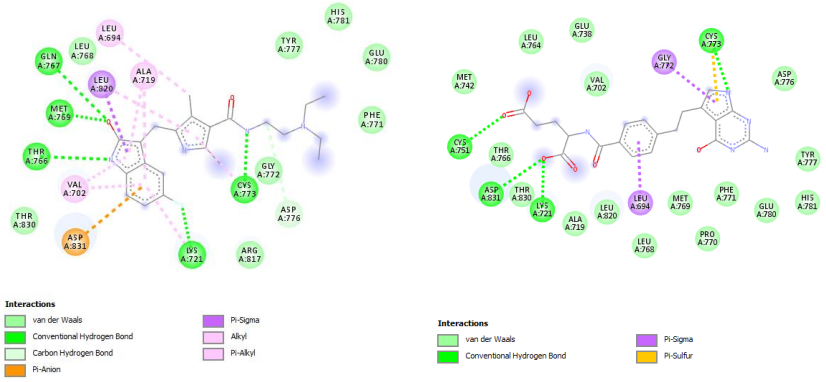

c d

Fig. 2. The diagrams of intermolecular interactions of Imatinib (a), Lapatinib (b), Sunitinib (c) and Pemetrexed (d) in the active site of the tyrosine kinase receptor (PDB ID: 1M17)

Conclusions. In view of the detailed analysis of the geometric location of the tested molecules of anticancer drugs in the active site of biological target, the formation between them of a number of intermolecular interactions arises due to the formation of hydrogen bonds between the molecules and residues of the target amino acids and stabilization of the formed complex of "molecule-target" by intermolecular interactions with charge transfer (π-σ, π – Sulfur, π – anion, carbon hydrogen bond, π – π, Alk, and π – Alk).

Alkyl, allyl and amide «linker» groups between cycles provide the flexibility of the molecule and enable it to adopt the most energetically favorable conformational position in the active site of biological target.

So, we can distinguish fragments that provide (improve) ligand-receptor interaction and offer recommendations for the rational design of effective tyrosine kinase receptor inhibitors, namely:

- It is required to have in the molecule alkyl, allyl, oxy, amino, halogen substituted nitrogen-containing cyclic fragments: pyridine, pyrimidine, piperazine, indole, pyrrole, quinazoline;
- Modification of molecules by a sulfonyl moiety, alkyl and halogen substituted aromatic nucleus, amide and dicarbonic residues is promising.

SYNTHESIS AND ISOMERISM OF 2-AMINO-4-ARYL-3-CYANO-8-METHOXYCARBONYL-5-OXO-5,6,7,8-TETRAHYDRO-4*H*-CHROMENES

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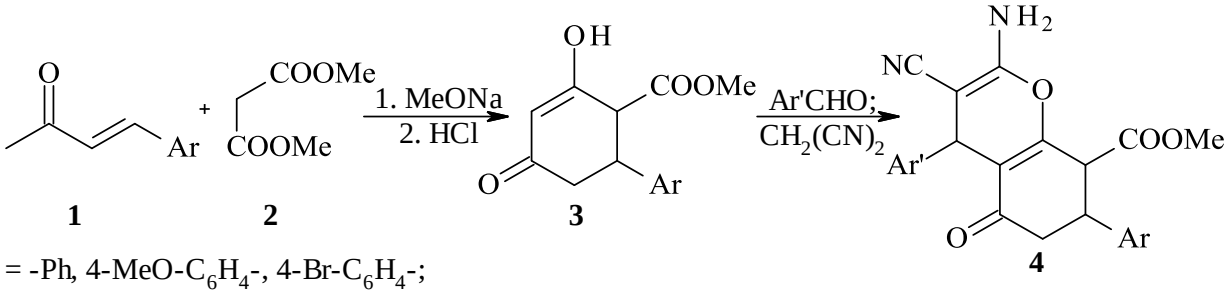
Introduction. Among chromene derivatives many compounds display a high level of different types of pharmacological activity (anti-inflammatory, antibacterial, anticoagulant, etc.) which causes the relevance of the synthesis of its new derivatives in order to find new biologically active substances.

Aim. In the present work we described the synthesis of derivatives of new derivatives of 2-amino-4-aryl-3-cyanochromenes via three-component one-pot interaction of esters of 2-hydroxy-4-oxo-6-arylcyclohexene-2-carboxylic acid with aromatic aldehydes and malononitrile.

