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COMPUTER AIDED DRUG DESIGN FOR HUMAN RHINOVIRUS FROM PHENOXY DERIVATIVES

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ABSTRACT

The receptor was docked to the commercially available antiviral agents that have broad serotype specificity. This family of antiviral agents Arildone was found to have limited antiviral activity by using Protein Structure Modeling Method, using INSIGHTII software. We tried to improve the binding efficiency and steric compatibility of Arildone against Rhinovirus. Several modifications were made to the probable functional groups which were interacting with receptor molecule. Analogs of the drug molecule were prepared using MODELLER9v1chemsketch and docked using INSIGHT II docking software. The modified drugs was sketched using chemsketch were found to be better than the convectional drugs available. Further from this work we can improve the steric compatibility and then Absorption, Distribution, Metabolism and Excretion (ADME) properties of the analogs can be analyzed using Insilco ADME tools.

KEYWORDS

Rhinovirus, Chemsketch, Protein and Ligand.

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INTRODUCTION

Bioinformatics is the science of using to understand biological phenomena and is conceptualizing biology in terms of molecule and applying “informatics techniques”. It is the part of the larger science of computational biology[1]. Computational biology is the application of quantitative analytical techniques in modeling and solving problems in biological systems. Bioinformatics is the mathematical statistical and computing methods that ago to solve biological problems using and DNA amino acid sequences and related information[2]. Understanding of basic mathematical

modulation techniques including stastical methods, probability and algorithms for sequence searching, pattern recognition etc[3].

Antiviral Drugs

Since there are over 100 different serotypes of rhinovirus, and because the virus can easily mutate its antigenic surface, development of a vaccine for the common cold has been impractical[4]. Despite the rhinovirus rather dynamic and diverse capsid structure, the Sterrling-Winthrop Research Inst. has synthesized a series of effects antiviral agents that have broad serotype specificity. This family of antiviral agents Arildone was found to have limited antiviral activity in cell culture, but subsequent changes in the chemical structure led to compounds with about a 1000-dole increased activity. The viral agents inhibits the infection of several piocornavirus include all strains of rhinovirus and certain strains of poliovirus and Coxrackie viruses[5]. The phenoxy derivatives used for docking was shown in Figure No.1.

Rhino Virus as a Drug Receptor

Process of piocornavirus infection

Rhinovirus, poliovirus, hepatitis A virus are among the smallest RNA containing animal viruses and belong to the piocornavirus family they have a molecular weight of approximately 8.5*10, and their external shells have icosahedra symmetry with diameter of about 300 A and each capsid is composed of 60 copies of four different viral proteins VP1, VP2, VP3, and VP4.

Piocornavirus infection can be divided into at least four steps. With each being a possible target for antiviral drug designs. The first stage in viral infection is cellular recognition. In the case of rhinovirus, it has been shown that the numerous serotypes bind to one of two bell surface proteins suggesting that although there are many amino acid differences between the different serotypes they exhibit very conservative binding interactions with their cellular receptors[5].

Structure of Rhinovirus

As previously mentioned, the structure of rhinovirus has been determined to resolution. Perhaps the most striking find was that the basic structural motif of the capsid was 60 copies of eight-stranded B-barrels (Figure No.2), just as was found previously with the small spherical RNA pl the basic structural motif of the capsid was 60 copies of eight-stranded B-barrels, just as was found previously with the small spherical RNA plant viruses and was found subsequently with other animal, plant, and insect viruses.

Approach to the denovo design of the antiviral lead is not an easy job to gestate, though it is obvious to state that common cold virus have been stuff to undergo rapid development of mutation upon on the developing lead molecules. However few lead molecules are good candidates for the virus at the time obnoxious to the host. The present study envisages the quality of design not deleterious to host at the cost of vulnerable to the virus, rationale mathematical drug virus interaction keeping pharmacokinetic and pharmacodynamics parachors intact with meticulous attention.

METHODOLOGY[6]

STEP: 1 First we search for the sequence of our target protein Rhinovirus. We search our protein sequence in NCBI. We should make sure that does not have a PDB structure.

STEP: 2 The FASTA format of the target sequence thus obtained from NCBI was submitted to BLAST tool Blastp compares an amino acid query sequence against a protein sequence database.

