QUANTUM-CHEMICAL SIMULATION AND PHARMACOKINETIC PROPERTIES OF LYSERGOL

КВАНТОВО-ХИМИЧЕСКОЕ МОДЕЛИРОВАНИЕ И ФАРМАКОКИНЕТИЧЕСКИЕ СВОЙСТВА ЛИЗЕРГОЛА

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Lysergol is a secondary metabolite of the ergoline family secreted by the parasitic fungi of *genus Claviceps*. Lysergol synergistically enhances the properties of some antibacterial drugs [1]. It was also found that lysergol can increase the bioavailability of some antibiotics [2]. This work presents the data of theoretical and semiempirical calculations of the lysergol molecule. Water was used as the solvent medium.

Лизергол является вторичным метаболитом семейства эрголинов, секретируемым паразитическими грибами рода *Claviceps*. Лизергол синергически усиливает свойства некоторых антибактериальных препаратов [1]. Также было установлено, что лизергол может повышать биодоступность некоторых антибиотиков [2]. В настоящей работе представлены данные теоретических и полуэмпирических расчетов молекулы лизергола. В качестве растворителя использовалась вода.

Keywords: B3LYP, TD-DFT, lysergol, spectrum, pharmacokinetic properties.

Ключевые слова: B3LYP, TD-DFT, лизергол, фармакокинетические свойства.

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The calculations were performed on a personal computer with an Intel Core i5 processor (2.3 GHz 2-core) with the macOS Ventura operating system installed. The MM+ method of the Chem3D package was chosen to calculate the starting geometry of the molecule [3]. The MM+ method was chosen because it is designed for organic molecules, takes into account the potential fields formed by all the atoms of the calculated molecule, and also allows a modification of the calculation parameters. The equilibrium geometry of the molecule calculated by the semiempirical MM+ method is shown in the Figure 1.

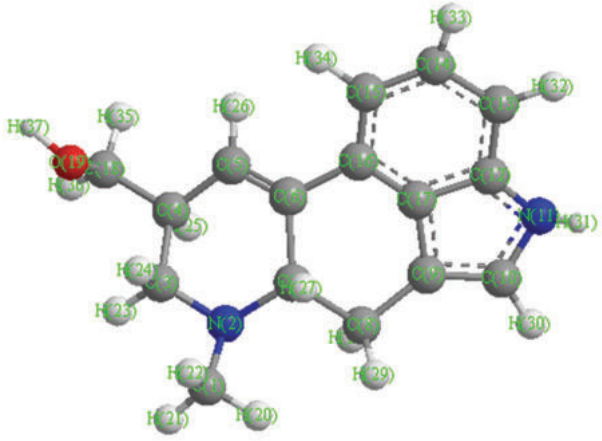

Figure 1 – MM+ optimized molecule

Method 1. Complete quantum-chemical modeling of the equilibrium geometry and electronic structure of the lysergol molecule.

Complete optimization and calculation of the electronic structure were performed using the most common methods DFT/B3LYP. This method is based on a hybrid functional in which the exchange energy is calculated using the exact result

obtained by the Hartree-Fock method. We also used the MIDIX basis set, which predicts charge distribution, molecular geometry, and partial atomic charges. The MIDIX basis sets, are heteroatom-polarized split-valence basis sets in which the polarization functions are optimized to predict realistic molecular geometries and atomic partial charges. The MIDIX basis set uses the core, inner valence, and outer valence basis functions of the MIDI basis set plus an additional Gaussian basis function. The calculated electronic absorption spectrum of the molecule in a solvent medium is shown in Figure 2. The calculation showed that the strongest electron transition is observed at the absorption maximum = 324.98 nm, f=0.2165. The transition refers to the transition of the electron to the excited singlet state: $S_0 \rightarrow S_1$. The other transitions have a small value of f and are forbidden by a symmetry. For full list of transitions see Table 1.

