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Benzopyranylpyrimidines: Potential Anti Dengue compounds in Silico Approach

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ABSTRACT

Dengue is mosquito borne viral disease, having no effective antiviral chemotherapy nor approved vaccine available. Therefore the design of new drugs to combat dengue virus replication is a challenge for researchers. Flavanone derivatives and substituted pyrimidine derivatives show antidengue activity in silico and in vitro. We report the docking study, ADME prediction of benzopyranylpyrimidine derivatives against the dengue virus NS2B/NS3 protease. The hydrogen bonding, hydrophobic interactions and Van der Waals forces between designed compounds with Lys74, Trp83, and Leu149 amino acid residues of the NS2B/NS3 protease is also discussed.

Keywords: Benzopyranylpyrimidines; Dengue Virus; Glide; Docking study

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INTRODUCTION

Dengue is the most common mosquito borne viral disease of humans that in recent years has become a major international public health concern as it infects 50-60 million people each year [1]. According to WHO, 2.5 billion people live in areas where dengue viruses can be transmitted. Dengue virus belongs to the family *flaviviridae* [2] and is caused by bite of the *Aedes agypti* mosquito. The infection severity ranges from dengue fever to dengue hemorrhagic fever and dengue shock syndrome. There are four serotypes of dengue viz. DEN-1, DEN-2, DEN-3, and DEN-4 [3].

Protease plays a vital role in virology of dengue virus replication. Hence the protease is most often targeted in designing the new scaffolds to combat dengue.

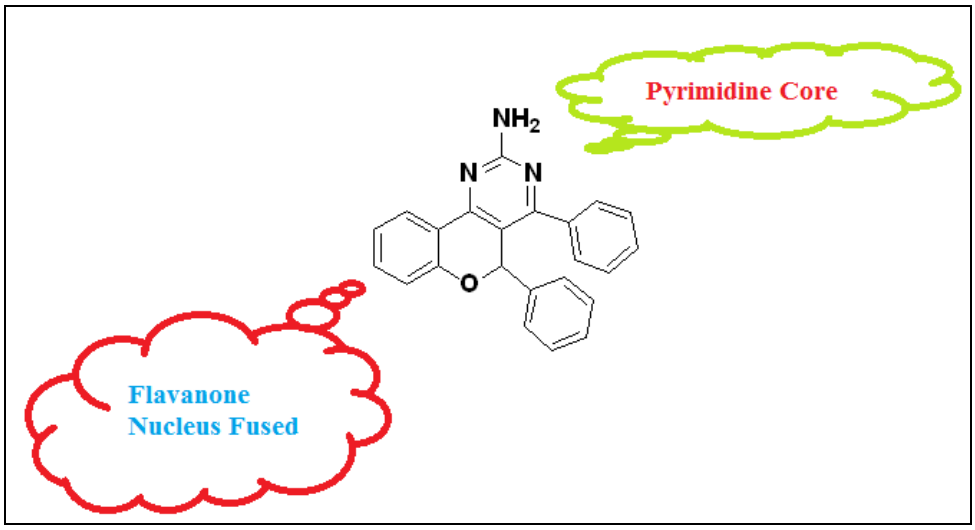
The dengue virus consists of three structural proteins capsid (C), premembrane (prM), envelope (E) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5) [3]. Dengue virus replication is dependent upon the correct cleavage of polypeptide and requires both host cell proteases and the virus-encoded two-component protease NS2B-NS3. NS3 contains a trypsin-like serine proteinase domain of 180 amino acid residues at its N-terminal, suggesting its role as a viral protease. The active region of dengue virus protease is located in catalytic triad His51, Asp75, and Ser135 [4].

To date, there is neither a vaccine nor any drug approved against dengue. Therefore there is a need for a safe, potent drug to combat dengue. Hence, efforts are being made to find potent antidengue scaffolds in *silico*.

Pyrimidines are reported to show anti-HIV, [5] antidengue [6] and anticancer [7] activity. Flavanones reported to exhibit antidengue activity [8]. Flavanones have potential antidengue characteristics in silico were also reported by us previously [9]. Combination of flavanone and pyrimidine generates benzopyranylpyrimidine. Benzopyranylpyrimidines have been reported to exhibit antiplatelet activity [10]. Hence we designed and synthesized [11] several benzopyranylpyrimidine cores to study their molecular informatics against dengue.

