In Silico analysis of Physicochemical, Pharmacokinetic and Toxicological properties of envelope protein inhibitors of yellow fever virus

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Abstract - Yellow fever is an Aedes aegypti mosquito-borne hemorrhagic disease that is conceivable related with jaundice and is brought about by yellow fever infection. There are no effective antiviral drugs to treat the dangerous malady and repress YFV replication would meet a squeezing medicinal need. Envelope protein of yellow fever virus has an important role in host cell viral infections. In this study, we performed molecular docking analysis of antiviral drug Rivavarin derivative against envelope protein (PDB Id: 6EPK) of YFV using Autodock 4.2 and ArgusLab 4.0.1 having binding energy -6.13 kcal/mol with AutoDock and -6.25 kcal/mol with ArgusLab, respectively. Further, ADME/Tox properties was calculated for Rivavarin derivative using preADMET and SwissADME web tools. Inhibitor showed satisfactory results for oral administration, because it qualifyes Lipinski, Veber and Egan parameters. Blood-brain barrier of inhibitor had penetration values < 1, lower strength in human gastrointestinal absorption and plasma protein binding. Other ADME/Tox properties of proposed inhibitor showed positive and satisfactory results.

Keywords: Rivavarin derivative, yellow fever virus, envelope protein, preADMET, SwissADME

I. INTRODUCTION

Yellow fever is endemic in many areas of South American and African countries. It is estimated that up to 1.7 million yellow fever cases happen in Africa every year, for the most part in West African countries, bringing about in 29,000–60,000 deaths (Monath, 2001). Since late 2016, yellow fever outbreaks have happened in the Southeast area of Brazil, with 792 confirmed cases, including 274 deaths (PAHO/WHO, 2017; Ministério and Saúde, 2017) in around a year. The transmission of YFV happens through the bite of mosquito vectors belonging to different species. Yellow fever is often an acute disease with a range of clinical manifestations, including fever, bradycardia and leukopenia. In 25 to 50% of cases, the acute phase can progress to an intoxication stage characterized by high fever, haemorrhagic syndrome, jaundice and kidney disease, which can be fatal. The patients surviving the acute period enter the convalescence phase, characterized by prolonged weakness and fatigue that can last several weeks (Paules and Fauci, 2017).

To be effective as a drug, a potent molecule must reach its target in the body in sufficient concentration, and stay there in a bioactive form long enough for the expected biologic events to occur. Drug development involves assessment of absorption, distribution, metabolism and excretion (ADME) increasingly earlier in the discovery process. Absorption is the exchange of a medication from its site of organization to the circulation system. Once a medication is consumed into the circulation system it can be conveyed all through the body. This procedure is called distribution. Medications are dispensed with from the body either unaltered through the kidneys and bile, or they may experience compound changes that enable them to be all the more effortlessly discharged. This procedure is called biotransformation or digestion. The total expulsion of the medication from the body is alluded to as end. Preclinical in vivo toxicology considers should be led in Rats and mice for intense and ceaseless presentation.

In this study, Drug development for Yellow fever infection has been in advance in few years. In this study, we docked Rivavarin derivatives with Yellow fever virus envelope protein using AutoDock4.2 and ArgusLab 4.0.1 tools. The docked complexes stability was evaluated by molecular dynamics simulation. In Silico physicochemical, pharmacokinetic and toxicological properties of inhibitors were perfomed by preADMET (Lee et al., 2003, 2004) and SwissADME (Daina et al., 2017) web tools.

II. MATERIALS AND METHODS

Molecular docking

Docking of Rivavarin derivative against envelope protein (PDB Id: 6EPK) structure was done using molecular docking program AutoDock 4.2 (Goodsell and Olson, 1990; Morriset al. 1998) and ArgusLab 4.0.1. During the docking

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procedure a Lamarckian Genetic Algorithm (LGA) were used for flexible ligand rigid protein docking calculation. 2D structure of Rivavarin derivative is shown in figure 1.

