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An approach of quantum chemical methods for the development and substantiation of the structure of new piperidine compounds

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Abstract

The main research direction uses computational computer programs that establish the structural features of new modified piperidine compounds. The analysis of molecular models of piperidine derivatives using the semiempirical PM3 method of the HyperChem program (version 8.0.8) shows the practicality of synthesizing seven drugs and thermodynamic stability for the structures. All compounds have one nucleophilic reaction (oxygen in benzoyl radical) based on the calculations of the piperidine charges and their derivatives. The chemical stability of piperidine derivatives directly depends on the highest occupied molecular orbital (HOMO) energy gap and the lowest unoccupied molecular orbital (LUMO). All investigated model structures 4, 6, 7, 10 are nucleophiles. Compounds 2, 3, and 15 acts as electrophiles, attributed to the absence of benzyloxy radical in their structure. Based on the calculations of dipole moments, all the considered compounds have high polarity and will be readily soluble in almost all polar solvents: water and alcohol. This confirms the possibility of obtaining various dosage forms based on the investigated compounds on an industrial scale.

Keywords: HyperChem; Piperidine; Electron Density; Reactivity; Charge Characteristics;

1. Introduction

A rational way to search for effective and safe biologically active compounds is to recognize the directed design of new molecules from pharmacophore structural fragments, among which saturated nitrogen heterocycles, which are synthetic analogues of natural alkaloids, occupy the leading positions. Alkyloxy, aryloxy, and heteroaryloxypropynyl carbinols of various structures [1, 2] have established themselves as convenient reactive "building blocks" in organic synthesis, including biologically active compounds.

Piperidine is a promising compound for the preparation of several chemical compounds. Many compounds of piperidine derivatives that used in medicine have been investigated [3-19]. Among them are peripheral neurotropic action anxiolytics [3, 4], antidepressants [5, 6], drugs that affect the cardiovascular system (coronary dilating, antiarrhythmic and antihypertensive) [7], and antiulcer

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drugs [8, 9]. Derivatives of piperidine with antidiabetic [10, 11], antituberculosis [12], antibacterial [13], antitumor [14], antioxidant [15], anti-inflammatory [16] activities are known. Developments of piperidine are underway to produce anticoagulants - factor Xa inhibitors [17], drugs for the treatment of leishmaniasis [18] and antiviral drugs [19].

The high pharmacological activity of nitrogenous heterocycles (4-hydroxypiperidine) is an integral part. Today, it has become an incentive to conduct many studies on the synthesis of their homologues, analogues, and various synthetic derivatives. Substituted piperidines belong to the so-called "privileged structures" since they serve as the basis for creating drugs with various types of biological action. In particular, much-paid attention to targeted scientific research on the search and creation of new harmless and highly effective drugs based on substituted 4-piperidones in the Laboratory of Chemistry of Synthetic and Natural Medicinal Substances of the Institute of Chemical Sciences named after A.B. Bekturov. As with all the development of new drugs, they took a long time and high economic costs. One of the practical "tools" for creating valuable drugs with a broad spectrum of pharmacological action is their molecular design using computational quantum chemistry methods. This line of research is the main novelty of scientific work.

The implementation of this work based on the computational computer programs that establish the features of the chemical structure of new piperidine derivatives and which will allow determining the evidence points for a small number of simulated compounds, which, in turn, will make a specific theoretical contribution to the chemistry of piperidine derivatives and significantly reduce the time for synthesis. The most biologically active of them, and, therefore, will reduce the economic costs of developing new drugs.

Research in this area covers applying molecular prediction methods for new compounds of piperidine derivatives, so far unknown to medical science. Such research on new piperidine derivatives will carry out for the first time on a national and international scale. Therefore, the results of this study will make a particular contribution to the development of new biologically active compounds with a broad spectrum of pharmacological action.

The synthesis of pharmaceutical preparations (drugs) of piperidine derivatives without computer simulation is associated with a more expensive and laborious process, which will require additional verification of the assessment of the biological properties of each potential drug in some experiments.

One way to solve this problem is to carry out molecular modelling to predict the features of the electronic, geometric structure and reactivity of new chemical compounds. Numerous computer programs are used to predict molecular properties [20-22], among which the HyperChem quantum chemical methods are the most acceptable. It noted that the solution of problems related to molecular modelling is quite the actual direction of modernity, simplifying and reducing the cost of pharmaceutical development of new medicines.

