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ЗБІРНИК МАТЕРІАЛІВ

V Всеукраїнська науково-практична конференція з міжнародною участю

YOUTH PHARMACY SCIENCE

10-11 грудня 2024 р.,
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МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ’Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

YOUTH PHARMACY SCIENCE

МАТЕРІАЛИ
V ВСЕУКРАЇНСЬКОЇ НАУКОВО-ПРАКТИЧНОЇ
КОНФЕРЕНЦІЇ З МІЖНАРОДНОЮ УЧАСТЮ

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Збірка містить матеріали V Всеукраїнської науково-практичної конференції «Youth Pharmacy Science», які представлені за пріоритетними напрямами науково-дослідної роботи Національного фармацевтичного університету. Розглянуто теоретичні та практичні аспекти синтезу біологічно активних сполук і створення на їх основі лікарських субстанцій; стандартизації ліків, фармацевтичного та хіміко-технологічного аналізу; вивчення рослинної сировини та створення фітопрепаратів; сучасної технології ліків та екстемпоральної рецептури; біотехнології у фармації; досягнень сучасної фармацевтичної мікробіології та імунології; доклінічних досліджень нових лікарських засобів; фармацевтичної опіки рецептурних та безрецептурних лікарських препаратів; доказової медицини; сучасної фармакотерапії, соціально-економічних досліджень у фармації, маркетингового менеджменту та фармакоекономіки на етапах створення, реалізації та використання лікарських засобів; управління якістю у галузі створення, виробництва й обігу лікарських засобів; інформаційних та освітніх технологій у фармації та медицині; суспільствознавства; філології.

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macroforms of metals into nanoforms using high temperatures, pressure, and vacuum. These methods require sophisticated equipment, are cost-intensive, and do not allow control over the size, geometry, and resistance to metal nanoparticles. “Bottom-up” methods are chemical and physico-chemical based on the reduction of metal cations to neutral metal atoms, which arbitrarily aggregate into nanoscale clusters.

Chemical synthesis is one of the primary methods for obtaining nanoparticles for medical purposes. By selecting appropriate reagents and reaction conditions, it is possible to control the size, shape, and properties of the nanoparticles. Advantages: control over the size, shape, and properties of nanoparticles; scalability of process for industrial production; relatively low cost. Disadvantages: posimble contamination by reaction by-products; nanoparticles require thorough purification. Key methods include chemical reduction, precipitation from solution, and biosynthesis. Chemical Reduction: Metal ions are reduced by an appropriate reducing agent to form nanoparticles. This method is most commonly used for the synthesis of nanoparticles from noble metals and metal oxides, such as gold, silver, and platinum. In medicine, nanoparticles obtained by this method are used as contrast agents for imaging, in photothermal therapy, and as antibacterial coatings.

Precipitation from Solution: This method involves the precipitation of nanoparticles from a solution by changing dissolution conditions, such as temperature, pH, or by adding precipitants. Cerium dioxide nanoparticles synthesized by precipitation of cerium salts with precipitant (like ammonia) exhibit antioxidant properties and are used as anti-inflammatory and anticancer agents.

Biosynthesis (Green Synthesis): This is ecologically safe method of obtaining nanoparticles using biological materials of plant or microbial origin as reducing agents and stabilizers. In this process are used plant extracts, microorganisms (bacteria, fungi, yeast), or biomolecules (enzymes, proteins, polysaccharides) which resduce metal ions and stabilize the formation of nanoparticlesatibility. Biosynthesis ensures high biocompatibility and low toxicity of the nanoparticles, while being a simple, inexpensive, and environmentally friendly approach.

Conclusions. Nanoparticles exhibit unique physicochemical properties that hold great potential in medicine. The synthesis of nanoparticles for medical purposes is a related area of nanotechnology and is actively being researched.

