

Geometric and electronic papaverine's structure and its acid strength

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ABSTRACT

Firstly the quantum-chemical calculation was done in the frames of molecular model by methods RHF/6-311G** and DFT-PBE0/6-311G** of papaverine's molecule. Received optimization geometric and electronic structure of this compound. Theoretically appreciated its acid strength. It is proved, that the papaverine's molecule belongs to the class of very weak acid ($pK_a > 14$). It is shown, that 3,4-di(methoxy)benzyl group is the electron-donor assistant. It is considered, that influence of dimethoxy-group and 3,4-di(methoxy)benzyl group on the distribution of electronic density and significance of the pK_a .

Keywords: quantum-chemical calculation; RHF/6-311G** and DFT-PBE0 / 6-311g ** methods; papaverine; dimethoxy-group; 3,4-di(methoxy)benzyl group; acid strength.

1. INTRODUCTION

Papaverine (the Nobel Prize, Robenson Robert, 1947) belong to the group of miotrop spasmolytics, that is medicinal preparations, taking off the spasms of smooth muscular of inner organs and walls of blood vessels by influence is method directly on cells of muscles[1].

Pharmacological action of papaverine is connected with suppressing of ferment phosphodiesterase (FDE), that calls the accumulation in the cell cyclic mononucleotides [2]. Accumulation of cyclic mononucleotides puts on the brakes the connection of miosinis albumen with the other albumen named actin in the result of that can found actomiosin, brining the contraction of muscular fibers[3]. This way, papaverine

suppresses spasms of smooth muscular of inner organs and the walls of blood vessels. More active it influences on the smooth muscular of gastrointestinal tract, gall-leading ways, pancreatic duct, bladder's ways, sexual system and bronchial tubes. In less degree papaverine takes off the spasms of artery is walls, that promotes the increase of circulation of the blood, that way in the heart sphere and the head brain (spasms of head brain vessels decreases less), so decreases the blood pressure. In large doses papaverine decreases the excitability of heart muscle and reduces the inner heart conductivity.

Structural formula of papaverine - 1-(3,4-dimethoxy)-6,7-dimethoxyisoquinoline hydrochloride is shown on figure 1, and its UV-spectrums are shown on figure 2.

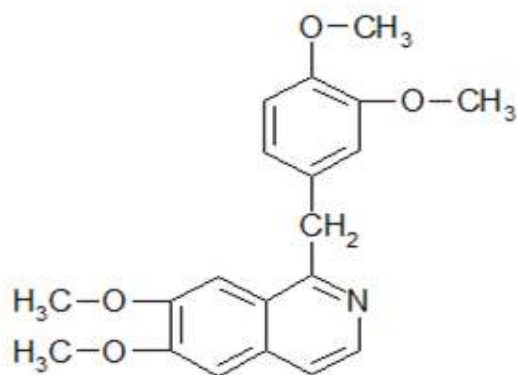


Fig. 1. Structural formula of papaverine[3].

