VOL 1, No 1 (1) (2016)

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
All articles are reviewed
Free access to the electronic version of journal

«The scientific heritage»
Editorial board address: Budapest, Kossuth Lajos utca 84,1204
E-mail: public@tsh-journal.com
Web: www.tsh-journal.com

EARTH SCIENCES

SOCIAL SCIENCES

TECHNICAL SCIENCE

PHARMACEUTICAL SCIENCES

PHILOSOPHICAL SCIENCES

CHEMICAL SCIENCES

ECONOMIC SCIENCES

CHEMICAL SCIENCES

Syrovaya A.O.
Kharkiv National Medical University, professor

Goncharenko N.A.
Taras Shevchenko National University of Kiyv, PG student

Levashova O.L.
Kharkiv National Medical University, PhD assistant

Chalenko N.N.
Kharkiv National Medical University,PhD assistant

INVESTIGATION OF QUANTUM-CHEMICAL PROPERTIES OF MELOXICAM

ABSTRACT

Meloxicam is a nonsteroidal anti-inflammatory drug that is commonly used in medical practice.

We have studied the quantum-chemical properties of meloxicam, which are vital for understanding of mechanisms of biological and pharmacological activity at a molecular level. The geometry optimization for meloxicam molecule was performed by PM3 method, Polak-Ribiere algorithm. We have determined the distance between atoms, total charge density, characteristics of molecular orbitals (HOMO, LUMO) of meloxicam molecule.

Established quantum-chemical properties of meloxicam molecule are the basis of molecular mechanisms of its anti-inflammatory and analgesic action.

Keywords*: meloxicam, spatial structure, quantum-chemical properties.*

INTRODUCTION

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic activity.

The drug has been used successfully for the pain treatment in joints and spine for various rheumatic diseases and osteoarthritis, neurology and other area of medicine.

The safe usage of NSAIDs is a topical problem especially for elderly patients suffering from acute, chronic pain and requires long-term administration. The basic requirements for these drugs are: high anti-inflammatory and analgesic activity, minimal risk of unwanted side effects.

Meloxicam is a selective conjugate of a cyclooxygenase-2 (COX-2) activity that involves in the synthesis of prostaglandins and leukotrienes in the inflammation area. Selectivity coefficient for meloxicam is 2 [1]. Meloxicam has low risk of the mucous membrane ulcerative lesions development in the gastrointestinal tract, which is an advantage over non-selective NSAIDs [2].

Comparative studies of the acute renal failure (ARF) development during meloxicam, ibuprofen and indomethacin administration showed that meloxicam has the lowest risk of the ARF development among these NSAIDs [3, 4].

Addition of meloxicam to the standard therapy of acute coronary syndrome (recurrent angina, myocardial infarction) has led to a decrease in the frequency of adverse outcomes from 38.3% to 15% during the hospital stay and from 48.3% to 26.7% in 90 days after treatment [5]. However, despite of widespread occurrence in world practice data about quantum-chemical properties and spatial structure of meloxicam in scientific literature are not available.

Objective. The objective of this study is to carry out quantum-chemical researches of meloxicam molecule. This work is a part of the scientific research of the Medical and Bioorganic Chemistry Department of Kharkiv National Medical University. Earlier we have performed quantum-chemical studies of NSAIDs molecules having different chemical structure [6,7].

MATERIAL AND METHODS

Research of quantum chemical and pharmacological properties of meloxicam was conducted by the method of molecular mechanic MM+ and semi empirical method PM3 [8-13].

All calculations were carried out using the Polak – Ribiere conjugate gradient algorithm.

During the research, the following parameters were studied: interatomic dis-tance (E), atomic charges (a.u./eV), distribution of electron density of outer-shell electrons, the total energy (kcal/mol), bonding energy (kcal/mol), electronic energy (kcal/mol), nuclear 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) [14].

The global hardness corresponds to the gap between the HOMO and LUMO orbitals. The larger the HOMO-LUMO energy gap, the harder the molecule is. Absolute hardness of the paracetamol molecule was determined by the equation.

$\eta = ½ (E_{LUMO} – E_{HOMO})$

RESULTS AND DISCUSSIONS

Meloxicam belongs to the chemical class oxicams and

chemically designated as 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.

