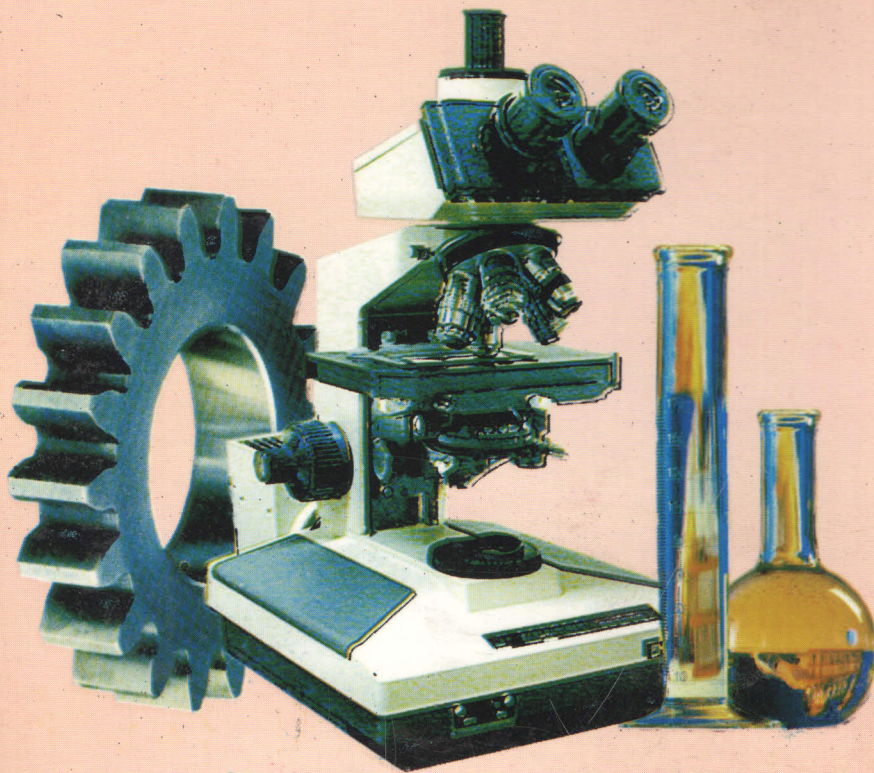


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Drug target selection for malaria: Molecular basis for the drug discovery process

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ABSTRACT: Diseases such as Malaria, Tuberculosis, Trypanosomosis and HIV/AIDS are prevalent in Africa. These are life-threatening diseases transmitted from person to person directly or through different parasites. The most lethal form of malaria is caused by the parasite *Plasmodium falciparum* (PF). The increasing problem of parasite resistance to currently used anti-malarials has led to an urgent need to develop new and effective antimalarial drugs.

The enormous pressure that the pharmaceutical and biotechnology companies are facing has created the need to apply all available techniques to decrease attrition rates, costs and the time to bring drugs to the market. Currently, two of the widely applied techniques in drug discovery are computational chemistry and molecular modeling. In this paper, we present a list of potential drug targets for malaria which can be further investigated to see if they can be synthesized into drugs.

Keywords: Drug Targets, Malaria, Druggability, Drug Validation.

1. Introduction

Malaria kills more than 1 million people each year and is the leading cause of death in children in the developing world. Each year, there are around 500 million clinical episodes of this disease (Snow *et al.*, 2003, 2005). The main transmitter of malaria in Africa is the female anopheles mosquito.

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The malaria parasite PF is of particular interest because it has a complex life style, contributing to the challenge of developing a successful vaccine. One problem of malaria is drug resistance. We need to understand the mechanism of drug resistance and to study the genomic difference between chloroquine sensitive and chloroquine resistant malaria parasite and then carry out a comparative genomic analysis of the genes of each parasite.

Malaria is a devastating infectious disease and a major cause of morbidity and mortality throughout the world. The World Health Organization estimates that malaria kills an African child every 30 seconds (Marsh 1998); approximately 40% of the world's population lives in malaria endemic areas. 90% of cases and most deaths occur in tropical Africa. There are up to 500 million clinical cases and 3 million deaths annually (White 2004). Malaria is now mainly confined to Africa, Asia, and Latin America. The problems of controlling malaria in the endemic countries are aggravated by inadequate health structures and poor socioeconomic conditions. The situation has become more complex over the last few years with the increase in resistance to the drugs normally used to combat the parasite that causes the disease.

