

Original Research Article

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Search for Selective and Novel Inhibitors of N-Myristoyl Transferase-Pharmacophore Modeling, Atom-Based 3D QSAR and Virtual Screening Approaches in Antimalarial Drug Discovery

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ABSTRACT

Malaria is one of the killer diseases posing serious threat across the globe. Managing malaria has become a big challenge due to the drug resistance. Now considering the global trend, there is an immense need to discover novel antimalarial drug. There is variety of routes available, in that especially, computer aided molecular drug discovery is one of the successful emerging platform to develop drug molecules. Vivax malaria is the one area which is not addressed in depth at the global level due to the lack of attention towards the severity and relapse patterns of the disease. N- Myristoyl transferase is one of the iconic molecular drug targets in protozoans and also recently validated as significant target for *Plasmodium vivax*. Nucleus of the study is to discover obvious and selective NMT inhibitor by constructing a pharmacophore model, atom based 3D-QSAR using thirty two known NMT small molecule inhibitors. Our effort was to construct a five point pharmacophore model with three hydrogen bond acceptor (A), one hydrophobic group (H), and one aromatic ring (R) so that they are more biologically responsive. Followed by that, attempt to build robust 3D-QSAR model yielded significant values such as regression R² (0.9311) and correlation co-efficient Q² (0.7909) which further highlights that we have identified the best -in -class QSAR model. Resultant best model was employed as a 3D query to screen against large chemical database, Zinc in order to find new scaffolds. Docking studies of the newly identified scaffolds revealed five new hit molecules possessing unique ability to interact with NMT. It further warrants that the identified molecules could be taken further to assess its efficacy under *in vitro* and *in vivo* conditions. Above all, this study may serve as a new horizon in the antimalarial drug discovery.

Keywords

Malaria, *Plasmodium vivax*, N-myristoyl transferase, Pharmacophore modeling, QSAR, Antimalarial drug discovery

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Introduction

Malaria is still an unresolved problem from the historical period and exists as a devastating issue in tropical developing countries with malaria cases more than 200 million and more than 600,000 deaths each year (Murray *et al.*, 2012; World Health Organization, 2012; Hay *et al.*, 2010). Approximately 40% of the total population of the world is at risk of getting malaria through mosquito bite and several other factors (Gething *et al.*, 2011; Guerra *et al.*, 2010; Battle *et al.*, 2012; Gething *et al.*, 2012). *Plasmodium vivax* has an extensive geographical distribution with an estimated 2.5 billion number of human beings are at risk (Gething *et al.*, 2011). India is a major contributing nation to the worldwide burden of *P. vivax*. Vivax malaria makes up the majority of cases in India, with 45% of cases being caused by *P. falciparum* (www.nvbdc.gov.in). The persistence of vivax malaria in the Indian subcontinent could be owing to several factors, such as the poor economy that encourages population migration between major cities and endemic areas, or the presence of various *P. vivax* 'strains' that differ in the basis of their relapse pattern or drug response. In addition, the harsher weather and terrain in certain areas all favor the continued presence of the more robust species (Gogtay *et al.*, 1999).

Chloroquine (CQ) is the first line antimalarial drug for the treatment of *P. vivax* in India, however there are some few places parasite clearance rate is very low and subsequent resistance was reported (Dua *et al.*, 1996; Garg *et al.*, 1995; Kshirsagar *et al.*, 2000) and also high relapse rate of 40% has been observed (Srivastava *et al.*, 1996). Other drugs such as primaquine and sulphadoxine-pyrimethamine are also resistant to Pv in India (Hema Joshi *et al.*, 2008). Now days the severity and relapse trend of vivax malaria is

considerably increasing. Just recently severe *Plasmodium vivax* cases have been recorded from Bikaner in North-western India and relapse pattern of vivax malaria has been found in Delhi, India (Dhanpat *et al.*, 2009; Adak *et al.*, 1998). Development of multi drug resistance in India demands the need to design a highly selective antimalarial with desired pharmaceutical traits.

N-myristoyltransferase (NMT, EC 2.3.1.97) catalyses transfer of the lipid myristate (C14:0) from myristoyl coenzyme A (Myr-CoA) to specific substrate proteins in eukaryotes (Wright *et al.*, 2009) and it has been discovered preclinically as a molecular target in fungal (Ebiike *et al.*, 2002) and trypanosome infections (Frearson *et al.*, 2010), and more over suggested as a potential target in malaria and leishmaniasis. N-myristoylation regulates membrane localization and protein complex assembly in eukaryotes, and selective inhibition of NMT is hypothesized to lead to pleiotropic effects on the parasite through multiple downstream substrates. It is the recently identified and emerged as druggable target in the symptomatic blood stage of the most important human malaria parasite. NMT inhibition results in a catastrophic and irreversible failure to form critical parasite subcellular structures, followed by rapid parasite cell death (Tate *et al.*, 2014; Wright *et al.*, 2014).