Our aim is to study the binding interactions between benzopyranylpyrimidine derivatives and the dengue virus NS2B/NS3 protease. We report the docking studies performed on benzopyranylpyrimidine derivatives as antidengue compounds using Glide software. We hope our study will be useful for understanding the protease inhibition of dengue virus in silico.

The designing of new antidengue cores can be best disclosed as shown below.



MATERIALS AND METHODS

Hardware and Software: All the molecular modeling studies described herein were performed on Lenovo Ultra Book Laptop (Intel® Core™ i5-3317U CPU @ 1.70 GHz, RAM 4 GB) running Windows 7 Home Basic Operating System. Schrödinger Small-Molecule Drug Discovery Suite Release 2013-1 and the products included therein were used for performing various molecular modeling studies described in this manuscript.

Docking Studies:
Glide [12] version 5.7, as implemented in Schrödinger suite 2013-1, was used for performing molecular docking studies. Table 1 show the molecules used in the docking studies against the target dengue virus protease. The crystal structure of dengue virus NS2B/NS3 protease (PDB ID 2FOM) is obtained from protein data bank (www.rcsb.org). The crystal structure of Dengue virus NS2B/NS3 protease (PDB ID 2FOM) was imported in Maestro 9.4 and subjected to *Protein Preparation*. All the default settings were used as implemented. The termini were capped, missing side chains were added, H-bonds were optimized and in the end, restrained minimization was performed wherein the heavy atoms were converged to root mean square deviation (RMSD) 0.3 Å. All the water molecules were removed from the structure during *Protein Preparation*. The prepared protein was then subjected to *Receptor Grid Generation* using Glide 5.9. Receptor grid was generated at the catalytic triad region of dengue virus NS2B/NS3. The grid, generated using the default settings, was then used for the docking studies of the ligands.

Small Molecule Ligands Preparation. The ligand structures were built in Maestro. All the structures were then subjected to *LigPrep 2.6*, as implemented in Schrödinger suite 2013-1. All the default settings were used. This set of molecules was then subjected to the docking studies. For docking studies, *Extra Precision* (XP) mode was used. The docked poses were minimized and RMSD to input ligand geometries were calculated. The output consisted of one docked pose (best pose). All other default settings were used during the docking analyses. The docked poses were critically analyzed for the number of intermolecular H-bonds, hydrophobic interactions, etc. The docking score and list of interacting amino acid residues with designed compounds is presented in **Table 1**. Figure 1 show the docking poses of representative molecules into the active site of dengue virus NS2B/NS3 protease. H-bonding interactions, if any, with the binding site residues, are shown as yellow dotted lines. The docked complexes were then used for predicting the binding free energies using *Prime MM-GBSA* calculations. The complexes were taken from the Maestro Pose Viewer files. The solvation model used was VSGB as implemented. The sampling method – Minimize – was used during the calculations. The MM-GBSA binding free energies for all the molecules are presented in Table 1.

ADME prediction: Another filter in the drug design is the prediction of drug-like characteristics of the newly designed molecules. For this purpose, the ADME properties [13] i.e. absorption, distribution (binding to plasma

protein), metabolism and excretion prior to the experimental studies is one of the most important aspect in the drug discovery and development. Drug may fail to reach the market phase if these properties are not fulfilled by the drug candidate. ADME properties of the designed benzopyranylpyrimidines are summarized in Table 2.

ADME properties of virtually designed benzopyranylpyrimidines were calculated using Qikprop 2.5 tool of Schrodinger software. It predicts both physicochemically significant descriptors and pharmacokinetically relevant properties. QikProp provides ranges for comparing a particular molecule's properties with those of 95% of known drugs. QikProp also flags 30 types of reactive functional groups that may cause false positives in high throughput screening (HTS) assays. It also evaluates the acceptability of designed compounds based on Lipinski's rule of five, which is essential to ensure drug-like pharmacokinetic profile while using rational drug design. All the analogs were neutralized before being used by Qikprop.

RESULTS AND DISCUSSION

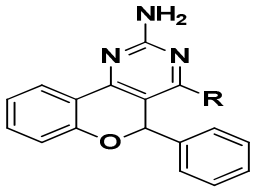
Docking of the benzopyranylpyrimidine derivatives against dengue virus NS2B/NS3 protease shows interaction with important amino acid residues. The antidengue compounds interact with Leu149, Lys74, Trp83 Asn152, Val147 and Ser135 is reported in the literature [14]. The designed compounds were found to interact with Lys74 and Trp83. This indicates designed compounds have potential to exhibit antidengue characteristics in *silico*.

