



No 16 (16) (2017)

P.1

The scientific heritage

(Budapest, Hungary)

The journal is registered and published in Hungary.

The journal publishes scientific studies, reports and reports about achievements in different scientific fields. Journal is published in English, Hungarian, Polish, Russian, Ukrainian, German and French.

Articles are accepted each month. Frequency: 12 issues per year.

Format - A4

ISSN 9215 — 0365

All articles are reviewed

Free access to the electronic version of journal

Edition of journal does not carry responsibility for the materials published in a journal. Sending the article to the editorial the author confirms it's uniqueness and takes full responsibility for possible consequences for breaking copyright laws

Chief editor: Biro Krisztian

Managing editor: Khavash Bernat

- Gridchina Olga - Ph.D., Head of the Department of Industrial Management and Logistics (Moscow, Russian Federation)
- Singula Aleksandra - Professor, Department of Organization and Management at the University of Zagreb (Zagreb, Croatia)
- Bogdanov Dmitrij - Ph.D., candidate of pedagogical sciences, managing the laboratory (Kiev, Ukraine)
- Chukurov Valeriy - Doctor of Biological Sciences, Head of the Department of Biochemistry of the Faculty of Physics, Mathematics and Natural Sciences (Minsk, Republic of Belarus)
- Torok Dezso - Doctor of Chemistry, professor, Head of the Department of Organic Chemistry (Budapest, Hungary)
- Filipiak Pawel - doctor of political sciences, pro-rector on a management by a property complex and to the public relations (Gdansk, Poland)
- Flater Karl - Doctor of legal sciences, managing the department of theory and history of the state and legal (Koln, Germany)
- Yakushev Vasilij - Candidate of engineering sciences, associate professor of department of higher mathematics (Moscow, Russian Federation)
- Bence Orban - Doctor of sociological sciences, professor of department of philosophy of religion and religious studies (Miskolc, Hungary)
- Feld Ella - Doctor of historical sciences, managing the department of historical informatics, scientific leader of Center of economic history historical faculty (Dresden, Germany)
- Owczarek Zbigniew - Doctor of philological sciences (Warsaw, Poland)
- Shashkov Oleg - Candidate of economic sciences, associate professor of department (St. Petersburg, Russian Federation)

«The scientific heritage»

Editorial board address: Budapest, Kossuth Lajos utca 84,1204

E-mail: public@tsh-journal.com

Web: www.tsh-journal.com

CONTENT

ART STUDIES

Zahladko A.A.
THE PROBLEM OF INTERPRETATION IN
THE MIRROR OF THE KIEV PRESS OF THE
LATE 60'S-EARLY 80'S XIX
CENTURY4

CHEMICAL SCIENCES

*Syrova A.O. , Kozub S.N. , Tishakova T.S. ,
Levashova O.L. , Chalenko N.N.*
INVESTIGATION OF QUANTUM-
CHEMICAL PROPERTIES OF
INDOMETHACIN 11

ECONOMIC SCIENCES

Hatska L.P.
THE POSSIBILITY OF IMPLEMENTATION
OF THE INDEPENDENT FISCAL
INSTITUTIONS IN THE ECONOMY OF
UKRAINE16

Ivleva E.V., Dyakov S.A.
THE CAUSES OF ECONOMIC CRISES19

Semyashkin G.M. , Semyashkin E.G.
THE DEPENDENCE OF STAFFING APK
FROM PROFITABILITY22

Timchenko D. , Dyakov S.A.
FEATURES PERSONNEL MANAGEMENT IN
A CRISIS SITUATION..... 28

Dyakov S.A., Chichkanova E.S.
ANTI-CRISIS MANAGEMENT AS THE
FACTOR OF ENSURING ECONOMIC
SAFETY AT ENTERPRISE 31

PHILOLOGICAL SCIENCES

Burtseva Zh.V.
NORTH AS A WAY OF LIFE IN THE WORKS
OF A.N. KRIVOSHAPKIN36

Efremova E.M.
ARCHETYPES AND IMAGINATIVE
IMPLEMENTATION IN POETRY OF I.M.
GOGOLEV37

Kirillina M.A.
THE COMEDY-TRILOGY "NAARA SUOKH"
OF I.M. GOGOLEV AND THE POPULAR
HUMOR AND FOLK CULTURE..... 39

Nadolynska A.
REPRESENTATION OF THE "LOVE"
CONCEPT IN UKRAINIAN
LINGUOCULTURAL SPACE 41

PHILOSOPHICAL SCIENCES

Lysokolenko T.V.
GAME AS THE OTHER BEING IN THE
WORK OF M.BAKHTIN "AUTHOR AND
HERO IN THE AESTHETIC ACTIVITY"44

PHYSICS AND MATHEMATICS

Ibragimov A.A. , Khodzhabaev F.D.
ANALYSIS OF TOTAL ERROR OF
INTERVAL OPTION OF PENTA-POINT
RUN47

CHEMICAL SCIENCES

INVESTIGATION OF QUANTUM-CHEMICAL PROPERTIES OF INDOMETHACIN

Syrovaya A.O.