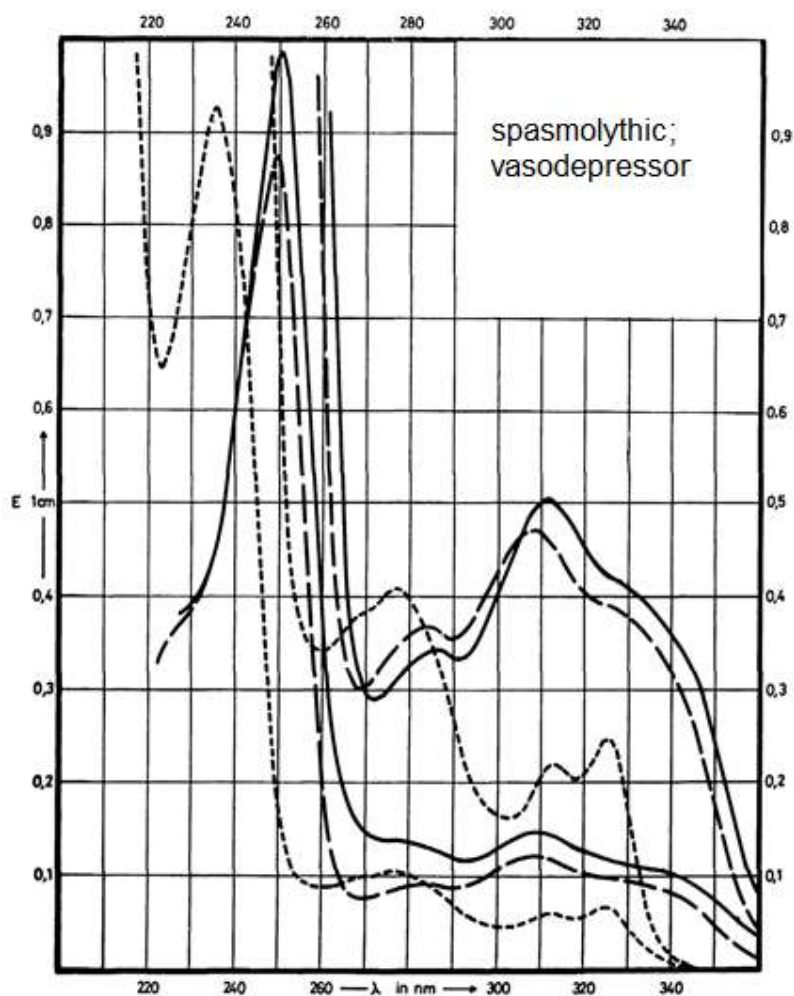


Fig. 2. UV-spectrum of papaverine (the conditions obtaining of spectrum in table 1)[3]

Table1. Parameters of UV-spectrum (methanol, 0.1M HCl, 0.1M NaOH).

Concentration – 0.5mg /100 ml and 2.0 mg/100ml				
Solvent	Methanol	0.1M HCl	0.1M NaOH	
	—————	-----	*****	
Maximum of	311 nm	308 nm	326 nm	

absorption	250 nm	284 nm 249 nm	277 nm 236 nm
$E_{1\%}^{1\text{cm}}$	244 1910	228 178 1700	117 196 1800
ϵ	9170 71800	8570 6690 63900	4400 7370 67670

Parameters of UV-spectrum of papaverine correspond to the availability π -systems of aromatic and nitrogen containing of heterocycles and p-electrons of nitrogen's atom in the heterocycle (π - π and n- π crossings). UV-spectrums of hydrochloride of papaverine correspond to the spectrum of comparison, and so UV – spectrums of solutions of preparations in ethanol (280, 315, 825, 238 nm) and in 0.01M in solution of HCL (hydrochloric acid) (250 and 309 nm). Identify the papaverine hydrochloride (in 0.0025% solution) can according to the second derivative UV-spectrum of absorption, finding by method of numerous differentiation. This method is more objective, than analyses under positions of maximum absorption.

As seen from figure 1 and table 1 position and intensiveness of maximum of absorption in the UV-spectrum of papaverine is defined by pH-environment. The largest significance of maximum absorption is observed for the structure, forming in alkaline environment. Probably in the alkaline environment manifests H-acidity of methylene-group, situated between two aromatic nucleuses. Obviously, that acid strength of papaverine depends on the environment and defines its properties and pharmacological action. That's why the doubtless interest presents also the appraisal of its acid strength in gas phase, and, in particular, through the calculation of quantum-chemical methods of the maximum charge on the hydrogen atom ($q_{\max}^{\text{H}^+}$)

2. MATERIALS AND METHODS

For the appraisal of acid strength of papaverine were used the formula (1) $pK_a = 49.04 - 134.61 \cdot q_{\max}^{\text{H}^+}$ [9] and (2) $pK_a = 51.048 - 150.078 \cdot q_{\max}^{\text{H}^+}$, where pK_a is a universal measure of acidity, and $q_{\max}^{\text{H}^+}$ - maximum charge on the hydrogen is atom of papaverine, received from the calculation by the method RHF/6-311G** for formula(1) and by method DFT-PBE0/6-311G** [4-5] (Nobel Prize, W. Kohn, 1998) for formula (2), received by authors. Namely by the only these methods and in these bases were received the

formulas (1) and (2) with maximum highest coefficients of correlation.

