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CONTENT

PLENARY LECTURES

Synthesis of substances with high anti-cancer and anti-parasitic activity based on a new type of reactivity of aliphatic nitro compounds

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Creating new classes of drugs is an urgent task, the solution of which involves a significant number of research teams. A special place is intended to search for new molecular scaffolds on base of which anticancer drugs can be found and more effective ways of synthesizing already known structures with anticancer activity.

Recently, among the new synthetic methods of great importance can be distinguished: metalfree C-H -functionalization, transannulation, ring economy - processes. this report is devoted to the development of such methodologies in combination with the methodology of “smart reaction medium”, which is being successfully developed in our laboratory. It includes the development of synthetic methods based on the reaction of indoles with unsaturated nitro compounds and nitroalkanes. Based on this methodology, it was possible to obtain a large number of compounds with high anticancer activity, and a number of substances exhibit a rare property — reverse differentiation. Some compounds have antiparasitic activity against leishmaniasis.

This work was supported by the Russian Science Foundation № 18-13-00238.

Selective Inhibitors of BET-Proteins as Epigenetic Strategy in Oncology

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BET proteins have multiple functions, including the initiation and elongation of transcription and cell cycle regulation. BET inhibitors provide a novel approach to epigenetic anticancer therapy. These inhibitors exhibit selectivity for tumor cells by preferentially binding to regions of DNA critical for the transcription of genes that determine a cell's identity.

Using the combination of different computational and experimental methods: virtual screening and FRET-methodologies, organic and diversity-oriented target-focused synthesis (DOTS), as well as crystallographical and biochemical approaches, several inhibitors of human BET-proteins with unforeseen selectivity profiles were identified. The hit-compounds contain xanthine, triazolopyrimidinyl and tetrahydrobenzazepine scaffolds and are able to bind preferentially to Brd4(BD1) and Brds(BD1) sites of BET-proteins and to provide the dose-response downregulation of c-Myc levels.

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Translational Approach to the Development of Drugs on the Example of Regulating the Activity of Signaling Proteins

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The modern term “translational research” describes efforts aimed at on-the-fly use of fundamental results to develop potential methods for the treatment of diseases.

One of the most promising objects in the targeted therapy of tumor diseases is the tumor suppressor p53 protein, which makes the vital activity of cancer cells impossible due to the activation of various signaling pathways. However, after the first successes in the rational development of small molecule p53 reactivators, problems were revealed. It was shown that when using MDM2-p53 protein-protein interaction inhibitors, the formation of resistant tumor cell subpopulations is observed. In such a situation, the main function of an effective drug is to trigger the most aggressive and selective mechanisms for the destruction of cancer cells [1]. Our aim is to establish the relationship between the structure of MDM2 inhibitors and the direction of transcriptional activity of the p53 protein saved from proteolysis.

Multiple responses to the effects of small molecule compounds are not less pronounced in the case of AMPK, a key kinase that maintains energy homeostasis at the cellular and whole-body levels. Ubiquitous expression, as well as the presence of direct and indirect activation mechanisms determines the possibility of energy control of a large number of various processes occurring in the body. Three sites of direct binding for small molecule compounds, as well as the two-step nature of the AMPK activation allows varying the activation degree of within two orders of magnitude and, accordingly, achieving different effects [2]. In this case, our aim is to establish the relationship between the structure of the activator and integral effects of the AMPK activation.

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

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Dipeptide mimetics of neurotrophins: design and pharmacological properties

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Neurotrophins are a small family of closely related proteins that controls many aspects of the survival, development and functioning of neurons. There are 4 neurotrophins - NGF, BDNF, NT3 and NT4 – expressed in mammals. They are variously involved in the growth, differentiation of neurons, in neurogenesis, synaptogenesis and brain plasticity. Neurotrophins carry out their main effects through Trk tyrosine kinase receptors, which are activated due to dimerization caused by the ligand and subsequent autophosphorylation of tyrosine residues of the cytoplasmic domain. As a result, the binding sites of adapting and signaling proteins are formed on Trk. The complexes of these proteins with Trk activate the signaling cascades PI3K/AKT, MAPK/ERK and PLC-γ. These cascades are involved in neuroprotection, differentiation, synaptic plasticity and neurogenesis. The most studied neurotrophins are NGF and BDNF, which interact with TrkA and TrkB, respectively. BDNF plays the key role in depression and NGF in the pathogenesis of neurodegenerative disorders such as cerebral ischemia, Alzheimer's disease and Parkinson et al. Full-length neurotrophins are pharmacologically unusable due to their pharmacokinetic limitations and the presence of serious side effects such as hyperalgesia, catastrophic loss of weight, carcinogenesis. In this case, for example, hyperalgesia caused by NGF is due to the activation of MAPK. However, it is known that the ability of neurotrophins to prevent the development of apoptosis is caused by the activation of the AKT signaling pathway. Neurotrophins are represented as symmetric homodimers, the monomeric units of it contain 7 beta turns connected by 4 hairpin loops, three of which are exposed to the outside (loops 1, 2, 4) and are most important for receptor recognition. We hypothesized that different loops of neurotrophins activate different post-receptor signaling pathways, while the pharmacophores are the central fragments of the beta-turns of these loops. In the framework of this hypothesis, homodimeric dipeptide mimetics of individual NGF and BDNF loops were obtained. The compounds were designed according to a single plan - the central dipeptide region of beta-turn has been saved, preceding amino acid residue has been replaced with its bioisostere, dimerization was carried out at the C-termini with hexamethylenediamine. It was shown by Western blot analysis that NGF mimetics activate TrkA, and BDNF mimetics activate TrkB. The mimetic of the 4th loop of NGF (GK-2) and the mimetic of the 1st loop of BDNF (GSB-214) selectively activated AKT, and the mimetic of the 2nd loop of BDNF (GTS-201) - ERK. The mimetics of the 1st NGF loop (GK-6) and of the 4th BDNF loop (GSB-106) activated both pathways. The mimetics activating both cascades were similar in their effects to the corresponding native neurotrophins. GK-6 possessed both neuroprotective and differentiating activity and reduced the pain sensitivity in rats. For GSB-106 anti-depressant activity was detected which is specific for BDNF. On the other hand, GK-2, having pronounced neuroprotective activity, did not affect the differentiation and did not cause hyperalgesia, while GSB-214 and GTS-201 exhibited neuroprotective activity and not antidepressant activity. No one of the mimetics caused weight loss. Thus, the patterns

of activation of post-receptor pathways are fully consistent with the spectrum of the registered pharmacological effects. The principal and priority evidences are that activation of both PI3K/AKT and MAPK/ERK is necessary for the manifestation of antidepressant activity, and for neuroprotection activation of the AKT signaling pathway is enough. The most active mimetics GK-2 (hexamethylenediamine bis- (N-monosuccinyl-L-glutamyl-L-lysine)) and GSB-106 (hexamethylene diamide bis- (N-monosuccinyl-L-seryl-L-lysine)) were selected for development as potential drugs for the treatment of acute disorders of cerebral circulation and depression, respectively. At present time, these drugs have undergone a full cycle of preclinical and pharmaceutical research in the framework of the Federal Target Program PHARMA 2020 (State Contracts No. 14.N08.12.0051 and No. 14.N08.12.0086).

Biocompatible polyolates of biogenic elements in the sol–gel synthesis of potential medicines

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Previously we proposed a design strategy for the sol-gel synthesis of bioactive hydrogels. The essence of the strategy is that polyolates of biogenic elements, mainly silicon glycerolates, are used as biocompatible precursors, as a rule, in the form of a solution of the corresponding polyol approved for medical application [1, 2]. Thus combined element-containing polyolates are used to achieve a synergistic pharmacological effect; and bioactive additives or medicines serve as templates and/or as the property modifiers for the formed hydrogel.

Based on the strategy, fairly extensive series of works on sol-gel synthesis was realized, and the study of composition, structure, and physicochemical properties of novel hydrogels based on biogenic elements polyolates (Si, Zn, B, Ti, and others), was performed [1-4]. The influence of various factors (pH, molar ratio of precursor / polyol / water, gel-forming additives) on the process of gel formation was studied. General regularities and features of gelation process were established for various element-containing precursors in comparison with traditional alkoxy precursors. In some cases biologically active compounds, such as chitosan and hydroxyapatite, were used as templates and property modifiers in sol-gel synthesis [5, 6].

These hydrogels are non-toxic and possess a broad spectrum of pharmacological activity (reparative, regenerative, transcutaneous, and antimicrobial). They can be used in medical and veterinary practice for topical treatment of the skin, soft tissues and mucous membranes diseases of various etiologies.

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This work was carried out in the framework of the state assignment (theme no. AAA-A-A19-119011790134-1)

Natural sesquiterpene lactones - perspective scaffolds for creating of hybrid molecules with antitumor properties

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Sesquiterpene lactones are a large group of biologically active plant secondary metabolites. These compounds have a wide spectrum of biological activity and are considered as a promising class of natural compounds designed for rational target-based synthesis on their basis of potential antitumor drugs with multitarget action [1]. A number of natural sesquiterpene lactones and their synthetic derivatives are currently at different stages of clinical research [2]. The mechanisms of their action on tumor cells are associated with effects on specific signaling pathways and biochemical targets. A promising direction in the use of natural sesquiterpene lactones is their directed chemical modification, the production of hybrid molecules with pharmacophoric fragments. The purpose of such modifications is both an increase in biological activity and targeting to a specific molecular target.

This paper summarizes the authors' own results and literature data on the study of antitumor activity of sesquiterpene lactones, discusses methods for the isolation, modification and main biochemical targets, mechanisms of action, structural requirements and promising areas of research.

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Filling the void: synthetic strategies towards and biological profiling of spirocyclic and medium-sized heterocyclic compounds

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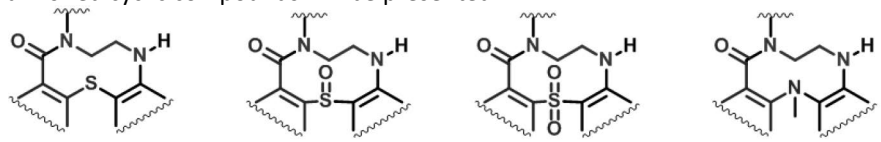
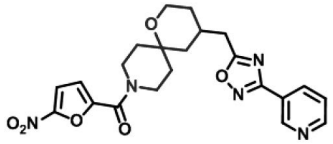
Medium-sized (9-14-membered) heterocycles are notoriously difficult to make using conventional cyclization strategies. At the same time, these cyclic frameworks have emerged as a privileged scaffold platform for drug design due to its possessing an optimal balance between rigidity and conformational flexibility. This, in turn, helps increase the likelihood of finding the optimal fit for a protein target without compromising the molecule's absorption and permeability characteristics. Several recent findings in the area of constructing such medium-sized cyclic compounds will be presented.



Similarly, spirocycles are very much sought after as scaffolds for drug design due to their inherent three-dimensionality and high degree of saturation – i.e., the combination of characteristics that are also favorable both from the prospective of small molecule's complementarity to the protein target and its physicochemical profile (mostly, solubility). We will present several strategies developed in our laboratories toward spirocycles and will discuss a number of medicinal chemistry applications of these scaffolds in the therapeutic areas as diverse as anti-infectives, antidiabetic compounds and anti-inflammatory agents.



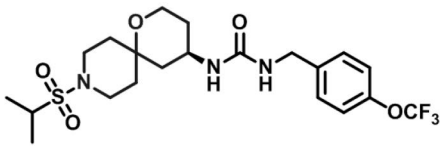
Lead compound

M. tuberculosis:

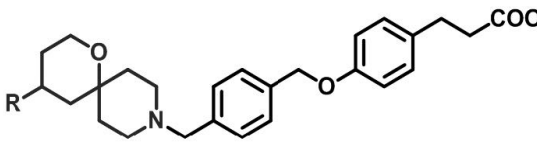
	MIC
H37Rv (drug sensitive)	1.6 μg/mL
2712 (MDR)	1.6 μg/mL
5023 (MDR)	3.1 μg/mL
7106 (MDR)	6.2 μg/mL

ESKAPEpathogens:
No activity

LD_{50} = 616.7 ± 74.44 mg/kg



Orally bioavailble inhibitor of soluble epoxide hydrolase (sEH): IC_{50} = 5 nM



Agonist for free fatty acid receptor 1

Design of Amino Acid-Based Pharmaceutical Agents for Cancer Therapy and Diagnostics

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Natural amino acids are diverse in structure, commercially available, possess high optical purity, and represent a unique starting material for the synthesis of extensive libraries thereon to design various medicinal agents. It is very important that there is the alpha-amino acid residue in the structure of these compounds, which ensures the bioavailability and selective transport of their derivatives.

At the Postovsky Institute of Organic Synthesis, methods for the synthesis of a large group of nitrosoureido derivatives of diaminocarboxylic acids have been developed and their antitumor activity has been studied. Research (in cooperation with the Blokhin National Medical Research of the Ministry of Healthcare of Russia, Moscow) resulted in designing the original antitumor agent Lysomustin that is currently used for the treatment of melanoma and lung carcinoma in clinics. Preclinical study of antitumor agent Ormustin for the treatment of primary and metastatic brain tumors has been successfully completed.

A number of peptide-like compounds derived from carboranes, which is of interest for application in boron neutron capture therapy of tumors, was synthesized.

Recently, methods for the synthesis of purine conjugates with amino acids and dipeptides possessing various types of biological activity have been developed.

Modification of magnetic magnetite-based nanoparticles made it possible to obtain materials promising for cancer diagnostics.

The conducted studies have shown the promise of using amino acids to design innovative pharmaceuticals.

The study was carried out in the framework of the State Assignment of Russia (project no. AAAA-A19-119011790130-3).

Transition metals complexese on the basis of natural plant substances: prospects for use in medicine

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The chemistry of transition metals and bioligands is an actively developing area of modern chemistry, where extensive information about new research appears each year, and new points of growth appear. This is a field of chemistry where such areas as asymmetric synthesis, metal complex catalysis, biochemistry, medical chemistry, pharmacology intersect and feed each other. The limitless possibilities of designing new metal-complex structures are determined by the diversity of natural bioligands and their hybrid derivatives, a wide range of metals. Terpenoids possess a wide spectrum of biological action in living nature, their structural diversity is represented by almost all classes of organic compounds, they can be obtained from renewable plant materials in the form of individual stereoisomers. All this determines their value as starting compounds for the synthesis of a huge number of new chiral derivatives, including ligands for solving problems of coordination chemistry.

Metal complexes with various chiral ligands are extensively studied as promising anticancer drugs [1,2]. Despite the diversity of metal complexes obtained on the basis of bioligands, studies of their biological activity are of a limited character.

The report will demonstrate modern achievements in the synthesis of metal-complex compounds containing polyfunctional derivatives of natural terpenoids and porphirins as ligands [3]. The results of studies on the biological activity of compounds of this class will be analyzed.

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Physiologically active metal-based compounds with controlled mode of pharmacological action

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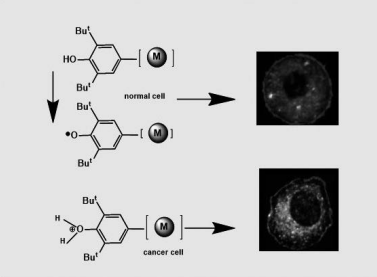
Metal-based drugs represent a relevant sector of the pharmaceutical market with potential development in the treatment of incurable diseases. There is an urgent need for the discovery of new drugs with novel modes of biological action, because several diseases develop resistances to known drugs. Metal compounds (metal-based drugs) might offer biological and chemical diversity that is distinct from that of organic substances. It has become increasingly apparent that metal-based pharmaceuticals can play a crucial role in oncology, treatment of metabolism- and genetic disorders, cardiovascular disease, gene therapy, inflammation, stroke, diabetes, malaria, and neurological disease. The goal of medicinal chemists is to create new inorganic/organometallic molecules as drug candidates.

We will discuss the need for rationalization of the investigational approaches available to create hybrid metal-based drugs. Our key approaches were (**1**) to maintain the interaction with the target, and (**2**) to keep the balance between the antitumor potency and general toxicity (Scheme).



Our study is focused on a novel approach to design hybrid metal-based physiologically 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 based on either biogenic metals (Fe, Mn, Co, Cu, Zn, Ni) or exogenic metals (Sn, Au) are presented and discussed.

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

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From natural amino acids to bifunctional chiral isocyanides

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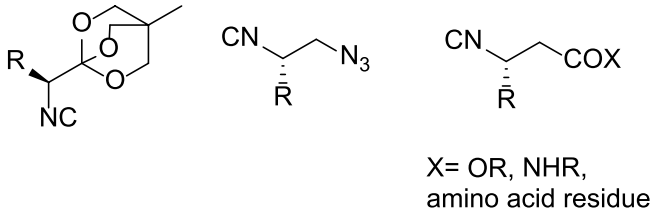
Ugi and Passerini reactions are most efficient way to molecular complexity. They open access to peptides and depsipeptides bearing the α-amino acid and α-hydroxy acid moiety in only one synthetic step using isocyanides as a key building blocks. Out of four or three imputs of this multicomponent reactions isocyanides are most important reagents. On the other hand family of these unique compounds is very limited. Using natural amino acids we elaborated efficient synthesis of some polifunctional isocyanides and demonstrated their high synthetic utility (Scheme 1). For example, a family of nonracemizable isocyanoacetic acid derivatives, azido substituted isocyanides and β_3-isocyanopropionates was elaborated. These reagents can be used for peptide decoration of various biologically active compounds to improve their properties.



Meglumine as a green, efficient and reusable catalyst for synthesis and molecular docking studies of bis(indolyl)methanes as antioxidant agents

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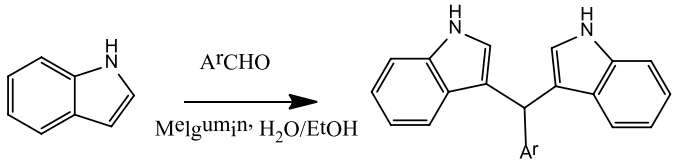
Indoles represent an important group of N-heterocycles, which are known to have potent pharmaceutical and biological properties. Indoles and their derivatives are one of the important classes of heterocyclic compounds that are present in various natural products, pharmaceuticals, agrochemicals and other compounds of importance. Among them, bis(indolyl)methanes (BIMs) are frequently found in natural products, drugs and biological molecules and also identified to possess wide range of applications in pharmacology, biochemistry and medicinal chemistry. BIMs and their derivatives are found in terrestrial and marine metabolites. In fact, bis(indolyl)alkanes exhibit a wide spectrum of biological activities viz., cytotoxic, antitumor, antiviral, antimicrobial, anti-inflammatory, and antioxidant. The BIM is also a privileged scaffold in alkaloids including ramiflorine A and ramiflorine B, vibrindole A, streptindole, deoxytopsentin, bromodeoxytopsentin, and sponges. Because of the unique pharmacological activities and the prevalence of indole moiety in many natural products, a great deal of interest has been focused on the development of efficient synthetic protocols for the preparation of bis(indolyl)alkanes. A number of synthetic methods for their preparation have been reported. Catalyst is an important aspect of green chemistry. The design and application of new catalysts and catalytic systems are playing a vital role in achieving goals of environmental defense and economic assistance. Reusability of the catalyst without any loss of activity is an indispensable fact of green chemistry. However, the use of toxic reagents, high temperature, and volatile organic solvents are among the drawbacks of most of these protocols. Hence, there is a need for a new, efficient, and inexpensive synthetic methodologies based on green chemistry processes in organic synthesis. In the present communication, herein we report the use of meglumine as a catalyst for the synthesis of bis(indolyl)methane derivatives.



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Ionotropic Glutamate Receptor Modulators: Design of New Scaffolds

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Ionotropic glutamate receptors attract a growing attention in the last decades as promising targets for development of drugs for the treatment of serious neurological and psychiatric disorders, such as schizophrenia, depression, age-related cognitive and memory disorders, Parkinson's disease, Alzheimer's disease, etc. AMPA receptor positive allosteric modulators were shown to reveal such neurophysiologic effects as induction of long-term potentiation of synaptic excitation, considered as a foundation for learning and memory, and significant increase of nerve growth factors expression, making them promising compounds for the development of nootropics and neuroprotectors.

Techniques for computer-aided design of AMPA receptor modulators based on new scaffolds as well as the approaches to their synthesis and the results of physiological activity studies are considered. The molecular dynamics simulations for a series of AMPA receptor PAMs bound on the interface between two glutamate-binding domains have demonstrated a good correlation of calculated binding energies with the experimental pEC_{50} values. The Molecular Field Topology Analysis (MFTA) QSAR method was quite helpful in the modeling of ligand selectivity and multi-target activity in terms of local properties such as the atomic charges, group van der Waals radii, and local lipophilicity. In addition, the 3D QSAR and pharmacophore models of the AMPA receptor PAMs have been constructed. The *de novo* design of structures fitting the PAM binding site and based on new scaffolds allowed us to find novel highly potent positive allosteric modulators of AMPA receptors that have a unique combination of properties.

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Three Decades of Computer Program PASS: From Prediction of Biological Activity Spectra to Systems Pharmacology

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PASS development started thirty years ago in the framework of the National System for Registration of New Chemical Compounds Synthesized in the USSR to create a computational method that predicts biological activity spectra for diverse drug-like molecules. PASS prediction is based on the analysis of structure-activity relationships of the training set included more than one million biologically active molecules. The average prediction accuracy calculated by the leave-one-out cross-validation procedure for the whole training set and over five thousand kinds of biological activity is about 95%. Both local PASS version and freely available via Internet dozen web services are developed (http://way2drug.com/projects). PASS Online is currently used by >22,000 researchers from 91 countries of the world. Over 835,000 predictions obtained and used to select the most promising molecules for synthesis and appropriate bioassays.

Our latest web service called AntiHIV Pred (http://way2drug.com/hiv) predicts the interaction of drug-like compounds with five antiretroviral targets and a few dozen biological activities relevant for the treatment of HIV-associated comorbidities. Also, predictions for about 250,000 compounds from Open NCI database allow ordering the samples for biological testing from NCI/NIH.

Based on PASS estimates, the systems pharmacology approach allows predicting therapeutic and adverse effects for new pharmacological agents under study.

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A new class of antiviral azoloazines. Medicine “Triazavirin”

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The design of new effective drugs for preventing and treating viral diseases is an actual task due to the high danger of viral infections, the variability of viruses, and the emergence of highly dangerous strains. A new original class of non-nucleoside antiviral etiotropic substances, azolo[5,1-c]-1,2,4-triazines and azolo[1,5-a]pyrimidines, effective against diseases caused by influenza, herpes, tick-borne encephalitis viruses, and various hemorrhagic fevers was developed during research projects at the Ural Federal University, the Institute of Organic Synthesis of the Ural Branch of the Russian Academy of Sciences, the Scientific Research Institute of Influenza of the Ministry of Health of the Russian Federation, and a number of other organizations

The main methods for construction of these bicyclic azoloazine structures include annelation of the azine cycle to the azole one, which allows the use of a wide range of aminoazoles and available synthons, such as derivatives of acetic acid or acetonitrile [1].

The obtained data results in the real basis for creating a series of effective domestic antiviral drugs. Triazavirin (dihydrate of the sodium salt of 2-methylthio-6-nitro-1,2,4-triazolo[5,1-c]-1,2,4-triazin-7-one) is the first drug created on the basis of this class of compounds and was included in the register of medicines of the Russian Federation in 08.28.2014, number LP-002604. During the clinical application of Triazavirin, it has been shown that its use in etiotropic therapy of influenza and acute respiratory viral infections facilitates reduce of the main symptoms duration of the disease include fever and level of re-isolation of influenza viruses in patients and outperforms Tamiflu and Arbidol by efficiency [2,3].

Furthermore, the inclusion of Triazavirin in the complex therapy of tick-borne encephalitis, including severe patients with the meningeal form, leads to a reduction in all clinical manifestations [4].

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How can we respond to modern challenges in medicine

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The most important direction of medical chemistry, allowing to obtain new, effective drugs, is the use of synthetic transformations of natural compounds. The most effective is the involvement in the synthesis of compounds with native biological activity and having an available raw material base.

The main efforts of our team are focused on creating agents in the most sought-after therapeutic classes - oncology, various viral infections, neurodegenerative diseases, cardiology.

In all the listed areas, leading compounds were found, the majority of which passed the cycle of preclinical trials.

Thus, the antiviral agent Camfecine, a derivative of natural camphor, was discovered, which possesses not only outstanding activity against the H1N1 strain of the influenza virus, but is also able to actively inhibit a wide range of other strains of the influenza virus.

The derivative of natural usnic acid is an effective inhibitor of Tyrosyl-DNA-phosphodiesterase 1 (Tdp1), which is an important enzyme of the DNA repair system responsible for the drug resistance of many malignant diseases. The combined use of this agent and cytostatic campotecin allows us to hope for success in the treatment of such a difficult cancer as lung cancer.

Serious progress was achieved in the creation of drugs that relieve life-threatening arrhythmia. One drug based on the natural toxin - botulinum toxin prevents the transmission of nerve signals that stimulate arrhythmia. The other is aimed at achieving the effect of ablation of the heart muscle with the help of chemicals, which is much more effective compared to the currently used radiofrequency ablation.

The development of new anti-inflammatory drugs based on the fluorinated het(aryl)derivatives

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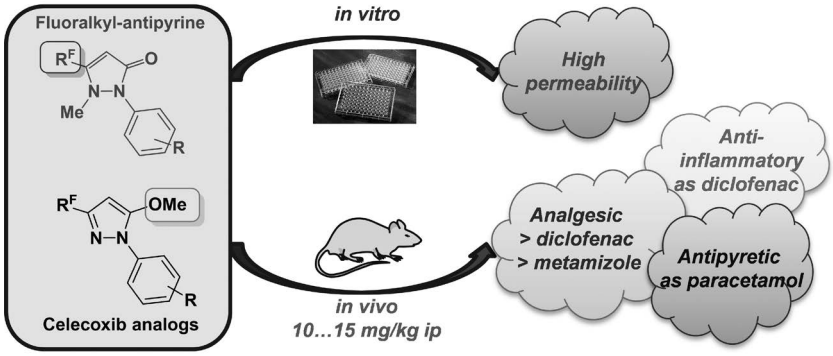
The report is devoted to the development of new non-steroidal anti-inflammatory drugs based on the fluorinated derivatives of salicylic acid and pyrazole. The effective methods for synthesis and modification of polyfluorosalicylic acids were suggested. The fluorinated analogues of the clinically used salicylates, metal complexes and amino-modified polysalicylates were obtained. The biological tests allowed to reveal a number of derivatives with high analgesic and anti-inflammatory properties [1, 2], tuberculostatic [3], antibacterial and anti-fungicidal actions. The method lowering the acute toxicity of polyfluorosalicylates by substitution of fluorine atom on the amine pharmacophore moiety was found [2]. Besides, the methods for regioselective methylation of polyfluoroalkylpyrazoles with a different set of ambident nucleophilic centers were developed, resulting in analogues of antipyrine and celecoxib [4, 5]. The research of biological properties of new derivatives in tests *in vitro* and *in vivo* allowed to discover leader compounds, perspective for preparation of new medicines [6].



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Chemical Probing of Gene Transcription: Molecular Mechanisms as Antitumor Drug Targets

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Targeting gene transcription remains attractive for antitumor drug design. Formation of stable complexes with DNA and interference with template syntheses (actinomycin D as a prototype) are efficient for transcriptional block. Following this direction, the antibiotic olivomycin A has been modified to yield a derivative potent in *in vivo* tumor model at tolerable doses. Rational design of DNA binders as transcriptional inhibitors is based on structural knowledge about the target and a precise positioning of the chemical compound on the target. Olivomycin A inhibits transcription of dozens of genes although general toxicity might limit the therapeutic potential of this class of transcriptional antagonists. Recent advances in synthetic chemistry opened novel opportunities in modulation of transcription using low molecular weight compounds. Selective inhibitors of individual transcriptional mechanisms entered clinical trials as gene- and situation specific pharmacological blockers (inhibitors of CDK8/19 Mediator kinases as a robust example). This approach is straightforward for prevention of emergence of drug resistance and attenuation of growth of metastatic foci, the mechanisms mediated via CDK8/19. However, the complexity of transcriptional machinery makes many responses independent of this mechanism. In these situations targeting at a post-mRNA synthesis level, that is, by deregulation of RNA splicing, is worth pursuing. Chemical inactivation of individual members of splicing protein kinases families DYRK (dual specificity tyrosine-phosphorylation-regulated kinase) and Clk (CDC-like kinase) induced cell death via DNA damage responses specific for cell cycle phases. Expanding medicinal chemistry of transcriptional modulators provides new antitumor drug candidates suitable in different contexts.

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Modifications of plant terpenoids and coumarins *via* the transition metal catalyzed reactions as a promising direction in the development of selective antibacterial agents

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Natural diterpenoids and coumarins are attractive platforms for the synthesis of new biologically active compounds, including potential medicinal agents. The directed catalytic transformations of the mentioned polyfunctional compounds allows their directional, selective modification and, accordingly, to find more effective and less toxic analogs and derivatives.

The report summarizes the results of our research on the application of reactions proceeding under the action of metal complex catalysts to plant metabolites and their derivatives (eudesmane type methylenlactones, coumarins, isopimaric acid). The cross-coupling reactions, cross-coupling-cycloisomerization reactions, copper(I)-catalyzed Mannich reaction, eco-friendly copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition (CuAAC reaction) were the main routes of synthesis used in this investigation.

A synthetic route for obtaining of 6-substituted furo[2,3-d]pyrimidines including the Sonogashira coupling reaction of (11*R*)-[5-bromouracyl-yl]eudesma-4(15)-en-8β, 12-olides with (trimethylsilyl)acetylene, desilylation, Cu-catalyzed Mannich reaction of (11*R*)-[(5-ethynyl)uracyl-1-yl]eudesmanolide with amines and formaldehyde and cyclization into the furo[2,3-d]pyrimidines.

Cycloisomerization of isopimaric acid N-propargyl amide in the presence of $ZnCl_2$ and selective bromination led to terpenoid 5-(bromomethyl)oxazole which was further transformed to azide. CuAAC reaction of the terpenoid azide with several alkynes, including amino acid alkynes led to the terpenoid substituted biheterocyclic or triheterocyclic derivatives.

Series of coumarins and bicoumarins, interconnected by spacers of various lengths containing the triazole substituent in the 3-th and 6-th positions were synthesized on the basis of plant accessible coumarins peuruthenicin and peucedanin.

Studies of toxicity and pharmacological properties of synthesized compounds are conducted jointly with the Novosibirsk State medicinal University. Some data of antimicrobial and also antitumor activity of the synthesized groups of compound are discussed. A number of compounds very interesting from the biological point of view have been mentioned.

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Is it possible to create synthetic opioid analgesics without narcogenic potential?

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Opioid analgesics remain the «gold» standard in the management of pain. However, the development of drug dependence limits their clinical efficacy. Currently, it has been convincingly proven that opioid-induced analgesia is the result of the activation of the G_i-protein signal transduction pathway, whereas the addictive potential is due to involvement of the β-arrestin cascade of intracellular reactions. According to the concept of functional efficiency of the GPCR dependent on the ligand, the opioid receptor adopts different conformations and directs the GPCR signaling along the G_i-protein or the β-arresting pathway of the regulatory process. G_i-biased mu- and kappa-opioid agonists (PZM21, Noribogaine, Oliceridine, Herkinorin) have been identified [1, 2]. These facts served as a prerequisite for the development of functionally selective opioid ligands having properties of highly efficient G_i-activators and β-arrestin-biased antagonists.

Using computer simulation, docking to the specific binding site of the human kappa-opioid receptor X-ray model (PDB ID 4DJH) and subsequent structural optimization of virtual molecules, an integral 2-*p*-fluorophenylimidazo[1,2-*a*]benzimidazole scaffold of G_i-biased kappa-agonistic activity was built, which is different from those of the known opioid ligands. For further development of conformation-selective agonists, one of the most promising molecules RU-1205 (K_i 36.7 nM) was selected. Analysis of the molecular mechanism of binding of RU-1205 to the kappa-opioid receptor site (LigandScout 4.1) revealed 7 hydrophobic, 2 π-π stacking and 1 hydrogen bond interaction with Met130, Leu200, Val218, Trp274, Ile277, Ile281, and Tyr869, which permits stabilization of the receptor conformation, initiation of G_i-signaling pathway, and block of the β-arrestin cascade. Panel of *in vivo* tests on the central models of algesia demonstrated that test substance has naloxone-, norBNI-reversible analgesic effect, exceeding the potency of morphine and butorphanol 12 and 4 times, respectively. Unlike reference drugs, compound RU-1205 does not show pharmacological properties that contribute to the formation of physical dependence, addiction, and dysphoria [3, 4].

Thus, the development of G_i-biased agonists can serve as a basis for creation of new generation of synthetic opioid analgesics without the narcogenic potential.

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Лекарственные препараты для иммунотерапии злокачественных новообразований: настоящее и будущее онкологии

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Биотехнологическая компания BIOCAD

В последние годы особое внимание мирового профессионального сообщества сконцентрировано на иммунотерапевтических подходах к лечению онкологических заболеваний. Особенностью подобных методов лечения является активация собственного противоопухолевого иммунитета пациента. Одними из первых в разработке, а затем и в клинической практике, появились препараты-блокаторы рецептора PD-1 или его лигандаPD-L1, которые продемонстрировали многообещающие успехи в лечении ряда заболеваний. Полученные еще на ранних фазах клинических исследований результаты иммунотерапии таких заболеваний, как меланома и рак легкого, были столь значительны, что изменили парадигму лечения злокачественных новообразований.

Первым российским блокатором PD-1, разработанным компанией BIOCAD, является BCD-100 (МНН: пролголимаб), — это полностью человеческое антитело, способное с высокой аффинностью и специфичностью связываться со своей мишенью. Препарат разрабатывался с учетом свойств других антител-блокаторов PD-1 и результатов их исследований. Одной из отличительных особенностей данного препарата в сравнении с имеющимися блокаторами PD-1 является принадлежность к классу IgG1 (пембролизумаб и ниволумаб относятся к IgG4). Преимущество использования IgG1 заключается в большей термодинамической и агрегационной стабильности антитела, в результате чего имеется возможность получения высококонцентрированной формы для подкожных инъекций. Еще одной особенностью препарата BCD-100 является наличие в Fc-фрагменте молекулы так называемой мутации LALA (Leu234Ala/Leu235Ala), которая минимизирует эффекторные свойства антитела и предохраняет, таким образом, PD-1-экспрессирующие лимфоциты от разрушения другими иммунокомпетентными клетками. Препарат продемонстрировал высокую активность по результатам экспериментов с клеточными линиями, мышами-ксенографтами, а также примлемый профиль безопасности и достаточные фармакокинетические показатели в рамках исследований на релевантной животной модели (нечеловекообразные приматы).

Результаты завершенного клинического исследования пролголимаба при метастатической меланоме свидетельствуют о высокой эффективности препарата BCD-100. Так, при применении в минимальной дозе 1 мг/кг один раз в две недели, общая частота ответа (ОЧО) и контроль над заболеванием в популяции perprotocol составили 40,68% и 67,80%, соответственно. В популяции mITT наблюдались схожие показатели эффективности.

Результаты анализа эффективности по вторичным конечным точкам подтвердили заключение о достаточной эффективности препарата BCD-100. Показатели беспрогрессивной выживаемости (БПВ), общей выживаемости (ОВ), длительности ответа были сопоставимы с таковыми лучших в классе ингибиторов PD-1.

При применении в минимальной дозе 1 мг/кг один раз в две недели, 12-месяч-

ная БПВ составила 41,27%.При медиане наблюдения 13,8 месяца (95% ДИ 13,2-14,7) медиана общей выживаемости не была достигнута.12-месячная ОВ составила 74,6%. Препарат BCD-100 был равно эффективен как при применении у не леченных прежде пациентов, так и при применении у ранее получавших терапию пациентов.

Таким образом, высокая эффективность препарата BCD-100 в минимальной дозе 1 мг/кг была подтверждена и по параметрам долгосрочной эффективности (общей и беспрогрессивной выживаемости), данный дозовый режим может быть рекомендован к клиническому применению у пациентов с распространенной меланомой.

Завершены клинические исследования 1 фазы еще двух иммуноонкологических препаратов компании BIOCAD- анти-CTLA-4 и анти-PDL1. Планируются клинические исследования комбинаций этих препаратов с анти-PD-1 и/или другими разрабатываемыми чекпойнт-ингибиторами с целью разработки лучшего в классе иммуноонкологического препарата.

В настоящее время проводится клиническое исследование 2 фазы «коктейля» анти-PD1 и анти-CTLA-4 антител – смеси двух оригинальных антител в одном флаконе, оказывающих синергетическое действие при совместном применении. Предполагается, что компоненты препарата, обладающие различными механизмами действия, при применении у больных со злокачественными новообразованиями будут обеспечивать более высокую эффективность в сравнении со всеми существующими иммуноонкологическими препаратами. «Коктейли» различных антител в одном флаконе – способ повысить эффективность терапии при использовании комбинаций лекарственных препаратов, при снижении стоимости лекарственной терапии в сравнении со стоимостью совместного применения отдельных препаратов.

Завершена разработка, ведутся доклинические исследования трех иммуноонкологических препаратов, аналоги которых отсутствуют на рынке. BCD-144 активирует противоопухолевые Т-лимфоциты, которым возвращена способность распознавать опухолевые клетки с помощью анти-PD1 препаратов. BCD-106 делает опухолевые клетки видимыми для еще одной популяции клеток иммунной системы – для фагоцитов. BCD-180 активирует еще одну популяцию иммунокомпетентных клеток, обладающую выраженным противоопухолевым эффектом – NK-клетки (натуральные киллеры).

Данные препараты позволят создавать новые высокоэффективные комбинации, потенциально обладающие эффективностью в тех областях онкологии, где иммунотерапия не всегда эффективна, или заболевание становится устойчиво к воздействию одного препарата.

Для того, чтобы добиться высоких результатов лечения при плохо отвечающих на иммунотерапию опухолях, необходим целый ряд иммунотерапевтических препаратов с различными точками воздействия. Компания стремительно расширяет свой портфель иммуноонкологических препаратов и разрабатывает в настоящее время более 15 различных молекул.

ORAL LECTURES

Nitroalkanes as precursors for azoles synthesis

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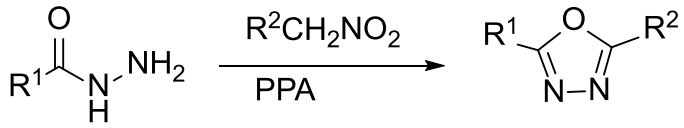
In our previous works we had shown nitroalkanes in polyphosphoric acid meduim serves as flexible reagent undergoing different transformations on various substrates under pretty similar conditions. Methods of amination, carbamoylation of arenes was developed which are in the base of many heterocyclization processes that was found in our laboratory past years. In such a manner, benzoxazoles, benzimidazoles, isatins, isoquinolines can be prepared.

Oxadiazole ring are matter of particular interest in terms of biological activity, being present in a large number of active substrates. This makes this fragment one of the most favored in the search for new drugs. On the base of previous works we have proposed that acylhydrazides and nitroalkanes can act as precursors of 1,3,4-oxadiazoles. When we tested this approach we had found that 1,3,4-oxadiazole can be prepared in polyphosphoric acid medium with yields from good to quantative.



As a development of this ideas thiadiazoles can be prepared or 2-pyridylhydrazines can be involved into this reaction to give corresponding 3-methyl-[1,2,4]triazolo[4,3-a]pyridines

This work was financed by the Russian Foundation for Basic Research (grant #18-33-20021 mol_a_ved).

Physiological activity of new 1,3,4-thiadiazine derivaties

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New 1,3,4-thiadiazine derivatives were synthetized at the I.Ya. Postovsky Institute of Organic Synthesis of Russian Academy of Sciences (Yekaterinburg, Russia) under the leadership of academician O.N. Chupakhin. The 1,3,4-thiadiazine class is known for a wide range of physiological activity. The aim of our work was to study the effects of new 1,3,4-thiadiazins on the energy processes of rat liver mitochondria *in vitro* as a result of determining succinate dehydrogenase activity (SDH; EC 1.3.99.1), one of the key mitochondrial Krebs Cycle and electron transport chain (ETC) enzymes involved in the adenosine triphosphate (ATP) formation [1].

The liver mitochondria of *Wistar* rat male (n=7, m=300±50 g) were isolated by differential centrifugation. Mitochondria were incubated for 10 min with solutions of 1,3,4-thiadiazines at a concentration of 10 mg / ml. The SDH activity of mitochondria was determined by the ferricyanide method.

The SDH activity in liver mitochondria of the control rats was 10.1±2.5 nmol/min per 1 mg of protein (Fig. 1). The 1,3,4-thiadiazine derivatives, with the exception of compound L-6, had an inhibitory effect on the enzyme activity to varying degrees: L-2 reduced the SDH activity by 30%; L-5, L-8 - by 50%; L-4, L-7, L-14 - by 67%; L-9, L-17 - by 80%; L-10, L-29 - by 86% (Fig. 1). The inhibitory effect of 1,3,4-thiadiazine derivatives on the SDH activity is due to the presence of the morpholine derivative in their chemical structure and depends on the nature of the substituent in the in the 2nd and 5th positions of the thiadiazine ring.

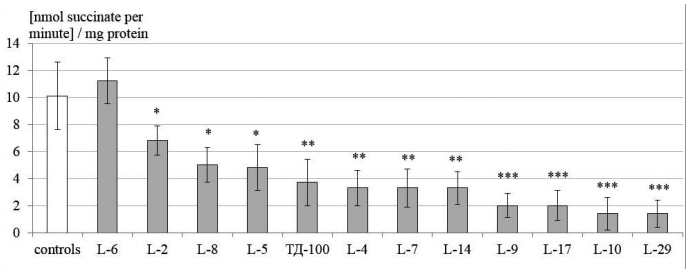

Fig. 1. *SDH activity in rat liver mitochondria before and after exposure to 1,3,4-thiadiazine derivatives (* - differences are significant at p <0.05, ** - at p <0.01, *** - at p <0.001, relative to the control, using the Kruskal-Wallis statistical test).*

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Early drug discovery for type 2 diabetes mellitus: An academia perspective

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Type 2 diabetes mellitus and related metabolic disorders represent a major health concern and growing burden worldwide and in Russia. Underlying molecular mechanisms are also largely involved in other pathologies, including obesity, cancer, aging, neurodegeneration, and cardiovascular diseases. Therefore, identification of new compounds with antidiabetic potential is of great interest in the metabolic disease area.

The majority of drugs today come from commercial pharmaceutical and biotech companies [1] which heavily rely on high-throughput screening campaigns to identify novel biologically active entities. Hit identification rates are way below 1% [2] while R&D costs are high. Drug development in academia is hampered by limited resources, lack of know-how, and lack of a regional ecosystem. At the same time, academic expertise empowered with modern approaches and collaborative networking may provide a cost-effective venue for valuable early-stage drug discovery.

In our current project, we pursue potential antidiabetic agents. Collection of ca. 2500 drug-like compounds was obtained through collaboration with 9 academic institutions. ChEMBL mining afforded published active compounds against therapeutically relevant targets. Pharmacophore fingerprint calculation coupled with expert examination was used to build focused libraries of previously untested ca. 500 compounds. Biochemical screening with subsequent disqualification of apparent hits (poorly soluble, aggregators, redox-active) identified 49 true hits against 7 target proteins. Follow-up cellular and animal assays provided validated leads for further development of first-in-class antidiabetic agents: micromolar MST1 and PTP1B inhibitors, glucokinase activator, and submicromolar AMPK activator and GSK3B inhibitor.

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Reactions of tertiary cyanothioacetamides with azides

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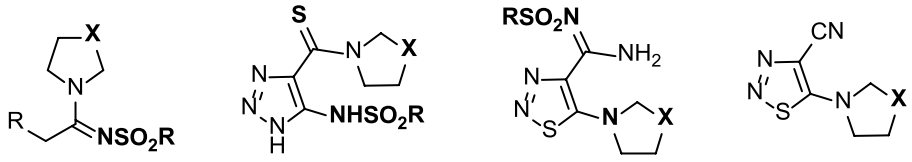
Sulfonyl azides, mostly tosyl and mesyl azides, exhibit diverse reactivity and are widely used in organic synthesis. They serve as diazo transfer agents, allowing to synthesize various types of diazo compounds from C–H acidic compounds, azides from amines and *N*-unsubstituted 1,2,3-triazoles from enamines. In cycloaddition reactions onto acetylenes leading to 1-sulfonyl-1,2,3-triazoles they are the source of the sulfonyl triaza fragment. In the synthetic approach to *N*-sulfonyl derivatives of diamino alkenes by reactions with enamines they serve as the source of sulfonyl imino fragments. In the last decade, two powerful synthetic methods were developed based on metal catalyzed processes for the generation of *N*-sulfonyl azavinyl carbenoids and *N*-sulfonyl ketenimines from acetylenes and sulfonyl azides followed by interactions with various nucleophilic reagents to form a huge variety of different types of valuable heterocyclic and organic compounds, such as amidines, sulfonamides, azadienes, α-aminoketones, cyclopentadienes, etc. Also in these reactions sulfonyl azides provide sulfonyl imine fragments to the reaction products. Reactions of sulfonyl azides with various kinds of thioamides are carefully studied by Hatanaka and Bakulev groups [1, 2]. These reactions being carried out in the absence of a base are given an access to N-sulfonyl amidines. Recently we have shown that cyanothioacetamides react with azides to form 1,2,3-triazoles **2** and 1,2,3-thiadiazoles **3** and **4** depending on the nature of azide and thioamide and base used.

Short review on reactivity of azides towards thioamides will be presented here.



1 **2** **3** **4**

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Design of pyridoxine-based hybrid and dipharmacophore structures

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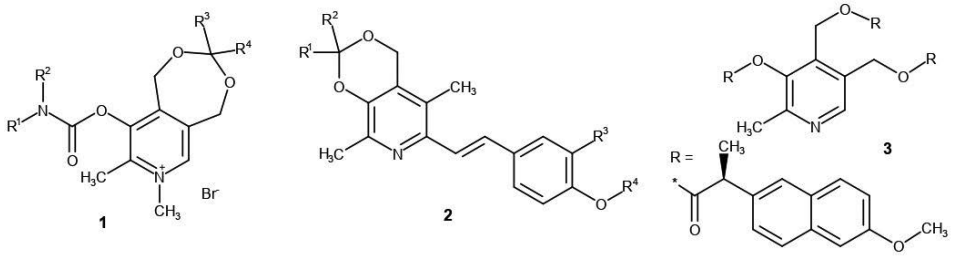
The design of hybrid and dipharmacophore structures is a valuable approach in medical chemistry, which allows us to harness the potential of the synergistic interaction of the initial pharmacophores. The pyridoxine molecule (vitamin B6) provides rich opportunities for chemical functionalization and med-chem design. In the present work, three examples of the development of promising pyridoxine-based drug candidates in actual therapeutic areas are discussed: anticholinesterase carbamates **1** [1], antitumor analogs of *trans*-stilbene modulators of estrogen receptors **2** [2], and anti-inflammatory dipharmacophore **3** [3]. In all of these cases, the use of the above strategy in combination with the bioisosteric approach has led to a significant improvement in the activity and/or safety profiles of the original pharmacophores.



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Derivatives of Glycyrrhizinic acid as inhibitors of Dengue and Zika viruses

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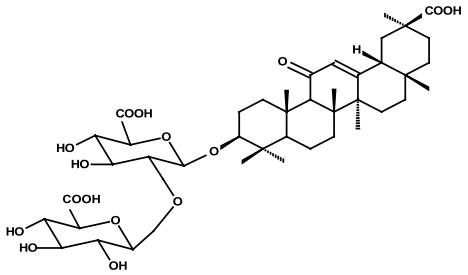
Dengue (DENV) and Zika (ZIKV) flaviviruses distributed by *Aedes sps.* mosquitoes, have caused epidemics in Asia, the Caribbean, Central and South America in recent years, and there are no licensed vaccines and post-infectious therapy against them [1,2]. ZIKV infection is especially dangerous for pregnant women, as it can lead to fetal microcephaly [2]. The preferred strategy of modern medical chemistry is the use of natural compounds with established activity as platforms to create new antiviral agents [3].

This work is devoted to the synthesis of a focused library of Glycyrrhizic acid (GA) derivatives, the main triterpene glycoside of licorice roots (*Glycyrrhiza glabra L., Gl. uralensis Fisher*) and the screening of the antiviral activity of the compounds obtained for DENV and ZIKV *in vitro*. Benzal hydrazides, amino acid and dipeptide conjugates of GA have been synthesized, among which highly active compounds have been found for the first time inhibiting the cytopathic effect, infectivity and the release of DENV2 and ZIKV viruses *in vitro*.



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The new synthesis of *N*-aryl-4-(5-nitrofuran-2-yl)-pyrimidin-5-amines and their antitubercular activity

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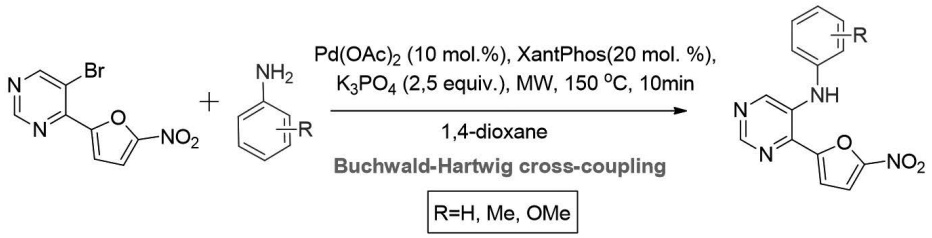
In previous paper 5-arylamino-4-(5-nirtofuran-2-yl)pyrimidines by the Buchwald-Hartwig cross- coupling with various anilines has been derived [1]. All synthesized compounds demonstrated a significant level of *in vitro* antibacterial activity against *Nesseria gonorrhoeae, Streptococcus pyogenes* and *Staphylococcus aureus*, including their drug-resistant stains, and low cytotoxic effect on McCoy B cells as compared to commercial drug Spectinomycin as a standard.

In the present studies, the reaction conditions have optimized. The starting 5-bromo-4-(furan-2-yl)pyrimidine was coupled with the corresponding anilines under microwave irradiation in presence of XantPhos as a most effective ligand, that reduced the reaction time from 15 h to 10 min and allowed to increase yields. The obtained compounds were screened for their antimicobacterial activity.



The synthetic path was supported RFBR No18-33-00103 mol_a. The biological assay was supported RSF (project No 15-13-00077 P).

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Mechanism of the antiviral action of camphecene analogs: molecular modeling

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According to the results of theoretical studies and biological experiments [1] camphecene (product of interaction between camphor and aminoethanol) can bind in two of the possible active hemagglutinin (HA) sites: on the border of subunits of HA1 and HA2 in the region of the fusion peptide and in the lower part of the protein in the region close to the proteolytic cleavage site. The binding of it in the second active site of HA lead to V615L mutation and to form camphecene-resistant virus strain. However these arguments do not deny the possible influence of camphecene on another potential biological target. The possibility of it interaction with proton M2 channel was estimated by molecular dynamic method (figure). Ligand locates into the channel and form hydrogen bonds with ASN31. This allows us to consider camphecene as a potential multitargent ligand.

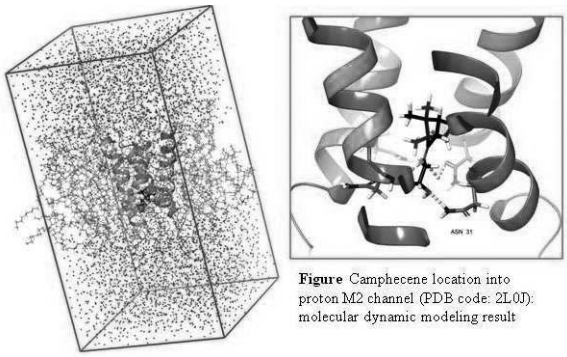

Figure Camphecene location into proton M2 channel (PDB code: 2L0J): molecular dynamic modeling result

Camphor imine derivatives [2] (camphecene analogies) also show pronounced antiviral activity. It is possible that these compounds inhibit only hemagglutinin through interaction with one active center or with both. Can be camphecene analogues also multitarget drug-like molecules? Then we will describe mechanism antiviral activity of new potential antiviral agents using molecular modeling methods.

This work was financially supported by the Russian Sceintific Foundation (Grant No. 15-03-00193)

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The approach to polyfluoroalkylated pyrazoles with multiple biological activities

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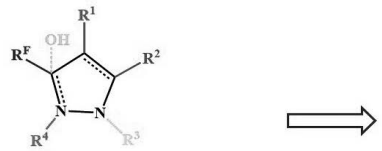
Pyrazoles are pharmacologically privileged structures, since their derivatives not only exhibit the wide range of diverse biological effects but they are actively used in clinical practice.

In the report, the features of the formation of polyfluoroalkyl-containing pyrazole framework, as well as the possibility of its modification are considered. The reaction of alkylation, ribosylation, alkoxy - and hydroxymethylation, nitrosation, azo-coupling, reduction, cross coupling, and others were used as methods for chemical modification. The functionalized polyfluoroalkylpyrazoles with different substituents at the various positions were synthesized. The tuberculostatic, antibacterial, antifungal, antioxidant, cytotoxic activities of the synthesized compounds were evaluated *in vitro* tests. Their analgesic activity and acute toxicity were established *in vivo* experiments. The most promising compounds for following chemical modifications and biological testing were revealed. The "structure – activity" regularities, which can be useful for the drug design based on pyrazole scaffold, were determined.

Possibilities of chemical modification:



R^F = CF_3, CF_2H, C_2F_5, C_2F_4H, C_3F_7, C_4F_9, etc;
R^1 = H, Ar, Het, CO_2X, N=NAr(Het), 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)

Biological activities:

- **analgesic,**
- **anti-inflammatory,**
- **antiviral,**
- **antifungal,**
- **anti-tuberculosis,**
- **hypoglycemic,**
- **antibacterial**

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This work was financially supported by the Russian Science Foundation (grant № 16-13-10255).

Chiral terpenophenols as a platform of new highly active biomolecules for medicine

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Natural compounds are bioactive and have high bioavailability due to their specific interactions with target macromolecules in living organisms. Therefore, the sequence motif and the basic skeletons of bioactive natural compounds can serve as guidelines for the synthesis of new molecules with high biological significance. Phenols can be highlighted among the various compounds of natural origin. It is an important and very common in nature class of compounds, many of which are found in plants and involved in a variety of growth and development processes. The presence of phenolic compounds often causes the medicinal properties of plants. Substituted phenol can be defined as structural unit of many biologically and pharmacologically active compounds. The search for approaches to the synthesis of analogues of natural biologically active phenols and new polyfunctional derivatives of phenols is a promising line of research.

We have developed methods for the selective synthesis of terpenophenols [1]. A series of analogs of natural phenolic compounds have been obtained: chroman type ethers, prenylphenols, diarylalkanoids, coumarins, chalcones [2]. Synthesis of new *N,O,S*-containing derivatives of isobornylphenols has been carried out [3]. Synthesized racemic and enantio enriched isobornylphenols and their derivatives are promising compounds for the creation of drugs of various actions [4].

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Synthesis of Nanomaterials Based on Fe_3O_4 Magnetic Nanoparticles and pH-Targeted Peptide pHLIP

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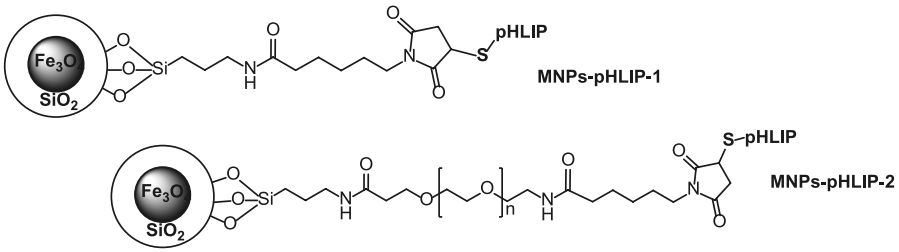
It is known that pH-low insertion peptide (pHLIP) can be used as a targeting molecule for delivery of nanoparticles or diagnostic agents to tumor tissues. The purpose of this work is to obtain nanomaterials based on Fe_3O_4 magnetic nanoparticles (MNPs) and pHLIP, as well as to study the peculiarities of their biodistribution in the bodies of tumor-bearing animals.

MNPs (10 nm) obtained by co-precipitation method from solutions of Fe^{3+} and Fe^{2+} salts, coated with SiO_2 and modified with 3-aminopropylsilane were used. pHLIP was conjugated either using 6-maleimidohexanoic acid *N*-hydroxysuccinimide ester as a linker (bearing an activated carboxyl group to bind to amino groups on MNP surface, and maleimide group to bind to thiol group of the peptide) by analogy with [1] (**MNPs-pHLIP-1**) or using polyethylene glycol containing similar terminal groups in its structure (**MNPs-pHLIP-2**).



The possibility of specific accumulation of MNP conjugates with pHLIP in media with a low pH was demonstrated in experiments *in vitro* and *in vivo*. As an example, the possibility of **MNPs-pHLIP-2** binding to tumor cells and MRI imaging of a tumor *in vivo* was shown.

This work was financially supported by the Russian Foundation for Basic Research (project no. 18-015-00319) (in part of synthesis and biological investigations of nanoconjugates). Characterization of nanoparticles by physical and chemical methods was carried out in the framework of the State Assignment of Russia (project no. AAAA-A19-119011790130-3).

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Drug Interaction Prediction using Chemoinformatics Methods

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Drug-drug interaction (DDI) phenomenon may occur when several drugs are combined. Many DDIs are associated with changes in drug metabolism that performed by Drug-Metabolizing Enzymes (DMEs). In this case, DDI manifests itself as a result of the effect of a one drug on the biotransformation of other drug(s), its slowing down (in the case of inhibiting DME) or acceleration (in case of induction of a DME), which leads to a change in the pharmacological effect of the combined drugs.

We used one of the most advanced DDI severity classification systems - the OpeRational ClassificAtion (ORCA) system for the classification of DDI, that was created for doctors to assess the risk of co-administration of two drugs. ORCA divides DDI into five classes: contraindicated (class 1), provisionally contraindicated (class 2), conditional (class 3), minimal risk (class 4), no interaction (class 5). For a computer prediction of DDI severity, we assembled a training set consisting of several thousands of drug pairs. DDI classes prediction is based on a combination of modified MNA PoSMNA descriptors (multilevel neighborhoods of atoms) and a classification algorithm implemented in the PASS (Prediction of Spectra Activity for Substances software).

The average accuracy of DDI classes is about 0.9.

The Russian Science Foundation (grant No. 17-75-20250) has supported the work.

Conformationally fixed tricarbocyanines modified with β-alanine, as the basis for the vector delivery of biogenic molecules

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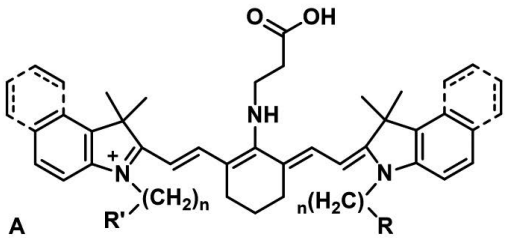
The effective fluorescence of tricarbocyanine dyes in the near infrared region allows their use in medicine and biology. The formation of complexes with transport proteins of the blood (for example, serum albumin HSA) is another key factor due to which they can be used in angiography [1].

As reagents that effectively participate in the modification of conformationally fixed tricarbocyanines at the meso-position, ω-amino acids, for example, β-alanine, have been described [2]. In the framework of this study, a series of symmetric conformationally fixed tricarbocyanines based on indolenin and benzindolenin was synthesized and a meso-position was modified by β-alanine. The molecular docking method was used to evaluate the possibility of binding the previously described modified dyes **A** with HSA and it was shown that the interaction of the ligand with the protein is possible at three binding sites of IIA, IIIA and IIB. The optical properties of the dye-albumin complexes were studied using spectrofluorimetry and time-resolved fluorimetry (TCSPC). The binding constants of modified tricarbocyanines **A** with BSA are determined.



A

R'=R = CH_3 (n=2)
SO_3^- (n=4)
C(O)OEt (n=4)

R'= SO_3(n=4) R = C(O)OEt (n=4)

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Nucleoside analogues as promising inhibitors of DNA repairing enzymes

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Alkylating drugs that react with heterocyclic bases of nucleic acids and cause DNA damage are used in the treatment of many forms of cancer. DNA repair systems resist the action of alkylating drugs that damage DNA. Thus, the therapeutic effect depends on the effectiveness of DNA repair systems. Selective inhibition of DNA repairing enzymes in combination with alkylating drugs can be the basis of a very effective anticancer therapy. The DNA repairing enzymes poly(ADP-ribose) polymerase-1 (PARP) and tyrosyl-DNA-phosphodiesterase 1 (Tdp1) can be considered as promising therapeutic targets for the treatment of oncological diseases [1, 2]. Recently we have identified a novel class of Tdp1 inhibitors based on disaccharide nucleosides and some related compounds. We have tested more than 50 compounds with half-maximal inhibitory concentration being in 0.4-18.5 μM range for the most effective inhibitors investigated in this experiment. Some disaccharide compounds and their derivatives were also tested with human recombinant PARP-1. The most effective inhibitors of Tdp1 on the basis of thymine, guanine and 5-iodouracil, which contained two D-ribose residues, linked together with β-(1→2)-*O*-glycosidic bond and modified with several benzoyl groups, demonstrated relatively low own cytotoxicity and strengthened the action of the anticancer drug topotecan in 2-6 times.

This work was supported by Russian Foundation for Basic Research (project № 18-29-09037).

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Drug-drug cocrystals of antituberculous 4-aminosalicylic acid

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4-Aminosalicylic acid (PASA) is a second-line drug used in the treatment of multidrug-resistant tuberculosis [1]. According to the Biopharmaceutical Classification System, PASA is located on the boundary between classes II and IV with low solubility and permeability about 80% [2]. Additionally, PASA is an unstable compound, which is inclined to irreversible decarboxylation with formation of toxic 3-aminophanol in solid state and aqueous solution [3, 4]. One of the perspective approaches to improve solubility and stability of active pharmaceutical ingredients is cocrystallization. Cocrystal is multi-component crystal that is formed between two (and more) compounds that are solids under ambient conditions and held together by non-covalent interactions [5]. The aim of our investigation is to find novel cocrystals of PASA, characterize them using a wide range of experimental methods (powder and single crystal X-ray diffraction, differential scanning calorimetry, thermogravimetric analysis) and study dissolution processes and stability in solutions. Pyrazinamide (PyrAm), nicotinamide (NAM), isonicotinamide (iNAM), isoniazid (IZN), caffeine (Caf) and theophylline (Tph) were selected as the second cocrystal compounds – coformers. Three new PASA cocrystals with pharmaceutically acceptable components (iNAM, Caf, Tph) have been prepared by both solvent-drop grinding and solution techniques. The thermochemical and solubility properties for all the obtained cocrystals have been studied. Cocrystallization has been shown to lead not only to PASA solubility improving but also to its higher stability against the chemical decomposition.

This work was supported by the Russian Science Foundation (No. 17-73-10351)

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Efficacy and safety of ligands for TRPV1 receptors

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Solve the problem of pain treatment and minimize undesirable manifestations, possibly acting on a single pain target, selectively modulating pain receptors. Pharmacogenetic approaches have identified molecular targets - TRPV1 receptors. Sensitive neurons that detect TRPV1 play the role of an integrator of pain-sensing stimuli (Freichel et all., 2001, Levine et all., 2007), which makes it possible to study the receptor as a promising therapeutic target in treating and arresting painful stimuli (Caterina et all. , 2001, Szallasi et all., 2007). From the extract of sea anemone Heteractis crispa, natural polypeptide modulators TRPV1, called Analgesic Polypeptide Heteractis Crispa (APHC) (Philyppov et all., 2012), were isolated. The ARNS1 polypeptide (Mr ~ 6187Da), ARNS2 (Mr ~ 6185Da), the amino acid sequence of which differed from ARNS1 by a single substitution of Val31 by Pro31 (Andreev et al. 2009) and ARNS3 (Mr ~ 6111Da) differing from APCH1 by replacing Arg18 by Pro18 and Ala52 by Gly52 (Kozlov et all., 2009). Selected polypeptides not only inhibit the TRPV1 receptor in model experiments in vitro, but also change the effect on potentiating when using small concentrations of activating agents. After analyzing the constructed three-dimensional models of the APHC1 and APH3 peptides, they identified several functionally important residues of modulating TRPV1 and collected them in a new hybrid molecule, A13 (Dyachenko et al. 2017). The study was performed on laboratory animals, rats, mice.

The results showed that a single substitution of the amino acid chain can lead to a change in activity (a drop in the analgesic ability of APCH3> APCH1> APCH3 and a complete change in the pharmacological properties of the molecule. The analgesic activity of the APCH 1-3 and A13 polypeptides in the biomodels of pain, directed through the TRPV1 receptor, It has a pharmacological effect in the dose range of 0.01–10 mg / kg. The polypeptide compounds APCH1-3 do not affect the hemostasis system, structural changes and can affect the CVS. APCH1-3 have an analgesic effect This activity, as in the tests related to the functioning of the TRPV1 receptor (capsaicin test, hot plate, CFA test), and standard pain models (formalin test, acetic cramps). Toxicological studies revealed a high safety of the studied substances.

The use of GLP-technology in conducting preclinical studies of drugs

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In the Russian Federation, preclinical studies of medicinal products for medical use are monitored by Roszdravnadzor by conducting routine on-site inspections of the organization that performs them. The subject of such inspections is the assessment of compliance with the requirements established by: Federal Law No. 61-ФЗ dated April 12, 2010 “On Appeals of Drugs”; by order of the Ministry of Health dated 01.04.2016 No. 1999n “On the approval of the rules of good laboratory practice”; GOST 33044-2014 “Principles of good laboratory practice” (GLP). Information on the results of on-site scheduled inspections of organizations performing preclinical studies of drugs for medical use can be found on the Roszdravnadzor website.

In addition to scheduled inspections of Roszdravravnadzor, in accordance with Government Decree No. 1172 of December 17, 2013 “On recognition and assessment of the compliance of testing laboratories (centers) with the principles of good laboratory practice ...” organizations performing preclinical studies (testing laboratories) can apply to the Federal Accreditation Service (Rosaccreditation), which is appointed by the testing laboratories monitoring body for their compliance with the principles of GLP. The recognition of compliance with GLP principles is obtained by testing laboratories on a voluntary basis. Information about the results of inspections Rosakkreditatsii recorded in the appropriate registry, which can be found on the site. Testing laboratories on a voluntary basis can receive recognition of compliance with the GLP principles in Rosakkreditatsiya, which may indicate the basis of the Federal Law dated December 22, 2014 No. 429-ФЗ “On Amendments to the Federal Law“ On Circulation of Drugs ”. Information on the results of inspections Rosakkreditatsiya can be used by the Ministry of Health of Russia in assessing the results of preclinical studies in order to make decisions about the registration of a medicinal product or to issue a permit for conducting clinical trials.

2,5-substituted 1,3,4-*6H*-thiadiazines in the correction of regenerative processes in experimental diabetes mellitus

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Successful correction of hyperglycemia, oxidative stress and protein glycation by 2,5-substituted 1,3,4-*6H*-thiadiazines [1] became the basis for further study of the mechanisms of experimental diabetes mellitus (DM) correction of by compounds of this class.

In a series of experiments *in vivo* in models of DM type 1 (alloxan diabetes) and type 2 (streptozotocin-nicotinamide diabetes) in rats was demonstrated the possibility of a joint correction of hyperglycemia, hypoinsulinemia, protein glycation, oxidative stress and systemic inflammatory response, as well as structural indicators of the pancreatic islets and kidney, by compounds L-17 (2-morpholino-5-phenyl-1,3,4-*6H*-thiadiazin, hydrobromide) and L-14 (2-aminopropylmorpholino-5-phenyl-1,3,4-*6H*-thiadiazin, dihydrobromide). Compound L-17 reduced the severity of kidney and pancreatic lesions characteristic of experimental DM. Compound L-14 injections increased the degree of apoptosis and proliferative activity of cells, but no significant reduction in destructive changes in the kidney was observed. The introduction of both compounds, to a greater extent L-17, led to a decrease in levels of IFN-γ, IL-1α, IL-10 and reduced the number of phenotype M2 macrophages in pancreatic tissue in alloxane DM. With the introduction of both compounds, the concentration of IFN-γ in the blood, increased in the simulation of type 2 DM, decreases sharply, which affects the indicators of hyperglycemia, hypoinsulinemia and the level of apoptosis in tissues.

Thus, the compounds of 1,3,4-*6H*-thiadiazines class, which differ in the nature of the substituent in the positions of the 2 - and 5 - thiadiazine cycle, have a pleiotropic effect on metabolic and immuno-inflammatory mechanisms of experimental DM development, modulate regenerative processes in this pathology, and are promising for further study of antidiabetic activity.

The work is supported by RSF grant, project № 16-15-00039.

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Modification of 5,7-dioxycoumarins with azines by nucleophilic substitution of hydrogen

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5,7-Dioxycoumarins are a widespread among nature compounds, which are demonstrated a broad spectrum of activity including anti-HIV, antitubercular and antioxidant. However, often the activity of these compounds does not meet the requirements of modern pharmacological drugs. In this connection chemists use such a method as modification of natural coumarins in order to search more active analogues. According to statistics, 2 out of 5 sold drugs have an azaheterocyclic fragment in their structure. Therefore, the development of methods of the direct modification of 5,7-dioxycoumarins with azines represents an important trend in this area.

The classic approach to the preparation of azine-coumarin conjugates is the direct reaction of cross-coupling of halogen- or pseudohalogen derivatives of coumarin compounds with azaheterocycles in the presence of transition metals as catalysts. In recent time, methodology nucleophilic substituted of hydrogen (S_N^H) has been developed, allowing C-H/C-H coupling in one simple step without prior functionalization of the starting compounds to be carried out.

In the present work we have shown the possibility of using 5,7-dioxycoumarins as nucleophilic agent in the S_N^H reactions.

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Substituted dihydroazolopyrimidines. Synthesis and tuberculostatic activity.

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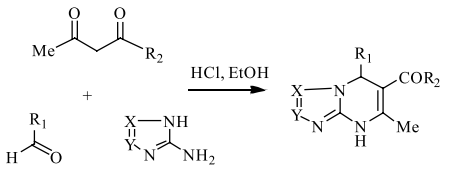
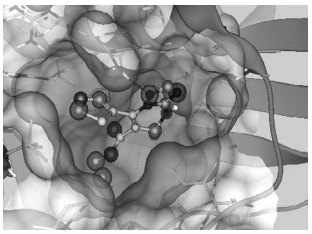
7-Aryl-substituted dihydroazolopyrimidines are of great interest as pharmacologically active compounds, as they exhibit a wide range of biological activities. We have synthesized a number of dihydroazolopyrimidines with various (het)aryl substituents (R_1), ether, amide (R_2) and azole fragments by the multicomponent Biginelli reaction. Tuberculostatic activity of synthesized compounds has been studied.



1, X = N, Y = CH, R_1 = Ph, R_2 = OEt, MIC = 1.5 μg/ml
2, X = N, Y = CH, R_1 = 2-NO_2Ph, R_2 = OEt, MIC = 1.5 μg/ml
3, X = N, Y = CH, R_1 =2,3-MeOPh, R_2 = OEt, MIC = 12.5 μg/ml
4, X = N, Y = CH, R_1 = 4-COOHPh, R_2 = OEt, MIC = 12.5 μg/ml
5, X = N, Y = CH, R_1 = 2-Thiophen, R_2 = OEt, MIC = 0.7 μg/ml
6, X = N, Y = CH, R_1 = 3-Thiophen, R_2 = OEt, MIC = 3.1 μg/ml
7, X = N, Y = CH, R_1 = 2-Thiophen, R_2 = OMe, MIC = 12.5 μg/ml
8, X = N, Y = CH, R_1 = 2-Thiophen, R_2 = O*i*Bu, MIC = 12.5 μg/ml
9, X = N, Y = CH, R_1 = 2-Thiophen, R_2 = NH_2, MIC = 12.5 μg/ml
10, X = N, Y = N, R_1 = 2-Thiophen, R_2 = OEt, MIC = 12.5 μg/ml

Leader compound **5** showed high activity towards the typical, atypical mycobacterium and the multi-drug resistant strains (MDR)[1], demonstrated high efficacy in the treatment of experimental tuberculosis (mice and guinea pigs) combined with low toxicity. The compound has no toxic effect on the liver, kidneys, pancreas and does not affect red blood. Dihydroazolopyrimidine **5** is recommended for preclinical studies.

Compound	**Minimal inhibition concentration (μg/ml)**				**LD_{50}, mg/kg**
	$H_{37}RV$	*M.Avium*	*M.Terrae*	MDR	
Racemate 5	0.7	0.7	0.7	1.5	>4000
(R)-5	0.7	0.7	0.7	0.7	
(S)-5	0.7	**0.3**	**0.3**	**0.7**	
Izoniazid	0.1	0.1	0.1	-	200



The location of compound **5** *in the pocket of DHFR*

Patent RU 2654463 (2018)

The work was financially supported by the the Russian Foundation for Basic Research (№ 16-29-10757-ofi_m) in the part of obtaining the enantiomers of the leader compound and the Russian Science Foundation (№ 15-13-00077P) in the part of synthesis and evaluation of activity of dihydroazolopyrimidines.

Targeted Molecular Docking of Antiviral Drug Riamilovir and HSP90

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HSP90 (heat shock protein 90) is one of human proteins which plays a key role in different phases of development of many viral infections, what makes HSP90 a promising antiviral drug target. Already in vitro studies showed that inhibition of HSP90 decreases replication of hepatitis C virus. [1] One of potential HSP90 inhibitors appears to be riamilovir, it belongs to the family of azolazines and theoretically it can be ligand to the purine protein site of HSP90. [2]

For determination the possibility of interaction between HSP90 and riamilovir was used targeted molecular docking with AutoDock Tools 1.5.6, crystallographic structure of HSP90α N-domain, (PDB ID: 5XRB) was taken for analysis. Before targeted docking was made control docking with known HSP90 inhibitor (PBD ID: 8DU): was found binding site, it forms the following amino acide residues - ASN51, ASP54, ALA55, ASP93, GLY135, PHE138, TYR139, VAL150, TRP162, THR184, VAL186; binding energy is -8.31 kcal/mol, were detected van der Waals interactions and H-bonds. The targeted docking with riamilovir showed binding energy is -5.06 kcal/mol, were also detected van der Waals interactions and H-bonds that form interections with the next amino acid residues: GLN23, ILE26, ILE104, LEU103, GLY108, PHE138, TYR139, TRP162, PHE170.

Both ligands are docked in the same binding pocket and form interactions with PHE138, TYR139. The presence of H-bond in best conformation of riamilovir with HSP90α N-domain suggests that this conformation is stable. The current data permits to relate riamilovir to HSP90 inhibitors.

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Functionalized polyfluoroalkylazoles as perspective structures in analgesic drugs design

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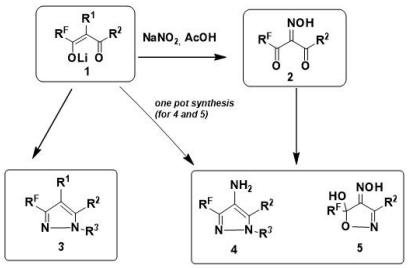
Pyrazole and isoxazole derivatives overall are of great importance for drug design and that renders development of new approaches to the synthesis of these structures [1]. Based on the available fluoroalkyl-containing synthons, lithium 1,3-diketonates **1**, we developed efficient methods for the synthesis of pyrazole derivatives **3, 4** [2] and ones of isoxazole **5** (R^F=CF_3, HCF_2, C_2F_5, $H(CF_2)_2$; R^1=H, R^2=Alk, Ar, Het; R^1+R^2= $(CH_2)_3$, $(CH_2)_4$; R^3 = H, Ph, Het). For the compounds **4** and **5**, the "step by step" and "one pot" synthesis options (both with and without the separation of oximes **2**) were implemented. Further transformations of the structures **4** and **5** at functional groups are possible for the purpose of expanding the series of analogs.



The antinociceptive effect of substituted pyrazoles is well known while isoxazoles are less explored in this regard. Some of compounds **3-5** were evaluated in the hot plate test (rats, 15 or 25 mg/kg, *ip*). For N-unsubstituted pyrazoles **3** and **4**, moderate activity was observed, which disappeared with the introduction of the pyrimidine substituent (R^3). A weak to moderate, antinociceptive effect for **5** was also detected, and in some cases, an activity was manifested on male animals only. The phenomenon of gender differences in pain and analgesia is known [3], however additional study is required for elucidation whether any fundamental reasons underlie gender differences for isoxazoles **5**. Most of the studied compounds **3-5** did not show acute toxicity at the dose of 150 mg/kg (mice, *ip*) with exception of compound **3** (R^F=$H(CF_2)_2$; R^1=R^3=H, R^2=Th), the expected LD_{50} value for which lies in the range of 30–75 mg /kg.

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Protein Kinase CK1 inhibitors as Potential Drugs

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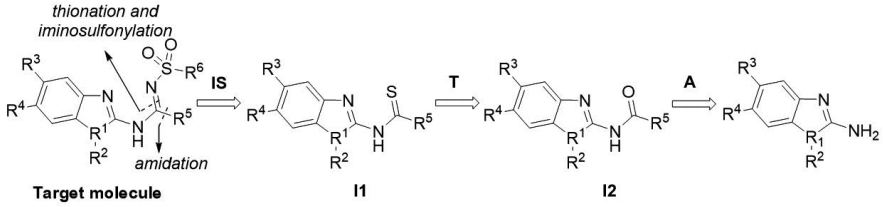
The CK1 family is an independent phylogenetic family of highly conserved, monomeric, and second messenger-independent serine\threonine-specific kinases. In humans six isoforms of CK1 (α, γ1, γ2, γ3, δ, ε) as well as several splice variants were identified.[1] Members of the CK1 family phosphorylate numerous proteins which are involved in the regulation of important cellular processes: differentiation, proliferation, DNA repair and other. Inhibition of CK1 isoforms has shown beneficial effects on the viability and proliferation of tumor cells *in vitro* and *in vivo.*

Benzimidazole nucleus is a part of numerous therapeutic agents while its derivatives exhibit various types of bioactivity including antioxidant, anticancer, analgesic, antimicrobial, antiviral, anti-inflammatory, antiparasite etc. We report a novel synthetic approach to new benzimidazole, benzothiazole and benzoxazole derivatives bearing *N*-sulfonyl acetamidine groups and preliminary data on their inhibition of casein kinases (Scheme 1).



Scheme 1

Selected compounds were initially screened for their activity against different CK1 isoforms.

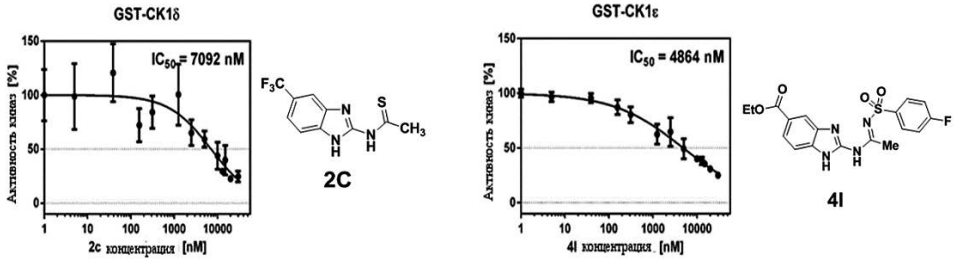


Figure 1

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Development of small molecule inhibitors of Bruton's tyrosine kinase (BTK)

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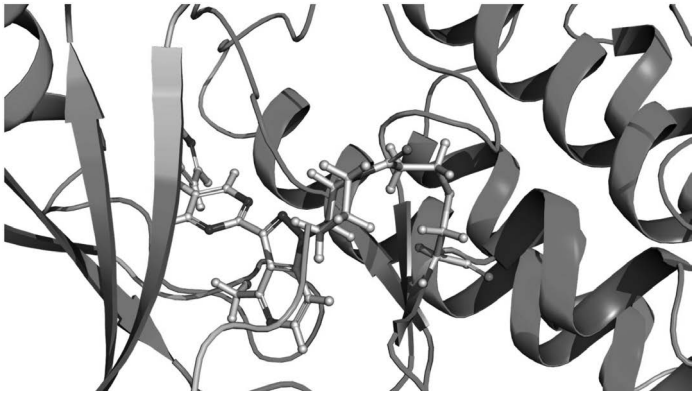
Bruton's tyrosine kinase (BTK) is a validated target in B-cell malignancies. Btk is a cytoplasmic tyrosine kinase, a member of the Tec family kinases. Btk plays a crucial role in the BCR signaling, which mediates B-cell proliferation, migration, and adhesion.

Ibrutinib, first-in-class BTK inhibitor, approved by FDA in 2013, has been in clinical use for the treatment of chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenstrom's macroglobulinemia [1, 2].

Based on structure of the target we designed and synthesized a few series of compounds, that possess nanomolar BTK affinity and bind irreversibly to BTK protein. Due to the rational design of chemical structures, it was possible to achieve better activity/toxicity profiles than Ibrutinib.

Obtained compounds show promising activity as next in class BTK inhibitors.



In silico modelling of irreversible binding to Cys481 in the kinase domain of BTK.

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Metal complexes of natural chlorins as diagnostic and therapeutic agents in oncology

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For the entire duration of this scientific work, a strategy has been developed for the synthesis of gold (I) thiolate complexes based on natural chlorins. The basis of this strategy is the synthesis of complexes based on sulfur-containing biologically active compounds (cysteine and amiethanethiol) and triphenylphosphineaurate chloride, followed by amidation of the leader PS - dipropoxyBPI. This path was chosen due to the fact that the direct synthesis of gold (I) complexes with thiol-containing bacteriopurupurinimide derivatives causes oxidation and disulfides are formed. Using this approach, a series of gold (I) thiolate complexes was synthesized, the most interesting of which was a compound containing two cysteine-TPPA residues. In vitro tests of the obtained complexes were carried out on cells with increased resistance to oxidative stress Hep2, HCT116 and HCT116p53KO. In all the complexes, both dark and photoinduced biological activity and increased efficiency were found in comparison with dipropoxyBPI and disulfide PS. Analysis of the obtained data allowed us to identify the leader compound for further in vivo testing. This compound was a PS modified by two gold (I) cysteine complexes. Its effectiveness was 2.5-3 times higher than that of the original PS - dipropoxy - BPI. In vivo tests were performed on mice with S37 sarcoma. During tests of this complex, both dark and photoinduced activities were detected.

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Transformation of the triterpenic ring A in synthesis of biologically active agents

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The development of multidrug resistance (MDR) of tumor cells, as well as of the drug-resistant strains of microorganisms and viruses against the high toxicity background of the majority of modern chemotherapeutical drugs necessitate the creation of medicines that would overcome various mechanisms of resistance. The plant-derived polycyclic triterpenoids are popular as synthetic platforms for the development of biologically active agents. In our exploratory studies, we used the lupane (betulone, betulonic and betulinic acids) and oleanane (allobetulin, allobetulone) derivatives of the pentacyclic triterpenoid betulin as the main component of birch bark.

To obtain original structures, apart from the directed transformation of functional groups of triterpenoids which is traditional for the chemistry of natural compounds, the methods for modifying the triterpenic skeleton by the selective fragmentation and subsequent intramolecular regioselective cyclization proceeding with contraction or expansion of the ring A and leading to the formation of new pharmacophoric fragments in triterpenic ring A have been developed. As a result of the conducted research, original 1,3-, 1,10-, 2,3-, and 3,4-secotriterpenoids with new functional groups at C3, C20, C28, C29, and/or C30 position, as well as C1, C2, C3, C4, and/or C5 functionalized 1,3-, 1,31-, 2,31-, and 2,24-cyclic triterpenoids with fragments of nitrile-diene, nitrile-hydroxyketone, nitrile-hydroxymine, nitrile-ketone, nitrile-enone and enamino-nitrile in the five-, six- or seven-membered ring A have been synthesized.

The antiviral properties of a number of the compounds were confirmed *in vitro* against HIV-1, herpes simplex virus of 1 and 2 types (including the acyclovir-resistant strain of the herpes virus) and tested under conditions of experimental skin herpes of laboratory animals. The ester and amide derivatives of 2,3-secotriterpenoids with virucidal properties that effectively suppress HIV-1 by direct contact with the virus particles and are promising for the development of anti-HIV microbicides are of practical interest. The triterpenoids that are highly cytotoxic against various tumor cell lines and their MDR-variants, the mechanism of action of which is governed by induction of apoptosis of the cancer cells with activation of caspases 8, 3/7 and inhibition of the functions of the transport protein P-gp responsible for development of MDR have been selected.

The work was sponsored by a Complex Program of the Ural Branch of the RAS (№ 18-7-3-4).

Synthesis of novel *nido*-carboranyl amino acid analogues, potential BNCT agents

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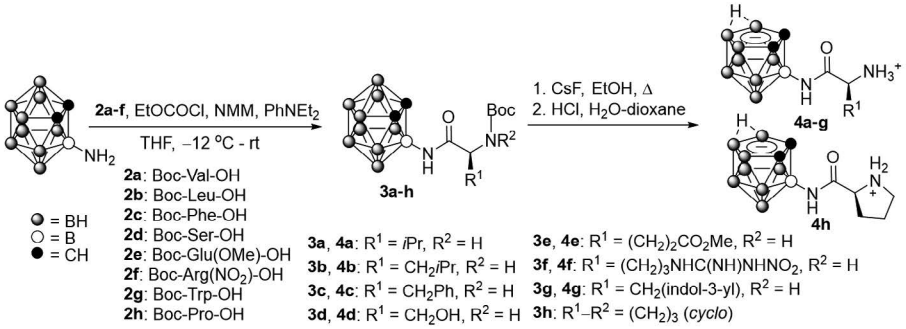
Boron neutron capture therapy (BNCT) is an efficient method for treatment of tumors. It is based on the combined use of preparations containing boron-10 nuclei and thermal neutron irradiation [1, 2]. Boron-containing amino acid derivatives are attractive agents for targeted boron delivery into tumor [3].

We synthesized a series of novel analogues of natural amino acids containing a 7,8-dicarba-*nido*-undecaborane (*nido*-carborane) fragment. Acylation of 3-amino-*closo*-carborane (**1**) with *N*-Boc-(*S*)-amino acids readily afforded amides **3a-h**. Deboronation under the action of CsF followed by *N*-deprotection resulted in the formation of *nido*-carboranyl derivatives **4a-h** as zwitter-ions.



nido-Carboranyl-amino acids **4** (in the form of salts) are highly soluble in aqueous media that makes them the promising BNCT agents suitable for biological tests.

The work was financially supported by the Ministry of Science and Higher Education of the Russian Federation (project no. AAAA-A19-119012490007-8).

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Photocatalitic activity of chlorine complexes with polyvinipyrrolidon and polysaccharides as agents for antibacterial photodynamic therapy

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Bacterial infections have been a constant threat to human health throughout the history of mankind. Progressing growth of the microorganisms' resistance to antibacterial drugs, primarily to antibiotics, which is observed in the last years, has acquired a more serious character and leads to difficulties in the use of a whole series of such drugs for the treatment of infections caused by antibiotic-resistant microbial strains. Antibacterial photodynamic therapy (APDT), based on the oxidative destruction of pathogenic microorganisms with laser irradiation of affected tissues, preliminarily treated with a photosensitizer (PS), may become a full alternative to antibiotic therapy. The main advantage of photosensitized cell destruction is the possibility of influencing strains of bacteria and fungi that are resistant to antibiotics. It was shown previously that the use of the porphyrin with amphiphilic polymers (AP) increases the efficiency of PDT of neoplasms and purulent wound of laboratory rats and patients complicated burns [1].

In this work for increasing the efficiency of antimicrobial PDT with new types of porphyrin photosensitizers complexed with amphiphilic polymer – polyvinylpyrrolidone (PVP) and polysaccharides (PS) which had their own bactericidal activity, were created. Trisodium salt of chlorin e6 (Chl e6) and photoditazine (dimethylglucamine salt of chlorin e6, PD) were used as porphyrin photosensitizers, polysaccharides (sodium alginate and hyaluronic acid) as possible antibacterial agents.

The presence of polysaccharides appears to increase the effective rate constant (k_{eff}) of tryptophan photoxidation (test reaction for evaluation of the photosensitizers efficiency), compared to the rate (k_{eff}) of free porphyrins. Moreover, the addition of the PVP to the system porphyrin-polysaccharide leads to a further increasing of the effective rate constant k_{eff}. Such increase of effective rate constant is believed to be linked with the formation of double (porphyrin-PVP) and triple (porphyrin-polysaccharide-PVP) complexes with the photosensitizer being in disaggregated state. To confirm the obtained data about formation of complexes PD-PVP and PD-polysaccharide-PVP, the light scattering and luminescence spectra were obtained. The results showed that there are shifts in the spectra of PD to a longer wavelength region with addition of PVP and polysaccharides.

Thus, it can be assumed that PVP and polysaccharides, which don`t have their own photochemical activity, are able to increase the photocatalytic activity of PD in the singlet oxygen generation and also to lead to partial destruction of possible porphyrin associates. The interpenetration character of a polymer components in the forming complex systems was established by atomic-force microscopy (AFM) of the site of surface pellicle forming by evaporation of double (PD-PVP and PD-PS) and triple systems (PD-PVP-PS).

The methods of dynamic light scattering, X-ray diffraction and resonant scattering, we will measure the size of the formed compositions and the degree of PS aggregation (which mainly determine the activity of the studied systems in the $^1O_2$ photogeneration) for the most active quaternary polymer compositions.

Thus, it becomes possible to use such triple complexes for antibacterial photodynamic therapy as an effective method for treating of infectious and inflammatory diseases of the skin and soft tissues.

Acknowledgments

This work was supported by the Russian Foundation for Basic Research (RFBR) (project No. 17-02-00294).

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Highlights on Specific Biological Targets; Cyclin-Dependent Kinases, Epidermal Growth Factor Receptors, Ras Protein, and Cancer Stem Cells in Anticancer Drug Development.

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Cancer is the second leading cause of death in worldwide, because of that we need a great effort to discover, determine and understand the main pathways and mechanism of action of new novel anticancer drugs, which highly selective on the cancerous cells over the normal cells. The traditional approaches to the treat cancer depend on surgery, radiotherapy, and chemotherapy, according to the medicinal reports the chemotherapy is still the main procedure in the cancer cure or treatment till nowadays, and it is one of the main factors that drops the mortality of cancer in the last years. In the past decades the chemotherapeutic agents were used in the cancer treatment without clear understand on which target, protein, or enzyme that is working, and it was making the inhibition on the whole family of enzymes or receptors which lead to high toxicity and side effects, but nowadays the anticancer agents work with high selectivity on specific subtype of clear targets, and these targets usually present in high percentage in the cancerous cells. We will summarize some of these specific targets for anticancer drugs like Cyclin-dependent kinases (CDKs), epidermal growth factor receptors (EGFR), Ras protein, and Cancer stem cells, finally, we will mention some anticancer drugs which approved by FDA in 2018 which work on specific targets.

Intraocular pressure-lowering effects of imidazo[1,2-a]- and pyrimido[1,2-a]benzimidazole compounds in ocular-normotensive and ocular hypertensive rats

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Ocular hypertension is believed to be involved in the etiology of primary open-angle glaucoma. Although many pharmaceutical agents have been shown to be effective for the reduction of intraocular pressure (IOP), a significant opportunity to improve glaucoma treatments remains. In an effort to find new ocular hypotensive drug candidates, a total of 27 condensed benzimidazoles based compounds were screened. The first part of study (**Study I**) was done in normotensive rats and rebound tonometry was used to estimate IOP. All compounds were topically applied as a single drop, unilaterally, at 3 different concentrations (0.1%, 0.2% and 0.4%). The contralateral eye was instilled with vehicle and served as control. The IOP reduction was measured up to 6 h. It was observed that with a single topical instillation, compounds RU 551, RU 555, RU839 (pyrimido[1,2-a] benzimidazole derivatives), and RU 615 (imidazo[1,2-a]benzimidazole derivative) showed significant IOP lowering activities in ocular normotensive rats. All other compounds showed none, weak and inconsistent IOP lowering effect. The relationship between ability of IOP lowering and hypotensive activities was studied. According to the pharmacophore analysis, the class of pyrimido[1,2-a]benzimidazole is more promising than the class of imidazo[1,2-a] benzimidazole as a source of compounds with high IOP lowering activity. Pharmacophore analysis also showed that the critical features of high IOP lowering activity are methoxyphenyl and [phenyl]alkyl fragments, and non-conjugated six-membered heterocyclic ring. The next part of study (**Study II**) was aimed: (1) to evaluate the IOP-lowering effect of four compounds RU-551, RU-555, RU-839 (pyrimido[1,2-a]benzimidazole), and RU-615 (imidazo[1,2-a] benzimidazole) on steroid-induced ocular hypertension in rats after single drop and chronic applications; and (2) to test *in silico* and *in vitro* conventional rho-associated kinase (ROCK) inhibitory activity of the selected compound. This study demonstrated that RU-551, RU-555, RU-839, and RU-615 significantly reduced IOP in Sprague Dawley rats with dexamethasone (DEXA) induced ocular hypertension after single drop administration (0.1%), however RU-615 showed the best IOP lowering effect as indicated by maximum IOP reduction of 22.32%. Repeated dose topical application of RU615 caused sustained reduction of IOP from baseline

throughout the 3 weeks of treatment with maximum IOP reduction of 30.31% on day 15. This study also showed that the steroid-induced increase in IOP is associated with increased retinal oxidative stress and significant retinal ganglion cells (RGCs) loss. Prolonged treatment with RU615 over 3 weeks results in normalization of IOP in DEXA-treated rats with partial restoration of retinal antioxidant status (catalase, glutathione and superoxide dismutase) and subsequent protective effect against RGC loss. Thus, IOP lowering activity of RU615 together with antioxidant properties might be the factors that contribute to prevention of further RGC loss. *In vitro* part of this study explored the ROCK inhibitory activity of RU-615 using dexamethasone-treated human trabecular meshwork cells as a possible mechanism of action of its IOP lowering activity. However, this study didn't show conventional ROCK inhibition by RU-615 which was later confirmed by *in silico* consensus prediction. Therefore, in the future studies it is important to identify the upstream target receptors for RU-615 and then delineate the involved intracellular signaling pathways which are likely to be other than ROCK inhibition.

Funding statement: We gratefully acknowledge financial support from by the MOH (Malaysia) under the project 600-RMI/RAGS 5/3 (46/2014).

