Geometric and Electronic Structure of Papaverine and Its Acid Strength

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Authors' contributions

Article Information

Original Research Article

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ABSTRACT

For the first time ever, the quantum-chemical calculation of papaverine molecule was performed within the framework of molecular model by methods RHF/6-311G** and DFT-PBE0/6-311G**. Optimized geometric and electronic structure of this compound was obtained. Its acid strength was also theoretically estimated. It was proved that papaverine molecule belongs to the class of very weak acids (pKa>14). It was shown that 3.4-di(methoxy)benzyl group is the electron-donating substituent. It is revealed, that dimethoxy-group and 3.4-di(methoxy)benzyl group influence on the distribution of electronic density and pKa value.

1. INTRODUCTION

Papaverine (the Nobel Prize, Robenson Robert, 1947) belongs to the group of miotropicspasmolytics, i.e. medicine curing convulsions of the unstriated muscles of visceral organs and of the walls of blood vessels by direct influence on the muscles cells [1].

Pharmacological action of papaverine is connected with suppressing the phosphodiesterase ferment (FDE), that induces accumulation of cyclic mononycleotides in the cell [2-4]. Accumulation of cyclic mononycleotides slows downbanding of protein myosin and another protein named actin, which could lead to production of actomiosin, which induces contraction of muscular fibers [5]. Thus, papaverine suppresses convulsions of the unstriated muscles of visceral organs and of the walls of blood vessels. Its most active influence is on the unstriated muscles of gastrointestinal tract, gall-leading ways, pancreatic duct, bladder's ways, genital system and bronchial tubes. In somewhat less degree papaverine cures the convulsions of the arteries walls, which induces the increase of blood circulation, including in the area of heart and brain (convulsions of brain vessels are relieved insignificantly), blood pressure also becomes lower. In large doses, papaverine decreases the excitability of heart muscle and reduces the inner conductivity of the heart.

Structural formula of papaverine -1-(3.4-dimethoxy)-6.7-dimethoxyisoquinoline hydro-chloride is shown on Fig. 1, and its UV-spectra are shown on Fig. 2.

Parameters of UV-spectrum of papaverine correspond to presence of π-systems of aromatic and nitrogen-containing heterocycles and p-electrons of nitrogen atom in the heterocycle (π-π and n-π jumping). UV-spectrums of hydrochloride of papaverine correspond to the comparison spectrum, and alsoto UV-spectrums of medication solutions in ethanol (280, 315, 825, 238 nm) and in 0.01 M hydrochloric acid solution (250 and 309 nm). Papaverine hydrochloride can be identified (in 0.0025% solution) by the second derivative of UV absorption spectrum, calculated by method of numerical differentiation. This method is more objective, than analysis by positions of absorption maxima.

As seen from Fig. 1 and Table 1, position and intensiveness of absorption maxima in the UV-spectrum of papaverine is defined by pH-environment. The largest value of absorption maximum is observed for the structure forming in alkaline environment. Probably H-acidity of methylene-group, situated between two aromatic nucleuses, is evident in the alkaline environment. Obviously the acid strength of papaverine depends on the environment and defines its properties and pharmacological action. That's why not without interestare the estimations of its acid strength in vapor phase, in particular, through the calculation of the maximum charge on the hydrogen atom (q_{max}^{H+}) by quantum-chemical methods.
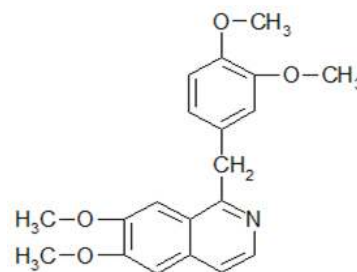

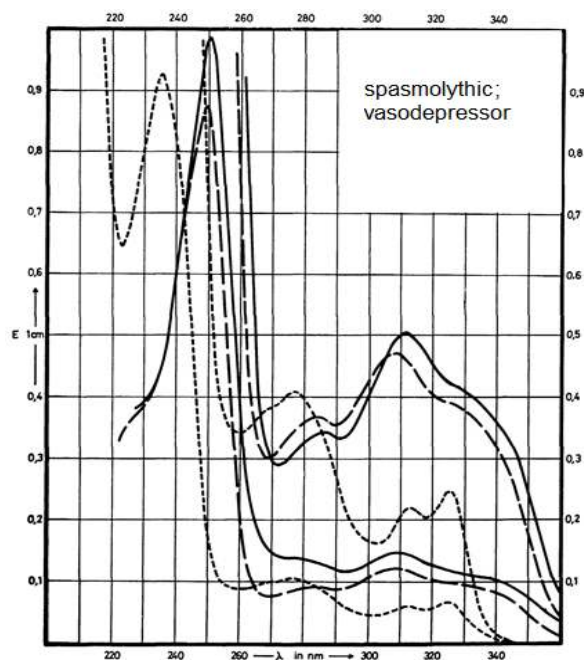**Fig. 1. Structural formula of papaverine [5]**

Fig. 2. UV-spectrum of papaverine (the conditions of spectrum reading are indicated in Table 1) [5]