Materials and methods. Starting compounds and reagents: arylidene acetones, dimethyl malonate, aromatic aldehydes, malononitrile, triethylamine, ethanol. The methods of organic synthesis and IR-, ^{1}H, ^{13}C NMR spectroscopy, chromatography-mass spectrometry methods were applied in the course of the research.

Results and discussion. Interaction between arylidene acetones (1) and dimethyl malonate (2) proceeds in the presence of sodium methylate with refluxing in ethanol for 3 hours as domino transformation by the «Michael addition / Claisen condensation» type. As a result, methyl esters of 2-hydroxy-4-oxo-6-arylcyclohexene-2-carboxylic acid were obtained (3).

A series of new 2-amino-4-aryl-3-cyano-8-methoxycarbonyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes (4) were synthesized in high yields via three-component interaction of methyl esters (3) with aromatic aldehydes and malononitrile in the presence of catalytic quantity of triethylamine in ethanol medium.

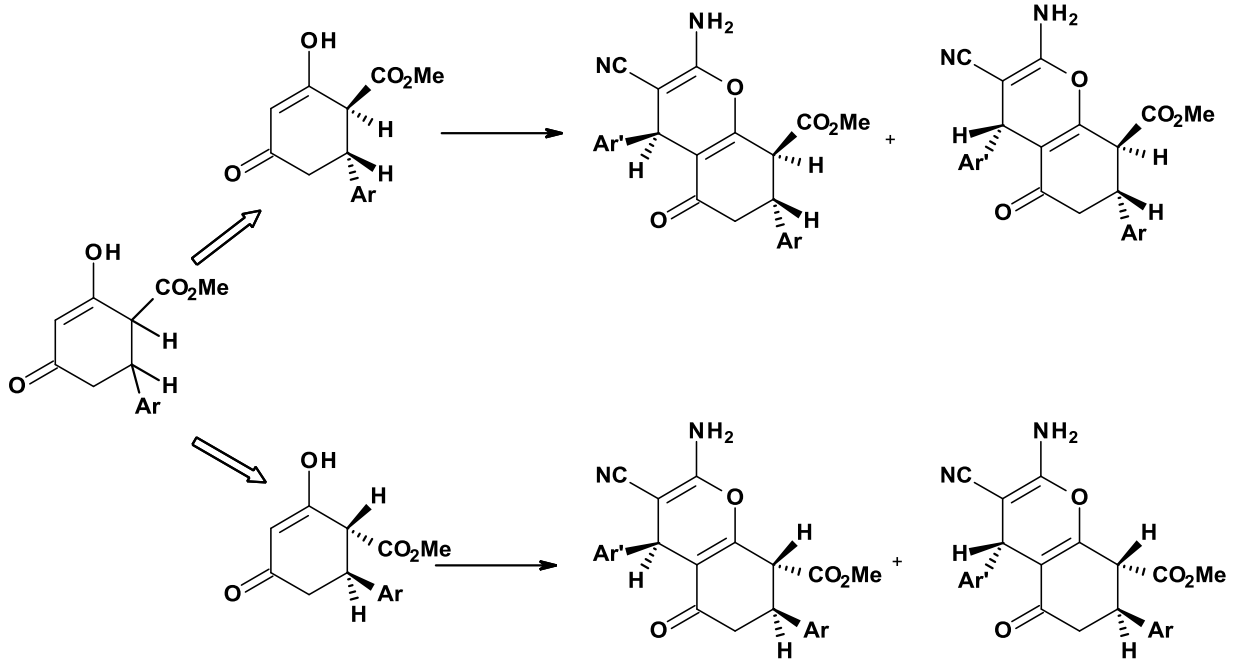


1 **2** **3** **4**

Ar = -Ph, 4-MeO-C_6H_4-, 4-Br-C_6H_4-;

Ar' = -Ph, 4-MeO-C_6H_4-, 2-MeO-C_6H_4-; 4-Br-C_6H_4-.

One of the important aspects of the studies conducted is to establish the structure of the synthesized compounds. The starting esters 3 contain two asymmetric carbon atoms and can exist as two pairs of enantiomers. Analyzing the ^{1}H NMR spectrum of the starting methyl ester of 2-hydroxy-4-oxo-6-phenylcyclohexene-2-carboxylic acid, we can conclude that the substance during the synthesis is formed in the form of trans-isomer. Thus, as reaction products, the formation of the following isomers is possible:



Conclusions. New 2-amino-4-aryl-3-cyano-8-methoxycarbonyl-5-oxo-5,6,7,8-tetrahydro-4H-chromenes were obtained. These investigations will be a base for further pharmacological researches.