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QUALIFICATION WORK

on the topic: «**PREDICTION THE PHARMACOKINETIC PROFILE OF PROMISING DIURETIC SUBSTANCES**»

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ANNOTATION

In order to optimize the search for promising diuretic candidates among thiadiazole derivatives, an approach has been applied that involves the use of in silico methods to predict the pharmacokinetic profile and potential toxicity of substances prior to experimental testing. This approach reduces the time and costs associated with drug discovery.

Key words: toxicity, thiadiazole, pharmacokinetic profile, in silico methods.

АНОТАЦІЯ

З метою оптимізації пошуку перспективних кандидатів в діуретики серед похідних тіадіазолу застосовано підхід, який передбачає використання методів in silico для прогнозування фармакокінетичного профілю та потенційної токсичності субстанцій ще до проведення експериментального тестування. Такий підхід дозволяє скоротити час і витрати, пов'язані з відкриттям лікарських засобів.

Ключові слова: токсичність, тіадіазол, фармакокінетичний профіль, методи in silico.

CONTENT

LIST OF SYMBOLS

APIs	Active pharmaceutical ingredients
PSA	Molecular surface area
HBD	Number of hydrogen bond donors
HBA	Number of hydrogen bond acceptors
M	Molecular weight
log P	Distribution coefficient in the octanol/water system
TPSA	Polar surface area of the molecule

INTRODUCTION

Relevance of the topic. The process of finding new drugs has changed significantly throughout the history of their use. The first doctors used only medicines of plant and animal origin, which have retained their importance to this day. In the second half of the 19th century, due to the development of chemistry, the active ingredients of many drugs were identified and the first synthetic drugs were introduced into medicine. As recently as 30 years ago, the selection of biologically active compounds was carried out on animals and tens of grams of a compound were required for initial testing. To reduce costs, scientists gradually began to screen isolated organs and then switched to single-cell studies. Advances in biotechnology and the emergence of databases of biomacromolecules (enzymes, receptors, etc.) have made it possible to significantly reduce the weight of test substances and significantly accelerate the time for total screening. The first half of the 20th century was marked by the discovery, isolation, active use and introduction of animal and microbial metabolites (antibiotics, vitamins, hormones, etc.) into medical practice. The term ‘new medicinal product’ has come to mean that a new molecule with a new (or improved) mechanism of action has been created, or scientists have modified an already known molecule, or developed a new system for delivering a medicinal product to a diseased target organ. At the same time, the main requirement for a new drug is to provide a therapeutic effect with a minimum dose of a new substance, preferably in the absence of side effects. Improvements in organic synthesis methods have led to the discovery of new drugs that are traditionally researched and developed using in vitro screening and in vivo biological activity testing. The sources of ideas for new medicines include accidental discoveries, new fundamental scientific hypotheses, and the emergence of new views on the course of disease. The continuous improvement of the process of developing new medicines is due to its interdisciplinary nature, and the process currently combines experimental synthetic methodologies of organic synthesis and pharmacological methods with in silico approaches, i.e. the ability to

use the latest advances in related sciences. In silico is a concept that involves creating models of natural or laboratory experiments on a computer. The resulting in silico models partially replace experiments. Currently, more than 4,500 companies are developing new medicines. A huge amount of research is being conducted around the world in the field of pharmacy and medicine, but it takes a very long time for it to be implemented. On average, it takes 10 to 16 years between the creation of new drugs and the start of their use in practical medicine. The cost of clinical testing of one drug candidate compound ranges from USD 500 million to USD 1 billion. Only one out of ten new drugs that reach the very last stage of clinical trials eventually becomes available for sale.

The concept of receptors and the subsequent determination of their specific structure has become the basis for rational drug design. Based on the discovery and structural identification of the main potential drug targets, Paul Ehrlich developed the concept of chemoreceptors, based on the idea that differences in the interaction of different substances with receptors can be used for therapeutic purposes. At present, scientists around the world synthesize only those compounds that are promising for the search for new drugs based on in silico research. The main advantages of using in silico technologies in drug design are shorter time to market for new drugs and lower development costs. In order to optimize the targeted search for diuretic substances and to justify the feasibility of experimental screening in the laboratory, an approach was applied that involves the use of in silico methods to predict the biological activity, pharmacokinetic profile and potential toxicity of active pharmaceutical ingredients before experimental testing. This approach makes it possible to reduce the time and costs associated with drug discovery. In this work, computational medicinal chemistry approaches will be applied to a number of thiadiazole derivatives to identify promising drug candidates for further experimental testing.

The aim of study. The aim of our study was to evaluate the drug-like properties, pharmacokinetic parameters, and to predict the probable toxicity and possible carcinogenicity of the new synthesized compounds anilides of 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid, which may become an obstacle at the last stage of clinical trials.

Objectives of the study:

- ✓ Analyze literature data about diuretics;
- ✓ Select objects and in silico activity prediction methods;
- ✓ Test new thiadiazole derivatives synthesized for compliance with the Lipinski's Rule of Five, Weber, and Mugge's Rules;
- ✓ Test pharmacokinetic profile new compounds;
- ✓ Analyze the results and select promising compounds for biological testing for activity in vivo experiments.

Object of study: New 8 compounds of thiadiazole derivatives synthesized at the National pharmaceutical University.

The subject of research. Online prediction of bioavailability and safety of 8 compounds of thiadiazole derivatives.

Research methods. Calculation physico-chemical and toxicity properties.

Practical significance of the results. It has been proved that tested thiadiazole derivatives are perspective for the experimental studies of activity and search potential diuretics.

Structure and scope of the qualification work. The qualification work includes an introduction, a review of scientific and patent literature, two experimental chapters, general conclusions, and a list of references. The work is presented on 49 pages, includes 1 scheme, 9 tables, 4 figures, 39 sources of literature.

CHAPTER I

DRUGS THAT AFFECT THE EXCRETORY SYSTEM

Review of literature

Water constitutes about 60% of the average adult body weight and is responsible for many physiological processes in the human body. Thus, fluid and electrolyte homeostasis is critical for human survival, as exemplified by the potentially devastating consequences of fluid imbalance. The balance of total body fluid is an extremely well-regulated process that ensures the maintenance of a balance between fluid gain and loss through different physiological mechanisms such as neural regulation of thirst, hormonal regulation (vasopressin and natriuretic peptides), management through the skin, hemodynamic changes, and renal control of salt and water excretion. Drugs that affect the body's excretory system are called diuretics (lat. "diuretica" – excrete urine) or diuretic drugs. Diuretics are drugs that pharmacologically tilt the renal fluid regulation in favor of the excretion of water and electrolytes. Diuretics are drugs that increase the renal excretory function of the kidneys and increase the amount of urine volume [1].

Drugs of this pharmacological group cause enhanced excretion of salt (primarily Na^+) and water from the body. Therefore, they are used mainly for the treatment of edema, arterial hypertension and disorders of kidney excretory function. The classification of diuretics takes into account the localization of their effect in the nephron, the mechanism of their action, as well as the chemical structure [2]. Diuretics fall into several classes and subcategories depending on their mechanism and site of their action along the nephron. Diuretics are widely used both alone and in combination with other drugs. The main effect of diuretics - increasing renal excretion of sodium ions, followed by water – primarily found application to overcome the retention of sodium and water, to eliminate oedema syndrome. Having an effect on electrolyte and water balance, circulating blood volume and vascular tone, diuretics are especially used as antihypertensive agents.

As reported in the literature, the first highly active diuretic drugs appeared about 80 years ago, when the diuretic effect of mercury compounds used for the treatment of syphilis was accidentally discovered. Due to their high toxicity, the mercury diuretics are no longer used today. Modern diuretics of various chemical structures (e.g. hypothiazide, furosemide, spironolactone), developed over the last 50 years, are among the most widely used in medicine.

In recent years, along with the well-known efficacy of diuretics in the treatment of renal failure, hypertension, glaucoma, epilepsy or diabetes insipidus, pharmacologists and physicians have been increasingly interested in such unusual areas of extrarenal diuretic effects as the treatment of bronchial obstruction syndrome, cancer and a number of other diseases. Diuretics are particularly interesting for practical medicine, as in addition to diuretic activity, they also have anti-inflammatory, antioxidant, antimicrobial, choleretic, hepatoprotective, hypolipidemic and other beneficial properties.

Diuretics are also used in the treatment of heart failure, liver disease and certain types of kidney disease. But the use of diuretics is often accompanied by side effects, which primarily concern water-electrolyte homeostasis, acid-alkaline balance, metabolism of carbohydrates and lipids, phosphates, uric acid. There are also specific types of side effects, e.g.

The main effect of diuretics - increasing renal excretion of sodium ions, followed by water – is primarily used to overcome the retention of sodium and water, to eliminate oedema syndrome. Having an effect on electrolyte and water balance, circulating blood volume and vascular tone, diuretics are especially often used

There are also specific types of side effects, for example, endocrine disorders in the treatment with spironolactone, ototoxic – when using loop diuretics [3]. Over the past 40 years, no new drugs claimed primarily as diuretics have appeared on the world pharmaceutical market. The latest technological achievements in this field, if they are used, are only used to improve certain

properties of already known substances by creating new dosage forms on their basis.

Classification of diuretics are distinguished [4]:

1. Saluretics:

a. Carbonic anhydrase inhibitors (sulfamides) – act on the proximal tubules: acetazolamide (diacarb);
b. Loop saluretics (derivatives of sulfamoylantranilic, sulfamoylbenzoic, dichlorophenoxyacetic acid) – act on the thick ascending limb of the loop of Henle: furosemide, bumetanide, ethacrynic acid;
c. Thiazides (benzothiadiazines) and thiazide-like saluretics – act on the distal tubules: hydrochlorothiazide, cyclopentazide, chlortalidone, clopamide, indapamide;

2. Aldosterone antagonists (potassium-sparing) – act on the distal and cortical collecting tubules: spironolactone, amiloride, triamterene;

3. Osmotic diuretics – act in luminal hyperosmolarity in the renal tubules without affecting electrolyte balance, whereas aquaretics are substances that act directly by only affecting the excretion of water: mannitol, urea;

4. Diuretics of different groups:

a. xanthine derivatives (purine alkaloids) – act on the glomerulus of nephron: euphylline, and theobromine.
b. acid-producing diuretics.