Synthesis of Abietane-type Thiols and Monosaccharide Derivatives Based Thereon

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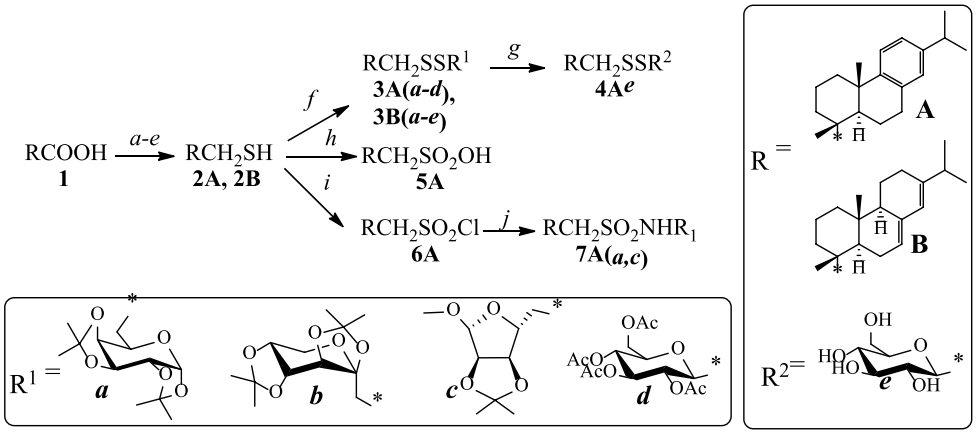
Diterpene resin acids are important defense compounds of conifers against potential herbivores and pathogens. Having a broad spectrum of biological activity, they find application in pharmaceutical industry for searching on their basis for new medicals. Abietic (AA) and dehydroabietic (DHA) acids are the main components of pine rosin, their derivatives exhibit antimicrobial, antiviral, antiulcer activities, inhibit the growth of malignant cells of intestine and lungs. The introduction of sulfur atom into a molecule is known to increase biological activity or change it to other one. But currently there is hardly any information about preparation and application of sulfur-containing abietane-type compounds as well as their properties.



a. EtBr, K_2CO_3, DMF; *b.* $LiAlH_4$, Et_2O; *c.* I_2, PPh_3, PhMe; *d.* AcSK, DMF; *e.* $LiAlH_4$, Et_2O; *f.* I_2, EtOH; *g.* MeONa, MeOH; *h.* ClO_2, Py; *i.* ClO_2, $VO(acac)_2$, CH_2Cl_2; *j.* Amine, $CHCl_3$, reflux

In this work, proceeding from AA and DHA, for the first time, we synthesized diterpene thiols **2**, and disulfides **3**, containing in addition to a terpene fragment a monosaccharide one (acetone, or acetyl protected galactose, fructose, ribose, glucose). Based on DHA, we also obtained sulfonic acid **5A**, sulfochloride **6A**, and sulfonamides **7A** with acetone protected ribofuranose and galactopyranose residues.

This study was performed under financial support of the Russian Foundation for Basic Research (project no. 18-33-00486 мол_а).

Modified Aptamers – EGFR Blockers for Cancer Theranostics

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When creating targeted drugs, oligomers are optimal comparing to low molecular weight compounds and macromolecules. Therapeutic nucleic acids include aptamers, oligonucleotides with a complex tertiary structure, which provides binding targets specifically and with high affinity; they are called “chemical antibodies”. The work is devoted to the development of epidermal growth factor receptor (EGFR) aptamers, blockers of the signal transduction, which supports increased cell proliferation, which is often associated with the occurrence of tumors. Depending on the type of modification of the aptamer, it could be used both to visualize the tumor and to suppress cell proliferation. In this sense, aptamers are effective and promising agents for theranostics.

A selection of a combinatorial library of oligonucleotide DNAs, containing modified nucleotide units able for click chemistry, yielded families of modified aptamers to the extracellular domain of human recombinant EGFR. Individual aptamers were synthesized and characterized for affinity to the receptor by surface plasmon resonance, as well as for interactions with cell lines, having a different number of EGFR receptors, using flow cytometry.

In addition, an analysis of the aptamers, described in the literature, was carried ou,t and their original derivatives were made, which were also characterized, as indicated earlier. The inhibitory effect of aptamers on the signal transduction system by phosphokinases was evaluated, and compared with antibodies for clinical immunotherapy.

Fluorescent aptamers were synthesized, their interaction with cells of various nature, including cancer cells, was studied using flow cytometry. A comparison of aptamers and antibodies, used in clinical immunotherapy, was made. With financial support from the Ministry of Education and Science of the Russian Federation (RFMEFI57617X0095).

Nephroprotective action of the novel inhibitor of collagen glycation end-products synthesis in experimental diabetes mellitus

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The prevention and treatment of complications of DM is one of the most important problems in modern medicine. One of the pathogenetic factors in the development of late complications of DM is considered to be the non-enzymatic interaction between free amino groups of proteins and carbonyl groups of reduced sugars, leading to the formation of the glycation end-products (AGEs).

The aim of the work was to study the effect of sodium salt of 4-oxo-1,4-dihydropyrazolo [5,1-c] -1,2,4-triazine-3,8-dicarboxylic acid monohydrate diethyl ester under the code AV-19 on the development of DM nephropatic complications.

Experimental diabetes mellitus (EDM) was modeled by a single i.v. administration of streptozotocin (Sigma, United States) in 60 adult male Sprague-Dawley rats. The fasting blood glucose level was determined by glucose meter "Glucocard Sigma-Mini" (Russia). Animals with fasting glucose levels not less than 15 mmol/l were taken into the experiment. One week after the injection of streptozotocin, the animals were divided into groups of 15 rats. Control groups: intact animals and rats with EDM were administered with distilled water (1 ml/100 g); the experimental groups: the test substance AV-19 (20.0 mg/kg) and the etalon drug aminoguanidine (50.0 mg/kg) were administered through an intragastric tube once daily within 12 weeks. The level of glycated hemoglobin was determined using the DIABET-TEST kit (Phosphosorb, Russia). The content of glycation end products (AGEs) in blood serum was determined immunochemically using the Rat AGEs ELISA kit (Cusabio, China) at Infinite 200 PRO multifunctional microplate reader (Tecan, Austria).

To determine the function of the kidneys every 4 weeks in rats the daily excretion of albumin and creatinine were examined. Urine protein concentrations were determined using the Vital Diagnostics kit, (Russia). Determination of serum creatinine and urine concentrations was performed using the Total Protein-002 kit (Olvex-Diagnosticum, Russia) and creatinine clearance [1] was calculated. The level of AGEs in kidneys was determined by the method [2] measuring AGEs fluorescence intensity at excitation / emission wavelengths of 370/440 nm using an Infinite 200 PRO microplate reader (Tecan, Austria). For immunohistochemical studies monoclonal antibodies to carboxymethyl lysine were used (Abcam, CMS-10).

Statistical analysis was carried out using a paired Student's t-test and the non-parametric Mann-Whitney U-test) with Bonferroni correction in Statistica 6.0 (StatSoft, USA), GraphPadPrism 5.0 and Microsoft Excel (Microsoft, USA).

It was shown that the blood glucose level in rats of all experimental groups with DM remained significantly high throughout the experiment, exceeding the values of the intact group of animals on average 4.9 times - the 1st month, 5.8 times - 2 month, 5.26 times -

the 3rd month ($p < 0.05$). The results were confirmed by a statistically significant increase in the level of HbA1c in all experimental groups of rats with streptozotocin diabetes with a duration of 3 months relative to intact animals by an average of 2.8 times ($p < 0.05$). The level of AGEs significantly increased in the serum of rats with EDM in relation to the intact group by 45.9%. AV-19 resulted in a significant decrease in the HbA1c content by 51.5% ($p<0.05$), the etalon drug aminoguanidine reduced HbA1c by 37.9% ($p < 0.05$) in relation to the EDM group. Studied AV-19 reduced the AGEs concentration in relation to the indicator of animals with EDM by 21.9% ($p < 0.05$), and the reference drug aminoguanidine reduced AGEs by 24.3% relative to rats with EDM.

The control animals with EDM throughout the experiment demonstrated a significant increase in the level of protein in the urine compared with the values of the intact group of rats (2.6 times - the 1st month, 3.2 times - the 2nd month, 3.3 times - the 3rd month). AV-19 and aminoguanidine led to a gradual decrease in proteinuria and statistically significantly reduced it after 3 months by 52% and 48%, respectively. It is established that during EDM, creatinine clearance increases significantly with respect to intact control. AV-19 led to a significant decrease in this indicator in relation to the group of DM control, similar to aminoguanidine, and the index returned to normal after 3 months of administration of AV-19, whereas aminoguanidine did not lead to a complete normalization of clearance. Animals with experimental diabetes mellitus showed an increase in the AGEs level in kidney tissue by 32.6% relative to those of the intact control group ($p<0.05$). Substances AV-19 and aminoguanidine lead to a significant decrease in the content of glycation end products in the kidneys of experimental animals by 21% and 19%, respectively.

Animals with 3 months diabetes developed microvascular disorders in the renal glomeruli, as evidenced by histological and histochemical impairments, in particular, a significant increase in the absolute and relative area of AGEs-positive material and connective tissue compared to the intact control. AV-19, when administered for 3 months at a dose of 20 mg / kg, significantly reduced the amount of AGEs-positive material, as well as connective tissue, exceeding aminoguanidine in its effect on the level of AGEs.

Thus, on the basis of compound AV-19, acting on the glycation end-products of collagen, a new drug can be developed for the prevention and treatment of complications of DM.

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Coping with “rules of thumb” based biases: practical approaches

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The “rules of thumb” guiding the selection of the promising molecules with low potential for bioavailability problems are limiting the diversity of compounds applied to screening [1, 2]. Although the rules continue to occupy an important place in choosing compounds for screening libraries, their influence has weakened substantially since 2000s which underlines the difficulties in creating unified filters for such multi-parameter systems. The declining trend was in part due to concern that potentially perspective compounds may be eliminated from screening programs, while growing number of successful compounds appeared to be beyond the “rules of thumb” [3].

Monitoring and balancing combination of the studied molecules properties is a key for successful outcome. However, among all the diverse *in vitro* assays available for the properties evaluation in early preclinical study, an average medicinal chemistry laboratory may only afford a limited number of techniques. Thus, the need for identifying minimal practical testing systems sets which generate the data guiding further steps in compounds selection and / or structure optimization is apparent. It is especially important to assess substances gastrointestinal absorption and their metabolic stability *in vivo*. Therefore, the set may include methods which require low quantity of compounds and enable acceptable throughput – such as PAMPA for permeability assessment and metabolic stability in plasma and sub-fraction of liver homogenate S9 accompanied by chromatography [4, 5].

Several sets of oxo-derivatives of heterocyclic compounds with different characteristics (i.e. molecular weight, lipophilicity, solubility, number of H-bond donors and acceptors, etc.) were evaluated based on rules as well as in set of tests *in vitro* and *in vivo* [6, 7]. It may be concluded that unbiased and consistent compounds investigation conducted despite the “rules of thumb” filters may lead to unexpected and encouraging results. Additionally, an important role of formulation in animal experiments is underlined.

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Main directions in the search for antithrombogenic agents

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Inhibition of platelet aggregation is a major strategy for prevention of thrombotic states. Molecular mechanisms that trigger activation of platelet hemostasis are associated with receptors exposed on the plasma membrane of platelets, which participate in cell-cell interactions and interactions of cells with the subendothelial matrix. These, in turn, lead to post-receptor activation of the prostacyclin-thromboxane system via intracellular calcium influx, the formation of phospholipid-derived second messengers, activation of downstream protein kinases and phosphodiesterases, modification of the functional activity of endothelium. Therefore, the use of current antiplatelet therapies significantly reduces the risk of thrombotic complications. The present antiplatelet agents are able to inhibit platelet function through various mechanisms of action with a high level of clinical efficacy evidence. The most notable classes are inhibitors of cyclooxygenase (COX) - acetylsalicylic acid, $P2Y_{12}$ purine receptor blockers - thienopyridines, e.g. ticlopidine, clopidogrel, prasugrel, and non-thienopyridines derivatives - ticagrelor and kangrelor, and glycoprotein (GP) IIb/IIIa receptor blockers for intravenous administration - abtsiksimab, eptifibatide, tirofiban. However, the effectiveness of these drugs remains hampered due to the fact that one or another mechanism of adhesion, activation, and/or aggregation of platelets remains unblocked, leading to the different effects on the thrombogenic potential of blood. Therefore, search, study, and development of novel agents that block several ways of platelet hemostasis activation is an urgent problem in the prevention of thrombotic states.

Design and synthesis of potential anti-thrombogenic agents could be facilitated with computer-aided solutions such as PASS system and information technology (IT) “Microcosm” to determine the similarity of main scaffolds that determine the antiplatelet effect of drugs. The present report will provide an overview of a target-oriented search for compounds that affect platelet COX_1, $P2Y_1$, $P2Y_{12}$, PAR1, and thromboxane receptors, as well as types of activity indirectly indicating the presence of antiplatelet action, namely, antioxidant and anti-serotonin.

As a result of a target-oriented search for inhibitors of glycoprotein IIb/IIIa platelet receptors using flow cytometry, the highly active compound F-168 (3-methyl-8-(piperazin-1-yl)-7- (tietan-3-yl)-1-ethyl-1H-purin-2,6(3*H*,7*H*)-dione hydrochloride), synthesized in Bashkir State Medical University (Ufa, Russia). This compound exceeds antithrombotic activity of IIb/IIIa glycoprotein receptors inhibitors eptifibatide and tirofiban on models of arterial thrombosis induced by ferric chloride, electric current, adrenaline-collagen mixture,

on the Global Thrombosis Test (Gogor) model, and also on the venous thrombosis model. Currently, a full preclinical study of its infusion dosage form Angipur for the treatment of acute coronary syndrome has been completed and the drug developed is approved for entering phase I clinical trials. Preclinical study of the benzimidazole derivative RU-891 (9-(3,4-dihydroxyfenacyl)-2,3-dihydroimidazo[1,2-*a*]benzimidazole hydrobromide) synthesized in Southern Federal University (Rostov-on-Don, Russia) is currently underway. RU-891 simultaneously blocks two targets of platelet activation - $P2Y_{12}$ receptors and thromboxane A_2 synthesis and its ameliorating effect on blood thrombogenic potential exceeds acetylsalicylic acid and clopidogrel. Other active compounds identified include the ones that affect PAR1 platelet receptors, which human-specific, platelet phosphodiesterase, Na+/H+ exchanger of the first isoform (NHE-1), and protein-tyrosine phosphatase (PTP1B).

Thus, for synthesis and development of anti-thrombogenic drugs, it is essential to use a comprehensive approach that includes *in silico* methods and *in vitro* target confirmation, as well as *in vivo* evaluation on relevant thrombosis models, since the study of novel anti-thrombogenic agents may reveal valuable pleiotropic effects.

Development of biodegradable prosthesis for tear duct reconstruction

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Lacrimal passage reconstruction with tubular implant is one of the most effective solution for surgical treatment of dacryocystitis - lacrimal ducts obstruction. Currently used non-degradable artificial tear ducts have a number of disadvantages such as unstable fixation, surrounding tissue granulomatous growth and absence of surrounding tissue epithelialization. All patients require lifelong implant wearing and medical follow-up.

This study was aimed to develop a slowly degradable implant stimulating formation of a connective tissue tunnel around itself, which will be a bio-frame after the implant is decomposed or removed. Thus, a new lacrimal duct will be formed from the patient's own tissues.

Macromonomers based on polytrimethylene carbonate and poly (trimethylene carbonate-co-L-lactide) of linear and branched structure were synthesized and their homopolymerization and copolymerization with N-vinylpyrrolidone and vinyl acetate were studied. The rate of in vitro hydrolytic degradation in phosphate buffer solution (PBS), the swelling kinetic in water, PBS and acetone, tissue reaction and general in-vivo toxicity in guinea pigs with histological tissues examination after 14, 28 and 60 days of the obtained cross-linked polymers were investigated.

Obtained polytrimethylene carbonate copolymers with N-vinylpyrrolidone were used to make degradable tear duct implants, which were used for lacopronostomy operation in rabbits in comparison to commercial silicone implants from FCI. Histological studies in 2 and 3 months after implantation has shown that, unlike silicone implants, developed implants stimulate adjacent tissue vascularization with formation of new collagen fibers, what indicates formation of new lacrimal canal which will be able to function without implant.

Synthesis and Biological Activity of New Purine Conjugates with Amino Acids, Dipeptides and Chiral Heterocyclic Amines

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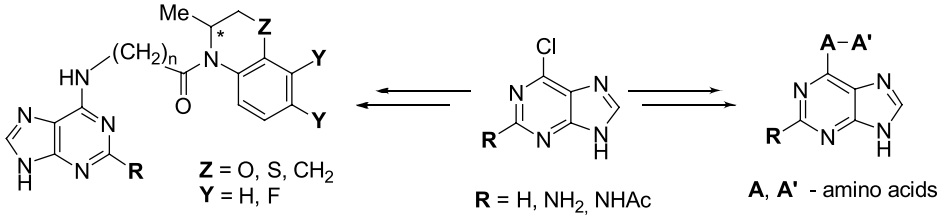
Purine and its derivatives play a unique role in the metabolism of living organisms, so the synthesis and study of purine conjugates is of great interest for designing efficient medicinal agents based thereof. The purpose of this work was the synthesis of novel purin-6-yl derivatives of amino acids, dipeptides, and heterocyclic amines and the study of their tuberculostatic and antiviral activity, including that against multidrug-resistant strains.

The starting compounds for the preparation of these substances were 6-chloropurine derivatives, from which the target products were obtained *via* the nucleophilic substitution of the chlorine atom with an amino acid followed by the introduction of the second amino acid or heterocyclic amine. To obtain purine conjugates with amino acids, we used the strategy of sequential protection–deprotection. The methods for determination of optical purity of the target compounds have been developed.



The study of the biological activity of the compounds obtained in experiments *in vitro* has demonstrated that among them there are substances with high antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv, *M. avium*, *M. terrae* and multidrug-resistant strains [1]; the most promising compound is currently undergoing preclinical study. The study of the antiviral activity of novel purine conjugates against herpes virus type 1 allowed identifying highly active compounds, including those against acyclovir-resistant strain.

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2-Oxindole as privileged structure for antiglaucomic and antidiabetic drug design: synthesis and biological activity

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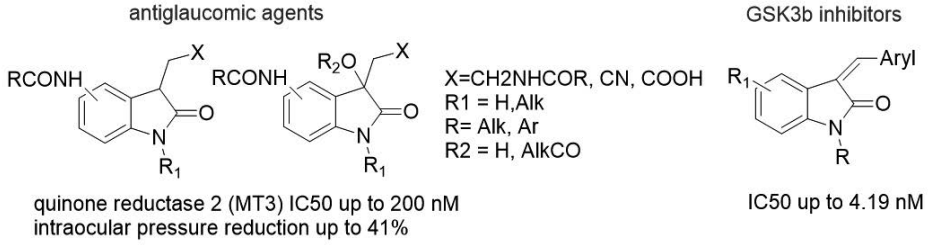
New amide-substituted oxindoles were synthesized using catalytic hydrogenation of corresponding nitro-derivatives and their biological activity was investigated [1]. The synthesis of new ligands of quinone reductase 2 (QR2, proposal MT3 receptor) [1-4] and kinase-3β glycogen synthase (GSK3β) [5] based on 2-oxindole scaffold was performed using condensation of isatin and 2-indolinone derivatives with appropriate compounds. The ability of oxindole-based QR2 ligands to reduce the intraocular pressure (IOP) was studied in vivo in normotensive rabbits. The lead compound was found to reduce IOP at 41% (more, then reference drug timolol (32%)) and had the long-lasting hypotensive effect (>6h). It was shown that 3-arylidene-substituted 2-oxindoles were effective inhibitors of kinase-3β glycogen synthase and exhibit pronounced anti-diabetic activity under conditions of the glucose-tolerant test in vivo [5]. The lead compound showed moderate cytotoxicity in the micromolar range which creates a sufficient therapeutic window for the design of potential antidiabetic drugs based on this compound.



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Cognitive enhancement by novel specific dopamine reuptake inhibitor

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Age related dementia and cognitive impairments are severe problems in industrial societies with high life expectancy. Cognitive functions can be influenced and improved by a series of chemical compounds which target the dopamine transporter (DAT). The dopamine transporter reuptakes extracellular dopamine into the synapse. Inhibitors of DAT increase the extracellular concentration of dopamine, which then can lead to an improvement of learning and memory. Commonly used inhibitors however exert un-sufficient specificity for DAT and also inhibit noradrenaline and serotonin transporters, which causes unwanted side effects, like increased states of arousal and depressive attacks. Therefore, we tested a newly synthesized compound with higher specificity for DAT in two spatial learning and memory tasks, a food reward related hole-board task and in the water-maze. Dosages at 1, 5, and 10 mg/kg body weight do not affect behavioral performance in young male rats. The highest dosage, however improved task acquisition as well as long-term memory in aged rats in the reward but not the water maze task.

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Chiral voltammetric sensor platforms based on supramolecular frameworks for recognition and detection of enantiopure drug compounds

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The appearance on the market of enantiopure drugs required the development of appropriate methods for determining individual enantiomers both in mixtures of optically active isomers and in objects of arbitrary composition against the background of optically inactive compounds. There are methods of chiral chromatography, mass spectrometry, capillary electrophoresis, electrochemical (voltammetric) sensors [1, 2] which are mainly used for these purposes. The most of the developments exploited so far were based on using inclusion complexes, molecularly imprinted polymers, nanomaterial's, elements of living systems and their analogues, as well as other chiral platforms based on organic and inorganic structures.

In the report were observed theoretical and experimental approaches on the development, research and application of enantioselective voltammetric sensors based on glassy carbon and carbon-paste electrodes modified by chiral supramolecular assemblies and metal-organic frameworks (MOF) and their composites [3, 4] to recognize and control enantiomer excess of pharmaceuticals (propranolol, atenolol, warfarin, baclofen, etc.). The studies on the interactions selectivity of enantiomers with supramolecules of uracil, melamine, cyanuric acid and polycarboxylate chiral MOF have been conducted using the methods of quantum chemistry, molecular dynamics simulations and chromatography. The ranges of structural selectivity of chiral platforms were established depending on the modifier nature of the detectable compounds and solvent.

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Multifunctional inhibitors of cholinesterases as innovative drugs for Alzheimer's disease (AD) treatment

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Neurodegenerative diseases are multifactorial; therefore, their treatment requires drugs that can act simultaneously on multiple pathogenic targets. One of the modern approaches for creating multitarget agents for AD treatment is building hybrid molecules that are conjugates of two or more different pharmacophores linked through spacers. Cholinesterase inhibitors are often used as one of the pharmacophores. We synthesized several series of hybrid compounds combining pharmacophores considered useful for neurodegenerative disease treatment: γ-carbolines, carbazoles, phenothiazines, aminoadamantanes, and tacrines. Inhibitory activity of these conjugates against acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and carboxylesterase (CaE) was studied. In addition, their ability to competitively displace propidium iodide from the peripheral anionic site (PAS) of AChE was determined to assess their potential effect on AChE-induced aggregation of β-amyloid. Antioxidant properties were examined computationally with the DFT method and experimentally using ABTS and ORAC-FL assays. Binding modes of conjugates to AChE and BChE were studied using QM-assisted molecular docking. Results revealed conjugates that were selective inhibitors of BChE (γ-carbolines/phenothiazines, carbazoles/aminoadamantanes) or that combined high potency and selectivity toward BChE with high radical-scavenging activity, e.g., γ-carbolines/carbazoles. Conjugates of γ-carbolines with Methylene Blue and bis-γ-carbolines demonstrated high potency against AChE and BChE combined with effective displacement of propidium from the PAS of AChE. Additionally, the conjugates were extremely active in both antioxidant tests. Potent inhibitors of cholinesterases with antiaggregant and radical-scavenging activity were found among tacrine conjugates with sulfamides and thiadiazoles, and the spectrum of their activity significantly depended on the spacer structure. All conjugates were poor CaE inhibitors, and were therefore expected to lack drug-drug interactions by this pathway. Good agreement was found between experimental and computational results. Promising compounds were identified to develop innovative multi-target drugs for AD treatment that combined cognition enhancement with neuroprotective and disease-modifying potential.

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Multicomponent reactions in the synthesis of furanoditerpenoid and steroid pyrazoles

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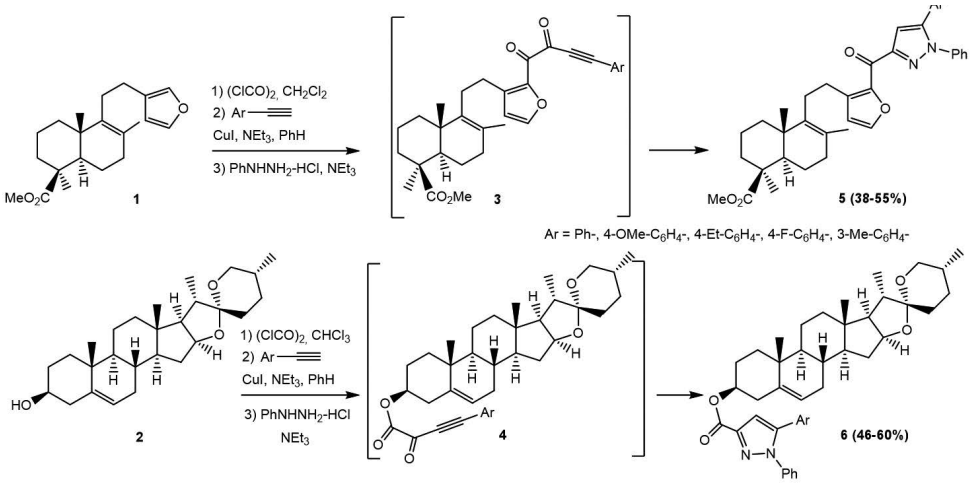
Early performed synthetical transformations of plant derived phlomisoic acid **1** and diosgenin **2** with introduction of additional heterocycle moiety on the furan ring or on the hydroxylic group have led to a number of valuable pharmacological agents [1, 2]. In the present work is described modification of phlomisoic acid **1** and diosgenin **2** with introduction of additional pyrazole moiety by the help of multicomponent reactions which includes oxalyl chloride acylation, Stephens-Castro cross-coupling and heterocyclization of intermediate alkyne-1,2-diones **3**, **4** with phenylhydrazine. The reaction goes regioselectively and leds to the formation of labdanoid and spirostanic 1,5-diaryl-1*H*-pyrazoles **5**, **6**.



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Development of fast anxiolytic based on TSPO ligand

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Creating a safe fast anxiolytic is an actual problem of modern pharmacology and medicinal chemistry. Translocator protein 18 kDa (TSPO) is a new target for creating effective anxiolytics free from side effects of benzodiazepines. This receptor is responsible for the activation of the biosynthesis of neurosteroids - positive allosteric modulators of the $GABA_A$ receptor, which play a crucial role in the pathophysiology of anxiety disorders.

In Zakusov Research Institute of Pharmacology was designed and synthesized new TSPO ligand GML-1 (*N*-benzyl-*N*-methyl-1-phenylpyrrolo[1,2-a]pyrazine-3-carboxamide). Radioligand method showed that GML-1 has a high affinity for TSPO ($Ki = 5,2*10^{-8}$ M). *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). It was found that GML-1 does not have diazepam side effects. Moreover, GML-1 demonstrated a pronounced positive nootropic effect. 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 neurosteroidogenesis.

It is established that GML-1 is a low-toxic substance, it does not cause dependence and addiction. Pharmacokinetic studies of GML-1 showed that it quickly (from the 5th minute) and in sufficient quantity reaches the target organ – brain. The relative bioavailability of GML-1 after intragastric administration to rabbits is 101.72±

Features of Hydrolytic Decomposition of Antitumor Agents Lysomustine and Ormustine

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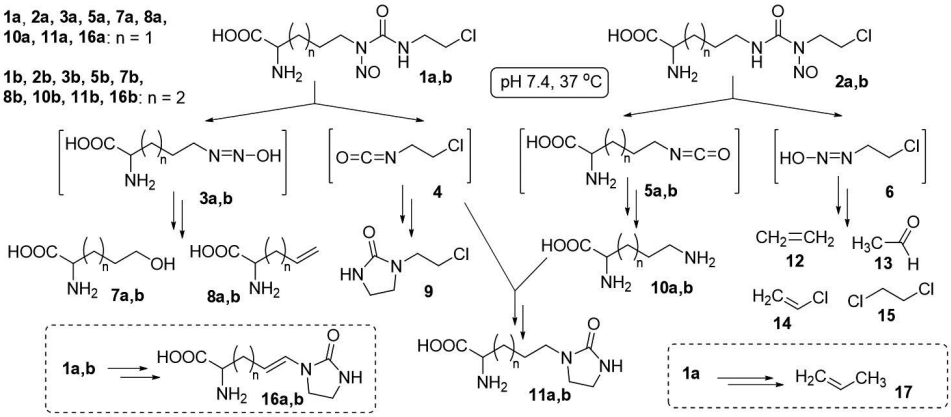
Active pharmaceutical substances of antitumor agents Ormustine and Lysomustine belonging to *N*-alkylnitrosoureas (ANUs) are mixtures of regioisomers **1a–2a** (78:22) and **1b–2b** (75:25). Pharmacological effect of ANUs is due to their ability to hydrolytic decomposition under physiological conditions with the formation of cytotoxic products; therefore, the study of this process is an important task. Non-volatile (**7-8a,b**, **9**, **10-11a,b**) and volatile (**12-15**) products formed during decomposition of mixtures **1a–2a** and **1b–2b** and individual isomers **1a** and **1b** under conditions close to physiological (pH 7.2-7.4, 37 °C were identified by high-resolution mass-spectrometry and gas-liquid chromatography. The data obtained are consistent with the scheme of ANU decomposition described in the literature, which proposed the formation of alkyldiazohydroxides **3a,b** (in case of **1a,b**), **6** (in case of **2a,b**) and alkylisocyanates **4** (in case of **1a,b**), **5a,b** (in case of **2a,b**). In the reaction mixture, compounds **16a,b** and **17** were also identified; these products are likely to be formed during intra- or intermolecular transnitrosation of isomers **1a,b**.



The work was carried out in the framework of the State Assignment (project AAA-A-A19-119011790130-3).

Anticancer Pt and Ru compounds with a targeting mode of action

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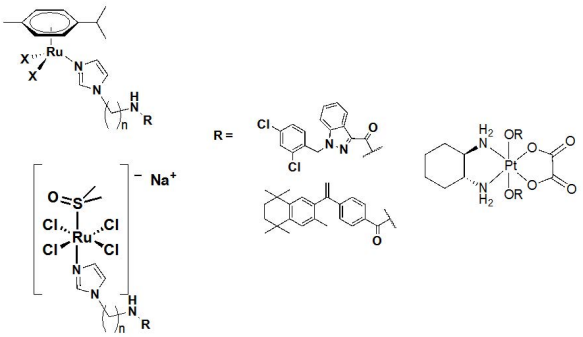
The majority of new metal-based anticancer compounds contain cytotoxic platinum moiety [1]; however, in recent years there has been a shift of interest in the development of non-classical platinum or non-platinum anticancer drugs and the Pt(IV) and ruthenium-based compounds are the most actively studied candidates.

The activity and specificity of metal-based anticancer compounds can be modulated by ligand environment. A dual drug concept is a modern approach in the anticancer drug design. Attachment of Pt or Ru moiety to the targeting biologically active organic molecules can drastically increase anticancer properties and provide a multitargeting mode of action. In our group, we applied lonidamine, bexarotene moiety as targeting bioligands [2,3]. Lonidamine is known to inhibit the aerobic glycolysis in cancer cells while simultaneously enhancing glycolysis in the normal cells. Bexarotene is known as an agonist of the retinoid X receptor and specific against T-cell lymphoma.

In our presentation will focus on the hybrid complexes based on lonidamine, bexarotene tethered to the ruthenium or platinum unit. Pt(IV), Ru(II) and Ru(III) compound found to be highly cytotoxic against the number of the human cancer cell lines and show good potential in *in vivo* studies.



This work was supported by RSF (project № 19-13-00084).

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Novel bivalent AMPA-receptor ligands of bis(pyrimidine) series

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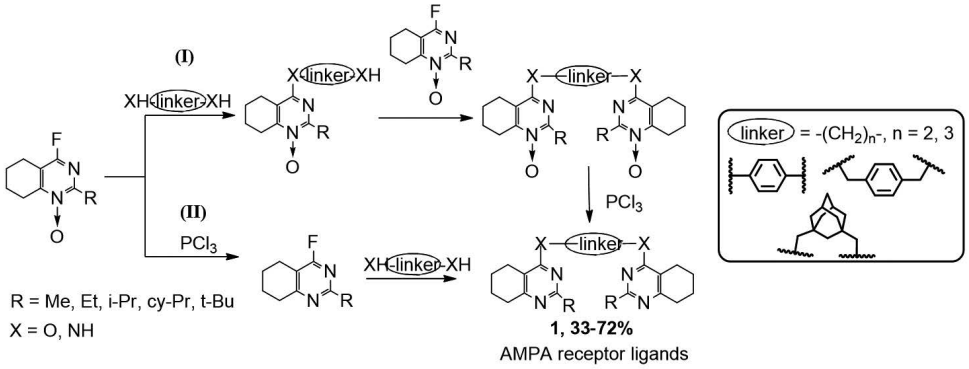
AMPA-receptors are the attractive targets for treatment of a series of neurological disorders. Positive AMPA-receptors modulators can be useful for treatment of the cognitive impairments improving learning and memory, whereas in contrast negative modulators (or blockers) are perspective agents for treatment of epilepsy. Here we present the synthesis of a novel series of bispyrimidines **1** which were supposed to act as bivalent AMPA-receptors ligands. Based on our previously described synthetic approaches [1] we obtained the targeted heterocycles **1** using two routes: (I) double S_NAr reaction of 4-fluoropyrimidine *N*-oxides with different bisnucleophiles and subsequent reduction of *N*-oxide fragment, or (II) reduction of starting 4-fluoropyrimidine *N*-oxides and subsequent S_NAr reaction with bisnucleophiles.



Obtained compounds **1** were tested in patch-clamp experiments for the influence on the kainate-induced currents recorded for the Purkinje cells extracted from the rat cerebellum. Several compounds **1** showed high positive (increase of the kainate-induced currents for 35-60% at 0.001-0.1 μM) or negative modulating effect [2].

This work was supported by the Russian Science Foundation, grant no. 17-15-01455.

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Novel taurine derivative as potential nootropic drug: QSAR, synthesis and biological activity

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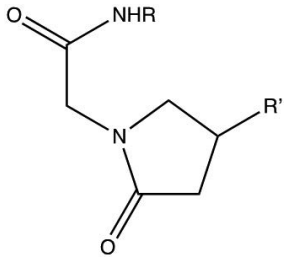
The main disadvantages of a number of nootropic (neurometabolic) drugs such as 2-pyrrolidone derivatives, in particular, Piracetam (**1**), Phenotripyl (**2**) [1], include blood pressure increase, psychomotor agitation and insomnia. Such side effects make it difficult to effectively use these drugs for long-term medication, age-related disorders, insults, cerebral ischemia and another disorders that require prolonged treatment or recovery course.



R = R' = H (1), R = H, R' = Ph (2), R = $(CH_2)_2SO_3K$, R' = Ph (3)

Our strategy for searching for a leading substance using *in silico* methods (QSAR) led to creation of new efficient substance of the pyrrolidone series based on taurine derivative **3** devoid of above-mentioned disadvantages [2]. Biological tests for *in vivo* models for cytoprotective activity, glutamate excitotoxity and for laboratory animals have reliably demonstrated the superiority of compound **3** over commercially available drugs based on compounds **1** and **2**. In *in vivo* studies no side effects such as increase blood pressure and psychomotor agitation have been found.

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Novel Doxorubicin Nanoform, Preclinical Study: Anti-Tumor Activity, Pharmacokinetics, and Safety

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Objective: Preclinical study of Doxolip.

Object of study: Doxolip (IBMCh, Russia), the drug on the basis of Doxorubicin (DR) encapsulated into phospholipid nanoparticles, powder for infusion solutions. Comparison drugs: Doxorubicin-TEVA (Pharmachemie B.V., Netherlands), Caelyx (TTY Biopharm Company Limited, China)

Methods: Evaluation of the anti-tumor (ITG, %) and anti-metastasis (IM, %, ILS, %) activity of DR *in vivo* in mice with transplanted tumors (P388 lympholeukemia, Ca755 breast carcinoma, and LLC Lewis lung carcinoma), study of pharmacokinetics in rats and rabbits using analysis of blood plasma components, normal and tumor tissues, and the estimation of safety of the drug with regard to its general and specific toxicity in rodents and rabbits.

Results.

It has been shown by comparison of Doxolip with Doxorubicin-TEVA that encapsulated DR binds to high-density lipoproteins in blood plasma more tightly than free DR, and because of that it circulates in the blood stream for a longer time and is absorbed by tumor tissue more efficiently. The “benefit/risk” ratio for the protected DR is higher than that for the uncoated drug. The ratio depends on the therapeutic interval (TI) and the toxicity of various forms of DR. In P388 model, the TI indices determined 6 days after the final infusion varied from 9.8 to 15.0 mg/ml for Doxolip, from 8.8 to 10.0 mg/ml for Doxorubicin-TEVA, and from 5.5 to 15.0 mg/ml for Caelyx. In LLC model, the drugs after a single infusion in non-toxic (6-10 mg/kg) and toxic (12-18 mg/kg) doses form the following series with regard to their TI indices: Caelyx (8.2-12.2 mg/kg)>Doxolip (10.0-12.8 mg/kg)>Doxorubicin-TEVA (9.3-10.1 mg/kg). For triple infusion of the protected DR, the three-day interval between the infusions (with regard to all studied indices) was the most efficient, whereas for the uncoated DR such regimen came out as the most toxic, and the seven-day interval was less toxic and the most efficient.

Conclusion.

The study demonstrated the advantages of the protected DR both in the form of phospholipid nanoparticles (Doxolip) and in liposomal pegylated form (Caelyx) over Doxorubicin-TEVA: judging by TI, the encapsulated drugs are less toxic and have higher efficacy.

Silicon-hydroxyapatite-glycerohydrogel as a promising biomaterial for dentistry

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The development of novel tooth enamel remineralization system has significantly progressed in recent years. Hydroxyapatite (HA) is known to have been used for this aim. HA is the main inorganic compound of tooth enamel and has superior biocompatibility and excellent bioactivity characteristics [1]. It is also known that silicon in the enamel imparts its required strength [2].

In this work novel nanocomposite silicon-hydroxyapatite-glycerohydrogel (Si-HA-gel) having HA content 1.75 wt.% and the content of Si 2.04 wt.% was obtained by the sol-gel method using glycerol solution of silicon tetraglycerolate [3] as a biocompatible precursor and aqueous colloid suspension of HA [4] as a template and property modifier. TEM studies demonstrated that HA in the Si-HA-gel is in the nanoscale crystalline state. The atomic force microscopy method was applied to study the remineralizing properties of Si-HA-gel on human teeth extracted for orthodontic reasons. It was found that Si-HA-gel has a pronounced remineralizing effect, namely, it reduces the roughness of tooth enamel. Silicon in a biologically active and accessible form causes an additional positive effect on the process of remineralization. Using the method of energy dispersive X-ray analysis, it was demonstrated that Si content increased in the tooth enamel; the Vickers microhardness was found to increase.

The analysis of the obtained data allows the Si-HA-gel to be considered as a promising biomaterial to be applied for tooth enamel remineralization.

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MINI-ANTIBODIES AGAINST MUC1 BASED ON MONOCLONAL ANTIBODIES ICO-25

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MUC1 is a component of the physiological barrier that protects epithelial cells from damage caused by free radicals, pH, toxins and other stress factors. MUC1 is a multifunctional protein with a high structural diversity that allows it to influence different cellular events. In malignant transformation, MUC1 plays an important role in the modulation of transcription of regulatory genes associated with invasiveness, metastasis, angiogenesis, proliferation and resistance to hypoxia, which ultimately affects cancer cell survival. In malignant transformation of MUC1 cells hyperexpressed, as well as changing the pattern of glycosylation, while opening areas of the protein core, previously inaccessible to the recognition of antibodies. MUC1 is a promising target for the development of new monitoring and therapeutic approaches for the treatment of patients with malignant tumors.

Previously, professor A. Yu. Baryshnikov obtained monoclonal antibodies ICO-25 against MUC1. In Lobachevsky University nucleotide sequence encoding the variable domains of antibodies have been sequenced and cloned. Then recombinant mini-antibodies (scFv) against MUC1 were obtained, which are variable fragments of heavy and light chains of ICO-25 antibodies bound into one molecule by a linker. Mini-antibodies was fused with a fragment of rotavirus enterotoxin NSP4, capable of causing cancer cell apoptosis. Peptides were expressed in E. coli, cleaned, was held their refolding. The productivity of the bacterial system was more than 1 mg/ml. Peptides interact with MUC1 isolated from breast tumor, MUC1-positive cell lines MCF7 and Colo205 and do not react with MUC1-negative cell line Caco2.

Recombinant peptides completely inhibited the metabolic activity of the cell lines Colo 205 and MCF-7. At the same time, the maximum effect of ICO-25 monoclonal antibodies was only 20%. The half-year dose for scFv miniantibodies was 10 μg, and for scFv-NSP4 peptide - 200 μg per milliliter of culture fluid. Cytometric analysis of cells incubated with peptides and stained with annexin V and propidium iodide showed that they induce apoptotic death of tumor cells. In addition, the level of Bax expression increased in cells, exceeding the level of BCL-2 expression, which is typical for cell death by apoptosis, the level of mRNA Fas increased, the cell cycle was arrested. Differences in the action of recombinant antibodies and ICO-25 antibodies are likely to be associated not only with the presence of rotavirus toxin, but also with the size of molecules and are associated with the ability of recombinant single-chain antibodies to recognize epitopes of MUC1 protein inaccessible to classical antibodies. This allows us to consider them as a prototype of therapeutic antibodies.

Synthetic application of 4-pyrones for the preparation of diketoacids as potential HIV integrase inhibitors

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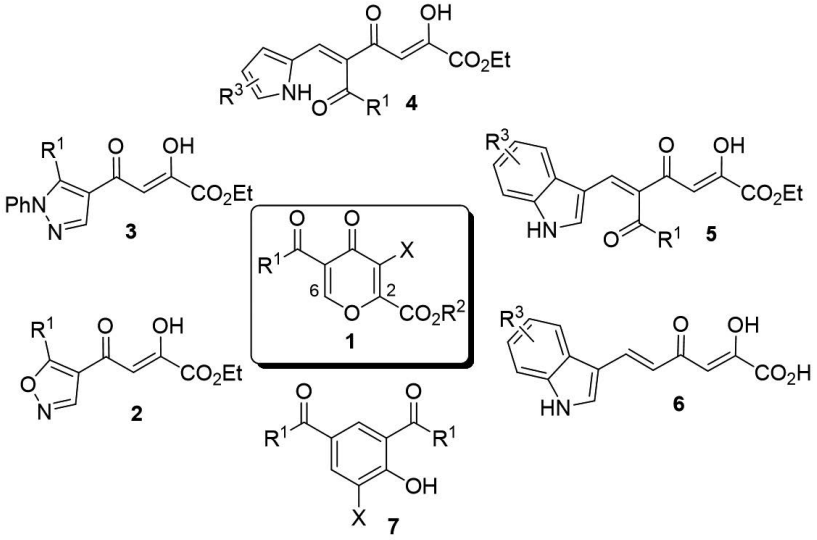
4-Pyrones are available highly active substrates that easily undergo ring-opening reactions leading to a variety of heterocyclic structures. Derivatives of 5-acylcomanic acid **1** are hidden polycarbonyl systems containing the pharmacophore moiety of diketobutanoic acid, which is necessary for the design of modern HIV integrase inhibitors, and due to the presence of electron-withdrawing substituents on the pyrone ring, these compounds can easily react with a wide range of nucleophiles. The transformations of pyrones **1** under action of binucleophiles lead to derivatives of (hetaryl)diketobutanoic acids **2,3** as the result of cyclization at the C-6 position of the pyrone ring and the acyl fragment. The use of indoles and pyrroles as nucleophiles makes it possible to obtain substituted diketohexenoic acids **4–6** [3]. In addition, an unusual self-condensation of enaminodiones was observed during the synthesis of pyrones **1** to give phenols and catechols **7** [4].



This work was financially supported by the Russian Science Foundation (Grant 18-73-00186).

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Biomolecular Release from Alginate-modified Electrode Triggered by a Biocatalytic Cascade – a promising technology for drug delivery

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Biocatalytic cascades involving more than one or two enzyme-catalyzed step are inefficient inside alginate hydrogel prepared on an electrode surface. The problem originates from slow diffusion of intermediate products through the hydrogel from one enzyme to another. However, enzyme activity can be improved by surface immobilization. We demonstrate that a complex cascade of four consecutive biocatalytic reactions can be designed, with the enzymes immobilized in an LBL-assembled polymeric layer at the alginate-modified electrode surface. The product, hydrogen peroxide, then induces dissolution of iron-cross-linked alginate, which results in release process of entrapped biomolecular species, here fluorescently marked oligonucleotides, denoted F-DNA. The enzymatic cascade can be viewed as a biocomputing network of concatenated AND gates, activated by combinations of four chemical input signals (maltose, NAD^+, pyruvate and dissolved O_2), which trigger the release of F-DNA. The reactions, and diffusion/release processes were investigated by means of theoretical modeling. The developed system provides a model for biochemical actuation triggered by a biocomputing network of reactions.

Alginate gel, crosslinked with Fe^{3+} ions, effectively concentrates biomolecules (DNA, proteins, etc.) that are used today for the treatment of cancer. The developed system allows them to be released in the presence of lactic acid, which is produced by many cancer cells (Warburg effect), thus becoming a promising system for targeted delivery of anticancer drugs.

The work was done with the financial support of the Russian Scientific Foundation (project No. 18-73-00224).

Interactions of Liposomes Loaded with a Methotrexate Lipophilic Prodrug with Human Blood Phagocytes

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Incorporation of methotrexate into bilayer of nanosized liposomes in the form of a lipophilic prodrug (methotrexate 1,2-dioleoylglyceride ester, MTXDG) allowed to decrease its toxicity and improve antitumor effect in experiments in vivo [1]. However, the liposomes were found to activate complement (C) in vitro, apparently, through binding and hydrolysis of the C3 factor on the bilayer surface [2–4]. The aim of the work was to study interactions of the drug-loaded liposomes with blood phagocytes (monocytes and neutrophils) by flow cytometry. Fluorescently labeled (1 mol. % PC probe) liposomes (100 nm) were prepared from egg yolk phosphatidylcholine (ePC) **1**, ePC–MTXDG, 9 : 1 **2**, ePC–phosphatidylinositol (PI) (ePC–PI, 9 : 1) **3**, and ePC–PI–MTXDG, 8 : 1 : 1 **4** by extrusion and incubated with human whole blood (10 : 1 by vol.). After 30 min of incubation smaller fraction of cells consumed drug-loaded ePC–PI–MTXDG liposomes **4** than ePC–MTXDG liposomes **2**. Yet even greater effect on liposome accumulation in monocytes was caused by the presence of the prodrug in the bilayer, either carrying PI or not. For example, introduction of MTXDG in the ePC–PI bilayer caused increase in the number of monocytes having consumed the liposomes from 12 ± 3% for sample **3** to 32 ± 10% for sample **4** after 30 min of incubation. Cell receptors probably recognize plasma proteins associated with liposomes, in particular, IgG and C3 and its fragments; the presence of these proteins in liposome–protein complexes formed upon the liposome incubation with human plasma has been the most pronounced for the ePC–PI–MTXDG **4** formulation [3, 4]. Liposome consumption rate by blood phagocytes also correlates with values of liposomes total protein binding in plasma ranging from ~30 g protein/mol lipids for formulations **1** and **3** to 55 and 84 g protein/mol lipid for MTXDG-loaded liposomes **2** and **4**, respectively. *The work was supported by the Russian Foundation for Basic Research (project no. 16-04-01585).*

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^{69m}Zn complexes with thiazine and 2-aminopyrimidine derivatives

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Modern radiopharmaceuticals can contain two active anticancer components: a suitable radionuclide and a chelator that has not only a vector but also a therapeutic effect. Among the possible chelators should be allocated 2-aminopyrimidine cycle - one of the most important pharmacophore. Of great interest are thiazine derivatives, being the inhibitors of iNO synthases. Salicylates (Sal) and metal ions, among which an important place is occupied by zinc are also demonstrating useful properties.

As a radionuclide, we used ^{69m}Zn produced from the photonuclear reaction ^{71}Ga (γ, np) ^{69m}Zn on a split microtron. ^{69m}Zn was isolated by extraction and ion exchange chromatography (yield ~ 60%, radiochemical purity is not less than 99%). The chelators were 2-aminopyrimidine (L^1), 2-aminopyrimidine salicylate (L^2), N(5,6-dihydro-4*H*-1,3-thiazin-2-yl)benzamide (L^3), and $[L^1]_2ZnCl_2$ (I), and the first time obtained and characterized $[L^2]_2Zn$ (II), L^3ZnCl_2 (III). The studies were carried out using spectrophotometry, confocal microscopy, TLC, ARG, as well as MTT tests and flow cytometry on different leukemia cell lines compared of mononuclear cells of healthy donors.

It has been shown that the compounds containing ions of zinc, salicylate and aminopyrimidine (or its derivatives) in various combinations may increase the specificity towards different types of leukemia. Introduction of aryl and acyl substituents can enhance the magnitude of the therapeutic window. The chelating of ^{69m}Zn by ligands L^1 and L^2 led to the formation of radiolytic stable complexes (log $K_{binding}$ > 10 for both complexes), which were characterized by TLC and ARG methods. A study on the distribution of zinc complexes in organs was carried out on a mouse model. Complex III, which has a number of advantages, proved to be stable in alcohol, but unstable in aqueous and physiological solutions, which requires its packaging into polymeric carriers It is important that zinc complex, even at low concentrations, is able to overcome the cell membrane.

Phenotypic Screening of Tick-Borne Encephalitis Virus Reproduction Inhibitors

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Tick-borne encephalitis (TBE) is an arboviral disease important for Russia and Europe, often leading to death or disability when affecting nervous system. It is caused by TBE virus (TBEV; genus *Flavivirus*, family *Flaviviridae*), transmitted to humans after an infected tick bite. Despite the availability of several effective vaccines, vaccination coverage in endemic regions remains insufficient, along with growing TBEV area justifying the need for small molecule antivirals [1].

We have developed a phenotypic screening technique for selection of small molecule inhibitors of TBEV reproduction. Inhibitiory activity of more than 500 nucleosides and non-nucleoside small molecules from different classes was assessed against TBEV and other tick-borne flaviviruses [1-8]. Most classes of small molecules showed EC_{50} values at micromolar and submicromolar level [1-5], whereas rigid amphipathic fusion inhibitors (RAFIs), containing perylene moiety, inhibited TBEV reproduction in nanomolar concentrations [1,6-8]. Mechanism of action studies showed that majority of the compounds inhibited the early stages of the viral lifecycle, corresponding to the viral entry.

Hit compounds identified during these studies will serve as starting points for further optimization and development. Similarity of the *Flavivirus* genus members, such as dengue virus, yellow fever virus, Zika virus, etc., to TBEV will allow an easy repurposing of the compounds and eventually lead to broad-spectrum anti-flaviviral drugs.

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On some opportunities of using Keplerate-type polyoxomolybdates in biomedicine

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The possibilities of using nanocluster polyoxomolybdates (POM) in biomedicine are determined by the structure, physicochemical, and biochemical properties of these compounds. The porous spherical structure of the Keplerate-type nanoclusters Mo_{132}, $Mo_{72}Fe_{30}$ with a diameter of 2.5-3.2 nm is formed by the oxygen coordination polyhedra of molybdenum, including the dimolybdenum octahedral configurations and pentagonal bipyramids. Nanoclusters are usually stabilized by the acetate groups and water molecules, which conditions the POM anions hydrophilicity. Molybdenum ions can be replaced, for example, with iron (III), which reduces the toxicity of POM to a safe level. The presence of charge in POM macroanions makes it possible to use an electric field for their transport — iontophoresis, including percutaneous. The association of POM with surfactant molecules allows to adjusting the hydrophilic-hydrophobic characteristics. The interaction of nanoclusters with drug molecules (vitamins, antibiotics, insulin, etc.) makes it possible to efficiently transporting the cures carried with POM. Moreover, the Keplerate POM can penetrate through the natural histo-hematic barriers, selectively adsorbed by the transformed and normal cells, increase the permeability of cell membranes for chemotherapeutic agents. Furthermore, a patent has been received for the use of $Mo_{72}Fe_{30}$-drug for the treatment of post-hemorrhagic anemia. In addition, a new coordination compound based on $Mo_{72}Fe_{30}$ has been synthesized and studied, which can potentially serve as a donor of nitric monoxide in the body.

In context of bioinspired applications, the stabilization of the Keplerate $Mo_{72}Fe_{30}$ was found due to its association with serum proteins that increases the POM lifetime. This phenomenon can be used to create a depot for preparations of prolonged action. Prospective studies aimed at the development of drug release systems with feedback containing POM and dyes, in particular, with a luminescent indication of the residual dose of drugs, are proposed.

Synthesis and *in vitro* antitumor activity of pyridoxine-based dehydrozingerone mimetics containing phosphonium group

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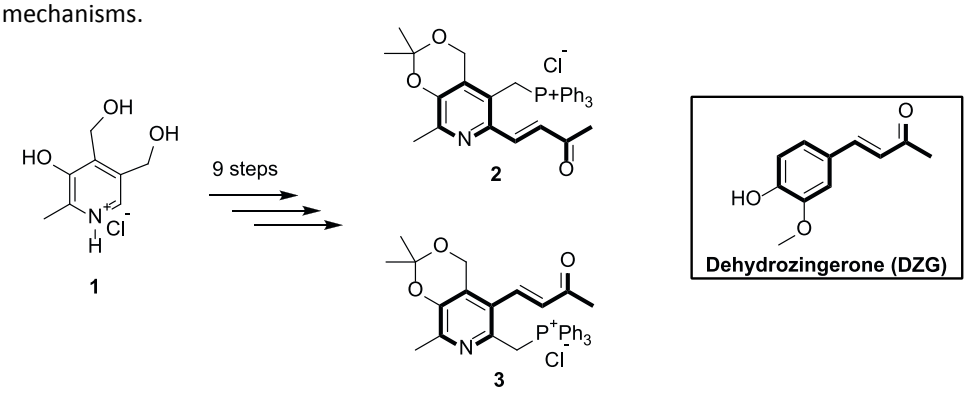
Herein we report synthesis and antitumor properties of novel phosphonium derivatives of pyridoxine-based Dehydrozingerone (DZG) mimetics. DZG represents an example of natural metabolite that possesses expressed antitumor properties and pro-apoptotic activities [1]. Anticancer activity of various pyridoxine based phosphonium salts has also been reported [2]. The underlying idea of this work is to explore antitumor activity of novel molecular constructs that contain both pharmacophore motifs. The pyridoxine-based phosphonium salts of bioisosteric analogs of dehydrozingerone **2**, **3** have been obtained in 9 stages starting from pyridoxine. *In vitro* cytotoxicity study has demonstrated that compounds **2** and **3** have high antitumor activity against 10 cancer cell lines (IC_{50} = 0.7-11.7 μM). It has also been found that compounds **2**, **3** increase concentration of reactive oxygen species up to 7-fold from baseline. At the same time, they decrease mitochondrial potential of cells by 30 and 20%, respectively. The obtained results suggest that both chemotypes represent promising starting points for the development of new anticancer drugs acting via pro-apoptotic mechanisms.



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Modified GDNF and it prospects for therapy in neurodegenerative diseases

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GDNF therapy can be effective in restoring and maintaining the viability of dopaminergic neurons that die in neurodegenerative diseases. In humans, at least two GDNF isoforms have been found, differing from each other in the size of the pro-region. It is possible that pre- (α) pro-GDNF is required for normal neuronal survival, and pre- (β) pro-GDNF serves as an SOS system and is expressed during traumatic neuronal damage or in neurodegenerative diseases. To study the significance of the pro-region for the inducer functions of GDNF, as well as its need for transport of the factor from the cell, several modifications of GDNF were obtained, differing from each other by the presence / absence of pre- and pro-regions. Constructs with modified GDNF were transfected into HEK293 cells. It has been shown that all GDNF isoforms are secreted from transgenic cells into the medium. The effectiveness of GDNF modifications as neural inductors was tested on a rat fetal spinal ganglion model. It has been shown that the removal of the pro region significantly increases the effects of GDNF as a stimulator of neural differentiation of progenitor cells. When using another research model - the model of the embryonic dissociated spinal ganglion of the rat - a quantitative analysis of the neural inducer properties of the GDNF modifications was carried out. Deletion of both pre- and pro-regions enhances trophic activity of GDNF (mGDNF). Spinal ganglia cultured in the presence of medium obtained after cultivation of transgenic cells producing mGDNF, showed an active growth of β-3-tubulin-positive processes already on the 4th day. Then we demonstrate neurotrophic effect of mGDNF for PC12 cells in vitro and showed that on this model also the sprouts of beta-3 tubulin positive. To confirm the neuroinduced properties of mGDNF on human cells, we used a human neuroblastoma cell line. It was found that the addition of mGDNF to the culture medium with neuroblastoma cell significantly increased the number of βIII tubulin positive cells in this culture. In the mouse model, we demonstrated the positive effect of mGDNF on dopaminergic neurons in the in vivo area of the substantia nigra. A model of Parkinson's disease was used, which was obtained by subcutaneous injection of MPTP in C57Bl / 6 mice. Implantation of cells producing mGDNF in caudateum-putamen smoothed the symptoms of Parkinson's disease in motility tests and increased the number of tyrosine hydroxylase-positive cells in the substantia nigra. This work was supported by the basic research programs of the Presidium of the Russian Academy of Sciences ICD and the Fundamental Foundations of the Technology of Physiological Adaptations.

Formation of carboxyalkyl chitosans based hydrogel materials for regenerative medicine products

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The contemporary breakthrough in development of regenerative medicine materials is primarily due to the raw and synthetic availability of biodegradable artificial [1] polymers. Indeed, the bio-friendly nature of natural polysaccharides and their ability to create the final material in accordance with the tasks of regenerative medicine make these polymers unique for the medicine development. Recent studies showed that hydrogel fiber materials can be successfully used to restore nervous tissue after a stroke [2].

In the present research we propose the use of chitosan carboxyalkyl derivatives for new bioabsorbable surgical and regenerative medicine materials formation, such as hydrogels with deposited therapeutic agents and controlled degradation time, hydrogels containing biological agents, hydrogels for the purposes of bone tissue regeneration and rehabilitation of the surgical area, bio-safe non-silicone hydrogels with adjustable swelling degree for the purposes of soft tissue defects treatment. The listed materials as chitosan derivatives are bio safe, do not cause toxic effects, tissue irritation, have long resorption time in human body and allow controlling their swelling degree and mechanical strength depending on the method of obtaining. Effect of polymers crosslinking method and method of sterilization on hydrogels structure and properties is experimentally revealed.

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Inhibitors of c-Jun N-terminal kinase (JNK) as perspective neuro-and cardioprotectors

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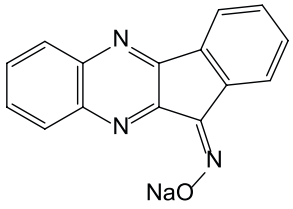
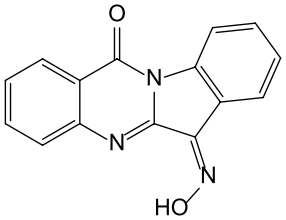
Ischemia and tissue recirculation / re-oxygenation are accompanied by oxidative stress with subsequent JNK activation and cell death due to necrosis and apoptosis. Pan-JNK inhibition weakens ischemic and reperfusion injury but is accompanied by a variety of side effects, which can be avoided by using compounds that selectively inhibit JNK3, expressed mainly in brain and myocardial tissue.

New analogs of 11*H*-indeno[1,2-*b*]quinoxaline-11-one-oxime (IQ-1S) and tryptanthrin-6-oxime were synthesized, having a high affinity for JNK1 and JNK3 and the properties of inhibitors of these kinases according to molecular modeling and kinase profile studies [1].



IQ-1S



Tryptanthrin-6-oxime

In the model of focal cerebral ischemia in rats, treatment by IQ-1S and tryptanthrin-6-oxime reduced the infarction area and weakened the severity of neurological deficit. Under conditions of global cerebral ischemia in rats, the neuroprotective effect of IQ-1S was manifested in the preservation of neurons of the hippocampus CA1 zone, improvement of microcirculation in the brain tissue, as well as in decrease of blood viscosity and severity of endothelial dysfunction. The cardioprotective effect of IQ-1S in the model of acute myocardial reperfusion in rats was manifested in a decrease of the infarction area and in improvement in the contractile function of the myocardium.

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Synthesis and pharmacological screening of water soluble derivatives of 4-R-2-hydroxy-4-oxobut-2-enoic acids

Pulina N.A.[1], Sobin F.V.[1], Kuznetsov A.S.[1], Krasnova A.I.[1], Lipatnikov K.V.[1], Yushkova T.A.[1], Starkova A.V.[1], Chashchina S.V.[1], Kozhukhar V.U.[1]

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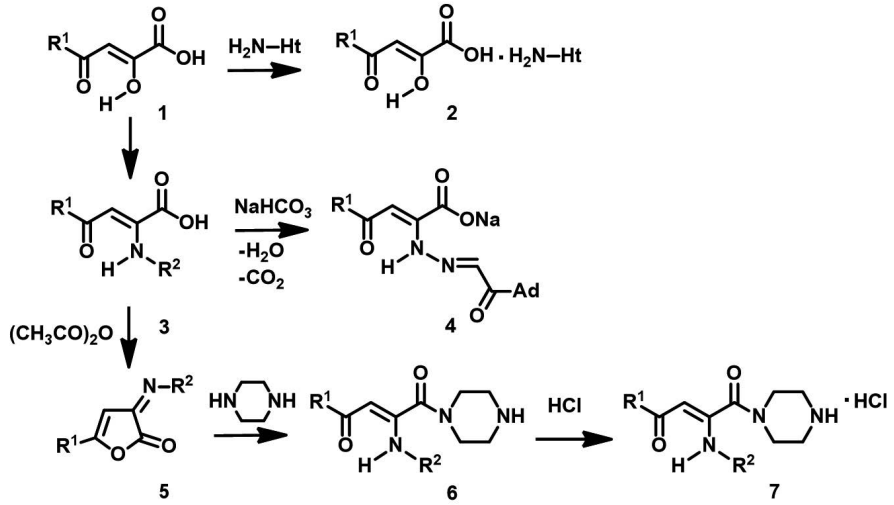
An important biopharmaceutical property of pharmacologically active molecules is solubility in the body's natural fluids [1]. We synthesized water soluble compounds 2,4,7 by chemical modifications of the 4-R-2-hydroxy-4-oxobut-2-enoic acids (1): a) through interaction of acids 1 with heterocyclic amines; b) by formation of sodium 4-(het)aryl-2-{2-[2-(3-R-adamanthane-1-yl)-2-oxoethylidene]hydrazinyl}-4-oxobut-2-enoats (4); c) by decyclization of 3-iminofuran-2-ones 5 and subsequent obtaining of salts 7. The effects of the synthesized products on CNS, anticoagulant, hemostatic, analgesic, anti-inflammatory, wound healing, hypoglycemic, larvicidal, gastroprotective and immunomodulation activities were studied. Low toxic compounds with activities exceeding those of the reference drugs were revealed.



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Design of Dual-Target Wnt Pathway Inhibitors Using Hybrid Machine Learning / Molecular Modeling Approaches

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The simultaneous inhibition of the PI3Kα (phosphoinositide-3-kinase α) and tankyrase enzymes involved in the Wnt pathway has synergistic effects making it a promising approach to the colorectal cancer therapy. The design of their dual-target inhibitors represents an interesting problem of rational polypharmacology. We have shown that the reliable prediction or ranking of activities towards multiple relevant targets can be achieved by using hybrid machine learning models (especially Deep Neural Networks) based on the molecular modeling data.

The molecular docking-based virtual screening workflow can be significantly enhanced by the machine learning approach to the development of target-specific scoring functions. Using the empirical potential values derived from the Smina scoring functions as descriptors, the Deep Neural Network classification models achieve high external test AUC ROC values. [1]

To predict binding affinities from the analysis of short molecular dynamics trajectories, they can be considered as multidimensional time series represented by 2D tensors containing the ligand-protein interaction descriptor values for each timestep. The convolutional neural network models trained on a relatively small dataset provide the best predictive power, outperforming the commonly employed molecular docking and MM-PBSA scores. Thanks to its relatively low computational complexity and the increasing GPU power, this approach can be used as an advanced virtual screening filter for compound prioritization. [2]

Using these methods, we have successfully performed virtual screening and design of potential dual-target PI3Kα and tankyrase inhibitors and identified a number of promising scaffolds.

This study was supported by the Russian Foundation for Basic Research (project no. 18-515-80028) under the BRICS STI cooperation program.

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Nonstoichiometric titanium dioxide photocatalyst for medical chemistry

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Last decade the nanostructured titanium dioxide attracts great attention of the researchers all over the world because this material can be used as a photocatalyst for the synthesis of organic molecules with high efficiency and within the green chemistry [1]. Currently, the material design engineering is widely employed to create the nanostructured materials with enhanced properties [2]. One of the efficient ways for the modification of titanium dioxide materials is creating atomic vacancy defects, which leads to the nonstoichiometry of the material, change the crystal structure, as well as the optical and electronic properties of the material. In terms of vacancies, the defects lead to the formation of additional energy levels within the band gap of titanium dioxide that correspondently results in a shift of the spectral response to the visible region and in a decrease in the optical band gap [3].

In present work the authors demonstrate the nonstoichiometry in titanium dioxide due to oxygen vacancies, which leads to higher catalytic activity in synthesis of organic molecules under visible light illumination, which are useful in medical chemistry for the synthesis of existing or new medicals.

Acknowledgements

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Synthesis and Biological Activity of *S*-, *O*-, *N*-, and *F*-containing Terpenoids

Rubtsova S.[1], Sudarikov D.[1], Pestova S.[1], Gyrdymova Yu.[1], Izmest'ev E.[1], Lezina O.[1], Grebyonkina O.[1], Shevchenko O.[2], Kutchin A.[1]

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We have carried out a synthesis of polyfunctional S-, O- N-, F-containing derivatives of mono- and sesquiterpenoids as well as evaluated their membrane-protective and antioxidant activities on the basis of an ability to inhibit H_2O_2-induced hemolysis of mammalian erythrocytes and retard the accumulation of secondary products of lipid peroxidation.

The ability of monoterpenic sulfides and sulfoxides with carbohydrate fragments to protect cells under conditions of acute oxidative stress depends on the structure of the carbohydrate moiety: sulfides and sulfoxides with galacto- and fructopyranose fragments turned out to be more active compared to compounds with the glucopyranose one. Both symmetric and asymmetric disulfides with *cis*-myrtanyl and myrtenyl fragments showed the highest membrane-protective activity, while the activity of compounds with a galactopyranose fragment was slightly higher than that of similar structures with a fructopyranose fragment. The introduction of an ethane bridge between sulfur atoms leads to a decrease in the toxicity of bis-sulfides compared with disulfides that do not contain such a fragment, as well as to an increase in membrane-protective and antioxidant activity compared to sulfide and disulfide.

We also showed that neomenthane- and isobornane-type sulfanylimines possess membrane-protective and antioxidant activity in the model of oxidative hemolysis of erythrocytes of warm-blooded animals. We established that some sulfen- and sulfinimines, as well as fluorine-containing sulfinamides based on 4-caranethiol, have antibacterial and antifungal activity with respect to *Acinetobacter baumannii* and *Candida albicans*. Pinane-type thiosulfonates showed activity against *Candida albicans*, *Staphylococcus aureus* and *Cryptococcus neoformans*.

Primary screening of caryophyllane sulfides for antifungal activity showed that sulfide with the *p*-nitro benzyl fragment is the most active against *C. Albicans*. In addition, thiols, di- and bis-sulfides exhibit antioxidant properties.

This study was performed under financial support of RFBR (project no. 19-03-00951) u Comprehensive program of UrB of the RAS (project no. 18-3-3-17).

Domino Reactions as a Potential Tool for the Synthesis of Biologically Prevalent Ring Systems

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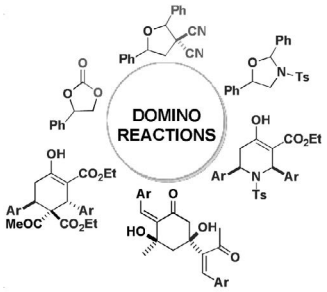
Introduction: Domino reactions could be defined as an efficient synthetic tool for the construction of two or more chemical bonds in a single reaction step.[1] This technique has been frequenty utilized by the synthetic organic chemists for the synthesis of complex molecular entity in a very simple, and step economic ways in the presence of either a metal or organo-catalyst.[2]

Methods: In this continuation, our group is focused in developing newer catalyst system for the synthesis of functionalized heterocyclic derivatives via the utilization of suitable domino reaction strategy.



Results & Discussions: We have successfully installed CO_2 to obtain cyclic carbonate from epoxide in the presence of bis-imine containing Hydrogen Bond Donor (HBD) catalyst. This methodology has been further extended for the synthesis of highly functionalized, tetrahydro furan and isooxazolidine derivatives.[3] Prior to that, we have also developed different stoichiometric domino strategies for the synthesis of highly functionalized 2,6-disubstituted piperidines and all carbon quaternary center containing cyclohexanone derivatives.[4]

Conclusions: In this abstract, Hydrogen Bond Donor (HBD) catalyzed domino strategy has been explained for the synthesis of various functionalized heterocyclic in excellent yields and selectivity.

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New nitric oxide (NO) delivery systems for chemotherapy of socially significant diseases

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Since the discovery of the important role of nitric oxide in biology [1,2], there has been an exponential growth of interest in its biochemistry and in studying nitrosyl transition metal complexes, particularly, biomimetic complexes of iron [3]. During the latest decade, nitrosyl complexes of tetrahedral iron with functional sulfur-containing ligands, being mimetics of active centers of nitrosyl non-heme [nFe-mS] proteins, have been of interest for researchers as the basis for developing innovative medicines [3]. This work presents the data on the development of a new therapeutic approach (NO-therapy) for the chemotherapy of social diseases. It is the development of new-generation medicines based on nitrosyl ferredoxin mimetics and the study of the fundamental principles of their pharmacological activity.

New NO-generating hybrid systems namely compounds with natural $[Fe(NO)_2]$ fragment(s) and thioanalogues of pyridine DNA bases, thioureas, thiotriazoles, thioamides and thiocarbasides were synthesized. Chemical and pharmacological characteristics of synthesized compounds and their polymer composites have been obtained for the standardization and certification their as prodrugs. Results from different studies of new iron nitrosyl complexes pharmacological effects will be presented and discussed.

The work has been performed in accordance with the state task (State registration № 0089-2019-0014).

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Synthesis and antimicrobial activity of quaternary ammonium salts based on pyridoxine derivatives and fatty acids

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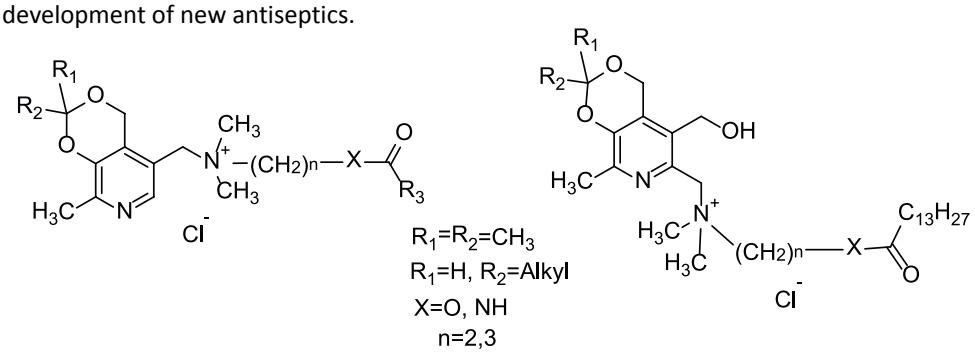
Antimicrobial resistance is one of the most serious problems of modern health care. Antimicrobial resistance (AMR) threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi. In our previous works we reported a synthesis of various quaternary ammonium salts based on pyridoxine derivatives [1-2]. The antibacterial activity of some compounds was higher or comparable with widely used antiseptics miramistin and benzalkonium chloride.

In this work the diverse library of new quaternary ammonium pyridoxine derivatives with fatty acids has been obtained in 3-5 stages. Out of more 30 new compounds, five exhibited high antibacterial activity *in vitro* inhibiting the growth of various Gram-positive and Gram-negative bacteria at 0.5-8 μg/ml and were able to eradicate bacterial biofilms at 2-4×MBC, that exceeded activity of miramistin and was comparable to that of benzalkonium chloride. No resistance development has been observed in series of 14 passages in presence of sublethal concentrations of all leading compounds, as well as no DNA-damage or mutagenic activity was detected in SOS-chromotest and in the Ames test. Cytotoxicity test on HSF (human skin fibroblasts) cells revealed lower toxicity in compare with reference drugs. These data allow suggesting active compounds a promising starting point for the development of new antiseptics.



The work has been supported by the Russian Foundation for Basic Research (RFBR) (project No. 18-33-20051 “mol_a_ved”).

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New antiglycating agents for diabetes therapy: current progress and perspectives

Savateev K.[1], Ulomsky E.[1], Rusinov V.[1], Chupakhin O.[2], Charushin V.[2], Sapozhnikova I.[1], Kotovskaya S.[1], Litvinov R.[3], Babkov D.[3], Spasov A.[3]

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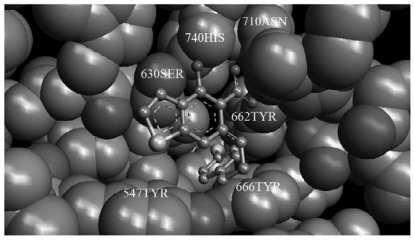
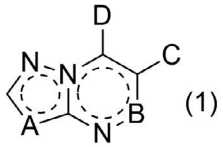
In 2015, there were an estimated 415 million people diagnosed with DM in the world. DM disability and mortality are directly associated with late vascular complications (cardiovascular disease, retinopathy, renal failure, encephalopathy, impaired peripheral blood circulation, and others). Accumulation of advanced glycation end products (AGEs) in tissues is considered as a main driver of these complications. Non-enzymatic glycation of proteins (Maillard reaction) is the way of AGEs formation.





(1)

AGE inhibition, IC_{50} in the range of $48.13…690.75*10^{-6}$ mol

We have proposed a synthetic scheme towards promising class of azoloazine heterocycles (1) and proved antidiabetic potential of these compounds by computational methods and experiments *in vitro*. It was shown that azoloazines (1) demonstrated higher antiglycation activity than reference compound, aminoguanidine, and have some potential as dipeptidylpeptidase-4 inhibitors. By given results this class of heterocycles can be considered as candidate for extended studies to develop drugs against complications of T2DM [1-3].

This work was supported by Russian Federation Ministry of education and science (grant № 4.6351.2017/8.9) and Russian Foundation for Basic Research (grant № 18-03-00787).

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Synthesis and biological activity of the first triazole pyrimidine nucleoside analogues

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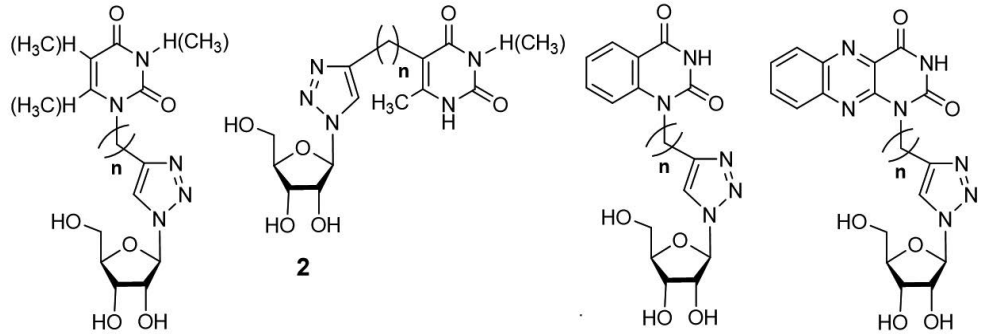
Native nucleosides are a productive platform for creating therapeutic agents with high physiological activity. Synthetic nucleosides are divided into two large groups, namely classical and formal nucleoside analogs. The first group includes derivatives that retain the structure of N-glycosides, for example, the antiviral drugs azidothymidine, stavudine, and others, anticancer drugs gemcitabine, floxuridine and others. The second group includes derivatives of native nucleosides, in which the sugar residue is replaced by carbo(hetero) cycle, the nucleic base is replaced with another heterocycle, and the glycosidic bond C1'-N is replaced with the bond C1'-CH2-N. These include, for example, antiviral drugs abacavir, lamivudine, *etc*.

The report is dedicated to the synthesis and biological activity of a series of previously unknown formal analogues of pyrimidine nucleosides **1-4**, in which ribofuranose moiety is attached to the



1 **2** **3** **4**

nucleobase (uracil, thymine) or their derivatives (6-methyluracil, 3,6-dimethyluracil, quinazolin-2,4-dione, alloxazine) through a 4-alkylene-1,2,3-triazole fragment. The influence on the biological activity of the nature of the nucleic base or its derivative, as well as the length of the alkylene linker is discussed.

The research was financed by Russian Science Foundation, grant number 19-13-00003.

Nanohydroxyapatite and its hierarchical textures as carriers of medical radionuclides

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Modern development of nuclear medicine cannot be imagined without introducing new promising diagnostic and therapeutic radionuclides and radiopharmaceuticals based on them. Due to their nuclear-physical and chemical properties, short-lived alpha-emitters (Ra-223, Ac-225, Bi-213, Pb-211) are effective for treating cancer and are successfully passing clinical trials. However, the scope of their use is limited by the availability of suitable means of delivery to cancer cells. Organic and inorganic nanotransporters are increasingly used as delivery system. In this work, we proposed nanosized hydroxyapatite (HAP), which has both complete biocompatibility and, in many cases, bioactivity, for the target transport of the mentioned radionuclides. It does not accumulate, but is completely metabolized in the body and has long been widely used in medical practice, including as a carrier of medicines. The HAP is able to form various hierarchical textures, each of which can find its application in different variants of nuclear medicine. In our work, the focus was on identifying patterns of sorption interaction between the selected radionuclides and HAP of several morphological and textural forms. The kinetics and isotherms of sorption and desorption of radionuclides on HAP from aqueous solutions were studied. The diffusion of radionuclides in a granular sorbent or in its watered layer was studied and the diffusion coefficient in these media was estimated (for Ra and Ac). For the binding of the radionuclide and carrier, a cocrystallization method was also proposed, when the target radionuclide is introduced directly into the synthesis of the sorbent itself (in this case, HAP).

This work was supported by the RFBR grant No. 18-03-00432.

Orexin OX1R receptors as a new target for creating pharmacological agents for the treatment of addiction diseases

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The aim of the work was to evaluate the Orexin peptide system as a new molecular target for the creation of pharmacological agents for the treatment of alcoholism and drug addiction. In our laboratory, it has been found by the methods of physiological analysis that the structural and functional basis of reinforcement in the test of self-stimulation of the lateral hypothalamus in rats is a system of extended amygdala (SEA)structures, including the central nucleus of the amygdala, the bad nucleus of the striaterminal, the medial portion (shell) of the nucleus accumbens and the innominate substance.Orexin peptides (orexin-1, orexin-2) of SEA are not directly involved in providing emotional response in the study of the phenomena of self-stimulation, but mediate dopamine and glutamatergic reinforcement mechanisms. The introduction of OX1R orexin receptor antagonists into SEA may have a direct effect on the central mechanisms of psychostimulants and hypnosedatives with narcotic potential. This gives basis to consider Orexin antagonists as possible promising agents of prevention and treatment of addictive disorders. The antagonists of Orexin receptors OX1R SB-408124 (a classic antagonist) and the new genetically engineered drug Antorex, created and studied in the Institute of Experimental Medicine, have the greatest antagonistic activity against the psychoactivating action of amphetamine. SB-408124 was most effective when locally injected into the bad nucleus of the striaterminal and the central nucleus of the amygdala. After administration into the lateral ventricle and the medial part of the nucleus accumbens, the antagonistic efficacy of SB-408124 on the reinforcing properties of addictive drugs is reduced.Antorex, which is a peptide with a molecular mass of about 4.2 kDa, showed high activity when administered intranasally to rats. Orexin OX1R receptor blockade with SB-408124 or Antorex administered to the ventricles of the brain or SEA reducedor inverted the psycho-activating properties of psychostimulants (amphetamine, phencyclidine) and hypno-sedative drugs (trimeperidine) on the self-stimulation of the lateral hypothalamus acting as the suppressive drugs. The antagonistic effects of SB-408124 on the reinforcing properties of the self-stimulation of the lateral hypothalamus are manifested by the following pattern: phencyclidine>amphetamin e>trimeperidine. Orexin with local and intraventricular administration does not significantly change the main indicators of spontaneous self-stimulation of the lateral hypothalamus, as well as its combination with OX1R antagonists of SB-408124 or Antorex, which indicates only the modulating type of action of both agents on self-stimulation of the brain.

Highly efficient and selective inhibitors of carboxylesterases based on polyfluoroalkyl-2-imino-1,3-dione scaffold.

Shchegolkov E.[1], Burgart Ya.[1], Elkina N.[1], Khudina O.[1], Boltneva N.[2], Kovaleva N.[2], Rudakova E.[2], Makhaeva G.[2], and Saloutin V.[1]

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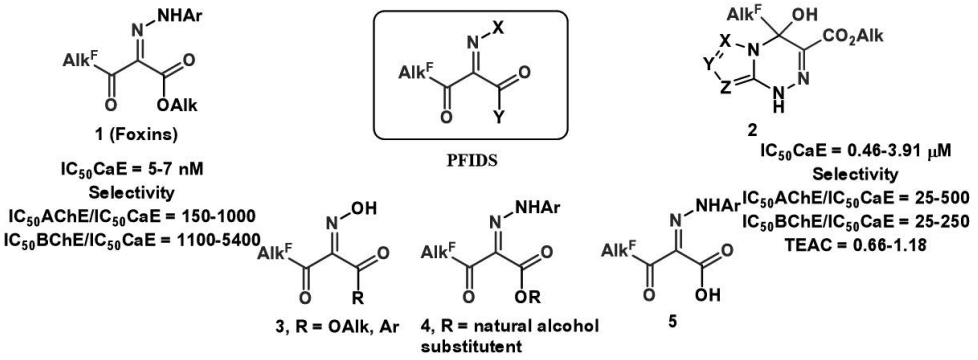
Recently, an attention rises sharply to the carboxylesterases (CaE), playing an important role in activation, detoxication and biodistibution of xenobiotocs. They include a plenty of drugs with ester, amide and carbamate group, responding for phase I of their metabolism.

To create the effective CaE inhibitors, we suggested the original polyfluoroalky-2-imino-1,3-dione scaffold (PFIDS) [1], combining two the known chemotypes in one molecule – trifluoromethylketone and 1,2-dione. These fragments provide an inhibitory activity and selectivity in relation to CaE. We have found that alkyl 2-arylhydrazinylidene-3-oxo-polyfluoroalkylpropionates **1** (Foxins) have the most anti-CaE activity, inhibiting this enzyme in nanomolar range, while ester **4** bearing natural alcohol substituents demonstrate the most selectivity in CaE inhibition comparing to functionally related esterases. Interestingly, acids **5** have the significant anti-CaE action along with antiradical activity. The effective and selective CaE inhibitors also were found among 4,7-dihydroazolo[5,1-c][1,2,4]triazines **2** (the cyclic isomers of Foxins **1**) and analogs of PFIDS **3**, having the hydroxyl substituent instead of arylamino group.



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1,2,4-Oxadiazole/2-imidazoline hybrids: Multi-target-directed weapons for the combat of infectious diseases and cancer

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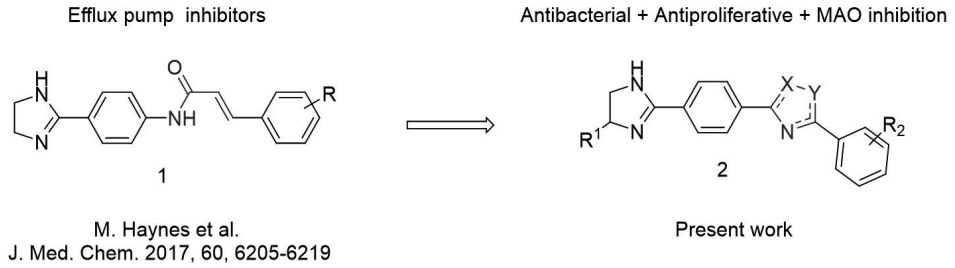
A development of novel antibacterial scaffolds for treatment infectious diseases is one of the greatest challenges to human health in our days. Replacement of amide moiety with 1,2,4-oxadiazole core in the scaffold of recently reported efflux pump inhibitors [1] afforded a novel series of oxadiazole/2-imidazoline hybrids. An antimicrobial and cytostatic potency of the library of synthesized compounds was evaluated on Gram-positive, Gram-negative bacterial strains (*E.coli*, *S.aur.*, *B.subtillis* etc.) and pancreas ductal adenocarcinoma (PANC-1) cell line.



Some of investigated compounds exhibited attractive antibacterial profile reaching MIC values between 8 and 32 μg/mL which makes them undoubtedly promising for further evaluation. Several frontrunners (**2a** (X=N, Y=O, R_1=Me, R_2 = 3,4-di$ClC_6H_{3)}$, **2b** (X=O, Y=N, R_1=H, R_2 = 3-$ClC_6H_{4)}$, **2c** (X=O, Y=N, R_1=H, R_2 = 3-$MeOC_6H_{4)}$, **2d** (X=O, Y=N, R_1=Me, R_2 = 4-$MeC_6H_{4)}$, and **2e** (X=O, Y=N, R_1=Me, R_2 = 3-$ClC_6H_{4)}$) have been studied in more details and showed pronounced bacteriostatic properties against drug-resistant strains, as well as substantial antiproliferative activity against PANC-1 cell line. In the meantime type-selective MAO inhibitory profile revealed for the most active compounds is favorable for them to demonstrate good side-effect characteristics in further development [2]. Finally, we strongly believe that this scaffold may gain attention of medicinal chemists as easily accessible privileged structure serving as starting point for novel libraries of biologically active compounds.

Funding: *This work was financially supported by the Russian Foundation for Basic Research (RFBR) grant No. 18-33-01108*

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Gamma-carbolines as the promising pharmacophores for the new neuroprotective drugs

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The increase in life expectancy leads to a significant rise in age-dependent sporadic forms of neurodegenerative diseases and an expansion in the relevance of creating new drugs for their treatment.

Neurodegenerative diseases are multifactorial and have extremely complex etiopathology and involve two or more pathophysiological indications and so current paradigm of drug design is development of a single entity with multiple pharmacological activities including the neuroprotective potential. Derivatives of gamma carbolines are of particular interest as a basis for the creation of such drugs, the first of which was dimebon and one of the most important targets of Dimebon are mitochondria [1,2]. Mitochondria and specific process of mitochondrial permeability transition (MPT) are the key stage of cell death and so are the main targets for realizing the neuroprotection. The increasing sensitivity of mitochondria to agents inducing MPT is not only a typical feature inherent in aging, but also an important component of the neurodegenerative process. It is shown that dimebon and lead compound among its fluorine-containing derivatives stimulate the neurogenesis and this type of activity is also possibly closely related to their ability to suppress MPT [3]. Large number of gamma-carboline derivatives including their binary complexes and conjugates with some other promising pharmacophores has been synthesized at the IPAC RAS, and their interaction with mitochondria, as well as with a number of targets capable of providing a compensatory cognitive-stimulating effect (glutamate receptors, cholinesterase), or disease-modifying effect (microtubule stabilization) has been studied. Lead compounds of interest for further preclinical trials have been identified.

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Modeling of E5 human papillomavirus ion channel

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Human papillomavirus (HPV) belongs to the papillomavirus family and is quite common in the world. Currently, there are more than 170 types of this virus, of which about 30 can cause cancer. Despite the availability of a vaccine, the development of methods of medical treatment of diseases caused by HPV is still appropriate.

Human papillomavirus virions contain several targets for possible chemotherapeutic intervention. One of the most promising targets is the ion channel E5, which is involved in the proliferation of human keratinocytes and their transformation into a malignant tumor. It is known that the E5 ion channel has a rather large internal cavity, as well as side pockets located near the bilipid membrane and containing lipophilic and hydrophilic regions.

During the work on the project, the E5 HPV ion channel was modeled and molecular docking was performed. The structures contained adamantane, homo-adamantane and bicyclo [3.3.1] nonane moieties, which facilitate penetration through the membrane to the target and its binding to lipophilic sites, connected with aromatic, and / or non-aromatic carboxy and heterocycles containing hydrogen bond donors and acceptors for interaction with hydrophilic amino acid residues within binding sites. For the structures that showed the highest binding energies, the blocking of the HPV channel was verified using molecular dynamics, and the influence of the structure of the molecule on its binding energy to the HPV ion channel was evaluated. On the basis of the data obtained, the leading structures and the most promising directions for their modification were selected.

The research is funded by RFBR project 19-03-00973.

A modern approach to development of antitumor drugs: the case of somatostatin analogue

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In this report the processes involved in drug development and the methods used for this purpose will be presented that will be illustrated by new antitumor drug created in N.N. Blokhin NMRCO - somatostatin analogue (SA) intended to neuroendocrine tumors (NET) management. As the disease has been agreed on, the drug's target has been also identified - somatostatin receptors of five types (SSR1-5), that are expressed by NET. A SAs "cluster" with specific amino acids sequence to bind with SSRs has been synthesized, and the most active pentapeptide compound judged based on IC50 value in vitro has been chosen. To examine structure-activity relationship expression of SSR in animals experimental tumors has been shown. Lead compound synthesis has been optimized for higher purity, its physicochemical and pharmacological properties have been researched to determine quality target product profile (QTPP): uncoated tablets, oral administration, unmodified release, dose - 6 mg/ tablet. Pharmaceutical development allowed to choose SA tablets optimal composition to obtain drug with characteristics corresponding to QTPP, PhEu and PhRu: desintegration time less than 15 min, resistance to crushing ≥ 30 N, weight variation <7.5 %, active substance content closed to nominal and consistent SA distribution in the batch. In preclinical study SA high antitumor efficacy has been shown on transplatable cervical cancer RShM5 and adenocarcinoma Ca755 (86% of tumor growth inhibition, TGI). Also SA was effective on the advanced tumor (TGI = 79-76%) and demonstrated antimetastatic effect (61% MGI) in combination with the surgical treatment. Pharmacokinetic studies informed on drug ability to all investigated organs and tissues including brain and tumor and its speed absorption and distribution and excretion by kidney in 72 hours. Preclinical toxicology studies showed SA safety with slight functional and morphological changes in organs and permitted to estimate the initial dose for clinical trials phase I. First experience of SA use in human showed drug satisfied safety and acceptability of the treatment.

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High-Spin Coordination Complexes in Magnetic Responsive Hybrid Materials: Prospective for Biomedical Applications

Shvachko Yu.N.[1] , Starichenko D.V.[1] , Boukhvalov D.W.[2] , Chizhov D.L.[3] , Pestov A.V.[3] , Rusinov G.L.[3], Chupakhin O.N.[4]

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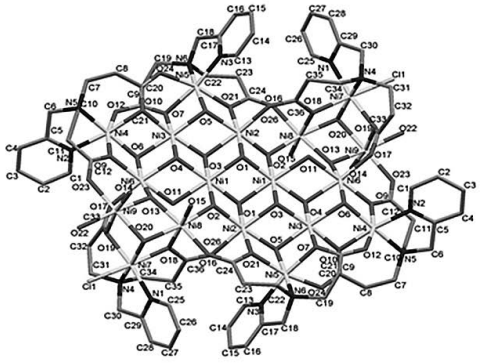
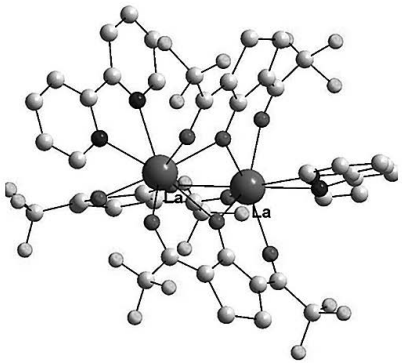
We discuss the potential biomedical applications of the magnetic responsive hybrid materials based on high-spin coordination complexes: planar Ni(II) hydroxo complexes $[Ni_6(pymeid)_6Ni_{12}(OH)_6(\mu_3\text{-}OH)_{16}Cl_2(H_2O)_2]\cdot 38H_2O$ (left structure) and complexes of rare-earth metals La(III) with fluorinated 1,3,5-triketones $[La_2(hfdacp)_3(bpy)_2]$, La=Dy, Ho (right structure) embedded in polymer matrixes.





The Single-Molecule Magnet (SMM) behavior is shown for both types of the original exchange- coupled metal complexes [1, 2]. The magnetic dc- and ac- characteristics are presented and analyzed in the framework of calculated electronic spectra. Two synthetic strategies are discussed: incorporation into nanopores and covalent bonding, including ligand functionalization for specific labeling.

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Camphor and borneol derivatives as effective inhibitors of orthopoxivrus and filovirus infections

Sokolova A.S.[1], Baranova D.V.[1,2], Yarovaya O.I.[1], Zybkina A.V.[3], Shcherbakov D.N.[3], Bormotov N.I.[3], Shishkina L.N.[3], Salakhutdinov N.F.[1]

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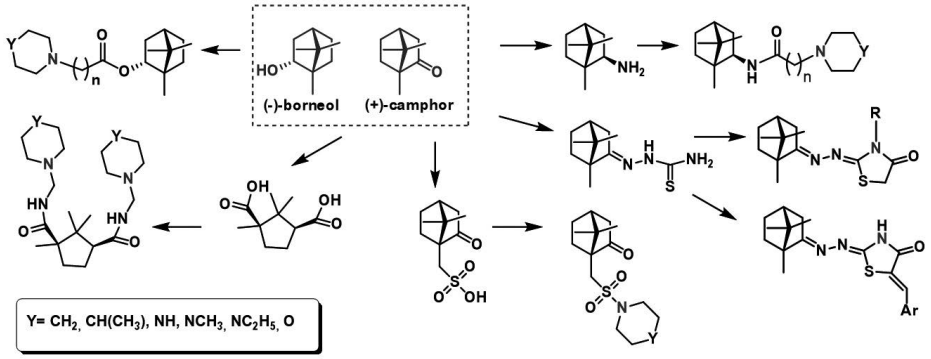
The family *Filoviridae* includes hemorrhagic fevers Marburg and Ebola, which are characterized by high viremia, multiorgan failure with a mortality rate from disease up to 90%. The *Orthopoxvirus* genus belongs to the Poxviridae family and includes variola virus (smallpox), cowpox virus, monkeypox virus and vaccinia virus. Smallpox is considered one of the great epidemic disease scourges in human history. There is currently no antiviral therapy for these viral infections. The purpose of this work is the synthesis of heterocyclic camphor and borneol derivatives for the subsequent study of antiviral activity against orthopoxviruses and filoviruses. Scheme 1 shows the chemical transformations to the target derivatives. Two key structural fragments that are present in the synthesized derivatives can be isolated: 1,7,7-trimethylbicyclo [2.2.1] heptan scaffold and six-membered N-containing heterocycle.



Scheme 1.

Among the synthesized compounds, camphor thiosemicarbazone and its derivatives displayed very good inhibitory activity against vaccinia virus and smallpox. The highest antiviral activity against filoviruses was shown for (-)-borneol based esters and (+)-isobornyl based amides and (+)-4-methylpiperazin-10-sulfonyl-camphor.

This work was supported by the Russian Science Foundation No. 17-73-10153.

Trace amine associated receptor 1 and their role in the treatment of some neuropsychiatric diseases

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Trace amine associated receptors 1 (TAAR1) are related to the family of G protein-coupled receptors revealed in 2001 [1]. TAAR1 were found in catecholamine areas of CNS [1]. There is growing evidence that TAAR1 can modulate the central catecholaminergic activity [1]. The clinical trials of two TAAR1-activating compounds for schizophrenia treatment are in progress [2]. Despite the clinical studies has been yet commenced, the information about the possible therapeutic effects of TAAR1 activation on the other neuropsychiatric disorder, in the pathophysiological mechanism of which the disturbances of catecholamine levels are involved, is still scarce. The present study was aimed to indicate the effects of TAAR1 activation in the preclinical models of such neuropsychiatric disorder like OCD, ADHD, and drug addiction.