DETERMINATION OF MOLECULAR MECHANISMS OF ANTI-INFLAMMATORY ACTIVITY OF A [1,2,4]TRIAZOLO[1,5-c]QUINAZOLINE DERIVATIVE

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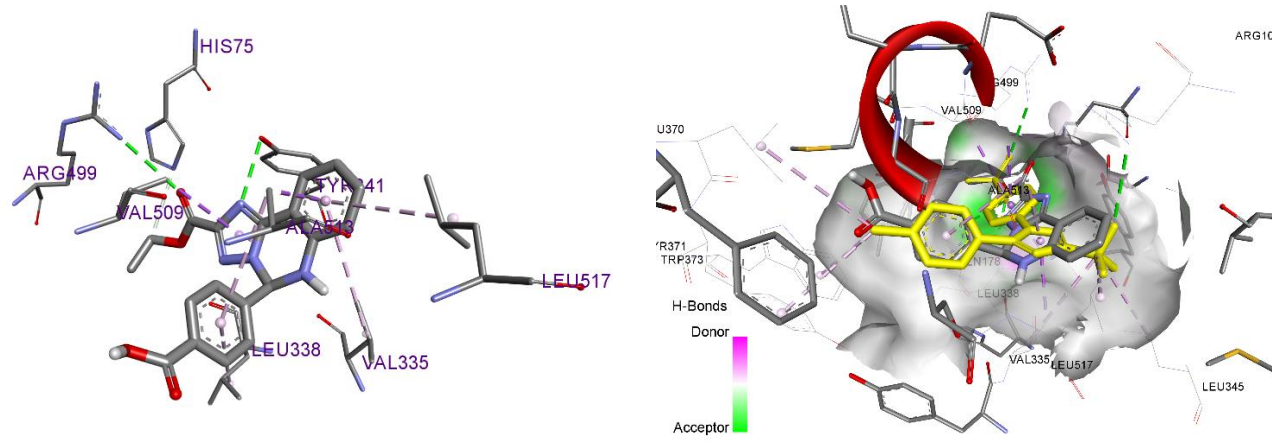
Introduction. Non-steroid anti-inflammatory drugs (NSAIDs) are among the most widely used medications for treatment of pain, fever, inflammation etc. Mechanism of their action as usual associated with inhibition of cyclooxygenases (COX) and biosynthesis of inflammation mediators – prostaglandins. However, abovementioned mechanisms inseparably associated with various side effects including ulcerogenicity, hepatotoxicity, nephrotoxicity, and others. Abovementioned side effects frequently observed during the long-term administration of NSAIDs. Thus, improvement of the NSAIDs safety profile is one of the most urgent tasks of modern medicinal chemistry and pharmacology. Current anti-inflammatory therapeutics focus mainly on reducing the production or

activity of inflammatory eicosanoids or certain cytokines or blocking their receptors, while others can block lymphocyte trafficking into tissues, prevent the binding of monocyte-ymphocyte costimulatory molecules, or reduce the number of circulating B lymphocytes. Under the guidance of Professor Kovalenko S.I. Kovalenko, the expressed anti-inflammatory activity of the new derivative [1,2,4]triazolo[1,5-c]quinazolin was synthesized and proved in animal experiments.

Aim. The aim of our study was to determine the molecular mechanisms of anti-inflammatory activity of the 4-(2-(ethoxycarbonyl)-5,6-dihydro[1,2,4]triazolo[1,5-c]quinazolin-5-yl)benzoic acid.

Materials and methods. BIOVIADraw 2021, AutoDockTools-1.5.6., AutoDock Vina, Discovery Studio Visualizer 2021 programs were used for experiments.

Research results. The *in silico* study of compound 3.2 affinity to the active sites of key for inflammatory processes enzymes COX-1 and COX-2 was conducted. The quantitative characteristic of ligand affinity towards the COX-1 exceeds the values of reference compound diclofenac (-9.2 kcal/mol and -8.5 kcal/mol correspondingly). However it should be mentioned that ligand forms hydrogen bonds via ethoxycarbonyl group (Ser530, 2.52 Å) and Nitrogen of triazole cycle (Tyr385, 2.67 Å). At the same time carboxylic group does not take part in fixation of conformation. The formation of the interactions with methionine (Met522) and leucine (Leu384) was established. The latter are not amino acids of active site but are visualized in the nearest environment at fixation of diclofenac. It was estimated that ligand has high affinity towards the COX-2 enzyme. However, the affinity of studied compound (-11.1 kcal/ mol) is slightly inferior to the affinity of the reference compound celecoxib (-12.2 kcal/mol). The fixation in hydrophobic pocket occurs solely via interactions with amino acid moieties that form active sites in experiment. It should be noted that interactions with non-polar amino-acids moieties valine (Val509, 335), alanine (Ala513) and leucine (Leu338) (length < 4 Å) that are essential for formation of stable conformations and coxib's inhibitory effects were observed as well.



a) b)

Fig. Interaction of ligand with amino acid's moieties of COX-2 active site (a) and combined conformation with native celecoxib (b) (yellow molecule)

Conclusion. The results *in silico* studies established the COX-2 inhibition as probable mechanism of anti-inflammatory activity of 4-(2-(ethoxycarbonyl)-5,6-dihydro[1,2,4]triazolo[1,5-c]quinazolin-5-yl)benzoic acid. Molecular docking showed the possibility of COX-1 inhibitory activity of obtained compounds, abovementioned property should be proven by experiments *in vitro*.

