RESEARCH STUDIES

Computer prediction of biological activity spectra of substituted and fused methylxanthines

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Abstract

Based on the chemical structure and mathematical algorithm of the Prediction of Activity Spectra for Substances software, computer prediction of possible types of biological activity of 121 substances substituted and fused derivatives of methylxanthine, has been done. The structure of compounds synthesized has been confirmed by modern physical and chemical methods: elemental analysis, UV-, IR-, HNMR- and mass-spectrometry, counter synthesis. The purity of the synthesized compounds has been controlled by thin layer chromatography. These substances are white crystalline powders, odorless, of a bitter taste, insoluble in water, soluble in dimethylformamide and dimethylsulfoxide and practically insoluble in alcohol, ether, chloroform, glacial acetic acid. Chemical structures of tested compounds have been introduced by a computer program "Java 6 Standart Edition" and posted on the official site of biological spectra prediction (http://195.178.207.233/PASSNew/predsct.php) in the form of the original multi-atomic orbital descriptors (Multilevel Neighborhoods of Atoms). The results of the computer prediction of the diuretic activity have been considered positive if the predicted activity probability of the substance Pa has been > 0.5. It has been specified that the newly synthesized derivatives of methylxanthine are able to demonstrate the following pharmacological activities: diuretic, neurotropic, antihypoxic, analgesic, anti-inflammatory and metabolic. By the method of computer prediction for substituted and fused methylxanthine derivatives it has been found that the highest diuretic activity is characteristic of the compound γ-6713 - pyrrolidine 1,7-dimethylimidazo[1,2-f]xanthinyl acetate. The substituted and fused derivatives of methylxanthine present a promising group of compounds for further synthesis and screening of new pharmacological substances with diuretic properties.

Key words: methylxanthine, PASS software, computer prediction, biological activity.

Introduction

Currently, in the developing world new drugs screening is based mainly on *in vitro* screening of a great number of chemical substances having a relatively small range of biological activity. The experience in medicinal chemistry and experimental pharmacology does not indicate absolutely specific actions for the known drugs: they all cause different pharmacological effects, some of which are used for the treatment of certain pathologies, and others cause side effects and toxicity. The full set of pharmacological effects that any substance has in different experimental conditions is the spectrum of its biological activity [1, 2].

The properties of the core structures are further optimized by the synthesis and study of a large number of their analogues. A lot of types of biological activity specific to substances remain unstudied and present side effects of the chosen direction of the research [3].

The computer prediction is based on the assertion that the biological activity of the substance is a function of its chemical structure. In medicinal chemistry while analyzing chemical structure of compounds with known biological activity, the fragments responsible for the pharmacological effects are isolated, and molecules of more active and less toxic analogues are synthesized then [4, 5].

The PASS (Prediction of Activity Spectra for Substances) software is based on the analysis of "structure-activity" dependence for the sample of compounds containing more than 45000 different biologically active substances (substances of known drugs and pharmacologically active compounds). The mathematical algorithm used in the PASS software is selected by targeted analysis and comparison of the efficiency of a large number of different methods. This algorithm provides a persistant type of "structure-activity" dependence and forecasts the results [6, 7].

The current version of the PASS software predicts 783 types of biological activity, based on its chemical structure formula, using a description of the chemical structure and mathematic algorithm of "structure-activity" dependence, including main and side pharmacological effects, mechanisms of action, mutagenicity, oncogenicity, teratogenicity and embryotoxicity [8, 9].

The results of the computer prediction are released in the form of a list of activities with calculated estimated probabilities of activity (Pa) and the absence of each kind of activity (Pi), with values from 0 to 1. This probability is calculated on the samples of active and inactive compounds and their sum is not equal to 1. Pa and Pi are interpreted as the evaluation measures of substances belonging to the class of active and inactive compounds. The higher the activity for a particular value of Pa is and the lower the Pi value is, the greater the

chance to detect this activity in the experiment is. If the analysis of the predicted list of activities is done for the compounds where Pa > 90%, we can make an assumption about 90% actually active compounds; for Pa > 80% - only 80% of active compounds. The smaller Pa is, the higher the risk of a negative result in the experiment is, however, the originality of such a structure is also higher [10, 11].