The results of the present study demonstrated that TAAR1 agonist RO5263397 decreases specifically the adjunctive drinking in one of the preclinical OCD models and this effect is maintained with repeated drug administration without the development of tolerance [3]. TAAR1 activation is able to decrease basal hyperactivity in DAT-KO rats, the novel ADHD model *in vivo* [4], additionally RO5263397 was shown to slightly affect impulsive choice in rats. Pretreatment with the TAAR1 agonist RO5263397 dose-dependently decreased nicotine-induced hyperlocomotion in rats habituated to locomotor boxes, prevented the development of nicotine sensitization and blocked hypermotility in nicotine-sensitized rats at the highest tested dose (10 mg/kg) [5]. Generally, these results further support the previously proposed view that TAAR1 is a promising target for the neuropsychiatric disorder.

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Synthesis of Novel Organophosphorus Compounds as Drug Candidates

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In the past decades, organophosphorus compounds (OPC's) have been widely employed as substrates in the synthesis of both natural and synthetic products with significant bioactivity. These OPC's exert strong effect on the biological properties due to their unique physiochemical properties. They are used as drugs in medicine for veterinary & human diseases and pesticides in agriculture & horticulture [1]. They have been also used as potent enzyme inhibitors, antimicrobial, antitumor, antioxidant, antiviral and antidiabetics.

Pharmacophore hybrid approach is one of the most effective methods in medicinal and pharmaceutical chemistry to develop new drugs. It includes the fusion of two or more pharmacophoric groups in a single molecule to attain synergetic bioactivity. It also affords an improved selectivity profile with enriched pharmacokinetic and pharmacodynamic boundaries, decrease of antagonistic side effects, dual or numerous modes of action and lesser drug-drug interactions. This method has been successfully exploited out in our research through incorporation of a phosphonate motif with a new C-P bond into various biologically potent acyclic, cyclic and heterocyclic moieties. These hybrid pharmacophoric compounds show very remarkable results on the target compounds having diverse activities such as anticancer [2], antioxidant [3], antimicrobial [4], antidiabetic [5], pesticidal [6] and so on.

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New biologically active derivatives of adamantane and heteroadamantanes containing monotherpenoid fragments

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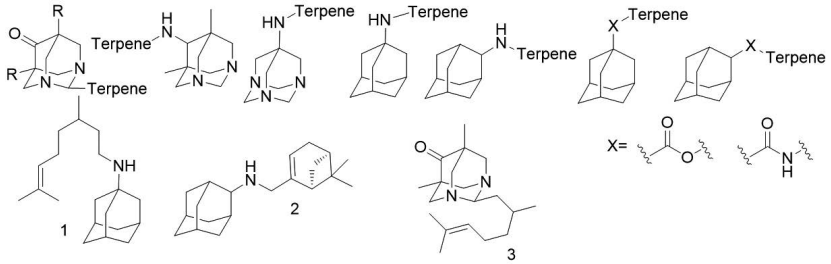
One of the approaches to the creation of new medicinal agents is the transformation of natural biologically active metabolites, for example, monoterpenoids. Adamantane derivatives find widespread use in clinical practice because that have a variety of biological activity. At the same time azaadamantanes 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 [1-4].



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.

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The Development of a New Class of Factor Xa Inhibitors as an Example of Structure-Based Drug Design with Feedback

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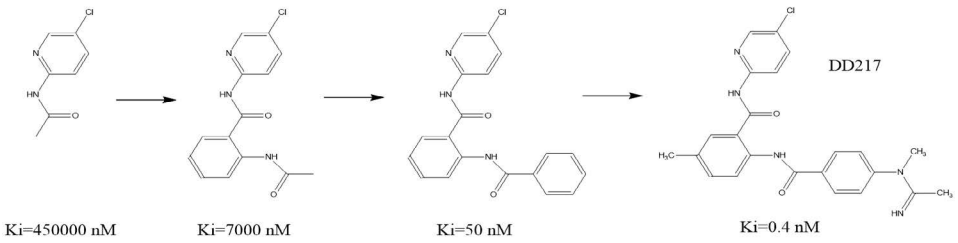
The original technology for the development of a new chemical compounds was created. It based on: - numerical methods for the predicting of the interaction of small molecules with proteins [1, 2]; - organic synthesis; - “in vitro” measuring their biological activity; - “in vivo” preclinical trials. The core idea of the approach is in combination of two groups of methods: one is based on physical models and chemical rules and another one uses experimental data. The main difference our approach from other known methods was in that both active and not active molecules have been used to adjust it.

Using our method we have developed a new class of the compounds that inhibit protein factor Xa (FXa) - one of the most attractive targets for new antithrombotic agents. The inhibition constants of the protein FXa by these compounds were closely to the best known analogues in the world. Moreover the most important indicator for hemostasis being measured showed the concentration of the substance DD217, which doubles the prothrombin time on human plasma, was less than 100 nM - the best result among the known inhibitors according to literature data.



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Innovative Anticoagulant Drug, Direct Factor Xa Inhibitor Development - DD217

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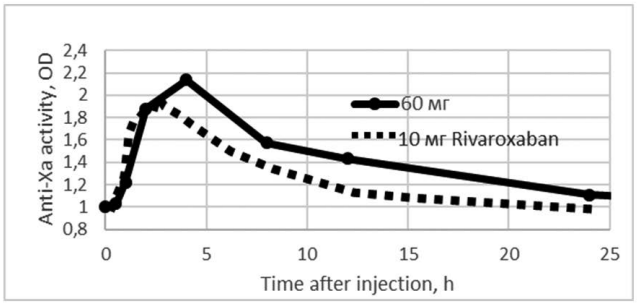
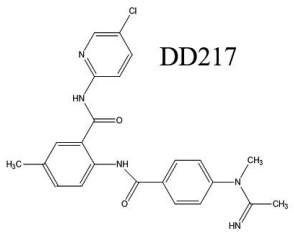
Factor Xa (FXa) plays a central role in a blood coagulation cascade and considered to be one of the most attractive targets for oral anticoagulants of new generation. The substances like R_1-(CONH)-R_2-(CONH)-R_3 are being developed using our own docking and screening methods[1], where R_1, R_2, R_3 are some chemical groups, (CONH) are amid bonds. Subnanomolar potency of several developed compounds was achieved. For some developed compounds was measured the concentration that doubled the prothrombin time (PTx2). PTx2 concentration of the compound DD217 less than 100 nM proves the efficacy of the compound, which makes it promising for the future trials[2].

A clinical study of Phase 1 (for healthy volunteers) was carried out for the DD217. The results have showed that DD217 is absorbed more slowly and leaves the blood more slowly compared Rivaroxaban with the same therapeutic doses, that is, it acts “softer”, which can allow it to maintain a more stable blood concentration once a day. Therefore, it can lead to greater predictability, efficiency and security of DD217.

At the moment, a multi-center, randomized, double-blind, placebo-controlled prospective study is being organized for DD217 to select optimal doses and assess the safety and efficacy of DD217 as a means of preventing venous thromboembolic complications in knee arthroplasty.





Relative change in anti-Xa activity with a single dose of DD217 and Rivaroxaban on healthy volunteers.

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Phase and Microelement Composition of the Kidney Stones of Ob' River Watershed Residents

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Kidney stone disease, also known as urolithiasis, occupies one of the first place among urological diseases in the World. However, the causes of urolithiasis are not clearly understood wherein urolithiasis depends on the individual characteristics of the patient and adverse environmental factors (ecology, food, etc.). For the treatment of urolithiasis, the following methods are traditionally used: surgery, ultrasonic chipping stones, drug dissolution urolites, etc. It should be noted that more than half the cases of the simple urolite removal leads to relapse of urolithiasis without further correction of the patient's diet.

The phase and elemental composition study's of the urolites is an effective way to identify patterns of their growth processes and scientifically based approach to the prevention of stone formation. The phase composition was studied by powder diffractometer Shimadzu XRD-7000. The elemental composition was studied by ICP OES spectrometer Thermo Scientific iCAP-6500. We investigated the uroliths of residents from various regions of the Russian Federation. The concretions «Invitro» are provided (in the framework of joint research of NIIC SB RAS and «Invitro»). More than 2,500 stones of residents of the Ob basin (Novosibirsk, Omsk and Chelyabinsk regions) and more than 15,000 stones of residents of the Russian Federation were analyzed.

We noticed significant changes in the phase composition of kidney stones studying the X-ray results for the residents of the Novosibirsk, Omsk and Chelyabinsk regions (for 10-15 years). The oxalate stones amounts increased by 10%, the phosphate stones amounts decreased by 5-10%. The phosphate stones are more common in Novosibirsk and Omsk regions – 10-12%; uric acid and its salts – in Chelyabinsk region (21%). The ICP OES data showed, that in X-ray amorphous stones are contained Ca, P, Mg, Na, K (more than 0.1% wt.); Ba, Bi, Cd, Cr, Cu, Co, Fe, Mn, Mo, Ni, Re, Rb, Si, Sr, Ta, Zn, Pb, Al, W (0.001-0.1% wt.). The elements Na, Mg, K more common in oxalate; Na, K, Zn, Sr – in phosphates; Na, Ca, K, P – in urinary stones.

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Search and development of drugs for the correction of endothelial dysfunction

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This report will consider issues dealing with the role of nitric oxide and endothelial function/dysfunction in providing a number of physiological and pathophysiological processes and various body systems functioning. It also covers in details the possible ways of pharmacological management of endothelial dysfunction (ED) using drugs of different pharmacological groups (classes). Diverse pharmacological effects which have various degree of intensity and presented at various stages of ED pathogenesis are discussed. The value and urgency of search and development of agents with endothelial protection potential are studied in available experimental and clinical works on the considerable role of endothelial system in cardiovascular diseases and lack of specific means for prevention and treatment of endothelial dysfunction. Integrated morphological-functional approach to assessment of ED and endothelial protection of substances was developed and implemented in experimental practice in Cardiovascular

Agents Laboratory of the Volgograd State Medical University Research Institute of Pharmacology. Various ED models were tested and most valid ones were selected. Endothelial protection of new compounds such as Salifen and Flavicin are considered and compared with cardiovascular drugs (ACE inhibitors, angiotensin receptor blockers, statins, etc.), antioxidants etc.

Azolo[1,5-a]pyrimidimes and their derivatives in searching the agents against sepsis

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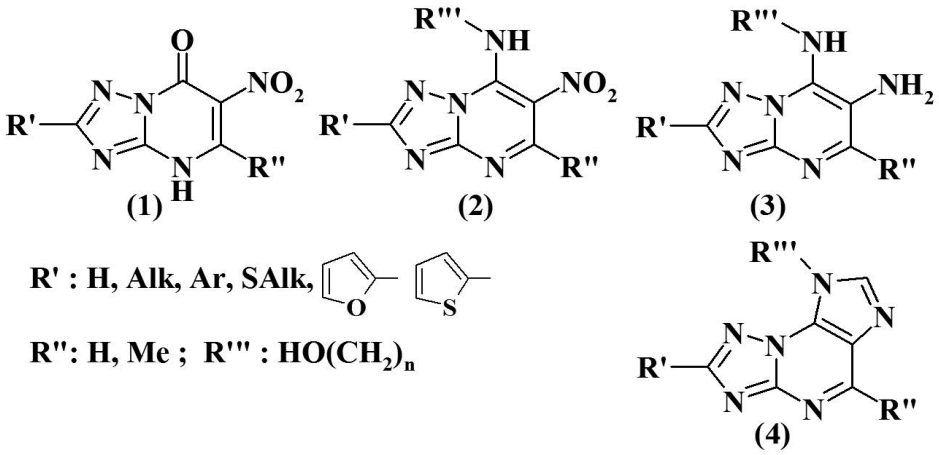
Sepsis which has microbial and viral nature is serious sequela of infectious diseases. The significant funds and intellectual resources of major scientific research collectives are expended to fight the sepsis. The picture of biochemical processes of the sepsis is very diverse, but it has been attracted the attention to the key role of the receptors action in the activation and inhibition of sepsis in recent years. One of the important objects in this direction are adenosine receptors (A_1, A_{2A}, A_{2B}, A_3) and compounds acting on them (agonists and antagonists). The molecular structure of such receptor effectors simulates purines, their azoloannelated analogues and and non-natural nucleosides in most cases.

The objects of the development and creation of agents against sepsis as assumed A_{2A} inhibitors of receptors became triazolopyrimidines (1-3) and triazolopurines (4) which is close in structure to purines.



There were analyzed the database, offered the most promising objects, were developed the methods of synthesis and were found the first active compounds in the study. As the most promising members of the group were identified representatives among water-soluble compounds such as (1) which showed an active activity against sepsis. It should be noted that the compounds do not have antimicrobial activity indicating their impact on the regulated processes by receptors.

We thank the Russian Science Foundation grant № 17-13-01096.

Research and development of fluorinated derivatives of Dimebon as potential drugs for the treatment of neurodegenerative diseases

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A large number of clinically different neurodegenerative disorders are grouped under one term – proteinopathies having a formation of insoluble fibrillar structures and depositions in the form of histopathological inclusions in the nervous system as a major hallmark of pathology. Results of previous studies suggested that fluorinate derivatives of Dimebon might act as neuroprotectors in the nervous system affected by neurodegenerative processes of protein aggregation [1, 2]. We used a model of fatal neurodegeneration caused by expression of the C-terminally truncated human FUS (heterozygous FUS(1-359) [3] to assess the effect of chronic administration of Dimebon and its fluorinated derivates DF302 and DF402 on the disease onset and duration, and animal lifespan. In contrast to Dimebon, fluorinated derivates showed pronounced effect on the disease duration leading to increased lifespan of transgenic animals. We used Noldus CatWalk gait analysis system to test FUS(1-359) and wild type littermates starting at the age of 30 days and continued until the symptoms were visible. After classification of footprints we employed R algorithm to perform multi-dimension scaling analysis. Data from 499 mice and 308 parameters were analyzed. We were able to select a set of parameters distinguishing between transgenic and wild type mice long before clinical signs of neurological pathology become visible. As a result, we conclude that more detailed characterization of the effect of DF402 on animal nervous system at presymptomatic stage is required for better understanding of the mechanism of the drug action. Yet, the studied fluorinated compounds showed high degree of efficacy which is supported by our findings of extended lifespan and reduced age of onset as well as delayed motor deficits. The study of fluorinated compounds was supported by RSF #19-13-00378. Animals were supported by IPAC RAS Bioresource Collection (No. 0090-2017-0016); Centre for Collective Use IPAC RAS was used for CatWalk data collection in the framework of the State Assignment of IPAC RAS (0090-2017-0019) and research program of the Presidium of the RAS “Fundamental research for biomedical technologies.”

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Oxidative C-H functionalization in the synthesis of "azine-metallocene" ligands systems

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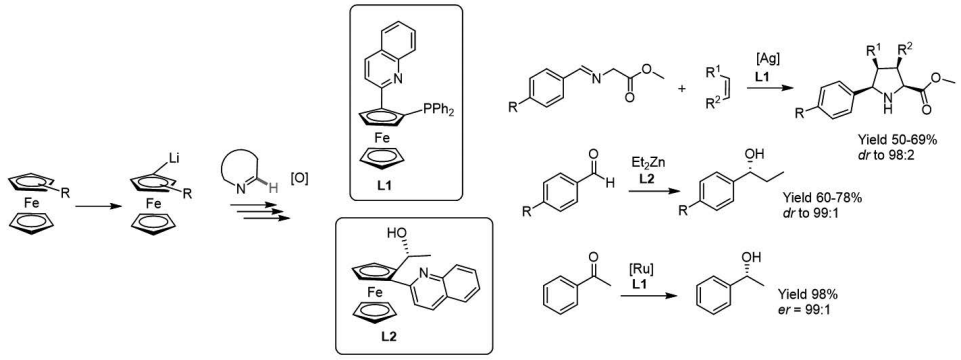
Enantiomerically enriched metallocenes compounds as well as bi(hetero)aryls, binaphthyls are included in the list of ligands of primary importance in the field of asymmetric synthesis. Among the metallocenes ligands homoannularly substituted planar chiral azinylmetallocenes using as catalysts in various reactions of asymmetric synthesis deserve special attention.

Based on the C-H functionalization reactions in azines (S_N^H reactions) by chiral lithium metallocenes a new low-stage and atom-economical method has been developed to production of *P,N*-ferrocenlylazines ligands [1]. To use of S_N^H reactions allows to increase the yields and enantiomeric purity of planar chiral azinylferrocenes, avoiding application of palladium catalysts and halogenated azines. It has been found that the synthesized enantiomerically enriched *P,N*-ligands **L1,2** has shown high catalytic activity in the reactions of asymmetric [3+2] cycloaddition, reduction as well as in the addition reactions of diethyl zinc to aldehydes.



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Acylative Kinetic Resolution as an Efficient Method for Preparation of Enantiomerically Pure Amines and Acids

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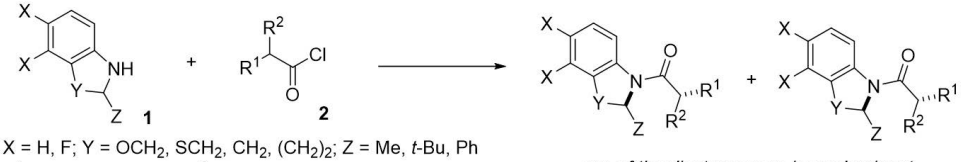
A constant interest in developing efficient synthetic approaches to individual enantiomers of organic compounds is attributed to their practical value, especially, for medicinal and analytical chemistry. The optical kinetic resolution (KR) is one of widespread approaches to obtain enantiopure compounds [1]. The acylative KR is a versatile method that can be used for the preparation of both enantiopure amines and acids.

A study on acylative KR of chiral amines (**1**) and 2-oxyacids (**2**) of various structures was carried out. An influence of the reagents' structure on the stereochemical outcome of the acylation was studied. To explain the observed stereoselectivity, DFT modelling of the transition states (TSs) in acylation of chiral 3-methylbenzoxazines with 2-oxyacyl chlorides was performed. It has been found that acylation proceeds *via* a S_N2-like concerted mechanism. From the calculation results, it follows that the acylation stereoselectivity is determined by the combined effect of steric and electronic factors. In this case, aromatic interactions between the reagents' molecules in TSs, presumably, play a crucial role in the observed stereoselectivity.



1 **2**

X = H, F; Y = OCH_2, SCH_2, CH_2, $(CH_2)_2$; Z = Me, *t*-Bu, Ph
R^1 = Me, Ph, Bn, *i*-Pr; R^2 = OMes, $OC_6H_4(4\text{-}NO_2)$, $OC_6H_4(4\text{-}F)$, $OC_6H_3(2,6\text{-}Cl_2)$

one of the diastereomers is predominant

The obtained results were used to develop the methods for preparation of individual enantiomers of 3-methylbenzothiazine (**1**: X = H, Y = SCH_2, Z = Me) and 3-*tert*-butylbenzoxazine (**1**: X = H, Y = OCH_2, Z = *t*-Bu), as well as a number of 2-oxysubstituted carboxylic acids (*ee* up to 99%), including practically valuable ones.

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The work was financially supported by the Russian Foundation for Basic Research (grant 18-33-00027 mol_a).

Neural network modeling of the poly-functional multi-target pharmacological active compounds

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By the method of artificial multilayer perceptron neural networks in Statistica program [1], the classification dependences of the level of RAGE inhibitory activity on the calculated affinity of compounds for significant target proteins of the RAGE–NF-kB signaling pathway were constructed. The training set included information about 183 known RAGE inhibitors from the patented database [2]. With the use of AutoDock Vina program [3], an ensemble docking of these structures in sites of 66 valid 3D models of 22 relevant target-proteins of the RAGE–NF-kB signaling pathway was performed, and the minimum docking energy values for each compound in relation of each target were determined. Three high significance neural network models were found ($p<<0.001$), the predictive accuracy of which, according to the ROCK analysis, was 90%, 86% and 81% for high, moderate and low active RAGE inhibitors, respectively. The sensitivity analysis of these neural networks has shown that, for a high level of RAGE inhibitory activity, the most significant bio-targets of the RAGE–NF-kB signaling pathway are 8 protein kinases ERK2, MAPK14, JNK1, JNK3, PRKCA, PRKCG, PRKCD, PRKCQ and transcription factor NF-kB1.

Similarly, two neural network dependences for SERT and NET inhibitory activities of 1,3,4-thiadiazine derivatives on their affinity for 13 proteins, which determine the effectiveness of these compounds under correction of the systemic stress response, are constructed. It is shown that for this action the most significant are 7 bio-targets: tyrosine kinase JAK3; transporter proteins SERT, NET, DAT; receptors CHRM1, DRD1, DRD2.

The work was funded by the Russian Foundation For Basic Research, 18-015-00499 project.

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Direct C-H functionalization of pyrimidine derivatives to development of antibacterial agents

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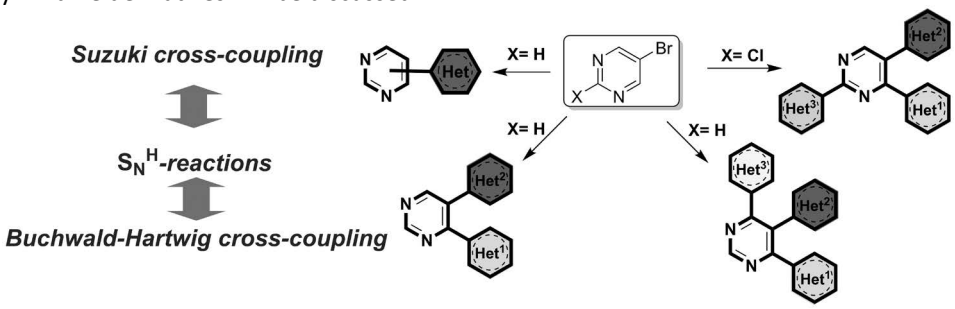
The report will present data on the functionalization of pyrimidine derivatives using various combinations of nucleophilic aromatic substitution of hydrogen, cross-combinations of Suzuki and Buchwald-Hartwig. In addition, the results of studies on biological activity assay (antituberculosis and antibacterial activities) for synthesized mono- and polysubstituted pyrimidine derivatives will be discussed.



Acknowledgements

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New Types of bis-Quaternary Pyridinium Salts Possessing Antibacterial and Antifungal Activity

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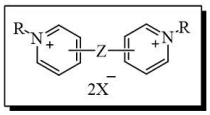
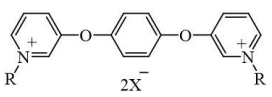
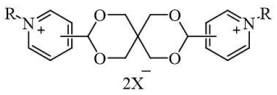
The most part of antiseptics on contemporary Russian medical market are based on quaternary ammonium compounds (QACs). The most known and effective antiseptics are benzalkonium chloride, cetylpyridinium chloride, Miramistin (all based on mono-QACs), chlorhexidine, alexidine, octenisept, mestamidine (based on bis-QACs). The active ingredient of the last two drugs is the bispyridinium quaternary salt of octenidine hydrochloride, produced in Germany. It is known that various strains of bacteria, including pathogens, develop resistance to antimicrobial drugs [1,2]. Therefore, the search for new chemicals with biocidal properties against a wide range of pathogenic and potentially pathogenic microorganisms, as well as viruses, is very important.

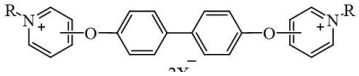
We have been proposed an original approach to the synthesis of several new types of bispyridinium salts with significant antibacterial activity against a wide range of pathogenic bacteria (both gram-positive and gram-negative) and fungi, exceeding the activity of known antiseptics. The undoubted advantage of the obtained bispyridinium salts is their high selectivity of action against pathogens such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Candida albicans*, *Cryptococcus neoformans*.

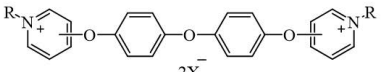


$R = C_nH_{2n+1}$, n = 7-16
X = Cl, Br, I









This work was supported by the Russian Science Foundation (grant № 17-73-20260).

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Liposomes and Nanomedicine

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The use of liposomes – phospholipid vesicles – as drug delivery systems today is a recognized approach to increasing the efficiency of treatment and improving the quality of life of cancer patients [1]. Liposome-based products are leading among nanomedical drugs intended for systemic administration, since liposomes are characterized by the highest bio- and hemocompatibility and the lowest toxicity. Moreover, phospholipids themselves possess a useful pharmacological activity. In recent years, the technologies of liposome production have been improved, methods of the inclusion of diverse substances – from small molecule drugs to peptides, oligonucleotides or non-large proteins – have been developed. However, the range of active pharmaceutical ingredients presented in liposomal formulations on the market is small. This is largely due to the problem of nanoscale carrier loading efficiency. One of the ways to solve it is the inclusion of drugs in the form of lipophilic prodrugs in the bilayer of liposomes. In the Laboratory of Lipid Chemistry, Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, liposomes based on natural phospholipids loaded with dioleoylglyceride ester conjugates of chemotherapeutic drugs melphalan and methotrexate have been developed [2]. Physicochemical characteristics and biological activity of liposomes, including those equipped with tetrasaccharide address molecule Sialyl Lewis X for delivery to angiogenic endothelium of tumors, were studied *in vitro* and *in vivo* [3-6].

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Nitroazolo[5,1-*c*][1,2,4]triazines and their derivatives as inhibitors of adenosine A2a-receptors

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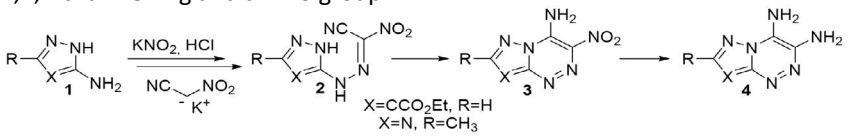
Adenosine A2a-receptors play an important role in the regulation of cellular functions [1]. The interruption of purinergic signal transmission between cells leads to the development of various neurodegenerative pathologies, in particular, associated with the work of adenosine A2a-receptors: Parkinson's disease, Alzheimer's disease and sepsis.

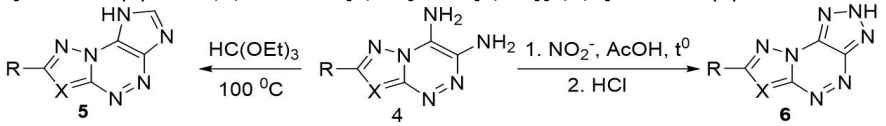
One of the most effective antagonists of adenosine A2a-receptors is the compound ZM-241385 [2], which belongs to the class of azolo[5,1-*c*][1,3,5]triazines. The structural similarity of the azolo[5,1-*c*][1,2,4]triazines being developed with the reference compound ZM-241385 suggests effective receptor inhibition.

Quantum-chemical calculations showed inhibitory activity of some representatives of the azolo[5,1-c][1,2,4]triazine series being developed in relation to adenosine A2a-receptors.

The synthesis of azolo[5,1-*c*][1,2,4]triazines consists in the diazotization of aminoazoles **1** and azacoupling of diazoazoles with the potassium salt of nitroacetonitrile. The resulting hydrazones **2** are undergone intramolecular cyclization of the nitrile group with the closure of the 1,2,4-triazine ring and amino group.



The subsequent reduction of nitroamines **3** leads to the formation of diamines **4**, the cyclization of which produces tricyclic analogs of natural purines - imidazo[4,5-*e*]azolo[5,1-*c*][1,2,4]triazines (**5**) and 1,2,3-triazolo[4,5-*e*]azolo[5,1-*c*][1,2,4]triazines (**6**).



Thus, methods for the synthesis of nitroazolo[5,1-c][1,2,4]triazines and their derivatives as promising inhibitors of adenosine A2a-receptors were developed.

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Monoterpenoids as Promising Agents for the Treatment of Parkinson's Disease

Volcho K.P.[1], Ardashov O.V.[1], Pavlova A.V.[1], Mahato A.K.[2], Sidorova Y.A.[2], Morozova E.A.[1], Tolstikova T.G.[2], and Salakhutdinov N.F.[1]

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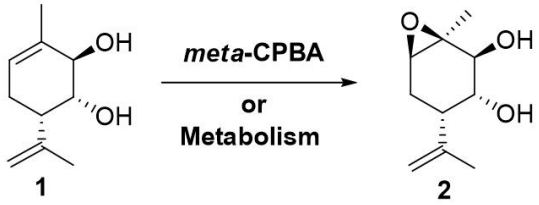
We previously had showed that monoterpenoid diol **1** alleviates motor manifestations of Parkinson's disease (PD) in MPTP rodent models [1]. It was further demonstrated that administration of diol **1** is effective in all main rodent models of PD based on injection of neurotoxins or medications causing drug-induced Parkinsonism [2], thus making further development of this compound highly promising.

In the current work, all four possible monoepoxides were synthesized and their biological activity in the MPTP mouse model of PD was evaluated. Two of the epoxides demonstrated promising anti-PD activity, with *trans*-epoxide **2** been the most active. Note, that we identified epoxide **2** as a metabolite of diol **1** in the blood and brain of experimental animals.

Epoxide **2** was found to robustly promote the survival of cultured dopamine neurons and trigger the mitogen-activated protein kinase (MAPK) signaling cascade in cells of neuronal origin. In the MPTP mice model of PD, compound **2** substantially increased the striatal dopaminergic fiber density.

Taken together, these data indicate that epoxide **2** can be a promising compound for further development as a neuroprotective and neurorestorative drug to treat Parkinson's disease.



1 **2**

We are grateful to Russian Foundation for Basic Research (Grant No 19-03-00071a) for the financial support.

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Anthrafurancarboxamides: Diversity of Structure and Antitumor Properties

Volodina Y.L.[1], Dezhenkova L.G.[2], Tikhomirov A.S.[2], Isagulieva A.K.[2], Tatarskiy V.V.[1,3], Moisenovich A.M.[4], Moisenovich M.M.[4], Kaluzhny D.N.[5], Tsvetkov V.B.[6], Shtil A.A.[1,3] and Shchekotikhin A.E.[2]

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Derivatives of anthraquinone represent an important class of antitumor agents. However, doxorubicin, mitoxantrone and other clinical drugs are less effective against resistant tumors. Optimization of the anthracycline structure allowed us to develop the furan containing derivatives (anthrafurandiones) with cyclic diamines in the side chain. New anthrafurancarboxamides demonstrated a high antiproliferative potency against tumor cells of different species and tissue origin, including the resistant sublines with P-glycoprotein overexpression or p53 dysfunction. Anthrafurancarboxamides form stable complexes with double stranded DNA, inhibit topoisomerases 1/2, cause DNA damage, cell cycle perturbations, and apoptosis. Furthermore, the lead compound LCTA-2034 inhibited individual protein kinases and demonstrated an antitumor efficacy *in vivo*. Importantly, structurally close compounds of this class differed significantly in their biological properties such as cytotoxicity, intracellular distribution, effects on cell cycle, DNA binding affinity, topoisomerase inhibition and therapeutic efficacy on transplanted tumor models. Nevertheless, the ultimate outcome of cell exposure was the same for individual derivatives, namely, a caspase dependent apoptosis. Thus, versatility of structural modifications of anthrafurancarboxamides expand their antitumor potential, strongly suggesting a perspective of this class for an in-depth SAR analysis and design of novel drugs efficient for resistant tumors.

The study was funded in part by the DST-RFBR in the framework of the scientific project № 17-53-45105 IND_a.

Derivatives of oximes of 3 - and 4 - benzoylpyridine – a new class of compounds with anti-epileptic properties

Voronina T.A.[1], Litvinova S.A.[1], Gmurenko L.A.[2], Gaidukov I.O.[1], Mokrov G.V.[2], Gudasheva T.A.[2], Durnev A.D.[1]

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New derivatives of oximes 3 - and 4-benzoylpyridine were synthesized and evaluated In Zakusov Research Institute of Pharmacology. The research of the antiepileptic activity of the original oximes 3 - and 4-benzoylpyridine derivatives was carried out with methods of assessing motor convulsive manifestations and electroencephalographic (EEG) method to study the epileptic activity (EpA) in different brain structures. It was found that the original derivatives of oxymes 3 - and 4-benzoylpyridine have the ability to eliminate seizures in the maximal electroshock seizure (MES) test and activity of the compounds depends on the presence of ethylmorpholine or dimethylaminoethyl groups in the structure and is not determined by the position of the nitrogen atom (3rd or 4th) in the pyridine ring. It is shown that the compound GIZH-298 (dialkylaminoethyl ether of oxyme 4-benzoylpyridine) has the highest activity (ED50 = 16.4 mg/kg, MES test), and also has the ability to eliminate audiogenic convulsions in Krushinsky-Molodkin rats, as well as antihypoxic activity. GIZH-298 has high therapeutic index (TI=19.3 in the ratio LD50/ED50). In the model of chronic focal cobalt-induced epilepsy in rats, GIZH-298 reduces both the number and duration of epileptic discharges. GIZ-298 has the ability to eliminate EEG (EpA discharges) and motor (secondary generalized tonic-clonic seizures, complex convulsive movements, drumming, etc.) manifestations of homocysteine thiolactone-induced epileptic status in rats with cobalt-induced epilepsy with 100% animal survival. GIZH-298 is superior to valproic acid and topiramate in activity, affectivity and speed of onset. GIZH-298 electrophysiological mechanism of action at the stage of formation of the epileptic system is determined by its influence on the primary foci of EpA in the ipsilateral cortex and hypothalamus, and at the stage of the epileptic system stabilization – influenced by generating of EpA in the secondary dominant foci in the contralateral cortex and hypothalamus.

Blockade of 5-HT$_{2A}$ receptors as a strategy for the development of new antimigraine drugs

Yakovlev D.[1,2], Spasov A. [1,2], Agatsarskaya I.[1,2], Sultanova K.[1], Kornilov V.[1], Morkovnik A.[3], Zhukovskaya O.[3], Anisimova V.[3]

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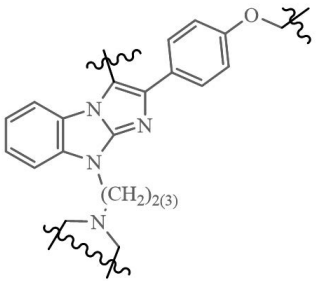
A modern approach to the development of new drugs for the migraine treatment is the reduction of excessive serotonergic impulses by 5-HT2A receptor antagonists, which improves cerebral circulation at an early stage of attack by inhibition the effects of serotonin [1].

The number of highly active compounds were identified using a target-oriented approach to search for new 5-HT$_{2A}$ receptor antagonists among indole and benzimidazole bioisosteres (synthesis: Southern Federal University, Lomonosov Moscow State University). The structure-activity dependence was investigated using productive screening, transfected cell technologies, in-vitro pharmacological analysis methods and in vivo methods [2].

Key molecular scaffold responsible for the presence of high 5-HT2A-antagonistic action was identified:



Pharmacological and pharmaceutical development of a new in the class drug for migraine treatment have been carried out based on the most active compound of 9-(2-diethylaminoethyl) -2- (4-methoxyphenyl) imidazo [1,2-a] benzimidazole dihydrochloride [3], the full cycle of preclinical studies, justifying the expediency of conducting clinical trials is finishing.

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[3] Patent RU 2465901

New TDP1 DNA Repair Enzyme Inhibitors Increasing Temozolomide Efficacy against Glioblastoma Multiforme

Yarovaya O.[1,2], Kovaleva K.[1,2], Oleshko O.[2], Cheresiz C.[2,4], Mamontova E.[3], Zaharenko A.[3], Zaharova O.[3], Pokrovsky A.[2], Lavrik O.[3], Salakhutdinov N.[1,2]

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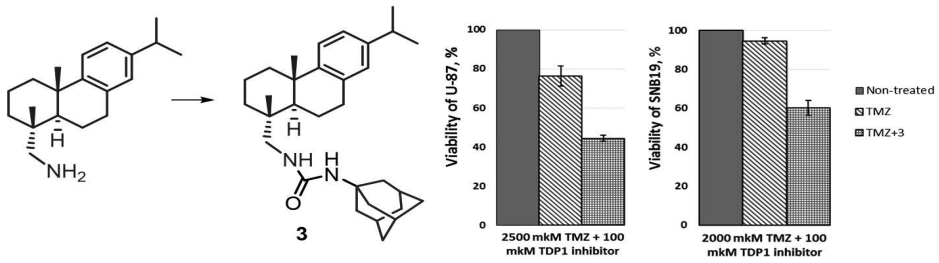
Chemotherapeutic DNA damaging agents are used as an adjuvant therapy for glioblastoma. However, in some patients the use of adjuvant chemotherapy does not achieve the desired effect, significantly increases the cost of treatment and is complicated by significant toxicity. A scarce number of chemotherapeutic agents is used for the treatment of glioblastoma, which creates significant difficulties for the development of individual treatment regimens in the struggle for the patient's life.

We synthesized a library of compounds based on tricyclic terpenoid dehydroabiethylamine. As a result of the screening, the obtained ureas, thioureas and heterocyclic derivatives were shown to inhibit the enzyme tyrosyl DNA phosphodiesterase 1 (TDP1) in concentrations of 0.09-3.7 μM.



The most effective TDP1 inhibitors were shown to have no cytotoxic effect against a number of tumor cell lines. It was established that the leader compound 3 sensitizes glioblastoma cells (U87MG, SNB-19) to the action of the anticancer drug temozolomide (TMZ).

Structural manipulations with lipophilic moieties

Zefirova O.N.[1,2], Nurieva E.V.[1], Alexeev A.A.[1], Zefirov N.A.[1,2], Kuznetsov S.A.[3]

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In the process of drug design it is often required to vary the lipophilic moieties in the designed structure. This modification can both provide additional hydrophobic interactions with molecular target and improve pharmacokinetic or pharmacodynamic parameters of the compound (modify its aqueous solubility or make it able to cross blood brain barrier etc.). In this report we present two examples of variations of lipophilic moieties recently fulfilled in our investigations in drug design.

The first type of the works was aimed to the synthesis of inhibitors of nitric oxide synthase (mostly inducible and endothelial isoforms) with prolonged vasoconstrictive activity. For the prolongation of action it was proposed to apply an isosteric replacement of monocycle in the lead compounds (thiourea derivatives) with either annelated bicyclic core or bridged or cage moiety. The target compounds were synthesized and two compounds were found to cause pronounced and prolonged vasoconstrictive effect *in vivo*.

In the second type of works we designed and synthesized a series of unusual analogues of well-known tubulin targeted compounds combretastatin A-4 and 2-methoxyestradiol bearing lipophilic adamantane moiety. The compounds were moderately cytotoxic to cancer cells, caused apoptosis of these cells and stimulated full depolymerization of their microtubules. These compounds represent novel structurally unusual type of the ligands of colchicine binding site in tubulin.

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Experimental basis for the introduction of drugs that acting via P2 receptors

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It is known that under physiological conditions the role of P2 receptors, the main mediators of which is ATP, is not dominant in most cases, they only complement or modulate the action of other neurotransmitters. However, in pathological conditions, the role of P2 receptors increases dramatically and often takes a leading position in the pathogenesis of a particular disease. This opens up prospects for the creation of new drugs acting through the involvement of P2 receptors [1]. Studies in recent decades show the real possibility of using P2 receptor agonists and antagonists in clinical practice. One of the significant achievements of pharmacology in recent decades has been the introduction into clinical practice antagonists of platelet $P2Y_{12}$ receptors (ticlopidine, clopidogrel) as effective antiplatelet agents that are widely used for the prevention of thrombotic processes in the cardiovascular system. Another direction in the clinical use of drugs acting through P2 receptors was the introduction of the $P2Y_2$ receptor agonist diquafosol, which is currently approved for use in Japan in the treatment of dry eye syndrome as an inducer of the production of intraocular fluid and mucin. Various other P2 receptor agonists and antagonists are currently undergoing different stages of preclinical and clinical trials. The great diversity and wide representation of P2 receptors make them very attractive as potential targets for the action of new drugs, so research in this area is certainly relevant. Obviously, due to the growing interest in this area of many pharmaceutical companies, in the near future we can expect the emergence of new drugs that are P2 receptor agonists or antagonists that will be effective in treating various human diseases.

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PASE-methodologies for obtaining drug candidates of aza-heterocyclic series

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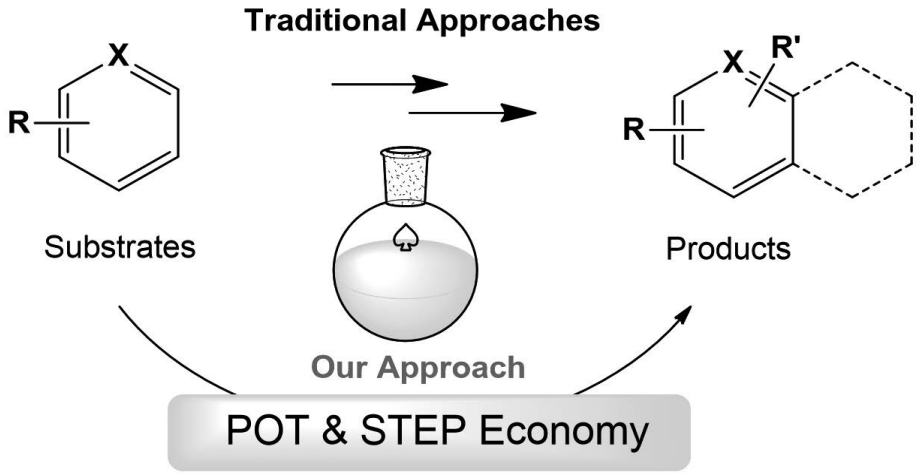
Compounds, containing (aza)aromatic scaffolds are well known as synthetic and natural drug candidates as well as chemosensors, ligands and fluorophores for various purpoces. In addition to traditional routes to synthesize the above mentioned compounds the so-called PASE (Pot, step, atom economic)-based/green approaches are of growing popularity.

In this report the most recent results in these area obtained by us will be reported.



Acknowledgements

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Новый лекарственный препарат «Арглабин» в онкологии. Фармакологические и клинические исследования.

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Введение. В настоящее время внимание исследователей привлекают сесквитерпеновые лактоны, как перспективные источники природных противоопухолевых средств. Одним из таких природных соединений является сесквитерпеновый γ-лактон арглабин, выделенный из Artemisia glabella Kar et Kir. На основе гидрохлорида диметиламиноарглабина разработан оригинальный противоопухолевый препарат «Арглабин». Препарат «Арглабин» изучался в Национальном медицинском исследовательском центре имени Н.Н. Блохина (г.Москва, Россия), клинике MD Anderson, компании NuOncology Labs Inc. (г.Хьюстон, США), Leonardis Klinik (г.Бад-Хайльбрун, Германия), Национальном центре онкологии Республики Грузия (г.Тбилиси), Национальном центре онкологии Кыргызстана (г.Бишкек) и во всех онкологических клиниках Республики Казахстан при лечении рака печени, пищевода яичников, шейки матки, легких и молочной железы как в монотерапии, так и в сочетании с другими химиотерапевтическими средствами и лучевой терапией. Препарат «Арглабин» исследован в клинике на более 3000 онкологических больных, при этом положительный эффект составляет 76 % по шкале Карновского. Выявлено, что данный препарат является конкурентным ингибитором фарнезилирования RAS-онкобелков, снижает экспрессию RAS-генов и содержание АТФ, вызывая апоптоз опухолевых клеток. В дозе, эквивалентной 500 мг/м^2 не влияет на периферическую кровь, что свидетельствует о его низкой токсичности по отношению к органам кроветворения. Доказано его иммуномодулирующее действие, зависимое от дозы препарата, проявляющееся преимущественным влиянием на Т-клеточное звено иммунитета и способность корректировать иммунодепрессивный эффект цитостатиков.

Цель исследования. Эффективность препарата «Арглабин» при различных клинических исследованиях.

Материалы и методы. Клинические испытания препарата «Арглабин» при местно-распространенном раке молочной железы, первичном раке печени, раке шейки матки.

Результаты. Применение препарата «Арглабин» внутривенно в дозе 10 мг/ кг или 370 мг/м^2 при комбинации с лучевой терапией приводит к снижению коэффициента липопероксидации перед операцией в 1,5 раза, снижает процент постлучевого эпидермита в 2 раза, число послеоперационных осложнений в 4,5 раза ниже по сравнению с только лучевой терапией, повышает 2-х и 3-летнюю кумулятивную выживаемость на 30%.

Применение препарата «Арглабин» у больных первичным раком печени в монорежиме в дозе 185 мг/м^2 и в комбинации с 5-фторурацилом вызывает достоверно меньшее число осложнений по сравнению со стандартной схемой с включением цис-

платина и 5-фторурацила. Монотерапия препаратом «Арглабин» приводит к развитию лечебного патоморфоза гепатоцеллюлярной карциномы печени, вызывая гибель опухолевых клеток путем апоптоза и парциального некроза.

Препарат «Арглабин» обладает химиосенсибилизирующей способностью. При его применении в дозах 10 мг/кг и 15 мг/кг в комбинации с химиотерапией у инкурабельных и ослабленных больных при выраженном прогрессировании процесса и устойчивости к стандартной химиотерапии получен положительный эффект в 44%.

Радиомодифицирующий эффект препарата «Арглабин» подтвержден у больных раком шейки матки, раком слизистой полости рта при введении препарата внутривенно капельно на 200 мл физиологического раствора из расчета 370 мг/м^2.

Заключение. Таким образом, препарат «Арглабин» в дозе 10 мг/ кг или 370 мг/м^2 в наиболее часто применяемых схемах полихимиотерапии повышают эффективность лечения. Его использование в комбинации с химиопрепаратами или лучевой терапией в подавляющем большинстве случаев приводит к стабилизации процесса, улучшает показатели выживаемости и качества жизни онкобольных.

О ПРОБЛЕМЕ ВВЕДЕНИЯ РАДИОФТОРА В КАТЕХОЛАМИНЫ

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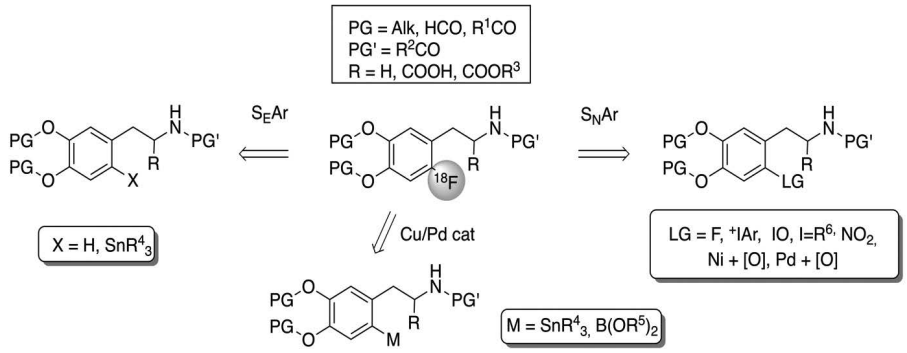
В патогенезе многих социально значимых заболеваний – нейродегенеративных деменций и нейроэндокринных опухолей – лежит процесс нарушения нейромедиаторного обмена. Из всех существующих нейровизуализационных методов диагностики перечисленных заболеваний наиболее совершенным и информативным является позитронно-эмиссионная томография (ПЭТ). Применимость ПЭТ в значительной степени определяется арсеналом доступных меченых соединений – радиофармпрепаратов (РФП), предварительно вводимых в организм человека. В нашем обзоре [1], созданном при поддержке гранта РНФ, собраны и систематизированы сведения о современном состоянии дел по применению РФП группы катехоламинов, позволяющих объективно оценивать состояние симпатической и центральной нервных систем, в клинической практике, методах их синтеза и существующих проблемах.



В докладе обсуждаются имеющиеся в области получения меченых ^{18}F катехоламинов проблемы и методы их решения (Схема). На данном этапе развития методов и методик получения меченых катехоламинов наиболее перспективными является метод асимметрического алкилирования с использованием хиральных межфазных катализаторов и медь-катализируемое фторирование бороновых эфиров.

Подробно обсуждаются методы нуклеофильного введения фтора в неактивированные ароматические субстраты, такие как фенолы и эфиры фенолов.

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Динамика и лиганд-индуцированные изменения структуры N-концевого домена белка-онкогена Mdm2

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В ходе дизайна ингибиторов белка-онкогена Mdm2, проведён анализ структур из базы PDB, полученных экспериментальным путём (ЯМР-спектроскопия и рентгеноструктурный анализ). Установлено две группы структур: с разрешённым N-концевым участком (Met1-Gln18) Mdm2 и без него. Причина – высокая подвижность домена, затрудняющая анализ методом PCA[1]. Из литературных источников установлено, что для белка Mdm2 характерно существование «открытой» и «закрытой» форм, зависящих от динамики петли Met1-Gln18 N-концевого домена и лиганда в p53-связывающей полости[2]. В ходе исследований проведены расчёты молекулярной метадинамики свободного Mdm2, ряда комплексов с актуальными и малоактивными ингибиторами. В качестве контрольных параметров динамики использованы величины междоменного угла и расстояния до активной полости Mdm2. Анализ траекторий показал, что для активных структур характерно смещение равновесия в сторону «закрытой» формы, что совпадает с минимумом свободной энергии ΔG. Профиль свободной энергии безлигандного Mdm2 демонстрирует равновесие между конформациями, в пределах локальных минимумов ΔG. Малоактивные структуры – напротив стимулируют формирование «открытой» конформации. Динамика лиганд-белковых контактов во времени указывает наличие гидрофобных контактов с N-концевым доменом (в частности с Pro9). Данное явление характерно только для активных молекул. Для валидации данной модели проведён ряд симуляций с точечными мутациями белка, а также модифицированных вариантов ингибиторов Mdm2, подтверждающих гипотезу о гидрофобном контакте исключительно активных лигандов с участком Met1-Gln18 N-концевого домена, что позволит уточнить стратегию дизайна ингибиторов белка-онкогена Mdm2. Работа выполнена при поддержке гранта РНФ 16-13-10358

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Технология «молекулярного портрета» в конструировании биологически активных соединений

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Детальный анализ свойств молекулярных поверхностей играет важную роль в процессах распознавания, взаимодействия и передачи сигналов в биомолекулярных системах. Технология «молекулярного портрета» представляет собой современный подход к расчету и 3-мерной визуализации различных физико-химических характеристик поверхности биомолекул. Эффективное использование таких подходов требует создания специальных методов компьютерной обработки, анализа и представления «молекулярных портретов». В настоящей работе описано применение указанных методов в работе с белками, мембранами и их комплексами. Показано, что в результате удается повысить точность решения задач молекулярного докинга белок-лиганд [1] и белок-белок [2]. Кроме того, предложен оригинальный метод «белковой топографии» (МБТ) [3], который позволяет наглядно представить полную поверхность молекулы белка в виде двумерных карт. МБТ применяется также для выявления конформационных изменений между различными состояниями молекул, для проведения сравнительного анализа групп биообъектов, нахождения в них общих и специфических характеристик. Методы «молекулярного портрета» в значительной степени дополняют современные технологии докинга, наглядно иллюстрируют комплементарность свойств поверхностей лиганда и белка-рецептора. Использование подобных технологий совместно с экспериментальными и независимыми вычислительными методами создает надежную основу для рационального конструирования новых биологически активных соединений с заданными свойствами [4].

Работа выполнена при поддержке РНФ (грант 18-14-00375), РФФИ (19-04-00350), в рамках Программы фундаментальных исследований НИУ ВШЭ и с использованием средств субсидии в рамках государственной поддержки ведущих университетов РФ «5-100».

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Неоантигены в иммунотерапии рака

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Достаточно часто развитие опухолевого процесса сопровождается нарастанием количества различных генетических мутаций в раковых клетках. Клетки в процессе развития опухоли накапливают много мутаций соматических генов, как правило, не имеющих прямого воздействия на опухолевый процесс. В результате таких генетических мутаций в опухолевых клетках образуются антигены, специфичные только для клеток опухоли и отсутствующие в нормальных тканях. Они получили название «неоантигены». Такие неоантигены могут быть высоко иммуногенными и рассматриваются в качестве молекул-мишеней, воздействие на которые может привести к отторжению опухоли. В свое время было обнаружено, что у ряда онкологических больных с опухолями, отличающимися высокой генетической нестабильностью, при лечении с помощью адоптивной иммунотерапии развивался сильный Т-клеточный иммунный ответ против неоантигенов. Эти мутации были в большинстве случаев уникальны для каждого конкретного пациента. С повышением доступности NGSсеквенирования для детекции всех мутаций в опухолях и появлением специализированных биоинформационных алгоритмов стало возможным использование феномена неоантигенов в терапии опухолей с последующей активацией иммунного ответа.

В современном понимании проблемы неоантигеныявляются перспективными мишенями для персонализированных противоопухолевых вакцин, позволяющих целенаправленно контролировать опухоль, не задевая нормальные ткани. Пока на сегодняшний деньнедостаточно клинических испытаний для того, чтобы сделать объективный вывод об их эффективности, но работы активно ведутся как за рубежом, так и в России. Проведенные разными группами исследованияимеют много общих черт, подтверждая, что для эффективного контроля опухоли одного метода терапии неоантигенными пептидными или РНК-вакцинами недостаточно.Использование в противоопухолевых неоантигенных вакцинах иммуностимулирующих или иммуномодулирующих адъювантов, которые преодолеваюттолерантность опухолевого микроокружения и вызывают мощный противоопухолевый иммунный ответ,может обеспечить эффективность вакцинотерапии. Также требуют прояснения и оптимизации практические вопросы производства и применения персонализированных вакцин со стороны регулирующих нормативных актов.

Синтез и фармакологические свойства нового антитромботического лекарственного средства

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Причиной острого коронарного синдрома, инфаркта миокарда и ишемического инсульта чаще всего служит атеросклероз, развивающийся вследствие повышения агрегационной активности тромбоцитов. Ввиду высокой смертности и инвалидизации от сердечно-сосудистых заболеваний актуален поиск новых средств профилактики и лечения тромбообразования.

Для решения обозначенной проблемы нами предлагается инновационный ингибитор агрегации тромбоцитов, созданный на основе новой молекулы – производного индолинона (кодовое наименование – GRS).

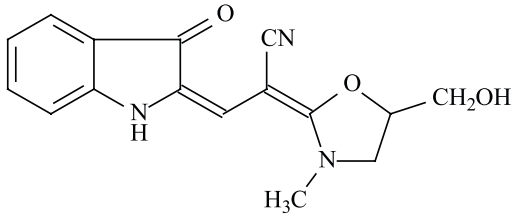

Рисунок 1 *– Структурная формула GRS*

Разрабатываемый антиагрегант с новым механизмом действия – экзогенный донор оксида азота, обладает антигипертензивными и кардиопротекторными свойствами. Новое соединение получено последовательностью следующих превращений: конденсация N-ацетилиндоксила с этоксиметиленмалононитрилом; обработка продукта уксусным ангидридом; взаимодействие с 3-(метиламино)-1,2-пропандиолом; дезацетилирование в первом положении индольного фрагмента.

В рамках доклинических испытаний фармацевтической субстанции и готовых лекарственных форм на ее основе разработаны методы контроля качества, проведены исследования специфической активности, острой и хронической токсичности, эмбриотоксичности и мутагенности, репродуктивной токсичности и иммунотоксичности, фармакокинетики при различных дозах и путях введения, экскреции и распределения по органам.

Поли(азагетеро)циклические ансамбли как флуоресцентные хемосенсоры и зонды для биоактивных объектов

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Флуоресцентный метод анализа остается одной из динамично развивающихся областей сенсорных технологий [1]. Благодаря высокому уровню чувствительности, быстрому времени отклика, способности использования во временном и пространственном *in vivo* изображении живых систем, флуоресцентные хемосенсоры широко применяются в биологии, физиологии, экологии, криминалистике и др. [2]. Множество (био)химических аналитов могут быть детектированы флуоресцентным методом анализа: взрывчатые соединения, биологически активные соединения, техногенные отходы, газы (в т.ч. нервнопаралитические), органеллы клетки и др., что является национальной задачей сохранения здоровья населения любого государства [3]. В отличие полимерных материалов мономолекулярные флуорофоры, широко растворимы в обычных растворителях, что делает их легко доступными для изготовления с целью применения на практике. Целью доклада является рассмотрение новейших разработок нашим коллективом молекулярных сенсоров/зондов (проб) на основе таких поли(гетеро)ароматических хромофоров как иптицены, пирен и его производные, азаантрацен и его производные, лиганды 2,2’бипиридинового ряда и их металлокомплексы для обнаружения биологически активных соединений, техногенных отходов, реализации отклика на изменения окружающей среды, присутствия анионов и катионов металлов и т.д.

Благодарности

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POSTER PRESENTATIONS

Antiproliferative activity of 6-hydroxyxanthanodiene conjugates with pharmacophoric azines

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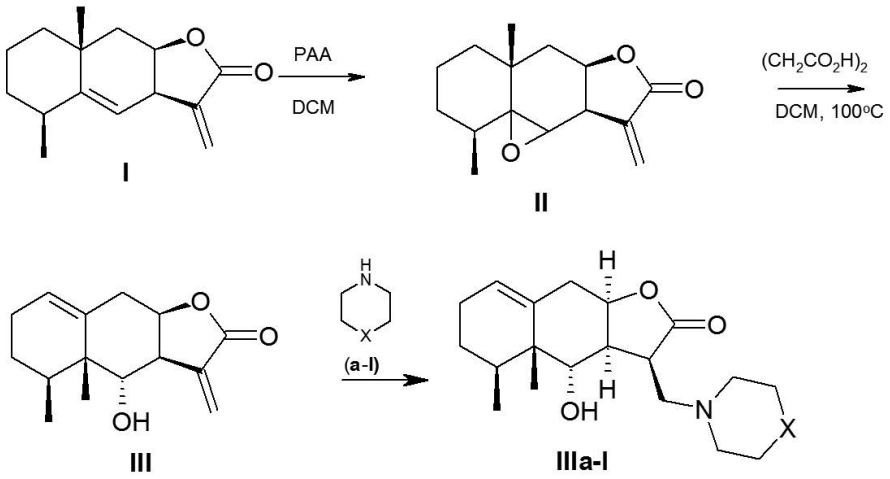
It is known that natural sesquiterpene lactones and their amino derivatives have a cytotoxic effect [1]. The natural sesquiterpene lactone of the eremophilane series, 6-hydroxyxanthanodiene (**III**), obtained from the readily available component of the plant *Inula helenium* L. alantolactone (**I**) via epoxy derivative **II** [2] was chosen as the object for amination. Lactone **III** react easily with N-nucleophiles (pharmacophoric piperidines and piperazines) by Michael-type addition.



X = C(OH)NC_6H_4Cl-4 (**a**), C(OH)Bn (**b**), NCO_2Et (**c**), $NC_6H_4CF_3$-3 (**d**), NC_6H_4F-4 (**e**), NC_6H_4OMe-4 (**f**), NC_6H_4OMe-3 (**g**), NC_6H_4Cl-3 (**h**), NC_6H_4CN-4 (**i**), $NCH(C_6H_4F\text{-}4)_2$ (**j**), NC_6H_3Me-2-Cl-5 (**k**), NPy-2 (**l**)

The obtained azino derivatives **IIIa-l** were tested against a number of tumor cell lines (A549, MCF7, HCT116, RD and Jurkat), many of them showed cytotoxic activity at the level of

10^{-7}–10^{-8} mol/l. The leading compounds were found, which confirms the promise the use of such molecules for the development of modern anticancer drugs.

The work was performed in the framework of the State assignment (№ 0090-2017-0018).

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Development of methods for the synthesis of 4-hydroxyimino-5-polyfluoroalkylpyrazol-3-ones and evaluation of their biological properties

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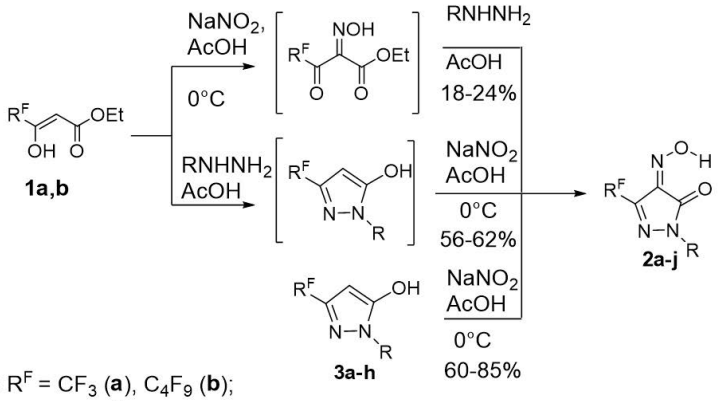
A pyrazole scaffold presences in a number of compounds using as drugs (metamizole, celecoxib, phenylbutazone, edavarone, etc.) [1, 2]. Thus, it is necessary to create the new derivatives of this class and the investigation of their biological properties. We have suggested the various approaches to the synthesis of 4-hydroxyimino-5-polyfluoroalkylpyrazol-3-ones **2a-j** [3], where an one-pot subsequent treatment of polyfluoroalkyl-3-oxoethers **1a,b** with hydrazine and sodium nitrite in acetic acid was the simplest and convenient route. However, the nitrosation of the early prepared 3-polyfluoroalkylpyrazol-5-ols **3a-h** was the most productive (yields is up to 85%) method. Among obtained pyrazolones **2** were revealed the compounds with analgesic activity comparable to diclofenac. The introduction of a substituent to the atom N1 promoted to increase the analgesic activity. In addition, compounds **2** demonstrated a moderate antiradical activity. All compounds are less toxic than diclofenac.



1: R^F = CF_3 (**a**), C_4F_9 (**b**);
2,3: R = H, R^F= CF_3 (**a**), C_2F_5 (**c**), $H(CF_2)_2$ (**e**), C_3F_7 (**f**), C_4F_9 (**g**);
R = Ph, R^F= CF_3 (**b**), C_2F_5 (**d**), C_4F_9 (**h**); R = Me, R^F = CF_3 (**i**), C_4F_9 (**j**)

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Pd^{II}-catalyzed C–H/N–H cross-coupling of 2*H*-imidazole 1-oxide with azoles in the design of novel biheterocyclic systems

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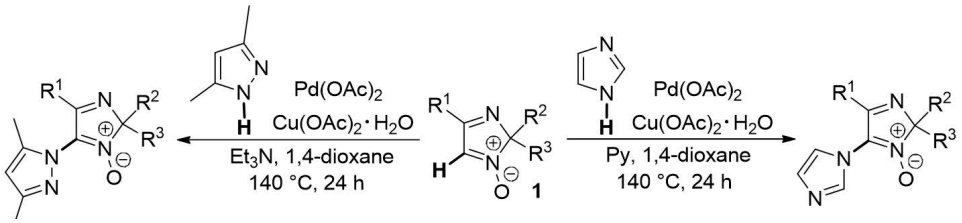
2*H*-Imidazole 1-oxide derivatives **1** (Scheme 1) represent non-aromatic compounds belonging to a class of cyclic nitrones, which are known to be of interest in the recent years. This is accounted for the specific properties inherent in such *N*-oxide-containing molecules. In particular, it has been shown that due to their spin-trapping capabilities, these azaheterocycles can be applied not only for analytical purposes, but also as potential antioxidant agents.

Earlier, we developed in our research group a number of strategies towards the direct C(sp^2)–H modification of 2*H*-imidazole 1-oxide derivatives **1**, leading to the formation of novel C–C bonds. These include an approach towards the Pd^{II}-catalyzed functionalization of such nitrones with five-membered π-excessive heteroarenes fragments. [1,2] Later, however, we found out that the application of catalytic conditions, essentially identical to those used in the above method, can also contribute to the generation of new C–N bonds in case of interaction with π-amphoteric azoles, such as 1*H*-imidazole or 3,5-dimethylpyrazole (see Scheme 1). Structures of the C–H/N–H coupling products obtained were confirmed via both 2D NMR spectroscopy and X-ray diffraction studies.



Scheme 1. *Pd^{II}-catalyzed C–H/N–H cross-coupling of 2**H**-imidazole 1-oxide with azoles*

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New derivatives of hydroxamic acids as highly effective antioxidants

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Oxidative stress plays a leading role in the development and progression of many human diseases primarily due to the intensification processes of lipid peroxidation (LPO) in biological membranes by the action of free radicals. It leads to the disruption of mitochondrial function and as a consequence to the release of apoptogenic factors and cell death. Cyclic hydroxamic acids (CHA) are interesting as agents, which inhibit oxidation processes. In addition to the complex antioxidant activity, these compounds also modulate the action of the enzymes such as histone deacetylase and lipoxygenase which are involved in the development of cancer and neuro-inflammatory processes.

A number of new cyclic hydroxamic acids, which are derivatives of 3-hydroxy-2,3-dihydroquinazoline with a spirocyclic fragment, have been synthesized and antioxidant potential of these compounds have been investigated in this work.

When we studied the biological activity of the researched compounds, it was found that most of them showed the effective inhibiting ability of LPO initiated by both Fe(II) ions and tert-Butyl hydroperoxide. This suggests that the antioxidant activity of CHA associated with both their iron chelating and anti-radical properties. The ability of hydroxamic acids to form coordination bonds with iron ions and directly bind free radicals was studied, when establishing the mechanism of antioxidant activity. Thus, the percentage of Fe(II) ions binding by CHA OVF-29, OVF-33-50 varied from 65% to 78%, and antiradical activity was found for 17 of the 18 studied compounds. These results indicate a high antioxidant activity of cyclic hydroxamic acids and allow us to consider these compounds as the basis for the creation of potential therapeutic agents.

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Mucoadhesive liposomes as carriers of antiviral and antituberculosis drugs

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Liposomes are excellent carrier systems in a variety of applications and are particularly ideal for drug delivery to the tissues due to their similarity to natural cells. Indeed, the therapeutic index of various drugs can be increased through their incorporation into liposomes, which can act as a non-toxic, biodegradable system for solubilizing drugs of low aqueous solubility. Addition of positive charged small molecules and biopolymers to liposomal compositions may produce liposomes with a prolonged release and mucoadhesive properties. To date, most of the concern about mucoadhesive liposomal systems has been focused on chitosan coated negative liposomes. In the European Union and USA these systems are approved for biomedical use in nasal drug delivery [1].

Our research group is focused on chemical modification of liposome surface with following evidence of mucoadhesive properties. In this case, the side groups introduced into the liposome structure provide electrostatic repulsion and additional steric stabilization in solutions. Mucoadhesive activity is usually explained on the basis of attraction underlying interaction between liposomes surface and mucin secreted from epithelial cells. Therefore, we introduce positively charged additives like palmitoylcholine and biopolymers like modified chitosan [2].

The aim of the present work was to obtain stable mucoadhesive liposomes loaded with hydrophobic antiviral drug Rimantadine and to define the release profile of this active substance. We tested the possibility of obtaining positively charged liposomal composition and its coating with modified biopolymers. The obtained liposomal form was shown to be stable for three months or longer and possess high mucoadhesive properties. In addition, the optimal parameters were determined for producing liposomal carriers for the delivery of another hydrophobic drugs with antituberculosis activity.

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Minor natural sesquiterpene lactones isotelekin, reynosin and santamarine as a platform for the creation of antineoplastic drugs

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The actual problem of current medicinal chemistry is the search for new groups of highly effective and low-toxic antineoplastic drugs. We assumes the use of the minor natural sesquiterpene lactones, isotelekin, reynosin, and santamarine, as a platform for the creation of such therapeutics, the biological properties of which have been poorly studied due to the low content of these compounds in plants. As a rule, drugs of plant origin, which possess antitumor and antimetastatic properties, have complex activity and are better tolerated by the body. We propose a new approach to the synthesis of minor sesquiterpene lactones, which makes it possible to obtain them in quantities sufficient for carrying out pharmacological studies. Preparative methods for the preparation of isotelekin, reynosin and santamarine from readily available lactones of isoalantolactone and costunolide are developed.

The cytotoxic activity of these compounds with respect to lines of tumor cells RD (rhabdomyosarcoma), A549 (lung carcinoma), HCT116 (colon carcinoma), and MCF7 (breast adenocarcinoma) was measured by the MTT-test. The test results showed that the cell line MCF7 is the most sensitive to the action of isotelekin, the cell line RD is the most sensitive to the action of reynosin and the cell line HCT116 is the most sensitive to the action of santamarine (see the table).

Table

Cytotoxicity of isotelekin, reynosin and santamarine

Compounds	IC_{50}, μM			
	A549	HCT116	MCF7	RD
Isotelekin	67.50±6.11	42.25±4.47	39.06±2.62	63.52±1.96
Santamarine	156.85±10.22	47.03±0.53	74.15±0.43	85.24±1.45
Reynosin	120.72±5.18	71.71±2.06	75.68±5.03	32.65±1.09

The study of the mechanisms of the antiproliferative effect of isotelekine, reynosine, santamarine will help elucidate the fundamental aspects of the biological activity of the sesquiterpene lactones of the Asteraceae family, and thereby contribute greatly to the development of medicinal chemistry of natural compounds.

The work was supported by RFBR Grant №18-33-00567-мол-а.

CONSENSUS PREDICTION OF ACUTE TOXICITY OF RAGE RECEPTOR INHIBITORS

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The aim of the research was a consensus prediction of acute toxicity LD_{50} oral for rats and the toxicity class of RAGE inhibitors with different levels of activity.

183 RAGE inhibitors were clustered on activity to 4 groups: 38 high active, 61 moderate active, 39 low active and 45 inactive. For all compounds, a prediction of acute toxicity LD_{50} oral for rats and toxicity class C_{tox} was performed using GUSAR and ProTox-II internet resources and original Microcosm ADMET system. The consensus estimates of LD_{50} and C_{tox} were calculated as the arithmetic mean of the three primary estimates. In each group of RAGE inhibitors, the medians and 95% confidence intervals for them in the series of consensus estimates of LD_{50} and C_{tox} was determined.

The following median estimates of toxicity for 4 groups of RAGE inhibitors were obtained: high active – LD_{50} = 1415 (1330 – 1689) mg/kg, C_{tox} = 4 (4 – 4); moderate active – LD_{50} = 1500 (1387 – 1795) mg/kg, C_{tox} = 4 (4 – 4); low active – LD_{50} = 1276 (1115 – 1561) mg/kg, C_{tox} = 4 (4 – 4); inactive – LD_{50} = 1475 (1163 – 1885) mg/kg, C_{tox} = 4 (4 – 4). In terms of toxicity classes, the compounds were distributed as follows: high active – 86,8% 4th class and 13,2% 5th toxicity class ; moderate active – 81,9% 4th class and 18,1% 5th class; low active – 92,3% 4th class and 7,7% 5th class; inactive – 91,1% 4th class and 8,9% 5th toxicity class.

Thus, according to the sets of two median estimates, RAGE inhibitors belong to the class of low toxic substances.

Performed using three different computer systems, a consensus prediction of acute toxicity indicators of RAGE inhibitors showed that these compounds belong to the class of low toxic substances. The obtained data can be used to search for new low-toxic inhibitors of RAGE receptors.

The work was funded by the Russian Foundation for Basic Research, 18-015-00499 project.

Anti-glycating and antiplatelet activity of some 3,6-disubstituted 1,2,4,5-tetrazines

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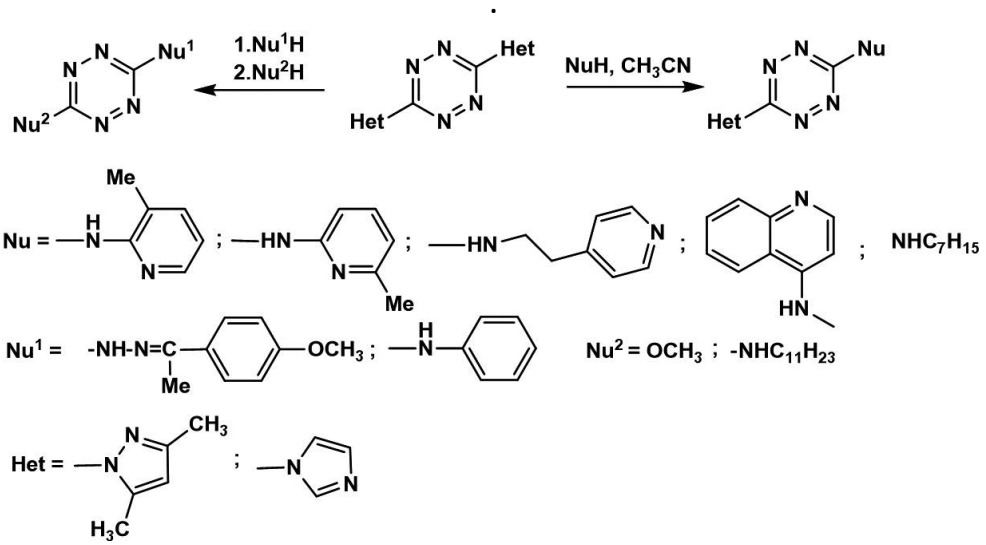
A number of 3,6-disubstituted 1,2,4,5-tetrazines, potential inhibitors of the Maillard reaction, have been synthesized based on quantum chemical prediction of biological activity. A series of compounds with high antiglycating activity was found. The effect of the identified glucose protein glycation inhibitors was studied on a model of ADP-induced rabbit platelet aggregation in vitro. Seven compounds definitely inhibited platelet aggregation. Two compounds showed the highest antiplatelet activity, significantly exceeding the reference drug, acetylsalicylic acid.



The set of biological effects of these compounds is actual for modern medical chemistry.

The work was performed in the framework of the project of the state task AAAA-A19-119011790134-1 using the equipment of the Center for Collective Use "Spectroscopy and Analysis of Organic Compounds" (PCU "SAOC»).

Hydroxylated imidazo[4,5-b]pyridine derivatives - potential antidiabetic agents

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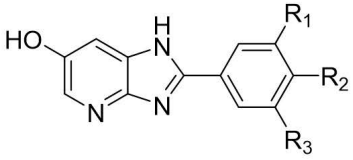
National Research Mordovia State University, 430005, Russia, Saransk, Bolshevistskaya, 68

The restoration of the functional mass of beta-cells is an important therapeutic goal in the treatment of diabetes mellitus of both type 1 and 2. It was shown [1], that stimulation of beta-cell proliferation is mediated by the inhibition of the DYRK (dual-specificity tyrosine-regulated kinases) and CLK (CDC-like kinases) family kinases. It is known that imidazo[4,5-b] pyridine derivatives [2] can act as promising double inhibitors of DYRK1/CLK1. On the other hand, given the important role of lipid peroxidation activation in the pathogenesis of diabetes mellitus, the positive effect of antioxidant-type preparations, in particular, pyridinol-3 derivatives, was established in the treatment of this pathology [3].

In the course of our study, a number of new hydroxylated imidazo[4,5-b]pyridine derivatives containing a pyridinol-3 fragment were synthesized.



R_1	R_2	R_3
H	OH	H
OH	OH	H
OH	H	OH
OH	OH	OH

Derived derivatives can be considered as potential antidiabetic agents, the activity of which is due to the possibility of exposure both through inhibition of kinases and by suppressing lipid peroxidation processes.

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Synthesis of Intermediates for Preparation of d,l-3,4-Dihydroxyphenylalanine

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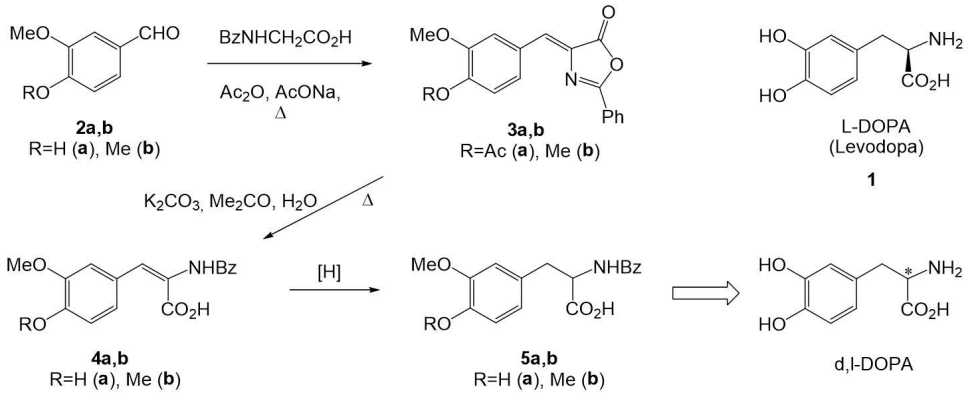
Levodopa **1** is an important drug for the treatment of Parkinson's disease and is used as a natural precursor for the in-vivo synthesis of dopamine, an endogenous neurotransmitter, the concentration of which is reduced in people with this disease [1].



A method for the synthesis of racemic d,l-dioxyphenylalanine (DOPA) via series of intermediates, including 2-benzamido-3-arylpropanoic acids **5a,b**, is proposed. At the first step, according to the classical method of the synthesis of azlactones [2], vanillin **2a** is condensed with hippuric acid giving of azlactone **3a** (89%).

In the second step, the azlactone ring is opened, leading to trans-benzamidocinnamic acid **4a** (55%). At the same time, the hydrolysis of the acetoxy group occurs, although it was shown in a previously published work, that the acetoxy group retains after **3a** was hydrolized under similar conditions. Then benzamidocinnamic acid **4a** is reduced to N-benzoyl-O-methylDOPA **5a**, a key intermediate in the synthesis of racemic DOPA. This synthetic scheme was also performed using veratraldehyde **2b** as the starting compound.

Therefore, proposed methods of synthesis of intermediates **5a,b** are attractive due to simplicity of implementation, good yields and low cost of starting materials.

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Synthesis and biological activity of polyfunctional pyrazoles based on trifluoroalkylated 1,2,4-triketone analogs

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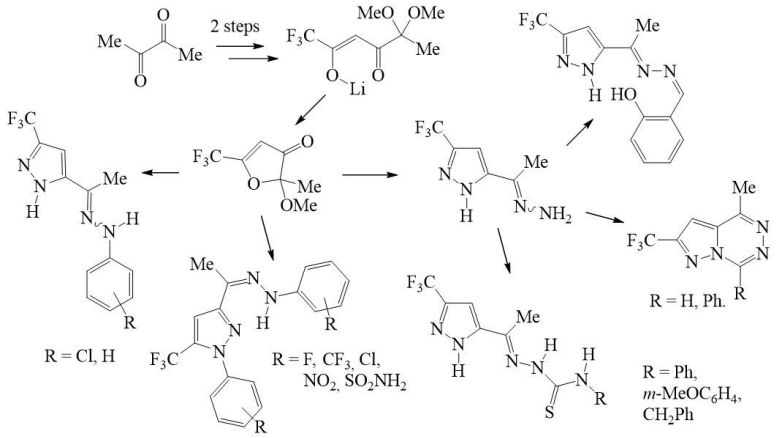
The search for compounds with a multi-target activity is considerably increased in the past decade. In this context, functionalized pyrazoles are of great interest due to the broad spectrum of their biological activities. Recently we have elaborated a useful approach to polysubstituted pyrazoles based on 1,2,4-triketone analogs [1-3]. The investigations of synthesized compounds have revealed the promising low toxic bioactive candidates. The introduction of thiosemicarbazone fragment in the structures of pyrazoles resulted in high antioxidant and analgesic activity. In addition, thiosemicarbozones demonstrated high cytotoxicity for cancer cells of the HeLa line, combined with low toxicity for normal human fibroblasts. There are several examples with moderate anti-*M. Tuberculosis* activity.



The work was financially supported by the Russian Foundation for Basic Research (project № 18-33-20124). K.Y.S. is thankful to the Council for grants of the President of Russian Federation (grant no. 1453.2019.3).

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Synthesis of 2-substituted 6-polyfluoromethyl-4-pyrimidinecarbaldehydes

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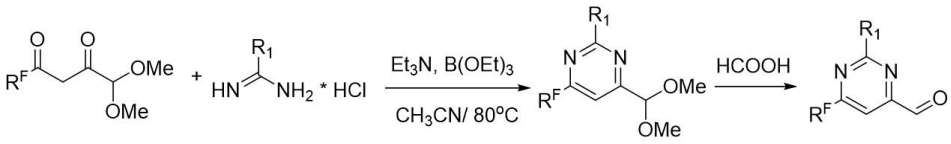
Pyrimidines and their derivatives are of great interest owing to a wide spectrum of their biological activity, namely anticancer, antiviral, antibacterial, anti-inflammatory and other. Therefore, synthesis of the novel pyrimidine derivatives remains an actual goal.

Recently we have described 3-(polyfluoroacetyl)pyruvaldehyde dimethyl acetals – a novel fluorinated building-block [1]. They can be used for the synthesis of heterocycles containing both fluoroalkyl and aldehyde groups in their structure. The aldehyde group is of considerable interest for further modification of the resulting heterocyclic compounds [1, 2].

Here we report on application of this building-block for preparation of fluorine-containing pyrimidine-4-carbaldehydes. It was found that 3-(polyfluoroacetyl)pyruvaldehyde dimethyl acetals react with amidines in refluxing acetonitril affording the substituted pyrimidine-4-carbaldehyde dimethyl acetals. However, the conversion of reagents was incomplete in 12 hours. We found that addition triethylborate accelerats significantly the heterocyclization (full conversion in 4-8 hours). As a result, 2-substituted 6-R^F-4-pyrimidinecarbaldehyde dimethyl acetals were isolated in high 74-96% yields.



R^F = CF_3, HCF_2
R_1 = Ph, 3-Py, 1-pyrazolyl

Hydrolysis of their acetal group in acid condition furnishes the corresponding 6-R^F-4-pyrimidinecarbaldehydes in good yields.

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Synthesis and biological evaluation of 3- arylidene 2-oxindole derivatives as new agents for treatment of diabetes mellitus

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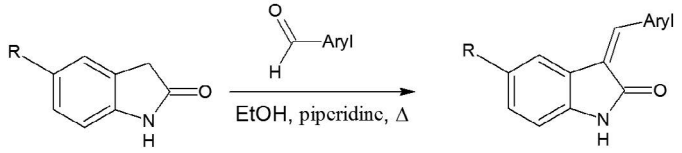
2-Oxindole scaffold was used for targeted design and synthesis of a number of novel compounds with pronounced antidiabetic activity[1]. Condensation of 2-oxindoles with 2-substituted heteroaromatic aldehydes was E/Z selective and resulted in one isomer predominancy.



43 - 99 %

R = H, BzNH, (2-furoyl)NH, $CH_3C(O)NH$, MeOC(O)NH, Br, NO_2
Aryl = 2-pyridyl, 4-Br-Ph, 4-OH-Ph, 3,4,5-tri-MeO-Ph, 3-OH-Ph, 4-NO_2-Ph, 3-pyridyl, 4-pyridyl, 2-thienyl, 2-furyl, 3,4-dimethyl-pyrazol-4-yl

The inhibitory activity of obtained compounds was tested *in vitro* on two molecular targets for diabetes mellitus therapy, glycogen synthase kinase 3β (GSK-3*β*) and α-glucosidase [2,3,4]. The lead compounds were shown to inhibit GSK-3*β* and *α*-glucosidase with IC_{50} 4.19 nM and IC_{50} 6.78 *μM* respectively. Even though GSK-3*β* ligands and α-glucosidase inhibitors share similar scaffold, lead compounds in screenings on these two molecular targets were structurally different which suggests a possibility for further structural optimization and search for selective ligands based on 2-oxindole scaffold for both enzymes. Lead compounds for each of two enzymes displayed significant antidiabetic effect in oral glucose tolerance test in rat model of type 2 diabetes mellitus.

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Synthesis and hypoglycemic activity of 2,4,5-trifluorostilbene derivatives

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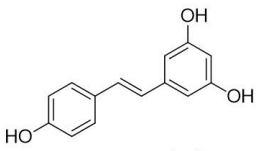
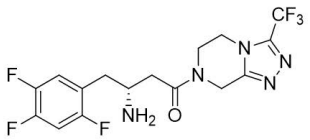
Diabetes mellitus type 2 is a metabolic disease characterized by impaired glucose control in the blood. Among modern oral medications used in the treatment of DM-2, a significant share of the market is occupied by drugs that inhibit DPP-4 (gliptins). The advantages of this class of compounds are that they do not cause hypoglycemia, so they do not act when the level of glucose in the blood is normalized. Some of the natural compounds, such as resveratrol, has ability to inhibit DPP-4. Despite the fact resveratrol has a high affinity for DPP-4 and binds to the same binding site as gliptins, its action is extremely non-selective [1].

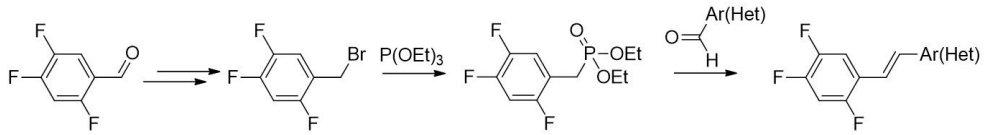
We have synthesized compounds containing a vinylphenyl fragment, which is common to natural DPP-4 inhibitors, including resveratrol, with a 2,4,5-trifluorophenyl structural unit of the marketed drug sitagliptin, whose specific binding to the active site of the enzyme has been confirmed by numerous studies. New compounds were synthesized in 4 stages with good yields using commercially available 2,4,5-trifluorobenzaldehyde and various aromatic aldehydes. Some of them showed hypoglycemic activity in GTT in mice at a dose of 10 mg/kg.



resveratrol,
IC_{50}=0,8 nM



sitagliptin



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Esters of 3-oxo-2-tolylhydrazinylidene-4,4,4-trifluorobutanoic acid and natural alcohols as new selective carboxylesterase inhibitors

Boltneva N.P.[1], Serebryakova O.G.[1], Lushchekina S.V.[1,2], Rudakova E.V.[1], Elkina N.A.[3], Shchegolkov E.V.[3], Radchenko E.V.[4], Palyulin V.A.[4], Burgart Ya.V.[3], Makhaeva G.F.[1], Saloutin V.I.[3], Richardson R.J.[5]

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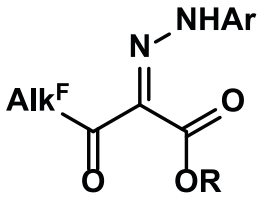
Carboxylesterases (CES, EC 3.1.1.1) are key enzymes of hydrolytic metabolism for major therapeutic agents that contain ester groups. Inhibitory activity of 3-oxo-2-tolylhydrazinylidene-4,4,4-trifluorobutanoates bearing natural alcohol moieties (R) of the general formula **I**



I

against porcine liver CES and two isoforms of human CES (hCES1 and hCES2), along with two related serine hydrolases, acetylcholinesterase and butyrylcholinesterase, were investigated using enzyme kinetics and molecular docking.

Analysis of the esterase profile demonstrated that these compounds are effective and highly selective inhibitors of CES. Moreover, the esters **I** based on geraniol and adamantol are nanomolar inhibitors of hCES2, while the bornyl- and isobornyl-containing esters **I** are more active and selective against hCES1. All compounds have favorable ADMET profiles, possess high antiradical activity, and exhibit low acute toxicity. The tested compounds are of interest as potential candidates for CES inhibition in biomedical applications.

This work was supported by Russian State assignment 0090-2017-0019 to IPAC RAS (biological assay) and AAAA-A19-119011790134-1 to IOS UB RAS (synthesis).

STUDY OF THE STRUCTURE AND PROPERTIES OF PERSPECTIVE MEDICAL MATERIALS BASED ON Ti-O-N SYSTEM

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The study of thin bioactive titanium-based films has recently attracted unabated interest due to the importance of the problem of increasing of medical implants resistance. The oxynitride coatings with the formula TiN_xO_y are widely used as a biocompatible coating of the medical implants [1]. Doping of the oxide film by nitrogen with technological replacement of oxygen by nitrogen atoms changes the properties of the material: antithrombogenic qualities appear and the level of hemocompatibility increases.

The purpose of this work was studying the influence of sputtering regimes and the composition of the sprayed gases on the structure and properties of the coating. Samples of biocoatings were obtained by the method of reactive magnetron sputtering using the experimental setup UVN-200MI, (TPU, Tomsk) [2]. For the estimation of coatings corrosion properties we used modern spectral analysis methods such as: gas chromatography, polarization method for studying the anodic behavior of the Ti-O-N ternary system. It was revealed a number of unique properties of the biocoatings: chemical and thermal stability, corrosion resistance in various biological environments. Upon contact with model biological fluids, compounds with N – O bonds are released from the coating forming nitrite / nitrate of nitrogen, which is an important compound for a living organism [3].

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Reactions of 10*H*-spiro[anthracene-9,5′-oxazolidin]-10-ones: synthesis of substituted pyrrolidines

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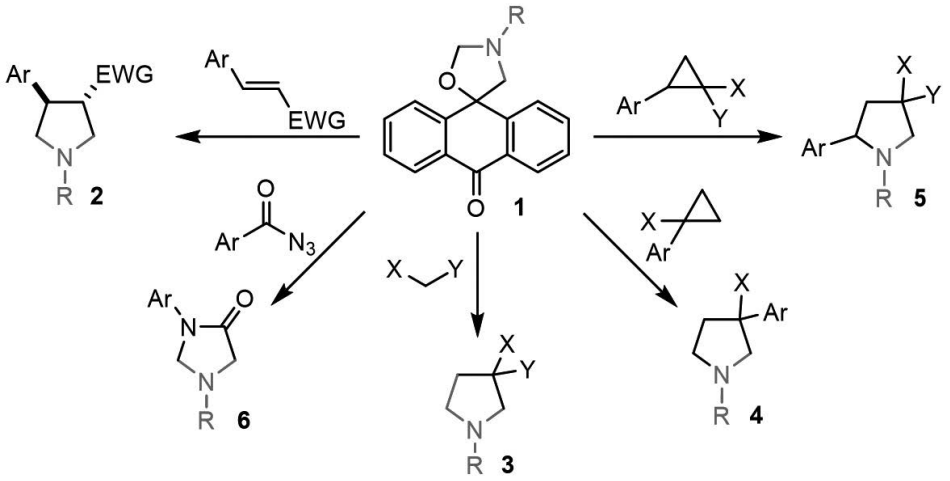
In order to develop new convenient and straightforward approaches to the synthesis of various azaheterocycles, including natural compounds, as well as saturated azaheterocycles with potential biological activity, the main direction of research in our laboratory is the reactions of nonstabilized azomethine ylides.

Proposing methodology is based on the cycloreversion of 10*H*-spiro[anthracene-9,5′-oxazolidine]-10-ones **1**, readily available from anthraquinone, *N*-alkylglycine and paraformaldehyde. These spiro-oxazolidines possess an ability to regenerate nonstabilized azomethine ylide at temperature above 120 °C. It was found that spiroanthraceneoxazolidines **1** possess a versatile reactivity and able to form substituted pyrrolidines **2**–5 with various starting materials: activated alkenes, active methylene compounds or cyclopropanes *via* domino process. Spiro-oxazolidines **1** also can be used for the synthesis of oxazolidines, aminoalcohols or imidazolidin-4-ones **6**.



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Novel 5-cyanopyrimidine derivatives induces inhibition EGFR signaling pathways in cancer lines

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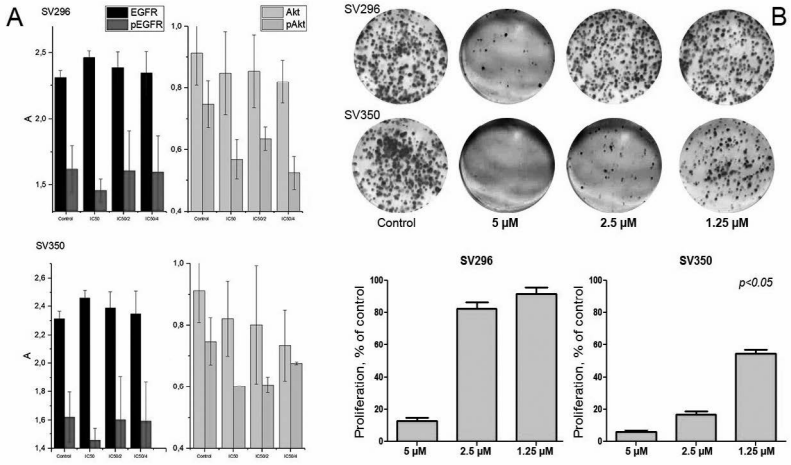
To identify novel EGFR inhibitors with better biological function, a 5-cyanopyrimidine-based compound library containing 48 derivatives was synthesized and compared in the present study. The in vitro cytotoxic activity of all compounds was screened against 7 cancer cell lines (T47D, SK-BR-3, MCF-7, HaCaT, A375, A549, A431) by MTT cell viability assay. The results indicated that all compounds exhibited certain degree of inhibition to cancer cells in range (IC_{50}=0.485–49 μM), in which compounds SV296 and SV350 displayed excellent cellular activity. To investigate the effect of selected compounds on signal transduction mechanism, we performed In-Cell ELISA colorimetric assay of EGFR and its downstream signaling pathways: extracellular signal regulated kinase (ERK1/2) and Akt. As shown in Fig. 1A, A549cells that express high EGFR were treated with IC50 concentrations of SV296 and SV350 and demonstrated a decrease in phosphorylation of EGFR and Akt, but not ERK1/2. Also, we study the effects of SV296 and SV350 on colony-forming potential of A549 and A431 cell line (Fig.1B). Both compounds significantly inhibited the clonogenicity in A549 and A431 cells. Therefore, selected SV296 and SV350 derivates may be promising for further development of novel EGFR inhibitors.



The reported study was funded by RFBR according to the research project № 18-015-00321, and partly research project № 18-33-00666.

Novel 5-cyanopyrimidine derivatives induces apoptosis in THP-1 and A549 cancer cell line

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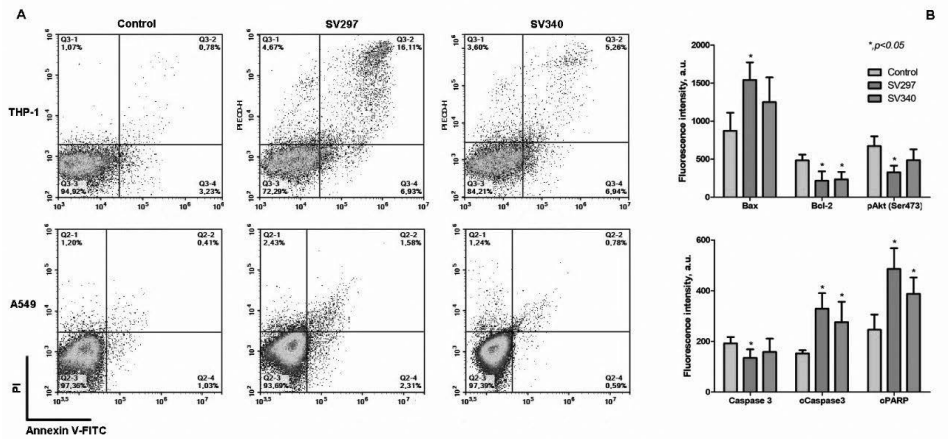
To identify novel 5-cyanopyrimidine derivatives with better cytotoxic action we performed apoptosis analysis by flow cytometry and evaluate expression of apoptosis mediators in cancer cells. For this a 5-cyanopyrimidine-based compound library containing 48 derivatives was synthesized and the in vitro cytotoxic activity of all compounds was screened against A549 and THP-1 cancer cell lines by MTT cell viability assay. The results indicated that all compounds exhibited certain degree of inhibition (IC50) to THP-1 cancer cells in range 0.485–2.20 μM and A549 cancer cells in range 17.30–46.56 μM, in which compounds SV297 and SV340 displayed pronounced cytotoxic activity. To investigate the cytotoxic effect of selected compounds we performed the apoptosis analysis (Fig.1A). SV297 and SV340 compounds on THP-1 cells showed a decrease in the number of living cells to 72.29% and 84.21% after 48h of incubation, respectively. On A549 cells that were treated with IC50 concentrations of SV297 we demonstrated a slight decrease in in the number of living cells to 93.69% and without change in living cells counts for SV340. For both compounds we also study the mechanisms of apoptosis induction by immunofluorescence assay after 24 h incubation with compound (Fig.1B). As shown, induction of apoptosis by 5-cyanopyrimidine derivatives accompanied by a decrease in anti-apoptotic signaling molecules (bcl-2, pAkt (Ser473) and an increase in the expression of proapoptotic molecules (Bax, cCaspase-3, cPARP). Therefore, selected SV297 and SV340 derivates may be promising for further development of novel target inhibitors.



