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Computer Aided Docking Studies on Antiviral Drugs for SARS

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***Abstract*—**Severe acute respiratory syndrome (SARS) is a respiratory disease in humans which is caused by the SARS coronavirus. The treatment of coronavirus-associated SARS has been evolving and so far there is no consensus on an optimal regimen. The mainstream therapeutic interventions for SARS involve broad-spectrum antibiotics and supportive care, as well as antiviral agents and immunomodulatory therapy. The Protein- Ligand interaction plays a significant role in structural based drug designing. In the present work we have taken the receptor Angiotensin converting enzyme 2 and identified the drugs that are commonly used against SARS. They are Lopinavir, Ritonavir, Ribavirin, and Oseltamivir. The receptor Angiotensin converting enzyme 2 (ACE-2) was docked with above said drugs and the energy value obtained are as follows, Lopinavir (-292.3), Ritonavir (-325.6), Oseltamivir (-229.1), Ribavirin (-208.8). Depending on the least energy value we have chosen the best two drugs out of the four conventional drugs. We tried to improve the binding efficiency and steric compatibility of the two drugs namely Ritonavir and Lopinavir. Several modifications were made to the probable functional groups (phenylic, ketonic groups in case of Ritonavir and carboxylic groups in case of Lopinavir respectively) which were interacting with the receptor molecule. Analogs were prepared by Marvin Sketch software and were docked using HEX docking software. Lopinavir analog 8 and Ritonavir analog 11 were detected with significant energy values and are probable lead molecule. It infers that some of the modified drugs are better than the original drugs. Further work can be carried out to improve the steric compatibility of the drug based upon the work done above for a more energy efficient binding of the drugs to the receptor.

***Keywords*—**Protein data bank, Rasmol, Marvin sketch, Hex docking.

I. Introduction

SEVERE acute respiratory syndrome or SARS is a respiratory disease in human, caused by the SARS coronavirus. There was one major epidemic between November 2002 and July 2003, with a mortality rate of 9.6% according to WHO's April 21, 2004 concluding report [1].

The treatment of coronavirus-associated SARS has been evolving and sofar there is no consensus on an optimal regimen. The mainstream therapeutic interventions for SARS involve broad-spectrum antibiotics and supportive care, as well as antiviral agents and immunomodulatory therapy. Assisted ventilation in an invasive or non- invasive form would be instituted in SARS patients complicated by respiratory failure [2, 3]. Apart from these therapies, in majority of the cases protease, inhibitors like Lopinavir-ritonavir co-formulation is normally used to treat human immunodeficiency virus (HIV) infection. Preliminary analysis suggests that the addition of lopinavir-ritonavir to the contemporary use of ribavirin and corticosteroids might reduce incubation and mortality rates, especially when administered early, but the survival rate of the patients is low [4]. To overcome these problems people made efforts in non conventional methods of drug designing by the use of Bioinformatics approaches.

Bioinformatics is seen as an emerging field with the potential to significantly improve how drugs are found, brought to the clinical trials and eventually released to the marketplace. Bioinformatics can be thought of as a central hub that unites several disciplines and methodologies. Computer – Aided Drug Design (CADD) is a specialized discipline that uses computational methods to simulate drug – receptor interactions. CADD methods are heavily dependent on bioinformatics tools, applications and databases. As such, there is considerable overlap in CADD research and bioinformatics.

Methods developed to facilitate and speedup the drug designing process are Rational Drug Design (RDD). These processes are used in biopharmaceutical industry to discover and develop new drugs. RDD uses a variety of computational methods to identify novel compounds. One of those methods is docking of drug molecules with receptors. The site of drug action, which is ultimately responsible for the pharmaceutical affect, is a receptor.

Fig. 1 Structure of ACE-2

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Angiotensin Converting Enzyme (ACE) [Fig. 1] is a receptor, which is an essential regulator of cardiac function and facilitates the entry of SARS-CoV into the cell by serving as its primary receptor. It has two isoforms with 43% homology. It is responsible for initiation of viral infection. In normal practice the conventional drugs like Ribavirin, Ritonavir, Oseltamivir, Lopinavir are used inhibit viral infection, which are specific to ACE [5]. Keeping rational drug designing approach in mind, we made an effort to design modified drugs for SARS, using conventional drugs like Lopinavir and Ritonavir by docking against ACE-2 receptor.

