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POTENTIAL DRUG BIS (2-ETHYLHEXYL) PHTHALATE TARGET THROUGH DOCKING ANALYSIS OF THE PROTEIN N-MYRISTORYLTRANSFERASE (PDB ID: 4BBH) OF PLASMODIUM VIVAX

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ABSTRACT

Malaria is a debilitating disease transmitted by mosquitoes and caused by protozoa of the genus Plasmodium. The disease is most commonly transmitted by an infected female Anopheles mosquito. The mosquito bite introduces the parasites from the mosquito's saliva into a person's blood. The parasites travel to the liver where they mature and reproduce. Chemical validation of new ant malarial targets is recently required in view of rising resistance to current drugs. The target receptor enzyme N-myristoyltransferase of *Plasmodium vivax*, which catalyzes **N**-myristoylation of protein substrates by the drug molecule, Bis (2ethylhexyl) phthalate. This work was aimed at the components obtained from the GC-MS analysis of *Kalancho epinnata* leaf extract and it act as lig and to bind with receptor protein molecules of malarial parasite. The docking simulation of compound is active on the active site of the *Plasmodium vivax* has been analysed. The result is suggested to found that phytochemical Bis (2 ethylhexyl) phthalate works more efficiently against the receptor protein of P. vivax. The screened inhibitors are effective and showed optimal binding affinity to the binding receptor of P.vivax. Its molecular properties and its binding affinity make it acceptable as a potential therapeutic against malaria.

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INTRODUCTION

Malaria is a mosquito-borne infectious disease affecting humans and other animals caused by parasitic protozoans belonging to the *Plasmodium* type (Caraballo, 2014). Malaria causes symptoms that typically include fever, feeling tired, vomiting, and headaches. In severe cases it can cause yellow skin, seizures, coma, or death (WHO, 2014). Symptoms usually begin ten to fifteen days after being bitten. If not properly treated, people may have recurrences of the disease months later. In those who have recently survived an infection, reinfection usually causes milder symptoms.

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This partial resistance disappears over months to years if the person has no continuing exposure to malaria. The disease is most commonly transmitted by an infected female *Anopheles* mosquito. The mosquito bite introduces the parasites from the mosquito's saliva into a person's blood (Caraballo, 2014). The parasites travel to the liver where they mature and reproduce. Five species of *Plasmodium* can infect and be spread by humans (WHO, 2014). Most deaths are caused by *P. falciparum* because *P. vivax*, *P. ovale*, and *P. malariae* generally cause a milder form of malaria (Caraballo, 2014). The signs and symptoms of malaria typically begin 8–25 days following infection (Fairhurst, 2010). However, symptoms may occur later in those who have taken antimalarial medications as prevention (Nadjm, 2012). Initial manifestations of the disease—common to all malaria species—are similar to flu-like symptoms (Bartoloni, 2012) and can resemble other conditions such

as sepsis, gastroenteritis, and viraldiseases (Beare *et al*., 2016). The presentation may include headache, fever, shivering, joint pain, vomiting, hemolytic anemia, jaundice, hemoglobin in the urine, retinal damage, and convulsions (Collins, 2009). Anopheles (Angus Stevenson, 2010) is a genus of mosquito first described and named by J. W. Meigen in 1818 (Meigen, 1818). About 460 species are recognized; while over 100 can transmit human malaria, only 30–40 commonly transmit parasites of the genus *Plasmodium*, which cause malaria in humans in endemic areas. *Anopheles gambiae* is one of the best known, because of its predominant role in the transmission of the most dangerous malaria parasite species (to humans) – *Plasmodium falciparum*. Some species of *Anopheles* also can serve as the vectors for canine heartworm *Dirofilariaimmitis*, the filariasis-causing species *Wuchereriabancrofti* and *Brugiamalayi*, and viruses such as one that causes fever. An association of brain tumor incidence and malaria suggests the *Anopheles* might transmit a virus or other agent that could cause a brain tumor (Steven, 2010).