The main research direction is computational computer programs that establish the structural features of new chemically modified piperidine compounds. Theoretically grounded piperidine derivatives have been created based on these studies, which have potential properties of medicinal substances. It will be appreciated by quantum chemical reactivity indices (bond lengths and charge characteristics, the value of electron densities and standard enthalpies of formation, the energy of the highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbital). It compared the obtained dipole characteristics using the Hyperchem program with the similar characteristics of the polar solvents most often used in pharmacy (water and ethyl alcohol) and taking into account the liquid state of the latter. It noted that the investigated model piperidine molecules could have significant polarity. This allows us to predict the sufficient solubility of piperidine derivatives both in water and in ethyl alcohol. The standard enthalpy of formation is the amount of internal energy of a system (molecule) that ensures the stability of a molecule as a structure. The effective charges on atoms in the structures of piperidine compound calculated by the RM 1 method of the Hyperchem program helped establish the reaction centres in the studied molecules. The boundary molecular orbitals of HOMO and LUMO are energies that determine the ability of a system to give away an electron (HOMO) or to receive an electron (LUMO). They are the main elements of the orbital boundary theory, which predict the reactivity of compounds. The central postulate of the theory of boundary orbitals: reactions proceed most easily in the case of maximum overlap of boundary MOs that make the most significant contribution to the energy of interacting

substances (reagents). Overlapping leads to charge transfer from the highest occupied orbital of the donor to the lowest free acceptor. For a nucleophilic attack, the most optimal position is the highest boundary density of the lowest free orbital; for an electrophilic attack, the position with the highest boundary density of the highest occupied orbital. When the charge transfer between the highest occupied orbital of one reactant and the lowest unoccupied orbital of the other, there is an increase in the density of the boundary region of overlap. Boundary molecular orbitals (MO), highest occupied MO (HOMO) and lowest unoccupied (vacant) MO (LUMO) make it possible to estimate not only the reactivity of a molecule but also its kinetic stability. The value of the HOMO – LUMO energy gap (the difference between their energies) determines the chemical stability of the compound. The resistance to deformation of the electric field and the effect of chemical reactions determines the chemical rigidity of the molecule (η), and the growth of which is associated with an increase in the molecule's stability – the high polarizability of the molecule determined by the high value of chemical softness (s). The compound's total reactivity determined by the compound's electrophilicity index, which corresponds to the value of the stabilization energy upon receipt of additional electron density and characterizes the electron transfer and stability [23].

Thus, empirical research on medicinal substances development is laborious and problematic and requires new solutions based on computer technology. It led to the creation of a database of quantum chemical methods for chemical compounds of piperidine derivatives.

Quantum-chemical studies give a reliable description of the reactivity of the compounds, make it possible to determine the stability of the chemical structure and the type of reaction forming it, which determines the course of synthesis. Quantum chemical calculations make it possible to obtain data on the geometry of molecular structures, ionization energies, dipole moment, electron density distribution, reactivity, etc. For the calculations, the semi-empirical methods AM1, PM3, RM1 were used.

The study aims to analyze molecular models of piperidine derivatives to study the chemical properties and the practicality of synthesizing potential medicinal substances.

2. Experimental

2.1. *Materials*

Computer studies of properties were performed using HyperChem programs. The experiment carried out for modelled 17 chemical structures of piperidine derivatives. The spatial characteristics of piperidine were calculated using the HyperChem program (version 8.0.8) by three semiempirical methods AM1, PM3, RM1. The AM1 method belongs to the self-consistent field (SCF) methods. It is used for organic molecules containing elements from the main subgroups 1 and 2 in the periodic table. This method identifies molecules containing nitrogen and oxygen. It calculates the electronic structure, optimizes the geometry and the total energy and heats of formation. The PM3 method is a modified version of the AM1 method and differs from AM1 only in the values of the parameters. The parameters for PM3 obtained by comparing a large number and type of experiments with the calculated results. Non-covalent interactions in PM3 are less repulsive than AM1. PM3 was initially intended to calculate organic molecules, but later it was also parameterized for several other groups of elements, particularly for transition metals. This SCF method allows the most accurate reproduction of intermolecular potentials. The RM1 method, proposed in 2006, is identical to the AM1 method, but its performance has been improved with updated and better-fitted parameters. In most cases, RM1 gives better results for organic compounds and biomolecules compared to AM1 and PM3 methods. The RM1 method is a reparametrized AM1 method for 10 elements: H, C, N, O, P, S, F, Cl, Br, I [24, 25]. The accuracy of the RM1 method in comparison with the AM1 and PM3 methods [26] is shown in Table 1.

A quantum calculation scheme for 17 models of chemical compounds is presented using HyperChem. After opening HyperChem, it is advisable to expand the window to full screen. Open the item "Default" element in the "Build" menu. It contains the dialogue menu "Element Table" - the periodic table of elements of D.I. Mendeleev. The Model is created with the addition of the "Explicit hydrogens" manipulation. Setup-> Semi-empirical-> PM3 File-> Start Lock-> Save Compute-> Geometry Optimization-> Ok Yes appears at the bottom of the screen line (calculation completed) File-> Stop lock, the final stage is the interpretation of the data obtained.