Diuretics are generally safe. Side effects include: urinating more often, too little sodium in the blood, too little potassium in the blood.

1. *SALURETICS*

The common structural fragment of the most saluretics is a sulfonamide group, connected with a benzene or heterocyclic nucleus [5].

Carbonic anhydrase inhibitors

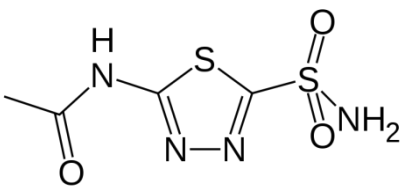
The starting point for the development of the first diuretics based on heterocyclic compounds was the development of acidosis in patients treated with antibacterial sulfonamides in 1949 [6]. As it turned out, this effect was due to

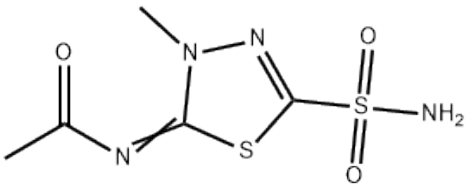
competitive inhibition of carbonic anhydrase in the kidneys, and increased urination under the influence of such substances was associated with the ability to block the same enzyme.

Almost at the same time, Krebs discovered another important pattern for further research: aromatic and heterocyclic compounds with an unsubstituted sulfamide group can effectively inhibit carbonic anhydrase [7].

The end result was not long in coming, and in 1951, after the experimental study of several dozen heterocyclic sulfamides, 2-acetylamino-1,3,4-thiadiazole-5-sulfamide - acetazolamide was introduced into medical practice as a new diuretic.

Acetazolamide (Acetazolamidum) Methazolamide (Methazolamidum)





Carbonic anhydrase is an enzyme which is catalyze the reaction of hydration of CO_2 in tubular epithelial cells and supports the acid-base balance by bicarbonate absorption:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

When the activity of carbonic anhydrase is inhibited, the rate of formation of carbonic acid in the tubules, and, consequently, the number of H^+ ions is decreased. The drugs of this group decrease intraocular and intracranial pressure, reduce the excitability of neurons in the brain, increase the excretion of potassium in urine. Substitution of H^+ on Na^+, as well as resorption of Na^+ with the renal epithelium is decreased. Inhibitors of carbonic anhydrase activity profoundly depress HCO_3^- reabsorbtion in the proximal tubules. They're used to treat glaucoma, metabolic alkalosis, acute mountain sickness and epilepsy. They can cause side effects such as hypokaliemia, hypercalciuria, hyperchloremic acidosis.

To manifest a diuretic action a sulfonamide group must be unsubstituted.

Diuretic effect is increased when the sulfonamide group is connected with the heterocyclic ring. Introduction to the m-position of the aromatic ring of the other sulfonamide group has a positive effect on the activity, which is amplified and prolonged as in the case of the introduction to the structure of the drug halogen or nitro group. The main use of carboanhydrase inhibitors is in the treatment of glaucoma. Carboanhydrase is a functionally important enzyme in the eye, where it plays a key role in the formation of aqueous turbinate. The absence of this ocular enzyme reduces the rate of aqueous turbinate formation, thereby reducing the pressure within the eye associated with glaucoma. Interestingly, the reduction in intraocular pressure is usually resisted once resistance works on the renal effects of carboanhydrase inhibitors. Carboanhydrase inhibitors are used prophylactically to counteract acute mountain sickness, as useful in the treatment of epilepsy, and, to create an alkaline environment in the urine in an attempt to, more quickly excrete certain harmful weak acids by the kidneys or, to maintain the urinary solubility of certain water-soluble, intrinsic, weak acids (e.g., uric acid).

Acetazolamide and Methazolamide are representatives of carboanhydrase inhibitors [8]. Methazolamide is a derivative of acetazolamide in which one of the active hydrogens has been replaced by a methyl group. This decreases the polarity and permits a greater penetration into the ocular fluid, where it acts as a carbonic anhydrase inhibitor, reducing intraocular pressure.

Clinically available carboanhydrase inhibitors are well absorbed from the gastrointestinal tract, distributed to sites of major importance, undergo little biotransformation, and are excreted initially by the kidneys. All carboanhydrase inhibitors reach relatively high concentrations in the renal fluid (by a combination of filtration in the glomeruli and active tubular secretion) as well as in the proximal tubular cells.

They are well absorbed in the gastrointestinal tract and uniformly distributed in the body; is excreted completely from the plasma by the kidneys for 24 hours, is not biotransformed.

Loop diuretics

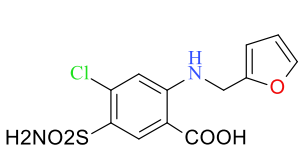
The group of loop diuretics includes sulfonamide-derived (sulphamoyl anthranilic) and and non sulfonamide-derived (dichlorophenoxyacetic acid derivatives). These drugs act primarily on the ascending loop section of Henle. The most important representatives of loop diuretics are *furosemide* and *ethacrynic acid*.

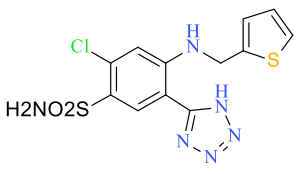
Sulfonamide-derived loop diuretics

In the mid-50s of the last century, Sturm [9] studied the reaction of 2,4-dihalogen-5-sulfamoylbenzoic acids with primary and secondary amines. Pharmacological studies of the N-substituted anthranilic acids synthesised in this way revealed that one of the compounds, 4-chloro-N-(2-furylmethyl)-5-sulfamoylanthranilic acid, in addition to its powerful diuretic activity, also exhibited hypotensive effects. This substance soon entered medical practice under the name furosemide and is now used in many countries around the world [10].

The discovery of such an effective diuretic as furosemide marked the beginning of a large series of studies on aromatic carboxylic and sulfonic acid derivatives. The most commonly used loop diuretics are furosemide, bumetanide, and torsemide, which are sulfonamide derivatives. Furosemide, azosemide, bumetanide are a representative of carboanhydrase inhibitors [11]. The most important use of furosemide or bumetanide is in the treatment of pulmonary edema.

Furosemide Azosemide

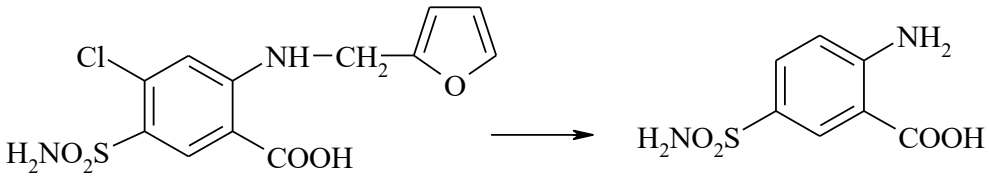




Loop diuretics inhibit $Na^+/K^+/2Cl^-$ transporter in the thick ascending limb of Henle's loop. By inhibition this transporter, the loop diuretics reduce reabsorbtion of NaCl, increase K^+, Ca^{2+} and Mg^{2+} excretion. Loop agents have direct effects on blood flow through several vascular beds. The loop diuretics are rapidly absorbed.

They are eliminated by the kidney by glomerular filtration and tubular excretion. Furosemide increases renal blood flow. No other group of diuretics is more effective than loop diuretics in this situation. When loop diuretics are used in the treatment of pulmonary edema that may accompany a close cardiac arrest, it is of prime importance to avoid their over-fanatical use. Such use may lead to an acute reduction in plasma volume, decreased venous return and cardiac output, and increased heart rate. The duration of effect for furosemide is usually 2-3 hours. Half-live depends on renal function.

In the liver 20% of the drug is biotransformed with the formation of 5-sulfamoylantranilic acid, 80% is excreted by the kidneys in unchange form. 20% of the drug undergoes biotransformation with the formation of acid 5-sulphamoyl anthranilic in the liver; 80% is excreted by the kidneys unchanged (Fig. 1.2).



furosemide 5-sulfamoyl anthranilic acid

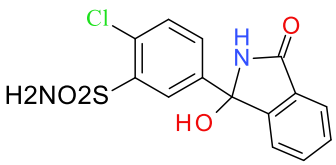
Fig. 1.2. Metabolism of furosemide.

In addition, furosemide has been used to treat hypertension. However, some investigators believe that because of its relatively short duration of action, it may be less effective than thiazide or thiazide-like diuretics. It has been suggested that furosemide be reserved for hypertensive patients with fluid retention, insensitive to thiazide or for patients with renal function [12]. Despite the differences in chemical structure, the pharmacodynamics of these drugs in chronic heart failure is approximately the same. Loop diuretics can cause a variety of adverse effect: allergic reactions, hypokalemic metabolic alkalosis, ototoxicity, hyperuricemia, hypo-magnesemia. These side effects are mostly related to fluid and electrolyte loss or depletion, and they may vary in severity between each drug in the class and

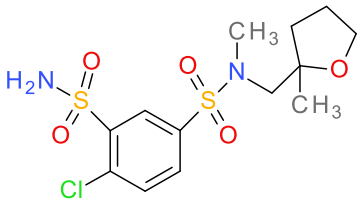
the dosing prescribed for your condition. The prevalence of side effects may increase with high doses of loop diuretics. Ototoxicity can occur with any of the loop diuretics, especially with the concomitant use of aminoglycosides and renal impairment. Furosemide has an increased risk for ototoxicity in those with hypoproteinemia (those with nephrotic syndrome). At the same time, torasemide therapy has a number of advantages over treatment with the reference diuretic furosemide: it has better bioavailability and prolonged effect, less often causes the ‘ricochet’ phenomenon, does not affect the function of the proximal renal tubules, and therefore its potassium-lowering effect is much less pronounced.

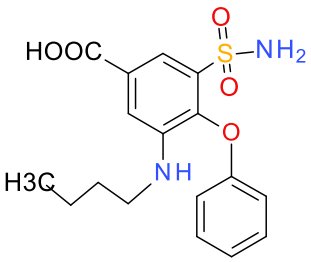
Thus, azosemide, chlorthalidone, mefruside (containing a tetrahydrofuran cycle), bumetanide (phenoxybenzoic acid derivative), clorexolone (isoindole diuretic) and pyrethanide (pyrrolidinylbenzoic acid derivative) [13].

