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***In Silico* Resources for Malaria Drug Discovery**

Pieter B. Burger and Fourie Joubert
University of Pretoria
South Africa

1. Introduction

Drugs currently in use against the malaria parasite have been derived from known natural compounds, or discovered serendipitously. The completion of the *Plasmodium falciparum* genome project at the turn of the century (Gardner *et al.*, 2002) raised great hopes for the identification of a wealth of targets against which to design new and novel drugs. However, it soon became apparent that the challenges associated with the annotation of the malaria proteome was creating a significant hurdle to be overcome already in the early stages. In addition, the complexity introduced by the multitude of factors that need consideration in selecting suitable drug targets made it difficult to perform the selection of target proteins in a high-throughput automated fashion. The need for the development of effective *in silico* approaches required to successfully address these problems were identified and addressed by the malaria community.

This chapter focuses on *in silico* resources that are available to support researchers working in the area of malaria drug discovery. It aims to facilitate the researcher's entry into early phase drug discovery by lowering the initial barrier to data mining sometimes perceived as a daunting task due to information overload. While *in silico* experimentation is not intended to replace detailed experimental work, it may be extremely useful in decreasing the size of the protein and chemical space to be investigated *in vitro*, and may help guide the experimentalist's decision making during the selection process. These resources are intended to assist the researcher in rationally selecting a relatively small number of targets out of the whole for further detailed investigation. The *in silico* resources discussed here vary from primary data repositories, to advanced data mining systems, and provide information on a variety of different levels in discovery research.

Genome databases are often the first point of access. Whereas they always contain the primary data generated during the genome project, they usually contain significant amounts of annotations regarding gene structures and gene products including nucleotide and protein sequences. The annotation detail may vary, as is the case with the malaria genomes. *Plasmodium falciparum* has been annotated extensively, but the level of annotation for the other Plasmodia may range widely. The genome database for malaria parasites additionally provides extensive information on gene variation, protein features, expression and a wide variety of other molecular properties and is a rich resource from which to embark on further study. Each entry also provides many external links for exploration.

The more specialized databases are typically derived from the data present in the genome database, and provide focussed information on specific aspects related to the molecules available. There are several resources containing information around metabolic pathways of the malaria parasites, assisting researchers in understanding the pathways present in the organisms, and the role of specific proteins or compounds in the organisms’ metabolic activity, which is especially useful in deciding on aspects of the parasite metabolism that may be selected for interference. Protein-protein interaction resources highlight interacting proteins, but additionally allow the researcher to begin understanding the interaction and regulatory network that the parasite requires for growth and survival, together with possible ways to manipulate this homeostasis. Gene expression resources provide insights into the regulatory mechanisms of gene expression, especially in terms of changes in expression profiles over the different stages of the parasite. Functional prediction resources attempt to expand the annotation of novel and unassigned proteins produced by the parasites, particularly by attempting to use methods that may be independent from the protein sequence of the molecule using eg. guilt-by-association approaches. Protein structure databases provide the researcher with experimentally-determined structures or models to help understand molecular mechanisms, and for further use in comparative undertakings and molecular modeling projects. Literature resources focus on articles published on the many aspects of malaria and its molecules, and may attempt to automatically extract value-added information from the text. Drug discovery resources attempt to integrate many of the aspects already mentioned here into a single system, where researchers may perform the selection and scoring of possible drug targets and lead compounds in an automated or semi-automated fashion.

A summary of the resource discussed in this Chapter is presented in Table 1.

Name	URL
PlasmoDB	http://www.plasmodb.org
Malaria Parasite Metabolic Pathways	http://sites.huji.ac.il/malaria
PlasmoCyc	http://plasmocyc.stanford.edu
KEGG	http://www.genome.jp/kegg
PlasmoMap	http://www.cbil.upenn.edu/plasmoMAP
IDC Strain Comparison Database	http://malaria.ucsf.edu
PlasmoDraft	http://www.atgc-montpellier.fr/PlasmoDraft
Protein Structure Database	http://www.pdb.org
TDI Kernel	http://tropicaldisease.org/kernel
ModBase	http://modbase.compbio.ucsf.edu
Malaria Literature Database	http://carrier.gnf.org/publications/Py
ChEMBL	http://www.ebi.ac.uk/chembl/db
TDR Targets	http://tdrtargets.org
Discovery	http://discovery.bi.up.ac.za

Table 1. A summary of resources discussed in this chapter

2. Malaria genome databases

2.1 PlasmoDB

URL: <http://www.plasmodb.org>

PlasmoDB (Aurrecochea *et al.*, 2009) is the primary resource for malaria genome information, and is part of the larger EuPathDB project (Aurrecochea *et al.*, 2010) which is focussed on eukaryotic pathogens. The PlasmoDB resource contains genome data for *P. falciparum*, *P. vivax*, *P. yoelii*, *P. berghei*, *P. chabaudi* and *P. knowlesi*. PlasmoDB is regarded as the primary distribution point for malaria sequence data, and while genome and proteome data are available for download, an advanced data mining system is provided for complex queries in gene, protein and related features. The most basic mechanism to access the PlasmoDB site is by searching using either a known accession number or a keyword. The more useful approach is to perform a text-based query, where series of species and data fields may be selected for searching. This will provide the user with a list of entries matching the search criteria. When an entry is selected, a page for the molecule is displayed, containing the genomic context, together with annotation, protein, expression and sequence information.

Each of these categories has a rich subset of information, which may be selected for display, including single nucleotide polymorphisms, sequence alignment vs. the other malaria species, links to annotation information in other databases, orthologs and paralogs, ontology information, metabolism information, physical-chemical information, structural information, immunological information, microarray and proteomics results (Figure 1). Some of the additional data is generated by the PlasmoDB group, while other data is linked to 3rd-party sites and research groups.

While a simple text search may be useful in straight-forward cases, the powerful query engine underlying the resource provides the user with the capability to select molecules based on a range of properties, in a sequential or branched fashion. Filters may be based on a wide range of properties as described in the previous paragraph. As an example, a scenario is illustrated where the user is interested in finding all *P. falciparum* proteins matching the text term “synth*” where the effect of SNPs may be predicted on a 3D level. An initial query may be performed by selecting all proteins containing the annotation “synth*”. The user is then presented with a graphical view of his query results, showing the number of initial results (119 in this case). An additional intersect filter may then be added to only show proteins where SNP information is available (68 genes). This may then be further filtered to only show proteins where predicted 3D-structures are also available (12 genes). The complete search strategy is visualized graphically as a pipeline (Figure 2), where the user interactively may alter points in the search strategy, create branches and set weighting for different aspects of the search. In a search strategy, unions and intersects will sum the weights, giving higher scores to items found in multiple searches. This interface is regarded as one of the most powerful, user-friendly and intuitive for all biological databases.

Users may create a personal account on the site, and search strategies as well as results may be saved in this way. In addition to the database searches, a series of tools are also

available at PlasmoDB. These tools enable the user to perform BLAST searches against the malaria data, retrieve sequences by lists of gene IDs, access links to the PubMed and Entrez sites, access the malaria genome data in the GBrowse genome browser interface (Stein *et al.*, 2002), predict apicoplast-targeting signals, predict mitochondrial transit peptides and access the PlasmoCyc metabolic pathway annotations. Additionally, a web services WADL (Web Application Description Language) specification for searches against PlasmoDB is provided.

PlasmoDB is carefully curated, highly quality controlled and updated at a very regular frequency. Information about the available data is easily accessed from the data summary section on the front page of the resource. PlasmoDB would be the first resource to visit for a researcher embarking on a malaria drug discovery project, to obtain data about the availability of genes and proteins of interest, together with the relevant annotations and value-added information.

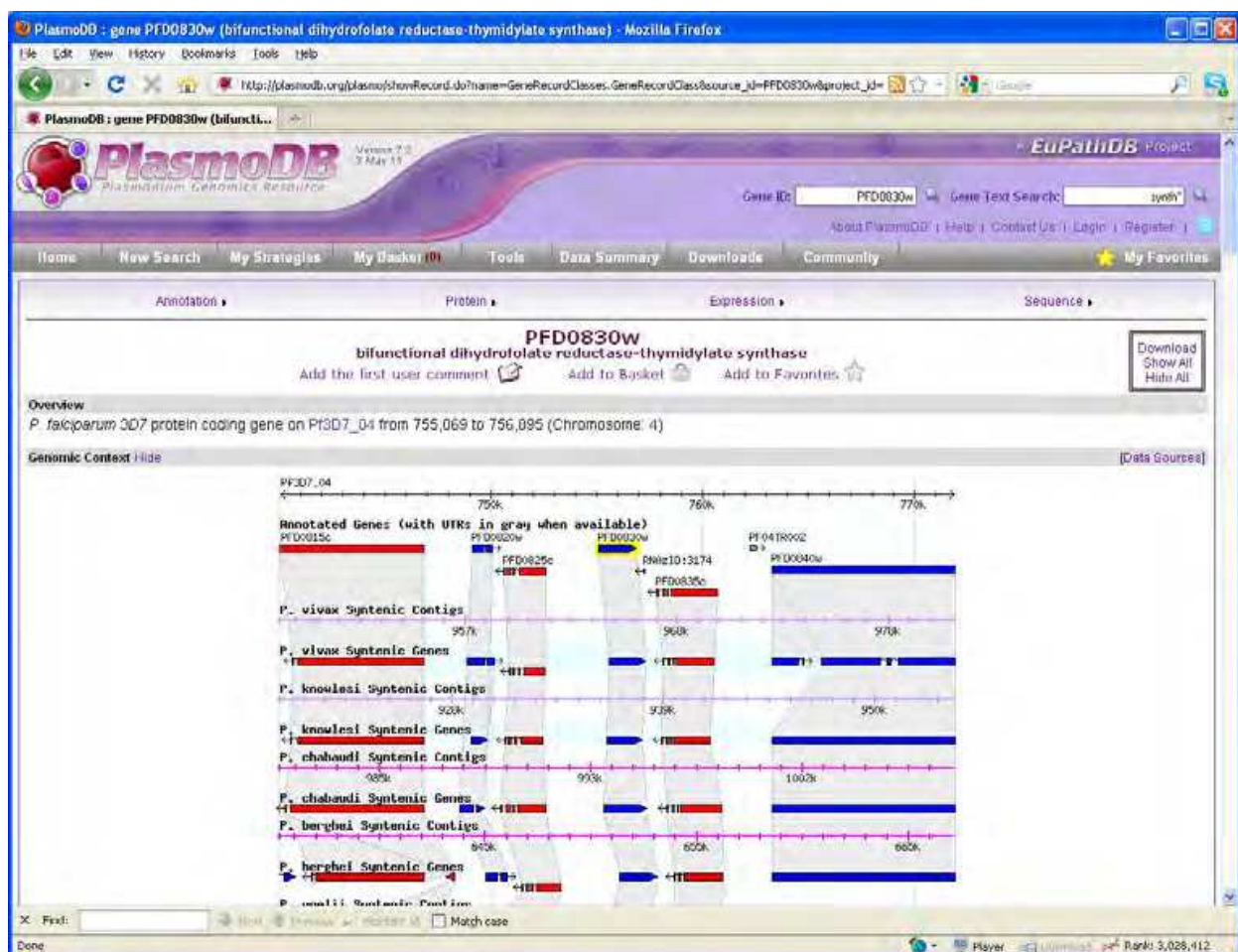


Fig. 1. The result view for the protein PFD0830w (bifunctional dihydrofolate reductase-thymidylate synthase from *P. falciparum*) in the PlasmoDB, showing the genomic context together with syntenic genes in other species. The rest of the detailed gene information mentioned in the text is not visible in this figure but continues lower down the browser screen.