Table 1: Comparative characteristics of the accuracy of methods AM1, PM3 RM1

Atoms	Characteristics	Average error			
		AM1	PM3	RM1	Number compounds
C, H, N, O	Heats of Formation (kcal/mol)	9.06	5.98	5.04	986
	Dipole moments (D)	0.26	0.29	0.23	59
	Ionization potentials (eV)	0.48	0.55	0.42	102
	Valence angles (º)	0.027	0.023	0.02	618
	Bond lengths (Å)	6.06	7.33	7.05	737
P, S	Heats of Formation (kcal/mol)	12.6	14.64	7.4	167
	Dipole moments (D)	0.74	0.56	0.49	16
	Ionization potentials (eV)	0.52	0.47	0.42	38
	Valence angles (º)	0.069	0.061	0.05	84
	Bond lengths (Å)	6.75	6.39	7.77	72
F, Cl, Br, I	Heats of Formation (kcal/mol)	16.71	10.62	7.12	327
	Dipole moments (D)	0.37	0.43	0.42	52
	Ionization potentials (eV)	0.77	0.59	0.49	92
	Valence angles (º)	0.051	0.038	0.039	202
	Bond lengths (Å)	3.94	4.88	4.43	101

The semiempirical methods available in the HyperChem program refer to the valence approximation methods. This means that they consider only the valence electron in the valence shell Atomic Orbitals, which differs from ab initio methods. All methods of this group characterized by the fact that they solve the Schrödinger equation for atoms and molecules in an approximate and simplified version, neglecting the integrals of specific interactions. For the solution, the standard non-optimized basis functions of electron orbitals and some experimental parameters are used, which in these methods eliminates the need to calculate several quantities and correct the erroneous results of the approximations.

3. Results and discussion

The spatial characteristics of 17 models for new chemical structures of piperidine derivatives calculated using HyperChem software (version 8.0.8) by methods AM1, PM3 and RM1, as shown in Table 2. The calculated accuracy of the RM1 method compared to the AM1 and PM3 methods are shown in Tables 3 and 4.

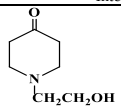
The spatial structure for 17 model molecules of piperidine derivatives was calculated using the AM1, PM3 and RM1 methods. In the studies, the bond lengths of C=O, C–H, C=C (sp2 – hybridization of the carbon atom) and C–N calculated by the indicated methods were compared. The obtained data were compared with experimental data [27-29]. The C=C bond (a double carbon bond located in the benzene ring; the experimental value of the bond length is 1.395 Å) was calculated quite accurately by all methods, with a deviation ranging from –0.005 to +0.005. The C=O bond (a carbon-oxygen double bond is a component of the carboxyl group; the experimental value of the bond length is 1.215 Å) was most accurately calculated by the PM3 method (calculations by AM1 method – deviation in the range from +0.01 to +0.02; calculations PM3 - deviation in the range from - 0.002 to 0.001; RM1 calculations - deviation in the range from –0.002 to +0.001). The C–N bond (included in the piperidine heterocycle; the experimental bond length (1.47 Å) was calculated with the same accuracy by both the PM3 method and the RM1 method (deviation from +0.005 to +0.025). The AM1 method gives a deviation in the range from –0.02 to –0.025; therefore, it is the most inaccurate. The C–C bond (present as in heterocycles and acts as a connecting link with other radicals; the experimental value of the bond length is 1.54 Å) was calculated by the AM 1 method (deviation ranging from –0.045 to +0.005). Calculations by the PM3 method show a deviation ranging from –0.004 to –0.015. Calculations RM1 - deviation in the range from –0.055 to –0.015.

As shown from the comparison results, most approximate to the experimental data (according to the values of the C=O, C-C, C=C) data were obtained by PM3 and selected for further studies. To identify the most energetically stable structures, semi-empirical method PM3 enthalpies of formation models piperidine derivatives are calculated. An analysis of the results presented in Table 5 shows that of the 17 model molecules of piperidine derivatives, seven compounds are the most stable.

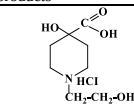
In search conditions corresponding to the most excellent stability, the system always tends to the minimum energy. The seven most stable models of piperidine derivatives after optimization by the PM3 method, the spatial structures of the compounds with the numbering and arrangement of atoms, presented in Figures 1-7 in 3D format, were obtained on chemical modelling.

