# Heme metabolism as a therapeutic target against protozoan parasites

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## Supplemental material

Table S1: A List of targets annotated for Dihydroartemisinin (DHA) in drugbank (www.drugbank.ca).

| Drug | Target | Organism | Heme binding protein* |
|---|---|---|---|
| **DHA** | Actin, cytoplasmic 2 | Human | Heme binding protein |
| **DHA** | Alpha-aminoadipic semialdehyde dehydrogenase | Human | |
| **DHA** | Annexin A2 | Human | |
| **DHA** | ATP synthase subunit alpha, mitochondrial | Human | Heme binding protein |
| **DHA** | ATP synthase subunit g, mitochondrial | Human | Heme binding protein |
| **DHA** | ATP synthase subunit O, mitochondrial | Human | Heme binding protein |
| **DHA** | Calpastatin | Human | |
| **DHA** | T-complex protein 1 subunit gamma | Human | |
| **DHA** | Cofilin-1 | Human | Heme binding protein |
| **DHA** | Chloride intracellular channel protein 1 | Human | |
| **DHA** | Cysteine and glycine-rich protein 1 | Human | |
| **DHA** | Dihydropyrimidinase-related protein 2 | Human | |
| **DHA** | Desmoplakin | Human | |
| **DHA** | Elongation factor 1-alpha 1 | Human | Heme binding protein |
| **DHA** | Alpha-enolase | Human | |
| **DHA** | Filamin-A | Human | |

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|---|---|---|---|
| **DHA** | Alpha-ketoglutarate-dependent dioxygenase FTO | Human | |
| **DHA** | Glucose-6-phosphate 1-dehydrogenase | Human | |
| **DHA** | Glyceraldehyde-3-phosphate dehydrogenase, testis-specific | Human | Heme binding protein |
| **DHA** | Glucose-6-phosphate isomerase | Human | |
| **DHA** | Heterogeneous nuclear ribonucleoproteins A2/B1 | Human | |
| **DHA** | Heterogeneous nuclear ribonucleoprotein D0 | Human | |
| **DHA** | Heterogeneous nuclear ribonucleoprotein K | Human | |
| **DHA** | Heterochromatin protein 1-binding protein 3 | Human | |
| **DHA** | Heat shock protein beta-1 | Human | |
| **DHA** | Ras GTPase-activating-like protein IQGAP1 | Human | |
| **DHA** | Far upstream element-binding protein 2 | Human | |
| **DHA** | L-lactate dehydrogenase A chain | Human | |
| **DHA** | L-lactate dehydrogenase B chain | Human | |
| **DHA** | Galectin-1 | Human | |
| **DHA** | Microtubule-associated protein 4 | Human | |
| **DHA** | Malate dehydrogenase, cytoplasmic | Human | |
| **DHA** | Puromycin-sensitive aminopeptidase | Human | |
| **DHA** | Profilin-1 | Human | |
| **DHA** | Phosphoglycerate kinase 1 | Human | |
| **DHA** | Pyruvate kinase PKM | Human | |
| **DHA** | Peptidyl-prolyl cis-trans isomerase A | Human | |
| **DHA** | Peroxiredoxin-1 | Human | Heme binding protein |
| **DHA** | 60S ribosomal protein L10 | Human | |
| **DHA** | 60S ribosomal protein L14 | Human | |
| **DHA** | 60S ribosomal protein L18 | Human | |
| **DHA** | 60S ribosomal protein L23a | Human | |
| **DHA** | 60S ribosomal protein L35 | Human | |
| **DHA** | 60S ribosomal protein L4 | Human | |
| **DHA** | 40S ribosomal protein S13 | Human | |
| **DHA** | 40S ribosomal protein S17 | Human | |
| **DHA** | 40S ribosomal protein S18 | Human | |
| **DHA** | 40S ribosomal protein S19 | Human | |