(PubChem). The ligand structures of (+)-catechin-anion, and (-)-epicatechin-anion were drawn by computer program ACD/ChemSketch. The active site of the docking protein was identified utilizing the Computed Atlas for Surface Topography of Proteins. As a standard was taken diclofenac sodium.

Research results. All studied compounds have a high level of affinity for the structure of the COX-2 enzyme. (+)-catechin-anion had the highest free energy value (-10.83 kcal/mol), followed by epicatechin-anion (-10.80 kcal/mol). When comparing the obtained results with the diclofenac sodium standard, the affinity of (+)-catechin-anion with the COX-2 active site was 88%, and in the case of epicatechin-anion, 87% more than that of diclofenac sodium, respectively. Comparing compounds with non-ionized form it was observed that the level of free energy of ionized form was higher 29 and 50% for (+)-catechin and epicatechin, respectively.

Table

Results of molecular docking of the compounds with the COX-2 structure

Ligand	COX-2		
	ΔGbind[a] (kcal/mol)	Ki[b] (mmol)	K[c] (mg/kg)
Epicatechin	-7.20	0.00526	0.55
Epicatechin-anion	-10.80	0.0000122	0.0011
(+)-Catechin	-8.40	0.00070	0.10
(+)-Catechin-anion	-10.83	0.0000116	0.0011
Diclofenac sodium	-5.76	0.05977	5.85

Conclusion. It was established that (+)-catechin anion and epicatechin anion have a higher level of affinity than non-ionized (+)-catechin and epicatechin for the active centers of COX-2. So, the degree of ionization is an important factor influencing the pharmacological activity of individual substances.

SYNTHESIS AND STUDY OF A TETRAZOLE-5-THIOLE DERIVATIVE

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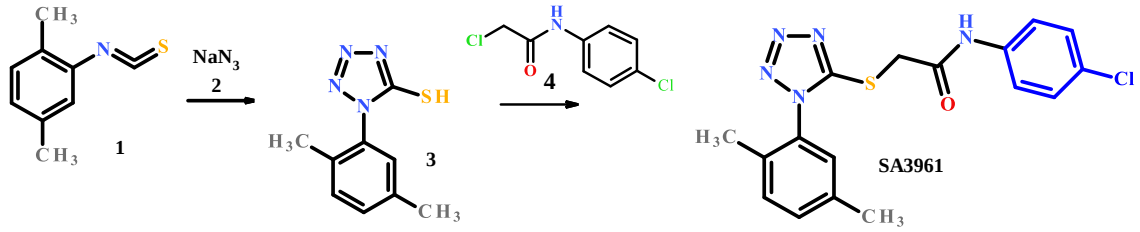
Introduction. The search for new biologically active substances in the series of heterocyclic compounds has been relevant for many decades. A special place among nitrogen-containing heterocycles in this area is occupied by tetrazole derivatives. The analysis of scientific publications in the field of chemistry and medicinal chemistry of tetrazoles revealed an intensive growth in the number of bibliographic sources. This is due to the physicochemical properties of tetrazole derivatives, their favorable safety profile for the body, ease of obtaining them from a wide range of starting materials, which makes them available for organic synthesis, and their unique biological properties. Tetrazole derivatives exhibit a variety of properties and are used in the treatment of infectious diseases, such as bacterial, viral and fungal diseases, cancer, high blood pressure, asthma and others. Many publications deal with the study of the effect of tetrazole derivatives on the central nervous system and the possibility of their use in the fight against diseases such as epilepsy,

Alzheimer's disease, Parkinson's disease, depression, anxiety, and others. In 2019, the Food and Drug Administration introduced the innovative drug Cenobamate, which contains a tetrazole cycle as its main structural fragment, into medical practice. Therefore, the development of new drugs against epilepsy is extremely important to solve existing problems, improve treatment, and raise the standards of medical care.