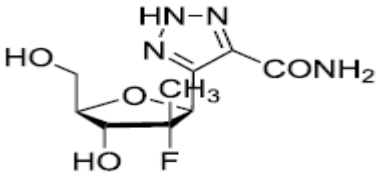

Figure 1: Rivavarin derivative

Physicochemical, Pharmacokinetic and Toxicological Properties of the Inhibitors

The preADMET (Lee et al., 2003, 2004) server calculates parameters such as human intestinal absorption, cellular permeability Caco-2 in vitro, cell permeability Maden Darby Canine Kidney (MDCK), skin permeability, plasma protein binding, and penetration of the blood brain barrier, carcinogenicity and mutagenicity. SwissADME compute physicochemical descriptors as well as to predict ADME parameters, pharmacokinetic properties and druglike nature of small molecules to support drug discovery.

III. RESULTS AND DISCUSSION

Molecular Docking

Optimal interactions and the best score were used as criteria to interpret the best conformation among the conformations generated by AutoDock and ArgusLab tools. Both docking programs showed almost similar results as shown in table 1.

Table 1: Binding energy of Rivavarin derivative with envelope protein resulted by AutoDock 4.2 and ArgusLab 4.0.1.

Sl. No.	Derivative	Binding Energy (Kcal/mol)	Binding Energy (Kcal/mol)
1	Rivavarin	-6.13	-6.25

Physicochemical, Pharmacokinetic and Toxicological Properties of compound

Inhibitor in SMILES format was entered in the online SwissADME (Daina et al., 2017) web tool for generating physicochemical parameters such as molecular weight, the number of heavy atoms, the number of aromatic heavy atoms, the fraction of carbon bond saturation (Csp3), number of rotatable bonds, the number of H-bond acceptors, the number of H-bond donors, Molar Refractivity and TPSA. Drugs entering the brain typically have a TPSA value of less than 60–70 $Å^2$ (Kelder et al., 1999). Inhibitor had TPSA >70 $Å^2$. Druglikeness of inhibitor was accessed by five different rule-based filters such as Lipinski (Lipinski et al., 2001) filter implemented rule-of-five, Ghose (Ghose et al., 1999), Veber (Veber et al., 2002), Egan (Egan et al., 2000) and Muegge (Muegge et al., 2001) methods, respectively. In analyzing the parameters of inhibitor, we observed that all had values within Lipinski, Veber and Egan parameters, as shown in table 2 & 3.

Table 2: Physicochemical Properties of inhibitor

Physicochemical Parameter	Ribavirin derivative
Molecular weight	262.24 g/mol
Num. heavy atoms	18
Num. arom. heavy atoms	0
Fraction Csp3	0.67
Num. rotatable bonds	3
Num. H-bond acceptors	6
Num. H-bond donors	6
Molar Refractivity	67.23
TPSA	128.87 $Å^2$

Table 3: Druglikeness of inhibitors.

Parameters	Ribavirin derivative
Lipinski	Yes; 1 violation: NHorOH>5
Ghose	No; 1 violation: WLOGP<-0.4
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: H-don>5
Bioavailability Score	0.55

The SwissADME predictions for passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeation both consist in the readout of the BOILED-Egg model (Butina et al., 2002) as shown in table 4. Human gastrointestinal absorption (HIA) properties are determinant for the drug development that purports to be administered orally. Analyzing the ADME tests of inhibitor using preADMET, it was observed that the compound presented low human gastrointestinal absorption (HIA) 24.276018 as shown in table 5. Caco-2 cell model and MDCK cell model has been recommended as a reliable *in vitro* model for the prediction of oral drug absorption (Yamashita et al., 2000). Inhibitor calculated, it was found that the P_{CaCO2} (nm/s) was low permeability has 20.0785 nm/s, standard range is (P_{CaCO2} >70 nm/sec) (Yazdanian et al., 1998). The cell permeability in vitro in MDCK system is used as a tool for the rapid analysis of permeability (Irvine et al., 1999). Analyzing the data in this MDCK system in the inhibitor shown in table 5, it is found that the permeability has low value is 0.577284 nm/s.

Table 4: Pharmacokinetics of compounds using SwissADME.

Parameters	Ribavirin derivative
GI absorption	Low
BBB permeant	No
Log K_p (skin permeation)	-8.19 cm/s

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Table 5: Absorption properties of compound using preADMET.