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|---|---|---|---|
| **DHA** | 40S ribosomal protein S28 | Human | |
| **DHA** | 40S ribosomal protein S5 | Human | |
| **DHA** | 40S ribosomal protein S6 | Human | |
| **DHA** | 40S ribosomal protein S8 | Human | |
| **DHA** | 40S ribosomal protein S9 | Human | |
| **DHA** | Splicing factor 1 | Human | |
| **DHA** | Splicing factor, proline- and glutamine-rich | Human | |
| **DHA** | Small nuclear ribonucleoprotein Sm D2 | Human | |
| **DHA** | Signal recognition particle 14 kDa protein | Human | |
| **DHA** | Serine/arginine-rich splicing factor 4 | Human | |
| **DHA** | Transgelin | Human | |
| **DHA** | Transgelin-2 | Human | |
| **DHA** | Triosephosphate isomerase | Human | |
| **DHA** | Tropomyosin alpha-1 chain | Human | |
| **DHA** | Tubulin alpha-1A chain | Human | Heme binding protein |
| **DHA** | Vimentin | Human | |
| **DHA** | Zyxin | Human | |
| **DHA** | Heat shock cognate 71 kDa protein | Human | Heme binding protein |
| **DHA** | Tubulin beta-6 chain | Human | Heme binding protein |
| **DHA** | Tubulin beta-4A chain | Human | Heme binding protein |
| **DHA** | Tubulin beta chain | Human | Heme binding protein |
| **DHA** | Fructose-bisphosphate aldolase A | Human | |
| **DHA** | Glyceraldehyde-3-phosphate dehydrogenase | Human | Heme binding protein |
| **DHA** | Cytochrome c | Human | |
| **DHA** | Phosphoglycerate mutase 1 | Human | |
| **DHA** | Myosin-9 | Human | |
| **DHA** | Protein disulfide-isomerase | Human | |
| **DHA** | Probable ATP-dependent RNA helicase DDX5 | Human | |
| **DHA** | Serine hydroxymethyltransferase, mitochondrial | Human | |
| **DHA** | Serum albumin | Human | |
| **DHA** | Spliceosome RNA helicase DDX39B | Human | |
| **DHA** | Temporary name for P06748 | Human | |
| **DHA** | Translationally-controlled tumor protein homolog | *Plasmodium* | |

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|---|---|---|---|
| | | *falciparum* | |
| **DHA** | P-type Ca2+-transporting ATPase | *Plasmodium falciparum* | |
| **DHA** | Ornithine aminotransferase | *Plasmodium falciparum* | |
| **DHA** | Elongation factor 1-alpha | *Plasmodium falciparum* | Heme binding protein |
| **DHA** | Multidrug resistance protein | *Plasmodium falciparum* | |
| **DHA** | Elongation factor 2 | *Plasmodium falciparum* | Heme binding protein |
| **DHA** | Actin-1 | *Plasmodium falciparum* | Heme binding protein |
| **DHA** | Glyceraldehyde-3-phosphate dehydrogenase | *Plasmodium falciparum* | Heme binding protein |
| **DHA** | Fructose-bisphosphate aldolase | *Plasmodium falciparum* | |
| **DHA** | Cell division cycle protein 48 homologue,putative | *Plasmodium falciparum* | |
| **DHA** | Heat shock protein 90 | *Plasmodium falciparum* | |
| **DHA** | Eukaryotic initiation factor 4A | *Plasmodium falciparum* | |
| **DHA** | Pyruvate kinase | *Plasmodium falciparum* | |
| **DHA** | L-lactate dehydrogenase | *Plasmodium falciparum* | |
| **DHA** | Protein disulfide-isomerase | *Plasmodium falciparum* | |
| **DHA** | Thioredoxin-related protein, putative | *Plasmodium falciparum* | |
| **DHA** | Spermidine synthase | *Plasmodium falciparum* | |