Table 2: Piperidine derivatives models

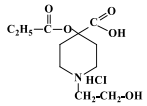
Intermediate and reaction products



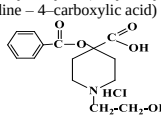
№ 1. 2–hydroxyethyl)–piperidine–4–one



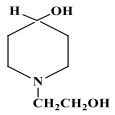
№ 2. 4–hydroxy–1–(2–hydroxyethyl) piperidine – 4–carboxylic acid)



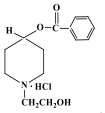
№ 3. 1–(2–hydroxyethyl)–4–(propanoyloxy)–piperidine–4–carboxylic acid



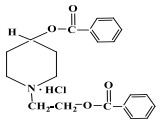
№ 4. (4–(benzoyloxy)–1–(2–hydroxyethyl)–piperidine–4–carboxylic acid)



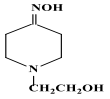
№ 5. 1–(2–hydroxyethyl)–piperidine–4–ol



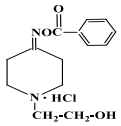
№ 6. 1–(2–hydroxyethyl)–piperidine–4–yl benzoate



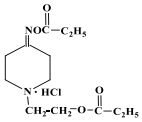
№ 7. 2–[4–(benzoyloxy)–piperidine–1–yl]ethyl benzoate



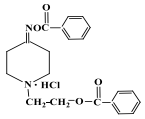
№ 8. 2–[4–hydroxyimino)–piperidine–1–yl] ethanol



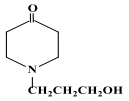
№ 9. [1–(2–hydroxyethyl) piperidine–4–ylidene] aminobenzoate



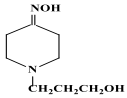
№ 10. {1–[2–(propanoyloxy)–ethyl]–piperidine–4– ylidene} aminopropanoate



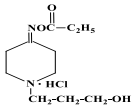
№ 11. 2–{4-[(benzoyloxy)–imino]–piperidine–1– yl} ethyl benzoate



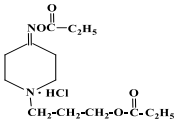
№ 12. 1–(3–hydroxypropyl)–piperidine–4–one



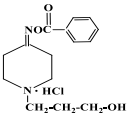
№ 13. 3–[4–(hydroxyimino)–piperidine–1–yl] propan–1–ol



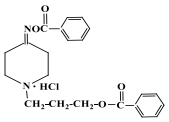
№ 14. [1–(3–hydroxypropyl)–piperidine–4–ylidene] aminopropanoate



№ 15. {1–[3–(propanoyloxy)–propyl]–piperidine–4–ylidene} aminopropanoate



№ 16. [1–(3–hydroxypropyl)–piperidine–4–ylidene] aminobenzoate



№. 17 {1–[3–benzoyloxy propyl]–piperidine–4–ylidene)-aminobenzoate

Table 3: The bond lengths C=C and C=O in model molecules of piperidine and its derivatives, Å

Connection name	AM1	PM3	RM1	AM1	PM3	RM1
	Bond length					
	C=C	C=C	C=C	C=O	C=O	C=O
№ 4. 4–(benzoyloxy)–1–(2–hydroxyethyl)–piperidine–4–carboxylic acid	1.3981 (16-18) 1.3943 (19-20) 1.3931 (17-21) 1.395 (exp.)	1.3908 (17-21) 1.3915 (19-20) 1.3941 (16-18) 1.395 (exp.)	1.3822 (16-18) 1.38 (17-21) 1,3814 (19-20) 1.395 (exp.)	1.2324 (11-12) 1.2316 (14-15) 1.215 (exp.)	1.2173 (11-12) 1.2125 (14-15) 1.215 (exp.)	1.2182 (11-12) 1.2150 (14-15) 1.215 (exp.)
№ 6. 1–(2–hydroxyethyl)–piperidine–4–yl benzoate	1.3953 (18-19) 1.4001 (14-15) 1.3949 (16-17) 1.395 (exp.)	1.3961 (14-15) 1.3896 (16-17) 1.3907 (18-19) 1.395 (exp.)	1.3821 (14-15) 1.3807 (16-17) 1.3814 (18-19) 1.395 (exp.)	1.2324 (12-13) 1.215 (exp.)	1.2149 (12-13) 1.215 (exp.)	1.2163 (12-13) 1.215 (exp.)
№ 7. 2–[4–(benzoyloxy)–piperidine–1–yl]ethyl benzoate	1.4 (22-23) 1.3945 (26-27) 1,395 (24-25) 1.3947 (14-15) 1.3939 (16-17) 1.3996 (12-13) 1.395 (exp.)	1.3960 (12-13) 1.3910 (14-15) 1.3895 (16-17) 1.3959 (22-23) 1.3910 (24-25) 1.3897 (26-27) 1.395 (exp.)	1.3834 (12-13) 1.3811 (14-15) 1.3811 (16-17) 1.3827 (22-23) 1.3813 (24-25) 1.3809 (26-27) 1.395 (exp.)	1.2321 (20-21) 1.2315 (10-11) 1.215 (exp.)	1.2140 (10-11) 1.2147 (20-21) 1.215 (exp.)	1.2166 (10-11) 1.2167 (20-21) 1.215 (exp.)
№ 9. [1–(2–hydroxyethyl) piperidine–4–ylidene] aminobenzoate	1.4017 (14-15) 1.3956 (16-17) 1.3946 (18-19) 1.395 (exp.)	1.3996 (14-15) 1.3916 (16-17) 1.3891 (18-19) 1.395 (exp.)	1.3832 (14-15) 1.3816 (16-17) 1.3814 (18-19) 1.395 (exp.)	1.229 (14-15) 1.215 (exp.)	1.216 (14-15) 1.215 (exp.)	1.2157 (12-13) 1.215 (exp.)
№. 17 {1–[3–benzoyloxy propyl]–piperidine–4–ylidene)-aminobenzoate	1.3947 (25-26) 1.3939 (27-28) 1.3998 (23-24) 1.4023 (15-16) 1.3956 (17-18) 1.3952 (19–20) 1.395 (exp.)	1.3905 (25-26) 1.3892 (27-28) 1.3958 (23-24) 1.399 (15-16) 1.3915 (17-18) 1.3895 (19–20) 1.395 (exp.)	1.3905 (25-26) 1.3892 (27-28) 1.3958 (23-24) 1.3827 (15-16) 1.3817 (17-18) 1.3815 (19–20) 1.395 (exp.)	1.2269 (12-13) 1.2312 (21-22) 1.215 (exp.)	1.2162 (12-13) 1.2141 (21-22) 1.215 (exp.)	1.216 (12-13) 1.2148 (21-22) 1.215 (exp.)

