TRIAZAVIRIN – POTENTIAL INHIBITOR FOR 2019-nCoV CORONAVIRUS M PROTEASE

ТРИАЗАВИРИН – ПОТЕНЦИАЛЬНЫЙ ИНГИБИТОР ПРОТЕАЗЫ КОРОНАВИРУСА 2019-nCoV

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In order to find candidate drugs for 2019-nCoV, we have carried out a computational study to screen for effective available drug Triazavirin ($C_5H_4N_6O_3S$) which may work as inhibitor for the Mpro of 2019-nCoV. In the present work, first time the molecular structure of title molecule has been investigated using Density Functional Theory (DFT/B3LYP/MidiX) in gas phase.

Проведено полное квантово-химическое моделирование Триазавирина ($C_5H_4N_6O_3S$), способного разрушить белковую структуру коронавируса 2019-nCoV. В настоящей работе впервые исследована молекулярная структура молекулы Триазавирина с применением метода теории функционала плотности (DFT/B3LYP/MidiX) в газовой фазе.

Keywords: Triazavirin, DFT, 2019-nCoV Coronavirus, Docking.

Ключевые слова: Триазавирин, ДФТ, Коронавирус 2019-nCoV, Докинг.

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Triazavirin (TZV) is a synthetic analogue of the bases of purine nucleosides (guanine). It belongs to azoloazines - heterocyclic compounds structurally resembling the nitrogenous bases of which DNA and RNA are composed. Research on azoloazines began at the UPI in 1993.

Triazavirin (Fig. 1) is an antiviral drug synthesized in Russia through a joint effort of Ural Federal University, Russian Academy of Sciences, Ural Center for Biopharma Technologies and Medsintez Pharmaceutical. Triazavirin has a wide spectrum of antiviral action and effectively inhibits not only many epidemic strains of influenza viruses type A such as H1N1 (swine flu), H3N2, H5N1 (avian influenza), H5N2, H7N3, H9N2, including the pandemic strain H1N1 pdm 2009, but also influenza viruses Type B. TZV has also been found to have antiviral activity against a number of other viruses including Tick-borne encephalitis virus, Forest-Spring Encephalitis virus and is also being investigated for potential application against the Coronavirus 2019-nCoV. The efficiency index of Triazavirin in animal experiments for influenza viruses Types A and B is 65–85%. The effectiveness of the drug against fever of Rift Valley, West Nile, tick-borne encephalitis and other dangerous infections has been established.

Clinical trials have confirmed the high therapeutic effect of Triazavirin; it was registered by the Ministry of Health of the Russian Federation as a medicament for the treatment of the influenza virus (registration certificate LP-002604). At present, studies are continuing on the mechanism of action of this drug. The study of the crystal structure of the drug gives an idea about a set of spatial and electronic features that can be used in the search for responsible biological targets and molecular modeling of new useful compounds. In 2019, a novel Coronavirus 2019-nCoV was found to cause Severe Acute Respiratory symptoms and rapid pandemic in China, France, United States of America, Germany, Italy, Japan, Russia. In order to find candidate drugs for 2019-nCoV, we have carried out a computational study to screen for effective available drug Triazavirin which may work as inhibitor for the Mpro of 2019-nCoV. The molecular docking approach used to model the interaction between a small molecule and a protein at the atomic level, which allow us to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes.

The quantum chemical calculations have performed for the most stable conformation and optimized the using the Density Functional Theory (DFT/B3LYP) method with MidiX basis sets by the Gaussian 09W program package [1] on a Pentium IV/4.28 GHz personal computer. We have used Time Dependent Density Functional Theory (TD-DFT) for calculation of the electronic transitions of the lowest energy conformation of the title compound. The electronic properties such as EHOMO, ELUMO, HOMO-LUMO energy gap, dipole moment (μD), point group, Mulliken atomic charges, and natural charge of the title structure were calculated [2]. The optimized molecular structures, molecular electrostatic potential

(MEP) surface, HOMO and LUMO surfaces were visualized using GaussView 05 program [3]. Interaction between structures of Coronavirus 2019-nCoV and Triazavirin has been investigated by HyperChem Professional 08, PyMOL and Molegro Molecular Viewer software programs. The protein sequences of 2019-nCoV was downloaded from GenBank.