One of the directions of the research in this area is a chemical modification of known physiologically active xanthines. The aim of the focused synthesis is to obtain more active analogues with increased selectivity and fewer side effects. The structure optimization consists of increasing the main activity and reducing the side effects and toxicity [8, 12].

The variety of pharmacological activities of methylxanthine derivatives and their high reactivity causes the relevance of the synthesis of new structures. The derivatives of xanthine are involved in the many regulation processes that occur in the body. In this regard, the design of the new compounds based on them is promising.

The aim of this work has been to make a prediction of biological activity spectra of synthesized substituted and fused derivatives of methylxanthine using the PASS software.

Connection with scientific programs, plans, themes. The research is performed according to the basic scientific plans of Kharkov Academy of Animal Health, Kaunas Medical University, National University of Pharmacy of Zaporozhye and State Medical University of Zaporozhye and is a part of the research on the topic "Preparation of Xenobiotics, Their Physical and Chemical Properties, Biological Effects and the Effects on Metabolic Processes" (state registration № 0105U002815, ID code 15.00.02.01).

The aim of the study has been to make a computer prediction of the biological activity of substituted and fused derivatives of methylxanthine and establish the "structure-activity" dependence.

Material and methods

The objects of the study have been 121 compounds of substituted and fused methylxanthine derivatives, synthesized by the Biological Chemistry Department, Zaporozhye State Medical University, under the guidance of the Doctor of Pharmacy, Professor Romanenko N.I.

The structure of the synthesized compounds has been confirmed by the modern physical and chemical methods: elemental analysis, UV-, IR-, HNMR- and mass-spectrometry, counter synthesis; the purity of the synthesized compounds has been controlled by thin layer chromatography. These substances are white crystalline powders, odorless, of a bitter taste, insoluble in water, soluble in dimethylformamide and dimethylsulfoxide and practically insoluble in alcohol, ether, chloroform, glacial acetic acid.

The chemical structures of the tested compounds have been introduced by a computer program "Java 6 Standart Edition" and posted on the official site (http://195.178.207.233/PASSNew/predsct.php) of biological spectra prediction in the form of the original multi-atomic orbital descriptors (Multi-level Neighborhoods of Atoms). The results of the computer prediction of diuretic activity have been considered positive if the predicted activity probability of the substance Pa has been > 0.5.

Results and discussion

Based on the chemical structure and mathematical algorithm of the PASS software, the computer prediction of possible types of biological activity of 121 substances of substituted and fused derivatives of methylxanthine has been made. The prediction results are presented in table 1 in the form of a list of possible types of activity with calculated estimates of probable activity Pa and the probable inactivity Pi, with values from 0 to 1. This algorithm has ensured obtaining the sustainable results based on the "structure-activity" dependence.

The analysis of the computer prediction results has showed that the studied derivatives of substituted and fused methylxanthines have a wide range of biological activity, with Pa > 0.7 and Pi < 0.4 in most of the cases, indicating broad prognostic possibilities of pharmacological activity in the absence of close chemical analogues. At the same time, the variety of possible pharmacological activity implies significant non-desirable side effects on the human body (tab. 1).

