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Research Paper

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Blind Docking Analysis of Potential Drugs against SARS-COV-1 and SARS-COV-2 Proteins

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***Abstract*—** In this short communication, more than 300 drugs were investigated by Blind Docking approach, by Autodock Vina Scoring Function with Pyrx Software. From Blind Docking Results, Deslanoside, Dactinomycin, Teicoplanin aglycone, Conivaptan, Paritaprevir, Acetyldigitoxin, Nafarelin, Lanatoside_C, Dydroergocristine, Dydroergotamine, Tirilazad, and Ubrogepant are potential candidates against SARS-COV-1 and SARS-COV-2 proteins. Particular attention, Acetyldigitoxin, Dactinomycin, and Deslanoside with Binding Energy about -12 .00 kcal mol $^{-1}$ are higher binding Energies values against SARS-COV-2 M^{pro}. Regarding SARS-COV-2 RBD, Teicoplanin aglycone and Dactinomycin have a potentially significant role with a binding energy value of -12.50 kcal mol $^{-1}$.

***Keywords*—** Autodock Vina, PyRx

I. INTRODUCTION

In this short communication, a rapid computation analysis on the prediction of the Binding Energies (kcal mol^{-1}) of several biological molecules was reported, through Autodock Vina with Pyrx programme [1], on SARS-COV-1 and SARS-COV-2 proteins.

The virus primarily spreads between people through close contact and via aerosols and respiratory droplets that are exhaled when talking, breathing. It mainly enters human cells by binding to angiotensin converting enzyme 2 (ACE2 receptor. [2]

As has been shown by several Bioinformatic studies reported in scientific Literature, both SARS-COV-1 and 2019 novel coronavirus (2019-nCoV) have high sequence homology, although they are partly different [2].

A powerful technique widely used today by computational researchers is Virtual screening (VS). This is an In Silico technique used in drug discovery to search small molecule libraries in order to identify which of them that are most likely to bind to a drug target [3]. The most known function score based on prediction binding energies of drugs complexed in target protein is AutoDock Vina which is a known open-source program for doing molecular docking.

It was originally designed and implemented by Dr. Oleg Trott in the Molecular Graphics Lab (now CCSB) at The Scripps Research Institute [4].

II. RELATED WORK

The aim of this work is to identify potential drugs that have excellent Binding Energies are able to bind effectively against SARS-COV-1 and SARS-COV-2 proteins.

III. METHODOLOGY

All proteins analyzed have been downloaded from the Protein Data BANK database, (https://www.rcsb.org/) by Autodock Vina and they are accurately prepared before docking analysis.

The First step of protein preparation, before obtaining predicted Vina scores in terms of Binding Energies, kcal mol -1, was the removal of Co-crystallized ligands and water using Chimera software [5].

Later, Polar Hydrogens and Kollmann charges were added AutoDockTools , [6] . Finally, they were added to the protein, any missing amino acids and the whole protein was minimized with the Swiss PDB Viewer Software [7].

Regarding the preparation of the Ligands, all biological molecules were downloaded by PUBCHEM database (https://pubchem.ncbi.nlm.nih.gov/) In 3D Format and they are minimized with MMFF94 force field [8], and opened by Pyrx software (https://pyrx.sourceforge.io/) [1] .

Parameters Grid Box for Blind Docking, by Autodock Vina with PyRx Tool*:*

- ID PDB 2GHV (DOI: 10.2210/pdb2GHV/pdb)

"Crystal structure of SARS spike protein receptor binding domain":

Center X (= 5.7757); Centre (Y = -22.0612); Centre Z (=14.493); Dimensions (Angstrom) (Å) X, Y, Z [= 52.0406406784 =, 59.1997179031, = 87.4564460754]; exhaustiveness = 8.

- ID PDB 6VSB (DOI: 10.2210/pdb6VSB/pdb)

"*Prefusion 2019-nCoV spike glycoprotein with a single receptor-binding domain up"*

Center X (= -8.93236722151); Centre (Y = -3.48295928048); Centre Z (=257.17572961); Dimensions (Angstrom) (Å) X, Y, Z [= 111.863248639=, 83.1357113888, = 83.9744478425]; exhaustiveness = 8.