Kharkiv National Medical University, professor

Kozub S.N.

Kharkiv National Medical University, assistant professor

Tishakova T.S.

Kharkiv National Medical University, assistant professor

Levashova O.L.

Kharkiv National Medical University, PhD assistant

Chalenko N.N.

Kharkiv National Medical University, PhD assistant

Abstract

The quantum-chemical properties of indomethacin were determined. These properties are very important for understanding explanation the causes of the manifestation of certain biological effects. The geometry optimization for indomethacin molecule was performed by PM3 method, Polak-Ribiere algorithm.

Pharmacological activity of a molecule depends not only on the character and sequence of atoms, but also on their spatial distribution in the molecule, atomic charges, position of the functional groups and active radicals, quantum-chemical properties.

Keywords: Indomethacin, spatial structure, quantum-chemical properties.

INTRODUCTION

Indomethacin ([1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]-acetic acid) is an effective anti-inflammatory, analgesic and antipyretic medicine from the NSAID group [2, 8]. Indomethacin has a wide spectrum of action: it is used in ophthalmology, gynecology, surgery, and is effective in the treatment of neuralgia. Indomethacin as a powerful anti-inflammatory agent allows rapid clinical improvement in inflammatory rheumatic diseases. Thus, it is helpful for pain suppression in a treatment of acute arthritis, gout, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and various injuries of soft tissue of the body. It shows a significant reduction of the morning stiffness and the number of inflamed joints, as well as a decrease in the sedimentation rate of erythrocytes (ESR) and C-reactive protein (CRP) in the rheumatoid arthritis treatment [11, 14].

Indomethacin causes weakening or disappearance of the pain syndrome having rheumatic and non-rheumatic nature, including pain in joints at rest and during movement, decrease of a morning stiffness and joints swelling. It contributes to an increase in the volume of movements, in inflammatory processes that occur after operations and injuries, quickly facilitates both spontaneous pain and pain when moving, and reduces inflammatory swelling at the wound site [6, 14].

Indomethacin suppresses the activity of anti-inflammatory factors, reduces the aggregation of platelets. Inhibiting both cyclooxygenases 1 and 2 (COX-1 and COX-2, giving preference to COX-1), it disrupts the metabolism of arachidonic acid, suppresses the exudative and proliferative phase of inflammation, reduces the amount of prostaglandins in both the inflammation focus and in healthy tissues [4, 12, 15].

In this paper, calculations of quantum-chemical properties of indomethacin molecule were carried out

with the aim of explanation of specific acting centers of this molecule.

MATERIAL AND METHODS

Research of quantum chemical and pharmacological properties of indomethacin was conducted by the method of molecular mechanic MM+ and semi empirical method PM3 [3, 7, 9]. All calculations were carried out using the Polak – Ribiere conjugate gradient algorithm. During the research, the following parameters were studied: charges of atoms (a.u./eV), distribution of electron density of outer-shell electrons, the total strain energy (kcal/mol), bonding energy (kcal/mol), electronic energy (kcal/mol), inter-nucleus interaction energy (kcal/mol), heat of formation (kcal/mol), localization and energy of highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals (eV) and absolute hardness (η , eV) [16].

Absolute hardness of the indomethacin molecule was determined by the following equation:

$$\eta = \frac{1}{2} (E_{\text{LUMO}} - E_{\text{HOMO}})$$

RESULTS AND DISCUSSION

Molecular model of indomethacin molecule was calculated based on geometrical optimization depicted in Figure 1; atoms numeration used in calculation of quantum chemical parameters are shown in Figure 2.

Calculated charges for each atom in the indomethacin molecule are presented in Figure 3. The regions of high electron density reside on oxygen atoms (-0.369; -0.316; -0.303 a.u.) as well as on nitrogen atom (-0.189 a.u.). The electron density on C₁, C₅, C₈, C₃₁ atoms: -0.143, -0.176, -0.163 and -0.179 respectively.