Lys74 is bonded directly to Asp75, catalytic triad residue. The observed hydrophobic interaction between Lys74 and all designed compounds will induce direct conformational change on Asp75 that is at the catalytic triad region. This could disrupt the electron transfer process required for substrate binding at the active site, hence affecting the activity of the protease.

Trp83 forms hydrophobic interaction with all designed compounds except compound. The importance of Trp 83 residue is reported in literature [15, 16]. Therefore, designed compounds have potential antidengue characteristics in silico.

The 2D and 3D images of docking poses of each compound is presented in supporting information file 1.

Table 1 :Docking result including MM-GBSA



Benzopyranylpyrimidine derivatives

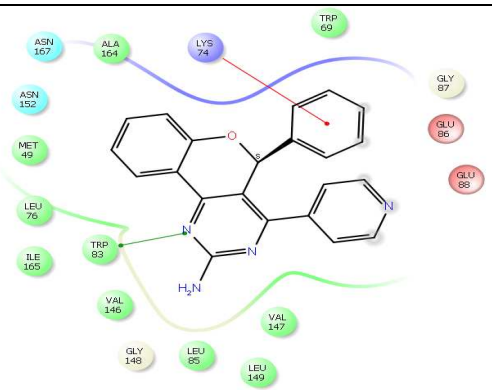
No	Compound Code	R	G-Score	Interacting amino acid residues	MM-GBSA
1	Compound 1	4-Pyridyl	-5.39	Lys74, Trp83	-41.67
2	Compound 2	2-Furyl	-3.76	Lys74, Trp83	-33.09
3	Compound 3	4-Fluorophenyl	-3.76	Lys74, Trp83	-40.22
4	Compound 4	4-Chlorophenyl	-3.66	Lys74	-36.18
5	Compound 5	4-Bromophenyl	-3.58	Lys74, Trp83	-41.20
6	Compound 6	Phenyl	-3.56	Lys74, Trp83	-38.28
7	Compound 7	4-Methoxyphenyl	-3.56	Lys74, Trp83	-41.48

All designed benzopyranylpyrimidines show ADME properties in acceptable range and properties are summarized in Table 2.

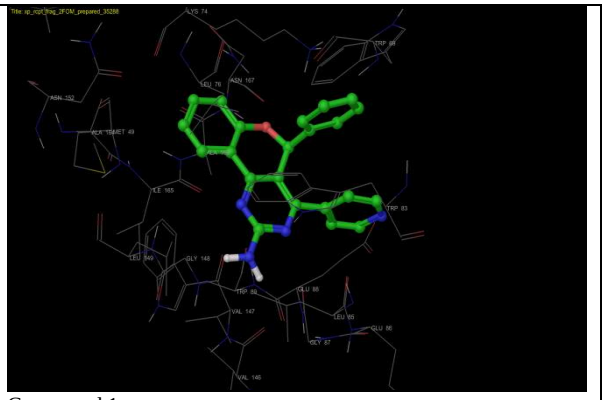
Table 2 :ADME properties

Compound Code	H-bond donor	H-bond acceptor	LogPw	Log Po/w	Log S	LogBB	CNS
Compound 1	2	4.75	12.18	3.57	-4.79	-0.53	0
Compound 2	2	3.75	11.27	3.89	-4.99	-0.26	0
Compound 3	2	3.25	10.59	4.66	-5.75	-0.24	0
Compound 4	2	3.25	10.56	4.89	-6.06	-0.19	0
Compound 5	2	3.25	10.68	5.143	-6.54	-0.19	0
Compound 6	2	3.25	10.79	4.42	-5.39	-0.34	0
Compound 7	2	4	11.011	4.52	-5.53	-0.41	0

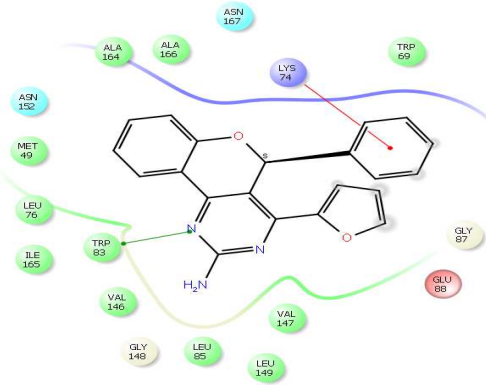
Figure 1: 2D and 3D poses of docked molecules.



