აკაკი წერეთლის სახელმწიფო უნივერსიტეტი
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II საერთაშორისო სამეცნიერო–პრაქტიკული ინტერნეტ-კონფერენცია

# თანამედროვე ფარმაცია – მეცნიერება და პრაქტიკა

# შრომათა კრებული

**THE II INTERNATIONAL SCIENTIFIC-PRACTICAL INTERNET-CONFERENCE**

# MODERN PHARMACY – SCIENCE AND PRACTICE

# PROCEEDINGS

ქუთაისი
KUTAISI. GEORGIA
01.12.2020-21.12.2020

AKAKI TSERETELI STATE UNIVERSITY
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# THE 2nd INTERNATIONAL SCIENTIFIC-PRACTICAL INTERNET -CONFERENCE

## MODERN PHARMACY – SCIENCE AND PRACTICE

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PHARMACY

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# IN SILICO PREDICTION OF PHYSICAL, CHEMICAL AND BIOPHARMACEUTICAL PROPERTIES OF THIOCTIC ACID

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*To determine the possible behavior when interacting with excipients and the human biological environment, the properties of thioctic acid were predicted by searching for quantitative structure-activity/structure-property ratios using ChemAxon, ChemBioOffice 2010 software. Thioctic acid complies with Lipinski's "rule of five" and can be used for oral administration: the molar mass does not exceed 500, it has in its structure not more than 10 H-bond acceptors and rotation connections, not more than 5 H-bond donors, logP is not more than 5. Calculated Structural-Molecular descriptors such as constitutional, geometric, topological, and quantum-chemical allow concluding that it is advisable to create a complex of thioctic acid with a high-molecular carrier, which will ensure its stability and predicted permeability to various parts of the gastrointestinal tract.*

**Introduction and aim:** an alternative to experimental research methods for determining the physicochemical and biopharmaceutical properties of substances is the methodology of QSPR (Quantitative Structure-Property Relationship) and QSAR (Quantitative Structure-Activity Relationship). To establish the structure-property relationship, descriptors such as molecular weight, polar surface area, solvent surface area, number of H-bond donors and acceptors, and so on are used. Despite very significant differences in the algorithms of different software, the general methodological prerequisite for QSAR/QSPR studies is the assumption that there is an objective existence of a relationship between the structure of a substance expressed using descriptors and its chemical properties and biological activity.

**Research methodology:** the main directions in each method of analyzing the structure-properties relationship are to determine the indicator to be investigated and describe the structural parameters (descriptors) of the $d_j$ object. ChemAxon, ChemBioOffice 2010 software was used to find the structure-activity/structure-property relationships of thioctic acid using the following descriptors: electron effects that affect the ionization or polarity of the substance, steric features of the structure that play an important role in assessing the strength of binding to a biotarget, lyophilicity, which characterizes the ability of an API to pass membrane cells – permeability.

**Results and implications:** the solubility of the active pharmaceutical ingredient is the main factor in predicting the bioavailability of the product, being developed. Its quantitative indicators are the dissociation constant (pKa), logarithms of distribution in the octanol/water system in ionized (logD) and non-ionized form (logP).

Most APIs are weak acids or bases, so they can exist in both ionized and non-ionized forms. The hydrogen index of the medium controls the ratio of ionized/non-ionized forms of the substance along the gastrointestinal tract and, consequently, absorption. The relationship between ionization and oral absorption is that non-ionized molecules are more permeable than ionized molecules, and therefore the non-ionized state is the defining form for passive diffusion. The degree of ionization of a molecule at a particular pH can be determined using the acid dissociation constant pKa, which is a critical parameter in determining the properties of the API. The dissociation constant is an indirect indicator of the lyophilicity of a substance because there is no constant value of the hydrogen index in the body and its consideration is important when predicting the behavior of the active pharmaceutical ingredient in vivo.

The pKa of thioctic acid has a value of 4.52, which indicates the strong acidic properties of the molecule. With an increase in the value of the hydrogen index above 4.5, thioctic acid is in a dissociated state. As the pH increases, the hydrophilicity increases significantly. This makes it possible to predict a

low degree of intestinal permeability. The obtained data indicate that TA at physiological pH values is completely ionized and therefore is practically not absorbed by diffusion, but is transferred by active transport or filtration.

The absorption and distribution of xenobiotics in organs and tissues is always associated with the transport of its molecules through barrier membranes, which is characterized by an isoelectric point. It corresponds to the pH of the solution at which the concentration of positive and negative charged ions is the same. This indicator directly correlates with the dissociation constant.

According to the results of the study, it was found that the isoelectric point has the following values for physiological pH values: 1,2 – -0,001; 4,5 - -0,487; 6,8 – -0,995. At PH 1.7, thioctic acid has limited diffusion, which reduces solubility. The result obtained may indicate poor solubility of the API in the stomach. The choice of excipients when developing the composition of medicines with thioctic acid should be based on the fact that they should not reduce the pH of the medium. As the pH increases, thioctic acid molecules form a stable dispersion, which contributes to an increase in TA solubility and a decrease in lyophilicity. The data obtained confirm the logD calculation.

Lyophilicity is one of the factors of intestinal absorption. Its main indicator is the distribution coefficient (log P), which depends on the interaction degree of inter- and intramolecular forces of the functional hydrophobic and hydrophilic groups of the molecule. For a complete picture of the lyophilicity of a substance, the logD value is used, which is calculated for a specific pH and takes into account the dissociation constant of the substance.