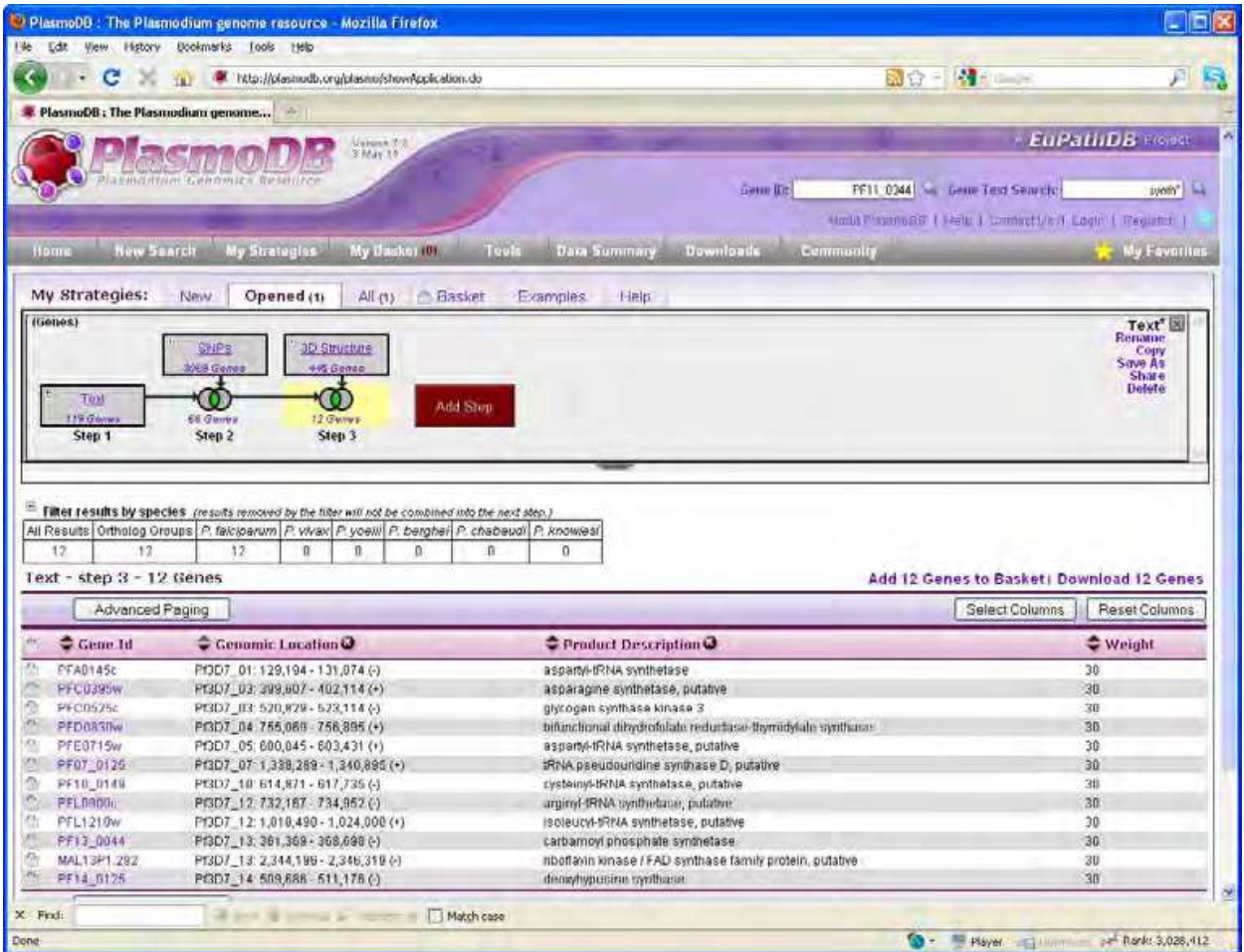


Fig. 2. The advanced result display interface of PlasmoDB, at the top graphically showing the data query pipeline with filtering steps performed using an initial text query followed by the availability of SNP information and 3D structural information. The resulting hits from the query are shown at the bottom. These steps may be edited again, or further branched and expanded.

3. Malaria metabolism databases

3.1 Malaria Parasite Metabolic Pathways (MPMP)

URL: <http://sites.huji.ac.il/malaria>

The Malaria Parasite Metabolic Pathways resource is maintained by Hagai Ginsburg, and is the most complete and up-to-date source of information for metabolic pathways in malaria (Ginsburg, 2009). Researchers may be interested in exploring information about the different enzymes in a pathway together with their characteristics, or alternatively in seeing the role that a specific enzyme plays in one or more pathways. MPMP has been constructed based on enzymes annotated in the parasite and on pathways known to occur in unicellular eukaryotes. While the pathways have been cross-checked against PlasmoDB, not all enzymes and reactions have been validated in malaria. The site also includes information related to cell-cell interactions, invasion of the erythrocyte and transport functions. The site

provides information in a hierarchical fashion, starting with grouped pathways based on chemical component or biological process. This is followed by specific pathways or process, chemical structures and enzymes together with their genes. To browse the site, the user selects a primary category, such as carbohydrates. This is followed by the selection of a specific category. In this example, first carbohydrate metabolism and then specifically the glycolysis pathway was selected for visualization. A graphical overview of the glycolysis pathway is displayed. The overview shows the enzyme names, EC numbers, co-factors and metabolites of the pathway, as well as links to other metabolic pathways (Figure 3). The site may also be searched using enzyme names, EC numbers, other protein names or the names of metabolites.

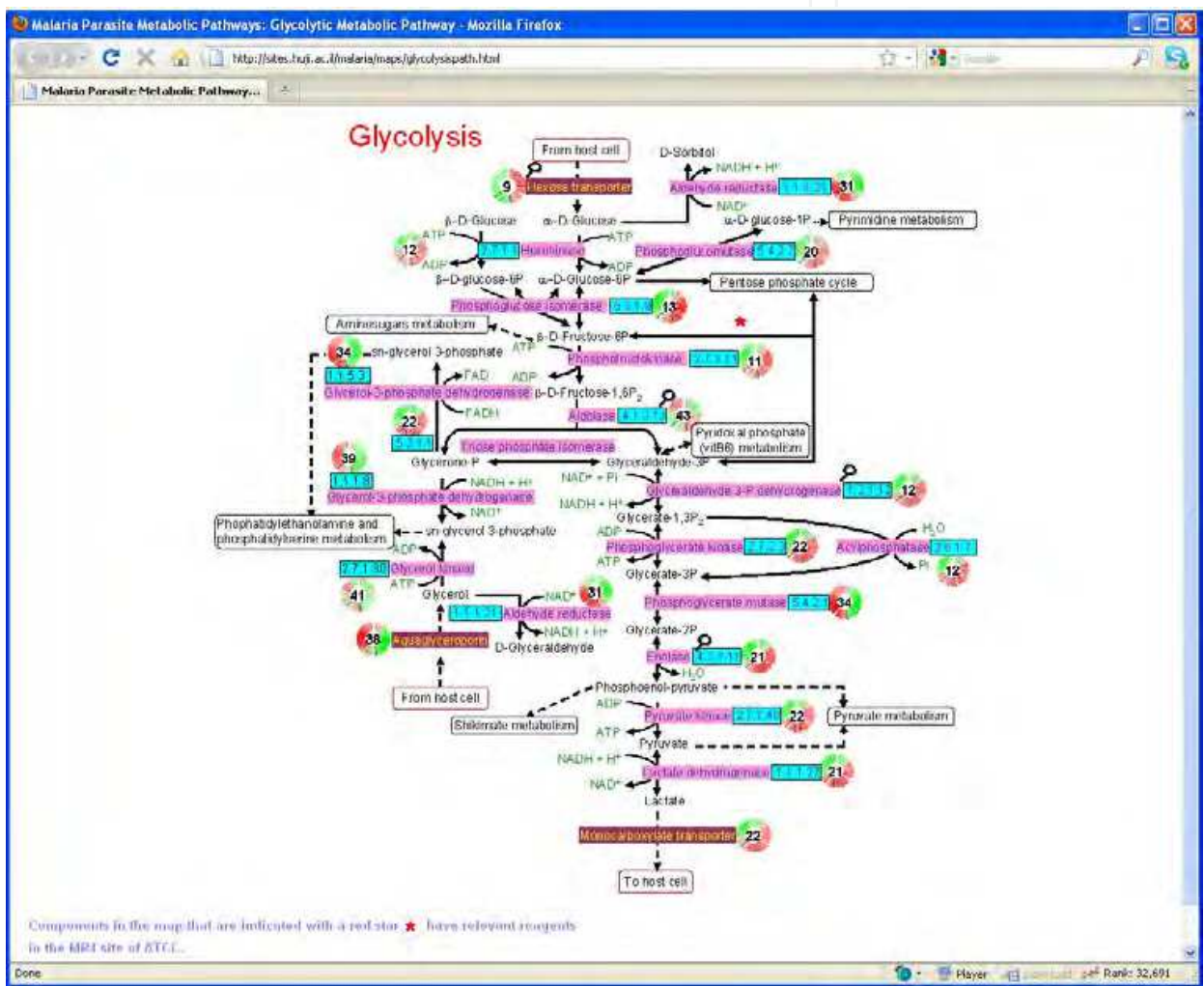


Fig. 3. The glycolysis pathway, as shown in Malaria Parasite Metabolic Pathways. The enzymes and well as chemical compounds and co-factors are visible. A small glyph showing stage-specific expression information is also shown where available.

