

Virtual Screening of Natural Products and Drugs as Inhibitors against Aspartate Transcarbamoylase and Orotidine-5'-Monophosphate Decarboxylase in *Plasmodium falciparum*

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RESEARCH ARTICLE

Abstract

Background: Malaria remains to be one of the major health problems in tropical areas of the world. It puts at least one-third of the world population at risk of infection and afflicts over 200 million people worldwide, approximately 7000 of whom are Filipinos. In spite of available drugs, malarial chemotherapy is still insufficient. The increased resistance of *Plasmodium falciparum* strains to existing antimalarial drugs prompts the discovery of new therapeutic agents for malaria.

Objective: This study aimed to uncover, through molecular docking technique, new chemical entities that can be developed as new drugs for malaria.

Methodology: In this study, 2,527 approved and 5,755 experimental drugs from DrugBank and 4,687 natural compounds from Analyticon MEGx database were docked against *Plasmodium falciparum* aspartate transcarbamoylase (PfATC) and orotidine-5'-monophosphate decarboxylase (PfOMPDC), two key enzyme targets involved in the *de novo* biosynthesis pathway of the pathogen.

Results: A total of 39 compounds (1 approved drug, 19 experimental drugs, 19 natural products) had larger binding energy (BE) values than the known ligands 2,3-naphthalenediol ($BE_{PfATC} = -7.0$ kcal/mol) and uridine 5-monophosphate ($BE_{PfOMPDC} = -9.0$ kcal/mol). The top 3 hits were natural products: dihydrotrichotetronine ($BE_{PfATC} = -21$ kcal/mol, $BE_{PfOMPDC} = -18$ kcal/mol), ginkgolide A ($BE_{PfATC} = -19$ kcal/mol, $BE_{PfOMPDC} = -15$ kcal/mol), and ginkgolide C ($BE_{PfATC} = -16$ kcal/mol, $BE_{PfOMPDC} = -16$ kcal/mol).

Conclusion: Based on calculated binding energy and ADMET properties, dihydrotrichotetronine, ginkgolide A, and ginkgolide C are the best natural product candidates for further development as dual inhibitors for both PfATC and PfOMPDC enzymes. Furthermore, myricetin ($BE_{PfATC} = -9$ kcal/mol, $BE_{PfOMPDC} = -10$ kcal/mol) and tolcapone ($BE_{PfATC} = -9.1$ kcal/mol, $BE_{PfOMPDC} = -9.2$ kcal/mol) may also be repurposed as anti-malarial drugs.

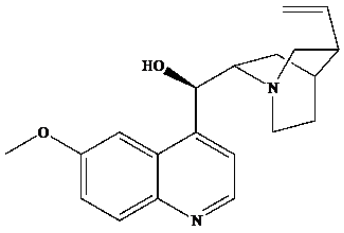
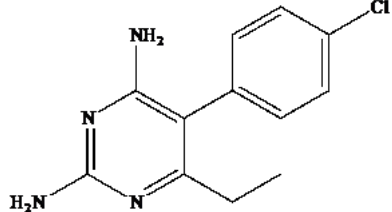
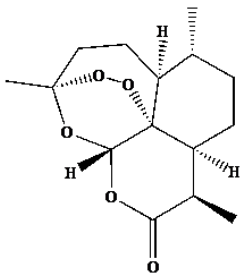
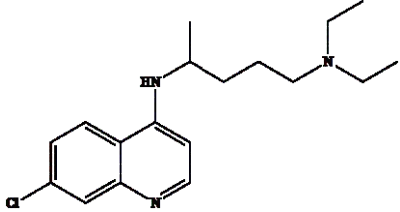
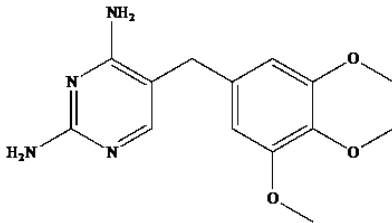
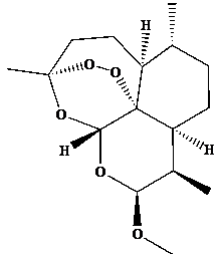
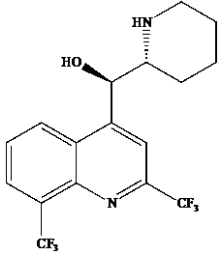
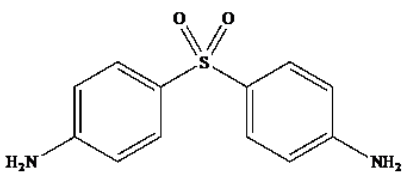
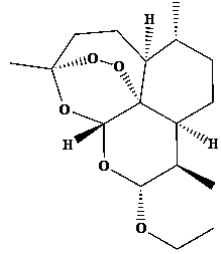
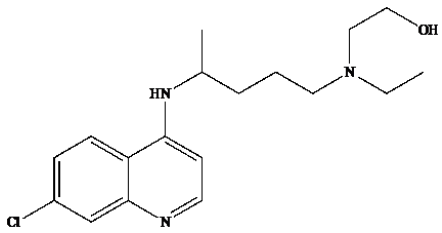
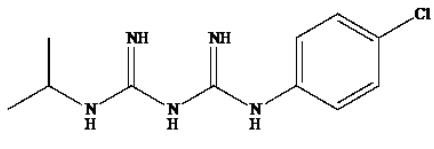
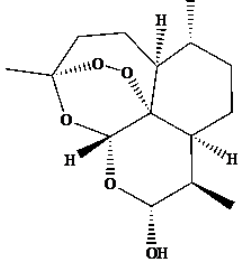
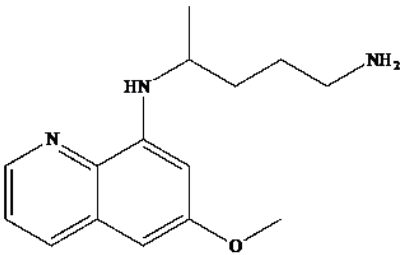
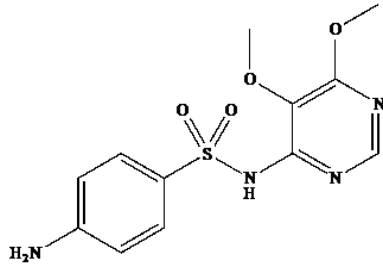
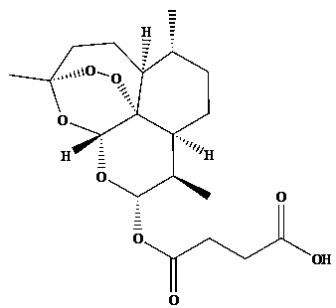
Keywords: Malaria, *P. falciparum*, PfATC, PfOMPDC, Virtual Screening