Aim. The aim of the present study is to synthesize and prove the structure of a new N-(4-chlorophenyl)-2-[1-(2,5-dimethylphenyl)tetrazol-5-yl]sulfonyl acetamide.

Materials and methods. General methods of organic synthesis were used to synthesize the substances; melting point and UV-spectroscopy were used to prove the course of reactions and chemical structure. Schemes were visualized using BIOVIADraw 2021.

Research results. The starting 1-(2,5-dimethylphenyl)tetrazol-5-thiol (3) was previously obtained at the Department of Pharmaceutical Chemistry of the National University of Pharmacy by boiling 2,5-dimethylphenylisothiocyanate (1) and sodium azide (2) in aqueous solution with stirring. The task was to carry out the reaction of interaction between tetrazol-5-thiol (3) and 2-chloro-N-(4-chlorophenyl)acetamide (4) according to scheme:



The alkylation of tetrazol-5-thiole (3) with the corresponding 2-chloro-N-(4-chlorophenyl)acetamide (4) was carried out under the conditions of basic catalysis – in the presence of potassium hydroxide in ethanol by boiling with refluxing for 3 hours. Then the solution was poured into water and as a result, a crystalline compound, N-(4-chlorophenyl)-2-[1-(2,5-dimethylphenyl)tetrazol-5-yl]sulfonyl acetamide, was obtained, which was assigned the code SA3961. The substance had a yellowish and sometimes brownish color, so to purify it, a recrystallization process from propanol-2 was carried out, which allowed to obtain a lighter substance. The compound was dried in an oven at 60 °C. It was found that it is insoluble in water, soluble in ethanol and propanol-2 when heated, dioxane, DMFA, and DMSO. The melting point of the SA3961 was 195-198 °C. The absorption spectrum of the substance SA3961 under study is characterized by two absorption maxima in the UV spectrum at 238 and 285 nm. In addition, it should be noted that the original 2,5-dimethylphenyltetrazol-thiole (3) had a single absorption maximum in this region of the spectrum, indicating the appearance of additional chromophores in the structure

Conclusion. The synthesis of the new derivative N-(4-chlorophenyl)-2-[1-(2,5-dimethylphenyl)tetrazol-5-yl]sulfonyl acetamide was carried out. Its melting point was measured, solubility in various solvents and absorption spectrum in the ultraviolet region were determined.

Research results. Obtaining the total extractives. 500 g of dried, crushed roots were extracted with ethanol alcohol *(>99% Merck KGaA, EMD Millipore Corporation*) three times, each extraction lasting one day. The resulting extract was filtered and concentrated using a rotary evaporator over a water bath. 41 g of brown residue is obtained. The extraction yield from the raw material was 8.2%. A 5 g portion of resin was dissolved in a small amount of ethyl alcohol and subjected to chromatography on a glass column (h-1m, d=3.5 cm) filled with neutral Al2O3, with Brockman II activity. The ratio of resin to sorbent is 1:10. The chromatographic separation was conducted using petroleum ether (20 fractions), petroleum ether + chloroform (40 fractions in 9:1, 8:2, 7:3, 6:4, 1:1, 1:2, 1:3, and 1:4) ratios, chloroform (35 fractions), and petroleum ether + acetone (15 fractions in 4:1, 3:2, and 1:1 ratios).

An oily mass was obtained from fraction 25-36 of the chromatography column eluted with petroleum ether + chloroform (8:2). In our future work, we intend to study the component composition of this fraction using GC-MS (gas chromatography-mass spectrometry).

Conclusion. The roots of *H. asperum* is a perspective object for the further pharmacognostic research.