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|---|---|---|---|
| **DHA** | Probable ATP-dependent 6-phosphofructokinase | *Plasmodium falciparum* | |
| **DHA** | Glutamate dehydrogenase | *Plasmodium falciparum* | Heme binding protein |
| **DHA** | Endoplasmin homolog, putative | *Plasmodium falciparum* | |
| **DHA** | Hypoxanthine-guanine-xanthine phosphoribosyltransferase | *Plasmodium falciparum* | |
| **DHA** | Enolase | *Plasmodium falciparum* | |
| **DHA** | 40S ribosomal protein S3 | *Plasmodium falciparum* | |
| **DHA** | Non-SERCA-type Ca2+-transporting P-ATPase | *Plasmodium falciparum* | |
| **DHA** | Tubulin alpha chain | *Plasmodium falciparum* | Heme binding protein |
| **DHA** | Knob-associated histidine-rich protein | *Plasmodium falciparum* | |
| **DHA** | S-adenosylmethionine synthase | *Plasmodium falciparum* | |
| **DHA** | V-type H(+)-translocating pyrophosphatase, putative | *Plasmodium falciparum* | |
| **DHA** | 60S ribosomal protein L4 | *Plasmodium falciparum* | |
| **DHA** | Phosphoethanolamine N-methyltransferase | *Plasmodium falciparum* | |
| **DHA** | 40S ribosomal protein S3a | *Plasmodium falciparum* | |
| **DHA** | Conserved Plasmodium membrane protein | *Plasmodium falciparum* | |
| **DHA** | 60S ribosomal protein L3 | *Plasmodium falciparum* | |
| **DHA** | High molecular weight rhoptry protein 2 | *Plasmodium* | |

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|---|---|---|---|
| | | *falciparum* | |
| **DHA** | Serine repeat antigen 5 | *Plasmodium falciparum* | |
| **DHA** | 40S ribosomal protein S19 | *Plasmodium falciparum* | |
| **DHA** | Glycophorin-binding protein | *Plasmodium falciparum* | |
| **DHA** | Calcium-transporting ATPase | *Plasmodium falciparum* | |
| **DHA** | V-type proton ATPase catalytic subunit A | *Plasmodium falciparum* | |
| **DHA** | 60S ribosomal protein L2 | *Plasmodium falciparum* | |
| **DHA** | Acyl-CoA synthetase | *Plasmodium falciparum* | |
| **DHA** | Plasmepsin IV | *Plasmodium falciparum* | |
| **DHA** | Plasmepsin-1 | *Plasmodium falciparum* | |
| **DHA** | Chloroquine resistance transporter | *Plasmodium falciparum* | |
| **DHA** | 14-3-3 protein | *Plasmodium falciparum* | |
| **DHA** | Isoleucine--tRNA ligase, putative | *Plasmodium falciparum* | |
| **DHA** | Plasmodium exported protein | *Plasmodium falciparum* | |
| **DHA** | Tubulin beta chain | *Plasmodium falciparum* | Heme binding protein |
| **DHA** | 60S ribosomal protein L27 | *Plasmodium falciparum* | |
| **DHA** | Sec62, putative | *Plasmodium falciparum* | |

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| **DHA** | Autophagy-related protein 18, putative | *Plasmodium falciparum* |
| **DHA** | Mature parasite-infected erythrocyte surface antigen | *Plasmodium falciparum* |
| **DHA** | Importin-7, putative | *Plasmodium falciparum* |
| **DHA** | Karyopherin alpha | *Plasmodium falciparum* |
| **DHA** | Peptidyl-prolyl cis-trans isomerase | *Plasmodium falciparum* |
| **DHA** | DnaJ protein, putative | *Plasmodium falciparum* |
| **DHA** | Merozoite surface protein 1 | *Plasmodium falciparum* |
| **DHA** | Glutamate--tRNA ligase | *Plasmodium falciparum* |
| **DHA** | T-complex protein 1 subunit eta | *Plasmodium falciparum* |
| **DHA** | Plasmepsin-2 | *Plasmodium falciparum* |
| **DHA** | Chaperone, putative | *Plasmodium falciparum* |
| **DHA** | Rhoptry neck protein 3 | *Plasmodium falciparum* |
| **DHA** | 40S ribosomal protein S5, putative | *Plasmodium falciparum* |
| **DHA** | Skeleton-binding protein 1 | *Plasmodium falciparum* |
| **DHA** | Purine nucleotide phosphorylase, putative | *Plasmodium falciparum* |
| **DHA** | Adenosylhomocysteinase | *Plasmodium falciparum* |
| **DHA** | Adenosine deaminase | *Plasmodium* |

