International Journal of Advances in Bio-Informatics and Bio-Technology– IJABB
Volume 1 : Issue 2 [ISSN 2475-2258]
Publication Date : 30 September, 2014

OPEN SOURCE DRUG DISCOVERY FOR CHIKUNGUNYA

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***ABSTRACT*—Chikungunya is viral disease is transmitted to human beings by mosquito bite [2]. Chikungunya can cause fever, chills, nausea, vomiting, joint pain, head ache, and swollen in the joints. A cause of Chikungunya is mainly due to the replication of Chikungunya virus in the human body [5]. The protein E1 was used in the study which is monomer with molecular weight 50KDa which is anchored in the membrane of CHIKV. The structure of E1 was retrieved from Protein Data Bank. The PDB ID for E1 was 3N41 , which is responsible for Chikungunya virus replication. CHIKV replication is resistant to inhibition by interferon once RNA replication has been established and that CHIKV actively suppress the antiviral IFN response by preventing IFN-induced gene expression there by making host to shut-off [4,2].The report have shown that the intensity of the infection has increased with every passing year with 45%–63% attack rates in world during outbreaks India is endemic to dengue fever and due to overlapping symptoms; CHIK infection is generally mistaken to be the former thereby leading to misdiagnosis. CHIKV infection is considered an important public health problem due to the morbidity and disability caused by chronic arthralgia [2] . The social and economic burden caused by CHIKV fever is tremendous. Hence, there is an urgent need for an effective vaccine or antiviral therapy against CHIKV infection. The Homology Modeling was used to predict the 3-Dimensional structure of 3N41[4]. Docking studies were carried out with various inhibitors and it was found that ligand 1IKW had a most stable interaction with 3n41. Indicate that LIGAND 1IKW is the most promising inhibitor for CHIKV.**

Keyword: CHIKV, drug design, OSDD, E1 protein, Efavirenz , Rimantidine

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INTRODUCTION

The CHIKV infection reemerged in seven states in 2005 and by the latest report in 2010, has spread to more than 18 states/Union Territories within the country affecting more than 3.7 million individuals [8]. Moreover, the number of cases has been grossly under reported due to mistaken diagnosis of dengue and non-reporting of suspected cases and related deaths thereby making the number of CHIK infection much more than reported [11].Since its reemergence, the intensity of the infection has increased with every passing year with 45%–63% attack rates in several areas during outbreaks India is endemic to dengue fever and due to overlapping symptoms; CHIK infection is generally mistaken to be the former thereby leading to misdiagnosis[5, 6]CHIK infection is considered an important public health problem due to the morbidity and disability caused by chronic arthralgia [4]. The social and economic burden caused by CHIK fever is tremendous. Hence, there is an urgent need for an effective vaccine or antiviral therapy against CHIKV infection [2].Chikungunya (CHIKV) virus has recently reemerged as an important pathogen causing epidemics of the disease in several countries . Epidemic resurgence of CHIKV was recorded in 2000 in the Democratic Republic of Congo(DRC), in Indonesia during 2013 [2 6]. There is no specific treatment (therapies) or vaccines are available for CHIKV due to which there is high morbidity and loss in daily activity associated with CHIKV infection . This emphasizes the need to have a drug design for chikungunya. We found Proteins E1 and E2 both having a molecular weight of roughly 50kDa, forms a heterodimer anchored in the membrane which is a major causes an illness . Recent Chikungunya virus outbreaks presented a prospect for genetic analysis of patients with the illness, revealing a point mutation at the amino acid 226 (Ala mutated to Val) of the E1 gene [7]. This point mutation was confirmed to be responsible for an improved capacity of CHIKV strains to infect and replicate in the Aedes albopictus, enabling virus transmission to anaive human population.

MATERIALS AND METHOD

Ligand selection

PubChem Database compound contains validated chemical depiction information. Structures that are stored in PubChem contain calculated properties and description which helps in searching and filtering of chemical structures. The ligand for 3n41 protein was retrieved from PubChem Compound in Sdf file format and converted to pdb.