Application of computational tools in drug discovery and development process has become enormously significant and it is rapidly gaining in popularity and implementation (Kapetanovic, 2008). They have dramatically revolutionized the way in which we approach drug discovery and leading to the explosive growth in the field of medicinal chemistry (Yan *et al.*, 2009).

Pharmacophore approaches have become one of the foremost tools in drug discovery after

the past century's development and many successful stories of pharmacophore approaches in facilitating drug discovery have been reported in recent years (Kubinyi, 2006; Mustata *et al.*, 2009). QSAR is a top notch computational method to quantify the association between the chemical structures of a series of compounds and a particular chemical or biological process. The fundamental theory behind QSAR method is that similar structural or physiochemical properties yield similar activity (Kamatsu, 2002; Verma *et al.*, 2009).

This whole work is to make use of the validated drug target N-myristoyl transferase to engage that with contemporary computational tools such as pharmacophore modeling, 3D QSAR and virtual screening to identify promising molecules retaining features to become an antimalarial drug.

Materials and Methods

Protein

The PDB is a key resource in areas of structural biology, such as structural genomics. Most major scientific journals, and some funding agencies, such as the NIH in the USA, now require scientists to submit their structure data to the PDB. Three dimensional crystal structure of *Plasmodium vivax* N-myristoyltransferase in complex with a benzothiophene inhibitor (compound 34a) was obtained and saved in pdb format. This would act as the receptor target for performing the docking analysis.

Ligands

ACD/Chemdraw freeware is a drawing package that allows us to draw chemical structures including organics, organometallics, polymers, and markush structures. It also includes features such as calculation of

molecular properties (e.g., molecular weight, density, molar refractivity etc.), 2D and 3D structure cleaning and viewing, functionality for naming structures (fewer than 50 atoms and 3 rings), and prediction of logP. Thirty two ligand molecules were exacted from the literature (Mark *et al.*) and drawn using Chemdraw (<http://www.cambridgesoft.com>).

Database

The ZINC Database contains commercially available compounds for structure based virtual screening. It currently has about 21 million compounds that can simply be purchased. It is provided in ready-to-dock, 3D formats with molecules represented in biologically relevant forms. It is available in subsets for general screening as well as target, chemotype- and vendor-focused subsets. ZINC is non-commercialised and can be downloaded at the website zinc.docking.org. Ten lakh lead like small molecules were downloaded from Zinc database and they are used for pharmacophore based virtual screening to find the good scaffolds.

Schrodinger

Maestro is Schrödinger's powerful, united, multi-platform graphical user interface (GUI). It is designed to simplify modeling tasks, such as molecule building and data analysis, and also to facilitate the set up and submission of jobs to Schrödinger's computational programs.

Pharmacophore modeling and 3D QSAR

(PHASE, 2013) is a versatile product for pharmacophore perception, structure alignment, activity prediction, and 3D database searching. PHASE provides support for lead discovery, SAR development, lead optimization, and lead expansion. Using PHASE, a best pharmacophore hypothesis

having pharmacophore feature, three hydrogen bond acceptor (A), one hydrophobic group (H), and one aromatic ring (R) was identified.

The 3D-QSAR studies were carried out using PHASE version 3. Atom-based QSAR models were generated for the selected hypothesis using the 25-member training set using a grid spacing of 1.0 Å. The best QSAR model was validated by predicting activities of the 7 test set compounds. A three component (PLS factor) model with good statistics was obtained for the dataset.

Pharmacophore based virtual screening

Once a pharmacophore model is generated by either the ligand based or the structure-based approach, it can be used for querying the 3D chemical database to search for potential ligands, which is so-called 'pharmacophore-based virtual screening' (VS). This is done using "find matches to hypothesis" in the PHASE module. The best resultant QSAR model was screened against the 10, 00,000 compounds from Zinc database for obtaining the similar scaffold and that would serve as the input for the molecular docking studies.

Molecular docking analysis

Molecular docking has become an increasingly important tool for drug discovery. The goal of ligand—protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure. Successful docking methods search high-dimensional spaces effectively and use a scoring function that correctly ranks candidate dockings. Docking can be used to perform virtual screening on large libraries of compounds, rank the results, and propose structural hypotheses of how the ligands inhibit the target, which is invaluable in lead optimization (Garrett *et al.*, 2008). Molecular docking analysis was carried out

after removing the co-crystal ligand from the crystal structure of protein target. In this study, Glide (Zhao, 2007; Glide, 2013) embedded in the Schrodinger is used to carry out the docking analysis.

