Plasmodium falciparum dihydroorotate dehydrogenase (*Pf*DHODH): A promising target for discovery of novel antimalarial agents

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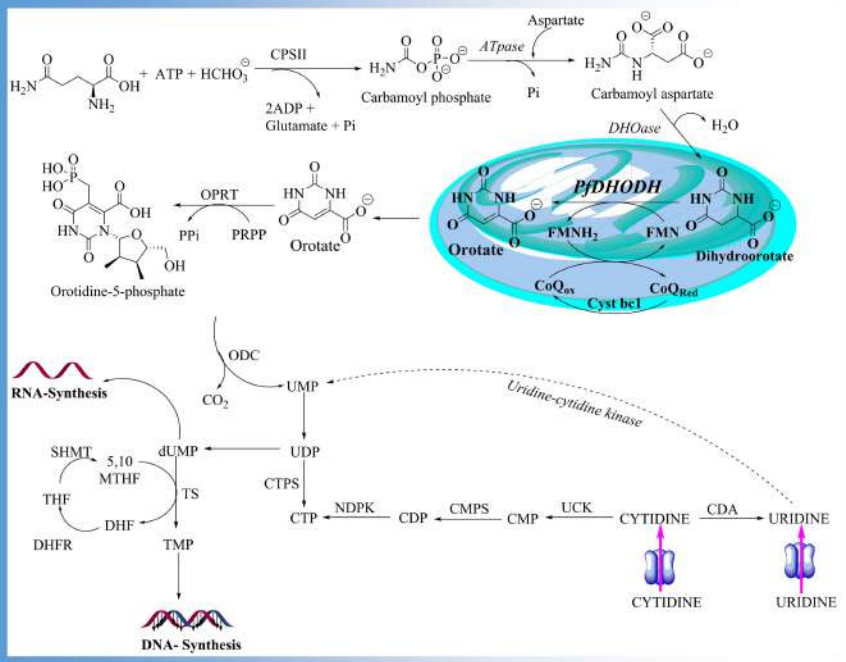
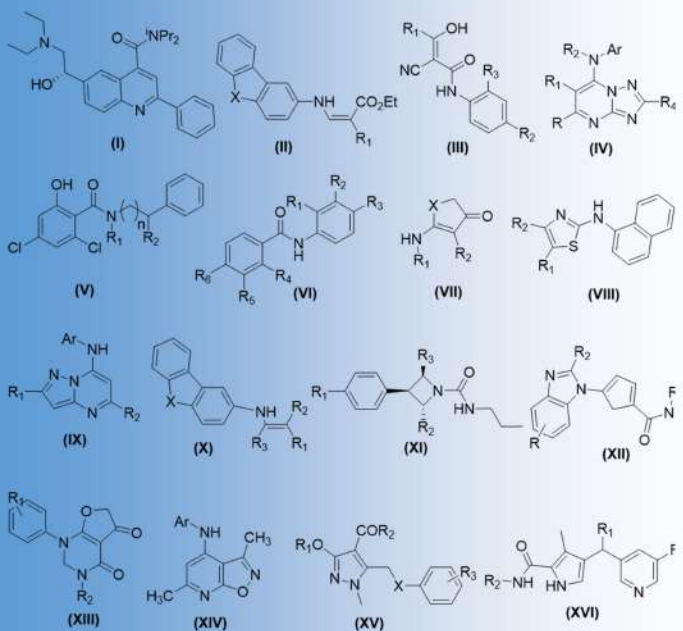
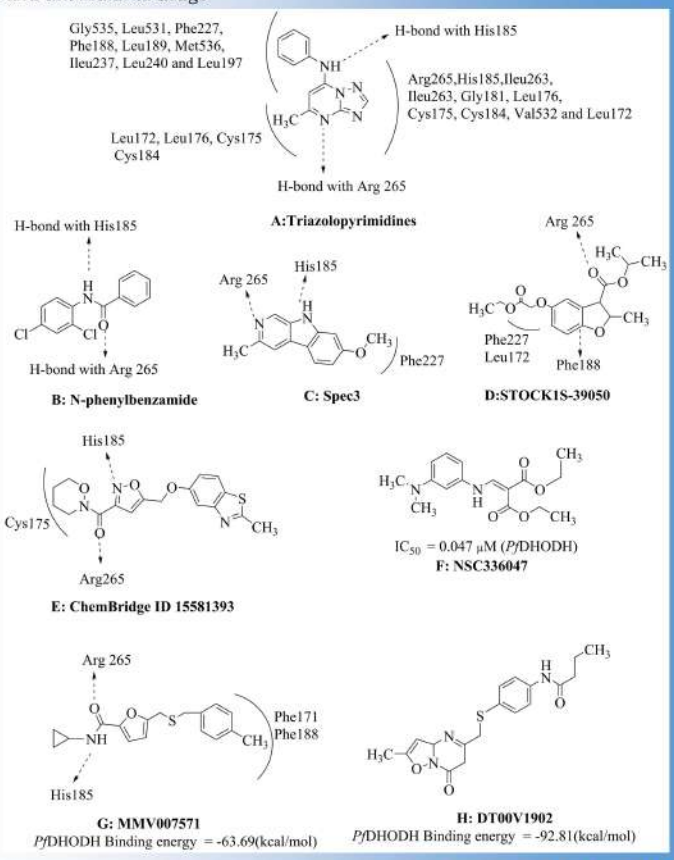
Malaria is a severe human disease that, despite extensive research, is often a global problem due to drug resistance strain. The drugs reported to date to prevent the growth of *Plasmodium* parasites target various phases of parasites' life cycle. Some antimalarial drugs can inhibit key enzymes which are responsible for cellular growth and development of parasites. *Plasmodium falciparum* dihydroorotate dehydrogenase (*Pf*DHODH) is one such enzyme, which is necessary for *de-novo* pyrimidine biosynthesis. Absence of pyrimidine salvage pathway in Plasmodium species make them completely dependent on de novo pathway for cellular growth and developments. This review mainly focuses on various biology, pharmacology and medicinal chemistry approaches used by the scientists and researchers for the discovery and identification of selective *Pf*DHODH inhibitors as antimalarial agents. This comprehensive review will provide recent advances of pharmacological, and biochemical approaches for selective therapeutic activity of distinct chemical class of chemical compounds and their activities and structural insights as *Pf*DHODH inhibitors and antimalarial drugs.