The synthesis of 5-aryl-azolo[1,5-a]pyrimidines – perspective therapeutic agents

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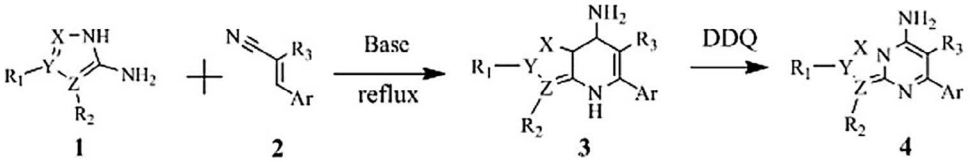
The development of the novel azoloazine-based therapeutic agents is still a relevant area of organic and medicinal chemistry. It has been established that derivatives of azolopyrimidines can be involved in the regulation of a wide range of biochemical processes, among which inflammatory processes take a special position. The limited range of azolo[1,5-a]pyrimidines 4 was obtained under the reaction conditions of Michael addition from the corresponding aminoazole **1** and benzylidenemalononononitrile previously **2 (**R2 = CN) [1].



1 **2** **3** **4**

X, Y, Z = N, C
R_1 = -H, -SMe, $-CH_3$, -furan-2'-yl, $-CF_3$
R_2 = -H, -COOEt
R_3 = -CN. $-NO_2$
Ar = -Ph, -Ph(4'-OMe), -Ph(4'-NMe_2), -furan-2'-yl

It is proposed to expand the series of azolo[1,5-a]pyrimidines in the present work (Scheme 1). One of the most attractive aspects of this work is the use of arylidenenitroacetonitriles(2, R2 = -NO2) [2] as a building block to obtain a previously unknown series of 5-aryl-6-nitro-7-aminoazolo[1,5-a]pyrimidines and corresponding azolo[5,1-b]purines. High affinity for adenosine A2a receptor in comparison with selective inhibitors was established by docking study for these compounds. One of the lead compounds - 7-amino-6-cyano-3-(2'-furyl)-5-phenyl(4'-methoxy)- [1,2,4]triazolo[1.5-a]pyrimidine has binding free energy -9.71 kcal / mol, which indicates higher affinity towards A2a receptor than affinity of the selective antagonist ZM241385 (-9.05 kcal/mol). Thus, compounds of this series can be considered as promising anti-inflammatory agents.

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Production of composites based on oxidized bacterial cellulose and prospidin in the form of porous napkins

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The aim of the study was to develop a method for obtaining the prolonged form of prospidin (N, NIII-Bis (2-hydroxy-3-chloropropyl) -NI, NII-dispyrotripiperazinium dichloride monohydrate) based on oxidized bacterial cellulose in the form of a porous napkin for local use in oncology and surgery.

In the system nitric oxide (IV) - trichloromethane, the influence of the conditions of dehydration of bacterial cellulose, oxidation and additional treatment of oxidized bacterial cellulose in the washing process on the composition, morphology of the polymer network, and water holding capacity is studied. A method has been developed for the inclusion of carboxyl groups in the range of 5.7 – 14.9% in the gel-films of bacterial cellulose with the maximum preservation of its porous structure. It has been established that oxidized bacterial cellulose undergoes biodegradation in phosphate buffer solution with pH = 7.4, the fullness and duration of which is determined by the content of carboxyl groups. The obtained samples of oxidized bacterial cellulose are elastic translucent films or sponges that rapidly swell in water (3-5 minutes). In appearance, wet gel films based on the interaction products of oxidized bacterial cellulose with prospidin are similar to the original bacterial cellulose, i.e. are super absorbent films that can sorb exudate in a wound.

The sorption ability of the synthesized porous napkins based on bacterial cellulose with different content of carboxyl groups in relation to prospidin was investigated depending on the concentration of cytostatic in aqueous solutions. It has been established that the obtained films of oxidized bacterial cellulose have a high sorption capacity with respect to cytostatics, a high degree of water absorption and elasticity. Based on the kinetic curves of prospidin release and biomedical research in *in vitro* experiments, it was concluded that the resulting wound tissue based on oxidized bacterial cellulose with included cytostatics has a prolonged antitumor effect.

GETTING TISSUE CULTURE CALLUNA VULGARIS L.

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Laboratory of Population Biology and Forest Dynamics, Botanical Garden, Ural Branch of the Russian Academy of Sciences, 620144, Russia, Yekaterinburg, 8 mattes, 202 a

The actual task of biotechnology is to obtain drugs from plant materials with a constantly high content of biologically active substances (BAS). The use of tissue culture methods for solving this problem has a number of significant advantages (independence from environmental conditions, year-round growth, high yield of biologically active substances) in comparison with the use of a plantation method of growing the resource base, as well as collecting plants from natural places of growth. Common heather (*Calluna vulgaris* L.) is a short, evergreen shrub included in various regional red books, the extract of which has more than 80 medicinal compounds, including phenolic acids, and exhibit antioxidant, anti-inflammatory and antiproliferative activity [1]. The main range of heather falls on the European part of Russia, as well as Europe, where it grows on the wet substrates and forms the heathland. In western Siberia, this species forms a disjunctive area, grows under the forest canopy and is rarely in open places, preferring to force itself near high bogs. With ecogeographic heterogeneity of growing conditions, heather is characterized by significant variability of the quantitative composition of biologically active substances in extracts. Since heather ordinary, being a promising pharmacopoeial plant, classified as a protected plant species, has a slow growth of vegetative shoots, weak renewal, as well as an unstable composition of biologically active substances, tissue culture can be considered the best way to obtain raw materials for pharmacology.

To date, strains of steadily growing callus culture in vitro have already been obtained, and in some culture strains it has been possible to increase the content of some biologically active substances (for example, chlorogenic acid, quercetin, kaempferol) in relation to plants that grow in natural conditions and become mother plants. The main objective of the study is to find factors that can increase the productivity of the culture, both for individual compounds and for groups in general. And the removal of stably growing strains of a culture of *C. vulgaris* with different controlled content of biologically active substances is a promising area of research.

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Synthesis of tetrahydro-5- (methylsulfonyl) oxocino [2,3-c] pyrazole-7-amine derivatives

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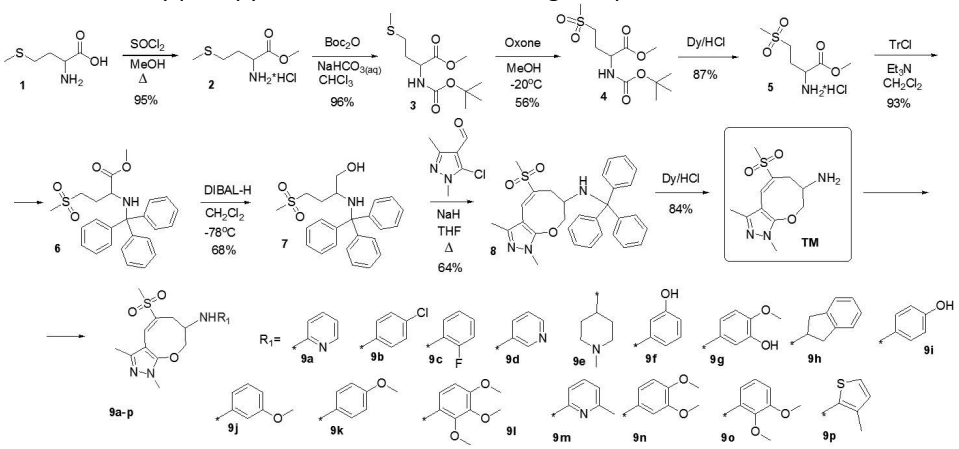
Pyrazole and its derivatives are widely used for the synthesis of a wide variety of heterocyclic compounds, and are also the starting material for the production of medicines. Interest in pyrazole derivatives is due to their wide range of biological activity. They inhibit the growth of tumors, have antiviral, antibacterial, antifungal effects, affect the central nervous system. In this regard, obtaining new derivatives of pyrazoles studying their properties, using as building blocks for the synthesis of other heterocyclic structures is an urgent and promising task.

For the synthesis of a focused library of tetrahydro-5- (methylsulfonyl) oxocino [2,3-c] pyrazole-7-amine derivatives (18 compounds) and the study of their biological activity, an effective synthetic strategy was proposed, allowing to obtain the target compound (TM) in eight stages from the commercially available amino acid methionine, with a total yield of 15%. It is important to note that with the use of L-methionine, it is possible to synthesize enantiomerically pure pyrazole derivatives according to a proven scheme.



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Acylative Kinetic Resolution of 6-Substituted 2-Methyl-1,2,3,4-tetrahydroquinolines with (*R*)-*O*-Phenyl Lactic Acid Chloride

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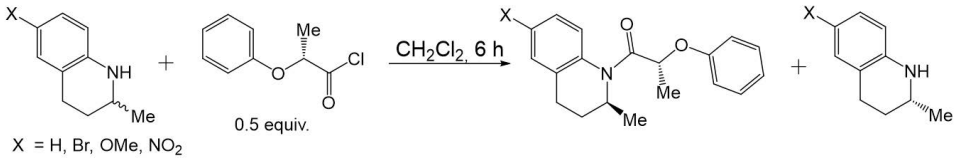
Kinetic resolution (KR) using diastereoselective acylating agents is a convenient method for the preparation of optically pure amines.

In this work, we studied the effect of donor and acceptor substituents in the aromatic fragment in the amine on the acylative KR of 6-substituted 2-methyl-1,2,3,4-tetrahydroquinolines with (*R*)-*O*-phenyl lactic acid chloride. The acylation was carried out in dichloromethane at +20 °C. The diastereomeric excess of the resulting amides (*de*) and the enantiomeric excess of unreacted amines (*ee*) were determined by HPLC. Based on the data obtained we were able to calculate the conversion of the starting racemate ($C = [ee_{amine}/(ee_{amine}+de_{amide})]\times100\%$) and the selectivity factor ($s = \ln[(1-C)\times(1-ee_{amine})]/\ln[(1-C)\times(1+ee_{amine})]$).



Amine, X =	**(*R,S*)-Amide*, de*, %**	**(*R*)-Amine*, ee*, %**	***C*, %**	***s***
H	**58.7**	**47.8**	**45**	**6**
Br	**64.2**	**32.4**	**34**	**6.2**
OMe	**62.9**	**62.3**	**50**	**8.1**
NO_2	**88.1**	**52.3**	**37**	**26.6**

It has been found that in all cases the (*R*)-*O*-phenyl lactic acid chloride reacts faster with the (*S*)-enantiomers of amines. Comparing the results of acylation of 6-substituted amines with unsubstituted, the following conclusions can be made: the presence of a bromine atom in the amine structure does not affect the selectivity of acylation, the presence of the donor MeO group leads to a slight increase in the selectivity (*s* 8.1), and the presence of an acceptor NO_2 group leads to the highest selectivity (*s* 26.6). The observed difference in selectivity is due to different interactions between the aromatic fragments of the reagents.

The work was financially supported by the Russian Foundation for Basic Research (grant no. 18-33-00027 mol_a)

Preparative HPLC Separation of Enantiomers of Praziquantel

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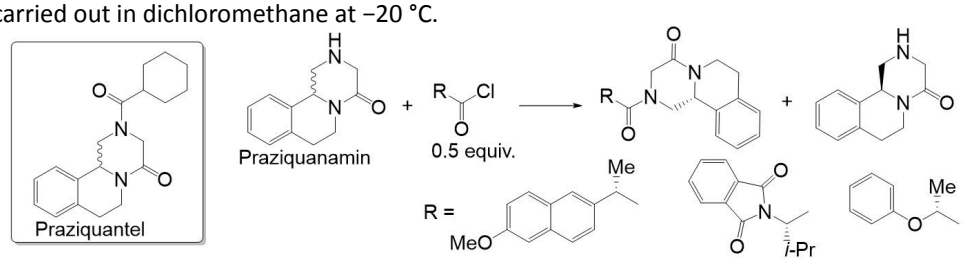
Praziquantel is a broad-spectrum antihelminthic agent. It is known that (*R*)-enantiomer exhibits a greater antihelminthic activity than (*S*)-enantiomer.

Enantiomers of praziquantel can be obtained by separation of the racemate by preparative HPLC or from the corresponding precursors, the enantiomers of praziquanamine, which can be obtained by acylative kinetic resolution using chiral acyl chlorides. In this work, we explored these two approaches.

The acylative kinetic resolution of praziquanamine with chiral acyl chlorides such as (*S*)-naproxen chloride, *N*-phthaloyl-(*S*)-leucyl chloride and (*R*)-*O*-phenyl lactic acid chloride was carried out in dichloromethane at −20 °C.



It has been found that all studied acyl chlorides react predominantly with (*R*)-enantiomer of praziquanamine, but the diastereomeric excesses of the amides obtained do not exceed 17%, which makes this method unsuitable for the preparation of praziquanamine.

Preparative HPLC separation of the praziquantel enantiomers was carried out on a Chiralcel OD-H (250×20 mm) chiral column, eluent hexane–*i*PrOH–MeOH 5:1:0.1, detection at 220 nm, flow rate 10 ml/min. The fractions containing individual enantiomers (*ee* 100%) were collected, and the fractions containing mixtures of enantiomers were re-resolved. The target product was crystallized from hexane. As a result, the individual enantiomers of praziquantel were obtained in 19% yield relative to the starting racemate.

The study was carried out in the framework of the State Assignment of Russia (theme no. AAAA-A19-119011790134-1).

Adamantylation of azolo-1,2,4-triazines

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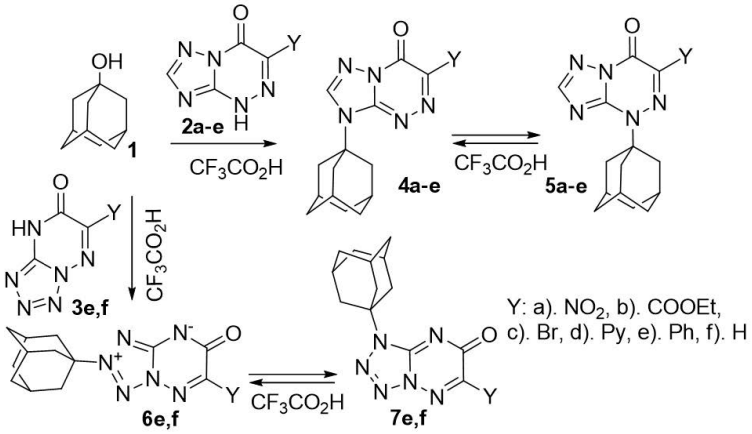
Incorporation of adamantane fragment into the structure of nitrogen-containing heterocycles is one of the approaches to the synthesis of compounds with a different spectrum of biological activity. The synthesis of tetrazole and imidazole derivatives containing the adamantyl fragment showed the efficiency of this method for obtaining compounds with activity against different strains of influenza viruses [1,2].

Herein, we report an efficient general method for incorporation adamatyl moiety into structure of 1,2,4-triazolo[5,1-*c*][1,2,4]triazin-7-ones **2a-e** and tetrazolo[1,5-*b*][1,2,4] triazines **3e,f** by use 1-adamantanole **1** in solution of trifluoroacetic acid.



The investigation of these processes allowed determination that adamatylation of compounds **2a-e** and **3e,f** led to formation of structures **4a-e** and **6e,f**, correspondingly. Then adamantylated derivatives **4a-e** and **6e,f** underwent isomerization to heterocycles **5a-e** and **7e,f**.

The study of the antiviral effect respiratory syncytial virus showed that structures **5a,b** possess moderate activity.

This work was supported by the Russian Ministry of Education and Science (State contract 4.6351.2017/8.9), the Russian Foundation for Basic Research (grant 17-03-01029).

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Design, synthesis and the pharmacological properties study of the novel dipeptide TSPO ligand

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The translocator protein (18 kDa, TSPO) is involved in cholesterol transport from the outer to the inner mitochondrial membrane, and it is the limiting step in the neurosteroids biosynthesis [1]. Neurosteroid hormones interact with the GABA receptor site, which differs from the benzodiazepine site and therefore have anxiolytic activity without side effects of benzodiazepine anxiolytics.

Using the original peptide design strategy [2], the first dipeptide TSPO ligand, N-carbobenzoxy-L-tryptophanyl-L-isoleucine amide (named GD-23), was obtained [3]. GD-23 expressed the anxiolytic activity in two pharmacological tests in rodents in the dose range of 0.1-1.0 mg/kg i.p. and p.o. Using the pharmacological inhibitory analysis the TSPO ligand properties of GD-23 have been proved [4]. The molecular docking of GD-23 using the Glide software specified the structure of the dipeptide ligand: the side chain of the isoleucine residue was replaced with a less branched leucine residue, and the carbobenzoxy moiety was replaced with a phenylpropionyl moiety. A new dipeptide ligand, the amide N-phenylpropionyl-L-tryptophanyl-L-leucine, was synthesized (named GD-102). GD-102 was obtained by the activated succinimide esters method. GD-102 possessed anxiolytic activity in doses of 0.01, 0.05, 0.1 mg/kg i.p. ($p < 0.05$) in the test "Illuminated open field" in BALB/c mice, in doses of 0.1, 0.5, 1.0 mg/kg i.p. ($p < 0.05$) in the test "Elevated plus maze" (EPM) in ICR mice Preliminary administration of the selective TSPO antagonist, compound PK11195, completely blocked the anxiolytic effect of GD-102 in the EPM test. GD-102 showed antidepressant activity in doses of 0.01 and 0.05 mg/kg i.p in BALB/c mice in the "forced swimming" test according to Porsolt technique.

A series of GD-102 analogues were synthesized and their structure - anxiolytic activity relationship was studied. It was shown that in the structure of the dipeptide ligand TSPO for the manifestation of the anxiolytic effect are necessary the presence of tryptophan and leucine residues in their natural L-configuration, N-phenylpropionyl radical, unsubstituted amide group at the C-terminus of the dipeptide.

Thus, we obtained a novel dipeptide ligand TSPO, compound GD-102 with the minimum effective dose in an order of magnitude lower than the effective dose of the previous dipeptide ligand, compound GD-23.

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Gramicidin S complex with β-cyclodextrin for innovative drug formulation

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Gramicidin S is a natural peptide which exhibits strong antibiotic activity towards Gram-negative and Gram-positive bacteria and several pathogenic fungi as well [1]. However, due to its hemolytic activity at low concentration Gramicidin S application is limited to the topical formulation [2].

In the present work, Gramicidin S was loaded in nanocomplexes based on β-cyclodextrine obtained by co-precipitation method [3].

The main aim was to release Gramicidin S overtime in a constant rate and under pH control to ensure its activity and avoid the side-effects.

The encapsulation efficiency of gramicidin S was determined as 25-30 % of the drug depending on the components ratio.

The obtained complexes were investigated using DLS, FTIR and SEM methods comparing to raw materials which have proved the encapsulation.

The release of the drug was performed at the solutions with pH 2.0, 4.3 and 7.4 resulting in different release profiles. In vitro assays reveals β-cyclodextrine-chitosan nanoparticles as promising candidate to develop innovative formulation based on Gramicidin S for future oral and parenteral administration.

Antimicrobial properties study of the complex in comparison with the raw materials demonstrated enhanced activity of the complex against *C. Albicnans*.

As a result gramicidin S complex with β-cyclodextrine can be regarded as promising antimicrobial agent which demonstrates a great potential for future drug development.

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New methods for the synthesis of biologically active triazolo [5,1-c] [1,2,4] triazines

Drokin R.A.[1], Tiufiakov D.V.[1], Voinkov E.K.[1], Ulomsky E.N.[1], Volobueva A.S.[2], Esaulkova Y.L., Sinegubova E.O.[2], Zarubaev V.V.[2], Rusinov V.L.[1]

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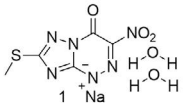
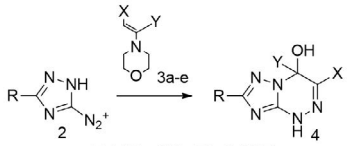
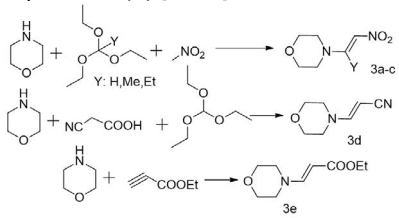
The antiviral drug "Triazavirin" (**1**) belongs to azolotriazine series - a class of compounds with a wide range of biological activity.



We have developed a new synthetic approach to the synthesis of triazolotriazines (**4**).



For synthesis of triazolotriazines (**4**) we synthesized a series of previously described derivatives of N-ethylenemorpholines (**3**) [1,2,3].



Biological activity of the synthesized triazolotriazines was studied at the Saint-Petersburg Pasteur Institute.

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The results obtained in the framework of the state order Ministry of Education of Russia (4.6351.2017/8.9)

Thermodynamics of formation of 4-aminobenzoic acid multi-component crystals

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4-Aminobenzoic acid (PABA) is known as vitamin B10 and is involved in the production of folic acid in bacteria [1]. PABA has been the subject of many scientific investigations, due to not only its pharmaceutical and biological properties, but also its ability to form various multi-component solid forms: salts, cocrystals, solvates, complexes with cyclodextrins and etc. Cocrystal formation of 4-aminobenzoic acid (PABA) has been screened with a variety of pyrimidine, pyridine and benzamide derivatives. Four new cocrystals with 6-methyluracil, barbituric acid, 2-hydroxybenzamide, 4-hydroxybenzamide and one salt with emoxypine have been successfully obtained from solvent evaporation experiments. All the solid forms are characterized by X-ray diffraction and thermal techniques. Thermodynamics of formation of PABA multi-component crystals with 6-methyluracil (6-MeUr), pyrazinamide (PyrAm) and emoxypine (EMX) was studied using two approaches: phase solubility diagrams and competitive reactions in planetary micromill. Phase solubility diagrams were constructed based on the solubility data of components in buffer pH 7.4 at 293 K, 298 K, 303 K, 308 K and 313 K. The order of magnitude for PABA multi-component crystals thermodynamic stability is [PABA+EMX]>[PABA+PyrAm]>[PABA+6-MeUr] in both used approaches.

This work was supported by the Russian Science Foundation (No. 17-73-10351)

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The effect of phenylsulfanyl (selenyl) derivatives of natural sesquiterpene lactones on the survival of neuroblastoma SK-N-MS cells under the toxic effect of hydrogen peroxide

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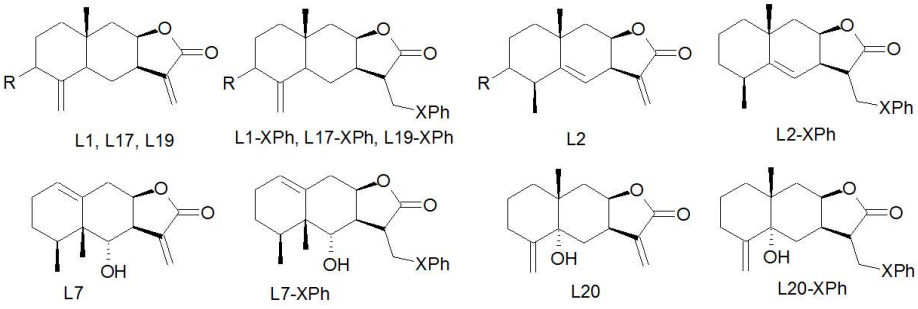
Neurodegenerative diseases, although different in nature, have common mechanisms of cell damage. Oxidative stress plays an important role in the pathogenesis of these diseases [1]. SPh-and SePh-derived sesquiterpene lactones of Asteracea family plants were synthesized and their effect on oxidative stress on SK-N-MC neuroblastoma culture cells was studied. The model of induction of neurotoxicity under the action of hydrogen peroxide was used. Pre-treatment of cells with lactones followed by exposure to H_2O_2 increased the percentage of viable cells compared to control (H_2O_2-treated) cells. We have previously shown that some of the investigated lactones have antioxidant properties [2].



X = S, Se; R = H (L1), b-OH (L17), a-OAc (L19)

It has been found that the introduction of both SPh and SePh groups into the L1, L2, L19, L20 lactones reduces their cytotoxicity. L1-SePh and L2-SePh have been shown to protect cells when toxicity is induced by H_2O2, in contrast to L1-SPh and L2-SPh. L17 also protects neuroblastoma cells as effectively as L2-SePh. The results revealed active compounds promising for the development of effective neuroprotective agents.

This work was supported by the RFBR grant No. 18-33-00567 mol_a.

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Drug development for the treatment of epilepsy

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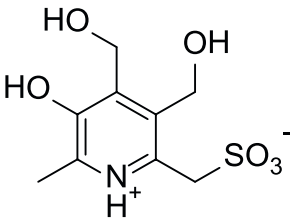
Approximately 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally. People with epilepsy respond to treatment approximately 70% of the time. Epilepsy has significant economic implications in terms of health care needs, premature death and lost work productivity. About three fourths of people with epilepsy living in low- and middle-income countries do not get the treatment they need [1].



KFU-06 is a first-in-class agent for the treatment of epilepsy [2,3]. It was discovered as a result of long-lasting project on synthesis and screening of CNS-active drugs. The mechanisms of its action is based on inhibition of glutamatergic neurotransmission, activation of GABA release from presynaptic neurons, and inhibition of postsynaptic GABA(A) receptors. The drug candidate penetrates the blood-brain barrier and forms a stable concentration in brain tissues demonstrating prolonged pharmacokinetics profile. Safety profile includes: low acute toxicity, LD_{50}>5000 mg/kg (mice and rats i.g.); LD_{50} >2000 mg/kg (mice and rats i.p.); LD_{50} >2000 mg/kg (rabbits i.g.); no influence on behavioral and psychoemotional status of rats at doses up to 100 mg/kg; low neurotoxicity after i.g. administration (daily for 1 month) at doses up to 250 mg/kg. *In vivo* efficacy of KFU-06 is comparable to the reference drug (sodium valproate) in models of corazol and picrotoxin induced seizures and significantly exceeds the reference drug in models of maximal electroshock and penicillin induced seizures.

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Synthesis methods of 5-substituted-6-nitroazolo [1,5-a] pyrimidines - precursors of structural analogues of Wyosine

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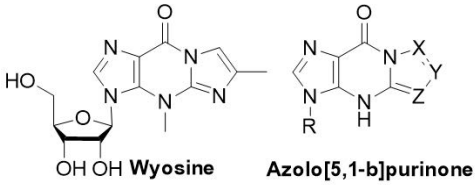
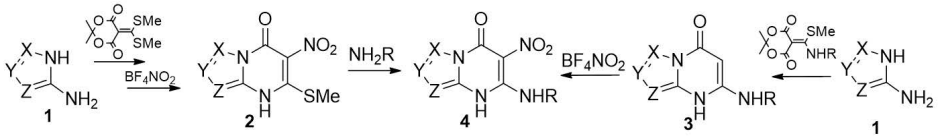
Post-transcriptional modifications are crucial to fine-tune the interactions of tRNA molecules with the other partners of the translation apparatus. One of the most hypermodified nucleosides are derivatives of Wyosine - linear imidazopurines. Such tricyclic modifications of guanosine are located in the $tRNA^{Phe}$ anticodon loop region - the area of the most complex modifications that require a number of enzymatic steps.

Structural analogues of Wyosine have the potential for competitive inhibition of enzymes whose substrate is modified linear tricyclic nucleosides. Such an impact disrupts the decoding, translation accuracy and integrity of tRNAs. Practical significance is revealed point of view of the search for antimicrobial and anticancer drugs.



This work presents methods for the synthesis of the precursors of azolopurins, potential inhibitors of the enzymatic reactions of the biosynthesis of hypermodified nucleosides.



The initial substrate is aminoazole **1**. The key to building the purine moiety is the placement of nitrogen-containing functional groups in 5 and 6 positions of the azolopyrimidine. In the framework of this work, this was achieved by nitration of the 6th position of thioanalogue **3** to obtain 5-methylthio-6-nitroazolopyrimidone **2.** The leaving group was subsequently replaced by an amine.

An alternative method is the nitration of 5-aminoazolopyrimidinone **3**, however, it should be borne in mind that the substituent at the N-atoms can be nitrated.

The results were obtained within the framework of the state task of the Ministry of education and science of Russia (4.6351.2017/8.9).

New express microwave-assisted synthesis of substituted 3-hydroxy-2-oxindoles for antiglaucomic drug discovery

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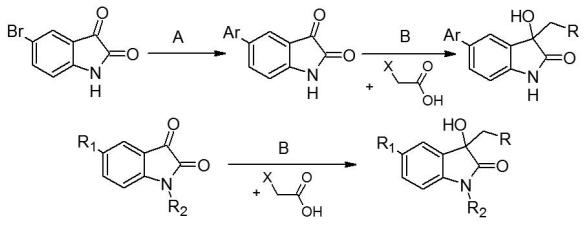
Suzuki reaction, catalyzed by Pd(dppf)Cl2 was used to obtain new 5-arylisatin compounds [1]. Novel 3-hydroxy-2-oxindole derivatives were synthesized using the microwave-assisted (MW) decarboxylative condensation of substituted isatins with malonic and cyanoacetic acids. Various compounds were synthesized using MW activation for 5-10 min with high yields (up to 98%). The binding affinity of synthesized compounds to quinone reductase 2 (possible molecular target for intraocular pressure (IOP) reduction) was analyzed using molecular docking simulation [2]. The influence of novel compounds on IOP was studied in vivo on normotensive rabbits. The obtained compounds were found to reduce the IOP nearly as fine as timolol (reference drug). Moreover, hypotensive effect of selected compounds appears to be way more long-lasting (>7 hours). Obtained results allow us to make an assumption about high efficiency of synthesized compounds in glaucoma therapy.



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Synthesis of Analgesic Active 5-Polyfluoroalkylpyrazolo[1,5-a]pyrimidines

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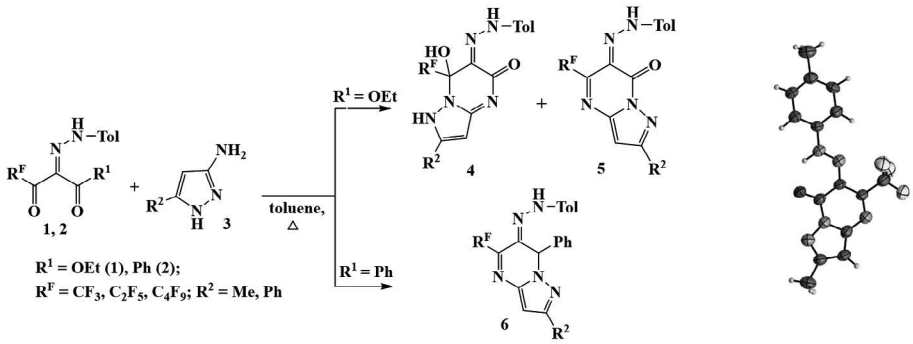
Pyrazolo[1,5-a]pyrimidines are promising for the creation of bioactive compounds [1]. Their derivatives are a basis for a wide class of sedative and anxiolytic drugs. We have developed a method for the synthesis of functionalized pyrazolo[1,5-a]pyrimidines based on the cyclization of polyfluoroalkyl-containing 2-arylhydrazono-1,3-dicarbonyl compounds **1, 2** with 5-aminopyrazoles **3**. Moreover, the cyclization of phenyl-substituted 2-tolylhydrazinylidene-1,3-diketones **2** into pyrazolo[1,5-a]pyrimidines **6** proceeded a regioselectively, while 2-tolylihydrazinylidene-3-oxoethers **1** formed analogous pyrazolo[1,5-a]pyrimidines **5** along with the stable 7-hydroxy-6-(2-tolylhydrazinylidene)-6,7-dihydropyrazolo[1,5-a]pyrimidine-5-ones **4**.



An investigation of the biological properties of the obtained heterocycles demonstrated an effective analgesic action of 5-polyfluoroalkylpyrazolo[1,5-a]pyrimidines **5** at the level of the reference drug diclofenac and higher in the “hot plate” test on SD rats. A study of acute toxicity in mice of the CD-1 line showed that these compounds at a dose of 300 mg/kg were non-toxic.

This work was financially supported by the Russian State assignment AAA-A-A19-119012490007-8.

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Study of antioxidant activity of substituted 1,3,4-*6H*-thiadiazines

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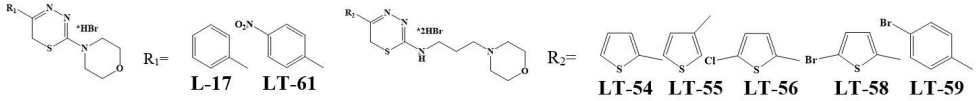
In previous studies, representatives of the 1,3,4-*6H*-thiadiazines class, characterized by the nature of the substituent in the provisions of the 2-and 5 - tiadiazine cycle, revealed a combination of antioxidant, antiglycative and antihyperglycemic action, which allows us to consider them as promising antidiabetic compounds [1]. The aim of the study was to identify the antioxidant activity of newly synthesized substituted 1,3,4-*6H*-thiadiazines for further selection of screening leaders in the experiment to assess the antidiabetic effect.

Investigated the antioxidant properties of the group of the synthesized compounds LT-54, LT-55, LT-56, LT-58, LT-59 (2-aminopropylmorpholino-5-aryl - and 2-aminopropyl-morpholino-5-heteryl-1,3,4-*6H*-thiadiazines, dihydrobromides), as well as compounds L-17 and LT-61 (2-morpholino-5-aryl-1,3,4-*6H*-thiadiazines, hydrobromides) *in vitro* to predict their action in the body in conditions of oxidative stress.



The redox properties of the compounds were studied in the pH=5-7 range. The method of cyclic voltamperometry of electrochemical activity was not registered in the entire pH range. However, activity with respect to the non-radical nature oxidizer potassium hexa-cyanoferrate (III) showed L-17, LT-59, LT-61 at pH=5-6. Antioxidant capacity of compounds decreased in the series LT-61>L-17>LT-59. Half-conversion periods ($\tau_{1/2}$) of these compounds amounted to 40-50 minutes, which is much higher than $\tau_{1/2}$ of natural antioxidants and could be of interest from the point of view of their prolonged action.

Thus, the results of the study allow us to recommend the compounds LT-61, L-17, LT-59 from the class of substituted 1,3,4-*6H*-thiadiazines for further study of antidiabetic activity.

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Anti-influenza activity of compounds of the class of azolo-azines in *in vitro* experiments

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Influenza virus is a cause of severe respiratory disease, which often results in dangerous health complications. Due to the characteristics of the viral genome, the virus is of high variability, which ensures the rapid development of resistance to clinically available anti-influenza drugs. As the consequence, there are annual epidemics of influenza that ending up with number of victims. Therefore, the study and search for new antiviral drugs is one of the most important tasks for scientific community. To complete this task, at primary stages of drug development the screening of libraries of chemical compounds *in vitro* is used.

The aim of the research was to study the anti-influenza activity of new compounds of the azolo-azine class.

The study was made *in vitro* on MDCK cell culture (Madin Darby canine kidney) using influenza A / Puerto Rico / 8/34 (H1N1) virus.

Infectious titer of the virus was evaluated in the presence of the compound in a range of concentrations: from 300 to 3 μg/ml. Cytotoxicity of each compound was evaluated using the methyltetrazolium test (MTT). Antiviral activity of the substances was evaluated using virus titration followed by its detection in the hemagglutination reaction with chicken erythrocytes. Based on the obtained data, values of 50% cytotoxic dose (CC_{50}), 50% effective concentration (EC_{50}), selectivity index (the ratio of CC_{50} to EC_{50}) were calculated for each compound. A compound was considered promising if the selectivity index value was higher than 10.

Among 32 compounds under investigation, 13 promising compounds were identified. Most of these substances appeared non-toxic *in vitro* at the studied concentrations (CC_{50}>300 μg/ml). The effective concentrations have been also calculated, for active compounds they were 3-25.2 μg/ml. Based on these data, we calculated the selectivity indices, which lay down between 11.3 and 57.1. That indicates a high selectivity of compounds and therefore one can call these compounds promising. Further research of given azolo-azine derivatives in *in vivo* systems is needed.

Thus, azolo-azines are a promising group of drugs and further development and research of compounds is required. It is also necessary to study toxicity and anti-influenza activity of given compounds using other strains of influenza virus and *in vivo* systems.

Sinthesis and antioxidative activity of 2-[5-(aryl)-6-R-3-phenyl-5,6-dihydro-4H-[1,2,4,5]tetrazin-1-yl]-benzothiazoles.

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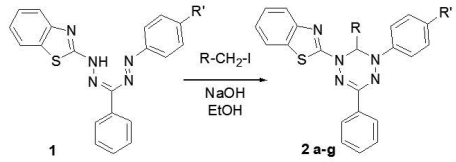
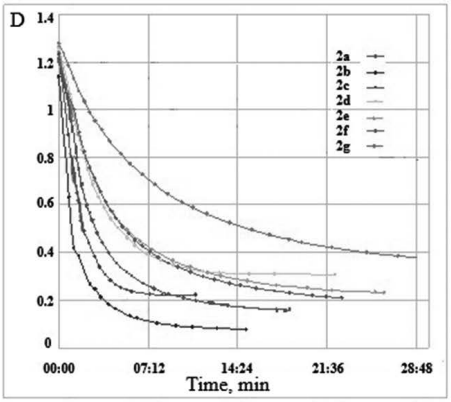
The cause of many diseases of humans and animals are free radicals. Protection against free radicals is provided by the antioxidant system of the body. However, in modern practice, antioxidants are widely used for neutralization of free radicals and protection of the cell from oxidation. 2-[5-(Aryl)-6-R-3-phenyl-5,6-dihydro-4H-[1,2,4,5]tetrazin-1-yl]-benzothiazoles were synthesized by alkylation of corresponding formazanes [1]. These comoundes are easily oxidized, therefore, they may be of interest as antioxidants.



R = H;
R' = H;

R' = H (**a**); MeO (**b**); F (**c**); Cl (**d**);
R = Me (**e**); Et (**f**); CH_2=CH- (**g**)



Antioxidative activity of the obtained compounds was determined by the DPPH antioxidant assay. The best results were obtained for the tetrazines with F or MeO substituents in the aromatic fragment in the 5 position of tetrazine ring, because of donor mesomeric effect of these groups. Replacement of the hydrogen in 6 position of tetrazine ring decrease the antioxidative activity.

The work was carried out in the framework of the project of the state task AAA 19-119011790130-3 using the equipment of the Center for collective use «Spectroscopy and analysis of organic compounds»

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Synthesis and biological activity of analogues of natural prenylphenols

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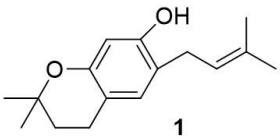
Prenylated phenols form a group of natural compounds that are related to substances of conjugated biosynthesis - meropenoids. Prenylphenols are involved in many biological processes and show a wide range of pharmacological activity. However, their content in natural raw materials is insignificant, and their production is often labor-intensive and very costly. Therefore, the development of methods for the analogues synthesis of natural biologically active compounds is an important area of research.

We have developed selective methods for the synthesis of 2,2-dimethylbenzopyranes, mono- and diprenylphenols based on monatomic phenols and dihydroxybenzenes. An initial assessment of the toxicity, membrane-protective and antioxidant activity of the synthesized compounds on the model of oxidative hemolysis of erythrocytes (in vitro) has been carried out. It has been established that the activity of the studied phenols varies in a wide range and significantly depends on the structure of the molecule. According to the set of indicators, compound **1** has shown the highest activity. The antiradical activity (ARA) has been studied in a test with diphenylpicrylhydrazyl (DPPH). The largest ARA has been detected for chroman **2** and prenylphenol **3** [2, 3].



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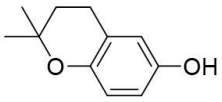

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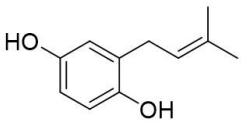

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Non-natural nucleosides based on triazolo[1,5-*a*]pyrimidines

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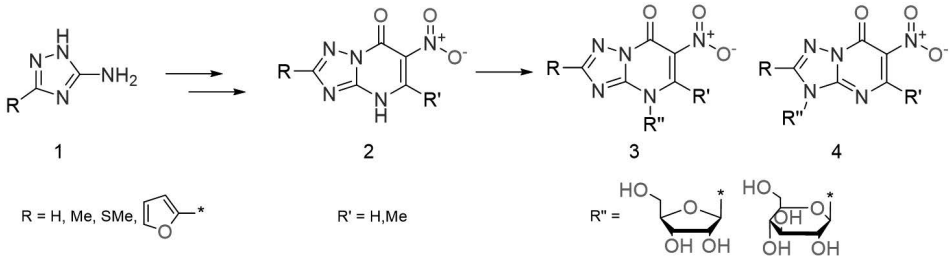
The importance of the development of the methods for synthesis of non-natural nucleosides is conditioned by the constant need to find new means of dealing with dangerous and infection diseases above all. Structural analogues of natural nucleosides are active against the simplex virus of herpes, varicella-zoster viruses, cytomegalovirus, hepatitis B viruses and human immunodeficiency viruses. In this respect, an interesting example of the synthesis of non-natural nucleosides is the use of the nitrogenous base in the form of triazolo[1,5-a]pyrimidines that proved themselves to be the structures of wide spectrum of beneficial biological effects.

Thus, the development of the methods of synthesis for triazolo[1,5-a]pyrimidine-based derivatives of nucleosides is an important scientific task.

To make the synthesis of nucleoside derivatives glycosylation by the method of Vorbruggen [1] was used in this paper. This approach involves the interaction of glycoside with a suitable silylated base in the presence of Lewis acids.



As a result, a method for synthesis of nucleosides 3, 4 in the presence of tin tetrachloride as Lewis acid and BSTFA as a silylation agent was developed and an approach to the synthesis of triazol [1,5-a]pyrimidines-based non-natural nucleosides was introduced.

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The results were obtained within the framework of the state task of the Ministry of education and science of Russia (4.6351.2017/8.9).

The design of new usnic acid derivatives as Tdp1 inhibitors

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Institute of chemical biology and fundamental medicine[3]:
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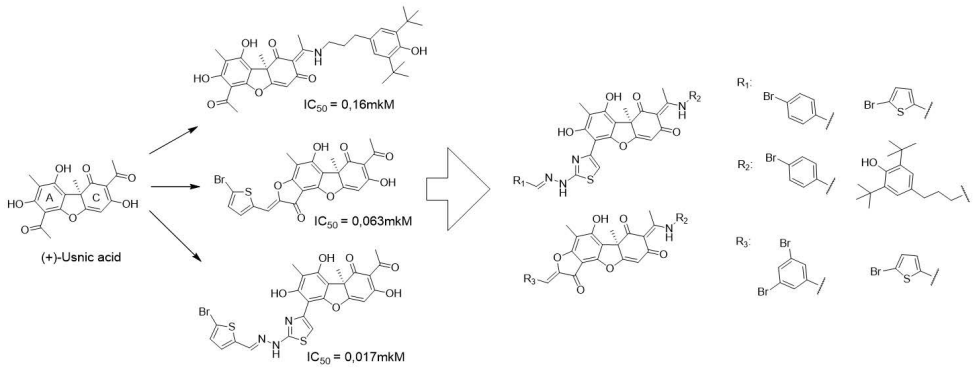
Developing inhibitors for DNA repair enzymes is a promising approach to improve anticancer therapy, in particular for drug-resistant tumors. Tyrosyl-DNA-phosphodiesterase (Tdp1) plays an important role in the repair of DNA damage produced by the action of anticancer drugs, for example, drugs of the camptothecin group, which makes it a promising target in the treatment of cancer.

The major metabolite of lichens, usnic acid, belonging to polyphenols, exhibits antiviral, antibiotic, anti-cancer properties in addition to the antioxidant properties of phenols [1]. Usnic acid derivatives, modified both by ring A and ring C of the natural compound, have shown themselves to be effective Tdp1 inhibitors acting in the concentration range 10^{-7}-10^{-8} M. We have synthesized new derivatives of usnic acid, modified simultaneously in two positions by introducing substituents that previously led to an increase in the inhibitory activity.



It was shown that the synthesized compounds have inhibitory activity against Tdp1 in the concentration range of 0.15 - 1 μM, which is comparable with the activity of compounds modified in ring C.

References

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Synthesis of new biocompatible bifunctional coatings for titanium implants based on phosphonic acid derivatives modified by an integrin-active RGD peptide

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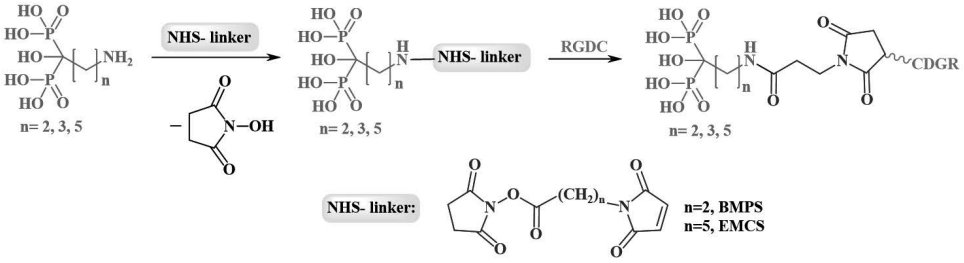
Bifunctional molecules were obtained by conjugating of amino acid bisphosphonates (synthesized on the base of β-alanine, γ-aminobutyric acid and ε-aminocaproic acids) with N-maleimido-succinimide linkers - BMPS, EMCS, followed by the introduction of RGDC tetrapeptide by Michael's reaction.



The obtained compounds were deposited on PEO-modified Ti surface by physicochemical adsorption from solutions. A significant decrease in the adhesion and proliferation of mesenchymal stem cells was observed in the case of long-chain derivatives containing the EMCS linker, as well as RGDC-BMPS-ε, while the short-chain RGDC-BMPS-β and RGDC-BMPS-γ did not lead to a statistically significant decrease in cell activity on surface. A significant (30%) increase in fibroblast adhesion was observed when using organic coatings RGDC-BMPS-β and RGDC-BMPS-γ. Samples coated with RGDC-BMPS-β provided the best adhesion of human osteosarcoma osteoblasts MG-63.

This work was financially supported by the Russian Foundation for Basic Research (Grant No. 17-03-01042a)

An effective approach to the synthesis of azolo[1,5-*a*]pyrimidines containing a primary amino group

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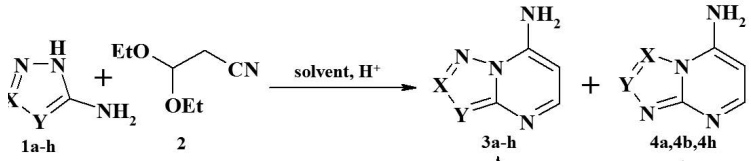
Azoloannelated pyrimidine is a promising scaffold which numerous applications in medicinal chemistry. In a recently published review by Killian Oukoloff et al. [1] present examples of using compounds that include triazolo[1,5-*a*]pyrimidine moiety as antiviral, antibacterial, antiparasitic, antitumor agents and other applications.

A large number of azolopyrimidines exhibiting biological activity contain a substituted amino group in the 7th position. However, the general procedure for the synthesis of such structures involves undesirable chlorine deoxygenation stage. At the same time, there are very few examples of the preparation of azolopyrimidines containing a primary amino group followed by modification [2].

The data given above make the development methods for the synthesis of azolopyrimidine-7-amines relevant. So the interaction of the corresponding aminoazole with commercially available 3,3-diethoxypropionitrile resulted in obtaining key compounds **3a-h** with good yields. Interestingly, the interaction of aminotriazoles **1a,1b** and **1h** led to a mixture of products azolo[1,5-*a*] and azolo[4,3-*a*]pyrimidines. Subsequently, the resulting mixture undergoes Dimroth's rearrangement under the basic conditions, which leads to the complete conversion of the mixture to azolo[1,5-*a*]–pyrimidine.



a: X=CH, Y=N;1b: X=C-SMe, Y=N;
c: X=C-CF_3, Y=N; 1d: X=N, Y=N;
e: X=CH, Y=C-COOEt;1f: X= C-Thienyl, Y=N;
g:X=C-Furyl, Y=N; 1h: X=C-CH_3, Y=N

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The work was performed in the framework of the project of the state task AAAA-A19-119011790134-1 using the equipment of the Center for Collective Use "Spectroscopy and Analysis of Organic Compounds" (PCU "SAOC").

Investigation of the rate of Miramistin release from gel-forming wipes based on cellulose phosphate *in vitro*

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Miramistin has antifungal, antimicrobial, and local immunoadjuvant effects. Miramistin is widely used in medical practice in various dosage forms, both for systemic action and for local therapy. One of the promising dosage forms of Miramistin for local anti-inflammatory therapy is hydrogel wound coverings. The purpose of this work is to compare the release profiles of Miramistin from hydrogels based on cellulose phosphate and the injectable form of Miramistin.

To determine the speed of Miramistin release, a quantitative analysis of Miramistin in hydrogels was developed using the HPLC method, which within the range of 0,018-0,033 mg / ml meets the acceptance criteria for validation characteristics: specificity, accuracy, precision and linearity.

Analysis of the kinetic profiles of the release of active substances into the external solution indicates that the release process consists of two stages. The first phase of the process lasts 15 to 30 minutes, it is characterized by the highest rate of release of active substances, which is determined by the diffusion of Miramistin molecules from the surface of the polymer carrier. During the next period, the release proceeds to the second stage, characterized by almost constant speed. At this stage, unlike an aqueous solution, the release of Miramistin from cellulose phosphate hydrogel is observed over a much longer period: in 24 hours, the total amount of released Miramistin is only 54.4%, i.e. the antimicrobial substance is desorbed from the hydrogel not only at a much lower rate, but also to a lesser extent. Thus, the prolonged release of Miramistin is determined by slow diffusion due to the electrostatic interaction of the active substance with the phosphoric acid groups of the hydrogel wound cover.

Sonosensitizing effect of phthalocyanine derivatives

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In recent years the range of therapeutic methods in oncology has been supplemented by the sonodynamic therapy. This method consists in exposing a tumor to an ultrasound of medium intensity in the presence of special substances – sonosensitizers – previously introduced into it.

The mechanism of sonodynamic destruction remains debatable. The main destructive factor is believed reactive oxygen species arising from the ultrasonic effect on the medium containing the sensitizer and molecular oxygen. In this case, the generation of reactive oxygen species, in turn, is associated with acoustic cavitation. However, there are other possibilities. In particular, a decrease in both the strength of cell membranes and the cavitation strength of the medium after the introduction of a sensitizer, which can lead to destruction of tumor tissue by cavitation events.

In the present work the sonosensitizing effect of two phthalocyanine derivatives — octa sodium salts of cobalt octacarboxyphthalocyanine (teraftal) and zinc octacarboxyphthalocyanine — was evaluated. The evaluation was carried out in aqueous solution, on bacteria, cells and experimental animals. The generation of reactive oxygen species in aqueous solutions was evaluated by extraction spectrophotometry. It was shown that in the presence of the above-mentioned phthalocyanine derivatives the generation of reactive oxygen species increases. In experiments on cells, bacteria and animals the introduction of these phthalocyanines leads to an increase in the destructive action of ultrasound. Thus, the combined effect of ultrasound and teraphthal on the tumors of experimental animals leads to a significant inhibition of their growth – up to 2-3 times compared with the control.

Thus, teraftal and octa sodium salt of zinc octacarboxyphthalocyanine may be promising sonosensitizers in the sonodynamic therapy of cancer.

The research was carried out with the financial support of the Russian Foundation for Basic Research, grant 18-08-01197.

Design of new bioactive 4-trifluoromethyl-6-alkyl(aryl)-pyridin-2-ones

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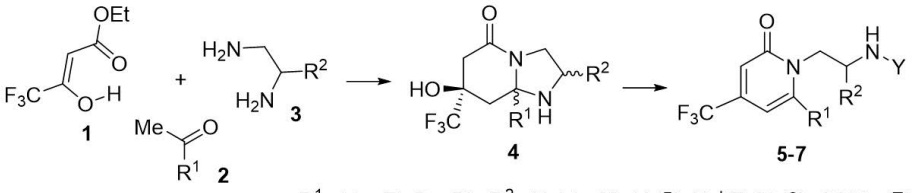
2-Pyridones are an important group of heterocyclic compounds, and their derivatives are successfully used in medicine. For example, the 2-pyridone core present in the drugs Amrinone, Milrinone, used for the treatment of cardiac failure [1], in the antimycotic agent Cyclopirox [2], in the antiepileptic drug Perampanel [3], in the memory-enhance alkaloid Ricinine [4] and the cytokine inhibitor Pirfenidone [5].

We have found a new approach to trifluoromethyl containing 2-pyridones. It was shown that the three-component reaction of polyfluoroalkyl-3-oxo esters **1**, methyl ketones **2** and 1,2-diamines **3** resulted in the formation of hexahydroimidazo[1,2-a]pyridin-5-one **4** [6]. Under dehydration, both the water molecule elimination and imidazolidine cycle opening proceeded to give 4-trifluoromethyl-6-alkyl(aryl)pyridin-2-ones **5-7**. Pyridones 7 with an ethyl or butyl substituent at the 6-position were found to have high tuberculostatic *in vitro* activity against *Mycobacterium tuberculosis* $H_{37}Rv$, M. *avium*, M. *terrae* and MDR strains (MIC = 1.5 μg/mL). In addition, the phenyl-substituted analogue showed moderate analgesic activity in the *in vivo* hot plate test.



R^1= Me, Et, Bu, Ph; R^2= H, Me; Y= H (**5**); H_2^+ TsO^- (**6**); COMe (**7**)

This research was financially supported by RFBR (grant no. 18-03-00342).

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Development of Multitarget Anticancer Agents Based on Mdm2 Inhibitors

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One of the key mechanisms of cancer cell resistance to the therapy is the release of the active substance from the cell as a result of its binding to P-glycoprotein. Even in the case of tumors that are initially sensitive to the therapy, hypertrophy of this mechanism can lead to remission with the formation of chemoresistant cells.

Modern P-glycoprotein inhibitors do not have their own therapeutic effect; they can be used only in the combination with drugs of a different targeting.

In the present work, we discuss the possibility of developing a drug that combines properties required for the parallel activation of two mechanisms impaired in tumors: a) the introduction of agents into the cell due to P-glycoprotein inhibition and b) reactivation of pro-apoptotic p53 protein.

Inhibitors of p53-Mdm2 protein-protein interaction are used as the basis since the p53 activity is suppressed in tumors of various etiologies as a result of overexpression of the Mdm2 protein that binds it. The rigid spatial structure of binding sites of the protein allows rational design of inhibitors based on the pharmacophore hypothesis, reflecting the key interactions of the p53 alpha helix with the Mdm2 hydrophobic cavity.

The activity towards P-glycoprotein is noted for several Mdm2 inhibitors, and the analysis of known inhibitors suggests that a unified pharmacophore hypothesis can be developed for them. The study of the spatial structure of P-glycoprotein allowed us to identify potential binding sites for inhibitors, and docking of the library of candidates using the identified sites allowed us to reveal compounds that are optimal in terms of “p53 reactivation — P-glycoprotein inhibition”.

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

Design and synthesis of 1-({4-[(4-chlorobenzoyl)amino]phenyl}sulfonyl-L-proline, new pharmacologically active inhibitor of matrix metalloproteinase 9

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Matrix metalloproteinases 2 (MMP-2) and 9 (MMP-9) (gelatinases) [1] belong to the family of zinc-dependent endopeptidases and play an important role in postinfarction myocardial remodeling, participating in the degradation of collagen chains [2]. In the study of patients with myocardial infarction (MI), an increase in the concentration of MMP-2 and MMP-9 in the blood was detected after 24 h and 6 months after MI [3]. It is believed that the activity of MMP-2 and MMP-9 plays a major role in undesirable changes in the tissues of the cardiovascular system, and the prognosis of early post-infarction heart remodeling depends on the level of their activity in the ischemic myocardium [3]. In this regard, the development of new potential selective inhibitors of MMP-2 and MMP-9 is relevant.

The new MMP-9 inhibitor 1-({4-[(4-chlorobenzoyl)amino]phenyl}sulfonyl-L-proline (AL-828) was designed on the basis of these structural requirements for selective gelatinase inhibitors. For a theoretical assessment of the viability of the proposed compound as an inhibitor of MMP-9, molecular docking was performed (Glide software (Schrodinger, Inc.)) and the theoretical $IC_{50} = 4*10^{-5}$ M was calculated. The compound AL-828 was synthesized from 4-chlorobenzoyl chloride, aniline, chlorosulfonic acid and L-proline in 3 stages with a total yield of 50%. The pharmacological activity of AL-828 was studied by using a model of acute myocardial infarction induced by ligation of the left coronary artery. MMP-9 was established using the "sandwich"-method of enzyme-linked immunosorbent assay ("Chem Well 2910 Combi", RMP900 kit for R & D Systems, USA). The only FDA-registered inhibitor of MMP-9, doxycycline-the tetracycline antibiotic was used as a comparator drug [4]. The compound AL-828 at the dose of 20 mg/kg/day orally under conditions of acute myocardial infarction produced a significant decrease in the blood of rat MMP-9 level from baseline. This compound was as active as reference compound doxycycline. The compound has low toxicity, LD_{50} = 398.8 mg/kg.

Thus pharmacologically active MMP-9 inhibitor, 1-({4-[(4-chlorobenzoyl)amino]phenyl} sulfonyl-L-proline (AL-828), which can be basis for drug development for the treatment and prevention of postinfarction myocardial remodeling was obtained.

This work was supported by the RFBR grant No. 18-015-00244.

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The concept of novel drug releasing system with feedback function based on inorganic-organic hybrid material

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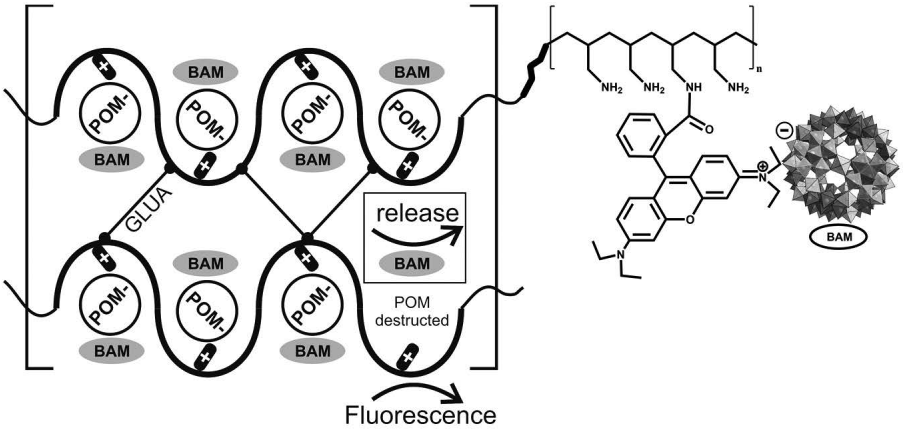
Design of novel drug delivery systems is vital important task of modern biotechnologies. At that, there are many bioactive molecules (BAM) have to be administrated into the human body by the longwise period: hormones, some proteins (insulin e.g.), chemotherapeutical agents etc. These longtime-drug-releasing systems (LDRS) allow to decreasing the toxicity action and some side effects, which could occur in case of traditional tablets carrying the too high concentration of BAM. In context, new LDRS with possibility to control the residual concentration of drug is suggested based on the giant polyoxometalates (POM) Keplerates $Mo_{72}Fe_{30}$ or Mo_{132} and polyallylamine (PAA) grafted with xanthene dye (rhodamine B, RhB). Due to the electrostatic and van-der-Waals interactions and H-bonds, the POM could be conjugated with different BAM as universal drug-carrier [1]. The embedding of POM-BAM conjugates into the polymer network, cross-linked with glutaraldehyde (GLUA), would be realized through the electrostatic interaction with dye (RhB), which fluorescence is dramatically quenched at the POM presence [2]. During the POM destruction under the physiological pH (7.2-7.4), the BAM releasing occurs, and RhB fluorescence recoveries. Thus, presented LDRS can be used as subcutaneous implant with function of monitoring the pharmacokinetic on-line.



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Chiral palladium complexes with terpene ligands: synthesis and biological activity

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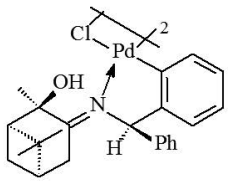
Metal complexes with a variety of chiral ligands are widely studied as promising therapeutic substances [1]. However, despite the huge variety of synthesized and described terpene-containing ligands and metal complexes based on them, their biological activity has not been practically studied.

This paper discusses the synthesis of various types of chiral palladium complexes – with cyclometallated ligands (1), *N,N*-bidentate chelating ligands (2) and *N,N,O*-tridentate salen type ligands (3) [2,3]. As examples, complexes based on imines of the pinane series are given. The corresponding amines and imines of the pinane and bornane series and palladium complexes based on them were obtained.



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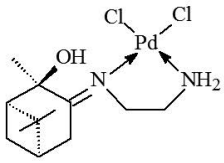

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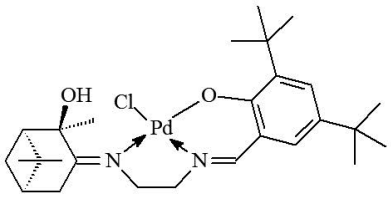

3

Positive results of antimicrobial and antifungal activity of the synthesized palladium complexes were obtained. Tests were performed *in vitro* on the main ESCAPE pathogen strains based on The Community for Open Antimicrobial Drug Discovery (Australia). Activity was determined by inhibition of the growth of cells of five species of bacteria (*Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Staphylococcus aureus*) and two species of fungi (*Candida albicans* and *Cryptococcus neoformans*). It was established that all the studied complexes have antimicrobial activity against *Staphylococcus aureus* (inhibition zone 82–96%), *Candida albicans* (inhibition zone 97–100%) and *Cryptococcus neoformans* (inhibition zone 81–98%).

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Novel [1,4]-benzodiazepine derivatives as potential anticancer agents

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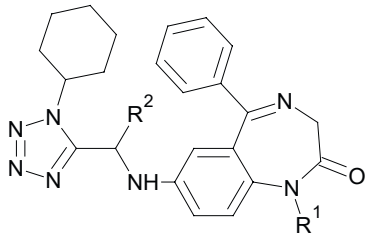
Recently the interest in [1,4]-benzodiazepine derivatives as components of potential anticancer drugs has increased significantly. This is due largely to the ability to form the antibody- drug conjugates for the targeted drug delivery [1].

A number of derivatives of [1,4]-benzodiazepines with a positive computer forecast was synthesised by the four-component Ugi reaction. All compounds contain reactive functional groups which are suitable for further chemical modification in order to obtain the original biologically active compounds. Structures of all obtained compounds have been confirmed by the spectral analysis.



R^1, R^2 = H, Alk or Ar

A quantitative forecast of the profiles of antitarget interaction of chemical compounds was carried out using the GUSAR software (http://www.way2drug.com/gusar/antitargets.html). In this work materials collected by PhD Apryshko G.N. were also used. In the preclinical study of the compounds, the MTT-test on 9 lines of tumor cells and transplanted tumors of mice from the bank of tumor strains of N. N. Blokhin Russian Cancer Research Center of Ministry of Health of Russia (P-388 lymphocytic leukemia and epidermoid lung carcinoma Lewis LLC) were used. The obtained results demonstrate the activity of the synthesized [1,4]-benzodiazepines with the prospect for further research.

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Rational design of novel tyrosyl-DNA phosphodiesterase 1 inhibitors as promising antitumor agents

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Inhibitors of DNA repair enzymes such as tyrosyl-DNA phosphodiesterase 1 (TDP1) may be applied in antitumor treatment for overcoming the resistance to traditional DNA-damaging chemotherapy [1]. TDP1 cleaves stalled complexes, caused by irinotecan and similar drugs, where a tyrosine side chain of topoisomerase is covalently attached to a DNA strand. The TDP1 catalytic cycle offers two potential therapeutic strategies: (1) the inhibition of the first step to prevent phosphoryl transfer and (2) the inhibition of the second step to prevent the hydrolysis of the phosphohistidine intermediate [2]. We have constructed molecular models to be used in virtual screening for potential TDP1 inhibitors: the apo form, the enzyme-substrate complex, and the intermediate with catalytic His263 covalently bound to the substrate's oligonucleotide. Analysis of the enzyme-substrate complex allowed us to identify the interactions crucial for competitive inhibition, and to reveal sulfonate-based compounds that can effectively interact with the apo form by hydrogen bonding with Lys265, Lys495, and other amino acid residues in the oligonucleotide's phosphate group binding sites. The Lead Finder program [3] and an in-house post-docking structural filtration algorithm were used to select compounds meeting the specified structural criteria. Also, we modeled the poses of recently discovered TDP1 inhibitors – usnic acid derivatives – and demonstrated their ability to bind to the TDP1 intermediate. They occupy a cavity adjacent to the active site and may affect its conformation, thus disrupting the reactive orientation of the intermediate phosphohistidine moiety and the nucleophilic water molecule.

The work was supported by RFBR (grant № 18-315-00389).

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Multifunctional mesoporous silica nanoparticles as a platform for drugs and diagnostic purposes

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Nowadays various nanostructured materials are used in different branches of industry and biotechnologies, including biomedicine for diagnostics and therapy. Optimized combinations of nanostructured compositions allow of designing the patient-friendly multifunctional platforms for the reduction of undesirable medicamental impact, decrease therapeutic dose of drug and frequency of its administration. Among various nanoscaled materials special attention is focused on mesoporous silica due to its unique structural features: large specific surface area, tunable size of pores, nontoxicity, high bioavailability and capability to biodegradation by microorganisms.

Presented investigation is devoted to the application of systems based on mesoporous silica of MCM-41 type and the amphiphile bearing triphenylphosphonium head group and hexadecyl hydrophobic tail (TPPB-16) as a platform for drug delivery and diagnostic purposes. Rhodamine B was selected as a model cargo for encapsulation in fabricated silica nanoparticles. Structural characteristics of non-modified MCM-41 and mesoporous silica noncovalently functionalized by TPPB-16 loaded with Rhodamine B were examined. Using dynamic and electrophoretic light scattering techniques it was shown, that modification of MCM-41 by TPPB-16 results in decrease of hydrodynamic diameter from 175 nm to 100 nm and shift of zeta potential from -40 mV to -5.5 mV. Using spectrophotometry technique quantitative encapsulation of model cargo in modified nanoparticles was demonstrated. Anticancer effect of fabricated nanoparticles has exhibited in terms of cytotoxic activity against M-Hela cell lines, while bioavailability and harmless toward healthy cells were tested (less than 10 % hemolysis at 63 μg/mL concentration).

This work was financially supported by Russian Science Foundation (project № 19-73-30012).

Quantitative determination of the main substances of some antiviral drugs from a number of azolo-azines with direct square-wave voltammetry

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Voltammetry (VA) is often not inferior in sensitivity and selectivity to the HPLC method in the analytical control of the active substance in pharmacy objects. At the same time, VA analysis is fast, simple, inexpensive and portable, which does not require the use of toxic organic solvents and the involvement of expensive personnel for its service.

For the first time it was established that an electrochemical activity of the new antiviral drugs from a number of azolo-azines as Triazavirin® (sodium salt of 2-methylthio-6-nitro-1,2,4-triazolo- [5,1-c] [1,2,4] triazine -7-it, dihydrate, TZ) and Triazid (5-methyl-6-nitro-7-oxo-4,7-dihydro-1,2,4-triazolo [1,5-a] pyrimidine L-arginine monohydrate, TD) is caused by electrochemical reduction of a nitro group bonded to a conjugated aromatic system. The electrochemical reduction processes take place in the region of potentials (-0.1) - (-0.4) V (Ep = -0.2 V, TZ) and (-0.3) - (-1.0) V (Ep = -0.6 V, TD). The presence of L-arginine in the TD molecule as a substituent shifts the analytical signal (AC) of the Triazide to the region of the dissolved oxygen reduction wave (-0.4) - (-1.0) V. It doesn't allow to obtain correct analytical information because of the superposition of two parallel flowing electrochemical processes. For rapid (within one minute) deoxygenation of the solution, chemical reduction of oxygen with sodium sulfite at a concentration of 1 mM was used at a pH of 7-8.

Methods for quantification of TZ in Triazavirin® capsules and TD in its pharmaceutical substance were developed and validated in accordance with the OFAS.1.1.0012.15. The methods developed meet the stated acceptance criteria and can be useful for pharmaceutical analysis and industry, including the control of technological processes.

This work was supported by the RSF № 17-13-01096

Preparation of novel carriers for drug delivery using the Ugi multicomponent reaction

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Microgels and nanocapsules developed from biopolymers are preferable over synthetic polymers due to their biocompatibility and have been used for *in vivo* delivery of various pharmaceuticals. Sub-micron particles made from polysaccharides can be ideal building blocks for drug delivery systems. However, considerable physical and chemical modifications including crosslinking should be made to improve the poor stability of the biopolymer particles. Our research program is focused on the modification of polysaccharides in aqueous suspensions, microemulsions, liposomal, micellar and microgels solutions [1].

For the preparation of novel carriers for drug delivery we explore multi-component reactions (MCRs), which have been highly useful in the modification of polysaccharides. Some MCRs, especially the Ugi reaction, can be accelerated up to 500-fold compared to organic solvents by conducting them in aqueous solutions of polysaccharides. In addition, the Ugi reaction can be applied to modification of various side groups including amine and carboxyl [2].

We will present the novel synthesis of the cross-linked microgels of pectin and cellulose with controlled colloidal properties (average hydrodynamic diameter in the range of 250-600 nm and polydispersity index 0.12-0.20) using the Ugi multicomponent reaction with polyamines. In this work we used isocyanides to promote the interaction between polysaccharides and polyamines. Microgels can be formed by the combination of mixture of isocyanides/polyamines and formaldehyde at optimize pH and room temperature. Natural oligomers have been incorporated inside the microgels during the synthesis.

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New potential antifungals among N- (4-oxo (tioxo) -1,3,5-triazinan-1-il) arylamides: in silico screening

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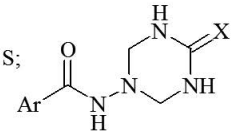
The effectiveness of modern antifungal therapy in the treatment of fungal infections is quite high. However, despite this fact, medicine needs new antifungal drugs. This is due to many factors. The determining factor is the emergence of drug resistance in some species of fungi. The present theoretical research is aimed at searching of new effective lanosterol 14 alpha-demethylase inhibitors among 5 N- (4-oxo (thioxo) -1,3,5-triazinan-1-yl) aryl amides with structural formulas 1-5 (Fig. 1) [1]. The enzyme lanosterol 14α-demethylase is present in a wide variety of organisms, this enzyme is studied primarily in the context of fungi, where it plays an essential role in mediating membrane permeability.

1 Ar = *n*-C_5H_4N, X = S; **2** Ar = *n*-$CH_3OC_6H_4$, X = S; **3** Ar = *m*-C_5H_4N, X = S;
4 Ar = *m*-$CH_3OC_6H_4$, X = S; **5** Ar = *o*-$CH_3OC_6H_4$, X = O;



1 - 5

Fig. 1. *Structural formulas of modeled compounds.*

Virtual screening was performed by molecular docking using the LeadIT 2.3.2 program with default parameters [2]. The positioning of the ligands was performed in chain A of the macromolecule with PDB ID 4wmz (www.rcsb.org). This macromolecule is a 3D model of the lanosterol 14 alpha-demethylase from Saccharomyces cerevisiae that catalyze ergosterol biosynthesis in baker's yeast. The selection of potentially bioactive conformations of ligands was performed using the FlexX scoring function. The radius of the sphere in the simulation was 12 Å. Its centering was performed automatically in the center of mass of the reference ligand (fluconazole) (www.rcsb.org).

All compounds were found to have a fairly high affinity with the active center of lanosterol 14 alpha-demethylase from Saccharomyces cerevisiae. The bioactive conformations and amino acids involved in their stabilization in the active center of the modeled enzyme were determined for all ligands. They are promising for testing as potential antifungal agents.

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New alpha amylase inhibitors among pyrazole and isoxazole derivatives

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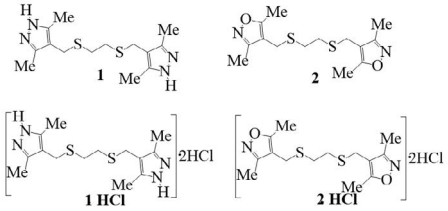
Recently [1], we have shown the ability to inhibit α-amylase with sulfanyl-substituted bis-3,5-dimethylpyrazole **1** and sulfanyl bis-3,5-dimethylisoxazole **2**, as a way to reduce the hydrolysis of carbohydrates in the intestine, preventing the development of type 2 diabetes. The synthesis of their water-soluble adducts with HCl has been carried out.



Using the LeadIT program, which implements the basic principles of flexible molecular docking, the positioning of these 4 ligands (Fig. 1) in the active sites of *Aspergillus niger* alpha-amylase has been studied. Molecular docking was performed with common default docking parameters. For parameters describing protein-ligand collisions, the maximum allowable amount of overlap was 5.0 Å^3. The coefficient of intra-ligand collisions with hydrogen atoms was 0.6. As potential biologically active conformations of the tested ligands, ligand conformations with the lowest energy were selected. By default, 50 conformations were automatically generated for each ligand, from which the best poses were selected using the FlexX evaluation function. The radius of the sphere in the simulation was 20 Å. Its centering was performed automatically in the center of mass of the reference ligand (maltose) (www.rcsb.org).

It was found that all 4 ligands **1**, **2**, **1·HCl** и **2 HCl** are able to effectively inhibit the catalytic activity of alpha-amylase. For all cases, bioactive conformations of simulated ligands were determined. The factors stabilizing their position in the active center of this enzyme are established.

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Copper(II) complexes of fluorinated diketonate ligands: synthesis and biological evaluation as potential antitumor drugs

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The development of new anticancer and antimicrobial agents is one of the fundamental goals in medicinal chemistry. The use of metal-based drugs presents one of the most important strategies in the search of new therapeutic and diagnostic agents. Investigations in this area are focused on the use of biologically active complexes formed by essential ions, such as copper.

Recently, we have synthesized and evaluated *in vitro* antimicrobial activity of several copper(II) complexes in comparing with the parent ligands [1,2]. The MIC values towards tested bacterial strains were in the range 64–512 μg/mL. It was shown that the biological activity is induced by intact complexes and is not resulted from the complex decomposition into copper(II) ions and the free ligand.

Since any essential metal which escapes its normal metabolic pathways can be very toxic to the organism (for example, copper in Wilson disease), complexes of such metals may serve as effective cytotoxic agents.

Herein we report the synthesis and biological properties of copper(II) complexes based on fluorinated aromatic β-diketonate ligands. Antibacterial and antifungal activities of ligands and their copper(II) complexes were evaluated towards *S. aureus*, *B. subtilis*, *E. coli*, *P. atrosepticum*, and *C. albicans*. Cytotoxic activity was tested with cultures of human cervical epithelioid carcinoma cells (HeLa) and African green monkey normal kidney cells (Vero) by the MTT assay.

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Novel biologically active monoterpene-containing substituted coumarins

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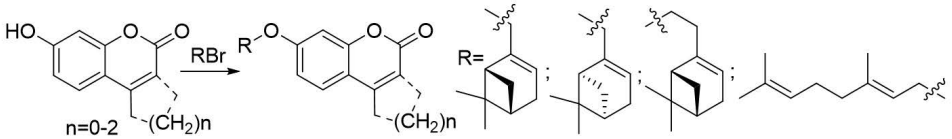
Monoterpenoids possess broad range of biological activities. Compounds with coumarin moiety also demonstrate various pharmacological activities including antiviral, antibacterial and antitumor activities. Therefore, incorporation of monoterpene fragments into the structure of coumarins is of great interest for medical chemistry. We have synthesized novel coumarin and monoterpene hybrids for testing their biological activity. Substituted coumarins were prepared by the reaction of monoterpenoid bromides with coumarins synthesized by the Pechmann condensation of resorcinol with β-keto esters.



New coumarin derivatives with monoterpene substituents turned out to be effective inhibitors of Tdp1 enzyme (IC_{50} about 1 μM), which is important target for antitumor therapy, in combination with low cytotoxicity (CC_{50} > 100 μM). These compounds showed synergistic effect in combination with known anti-cancer drug camptothecin, thus been promising as an important component for complex anti-tumor therapy.

The antiviral activity of the synthesized compounds was studied against the pandemic influenza virus A/California/07/09 (H1N1)pdm09. The compounds with a bicyclic pinane framework exhibit the highest selectivity indices (the ratios between the cytotoxicity and the active dose). The derivative of (-)-myrtenol, which is characterized by promising activity, low cytotoxicity, and synthetic accessibility, has the greatest potential among this group of compounds.

This work was supported by Russian Scientific Foundation (grant 19-13-00040).

Targeted Search for Small Molecule Inhibitors of p53-MDM2 Protein Interaction

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The tumor suppressor p53 protein, whose negative regulator is MDM2 E3 ligase, is the target of studies performed at Research Laboratory of Molecular Pharmacology. Small molecule inhibitors of the interaction of these two proteins, which allow increasing the lifetime of p53 and regenerating its function consisting in the induction of apoptosis in cancer cells, are at the stage of the development.

Gibbs energy, binding constant and scoring value for the studied compounds (a series of substituted indole-2,3-diones with structural fragments of Schiff bases and Mannich bases) are calculated during computer simulation. Since the N-terminal domain of MDM2 is labile, the MDM2 conformation is taken into account when calculating these parameters.

A number of compounds, obtained from computer simulation, that meet certain requirements are synthesized and studied in the cell model (modified human osteosarcoma cell line U2OS) using the Operetta imaging system, which allows to evaluate the target activity of the compounds, select the structures to be optimized, and identify structural fragments with the greatest contribution to the activity of the compounds. In addition, a number of biological experiments aimed at identifying the mechanisms of the effect of the active compounds is carried out.

As a result of the research, a number of small molecule compounds with high target activity were obtained, which are currently tested *in vivo* in *Danio Rerio* fish.

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

Esterase profile and antiradical activity of 3-oxo-2-(2-arylhydrazinylidene)-3-polyfluoroalkylpropanoic acids

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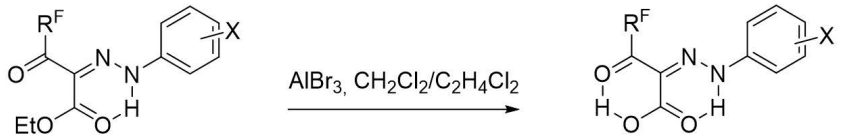
We have developed the effective method for producing 3-oxo-2-(2-arylhydrazinylidene)-3-polyfluoroalkylpropanoic acids **2a-k** by dealkylation of readily available ethyl 3-oxo-2-(2-arylhydrazinylidene)-3-polyfluoroalkylpropanoates **1a-k** in refluxing dichloromethane (1,2-dichloroethane) under the action of $AlBr_3$ as Lewis acid. The usual acid catalyzed hydrolysis does not allow to obtain the target acids **2**.



1a-k **2a-k**

R^F = HCF_2, CF_3, CF_2CF_2H, C_2F_5, C_3F_7, C_4F_9, X = 4-Me, 4-OMe,4-CO_2Et, 4-NO_2, 2-CO_2Et

The esterase profile was investigated for compounds **2**. It was established that acids **2** do not inhibit acetylcholinesterase, butyrylcholinesterase, but have a high inhibitory activity against carboxylesterase (when R = perfluoroalkyl substituent and X = 4-Me, 2-CO_2Et) with IC_{50} values in the range of 2.01×10^{-8} - 6.3×10^{-7} M. Antioxidant activity for compounds **2** was determined by their ability to bind free radicals in the ABTS-test. The acids **2** having polyfluoroalkyl substituent and (4-methyl- or 4-methoxyphenyl)hydrazinylidene group exhibited high antiradical activity, exceeding 1.45 - 2 times the activity of the standard antioxidant Trolox and the known antioxidants such as ascorbic acid and pyrocatechin. For compounds **2**, a high initial rate of the $ABTS^+$ radical binding reaction (up to 75.8% after 1 minute) was observed, similar to that of Trolox, which suggests the SET-mechanism (single electron transfer) of the antiradical action of the compounds studied.

This work was financially supported by the Ural Branch of the Russian Academy of Sciences (grant 18-3-3-13).

Results on medicinal chemistry research in Russian Chemical Bulletin

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Russian Chemical Bulletin is the leading journal in chemistry, covering practically all areas of fundamental chemical research including Chemistry of Natural Compounds, Bioorganic, and Medical Chemistry. Papers on interdisciplinary topics are also accepted for publication.

The journal publishes materials containing the theoretical and experimental results of original chemical research in the form of Full Articles, Brief Communications and Letters to the Editor, as well as Author Reviews and Analytical Reviews on topical issues of chemical science.

The journal is refereed and cited by all leading refereed journals, including SCOPUS and Web of Science. Among all Russian scientific journals has the highest rate of downloads of full-text article files. Contents, graphical abstracts, and annotations of articles are available free on website (russchembull.ru).

In addition to the usual issues containing materials in different areas of chemical science, the journal produces specialized issues. Specialized issues containing the articles on materials of conferences on medicinal chemistry are published every year (see, for example issue 5, 2019).

Editorial Board of the Journal is planning to publish the results presented at the All-Russian Conference on Medicinal Chemistry and MOBI-Chem Pharma2019 and inviting authors with new interesting materials to participate in the preparation of this issue.

Perfectly prepared articles are published in 4 months, for Letters to the Editor this period is even shorter (2 months).

The synthesis of 10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles with pentafluorophenyl substituent

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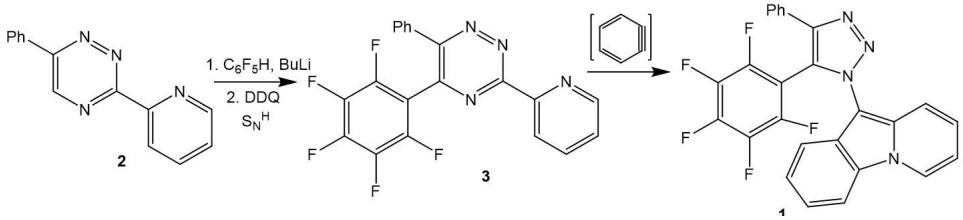
Derivatives of pyrido[1,2-*a*]indoles are of interest as promising compounds for medical chemistry. We have proposed a convenient synthetic approach to derivatives of 10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles **1** with a pentafluorophenyl substituent in position 4 of the triazole. The synthesis is based on using the methodology for nucleophilic substitution of hydrogen in the 3- (2-pyridyl)-1,2,4-triazines **2** and the subsequent interaction of compound **3** with the aryne intermediates generated *in situ*. Pentafluorophenyl lithium obtained *in situ* on the basis of pentafluorobenzene was used as a nucleophile at the first stage of the synthesis. The formation of the pyrido[1,2-*a*]indole system occurs at the second stage as a result of the rearrangement described by us in 2013[1]. The introduction of a pentafluorophenyl substituent into the triazine does not change the direction of the reaction.



The structure of the product **1** was confirmed by the NMR ^{1}H, ^{19}F, mass-spectrometry and elemental analysis data.

Acknowledgment

The study was carried out with the financial support of the Russian Foundation for Basic Research in the framework of a research project 18-33-00226.

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Antifungal and antiglycation activity of [1,2,4]triazolo[1,5-*b*][1,2,4,5]tetrazines

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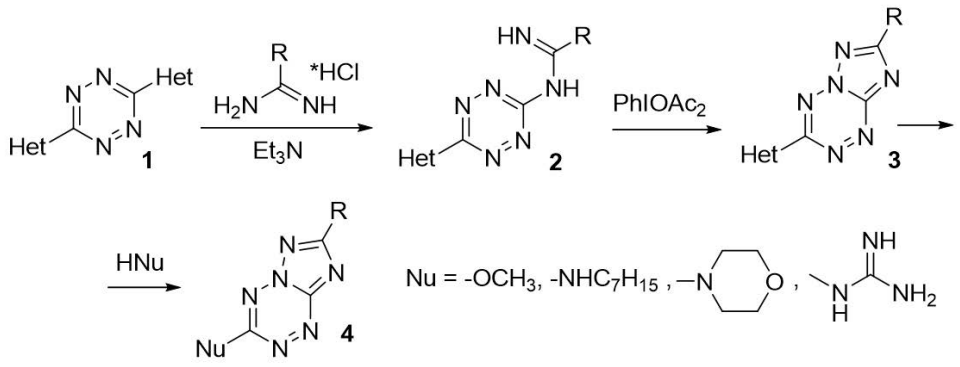
Azoloannulated azines are purine isosters and are of great interest for modern medicinal chemistry as potential biologically active compounds. Derivatives of azoloannulated 1,2,4,5-tetrazines have been found to have pronounced antimicrobial activity (1,4-dihydroimidazo[1,2-*b*][1,2,4,5]tetrazines), antituberculosis activity (triazolo[4,3-*b*]- and imidazo[1,2-*b*][1,2,4,5]tetrazines), antibacterial and fungistatic action (thiazolo[3,2-*b*][1,2,4,5]tetrazines), as well as antitumor activity (triazolo[4,3-*b*][1,2,4,5]tetrazines and imidazo[1,2-*b*][1,2,4,5]tetrazines).

By oxidative cyclization of products containing an amidine fragment **2** obtained by nucleophilic substitution, a number of derivatives of the new heterocyclic system [1,2,4]triazolo[1,5-*b*][1,2,4,5] tetrazine **3** was synthesized. Nucleophilic substitution reactions were carry out in this system with N- and O-nucleophiles. For the synthesized compounds, biological activity was investigated with respect to mycelial anthropophilic and zooanthropophilic dermatophyte fungi (*Trichophyton*, *Microsporum* and *Epidermophyton*), which cause diseases of the skin and its appendages (hair, nails), as well as the antiglycation activity of these derivatives.



This work was done with the financial support of the Russian Science Foundation (grant 15-13-00077-P)

Tantalum oxide nanoparticles as a perspective platform for theranostic agent

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The present work is aimed to investigate the potential of Ta_2O_5-based nanoparticles for multimodal theranostic applications. Theranostics is a novel approach to create pharmaceuticals which combine both therapeutic and diagnostic capabilities. Tantalum oxide nanoparticles offer an excellent platform for developing multimodal theranostic agents because they inherently possess biocompatibility, radiosensitising properties and X-ray contrast performance. Moreover, Ta_2O_5 is an excellent host matrice for rare-earth element dopants giving rise to adjustable luminescent properties, including upconversion ones. This enables to design a converter for the radical destruction of malignant cells for enhanced radiotherapy, which at the same time offer dual imaging capabilities (luminescence and X-ray diagnostics). An additional point is high chemical inertness that makes Ta_2O_5 nanoparticles safe for human organism while being non-irradiated.

It is known that such type of materials should have a narrow particle size distribution, small size of core (up to 50 nm), stability in water and physiological conditions, as well as low cytotoxicity. In this regard, the developing of synthesis procedure of tantalum oxide nanoparticles, including nanoparticles doped by rare-earth elements (Eu, Er, Yb), that satisfying the above mentioned requirements was performed. Solvothermal and sol-gel methods were chosen as backbone synthesis techniques and influence of different synthesis conditions on the properties of the obtained materials was investigated. The phase composition, morphology, surface properties and thermal behavior of obtained materials were characterized by XRD, TEM, FTIR, BET, TG/DSC. Luminescent properties of doped nanoparticles were investigated by using mercury lamp and NIR laser as sources of excitation. Stability and colloid-chemical characteristics of sols were studied by microelectrophoresis, dynamic light scattering and potentiometric titration. In Vitro Cytotoxicity and In Vivo Acute Toxicity studies were performed for the obtained materials.

Acknowledgement
This work was supported by the Grant of Russian Foundation for Basic Research, N 18-29-11078.

Ligands of Sig1R on the basis of quinolizidine alkaloid (-)-cytisine

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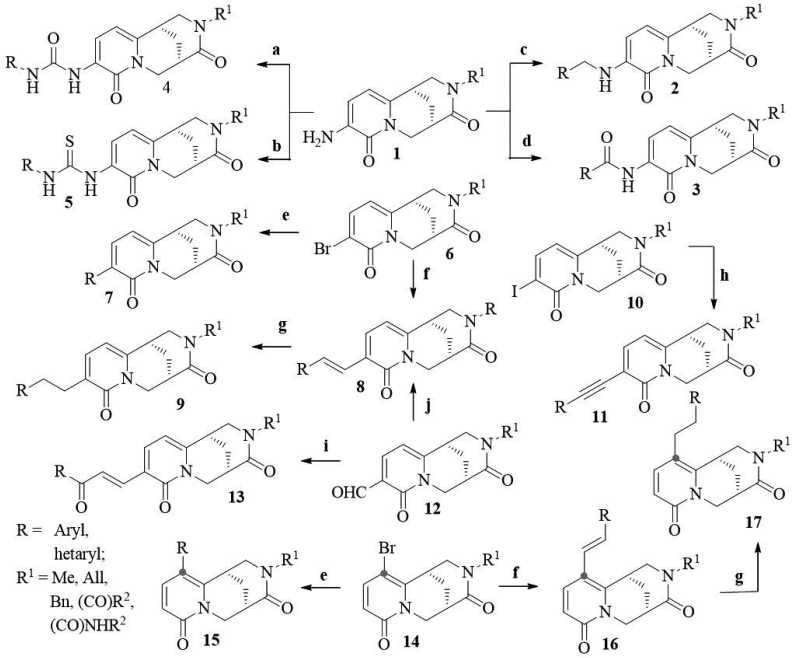
Based on the amino, halo and formyl derivatives of quinolizidine alkaloid (-)-cytisine novel potential ligands of the Sig1 receptor (it takes part in regulation of various central nervous system functions) with aromatic/heteroaromatic substituents at 3, 9 and 11 carbon atoms of starting molecules were synthesized.



Reagents and conditions: *a) RNCO, benzene, 80 °C, 48 h.;* **b***) RNCS, benzene, 80 °C, 48 h.* **c***) C_6H_5CHO, benzene, 80 °C, 12 h.; $NaBH_4$, MeOH, 0 °C, 1 h;* **d***) R(CO)Cl, Py, 20 °C, 2 h;* **e***) $PdCl_2(PPh_3)_2$, $RB(OH)_2$, Na_2CO_3, toluene, EtOH, H_2O, 80 °C, 16 h.;* **f***) $R(CH=CH_2)$, $Pd(OAc)_2$, $(o\text{-}Tol)_3P$, Na_2CO_3, DMF, Ar, 120 °C, 10 h.;* **g***) Pd/C, H_2, MeOH, 20 °C, 8 h.;* **h***) $R(C\equiv CH)$, $PdCl_2(PPh_3)_2$, Ph_3P, CuI, Et_3N, toluene, Ar, 110 °C, 8 h.;* **i***) $RCOCH_3$, NaOH (10%), H_2O, 20 °C, 5 h.;* **j***) $[Ph_3PRCH_2]+Br^-$, NaOMe, MeOH, 20 °C, 1 h.*

Ability of synthesized compounds to interact with the 5NK1 active site of Sig1R (reference ligand – agonist PD144418) was evaluated *in silico* using the software package Schrödinger Suite 2018-4: QipProp, version 4.2 (Schrödinger, LLC, New York, NY, 2018). The most perspective compounds (derivatives of 4-oxo-3-*N*-benzylcytisine with substituents in the 11 position of starting molecule) were revealed; their neuroprotective properties were proved *in vivo*.

This work was supported by RFBR, project No 18-03-00153_a.

Conjugates of tacrine and its cyclic homologues with *p*-toluenesulfonamide as novel cholinesterase inhibitors and antiaggregants

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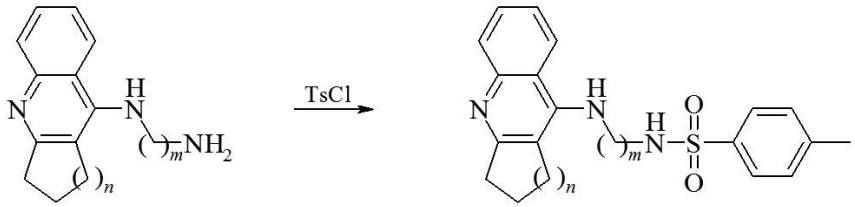
New hybrid compounds of tacrine and its cyclic homologues (n=1-4) with *p*-toluenesulfonamide, combined by spacers of different lengths (m=3-5) (**2**), were synthesized and their biological activity was studied with the aim of searching for the new multifunctional drugs to the treatment of Alzheimer's disease.



1 **2**

It was shown that the compounds **2** effectively inhibited acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) with predominant inhibition of BChE (IC_{50}=29-470 nM) and also displaced propidium from the peripheral anionic site (PAS) of *E.eel* AChE. At the same time, they exhibited very low potencies against carboxylesterase (CaE), thus precluding potential drug-drug interactions arising from CaE inhibition.

The characteristics of the efficiency and selectivity of cholinesterases inhibition by the compounds **2**, as well as their ability to bind to the PAS of AChE and to block AChE-induced β-amyloid aggregation were confirmed by the results of molecular docking.

The study shows the promise of the hybrid compounds based on tacrine derivatives with *p*- toluenesulfonamide for further optimization as potent multitarget agents for the treatment of Alzheimer's disease.

This work was supported by the Russian State assignment to IPAC RAS # 0090-2017-0019 (biological assay) and by RFBR grant #17-03-00984 (synthesis).

Synthesis and *in vitro* anti-tuberculosis activity of 2-aminomethylidene-3-oxo esters

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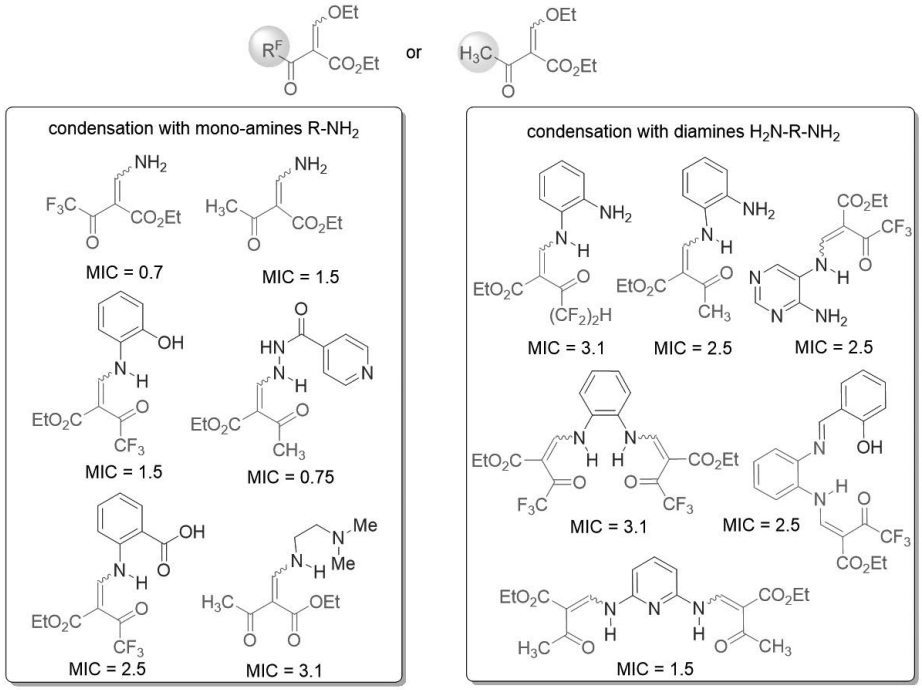
Tuberculosis (TB) is a global public health problem [1]. An increase in drug-resistant strains of *Mycobacterium tuberculosis* has stimulated the search for new anti-TB drugs. Based on the reactions of 2-ethoxymethylene-3-oxo esters with mono- and diamines, we have synthesized a number of amino-derivatives, which exhibited inhibitory properties against *Mycobacterium tuberculosis* $H_{37}Rv$ strain. The examples with high level of anti-*M. Tuberculosis* activity (MIC ≤ 3.1 μg/mL) are shown below.