The following logD values for physiological pH values have been determined: 1,2 – 2,114; 4,5 – 1,824; 6,8 - -0.141. The results obtained indicate unsatisfactory bioavailability of thioctic acid in the lower gastrointestinal tract. The calculated log P is 2.11, which indicates possible spontaneous penetration through biological membranes.

Most methods used in silico calculate the eigenvalue of solubility for each API in the form of the solute concentration that is in equilibrium with the solid phase when dissolved.

From the obtained data, it can be concluded that the maximum solubility value of API is at pH 7.2 and is logS=0 (266.32 mg/mL). At physiological values of the hydrogen index in the stomach, thioctic acid has practically no solubility. Thus, the LogS value is in the range of -2.93 – 2.79, which is 0.242 mg/mL – 0.314 mg/mL. The results obtained correlate with the calculated logD and logP values and suggest a low degree of oral bioavailability of thioctic acid.

Also, to establish the composition-structure relationship, topological descriptors are used, which characterize both the chemical and geometric properties of a substance. A significant role in determining the structure of a substance is played by the value of the topological surface, which correlates with the value of solubility and indicates the degree of interaction with the solvent due to the formation of bonds, their angle, and changes in the surface geometry. Semi-empirical calculations of modeling the thioctic acid structure under energy minimization conditions were performed to find the transition state and change the surface value available for the solvent. Calculations were performed considering the radius of water molecules (1.4 Å).

Visualization of this descriptor makes it possible to observe the presence of an increase in the degree of curvature of the solid sphere of the dissolved thioctic acid molecule, which is available for the solvent. The obtained data indicate a possibly higher solubility of the TA molecule at different dissolution conditions. This finding confirms the presence of undivided electron pairs (lp) and changes in binding angles. The structure of the molecule becomes less rigid, which facilitates the increase in the dissolution degree.

According to the calculated structural and molecular descriptors such as constitutional (number of atoms, their types), geometric (surface, volume), topological (binding indices), and quantum-chemical

(dipole moment, polarity, energy), which are components of the Lipinsky's rule and the Wiener index, it is possible to conclude of unstable behavior at the time of passage through the gastrointestinal tract and the possibility of changing its physicochemical properties by changing the thermodynamic conditions for obtaining the drug.

**Conclusion:** thus, the results obtained allow us to conclude on the advisability of changing the physicochemical properties of thioctic acid in order to ensure its stability and predicted permeability to various parts of the gastrointestinal tract.

**Keywords:** thioctic acid, structural parameters, physical and chemical properties

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## თიოქტის მჟავას ფიზიკური, ქიმიური და ბიოფარმაცევტული თვისებების პროგნოზირება IN SILICO

**ინა კოვალევსკა, ოლენა რუბან**
**ფარმაციის ეროვნული უნივერსიტეტი. წამალთა საქარხნო ტექნოლოგიის კათედრა. ხარკოვი. უკრაინა რეზიუმე**

იმისათვის რომ გაგვესაზღვრა თიოქტის მჟავას დამხმარე ნივთიერებებთან და ადამიანის ბიოლოგიურ გარემოსთან ურთიერთქმედებისას შესაძლო ქცევა, თიოქტის მჟავას თვისებების პროგნოზირება მოხდა რაოდენობრივი თანაფარდობების: სტრუქტურა-აქტივობა/სტრუქტურა-თვისება განსაზღვრის მეთოდით ChemAxon, ChemBioOffice 2010 კომპიუტერული პროგრამების გამოყენებით. თიოქტის მჟავა აკმაყოფილებს ლიპინსკის „ხუთეულის წესს" და შეიძლება გამოყენებულ იქნას პერორალური მიღებისას: მოლური მასა არ აღემატებოდა 500-ს, თავის სტრუქტურაში მას აქვს არაუმეტეს 10 წყალბადური ბმის აქცეპტორული და როტაციური კავშირები არაუმეტეს 5 წყალბადური ბმის დო-

ნორთან, ხოლო logP არ აღემატებოდა 5. გამოთვლილი იქნა სტრუქტურულ-მოლეკულური აღწერილობები, როგორიცაა ქიმიური შემადგენლობა, სტრუქურა, გეომეტრიული და კვანტურ-ქიმიური სტრუქტურა. კვლევის შედეგები საშუალებას იძლევა დავასკვნათ, რომ სასურველია შეიქმნას თიოქტის მჟავას კომპლექსი მაღალმოლეკულური მატარებლით, რაც უზრუნველყოფს მის სტაბილურობასა და პროგნოზირებად ბიოშეღწევადობას კუჭ-ნაწლავის ტრაქტის სხვადასხვა ნაწილში.

თანამედროვე ფარმაცია
მეცნიერება და პრაქტიკა

**SOME MEDICINAL PLANTS OF THE FAMILY CONDITIONS**

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**ABSTRACT**

The use of plant diseases and improve the health of ancient times.People are still using primitive nature.Medicinal properties of plants currently transmitted from generation to generation,and how they are used,mentioned in ancient legends and myths and the legends.The article discusses The Therapeutic value of Coriander and European horse-chestnut, and their family in terms of production rules.

თანამედროვე ფარმაცია
მეცნიერება და პრაქტიკა

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## მიმართულება 2. თანამედროვე ქიმიურ-ფარმაცევტული, კოსმეტიკური და ბიოტექნოლოგიური პრეპარატების რეცეპტურისა და ტექნოლოგიის შემუშავება, ბიოფარმაცევტული შესწავლა