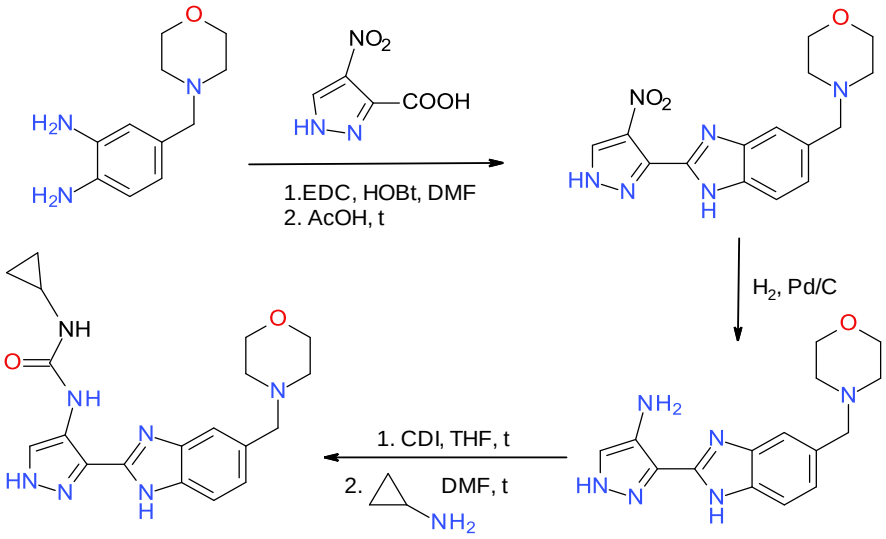
Synthesis of compound 7 can be carried out according to the following scheme:



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.

The antimicrobial activity was determined on the model of daily double serial dilutions in the nutrient medium – meat-pumped broth and on the model of paper disks impregnated with solutions of investigated substances of different concentrations applied to nutrient agar, in comparison with some antibiotics and antimicrobial preparations.

Results and discussion. The synthesized substances showed a weak anti-inflammatory effect, which did not exceed the product of comparison voltaren, diuretic activity revealed some compounds with activity exceeding the activity of hypothiazide in 2 times, according to the bacteriostatic activity the presented compounds do not exceed the test preparations in the concentration of 31,2-250 mg/ml nutrient medium. The study of acute toxicity of DL50 of the most active compounds allowed to establish their low toxicity by K.K. Sidorov's classification, which was 2900-3500 mg/kg.

Conclusions. It is reasonable to study derivatives of β-N-aryl sulfohydrazides of 2-methyl-5- (6) - nitrooxanilic acids as potential diuretic agents.

THE USE OF THE MOLECULAR DOCKING TO ESTABLISH THE POSSIBLE MECHANISM OF THE ANTICONVULSANT ACTION OF 5-R-2- (R_1-AMINO)-1,3,4-THIADIAZOLE DERIVATIVES

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Introduction. An important direction in the development of modern medical chemistry is the use of computer simulations in the process of finding new drugs. Molecular docking, in which the parameters of binding of ligands to receptors is evaluated, is now preceded by pharmacological studies. Its use makes it possible to optimize the structure of the leader compounds; to simulate binding ligand – target; to conduct a virtual screening to determine the affinity of the compounds for a particular biological target and to select compounds for which there is a certain type of pharmacological activity for further experimental studies. Such an approach to solving the problem will help to reduce the cost of money and the number of laboratory animals.

Aim. Research of probable mechanisms of anticonvulsant action of new derivatives of 5-R-2-(R_1-amino)-1,3,4-thiadiazole on the cell and subcellular levels using the molecular docking method..

Materials and methods. New derivatives of 5-R-2-(R_1-amino)-1,3,4-thiadiazole were selected as objects of docking researches. The active site of the Protein Data Bank (PDB) macromolecule of the GABA-aminotransferase enzyme (PDB code 1OHW) was used as the biological target. Autodock 4.2.6 was used for flexible molecular docking. Preparation of ligands was carried out using Vega ZZ (command line) and MGL Tools 1.5.6. programs. A visual analysis of the complexes of substances in the active site of the GABA-aminotransferase enzyme (PDB code 1OHW) was performed using Discovery Studio Visualizer 4.0.

Results and discussions. According to the results of the conducted molecular docking, the scoring function values were calculated. The calculated values (EDoc = from -5.13 to -8.44 kcal/mol) of all tested compounds in complexes with the GABA-aminotransferase enzyme exceed the values of these functions for sodium valproate (EDoc = -5.29 kcal/mol). The conducted analysis of the geometric location of the molecules of the synthesized substances in the active site of the GABA-aminotransferase enzyme shows that the formation and stability of the complexes between the ligands and the amino acids side chains residues is realized due to the hydrogen bonds between them, intermolecular electrostatic and donor-acceptor interactions. Substances that contain a trifluoromethyl substituent and an additional thiadiazole ring have the best affinity for the convulsive target.

Visualization of the results of molecular docking of the leader compounds is presented in Fig. 1