therapeutic applications: it is water soluble, has no toxicity.The new trend in drug design is synthesis of cobalamin derivatives, which remain their functionality as vitamin and cofactor in the cell, but are able to carry the organic and inorganic chemotherapeutic drugs, binding to the vitamin, into fast proliferation cells [6,7]. An alternative strategy is the development of structurally perfect, but catalytically inactive semi-artificial B_{12} surrogates [2]. Both strategies in drug design will be discussed in this talk.

This work was supported by Russian Science Foundation, Agreement no. 14-23-00204.

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Scientific session «Natural-product-based drug design»

Hybrid biomolecules based on natural and semisynthetic terpenoids, porphyrins and polysaccharides

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Natural and semisynthetic terpenoids, porphyrins and polysaccharides are a promising platform for the synthesis of new biologically active substances. The results of the synthesis of hybrid biomolecules based on natural and semi-synthetic porphyrins, and terpenoids and the results of the preliminary assessment of the useful properties of the obtained compounds will be presented in the report.

Work is carried out with the support of Russian Science Foundation (project № 16-13-10367).

DESIGN OF MODERN DRUG – GLOBAL TRENDS AND OUR OPPORTUNITIES

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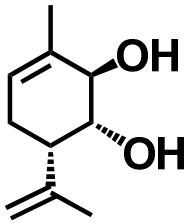
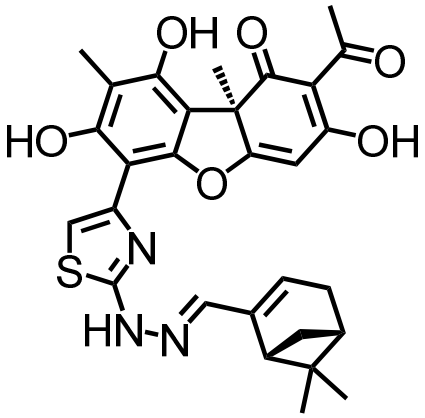
Important way of medicinal chemistry, which allows to get new, effective drugs is the use of synthetic transformations of natural compounds. The most effective is the involvement in the synthesis of compounds having an ative biological activity and having an available resource base.

So, one of the most vivid embodiment of this approach is to create a perspective antiparkinsondrug Diol, preclinical tests which have recently been successfully completed.



Diol



Tdp1 inhibitor

Another example is thedetection ofthe most effective inhibitors of tyrosyl-DNA phosphodiesterase1(Tdp1),which isan importantDNA repair enzyme system responsible fordrug resistance of many cancer tumors. Inhibition Tdp1,conducted by aderivative of the natural usnic acid, may help to solve this problem.

The Reason for Antitubercular Activity of Natural Terpenoids. New Targets

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The cause of antitubercular activity of natural terpenoids should be sought among the reasons for the survival and virulence of *Mycobacterium tuberculosis* in the human body. The report focuses on recent works of molecular geneticists and biologists devoted to the study of the *M. Tuberculosis* genome (strain H37Rv). Of particular interest are recently identified genes Rv3377c and Rv3378c which encode enzymes diterpene cyclase DTC (Rv3377c) and tuberculosinol phosphatase TP (Rv3378c), respectively. The first enzyme cyclizes geranylgeranil diphosphate into tuberculosinol diphosphate, and the latter one turns it into tuberculosinol, 13 (*R*)-tuberculozinol, and 13(*S)*-iso-tuberculosinol. These terpenoids inhibit the formation of phagolysosomes which serve to kill *M. tuberculosis* in human alveolar macrophages, thereby promoting the survival of the pathogen. It is interesting that Rv3377c gene was detected only in virulent strains of *M. tuberculosis*. Thus, it was established that exactly Rv3377c gene is responsible for the pathogenicity of *M. tuberculosis*, and tuberculosinol type diterpenoids synthesized by DTC (Rv3377c) and TP (Rv3378c) enzymes allow the pathogen to penetrate the human immune system. Structures of DTC (Rv3377c) and TP (Rv3378c) *M. Tuberculosis* enzymes determined by X-ray analysis are presented in the report. Active centers of the enzymes are hydrophobic cavities in which substrates (terpenoid diphosphates) are placed. Structures of enzyme-terpenoid complexes, as well as examples of molecular docking of complexes of these enzymes with some synthesized inhibitors of the nontepenoid nature are also presented in the report.

It is suggested in the report that the cause of antitubercular activity of natural terpenoids is as follows. Molecules of "foreign" terpenoids having dimensions that correspond to the size of the active cavities of these enzymes occupy these cavities and interfere with the cyclization of geranylgeranyl diphosphate into tuberculosinol diphosphate. Such competitive binding interferes with the synthesis of tuberculosinols, which ensure the survival of *M. tuberculosis* in human macrophages. Thus, enzymes DTC (Rv3377c) and TP (Rv3378c) are promising targets for the synthesis of a new generation of antitubercular agents based on natural terpenoids.

The speaker is grateful to the Russian Science Foundation (grant no. 14-50-00014) for the financial support.

New antiviral agents based on terpene scaffold

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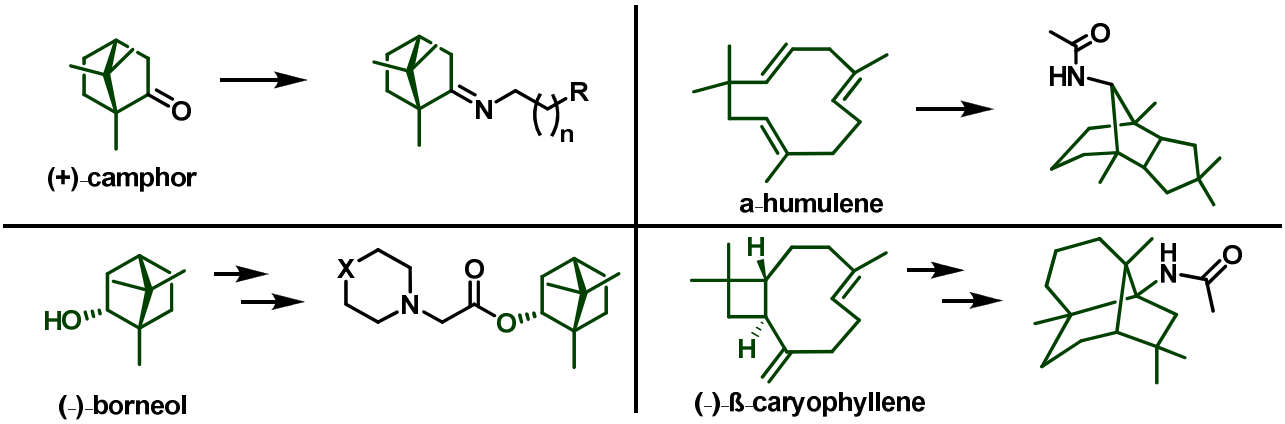
Search for new antiviral agents active against drug-resistant strains of viruses is particularly important against the background of recent influenza pandemic 2009 year, seasonal epidemics and the threat of the spread of influenza virus strains of avian origin. We have previously shown that compounds that have one or two imine group and a fragment of camphor in their skeleton exhibit antiviral activity [1, 2]. In the context of the identification of the lead compound, we have synthesized chemical library on the basis of natural (+)-camphor [3] and carried out a study on the structure-activity relationship [4, 5]. With a view to detecting the effects of the nature frame fragment on biological activity of target compounds, we have synthesized the library of heterocyclic derivatives of (-)-borneol, and identified the key structural blocks responsible for antivirus activity [6]. A high level of anti-viral activity has been detected for the compounds based on α-humulene and (-)-β-caryophyllene.



As a result of the work compounds were discovered, whose therapeutic index against the most dangerous influenza virus A(H1N1)pdm09 exceeded that of reference drugs hundred- or more- fold. In fact, we have identified a new class of antiviral agents based on terpenoids. It is shown that compounds containing in their scaffold frame fragment are extremely attractive platform for design of antiviral agents.

This work was supported by Foundation by the Russian Foundation Research (N 15-03-00193A)

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New polysulfur-containing biologically active compounds, analogues of natural varacins

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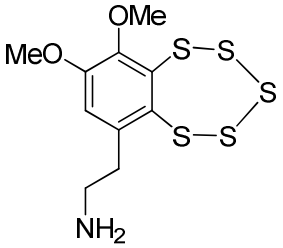
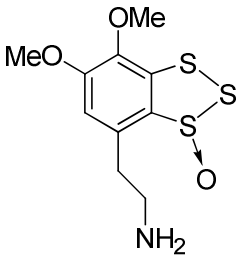
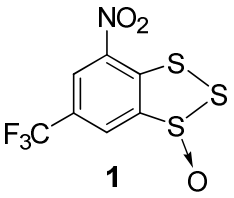
Varacins, cyclic polysulfides annelated to benzene ring are unique natural compounds isolated from marine ascidians [1]. They can contain five (benzopentathiepine derivatives, for example Varacin) or three (benzotrithiole derivatives, for example Varacin C) atoms of sulfur in the ring, in the latter case one in the oxidized state. Most natural varacins demonstrate various biological activities including antibacterial and antitumor one, but are synthetically difficultly accessible compounds. We found that substantially more accessible synthetic analogues of natural varacins also possess high biological activity. For example, compound **1** (Varacin C analogue) exhibits the cancer preventive activity at dose into 100 times lower than its cytotoxic concentrations [2], while pentathiepine **2** known also as TC-2153 demonstrates different biological activities including antidepressant, analgesic, anticonvulsant ones and so on [3]. Some derivatives of compound **2** turned out to be effective inhibitors of Tdp1 enzyme, which is important target for antitumor therapy.



Varacin



Varacin C



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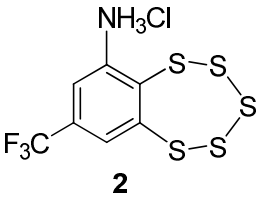

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This work was supported by Russian Scientific Foundation (grant 16-13-10074).

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Anti-influenza drug camphecene: mechanism of activity and resistance

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Influenza A virus is a respiratory pathogen that substantially affects human health worldwide and is responsible for 500,000 deaths per year. Two groups of antivirals are currently used for treatment of influenza [1, 2]. The clinical use of both groups is limited due to the drug resistance [3, 4]. The search for new antivirals with alternative target(s) and mechanism of activity is, therefore, of high importance. Recently we have identified the novel group of cage compounds with high anti-influenza activity. Among about 200 tested compounds, camphecene (1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene-aminoethanol) appeared one of the most potent. We performed in vitro selection of drug-resistant mutant by cultivating the virus at increasing concentrations of camphecene. Five serial passages resulted in formation of resistant virus with 50% inhibiting concentration (IC50) value of 150 micrograms/mL that is 150 times higher than for initial virus. This virus carried two amino acid substitutions one of which was localized in the receptor-binding site and reflected an adaptation to cell culture. Another substitution was located within the stem domain close to fusion peptide thus substantiating the resistance to camphecene. No substitutions were found in M2 transmembrane domain thus confirming that despite structural similarity to rimantadine, their targets and mechanisms of activity differ. The pathogenicity of resistant virus was sharply decreased. Mouse infected with susceptible virus demonstrated severe weight loss and 100% mortality at day 8 post infection while infection with equal dose of resistant variant did not result in either weight loss or animals' death. Therefore, gain of camphecene resistance is accompanied with loss of pathogenicity of influenza virus.

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Usnic Acid Derivatives – new role in anticancer treatment

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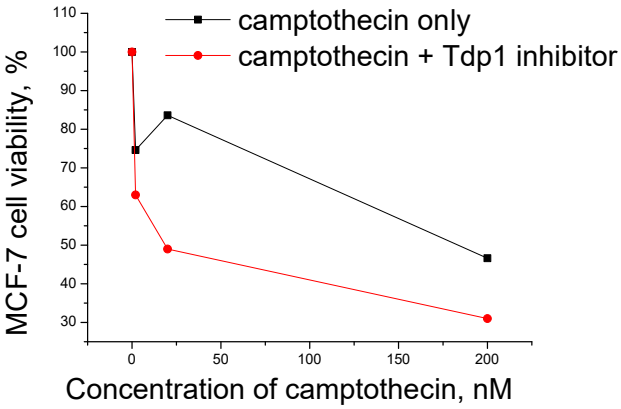
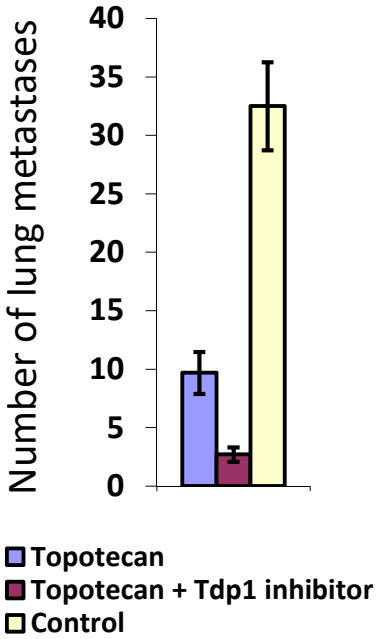
The future of cancer therapy is the fight against the protective system of cancer cells. One of the enzymes that play a key role in removing DNA damage from chemotherapy is tyrosyl-DNA-phosphodiesterase1 (Tdp1). It has been shown experimentally that selective inhibition of the activity of this enzyme may lead to an increase in the therapeutic effect of the widely used in chemotherapy derivatives of camptothecin (topotecan, etc.). The Tdp1 inhibitors described in the literature generally have mild inhibitory effects in the concentration range of 0.15 - 100 μM. We have shown that some derivatives of the lichen origin natural compound usnic acid are highly effective inhibitors of Tdp1 (IC50 0.01-0.1 μM), are low-toxic for cells (CC50 >50 μM) and enhance the cytotoxic effect of camptothecin in vitro. It was found that the compounds enhance the antimetastatic effect of topotecan therapy.





This work was supported by Russian Science Foundation (grant 16-13-10074)

The description of mechanism antiviral action of camphene and its analogues on the influenza virus

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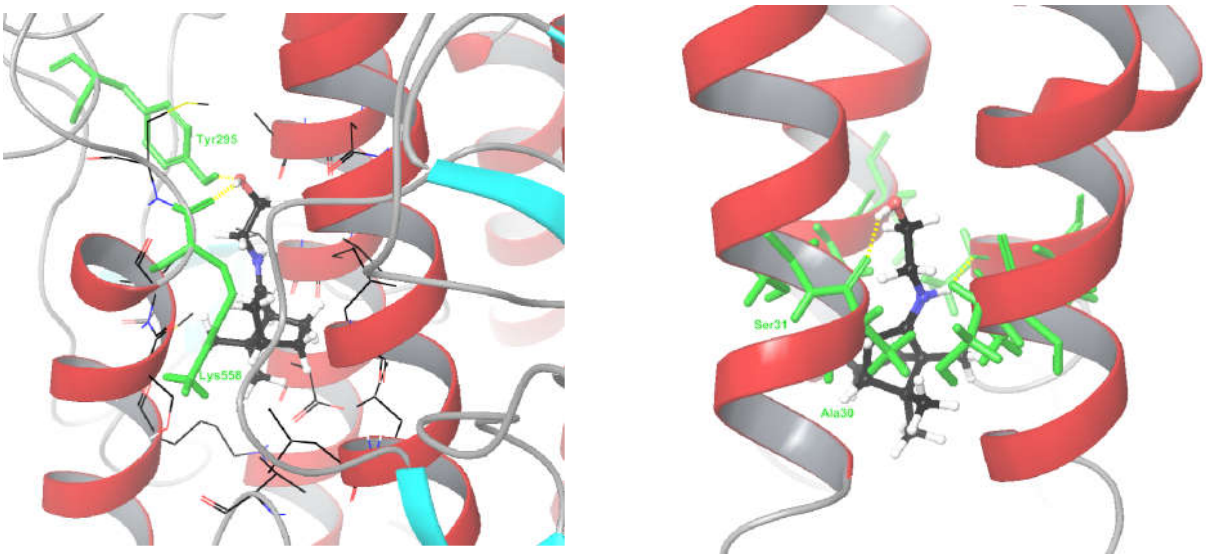
Camphecene is product of interaction between camphor and aminoethanol. According to the biological experiments [1] camphecene and its analogues possess pronounced antiviral activity against influenza virus H1N1. The maximum efficiency is observed at the initial stages of infection (0-2 hours). In this case the surface proteins (proton M2 channel and haemagglutinin) can be considered as the potential biological targets. We have estimated the binding energy of camphecene and its analogues in the ligand-protein complex with these proteins. All calculations were performed by molecular docking methods with help of Schrödinger Suite Maestro release 2015-4.



a b

Figure: the locations of lead-compound in the binding site of haemagglutinin (a) and proton M2 channel (b): functional amino acids are represented by green color; H-bridges are shown yellow dotted lines.

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Pharnesyltransferase and its inhibitors as a promising strategy for cancer therapy

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The Ras superfamily consists more than 100 proteins, involved in the regulation of proliferation, differentiation, cell adhesion andapoptosis of cells. Each mammalian cell contains at least three associated genes, H-ras, K-ras and N-ras. Some of these proteins are small G proteins that deliver signals from cell-surface receptors, and then transmit the signals to several different pathways, ultimately affecting mitogenic functions.

The incidence of mutated Ras gene isoforms in human tumorsis about 30%. Farnesylation is a type of lipid modification called protein prenylation that is critical for biological functionality, including membrane association of Ras proteins.Farnesyltransferase (FTase) is a cytoplasmic protein that catalyzes this process which involves the transfer ofa 15-carbon farnesyl group to a cysteine amino acid in the carboxyl end of Ras proteins.

Known farnesyltransferase inhibitors (FTIs) are classified based on the mechanism by which they inhibit a target enzyme: i) peptide analogues, designed to mimic and compete with thetypical CAAX motif; ii) farnesyl pyrophosphate (FPP) analogues, designed to compete with the FPP substrate; iii) bisubstrate analogues, that combine properties of both FPP and CAAX peptide substrates; and iv) nonpeptidomimetic inhibitors. FTIs are being investigated in clinical trials and up to date FTIs are promising basis for new antineoplasts development.

The one of probable mechanisms of sesquiterpene lactone action on tumor cells is the apoptosis induction through the inhibition of key enzyme farnesyltransferase. The most known lactone with farnesyltransferase inhibition activity is well known arglabin. We developed a series of natural and modified sesquiterpene lactones and tested them on cytotoxicity, apoptosis induction, ability to inhibit farnesyltransferase. Our experiments reveal several natural and modified lactones with high cytotoxic activities (nanomole level), apoptosis induction, farnesyltransferase inhibition. This data allows us to suggest that antineoplastic effects of the sesquiterpene lactones is wider than the Ras-inhibition and is connected also with inhibition of Ras/MAPK and PI3K signal transduction pathways. It was demonstrated the prospect of using sesquiterpene lactones for developing of effective antineoplasts on their basis.

Scientific session «Computational drug design»

Computational Platform Way2Drug: From Prediction of Biological Activity to Drug Repurposing

D.S. Druzhilovskiy [1], A.V. Rudik [1], D.A. Filimonov [1], T.A. Gloriozova [1], A.A. Lagunin [1,2], A.V. Dmitriev [1], P.V. Pogodin [1], V.I. Dubovskaya [1], S.M. Ivanov [1,2], A.S. Gaur [3], G.N. Sastry [3], V.V. Poroikov[1]

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Information-computational platform Way2Drug (www.way2drug.com/dr) provides access to the data on drugs approved for medicinal use in U.S. and Russia, as well as computational tools for prediction of the biological activity of drug-like organic compounds. Currently realized computational components of the platform allow prediction of several thousand kinds of biological activity [1] including interaction with molecular targets [2], pharmacotherapeutic and side effects [3], acute rat toxicity [4], cytotoxicity to the tumor and non-tumor cell lines [5], metabolism [6] and other characteristics necessary for estimation how promising are particular drug-like compounds as potential human medicines. Using Way2Drug, one may not only select the most promising hits for synthesis and study of biological activity [7], but also reveal new indications of launched drugs [8].

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Consensus in silico and in vitro search for antidiabetic compounds with combined antiglycation and targeted hypoglycemic activities

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In diabetes mellitus there is an intensive non-enzymatic glycation of proteins (Maillard reaction), which leads to the development of severe complications [1]. Currently, there are no approved for clinical use drugs that inhibit the Maillard reaction. Modern therapy of diabetes type 2 is based on the use of oral hypoglycemic agents. Thus, it is very promising to search for Maillard reaction inhibitors that additionally act on bio-targets that are important for the regulation of disorders of carbohydrate metabolism in diabetes type 2. Such compounds can become the basis for creating antidiabetic drugs of a fundamentally new type.

Virtual screening of 3000 structurally dissimilar compounds was carried out with using a consensus of prediction estimates obtained by means of four computer systems: IT Microcosm [2], PASS [3], AutoDock Vina [4] QSAR QMM [5]. The following activities were predicted: Maillard reaction inhibitors (MRI), dipeptidyl peptidase 4 inhibitors (DPP4), agonists of PPAR gamma receptors (PPARg), glycogen phosphorylase inhibitors (PYGL), glucokinase inhibitors (HK4), AMP-kinase activators (AMPK), protein tyrosine phosphatase 1B inhibitors (PTP1P), alpha glucosidase inhibitors (MGAM).

By results of in silico screening, 340 compounds were selected and studied in vitro to inhibit the Maillard reaction. 172 substances were found, that were exceeded the activity of the reference drug aminoguanidine. Among these substances, 81 compounds were found showing a second high targeted hypoglycemic activity: MRI & DPP4, 40 substances; MRI & PYGL, 3 substances; MRI & HK4, 5 substances; MRI & AMPK, 13 substances; MRI & PTB1B, 3 substances; MRI & MGAM, 17 substances.

Thus, with the consensus in silico and in vitro search for compounds with combined antiglycation and hypoglycemic activities, the enrichment coefficient was equal 37 times, and the search efficiency among the experimentally studied substances was 23.8%.

81 compounds with double antiglycation and targeted hypoglycemic activities were found.

The work was funded by the Russian Science Foundation, 14-25-00139 project.

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New Thiamine diphosphate activation model and therefore new paradigm on ThDP structural function

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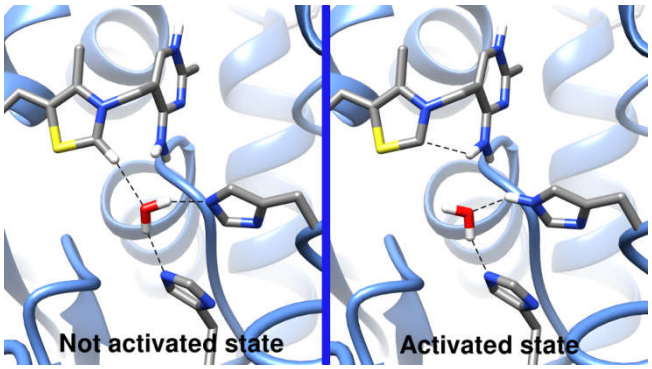
Thiamine diphosphate (ThDP)-dependent enzymes form a vast, diverse class of proteins, catalysing a broad variety of enzymatic reactions including the formation or cleavage of carbon-sulfur, carbon-oxygen, carbon-nitrogen, and especially carbon-carbon bonds. For novel therapeutic approaches, ThDP-dependent enzymes of human origin have been identified as being involved in a variety of diseases[1]. ThDP activation is the initial and crucial reaction common to all ThDP-dependent enzymes, and has been the subject of controversy over the past thirty years [2].

Of the ThDP-dependent enzymes, transketolase (TK; E.C.2.2.1.1) is one of the most extensively studied, judging by the abundant data available in the literature. TK is therefore a highly useful model for investigating the ThDP activation process.

Based on the limitations of the current ThDp activation model, this presentation will show the process followed by molecular modeling which leads to the presentation of this new ThDP activation model[3] and its comparison with the experimental results.



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Modern approaches to the design of p53 oriented drugs

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The p53 protein is considered as the major tumor suppressor in human cells. It is an attractive target for the development of new targeted anticancer therapies because it is commonly affected in cancers. However, until recently p53 was regarded as "undruggable".

To date, this situation has changed, as several compounds that are able to restore wild-type properties of p53 become available. Among them there are compounds that prevent the binding of MDM2 to wild type p53, thereby blocking its degradation.

The majority of the developed structures of p53-MDM2 interaction inhibitors are based on the common pharmacophore hypothesis, consisted in the simulation of the interaction between three hydrophobic amino acid residues F19, W23, L26 located in the p53 transactivation domain and the N-terminal domain of MDM2.

However, despite the availability of active p53-MDM2 interaction inhibitors, the predictive power of the model considering only the three-centered ligand-receptor interaction remains extremely low, which is associated with the features of the N-terminal domain structure of MDM2. The MDM2 region from 1 to 20 amino acids is an unstructured, highly mobile fragment. No structural data have been obtained by X-ray diffraction analysis for this region yet; it was only studied by NMR in recent years. Dynamics studies of the protein region allowed to determine that MDM2 is able to bind to p53 only at a certain position of the mobile N-terminal domain region, while the most active inhibitors of the p53-MDM2 interaction not only shield the MDM2 binding cavity but also stimulate such changes in the spatial structure of MDM2, which make the binding between p53 and MDM2 absolutely impossible.

Thus, we propose the ability of small molecule compound to induce directly the energetically favorable structural rearrangement of the MDM2 protein due to the four-centered interaction as a criterion of high activity of the p53-MDM2 protein-protein interaction inhibition.

Compounds based on the indolinone scaffold developed in our laboratory [1] showed a pronounced ability to stimulate similar rearrangement of the N-terminal domain of MDM2, which results in a conformation incapable of the p53 binding in studies by molecular dynamics methods. A feature of the series is the ability to induce the formation of alpha-helix in the region of 1-20 amino acids of MDM2, which is an additional factor of energy expediency.

The ability to develop resistance, which is noted for a number of tumor cell lines, is one of the serious factors that must be taken into account during the development of modern p53 targeting drugs. In a number of cases, this is determined by the generation of tetraploid cell clones after the treatment with MDM2 inhibitors and cell cycle arrest. Such clones are not susceptible not only to the repeated treatment of the original drug, but also to radiotherapy and platinum derivatives, which is associated with mutations in the p53 transactivation domain. The resistance effect can be explained by preferential expression of the p21 protein, which is the main transcriptional target of p53; p21 provokes cell cycle arrest only, while the expression of the apoptotic proteins PUMA and BAX leads to cancer cell death. We can induce rapid apoptosis without a delay in cell cycle progression, which promotes the development of resistant mutant cells, by changing the profile of expressing proteins in favor of PUMA and BAX.

The study on indolinone derivatives developed in our laboratory showed their ability to significantly induce the expression of the apoptotic protein PUMA, in contrast to the known highly active inhibitors of the p53-MDM2 interaction.

This work was supported by the Russian Science Foundation, project no. 16-13-10358.

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Predictive approaches in synthetic chemistry: case of protective groups cleavage

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Synthesis of chemical compounds is one of the major issue of drug development process. It is important problem for both lead optimization, and drug candidate synthesis scaling. Despite chemo- and bioinformatics approaches are widely used at different stages of drug design they rarely applied for synthesis planning. Here, we propose a prototype of the expert system [1] able to predict optimal reaction conditions. In its present version, it can be used for protective group cleavage reactions by catalytic hydrogenation.

For any query reaction, the expert system finds the most similar reactions in the reaction database extracted from Reaxys information system and on the basis of special algorithm assigns experimental conditions to the query. Quantitative assessments of pairwise reaction similarity are performed with the help of the Condensed Graph of Reaction approach transforming a given chemical reaction in one sole molecular graph.

Developed expert system has been assessed correctly predicts the optimal catalyst for some 80% reactions in the external dataset. It was also able to tackle the selectivity problem if several protective groups are present in the substrate.

Research was supported by Russian Science Foundation, grant No 14-43-00024. Authors acknowledge Reaxys database (RELX Group, Switzerland) for the dataset.

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ViralChEMBL: Enhancement of Antiviral Activity Data from ChEMBL

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Emergence of novel viruses, such as Ebola virus and Zika virus, and resistance of known ones, such as influenza virus, HCV, and HIV, justifies discovery and design of new antiviral drugs as a very important branch of medicinal chemistry. Drug discovery based on previously obtained data is a widely accepted approach. The most widely used public repository ChEMBL provides access to a large amount of antiviral activity data, but these data are often insufficiently annotated and poorly curated. To overcome this problem, we developed an algorithm of semi-automatic curation of ChEMBL data based on mapping lists for assay organism and target organism data and a dictionary of virus-related terms. With the help of this algorithm ChEMBL 20 and ICTV taxonomy 2014 were used for the generation of the first version of antiviral activity database ViralChEMBL, which provided the most comprehensive and the best annotated antiviral activity profiles for small molecule compounds to date. Applicability of ViralChEMBL for antiviral chemical space mapping was illustrated using the approach of self-organised maps.

This work was supported by Russian Science Foundation grant no. 16-15-10307.

Machine Learning Approach to Target-Oriented Scoring Functions for Molecular Docking and Virtual Screening of Multi-Target Drugs: A Case of Tankyrase and PI3K Inhibitors

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Nowadays, along with the classical approach to target-selective drug design, the methods of rational polypharmacology are on the rise. They aim to develop the compounds acting on several targets or pathways simultaneously. A popular solution in the design of both selective and multitarget drugs is based on virtual screening of large compound libraries. In this approach, the quality of a scoring function used in the screening process plays a critical role. Most of the scoring functions currently used in molecular docking are of general nature, attempting to provide binding energy estimates across a wide range of targets. However, their accuracy is often limited, and this can cause problems in the design of multitarget drugs that involves virtual screening against several targets, leading to the multiplication of uncertainty. Thus, in order to differentiate between decoys and actives, it is necessary to select a suitable scoring function for each target or to construct scoring functions specifically for particular targets. We have developed an approach to constructing such functions using the machine learning methods. The empirical potentials calculated using the AutoDock Vina docking software are used as descriptors. The models were built using the RF, SVM, LDA, ANN and kNN machine learning techniques. This approach was successfully used to design multitarget inhibitors of Tankyrase and PI3Kα enzymes that have good potential for the development of drugs against colon cancer. The results based on the classification models are also compared to the application of the built-in scoring functions in AutoDock Vina software.

Identification of molecular mechanisms of hepatotoxicity through the bi-clustering analysis of drug-induced gene expression data

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Hepatotoxicity is one of the main reasons for drug withdrawn from the market and clinical trials, which is caused by shortcomings of existing methods of its evaluation [1]. To develop new approaches, including methods *in vitro*, the more complete understanding of the molecular mechanisms of hepatotoxicity is required. Within the framework of our study, we used the bi-clustering algorithm [2] for analysis of drug-induced gene expression data for more than 140 drugs, which was previously obtained using human hepatocytes *in vitro* and rat liver *in vivo* and is available on the Open TG-GATEs website (http: //toxico.nibiohn.go.jp/). Each bicluster contains information on co-expressed genes, which have common functions in the cell, and compounds, which affect the transcription of these genes in the same way (hyper- or hypo-expression). Analysis of the functions of genes from each bicluster allowed us to characterize a variety of cellular processes, the disruption of which by drugs under study can lead to the induction of hepatotoxicity. The use of a large amount of *in vitro* and *in vivo* data has made it possible to obtain the most complete description of the molecular mechanisms of drug hepatotoxicity at the level of drug-induced gene expression. The obtained results may potentially be used for the estimation of hepatotoxicity at the earliest stages of drug development.

This work was supported by the Russian Foundation for Basic Research grant 16-34-01077.

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Advanced approaches to prediction of ADMET properties of drug compounds

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The pharmacokinetic properties and toxicity of potential drug compounds (ADMET properties: absorption, distribution, metabolism, excretion, toxicity) critically affect their efficacy, pharmacological profile, administration protocol and safety. Their optimization is an important aspect of drug discovery and development process, and the ability to predict these properties for new structures can substantially improve its speed and efficiency. We have developed a general methodology for the prediction of ADMET parameters based on the application of artificial neural networks and fragmental descriptors to extensive and verified experimental data sets. The fragmental descriptors for a structure are the occurrence counts of the paths, cycles and branches of varied size using a hierarchical atom type classification, providing a 'holographic' representation of a molecule. During the model construction, the GPU-based deep learning and double cross-validation are used to achieve optimal performance and model predictivity. During the prediction, a graphic map highlighting the parts of a molecule that make positive or negative contributions to the predicted property is generated as an additional guidance for the ADMET optimization. The models built by us are implemented in an integrated online service available on the Internet (http://qsar.chem.msu.ru/admet/). It supports convenient prediction of important properties (in particular, lipophilicity, blood-brain barrier permeability [1], human intestinal absorption [2], hERG-mediated cardiac toxicity [3], etc.) as well as qualitative and semi-quantitative estimation of their suitability for drug-like compounds. This integrated prediction system may be used in the research in various areas of medicinal chemistry and pharmacology. This work was supported by the Russian Foundation for Basic Research (grant #15-03-09084).

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Poster session №1

NOVEL MODIFIED PYRIMIDINE NUCLEOSIDES AS POTENTIAL ANTIBACTERIAL AGENTS

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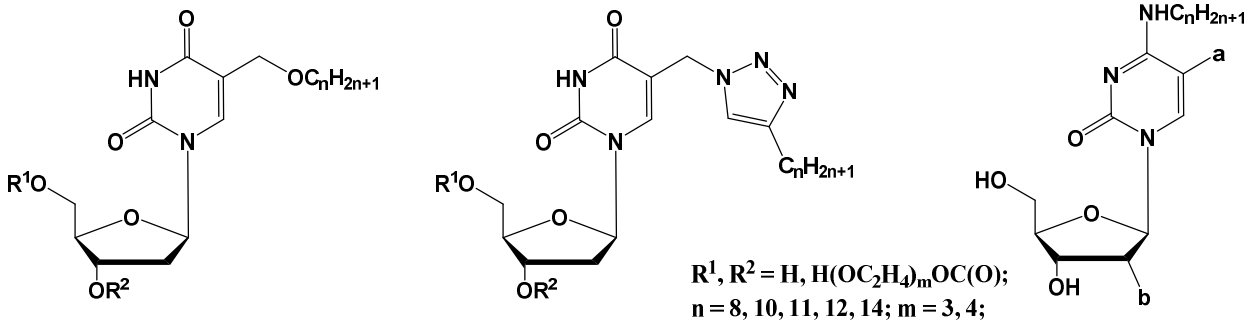
The development of new classes of antibiotics has lagged nowadays far behind the growing need for such drugs whereas resistance to clinically significant antibacterial agents has evolved to nearly all antibiotics used [1]. There is the urgent need to design radically new drugs acting on new targets and active against resistant strains of patogenes. Nucleoside analogues play an important role in medicine as antiviral agents [2]. Only at the beginning of the XXI century several groups reported a few sets of modified nucleosides that displayed *in vitro* antimycobacterial activity [3].Recently we synthesized a set of 2'-deoxypyrimidine nucleoside derivatives bearing extended alkyloxymethyl (**1**, R^1, R^2 = H) or alkyl(1,2,3-triazol-1-yl)methyl (**2**, R^1, R^2 = H) substituents at C-5 position and demonstrated their effective bacteriostatic activity against a series of microorganisms including *Mycobacterium tuberculosis* strains [4]. However, the nucleosides with large hydrophobic fragments are insoluble in water, thus, limiting the biological investigations. The goals of this work were the synthesis of a set of more soluble in water derivatives of 5-modified 2'-deoxyuridines (**1**, **2**, R^1 or R^2=$H(OC_2H_4)_mOC(O)$-) and new N^4-derivatives of cytidine (**3**), with additional modifications in base as potential microorganism growth inhibitors and evaluation of their stability in human blood serum, cytotoxicity and antibacterial activity towards a wide range of microorganisms.



1 **2** **3**

Most of the compounds showed low cytotoxicity in K562, *Jurkat* and *Vero* cell cultures. The antimicrobial activity will be reported. According to the preliminary data a significant part of the synthesized compounds effectively inhibited the growth of a set of microorganisms (including *Mycobacterium Smegmatis*, drug-resistant strains of *Mycobacterium tuberculosis, Staphylococcus aureus, Mycrococcus luteus,* and / or *Leuconostoc mesenteroides)*.

The study of antibacterial activity and cytotoxicity and physicochemical analysis of all compounds were supported by the Russian Science Foundation (grant No. 14-50-00060). Chemical synthesis was supported by the Russian Foundation for Basic Research (grant No. 17-04-00536).

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ANTIPROLIFERATIVE PROPERTIES OF CONJUGATE OF DAUNORUBICIN WITH EPOXYISOALANTOLACTONE

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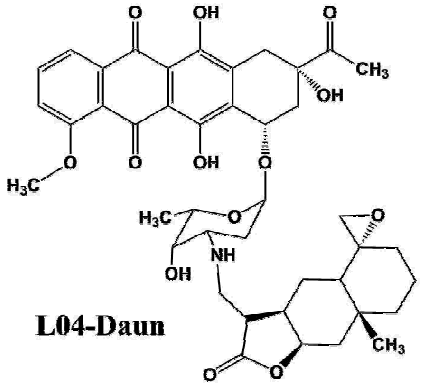
The antitumor activity of sesquiterpene lactones of plant *Inula helenium L*. has long been known and is realized mainly through apoptosis induction [1, 2]. By Michael reaction [3] we received new conjugate of anthracycline antibiotic daunorubicin with minor sesquiterpene lactone epoxyisoalantolactone – compound L04-Daun.



The study of the antiproliferative activity of the obtained conjugate *in vitro* demonstrated high cytotoxicity of L04-Daun against human tumor-cell cultures comparable to daunorubicin (Daun) and far superior cytotoxicity of original epoxyisoalantolactone (L04). The effect of obtained conjugate against tumor-cell culture was stronger than previously synthesized conjugates alantolactone with daunorubicin and doxorubicin [4].

Compound	IC_{50}, μM				
	A549	HCT116	MCF7	RD	HEK293
L04-Daun	0,27±0,01	0,02±0,00	1,99±0,27	0,63±0,02	11,41±0,53
Daun	0,33±0,01	0,12±0,00	0,84±0,17	0,63±0,03	12,31±1,17
L04	83,51±0,26	21,40±0,32	31,87±0,14	18,60±0,21	105,68±4,13

The work was sponsored by RFBR Grant № 15-04-3940.

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INFLUENCE OF ALKYL SUBSTITUTION IN THE IMIDAZOLE-4,5-DICARBOXYLIC ACID RING ON NMDA-INDUCED CONVULSIONS

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1- And 2-alkyl substituted imidazole-4,5-dicarboxylic acids (4,5-IDC) are interesting not only as drug intermediates (for example, Etimizole, Cardosal) but also as a biologically active compounds. It is known that 4,5-IDC derivatives are ligands of the NMDA-receptors [1]. However lipophilicity plays the key role in the interaction of these compounds with the NMDA-receptor. Lipophilicity of 4,5-IDCs is due to the position and size of the alkyl substituent in the imidazole ring.

Bioactivity of 1- and 2-monosubstituted 4,5-IDCs is studied extensively. But bioactivity of 1,2-disubstituted 4,5-IDCs has not been studied yet. It is due to that fact that one of the most common methods for the synthesis of 4,5-IDCs is oxidation of benzimidazoles. But harsh oxidative conditions involves elimination of the 1-substituent [2]. That is why we have optimized the oxidation procedure to develop the common method for the synthesis of 1-, 2- and 1,2-substituted 4,5-IDCs and have synthesized 1,2-disubstituted 4,5-IDCs by oxidation of benzimidazoles with hydrogen peroxide for the first time.

Examination of the anticonvulsant activity of the compounds was carried out on NMDA-induced convulsions caused by NMDA (340 mg/kg) intraperitoneal injections to the CBA mice. It was shown that 2-methyl-1-propyl-4,5-IDC (0.5 mmol/kg) reduced the latency time and increased the intensity of tonic and clonic convulsions compared with the control group that had only NMDA injections. The potentiating action of this compound on the NMDA-induced convulsions is also greater than the action of monosubstituted 1-propyl-4,5-IDC (0.5 mmol/kg). 1-Propyl-4,5-IDC reduced the convulsion percent from 100% in 2-methyl-1-propyl-4,5-IDC and control groups to 68%.

As an initial conclusion we can say that the second alkyl substituent in the imidazole ring of 4,5-IDC cause the increase of the potentiating action of the compound on the NMDA-induced convulsions.

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NEW STRUCTURE APPROACHES TO DEVELOPMENT OF TARGET-ORIENTED HUMAN SOLUBLE EPOXIDE HYDROLASE INHIBITORS

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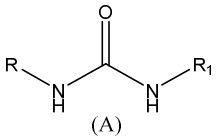
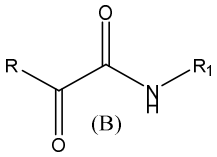
New structure approaches to development of target-oriented human soluble epoxide hydrolase inhibitors (sEH, E.C. 3.3.2.10) based on adamantylcontaining 1,3-disubstituted ureas (A) and thioureas, derivatives of parabanic acid (C) and oxalic acid amides were implemented. Methods for the preparation of precursors for new inhibitors were developed. Inhibitors with altered primary pharmacophore group (A), including spacers between adamantyl R and urea groups, donor, acceptor and sterically hindered substituents in adamantyl radical R were synthesized.



(A)



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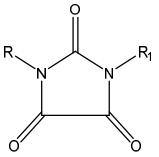

(C)

Influence of structure factors of primary pharmacophore group on inhibitory potency against human, rat and mouse soluble epoxide hydrolases were investigated. Effects of inhibitor structure on IC_{50} depending on type of enzyme were investigated. Mouse and Rat sEH more sensible to the structure of primary pharmacophore than human sEH which can witness about the different mechanisms of inhibition of these enzymes. Structure factors of inhibitor which influence its important properties such as water solubility and mp were affirmed. The positive role of sulfur in primary pharmacophore was accounted. Microsomal stability of leads were investigated on human and mouse liver microsomes (s9).

This work was supported by Russian Foundation for Basic Research (project no. 16-43-340116 r_a), (project no. 16-33-00172 mol_a) and by the Ministry of Education and Science of the Russian Federation (base part of state assignment for 2017–2019; project no. 4.7491.2017/BCh).

CYTISINE DERIVATIVES AS POTENT ANTIVIRALS THAT INHIBIT REPLICATION HUMAN INFLUENZA VIRUSES *IN VITRO*

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Influenza is currently one of the most common diseases in the world. It causes epidemics and pandemics and leads to a significant morbidity and mortality in people of all age groups. The impact of influenza virus infections is estimated to run into billions of dollars worldwide with an estimated 3,5 million cases of severe illness and 250000-500000 deaths annually. There are several drugs for influenza treatment. In some cases they are not effective because of appearance of resistant strains. Therefore, there is a need to search for new compounds that are effective against viruses resistant to the action of already available drugs. At first, we evaluated *in vitro* the antiviral activity of 40 synthetic derivatives of cytisine against influenza virus A/Puerto Rico/8/34). The selectivity index was calculated for each analyzed compound. According to the received data, 12 of 40 synthetic cytisine derivatives have antiviral effect against the virus. Fufrther, the antiviral effect of these compounds has been studied for other subtypes of influenza A (A/California/7/09(H1N1) pdm09, A/Aichi/2/68(H3N2), A/Mallard/Pennsylvania/10249/84(H5N2)) and influenza B (B/Malaysia/2506/04, B/Florida/04/06). Three of tested derivatives have antiviral effect against all subtypes of the influenza A and one - against all subtypes of influenza A and B viruses. Next, we used a time-of-addition assay to identify when in the virus life cycle an inhibitor acts. Reduction in viral titer indicate that tested compound acts later in the replication cycle and may be affecting processes such as viral budding and release. We also performed an electron microscopic study of influenza-infected cells treated with cytisine derivative. It was showed that infected cells in the presence of tested compound release less virions comparing to drug-free specimens. We assume that viral proteins such as neuraminidase, polymerase, matrix protein, or transport proteins of the cell may be possible targets for these compounds. Obtained data serve as the basis for further development of the compounds of this group as a means for the treatment of influenza infection.

BIOLOGICAL ACTIVITY OF SUBSTITUTED 4-QUINOLONES: BEYOND ANTIBACTERIALS

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The 4-quinolone fragment is present in a diverse range of biologically active compounds. When it comes to the marketed drugs, this motif belongs predominantly to antibacterials, however, it serves as a lead chemotype in drug discovery toward various therapeutic indications beyond antibacterials. Notwithstanding, the explored diversity around the 4-quinolone fragment, particularly among annulated derivatives, still requires medicinal chemistry efforts. Comparatively limited data is published on the synthesis and biological activity of [*b*]-annulated derivatives, although they represent a very promising subset of 4-quinolone derivatives. Differently substituted pyrrolo[b]quinolones are described as prominent inhibitors of phosphodiesterase type 5 related to male erectile dysfunction [1]. Their inhibitory properties toward tumor necrosis factor function and anti-acetylcholinesterase activity which is associated with Alzheimer disease were reported. Pyrazolo-, pyrimido- and thieno[*b*]quinolones demonstrated antimalarial activity as well as cytotoxycity against several cancer cell lines [2-4].

The simple approach to [*b*]-annulated 4-quinolone which is based on the reactivity of 2,3-bifunctionalized core fragment was developed. Reactions with a range of mono- and binucleophiles lead to rings systems containing three to five cycles: 4-quinolones annulated with pyrrolone, oxazolopyrrolone, piperazinopyrrolone and other heterocycles.

Biological activity and toxicity profile for selected set of 4-quinolone derivatives were studied and some ADME related properties *in vitro* and *in vivo* were evaluated. Compounds with analgesic activity *in vivo,* superior to diclofenac, were found. The results of inhibitory activity study against COX-1 and COX-2 revealed that these enzymes most likely do not represent the main biological targets of studied 4-quinolone derivatives.

The experimental data for [*b*]-annulated 4-quinolones as well as for not annulated ones will be compared and discussed.

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PHARMACOLOGICAL EVALUATION OF OPIOID RECEPTOR ANTAGONISTS

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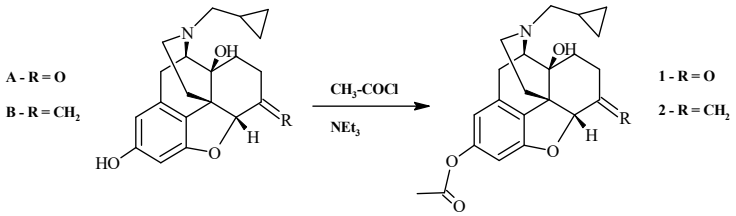
The uncontrolled use of opioid analgesics poses a threat to the human health. The pharmacological activity of substances acting on the central nervous system is largely due to their lipophilicity. Analysis of log P values of opioid receptor agonists and antagonists is of great practical interest in the search for drugs for the treatment of opioid poisoning. For the treatment of opioid poisoning, it is essential that opioid analgesics and their antidotes have comparable lipophilicity indices. Thus we have synthesized 3-acetates **1**, **2** of naltrexone (A) and its 6-methylene analogue, nalmefene (B), previously proposed only to increase the oral and transdermal bioavailability of these drugs for the treatment of dependencies. We have also conducted a comparative evaluation of their lipophilicity by calculation methods using ACD/Percepta software, designed for toxicokinetic studies.



Opioid receptor agonists	Predicted Log P	Opioid receptor antagonists	Predicted Log P
Morphine	0,69 (0,76)	Naloxone	1,53 (1,50)
Diacetylmorphine	1,89 (1,58)	Naltrexone **A**	1,63 (1.92)
Acetylphentanyl	3,75	Nalmefene **B**	2,42 (2,66)
Methadone	4,44 (3,93)	O-acetyl–naltrexone **1**	1.89
Phentanyl	4,09 (3,89)	O-acetyl–nalmefene **2**	2,71

The experimental values of logP are given in parentheses.

The pharmacological evaluation showed the lipophilicity of the molecules obtained by acetylation of opioid receptor antagonists to increase in comparison with the initial drugs, which may contribute to their faster and more pronounced pharmacological effect on the CNS for emergency therapy of life-threatening socially significant diseases.

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HYPOGLYCEMIC ACTIVITY OF NOVEL GPR119 RECEPTOR AGONISTS

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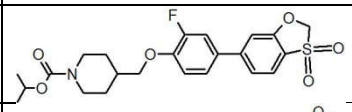
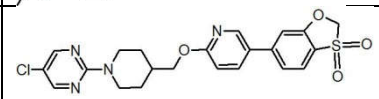
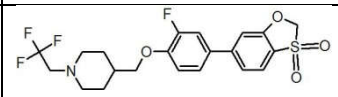
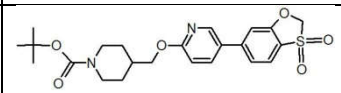
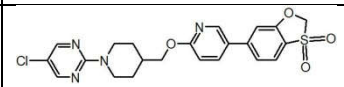
The GPR119 receptor is a promising pharmacological target for the treatment of type 2 diabetes mellitus, metabolic syndrome and obesity. GPR119 agonists have glucose-dependent hypoglycemic action that is realized by increasing incretins and insulin secretion. To date, 10 GPR119 agonists have reached stage I and II clinical trials as drugs for the treatment of type 2 diabetes and obesity [1].The purpose of this study was the evaluation of hypoglycemic activity of some novel GPR119 agonists in animals with experimental diabetes mellitus.

The study was performed on Wistar rats with streptozotocin-nicotinamide-induced (65/230, mg/kg, i.p.) diabetes mellitus (DM) [2]. The investigated GPR119 agonists (formulas and activity (EC) are presented in Table), synthesized in Chemical Diversity Research Institute, Russia, were administered for 4 weeks in three doses (0.1, 1 and 10 mg / kg, per os). The hypoglycemic activity of the compounds was assessed after 7, 14 and 28 days of therapy by evaluation of fasting glucose and the rate of glucose utilization during the oral glucose tolerance test (OGTT).

The chemical structure and activity of GPR119 agonists

Compound	Chemical structure	EC_{50} M*
ZB-16		$7{,}25E^{-09}$
ZB-17		$1{,}25E^{-08}$
ZB-18		$6{,}35E^{-08}$
ZB-19		$1{,}1E^{-08}$
ZB-20		$2{,}93E^{-08}$

*Note: * – specific activity (EC50) of the compounds was established previously in vitro conditions using the CHO-K1 cell line expressing human GPR119 (hGPR119) receptors [3]. The agonistic activity of the ZB-16 was estimated by the increase in intracellular cAMP concentration, as it is known that, when activated, hGPR119 receptors cause subsequent activation of cellular adenylate cyclase, which increases intracellular cAMP levels [1]. Lance Ultra cAMP kit (Perkin Elmer, Waltham, MA, USA) was chosen as the experimental platform. Known agonists of hGPR119 receptors (Arena) were used as positive controls and to determine the upper limit (maximal signal) of the experiment*

The administration of GPR119 agonists to animals with experimental diabetes led to a decrease in fasting glycemia and an increase in the rate of glucose utilization during OGTT. The most pronounced hypoglycemic activity had the compound ZB-16 in a dose of 1 mg/kg, with a significant effect observed after 7 days.

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STUDY OF EFFICACY OF DIURACILE DERIVATE AS SELECTIVE ACETYLCHOLINESTERASE INHIBITOR IN MYASTHENIA GRAVIS ANIMAL MODEL

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Myasthenia gravis (MG) is an autoimmune disorder characterized by skeletal muscle weakness, in which antibodies decrease the number of acetylcholine receptors on the postsynaptic membrane of the neuromuscular junction [1].

The using of anticholinesterase drugs for MG therapy is only the way in most cases. However, during MG therapy not only AChE, but also BuChE is inhibited and there are a number of side effects from the smooth muscles, which limits quality of patients life.

A number of diuracile derivatives were synthesized in the A.E. Arbuzov Institute of organic and physical chemistry and tasted for the ability to inhibit AChE and BuChE *in vitro*. For leader compound (No. 86) extremely high selectivity for AChE vs. BuChE was shown. AChE was inhibited at the concentration 400,000 times lower than BuChE.