These formulas received by other methods and in other bases have coefficients of correlation less, than in formulas (1) and (2), that naturally tell upon the precision of calculation pK_a . Optimization of geometry of molecular papaverine's system were done on all parameters by the gradient method built into the Firefly [4,5], which is the fundamental basis of the stationary Erwin Schrodinger's equation (Nobel Prize, 1933). The calculation has been performed in an approximation of an isolated molecule within the molecular model in the gas phase.

The total charge of papaverine's molecule was zero, and the multiplicity is $M = 2S + 1 = 1$ (all electrons are doubled in connection with that the total spin of studied, molecular system is zero. For a visual representation of the molecular model of papaverine the MacMolPlt[6] program has been used.

3. EXPERIMENT, RESULTS AND DISCUSSION

Optimization geometric and electronic structure, the total energy of papaverine is molecule was received by the methods RHF/6-311G** and DFT-PBE0/6-311G** and are shown on figure 3-4 and in the tables 2-3. Find the significance of acid strength (pK_a) by formulas, received by authors for considered methods as analogously described in [7].

$pK_a = 49.04 - 134.61 \cdot q_{\max}^{\text{H}^+}$ (for method RHF/6-311G**, $pK_a = 30$),

$pK_a = 51.048 - 150.078 \cdot q_{\max}^{\text{H}^+}$ (for method DFT-PBE0/6-311G**, $pK_a = 27$),

where $q_{\max}^{\text{H}^+} = 0.14$ (for method RHF/6-311G**) and $q_{\max}^{\text{H}^+} = 0.16$ (for method DFT-PBE0/6-311G**)- maximum charge on the atom of hydrogen, see Tables 2-3 – and Figures 3-4, pK_a is a universal measure of acidity.

Consider issues of mutual influence of atom of papaverine's molecule (figure 3-4, tables 2-3). In

benzene cycle of isoquinoline's structure (method RHF/6-311G**) the atoms of hydrogen C(3) and C(4) bring negative charge accordingly -0.13 C(3) and -0.09 C(4). These atoms are situated relatively each other in p-situation and in o-situation to the electron-donor methoxy-group (p- π effect). The negative charge on the main atom C(6), which is situated in the para-situation to the methoxy group also negative and is -0.17. The largest electronic density (-0.43) is localized on the hydrogen's atom N(14) (table 2) indivisible pair of electrons, localized on this atom. The highest electronic density on the oxygen's atoms O(6) and O(7) methoxy-group (-0.43 and -0.44) is discussed the presence of indivisible pair of electrons on these atoms, crossing with π -electrons bicyclic system of isoquinoline.

3,4-di(methoxy)benzyl group is the only electron-donor assistant, so the charge on the carbon's atom C(19) methylene group is negative (-0.12). Geometric and electronic structure of papaverine's molecule, received by method DFT-PBE0/6-311G** confirmed received results on the distribution of electronic density. The charge on the atom C(4) is -0.06 (and is -0.09 for method RHF/6-311G**), on the atom C(6) is -0.14 (and is -0.16 for method RHF/6-311G**). 3,4-di(methoxy)benzyl group also was shown itself as electron-donor assistant, however the atom of carbon C(19) methylene group was more negative (-0.23).