Preparation of protein

The preparation of a protein involves a number of steps. The procedure assumes that the initial protein structure is in PDB-format file, includes a co-crystallized ligand, and does not include explicit hydrogens. The result is refined, hydrogenated structures of the ligand is used for further applications in Schrodinger module. Protein Preparation Wizard (Protein preparation Wizard Maestro, 2013) is used to prepare the protein.

Grid generation and ligand docking

Grid files represent physical properties of a volume of the receptor (specifically the active site) that are searched when attempting to dock a ligand. In the given workspace, prepared ligands are docked into the generated grid over the receptor surface. In the glide module, XP method is followed to filter the ligands.

Pharmacodynamics and kinetics study of hit molecules

QikProp

(QikProp, 2013) is a quick, accurate, easy-to-use absorption, distribution, metabolism, and excretion (ADME) prediction program designed by Professor William L. Jorgensen. QikProp predicts physically significant descriptors and pharmaceutically relevant properties of organic molecules, either individually or in batches. In addition to predicting molecular properties, QikProp provides ranges for comparing a particular molecule's properties with those of 95% of

known drugs. QikProp also flags 30 types of reactive functional groups that may cause false positives in high-throughput screening (HTS) assays. Finally, identified hit molecules were checked for its efficacy to predict the pharmacodynamics properties.

Results and Discussion

Pharmacophore model

To find the common pharmacophore hypothesis, for the energy minimized NMT inhibitors were imported into PHASE and these molecules were divided into active and inactive molecules (Fig. 1–4). NMT inhibitors with pIC_{50} value higher than 8.500 were considered as active and pIC_{50} value less than 6.000 were considered as inactive respectively. The top pharmacophore model were found to be associated with the five point pharmacophore hypotheses containing three hydrogen bond acceptor (A), one hydrophobic group (H), and one aromatic ring (R) and was donated as AAAHR. The distance between the pharmacophoric sites was reported in figure 5. Angle between the pharmacophoric sites is shown in figure 6. The alignment of training set molecules with best common pharmacophore hypotheses were depicted in figure 7. Statistically significant 3D-QSAR models were generated using PLS factor based on the training set compounds by validated with test set compounds. The training set correlation is characterized by PLS factors ($R^2=0.9311$, $SD=0.2275$, $F=94.6$, $P=2.30.7e-012$). The test set correlation is characterized by PLS factors ($Q^2=0.7907$, $RMSE=0.1645$, $Pearson-R=0.9013$). The results of PLS statistical of atom-based 3D-QSAR are shown in Table 1.

Atom-based 3D-QSAR models

Additional insights into the inhibitory activity can be gained by visualizing the 3D-QSAR model in the context of one or more ligands in

the series with diverse activity. The contour maps were obtained from atom-based 3D-QSAR. The atom based 3D-QSAR with combined effect of hydrogen bond donor and electron-withdrawing were considered in this study.

Figure 8a and 8b represents the hydrogen bond donor property of the most active (compound 34C) and least active compound (compound 6A) from the ligand dataset.

The blue color region indicates the favorable features to contributing to the ligand interactions with target enzyme, while red color region indicate unfavorable region of the activity.

Piperidin ring of the compound 34C increases the hydrogen bond donor property. Electron withdrawing property of most active and least active compound is depicted in 9a and 9b respectively. Graph of actual versus predicted pIC_{50} of training set and test set using atom-based 3D-QSAR is depicted in figure 10a and 10b respectively.

Pharmacophore based virtual screening

One efficient approach to drug discovery is virtual screening of molecule libraries. Pharmacophore-based virtual screening is a fast and precise method using commercially available chemical database aiding in the identification of novel and potential leads by filtering the inactive compounds. Initially, the well validated pharmacophore model (AAAHR) of NMT inhibitors were used as 3D structural query for obtaining a potential compound with desired properties from Zinc database with fitness value ranges >1 .

Out of a hit list of 1056 compounds matching the pharmacophore model were obtained then the hits were selected based on their good fitness value of the pharmacophore site >1 .