The ability of compound No. 86 to eliminate the symptoms of muscle weakness was tested. Experimental autoimmune model of myasthenia gravis (EAMG) was triggered as described by Baggi et al. [2]. The muscle weakness symptoms was judged by the ratio of the amplitudes of the 1st and 200th M-responses of the hind limbs muscles of the rats (decrement test). We determined the dose of compound No. 86, which restored the amplitude of the 200th M-response of animals with EAMG until the level of healthy rats. This dose was 0.01 mg / kg with the intraperitoneal route of administration.

The therapeutic index for this compound is 1/2000 of LD_{50}, which shows significant safety for the use for the treatment of MG.

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NEW APPROACHES TO AN OBJECTIVE ASSESSMENT OF THE PAIN SYNDROME: DIFFERENTIAL VAS, PRESSURE ALGOMETRY AND NATURAL ANTIBODIES TO ENDOGENOUS PAIN REGULATORS

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Many specialists are faced with the problem of low effectiveness of analgesia. For the successful realization of the analgesic program, a dynamic control of pain is necessary during the entire period of the patient's treatment. In this regard, the actual task is to create and modernize methods of objective pain assessment. In order to more accurately assess pain, we proposed the following methods: Differential visual analogue scale - a method in which the patient evaluates the severity of pain on a 100mm scale, being in different functional states (at activity (ACT), spontaneous pain (SPONT), rest (POC), night (NIGHT) pain); Pressure algometry, in which the thresholds of pain intolerance (PITs), caused by the pressure of the applicator Kuznetsov, located under the cuff of the tonometer, are measured; ELISA of the content of natural antibodies (nAb) against bioregulators of the pain signal (β-endorphin, orphanin, serotonin, dopamine, histamine and angiotensin) in the blood serum of patients and the composing of individual nAb profiles.

We examined 189 patients (88 men and 101 women) with radicular (RP) and myofascial (MP) chronic back pain (lumbosacral section). The severity of pain, PITs and eAt levels were measured on 1, 10 and 21 days of the treatment. The intensity of pain according to VAS, depending on the functional state on day 1, decreased as follows: SPONT> ACT> NIGHT> POC, both in the RP group and in the MP group. By the 21st day of treatment, the severity of pain significantly decreased in all groups, and the intensity distribution had the same order. At the same time, the SPONT and NCH indicators in the women's RP group and all the indicators in the male RP group were significantly higher than the corresponding indicators in the MP groups. This fact suggests a deeper damage at the radicular syndrome and a longer recovery process. Measurement of PITs (day and night) showed that low daily PITs (<20 c.u.) was found at 35-45% of men and at 58-78% women. Women's PITs were 16-30% higher than men's PITs. A comparison of the PITs between RP-group MP-group showed that PITs in the RP-group were higher than in the MP-group, however, these differences were not significant.

Determination of the nAbs levels to pain bioregulators showed that in most patients (65% -85%) the nAb levels were high and elevated. The highest levels were detected for nAbs to β-endorphin, orphanin, which are ligands of the opiate system - the main endogenous analgesic system. Pairwise comparison of the number of patients in subgroups with high and elevated nAb levels at 21 days between the RP and MP groups did not reveal statistical differences, which indicates that the change in these parameters is slower than the regression of pain, which can be involved in the maintenance of the chronic pain state.

Thus, this research has shown the possibility of objectifying the pain estimation on the basis of the pressure algometry results and the analysis of individual profile of the nAbs to the pain signal regulators. The task requires a longer monitoring of patients with chronic pain.

DEVELOPMENT OF NOVEL COUMARIN DERIVATIVES WITH ANTI-INFLAMMATORY AND ANALGESIC ACTIVITY

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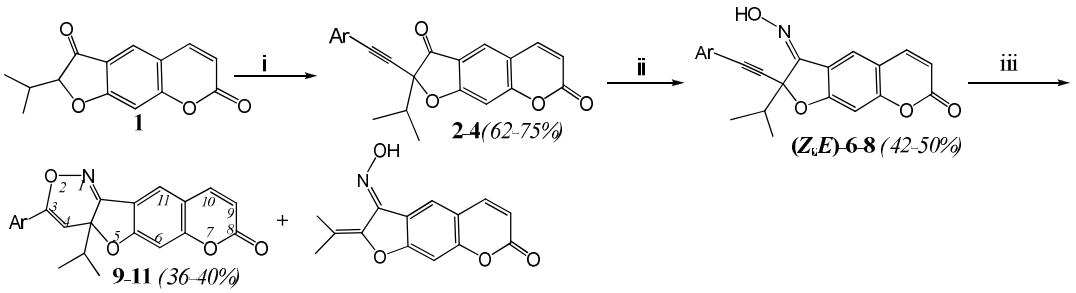
Furocoumarins are widely presented in plants, including Orchidaceae, Rutaceae and Apiaceae, and both synthetic and plant-derived furocoumarins are utilized in a wide range of applications in chemical, pharmaceutical and agricultural industry [1]. These compounds are also important ingredients of plants used as anti-inflammatory remedies in traditional medicine [2]. A number of semisynthetic derivatives of these molecules, possess high medicinal efficiency including cytotoxic, photosensitizing, antibacterial, antiviral (HIV-1), and anti-inflammatory activity. Even small structural changes in furocoumarin core were reported to lead to significant changers in their activity, making a convincing case for the study of structure-activity relationships in this class of compounds. Starting from available furocoumarin oreoselone **1** was obtained a new group of heterocyclic compounds – 1,2-oxazine fused linear furocoumarins **9-11** by using of the gold(III)-catalyzed cycloisomerization of furocoumarin β,γ-acetylenic oximes **6-8**.



i $TsCl$, Et_3N, $Pd(PPh_3)_2Cl_2$, THF, 60°C, 5h, then $ArC{\equiv}CH$, 60°C, 3–7 h;
ii $NH_2OH{\cdot}HCl$, 10% NaOH, EtOH, 55–60°C, 10h;
iii $AuCl_3$, MeCN, 30°C, 6–8 h

Ar = Ph (2,6,9), 4-F-C_6H_4 (3,7,10), 2-OMe-3-OMe-4-OMeC_6H_2 (4,8,11)

Structures of compounds were confirmed with spectral methods and elemental analisys data. Experimental studies based on mouse models reveal anti-inflammatory and analgesic activity for these new type of heterocyclic compounds. Docking studies were undertaken to gain insight into the possible binding mode of oxazine fused linear furocoumarins with phosphodiesterase (PDE-4B) binding site.

This work was supported by the Russian Foundation for Basic Research (grant №17-73-10099).

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SPECIFIC ACTIVITY OF THE NOVEL DERIVATIVE OF QUATERNARY AMMONIUM SALTS AGAINST GRAM-POSITIVE AND GRAM-NEGATIVE BACTERIA

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Quaternary ammonium compounds (QAC) are currently one of the promising classes of disinfectants. However, its common use for medical application is limited due to bacterial resistance to these compounds. The creation of new antimicrobial agents can solve this problem.

In this work we studied a novel of promising antimicrobial agent based on QACs (AM17). This compound was synthesized in Department of Medical Chemistry of Scientific and Educational Centre of Pharmaceutics. At first the minimal inhibitory and bactericidal concentrations for several museum strains of microorganisms was identified by serial dilution method. For AM17 a relatively high antimicrobial activity against gram-positive and gram-negative bacteria was shown. Further, the effect of AM17 on the test microorganisms growth (*Staphylococcus aureus 209P* and *Escherichia coli CDC F-50*) was studied. The compound showed high inhibitory action against test-microorganisms, more powerful than miramistin.

And finally, the ability of the synthesized compound to change the electric potential of the bacterial membrane was studied through the use of membrane-potential-sensitive cyanine dye DiOC2(3). It was shown that the AM17 can cause membrane depolarization. As a result, the ability of AM17 to damage the bacterial membrane was identified.

The obtained data give evidence that this compound represents a real interest for development and creation of promising antiseptics and disinfectants.

THE AMINO-ADAMANTANE DERIVATIVE TG2113X AS A POTENTIAL NEUROPROTECTIVE COMPOUND

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Alzheimer's disease is one of the most common forms of senile dementia, the main symptoms of which are memory dysfunction, the violation of the synthesis of the neurotransmitter acetylcholine, the formation of beta-amyloid and tau protein [1, 2]. Currently, there is not developed a sufficiently effective treatment of the disease and it is important to development of new drugs. Here, effects of the amino-adamantane derivative TG2113X on memory of 3-month-old C57Bl6 mice were studied in models of scopolamine-induced amnesia and stress-induced behavioral abnormality.

TG2113X+scopolamine-treated and Vehicle+Vehicle (control group) mice showed the similar level of freezing behavior in the fear conditioning test, both in fear conditioning and memory extinction sessions, although, TG2113X+Vehicle mice did not show significantly increased memory in the test. The obtained results suggest that TG2113X eliminates the amnesic effect of scopolamine and, probably, has a neuroprotective effect. However no effects on stress-induced depressive-like behavior in tail suspension, dark-like box, sucrose preference test were observed.

To assess the effect of TG2113X on the general behavior of mice, the open field test was additionally performed. TG2113X did not change the average speed, travel distance and time in comparison to the control mice. The number of entrances to the center of TG2113X-treated mice was not differ from the center entries of mice from the control group

Thus, it can be suggested that TG2113X has pro-cognitive functions, without alters in the motor activity of mice, anxiolytic or anxiogenic effects.

The financial support of RSF grant 14-23-00160P is gratefully acknowledged.

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SYNTHESIS OF NEW ANTIBACTERIAL EREMOMYCIN CARBOXAMIDES

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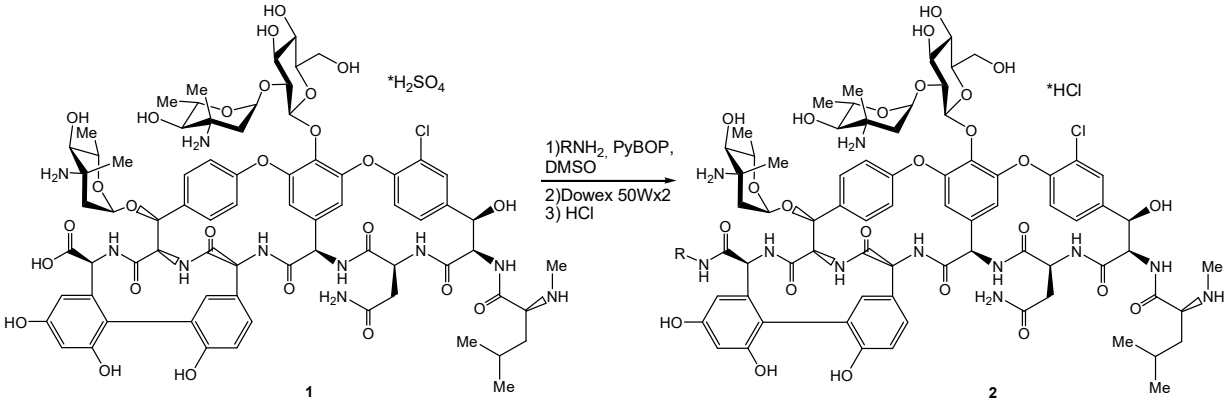
Eremomycin (**1**) is a glycopeptide antibiotic produced by *Nocardia orientalis* discovered in 1979 by G.F. Gause. Though eremomycin has higher activity than vancomycin and other natural glycopeptides, it has low activity against some resistant strains as GISA (Glycopeptides Intermediate-resistant *S. aureus*) and VRE (Vancomycin Resistant *Enterococcus*). Thereby, the searching of new semi-synthetic eremomycin derivatives which could circumvent the bacterial resistance is a perspective direction for the development of new antibacterial agents.

One of the most promising ways of modification of glycopeptides is a transportation of C-terminus of the peptide core into carboxamide group [1]. Also well known that potency of glycopeptides can be increase by the introduction of hydrophobic substituent [2]. Taking into account these data, the new series of eremomycin carboxamides**2** were obtained. The condensation of **1** with amines was carried out by PyBOP in the presence of the base (DIEA) in DMSO. Crude products were purified by ion exchange chromatography on a Dowex 50Wx2 resin.



Several derivatives from series of new amides of eremomycin were more active than vancomycin against both sensitive and resistant strains of gram-positive bacteria: 5-10 times against sensitive strains of *S. aureus* and *E. faecalis* and 10-25 times against resistant strains of *E. faecium* and *E. gallinarum*. Thus, some perspective modifications of eremomycin (**1**) for the searches of candidates for further development of a new generation of glycopeptide antibiotics have been selected.

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GML-1 – 18 KDA TRANSLOCATOR PROTEIN LIGAND – NOVEL PROMISING ANXIOLYTIC

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Translocator protein 18 kDa (TSPO) is a new target for creating effective anxiolytics free from side effects of benzodiazepines. This receptor activates cholesterol transport from the outer to the inner mitochondrial membrane that is the rate-limiting step of neurosteroids biosynthesis. Neurosteroids are potent positive allosteric modulators of GABAA receptor, which plays an important role in the pathophysiology of anxiety disorders.

Based on the pharmacophore model of the structures of TSPO ligands and using the molecular docking method, we constructed a molecule of GML-1 (*N*-benzyl-*N*-methyl-1-phenylpyrrolo[1,2-a]pyrazine-3-carboxamide) [1]. *In vivo* experiments in standard rodent anxiety tests demonstrated that GML-1 in the dose range of 0.1-5.0 mg/kg has anxiolytic activity both using intraperitoneal and oral administration. The activity of GML-1 was not inferior to effect of known benzodiazepine tranquilizer diazepame (1,0 mg/kg) [2]. It was found that GML-1 does not have diazepam side effects. Moreover, GML-1 demonstrated a pronounced positive mnemotropic (nootropic) effect.

Radioligand method showed that GML-1 has a high affinity for TSPO ($Ki = 5,2*10^{-8}$ M). It was proved that the mechanism of anxiolytic action of the compound GML-1 is due to its ligand properties to TSPO and its ability to activate neurosteroids [3]. GML-1 has a low acute toxicity (LD_{50}> 1000 mg/kg), and it well penetrates the BBB. The oral dosage form of GML-1 has been developed.

Currently, GML-1 is at the final stage of preclinical study as a potential anxiolytic drug (State contract No. 14.N08.12.0087).

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DEVELOPMENT OF VACCINE BASED ON SYNTHETIC IMMUNOGEN FOR DRUG ADDICTION ANTI-RELAPSE TREATMENT

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The most acute problem of narcology is the lack of effective means of drug addiction anti-relapse treatment. Approaches available have shown their low efficiency and high risk of side effects. Therefore, new generation drugs being developed nowadays are vaccines that are synthetic immunogens for the production of anti-narcotic antibodies. After the course of vaccination, specific antibodies are produced and bind the drug if it enter into the body. Antibodies act at the peripheral level, preventing the passage of drugs through the blood-brain barrier, reducing their toxic effect. The patient does not receive relief from narcotic cravings and gradually loses motivation to take drugs. Such therapy is much more safe than the existing anti-relapse drug treatment, associated with high addictivity or having serious side effects.

We proposed the structure of synthetic immunogen, which contains a natural human serum protein (human gamma globulin HGG or human serum albumin HSA) and a hapten (morphine or naltrexone derivative) conjugate bound to a polymer matrix to enhance the immune response. Poly-4 (nitrophenyl) acrylate (PNPA) as a high-tech polymer, and a copolymer of 2-methyl-5-vinylpyridine and N-vinylpyrrolidone (MVP-VP) were used as polymers.

Preclinical study of acute toxicity of PNPA showed that the polymer belongs to the 5th toxicity class, i.e. to practically non-toxic substances (LD_{50}> 2500 mg / kg). The MVP-VP polymer is also non-toxic according to previous studies.

Various combinations of protein carrier and hapten conjugates and a polymer matrix have been synthesized. The ratios for HGG, HSA and hapten (morphine, naltrexone) were in the range from 9 to 43 (for HGG) and from 5 to 15 (for HSA) moles of hapten per mole of macromolecular carrier. The substitution of the polymer matrix with the conjugate was 1:2 to 1:20. The study of epitope accessibility and specificity of antigenic determinants in synthesized immune complexes was carried out by means of enzyme immunoassay (ELISA). Antigenic determinants are not screened in a ratios conjugates : polymer up to 1:10 for HGG and HSA conjugates.

The ability of synthesized immunogens to rase the production of specific antibodies was investigated by immunizing rats with complexes hapten : protein: PNPA and hapten: protein: MVP-VP. It has been shown that immunogens containing MVP-VP cause the formation of antibodies with a higher titer, which is probably explained by the best adjuvant properties of the copolymer.

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BIOLOGICAL ACTIVITY OF DAUNORUBICIN AND DOXORUBICIN DERIVATIVES

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One of the important directions of chemotherapy of oncological diseases is the use of various antitumor antibiotics. It is possible to allocate among them a special group of antitumor antibiotics - anthracyclines - which have high antimitotic activity and are widely used in medical practice. Alongside with their significant advantages, they have a lot of serious limitations - first of all their high and irreversible cumulative dose-dependent cardiotoxicity, which is mainly caused by free radical damage to myocardial cell membranes.

The series of conjugates of known anthracycline antitumor antibiotics daunorubicin and doxorubicin with natural or modified sesquiterpene lactones from plants of the Asteraceae family were synthesized. Due to our previous data we propose that in particularly some of new conjugates may possess the antioxidant properties and will be capable to influence on the key stages of cardiotoxicity formation without significant decrease of antitumor activities.

At the initial stage, the effect of test compounds on the survival of different human tumor cells was studied to compare the level of activity with the initial anthracyclines. It was shown that all test substances demonstrate high cytotoxic activity. For some conjugates, cytotoxic activity is significantly higher than of the initial antibiotics.

The next step was to study the effect of anthracyclines and their derivatives on the process of lipid peroxidation of rat brain homogenate to detect antioxidant activity. As expected, unlike the scaffold antibiotics, which do not have antioxidant activity, some conjugates effectively suppressed the process of lipid peroxidation.

Thus, modification of anthracycline antibiotic by sesquiterpene lactones can act as a basis for the development of effective antitumor agents with reduced toxicity in relation to healthy cells.

This work was supported by Russian Science Foundation (grant 17-73-10461).

NEW BIOCHEMICAL MARKERS OF HIV/AIDS: BLOOD SERUM ANTIBODIES HYDROLYZING HISTONES

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Histones and its post-translational modifications play key roles in chromatin remodeling and gene transcription. Besides intranuclear functions, histones act as pathology associated molecular pattern molecules when they are released into the extracellular space. Administration of exogenous histones to animals leads to systemic inflammatory and toxic responses.

Here, using ELISA we have shown that sera of HIV-infected patients and healthy donors contain autoantibodies against histones. Autoantibodies with catalytic activity are distinctive feature of autoimmune diseases. It was interesting whether antibodies from sera of HIV-infected patients can hydrolyze human histones.

Electrophoretically and immunologically homogeneous IgGs were isolated from sera of HIV-infected patients by chromatography on several affinity sorbents. Here we present first evidence that 100% of IgGs purified from the sera of 32 HIV-infected patients efficiently hydrolyze from one to five human histones. Several rigid criteria have been applied to show that the histone-hydrolyzing activity is an intrinsic property of IgGs of HIV-infected patients.

The relative efficiency of histone hydrolysis (H1, H2a, H2b, H3, and H4) significantly varied for IgGs of different patients. IgGs from the sera of 40% of healthy donors also hydrolyze histones but with an average efficiency approximately 16-fold lower than that of HIV-infected patients.

Similar to proteolytic abzymes from the sera of patients with several autoimmune diseases, histone-hydrolyzing IgGs from HIV-infected patients are inhibited by specific inhibitors of serine and of metal-dependent proteases, but an unexpected significant inhibition of the activity by specific inhibitor of thiol-like proteases was also observed. Because IgGs can efficiently hydrolyze histones, a negative role of abzymes in development of acquired immune deficiency syndrome cannot be excluded.

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SYNTHESIS AND BIOLOGICAL PROPERTIES OF 7-(*R*)-DIHYDROOLIGOMYCIN A

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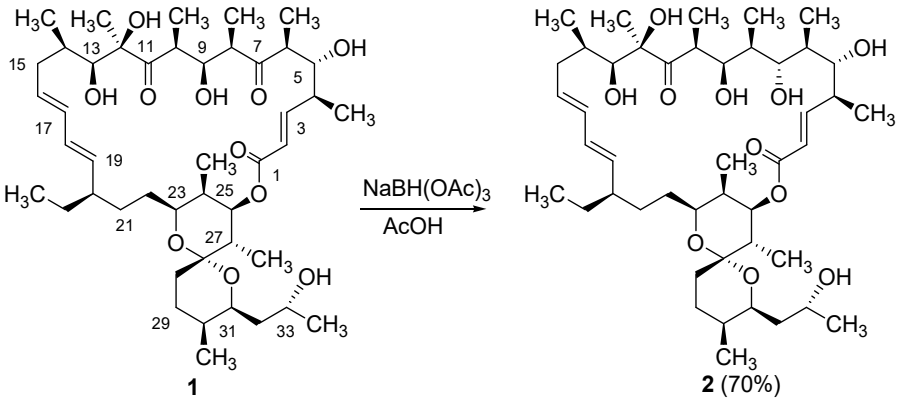
Oligomycins are produced by actinomycetes *Streptomyces* [1] and belong to the class of polyfunctional macrolide antibiotics. Oligomycin A (**1**) inhibit F_1F_0 ATP-synthase [2], which is regarded as a molecular target for new drugs in the treatment of tumors and infections. Synthesis and biological studies of new derivatives of oligomycin A will provide important SAR-data and evaluation of the detailed mechanism of chemotherapeutic activity of oligomycins.

Previously, a stepwise nonstereospecific reduction of the 7-keto and the 11-keto groups of the oligomycin mixture (A, 65%; B, 20%; C, 15%) by treatment with sodium borohydride in ethanol solution was described [3]. Based on this point, we have studied a borohydride-mediated reduction of pure oligomycin A more carefully. The best results were obtained by reduction of oligomycin A (**1**) with $NaBH(OAc)_3$ in AcOH. The reaction proceeds smoothly with high regio- and stereoselectivity, giving 7-(*R*)-dihydrooligomycin A (**2**) in a good yield.



1 **2** (70%)

Structure of compound **2** was confirmed by high resolution mass spectrometry and NMR spectroscopy. Relative configuration at C7 position was unambiguously determined by detecting correlations between neighboring protons in ^{1}H-^{1}H ROESY spectrum. Obtained biological data revealed that 7-(*R*)-dihydrooligomycin A (**2**) slightly less potent than native antibiotic **1**.

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NOVEL ANTIMICROBIAL TRIINDOLYLMETHYLLIUM DERIVATIVES: SYNTHESIS AND BIOLOGICAL PROPERTIES

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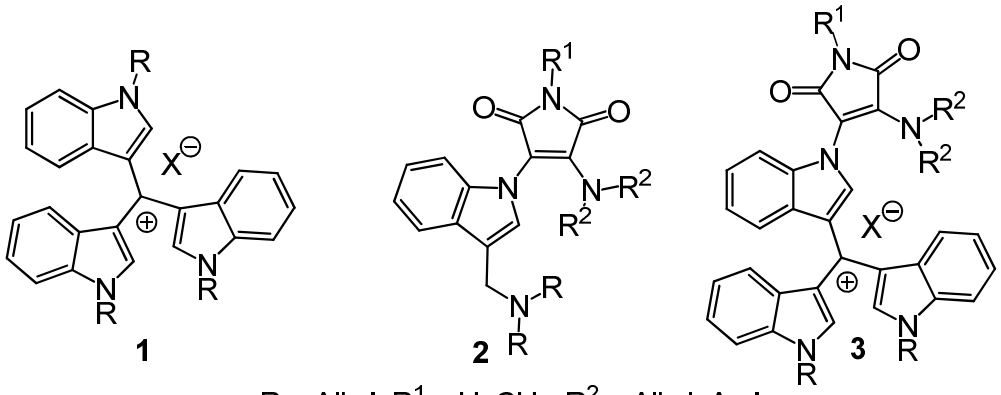
Development of new antibiotics is now possible either by search of new naturally occurring biologically active compound or by means of total synthesis [1,2]. Recently we synthesized tris-(1-alkylindol-3-yl)methyllium salts (**1**), which showed high antibacterial and antifungal activity [2,3], and 4-substituted 3-[3-dialkylaminomethyl)indol-1-yl]maleimides (**2**), which are capable of inhibition of vital protein kinases [4]. It seems promising to combine these two classes into hybrid molecules (**3**) in an attempt to make more active compound bearing both pharmacophore fragments simultaneously.



More than 25 compounds of the structure **3** and an array of related compounds were synthesized and tested for antibacterial and antifungal activity [5]. Some of them turned out to be active against mycelial fungi, yeasts and bacteria, including antimicrobial-resistant strains.

The study was carried out with the support of the Russian Science Foundation (project №16-15-10300)

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PSYCHOTROPIC PROPERTIES OF NEW ANALOGUES OF THE TRANQUILIZER «PHOSENAZID»

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Phosenazid 1 is a sample of hydrazides of phosphorylated carboxylic acids. Its psychoactive properties were investigated in the pharmacology department of KSMU. Phosenazid 1 was introduced into practical medicine as a tranquilizer and anti-alcohol cure.

Currently psychotropic properties of the new representatives of hydrazides of phosphorylated carboxylic acids – analogues of tranquilizer phosenazid were studied on behavioral models of laboratory animals. These researches have shown that all substances are significantly less toxic than phosenazid and demonstrate psychoactive properties, which depend on the chemical structure. It was found that compound 2, where the phosphoryl and hydrazide fragments are directly connected, characterized by inhibiting the action in the "open field" and anxiolytic properties on the model of "conflict" and "cruciform labyrinth" without appearing muscle-relaxing effects, characteristic of tranquilizers. Compounds 3 and 4 have additional 1,4-phenylene spacer between the phosphoryl and hydrazide fragments. This compounds do not exhibit anxiolytic activity and depressive action, on the contrary, in an "open field" increase the number of "looking" into the holes. The "phosenazid" in studied aquatoxicity doses did not show activity. The results of the experiments indicated the feasibility of directed synthesis and study of the psychotropic activity of several new analogues phosenazid. Researches, were conducted with using video tracking and computer programs of the company "Noldus" (Netherlands).

$Ph_2P(O)CH_2CONHNH_2$	$Et_2P(O)CONHNH_2$	$Et_2P(O)CH_2C_6H_4CONHNH_2$	$Et_2P(O)CH_2C_6H_4CONHNH_2$
1	**2**	**3**	**4**

The work was made with financial support of the Ministry of education and science of the Russian Federation, performed in the framework of the base part of state assignment in the field of scientific activities on the project № 4.5348.2017/BCh.

NOVEL SEMISYNTHETIC DERIVATIVES OF BILE ACIDS AS EFFECTIVE TIROSYL-DNA PHOSPHODIESTERASE 1 INHIBITORS

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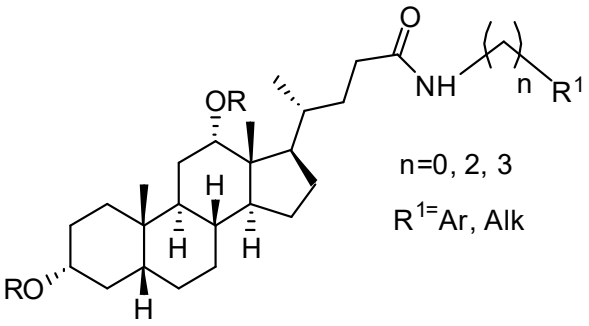
Tirosyl-DNA phosphodiesterase 1 (Tdp1) is an enzyme that has been associated with repair of topoisomerase 1 (Top1) cleavage complexes by its ability to hydrolyze the phosphodiester linkage a tyrosine residue and DNA 3'-phosphate [1]. Tdp1 inhibitors have been regarded as a potential therapeutics in combination with Top inhibitors, such as campotothecin derivatives, which are used to treat human cancers. It should be note, at date, only a small number of Tdp1 inhibitors have been characterized [2, 3].



R= H, Ac;

In this work, we describe a new class of semisynthetic small molecule Tdp1 inhibitors that were originally identified by molecular docking. Herein we present the successful synthesis and evaluation of inhibitors, which are based on the bile acid scaffold. The substances were synthesized by modification of carboxylic group via formation of chloroanhydride and its reaction with corresponding amines. Structures of all new compounds were confirmed by ^{1}H and ^{13}C NMR and high resolution mass spectrometry. The *in vitro* studies demonstrate the ability of semisynthetic derivatives to effectively inhibit Tdp1 (IC_{50} values in the range 0.2-6.0 μM)

This work is supported by Russian Science Foundation under grant 16-13-10074.

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SYNTHESIS OF DIASTEREOMERS OF THE DIMERIC DIPEPTIDE MIMETIC OF THE NERVE GROWTH FACTOR GK-2 AND STUDY ITS NEUROPROTECTIVE ACTIVITY IN VITRO

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A dimeric dipeptide mimetic GK-2 (*bis*-(*N*-monosuccinyl-*L*-glutamyl-*L*-lysine) hexamethylenediamide) was designed on the basis of the β-turn structure of the NGF loop 4. [1] Dipeptide GK-2, like NGF, induced the activation of specific TrkA receptors, but unlike the latter selectively activated PI3K/Akt post-receptor signaling pathway involving in neuroprotection [2]. GK-2 exhibited neuroprotective activity in *in vitro* experiments in the concentration range 10^{-5}-10^{-9}M. In *in vivo* experiments (in doses of 0.05-5 mg/kg ip), GK-2 was active in the experimental models of Alzheimer's and Parkinson's diseases, as well as in the models of and chronic cerebral ischemia in rats [3]. At the moment, GK-2 is at the final stage of preclinical study as a potential neuroprotective drug.

To increase the knowledge of the mechanism of interaction of GK-2 with the TrkA receptor we have studied the stereospecificity of its neuroprotective effects. For this purpose, its L, D- and D, L-diastereomers were synthesized and their neuroprotective activity *in vitro* was studied under conditions of oxidative stress caused by H_2O_2 in the concentration range 10^{-5}-10^{-8} M on the HT-22 neuronal culture.

Synthesis of the diastereomers was carried out by classical peptide synthesis in solution by elongation of the peptide chain from the C-terminus, using the Z/Boc strategy of protecting groups and the activated *N*-hydroxysuccinimide esters method. The homogeneity of target products was confirmed by TLC and HPLC. The structure and diastereomeric purity of the resulting compounds were confirmed by ^{1}H-NMR.

It was found that replacement of *L*-lysine residue by *D*-lysine leads to reduction of activity, and the replacement *L*-glutamic acid residue by its *D*-stereoisomer - to its disapperence. Thus the neuroprotective effect of GK-2 is stereospecific and depends on the configuration of the both amino acid residues.

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MOLECULAR MODELING OF MODULATORS OF AMPA-RECEPTOR IN A ROW OF SOME (-)-CYTISINE DERIVATIVES

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According to in vivo tests, a number of (-)-cytisine derivatives possess pronounced neurotropic activity, comparable with the activity of piracetam. It's known that piracetam acts as a weak positive modulator of AMPA receptor [1]. We can assume that mnestic activity of some derivatives of the (-)-cytisine (Fig.1) may be associated with their affect the work of the AMPA receptor.

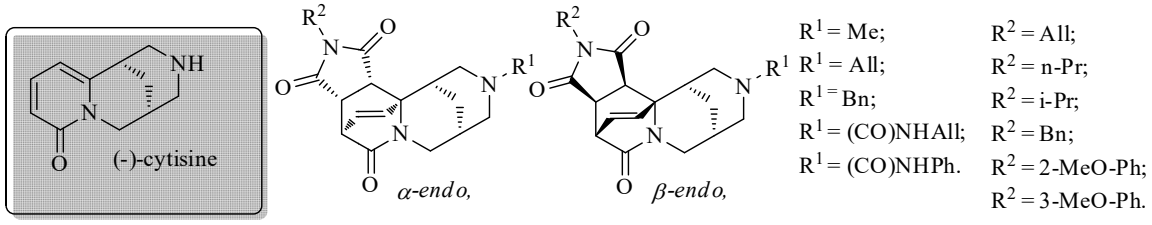
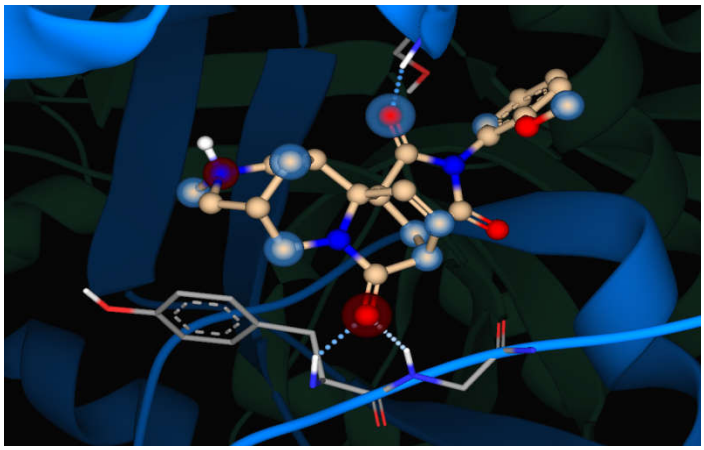


Fig.1. Some derivatives of the (-)-cytisine.

Molecular modeling was carried out using the software package LeadIT v. 2.2.0. The lead-compound locates in the U-shaped cleft of ligand-binding domain S1S2 AMPA receptor forming hydrogen bridges between the carbonyl oxygen of the ligand and tyrosine, serine and glycine residues (Fig. 2).



Ligand	Mnestic Activity, %	ΔG_{bind}, kJ/mol
Leader	90,5	-18
Piracetam	71,7	-8

Fig.2. The location of lead-compound in the active site of AMPA-receptor: H-bridges are shown blue color.

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NOVEL MONOAMINE OXIDASE INHIBITORS BASED ON PRIVILEGED 2-IMIDAZOLINE SCAFFOLD

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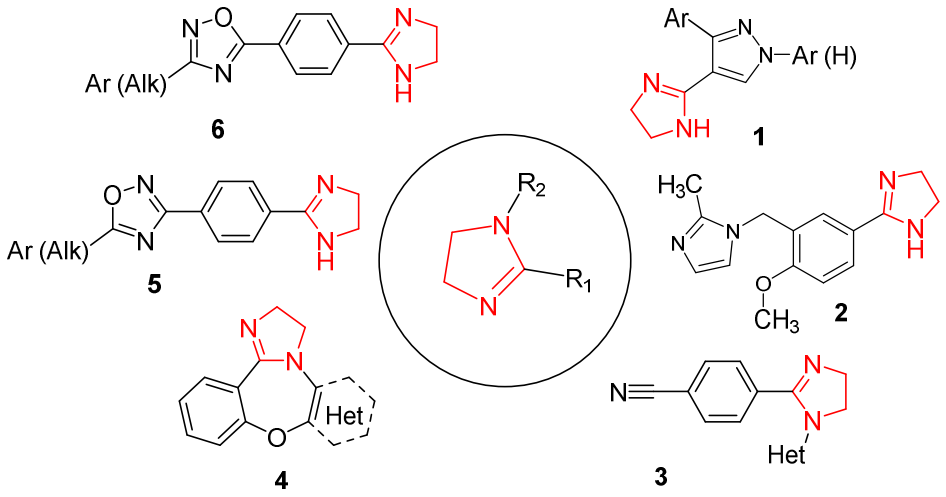
Good potency inhibitors of both human monoamine oxidase (hMAO) isoforms may be useful for the treatment of neuropsychiatric and neurodegenerative disorders such as depression and Parkinson's disease, and future application for the treatment of prostate cancer, congestive heart failure, and Alzheimer's disease. The pilot series of structurally diverse 2-imidazoline derivatives have been synthesized by condensation of substituted aldehydes with ethylenediamine (**1, 2**), Pd-catalyzed N-arylation of 2-imidazolines (**3**), transition-metal free dehalocyclization reaction (**4**) and by the formation of 1,2,4-oxadiazoles from 2-imidazoline-containing precursors (**5, 6**) and were evaluated as potential inhibitors of hMAO isoforms.



Among the 2-imidazolines, good potency inhibitors were discovered with compound **5** (Ar = 4-$CH_3C_6H_4$, IC_{50} = 0.071 μM) being the most potent MAO-B inhibitor, while compound **6** (Ar = 4-$(CH_3)_3C_6H_4$, IC_{50} = 0.751 μM) was the most potent MAO-A inhibitor of the series. These potencies are in the same range as those of reference MAO inhibitors used in the clinic.

THE SEARCH OF NEW COMPOUNDS NORMALIZING THE STRUCTURE OF THE MICROTUBULES AS POTENTIAL THERAPEUTIC AGENTS FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

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Reduced microtubule stability has been observed in several neurodegenerative disorders (ND) such as Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis, amyotrophic lateral Lateral (ALS), and tauopathies like Progressive Supranuclear Palsy [1]. In recent years, in the search for new drugs for the treatment of such diseases a great importance is paid to the microtubules stabilization properties of new potential drugs. Even more important are the studies on the effect of potential drugs on the assembly and structure of microtubules (MT), obtained from tubulin (TB) and microtubule-associated proteins (MAPs) isolated from postmortem brains of AD patients or from the brains of animals proposed as models of neurodegenerative diseases. Mouse neurospecific expression of shortened forms of DNA/RNA-binding protein FUS [1-359] (FUS-TG F19) is a vivid example of an ALS and frontotemporal lobar dementia (FTLD) model. These ND also characterized by microtubules impairments.

Previously, we have discovered that *in vitro* assembly of MT from TB-MAPs, isolated from brain of AD patients, had abnormal structure [2]. Moreover anti-AD drug Amiridin is capable to restore the normal structure of MT unlike another anti-AD drug – Tacrine[3].

Polymerization of TB-MAPs isolated from brain cortex of FUS-TG F19 mice (FUS-MT-MAPs) also leads to formation of abnormal structures similar to the discovered earlier for AD-TB-MAPs (tangled bundles of different degree of density, rings and coiled structures). Screening for potential microtubules stabilizing properties among new conjugates of adamantane and carbazole derivatives revealed the compounds, which able in some degree to restore the normal structure of MT formed from the FUS-MT-MAPs. In addition, some of such compounds induced the concentration-dependent inhibition of GSK-3β. Activity of this kinase is tightly connected with the hyperphosphorilation of tau-protein - one of the main microtubules-stabilizing MAPs. We believe that this effect may at least partly determine compounds ability to normalize the structure of microtubules during their assembly from FUS-MT-MAPs.

These data reaffirms the use of FUS-TG F19 mice as a model of ND with microtubules impairments.

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NOVEL MULTITARGET CONJUGATE OF CARBAZOLE- AND AMINOADAMANTANE DERIVATIVES AS POTENTIAL NEUROPROTECTORS

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The low efficiency of currently available mono-targeted drugs for treatment of Alzheimer's disease (AD) and other types of dementia is directly related to the multifactorial nature of such neurodegenerative disorders. In this connection, the concept of multi-target drugs affecting simultaneously a number of key biotargets involved in pathogenesis of the disease looks as a promising approach for the development of original disease-modifying agents for AD treating [1]. In the present work we describe activity of some lead-compounds, representing series of novel conjugates of neuroactive pharmacophore fragments, namely, carbazole- and aminoadamantane derivatives and possessing the properties of multitarget potential drug for treatment of AD.

A new group of compounds, based on conjugates of aminoadamantane and carbazole derivatives was synthesized and investigated in *in vitro* targets assays [2]. The lead compounds was found to interact with a group of targets that play an important role in the development of AD diseases: not only selectively inhibit butyrylcholinesterase and/or block NMDA receptors, but also exert microtubules stabilizing properties and/or influence mitochondrial functions – protect against calcium-induced mitochondrial permeability transition. Neuroprotective potential for some compounds has been confirmed by it's ability to protect nerve cells from calcium overload death paradigm. It was of significant interest that one of the lead-compounds, TG2112x, effectively protect neurons against excitotoxicity without any effect on calcium intracellular dynamics.

The TG2113x, the lead compound with properties of microtubules stabilizer, significantly increase the associative memory in contextual FC test with 16-month mice without such effect on younger mice and display considerable protective effect on the associative memory in contextual FC test at scopolamine amnesia model.

Thus, our results confirm that novel conjugates of carbazole- and aminoadamantane derivatives has significant potential as a neuroprotector and enhancer of cognitive function in conditions of impaired memory and could be discussed as a perspective multitarget drug-candidate for the treatment of AD and related disorders.

The financial support of compound synthesis and primary screening by RSF grant 14-23-00160P is gratefully acknowledged.

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THE CYTOTOXICITY OF EPOXYALANTOLACTONE AND ITS AMINO DERIVATIVES AGAINST SUSPENSION TUMOR CELL LINES

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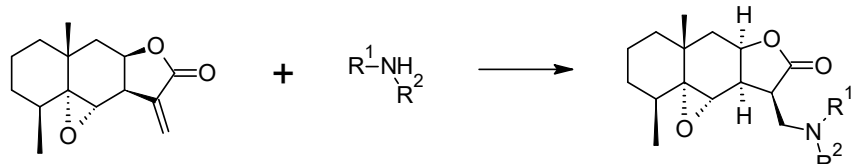
The primary basis for a diverse spectrum of biological effects of most sesquiterpene lactones is the presence of an α-methylene-γ-lactone functional group in their structure. In recent years, much attention has been paid to the modification of natural α-methylene-γ-lactones by amines. The reaction with epoxyalantolactone **1** and amines **2-9**, containing in their structure a pharmacophore fragment, was carried out.



1 **2-9** **1--2...9**

Previously, we studied the effect of natural epoxyalantolactone and its derivatives on the survival of the MCF7 cell line [1]. In the present study we investigated the influence of these compounds on the suspension cell lines (K562, Jurkat) and show a higher activity of modified lactones compared with the original.

The work was supported by RFBR grant №15-04-03940.

Compound, 5 uM	Viability, %		Compound, 5 uM	Viability, %	
	K562	Jurkat		K562	Jurkat
Camptothecin	23	21	**1-5**	54	30
1	40	34	**1-6**	58	26
1-2	---	34	**1-7**	29	---
1-3	60	49	**1-8**	46	32
1-4	48	31	**1-9**	30	---

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ANTIVIRAL ACTIVITY OF N-CONTAINING BORNYL ESTER DERIVATIVES AGAINST INFLUENZA VIRUS AND MARBURG VIRUS

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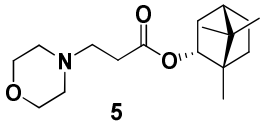
We studied activity of N-containing bornyl ester derivatives toward Marburg virus entry into the cell using a VSV capsid-based pseudovirus system. For all studied compounds, the half maximal inhibitory concentration (IC_{50}) was determined for rVSV-ΔG-MarV and rVSV-ΔG-G*, pseudoviruses. Further, the selectivity index (SI), a ratio of compound toxicity to inhibitory activity against the Marburg virus ($CC_{50}/ICMarV_{50}$), and the inhibitor specificity coefficient (SC), a ratio of half maximal inhibitory concentrations for two pseudoviruses ($ICMarV_{50}/ICVSV_{50}$), were calculated for each compound. Among the synthesized borneol derivatives, four compounds **1-4** turned to be more specific inhibitors of Marb-GP-mediated infection (SC>10).

Compound	CC_{50} (μM)	IC_{MarV50}, (μM)	IC_{VSV50}, (μM)	SI	SC
1	302±23	9±1	121±7	35	14
2	215±25	4±1	79±19	60	34
3	421±4	19±1	318±23	20	16
4	474±29	10±2	106±5	47	11
verapamil	280	13±1	>200	>21	>15

Also the activity against influenza virus A/Puerto Rico/8/34 (H1N1) was studied. Among these novel derivatives, compounds **5** and **6** with 1,7,7-trimethylbicyclo[2.2.1]heptan and morpholine fragments were found to possess the highest efficacy in virus inhibiting. Analysis of the structure-activity shown the increase of the linkers length leads to enlargement of the toxicity. The results obtained suggest that 1,7,7-trimethylbicyclo[2.2.1]heptan scaffold was necessary for activity [1].



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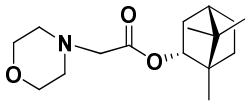

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Cis-imidazolines as precursors for creation potential antitumor agents

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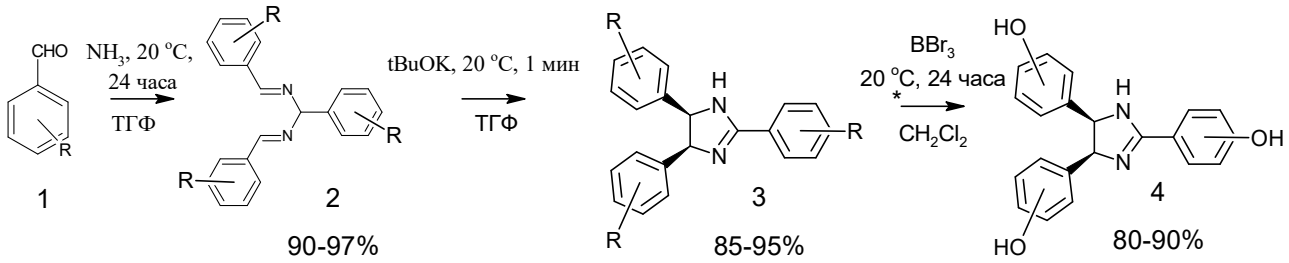
New structures that possess antitumor activity found out to be one of the promising areas of research in medical chemistry. The preparation of *cis*-imidazoline derivatives from aromatic aldehydes with ammonia is a convenient and simple synthesis of the precursors of the known inhibitors Mdm2-p53 interaction. We synthesized a series of *cis*-imidazolines by this method and measured their cytotoxicity.



The micromolar cytotoxicity of the derivatives obtained has a high potential for further research and modifications of these compounds. For example, the cytotoxicity of *methoxy* derivatives is in the range of 9-30 μM, while their *hydroxy* analogs do not exhibit a similar effect.

This work was supported by the RFBR grant No. 14-03 -1320/17 and the Fund for the Promotion of Innovation (Program"Umnik" № 11651ГУ/2017).

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF DUAL-ACTING ANTIBIOTICS ON THE BASIS OF BENZOXABOROLES AND AZITHROMYCIN

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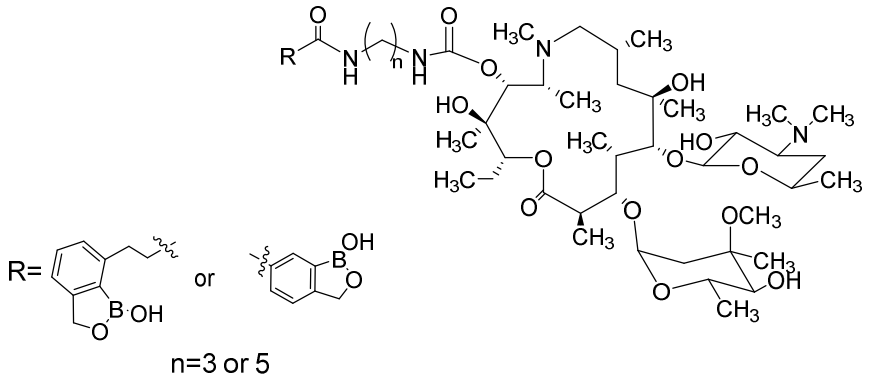
Benzoxaboroles, a privileged structure in medicinal chemistry due to its desirable physicochemical and drug-like properties, were used for the synthesis of azithromycin – benzoxaborole conjugates in which benzoxaborole fragment was attached to the 11-hydroxy group of antibiotic via aminoalkylcarbomoyl spacer.



The reaction of azithromycin with ethylene carbonate gave 11, 12-cyclic carbonate of azithromycin, 2'-O-hydroxyl group was protected with an acetyl group by interaction of 2 with acetic anhydride in pyridine. The resulting derivative was introduced into the reaction with propylenediamine or pentylendiamine what led to the opening of the 11, 12-cyclic carbonate ring and simultaneous splitting of the 2'-acetyl group. The obtained azithromycin derivative containing amino group was acylated by the benzoxaboroles that contain carboxylic group in the presence of DCC and HOBt. The obtained azithromycin – benzoxaborole conjugates demonstrated wide spectrum of antibacterial activity, especially against susceptible *S. pneumonia* strain although the investigated modification didn't result in the overcoming of bacterial resistance in MRSA. Further investigations including some SARs are under way.

The reported study was funded by the Russian Foundation for Basic Research according to the research project № 16-34-60110.

IMIDAZO[2.1-B]BENZOTHIAZOLES: A NOVEL MOLECULAR SCAFFOLD FOR THE $GABA_A$ RECEPTORS MODULATORS

Tikhonova T.A. [1], **Rassokhina I.V.** [1], **Kondrakhin E.A.** [2], **Sharonova I.N.** [3], **Kovalev G.I.** [2], **Volkova Y.A.** [1], **Zavarzin I.V.**[1]

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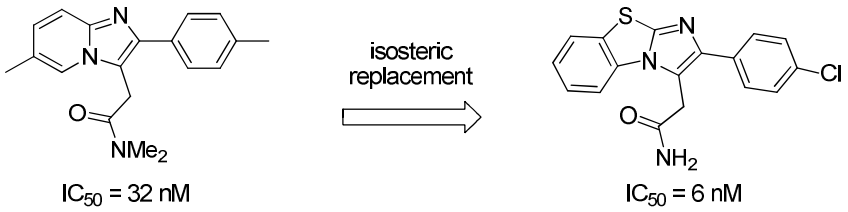
$GABA_A$Rs (γ-aminobutyric acid type A receptors) are pentameric proteins that form Cl^--permeable ion channels activated by the neurotransmitter GABA. Severe neurological disorders, such as epilepsy, Alzheimer's disease, Parkinson's disease, stroke and multiple sclerosis, are suggested to involve alterations in the function of synaptic $GABA_A$R. They participate in two types of inhibitory control: transient activation of synaptic $GABA_A$Rs is responsible for conventional phasic inhibition, and the continuous activation of extrasynaptic $GABA_A$Rs can generate a form of tonic inhibition. Thus the positive allosteric modulators of $GABA_A$R have sedative hypnotic, anticonvulsant, and anxiolytic effects. In recent years, much attention has been given to the production of novel alternate scaffolds for $GABA_A$R modulation through 'scaffold hopping' exercises to suggest novel structures de novo [1].

In the present study, we purported the rational design of a novel $GABA_A$R modulator core containing a central imidazo[2.1-b]benzothiazoles scaffold in which appropriate substitution would further challenge the liganding behavior of this therapeutically relevant target. A facile route to the desired imidazo[2.1-b]benzothiazole scaffold proceeded *via* tandem copper-catalyzed *5-exo dig* condensation of acetylenes with Schiff bases derived from 2-aminobenzothiazoles and aromatic aldehydes [2,3]. These compounds have demonstrated competitive $GABA_A$R benzodiazepine (BDZ) site binding and exhibit anxiolytic potency.