From each enzyme, links are available to a set of other metabolic pathways databases including BRENDA (<http://www.brenda.uni-koeln.de>), ExPASy ENZYME (<http://www.expasy.org/enzyme>) and the IUBMB reaction schemes (<http://www.chem.qmul.ac.uk/iubmb/enzyme/reaction>). Links are also provided to PlasmoDB

(<http://plasmodb.org>), and *P. falciparum* GeneDB (<http://www.genedb.org>). From metabolites, links are provided to KEGG (<http://www.genome.jp/kegg>) which provides chemical structures and formulas. The links provide access to a wealth of information including enzymatic activity, enzyme assays, kinetic parameters and inhibitors. Stage-dependent transcription of each enzyme is also shown as a pie-chart, based on the DeRisi/UCSF transcriptome database (<http://malaria.ucsf.edu>).

3.2 PlasmoCyc

URL: <http://plasmocyc.stanford.edu>

PlasmoCyc (Yeh *et al.*, 2004) forms part of the larger MetaCyc resource, where metabolic pathways for a range of organisms have been modeled. PlasmoCyc was initially constructed automatically using annotated EC terms as input to the PathoLogic tools (Caspi *et al.*, 2006). Additional enzymes and reactions were then manually added afterwards based on information obtained from literature. The pathways constructed in this fashion were then further expanded using data from the Malaria Parasite Metabolic Pathways resource. The PlasmoCyc site additionally hosts a set of potentially-interesting drug target proteins, together with motivations for their choice and literature references. PlasmoCyc may be accessed by searching for an enzyme name or EC number, using an ontology browser, or choosing from a list of pathways, proteins or compounds. Pathways may be viewed at different levels of detail. The initial view shows enzyme names, and the next level adds PlasmoDB IDs, EC numbers, compounds and co-factors. The subsequent level provides chemical structures of the compounds. In this example, the glycolysis pathway was selected for display (Figure 4). A useful functionality is the species comparison tool, where metabolic pathways may be compared between several different species to test for differences in the presence of pathway components and to identify unique enzymes for target selection.

3.3 Kyoto Encyclopedia of Genes and Genomes (KEGG)

URL: <http://www.genome.jp/kegg>

KEGG is a very comprehensive database on metabolism in many species, and includes malaria. KEGG includes information for pathways, diseases, drugs, orthology, genes, genomes, compounds and reactions (Kanehisa & Goto, 2000; Kanehisa *et al.*, 2010; Kanehisa *et al.*, 2006). KEGG contains pathway representations for *P. falciparum*, *P. vivax*, *P. yoelii*, *P. berghei*, *P. chabaudi* and *P. knowlesi*. KEGG may be accessed using various approaches. A common approach for browsing pathways is to select the KEGG pathway entry point, followed by a reference pathway of interest. Subsequently, an organism may be selected. Enzymes identified in the organism are then highlighted using color coding. In this example, the glycolysis pathway was selected for display (Figure 5). Selecting an enzyme on the pathway will provide a detailed page of information on the enzyme, including the sequence, known motifs and links to other databases such as SSDB, GenBank, PlasmoDB, GeneDB and UniProt. Selecting a compound will provide a detailed page including physical-chemical properties, the structure, reactions linked to the compound, pathways linked to the compound, enzymes linked to the compound and links to other databases such

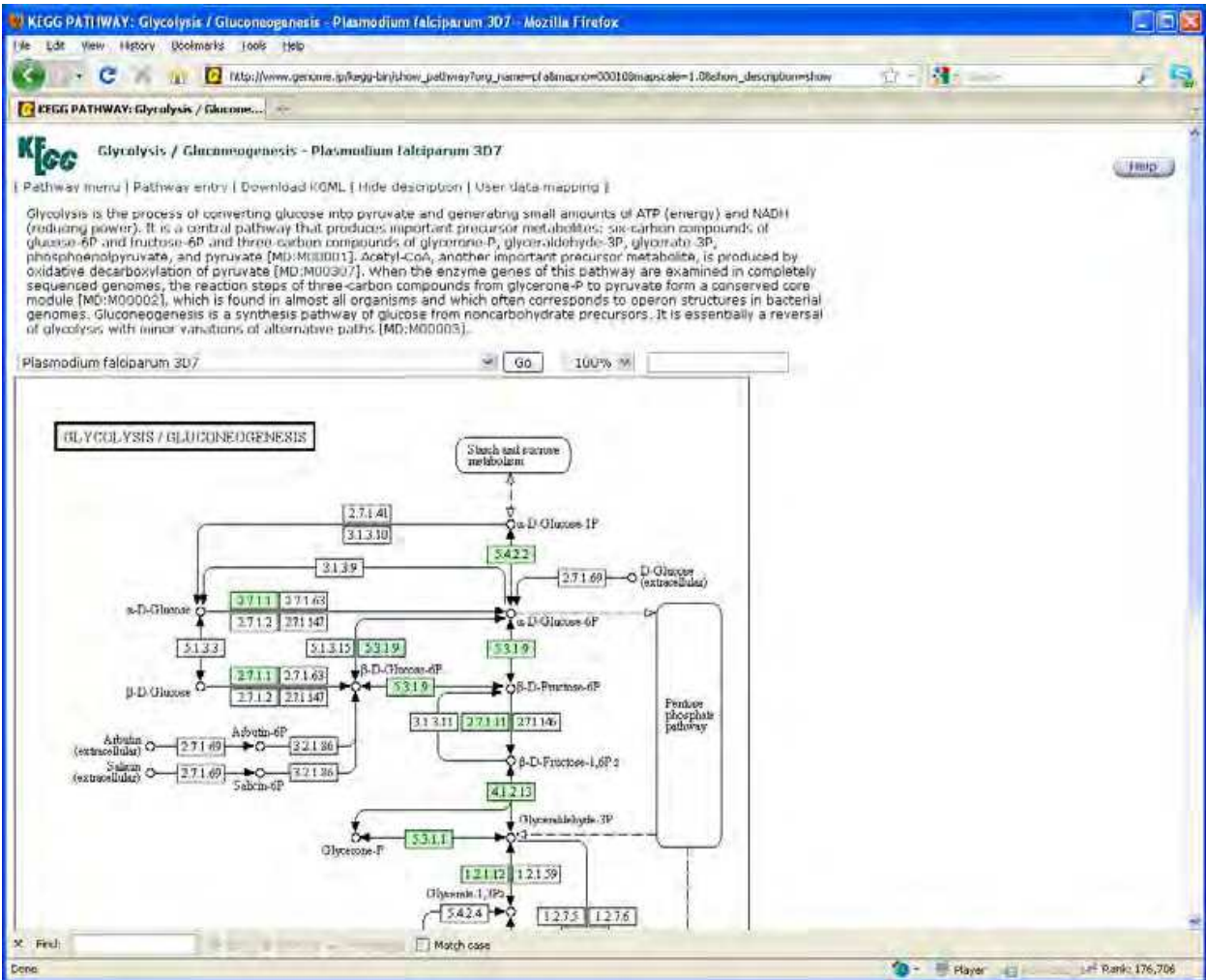


Fig. 5. The glycolysis pathway, as shown in KEGG. EC numbers and chemical compounds names are shown.

4. Protein-protein interaction databases

4.1 PlasmoMAP

URL: <http://www.cbil.upenn.edu/plasmoMAP>

PlasmoMAP is focussed at functional interactions between proteins in *P. falciparum* (Date & Stoeckert, 2006), with the goal of eventually illustrating a complete interactome. It is based on the reconstruction of functional genomics and computational data using a Bayesian framework. The interaction network covers around 68% of the parasite genome and infers information for nearly 2000 uncharacterized proteins. PlasmoMAP contains data for *P. falciparum* strains HB3, 3D7 and Dd2. The resource allows the user to access the data by either generating a complete protein-protein interaction dataset at a specified cut-off value, or by specifying a protein name for which to generate interaction partners. The PlasmoMAP network data is made available for download in LGL format, so that the networks may be viewed using the LGLView application. Additionally, the raw functional genomics data may be downloaded, as well as various subsets of the interaction data by confidence, by KEGG category, by GO category and by linkages detected in other apicomplexan organisms.

5. Gene expression databases

5.1 Malaria IDC strain comparison database

URL: <http://malaria.ucsf.edu>

The IDC site presents the data from the DeRisi lab studies on the transcriptome analysis of *P. falciparum* (Bozdech *et al.*, 2003; Llinás *et al.*, 2006). Queries may be executed using a variety of terms, including PlasmoDB ID, ORF description, oligonucleotide ID, automated prediction, automated description, GO annotation, GO number, common gene name, functional group, chromosome or by providing a list of ORFs or oligonucleotides. Strain, time, Fourier, amplitude and CGH constraints may be set for queries. In this example of viewing the expression of a specific gene, a query was performed for the PlasmoDB ID PFD0830w (bifunctional dihydrofolate reductase-thymidylate synthase) and the expression data for the d33539_76 oligonucleotide was visualized for the 3D7 isolate (Fig 6). The chromosomal