Chlorthalidone

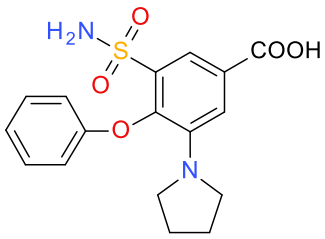


Mefruside





Bumetanide



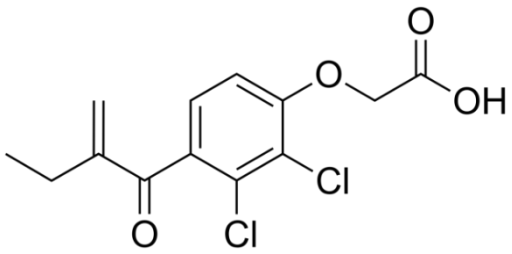
Pyrethanide

Generally, furosemide or bumetanide are preferred over ethacrynic acid (the other site 2 diuretic) because they have a broader dose response curve, less ototoxic, and less gastrointestinal toxicity.

Non sulfonamide-derived loop diuretics

Ethacrynic acid is rarely used but is an alternative in patients who have a hypersensitivity reaction to a typical loop diuretic. Ethacrynic acid is not a sulfonamide derivative, it is a phenoxyacetic acid derivative containing an adjacent ketone and methylene group [14]. Loop diuretics are the most efficacious diuretics agents currently available.

Ethacrynic acid (Acidum etacrinicum)



Ethacrynic acid is binded at 90% with plasma proteins and metabolized in the liver to an active metabolite. It excreted in the urine and stool mainly by the kidneys in unchange form (60-80%) and as conjugates with glutathione. The half-life of the drug is 2–4 hours. The methylene group forms an adduct with the free sulfhydryl group of cysteine. The cysteine adduct appears to be an active form of the drug. (Fig. 1.3).

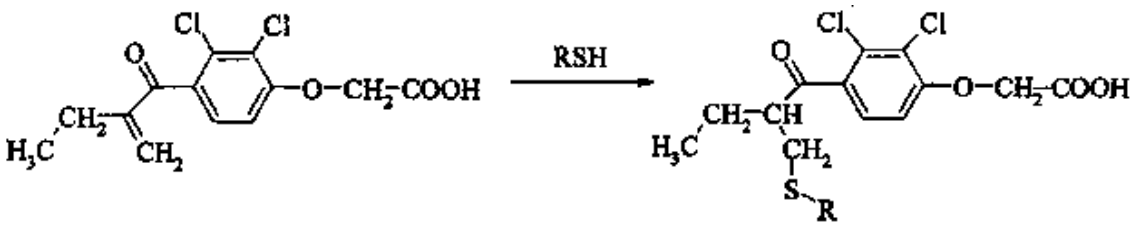


Fig. 1.3. Metabolism of Ethacrynic acid.

In oral use an onset of action after 30 minutes and duration – from 6 to 8 hours; parenteral use – onset of action within 5 minutes and duration, from 2 to 3 hours. Ethacrynic acid has been known to have a more ototoxic potential than the other members and can lead to permanent sensorineural hearing loss without proper caution of its use, especially concomitantly with another loop diuretic [14].

Thiazide (benzothiadiazines) and thiazide-like saluretics

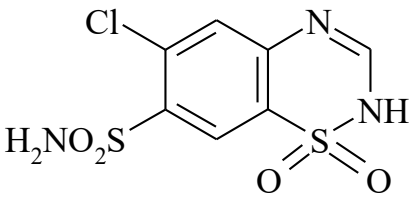
Subsequent extensive studies of compounds chemically similar to acetazolamide led to the development of benzothiazide diuretics [15], the ancestor of which was chlorthiazide. However, 3,4-dihydrogen derivatives of benzothiazines, which constitute the largest group of diuretics approved for medical use and brought to industrial production, have become more important for medical practice Like carbonic anhydrase inhibitors and many loop diuretics, all of the thiazides have an unsubstituted sulfonamide group. Thiazides are the best first choice for hypertension, as concluded in a recent Cochrane review, and chlorthalidone is the best first-line agent among all the anti-hypertensive compared according to the 2017 American college of cardiology hypertension guidelines [16]. Chlorthalidone, with its longer duration of action and longer half-life at lower doses, was found to significantly reduce the risk of cardiovascular events when compared to other anti-hypertensive medications. Indapamide has lower metabolic adverse effects when compared to chlorthalidone due to its non-interference in lipid or glucose metabolism and much safer for use in hypertension, making it suitable for patients with diabetes. Direct vasodilatory effects of thiazide-like diuretics also contribute to lowering blood pressure on long-term therapy. On the other hand, loop diuretics may be the preferred agent when hypertension is associated with chronic kidney disease or glomerular filtration rate less than or equal to 30 mL/min (though some recent reports still favor thiazides in this setting) and potassium-sparing diuretics are used in hypertensive patients with K^+ or Mg^{2+} loss. [16]

Thiazides inhibit NaCl reabsorbsion in distal convoluted tubule. In contrast to loop diuretics, which inhibit Ca^{2+} reabsorbtion, thiazides actually enhance Ca^{2+} reabsorbtion.

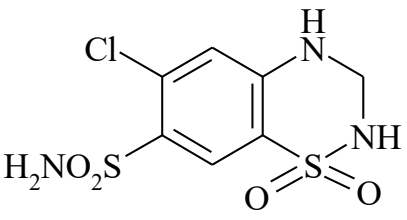
In 1957, benzothiadiazine derivatives with pronounced diuretic activity were obtained. The first drug of the thiazide diuretic group was chlorothiazide, which was later replaced by the more effective and the best known hydrochlorothiazide. Hydrochlorothiazide, which is obtained by condensing 4-amino-6-chlorobenzene-1,3-disulfamide with an aqueous solution of formaldehyde or paraformaldehyde.

This agent is much more active than its non-hydrogenated predecessor and is widely used today.

Chlorothiazide



Hydrochlorothiazide



The peculiarity of the pharmacological action of the compounds of this group is that they contribute to the excretion of Na^+ ions not as $NaHCO_3$, but as NaCl. Thus, when using benzothiadiazinium, Na^+ and Cl^- ions are excreted with urine in equimolar amounts. Therefore, when they are prescribed, the reaction of the urine is not changed to the alkalinity increasing and no acidosis of the blood is observed. Benzothiadiazines can be used as antihypertensive drugs, however, they are ineffective at glaucoma and epilepsy.

In the study of the relationship between the chemical structure and the diuretic effect of benzothiadiazines it was found:

- For the manifestation of the diuretic effect benzothiadiazine must contain sulfamide moieties in position 7. In the absence of this moieties or moving it to another position, specific activity is lost;
- Introduction to possition 6 of halogen atoms or nitro groups leads to a substantial increase of activity of compounds.
- The replacement of chlorine by fluorine leads to the same result. For example, flumetazide which contains the fluorine atom in position 6 is 10 times more active than chlorothiazide.
- when the double bond is restored in the thiadiazine ring, diuretic activity is increased almost in 20 times (hydrochlorothiazide).

A special feature of this group of substances is that they are derived from the body Na^+ ions not in the form of $NaHCO_3$, but in the form of NaCl. That's why the

reaction of urine does not change in the direction of increasing of alkalinity and acidosis of blood is not observed [16].

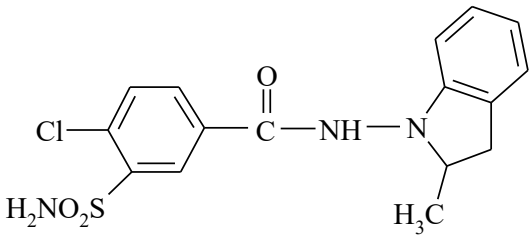
Thiazides are not metabolized, are excreted by the kidneys in unchange form. The major indications for thiazide diuretics are hypertension, heart failure, nephrolithiasis due to idiopathic hypercalciuria and nephrogenic diabetes insipidus. Thiazides have exacerbated or activated systemic lupus erythematosus; consider possibility with this therapy as well. Thiazide-like diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Toxicity of thiazides: hypokalemic metabolic alkalosis, impaired carbohydrate tolerance, hyperlipidemia, allergic reaction.

Hydrochlorothiazide is used at hypertension, heart failure, nephrosis, nephritis, glaucoma. Hydrochlorothiazide is must be store in a dry place at room temperature, in well-sealed containers.

Indapamide (Indapamidum)

Arifon (Arifonum)



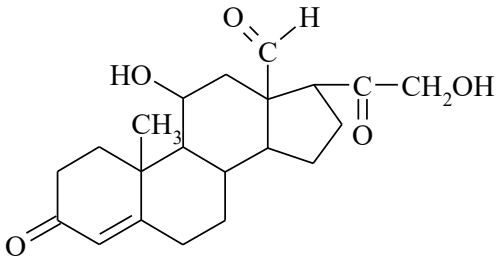
.

Indapamide belongs to the thiazide-like diuretic group, which is not a benzothiadiazine derivative, but contains an ortho-chlorobenzene sulfamide moiety in its structure. Indapamide is a representative of a new class of antihypertensive diuretics – derivatives of indoline. It is an orally active sulphonamide diuretic agent that can reduce blood pressure by decreasing vascular reactivity and peripheral vascular resistance. Indapamide is also can reduce left ventricular hypertrophy. It shows a pronounced and prolonged hypotensive effect. Its mechanism of action is associated with the effect on transmembrane ion exchange (reduction of intracellular calcium transport) and stimulation of the synthesis of prostaglandins E_2, which exhibits a vasorelaxant and hypotensive effect.

Indapamid is flavourless white crystalline powder, insoluble in water. Indapamide is evenly distributed in all tissues of the body, binds to plasma proteins (about 80%). It is metabolized in the liver by glucuronidation and sulfation, 60-70% of indapamide is excreted by the kidneys (with only 5-7% unchanged), 20-23% through the intestine. Indapamide is used in the form of tablets and capsules as a diuretic, hypotensive agent.