Introduction

Malaria remains a major cause of morbidity and hospitalization in many tropical and subtropical countries in the world. It puts 3.3 billion people at risk of infection, affecting 219 million people, and causing approximately half a million deaths in 2017 [1]. In the Philippines, there were 6,922 malaria cases reported nationwide in 2016 alone [2]. Fueled by climate fluctuations, increasing urbanization, and lower rates of sanitation, malaria remains to be a significant threat to global health. The clinical manifestations of malaria range from chills and high fever, to severe malaria-associated organ failures, and cerebral malaria in which the parasite accumulates in the capillaries eventually leading to coma [3].

Antimalarial chemotherapy has long been the gold standard for the treatment and management of the disease. Specifically, artemisinins and chloroquines are the primary drugs used to treat malaria. These drugs work by disrupting the hemoglobin metabolism of the parasite [4]. Antimalarial drugs are mainly categorized in three groups: quinine and derivatives, antifolates, and artemisinin combination therapy [5]. Quinine-based antimalarials include chloroquine, mefloquine, and primaquine (Table 1). The structures of antifolates are quite diverse, whereas the artemisinin drugs share a common tricyclic motif. Unfortunately, resistance to these drugs has been noted to be more and more prevalent (*i.e.* reaching to almost 100%) making it a primary concern in

Table 1. Chemical Structures of Anti-Malarial Drugs.

Quinine and Derivatives	Antifolates	Artemisinin and Derivatives
 <p>Quinine</p>	 <p>Pyrimethamine</p>	 <p>Artemisinin</p>
 <p>Chloroquine</p>	 <p>Trimethoprim</p>	 <p>Artemether</p>
 <p>Mefloquine</p>	 <p>Dapsone</p>	 <p>Artemitol</p>
 <p>Hydroxychloroquine</p>	 <p>Proguanil</p>	 <p>Arterimol</p>
 <p>Primaquine</p>	 <p>Sulfadoxine</p>	 <p>Artesunate</p>

malaria management [6,7,8]. Furthermore, the rise and spread of drug resistance in Southeast Asia, their toxicity, low efficacy of vaccines, and the high number of infections and morbidity entail urgency in the need to discover and develop new antimalarial drugs [9,10,11,12,1,2].

The causative agent of malaria is a group of protozoans belonging to the genus *Plasmodium*, namely, *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium vivax*, with *P. falciparum* being responsible for majority of the morbidity caused by the disease [13]. It is therefore imperative to screen chemical compounds against druggable targets in crucial biochemical pathways of *P. falciparum*. One such pathway is the *de novo* pyrimidine biosynthesis. Unlike humans, *P. falciparum* lacks the pyrimidine salvage machinery, relying solely on *de novo* pathway as the means of producing the essential precursors for the synthesis of DNA and RNA [3]. Parasite enzyme inhibitors of the *de novo* pathway have been found to have strong antimalarial activity against *in vitro P. falciparum* growth [3,14]. Mammalian hosts, however, can utilize both the *de novo* and salvage pathways. In addition, mature human erythrocyte lacks the *de novo* pyrimidine pathway, thus the obstruction of this pathway could lead to selective death of the intraerythrocytic parasite [14].