4. CONCLUSION

Thus, quantum-chemical calculation of papaverine's molecule was done by us with methods RHF/6-311G** and DFT-PBE0/6-311G**. Received an optimized geometric and electronic structure of this compound. Theoretically appreciated its acid strength $pK_a=30$ (for RHF/6-311G**) and $pK_a=27$ (for DFT-PBE0/6-311G**) that is situated in enough good accordance with appraisal pK_a , done in work [8]

It is considered, that papaverine belongs the class of very weak H-acids ($pK_a>14$). Examined the questions of mutual influence of atom in the papaverine's molecule and is shown, that 3,4-di(methoxy)benzyl group is the electron-donor assistant, so the charge on the carbon's atom C(19) methylene group is negative (-0.12). It is shown, how simultaneous introduction the dimethoxy group into the benzyl cycle of isoquinoline and 3,4-di(methoxy)benzyl group into ortho-situation to the nitrogen's atom of pyrimidine cycle influences on the distribution of electronic density and significance of pK_a .

Finally, made quantum-chemical calculations can promote the elaborations of new, more effective spasmolytics, for example, according the algorithms proposed in [8].

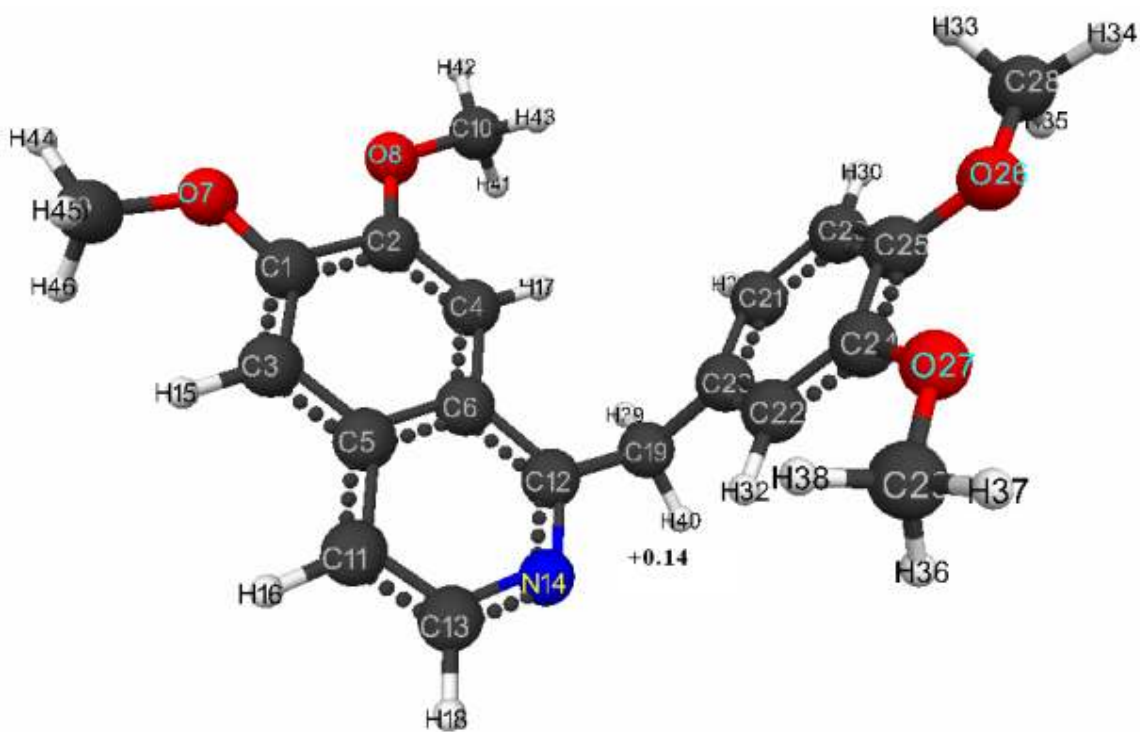


Fig. 3. Geometric and electronic structure of papaverine's molecule received by the method of RHF/6-311G** ($E_0 = -2\,949\,707$ kJ/mol)

Table 2. The Optimized Bond Lengths, Valence Angles and the Charges on the Atoms of the molecule of papaverine, received by the method of RHF/6-311G.**