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

Calculated charges for each atom in the meloxicam molecule are presented in Figure 3. The regions of high electron density reside on oxygen atom of sulfo-, oxo- and hydroxo- groups (-0,931; -0,914; -0,322; -0,251 a. u. correspondingly) as well as on nitrogen atoms (-0,735; -0,271; -0,160 a. u.). The electron density is significantly different on the carbon atoms not directly associated with the nitrogen, oxygen and sulfur atoms: -0,150 a. u. (C_{19}), 0,039 (C_8); -0,147 and -0,094 on the carbon atom of methyl group C_{20} и C_{21} respectively. The carbon atoms of the thiazole rings have excess of electron density in the range of -0,814 (C_{17}) to 0,013 (C_{10}) a. u. The electron deficient areas are observed on carbon atoms directly bonded to oxygen (C_7, C_{10}) and nitrogen (C_8) (0,375; 0,013; 0,039; a.u.). Positive charges are located on hydrogen atoms (from 0,154 yo 0,087 a.u.).

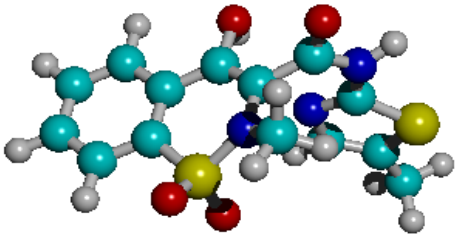

Figure. 1. Structure of meloxicam molecule – green colour correspond to carbon atoms, red - oxygen, blue – nitrogen, yellow – sulfur, grey - hydrogen.

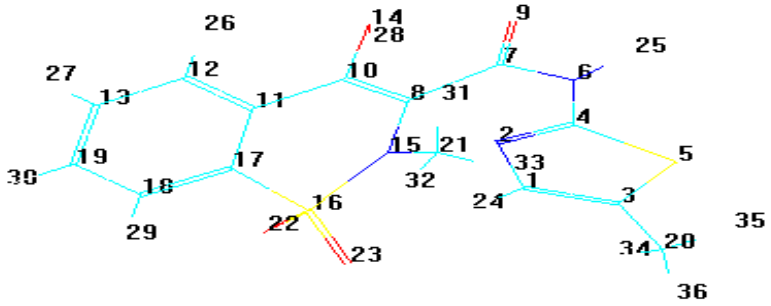

Figure. 2. Atom numeration of meloxicam molecule used in calculation of quantum chemical parameters.

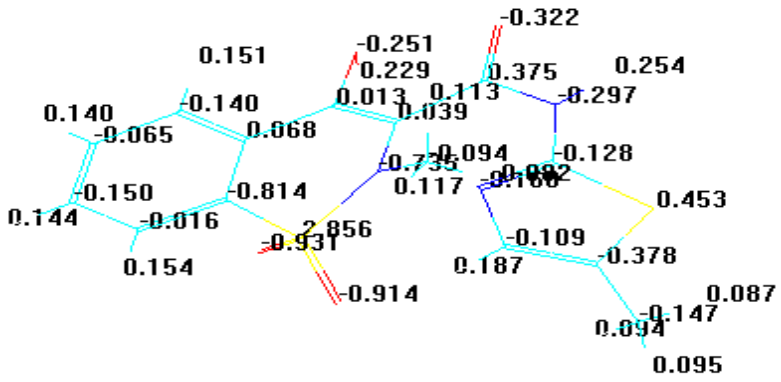

Figure. 3. Atom charges in meloxicam molecule.

Dipole moment of a molecule represents a sum of dipole moments of each chemical bond and having the directionality from the center of negative charges to the center of positive charges. It characterizes the asymmetry of charge distribution in electroneutral system. Dipole moment quantitatively determines a static polarization of particle. Its value is a measure that defines the activity of chemical interaction.

The total dipole moment of meloxicam molecule is 4,6188 D. The distances at axes are X = 1,5273 D, Y = -0,9881 D, Z = 4,2455 D (Fig. 4). The low value of the dipole moment denotes the low solubility of meloxicam.

The distribution of electron density of outer valence electrons of the meloxicam is shown in Figure 5. The highest electron density is observed on oxygen, nitrogen C_{10}, C_{11}, C_{17}, C_{18} and C_{19} carbon atoms. Hydrogen atoms directly bonded to oxygen and nitrogen are capable to hydrogen bond with electro neutral atoms of other molecules (oxygen or nitrogen of amino acids at the bonding place with receptors.