The *de novo* pathway is composed of 6 enzyme-catalyzed reactions [15]. The initial reaction is the formation of carbamoyl phosphate catalyzed by carbamoyl phosphate synthetase [16]. Aspartate transcarbamoylase (PfATC) then catalyzes the condensation of carbamoyl phosphate and L-aspartate to form N-carbamoyl-L-aspartate and orthophosphate [17]. The subsequent reactions form the pyrimidine ring from carbamoyl phosphate. Uridine 5-monophosphate (UMP) is formed in the final two steps by the addition of a ribose phosphate moiety to orotate and the subsequent decarboxylation of the resulting orotidine 5'-monophosphate (OMP) by orotidine-5'-monophosphate decarboxylase (PfOMPDC). Reactions 5 and 6 are catalyzed by orotate phosphoribosyl transferase (OPRT) and PfOMPDC, collectively known as the UMP synthase [18]. Together, these enzymes exist as a bifunctional UMP synthase. PfOMPDC and OPRT exist as a heterotetrameric enzyme containing two subunits each from PfOMPDC and OPRT, which are expressed and encoded in two separate genes [19].

PfATC catalyzes the committed step in the pathway that will ultimately produce pyrimidine nucleotides such as cytidine triphosphate (CTP) [20]. It exists as three identical regulatory dimers and 2 trimers of catalytic units. The arrangement between these subunits enables the enzyme a strong allosteric behavior with respect to its substrates [21]. On the other hand,

PfOMPDC catalyzes the decarboxylation of OMP to UMP, which is an essential ribonucleotide for the formation of various pyrimidine nucleotide precursors used for the synthesis of nucleic acids [22,23]. PfOMPDC always exists catalytically as a dimer with essentially identical subunits regardless of it being monofunctional or bifunctional enzymes [16,18]. Biochemical differences of these enzymes between the parasite and host provide a rational basis for the development of antimalarial drugs. PfOMPDC is a highly selective target. Kinetic profiles, ability to function in diverse conditions, affinity towards inhibitors, are significantly different for PfOMPDC enzymes from different sources such as *E.coli*, mice, humans, and *P. falciparum* [23,24,25].

Hence, the compounds that can inhibit both PfATC and PfOMPDC have the potential ability to compromise the growth, development, and multiplication of the parasite. Moreover, a drug that can act on two druggable enzymes has potential advantages over those that act on just one single drug target. Multi-targeted drugs are intuitively more potent and are less prone to drug resistance [26,27].

The traditional method of drug discovery, however, is an expensive and sluggish process. It takes a long time and ample resources to find drug leads that are both effective and non-toxic for human use. However, the recent application of computational techniques in drug discovery has remarkably streamlined and hastened the individual stages of the drug discovery process. Virtual screening of new bioactive agents based on, for example, their binding affinity with the macromolecular target of interest has been routinely employed in any drug discovery ventures in recent decades. In fact, the new drugs in the market today are mostly products of computer-aided drug discovery (CADD). Matter-of-factly, CADD routinely involves molecular docking, a computational procedure that predicts theoretical binding between a macromolecule (*i.e.*, receptors) and a smaller molecule (*i.e.*, ligand or drug).

In this study, molecular docking was done to screen over 12,000 database compounds including drugs and natural products against PfATC and PfOMPDC targets. Subsequently, the top hits were further evaluated *in silico* for pharmacokinetics and pharmacodynamics properties through ADMETox calculations.

Methodology

The molecular docking study was performed with the use of Python Prescription (PyRx) software (<https://pyrx.sourceforge.io>) installed on a computer running on macOS Sierra Version

10.12.6 with an Intel Core™ i7-4770K CPU, 3.10 Ghz processor, NVIDIA GeForce 750M graphics card, and 16.00 GB RAM. SDF files of the approved and experimental drugs were obtained from DrugBank (<https://www.drugbank.ca/>) on May 28, 2018. The structures of purified natural products were obtained from the Analyticon MEGx database (<https://ac-discovery.com>). DataWarrior (<http://www.openmolecules.org/datawarrior/>) was used to organize the data by setting the ID of each compound with their respective DrugBank ID. Using PyRx Open Babel software, the organized sdf files were minimized and converted to pdbqt files as ligands for molecular docking.

The three-dimensional structure of the drug targets, PfATC (PDB ID:6FBA) and PfOMPDC (PDBID:3N2M), were retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) (<http://www.rcsb.pdb.com>) on May 14, 2018. The enzymes were prepared using sequence analysis with PyMOL (<https://pymol.org>). The structure file was then converted to pdbqt file in PyRx.

The binding sites were identified based on previous accounts on the interactions of the enzymes and their respective known ligands. The Vina grid box was then positioned and manipulated to ensure that the relevant amino acids were within the defined binding site. The redocked ligand was superimposed with the experimental structure available from RCSB and the root-mean-square deviation (RMSD) values were determined using UCSF Chimera (<https://www.cgl.ucsf.edu/chimera/>).

