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Comparative study on quantum descriptors, Molecular docking and dynamic simulation of antiviral drugs with Covid-19

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Molecular Docking and Dynamics Simulation of Antiviral Drugs With COVID-19

Abstract:
Covid-19 is a beta-coronavirus that was first identified during the Wuhan COVID-19 epidemic in 2019. This study is focused on the quantum descriptors of the proposed antiviral drugs, molecular docking, and dynamics simulation with the main protease of coronavirus. Such drugs are Baloxavir, Chloroquine, Avigan, Plaquenil, oseltamivir, Remdesivir, Arbidol, and Sofosbuvir were used for comparison. Density functional theory (DFT) may help find the relevancy of quantum chemical descriptors to explain the potential antiviral activity. Some quantum descriptors such as $\Delta E$; the energy gap, $\eta$; global hardness, $S$; global softness, $I$: ionization potential, $A$: electron affinity, $\chi$: absolute electronegativity, $\omega$; $\Delta E_{\text{Back-donation}}$; the back donation were calculated based on $E_{\text{HOMO}}$; energy of the highest occupied molecular orbital, and $E_{\text{LUMO}}$; energy of the lowest unoccupied molecular orbital. Fukui indices ($f^+, f^-$); for local nucleophilic and electrophilic attacks are investigated for the investigated antiviral drugs. The reported genomic sequence of Covid-19 main protease in complex with an inhibitor N3 (DOI: 10.2210/pdb6LU7/pdb) was used as a precursor for docking with the selected drugs after removing the attached inhibitors N3 and water. Molecular docking was performed using Autodock 4.2, with the Lamarckian Genetic Algorithm, and was analyzed by Autodock 1.5.6 and Pymol version 1.7.4.5 Edu, However, further research is necessary to investigate their potential medicinal use.

Keywords: Virtual Screening, Molecular Docking, Anti-Viral drugs, Coronavirus, COVID-19

Introduction:
Coronaviruses can be classified into four genera: Alphacoronavirus, Beta-coronavirus, Gamma-coronavirus, and Delta-coronavirus. Among them, alpha- and beta-coronaviruses infect mammals, gamma-coronaviruses infect avian species, and delta-coronaviruses infect both mammalian and avian species [1]. Structure, Function and Evolution of Coronavirus Spike Proteins were reviewed [2]. In general, coronaviruses COVID-19 infects humans causing a variety of highly prevalent and severe diseases, including Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [3]. Its main protease (Mpro) plays an important role in viral replication and transcription. So, it can be an attractive drug target for this virus [4]. Virtual drug screening was carried out to identify new drug leads that target the COVID-19 virus main protease (Mpro)[1]. Different compounds were tested against Covid-19[5] including Sofosbuvir, IDX-184, Ribavirin, Remissive, Guanosine triphosphate (GTP), Uracil triphosphate (UTP), Cinnamaldehyde, and Thymoquinone, Chloroquine was reported to be strong in vitro and in vivo antiviral activities against HCoVOC43 [6]. Sofosbuvir, Ribavirin, and Remissive can be used against the new strain of coronavirus that emerged with promising results. GTP derivatives may be used as specific inhibitors against COVID-19 [5]. Avigan (Favipiravir) was reported that it can be a substitute for compassionate use in COVID-19 based on its mechanism of action inhibiting virus RdRp [7]. Modification of oseltamivir was investigated as a neuraminidase inhibitor of influenza A virus subtype H1N1 [8]. Based on molecular docking, three molecules out of 67 natural product extracts pronounce to be SARS-CoV-2 antiviral [9]. Up till now, no antiviral therapy or vaccine is available against coronavirus infection and attempts in this trend are accelerated to combat the current epidemic outbreak[10], [11] Binding site analysis of potential protease inhibitors of COVID-19 were determined using AutoDock [16]. It is of interest to investigate eight of FDA approved drugs (i.e., (Baloxavir [12], Chloroquine [6, 7], Avigan [7], Plaquenil [14], oseltamivir [8], Remdesivir [11], Arbidol [15], and Sofosbuvir [5]) to be docked to the main protease structure of CoVis-19 for understanding their potential antiviral activity against the new epidemic coronavirus. The selected drugs Baloxavir, Chloroquine Avigan, Plaquenil, oseltamivir, Remdesivir, Arbidol, and Sofosbuvir are designated L1, L2, L3, L4, L5, L6, L7 and L8, respectively.
Computational methodology