The two most widely used antimalaria drugs, chloroquine and sulphadoxine pyrimethamine, are failing at an accelerating rate in most malaria endemic regions because of the development of resistance to these agents. Other antimalaria drugs such as mefloquine, halofantrine, atovaquone, proguanil, artemether, and lumefantrine retains efficacy but have limitations, one of which is their high cost. The drugs currently used for malaria come from three families: the quinolines (quinine, chloroquine, mefloquine, primaquine), the antifolates (sulfadoxine, pyrimethamine) and the artemisinin derivatives (Von Seidlen and Greenwood, 2003).

The increasing serious problem of malaria parasite resistance to currently used anti-malarials has led to an urgent need to develop new and effective antimalarial molecules. This goal can be achieved in two ways: either by focusing on validated targets in order to generate new drug candidates; or by identifying new potential targets for malaria chemotherapy. The advent of functional genomics and structure-based drug design has helped in the search for new targets. The genomic sequences of parasitic diseases are rapidly becoming available and recently, the full sequence of *Plasmodium falciparum* was published. Much has been promised from this genomic revolution including the identification of new drug targets and novel chemotherapeutic treatments for the control of parasitic diseases. A goal of sequencing the PF genome is to find gene products that function at sensitive stages of the parasite life cycle, offering targets for drug therapy or vaccine development.

Bioinformatics has become a very powerful tool for research on malaria. The exploitation of the vast amount of information in the various genome sequence databases is dependent on our ability to assign functions to the sequences. The currently used methods which include global sequence alignment and local sequence motif identification are limited by the extent of similarity between the new sequence and a sequence of known function. A new method that could be useful for identification of protein function based on direct sequence-to-sequence-to-structure-to-function paradigm has been suggested.

2. Background information on malaria

The recently concluded Plasmodium genome sequencing project has led to a dramatic increase in the amount of genome data available in public databases. A major challenge confronting researchers on malaria is how to analyze and mine the data from this database. It has, therefore, become important to develop computational tools for data mining in novel genomes. The phenomenon of parasite resistance to drugs has also compounded the problem of malaria control. Chemotherapy is one of the major control strategies in the fight against the malaria parasite. However, the development of drug resistance to many of the currently available drugs is causing a crisis in malaria endemic areas. The mechanism of drug resistance is still poorly understood, and if the problem is to be tackled successfully, new antimalarial drugs must be found to replace those that have been rendered ineffective in controlling malaria.

The challenge to use this information effectively will require functional genomic tools such as bioinformatics, micro arrays, proteomics and chemical genomics to identify potential drug targets, and to allow the development of optimized lead compounds. The information generated from these tools will provide a crucial link from genomic analysis to drug discovery. It is well understood that the development of new chemotherapeutics agents is a long and expensive process, and that many potential targets and lead compounds will fail at various steps in the process. The sequence of the different parasite genomes has already revealed a long list of potential drug targets. If promising candidates are to be identified, it will be essential to have simple cost-effective and rigorous screening methods to identify and validate just the very best new targets at an early stage in the process.

The combination of proteomics with chemical genomics has huge potentials to produce lead compounds in a relatively short time period and can enable screening for inhibitors with increased selectivity for the target which should reduce potential side effect problems in the host (Stausberg *et al.*, 2003).

An important aspect for the identification and validation of a drug target is that they should be essential for growth of the organisms (Van Duin *et al.*, 2003). Drug target validation respects an efficient way of sorting and prioritizing a large number of candidate genes identified from genome sequences. The target genes can be validated:

1. Genetically, by showing that gene disruption and loss-of-function of the protein results in a non-viable or severely disabled parasite; and
2. Chemically, by demonstrating that a compound can specifically and selectively inhibit the function of the target protein, resulting in the death of the parasite.

Bioinformatics is an emerging field with the potential to significantly improve how drugs are found, brought to clinical trials and eventually released to the market. A validated drug target is an effector of a therapeutic compound such that, when modulated in humans, it has a desirable chemical use. Target validation requires biological information on the physiological role of the putative targets. Such targets are biomolecules that in most cases are protein such as receptors, enzymes and ion channels. These drug targets are proteins whose crystal structures (3-dimensional structures) are

either known (i.e determined by x-ray crystallography or NMR) or unknown, which has to be modeled.