The results of computer prediction have showed that substituted and fused derivatives of methylxanthines can, probably, show an increased urinary kidney function. So, for the first synthesized substances γ-6237, γ-4704, γ-5847, γ-5856, γ-5857, γ-5869, γ-5871, γ-7434, γ-7437F, γ-7435, γ-7440, γ-7441, γ-7443, γ-7444, γ-7992, γ-6492, γ-6504, γ-6520, γ-4237, γ-4249B, γ-6387, γ-6713, γ-6728, γ- 7964, γ-7965, γ-7966, γ-7967, γ-7968 the activity probability Pa has ranged from 0.413 to 0.815. The presence of expressed increased urinary renal function has also been predicted for ammonium salts of 1,3,7-trimethylimidazo[1,2-f]xanthinyl-8-butanoate. The highest factor of their diuretic activity (Pa = 0.815) has been predicted for the compound γ-6713 – ammonium salt of pyrrolidine 1,7-dimethylimidazo[1,2-f]xanthinyl acetate. The substitution in the 1st position of the molecule of 1,7-dimethylimidazo[1,2-f]xanthinyl acetate of hydrogen atom by the methyl radical (γ-6728) reduces the probability of diuretic activity (Pa = 0.802). The replacing of pyrrolidine ammonium salt (γ-6713) for morpholine (γ-7963), for piperidine (γ-7964), for β-hydroxyethylammonium (γ-7966), N, N-di(β-hydroxyethyl)ammonium (γ-7967), diethylammonium (γ-7968) leads to the presence of the diuretic activity. The blockade of A_1 receptors enhances diuresis and natriuresis due to the inhibition of proximal tubular reabsorption of sodium ions. The stimulation of urinary kidney function is also associated with the decreased reabsorption of sodium in renal tubules of nephrons, accompanied by a reduction of the reabsorption of water and the increased urination. Most of these substances can be used as regulators of water and electrolyte balance in the body of the patient.

The peripheral vasodilator activity (Pa = 0,413-0,664) has also been predicted for the tested compounds, indicating the feasibility of using these substances to enhance distal venules

Table 1

Analysis of the possible types of pharmacological activity for substituted and fused derivatives of methylxanthine