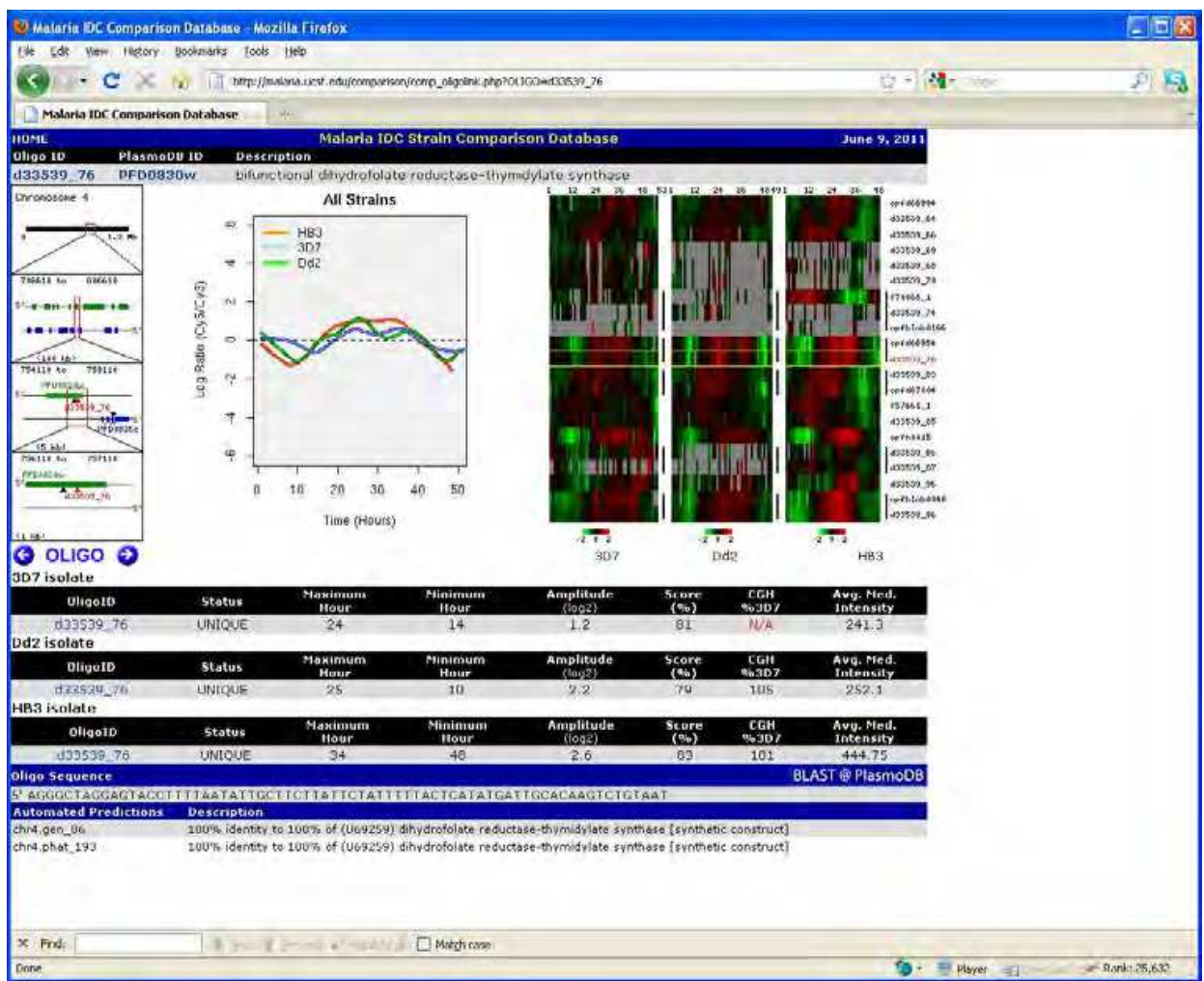


Fig. 6. The expression profile of PFD0830w (bifunctional dihydrofolate reductase-thymidylate synthase from *P. falciparum*) visualized in the Malaria IDC Strain Comparison Database as measured using the d33539_79 oligonucleotide probe. The chromosomal position is shown on the left. The expression of the gene over time is visible as a graph for the different parasite strains, and a heat map of expression measured by other probes are shown on the right. Detailed information is provided at the bottom.

location, log-ratio of expression over time and strain comparison heat map are shown together with a table providing more detailed time, median and scoring information. When a search is performed using specific constraints over the complete dataset, matching genes are shown in a tabular fashion, together with a miniaturized heatmap of the expression profile. The IDC data is also made available for download in normalized as well as non-normalized formats. Furthermore, the raw image files from the study may also be obtained.

6. Functional prediction databases

6.1 PlasmoDraft

URL: <http://www.atgc-montpellier.fr/PlasmoDraft>

The PlasmoDraft database predicts GO terms for genes from *P. falciparum*. It is based on a Guilt By Association (GBA) predictor named Gonna, measuring the profile of a gene's similarity using data from transcriptome, proteome and interactome studies to genes in the GeneDB database (Bréhélin *et al.*, 2008). The database may be viewed globally for each gene ontology category (Molecular Function, Biological Process and Cellular Component). The GO term is displayed, followed by its parameters for a series of parasite strains. These include prior probability (indicating term frequency), the best global degree of belief (GDB) and its confidence (TDR: True Discovery Rate). These are indicated using a color code varying from green to red (Figure 7). The database may also be searched using a gene, a GO term identifier or a keyword. This approach to functional prediction is complementary to the classical sequence based-approaches. Around 60% of genes lacking annotations are included, in addition to genes already annotated in GeneDB. Particularly useful is the ability to identify GO terms attached to a specific gene, and also genes attached to a specific GO term.

7. Protein structure databases

7.1 PDB

URL: <http://www.pdb.org>

Although not malaria-specific, the PDB database is the global repository for all protein structure information, derived primarily from X-ray crystallography and NMR studies (Bernstein *et al.*, 1977). At the time of writing, there were 59 structures from Plasmodia, of which some were duplicates of the same protein with different ligands or with single / multiple mutations. The PDB database may be searched using an extensive range of criteria, but the main approaches are using a text term search or performing a BLAST search using a protein sequence to find homologous proteins. The results view of a protein structure includes a preview of the protein structure, literature information, a molecular description, information about related PDB entries and information about associated ligands (Figure 8). The structure may be interactively viewed using Jmol (<http://www.jmol.org>). The structural and sequence data may be downloaded in a range of formats for further investigation.

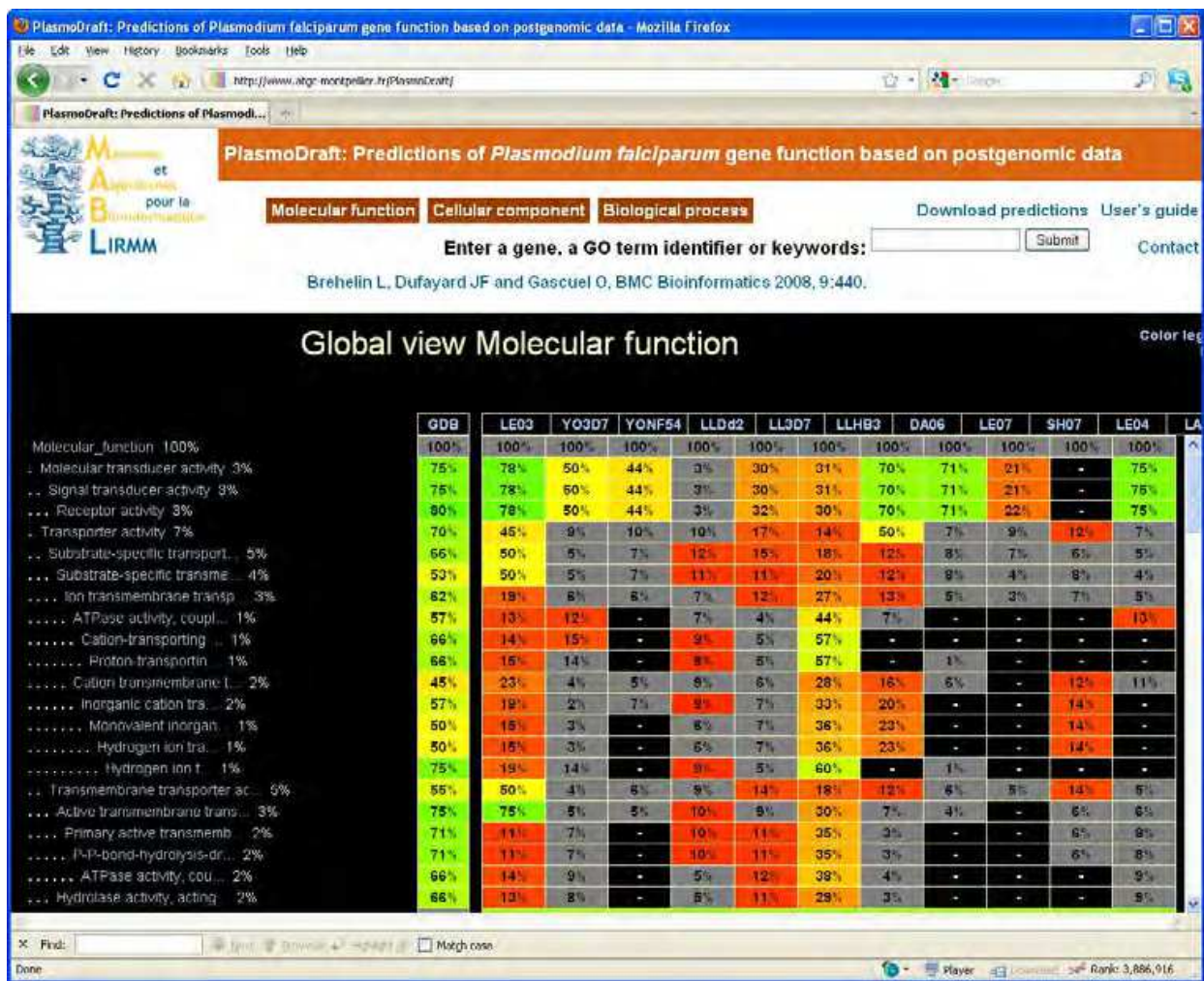


Fig. 7. A global view for a series of parasite strains based on the GO Molecular Function classification in PlasmoDraft. GO categories are listed on the left of the table, and the results are shown in columns for a series of different parasite strains.

7.2 TDI Kernel

URL: <http://tropicaldisease.org/kernel>

The TDI Kernel strongly supports the Open Source approach to drug discovery, and is aimed at the prediction of binding sites and ligand interactions through homology modeling approaches (Ortí *et al.*, 2009). Targets may be searched by organism, which includes *C. hominis*, *C. parvum*, *L. major*, *M. leprae*, *M. tuberculosis*, *P. falciparum*, *P. vivax*, *T. brucei*, *T. cruzi* and *T. gondii*. Further search criteria include keywords, UniProt IDs, DrugBank IDs, PDB Ligand ID and homology modeling parameters. At the time of writing, 28 templates had been analyzed for *P. falciparum*. The detailed view of a target shows the templates used for homology modeling, provides the generated models and shows the ligand predictions for the selected target (Figure 9). Each of these may be investigated further through links to PDB, MSD (<http://www.ebi.ac.uk/msd>) and DrugBank (Wishart *et al.*, 2008). For each prediction, the result may be expanded to further show a figure of the ligand bound in the active site, drug category information for the ligand, and current uses of the drug.