The bond lengths	R, Å	The valence angles	Degree	Atom	The charges on the atoms
C(2)-C(1)	1.44	C(5)-C(3)-C(1)	121	C(1)	+0.28
C(3)-C(1)	1.35	C(6)-C(4)-C(2)	121	C(2)	+0.25
C(3)-C(5)	1.42	C(2)-C(1)-C(3)	120	C(3)	-0.13
C(4)-C(2)	1.35	C(11)-C(5)-C(3)	122	C(4)	-0.09
C(4)-C(6)	1.43	C(6)-C(5)-C(3)	120	C(5)	+0.08
C(5)-C(11)	1.41	C(1)-C(2)-C(4)	120	C(6)	-0.17
C(6)-C(5)	1.40	C(5)-C(6)-C(4)	119	O(7)	-0.43
O(7)-C(1)	1.33	O(8)-C(2)-C(4)	126	O(8)	-0.44
O(8)-C(2)	1.34	C(12)-C(6)-C(4)	123	C(9)	-0.04
C(9)-O(7)	1.40	C(13)-C(11)-C(5)	119	C(10)	-0.05
C(10)-O(8)	1.40	C(11)-C(5)-C(6)	118	C(11)	-0.21
C(11)-C(13)	1.35	C(2)-C(1)-O(7)	115	C(12)	+0.18
C(12)-C(6)	1.43	C(1)-C(2)-O(8)	115	C(13)	+0.12
C(13)-N(14)	1.35	C(1)-O(7)-C(9)	120	N(14)	-0.43
N(14)-C(12)	1.30	C(2)-O(8)-C(10)	119	H(15)	+0.10
H(15)-C(3)	1.07	N(14)-C(13)-C(11)	124	H(16)	+0.08
H(16)-C(11)	1.07	C(5)-C(6)-C(12)	118	H(17)	+0.13
H(17)-C(4)	1.07	C(12)-N(14)-C(13)	119	H(18)	+0.10
H(18)-C(13)	1.08	C(6)-C(12)-N(14)	122	C(19)	-0.12
C(19)-C(12)	1.52	C(19)-C(12)-N(14)	116	C(20)	-0.15
C(20)-C(19)	1.52	C(1)-C(3)-H(15)	121	C(21)	-0.10
C(21)-C(20)	1.37	C(5)-C(3)-H(15)	118	C(22)	-0.09
C(22)-C(20)	1.40	C(13)-C(11)-H(16)	121	C(23)	-0.14
C(23)-C(21)	1.40	C(2)-C(4)-H(17)	120	C(24)	+0.26
C(24)-C(22)	1.37	C(6)-C(4)-H(17)	119	C(25)	+0.24
C(24)-C(25)	1.41	N(14)-C(13)-H(18)	115	O(26)	-0.44
C(25)-C(23)	1.37	C(6)-C(12)-C(19)	122	O(27)	-0.44
O(26)-C(25)	1.35	C(12)-C(19)-C(20)	114	C(28)	-0.04
O(27)-C(24)	1.34	C(19)-C(20)-C(21)	122	C(29)	-0.04
C(28)-O(26)	1.40	C(22)-C(20)-C(21)	118	H(30)	+0.10
C(29)-O(27)	1.40	C(19)-C(20)-C(22)	120	H(31)	+0.08
H(30)-C(23)	1.07	C(25)-C(24)-C(22)	120	H(32)	+0.13
H(31)-C(21)	1.08	C(20)-C(21)-C(23)	121	H(33)	+0.08
H(32)-C(22)	1.07	C(20)-C(22)-C(24)	121	H(34)	+0.11
H(33)-C(28)	1.09	C(23)-C(25)-C(24)	119	H(35)	+0.09
H(34)-C(28)	1.08	O(26)-C(25)-C(24)	116	H(36)	+0.09
H(35)-C(28)	1.09	C(21)-C(23)-C(25)	121	H(37)	+0.11
H(36)-C(29)	1.09	C(23)-C(25)-O(26)	125	H(38)	+0.09
H(37)-C(29)	1.08	C(22)-C(24)-O(27)	125	H(39)	+0.11
H(38)-C(29)	1.09	C(25)-C(24)-O(27)	116	H(40)	+0.14
H(39)-C(19)	1.08	C(25)-O(26)-C(28)	119	H(41)	+0.09
H(40)-C(19)	1.08	C(24)-O(27)-C(29)	120	H(42)	+0.12
H(41)-C(10)	1.09	C(21)-C(23)-H(30)	119	H(43)	+0.10
H(42)-C(10)	1.08	C(20)-C(21)-H(31)	120	H(44)	+0.12
H(43)-C(10)	1.09	C(20)-C(22)-H(32)	118	H(45)	+0.09
H(44)-C(9)	1.08	O(26)-C(28)-H(33)	112	H(46)	+0.09
H(45)-C(9)	1.09	O(26)-C(28)-H(34)	106		
H(46)-C(9)	1.09	O(26)-C(28)-H(35)	112		
		O(27)-C(29)-H(36)	112		
		O(27)-C(29)-H(37)	106		
		O(27)-C(29)-H(38)	111		
		C(12)-C(19)-H(39)	110		
		C(12)-C(19)-H(40)	106		
		O(8)-C(10)-H(41)	111		
		O(8)-C(10)-H(42)	106		
		O(8)-C(10)-H(43)	111		