Table 4: C–N and C–C bond lengths in model molecules of piperidine and its derivatives, Å

Connection name	AM1	PM3	RM1	AM1	PM3	RM1
	Bond length					
	C–N	C–N	C–N	C–C	C–C	C–C
№ 4. 4–(benzoyloxy)–1–(2–hydroxyethyl)–piperidine–4–carboxylic acid	1.4545 (4–5) 1.4468 (4–7) 1.4562 (3–4) 1.47 (exp.)	1.4919 (3–4) 1.4908 (4–5) 1.4874 (4–7) 1.47 (exp.)	1.4864 (3–4) 1.4859 (4–5) 1.,4778 (4–7) 1.47 (exp.)	1.5433 (1–2) 1.5261 (2–3) 1.5268 (1–6) 1.5268 (5–6) 1.5375 (7–8) 1.475 (14–16) 1.54 (exp.)	1.5483 (1–2) 1.5205 (2–3) 1.5407 (1–6) 1.5229 (5–6) 1.54 (exp.)	1.5198 (1–2) 1.5196 (2–3) 1.5198 (5–6) 1.5290 (1–6) 1.54 (exp.)
№ 6. 1–(2–hydroxyethyl)–piperidine–4–yl benzoate	1.4563 (4–5) 1.4568 (3–4) 1.4471 (4–7) 1.47 (exp.)	1.4903 (4–5) 1.4907 (3–4) 1.4826 (4–7) 1.47 (exp.)	1.4886 (3–4) 1.4875 (4–5) 1.4797 (4–7) 1.47 (exp.)	1.5258 (1–2) 1.5270 (2–3) 1.5223 (1–6) 1.5260 (5–6) 1.5373 (7–8) 1.,4769 (12–14) 1.54 (exp.)	1.5334 (1–2) 1.5238 (2–3) 1.5326 (1–6) 1.5219 (5–6) 1.54 (exp.)	1.5180 (5–6) 1.5186 (2–3) 1.5227 (1–2) 1.5190 (1–6) 1.54 (exp.)
№ 7. 2–[4–(benzoyloxy)–piperidine–1–yl]ethyl benzoate	1.4569 (3–4) 1.4572 (4–5) 1.4451 (4–7) 1.47 (exp.)	1.4921 (3–4) 1.4913 (4–5) 1.4849 (4–7) 1.47 (exp.)	1.4887 (3–4) 1.4890 (4–5) 1.4776 (4–7) 1.47 (exp.)	1.5255 (1–2) 1.5267 (2–3) 1.5220 (1–6) 1.5251 (5–6) 1.4771 (20–22) 1.4756 (10–12) 1.5373 (7–8) 1.54 (exp.)	1.5324 (1–2) 1.5217 (2–3) 1.5319 (1–6) 1.5209 (5–6) 1.54 (exp.)	1.5170 (5–6) 1.5180 (1–6) 1.5202 (2–3) 1.5251 (1–2) 1.54 (exp.)
№ 9. [1–(2–hydroxyethyl) piperidine–4–ylidene] aminobenzoate	1.4482 (3–4) 1.4489 (4–5) 1.4439 (4–7) 1.47 (exp.)	1.4842 (3–4) 1.4841 (4–5) 1.4845 (4–7) 1.47 (exp.)	1.4775 (3–4) 1.4778 (4–5) 1.4777 (4–7) 1.47 (exp.)	1.5057 (1–2) 1.5312 (2–3) 1.5007 (1–6) 1.5307 (5–6) 1.4678 (12–14) 1.54 (exp.)	1.5046 (1–2) 1.5274 (2–3) 1.499 (1–6) 1.5282 (5–6) 1.54 (exp.)	1.4909 (1–2) 1.5220 (2–3) 1.4835 (1–6) 1.5225 (5–6) 1.54 (exp.)
№. 17 {1–[3–benzoyloxy propyl]–piperidine–4–ylidene)-aminobenzoate	1.4486 (4–5) 1.4475 (3–4) 1.4488 (4–7) 1.47 (exp.)	1.4834 (4–5) 1.4842 (3–4) 1.486 (4–7) 1.47 (exp.)	1.4777 (4–5) 1.4875 (3–4) 1.4824 (4–7) 1.47 (exp.)	1.525 (5–6) 1.5012 (1–6) 1.5062 (1–2) 1.5288 (2–3) 1.468 (12–15) 1.5301 (7–8) 1.5167 (8–9) 1.54 (exp.)	1.5277 (5–6) 1.499 (1–6) 1.5045 (1–2) 1.5261 (2–3) 1.4823 (12–15) 1.5276 (7–8) 1.5242 (8–9) 1.54 (exp.)	1.5211 (5–6) 1.4827 (1–6) 1.488 (1–2) 1.5224 (2–3) 1.4585 (12–15) 1.5207 (7–8) 1.5193 (8–9) 1.54 (exp.)