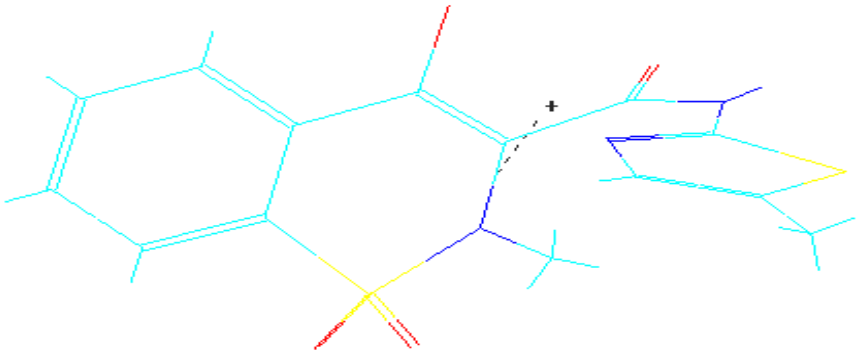

Figure 4. Direction of dipole moment in the meloxicam molecule.

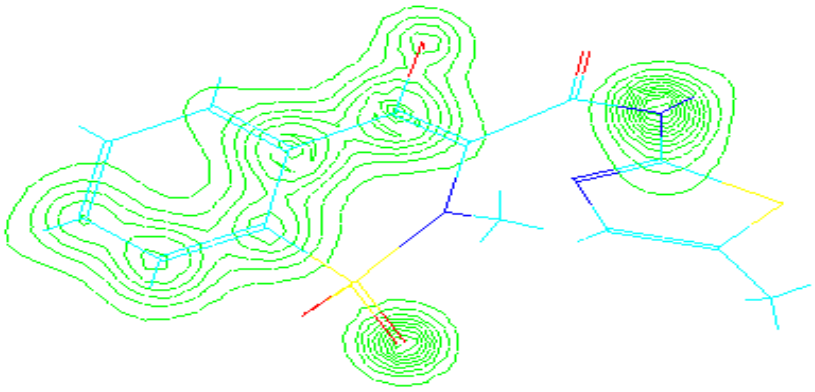

Figure. 5. Distribution of electron density of outer valence electrons in the meloxicam molecule.

The reactivity of the molecule is characterized by the localization of HOMO LUMO (H. Fukui theory) [17]. Table 1 shows some electro-optical parameters of the meloxicam molecule. Localization of electron density of HOMO LUMO depicted in Fig. 6 (a, b).

Table 1.

Electro-optical properties of meloxicam

Property	Value
Total energy (E) (kcal/mol)	-98249,7958
Binding energy (kcal/mol)	-3822,8415
Electronic energy (kcal/mol)	-689545,8675
Nuclear energy (kcal/mol)	591296,0717
Heat of formation (kcal/mol)	-43,0195
Hydration energy (kcal/mol)	-10,30
Polarizability (A)	28,01
HOMO (eV)	-9,199413
LUMO (eV)	- 0,9615749
Hardness (η, eV)	4,118919

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 meloxicam molecule.

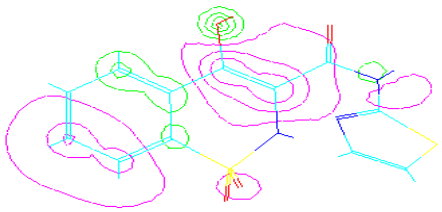

Figure 6a. Localization of HOMO in the meloxicam molecule

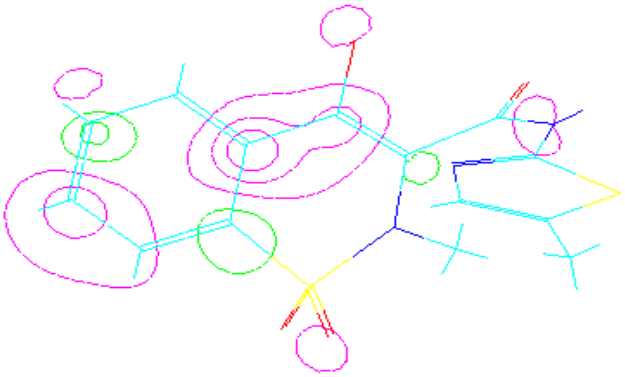

Figure. 6б. Localization of LUMO in the meloxicam molecule

Molecular parameters such as hardness can be computed using data from Table 1. Based on the values obtained for HOMO and LUMO, the hardness is equal to 4,118919 ($\eta = ½ E_{LUMO} – E_{HOMO}$).