II. Materials and Methods

For the present study bioinformatics online databases and software like Marvin Sketch and Hex docking were used. The databases and software used are as fallows:

PubMed [6], developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM). The database is designed to provide access to citations from biomedical journals. From PubMed we have collected literatures on SARS, receptors and antiviral drugs. Based on the literature, the present study was confined to ACE-2 receptor and the analogs of conventional drugs like Lopinavir and Ritonavir.

The structure of angiotensin converting enzyme 2 (ACE-2) was retrieved from Protein data bank (PDB) [7]. PDB is a repository for the processing and distribution of 3D- structure data of large molecules of proteins and nucleic acids. Most were determined by X-ray crystallography and some by NMR.

The retrieved structure of ACE-2 was analyzed by using RasMol. RASMOL [Raster Display of Molecules] is a molecular graphics program intended for the structural visualization of proteins, nucleic acids and small biomolecules. RasMol runs on wide range of architectures and operating systems. The program reads the molecule coordinate file and interactively displays the molecule on the screen in a variety of color schemes and molecular representations.

The structures of conventional drugs like Lopinavir and Ritonavir were retrieved from PDB and the structural analogs of these drug molecules were created by using MarvinSketch. MarvinSketch is a Java based chemical drawing tool which allows creating and editing of molecules in various file formats.

The docking analysis of Lopinavir and Ritonavir structural analogs with ACE-2 was carried by HEX Docking software. Docking is the process of fitting together of two molecules in 3-dimensional space. Docking allows the scientist to virtually screen a database of compounds and predict the strongest binders based on various scoring functions. It explores ways in which two molecules, such as drugs and an enzyme receptor ACE-2 fit together and dock to each other well, like pieces of a three-dimensional jigsaw puzzle. The molecules binding to a receptor, inhibit its function, and thus act as drug. The collection of Lopinavir, Ritonavir and ACE-2 receptor complexes was identified via docking and their relative stabilities were evaluated using molecular dynamics and their binding affinities, using free energy simulations.

III. Results

Docking results tabulated between ACE-2 and the conventional drug Lopinavir (Table I) as well as with the modified drugs are shown below along with the changes or modification within them.

Docking results tabulated between Angiotensin converting enzyme-2 and the conventional drug Ritanovir (Table II) as well as the modified drugs are shown below along with the changes or modifications within them.

TABLE I
Docking Results of ACE-2 with Lopinavir Analogs

Drug docked	E-value
Lopinavir	-292.3
Lopinavir Analog 1	-301.3
Lopinavir Analog 2	-300.7
Lopinavir Analog 3	-310.5
Lopinavir Analog 4	-301.3
Lopinavir Analog 5	-302.4
Lopinavir Analog 6	-332.4
Lopinavir Analog 7	-316.2
Lopinavir Analog 8	**-332.7**
Lopinavir Analog 9	-317.6
Lopinavir Analog 10	-313.5

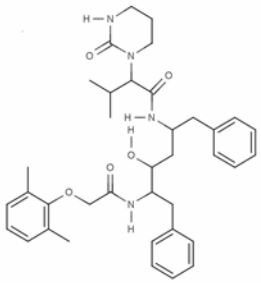

Fig. 2 Structure of Lopinavir

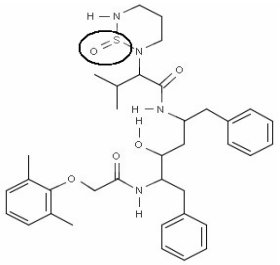

Fig. 3 Structure of Lopinavir Anolog 8

IV. Discussion

Based on the literature it has been shown clearly that the drugs Lopinavir and Ritonavir have been used to target receptor ACE-2. Lopinavir and Ritonavir on docking with ACE-2 produced an energy value of -292.3 and -325.6 respectively. It was observed using RasMol that the carbonyl group present in the drug lopinavir was the site of binding to the receptor (ACE-2) and phenylic and a kenotic functional groups present in the Ritonavir was the site of binding to the receptor (ACE-2) Several modifications were made to these

probable functional groups, which resulted in a decrease in the energy values. These modifications were made using Marvin Sketch and the energy values were calculated using Hex. This way the pharmacophoric part of the drug was partially identified.