The ligands were docked with the use of PyRx Version 0.9.0.6, which utilizes a hybrid scoring function. PyRx is a virtual screening software that uses an open-source software including AutoDock Vina for molecular docking,

AutoDockTools for input file generation, and Open Babel for importing files, salt removal, and energy minimization. The top hits (*i.e.* those with binding energy larger than the control) were further analyzed by generating their respective interaction maps using the DS Visualizer, a Discovery Studio (DS) visualization software (<https://www.3dsbiovia.com>). The top hits were further evaluated for their predicted adsorption, distribution, metabolism, excretion, and toxicity (ADMET) profile using ADMETSar (<http://lmmd.ecust.edu.cn>).

Results and Discussion

Pyrimidine nucleotides are essential metabolites. In principle, they are acquired from two different sources namely the *de novo* biosynthetic pathway and the salvage pathway. Unlike humans, however, *P. falciparum* species are exclusively dependent on the *de novo* synthesis for synthesized nucleotides due to the absence of the salvage pathway, which recovers product pyrimidine bases or nucleotides from the extracellular environment [3,22]. PfATC and PfOMPDC catalyze the second and fifth steps of the *de novo* pyrimidine biosynthesis. Due to the essential role of the nucleotides in various cellular processes and disease conditions, selective inhibition of PfOMPDC and PfATC could be a potential strategy for the development of drugs for malaria.

PfATC is a trimer molecule in an asymmetric unit. Figure 1 shows the 3D representation of PfATC in complex with a known ligand 2,3-naphthalenediol, a novel inhibitor that binds in close proximity to the active site of PfATC, implying an allosteric mechanism of inhibition [17]. The intersubunit cavity of PfATC hosts a unique pair of cysteines (*i.e.*, Cys100 and Cys112), which are mainly observed in *Plasmodium* species [17]. No ATC from other homologous organisms

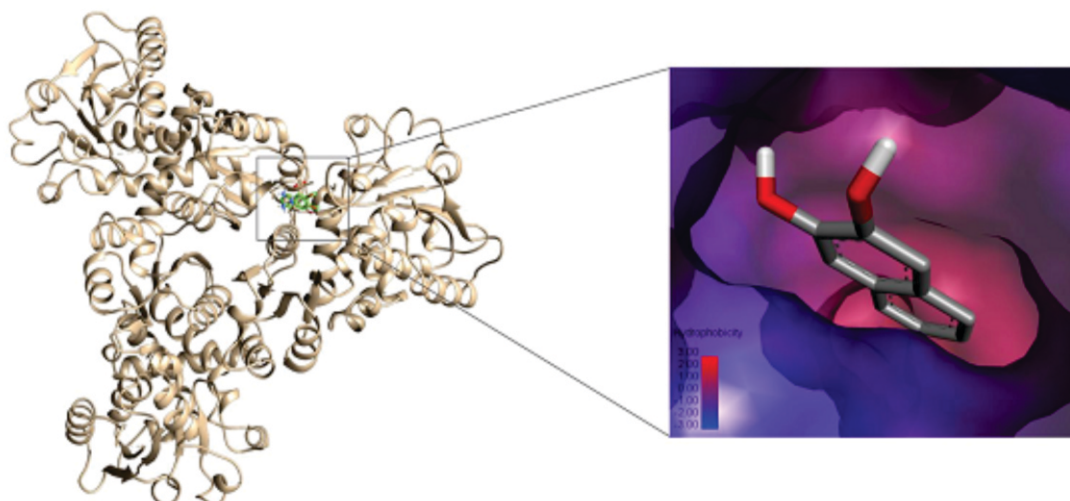


Figure 1. Overview of the 3D representation of the binding of PfATC with 2,3-naphthalenediol.

with a sequence identity of over 30% possess either Cys100 or Cys112, hence, selective targeting is possible. On the other hand, the active site residues in PfOMPDC are involved in extensive hydrogen-bonding network (Figure 2) [29]. An analysis of the catalytic site of PfOMPDC with RCSB NGL reveals the presence of the following amino acids: Asp23A, Lys102A, Asn104A, Asp136A, Asp141B, Thr145B, Thr195B, Gln269A, Arg293A, and Arg294A [30].

To evaluate the validity of the docking protocol, the respective ligands of PfATC and PfOMPDC were redocked to these target enzymes. The RMSD is the most commonly used quantitative measure of the structural similarity between two superimposed structures [31]. The RMSD value is small if the structures are more similar to each other. Figure 3 clearly shows that the redocked ligands closely resemble the disposition of the bound ligands in the experimental crystal structures, with RMSD values of 0.434 Å and 0.864 Å for 2,3-naphthalenediol and uridine-5'-monophosphate (U5P), respectively. An RMSD value lower than 1.500 Å indicates high structural similarity and thus high binding mode reproducibility [32].