MIC - min inhibitory concentration, μg/mL; Reference drug Isoniazid, MIC = 0.15 μg/mL

Financial support from the Council for grants of the President of Russian Federation (grant no. MK-1453.2019.3) is gratefully acknowledged.

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Conjugates of phenylpropanoic acid and terpenoids as potential FFA1 agonists

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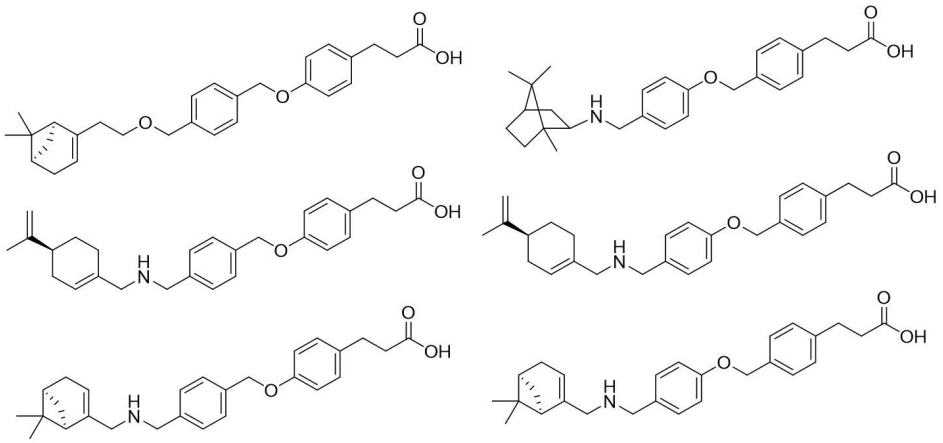
Diabetes mellitus type 2, representing over 85% of diabetes cases, is a progressive disease characterized by insulin resistance resulting in insufficient insulin action.

One of promising target is free fatty acid receptor 1 (FFA1), also known as GPR40, whose activation leads to increase of insulin secretion. The insulinotropic effect being glucose-dependent, FFA1 agonists have the therapeutic potential to treat diabetes with a low risk of hypoglycemia [1].

Phenylpropanoic acid derivatives were shown to be potent FFA1 agonists. Earlier, we have synthesized the series of compounds combining phenylpropanoic acid scaffold with bulky nature-derived amines. Among them, camphor-based compound shows the better results in *in vitro* and *in vivo* tests. In order to further optimization, we have developed different approaches to the synthesis of phenylpropanoic acid derivatives bearing terpenoid's moieties.



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INFLUENCE OF AMPHIPHILIC POLYMER - PLURONICS F-127 ON THE ACTIVITY OF SOLUBILIZED CONJUGATES OF PYROPHEOPHORBIDE a

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In recent years, to improve the efficiency of photodynamic therapy (PDT) of malignant neoplasms, photosensitizers (PS) modify biologically active molecules that increase the affinity of PS to certain cells and tissues [1]. In this work, we studied the photosensitizing activity in the generation of singlet oxygen $^1O_2$ (playing the role of an active agent in PDT) hydrophobic PPS - steroid conjugates of pyropheophorbide a (PPa) containing testosterone (PPT) and dihydrotestosterone (PPdT), as well as isomers of PPT with a lipophilic fragment – hexadecylamine (PPTH –I,II), solubilized with non-toxic polymeric surfactant - pluronic F-127 in the model photooxidation reactions of tryptophan in water and anthracene in chloroform [2]. Previously it was shown that PSs modified with testosterone and dihydrotestosterone molecules have affinity for androgen-dependent cancer cells — prostate carcinoma cells [3]. It was shown that Pluronic has little effect on the effective rate constant k_{eff} for all conjugates in the reaction of photooxidation of anthracene in chloroform (a test reaction for determining PS activity in $^1O_2$ generation). At the same time, the k_{eff} value increases with increasing polymer concentration in the model reaction photooxidation tryptophan in water in the presence of solubilized substituted pyropheophorbides. The observed effects are associated with the disaggregation of PS molecules due to the formation of the Pluronic F-127-PS complex. The obtained regularities of k_{eff} changes are confirmed by electron and fluorescence spectroscopy data. Thus, the process of solubilization by Pluronic makes it possible to obtain watersoluble forms of modified PS which they are active in photooxidation and generation of $^1O_2$.

This work was supported by the Russian Foundation for Basic Research (project 17 -02 -00294) and within the government assignment (topic V. 46.14, № 0082-2014-0006).

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Synthesis and biological activity of 3-alkylamino-5-trifluoromethylphenols

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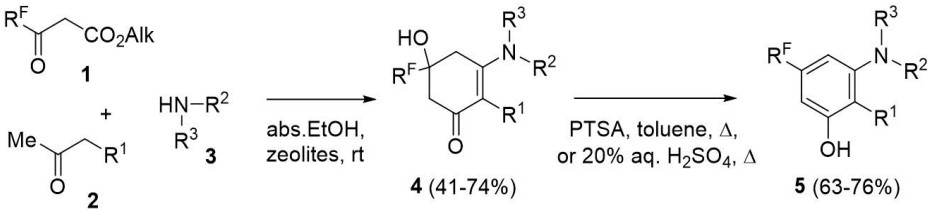
The development of 3-aminophenols synthetic methods has significant potential, because biologically active compounds [1] and selective fluorescent chemosensors [2] were found among them. We proposed a new approach to 3-alkylamino-5-polyfluoroalkylphenols **5** based on the dehydration of the aminocyclohexenones **4**. The products **4** were prepared by one-pot three-component cyclization of polyfluoroalkyl-3-oxoesters 1, methyl ketones **2** and monoamine **3** [3]. Synthesized 3-alkylamino-5-polyfluoroalkylphenols **5** exhibited moderate antifungal activity against eight pathogenic fungal strains. The presence of a CH2 group in the alkylamino residue at position 3 of compound **5** has an effect on antimycotic activity. The further variation of an alkylamino substituent in phenols **5** implies a promising route to anti-fungicidal agents.



R^F= HCF_2, CF_3, $H(CF_2)$, C_2F_5, C_3F_7; R^1= H, Me, Pr; R^2= H, R^3= c-C_3H_5, c-C_6H_{11}, C_8H_{17}, $C_{12}H_{25}$, $(CH_2)_2N(Me)_2$, CH_2Ph, $CH_2C_6H_4F$, $CH_2C_6H_3(OMe)_2$, furfuryl; R^2,R^3= pirrolidinyl, piperidinyl; R^4= H, Me, Ph; R^5= H, Ph.

This research was financially supported by the Russian Foundation for Basic Research (grant no. 18-03-00342).

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Supramolecular systems based on piperidinium surfactants to increase the bioavailability of anti-inflammatory drugs

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Supramolecular systems based on amphiphilic compounds are widely used as effective nanocontainers for targeted drug delivery, which can increase drugs solubility and bioavailability. Implementation of these substances in biomedicine and pharmacology requires them to meet the following criteria: low toxicity, biocompatibility and high efficiency at low concentrations.

In the present work, new surfactants containing piperidinium or 3-hydroxypiperidine fragment in the head group (PP-n and HPP-n series) were synthesized and further characterized. By using complex of physicochemical methods, the critical micelle concentration (CMC), the Kraft point, adsorption parameters on the air-water interface, sizes and aggregation numbers of these compounds in aqueous solutions were determined. To quantitatively characterize the solubilization capacity of surfactant solutions toward anti-inflammatory drugs quercetin and indomethacin adsorption spectrophotometry was used. Our study demonstrated that cationic surfactant HPP-16 allows achieving a 3 to 8-fold increase in the solubility of these drugs at a concentration of 3mM. It is worth noting that the effectiveness of solubilization significantly depends on the solution pH. The incorporation of hydroxy fragment into surfactant molecule is revealed to enhance the solubilization effect of HPP-16 compared to its nonfunctionalized analog. The transition from micellar solutions to biocompatible microemulsions based on Tween 80 with the addition of HPP-16 allows of increasing the solubilization capacity of the anti-inflammatory drugs by more than an order of magnitude.

Acknowledgment: This work was supported by the Russian Foundation for Basic Research and the Government of the Republic of Tatarstan (project № 18-43-160015).

Targeted drug delivery to dopaminergic neurons by the functionalized derivative of the dopamine transporter inhibitor GBR12909: a proof of concept

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One of the key challenges in medical chemistry is the targeted delivery of therapeutic molecules to the intended site of action. A possible solution is to design hybrid molecules that combine an address part directed at a specific target on the cell membrane and the active substance itself. The aim of this work is to create a construct capable of selectively delivering active molecules to dopaminergic neurons. The applicability of creating such drugs is explained by the need to protect dopaminergic neurons, which progressively die in Parkinson's disease. A convenient and adequate target for delivery of such drugs is the membrane dopamine reuptake transporter (DAT). As the address part of the prototype drug, we have chosen DAT inhibitor GBR12909, which differs from other known inhibitors by high selectivity and affinity for DAT. The synthesis of a universal functionalized analog carrying a primary aliphatic amino group was developed, which is subsequently further modified by attaching linkers with other functional groups for conjugation with therapeutically significant molecules. To test the applicability of this design for the targeted delivery of active substances to dopaminergic neurons, a fluorescent analogue of functionalized GBR12909 was synthesized with a BODIPY-FL fluorophore. The study of the internalization of this substance by cells containing active DAT showed that the fluorescent analogue penetrates into the PC12 pheochromocytoma cells and the rat brain dopaminergic neurons through selective transport using DAT. Thus, it has been established that the fluorescent analogue GBR12909 is a ligand of the dopamine transporter and DAT system can be used for the targeted delivery of active compounds to dopaminergic neurons.

The work is supported by the Research Program of the Presidium of the Russian Academy of Sciences «Fundamental research for biomedical technologies», project No. 0108-2018-0006.

Selective cytotoxicity of Arg/Lys-enriched peptides and the possibility of their use for anticancer therapy

Lushnikova A.A.[1], Rudakova A.A.[1], Onyan A.V.[1], Kostarev A.V.[2], Ponkratova D.A.[1], Kozhikhova K.V.[3] , Andreev S.M.[3], Balbutsky A.V.[1], Baryshnikova M.A.[1]

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Introduction. .Molecular-directed antitumor therapy is a challenge of modern oncology. A number of cationic peptides (CP) with low molecular mass and arginine (Arg/R), lysine (Lys/K) –rich residues exhibit a selective toxicity against solid tumor cells without affecting the physiology of normal cells at low concentrations. The selective cytotoxicity of CP is based on the differential expression of chaperone proteins nucleophosmin/NPM and nucleolin/ NCL in tumor and normal cells. **Purpose**.Analysis of mechanisms of selective cytotoxicity for CP and a search for their molecular targets. **Materials and methods**. Human transplantable cell lines (CL) were used: cutaneous melanoma - melIS, melH, mel Ibr, breast cancer (BC) and drug - resistant breast cancer (MDR)-HBL – 100, HBL 100 - ID120, hepatocarcinoma and hepatoblastoma-Huh – 7 and HepG2, pancreatic cancer – Panc 1, MiaPaCan2, AsPc1, CaPa2, ovarian cancer - CrovCel, glioblastoma -GLB _Sh and Glb_17; lines of skin fibroblasts Wi - 38 and H1036- as a control. Seven CPs were tested using MTT tests, flow cytometry, western blotting, IGH and RT-PCR to analyze the expression of p53, NPM and NCL. The results of *in vitro* cell cultivation with these CPs (C=0,25 – 4 mg/ml, 2-3 days.) were observed under a fluorescent microscope using cyanine labeled Cy5-KP:Cy5*-R_8-K_4K_2KAC-NH_2. Intermolecular interactions and molecular dynamics were modeled and evaluated in Maestro 11 program. **Results.** All the CLs under study have revealed a high selective cytotoxicity for tested CPs: IC50 ranged from 0.5 to 1 μg, with induction of apoptosis. Control fibroblast CLs survival has not changed significantly. In the course of 2-6 hours of cultivation of tumor cells in 96 well cell cultured clusters and micro-wells, activation of caspase 3, 8 and 9 was detected along with increased frequency of DNA double-strand breaks, degradation of chromatin and mitosis spindle. Tumor cell apoptosis was revealed in MDR breast cancer line HBL-100-ID120, apparently associated with the activation of the cas2 and NCL-RFWD-p53 signal cascade. Molecular interactions were confirmed by pair docking. A modeling of the interactions of CPs with cell surface NCL and NPM pentamer has revealed a high scores and preferred amino acid residues that are forming hydrogen bonds with these proteins. The dynamics of processes and specific cytotoxicity of tested CPs were evaluated.

Synthesis of new 6-nitroazolo [1,5-a] pyrimidines with the possibility of further modification into azolopurines

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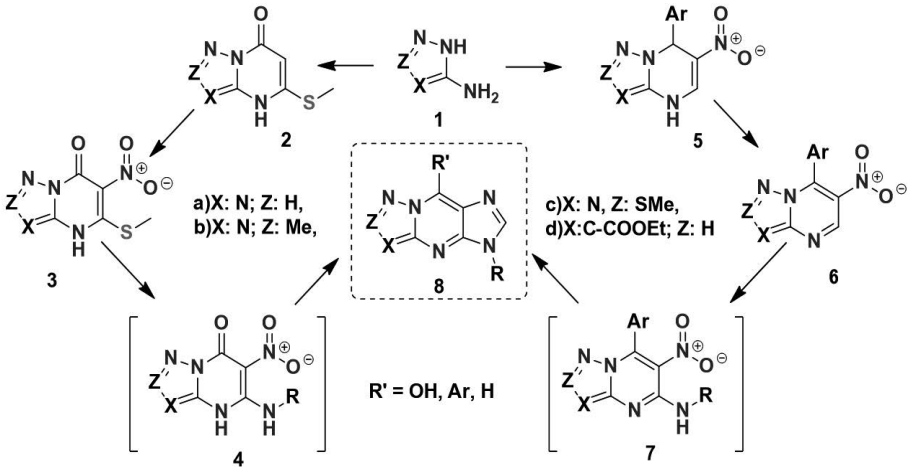
The role of purine nucleosides in the life of the organism is very diverse: inclusion in the structures of DNA and RNA, regulatory functions, and so on. Structural analogs of endogenous purines are often able to replace them in key metabolic processes, which allows to create drugs. One of the promising classes of compounds that model the biological behavior of purines is azaindolizines, specifically azolo[1,5-a]pyrimidines, since they are isosters of purines. Moreover, azaindolizines similar structures are used independently as drugs (vasodilators, antiviral and antibacterial drugs) in countries such as Germany, Japan, Russia, etc. Assuming that the heterocyclic system that is a hybrid of purine and azaindolizine has more opportunities to affect important biological receptors, we set a goal to synthesize azolo [1,5-a] pyrimidines to study their biological activity, as well as their subsequent transformation in the linear azolo [1,5-a] purines **8**.



Azolopyrimidines **3** and **6** were chosen from the point of view of possibilities for further structural modification - the pyrimidine ring should be similar to guanine and adenine; the nitro group acts as a hidden N-atom of the imidazole ring. In addition, in the drugs «Triazavirin» and «Triazid», the nitro group is an important structural element in terms of the mechanism of action. In the resulting aromatic 6-nitroazolo[1,5-a]pyrimidines **3,6**, position 5 is functionalized by the introduction of actual amines. In both cases, the cyclization is performed in similar ways.

Thus, new methods were developed for the synthesis of 6-nitroazolo[1,5-a]pyrimidines **3,6**, which are a promising matrix for the creation of new non-natural purine nucleosides.

2-Cyano-4-pyrone as a substrate for the preparation of pyrazoles and pyridones

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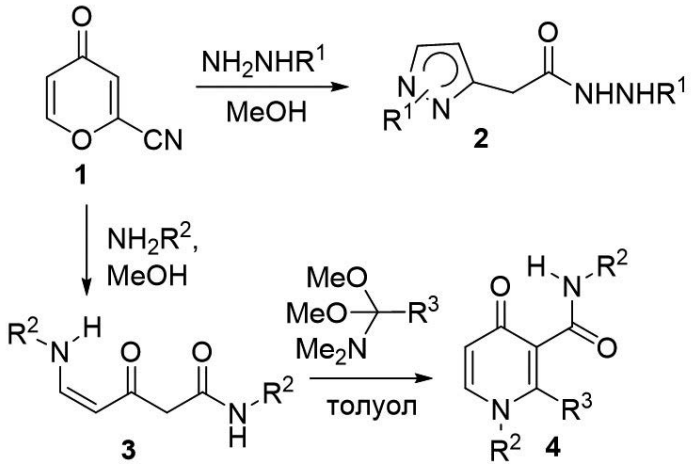
2-Cyano-4-pyrone **1** is the simplest representative of 2-cyano-4-pyrones and a scarcely studied molecule. We have found that pyrone **1** reacted with hydrazines to give pyrazoles **2** in good yields. In the case of unsubstituted hydrazine, the transformation proceeded selectively. When phenylhydrazine was used as a nucleophile, a mixture of regioisomers was obtained, which can be prepared in pure form by recrystallization.

Under the action of primary amines, cyanopyrone **1** undergoes a pyrone ring opening transformation to produce carbamoylated enaminones **3**. These compounds led to 4-pyridone-3-carboxamides **4** by the reaction with DMF-DMA or DMA-DMA.

The obtained compounds **2** and **4** bear the pharmacophore moieties, the pyrazole or pyridone rings, and are of interest for medical chemistry.



A novel acetazolamide cocrystal

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Acetazolamide (ACZ), 5-acetamido-1,3,4-thiadiazole-2-sulfonamide, is an inhibitor of carbonic anhydrase II and has been included in the WHO Model List of Essential Medicines. ACZ is used mainly for the treatment of glaucoma, but is explored also for the management of epilepsy, acute mountain sickness, respiratory diseases and, recently, for the symptomatic treatment of idiopathic intracranial hypertension [1, 2]. ACZ has low solubility and poor permeability, which makes the discovery and identification of new solid forms of ACZ (cocrystals) relevant to improve its physical and chemical properties. Today set of ACZ cocrystals with 4-hydroxybenzoic acid, 2-hydroxybenzamide, nicotinamide, picolinamide, 2,3-dihydroxybenzoic acid are reported [1]. The mechanochemical approach (liquid-assisted grinding) has been demonstrated as a powerful technique for screening new cocrystals and their polymorphs. The aim of our study was to investigate the influence of solvent on the acetazolamide cocrystal screening by liquid-assisted grinding. 4-Aminobenzoic acid was employed in grinding experiments as coformer with acetazolamide. For estimation of solvent role, 7 solvents of different polarity were chosen: ethanol, methanol, tetrahydrofuran, ethyl acetate, water, acetone and acetonitrile. A novel ACZ cocrystal with 4-aminobenzoic acid was identified only by grinding physical mixture with acetonitrile. Cocrystal was characterized by DSC and single crystal X-ray diffraction analysis and was investigated it solubility and dissolution rate in water.

This work was supported by the Russian Science Foundation (No. 17-73-10351)

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Synthesis of highly lipophilic organophosphorus derivatives of naltrexone

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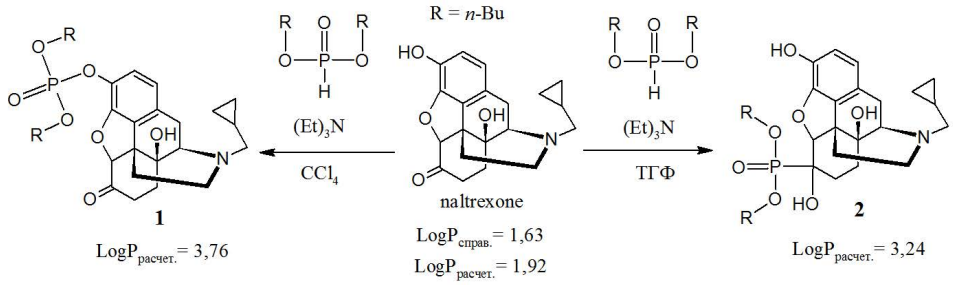
Naloxone is an opioid receptor antagonist which most commonly used as an antidote for poisoning with narcotic analgesics in medical practice, however, due to insufficient affinity and suboptimal pharmacokinetic properties it is not always effective [1]. Naltrexone and its derivatives which are pharmacological agents with clinical experience have high potential for the development of treatment of acute poisoning by narcotic analgesics.

We obtained new naltrexone derivatives: among them are phosphate **1** and phosphonate **2**, and also calculated lipophilicity indicators for the obtained and initial compounds using the standard ACD / Percepta.



Compound **1** has the greatest lipophilicity among the presented compounds and is positioned by us as a naltrexone prodrug, and compound **2** may have a completely different affinity for opioid receptors and accordingly a different pharmacological profile due to the position of the phosphoryl group.

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Design and synthesis of quinazoline dopped hydroxamic acid derivatives as VEGFR/HDAC inhibitors

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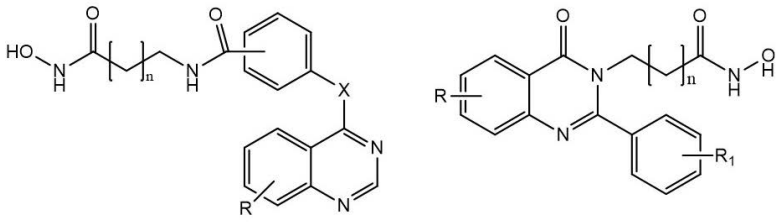
Chemistry of hydroxamic acids is an intensively developing section of synthetic organic chemistry. In medical chemistry, derivatives of hydroxamic acids are mainly considered as inhibitors of histone deacetylase, which are essential targets in the treatment of cancer [1].

The chemical flexibility of the hydroxamate group allows its use in a variety of natural and synthetic compounds, as well as in well-known preparations [2], resulting in a clearer therapeutic effect. Multi-purpose hybrids based on histone deacetylase inhibitors are becoming new methods of anticancer therapy [4].

The report discusses the strategy for creating bifunctional compounds by conjugating hydroxamic acid derivatives with a quinazoline or quinazolon fragments.

The results of the work on the synthesis of new compounds containing hydroxamic acid and a heterocyclic fragments are presented.



R=Alk, AlkO, Hal; R_1=Alk, AlkO, Hal, Ar, HetAlkyl, HetAr

The synthesized compounds are potential bifunctional antitumor agents acting on histone deacetylase and various tyrosine kinases.

This work was supported by the Ministry of Education and Science of the Russian Federation (grant agreement № 075-11-2018-172, RFMEFI62418X0051).

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The method of address covalent immobilization of proteins on the surface of the working electrode through the reaction of copper-catalyzed azide-alkyne cycloaddition (CuAAC)

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A key part in electrochemical immunosensors creation is a method of antibodies immobilization on the surface of the working electrode. Address covalent immobilization can improve the analytical characteristics of the sensor. A promising method of bio-orthogonal immobilization is the CuAAC reaction, characterized with expressivity, high product yield, low toxicity of the reagents and products. The “mild conditions” of the click-reaction are also an undeniable advantage during working with protein structures.

The aim of this work was to develop a method for covalent immobilization of proteins on the surface of a working carbon-containing electrode through the reaction of CuAAC using as a catalyst copper particles included in an electrodeposited film of polyvinylbenzylazide on the electrode.

Protein immobilization was carried out in three stages: forming a polymer film with copper particles on the surface of the working electrode, conducting click-reaction between the azide groups of the polymer film and the acetylene fragment of propargyl-N-hydroxysuccinimide ester, and incubation in a protein solution. The formation of the polymer layer, the reaction of the copper-catalyzed azide-alkyne cycloaddition and the immobilization of the protein on the electrode were controlled by the method of cyclic voltammetry and electrochemical impedance spectroscopy using an Autholab Type III analyzer. $K_4[Fe(CN)_6]/K_3[Fe(CN)_6]$ was used as a mediator system.

The working conditions for the electropolymerization of vinylbenzylazide, the click-reaction and the immobilization of the protein on the surface of the working electrode were chosen. The results obtained make it possible to make the address covalent immobilization of protein on the surface of a carbon-containing electrode.

This work was supported by the Russian Scientific Fond (grant number 17-13-01096)

The use of carbamate-bearing surfactants to improve the solubility of meloxicam

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Amphiphilic compounds are mainstream in the design of building blocks for nanoscale supramolecular systems showing high interface activity and wetting effect on hydrophobic surfaces, exhibiting improved solubilization and transport effect, controlling the stability and properties of guest molecules. Employment of these substances in biotechnologies, pharmacology, and medicine make requirements of their properties such as high performance under mild conditions and in the low concentration range, low toxicity, and the ability to overcome biological barriers. In this work, a series of new carbamate-bearing cationic surfactants with hexadecyl tail and varied structure of head group was synthesized and characterized. Their aggregation parameters (critical micelle concentration, size, surface potential, degree of counterion binding, aggregation numbers) have been determined. The solubilization capacity of carbamate-bearing surfactants was evaluated in relation to the anti-inflammatory drug meloxicam by a spectrophotometric method. Due to low solubility of meloxicam at pH <5.5 it dissolves and absorbed only in the intestinal tract rather than in the stomach upon the oral administration, which significantly slows down its therapeutic effect. It has been shown that the carbamate-bearing surfactants can be related to the class of moderately toxic compounds. The use of this surfactants in a concentration of about 0.1% allows of increasing the solubility of meloxicam in acidic media by more than an order of magnitude. Using carbamate-bearing surfactants in binary compositions with nonionic amphiphiles (Tween 20, Tween 80, Tyloxapol) allows us to reduce the toxicity of the systems, while maintaining a high level of their solubilizing action.

Acknowledgements

This work is supported by the Russian Science Foundation (grant № 19-73-30012).

Novel viral entry inhibitors for the treatment of chronic hepatitis B

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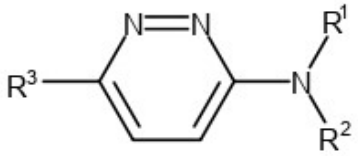
Treatment of chronic viral hepatitis remains a serious medical problem. One of the promising solutions is the development of virus entry inhibitors capable of blocking the function of Sodium/Taurocholate Co-transporting Polypeptide (NTCP), the cellular receptor for hepatitis B and D viruses, and thereby preventing the viral infection of liver cells [1].

During a systematic study that included the stages of computational simulation of interaction of NTCP and its known ligands, and construction of QSAR models and 3D pharmacophore models, a number of promising chemotypes of heteroaromatic compounds were identified. Effective synthetic approaches were developed to obtain the appropriate combinatorial series of compounds, and the resulting synthesized products were investigated in an *in vitro* model to assess their ability to prevent the hepatitis virus entry into the cell by inhibiting NTCP. In particular, 6-aryl-substituted pyridazin-3-amines were identified as potent NTCP inhibitors (IC_{50} from 10 μM to less than 0.1 μM) with low cytotoxicity (CC_{50} > 30 μM). At present, systematic preclinical studies of the most active leading compounds in *in vivo* models have been initiated.



R^1, R^2 = alkyl, cycloalkyl; R^3 = aryl

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Synthesis of hybride compounds on the basis of fluoroquinolones as potential antitubercular agents

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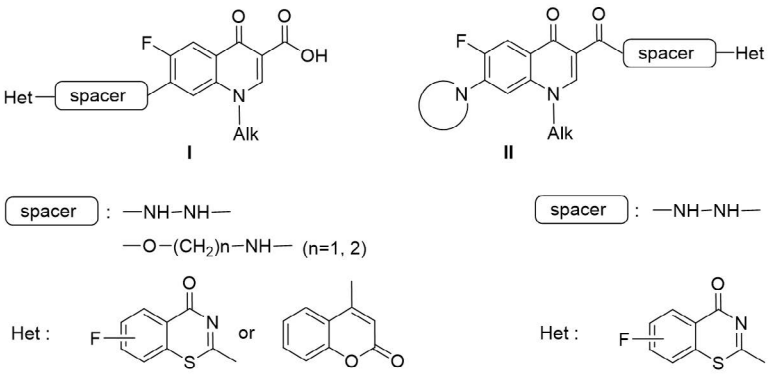
Design of antibiotics with dual action is considered nowadays as the relevant strategy directed to creation of the medicines with the broadened range of action in comparison with initial antibiotics and which are slowing down the development of the resistance to antibiotics. Fluoroquinolones are perspective candidates for the creation of hybrid antibiotics on their basis because from the chemical point of view fluoroquinolones are characterized as rather stable compounds and can be successfully modified without the loss of antibacterial activity [1,2].

Efficient synthetic approaches to antibacterial agents with dual mechanism of action, hybride fluoroquinolone compounds with covalent bond between fluoroquinolone fragment and coumarine or benzothiazinone core (**I**, **II**), were developed.



The structure of compounds obtained was confirmed by the data of NMR and mass spectra.

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The work was carried out with financial support from the Russian Scientific Foundation (grant 15-13-00077-P) and from the Ministry of Education of Russian Federation (State Contract 4.6351.2017/8.9).

Multimodal Polymeric Adsorbent for Extracorporeal Therapy of Sepsis

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JSC Efferon, 143026, Russia, Moscow, Skolkovo, Nobel str, 7

Sepsis is a severe complication of generalized infections with high mortality up to 40%. Primary trigger of sepsis is the translocation of bacterial or fungal cell components into the bloodstream which provokes an excessive immune response. Typical therapeutic targets are the endotoxins of gram-negative bacteria (lipopolysaccharides, LPS). A number of clinical studies have shown the LPS-selective and non-selective extracorporeal removal of LPS from the patient's blood improves outcome of patients with sepsis. However, there is not a single extracorporeal adsorber that is able to simultaneously remove both LPS molecules and internal inflammatory mediators, such as cytokines.

Multimodal macroporous hypercrosslinked polystyrene adsorbent was developed in this work. The surface of the polymer was modified with synthetic ligand complemental to conservative moiety of bacterial endotoxins. A series of *in vitro* tests was conducted to determine the efficacy and safety of the sorbent. The main results are shown below. Endotoxin concentration decreased by 18.5 times in 0.9% saline after 2 hours of perfusion wherein the residual adsorption capacity of the sorbent was maintained at initial level.

Erythrocyte suspension and freshly prepared donor blood perfusion through adsorbent did not cause the appearance of cytolytic markers but a twofold decrease of free hemoglobin concentration, a decrease in the level of significant cytokines (IL-8, IL-10, etc.) and small molecules (bilirubin, creatinine, β_2-microglobulin, etc.) by 1.5-4 times was determined in the same time. Also it was demonstrated that bacterial endotoxin level dramatically decreased (more than 10 times after 1 hour) during perfusion of contaminated bovine blood.

Additionally *in vivo* study using septic shock swine model was carried out. Septic shock was induced by i.v. injection of *E.coli* O55:B5 LPS (20 000 000 EU). It was shown that hemoperfusion can stabilize the condition of animals and in some cases even prevents of septic shock manifestation.

Thus a number of carried out *in vitro*, *in vivo* and *ex vivo* experiments persuasively demonstrated the efficacy and safety of an innovative cross-linked polystyrene adsorbent in the extracorporeal sepsis treatment.

TRANSITION METALL-FREE C-H/C-Li COUPLING OF PENTAFLUOROPHENYLLITHIUM WITH 1,2,4-TRIAZINES – PASE METHOD TOWARDS POLYFLUORO AZAGETEROCYCLIC SYSTEM

Moseev T.D. [1], Varaksin M.V.[1,2], Kopchuk D.S. [1,2], Gorlov D.A.[1], Nikiforov E.A.[1], Lavrinchenko I.A.[1], Charushin V.N.[1,2], Chupakhin O.N.[1,2]

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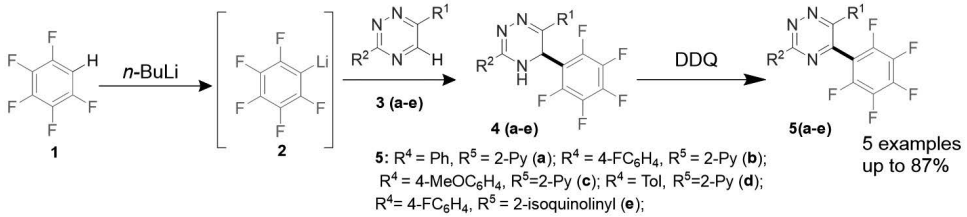
Development of atom and stem economical (PASE) methods for the synthesis of organic compounds is one of the key challenge in modern organic chemistry. These methods are attractive because they correspond to basic principles of green chemistry and do not require catalysis by transition metals.

Due to special properties of polyfluoro organic compounds, these compounds are widely used in the fields of molecular electronics (OLED) and as biomarker for detection and treatment of social diseases (PET).

There are a lot of known methodologies to construct C-C bond. In particular, reaction of nucleophilic substitution of hydrogen (S_N^H) in 1,2,4-triazines under the action of pentafluorophenyl lithium **2** prepared from pentafluorobenzene **1** and *n*-BuLi is one the most attractive complying with the basic principles of green chemistry.

According to the modern concept of S_N^H reactions, this coupling is a two-stage process by the addition-oxidation mechanism (S_N^HAO). On the first stage, pentafluorophenyl lithium **2** interacts with C(5)-carbon atom of 1,2,4-triazine **3(a-e)** to lead to stable σ^H-adduct **4(a-e)**. These compounds are able to be aromatized into 5-pentafluorosubstitution-1,2,4-triazines **5(a-e)** by action of oxidative agent (DDQ).



As a result, a number of 5-pentafluorophenyl-substituted 1,2,4-triazines have been obtained. The resulting compounds are of particular interest in the field of medical chemistry, molecular electronics, and coordination chemistry.

M.V. Varaksin, T.D. Moseev, V.N. Charushin, O.N. Chupakhin, J. Organomet. Chem., 2018, https://doi.org/10.1016/j.jorganchem.2018.01.020

The study was carried out with the financial support of the Russian Foundation for Basic Research in the framework of a research project 18-33-00226.

NUCLEOPHILIC SUBSTITUTION OF HYDROGEN (S_N^H) IN THE SYNTHESIS OF PENTAFLUOROPHENYL-CONTAINING 2*H*-IMIDAZOLES AND N-OXIDES

Moseev T.D. [1], **Varaksin M.V.**[1,2], **Gorlov D.A.**[1], **Nikiforov E.A.**[1], **Lavrinchenko I.A.**[1]
Charushin V.N.[1,2], **Chupakhin O.N.**[1,2]

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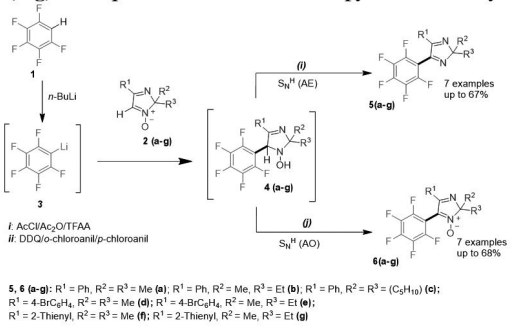
Organic molecules containing polyfluorinated moiety have found various applications in many areas of science and technology as promising materials for medical and cryochemistry, molecular electronics, as well as in the field of biologically active substances exhibiting chaperone activity.

Due to unique physical properties of fluorine atom, the introduction of this atom into an organic molecule allows obtaining substances with such desired properties as increased bioavailability, improved photophysical indicators, resistance to undesirable degradation transformation.

Thus, the development of new efficient methods of unknown azaheterocyclic pentafluorophenyl-substituted compounds is a key challenge in modern organic synthesis. The methodology of nucleophilic substitution of hydrogen in 2*H*-imidazole N-oxides by the action of pentafluorophenyllithium **2** is one of the most effective strategy for this transformation that does not require additional catalysis and using the protective group.

This transformation can be implemented in two ways. After the formation of adduct **4(a-g)**, when a deoxygenating agent is present in the reaction mass, the reaction proceeds according to the addition-elimination scheme S_N^H(AE) furnishing the formation of products **5(a-g)**. Contrarily, if an oxidant is present instead of deoxygenating agent, the reaction would proceeds according to addition-oxidation mechanism S_N^H(AO) resulting in compounds **6(a-g).**



Scheme 1. Coupling of pentafluorophenyl lithium with 2H-imidazole-1-oxide

The new pentafluorophenyl-containing 2*H*-imidazoles were obtained from good to excellent yields, which are of particular interest in the field of medical chemistry and molecular electronics.

The study was carried out with the financial support of the Russian Science Foundation as part of a research project 18-73-00088.

Synthesis of amides and thioamides combining adamantane and monoterpene fragments

Mozhaitsev E.S.[1], Munkuev A.A.[1,2], Zakharenko A.L.[2,3], Suslov E.V.[1], Korchagina D.V.[1], Zakharova O.D.[2,3], Vasil'eva I.A.[3], Chepanova A.A.[3], Volcho K.P.[1,2], Salakhutdinov N.F.[1,2], Lavrik O.I.[2,3]

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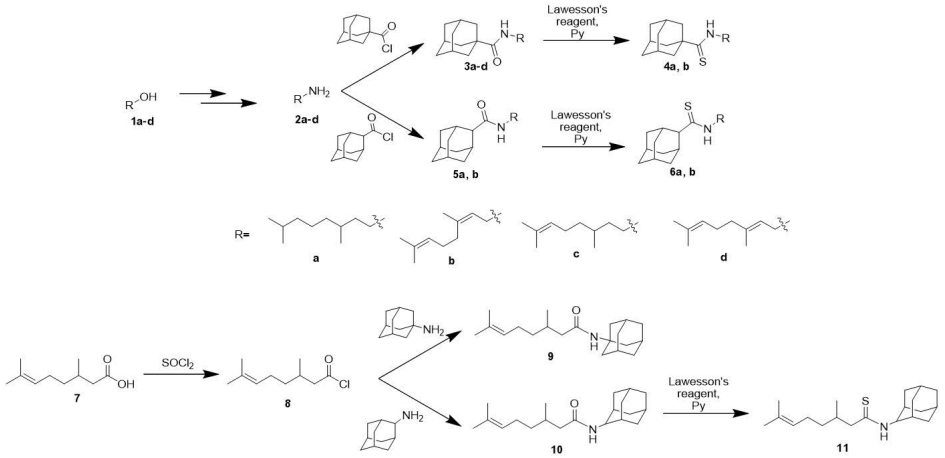
[2] Novosibirsk State University, 630090, Russian Federation, Novosibirsk, Pirogova Str., 2.
[3] Institute of Chemical Biology and Fundamental Medicine, Siberian Branch of Russian Academy of Sciences, 630090, Russian Federation, Novosibirsk, Lavrentiev Ave., 8.

A number of 1- and 2-adamantane carboxylic acid amides were synthesized by interaction of corresponding acid chlorides with monoterpene amines. Preliminary, amines were obtained from corresponding monoterpene alcohols. Some amides obtained were boiled with Lawesson's reagent yielding thioamides. To investigate «structure – biological activity» relation a number of citronellic acid amides were synthesized as well as thioamide was obtained from 2-adamantane substituted isomer.



A most of adamantane derivatives were shown being active according to human DNA repair enzyme Tdp1 at micromolar concentrations.

The work was supported by the Russian Science Foundation under Grand № 19-13-00040.

Study of the neuroprotective properties of the anti-amyloid agent Amylovis as a promising drug for the treatment of neurodegenerative diseases

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The major obstacle of drug research of a wide range of central nervous system (CNS) diseases lies in the development of scientific and experimental methodologies for generation of proper therapeutics acting on the core stages of pathogenesis permanently halting the progression of the pathological process (the so-called "disease-modifying drugs") and not temporarily improving the disease symptoms ("symptomatic action" drugs).There is an urgent need for a reliable method for selecting and evaluating potential new compounds, as well as the evidence-based approach for designing and screening of drugs acting on the central nervous system biotargets. The relevance of the current study is based on the use of adequate models of neurodegenerative disease, which recapitulates the main features of the molecular processes found in such pathologies as Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and a number of others. The core pathological process that is reproduced in our models is based on protein aggregation at an early stage of development of disease in the brain (neuropathology). The development of innovative approaches in genetic modeling neurodegenerative processes both *in vitro* and *in vivo* is one of the primary objectives of our Institute. At the moment, there are several lines of transgenic animals which recapitulate major different steps of proteinopathy pathogenesis whereas our colleagues Cuban Neuroscience Center (CNEURO) has developed and patented a set of compounds called Amylovis which were shown to bind with senile plaques*in silico*, *in vitro* and *in vivo* studies. The combination of adequate models of neurodegenerative diseases and computer screening techniques prior to selection of prospective structures from the Russian side with the synthesis of original compounds provided by the Cuban colleagues, blends into a unique opportunity for a comprehensive solution of the global scientific challenges to develop "disease-modifying" neuroprotective drugs.The study is supported by Skolkovo Resident LLC "BioNeuroPharma".

Evaluation of the prospects for the combined use of ultrasound and ionizing radiation in the in the cancer therapy

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The main focus in the therapy of cancer is the development of integrated methods that focus on individual patients. The aim of the work was an experimental study on models of different levels of complexity of the effects of the combined action of ultrasound and ionizing radiation. The prospects of such a combination, is determined by the mutual addition of a number of therapeutic factors of the two methods of treatment.

The objects of study were octa sodium salt of cobalt octa-4,5-carboxyphthalocyanine (teraphthal), the enzyme alkaline phosphatase and bacteria Lactobacillus casei. Irradiation of objects with ionizing radiation was carried out on a ^{137}Cs γ-400 facility (2 Gy/min), ultrasound – on an Albedo setup (frequency 0.88 MHz, intensity 2 W/cm^2). The results were assessed by the change in the teraphthal optical spectra, enzyme activity and survival and the size distribution of bacterial cells.

The presence of a synergetic effect of changes in the structurally dependent parameters of the enzyme alkaline phosphatase and the bacteria Lactobacillus casei was revealed. It is established that the magnitude of the effect depends on the complexity of the object, the order of exposure, the magnitude of absorbed doses and the presence of a sensitizer – a substance that enhances the action of ultrasound [1]. Comparison of the size distribution functions of bacteria that survived after various exposures showed that larger cells with more than 15 μm length are eliminated first. The role of post-effects in the combined action of ultrasound and ionizing radiation is revealed. A tumor model has been selected for in vivo experiments.

The obtained results demonstrate the perspectivity for the development of research in the field of the combined use of ultrasound and radiation medicine in the cancer therapy. This work was supported by the RFBR grant No. 18-08-01197/19.

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Antiviral activity of perilene derivatives against respiratory viruses – influenza, parainfluenza and respiratory-syncytial virus.

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The project aims to solve acute medical and social problems - the search for new means of combating respiratory viral infections. SARS annually affects up to 30% of the population, half of which are children. Mortality from respiratory diseases (including influenza, respiratory syncytial infection, etc.) is about 4.25 million cases per year [1].

Despite the fact that there are a large number of drugs on the pharmaceutical market for the treatment of respiratory diseases, most of them are symptomatic drugs, and in some cases even homeopathic medicines. In addition, for a number of respiratory infections, such as adenoviral or parainfluenza, etiotropic drugs do not exist at all.

At present work we had investigated antiviral activity of 6 perilene derivatives against three respiratory viruses – influenza, parainfluenza and respiratory-syncytial virus. 5 compounds had shown significant activity against influenza virus (SI more than 100) and also significant, but a little bit reduced activity against respiratory-syncytial virus. Interestingly, all compounds tested were active against parainfluenza, having SI higher than for influenza virus.

Thus, we can make a conclusion about high potential of this group as respiratory viruses inhibitors.

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Synthesis and Study of Psychotropic Activity of 1-Substituted 4-Amino-5-oxoprolines

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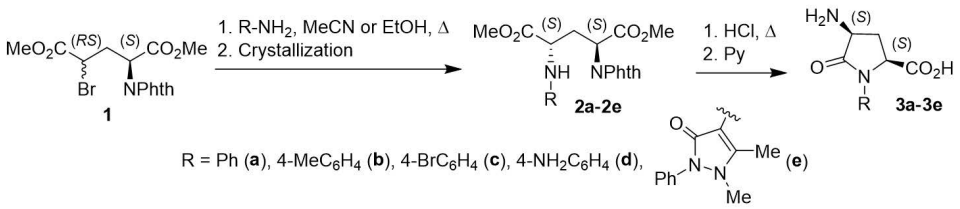
4-Aminobutyric acid (GABA) is a neurotransmitter of CNS inhibition. GABA derivatives exhibit psychotropic and anticonvulsant properties. The purpose of this work was to prepare and study psychotropic activity of 1-substituted 4-amino-5-oxoprolines that can be considered both as cyclic GABA analogues and as pyroglutamic acid derivatives.

Nucleophilic substitution of halogen in dimethyl (2*S*,4*RS*)-4-bromo-*N*-phthaloylglutamate (1) with arylamines or 4-aminoantipyrine followed by the isolation of predominant (2*S*,4*S*)-diastereoisomers gave compounds 2a-2e. Heating of compounds 2a-2e in an acidic medium resulted in removal of protecting groups and lactamization, which afforded 1-substituted 4-amino-5-oxoprolines 3a-3e. The structure of the target compounds was confirmed by NMR spectroscopy and elemental analysis.



The study of psychotropic activity of compounds **3a-3e** was carried out on white outbred female rats using 1/60, 1/30 and 1/15 equimolar doses. Compounds were administered intraperitoneally 30 min before testing. It has been found that compound **3d** causes a moderate increase in motor activity in the open field test and anxiolytic action in the elevated plus maze test. Compounds **3b-3d** showed nootropic properties (they improved the formation and maintenance of a memory trace) in the passive avoidance and extrapolation deliverance tests.

The study was carried out in the framework of the State Assignment of Russia (project no. AAAA-A19-119011790130-3).

Fluorinated benzothiazinones possessing cytotoxicity

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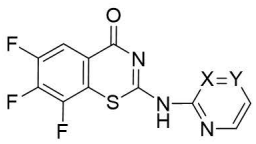
The benzothiazine fragment is scarcely presented in the structure of natural compounds, however many synthetic benzothiazines are biologically active, which play an important role in treatment of various diseases. We developed effective synthetic approaches to fluorine-containing 2-substituted 1,3-benzothiazin-4-ones **1, 2** based on nucleophilic addition of heterylamines or cycloalkylamines to polyfluorobenzoyl isothiocyanates and subsequent intramolecular cyclization. Cyclocondensation of polyfluorobenzoyl chloride with azolylthiones represents a convenient approach to [*b*]-annelated fluorine-containing benzothiazinones **3**, linear structure of tetracyclic derivatives has been proved.

In the frames of Open HTS Cell Cytotoxity Project (Medicinal Chemistry Center, Togliatti State University) three types of fluorinated 1,3-benzothiazin-4-ones **1**-**3** were studied for their cytotoxicity towards epidermal carcinoma (A431). Among 2-heterylamino-6,7,8-trifluoro-1,3-benzothiazin-4-ones **1** pyrazinyl derivative (X = CH, Y = N) demonstrated the best result (48.8% of survived cells). In the series of 2-piperazinyl-6,7,8-trifluoro-1,3-benzothiazin-4-ones **2** arylpiperazinyl derivative (R = 2-fluorophenyl) proved to be the most perspective (38.4% of survived cells).



1

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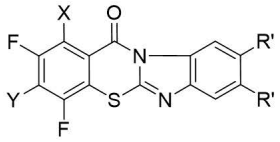

3

Benzimidazo-annelated benzothiazinones **3** were also tested, tetrafluoro derivative (X = Y = F, R' = H) demonstrated the lowest percentage of survived cells (33.3 %). All mentioned compounds exhibited EC_{50} < 10 μmol/mL and were selected for further investigations.

The work was carried out with financial support from the Ministry of Education of Russian Federation (State Contract 4.6351.2017/8.9).

Development of Approaches to the Efficient Isolation of Isomerically and Optically Pure MDM2 Inhibitors of Pyrrolidin-2-one Series

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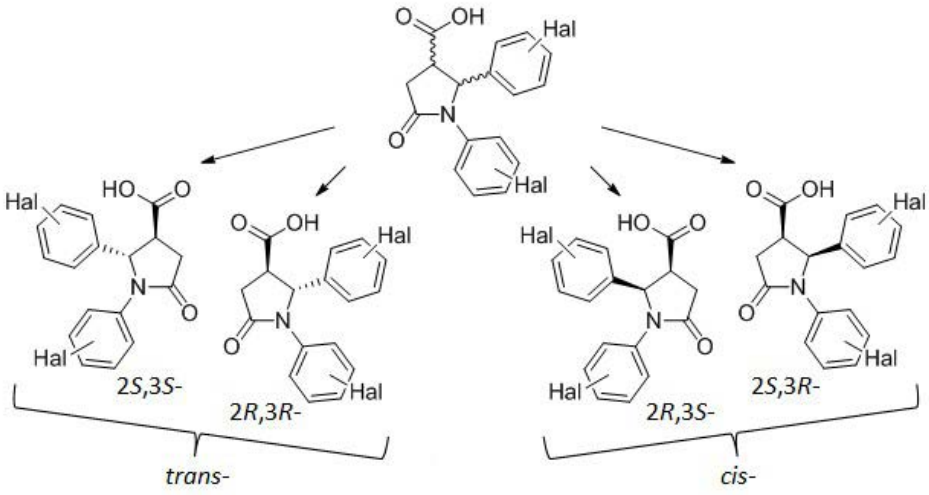
A number of structures based on the pyrrolidone scaffold was identified during screening of a focused library of compounds in order to identify new inhibitors of the MDM2-p53 protein-protein interaction [1]. Synthesis of the identified active compounds is carried out by the cyclization of various Schiff bases with succinic anhydride with the formation of Castagnoli-Cushman acids [2] and their subsequent amidation.

The main feature of the present class of compounds is the presence of both *cis*-/*trans*- and optical isomers. In this study, we consider possible pathways for the derivatization of the Castagnoli-Cushman acids formed during the synthesis, which allow isolating geometrically and optically pure isomers to identify the most active ones according to the used pharmacophore hypothesis, as well as factors that allow shifting the isomeric ratio towards the minor *cis*-form.



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

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Synthesis of macrocyclic ketones as potential precursors for antitumor drugs

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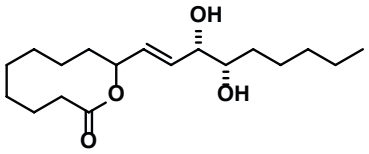
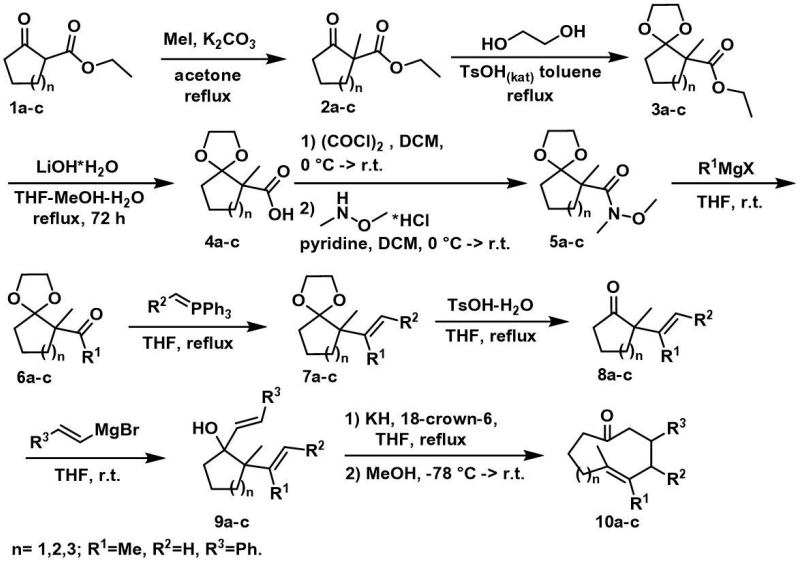
The most important and popular problem in modern science is discovery of new efficient drugs against human cancer cells. Macrocycles is a large part of natural compound which have wide biological activity against different biological targets including tumor cells. Recent investigations show that more new compounds isolated from vegetal materials contain in its structure 9-11 membered carbocycle or heterocycle. These cycles can contain such fragments as ketone, lactone or amide. An example of such substance illustrated bellow.



This compound was isolated from seaweed and showed activity against human cancer cell lines U373 (glioblastoma–astrocytoma), A549 (lung carcinoma) [1].

We reported simple synthetic method of obtaining new 9, 10 and 11 membered macrocyclic ketones by oxy-Cope rearrangement.



n= 1,2,3; R^1=Me, R^2=H, R^3=Ph.

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Features of formation and structure of silicon–polysaccharide-containing polyolate hydrogels obtained by the method of biomimetic mineralization

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Previously we synthesized novel hybrid silicon-glycerol-chitosan hydrogels by biomimetic sol-gel method using silicon tetraglycerolate as biocompatible precursor and chitosan as template and properties modifier [1−3].

In this work we demonstrated that water-soluble biocompatible polyolate precursors of silicon tetraglycerolate and silicon tetrapolyethylene glycolate [4] can be successfully utilized in biomimetical mineralization of polysaccharides of different nature. By the example of chitosan (cationic), xanthan gum (anionic), and hydroxyethyl cellulose (uncharged) polysaccharides, an accelerating effect on the gelation has been demonstrated and a stabilizing effect has been revealed on the hydrogels formed as transparent monoliths showing resistance to syneresis. Structural features of silicon–polysaccharide-containing hydrogels were investigated using advanced physical methods of CryoSEM and TEM. Thus formed silicon-containing 3D-network of gels is found to be polymeric and appears to have an ordered amorphous morphostructure, which can be explained as caused by the effect of polysaccharides serving as templates. The difference in the reactivity of precursors leads to the peculiarities of the gelation process in the presence of the polysaccharides under study, as well as to the difference in the composition of the formed products.

The sol-gel process utilized to obtain the silicon–polysaccharide-containing hydrogels proceeds under the mild conditions with no catalyst or any organic solvent, and thus can be regarded as belonging to the green chemistry methods.

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Antienteroviral activity of N^6-substituted adenosines

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N^6-Substituted adenosines are a perspective group of nucleoside analogs with wide spectrum of biological activity [1]. Recently, we have shown that naturally occurring cytokinin nucleosides N^6-benzyladenosine and N^6-isoprenyladenosine inhibit reproduction of human enterovirus (EV) A71, but have been cytotoxic [2,3].

In this study we report a phenotypic screening of a large series of N^6-substituted adenosines, as well as several purine nucleoside derivatives modified in different positions, against several enteroviruses. EVA71 from *Enterovirus A* species was chosen for the initial screening as the most clinically relevant member of our panel. Coxsackievirus (CV) A16, Echoviruses (E) 13 and 30, and poliovirus (PV) type 1 and CVA21 were chosen as additional epidemiologically significant members of *Enterovirus A, Enterovirus B*, and *Enterovirus C* species, respectively.

It turned out that large number of our nucleosides inhibited reproduction of EVA71 and most compounds active against EVA71 were inactive against E30. Only a few of studied compounds inhibited the reproduction of E30. N^6-Benzyladenosine and some of its analogs containing different groups in the phenyl moiety demonstrated similar EC_{50} values against CVA16 and EVA71 of *Enterovirus A* species. Near the same results were observed in the case of E13 and E30 of *Enterovirus B* species. N^6-Substituted adenosines containing additional substituents in different positions of the purine heterocycle, as well as O^6-substituted inosine and guanosine derivatives, were completely inactive against all of the enterovirus species.

This work was supported by the Russian Foundation for Basic Research (17-04-01939).

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Dihydroazolopyrimidine crownophanes. Synthesis and tuberculostatic activity

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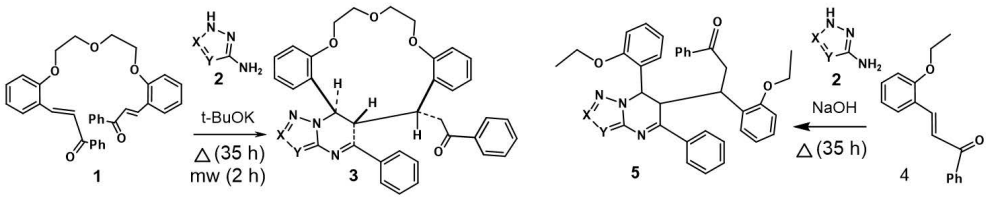
One of the strategies used in medical chemistry to increase biochemical activity, in particular, azolo [1,5-a] pyrimidines is the incorporation into the pharmacophoric core of functional groups, which are responsible for the solubility and transport ability of these compounds. In our studies, the positive effect of the polyester moiety on increasing the activity and reducing the toxicity of azolopyrimidine bacteriostatics has been demonstrated.

Crownophanes **3a**-**c** and their 6,7-dihydroazolo[1,5-a]pyrimidine acyclic analogs **5a**-**c** were synthesized as a result of a one-pot cascade sequence of intermolecular and intramolecular Michael addition reactions and heterocyclization at the final stage of the interaction of chalcone podand **1** or 2-ethoxy-trans-chalcone **4** with amino azole **2**.



(*R,S,R*)-**3a(X=CH,Y=CH),b(X=CH,Y=N),c(X=Y=N)** (*R,S,S*)-**5a(X=CH,Y=CH),b(X=CH,Y=N),c(X=Y=N)**

Tuberculostatic activity of crownophanes **3a**-**c** and their acyclic derivatives **5** *in vitro* was investigated towards the typical laboratory strain of *M. tuberculosis* $H_{37}Rv$. It has been established that the incorporation of the ionophoric crown ether fragment into compounds **3** contributes to an increase in tuberculostatic activity by an order of magnitude to a MIC 6.2 μg/ml (**3b**, **c**) in comparison with a MIC of 12.5 μg/ml for acyclic analogues **5a**-**c**. Compound **3a** has the highest tuberculostatic activity (MIC 3.15 μg / ml).

The work was financially supported by the Russian Science Foundation (project no. 15-13-00077-P).

Key factors for the effectiveness of cooperation between the pharmaceutical industry and academic institutions in drug discovery and development.

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The complexity and cost of the process of developing new drugs in the modern world leads to the fact that various stakeholders interested in the result of this process find ways to combine their efforts and resources to achieve goals. In Russia and in other countries the partnership between pharmaceutical companies and academic institutions in the field of drug development is very common and is developing quite intensively. The forms of such partnerships vary as well as its results - from colossal breakthroughs to serious failures. Some researchers are trying to determine what the preconditions for effective cooperation of commercial companies and scientific organizations are [1, 2], however, the specific conditions of Russia require the special researches in this area. Understanding exactly which factors increase the chances of partnership between industry and academic science for success, and which interfere with efficiency, it would certainly be useful for both parties to assess the potential of joint projects and select partners for cooperation.

Based on the data of the last 30 years, the report analyzes key factors affecting the effectiveness of cooperation between the pharmaceutical industry and academy, identifies the main problems and assesses the prospects for improving the efficiency of joint pharmaceutical business projects and research institutions in Russia. It was shown that such factors as the therapeutic area, type of drug, and development stage correlate most strongly with the degree of effectiveness.

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Heck reaction of sesquiterpene lactones with halogen-substituted quinolines. Synthesis and biological activity of 13-quinolinyleudesmanolides

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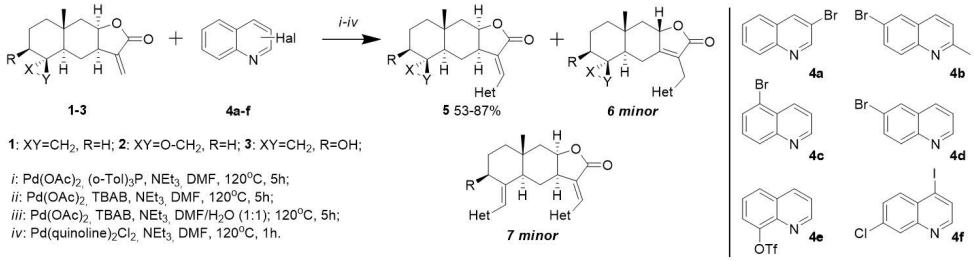
Quinoline derivatives are of interest for the development of antitumor, antiviral and antimicrobial agents [1,2]. In this work, we propose one-pot method for the synthesis of hybrid structures containing a fragment of quinoline and sesquiterpene lactone fragment, using Pd- catalyzed cross-couplig reaction. The interaction of isoalantolactone **1** with halogen-substituted quinolines **4a-f** catalyzed by $Pd(OAc)_2$ in the presence of NEt_3 and TBAB leads to 13-(*E*)-(quinolinyl)isoalantolactones **5a-f** with high yields. Additionally, the products of isomerization of 11,13-double bond **6a-f** and 13,15-bis(quinolinyl)isoalantolactones **7a-f** were obtained depending on the condition of the reaction, the structure of quinoline and methylenelactone, the nature of catalytic systems. High catalytic activity of $Pd(quinoline)_2Cl_2$ in the reaction of sesquiterpene lactones with 3-bromquinoline was shown.

The ways of formation of reaction products are discussed, as well as the results of studies of the biological activity of synthesized quinoline derivatives *in vitro* and *in vivo*.



This work was supported by the Russian Science Foundation (project No 18-13-00361).

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N-propargylation of indolo-triterpenoids and their application in Mannich reaction

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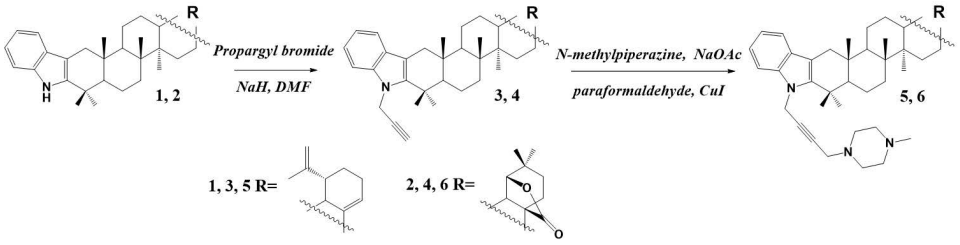
One of the priority topics in the chemistry of triterpenoids is the synthesis of various heterocyclic derivatives. According to previous reports, some indolo-fused lupanes showed α-glucosidase inhibitory activity and cytotoxicity. At the same time, there are no reports about synthesis of *N*-substituted indole-fused triterpenoids, which in turn opens up possibility for obtained of new conjugates. In this work, the first example of *N*-propargylation of indolo-triterpenoids is described and their application for Mannich reaction is presented. As starting material we used 2,3-indolo-derivatives with one reaction center for propargylation, were obtained according to the methods described previously. Then the reaction of compoumds **1** and **2** with propargyl bromide in the presence of NaH in DMF provided N-substituted derivatives **3** and **4**. The structure of compounds **3** and **4** was ascertained by NMR spectroscopy. Thus, was observed disappearance of proton NH-group's of indolo-fragment at δ 7.71 and 7.76 ppm. The signals of the acetylene at *δ* 72.2-80.1 ppm (^{13}C NMR) as well as methylene group (*δ* 5.02-5.04 ppm (^{1}H NMR)) were characteristic. The reaction of *N*-propargylindoles **3** and **4** with *N*-methylpiperazine using Mannich reaction (secondary amine, paraformaldehyde, NaOAc, CuI) gave indole-*N*-methylpiperazine conjugates **5** and **6** with 72 and 77% yields. The NMR spectra of Mannich bases **5** and **6** showed signals of all functional groups typical for this derivatives.

Thus, the first synthesis of triterpenic *N*-propargylindoles, which are promising for following biological studies is described.



Synthesis and cytotoxity of *A*-azepanodammarandiene

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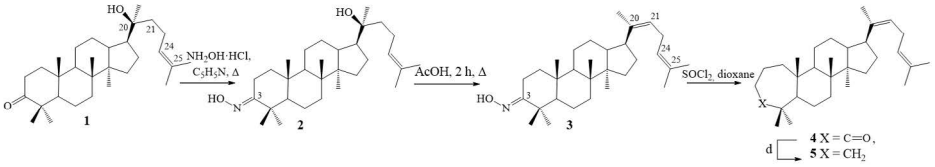
Semisynthetic derivatives of triterpenoids containing azepane ring shows a broad spectrum of biological activity, including anti-cancer, anti-tuberculosis and anti-diabetic properties. In this work the first synthesis of a dammarane triterpenoid with an *A*-azepane cycle was carried out. As starting compound we used dipterocarpol, the main metabolite of the resin of the tropical tree *Dipterocarpus alatus*, possessing anti-cancer, antiviral, immunostimulating types of activities.

The reaction of dipterocarpol **1** with $NH_2OH{\cdot}HCl$ in pyridine yields to oxime **2**, following treatment by acetic acid led to the dehydration of the hydroxy group and the formation of *syn*-oxime **3** with a 20(21)-double bond in side chain. The azepanone **4** was obtained by Beckmann's rearrangement I type of compound **3** ($SOCl_2$, dioxane), with following reduction using $LiAlH_4$ in THF to azepane **5** with 62% yield. Structures of all compounds were confirmed by NMR spectra.



The cytotoxic activity of all compounds was investigated on 60 cells lines of nine types of human tumors. The compounds **4** and **5** showed a broad spectrum of activity against the all range of tumor cells. A new *A*-azepandammarandiene **5** showed marked antitumor activity against nine types of cancer cells (growth from-15.72% to -82.08%). Thus, the presence of azepane fragment in ring A leads to a significant increase in cytotoxicity.

This work was supported by the Russian Foundation for Basic Research (project no. 18-53-54005 Viet_a to Irina E. Smirnova).

Synthesis and antidiabetic activity of *β*-sitosterol derivatives

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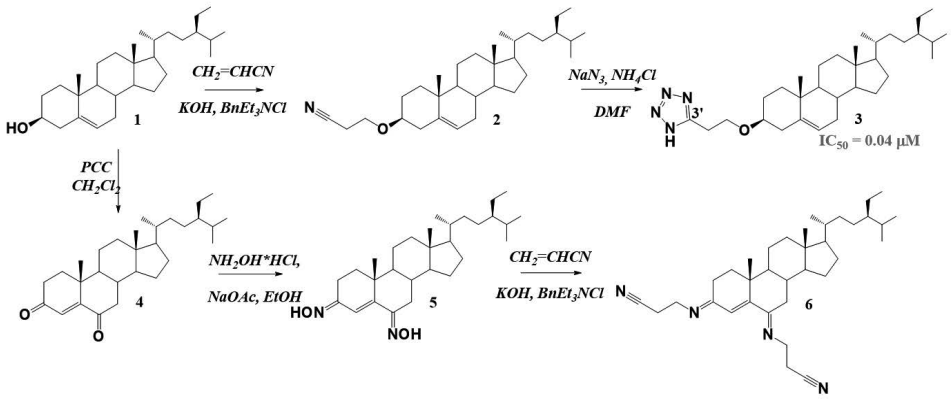
Steroidal compounds display a variety of biological functions and play a very important role in life. The steroidal drugs are widely used in traditional medicines, such as antibacterium, hormone kind medication, etc. The introduction of heteroatom in steroids often affects the chemical properties of the steroidal molecule and results in alterations of biological activities.

In this work first synthesis of cyanoethyl-derivatives of β-sitosterol is described. Thus, using **1** and dioxo-derivative **4**, obtained via oxidation of **1** with pyridinium chlorochromate (PCC) as a starting materials, three new compounds were synthesized. First, cyanoethylation of **1** using acrylonitrile in presence $BnEt_3NCl$ and 30% KOH proceeds with formation of 3-cyanoethoxy-sitosterol **2**, with following reaction with NaN_3 in the presence NH_4Cl to 1*H*-tetrazol-5-yl-derivative **3**. The reaction of **4** with hydroxylamine hydrochloride offers the dioxime **5**. Cyanoethylation of **5** under the conditions described above gave corresponding dicyanoethoxyimino-derivative **6.** The structure of obtained compounds was identified by NMR spectroscopy. In ^{13}C NMR spectra of compounds **2** and **6** signals of cyano- group at ~118-120 ppm were characteristic. The ^{1}H NMR spectrum of **3** contained signals of the methylene protons of the tetrazolylethyl fragment at δ 3.22–3.90 ppm, and the ^{13}C NMR spectrum characteristically displayed signals of the tetrazole carbon atom at δ 154.35 ppm ($C^{3'}$). The screening of *in vitro α*-glucosidase enzyme inhibition activity of compounds **1**-**6** revealed lead 3*β*-tetrazolylethoxy-derivative **3** with IC_{50} of 0.05 μM.



This work was supported by the Russian Foundation for Basic Research (project no. 18-33-00313 mol_a to Anastasiya V. Petrova)

The assessment of 1,2,3-triazolo[5,1-b]1,3,4-thiadiazines stimulating action on skin fibroblasts synthetic activity during regeneration caused by burn injury

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Together with fibroblasts proliferative activity, the intensity of collagen synthesis is another important hallmark of tissue functional state. Previously derived by us thiadiazines induced fibroblasts proliferation [1]. Hence, we investigated the stimulatory effect of 1,2,3-triazolo[5,1-b]1,3,4-thiadiazine *(STT)* on synthetic activity under burn injury regeneration.

The study included 3rd degree burn injury model in rats. The experiment utilized 18 male Wistar rats. Experiment involved 3 groups, such as naïve control, animals exposed to lanolin, and animals exposed to *STT*. The substances were applied epicutaneously in dose of 0.2 g. Animals were sacrificed on the 21st day of the experiment. Histologic analysis included standardized histological methods. Sections were dyed by picro-fuchsin. Microscope Olympus, TopView, and Image J software were used to count fibroblast number and measure the thickness and area of collagen fibers. Statistical analysis was conducted in Microsoft Excel and Statistica10 (Manna-Whitney U-test) software.

The results shown the stimulatory effect of *STT* on skin fibroblasts synthetic activity. Thuswise, the thickness (90,628±3,143 μm) and area (81,141±1,247 %) of collagen fibers in *STT* group derma are higher than in other groups: control - 61,005±5,289 μm; 76,930±2,650 %, and lanolin group - 81,269±3,236 μm; 76,359±1,479 %, respectively. Nevertheless, it cannot be explained by the increase of fibroblasts proliferative activity, as their number is statistically similar between groups.

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Inhibitors of flu virus A (H1N1) reproduction on the basis of natural and synthetical 2-pyridones

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Novel Diels-Alder adducts of *N*-substituted 2-pyridones, di- and tricyclic quinolizidine matrixes containing 2-pyridone core, with *N*-substituted imides of maleic acid were synthesized (Figure 1).

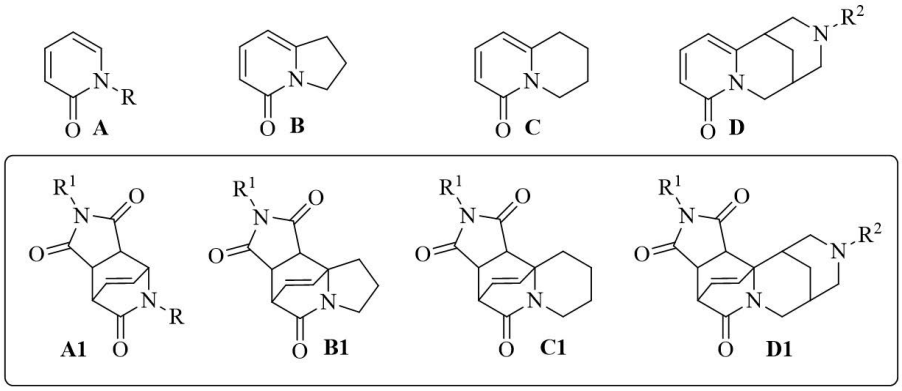

Fig. 1 – *Starting heterocyclic matrixes* **A-D** *and libraries of Diels-Alder adducts* **A1-D1**

Among obtained compounds effective inhibitors of flu virus A (H1N1) were identified with selectivity indexes (SI = CC_{50}/IC_{50}) more than 1.5-3 times higher than that of reference drug ribavirin and more than 29 times of rimantadin. It was established, that synthesized adducts demonstrated maximal virus-inhibiting activity at the middle and last stages of flu virus life cycle.

Docking of all derivatives included in the libraries **A1-D1** into the 4B7R active site of neuraminidase, 5VPT of endonuclease and 5JUN of PB2 domain of polymerase of A (H1N1) flu virus (reference ligand zanamivir) was carried out using the software package Schrödinger Suite 2018-4: QipProp, version 4.2 (Schrödinger, LLC, New York, NY, 2018); it was shown, that with a high degree of probability exactly PB2 is the target for the most of **A1-D1** adducts.

This work was supported by RFBR, project No 18-33-00877_mol_a.

Design and synthesis of new N-sulfonyl and N-acylsubstituted derivatives of indole-3-carboxylic acids – highly effective Angiotensin II AT_1 receptor blockers

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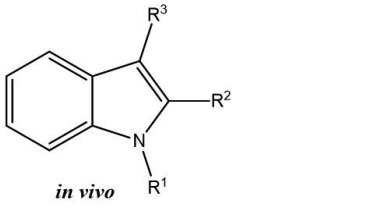
Arterial hypertension is one of the most common diseases of the cardiovascular system according to the WHO. Although, there are a number of known anti-hypertensive drugs, such as diuretics, β-blockers, angiotensin-converting enzyme inhibitors, calcium channel antagonists, namely angiotensin receptor blockers have the maximum therapeutic benefit with the minimum possible side effects.

This research presents new N-sulfonyl- and N-acylsubstituted indole-3-carboxylic acid derivatives prepared from commercially available 2-iodoaniline; it should be noted that *tert*-butylsubstituted phthalocyanine palladium was used for the first time in tandem reaction at one of the step.

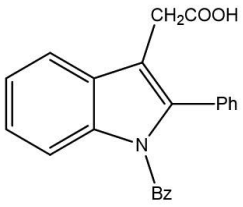


in vivo

R^1 = H, Ms, Ts, Bz, Ac, $COCF_3$

R^2 = Ph, Hex, Propargyl, 

R^3 = COOH, CH_2COOH, $CONH_2$, CH_2CONH_2,



$K_I = 0,64 \pm 0,07$ nM

$IC_{50} = 0,72 \pm 0,08$ nM

The obtained compounds were characterized by physicochemical methods: FTIR, ^1H, ^{13}C NMR spectroscopy, HRMS, and thermogravimetric analysis. To assess the possible use of synthetized compounds in the treatment of cardiovascular diseases we have conducted *in vitro* and *in vivo* studies. The most effective compound was the indole derivative whose structure was shown in the figure, which showed high selectivity for the angiotensin II receptor AT_1 and its effectiveness when orally administered to white rats (ED_{50} = 3 mg / kg, blood pressure decreased by 52 mmHg, the duration of the antihypertensive effect – 12 hours).

The work was supported by the Russian Science Foundation (project 18-73-00216).

Synthesis of ω-Fluoro-substituted of Fatty Acids and their Ethers with the Use of Cyclic Ketones

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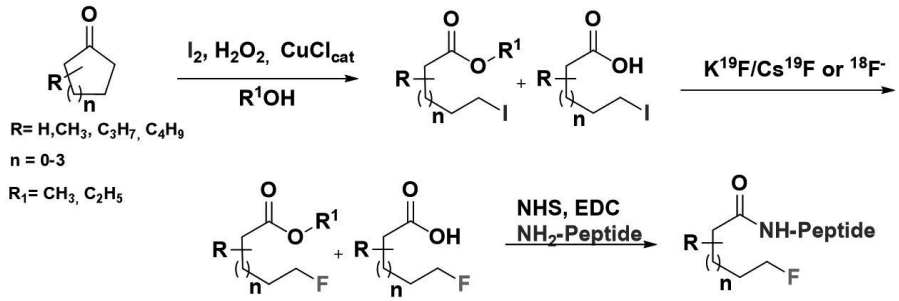
One of the directions of our research is not only the development of technologies for producing iodine-containing compounds as target substances, but also use their in the synthesis of equally valuable fluorine-containing compounds. This means the iodine-containing organic compounds synthesized by us are excellent precursors not only for introducing iodine-123 radioactive label, but also for use as a linker in creating radiopharmaceutical preparations based on ^{99m}Tc, as well as for obtaining fluorine-containing carboxylic acids valuable for PET diagnostics.



Scheme 1 - Obtaining ω-fluorocarboxylic acids and their esters

To this end, we have developed a technology for obtaining valuable fluorine-containing carboxylic acids on the basis of ω-iodaliphatic carboxylic acids and their esters (Scheme 1).

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New analogs of carboplatin as the basis for the structural design of compounds with high antitumor activity

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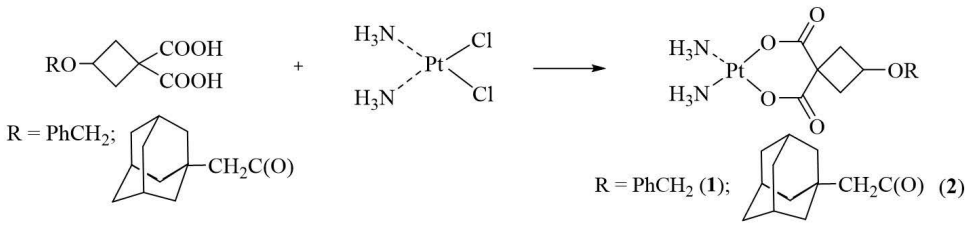
Oncological diseases are today one of the global problems for health care. However, previously found highly effective drugs lose their relevance due to the fact that tumor cells and tissues that have undergone therapy with the aforementioned drugs quickly enough acquire the multidrug resistance phenotype, manifested, to a greater extent, in reducing the intensity of accumulation of these drugs in transformed tissues, and decrease, thereby, efficiency of their action. In this regard, the creation of new forms of chemotherapy does not cease to be a promising direction. The most developed and studied are platinum complexes Pt (II) or Pt (IV) .1

As part of this study, the synthesis of new 3-hydroxycarboplatin derivatives was carried out, their activity on a series of cells was investigated.



As a result of the studies, a good antitumor potential of compound **1** was revealed, which manifests itself in high activity against the cisplatin-resistant A549^{Pt} line (IC_{50} 51.8 μM (**1**) and 179.3 μM (cisplatin)), as well as a pronounced ability to induce apoptosis after 6 hours of incubation comparison of cisplatin (12 hours of incubation) and complex **2**.

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Synthesis of di- and triazaadamantane derivatives containing monoterpene fragments

Ponomarev K.Yu.[1], Suslov E.V.[1], Pavlova A.V.[1], Morozova E.A.[1], Korchagina D.V.[1], Tolstikova T.G.[1,2], Volcho K.P.[1,2], Salakhutdinov N.F.[1,2]

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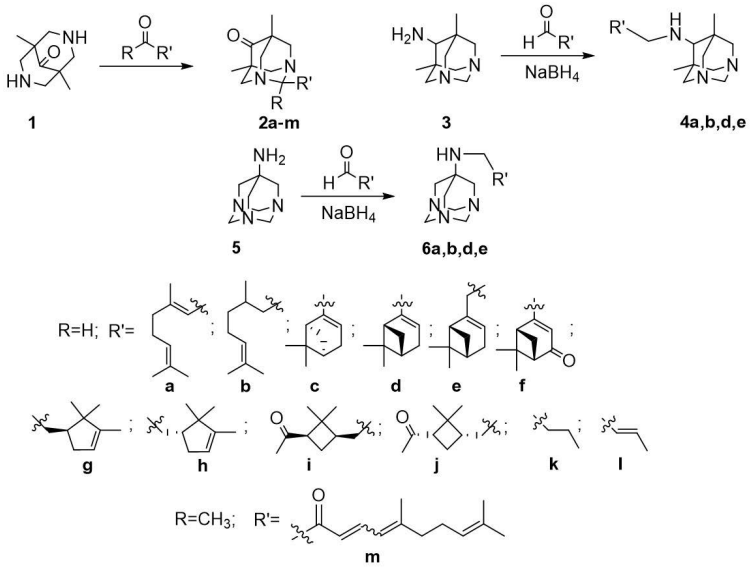
Studies of the biological activity of azaadamantanes are currently represented by a small number of studies in which a narrow range of substrates has been studied, mainly containing only aromatic or simple aliphatic substituents [1].



A library of di- and triazaadamantanes was synthesized started from the natural compounds of the terpene series (citronellal, citral, (-)- and (+)- myrtenal, (-)- and (+)- camphor aldehyde, pseudoionone, etc.), by the interaction with 1,5-dimethylbispidin-9-on, 6-amino-5,7-dimethyl-1,3-diazaadamantane, 7-amino-1,3,5-triazaadamantane. Some of the synthesized compounds showed high analgesic activity in combination with low toxicity.

This work was supported by Grant RFBR No. 18-03-00437 A.

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New 4-methyl-2*H*-chromen-2-one derivatives with terpene substitutes: Synthesis and biological evaluation

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Coumarins are a class of heterocyclic compounds widely distributed in nature and exhibited a variety of biological and pharmacological activities [1]. The different types of substitutes in the coumarin basic structure can influence on the biological activity of molecule. Recently coumarin derivatives with terpene moieties have been recognized as interesting and valuable biologically active compounds [2]. At the same time, chemical modification of natural bioregulator analogs is one of the most promising methods for the synthesis of new biologically active compounds. It was revealed that insertion of monoterpene substituent in the phenols molecules reduces hemolytic and significant increases antioxidant activity [3]. This work is a continuation study of the synthetic potential of terpenophenols to obtain highly biologically active compounds. We synthesized 4-methylcoumarins with isobornyl and isocamphyl substituents and assessed the effect of the presence and isomerism of terpene group on the antioxidant and membrane-protective activity [4].

It is plausible to assume that the complex of factors influence the antioxidant activity of coumarin derivatives, including the number, isomerism and position of alkyl substituents in the coumarin scaffold. Indeed, if only coumarins with an isobornyl moiety were significantly superior to 7-hydroxy-4-methylcoumarin in radical scavenging activity in a reaction with a stable DPPH radical, then on the substrate containing the brain lipids of the laboratory mice, already all the derivatives synthesized were more active than unsubstituted 7-hydroxy-4-methylcoumarin.

The work was carried out within the framework of the State Assignments (registration No. AAAA-A18-118012490385-8, AAAA-A18-118011120004-5).

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Synthesis and antitumor activity of pyridoxine-based saccharumoside-B mimetics

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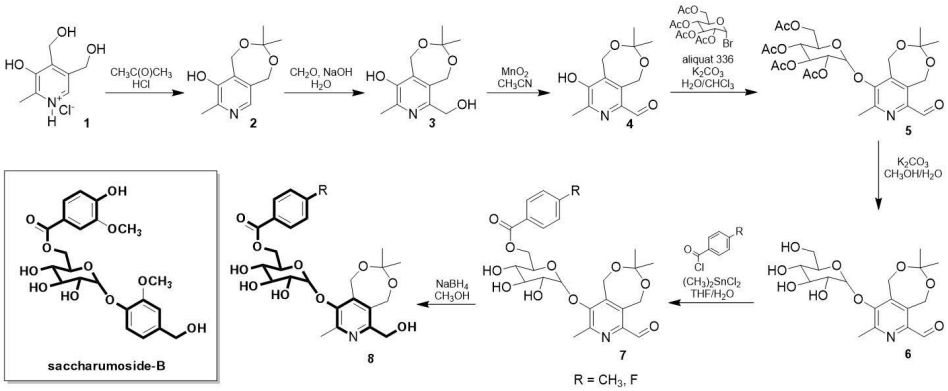
Synthesis of novel biologically active substances with high efficiency and safety is one of the most important tasks solved in medicinal chemistry. It is known that saccharumoside-B and its bioisosteric analogues possess antiproliferative and pro-apoptotic activities [1-3].

As a continue to the systematic research of bioisosteric analogues of saccharumoside-B we obtained new derivatives containing a fragment of pyridoxine. Target products were synthesized from pyridoxine in 7 stages, using classical methods of organic synthesis. *In vitro* study of cytotoxicity of obtained substances revealed that some of them have high antitumor activity against breast cancer cells *MCF-7* and prostate cancer cells *PC-3* (IC_{50} = 7.7-10.0 μM) and low toxicity against conditionally normal skin fibroblasts cells (CC_{50} = 118 μM).



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Arteannuin B aminoderivatives inhibit the growth of various cancer cell lines

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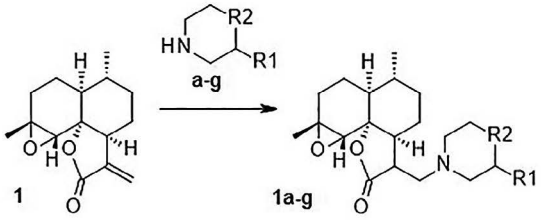
Arteannuin B, one of the main sesquiterpene lactone of *Artemisia annua* L., show antifungal activity [1] and it is assumed that the methylene group is necessary for activity against leukemia P 388 cells [2]. In the present study, we modified the molecule of arteannuin B (**1**) by Michael-type addition with a number of amines (**a**-**g**) and investigated the activity of the synthesized compounds (**1a**-**g**) against to a panel of cancer cell lines.



R1: H, R2: CH_2 (**1a**)
R1: CH_3, R2: CH_2 (**1b**)
R1: CO_2Et, R2: CH_2 (**1c**)
R1: H, R2: $CHPh_2OH$ (**1d**)
R1: H, R2: NC_6H_4OMe-2 (**1e**)
R1: H, R2: NC_6H_3Me-2-Cl-5 (**1f**)
R1: H, R2: $NCH_2C_6H_3(CH_2OCH_2)$-3,4 (**1g**)

Arteannuin B derivatives with 2-methoxyphenylpiperazine and ethyl piperidine-3-carboxylate turned out to be the most active. The IC50 for these conjugates ranged from 5 to 20 μM for A549, MCF7, HCT116, RD and Jurkat cells, and data on the induction of apoptosis by flow cytometry were obtained for various cell lines. A comprehensive assessment of the effect of these substances on the mitochondrial characteristics suggests that their antiproliferative activity is associated with the induction of the mitochondrial pathway of apoptosis.

The reported study was funded by RFBR according to the research project № 18-33-20209.

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Chitosan derivatives: between nutrition and drug

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Chitosan exhibits a variety of physicochemical and biological properties resulting in numerous applications such as waste and water treatment, agriculture, cosmetics, nutritional enhancement and food processing. Due to its biocompatibility, biodegradability and bioactivity it became a very attractive substance for diverse applications as a biomaterial in pharmaceutical and medical fields. As a non-toxic and non-allergenic bioadhesive polymer, chitosan has been extensively studied for its antimicrobial properties, tissue regeneration, wound healing and immunogenic activities. Chitosan used as a feed additive for poultry and pigs has some beneficial, biological effects, including immunomodulatory, anti-oxidative, antimicrobial and hypocholesterolemic properties. These properties of chitosan, unlike many other kinds of feed additives, were often reflected in improved growth performance (body weight gain and/or feed conversion ratio) of young animals, that is, broiler chickens and weaned pigs [1].

An amino acid, taurine, is considered to have effects on cell proliferation, inflammation and collagenogenesis. The effect on skin wound healing of taurine-containing chitosan gel, which releases taurine slowly, has been investigated in [2]. It has been shown that such dosage form could be effective for rapid collagen production and enhance the re-epithelization and tensile strength of wounds.

In the previous work [3], we have described a simple and effective synthesis method of N-(2-sulfoethyl)chitosan, a taurine derivative, and structural analogue N-(2-carboxyethyl) chitosan, a β-alanine derivative. Herein we report the investigation of their toxicity and effect on body weight in white mice.

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Supramolecular vesicles formed by modificated calix[4]resorcinols and chitosan for drug delivery

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Stimuli-responsive supramolecular aggregates have aroused wide attention in recent decades as containers for drug delivery. The particles of nanodimensions can facilitate the absorption of drugs by cells and their passage through the biological barriers, thus providing better integration. In this work, the aggregates based on functionalized calix[4]resorcinols and chitosan were studied. Chitosan is biocompatible, biodegradable and nontoxic polysaccharide. In addition, it possesses a polycationic character because of the protonation of amine groups in acidic medium. Due to presence of negatively charged sulfonate groups in macrocycles the electrostatic interactions with the protonated amino groups of chitosan with formation of aggregates are observed.

The particles obtained are capable of encapsulating hydrophilic rhodamine B and doxorubicin. Doxorubicin encapsulation exceeds 98% in the system with calix[4]resorcinol with sulfonated groups on the lower rim and 51% in the case of macrocycle with sulfonated groups on the upper rim. The method of dynamic light scattering revealed the stability of the systems obtained: triple systems with encapsulated rhodamine B vary in size significantly rather than the aggregates with doxorubicin, i.e. supramolecular polymers with doxorubicin are stable at least for 8 days. Therefore, transmembrane transfer was studied by flow cytometry, where it was found that the resulting systems penetrate the cells, and doxorubicin is more efficiently transferred due to calixarene with sulfonated groups on the upper rim regardless of the drug concentration. It is interesting to note that in the study of cytotoxicity a selective effect on the tumor cell line was achieved, while the triple doxorubicin system with macrocycle with sulfonated groups on the upper rim is less toxic to healthy liver cells. The results obtained show the possibility of spontaneous vesicles formation in the investigated systems. The present supra-amphiphilic assemblies promise potential applications in the biomedical field such as drug delivery and controlled release.

This work was supported by Russian Science Foundation, grant no. 17-73-20253.

Selective butyrylcholinesterase (BChE) inhibitors with antioxidant activity as potential multifunctional drugs for the treatment of Alzheimer's disease (AD)

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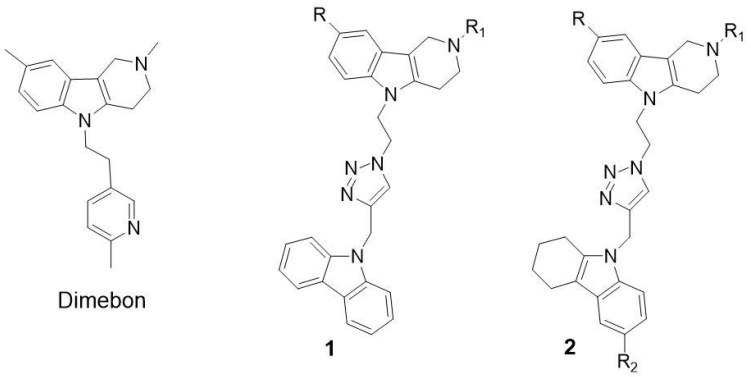
The growing interest in the search for selective BChE inhibitors is due to both an increasing of BChE activity in AD progression, and the lack of cholinergic side effects of BChE inhibitors that are typical for acetylcholinesterase (AChE) inhibitors.

We have synthesized new hybrid compounds combining the g-carboline fragment of the Dimebon with carbazole (**1**) and tetrahydrocarbazole derivatives (**2**) in one molecule via a triazole-containing spacer.



The study of the esterase profile — the inhibitory activity of the compounds against AChE, BChE and the structurally related carboxylesterase enzyme showed that all conjugates **1** and **2** are effective and selective inhibitors of BChE, with IC_{50} values in the micromolar concentration range. Moreover, according to the results of the ABTS test, conjugates **1** and **2** are scavengers of free radicals, similar in activity to the standard antioxidant Trolox. The replacement of the carbazole moiety (**1**) by the tetrahydrocarbazole (**2**) was shown to have virtually no effect to the anti-BChE activity of the conjugates, but significantly increases their ability to scavenge free radicals. Whereas the presence of electron-withdrawing substituents in the tetrahydrocarbazole fragment **2** (R_2 = F, OCF_3) reduces both of these activities.

Thus, conjugates **2**, which effectively and selectively inhibit BChE and possess high radical-scavenging activity, are of interest for the further development of the safe multifunctional drugs for AD therapy.

This work was supported by the Russian State assignment # 0090-2017-0019 to IPAC RAS.

The receptor layer structuring of electrochemical immunosensors by electrographing salts of carboxy-1,2,4-triazolediazonium and carboxyphenyldiazonium

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Modern medicine requires the development and creation of analytical devices combining high specificity and sensitivity with fast definition rate, simplicity, and portative design. These properties have electrochemical immunosensors. It is sensor that includes antigen or antibody immobilized on the surface of the transducer as an element of bio-recognition.

One of the prevalent methods of electrode fictionalization for the subsequent covalent immobilization of a bioreceptor is electrografting of aryldiazonium salts. The process usually is accompanied by the formation of thick polylayers on the electrode surface formed as a result of free radical substitution in the aryl ring of the first modifier layer. Such layers reduce the rate of electron transfer and therefore have a negative effect on the analytical characteristics of electrochemical immunosensors.

The aim of the work was a comparative study of the effect of the modifying layer structure formed by electrographing of 4-carboxyphenyldiazonium and 3-carboxy-1,2,4-triazolediazonium salts, the subsequent immobilization of antibodies against carcinoembryonic antigen by the method of carbodiimide crosslinking on the analytical characteristics of label-free electrochemical immunosensors.

The results indicate differences in the electrographing mechanisms of the investigated diazonium salts on the surface of a gold disk electrode under selected operating parameters.

This work was supported by the Russian Scientific Fond (grant number 17-13-01096)

Amidation Reactions of Terminal Alkynes with Benzenesulfonamide: Metal-Free Synthesis of α-Sulfonylamino Ketones

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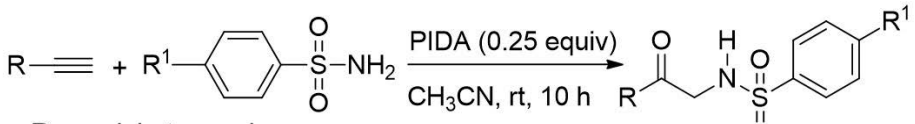
α-Amino ketones assist a significant role in organic chemistry as they are found in a large variety of biologically active natural products. Commercial medicines such as mephedrone [1] and bupropion [2] hold α-amino ketones as well as the proteasome inhibitor epoxomicin [3]. In organic synthesis, this moiety is also very valuable for the preparation of 2-amino alcohols and nitrogen-containing heterocycles [4].

Owing to their importance, synthetic organic chemists have endeavored various methodologies based on different modifications. Herein, we are pleased to report an efficient and regioselective methodology for the synthesis of α-sulfonylamino ketones derivatives by the coupling of terminal alkynes with sulfonamides in presence of PIDA at room temperature under ambient air [5].



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Triazolo[5,1-*c*][1,2,4]triazine: synthesis and bioactivity

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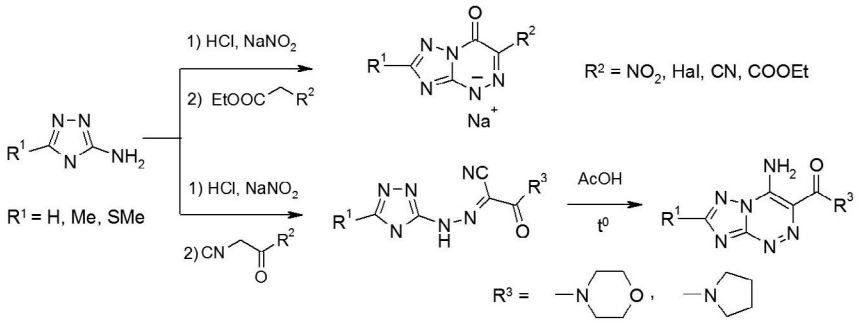
The rapid growth in the incidence of diabetes mellitus throughout the world determines the relevance of the search for new drugs against diabetes. In addition to drugs that eliminate hyperglycemia, also of interest are compounds that can inhibit non-enzymatic glycosylation of proteins, leading to the accumulation of advanced glycation end-products and the development of multiple complications of diabetes mellitus [1].

A large amount of biologically active compounds was found among the condensed azolotriazines. In particular, it was previously shown that the derivatives of pyrazolo- and 1,2,4-triazolo[1,2,4]triazines have a considerable anti-glycating activity [2].



Several 4-oxo-1,2,4-triazolo[5,1-*c*][1,2,4]triazines and 4-amino-1,2,4-triazolo-[5,1-*c*] [1,2,4]triazines were synthesized and evaluated *in vitro* as inhibitors of advanced glycation end-products formation. Some of the studied compounds showed higher activity than that of the reference drug aminoguanidine.