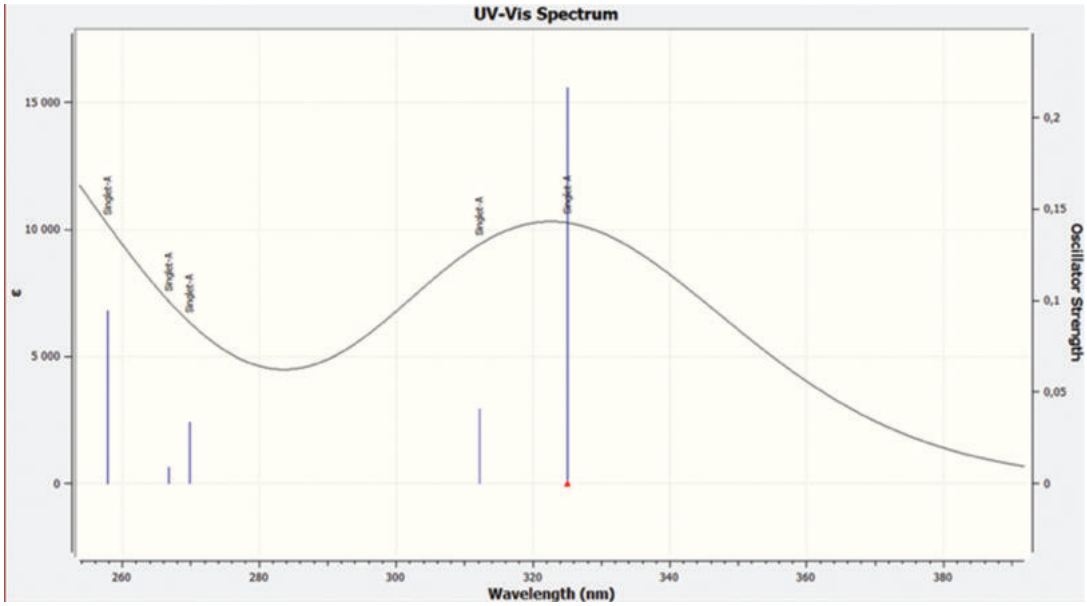

Figure 2 – UV-Vis absorption spectrum

Table 2

Calculated electronic absorption spectrum of the molecule

Excited State	Wavelength	Transition energy, eV	Cluster decomposition of full configuration interaction wave	Oscillator (f)
$S_0 \rightarrow S_1$	324.98 nm	3.8151	89 -> 91 0.20655 90 -> 91 0.66007	0.2165

Method 2. Pharmacokinetic properties of the lysergol molecule

For the study of ergotamine derivatives Lipinski's Rule of Five was used. Parametrs such as ligand molecular weight (<500 Da), high lipophilicity (LogP<5), number of hydrogen bond donors (<5), number of hydrogen bond acceptors (<10), and molar refraction (40–130) (Goze's Rule). Molinespiration software was used for calculation. Values are given in the table 2.

Table 2

Pharmacokinetic properties of the title compounds

Name	LogP	Molecular weight	Rotatable bonds	Topological polar surface area	Fraction Csp3	LogS
Lysergol	2.41	254.33 g/mol	1	39.26 Å²	0.38	-3.06

The bioactivity of the molecule was measured as the ability to bind to the GPCR, act as a modulator of ion channels, and inhibit kinases, proteases, and enzymes. Calculations were performed on the online platform Molinspiration (www.molinspiration.com). The results are shown in Table 3. Lysergol is a molecule similar to G-protein-coupled receptors ligands, exhibiting properties of an ion channel modulator, kinase and enzyme inhibitor. One of the main useful properties potentially present in lysergol is its similarity to GPCR ligands. GPCRs are some of the most abundant receptors in the human body, when bound to a ligand the receptor changes conformation and activates signal transduction through signaling, what makes lysergol a drug to explore its interests as a GPCR lignad in a wide variety of metabolic pathways. Also, the molecule has a small size.