Malaria parasites belong to the genus *Plasmodium* (phylum Apicomplexa). In humans, malaria is caused by *P. falciparum*, *P. malariae*, *P. ovale*, *P. vivax* and *P. knowlesi* (Mueller, 2007; Collins, 2012). Among those infected, *P. falciparum* is the most common species identified (~75%) followed by *P. vivax* (~20%) (Biswas, 2011). Although *P. falciparum* traditionally accounts for the majority of deaths[20], recent evidence suggests that *P. vivax* malaria is associated with potentially life-threatening conditions about as often as with a diagnosis of *P. falciparum* infection[9]. *P. vivax* proportionally is more common outside Africa (Baird, 2013). There have been documented human infections with several species of *Plasmodium* from higher apes; however, except for *P. knowlesi*—a zoonotic species that causes malaria in macaques (Okwu, 2011)—these are mostly of limited public health importance (Arnott *et al*., 2012). *Plasmodium vivax* is a protozoan parasite and a human pathogen. The most frequent and widely distributed cause of recurring (Benign tertian) malaria, *P. vivax* is one of the five species of malaria parasites that commonly infect humans (White *et al*., 2008). It is less virulent than *Plasmodium falciparum*, the deadliest of the five, but vivax malaria can lead to severe disease and death due to splenomegaly (a pathologically enlarged spleen (Baird, 2007). *P.vivax* is carried by the female *Anopheles* mosquito, since it is only the female of the species that bites (Anstey *et al*., 2012). In the present study molecular docking studies were performed using secondary metabolites selected from the plants *Kolanchoe pinnata* against the N-myristoyltransterase protein of plasmodium vivax.

MATERIALS AND METHODS

SELECTION OF CANDIDATE PLANT

The computational prediction of potential candidate by the process of molecular docking, the important phytochemicals of the plant *kalanchoe pinnata*. Such as Bis (2-ethylhexyl) phthalate and Triacontanewere related from ethyl acetate extract of plant leaf by using GC-MS analysis.

MOLECULAR DOCKING

This work was aimed at the components obtained from the GC-MS analysis of *Kolanchoepinnata* it act as ligand (drug molecule) and bind with receptor protein molecules of malarial parasites. The docking simulation of compound is active on the activesite of the plasmodium vivax has been analysed. Molecular docking is a well-established computational technique which predicts the interaction energy between two molecules. This technique mainly incorporates algorithms like molecular dynamics, Monte Carlo stimulation and fragment based search. Molecular docking studies are used to determine the interaction of two molecules and to find the best orientation of ligand which would form a complex with overall minimum energy. The small molecule, known as ligand usually fits within proteins cavity which is predicted by the search algorithm. These protein cavities become active when they come in contact with any external compounds and are thus called as active sites. Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational drug design. Given the biological and pharmaceuticals significance of molecular docking, considerable efforts have been directed towards improving the methods used to predict docking.

Molecular docking studies

Preparation of Protein Structure

The crystal structure of Plasmodium vivax N-myristoyltransferase (PDB ID: 4BBH), was recovered from the Protein Data Bank (www.rcsb.org/pdb) (Mark *et al*., 2013). After selected the protein structure, The all unwanted water molecules were removed from the protein structure, hydrogen atoms were added and metal were treated, all atom force field (OPLS-2005) charges and atom types were assigned. Protein structure energy was minimized until the average root mean square deviations of non-hydrogen atoms reached 0.3Å (Ligprep, 2013).

Preparation of Ligand

The compound structure was not present in pubchem database so we use chemsketch to draw the chemical structure and save in the mol file format. All the chemical compounds structures were prepared for insilico docking studies using ligprep version 2.3 (Taylor *et al*., 2002). The chemical compounds structure energy was minimized, partial atomic charges were computed using the OPLS-2005 force field by using Schrödinger suite.

Active Site Prediction

The crystal structure of Plasmodium vivax N-myristoyltransferase (PDB ID: 4BBH) was retrieved from protein data bank. The c-crystal ligand benzothiophene inhibitor was indentified. Active site residues: phe 30, trp 31, tyr 95, val 96, val 160, leu 163, val 165, leu 202, arg 173, ala 175, ser 171, ile 179, ala 194, tyr 196, tyr 183.

Molecular docking protocol

All the synthesized molecules (3a-g) with Plasmodium vivax N-myristoyltransferase (PDB ID: 4BBH), the molecular docking studies were performed using the schrodinger 9.5