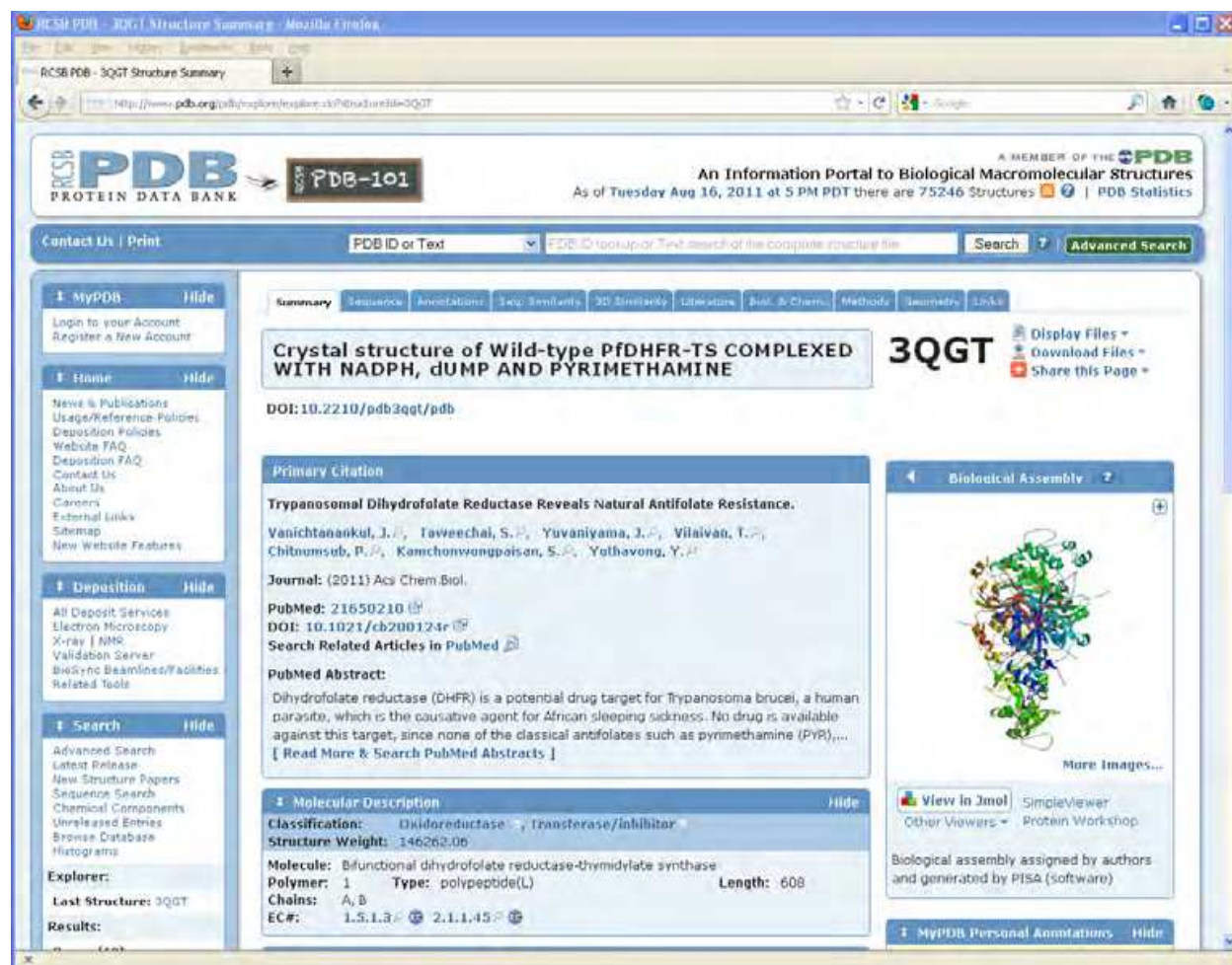


Fig. 8. The PDB results page for a structure of PFD0830w (bifunctional dihydrofolate reductase-thymidylate synthase from *P. falciparum*). A summary of the protein's information is shown in the centre, with a structural overview on the right.

7.3 ModBase

URL: <http://modbase.compbio.ucsf.edu>

ModBase is an extensive collection of homology models for a variety of species, including *P. falciparum* and *P. vivax* (Pieper *et al.*, 2009). The homology models have been constructed using ModPipe, a pipeline which uses mainly PSI-BLAST (Altschul *et al.*, 1997) and Modeler (Eswar *et al.*, 2006) for model building. At the time of writing, ModBase contained models for 2599 *P. falciparum* and 2359 *P. vivax* proteins. Searches may be performed using text terms or protein sequence, and results may be displayed as either a model overview, detail regarding the model or a sequence overview. The detailed view contains information about the model coverage of the protein sequence, model quality parameters, graphical representations of the protein structure and a wide range of external links to other relevant databases (Figure 10). Where available, SNP information and ligand binding sites may also be viewed.

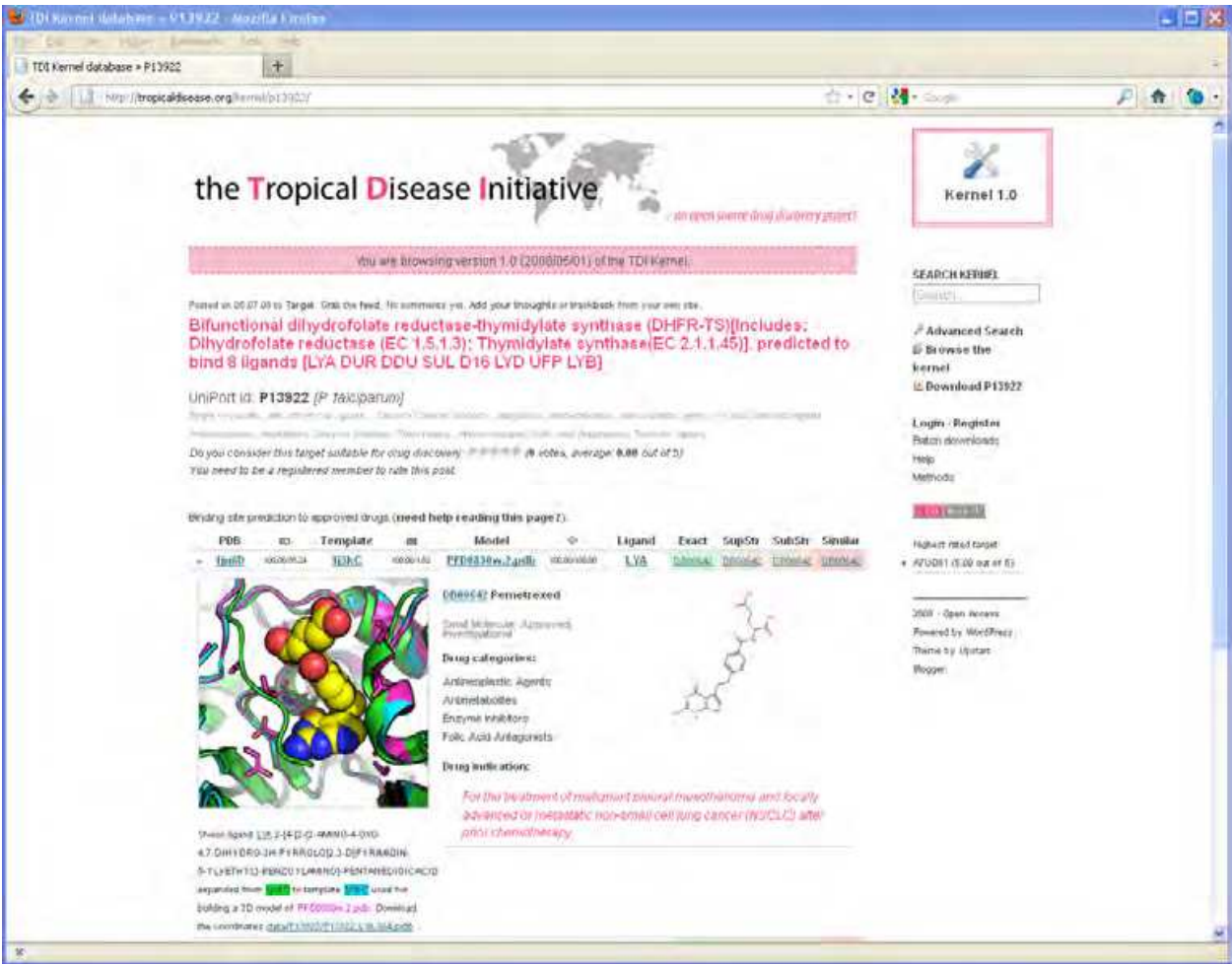


Fig. 9. The result view for PFD0830w (bifunctional dihydrofolate reductase-thymidylate synthase from *P. falciparum*) with LYA in the TDI Kernel resource. A structural view of the ligand in binding site is shown, as well as additional information about the protein and ligand.

8. Literature databases

8.1 The malaria literature database

URL: <http://carrier.gnf.org/publications/Py>

The Malaria Literature Database is compiled by the Genomics Institute of the Novartis Research Foundation. Whereas most literature searches focus only on abstracts, Google Scholar and Scirus is used to search in the body of Open Access papers for the presence of gene names. Gene name - publication pairs are then collected and indexed. Additionally, searches may be performed for genes, orthologs and published papers. Gene results are displayed with PlasmoDB links, and ortholog results are shown. Literature results are shown together with PubMed PMID links for easy access to the abstracts and papers. It is also possible to download all data in batch format.

