International Journal of Scientific Research in Computer Science and Engineering
Vol.9, Issue.6, pp.79-81, December (2021)

Research Paper

E-ISSN: 2320-7639

Lapatinib (Tyverb®) Against Zika Virus

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Available online at: www.isroset.org

Received: 09/Nov/2021, Accepted: 20/Nov/2021, Online: 31/Dec/2021

***Abstract*—** After Docking analysis of over 300 drugs, processed with Pyrx, a small Virtual Screening software, into the active site of protein of RNA-directed RNA polymerase NS5, (ID PDB 6LD3 chain A), could be an excellent candidate drug against Zika virus. Indeed, from the results of Autodock Vina has a good Binding affinity value, ca. -9.6 kcal mol $^{-1}$, good estimation inhibitory constant (Ki) value ca. 91 nM and goof Ligand efficiency ca -0.24 kcal mol $^{-1}$. These results are higher to the crystallized ligand G8O (2,4-dimethoxy-5-thiophen-2-yl- benzoic acid) complexed in this studied protein.

***Keywords*—** Lapatinib, Zika virus (ZIKV), Autodock 4, Autodock Vina

I. INTRODUCTION

Zika virus belongs to the family Flaviviridae and the genus Flavivirus, thus is related to the dengue, yellow fever, Japanese encephalitis, and West Nile viruses. Like other flaviviruses, Zika virus is enveloped and icosahedral and has a no segmented, single-stranded, 10 kilo base, positive-sense RNA genome [1]. ZIKV remains a potentially significant public health concern because it can cause teratogenic effects, such as microcephaly in newborns and neurological disease, like Guillain-Barre syndrome. Together with efforts to develop a vaccine, the discovery of antiviral molecules is important to control ZIKV infections and to prevent its most severe symptoms [2].

II. RELATED WORK

In this short communication, we investigated about 300 drugs, through In Silico Docking approach, downloaded from PubChem Database (https://pubchem.ncbi.nlm.nih.gov/).

Particular attention, I have focused on Autodock Vina, estimated with Pyrx software, a simple Virtual Screening library software for Computational Drug Discovery (https://pyrx.sourceforge.io/) [3] based on prediction the binding orientation and affinity of a ligand and Autodock 4 ,opened by AMDOCK software [4]. Both Scoring Functions, were supplied by The Scripps Research Institute [5, 6].

III. METHODOLOGY

PDB format (6LD3) ["Zika NS5 polymerase domain, RNA-directed RNA polymerase NS5 Chain A"] was downloaded from Protein Data Bank (https://www.rcsb.org/structure/6LD3) [7] and prepared manually using several software, before molecular docking analysis.

The second step were removed all unnecessary docking chains. In fact, in this case we are only Chain A has been maintained and re-saved in pdb format. (See below figure 1). The following step, were the removal of ligands and crystallized water using Chimera software [8]. Later, polar Hydrogens and Kollmann charges were added with MGL Tool [6] , As a last step they were added to the protein, any missing amino acids and the whole protein was minimized with the Swiss PDB Viewer Software [9].

On the other hand, for Ligand Preparation steps, the first step, was to separate the crystallized ligand G8O (2,4-dimethoxy-5-thiophen-2-yl-benzoic acid) from its protein, manually add all the hydrogens and their charges (with the MGL Tool software) and minimize it with MMFF94 force field [10], and opened by Pyrx software (https://pyrx.sourceforge.io/) [3].

Parameters Grid Box for Docking in Ligand Binding Site Pocket for Repeatability Binding Affinity by AMDock Software calculated with Autodock Vina and Autodock 4 [4].

- ID PDB 5UHB Chain: Center X (= 77.72); Centre Y (=-3.94); Centre Z (=13.13); Dimensions (Angstrom) (Å) X, Y, Z [= 12.50=, 13.65, =14.77]; exhaustiveness = 8.

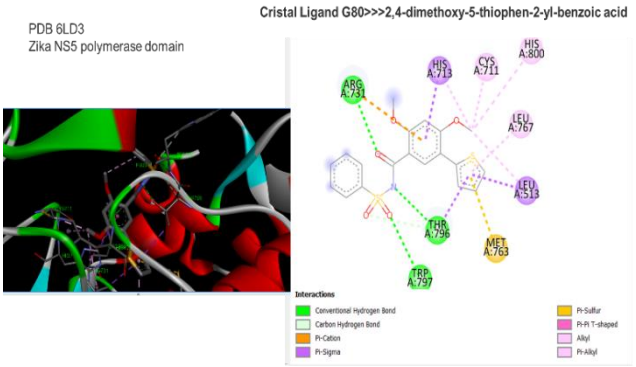

Figure 1. 3D an 2D of RNA-directed RNA polymerase NS5 complexed Crystal Ligand G8O (2,4-dimethoxy-5-thiophen-2-yl-benzoic acid) (PDB 6LD3). Figure reproduced by Discovery studio Biovia.