The electron deficient areas are observed on carbon atoms directly bonded to oxygen and nitrogen atoms (0.369, 0.311, 0.071 a.u.). Positive charges are located on hydrogen atoms (from 0.167 to 0.072 a.u.).

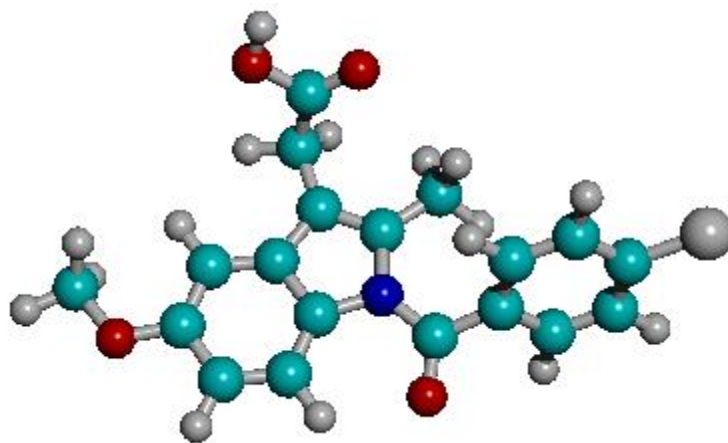


Figure 1. Structure of indomethacin molecule – green colour correspond to carbon atoms, blue – nitrogen, red - oxygen, grey – hydrogen.

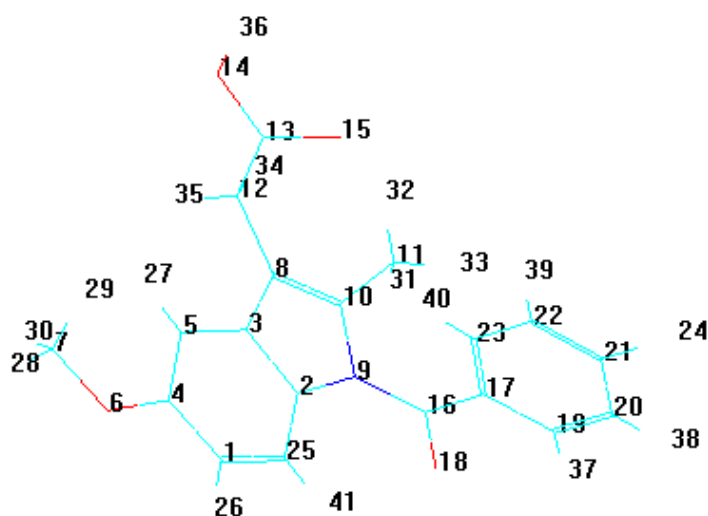


Figure 2. Atom numeration of indomethacin molecule used in calculation of quantum chemical parameters.

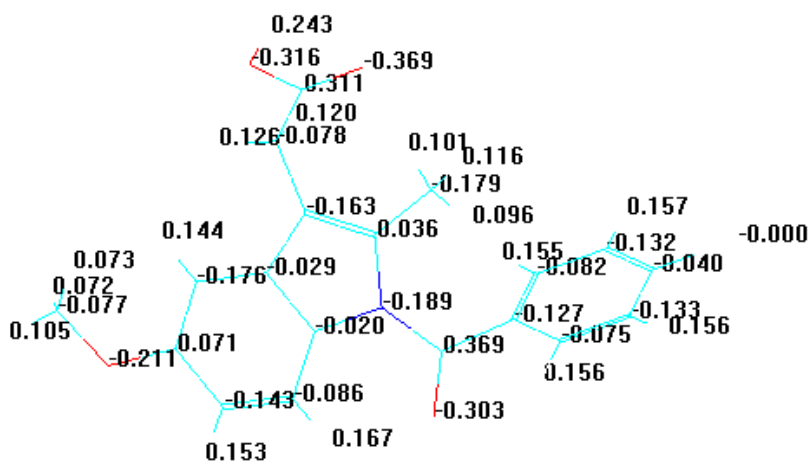


Figure 3. Atomic charges in indomethacin molecule.

The adsorption of the drug molecule from the intercellular fluid to the surface of the biomembrane depends on the projection of the vector of the dipole moment on the plane. It characterizes the extent of charge separation within a molecule. Dipole moment quantitatively determines a static polarization of particle. Its value is also a measure that defines the activity of chemical interaction (Figure 4).