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|---|---|---|
| | | *falciparum* |
| **DHA** | Methionine--tRNA ligase | *Plasmodium falciparum* |
| **DHA** | Carbamoyl phosphate synthetase | *Plasmodium falciparum* |
| **DHA** | Aspartate carbamoyltransferase | *Plasmodium falciparum* |
| **DHA** | Signal recognition particle receptor, beta subunit | *Plasmodium falciparum* |
| **DHA** | Parasite-infected erythrocyte surface protein | *Plasmodium falciparum* |
| **DHA** | Coatomer alpha subunit, putative | *Plasmodium falciparum* |
| **DHA** | Hexokinase | *Plasmodium falciparum* |
| **DHA** | Proteasome subunit alpha type | *Plasmodium falciparum* |
| **DHA** | Haloacid dehalogenase-like hydrolase | *Plasmodium falciparum* |
| **DHA** | Insulinase, putative | *Plasmodium falciparum* |
| **DHA** | 40S ribosomal protein S21 | *Plasmodium falciparum* |
| **DHA** | Ubiquitin-conjugating enzyme E2 | *Plasmodium falciparum* |
| **DHA** | Eukaryotic translation initiation factor 3 subunit C | *Plasmodium falciparum* |
| **DHA** | 60S ribosomal protein L24, putative | *Plasmodium falciparum* |
| **DHA** | 60S ribosomal protein L23 | *Plasmodium falciparum* |
| **DHA** | 60S ribosomal protein L17, putative | *Plasmodium falciparum* |

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| **DHA** | NADP-specific glutamate dehydrogenase | *Plasmodium falciparum* | |
| **DHA** | HAP protein | *Plasmodium falciparum* | |
| **DHA** | Heat shock protein 110, putative | *Plasmodium falciparum* | |
| **DHA** | 60S ribosomal protein L10, putative | *Plasmodium falciparum* | |
| **DHA** | Lysophospholipase, putative | *Plasmodium falciparum* | |
| **DHA** | Polyadenylate-binding protein | *Plasmodium falciparum* | |
| **DHA** | Ubiquitin-60S ribosomal protein L40 | *Plasmodium falciparum* | |
| **DHA** | Phosphoribosylpyrophosphate synthetase | *Plasmodium falciparum* | |
| **DHA** | Thioredoxin peroxidase 1 | *Plasmodium falciparum* | Heme binding protein |
| **DHA** | Protein transport protein SEC31 | *Plasmodium falciparum* | |
| **DHA** | Dipeptidyl aminopeptidase 1 | *Plasmodium falciparum* | |
| **DHA** | Ring-infected erythrocyte surface antigen | *Plasmodium falciparum* | |
| **DHA** | ATP-dependent RNA helicase UAP56 | *Plasmodium falciparum* | |
| **DHA** | Calcium-dependent protein kinase 4 | *Plasmodium falciparum* | |
| **DHA** | GTP-binding nuclear protein Ran | *Plasmodium falciparum* | |
| **DHA** | Nucleoside transporter 2 | *Plasmodium falciparum* | |
| **DHA** | Anamorsin homolog | *Plasmodium* | |

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|---|---|---|---|
| | | *falciparum* | |
| **DHA** | Glutamine synthetase, putative | *Plasmodium falciparum* | |
| **DHA** | 60S ribosomal protein L30e, putative | *Plasmodium falciparum* | |
| **DHA** | Casein kinase 2, alpha subunit | *Plasmodium falciparum* | |
| **DHA** | Threonine--tRNA ligase | *Plasmodium falciparum* | |
| **DHA** | cAMP-dependent protein kinase regulatory subunit | *Plasmodium falciparum* | |
| **DHA** | Elongation factor 1-gamma, putative | *Plasmodium falciparum* | Heme binding protein |
| **DHA** | Thioredoxin-like protein | *Plasmodium falciparum* | |
| **DHA** | 60S ribosomal protein L21 | *Plasmodium falciparum* | |
| **DHA** | 60S ribosomal protein L14, putative | *Plasmodium falciparum* | |
| **DHA** | Inner membrane complex sub-compartment protein 3 | *Plasmodium falciparum* | |
| **DHA** | HSP40, subfamily A, putative | *Plasmodium falciparum* | |
| **DHA** | Pyridoxal 5'-phosphate synthase subunit Pdx1 | *Plasmodium falciparum* | |

* Heme-binding proteins according to Li. X, et al, 2003. A novel approach for identifying the heme-binding proteins from mouse tissues. Genomics. Proteomics Bioinformatics 1, 78–86.

