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In silico molecular docking and ADME-toxicity studies on Quinacrine derivatives against NS5-methyltransferase of dengue virus

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ABSTRACT

Dengue is a standout amongst the most vital mosquito-borne viral infections on the planet, and is endemic in roughly 120 nations. Dengue fever is showed as a weakening infection in more seasoned youngsters, youths, and grown-ups. In this work, we screened Quinacrine derivatives from PubChem compound database and docked with NS5-methyltransferase of dengue virus. Among docked compounds, we got two best-predicted compound CID 217476 and CID 71471828 having binding affinity -7.34 kcal/mol and -7.76 kcal/mol with NS5-methyltransferase. This predicted compound was evaluated by preADMET tool for ADME-toxicity properties. Predicted compounds had good result in oral administration. HIA value of compounds belongs in the range of well-absorbed compounds. PCaCO2 value of compounds belongs in standard range. Skin permeability of compound had negative value and strongly binds to plasma proteins. The Ames test result predicted that compound was mutagenic and carcinogenicity showed that compound had positive value in mouse and negative value in rat.

Keywords: Quinacrine derivatives; NS5-methyltransferase; Dengue virus; ADME/Tox.

INTRODUCTION

Dengue virus is flavivirus place with the family flaviviridae and is transmitted to people by Aedes mosquitoes, mainly Aedes aegypti. Four serotypes DENV-1, DENV-2, DENV-3 and DENV-4 were identified based on neutralization assay data. DENV infection is a noteworthy reason for disease in tropical and subtropical regions, with a reported 50 million infections happening every year and more than 2.5 billion individuals being at danger of contamination (Guha-Sapir and Schimmer, 2005). It has been assessed that there are 50–100 million instances of dengue fever and 3.6 billion individuals are in danger of disease (Ng, 2012). It is rising and re-developing in the tropics and as of now represents the most huge arboviral risk to people. What was before an infection with low assault rates, moderate pathogenicity, and rare pandemics has moved toward becoming, over the most recent two decades, the main arboviral reason for disease and demise in people (Gubler, 2006). The recurrence of dengue flare-ups is expanding and spreading, with Asian nations encountering such flare-ups each three to five years (WHO, 2009). Infection with any of the DENV serotypes might be asymptomatic in the greater part of cases or may result in a wide range of clinical side effects (Harris et al., 2000), running from a mellow influenza like disorder known as dengue fever (DF) to the most serious types of the infection, which are described by coagulopathy, expanded vascular delicacy, and permeability (dengue hemorrhagic fever [DHF]). In Asia the danger of creating serious sickness is more prominent in DENV-tainted kids (15 years) than in

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grown-ups (Carlos et al., 2005; Guzman et al., 2002; Kittigul et al., 2007; Nguyen et al., 2004). Interestingly, in the Americas primarily the grown-up populace is influenced, bringing about mellow sickness (Halstead, 2006; Pinheiro and Corber, 1997; Pongsumpun et al., 2002), despite the fact that an expanding pattern of cases advancing toward DHF/DSS has additionally been seen in grown-ups there (Guzman and Kouri, 2003; Pongsumpun et al., 2002).

To reach a molecule in clinical trial of dengue virus, the most probable method was to repurpose FDA approved drugs derivatives. Special priority was given to that Quinacrine antiviral that were shown to be active against flaviviruses. In this study, we have screened Quinacrine derivatives from pubchem compound database and performed molecular docking analysis against NS5-methyltransferase of dengue virus in order to observe the binding affinity of these derivatives. Among these derivatives having minimum binding energy has been considered as the lead drug molecule and their ADME/Tox properties were calculated.

MATERIALS AND METHODS

Protein target structure

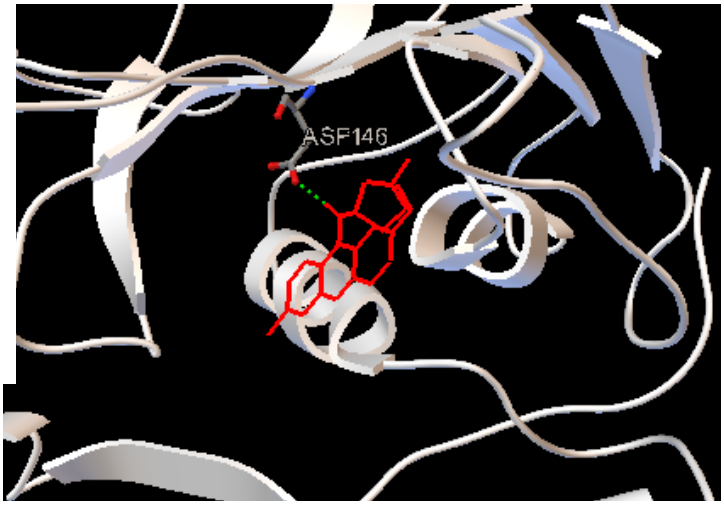
Crystal structure of dengue-2 virus methyltransferase complexed with S-adenosyl-L-homocysteine (PDB Id: 3EVG) was retrieved from Protein Databank (http://www.rcsb.org/). The structure was optimized using the chimera tool **(**Pettersen, 2004).