The total dipole moment of indomethacin molecule is 2.5473 D. The distances at axes are $X = -2.1338$ D, $Y = 1.1464$ D, $Z = 0,7884$ D.

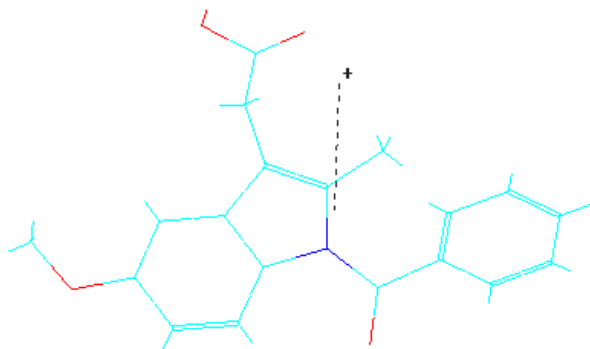


Figure 4. Dipole moment of indomethacin molecule

The distribution of electron density of outer valence electrons of the indomethacin molecule is shown in Figure 5. The highest electron density is observed on oxygen nitrogen and chloride atoms, C₂, C₃, C₅, C₁₇ and C₂₀ atoms. C₅ atom (+0.176) as a potential electrophile

may react with nucleophilic reagent. Hydrogen atoms directly bonded to oxygen are capable to form hydrogen bonds with electro neutral atoms of other molecules.

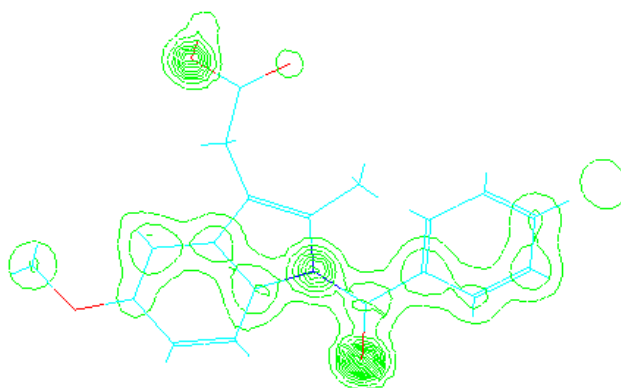


Figure 5. Distribution of electron density of outer valence electrons in the indomethacin molecule

The reactivity of the molecule characterizes by the localization of HOMO LUMO (H. Fukui theory) [1, 10, 19]. HOMO characterizes the molecule ability to interact with electron acceptors, LUMO – with electron donors. According to the Koopmans' theorem, energies of boundaries surfaces correspond to the ionization energy (HOMO energy) and electron affinity (LUMO energy). The frontier orbitals are delocalized in the indomethacin molecule.

The calculations of the energy levels of the electron orbitals allowed to quantify the value of the HOMO and LUMO energies; -8.6683eV and -0.7765 eV respectively. The value of the HOMO indicates that the molecule of indomethacin is a donor of electrons. Possible centers that can accept or donate electrons are indicated on the Figure 6 (a, b).