The redocked 2,3-naphthalenediol has retained almost all important interactions with PfATC, namely, pi-sigma bonding with Ile148A and pi-alkyl bonding with Arg109A and Leu109B (Figure 4). On the other hand, the ligand interactions of the redocked U5P has featured conventional hydrogen bonding interactions with Lys102A, Asp136A, Thr195A, Gln269A, Asn291A, and Gly293A and pi-alkyl bonding with Ile142B and Pro264A of PfOMPDC, as described above for the experimental structure. The redocked known inhibitors, 2,3-naphthalenediol and U5P, yielded binding energy values of -7.0 and -9.0 kcal/mol, respectively. Using the optimized coordinates of the docking site, the compounds from DrugBank and MEGx databases were docked against PfATC and PfOMPDC in our quest for possible inhibitors of these druggable targets in *P. falciparum*.

The molecular docking of the 2,704 approved drugs and 5,584 experimental drugs from DrugBank, and 4,558 purified natural products from Analyticon MEGx yielded 1,262, 3,085, and 2,034 compounds, respectively, that have larger (or more negative) binding energies than the known inhibitor of PfATC – 2,3-naphthalenediol. These compounds were subsequently

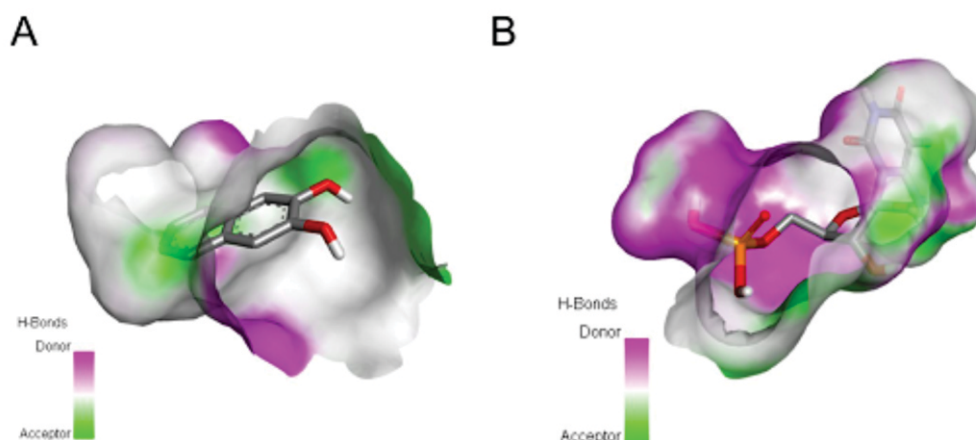


Figure 2. Illustration of the H-bonding properties of (A) PfATC and (B) PfOMPDC with their ligands, 2,3-naphthalenediol and uridine-5'-monophosphate, respectively.

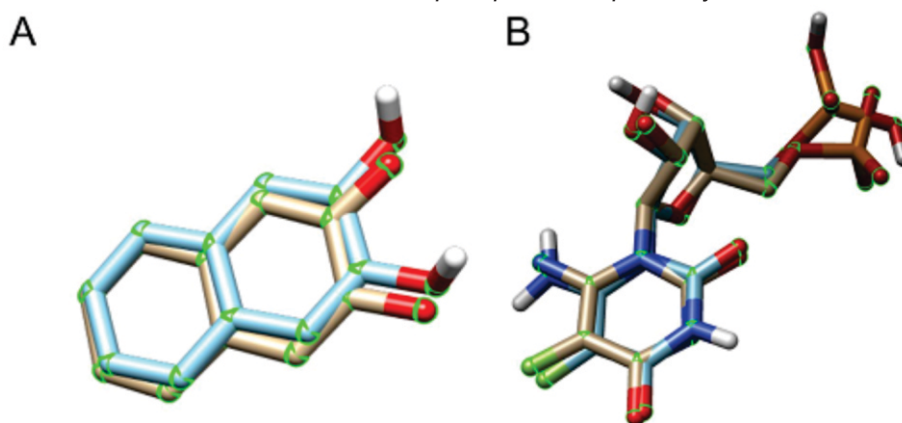


Figure 3. Superimposed original crystallized structure (in blue) against the redocked ligand (in brown) of (A) 2,3-naphthalenediol and (B) uridine-5'-monophosphate.

docked to the PfOMPDC target to furnish 1, 19, and 19 compounds, respectively, that have potentially greater binding affinity than uridine-5'-monophosphate. In summary, 39 from a total of 12,846 compounds were able to pass both screens and can potentially serve as dual inhibitors of PfATC and PfOMPDC, two crucial targets in malaria drug discovery. The binding energies of these compounds are in the range of -7.1 to -21.1 kcal/mol for PfATC and -9.1 to -17.7 kcal/mol for PfOMPDC. It was observed that the compounds that displayed large binding energies have similar structures with high molecular weights ranging from around 200 up to 900 amu, presence of multiple rings, and N-, S- and O- rich functional groups.