		O(7)-C(9)-H(44)	106		
		O(7)-C(9)-H(45)	111		
		O(7)-C(9)-H(46)	111		

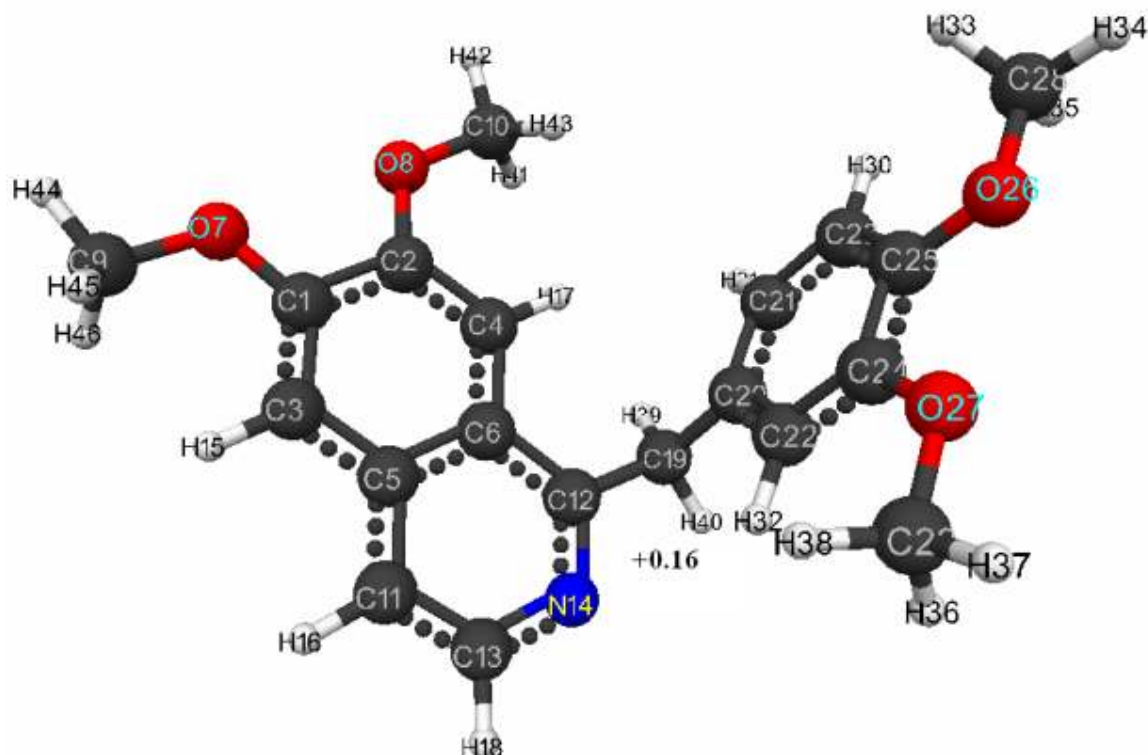


Fig. 4. Geometric and electronic structure of papaverine's molecule, received by the method of DFT-PBE0/6-311G** ($E_0 = -2\,964\,573$ kJ/mol)