Fig.1 Pharmacophore hypothesis and distance between pharmacophoric sites.
All distances are in Å unit

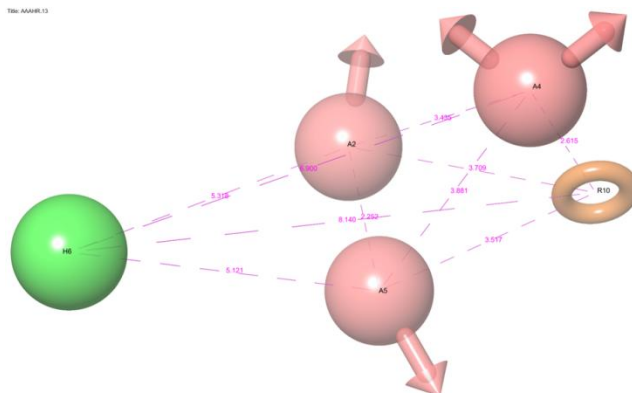


Fig.2 Pharmacophore hypothesis and angle between pharmacophoric sites.
All distances are in Å unit

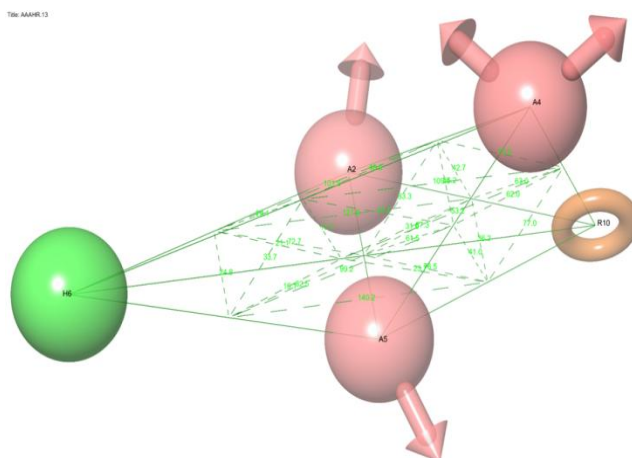


Fig.3 Alignment of the most active compound with the best hypothesis

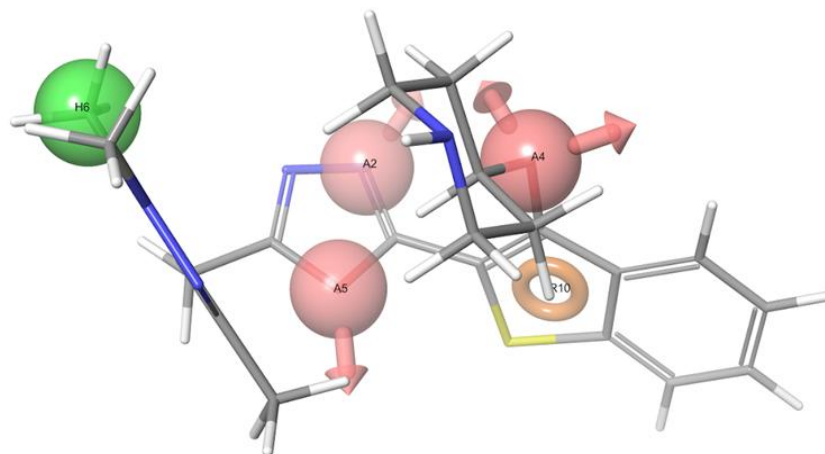


Fig.4a and 4b H₂ bond donor features for most active compound and least active compound

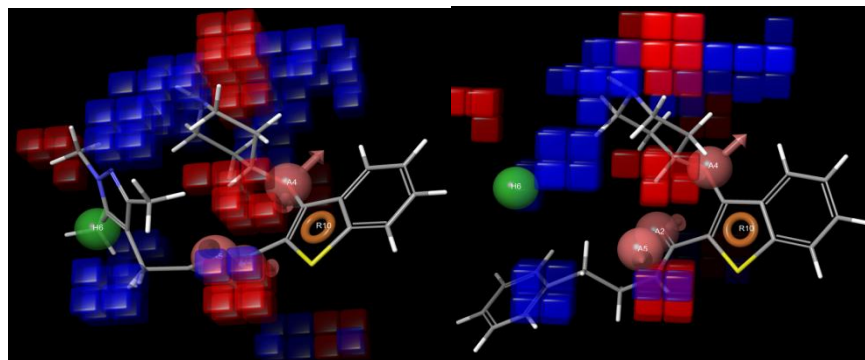


Fig.5a and 5b Electron with drawing feature for most active compound and least active compound