Table 1. Parameters of UV-spectrum (methanol, 0.1M HCl, 0.1M NaOH)

Concentration – 0.5 mg /100 ml and 2.0 mg/100 ml			
Solvent	Methanol	0.1M HCl	0.1M NaOH
	▬▬▬	▬ ▬ ▬	··········
Absorption maximum	311 nm	308 nm	326 nm
	250 nm	284 nm	277 nm
		249 nm	236 nm
$E_{1\%}^{1cm}$	244	228	117
	1910	178	196
		1700	1800
ε	9170	8570	4400
	71800	6690	7370
		63900	67670

2. MATERIALS AND METHODS

Estimation of papaverineacid strength wasmade using formulae (1) pKa=49.04-134.61·q_{max}^{H+} [6] and (2) pKa=51.048-150.078· q_{max}^{H+}, where pKa is universal measure of acidity, and q_{max}^{H+}- maximum charge on the hydrogen atom of papaverine, obtained from the calculation by the method RHF/6-311G** for formula (1) and by method DFT-PBE0/6-311G** [7,8] (Nobel Prize, W. Kohn, 1998) for formula (2), deduced by the authors. Formulae (1) and (2) with the highest coefficients of correlation were deduced exactly by these methods and within these frames of references. These formulae deduced by other methods and within other frames of references have coefficients of correlation which are less than in formulae (1) and (2), that naturally affects the precision of calculation of pKa. Optimization of geometry of papaverine molecular system was performed in accordance with all parameters by classical gradient method built into the Firefly software [7,8] based on the stationary Erwin Schrodinger equation (Nobel Prize,1933). The calculation was performed in fundamental state in vapor phase in an approximation of an isolated molecule within the molecular model.

The total charge of papaverine molecule was zero, and themultiplicity was M=2S+1=1 (all electrons are doubled, therefore the total spin of the studied molecular system is zero. Visual presentation of papaverine molecular model was made using MacMolPlt software [9].

3. EXPERIMENT, RESULTS AND DISCUSSION

Optimized geometric and electronic structure, the total energy and electron energy of papaverine molecule were obtained by the methods RHF/6-311G** and DFT-PBE0/6-311G** and are shown on Figs. 3-4 and in the Tables 2-3. The value of acid strength (pKa) is calculated by formulae, deduced by the authors for considered methods as analogously described in [10].

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pKa= 49.04-134.61·q_{max}^{H+} (for method RHF/6-311G**,pKa=30),

pKa= 51.048-150.078· q_{max}^{H+}(for method DFT-PBE0/6-311G**,pKa=27),

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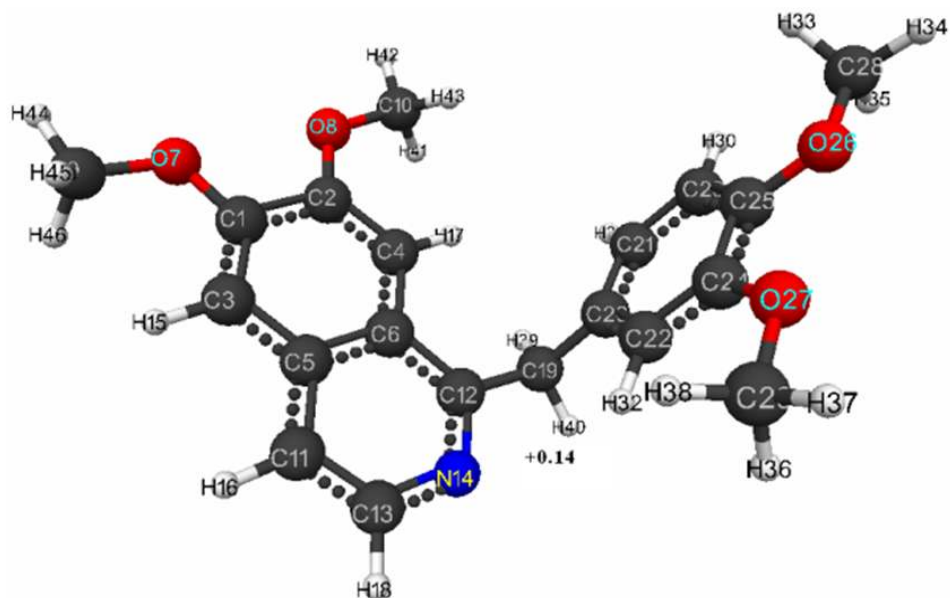

Fig. 3. Geometric and electronic structure of papaverine molecule obtained by method of RHF/6-311G(E$_0$= -2 949 707 kJ/mol)**

Table 2. The optimized bond lengths, valence angles and the charges on the atoms of papaverine molecule, obtained by method of RHF/6-311G**