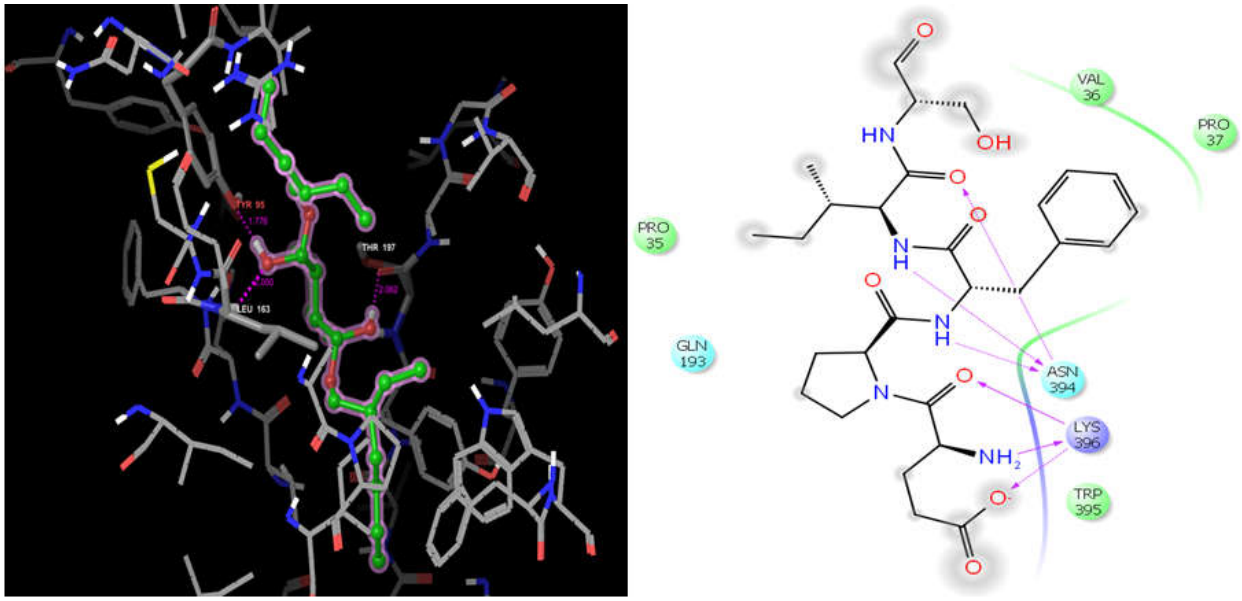

Figure 1: this figure show that target structure of target protein Plasmodium vivax N-myristoyltransferase and drug compound Bis(2-ethylhexyl)phthalate

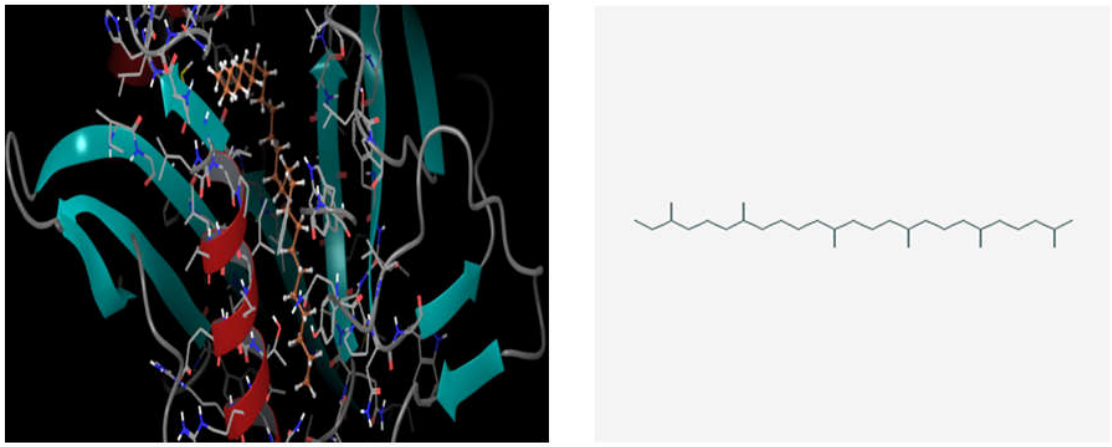

Figure 2: this figure show that target structure of target protein Plasmodium vivax N-myristoyltransferase and drug compound Triacontane

software (Glide, 2013; Thomayant Prueksaritanont, 2012). To analyze the docking results and execute the protocol, the maestro users inter face was employed and the validating of the protocol was evaluated by redocking. Glide grid generation wizard has been used to define the docking space. Docking was performed using XP docking protocol. The ADME properties were carried out using Qikprop 3.7 (Qikprop, 2013; Lipinski, 1997).