Table 5: Calculations of the enthalpy of formation of models of new piperidine derivatives

№	Connection name	Δ H (kcal/mol)		
		AM 1	RM 1	PM 3
1	2–hydroxyethyl)–piperidine–4–one	–98.8779	335.1968	–100.3387
2	4–hydroxy–1–(2–hydroxyethyl) piperidine – 4–carboxylic acid)	–194.938	413.3604	**–189.031**
3	1–(2–hydroxyethyl)–4–(propanoyloxy)–piperidine–4–carboxylic acid	–226.099	595.5402	**–228.174**
4	(4–(benzoyloxy)–1–(2–hydroxyethyl)–piperidine–4–carboxylic acid)	–183.432	**852.0896**	**–186.909**
5	1–(2–hydroxyethyl)–piperidine–4–ol	–110.099	268.8917	–103.0562
6	1–(2–hydroxyethyl)–piperidine–4–yl benzoate	–105.737	**709.1277**	**–106.312**
7	2–[4–(benzoyloxy)–piperidine–1–yl]ethyl benzoate	–103.782	**1150.4418**	**–111.147**
8	2–[4–hydroxyimino)–piperidine–1–yl] ethanol	–57.9488	275.5678	–52.3671
9	[1–(2–hydroxyethyl) piperidine–4–ylidene] aminobenzoate	–50.8755	718.1104	–52.3630
10	{1–[2–(propanoyloxy)–ethyl]–piperidine–4–ylidene} aminopropanoate	–130.681	632.2168	**–140.050**
11	2–{4-[(benzoyloxy)–imino]–piperidine–1– yl} ethyl benzoate	–47.6969	1152.4050	–54.7750
12	1–(3–hydroxypropyl)–piperidine–4–one	–98.8855	335.1960	–100.3394
13	3–[4–(hydroxyimino)–piperidine–1–yl] propan–1–ol	–64.9334	306.5564	–58.4963
14	[1–(3–hydroxypropyl)–piperidine–4–ylidene] aminopropanoate	–100.993	485.1984	–101.7519
15	{1–[3–(propanoyloxy)–propyl]–piperidine–4–ylidene} aminopropanoate	–140.624	662.5659	**–146.348**
16	[1–(3–hydroxypropyl)–piperidine–4–ylidene] aminobenzoate	–57.7594	749.0080	–58.5663
17	{1–[3–benzoyloxy propyl]–piperidine–4–ylidene)-aminobenzoate	–52.1262	1189.9533	–61.7484

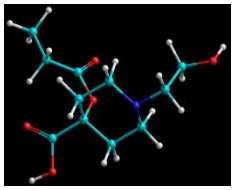


Fig. 1. 4–hydroxy–1–(2–hydroxyethyl) piperidine–4–carboxylic acid (**№ 2**)