Among the screened compounds, dihydrotrichotetronine from the Analyticon MEGx library yielded the largest binding energy of -21.1 kcal/mol against PfATC and -17.7 kcal/mol against PfOMPDC (Table 2). Dihydrotrichotetronine binds mostly through conventional hydrogen bonds and π stacking interactions (*i.e.*, π -cation and π -alkyl) with the polycyclic hydrocarbon moiety. Specifically, it forms conventional hydrogen bonding with Arg159A, Arg226, Gln297A, Arg336A, amide- π stacked interactions with Arg109A, π -cation interaction with Arg295A, and π -alkyl interaction with Pro333A of PfATC. Moreover, the entire length of dihydrotrichotetronine, which is 16 carbon long, plays a huge contribution to the van der Waals interactions.

After dihydrotrichotetronine, ginkgolide A and ginkgolide C ranked second and third, respectively. The other natural product top hits include quercetin, catechin, galliccatechin, epicatechin, dihydroluteolin, galangin, norwogenin, pinobanksin, 2',5,8-trihydroxy-7-methoxyflavone, (+)afzelechin, 7-O-methyleryodictyol, gibberellic acid, 3',4',7-trihydroxyflavone, 5,6,7-trihydroxyflavone, viscidulin, and compounds with formulas $C_{34}H_{36}O_{14}$ and $C_{26}H_{38}O_5$.

Among the experimental drugs, myricetin showed the largest binding energy (-9.1 kcal/mol with PfATC and -10.4 kcal/mol with PfOMPDC). The known enzyme targets of myricetin include phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit gamma isoform and tyrosine-protein kinase JAK1 (<https://drugbank.ca>). Myricetin, a flavonol, was found to bind with PfATC primarily through hydrogen bonds and hydrophobic bonds. Specifically, it forms conventional H-bonds with Arg159A, Gln190A, Arg226A, and Arg363A, in addition to the π -alkyl bond with Pro333A and π -cation bond with His187A. Moreover, myricetin binds with PfOMPDC more strongly than with PfATC. Myricetin observably forms more bonds with PfOMPDC, particularly conventional hydrogen bond with Asn104A, Asp141B, Asp136A, Thr195A, Ile266A, Gln269A, and Gly293A against PfOMPDC. Myricetin also forms π -cation bonding with Lys102A, Lys138A, and Arg294A; and π -alkyl bonding with Pro264A and Ile142B (Figure 5).

The other top hits from Experimental Drugs include taxifolin (DB02224), epigallocatechin (DB02375), 5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-4H-chromen-4-one (DB08230), thymidine-5'-diphosphate (DB03103), 3,7,3',4'-tetrahydroxyflavone (DB07795), kaempferol (DB01852), guanosine-5'-diphosphate (DB04315), 1-[2-deoxyribofuranosyl]-2,4-difluoro-5-methylbenzene-5'-monophosphate (DB07652), 2-({2-[(3-hydroxyphenyl)amino]pyrimidin-4-yl}amino)benzamide (DB07268), 5-aminocarbonyl-3-nitrophenyl- α -D-galactopyranose (DB02802), 1-(5'-phospho- β -D-ribofuranosyl)barbituric acid (DB03668), 6-hydroxyuridine-5'-phosphate (DB02890), 5-methylcytidine-5'-monophosphate (DB01995), 3-fluoro-N-[3-(1H-tetrazol-5-yl)phenyl]benzamide (DB07729), FUDP (DB04068), nicotinamide mononucleotide (DB03227), phosphomethylphosphonic acid guanosyl ester (DB03486), and pseudouridine-5'-monophosphate (DB03829).