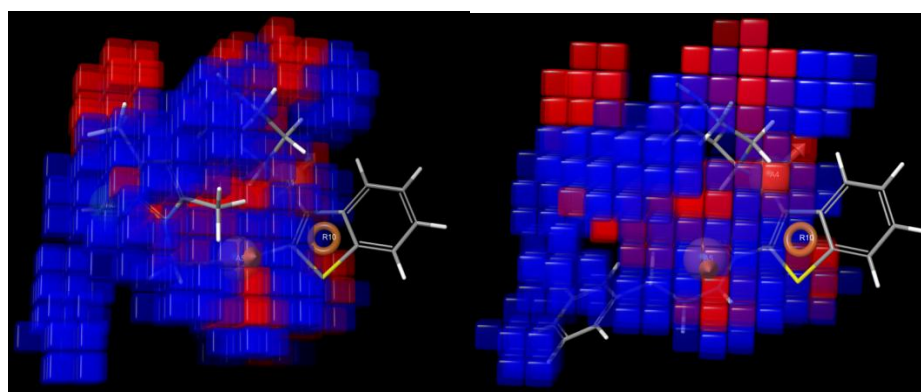


Fig.6a and 6b Scatter plot of actual versus predicted Pic50 of training set

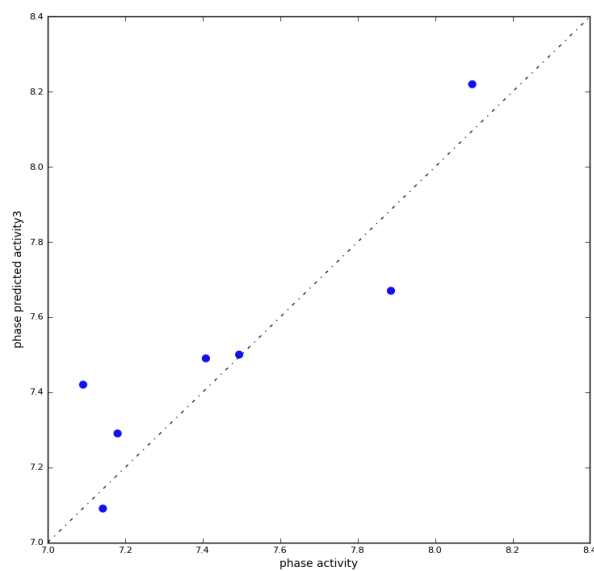
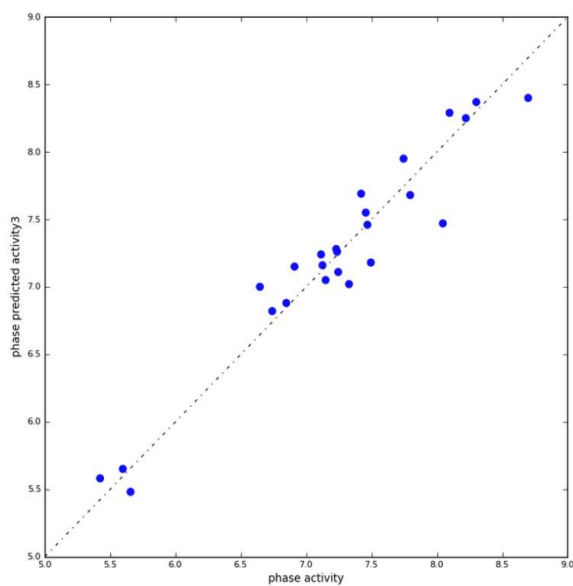


Fig.7 Docking view of Zinc 23978306 with the target protein. **Fig.8** Docking view of Zinc72101419 with the target protein.

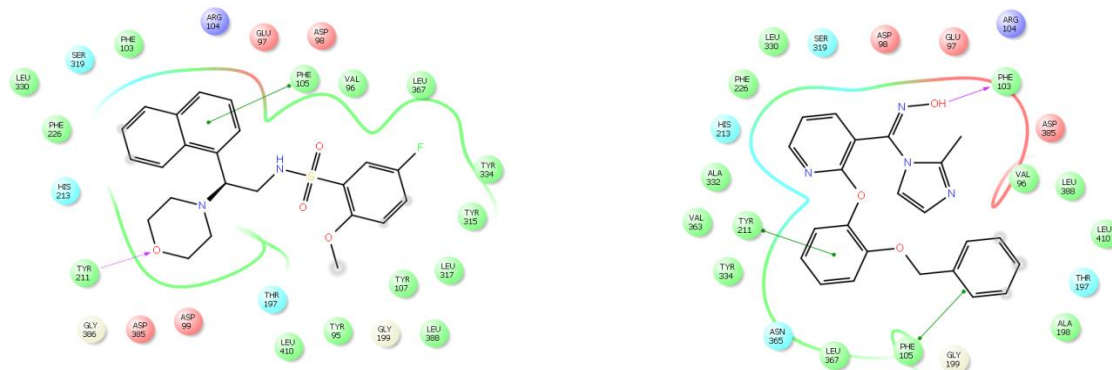


Fig.9 Docking view of Zinc23371891 with the target protein. **Fig.10** Docking view of Zinc49095919 with the target protein

