NEW PHARMACOPHORIC GROUPING IN SYNTHESIS OF CYSTOSTATIC MEDICINES

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Introduction. It is known that every third man and every fourth woman living on the Earth during a lifetime get cancer (so, in 2017, more than 17 million were sick and 8 million people died, and in Russia every day, only according to official statistics, from this 1000 people die). In connection with this, the problem of these diseases is the survival of mankind as a whole on the planet. Purpose of the study. Existing drugs for today have different pharmacophore groups, one third of them are alkylating. They are united by the fact that they are extremely toxic, many are carcinogenic and terrigenous, expensive and not all patients can afford or sustain chemotherapy courses. We propose analogues of natural compounds containing cyano groups (more than 3000 plants synthesize them-cyanogenic glycosides).

The **aim** of our study. Is to create alkylators-analogues of natural or structurally obviously active organic compounds saturated with cyano (carbonitrile) groups (1-4) in neighboring carbon atoms.

Materials and methods. As the cyanating agent, tetracyanoethylene (TCE), which we have studied well, is the most convenient. Tests of cytostatic activity were conducted at the National Cancer Institute, Maryland, USA on 66 pure cancer cell lines.

Results and discussion. TTE interacts easily and quickly with a variety of organic compounds and often with high and quantitative yields it makes it possible to obtain polycyano-organic (often with tetracyanoethyl) compounds. Thus, we obtained for the first time cyanosubstations - natural analogues: tricyanovinyl derivatives of substituted p-menthane-8-ol and o-cimenols, 3((R-hydrazohydrazono) methyl) cyclobutane-1,1,2,2-tetracarbonitriles, 3((2R-hydrazono) methyl)-6-methylcyclohex-4-ene-1,1,2,2-tetracarbonitriles, 1,1,2,2-tetracyanocyclopentanes, 1,3,5-triaryl-2,4-diazapentane-1,4-yenes, tricyanobicyclimines, cyanopyrans and cyanotetrahydropyridines. Tests of the antiproliferative activity of compounds in the concentration of 10-5 moles according to the program Onne-Dose Scrieen on cells obtained from tumors of the lungs, large intestine, brain, ovaries, kidneys, prostate, breast, and leukemia and human melanoma. At a concentration of 10 μM, significant inhibition of tumor cells was detected. This is especially true for leukemia, as the growth of test cultures is suppressed (CCRF-CEM, YL-60 (TB), K-562 <MOLT-4, RPMI-8226, SR). The average inhibition of these lines is 88.4%, the maximum value is 95.4% (SR).

Conclusions. Polycyanoorganic fragments in organic molecules are fundamentally new pharmacophores in the chemistry of cytostatic drugs.

SYNTHESIS AND BIOLOGICAL ACTIVITY INVESTIGATION OF NOVEL 1,2-BENZOXATHIIN-4(3*H*)-ONE 2,2-DIOXIDE DERIVATIVES

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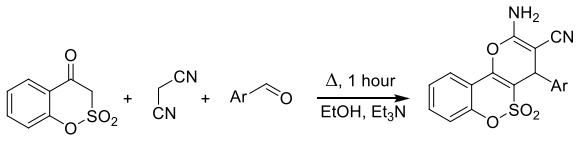
Introduction. The concept of isosterism is a powerful tool for purposeful searching of novel biologically active compounds. For example, among 4-hydroxycoumarin derivatives anticoagulant drugs are well-known. That is why 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide core, as isostere of this famous pharmacophore, attracted our attention in the course of synthesis and investigation of biological activity of new heterocycles. Besides this compound contains in its structure $COCH_2SO_2$ moiety and can be used as promising building-block for construction of new condensed heterocyclic systems in particular applying multicomponent format for these interactions.

Aim. The purpose of the research was to synthesize 2-amino-4-aryl-4*H*-pyrano[3,2-*c*][1,2]benzoxathiine-3-carbonitrile 5,5-dioxides and to explore the anticoagulant properties of the obtained compounds.

Materials and methods. 1,2-Benzoxathiin-4(*3H*)-one 2,2-dioxide, malononitrile and series of substituted aromatic aldehydes were applied as starting materials. The Burker method was used to study the influence of the synthesized compounds on blood coagulation.

Results and discussion. The reaction of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (1) with malononitrile (2) and aromatic aldehydes (3a-e) proceeded smoothly in refluxing ethanol for 1 hour in the presence of triethylamine as a catalyst.



Cmp	Ar	Yield,%
4a	C_6H_5	65
4b	2-MeO-C_6H_4	58
4c	4-MeO-C_6H_4	85
4d	3-Cl-C_6H_4	78
4e	4-Cl-C_6H_4	40

Among the synthesized 2-amino-4-aryl-4*H*-pyrano[3,2-*c*][1,2]benzoxathiine-3-carbonitrile 5,5-dioxides (4a-e) the compound 4d in concentration of 1 mg/ml revealed a significant increase in the time of blood coagulation (1.9 times compared with the control), that indicates its anticoagulant properties.

Conclusions. Series of novel 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide derivatives were synthesized and according to the research assumption anticoagulant activity was detected for one of the obtained compounds, that gives the opportunity for further investigations in this field.

THE PSYCHO- AND NEUROTROPIC PROPERTIES OF 3-(N-R,R'-AMINOMETHYL)-2-METHYL-1H-QUINOLIN-4-ONES: *IN VIVO* VS *IN SILICO*

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Introduction. Methods “in silico” are the powerful tools for searching new biologically active compounds on the early stages of research. They allow to greatly optimize the selection of candidates for further experimental studies *in vitro* and *in vivo*.

Aim. The aim of the work was comparative analysis of the results of screening *in vivo* studies and retrospective *in silico* prediction of psycho- and neurotropic properties of 3-(N-R,R'-aminomethyl)-2-methyl-1H-quinolin-4-ones using the PASS Online service.

Materials and methods. Analysis of the results of previous screening *in vivo* studies of the psycho- and neurotropic properties of 3-(N-R,R'-aminomethyl)-2-methyl-1H-quinolin-4-ones was based on the data published previously. Computer-aided prediction of the spectrum of the biological properties of 3-(N-R,R'-aminomethyl)-2-methyl-1H-quinolin-4-ones was carried out retrospectively using the PASS Online system.

Results and discussion. The results of *in vivo* screening studies have shown that most of the compounds studied has pronounced nootropic properties that for some derivatives combine with high antidepressant activity, anti-anxiety effect, sedative or, conversely, stimulant properties. Analysis of certain subgroups of derivatives allowed us to reveal relationships between chemical structures and biological effects of the compounds. Thus, an analysis of *in vivo* studies of neurotropic properties of 3-(N-R,R'-aminomethyl)-2-methyl-1H-quinolin-4-ones has proven that this class of compounds is promising for further search of new objects.

According to the of PASS prediction results, the most probable biological effects are the ability to act as inhibitors of ubiquinol-cytochrome C reductase, gluconate 2-dehydrogenase, plastoquinol-plastocyanine reductase, kinase of platelet-derived growth factor (PDGF) receptors and enhancers of 3-