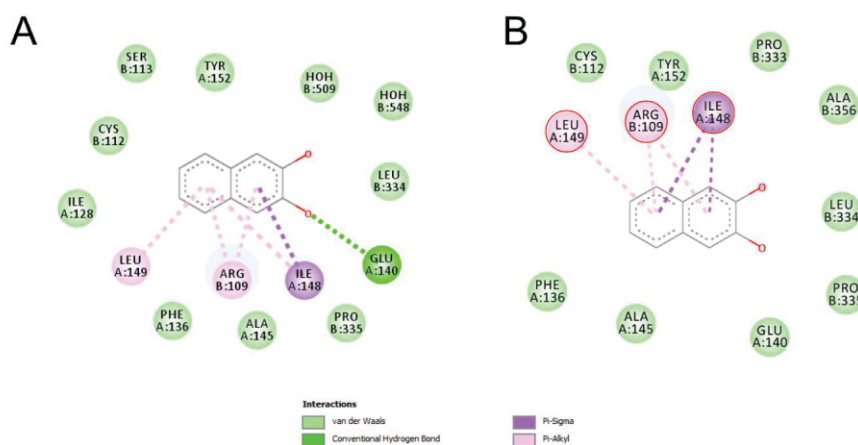
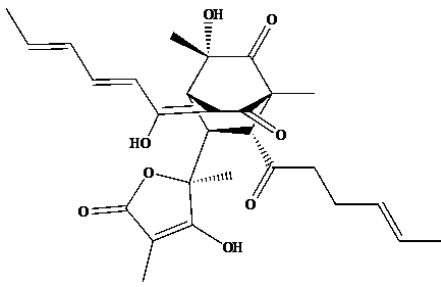
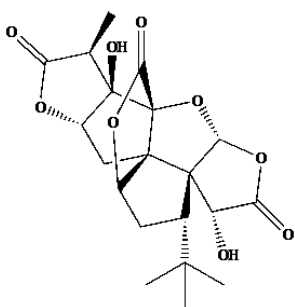
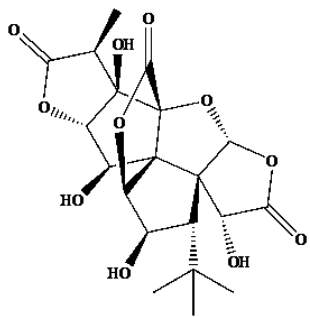
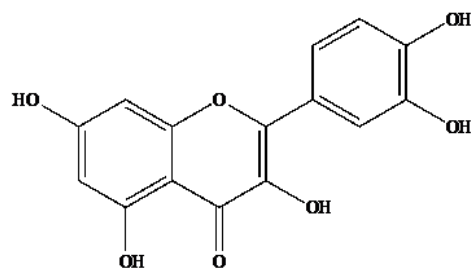


Figure 4. (A) Interaction diagram for the crystal structure of PfATC with 2,3-naphthalenediol. (B) Interaction diagram for redocked 2,3-naphthalenediol with the optimized PfATC structure (retained amino acids are encircled in red).

Table 2. Structures and Binding Energies of Selected Virtual Screening Top Hits Against PfATC and PfOMPDC.

Library	Structure	Binding Energy with PfATC (kcal/mol)	Binding Energy with PfOMPDC (kcal/mol)
Analyticon MEGx	 <p>Dihydrotrichotetrone</p>	-21.1	-17.7
Analyticon MEGx	 <p>Ginkgolide A</p>	-18.6	-15.1
Analyticon MEGx	 <p>Ginkgolide C</p>	-16.4	-16.2
Analyticon MEGx	 <p>Quercetin</p>	-10.0	-10.0

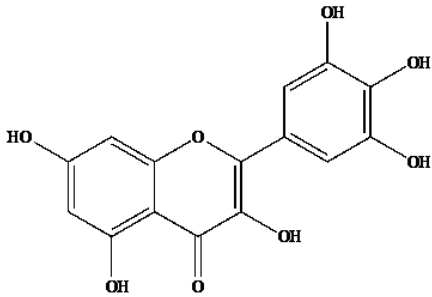
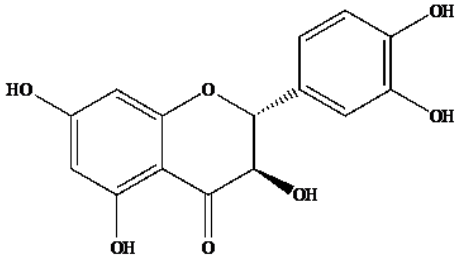
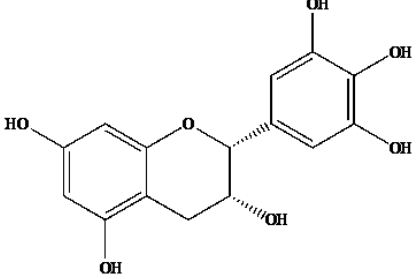
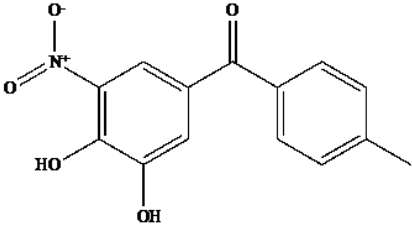
Library	Structure	Binding Energy with PfATC (kcal/mol)	Binding Energy with PfOMPDC (kcal/mol)
DrugBank (Experimental)	 <p data-bbox="565 600 685 655">Myricetin (DB02375)</p>	-9.1	-10.4
DrugBank (Experimental)	 <p data-bbox="565 1020 685 1075">Taxifolin (DB02224)</p>	-8.9	-10.1
DrugBank (Experimental)	 <p data-bbox="535 1440 717 1495">Epigallocatechin (DB02375)</p>	-8.6	-10.1
DrugBank (Approved)	 <p data-bbox="565 1860 685 1915">Tolcapone (DB00323)</p>	-9.1	-9.2

Table 3. ADME-Tox properties of Top Hits.