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N. Name, N. Name, and N. Name, *Journal.* **2008**, *0000*, xx-xxx

Synthesis of pharmacologically active analogue of dimeric dipeptide mimetic BDNF 4th loop GSB-106

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A dimeric dipeptide mimetic GSB-106 (*bis*-(*N*-monosuccinyl-*L*-seryl-*L*-lysine) hexamethylenediamide) was designed on the basis of the β-turn structure of the BDNF loop 4. [1] Dipeptide GSB-106, like BDNF, induced the activation of TrkB receptors, and activated ERK and AKT post-receptor signaling pathways [2], exhibited neuroprotective activity on neuronal cell cultures in the concentration range 10^{-5}-10^{-8} M and possessed specific for BDNF antidepressive activity in a series of rodent tests in doses of 0.1, 0,5 and 1.0 mg/kg ip [3].

To study the role *N*-acyl radical in activity of GSB-106 its acetyl analog (*bis*-(*N*-acetyl-*L*-seryl-*L*-lysine) hexamethylenediamide (GTS-106Ac) was synthesized, in which monosuccinyl radical was replaced by acetyl radical, and its neuroprotective activity *in vitro* and antidepressive activity *in vivo* were studied.

Synthesis of dipeptide GTS-106Ac 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 and pentafluorophenyl (for protected serine) esters method.

In the first stage, activated *N*-hydroxysuccinimide esters of *N*α-Z, *N*ω-Boc-protected lysine, acetic acid and pentafluorophenyl ester of serine were synthesized, and dicyclohexylcarbodiimide was used as a condensing agent. Reactions were carried out with cooling to +10°C for *N*-hydroxysuccinimide esters and to 0 - +5 °C for pentafluorophenyl esters. The reaction yield was 90-95%. In the second stage Z-Lys(Boc)-OSu was condensed with hexamethylenediamine in DMF for 12 h, getting appropriate hexamethylenediamide with a yield of 92%, which was then *N*-deblocked by catalytic hydrogenolysis in the presence of 10% Pd/C. The resulting bis-peptide was condensed with Z-serine pentafluorophenyl ester in DMF at room temperature. Then Z-protected bis-dipeptide was subjected to catalytic hydrogenolysis and entered into reaction with acetic acid *N*-hydroxysuccinimide ester. Reaction was carried out at room temperature in DMF, getting product with a yield of 77%. In the final stage *t*-butyloxycarbonyl protecting groups were removed by anhydrous TFA in CH_2Cl_2 and then obtained GTS-106Ac trifluoroacetate was conversed to acetate by 5x treatment with 10% acetic acid. Overall yield of homogeneous according to TLC and RP-HPLC GTS-106Ac was 57%. The structure and diastereomeric purity of the resulting and intermediate compounds were confirmed by ^{1}H-and ^{13}C-NMR.

The study of neuroprotective activity on neuronal cell culture HT-22 under conditions of oxidative stress caused by H_2O_2 showed that GTS-106Ac in the concentration range 10^{-5}-10^{-8} M increased neuronal survival and demonstrated neuroprotective effect which by severity was comparable to the activity of GSB-106. The study of antidepressive activity of GTS-106Ac in Porsolt learned helplessness test when administered intraperitoneally in mice at

doses of 1–5 mg/kg, a significant decrease in the immobility time was detected compared with animals from the control group. The severity of the effect of GTS-106Ac did not differ from the severity of the effect of GSB-106 in the same dose (1 mg/kg).

Thus, the replacement of the monosuccinyl radical with acetyl in the structure of GSB-106 does not lead to a change in the pharmacological activity of the latter.

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New mitochondria-targeted antioxidants based on trans-resveratrol heteroanalogs

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Mitochondria are a key source of reactive oxygen species (ROS) in the cell. Antioxidants that can be accumulated and act directly in the mitochondria attract attention, preventing ROS from entering the cytoplasm of the cell and thus protecting it from oxidative stress. The vectors for the delivery of antioxidants into mitochondria are lipophilic cations, which easily penetrate into it due to the large negative membrane potential inside the organelle [1].

Previously, we synthesized a number of hydroxyl-substituted *trans*-stilbazole derivatives (analogues of natural polyphenol – resveratrol) and their higher antioxidant activity compare with the prototype was shown [2]. The obtained compounds can easily be converted into lipophilic cations by quaternization of the pyridine nitrogen atom. There are some examples of the pyridinium derivatives using as mitochondria-directed transporters in the literature [3]. The calculated coefficient of accumulation obtained taking into account the membrane potential and the difference in pH values in the intercellular space and the mitochondrial matrix predicts the better penetration of the studied compounds into the organelles compare to the original substances.

The target compounds were synthesized and their antioxidant activity was studied on the model of peroxidation of lipids in mitochondrial membranes in the MDA test. A significant decrease in the concentration of MDA compared with the control was shown in the concentrations of more than 15 μM, which is better than the values obtained in the same test for non-quaternized initial stilbazoles.

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New nitrogen-containing ursolic acid heterocycles with thiol group: synthesis and biological activity

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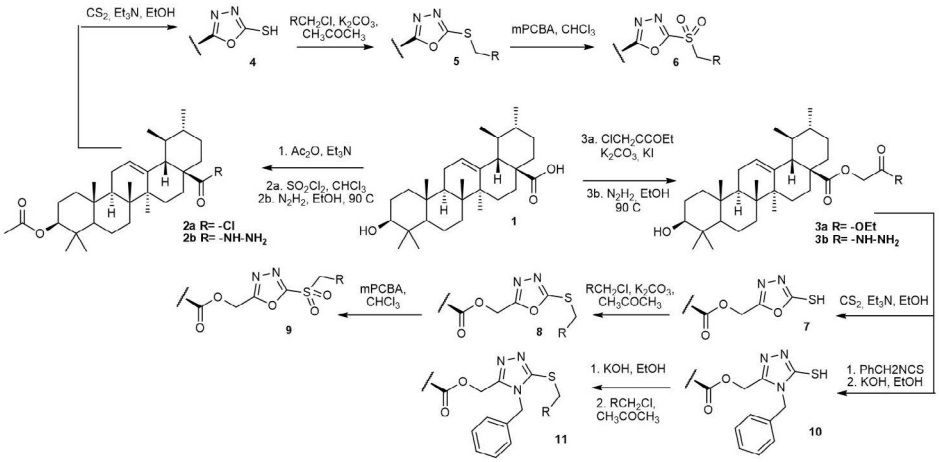
New ursolic acid derivarives containing fragments of 3-mercapto-1,2,4-triasoles and 2-mercapto-1,3,4-oxadiasoles have been synthesized. The derivatives potentially posess biological activity.



Hydrasides 2 и and 3b have been obtained from ursolic acid 2a and 3a. Heterosyclic derivatives have been synthesized from hydrasides obtained according sheme 1, and conditions for derivatives alkylation nave been found. We have stydied the selective oxidation conditions from sulfides to sulphons as anticancer activity has been detected [1] in 1,3,4-oxadiasoles having the sulphone group. The compounds obtained nave been send to explore anticancer activity. We have been investigating the sulphones and N-, S-nucleophiles interaction.

This work was supported by the grant RFBR 18-53-76001.

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Synthesis of 1,2,4-triazolo[4,3-a]azines through oxidative cyclization strategy

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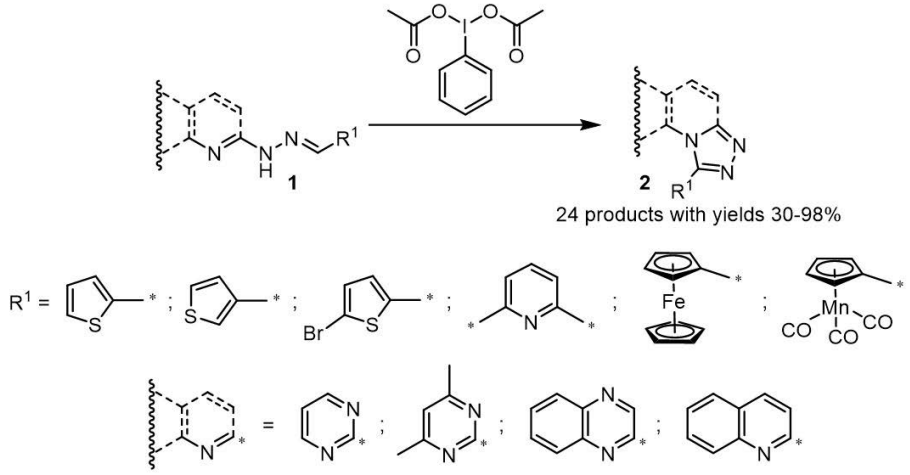
Triazoloazines constitute an important class of heterocyclic compounds. They are part of various biologically active compounds, for example, antibacterial, anti-inflammatory and herbicidal agents. Therefore, the current task of organic synthesis is development of new methods for the synthesis of azoloazines, which make it possible to obtain potential biologically active compounds from commercially available compounds under mild conditions.

In this research, the oxidative cross-dehydrogenative cyclization was demonstrated for the synthesis of 1,2,4-triazolo[4,3-*a*]azines from corresponding azinylhydrazones in the presence of hypervalent iodine(III) (Scheme 1). So, the new 1,2,4-triazolo[4,3-*a*] azines containing both heterocyclic (thiophene, pyridine) and metallocene (ferrocene, cymantrene) fragments have been received. The hypervalent iodine(III) are attractive for these transformations, because it has a low toxicity and a high oxidative properties and stability.



The research was financially supported by the Russian Foundation for Basic Research (18-33-00927), the Ministry of Education and Science of the Russian Federation grant number 4.6351.2017/8.9.

Synthesis of new hydrophobic analogues of aminophosphonic acids

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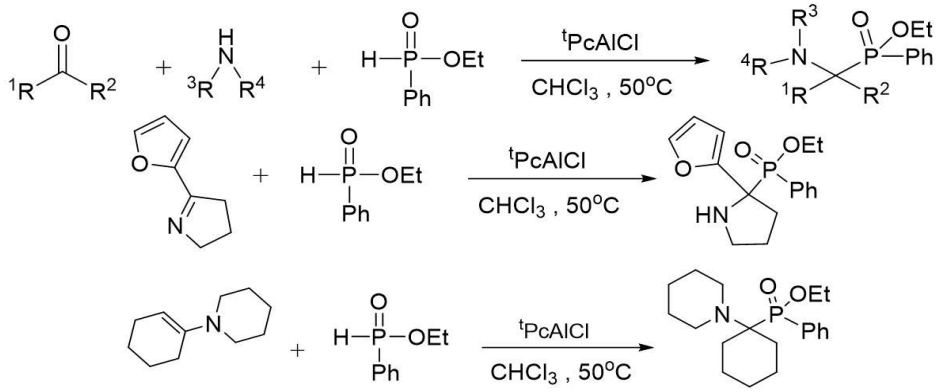
α-Aminophosphinic acids and their derivatives are of great interest for medical chemistry, as they have a high potential for creating structural diversity and have a range of pharmacological activities, including Alzheimer's disease, hepatitis, HIV, malaria. This makes them a promising tool in the development of new drugs [1].

Previously, we developed a universal catalytic method for the synthesis of phosphorus peptidomimetics using tetra-*tert*-butylphthalocyanine aluminum chloride (^{t}PcAlCl) as a catalyst for three-component (Kabachnik-Fields) and two-component (Pudovik) hydrophosphorylation reactions. The effectiveness of this catalyst has been confirmed in our previous studies [2]. Continuing to study the possibilities of this catalytic method, we used it to create an aminophosphinate site [3].

In the present work, we have obtained hydrophobic analogs of aminophosphonic acids - α-aminophosphinates based on secondary cyclic amines, including biogenic ones. The conditions of the three-component hydrophosphorylation reaction were also optimized for the production of α-aminophosphinates.



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Nanohydroxyapatite and its hierarchical textures as carriers of medical radionuclides

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Modern development of nuclear medicine cannot be imagined without introducing new promising diagnostic and therapeutic radionuclides and radiopharmaceuticals based on them. Due to their nuclear-physical and chemical properties, short-lived alpha-emitters (Ra-223, Ac-225, Bi-213, Pb-211) are effective for treating cancer and are successfully passing clinical trials. However, the scope of their use is limited by the availability of suitable means of delivery to cancer cells. Organic and inorganic nanotransporters are increasingly used as delivery system. In this work, we proposed nanosized hydroxyapatite (HAP), which has both complete biocompatibility and, in many cases, bioactivity, for the target transport of the mentioned radionuclides. It does not accumulate, but is completely metabolized in the body and has long been widely used in medical practice, including as a carrier of medicines. The HAP is able to form various hierarchical textures, each of which can find its application in different variants of nuclear medicine. In our work, the focus was on identifying patterns of sorption interaction between the selected radionuclides and HAP of several morphological and textural forms. The kinetics and isotherms of sorption and desorption of radionuclides on HAP from aqueous solutions were studied. The diffusion of radionuclides in a granular sorbent or in its watered layer was studied and the diffusion coefficient in these media was estimated (for Ra and Ac). For the binding of the radionuclide and carrier, a cocrystallization method was also proposed, when the target radionuclide is introduced directly into the synthesis of the sorbent itself (in this case, HAP).

This work was supported by the RFBR grant No. 18-03-00432.

Antimicrobial activity of hydrogels based on silicon, zinc, and boron glycerolates: comparative evaluation

Shadrina E.[1], Nikitina E.[1], Permikin V.[1], Khonina T.[1,2], Evstigneeva N.[3], Kokhan M.[3], Polishchuk A.[3], and Chupakhin O.[1,4]

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Growing resistance of pathogenic and conditionally pathogenic bacteria and fungi to antimicrobial drugs is dangerous for public health. Previously we synthesized by the sol–gel method pharmacologically active hydrogels based on glycerolates of silicon $Si(C_3H_7O_3)_4$, zinc $ZnC_3H_6O_3$, and boron $HB(C_3H_6O_3)_2$: Si-gel [1], Si–Zn-gel [2], Si–B-gel [3], and Si–Zn–B-gel [4].

The purpose of this work was the comparative study of antimicrobial (antibacterial and antimycotic) activity of these gels. The antimicrobial activity was studied by agar well-diffusion and serial dilutions methods using conventional test cultures. Tetracycline and Exoderil were used as positive control.

It was shown that Si–Zn–B- and Si–B-gel possessed the highest antibacterial activity comparable to Tetracycline. Si–Zn-gel was less active, Si-gel demonstrated no antimicrobial properties. Si–Zn–B-gel showed high fungicidal activity, in particular with respect to *Candida albicans*, exceeding Exoderil. Correlation of composition, structure, and antimicrobial properties of the hydrogels was considered. Explanation of the higher antimicrobial activity of Si–Zn–B-gel was proposed.

Si–Zn–B- and Si–B-gel could be an effective and safer alternative to conventional topical antimicrobial agents for treatment of diseases of skin and mucous membrane.

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Homotaurin-containing Derivatives of Lactams and Pyrimidines: Synthesis, Structure and Biological Activity

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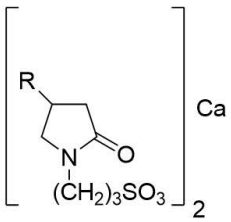
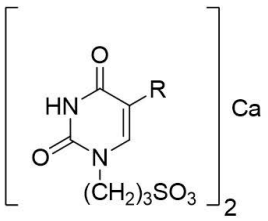
One of the directions for creating new perspective biologically active compounds is the combination of different pharmacophoric fragments in one molecule. In this regard, derivatives of *N*-substituted lactams and pyrimidines are of interest, because they have a broad spectrum of biological activity (active ingredients of such drugs as Nootropil (Piracetam), Fenotropil, anti-epileptic agent Keppra, anticoagulant Apixaban) [1-2]. The biological activity of homotaurine-containing cyclic amides is currently less studied [3].

Based on *in silico* (QSAR) methods we synthesized compounds **1a-d** and **2a-b** (**Fig. 1**), selected as the "leader" substances, by the reaction of *N*-sylylated lactams and pyrimidines with 1,3-propanesultone, with subsequent processing of resulted sulfonic acid by CaO or $CaCO_3$.

1a: n = 1, R = H
1b: n = 1, R = Ph
1c: n = 2, R = H
1d: n = 3, R = H



1a-d



2a-b

2a: R = H
2b: R = CH_3

Fig 1

In preliminary biological activity tests for all synthesized substances high efficacy in antioxidant and cytoprotective activity was shown. The data correlates well with the computer prediction results using ***Pass Online*** Program.

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Amino-functionalized 1-(2-hydroxypolyfluorophenyl)prop-2-ene-1-ones: synthesis and antimycotic activity

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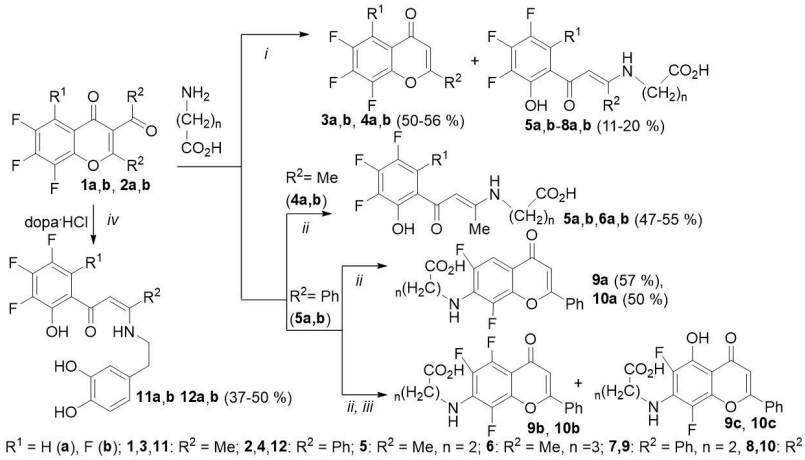
The reactions of 3-acetyl- and 3-benzoyl-substituted polyfluorochromones **1a**,**b**, **2a**,**b** with amino acids and dopamine were shown to be realized by two alternative routes with the formation of *N*-substituted aminoenketones **5-8**, **11**, **12**, due to the pyrone cycle opening and deacylation, and/ or the products of nucleophilic aromatic substitution of fluorine atoms **3**, **4**, **9**, **10**, depending on the nature of the substrates, nucleophilic reagents and reaction conditions. As a result of a microbiological study, it was determined that aminoenketones **5b**, **6b**, **7a**, **8b**, **11a**,**b**, **12b** exhibit an antimycotic effect against dermatophyte test strains from moderate to high values. Data on the most active compounds **8b**, **12b** are given in the table.



R^1 = H (**a**), F (**b**); **1**,**3**,**11**: R^2 = Me; **2**,**4**,**12**: R^2 = Ph; **5**: R^2 = Me, n = 2; **6**: R^2 = Me, n =3; **7**,**9**: R^2 = Ph, n = 2, **8**,**10**: R^2 = Ph, n =3;
i: EtOH, $AcONa*3H_2O$, DIPEA (50 % mol) ,23°C, 96 h; *ii*: EtOH, 0.5M carbonate buffer, MW, 20 W, 80°C, 0.1 MPa, 4 h,
iii: EtOH, 0.5M carbonate buffer, MW, 50 W, 130°C, 0.9-1.0 MPa, 4 h; *iv*: $EtOH_{abs}$, Et_3N, 23 °C, 10 h, inert atmosphere

Compound	*Antimycotic activity, MIC, μg/mL*							
	T. rubrum	*T. gypseum*	*T. tonsurans*	*T. violaceum*	*T. interdigitale*	*E. floccosum*	*M. canis*	*C. albicans*
8b	**1.56**	25	50	200	200	50	**1.56**	>200
12b	**1.56**	25	**3.12**	**3.12**	200	12.5	**1.56**	12.5

The work was supported by the state project AAAA-A19-119012290115-2

SEARCH FOR ACETYLCHOLINESTERASE INHIBITORS AMONG THE SUBSTITUTED 1,3-DIHYDRO-2-OXO-1H-BENZIMIDAZOLE-1-CARBOXAMIDES

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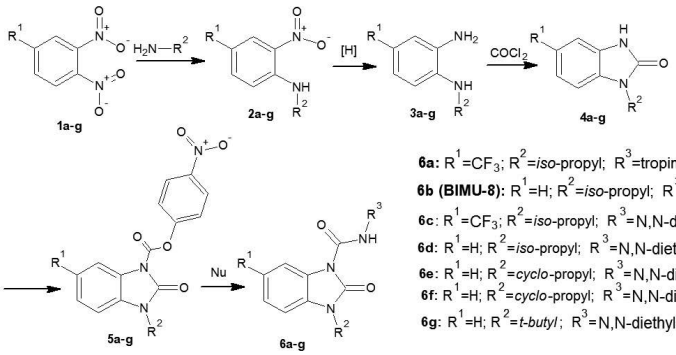
2,3-Dihydro-2-oxo-1H-benzimidazole-1-carboxamides, benzimidazolone derivatives are biologically active substances. Among these compounds are selective serotonin receptor ligands, inter alia, ligands of unique 5-HT4a subtype such as BIMU-8 (**6b**). The latter is located in the brain region called "pre-Bötzinger complex". This region ensures respiratory rhythm generation in humans [1]. Additionally, it was found that BIMU-8 has a positive effect on cognitive function, which is caused by the regulation of serotonin receptors. Improvement of cognitive functions may also be due to the inhibitory effect of this compound on cholinesterase, however, studies confirming this assumption have not been previously conducted.

We have developed an efficient general approach to the synthesis of 2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxamide derivatives based on nucleophilic substitution of ortho-dinitrobenzenes.



6a: R^1=CF_3; R^2=*iso*-propyl; R^3=tropine; K_i(μM)=41.7;
6b (BIMU-8): R^1=H; R^2=*iso*-propyl; R^3=tropine; K_i(μM)=363.9;
6c: R^1=CF_3; R^2=*iso*-propyl; R^3=N,N-diethyletheleniamine; K_i(μM)=39.66;
6d: R^1=H; R^2=*iso*-propyl; R^3=N,N-diethyletheleniamine; K_i(μM)=97.3
6e: R^1=H; R^2=*cyclo*-propyl; R^3=N,N-diethyletheleniamine; K_i(μM)=228.2
6f: R^1=H; R^2=*cyclo*-propyl; R^3=N,N-dimethyletheleniamine; K_i(μM)=348.2;
6g: R^1=H; R^2=*t-butyl*; R^3=N,N-diethyletheleniamine; K_i(μM)=176.8

For the synthesized 1,3-dihydro-2-oxo-1H-benzimidazole-1-carboxamides (**6a-g**), including BIMU-8 (**6b**), the inhibition constants (K_i) of acetylcholinesterase were determined by the modified Ellman tablet method.

Analysis of the results showed the presence of inhibitory activity in the obtained products (**6a-g**), which made it possible to consider these compounds as potential acetylcholinesterase inhibitors, which are known to be used in the supportive treatment of Alzheimer's disease. It was established that the introduction of the trifluoromethyl group into the phenyl fragment of benzimidazolone increases the activity tenfold.

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Metal complexes of polyfluorosalicylates as promising antifungal and antimicrobial agents

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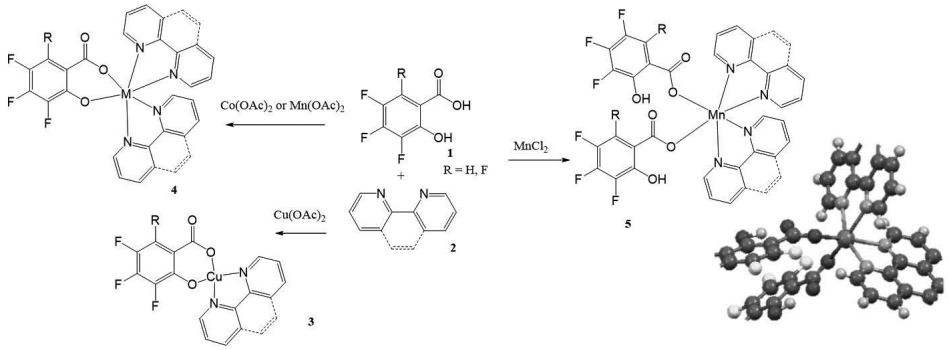
The salicylic acid and its derivatives are widely used as medicines. Metal complexes based on salicylic acid possess anti-*Candida* [1] and antitumor [2] activity. Recently, we have developed the methods for synthesis of polyfluorosalicylic acid **1** and their derivatives, which were revealed anti-inflammatory [3] and tuberculostatic [4] action. Metal complexes **3-5** were obtained *via* the reaction of acids **1** with the transition metal salts {Co(II), Cu(II), Mn(II)} followed by treatment with 2,2'-bipyridine or 1,10-phenanthroline. According to the X-Ray analysis, elemental analysis and mass-spectrometry, the structure of metal complexes was found to depend on a nature of being used salt.



The biological investigation of metal complexes **3-5** showed that Co(II) and Mn(II) polyfluorosalicylate derivatives had the high antifungal activity (minimum inhibitory concentration (MIC) is up to 3.12 mg/ml). In addition, Cu(II), Co(II) and Mn(II) complexes of tetra- and trifluorosalicylates demonstrated antibacterial action against three opportunistic strains at MIC to 15.6 mg/ml, but against *Neisseria gonorrhoeae* – at MIC to 3.9 mg/ml.

This work was financially supported by Program UB RAS (Project № 18-3-3-16).

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Synthesis, anticholinesterase activity and molecular modeling of 9,10-dihydroacridines

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The increase in life expectancy and population ageing inevitably leads to an increase in the number of neurodegenerative diseases. The most common type of dementia in older people is Alzheimer's disease, a multifactorial and fatal neurodegenerative disorder, which is characterized by a constant decrease in cognitive function and memory, up to the complete degradation of the individual. Modern methods of treatment alleviate the symptoms, but do not yet allow stopping or slowing the progression of the disease. Currently, disease therapy is based on cholinesterase inhibitors, which are capable of increasing the concentration of acetylcholine in cholinergic synapses. The first drug of this type was Tacrin, however, it had already been withdrawn from the clinical use due to its hepatoxicity. Currently, the number of approved drugs is limited to only three cholinesterase inhibitors (rivastigmine, donepezil and galanthamine), as well as one NMDA antagonist (memantine). Therefore, the search and creation of effective and safe drugs for the treatment of Alzheimer's disease is of great scientific interest.

We have previously obtained the amino derivatives of acridine compounds that possess the properties of effective cholinesterase inhibitors and exhibit high radical-scavenging activity, which makes them promising for use in the creation of multifunctional drugs for the treatment of neurodegenerative diseases, such as Alzheimer's disease [1]. This work involves the directed synthesis of new amino compounds of acridine, which would show a more pronounced inhibitory activity against cholinesterase.

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BRCA1 and estrogen receptors alpha and beta expression regulation in breast cancer cell lines

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Introduction. BRCA1-associated cancer mainly develops in estrogen dependent tissues. The aim of the research is the study of BRCA1 and ERα/β expression in breast cancer cells in the circumstances characterized with epigenetic regulation of gene expression: prolonged hypoxia [1] and phytoestrogen influences inducing core histones modifications [2].

Materials and methods. MCF-7 breast cancer cell line was exposed to moderate (1% O_2) prolonged hypoxia (1, 4, 6 and 10 days) in DMEM medium with 10% of fetal bovine serum. MCF-7 breast cancer cells were incubated with phytoestrogen genistein at concentrations 7,5 μM, 15 μM, 30 μM and 60 μM during 24 hours in DMEM medium with 10% of fetal bovine serum without steroids. Marker expression parameters (BRCA1, ERα and ERβ being the main phytoestrogen target) were determined using immunofluorescent method associated with flow cytometry and Kolmogorov-Smirnov statistical method. Expression level - the portion (in percent) of specifically fluorescent cells comparatively to the control cells (staining with secondary antibodies); and expression intensity: the specific fluorescent intensity of the cells.

Results. 1. The increase of MCF-7 breast cancer cells exposure to hypoxia from 1 to 4, 6, 10 days led to the decrease of BRCA1 expression level in 1.3; 1.4; 1.5 and 1.9 folds, respectively, comparatively to the control (incubation of the cells at normal O_2 content (21%)), whereas the marker expression intensity did not change significantly. 2. Incubation of MCF-7 cells during prolonged hypoxia induced at 10 days the diminution of ERα expression level in 1.5 fold and the marker expression intensity – in 2.1 folds comparatively to the control. 3. The increase of genistein concentration from 7.5 μM to 30 μM led to the augmentation of BRCA1 expression intensity with maximum 1.4 folds at the genistein concentration 30 μM. Higher genistein concentrations (60 μM) did not induce the increase of the marker expression intensity. 4. Genistein in the concentrations 7.5 μM, 15 μM and 30 μM also increased ERβ expression intensity in 1.6; 1.3 and 1.7 folds, respectively, without influence on ERβ expression intensity at the concentration 60 μM. 5. Incubation with genistein at the concentrations 7.5 μM, 15 μM, 30 μM and 60 μM diminished ERα expression intensity in 1.4; 1.3; 1.4 and 1.9 folds, respectively.

Conclusion. Results of the study demonstrate the decrease of BRCA1 and ERα expression at the prolonged hypoxia. Phytoestrogen genistein did not influence similarly the BRCA1, ERα and ERβ expression: it increased BRCA1 and ERβ expression and reduced ERα expression. Therefore, the data obtained point to different effects of phytoestrogen genistein on breast cancer markers and open perspectives of the research of molecular mechanisms involved in these processes. (RFBR grant 18-29-09017).

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Berberine derivatives as Tdp1 inhibitors

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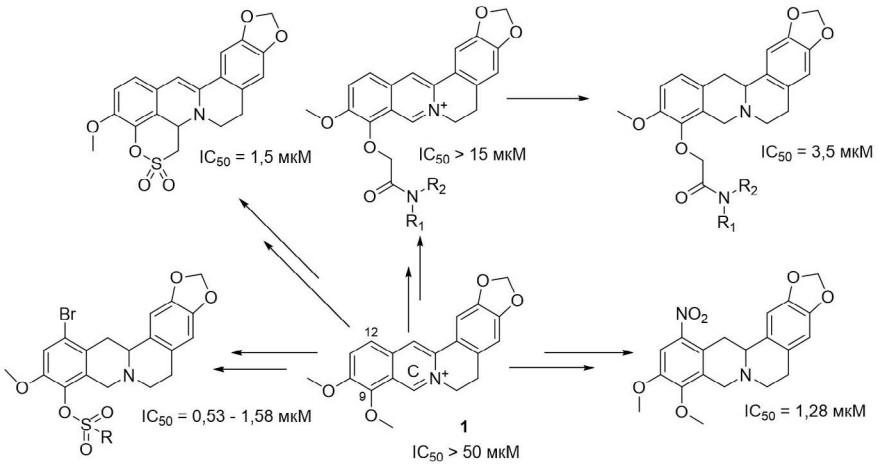
Berberine **1** is an isoquinoline plant alkaloid which shows multiple biological activity. One of the important properties of berberine and its derivatives is anticancer activity. Tdp1 is a human DNA repair enzyme. It is considered to be a potential target for adjuvant therapy of cancer treatment. Tdp1 inhibitors can be used in combination with topoisomerase inhibitors and other antitumor agents. Information about protoberberine structures as potential Tdp1 inhibitors is not described in literature yet. Newly synthesized berberine derivatives containing reduced ring *C* and some substituents at 9- and 12-positions have shown to be capable to inhibit Tdp1 at micromolar concentrations in screening tests.



This work was supported by Russian Science Foundation (grant 19-13-00040)

New structural types of carbocyanines with two chromophore groups: synthesis and properties

Shmykova A.M.[1], Kriveleva A.S.[1,2], Mestergazi M.G.[1,2], Kostyukov A.A.[2], Kuzmin V.A.[2], Shtil A.A.[3], Podrugina T.A.[1,2]

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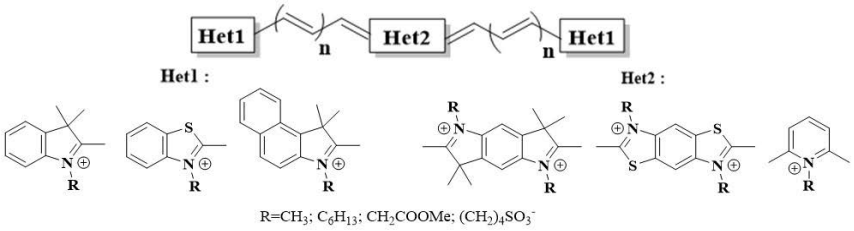
Due to their highly effective fluorescent properties, carbocyanine dyes are successfully used in biology and medicine to investigate the mechanisms of action of drugs, as well as a means of early diagnosis and as therapeutic agents. The carbocyanines containing two chromophore fragments are the least studied in this area [1]. The structure of the dye containing four heterocyclic cores allows to significantly expand the combinatorial possibilities for the directed design of the structures in order to optimize the photophysical and pharmacophoric properties.

In the present investigation, the synthesis of a series of new biscarbocyanine dyes based on a combination of heterocycles of different structural types and hydrophilic and lipophilic substituents at nitrogen atoms was performed. It has been shown that the photophysical properties (absorption maximum, extinction coefficient, fluorescence quantum yield, etc.) depend both on the replacement of the heterocyclic system and on the variation of functional groups in the substituent at the nitrogen atom. For example, it was shown on the HCT116 cell line that dyes containing hydrophobic alkyl groups have pronounced cytotoxicity, and the introduction of hydrophilic sulfo groups into a substituent at the nitrogen atom leads to sharp decrease of the cytotoxicity.



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Synthesis, antibacterial and antitumor activity of quaternary ammonium salts of pyridoxine functionalized 2-amino-6-sulfanylpyridine-3,5-dicarbonitriles or pentaerythritol ethers

Shtyrlin N.[1], Grigor'ev A.[2], Gabdrahmanova A.[1], Gabbasova R.[1], Zeldi M.[1], Grishaev D.[1], Balakin K.[1], Nasakin O.[2] and Shtyrlin Y.[1]

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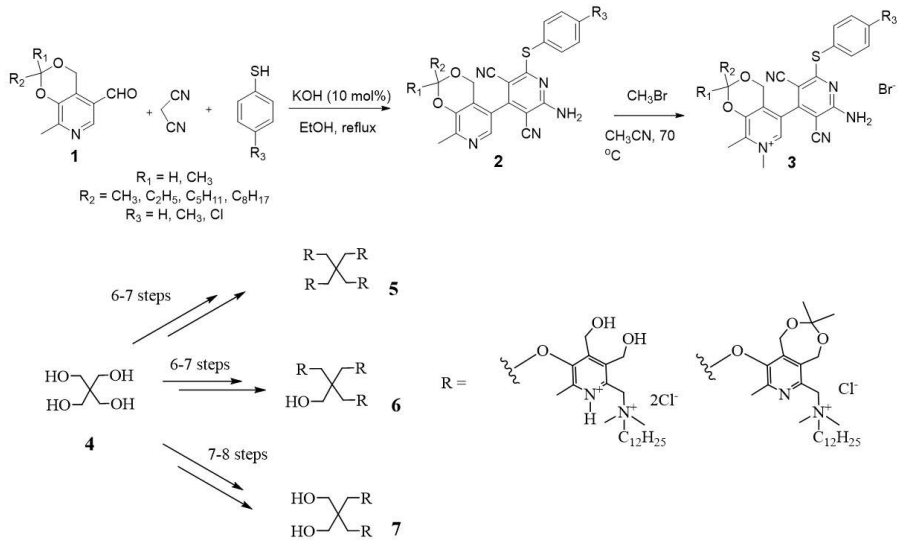
A library of 21 quaternary ammonium salts of pyridoxine functionalized with 2-amino-6-sulfanylpyridine-3,5-dicarbonitrile or pentaerythritol moieties was synthesized. Compounds **3** were obtained using a three-component one-pot reaction of aldehyde derivatives of pyridoxine **1**, malononitrile and thiophenol [1]. Compounds **5-7** were synthesized from pentaerythritol **4** and the corresponding 6-hydroxymethyl derivatives of pyridoxine in 6-8 stages. The obtained bi-, three- or tetrapyridine structures demonstrated expressed antibacterial activity with MICs in the range of 0.5-4 μg/mL against the three studied Gram-positive strains and 2-64 μg/mL against three Gram-negative strains, which was comparable or better than activity of the reference antimicrobial agents myramistin and benzalkonium chloride. Several compounds also demonstrated high cytotoxic activity against MCF-7, SNB-19 and HCT-116 tumor cells.



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Influence of ligand environment on the stability and activity of Ru(II)-arene anticancer compounds with targeting ligands

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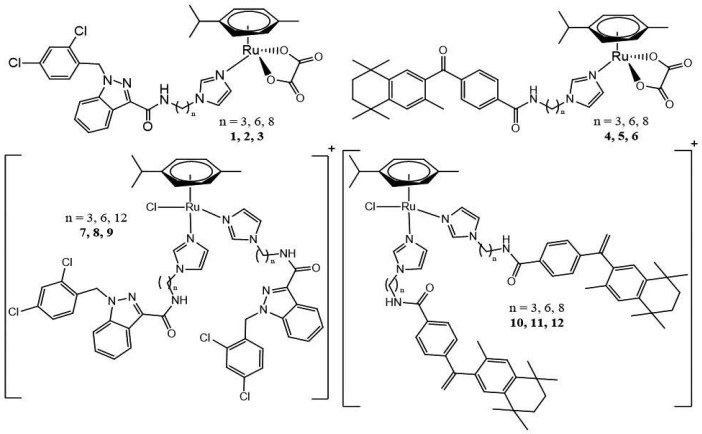
Cisplatin and other platinum-based compounds are most widely used in clinics for the treatment of various types of cancer. Ruthenium coordination and organometallic compounds are a promising alternative in the search of the new metal-based antitumor agents. Different approaches have been explored, including mono- and bifunctional compounds such as RAPTA compounds, targeted approaches, protein kinase inhibitors, ruthenium-arene clusters. Recently we reported new highly active organometallic Ru(II)-arene compounds [1] based on imidazole modified targeting ligands such as lonidamine and bexarotene. However, reported compounds showed fast partial ligand exchange behavior in DMSO solution which is widely used in the MTT assay to support solubility of new metal-based anticancer compounds.



In this work, in order to increase stability, we modified ligand environment at the ruthenium moiety by substitution chloride ligand with oxalate ligand **(1-6)** or by an introduction of the second ligand in the coordination sphere and obtaining charge complexes **(7-12)**. All synthesized compounds showed resistance to the ligand exchange in DMSO solutions. Interestingly, that new compounds **(1-12)** in the MTT test show a similar level of antiproliferative activity compare to the early reported compounds.

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This work was supported by Russian Science Foundation (19-13-00084)

Sterically hindered catechol thioethers: synthesis, electrochemistry, antioxidant and cryoprotective activities

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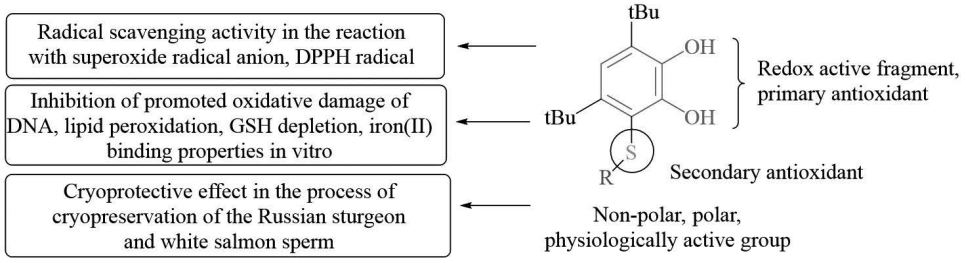
A number of asymmetrical thioethers based on 3,5-di-*tert*-butylcatechol containing sulfur atom bonding with non-polar, polar or physiologically active groups in the sixth position of aromatic ring have been synthesized and the electrochemical properties, antioxidant, cryoprotective activities of new thioethers have been evaluated.



Cyclic voltammetry was used to estimate the oxidation potentials of thioethers in acetonitrile and to propose the mechanism of oxidation. The reaction of electrogenerated superoxide radical anion (or KO_2) with the target compounds was researched. The antioxidant activities of the compounds were determined using 2,2'-diphenyl-1-picrylhydrazyl radical (DPPH) assay, experiments on the oxidative damage of the DNA, the reaction of 2,2'-azobis(2-amidinopropane hydrochloride) (AAPH) induced glutathione depletion (GSH), the process of lipid peroxidation of rat liver (Wistar) homogenates *in vitro*, and iron(II) chelation test. The variation of different groups at sulfur atom allows to regulate lipophilic properties and antioxidant activity of compounds. Several thioethers demonstrate the combination of radical scavenging, antioxidant activity and iron(II) binding properties. The catechols were studied as cryoprotectants of the media for cryopreservation of the fish sperm. A cryoprotective effect of an addition of the thioethers depends on the structure of groups at sulfur atom.

The work was supported by the Russian Science Foundation grant 17-13-01168.

Reaction of 5-aryloxazolidines with CH-acidic compounds

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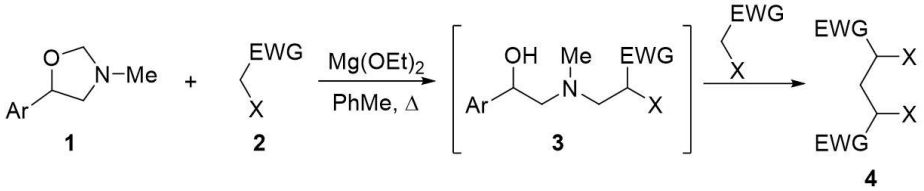
Institute of Natural Sciences and Mathematics, Ural Federal University, 620002, Russian Federation, Ekaterinburg, Mira Street, 19

An oxazolidine ring is well known and widely used in organic chemistry. Despite the simplicity of this heterocyclic system it possesses a versatile reactivity. In particular, general direction of the reactivity of oxazolidines is their ring-opening by nucleophilic attack at C-2, located between two electron-deficient atoms (N and O), resulted in the amino alcohol formation.



X = CO_2Et, CO_2Me, Ph; EWG = CO_2Et, CO_2Me, Bz

However, the reaction of 5-aryloxazolidines **1** with 1,3-dicarbonyl compounds has not been investigated. It was found that the reaction of oxazolidine **1** with methylene-active compound **2** in the presence of catalytic amounts of $Mg(OEt)_2$ did not stop at the formation of amino alcohol **3**, and proceeded further *via* decomposition of Mannich base and elimination of the amino alcohol. The formed terminal alkene reacted with a second molecule of CH_2-active compound **2**. As a result, methylene-bridged bis-1,3-dicarbonyl compounds **4** were obtained in 39 to 71% yield. Thus, the oxazolidine ring appears to be the synthetic equivalent of formaldehyde.

This work was financially supported by the Russian Science Foundation (Grant 17-73-20070).

Direct C-H functionalization in the synthesis of potential agents for boron-neutron capture therapy (BNCT)

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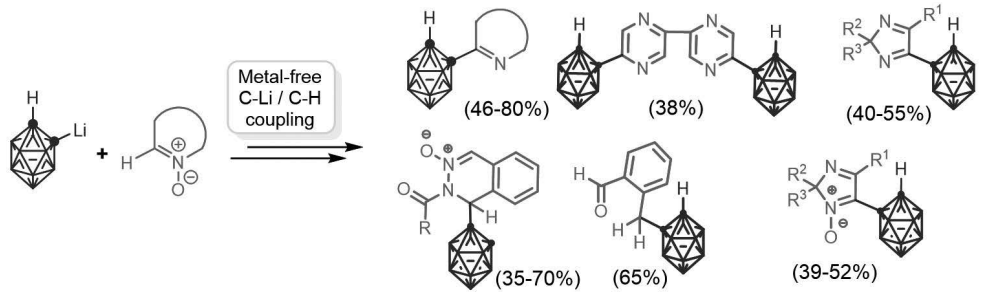
Boron neutron capture therapy (BNCT) is an experimental method of treating malignant tumors, based on the nuclear capture and fission reactions that takes place, when nonradioactive boron-10 is irradiated with thermal neutrons to yield high linear energy transfer particles that can lethally damage cancer cells.

One of the limitations of this method is associated with the design of effective boron delivery agents to target tumors. A convenient approach for the modification of carboranes, which are of particular interest as potential agents for BNCT has been developed. It has been found that the direct, nucleophilic functionalization of C(sp^2) -H bond in aromatic and nonaromatic *N*-oxides by action of carboranyllitium leads to the formation of various boron-enriched azaheterocyclic derivatives [1-3].



This study was supported by the Russian Ministry of Education and Science (State contract 4.6351.2017/8.9).

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Mavoglurant analogues synthesis via the aza-Coupe-Mannich rearrangement

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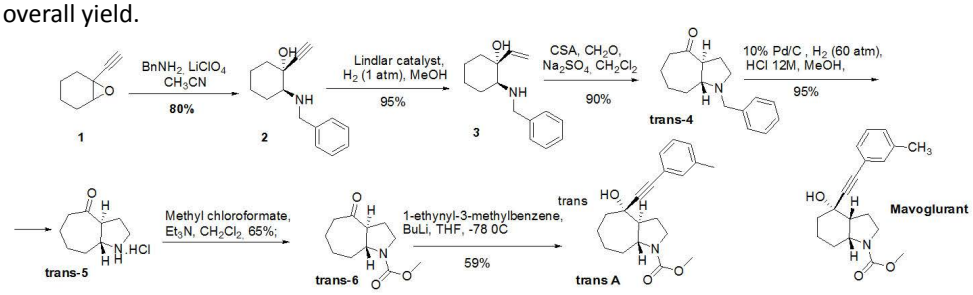
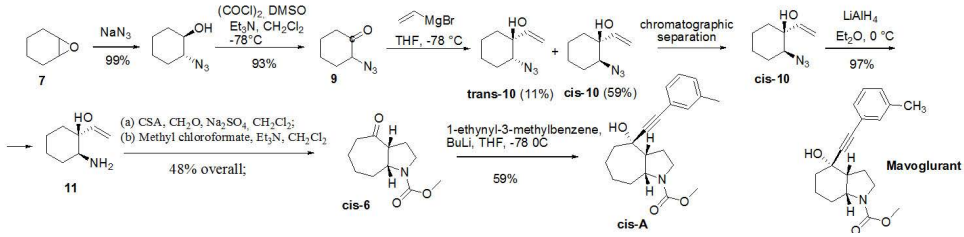
One of the urgent tasks of modern medical chemistry is the search and creation of new effective drugs. This is directly related to the synthesis of new analogues of the drug Mavoglurant, for which anti-prion activity has recently been discovered [1].

Earlier in our group an approach to the synthesis of bicyclic ketones, analogues of octahydroindole, was proposed via aza-Coupe-Mannich rearrangement [2]. This approach was used to synthesize Mavoglurant analogues with cis- and trans-fused cycloheptane and pyrollidine rings.. For the synthesis of the trans-fused analogue a six-step transformation was used, as a result of which we were able to obtain the target compound **trans-A** in 25% overall yield.



For the synthesis of the cis-articulated analogue, a six-step conversion from commercially available epoxide 7 is used, which makes it possible to obtain cis-A with a total yield of 31%.



This work was supported by RFBR (18-33-20215).

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Synthesis and tuberculostatic activity of podands with a dihydropyrimidine fragment

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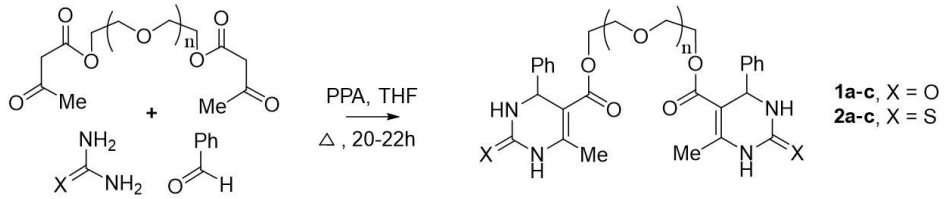
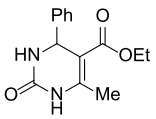
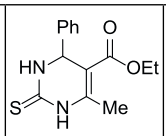
[2]Ural Federal University, 620002, Russia, Yekaterinburg, Mira St.,19

Among numerous dihydropyrimidine derivatives, hetero cycles comprising a transport polyether spacer are of special interest. We have demonstrated that joining a polyether (podand) and dihydropyrimidine moieties in a molecule results in an increase of activity and specifi city against Mycobacterium tuberculosis[1].

Podands **1a-c** and **2a-c** were synthesized via the polyphosphoric acid (PPA)-catalyzed three-component Biginelli condensation using polyethers containing 3-oxobutanoyl moieties as CH-active components.



Tuberculostatic activity of podands 1a-c and 2a-c *in vitro* has been studied towards the typical laboratory strain of *M. tuberculosis* $H_{37}Rv$.

		**1a** *n = 0*	**1b** *n = 1*	**1c** *n = 2*		**2a** *n = 0*	**2b** *n = 1*	**2c** *n = 2*
MIC, μg·ml^{-1}	*>100*	*12*	*12*	*3.1*	*50*	*1.5*	*3.1*	*6.2*

It was shown that among dihydropyrimidinethione podands **1a-c** tuberculostatic activity against $H_{37}Rv$ strain increases with elongation of the polyether unit, whereas for dihydropyrimidinethione podands **2a-c** an inverse dependence was observed.

References

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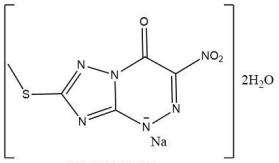
The work was financially supported by the Russian Science Foundation (project no. 15-13-00077-P).

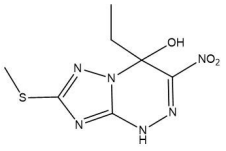
4-ALKYL-AZOLO[5,1-C] [1,2,4] TRIAZINES AS ANALOGS OF TRIAZAVIRIN

Tiufiakov D.V.[1], Drokin R.A.[1], Voinkov E.K.[1], Ulomsky E.N.[1], Rusinov V.L.[1], Volobueva A.S.[2], Esaulkova Y.L.[2], Sinegubova E.O.[2], Zarubaev V.V.[2]

[1]Ural Federal University, 620002, Russia, Ekaterinburg, Mira 19
[2]Saint-Petersburg Pasteur Institute, 197101 Russia, Saint-Petersburg, Mira 14



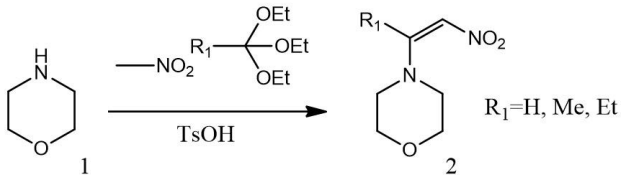
TRIAZAVIRIN



DT-152

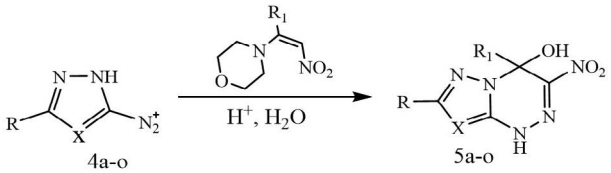
In current work were synthesized a series of 6-nitroazolo [5,1-c] [1,2,4] triazines, not previously mentioned in the literature.

By analogy with the previously described experiments, ternary condensation of 2-morpholine-1-nitroalkenes [2] (2) was obtained.



1 2

Then was developed a method for producing 6-nitroazolo [5,1-c] [1,2,4] triazines (5a-5o) by azo coupling with obtained compounds (2).



4a-o 5a-o

a-l:R=H,Me,SMe,CF_3, R_1=H, Me, Et, X=N;
m-o: R=H, X=CCOOEt, R_2=H, Me, Et.

As a result, a series of promising 4-alkyl – 3-nitro-1,4-dihydro- [1,2,4] triazolo [5,1-c] [1,2,4] triazin-4-ols and two new nitroenamines, not previously mentioned in literature.

A close analogue (DT-152) of the known drug triazavirin confirmed antiviral activity.

The work was supported by Russian Science Foundation grants № 17-13-01096.

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Synthesis and *in silico* identification of candidate drugs for *Neisseria gonorrhoeae* among heteroaryl-substituted indole and pyrrole derivatives

Trestsova M.[1], Sarapultsev A.[1], Utepova I.[1,2], Vassiliev P.[3], Ianalieva L.[3], Appazova D.[3], Chupakhin O.[1,2]

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[2]Institute of Organic Synthesis, Ural Branch of RAS, 620990, Russia, Ekaterinburg, S. Kovalevskaya Street, 22
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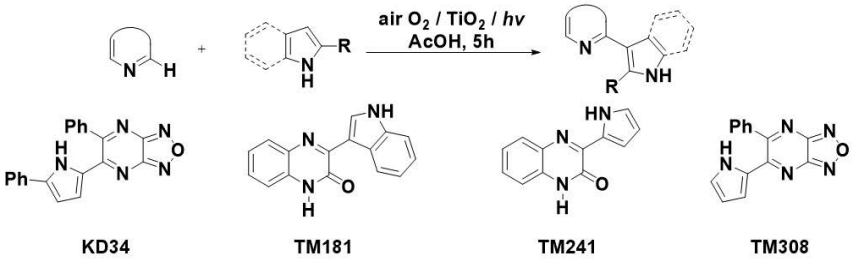
Neisseria gonorrhoeae (GC) is a Gram-negative bacterium and a human-specific pathogen that causes gonorrhea. Pharmaceutical interventions against GC infections are limited to the common antibiotic regimens, but no specific drug is available. Thus, the aim of the study was the identification of indolyl- and pyrrolyl-substituted heteroaryl derivatives with the pronounced activity against GS with the additional activity against Gram-positive bacteria (*S. aureus*).

Synthesis of indolyl- and pyrrolyl-substituted heteroaryls was performed by the direct C-H functionalization of heteroarenes (S_N^H reaction) using a heterophase oxidative system air O_2 / TiO_2 photocatalyst / light irradiation.



In silico prediction of the compounds with high antibacterial (anti-GS) activity was made using IT Microcosm. According to the results of the *in silico* prediction, three molecular targets for GC were set as perspective: *GTP-binding protein Rheb* (I), *UDP-N-acetylmuramoyl-tripeptide-D-alanyl-D-alanine ligase* (II) and *Anthranilate phosphoribosyltransferase* (III). Five molecular targets for *S.aureus* were set as perspective. Among 60 compounds studied, one compound was estimated to be highly active against I, four compounds - against II and 26 compounds - against III. The possible action on two molecular targets (II and III) was predicted for four compounds (KD34 (5-phenyl-6-(5-phenyl-1*H*-pyrrol-2-yl)-[1,2,5] oxadiazolo[3,4-*b*]pyrazine), TM181 (3-(1*H*-indol-3-yl)quinoxalin-2(1*H*)-one), TM241 (3-(1*H*-pyrrol-2-yl)quinoxalin-2(1*H*)-one) and TM308 (5-phenyl-6-(1*H*-pyrrol-2-yl)-[1,2,5] oxadiazolo[3,4-*b*]pyrazine)). Of these four compounds, three were identified as potentially active against *S. aureus* - due to exposure to *DNA ligase* (KD 34, TM308) and *methionyl-tRNA synthetase* (TM241), which has determined their choice for future *in vitro* testing.

Synthesis of biologically active hetarylindole derivatives by the direct C-H functionalization of heteroarenes using a heterophase oxidative system air O_2 / TiO_2 photocatalyst / light irradiation

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[2]Institute of Organic Synthesis, Ural Branch of Russian Academy of Sciences, 620990, Russia, Ekaterinburg, S. Kovalevskaya Street, 22
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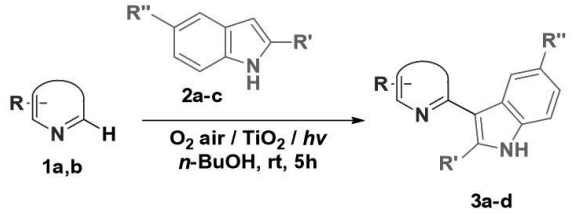
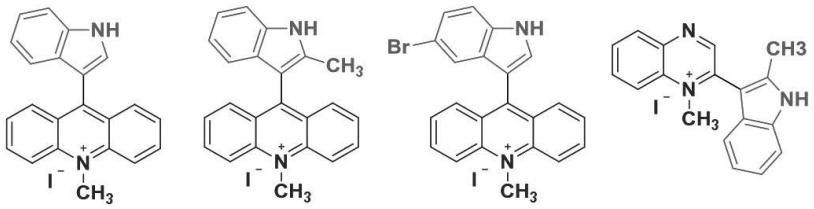
Interest in the indole derivatives study is related due to exhibit their high biological activity. Among them are known compounds with anti-cancer, anti-inflammatory and antibacterial activity.

We have developed a simple method for the synthesis of heteroaryl substituted indole derivatives. The compounds **3** were obtained by the direct C-H functionalization of heteroarenes **1** by indole derivatives **2** (S_N^H reaction) using a heterophase oxidative system air O_2 / TiO_2 photocatalyst / light irradiation [1],[2].





The results of the initial biological tests show that the compounds **3a-d** have antibacterial activity.

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This work was supported by the Russian Foundation for Basic Research, project 18-33-00927.

Synthesis of new inhibitors of excitatory amino acid carriers (EAATs)

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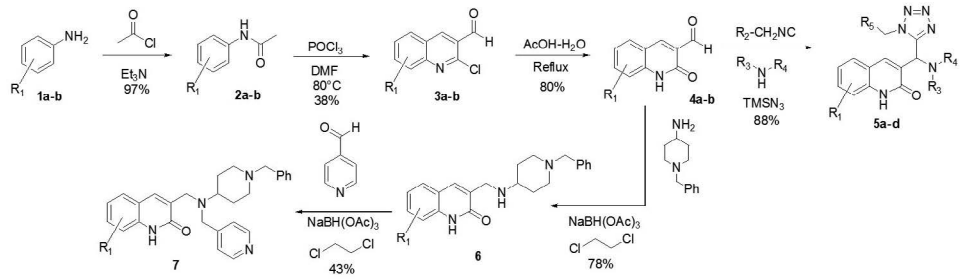
Dysfunction of excitatory amino acid transporters (EAATs) has been implicated in the pathogenesis of various neurological disorders, such as stroke, brain trauma, epilepsy, and neurodegenerative diseases, among others. EAAT2 is the main subtype responsible for glutamate clearance in the brain, having a key role in regulating transmission and preventing excitotoxicity. Therefore, compounds that increase the expression or activity of EAAT2 have therapeutic potential for neuroprotection. Previous studies identified that derivatives of 3-(aminomethyl)quinoline-2(1H)-one increase the speed of glutamate translocation, without affecting the substrate interaction, suggesting an allosteric mechanism. Identification of these new positive allosteric modulators EAAT2 offers an innovative approach to the development of treatment methods based on enhancing glutamate transport.

Recently, research was conducted in our laboratory to obtain and study the biological properties of 3-(aminomethyl)quinoline-2(1H)-one derivatives. A focused library of 3-(aminomethyl)quinoline-2(1H)-one derivatives was synthesized to search for the leader compounds among the synthesized compounds.



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Analytical Provision of Boron Neutron Capture Therapy of Cancer

Tsygankova A.[1,2], Guselnikova T.[1], Zavyalov E.[2,3], Kanygin V.[2], Kasatova A.[2,4], Razumov I.[2,3], Sibirtsev R.[2,5]

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[3]FRC IC&G SB RAS, 630090, Russian Federation, Novosibirsk, Acad. Lavrentiev Ave., 10
[4]BINP SB RAS, 630090, Russian Federation, Novosibirsk, Acad. Lavrentiev Ave., 11
[5]Novosibirsk State Medical University, 630091, Russian Federation, Novosibirsk, Krasny Pr. 52

Boron Neutron Capture Therapy (BNCT) is a noninvasive therapeutic modality for treating locally invasive malignant tumors such as primary brain tumors and recurrent head and neck cancer, for example, anaplastic astrocytoma or glioblastoma. The development of BNCT requires an integrated approach with the participation of specialists from various fields, including physicists, biologists, chemists and doctors. At the BINP SB RAS, a source of accelerator-type epithermal neutrons was proposed and constructed. We carried out a series of preclinical experiments on BNCT on cell cultures and laboratory animals. We used immunodeficient 8-10 week old male SCID mice of the SPF status. 18-21 days before the start of the experiment, U87 human glioblastoma cells were prepared, brought to concentration of 100 thousand cells in 1 µl and injected intracranially to obtain intracerebral mass formation. BPA L-p-borfenylalanine and BSH borkaptat were used as a drug for targeted delivery of boron B^{10} monoisotope.

To assess the effectiveness of the accumulation of BPA and BSH in the tumor and constructing the kinetic curves of excretion of drugs, we investigated the tissues of the organs of laboratory animals (blood, kidneys, liver, brain and tumor). The boron content was determined by the ICP OES method on an iCAP-6500 spectrometer (Thermo) after acid digestion in a MARS-5 microwave system (we used HNO_3, H_2O_2, $HClO_4$ and their mixtures). We checked the accuracy and specificity by analyzing the reference material and using spike method. The calibration function was built using a single-element solution of boron ions «ГСО 7345-96». The registration of emission spectra was performed under the conditions recommended by the manufacturer. We used the method of sequential dilutions.

We identified organs and tissues in which the accumulation of B10 is maximal. We find out the ratio of accumulated B^{10} in the tumor and brain tissue. The optimal times of exposure were chosen when the ratio of accumulated B^{10} in the tumor and brain is maximal.

The study was carried out on the basis of the Center for Genetic Resources of Laboratory Animals, SPF Animal Farm, FRC IC&G SB RAS. Financial support of the Russian Foundation for Basic Research in the framework of the research project No. 18-29-01007.

Synthesis of novel ligands for quinone reductase 2 (MT3/QR2) through specific cyanation and selective reduction of 2-oxindole derivatives

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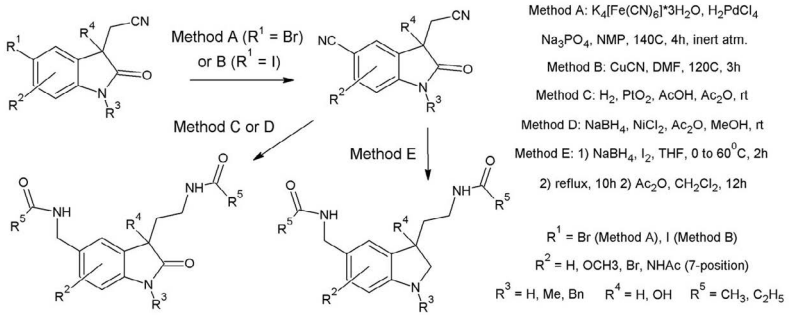
MT3/QR2 is a low-affinity melatonin receptor, which functions include neuroprotective and antioxidant activity, as well as decreasing of the intraocular pressure (IOP). A new method of obtaining MT3/QR2 (and MT1, MT2 in case of 2,3-dihydroindoles) affinic ligands based on 2-oxindole scaffold is proposed. It was previously shown, that amido-group in 5-position of the indole scaffold is a pharmacophore one and is necessarily present in many MT3-active compounds[1].

According to molecular docking and X-ray crystal diffraction analysis, the substituent in 5-position must be modified by adding a -CH_2- spacer before the amido-group. Supposedly, when the amido-group is situated one carbon atom further from the indole core, less water can be confined in the binding site of QR2 (less free space), making the binding more efficient.

Cyano-derivatives were chosen as precursors, as they can be reducted to amines and then acylized together with the other cyano-group in 3-position, which leads to minimization of reaction stages. Pd-catalyzed cross-coupling and Rosenmund-von Braun reactions were used in the cyanation of oxindoles for the first time. A new method of selective reduction of cyano-groups and the amido-group in 2-position of the indole scaffold is proposed. The conditions were optimized to obtain indole- or 2,3-dihydroindole derivatives with good yields.



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This work was supported by the Russian Foundation for Basic Research (Project 17-03-01320)

Urocanic acid derivatives as novel cytotoxic agents

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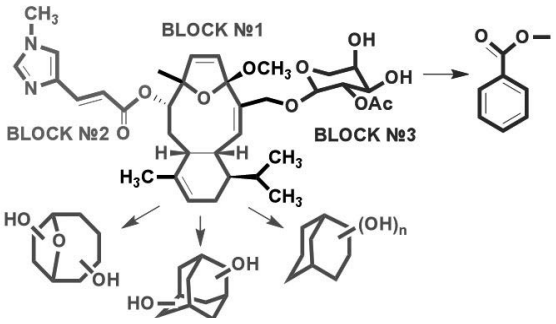
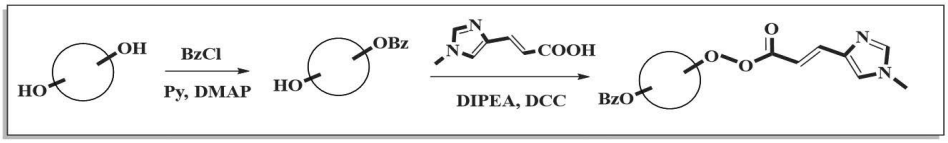
Cancer is the second major cause of death in highly industrialized countries. Chemotherapy of cancer usually involves the use of cytotoxic agents (such as taxol and eleutherobin [1]).

During molecular modeling we formulated the main principles of design of simplified eleutherobin analogues. We assumed that some polycyclic structures (e.g. adamantane, oxabicyclooctane, bicyclononane) could play the role of the central block. They should contain at least two hydroxyl groups, one of them esterified with N-methylurocanic acid (as in eleutherobin, Block №2) and the other one with benzoic acid (as in taxol, Block №3).



We synthesised a series of individual novelanalogs of eleutherobin which are toxic against three human tumor cell lines (breast MCF7, ovarian SKOV and colon HCT116) in the micromolar range of concentrations. These compounds caused cell rounding and death which could be an evidence of taxol-like effect on tubulin polymerization.



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Acknowledgments:
This work was supported by the Russian Foundation for Basic Research (Project 17-03-01320)

Synthesis of Fluorescent Derivative of RGD Peptide

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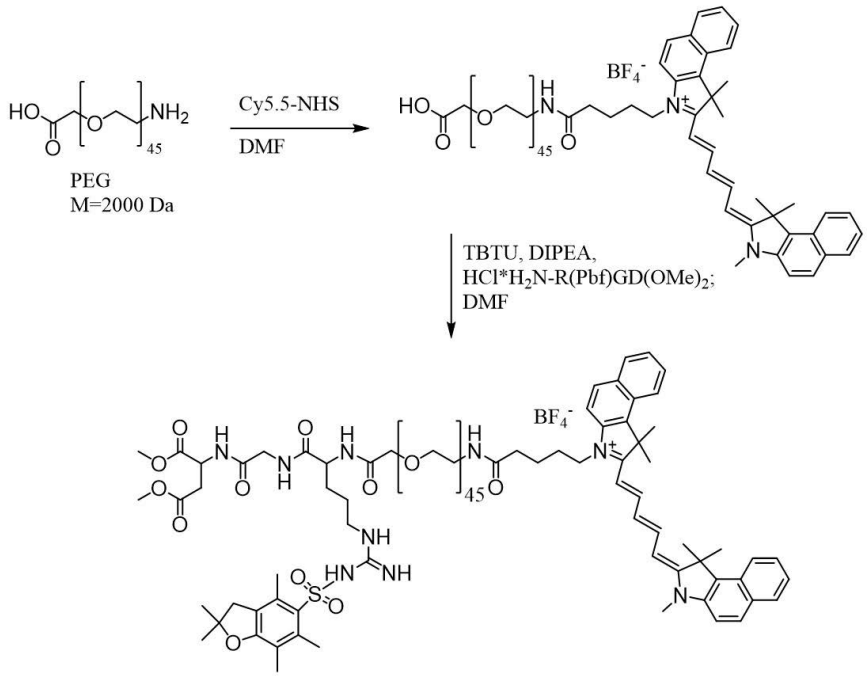
It is known that RGD peptides containing the amino acid sequence *S*-Arg-Gly-*S*-Asp are capable of specific binding to integrins, for example, $\alpha_v\beta_3$, distributed on the surface of tumor cells. It is makes it possible to use peptides of this family as molecular vectors. The purpose of this work is to obtain the RGD peptide derivative containing a polyethylene glycol (PEG) molecule as a linker and a fluorescent label (cyanine dye Cy5.5).



The introduction of bifunctional PEG into the molecule increases the hydrophilicity of the conjugate molecule and spatially removes the fluorescent label from binding site to integrin. The peptide was synthesized starting from the corresponding protected *S*-amino acids by the methods of classical solution peptide chemistry according to the Fmoc-strategy. The structure and purity of the target product was confirmed by physical and chemical methods (^{1}H NMR and UV spectroscopy, HPLC, MS, and fluorimetry). The data obtained can be further used for designing the agents for specific staining tumor cells and tissues.

The study was carried out in the framework of the State Assignment of Russia (project no. AAAA-A19-119011790130-3).

HPLC Analysis of Enantiomeric Composition of 2-Aryloxy Propionic Acids on a Chiral Stationary Phase

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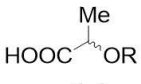
2-Aryloxycarboxylic acids are precursors and structural fragments of physiologically active compounds and agrochemical agents. The purpose of the work was to develop chromatographic conditions for the determination of enantiomeric composition of 2-aryloxy propionic acids **1–4** being of practical interest (Fig. 1).



1-4

1: R = Ph
2: R = 2,6-Cl_2-C_6H_3 (precursor of Lofexidine, an α_2-adrenoreceptor agonist)
3: R = 2-Me-4-Cl-C_6H_3 (pesticide Mecoprop)
4: R = 4-I-C_6H_4 (precursor of hypervalent iodine-based chiral catalysts)

Figure 1. *The objects of study – racemic acids* **1–4**

Determination of the enantiomeric composition of compounds **1-4** was carried out in normal-phase (NP) and reversed-phase (RP) modes on chiral columns. The optimal conditions for HPLC analysis (chromatographic columns, mobile phase, and elution rate) were found, which made it possible to achieve successful separation of the enantiomers of 2-aryloxy propionic acids. Spectrophotometric and polarimetric (Chiralyser-MP) detectors were used to identify the enantiomers of acids **1–4** (Fig. 2).

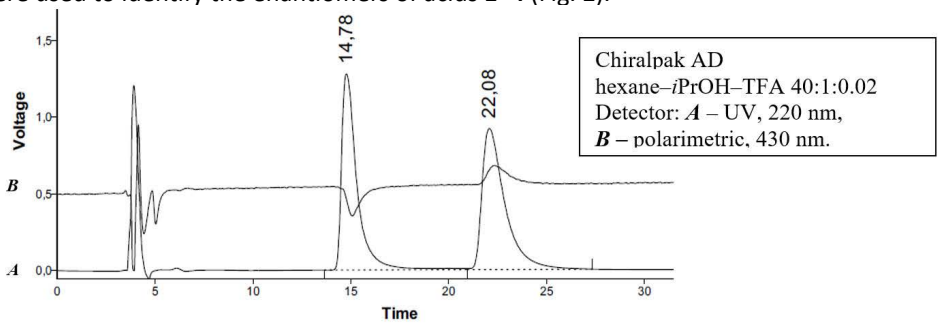


Figure 2. *HPLC chromatogram of racemic 2-phenoxy propionic acid (***1***)*

The best separation (separation factor α= 1.93) of the optical isomers was achieved for acid **2** on a (*S,S*) Whelk-O1 column in the NP analysis mode using a hexane–*i*PrOH–TFA 50:1:0.02 mixture as an eluent (flow rate 1 ml/min).

The work was financially supported by the Russian Foundation for Basic Research (project 18-33-00027 mol_a).

SYNTHESIS AND AGGREGATION OF ISOTHIOURONIUM SURFACTANTS IN AQUEOUS SOLUTION

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Cationic surfactants have a number of practically important functional properties, for example, antimicrobial activity, the ability to solubilize water-insoluble substances and medicines. The aggregation behavior of surfactants in solution depends on the nature of the head group and the length of the alkyl tail. Among the cationic surfactants, amphiphiles with a sulfur atom in the head group are the least studied. There are only a few works devoted to the study of the surface-active properties of isothiouronium amphiphiles [1,2]. In the present work, a homologous series of isothiouronium surfactants was synthesized (Fig. 1, where n = 9, 11, 13, 15, 17), and their aggregation and solubilization activity was investigated by the methods of tensiometry, conductometry, fluorimetry, spectrophotometry, dynamic and electrophoretic light scattering.

The values of the critical micelle concentration and the hydrodynamic diameter of the aggregates were determined, as well as the solubilization capacity towards the hydrophobic dye Orange OT was calculated.

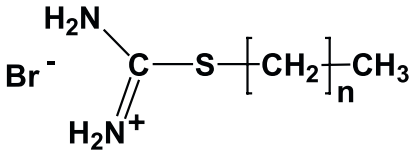

Figure 1. *The chemical structure of isothiouronium surfactants*

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F.V., T.K., G.G. and L.Z. thank the Russian Science Foundation, project 19-73-30012 (self-organization and functional activity of surfactant systems); I.G. and D.B. thank for the subsidy allocated to Kazan Federal University for the state assignment in the sphere of scientific activities (№ 4.5888.2017/8.9) (synthesis of surfactants).

Neutral Glycoglycerolipids Are the Novel Class of Antitumor Agents

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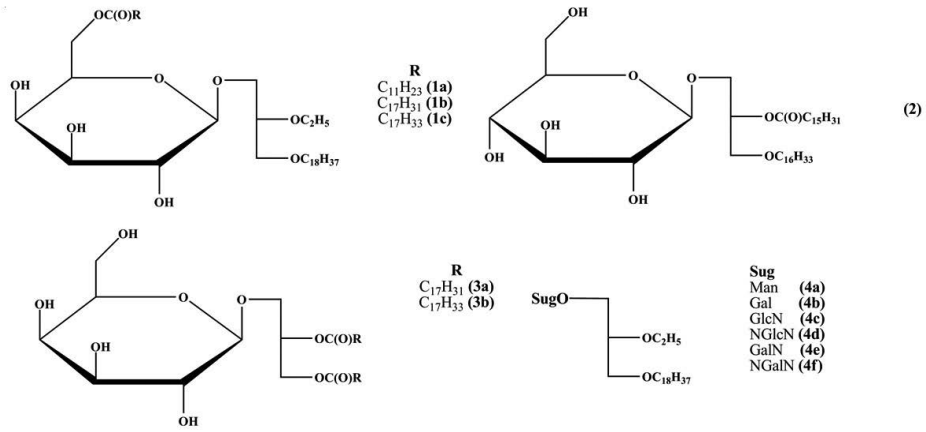
Cationic alkyl glycerolipids have been investigated as antitumor compounds [1]. Hemolysis, a side effect of these compounds, limits their practical use. Therefore, search for other classes of glycerolipids, particularly the neutral ones, in which cytotoxicity is preserved but the hemolytic activity is minimal, is worthy.



New glycoglycerolipids of mixed structure (**1a-c**) cause virtually no death of tumor cells (IC_{50}> 50 μM). The analog **2** containing alkyl and acyl substituents in the glycerol backbone showed a weak activity in all cell lines except the colon carcinoma HCT116 (IC_{50}= 23.6 ± 1.2 μM). Glycoglycerolipids with substituents at C2 and C3 positions of glycerol **(3a-b)** were most active for the K562 line (leukemia) (**3a**, IC_{50}= 6.72 ± 0.71 μM) and SCOV-3 (ovarian cancer) (**3b**, IC_{50}= 3.41±0.15 μM), significantly exceeding the respective values of **1a-c**. Among the alkyl glycoglycerolipids, the aminoglycerolipids **4c-f** showed the best results on the K562 cell line (IC_{50}≤8±0.2 μM). Lead compounds did not cause hemolysis at concentrations that induced tumor cell death. Thus, charge neutralization led to a reduced hemolytic activity of glycoglycerolipids whereas the cytotoxic properties of compounds were preserved.

Reference

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Preparation of copper complexes based on α,ω-bis-(2-trifluoroacetoacetylphenoxy)alkanes

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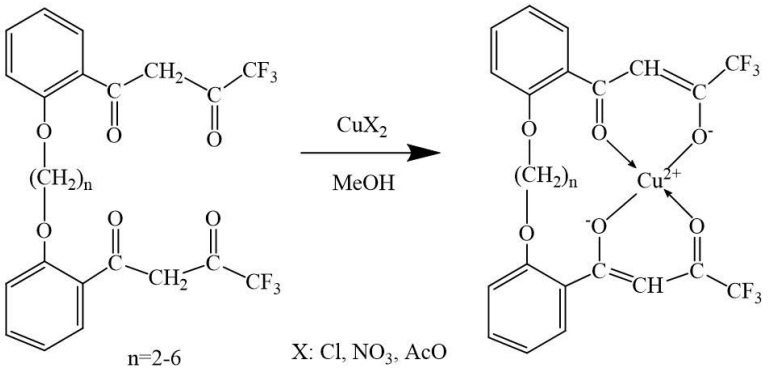
Complexes with organic ligands play an essential role in biochemical processes. Thus, metalloenzymes are important catalysts for a wide range of chemical reactions occurring in a living cell. Exogenous transition metal complexes possess a wide spectrum of biological activity. Previously, bacteriostatic and fungistatic activities of the Cu(II) complexes with organic ligand based on 1,1,1-trifluoro-4-(2-methoxyphenyl)butane-2,4-dione were described [1].

In the present work, we consider an attempt of synthesis of Cu(II) complexes based on α,ω-bis(2-trifluoroacetoacetylphenoxy)alkanes, chelating triketone-like ligands. The synthesized chelating ligands were characterized by elemental analysis, FT-IR spectroscopy, and ^{1}H NMR spectroscopy.



The preparation of the complexes was carried out by the exchange reaction of the corresponding salt in methanol in the presence of a base. The composition and the estimated structure of the complexes were characterized by elemental analysis and FT-IR spectroscopy.

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Synthesis of Purine Conjugates with *N,S*-Heterocycles as Potential Antiviral Agents

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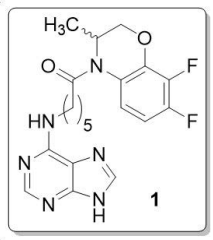
[2]Institute of Chemical Engineering, Ural Federal University, 620002, Russia, Ekaterinburg, Mira St., 19



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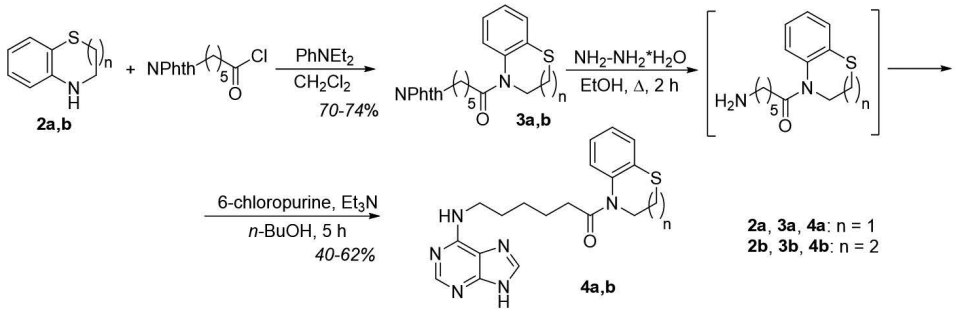
The development of synthetic approaches to new biologically active compounds is the important task of medicinal chemistry. Previously we synthesized the purine conjugate with (*RS*)-7,8-difluoro-3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazine attached by a 6-aminohexanoyl fragment (compound **1**). It has been shown that compound **1** exhibits high antiviral activity against herpes simplex virus type 1 [1]. In the present work we obtained new purine conjugates containing fragments of *N*,*S*-heterocycles such as 3,4-dihydro-2*H*-[1,4]benzothiazine (**2a**) and 2,3,4,5-tetrahydro-1,5-benzothiazepine (**2b**), structural analogues of lead-compound **1**. Acylation of amines **2a,b** with 6-phthalimidohexanoyl chloride in dichloromethane in the presence of *N,N*-diethylaniline afforded amides **3a,b** in good yields; subsequent removal of the phthaloyl protection by hydrazinolysis in refluxing ethanol led to corresponding amines that were used (without purification) as nucleophiles in the nucleophilic substitution of chlorine atom in 6-chloropurine (*n*-BuOH, TEA, 90 ° C). The target purine conjugates **4a,b** with *N,S*-heterocycles are of interest as potential antiviral agents.



The work was financially supported by the Russian Science Foundation (project 19-13-00231).

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Induction of apopotosis of melanoma B16 cells under the action of preparation, containing TNF-α and ds-RNA, in vitro.

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IMBT FBU SSC VB Vector, 630010, Russia, Berdsk, Khimzavodskayastreet, 9

Attempts to use cytokines in cancer therapy do not yet give stable positive results, so the development of an acceptable strategy for the treatment of cancer using different models continues. The preparation of recombinant human TNF-alpha in nanoparticles, containing high-polymer purified double-spiral RNA from Saccharomyces cerevisiae, so called virus-like particles, VLP [1], developed in IMBT, showed increased antitumor activity in vivo on tumor-bearing mice, as well as tropicity to tumor tissue and skin [2,3].

The aim of this study was to assess the direct toxic effect of the drug form VLP-TNF-alpha and its individual components on melanoma cells B16-F10. Analysis of cytotoxic action of TNF-alpha, ds RNA and complex preparation VLP - TNF-alpha was performed by MTT test, apoptosis of melanoma cells was evaluated by flow cytometry with FITZ-annexin V. It was shown that the cytotoxic effect of VLP - TNF-alpha significantly exceeds the total cytotoxic effect of TNF-alpha and ds RNA separately (LD50 is respectively for VLP-TNF-alpha -0.05 μg/ml, TNF-alpha - 9.5 μg/ml, ds RNA > 20 μg/ml). Complex preparation had more pronounced apoptogenic effect. Preparation VLP-TNF-alpha can be a promising drug for the treatment of malignant tumors, including melanoma.

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3. A. V. Bateneva, S. G. Gamaley, L. R. Lebedev, E. D. Danilenko, 2019 , Russian immunological journal in press

Selective effect of 1,2,3-triazolo [5,1-b] 1,3,4-thiadiazines on the proliferation of cultured normal and tumor cells

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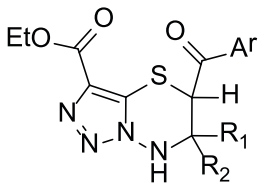
s-Triazolo[3,4-b]1,3,4-thiadiazines show *in vitro* cytotoxic activity against various tumor cell lines [1-3]. Previously, we developed a method for the synthesis of *a*-triazolo[5,1-b]1,3,4-thiadiazines **1** [2]. The influence of compounds **1** on seed germination and development of seedlings of *Pinus sylvestris* L. and *Solanum lycopersicum* L. has been determined [3,4].



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In this current study have been shown that 1,2,3-triazolo[5,1-b]1,3,4-thiadiazines have selective biological activity against animal cells. It has been determined that HeLa tumor cell culture is hypersensitive to the cytotoxic effect of the substances. At the same time, rhabdomyosarcoma cells, especially the normal cell lines, are more resistant to the damaging effects of these substances. Interestingly, stimulation of the proliferative and functional activity of dermal fibroblasts with simultaneous suppressive action on tumor cells under the influence of low concentrations of substances was observed.

This research was supported by the Russian Foundation for Basic Research (grant № 18-316-20018).

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Preparation and properties of porous cellulose phosphate matrices

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Ultrathin fibrillar structures in the form of porous matrices are of interest as modern functional materials with specific properties due to the high ratio of surface to volume of an individual fiber, and can be used in biomedicine and cell engineering.

In this work, the esterification reaction of cotton cellulose in the system orthophosphoric acid – tributyl phosphate – phosphorus (V) oxide was studied. The physicochemical characteristics of gel-forming cellulose phosphates obtained under different synthesis conditions are compared. The influence of the composition of the esterifying mixture, the length of the hydrocarbon radical in the diluent (trialkyl phosphate), the temperature and reaction time on the composition of the phosphorylation reaction products, the yield of the gel fraction and the degree of swelling of hydrogels are analyzed. A quantitative assessment of the kinetic process of polysaccharide phosphorylation was performed using the equation of polychronic kinetics. Based on the kinetic parameters of the equation and the values of the activation energy, it was concluded that diffusion is the limiting stage of the process of polysaccharide phosphorylation.

The composition and properties of phosphorylated cellulose were determined using IR spectroscopy, potentiometric titration, elemental analysis, X-ray diffraction, electron microscopy. It was established that cellulose phosphate is a sponge constructed from individual microfibers with a thickness in the range of 1 – 5 microns and having interpenetrating through pores with sizes ranging from 10 to 150 microns. The cellulose phosphates obtained in this work are dibasic cation exchangers with a full exchange capacity in the range of 1.8 – 9.8 mg-eq/g.

On the basis of the studied physicochemical properties of cellulose phosphate hydrogels, it was concluded that they can be used as wound dressings, ensuring the creation of an optimal moist environment on the wound, absorption of exudate, and targeted delivery of active substances.

Investigation of the structure of the reaction products of cisplatin with oxidized bacterial cellulose

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Oxidized bacterial cellulose (OBC) has a high water retention capacity, biocompatibility, ability to control biodegradation, elasticity, atraumatic removal from wounds and can be used as wound coverings, temporary skin substitute in the treatment of wounds and burns, as well as matrices for prolonged and targeted delivery medicinal substances. The purpose was to study the nature of the interaction of cisplatin with the OBC, clarifying the structure and properties of the resulting reaction products.

The sorption properties of OBC with different contents of carboxyl groups were studied depending on the cisplatin concentration in the external solution and the time of the sorption process. The sorption capacity of the cation exchanger with respect to cisplatin, the degree of extraction of cytostatic agents from the external solution, the degree of swelling of composites of the OBC-cisplatin were determined, and the distribution coefficients were calculated. It has been shown that the degree of cisplatin recovery by OBC from solutions increases as the content of carboxyl groups in its composition increases. It has been established that the cation exchanger with the highest content of carboxyl groups exhibits the highest selectivity for cisplatin: the distribution coefficient for OBC is 3.7, while for bacterial cellulose it is 0.04. It was established that the introduction of cisplatin molecules into the composition of cation-exchange polysaccharides leads to a decrease in their degree of swelling and degree of water absorption. It is shown that the sorption of cisplatin on the OBC has a presumably ion-coordination character.

On the basis of the established regularities, the possibility of obtaining a porous wipe based on an OBC with cisplatin included in a therapeutic dose is shown.

TDP 1 Inhibitors as Potential Antitumor Drugs

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DNA repair mechanisms and their regulation are closely related to the diagnosis and search for treatment of various diseases, including cancer. Traditional cancer therapy is aimed at damaging the DNA of malignant cells, and treatment outcome depends on the effectiveness of their DNA repair systems. Currently, the use of DNA repair inhibitors is considered as perspective adjuvant cancer therapy.

One of the promising target enzymes for the treatment of oncological diseases is tyrosyl-DNA-phosphodiesterase 1 (Tdp1). This enzyme plays an important role in the removal of DNA damage caused by anti-cancer drugs such as topotecan, irinotecan, etoposide, temozolomide and others [1]. It is suggested that Tdp1 contributes to the drug resistance of some cancers, and combination of antitumor drugs and Tdp1 inhibitors can significantly increase the effectiveness of chemotherapy [2].

We discovered a wide range of inhibitors of Tdp1 - derivatives of natural biologically active substances. Many of these compounds did not show toxicity against cell lines, which is an important for creating a safe adjuvant therapy. We found that some of these Tdp1 inhibitors could enhance the cytotoxic effect of Top1 poison topotecan on different types of cell lines and in murine tumor models of lung Lewis carcinoma and ascites carcinoma Krebs-2 mice [3,4].

This work was supported by Russian Foundation for Basic Research (grant 18-29-09037) and Russian Science Foundation (grant 19-13-00040)

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New C (6) -derivatives of the natural phaeosphaeride A

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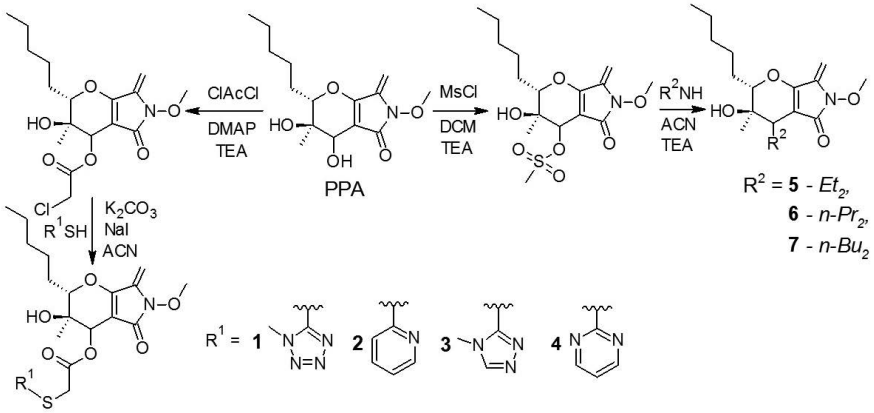
Phaeosphaeride A (PPA), isolated from the solid culture of the fungus *Phoma* sp. N 19 in 2011 at the All-Russian Institute of Plant Protection, found a high antitumor activity in the absence of toxicity in relation to healthy cells. In this connection, the introduction of pharmacophore groups into the PPA molecule seems to be an important direction in the search for new drug substances for the treatment of cancer.

Earlier [1], we obtained a series of PPA derivatives, among which C (6) -mercaptobenzothiazole showed the greatest cytotoxic effect. Based on the fact that azaheterocyclic mercaptans possess biological activity [2], a number of C (6) acyloxymercaptoazaheterocyclic derivatives of PPA **1**–**4** were synthesized in this work. In addition, PPA derivatives have been obtained in which hydroxyl at the C (6) atom is replaced by secondary amines **5**-**7** through the corresponding mesylate.



Synthesized substances will be tested for biological activity.

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Synthesis of 4,7-dihydroazolo [1,5-a] pyrimidines via multicomponent Biginelli reaction

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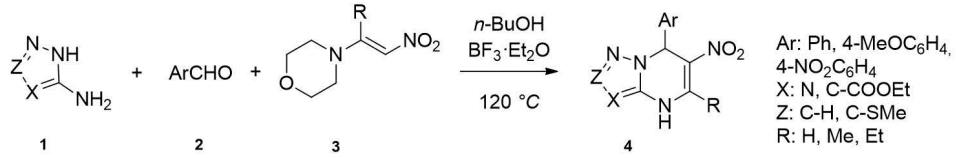
Today one of the most important problems of organic chemistry is synthesis of useful compounds. One of the uses is searching and synthesis of the biologically active molecules used as a base for creation of new modern drugs.

A relatively new class of compounds with a wide range of useful biological activity are azoloazines. It was previously shown that compounds of this range can exhibit antiviral, antidiabetic activity, and also act as antagonists of the azine A_{2A} receptor [1]. In addition, being similar in structure to natural nucleosides, these compounds are inhibitors of purine receptors.

In this work, a new approach was proposed for the preparation of 6-nitro-4,7-dihydropyrazolo [1,5-a]pyrimidines. An element of the novelty of the developed approach is the use of morpholinonitroethylenes as a stable form of nitroacetaldehyde.



1 2 3 4

As a result of multicomponent condensation 6-nitro-4,7-dihydropyrazolo[1,5-a] pyrimidine **4** is formed. The structure of products **4** was found via ^{1}H, ^{13}C NMR spectroscopy, IR spectroscopy, chromatography-mass spectrometry and elemental analysis. The use of a nitro group as a substituent in morpholinoethylenes is due to the possibility of its further recovery to create a purine cycle [2].

Thus, a new method was developed for the synthesis of previously unknown 6-nitro-5-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidines. The resulting compounds **4** have the potential for further functionalization in order to obtain aromatic analogues, azolopurines or other azaheterocycles.

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EXPERIENCE OF APPLICATION OF "CISPLACEL" MEDICINE IN ONCOLOGICAL SURGERY OF THE SPINE

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Relevance. According to several authors, the progression of the tumor process in the spine and paravertebral tissues in the surgical area is observed in 69% of patients within 1 year after the intervention and in 96% of patients within 4 years after the intervention[1]. A promising method of reducing the incidence of local recurrences of the tumor process in the spine and paravertebral tissues after performing a surgical procedure may be local intraoperative chemotherapy. Currently in the Republic of Belarus 2 drugs are developed, tested and successfully used for local chemotherapy operations: ''Cisplacel'' (it is cisplatin immobilized on oxidized cellulose wipes (1.0 +/- 0.15 mg cisplatin per 1 cm2) and "Temodex" (represents temozolomide immobilized on a polymeric carrier - dextran phosphate).

Purpose. To analyze the experience of using "Cisplacel" in the treatment of patients with spinal tumors in the N.N. Alexandrov National Cancer Center of Belarus.

Materials and research methods. The material was data on 109 patients with tumors of the spine. To them in the N.N. Alexandrov National Cancer Center of Belarus in the period 2014-2018 the drug "Cisplacel" was used to perform local intraoperative chemotherapy.

In the analyzed group there were 42 women (mean age 56.8 years) and 67 men (mean age 56.4 years). The distribution of patients depending on the diagnosis: sarcoma - 17, lung cancer - 11, prostate cancer - 10, breast cancer - 9, cancer from unspecified source - 8, colorectal cancer - 8, myeloma - 7, kidney cancer - 4 , chordoma - 4, cancer of the salivary gland - 3, melanoma - 3, liver cancer - 3, cancer of the tongue - 2, cancer of the esophagus - 2, germ cell tumor - 2, and another - 16 patients.

Results. In the postoperative period, the majority of patients showed satisfactory tolerability of local intraoperative chemotherapy. In 10% of patients, a systemic reaction was observed in the form of chills, general weakness, dizziness. This effect completely disappeared within 3 days. Two patients in the postoperative period developed complications that could be associated with the use of "Cisplacel" and required repeated surgical intervention. There were no fatal outcomes during hospitalizations. Evaluation of long-term treatment outcomes is for further study.

Findings. 1. Local chemotherapy in oncological surgery of the spine is a relevant and safe treatment method. 2. The use of " Cisplacel" in oncological surgery of the spine is for further study.

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Preparation of poly(trimethylene carbonate) based hydrogel materials for regenerative medicine products

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The contemporary breakthrough in the development of materials for regenerative medicine is primarily due to the raw and synthetic availability of biodegradable artificial [1] polymers. Indeed, the bio-friendly nature of natural polysaccharides and the ability to create the final material in accordance with the tasks of regenerative medicine make these polymers unique for the development of medicine. Recent studies show that the hydrogel fiber materials can be successfully used to restore nervous tissue after a stroke [2].

In the present research we propose the use of poly(trimethylene carbonate) solutions for new bioabsorbable surgical and regenerative medicine materials creation, such as hydrogels with deposited therapeutic agents and controlled degradation time, hydrogels containing biological agents, hydrogels for the purposes of bone tissue regeneration and rehabilitation of the surgical area, bio-safe non-silicone hydrogels with adjustable swelling degree for the purposes of soft tissue defects treatment. The listed materials as aliphatic polycarbonates derivatives are bio safe, do not cause toxic effects, tissue irritation, are able to resorb in human body without pH change in the surrounding tissue and allow controlling their swelling degree and mechanical strength depending on the method of obtaining.

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Synthesis of hetaryl containing ferrocifen as a potential antitumor drugs

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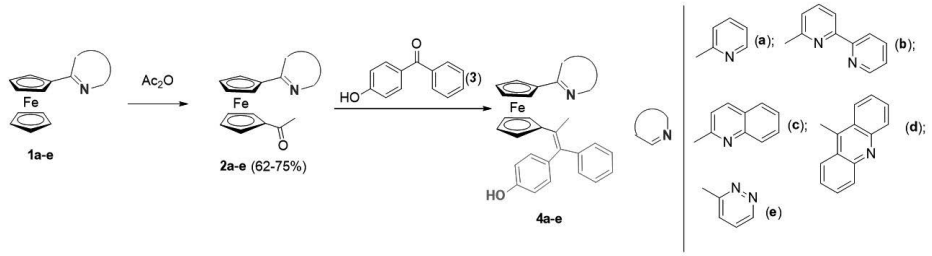
Chemical stability, lipophilicity, high permeability through membranes, low toxicity, well defined and reversible redox behavior are the factors allowing to use of the ferrocene in the development of the new generation of anticancer agents. It has been known, that ferrocifens as tamoxifen analogues have high antitumor activity.