IC_{50} = 32 nM IC_{50} = 6 nM

Screening of imidazo[2.1-b]benzothiazoles affinity for BDZ binding site of $GABA_A$R using competitive radioligand binding studies reviled high-affinity interactions (IC_{50} 10-2000 nM) comparable with zolpidem reference drug (IC_{50} 32nM). Using conventional whole-cell patch clamp techniques we have studied the effect of imidazo[2.1-b]benzothiazoles on $GABA_A$R channels in acutely isolated Purkinje neurons from rat cerebellum. Anxiolytic-like effects *in vivo* and low toxicity were estimated using zebrafish (Danio rerio) model.[4]

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GAMMA-CARBOLINE DELAYS DEBUT OF SYMPTOMATIC STAGE OF FUS-PROTEINOPATHY AND INHIBITS NEURODEGENERATIVE PROCESSES IN TRANSGENIC MODEL OF AMYOTROPHIC LATERAL SCLEROSIS

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Aggregation of specific proteins is a key molecular event in pathogenesis of neurodegenerative diseases known as proteinopathies. Various products of this pathological aggregation cause neuronal dysfunction and inevitable cell death. Prevention of protein aggregation at initial stages of this multistep process is seen as an important therapeutic hallmark for intervention into pathogenesis of proteinopathies. We used a transgenic mouse model of proteinopathy with the overexpression of the aberrant isoform of FUS protein which is found to play a causal role in Amyotrophic Lateral Sclerosis and Frontotemporal degeneration. The developed transgenic mouse model is characterized by the formation of neuronal inclusions in the spinal cord and brains that are similar to the human disease states [1]. These transgenic mice were used in this work to study the neuroprotective effect of the gamma-carboline group on the progression of the model neurodegenerative process. It was previously shown that Dimebon is able to decelerate the progression of other model proteopathies [2-3]. We also found that Dimebon exhibits a geroprotective effect in the experiments with C57BL/6 mice. For this reason, Dimebon was selected as the basic compound in the series of gamma-carbolines series for testing in the FUSopathy model. Transgenic Thy-1/FUS animals were treated with Dimebon at dose of 11 mg/kg in drinking water. Chronic treatments started at the age of 35 days which was before the registered onset of the pathological symptoms (90 days). A statistically significant increase (29% higher) in the mean lifespan of the mice treated with the drug was observed in the experimental group compared to the untreated transgenic control animals [4]. Dimebon administration also statistically significantly delayed the debut of clinical symptoms manifestation of the neurodegenerative process in transgenic animals. Moreover, chronic treatments prevented overall weight loss which was a characteristic feature of the undertreated controls. Yet, the dynamics of eventual symptoms even in Dimebon treated animals were similar to the control group. Thus, our study suggests that chronic administration of Dimebon significantly prolongs the pre-symptomatic stage of FUS-proteinopathy in mice postponing the debut of clinical symptoms but not affecting the symptomatic stages of the pathology. It is likely that Dimebon decelerates the progression of the neurodegenerative process that is accompanied by the death of motor neurons in the model FUS-proteinopathy. The study was carried out with the support of the Russian Scientific Foundation (RSF) grant No. 14-23-00160П.

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A ROLE OF POSITIONING OF THE PHARMACOPHORE CARBOXAMIDE GROUP IN ANTITUMOR PROPERTIES OF ANTHRAFURANDIONES

Yu.L. Volodina [1], L.G. Dezhenkova[2], A.S. Tikhomirov [2], D.N. Kaluzhny[3], V.B. Tsvetkov [4], A.E. Shchekotikhin[2], A.A. Shtil[1]

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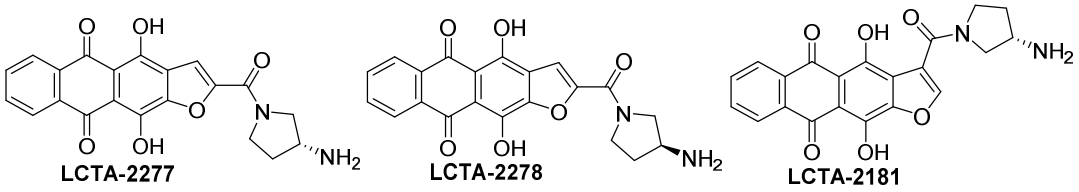
Anthraquinones are a perspective class of antitumor drugs. Previously we have synthesized a series of anthrafuran-3-carboxamides and demonstrated their ability to inhibit tumor cell proliferation and induce death in parental and drug resistant cells including those that express P-glycoprotein or a non-functional p53 [1]. Eventually the new derivatives of anthrafuran-2- and -3-carboxamides have been obtained from the respective anthrafuran-2- and -3-carbonic acids [2,3].



The majority of new anthrafuran-3-carboxamides (e.g., **LCTA-2181**) were potent in a panel of tumor cell lines including resistant variants (IC_{50}=0.4-9.2 μM). Compound **LCTA-2181** (in which the carboxamide moiety is in the position 3) caused cell cycle arrest in S and G2 phases. This agent can bind to the duplex DNA but weakly attenuated topoisomerase 1 (Top1) at 0.5-10 μM. In contrast, (*R*)- and (*S*)-isomeric anthrafuran -2-carboxamides **LCTA-2277** and **LCTA-2278** with the carboxamide moiety at the position 2 were cytotoxic only for suspension cells at micromolar or submicromolar concentrations whereas the adherent cell lines werevirtually insensitive(IC_{50}>50 μM). Both isomers triggered a G1 arrest. **LCTA-2277** and **LCTA-2278** were more potent Top1 inhibitors although their affinity to DNA was less pronounced. Stereochemical difference played no role in these characteristics. This set of data should be considered for SAR analysis of antitumor anthrafuran-2- and -3-carboxamides.

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EVALUATION OF HEPATOPROTECTIVE AND ANTIOXIDATIVE ACTIVITY OF THE XYMEDONE DERIVATIVE WITH ASCORBIC ACID

A. Vyshtakalyuk [1], V. Semenov [1,2], I. Sudakov [1,2], A. Parfenov [1,2], N. Nazarov [1,3], L. Gumarova [1], D. Kondrashina [1], I. Galyametdinova [1], V. Zobov [1,4]

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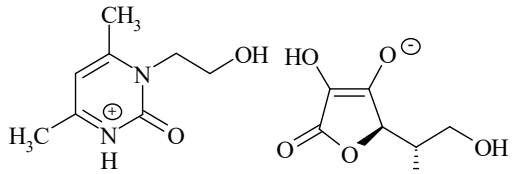
The series of pyrimidine derivatives that are compounds like salts were created in the studies on modification of the active substance of Xymedon remedy. They are conjugates of two fragments, one of the fragment is Xymedone and other is metabolic agent. It was shown the derivative of Xymedone with ascorbic acid (derivative (I)) possesses the highest hepatoprotective activity in comparison with other derivatives of pyrimidine. Its formula is shown in the figure:



(1)

Under action of derivative (I) the survival increased and structural morphological injuring of liver decreased in rats that were subjected to the toxic influence of carbon tetrachloride. The advantages of derivative (I) in comparison with Xymedone and Thiotriazoline preparations were shown.

In results of the study of antioxidative properties of the derivative (I), Xymedone and ascorbic acid by method of luminol chemiluminescence on the LUM-100 device was shown the Xymedone molecule doesn't possess of anti-radical properties. In contrast Xymedone the derivative (I) has ability to inhibit free radicals same as ascorbic acid. In comparison with ascorbic acid the derivative (I) shows a less pronounced pro-oxidant properties.

This study was supported by the Russian Science Foundation, project № 14-50-00014.

DEVELOPMENT AND TESTING OF A METHOD FOR EVALUATION THE DRUGS BELONGING TO SUBSTRATES, INDUCERS AND INHIBITORS OF THE TRANSPORTER P-GLYCOPROTEIN

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P-Glycoprotein (Pgp, ABCB1-protein) is an efflux transporter that plays an important role in the pharmacokinetics of drugs (Ds), which are its substrates, and the resistance of tumor cells to chemotherapy [1]. The FDA and EMA recommend that all new Ds be tested for belonging to Pgp substrates, inducers and inhibitors. The aim of the study was to develop a method for assessing the affinity of Ds for Pgp substrates, inducers and inhibitors in an in vivo experiment, in the example of mexidol, afobazole and noopept. Materials and methods. The work was performed on male chinchilla rabbits weighing 3000 ± 300 g. The belonging of test drugs to Pgp substrates was assessed by their pharmacokinetics before and after administration of Pgp inducer (rifampicin per os 20 mg/kg 14 days) and Pgp inhibitor (verapamil per os 80 mg/kg for 14 days). The affiliation of mexidol, afobazole and noopept to inhibitors/inducers of Pgp was determined by their effect on the pharmacokinetics of the marker Pgp substrate - fexofenadine (per os 67,5 mg/kg). The concentration of test substances and fexofenadine was determined by HPLC with UV detection. Results. It has been established that mexidol, afobazole and noopept are not substrates of Pgp, because their pharmacokinetics do not change after verapamil and rifampicin introduction. Noopept introduction (per os at a dose of 10 mg/kg 3 times a day for 14 days) did not affect the pharmacokinetics of fexofenadine, indicating that noopept does not affect Pgp activity. Mexidol administration (per os at a dose of 50 mg/kg 3 times a day for 10 days) caused an increase in C_{max} of fexofenadine by 47,0%, AUC_{0-24} by 86,5% ($p<0,05$), which characterizes mexidol as an inhibitor of Pgp. Afobazole administration (per os at a dose of 3,8 mg/kg 3 times a day for 14 days) was accompanied by an increase in AUC_{0-24} fexofenadine by 105,1% and a decrease in its total clearance by 56,8% ($p<0,05$), which indicates the inhibition of Pgp Conclusions. In vivo method for evaluation of drugs belonging to Pgp substrates, inducers and inhibitors has been developed and tested. The method is relevant for the search for new molecules of Pgp inhibitors. It has been shown that mexidol and afobazole are Pgp inhibitors, noopept does not affect its activity.

This work was supported by the Russian Foundation for Basic Research (project 16-44-620292 p_a).

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6-METHYLURACIL DERIVATIVES AS DUAL BINDING SITE ACETYL-CHOLINESTERASE INHIBITORS FOR ALZHEIMER DISEASE TREATMENT

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Alzheimer's disease (AD) is an age-related neurodegenerative disorder that is characterized by deterioration of higher cognitive functions and deficits in hippocampal-dependent spatial memory [1, 2]. The brain of AD patients exhibits extracellular plaques of aggregated β-amyloid protein (Aβ) and intracellular neurofibrillary tangles [3, 4]. Currently all approaches for treatments of AD are nosotropic and focus on the inhibition of brain acetyl-cholinesterase (AChE) [5]. It is important to emphasize that AChE itself promotes the formation of Aβ plaques in the cerebral cortex of transgenic mouse models of AD [6]. This property of AChE results from interaction between Aβ and the peripheral anionic site of the enzyme (PAS) [7]. Thus dual inhibitors of both catalytic active site (CAS) and PAS can simultaneously improve cognition and slow down the rate of Aβ plaque formation and can be a promising multifunctional drug candidate for AD.

In previous work we determined the effective dose (5 mg/kg, i.p.) of compound 3d (6-methyluracil derivative), that improved memory and significantly reduced the number and area of Aβ plaques in the brain of APP/PS1 transgenic mice [8]. Thus research objective is to check whether PAS inhibitors based on 6-methyluracil derivatives slow the progression of the disease by reducing the amount of Aβ deposits. In our experiments we work with APP/PS1 mice model. Mice were assigned to 4 groups including transgenic mice treated with compound 3d(5 mg/kg, i.p.), donepezil(0.75 mg/kg, i.p.), or water, and wild-type (WT) mice as positive control. Mice were injected once a day for a total of 18 successive days. After 18 days treatment was discontinued and behavior test was conducted. To evaluate memory performance mice were tested in the T-maze [9]. On each of 14 training days mice were given 6 pairs of training trials. The criterion for a mouse having learned the rewarded alternation task was 3 consecutive days of at least 5 correct responses out of the 6 free trials. Compound 3d (5 mg/kg, i.p.) treatment significantly improved the percentage of reaching behavioral criterion in T-maze task, whereas donepezil treatment (0.75 mg/kg, i.p.) did not rescue this parameter. After experiments in T-maze, a histological study of the cerebral cortex was performed. Compound 3d injections significantly reduced percentage of summary area and number of β-amyloid peptide deposits visualized in sections of cerebral cortex in APP/PS1 mice. Amount of amyloid aggregates in group treated with compound 3d was 46% less than in transgenic mice control group, whereas in group of mice treated with donepezil, the amount of amyloid aggregates was only 16% less than in control.

Thus, the use of AChE inhibitors whose binding sites include both peripheral anionic site and catalytic active site appears to be promising agents for increasing the efficacy of AD therapy by slowing the progression of the disease.

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Poster session №2

SYNTHESIS AND STEREOCHEMISTRY OF NATURAL PHAEOSPHAERIDES A AND B DERIVATIVES

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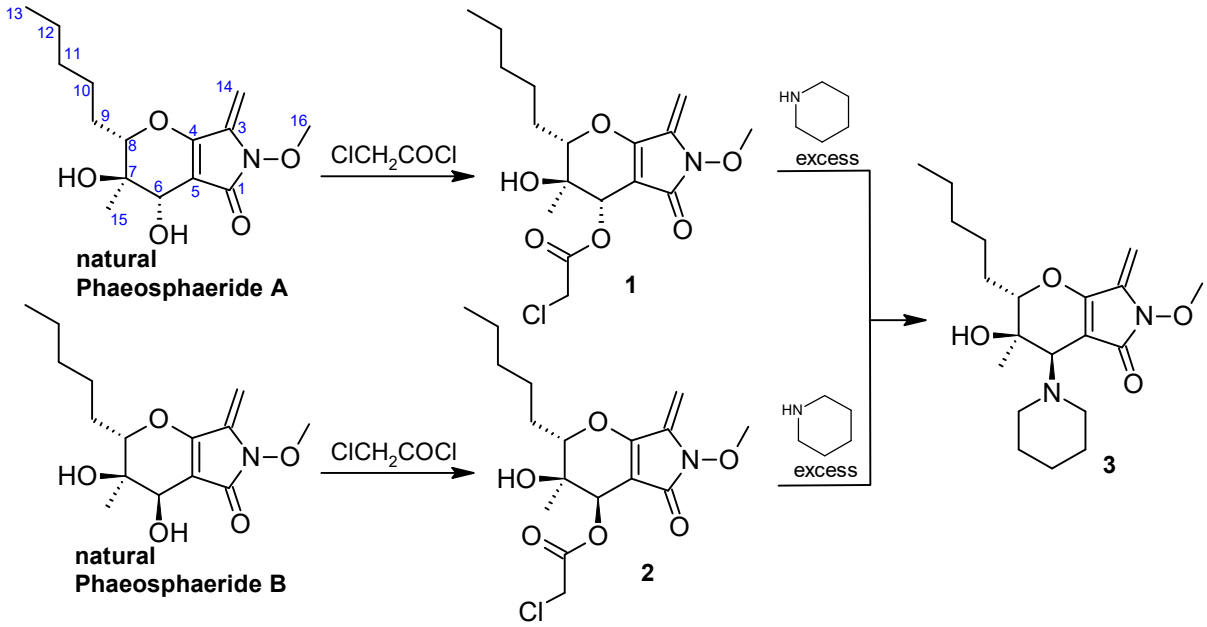
Phaeosphaeride A (PPA) is a natural potent inhibitor of STAT3/DNA binding with an IC50 of 0.61 mM, while exhibiting promising cell growth inhibition in STAT3-dependent U266 multiple myeloma cells with an EC50 of 6.7 μM [1]. Previously, we synthesized a series of PPA derivatives and evaluated the influence of the structural fragments in the molecules of PPA and its derivatives on cytotoxic activity [2, 3]. Our research highlighted the functionalization of PPA at the C-6 atom as an effective way to optimize the biological activity of phaeosphaeride A. The C-6 acyloxy derivative 1 exhibited more potent cytotoxicity (EC50 = 33 ± 7 μM) against A549 cancer cells than natural phaeosphaeride A (EC50 = 46 ± 5 μM).



Herein the synthesis and stereochemistry of new phaeosphaerides A and B derivatives will be discussed.

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SYNTHESIS OF CONJUGATES OF PSMA LIGANDS WITH PACLITAXEL AND BIOLOGICAL TESTING

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Prostate cancer (PC) is the most prevalent malignancy spread widely among men and the second leading cause of cancer-related death [1]. Despite a wide range of approaches to treatment, none of them does not effectively treat metastatic tumors. Also these methods show various undesirable side effects. Targeted drug delivery can be one of possible solutions. Prostate specific membrane antigen (PSMA) is an established prostate cancer marker and has been considered as a biological target for anti-PC drug delivery. The protein was found to be overexpressed in PC cell and their metastases more than 10000 times. There are several small molecules, that selectively bind with PSMA [2,3].

In the present work conjugates with PSMA selective ligands and anti-tumor drug Paclitaxel were synthetized and characterized. Compounds were consist of three fragments, one of them provided selective binding to PSMA (vector). This fragment binds with active molecule (paclitaxel) via carbon linker, which provides release of drug inside cell. Length of linker varied from 5 to 10 carbon atoms. Vector and linker were connected through amide or ureide junction.

All synthetized compounds was characterized by ^{1}H and ^{13}C NMR spectroscopy. Purity of conjugates was controlled with HPLC/MS. Also conjugates were tested *in vitro* and *in vivo*.

Five conjugates were synthetized. In vitro and in vivo tests were performed on prostate cancer cell lines LNCaP (PSMA +), 22Rv1 (PSMA +) and PC3 (PSMA -). Conjugates with amide junction showed toxicity close to paclitaxel, but low selectivity to PSMA-expressing cells. Conjugate with amide bond and 5-atom carbon linker was tested in vivo. This compound showed ability to inhibit growth of tumor comparable to original drug.

As a result of present work five conjugates were synthetized. Their structure was approved through NMR ^{1}H and ^{13}C spectroscopy, high resolution mass spectrometry. Purity of compounds was confirmed by HPLC/MS. In vitro and in vivo testing was performed.

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SYNTHESIS AND PROMISING ANTI-DIABETIC PROPERTIES OF 2-PHENYLCHROMANE-7-DITHIOACETALS

Edward E. Korshin [1], Naomi Rozentul [1], Yosef Avrahami [2], Moran Shubely [1],Guy Cohen [2],Erol Cerasi [3], Shlomo Sasson [2], and Arie Gruzman [1]

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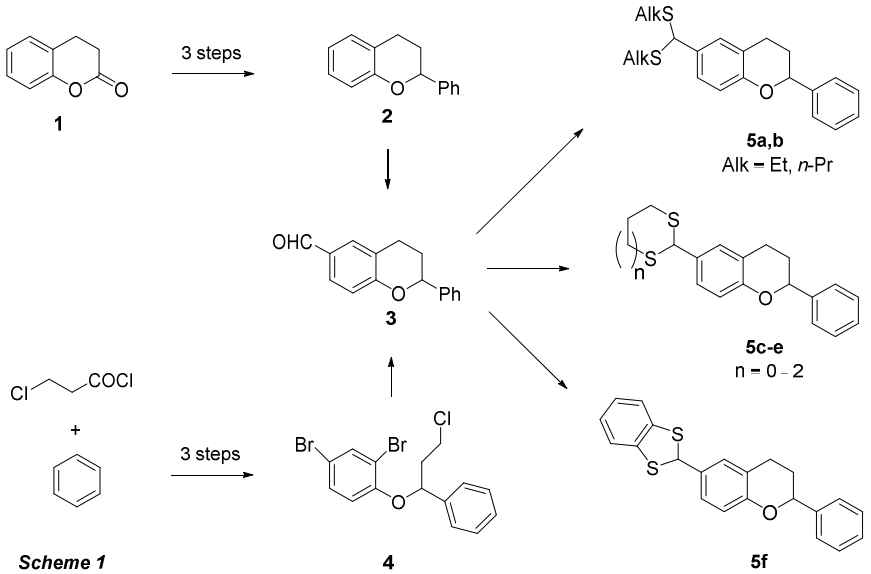
The etiology of type 2 diabetes is associated with the development of insulin resistance, characterized by inability of peripheral tissues (*e.g.*, skeletal muscles) to utilize glucose effectively. The resulting hyperglycemia promotes the damage by further down-regulation the glucose transport and utilization. Insulin-independent diabetes mellitus has reached almost pandemic level and a number of type 2 diabetic patients is expected to increase dramatically in the nearest future. Nevertheless, in spite of enormous efforts toward development of efficient antihyperglycemic chemotherapy, generally applicable, potent and non-expensive drugs against type 2 diabetes are still lacking. We report the synthesis and promising *in vitro* antihyperglycemic potency of novel 2-phenylchromane-7-dithioacetals **5**. The dithioacetals **5** were prepared by Me_3SiCl-catalyzed condensation of the aldehyde **3** with thiols or dithiols (Scheme 1). The aldehyde **3** was synthesized in 4 steps from either dihydrocoumarin **1** or from benzene and β-chloropropionyl chloride. The most potent cyclic dithioacetal **5e** (n = 2) significantly increased the rate of glucose uptake in L6 myotubes and insulin secretion in INS-1E cells via activation of the LKB1-AMPK pathway.



Scheme 1

3-NITROPYRIMIDO[1,2-*A*]BENZIMIDAZOLES: SYNTHESIS AND PROPERTIES

V.V. Fedotov [1], E.N. Ulomsky [1], K.V. Savateev [1], R.A. Drokin [1], D.N. Lyapustin [1], V.L. Rusinov [1].

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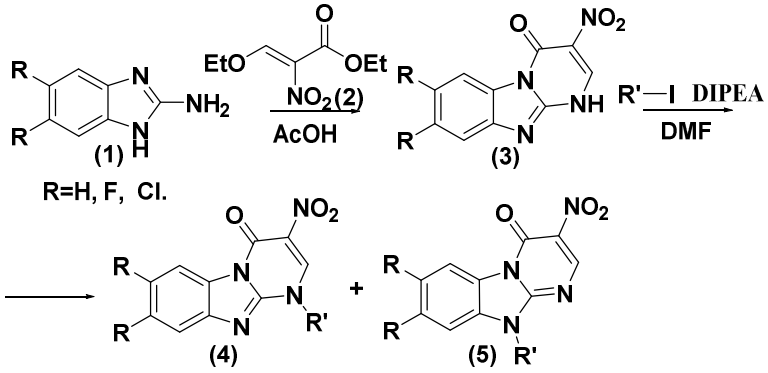
Synthesis of heterocyclic compounds close in structure to natural purines has traditionally attracted interest from the point of view of searching for inhibitors of natural purine nucleoside receptors - adenosine, guanosine. Promising representatives of this class of compounds are pyrimido [1,2-a]benzimidazoles that are structurally related both to benzimidazoles and azolo[1,5-a] pyrimidines. The intercalating ability of pyrimido[1,2-a]benzimidazoles with respect to DNA molecules is associated with the structural similarity to quinolones, because the studied compounds represent stretched-out analogs of quinolones. The relevance of the synthesis of pyrimido [1,2-a] benzimidazoles is also due to the wide representability of arenoimidazole and azoloazine compounds in medical practice.



A synthesis method for the preparation of pyrimido [1,2-a] benzimidazoles (3) was developed that involves condensation of components (1) and (2) in acetic acid. In contrast to the precedents described in the literature, we found that the initial pyrimidobenzimidazoles (3) react with alkyl iodides in DMF with the formation of two regioisomers in the presence of DIPEA. The N1-alkylation products (4) prevailed in all cases (60%). The content of N10 regioisomer decreased sharply (10%) due to the spatial difficulties when bulky *iso*-propyl iodide was used in this reaction.

We thank Russian Scientific Foundation (grant 16-13-00008) for financial support.

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NOVEL AZOMETHINES WITH ALKYL CHAINS OF VARIOUS LENGTHS

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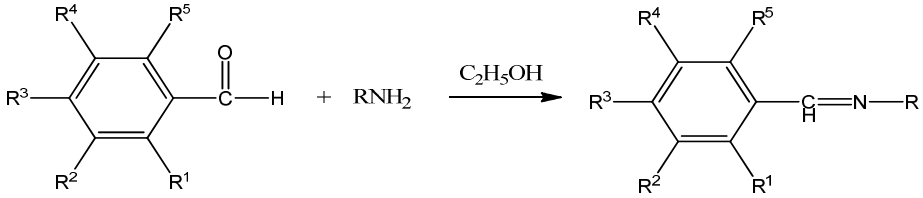
The condensation of do-, tetra-, hexa- and octadecan-1-amines with substituted benzaldehydes yielded a series of Schiff bases in good yields.

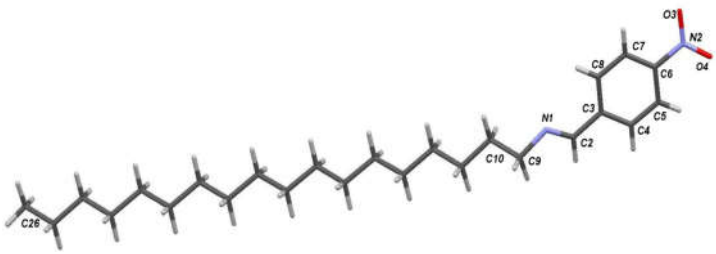


1 20

(1) R = $C_{12}H_{25}$, R^3 = Cl;
(2) R = $C_{12}H_{25}$, R^3 = Br;
(3) R = $C_{12}H_{25}$, R^3 = F;
(4) R = $C_{12}H_{25}$, R^3 = NO_2
(5) R = $C_{16}H_{33}$, R^3 = Cl;
(6) R = $C_{16}H_{33}$, R^3 = Br;
(7) R = $C_{16}H_{33}$, R^3 = F;
(8) R = $C_{16}H_{33}$, R^3 = NO_2
(9) R = $C_{18}H_{37}$, R^3 = Cl;
(10) R = $C_{18}H_{37}$, R^3 = Br;
(11) R = $C_{18}H_{37}$, R^3 = F;
(12) R = $C_{18}H_{37}$, R^3 = NO_2

(13) R = $C_{12}H_{25}$, R^1 = R^2 = OCH_3;
(14) R = $C_{14}H_{29}$, R^1 = R^2 = OCH_3;
(15) R = $C_{16}H_{33}$, R^1 = R^2 = OCH_3;
(16) R = $C_{18}H_{37}$, R^1 = R^2 = OCH_3;
(17) R = $C_{12}H_{25}$, R^1 = OH, R^4 = Br;
(18) R = $C_{14}H_{29}$, R^1 = OH, R^4 = Br;
(19) R = $C_{16}H_{33}$, R^1 = OH; R^4 = Br;
(20) R = $C_{18}H_{37}$, R^1 = OH, R^4 = Br;

New Schiff bases were synthesized and their structures were determined by IR, NMR, TG-DSC and X-ray analysis. The antimicrobial activity was measured. So, it may be concluded from our results that the synthesized compounds are potent nanoantimicrobial agents against pathogenic bacteria and fungi. We have also reported the first crystal structures of these compounds.



Structure of the molecule of 12 in crystal.

This work was funded by the subsidy allocated to Kazan Federal University for the state assignment in the sphere of scientific activities.

HYBRID MICRO CONTAINERS FOR HIGHLY EFFICIENT DELIVERY OF SMALL INTERFERING RNA

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The effectiveness of many biologically active compounds is limited by their low selectivity, bioavailability, limited solubility, etc. There are methods that are used to increase the biological activity of drug compounds, for example, chemical modification allows the introduction of new functional groups into the structures of drug compounds, increasing their bioavailability. In addition, now the methods of targeted delivery based on the use of various carriers (nanocapsules, nanoparticles, liposomes, micelles, etc.) are widely used, with the help of which the delivery of drugs to target cells or organs is carried out. In our studies [1], a high potential of micro-containers obtained using "Layer-by-Layer" technology for targeted delivery of biologically active compounds was demonstrated.

The purpose of this work was to create microcarriers for the delivery of small interfering RNA (siRNA). New hybrid microcontainers with low toxicity, high biocompatibility, ability to protect the encapsulated material from the aggressive external environment were obtained. The resulting microcontainers were characterized by confocal and electron microscopy. *In vitro* studies were conducted on the A549 human lung carcinoma cell line. Also in comparison with other polycationic systems: chitosan, polyethyleneimine, and commercial reagent Lipofectamine 2000 was estimated the delivery capacity of microcontainers.

The work was supported by the Russian Foundation for Basic Research (grant no. 16-33-00966 mol_a).

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REDUCTIVE ACID-CATALYZED REARRANGEMENT OF 3-(2-NITROBENZYL)QUINOXALIN-2(1*H*)ONES – AN EFFICIENT METHOD FOR THE SYNTHESIS OF 2-(INDOL-2-YL)BENZIMIDAZOLES

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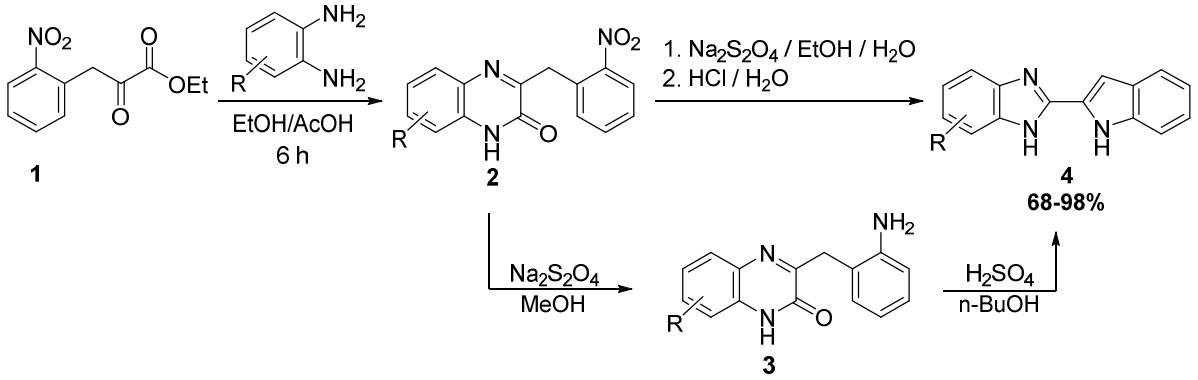
Since biaryl structures that contain an indole nucleus occur in many pharmaceuticals, biologically active compounds, and functional materials, indole–arene cross-coupling reactions have received great attention from synthetic chemists [1]. However, reported protocols generally depend on precious palladium catalysts combined with copper- or silver-based terminal oxidants.

In continuation of our ongoing interest in the green synthesis of indoles [2] and benzimidazoles [3],we have developed an efficient one-pot transition-metal-free method of the synthesis of 2-(indol-2-yl)benzimidazoles from 3-(2-nitrobenzyl)quinoxaline-2(1*H*)-ones. The method is based on the transformation of the 3-(2-aminobenzyl)quinoxalin-2(1*H*)-ones formed *in situ* when exposed to $Na_2S_2O_4$ under reaction conditions. The process involves the Mamedov heterocycle rearrangement as the key step [3].



The method is highly efficient and free from drawbacks. A brief account of our work and its main findings as well as the advantages of this method over the existing synthetic routes is discussed in this report.

This work was financially supported by the Russian Science Foundation (Project No. 14-23-00073-n).

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THIIRANES IN THE SYNTHESIS AND DEVELOPMENT OF INNOVATIVE DRUGS THAT AFFECT THE HEMOSTASIS SYSTEM

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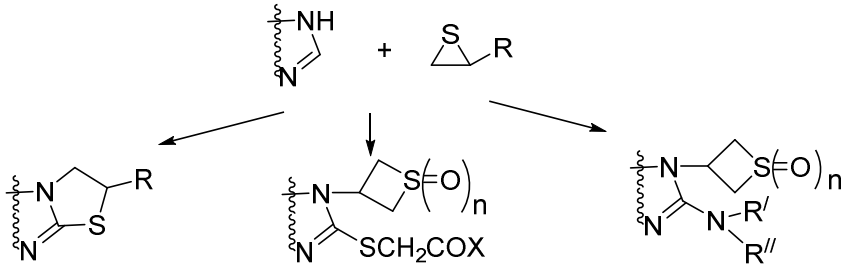
Cardiovascular disease and stroke are major causes of morbidity and mortality. Although many factors contribute to the development of cardiovascular disease, thrombus formation is the main trigger event in acute coronary syndrome and stroke. Therefore, an intense research activity is devoted to drugs showing antiaggregatory potency. The thiiranes are very reactive and promising for the development of innovative drugs for correcting the hemostasis violations [1].

Investigation of the reactions of thiiranes with nitrogen-containing heterocycles (xanthines, 1,2,4-triazoles, imidazoles and benzimidazoles) and study of the biological activity of more than 1500 synthesized compounds have shown their ability to effect on the hemostatic system [2-4] and have antiplatelet effect comparable to or greater than those effect of tirofiban and eptifibatide.



Thus, the products of reaction of thiiranes with azoles are promising for the development of innovative drugs with antiaggregant activity.

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5-[BROMO(*O*-NITROPHENYL)METHYL]-2,2-DIMETHYL-1,3-OXAZOLIDIN-4-ONE ON THE WAY TO INDOLE-2-CARBOXYLIC ACID DERIVATIVES

G.Z. Khikmatova[1,2], V.L. Mamedova[2], D.E. Korshin[1,2], and V.A. Mamedov[1,2]

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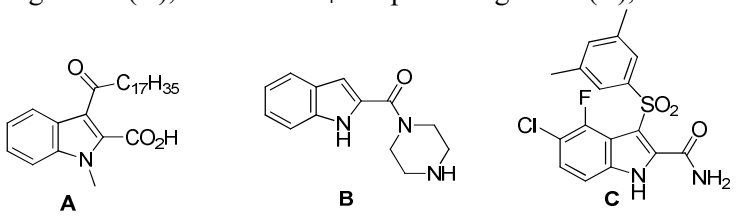
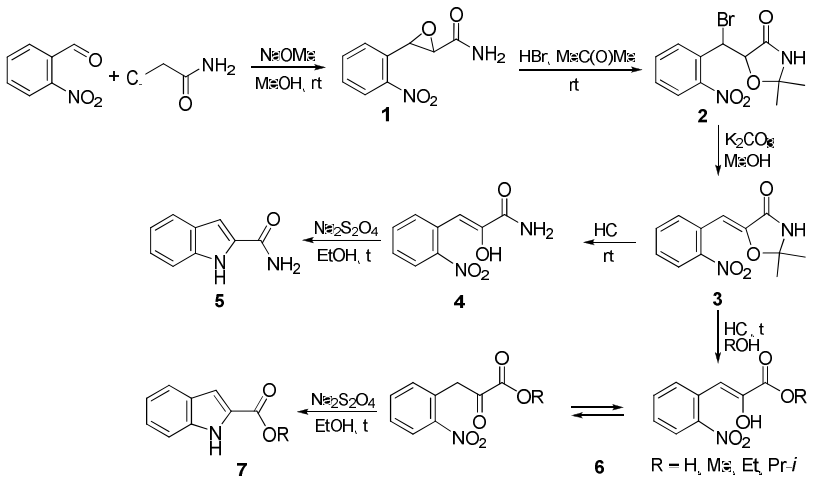
Indole-2-carboxylic acid derivatives display a wide range of biological functions such as cytosolic phospholipase A_2 (cPLA$_2$) ingibition (**A**), histamine H_4 receptor antagonism (**B**), HIV-1 ingibition (**C**) [1].



Although the significance of this class of compounds is obvious, the synthesis of indole-2-carboxylic acid derivatives has surprisingly, remained largely unexplored. The main limitation of the known methods is the impossibility of their use in the synthesis of indole-2-carboxylic acid derivatives **1** with no substituent. Such derivatives are very important for the synthesis of parent indoles to which various substituents can then be introduced in various positions.

In this work, the methods of the synthesis of indole-2-carboxylic acid and its derivatives have been developed for the first time by the following reactions:



The approach is based on the use of 5-[bromo(aryl)methyl]-2,2-dimethyl-1,3-oxazolidin-4-ones easily available from 3-aryl-2,3-epoxypropionamides, which are, in their turn, obtained under mild conditions with the help of Darzens condensation [2].

This work was financially supported by the Russian Science Foundation (Project No. 14-23-00073).

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SYNTHESIS OF LUPANE TRITERPENOID−AMINO ACID−CYCLIC B-TRIKETONE HYBRIDS

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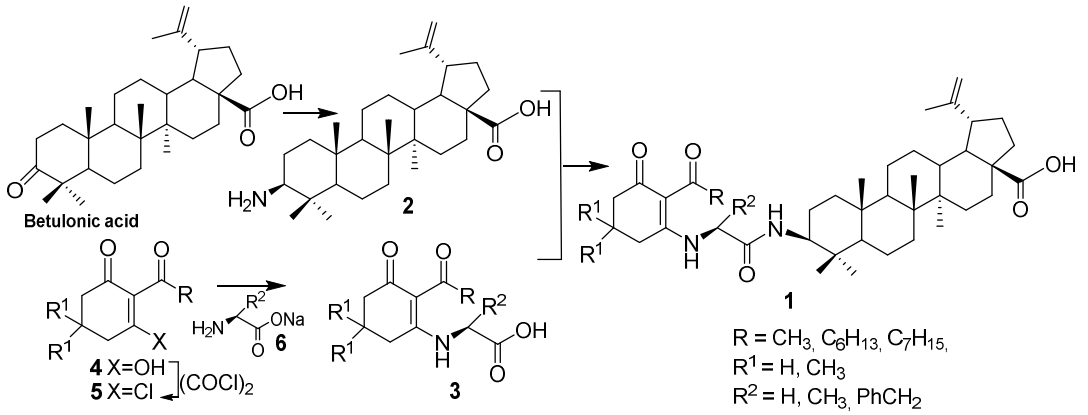
The hybridization of bioactive natural and unnatural compounds is one of the most promising and fundamentally novel approaches for the design of new leading structures and the discovery of new and potent drugs in the field of medicinal chemistry [1]. Pentacyclic triterpenoids such as betulonic acid, betulinic acid and their derivatives attract much attention due to high medical efficiency including anticancer, anti-inflammatory, anti-HIV and other activities [2]. Reports have shown that the introduction of amino acid or dipeptide to triterpenes could improve selective cytotoxicity as well as water solubility [3]. A structural fragment of cyclic β-triketons is found as a part of many biologically active compounds produced by various plants, insects and microorganisms [4].



A protocol for the synthesis of novel lupane triterpenoid−amino acid−cyclic β-triketone hybrids **1** has been developed. The synthetic pathway includes transformation of betulonic acid by reductive amination into 3β-amino-3-desoxybetulinic acid **2**. For the first time a series of hybrids **1** have been synthesized *via* an condensation of corresponding natural amino acid (glycine, L-alanine, L-phenylalanine) derivatives of triketones **3** with acid **2** under an action of DCC in the presence of DMAP in THF in 50−65% yield. Enamines **3** were prepared by an interaction of chloride **5** with corresponding amino acid sodium salt **6** in methanol in 65−78% yield.

This work was supported by the Belarussian Foundation for Fundamental Research (grant X15CO-001, X16K-037).

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NEW SYNTHESIS OF THIETHANE DERIVATIVES WITH ANTIDEPRESSANT ACTIVITY

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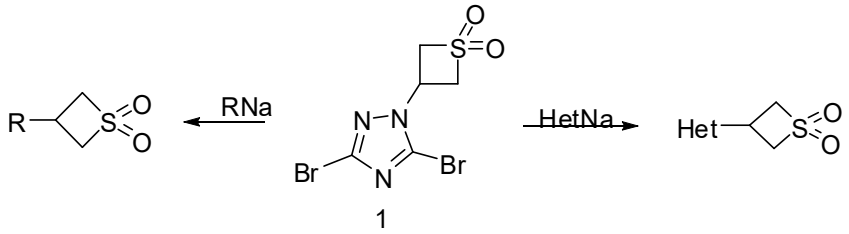
According to WHO predictions, depression will by 2030 be the leading cause of the burden of diseases in the world. Therefore, development of innovative medicines for treatment psychiatric disorders is crucial. In this respect, thietane derivatives that exhibit antidepressant activity are promising for design «first in class» drag candidate for the treatment of depressive disorders [1-3]. However, a broad study of compounds of this class is limited because of their unavailability.

We proposed a new one-stage method of synthesis of 3-substituted thietane 1,1-dioxides based on 3,5-dibromo-1-(1,1-dioxothietanyl-3)-1,2,4-triazole (1) as dioxothietanylation reagent [4]. 3-Alkoxy-, 3-aryloxy-, 3-alkyithio-, 3-phenylthio- and 3-azolylthietane 1,1-dioxides are formed in good yields.



1

R = OAlk, OAr, SAlk, SAr,
Het = 1,2,4-triazolyl, imidazolyl, benzimidazolyl, xanthinyl

Antidepressant activity of 3-substituted thietane 1,1-dioxides was assessed in psychopharmacological tests. It was found that some synthesized compounds exhibited significant antidepressant activity greater than those of the traditional antidepressants (fluoxetine, imipramine) and have low toxicity.

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SIMPLE SYNTHESIS OF 3-HYDROXYQUINOLINES AND THEIR TRANSFORMATION

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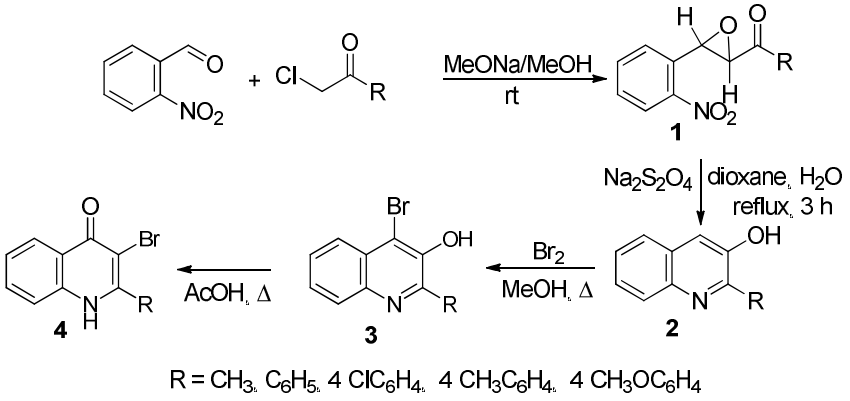
Quinolines are widely found in natural products[1] and broadly used in medicinal chemistry[2] among them, 3-hydroxyquinolines (quinolin-3-ols) are of extreme importance. Although the significance of this class of compounds is obvious, only a few methods have been reported.[3] The main limitation of these methods is the impossibility of their use in the synthesis of 3-hydroxyquinolin-2(1*H*)-one derivatives with no substituent in position 4. Such derivatives are very important for the synthesis of 3-hydroxyquinolines to which various substituents can then be introduced in this position.

Herein, an efficient sodium dithionite ($Na_2S_2O_4$) mediated method for construction of 3-hydroxyquinolines **2** via *in situ* Meinwald rearrangement/intramolecular reductive cyclization of *o*-nitrobenzalacetophenone oxides **1** has been developed.

Further manipulations resulted in 3-bromoquinoline-4-ones **4**, representatives of the class with a broad spectrum of biological activity.[4]



This work was financially supported by the Russian Science Foundation (Project No. 14-23-00073-p).

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SYNTHESIS OF NEW ANALOGUES OF NEUROTROPIC PREPARATION «PHOSENAZID»

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One of the representatives of phosphorylated carboxylic acids hydrazides, which possess significant action on central nervous system is diphenylphosphinylacetic acid hydrazide named «phosenazid». They basically differed one from another by the substituents at P(IV). It was established by studying «structure – biological activity» dependence that phosphoryl and unsubstituted hydrazide groups are responsible for exhibiting neurotropic properties. Changing link structure connecting these groups (spacer) we suggest new general formula for «phosenazid» and its analogues. It considerably expands range of synthesizing substances for searching compounds possessing neurotropic activity.

$$R_2P(O)(CHX)_n(C_6H_4)_mCONHNH_2$$
$$X = H, R_2P(O), OR;\ n = 0, 1, 2;\ m = 0, 1$$

New «phosenazid» analogues were synthesized on following schemes:

$$4\text{-}Br_2CHC_6H_4CHBr_2 \xrightarrow[ZnCl_2]{HC(OMe)_3} 4\text{-}Br_2CHC_6H_4CHO \xrightarrow[H^+]{HC(OMe)_3} 4\text{-}Br_2CHC_6H_4CH(OMe)_2 \longrightarrow$$

$$\xrightarrow[reflux]{NBS,\ h\nu} 4\text{-}Br_2CHC_6H_4COOMe \xrightarrow[ZnCl_2]{2HC(OMe)_3} 4\text{-}(MeO)_2CHC_6H_4COOMe \xrightarrow{R_2PCl} \longrightarrow$$

$$\longrightarrow 4\text{-}[R_2P(O)CH(OMe)]C_6H_4COOMe \xrightarrow[\Delta]{H_2NNH_2 \cdot H_2O} 4\text{-}[R_2P(O)CH(OMe)]C_6H_4CONHNH_2$$

R = Et, Ph

$$Et_2P(O)COOMe \xrightarrow{H_2NNH_2 \cdot H_2O} Et_2P(O)CONHNH_2$$

Biological activity forecasting on PASS program and determination of toxicity and neurotropic activity of new «phosenazid» analogues are carried out.

The work was made with financial support of the Ministry of education and science of the Russian Federation, performed in the framework of the base part of state assignment in the field of scientific activities on the project № 4.5348.2017/BCh.

SYNTHESIS OF BIS-DICARBOCYANINES ON THE BASIS OF BENZODIPYRROLENINS CONTAINING ALKYLSULFONATE SUBSTITUENTS

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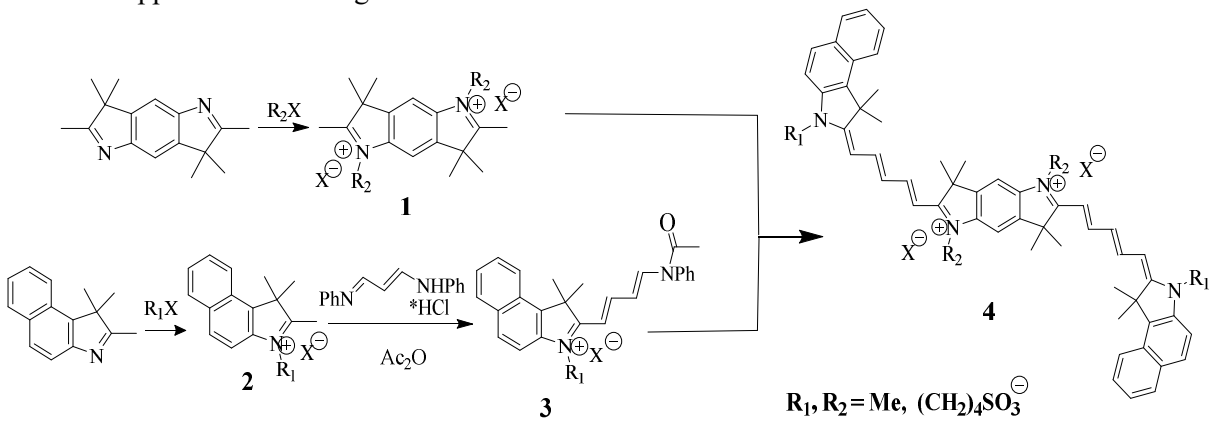
Carbocyanine dyes, due to their ability to effectively bind to transport proteins, can serve as biomarkers. In this connection, one of the promising directions in medicinal chemistry is currently a synthetic design based on carbocyanine fluorophores in order to create structures with given photophysical properties. The main requirements for such structures are a high extinction coefficient and a high quantum yield of fluorescence. The absorption and fluorescence interval in such structures is convenient to change due to the variation of the substituents in the structural fragments.

The least studied in this class of compounds are bichromophores based on benzodipyrrolenin and benzindolenine heterocycles, presented in the literature as several examples containing only methyl substituents at nitrogen atoms [1, 2].

In the framework of this study, a scheme for the synthesis of bis-dicarbocyanines with benzodipyrrolenin scaffold **4** and containing several hydrophilic groups has been developed.

The work was carried out with the financial support of the Grant of the President of the Russian Federation for the state support of the leading scientific schools of the Russian Federation NSh-10268.2016.3.



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A FACILE METHOD FOR THE SYNTHESIS OF BENZIMIDAZOLE-5(6)-CARBOXYLIC ACID DERIVATIVES

M.S. Kadyrova [1,2], N.A. Zhukova [1,2], T.N. Beschastnova [1,2], I.Kh. Rizvanov [1], V.V. Syakaev [1], Sh.K. Latypov [1], O.G. Sinyashin [1,2], and V.A. Mamedov [1,2]

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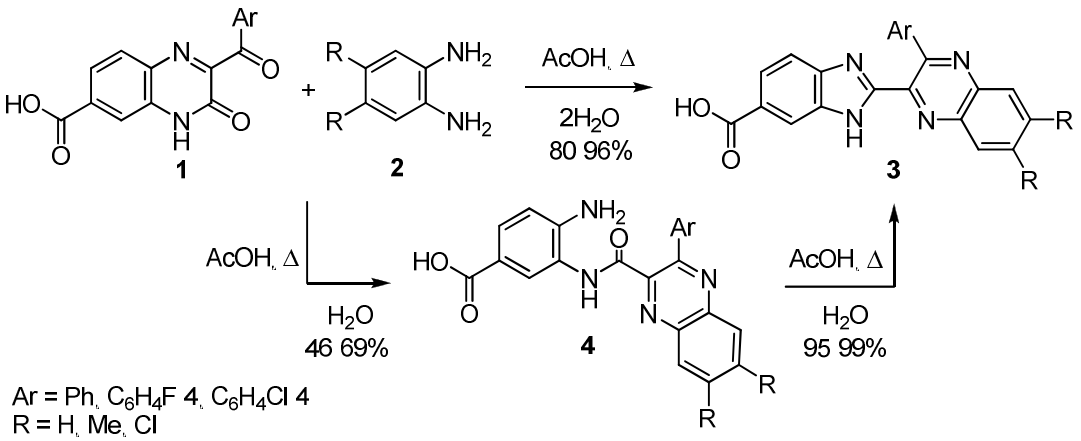
Substituted benzimidazole-5(6)-carboxylic acid and acid derivatives were widely used in the design of antineoplastic, antihypertensive, and antimicrobial agents, hepatitis C virus polymerase inhibitors, inhibitors of kinesin spindle protein (KSP), and nonpeptidic angiotensin II AT1 receptor antagonists. Although the significance of this type of compounds is obvious, the synthesis of substituted benzimidazole-5(6)-carboxylic acid and acid derivatives has surprisingly, remained largely unexplored.
In this work, the methods of the synthesis of substituted benzimidazole-5(6)-carboxylic acid derivatives have been developed for the first time by the following reactions, involving the Mamedov heterocycle rearrangement [1,2] as the key step:



The work was supported by the Russian Scientific Foundation (Grants No. 14-23-00073, 14-23-00073-p).

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SYNTHESIS OF NAPHTHOINDOLE ANALOG OF ANTICANCER ANTHRAFURAN

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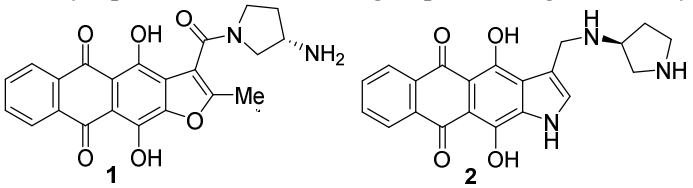
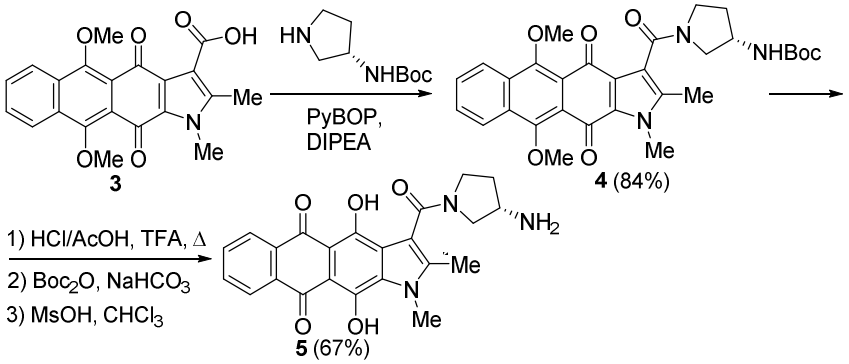
Arene-and hetarene-fused derivatives of anthracene-9,10-dione represent a potent class for the development of new antitumor drugs. Inparticular, anthra[2,3-*b*]furan-3-carboxamide and 3-aminomethylnaphto[2,3-*f*]indoles(e.g.,**1**,**2**,respectively)inhibit topoisomerase 1 and 2, Aurora B kinase,and *invivo* block cancer grown[1,2]. In a continuation of research we synthesize d naphto[2,3-*f*]indole analogue of **1** to estimate an influence of heteroatom and carbonyl spacer of carboxamide group on biological activity.