IV. Results and Discussion

We report first time a potential candidate Drug Lapatinib against Zika virus, by in Silico approach, using Autodock Vina and Autodock 4 (or MGL Tool), estimated with Pyrx and AMDock Software, calculating three different important parameters: Binding Affinity (kcal/mol), estimated Ki (in nM units) and Ligand Efficiency (L.E. in kcal/mol). This drug is used to treat advanced hormone-related breast cancer that has progressed or spread after treatment with other cancer medicines. Lapatinib is used for this condition only if your tumor tests positive for a protein called human epidermal growth factor receptor 2 (HER2) [11].

After a selective analysis of over 300 drugs, processed with Pyrx, I individuated three good estimation docked parameters ,regarding the drug Lapatinib, concluding that it could be an good candidate for this type of infection. Indeed, from the results of Autodock Vina and Autodock Vina 4 (or AutoDock 4.2), implemented with Lamarckian genetic algorithm, LGA, trough AMDock Software Lapatinib has a good Binding affinity value, ca. –9.6 kcal mol $^{-1}$, a estimation inhibitory constant (Ki) value ca. 91 nM and Ligand efficiency ca -0.24 kcal mol $^{-1}$. These results are higher to the Crystallized ligand G8O (2,4-dimethoxy-5-thiophen-2-yl-benzoic acid) in the above-mentioned protein, used against in the crystalized Protein 6LD3. (See below Figure 1-2 and Table 1- 2) .

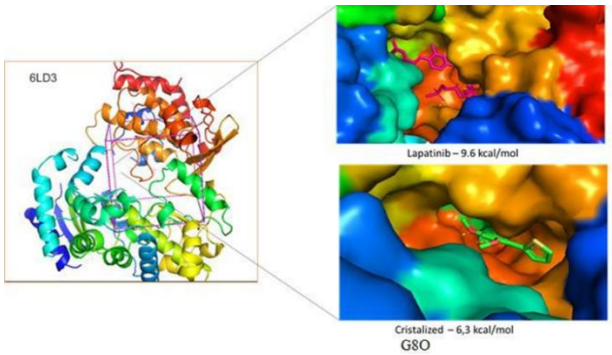

Figure 2. Comparison between docked ligand 680 and drug docked Lapatinib by Autodock Vina.

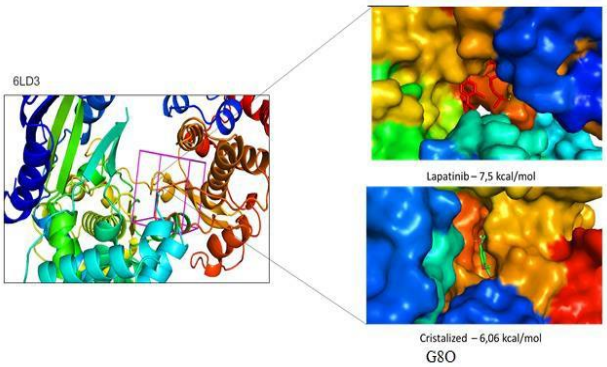

Figure 3. Comparison between docked ligand 680 and drug docked Lapatinib by Autodock 4.

Table 1. Comparison results of Binding Energies between Crystalized ligand 680 (2,4-dimethoxy-5-thiophen-2-yl-benzoic acid) and Lapatinib, calculated by AutoDock Vina and by AutoDock 4, estimated by PyRx and AMDock Software respectively.

Drugs	***Binding Energy (Kcal mol $^{-1}$) by Autodock Vina***	***Binding Energy (Kcal mol $^{-1}$) Autodock 4***
Lapatinib	***-9.6***	-7.53
Crystallized ligand G8O	-6.3	-6.06

Table 2. Comparison results of estimation inhibitory constant (Ki) and Ligand efficiencies, between Crystalized ligand 680 and Lapatinib, calculated by AutoDock Vina, estimated by AMDock Software .

Drugs	Estimation inhibitory constant (Ki)	Estimation Ligand efficiency (Kcal mol $^{-1}$)
Lapatinib	***91.87 nM***	-0.24
Crystallized ligand G8O	24.10 µM	-0.35

V. Conclusion and Future Scope

Here, this communication report, first time, a potential Drug Lapatinib against Zika virus (ZIKV), by in Silico approach, estimated with Pyrx and AMDock Software, calculating three different important parameters: Binding Affinity (kcal mol $^{-1}$), estimated Ki (in nM units) and Ligand Efficiency (L.E. in kcal mol $^{-1}$).

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Ivan Vito Ferrari has published more than 10 research papers in reputed international journals and His main research work focuses on Bioinformatic Tools, Electrochemistry field and Polymer Science. He obtained PhD in Industrial Engineering and Master Degree in Industrial Biotechnology at the University of Rome Tor Vergata.

