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In silico molecular docking and ADME-toxicity studies on Berberine derivatives against NS3 protein of Zika virus

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ABSTRACT

Zika virus causes large epidemics in worldwide. Its infection causes a serious birth defect during pregnancy. In this work, we screened berberine derivatives from PubChem compound database and docked with NS3 protein of Zika virus. Among docked compounds, we got one best-predicted compound CID 52948350 having binding affinity -9.44 kcal/mol with NS3 protein. This predicted compound was evaluated by preADMET tool for ADME-toxicity properties. Predicted compound had good result in oral administration. HIA value of compound belongs in the range of well-absorbed compounds. PCaCO2 value of compound 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 negative value in mouse and positive value in rat.

Keywords: Berberine derivatives; NS3 protein; Zika virus; ADME/Tox.

INTRODUCTION

Zika virus belong to flaviviridae family and categarised in with dengue, West Nile, yellow fever viruses (Kuno et al., 1998). Zika infection was segregated in 1947 from a rhesus monkey in the Zika forest close to Entebbe, Uganda (Simpson, 1964). In 2006, genome of Zika virus was sequenced (Kuno and Chang, 2007). There is serologic proof of human Zika virus infection in Asia and Africa and isolated from people in Nigeria, Uganda and Senegal (Pond, 1963; Smithburn, 1954; Jan et al., 1978; Adekolu-John and Fagbami,1983; Darwish et al., 1983; Monlun et al., 1993; Moore et al., 1975). Zika infection is accepted to be transmitted to people by infected mosquitoes and has been confined from Aedes africanus, Aedes aegypti and Aedes luteocephalus (Gubler et al., 2001; Dick, 1952; Lee and Moore, 1972; Marchette et al., 1969). Fourteen humam infected cases of zika virus was recored till 2007 (Fagbami, 1979; Filipe et al., 1973; Olson et al., 1981). In the month of may 2007, doctors on Yap Island, Federated States of Micronesia, noticed an episode of sickness described by rash, conjunctivitis, fever, arthralgia, and joint pain. Although 3 patients having positive test in dengue IgM kit, the doctors had the feeling that this illness was clinically distinct from past two outbreaks of dengue in Yap Island (Durand et al., 2005; Savage et al., 1998). Centers for Disease Control and Prevention reported 10 cases out of 71 sample of Zika virus in june 2007(Mark et al., 2009).

There is essentially more data on the related flavivirus such as dengue virus, which had computational drug discovery efforts resulted many drug like molecules. To reach a molecule in clinical trial of Zika virus, the most probable method was to repurpose FDA approved drugs derivatives. Special priority was given to that berberine antiviral that were shown to be active against other flaviviruses such as dengue virus, yellow fever, Japanese encephalitis, etc. In this study, we have screened berberine derivatives from pubchem compound database and performed molecular docking analysis against NS3 protein of ZIKV 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

Receptor x-ray structure

Protein target structure

Crystal structure of Unlinked NS2B-NS3 Protease from Zika Virus and its complex with a Reverse

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Peptide Inhibitor (PDB Id: 5GPI) was retrieved from Protein Databank (http://www.rcsb.org/). The structure was optimized using the chimera tool (Pettersen, 2004).

Inhibitors dataset

Twenty Berberine derivatives screened from 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 twenty berberine derivatives screened from pubchem compound database against NS3 protein of Zika 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 NS3 protein 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 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, twenty berberine derivatives were screened from PubChem compound database was shown in table 1. In docking studies of berberine derivatives with NS3 protein, lower binding affinity was used as criteria to select best conformation among 30 generated conformations by AutoDock. Docking result of berberine derivatives with NS3 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. Docked complex depicting compound formed one H-bond with GLN167 of protein, which is represented by green dotted sphere. GLN167 is represented by sticks and balls and colored by atom type. Compound is represented by lines.

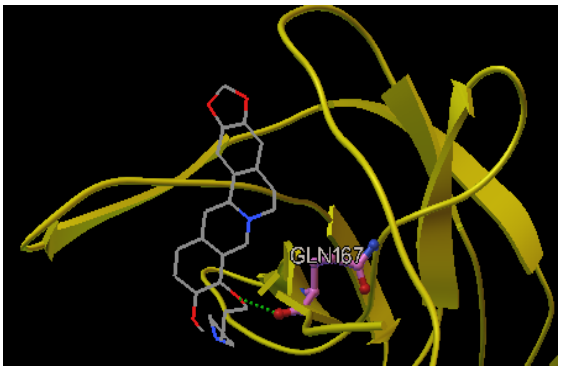


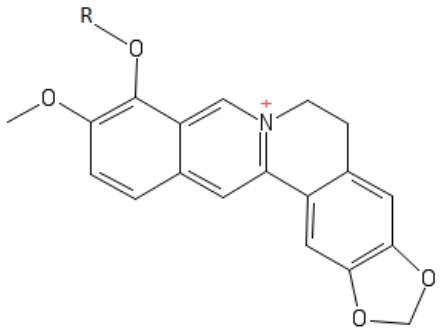
Figure 1: Docking orientation of compound CID 52948350 with NS3 protein.