- ID PDB 3SCI (DOI: 10.2210/pdb3SCI/pdb)

"Crystal structure of spike protein receptor-binding domain from a predicted SARS coronavirus human strain complexed with human receptor ACE2"

Center X (= 9.6301); Centre (Y = 15.5594); Centre Z (=26.6244); Dimensions (Angstrom) (Å) X, Y, Z [= 109.284019661=, 106.461824074, = 133.588461418]; exhaustiveness = 8.

- ID PDB 6VW1 (DOI: 10.2210/pdb6VW1/pdb)

"Structure of SARS-CoV-2 chimeric receptor-binding domain complexed with its receptor human ACE2"

Center X (= 84.5363); Centre (Y = 16.1512); Centre Z (=138.72); Dimensions (Angstrom) (Å) X, Y, Z [= 123.976492481=, 155.958715973, = 79.8628112602]; exhaustiveness = 8.

- ID PDB 1P9U (DOI: 10.2210/pdb1P9U/pdb)

"Coronavirus Main Proteinase ($3CL^{pro}$) Structure: Basis for Design of anti-SARS Drugs"

Center X (= 40.2076); Centre (Y = 87.4228); Centre Z (=67.7708); Dimensions (Angstrom) (Å) X, Y, Z [= 123.976492481=, 155.958715973, = 79.8628112602]; exhaustiveness = 8.

- ID PDB 6M2N (DOI: 10.2210/pdb6M2N/pdb)

"SARS-CoV-2 3CL protease ($3CL^{pro}$) in complex with a novel inhibitor"

Center X (= -45.2674); Centre (Y = -29.8437); Centre Z (=27.3077); Dimensions (Angstrom) (Å) X, Y, Z [= 94.4420667183=, 103.291257477, = 103.901556377]; exhaustiveness = 8.

- ID PDB 1O86 (DOI: 10.2210/pdb1O86/pdb)

"Crystal Structure of Human Angiotensin Converting Enzyme in complex with lisinopril"

Center X (= 41.555683131); Centre (Y = 34.0342297868); Centre Z (=47.2872633005); Dimensions (Angstrom) (Å) X, Y, Z [= 25.00=, 25.00, = 25.00]; exhaustiveness = 8.

- ID PDB 4L8U (DOI: 10.2210/pdb4L8U/pdb)

"X-ray study of human serum albumin complexed with 9 amino camptothecin"

Center X (= 29.2318236119); Centre (Y = 5.84206757766); Centre Z (=30.9706765041); Dimensions (Angstrom) (Å) X, Y, Z [= 25.00=, 25.00, = 25. 00]; exhaustiveness = 8.

IV. RESULTS AND DISCUSSION

The present study, is intended to investigate more than 1000 drugs and biological compounds by Bioinformatic approach, using Autodock Vina tool with Pyrx Software, evaluating the binding energies scores, in order to find the best Ligand-protein complex against SARS-COV-1 and SARS-COV-2 proteins.

For this purpose, the best results of about 30 selected molecules from an initial screening with over 1000 compounds are reported against SARS-COV-1 and SARS-COV-2 , in Figure 1, Figure 2 and Figure 3 respectively.

As we remark, from "Vina" results, there are selected 30 proposal drugs that have obtained higher binding energies out of a total of 1000 drugs scanned. In fact, figure 1 evaluates the comparison of the SARS-COV-1 Main protease (PDB 1P9U) and SARS-COV-2 Main protease (PDB 6M2N). In Figure 2 are reported docking results between SARS-COV-1 Spike Glycoprotein (PDB 2GHV) and SARS-COV-2 Spike Glycoprotein (PDB 6VSB) and SARS coronavirus human.

Furthermore, the same compounds have also been investigated in the Crystal Structure of Human Angiotensin- Converting Enzyme (PDB 1O86) and in the Crystal Structure of human serum albumin (PDB 4l8u).

All results were obtained through Scoring function Autodock Vina with PyRx software, using a Blind Docking approach (all the protein was docked).

The main results of "Blind "docking (See Figure 1) showed that ten pharmacological molecules active against SARS-COV1 M-^{pro}.

Putting their Binding Energies in ascending order (from the most negative to the most positive) we find:

Deslanoside with -12.2 kcal mol $^{-1}$; Tirilazad and Dactinomycin with -11.8 kcal mol $^{-1}$; Dydroergotamine, Acetyldigitoxin and Teicoplanin aglycone with -11.5 kcal mol^{-1}; Dydroergocristine with -11.3 kcal mol $^{-1}$ and Triptorelin with -11.2 kcal mol $^{-1}$.