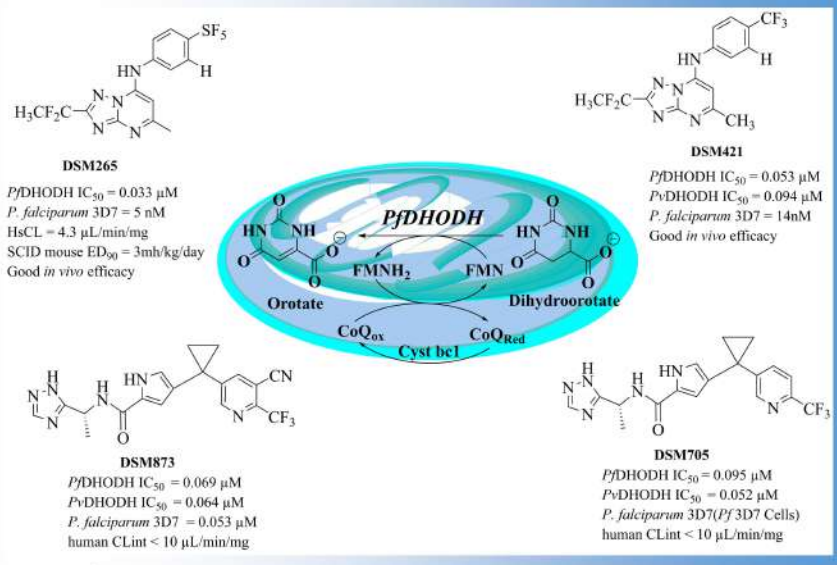
De novo pyrimidine biosynthesis pathway



2-Phenylquinoline-4-carboxylic acid (related to brequinar) **(I)**, diethyl 2-(arylamino)methylene) malonate **(II)**, biphenylanilines **(III)**, triazolopyrimidines **(IV)**, N-substituted salicylamides **(V)**, N-phenylbenzamide **(VI)**, dihydrothiophenones **(VII)**, thiazoles **(VIII)**, 7-arylaminopyrazoles **(IX)**, tricyclic beta-amino acrylates **(X)**, azetidine-2-carbonitriles **(XI),** N-alkyl-thiophene-2-carboxamides **(XII)**, pyrimidones **(XIII)**, isoxazolopyrimidines **(XIV)**, hydroxyazoles **(XV)**, pyrroles **(XVI)**



Amino acid residues involved in docking study with *Pf*DHODH



Clinical trial candidates with their antimalarial activities

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