1. Aldosterone antagonists (potassium-sparing)

The group of drugs so-called "potassium sparing diuretics" represent an important part of our modern therapeutic arsenal. Their "weak diuretic" properties are especially beneficial in cirrhotic patients with ascites, when highly effective loop diuretics may be hazardous. Representatives of potassium sparing diuretics are (amiloride, triamterene). The mechanism of aldosterone antagonists pharmacological action is to inhibit the secretion of the aldosterone - mineralocorticosteroid hormone, which promotes the reverse resorption of Na^+ for the needs of the body.



aldosterone

All potassium-sparing diuretics act at the late distal convoluted tubule. Potassium-sparing diuretics reduce Na^+ absorbtion and prevent K^+ secretion by antagonizing the effect of aldosterone at the distal and cortical collecting tubules. Inhibition may occur by direct pharmacological antagonism of mineralocorticoid receptors (spironolactone), or by inhibition of Na^+ influx through ion channel in the luminal membrane.

Clinical indications of potassium-sparing diuretics are hyperaldosteronism, due either to primary hypersecretion (Conn’s syndrome, ectopic adrenotropic hormone production) or secondary aldosteronism (evoked by heart failure, hepatic

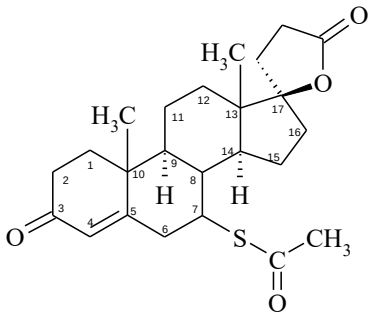
cirrhosis, nephrotic syndrome). With potassium-sparing diuretics, water and Na^+ loss is accompanied by preservation of plasma K^+, because the reduced Na^+ reabsorption limits ATP-dependent Na^+ exchange with K^+. When used together with outher groups, potassium-sparing diuretics reduce or eliminate the excess urinary K^+ loss.

Potassium sparing diuretics have not only the advantage of avoiding potassium loss, but can potentiate the effects of diuretics acting in distal tubules and Henle's loop also. They may be combined by each other or ACE inhibitors too, taking the necessary precautions and laboratory monitoring. Their indications include the hypertension and special diseases as Conn's, Bartter's, Liddle syndromes and hirsutism. The broad clinical usefulness justifies the drug inventory ambition to develop new, more effective potassium sparing compounds without side effects [17].

Amiloride and triamterene have a different mechanism of action: they directly block the ENaC at the luminal surface of the renal tubule. Their action is independent of the presence of aldosterone. At increased secretion of aldosterone, the reverse resorption of sodium ions is increased, which leads to the formation of edema. Antagonists of aldosterone, on the contrary, inhibiting its action, promote the release of sodium ions and reduce the release of potassium ions. Spironolactone which was synthesized in 1951is the most effective drug among the competitive aldosterone antagonists. Spironolactone stimulates the removal of Na^+ ions from the body and to a lesser extent of Cl^- ions, but does not affect the output of K^+, H^+ and urea, and therefore it is effective in acidosis and alkalosis. Toxicity: hyperkaliemia, hyperchloremic metabolic acidosis, gynecomastia (synthetic steroids may cause endocrine abnormalities by action on other steroid receptors), kidney stones (triamterene).

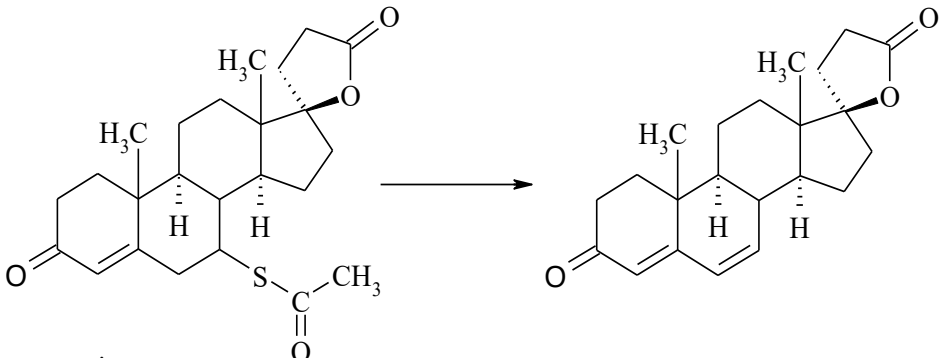
Spironolactone (Spironolactonum)

Verospiron (Verospironum)



Spironolactone is a yellowish-white or light yellowish-brown powder, practically insoluble in water, slightly soluble in ether, soluble in ethanol. Spironolactone is a synthetic steroid which that act as a competitive antagonism to aldosterone. Overall, spironolactone has a rather slow onset of action, requiring several days before full therapeutical effect is achieved.

It belongs to the prodrug group. Under the influence of cytochrome P-450 it is metabolized in the liver to form the active metabolite of canrenone (Fig. 1.4.).



spironolactone canrenone

Fig. 1.4. Metabolism of spironolactone.

Spironolactone, canrenon and eplerenone are the only diuretics that do not act at the luminal membrane of the tubular cells. Spironolactone and eplerenone only work in the presence of aldosterone. More importantly, spironolactone and eplerenone have been shown to have a survival advantage in heart failure, making them a critical drug in the treatment of that condition.

Spironolactone is used in the form of tablets, capsules, lyophilized powder for injection as a diuretic and hypotensive agent. Store in an airtight container.

2. *OSMOTIC DIURETICS*

An osmotic diuretic is a type of medication that increases water excretion more than sodium excretion, helping to maintain urine volume even when the kidney filtration rate is low. Osmotic diuretics include some inorganic salts potassium nitrate, potassium chloride, potassium acetate, (KNO_3, KCl, CH_3COOK), as well as a number of organic substances (mannitol, sorbitol, urea).

Osmotic diuretics have their major effect in the proximal convoluted tubule and the descending limb of the Loop of Henle. These sites are freely permeable to water. Osmotic diuretics descending limb in Henle's loop. Osmotic diuretics do not act directly on the kidneys. With their introduction at hypertonic concentrations into the body, an increase of the osmotic pressure of blood plasma occurs. This, in turn, leads to the entry of water from the tissues into the blood. As a result of this process, the osmotic pressure on the filtrate of the glomeruli increases in the kidneys, which prevents the reverse resorption of Na^+ and water into the renal tubules.

The introduction of osmotic diuretics into the body in hypertensive concentration increases the osmotic pressure of blood plasma. This leads to a transition of water from tissues into the blood. As a result of this process in the kidneys increases the osmotic pressure on the filtrate glomerulus is increased, which prevents the resorption of Na^+ and water in the renal tubules. Osmotic diuretics toxicity includes dehydration and hyperkaliemia.

Potassium acetate (Kalii acetas)

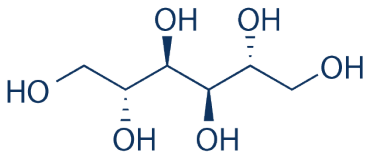
CH_3COOK

Potassium acetate is a medication used to treat hypokalemia. Potassium acetate is white crystalline powder or colorless crystals; very easily soluble in water, easily soluble in 96% ethanol.

Potassium is the major positive ion inside animal cells, while sodium is the major cation outside animal cells. The concentration difference of these charged particles causes a difference in electric potential between the inside and outside of cells, known as the membrane potential. The balance between potassium and sodium is

maintained by ion pumps in the cell membrane. The cell membrane potential created by potassium and sodium ions allows the cell generate an action potential - a "spike" of electrical discharge. The ability of cells to produce electrical discharge is critical for body functions such as neurotransmission, muscle contraction, and heart function. Potassium is also an essential mineral needed to regulate water balance, blood pressure and levels of acidity. Potassium acetate is used in the form of powders and capsules as a diuretic for edema associated with impaired blood circulation, and as a source of potassium ions for hypokalemia. Store in an airtight container.Today, mannitol, a 6-carbon polyol, is the most widely used osmotic diuretics that is metabolically inert in humans and is naturally found, as sugar alcohol, in fruits and vegetables. Synonyms of this drug are osmosal, osmitrol, renitrol, and others.

Hypertonic mannitol



Hypertonic mannitol is an osmotic diuretic that is commonly used in the osmotherapy of cerebral edema. Hypertonic mannitol is effective in treating all forms of cerebral edema. It raises osmotic pressure in renal tubules, thus reducing reabsorption of water in the nephrons. As a result, a large quantity of free water is released, sodium secretion increases, and as a rule, an insignificant amount of potassium is secreted.

It acts by creating an osmotic gradient between the blood and brain, withdrawing water from the brain. These effects are temporary because an equilibrium concentration is reached after a few hours.

Acid-forming diuretics

Amonium chloride belongs to an acid-forming diuretic. Since our first successful use of ammonium chloride, this salt has received a thorough trial in different types of nephritis with edema.

Amonium chloride (Ammonii chloridum)

NH_4Cl

Ammonium chloride is white crystalline powder or colorless crystals; easily soluble in water. Ammonium chloride is easily absorbed in the digestive tract; metabolized in the liver to form urea:

$2NH_4Cl + CO_2 \rightarrow CO(NH_2)_2 + 2HCl + H_2O$

Due to the release of hydrochloric acid it is an effective means for alkalosis correction. It is excreted through the kidneys with an appropriate amount of water causing a diuretic effect. In many it produced prompt diuresis, with rapid disappearance of the edema. In others, its beneficial effects were temporary and slight. In the latter cases, the organic mercury compound novasurol was administered, and as a rule the resulting diuresis was most striking.

Ammonium chloride applied in the form of an aqueous solution, powders and capsules as a diuretic. Store in an airtight container.