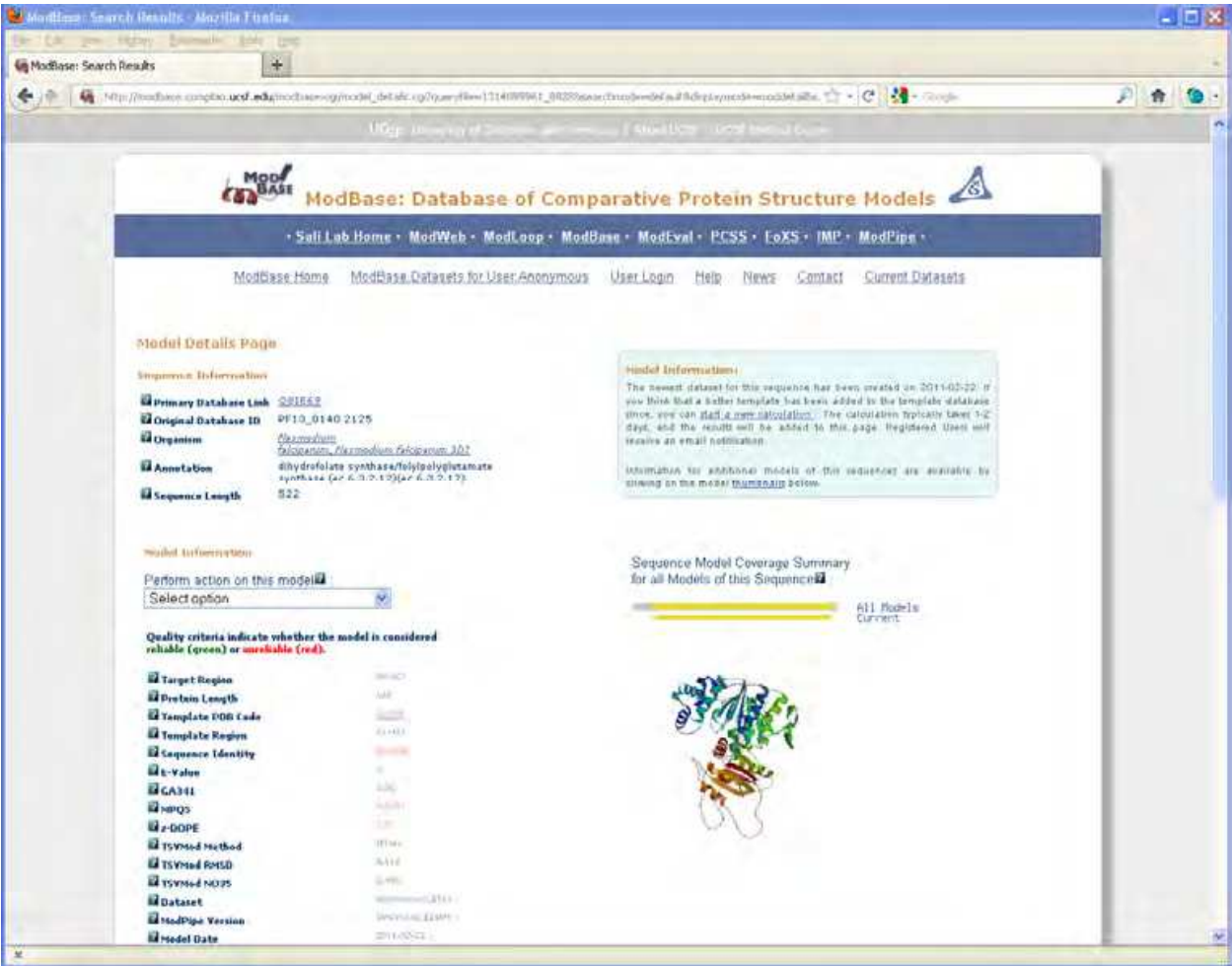


Fig. 10. A detailed view of a homology model of PFD0830w (bifunctional dihydrofolate reductase-thymidylate synthase from *P. falciparum*). Model parameters are shown on the left, with an alignment overview and graphical representation of the protein structure on the right.

9. Drug discovery databases

9.1 ChEMBL

The ChEMBL database is primarily a database of bioactive small molecules, and provides access to a wide range of targets and chemical compounds, including industry-generated datasets such as the GSK TCAMS malaria dataset and the Novartis-GNF malaria box set in the ChEMBL-NTD section (Overington, 2009). The targets section may be searched using either a keyword, protein sequence or a ChEMBL ID. The results for a specific target include bioactivity data, assay categories and parameters available for the target and a chemical classification of the related compounds by molecular weight, logP and PSA (Figure 11).

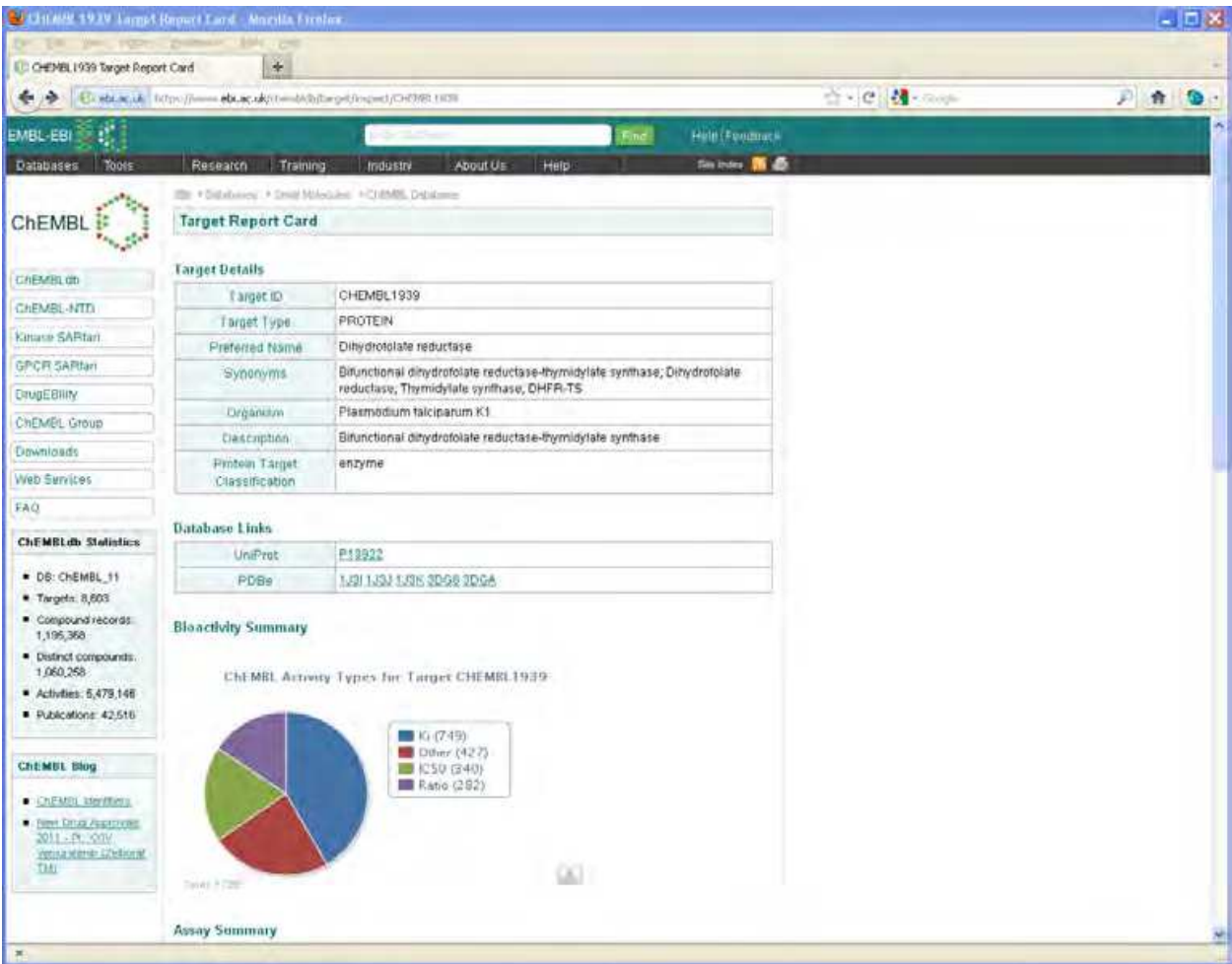


Fig. 11. The result view for PFD0830w (bifunctional dihydrofolate reductase-thymidylate synthase from *P. falciparum*) in ChEMBL. The protein’s details are shown at the top, with database links followed by a graphical summary of available binding data at the bottom.

These are presented as a graphical summary view, where each section may be explored further. The next level of results is a table showing the compound structure, bioactivity, assay type, assay source, results and literature reference (Figure 12). Links between proteins and compounds are established through manual literature curation.

Chemicals may be searched using text-based queries or chemical structures. Results are returned in a tabular format with chemical structures and detailed chemical properties. When a compound is selected for further exploration, clinical trials relevant to the compound, bioactivity, assay and protein target information are also shown together with links to external databases. A search functionality for assays is also available. The ChEMBL database additionally contains specific resource areas for kinases (Kinase SARfari) and for G protein-coupled receptors (GPCR SARfari). It also contains the DrugEBility resource focussed on structure-based drugability.

ChEMBLdb - Mozilla Firefox

ChEMBLdb

ebi.ac.uk https://www.ebi.ac.uk/chembl/bioactivity/results/1/compound/chembl115483/0

Fig. 12. A more detailed view for PFD0830w (bifunctional dihydrofolate reductase-thymidylate synthase from *P. falciparum*)-related compounds in ChEMBL. The chemical structures of the parent compound (if applicable) and the specific chemical ingredient are shown on the left, followed by columns containing detailed assay and target information.

9.2 TDR Targets

URL: <http://tdrtargets.org>

The TDR Targets database is a comprehensive integrated resource for the selection of drug targets and lead compounds in several different infectious diseases. It is the product of a collaboration of many research groups, and contains very extensive data for *P. falciparum* and *P. vivax*, but also for *T. gondii*, *M. tuberculosis*, *M. leprae*, *T. brucei*, *T. cruzi*, *L. major*, *B. malayi*, *S. mansoni* and *W. bancrofti* (Crowther *et al.*, 2010). It also contains chemical compounds. The TDR Targets database provides pre-compiled lists of targets, but also allows users to perform their own target selection based on a series of molecular properties. Gene information includes a series of fields such as gene ID, gene name, gene product name, exon count, length of gene, length of the protein, molecular weight of protein, isoelectric point of protein, hydrophobicity of proteins, number of transmembrane domains and presence of a signal peptide. Genes are additionally classified into enzymes, transporters and receptors. Functional annotation data includes InterPro domains (Hunter *et al.*, 2009), Pfam domains (Bateman *et al.*, 2004), GO data (Ashburner *et al.*, 2000) and EC numbers.

Structural data contains links to experimentally-derived 3D structures but also to homology models generated as part of the ModBase project. Expression data contains links to a series of microarray experiments. Antigenicity data was generated using the Kolaskar and Tongaonkar method (Kolaskar & Tongaonkar, 1990) as implemented in the EMBOSS antigenic module (Rice *et al.*, 2000). Phyletic distribution information was obtained from the OrthoMCL database (Li *et al.*, 2003). Essentiality data is based on gene knockout and knockdown studies in selected organisms. Drugability data is based on orthology to proteins in the Inpharmatica SAR database which is maintained by the ChEMBL group at the EBI. Drug-to-gene association data is mined from DrugBank and ChEMBL using orthology approaches. Assayability data is primarily obtained from the BRENDA database (Scheer *et al.*, 2011). Literature data originates from PubMed or from curators.

The chemical datasets in TDR Targets is a combination of small molecule data from a variety of sources. This includes properties such as names, synonyms, structure, InChi keys, molecular weight, LogP, hydrogen-bonding donors and acceptors, pharmacological activity and rating according to the Lipinski Rule-of-Five (Lipinski *et al.*, 2001). Bioactivity data is also available.