5,10-Dimethoxy-1,2-dimethylnaphtho[2,3-*f*]indol-3-carboxylic acid **3** [3] was chosen as a starting for required transformation.The coupling of **3** with (*S*)-*N*-Boc-3-aminopyrrolidine in presence of PyBOP led to amide **4**. Cleavage of 5,10-methoxygroups of **4** by treatment with 9% solution of HCl in a mixture of AcOH-TFA accompanied by isomerization into 4,11-dihydroxyderivative. Reaction of crude amide **5** with Boc_2O, a column chromatography followed by treatment with MsOH gave the final naphto[2,3-*f*]indole-3-carboxamide **5**.



Screening of cytotoxic activity revealed that compound **5** inhibited proliferation of L1210 murinel eukemia; lymphoblasticleukemia CEM and human cervical carcinoma HeLa cells at a low micromolar concentration.

«The reported study was funded by RFBR according to the research project № 17-53-45105»

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SPECIFIC FEATURES OF NUCLEOPHILIC SUBSTITUTION IN 4-ALKYLAZOLO[5,1-C] [1,2,4]TRIAZIN-7-ONES

D.N. Lyapustin, E.N. Ulomsky, E.M. Mukhin, E.K. Voinkov, V.V. Fedotov, K.V. Savateev, O.S. Eltsov, E.B. Gorbunov, R.A. Drokin, V.L. Rusinov, O.N. Chupakhin.

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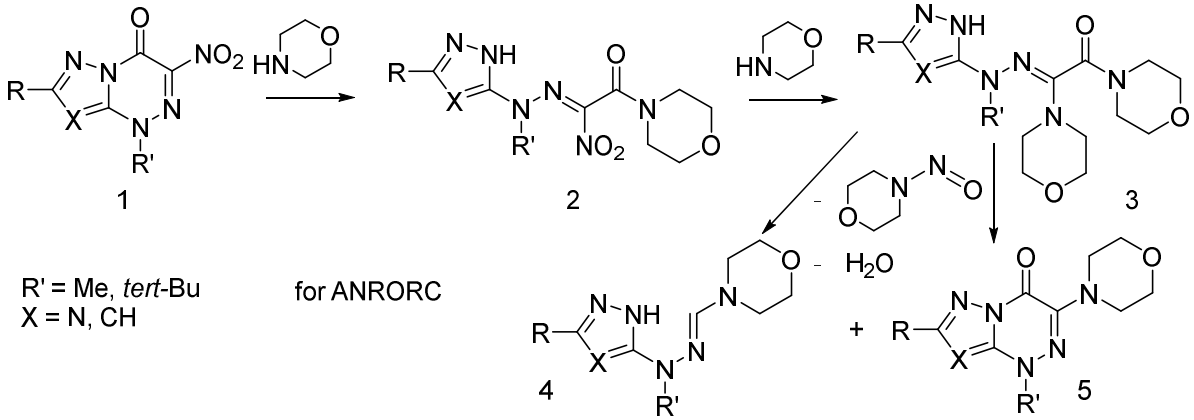
One of factors of topicality of such studies is that the compounds of this group exhibit a wide range of biological effects [1]. The possibility of transformations of such compounds under the action of biogenic nucleophiles is very important from the point of view of their possible transformations in the organism.



The first stage of the nucleophilic substitution in 4-alkyl-6-nitroazolo[5,1-c][1,2,4]triazine-7-ones **1** is an A_N process not at the most obvious center of the *ipso*-attack next to the leaving group, but at the carbonyl moiety with the formation of unstable anionic adducts readily opening into hydrazones **2**. Subsequent transformations of **2** proceed via substitution of the nitro group to form dimorpholinoethanones **3** and their subsequent cyclization to morpholintriazinones **5.** The reason for the appearance of morpholinomethanes **4** is the formation of water and the hydrolysis of amide **10.**

Thus, the nucleophilic substitution of the nitro group in the described series of compounds proceeds not according to the *ipso*-substitution type, but in accordance with the ANRORC mechanism.

The work was carried out with the support of the state task of the Russian Science Foundation grant № 16-13-00008.

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N^1-(2-CARBOXYPHENYL)-N^2-(3-METHYLPHENYL)OXALAMIDES AS VERSATILE REAGENTS IN ORGANIC SYNTHESIS

V.L. Mamedova[1,2], A.T. Gubaidullin[1], T.A. Kushatov[2], G.Z. Khikmatova[1,2], and V.A. Mamedov[1,2]

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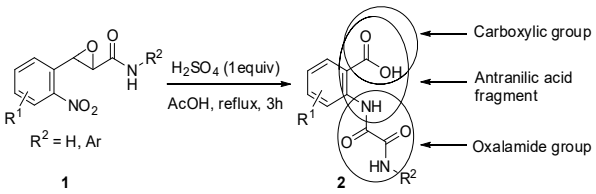
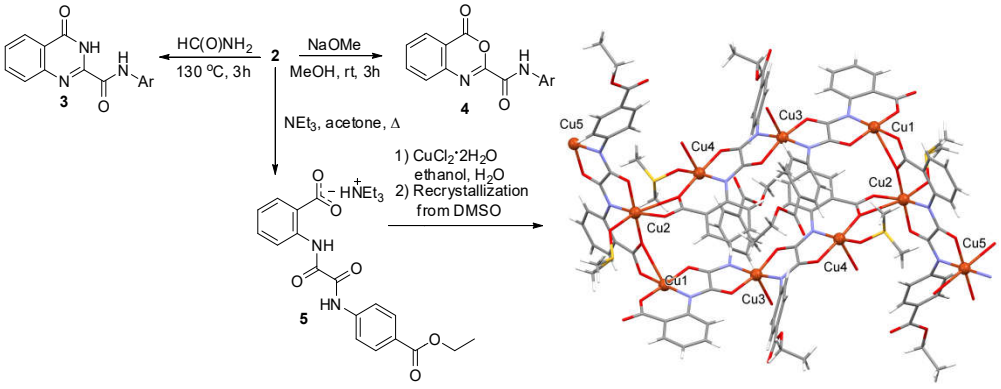
A molecule of N^1-(2-Carboxyphenyl)-N^2-(3-methylphenyl)oxalamide, **2** [1], contains at least three functional groups: a carboxylic acid, an oxalamide moiety and an antranilic acid fragment. Combination of these potential three reaction centers in the molecule results in exceptional reaction diversity and broad synthetic potential of these compounds.



In this work, the methods of the synthesis of quinazolin-4(3*H*)one-2- (**3**) and benzo[d][1,3]oxazin-4-one-2- (**4**) carboxamide derivatives and one new Cu(II) coordination 1D-polymer (**6**) with the formula of $[9Cu{\cdot}6(CarPhPhQxal){\cdot}5DMSO]_n$ based on N^1-(2-carboxyphenyl)-N^2-(aryl)oxalamides (CarPhPhQxal) **2** have been developed by the following reactions:



Single-crystal X-ray analysis shows that compound **6**is triclinic and crystallizes in space group P-1, with a 13.337 (2), b 16.891 (3), c 22.394 (3) A, and α 96.097 (2), β 104.437 (2), γ 105.781 (2), V 4619 (1) A3, Z = 2; Final R = 0.076. The symmetrically independent part of the triclinic unit cell of the complex consists of 4.5 Cu atoms, five DMSO molecules and three CarPhPhQxal molecules. Due to the coordination bonds, centrosymmetric cyclic clusters are formed in the crystal, which are monomeric units of the coordination polymer and consist of 8 Cu atoms (Cu1 – Cu4 in Figure). In such clusters, Cu atoms have a coordination number of 5 or 6, but differ in the type of ligand coordination. Two of Cu atoms are coordinated directly with solvate DMSO molecules. The binding of such clusters to the 1D-polymer is accomplished by one of the copper atoms (Cu5) located in a special position - the center of symmetry.

This work was financially supported by the Russian Science Foundation (Project No. 14-23-00073-p).

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SYNTHESIS, STRUCTURE AND ANTIMICROBIAL ACTIVITY OF NOVEL CARBOXYLATE PHOSPHABETAINES

M. Morozov[1], D. Bakhtiyarov[1], R. Minnullin[1], Kh. Khayarov[1], Yu. Bakhtiyarova[1], M. Shulaeva[2], O. Pozdeev[2], I. Galkina[1]and V. Galkin[1]

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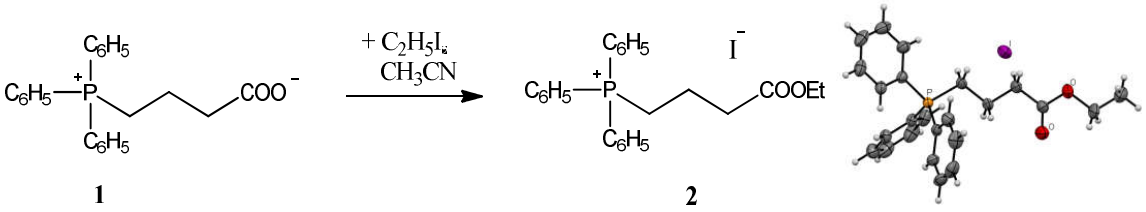
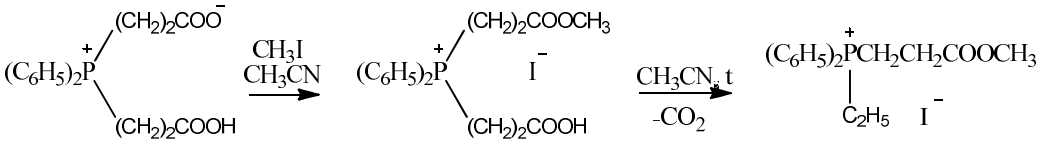
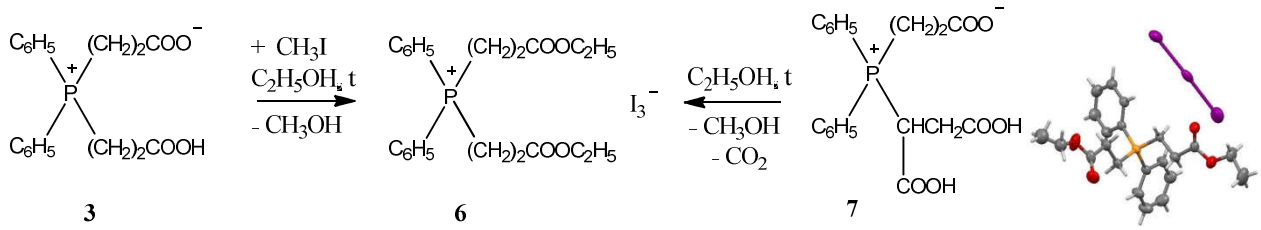
Organic and pharmaceutical chemists are trying to synthesize new drugs with better pharmacokinetic and dynamic properties. In this study we prepared triphenyl-substituted phosphonium salts (**2,4-6**) on the basis of reaction of alkylation by methyl iodide carboxylate phosphabetaine 1 in good yields.



1 **2**



3 **4** **5**



3 **6** **7**

New phosphonium salts were synthesized and their structures were determined by IR, NMR, TG-DSC and X-ray analysis (for compounds **2** and **6**). Microbiological results indicate that the synthesized compounds – phosphonium iodides **2**, **4-6** possess a broad spectrum of activity against the tested pathogenic microorganisms.

This work was funded by the subsidy allocated to Kazan Federal University for the state assignment in the sphere of scientific activities.

TOPOISOMERASE 1 INHIBITORS ON HELIOMYCIN SCAFFOLD

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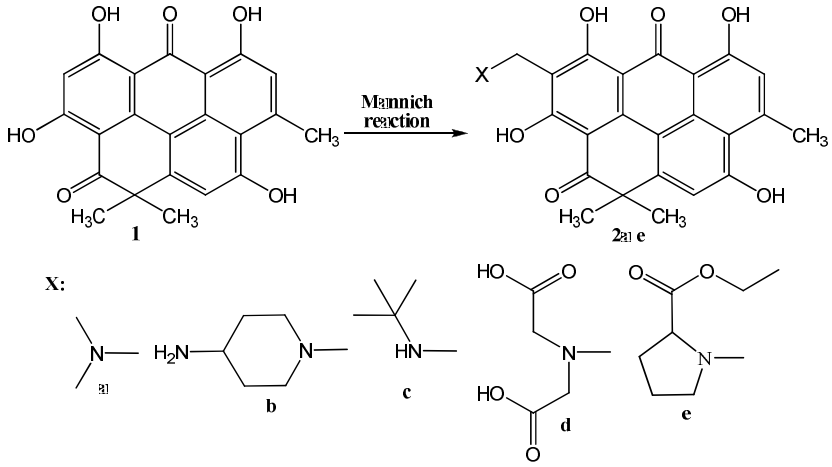
Heliomycin (resistomycin) is an antibiotic, produced by *Streptomyces resistomycificus*, which has antiviral, antibacterial activity and could be useful scaffold for the development of new chemotherapeutic agents [1,2]. Despite the fact that heliomycin has a promising biological activity, there is not any data about their chemical transformations and evaluation of its derivatives. Thereby, the main goal of our study was a development of methods of transformation of heliomycin into new semisynthetic derivatives targeted topoisomerase 1 and evaluation of their biological activity.

So, we have synthesized the new derivatives by Mannich reaction, through the aminomethylation into 4-position of heliomycin **1**. Next, we examined the ability of **1** and its derivatives **2a-e** to inhibit relaxation of supercoiled plasmid DNA by topoisomerase 1. We observed, that **1** had no effect on the relaxation of the plasmid DNA even at 20 μM, while **2a**,**e**,**d**,**b** inhibited the enzyme at concentrations ≤20 μM. Compound **2b** displayed the highest activity, as well as displayed low micromolar IC_{50} against some cancer cell lines in *invitro* tests. Thus, aminomethylation of **1** improved Top1 inhibitory potency and water solubility of this antibiotic.



Scheme. Synthesis of heliomycin derivatives 2a-e.

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SYNTHESIS OF CYCLIC HYDROXAMIC ACIDS, POTENTIAL INHIBITORS OF HISTONE DEACETYLASE

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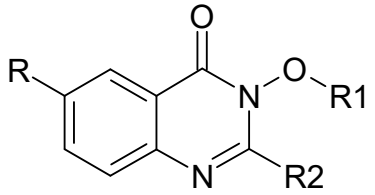
Histone deacetylases (HDACs) are a group of enzymes that remove acetyl groups from histones, regulate the expression of tumor suppressor genes and induce apoptosis, cell cycle arrest, aging, differentiation, immunogenicity of cells and inhibit angiogenesis in certain cancers. Hydroxamic acids exhibit strong chelating properties to metal ions, and therefore can be used as inhibitors of metal-containing enzymes [1]. Among the inhibitors of HDACs, the most important and numerous group are derivatives of hydroxamic acids (Vorinostat, Romidepsin, Belinostat) [2]. The hybrid molecule CUDC-101, created as a multipurpose inhibitor of EGFR, HER2 and HDACs, containing the quinazoline fragment of Lapatinib [3], showed antiproliferative and antitumor activity against a number of tumor models, including those resistant to Lapatinib and Erlotinib, and is in phase I clinical trial.

On the basis of anthranilic acid derivatives, we synthesized a number of new cyclic hydroxamic acid derivatives containing quinazoline-4(3H)-one (**1**) and dihydroquinazoline-4(1H) -one (**2**) fragments.



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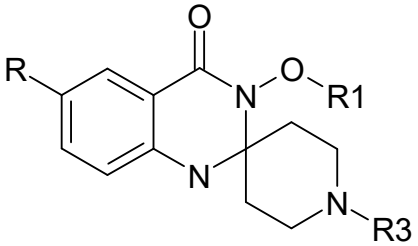

2

At present, the biochemical and cytotoxic properties of the compounds are being studied.

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SYNTHESIS OF POLYCATIONIC GLYCEROLIPIDS BY UGI REACTION

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Non-phosphorous cationic alkyl glycerolipids are known to be investigated as promised antitumor chemotherapy agents. Cationic glycerolipids are metabolitically stable and do not cause hemolysis of erythrocytes [1]. We synthesized polycationic glycerolipids with various long-chain alkyl substituents in lipophilic domain and with natural or synthetic polyamines as polar domain. Compounds synthesized possessed selective cytotoxicity against tumor cells. However, elaborated syntheses were multi-stage and provide lipids in low yields. Alternative strategy for polycationic glycerolipids preparation base on multicomponent ugi reaction as a single stage molecules assemble. Ugi reaction includes four components: isocyanide, carbonic acid, secondary amine and formaldehyde [2].

We designed and synthesized required structure components of glycerolipids for ugi reaction. But, at first, we carried out model reaction of more simple compound, because polycationic lipids are complex for synthesis due to amphiphilic nature. Model ugi reaction with *tert*-butylisocyanide, dibenzylethylendiamine, formaldehyde and *n*-acetilglycine in methanol resulted in formation of desirable molecule, which make possible to carry out synthesis of polycationic glycerolipids.

This study was supported by the RFBR grant No. 17-03-01354.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1,2,4-OXADIAZOLES OF GLYCYRRHETINIC AND DEOXYCHOLIC ACIDS

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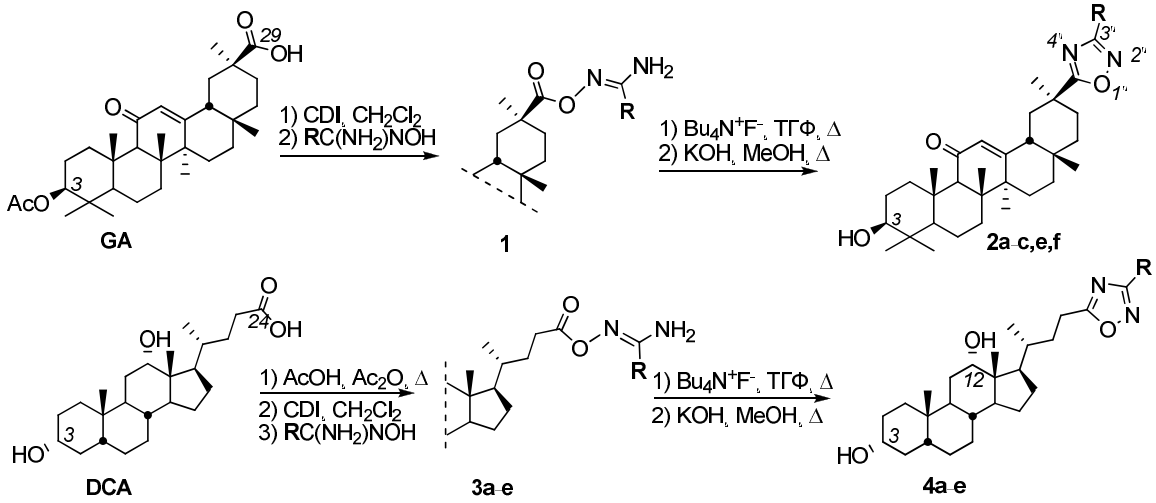
Oxadiazoles are metabolically stable bioisosteres of carboxylic acids and their derivatives (esters, amides) and can also be used as linkers in the synthesis of hybrid molecules [1]. Furthermore, oxadiazoles are important structural fragment of a wide range of biologically active substances with useful pharmacological properties (anti-inflammatory, analgesic, antimicrobial, etc.).



R = Me (**a**), Ph (**b**), *o* Py (**c**), *m* Py (**d**), *p* Py (**e**), *t* Bu (**f**)

The objects of this study are glycyrrhetinic (GA) and deoxycholic (DCA) acid, which are natural compounds of plant and animal origin, respectively, with a broad spectrum of native biological activities [2,3]. In our work new derivatives of GA and DCA were synthesized by transformation of native carboxyl group to the 1,2,4-oxadiazole rings containing *t*-Bu, Me, Ph and pyridine (Py) substituents. The synthesized compounds were tested *in vivo* on models of inflammation induced by histamine (exudative inflammation) and lectin concanavalin A (immunogenic inflammation of the B cell type). Antioxidant and hepatoprotective properties were investigated on models of acute hepatitis induced by 1-isothiocyanatonaphthalene and tetracycline. A structure – activity relationship has been established for the studied compounds. It is shown that DCA derivatives have a more pronounced anti-inflammatory effect than the GA derivative. The dependence of the compounds antioxidant and hepatoprotective activity on the substituent in the molecule was revealed.

This work was supported by RFBR № 16-33-00414.

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SYNTHESIS OF 5-(PERYLEN-3-YLETHYNYL)URACIL-1-YL ACETIC ACID DERIVATIVES FOR ACTIVITY EVALUATION AGAINST ENVELOPED VIRUSES

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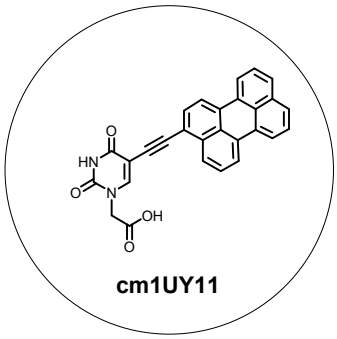
5-(perylen-3-ylethynyl)-2'-deoxy-uridine (**dUY11**) and it's arabino-containing analogue (**aUY11**) are known as replication inhibitors of enveloped viruses [1,2]. Nowadays there are two hypotheses of antiviral activity mechanism: first of them - preventing viral activity are reaching by inhibition of viral and cell fusion; according to the second theory, these compounds generate singlet oxygen molecules and peroxidate membrane lipids, thus, destroys viral particle [3].

In any case, interaction between perylen moiety and lipid membrane is the most important stage. 5-(perylen-3-ylethynil)uracil-1yl acetic acid (**cm1UY11**) was synthesized to study structure-activity relationship. Thus, compound is analogue of nucleoside in which hydrocarbon moiety was changed to carboxymethyl group.

Many branched derivatives with different pharmacophore moiety were synthesized from **cm1UY11** acid. These compounds were synthesized by copper-catalyzed cycloaddition (CuAAC) between azide-containing branching "core" and propargylamide of **cm1UY11** acid, which protected by pivaloyloxymethyl group (**Pom**) in the third position. Azides, which were based on pentaerythritol and synthesized by our group, were used as a "core" [4]. **Pom**-group can be used for increasing of compound's solubility and simplification of their treatment. A method for removing **Pom**-group was developed for key compounds.



cm1UY11

All these compounds were found to be efficient reproduction inhibitors of tick-borne encephalitis virus (TBEV) with IC_{50} values in the micromolar range.

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TRIAZOLO[1,5-A]PYRIMIDINES AND THEIR DERIVATIVES AS PERSPECTIVE MOLECULES AGAINST SEPTIC CONDITIONS

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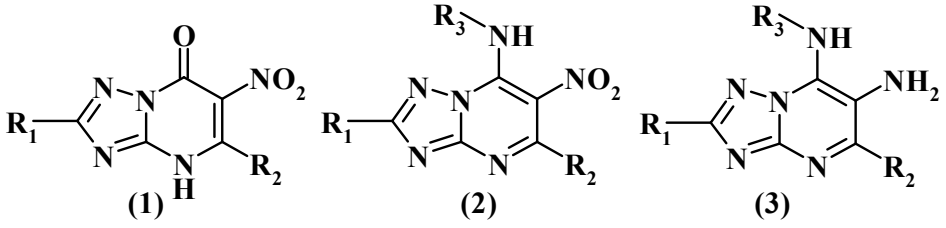
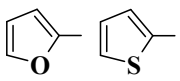
Sepsis is a viral and microbial serious complication of infectious diseases. Recently, a significant number of works devoted to the development of drugs and tools against sepsis have been published. The picture of biochemical processes in sepsis is quite complex and diverse, however, most researchers give a key role in the activation and inhibition of sepsis to the receptor mechanisms. One of the promising directions in this area is the group of adenosine receptors (A_1, A_{2A}, A_{2B}, A_3) and molecules that interact with them (agonists and antagonists). The molecular structure of such effectors, in most cases, is purines, azole-annelated purine analogs and anomalous nucleosides.

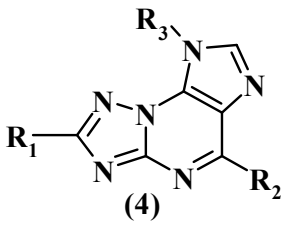
Nitrogen-containing heterocycles of the triazolopyrimidines and triazolopurines series became objects of synthesis and tests for activity against sepsis *in vivo* in present work. Synthetic approaches have been developed for the preparation of such heterocycles, since 6-nitro-7-alkylaminotriazolopyrimidines and their analogs have not been described in the literature previously.



R_1 : H, Alk, Ar, SAlk,



R_2: H, Me ; R_3 : $HO(CH_2)_n$



Thus, the possible structures for synthesis were analyzed by quantum-chemical calculations for the A_{2a} receptor affinity, synthetic approaches to the most promising molecules were developed, and biological tests *in vivo* were performed with synthesized heterocycles. The most promising structures were water-soluble 6-nitrotriazolo[1,5-*a*]pyrimidones (1), which demonstrated antiseptic activity *in vivo*. However, alkylamino derivatives of the series (2) also showed, although less, activity [1,2]. It should be noted that the above-mentioned nitrogen-containing heterocycles did not demonstrate antimicrobial effect, indicating that the regulation of septic process through action on adenosine receptors.

We thank Russian Scientific Foundation (grant 17-13-01096) for financial support.

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4-FLUOROTETRAHYDROQUINAZOLINE *N*-OXIDES AS VERSATILE PRECURSORS OF HETEROCYCLIC COMPOUNDS WITH PRACTICABLE PROPERTIES

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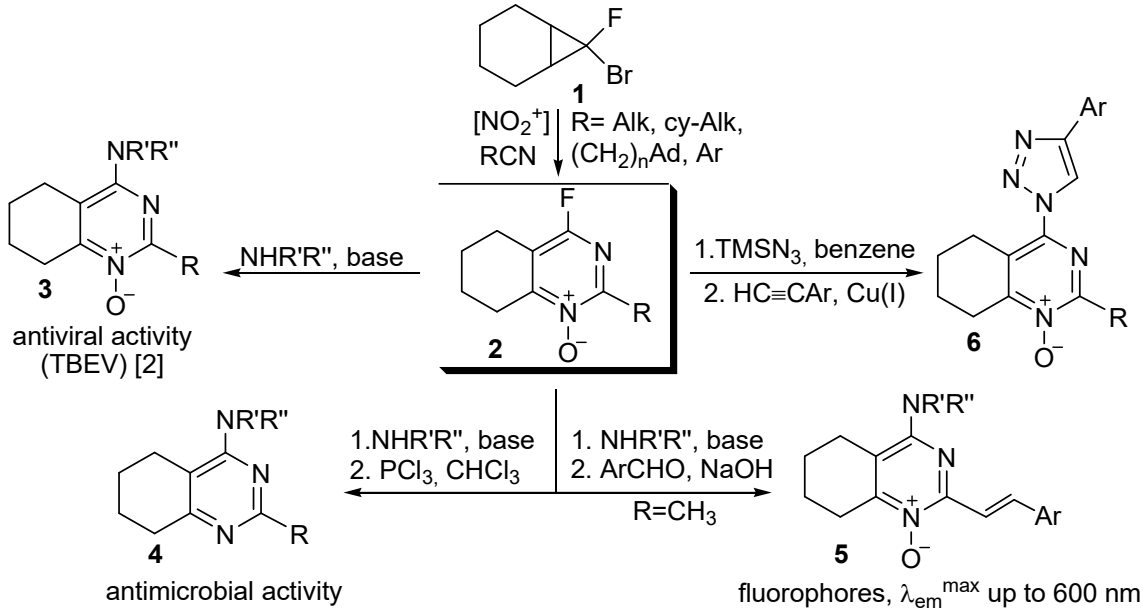
Three-component heterocyclization of *gem*-bromofluorocyclopropanes under the treatment with nitrosating and nitrating agent in presence of organic nitriles yielding previously unknown 4-fluoropyrimidine 1-oxides **2** was found in our laboratory [1].



Starting from highly reactive structures **2**, simple and efficient preparative approaches to 4-aminotetrahydroquinazoline N-oxides **3** and 4-aminotetrahydroquinazolines **4**, structures with extended π-system and intramolecular charge transfer **5** and 4-triazolyl substituted heterocycles **6** were elaborated, employing aromatic nucleophilic substitution, deoxygenation, Knoevenagel-type condensation of activated CH_3-group and CuACC-reactions. A number of the obtained heterocyclic derivatives are characterized with valuable biological activity and photophysical properties.

This work was supported by RNF (project 17-73-10281).

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PHOSPHONATE-SUBSTITUTED PEPTIDOMIMETICS BASED ON CYCLIC SECONDARY AMINES

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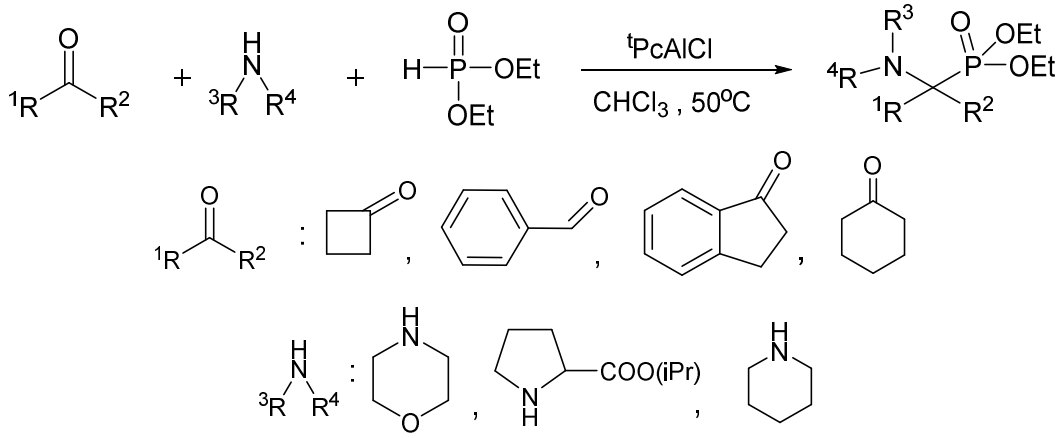
α-Aminophosphonates and α-aminophosphonic acids – bioisosteric analogs of natural aminoacids – are widely used in the organic and medicinal chemistry. They have low toxicity, good solubility in water and resistance to enzymatic hydrolysis. Aminophosphonates are used as antitumor, antiulcer, antituberculosis, antiviral and antithrombotic agents, plant growth regulators, fungicides, enzyme inhibitors, including HIV protease [1].

In the present work, α-aminophosphonates based on biologically active cyclic amines (piperidine, proline) were synthesized using tetra-*tert*-butylphthalocyanine aluminum chloride (^{t}PcAlCl) as a catalyst for the Kabachnik-Fields reaction, the effectiveness of which has been confirmed in our previous studies [2].

The work was carried out with the financial support of the Grant of the President of the Russian Federation for the state support of the leading scientific schools of the Russian Federation NSh-10268.2016.3.



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PERSPECTIVE BICHROMOPHORES WITH PYRIDINE SCAFFOLD

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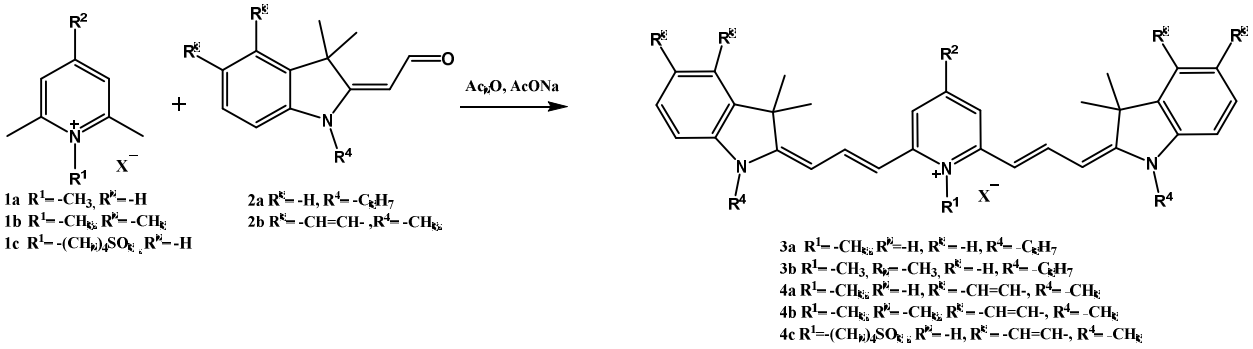
At present carbocyanine dyes are widely used in medicine, particular attention is given to their use as biomarkers. The combination of certain hydrophilic and lipophilic properties, and also photostability and quantum yield of fluorescence is important for these dyes [1]. In this regard the synthetic design of carbocyanines for the purpose of the directed change of their photophysical properties is an actual problem. So far the least studied class are carbocyanines containing in their structure two chromophore fragments [1,2].

This work is devoted to the synthesis of a previously unknown class of bichromophoric carbocyanines based on 2,6-lutidine and 2,4,6-collidine. The compounds obtained were characterized by electronic spectra of the absorption. The spectral range of absorption maxima of the carbocyanines **3-4** is 620-670 nm (620-630 nm for **3a-b**, 660-670 nm for **4a-c**).

The work was carried out with the financial support of the Grant of the President of the Russian Federation for the state support of the leading scientific schools of the Russian Federation NSh-10268.2016.3.



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ANTIVIRAL ACTIVITY OF ISOCARYOPHYLLENE DERIVATIVES AGAINST INFLUENZA VIRUS.

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Influenza is a contagious respiratory disease causing annual epidemics, involving a big number of people all over the world. Only two groups of anti-influenza drugs are available in Russia – M2 protein blockers (rimantadine and amantadine) and neuraminidase inhibitors (oseltamivir and zanamivir). Circulating strains of influenza virus are totally resistant to rimantadine. Resistance to compounds of the second group is not observed now, but in 2008-9 a high prevalence of resistant strains was observed. Also, both drugs are relatively expansive comparatively to symptomatic ones. Thus, there exists a necessity to develop some novel anti-influenza drugs, available to broad groups of population and effective against actual strains of influenza virus.

At present work we had investigated a spectrum of activity and potential mechanism of action of 5 isocaryophyllene derivatives, whose activity had been shown in our previous work. All the compounds were highly active against influenza viruses A/PR/8/34 (H1N1) and A/California/7/09 (H1N1)pdm09, but didn`t show any activity against viruses of other antigen subtypes.

“Time-of-addition” assay had shown that all compounds of the group are active at late stages of influenza infection. These data, coupled with previous ones give us ability to make a suggestion that type 1 neuraminidase is a possible target for compounds of this group. Final answer to this question requires additional investigations.

NEW BIOLOGICALLY ACTIVE DERIVATIVES OF MONOTERPENES CONTAINING ADAMANTANE AND HETEROADAMANTANE MOIETIES

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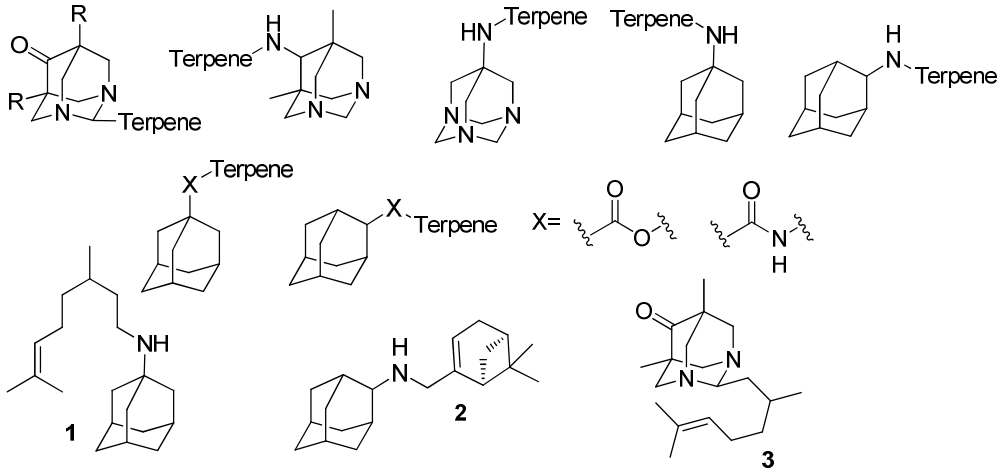
One of the approaches to the creation of new medicinal agents is the transformation of natural biologically active metabolites, for example, monoterpenoids. Adamantane derivatives find widespread use in clinical practice because that have a variety of biological activity. At the same time azaadamantanes which contain nitrogen atoms at the bridgeheads are much less studied. The aim of our work was to combine these two types of pharmacophore fragments in one molecule.

As a result of our studies, we synthesized libraries of monoterpenoid derivatives (acyclic, monocyclic, bicyclic) which contain fragments of adamantane, diazadamantane and triazadamantane [1-5].



These compounds were tested for various types of biological activity: antiviral (influenza virus, herpes virus), antibacterial, fungicidal, analgesic and anxiolytic activities, as well as inhibitory activity towards human DNA repair tyrosyl-DNA phosphodiesterase 1 (Tdp1), plays an important role in the formation of resistance of cancer cells to antitumor drugs. In almost all cases, we found compounds that showed high biological activity. In particular, both derivatives of aminoadamantanes (compounds **1** and **2**) and diazadamantane (compound **3**) also showed significant activity against Tdp1.

This work was supported by Russian Scientific Foundation (grant 16-13-10074).

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SYMPLIFIED BICYCLO[3.3.0]NONANE-BASED ANALOGS OF ELEUTEROBINE AND TAXOL AS NOVEL ANTICANCER AGENTS

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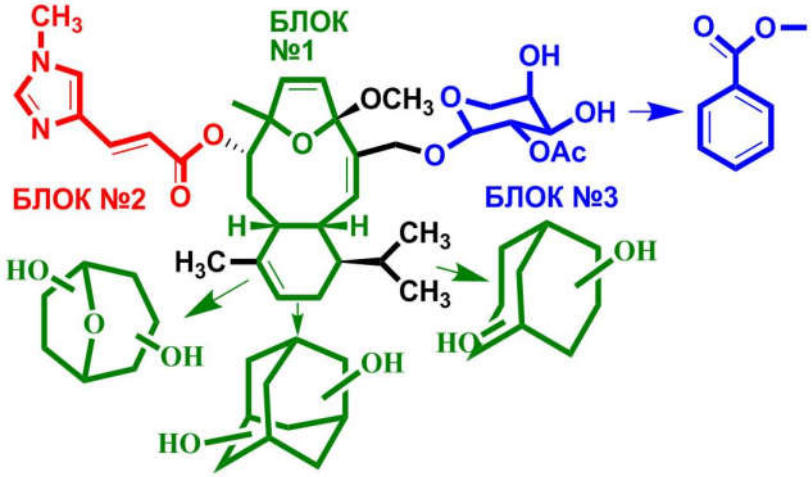
The work presents design, synthesis and evaluation of novel symplified bicyclo[3.3.0]nonane-based analogs of eleuterobine and taxol. These compounds demonstrated significant potential as novel anticancer agents.



The work has been supported by RFBR grant 17-03-01320.

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NOVEL SYNTHETIC APPROACH TO 4-NITROISOXAZOLES – VERSATILE PRECURSORS FOR BIOACTIVE COMPOUNDS

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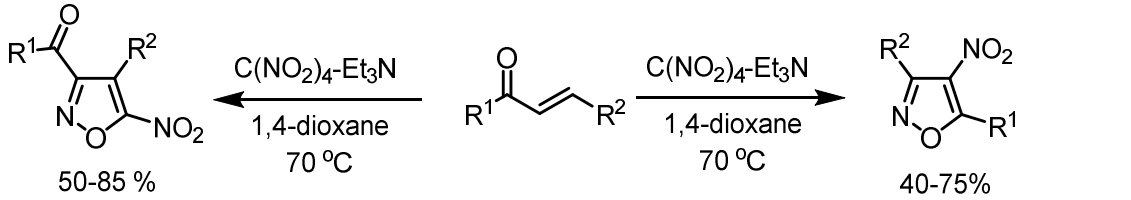
Recently we have developed a general synthetic approach to polysubstituted 5-nitroisoxazoles based on heterocyclization of electrophilic alkenes under the treatment of activated tetranitromethane (TNM) [1,2]. Using this methodology we elaborated convinient synthetic routes to isoxazole derivatives bearing a variety of functional groups [1-3]. However, studying the heterocyclization of aryl vinyl ketones under standard conditions we unexpectedly found a novel reaction resulting in 4-nitroisoxazoles.



50-85 %
R^1 = H, Alk, Ar
R^2 = H, Alk

40-75%
R^1 = Ph, Me, biphenyl
R^2 = Ph, 4-(MeO)C_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, furyl, thiophenyl

Up to date we systematically investigated a series of α,β-unsaturated ketones possessing aryl substituents in the reactions with TNM-Et_3N complex. The scope and limitations of this novel reaction were revealed. A large series of polysubstituted 4-nitroisoxazoles was obtained in good preparative yields.
Some of isoxazole derivatives were estimated as perspective ligands of NMDA and AMPA receptors according to computational studies.

This work was supported by RSF (Project 17-15-01455).

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SYNTHESIS AND EVALUATION OF NEUROPROTECTIVE ACTION OF NOVEL HYDROXYBENZOIC DERIVATIVES WITH AMINO ACIDS

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In order to study cerebroprotective activity, we obtained water-soluble sodium, potassium and lithium salts of 4-hydroxybenzoic acid amides with amino acids (glycine, GABA). The test compounds (and to a greater extent C40) contributed to the preservation of cerebral blood flow at a higher level in relation to the index of the animals of the control group [1,4].

Full text of the abstract can be found in the Russian version of the conference abstract book.

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1-MORPHOLINO-2-NITROETHYLENE AS A PRECURSOR OF NITROACETALDEHYDE IN THE SYNTHESIS OF 3-NITRO-4-HYDROXY-1,4-DIHYDROAZOLO[5,1-C][1,2,4]TRIAZINES

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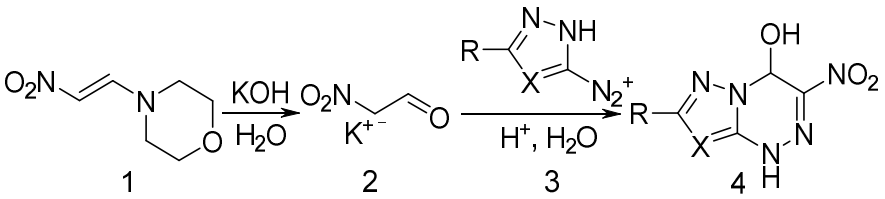
The number of papers with the application of nitroacetaldehyde is small: it is used for the synthesis of biologically active nitrogen heterocycles, some natural polycyclic structures and carbasugars [1,2,3]. Nitroacetaldehyde is a highly reactive compound, the actual building block that contains both nucleophilic and electrophilic centers. This structural feature of nitroacetaldehyde is the reason of its extremely low stability. To show its wide synthetic potential we developed new efficient method of preparation and use of nitroacetaldehyde potassium salt *in situ*.

The nitroacetaldehyde potassium salt **2** which is prepared by the treatment of nitroethylene **1** with aqueous solution of potassium hydroxide interacts with azolyldiazonium salts **4** to obtain 3-nitro-4-hydroxy-1,4-dihydroazolo[5,1-c][1,2,4]triazines **4** with a yield of 9-49% which are of practical interest [4].



a: R=H, X=N; b: R=Me, X=N; c: R=SMe, X=N;
d: R=COOEt, X=N; e: R=Ph, X=N; f: R=CF_3, X=N;
g: R=α-Thienyl, X=N; h: R=H, X=CCOOEt

The azocoupling reaction with nitroacetaldehyde can take place both with isolated one and *in situ*, which is an advantage of the developed approach.

The hydroxy group in azolotriazines **4** is mobile, i.e. is easily replaced by C- or O-nucleophiles. This way, one can introduce additional pharmacophore groups that can make other kinds of biological action.

Thus we have developed a new effective and simple method for the synthesis nitroacetaldehyde potassium salt and synthesized new azolo[5,1-c][1,2,4]triazines using this synthetic equivalent.

The work was supported by Russian Science Foundation grants № 16-13-00008.

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SYNTHESIS OF NEW BETULIN AND N-ACETYLGALACTOSAMINE GLYCOCONJUGATES

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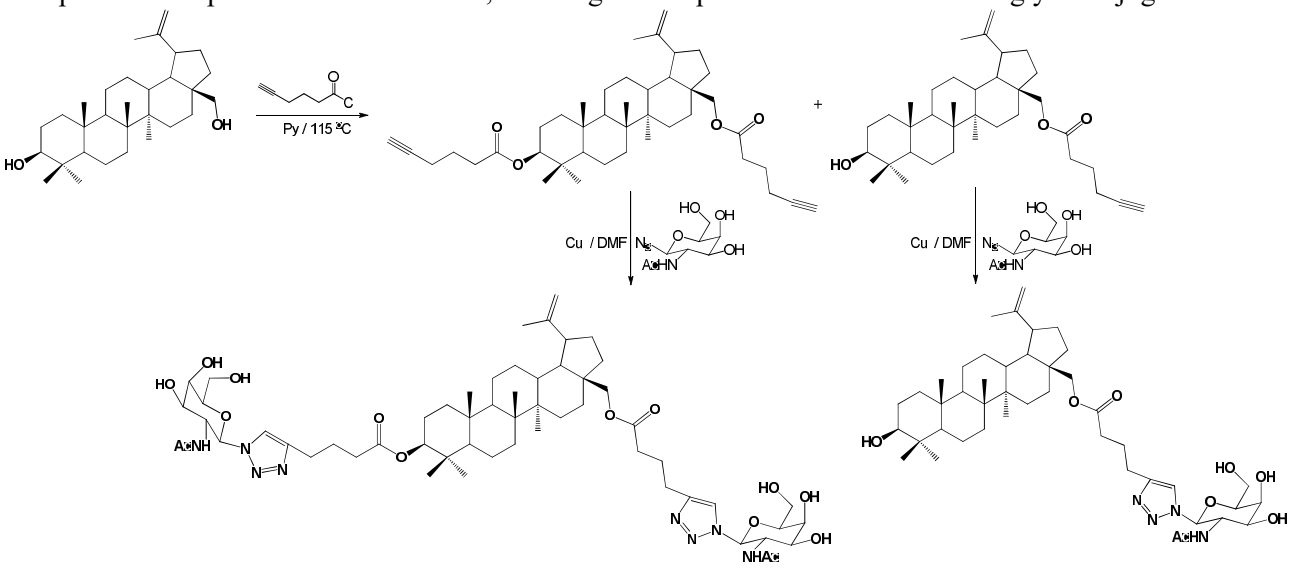
To date, the key approach in optimizing the pharmacological profile of antitumor drugs is delivery to validated biological targets (receptors, biomarkers, antigens, etc.). Among the targeting drug delivery to the liver, the strategy of creating specific compounds to asialoglycoprotein receptor takes leading roles [1]. Similar developments are also being made with drugs for treating hepatocellular carcinoma [2]. Besides, glycoconjugated systems allows to improve significantly the pharmacological profile of the initial molecules, which is especially important for natural triterpenoids.

At present work, two covalent conjugates of betulin and N-acetylgalactosamine were synthesized and characterized. Initially, esters of betulin and 5-hexynoic acid were obtained. The subsequent interaction of azido derivatives of N-acetylgalactosamine with acetylenic moieties allowed selective conjugation of triterpenoid and specific monosaccharide, resulting in new potential bivalent ASGPR glycoconjugates.



The study was supported by a grant from the Russian Science Foundation (project No. 17-74-10204)

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A FACILE METHOD FOR THE SYNTHESIS OF POLYSUBSTITUTED TETRAHYDROINDOLES

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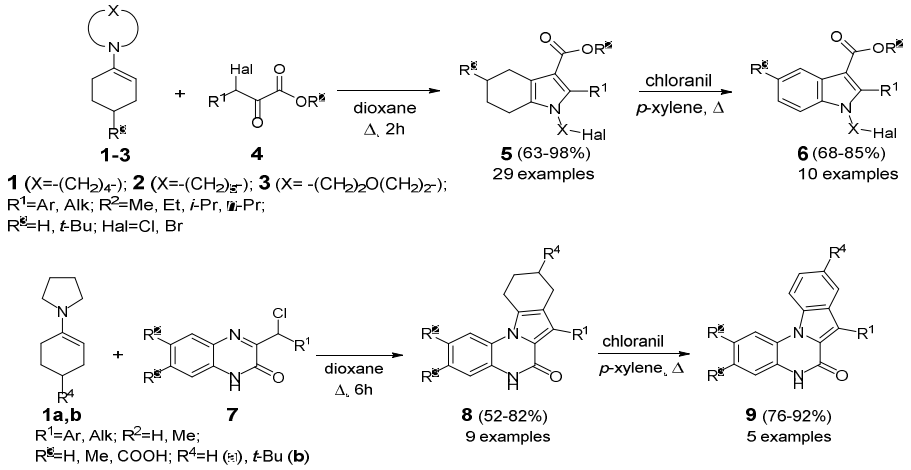
Indole derivatives widely exist in natural and artificial synthetic compounds. Extensive studies indicated that these compounds possess a wide range of bioactivities such as antibacterial, antifungal, cytotoxic and insecticidal properties [1]. Therefore, the syntheses of these valuable compounds are always the hotspot in organic chemistry, and numerous methods based on more than 25 name reactions have been developed [2]. However, in spite of all known procedures, efficient and simple protocols for the preparation of polysubstituted indoles, a subject of great interest for the synthesis of biologically active compounds, are still an active research field [3]. The simplicity and the availability of the requisite starting materials, the tolerance of functional groups, the selectivity of the substitution process, and the broad scope of the method are all issues of particular relevance often difficult to combine in a synthetic process.
In this work, the methods of the synthesis of polysubstituted indoles and their various condensed derivatives have been developed by the following reactions [4]:



This work was financially supported by the Russian Science Foundation (Project No. 14-23-00073-n).

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KAZCAINE, TRIMECAINE, PIROMECAINE AND TOLPERISONE BASED IONIC COMPOUNDS: SYNTHESIS, PREDICTION AND EVALUATION OF BIOLOGICAL ACTIVITY

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The combination of N-ethoxyethylpiperidine derivatives, trimecaine, piromecaine and tolperisone in form of a base with different alkyl halides bring via N-alkylation reaction to the range of new biological activity and/or reduce toxic effects of parent compounds.

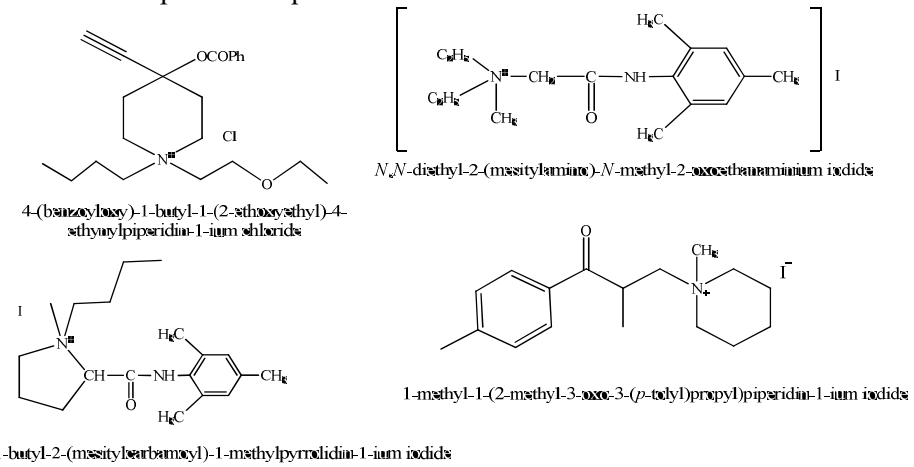

Figure 1. New ionic compounds based on kazcaine, trimecaine, piromecaine and tolperisone respectively

Herein we report synthesis and PASS (Prediction of Activity Spectra for Substances) prediction of potential biological activity and potential toxic effects for obtained ionic compounds [1]. N-ethoxyethylpiperidine derivatives (kazcaine) showed ovulation inhibitor, spasmolytic and gestagen antagonist as potential activities. Trimecaine derivatives showed cardiotonic, spasmolytic and calcium channel activator effects. Piromecaine derivatives showed gastrin inhibitor, membrane integrity antagonist and general pump inhibitor potential activity. Tolperisone derivatives showed acetylcholine neuromuscular blocking agent and spasmolytic potential activities.

