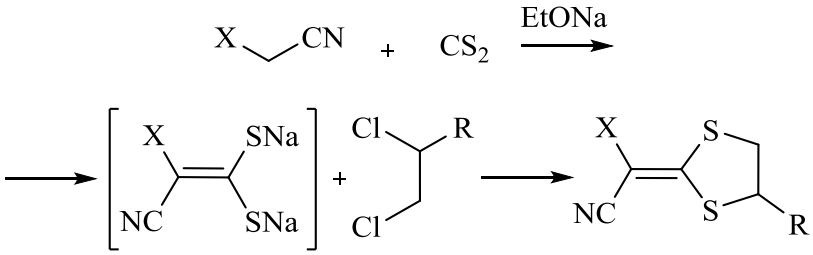
Scheme 1

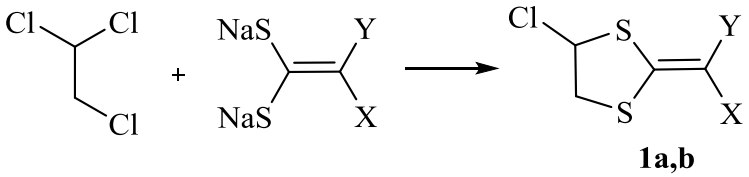


X = CN, $CONH_2$; R = H, CH_3

Materials and methods. Malononitrile and cyanacetamide were used as the methyleneactive compound. 1,1,2-Trichloroethane was used as the chloro-substituted reagent.

Results and discussion. It was found that less reactive trichloroalkanes, in particular, 1,1,2-trichloroethane, can be involved in the interaction. As a result, a method of producing chloro-substituted 2-ylidene-1,3-dithiolanes 1a,b (scheme 2) was developed. The outputs of compounds 1a,b amounted to 75-82%.

Scheme 2



1a,b

X=CN, Y=CN (1a), X=CN, Y=$CONH_2$ (1b)

In the case of ethyl 2-(4-chloro-1,3-dithiolan-2-ylidene)-2-cyanoacetamide **1b**, a mixture of E- and Z-isomers is formed, according to 1:1 NMR spectroscopy.

The structure of the synthesized compounds was confirmed by IR, ^{1}H, ^{13}C NMR and mass spectrometry.

In the IR spectra of dithiolans 1, there are intense absorption bands of stretching vibrations of the conjugated cyano group in the region of 2192-2208 cm^{-1} and intense absorption bands in the region of 1457-1461 cm^{-1}, corresponding to stretching vibrations of the C=C bond. In the case of compound 1b, characteristic signals of the amide group are also present in the IR spectra. The ^{1}H NMR spectra of the compounds obtained are characterized by signals from protons of alkyl substituents and the amide group in the case of compound 1b. The ^{13}C NMR spectra contain all the characteristic signals consistent with the reference data. In the mass spectrum there is a peak of molecular ion with an intensity of 10-30% with a characteristic ratio of isotopes.

Conclusions. Thus, an original method has been developed for the synthesis of chloro-substituted 2-ylidene-1,3-dithiolanes, which makes it possible to produce complex heterocycles in one stage. The obtained dithiolanes 1a,b were synthesized for the first time.

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FRAGMENT-BASED AURORA KINASE INHIBITORS DESIGN

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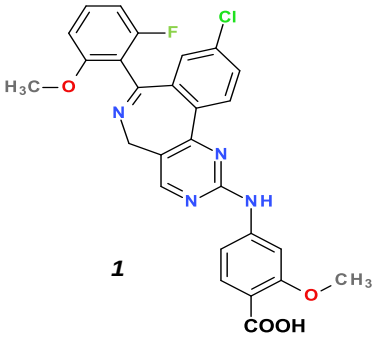
Introduction. Fragment-based design is a method of searching for new drugs, which is based on the study and identification of ligands for a specific receptor, followed by an increase or combination of these fragments in a single "druglike" molecule.

Aim. Identify the advantages of fragment-based design by the example of the search for Aurora kinase inhibitors.

Materials and methods. As a part of our work, we used a variety of available information on the Internet, data from specialized textbooks and periodicals. For the study was applied the method of analysis of the most valuable information and the methods of induction.

Results and discussion. Aurora family kinases are important for the normal course of cell division. Disruption of the cell cycle is typical of tumor cells. Uncontrolled proliferation, nondisjunction of chromosomes, chromosomal aberrations are the result of changes in the regulation of the cell cycle, which can occur both in the process of tumor development and cause its appearance. During the last decade, several inhibitors of Aurora kinases (1-3) were found, for example, Alizertib (1), is undergoing clinical studies in the treatment of breast cancer, lung cancer, t-cell lymphoma, ovarian cancer.



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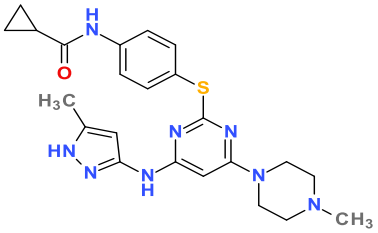

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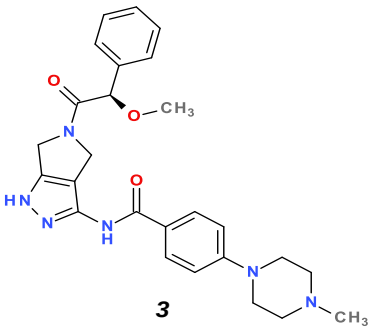