Quantum descriptors

The COVID-19 main protease’s crystallographic structure was recently made publicly available through the Protein Data Bank (PDB) as a complex with an N3 inhibitor (PDB ID: 6lu7) [2, 15]. By using Autodock4.2, water and associated inhibitor chain were removed from the (pdb) file, then hydrogen and Kollman charges were added to the protein, then the (pdb) file was saved as (pdbqt) file. The structure of the approved drug was retrieved from PubChem [18] as a 3D conformer and saved as (sdf) file, then generated to a (pdb) file using Discovery Studio visualizer v 20.1.0.

All quantum descriptors are calculated using ORCA 4.0 applying functional B3LYP OPT def2-TZVP/J NormalPrint Grid4 Normal SCF [19], with Avogadro 1.2 as Graphical user interface GUI. The obtained HOMO and LUMO orbitals for the selected drugs can be visualized in Figure 1 and their energy $E_{\text{HOMO}}$ and $E_{\text{LUMO}}$ values are listed in Table 1. The following descriptors [20]: the energy gap; $\Delta E_{\text{gap}} = (E_{\text{LUMO}} - E_{\text{HOMO}})$, Ionization potential; ($I = -E_{\text{HOMO}}$), electron affinity; ($A = -E_{\text{LUMO}}$), the electronegativity; ($\chi = (I+A)/2$), global hardness; ($\eta = (I-A)/2$), and softness ($S = 1/\eta$), can be calculated based on the energy of the HOMO and the LUMO [22]. The local reactivity of ligand molecules is analyzed using Fukui’s indices [23].

Molecular docking and dynamics simulation

The sequence of docking is explained in supplementary text (A) Autodock 1.5.6 used for protein optimization, by removing water and other atoms, then adding a polar hydrogen group [24]. Autodock 4.2 was supported by Autodock tools and MGL tools. Autogrid, then was determined the native ligand position on the binding site by arranging the grid coordinates (X, Y, and Z). Ligand tethering of the protein was performed by regulating the genetic algorithm (GA) parameters, using 10 runs [25]. The default force-field parameters for these atom types can be overridden using the "parameter file" command in the GPF and DPF. This command requires one argument, namely the filename of the "dat" file that contains the linear free energy model's coefficients and the atom parameters; the default values can be found in "AD4_parameters.dat" which resides in the source code distribution. All of the conformations obtained from the molecular
docking were energy-minimized using molecular mechanics (MM) force-field. MD simulations were then applied to multiple conformations of the protein-ligand complexes. Among the 10 highest-scoring docking poses saved for each compound, the obtained protein-ligand complexes with the optimum binding energy were analyzed using Pymol [26].

**Results and Discussion:**

The frontier molecular orbitals of selected drugs are graphical represented in Figure 1. The highest-energy occupied (HOMO) and lowest-energy unoccupied molecular orbitals (LUMO). HOMO is logically viewed as nucleophilic or electron donating, while the LUMO is electrophilic and electron accepting [27]. According to the obtained $E_{\text{HOMO}}$ and $E_{\text{LUMO}}$ as shown in Table 1. The highest value of $E_{\text{HOMO}}$ of the investigated drugs indicated the ease of electron donation of the ligand to the target proteins. It is observed that the ease of electron donation increases in the following order; L4 (-5.29 eV) > L7 (-5.48 eV) > L2 (-5.72 eV) > L6 (-5.74 eV) > L1 (-5.82 eV) > L3 (-6.47 eV) > L8 (-6.80 eV). The lower the $E_{\text{LUMO}}$ the easier is the acceptance of the electron from protein molecule. The order of $E_{\text{LUMO}}$ of selected ligand can be arranged in the order; L3 (-2.14 eV) > L4 (-1.87 eV) > L1 (-1.71 eV) > L5 (-1.37 eV) > L2 (-1.34 eV) > L8 (-1.22 eV) > L7 (-0.91 eV) > L6 (-0.67 eV).