We also carried out an experimental test of the biological activity of the obtained substances. Three groups of bioactivity were tested: a) antimicrobial by spot-test (no antimicrobial activity); b) growth stimulating activity (Trimecaine derivatives showed the higher energy of germination in comparison with the used growth stimulant; c) N-ethoxyethylpiperidine derivatives showed myelostimulating activity (in laboratory mice).

These novel ionic compounds can be applied for synthesis of ionic compounds and drug candidates.

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REARRANGEMENT OF 3-(BROMOMETHYL)- AND 3-(A-BROMOETHYL)QUINOXALIN-2(1*H*)-ONES WHEN EXPOSED TO A-PICOLINE: A SIMPLE METHOD FOR THE SYNTHESIS OF 2-(INDOLIZIN-2-YL)BENZIMIDAZOLES

N.A. Zhukova [1,2], M.S. Kadyrova [1,2], T.N. Beschastnova [1,2], A.O. Isaeva [2], V.V. Syakaev [1], Sh.K. Latypov [1], and V.A. Mamedov [1,2]

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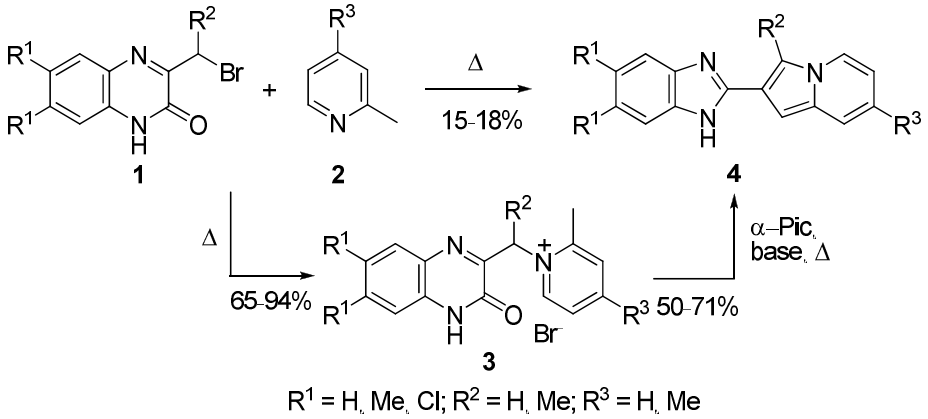
Indolizines are fundamentally important nitrogen containing heterocyclic systems. Many synthetic and naturally occurring indolizine derivatives have found wide applications in pharmaceuticals, such as in anti-inflammatory agents, H3 receptor antagonists, anti-HIV agents, and usage as molecular probes. They are of interest also as key intermediates for the preparation of indolizidines, biindolines, cyclophanes, cyclazines and a range of biologically important alkaloids. Consequently, the development of efficient especially convergent methods for rapid construction of indolizines has stimulated considerable interest.
In this work a simple method for the synthesis of 2-(indolizin-2-yl)benzimidazoles has been developed by the following reactions.



The method is based on the reaction of 3-(bromomethyl)- (**1**, R^2 = H) and 3-(α-bromoethyl)- (**1**, R^2 = Me) quinoxalin-2(1*H*)-ones with α-picolines **2**. The process involves the Mamedov heterocycle rearrangement [1, 2] as a key step.

The work was supported by the Russian Scientific Foundation (Grants No. 14-23-00073, 14-23-00073-p).

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CHEMOENZYMATIC SYNTHESIS AND ANTIHERPES ACTIVITY OF FLUOROBENZIMIDAZOLE NUCLEOSIDES

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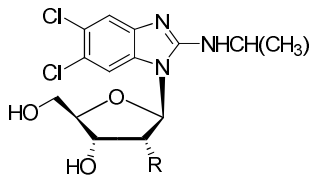
It is well known that nucleoside analogues, such as acyclovir, ganciclovir, penciclovir, as well as cidofovir, are widely used in medical practice for treatment of herpes simplex virus type 1 (HSV-1) and cytomegalovirus infection (CMV).It has been established that benzimidazole derivatives belong to a promising family of antiviral compounds with a broad spectrum of biological activity. We have synthesized the family of fluorobenzimidazole nucleosides by using the transglycosylation reaction catalyzed by nucleoside phosphorylases *E. coli* [1, 2].



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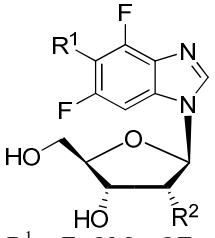
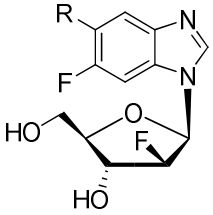
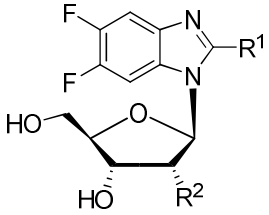


R^1 = F, OMe, OEt, morpholino, pyrrolidino
R^2= OH, H



R = F, OMe, OEt, O-*i*Pr, morpholino, N-methyl-piperazino



R^1 = NH_2, $NHCH(CH_3)_2$
R^2= OH, H, arabinoF

Cytotoxicity and biological activity of nucleosides can be changed not only by introduction of substituents into heterocyclic base, but also by replacing of natural sugar residues. Benzimidazole-β-D-arabinofuranosides (both di- and trisubstituted in positions 4-6 of benzene cycle and nonsubstituted) synthesized with help of enzymatic transglycosylation. 1-(β-D-Arabinofuranosyl)benzimidazole was synthesized by glycosilation of N-trimethylsilyl-benzimidazole with 1-chloro-2,3,5-O-methoxymethyl-D-arabinose. Using the enzymatic transglycosylation reaction β-D-ribo- and 2'-deoxyribofuranosides of 2-amino-5,6-difluorobenzimidazole nucleosides have been synthesized.

2-Amino-5,6-difluoro-benzimidazole riboside proved to exhibit a selective antiviral activity (selectivity index >32) against a wild strain of the herpes simplex virus type 1, as well as towards virus strains that are resistant to acyclovir and cidofovir.

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Poster session №3

CHRONOPULSE-KINESIOMETRY AS A METHOD OF DIAGNOSIS, TREATMENT AND EVALUATION OF THE EFFECTIVENESS OF DRUGS

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Chinese chronopuncture is the most promising direction of Chinese medicine, represented by the methods of zhen-chiu and qigong. The method of zhen-chiu therapy always took into account the presence of a certain synchronization between the time cycles (seasons of a year, months, days and hours) and the state of a person (Akhtyamov I.Sh., Paltseva IS, 2011) [1]. Chronopulse-Kinesiometry is a clinical chronometry of the regulatory function of the transport function (i.e., ensuring the progress of lymph, blood and CSF) of a self-regulating cardiovascular system through modernized Chinese pulse diagnostics performed under kinesiological control.

There is an idea of "physiological homeostasis" realized at the level of tissues, organs, physiological systems of the organism and the system organism - environment ("micro-macrocosmos"). The internal environment of the body is blood, lymph, intercellular fluid, as well as internal organs, which are in constant interaction with the liquid media of the body. Earlier, my colleagues and I were offered an explanation of the physiological basis for the separation by ancient physicians of a single stream of body fluids ("jin-e, hsueh, chi") along two propagation paths, namely, "jung (in-chi) and wei (wei-chi)" [2], which allowed the effective use of knowledge on pulse diagnostics.

In our practice, when testing by methods of applied kinesiology (PC) - manual muscle testing, therapeutic localization and provocation, we combine the assans and mudras (used in PCs), while evaluating the relative location of "areas and sections" of the patient's body in space in accordance with the views of Chinese physicians on the ancient triad "sky-man-earth." Pulseokinesiometry is carried out taking into account the Yang ("the action of the disease on the breath of chi") and the Yin days ("the effect of the disease on the blood"), as well as days and hours for 9 (10) -day cycles.

Chronopulseokinesiometry that provides a clinical control of physiological homeostasis in real time (ie, "here and now") is useful to use in assessing the effectiveness of used and new drugs, investigating their interaction with each other.

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SYNTHESIS AND ANTIRADICAL ACTIVITY OF SOME RESVERATROL ANALOGUES

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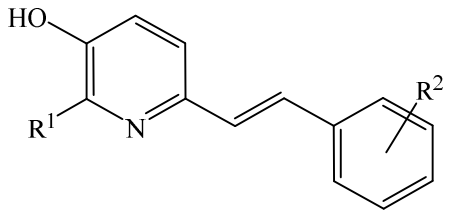
Previously, we reported on the synthesis and study of antiradical properties of some analogues of natural antioxidant –*trans*-resveratrol (TR) [1]. The strategy for modifying the prototype structure consisted in introducing the 3-hydroxypyridine fragment into its core and varying the number and position of the hydroxyl groups in the benzene ring. It is known that bulk alkyl substituents in the *ortho* position to the phenolic hydroxyl screen the radical center in the resulting phenoxy radical and increase its stability, which should promote the antioxidant activity increasing.

In the present study, we carried out the synthesis of hetero-analogues of TR (**2**) containing an ethyl group at the 6-position of the pyridine ring, and a theoretical and experimental evaluation of their antiradical activity.



R^1 = H (**1**), Et (**2**) R^2=4-OH (**a**), 3,4-$(OH)_2$(**b**)

Compound	BDE, kcal/mol	API, kcal/mol	IC_{50}, µM
1a	75,5	153,6	14,8
1b	69,5	151,9	5,8
2a	73,9	152,3	17,7
2b	73,1	149,6	5,0
TR	76,4	155,0	93,0

The enthalpy of dissociation of the O-H bond (BDE) and the adiabatic ionization potential (API) calculated by the DFT/B3LYP/6-311G(d.p) method using the GAMESS software package (US) were used as the antiradical activity descriptors. The antiradical activity of the compounds obtained was also investigated with respect to DPPH and a half inhibitory concentration (IC_{50}) was calculated. The data indicate that all hetero-analogues (**1**) and (**2**) have better antiradical activity in comparison with TR. At the same time, the introduction of the ethyl group has an ambiguous effect on the BDE value, but leads to a significant reduction in the API, facilitating the formation of the radical by the SET-PT mechanism. The best indicator in DPPH test is the compound (**2b**), the main candidate for the role of an effective antioxidant.

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MODELING OF THE ANTIOXIDANT ACTIVITY OF ORGANIC SULFIDES

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It is known that organic sulfides can exhibit significant antioxidant activity due to the ability to reduce hydroperoxides (R'OOH) to form the corresponding sulfoxides and sulfones:

$$RSR + R'OOH \rightarrow RSOR + R'OH$$
$$RSOR + R'OOH \rightarrow RSO_2R + R'OH$$

The flow of these reactions prevents the possibility of the decomposition of R'OOH into free radicals and blocks the nucleation of new oxidation chains [1,2].

In the present work, the quantum-chemical modeling of reactions of sulfides RS_nR (n = 1-4, R = CH_3, *n*-C_4H_9, *tert*-C_4H_9, Ph) with R'OOH by the density functional method (B3LYP/6-31++G(d,p)) was carried out using the computer program HyperChem 8.0. The thermodynamic probability of the considered reactions was estimated using the value of ΔE, calculated as the difference between the total energies of the final and initial structures.

The calculations did not reveal a significant effect of the number of sulfur atoms (n) on the value of ΔE for the hydroperoxides reduction reactions. Thus, modeling allows predicting antioxidant activity for di-, tri- and tetrasulfides in the case when such activity is observed for the corresponding monosulfide. For all the simulated reactions ΔE<0 (the energy is released, the course of the hydroperoxides reduction reactions is not energetically hindered). In general, for the considered series of sulfides, the nature of R has a weak effect on the value of ΔE.

The influence of disulfides (*n*-$C_4H_9)_2S_2$, (*tert*-$C_4H_9)_2S_2$, Ph_2S_2 on the rate of generation of $O_2^{\bullet-}$on the model system of adrenaline quinoid oxidation in alkaline bicarbonate buffer and on the SOD-protective activity of biopreparations – liver homogenates of the Russian sturgeon – is studied. Oxidation of adrenaline under these conditions simulates a quinoid pathway of adrenaline transformation. It was found that the investigated disulfides slightly increase the SOD-protective activity of the biopreparation, slowing down the rate of adrenaline oxidation, but the nature of R practically does not influence the antioxidant activity, which agrees with the results of model calculations.

In the case of tri- and tetrasulfides, according to the results of calculations, first of all, the sulfur atoms located in the middle of the -S_n- chain should undergo oxidation. The substitution of the hydrogen atom for the alkyl group (R') in the hydroperoxide results in a decrease in the absolute value of ΔE– hydrogen peroxidereacts more readily with sulfides than AlkOOH. For the oxidation of sulfoxides with n>1, calculations show that the formation of the corresponding sulfone is more likely than that of the isomeric oxidation product with two sulfoxide groups. In general, the reactions of formation of sulfones are accompanied by the release of more energy (ΔE = (-197.5) – (-243.0) kJ/mol) compared to the reactions of sulfoxides' formation (ΔE = (-125.0) – (-166.2) kJ/mol).

This work was supported by the Russian Science Foundation (grant no. 17-13-01168)

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SYNTHESIS AND STUDY ON THE POTENTIAL ANTICANCER ACTIVITY OF PHOSPHINOLINIUM-TYPE HALIDE SALTS

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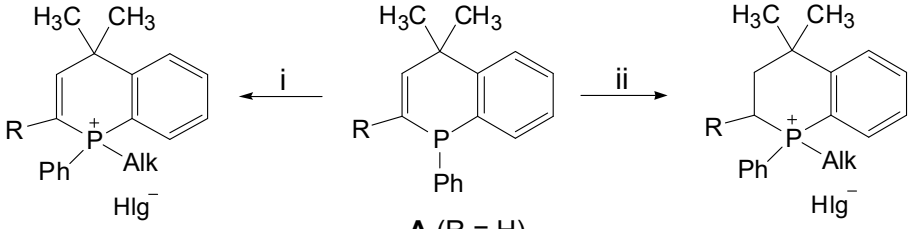
This research work deals with the synthesis of a series of phosphinolinium-type bromide and iodide salts**.** The cytotoxic activity of the newly synthesized compounds was evaluated against the two cell lines of human origin: A549 lung adenocarcinoma and U251 glioblastoma using SRB assay and MTT assay. The most active compounds were found to be **1**, **5**, **6** displaying a submicromolar GI_{50} values from 0.25 to 0.48 μM. They also have strongly pronounced cytostatic activity. Compounds **1**, **5**, **6** have a stronger effect on viability of two cell lines as compared to cysplatin. Extension of the alkyl chain leads to an increase of anticancer activity of the compounds, while the presence of bromine in the heterocycle ring does not have a noticeable effect on the cytotoxicity of the synthesized compounds. Initial phosphinolines **A**, **B** were synthesized by reduction of corresponding phosphinoline oxides [1].



1 - 5 **A** (R = H) **B** (R = Br) **6**

	R	Alk	Hlg
1:	Br	*n*-decyl	Br
2:	Br	ethyl	Br
3:	Br	ethyl	I
4:	H	ethyl	I
5:	H	*n*-decyl	Br
6:	H	*n*-decyl	Br

(i) AlkHlg, toluene, 120-150°C, 10-15 h;
(ii) 1) $HSiCl_3$, benzene, 100°C, 5 h;
2) AlkHlg, toluene, 150°C, 15 h

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AN ANALYSIS OF THE ANTIOXIDANT ACTIVITY IN RAT SERUM UNDER THE ACTION OF MELANIN

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Reactive oxygen species (ROS) induce lipid peroxidation (LPO) processes in biological membranes. One of the important indicators of pathological processes development is malonic dialdehyde (MDA), other endogenous systems of tissue protection from ROS are superoxide dismutase (SOD), catalase [1, 2]. SOD is an antioxidant enzyme that catalyzes the dismutation of superoxide anions in O_2 and H_2O_2 [3]. The complex determination of the above indicators with high accuracy makes it possible to determine the functional state of health and differentiate the phases of adaptation reactions.

In the literature it is reported that the melanin complex derived from *Inonotus obliquus* contains antioxidants due to the content of free radical molecules [2, 3].

The purpose of this work was to determine the indicators of LPO activity in serum samples in groups of rats that received oral solutions of melanin composites.

Our results indicate that the substances KM1 and KM2 reduce the activity of MDA and, in addition, affect the weight of rats, reducing it by an average of 2%. These substances also have the same effect on the indicators of SOD activity, reducing the activity of lipid peroxidation in the blood serum of rats. For the catalase activity in the serum of rats there were no statistically significant differences.

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SYNTHESIS OF CONFORMATIONALLY FIXED TRICARBOCYANINES

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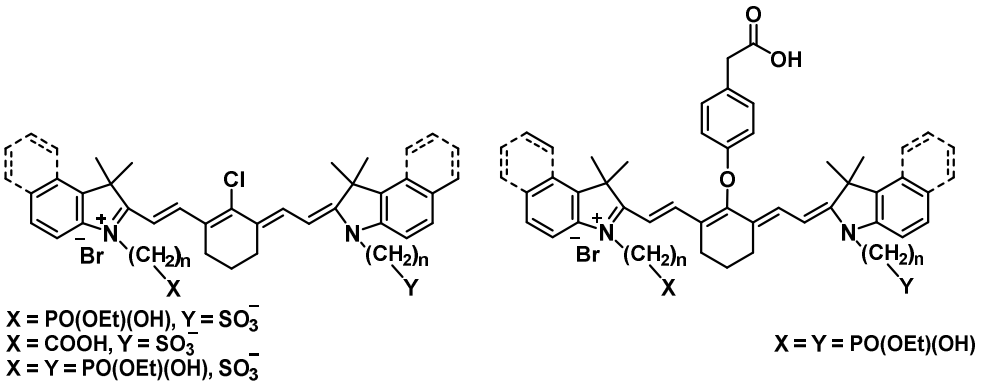
Optimization of the physicochemical characteristics of tricarbocyanine dyes (photostability, binding efficiency with transport proteins, the quantum yield of fluorescence) due to structural modifications is an actual problem. Recently, we have developed a method for the synthesis of tricarbocyanines containing a hydrophilic phosphonate group and have showed their ability to efficiently bind to transport proteins (BSA, HSA and α-fetoprotein) [1,2].

In the framework of this research, a number of water-soluble symmetrical and nonsymmetrical conformationally fixed tricarbocyanines containing hydrophilic groups (phosphonate, carboxyl and sulfonate) were synthesized and a modification of the *meso*-position of the polymethine linker was carried out for the further structural design of the drug-delivery conjugates.

The research was carried out with the financial support of the Grant of the President of the Russian Federation for the state support of the leading scientific schools NSh-10268.2016.3



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PROTECTIVE EFFECTS OF THE NATURAL SESQUITERPENE LACTONES AGAINST DAMAGE CAUSED BY GLUTAMATE AND PEROXIDE IN SK-N-MC CELLS: COMPARATIVE ANALYSIS

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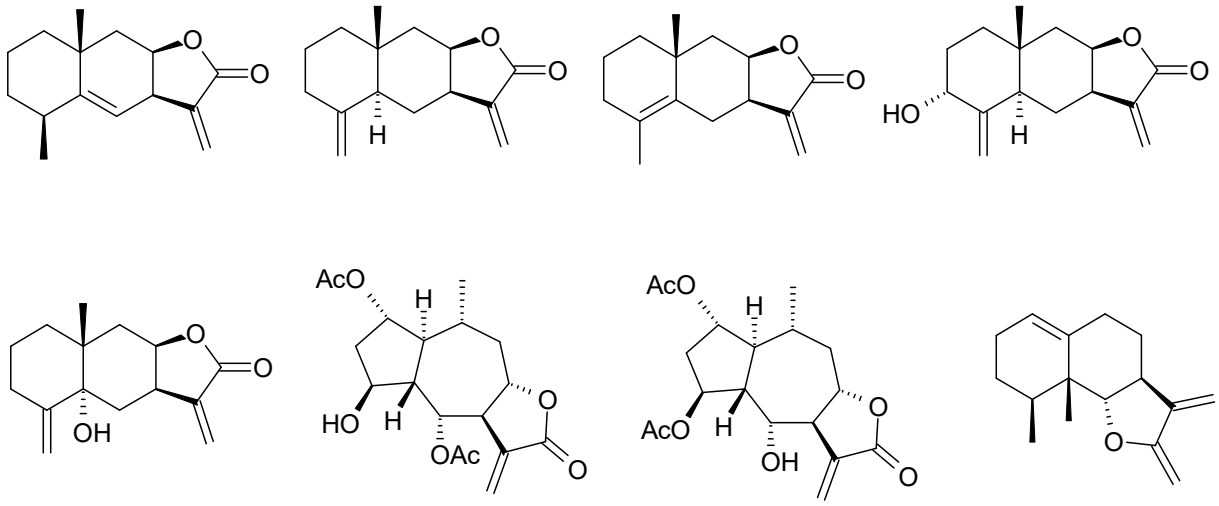
Neurodegenerative diseases, although different in nature, have common mechanisms of cellular damage. And oxidative stress, and glutamate toxicity plays an important role in the pathogenesis of these diseases [1]. The aim of this work is to study the effect of sesquiterpene lactones of plants of the family Asteracea (compound 1-20) on the SK-N-MC neuroblastoma cell line. We used *in vitro* models of glutamate-induced toxicity and toxicity caused by hydrogen peroxide. Pretreatment of the cell with lactones followed by exposure to glutamate or H_2O_2 were capable of restoring the viability of cells relative to the control (glutamate- or H_2O_2-treated) cells. Previously we have shown that some of the studied lactones possess antioxidant properties [2].



We found that the investigated lactones protect cells against glutamate-induced and H_2O_2 –induced damages, demonstrating selectivity. The results revealed the most active compounds promising for the development of effective neuroprotective agents.

The work is executed at financial support of RFBR grant No. 16-03-00674.

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Antianemic activity of Na-, Ca-, Fe-polygalacturonate of the model of combined iron deficiency and posthemorrhagic anemia of rats

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The work is devoted to study the influence of acute massive blood loss causing iron deficiency anemia.

As you know, anemia not only reduces the quality of life, but aggravates the underlying pathology and poses a threat of premature death of patients [1].

The aim of this work was to study the clinical efficacy and tolerability of drugs, including analysis of the clinical efficiency evaluated by the frequency of hematologic response and improvement of quality of life in the experience of the main receipts of iron in cells of the hematopoietic system was the drug of the totem and the complex of pectin FeCa.

The experiment was conducted on 57 albino rats using two routes of exposure:

1. At the beginning of the experiment, age 4-5 weeks, weight 110-140 g; modelling of anemia using iron-deficient diet, without blood loss;

2. At the beginning of the experiment, age 8-9 weeks, weight 214-240 g.; modeling by anemia of acute blood loss (3-fold at 1% of body weight, a total amount of about 50% of circulating blood volume), against feeding iron-deficiency diet.

In this work, we have obtained the following results:

1. In iron-deficiency anemia posthemorrhagic increase in the number of erythrocytes, hemoglobin and hematocrit under the influence of the pectin is Na-, Ca-, Fe-polygalacturonate at a dose of 60 mg/kg (equivalent to 50% of the dose of iron recommended in the treatment of other iron-containing drugs) is observed starting from 3 days of application.

2. Na-,Ca-,Fe-polygalacturonate at a dose of 60 mg/kg showed higher efficiency compared to an equivalent dose of the drug totem.

3. On the background of deficient iron intake, blood loss no, na-,ca-,fe-polygalacturonate at a dose of 120 mg/kg (equivalent 100% dose of iron recommended in the treatment of other iron-containing drugs) has an effect on the blood similar drug Totem.

The research was financed by the contract N 14.N08.12.1042.

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THE STUDY OF THE MECHANISM OF THE ANTITUMOR ACTION OF AURUM POLYACRYLATE

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Discovery of the strong antitumor activity in the group of platinum derivatives had been the reason for the intensive investigation of the various metalloorganic compounds containing the other noble metals as potential antitumor drugs.

Recently, the antitumor effect of the number of containing aurum compounds with different structures has been found. In particular, significant antitumor activity of aurum polyacrylate (aurumacryl) - the drug which belongs to such new for oncology group of compounds as polyacrylates of metals - has been revealed. It was previously shown that aurumacryl induced *in vivo* the inhibition of growth of such murine solid tumors as Lewis lung carcinoma, Acatol adenocarcinoma and Ca-755 adenocarcinoma by 80-90% as compared to control [1].

The study of the mechanism of antitumor action of aurumacryl on such *in vitro* model as MCF-7 human breast carcinoma cells line was the aim of this work.

The aurumacryl action in the wide range of concentrations (from 0.001 to 1 mg/ml) during various time of exposure (1-24 hours) on the cell survival as well as its effect on the such parameters as kinetics of cell proliferation, the ability to induce single- and double-stranded DNA breaks and to generate the reactive oxygen species (ROS) have been evaluated.

Cytotoxic and cytostatic effects of the drug upon tumor cells had been established. Dose dependant cytotoxic effect of aurumacryl was expressed as the death of the 70% of cells after 24 hours incubation of tumor cells with the drug in the dose equal to the 1 mg/ml.

Kinetics of proliferation of the fraction of survived tumor cells was also changed after the drug treatment. These alterations were expressed as accumulation of the 93% of cells in the phase of proliferative rest G_0 and in the strong decrease of the number of proliferating cells – till to the 7%. These data may be evaluated as the evidence of the loss of the reproductive activity of the most of MCF7 cells after aurumacryl treatment.

3D QSAR AND END-STATE FREE ENERGY CALCULATIONS FOR THE DEVELOPMENT OF NOVEL AMPA RECEPTOR POSITIVE ALLOSTERIC MODULATORS

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Positive allosteric modulators (PAMs) of the AMPA-sensitive glutamate receptors are expected to be helpful in treatment of learning and memory deficits, which could be caused, e.g., by the Alzheimer's disease. In this work we tried to create and tune a system for the estimation of PAMs activity using MM-PB(GB)SA approach and CoMFA. This system can be used in the refinement of the virtual screening results to identify novel PAM chemotypes.

Crystal structures of PAM complexes with GluA2 ligand binding domains dimers were used for ligand alignment for CoMFA. The best obtained model (Q^2 = 0.57) was created using MMFF94 charges. As one can note the increase in activity can be achived by filling the two symmetrical binding pockets which are formed by Ile502, Pro515, Ser750 and Lys751 (GluA2) [1].

Calculation of the binding free energy for a set of AMPA receptor PAMs was undertaken and a reasonable correlation was found for the obtained values and the available data for pEC_{50} of PAMs. Combining various calculated parameters we were able to construct a linear model for the pEC_{50} with the correlation coefficient (R^2) of 0.61 (MM-GBSA) on a large set of PAMs with highly diverse structures. In the considered case the overall performance of the MM-GBSA is comparable with the MM-PBSA method for solvation energy calculation. It was found for the MM-PBSA method that the default value of the dielectric constant is inappropriate in this case giving positive value for the binding energy. Variation of the internal dielectric constant led to achievement of the relatively high correlation coefficient (R^2 = 0.62). It should be noted that a usage of frames from the beginning of the trajectories leads to the noticeable decrease in the correlation coefficient which can be associated with the conformational changes in the structures of complexes. The inclusion of the calculated conformational entropy term did not improve the correlation both for MM-GBSA and MM- PBSA.

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APPROACHES TO THE DEVELOPMENT OF SUPRAMOLECULAR SYSTEMS WITH MODIFIED CYCLEN

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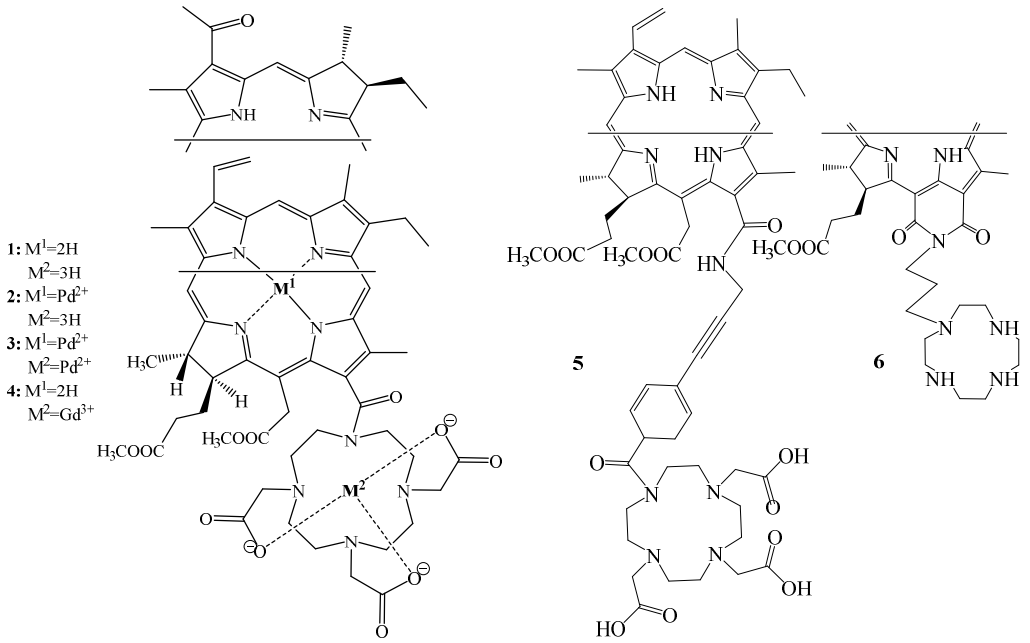
The subject matter of this work is the development of synthetic approaches to directed synthesis of conjugates of derivatives of natural chlorins and bacteriochlorins with 1,4,7,10-tetraazacyclododecane (cyclen). The binding of the above components into a single structure can be implemented either by direct opening of the cyclopentanone fragment in the molecules of the methyl esters of pheophorbide *a* and bacteriopheophorbide *a*, or through the spacer group with the chlorin derivatives *e6* and *p6*.

The existence of two coordination cavities in this kind of conjugates makes it possible to obtain homo- and heteronuclear metal complexes, which may be of relevance in the fluorescence diagnostics (FD), magnetic resonance imaging (MRI) and positron emission tomography (PET). The application of such contrast agents allows studying biological tissues at different depths with high resolution, which significantly increases the effectiveness of early cancer diagnostics.



Acknowledgements: Authors thank the Russian Science Foundation (grant RSF No. 16-13-10092) and the Russian Foundation for Basic Research (grant RFBR № 15-29-01150) for their support.

SELECTIVE HEMOSORBENT FOR EXTRACORPOREAL THERAPY OF SEPSIS

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Sepsis is a life-threatening complication of an infection when the body's immune defense system react in an extreme way. Despite all the advances in the treatment of infectious diseases, mortality could reach up to 25-40%. Development of sepsis begins with the spread of bacterial (less often fungal) infection in the bloodstream. At the same time, a strong immune response to the components of the cell walls of bacteria and fungi presented in the body, in particular, to bacterial endotoxins (lipopolysaccharides, LPS) develops.

A number of clinical studies have shown the effectiveness of extracorporeal therapy for sepsis treatment. In particular, the Toraymyxin™ column that selectively extracts bacterial endotoxins from the blood of patients is widely used in clinical practice. However, it has certain drawbacks, such as high cost and insufficient effectiveness to remove an excessive number of inflammatory mediators - cytokines.

In this work, a bimodal sorbent based on macroporous hyper-cross-linked polystyrene (HPS) was developed. On the surface of HPS a synthetic ligand, affine to bacterial endotoxins (BE), was immobilized (sorbent HPS-0516). Procedure simulating hemoperfusion was performed to estimate the efficiency of BE removal. Through a column filled with 5 ml of sorbent citrated blood (75 ml) was perfused at a rate of 100-150 ml/min, at 37 °C. Blood was previously contaminated with LPS at a concentration of 400 EU/ml. The content of LPS in the samples was determined by endpoint chromogenic LAL-assay (Pyrochrome, USA) after 30, 60, 90 and 120 min. A pure HPS without a ligand was used as the reference sample. Data are presented on the graph. As well as LPS decline, decrease in bilirubin content of 40% (initial concentration of 10 mg/ml), clinically significant cytokines, and hemolysis absence were also shown.

The work was supported by the Ministry of Education and Science of the Russian Federation (№ 14.577.21.0165 dated October 28, 2015)

INVESTIGATION OF THE PENETRATION OF A QUATERNARY AMMONIUM COMPOUND IN COMPLEX WITH FULLERENE C_{60} THROUGH A PLASMA MEMBRANE

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The design of drug delivery systems is an actual problem of pharmacology and medicinal chemistry. Such systems will increase the therapeutic effectiveness and reduce the toxicity and side effects of drugs. Delivery of low-molecular substances through the blood-brain barrier (BBB) can solve the problem of treating many neurotic diseases, for example, Parkinson's and Alzheimer's diseases.

We have shown the possibility of creating such systems based on fullerene C_{60}. We synthesized complexes of amino acid derivatives of fullerenes with hexonium of the general formula $[C_{60}(NH(CH_2)nCOOH)m \times (CH_3)_3N(CH_2)_6N(CH_3)_3]$. Hexonium is a bis-quaternary compound and is unable to penetrate the BBB. However, when hexonium as part of our complexes is administered to mice and rats it affects the central effects of nicotine: suppresses nicotine-induced convulsions, and also reduces motor activity [1].

Therefore, the aim of this work was to study the *in vitro* penetration of these complexes through the plasma membrane.

For this purpose, a solution of hexonium, as well as its complex with fullerene derivatives - compound IEM-2214 (1, 10, 100 and 1000 μg) was added to the culture of cells K-562 (chronic myelogenous leukemia of man). Cells were incubated with drug solutions for one hour. Staining of smears with a sturdy green dye showed the presence of green granules in cells incubated with the addition of complex. No staining was observed in control and hexonium groups. This indicates the penetration of hexonium in the composition of the complex through the plasma membrane.

Thus, we have shown that complexes based on fullerene C_{60} facilitate the transfer of quaternary ammonium compounds through the plasma membrane.

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HIGHLY EFFICIENT INTRACELLULAR DELIVERY OF GENOME EDITING TOOLS BASED ON MULTILAYER POLYELECTROLYTE MICROCAPSULES

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Currently, gene therapy is becoming increasingly popular as a therapy for a number of socially significant and incurable at the moment diseases. A new impetus for the development of the direction was the introduction of highly specific genome editing tools, one of the most promising of which is the CRISPR-Cas9 system. However, the lack of safe non-viral methods of delivery of editing tools sharply limits the use of this method in the clinic. One approach is the delivery of components of the CRISPR-Cas9 system by microencapsulation in containers based on biocompatible peptides and polysaccharides with their subsequent modification by various inorganic matrices and nanoparticles.

The aim of the work is the encapsulation of the matrix ribonucleic acid encoding the Cas9 protein (Cas9 mRNA) and guide RNA (gRNA) in polyelectrolyte microcapsules with their further in vitro delivery and evaluation of the functional activity of the delivered molecules. With the use of the technology of Layer by Layer (Polyarginine / Dextran sulfate) and sol-gel synthesis (Tetraethyl orthosilicate), new hybrid micro containers with low toxicity, high biocompatibility, ability to protect the encapsulated material from aggressive external influences and efficiently release genetic material into the cell. The resulting micro containers were characterized by confocal and electron microscopy.

To study the functional activity of the technology, a human embryonic kidney cell line (HEK293) carrying the reporter gene for fluorescent dTomato protein was created. As the deliverable editing tool, Cas9 mRNA and gRNA against this gene were included. In vitro studies to evaluate the efficiency of capsule transfection, their toxicity and biocompatibility, as well as the effectiveness of genomic editing of the target gene after internalization of the capsules into the cell were conducted. Confocal scanning laser microscopy, flow cytofluorimetry (FC), as well as other culture methods of analysis were used as research methods. As a comparison, the commercially available liposomal transfection system Metafectene pro (MF PRO) was used.

As a result of the work, a high frequency of cell and capsule association (97.2% according to FC data), low toxicity (the viability of the cell line at the control level during 7 days of observation after capsules injection into the cultural medium) and the high transfer ability of the microcapsules (FC data, along with Confocal microscopy demonstrates that capsules mediate a much higher transfection efficiency compared to MF PRO 76% versus ~ 50%). An estimate of the genome editing from the FC data showed knockout of the reporter gene in 32% of the analyzed cells on day 6 after delivery of the CRISPR / Cas9 system.

Thus, the created system based on polyelectrolyte microcapsules provides safe and efficient intracellular delivery of genome editing tools.

The work was supported by the Russian Foundation for Basic Research (grant no. 16-33-00966 mol_a).

METAL BASED ANTICANCER COMPOUNDS WITH TARGETING LIGANDS

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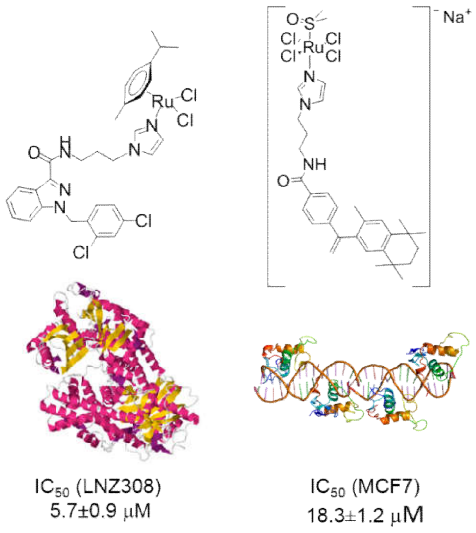
The development of metal-based anticancer compounds mainly focused on cytotoxic platinum compounds [1, 2]; however, recently attention shifted to the development of non-platinum anticancer drugs and it was shown that the ruthenium-based compounds could be clinical alternative of platinum drugs.

The tumor specificity of ruthenium compounds can be influence by ligand sphere around metal atom. Addition of Ru part to the targeting biologically active organic molecules can strongly increase anticancer properties. Lonidamine is known to inhibit the aerobic glycolysis in cancer cells while simultaneously enhancing glycolysis in the normal cells. Bexarotene is agonist of the retinoid X receptor and involved in the cell proliferation.

This presentation will focus on the hybrid compounds based on lonidamine and bexarotene tethered to the ruthenium unit via an imidazole group. Ru(II) and Ru(III) compounds found to be highly cytotoxic against number of the human cancer cell lines.



This work was supported by Russian Science Foundation (14-13-00483).

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Radiopharmaceuticals based on the somatostatin hormone analog

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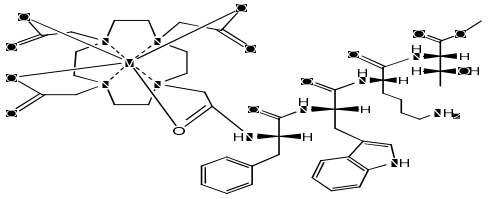
Conjugates [1], which are based on analogs of somatostatin hormone and labeled with various alpha, beta, auger and gamma-emitting radionuclides, can be used for more effective treatment and diagnosis of oncological diseases: ^{213}Bi, ^{90}Y, ^{67,68}Ga, ^{64,67}Cu, ^{44}Sc. (Picture 1)



M = ^{213}Bi, ^{90}Y, ^{67,68}Ga, ^{64,67}Cu, ^{44}Sc.

Picture 1

An important factor for the application of the obtained complexes is their stability in human body. Quantum chemical calculations of selected complexes (PBE0-D3/SBKJC PCM(H_2O)) have shown that binding of the peptide to DOTA does not alter the secondary structure of the peptide, so its affinity to the receptor should be maintained at the initial level.

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SYNTHESIS OF NEW METHIONINE-CONTAINING PHOTOSENSITIZER FOR PDT

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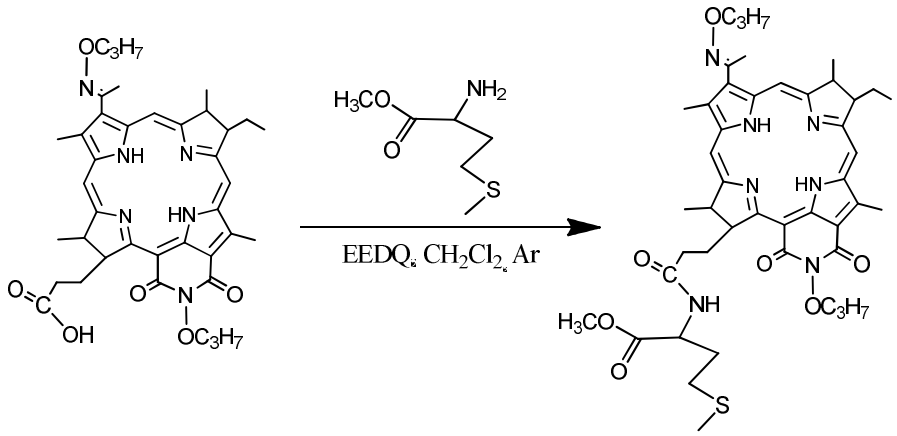
Methionine is sulphur-containing proteogenic amino acid. It takes part in such biochemical processes in organism as methyl group donation and antioxidant system. There is a phenomenon in methionine metabolism called “methionine dependence”. It consists in inability of some tumor cell lines to survive in environment where methionine is replaced by its precursor – homocysteine. Meanwhile normal cells can survive in such conditions. [1]

One of the main methods in oncology is photodynamic therapy (PDT), which consists in intravenous injection of photosensitizer (PS), its accumulation in tumor and then illumination of tumor by light with wavelength corresponding to the photosensitizer. PDT is modern, effective and minimal invasive method of treatment of cancer. Because of this and also because of such phenomenon as methionine dependence it was decided to synthesize methionine-containing PS. In the capacity of leader compound O-propyloxime-N-propoxybacteriopurpurinimide (DPBP) was used. DPBP has maximum of absorbance at 800 nm, it makes it a perspective PS, what was demonstrated in some biological studies [2]. Synthesis was carried out by modification of propionic tail in 17-th position of bacteriochlorin by methionine methyl ester. EEDQ was used as a condensising agent. In result methionine-containing conjugate of DPBP was synthesized and characterized.



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DERIVATIVES OF NATURAL BACTERIOCHLOROPHYLL *A* AND WITH SULFUR-CONTAINING AMINO ACIDS AND THEIR BIOLOGICAL PROPERTIES

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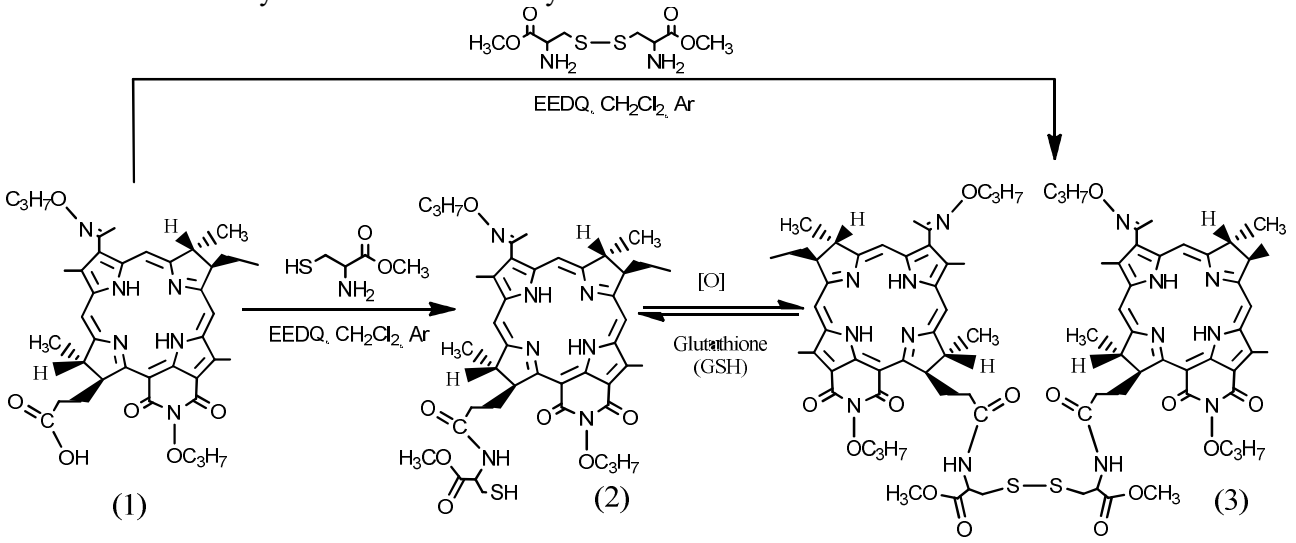
Reactive oxygen species (ROS) can be inactivated by intracellular glutathione and cysteine in the presence of specific enzymes glutathione and cysteine protease. These components form the an antioxidant system, the maintenance of the redox balance in the cell. This system can reduce the effectiveness of photodynamic therapy (PDT). Amino acids conjugated with photosensitizer (PS), will allow to increase the yield of ROS in physiological environments, disrupting the redox balance in cells and therefore increase the cytotoxicity of FS. In addition, amino acid residues increase the affinity of the photosensitizer to the membrane and thereby increases the selectivity of accumulation of PS.



O-propyloxime-N-propoxybacteriourpurinimide (Compound 1) was chosen as the leader compound was chosen, which proved to be well established in biological tests. Proteinogenic sulfur-containing amino acids were chosen for conjugation with PS, namely cysteine and cystine. Proteinogenic sulfur-containing amino acids (cysteine and cystine) for conjugation with PS were chosen. Compound 2 is not stable in air and oxidizes to form, forming a dimer (compound 3). Thus, compound 3 was synthesized directly using cystine was synthesized. Compounds 2 and 3 were examined on the HeLa cell line were examined. Studies showed a decrease in the half-maximal inhibitory concentration of the resulting conjugates 5-fold compared to the leader compound have shown.

TARGET CONJUGATES BASED ON NATURAL CHLORINES FOR PHOTODYNAMIC THERAPY AGAINST CANCER

A.M. Popkov[1], I.V. Pogrebnyak[1], N.V. Suvorov[1], A.V. Ivanova[1], A.E. Machulkin[2, 3], A.G. Majouga[2, 3], A.F. Mironov[1], M.A. Grin[1]

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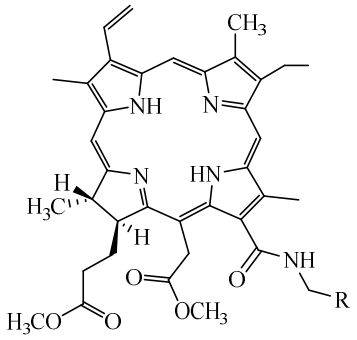
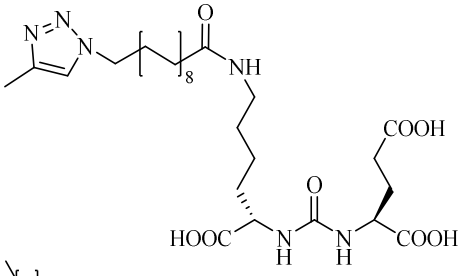
Photodynamic therapy (PDT) is a method of cancer treatment, based on the accumulation of a photosensitizer (PS) in tumor tissues and its irradiation with light at an appropriate wavelength, leading to the generation of reactive oxygen spices ($^1O_2$) and to the subsequent necrosis of the tumor. One main disadvantage of PDT is the lack of selectivity of PS uptake in tumor tissues, that can be solved by active targeting. This method is based on the usage of protein vectors that are capable to selective binding for the receptor, overexpressed on the target cell membrane surface.

In this study, new conjugates based on the chlorine e6 methyl ester were obtained with various target agents such as peptidomimetic **(1)** with the affinity for the prostate-specific membrane antigen and folic acid **(2a-d)** with the affinity for folate receptors α, which are overexpressed on different tumor types (lung, kidney, etc.). The structure of the obtained conjugates was studied with various physicochemical analysis methods. Biological *in vitro* and *in vivo* tests of the compounds **1**, **2a-d** will be carried out.

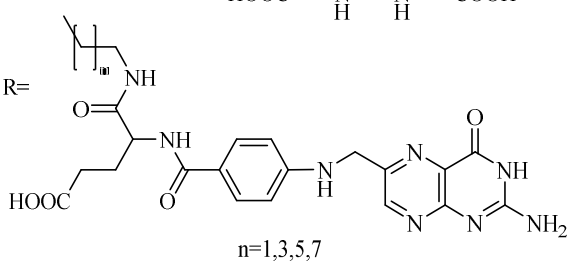


1,2a-d

1: R=



2a-d: R=



n=1,3,5,7

This work was supported by RFBR, research project №16-13-10092 and by the Grant of President of Russian Federation for state support of leading scientific schools of the Russian Federation № 7946.2016.11

DEVELOPMENT OF EFFECTIVE METHODS OF BETULIN ISOLATION AND PREPARATION OF BETULONIC ACID, SYNTHESIS OF NEW OF POTENTIALLY BIOACTIVE LUPANE DERIVATIVES

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Lupane triterpenoid derivatives exhibit various types of biological activities and they are widely used in the synthesis of compounds which are prospective for the treatment and prevention of dangerous diseases.
The authors developed a series of effective technological schemes for the extraction of triterpenoids using "green" solvents with complete extractant recycling. A new cost-effective technology for betulonic acid production comprising the direct oxidation of birch bark extracts in the extraction solvent with subsequent purification was proposed.
The series of covalent conjugates of triterpenoids of lupane series with the molecules of heterocycles-donors of H_2S and NO, which are promising in terms of anti-inflammatory, antioxidant and chemopreventive activity, were synthesized basing on betulinic and betulonic acids.

The preparation and *in vivo* biological activity of salts with inorganic and organic cations derived from betulonic acid derivatives were studied. Several salts were characterized by improved solubility and possess antioxidant and anti-inflammatory activity and hepatoprotective effect.

A NOVEL PT(IV) COMPLEX BASED ON OXALIPLATIN WITH PHENOL FRAGMENT

Yu.A. Gracheva[1], A.A. Antonets[1], I.D. Bronner[2], V.Yu. Tyurin[1], E.V. Kharitonashvili[1], E.R. Milaeva[1], and A.A. Nazarov[1]

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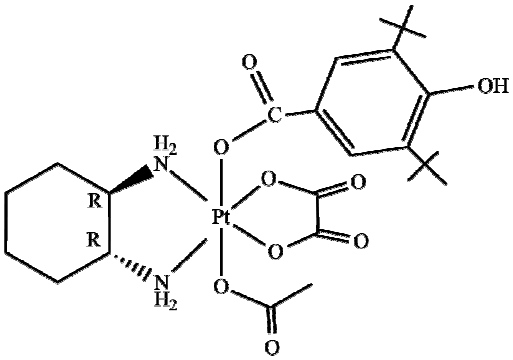
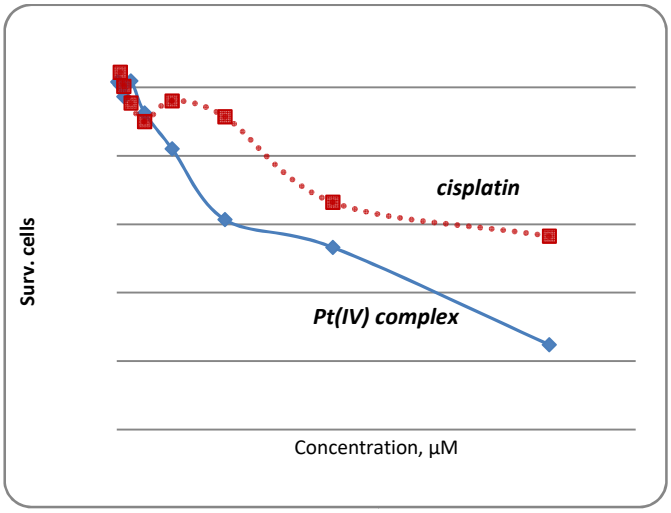
The focus of medical chemistry is the search for the new biologically active compounds. Incorporating the biologically active moiety into known pharmacologically active compound is one of the most common ways to design the new drugs. A novel platinum (IV) complex based on the oxaliplatin pharmacophore that contains an antioxidant phenol moiety to prevent the side effects was synthesized and characterized by NMR, IR and elemental analysis.