Regarding the main results of blind docking (See Figure 1) against SARS-COV-2-Mpro highlighted seven pharmacological molecules.

Putting their Binding Energies in increasing order (from the most negative to the most positive) we find:

Acetyldigitoxin with -12.1 kcal mol $^{-1}$; Dactinomycin with -12.1 kcal mol $^{-1}$; Deslanoside with -11.9 kcal mol^{-1}; Tirilazad with -11.5 kcal mol $^{-1}$, Ubrogepant with -11.1 kcal mol $^{-1}$, Rutin with -11 kcal mol $^{-1}$ and Nilotinib with -10.8 kcal mol^{-1}.

The main results of blind docking (See Figure 2) against SARS-COV-1 Spike Glycoprotein RBD (Receptor Binding Domain), highlighted eight pharmacological molecules.

Putting their Binding Energies in ascending order (from the most negative to the most positive) we find: Teicoplanin aglycone with -10.4; Deslanoside with -10.2 kcal mol^{-1}; Nilotinib, Conivaptan and Candicidin with -9.8 kcal mol $^{-1}$; Tirilazad with -9.7 kcal mol $^{-1}$and Dydroergotamine with -9.6 kcal mol $^{-1}$.

The results of Blind docking are shown in Figure 2, against SARS-COV-2 Spike Glycoprotein RBD, putting the Binding Energies in ascending order (from the most negative to the most positive):

Dactinomycin and Teicoplanin Aglycone with -12.4 kcal mol^{-1}; Tirilazad with -11.3 kcal mol^{-1}; Candicidin with -11.1 kcal mol-1; Paritaprevir with -10.9 kcal mol -1; Deslanoside with -10.6 kcal mol $^{-1}$; Dydroergocristine with -10.5 kcal mol $^{-1}$; Dydroergotamine -10.4 kcal mol $^{-1}$.

For more details on results obtained, see Figure 1, Figure 2 and Figure 3 respectively.

Drugs	SARS-COV-1- 3CL- protease (1P9U)	SARS-COV-2- 3CL- protease (6M2N)
Abivertinib	-10.1	-9.8
Acetyldigitoxin	-11.5	-12.1
Astemizole	-10.1	-9.7
Candicidin	-9.5	-10.3
Conivaptan	-9.9	-10.6
Dactinomycin	-11.8	-12.1
Deslanoside	-12.2	-11.9
Dihydroergocristine	-11.3	-10.4
Dihydroergotamine	-11.5	-10.1
Diosmin	-10.5	-10.0
Epirubicin	-10.7	-9.7
Idarubicin	-11.1	-10.1
Indinavir	-9.4	-9.8
Irinotecan	-10.5	-11.2
Keracyanin	-9.0	-10.5
Lanatoside	-10.3	-10.7
Meproscillarin	-10.2	-10.8
Montelukast	-10.1	-9.7
Nafarelin	-10.9	-11.5
Nilotinib	-11.7	-10.8
Paritaprevir	-10.1	-10.2
Raltegravir	-9.1	-9.7
Rutin	-10.4	-11.0
Tadalafil	-9.4	-9.9
Teicoplanin_aglycone	-11.5	-11.1
Tirilazad	-11.8	-11.5
Triptorelin	-11.2	-10.8
Ubrogepant	-11.7	-11.1

Figure 1. Comparison Binding Energies of best drugs in SARS-COV-1 M –^{pro} (PDB 1P9U) and SARS-COV-2 M –^{pro} (PDB 6M2N), by Autodock Vina with PyRx Tool.