RESULTS AND DISCUSSION

Molecular docking studies

Binding mode of compound Bis(2-ethylhexyl) phthalate into Plasmodiumvivax N-myristoyltransferase. Docking simulation of compound Bis (2-ethylhexyl) phthalatewithin the active site of the Plasmodium vivax N-myristoyltransferase has been analyzed. The Glide Score and Glide Energy value for compound Bis(2-ethylhexyl) phthalate were observed -10.7294Kcal/mol and -42.130Kcal/mol. Upon the examination of docking features between compound Bis(2-ethylhexyl) phthalate and Plasmodium vivax N-myristoyltransferase it was found only six hydrogen bond interactions. the hydrogen atom of the compound Bis (2-ethylhexyl) phthalate was well interacted with side chain oxygen atom of the polar residue of ASN 394. The side chain hydrogen atom of the polar residue of ASN 394 were strongly interacted with oxygen atom of the compound Bis(2-ethylhexyl) phthalate, backbone oxygen atom of the positive charged residue of LYS 396 were interacted with oxygen atom of the compound Bis(2-ethylhexyl) phthalate, hydrogen atom of the compound one were well interacted with backbone oxygen atom of the positive charged residue of LYS 96, side chain hydrogen atom of the positive charged residue of LYS 396 were interacted with oxygen atom of the compound Bis(2-ethylhexyl) phthalate. Furthermore VAL 36, PRO 37, TRP 395, PRP 35 a number of hydrophobic interactions were bound between compounds bis(2-ethylhexyl) phthalateinto Plasmodium vivax N-myristoyltransferase. Binding mode of compound Triacontaneinto *Plasmodium vivax* N-myristoyltransferase. Docking simulation of compound Triacontane within the active site of the Plasmodium vivax N-myristoyltransferase has been analyzed. The Glide Score and Glide Energy value for compound Triacontane were observed -6.421Kcal/mol and-32.152Kcal/mol.

Table 1. Glide Extra-precision (XP) Results for the Bis (2-ethylhexyl) phthalate, Pentacosane, by use of Schrodinger9.5.

Compound Name	Glide Score	Glide Energy	No of H bond interactions	Interacting Residue	Distance Å)
Bis (2-ethylhexyl) phthalate	-10.729	-42.130	6	LYS (3), ASN (3) TYR 95 THR 197 LEU 163	- 1.776 2.050 2.062
Triacontane	-6.421	-32. LYS (3) ASN (3) 152	-	-	-

Table 2: Qikprop properties of the with analoide molecule, by use of Schrodinger 9.5.

Compound	MW	HBD	HBA	QPLog Po/w	PMDCK	QPPCaco2	QPHERG	QPBB	%of human oral absorption
Bis(2ethylhexyl) Phthalate	400.641	2	6.8	5.617	1831	3357	-5.466	-1.098	100
Triacontane	436.847	0	0	15.46	5899	9906	-6.413	2.333	100

There is no hydrogen bond interaction was found between compound Triacontane with *Plasmodium vivax* N-myristoyltransferase. LYS (3) ASN (3)

ADME properties Prediction

We analyzed 44 physically significant descriptor and pharmaceutically relevant properties of Bis (2-ethylhexyl) phthalate, Pentacosane, among which were molecular weight, hydrogen bond donors, hydrogen bond acceptors, log p, log p , Human absorption according to Lipinski rule of five. Lipinski rule of five evaluate if a chemical compound having a pharmacological properties that would make it orally active drug for human. The compound was further evaluated by pharmacokinetic properties required for absorption, distribution, metabolism, excretion by using Qikprop. Like aqueous solubility, cell permeability QPPCaco2, QPPMDCK, HERG, Blood Brain Barrier. All the compounds are under acceptable range with predicted ADME properties were depicted in Table 2.

- Solute Molecular Weight = (130.0 / 725.0)
- Solute as Donor - Hydrogen Bonds = (0.0 / 6.0)
- Solute as Acceptor - Hydrogen Bonds = (2.0 / 20.0)
- QP log P for octanol/water = (-2.0 / 6.5)
- QP log Khsa Serum Protein Binding = (-1.5 / 1.5)
- Apparent MDCK Permeability (nm/sec) = (<25 poor, >500 great)
- Apparent Caco-2 Permeability (nm/sec) = (<25 poor, >500 great)
- HERG K+ Channel Blockage: log IC50 = (concern below -5)
- QP log BB for brain/blood = (-3.0 / 1.2)
- % Human Oral Absorption in GI (+-20%) = (<25% is poor).

Conclusion

The current study deals with computational analysis compound against P. vivax receptor (N-myristoyltransferase. From this study, it was found that phytochemical Bis (2ethylhexyl) phthalateworks more efficiently against the receptor protein of P.vivax. The screened inhibitors are effective and showed optimal binding affinity to the binding receptor P.vivax.

Its molecular properties and its binding affinity make it acceptable as a potential the rauptic against malaria.

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