Table 3. The Optimized Bond Lengths, Valence Angles and the Charges on the Atoms of the molecule of papaverine, received by the method of DFT-PBE0/6-311G**

The bond lengths	R, Å	The valence angles	Degree	Atom	The charges on the atoms
C(2)-C(1)	1.43	C(5)-C(3)-C(1)	121	C(1)	+0.19
C(3)-C(1)	1.37	C(6)-C(4)-C(2)	121	C(2)	+0.16
C(3)-C(5)	1.42	C(2)-C(1)-C(3)	120	C(3)	-0.10
C(4)-C(2)	1.37	C(11)-C(5)-C(3)	123	C(4)	-0.06
C(4)-C(6)	1.42	C(6)-C(5)-C(3)	119	C(5)	+0.06
C(5)-C(11)	1.41	C(1)-C(2)-C(4)	120	C(6)	-0.14
C(6)-C(5)	1.42	C(5)-C(6)-C(4)	119	O(7)	-0.33
O(7)-C(1)	1.34	O(8)-C(2)-C(4)	125	O(8)	-0.33
O(8)-C(2)	1.35	C(12)-C(6)-C(4)	123	C(9)	-0.19
C(9)-O(7)	1.41	C(13)-C(11)-C(5)	119	C(10)	-0.19
C(10)-O(8)	1.41	C(11)-C(5)-C(6)	118	C(11)	-0.18
C(11)-C(13)	1.37	C(2)-C(1)-O(7)	115	C(12)	+0.12
C(12)-C(6)	1.42	C(1)-C(2)-O(8)	115	C(13)	+0.07
C(13)-N(14)	1.35	C(1)-O(7)-C(9)	118	N(14)	-0.37
N(14)-C(12)	1.32	C(2)-O(8)-C(10)	117	H(15)	+0.11
H(15)-C(3)	1.08	N(14)-C(13)-C(11)	124	H(16)	+0.09
H(16)-C(11)	1.09	C(5)-C(6)-C(12)	118	H(17)	+0.14
H(17)-C(4)	1.08	C(12)-N(14)-C(13)	119	H(18)	+0.11
H(18)-C(13)	1.09	C(6)-C(12)-N(14)	123	C(19)	-0.23
C(19)-C(12)	1.51	C(19)-C(12)-N(14)	116	C(20)	-0.16
C(20)-C(19)	1.51	C(1)-C(3)-H(15)	121	C(21)	-0.09

