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Research Article

In silico Molecular Modelling and Docking Studies on Therapeutic Target Non Structural Protein 3 (NS3) of Dengue Virus 1

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ABSTRACT

Dengue virus (DENV) is a family member of flaviviruses, transfer their pathogenecity to humans by the vector mosquitoes and it is showing similar positive sense genomic RNA as such flavivirus, encodes single polyprotein in order to synthesize structural and non structural proteins. Non Structural protein 3 (NS3) has serine protease and RNA helicase activities. NS3 combined with the NS2B activator to form the heterodimer for the cleavage at intermolecular sites in polyprotein to generate other proteins. In the present study we build three dimensional model structure of Non Structural protein 3 (NS3) using modeller 9.10. Common drugs available in market for dengue virus, yellow fever virus and westinile virus used to find lead molecules against NS3 by molecular docking studies in Auto Dock Vina in Pyrx. Screening of ZINC database for mycophenolic acid analogues and its docking studies revealed that ZINC 78034162, 62001571, 62001658, 09813466 and 34527414 are showing least binding energy through hydrogen bond interactions. In conclusion the compounds which are showing high binding affinity with least binding energy better than mycophenolic acid is suggesting therapeutic lead molecule for inhibition of NS3 therapeutic target of dengue virus 1.

Keywords: Dengue virus, Molecular docking, Non Structural protein 3, Westinile virus.

INTRODUCTION

Dengue virus (DENV) is a family member of flaviviruses, transfer their pathogenecity to humans by the vector mosquitoes and it is showing similar positive sense genomic RNA as such flavivirus, encodes single polyprotein in order to synthesize structural and non structural proteins. Dengue diseases are caused by the four antigenically distinct dengue virus serotypes, DENV 1 to 4.[1] With the effect of pathogenicity transfer, approximately 2.5 billion people were contracting with dengue virus. Along with structural, Non-Structural proteins (NS) also act as therapeutic targets in development of anti dengue viral compounds due to its importance in viral multiplication. The Non-Structural proteins play very important role in the development of dengue fever such as NS1 involved in the RNA replication, NS2A and NS4A is a part of replication and induce the host immune system, NS2B cofactor for NS3 whereas NS3 act as serine protease and RNA helicase, NS4B modulates dengue virus replication and NS5 involve in post transcriptional modification.[2] The NS3 protease is an essential component for maturation of the virus and viable virus.[3] Sequence comparison revealed that multifunctional 69 kDa NS3 protein has a N-terminal region exist as trypsin-like protease domain and serine protease domain at 167 aminoacids,[4,5] at c- terminal have Nucleoside Triphosphatase (NTPase) and RNA helicase activities.[6] NS3 cleaves the non structural region of polyprotein by formation of heterodimer with activator NS2B. Activated heterodimer cleaves intramolecular cleavage at NS2A/NS2B and NS2B/NS3 and cleavage as intermolecular at NS3/NS4A and NS4B/NS5 sites in polyprotein.[7-9] The NS3 protease exhibits NS2B-independent activity with model substrates for serine proteases but enzymatic cleavage of dibasic peptides is markedly enhanced with the NS2B-NS3 co-complex and the presence of the NS2B activation sequence is indispensable for the cleavage of poly protein substrates in vitro.[10] Due to its significant role of NS3 protease in dengue virus, make it a valid molecular target for the development of antiviral compounds that are equally effective against the four dengue virus serotypes and related members of the Flaviviridae.[11, 12]

In the present study we build three dimensional model structure of Non Structural protein NS3, molecular docking studies with common drugs which are available in market for dengue virus, yellow fever virus and westinile virus and its analogs to find lead molecules.

MATERIALS AND METHODS

Molecular modelling

The molecular model generation needs query sequence; it is retrieved from NCBI database which specific identification as NP_722463.1 (Non-structural Protein 3 [Dengue virus 1]). The protein sequence of NS3 was used to found suitable template coordinates which have already crystallographic structure in PDB from NCBI BLAST. BLAST search generated a template, mutant type of same protein in same virus and its PDB id is 2WZQ (Chain A, Insertion Mutant E173gp174 of The NS3 Protease-Helicase from Dengue Virus [Dengue virus]). Preparation of template-sequence alignment and generation of model structure NS3 protein was done in Modeller 9 Version 10(Mod9v10)[13] using template and query protein sequence. The selections of final 3-D model NS3 from Modeller by least DOPE score values.