№	Possible activity, compounds code	Pa	Pi
1	Analeptic: γ-6236, γ-6574, γ-3427, γ-3428, γ-3947, γ-3948, γ-5847, γ-5856, γ-5857, γ-7434, γ-7435, γ-7437, γ-7440, γ-7441, γ-7443, γ-7444	0,547-0,891	0,003-0,161
2	Anxyolitic: γ-4832, γ-3842, γ-3952, γ-4238, γ-6236, γ-6237, γ-6491, γ-6492, γ-6503, γ-6520, γ-6540, γ-3825, γ-4237, γ-6369	0,252-0,358	0,051-0,091
5	Adenosine A_1 receptor antagonist: γ-6622, γ-4250, γ-3947, γ-3960, γ-4705, γ-4706, γ-4707, γ-5847, γ-5856, γ-5857, γ-5868, γ-5492, γ-4237, γ-4249Б, γ-6369	0,194-0,293	0,007-0,038
6	Adenosine receptors atagonist: γ-4250, γ-5132, γ-3947, γ-3960, γ-6491, γ-6492, γ-6538, γ-6539, γ-3825, γ-4237, γ-4249Б, γ-6369, γ-6713, γ-6728	0,328-0,522	0,006-0,012
7	Adenosine A_2 receptor antagonist: γ-4250, γ-3947, γ-3960, γ-6491, γ-6492, γ-6538, γ-6539, γ-6540, γ-4237, γ-4249Б, γ-6369, γ-6728	0,265-0,403	0,007-0,010
8	Alpha adreoreceptor antagonist: γ-4832, γ-3952, γ-4238, γ-4543, γ-3961, γ-4530, γ-4704, γ-5871, γ-7992, γ-7993, γ-7997, γ-7998, γ-7999, γ-8090, γ-6540	0,080-0,209	0,029-0,060
12	Interleukin-8 antagonist: γ-4853, γ-5132, γ-3427, γ-3428, γ-3947, γ-3948, γ-3960, γ-4705, γ-4706, γ-4707, γ-7839, γ-7840, γ-7841, γ-7842, γ-7843, γ-7845, γ-7846, γ-8055, γ-8057, γ-7999	0,142-0,238	0,008-0,026
15	Antiallergic: γ-4706, γ-7444, γ-7843, γ-8057, γ-7887, γ-7939, γ-7945, γ-7967, γ-7968	0,302-0,727	0,007-0,094
16	Antihistamine: γ-3428, γ-3952, γ-6236, γ-6237, γ-3427, γ-3428, γ-3947, γ-4530, γ-4704, γ-4705, γ-4706, γ-4707, γ-5871, γ-7434, γ-7435	0,172-0,343	0,012-0,112
17	Antidepressant: γ-4832, γ-4238, γ-4543, γ-6236, γ-6237, γ-4530, γ-4704, γ-5863, γ-5871	0,218-0,263	0,097-0,508
21	Antihypertensive: γ-5847, γ-5964, γ-5968, γ-7434, γ-7435, γ-7437Ф, γ-7440, γ-7441, γ-7443, γ-7444	0,273-0,350	0,058-0,094
22	Anti-ischemic, cerebral: γ-4832, γ-4835, γ-4853, γ-6622, γ-3842, γ-3952, γ-4237A, γ-4238, γ-4249A, γ-4543, γ-6236, γ-6237, γ-6574, γ-6575, γ-6560, γ-3427, γ-3428, γ-3947, γ-4530, γ-4704, γ-4705, γ-4707, γ-5847, γ-5871, γ-7434, γ-7435, γ-7437Ф, γ-7440, γ-7441, γ-7443, γ-7444, γ-7994, γ-8090, γ-7940	0,565-0,937	0,004-0,085
24	Sodium channel blocker: γ-4832, γ-4835, γ-6622, γ-3842, γ-3952, γ-4237A, γ-4232, γ-4249A, γ-4543, γ-6575, γ-6560	0,150-0,251	0,052-0,084
26	Bronchodilator: γ-4835, γ-4853, γ-3842, γ-5132, γ-4704, γ-4706, γ-5847, γ-7939	0,140-0,237	0,048-0,097
27	Vasodilator: γ-6236, γ-6237, γ-3428, γ-3947, γ-4704, γ-4707, γ-5847, γ-5871, γ-7434, γ-7435, γ-7437Ф, γ-7440, γ-7441, γ-7443, γ-7444, γ-7992, γ-7993, γ-7994, γ-7995, γ-7997, γ-7998, γ-7999, γ-8090	0,412-0,685	0,009-0,212
28	Vasodilator, coronary: γ-3428, γ-3947, γ-4705, γ-5847, γ-5871, γ-7434, γ-7435, γ-7437Ф, γ-7440, γ-7441, γ-7443, γ-7444, γ-7940	0,413-0,664	0,010-0,112
31	Diuretic: γ-6237, γ-4704, γ-5847, γ-5856, γ-5857, γ-5869, γ-5871, γ-7434, γ-7435, γ-7437Ф, γ-7440, γ-7441, γ-7443, γ-7444, γ-7992, γ-6492, γ-6504, γ-6520, γ-4237, γ-4249Б, γ-6387, γ-6713, γ-6728, γ-7964, γ-7965, γ-7966, γ-7967, γ-7968	0,413-0,815	0,003-0,112
32	Breathing analeptic: γ-6236, γ-6237, γ-6574, γ-3427, γ-3428, γ-3947, γ-3948, γ-4706, γ-5847, γ-5856, γ-5857, γ-5968, γ-7434, γ-7435, γ-7437Ф, γ-7440, γ-7443	0,403-0,853	0,005-0,062
33	Exciting activity: γ-4835, γ-6622, γ-3952, γ-4249A, γ-6236, γ-3427, γ-3428, γ-3947, γ-4705, γ-5847, γ-5857, γ-5871, γ-5968, γ-7434, γ-7435, γ-7437Ф, γ-7440, γ-7441, γ-7443, γ-7444, γ-7846, γ-7992, γ-7994, γ-7993, γ-7995, γ-7997, γ-7998, γ-7999, γ-8090, γ-7939, γ-7940	0,513-0,878	0,008-0,238