So azinylferrocenes **1a-e** obtained earlier have been entered into the reaction of regioselective acylation followed by coupling of heteroannular disubstituted acetylferrocenes **2** and benzophenone **3** by the McMurry reaction to analogues of the antitumor drug Tamoxifen (**4a-e**) (Scheme 1).



Scheme 1

It has been found the products **4** had been formed as a mixture of *cis*- and *trans*-isomers in a 1 to 2 ratio.

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*Open*HTS – открытая программа поиска новых хемотипов противоопухолевых соединений

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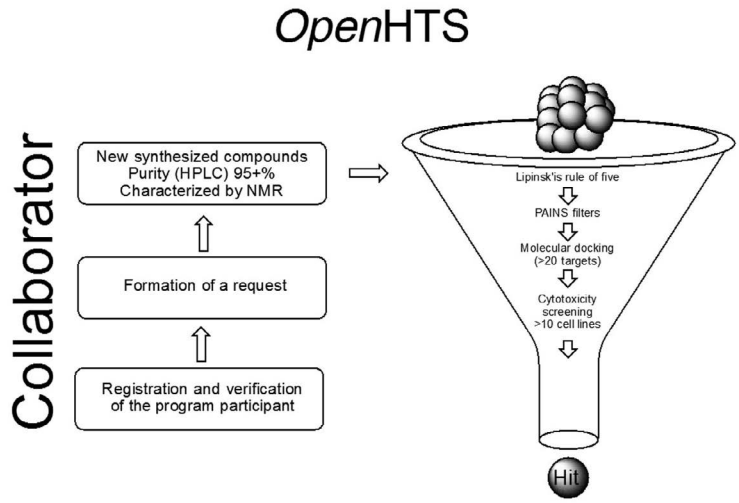
В докладе будут освещены основные этапы реализации программы поиска новых хемотипов противоопухолевых соединений среди низкомолекулярных органических соединений, полученных в академических и образовательных учреждениях России.



Работа выполнена при поддержке Программы развития Тольяттинского государственного университета, проект 2.1.

ОПЫТ ЛЕЧЕНИЯ МЕЛАНОМЫ С ИСПОЛЬЗОВАНИЕМ ЛАЗЕРНОГО ИЗЛУЧЕНИЯ 1264±5 нм В ЭКСПЕРИМЕНТЕ

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Актуальным является поиск новых, эффективных способов лечения меланом как в ветеринарной медицине, так и в медицине человека.

Цель работы. Оценить возможность использования лазерного излучения с длиной волны 1264±5 нм (спектр поглощения кислорода в инфракрасном диапазоне – светокислородный эффект) для лечения меланомы кожи.

Материалы и методы. Под наблюдением находились кошка и собака, со спонтанно возникшими меланомами, биологическое поведение опухолей у мелких домашних животных сходно с биологическим поведением соответствующих опухолей у человека. Больные – кошка и собака, возраст 12 и 9 лет соответственно, опухоли в морфологическом отношении представлены меланомой кожи, макроскопически представляли собой одиночные плотные пигментированные образования, расположенные на коже, локализация образований – область уха и пясти, диаметром 5 и 15 мм, при этом признаков регионарного и отдаленного метастазирования не обнаружено. В качестве источника лазерного излучения использовали экспериментальный диодный лазер - «Супер Сэб» (разработка ООО «Новые Хирургические Технологии», Россия), работающий в постоянном режиме, длина волны излучения 1264±5 нм, мощность варьируется от 0,3 до 3 Вт. В процессе проведения лечения проводили термометрию облучаемой области при помощи электронного термометра с термопарой.

Результаты. Облучение проводилось без седации, доза облучения составила 750-800 Дж\см^2, мощность излучения – 3 Вт, расстояние от источника излучения до опухоли составляло 1,5-2,5 см., при этом замеры температуры с поверхности опухоли ≈ 54°С. После проведения сеанса опухоль бледнела, а затем в течении 8-12 дней подвергалась некрозу и отторгалась, в последствии дефект тканей заживал по вторичному натяжению. Во всех случаях наблюдалась полная регрессия, у собаки через 3 месяца произошел рецидив опухоли, который потребовал проведения повторного сеанса облучения с тем же эффектом, на момент написания статьи период наблюдения составляет 3 месяца с момента рецидива, повторного рецидива не обнаружено.

Заключение. Использование лазерного излучения с данными параметрами, что обусловливает как светокислородный эффект, так и эффект гипертермии возможно применять для лечения меланомы кожи как самостоятельную методику, особенно пациентам с противопоказаниями к другим методам лечения. Необходимы дальнейшие исследования в этой области.

Ключевые слова: светокислородная терапия, светокислородный эффект, меланома, гипертермия.

ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ HRAS ОНКОБЕЛКОВ ПРИ РАКЕ МОЛОЧНОЙ ЖЕЛЕЗЫ

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Введение. Терапия рака молочной железы активно развивается благодаря изучению молекулярно-генетических механизмов опухолевых клеток и появлению препаратов целенаправленного действия. Учитывая гетерогенность злокачественного процесса и наличие устойчивых к терапии опухолей молочной железы, существует необходимость постоянного исследования биомаркеров, способствующих повышению эффективности проводимой терапии. Несмотря на то, что Ras редко мутирует при раке молочной железы, Ras активируется при раке молочной железы различными регуляторами восходящего потока, включая семейство рецепторов эпидермального фактора роста, в частности EGFR / HER1 / ErbB1 и HER2 / ErbB2 / Neu. Проведенные исследования показали, что экспрессию белка c-Ha-Ras можно использовать в качестве маркера для прогнозирования прогрессирования рака молочной железы, а также стратифицировать пациентов в зависимости от экспрессионного статуса и риска развития метастазирования для проведения предоперационных курсов химиотерапии.

Цель исследования. Поиск маркеров для проведения неоадъювантной терапии рака молочной железы.

Материалы и методы. Было проведено ретроспективное исследование архивного морфологического материала 100 пациентов с диагнозом рак молочной железы до и после неоадъювантной терапии и оперативного лечения в объеме радикальной мастэктомии по Маддену. Иммуногистохимическое определение экспрессии Hras онкобелка исследовалось перед курсами предоперационной химиотерапии. Интенсивность и распространенность экспрессии Hras оценивалась с помощью модифицированной шкалы иммунореактивности Remmele и Stegner (IRS). Непосредственные результаты предоперационной химиотерапии оценивалась с помощью модифицированной шкалы RECIST 1.1. Статистическая обработка данных выполнена с использованием пакетов прикладных программ Statistica 10.

Результаты и обсуждения. При иммуногистохимическом исследовании 100 материалов трепанбиопсии обнаружено наличие экспрессии ER-15, PR-15, Her2\neu-22, Ki67-34, Hras-20%. Эффективность предоперационной терапии составила: CR (полный ответ)-0, PR (частичный ответ)-55, SD (стабилизация заболевания)-33, PD (прогрессирование заболевания)-11. Корреляционный анализ выявил сильную прямую связь

экспрессии Hras до и после терапии со следующими иммуногистохимическими показателями: Her2\neu (R=0,78; R=0,76), Ki67 (R=,072; R=0,71), выявлена сильная обратная корреляция с периодом безрецидивной выживаемости (R=-0,76; R=-0,75), а также с данным показателем коррелировали Her2\neu (R=-0,78) и индекс пролиферации Ki67 (R=-0,72).

Выводы. В результате проведенного исследования, были изучены молекулярно-генетические особенности рака молочной железы в зависимости от стадии опухолевого процесса, а также определена корреляционная связь иммуногистохимических особенностей с онкобелками Hras, которые являются терапевтическими мишенями препарата арглабин.

Лазерно - фотодинамическая санация брюшной полости в лечении перитонита

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Введение: Лечение острого гнойного перитонита остается одной из актуальнейших проблем абдоминальной хирургии, что подтверждается высокими цифрами летальности, составляющим от 18 до 65 % и требует поиск новых методов санации брюшной полости.

Цель и задачи. Оценить целесообразность применения лазерно-фотодинамическую санации брюшной полости в лечение перитонита .

Материалы и методы:

Работа основана на анализе результатов обследования и лечения 108 больных в возрасте от 35 до 80 лет, которых, в зависимости от метода санации брюшной полости, разделили на 2 группы - основную (75), контрольную (33). В основной группе (п=75) пациентам внутривенно вводили фотосенсибилизатор «фотодитазин» в дозе 0.8 мг/кг, время максимального накопления фотосенсибилизатора в воспаленной брюшине составляло 2-2.5 ч. после введения, Для проведения ФДТ использовали светодиодный медицинский аппарат ЛАТУС-Т «Маска» с выходной мощностью 0,2 Вт, время экспозиции 100-120 сек на каждую область.

В контрольной группе (п=33), санацию проводили наиболее распространенным в клинической практике способом- 0.02% р-ром хлоргексидина.

Результаты: При сравнении результатов лечения двух групп больных установлено, что использование ФДТ позволило быстрее купировать признаки эндогенной интоксикации. Анализ осложнений, возникших в процессе лечения больных, показал, что в основной группе они развивались реже и спектр их был существенно меньшим, чем в контрольной группе. Наиболее часто в послеоперационном периоде отмечали нагноение послеоперационной раны - 6,2% в основной группе и 8,5% в контрольной.

Летальность у оперированных больных во многом определялась степенью распространения гнойного процесса. Минимальные значения летальности (4,5%) отмечены нами при местном перитоните в основной группе, и в контрольной (7,1%). Такая же динамика отмечена при других формах перитонита: при распространенном - основная группа -10,6%, контрольная - 16,8%, при разлитом - основная группа -22,1%, +контрольная - 38%.

Заключение: Анализ результатов применения разработанного метода нефармакологического потенцирования традиционной санации брюшной полости при различных форм гнойного перитонита лазерной фотодинамической терапией **показывает,** что предлагаемый метод санации брюшной полости обеспечивает лучшие результаты комплексного лечения данной категории больных.

Некоторые аспекты структурного дизайна карбоцианинов с одной и двумя хромофорными группами

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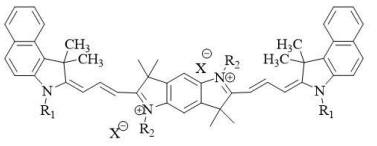
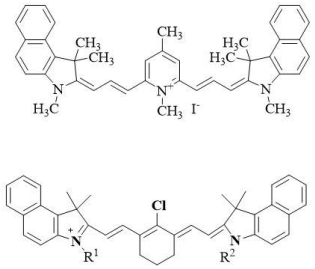
Флуоресцентное маркирование, как неинвазивный метод диагностики, находит все более широкое применение в медицинской практике. Важными для чувствительности, точности и достоверности метода являются флуоресцентные характеристики и оптический диапазон возбуждения применяемых маркеров. Среди существующих флуорофоров особое место занимают цианиновые красители. Они обладают непревзойдённо высоким коэффициентом экстинкции, хорошим квантовым выходом флуоресценции и малой полушириной полосы в спектрах возбуждения и поглощения. [1, 2]

В рамках нашего исследования мы синтезировали серии новых карбоцианиновых красителей с одним и двумя хромофорными фрагментами и разнообразным сочетанием гетероциклов и заместителей при гетероциклических атомах азота с целью выявить влияние особенностей структуры красителей на ряд ключевых фотофизических свойств и на характер их взаимодействия с биомакромолекулами. Исследована темновая цитотоксичность синтезированных соединений, показана возможность их накопления в раковых клетках HCT116, MCF7.



Y=C(CH$_3$)$_2$; S



R^1, R^2=SO$_3^-$, P(O)(OEt)$_2$, Alk, (CH$_2$COOR)

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ОЦЕНКА ЭФФЕКТИВНОСТИ ПРИМЕНЕНИЯ ЭНДОВЕНОЗНОЙ ЛАЗЕРНОЙ КОАГУЛЯЦИИ В ЛЕЧЕНИИ ВАРИКОЗНОЙ БОЛЕЗНИ НИЖНИХ КОНЕЧНОСТЕЙ

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Введение. В настоящее время актуальным для лечения варикозной болезни становятся малоинвазивные термические методы обляции магистральных подкожных вен, одним из них является эндовенозная лазерная коагуляция.

Цель. Оценить эффективности применения эндовенозной лазерной коагуляцией (ЭВЛК) с применением разных волн лазерного излучения и световодов при лечения варикозное расширение подкожных вен нижних конечностей .

Материалы и методы. Проведен анализ 232 оперативных вмешательств на большой подкожной вене (БПВ) с применением метода ЭВЛК с максимальным диаметром в приустьевом отделе БПВ до 11 мм (средний диаметр - 7,6±1,1 мм). Возраст оперируемых пациентов составил от 23 до71 года, из них 186 (80,2%) женщин и 46 (19,8%) мужчин, с классом клинических проявлений С2-С4 по международной классификации хронических заболеваний вен нижних конечностей СЕАР, проходивших лечение на базах ФГБУ «ГНЦ Лазерной медицины им. О.К. Скобелкина ФМБА России» с 2015 по 2018 год. ЭВЛК выполняли с помощью отечественных аппаратов ЛСП-«ИРЭ-Полюс» длиной волны 970 нм (одномикронный лазер), выходящей мощностью 20 Вт с торцевым многоразовых световодом в 135 случаях. В 97 случаях применялся аппарат ЛСП-«ИРЭ-Полюс» с длиной волны 1560 нм (полуторомикронный лазер) с мощностью 8 Вт, 48 из которых было выполнено с применением торцевым многоразовых световодов и 49 с радиальными одноразовыми световодами. Оперативное вмешательство выполнялось под УЗ контролем с применением тумесцентной анестезии с сочетанием с минифлебэктомией притоков. После проведение операции всем больным накладывался компрессионный бандаж. Послеоперационный контроль производился на 2,14,60 и 180 сутки.

Результаты и обсуждение: Случаев тромбоэмболии лёгочных артерий и тромбоза глубоких вен в послеоперационном периоде после проведения оперативного вмешательства нами не отмечалось.

В 3 (2,2%) случая после использования длины волны 970 нм с торцевым световодом и в одном (2,04%) случае при использование лазера длиной волны 1560 нм с радиальным световодом при УЗ-контроле лоцировались локальные тромбозы суральных вен связанные с перевезенной перфорантов при минифлебэктомии. В одном случае при проведении ЭВЛК БПВ лазером с длиной волны 1560 нм и торцевым световодом с удалением межсафенной вены методом минифлебэктомии нами при контрольном обследовании на вторые сутки после операции у пациента были лоцированы окклю-

зирующие тромботические массы в просвете МПВ на протяжении 5 см, источником которого явилась культя перевязанной вены.

Во время проведения ЭВЛК торцевым световодом при длине волны 970 нм пациенты ощущали чувство «жжения» разной интенсивности в области паховой складки в 52 (38,5%) случаях, при применение лазера длиной волны 1560 нм в 2-х (4,2%) случаях. При применение радиального световода при длине волны 1560 нм данных ощущений не отмечалось. Так же в 2 (1,5%) случаях было отмечено не закрытие просвета БПВ на протяжении 6 и 9 см от Сафено - феморального соустья после выполнения ЭВЛК лазерным аппаратом длиной волны 970 нм. Причиной реканализации мог послужить выраженный медиальный приток БПВ. В 7 (5,2%) случаях при ЭВЛК с помощью одно микронного лазера и торцевого световода и по одному случаю (1,03%) при ЭВЛК полуторомикронным лазером с применением двух видов световодов диагностировались парестезии по ходу коагулированной вены. В 2 (1,3%) случаях пальпировался плотный болезненный тяж по ходу коагулированной вены с образованием воспалительного болезненного инфильтрата. В ранний послеоперационный период при применении торцевого световода в 65(48,1%)случаях после ЭВЛК длиной волны 970 нм и 38 (40%) пациентов после ЭВЛК длиной волны 1560 нм отмечались экхимозы по ходу коагулированной вены, Надо заметить, что при применении излучения длиной волны 1560 нм площадь их была меньше. При применении радиального световода количество экхимозов снизилось, и составляло 34 (35,8%) случаев. По прошествии 2 недель у ряда пациентов по ходу коагулированной вены определялась пигментация, 5 (3,7%) случая при использование одно микронного лазера и по 1 (1,05%) случаю при использование полуторомикронного лазера с разными видами световодов.

Заключение. Анализ представленных результатов свидетельствует о эффективности применения для ЭВЛК аппаратов с длинной волны 1560 нм обусловленный меньшим количеством послеоперационных осложнений отсутствием эпизодов реканализации облитерированной вены. Существенной разницы в применение торцевых и радиальных световодов при облитерации БПВ диаметром до 11 мм мы не наблюдали.

РЕТИНОТОКСИЧНОСТЬ ПРОТИВООПУХОЛЕВЫХ ПРЕПАРАТОВ И ОТВЕТ КЛЕТОК МЮЛЛЕРА В СЕТЧАТКЕ ГЛАЗА КАК ОЖИДАЕМЫЙ МЕХАНИЗМ ЕЕ РЕГЕНЕРАЦИИ

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Регенерация сетчатки, наблюдаемая у амфибий, рыб и птиц, рассматривается как один из путей, направленных на терапию заболеваний человека, связанных с дегенерацией сетчатки. Одним из источников регенерации считаются глиальные клетки Мюллера (ГКМ). В ответ на дегенерацию и связанную с ней гибель ретинальных клеток, ГКМ, в норме покоящиеся, подвергаются де-дифференцировке, приобретают качества клеток-предшественников и вступают в клеточный цикл. В процессе деления они дифференцируются в разные типы ретинальных клеток, восстанавливая структуру и функцию сетчатки. Амфибии и рыбы полностью восстанавливают сетчатку, птицы – почти полностью. На способность ГКМ млекопитающих к регенерации существуют две точки зрения: 1 – ГКМ млекопитающих не способны к регенерации в силу их принципиальной неспособности к пролиферации; 2 – поскольку ГКМ способны к неограниченному делению в культуре, существуют какие-то факторы, ограничивающие их пролиферацию in vivo. Известно, что ГКМ в культуре способны даже дифференцироваться в нейроны и фоторецепторы. В то же время высокий уровень оксигенации сетчатки и клеточного метаболизма предполагают высокий уровень фоновой поврежденности ДНК в ней. Цель работы – определить повреждение ДНК в клетках Мюллера в связи с возможной причастностью этих повреждений к ограниченной пролиферации ГКМ in vivo. В качестве индукторов повреждения сетчатки были апробированы 4 алкилирующих агента, широко используемых в химиотерапии злокачественных опухолей различной природы – нимустин (ACNU), дакарбазин (DTIC), темозоломид (TMZ) и метилнитрозомочевина (МНМ). В результате показали, что они обладают ретинотоксическим действием in vitro и in vivo и располагаются по ретинотоксичности в ряд МНМ>TMZ>DTIC>ACNU. Поэтому в исследовании ГКМ использовали только МНМ. В ходе этих исследований решались следующие задачи: (1) разработать метод количественной оценки пролиферации клеток Мюллера в сетчатке у мышей в ответ на действие метилнитрозомочевины (МНМ); (2) охарактеризовать цитотоксическое действие МНМ, как индуктора дегенерации сетчатки у мышей; (3) оценить пролиферативную активацию клеток Мюллера в сетчатке у мышей в ответ на действие МНМ в разной концентрации; (4) определить повреждение ДНК в клетках Мюллера у мышей; (5) проанализировать связь пролиферации ГКМ в сетчатке мышей с индуцированными повреждениями и репарацией ДНК. Методология. Работа проводилась на мышах, которым однократно вводили внутрибрюшинно индуктор дегенерации сетчатки. Для маркирования ГКМ, оценки их пролиферации и повреждений ДНК через 24 ч вводили BrdU (2 дня по 2 инъекции в день). Из глаз извлекали сетчатку, из которой готовили клеточную суспензию и тканевые микросрезы. Использовались методы иммуноги-

сто- и иммуноцитохимии, TUNEL-детекция апоптоза, метод ДНК-комет. ГКМ, содержащие BrdU, детектировали по флуоресценции моноклональных анти-BrdU антитител, ассоциированных с флуорохромом Alexa594. Результаты. МНМ индуцировала в ДНК сетчатки метилирование оснований, которые репарировались с образованием однонитевых разрывов и щелочелабильных сайтов как временных аддуктов, по которым прослеживали формирование и репарацию повреждений ДНК. Спустя 14 ч индуцированные повреждения ДНК удалялись полностью. С этого момента включение BrdU в ДНК происходило только в клетках ГКМ за счет репликативного синтеза в них. Через 24 ч после инъекции МНМ (доза 70 мг/кг) наблюдалась нарастающая во времени дегенерация сетчатки у мышей в виде апоптоза фоторецепторов. Максимальная скорость гибели приходилась на 72 ч. Все остальные клеточные слои сетчатки не претерпевали деструктивных изменений. В ответ на гибель фоторецепторов возрастало число BrdU-позитивных клеток в сетчатке. Достигало максимума 2±1% от общей клеточности сетчатки на 72 ч и не изменялось до 108 ч., что говорит об ограничении дальнейшей пролиферации ГКМ. К этому времени клетки Мюллера завершали цикл репликации и по результатам метода комет содержали в ДНК большое количество разрывов. Эти разрывы не вызваны прямым действием МНМ на сетчатку. В сетчатке, обработанной МНМ, иммуноцитохимически обнаружено 3-кратное увеличение экспрессии p53, маркера и сенсора разрывов ДНК. Одна из функций этого белка состоит в том, чтобы предотвратить вхождение в цикл клеток с большим количеством повреждений ДНК. Таким образом, наличие разрывов в ДНК, экспрессия p53 являются факторами, ограничивающими пролиферацию клеток Мюллера и, возможно, регенерацию сетчатки у мышей после ретинотоксического стресса.

ОПЫТ ЛЕЧЕНИЯ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ С ИСПОЛЬЗОВАНИЕМ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ С ФОТОСЕНСИБИЛИЗАТОРОМ ФОТОСЕНС В ЭКСПЕРИМЕНТЕ

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Актуальной задачей в медицине и ветеринарии является поиск новых эффективных методов лечения опухолей молочной железы, в том числе с применение различных фотосенсибилизаторов.

Цель работы. Оценить возможность использования фотосенсибилизатора Фотосенс для фотодинамической терапии рака молочных желез (РМЖ) у возрастных пациентов. **Материалы и методы**. Пациентами были кошки (n=3), со спонтанно возникшими злокачественными опухолями молочных желез возраст от 16 до 19 лет (больные имели сопутствующую патологию - хроническая болезнь почек, при этом мочевина повышена в 2-4 раза от ВГН, креатинин повышен в 2-3 раза от ВГН), опухоли в морфологическом отношении представлены умеренно дифференцированным и высоко дифференцированным дольковым раком молочной железы, клинически представляли собой одиночные или множественные плотные бугристые образования, выбухающие за пределы молочной железы, диаметром от 2 до 4 см, подвижные относительно окружающих тканей или спаянные с окружающими тканями, при этом рентгенологически и ультрасонографически признаков регионарного и отдаленного метастазирования не обнаружено. В качестве фотосенсибилизатора использовался Фотосенс (Россия, регистрационный номер Р N000199/02 от 04.03.2010), который вводили внутривенно медленно болюсно, за 24 ч до облучения, в дозе 0,3 мг\кг массы тела. Источник лазерного излучения – диодный лазер излучающий на длине волны 660±2 нм (которая также попадает в полосу поглощения Фотосенса), мощностью 1,5 Вт. Доза облучения составляла 300-350 Дж/см^2. **Результаты.** Фотодинамическую терапию (ФДТ) проводили в монорежиме с захватом ткани окружающей опухоль на 0,5-1 см. Болюсное введение фотосенсибилизатора пациенты переносили без осложнений. Введение Фотосенса и последующая ФДТ не повлияли на сопутствующие патологии. После проведения ФДТ опухоли как правило бледнели и уменьшались в размере на 30-60 % в течении 8-14 дней, таким образом наблюдалась частичная регрессия. Для полного регресса РМЖ требовалось проведение 2-4 сеансов ФДТ, в последствии дефект тканей заживал по вторичному натяжению.

Заключение. ФДТ с фотосенсибилизатором Фотосенс возможно применять при раке молочной железы в ветеринарной медицине, с перспективой применения в медицине человека. Необходимы дальнейшие исследования в этой области, в том числе в направлении комбинированных методов лечения.

Ключевые слова: фотодинамическая терапия, рак молочных желез, фотосенс.

CORRESPONDENT PRESENTATIONS

Acyclogermanium: synthesis and study of antivirus activity in herpesvirus infection

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Acyclic nucleoside analogues (ANA), which have a selective effect on HSV DNA polymerase, are the drugs of choice in the treatment of herpes virus infection (HSVI), which is one of the most common and socially significant human infections. However, their use is not always effective be-cause of relatively moderate pharmacokinetic properties.Improving the bioavailability of AAS with the aim of increasing the effectiveness of GI therapy is an urgent task. We have synthesized a new acyclic analogue of acyclovir (ACV) - acyclogermanium, belonging to the class of small molecules and being a complex compound consisting of 2 germanium atoms, a fragment of ACV, connected by 4 citrate ions and an arginine fragment. The structure and chemical purity of acyclogermanium is confirmed by NMR, IR, HPLC, atomic absorption spectrometry and X-ray structural ana-lysis.Compound formula in general:GE2[C6H5O7]4[C8H11N5O3][C6H14N4O2].

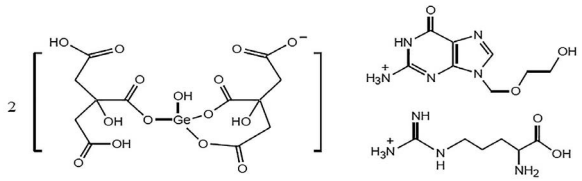

Fig 1. *Structural formula of acyclogermanium*

Bioavailability, cytotoxicity, antiviral activity of acyclogermanium on the HSVI model *in vitro* (in relation to HSV-1, strains: L2, L2/R-resistant to ACV, Kl, ES); HSV-2 (strain VN)) and *in vivo* (on a model of meningoencephalitis in mice, genital herpes in guinea pigs, ophthalmic herpes in rabbits) were studied in accordance with the procedure [2]. Studies have shown that the introduction of the organo-germanium component allowed to reduce the effective dose of ACV, and at the same time to obtain a drug that exceeds the parent compound (ACV) in its biopharmaceutical charac-teristics: higher water solubility (> 25% for acyclogermanium vs 0.13% for ACV) and biorelevant environments;higher bioavailability of the ACV fragment (> 90% in acyclogermanium vs 15-20% in ACV (oral)); expressed therapeutic activity due to the presence of a combined mechanism of act-ion (antiviral and immunotropic), the presence of activity against ACV-resistant HSV-1. The data indicate the prospects for the use of acycogermanium for the treatment of diseases caused by HSV.

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Novel Sn(IV) and Au(I) Complexes with Curcumin as Perspective Antioxidants

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The prevalence of degenerative diseases could be prevented if the body has an efficient antioxidant mechanism to scavenge the free radicals which are their main causes. Curcumin and its derivatives are widely employed as antioxidants. A series of new curcumin complexes Me_3SnL (**1**), Ph_3SnL (**2**), Me_2SnL_2 (**3**) and $Ph_3PAu(L)Cl$ (**4**) (L = curcumin) were synthesized and characterized. The radical scavenging activity of **L** and complexes **1-4** was monitored spectrophotometrically at 517 nm in reaction with stable 2,2-diphenyl-1-picrylhydrazyl radical (DPPH). Antioxidant activity was evaluated (Fig. 1) as the amount of antioxidant which is necessary to decrease the initial concentration of DPPH by 50% (Efficient Concentration = EC_{50}).

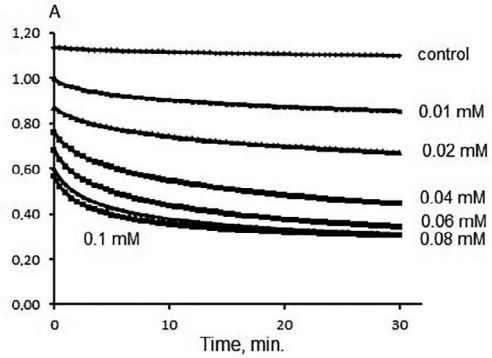

Fig. 1. *Reduction of the optical density of the DPPH solution in the presence of different concentrations of compound* **1** *at 517 nm (EtOH, 20 °C).*

The high activity of all compounds was demonstrated (Table 1). It was found that complex **3** is the most active that makes it promising for further research as an effective antioxidant.

Table 1. *EC_{50} values for* **L** *and complexes* **1-4** *in DPPH-test.*

Compound	**L**	**1**	**2**	**3**	**4**
EC_{50}, μM	31 ± 3	38 ± 4	41 ± 3	11 ± 4	38 ± 4

This work was supported by RFBR (Grants № 17-03- 01070, 18-03-00203).

Nanoparticles based on N-vinyl-2-pyrrolidone conjugated with cytokine TRAIL DR5-B/V114C induce cell death in colorectal carcinoma

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Previously we obtained an amphiphilic polymer based on N-vinyl-2-pyrrolidone, modified by maleimide at the hydrophilic end of the polymer chain for further covalent conjugation with antitumor cytokine TRAIL DR5-B/V114C by the cysteine-maleimide bond. This method provides conjugation strictly by the N-end of the protein, ensuring the correct orientation of protein molecules on the surface of the nanoparticle.

The polymer in concentration 1 mM was incubated overnight with TRAIL DR5-B/V114C protein with a 1:120 protein-to-polymer molar ratio in 150 mm NaCl solution, pH 7.5 at room temperature. The obtained nanoparticles were precipitated by centrifugation. The protein content was determined by Bradford assay. Polymer nanoparticles completely entrapped the protein from the solution, while the protein retained its solubility. The size of nanoparticles was investigated by dynamic light scattering. The average particle size was 1 μm.

The obtained conjugates induced up to 40% cell death in colorectal carcinoma cell lines HT-29 and HCT116 *in vitro*. Thus, cytokine TRAIL DR5-B/V114C conjugated with polymer nanoparticles based on N-vinyl-2-pyrrolidone retained cytotoxicity similar to that of soluble cytokine TRAIL DR5-B/V114C.

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Analysis of informativeness of immunohistochemical and flow cytometric methods for estrogen receptor α evaluation

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Informativeness of two methods – immunohistochemistry (IHC) and flow cytometry (FCM) – for the evaluation of estrogen receptor α (ERα) expression in breast cancer tissue was performed. We aimed to determine the frequency of false-positive and false-negative results of a routine IHC assay in clinical practice and to develop an algorithm to reduce the amount of tumor molecular phenotype errors. The study was performed on surgical breast cancer specimens of 60 patients operated in N.N. Blokhin National Medical Research Center of Oncology. The method of analysis was described in detail previously [1].

Two levels of the marker expression were determined by FCM – low and high (ERα were detected in ≤40 and >40% of the tumor cells, respectively). The same frequency of expression was revealed by both methods: 27% of ERα-negative and 73% ERα-positive cases. However, in the case of routine IHC determination, low level of the marker was detected in only 20% of the ERα-positive tumors. The evaluation of expression by FCM showed that the number of tumors with the low-level of ERα expression was more than twice higher – in 48% of cases. Conversely, the IHC results showed that frequency of high-level of ERα expression in tumors was more than 1.5 times greater than in the FCM assay (80 and 52%, respectively). Moreover, FCM revealed positive expression (23–60%) in 33% of IHC ERα-negative cases. Among IHC ER-positive cases, no ERα expression was detected by FCM in 12.5%.

The approaches to minimize errors in routine clinical evaluation of the estrogen receptor status were proposed. Any result of IHC assay should be verified by an additional IHC analysis in other tumor sections. We truly believe that in the case of ERα IHC-based negative status, the test must be verified three times, because, according to our data, the frequency of false-negative ERα results exceeds 30%. Only in the case of three negative results (optimally obtained using different clones of monoclonal antibodies), the conclusion that the tumor is ERα-negative should be recognized as final.

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Antiglycation, antiglycoxidation and copper chelation activitivities of Losartan, Eprosartan, Lipoic acid and Aminoguanidine

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Advanced glycation end-products (AGEs) are formed in non-oxidized glycation reaction (pirraline) and in oxidation-dependent conditions – glycoxidation (pentazidine, carboxymethyllysine). Both of them lead to the development of long-term diabetes mellitus complications (DMC). Anti-DMC agents Losartan (nephropathy), Eprosartan (nephropathy), Lipoic acid (neuropathy) and Aminoguanidine (experimental anti-DMC) (Sigma Aldrich) were tested *in vitro* for the presence of antiglycation, antiglycoxidatoin and copper chelation properties. Glycation reaction (described in [1]) conditions: in phosphate buffer solution (PBS, 0.05 M, 7.4 pH), 1 g/L bovine serum albumin (BSA)+0.5 M glucose+10-1000 µM compound (in DMSO) ➔ 60°C, 24 hours ➔ AGE's fluorescence detection (370 nm excitation, 440 nm emission, Infinite 200 Pro, TECAN); glycoxidation reaction conditions: in HEPES-buffer (0.01 M, 5.8 pH), 1 g/L BSA+0.5 M glucose+10 mg/L $CuSO_4$*5H2O+10-1000 µM compound (in double distilled water) ➔ 60°C, 24 hours ➔ AGE's fluorescence detection (370 nm excitation, 440 nm emission, Infinite 220 Pro, TECAN); chelation reaction (Cu^{2+} induced ascorbate autoxidation [3,4]) conditions: 1 step – compound (in DMSO)+$CuSO_4$*$5H_2O$ (in distilled water) ➔ 5 minutes, 37°C; 2 step – the "step 1" product add to the 2.5 ml of ascorbate solution (finally, 100 µM ascorbate+75 µM compound+95 µM Cu^{2+}) ➔ optical density (OD) detection (PD 303 UW, APEL) until the stop of OD loss becomes, half-time ($T_{1/2}$) of the OD loss calculation. Higher $T_{1/2}$ corresponds with stronger Cu^{2+}-inactivation. The result, IC_{50} glycation / IC_{50} glycoxidation / $T_{1/2}$ ascorbate autoxidation (respectively): 3.6 mM / 0.1 mM / 91.2 seconds (Losartan), 3.4 mM / 2.2 mM / 151.2 seconds (Eprosartan), 2.3 mM / 1.6 mM / 44.6 seconds (Lipoic acid) and 0.77 mM / > 10.0 mM / 32.4 seconds (Aminoguanidine) respectively. In conclusion, sartans and Lipoic acid, but not Aminoguanidine, stronger prevented AGEs production in oxidize-dependent conditions (with Cu^{2+}), suppressed prooxidative action of Cu^{2+}. Aminoguanidine was inactive in Cu^{2+}-contained medias.

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SYNTHEIS OF NOVEL PSMA LIGANDS WITH INCREASED WATER SOLUBILITY

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Prostate cancer (PC) is the most prevalent malignancy spread widely among men. There are 1,3 millions new cases of malignant prostate tumors [1]. A wide range of approaches to treatment exists, but none of them does not effectively treat metastatic tumors and can lead to various side effects. Targeted 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 over-expressed in PC cell and their metastases more than 10000 times [2]. There are several small molecules, that selectively binds PSMA [3-4].

In the present work PSMA selective ligands were synthesized and charachterized. Compouds were consists of vector, that provided selective binding to PSMA, and a linker. Linker had aromatic amino-acids for better binding with target. Lysine's amino-group was modified with substituted benzyl aldehydes, mostly polar nature (-NO_2, -OH).

All synthetized compounds was characterized by ^{1}H and ^{13}C NMR spectroscopy, high resolution mass spectrometry. Purity of ligands was controlled with HPLC/MS. 12 ligands with different aromatic substituents were synthesized and characterized. To find out relationship between position of polar group in aromatic ring, a series of nitro-group compounds were synthesized. In our previous work [5] ligands with urea linkage between vector and linker showed better selectivity. This time we synthesized para-nitro compound with dipeptide linker. All ligands proceeding in vitro testing.

As a result of present work twelve ligands 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.

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Immunoadhesion markers of tumour-infiltrating CD8+ lymphocytes significant for a preventive effect as well as for increasing the lifespan and quality of life in mice with spontaneous hepatocarcinogenesis

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The aim of this investigation was to evaluate the association between the expression of CD8, CD11a and CD11b antigens on tumour infiltrating lymphocytes (TILs) with the level of tumour formation, survival and quality of life in CBA mice under multiphytoadaptogene complex dry powder (DMPAC) preventive administration.

Materials and methods. Control male mice CBA/LacY (n = 90) received water, experienced mice (n = 170) – 0,3% DMPAC water-solution during the first month of life (preventive administration). DMPAC is a standardized pharmaceutical complex of forty plants, including adaptogenes. The TILs were examined immunohistochemically using the avidin-biotin peroxidase complex method. The number of positively stained CD8+ CD11a+ CD11b+ lymphocytes was counted in 10 fields of view. The average number of cells was determined.

Results. TILs were observed in low quantities (2.3 ± 0.2 cells/field of view) in the tumours of the control mice. The number of TILs was 118.6 ± 11.0 cells/field of view in the tumours of the experimental animals. It was detected that hepatocarcinomas of experimental mice were infiltrated with CD8+ cytotoxic lymphocytes expressing LFA-1 (CD11a) and Mac-1 (CD11b) leukocyte integrins. Hepatocarcinomas infiltration was significantly associated with tumour destruction, increased expression of these antigens on peripheral blood cells as well as with a decrease of interleukins 6 and 10 levels in the serum. At the same time in the DMPAC-exposed mice the tumours occurred with lower frequency (by 31%), the total hepatomas mass per one animal were lower (by 66%) than in the control animals. Moreover mice with CD8+ CD11a+ CD11b+ TILs had a better average lifespan and survival median (by 18 and 19% respectively) as well as somatic condition including motor activity.

Conclusion. When preventive exposed to DMPAC, CD8+ CD11a+ CD11b+ TILs can be significant for tumour process reducing and increasing the animals survival and quality of life.

Survival and quality of life in CBA mice with spontaneous hepatocarcinomas under multiphytoadaptogene complex dry powder preventive administration

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The aim of this investigation was to estimate survival and quality of life in CBA mice genetically predisposal to hepatomas that are predisposed to spontaneous hepatomas under multiphytoadaptogene complex dry powder (DMPAC) preventive administration.

Materials and methods. Control male mice CBA/LacY (n = 90) received water, experienced mice (n = 170) – 0,3% DMPAC water-solution during the first month of life (preventive administration). DMPAC is a standardized pharmaceutical complex of forty plants, including adaptogenes. The average lifespan and median survival (by Kaplan-Meyer method), body weight of mice (at the age of 4, 8 and 22 months) and coat state (at the age of 22 months) of animals were determined. **Results.** The average lifespan of DMPAC-administered mice was increased by 3.5 months ($p < 0.001$) compared to control mice (22 months). One experienced male lived 1001 days (33 months). It had one tumour the size of 520 mm^3. At the same time the median survival of experienced mice (25.3 months) was increased compared to control by 5 months ($p = 0.015$). The body weight values of the mice in both groups did not differ at the age of 4 and 8 months. At the age of 22 months, the control mice showed cachexia syndrome with a decrease in body weight from 32,0 ± 0,6 g to 28,0±0,4 g ($p=0,0003$). At the same time the body weight value (34.0 ± 0.3 g) and motor (behavioral) activity of DMPAC-administered mice corresponded to the state of eight months age. The coat state of experienced mice was normal in contrast to the control mice, which showed signs of alopecia in 20% of cases. The increased survival and quality of life in DMPAC-administered mice was significantly associated with magnification of LFA-1 and Mac-1 leukocyte integrins expression on peripheral blood cells, tumours infiltration with cytotoxic CD8+ CD11a+ CD11b+ lymphocytes, with a decrease of interleukins 6 and 10 as well as catabolic stress-hormone corticosterone levels in the serum, with an increase of anabolic hormone testosterone. These results were accompanied by a lower tumour formation frequency and hepatocarcinomas size.

Conclusion. So, data obtained demonstrate that the regulation of the immunoadhesive and stressor mechanisms during the DMPAC prophylactic administration adjust the antitumor reactions probably as well as the survival and quality of life in high-cancer animals.

SYNTHESIS OF HYBRID ORGANIC-INORGANIC MOLECULARLY IMPRINTED POLYMERS FOR SELECTIVE SORPTION OF GLUCOSE

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The molecular recognition of carbohydrates, especially of glucose, becomes remarkable due to their importance as biomarkers in different biological systems. In addition, selective uptake of glucose is actual for developing new approaches to the treatment of hyperglycemia and correction of blood glucose levels. Molecularly imprinted polymers (MIPs) for these purposes seem a viable alternative to expensive affine sorbents.

Novel granular organic-inorganic molecularly imprinted polymers (MIPs) based on 2-hydroxyethyl methacrylate (HEMA) and ethylene glycol dimethacrylate (EGDMA) were prepared by co-polymerization on the surface of selenium (Se) stabilized with poly(vinyl pyrrolidone) (PVP) nanoparticles (Se/PVP). Reactions of reduction of red amorphous Se (α-form) in the acidic environment of ascorbic acid and in alkaline medium β-mercaptoethanol were previously studied; the reactions were carried out in an aqueous solution of PVP (M_w = 55 000.) directly. HEMA-EGDMA@Se/PVP hybrid beads were synthesized under varying physico-chemical synthesis conditions (acidic or alkaline environment). The acidic environment was found to be better for the preparation of hybrid polymer beads in a narrow range of particle size. The surface HEMA-EGDMA layer was molecularly imprinted with glucose templates (6 mol%). The modification of HEMA-EGDMA@Se/PVP matrix with orthoboric acid (6 mol%) that forms reversible covalent bonds with 1,2-cis or cis-1,3 diols was studied, too. Therefore, we tried to create additional specific sorption centers in sorbents, as well as to prevent distribution of the associated glucose dimer and trimer molecules in the HEMA-EGDMA layer during molecular imprinting process. Thus, we tried to ensure the formation of highly specific imprint site around a single template molecule.

The following samples of sorbents were prepared: the non-modified non-imprinted polymer (NIP) as the reference sorbent, the modified with boric affine groups non-imprinted polymer (Aff-NIP), the polymer molecularly imprinted with glucose (MIP), and the imprinted polymer that was additionally modified with boric affine groups (Aff-MIP). The presence of boric affine groups in the matrix resulted in the formation of sorption sites with high specific affinity to glucose. In addition, thermodynamics of sorption showed different nature of specific affinity of imprint sites to glucose in the MIP and the Aff-MIP networks.

The work was financially supported by the Russian Foundation for Basic Research (projects no. 18-03-00835-a).

Early contrast MRI identification and magnetic thermo-chemo-therapy of the breast gland CA755 by combinations of nanoparticles with Furox

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Purpose of the study. Evaluation of early contrast MRI imaging of the centers of proliferation of malignant cells (CPMC) using Dextranmagnetite-Co^{2+} (DM-Co^{2+}) -Magnevist® (MV), (DM-Co^{2+}-MV) combinations and 40% DM-Co^{2+} anti-cancer activity during magnetic thermotherapy (MTT) of 40% sol DM-Co^{2+} Furox (DM-Co^{2+} -FO) with magnetic thermo-chemo-therapy (MTCT).

Materials and methods. From activated magnetite doped with Co^{2+}, DM-Co^{2+} was synthesized, consisting of nanospheres with diameters from 25 to 39 nm with a magnetite core with diameters from 5 to 11 nm, coated with dextran. 3 days after breast gland Ca755 cells inoculation, 6 ml of DM-Co^{2+} aqueous sol and 0.2 ml/kg MV were injected intravenously to 6 C57Bl/6j female mice. Mice were placed in the field "BioSpec BC 70/30 USR biospectrograph" ("Bruker") and MRI scans of tissues were performed in T1 weighted (W) and T2 W image acquisition modes. At MTCT 6 female mice with Ca755 were injected into CPMC tissue with a diameter of 21 ± 7 mm^3 with 80 mg/kg of super paramagnetic nanoparticles of citric magnetite with 50 mg/kg of Furox in 0.2 ml of water, the tissues of CPMC of mice were in the RF field 0.88 MHz, 150 W. The temperature of the CPMC increased from + 37 to +45 ° C.

Results. We developed combinations: 1) Dextranmagnetite-Co^{2+}-Magnevist (DM-Co^{2+}-MV) caused a reduction in the time of visualization of CPMC by 2-3 days; 2) Dextranmagnetite-Co^{2+} -Furox caused in mice a decrease in the volume of CPMC to 1.0 ± 0.3 mm^3; 3) 40% sol DM-Co^{2+} with MTT increased the lifespan of mice by 92%; 4) a combination of 40% sol DM-Co^{2+}-Furox with MTCT, resulted in an increased the lifespan of mice by 180%. The lifetime of mice of all groups vas compared, mean ± standard deviation ($\rho \leq 0.05$).

Findings. At the early stages of the development of tumors, CPMC was visualized and, during treatment, they received a significant increase in the efficiency of magnetic TCT.

Various aspects of this study were partially supported by grants from the Russian Foundation for Basic Research: 19-01-00056, 17-01-00037.

Studying the pharmacokinetics of CSL 1208

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CSL 1208 is a representative of the indolocarbazol class synthesized in the chemical synthesis laboratory of Research Institute for Experimental Diagnostics and Tumor Treatment. It is related to protein kinase C inhibitors and is currently going through clinical trials. A study of pharmacokinetics, according to [1], is an obligatory stage of pre-clinical studies of new medication. The lyophilized dosage form (DF) containing dimethyl sulfoxide (DMSO) has been developed due to the insolubility of the substance in water. To study pharmacokinetics a tritium labeled CSL 1208 (^{3}H-CSL 1208) was synthesized by means of tritium thermal activation method [2]. Radiochemical purity of ^{3}H-CSL was not less than 90%. The study was conducted on DBF male mice, weighing 23 g, with intramuscularly transplanted Lewis epidermoid carcinoma (LLC). The substance was introduced intravenously in the form of DF at a dose of 25mg / kg. The radioactivity of biological samples was counted with the help of the 1219 RackBeta LKB Wallac spectrometer.

Pharmacokinetic studies with ^{3}H-CSL 1208 used 15 tissues and organs of mice, including the LLC tumor, showed tropism for the liver, kidneys, bone marrow when administered intravenously in the dosage form. Selective accumulation in the tumor has not been detected. The cumulative excretion with urine and feces is 28.6% and 56.7% respectively, and generally ends at 24 hours of observation.

Thus, pharmacokinetic studies have shown ^{3}H-CSL 1208 intake in all the studied tissues and organs, including LLC tumor. Liver and kidneys are considered to be the organs of egestion, where the area under curve AUC 0-72h was respectively 10 and 3.6 times higher than in blood, and MRT average retention time was 18.3 and 14.2 hours respectively at 19-25 h for other organs. MRT for bone marrow was 39.3 hours. For tumor MRT was 28,7 hours.

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Synthesis and antioxidant activity of 4-methyl-2-prenylphenol derivatives

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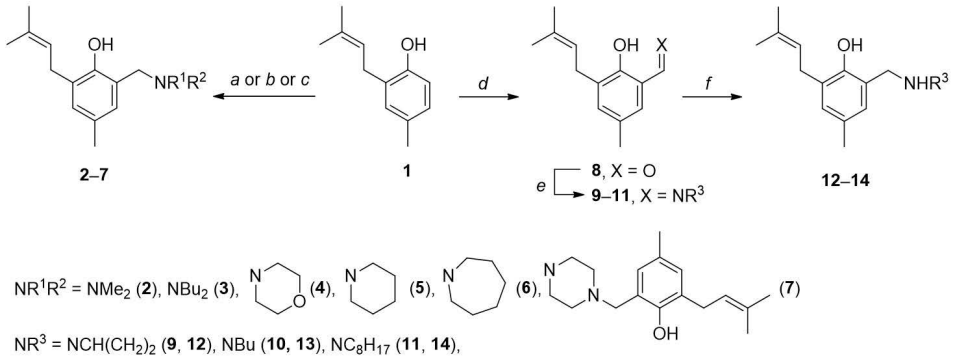
Novel Mannich bases containing tertiary and secondary amino groups were synthesized from 4-methyl-2-prenylphenol (**1**) (Scheme). For the synthesized derivatives **2–7**, **12–14**, radical-scavenging activity and antioxidant (AO) activity were assessed on an organic substrate containing animal lipids, as well as Fe^{2+}-chelation ability, AO-, and membrane-protective properties using red blood cells of laboratory mice. It was shown that with respect to a set of indicators characterizing the studied compounds as inhibitors of oxidative processes, the most optimal bioantioxidant was Mannich base with *n*-octylaminomethyl fragment (compound **14**) [1].



Scheme. *Reagents and conditions:* ***a****) HCHO (aq.),* Me_2NH *(aq.), MeOH, r.t., 24 h;* ***b****) HCHO, dibutylamine, morpholine, piperidine or azepane, PhH, reflux, 6–12 h;* ***c****) HCHO, piperazine,* $CaCl_2$*, 110°C, 35 min;* ***d****) HCHO,* $SnCl_4$*,* Bu_3N*, PhMe, reflux, 10 h;* ***e****) cyclopropylamine, butylamine or octylamine, molecular sieves 4 Å, PhH, reflux, 3.5 h;* ***f****)* $NaBH_4$*, EtOH, reflux, 30 min.*

The reported study was funded by RFBR, according to the research project No. 18-03-00950 a.

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Development of new hybrid nanomaterials based on lipids and sterical hindered phenols for targeted drug delivery

Burilova E.[1], Pashirova T.[1], Tagasheva R.[2], Gibadullina E.[1], Zueva I.[1], Nizameev I.[1,2], Sudakov I.[1], Vyshtakalyuk A.[1], Kadirov M.[1,2], Petrov K.[1], Burilov A.[1], Bukharov S.[2], Zakharova L.[1]

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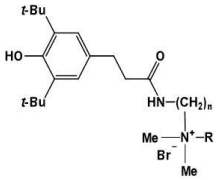
Currently, owing to the use of nanomaterials, targeted drug delivery systems are being actively developed. The latter include antioxidants of natural and synthetic origin. Among synthetic antioxidants, a special place belongs to the class of sterically hindered phenols (SHP). The prospect of using synthetic phenolic antioxidants in the treatment of Alzheimer's disease, Parkinson, etc., is limited by their low bioavailability, rapid degradation *in vivo* and the impossibility of passing through biological barriers. In order to solve these problems, in the present work new hybrid polyfunctional nanomaterials based on lipids and functionalized derivatives of SHP were developed. At the first stage, the process of self-association of SHP derivatives is investigated by a complex of physicochemical methods.



SHP-n-Bn, SHP-n-R, где n = 2, 3;R = CH_2Ph - (SHP -n-Bn); R = C_8H_{17} - (SHP -n-C-8); R = $C_{10}H_{21}$ - (SHP -n-C-10); R = $C_{12}H_{25}$ - (SHP -n-C-12); R = $C_{16}H_{33}$ - (SHP -n-C-16)

Quantitative characteristics of the resulting aggregates were determined, such as critical concentrations of association, solubilization capacity, aggregation numbers, hydrodynamic radius. L-α-phosphatidylcholine-based liposomes were obtained and modified by PZF; their physicochemical characteristics, size and zeta potential, were investigated. The studied systems were shown to be cholinesterase inhibitors with antioxidant properties.

This work was supported by the Russian Science Foundation, the project 19-73-30012.

Synthesis of new biologically active (+)-camphoric acid heterocyclic derivatives

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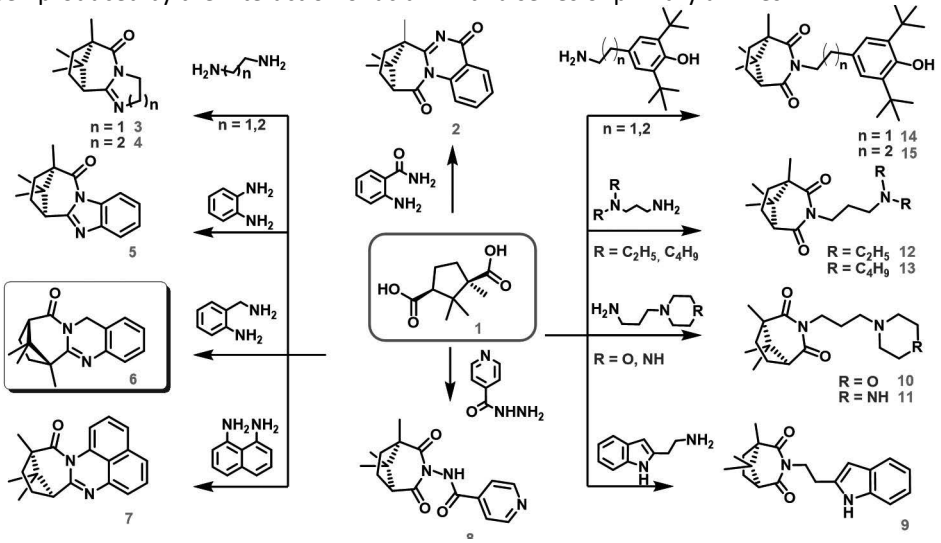
Use as a source of structural blocks in the synthesis of new libraries of biologically active substances of terpenic compounds is one of the most popular trends in modern medical chemistry. A series of polycyclic nitrogen-containing compounds (**2**-**7**), which can be attributed to analogues of alkaloids, has been synthesized by a one-stage interaction of (+)-camphoric acid 1 with diamines of various structures. A set of cyclic amides (**8**-**15**) has been produced by the interaction of acid **1** with a series of primary amines.



All the compounds described are tested as inhibitors of the influenza virus A and Hantaan virus. Compound **8**, which has structural similarity with quinazoline alkaloids, turned out to be the most active agent for A/Puerto Rico/8/34 (H1N1), A/Aichi/2/68 (H3N2), A/mallard/ Pennsylvania (H5N2) strains.

This work was supported by Foundation by the Russian Foundation Research № 18-03-00271 A.

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Synthesis of the complex of Ag(I) with cefuroxime

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A cefuroxime is the II generation of cephalosporin antibiotics. In vitro it has a significant antibacterial effect against gram positive and gram negative microorganisms.

Silver compounds have a bactericidal, antifungal and antiseptic effect. They are highly effective disinfectants against pathogens that cause acute infections.The combined presence of a silver ion and an antibiotic in the compound can lead to a synergistic effect against different bacteria.

The compound was synthesized in the molar ratio of metal ($AgNO_3$) to ligand (antibiotic) 1:1 in water medium, pH=3**.** A beige precipitate was formed in 1 hour. The compound was analyzed by elemental (C, H, N, S) and thermal analysis, X-ray diffraction and FT-IR spectroscopy (ЦКПИНиГСФУ). The compound had the chemical composition of $[Ag_2Cefur_2]•H_2O$. The complex was obtained in a crystalline form. Cell parameters were determined for the $[Ag_2Cefur_2]•H_2O$ is: a=9,408 Å, b=12,816 Å, c=7,614 Å, α=90,000°, β=104,149°, γ=90,000°, space group symbol: P 1 2/m 1 (centrosymmetric), space group number: 4 . The thermal behavior of the complex was determined in the temperature range of 273 – 773K under inert atmosphere. The thermal analysis of the compound $[Ag_2Cefur_2]•H_2O$ showed one molecule of crystallization water. Thermal decomposition of complex $[Ag_2Cefur_2]•H_2O$ evolved by emission of COS, CH_3OH, NH_3, HNCO.

To establish the type of coordination of cefuroxime to metal ions, the FT-IR spectra of sodium cefuroxime and $[Ag_2Cefur_2]•H_2O$ were analyzed. The FT-IR analysis of structures showed that the formation of the bond of one cefuroxime ion with one Ag (I) ion involved the oxygen atoms of lactam, carboxyl, and amide groups. A bridge between the silver atoms was assumed.

Hydration of the lipid film under normal and low-pressure in the technology of liposomal preparations

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The first stage in the technological process of obtaining liposomal preparation is the formation of a lipid film and its hydration to form a dispersion of multilamellar vesicles. Under normal conditions, at the stage of hydration of the film, the formation of foam is observed, which partially complicates the process of extrusion of liposomal dispersion. To suppress foaming, the possibility of film hydration under reduced pressure (under vacuum) is considered.

The aim of the study was to compare the quality of dispersion of "empty" liposomes and liposomes loaded with a drug obtained by hydration of the lipid film under normal and low-pressure. Liposomes were obtained from egg lecithin and cholesterol with the addition of pegylated phospholipid.

As a result of the analysis of the quality of liposomal dispersions obtained without and using the vacuum (150−200 mbar) during hydration of the film with water for injection, it was found that the reduced pressure can generally have a positive effect on the formation of liposomes. Formed in a low pressure environment of a dispersion of homogeneous appearance, no foam, the size of "empty" liposomes were 209±10 nm, liposomes with burglaries − 194±10 nm, with LHS-1269 − 523±23 nm. Without vacuum − 211±14, 212±13 and 379±20 nm, respectively. In addition, with the use of vacuum, an increase in the values of ζ-potential was noted: from -17.4 to -19.4 mV for liposomes with borchlorine and from -23.0 to 24.9 mV − with LHS-1269. The ζ-the potential of "empty" liposomes practically did not change and was at the level of -32.0 mV.

Thus it is shown that the hydration of the lipid film under reduced pressure contributes to the production of dispersions with higher quality indicators compared to the same stage carried out under normal conditions.

New derivatives of hydroxycinnamic acid

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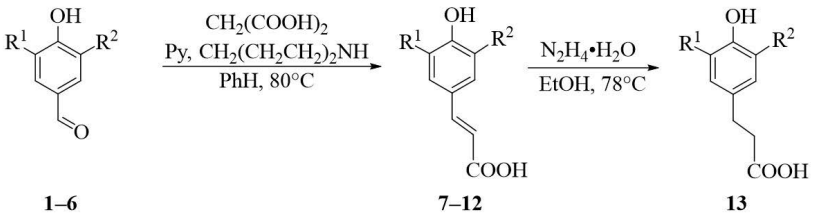
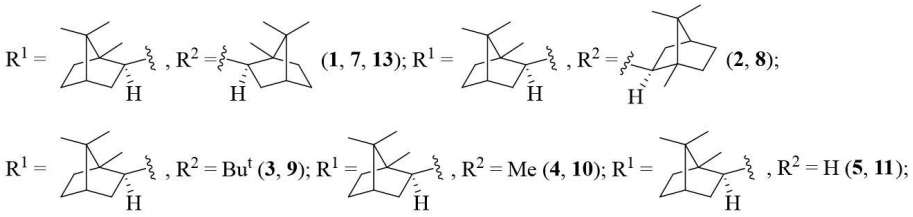
Derivatives of cinnamic acid are of great interest due to the wide range of biological activity, which is shown by representatives of this class of compounds. Terphenophenols with bornyl and isobornyl fragments with different pharmacological properties can serve as the structural basis for the synthesis of cinnamon acid derivatives. We have synthesized new *para*-hydroxy-cinnamic acid derivatives (**7**-**11** and **13**) with terpenic isobornyl substituents in the aromatic ring and evaluated their antiradical, antioxidant and membrane-protective activities on various *in vitro* models.



1–6 **7–12** **13**



$R^1 = R^2 = Bu^t$ (**6**, **12**)

Compounds **1**, **7** *and* **13** – ***meso****-stereoisomers,* **2–5**, **8–11** *– racemates (the diagram shows the structures of one of the enantiomers)*

It is shown that all compounds have low toxicity, membrane-protective properties and high antiradical activity. Judging by the totality of indicators, the largest antioxidant and membrane-protective activity have acid 7 and 8 that contains two isobornyl fragments.

The study was funded by RFBR according to the research project No 18-03-00950.

Biological Activity of 2-(2-Amino-6-methylpyrimidin-4-yl)-4-arylmethylidene- 5-methyl-2,4-dihydro-3-*H*-pyrazol-3-ones: Virtual Screening vs *in vitro* Evaluation

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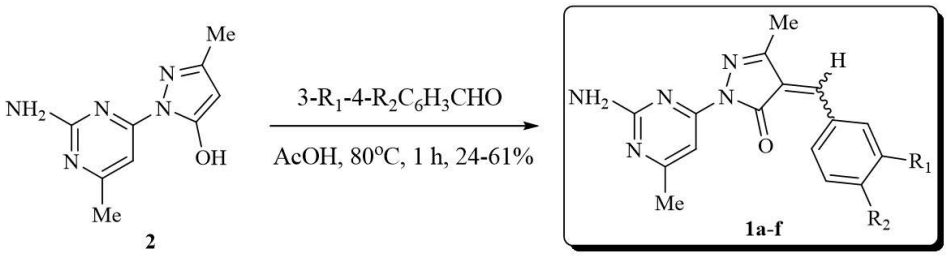
For a series of the title compounds described by general formula **1a-f**, antitubercular activity was predicted via Way2Drug predictive services. As for the calculated ratio of the values of P_a (probability to be active) and P_i (probability to be inactive), it was in the range of 2.7÷19.8.

Arylidenepyrazolones **1a-f** were obtained by Knoevenagel condensation from the corresponding 2-(pyrimidin-4-yl)-2*H*-pyrazol-3-ol **2**. Noteworthy that, of the aldehydes used, only those bearing an auxochromic substituent at *para*-position gave the target compounds upon reaction with hydroxypyrazole **2**. A number of spectroscopic parameters of arylidenepyrazolones **1a-f**, in particular ^{1}H, ^{13}C NMR and IR spectra, were in full agreement with their structures.



R_1 = H, R_2 = Me_2N (**a**); R_1 = H, R_2 = Et_2N (**b**); R_1 = H, R_2 = MeO (**c**);

R_1 = MeO, R_2 = HO (**d**); R_1 = EtO, R_2 = HO (**e**); R_1 = MeO, R_2 = MeO (**f**)

As the *in vitro* biological assay evidenced, the target compounds possessed various types of activity. Besides *Mycobacterium tuberculosis* $H37R_V$ (*MT*), they also readily inhibited growth of bacteria (*Staphylococcus aureus* ATCC 29213, *SA*) and fungi (*Candida albicans* 15, *CA*). The values of MIC_{100} (mmol·L^{-1}) for each of arylidenepyrazolones **1a-f** were the following: 0.074 (**1a**, *CA*); 0.069 (**1b**, *MT*), 0.069 (**1b**, *SA*); 0.155 (**1c**, *CA*); 0.074 (**1d**, *MT*), 0.074 (**1d**, *CA*); 0.142 (**1e**, *SA*), 0.074 (**1e**, *CA*); 0.142 (**1f**, *MT*).

Thus, *in vitro* biological activity of the title compounds turned out to be more diverse as compared to that *in silico* predicted. As a result, some of them were selected for advanced study.

The development of the HPLC-MS/MS method for the simultaneous quantitation of several antitumor peptide-based therapeutics.

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Objective: The development of the HPLC-MS/MS method for simultaneous quantitation of goserelin, buserelin, and octreotide in blood plasma.

Materials & methods: The research was carried out using blood plasma samples containing goserelin acetate, buserelin acetate, octreotide acetate and dalargin acetate (internal standard). The HPLC-MS/MS analysis was performed with the Nexera LC system (Shimadzu, Japan) coupled with triple quadrupole mass spectrometer LCMS-8040 (Shimadzu, Japan). Chromatographic separation was achieved using Jupiter® C18 column (5 µm, 4.6 x 50 mm, 300Å). The mobile phase consisted of 0,1% aqueous solution of formic acid (v/v) as solvent A and 0.1% formic acid (v/v) in acetonitrile as solvent B. Flow rate was 1,2 mL/min and gradient elution was used for better separation. The MS/MS detection was performed using positive electrospray ionization (5000V) in multiple reaction monitoring (MRM) mode. The samples were prepared using a simple method of protein precipitation with methanol in a 2:1 (v/v) ratio with plasma.

Results and discussion: The developed method was successfully validated according to the Guideline on the examination of drugs, as well as FDA (U.S. Food and Drug Administration) and EMA (European Medicines Agency) guidelines. This method showed a linear quantification range of 1 - 20 ng/mL (for buserelin and octreotide) and 2 - 20 ng/mL (for goserelin). The correlation coefficients (r) were above 0,99: 0,99774, 0,99821 and 0,99632 for goserelin, buserelin, and octreotide, respectively. The obtained values of relative standard deviation (RSD, %) and relative error (E, %) were within the acceptable limits according to the guidelines requirements (≤ 20% at the LLOQ level, and ≤ 15% at all other levels).

Conclusions: The developed HPLC-MS/MS method for simultaneous quantitation of goserelin, buserelin and octreotide in blood plasma is applicable to the pharmacokinetic studies. For instance, this method can be used during preclinical studies, where the lower analyte concentration is about 1-5 ng/mL.

Modification of anthracyclines by sesquiterpene lactones as a way of cardiotoxicity reducing

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One of the most important areas of anticancer chemotherapy is the use of various antitumor antibiotics. Anthracyclines can be identified in a special group of such substances. Anthracyclines have high antimitotic activity and are widely used in medical practice. The main disadvantage of such drugs is irreversible cumulative dose-dependent cardiotoxicity, which is caused by free radical damage of the myocardium cell membranes. To reduce toxicity to body healthy cells anthracycline antitumor antibiotics were modified by natural pharmacophores – sesquiterpene lactones. Conjugates with epoxy-isoalantolactone were selected from a modified doxo - and daunorubicin analogues series as the most effective compounds.

It has been shown that anthracycline lactone conjugates exhibit higher cytotoxic activity in relation to different tumor cell lines and reduced toxicity with respect to pseudonormal HEK293 cells compared to the parent antibiotics. The isolated mitochondria functioning, as the main link of the cell death cascade launch and the effect of compounds on glycolysis, as on the main pathway of metabolism in tumor cells, were studied to determine the cytotoxic action mechanism. The substance-leader is the daunorubicin conjugate with epoxy-isoalantolactone, which has depolarizing effect on the mitochondrial membrane and stimulates the process of Ca^{2+}-induced opening of mitochondrial pores, what can lead to the launch of the caspase-dependent pathway of apoptosis. Moreover, this substance effectively inhibits the process of glycolysis in A549 lung carcinoma cell line.

By comparison cardiotoxicity of daunorubicin and its conjugate with epoxy-isoalantolactone in analysis of morphological condition changes in the rats left ventricle, which once were injected the test substance, it was shown that the conjugate in comparison with the anthracycline causes less pronounced damaging effect on cardiomyocytes and on the vascular component of the myocardium stroma. Thus, the daunorubicin conjugate with epoxy-isoalantolactone has a higher cytotoxic effect on tumor cells and has a lower cardiotoxic effect in comparison with parent antibiotic.

Spectrophotometric study of interaction of aminonitroxyl platinum(IV) complexes with DNA

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The antitumor effect of platinum-based drugs is associated with the formation of adducts with DNA that prevent cell proliferation. In this regard, it is important to investigate the interaction of platinum-based complexes with DNA and the kinetics of this process. The goal of the work is a spectrophotometric study of the interaction of platinum complexes with DNA.

Cisplatin, JM216 and aminonitroxyl platinum(IV) complexes (ANPC) with the general structure of $Pt(IV)(NH_3)(R{\bullet}NH_2)Cl_2X_2$, where $R{\bullet}NH_2$ is the nitroxyl radical and X are axial ligands, were used in the work. The process of interaction of platinum complexes with DNA was studied using plasmid DNA pGL3-Basic Vector (Promega, USA).

It was found that solutions of ANPC have characteristic absorption peak at 230 nm, which probably corresponds to the nitroxyl radical. After incubation of complexes with DNA several characteristic changes in the absorption spectra are observed: a slight bathochromic shift of the main absorption peak of the ANPC (230 nm) and the hypochromic effect that develops over time in the 230-280 nm range. The JM216 complex is characterized by a hypochromic effect in the region of 220-270 nm. Changes in the spectral properties of cisplatin and DNA develop faster compared to investigated platinum(IV) complexes. For solution of cisplatin with DNA were also observed hyperchromic effect in the region of 230 nm and a bathochromic effect in the region of 260 nm.

The results show that the incubation of platinum complexes with DNA leads to a change in the absorption spectra, which reflects the formation of platinum-DNA complexes. For cisplatin, there is a faster dynamics of these changes, which reflects its higher reactivity.

Expanded in vivo studying of antineoplastic properties of amino-acid derivatives of the indolocarbazol

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Introduction. Introduction to the molecule of the active metabolites (amino acids) affects the physico-chemical and Pro-properties of derivatives of indolocarbazoles. On computers using the predicted probability antitumor activity of these compounds, with low probability of their cytotoxic activity in vitro [1]. Based on these data, conducted a study of 5 compounds in vivo [2].

Objective. Assessment of amino-acid derivates of glycosides of indolocarbazole as potential antitumor medications.

Materials and methods. Research antitumor activity of amino-acid derivates of glycosides of indolocarbazol was done using tumorous models of murine - cervical cancer CC- 5, epidermoid carcinoma Lewis (LLC), breast adenocarcinoma Ca755, melanoma B16. Sister compounds were injected to mice abdominally five-time, daily with interval of 24 hours. Supervision on animals were continued till their death. Antitumor effect of medications was assessed by criteria of tumor growth inhibition, increase in life expectancy of mice comparing to control animals.

Results. As a result of comparative assessment of antineoplastic activity of five APGIKs the L-threonine derivative was chosen for further study.

Conclusion. The expanded research *in vivo* of antineoplastic properties of the selected L-threonine APGIK- derivative is supposed.

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Study in vivo of LCS 1269 — derivative of indolocarbazols N-glycosides class

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Introduction. We studied in vivo the compound LCS 1269, derivative of a indolocarbazols N-glycosides class with cytotoxic and antitumor (a/t) properties [1].

The purpose of the study. Schemes of application and way of LCS 1269 introduction in an organism.

Materials and methods. The research was carried out in the experimental dosage form on models of mice solid tumors: cervical cancer CC5. epidermoid carcinoma Lewis Lung (LLC), adenocarcinoma, mammary gland Ca 755, colorectal adenocarcinoma AKATOL, B16 melanoma. Compound was injected intraperitoneally (in/p), subcutaneously (s/c), intravenously (in/v) and inside (per os) to mice in the modes: modes: five times, daily with 24 h interval (5x24h), the 1-st and 5-th days (2 x 96 h), one-time use (one). Animals were watched until their death. Score of a/t effect: inhibition of tumor growth (TGI%), increase in life expectancy (LEI%) of experienced mice relative to the control.

The results. LLC – at in/v injection the best a/t effect with TGI 94-51% up to 20 days after the end of treatment was in a dose of 60 mg/kg, mode 5x24h. At s/c injection TGI was=78-58 % up to 20 days, LEI -34 % in a dose of 60 mg/kg, mode 5x24h, in mode 2x96h, a dose of 100 mg/kg, (TGI%=80-68 up to 20 days). At introduction of per os TGI=69-61f % till 8 days in a dose of 150 mg/kg, mode 5x24h. Ca 755 – at s/c injection TGI=91-64 % till 20 days, LEI=41% in a dose of 60 mg/kg, mode 5x24h. Cervical cancer CC5 - at in/p injection TGI= 89-58% up to 25 days, in a dose of 60 mg/kg, mode 5x24h. AKATOL - at in /p injection TGI = 89-62% till 25days, in a dose of 60 mg/kg, mode 5x24h. B 16- at in/p injection TGI = 86-68% up to 26 days, LEI = 21%, in 5x24h mode, a dose of 60 mg/kg.

Conclusions. LCS 1269 showed a high a/t activity at different ways and modes of injection on mice cultivated solid tumors; in/v and s/c ways of injection were selected, which can be used for further preclinical treatment.

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Voltammetric analysis for the evaluation of platelets viability

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The search for additional independent methods for assessing cell viability is a relevant task due to the development of applied biotechnologies. The instrumental assessment of platelets quality is in demand in blood service [1]. In our previous work we found the correlation between the presence of granules in platelets and shift of the redox potential in blood plasma after cryodestruction of platelets [2]. Functionally complete platelets contain a large amount of low molecular weight antioxidants concentration of which can be estimated *via* cyclic voltammetry method (CV) [3].

Voltammetric analysis in platelet concentrate (PC) before and after the cryodestruction was carried out on platinum electrode in the potential range from -0.6 V to +1.1 V (sat. Ag/AgCl). The morphofunctional state of platelets was analyzed by the method reported in [1].

It was found that the height of electrooxidation peaks on polarization curves change depending on the content of granule-rich platelets in PC, indicating an increase in plasma content of substances capable of oxidizing (Fig. 1).

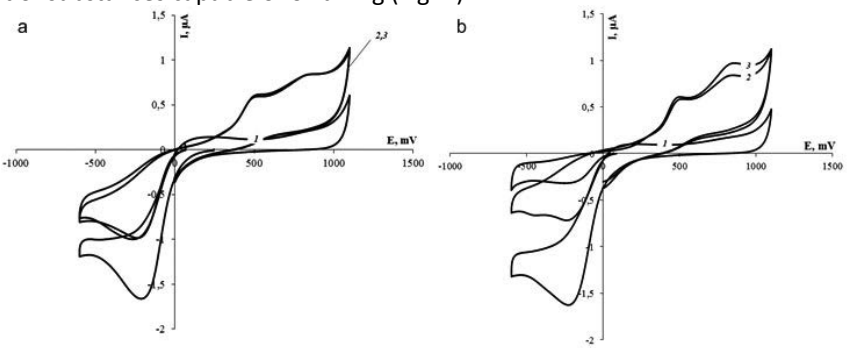

Fig.1. C*Vs in PC with content of granule-rich platelets 3% (a) and 36% (b): 1- background solution (0.15M NaCl), 2 – PC before freezing, 3 – PC after freezing.*

Voltammetric analysis provides additional information on the morphofunctional state of platelets and, in combination with other analyzes, can serve to assess the quality of blood cells.

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Cytotoxic activity of Sn (IV) complexes with fragments of polycyclic acids

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The interest in organotin compounds in the last decade is associated with their high biological activity. It is known that organotin derivatives of bile exhibit cytotoxic activity [1-2]. A series of Sn (IV) carboxylates with fragments of bile acids of the general formula $R_3SnOOCL$ (where R = Me, Ph; LCOOH is cholic (L^1), deoxycholic (L^2), lithocholic acid (L^3) were synthesized. The cytotoxic activity of the compounds was studied in MTT-test and IC_{50} values in MCF-7, A549, SW480 cancer cell lines and WI38 (fibroblasts from lung tissue) were determined. It was shown that high cytotoxicity is characteristic of all studied Sn complexes, however, the triphenyltin derivatives at the MCF7 and SW480 cell lines were the most active one in the MTT-test (IC_{50} = 0.18-0.25 μM). The analysis of apoptosis with annexin V protein and cell cycle were performed using flow cytometry (Fig. 1).

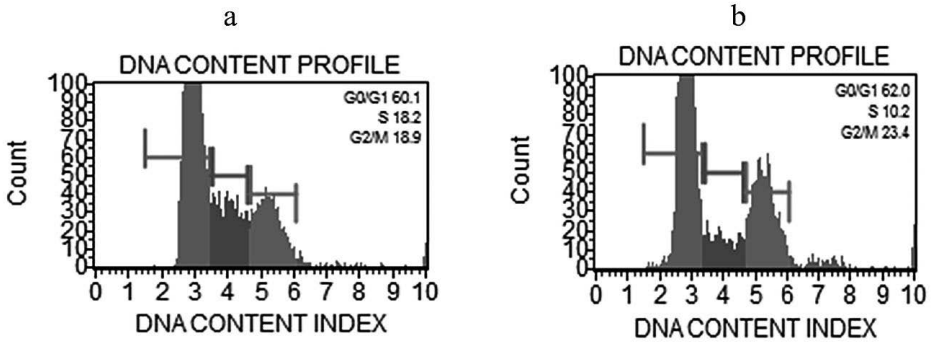

Fig. 1. *Cell cycle analysis in MCF7 breast cancer after treatment with Ph_3SnL^2 by flow cytometry. Cell were treated with 0.5 μM of compound for 24 h. (a - control, b - Ph_3SnL^2).*

It was demonstrated that blockade of the cell cycle occurs in the presence of $Ph_3SnOOCL$ in the G2/M phase (DNA replication / mitosis).

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Isolation and determination of the cytotoxic activity of macrocyclic tannins and their derivatives

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Chamenerin-I (*Oenothein B*), isolated from plant raw materials of fireweed of narrow-leaved *Chamaenerion angustifolium (L.)* is a dimeric macrocyclic tannin, among similar oligomers, trimeric and tetramer tannins, it is most active [1]. Chamenerin-I and related oligomeric ellagitannins exhibit various physiological activities *in vitro* or *in vivo*. We identified and described the properties of dimeric and trimeric ellagitannins isolated from shoots and inflorescences of *Chamaenerion angustifolium*. In *in vitro* studies, macrocyclic trimeric ellagitannins "2" (compound of a new type containing an oxide cycle) and II (*Oenothein A*), as well as a monosodium derivative of dimeric macrocyclic tannin - Chamenerin-I showed cytotoxic activity against kidney cancer SN-12, A498, breast cancer SK-BR-3, A549 adenocarcinoma, and hepatocellular carcinoma (Hep-2G).At the same time, the studied ellagitannins exhibit a greater cytotoxic effect on tumor cell lines than on normal human fibroblasts. The cytotoxicity mechanism of ellagitannins was studied using A549 cell lines and is associated with induction of apoptosis. ellagitannins caused a decrease in the migration activity of A549 tumor cells when examined by the method of wound healing and reduction of the formation of spheroids after 48 hours of cultivation with ellagitannins.

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Novel [1,4]-benzodiazepine derivatives as potential anticancer agents

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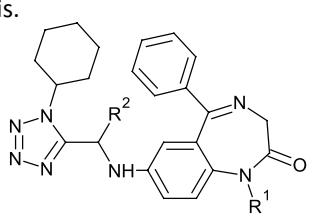
Recently the interest in [1,4]-benzodiazepine derivatives as components of potential anticancer drugs has increased significantly. This is due largely to the ability to form the antibody- drug conjugates for the targeted drug delivery [1].

A number of derivatives of [1,4]-benzodiazepines with a positive computer forecast was synthesised by the four-component Ugi reaction. All compounds contain reactive functional groups which are suitable for further chemical modification in order to obtain the original biologically active compounds. Structures of all obtained compounds have been confirmed by the spectral analysis.



R^1, R^2 = H, Alk or Ar

A quantitative forecast of the profiles of antitarget interaction of chemical compounds was carried out using the GUSAR software (http://www.way2drug.com/gusar/antitargets.html). In this work materials collected by PhD Apryshko G.N. were also used. In the preclinical study of the compounds, the MTT-test on 9 lines of tumor cells and transplanted tumors of mice from the bank of tumor strains of N. N. Blokhin Russian Cancer Research Center of Ministry of Health of Russia (P-388 lymphocytic leukemia and epidermoid lung carcinoma Lewis LLC) were used. The obtained results demonstrate the activity of the synthesized [1,4]-benzodiazepines with the prospect for further research.

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Comparative analysis of the energy spectra of the interaction of RAGE inhibitors with target proteins of the RAGE–NF-KB signaling pathway

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The impairments caused by advanced glycation end products (AGEs) are largely related to the interaction of AGEs and its receptors (RAGE) that mediate many signaling transduction pathways and pro-inflammatory responses, oxidative stress, and uncontrolled cell growth. AGE/RAGE interaction stimulates the activation of a diverse array of signaling cascades, including a number of protein kinases.

The purpose of this work was a comparative multidimensional statistical analysis of the energy spectra of the interaction with key bio-targets of RAGE–NF-kB signaling pathways AGE-receptors inhibitors with the different levels of activity. The nine most significant target proteins were selected by analyzing the neural network model of the RAGE–NF-kB signaling pathway. 3D models of six proteins ERK2 (PDB ID: 5BVD), APK14 (PDB ID:3ZS5), JNK1 (PDB ID: 3VUG), JNK3 (PDB ID: 2O0U), PRKCA (PDB ID: 3IW4), PRKCQ (PDB ID: 2JED), and NF-kB (PDB ID: 1SVC) were obtained from the database of experimental models PDBe; the 3D-models of the two proteins PRKCG (ModBase ID: f3056d7c42cd5e33cdb6b4d19b 34bd11) and PRKCD (ModBase ID: dc73c609e930eb6bf24d49d7f3dba2f) were taken from the database of theoretical models ModBase. All 3D-models were subjected to molecular dynamics (MD) in the GROMACS 5.0.7 program to equilibrium. The structures of RAGE inhibitors with the graded activity levels were taken from the patented database, and their conformations were optimized using by the MarvinSketch 17.1.23 and MOPAC2016 programs. Docking of RAGE inhibitors with different levels of activity in eight kinases and in NF-kB was performed in the AutoDock Vina 1.1.2 program. MD of ligand-protein complexes were made using GROMACS 5.0.7 program. The energy spectra were calculated using the MMPBSA 1.6 program. A comparative multidimensional statistical analysis of the energy characteristics of the trajectories of MD of RAGE inhibitors with different levels of activity was performed in the Statistica 8.0 program. For RAGE inhibitors with different levels of activity, a statistically high significant difference in the energy spectra of their binding with nine key bio-targets of the RAGE–NF-kB signaling pathway was shown.

The work was funded by the Russian Foundation For Basic Research, 18-015-00499 project.

Spectrophotometry for quantitative determination of LHS-1269 in the dosage form for injections

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LHS-1269 is an indolocarbazole derivative and a protein kinase C inhibitor, which has a marked antitumor function. A new dosage form of LHS-1269 for injections has been designed at N.N. Blokhin NMRCO. The aim of the study was to develop a methodology for quantitative evaluation of the active substance in the dosage form.

LHS-1269 is practically insoluble in water, but soluble in dimethylformamide (DMFA) and dimethyl sulfoxide (DMSO). Special studies have determined that LHS-1269 solutions in DMFA present specific electronic absorption spectra within the band range of 200 to 500 nm; the maximum intensive absorption value at the wavelength of 319±2 nm was chosen as the analytical one. The results demonstrated the linear absorption curve of LHS-1269 solutions in DMFA at the selected wavelength in the concentration range from 0.003 mg/ml to 0.010 mg/ml. LHS-1269 concentration of 0.005 mg/ml was chosen as the working concentration. The LHS-1269 dosage form is a solution for injections and includes a number of excipients. The findings demonstrated that the excipients had no effect on the spectral characteristics of the studied substance and the absorption of the excipient solution at the working concentration was insignificant. The methodology assumes using the standard sample of specially purified and characterized LHS-1269. This methodology has good reproducibility, sufficient accuracy and a high performance rate. The determination relative error does not exceed 2.0 %.

The developed methodology may be used for quantitative determination of LHS-1269 in the dosage form and for monitoring of the technological process of the drug manufacturing.

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Synthesis of biologically active isobenzofurans starting from 3-carene

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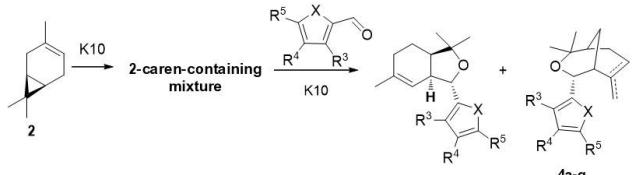
It is known that chiral hexahydroisobenzofurans formed by the interaction of (+)-2-carene **1** with aldehydes in the presence of montmorillonite K-10 [1] can exhibit high neuroprotective activity in Parkinson's disease model *in vivo* [2]. At the same time, (+)-2-carene is too expensive for practical use. It has been found recently that 2-carene is one of the major products of clay catalyzed isomerization of 3-carene **2** which is among main components of turpentine [3]. In this work, we developed the methods for hexahydroisobenzofurans starting synthesis from a mixture of monoterpenoids with a high content of (+)-2-carene **1** obtained by isomerization of available (+)-3-carene **2**.

When studying the reactions of a 2-caren-containing mixture with thiophene- and furan-2-carboxaldehydes and their derivatives in the presence of montmorillonite K-10, chiral isobenzofurans **3** were obtained with the yields 73% - 86%. In addition, products with oxabicyclo-[3.3.1]nonane framework **4** were formed in these reactions.



X=S, R^3=R^4=R^5=H ***(S)*-3a (78%), 4a**
X=S, R^4=R^5=H R^3=Me ***(S)*-3b (86%), 4b**
X=S, R^3=R^4=H R^5=Me ***(S)*-3c (85%), 4c**
X=S, R^3=R^4=H R^5=Br ***(S)*-3d (73%), 4d**

X=S, R^3=R^5=H R^4=Br **13e**
X=S, R^3=R^4=H R^5=NO_2 **13f**
X=O, R^3=R^4=H R^5=NO_2 **13g**

Among the synthesized compounds effective inhibitors of the TDP1 enzyme (IC_{50} <1 mkM) were found, which may be promising for use in complex therapy of cancer diseases.

The research was financially supported by BRFFR (grant Ch19RM-002) and RFBR (grant 19-53-04005 Bel_mol_a).

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Synthesis of novel derivatives of thiazolidine-2,4-dione and 1-thia-4,8-diazaspiro[4.5]decane-3-one

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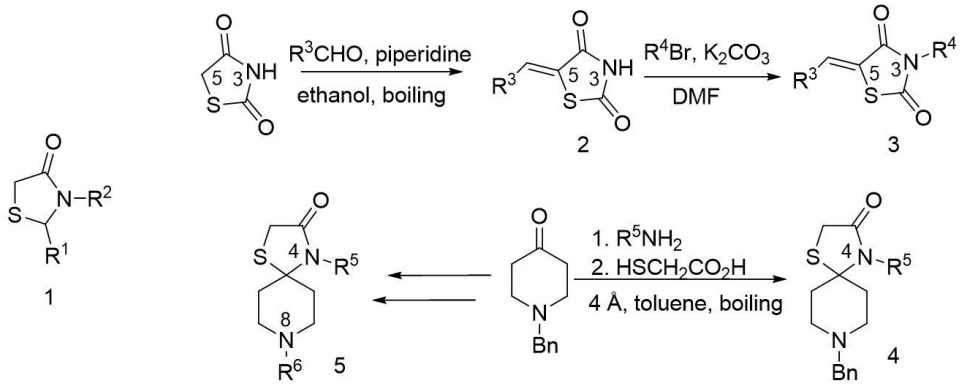
Nowadays, heterocyclic compounds based on 1,3-thiazolidine are considered as agents of great interest in medicinal chemistry due to their many-sided pharmacological activity [1]. Earlier, a series of thiazolidine-4-one derivatives (compounds **1**), which have shown to possess significant anti-ulcerative activity on indomethacin-induced model, has been synthesized in the laboratory of physiological active compounds of NIOCh SB RAS [2].

In order to expand a number of novel heterocyclic compounds with anti-ulcerative activity, we have synthesized several novel thiazolidine-2,4-dione derivatives containing various substituents in 3 and 5 positions (compounds **2** and **3**), as well as 1–thia-4,8-diazaspiro[4.5]decane-3-one with different substituents in 4 and 8 positions (compounds **4** and **5**).



Screening of anti-ulcerogenic activity *in vivo* on indomethacin-induced gastric ulcer in rats has demonstrated that some novel compounds at a dose of 100 mg/kg possess anti-ulcerative activity similar to the activity of drug omeprazole at the same dose.

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Comparison of two clones of 8F1 and FL297 ERCC1-specific monoclonal antibodies

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Excision repair enzyme ERCC1 is responsible for the DNA reparation in cells damaged by platinum agents, which are commonly used for treatment of different cancers. The data concerning the expression of ERCC1 protein in tumors and its prognostic significance remain controversial. This may be due to a variety of existing monoclonal antibodies to ERCC1 and their different specificity. It was shown that the most commonly used antibody clone 8F1 detects, in addition to ERCC1, another antigen – choline-phosphate cytidylyltransferase alpha. Thus, there is no strict specificity of this clone 8F1 to ERCC1. The clone FL297 can be considered as the most specific in relation to ERCC1 [1]. In this study, we compared the ERCC1 expression parameters obtained by using 8F1 and FL297 in the same tumor samples.

Quantitative evaluation of immunofluorescence parameters was performed by flow cytometry on ovarian cancer biopsy specimens (n=53). Tissue specimens were dispersed to a single-cell suspension, fixed and stained by indirect immunofluorescence.

Positive expression was found in all the studied tumor samples. ERCC1 expression differed significantly between patients (from 24 to 87% of positive cells per patient). Differences between ERCC1 expression measured by different assays (8F1 vs. FL297) was not statistically significant ($p = 0,06$; Shapiro–Wilk test).

Agreement between two different assays was estimated by correlation analyses and Bland-Altman plots. The data obtained using these antibodies are in good agreement with each other regardless of the concentration of the antibodies within the range studied, as well as the magnitude of the parameter measured. Thus, the insufficient specificity of the 8F1 monoclonal antibodies against ERCC1 cannot be the reason for the inconsistency of the data on the prognostic significance of the marker.

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Specifities of the cytotoxic action of Au complexes on colon cancer cells

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The biological impact of gold complexes $AuPPh_3Cl$ (1), PPh_3AuSR (2) with a protective antioxidant group (R=3,5-di-*tert*-butyl-4-hydroxyphenyl) and RSH on reactive oxygen species (ROS) intensity in human colon carcinoma (HCT-116) was investigated. Intracellular ROS were detected with DCFH-DA. Mitochondrial superoxide radical-anion ($O_2^{-\cdot}$) was detected with MitoSOX red. Quantitative fluorescence microscopy was performed in a wide-field fluorescence microscope Axioplan 2 imaging MOT equipped with digital camera and a mercury lamp. Obtained images were processed with AxioVision software .

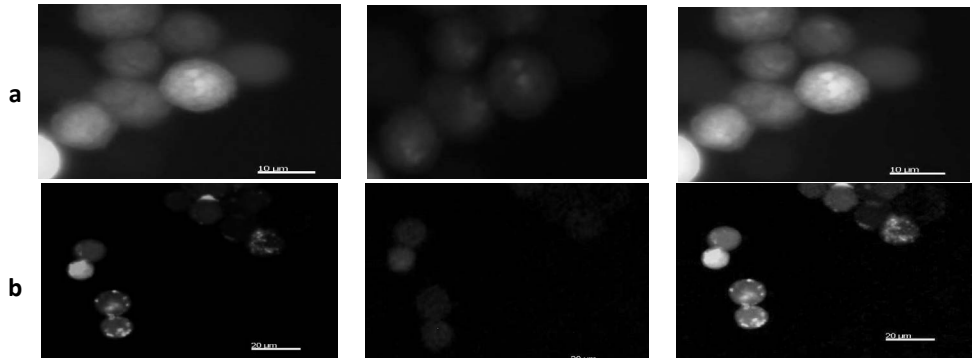

Fig. 1. *Morphological changes in MCF-7 cells treated with a) (1) for 1h and b) (2) for 1h. Then, cells were stained with DCFH-DA/MitoSOX monitored with a fluorescence microscope: (1) green chanell, (2) red chanell, (3) green+red channels.*

The $AuPPh_3Cl$ (1) complex is cytotoxic and initiates a diffuse increase in the level of ROS in the cells. MitoSOX revealed accumulation of $O_2^{-\cdot}$ in mitochondria. It was shown that “green” and “red” mitochondria are colocalized. The PPh_3AuSR (2) complex with antioxidant R group is weakly cytotoxic. However, ROS significantly accumulate in intracellular structures, and not diffusely in the cytosol. The accumulation of $O_2^{-\cdot}$ in the mitochondria is practically not observed.

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Cytotoxic effect of synthetic purpurin derivatives on chronic human myelogenous leukemia cells (K562)

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The search for new effective anticancer drugs that do not have side effects is considered highly relevant [1]. Purpurin (1,2,4-trihydroxyanthraquinone) is well known compound with antibacterial, antioxidant, antifungal and antitumor activity [2, 3]. Recently, purpurin was shown to suppress the proliferation of T49D breast cancer cells [4] and melanoma cells (A2058) [5]. The aim of the study was to evaluate the cytotoxic effect of synthetic fluorine-containing derivatives of purpurin on human chronic myelogenous leukemia cells (K562), which was analyzed in MTT test.

Purpurine or its fluorine-containing synthetic derivatives (P5, P6, P7, P8), dissolved in DMSO, in concentrations of 25, 50, 100 and 150 μM were added to cultures of K562 cells and cells were incubated for 48 hours [3]. During the study, we found that synthetic analogues of purpurin P5 and P8 exhibit cytotoxicity against K562 cells at concentrations of 50, 100 and 150 μM, while P6 and P7 significantly reduced the proportion of viable K562 cells only at concentrations of 100 and 150 μM, compared with the control cultures. At the same time, P5 and P8 at a concentration of 150 μM reduced the proportion of viable K562 cells to a greater extent as compared with similar cultures incubated in the presence of purpurin, while adding equimolar amounts of preparations P6 and P7 did not differ from the effect of the parent compound.

Thus, the synthesized derivatives of purpurin P5 and P8, used at a concentration of 150 μM, have the higher cytotoxic activity against K562 cells, comparing to purpurin, which indicates the prospects for further study of these compounds for targeted anti-cancer therapy.

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Catalitic system (teraphtal+ascorbic acid) is an inducer of heme oxygenase /ferritin system in leukemic cells

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It is known that the mechanism of cytotoxic action of antitumor agent – catalytic system (teraftal+ ascorbic acid) (TF+AC), associated with the generation of ROS in the cell and the induction of oxidative stress (OS) [1]. To protect against OS, hemoxygenase-1 / ferritin (HO-1 / Ft) system is present in the cells.

Purpose: Investigate the significance of the HO-1/Ft system in the protection of leukemic cells from (TF+AC) toxicity

Materials and methods. Human leukemic cell lines U937 is used in this study. The basal and drug-induced expression of HO-1/Ft at the level of mRNA and protein was studied by methods real-time PCR and Western blot; the concentration of ROS in the cells was evaluated using flow cytometry; cytotoxicity of drugs – the MTT method.

Results. According to our data the monocytes-like cell line U937 have constitutively active HO-1, and it is established that the (TF+AC) causes up-regulation of genes *HO-1/Ft*, the expression of which is increased in the mean by 4 and 1.5 fold respectively, compared to basal level. Preincubation U937 cells with iron chelator leads to an increase in their resistance to (TF+AC) by 2 fold, and in the presence of iron-containing analogue of TF the drug cytotoxicity increases by 2 fold.

Summary. The catalytic system (TF + AC) is an inducer of the co-expression of *HO-1/Ft* genes along the ROS-dependent pathway in cells with a constitutively active NO-1/Ft system. In the mechanism of action (TF + AC), the intracellular pool of labile “non-hemic” iron is involved, and cell sensitivity to the drug depends on its content. Our findings suggest that ROS-dependent activation of the HO-1/Ft system of drugs may affect the effectiveness of chemotherapy for patients with leukemia.

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Cancer drug delivery system

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Cancer (malignant neoplasm) is a group of diseases, each of which is capable of infecting any organs in the human body due to the pathological formation and proliferation of abnormal cells. The process of spreading such tissues to organs is called metastasis [1]. Many current anticancer drugs have less than ideal pharmaceutical and pharmacological properties [2]. From the aspect of pharmacokinetics, in particular drug distribution, these may cause low bioavailability of the anticancer drug at the site of action as well as high organ toxicity limiting the maximum tolerated dose. In recent years, drug delivery systems (DDS) have been developed, among with anticancer agents for those systems based on the concept of achieving a better clinical response and tolerability [2].

Low targeting efficiency limits the applications of nanoparticles in cancer therapy. The fact that mesenchymal stem cells (MSC) trapped in the lung after systemic infusion is a disadvantage for cell therapy purposes. It was demonstrated that MSC is used as lung cancer-targeted drug delivery vehicles by loading nanoparticles (NP) with anti-cancer drug. MSC showed a higher drug intake capacity than fibroblasts [3].

Calcium carbonate ($CaCO_3$) has broad biomedical utilizationsowing to its availability, low cost, and safety. Recently, there has been widespread interest in their application as drug delivery systems for different groups of drugs. Among them, $CaCO_3$ nanoparticles have exhibited promising potential as drug carriers targeting cancer tissues and cells [4].

Liposomes and protein-based drug delivery systems (DDS) are archetypal nanoscale DDS. Currently, numerous traditional anticancer drugs are encapsulated in liposomes and many of them have been approved for clinical use or are undergoing clinical trials. In addition, nanoparticle albumin-bound (nab)-paclitaxel has recently been approved for the treatment of metastatic breast cancer [2].