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Modelled NS3 protein validation

Protein validation parameter such as protein structure backbone dihydral angles ψ against ϕ of amino acid residues and empirical distribution of data points observed in a single structure was identified by Ramachandran plot in RAMPAGE crystallography and bioinformatics group (http://mordred.bioc.cam.ac.uk/~rapper/rampage.php). In Ramachandran plot, residues in favoured, allowed and outer lined regions were observed. The compatibility of atomic model with amino acids present in own structure based on amino acids possess their features was validated by Verify3D in SAVES-UCLA-DOE structure evaluation server (http://nihserver.mbi.ucla.edu/SAVES).

Docking and identification of binding geometry of ligands with NS3 protein

Therapeutic active drug compounds for common flavivirus such as Dengue, Yellow Fever and Westinile were selected from literature and downloaded from the Pubchem database in the form of SDF format to suitable for dock with target protein in docking software. The docking parameter, the drug compounds with target protein was run in the Auto Dock vina in the PyRx freely available offline software. Auto dock vina, is a program for molecular docking and virtual screening with sophisticated gradient optimization method in its local optimization procedure. [14] The drug compounds were subjected to the energy minimization and allow fitting in the ligand binding site of the protein with eight iteration or conformations for each drug compound. Docking results generated highest binding affinity drug with ligand binding site of the target protein was used to download its 90 and 80 percent ligand analogues molecules from the ZINC database. ZINC database have a biological relevant, three dimensional forms of chemical compounds. Downloaded ZINC chemical analogues were used to run structure based virtual screening approach with the target protein ligand binding site to evaluate finest binding affinity compound than reference drug compound. Structure-based virtual screening is most commonly implemented as the prediction of binding modes and binding affinities of each compound by means of high-throughput docking to an X-ray structure or model of the target.[15] From docking studies the lead molecules binding geometry in binding site of ns3 was observed in the PyMol visualizer. To understanding the structural principles that determine the strength of a protein/ligand complex in an accurate and fast docking procedure, the ability to visualize binding geometries and interactions are mandatory.[16]

Prediction of Lipinski rule of five for chemical structures

The selected drugs in evaluation process of drug properties should follow the Lipinski rule of five include molecular mass less than 500 daltons, high lipophilicity less than 5, less than 5 hydrogen bond donors and less than 10 hydrogen bond acceptors. The drug, activity in therapeutic important with successful Lipinski rule of five parameters has been able to act as potent inhibitor in the field of pharmacy. In this study the drug property parameters were calculated in Molinspiration online tool. Molinspiration is a sum of fragment-based contributions and correction factors with very robust and is able to process practically all organic and most organometallic molecules.[17]

RESULTS AND DISCUSSION

Template structural homology with target protein sequence identified in BLAST was 76% identity. The template sequence aligned with target sequence in the Clustal W sequence alignment programme (figure 1).

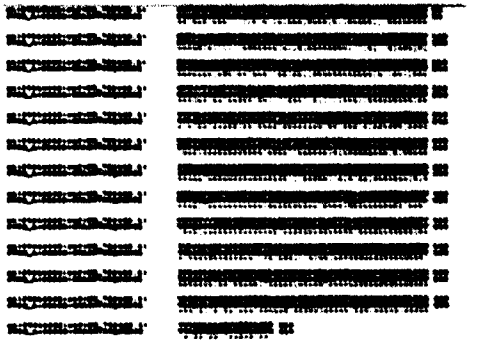

Figure 1: Target NS3 - template protein sequence alignment in CLUSTAL W sequence alignment tool.

The target protein three dimensional structures builded in modeller generate hundred low energy models, in which the finest lest energy protein model was picked out based on DOPE score energy value -62307.97266. The modelled protein and templates structure was superimposed in the PyMol visualizer to found how modeller bring on target sequence to build its tertiary structure based on template structure and the superimposed structure illustrated in figure 2.

Figure 2: visualization of NS3 modelled protein superimposition with the template structure (PDB: 2WZQ) in PyMol graphical visualization tool. The template structure viewed in green where as NS3 in cyan in colour.

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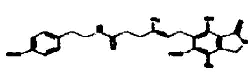
The selected model was validated through Ramachandran plot parameter generates 93% amino acids in favoured, 4.5% amino acids in allowed and rest of the amino acid percent in outer lined regions (figure 3). The validated target protein final model structure (figure3) has 16 Alpha helixes, 26 beta pleated sheets. The evaluation model of NS3 protein gave information which is suitable for further proteomic analysis.