Inhibitors dataset

Thirty five Quinacrine derivatives screened from

Figure 1: Docking orientation of compound CID 217476 with NS5-methyltransferase. Complex depicting compound formed one H-bond with ASP146 of protein, which is represented by green dotted sphere. ASP146 is represented by sticks and balls and colored by atom type. Compound is represented by red lines.

Figure 2: Docking orientation of compound CID 71471828 with NS5-methyltransferase. Complex depicting compound formed one H-bond with ASP146 of protein, which is represented by green dotted sphere. ASP146 is represented by sticks and balls and colored by atom type. Compound is represented by red lines.



Pubchem compound database (Wang et al., 2010) having similar compounds, score >=95. The 3D structures of these derivatives were downloaded in .sdf format and later converted in .pdb format with the help of open babel (O'Boyle et al., 2011) tool. All the compounds were subjected to energy minimization using the HyperChem software (HyperChem (TM) Release 7.5).

Molecular docking

Molecular docking was performed on thirty five Quinacrine derivatives screened from pubchem compound database against NS5-methyltransferasen of Dengue virus using AutoDock (Morris et al., 2009). Gasteiger charges was given to berberine derivatives using AutoDock tool (http://autodock.scripps.edu/resources/adt). Kollman charges and the solvation term were added to the NS5-methyltransferase structure. Lamarckian genetic algorithm was used in docking calculation.

ADME and Toxicological properties of compound

The predicted derivative was subjected for calculation of Absorption, distribution, metabolism, excretion and toxicological

ADME and Toxicological properties

Best anticipated compound fulfilled the Lipinski guideline of five to assess oral ingestion and was appeared table 2. Predicted compounds CID 217476 and CID 71471828 have human intestinal absorption (HIA) values are 100 and belong to in the range of well absorbed compounds (HIA: 70 ~ 100 %) (Yee, 1997) was shown in table 3. The cell penetrability in vitro Caco-2 is an imperative test to survey intestinal retention of medication compounds. It was discovered that the P_{CaCO2} (nm/s) estimation of compounds were 57.8758 nm/s and 56.4295 nm/s and arranged as low in standard range (P_{CaCO2} >70 nm/sec) (Yazdanian et al., 1998). In vitro in Maden Darby Canine Kidney (MDCK) framework was utilized as an instrument for the fast examination of cell permeability. MDCK estimation of compounds were 0.0450466 nm/s and 128.995 nm/s (table 3). This esteem had bring down MDCK esteem than mean range (Irvine et al., 1999). Predicted compound had negative permeability value was shown in table 3. Skin properties. Physicochemical properties like H-Bond donor count, H-Bond acceptor, molecular weight and XlogP value was calculated for predicted compound. ADME properties like percentage of human intestinal absorption, skin permeability, cell permeability, plasma protein binding, blood brain barrier and toxicological properties like mutagenicity and carcinogenicity were calculated using PreADMET tool (Lee et al., 2003, 2004).

RESULTS AND DISCUSSION

Molecular Docking

Based on R group, Thirty five Quinacrine derivatives were screened from PubChem compound database was shown in table 1. In docking studies of berberine derivatives with NS5-methyltransferase protein, lower binding affinity was used as criteria to select best conformation among 30 generated conformations by AutoDock. Docking result of berberine derivatives with NS5-methyltransferase protein was shown in table 1. Docked complexes were visualized by Python Molecular Viewer (Sanner et al., 1999) software for their interaction studies and best docked confirmation of compound with protein was shown in fig.1 & 2

permeability parameter is utilized in the pharmaceutical industry to evaluate the hazard synthetic products on the off chance that there is accidental contact with skin (Singh and Singh, 1993). The binding of drug to blood and plasma proteins can alter the half-life of the drug in the body of the individual (Godin, 1995; Pratt and Taylor, 1990). The best-predicted compound strongly binds with plasma protein as shown in table 4. Identified derivative CID 217476 was belong to active compound range (blood-brain barrier >1) and compound CID 71471828 belonging to inactive compound range (blood-brain barrier < 1) (Ma et al., 2005). The Ames test (Ames et al., 1972) determined mutagenicity of the compounds. Test predicted compounds mutagen (table 5). Carcinogenicity of compounds showed positive value in mouse and negative in rat was shown in table 5.