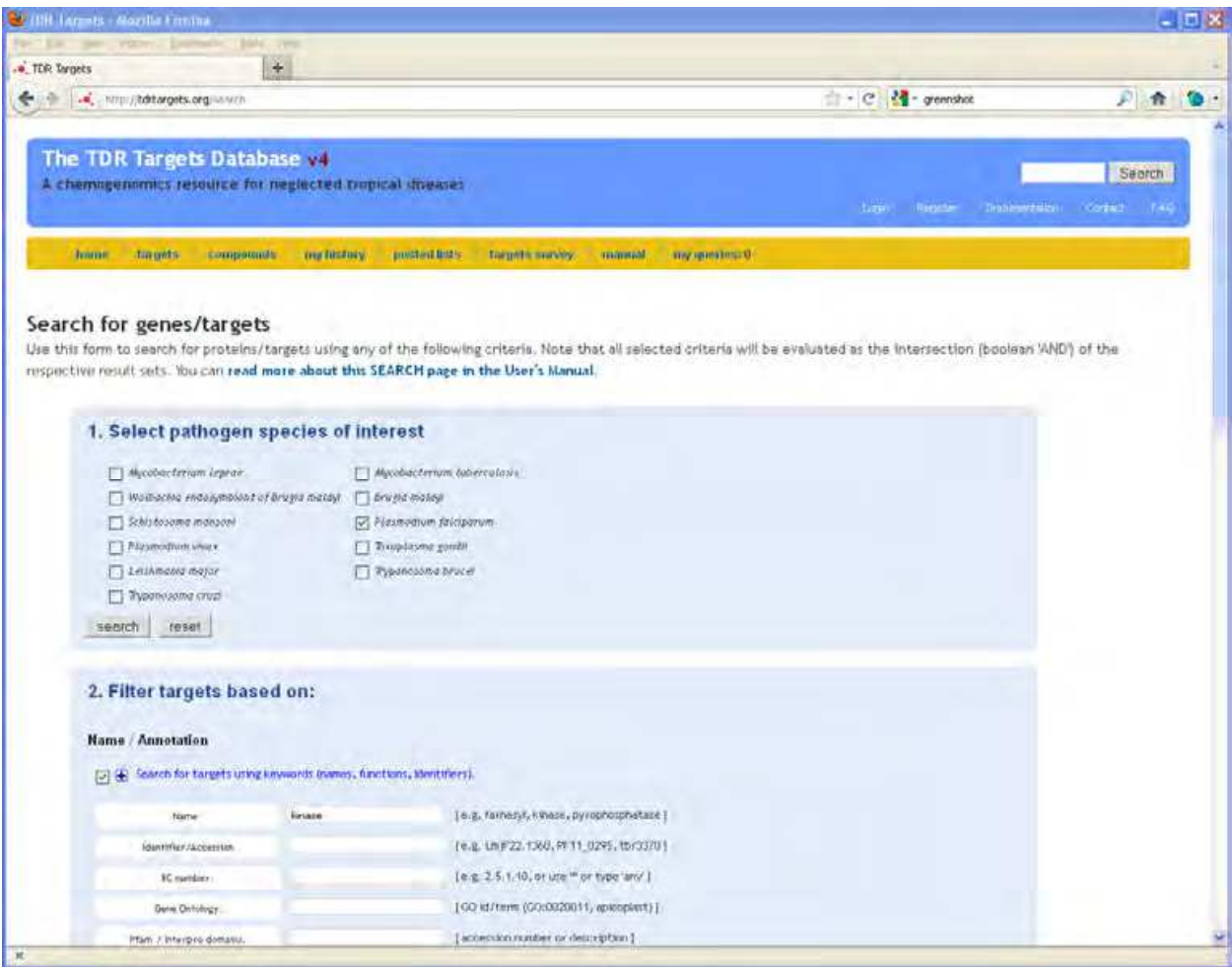


Fig. 13. The target search interface of the TDR Targets database. The different organisms available for searching are shown at the top, followed by possible search parameters at the bottom.

The target search functionality allows users to select proteins from the pathogen genome based on the very extensive criteria mentioned above, and queries may be saved for future reference. Searches are performed by first selecting the pathogen of interest, and this is followed by the addition of filtering criteria (Figure 13). Multiple queries may be executed, and subsequently cumulative search results may be generated by specifying unions, intersects or subtractions of the results. Weights and names may be associated with the different queries. When a target is explored, the view provides extensive information in all the categories listed above, sorted by category. Compound searches may be performed using text- or structure-based queries. Additionally, compound searches may be done based on chemical properties, activities and associated genes. A summary of resulting chemical structures is displayed together with basic properties, and a highly-detailed report for each compound may be obtained, including putative protein targets, activities and external resources for the compound (Figure 14). The TDR resource further provides a posted list feature for the sharing of data within the scientific community, as well as a targets survey page for gathering curated information from community experts.

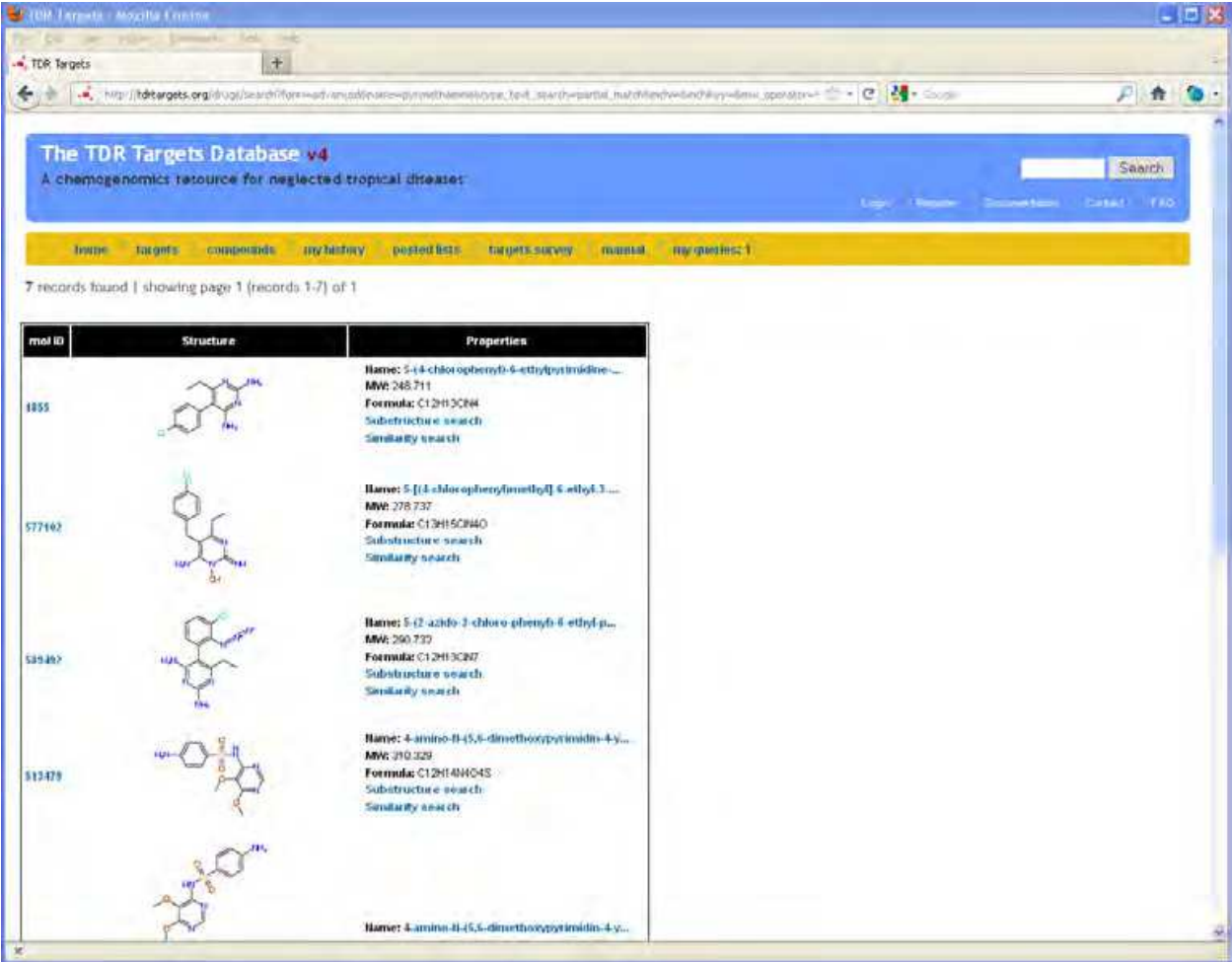


Fig. 14. The compound search results display of the TDR Targets database. Chemical identifiers and structures are shown on the left, with more detailed compound information on the right.

9.3 Discovery

URL: <http://discovery.bi.up.ac.za>

The Discovery resource is aimed at scientists who would like to explore primarily the *P. falciparum* genome for the selection of drug target proteins and lead compounds (Joubert *et al.*, 2009). Other parasite genomes included are *P. vivax*, *P. vivax*, *P. bergei*, *P. chabaudi* and *P. yoelii*. Also included for comparative purposes are the the human and mosquito genomes. The resource may be accessed by querying proteins or ligands. Proteins may be searched using simple keywords, combined terms or accession numbers. Protein data displayed includes orthology and sequence comparisons, ontology terms, functional annotations, metabolic pathways, structural information and possible ligand interactions based on orthology to sequences from DrugBank, PDB Ligand and KEGG. The new version of Discovery adds extensive data from ChEMBL, as well as literature mining and user annotation functionality (Figure 15).

