IN SILICO INVESTIGATIONS OF MOLECULAR MECHANISMS OF ANTI-INFLAMMATORY AND ANALGETIC ACTION OF DERIVATIVES OF 3-(AMINOXALYLAMINO)-2-(PHENYL)AMINOBENZOIC ACIDS

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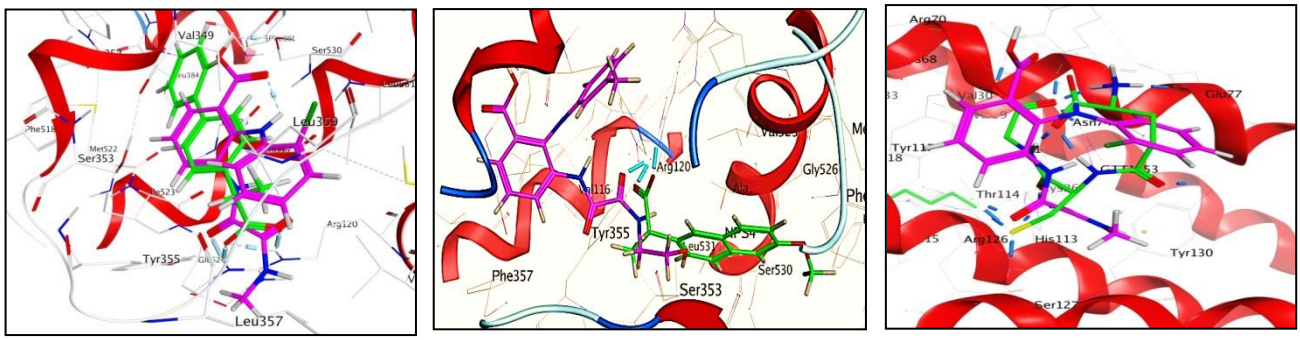
Introduction. An important direction in the development of modern medical chemistry is the development and improvement of theoretical (in silico) methods for investigating the mechanisms of drugs action, foreseeing their activity, and the virtual design of new "medicine-like" substances. New derivatives of 3-(aminoxalylamino)-2-(phenyl)aminobenzoic acids show manifest anti-inflammatory and analgesic properties. The results of the earlier conducted pharmacological screening have became the basis for further studies of the mechanisms of action of the investigated substances at the cellular and subcellular levels using the methodology of evaluating binding ligands with probable biological targets - molecular docking.

Aim. Establishment of the possibility of inhibiting the synthesis of prostaglandins by the derivatives of of 3-(aminoxalylamino)-2-(phenyl)aminobenzoic acids by inhibiting the activity of enzymes involved in different stages of the cyclooxygenase pathway of the arachidonic acid metabolism: COX-1, COX-2 and microsomal prostaglandin-E-synthase-1 (mPGES-1).

Materials and methods. For the docking studies, crystallographic structural models with a high separation capacity with Protein Data Bank were used: COX-1 in complex with α-methyl-4-diphenylacetic acid (pdb code 1Q4G), COX-2, crystallized with naproxene (pdb code 3NT1) and mPGES-1 in complex with glutathione (pdb code 4AL0). The flexible molecular docking was conducted using software package Molecular Operating Environment (MOE).

Results and discussions. According to the results of the docking studies four scoring functions were calculated (Affinity dG Scoring, Alpha HB Scoring, London dG Scoring, GBVI/WSA dG Scoring). The scoring functions for all substances under study have negative values and are comparable or exceed values of the scoring functions of voltaren, analgin, and naproxen. The values obtained indicate a thermodynamic probability and the energy capacity of the formation of complexes between the molecules of the investigated substances and the corresponding receptor, in which the arrangement of the ligands in the active center of the receptor and the amino acids residues of the side chains are similar to the geometry and binding types of the known inhibitors of COX-1, COX-2 and microsomal prostaglandin-E-synthase-1 (mPGES-1), established on the basis of crystallographic studies.

The visualization of the results of molecular docking is shown in Fig. 1.



a) b) c)

Fig. 1. Superpositions of the molecules under study in active centers COX-1(a), COX-2 (b) and mPGES-1 (c)

Thus, the results of a flexible molecular docking of derivatives of 3-(aminooxalylamino)-2-(phenyl)aminobenzoic acids to COX-1, COX-2 and mPGES-1 indicate the possibility of forming stable complexes between them, in which for all compounds studied binding between the ligand and the

receptor occurs with participation of oxygen atoms of the carboxyl group of 2-aminobenzoic acid or oxygen carbonyl atoms in the residues of dicarboxylic acids in the form of hydrogen, as well as π-H or π-π interactions involving the phenyl ring of 2-(phenyl)aminobenzoic acid.

Conclusions. The conducted docking studies have established that the pharmacological activity is connected with the possible inhibition of the synthesis of prostaglandins by new derivatives of 3-(aminoxalylamino)-2-(phenyl)aminobenzoic acids by inhibiting the activity of the enzymes COX-1, COX-2 and mPGES-1.

ASPECTS OF AMPHETAMINE USING IN MEDICINE AND OTHER AREAS (REVIEW)

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Introduction. Amphetamine, also known as α-methylphenylethylamine, was synthesized in Germany in 1887, but this substance attracted attention only in the 20s of the last century. It was a substitute for ephedrine in the treatment of asthma initially. Today, its use is limited, but amphetamine-based drugs are still known in medicine.

Aim. Systematization of data about the use of amphetamine (α-methylphenylethylamine) in the modern world.

Amphetamine is a recreational psychoactive substance that can cause mental dependence. Its trafficking is limited by international and national legislation. However, in America, amphetamine is used to treat attention deficit hyperactivity disorder (ADHD), narcolepsy and obesity, and is recommended for depression and chronic pain. It is known that prolonged use of high doses of amphetamine in some animals leads to problems in the dopaminergic system, but in people with ADHD such drugs improve brain function, as studies of MRI results have shown.

In one systematic review, it was demonstrated that as a result of a nine-month controlled use of amphetamine in therapeutic doses in children with ADHD, the intelligence coefficient increased by an average of 4.5%, attention was improved, and hyperactivity attacks became less common. Such therapy since childhood not only helps to combat the symptoms of ADHD, but also reduces the risk of developing disorders from the use of psychoactive substances in adulthood.

Children with ADHD who take stimulant drugs based on amphetamine tend to have a warmer relationship with peers and family members, better learn at school, are less distracted and less impulsive. In other reviews of ADHD treatment in children, adolescents, and adults with amphetamine, it was noted that although such drugs reduce the frequency of seizures, they are interrupted more often due to side effects. For example, in the treatment of ADHD in children with diseases such as Tourette's syndrome, these stimulants do not worsen the quality of life, but high doses of dextroamphetamine can lead to the appearance of a tick in some people.

In 2015, in a systematic review, it was noted that when used in low (therapeutic) doses, amphetamine causes small but noticeable improvements in intelligence – it stimulates working and episodic memory in healthy adults, and also makes them more attentive and favors the development of purposefulness.

Some students often use amphetamine as a stimulant – from 5% to 35% of students use it in small doses mainly to improve academic performance, but not as a recreational substance. Amphetamine-based drugs are popular with athletes to increase endurance and reaction speed, but its using in competitions is prohibited and regulated by collegial, national and international anti-doping agencies.

Conclusion. Amphetamine is not only used illegally as a recreational substance, but also used in medicine in other countries for the treatment of ADHD, depression and some other diseases.