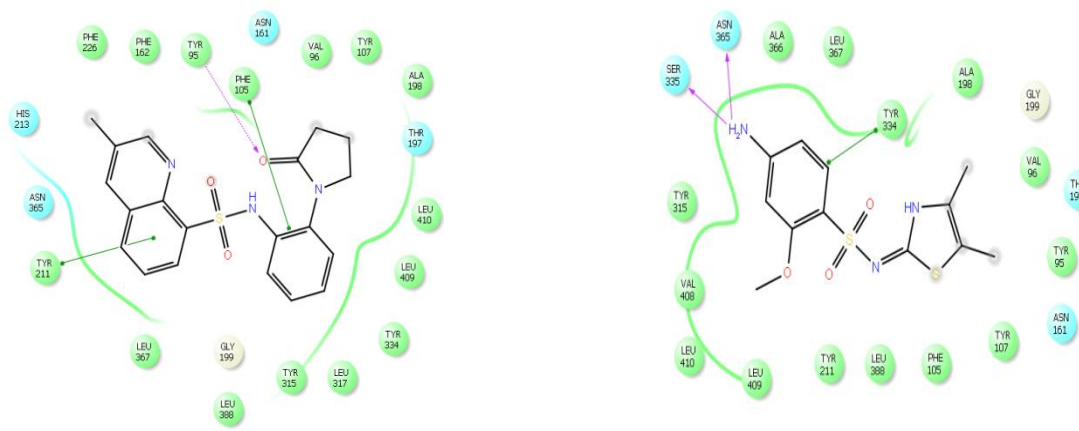


Fig.11 Docking view of Zinc13070677 with the target protein

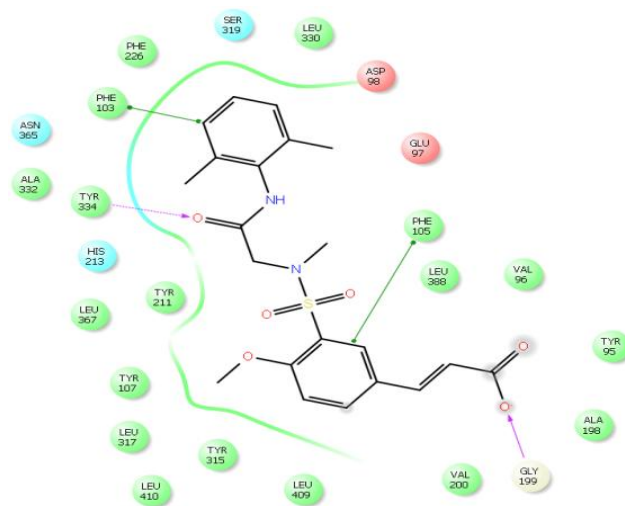


Table.1 Results of molecular docking analysis

S.no	Compound Name	Glide score	Interaction residues	No. of Hydrogen bonds
1	5-fluoro-2-methoxy-N-((2S)-2-morpholino-2-(1-naphthyl) ethyl) benzene sulfonamide	-9.958	TYR 211, PHE 105	1
2	- (2-(2-benzyloxyphenoxy)-3-pyridyl)-(2-methylimidazol-1-yl)methanone	-9.707	PHE 103, TYR 211, PHE 105	1
3	3-methyl-N-(2-(2-oxopyrrolidin-1-yl)phenyl)quinoline-8-sulfonamide	-8.481	TYR 95, TYR 211, PHE 105	1
4	4-amino-N-(4,5-dimethylthiazol-2-yl)-2-methoxy-benzenesulfonamide	-7.555	ASN 365, SER 335	2
5	-(E)-3-(3-((2-(2,6-dimethylphenyl)amino)-2-oxoethyl)-methyl-sulfamoyl)-4-methoxy-phenyl)prop-2-enoi	-7.515	TYR 334, GLY 199	2

Table.2 Assessment of drug-like properties of the hit molecules

Compound Name	MW	HBD	HBA	QPLog Po/W	Caco-2	MDCK	QPLog HERG	QPLogS	QPLogB/B
Zinc 23371891	381.448	1.0	8.5	2.18	611	290	-5.347	-3.950	-0.799
Zinc 23978306	444.520	1.0	8.95	2.46	406	329	-4.702	-1.748	-0.025
Zinc 49095919	313.389	1.5	5.75	1.85	358	301	-4.199	-3.963	-0.959
Zinc 72101419	400.436	1.0	6.45	4.02	236	125	-5.731	-3.668	-0.551
Zinc 13070677	432.490	2.0	9.75	2.66	37	18	-3.696	-4.060	-1.891