STEP: 3 Among the closely related template sequences, one sequence 1BFO with the highest similarity, best score and least gap is selected as template and compared with our query sequence was shown in Figure No.3.

STEP: 4 Comparative structural modeling by MODELLER, Preparing Input Files, Atom Files, Alignment File, Script File, Directories for Input Atom Files

STEP: 5 We can visualize our generated model using RASMOL using following commands in the terminal was shown in Figure No.4.

STEP: 6 The best structure selected is visualized in INSIGHTII were shown in Figure No.5 and 6.

STEP: 7 We then minimized its energy so that it attains the stable conformation. The steps of minimization are as follows. Select the builder module, Select Modify-> Hydrogen's-> Set pH to 7, Select Force Field-> Potential->Fix/Fix/Fix your potentials/partial charges/formal charges, Select Force Field->Select-> cvff.frc, Now to obtain the result of minimization we need to open filename, Output file.

STEP: 8 The minimized structure is automatically stored as a.cor file which can be used for docking was shown in Figure No 7 and 8.

STEP: 9 DOCKING

There are several ways for Docking i.e. Auto Docking, ZDOCK, Traction Beam Docking, GridDocking and other online server programs like Patch Dock, Cluspro and GrammX .We have done Grid Docking and PatchDock was shown in Table No.1.

RESULTS AND DISCUSSION

The work was done on an existing drug but the procedure used to dock a new drug is also the same, but the hurdle is to sequence amino acids as well as to determine its structure. However we predicted structure using Modeller 9v1. The Modeller required three input files

- The atom files which codes for the template structure
- The alignment files which is in PI forma
- The script file instructs the Modeller

The structure thus evolved from Modeller result then evaluated using SAVS (Structure Analysis and Validation Server). The SAVS consist of various programs which evaluate the structure based on stereo chemical quality, crystallographic model building & refinement, compatibility of an atomic model (3D). The procheck who analyzes the steriochemical quality displays the results in the form of Ramachandran's Plot. From the result it was clear that all amino acid are in allowed region except two glycine residues. The energy bond angle of each amino acid was studied by clicking to each black square (which implies amino acid residues) and G (Glycine). The generated model is further stabilized by energy minimization. Energy minimization was carried out using Discover 3module of insight II. The Energy minimization results with providing stable compact structure. The protein thus generated was checked for active site. The binding site module in insight II was used for doing so. The module pull down is used to get the sequence and also to active site prediction.

The structure was thus made ready docking to perform docking. There are several ways of docking that is Auto docking, Zdock, Traction Beam Docking, Grid Docking and other online server programs like Patch dock, Clus _ pro. Among the above aid some are used to perform protein-protein docking and some for protein drug docking and some for both. The Rhino virus docking was performed in Patch dock by Grid docking procedure. The same docking was also performed in an Auto dock. The docking brings about conformational changes in rhino protein. From the above work it was clear S11 derived drugs were more potent than drugs available.

- The protein sequence was retrieved from NCBI.
- The fasta format of raw sequence was submitted to blast search.
- The homologous sequence was selected through blast search.
- The homologous sequence thus obtained was selected as template over which model building of target was done.
- The structure of target protein was generated by Modeller 9v1.
- The generated model was then evaluated by SAVS. The best model was loaded in Patchdock.

Table No.1: Docked Structures

S.No	Structure –I		Structure -II	Structure -III	Structure -IV	Structure -V
1	R	CH_3	CH_3	CH_3	OCH_3	OH
2	R’	CH_3	COOH	O CH_3	COOH	CH_3