2.1 Plasmodium Life Cycle

The malaria parasite enters the human host when an infected mosquito takes a blood meal. Inside the human host, the parasite undergoes a series of changes as part of its complex life-cycle. The plasmodium falciparum life cycle is shown below.

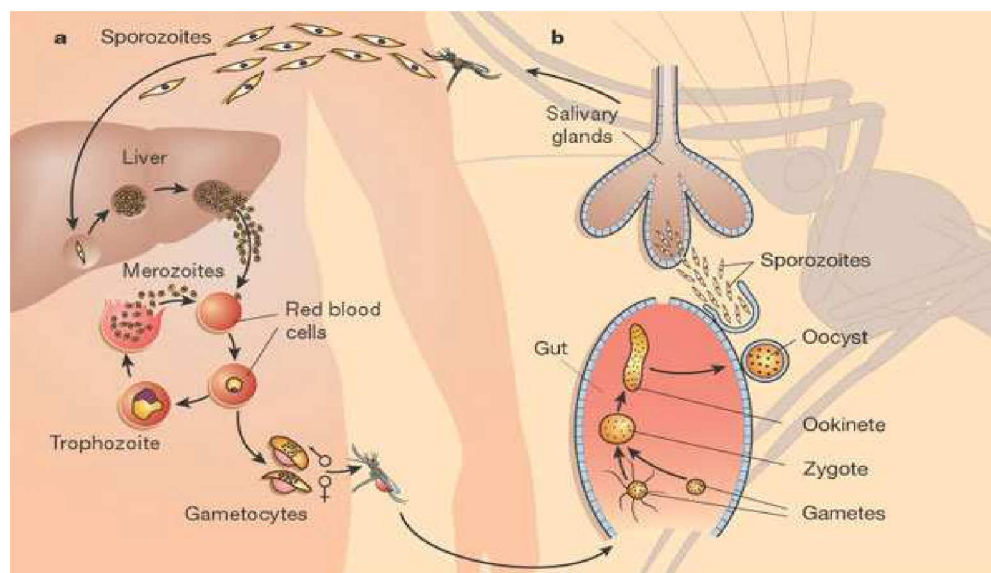


Figure: Life cycle of the parasite *Plasmodium falciparum*. (Dyann F. W., 2002).

a: When a parasite-infected mosquito feeds on a human, it injects the parasites in their sporozoite form. These travel to the liver, where they develop through several stages, finally producing merozoites which invade and multiply, via the trophozoite stage, in red blood cells. Eventually, up to 10% of all red cells become infected. (Clinical features of malaria, including fever and chills, anaemia and cerebral malaria, are all associated with infected red blood cells, and most current drugs target this stage of the life cycle.) The merozoites in a subset of infected red blood cells then develop into gametocytes.

b: When another mosquito bites the infected human, it takes up blood containing gametocytes, which develop into male and female reproductive cells (gametes). These fuse in the insect's gut to form a zygote. The zygote in turn develops into the ookinete, which crosses the wall of the gut and forms a sporozoite-filled oocyst. When the oocyst bursts, the sporozoites move to the mosquito's salivary glands, and the process begins again.

3. Motivation for the Study

The disease burden in Africa is one of the factors that have motivated our research in drug discovery in malaria. There are 500 million clinical cases of malaria per year

(White, 2004), well over a million deaths and over 95% of these deaths are in Africa while it is almost eradicated in Europe. These deaths occur mostly in children under age 5. Disability occurs due to the severe form of the disease. The burden is not just on individuals and the health sector, it is on the entire infrastructure and systems of the country that has to deal with the disease. We talk about disease burden in terms of morbidity and mortality. Malaria is found in tropical regions. The main disease burden is in Africa. Malaria has a link to poverty. If the map of the world is viewed according to poverty, it almost exactly overlaps the map of the malaria index. Where you have poverty, you have malaria. It is not just that poverty causes malaria. Malaria also feeds back into poverty. Malaria makes you less productive and the economy suffers; your health suffers as well. So, health and wealth are inextricably linked together.

