тэставання малекулы мірыцэтына ў якасці кандыдата на клінічныя выпрабаванні і патэнцыйнага агента звязвання з іншымі бялкамі, задзейнічанымі ў патагенезе хваробы Паркінсана.

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QUANTUM-CHEMICAL MODELING AND MOLECULAR DOKING OF THE BROMCRIPTINE MOLECULE

КВАНТОВО-ХИМИЧЕСКОЕ МОДЕЛИРОВАНИЕ И МОЛЕКУЛЯРНЫЙ ДОКИНГ МОЛЕКУЛЫ БРОМОКРИПТИНА

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Bromocriptine is a dopamine D2-receptor agonist with many bioactive properties. Bromocriptine is used in clinical practice as a drug for the treatment of hyperprolactinemia, Parkinson's disease, acromegaly, prolactinoma and other hormone-dependent pituitary adenomas and, more recently, diabetes and various other diseases [1].

Бромокриптин является агонистом дофаминовых D2-рецепторов и обладает многими биологически активными свойствами. Бромокриптин используется в клинической практике как препарат для лечения гиперпролактинемии, болезни Паркинсона, акромегалии, пролактиномы и других гормонозависимых аденом гипофиза, а в последнее время – сахарного диабета и ряда других заболеваний [1].

Keywords: B3LYP, TD-DFT, bromocriptine, spectrum.

Ключевые слова: B3LYP, TD-DFT, бромокриптин, спектр.

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

The calculation and complete optimization of the structure were performed using the non-empirical DFT/ RB3LYP method and the MidiX basis set [2]. The calculated electronic absorption spectrum of the molecule in a solvent medium is shown in Figure 2. The calculation demonstrated that the strongest electronic transition is observed at the absorption maximum $\lambda = 302.79$ nm, f=0.3286. The transition refers to the transition of an electron to an excited singlet state: $S_0 \rightarrow S_1$. The other transitions have a small value of f and are forbidden by symmetry. A complete list of transitions is given in Table 1.