C(21)-C(20)	1.38	C(5)-C(3)-H(15)	118	C(22)	-0.05
C(22)-C(20)	1.40	C(13)-C(11)-H(16)	121	C(23)	-0.15
C(23)-C(21)	1.40	C(2)-C(4)-H(17)	120	C(24)	+0.18
C(24)-C(22)	1.38	C(6)-C(4)-H(17)	119	C(25)	+0.18
C(24)-C(25)	1.41	N(14)-C(13)-H(18)	115	O(26)	-0.34
C(25)-C(23)	1.38	C(6)-C(12)-C(19)	121	O(27)	-0.34
O(26)-C(25)	1.35	C(12)-C(19)-C(20)	114	C(28)	-0.18
O(27)-C(24)	1.35	C(19)-C(20)-C(21)	122	C(29)	-0.19
C(28)-O(26)	1.41	C(22)-C(20)-C(21)	119	H(30)	+0.11
C(29)-O(27)	1.41	C(19)-C(20)-C(22)	120	H(31)	+0.08
H(30)-C(23)	1.08	C(25)-C(24)-C(22)	120	H(32)	+0.13
H(31)-C(21)	1.09	C(20)-C(21)-C(23)	121	H(33)	+0.12
H(32)-C(22)	1.08	C(20)-C(22)-C(24)	121	H(34)	+0.14
H(33)-C(28)	1.10	C(23)-C(25)-C(24)	119	H(35)	+0.12
H(34)-C(28)	1.09	O(26)-C(25)-C(24)	116	H(36)	+0.13
H(35)-C(28)	1.10	C(21)-C(23)-C(25)	121	H(37)	+0.14
H(36)-C(29)	1.10	C(23)-C(25)-O(26)	125	H(38)	+0.13
H(37)-C(29)	1.09	C(22)-C(24)-O(27)	125	H(39)	+0.14
H(38)-C(29)	1.10	C(25)-C(24)-O(27)	115	H(40)	+0.16
H(39)-C(19)	1.10	C(25)-O(26)-C(28)	117	H(41)	+0.12
H(40)-C(19)	1.09	C(24)-O(27)-C(29)	117	H(42)	+0.14
H(41)-C(10)	1.10	C(21)-C(23)-H(30)	119	H(43)	+0.14
H(42)-C(10)	1.09	C(20)-C(21)-H(31)	120	H(44)	+0.15
H(43)-C(10)	1.10	C(20)-C(22)-H(32)	118	H(45)	+0.13
H(44)-C(9)	1.09	O(26)-C(28)-H(33)	112	H(46)	+0.13
H(45)-C(9)	1.10	O(26)-C(28)-H(34)	106		
H(46)-C(9)	1.10	O(26)-C(28)-H(35)	112		
		O(27)-C(29)-H(36)	112		
		O(27)-C(29)-H(37)	106		
		O(27)-C(29)-H(38)	112		
		C(12)-C(19)-H(39)	110		
		C(12)-C(19)-H(40)	106		
		O(8)-C(10)-H(41)	111		
		O(8)-C(10)-H(42)	106		
		O(8)-C(10)-H(43)	111		
		O(7)-C(9)-H(44)	106		
		O(7)-C(9)-H(45)	111		
		O(7)-C(9)-H(46)	111		

REFERENCES

1. Kulbuach VO. Pharmaceutical Chemistry. Leningrad: Medicine - 1966. - 761p.
2. Belousova EA. Spasmolytics in gastroenterology: comparative characteristics and testimony for using. Pharmacology. - 2002. - № 9. 40-45 p
3. Kril'skiy DV, Slivkin AV. Heterocyclic medicinal substances (medicinal substances with heterocyclic structure) Teaching aid on pharmatsevtic chemistry. Voronezh. - 2007. - 234 p.
4. Granovsky Alex A., Firefly version 8, <http://classic.chem.msu.su/gran/firefly/index.html>
5. Schmidt MW, Baldrosge KK, Elbert JA, Gordon MS, Enseh JH, Koseki S and et al. General Atomic and Molecular Electronic Structure System. J. Comput. Chem. – 1993. - №14. –Pp. 1347-1363.
6. Bode BM and Gordon MS. J. Mol. Graphics Mod. - 16. – 1998. - Pp 133-138.
7. Babkin VA, Andreev DS, Fomichyov VT, Zaikov GE, Mukhamedzyanova ER. About the Correlation Dependence of the Universal Indicator of Acidity with the Maximum Charge on the Hydrogen Atom of H-acids. AM1 Method. Vestnik of the Kazan Technological University. – Kazan. – 2012. - №10. - Pp. 15-19.
8. Babkin VA, Zaikov GE. Nobel Laureates and Nanotechnologies of Applied Quantum Chemistry. - USA. New York : Nova Science Publishers. -2010. -351p
9. Babkin VA, Fedunov RG, Minsker KS, Ponomarev OA, Sangalov YA, Berlin AA, Zaikov GE. Connection of the universal acidity index of H-acids with the charge on Hydrogen atom (AB INITIO METHOD). Oxidation Communication – 2002. – 25. - №1. - Pp 21 - 47.