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«Chemical structure-antitumor activity» bond correlation of new indolo[2,3-a]pyrrolo[3,4-c]carbazoles of N-glycosides class

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Introduction. The research of «structure –activity» bond opens the best ways for the creation of new high selectivity and efficiency pharmaceutical products among the synthesized products of natural analogues or their structure chemical modification. The structure uniqueness and indolocarbazole N-glycosides biological properties stimulated the search and creation of active antitumor agents among their synthetic analogues and low-malecular derivatives.

Objective. The goal of the work is to conduct a comparative study of 8 N-glycosides domestic derivatives of indolo[2,3-a]pyrrolo[3,4-c]carbazoles (LCS) with various modifications on aglycone and glycoside residue during the «structure-activity» bond analysis.

Materials and methods. The research of the structure dependence of 8 indocarbasoles (LCS), synthesized in N.N. Blokhin Russian Cancer Research Center, and their antitumor activity was performed on transplantable mouse tumor models: lympoblastosis P388, lung Lewis epidermoid carcinoma (LLC) and B16 melanoma. The substances of conponds LCS were dissolved in dimethyl sulfoxide (DMSO) and diluted with saline to 10% of DMSO concentration. The compounds (LCS) were studies in doses of 25, 50 and 75 mg/kg with daily intraperitoneal administration for 5 days. The criteria for evaluation became the increase of life span of animals with P388 (ILS>25%) and the inhibition of solid LLC tumors and B16 (TGI>50%) growth.

Results. On P388 all the compounds LCS demonstrated activity on ILS=31-115%. The aglycone-modified LCS compounds with the same glycosides showed effectiveness on solid models: xylose (TGI=52-84%) or arabinose (TGI=54-91%). The LCS compounds, similar in aglycone, but with different glycosides (galactose, xylose, ribose), had no effect on LLC, on B16 – TGI=70-84%.

Conclusion. A comparative study of 8 N-glycosides derivatives of indolocarbazoles showed their effectiveness on P388 regardless of the modification changes in the aglycone structure. As for the LLC and B16 models, the antitumor LCS compounds activity depended on the structure of both, the aglycone and the glycoside residue. The obtained results can be proposed for analysis and synthesis of more active LCS compounds as new potential antitumor agents.

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BIOLOGICAL EFFECTS OF NEW CYANINE DYES

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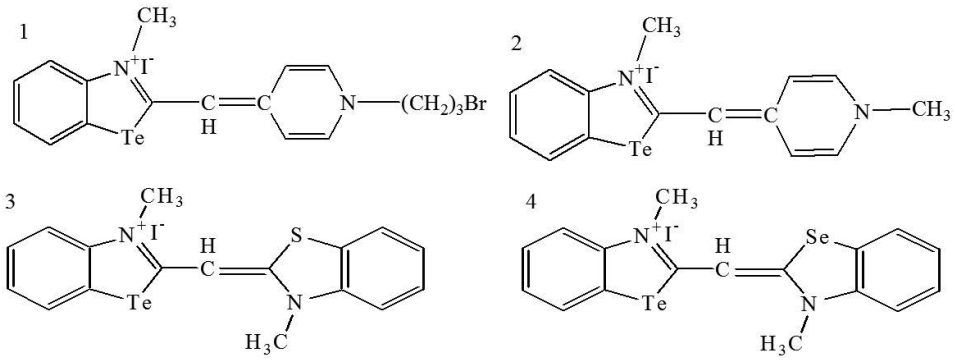
Compounds related to cyanine dyes possess intense fluorescence in the visible and near infrared spectral regions, because of which they have been used in various technologies [1]. Cyanine dyes, having in their composition various chalcogens, can be of considerable interest in biological and medical research. We have synthesized 4 new monomethion cyanine dyes containing tellurium, sulfur and selenium [2]:



In this paper, we studied the effects of these substances on the state of antioxidant protection of erythrocytes and acetylcholinesterase (AChE) activity in synaptosome membranes from rat brain in vitro. Substances 1 and 2 increase the level of reduced glutathione in erythrocytes, and substances 3 and 4 significantly increase the concentration of SH-groups in synaptosome membrane proteins. None of the substances had an effect on the activity of superoxide dismutase, but they significantly reduced the activity of erythrocyte catalase. Substances 3 and 4 have a significant inhibitory effect on the AChE of synaptosome membranes. The resulting substances can be the basis for the synthesis of more active antioxidants and inhibitors of brain ache used in the treatment of Alzheimer's disease.

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Determination of water in pharmaceutical substance (sodium salt of diethyl ether of 4-oxo-1,4-dihydropyrazolo[5,1-C]-1,2,4-triazine-3,8-dicarboxylic acid, monohydrate) by Karl Fischer method

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Quantitative determination of water content (capillary, absorption-bound, chemically bound and free) is necessary to control the quality of pharmaceutical substances. The exact concentration of water is needed to calculate the content of the active substance, as well as to predict such processes as weathering of water of crystallization in crystalline hydrate or absorption of moisture from the air by hygroscopic substances, hydrolysis, oxidation, decomposition, and possible appearance of toxic impurities.

There are many methods for determining the water content, including volumetric and coulometric Karl Fischer titrations, which are described in the pharmacopoeias of several countries and are used to determine water in the range of 10 μg -100 mg H_2O.

This paper describes the possibility of determining the water content by Karl Fischer titration in the pharmaceutical substance - sodium salt of 4-oxo-1,4-dihydropyrazolo [5,1-s] -1,2,4-triazine-3,8-dicarboxylic diethyl ester acid, monohydrate with anti-glycating activity [1], using a Karl Fischer 915 KF Ti-Touch volumetric titrator (Metrohm) and an Expert-006 coulometer (Econix-Expert). Also presents the results obtained by the method of drying.

The results are presented in the table.

	Volumetric titration	Coulometer titration	The method of drying
Water content of sample, %	5,78 ± 0,07	4,83 ± 0,46	5,90 ± 0,90

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Synthesis and photoinduced E-Z isomerization of enones of tetralone, 1,2,5-trimethylpiperidin-4-one and dienones of tropane-3-one.

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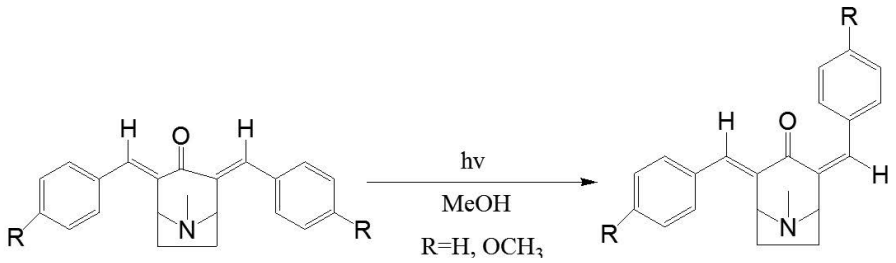
Enones and dienones derivatives of heterocycles such as substituted piperidine, tropane and tetralones are of importance because they can be a prolific source of drug candidate molecules displaying cytotoxic[1], antimicrobial[2] and other biological activities.

Synthesis of enones of tetralone, 1,2,5-trimethylpiperidine-4-one and dienones of tropane-3-one derivatives has been performed via aldol condensation reaction. All new products of condensation was observed as E - isomers. Photoisomerization of E - isomers led to the formation of new series of Z-isomers in methanol solution under UV light λ> 250 nm.



The study of the reaction photoisomerization of tropane-3-one dienone led to formation only E/Z isomer.

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Synthesis of novel N-(8-Methyl-8-azabicyclo[3.2.1]octane-3-iliden) benzohydrozide derivatives demonstrate antimigraine and anxiolytic types of activities.

Kostochka L.M.[1], Ganshina T.S. [1], Naplenkova P.L.[1], Narkevich V.B.[1], Voronina T.A.[2], Kudrin V.S.[2], Mirzoyan R.S.[2], Kurdymov I.N.[1], Gudasheva T.A.[2]

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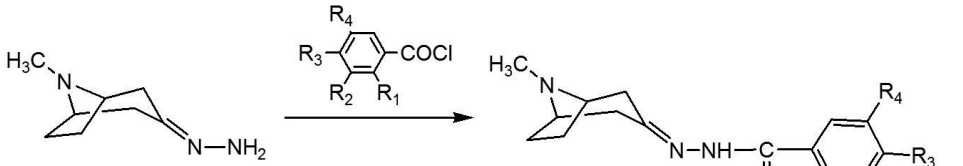
Design and synthesis of novel efficient antimigrane derivatives is still important aspect of modern medicine for treatment migraine onset. It is well known, that important role in initiating and progressing migraine onset plays serotonine hormone. Mostly well-known drugs, using in the medical practice are affecting and binding with 5HT1A/1B/1D/1 and 5HT2A/2B/C serotonine sub-types of receptors, that verify of their importance.

Design and synthesis of novel potent antimigraine drugs is interesting field for modern pharmacology and medicinal chemistry.

During our studies, has been synthesized line of the novel derivatives, considering as novel potential antagonists of benzohydrozide tropane-3-one derivatives:



Где а)$R_1=R_2=R_3=OMe$, $R_4=H$, б)$R_1=R_3=H$,$R_2=R_4=CH_3$
в)$R_1=R_3=H$, $R_2=R_4=OMe$, г)$R_1=R_2=R_3=R_4=H$

Pharmacologycal studies of synthesized compounds demonstrate that all of them exhibit antiserotonine-type of activity. Compound - 2,3,4-trimethoxy-N-(8-Methyl-8-azabicyclo[3.2.1]octane-3-iliden)benzohydrozide (a) is showing pronounced and stable antimigraine effect and also possess expressed anxiolytic type of activity that is very important for antimigraine drugs in mechanism of their action. It should be noted, that in literature there are only a few acetylated hydrazones tropane-3-one derivatives were shown. All of them were declared as anti-tuberculosis, stimulating, antidepressants drugs [1].

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Glycosylated amino acid derivatives of 4-(1-adamantyl)benzoic acid as potent prodrug nonsteroidal anti-inflammatory drugs

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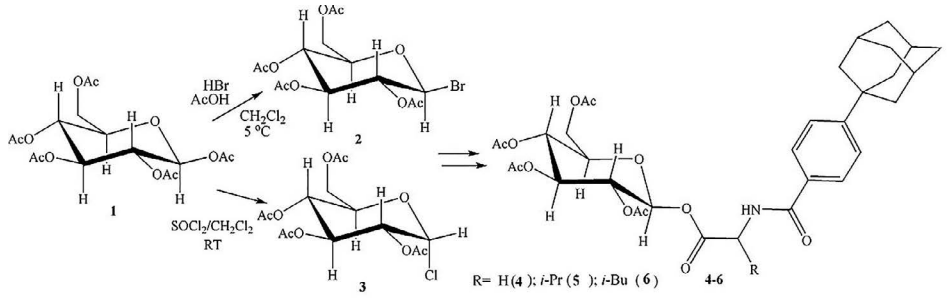
At the moment the need to use of nonsteroidal anti-inflammatory drugs (NSAIDs) remains high. Accordingly, there is a need for their modification in order to reduce or eliminate ultserogennogo [1].

In our scientific work, we proposed an NSAID in a molecule fragment of the monosaccharide using glycosylation reaction, which will be a prodrug [2].

The objects of the study were the amino acid derivatives of 4- (1-adamantyl) benzoic acid derivatives having anti-inflammatory activity [3].

Two methods of synthesis of glycosides (**4-6**), the condensation of the starting compounds with a α-D-bromide (**2**) and α-D-chloride (**3**) was investigated.



A comparative analysis of the results and provides a method, which leads to high yields of the final products and the most convenient in carrying.

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State of fluorine metabolism in young children in the conditions of the Ural region

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The effect of nutrition on health is a pressing issue in pediatrics, as the lack of trace elements has a negative effect on the child. The high incidence of symptoms of lesions of the musculoskeletal system is the clinical manifestation of fluorine deficiency in the child's body. The Ural region is an unfavorable biogeochemical territory for the content of fluoride in drinking water as the main source of its entry into the human body [1,2].

We evaluated the availability of fluorine in 95 children aged 1 month to 3 years with a clinical examination and a set of laboratory and instrumental research methods. Static analysis of research results was performed using computer programs Microsoft Excel XP, SPSS 12.0, STATISTICA 6.0. The examined children showed signs of deficiency of one of the main osteogenic minerals - fluorine - in the form of damage to milk teeth (delayed teething, darkening of tooth enamel and caries) and the presence of signs of osteomalacia. The state of fluorine availability was estimated by the level of fluorine excretion in the urine (fluoruria) with reference indices of fluorine in the urine of 0.5-0.7 mg/l [3]. A low level of fluoride was detected, which averaged 0.33 ± 0.01 mg/l. Fluorine deficiency can sustain and aggravate the processes of bone mineral density decrease, that dictates the need to develop fluorine-containing drugs.

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In silico preliminary assessment of ligand-receptor interactions for series of novel estrogen receptor steroidal modulators

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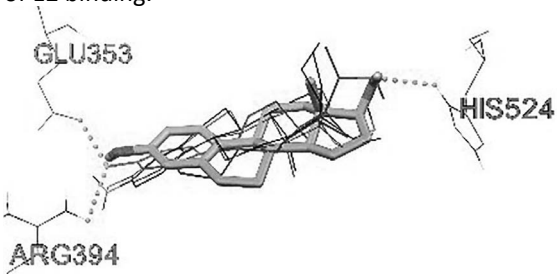
Recently, we have described the effective syntheses of 3-hydroxyestra-1,3,5(10)-trienes of natural and epimeric 13α-configuration with 17th-side chain bearing the second hydroxy group and 16,17-fused three- or six-membered carbocycle (or without it), evaluation of the relationship of their stereochemical and conformational features of the structures with their reactivity, study of the anticancer activity of the new compounds (antiproliferative activity, inhibition of estrogen receptor expression, and estrogen/antiestrogen activity). All target compounds suppressed the estradiol-induced ER transcriptional activity in MCF-7 cells with the exception of 16α,17α-cyclopropane derivative of 13-epi-series which proved to be an ER activator [1,2].

We performed the docking experiments using AutoDock Vina wherein two approaches were implemented – flexible and rigid docking. The flexible model implied the plasticity of the ligand-binding pocket (LBP) and showed that all the compounds can fit to LBP ER well. The rigid model implied a “frozen” protein conformation like in the X-ray structure of ER-estradiol complex. The latter showed that ER agonistic compound lies like estradiol (E2) while the antagonists are flipped in comparison with first one. The main difference is observed in the position of the second OH-group of the agonist which can form hydrogen bond characteristic of E2 binding.



Thus, docking studies using AutoDock Vina allowed us to evaluate possible differences of receptor binding modes causing different transcriptional activity. The combination of flexible and rigid docking models was found to be appropriate way for the primary assess of the potential ligand-receptor interactions in the case of previously unknown structures.

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Alternative method for joint determination of amlodipine, rosuvastatin and lisinopril in medical preparations using spectrophotometry

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Major pharmaceutical manufacturers produce combined medicines that allow taking one pill per day for the treatment, instead of three or four, which is very convenient for the consumer. Along with the pharmaceutical giants, there are generic companies, which are interested in developing substitutes for these original medical preparations and aim reducing the total cost of production. In order to achieve this goal, it is necessary to reduce the cost of analyzing the produced medicines. A spectrophotometric technique was developed as an alternative to cost HPLC methods.

This research is devoted to the development of method for the joint determination of amlodipine (AML), rosuvastatin (ROS) and lisinopril (LIS) in a combined drug using spectrophotometry. The developed technique involves the separation of the drug active ingredients due to its different solubility in water, 0.1 M HCl solution, alcohol, chloroform and their determination using selective reagents: bromocresol green (BCG), bromocresol purple (BCP) and alizarin (ALZ).

The determination of amlodipine is based on the formation of a colored product with BCP (λ_{max}=364 nm, pH=7,68, ε=5563). The range of the drug detectable concentrations was 0.020-5.3 mg/25 ml. The reaction contrast was 224 nm.

Rosuvastatin was determined using the BCG (λ_{max}=432 nm, pH=2,40, ε=7943). The linearity of the calibration curve is observed in the range of 0.050-5.0 mg/25 ml.

The determination of lisinopril was carried out with the help of ALZ (λ_{max}=434 nm, pH=8,7, ε=9067). The Bouguer-Lambert-Ber law is observed in the range of 0.40-30.0 mg/25ml.

Various molar ratios of the components were studied as part of the research: ROS- BCG, AML-BCP and LIS-ALZ, using methods of isomolar series, saturation, balance shift and Asmus. The results were confirmed by conductometric titration. The molar ratio of the components was [1: 2]. However, the result obtained by the Asmus method allows us to speak about the ratio of the components [1: 1].

The Babko method was used to calculate the stability constants ROS-BCG, AML- BCP, LIS-ALZ, which were respectively: $6.0 \cdot 10^9$, $5.0 \cdot 10^{10}$, $5.4 \cdot 10^9$.

The proposed technique has been successfully applied to the analysis of a drug containing ROS, AML and LIS. The determination error was 1.5–5%.

Photobiological properties of crown and phosphoryl-containing metal phthalocyanines. Comparative *in vitro* analysis.

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Nowadays, the study of well-known photosensitizers (PSs) for photodynamic therapy and search for new ones are intensively conducted. In the present work, crown- and phosphoryl-containing metal phthalocyanines (Pcs), $Mg[B15C5O)_8Pc]$ (**I**) and $Zn[R_4Pc]$ {R = -OPhP(O)(OH)(OC_5H_{11})} (**II**), were investigated as potential PSs and comparative in vitro analysis of their photobiological characteristics with respect to human adenocarcinoma cells, HeLa, was also carried out. As part of this study, the determination of toxicity and the intracellular level of the formation of reactive oxygen species (ROS) were performed in the presence of **I** and **II**. Cells were irradiated after their 24 hour incubation with Pcs. After rinsing the samples with phosphate buffer, the phototoxicity of both Pcs was determined using the MTT assay. For **I**, the light and dark toxicity (IC_{50} dose) were determined to be 1.83 and more than 25 μM, and for **II**, the IC_{50} values were determined to be 6.44 and more than 100 μM, respectively. Under cell irradiation in the presence of **I** and **II** (λ = 670 nm, power of incident light 8 mW·cm^2, room temperature), the ROS formed were determined with $DCFH_2$ as a fluorescence detector. The Pcs concentration values studied are in the range from 0.195 to 25 μM and from 0.195 to 100 μM for compounds **I** and **II**, respectively. Compound **I** was significantly more active than **II** in photo-induced generation of ROS. Using laser confocal microscopy, data on the accumulation and localization of I and **II** in HeLa cells were obtained. **I** was shown to be completely absorbed by HeLa cells at the concentration of 5 μM for 24 h. However, **II** accumulated in cells in a smaller amount as compared to **I**. When accumulated, both Pcs are localized mainly in the cytoplasm.

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A Free-radical-damaging ability of the selenium-containing humic substances from the brown coal

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Polymeric highly branched structure and highly functionalized composition of humic substances (HS) causes their bioactive effects on the body. It is known that some HS are able to neutralize free radicals formed in the focus of inflammation and which are inducers of destabilization and destruction of the cell membranes. The paper presents the results of a study of the using possibility of the nanocomposites from natural sources as materials with free-radicals damaging activity. With use modern physicochemical methods, we have described in detail HS from brown coals of Mongolia [1]. The humic substances isolated from brown coal by alkaline extraction by a procedure reported in [1] look like a black powder with a total ash content of 21.7%. The degree of oxidation (the oxygen to carbon, O/C, ratio) was 0.65, which characterizes them as highly oxidized. Synthesis of selenium nanocomposites was carried out by reduction of selenium dioxide by sodium borohydride in an aqueous medium in the presence of HS. A comparative study of the antioxidant activity of isolated HS and their selenium-containing nanocomposites showed that in vitro all samples inhibit model processes of lipid peroxidation of living cell membranes [2-3]. In addition, a pronounced damaging effect of HS and selenium nanocomposites based on them in relation to the free radicals of DPPH and ABTS was found. Moreover, the introduction of the selenium into the matrix of HS increases the antioxidant activity by 50%. For nanocomposites and initial HS, a pronounced antioxidant activity was established, comparable to that for succinic acid and ionol. Such biologically active substances are promising as antioxidant compounds, specific complexation agents with pharmacoactive elements, and can be used in the manufacture of drugs of combined action.

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Synthesis and in vivo study of biological effects of the selenium on the base of kappa-carrageenan

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Selenium is an essential biogenic element. It is part of the selenoproteins that perform a complex of vital functions in the organism. In particular, of particular importance is the function of antioxidant protection of cells against the action of aggressively directed free radicals, which are constantly synthesized in cells as a result of both natural metabolic processes and in increased amounts - in the case of cell interaction with pathogenic agents (viruses, microbes, toxins, inflammatory factors and factors of growth and decay of tumors). At present, the use of the elemental selenium nanoparticles (Se^0NPs), which, according to several studies, having a low toxicity along with a high biological activity, seems to be very promising for the correction of selenium-deficient states. As a result, the development of available and environmentally friendly methods for the synthesis of Se^0NPs, as well as the study of their effects on the organism, is urgent tasks. Thus, as a result of an oxidation of the selenide anions (previously generated from elemental bulk selenium in the hydrazine hydrate-alkali basic reduction system), we synthesized the water-soluble hybrid nanocomposites consisting of Se^0NPs of 4.6–11.0 nm in size stabilized by the biocompatible polysaccharide kappa-carrageenan. It is experimentally found the obtained nanocomposites have a pronounced hepatoprotective effect in toxic liver damage modeled by the administration of white rats CCl_4. This effect was expressed in the reduction and normalization of the blood biochemical indices (ALT and AST) in the group of selenium nanocomposite treated after seed CCl_4 compared with the group in which animals did not receive this nanocomposite. In addition, during the entire observation period (21 days), in the groups treated with selenium nanocomposite (on the backdrop of the seed CCl_4 and without it), no death of animals was recorded. Whereas in the group exposed to the action of the CCl_4 recorded death of 25% of animals. This indicates the non-toxicity of the studied nanocomposites. The obtained results determine the prospects of further research on the biological effect of these nanocomposites with the aim of developing biocompatible hepatoprotective preparations on their basis.

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Possibilities of Non-invasive Diagnostics of Nutritional Deficiency in Children

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Alimentary-dependent diseases occupy one of the leading places in the morbidity structure of children of preschool and primary school age [1]. Insufficiency of mineral substances that regulate metabolic processes, accompanied by a decrease in the adaptive capacity and leads to the development of a number of diseases [2].

We have evaluated the sufficiency of essential macro- and microelements in 66 children aged 3 to 11 years of age based on the level of their urine excretion (a method of spectral analysis with inductively coupled plasma). Static analysis of research results was performed using computer programs Microsoft Excel XP, STATISTICA 10.0.

High urinary excretion of sodium, detected in 61.1% of children of preschool and 46.9% of children of primary school age, indicates an increased consumption of foods with a high salt content. The average value of calcium excretion was reduced during normal excretion of phosphorus, which influenced the ratio of calcium: phosphorus and reflected the presence of latent calcium deficiency. Decrease in iron excretion was observed in 23.5% of preschool and 53.1% of primary school children. The level of excretion of zinc in the urine was almost two times lower than the reference values. Copper excretion with urine corresponded to the lower limit of reference values. The revealed changes prove the presence of combined macro- and microelementosis in children, requiring preventive and therapeutic measures.

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The determination of optimal cryoprotectant for lyophilization of liposomal forms derived indolocarbazole

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Lyophilization-is one of the effective methods used to stabilize and increase the shelf life of drugs. This process is influenced by many factors, the most important of which are the conditions of freezing and drying, the properties of medicinal and auxiliary substances [1]. In the case of obtaining high-quality lyophilizate liposomes, their sublimation drying is carried out with the addition of special substances − cryoprotectors that ensure the preservation of bilayer structures [2].

The aim of this work was to determine the optimal cryoprotectant and its amount, providing the production of lyophilisate liposomes of a new derivative of indolocarbazole LHS-1269. The monosaccharide mannose introduced into the dispersion in molar ratios (v/v) lecithin/cryoprotector 1:8 and 1:10 and the disaccharides sucrose and trehalose introduced into v/v lecithin/cryoprotector 1:4 and 1:5 were studied as cryoprotectors.

The results of the study showed that in appearance all lyophilizates were a dry porous mass of light yellow color, during rehydration of which a homogeneous dispersion was formed, without sediment and signs of stratification. At the same time, in all samples of dispersions, with the exception of sucrose-containing 1:4, the preservation of the initial size of liposomes was noted. However, the highest value of ζ-potential of liposomal dispersion had a sample of the lyophilisate, including in its composition a sucrose 1:5.

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Oxidation of uracils by ozone in aqua solutions

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RNA and DNA play an important role among biological macromolecules. They are keepers and messengers of genetic information. Pyrimidine bases are one of the building blocks of mentioned acids. It is considered that oxidative destruction lead to degradation of RNA and DNA chains. At the present day researches are conducted on the oxidative transformations of pyrimidine bases (on the example of uracil and its derivatives) under the action of various oxidative systems. However ozone which has gained wide popularity in cosmetology and medicine (prevention and treatment of many diseases) is not properly represented among the used oxidizers.

In the present work the kinetics of oxidation of uracil and its six derivatives (UD) by ozone was studied by UV spectroscopy with equal initial concentrations of reagents ($[UD]_0 = [O_3]_0 = C_0$). Analysis of the kinetic curves of concentration changes C showed that they are linearized well enough on the equation coordinates of second-order reaction. Using a bubbling installation it was found that 1 mole of absorbed ozone be accounted 1 mole of consumed UD. In this way reaction obeys the second order kinetic law (the first – on UD and the first – on ozone).

In this work the temperature dependence of the second-order rate constants was studied in the range of 285–309 K and the parameters of the Arrhenius equation were calculated for all uracils. The reactivity of uracils in relation to ozone (285 K) changes in the following row: 1,3-dimethylthymine > 5-bromo-6-methyluracil > uracil, 6-methyluracil > 5-nitro-6-methyluracil > 5-hydroxy-1,3,6-trimethyluracil > thymine. It was established that there is a linear correlation (or effect of compensation) between logarithms of pre-exponential factors and activation energies of the reaction of ozone with uracils which probably indicates a single mechanism of the limiting stage of ozonized UD oxidation.

The work was supported by the Russian Science Foundation, project 19-73-20073

Virtual screening of potential antiherpetic agents

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The purpose of the work was QSAR-modeling of some derivatives of 5-ethyluridine, N2-guanine and 6-oxopurine with a pronounced inhibitory activity against thymidine kinase (TK) of the herpes simplex virus of the first and second type of human (HVS-1 and HVS-2) [1-3]. Studies were conducted using the GUSAR 2013 program on the basis of two training and two test samples according to the method described in the work [4]. As a result, six statistically significant stable QSAR consensus models for the prediction of the numerical values of IC_{50} for the HVS-1 and HVS-2 TK inhibitors (Table 1). They are applicable for virtual screening and searching for new connections.

Table 1. *The statistical characteristics of consensus models M1-M6.*

Training set	*Models*	*N*	*R2TrS*	*R2TS*	*F*	*S.D.*	*Q2*	*V*
QSAR model based on QNA-descriptors								
TrS1	M1	75	0.880	0.940	62.116	0.563	0.849	7
TrS2	M4	76	0.886	0.917	80.793	0.605	0.866	6
QSAR model based on MNA-descriptors								
TrS1	M2	75	0.887	0.921	72.470	0.546	0.865	7
TrS2	M5	76	0.914	0.899	78.441	0.529	0.895	8
QSAR model based on MNA- and QNA-descriptors								
TrS1	M3	75	0.940	0.940	61.463	0.524	0.870	7
TrS2	M6	76	0.911	0.922	67.662	0.541	0.888	9

N – number of structures in the TrS; R^2_{TrS} - a multiple coefficient of determination calculated for compounds from the TrS; R^2_{TS} - a multiple coefficient of determination calculated for compounds from the TS; Q^2 – a cross-validated R^2 calculated during leave-one-out cross-validation procedure on data of the TrS; F – Fisher's coefficient; S.D. – standard deviation; V- the number of variables in the final regression equation.

Additionally, using the molecular docking method, the steric complementarity of the modeled compounds with the active center HSV-1 TK in humans was studied. Potential biologically active conformations were determined for all ligands, and binding sites to the active center were identified. This information may be useful in the development of new selective inhibitors of TCV HSV-1.

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Effect of Phytohermab on the myocardium of rats and mice

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Introduction. Phytohermab (PG) is a dosage form of a new biotechnological drug, humanized monoclonal recombinant therapeutic antibody against HER2 onco-antigen, obtained from a plant source in the laboratory of transgenic preparations of the FSBI «N.N. Blokhin NMRCO» Ministry of Health of Russia and is a plantianalog of Trastuzumab, the main toxic effect of which is cardiotoxicity.

Purpose of the study. Evaluation of the alleged cardiotoxic effect of PG with intravenous (I/V) or intraperitoneal (I/P) administration in rats and mice.

Materials and methods. The study was performed on 25 Wistar rats and 60 female SHK mice. Doses of PG were selected on the basis of literary data. PG was administered once I/V or I/P in doses of 2 and 20 mg/kg. ECG parameters in rats were assessed on days 3, 5, 7, and 9 of observation. Histological examination of the heart of rats was performed on days 7 and 9; mice - on the 3rd, 5th, 7th and 9th day of observation. The material was subjected to conventional histological processing, histological preparations were examined under a light microscope.

Results. It was established that PG with a single I/V and I/P administration to rats only at a dose of 20 mg/kg on day 7 of observation caused changes in the ECG of animals passing by 9 days: an increase in the PQ interval and heart rhythm disturbances. Histological examination of pathological changes in the myocardium of rats on days 7 and 9 was not observed. PG in doses of 2 and 20 mg/kg, regardless of the route of administration and for all periods of observation, caused changes in the myocardium of mice. Cardiac foci of cardiomyocytes with signs of dystrophy (swelling and disappearance of striated striation) and increased staining by eosin of their sarcoplasma (hypereosinophilia) were found in the heart muscle, which is associated with cell hypoxia and metabolic disturbances. In addition, PG at a dose of 20 mg/kg on the 3rd day of observation after I/P use and on the 5th day of observation after I/V use caused isolated mononuclear infiltrates in the myocardium of individual mice, which may be a manifestation of focal inflammation.

Conclusion. When administered once to rats, PG caused passing, independent of the route of administration, ECG changes only at a dose of 20 mg/kg, while no histological changes were noted in the heart of the rats. Slightly pronounced dystrophic and hypoxic changes of myocardial cells were noted histologically, irrespective of the dose and route of administration, in the heart of all mice. Focal inflammatory changes in the myocardium of mice were detected only with the use of PG at a dose of 20 mg/kg.

Pathomorphological criteria for preclinical study of domestic reproduced drugs and their analogues - reference drugs

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Introduction. Preclinical pathomorphological comparative study of reproduced drugs requires the use of criteria that allow to evaluate the macroscopic and histological changes in the internal organs of animals.

Purpose of the study. Determine the pathomorphological criteria for assessing the identity of the manifestations of the toxic effects of domestic reproducible anticancer drugs and reference drugs.

Materials and methods. In FSBI «N.N. Blokhin NMRCO» Ministry of Health of Russia conducted a comparative preclinical study of reproducible anticancer drugs cisplatin, carboplatin, oxaliplatin, methotrexate, vincristine and hydroxycarbamide. As the reference drugs used similar registered drugs. Reproduced drugs were administered to rats in parallel with the comparison preparations for 3-5 days in accordance with the required doses and the mode of administration - intravenously or orally. Pathomorphological study was performed on days 3 and 30 after discontinuation of the injections. An autopsy and a macroscopic examination of the internal organs were performed at the autopsy, and parts of the internal organs were taken, which were subjected to conventional histological processing.

The results of the study. Criteria for comparative evaluation are highlighted: external features of rats (condition of the skin, hair, mucous membranes, signs of diarrhea); macroscopic changes of the internal organs (increase / decrease, blood supply, consistency, edema, etc.); qualitative assessment of microscopic changes (cell dystrophy, signs of inflammation, hemorrhage, necrosis, regeneration sites, etc.); semi-quantitative assessment of histological changes on the scale: 1 - single small areas, 2 - large single areas, 3 - a large number of sites / diffuse changes; number of animals with changes in organs. We studied the dependence of changes on the dose and their reversibility. If the evaluation criteria coincided, the conclusion was made about the identity of the reproduced drug and its analogue.

Conclusion. Pathomorphological criteria were determined during a preclinical comparative study of domestic reproduced drugs and their analogues - reference drugs.

Biological activity of novel fluorinated quinazolines

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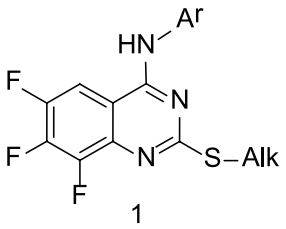
Quinazoline derivatives is an important class of heterocyclic compounds, among which antagonists of enzymes and of a number of receptors, compounds with antitumour, antiviral and antibacterial activity were found. A special place among these compounds is occupied by the fluorine-containing derivatives. We managed to develop a number of effective synthetic approaches to fluorinated quinazolines with different types of biological activity.

2-Alkylthio-4-arylamino-6,7,8-trifluoroquinazolines **1** were studied at State Scientific Center of Virusology and Biotechnology (Novosibirsk), Flu Institute (S.-Petersburg) and Phtiziopulmonology Institute (Ekaterinburg). Derivatives active towards pox-viruses, flu virus and tuberculosis micobacteria were found.



1

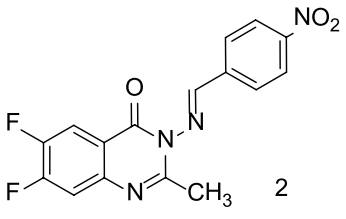
Antiviral activity:

Ar = Ph, Alk = Et	variolovaccine (VV) IC_{50} = 0.05 μg/mL, ektromelia (Ectr) IC_{50} = 0.05 μg/mL, monkeys smallpox (MPV) IC_{50} < 0.05 μg/mL;
Ar = 3,4-diFC_6H_3, Alk = Et	VV IC_{50} 0.09 μg/mL, Ectr IC_{50} 0.11 μg/mL, MPV IC_{50}<0.05 μg/mL; FLU VIRUS A (H_3N_2) $lgID_{50}$/50mL = 4.0

Antitubercular activity:

Ar = 2-$OMeC_6H_4$, Alk = Me	$H_{37}R_V$ 1,5 μ/ml; M. Avium 1,5 μ/ml; M. Terrae 1,5 μ/ml; MDR strain 1,5 μ/ml

We found that transformation of 3-aminoquinazolinones into arylydenamino ones represents a perspective way for search new fungistatic agents. 3-Arylydeneaminoquinazolines **2** were studied at Dermatology and Venereology Institute (Ekaterinburg).



2

Fungistatic activity:
Trichophyton mentagrophytes var. Interdigitale (MIC 3.12 mg/mL),
Trichophyton schoenleinii (MIC 1.5 mg/mL),
Epidermophyton floccosum (MIC 0.75 mg/mL),
Microsporum canis (MIC 25 mg/mL)

The work was carried out with financial support from the Ministry of Education of Russian Federation (State Contract 4.6351.2017/8.9).

Synthesis of pancreatic α-amylase inhibitors by endophytic fungi under solid-phase fermentation conditions

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Diabetes mellitus characterized by chronic hyperglycemia, which controlled by inhibiting α-amylase and α-glycosidase, leading to a strong delay in the digestion of carbohydrates.

Endophytic fungi, asymptomatically living in the intercellular space of various parts of plants, are capable of producing α-amylase inhibitors. Earlier, we isolated *Penicillium brevicaule alba Thom*-CC200 and *Aspergillus egypticus*-HT166S strains from medicinal plants *Celosia cristata* and *Heliantus tuberosus*, producing inhibitory activity compounds.

In order to optimize the cultivation conditions of selected endophytic strains to increase the level of production of metabolites with high inhibitory activity, as well as taking into account the cost-effectiveness of the solid-phase fermentation method, we conducted studies to determine the possibility of endophyte cultivation by the TFF method.

The strains were grown for 7 days on substrates containing oats, cereal waste, rice and wheat husks, hydrated with the Chapek-Doksa medium and nutrient-rich medium, containing various carbon sources.

It was shown, that all the used substrates are well suited for the successful development of the mycelium of both cultures, which grows deep into the substrate, forming a fluffy layer, more pronounced when hydrated with a nutrient-ruch medium containing glucose, maltose and glycerin, as compared to the Chapek-Doks medium.

In general, the level of production of α-amylase inhibitors in the extract of *P. brevicale alba Thom* - CC 200 is higher than in *A. egypticus* - HT166S, is dependent on the substrate used and is directly correlated with biomass growth. It was established that in the strain P. brevicale alba Thom - CC 200 on wheat husk, when hydrated with nutrient-rich medium, observations show maximum inhibitory effect of α-amylase at a level of 87.5% and inverse correlation with biomass growth. In the A. egypticus - HT166S strain, the maximum percentage if inhibition is low and amounts to only 20% when fermentation carried out in oats hydrated by nutrient-rich medium.

Thus, the P. *brevicale alba Thom* - CC 200 strain shows most promise as means of obtaining α-amylase inhibitors by the method of solid phase fermentation on wheat husk and substrate hydration via nutrient-rich medium.

Antiproliferative activity of imidazo[4,5-e]benzo[1,2-c; 3,4-c']difuroxans

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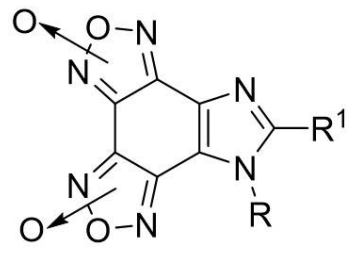
Nitric oxide affects the apoptosis of tumor cells at all stages of cancer development [1]. It's well know that benzimidazole derivatives exemplify one of the chemical classes that show strong cytotoxic. The aim of present study was to evaluate the antiproliferative activity of imidazo[4,5-e]benzo[1,2-c; 3,4-c ']difuroxans - the hybrid compounds with two furoxan rings and benzimidazole core. The antiproliferative activity of 19 imidazo [4,5-e]benzo[1,2-c; 3,4-c ']difuroxans with various substituents was tested against two human cancer cell lines: fibrosarcoma (HT1080) and glioblastoma (A-172) using the MTT assay. A-172 glioblastoma cells, on average, were more sensitive than HT1080 cells. It was determined that four compounds (Ks009, Ks052, Ks066, Ks067) demonstrated the insignificant or low antiproliferative activity (IC (50) more than 70 μM for both cell lines)and three (Ks010, Ks019, Ks025) showed the medium activity (IC (50) 50-70 μM for HT1080 and 15-30 μM for A-172). The other 12 compounds (Ks022, Ks023, Ks026, Ks032 Ks033, Ks034, Ks042, Ks050 Ks057, Ks064, Ks065, Ks068) displayed high antiproliferative activity (IC (50) 15-50 μM for HT1080 and 4-7 μM for A-172) .



The obtained data allow us to consider imidazo[4,5-e]benzo[1,2-c; 3,4-c']difuroxans as new crucial candidates in antitumor drug research and development.

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Comparative strength properties changes of polyfilament sutures Sabfil Plus and Mefpil under conditions of in vivo and in vitro destruction

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Replacement of expensive imported medical goods with identical in biological and mechanical properties domestic products, including surgical is currently a topic issue. Evaluation of biodegradable sutures biocompatibility and mechanical properties that satisfy their practical application areas is very important [1].

This work was aimed to determine the rate of mechanical strength change of “Mefpil” suture based on polyglycolide and “Sabfil Plus” domestic suture based on polyglycolide-co-D,L-lactide by chemical hydrolysis in a buffer solution and biological destruction in tissues.

The experiments were carried out on 3-month laboratory CBA mice weighing 22.0-24.0 g. The analysis of the samples mechanical properties showed an increase in destruction rate of the studied sutures when implanted into the subcutaneous tissue compared to chemical hydrolysis in phosphate buffer. Apparently, this is due to the enzymatic activity of serum proteases of the tissue fluid and the esterase activity of the inflammatory infiltrate cells. The shape analysis of “Mefpil” and “Sabfil plus” sutures strength curve indicates their degradation due to the automatic depolymerization mechanism. The rate of mechanical strength decrease in mice body of imported “Mefpil” and domestic “Sabfil plus” sutures are identical and amounts to 28 + 1.5 days. Histological analysis of muscle samples at the interface with the suture implant showed no pathological changes in the granulations in the case of “Mefpil” nor “Sabfil Plus”. Thus, based on the performed experiments, it can be concluded that the studied sutures “Mefpil” and “Sabfil plus” are identical in terms of destruction rate and histological pattern of tissue reaction at the border with the implant.

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Physiological Activity of Hindered Phenols with Pyridine Moiety

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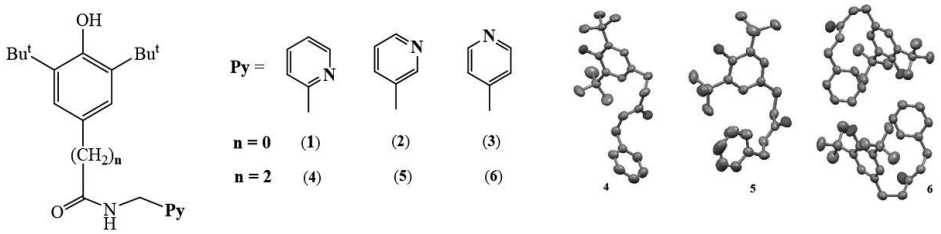
The search for antioxidants preventing oxidative stress and many pathological conditions is of a great importance. 2,6-Di-alkylphenols are widely used as vitamin E mimetics and stabilizers of organic substrates. Pyridine derivative Mexidol® is an inhibitor of free radical processes, membraneprotective, nootropic drug.

Presented work is aimed at the synthesis of hybrid compounds possessing both pyridine and hindered phenol groups and their water soluble hydrochlorides. Novel picolylamines with 2,6-di-*tert*-butyl moieties were synthesized and characterized. The structures of **4-6** were determined by X-ray analysis. Compound **6** appeared to be a homodimer in which two monomers are arranged in such a way that pyridine ring of one molecule is located opposite to the hindered phenol fragment of another one due to hydrogen bonds.



The activity of compounds as radical scavengers was evaluated in reactions with stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) and with $O_2^{\cdot-}$. On long time spans of about 24 h compounds were found to be slow antiradical scavengers with prolonged type of action and moderate inhibitors of lipoxygenase. The influence of compounds on rat liver homogenate lipid peroxidation was studied. The IC_{50} values in ^{t}BHP-induced lipid peroxidation varied in 0.5-11 μM range. The length of a linker and position of the nitrogen atom in pyridine cycle influenced the antioxidant activity of compounds. The results open up the perspectives for future application of these compounds as antioxidants and cytoprotectors.

Acknowledgement: The financial support of RFBR (18-03-00203, 17-03-01070) is gratefully acknowledged.

Design, synthesis and biological activity of 5-oxypyrimidine derivative

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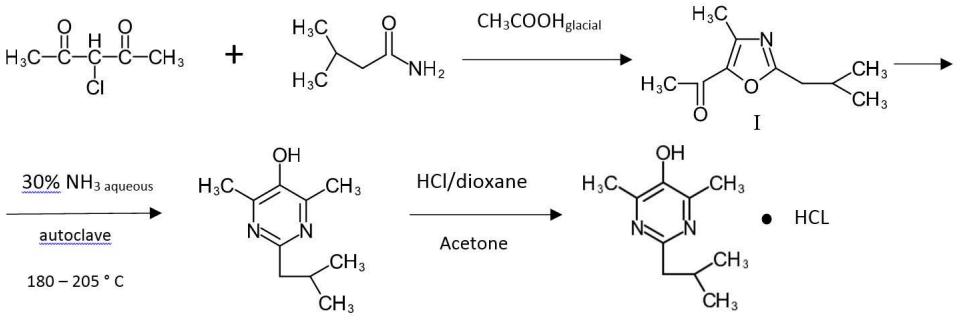
According to the World Health Organization, cancer is estimated to account for millions of deaths every year, and in the coming years, different cancer types are to become the top cause of death worldwide. As 20% of chronic inflammatory processes lead to cancer, and due to the fact that cancer is associated with different levels of immune homeostasis disorders, which depend on the age and genetic characteristics of patients, various directions of immuno-oncology are currently being actively developed. 5-oxypyrimidine derivatives, 2-isobutyl-4,6-dimethyl-5-oxypyrimidine (SNK-411) and its salt (SNK-578), demonstrate pronounced antitumor and antimetastatic activity on experimental solid tumor models, such as Lewis lung carcinoma, B-16 melanoma and cervical cancer. Synthesis ot the compounds (Figure 1) is carried out by the interaction of isovaleric acid amide with 3-chloro-2,4-pentanedione in glacial acetic acid to form oxazole.

Figure 1



The resulting oxazole is placed in an autoclave with a 10-fold excess of 30% aqueous ammonia solution and heated to 180-205°C for 24 hours, yielding SNK-411. Technical grade SNK-411 is dissolved in dry acetone. The solution is healed to 50°C, and hydrogen chloride is added dropwise to pH=3-4. The reaction mass is cooled, the precipitate is filtered, dried, refluxed in dry acetone, then allowed to cool. The precipitate is filtered and air dried; the resulting compound is SNK-578. ^{1}H NMR spectra and elemental analysis data agree with the proposed structures.

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Investigation of the stability of dried plasma spots samples containing antiviral agent camphecene under various storage conditions

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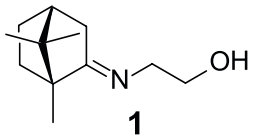

1

One of the urgent tasks of modern medicinal chemistry is the search for new physiologically active substances to create drugs, in particular, with antiviral properties. Earlier, our laboratory has developed a camphor derivative, camphecene **(1)**, which showed outstanding activity against the influenza virus A/H1N1 [1]. For pharmacokinetic studies, a method for quantitative determination of compound **1** in whole rat blood was developed, consisting in extraction of a dried blood spot and HPLC-MS/MS analysis of a sample [2]. The purpose of this work was to study the stability of compound **1** in dried plasma spots during storage under various conditions.

For the investigation, plasma samples were spiked with camphecene to obtain concentrations of 10, 25, 50, 100, 250, 500, 1000, 2500 and 5000 ng/ml. Aliquots of 20 µl plasma were spotted onto the Whatman Protein saver card 903® and air dried. One set of the calibration samples was processed and analyzed immediately after preparation, and linear calibration was built over whole concentration range. Analysis of the samples stored for 8 days at ambient temperature showed a decrease in the observed concentrations compared to baseline values, while camphecene concentrations in samples stored at -18°C were higher. As a conclusion, we suggest optimal storage conditions to be at +4° C: no changes in the concentrations of camphecene were observed in samples kept at this temperature. The obtained data on samples stability should be taken into account when developing methods for quantitative analysis of camphecene and collecting and keeping samples during clinical trials.

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Sorption of cholesterol on polymeric and hybrid organo-inorganic molecular imprinted sorbents

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Molecularly imprinted sorbents (MISs) are crosslinked polymers obtained in the presence of a target molecule as a template. After the template is removed by washing, cavities with molecular recognition sites that can bind selectively to the original template are stored in the polymer networks. MISs are highly selective to capture the target analyte as the antibody. But as artificial receptors, MISs are easy and rapid to prepare, very stable in harsh conditions, and allow the usage of a great variety of binding/eluting conditions without the risk of losing binding activity.

The aim of our study was to prepare cholesterol-imprinted sorbents (Ch-MISs) by the bulk and emulsion copolymerization. The bulk Ch-MISs were prepared by the Ch-imprinting in copolymerized hydroxyethyl methacrylate (HEMA) as an amphiphilic monomer and ethyleneglycol dimethacrylate (EGDMA) as a crosslinker in n-propanol. The Ch-imprinted core–shell particles were prepared by emulsion copolymerization. In this method, imprint-sites were formed in the HEMA-EGDMA copolymer layer at the surface of nanocomposites (NCs) of selen (Se) stabilzed with polyvinylpyrrolidone (PVP). An excess amount of Se/PVP-NCs in processes involving contact of comonomers and water, and then contact of water and butanol resulted in the formation of stabilized Pickering emulsions oil/water/oil.

In the process of plasma sorption in vitro, it was shown that the sorption selectivity increased on the Ch-imprinted sorbents if compare with the corresponding non-imprinted sorbents. At the same time, hydrodynamics of sorption on the hybrid sorbents were better than on the bulk sorbents due to more prominent amphiphilicity and narrow surface sorption layer in the hybrid networks.

The study was supported by the Russian Foundation for Basic Research (project no. 18-33-00710).

The influence of parabens on the development of pathology and human health

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According to the CAMP study, parabens cause an allergic reaction only in 1% of cases.

Parabens have low estrogenic activity and can initiate hormonal changes in organisms, cause the growth of tumors and adversely affect the reproductive system. So, scientists from the United States found that parabens can affect thyroid hormones during pregnancy.

A mixture of parabens can stimulate the formation of mitochondrial and cytosolic reactive oxygen species (ROS), which inhibits sperm motility and viability depending on the dose.

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Anthony F. Fransway, MD, Paulina J. Fransway, BS, Donald V. Belsito, MD, Erin M. Warshaw, MD, Denis Sasseville, MD, Joseph F. Fowler, Jr, MD, Joel G. DeKoven, MD, Melanie D. Pratt, MD, Howard I. Maibach, MD, James S. Taylor, MD, James G. Marks, MD, C. G. Toby Mathias, MD, Vincent A. DeLeo, MD, J. Matthew Zirwas, MD, Kathryn A. Zug, MD, Amber R. Atwater, MD, Jonathan Silverberg, MD, and Margo J. Reeder, MD // Parabens: Contact (Non) Allergen of the Year.- 2018.- American Contact Dermatitis Society- 5-7, 11-14

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Redox Properties and Antioxidant Activity of Diimine with Phenolic Fragment

Osipova A.[1], Polovinkina M.[1], Osipova V.[2], Berberova N.[1] and Kudryavtsev K.[3]

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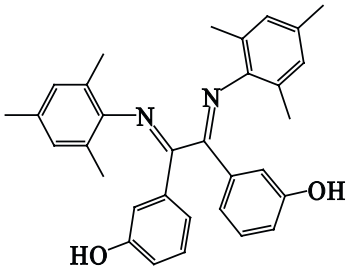
The redox properties and antioxidant activity of new aromatic diimine with phenolic fragment in comparison with BHT (2,6-di-*tert*-butyl-4-methylphenol) have been studied. The compound have been shown to react more readily in electron transfer processes (E_{pa}=1.21 V) as compared with BHT (E_{pa}=1.52 V). The interaction of compounds with an electrochemically generated $O_2^{\bullet-}$ in CH_2Cl_2 on a platinum electrode was studied.



The form of cyclic voltammograms of the electroreduction of oxygen were changed in the presence of BHT and diimine. The cathode peak increase of oxygen reduction, anode peaks decrease of oxygen oxidation and the new peak appeared in the anode region (E_{pa}= -0.1 V) were established. Decline anodic peak of current $O_2^{\bullet-}$ indicates that the compound react irreversibly with superoxide anion-radical. Based on the obtained voltammetric data, the rate constants of the interaction (k) of new aromatic diimine with phenolic fragment and BHT with $O_2^{\bullet-}$ were calculated [1], the values of these constants 361.0 and 8.0 L/mol·s. respectively.

The chelating of Fe^{2+} by compounds was estimated by the method of Dinis et al. [2]. In the presence of chelating agents, the formation of complex ferrozine with Fe^{2+} is disrupted with the result that the red colour of the complex is decreased. Measurement of colour reduction allows the estimation of the chelating activity of the existing chelator. The aromatic diimine with phenolic fragment and BHT demonstrated a low ability to chelate Fe^{2+}.

This work was supported by the Russian Foundation for Basic Research (grant № 17-03-00434).

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Hybrid Organo-Inorganic Composites on a Basis Chymotrypsin and Silver Nanoparticles

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The study of self-organization of hybrid organic-inorganic nanocomposites (NC), solution of stabilization problem, and obtaining of nanoparticles of predetermined size are the fundamental tasks of the modern chemistry of nanomaterials. The creation of such NC, in which every constituent provides different biological activity, at the present time is one of the most currently important trends of development of new therapeutic agents.

The increase in stability of enzymes reached during immobilization on polymers is most often accompanied by a significant decrease in their catalytic activity. This fact limits the wide application of immobilized enzymes in practical medicine. It was proved that a sharp increase in specific surface of nanoparticles (in comparison with known modificators) led to an increase in adsorption kinetics of substrate on enzyme active site. Furthermore, if the immobilization of enzymes is performed on nanoparticles which have their own biological activity, then the possibility of overlapping of different useful biological properties in one nanocomposite emerges.

In the report synthesis, spectral and dimensional properties of NC based on proteolytic enzyme chymotrypsin (CT) and silver (Ag) nanoparticles, and also their dimensional, enzymological, and bactericidal properties are considered. The synthesis of Ag with CT nanocomposites was performed during the reaction of nitrate sodium ($AgNO_3$) reduction by sodium borohydride ($NaBH_4$) in water medium at the presence of CT at atmospheric pressure and temperature of 20 °C:CT was simultaneously a stabilizer of silver nanoparticles in solution. Aggregatively stable nanocomposites were synthesized at a significant excess of $NaBH_4$ (12 fold increase in the stoichiometric ratio of the components.The proteolytic and bactericidal activities of the NC was determined in the aggregatively stable systems obtained in the absence of the mixture phase separation.

It was shown that proteolytic and bactericidal activity of Ag—CT nanocomposites, which are formed during the chemical reduction with sodium borohydride of Ag^+ cations in CT aqueous solutions, significantly depends on the ratio of concentrations of reagents and medium pH. The chemical reduction leads to the formation of stable nanocomposites which have polyfunctional biological activity in the presence of optimal amounts of CT which are effectively binding Ag^+ cations.

SOD-Protector Activity of New Heterocyclic Compounds

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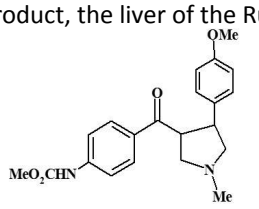
In this work the effect of compounds **1-3** on the rate of superoxide anion-radical ($O_2^{\bullet-}$) generation in the auto-oxidation reaction of adrenaline in an alkaline medium was investigated. The effect of the compounds on the SOD-protector activity of a biological product, the liver of the Russian sturgeon, was also studied.



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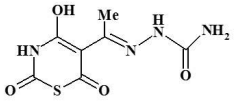

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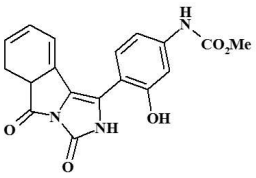

3

It was found that all compounds exhibited antiradical and SOD-protector activity (Fig.). Compounds **1-3** reduced the rate of adrenaline oxidation in alkaline bicarbonate buffer by 33%. Compound **3** showed the highest SOD-protector activity at the presence of the Russian sturgeon liver homogenate, reducing the $O_2^{\bullet-}$ generation rate by 60%, compound **2** slowed down the reaction rate by 66%. Compound **1** did not increase the SOD-protective activity of a biological product.

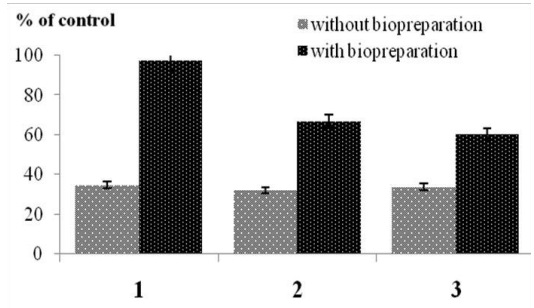

Fig. *The effect of compounds* **1-3** *on the rate of accumulation of the auto-oxidation products of adrenaline without a biopreparation and in the presence of the liver homogenate of Russian sturgeon ($C_{(1-3)}$=25 μM, λ=347 nm, $C_{adrenalin}$=5.46 mM). The rate of accumulation of the products of auto-oxidation of adrenaline in bicarbonate buffer in the presence of a biological product was taken as 100% (control).*

Thus, the antiradical activity of new heterocyclic compounds and their ability to increase the SOD-protector activity of the Russian sturgeon liver homogenate was discovered, which allows considering these compounds as potential inhibitor of lipid peroxidation.

This work was supported by the Russian Foundation for Basic Research (grant № 19-03-00006).

Search for new hepatoprotective agents based on available bile acids by *in silico* methods

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Today, there is an acute problem of finding new hepatoprotective agents due to the excess incidence of hepatobiliary system diseases of various origins. One of the hepatoprotective drugs classes exhibited on the pharmaceutical market is represented by medicines based on ursodeoxycholic acid (UDCA), which is one of the main human bile acids. This research is devoted to finding new hepatoprotective agents based on bile acids – UDCA, as well as cheaper and more available deoxycholic (DCA) and chenodeoxycholic (CDCA) acids. We have previously shown that the bioisosteric replacement of the native carboxyl group of DCA with the 1,2,4-oxadiazole enhances the anti-inflammatory, antioxidant, hepatoprotective, hypocholesterolemic and anti-mitotic properties in *in vivo* models compared to the original acid. We have created a virtual library of more than 100 derivatives of DCA, CDCA and UDCA containing the 1,2,4-oxazoazole substituted at position 3 instead of the native carboxyl group in the side chain, and various functional groups in the steroid backbone (native hydroxyl, carbonyl, ester and ether). All compounds from virtual library were analyzed by the molecular docking method. For the screening of new derivatives, possible molecular targets of anti-inflammatory and hepatoprotective effects were selected. Molecular docking of new studying bile acid derivatives was performed at the aromatase binding sites, Kelch domain Keap1, BTB domain Keap1, and IKK kinase. The leader compounds detected as a result of molecular docking were successfully synthesized and characterized for subsequent biological studies.

The reported research was funded by Russian Foundation for Basic Research and the government of the Novosibirsk Region of the Russian Federation, grant № 18-43-543031.

Development of method for quantitative analysis and pharmacokinetics study of a new anti-filoviral agent AS-358

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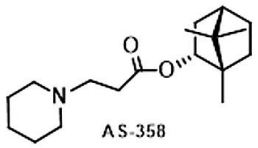

AS-358

Earlier, we have developed the agent AS-358 [1, 2], which showed high activity *in vitro* against Marburg and Ebola filoviruses. The next step in the study of the agent is an investigation of the activity of this compound using animal models, but such experiments are extremely expensive, since they can be carried out exclusively in BSL4 biolaboratories. To identify the dose and mode of administration of the compound it is necessary to study its pharmacokinetics profile.

We have developed and validated a method of quantitative determination of AS-358 in rat blood by HPLC-MS/MS using NaF as an additive to anticoagulant. The developed method was validated according to the following parameters: selectivity, LLOQ, calibration curve, accuracy and precision, carry-over, stability.

After oral administration of AS-358 to rats, the substance is absorbed after 20 minutes. After 1 h, the concentration of the substance in the blood drops, but then it increases, reaching the second maximum after 5 h (Fig. 1A). In addition to AS-358, its major metabolite, 3-(1-piperidinyl)-propanoic acid, was also detected in the blood, and its maximum concentration was achieved 2-2.5 hours after administration of the agent (Fig. 1B).

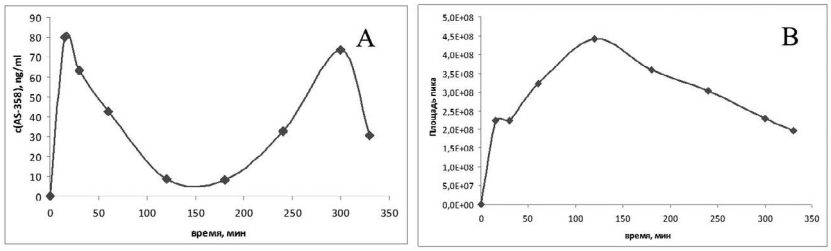

Fig. 1. *Concentration – time profiles of AS-358 (A) and 3-(1-piperidinyl)-propane acid (B).*

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Direct CH/CH coupling of tetramethylpiceatannol with 3,5-diphenyltriazine

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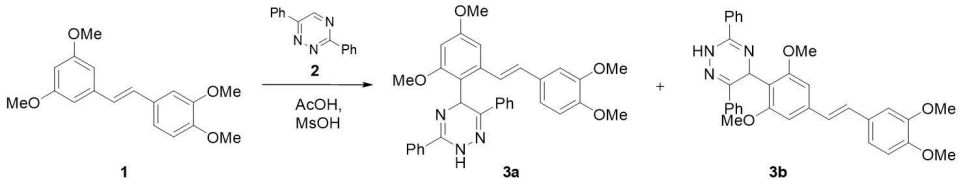
The past decade has witnessed tremendous natural derivatives phytoalexins, in particular resveratrol and piceatannol, primarily because of its promising activity against a collection of disease states including inflammation, heart disease, aging and cancer [1].

One of the possible directions in the modification of these stilbene derivatives is their coupling with aryl-1,2,4-triazines which may be useful in the treatment of Parkinson's disease [2], and also possess neuroprotective [3] and antitumor properties [4].

Herein, we present an example of CH/CH coupling of tetramethylpiceatannol **1** with 3,5-diphenyltriazine **2** using acid catalysis. Unfortunately, the reaction was not regioselective and a mixture of isomeric products **3a** and **3b** was formed in a 2: 1 ratio.



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Investigation of the properties of gadolinium oxide nanopowders to assess the possibility of delivery of biologically active substances

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The porosity of nanopowders obtained by the pulsed electron beam method was studied by the BET / BJH method. Also performed synchronous thermal analysis according to the DSC-TG method. The study was conducted for nanopowders with different concentrations of the SiO_2 dopant.

Based on the results of the BET and BJH analyzes, it can be concluded that the specific surface area and porosity of the samples are high. The analysis by the DSC-TG method confirms the porosity of the samples, and also indicates the hydrophilicity of the doped samples.

Table - Structural properties of Gd2O3 nanopowders obtained by the BET / BJH method

Sample	*S, m^2/g*	*Pore diameter, nm*	*Pore volume, cm^3/g*
Gd_2O_3-pure	163	18,9	0,64
Gd_2O_3-0,1%SiO_2	170	17,9	0,53
Gd_2O_3-1%SiO_2	177	21,9	0,96
Gd_2O_3-5%SiO_2	153	30,4	1,19

Thus, according to the results of the analysis performed, it can be concluded that the use of gadolinium oxide doped silica nanopros for the delivery of biologically active substances is promising.

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Gadolinium oxide nanopowders as the basis of X-ray contrast agents

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The possibility of using bioinert gadolinium oxide nanopowders obtained by the pulsed electron beam method as a radiopaque substance has been investigated. The study of radiopaque properties of nanopowders in Na-CMC gel was carried out on a medical X-ray unit, with exposure times: 160, 200, 250 ms. As reference standards, iodine-containing radiopaque drug Urografin was used, in a concentration of 38% and water. Further, using an MD100 microdensitometer, we measured the blackening density of the obtained X-ray images. To assess the absorption capacity, we calculated the ratios of the blackening density of the samples under study to the preparation “Urografin”.

Table - The ratio of the density of blackening of X-ray images of the studied samples to the drug “Urografin”

Sample	*Exposure time, ms*		
	160	200	250
Gd_2O_3-12,5%	1.02	1.08	1.11
Gd_2O_3-5%	1.22	1.38	1.71
Gd_2O_3-2,5%	1.33	1.58	1.88
H_2O	2.05	2.38	2.68

Thus, when the concentration of nanopowders is 12.5%, the results are close to the iodine-containing drug Urografin.

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Detection of related substances in LHS-1269

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A novel compound, an indolocarbazole derivative LHS-1269, has been synthesized at N.N. Blokhin National Medical Research Center of Oncology and it has demonstrated high antitumor potential. The aim of the study was to design a method for the control of related substances in the pharmaceutical substance LHS-1269.

The studies were performed with the liquid chromatograph Agilent 1200 equipped with diodematrix detector and chromatographic column «ZorbaxSB-C18» (3.0 mmx 150 mm, 3.5 µm). The results showed that optimal separation of LHS-1269 and possible related substances determined in the following chromatographic conditions: mobile phase is the mixture of acetonitrile – water–0.1% trifluoroacetic acid; elution gradient regimen is 10% to 95% of acetonitrile over 12.5 minutes; the flow rate of the mobile phase is 0.4 ml/min. Chromatogram registration time is 15 min. The detection was performed at the wavelengths of 220 nm, 285 nm and 315 nm. The separation results were similar in all samples at the given wavelengths. LHS-1269 retention time (RT) was 11 min. in the proposed conditions. Maximum number of impurities was detected at the wavelength of 315 nm: the chromatograms presented up to four peaks with RT bigger than that of LHS-1269, which spectra were identical to the main substance by signal location and relation of optical density at the D_{319}/D_{286}maximum. The impurity with the RT of 9.3min.has also an absorption spectrum similar to that of indolocarbazoles, though it is closer to LHS-1208 spectrum by the relation of D_{319}/D_{286} [1]. Thus, the studies demonstrated that all impurities detected in LHS-1269 include the indolocarbazole core and are related substances. Quantitative determination of any impurity was performed with the method of “internal normalization”. The results showed that in all studied substance samples the content of any single impurity does not exceed 1.5% and the sum is within the limits of 3%.

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Hemostatic properties of 3% carboxymethyl cellulose gel

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Carboxymethyl cellulose is widely used in the food and pharmaceutical industry as an emulsifier and stabilizer in suspensions and emulsions, as well as to adjust the consistency of substances of different fat content. This amorphous colorless substance has the properties of a weak, odorless and tasteless acid and is considered to be physiologically harmless. Carboxymethylcellulose promotes thickening of aqueous solutions, has stabilizing and binding properties and forms a transparent and durable film [1]. These physical and chemical properties of this compound suggest the possibility of using carboxymethylcellulose as a hemostatic agent.

In this regard, the aim of our study was to investigate hemostatic properties of 3% carboxymethyl cellulose gel. The blood of 35 male volunteers aged 20 years was used for the experiments. To study hemostatic activity of 3% carboxymethylcellulose gel, hematocrit was determined. Coagulation index was calculated in the control group using native blood and in the experimental group using gel at the beginning (CI T1) and at the end of coagulation (CI T2). Minimal values were associated with the most pronounced hemostatic effect. To determine the chemical interaction of gel and blood, a dry substance of the mixture of these substances was passed through infrared (IF) and ultraviolet (UV) spectrometers. The reliability of the results was evaluated using T-student's test.

In all cases, hematocrit increased due to the absorption of blood plasma by carboxymethyl cellulose. The decrease in plasma volume was on average 48% (0.3 ml). The addition of 0.1 ml of NaCl 0.9%, in contrast, led to an increase in the plasma volume by 17%, respectively, of the added value. The analysis of coagulograms showed that carboxymethyl cellulose gel reduced CI T1 by 24% (70,23±1,4) and CI T2 by 30% (65,23±2,3) relative to the control ($p<0,001$). After the IF and UV spectroscopy, no new spectrograms were detected, indicating no chemical interaction between carboxymethylcellulose and blood.

Thus, 3% carboxymethylcellulose gel has hemostatic properties, which are due to the absorption of the liquid part of the blood (plasma) by hydrophilic groups of carboxymethylcellulose and due to the matrix structure of the gel, detaining the formed elements of the blood and forming a lattice for the formation of a platelet clot.

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Synthesis, structure and physicochemical properties of hydrogels based on modified dextran for controlled delivery of prospidin

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The aim of the work was the regularities of the esterification of dextran in the orthophosphoric acid-urea system, to obtain hydrogels of dextran phosphates and the products of their interaction with prospidin, to create a hydrogel dosage form for local chemotherapy of malignant tumors.

The influence of the conditions of carrying out the esterification of dextran in the orthophosphoric acid – urea system on the chemical composition and the physicochemical properties of the reaction products has been established. It has been shown that the formation of monosubstituted phosphoric acid groups proceeds at a higher rate than in disubstituted phosphates, and the yield of gel fraction and the water-absorbing capacity of the modified dextran hydrogels are determined by the equilibrium between the cross-linking and degradation processes. Morphology, particle size, sensitivity to pH change and ionic strength of hydrogels have been determined. The parameters of the polymer network have been calculated: the average molecular weights between crosslinks, the crosslinking density and the pore size [1]. The values of ion-exchange and non-exchange components of sorption of antineoplastic substance of prospidin by hydrogels have been established [2]. It has been shown that the release of cytostatics from hydrogel forms consists of several stages, the amount of released substance is almost independent of the degree of crosslinking of the modified dextran and is determined by the content of functional groups in the polymer. In in vitro and in vivo experiments an increase in the antitumor activity and prolongation of the action of hydrogel forms of prospidin and cisplatin on the basis of dextran phosphates in comparison with injection forms of cytostatics has been demonstrated [3].

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Effect of lipid composition on the viscosity of liposomal dispersion

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The quality of the drug is evaluated by its compliance with the quality indicators and their normalized values specified in the corresponding normative documentation. Among the indicators that play an important role in the analysis of sterile dosage forms should include "Viscosity" [1]. Viscosity is important as the passport characteristics of the finished product and intermediate products. Since the viscosity of a multicomponent liquid depends on many parameters, it is an indirect and easy to determine the indicator of its purity and suitability for use [2].

The aim of the work was to assess the effect of lipid composition on the viscosity of liposomal dispersion. In the study, we obtained dispersions of liposomes from egg and soy lecithin (EL and SL, concentration 50 mg/ml) with different content of cholesterol (Chol) and distearoylphosphatidylcholine pegylated (PEG-DSPE).

As a result of the analysis of model compositions of liposomes obtained from both types of lecithin with molar ratios (v/v) lecithin/Chol in the range from 10:1 to 2:1, it was found that the viscosity of the dispersion has no direct dependence on the amount of Chol in the bilayer and averages from 9.4 to 13.2 MPa•s for liposomes from EL and from 10.2 to 14.6 MPa•s − from SL. For compositions with v/v lecithin/Chol 1:1, the viscosity value is at the level of 23.1−24.2 MPa•s. At the same time, a correlation between the viscosity index and the content of PEG-DSPE in the liposomal bilayer is observed. Thus, with an increase in the amount of PEG-DSPE in v/v lecithin/Chol in the range 1:0.002−1:0.030, there is a gradual increase in the viscosity of dispersions: for liposomes from EL − from 8.1 to 43.8 MPa•s, from SL − from 7.7 to 56.4 MPa•s.

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Synthesis and biological activity of N-α-(diethoxyphosphorylcyclopropyl-carbonyl)aminoacids

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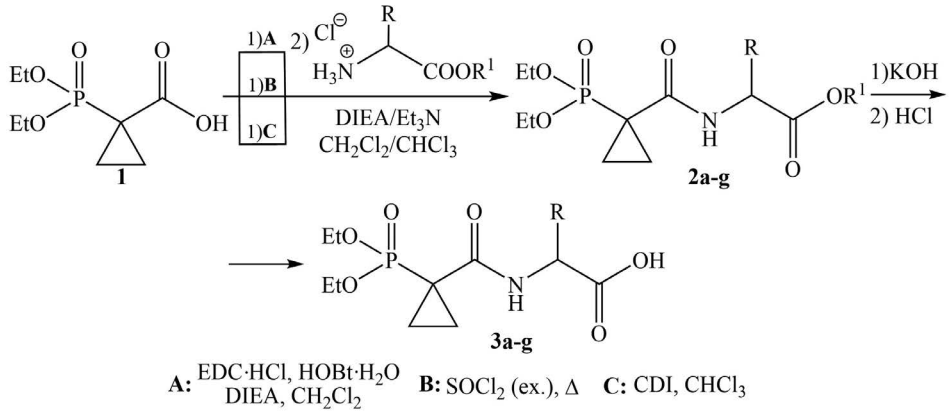
Phosphorus containing analogues of biogenic carboxylic acids and their derivatives show activity towards biological targets: phosphonoacetic acid (PAA) displays proved antiviral activity, and N-phosphonoacetyl-L-aspartate (PALA) shows cytostatic potency [1].

With a view to find new bioactive phosphonic acids derivatives, a number of esters of **N**-(α-diethoxyphosphorylcyclopropylcarbonyl)aminoacids **2a-g** ($R^1 = CH_3$, C_2H_5) were synthesized and then hydrolyzed to the relevant acids **3a-g**.



*Therefore, **N**-(α-diethoxyphosphorylcyclopropylcarbonyl)glycine (**3a**), -cysteine (**3b**), -methio-nine (**3c**), -aspartic acid (**3d**), -proline (**3e**), -phenylalanine (**3f**) and -γ-aminobutyric acid (**3g**) were obtained in good yields.*

Compounds **1**, **3a, 3c, 3d, 3g** were examined for a cytotoxicity against human cancer cell lines of mammary, skin and glioblastoma. In all cases there was no difference from control groups. Absence of outspoken activity may be caused by the presence of ester groups at the phosphorus component part [2]. The purposes of future research work are synthesis and examination of biological activity for acids obtained by the way of partial and total hydrolysis of phosphonic esters **3a-g**.

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Antioxidant and radical-scavenging activity screening for multiple pharmacological applications

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Reactive oxygen species are important elements of cell metabolism: they are involved in both physiological and pathophysiological processes associated with various diseases [1, 2]. To assess the antioxidant properties of compounds, chemical methods are used primarily to determine the radical-binding activity of the substance [3]. However, such methods have significant drawbacks, the main of which is the simplified nature of the in vitro reaction, which does not reflect the versatility of the processes occurring in a living organism. It leads to a large number of negative and positive false in results of testing. The main strategy in this case is to use several chemical methods for evaluating radical-binding activity, differing in the source of radicals and in the method of evaluation of the analytical signal, and to confirm it in test systems based on blood cells (for example, red blood cells) or microorganisms (for example, *E. coli*), reflecting the effect of substances on the integrity and function of the cell membrane and on the redox regulation of cellular activity, respectively [4].

The broad biological activity spectra of pyruvic acid and its derivatives, is largely attributed to their antioxidant properties and free radical scavenging ability [5]. We evaluated a set of the acyl-substituted methylpyruvates and their 2-arylaminoderivatives in two assays with AAPH and DPPH as free radical sources. In general, the IC50 values for the studied samples were approximately two orders of magnitude higher in the DPPH assay than in APPH assay, which reflects the difference in the concentrations of the substances used in the protocols for these test systems. The radical-scavenging activity in the AAPH test was superior for compounds containing electron-donating substituents in the acyl group and the N-aryl substituent. In the DPPH test, such dependence of activity from the properties of the substituent was not observed.

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Comparison of cytotoxic effect of platinum(IV) complexes with aminonitroxyl radicals on 2D and 3D cultures

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Introductions. 3D models of cell culture are closer than 2D models to the surrounding conditions of solid tumors *in vivo* and are broadly used for cytotoxicity and tumor chemoresistance screening. Platinum (II) complexes used in clinical practice have serious side effects and high toxicity, which limits their use and encourages further search for new active compounds containing platinum and having better tolerability. This work presents platinum (IV)-nitroxyl complexes containing residues of aliphatic carboxylic acids (acetic (VS118), butyric (VS146), valerian (VS131) as axial ligands, and Satraplatin (JM216) that are chemically more inert compared to platinum (II) complexes and hence have lower toxicity.

Purpose of research. Studying the cytotoxic effect of platinum (IV)-nitroxyl complexes on tumor spheroids compared to monolayer of cervical adenocarcinoma HeLa.

Materials and methods. Experiments were performed on HeLa cells grown both as monolayer (2D) and spheroids (3D). Spheroids were grown in agarose forms made with 3D Petri Dish 12-256 moldings (Microtissues, USA). Platinum (IV) complexes with the common structure of $Pt(IV)(NH_3)(R{\bullet}NH_2)Cl_2X_2$, where $R{\bullet}NH_2$ is a nitroxyl radical and X is an axial ligand, were applied to 2D and 3D cultures for 24 h. Cisplatin was used as a comparison drug. The viability of cells was evaluated with MTT-test.

Results. Tumor spheroids (3D) are more resistant to platinum (IV)-nitroxyl complexes than 2D culture. Various resistance degrees were demonstrated for compounds with different structures: for the complexes **VS118** and **VS131** the ratio between IC50 values for 3D culture and monolayer (the resistance index) were 1.4 and 1.7, and for **VS146** and **JM216** complexes the resistance indices were 2.0 and 2.5, respectively. Cisplatin exhibited the highest resistance index of 3.6. Our findings show that new compounds, aminonitroxyl complexes of platinum (IV), have lower resistance indices for tumor spheroids compared to cisplatin, which might be the result of their higher penetrating ability in 3D culture and it will explain their higher cytotoxity on spheroids.

BIOACTIVE MEMBRANE BASED ON POROUS GLASS FOR WATER TREATMENT

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At the present time, the most effective filters for water treatment are membrane filters of osmotic action. We have developed a disk membrane, which is a composite material, the matrix for which creation was high-silica glass (PG), obtained by etching in a solution of hydrochloric acid HCl of two-phase sodium borosilicate glass (ABS) of the original composition $7.6Na_2O{\cdot}20.4B_2O_3{\cdot}71.9SiO_2{\cdot}0.1Al_2O_3$ (mol.%) [1, 2]. Such high-silica PGs are chemically and biologically inert, have good longitudinal elasticity (Young's modulus = 23.9 GPa), and have a surface that can be easily modified. The obtained PG was modified by a silicon-molybdenum polyoxometallate, the bioactivity of which was previously studied against the gram-negative bacterium *Escherichia coli*, strain ML-35p; Gram-positive bacteria *Listeria monocytogenes*, strain EGD. Structural characteristics of the obtained composite: specific pore volume of 0.232 cm^3/g, total porosity of 34.4%, average pore diameter of 7.9 nm, specific surface area 156 m^2/g. The membrane fungicidal properties were studied in relation to the fungus of the genus Candida, Candida *albicans* species in the laboratory of bacteriology of the Russian Research Institute of Hematology and Transfusiology of the FMBA of Russia. The test data showed high bioactivity of the obtained composite, which was confirmed by the complete death of colonies of the fungus of the genus Candida, as well as by the presence of a zone of suppression of the growth of Candida *albicans* colonies on agar-agar (a zone of growth inhibition - 3 mm).

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The work was carried out within the framework of the research and development work of the IChS RAS (State registration № AAAA-A19-119022290087-1).

Antioxidant Activity Study Of The 2,6-Di-*Tert*-Butylphenols With Pyridine Moieties Using Cyclic Voltammetry

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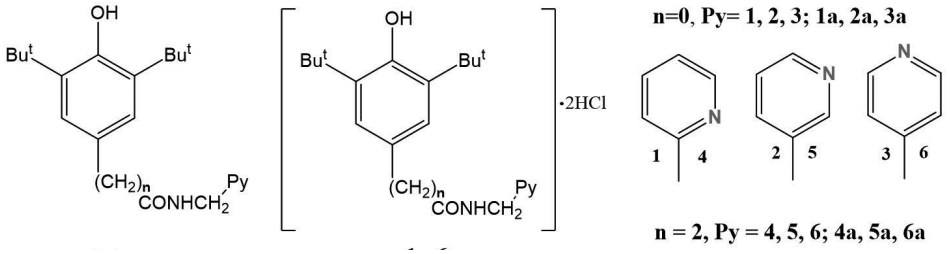
The search for novel antioxidant express assays as well as for polyfunctional antioxidants is still of great interest [1]. Novel ligands **1-6** and their hydrochlorides **1a-6a** containing N-donor pyridine rings and 2,6-di-*tert*-butylphenols fragments were synthesized and the electrochemical properties of these compounds were studied by cyclic voltammetry (CV) method. The feasible schemes of redox-transformations were proposed.



Antioxidant activity of **1-6** and **1a-6a** was measured using electrochemical method [2] based on the reaction with stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) rate measuring. It was shown that the redox behavior of phenols as well as antioxidant activity strongly depends on the structure of pendant in *para*-position and the length of hydrocarbonyl linker. The compounds **4-6** and hydrochlorides **1a-6a** demonstrated high activity. The correlation of redox-properties and antioxidant properties was demonstrated. The data of electrochemical study are in accordance with the results obtained spectrophotometrically in CUPRAC test thus proving the efficiency and reliability of approach proposed.

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Studying the effect of N^1,N^4,2,3-tetrahydroxysuccinamide on apoptosis in combination with platinum complexes

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Histone deacetylases (HDACs) are the family of enzymes playing an important role in the regulation of various cellular processes including cell proliferation and differentiation. Expression and activity of HDACs are increased in many tumors. Therefore, HDACs are considered as the promising molecular targets for tumor therapy. Great attention is paid to the class of hydroxamic acids, well-known HDAC inhibitors, for the development of anticancer therapy. It is known that HDAC inhibitors potentially improve the effectiveness of chemotherapy with anticancer drugs of different classes. Some representatives of this class, such as Vorinostat, Panobinostat and Belinostat, show high antitumor activity *in vitro* and *in vivo* and are approved for clinical use for the treatment of cutaneous T-cell lymphoma [1].

Here we describe a new hydroxamic derivative of tartaric acid, *N1,N4,2,3*-tetrahydroxysuccinamide (THSA), that contains two hydroxamate groups. The aim of the work was to study biological activity of THSA in cancer cell cultures *in vitro*: i) THSA effect on viability of cancer and normal cells, ii) THSA ability to affect toxicity of platinum complexes towards cancer cells; iii) influence of THSA on cell cycle and apoptosis of cancer cells.

Experiments were performed on cell lines M-HeLa (human cervical carcinoma), MCF-7 (human breast adenocarcinoma) and Vero (monkey African Green kidney). The viability of cells was evaluated with MTT staining. Cell cycle was studied with flow cytometry after propidium iodide DNA staining. Apoptic cell death was determined via detection of cleavage of proteins PARP and caspase-3 by Western-blotting.

THSA was shown to have higher toxicity towards tumor cells in comparison to normal cells. Normal cells were found to be more resistant to combinations of THSA and platinum complexes than tumor cells. THSA exhibited strong synergism with platinum complexes, and these combinations induced apoptosis in cancer cells.

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Functional microwave thermography of malignant neoplasms laboratory animals under chemotherapeutic effects

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In experimental and clinical oncology, the question of the sensitivity of malignant neoplasms of a number of nosoologies to the use of various therapeutic agents is very important, in particular, at the stage of neoadjuvant therapy. One of the indicators of therapeutic response is a change in the spectrum of temperature fluctuations in the area of tumor growth. The dynamics of changes in thermograms under the action of the following drugs was studied: aranose, ormustine, lysomustine, nitrulline. funds from this class [1]. Taking into account that the drug causes the death of melanoma cells by the mechanism of apoptosis, and not only the external, but also the mitochondrial signaling pathway is activated, there were grounds to believe that ormustin directly or indirectly changes the cell bioenergy and, therefore, this can be detected by functional microwave thermography [2]. Thermograms of a number of transplantable tumors were recorded: Lewis epidermoid carcinoma (LLC), RL-67 and B-16 melanoma in mice administered with ormustine at a therapeutic dose (125 mg/kg). The change in the nature of the thermograms of tumors under the action of ormustine was different for different types of tumors. The most significant response was observed for LLC's tumors - an increase in the trend of 1.5 ° C and an amplitude of thermal fluctuations of 3-4 times. For the RL-67 tumor, these figures were 0.4 ° C and 1.5 times, respectively. We received a weak response to changes in the thermogram on melanoma-B16, which may indicate that in the mechanism of action of ormustine on B-16 melanoma, the specific contribution directly from bioenergetic processes and / or microcirculatory processes is insignificant. Interesting thermograms of the LLC with the action of aranose. Stable, quasi-periodic fluctuations in the tumor growth zone, caused by the action of aranose, were observed. The study of their nature requires further research.

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New tamoxifen-based derivatives as potential anticancer agents

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Breast cancer (BC) is one of the most common types of cancer, along with lung cancer in 2018, 2.09 million new cases of morbidity and 607 thousand deaths caused by BC were recorded in the World according to WHO statistics [1].

Nowadays selective estrogen receptors modulators (SERMs) are effectively used in the treatment and diagnosis of hormone-dependent BC, they reduce the number of estrogen receptors in BC cells, which results in to a decrease in proliferation of atypical tissues and shrinking tumors.

Tamoxifen (TAM) is the first SERM which was obtained in the last century, and more than fifty years has been the standard for the treatment of BC. However, resistance to tamoxifen occurs after long-term treatment and it becomes ineffective. Moreover, the risk of developing pathology of the uterus among women taking tamoxifen is significantly increased [2].

So, Japanese scientists have synthesized 4-hydroxytamoxifen derivatives, which possess antagonistic properties in MCF-7 BC cells [3]. Twelve new pyrrolidinylethyloxy and piperidinyl ethoxy derivatives have been synthesized and showed the best antiproliferative activity [4]. A number of TAM derivatives are patented [5]. More recently, derivatives that are not inferior to TAM and fulvestrant have been obtained [6]. The TAM' triazolyl derivatives also showed high inhibitory activity against BC cells [7, 8]. At present, tamoxifen analogues have been obtained with an activity in 1000 times higher compared to TAM [9,10]. In addition, it has been demonstrated in recent papers that hybrids of other classes with tamoxifen have great potential [11, 12, 13].

The aim of further research is creating a fundamental new types of anticancer drugs – hybrids of steroid estrogens with tamoxifen, and studying their biological activity in preclinical studies.

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Radiopaque contrast nanosuspensions based of REE tantalates

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Tantalates YTaO4 yttrium and LaTaO4 lanthanum nanoparticles were received using radiation technologies from the targets produced from specified tantalates in microdimensional condition [1]. The received samples are powders with an average particles size of ~5 nm. According to the X-ray phase analysis and elektronografiya of nanopowders (NP) contain samples crystal and amorphous components. NPs placed in penicillinic vials with gel were photographed on the x-ray film. It is established that nanosuspension have more contrast, than the gel tantalic X-ray contrast means (RCM) containing substances on the basis of micropowders.

RKM contains tantalate NPs, and gel-forming organic component. The main problem which managed to be solved, consists in possibility of use as the agent for contrasting tantalates rare-earth elements in the form of nanoparticles with the average size of ~5 nm in a wide energy interval of the x-ray radiation, covering all range of energy of x-ray radiation for medical x-ray diagnostics. There were experimentally established interaction conditions of tantalates nanoparticles and the liquid dispersive environment in the form as an organic component. High sedimentative stability of means is apparently the consequence of generation on the surface of the adsorptive layer particles owing to sedimentation molecules of the organic component which existence complicates possibility of particles adhesion and consequently also formations of agregates.

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Разработка технологии создания противоопухолевых вакцин на модели мышиной меланомы

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Иммунотерапия – активно развивающееся направление лечения онкологических заболеваний. В последние годы в мире успешно проходят доклинические и клинические испытания противоопухолевые вакцины на основе неоантигенов для персонализированной терапии опухолей, создание которых стало возможным благодаря новым достижениям в области полноэкзомного секвенирования и биоинформатики. Предсказание наиболее иммуногенных для конкретного пациента неоантигенов позволяет создать пептидную вакцину, усиливающую иммуногенность опухоли.

Цель исследования – разработка технологии создания пептидной неоантигенной противоопухолевой вакцины на модели мышиной меланомы.

Материалы и методы. Меланому B16F10, полученную от мышей C57BL/6, секвенировали по протоколу Sequencing in Rapid Run Mode на платформе Illumina HiSeq2500. Полученные данные использовали для выявления мутаций и предсказания иммуногенных пептидов. Предсказанные пептиды синтезировали на пептидном синтезаторе ResPep SL (Производитель: Intavis, Germany) со стандартной конфигурацией (24-колоночный 10 микромолярный синтез). На мышах C57BL/6 оценивали эффект моделей вакцины, содержащих разное количество пептидов, по 100 мкг каждого пептида на мышь, в качестве адъюванта использовали Poly(I:C) по 50 мкг на 1 дозу. Исследуемые модели вакцины вводили подкожно, иммунизацию проводили в 0 и 7 день, на 12 день мышам перевивали опухоль меланому B16F10 в количестве 75 тыс. клеток на мышь, после чего еще дважды иммунизировали мышей на 14 и 21 день.

Результаты. Получены данные NGS транскриптомов и экзомов нормальной и опухолевой тканей мышей C57BL/6. На основании биоинформационного анализа полученных результатов было выбрано 44 иммуногенных пептида для синтеза и экспериментальной проверки. Модель вакцины, содержащая 18 пептидов и Poly(I:C) оказалась наиболее эффективной: торможение роста меланомы B16F10 составило 95%, у 50% животных опухоль не развилась в течение 90 дней наблюдения.

Заключение. Разработанная модель пептидной неоантигенной персонализированной противоопухолевой вакцины показала эффективность в профилактическом режиме у мышей с меланомой.

Исследование влияния состава липосомального препарата на проявление местного лечебного эффекта

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На основе масляных и водных экстрактов природных органоминеральных образований получены липосомальные структуры, которые представляют собой натуральные композиции [1-2]. Содержание основных компонентов в полученных препаратах варьируется в пределах 20-25% липофильной фазы, 64-74% гидрофильной фазы, вспомогательный компонент – 5-10% стабилизатор на фосфолипидной основе – 1%. Для изучения эффективности трансдермальной доставки биологически активных веществ различной природы с помощью полученных липосомальных частиц, использовали препараты с гидрофильным (водный комплекс гуминовых кислот) и липофильным (витамин Е) вспомогательными компонентами.

Исследования липосомальной препаративной формы на проявление местного лечебного и общебиологического эффектов проводили с помощью аппликации препаратов на кожной поверхности белых беспородных крыс-самцов, массой 200-300 г. Уровень липидов определяли методом тонкослойной хроматографии на пластинках «Sorbfil» размером 10 см на 15 см. Разделение нейтральных липидов проводили в системе растворителей гексан/этиловый эфир/этилацетат в соотношении 20:5:0,375, соответственно. Общие липиды определяли колориметрически [3].

Полученные результаты показали, что использование липосомальных препаративных форм на основе липидных и гидрофильных комплексов, извлеченных экстрагированием из природного органоминерального сырья и активных добавок, дает возможность получения препаратов широкого лечебно-косметического профиля с возможностью целенаправленного изменения их свойств, ускорению регенерации тканей, формированию антибактериальной активности, участию в процессах созревания, развития и старения клеток организма человека и животного.

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BIOCAD – одна из крупнейших биотехнологических международных инновационных компаний в России, объединившая научно-исследовательские центры мирового уровня, современное фармацевтическое и биотехнологическое производство, доклинические и клинические исследования, соответствующие международным стандартам.

Продуктовый портфель компании в настоящее время состоит из более чем из 50 лекарственных препаратов, 10 из которых – биологические. Более 40 продуктов находятся на разных стадиях разработки. Приоритетным направлением деятельности является разработка лекарств для лечения онкологических заболеваний.

Трастузумаб, бевацизумаб и ритуксимаб – наиболее востребованные системой здравоохранения препараты для терапии различных видов рака. С появлением в 2014 году биоаналогов компании BIOCAD уровень обеспеченности пациентов лекарственными средствами вырос в разы.

Начало новой эры в лечении онкологических заболеваний - иммуноонкология. BIOCAD имеет целый портфель препаратов для иммунотерапии злокачественных опухолей, находящихся на разных стадиях разработки:

- ингибиторы контрольных точек иммунного ответа, направленные на разные мишени сигнального пути программируемой клеточной гибели PD-1 (от англ. «Programmed cell Death pathway»): антиPD-1 и анти PD-L1

- ингибитор контрольных точек иммунного ответа анти-CTLA-4 (от англ. «cytotoxic T-lymphocyte associated protein 4»

- новые препараты, работающие на уровне рецепторов анти OX40 - вакцины, потенцирующие действие препаратов - ингибиторов контрольных точек иммунного ответа

- CAR-терапия и другие новейшие научные разработки

В компании **BIOCAD** работает более 2000 человек, из которых свыше 650 ученые и исследователи. Офисы и представительства компании расположены в США, Бразилии, Китае, Индии, Вьетнаме, ОАЭ, Финляндии, Республике Беларусь и других странах.

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КОМПАНИЯ НИКА-ПЕТРОТЭК в настоящее время активно развивается на рынке услуг по интенсификации нефтедобычи, имея в своем составе промышленные площадки по производству современных керамических расклинивателей (пропантов) и химреагентов, а также развитую научно-техническую базу.

Производство химических реагентов.

Технопарк «Камбарка», Удмуртская Республика

На базе технопарка «Камбарка», расположенного в Удмуртской Республике, налажено производство химических реагентов для интенсификации нефтедобычи, нефтепромысла, бурения и транспортировки нефтепродуктов. При производстве химических реагентов компания Ника-Петротэк проводит как внутренний контроль качества на всех этапах производства, так и независимую оценку для получения отраслевых сертификатов и разрешений.

Производство пропанта.

Площадка Семилукского огнеупорного завода, Воронежская область

Сегодня компания Ника-Петротэк владеет производственными мощностями Семилукского огнеупорного завода, на которых осуществляется выпуск пропанта, как основного элемента процесса гидроразрыва пласта. Крепкие традиции огнеупорного производства, а также сотрудничество с Российской Академией Наук, помноженные на модернизированное оборудование обеспечивают необходимую технологическую базу для производства пропанта – современного керамического расклинивателя. Высокотехнологичное оборудование позволяет выпускать широкую линейку пропантов для любых геологических условий интенсификации нефтедобычи, включая месторождения России, Ближнего Востока, Латинской Америки и стран Африки.

Научно-техническое подразделение. Екатеринбург

Для осуществления комплексного сервиса компания Ника-Петротэк имеет в своем составе научно- техническое подразделение, которое занимается сбором и анализом эксплуатационных характеристик фонда скважин для формирования уникального подхода к их обработкам. Наши специалисты способны разработать и реализовать технологический процесс интенсификации под геологические условия любой сложности. Наша команда регулярно участвует в отраслевых конференциях, включая ведущее международное сообщество инженеров-нефтяников SPE. Мы создали и запатентовали разработки химических систем и методики тестирования, включая оценку качества пропантов. Кроме того, в нашем распоряжении имеется обширная патентная база по всем группам продуктов. Научно-исследовательская деятельность Ника-Петротэк ведется совместно со специалистами Российской Академии Наук, при активном их участии.

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ООО “ФармаДиол”

В 2005-2007 годах нами была создана оригинальная технология разработки новых химических соединений, основанная на численных методах, органическом синтезе, измерении их биологической активности и тестировании на подопытных животных. С начала 2008г. мы занимаемся разработкой инновационного лекарства-антикоагулянта на собственные средства. В результате нескольких лет исследований сотрудниками ООО «ФармаДиол» был разработан и запатентован оригинальный класс веществ, ингибиторов Фактора Ха, наиболее перспективным из которых оказалось вещество Амидина гидрохлорид (условное название - DD217), обладающее уникальными характеристиками по активности (лучшее в мире по известным литературным данным). В 2014-2015 годах были успешно проведены доклинические исследования вещества DD217 с изучением общей и специфической токсичности, фармакокинетики и фармакологической активности препарата. В 2017 году было проведено клиническое исследование (КИ) 1 фазы на 24-х здоровых добровольцах и были получены данные о переносимости и безопасности использованных дозировок препарата, а также фармакокинетические и первичные фармакодинамические результаты, свидетельствующие об эффективности DD217. Оказалось, что DD217 имеет более «мягкое» действие по сравнению с другими препаратами данного класса и, потенциально, лучшую безопасность в классе оральных антикоагулянтов прямого действия (DOAC). В настоящее время проводится 2 фаза КИ препарата DD217 по показанию применения для предупреждения венозной тромбоэмболии после перенесенной операции эндопротезирования крупных суставов, что является стандартным начальным показанием при разработке антикоагулянта, относящегося к классу DOAC (т.н. «золотой стандарт»). При выборе такой стратегии перед DD217 откроются различные варианты для проведения КИ 3 фазы и, в случае подтверждения уникальности DD217 (на этапе проведения 2 фазы КИ) и обоснованности претензий на звание «лучшего в классе» препарата, будет возможна инициация процедуры регистрации препарата за рубежом.

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