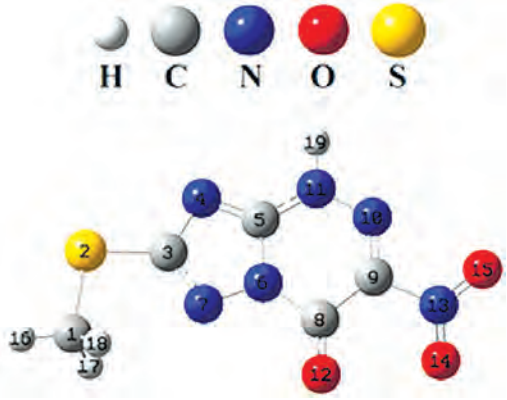

Figure 1 – Optimized structure of the TZV by B3LYP/MidiX method

The MEP Map of the optimized molecule TZV was calculated at B3LYP/MidiX level of theory and given in Fig. 2. The electrostatic potential of the molecule is related to the electronegativity and the partial charges on the different atoms [4]. The MEP map indicates the molecular shape, size, dipole moment and relative polarity of the molecule. The electrophilic and nucleophilic reactive sites of the molecular structure are also identified with the MEP map. The difference of the electrostatic potential at the surface is shown by different colors. The sites of electron rich, partially negative charge, slightly electron rich regions, positive charge or electron poor and neutral sites in the MEP maps are red, orange, yellow, blue, and green colors, respectively [5]. In MEP map of TZV, the oxygen atom (O12) of carbonyl group is found to be electron rich site (red color), which is due to the lone pairs of oxygen atoms. Also, the O14 and O15 atoms in the $–NO_2$ group with orange color are shown partially negative charge site. Therefore, the O12, O14 and O15 are nucleophilic sites. The H19 atom in the –NH group with blue color is shown electron poor and electrophilic site. The regions with green color in the molecule TZV show the sites with zero potential and neutral regions. The electrophilic and nucleophilic regions of the TZV illustrate the interaction with other molecules in chemical reactions.

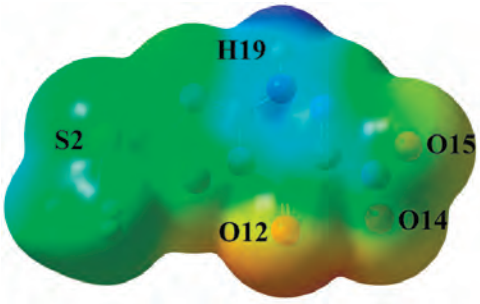

Figure 2 – MEP map of the molecule TZV calculated using the B3LYP/MidiX level of theory

The molecular docking analysis is an important tool for drug design and molecular structural biology [4]. The aim of molecular docking analysis is to predict the preferred binding location, affinity and activity of drug molecules and their protein targets. In the present work, the molecular docking studies of TZV molecule was performed against Coronavirus 2019-nCoV using HyperChem Professional 08, PyMOL and Molegro Molecular Viewer software programs. Molecular basis of interactions between Coronavirus 2019-nCoV molecule and the TZV can be understood with the help of docking analysis and interactions as observed in Fig. 6. The binding energy for Coronavirus 2019-nCoV and TZV is -36.900 kcal/mol that shows good binding affinity between TZV and 2019-nCoV. As seen from Fig. 3 two hydrogen bonding formation between reduce Asn 142 bonded with N atom of the TZV are observed. Also, His 172, Glu 166, Gly 138 and Phe 140 are contact with negatively and positively charged in the TZV binding environment. it was found that the ligand TZV shows the best affinity towards of the protein. The molecular docking binding energies (kcal/mol), intermolecular energy (kcal/mol) and inhibition constants (μm) were also obtained and listed in Table.

Table – Molecular docking energy data for mentioned ligand and Hydrogen bonding

Protein	Bonded residues	Hydrogen bond	Bond distance (Å)	Estimated Inhibition Constant (μm)	Binding energy (kcal/mol)	Intermolecular energy(kcal/mol)	Reference RMSD (Å)
2019-nCoV	Asn 142	1	1.5	6.53	-9.94	-8.57	83.15
2019-nCoV	Asn 142	1	1.6	4.39	-8.50	-8.66	87.35

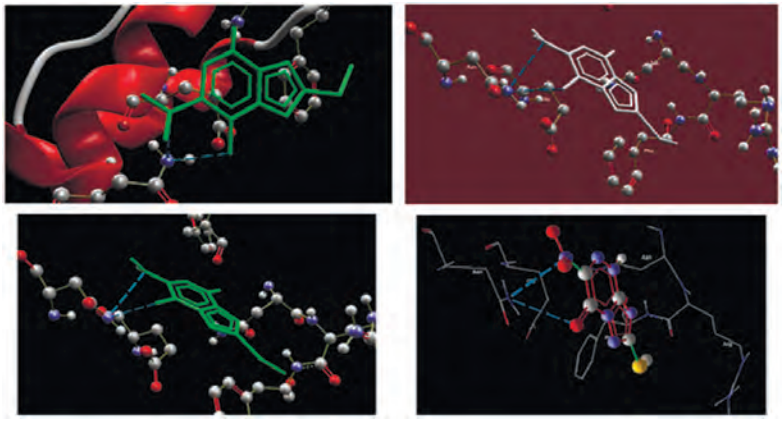

Figure 3 – Molecular docking of TZV to Coronavirus

In this present study quantum computational chemical calculations were carried out for 2-methylsulfanyl-6-nitro[1,2,4]triazolo[5,1-c][1,2,4]triazin-7(4H)-one molecule. The geometrical optimized bond lengths and bond angles were calculated theoretically. The binding energy for Coronavirus 2019-nCoV and TZV is -36.900 kcal/mol that shows good binding affinity between TZV and 2019-nCoV. TZV is also being used for potential application against the Coronavirus 2019-nCoV.

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ZIDOVUDINE – INHIBITOR FOR 2019-nCoV CORONAWIRUS M PROTEASE

ЗИДОВУДИН - ИНГИБИТОР ДЛЯ ПРОТЕАЗЫ КОРОНАВИРУСА М 2019-nCoV

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In order to find candidate drugs for 2019-nCoV, we have carried out a computational study to screen for effective available drug Zidovudine which may work as a strong inhibitor for the Mpro of 2019-nCoV. The interaction of the Zidovudine with the Coronavirus 2019-nCoV were performed by molecular docking studies.