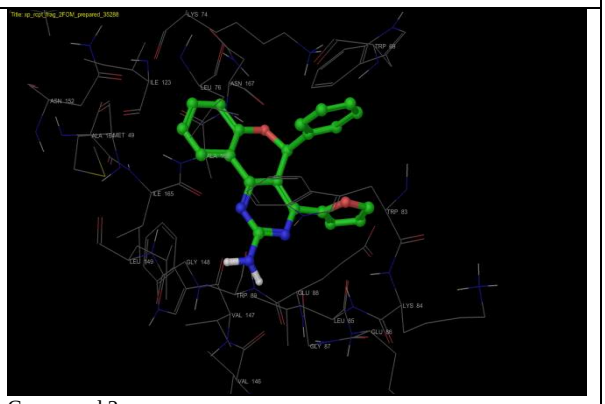
Compound 1



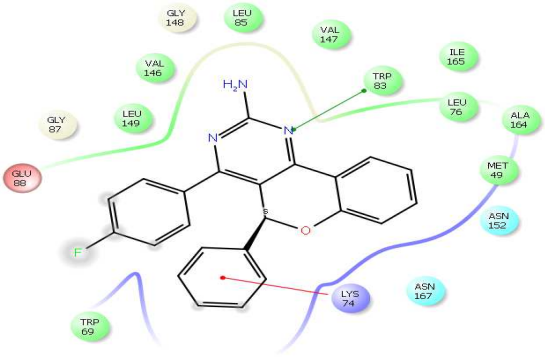
Compound 1



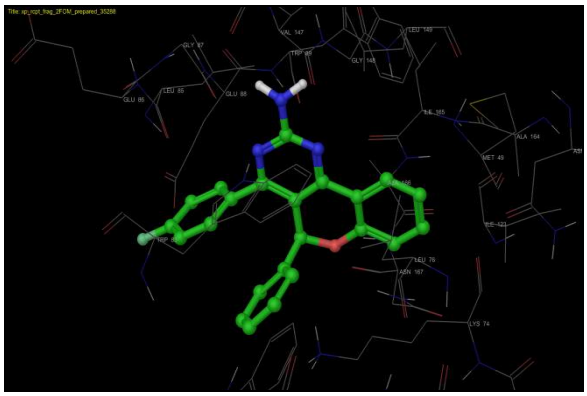
Compound 2



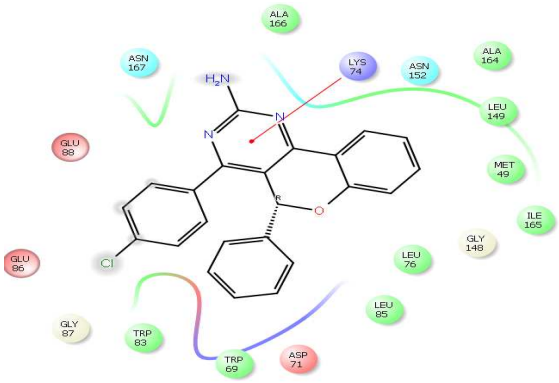
Compound 2



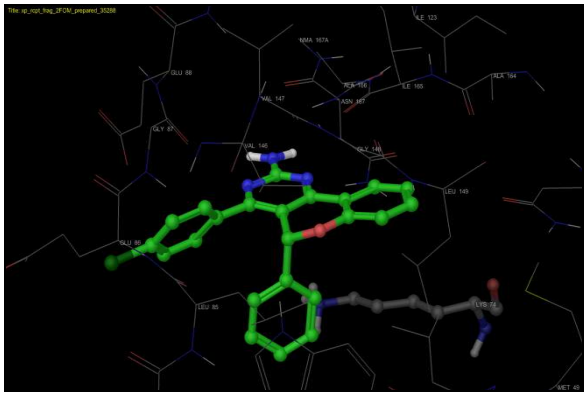
Compound 3



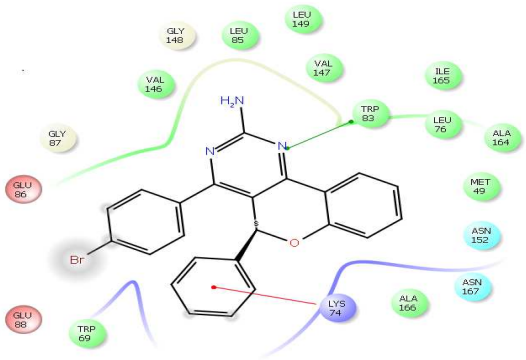
Compound 3



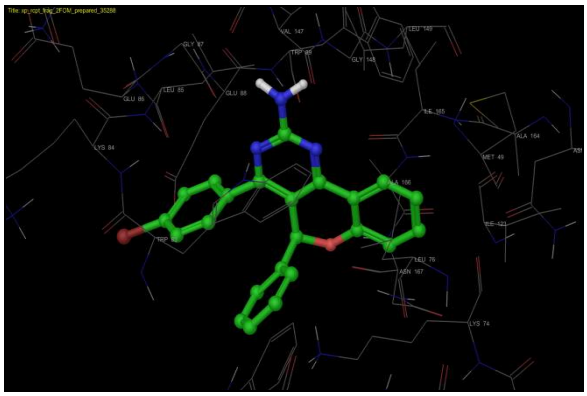
Compound 4



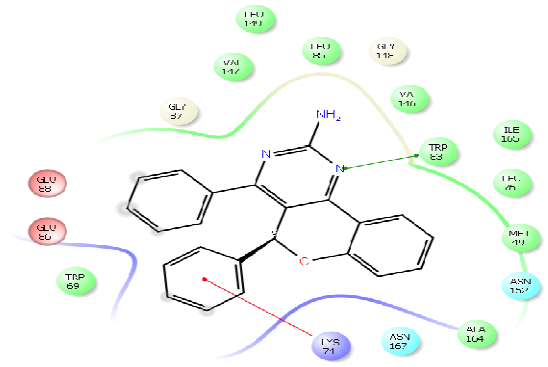
Compound 4



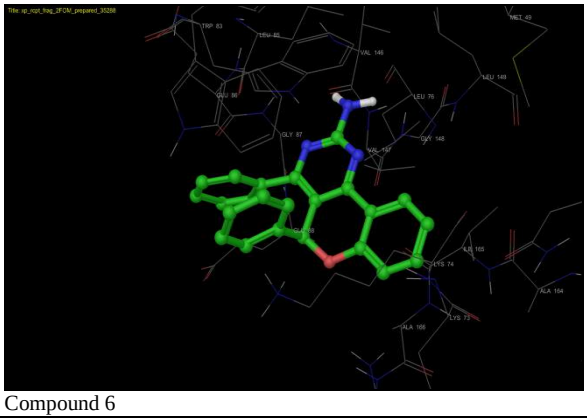
Compound 5



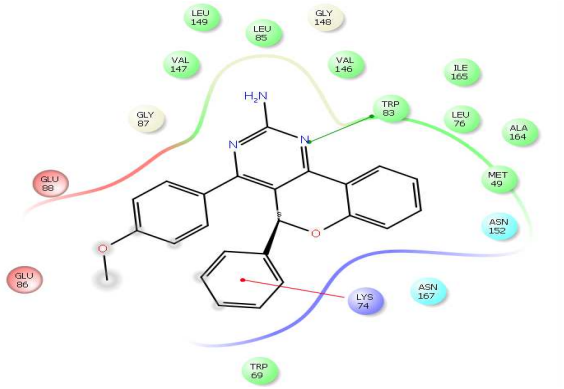
Compound 5



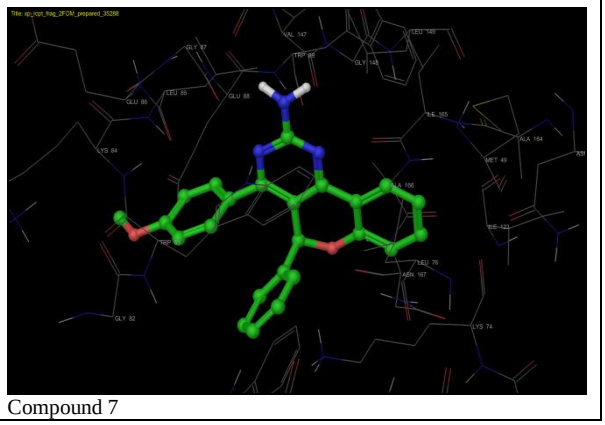
Compound 6



Compound 6



Compound 7



Compound 7

CONCLUSION

The designed benzopyranylpyrimidines were docked on dengue virus NS2B/NS3 protease using Glide docking software. Hydrophobic interactions were observed with amino acids other than catalytic triad of dengue virus protease. All compounds interact with Trp83 and Lys74 which is bonded directly to Asp75, one of catalytic triad, therefore indicating potential antidengue features in designed compounds. Observed ADME properties are in acceptable ranges. The docking results and ADME properties suggest the designed benzopyranylpyrimidines have potential antidengue characteristics in *silico.*

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