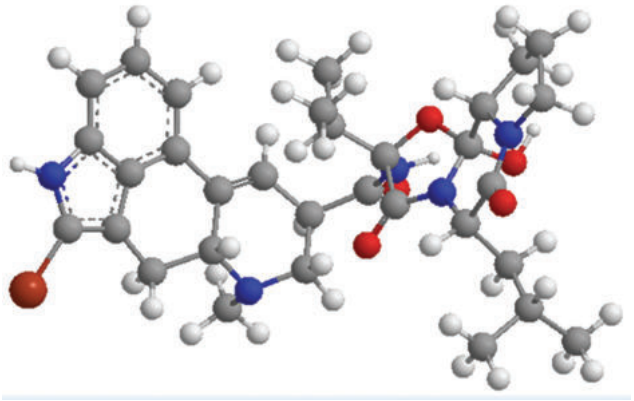

Figure 1 – MM+ optimized molecule

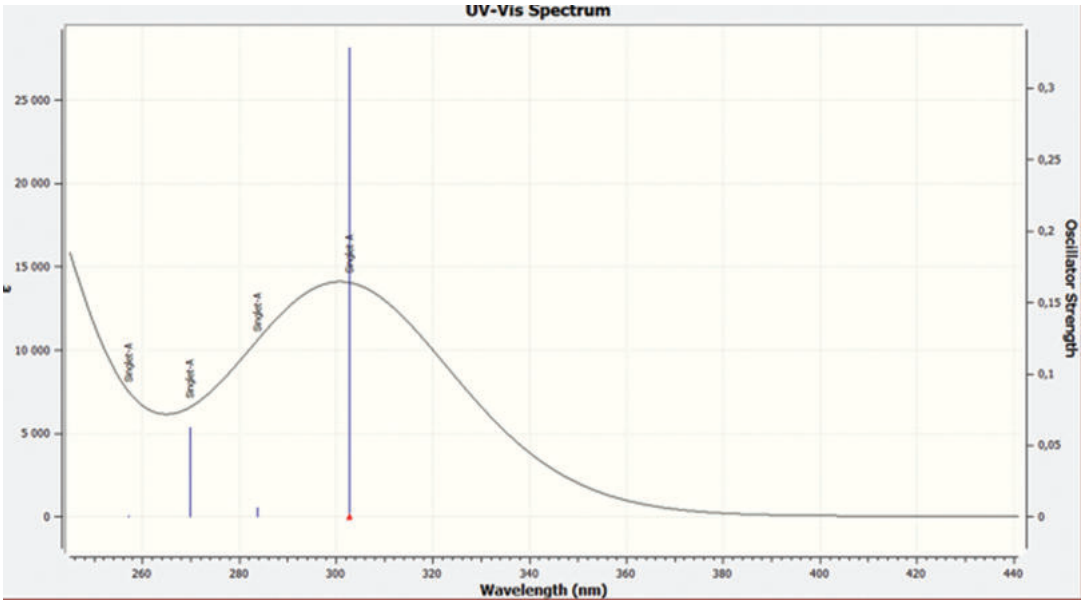

Figure 2 – UV-Vis spectroscopy

Table 1

Calculated electronic absorption spectrum of the molecule

Excited State	Wavelength, nm	Transition energy, eV	Cluster decomposition of full configuration interaction wave	Oscillator
$S_0 \rightarrow S_1$	302.79	4.0948	171 ->172 0.68553	f=0.3286
$S_0 \rightarrow S_2$	283.72	4.3699	170 ->172 0.69817	f=0.0067
$S_0 \rightarrow S_3$	269.80	4.5954	169 ->172 0.60129 171 ->174 0.30337 171 ->176 0.11120 171 ->178 -0.10526	f=0.0625
$S_0 \rightarrow S_4$	242.57	257.12	171 ->174 0.18794 171 ->175 0.66340	f=0.0006
$S_0 \rightarrow S_5$	242.57	5.1112	171 ->173 0.66760 171 ->176 0.15716	f=0.0060
$S_0 \rightarrow S_6$	237.02	5.2310	165 ->172 0.28194 166 ->172 0.34403 167 ->172 0.44525 168 ->172 -0.20657	f=0.1469

Excited State	Wavelength, nm	Transition energy, eV	Cluster decomposition of full configuration interaction wave	Oscillator
$S_0 \rightarrow S_7$	234.31	5.2916	165 ->172 -0.38970 166 ->172 0.47242 167 ->172 -0.12218 168 ->172 0.12901 171 ->174 -0.20622 171 ->178 -0.10781	f=0.1777
$S_0 \rightarrow S_8$	232.78	5.3263	162 ->173 -0.11923 163 ->173 -0.10877 163 ->176 0.10356 165 ->173 0.20765 165 ->174 -0.11860 165 ->176 0.27316 165 ->177 -0.14961 167 ->173 0.30700 167 ->176 0.10840 168 ->172 0.19196 170 ->173 0.24841 170 ->176 0.18287	f=0.0034
$S_0 \rightarrow S_9$	232.06	5.3427	162 ->173 0.10743 163 ->173 0.14832 165 ->172 0.10319 166 ->172 -0.14042 167 ->173 -0.15105 167 ->176 0.10619 171 ->173 -0.14622 171 ->174 -0.25019 171 ->176 0.46629 171 ->177 -0.16822	f=0.0212
$S_0 \rightarrow S_{10}$	231.54	5.3547	165 ->172 0.18831 167 ->172 0.18990 168 ->172 0.62462	f=0.0006

Method 2. Pharmacokinetic properties.

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 and Table 3.

Table 2

Pharmacokinetic properties of the bromocriptine molecule

miLog *P*	TPSA	Log *S*	Molecular weight	Fraction Csp3
4.06	118.21 Å²	-6.67	654.59 g/mol	0.59

Table 3

Bioactivity score

Name	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Bromocriptine	0.87	-0.22	-0.28	-0.40	0.32	-0.08

Method 3. Molecular docking was performed via the Chimera program, which provides docking and docking evaluation analysis. Chimera calculates and analyzes the interaction between the ligand and the target molecule based on binding energy as well as pi-bonding and hydrogen bonding. The target molecule in our study was an amyloid protein, and bromocriptine was used as the ligand. the study of molecular docking was performed using the Autodock/Vina program [19] and its algorithm, the Broyden-Goldfarb-Shanno algorithm. The crystal structure of the target protein was

taken from the PDB database (identifier: 2BEG). The docking position was visualized using Chimera (www.cgl.ucsf.edu/chimera) and Molegro Molecular Viewer 2.5 (www.clcbio.com/products/molegro/#molecular-viewer). The doking results are shown in Figure 5. Bromocriptine binds to the alzheimer's amyloid protein, and gives low binding energy -7.7 (Kcal/mol), indicating a strong bond.