A set of 1056 hit molecules were found to fit well with five point pharmacophore and using the fitness score the best fitted molecules were identified and the selected compounds were pre-filtered by Lipinski's rule of five. 300 hit compounds were selected from pre filtration then the selected compounds were further taken into molecular docking studies. Finally we identified five ligands based on the glide score, which interacted with active site of the NMT. The chemical name of the six hits with their corresponding database ID is: Zinc23978306- (5-fluoro-2-methoxy-N-((2S)-2-morpholino-2-(1-naphthyl)ethyl) benzene sulfonamide, Zinc 72101419 - (2-(2-benzyloxyphenoxy)- 3-pyridyl)- (2-

methylimidazol-1-yl) methanone, Zinc23371891 -3-methyl-N-(2-(2-oxopyrrolidin-1-yl) phenyl) quinoline-8-sulfonamide, Zinc49095919 -4-amino-N-(4,5-dimethylthiazol-2-yl)-2 - methoxy-benzene sulfonamide, Zinc13070677-(E)-3-(3-((2-(2,6-dimethylphenyl) amino)-2-oxo-ethyl)-methyl-sulfamoyl)-4 - methoxy-phenyl)prop-2-enoi.

Docking study

Binding mode analysis of hits

The molecular docking studies were performed by using Glide. The selected hit

compounds were docked into the active site of the protein. In order to ensure that the glide algorithm was able to properly dock the ligands to the active site of the target protein, These results suggest that the glide was eligible for docking of ligands to the protein (PDB ID:4CAF. The 2D structure of the four hits compounds structure Zinc13070677, Zinc49095919, Zinc23371891, Zinc 72101419, Zinc23978306 were reported in figure 11. The docking poses of the hits were depicted in figure 12 -16.

ADME properties prediction

The ADME properties of the five newly identified lead were assessed by the use of QikProp. The abovementioned six lead molecules are satisfied drug-like properties based on Lipinski's rule of five. All the pharmacokinetics parameters are fit well with the acceptable range defined for use of human. The results thus retrieved are also listed in the table 3.

Malaria due to *Plasmodium vivax* causes untold suffering to human beings. Recently the emergence of the drug resistance in malarial parasites accounted for severe situation and it is likely to keep the globe under the threat. The problem of the drug resistance is also highly pronounced today in India. Though the controlling of the arthropod vectors is an option to combat against malaria, however overcoming the drug resistance is the ultimate solution will neutralize the permanent establishment of parasites in the local scenario. Previous studies could able to focus only on validating the drug target. To develop an unprecedented antimalarial drug using computational tools is the core objective of the study. In this study, we have identified five potent NMT inhibitors by using ligand based pharmacophore modeling, atom-based 3D-QSAR and molecular docking. The robustness of the

statistical values reflects the goodness of the model developed. No wonder, these newly identified hit molecules may pass the *in vitro studies* if at all their efficacy are determined by molecular simulation also. In addition to that, ADME properties of the hit molecules are also falling under the acceptable range which signifies the success of the study. On the whole, the exceptional role of computational tools in discovery of drugs is so clear in this approach to identify small molecule inhibitor of N-myristoyl transferase. In near future this may actively play a role as drug and if passes all the events in the clinical trials and once favorable consistency of the molecule is attained, overcoming drug resistance is not far away. This study is just a lead in malaria drug research.

References

- Adak, T., V. P. Sharma, and V. S. Orlov Studies on the *Plasmodium vivax* relapse pattern in Delhi, India. *Am. J. Trop. Med. Hyg.*, 59(1), 1998, pp. 175–179.
- Battle KE, Gething PW, Elyazar IR, *et al.*,: The global public health significance of *Plasmodium vivax*. *Adv Parasitol* 2012; 80: 1-111.
- Dhanpat K. Kochar, Ashish Das *et al.*, Severe *Plasmodium vivax* Malaria: A Report on Serial Cases from Bikaner in Northwestern India *Am. J. Trop. Med. Hyg.*, 80(2), 2009, pp. 194–198.
- Dua, V.K. *et al.*, (1996) Chloroquine resistant *Plasmodium vivax* malaria in India. *Trop. Med. Int. Health* 1, 816–819
- Ebiike, H. *et al.*, Design and synthesis of novel benzofurans as a new class of antifungal agents targeting fungal N-myristoyl transferase. Part 2. *Bioorg. Med. Chem. Lett.* 12, 607–610 (2002).
- Frearson, J. A. *et al.*, N-myristoyl transferase inhibitors as new leads to treat sleeping sickness. *Nature* 464, 728–732 (2010).