The antiradical properties (DPPH test), electrochemical behavior (CVA) and cytotoxicity (MTT assay) on human colon carcinoma cells (HCT-116) have been studied. It was found that the Pt (IV) complex exhibits only moderate antioxidant activity. On the other hand the platinum complex exhibits cytotoxicity comparable to the cytotoxicity of cisplatin with the IC_{50} value 25,6 μM.

The financial support of RFBR (grants № 16-03-00743, 17-03-00892) is gratefully acknowledged.

A UNIVERSAL METHOD OF BISPECIFIC ANTIBODY PRODUCTION

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Fab-arm exchange was first shown *in vitro* and *in vivo* for IgG4. We have shown that this exchange takes place *in vivo* in human milk, as well as *in vitro* in the presence of glutathione and protein factor from human milk.
IgG molecules are presented as bivalent monospecific molecules with stable structures and two identical antigen-binding sites. However, we found that up to 54% of human milk IgG molecules comprise κ- and λ-light chains simultaneously. Such molecules contain two distinct antigen-binding and are bispecific. In human milk bispecific IgG molecules are presented mainly by IgG1 74%.
Here we show the role human milk in Fab-arm exchange leading to bispecific antibody generation. We established the mechanism of the HL-fragments exchange reaction, optimal concentrations of GSH and concentrations of other reaction components.
This approach can be used for bispecific antibody molecules generation *in vitro*.

The work is supported by RFBR grant 16-34-00163 mol_a, and also by the President grant for young scientists MK-410.2017.4.

CONJUGATES OF NATURAL BACTERIOCHLORIN WITH NAPHTHALIMIDES AS MODEL THERANOSTICS

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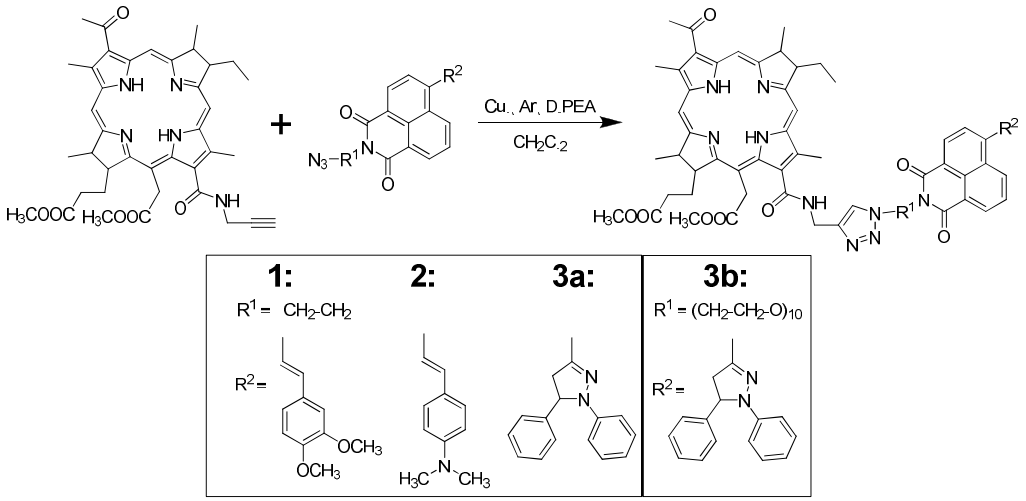
The use of bacteriochlorophyll *a* derivatives in the composition of theranostics is promising from the viewpoint of increasing the depth of photoinduced damaging effect. Naphthalimides have a narrow band of absorption and fluorescence and, at the same time, a large Stokes shift, which makes them promising for fluorescence diagnostics (PD) of tumors. A significant difference in the wavelengths of light absorbed by the dye and the photosensitizer makes it possible to realize separately fluorescent navigation and photodynamic therapy (PDT) using lasers with a tunable excitation wavelength.

Series of conjugates differing by substituents at the 4 position of naphthalimide and the linkers length between the active centers of the molecule was obtained by the reaction of azide-alkyne cycloaddition. The photophysical properties of bichromophores and their in vitro activity on mouse and human tumor cells have been studied. The efficacy of teranostics in vivo has also been studied. According to the results of the research, it is established that model systems based on bacteriochlorin and naphthalimide can successfully fulfill the role of theranostics in oncology.



EVALUATION OF DNA AND PROTEIN BINDING, DNA CLEAVAGE, MOLECULAR DOCKING AND *IN VITRO* CYTOTOXIC ACTIVITIES OF PD(II) AND PT(II) COMPLEXES FEATURING TETRAZOLYLACETIC ACIDS ESTERS

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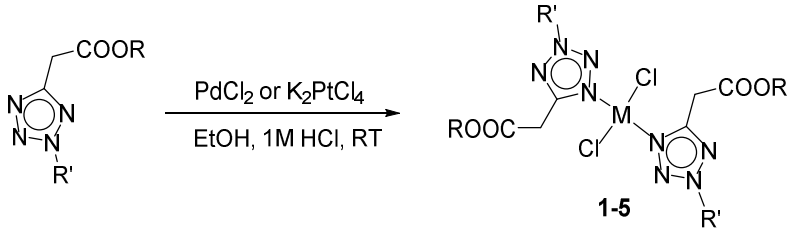
Tetrazole-containing coordination compounds of platinum group metal ions are promising compounds exhibiting antitumor activity [1]. In this study, two series of palladium(II) and platinum(II) complexes containing esters of tetrazolylacetic acids as ligands were synthesized and characterized by means of CHN analysis, HRESI-MS, ^{1}H and $^{13}C\{^{1}H\}$ NMR and IR spectroscopies.



M = Pd, R = H, R' = ^{t}Bu (**1**);
M = Pd, R = Et, R' = ^{t}Bu (**2**);
M = Pt, R = Et, R' = ^{t}Bu (**3**);
M = Pd, R = Et, R' = CH_2CH_2OH (**4**);
M = Pt, R = Et, R' = CH_2CH_2OH (**5**)

The interactions between the metal complexes with calf-thymus DNA (CT-DNA) and bovine serum albumin (BSA) were carried out by means of both experimental (UV, fluorometric and electrophoretic techniques) and theoretical methods. According to K_b (intrinsic binding constants) values determined all metal complexes show high DNA binding affinity. However, in the case of platinum complex this affinity is somewhat higher (K_b 2.58÷5.93 × 10^5 $M^{-1}$for Pd(II) complexes and K_b 8.82÷13.30 × 10^5 M^{-1} for Pt(II) complexes). The efficiency of interaction between BSA and metal complexes studied is proved by the corresponding binding constants (K_{bin}) which are in optimal range (K_{bin} 0.83÷4.12 × 10^5 L M^{-1}).
The molecular docking studies agree with the experimental data. According to the results obtained the DNA minor groove binding behavior of the tetrazole-containing palladium(II) and platinum(II) complexes ($\Delta G_{binding}$. -5.5 ÷ -6.2 kcal/mol) and efficiency of their binding to BSA *via* the favored binding site Trp-213 ($\Delta G_{binding}$ -7.2 ÷ -7.6 kcal/mol) were shown.

This work is supported by the Russian Science Foundation (grant 17-13-01124)

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SYNTHESIS AND SCREENING OF HEMOSTATIC ACTIVITY IN THE SERIES OF NEW DERIVATIVES OF 4-(HET)ARYL-2,4-DIOXOBUTANOIC ACIDS

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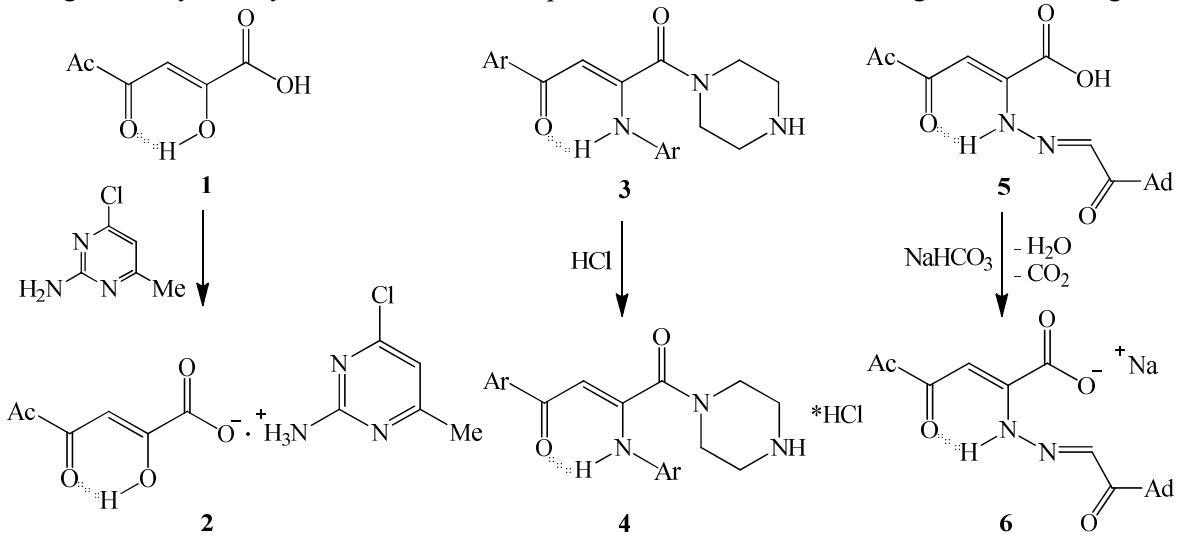
As it has been previously reported, the anticoagulant activity of hetarylammonium butenoates and sodium 2-(2-hetarylamino-2-oxoacetyl)phenolates is high [1,2]. However, the substances with hemostatic action among these derivatives were not found. Of interest was to investigate the influence of new water-soluble derivatives of 2,4-dioxobutanoic acids containing the fragments of pirimidyl, piperazinyl and adamantyl on blood coagulation system by *in vitro* tests. All compounds were obtained according to the following scheme:



It was revealed that derivatives 2, 4, 6 demonstrate low acute toxicity and pronounce hemostatic action. Some substances with activity exceeding that of the reference drug etamsylate were found. Regularities between the structure of the compounds and their effect on hemostasis were identified. It is needed for the further synthesis and search of potential pharmaceutical substances.

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HUMAN MILK EXOSOMES: ISOLATION, PROTEOMIC ANALYSIS, THERAPEUTIC POTENTIAL

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Milk is the unique biological fluid. In additional to its nutrients (lipids, sugars, and proteins), vitamins, minerals, protective enzymes (lysozyme), milk also contains various membrane structures, the most important of which are vesicles. One of the groups among vesicles found in milk are exosomes – membrane structures of endocytic origin with a 40-100 nm diameter. Exosomes performs many functions in the body, the most important of which is intercellular communication. A distinctive feature of exosomes is the ability of traverse biological barriers and naturally transport nucleic acids between cells. Existing delivery approaches are limited by concerns regarding their safety, toxicity, and efficacy. In contrast, exosomes as a natural cell-derived nanocarrier are immunologically inert if purified from a compatible cell source and possess an intrinsic ability to cross biological barriers. This makes exosomes an ideal candidate for the development of new mode of targeted drug delivery.

An important and relevant task is to develop a new effective method of isolation of pure exosomal preparations, suitable for various biological fluids, including milk, and various tissues. Now the main method of exosome isolation is the ultracentrifugation of samples leading to the exosomes sedimentation. This method is suitable for obtaining sufficiently pure preparations exosomes from biological fluids such as blood, urine and culture liquid. We have developed a method obtaining pure preparations of exosomes from complex biological fluids containing large amounts of protein impurities. We compared several methods of isolation, and proposed the original modification of the standard exosomes isolation protocol. Lack of protein and other impurities in exosome preparations has been verified by transmission electron microscopy and immunocytochemical staining using antibodies to crucial proteins marker on the surface of exosomes.

In addition, the protein composition analysis of the obtained preparations has shown the dependence of number and variety of proteins in the preparations on the method of exosomes isolation. Well-purified preparations of milk exosomes contain unpredictably small number of proteins, indicating that a significant number of milk proteins are not presented in exosomes.

Our results provide that with proper isolation technology milk may be a perspective source of exosomes needed for research and development on its basis of new therapeutic approaches of drug delivery.

BIOCHEMICAL FEATURES OF NEW MARKERS OF AUTOIMMUNE PATHOLOGY – BISPECIFIC ANTIBODIES

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Antibodies containing two different antigen-binding sites and capable binding two different antigens simultaneously are named bispecific. Perspectives of therapeutic use of bispecific antibodies in oncologic pathology promote the interest to these molecules from research laboratories and pharmacologic companies. Results, published in recent years are devoted to various ways of monoclonal bispecific antibody production, preclinical and clinical trials of these drugs, as well as possible prospects for their use.

We obtained natural bispecific antibodies in human milk, placenta and blood of healthy donors. The content of bispecific antibodies in these biological objects was determined, as well as the ratio of bispecific molecules to monospecific.

The literature data indicate that simultaneous expression of two light chain genes in one B lymphocyte clone is possible in pathologic processes (chronic lymphocytic leukemia, myeloma) as well as in artificial cells (hybridoma, induced plasmacytoma). These cases may be related to the secondary rearrangement of the immunoglobulin genes and to the fact that some peripheral populations of B lymphocytes avoid allelic exclusion.

According to our data, natural bispecific antibodies are formed in human body *in vivo* as the result of Fab-arm exchange. Our data indicate that this process occurs in the blood, milk and placenta between the IgG of all subclasses. We propose the possible biological role of Fab-arm exchange during pregnancy and lactation.

Here we show the potential use of natural bispecific antibodies as diagnostic tools in autoimmune processes.

The work is supported by RFBR grants 16-34-60066 mol_a_dk, 16-34-00163 mol_a, and also by the President grant for young scientists MK-410.2017.4.

THE ELABORATION OF PHOTOSENSITIZERS WITH IMPROVED SPECTRAL PROPERTIES FOR COMBINED THERAPY AND DIAGNOSIS

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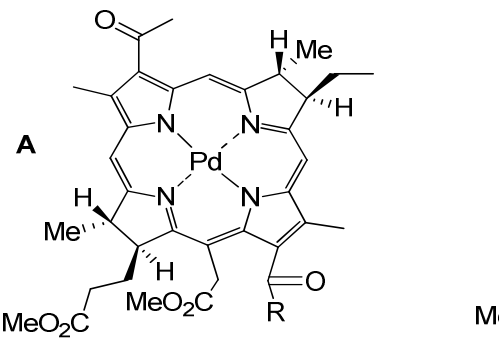
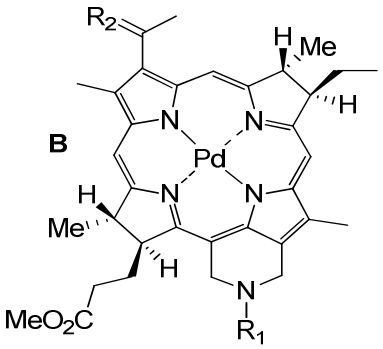
Nowadays the fluorescence diagnosis method (FD) has received wide recognition from malignancy diagnosis. Pd-complexes of natural bacteriochlorins as well as their derivatives with one more annulated ring E (anhydride or imide cycle) stand out among photosensitizers considered as FD agents. It is due to improved photophysical and spectral characteristics of such compounds which having red and near-infrared absorption [1]. The incorporation of palladium into bacteriochlorin derivatives leads to increased of their stability, variations in fluorescence and singlet oxygen quantum yield, and noticeably increased of macrocycle's photodynamical potential because of remarkable enhancement of molecule intersystem crossing rate into its ground triplet state [2].

As part of this effort, Pd-complexes of various bacteriochlorophyll *a* derivatives were synthesized, and photophysical and spectral properties of those were examined. The incorporation of palladium into bacteriochlorins coordination sphere (A) led to bathochromic shift of electronic absorption spectrum (EAS), decline in fluorescence intensity, and increased of singlet oxygen generation. At the same time the formation of bacteriocycloimide metallocomplexes (B) was accompanied by EAS hypsochromic shift, and increased of fluorescence intensity.



R: $NH(CH_2)_4NH_2$; $NH(CH_2)_6NH_2$; $NH(CH_2)_8NH_2$; 1,4,7,10 tetraazacyclododecane



R_1: NH_2; OC_2H_5; OC_3H_7

R_2: O; NOC_2H_5; NOC_3H_7

Thus, metals incorporation into bacteriochlorophyll *a* coordination sphere may leads to both increased and decreased fluorescence intensity, and likewise singlet oxygen quantum yield variations. By managing these two parameters one can obtain drugs suitable both for diagnosis and therapy of oncological diseases.

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WATER-SOLUBLE CONJUGATES OF BACTERIOCHLOROPHYLL *A* DERIVATIVES WITH POLOXAMERS

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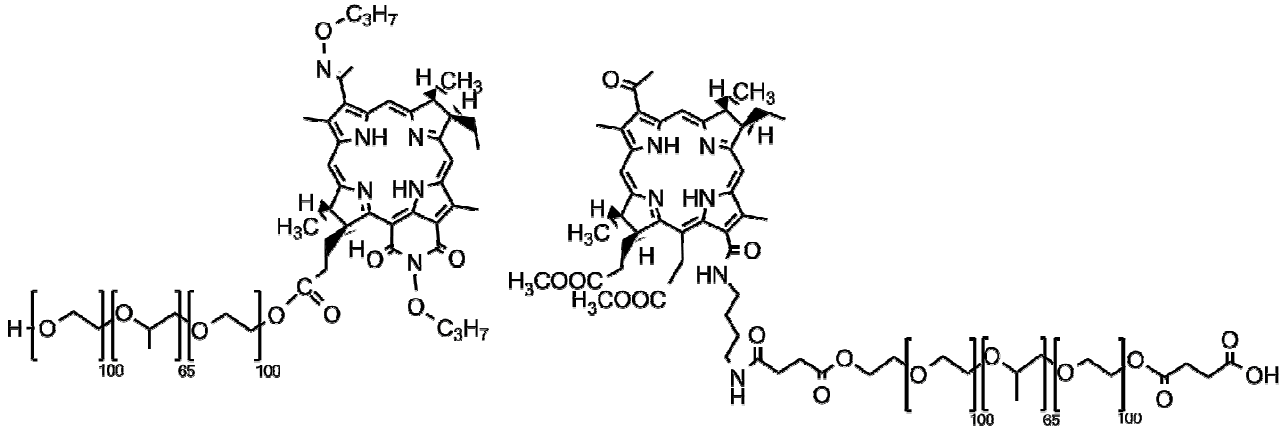
Photodynamic therapy (PDT) is a noninvasive method of oncotherapy, including the administration of photosensitizer (PS), its accumulation in the tumor and irradiation with light of an appropriate wavelength, which causes the generation of reactive oxygen species, and necrosis of tumor tissues. Among the most promising PS for PDT there are derivatives of chlorins and bacteriochlorins, which have absorption in the near-IR region. However, their use is limited due to their poor solubility in aqueous media. One of the methods to solve this problem is to synthesize conjugates of PS with amphiphilic polymers. The aim of this study was to obtain water-soluble conjugates of bacteriochlorophyll *a* derivatives with pluronic F-127.



In this work conjugate of O-propyloxime-N-propoxybacteriopurpurinimide with pluronic F-127 (**1**) and conjugate of an aminoamide derivative of bacteriopheophorbide with the modified pluronic F-127 (**2**) containing carboxyl groups at the terminal ends of the molecule were obtained. The compounds obtained were able to dissolve in water maintaining their photophysical properties. The structure of compounds **1** and **2** was confirmed by ^{1}H NMR spectroscopy. Biological *in vivo* tests were carried out in rats grafted with M1 sarcoma tumors.

EFFECTIVE PS FOR COMBINATION THERAPY OF CANCER BASED ON GOLD (I) MIXEDLIGAND COMPLEXES

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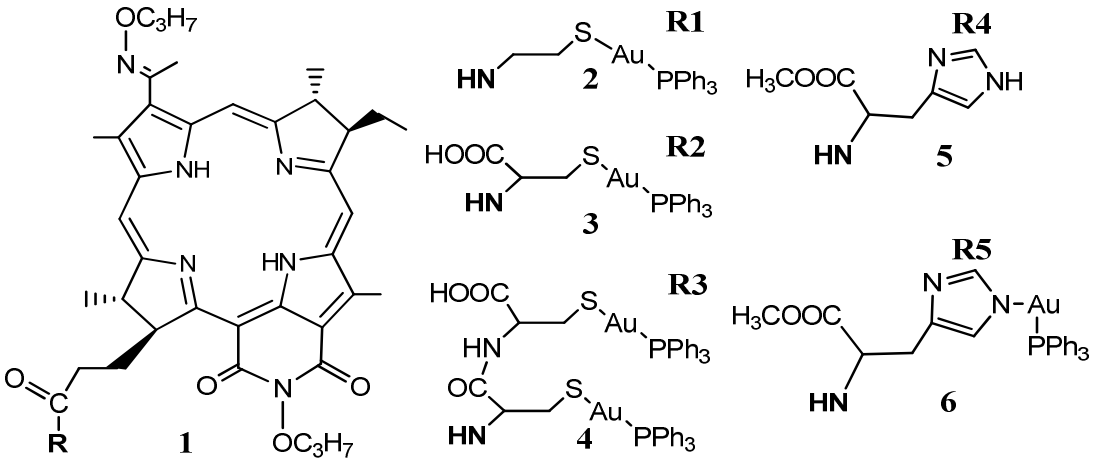
Reducing the resistance of cells to free radicals and oxidative stress can increase the effectiveness of photodynamic therapy (PDT), the main cytotoxic agent, which is singlet oxygen. As known thiolate and nitrogen-containing gold (I) complexes are able to inhibit thioredoxin reductase. This study includes the development of high-performance PS for combination therapy of cancer, based on dipropoxybacteriopurpurinimide (DP-BPI) (1) and gold (I) mixedligand complexes of triphenylphosphingold (TPPA).



In this work, a number of thiolate complexes of gold (I) were synthesized on the basis of DP-BPI (1). Biological in vitro tests showed the presence of dark and photoinduced toxicity in compounds 2, 3 and 4, according to the results of these studies, the most effective was compound 4. The next series of gold (I) complexes are histidine-based compounds. We synthesized compounds 5 and 6, compound 6 synthesized in two ways, namely by direct synthesis of a gold complex based on the histidine derivative DP-BPI (compound 5) or by synthesis with a previously synthesized histidine-TPPA complex.

The work was carried out with the financial support of the RFBR grant No. 16-03-00519.

EFFICIENT GENE EDITING VIA NON-VIRAL DELIVERY OF CRISPR-CAS9 SYSTEM USING POLYMERIC AND HYBRID MICROCARRIERS

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CRISPR-Cas9 is a revolutionary genome-editing technology that has huge potential for the treatment of genetic diseases. However, the lack of the safe, non-viral delivery systems has hindered its clinical application. Here, we first report the application of polymeric and hybrid microcarriers that are capable to deliver all components of the CRISPR-Cas9 system. We showed that these polymeric and hybrid microcarriers mediate more efficient transfection than a commercially available liposome-based transfection reagent (>70% vs. <50% for mRNA, >40% vs. 20% for plasmid DNA). For proof-of-concept, we delivered CRISPR-Cas9 components using our capsules to dTomato-expressing HEK293T cells – a model, in which loss of red fluorescence indicates successful gene editing. Notably, transfection of indicator cells translated in high-level dTomato knockout in app. 70% of transfected cells. In conclusion, we have shown the proof-of-principle to use our micro-sized containers as promising non-viral platform for efficient and safe gene editing.

The work was supported by the Russian Foundation for Basic Research (grant no. 16-33-00966 mol_a).

HUMIC SUBSTANCES AS A SOURCE OF NOVEL AGENTS AGAINST TEM-1 BETA-LACTAMASE

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The microbial resistance to antibiotics is a genuine global threat. Effectiveness of well-known single-molecule beta-lactamase inhibitors (BLIs) has diminished with the evolution of bacteria [1]. Hence, new multi-target agents are in high demand. In this respect, humic substances (HS) deserve particular attention. HS are the products of abiotic combinatorial synthesis yielding supramolecular mixtures of natural organic compounds formed mostly by phenolic and carboxylic units. It was reported that they possess a broad spectrum of biological activity, such as anti-inflammatory and antiviral [2]. Here we present a new BLIs and HS combination as an agent against TEM-1 beta-Lactamase.

Inhibitory activity was determined by measuring rate of CENTA cleavage using UV-absorbance at 405 nm. Two HS samples (humic acids (HA) and hymatomelanic acids (HMA)) obtained by standard protocol showed moderate activity against TEM-1. In order to determine active compounds HMA was fractionated using SPE extraction followed by gradient H_2O/CH_3OH elution. Molecular compositions of obtained fractions were determine by ultra-high resolution mass-spectrometry. Most hydrophobic fraction of HMA (hydrophFR) showed the highest inhibitory activity against TEM-1 close to commercial agent, e.g. sulbactam (Slb) and tazobactam (Tzb). Moreover, combination of HS samples with BLIs decreases the rate of CENTA cleavage product accumulation. Addition of hydrophFR of HMA showed a 55% increase of sulbactam inhibitory activity (Fig. 1). Therefore, using HS-related products may be a valuable option for patients infected with multidrug-resistant organisms.

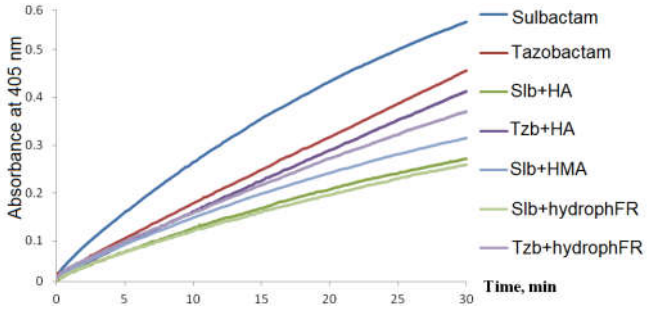

Fig. 1. Kinetic curve of UV-absorbance at 405 nm of reaction mixture of TEM-1, CENTA and BLI

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THE BIOLOGICAL EFFECTS OF SILVER NANOPARTICLES IN MOUSE PERITONEAL MACROPHAGES *IN VITRO* INFECTED WITH BCG *MYCOBACTERIA*

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The tuberculosis (TB) caused by *Mycobacterium tuberculosis* is currently an extremely widespread disease in the world, with high morbidity and mortality rates despite the significant advance in medicine. With the emergence and increase of *M. tuberculosis* resistant to multiple antibiotics, the development of new and effective antimicrobial reagents free of resistance is required for the successful treatment of TB infection. Due to their bactericidal properties, silver nanoparticles (Ag(0)-NPs) are the most frequently applied nanomaterials [1]. Previously, we have determined anti-mycobacterial activity of Ag(0)-NPs with different size 2-5, 10-15 and 35-40 nm at the 5.0 μg/ml concentration in mouse bone-marrow cells and peritoneal macrophages *in vitro* infected with the Bacillus Calmette-Guérin (BCG, a strain of attenuated live *M.bovis*) vaccine [2], because good concordance was found between the results on the sensitivity of *M. bovis* BCG and *M. tuberculosis* to diverse compounds [3]. Then, we have studied the molecular mechanisms of Ag(0)-NPs action, such as ROS (reactive oxygen species) generation, apoptotic or necrotic death, and inflammation (the production of TNFα, IFNγ, and IL-1α), in BCG-infected mouse peritoneal macrophages with or without the addition of the antioxidant GSH (reduced glutathione) and mitochondrial antioxidant LiCl. In a result, we revealed the activation of caspase 3/7 (CellEvent Caspase-3/7 Green Detection Reagent staining) and apoptotic death (Annexin V-FITC staining) in animal cells after 2, 4, and 6 hours of the Ag(0)-NPs treatment, but not after the exposure to BCG mycobacteria or isoniazid. We did not observe the hydrogen peroxide (H_2O_2, H_2DCFDA staining), the mitochondrial superoxide radical (O_2^-, MitoSOX Red indicator staining), and other ROS types (CellROX Deep Red Reagent staining) generation in the all investigated cell cultures for 2, 4, and 6 hours of the Ag(0)-NPs treatment. After 24 hours of experiments, we detected the elevated ROS type production, but not H_2O_2 and mitochondrial O_2^-, in some BCG-infected mouse macrophages treated with the 35-40 nm Ag(0)-NPs, that was reduced by GSH treatment. We supposed this phenomenon was associated with the determined intensification of BCG mycobacteria killing in host macrophage lysosomes (*Mycobacteria* lipoarabinomannan and LysoTracker Red DND-99 dye staining) at this time point.

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EFFECT OF THE MEDIUM ON THE RESISTANCE TO DEGRADATION OF THE HYDROXYAPATITE-BIOPOLYMER COMPOSITES USED AS DRUG DELIVERY SYSTEMS

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Composites based on hydroxyapatite (HAP) are of interest not only as materials for orthopedic reconstruction after bone diseases such as tuberculosis [1], but also as drug delivery systems.
We studied the dependence of the degradation rate of HAP-biopolymer composites in four model medium: SBF, HBSS, synovial fluid and liquid simulated saliva. Collagen, casein, alginate and chondroitin in various combinations and ratios have been used as biopolymers.
The initial hydroxyapatite was synthesized by the method of co-precipitation. Composites were prepared by mixing and distributing the gel into plates. The samples were dried by freezing and were formed as ceramic tablets with a diameter of 1 cm and a height of 2 mm. For treatment and reconstruction in the oral cavity (contact with saliva) samples with collagen and alginate showed best resorption.
The obtained data allow selecting the most optimal compositions for each of the media for studying the pharmacokinetics and pharmacodynamics of drugs delivery from these composites and evaluating the feasibility of their usage as drug delivery systems.

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PHOSPHORYLATED 1,3-ALKADIENE STRUCTURES IN REACTIONS WITH VARIOUS NUCLEOPHILES

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Text of this abstract can be found in the Russian version of the conference abstract book.

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Correspondent presentations

TARGET DESIGN OF NOVEL PHARMACOLOGICALLY ACTIVE 1-(DIPHENYLMETHYL)PIPERAZINES

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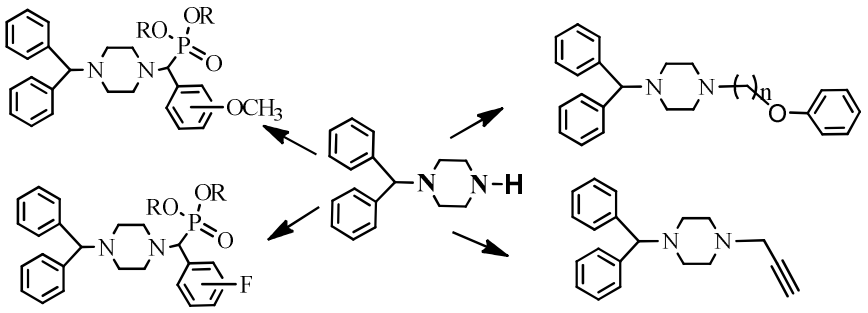
Due to the variety of practically useful structures, the purposed search for new pharmacologically active compounds is more rational than the empirical. At most the success of such studies depends on the original molecule. While choosing the basic synthesis method for our studies, the main criteria were: the synthetic potential of the compound; the simplicity of the intended modifications and, of course, the pharmacological potential of the original fragments. As a starting object the fragment 1- (Diphenylmethyl) piperazine has proved to be the most suitable one. This fragment is found to be a major component of following medicines: cinnarizine and flunarizine (slow calcium channels blockers), cetirizine (a metabolite of hydroxyzine, blocker of H1-histamine receptors).

The reaction of 1- (diphenylmethyl) piperazine with phenoxyalkyl and propargyl bromides in DMF and in the presence of powdered KOH, which proceeds for 1-2 days at room temperature, leads to the formation of 1- (phenoxyalkyl- and propargyl-)] - 4- (diphenylmethyl) Piperazine with high yield.



Aminophosphonates with a methoxy- and fluorophenyl fragments were obtained under conditions of a three-component "one-pot" Kabachnik-Fields reaction [1].

The tests on mice and rats revealed that synthesized molecules and their complexes with β-cyclodextrin have local anesthetic and antibacterial activities. Leukopoiesis stimulating action is found in aminophosphonates.

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BIOLOGICAL ACTIVITY OF NOVEL SN (IV) CARBOXYLATES WITH PROTECTIVE PHENOL GROUP

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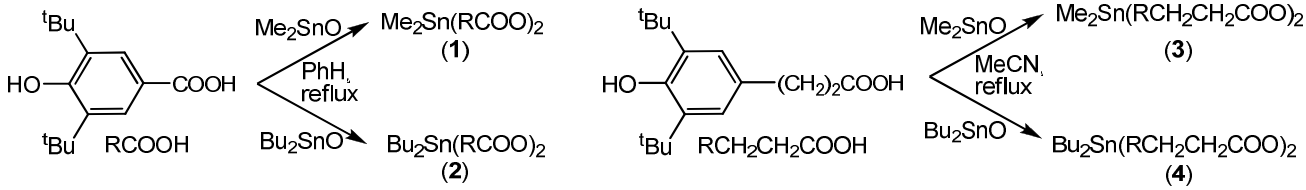
Tin (IV) complexes are perspective candidates for the creation of specific anticancer drugs. Moreover, hindered 2,6-di-*tert*-butylphenols are widely used antioxidants as vitamin E mimetics. To reduce the possible toxic side effects of tin (IV) compounds and to extend the spectrum of their therapeutic applications, two series of tin carboxylates were synthesized and characterized by NMR, IR spectroscopy, mass spectrometry and X-ray diffraction analysis.



The antioxidant activity of compounds **1**-**4** was monitored spectrophotometrically in reactions with stable 2,2-diphenyl-1-picrylhydrazyl radical (DPPH), in the Cu^{2+} reduction to Cu^{+} (CUPRAC test) and in reaction of inhibition of superoxide radical anion generated by xanthine oxidase (NBT assay). It was shown that organotin carboxylates are effective antioxidants.
The cytotoxic activity of complexes **1**-**4** was evaluated against colorectal cancer cell line (HCT-116) in MTT test. Complexes **2** and **4** demonstrate higher activity than cisplatin. The nature of organic group plays critical role in the toxicity mechanism. The introduction of the protective 2,6-di-*tert*-butylphenol group leads to a reduction in the overall toxicity of complexes that makes them perspective antitumor agents.

IC_{50}, μM (HCT-116)				
1	**2**	**3**	**4**	cisplatin
>50	3	>50	1.6	5

This work was supported by RSF (14-13-00483), RFBR (15-03-030557).

MUTAGENIC ACTION OF THE PHARMACEUTICAL SUBSTANCE– RAPITALAM

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The aim of this study is the identification and quantitative assessment of alkali-labile sites and DNA strand breaks in leukocytes of peripheral blood of male mice treated orally with Rapitalam.

Materials and methods: The test pharmaceutical substance of Rapitalam was dissolved in dimethyl sulfoxide to final concentration of solvent 5%. Rapitalam was administered to animals orally according to 2 schemes: a single acute dose (413 mg/kg, which corresponds to 1/5 LD50 dose) and once daily in a therapeutic dose (3 mg/kg) for 4 days. For analysis we used a peripheral blood of the mice obtained by incising the tip of the tail. The blood aliquots sampling (10 µl) of each animal was performed not later than 24 hours after the completion of treatment. Peripheral blood was sampled in tubes containing phosphate buffer and 1 mM EDTA, shook by vortex to prevent clotting and immediately used for preparation of agarous slides [1,2]. The preparations were analyzed using a fluorescence microscope "LUMAM I-3" ("LOMO", Saint-Petersburg, Russia). Image capture was performed with a digital camera "Nikon CoolPix 995" (Japan) with the subsequent transfer them to the computer. The processing of the photomicrographs was performed using specialized software, where there were implemented the algorithms of calculation of standard parameters of "comet" [3]. The analysis of parameters of DNA comets was performed with the stored digital images. As an indicator of DNA damage there was used the value of %TDNA - % DNA in the tail of the comet. Statistical analysis was performed using student's t-test ($p < 0.05$). The middle values presented as $M \pm SD$.

Research results: Table shows average values of DNA damage in groups while taking the drug and/or solvent for this drug.

Parameters	Acute dose, 1/5 of LD_{50}, 413 mg/kg		Therapeutic dose, 3 mg/kg	
	%TDNA	p	%TDNA	p
Rapitalam	23,25 ± 3,35	0,008	2,2 ±1,22 *	0,0009
DMSO, 5%	16,51 ± 3,75		16,77 ± 5,3	

Table 3. The influence of Rapitalam on the level of DNA damage in peripheral blood leukocytes of the mice (M ± SD).

* significantly different from the value for acute dose of Rapitalam ($p < 0.05$).

Conclusions:

1. Analysis of the level of DNA damage of blood leukocytes (%TDNA) in the groups with acute dose of Rapitalam showed significant differences between animals treated with the solvent from mice treated with dissolved in DMSO Rapitalam ($p = 0.008$). It indicates the presence of DNA-damaging activity of Rapitalam in the acute dose.
2. Analysis of the level of DNA damage of blood leukocytes (%TDNA) in groups with therapeutic dose of Rapitalam showed significant differences between animals treated with the solvent and animals treated with dissolved in DMSO Rapitalam ($p = 0.0009$).

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NEUROPROTECTIVE EFFECT OF LUPANE TRITERPENOID IN MODELS OF MULTIPLE SCLEROSIS

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Multiple sclerosis (MS) is a socially significant non-traumatic neurological disease resulting in expressed disability. MS currently remains incurable, mainly due to the fact that current drug therapy directed to correction of primary autoimmune inflammation and demyelination of the conductors of the spinal cord and brain does not yield positive response in case of secondary progression of the disease in chronic patients. It was found that early injury of neurons and their microenvironment (neuronal and oligodendrocyte dystrophy, axonopathy, and gliosis) has played a crucial role in pathogenesis of MS. This fact necessitated revising the strategy for treatment of MS to design the neuroprotective approaches.

In Novosibirsk Institute of Organic Chemistry the neuroprotective activity of terpenes of different structural classes is investigated. Among the lupane triterpenoids, an amide of betulonic acid with antioxidant, anti-inflammatory and immunomodulating activity was selected. The agent reduces the activity of cytotoxic T-lymphocytes in the hypersensitivity reaction and reduces the inflammation caused by the T-mitogen concanavalin A. It is shown that the triterpenoid is the inducer of the cytoprotective network Keap1-Nrf2-ARE.

The neuroprotective effect of amide was studied in C57Bl/6j mice in two models of MS: MOG-induced experimental autoimmune encephalomyelitis (EAE) and cuprizone-induced demyelination. The influence of agent on the functional activity of the central nervous system and morphological and ultrastructural injuries of the brain and spinal cord cells were investigated. It was found the triterpenoid restricted the development of the pathogenic features of MS in the both models. The neuroprotective effect was confirmed by MRI (carried out by A. V. Romashchenko, Institute of Cytology and Genetics SB RAS). The specific neuroprotective effect such as ability to reduce severity of demyelination, axono- and neuronopathy, oligodendrocyte dystrophy, inflammatory infiltration in the mouse spinal cord and brain tissues will be discussed.

The work is supported by the Basic Program of SB RAS V.48.1.5:

AN UNEXPECTED OXIDATION OF UNDECABORATE IONE AS A NEW METHOD PERSPECTIVE PHARMACOPHORES SYNTHESIS

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Boron chemistry is one of the leading branches of modern chemical science and technology. Carborane and metalcarborane derivatives, which are used in neutron capture cancer therapy [1], are of the most interest. Some carborane derivatives are known for their antimicrobial, antiviral, and neurotropic activity as well as enzyme inhibitors [2]. All of that outstands carboranes and metalcarboranes in the wide separate group of new perspective pharmacophores [3]. However the main and only raw compound for carborane obtaining was and is decaboran(14) – $B_{10}H_{14}$, and need in it is growing every year. That fact forced us to develop a new efficient method for decaboran synthesis. Using domestic and foreign works [4, 5] we concluded the most optimal and safe method of decaborane obtaining is two-step synthesis where at the first stage we synthesize undecaborate salt [6] from alkali metals boronhydrydes and haloic alkyls, at the second stage, we oxidize the salt with different oxidizers. The methods described in literature are either laborious at execution which causes raise of product cost price or not efficient enough and non-ecological [7]. That was the reason to find a new method of undecaborate oxidizing. The solution of that problem became ketones and carbonyl compounds as oxidizers. To be noted, that before this unusual reaction was unknown and unlike the common oxidizing methods of $NaB_{11}H_{14}$ [5, 7] it allows to obtain decaborane(14) with high yield.

$$2NaB_{11}H_{14} + 4R'C(O)R'' + H_2SO_4 + 6H_2O \rightarrow 2B_{10}H_{14} + 2H_3BO_3 + 4R'CH(OH)R'' + Na_2SO_4$$

where $R' = H, CH_3, C_2H_5, C_6H_5$

$R'' = H, CH_3, C_2H_5, C_6H_5, CH_2COCH_3$

Developing this direction the optimal technique of sodium undecaborate to decaborane(14) oxidizing reaction using ketones was invented and patented at industrial base of JSC GNIIChTEOS [8].

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ANTITUMOR ACTIVITY OF NEW DEHYDROZINGERONE DERIVATIVE

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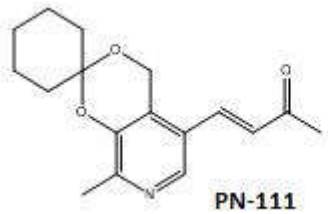
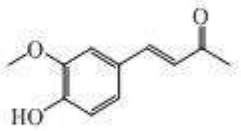
In the present research we investigated biological properties of the new synthesized alkenyl derivative of pyridoxine and dehydrozingerone (PN-111) as antineoplastic agent [1-3]. With the use of metabolic MTT-test we estimated cytotoxicity of the compound PN-111 concerning a number of cancer and conditionally normal human cells. According to the data the new derivative PN-111 is characterized by larger antitumor activity than dehydrozingerone and also his predecessor – curcumine concerning tumor cells of mammary gland, prostate adenocarcinoma, glioblastoma and colorectal carcinoma. The concentrations of semi-maximal inhibition of a tumor cells proliferation are in limits 3-10 μM. According to flow cytometry data PN-111 shows cytostatic action on a particular growth phase of tumor cells, namely initiates arrest of a cell-cycle in the G2/M phase, inhibiting further transition of cells to the G0/G1 phase. Similar action shows also dehydrozingerone and some commercial antineoplastic agents, in particular paclitaxel. Interestingly, that PN-111 makes rather slight attachment on a membrane potential of mitochondria and probably cannot serve as an apoptosis inducer. The new derivative PN-111, as well as dehydrozingerone, demonstrates antioxidant properties, reduces initially high content of the reactive oxygen species in tumor cells. By results of the research we can conclude that the new synthesized derivative of dehydrozingerone - PN-111 is perspective antineoplastic agent and can be recommended for further *in vivo* studying on a xenograft models.



PN-111



Dehydrozingerone

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF HYDROXYBENZOYL PYRIMIDINES

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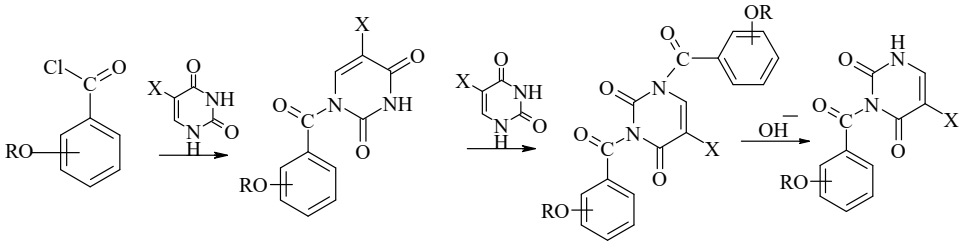
Hydroxybenzamides and their derivatives demonstrated a variety of pharmacological activity. It was shown that chemical modification of hydroxybenzoic acids by different fragments, pharmacophore groups, had given rise to unexpected change in biological action. N-hydroxybenzoyl derivatives of GABA and glycine were reported for psychotropic, antidepressant, cerebroprotective and anxiolytic activity [1]. N-hydroxybenzoyl derivatives of heterocyclic compounds such as morpholine [2] and imidazole [3] displayed analgesic, nootropic and cerebroprotective activities. In the past few years, the therapeutic interest of pyrimidine derivatives in pharmaceutical and medicinal field has been given a great attention to the medicinal chemists.

Literature reveals that pyrimidine derivatives are well known to have anticancer and antiviral activities. Thus, in this work, a series of novel N-hydroxybenzoyl derivatives of uracil and thymine were synthesized by acylation of a heterocycle with hydroxybenzoyl chloride. Prompted by many factors, the new procedure of hydroxybenzoyl chlorides preparation was attempted. The procedure included the usage of oxalyl chloride as chlorination agent in ratio acid:oxalyl chloride:DMFA 1:1.1:0.07 at boiling point. The advantage of this method resided in high yields of halides used without purification [4]. N^1-derivatives of uracil and thymine were prepared from the reaction of heterocyclic base with acyl chloride in ratio 1:1 in pyridine. N^1, N^3-htdroxybenzoylpyrimidines were synthesized in ration 1:2 in the same solvent. It is known that N^1, N^3-derivatives of heterocyclic bases are unstable in aqueous alkali, treatment of a solution of N^1, N^3-dihydroxybenzoylpyrimidines in pyridine with 0.25 M KOH followed by alkaline hydrolysis of the reaction mixture afforded N^3-derivative.



RO:2-OH, 3-OH, 4-OH, 2,3,4-OH, 2-OMe, 3-OMe, 4-OMe, 2,3,4-OMe, 2-OAc, 3-OAc, 4-OAc, 2,3,4-OAc, 2,4-OH, 2,4-OAc, 2,4-OMe; X: H, CH_3

A series of novel pyrimidine derivatives were tested for their biological activity. Several of them were found to exhibit activity as crosslink breakers that contribute to the restoration of the structure and function of structural proteins. The therapeutic potential of crosslink breakers for cardiovascular complications and dermatological alterations associated with aging, development of diabetes complications (angiopathy, cataract, ratinopathy, nephropathy, etc.), Alzheimer's disease (glycated formation of neurotoxic β-amyloid) and cancer [5].

In conclusion, our data show potential activity of newly synthesized pyrimidines and this may be a novel therapeutic strategy in the treatment of diabetes complications.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 15-43-02 445).

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POLYFLUOROALKYL-CONTAINING PYRAZOLES AS THE BASE TO OBTAIN BIOACTIVE MOLECULES

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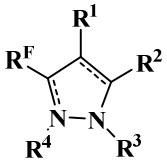
The pyrazole structural motif is presented in many molecules with different pharmaceutical actions [1, 2]. The prospect of obtaining bioactive substances on the basis of polyfluoroalkyl-containing pyrazoles is discussed in the report. We have developed approaches to the synthesis of variously substituted polyfluoroalkyl-containing pyrazoles. It is shown that "synthon" method based on cyclization of polyfluoroalkyl-1,3-dicarbonyl compounds with □-N,N-dinucleophiles is suitable to form functionalized pyrazoles. In addition, the advantages of changing the pyrazole skeleton in the reactions with electrophilic reagents are discussed. The possibilities of further chemical transformation of pyrazoles having carboxyl, hydroxyimine and amine substituents are shown. As a result, the paths for the synthesis of polyfluoroalkylpyrazoles with different set of substituents at all positions were found.



R^F = CF_3, CF_2H, C_2F_5, C_2F_4H, C_3F_7, C_4F_9, C_4F_8H, C_6F_{13} etc;
R^1 = H, Ar, Het, COR, CO_2X, N=NAr(Het), Hal, N=O, NH_2 etc;
R^2 = H, Alk, Ar, Het, OH, CO_2X;
R^3, R^4 = H, Alk, Ar, Het, $CSNH_2$, COAr(Het)

It has allowed to obtain the pyrazoles with anti-inflammatory, analgesic, tuberculostatic, antiviral, antifungal and hypoglycemic activities depending on the substituents.

This work was financially supported by RSCF (grant 16-13-10255)

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STRUCTURE AND ANTIOXIDANT ACTIVITY OF MAILLARD REACTION PRODUCTS IN *D*-LACTOSE – *P*-AMINOBENZOIC ACID SYSTEMS

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Amino-carbonyl interactions in carbohydrate – amine systems, known as Maillard reaction, represent the complex multistage process leading to formation a wide range of products, which show antioxidative, antimicrobial, antimutagenic and other physiologically important properties [1]. The majority of studied carbohydrate-amine systems include aliphatic amines and amino acids whereas properties of reaction products with arylaminocomponents as reagents are almost not investigated. In this research we presented results of sugar-amine reactions studying in *D*-lactose with *p*-aminobenzoic acid systems in subacid aqueous-ethanolic media in the presence of catalytic quantities of copper (II) ions, and antioxidative properties of the products are also valuated. The course of reactions was controlled by the TLC-method and UV-Vis spectrophotometry, fractionation of final products was carried out by dialysis, and the structure was confirmed based on FTIR- and mass spectroscopy data, the antioxidant activity was estimated on linoleic acid oxidation inhibition degree by iron-thiocyanate method in comparison with α-tocopherol. Due to results of researches presented the dependence of final product's structure on melanoidin formation duration has been established, in particular within the first three hours of synthesis the heteroaromatic nitrogen-containing substances are formed, including essential quantity of structural-linked carbohydrate rings which are transformed to conjugated polymeric heterocyclic structures, in particular substituted furans and furanones, forming pseudomelanoidinic component of browning product's structure. Studying of antioxidant activity has shown presence of the reducing properties both of early and of late isolated products that it is probably explained by the considerable electronic redundancy of the last, at the same time the maximum inhibition degree of oxidation, close to standard, characterizes the non-dialyzable high molecular weight structures.

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SYNTHESIS OF CARBORANE-BASED DELOCALIZED LIPOPHILIC CATIONS FOR DIAGNOSTICS AND CANCER TREATMENT

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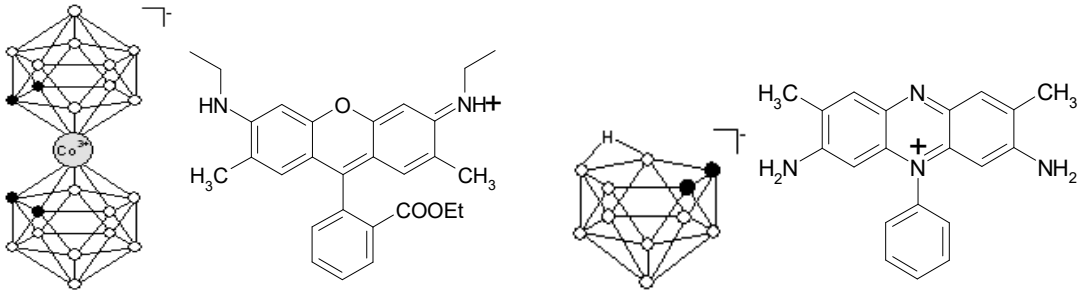
Carboranes and metalcarboranes represent the wide class of polyhedral boron compounds with low toxicity, high boron content and catabolic stability [1]. Applied in boron neutron capture therapy carboranes and metalcarboranes derivatives are of interest [2]. Furthermore, there are known carborane derivatives with antimicrobial, antiviral, anti-inflammatory and neurotropic activity, and inhibitors of some enzymes as well [3]. All of that sets apart carboranes and metalcarboranes in the separate broad group of perspective pharmacophores [4]. Carboranes containing the Delocalized Lipophilic Cations (DLCs) arouse big interest [5]. DLCs are perspective compounds for diagnostics and cancer treatment [6, 7]. Eight compounds based on fluorescent dyes Rodamine 6G, B, Safranin O and Nile Blue were synthetized and characterized in our laboratory.



Developing this direction the optimal methods of nido-7,8-dicarbaundecaborate and bis(dicarbollide) cobalt-based DLCs syntheses were invented.