Table 3

Bioactivity of lysergol

Name	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Lysergol	0.98	0.52	0.35	-0.21	0.00	0.45

Drug similarity is assessed using the rule of five, also known as Lipinski's rule, which includes four ranges of simple physicochemical parameters (MWT ≤ 500, log P ≤ 5, H-bond donors ≤ 5, H-bond acceptors ≤ 10). The miLog*P* values indicate good cell membrane permeability for these compounds, the results for the studied ligands are presented in the table Table 4. Using the intuitive BOILED-Egg model, we have demonstrated an estimate of the access of the lysergol molecule to the brain and gastrointestinal tract (Fig.3 and Fig. 4) This model works by calculating the lipophilicity and polarity of the molecule. As can be seen in the graph, lysergol is a drug that is able to cross the blood-brain barrier and is similarly absorbed in the gastrointestinal tract. Drug access to the brain and absorption through the gastrointestinal tract are important parameters to elucidate in the search for potential pharmacologic agents. Lysergol is able to cross the blood-brain barrier and is absorbed in the gastrointestinal tract, which gives lysergol a bioavailable drug.

Table 4

Bioavailability chart for lysergol

Log*P*	Molecular weight	Log*S*	Fraction Csp3	TPSA
2.41	254.33 g/mol	-3.06	0.38	39.26 Å²

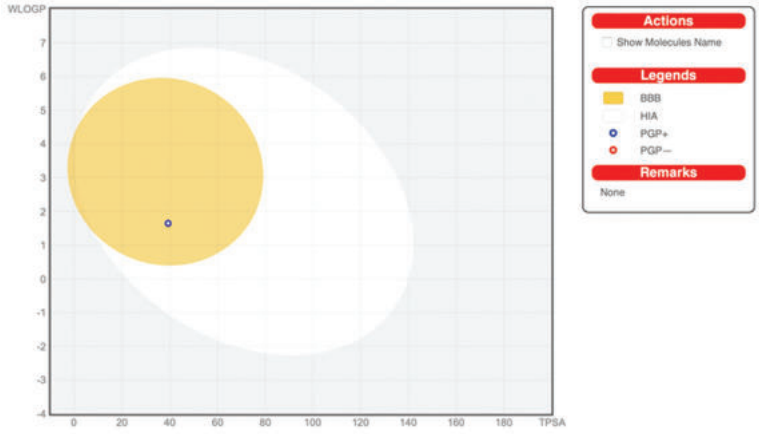

Figure 3 – Predicted «boiled egg» chart from the swissADME online web tool for lysergol

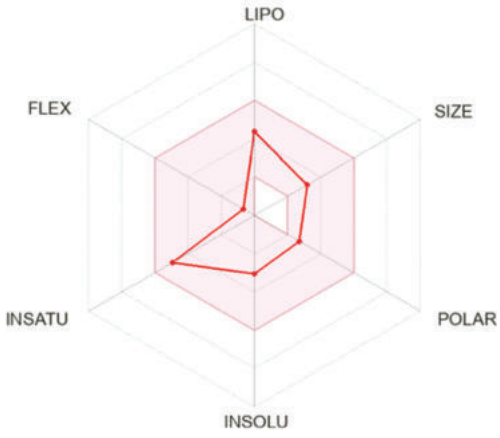

Figure 4 – Radar bioavailability chart for lysergol. The pink area is the optimal property range for oral bioavailability, and the red line is the predicted properties of lysergol