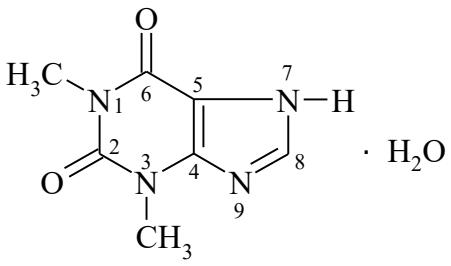
3. Diuretics of different groups:

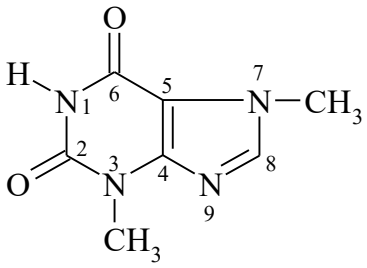
Xanthine derivatives (purine alkaloids)

Another type of bicyclic pyrimidine derivatives, the xanthines, deserves special attention. They are, of course, one of the most important chemical classes of adenosine receptor antagonists [17], and these compounds sometimes exhibit extremely high diuretic properties. The high diuretic activity of xanthines has been the subject of many pharmacological studies, which were mainly conducted with one goal in mind - to elucidate the physiological function of adenosine receptors in the kidneys. As a result, it has been convincingly demonstrated that blocking of adenosine A1 receptors is an important factor in the diuretic effect of xanthines. Natural sources of purine alkaloids are tea leaves, cocoa beans, coffee beans.

Representatives of diuretics of the purine alkaloids group are theophylline and theobromine.

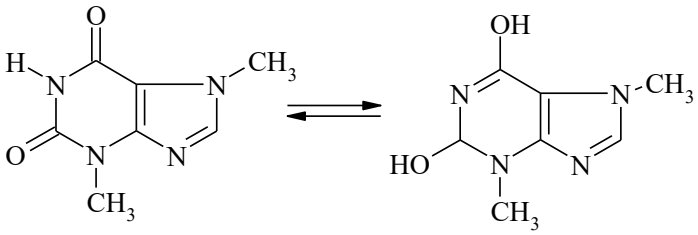
Theophylline (Theophyllinum) Theobromine (Theobrominum)





1,3 – dimethylxanthine 3,7 - dimethylxanthine

Today they are obtained synthetically from uric acid. The diuretic effect of theophylline and theobromine is mainly due to the vascular expansion of the renal arteries, which reduces the intake of water. Theobromine and theophylline are amphoteric compounds with a predominance of acidic properties (due to the mobile hydrogen atom at nitrogen in position 1 or 7). Lactam-lactym tautomerism is characteristic for theobromine:

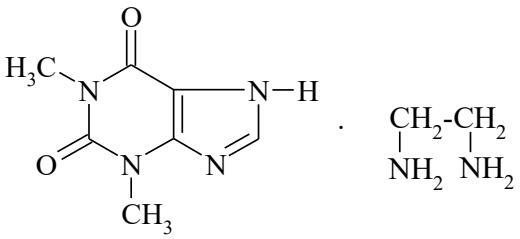


lactam form lactym form

The main metabolic ways of theophylline and theobromine are demethylation and oxidation. Theobromine and theophylline are used in the form of tablets, capsules, solutions for injection and suppositories as antispasmodic (vasodilator, bronchodilator) and diuretics. Usually, they are combined with diuretics of other groups to enhance the diuretic effect.

Aminophylline (Aminophillinum)

Euphylline (Euphyllinum)



Aminophylline is a theophylline salt with 1,2-ethylenediamine. Aminophylline is white, sometimes with a yellowish tinge crystalline powder with a weak ammonia smell soluble in water (aqueous solutions are alkaline). On the air it absorbs carbon dioxide, while its solubility is decreased**.** Theophylline is metabolized in the liver with the participation of several cytochrome P-450 isoenzymes. In the process of metabolism 1,3-dimethyl uric acid, 1 methyl uric acid and 3 methylxanthine are formed, which are excreted with the urine.

Aminophylline is used in the form of tablets, solutions for injection as a diuretic and hypotensive agent. It is prescribed at bronchial asthma, angina and other cardiovascular pathologies. The statistical data provided in the scientific literature indicate that diuretics are one of the pharmacological classes of drugs that require the most dynamic development. At the same time, many years of experience in the use of diuretics shows that there are practically no effective drugs that are absolutely harmless and safe, because they do not have absolute selectivity of action. Getting to the ‘target’, they can at the same time affect other organs and systems of the body, causing undesirable side effects. In addition, the studies conducted so far have revealed many interesting structural and biological patterns, which are fully described in this review.

One of the most convincing proofs of this statement, can be considered the extremely wide synthetic potential of 1,3,4-thiadiazole. Based on the above, the study of compounds of this series will be the key to success in the search for and introduction into clinical practice of new chemical compounds with diuretic action.

Conclusion to chapter 1

1. We have analysed structures, mechanisms of action, metabolism of diuretics of different pharmacological groups.

2. According to the analysis of literature data, the range of diuretics is large but they have many side effect.

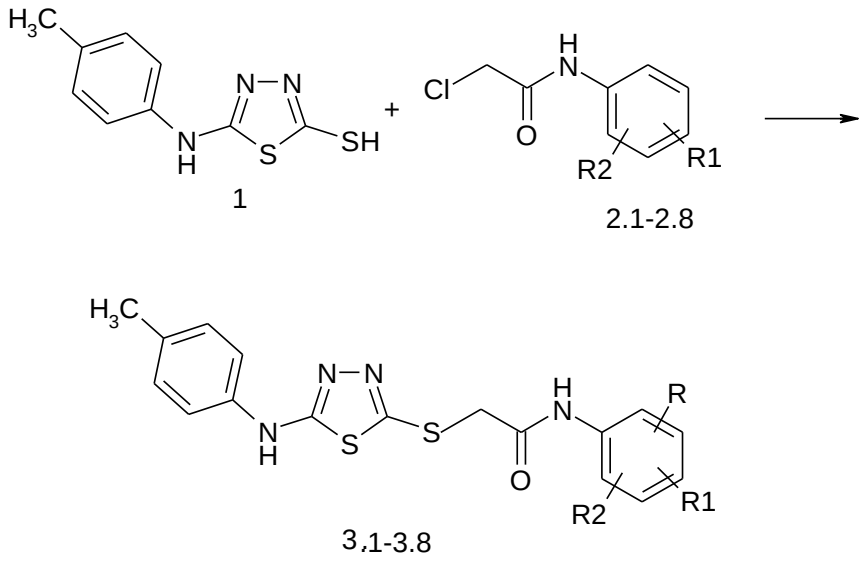
3. No new diuretics have been synthesised in recent years. It should be noted that this topic confirms the prospects for further work.

CHAPTER 2
RESEARCH SUBJECT AND METHODS USED IN THE STUDY

2.1. Synthesis of research subject - new anilides 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid.

1,3,4-Thiadiazoles are five-membered rings, which containing two carbons, two nitrogens, and one sulfur atom, and they exist in different forms. The interest in 1,3,4-thiadiazoles derivatives is primarily due to the wide range of their biological activity. 1,3,4-Thiadiazoles is perspective cycle for new diuretics search. Among the compounds of synthetic origin from a number of 1,3,4-thiadiazole derivatives, as well as condensed systems obtained on their basis, substances with various types of biological activity, namely: diuretic, nootropic, antiinflammatory, analgesic, antimicrobial, were found. In the recent years, molecules containing the pharmacophore 1,3,4-thiadiazole fragment and possessing interesting pharmacological, including diuretic, properties have attracted great interest as promising drugs. Among them, many of the substances on the basis of which drugs were created were found: etazol, diacarb.

New thiadiazole derivatives have been synthesized at the National University of Pharmacy. The reaction of 5-(4-methyl)-2-mercapto-1,3,4-thiadiazoles **1** with different amides of chloroacetic acid **2.1-2.8** was successfully performed in ethanol solution. S-alkylation of initial compounds 5-(4-methyl)-2-mercapto-1,3,4-thiadia-zoles ***1*** with chloroacetic acid amides **2.1-2.8.** in the presence of potassium hydroxide, allowed to obtain the research subject – target anilides 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid **3.1-3.8.** *(Scheme 2.1.).*



Scheme 2.1. Synthesis of anilides 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid **3.1-3.8.**

The target compounds were obtained with good yields (68-76 %). Their physicochemical properties were studied, their individuality and purity were confirmed. The synthesized compounds anilides 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid **3.1-3.8.** are white powder that are soluble in ethanol and insoluble in water.

For these tested substances, a prediction of diuretic activity was carried out with the help of docking studies. The forecast showed the affinity of the synthesized substances to the carbonic anhydrase enzyme. Therefore, there is a possibility that these substances may exhibit diuretic activity.

Before conducting experimental studies, it is advisable to predict the probable toxicity and characteristics.

2.2. Modern in silico technologies are methods used in the study

2.2.1. Assessment of drug-like properties

Lipinski Rule applies early in the process of discovery and research of new substances. It was formulated by Christopher A. Lipinski and his colleagues at Pfizer in 1997 based on the observation that most drugs are relatively small and lipophilic substances. In order to advance the discovery and development of new

drugs, great efforts are made to evaluate the similar, i.e., “drug-like” properties of molecules. A biologically active molecule must meet five conditions to potentially be used as an oral drug. Poor absorption or permeability would be most likely if:

Molar mass >500, number of H-bond acceptors >10, number of H-bond donors >5, LogP>5 (or MlogP>4.15).

Based on Lipinski's Rule of Five, the rating for an orally active drug ranges from “0” to “4,” meaning that a potential drug should have no more than one deviation from the criteria described. However, Lipinski notes that such molecules should not be completely excluded from further consideration; despite the widespread use of the rule of five, it has certain drawbacks. The two main drawbacks are the equal weight given to each of the rules and the sharp boundary marking a violation of one rule or another. Another disadvantage of this rule is that it does not include natural and biological compounds. Lipinski's rule of five does not include criteria related to metabolism. This rule does not predict whether a compound will be pharmacologically active. But its use is very relevant for the design and development of new pharmaceuticals, when a pharmacologically active lead structure is stepwise optimized to increase activity, selectivity, and pharmacokinetic properties [18-23].