4. Drug Discovery

The drug discovery process is complex, time consuming and very expensive. Typically, the time to develop a candidate drug is about 5 years, while the clinical phases leading, possibly, to the commercial availability of the drug are even longer (>7 years) for a total cost of more than 700 million dollars. The drug discovery process begins from the identification of an area of “unmet medical needs” and then proceeds by identifying “druggable” biological targets that could relieve the symptoms of the disease, or that are involved in the causative process of the disease. The pharmaceutical industry is moving from a symptomatic relief focus towards a more pathology-based approach where a better understanding of the pathophysiology should help deliver drugs whose targets are directly involved in the causative processes underlying the disease. The drug discovery process is very similar across different pharmaceutical companies. It consists of preclinical and clinical phases. In the target identification and validation step, “druggable” biological targets are identified. In the hit identification step, library of compounds ranging from tens to hundreds of thousands of compounds are screened against the “druggable” targets to identify those compounds that “hit” the targets using high throughput screening (HTS).

HTS methods based on experimental assays are reviewed extensively elsewhere. The number of compounds selected after this step is in the order of hundreds. By analyzing the structure of the selected compounds and identifying common active substructures, novel compounds containing those substructures are synthesized to significantly lower the number of lead compounds. This step is called lead identification. Structural bioinformatics and chemical informatics approaches to drug discovery are particularly useful in this step. However, widely used methods like structure-activity relationship (SAR) are outside the scope of this review. The leads identified are further refined to comply with pharmacokinetic constraints such as absorption and bioavailability, and to increase their potency and efficacy, while decreasing side effects and toxicity. This step is called lead optimization. Knowledge of the mode of action (MOA), that is, the identification of the therapeutic molecular target of the drug, can simplify the task of optimizing the drug candidate. Understanding the MOA can help predicting the effect of drug interactions and allow structure-activity relationships (SAR) to guide medicinal chemistry efforts toward optimization. However, for many drugs, the targets are unknown

and difficult to find among the thousands of gene products in a typical genome. Many new compounds fail when they are tested in humans due to lack of efficacy. Testing for efficacy early during the drug discovery process (i.e. before the clinical phases) is essential for reducing costs and time required. Therefore, the development of experimental and computational approaches to test for efficacy *in vitro* is critical. After the preclinical phases, a candidate compound is then selected and the clinical phase of the process can begin. This consists of clinical phase I, phase II, and phase III and possibly the launch into the market. Many compounds fail in the clinical phases of the process thus leading to consistent waste of time and money. A good review of the evolution of the drug discovery process can be found in Ratti et al. Computational biology and bioinformatics have the potential not only of speeding up the drug discovery process thus reducing the costs, but also of changing the way drugs are designed.

The increasing availability of genomic data for pathogens that cause tropical diseases has created new opportunities for drug discovery and development. However, if the potential of such data is to be fully exploited, the data must be effectively integrated and easy to interrogate. The development of the TDR Targets database (<http://tdrtargets.org>), which encompasses extensive genetic, biochemical and pharmacological data related to tropical disease pathogens, as well as computationally predicted druggability for potential targets and compound desirability information provide a means of accessing this data. By allowing the integration and weighting of this information, this database aims to facilitate the identification and prioritization of candidate drug targets for pathogens.

5. Three-dimensional Structure and the Drug Discovery Process

The past 30 years have seen an accelerating increase in our understanding of the molecular mechanism that underlie disease processes. This has had a fundamental impact on the process of drug discovery; the most of modern pharmaceutical research is based on target focused discovery, where the goal is to affect the biological activity of a particular molecular target to provide a cure for a disease. Since the 3D structures of some of these targets have become available, a range of experimental and computational methods have been developed to exploit that structure in drug discovery.

In a target focused approach, the cycle of discovery is very similar with or without a structure for the target. Initial hit compound are found that bind to the target and enters a medicinal chemistry cycle of making compound analogues and testing in suitable biological models. From these, the chemist builds hypothesis of what is important for the activities using experience (or inspired guesses). The chemist then makes changes that should improve the properties of the compound and the cycle of synthesis, testing and design begins again. These hypotheses develop a model of the conformations the compounds adopt, the chemical surfaces they project and the interaction made with the active site. Nowadays, an application of the 3D structure of both the compound and the target are a part of just about every drug discovery project. These targets can be experimentally determined, a model constructed on the bases of homology or a virtual model of the receptor created on the bases of the chemical structure of the known activity compound.