The values of the energy gap are listed in Table 1. The energy bandgap ($\Delta E_{\text{gap}}$), the difference between $E_{\text{LUMO}}$ and $E_{\text{HOMO}}$ is an indication of the reactivity of the molecules [28]. Accordingly, the smaller $\Delta E_{\text{gap}}$ is the more reactive molecule towards docking. So, the global reactivities of the investigated drugs are in the order; L4 (Plaquenil) > L1 (Baloxavir) > L3 (Avigan) > L5 (oseltamivir) > L2 (Chloroquine) > L7 (Arbidol) > L6 (Remedesvir) > L8 (Sofosbuvir).

The ionization potential; $I$ and the electron affinity; $A$, can be expressed as negative values of $E_{\text{HOMO}}$ and $E_{\text{LUMO}}$, respectively [29]. Ionization energy is a descriptor that indicates the chemical reactivity of atoms and molecules. Lower values of ionization energy indicate higher chemical reactivity and vice versa. Higher ionization potential indicates lower reactivity of the molecule, Table 1 shows values of the ionization potential of the investigated drugs. The lower ionization energy of L4 (Plaquenil) 5.29 (eV) indicates that it is the more reactive one out of the investigated
drugs. A good nucleophile can be characterized by low values of chemical potential $\mu$ [27, 29]. It is clear from the chemical potential values in Table 1 that the Avigan (L3) shows the lower chemical potential.

Fukui functions $f^+$ and $f^-$ are calculated to analyze the chemically active sites of a molecule using the following equations:

\[ f^- = q_{N+1} - q_N \quad \text{for nucleophilic attack} \tag{1} \]
\[ f^+ = q_N - q_{N-1} \quad \text{for electrophilic attack} \tag{2} \]

where $q_N$ is the Mullikan atomic charge for neutral molecule, $q_{N+1}$ the Mullikan atomic charge for positively charged molecule and $q_{N-1}$ the Mullikan atomic charge for negatively charged molecule.

The local reactivity of the molecule is analyzed using condensed Fukui indices (as attached supplementary Table (B). The most reactive sites of the investigated ligands are summarized in Table 2. The $f^+$ measures the changes of density while the molecules receive electrons and it corresponds to reactivity concerning the nucleophilic attack. As vice versa, $f^-$ denote to reactivity concerning electrophilic attack or when the molecule loses electrons. The nucleophilic attacks and the electrophilic attacks ($f^+$ and $f^-$) of molecules are listed in Table 2, where the red values indicate the atoms responsible for the nucleophilic attack and the blue ones indicate to the atoms liable to electrophilic attack. In the case of the site that is capable of nucleophilic or electrophilic attacks, the difference between the nucleophilic and electrophilic Fukui function (Dual descriptor $\Delta f$) is considered. If $\Delta f(r) > 0$, then the site is favored for a nucleophilic attack, whereas if $\Delta f(r) < 0$, then the site may be favored for an electrophilic attack. Several nucleophilic and electrophilic sites for each ligand are summarized in Table 2. From the values of Fukui functions $f^+$ and $f^-$, It is observed that the atoms seven atoms in Avigan molecule; 1O, 2O, 4N, 8C, 9C, and 10C) are susceptible for nucleophilic attack. Regarding Dual descriptor $\Delta f$ for Avigan, the result indicates that (1O, 2O, 9C, 10C) are strong nucleophilic sites. It is observed that Avigan has a lower molecular weight, lower molar volume, and lower relative ratio of Dipole moment/Molecular weight (D/Mw).
The main protease of coronavirus was docked with different eight drugs, Baloxavir, namely, Chloroquine, Avigan, Plaquenil, oseltamivir, Remdesivir, Arbidol, and Sofosbuvir was performed. In the rigid docking analyses, satisfactory results were found. It is observed that the binding energies shown in Table 3 are negative values ranging from -3.7 kCal/mol to -7.08 kCal/mol. For all ligands tested the mean RMSD are 0.0 Å. Lower RMSD value of the complex indicates its stability with the investigated drugs and provided a suitable basis for this study. The binding free energy was attributed to the $\Delta G_{vdw}$, $\Delta G_{hbond}$, $\Delta G_{elec}$, $\Delta G_{tor}$ and $\Delta G_{sol}$ and can be expressed in the following equation:

$$\Delta G_{binding} = \Delta G_{vdw} + \Delta G_{hbond} + \Delta G_{elec} + \Delta G_{tor} + \Delta G_{desolv} \quad (3)$$

The obtained molecular docking analysis and visualization using PyMol of Covid-19 binding with the investigated ligands (Table 4 A). The surface of covid-19 including the ligand in the pocket potential inhibitor of COVID-19 Mpro (Table 4 B). The hydrogen bonding between Covid-19 protease and the considered drugs obtained with individual docking are presented in Table 4 as dashed yellow lines. The binding energy obtained from docking Covid-19 are -8.0, -5.9, -5.1, -6.0, -5.8, -8.1, -6.1 and -7.4 kCal/mol for Baloxavir, Chloroquine, Avigan, Plaquenil, oseltamivir, Remdesivir, Arbidol, and Sofosbuvir, respectively. The interaction of most ligands with their binding sites can be characterized in terms of a binding affinity. In general, high-affinity ligand binding results from greater intermolecular force between the ligand and its receptor while low-affinity ligand binding involves less intermolecular force between the ligand and its receptor.

Conclusion:

Several parameters may indicate more potential antiviral activity of Avigan than the other investigated drugs. Such parameters are lower chemical potential, higher relative value of dipole moment/molecular weight (D/Mw), a greater number of nucleophilic atoms f+ as result of Fukui function analysis, and more hydrogen bonding between Avigan and COVID-19.
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**Fig. 1:** The HOMO and LUMO frontier molecular orbitals of selected drugs.

**Table 1:** Energy of the highest occupied molecular orbital; $E_{\text{HOMO}}$, the energy of the lowest unoccupied molecular orbital; $E_{\text{LUMO}}$, the energy gap; $\Delta E$, ionization potential; $I$, electron affinity; $\Delta$, absolute electronegativity; $\chi$, Chemical potential; $\mu$, Global hardness; $\eta$, global softness; $S$, Molar volume; $M_v$, Molecular weight; $M_w$, Dipole moment; $D$, and $D/M_w$ ratio.