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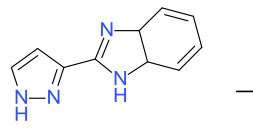
Consider a fragment-based design of Aurora-A kinase inhibitors based on pyrazole-benzimidazole derivatives, which was conducted by Astex Therapeutics (UK) scientists. Thus, according to x-ray diffraction analysis, pyrazole benzimidazole (4) showed good connections with the ATP-binding site of Aurora-A. The introduction of an acylated amino group into the pyrazole fragment leads to an increase in the affinity of the compound in Aurora-A. Acylation of the amino group with a p-fluorobenzoic acid residue improves pharmacokinetic properties. At the next design stage, the morpholine group was introduced in the 5th position of the benzimidazole cycle. The transition from the aminoacyl group to urea residues revealed greater efficiency due to the change in the conformation of the molecule. The study of substituents in the urea fragment proved that it was in the case of cyclopropyl that the interaction of compound 7 from the hydrophobic pocket of the enzyme was ideal, which was proved by X-ray structural analysis and NMR.



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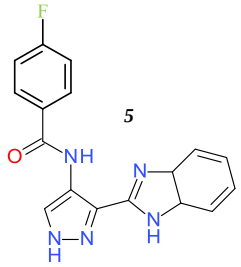

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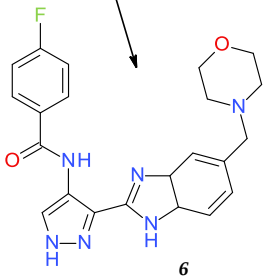

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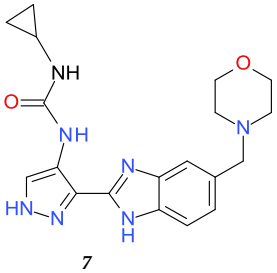

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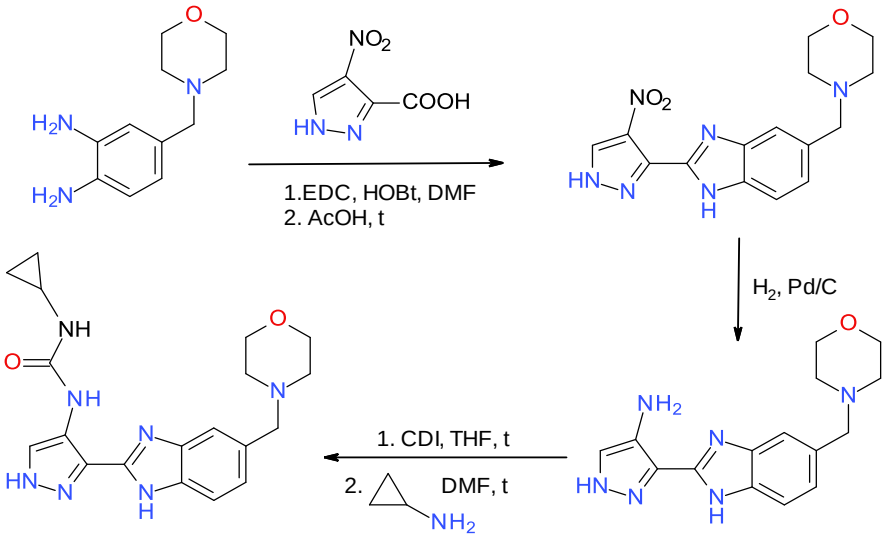
Synthesis of compound 7 can be carried out according to the following scheme:



According to British researchers, compound 7 showed antitumor activity in vivo in immunocompromised mice with the initial stage of human colon carcinoma HCT116.

Conclusions. The given example of using the "method of increasing fragments" in the search for antitumor agents proves that fragment-based design is perspective in the development of new drugs, since it requires the synthesis and research of a much smaller number of compounds.

β-N-ARYL SULFOHIDRAZIDES OF 2-METHYL-5- (6) –NITROCOXANYL ACID, THEIR PROPERTIES, ANTIMICROBIAL, DIURETIC AND ANTIMICROBIC ACTIVITY

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Introduction An annual increase in the number of diseases among the population associated with the pathological processes of various etiologies is actualized research aimed at the creation of new chemotherapeutic agents of the multiplet pharmacological orientation. Among the substituted β-N-aryl sulphohydrazides of 2-methyl-5-(6)-nitrooxanilic acids, the compounds were defined with significant antimicrobial, diuretic and antimicrobial activity against golden staphylococci, hay, intestinal, pseudopharynx, proteus and other commonly occurring microorganisms, most commonly causing infectious complications.

Aim The present study is devoted to the synthetic production of some substituted β-N-aryl sulfohydrazides of 2-methyl-5- (6) -nitrooxanilic acids, followed by the further study of anti-inflammatory and diuretic levels as well as antimicrobial activity against some strains of microorganisms.

Materials and methods. Synthesis of β-N-aryl sulfohydrazides of 2-methyl-5- (6) -nitrooxanilic acids was conducted by multi-stages method with high yields of target products. The yield of the target products was monitored by thin layer chromatography after the disappearance of the stains of the starting compounds.

The structure of compounds obtained has been confirmed by modern methods of analysis: infrared, ultraviolet, nuclear magnetic spectroscopy, and degree of purity – by thin-layer chromatography.

Anti-inflammatory activity was studied on a carrageenal edema model in mice 16-20 grams of weight. The compounds were administered once at a dosage of 10, 20 and 25 mg/kg orally. Voltaren was used as the reference drug, which was administered at a dosage of 8 mg / kg.

The diuretic activity was studued by introducing the test substances in a dosage of 50 mg/kg against a certain water load. As a drug of comparison hypothiazide was applied.