TABLE II
DOCKING RESULTS OF ACE-2 WITH RITANOVIR ANALOGS

Drugs Docked	E-Values
Ritonavir	-325.6
Ritonavir Analog 1	-325.9
Ritonavir Analog 2	-318.9
Ritonavir Analog 3	-318.9
Ritonavir Analog 4	-318.8
Ritonavir Analog 5	-328.5
Ritonavir Analog 6	-328.5
Ritonavir Analog 7	-328.5
Ritonavir Analog 8	-329.4
Ritonavir Analog 9	-315.7
Ritonavir Analog 10	-306.6
Ritonavir Analog 11	**-330.8**

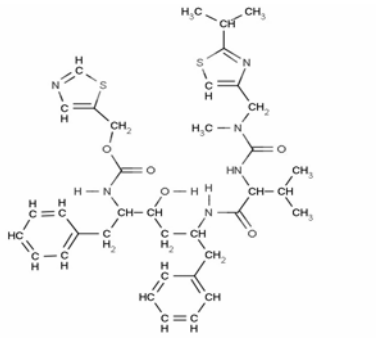

Fig. 4 Structure of Ritonavir

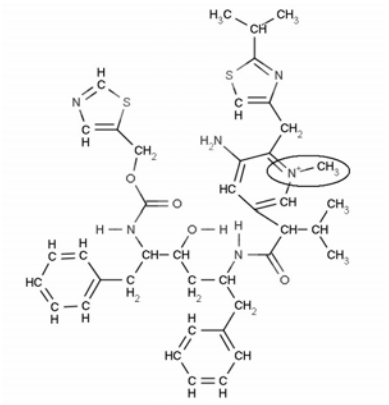

Fig. 5 Structure of Ritonavir Analog 11

An analog with additional S atom (Lopinavir analog 8) was prepared virtually using Marvin Sketch. This particular analog showed an increase in the energy values (-332.7) and an analog with additional functional group (Ritanovir Analog 11) was prepared virtually using MarvinSketch. This particular analog showed an increase in the energy values (-330.8) which means the analog (Lopinavir analog 8) and (Ritanovir Analog 11) was more compatible with the receptor than its predecessor. However, the binding site of the analog was similar to that of its predecessor, which means that functional groups involved were the same and by preparing the analog only the steric compatibility was increased.

V. CONCLUSION

The Protein-Ligand interaction plays a significant role in structural based drug designing. In the present work we have taken the receptor Angiotensin converting enzyme 2 and identified the drugs that were used against SARS. They are Lopinavir, Oseltamivir, Ribavirin and Ritonavir. When the receptor (ACE-2) was docked with four drugs the energy value obtained is: Lopinavir (-292.3), Oseltamivir (-229.1), Ribavirin (-208.8), Ritonavir (-325.6). Further extension of this, we have tried to look for the most probable analog of the respective drugs, which specified earlier. When the modified drugs were docked against the same receptor the energy value obtained was: Lopinavir analog 8 (-332.7), Ritonavir analog 11 (-330.8). From this we can conclude that some of the modified drugs are better than the original drugs. Of these molecules Lopinavir analog 8, Ritonavir analog 11 are probable lead molecules than the rest of the drugs for SARS owing to their high-energy value. This infers that the lead molecule is one with maximum interaction having high negative e-value.

Thus the concept of protein-Ligand interaction helps in designing new drugs for SARS (Severe Acute Respiratory Syndrome). Further work can be carried out to improve the steric compatibility of the drugs based upon the work done above for a more energy efficient binding of the drug to the receptor.

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