|                | L1  | L2  | L3  | L4  | L5  | L6  | L7  | L8  |
|----------------|-----|-----|-----|-----|-----|-----|-----|-----|
| $E_{\text{HOMO}}$ (eV) |     |     |     |     |     |     |     |     |
| $E_{\text{LUMO}}$ (eV) |     |     |     |     |     |     |     |     |
| $\Delta E$ Gap (eV)   |     |     |     |     |     |     |     |     |
| $I$ (eV)              |     |     |     |     |     |     |     |     |
| $\Delta$ (eV)        |     |     |     |     |     |     |     |     |
| $\chi$ (eV)          |     |     |     |     |     |     |     |     |
| Atoms  | f+     | f-     | Δf     | 4 nucleophilic sites (OS, SO, 6O, 6N) | 1 electrophilic site (4O) |
|--------|--------|--------|--------|----------------------------------------|--------------------------|
| Baloxavir (L1) | 0 S | 0.132528 | 0.062819 | 0.069709 | 4 nucleophilic sites (OS, SO, 6O, 6N) |
|         | 4 O   | 0.027527 | 0.056256 | -0.02873 | 1 electrophilic site (4O) |
|         | 5 O   | 0.064186 | 0.03724  | 0.026946 | 1 electrophilic site (4O) |
|         | 6 O   | 0.095134 | 0.07071  | 0.024424 | 1 electrophilic site (4O) |
|         | 9 N   | 0.049336 | 0.005432 | 0.043904 | 1 electrophilic site (4O) |
| Chloroquine (L2) | 0 Cl | 0.074293 | 0.111281 | -0.03699 | 2 nucleophilic sites (2N, 1N) |
|         | 1 N   | 0.072595 | 0.00409  | 0.072186 | 1 electrophilic site (0Cl) |
|         | 2 N   | 0.065985 | 0.011071 | 0.054914 | 1 electrophilic site (0Cl) |
| Avigan (L3) | 1 O   | 0.128789 | 0.098854 | 0.029935 | 4 nucleophilic sites |
|         | 2 O   | 0.135517 | 0.05896  | 0.076557 | 4 nucleophilic sites |
| Compound            | 4 N  | 8 C  | 9 C  | 10 C | (10, 20, 9C, 10C) |
|---------------------|------|------|------|------|------------------|
|                     | 0.053739 | 0.121402 | -0.06766 |       | 2 electrophilic sites (4N,5C) |
|                     | 0.094514 | 0.130743 | -0.03623 |       |                      |
|                     | 0.079055 | 0.038085 | 0.04097 |       |                      |
|                     | 0.059379 | 0.054885 | 0.004494 |       |                      |
| Plaquenil (L4)      | 0 Cl  | 2 N  | 3 N  | 4 N  | 2 nucleophilic sites (2N, 3N) |
|                     | 0.074441 | 0.00544 | 0.070175 |       | 4 electrophilic sites (0Cl, 4N, 12C, 18C) |
|                     | 0.070719 | 0.000544 | 0.070175 |       |                      |
|                     | 0.06862 | 0.011746 | 0.056874 |       |                      |
|                     | 0.052272 | 0.054748 | -0.00248 |       |                      |
|                     | 0.00179 | 0.070037 | -0.06825 |       |                      |
|                     | 0.013353 | 0.081995 | -0.06864 |       |                      |
| Osel tamivir (L5)   | 0 O   | 1 O  | 2 O  | 3 O  | 3 nucleophilic sites (3O, 25C, 16C) |
|                     | 0.038573 | -0.04633 | 0.075432 | -0.12196 | 3 electrophilic sites (0O,1O, 2O) |
|                     | 0.002311 | 0.144928 | -0.14262 |       |                      |
|                     | 0.064070 | 0.052985 | 0.011085 |       |                      |
|                     | 0.079429 | 0.052626 | 0.026803 |       |                      |
|                     | 0.061391 | -0.05055 | 0.111937 |       |                      |
| Remedesvir (L6)     | 8 O   | 10 N | 24 C | 32 C | 2 nucleophilic sites (10N, 24C) |
|                     | -0.00134 | 0.08170 | 0.056183 | 0.025517 | 2 electrophilic sites (8O,32C) |
|                     | 0.049006 | 0.056183 | 0.025517 |       |                      |
|                     | 0.083985 | 0.031964 | 0.052021 |       |                      |
| Arbidol (L7)        | 0 Br  | 1 S  | 2 O  | 11 C | 3 nucleophilic sites (1S, 2O,11C) |
|                     | 0.104061 | 0.069143 | 0.042164 | 0.026979 | 2 electrophilic sites (0Br, 13C) |
|                     | 0.111904 | 0.042164 | 0.026979 |       |                      |
|                     | 0.056183 | 0.025171 | 0.034484 |       |                      |
|                     | 0.049037 | 0.046184 | 0.002853 |       |                      |
|                     | 0.064756 | 0.076938 | -0.01218 |       |                      |
| Sofosbuvir (L8)     | 5 O   | 7 O  | 8 O  | 20 C | 2 nucleophilic sites (O5, O7) |
|                     | 0.054836 | 0.059581 | 0.060175 | 0.019921 | 3 nucleophilic sites (O8, C20, C23) |
|                     | 0.05122 | 0.020624 | 0.07646 | -0.05055 |       |
|                     | 0.003616 | 0.038957 | -0.01629 |       |                      |
|                     | 0.03616 | 0.038957 | -0.01629 |       |                      |
|                     | 0.02531 | -0.00942 | -0.05055 |       |                      |