	Immunomodulatory: γ-8107, γ-7841, γ-7845, γ-7940, γ-4237A, γ-3428, γ-3947, γ-3960, γ-4705, γ-7440, γ-7443, γ-8104, γ-8106, γ-7934, γ-7843, γ-7844, γ-8055, γ-7887, γ-7946, γ-6506, γ-4249Б	0,501-0,724	0,003-0,025
	Immunopotentiating: γ-3947, γ-3948, γ-4237A, γ-4249A, γ-4705, γ-4707, γ-6622, γ-7440, γ-7443, γ-7841, γ-7843, γ-7844, γ-7845, γ-7846, γ-7939, γ-7940, γ-8055, γ-8057	0,452-0,765	0,010-0,072
	cAMP phosphodiesterase inhibitor: γ-3952, γ-4237A, γ-4543, γ-6236, γ-6237, γ-3427, γ-3428, γ-3947, γ-3948, γ-4530, γ-4704, γ-4705, γ-4707, γ-5847, γ-5871, γ-5964, γ-5968, γ-7434, γ-7435, γ-7437Ф, γ-7440, γ-7443, γ-7992, γ-7993, γ-7997, γ-7998, γ-7999, γ-8083, γ-8032, γ-8050, γ-8051, γ-8090, γ-4237, γ-6728	0,607-0,875	0,013-0,058
34	Phosphodiesterase inhibitor: γ-4832, γ-3842, γ-3952, γ-4238, γ-4543, γ-5132, γ-6236, γ-6237, γ-6560, γ-6562, γ-3960, γ-4530, γ-4706, γ-5847, γ-8033, γ-8090, γ-7939, γ-7945, γ-6539, γ-4237, γ-7968	0,150-0,403	0,004-0,038
35	Neurogenic pain treatment: γ-4832, γ-6622, γ-3842, γ-3952, γ-4249A, γ-4237A, γ-4238, γ-4543, γ-5132, γ-6574, γ-6575, γ-6560, γ-6562, γ-3427, γ-3428, γ-3947, γ-3948, γ-3960, γ-3961, γ-4530, γ-4704, γ-4705, γ-4706, γ-4707, γ-5871, γ-7435, γ-7992, γ-7994, γ-7995, γ-7997, γ-7998, γ-7999	0,306-0,508	0,008-0,056
38	Nootropic: γ-4832, γ-4853, γ-6622, γ-3842, γ-3952, γ-4237A, γ-4238, γ-4249A, γ-4543, γ-6236, γ-6237, γ-6560, γ-6562, γ-4530, γ-5871, γ-7992, γ-7993, γ-7994, γ-7995, γ-7997, γ-7998, γ-7999, γ-8024, γ-8026, γ-8027, γ-8028, γ-8029, γ-8030, γ-8031, γ-8032, γ-8051, γ-8054, γ-8090, γ-4249Б	0,504-0,782	0,022-0,306
39	Peripheral vasodilator: γ-6236, γ-6237, γ-4530, γ-5847, γ-5871, γ-5964, γ-7434, γ-7435, γ-7440, γ-7437, γ-7441, γ-7443, γ-7444, γ-7992, γ-7993, γ-8090, γ-7966, γ-7967, γ-7968	0,600-0,836	0,004-0,222
40	Psychogenic: γ-4853, γ-6622, γ-3842, γ-3952, γ-4237A, γ-4249A, γ-6236, γ-6237, γ-6574, γ-6560, γ-3427, γ-3428, γ-3947, γ-3948, γ-4704, γ-4705, γ-4707, γ-5847, γ-5856, γ-5857, γ-5865, γ-5868, γ-7434, γ-7435, γ-7440, γ-7441, γ-7443, γ-7444, γ-8107, γ-7998, γ-7999, γ-8090, γ-3825, γ-4237, γ-6387, γ-6728	0,503-0,680	0,019-0,261
41	Anti-asthmatic: γ-5132, γ-6237, γ-3960, γ-4706, γ-5847, γ-7441, γ-7444, γ-7843, γ-8057, γ-7887, γ-7939, γ-7940, γ-7945, γ-4237, γ-7969, γ-7968	0,339-0,779	0,070-0,186
43	Antitumor: γ-4835, γ-3842, γ-3952, γ-4237A, γ-4249A, γ-4543, γ-6575, γ-6560, γ-3427, γ-3947, γ-3948, γ-3960, γ-4530, γ-4704, γ-4705, γ-4706, γ-3947, γ-7435, γ-7434, γ-7937, γ-7939, γ-3825	0,200-0,269	0,041-0,090
44	Anti-spasmatic, papaverine-like activity: γ-4835, γ-6236, γ-6574, γ-3427, γ-3428, γ-3947, γ-3948, γ-3960, γ-3961, γ-4530, γ-4704, γ-4705, γ-4706, γ-4707, γ-5856, γ-5857, γ-5868, γ-7434, γ-7435, γ-7444, γ-7846, γ-7939, γ-7943	0,340-0,696	0,004-0,041