Derivative	Absorption			
	HIA (%)	P_{Caco-2} (nm/sec)	MDCK(nm/sec)	Skin Permeability
Ribavirin derivative	24.276018	20.0785	0.577284	-5.55162

The skin permeability is used in the pharmaceutical industry to assess the risk chemical products in case there is accidental contact with skin (Singh and Singh, 1993). Proposed inhibitor showed negative permeability values as shown in table 4 & 5. The binding to plasma proteins can alter the half-life of the drug in the body of the individual (Godin, 1995; Pratt and Taylor, 1990). According to table 6 calculated inhibitor binded loosly to plasma proteins. Inhibitors analyzed showed had BBB values <1. The Ames test (Ames et al., 1972) assesses mutagenicity of the Inhibitors as shown in table 6. Inhibitor showed positive prediction as a mutagen. Carcinogenicity is a toxicity that causes cancer in body. When analyzing carcinogenicity in mice and rat the inhibitor was predicted as negative and positive, respectivey as shown in table 6.

Table 6: Distribution properties in percentages of PPB, penetration of the blood brain barrier, toxicological properties of mutagenicity (Ames test) and carcinogenicity (mouse and rat) of Ribavirin derivative using preADMET.

Derivative	Distribution		Carcinogenicity		Ames Test
	PPB (%)	BBB	Mouse	Rat	
Ribavirin derivative	4.502663	0.0419196	Negative	positive	mutagen

SwissADME predict Lipophilicity of compound based on five predictive models, such as XLOGP3 (Cheng et al., 2007), WLOGP (Wildman and Crippen, 1999), MLOGP (Moriguchi et al., 1992, 1994), SILICOS-IT, an hybrid method relying on 27 fragments and 7 topological descriptors and finally iLOGP, our in-house physics-based method relying on free energies of solvation in n-octanol and water calculated by the Generalized-Born and solvent accessible surface area (GB/SA) model. The consensus log Po/w is the arithmetic mean of the values predicted by the five proposed methods. Lipophilicity and Water Solubility of both compounds were shown in table 7 & 8.

Table 7: Lipophilicity of compound.

Parameter	Ribavirin derivative
Log $P_{o/w}$ (iLOGP)	0.21
Log $P_{o/w}$ (XLOGP3)	-0.41
Log $P_{o/w}$ (WLOGP)	-3.58
Log $P_{o/w}$ (MLOGP)	-1.81
Log $P_{o/w}$ (SILICOS-IT)	-1.95
Consensus Log $P_{o/w}$	-1.51

SwissADME predict water solubility of compounds based on two topological methods as ESOL model (Delaney, 2004) and second one was adapted from Ali et al. (Ali et al., 2012). SwissADME third predictor for solubility was developed by SILICOS-IT.

Table 8: Water Solubility of compound.

Parameters	Ribavirin derivative
Log *S* (ESOL)	-1.01
Solubility	2.57e+01 mg/ml ; 9.78e-02 mol/l
Class	Very soluble
Log S (SILICOS-IT)	-1.83
Solubility	3.86e+00 mg/ml ; 1.47e-02 mol/l
Class	Very soluble
Log *S* (SILICOS-IT)	-0.22
Solubility	1.59e+02 mg/ml ; 6.05e-01 mol/l
Class	Soluble

IV. CONCLUSION

Ribavirin derivative had binding energy -6.13 kcal/mol with AutoDock and -6.25 kcal/mol with ArgusLab, respectivley. Both the docking tool predicts almost same binding energy. Optimizatin of docked protein - inhibitor complexe shows its stability. Physicochemical, Pharmacokinetic and Toxicological properties of proposed Ribavirin derivative of envelope protein of yellow fever virus showed satisfactory results for oral administration, since they quaify the Lipinski, Veber and Egan parameters. It was observed that the compound presented low human gastrointestinal absorption and low permeability as P_{CaCO2} and MDCK system. Predicted inhibitors had negative skin permeability and low BBB value. The Ames test assessed that inhibitor had positive prediction as a mutagen. On analyzing carcinogenicity in mice and rat, inhibitors had Negative and positive prediction, respectivey. Predicted lipophilicity and water solubility of inhibitor showed satisfactory results.

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