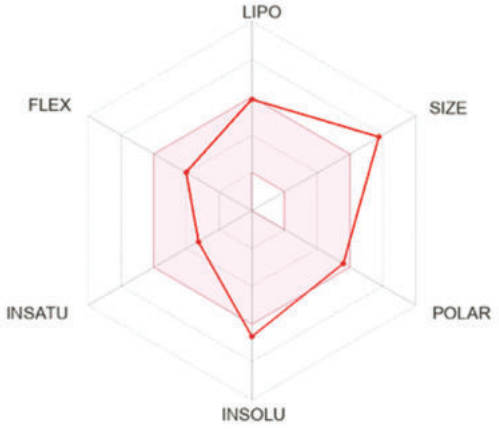

Figure 3 – Predicted «boiled egg» chart from the swissADME online web tool for bromocriptine

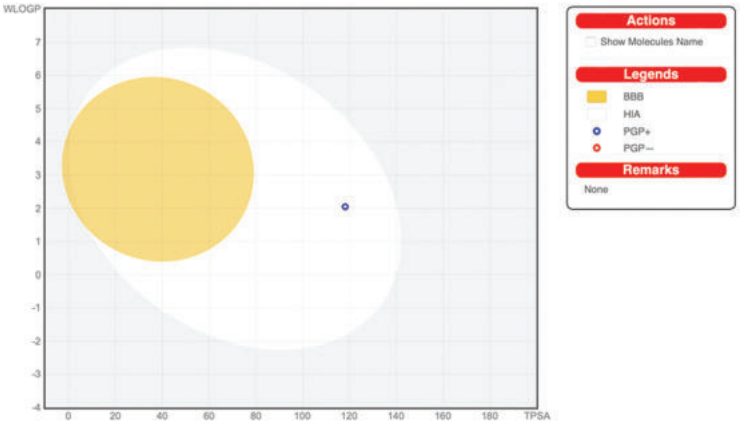

Figure 4 – Predicted «boiled egg» chart from the swissADME online web tool for bromocriptine

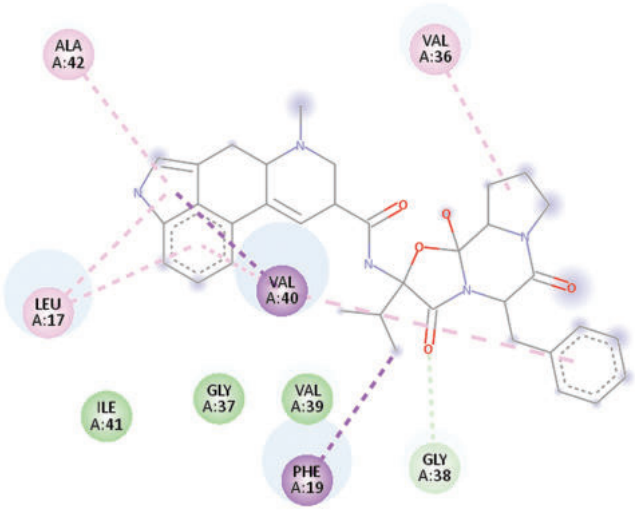

Figure 5 – Molecular docking of the 2BEG protein and bromocriptine

Bromocriptine fits all the criteria of Lipinski's rule, except for size, bromocriptine has a larger size, however, in other criteria bromocriptine shows itself as a bioactive substance, demonstrating protease inhibitor properties and having similarity to GPCR ligands. Bromocriptine does not inhibit cytochromes. It also has good permeability through the gastroenteric tract. this study involved molecular docking of bromocriptine with the amyloid protein of Alzheimer's disease, and its low binding energy makes bromocriptine a potential compound for studying its interaction with amyloid proteins. All these parameters make it a molecule of interest for further studies for various therapeutic applications.

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