and areterioles. The reduced venous flow to the heart and systemic vascular resistance may contribute to reducing pre- and postload on the myocardium, improve the functional activity of the heart, reducing myocardial oxygen necessity, reduce blood pressure and dilate blood vessels of muscles and kidneys. Antihypertensive (Pa = 0,273-0,350), antispastic, papaverine-like activities (Pa = 0,231-0,389), anti-ischemic and cerebral (Pa=0,565-0,937) activity respectively for compounds γ-5847, γ-5964, γ-5968, γ-7434, γ-7435, γ-7437F, γ-7440, γ-7441, γ-7443, γ-7444 have been predicted. For substituted and fused derivatives of methylxanthine the bronchodilatory activity (Pa = 0,140-0,237) has also been predicted.

For the tested substances γ-4832, γ-3952, γ-4238, γ-4543, γ-3961, γ-4530, γ-4704, γ-5871, γ-7992, γ-7993, γ-7997, γ-7998, γ-7999, γ-8090, γ-6540 the alpha adrenoreceptor inhibitory activity has been predicted, the Pa has ranged from 0.080 to 0.209 and the activity of vascular and breathing centers is increased (Pa = 0.513-0.878). For most compounds – γ-4832, γ-6622, γ-3842, γ-3952, γ-4249, γ-4237, γ-4238, γ-4543, γ-5132, γ-6574, γ-6575, γ-6560, γ-6562, γ-3427, γ-3428, γ-3947, γ-3948, γ-3960, γ-3961, γ-4530, γ-4704, γ- 4705, γ-4706, γ-4707, γ-5871, γ-7435, γ-7992, γ-7994, γ-7995, γ-7997, γ-7998, γ-7999 – the feasibility of their use for the treatment of neurogenic pain has been predicted (Pa = 0.306-0.508).

The tested compounds γ-4853, γ-6622, γ-3842, γ-3952, γ-4237, γ-4249, γ-6236, γ-6237, γ-6574, γ-6560, γ-3427, γ-3428, γ-3947, γ-3948, γ-4704, γ-4705, γ-4707, γ-5847, γ-5856, γ-5857, γ-5865, γ-5868, γ-7434, γ-7435, γ-7440, γ-7441, γ-7443, γ-7444,

γ-8107, γ-7998, γ-7999, γ-8090, γ-3825, γ-4237, γ-6387, γ-6728 (Pa = 0.503-0.680) can, probably, show a psychogenic influence on the function of the cerebral cortex and activate the mental and physical activities of the human body; they reduce reflex response time for stimulation of afferent receptors; they possess anxiolytic activity (Pa = 0.252-0.358), cause acceleration and increased respiratory excursions (Pa = 0.403-0.853); they expand bronchial tubes and act as bronchodilators (Pa = 0.140-0.237).

According to the computer prediction data, the most derivatives of substituted and fused methylxanthines have showed antagonism to interleukin-8 (Pa = 0.142-0.238), which indicates the presence of anti-inflammatory and analgesic activity of these substances.

Most derivatives of substituted and fused methylxanthines inhibit the activity of phosphodiesterase (Pa = 0.150-0.403), which leads to the cAMP and cGMP accumulation. The antihistamine activity (Pa = 0.172-0.343) has also been predicted for the tested substances, as these substances can be used as antiallergic agents (Pa = 0.302-0.727) in various pathological conditions and allergic diseases.

The presence of antitumor activity within the range of Pa = 0.340-0.696 has been predicted for the following compounds: γ-4835, γ-3842, γ-3952, γ-4237, γ-4249, γ-4543, γ-6575, γ-6560, γ-3427, γ-3947, γ-3948, γ-3960, γ-4530, γ-4704, γ-4705, γ-4706, γ-3947, γ-7435, γ-7434, γ-7937, γ-7939, γ-3825. They may possess an antimetabolic action and can be used to fight cancer diseases.

Thus, taking into account the results of the computer prediction of biological activity spectra of substituted and fused methylxanthine derivatives using the PASS software, we have planned a pharmacological screening for the following types of pharmacological activities: diuretic, neurotropic, antihypoxic, analgesic, anti-inflammatory and metabolic.