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THE FIRST TOTAL SYNTHESIS OF THE MARINE ACETYLENIC ALCOHOL, LEMBEHYNE B - A SELECTIVE INDUCER OF EARLY APOPTOSIS IN LEUKEMIA CANCER CELLS

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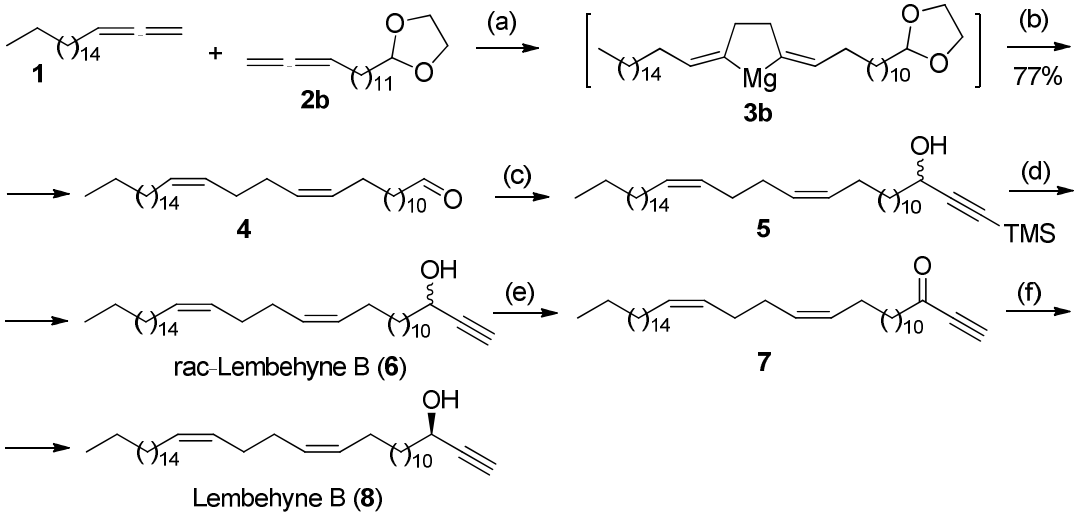
An original stereoselective method for the synthesis of lembehyne B was developed for the first time. The key stage of the synthesis was based on the new reaction that we developed, namely, Ti-catalyzed cross-cyclomagnesiation of oxygenated aliphatic 1,2-dienes with Grignard reagents [1,2].



(a) EtMgBr, Mg, Cp_2TiCl_2, Et_2O, rt; (b) H^+; (c) Lithium trimethylsilylacetylenide, THF, rt, 90%; (d) TBAF, THF, rt, 99%; (e) Dess-Martin periodinane, THP, rt, 83%; (f) Alpine-borane, THF, rt, 84%.

This method bears huge synthetic potential for the preparation of stereochemically pure lembehynes and their analogues by varying the structure of the starting 1,2-dienes.

By means of flow cytometry, it was shown for the first time that lembehyne B is a selective early apoptosis inducer for the Jurkat, HL-60, and K562 cell cultures. Currently, active research along this line is in progress in order to implement stereoselective methods for the synthesis of the whole range of natural lembehynes and their analogues for performing, in particular, full-scale pharmacological investigations of the biological activity and structure–activity relationships.

This work was financially supported by the Russian Science Foundation (Grant No. 16-13-10172).

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POTENT GLUCOKINASE ACTIVATORS BASED ON PYRIDOXINE DIPHARMACOPHORE DERIVATIVES

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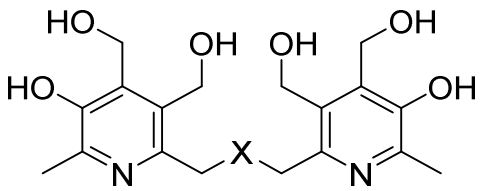
A series of novel symmetric molecular constructs, in which two pyridoxine moieties are connected via sulfur-containing linkers, have been synthesized and tested in vitro for glucokinase activation potential. The enzyme activation rates by two most active compounds at 100 μM (~150% and 130%) were comparable to that of the reference agent PF-04937319 (~154%). Both leading compounds demonstrated low cytotoxicity and excellent safety profile in acute toxicity experiment in rats after oral administration with LD_{50} exceeding 2000 mg/kg of body weight. Binding mode of the active compounds in comparison with the reference agent was studied using molecular docking. The leading compounds represent viable preclinical candidates for the treatment of type 2 diabetes mellitus, as well as a promising starting point for the design of structural analogs with improved activity.



X = S, S-S, SO, SO_2

ANTIOXIDANT ACTIVITY OF 5-PHENYL-*6H*-1,3,4-THIADIAZINE-2-AMINE ANALOGUES

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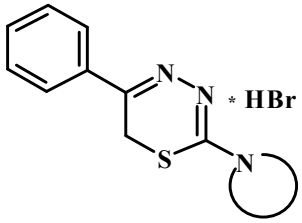
In study of biological activity in models of alloxan diabetes mellitus [1] and experimental pancreonecrosis [2], effective compounds of 1,3,4-thiadiazine class with various cycloalkylamine residues as substituents at position-2 were established to have antioxidant properties also.



= pyrrolidyl, piperidyl, morpholyl, thiomorpholyl

In order to investigate the mechanism of this action, an experiment for evaluation the effect of *6H*-1,3,4-thiadiazines containing phenyl or substituted phenyl at position-5 of the thiadiazine ring on the kinetics of ascorbic acid (AA) oxidation with air oxygen was set up.

It is known that in a solution AA may exist in two forms, reduced and reversibly oxidized (dehydroascorbic acid). With mild oxidation of the reduced form, it turns into a reversibly oxidized one, which under the action of reducing agents can again be transformed into the initial, reduced form.

Among the compounds studied, L-17 (2-morpholino-5-phenyl-6*H*-1,3,4-thiadiazine) was found to be the most effective inhibitor of AA oxidation with air oxygen. The rate of AA decrease without an inhibitor was 15.0 μg/L·h; in the presence of an equimolar amount of L-17, it decreased to 11.5 μg/L·h, and with a 2-fold excess of L-17, up to 8.5 μg /L·h. A half-maximal inhibitory concentration (IC_{50}) for L-17 was 1.47 moles of substance/mole of ascorbic acid. According to the experiment conducted, it can be assumed that the most probable mechanism of corrective action of compound L-17 is associated with its ability to convert to the corresponding pyrazole derivatives of thiol type, which reduce dehydroascorbic acid to AA.

The work was supported by the RSF (project No. 16-15-00039)

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GENOTOXICITY SCREENING OF TWO NEW CARBAZOLE DERIVATIVES

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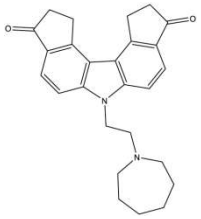
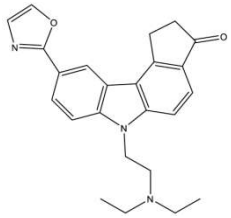
The class of carbazoles includes compounds with high biological activities and broad spectra of action [1]. PLX01107 and PLX01008 are xenomycins, a new subclass of antimicrobial carbazole derivatives demonstrating strong antifungal activity *in vitro* (minimal inhibitory concentrations against *A. fumigatus* are 1 – 5 ug/mL) [2]. In order to investigate the possible genotoxicity of these compounds three tests have been performed – a bacterial reverse mutation assay (Ames test), *in vitro* cytokinesis-block micronucleus (MN) assay [3], and chromosome aberration test in mouse bone marrow cells.



PLX01008



PLX01107

PLX01107 did not exhibit a positive response for *S. typhimurium* or *E. coli* strains in the absence or presence of S9, although it showed a cytotoxic response for strains TA98, TA100, and TA1535 without S9. In contrast, PLX01008 was mutagenic in *S. typhimurium* strains TA98 and TA1537, with or without S9 activation. Strain TA1535 showed a positive response only at 0.4 μg/mL in the absence of S9.

Treatment with 2, 10, or 50 ng/mL PLX01107 without S9 activation revealed a statistically significant, but not concentration-dependent, increase (up to 12-fold) in the total number of MN in binucleated cells. PLX01008 exposure also resulted in a significant increase of MN frequency at the same concentrations analyzed. The genotoxic effect of PLX01008 at the highest concentration was almost two-fold greater than for PLX01107. When cells were treated with PLX01107 in the presence of S9, MN levels at all tested concentrations were significantly higher in comparison with the background level. In contrast, in the case of PLX01008 with S9 activation significantly increased MN values were observed only at the highest concentration, 50 ng/mL. No statistically significant effects were seen for PLX01008 at 2 or 10 ng/mL with S9.

PLX01107, single dose, 15 mg/kg, failed to induce aberrant metaphases after 24 h exposure as compared to the control group. However, a dose of ≥ 30 mg/kg PLX01107 revealed a clear dose-dependent increase in the number of cells with chromosome aberrations. The highest clastogenic effect was recorded after treatment with 75 mg/kg PLX01107. The observed percentage of aberrant metaphases was greater than in the positive control group (35.4±13.6% *vs* 16.8±1.7%, respectively). The effect was characterized by a high percentage of severely damaged cells with numerous aberrations. At the same time, after 5 daily administrations of 15 mg/kg PLX01107, no significant clastogenic activity was detected.

A single PLX01008 injection, 6 mg/kg, failed to induce clastogenic activity, while PLX01008, 30 mg/kg, revealed a weak but statistically significant clastogenic effect, which was confirmed in the repeated experiment. PLX01008, administered in five daily 6 mg/kg doses, did not significantly change the frequency of aberrant cells.

Thus, despite their structural similarity, the two compounds had different genotoxicity profiles. PLX01008 showed positive effects in all assays. PLX01107 showed no mutagenicity in the Ames test but demonstrated strong cytogenetic activity *in vitro* and *in vivo*. This study shows genotoxicity of PLX01107 and PLX01008, limiting further development of these compounds as antifungal drugs. Moreover, our findings should be taken into consideration during discovery research on carbazole derivatives as lead compounds.

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“CHEMISTRY IN ENGLISH” – THE NEW EDUCATIONAL PROGRAM FOR HIGH SCHOOL STUDENTS OF MEDICAL PROFILE

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The educational training program "Chemistry in English" for high school students of specialized medical classes was developed according to the priority direction "Development of the system of profile education in the context of integration of general and additional education" (Educational Project “Medical class in the Moscow school” [1]) and is focused on pre-university training. The intention of the program is to introduce it in the system of general secondary education [2] and focuses on the subject profile orientation of high school students of partner schools in the educational space of the Sechenov University.

The content of the syllabus is integrated in the methodological plan and covers selected sections of related (and non-related) academic disciplines (physics, biology, algebra, geometry, informatics). The total laboriousness of the course “Chemistry in English” is 50 academic hours, the standard term of training is 6 months, the form of the final certification is an examination. The program includes an advanced study of the selected sections of chemistry in English (in medical applications) and provides:

- scientific terminology training in English;
- practice of reading, interpreting and solving of chemistry tasks in English;
- system of control test blocks for full and selective training in scientific chemical and medical terminology, monitoring the effectiveness of mastering students' knowledge, and assessing the level of practical skills acquirement;
- analysis of the thematic sections of the syllabus and the solution of the tasks of international examinations in chemistry.

As a result of mastering the course, the high school students must learn to:

- produce literate bilingual (English-Russian, Russian-English) oral and written translation of scientific chemical texts in accordance with the basic theoretical blocks;
- to solve test tasks and exercises in chemistry in English in accordance with the advanced program, to solve chemical problems and to give a written solution in English;
- independently work with educational, scientific and reference literature, effectively navigate in specialized chemical sites on the Internet in English;
- to apply the knowledges, theoretical and practical skills acquired in the studying of the educational program in reading, translating and solving chemistry tasks in English while mastering the future medical specialty.

The training and methodological support of the course “Chemistry in English” includes the unified educational complex, developed at the Sechenov University, which contains the textbook, the workbook, the bank of tests and written assignments, exercises and tasks [3]. The presentation of information is carried out using modern multimedia technologies on the base of cognitive computer graphics containing text, graphic information screens, and models, audio and video materials in chemistry in English. Since 2016 the educational program “Chemistry in English” has been successfully implemented in the system of additional medical-oriented pre-university education of high school students of Moscow Lyceum 1535 [4].

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SYNTHESIS OF NOVEL 6-{[METHYL(PHENYL)AMINO]METHYL}-S-DABO ANALOGS AS POTENTIAL ANTIVIRALS

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Dihydroalkylthiobenzyloxopyrimidines (S-DABOs) represent an extensive class of compounds capable of blocking HIV-1 reverse transcriptase functions due to allosteric interaction with hydrophobic pocket of this enzyme, thus being the non-nucleoside reverse transcriptase inhibitors (NNRTIs) [1,2]. Recently, novel NNRTIs containing an aminomethylene bridge linking the 6-position of the heterocycle to the aromatic moiety have been described [2]. These compounds are characterized by promising antiretroviral profile. In the last decade new areas of S-DABO application were discovered, in particular, the compounds of this class were found to inhibit reproduction of hepatitis B [3] virus and influenza virus [4].

In present work, we developed a method for the synthesis of novel S-DABO analogs bearing methyl(phenyl)aminomethyl fragment at the C-6 position of the heterocyclic core. Starting ethyl 4-[methyl(phenyl)amino]-3-oxobutanoate was obtained via condensation of N-methylaniline with ethyl acetoacetate using modified Zhang-Silverman protocol [5]. Resulting ketoester was condensed with thiourea [6] to give 6-{[methyl(phenyl)amino]methyl}-2-thioxo-2,3-dihydropyrimidine-4(1*H*)-one, which was subsequently alkylated with various benzylhalogenides and (phenoxy)ethyl bromides [1, 7] to give target S-DABO derivatives.

This work was supported by grants from the Russian Foundation for Basic Research (№ 15-44-02651) in part of the synthesis and from the Foundation for Assistance to Small Innovative Enterprises («UMNIK» program, № 0019419) in part of the spectral research.

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APOLIPOPROTEIN A-I STIMULATES PROLIFERATION OF BONE MARROW PROGENITOR CELLS

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Apolipoprotein A-I (apoA-I) is the main protein component of high-density lipoproteins (HDL), which is involved in reverse cholesterol transport from peripheral tissues to the liver for its subsequent utilization. We have previously demonstrated that apoA-I is able to stimulate protein synthesis in isolated liver macrophages [1], and complex of apoA-I with steroid hormones stimulates the biosynthesis of proteins and DNA in hepatocytes [2]. In this paper, the effect of apoA-I on the biosynthesis of DNA in the culture of bone marrow cells was studied. The cell fraction enriched in the progenitor cells was obtained by counterflow centrifugal elutriation of the initial suspension of bone marrow cells in Avanti J-26XP centrifuge (Beckman Coulter, USA) equipped with JE-5.0 elutriator rotor. It was found that incubation of the cells in serum-free RPMI-1640 medium was accompanied by a significant decrease in the rate of incorporation of [^{3}H] -thymidine into DNA. In contrast, the addition of HDL or apoA-I to the culture medium resulted in a dose-dependent increase in the DNA biosynthesis. A statistically significant ($p < 0.05$) increase in this parameter was observed already at 5 μg/ml of apoA-I. The maximum stimulating effect was achieved at a concentration 20 μg/ml of apoA-I and 80 μg/ml of HDL. To identify the target cells of apoA-I, we used a thymidine analogue of 5-ethynyl-2'-deoxyuridine (EdU), which is incorporated into the DNA in the stage of DNA replicative synthesis (S-phase). Identification of EdU-positive cells by Romanovsky-Giemsa stain showed that apoA-I stimulates the proliferation of monocyte (monoblasts, promonocytes) and granulocyte (myeloblasts, promyelocytes) progenitor cells, as well as a bone marrow stromal cells. Thus, our results suggest that apoA-I is a multifunctional protein that plays an important roles not only in lipid transport, but also in the regulation of proliferation of bone marrow cells. The results open the prospects for the creation a new drugs based on apoA-I for stimulation of hematopoiesis in the bone marrow.

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SEARCH FOR PERSPECTIVE PHARMACOLOGICAL PREPARATIONS WITH WOUND-HEALING PROPERTIES ON THE BASIS OF DEFENSIN SYNTHETIC FRAGMENTS

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It is known that for normal wound healing it takes involvement of, at least, three groups of cells: 1) leukocytes, including neutrophils, released during the inflammatory phase into injury zone the diverse biologically active compounds (such as mediators, cytokines, growth factors, and peptide antibiotic defensins) regulated a functional activity of cells participating in processes of wound healing; 2) fibroblasts synthesized and secreted the different components of extracellular matrix, including collagen and fibronectin, which are necessary for the formation of granulation tissue to be subsequently transformed into scar one; 3) epithelial cells produced external cell layers during wound re-epithelialization. Disruption of the intercellular and cell-matrix interactions in tissue injury zone is one of the reasons in the development of persistent nonhealing wounds. In this connection, search for compounds with capacity to regulate cell adhesive properties is currently central.

For the further analysis some defensin oligopeptide fragments containing positively and negatively charged amino-acid residues were chosen. It is known that in peptide/polypeptide molecules the most reactionary amino-acid residues contain charged side radicals to generate electrostatic bonds between side radicals of amino acids in peptide molecules and cell distinct receptor structures. The effect of defensin synthetic fragments on the adhesion of mammalian fibroblasts and epithelium-like cells to different substrates (polystyrene plastic, poly-L-lysine, fibronectin, gelatin) has been studied. It has been found that the investigated defensin-derived peptides are involved in the regulaton of adhesion of fibroblasts and epithelium-like cells. The effect of the studied peptides on the cell response depends on the substrate type and the mode in which the peptides were added to cell cultures.

A NEW STRATEGY IN THE SYNTHESIS OF SUBSTITUTED BICYCLO[4.3.1]DECA-2,4,8-TRIENES - PROMISING PRECURSORS IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

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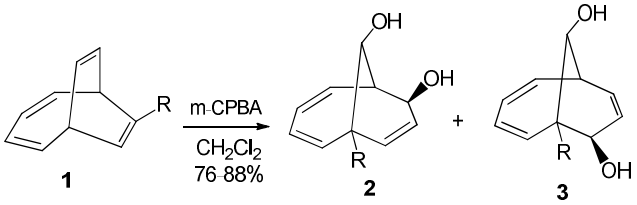
The bicyclo[4.3.1]decane core is the key structural unit of many natural biologically active compounds, for example, caryolane, phomoidride B, vibsanines, welwitindolinones, nakafuran-9, pallescensins C and D, florlides and so on, which exhibit anti-HIV, antitumor, antimicrobial, antibacterial, and antimicotic properties [1,2]. Earlier we developed an efficient method for the synthesis of bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols based on the oxidation reaction of substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes with m-chloroperbenzoic acid [3]. Our recent studies have shown that the obtained bicyclo[4.3.1]deca-2,4,8-trienones exhibit selective antitumor activity against various tumor cell lines (Hek293, Jurkat, K562, A549) [3]. Given the relevance of the results obtained for organic and medical chemistry, we carried out further studies on the oxidation reaction of substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes. It was found that the oxidation reaction of tolyl-, anisole-, halogenphenyl-, cycloalkyl-substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes **1** under the conditions developed leads to the formation of bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols **2**, **3** with high yields (76-88%).



R = 4-$CH_3C_6H_5$, 3-$CH_3C_6H_5$, 4-$OCH_3C_6H_5$, 4-BrC_6H_5, 3-ClC_6H_5, 4-FC_6H_5, $CH(CH_2)_2$, $CH(CH_2)_4$

This work was supported by RFBR, projects 15-03-01254, 16-33-00379, by a grant of the Republic of Bashkortostan for young scientists and youth research teams (2017).

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PHOSPHORYLATED DERIVATIVES OF BENZIMIDAZOLE –COMPOUNDS WITH PERSPECTIVE BIOLOGICAL ACTIVITY

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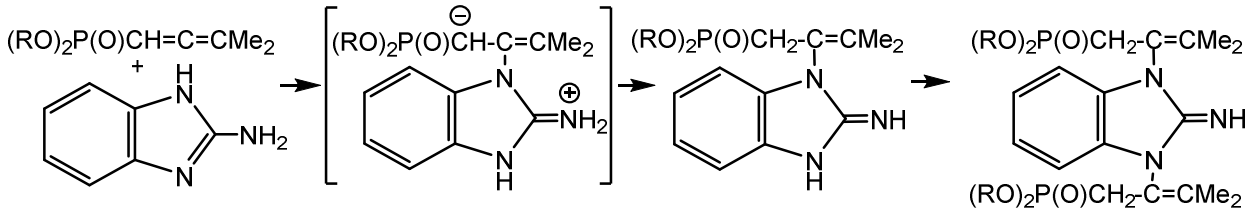
Alkyl- and alkenylphosphonates functionalized with nitrogen-containing pharmacophore moieties are promising for using as biologically active substances [1]. We previously showed that reactions of allenyl- and vinylphosphonates with imidazole lead to formation of the addition products with a strong bactericidal activity against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. While continuing studies in this line we examined the reactions of 3-methylbuta-1,2-dien-1-yl-phosphonates and vinylphosphonates with benzimidazole and 2-aminobenzoimidazole. The presence of two nucleophilic centers in the molecule of 2-aminobenzimidazole allows to consider its interaction with the unsaturated phosphonates on the two possible routes: with endocyclic nitrogen atom of heterocyclic compound, or the nitrogen atom of the exocyclic amino group [2]. On the basis of the data of ^{1}H, ^{13}C and ^{31}P NMR and mass-spectral studies we have shown that the more nucleophilic endocyclic nitrogen atom of 2-aminobenzimidazole is participating in the addition to the β-carbon atom of the cumulene or vinylene system of unsaturated phosphonates.



Also we have shown that 3-methyl-buta-1,2-dienylphosphonate reacts with 2-aminobenzimidazole via addition of two phosphonate molecules to endocyclic nitrogen atoms of 2-aminobenzimidazole.

Acknowledgements
The work is performed according to the Russian Covernment Program of Competitive Growth of Kazan Federal University.

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EFFECT OF TRIMETHYLTIN COMPLEX BASED ON 2,6-DI-TERT-BUTYL-4-MERCAPTOPHENOL ON GENERATION OF HYDROXYL RADICAL BY FENTON SYSTEM *IN VITRO*

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The aim of this work is to study the effect of (3,5-di-*tert*-butyl-4-hydroxyphenylthiolate) trimethyltin (Me_3S) on the generation of hydroxyl radical ($HO^{\bullet}$) in Fe^{2+}- EDTA-H_2O_2-deoxyribose system *in vitro* [1]. The effect of Me_3S was studied in comparison with trimethyltin chloride (TMT), with the DMSO.
Previously, antioxidant and antiradical (in DPPH-test) activity were established for Me_3S [2]. According to the data obtained, TMT and Me_3S as well as DMSO (0.09 mM) inhibit the generation of $HO^{\bullet}$ in this model system. Inhibition of the Fenton reaction in the presence of TMT can be due to the reaction of chloride ions with $HO^{\bullet}$, which competes with the main process [3]. In the present study, we found that the generation of hydroxyl radical was inhibited by solution of Me_3S in DMSO in a concentration-dependent manner with an IC_{50} value of 0.5 mM (Fig.).

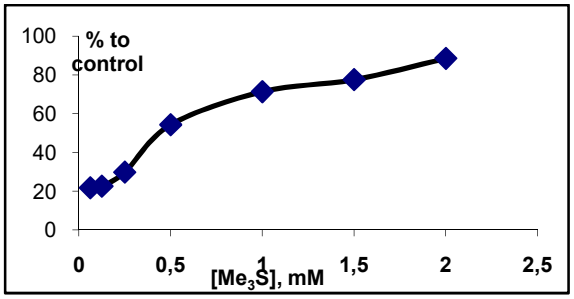

Figure - Effect of different concentrations of Me_3S on the degradation of deoxyribose under the action of $HO^{\bullet}$ in the Fenton reaction *in vitro*. Control - the degradation of deoxyribose in a similar model system without the addition of compounds. The average values of three independent experiments are given.

As the concentration of Me_3S increases, the inhibition decreases, indicating that the ability of DMSO to scavenge $HO^{\bullet}$ was higher than for trimethyltin complex. In conclusion, the present results provide evidence that trimethyltin complex based on 2,6-di-tert-butyl-4-mercaptophenol exhibit the hydroxyl radical-scavenging activity, which can be an important aspect of its cytoprotective activity under oxidative stress conditions.

Acknowledgements - we are grateful to RFBR (17-03-00434) for financial support of this work.

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NOVEL CONJUGATES OF TACRINE WITH 1,2,4,-THIADIAZOLES AS HIGHLY EFFECTIVE CHOLINESTERASE INHIBITORS, ANTIOXIDANTS AND BLOCKERS OF NMDA RECEPTORS FOR ALZHEIMER'S DISEASE TREATMENT

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[2]N.M. Emanuel Institute of Biochemical Physics RAS, 119334, Russia, Moscow, Kosygina Str., 4
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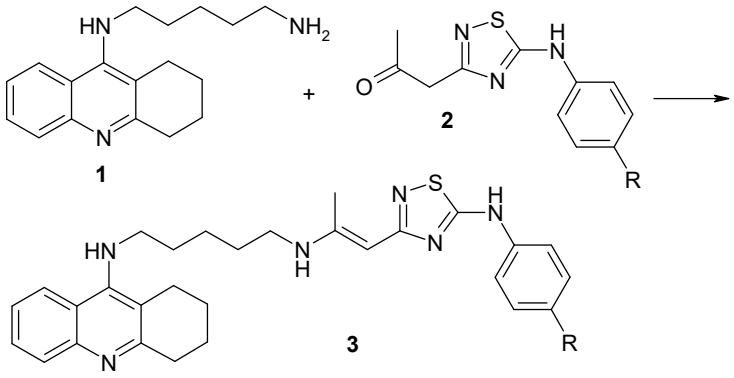
A novel series of tacrine derivatives was designed and synthesized by combining 1,2,4-thiadiazole derivatives with tacrine:



The synthesized tacrine conjugates (**3**) were evaluated as multifunctional cholinesterase inhibitors against Alzheimer's disease: their esterase profile, antioxidant activity and action on the key N-methyl-D-aspartate (NMDA) receptor binding sites were studied *in vitro*. The results showed that compounds **(3)** exhibited good multifunctional activities. They exhibited significant potency to inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) with predominant inhibition of BChE (IC_{50} = 1.28 – 2.29 μM for AChE, IC_{50} = 0.07 – 0.1 μM for BChE). Kinetic and molecular modeling studies indicated the conjugates as mixed-type inhibitors, binding simultaneously to the catalytic site and peripheral anionic site of AChE. Moreover, the conjugates also showed good radical-scavenging activity in the ABTS assay (Trolox Equivalent Antioxidant Capacity, TEAC = 1.28 – 1.45) and blocked simultaneously two binding sites of the NMDA receptor (for allosteric ifenprodil-binding site IC_{50} = 5.2 – 8.9 μM, for intra-channel MK-801 binding site: IC_{50}= 8.6 – 15.3 μM). Taken together, the results indicate that these new multi-functional compounds may be candidates with potential impact for further pharmacological development in Alzheimer's therapy.

This work was supported by RFBR grant №17-03-00984.

The use of a networked system for an antioxidant activity rapid assay of multifunctional organometal derivatives with redox active ligands

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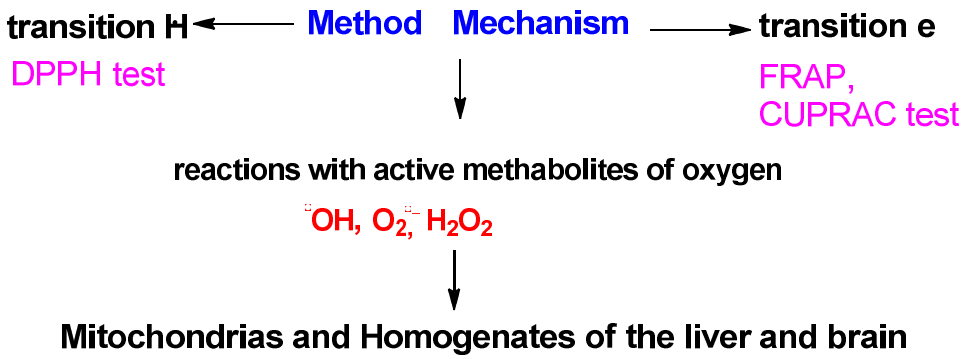
The oxidative stress is considered to be involved in the pathogenesis of many diseases and there is strong evidence that the antioxidants prevent some pathologies including cancer. The specific chemical properties of metal-based drugs containing functional groups with redox and antioxidant activity impart innovative pharmacological profiles to this type of therapeutic agents [1]. The antioxidant efficiency studies at present time are completed usually using 1-2 methods, that does not allow to evaluate the integral contribution of different types of activity in polifunctional compounds. The mechanism of activity may be due to the ability to inhibit radical reactions of ROS both due to the detachment of the hydrogen atom and as a result of electron transfer. To assess the overall antioxidant activity of such compounds, a networked system of methods including a series of rapid tests, electrochemical studies, model reactions and biological testing is proposed (Scheme 1).



The results of antioxidant studies obtained with use of networked system for the organometal compounds with redox-active fragments (the ferrocenes, complexes with di-(2-picolyl)amine ligand, thiols, phosphonates, porphyrins) were obtained [2, 3]. These data demonstrate the effectiveness of integrated approach and the need to combine a number of methods, in order to full characterize antioxidant effect of the multifunctional molecules.

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REDOX ACTIVATION RSH AND S_8 IN ELECTROSYNTHESIS OF BIOLOGICALLY ACTIVE ORGANIC POLYSULFIDES

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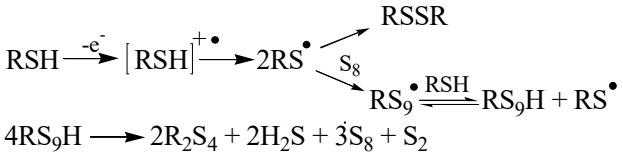
Currently one of the promising directions in organic and medicinal chemistry is associated with the production of straight-chain or cyclic mono-, di- and polyatomic sulfur compounds, as well as the study of their biological activity. Redox activation of thiols (RSH) and sulfur under electrochemical conditions causes the formation of polysulfides (R_2S_n, n = 2-4) at room temperature. Oxidative activation of RSH in the presence S_8 allows generating sulfur-centered radical intermediates. These particles undergo further transformations which lead to the formation of di- and tetrasulfides with a low current yields varying from 16.5 to 37.0%.



R = n-C_4H_9; n-C_5H_{11}; n-C_6H_{13}; cyclo-C_5H_9; cyclo-C_6H_{11}; C_6H_5; $CH_2C_6H_5$

On the example of butanethiol-1 shows that the change of sulfur concentration and carrying out of electrosynthesis at a potential of -1.15V increase the selectivity of the reaction with di-, tetrasulfides. This method allows increasing the yield of R_2S_4 by 10% in comparison with the electrochemical oxidation of RSH where the yield of R_2S_2 is unchanged. It was observed that the decrease the ratio (S_8:RSH) leads to sulfur conversion reduction by 30%, and the yield of the reaction products remains constant.

$$C_4H_9SH + S_8 \xrightarrow{\text{-1.15 V; } CH_2Cl_2\text{; 1h}} (C_4H_9)_2S_2 + (C_4H_9)_2S_4$$

$C(S_8)$ =1.5 mM	21%	29%
$C(S_8)$ =0.75 mM	17%	33%
$C(S_8)$ =0.375 mM	20%	12%

In case of cathodic sulfur activation at a potential of -1.30 V, the yield of the reaction products increases from 29.2 to 52.0% and depends on time of electosynthesis and the structure of the substituent at the sulfur atom. A comparable yield of R_2S_3 (40.0 – 47.7%) is observed in case of thiols with C_4-C_6 hydrocarbon groups. Di- and trisulphides are formed in reaction cycloalkanethiols with reduced sulfur species. In course of electrolysis S_8 with RSH with alkyl groups tetrasulfides are registered with a yield of up to 55.2%.

This work was financially supported by the Russian Science Foundation (grant No.17-13-01168)

NOVEL A-AMINOPHOSPHONATES AS CANDIDATES FOR MULTI-PURPOSE DRUGS

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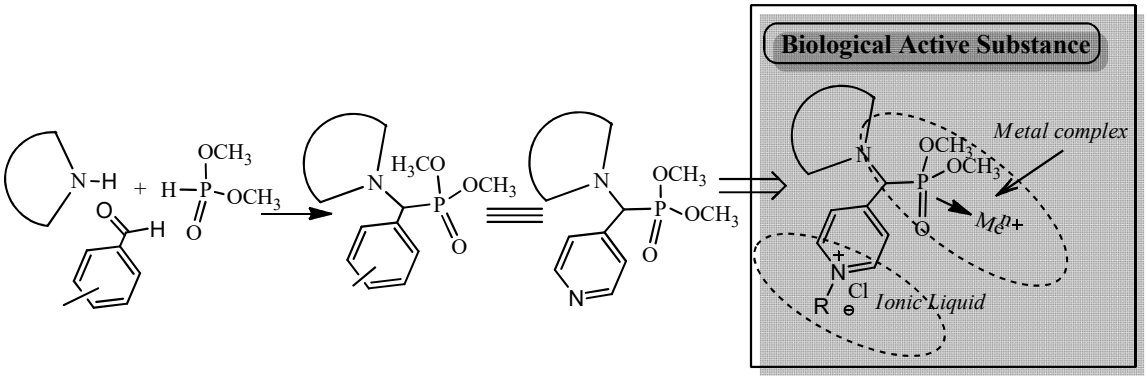
One important class of biologically active compounds are α-amino phosphonates. In recent years there has been tremendous interest in the synthesis and comprehensive study of these unique compounds as a promising substances of multipurpose practical purpose. Numerous studies have shown that α-amino phosphonates have the potential antibacterial, anticancer, antimicrobial and antithrombotic properties [1]. Aminopolyphosphonates as multidentate complexing agents are used in medicine to relieve metal overload in living organisms. The applicability of complexes for treating anemia of iron overload in the body is known.
A series of novel α-aminophosphonates had been synthesized:



For targeted synthesis of α-amino phosphonates it had been used triple one-pot Kabachnik-Fields reaction, consistent with the principles of Green Chemistry. Among synthesized α-aminophosphonates there are several ones having aromatic azaheterocycle capable of quaternization of nitrogen center (IL fragment) and a moiety for obtaining of complexes with transition biogenic metal (Co^{+2}, Mn^{+2}, Ag^{+}, Cu^{+2}, etc.).

The authors thank the Ministry of Education and Science of the Republic of Kazakhstan for financial support (0650/ GF4, 0650/ GF4, 1752/GF4).

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ANALYSIS OF MULTIPARAMETRIC BIOLOGICAL AND PHARMACOLOGICAL DATA FOR THE PURPOSE OF FORECASTING CLINICAL SIDE EFFECTS OF DRUGS

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Side effects are an integral part of any drug. Unfortunately, many of them are detected after the release of the drug on the market and often cause the discontinuation of production of this drug [1]. Therefore, it is necessary to predict in advance possible adverse side effects. Various side effects are usually associated with differences in the profile of target-specific drug activity. Is it possible to systematically detect this relationship and predict the side effects of the drug, by studying its target-specific activity? In this work, we tried to answer this question.

Using data from the FDA AERS database, which are publicly available, about one million reports were analyzed in which only one drug was prescribed to a patient. Of these reports, 255 most commonly used drugs were selected. For them, a side effect profile was compiled and for each side effect a PRR value was calculated that indicates the relationship between the drug intake and the specific side effect and is used as a descriptor for calculating the pairwise similarity coefficients of the side effect profile of the drugs. For the same compounds, using the ChEMBL database, a target-specific activity profile has been constructed, namely, all possible human biotargets have been selected, with respect to which these compounds exhibit in vitro activity, and the corresponding quantities quantitatively characterizing this activity. However, in connection with the often occurring variability of these values for the same compound in the ChEMBL database, they were replaced by more universal semi-quantitative coefficients for further calculation of the similarity coefficients of the target-specific profile.

On the basis of the obtained data, the coefficients of pairwise similarity of side effects and the target-specific action were calculated using the generally accepted similarity metrics (Tanimoto, Euclid and Hodgkin) using the continuous formulas. The calculated coefficients of pairwise similarity allowed us to cluster the investigated molecules using the method of hierarchical clustering (the Ward method).

As a result of assignment of compounds into clusters in accordance with the similarity profile of side effects, as well as the profile of the target-specific action, we showed that the structures of both hierarchies, corresponding to the profile of biotarget-specific activity and side effects, are found to be similar. In this way, an approach can be developed to assess the specific features of the side effects profile based on in vitro analysis of activity on a certain panel of biotargets.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF NEW BIS(1-(HETARYL-1,4-DIOXO-4-ARYLBUT-2-EN-2-YL)OXY)METALS

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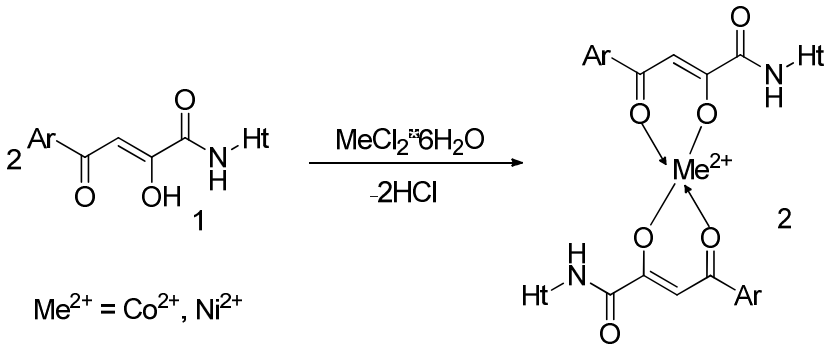
Complex compounds of divalent metals based on 2-hydroxy-N-(hetaryl)-4-oxo-4-arylbut-2-enamides are known to have hypoglycemic, antimicrobial and anti-inflammatory activity [1,2]. It was of interest to synthesize new chelates containing various combinations of electron-donor and electron-withdrawing substituents in both the heterocyclic and aromatic parts of the molecule and study their pharmacological activity. Bis(1-(hetaryl-1,4-dioxo-4-arylbut-2-en-2-yl)oxy)metals 2 were obtained by the reaction of 2-hydroxy-N-(hetaryl)-4-oxo-4-arylbut-2-enamides with alcohol solutions of salts of divalent metals in the ratio 2:1. The structure of compounds 2 was proved by IR spectroscopy and inductively coupled plasma mass spectrometry.



In the series of derivatives 2, substances with antimicrobial activity against test cultures of microorganisms *St. aureus* ATCC 6538-P and E. coli ATCC 25922, as well as antifungal activity against the test culture of C. albicans 885-653 ATCC were found. Some dependences of the pharmacological effect strength on the obtained compounds' chemical structure were revealed.

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Conjugates of γ-carbolines with methylene blue (MB) as new multifunctional agents for neurodegenerative diseases treatment.

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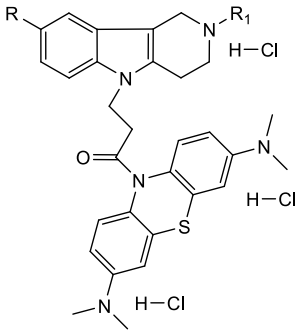
The multifactorial nature of neurodegenerative diseases assumes using drugs for treatment that are capable to act simultaneously on multiple targets involved in the disease pathogenesis. Conjugates of γ-carbolines with MB of general formula (I) have been earlier synthesized [1]:



(I) R = H, Me, F; R_1 = Alk.

We studied inhibitory activity of conjugates (I) against acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and a structurally close enzyme carboxylesterase (CaE), their ability to bind to the peripheral anionic center of EeAChE and competitively displace propidium iodide as well as their antioxidant activity by means of $ABTS^{\bullet+}$ and ORAC-FL assay. It is shown that the conjugates (I) effectively inhibit AChE and BChE with the IC_{50} values of 1-10 μM and very weak inhibit CaE that indicates the absence of potential drug-drug interactions. On molecular docking results, the compounds bind to the active site of BChE, while binding to AChE occurs in the region of peripheral anionic site, suggesting their effect on AChE-induced aggregation of beta-amyloid. Indeed, the compounds studied effectively displaced propidium from the peripheral anionic site of AChE (30-37% at 20μM). Additionally, conjugates (I) were extremely active in both radical-scavenging tests: their activity was comparable with that of Trolox in the ABTS test (TEAC = 0.96 – 1.08), while their ability to scavenge peroxyl radicals determined in ORAC-FL method considerably exceeded the Trolox one and ranged from 7 to 10 TE. The results show the promise of these conjugates for further optimization as multitarget neuroprotective agents for neurodegenerative diseases. This work was financially supported by RSF grant № 14-23-00160P.

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CYANO-CONTAINING CYTOSTATICS ON NANODIAMONDS

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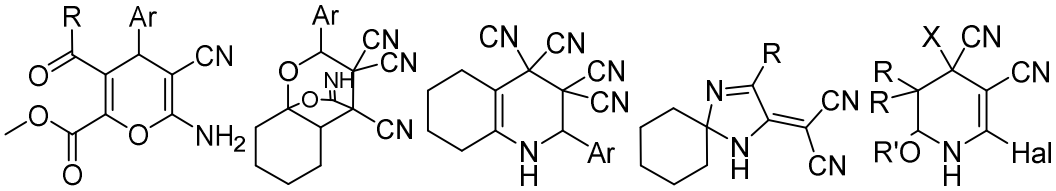
Recently, the attention of researchers in the search for new cytostatics has been focused on natural and synthetic cyano-containing derivatives [1]. In addition to obvious increase in the activity of organic compounds as anticancer substances, the cyano group is ideally suited for fixing substances on nanocarriers. It is compact (3.5 Å), does not create steric hindrance, has the highest adhesion to virtually all materials, which has found application in cyanoacrylate adhesives [2]. In 2011 E.K. Chow suggested that nanodiamonds (ND) are the ideal way to deliver drugs [3]. Recently (2015) it was established that ND are non-carcinogenic, non-mutagenic, non-toxic and biocompatible [3]. In connection with the above, we investigated the activity of the cytostatics we synthesized on ND. As substances on pure lines of cancer cells (National Cancer Institute, Maryland, USA) (cyano-substituted pyran (1), bicycloimines (2), tetrahydropyridines (3.5) and imidazoles (4). The results obtained show that the activity of the substances on ND exceeds that of ND. However, it should be taken into account that the concentration of the above (1-5) per ND did not exceed 5%.



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FORECAST OF BIOACTIVITY AND TOXICITY OF (2-HYDROXYPHENYLTHIO)ACETAMIDES

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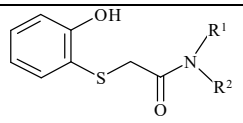
The forecast of the spectrum of biological activity and toxicity of (2-hydroxyphenylthio)acetic acid amides [1] is based on the structural formula of the compound and was performed using the PASS (*Prediction of Activity Spectra for Substances*) software on the basis of the structural formula of the compound. The results of the forecast are presented in the table with estimated probabilities of availability (P_a) and absence of each activity type (P_i). With the ratio $P_a > P_i$, it is assumed that there is a high probability that certain activity can be detected in the experiment.

	R^1 = H, R^2=CH(*i*-C_4H_9)$COOCH_3$		R^1 = H, R^2 =CH($(CH_2)_2CH_3S$)$COOCH_3$		R^1,R^2 = $(CH_2)_3CHCOOCH_3$		R^1,R^2 = $(CH_2)_2N(COCH_2S(o\text{-}HOPh))(CH_2)_2$	
	P_a	P_i	P_a	P_i	P_a	P_i	P_a	P_i
Nicotinic alpha4beta4 receptor agonist	0.675	0.024	0.838	0.004	0.832	0.005	0.678	0.023
Proteasome ATPase inhibitor	0.510	0.065	0.563	0.045	0.383	0.145	0.642	0.024
Muramoyltetrapeptide carboxypeptidase inhibitor	0.478	0.047	0.714	0.013	0.581	0.027	0.554	0.031
Oxygen scavenger	**0.335**	**0.143**	**0.469**	**0.061**	**-**	**-**	**0.384**	**0.105**
Rat Oral LD_{50} (mg/kg)	1379		1971		1574		1765	
Bioaccumulation factor Log10(BCF)	0.707		0.390		0.349		0.917	

The calculation of the BCF and the LD_{50} with a single oral administration of rats has been performed using the GUSAR software *in silico*. BCF values do not exceed 5, which, in accordance with the recommendations of application D of the Stockholm Convention, indicate low ecological toxicity of the compounds. The calculation of LD_{50} predicts low toxicity (class 4) of compounds, because the values in the limit of 500-5000 mg/kg. The biological activity of amides of (2-hydroxyphenylthio)acetic acid, in particular, as interceptors of reactive oxygen species, is predicted by the *in silico* method, these predictions correlate with the data obtained in *in vitro* experiments. The compounds show high activity in the reaction with electrochemically generated $O_2^{\bullet-}$, increase the SOD-protective activity of liver homogenates and gonads of Russian sturgeon and inhibit the oxidation of lipids of sturgeon tissue; it can be concluded that these amides possess antiradical activity.

This work was supported by the Russian Foundation for Basic Research (17-03-00434).

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[1] Patent RU 2473540. Published 27.01.2013, Bul. № 3.

NEW UNUSUAL METHOD OF COBALT DICARBOLLIDE SYNTHESIS IN ORGANIC ACIDS

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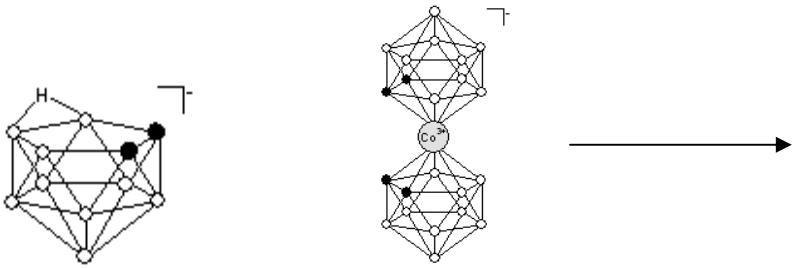
Metallacarboranes were first synthesized in 1965 [1, 2]. Now carboranes and metalcarboranes represent the separate wide group of new perspective pharmacophores [3]. Cobalt bis(1,2- and 1,7-dicarbollides) were the first metallacarboranes synthesized. The classical approach to the synthesis of the cobalt dicarbollide consists in the deprotonation of *nido*-[7,8-$C_2B_9H_{12}]^-$ or *nido*-[7,9-$C_2B_9H_{12}]^-$ with strong bases to dianions [7,8-$C_2B_9H_{11}]^{2-}$ or [7,9-$C_2B_9H_{11}]^{2-}$ followed by the reaction with cobalt (II) chloride ($CoCl_2$) [1, 2].

During the study of *nido*-[7,8-$C_2B_9H_{12}]^-$ and *nido*-[7,9-$C_2B_9H_{12}]^-$ protonation, as well as search for new synthetic routes for dicarbollide transition metals, the atypical formation of cobalt dicarbollide by the interaction of cobalt acetate [$Co(OAc)_2 \cdot 4H_2O$] with potassium and cesium nido-dicarbaundecaborates in the boiling organic acid medium (acetic and propionic) was established in our laboratory [4]. The reaction products [*commo*-3,3'-Co(1,2-$C_2B_9H_{11})_2$] and [*commo*-2,2'-Co(1,7-$C_2B_9H_{11})_2$] in the form of potassium or cesium salts were formed with high yield (85-95% recrystallized product) under stirring of initial components in boiling acetic or propionic acid for 4-12 hours, followed by separation. The study of product formation kinetics were carried using ^{11}B NMR-spectroscopy.



So the new methods of dicarbollide cobalt synthesis and the reaction process monitoring with ^{11}B NMR-spectroscopy were invented in our laboratory.

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SYNTHESIS AND ANTITUMOR ACTIVITY OF NOVEL ALKENYL DERIVATIVES OF PYRIDOXINE CONTAINING THE DEHYDROZINGERONE MOIETY

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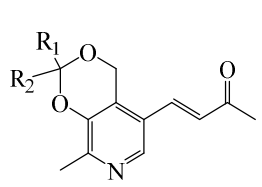
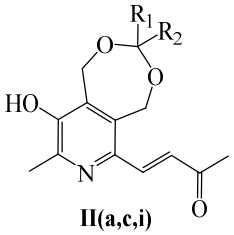
We report a novel class of pyridoxine monoalkenyl derivatives, structural analogs of dehydrozingerone [1-4]. The synthesized compounds were studied for antitumor activity and cytotoxicity *in vitro* using MTT-test. These compounds showed a high antitumor activity. Their cytotoxic concentration *in vitro* against the human embryonic kidney HEK-293 cells in the range of 1.2-38.5 μM and the human breast carcinoma MCF-7 cells with IC_{50} in the range of 0.4-27.2 μM. The 5-alkenyl substituted pyridoxine derivatives are the most active compounds. Acute toxicity studies using mice models demonstrated excellent safety profile of the most active compounds with LD_{50} in the range of 64.83 mg/kg (intravenous) and>2000 mg/kg (per os). Synthesized analogs of dehydrozingerone based on pyridoxine represent prospective biologically active agents for the development of the new antitumor drugs with an improved safety profile.



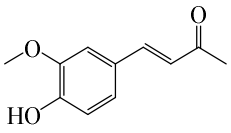
I(a-i)

IC_{50} (MCF-7) = 0.4-7.2
CC_{50} (HEK-293) = 1.2-35.6
SI (CC_{50}/IC_{50}) = 0.3-57.4



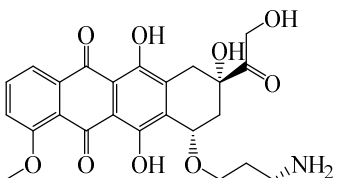
II(a,c,i)

IC_{50} (MCF-7) = 2.9-27.2
CC_{50} (HEK-293) = 1.4-38.5
SI (CC_{50}/IC_{50}) = 0.5-2.8



III – Dehydrozingerone

IC_{50} (MCF-7) = 74.6
CC_{50} (HEK-293) = 63.9
SI (CC_{50}/IC_{50}) = 0.9



IV – Doxorubicin

IC_{50} (MCF-7) = 1.4
CC_{50} (HEK-293) = 1.2
SI (CC_{50}/IC_{50}) = 0.9

a) $R_1 = R_2 = CH_3$; **b**) $R_1 = H$, $R_2 = C_2H_5$; **c**) $R_1 = H$, $R_2 = C_3H_7$; **d**) $R_1 = H$, $R_2 = C_4H_9$; **e**) $R_1 = H$, $R_2 =$ *tert*-C_4H_9;
f) R_1 $R_2 =$ *cyclo*-C_4H_8; **g**) R_1 $R_2 =$ *cyclo*-C_5H_{10}; **h**) $R_1 = H$, $R_2 = C_8H_{17}$; **i**) $R_1 = H$, $R_2 = CH(CH_3)C_9H_{19}$

*IC_{50}(μM) - Inhibition concentration 50%, *CC_{50}(μM) - cytotoxic concentration 50%, *SI – selectivity index

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NOVEL TERBINAFINE DERIVATIVE WITH POTENT ACTIVITY AGAINST FUNGAL AND BACTERIAL PATHOGENS INCLUDING THEIR BIOFILM-EMBEDDED FORMS

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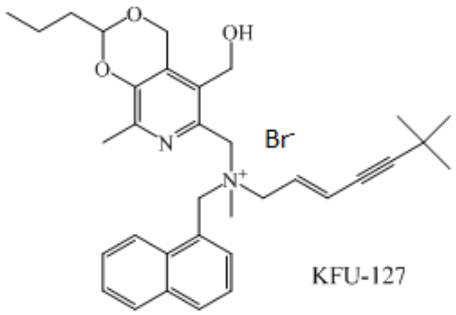
In this work we have obtained a novel derivative of terbinafine and pyridoxine KFU-127 and studied its antimycotic and antibacterial activity, and toxicity [1]. The compound exhibited excellent antimycotic and antibacterial activity, comparable or exceeding that of the reference antifungal (terbinafine, fluconazole) and antibacterial (miramistin, benzalkonium chloride, vancomycin) agents. In contrast to many antimicrobials, it was also active against biofilm-embedded *C. albicans, S. aureus, S. epidermidis,* and *E.coli*. While no biofilm structure destruction occurred, KFU-127 was able to diffuse into the biofilm matrix and inhibit biofilm growth and reduce the number of colony-forming units by 3 orders of magnitude at 8-16×MBCs. KFU-127 was slightly more toxic than miramistin and benzalkonium chloride and significantly more toxic than the reference antifungal drugs in *in vitro* cytotoxicity experiments. The results of the Ames test suggested the absence of mutagenic potential; at the same time, the tested compound as well as the reference biocides miramistin and benzalkonium chloride led to the development of SOS-response in cells at high concentrations. Acute toxicity studies using rats models demonstrated excellent safety profile of the obtained compound with LD_{50}>2000 mg/kg (per os). The obtained results suggest that KFU-127 represents a new promising broad spectrum antimicrobial agent with powerful effect.