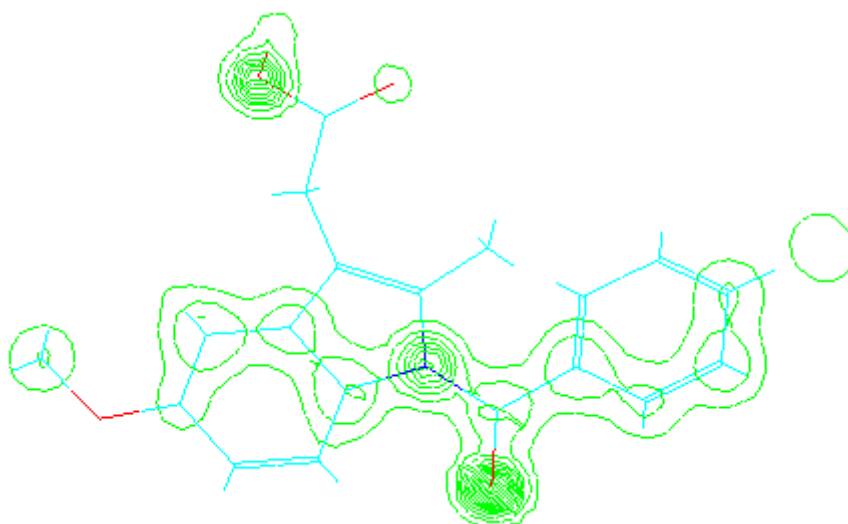


Figure 6a. Localization of HOMO in the indomethacin molecule

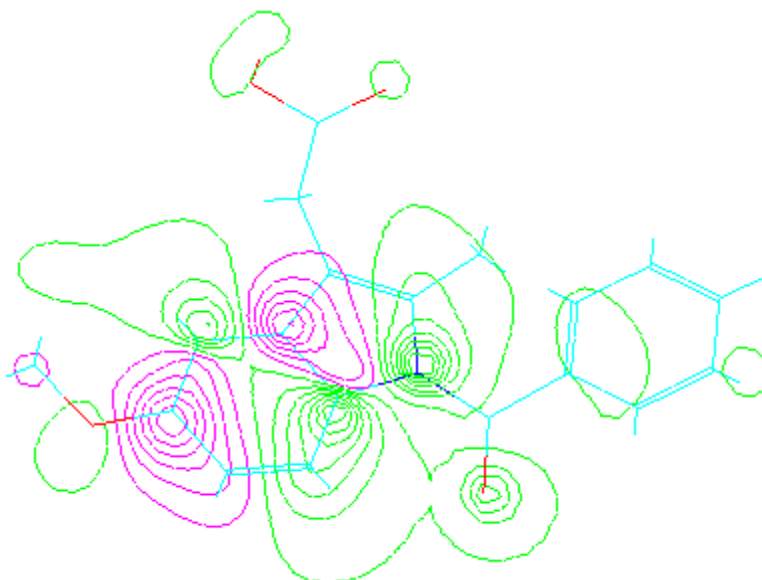


Figure 6b. Localization of LUMO in the indomethacin molecule

The value of absolute hardness represents the basis of the principles of soft and hard acids and bases. Soft substitutes make acids and bases softer, hard substitutes make them more rigid. The interaction energy increases with decrease of the reactants hardness.

Based on the energies of HOMO and LUMO, the absolute hardness of the molecule can be computed using data from Table 1. Based on the values obtained for HOMO and LUMO, the hardness of indomethacin molecule is equal to 3.9459.

Table 1.

Electro-optical properties of indomethacin

Property	Value
Total energy (E) (kcal/mol)	-104098.7758
Binding energy (kcal/mol)	-4547.99015
Electronic energy (kcal/mol)	-72.4094
Heat of formation (kcal/mol)	-87.2222
HOMO (eV)	-8.6683
LUMO (eV)	-0.7765
Hardness (η) (eV)	3,9459

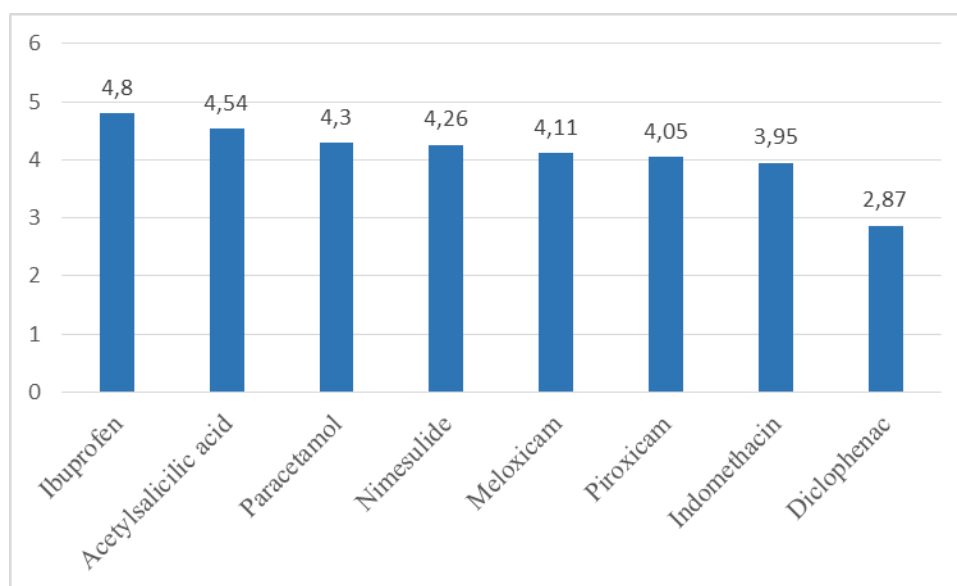


Figure 7. Hardness values (η)

By the comparison of hardness value (η) shown on Figure 7, we can conclude that the studied molecule can be considered as a soft reagent. Thus, indomethacin

most actively will react with soft reagents comprising cysteine residues in proteins as evidenced by the published data [5, 13, 17-20].