Drug discovery is an expensive and time consuming activity that mostly fails. Retrospective analysis of the pharmaceutical industry during the 1990s estimates that each new drug in the market takes an average of 14 years to develop, costing in the region of \$800 million. In addition, one in nine compounds that enters clinical trials makes it to the market. The failure rate in discovery research is similarly high. Depending on the company, therapeutic area and discovery strategy, at best only one in ten research projects that begin with a starting compound will generate an optimized candidate to enter clinical trials. For these reasons, most companies maintain a pipeline with a large number of projects in the early stages taking a diminishing number forward at each stage. The discovery process gets more expensive as you proceed; hence careful management of the portfolio is essential. The key is to make a right decision at the right time-knowing when to project is often more important than committing to continue.

Modern, target oriented drug discovery is usually organized into a series of stages. The definition of these stages differs from company to company and the details of the boundary will vary from project to project. Clear criteria needs to be established from one stage to another as, in general, the stages become progressively more resource and expense intensive.

6. Establishing a Target

Clearly, the starting point for a target oriented drug discovery is to identify a relevant target. In the pre-genomic era, targets were discovered through cellular and protein biochemistry methods, where a detailed understanding of the origins of a disease led to isolation and characterization of key protein molecules. The nature and significance of these targets were established before much of the modern machinery of molecular biology and genomics methods were available.

The approach to biological research has undergone dramatic changes in the past decade, with succession of omics technologies becoming available. Genomic has recorded the sequence of nucleic acid bases in many genomes, and continuing bioinformatics analysis is identifying the coding region. Comparing the genomes of both pathogens and host organisms can identify potential target genes. Transcriptomics methods monitored the identity and levels of RNA transcribed for each gene, and there have been high hopes that comparison of “normal” and diseased cells will identify targets.

Whatever the mechanism of identifying a target, there needs to be some level of validation before nominating it for a drug discovery project. The phrase “target validation” is much misused. A target cannot be said to be truly validated until a drug that uniquely affects that target is on the market. In general, the requirements for a target are to establish a biological rationale for why affecting the target will have desired therapeutic benefits. The best case for a target is to have a compound available that can provide the biological proof of concept. This is a compound that is sufficiently specific for the target of interest that can be studied either in cellular assays or in animal models or disease, to demonstrate that modulating a particular target will have the desired therapeutic benefit *in vivo*. In addition to biological validation, targets also need to be considered for what is termed druggability. That is, does the protein have a binding site

which can accommodate a drug-like compound with sufficient affinity and specificity? Although some experimental methods may be used to access these.

Enzyme active sites tend to be highly druggable consisting of a distinct clefts designed to bind small substrates and with defined shape and directional chemistry. For a structure based project, there is a clear structural gate - that is, the structure of an appropriate form of the target needs to be available. Sometimes (for example, in a small structure-based company), this is set as a strict gate, that is, unless the structure is available, hit identification cannot begin.

7. Potential Targets for New Anti-Malarial Drugs

Target-based drug discovery starts with the identification of target genes and their respective protein products (associated with or controlling a disease-relevant phenotype) that, when inhibited or activated, ameliorate the associated disease. To identify disease-relevant genes, robust tools are needed to allow biology-driven targets (Helmuth *et al*, 2005).

Drug-resistant strains of malaria parasites pose significant challenges to drug discovery efforts. This increasing resistance to multiple drugs may be the result of defective DNA repair or other pathways responsible for genomic stability (Trotta *et al*, 2004). The identification of promising novel drug targets is an essential but small part of the drug development process (Trouillar *et al*, 2002). Generating lead compounds from a validated target is a complex process requiring many steps, including appropriate expression of functional protein, assay development for high-throughput screening (HTS) and secondary assays for lead optimization. Though some chemical genomic strategies can help shortcut this process in many cases, it will still be essential. (Strausberg *et al*, 2003).

It will also be necessary to take the optimized lead through the complex and expensive process of toxicology clinical development. Even if the pharmaceutical industry were inclined to invest large sums of money in this process, it would not be possible to fully test and exploit all of the potential drug targets harvested from the genome information. Hence, it is vital to have stringent selection criteria early in the drug target identification and validation process in order to reduce the number taken forward for future development. New validated drug targets have already been identified for malaria and some important antimalarial drugs are in clinical trials (Lell *et al*, 2003).

Discovering new medicine is extremely difficult, takes a longtime and cost a lot of money. On the average, it cost over 800 million dollars and took 14 years from project inception for each drug that came to the market during the 1990s. It is also an activity where failure is expected and success is extremely rare. Analysis of drug development during the last decade suggests that only one in 10 drugs entering clinical trials eventually is available in the market.