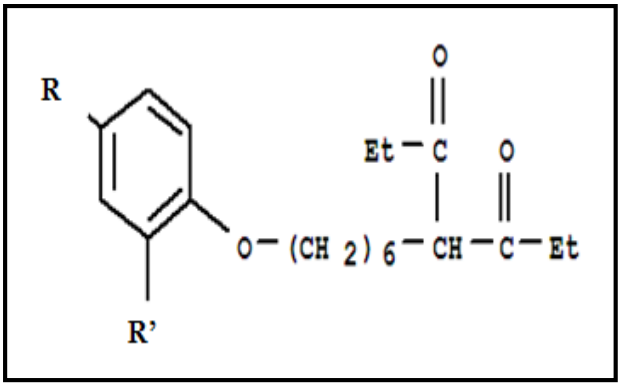

Figure No.1 Structure of Phenoxy Derivative

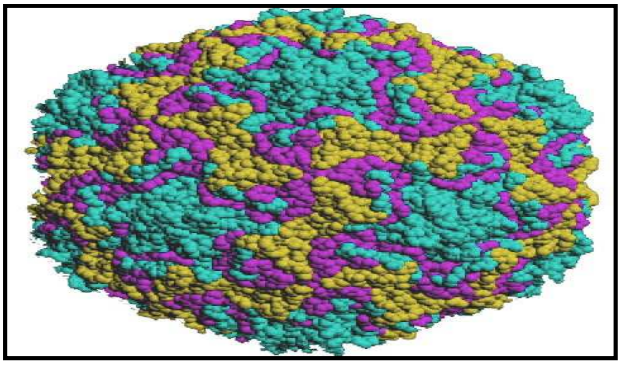

Figure No.2: Structure of Rhinovirus

Figure No.3: Template

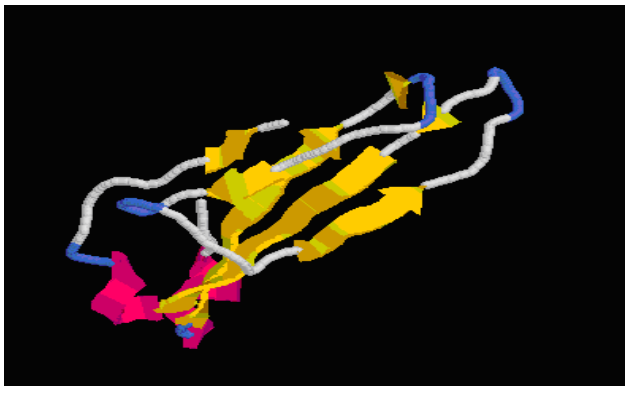

Figure No.4: Rhinovirus Protein Terminal

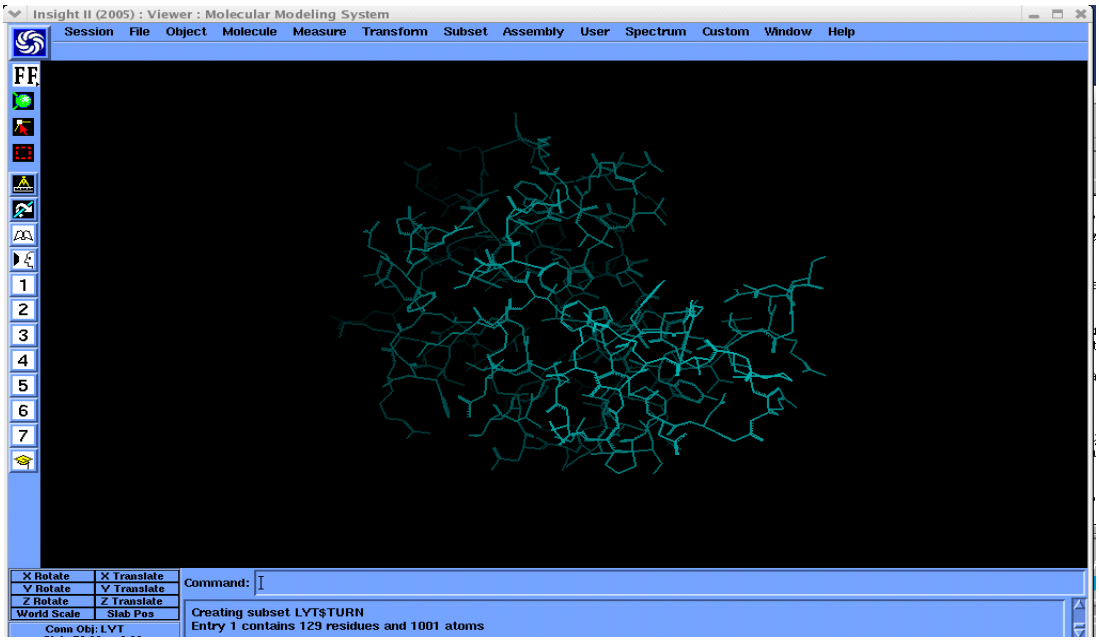

Figure No.5: The Best Structure Selected is Visualized in INSIGHT II