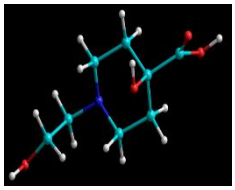


Fig. 2. 1–(2–hydroxyethyl)–4–(propanoyloxy)–piperidine–4–carboxylic acid (**№ 3**)

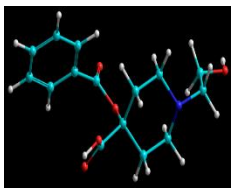


Fig. 3. 4–(benzoyloxy)–1–(2–hydroxyethyl)–piperidine–4–carboxylic acid (**№ 4**)

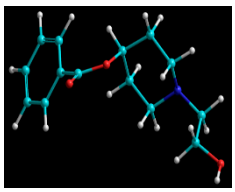


Fig. 4. 1–(2–hydroxyethyl)–piperidine–4–yl benzoate (**№ 6**)

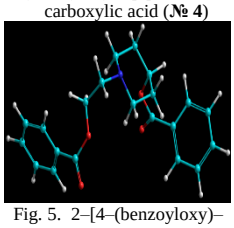


Fig. 5. 2–[4–(benzoyloxy)–piperidine–1–yl] ethyl benzoate (**№.7**)

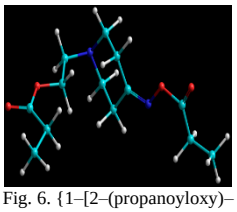


Fig. 6. {1–[2–(propanoyloxy)–ethyl]–piperidine–4–ylidene} aminopropanoate (**№ 10**)

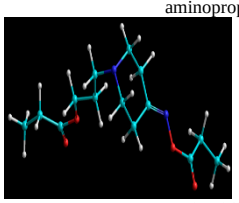


Fig. 7. {1–[3–(propanoyloxy)–propyl]–piperidine–4–ylidene} aminopropanoate (**№ 15**)

Calculations of the charge characteristics made it possible to determine that all compounds have one most probable nucleophilic reaction center, oxygen, with a double bond in the benzoyl oxide radical. In the presence of carboxyl groups, another reaction center will arise in the form of an oxygen atom with a double bond, which is in this group (Table 6).

Boundary molecular orbitals (MO), highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbital) make it possible to estimate not only the reactivity of a molecule but also its kinetic stability.

Reactivity indices for boundary MOs are determined by the ratios: $I = -\varepsilon$ HOMO; $A = -\varepsilon$ LUMO; $\chi = (\varepsilon \text{ HOMO} + \varepsilon \text{ LUMO}) / 2$; $\mu = -\chi$; $\eta = (\varepsilon \text{ LUMO} - \varepsilon \text{ HOMO}) / 2$; $s = 1 / (2\eta)$; $w = \mu 2 / (2\eta)$,

where ε HOMO and ε LUMO are the energies of HOMO and LUMO,

I is the ionization potential,
A - electron affinity,
χ - electronegativity,
μ - chemical potential,
η - stiffness,
s - softness,
w - the general electrophilicity index.

Next, the calculation made of the energy gap HOMO-LUMO (the difference between their energies); the calculation results are presented in Table 7. The obtained calculations concluded that model compounds No. 4, No. 6, No. 7, No. 10 have negative LUMO values, which defines them as nucleophiles, which confirms the conclusion made earlier analysis of charge characteristics. Concerning compounds No. 2, No. 3 and No. 15, it proved that they would act as electrophiles, which is explained by the absence in their structure of benzoyl radical or "compensator" in the form of an additional nitrogen atom (as in the case of compound No. 10), which contributes to the shift of the electron density towards oxygen atoms, defined as reaction centres. According to calculations, all compounds have a high stiffness coefficient, which indicates their low reactivity and high stability and allows to talk about their possible use as medicinal substances.

Based on the calculation of the dipole moments of the test compounds, it can determine the compounds that have high polarity (the lowest value is 1– (2 – hydroxyethyl)–4– (propanoyloxy)–piperidine – 4 – carboxylic acid: 2.004), and therefore, will be readily soluble in almost all polar solvents: water, alcohol, etc. It confirms the possibility of obtaining various pharmaceutical substances and dosage forms based on it. The compound 4–hydroxy–1–(2–hydroxyethyl) piperidine–4–carboxylic acid (No. 2) was an exception. The value for calculating the dipole moment was 1.024 D, which is lower than the experimental dipole moments of most solvents. Thus, the simulated compounds' spatial, electronic structure, and energy characteristics were calculated, piperidine derivatives was performed. Analysis of molecular models of potential piperidine derivatives shows that the most reactive compounds can claim the role of potential drugs and synthesized under industrial conditions. Based on the analysis of spatial and energy characteristics), seven compounds out of 17 had the most thermodynamically stable structures. The quantum-chemical calculations for 17 simulated piperidine compounds make it possible to estimate the spatial, electronic structure and reactivity of chemical structures used as drugs.