**Table 3:** The obtained Molecular docking analysis of several compounds against COVID-19 using Autodock 4.0.
| Reference RMSD | A    | 67.212 | 69.847 | 66.551 | 71.150 | 64.648 | 54.727 | 54.812 | 69.777 |
|----------------|------|--------|--------|--------|--------|--------|--------|--------|--------|
| Estimated Free Energy of Binding kcal/mol | -7.08 | -6.07  | -3.7   | -4.81  | -6.12  | -3.89  | -1.67  | -4.51  |
| Estimated Inhibition Constant, Ki uM | 6.48  | 35.81  | 1.93   | 298.54 | 32.49  | 1.4    | 59.8   | 493.54 |
| (1) Final Intermolecular Energy kcal/mol | -6.99 | -7.97  | -4.05  | -7.23  | -6.96  | -4.83  | -3.34  | -4.02  |
| vDW + Hbond + desolv Energy kcal/mol | -6.83 | -7.5   | -3.81  | -6.51  | -4.94  | -4.41  | -3.21  | -3.96  |
| Electrostatic Energy kcal/mol | -0.16 | -0.47  | -0.24  | -0.71  | -2.02  | -0.42  | -0.13  | -0.07  |
| (2) Final Total Internal Energy kcal/mol | -0.64 | -0.29  | 0.07   | -0.33  | -1.63  | -3.72  | -0.8   | -3.78  |
| (3) Torsional Free Energy kcal/mol | 0.55  | 2.2    | 0.27   | 2.74   | 2.47   | 4.66   | 2.47   | 3.29   |
| (4) Unbound System's Energy kcal/mol | 0     | 0      | 0      | 0      | 0      | 0      | 0      | 0      |

Table 4: Binding mode of Covid-19 - ligand complex using PyMol A. The surface of covid-19 including the binding pocket B. The dashed yellow line represents H-bonds.
| L1 | -7.08 | 3 | ASN142 (2.9) - HIS163 (2.8) – GLU166 (3.5) |
| L2 | -6.07 | 2 | ARG188 (2.7) - GLU166 (2.1) |
| L3 | -3.7  | 6 | ASN142 (3.3) - HIS163 (3.4) – HIS163 (2.7) - GLU166 (2.1) - PHE140 (2.5) – LEU142(1.9) |
| L4 | -4.81 | 4 | SER144 (2.2) - SER144 (2.8) – GLY143 (3.2) - GLN189 (2.1) |
| L5 | -6.12 | 1 | ASN142 (2.4) |
| L6 | [-3.89] | 4 | ASN142 (2.4) – HIS163 (3.1) – SER144 (2.4) – PHE140 (3.1) |
|----|---------|----|---------------------------------------------------------|
| L7 | [-1.67] | 3 | ASP289 (2.7) – GLU290 (2.7) – LYS137 (2.7)                |
| L8 | [-4.51] | 4 | SER158 (3.1) – ASP153 (3.2) – ASN151 (2.9) – GLN 110 (3.1) |