Drugs	ACE2/ SARS1-Spike Glycoprotein (3SCI)	ACE2/ SARS2-Spike Glycoprotein (6VW1)	SARS1-Spike Glycoprotein - RBD(2ghv)	SARS2-Spike Glycoprotein - RBD (6VSB)
Abivertinib	-8.6	-8.3	-7.5	-9.5
Acetyldigitoxin	-10.6	-11.4	-9.5	-10.2
Astemizole	-9.3	-9.3	-8.2	-8.6
Candicidin	-10.1	-10.4	-9.6	-11.1
Conivaptan	-11.5	-10.9	-9.8	-10.2
Dactinomycin	-13.1	-12.5	-9.4	-12.4
Deslanoside	-10.3	-10.0	-10.2	-10.6
Dihydroergocristine	-11.3	-10.4	-9.1	-10.5
Dihydroergotamine	-11.4	-12.3	-9.6	-10.4
Diosmin	-9.8	-10.3	-9.0	-9.7
Epirubicin	-9.8	-9.3	-7.6	-9.7
Idarubicin	-10.2	-9.5	-8.1	-9.6
Indinavir	-9.7	-10.3	-7.8	-9.7
Irinotecan	-9.7	-9.7	-9.4	-10.3
Keracyanin	-9.9	-10.0	-8.5	-8.4
Lanatoside	-11.2	-11.1	-9.2	-8.2
Meproscillarin	-10.4	-10.4	-8.9	-9.2
Montelukast	-9.0	-9.5	-7.6	-8.4
Nafarelin	-12.1	-11.0	-9.0	-10.2
Nilotinib	-11.1	-10.0	-9.8	-10.3
Paritaprevir	-12.9	-12.1	-8.9	-10.9
Raltegravir	-9.5	-8.7	-8.6	-8.6
Rutin	-9.8	-9.0	-8.0	-8.7
Tadalafil	-9.6	-9.5	-8.2	-9.0
Teicoplanin_aglycone	-12.5	-12.2	-10.4	-12.4
Tirilazad	-11.4	-9.6	-9.7	-11.3
Triptorelin	-10.5	-10.6	-8.5	-10.6
Ubrogepant	-11.3	-10.1	-10.1	-9.9

Figure 2. Comparison Binding Energies of best pose drugs in SARS-COV-1 Spike RBD (PDB 2GHV) and SARS-COV-2 M $^{-pro}$ (PDB 6VSB); and Comparison Binding Energies of best drugs in Crystal structure of spike protein receptor-binding domain from a predicted SARS coronavirus human strain complexed with human receptor ACE2 (PDB 3SCI) and Structure of SARS-CoV-2 chimeric receptor-binding domain complexed with its receptor human ACE2 (PDB 6VW1), by Autodock Vina with PyRx Tool.

Drugs	Human-ACE2 (1O86)	Drugs	Serum albumin (4L8U)
Abivertinib	-10.2	Abivertinib	-9.7
Acetyldigitoxin	-12.7	Acetyldigitoxin	-11.1
Astemizole	-9.6	Astemizole	-11.2
Candicidin	29.1	Candicidin	-9.4
Conivaptan	-11.4	Conivaptan	-12.6
Dactinomycin	-1.4	Dactinomycin	-12.7
Deslanoside	-13.0	Deslanoside	-11.7
Dihydroergocristine	-11.4	Dihydroergocristine	-12.4
Dihydroergotamine	-11.1	Dihydroergotamine	-13.0
Diosmin	-10.7	Diosmin	-10.5
Epirubicin	-9.8	Epirubicin	-9.5
Idarubicin	-11.1	Idarubicin	-9.6
Indinavir	-10.5	Indinavir	-11.0
Irinotecan	-11.7	Irinotecan	-11.6
Keracyanin	-10.2	Keracyanin	-10.9
Lanatoside	-12.4	Lanatoside	-11.1
Meproscillarin	-11.3	Meproscillarin	-9.7
Montelukast	-9.7	Montelukast	-11.0
Nafarelin	-10.8	Nafarelin	-10.7
Nilotinib	-11.9	Nilotinib	-11.9
Paritaprevir	-12.2	Paritaprevir	-11.8
Raltegravir	-10.2	Raltegravir	-9.4
Rutin	-10.7	Rutin	-10.9
Tadalafil	-10.1	Tadalafil	-11.6
Teicoplanin_aglycone	23.0	Teicoplanin_aglycone	-10.7
Tirilazad	-12.0	Tirilazad	-13.5
Triptorelin	-11.1	Triptorelin	-10.9
Ubrogepant	-12.9	Ubrogepant	-11.8

Figure 3. Comparison Binding Energies of best pose drugs in Crystal Structure of Human Angiotensin Converting Enzyme (PDB 1O86) and in Human Serum Albumin (PDB 4L8U), by Autodock Vina with PyRx Tool

V. CONCLUSION and Future Scope

Binding Energies values of Docking Vina results, theoretically demonstrated that Dactinomycin , antineoplastic antibiotic, and Teicoplanin aglycone, an antibacterial glycopeptide, as a possible anti- COVID-19 drug, even though further in vitro and in vitro studies are needed to confirm really their activity against this viral infection.

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Authors Profile

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