Mugge's Rule predicts that a chemical compound will be a successful drug molecule if it has certain characteristics. The restrictions in the Mügge Rule are more stringent than the Lipinski Five Rules. According to the requirements of the Mügge Rule, there are restrictions on the values of physicochemical parameters, namely:

M (molecular weight) - from 200 to 600;

log P (distribution coefficient in the octanol/water system) - from -2 to 5;

TPSA (polar surface area of the molecule) - less than 150;

Hd (number of hydrogen bond donors) - less than 5;

Rot B (number of rotating bonds) - less than 15;

HA (number of hydrogen bond acceptors) - less than 10;

The number of aromatic rings in the molecule is less than 7;

The number of heteroatoms in a molecule is less than 7.

The researcher Gaucher and his colleagues proposed their own range of values, which they suggested to use when developing libraries of drug-like chemicals. They recommended the following specific limits:

M (molecular weight) - between 160 and 480;

log P (partition coefficient in the octanol/water system) - between -0.4 and 5.6;

molar refraction - between 40 and 130;

total number of atoms - between 20 and 70.

According to Weber's research, molecular weight does not significantly affect bioavailability, so he does not take it into account, stating that two parameters are sufficient to determine good oral bioavailability for most compounds. According to Weber's Rules, promising compounds must meet two requirements:

Rot B (number of rotating bonds) - less than 10;

PSA (polar surface area) - less than 140 Å [24].

3.2.2 Assessment of toxicity

Computer prediction of toxicity can be performed on the basis of the structural formula without the use of laboratory animals and test organisms. The advantage of calculated estimates of toxicometric characteristics for BAS is the possibility to obtain them at early stages of the study. The online service «ProTox-II» was used to calculate physicochemical descriptors, as well as to predict drug-like properties. The virtual laboratory of the ProTox-II website was used to predict the toxicity of molecules [25-27]. It incorporates molecular similarity, propensity score, most frequent features, and (based on CLUSTER cross-validation fragment similarity) machine learning based on a total of 33 models to predict various toxicity endpoints such as acute toxicity, hepatotoxicity, cytotoxicity, carcinogenicity, mutagenicity, immunotoxicity, adverse outcome pathways (Tox21), and target toxicity. All methods, training set statistics, and cross-validation of results can be found on the website. The toxicity model report illustrates the significance of positive toxicity results compared to the average of

the hepatotoxicity class, carcinogenicity, etc. Therefore, when developing new drugs, hepatotoxicity; cardiotoxicity; nephrotoxicity; neurotoxicity; and hematotoxicity are predicted in advance [28-32].

Conclusions to Chapter 2

1. Objects for research were selected.

2. In silico methods for research were selected. Currently used method for predicting toxicity and «drug like» parameters were analyzed.

CHAPTER 3
PREDICTION OF DRUG-LIKE PROPERTIES AND TOXICITY OF THE TESTED SUBSTANCES

The aim of this study is to select promising compounds for experimental and biological testing for diuretic activity among new thiadiazole derivatives. In our study for 8 new anilides of 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid, for which possible toxicity and pharmokinetic profile were predicted using in silico methods as modern approaches used in medicinal chemistry to find new APIs.

3.1. Prediction of drug-like properties of the tested substances

The objects of the "drug-like" test were 8 new anilides of 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid.

Chemical names of the studied compounds are given according to IUPAC, structural 2D formulas of substances ***3.1-3.8*** were created in Mollinspiration online program and converted to mSMILES.

The resulting mSMILE looks like a sequence of atoms:

3.1 miSMILES: Cc3ccc(Cc2nnc(SC(=O)Nc1ccccc1)s2)cc3

3.2 miSMILES: Cc3ccc(Cc2nnc(SC(=O)Nc1ccccc1C)s2)cc3

3.3 miSMILES: CCc3ccc(NC(=O)Sc2nnc(Cc1ccc(C)cc1)s2)cc3

3.4 miSMILES: Cc3ccc(Cc2nnc(SC(=O)Nc1ccc(Cl)cc1)s2)cc3

3.5 miSMILES: Cc3ccc(Cc2nnc(SC(=O)Nc1ccc(Br)cc1)s2)cc3

3.6 miSMILES: Cc3ccc(Cc2nnc(SC(=O)Nc1cccc(C)c1)s2)cc3

3.7 miSMILES: CC(=O)c3cccc(NC(=O)Sc2nnc(Cc1ccc(C)cc1)s2)c3

3.8 miSMILES: Cc3ccc(Cc2nnc(SC(=O)Nc1cccc(C(F)(F)F)c1)s2)cc3

Identification of drug-like properties is one of the most important stages of drug discovery. The term "drug-like characteristics" encompasses the concept of the properties of compounds that are most important for their successful use as medicinal products. We analyzed the drug similarity using Lipinski's Rule of Five, Weber, Gaucher's and Mugge's Rules.

According to result all 8 compounds have optimal physicochemical parameters, meet the parameters of «drug-like» properties according to the Lipinski, Weber, Gaucher and Mugge rules, therefore they have good bioavailability and are likely to be drug-like [33-35](Table 3.1-3.8).

Table 3.1

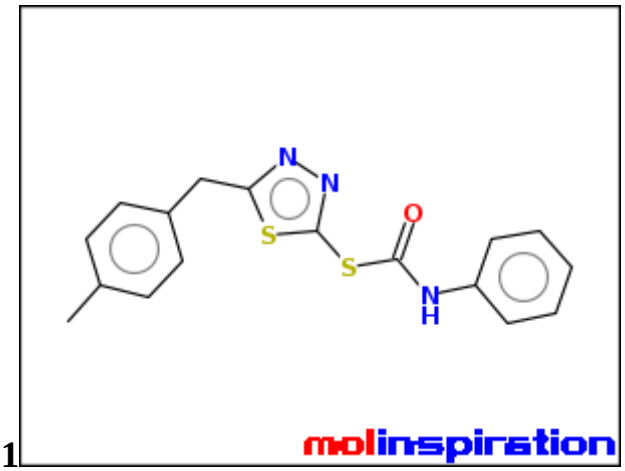
3.1 	miLogP 4.74 TPSA 54.88 natoms 23 MW 341.46 nON 4 nOHNH 1 nviolations 0 nrotb 5 volume 292.14
Anilide 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid	
Molweight	341.46
Number of hydrogen bond acceptors	5
Number of hydrogen bond donors	1
Number of atoms	24
Number of bonds	26
Number of rotable bonds	6
Molecular refractivity	100.43
Topological Polar Surface Area	108.42
octanol/water partition coefficient(logP)	4.74

Table 3.2

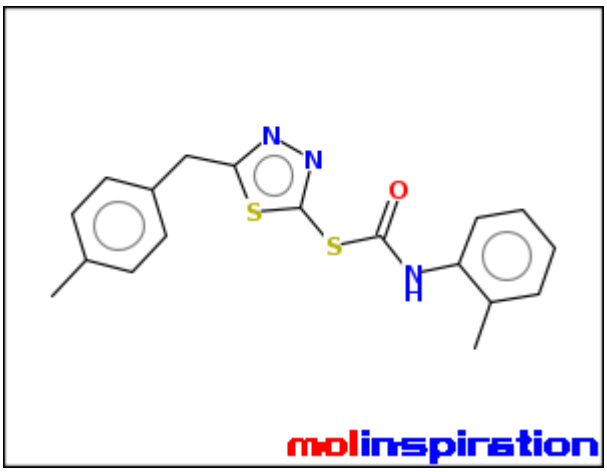
3.2 	miLogP 5.14 TPSA 54.88 n atoms 24 MW 355.49 nON 4 nOHNH 1 nviolations 1 nrotb 5 volume 308
2-Methylanilide 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid	
Molweight	355.48
Number of hydrogen bond acceptors	5
Number of hydrogen bond donors	1
Number of atoms	24
Number of bonds	26
Number of rotable bonds	6
Molecular refractivity	100.43
Topological Polar Surface Area	108.42
octanol/water partition coefficient(logP)	4.14

Table 3.3

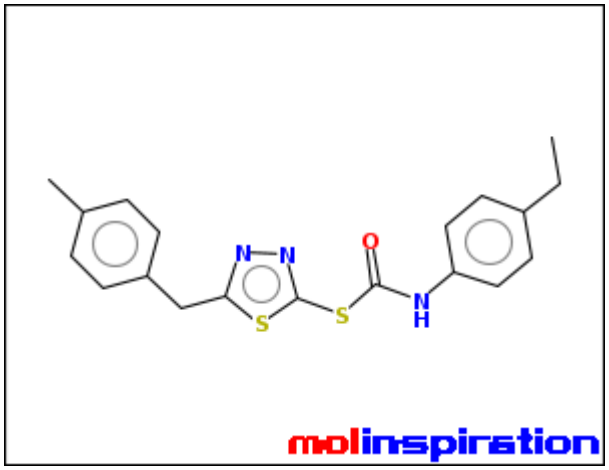
3.3 	miLogP 5.66 TPSA 54.88 n atoms 25 MW 369.51 nON 4 nOHNH 1 nviolations 1 nrotb 6 volume 325.50
2-Ethylanilide 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid	
Molweight	369.5
Number of hydrogen bond acceptors	5
Number of hydrogen bond donors	1
Number of atoms	25
Number of bonds	27
Number of rotable bonds	7
Number of rotable bonds	7
Molecular refractivity	105.24

Table 3.4

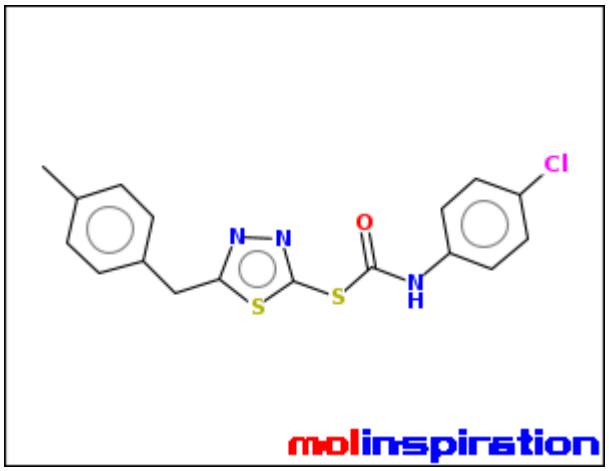
3.4  	miLogP 5.42 TPSA 54.88 natoms 24 MW 375.91 nON 4 nOHNH 1 nviolations 1 nrotb 5 volume 305.67
4-Chlorolanilide 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid	
Molweight	375.9
Number of hydrogen bond acceptors	5
Number of hydrogen bond donors	1
Number of atoms	24
Number of bonds	26
Number of rotable bonds	6
Molecular refractivity	100.48
Topological Polar Surface Area	108.42