KFU-127

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ASSESSMENT OF THE BIOLOGICAL ACTIVITY AND TOXICITY OF TRITERPENE SAPONINS

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The primary evaluation of the activity, in particular the adaptogenic action of saponin solutions, was carried out using an infusorian culture.

The index of biological activity of saponins on the model of damage to the culture of infusorians

A drug	The index of bioactivity in solutions with concentrations C, %								
	$1x10^{-1}$	$1 x 10^{-2}$	$1 x 10^{-3}$	$1 x 10^{-4}$	$1 x 10^{-5}$	$1 x 10^{-6}$	$1 x 10^{-7}$	$1x10^{-8}$	$1 x 10^{-9}$
Solutions of saponins - derivatives of quillic acid	**	**	0,88	0,98	**1,23**	1,09	0,95	0,86	0,76

From the data of the table it was established that the directivity of the studied saponins is identical to adaptogens, i.e. in large concentrations they act on the body depressingly, and in small concentrations, they exaggerate the general nonspecific resistance of the organism. It was also determined the affiliation of saponins - the derivatives of quillic acid to a certain class of toxicity with the intraperitoneal route of administration.

Materials and methods: 30 mice laboratory weight 18-22 g, males. The animals were on a standard vivarium diet, under natural light conditions, without restricting access to water and feed. Acute toxicity was determined according to the Guidelines for preclinical drug research (Ed. Mironova A.N., M .: Grif & K, 2012). After 2 weeks of quarantine, the animals were divided into groups of 6 individuals. An aqueous solution of the studied sample was injected intraperitoneally once with a probe at increasing doses of 250, 500, 1000, 2000, and 4000 mg / kg. After administration of the saponin solution, the mortality of the animals was evaluated. The number of dead mice during the first 24 hours of observation was used to calculate the lethal dose of LD_{50}. Further observations were conducted for 14 days, to monitor the appearance of signs of delayed toxicity. The established value of LD_{50} = 2854.2 makes it possible to classify the studied substance as a class **III** toxicity (**moderately dangerous**, 151-5000 mg / kg) with the oral route of administration according to GOST 12.1.007-76, SanPiN 2.1.4.1074-01 (I.V. Berezovskaya, 2003).

UNTARGETED SEARCH AND IDENTIFICATION OF METABOLITES OF ANTIVIRAL AGENT CAMPHECENE IN RAT URINE BY LC-MS/MS

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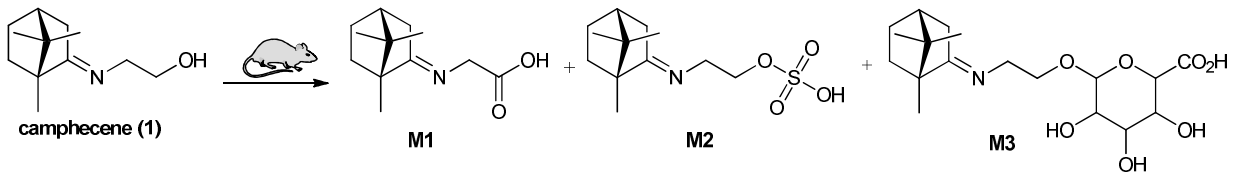
Recently we have developed a new class of camphor-based antiviral drugs. Leading compound, camphecene **1**, showed a wide spectrum of antiviral activity [1]. Later, we validated a bioanalytical method for quantitation of **1** in whole rat blood and assessed pharmacokinetic data of **1** following *i.v.* administration [2]. In this study, we performed an untargeted search and identified three major metabolites of camphecene formed in rats after *p.o.* administration.

Analysis of LC-MS chromatograms obtained in Q1 mode (6500 QTRAP spectrometer, SCIEX) using MarkerView™ software (SCIEX) showed that urine samples taken from animals received agent **1** contained three major compounds forming molecular ions with m/z = 210.4, 276.4 and 372.6 $[M+H]^+$. These compounds were absent in the samples of control group of animals and thus supposed to be camphecene metabolites (**M1**, **M2** and **M3** correspondingly). Upon collision-induced dissociation (CID) of molecular ions with m/z = 276.4 and 372.6 (**M2** and **M3**), fragment with m/z = 196.4 corresponding to protonated camphecene was formed. The observed losses of mass of 80 Da and 176 Da are characteristic for sulfates and glucuronides, correspondingly, which are often formed as metabolites of alcohols *in vivo*. CID of molecular ion with m/z = 210.4 led to the formation of several groups of ions which are characteristic for fragmentation pattern of camphor, the most intensive ion having m/z = 164.3 Da. The loss of 46 Da is often observed during ESI-MS/MS analysis of protonated aminoacids and corresponds to the elimination of CO and H_2O [3]. Thus, we suppose the **M1** to be a carboxylated derivative of camphecene. In addition to MS/MS experiments, all molecular formulae of metabolites **M1**-**M3** were confirmed by LC-QTOF method.



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POLYFLUOROALKYL-CONTAINING DIHYDROAZOLO[5,1-*C*][1,2,4]TRIAZINES AS SELECTIVE INHIBITORS OF SERINE HYDROLASES

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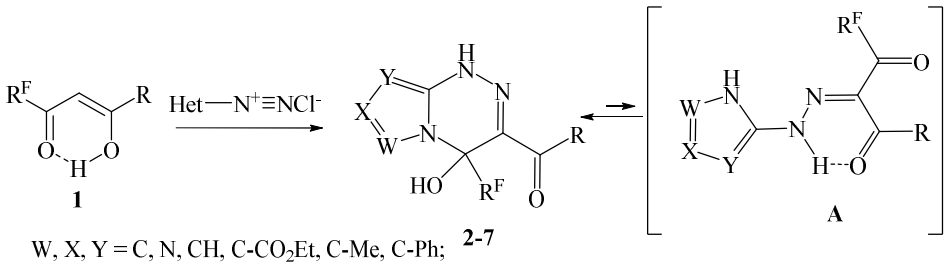
This report discusses the biological activity of 7-hydroxy-7-polyfluoroalkyl-4,7-dihydroazolo[5,1-*c*][1,2,4]triazines **2-7**, which have been obtained by the one-pot method *via* azocoupling polyfluoroalkyl-containing 1,3-dicarbonyl reagents **1** with hetaryldiazonium salts having an α-NH group [1].
By varying the heterocyclic component in the azocoupling reaction, we synthesized a series of dihydroazolotriazines **2-7**.



W, X, Y = C, N, CH, C-CO_2Et, C-Me, C-Ph;
R^F = CF_3, C_2F_5, C_3F_7, C_4F_9;
R = Alk, Ph, OAlk

Inhibitory activity of compounds **2-7** against acetylcholinesterase, butyrylcholinesterase, and carboxylesterase (CaE) were investigated using the methods of enzyme kinetics and molecular docking. It was shown that the tested compounds are reversible selective CaE inhibitors of mixed type [2]. Elongation of the polyfluoroalkyl radical and the presence of an ester group, preferably the ethoxycarbonyl group, enhance the inhibitory activity against CaE. The obtained kinetic data are well explained by the results of molecular docking. Furthermore, compounds with the tetrazole ring are more active against CaE than their triazole analogues. In the ABTS assay, pyrazolotriazines and tetrazolotriazines have a high antiradical activity comparable with a standard antioxidant Trolox.

This work was financially supported by RFBR (grant 16-03-00417)

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CYTOTOXIC ACTIVITY OF MODIFIED BILE ACIDS

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Steroids play an important role in living organisms. Bile acids are steroid acids and therefore are widely used as hepatoprotectors and anticholesteremic agents. The aim of this work is the synthesis and study of cytotoxic activity of cholic (1), litocholic (2) and modified bile acids.

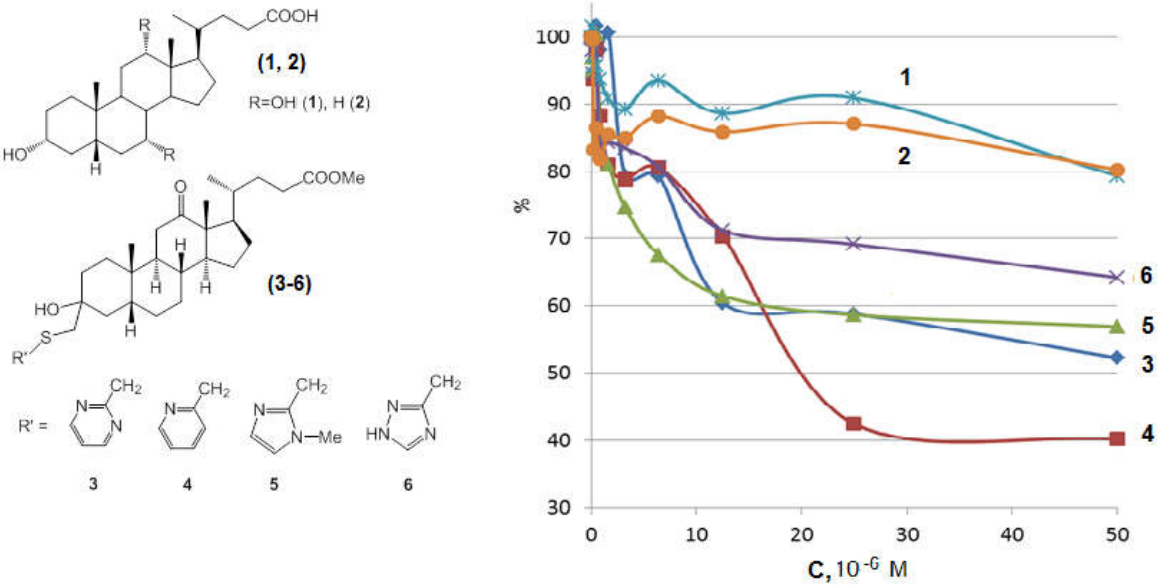

Fig. The cell viability for compounds **1–6** against HCT116 cell line.

Cytotoxic activity of compounds was evaluated on the human cancer cell lines (HCT116) in MTT test. The activity was compared with doxorubicin and cisplatin. It was shown that polycyclic acids possess moderate cytotoxic activity. The more pronounced effect was observed for compound 4 that contains pyridine moiety (IC_{50} = 20 μM). Thus, the high potential of the steroid acids in drug design can lead to novel multi-target drugs.

The financial support of RFBR (grant № 17-03-01070) is gratefully acknowledged.

ANTITUMOR ACTIVE RU(III) COMPOUNDS WITH TARGET SPECIFIC LIGANDS

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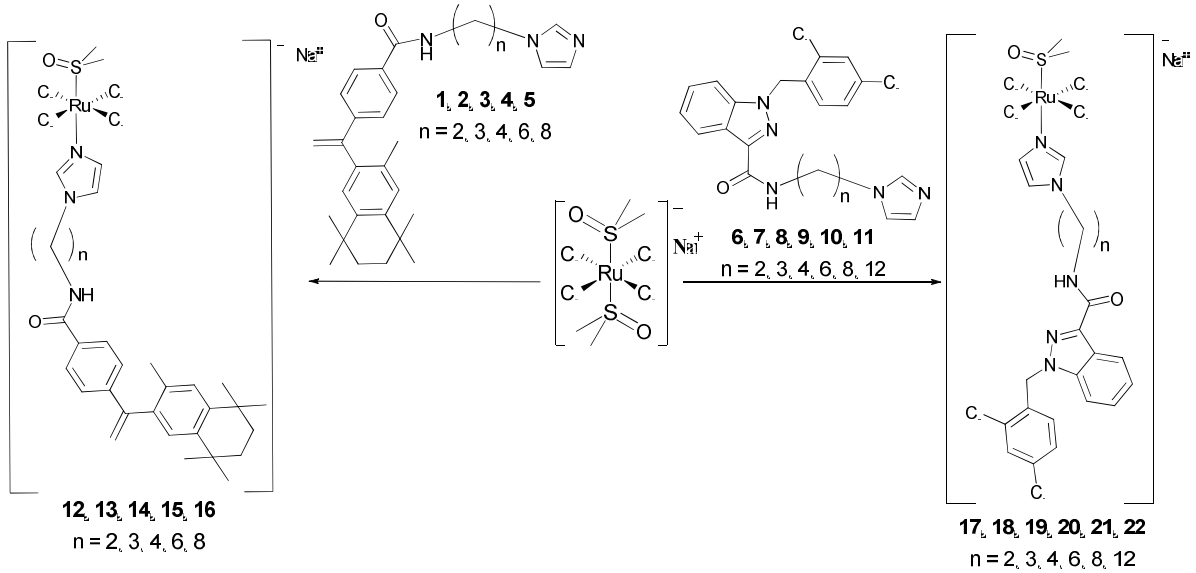
Platinum complexes dominate in the field of metal-based cancer chemotherapy. The success of these compounds incited the search for the new metal-based anticancer drugs. After platinum drugs, ruthenium compounds became the most promising antitumor agents with similar to cell cycle binding kinetics, different molecular targets and possibility for the active intracellular transport.

One of the approaches for design of new inorganic drugs is incorporating the biological active molecules into known anticancer metal complex. Synthesis and characterization of Ru(III) complexes with imidazole modified bexarotene and lonidamine ligands are presented (Scheme1).



The stability was investigated in solution simulating physiological conditions. It was shown that stability of ruthenium complexes **17-22** increase with increasing of linker length. The study of antiproliferative activity showed that obtained ruthenium complexes possess activity in the region of low micromolar concentrations.

Compounds	Stability $t_{1/2}$, s	IC_{50}, μM			
		A549	**MCF7**	**SH-SY5Y**	**SW480**
17	360±20	>30	20,39±0,04	25,8±4,5	21,4±1,8
18	330±20	>30	23,05±0,51	26,1±5,5	25±7,1
19	360±20	>30	>30	27,7±3,3	21±1,8
20	650±30	12,94±0,97	22,01±0,7	5,12±2,5	19,57±3,91
21	1390±70	5,95±2,57	17,06±0,3	2,64±1,5	9,28±0,09
22	2150±110	8,1±1,1	9,2±0,1	6,1±0,3	9,6±1,3

This work was supported by Russian Science Foundation (14-13-00483).

ELECTROSYNTHESIS OF DI- AND POLYSULFIDES ON THE BASIS OF CYCLOALKANES AND HYDROGEN SULFIDE UNDER MILD CONDITIONS

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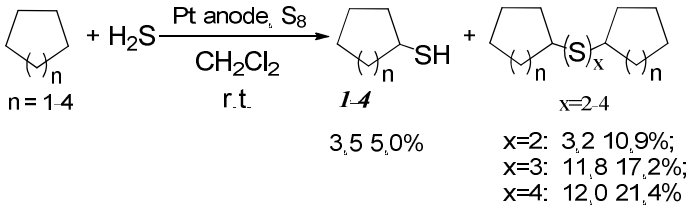
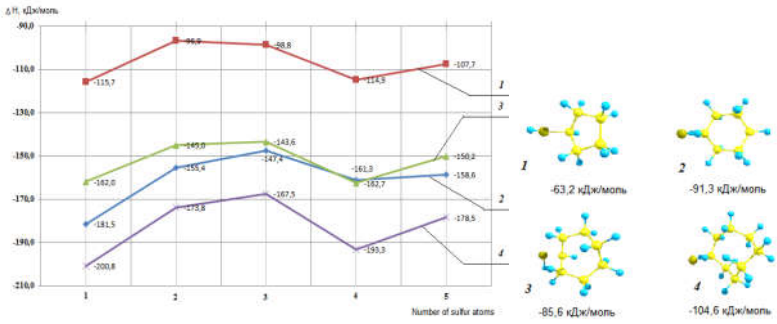
Due to the fact that organic polysulphides have a high biological activity, they are widely used in the pharmaceutical industry. It is known that the nature of the hydrocarbon radical does not affect the physiological activity of polysulfides, which are in the role of potential antifungal, antibacterial and antitumor agents. At present, there are no methods for obtaining polysulphides R_2S_n (n=2-4) based on cycloalkanes and H_2S under mild conditions. In this paper, the electrosynthesis of polysulfides based on the interaction ***1-4*** of cycloalkanes with hydrogen sulfide in the presence of sulfur (90 min) in CH_2Cl_2 is proposed.



The method consists in the anodic activation of hydrogen sulfide in the presence of S_8 and forming of a thiyl and hydropolysulfide radicals. Cycloalkanethioles are formed at the first stage of the reaction, which participate in further transformations with the formation of polysulfides. The largest yield of di- and R_2S_n (n=3,4) was achieved for the reaction of H_2S with cyclooctane (49,5%). The results of the electrochemical experiment were confirmed by quantum chemical calculations (method of density functional theory, functional and basis: B3LYP/6-31++G(d,p), Gaussian 98).



As can be seen from the graphical dependencies the formation of R_2S_4 is thermodynamically more advantageous than of di- or trisulfides.

The formation of sulfides was not fixed, since they are converted to polysulphides in the presence of a system H_2S-S_8. The total yield (28,1%) of these products ($\sum R_2S_2$, R_2S_3) was also maximum for the reaction of cycloalkane C_8 with H_2S. This is evidenced by the values of the thermal effects of the reactions. To obtain pentasulfides, it is necessary to increase the time of electrolysis up to 120-150 min.

This work was supported by RSF (grant № 17-13-01168)

CD SPECTRA OF DNA WITH BIOACTIVE FERROCENE AND COBALTOCENE COMPOUNDS

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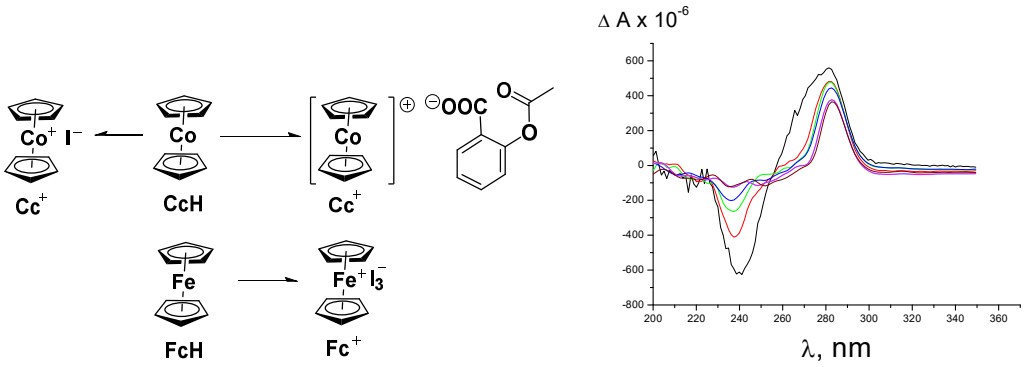
Since 1951 when ferrocene was discovered intensive research into novel drug candidates for the treatment of iron deficiency anemia, malaria, tuberculosis and especially cancer led to the development a new class of ferrocene-based compounds with significant antianemic, antimalarial, tuberculostatic, antiproliferative effectiveness [1]. At the same time, ferrocene units incorporated into some organic molecules or drugs and vitamins significantly decreased their acute toxicity.

In continuous our biological investigations a series of ferrocenium and cobaltocenium salts was studied by circulardichroism (CD) spectroscopy. Starting from commercially available ferrocene and synthetically prepared unstable (in air) cobaltocene *via* the one-electron oxidation reaction of neutral metallocenes with iodine or acetyl salicylic acid ferrocenium and cobaltocenium compounds were synthesized in quantitative to good yields.



Ferrocenium water soluble salts, as we found early *in vivo* experiments, inhibited virus induced Raucher eritroleucosis and 100% inhibition of the tumor growth and regression were found [2].

Conformational changes in double-stranded DNA were investigated by CD method. Decrease of intensity of both curves in positive and negative regions was demonstrated in CD spectra when metallocenium salts were added to DNA solutions (Fig.). Local changes in DNA conformation was due to the intercalation of metallocenium compounds between nucleic base pairs and the interaction of positive-charged metallocenium cations with phosphorus fragments of DNA.

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF THIOSEMICARBAZONE-BASED CAMPHOR DERIVATIVES

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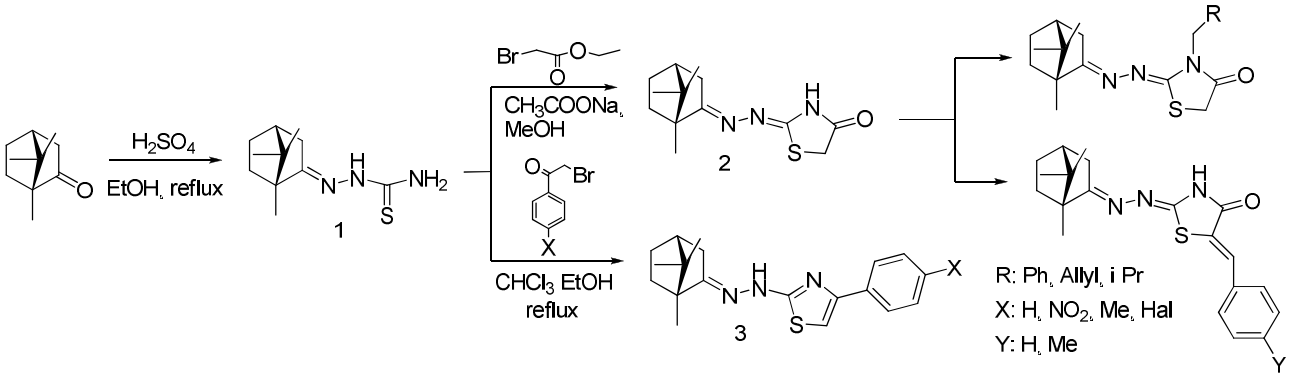
We have previously shown that the 1,7,7-trimethybicyclo [2.2.1]heptane scaffold is an important pharmacophore for the manifestation of antiviral activity [1], [2]. On the other hand, based on the literature data, heterocyclic fragments are important pharmacophore groups that are widely used in medical chemistry. Here we hybridized two pharmacophores, namely a bicyclic skeleton and a heterocyclic structure, in order to obtain novel inhibitors of especially dangerous viral infections. The synthetic scheme for constructing of target structures is presented in Scheme 1 and includes the synthesis of thiosemicarbazide **1** in the first stage. Further, by reacting the derivative **1** with ethyl bromoacetate, thiazolidinone **2** is synthesized, the subsequent modification of this compound includes two directions: alkylation at the nitrogen atom and Michael addition. An alternative pathway for the synthesis of potential inhibitors of particularly dangerous viruses involves the interaction of thiosemicarbazide **1** with α-bromo-substituted acetophenones, which leads to a set of thiazole camphor derivatives **3**.



Scheme 1

Among the synthesized derivatives, compound **3** (X=H) shown antiviral activity against Marburg virus entry into the cell using a VSV capsid-based pseudovirus system.

This work was supported by the Russian Science Foundation (N 17-73-10153).

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THE SEARCH FOR ANTI-INFECTIVE DRUGS IN N-PHENETHYLPIPERIDINES FAMILY

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K. Praliyev[2], V. Yu[1,2]

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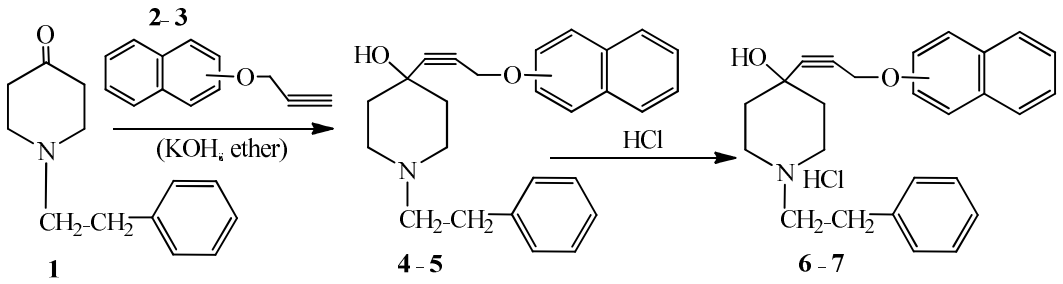
Currently, there is such a tendency when there sistance of infectious agents to various groups of drugs is increasing. This makes the process of identifying and treating infectious diseases become a complex issue.
While searching for new drugs having pronounced antimicrobial activity, previously it was found out byus, that the combination of naphthoxypropyne and piperidine moeitiesin the one molecule significantly increases the range of antimicrobial acitivity. Continuing these investigations, in the framework of the current Research 1-(2-phenylethyl)-4-naphthoxypropynylpiperidine-4-ols (**6,7**) have been synthesized.



The synthesis was carried out by condensationof 1-(2-phenylethyl)-4-oxopiperidine (**1**) with 1- or 2-naphthoxypropyne (**2,3**) under Favorskii reaction conditions, and the subsequent treatment of piperidols (**4,5**) with diethyl ether solution of HCl resulted in the formation of hydrochlorides (**6,7**).
It has been found out, that **6** and **7** are active towards the following museum strains: *Escherichia coli* ATCC 25922, *Escherichia coli* ATCC-BAA-196, *Klebsiella pneumonia* ATCC 10031, *Staphylococcus aureus* ATCC 6538-P, *Candida albicans* ATCC 10231.

The authors thank the Ministry of Education and Science of the Republic of Kazakhstan for financial support (0251/ STP).

SYNTHESIS AND STRUCTURE OF ANTIMICROBIAL MEISENHEIMER ADDUCTS

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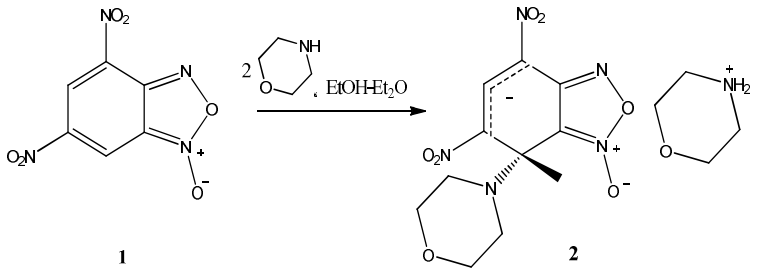
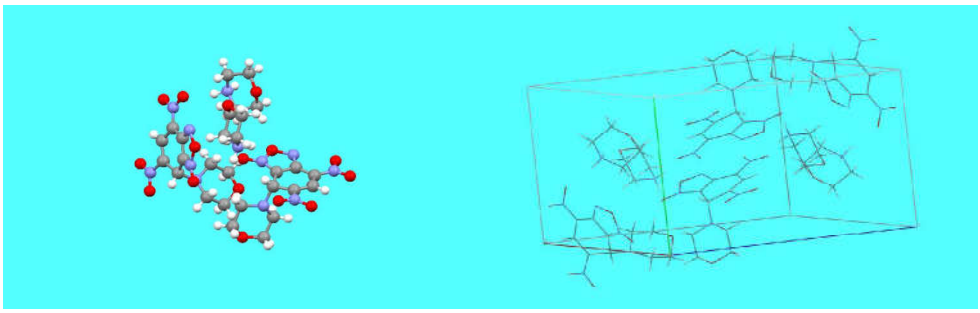
For a long time in our laboratory we have been investigating the reactions of electron-deficient heteroaromatics like 4,6-dinitrobenzofuroxan and -furazan with electron-rich reagents – different amines. Stable crystalline σ-complexes (Meisenheimer adducts) were isolated for the first time in the reactions of superelectrophilic 4,6-dinitrobenzofuroxan (**1**) with morpholine (**2**), and their structure was determined by X-ray analysis.





Structure of Meisenheimer adduct **2** and fragment of crystal packing according to the X-ray diffraction data.

Meisenheimer complexes are important intermediates in Nucleophilic Aromatic Substitution Reactions (S_NAr). They are formed by the addition of electron rich species to polynitro aromatic compounds or aromatic compounds with strong electron withdrawing groups It is believed that this reaction generally proceeds through an addition-elimination mechanism. Typically, this intermediate with a tetrahedral (sp^3) carbon is unstable, and the reaction could either proceed forward by rearomatization to generate the substituted product or simply revert back to the reactants.

Compound **2** exhibited an excellent percentage growth inhibition against the wide spectrum of tested pathogenic microorganisms.

This work was funded by the subsidy allocated to Kazan Federal University for the state assignment in the sphere of scientific activities.

2-AMINOPROPYLMORPHOLINO-5-THIENYL-6H-1,3,4-THIADIAZINE, DIHYDROBROMIDES AS A POTENTIAL ANTIPLATELET AGENTS

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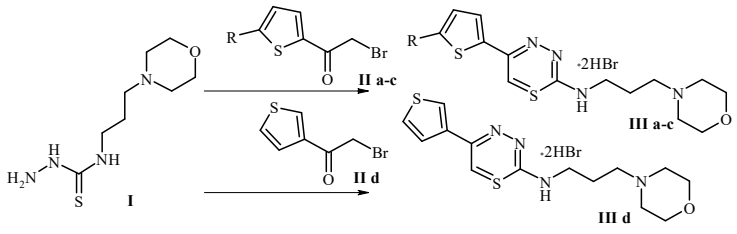
The important task of medical chemistry is to search for pharmacological agents that reduce platelet aggregation and, thus, prevent the development of a number of pathologies of the cardiovascular system. The search for and development of methods for the synthesis of novel antiplatelet agents is carried out, as the drugs used have a number of serious disadvantages: time of exposure requiring individual adjustment, constantly emerging danger of internal bleeding, and low selectivity.

2-Aminopropylmorpholino-5-aryl-6H-1,3,4-thiadiazine, dihydrobromides, previously obtained and patented, has a high antiplatelet activity in vivo [1]. An important characteristic of these substances, as antiplatelet agents, was a good solubility in water and, consequently, the possibility of their use with an intravenous administration with an acceleration of the effect, which can be used to create «rescue drugs».

We synthesized new original compounds – analogues of active antiplatelet agents having a thiophene fragment in position-5 of the thiadiazine ring.



a: R=H; **b**: R=Cl; **c**: R=Br

In addition, it became possible to vary the position of the thiophenic fragment attachment, which may result in an expansion of the range of activity of these substances.

The results were obtained within the framework of the State task of Russian Federation Ministry of Education and Science of (4.6351.2017 / 8.9).

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A NEW APPROACH TO THE SYNTHESIS OF BIOLOGICALLY ACTIVE POLYHETEROATOMIC O-, S-CONTAINING COMPOUNDS

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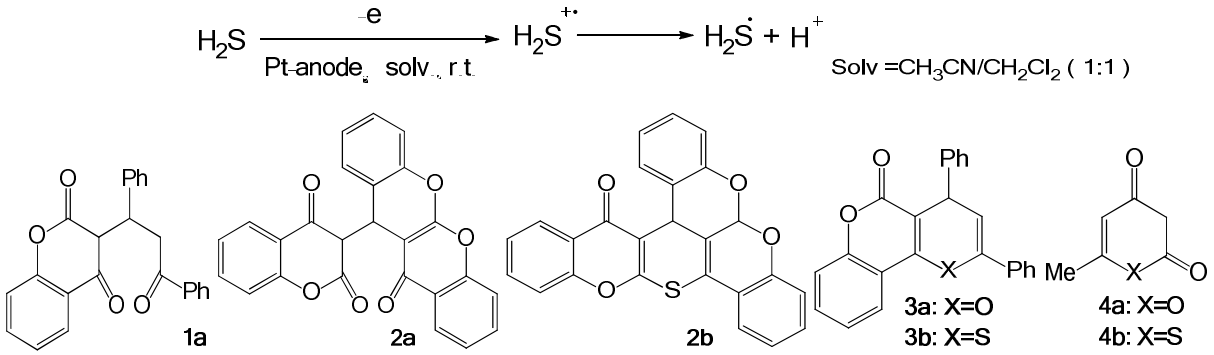
Heterocyclic compounds containing a coumarin fragment are known as therapeutic agents. The activity of coumarin derivatives is detected against Alzheimer's disease, cancerous tumors, hepatocellular carcinoma, hepatitis C, as well as in the fight against bacteria of Golden Staphylococcus and anthrax. Thus, coumarins exhibit antiviral, antibacterial, anti-cancer activity, and can be used as a medicine against diseases that come with age.

In this work the possibility of introducing a sulfur atom into polyheteroatomic compounds **1a**-**4a** in conditions of electrolysis is considered. The S-cyclization and S-recyclization reactions (90 min) of the starting substrates were carried with the participation of hydrogen sulfide out without the traditional use of strong acids (CH_3COOH, CCl_3COOH, $HClO_4$, etc.). As a result, the sulfur-containing reaction products **2b**-**4b** were obtained due to the fragmentation of the oxidized form of hydrogen sulfide (1,7 V) at the room temperature:



Moreover, the heterocyclic compound **2b** was prepared from compounds **1a** and **2a** with a current yield of 46,8% and 39,5%, respectively. The current yield of the compounds **3b**, **4b** was 50,9% and 48,7%. The first stage of the reaction is the protonation of substrates the conversion of which varies from 55.3 to 81.8%, depending on the structure. The presence of several heteroatoms of different nature in the structure of organic compounds has a positive effect from the standpoint of their biological activity. Calculations performed using the PASS program show that the following types of biological activity (antitumor, anti-seborrheic and for the treatment of restenosis) with the greatest probability are characteristic for the synthesized reaction products **2b**-**4b**.

This work was supported by RFBR (grant № 16-03-00730)

SYNTHESIS AND STUDY OF BASICITY OF NOVEL DERIVATIVES OF *N*-[(ADAMANTAN-1-YL)METHYL]ANILINE

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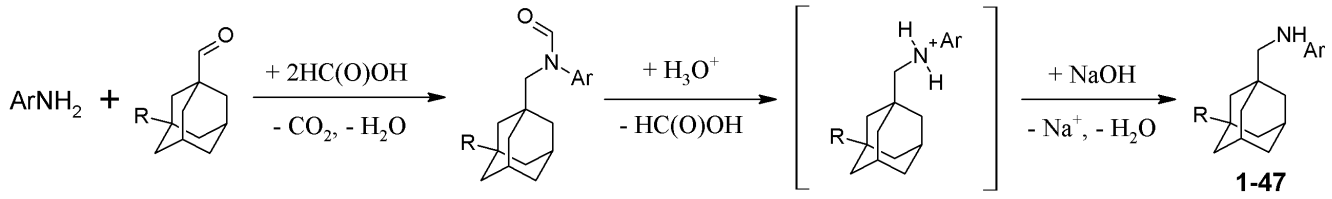
Using the Leuckart–Wallach reaction novel derivatives of *N*-[(Adamantan-1-yl)methyl]aniline have been synthesized - conformationally mobile analogs of a synthetic adaptogen "Bromantane".



R = H, Br, Cl, CN, OH

Ar = Ph, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 4-$H_2NC_6H_4$, 3-$H_2NC_6H_4$, 4-HOC_6H_4, 4-MeC_6H_4, 4-BrC_6H_4, 1-$C_{10}H_7$, 2-$C_{10}H_7$

For synthesized compounds, an experimental (in nitromethane) and theoretical evaluation of basicity - pK_{BH}^+ was performed to determine the preferred candidates for further biological studies. In addition, the study of the basicity of the compounds **1-47** was carried out in order to assess the ability of the 1-AdCH_2-fragment to transfer the inductive influence of the substituent located in position 3 of the adamantane skeleton, and also to study the combined effect of the substituents in the aromatic moiety and in the adamantane skeleton on the investigated indicator (pK_{BH}^+).

As a result, it was found that the ability of the 1,3-adamantylene link to transfer induction effects of the substituents influences the value of the basicity of amines in nitromethane.The basicity values of the amines studied and the values of the induction constants of the substituents in the third position of the adamantane sceleton correlate satisfactorily within the framework of the linear equation $pK_{BH}^+ = f(\sigma^*)$.

The work was supported by the RNF, grant № 16-13-00100.

PT(IV) ANALOGS OF OXALIPLATIN WITH AXIAL BEXAROTENE LIGANDS

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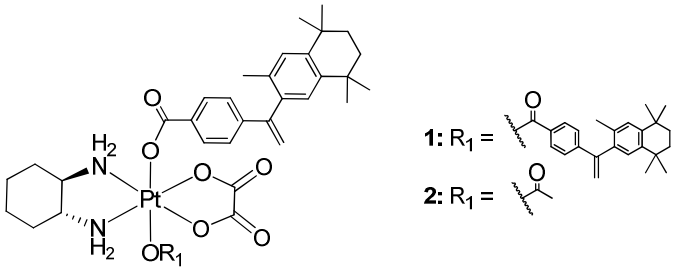
Currently Pt(II) complexes (cisplatin, carboplatin and oxaliplatin) remain major drugs in cancer treatment. However, despite the success of platinum containing drugs, the intrinsic or acquired resistance, general toxicity and other severe side effects are clinically unfavorable. Octahedral Pt(IV) complexes are of interest because of their kinetic inertness, low general toxicity and possibility for oral administration.

Combinations of two drugs in one molecule are extensively used in modern drug discovery. Bexarotene, a selective agonist of retinoid X receptors, is used to treat cutaneous T-cell lymphoma by inducing cell differentiation and apoptosis and inhibiting metastasis.

In this presentation synthesis and characterization by NMR, ESI-MS of new Pt(IV) complexes **1** and **2** with bexarotene as axial ligand are reported. Anticancer activities of the complexes were estimated on MCF7, MCF7D, SW48, A549 and HaCat cell lines by means of standard MTT colorimetric assay (Table). The complex **1** with two axial bexarotene ligands was found to be inactive, but **2** with one bexarotene ligand showed a higher cytotoxicity than cisplatin [1]. *This work was supported by RFBR (grant № 16-03-00743).*



Compounds	IC_{50} (μM)				
	SW480	**A549**	**MCF7**	**MCF7D**	**HaCat**
1	>100	83±16	>100	>100	>100
2	11±1.6	10±1	0.47±0.07	4.8±0.5	8±1.3
Cisplatin	14±4.4	29.0±10	14±7	75±5.8	30±10

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CONDITIONS OPTIMIZATION OF THE *CYLINDROTHECA CLOSTERIUM* (EHRENBERG) REIMANN ET LEWIN CULTIVATION IN ORDER TO OBTAIN A HIGH YIELD OF FUCOXANTHIN

Zheleznova S.N., Gevorgiz R.G., Nekhoroshev M.V.

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Microalgae synthesize a number of substances that have high biological activity [2]. Among the many microalgae species of particular interest are diatoms, in which the photosynthetic apparatus includes xanthophyll — fucoxanthin. Fucoxanthin (Fc) - one of the most active carotenoids of marine organisms widely used in medicine [4,7,8]. It has been experimentally proven its high activity in inhibiting the growth of cancer cells of the prostate gland, in cancer of the skin, large intestine, and leukemia [5]. Objective of the work wasto optimize the cultivation conditions of *Cylindrotheca closterium* in order to obtain biomass with a high fucoxanthin content .

We used diatom alga Cylindrotheca closterium (Ehrenb.) Reimann et Lewin from the collection of microalgae cultures of the department of ecological physiology of algae IMBI them. A.O. Kovalevsky Institute of the Russian Academy of Sciences. The culture of C. closterium, obtained from the museum, was adapted to the RS [1] nutrient medium developed by us on a luminostate at a constant temperature of 19-20 C C and 24-hour illumination with LB-40 fluorescent lamps.

The culture of C. closterium was grown in a nutrient medium RS at a nitrogen / phosphorus ratio of 15, in a mode of accumulation culture in photobioreactors of a plane-parallel type with a working volume of 2 l, a layer of 5 cm, at a constant temperature of 15 ± 1 ○ C and 24-hour illumination of 10 cl. During the cultivation process, the culture was bubbled with air (0.5 L of air per liter of culture).

The density of the culture was determined by direct weighing of C. colosterium raw biomass in polypropylene test tubes on analytical scales (CAUY-120 with an absolute error of 1 mg) after cell precipitation by centrifugation (3000 rpm for 2 minutes). To recalculate the obtained data on a dry mass, the experimental coupling coefficient between dry and raw biomass (k = 0.1) was used. To determine the dry mass of the algae, the weights were dried to constant weight for 24 hours at 105 ° C [3].Fucoxanthin was determined by thin layer chromatography [1].

Below is a storage curve with the calculation of nutrients in the nutrient medium for a maximum culture density of 3 g / l dry weight. It can be seen from Fig. 1 that the maximum density of culture reached the calculated values for 5 days of the experiment, and the maximum productivity of the culture of *C. closterium* was 1.2 g / l.

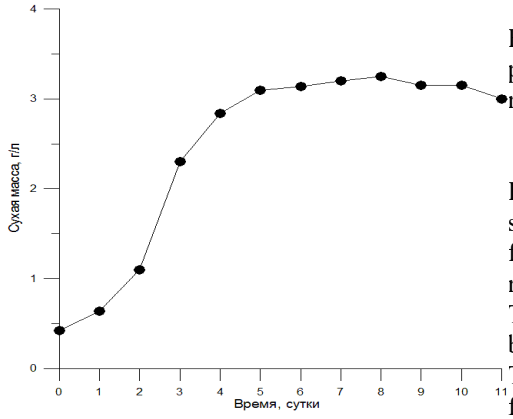

Fig.1 Dynamics of the density of *C.closterium* storage culture in plane-parallel photobioreactors on RS nutrient medium at a nitrogen / phosphorus ratio of 15, calculated for a maximum culture density of 3 g / l

In this case, the stationary growth phase lasted 6 days. At the end of the stationary growth phase, on the 11th day of the experiment, the maximum fucoxanthin content in the biomass was recorded, the Fc concentration reached 2.3% dry weight (23 mg / g dry weight).

The maximum productivity of FC in the stationary phase was 2.5 mg / g dry biomass per day.

To obtain biomass *Cylindrotheca closterium* with a high content of fucoxanthin, it is necessary to maintain an intensive culture at a temperature of 15C and an illumination of 15 kl. Under these conditions, the concentration of fucoxanthin reaches 23 mg / g dry weight (2.3% dry weight).

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POSTER SESSION №3

Synthesis of water soluble sulphur containing phosphorylated sterically hindered phenols potentially possessing bactericidal activity

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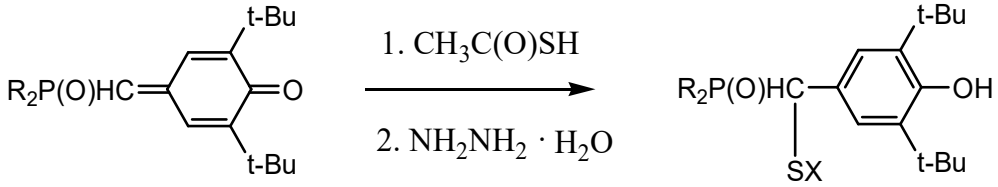
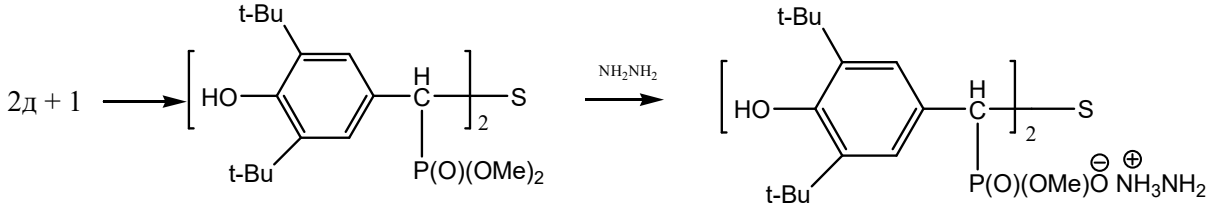
In elaboration of research of sterically hindered phenols with bifunctional antioxidant effect mechanism we developed method for synthesizing of phosphorylated α-ethanoylthioderivatives of these phenols – synthetic analogues of coenzyme A by addition of thiolacetic acid to phosphorylated methylenequinones.



1 2,3

где 2, X = MeCO, R = MeO (a), EtO (b), Et (c), Ph (d);
3, X = H, R = MeO (a), Ph (b).

By working up with hydrazine hydrate compounds 2a and 2d are transformed into corresponding α-mercaptoderivatives: O,O-dimethyl-α-mercapto-4-hydroxy-3,5-di-tert-butylbenzyl phosphonate 3a and α-mercapto-4-hydroxy-3,5-di-tert-butylbenzyldiphenylphosphinoxide 3b. Addition of substance 3a to phosphorylated methylenequinone 1 results in formation of sulphide 4a. Hydrazinolis of latter by anhydrous hydrazine leads to formation of water soluble hydrazinium salt 5a.



4a 5a

It was shown experimentally that compound 5a possesses bactericidal activity.

The work was made with financial support of the Ministry of education and science of the Russian Federation, performed in the framework of the base part of state assignment in the field of scientific activities on the project № 4.5348.2017/8.9.

Round table materials

Education in medicinal chemistry: toward an actual interdisciplinarity and market-oriented programs

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The profession of a medical chemist can be considered completely formed, the duties of such a specialist and the requirements for his qualification are understandable and almost standard. Until recently the only way that the qualification of a medical chemist has been acquired was to obtain the necessary experience by an organic chemist in the laboratory and / or workplace, but now the limitations and shortcomings of this path of professional development become apparent [1, 2]. The question of options for obtaining the appropriate education as efficiently and quickly as possible therefore is of high importance.

Obviously, the programs for training specialists and bachelors in medical chemistry will not be in demand or effective. The most promising are the master programs for and a variety of continuing education programs - from long-term training to several days. Such a format allows to optimally combine in the educational process the acquiring of a broad interdisciplinary scientific outlook and a set of knowledge and practical skills required for work.

This report examines the main problems and prospects for the development, promotion and implementation of these types of programs, analyzes the world experience and domestic practice of similar successful educational programs in other areas of professional activity.

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Educational cluster “The basis of drug design”: Tripartite teaching composition

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At the chemistry department of M.V. Lomonosov Moscow State University the practically oriented educational cluster “The basis of drug design” was recently elaborated. The cluster is aimed to provid elisteners with the professional knowledge of main principles of lead compounds search and optimization and with ability to apply this knowledge for the rational drug design. The educational cluster consists of three courses “The general aspects of medicinal chemistry”, “Methods of organic and medicinal chemistry in the lead optimization” and a practical course “Synthesis of the lead-compound analogues in drug design”.

The first course deals mainly with the principles of choice or structural design of lead-compounds (structural prototypes of the drugs), and the general accent is made on the discussion of interrelation between the drug structure and the structure of its biological target. Different aspects of improvement of lead-compound pharmacokinetic properties are also discussed, and many examples of structural design of compounds with different types of physiological activity are provided. The second course of the cluster presents the main principles of lead-compound optimization (e.g., conformational restriction, bioisosteric replacement, design of peptidomimetics, prodrugs, twin-drugs etc.). The practical course provides the students an ability to elaborate the strategies of synthesis of lead-compound analogues. The examples of structural modifications by methods of combinatorial chemistry are also included to the program.

In the end of each course the students should prepare a homework based on the analysis of papers published in scientific journals (e.g. Journal of Medicinal Chemistry) and to present a report. The detailed discussion of the purpose, ideas and the results of work is required as well as a conclusion concerning the synthetic details, the structure–activity relationship etc.

Innovative drug portfolio of Scientific and Educational Center of Pharmaceutics (SECP) of Kazan Federal University

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The Scientific and Educational Center of Pharmaceutics (SECP) of Kazan Federal University is one of the leading university centers of Russian Federation working in the field of drug discovery and development. SECP was created in the framework of the Federal Targeted Program Pharma-2020 in 2011-2014. Among the SEPC employees, there are more than 100 scientists, including chemists, biologists, pharmacologists, etc. At this moment, SECP has original innovative drug candidates, including anti-inflammatory, anticancer, antibacterial, antidiabetic, antifungal and other agents in actual therapeutic areas.

The speaker will present the actual innovative drug portfolio of SECP which can be of interest for further collaborative development with the industrial partners.

The systematic and industry-specific problems of innovative drugs' market launch in Russia.

I. Narkevich [1], A. Semin [1], and N. Kartashova [1]

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The innovative transformation of the Russian economy is the systemic tool that could help the Government of the Russian Federation to ensure the national competitiveness in the long term and to solve successfully the accumulated problems in the social and economic sphere.

However, at present, there is no continuous chain of value creation in Russia at all stages of its implementation (from the order for research and innovative development to their implementation into production and the creation of innovative companies).

As a result, the implementation of R & D into the production and the commercialization of innovative ideas are more like the exceptions rather than the rule in the current system of innovation administration

The existing systemic and sectoral problems on the way to the introduction of innovative medicines on the market were identified. The necessity of adjusting the state policy in the field of innovations was proved.

At the same time, one of the major sectoral problems is the imbalance in financing of the drug development stages:

1) There is a significant excess of applied research over search and fundamental research, which is caused by a low probability (0.35%) of conversion of the active substance into a drug that grows as the results are transferred to the next stage of the life cycle, and only after the phase III clinical trials Will be 65% [1]:

2) There is a lack of funding for applied research and R & D aimed at developing methods and technologies for the production of pharmaceuticals and pharmaceutical substances. At the same time, technologies for obtaining active pharmaceutical substances by local producers are needed for the needs of national markets, with the following advantages:

The lowest operating costs, repeatability, stability and safety of production processes;

Low capital costs due to the compactness of production site;

Low capital costs due to the high safety of the production method itself [2].

3) Lack of support for clinical trials influences on the results of preclinical studies that are actively supported by the state in recent years - they remain unclaimed.

Given the continuing potential and competitive advantages of Russian science, these negative factors and trends create the risks of Russia's lagging behind countries-world technological leaders and the devaluation of domestic investments in science and technology, reduce Russia's independence and competitiveness in the world and jeopardize national security. In the context of significant restrictions on other opportunities for the development of the Russian Federation, these risks and threats become a significant barrier that hinders the long-term growth of society's welfare and the strengthening of Russia's sovereignty.

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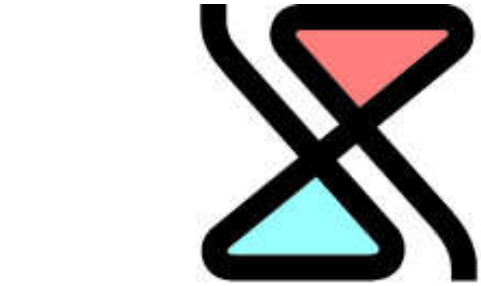
Information from the Industrial Partners

The conference organizers cordially thank the industrial partners, who have provided substantial support in organizing the conference, and wish them great success in science and business!



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ChemRar group of companies integrates research, production and investment companies in the field of innovative pharmaceutics for the development and commercialization of innovative pharmaceuticals, diagnostics, prevention, and new methods for the treatment of life-threatening diseases in Russia and abroad.

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За долгие годы работы компания накопила незаменимый опыт оснащения лабораторий и производственных участков. МИЛЛАБ, являясь интегратором технических решений, обеспечивает оптимальный выбор оборудования с учётом всех особенностей процесса, для которого предназначена установка. Каждая решенная нестандартная задача сделала свой вклад в развитие наших знаний, благодаря чему компания может успешно передавать и создавать новые современные технологии для своих клиентов.

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Компания, занимающаяся доклинической разработкой лекарственных препаратов, а также работающая в смежных областях. Ключевыми областями компетенции компании являются разрабтка мультитаргетных лекарственных препаратов, разработка противоопухолевых лекарств и препаратов для лечения нейродегенеративных заболеваний и других возрастных болезней, а также разработка геропротекторов. Компания специализируется на компьютерном драг-дизайне, QSAR, молекулярном моделировании, органическом синтезе и пр. Также компания предоставляет решения в области управления проектами по разработке новых лекарственных средств.

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