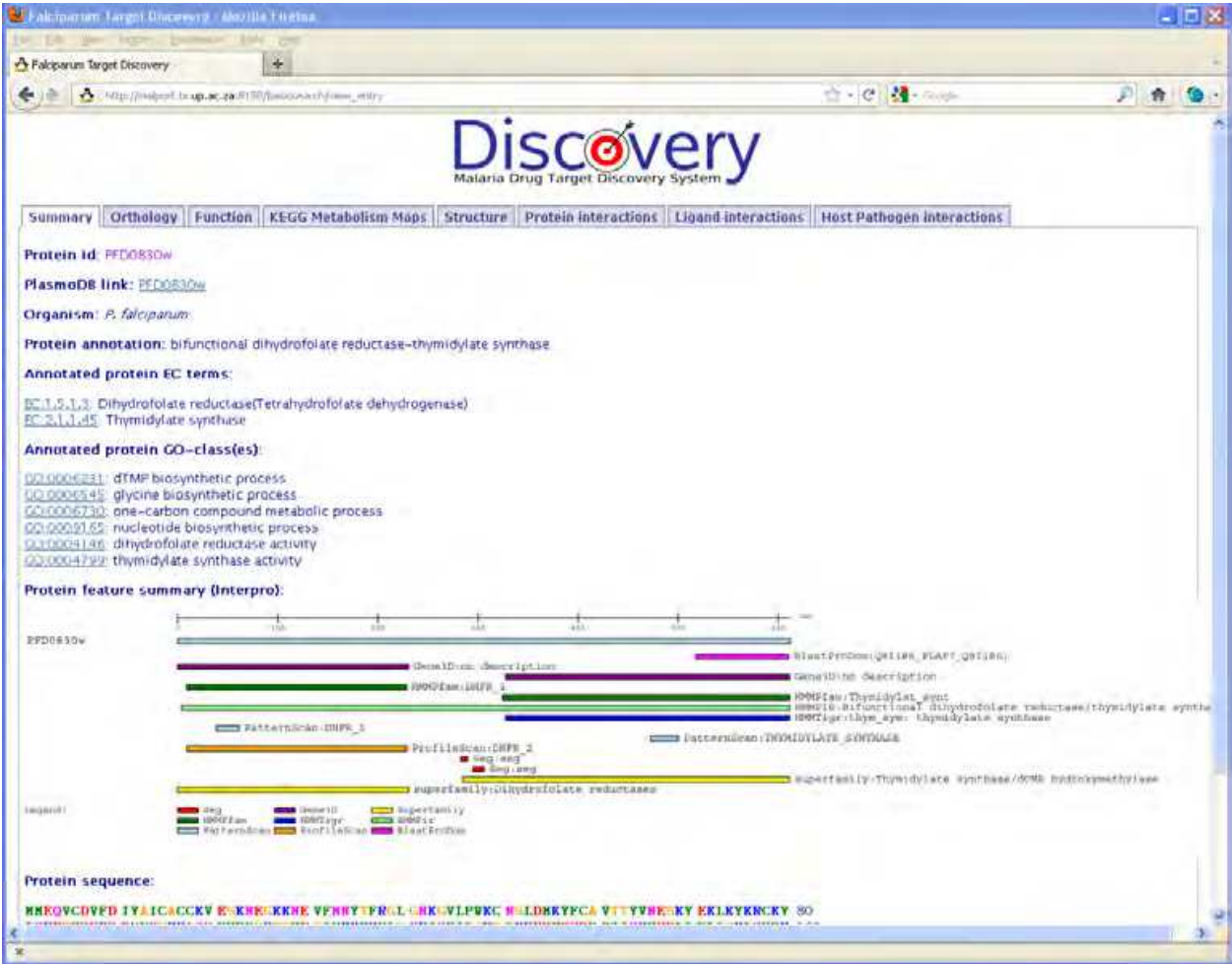


Fig. 15. The Discovery protein results view for PFD0830w (bifunctional dihydrofolate reductase-thymidylate synthase from *P. falciparum*). A summary of protein annotations is shown at the top, followed by a graphical representation of sequence motifs in the molecule. The other types of results that may be viewed can be seen as tabs at the top of the screen.

Chemical compounds may be searched using text terms or chemical structures, and searches are powered using the ChemAxon JChemBase software (<http://www.chemaxon.com>). Several different types of searches are available. Results are displayed in a tabular fashion, and compounds may be selected for further inspection. Additional detail is then provided, including the structure, ADMET properties and putative protein interactions (Figure 16).

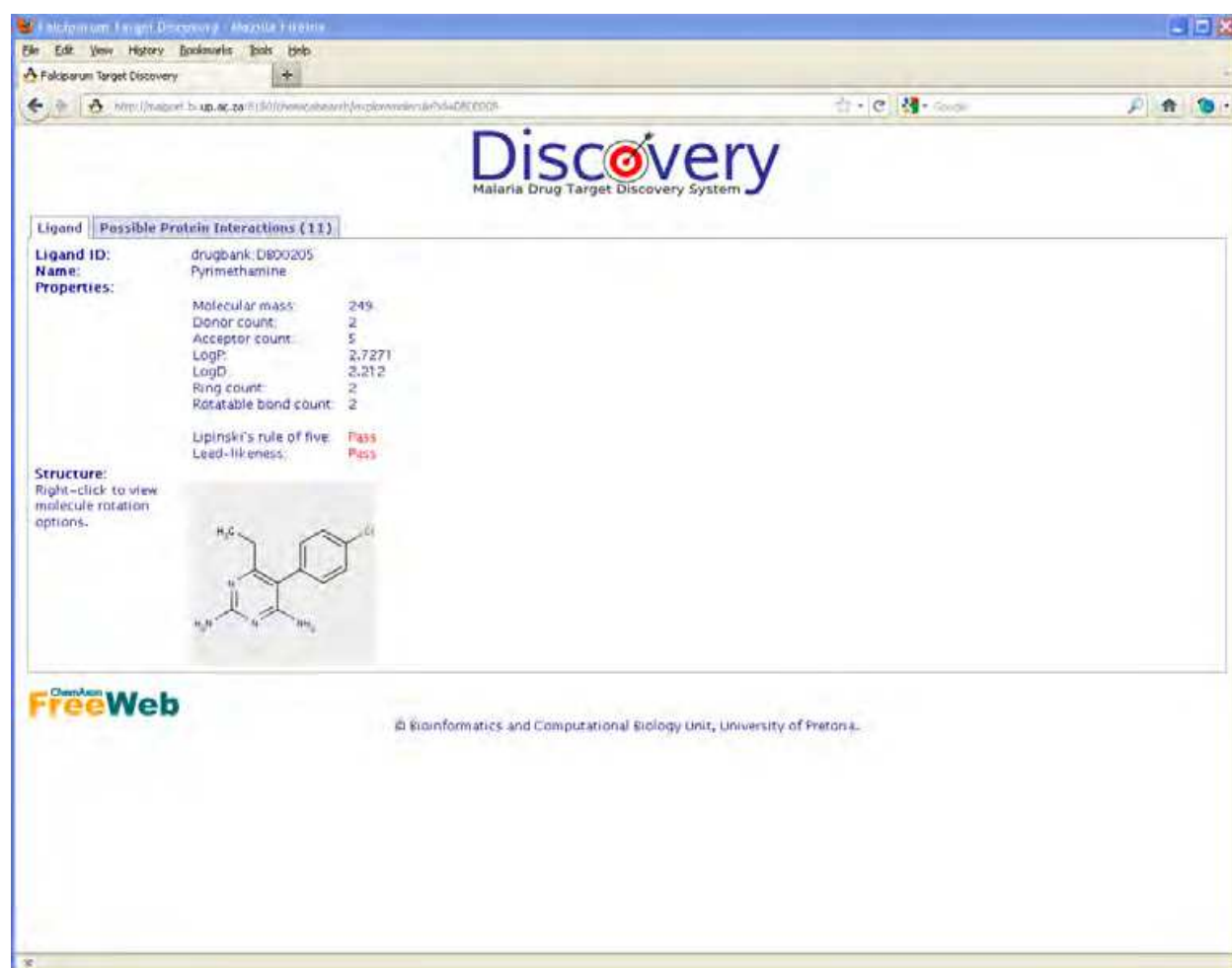


Fig. 16. The Discovery chemical results view for pyrimethamine. The chemical properties are shown at the top, followed by the structure of the compound at the bottom. The tab for viewing possible protein interactions is visible at the top of the page.

10. Conclusion

Researchers face many different challenges when embarking on the discovery of new drug targets. Here we provide an overview on valuable resources that will enable scientists to perform comprehensive searches and make numerous comparisons between targets prior to selection. In addition these tools can be used in the evaluation and data mining of existing targets, which can easily be overlooked using conventional methods and should therefore be used before committing expensive and time-consuming resources. Of primary concern is the properties that need to be taken into account when selecting putative drug proteins or lead compounds. The term “drugability” is widely used for describing the suitability of both proteins and compounds as targets and leads, but specific properties and parameters related

to this can be difficult to formalize. Various examples of studies proposing drugability properties and possible scoring systems are available in the literature (Crowther *et al.*, 2010; Fauman *et al.*, 2011; Halgren, 2009; Hasan *et al.*, 2006; Nicola *et al.*, 2008; Schneider, 2004).

Whereas the resources discussed in the first part of the chapter mostly address resources with single specialized foci, the latter two resources have attempted to integrate the most relevant properties related to protein and compound suitability for drug design during the design of the search strategies. These resources make it possible for researchers to start out with a large number of proteins or compounds, and filter them sequentially based on a series of properties related to “drugability”, therefore producing a smaller list of candidate molecules that may be explored further in greater detail using the more focussed sites, and through experimental approaches. These integrated resources make it possible for researchers to in effect start out with all proteins encoded by a genome or all compounds in a database, and rapidly decrease the potential candidate list to a manageable number using the rational application of filters to properties of their choice.

11. Glossary

A brief glossary of some terms that may not be familiar to all readers:

Bayesian:	A method employing Bayes’ theorem on conditional probability
BLAST:	Basic Local Alignment Search Tool which is used for searching sequences vs. databases
EC number:	Enzyme Commission number defining the type of reaction catalyzed by an enzyme
Essentiality:	An indication of whether the organism can survive after an enzyme has been knocked out or inhibited
Homology model:	A model of a protein structure calculated by using the structure of another homologous protein as template
Lipinski rule-of-five:	A rule of five parameters proposed by Lipinski and colleagues which is used predict the pharmacological or biological activity of a chemical compound
Ontology:	A biological ontology term or identifier forms part of the Gene Ontology (GO) Consortium classification which provides a vocabulary describing gene product characteristics
ORF:	An Open Reading Frame in a nucleic acid sequence which potentially encodes a peptide region
Orthologs:	Sequences which are related to a common evolutionary ancestor but have diverged due to speciation
Paralogs:	Sequences which are related to a common evolutionary ancestor but have diverged due to gene duplication
Proteome:	The complete set of proteins produced by an organism or tissue

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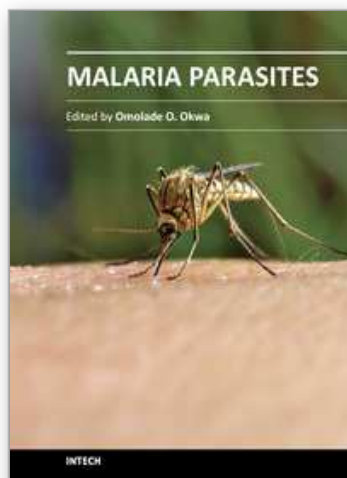
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Malaria Parasites

Edited by Dr. Omolade Okwa

ISBN 978-953-51-0326-4

Hard cover, 350 pages

Publisher InTech

Published online 30, March, 2012

Published in print edition March, 2012

Malaria is a global disease in the world today but most common in the poorest countries of the world, with 90% of deaths occurring in sub-Saharan Africa. This book provides information on global efforts made by scientist which cuts across the continents of the world. Concerted efforts such as symbiont based malaria control; new applications in avian malaria studies; development of humanized mice to study *P.falciparum* (the most virulent species of malaria parasite); and current issues in laboratory diagnosis will support the prompt treatment of malaria. Research is ultimately gaining more grounds in the quest to provide vaccine for the prevention of malaria. The book features research aimed to bring a lasting solution to the malaria problem and what we should be doing now to face malaria, which is definitely useful for health policies in the twenty first century.

How to reference

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Pieter B. Burger and Fourie Joubert (2012). In Silico Resources for Malaria Drug Discovery, *Malaria Parasites*, Dr. Omolade Okwa (Ed.), ISBN: 978-953-51-0326-4, InTech, Available from:
<http://www.intechopen.com/books/malaria-parasites/in-silico-resources-for-malaria-research>

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51000 Rijeka, Croatia
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