Compound	Water Solubility	Human Intestinal Absorption (Probability)	CYP450 2D6 Inhibition (Probability)	Carcinogenicity (Probability)	Ames Mutagenicity (Probability)	Biodegradation (Probability)
Dihydrotrichotetronine	Soluble	+ (0.93)	– (0.95)	– (0.94)	– (0.60)	– (0.88)
Ginkgolide A	Soluble	+ (0.93)	– (0.97)	– (0.92)	– (0.51)	– (0.99)
Ginkgolide C	Very soluble	+ (0.89)	– (0.95)	– (0.89)	– (0.80)	– (0.97)
Quercetin	Soluble	+ (0.97)	– (0.93)	– (0.95)	– (0.72)	– (0.87)
Myricetin	Soluble	+ (0.97)	– (0.93)	– (0.95)	– (0.72)	– (0.87)
Taxifolin	Soluble	+ (0.97)	– (0.93)	– (0.95)	– (0.72)	– (0.87)
Epigallocatechin	Soluble	+ (0.97)	– (0.92)	– (0.95)	– (0.77)	– (0.79)
Tolcapone	Soluble	+ (0.90)	– (0.91)	– (0.61)	– (0.91)	– (0.94)

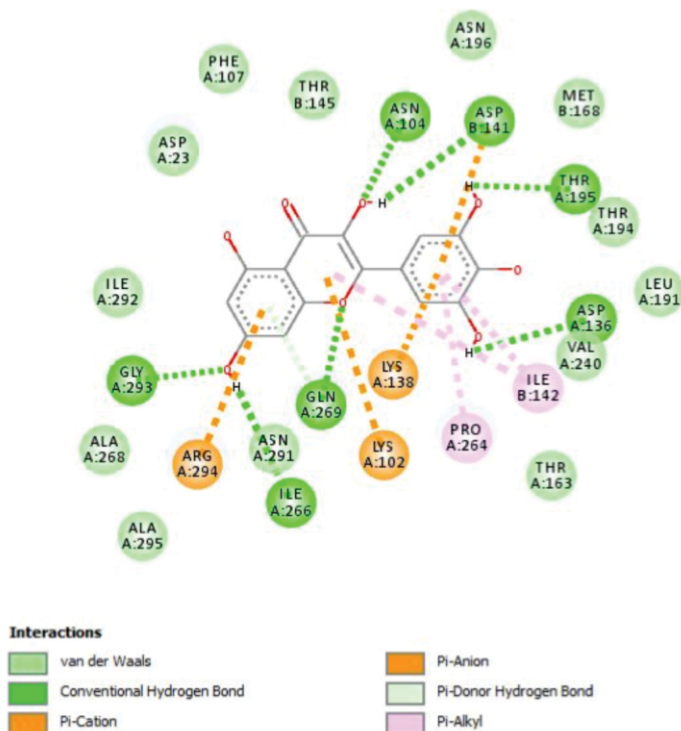
Among the Approved Drugs, tolcapone showed the highest binding affinity and the only drug that had a binding energy that is greater than the control. Although already withdrawn from the market, Tolcapone was used to inhibit the enzyme catechol-O-methyl transferase. It was used in the treatment of Parkinson's disease as an adjunct to Levodopa/Carbidopa drugs (<https://drugbank.ca>). Tolcapone forms conventional hydrogen bonds with Arg109A, Arg159A, His187A, Thr227A, Arg295A, Pro333A, and Leu334A. Furthermore, it bonds with Lys134A

and Asp141B through π -anion and π -cation bonding and alkyl and π -alkyl bonding with Ile142B, Val240A, and Pro264A.

The predicted ADME-Tox profile of the top hits are shown in Table 3. The data showed that except for ginkgolide C which is very soluble, the top hits are all soluble in water (*i.e.* log S values within 2-4 units). Interestingly, the top hits have very high probabilities of being absorbed by the human intestine. The ability of these compounds to be dissolved in aqueous biological medium and be absorbed by the intestine is indicative of good oral bioavailability. The top hits are also non-inhibitor of cytochrome P450 (2D6), a desirable property of a drug. Otherwise, these compounds could interfere with the metabolism of other drugs. Delightfully, all hits are predicted to be non-mutagenic and noncarcinogenic, albeit they are likely to be nonbiodegradable.

Conclusion

The approved and experimental drugs from DrugBank, and isolated natural products from Analyticon MEGx database were screened virtually against both *Plasmodium falciparum* aspartate transcarbamoylase (PfATC) and oritidine-5'-monophosphate decarboxylase (PfOMPDC), two highly druggable targets in *P. falciparum*, the causative agent of malaria. Molecular docking studies and ADMET predictions revealed a good number of approved and experimental drugs, and natural products that may act as promising dual inhibitors of PfATC and PfOMPDC. Specifically, dihydrotrichotetronine, ginkgolide A, ginkgolide C, and 16 other natural products may be further developed as new classes of compounds against malaria. Furthermore, myricetin and tolcapone along with 18 other experimental drugs may also be repurposed as anti-malarial drugs.

**Figure 5.** 2D Interaction map for myricetin with PfOMPDC.

Acknowledgement

The authors are grateful to the Emerging Inter-Disciplinary Research (EIDR) program (OVPA-EIDR 12-001-121102) for the use of its computational facilities.

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