Table 3.5

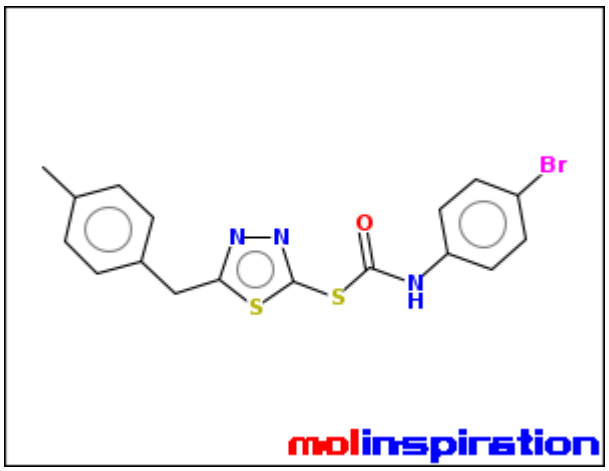
3.5 	miLogP 5.55 TPSA 54.88 natoms 24 MW 420.36 nON 4 nOHNH 1 nviolations 1 nrotb 5 volume 310.02
4-Bromolanilide 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid	
Molweight	420.35
Number of hydrogen bond acceptors	5
Number of hydrogen bond donors	1
Number of atoms	24
Number of bonds	26
Number of rotable bonds	6
Molecular refractivity	103.17
Topological Polar Surface Area	108.42

Table 3.6

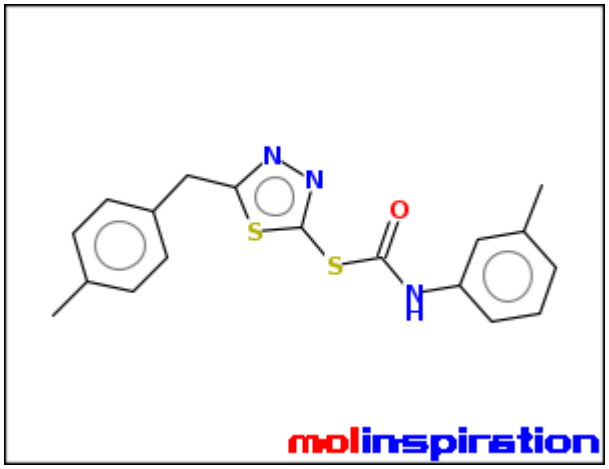
3.6 	miLogP 5.17 TPSA 54.88 n atoms 24 MW 355.49 nON 4 nOHNH 1 nviolations 1 nrotb 5 volume 308.70
5-Methylanilide 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid	
Molweight	355.48
Number of hydrogen bond acceptors	5
Number of hydrogen bond donors	1
Number of atoms	24
Number of bonds	26
Number of rotable bonds	6
Molecular refractivity	100.43
Topological Polar Surface Area	108.42
octanol/water partition coefficient(logP)	4.14

Table 3.7

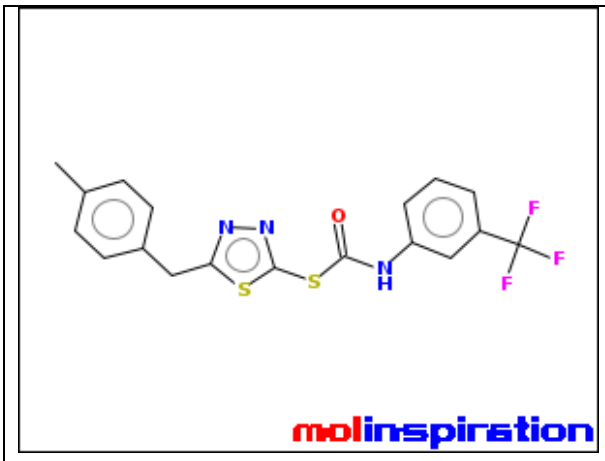
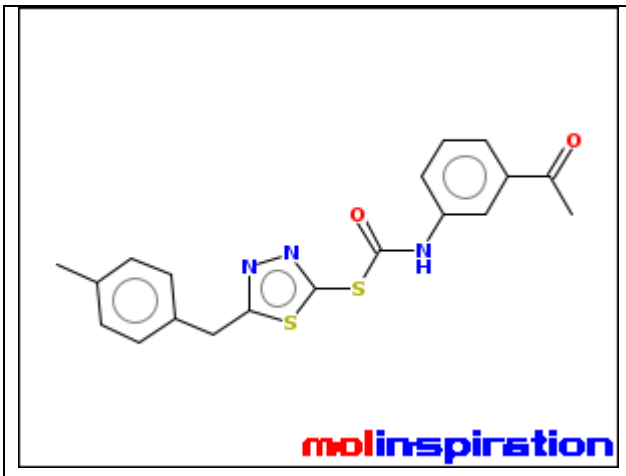
 **3.7**	miLogP 4.62 TPSA 71.95 natoms 26 MW 383.50 nON 5 nOHNH 1 nviolations 0 nrotb 6 volume 327.68
3-Acethylanilides 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid	
Molweight	383.49
Number of hydrogen bond acceptors	6
Number of hydrogen bond donors	1
Number of atoms	26
Number of bonds	28
Number of rotable bonds	7
Molecular refractivity	105.66
Topological Polar Surface Area	125.49

Table 3.8.

 ***3.8***	miLogP 5.61 TPSA 54.88 natoms 27 MW 409.46 nON 4 nOHNH 1 nviolations 1 nrotb 6 volume 323.43
2-Threeftormethylanilides 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid	
Number of hydrogen bond acceptors	5
Number of hydrogen bond donors	1
Number of atoms	27
Number of bonds	29
Number of rotable bonds	7
Molecular refractivity	100.47
Topological Polar Surface Area	108.42
octanol/water partition coefficient(logP)	4.85
Number of hydrogen bond acceptors	5

Testing of 8 compounds for compliance of physicochemical parameters with was carried out. Testing of the research objects for “drug-like” showed their compliance with Lipinski's Five Rules, Weber, Gaucher, and Mugge's Rules.

The results obtained indicate that the tested compounds are «drug-like». Prediction of pharmacokinetic potential of new compounds indicates their favorable pharmacokinetic profile and prospects for in vivo studies.

3.2. Prediction of toxicity properties of the tested substances

We calculated the toxicity parameters with using online service «ProTox-II». The calculated toxicity parameters of the studied substances **3.1-3.8** are presented in Table 3.9

Table 3.9

Values of predicted toxicity parameters calculated using the ProTox-II service

	Toxicity in case of oral administration		**Predicted specific toxicity** [#]				
	Toxicity class **	LD_{50}, мг/кг	HT	CG	IT	MG	CT
3.1	4	1000	yes 0.50	yes 0.51	no	no	no
3.2	4	2000	yes 0.55	yes 0.66	no	no	no
3.3	4	1000	yes 0.61	yes 0.52	no	no	no
3.4	4	1000	yes 0.54	yes 0.64	no	no	no
3.5	4	1000	yes 0.54	yes 0.64	no	так	no
3.6	4	2000	yes 0.57	yes 0.65	no	no	no
3.7	4	2000	yes 0.54	yes 0.64	no	no	no
3.8	4	2000	yes	yes	no	no	no

			0.68	0.56			

* – Class I: lethal if swallowed (LD50 ≤ 5); Class II: lethal if swallowed (5 < LD50 ≤ 50); Class III: toxic if swallowed (50 < LD50 ≤ 300); Class IV: harmful if swallowed (300 < LD50 ≤ 2000); Class V: May be harmful if swallowed (2000 < LD50 ≤ 5000); Class VI: Non-toxic (LD50 > 5000); # - Model toxicity report describes the reliability of the toxicity compared to the average of the defined class.

Types of activity: HT (Hepatotoxicity), CG (Carcinogenicity), IT (Immunotoxicity), MH (Mutagenicity) and CT (Cytotoxicity). According to the results of the calculations, all the tested substances belong to the Predicted Toxicity Class: 4, their Predicted LD50 is in the range of 1000mg/kg to 2000mg/kg. Drug intoxication of the liver is always a serious problem. Hepatotoxicity testing is important in the development of new drugs [36]. According to our calculations, all tested compounds **3.1**-**3.8** with a probability in the range of 50-60 percent can be hepatotoxic. But at the same time they do not show mutagenicity, cytotoxicity, immunotoxicity. The most promising of this group of compounds is compound **3.1**.It has the lowest probability of side effects.

In silico toxicity prediction helps to predict toxicological effects in advance by modeling the effects of high doses of drugs or their long-term use, contributing to safer clinical trials [37]. In addition to its practicality in obtaining data for further study, the computer calculations demonstrate that in silico assessment of pharmacokinetic properties and toxicity allows for faster data acquisition compared to experimental studies.

Conclusion to Chapter 3

1. Computer evaluation of the pharmacokinetic profile, toxicity of new substances was performed.

2. Testing of the research objects for «drug-like» showed their compliance with Lipinski's Five Rules, Weber, Gaucher, and Mugge's Rules.

3. Computer predictions of toxicity, carcinogenicity, hepatotoxicity, cardiotoxicity, immunotoxicity, мutagenicity and cytotoxicity of new compounds were made using the online service «ProTox-II».

4. All the tested substances belong to the Predicted Toxicity Class: 4, their Predicted LD50 is in the range of 1000mg/kg to 2000mg/kg.

5. All tested compounds **3.1**-**3.8** with a probability in the range of 50-60 percent can be hepatotoxic and carcinogenic.

6. The tested compound anilide 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid **3.1** is promising for experimental studies on the presence of diuretic activity in vivo.

GENERAL CONCLUSIONS

1. Objects anilides 5-(4-methyl)phenylamine-1,3,4-thiadiazol-2-yl-thioacetic acid and in silico methods for research were selected.