Table 6: The values of the charge characteristics on atoms in the investigated piperidine derivatives

№	Connection name	–Δ q, units charge						+Δ q, units charge			
2	4–hydroxy–1–(2–hydroxyethyl) piperidine–4–carboxylic acid	9	O	10	O	12	O	–0.3032 –0.2970 –0.3966	11	C	0.3441 0.1257
		13	O	4	N			–0.2931 –0.0748	1	C	
3	1–(2–hydroxyethyl)–4–(propanoyloxy)–piperidine–4–carboxylic acid	9	O	10	O	13	O	–0.3042 –0.2513 –0.3327 –0.4066	1	C	0.1256 0.3610
		16	O	17	O			–0.2828	11	C	0.3626
									12	C	
4	4–(benzoyloxy)–1–(2–hydroxyethyl)–piperidine–4–carboxylic acid	9	O	15	O			–0.3049 –0.3238 –0.3785 –0.2355	14	C	0.4151 0.3472
		12	O	10	O				11	C	
6	1–(2–hydroxyethyl)–piperidine–4–yl benzoate	9	O	13	O	11	O	–0.3063 –0.3390 –0.2355	12	C	0.4055
7	2–[4–(benzoyloxy)–piperidine–1–yl] ethyl benzoate	9	O	11	O	19	O	–0.2383 –0.3353 –0.2366 –0.3390	20	C	0.4071 0.4071
		21	O						10	C	
10	{1–[2–(propanoyloxy)–ethyl]–piperidine–4–ylidene} aminopropanoate	9	O	11	O			–0.2341 –0.206 –0.3390	12	C	0.37310.3450
		13	O	15	O			–0.3265	14	C	
15	{1–[3–(propanoyloxy)–propyl]–piperidine–4–ylidene} aminopropanoate	10	O	12	O	16	O	–0.2469 –0.3301 –0.2059	11	C	0.3477 0.3740
									17	C	

Table 7: The energies of HOMO and LUMO in the investigated models of new piperidine derivatives

№	Connection name	eHOMO	эВ	eLUMO	эВ
2	4–hydroxy–1–(2–hydroxyethyl) piperidine–4–carboxylic acid	–9.2503	38	0.7265	39
3	1–(2–hydroxyethyl)–4–(propanoyloxy)–piperidine–4–carboxylic acid	–9.3579	49	0.3161	50
4	4–(benzoyloxy)–1–(2–hydroxyethyl)–piperidine–4–carboxylic acid	–9.2647	57	–0.3913	58
6	1–(2–hydroxyethyl)–piperidine–4–yl benzoate	–9.1064	49	–0.4569	50
7	2–[4–(benzoyloxy)–piperidine–1–yl] ethyl benzoate	–9.1677	68	–0.4076	69
10	{1–[2–(propanoyloxy)–ethyl]–piperidine–4–ylidene} aminopropanoate	–9.5864	54	–0.0037	55
15	{1–[3–(propanoyloxy)–propyl]–piperidine–4–ylidene} aminopropanoate	–9.4847	57	0.2244	58

4. Conclusion

Quantum-chemical studies of the model derivatives of piperidine, carried out by the semi-empirical PM3 method, made it possible to substantiate spatial, electronic, and energy characteristics for determining the chemical structure of new compounds. Analysis of the calculated enthalpies of formation model molecules shows that seven compounds are the most thermodynamically stable: 4–hydroxy–1–(2–hydroxyethyl) piperidine–4–carboxylic acid (**№ 2**); 1–(2–hydroxyethyl)–4–(propanoyloxy)–piperidine–4–carboxylic acid (**№ 3**); 4–(benzoyloxy)–1–(2–hydroxyethyl)–piperidine–4–carboxylic acid (**№ 4**); 1–(2–hydroxyethyl)–piperidine–4–yl benzoate (**№ 6**); 2–[4–(benzoyloxy)–piperidine–1–yl] ethyl benzoate (**№ 7**); {1–[2–(propanoyloxy)–ethyl]–piperidine–4–ylidene} aminopropanoate (**№ 10**); {1–[3–(propanoyloxy)–propyl]–piperidine–4–ylidene} aminopropanoate (**№ 15**). Calculation models represent chemical compounds and reactivity, which are essential for proving their chemical structure. The analysis of molecular models of medicinal compounds based on piperidine derivatives is of practical interest for pharmacological properties. Based on theoretically created chemical compounds, drugs will be synthesized as pharmaceutical substances for launching a production series of drugs.

5. Conflict of interest.

Authors declare no conflict of interest.

6. References

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