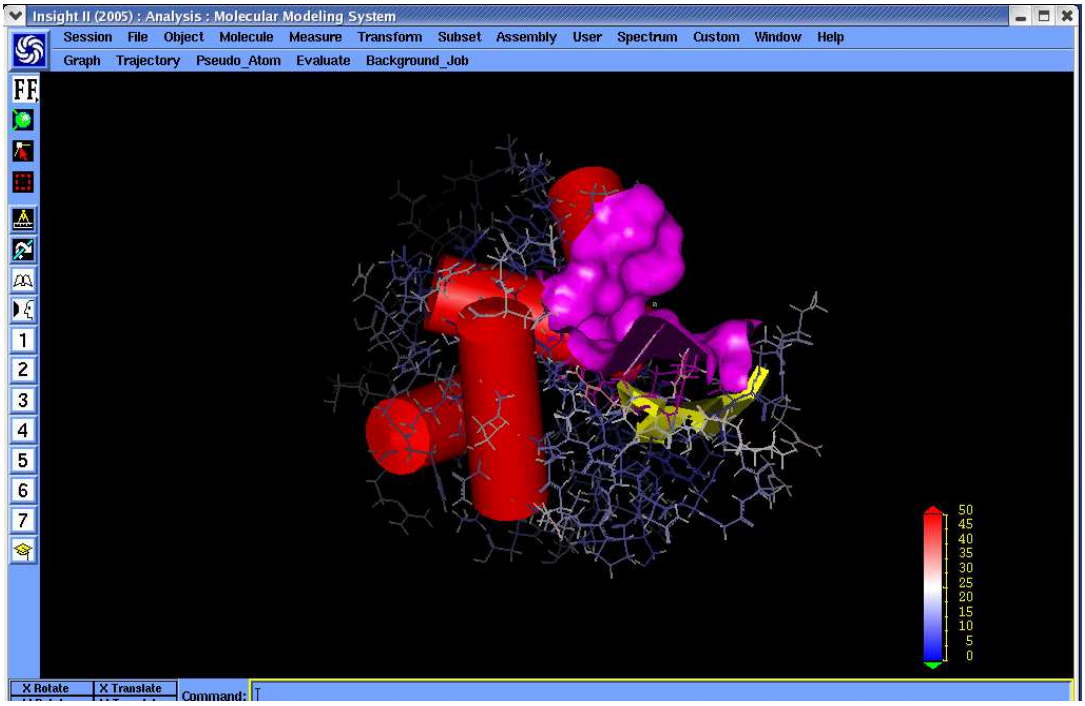

Figure No.6: Active Site Prediction

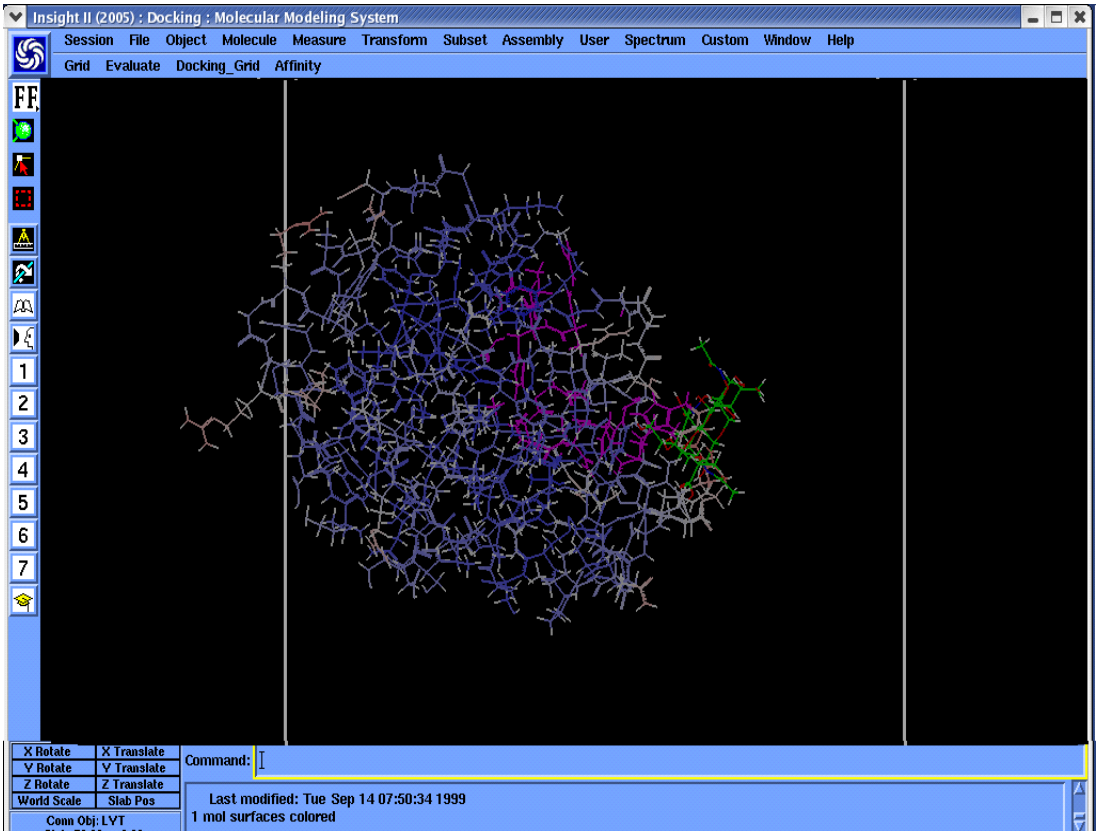

Figure No.7: Docking Result of Naproxen

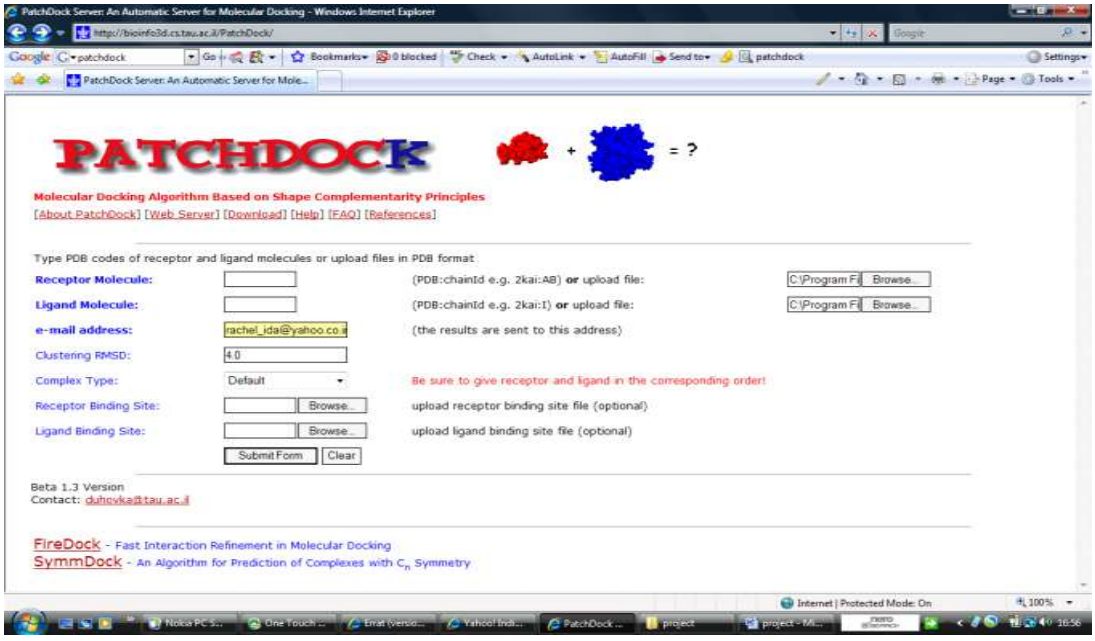

Figure No.8: Docking by Online Tool

CONCLUSION

The drug was build by using Chemsketch tools. The best generated model was subjected to energy minimization to attain stable configuration. Finally docking was performed. Thus model building of docking with rhino virus was performed. The best structures are docked from phenoxy derivative, It may give more biological activity when compare to phenoxy group.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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