Table 1: Novel drug targets for malaria

S/No	TARGETS	ENZYME/RECEPTOR	INHIBITOR/CANDIDATE MOLECULE	PDB CODE
1.	Food Vacuole	Plasmeppsins	Leupeptin, Pepstatins, Epoxysuccinate E64, Hydroethylamines, Chymostatin	Peptatin A from P.vivax (1QS8), Plm IV from Pf (1LS5), Plm II from Pf (3F9Q), Plm inhibitor (1W6H), Plm & inhibitor (1W6I), (1XDH), (1XE5)
2.	Food Vacuole	Falciplains	Statins, Semicarbazones, Epoxysuccinate E64, Leupeptin , Vinylsulfones, Isoquinolines	Falcipain 3 & Leupeptin (3BPM), Falcipain 2 & E64 (3BPF), Falcipain 2 from Pf (2GHU), Pf Falcipain 2 (1YVB), Falcipain 2 & inhibitor, K11017 (3BWK)
3.	Food Vacuole	Proteases	1,4-Bis(3-amino propyl) piperazine derivatives	CVB3 3C Protease & EPDTC (2ZTX)
4.	Food Vacuole	Peptidases	1,4-Bis(3-amino propyl) piperazine derivatives	Peptidase 4 – USP4 (3JYU), Human PPPDE1 (3EBQ) (Permitted Papain fold Peptidases of DS RNA viruses & eukaryotes 1)
5.	Food Vacuole	Methionine amino-peptidase	2-(2-pyridinyl)-pyrimidine	Human MAP-2 & SB-587094 (20AZ),MAP Inhibitors (2GGO, 2GG2, 2GG3, 2GG5, 2GG7, 2GG8, 2GG9, 2GGB, 2GGC)
6.	Shikimate Pathway	5-enolpyruvyl shikimate 3-phosphate synthase (EPSP synthase)	Glyphosate, 6-S-fluoroshikimate, 6-R-fluoroshikimate	EPSP & Shikimate (2AA9), EPSP & Shikimate & glyphosate (2AAY), EPSP & shikimate-3-phosphate & glyphosate (1G6S), EPSP & shikimate-3-phosphate (1G6T)
7.	Apicoplast	DOXR Reductoisomerase	Fosmidomycin	DOXP from Mycobacterium Tuberculosis (2JCV, 2JCX, 2JCY)
8.	Apicoplast	Acetyl-CoA Carboxylase (ACCase)	Acryloxy phenoxy propionate	Carboxyltransferase subunit of ACC from E.Coli (2F9Y)

S/No	TARGETS	ENZYME/RECEPTOR	INHIBITOR/CANDIDATE MOLECULE	PDB CODE
9.	Apicoplast	Purine nucleoside phosphorylase (PNP)	5-methylthio-iimucilin H	P.vivax PNP & Sulphate (3EMV), Human PNP & 2-mercapto(3H) quinazolinone (3D1V), Human PNP & 2-fluoroadenine (3GB9), Human PNP & 2-fluoro-2-deoxyadenosine (3GGS)
10.	Apicoplast	Histone Deacetylase (HDAC)	Trichostatin A (TSA), Apicidin, Salicyl hydroxamic acid (SHA), Vorinostat (SAHA) and Azelaic bis hydroxamic acid (ABHA), Suberoic bis hydroxamic acid (SBHA)	HDAC8 (1T64), HDLP (1C3R), SAHA (1T69-HDAC8, 1C3S-HDLP), TSA (1T64-HDAC8, 1C3R-HDLP), Human HDAC8 D101L (3EW8), Human HDAC8 H143A & substrate (3EWF), D101N (3EZP), D101E (3EZT), D101A (3F06)
11.	Redox System	Thioredoxin reductase (PfTrxR)	5,8-dihydroxy-1,4-naphthoquinone and 5-nitro-2-furanacrolein	Human TrxR 1 (2CFY), Human TrxR 1 (SeCys 498 Cys) (2ZZ0), Human TrxR 1 & Terpyridine Platinum II (2ZZB)
12.	Redox System	Gamma-Glutamylcysteine synthetase (Gamma-GCS)	Buthionine Sulfoximine	Michaelis Gamma-GCS (2D32), Gamma-GCS with Aluminium fluoride (2D33), Gamma-GCS from E.Coli B (1V4G)
13.	Redox System	Glutathione reductase	2-AAPA, Carmustine, Ariloxazines, Methylene blue, Buthionine Sulfoximine	Human GR (3GRS), E.Coli (1GER), Human GR near 1 Å resolution (3DJG, 3DJJ, 3DK4, 3DK8, 3DK9)
14.	Purine Metabolism	HGPRT – Hypoxanthine-guanine-xanthine phosphoribosyltransferase	Immucillin-H	Chimera of Pf and Human HGPRT (2VFA), Human HGPRT (1Z7G)
15.	Purine Metabolism	Adenosine deaminase (ADA)	Erythro-9-(2-hydroxy-3-nonyl) adenine, 2-deoxycoformycin (DCF)	P.yeoli ADA (2AMX), P.vivax ADA (2PGF), Ligands DCF (2PGR), Guanosine (2QVN), P.vivax ADA & MT-Coformycin (3EWC), Human ADA (3IAR)