The bond lengths	R,A	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

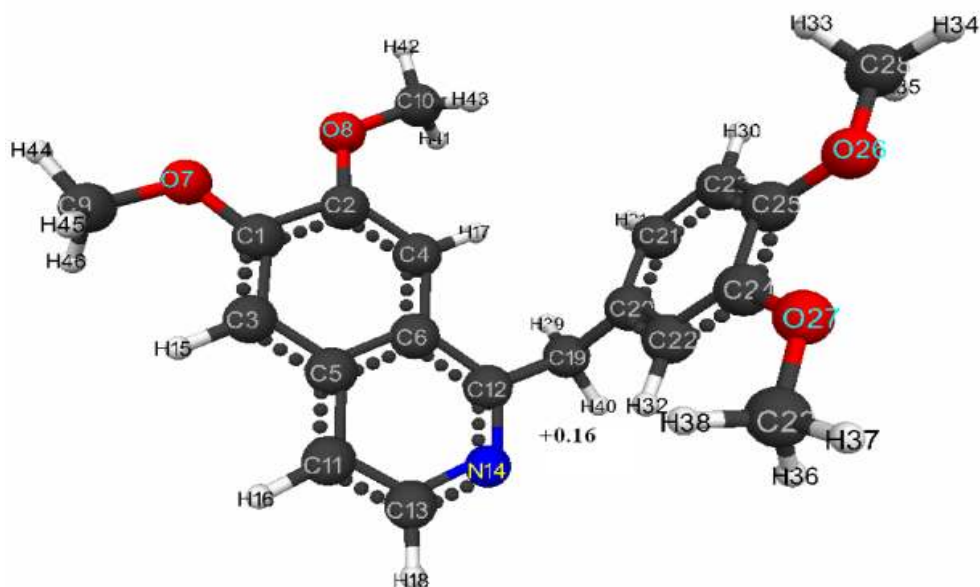| The bond lengths	R,A	The valence angles	Degree	Atom	The charges on the atoms
C(24)-C(25)	1.41	N(14)-C(13)-H(18)	115	O(26)	-0.44
C(25)-C(23)	1.37	C(6)-C(12)-C(19)	122	O(27)	-0.44
O(26)-C(25)	1.35	C(12)-C(19)-C(20)	114	C(28)	-0.04
O(27)-C(24)	1.34	C(19)-C(20)-C(21)	122	C(29)	-0.04
C(28)-O(26)	1.40	C(22)-C(20)-C(21)	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 molecule, obtained by method of DFT-PBE0/6-311G (E_0= -2 964 573 kJ/mol)**

Let us consider the issues of mutual influence of the atom of papaverine molecule (Figs. 3-4 and Tables 2-3). In benzene nucleus of isoquinoline structure (method RHF/6-311G**) the atoms of hydrogen C(3) and C(4) have negative charge of -0.13 C(3) and -0.09 C(4), respectively. These atoms are in p-situation with respect to each other and in o-position with respect to the electron-donatingmethoxy-group (p-π effect). The negative charge on the main atom C(6), which is in the para-position to the methoxy group, is also negative and equals to -0.17. The largest electronic density (-0.43) is localized on the hydrogen atom N(14) (Table 2) of unshared electron pair, localized on this atom. The highest electronic density on the oxygen atoms O(6) and O(7) of methoxy-group (-0.43

and -0.44) is due to the presence of unshared electron pair on these atoms, crossing with π-electrons of isoquinoline bicyclic system.3.4-di(methoxy)benzyl group is the only electron-donating substituent because so the charge on the carbon atom C(19) of methylene group is negative (-0.12). Geometric and electronic structure of papaverine molecule, obtained by method DFT-PBE0/6-311G**, confirmed the results on the distribution of electronic density. The charge on the atom C(4) is -0.06 (and -0.09 for method RHF/6-311G**), on atom C(6) it is -0.14 (and -0.16 for method RHF/6-311G**). 3.4-di(methoxy)benzyl group also showed itself as electron-donating substituent, however, the atom of carbon C(19) methylene group proved more negative (-0.23).

Table 3. The optimized bond lengths, valence angles and the charges on the atoms of the papaverine molecule, obtained by method of DFT-PBE0/6-311G**

The bond lengths	R,A	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

The bond lengths	R,A	The valence angles	Degree	Atom	The charges on the atoms
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		

4. CONCLUSION

Thus, quantum-chemical calculation of papverine molecule was done by methods RHF/6-311G** and DFT-PBE0/6-311G**. An optimized geometric and electronic structure of this compound was obtained. Its acid strength was estimated as pKa=30 (for RHF/6-311G**) and pKa=27 (for DFT-PBE0/6-311G**) which is in enough good accordance with pKa estimation, made in publication [11].

It was established that papaverine belongs to the class of very weak H-acids (pKa>14). The questions of mutual influence of atoms in papaverine molecule were considered and it was shown that 3.4-di(methoxy)benzyl group is electron donating substituent since the charge on the carbon atom C(19) of methylen group is negative (-0.12). It is shown how simultaneous introduction of the dimethoxy groups into the benzene nucleus of benzmine and 3.4-di(methoxy)benzyl group into ortho-position with respect to the nitrogen atom of pyrimidine cycle influences on the distribution of electronic density and significance of pKa.

Eventually the performed quantum-chemical calculations could promote the development of new, more effective spasmolythics in accordance with the algorithms proposed in [11,12].

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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