Table S2: Hemeproteins from human pathogenic Kinetoplastids with heme (HEM) as

ligand in PDB (www.rcsb.org).

| PDB ID | Protein | Organism | PDB DOI | Ligand ID |
|---|---|---|---|---|
| **3L4D** | Sterol 14-alpha demethylase | *Leishmania infantum* | 10.2210/pdb3l4d/pdb | HEM |
| **5VIA** | Pseudoperoxidase | *Leishmania major* | 10.2210/pdb5via/pdb | HEM |
| **5AMM** | Ascorbate peroxidase | *Leishmania major* | 10.2210/pdb5amm/pdb | HEM |
| **5ALA** | Ascorbate peroxidase | *Leishmania major* | 10.2210/pdb5ala/pdb | HEM |
| **5AL9** | Ascorbate peroxidase | *Leishmania major* | 10.2210/pdb5al9/pdb | HEM |
| **4GED** | Ascorbate peroxidase | *Leishmania major* | 10.2210/pdb4ged/pdb | HEM |
| **4DY9** | Cytochrome c | *Leishmania major* | 10.2210/pdb4dy9/pdb | HEM |
| **3RIW** | Ascorbate peroxidase | *Leishmania major* | 10.2210/pdb3riw/pdb | HEM |
| **3RIV** | Ascorbate peroxidase | *Leishmania major* | 10.2210/pdb3riv/pdb | HEM |
| **4G7G** | Sterol 14-alpha demethylase | *Trypanosoma brucei* | 10.2210/pdb4g7g/pdb | HEM |
| **4G3J** | Sterol 14-alpha demethylase | *Trypanosoma brucei* | 10.2210/pdb4g3j/pdb | HEM |
| **4BJK** | Sterol 14-alpha demethylase | *Trypanosoma brucei* | 10.2210/pdb4bjk/pdb | HEM |
| **3TIK** | Sterol 14-alpha demethylase | *Trypanosoma brucei* | 10.2210/pdb3tik/pdb | HEM |
| **3P99** | Sterol 14-alpha demethylase | *Trypanosoma brucei* | 10.2210/pdb3p99/pdb | HEM |
| **3GW9** | Sterol 14-alpha demethylase | *Trypanosoma brucei* | 10.2210/pdb3gw9/pdb | HEM |
| **3G1Q** | Sterol 14-alpha demethylase | *Trypanosoma brucei* | 10.2210/pdb3g1q/pdb | HEM |
| **2X2N** | Sterol 14-alpha demethylase | *Trypanosoma brucei* | 10.2210/pdb2x2n/pdb | HEM |
| **2WV2** | Sterol 14-alpha demethylase | *Trypanosoma brucei* | 10.2210/pdb2wv2/pdb | HEM |
| **5AJR** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb5ajr/pdb | HEM |
| **4UVR** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb4uvr/pdb | HEM |
| **4UQH** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb4uqh/pdb | HEM |
| **4H6O** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb4h6o/pdb | HEM |
| **4COH** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb4coh/pdb | HEM |
| **4CKA** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb4cka/pdb | HEM |
| **4CK9** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb4ck9/pdb | HEM |
| **4CK8** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb4ck8/pdb | HEM |
| **4C28** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb4c28/pdb | HEM |
| **4C27** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb4c27/pdb | HEM |
| **4C0C** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb4c0c/pdb | HEM |
| **4BY0** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb4by0/pdb | HEM |
| **4BMM** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb4bmm/pdb | HEM |

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| **3ZG3** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb3zg3/pdb | HEM |
| **3ZG2** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb3zg2/pdb | HEM |
| **3KSW** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb3ksw/pdb | HEM |
| **3KHM** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb3khm/pdb | HEM |
| **3K1O** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb3k1o/pdb | HEM |
| **2WX2** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb2wx2/pdb | HEM |
| **2WUZ** | Sterol 14-alpha demethylase | *Trypanosoma cruzi* | 10.2210/pdb2wuz/pdb | HEM |