S/No	TARGETS	ENZYME/RECEPTOR	INHIBITOR/CANDIDATE MOLECULE	PDB CODE
16.	Pyrimidine Metabolism	Thymidylate Synthase	5-fluoroorotate and N ⁵ -N ¹⁰ -methylene tetrahydrofolate analogues	Human Thymidylate Synthase with Dump and Tomudex (1I00)
17.	Cyclin-dependent protein kinases	Pfmrk	Quinolinones, Oxindoles, Thiophene Sulfonamide	hCDK2 (1QMZ), hCDK7 (1UA2)
18.	Glycogen Metabolism	Pyruvate Kinase (PfPyrk)	Fluorophosphate, ATP, Citrate, Ca ²⁺	Human Pyruvate Kinase M2 (3H60, 3GQY, 3GR4)
19.	Folate Pathway	Dihydrofolate reductase (PfDHFR)	Pyrimethamine, Cycloguanil	Human DHFR (1DHF), E.Coli DHFR (1RA9), Chicken liver DHFR (8DFR), DHFR/Thymidylate synthase (3K2H), DHFR inhibitor (3GHW)
20.	Heam Detoxification Pathway	Nicotinic Acid (ALH5)	β-Heamatin	Nicotinic Acid mononucleotide adenylyl-transferase from Bacillus anthracis (3DV2)
21.	Human Erythrocyte	Heat Shock Protein 90 (PfHsp90)	Geldanamycin	Yeast Hsp90 (2CG9), Pf Hsp90 & AMPPN (3IED), Human Hsp90 N-terminal (1YET), Yeast Hsp90 N-terminal (1AM1), Yeast (2CG9), Yeast Hsp90 Aha1 (1USU)
22.	Metabolic Pathway	Protein Farnesyl transferase (PFT)	Tetrahydroquinoline (THQ) Analogues	PFT with FPP & caged TKCVIM substrate (3DPY), Rat PFT (1SA5)

Structure based method provide a sobering reminder that there is little new in the ideas of the current wave of structure based discovery and exemplify the two long standing applications of structural method in drug discovery. The first is to provide detailed understanding of the mechanism of action of the protein molecules and how this relate to its biological factors. Such understanding can be important in designing strategy for modulating the activity of the target and the design of the in vitro and in vivo assays on which drug discovery depends. The second conventional use of structural method is to use the structure of a lead molecule bound to the target to guide the design of modifications to improve compound affinity, selectivity or drug like properties. These protein crystal structures are important in moving drug discovery to be more rational and target oriented. As more structural information become available, an increasing number of drug discovery projects use rational, target oriented approaches that rely on either explicit or model structures of the target.

Table 1 presents novel drug targets for *Plasmodium falciparum*. We have presented a summary of drug targets and candidate molecules for malaria parasite. The enzyme/receptors are also specified. The Protein Data Bank (PDB) codes are also given for molecules whose structures are available.

8. Conclusion

Nigeria is a malaria endemic country and there is a global effort to eradicate malaria. The development of new anti-malaria interventions is urgently needed to combat the growing mortality and morbidity caused by malaria and the increasing prevalence of drug resistance to plasmodium parasites. We have principally identified putative molecular targets based on various aspects of the malaria parasite. These putative targets could be helpful for the future development of new antimalarial drugs.

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