SMART screening

DS-smarts screening filter was used to screen the screened ligands from the library of thecompounds using the Discovery studio2.5. Discovery studio package contains the smiles of the

Reactive functional group of the database and the compounds screened using the DS_ smarts. Usually many drugs fail in clinical trials because of unrelated side effects and Bio- Unavailability. To overcome these problems, we screened drug like molecules that exhibit physicochemical properties for favorable absorption, distribution, metabolism, excretion and toxicological parameters. Key physicochemical properties of compounds such as Molecular.

Homology modeling:

Homology modeling was carried out in order to study three dimensional structure of protein of E1(3N41).the study was carried out using **PHYRE2.**

- Protein HomologY Recognition Engine developed by Lawrence Kelley. PHYRE2 was used for protein structure prediction. It was web-based services for protein structure prediction.PHYRE2 was used to predict the 3-D structure of a protein using the principles and techniques of Homology Modeling, Secondary Structure Prediction and Domain analysis.

3D LIGAND SITE SEARCHING

3DLigandSite is a web server was used to predict the ligand binding sites based upon the structure similar to the protein submitted as query. Ligands bound to structures similar to the query were superimposed onto the model. This model used to predict the binding site. 3DLigandSite was used to predict the binding sites using ligands from homologous structure of query protein E1.

Docking

Docking was used to predict both ligand orientation and binding affinity. In this method the preferred orientation of one molecule with relation to a second, when bound to each other to form a stable complex in three dimensional spaces is predicted. Docking was used for finding the orientation of drugs in particular target. Knowledge of the preferred orientation in turn was used to predict the strength of association/binding affinity between two molecules using scoring functions. We took the PDB ID of E1 protein monomer(3N41). Ligands for the particular proteinis taken expected output from it. We have checked the properties of these ligands in pubchem database and chosen few lead molecules out of them. Using Patch dock we checked the protein -protein interactions. The Docking interactions were observed in Pymol.

- **PATCHDOCK**: patchdock study was carried out in order to study the interaction between ligand and protein of interest.the result yielded Atomic Configration Energy with surface area
- **HEX :**Hex is an interactive protein docking and molecular superposition program.Hex understands protein and DNA structures in PDB format, and it can also read small-molecule SDF files and include CUDA support for Nvidia GPUs. It uses KBDOCK KBDOCK is a database of all known structural domain-domain interaction, built directly from the PDB and Pfam . If structural homologues exist for your docking target, KBDOCK finds homology templates, it can also be used as a handy way to launch a docking job with HexServer.

UNITS

Energy value in Kilojoules per mole (kj/mol), interaction Energy in Kilo Calories per mol (kcal/mol)

RESULT

TABLE 1: SHOWING DIFFERENT LIGANDS AND ITS INFORMATION

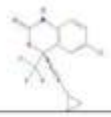
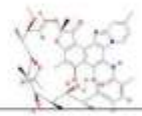
NAME	PDB ID	STRUCTURE	MOLECULAR FORMULA	MOLECULAR WEIGHT(g/mol)
EFAVIRENZ	PDB/1FK9 PDB/1FKO PDB/1FKP PDB/1IKW		$C_{14}H_9ClF_3NO_2$	315.67
RIFAXIMIN	1H4V		$C_{43}H_{51}N_5O_{11}$	785.87854
RIFAPENTINE	PDB/2A69 PDB/2A6E PDB/2BE5		$C_{47}H_{64}N_4O_{12}$	877.030660