Despite the fact that lysergol and other secondary metabolites of ergot have been known to mankind since ancient times, they mainly focus on their toxicity, I use them only in narrow areas of pharmacology, for example, as a drug that synergistically enhances the effect of antibiotics of the nalidix series, however, lysergol as an independent molecule shows excellent pharmacological properties and requires further study of all potential effects. As can be seen from the results, lysergol meets all the requirements of Rule Five, making it a potentially interesting molecule for further study, and it also has excellent permeability through the gastrointestinal tract and blood-brain barrier, making it a molecule with active pharmacokinetics and bioavailability. Also, lysergol derivatives have a pronounced effect on the human neural system, including the higher nervous activity, the mechanism of such an effect is not fully understood at the moment, but it was previously found that its derivatives are able to bind to a large number of serotonin receptors, which makes lysergol an interface for the synthesis of new compounds, which has the properties of ligands the receptor of the nervous system. As it was indicated in our calculations, lysergol shows similarities in GPCR ligands, and this gives a great field for studying the interaction of lysergol with neurotransmitter receptors, since many of them are GPCRs. Like other secondary metabolites of fungi of the *Claviceps* genus, lysergol, according to preliminary calculations, proved to be an interesting molecule for further study of all its properties.

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КВАНТОВО-ХИМИЧЕСКИЙ РАСЧЕТ ПРОИЗВОДНОГО ХАЛКОНОВ 4-(2-БРОМФЕНИЛ)-6-(4-БРОМФЕНИЛ)-1,6-ДИГИДРОПИРИМИДИН-2-АМИНА

QUANTUM-CHEMICAL CALCULATION OF THE CHALCON DERIVATIVE 4-(2-BROMOPHENYL)-6-(4-BROMOPHENYL)-1,6-DIHYDROPYRIMIDINE-2-AMINE

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В работе приведены данные полуэмпирических и теоретических расчетов молекулы дигидропиримидина 4-(2-бромфенил)-6-(4-бромфенил)-1,6-дигидропиримидин-2-амина, синтезированного на основе халконов, в среде растворителя, их спектр поглощения и оптимизированная структура с значением полной энергии системы.

The paper presents the data on semi-empirical and theoretical calculations of 4-(2-bromophenyl)-6-(4-bromophenyl)-1,6-dihydropyrimidin-2-amine molecule, that was synthetized on the basis of chalcones, in the solvent, their absorption spectrum and the optimized structure with the value of the total energy of the system.

Ключевые слова: PM6, DFT, спектр, дигидропиримидины, производные халконов.

Keywords: PM6, DFT, spectrum, dihydropyrimidines, chalcone derivatives.

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Предварительное квантово-химическое моделирование молекулы. Для расчетов использован персональный компьютер с процессором intel core i7 (2.21 GHz CPU) с установленной операционной системой Ubuntu 18.04. При вычислениях стартовой геометрии молекулы с дигидропиримидиновым основанием выбран метод молекулярной механики ($ММ^+$) программного пакета HyperChem 08. Выбор метода $ММ^+$ обоснован тем, что он разработан для органических молекул, учитывает потенциальные поля, формируемые всеми атомами рассчитываемой системы, и позволяет гибко модифицировать параметры расчета в зависимости от конкретной задачи. Стартовую геометрию молекулы дополнительно оптимизировали в среде растворителя этанола (ethanol) полуэмпирическим методом PM6 программного пакета Gaussian 16 до достижения глобального минимума полной энергии изучаемых систем. Для нахождения глобального энергетического минимума и наиболее устойчивых конформеров анализировали все стационарные точки на поверхности потенциальной энергии молекул. Методом PM6 находят оптимизированные геометрические конфигурации, общую энергию молекул, электронные свойства и энтальпию образования веществ [1, 2]. Для визуализации результатов использована программа Gauss View 06. Равновесная геометрия молекулы полуэмпирическим методом PM6 приведена на рисунке 1.

E = -807.85 Hartree

Полное квантово-химическое моделирование равновесной геометрии и электронной структуры молекулы. Полная оптимизация и расчет электронной структуры проводились неэмпирическим методом DFT/RB3LYP в базисе LanL2DZ. Данный метод используется для расчета оптимизированных геометрий, электронных абсорбционных спектров, значений полной энергии и теплоты образования и применен нами для расчета электронного спектра поглощения молекул. Электронный спектр молекулы рассчитан для 20 одноэлектронных возбуждений. Результаты расчета абсорбционного спектра даны в таблице 1.