Indian Journal of Biochemistry & Biophysics
Vol. 60, January 2023, pp. 55-57
DOI: 10.56042/ijbb.v60i1.64604

Blind docking of 4-Amino-7-Chloroquinoline analogs as potential dengue virus protease inhibitor using CB Dock a web server

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Received 18 July 2022; *revised 01 October 2022*

Currently, there is no approved drug to combat dengue. Various quinoline derivatives are known for potential antimalarial, antiviral activities, *etc*. In the present work docking between 4-Amino-7-Chloroquinoline analogs was performed with dengue virus NS2B/NS3 protease using CB dock, a web server. Lys74, Ile165, Val147, Asn152, Asn167, Trp83 and Leu149 amino acid residues were found to be in contact with designed 4-Amino-7-Chloroquinoline analogs. Different modes of binding like hydrogen bonding, hydrophobic interactions, *etc* with designed compounds improve potential anti-dengue characteristics *in silico*. ADME results are in acceptable range.

Keywords: 2FOM, ADME, Amino Acids, Drug design, Quinoline

Dengue is a viral diseasecaused due to the bite of *Aedes aegypti* type mosquito[1-2]. DEN 1, DEN 2, DEN 3 and DEN 4 are four serotypes of dengue. Dengue virus contains capsid, pre-membrane and envelope as structural proteins. Whereas. NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 are seven nonstructural proteins[3]. The dengue virus replication is due to cleavage between host cell protease and virus-encoded two component protease NS2B/NS3 proteins. The active site of dengue virus protease is located between His51, Asp75, and Ser135 residues[3].

Quinoline derivatives show antiviral activity[4]. Moreover, the quinoline class also shows activity against the dengue virus[5]. Quinoline derivatives have potential anti-dengue characteristics against dengue *in silico* approach[6]. Substituted amino chloro quinoline derivatives were known to exhibit antiprotozoal[7], anti-HIV[8], anti-zika[9], antimalarial[10], and anticancer[11]activities. For the development of the new drug, docking is commonly used. It requires an understanding of the protein drug interactions. These interactions can be studied by using software like an autodock, glide, *etc*. Virtual screening of compounds can be easily done using docking[12-14].

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Suppl. Data available on respective page of NOPR

In the present work, the docking between new 4-Amino-7-Chloroquinoline derivatives and dengue virus protease is performed using CB Dock, a web-based server12. We hope our study will be helpful in designing new entities against the dengue virus.

Experimental Section

Materials and Methods

Hardware

Molecular docking studies described herein were performed on Dell Inspiron 15R Laptop (Intel® Core™ i3-processor) running Windows 7 Home Basic Operating System.

Docking studies

Docking between ligands and protein were performed on CB Dock web server. (https://cadd.labshare.cn/cb-dock2/php/index.php)[15].

Dengue virus NS2B/NS3 protease proteins were downloaded from www.rcsb.org website in.*pdb* format. (PDB ID: 2FOM)[16-17]. Water molecules and other heteroatoms were removed automatically from protein when uploaded on CB Dock web server (Table 1).

Ligands Preparation

Ligands were drawn on Chemdraw software and saved in *.sdf* file format for docking using CB dock web server.

Table 1 — Dock score of designed molecules

Sr No	Compound	R chain	Dock score	Hydrogen bonding, Hydrophilic interactions with following amino acids
1	Compound 1	H	–5.8	Lys74, Ile165, Val147, Asn152, Asn167, Trp83 and Leu149
2	Compound 2	Methyl	–6.9	Lys74, Ile165, Val147, Asn152, Asn167, Trp83 and Leu149
3	Compound 3	Ethyl	–7.3	Lys74, Ile165, Val147, Asn152, Asn167, Trp83 and Leu149
4	Compound 4	n-Propyl	–7.7	Lys74, Ile165, Val147, Asn152, Asn167, Trp83 and Leu149
5	Compound 5	n-Butyl	–8.0	Lys74, Ile165, Val147, Asn152, Asn167, Trp83 and Leu149
6	Compound 6	n-Pentyl	–8.3	Lys74, Ile165, Val147, Asn152, Asn167, Trp83 and Leu149
7	Compound 7	n-Hexyl	–8.9	Lys74, Ile165, Val147, Asn152, Asn167, Trp83 and Leu149
8	Compound 8	n-Octyl	–9.5	Lys74, Ile165, Val147, Asn152, Asn167, Trp83 and Leu149
9	Pinostrobin[3]	-	–7.8	Lys74, Ile165, Val147, Asn152, Asn167, Trp83 and Leu149

Table 2 — Dock score of designed molecules

	ADME Prediction						
Compound	H-bond acceptors	H-bond donors	Consensus Log P	GI absorption	BBB permeant	log Kp (cm/s)	Lipinski violations
1	1	1	2.1	High	Yes	–5.78	0
2	1	1	2.61	High	Yes	–5.05	0
3	1	1	2.94	High	Yes	–4.88	0
4	1	1	3.3	High	Yes	–4.59	0
5	1	1	3.63	High	Yes	–4.42	0
6	1	1	3.98	High	Yes	–4.13	0
7	1	1	4.32	High	Yes	–3.82	0
8	1	1	5.06	High	Yes	–3.22	0
9	4	1	2.66	High	Yes	–5.68	0

Swiss ADME program helped in computing the drug-likeness of designed compounds given in Table 1. Table 2 shows predictions of pharmacological properties. The pharmacokinetics of compounds that were analyzed using the descriptors and pharmaceutically relevant properties of ligands.

ADME Prediction

The swiss ADME program is used to predict physicochemical parameters and ADME parameters (http://www.swissadme.ch/) (Table 2).

Results and Discussion

Designed 4-Amino-7-Chloroquinoline derivatives were docked on dengue virus protease using CB dock web server. Previously reported anti-dengue compounds contains either hydrogen bonding or hydrophobic interactions with amino acids residues including Ile165, Lys74, Asn152, Leu149, Trp83, Ser135 and Val 147[18-24]. Pinostrobin[3] a flavanone derivative is known to exhibit anti-dengue activity with a docking score of –7.8 and it comes in contact with Lys74, Leu149, and Trp83 which are responsible for anti-dengue activity as per literature[3].

Compound 1 to compound 9 were found to exhibit hydrogen bonding and/or hydrophilic interaction with Lys74, Leu149 and Trp83. It Indicates, the 4-Amino-7-Chloroquinoline class has potential for anti-dengue activity *in silico*. The docking score increases as the carbon chain at the fourth position increases. The docking score is found to be comparable with Pinostrobin[3].

Therefore, it can be concluded that the 4-Amino-7-Chloroquinoline class has a potential anti-dengue character.

The supporting images are provided in the supporting information file. The designed 4-Amino-7-Chloroquinoline compounds contact with amino acid residues is summarized in table.

Conclusion

It can be concluded that 4-Amino-7-Chloroquinoline analogs have potential anti-dengue activities *in-silico*. The interacting amino acid residues have a role in proteolytic cleavage in dengue replication, which is observed in designed 4-Amino-7-Chloroquinoline analogs indicating potential anti-dengue character. Blind docking helps in identifying potential target molecules for their activity against the dengue virus. CB dock program helps in predicting the potential anti-dengue compounds from dock score in less time.

Acknowledgement

Authors Prasanna Ranade and Dinesh Navale gratefully acknowledge the use of central instrumentation facilities at Vivekanand Education Society's College of Arts, Science and Commerce (Autonomous) funded by FIST-DST (Ministry of Science and Technology Govt. of India. and DBT STAR college scheme.

Conflict of interest

All authors declare no conflict of interest.

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