2. Computer evaluation of the pharmacokinetic profile, toxicity of new substances was performed.

3. Testing of the research objects for «drug-like» showed their compliance with Lipinski's Five Rules, Weber, Gaucher, and Mugge's Rules.

4. Computer predictions of toxicity, carcinogenicity, hepatotoxicity, cardiotoxicity, immunotoxicity, mutagenicity and cytotoxicity of new compounds were made using the online service «ProTox-II».

5. All the tested substances belong to the Predicted Toxicity Class: 4, their Predicted LD50 is in the range of 1000mg/kg to 2000mg/kg.

6. The most promising for experimental studies on the presence of diuretic activity in vivo compound **3.1** was selected, which has the favorable pharmacokinetic profile and least probability be hepatotoxic and carcinogenic.

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Ф А 2.2.1–32-366

National University of Pharmacy

Pharmaceutical faculty
Pharmaceutical chemistry Department
Level of higher education master
Specialty 226 Pharmacy, industrial pharmacy
Educational and professional program Pharmacy

APPROVED
The Head of Department
Victoriya GEORGIYANTS
"3" September 2024

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Mohamed BOURAKI

1. Topic of qualification work: «Prediction the pharmacokinetic profile of promising diuretic substances», supervisor of qualification work: professor of higher education institution of department of pharmaceutical chemistry, DSc, professor Lina PEREKHODA, approved by order of NUPh 237 from " 27" of September 2024.

2. Deadline for submission of qualification work by the applicant for higher education: April 2025.

3. Outgoing data for qualification work: Calculations of physicochemical and ADMET properties will be conducted to predict the compounds' potential drug-likeness and safety profile.

4. Contents of the settlement and explanatory note (list of questions that need to be developed): _ Analyze literature data on modern approaches used in medicinal chemistry to find new active pharmaceutical ingredients; select objects, *in silico* activity prediction method, test compounds for compliance with the Lipinski's Rule of Five, Weber, and Mugge's Rules; analyze the results and select promising compounds for biological testing for diuretic activity in vivo experiments. _

5. List of graphic material (with exact indication of the required drawings):
Tables – 9, pictures – 4 , schemes – 1

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
Chapters 1	Lina PEREKHODA, professor of higher education institution of department pharmaceutical chemistry, professor	September 2024	September 2024
Chapters 2	Lina PEREKHODA, professor of higher education institution of department pharmaceutical chemistry, professor	November 2024	November 2024
Chapters 3	Lina PEREKHODA, professor of higher education institution of department pharmaceutical chemistry, professor	January 2025	January 2025

7. Date of issue of the assignment: «3»September 2024

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1	Writing a literature review	Oct.-Nov. 2024	**done**
2	Planning a research subject and methods used in the study	Nov. 2024 – Jan. 2025	**done**
3	Prediction of drug-like properties and toxicity of the тested substances	Jan. – March 2025	**done**
4	Formalization of the qualification work	April 2025	**done**

An applicant of higher education _____ Mohamed BOURAKI

Supervisor of qualification work _____ Lina PEREKHODA

ФА2.8-03-317

ВИСНОВОК

експертної комісії про проведену експертизу
щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

«04» травня 2025 р. № 331111302

Проаналізувавши кваліфікаційну роботу здобувача вищої освіти Буракі Мохамед, групи Фм20(4.10д)англ-03, спеціальності 226 Фармація, промислова фармація, освітньої програми «Фармація» навчання на тему: «Прогнозування фармакокінетичного профілю перспективних речовин діуретичної дії / Prediction the pharmacokinetic profile of promising diuretic substances», експертна комісія дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,
проректор ЗВО з НПР,
професор **Інна ВЛАДИМИРОВА**

ВИТЯГ З НАКАЗУ № 237

По Національному фармацевтичному університету

від 27 вересня 2024 року

Затвердити теми кваліфікаційних робіт здобувачам вищої освіти 5-го курсу Фм20(4.10д) 2024-2025 навчального року, освітньо-професійної програми – Фармація, другого (магістерського) рівня вищої освіти, спеціальності 226 – Фармація, промислова фармація, галузь знань 22 Охорона здоров'я, денна форма здобуття освіти (термін навчання 4 роки 10 місяців), які навчаються за контрактом (мова навчання англійська та українська) згідно з додатком № 1.

Прізвище, ім'я здобувача вищої освіти	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі фармацевтичної хімії**				
Буракі Мохамед	Прогнозування фармакокінетичного профілю перспективних речовин діуретичної дії	Prediction the pharmacokinetic profile of promising diuretic substances	проф. Перехода Л.О.	проф. Гонтова Т.М.

Ректор

Вірно. Секретар

Ф А 2.2.1-32-353

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy

Mohamed BOURAKI

On the topic: «Prediction the pharmacokinetic profile of promising diuretic substances »

Relevance of the topic. Mohamed BOURAKI's qualification work is devoted to the targeted search for new biologically active substances with diuretic action in a series of thiadiazole derivatives based on modern computer prediction methods.

Practical value of conclusions, recommendations and their validity. All scientific positions and conclusions formulated by Mohamed BOURAKI are based on the results of theoretical and experimental studies, are presented correctly and are scientifically sound. The reliability of the obtained research results is beyond doubt, given that the most modern, well-known computer programs developed in European countries were used to conduct in silico studies.

Assessment of work. The work is relevant, modern, performed at a high scientific level, has theoretical and practical significance. The conclusions are reasonable substantiated and logically result from the experimental material described. The overall evaluation of the work is positive.

General conclusion and recommendations for admission to defense. Mohamed BOURAKI's qualification work meets the existing requirements in terms of relevance and scope of research and can be recommended for defense by the Examination Commission.

Scientific supervisor _____ **Lina Perekhoda**

« 12» травня 2025 р.

Ф А 2.2.1-32-356

REVIEW

for qualification work of the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy

Mohamed BOURAKI

On the topic: «Prediction the pharmacokinetic profile of promising diuretic substances »

Relevance of the topic. In order to optimize the targeted search for diuretic substances and to justify the feasibility of experimental screening in the laboratory, an approach was applied that involves the use of in silico methods to predict the pharmacokinetic profile and potential toxicity of active pharmaceutical ingredients before experimental testing. The qualification work of Mohamed BOURAKI is devoted to optimizing the development of new drugs by using computer technologies that save money and reduce the number of laboratory animals in the experiment, which is always a pressing task in pharmaceutical science.

Author's proposals on the research topic. Based on the results of computer prediction, the prospects for the synthesis of 8 investigated thiadiazole derivatives were determined and experimental testing of one compound for diuretic activity in laboratory animals was recommended.

Practical value of conclusions, recommendations and their validity. Computer prediction of diuretic activity is a theoretical and practical basis for the further experimental studies of the diuretic activity of a new substance from the thiadiazole group. This approach makes it possible to reduce the time and costs associated with drug discovery. In this work, computational medicinal chemistry approaches was be applied to a number of thiadiazole derivatives to identify promising drug candidates for further experimental testing.

Limitations of the work. No significant shortcomings were found.

General conclusion and evaluation of the work. The qualification work of Mohamed BOURAKI is performed at a high scientific level, neatly executed, meets all the requirements in terms of the volume of research conducted and can be recommended for defense at the EC.

Reviewer _____ Prof. Tetiana GONTOVA

« 14 » травня 2025 р.

ФА2.2.1-91-287

ВИТЯГ

з протоколу засідання кафедри фармацевтичної хімії

№ 14 від 16 травня 2025 р.

Засідання проводилось з використанням ZOOM технологій з 12 год. 05 хв. по 12 год. 50 хв.

Чисельний склад кафедри: 16 штатних науково педагогічних працівників, з них присутні – 16 осіб.

ПРИСУТНІ: проф. Георгіянц В. А., проф. Баюрка С.В., проф. Перехода Л. О., проф. Северіна Г. І., проф. Сидоренко Л. В., доц. Абу Шарк А. І., доц. Бевз Н. Ю., доц. Віслоус О. О., доц. Головченко О. С., доц. Гриненко В. В., доц. Кобзар Н. П., доц. Рахімова М. В., доц. Яременко В.Д., доц. Михайленко О.О., доц. Петрушова Л. О., ас. Григорів Г. В., аспіранти: Гуріна В. О., Асмолов В. Є., Суржиков І. О., Мураль Д. В., Сайфудінова Р. П., Куцанян А. А., Сулейман Р. М., Гончар О.О., Коптєлов А.С.

ПОРЯДОК ДЕННИЙ:

Звіт про стан виконання кваліфікаційної роботи здобувача вищої освіти фармацевтичного факультету групи Фм20(4.10д)англ-03 (226 Фармація, промислова фармація освітньої програми Фармація) Мохамеда БУРАКІ на тему: «Прогнозування фармакокінетичного профілю перспективних діуретиків».

СЛУХАЛИ: доповідь здобувача вищої освіти фармацевтичного факультету групи Фм20(4.10д)англ-03 (226 Фармація, промислова фармація освітньої програми Фармація) Мохамеда БУРАКІ на тему: «Прогнозування фармакокінетичного профілю перспективних діуретиків», керівник професор каф. фармацевтичної хімії, д.фарм.н., проф. Ліна ПЕРЕХОДА.

УХВАЛИЛИ: рекомендувати кваліфікаційну роботу Мохамеда БУРАКІ до офіційного захисту в Екзаменаційній комісії.

Голова:

зав. кафедри, доктор фарм. наук,

професор Вікторія ГЕОРГІЯНЦ

Секретар:

доцент, канд. фарм. наук Марина РАХІМОВА

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Мохамед БУРАКІ до захисту кваліфікаційної роботи за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Прогнозування фармакокінетичного профілю перспективних діуретиків».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Микола ГОЛІК /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Мохамед БУРАКІ виконав кваліфікаційну роботу у повному обсязі у відповідності до виданого завдання та у встановлені терміни.
Керівник кваліфікаційної роботи

_____ Ліна ПЕРЕХОДА
« 12» травня 2025 р.

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Мохамед БУРАКІ допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувачка кафедри
фармацевтичної хімії

_____ Вікторія ГЕОРГІЯНЦ

«16» травня 2025 р.

Qualification work was defended

of Examination commission on

« » of June 2025

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Volodymyr YAKOVENKO/