- Garg, M. *et al.*, (1995) Vivax malaria resistant to chloroquine: case reports from Bombay. *Trans. R. Soc. Trop. Med. Hyg.* 89, 656–657.
- Garrett M. Morris, Marguerita Lim-Wilby Molecular Docking Methods Molecular Biology™ Volume 443, 2008, pp 365–382.
- Gething PW, Elyazar IR, Moyes CL, *et al.*,: A long neglected world malaria map: *Plasmodium vivax* endemicity in 2010. *PLoS Negl Trop Dis* 2012; 6:pp. e1814.
- Gething PW, Patil AP, Smith DL, *et al.*,: A new world malaria map: *Plasmodium falciparum* endemicity in 2010 *Malaria J* 2011; 10: pp. 378.
- Gething PW, Van Boeckel TP, Smith DL, *et al.*, Modelling the global constraints of temperature on transmission of *Plasmodium falciparum* and *P. vivax*. *Parasite and Vectors.* 2011; 4:92.
- Glide, Version 6.0 (2013) Schrodinger, LLC, New York, NY.
- Gogtay, N.J. *et al.*, (1999) Efficacies of 5- and 14-day primaquine regimens in the prevention of relapses in *Plasmodium vivax* infections. *Ann. Trop. Med. Parasitol.* 93, 809–812.
- Guerra CA, Howes RE, Patil AP, *et al.*, The international limits and population at risk of *Plasmodium vivax* Transmission in 2009. *PLoS Negl Trop Dis* 2010; 4: pp. e774.
- Hay SI, Okiro EA, Gething PW, *et al.*,: Estimating the global clinical burden of *Plasmodium falciparum* Malaria in 2007. *PLoS Med* 2010; 7: pp.e1000290.
- Hema Joshi, Surendra K. Prajapati *et al.*, *Plasmodium vivax* in India Trends in Parasitology Vol.24 No.5,2008. <http://www.cambridgesoft.com>
- Kamatsu M. Current State and Perspectives of 3D-QSAR. *Curr. Top. Med. Chem.*, 2002; 2: 1381–1394.
- Kapetanovic, I.M. Computer-aided drug discovery and development (CADD): *In silico*-chemico-biological approach. *Chemico-Biological Interactions* 171 (2008) 165–176.
- Kshirsagar, N.A. *et al.*, (2000). An unusual case of multidrug-resistant *Plasmodium vivax* malaria in Mumbai (Bombay), India. *Ann. Trop.Med. Parasitol.* 94, 189–190.
- Kubinyi, H. (2006) Success stories of computer-aided design. In *Computer Applications in Pharmaceutical Research and Development* (Ekins, S., ed.), pp. 377–424, Wiley–Interscience.
- Mark D. Rackham *et al.*, Design and Synthesis of High Affinity Inhibitors of *Plasmodium falciparum* and *Plasmodium vivax* N-Myristoyl transferases Directed by Ligand Efficiency Dependent Lipophilicity (LELP).
- Murray CJ, Rosenfeld LC, Lim SS, *et al.*, Global malaria mortality between 1980 and 2010: a systematic analysis. *Lancet* 2012; 379: pp. 413–431.
- Mustata, G. *et al.*, (2009) Discovery of novel Myc-Max heterodimer disruptors with a three-dimensional pharmacophore model. *J. Med. Chem.* 52, 1247–1250.
- PHASE, version 3.6. Schrödinger, New York, NY, 2013.
- Protein preparation Wizard Maestro (2013) New York: Schrodinger LLC
- QikProp, Version 3.7, LLC, New York, NY, 2013.
- Srivastava, H.C. *et al.*, (1996) Studies on *Plasmodium vivax* relapse pattern in Kheda district, Gujarat. *Indian J. Malariol.* 33, 173–179.
- Tate, E.W., Bell, A.S., Rackham, M.D. and Wright, M.H. N-myristoyl transferase as a potential drug target in malaria and leishmaniasis. *Parasitology.* 2014 Jan; 141(1): 37–49.
- Verma RP, Hansch C. Camptothecins: A SAR/QSAR Study. *Chem. Rev* 2009; 109: 213–235.

- World Health Organization: World Malaria Report. Geneva: World Health Organization, 2012.
- Wright MH, Clough B *et al.*, Validation of N-myristoyl transferase as an antimalarial drug target using an integrated chemical biology approach. *Nat Chem.* 2014 Feb; 6(2): 112-21.
- Wright, M. H., Heal, W. P., Mann, D. J. and Tate, E. W. Protein myristoylation in health and disease. *J. Chem. Biol.* 3, 19–35 (2009).
- www.nvbdc.gov.in.
- Yan A. Ivanenkov, Nikolay P. Savchuk, Sean Ekins and Konstantin V. Balakin Computational mapping tools for drug discovery, *Drug Discovery Today* Volume 14, Numbers 15/16 August 2009.
- Zhao, H. (2007) Scaffold selection and scaffold hopping in lead generation: a medicinal chemistry perspective. *Drug Discov. Today* 12, 149–155.

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