TABLE 2: PROTEIN (MACROMOLECULE) INFORMATION

PROTEIN NAME	SOURCE	PDB ID& CHAIN	PDB STRUCTURE
E1-PROTEIN	CHIKUNGUNYA VIRUS	3N41	

TABLE 3:LIGAND (SMALL MOLECULE) INFORMATION

LIGAND NAME	SOURCE	PDB ID	PUBCHEM STRUCTURE
EFAVIRENZ	CHEMICAL SYNTHESIS	1IKW	

TABLE 4: QUANTUM ENERGY COMPARISON FOR LIGAND AND PROTEIN

LIGAND NAME	ESTIMATED VALUE	BINDING VALUE
EFAVIRENZ	-1.80 kj/mol	-15.80 kj/mol
RIMANTIDINE	-3.98 kj/mol	

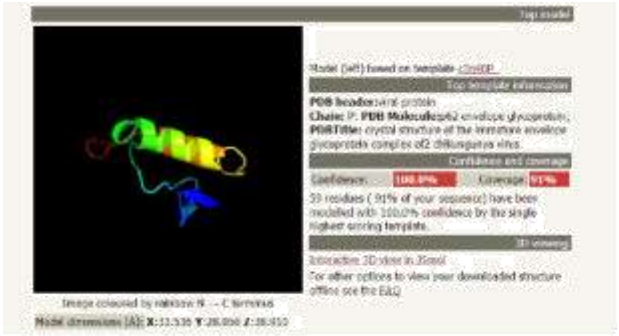


FIG1: PHYRE RESULT FOR E1 PROTEIN

FIG2: DETAILS OF E1 PROTEIN CHIKUNGUNYA VIRUS

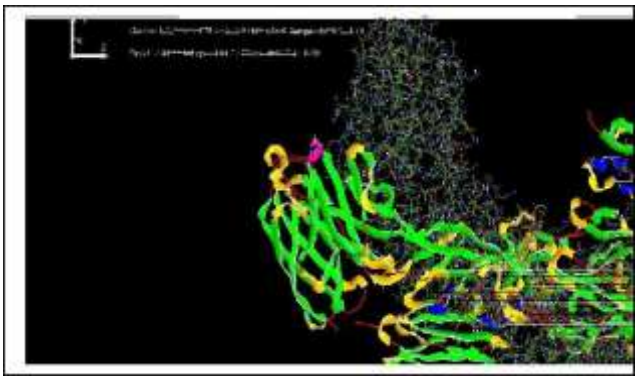
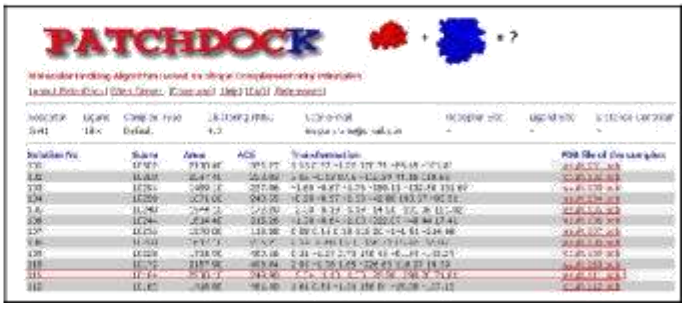


FIG 3: THE INTERACTION ENERGY OF DOCKING WAS CALCULATED USING THE HEX SERVER BETWEEN PROTEIN(3N41) AND LIGAND(1IKW) (WITH HYDROGEN BONDING) WITH INTERACTION ENERGY -144.79 KCAL MOL(-1)



PATCHDOCK RESULTS FOR 1IKW AND 3N41

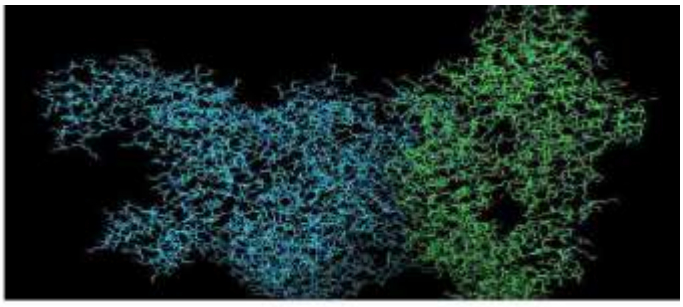


FIG 4: PYMOL VIEW OF PATCHDOCK (DOCKING BETWEEN LIGAND (EFAVIRENZ.) AND PROTEIN(3N41)WITH ATOMIC CONFIGRATION ENERGY -249.98KJ.MOL(-1).