By the comparison of hardness value (η) of other NAISD molecules (η, eB) such as paracetamol – 4,364926 eV, ibuprofen – 4,8036968 eV, that are soft molecules, we can conclude that the studied molecule can be considered as a soft reagent. Thus, meloxicam most actively will react with soft reagents comprising cysteine residues in proteins and glutathione [6-7].

CONCLUSIONS

Main geometrical and energetic parameters were established for meloxicam molecule.

It is shown that negative electrostatic potential in meloxicam molecule is observed on oxygen, nitrogen atoms.

Meloxicam is a mild reagent according to the values of the HOMO and LUMO energies and the absolute hardness.

References

1. Compendium 2014: Sat. Medical drugs. ed. by Kovalenko VN, Kiev: Moryon; 2014. - 24448 p.

2. Mashkovskii M.D. Medicinal product. – Moskow: New wave, 2012. - 1216 p. [Russian]

3. Winkelmeyer W. C., Waikar S. S., Mogun H., Solomon D. H. Nonselective and Cyclooxygenase-2-Selective NSAIDs and acute kidney injury // Am. J. Med., 121, 2008.

4. Kozchok 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].

5. Altman R., Luciardi H. L., Muntaner J. et al. Efficacy assessment of meloxicam, a preferential cyclooxigenase-2 inhibitor, in acute coronary syndromes without ST-segment elevation: The Nonsteroidal Anti-Inflammatory Drugs in Instable Angina Treatment –2 (NUT-2) Pilot Study // Circulation, V. 196, 2002.

6. Syrovaya A. O. Investigation of quantum-chemical properties of paracetamol / A. O. Syrovaya, O. L. Levashova, S. V. Andreeva // Journal of Chemical and Pharmaceutical Research, № 7 (1), 2015.

7. Tishakova T. S. Investigation of quantum-chemical properties of ibuprofen / T. S. Tishakova, Levashova, Singh Sukhdeep et al. // Europian applied science, Kharkiv, 14–15 May 2015: abstract book / KhNMU. – Kharkiv, №5, 2015.

8. 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].

9. Chekman I.S., Gorchakova N.O., Tumanov V.A. et al.; Chekman I.S. (Ed.) Pharmacology. Kiiv: Visha shkola, 2001. - 598 p. [Ukrainian].

10. Chekman I.S. Quantum Pharmacology. – Kiiv: Naukova dumka, 2012. - 180 p. [Ukrainian].

11. Chekman I.S. Quantum-chemical and topological descriptors in studies of “structure – activity” relationship. / I.S. Chekman, O.O. Kazakova, T.U. Nebesna // Journal of the Academy of medical sciences of Ukraine, 14, № 4, 2008 [Ukrainian].

12. Minkin V.I., Simkin B.Y., Miniaev R.M. Theory of molecules structure. Rostov-on-Don: Phoenix, 1997. - 560 p. [Russian]

13. Nebesna T.U., Zagorodnii M.I., Yagupova A.S., Gorchakova N.O., Chekman I.S. The study of molecular structure and chemical properties of quantum-acetylcysteine // Ukrainian Scientific Medical Youth Journal, № 1-2, 2007 [Ukrainian].

14. Soloviev M.E., Soloviev M.M. Kompyuternaya chimiya. Moskow: Solon-press, 2005. - 325 p. [Russian].

15. Apostolova E.S., Michayluk A.I., Tserelson V.G. Quantum chemical de-scription of reactions. Moskow: Izdat. Center MORPH, 1999. - 45 p. [Russian].

16. Molecular orbital studies in chemical pharmacology // A symposium held at Battele Seatle research center / Ed. By L.B. Kier. – New York, 1969. -284 p.

17. William O Foye; Thomas L Lemke; David A Williams / Foye’s principles of Medicinal Chemistry 6th edition.– Philadelphia : Lippincott Williams & Wilkins, 2008. - 1377 p.