CONCLUSION

We got two best predicted compounds CID 217476 and CID 71471828 having lower binding energy -

7.34 kcal/mol and -7.76 kcal/mol with NS5-methyltransferase, respectively. In silico ADME and toxicological properties of predicted compounds showed satisfactory results. Therefore it is predicted that Quinacrine derivatives CID 217476 and CID 71471828 could be promising drug like compounds for NS5-methyltransferase as drug target yet experimental studies have to confirm it.

Table 1: Docking results of quinacrine derivatives against NS5-methyltransferase.

S.No.	PubChem CID	BE	IME	IE	TorE	VdwE	EE
1	217476	-7.34	-9.43	-0.56	2.09	-8.58	0.86
2	10883202	-6.45	-8.54	-0.96	2.09	-806	-0.49
3	71471828	-7.76	-8.65	-0.63	0.89	-7.84	-0.82
4	73892290	-6.17	-9.4	-0.83	2.68	-8.76	-0.64
5	123281369	-6.31	-8.99	-0.77	2.68	-8.77	-0.22
6	123176653	-5.67	-9.25	-0.85	3.58	-9.06	-0.2
7	101758534	-6.66	-9.34	-0.77	2.68	-8.78	-0.56
8	101758533	-5.72	-8.41	-1.92	2.68	-7.83	-0.57
9	87421478	-5.89	-9.17	-1.39	3.28	-8.82	-0.35
10	73892291	-5.53	-8.81	-2.24	3.28	-8.51	-0.3
11	73892289	-5.34	-7.43	-0.7	2.09	-7.89	-0.46
12	73892277	-5.3	-7.39	-0.68	2.09	-6.81	-0.58
13	73892276	-5.04	-7.12	-1.05	2.09	-6.67	-0.45
14	73892275	-4.9	-8.18	-2.0	3.28	-8.1	-0.08
15	71594713	-5.26	-8.55	-2.22	3.28	-8.36	-0.19
16	24897	-6.45	-8.54	-0.96	2.09	-806	-0.49
17	71471955	-4.99	-8.27	-2.81	3.28	-7.96	-0.31
18	71471759	-4.91	-8.19	-1.68	3.28	-7.71	-0.46
19	71471684	-4.55	-7.83	-2.65	3.28	-7.41	-0.42
20	71471620	-4.82	-8.1	-2.58	3.28	-7.99	-0.11
21	71406674	-6.97	-9.06	-1.0	2.09	-8.06	-1.0
22	54039272	-6.77	-8.86	-0.83	2.09	-7.85	-1.01
23	53475643	-6.36	-8.45	-1.1	2.09	-7.82	-0.63
24	53437482	-5.8	-7.88	-0.84	2.09	-7.99	-0.1
25	108129	-6.55	-9.24	-1.03	2.63	-8.92	-0.33
26	44533202	-6.88	-9.26	-1.58	2.39	-9.12	-0.14

27	44531435	-6.3	-8.39	-0.84	2.09	-7.55	-0.84
28	44531431	-6.77	-8.86	-0.83	2.09	-7.85	-1.01
29	21791491	-6.08	-8.47	-1.66	2.39	-8.34	-0.12
30	20650225	-5.06	-7.15	-0.47	2.09	-6.68	-0.47
31	15570035	-5.77	-9.35	-1.51	3.58	-8.71	-0.64
32	15329119	-6.69	-9.38	-0.76	2.68	-8.92	-4.46
33	12207957	-4.9	-8.18	-2.0	3.28	-8.1	-0.08
34	3021136	-6.41	-8.79	-1.41	2.39	-8.81	-0.02
35	623427	-5.34	-7.43	-0.7	2.09	-7.89	-0.46

BE: Binding Energy, IE: Internal Energy, IME: Intermolecular Energy, TorE: Torsional Energy, EE: Electrostatic Energy, VdwE: vdW + Hbond + desolv Energy.

Table 2: Physicochemical properties of best-predicted compounds.

PubChem CID	Molecular Weight (g/mol)	Donor	Acceptor	XLogP
217476	378.297	2	4	4.7
71471828	341.839	1	4	4.3

Table 3: Absorption properties of predicted compounds.

PubChem CID	Absorption			
	HIA (%)	P_{Caco-2} (nm/s)	MDCK (nm/s)	Skin Permeability
217476	100.000000	57.8758	0.0450466	-2.87485
71471828	100.000000	56.4295	128.995	-3.53227

Table 4: Distribution properties of best-predicted compounds.

PubChem CID	Distribution	
	PPB (%)	BBB
217476	84.675328	2.76122
71471828	81.787171	0.224683

Table 5: Toxicological properties of best-predicted compounds.

PubChem CID	Ames Test	Carcinogenicity	
		Mouse	Rat
217476	Mutagen	Positive	Negative
71471828	Mutagen	Positive	Negative

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