TABLE 5: ATOMIC CONFIGURATION ENERGY AND SURFACE AREA COMPARISON FOR DIFFERENT LIGANDS WITH PROTEIN (3N41) USING PATCHDOCK

LIGAND NAME	PDB ID	ACE	SURFACE AREA
EFAVIRENZ	1FKO	-356.86	1950.60
RIFAPENTINE	2A69	-292.73	842.20
EFAVIRENZ	1FK9	-296.14	1689.40
EFAVIRENZ	1FKP	-346.93	1421.30
EFAVIRENZ	1IKW	-249.98	2230.10
RIFAXIMIN	1H4V	-298.70	3136.30
RIFAPENTINE	2A6E	-298.84	1754.20
RIFAPENTINE	2BE5	-295.78	1298.2

CONCLUSION:

This study describes about the 3n41 protein that have demonstrated to be a promising drug target for the treatment of Chikungunya. The interaction between Chikungunya 3n41 protein against the ligands was studied by using various computational methods. Based on the hydrogen bonds, docking score ,the docking result was analyzed. The results were compared based on patchdock , quantum energy within themselves to find out the best ligands which can inhibit the property of the viral protein. Based on this observations LIGAND EFAVIRENZ. is found to bind with the target more efficiently than other ligand compound with best hydrogen bonding interactions with the peripheral site key residue. Hence, LIGAND EFAVIRENZ. has been emerged as a promising Anti-viral drug candidate with potential symptomatic and disease-modifying effects. Further, QSAR studies can be done to identify conformational changes. The open source tools used to study the docking gave positive results and hence we shortlisted the ligand molecule to be Efavirenz.. Our future goal is to optimize the ligand and prepare the Drug for and make it available for Market .

APPENDIX:

Abbreviations and Acronyms

Abbreviations	Acronyms
CHIKV	Chikungunya virus
DRC	Democratic Republic of Congo
IFN	Interferon
kDa	Kilo Dalton
Ala mutated to Val	Alanine mutated to Valine
OSDD	Open source Drug Discovery
GB RAM	GIGABYTE,Random Access Memory
PDB	Protein Data Bank
SDF	Standard Data File
DS	Discovery studio
HBA	Hydrogen Bond Acceptor
HBD	Hydrogen Bond Donor
ClogP	Concentration log Partition value
PHYRE	Protein HomologY Recognition Engine
SAVS	Stuctural Analysis and Verification Server

5.

ACKNOWLEDGMENT

Apart from the efforts of OSDD Team, the success of any project depends largely on the encouragement and guidelines of many others. We take this opportunity to express our gratitude to the people who have been instrumental in the successful completion of this.

We would like to express my special gratitude and thanks to my Principal, **Dr. B. S. Satyanarayana,** R.V. College of Engineering, for giving us vast resources, facilities and inspiration for all that we could do today

With due respect and immense pleasure we express my special thanks of gratitude to Dr.H.G.ASHOK KUMAR, Head of the department, BIOTECHNOLOGY, and DR.VIDYA NIRANJAN, Associate Professor who gave us the golden opportunity along with constant support and motivation for presenting my work.

We take this opportunity to express our profound gratitude and deep regard to our Professor, Dept OF BIOTECHNOLOGY, for their exemplary guidance, monitoring and constant encouragement throughout the course of this work. The blessing, help and guidance given by them time to time shall carry me a long way in the journey of life on which we are about to embark.

We are obliged to staff members of the department, for the valuable information provided by them in their respective fields. We are grateful for their cooperation during the period of our work.

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