Conclusions

1. By the computer prediction for substituted and fused methylxanthine derivatives it has been found that the highest diuretic activity (Pa = 0.815) belongs to the compound γ-6713 – pyrrolidine 1,7-dimethylimidazo[1,2-f]xanthinyl acetate.

2. The derivatives of substituted and fused methylxanthines present a promising group of compounds for the further synthesis and screening of new pharmacological biologically active substances with diuretic properties.

References

1. Martynova NB, Filimonov DA, Poroykov VV. Komputernoe prognozirovanie spektra biologicheskoy aktivnosti nizkomolekulyarnykh peptidov i peptidomimetikov [Computer prognostication of the spectrum of biological activity of low-molecular peptids and peptids mimetiks]. *Bioorganicheskaya khimiya* [Bioorganic chemistry], 2000;26(5):330-339.
2. Anzali S. Discriminating between drugs and nondrugs by Prediction of Activity Spectra for Substances (PASS). *J. Med. Chem.* 2001;4(15):2432-2437.
3. Filimonov DA, Poroykov VV. Srednyaya tochnost prognoza pri otsenke farmakologicheskikh effektov ryada biologicheski aktivnykh veshchestv s pomoschyu sistemy PASS [An average accuracy of the prognosis at the estimation of pharmacological effects of a number of bioactive substances by means of the system PASS]. *Voprosy med. Khimii [The issues of medical chemistry].* 1997;43:41-57.
4. Glouizova TA, Filimonov DA, Lagutin AA, et al. Testirovanie komputernoy sistemy dlya predskazaniya biologicheskoy aktivnosti PASS na vyborke novykh khimicheskikh soedineniy [Testing of the computer system for the prediction of biological activity of PASS on the selection of new compounds]. *Khim.-Pharm. zhurnal.* 1998;32(12):32-39.
5. Poroykov VV, Filimonov DA. Instruktsiya dlya chlenov assotsiatsii polzovateley PASS po popolneniyu obuchayushchey vyborki [Instruction for the members of the association of PASS users on the completion of the teaching selection materials]. M., 2002;40.
6. Lagutin AA, Filimonov DA, Poroykov VV. Komputerny poisk potentsialnykh antigipertenzivnykh soedineniy kombinirovannogo deystviya [Computer search of potential antihypertension compounds of the combined action]. *Khim.-Pharm. zhurnal.* 2001;35(7):28-34.
7. Filimonov D. Chemical similarity assessment through multilevel neighborhoods of atoms: definition and comparison with the other descriptors. *J. Chem. Inf. Comput. Sci.* 2009;4:666-670.
8. Poroykov VV. Kompyuternoe predskazanie biologicheskoy aktivnosti veshchestv: predely vozmozhnogo [Computer prediction of the biological activity of substances: limits of the possible]. *Khimiya v Rossii* [*Chemistry in Russia*]. 1999;2:8-12.
9. Poroykov VV. Top 200 medicines: can new actions be discovered through computer-aided prediction? *SAR and QSAR in Environmental Research*. 2004;12(4):327-344.
10. Poroykov VV. Komputernyy prognoz biologicheskoy aktivnosti khimicheskikh soedineniy kak osnova dlya poiska i optimizatsii bazovykh struktur novykh lekarstv. V sb. Azotistye geterostykly i alkaloidy [Computer prognosis of the biological activity of chemical compounds as a basis for a search and optimization of basic structures of new medications. In the compendium Nitrogenous Heterocycles and Alkaloids]. Moskva: Iridium-press, 2001;1:123-129.
11. Poroykov VV. Computer-aided prediction of biological activity spectra. Application for finding and optimization of new leads. In: Rational Approaches to Drug Design, Eds. H.-D. Holtje, W. Sippl. Barcelona: Prous Science, 2005;403-407.
12. Filimonov DA, Poroykov VV. Komputernaya otsenka svoystv khimicheskikh soedineniy s pomoshchyu sistemy PASS [Computer estimation of the properties of chemical compounds by means of the system PASS]. *Khim.-Pharm. zhurnal.* 1998;32:32-39.