PREDICTION OF ANTAGONISM TO NMDA RECEPTORS BY BIOLOGICALLY ACTIVE SUBSTANCES OF *MATRICARIA DISCOIDEA DC.*

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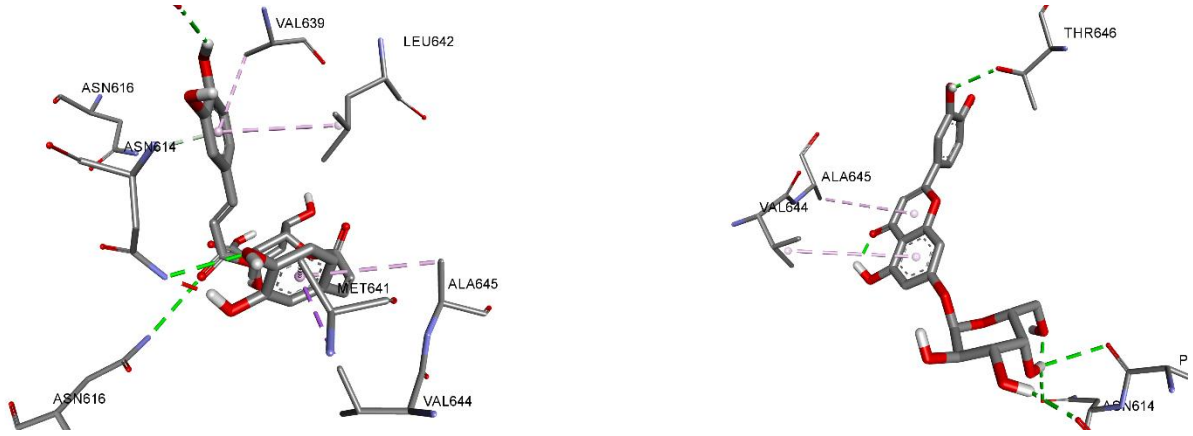
Introduction. *Matricaria discoidea DC.* is widely spread in Europe and North America, but it is not cultivable. M. discoidea has an ethnomedical background dating back to the 19th century, with the plant having been mainly used in the form of tea or a tincture for its anti-inflammatory and spasmolytic properties. According to the literature. in general, of 44 compounds (essential oils) were found in M. discoidea. Biologically, the most relevant compounds were (Z)-enyne-dicycloether, (E)-βfarnesene, geranyl isovaleriate, palmitic acid, and myrcene. Prof. Koshovyi also found a total of 16 phenolic compounds were identified in the herb dry extracts, and nine terpenoids were identified in the *M. discoidea* essential oil. Traditionally, chamomile is used as a sleep-inducer and mild tranquilizer. According to the literature, the sedative effect observed here could be related to apigenin, which binds to GABA and benzodiazepine receptors in the brain. According to the literature, the sedative effect observed here could be related to apigenin, which binds to GABA and benzodiazepine receptors in the brain. The authors suggested that chamomile extracts may have anxiolytic effects in persons with mild to moderate generalized anxiety disorder. Scientists at the National Universiti of Pharmacy have proven that dry extracts of *M. discoidea* in animal experiments showed non-toxicity, analgesic and hypnotic activity.

Aim. The aim of the study was to determine the affinity of the corresponding biologically active substances to the active centers of the central nervous system biotargets responsible for the hypnotic activity of plants.

Materials and methods. BIOVIADraw 2021, AutoDockTools-1.5.6., AutoDock Vina, Discovery Studio Visualizer 2021 programs were used for experiments.

Research results. Macromolecule from the Protein Data Bank was used as target protein: ionotropic NMDA glutamate receptors in conformation with a non-competitive direct-acting antagonist, ketamine (PDB ID 7EU7). Affinity prediction was performed for 17 biologically active substances of *M. discoidea.* For most of the ligands studied here, the calculated values for the scoring functions for binding to the active site of the NMDA receptor were lower than that for the reference ligand ketamine (excluding vanillic acid, caffeic acid, and 3,4-dihydroxyphenylacetic acid). The inhibition of the NMDA receptor by ketamine occurs by fixing it in the channel pore through the participation of three hydrophobic bonds with Val644 and Leu642. Therefore, the amino acid interactions of the ligands were investigated, and the results showed that only dicaffeoylquinic acids and luteolin have the ability to bind the channel pore through interactions with Val644 and Leu642 (Figure). As shown in Figure 1, a hydrophobic fixation is possible only through a benzopyranone ring interaction with Val644 (for example, in luteolin-7-O-glucoside). The other fragments of the molecule only formed hydrogen bonds with amino acids that are not essential for the manifestation of activity, and this does not ensure conformational stability and inhibition of the receptor.



a) b)

Fig. Visualization of the interaction of 4,5-dicaffeoylquinic acid (a) and luteolin-7-O-glucoside (b) with amino acid residues in the active site of the NMDA receptor

Conclusion. The results of the molecular docking analyses of the identified BASs of *M. discoidea* demonstrated a high probability of NMDA receptor antagonism.