CONCLUSIONS

Main geometrical and energetic parameters were established for indomethacin molecule. It was shown that negative electrostatic potential is on the oxygen and nitrogen atoms. It was shown that indomethacin is a soft reagent ($\eta=3.9459$). The quantum-chemical properties of indomethacin could be the basis of the molecular mechanisms of its pharmacological action.

References

1. Apostolova E.S., Michayluk A.I., Tserelson V.G. Quantum chemical description of reactions. Moscow: Izdat. Center MORPH, 1999. - 45 p. [Russian].
2. Compendium 2014: Sat. Medical drugs. ed. by Kovalenko VN, Kiev: Moryon; 2014. - 24448 p. [Russian].
3. Chekman I.S. Quantum-chemical basis of pharmacokinetics / I.S. Chekman, N.O. Gorchakova, T.U. Nebesna et al. // Medical business, № 3/4, 2012 [Ukrainian].
4. Chekman I.S., Gorchakova N.O., Tumanov V.A. et al.; Chekman I.S. (Ed.) Pharmacology. Kiiiv: Visha shkola, 2001. - 598 p. [Ukrainian].
5. Chekman I.S., Syrovaya A.O., Levashova O.L., Kozub S.N. Investigation of quantum chemical properties of diclofenac. Reports of the National Academy of Sciences of Ukraine, 2016. - № 9. - P. 94-98. [Ukrainian].
6. Granik V.G. Fundamentals of Medicinal Chemistry. - M.: Vuzovskaya kniga, 2001. - 384 p. [Russian].
7. Kozhok N.N., Seluk S.A., Bichkova S.A., Besacha V.V. The optimal choice of NSAID in modern clinical practice. News of Medicine and Pharmacy, 8/218, 2007 [Russian].
8. Mashkovskii M.D. Medicinal product. - Moscow: New wave, 2012. - 1216 p. [Russian].
9. Minkin V.I., Simkin B.Y., Miniaev R.M. Theory of molecules structure. Rostov-on-Don: Phoenix, 1997. - 560 p. [Russian]
10. Molecular orbital studies in chemical pharmacology // A symposium held at Battelle Seattle research center / Ed. By L.B. Kier. - New York, 1969. - 284 p. [English].
11. Nasonove E. L. Nonsteroidal anti-inflammatory drugs for rheumatic diseases: treatment standards //RMG. 2001. № 7-9. p. 265-270 [Russian].
12. Neurology: национальное руководство / ed. E.I. Gusev, A.N. Konovalova, V.I. Skvortsova, A.B. Gecht. - M.:GEOTAR-Media, 2010. - 1040 p. [Russian].
13. Non-steroidal anti-inflammatory drugs in quantum chemistry: Monograph / I.S. Chekman, A.O. Syrovaya, O.L. Levashova et.al. - Kiev, Kharkov: "Planeta-print" Ltd, 2016. - 84 p. [English].
14. Tannenbaum H., Bombardier C., Davis P., Russel A. For the Third Canadian Consensus Conference Group//J. Rheumatology. 2005; 33: 140-157 [English].
15. Pharmaco-prescription guide of a pediatrician / ed. A.V. Sukalo, A.A. Kozlovsky. - Minsk: Belarusian Science, 2013. - 373 c. [Russian].
16. Soloviev M.E., Soloviev M.M. Kompyuternaya chimiya. Moscow: Solon-press, 2005. - 325 p. [Russian].
17. Syrovaya A.O., Levashova O.L., Andreeva S.V. Investigation of quantum chemical properties of paracetamol. Journal of chemical and Pharmaceutical Research, 2015. - 7(1). - P. 307-311. [English].
18. Syrovaya A.O., Tishakova T.S., Levashova O.L., Alekseeva Investigation of quantum chemical properties of ibuprofen. European applied sciences, 2015. - №5. -P. 82-85 [English].
19. Syrovaya A.O., Goncharenko N.A., Levashova O.L., Chalenko N.N. Investigation of quantum-chemical properties of meloxicam. The scientific heritage, 2016. - Vol. 1, № 1 (1). - P. 93-96 [English].
20. Zvyagintsev T.V., Syrova G.A., Chekman I.S., Celestial T.Y. Prediction pharmacological activity of potassium salt of 2,4-dyhlorbenzoynoyi acid. Pharmaceutical Journal, 2010. - №1. - P. 75-79 [Ukrainian].