ADME and Toxicological properties

Best anticipated compound fulfilled the Lipinski guideline of five to assess oral ingestion and was appeared table 2. Predicted compound CID 52948350 had human intestinal absorption (HIA) value 97.822744 and belong to in the range of well absorbed compounds (HIA: 70 ~ 100 %) (Yee, 1997). The cell penetrability in vitro Caco-2 is an imperative test to survey intestinal retention of medication compounds. It was discovered that the PCaCO2 (nm/s) estimation of compound was 56.2101 and arranged as low in standard range (PCaCO2 >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 compound was 0.240294 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 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 was having a place with inactive compound range (blood-brain barrier < 1) (Ma et al., 2005). The

Ames test (Ames et al., 1972) determined mutagenicity of the compounds. Predicted compound was mutagen (table 5). Carcinogenicity of compounds demonstrated negative value in mouse and positive in rat was shown in table 5.

Table 1: Berberine derivatives on the basis of different R group.



Sl.No.	PubChem CID	BE	IME	IE	TorE	VdwE	EE
1	76974413	-7.04	-8.83	-1.15	1.79	-8.74	-0.09
2	71517543	-8.72	-9.91	-0.75	1.19	-9.94	0.03
3	57580945	-8.07	-10.76	-0.82	2.68	-10.56	-0.2
4	57580940	-7.4	-9.19	-1.02	1.79	-9.06	-0.13
5	57580935	-8.72	-9.91	-0.75	1.19	-9.94	0.03
6	52948350	-9.44	-11.23	-0.77	1.79	-11.34	0.1
7	52948173	-8.75	-11.14	-1.01	2.39	-11.11	-0.03
8	52946524	-8.41	-10.2	-0.78	1.79	-10.24	0.04
9	52945895	-7.71	-9.5	-1.78	1.79	-9.5	0.0
10	49865302	-8.53	-9.73	-1.04	1.19	-9.72	0.0
11	49865411	-7.0	-9.68	-2.05	2.68	-8.71	-0.97
12	52942029	-8.64	-9.84	-0.78	1.19	-9.87	0.03
13	44583336	-8.57	-9.77	-0.71	1.19	-9.77	0.0
14	44583270	-7.14	-9.82	-2.7	2.68	-9.73	-0.09
15	44578156	-8.73	-10.22	-0.74	1.49	-10.2	-0.02
16	44578154	-5.84	-8.52	-2.39	2.68	-8.44	-0.08
17	15061309	-8.52	-10.9	-0.96	2.39	-10.9	-0.01
18	15061303	-9.12	-10.32	-0.95	1.19	-10.24	-0.07
19	15061299	-8.35	-10.73	-1.06	2.39	-10.79	0.06
20	10790783	-6.31	-8.1	-1.24	1.79	-8.14	0.04

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 compound.

PubChem CID	Molecular Weight (g/mol)	Donor	Acceptor	XLogP
52948350	433.528	0	5	4.5

Table 3: Absorption properties of predicted compound.

PubChem CID	Absorption			
	HIA (%)	P_{Caco-2} (nm/s)	MDCK (nm/s)	Skin Permeability
52948350	97.822744	56.2101	0.240294	-4.50726

Table 4: Distribution properties of best-predicted compound.

PubChem CID	Distribution	
	PPB (%)	BBB
52948350	17.429351	0.0364227

Table 5: Toxicological properties of best-predicted compound.

PubChem CID		Carcinogenicity	
		Mouse	Rat
52948350	mutagen	negative	positive

CONCLUSION

We got one best-predicted compound CID 52948350 having lower binding energy -9.44 kcal/mol with NS3 protein of Zika virus. In silico, ADME and toxicological properties of predicted compound had satisfactory results. Therefore, it is predicted that berberine derivative CID 52948350 could be promising inhibitor for NS3 protein as drug target yet experimental studies have to confirm it.

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