Figure 3: NS3 modelled protein validation report in respect of Ramachandran plot predicted in Rampage. The final refined three dimensional model structure of the NS3 generated from Modeller 9.10.

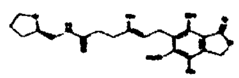
The drug Mycophenolic acid identified in preliminary docking studies of common drugs for flaviviruses with NS3 protein. Further docking studies with 440 analogues of mycophenolic acid form the ZINC database was identified that top five lead molecules such as ZINC 78034162, 62001571, 62001658, 03813466 and 34527414. These compound structures have least binding energy through hydrogen bond interaction, bond lengths and bond angles with NS3 target protein comparatively by means of reference drug mycophenolic acid represented in table 1 and 2.

The top five lead molecules have least binding energies in between -9.4 and -8.8. The ZINC 78034162 has shown highest binding affinity (-9.4) with least binding energy in ligand binding site of target NS3 and which have three hydrogen bond interactions with lysin389 and met 538. The lysin389 zeta N atom interact O24 of lead molecule with 3.2 Å bond length and 92.9 bond angle. The metheonine538 have shown two interactions such as oxygen atom interacts H0 and O9 with bond length 2.4, 3.2 Å plus bond angles 114.2, 134.9 respectively. The ligand binding site in target protein contained few amino acids play a crucial role in hydrogen bond interactions with top five lead molecules in which Lys 389 Met 538, Ser 1, Arg 388, His 488, Met 38, Asp 542, Thr 601, Gly 29 and Met 59 are noticed and illustrated in figure4.

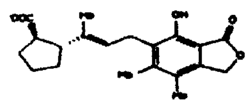
Table 1: identified five lead chemical compound structures in docking studies with NS3 therapeutic target



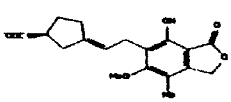
78034162



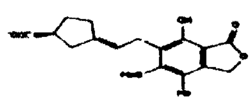
62001571



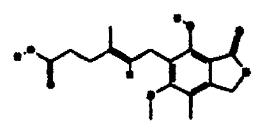
62001658



03813466



34527414



Mycophenolic acid

Table 2: The summary of molecular interaction studies of lead compounds with NS3 target protein based on binding affinity. The atoms involved in hydrogen bonding, the bond lengths and bond angles are represented.

[illegible]	-9.4	Lys 389 CE-ZN—O24-C22; Met 538 C-O—H0-O8; C-O—O9-C8	[illegible]	[illegible]
[illegible]	-9.2	Ser1 [illegible]; Arg 388 [illegible] His 488 [illegible]	[illegible]	[illegible]
[illegible]	-9.2	Met 38 C-O—[illegible]; Asp 542 [illegible] Thr 601 [illegible]	[illegible]	[illegible]
[illegible]	-9.1	Ser 1 [illegible] Met 538 [illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

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Table 3: Insilico prediction of drug properties in Molinspiration for top five lead molecules

78034162	373.425	1.296	6	1	[illegible]	[illegible]
63001571	459.595	4.958	7	2	[illegible]	[illegible]
63001658	409.475	2.886	7	2	[illegible]	[illegible]
03813486	349.389	1.416	5	1	[illegible]	[illegible]
94527414	391.944	-0.19	6	1	[illegible]	[illegible]
Mycophenolic acid	320.341	2.632	6	2	[illegible]	[illegible]

Figure 4: Docking study generated top five lead molecules interactions in the ligand binding site of NS3 target protein visualized in PyMol, where the hydrogen bond (dotted red lines) interactions of lead molecules (sticks)with amino acids of NS3 protein.

Screened out final five lead compounds is need to follow the pharmacological suitable and important drug properties, for that, all those lead molecules subjected to Molinspiration drug property prediction programme. Molinspiration calculated molecular weight, *miLog P*, TPSA, nON, nOHNH and nrotb of selected chemical compounds were represented in table 3.

All the lead molecules are obey the pharmacological properties of drugs in computationally and the compound 78034162 showing high binding affinity with NS3 protein contains molecular weight 373.425, *miLogP* 1.296, *nON* 6, nOHNH 1, TPSA 95.895 and nrotb 5 as similarity with reference drug Mycophenolic acid.

CONCLUSION

In conclusion the compounds which are showing high binding affinity with least binding energy better than mycophenolic acid is suggesting therapeutic lead molecule for inhibition of NS3 therapeutic target of dengue viurs1.

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