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Development of inhibitors of the cysteine proteases rhodesain of *T. b. rhodesiense* and falcipain-2 of *P. falciparum*

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Neglected tropical diseases (NTDs) are a group of disabling infections particularly endemic in developing regions of Africa, Asia and the Americas. Over one billion people suffer from one or more NTDs, two of the most important are Human African Trypanosomiasis (HAT) and malaria. Although a number of antitrypanosomal and antimalarial agents are available, these suffer from problems like increasing drug resistance, toxicity and route of administration. Thus, there is an urgent need to identify new effective drugs, ideally directed against novel targets. The cathepsin L-like cysteine proteases rhodesain and falcipain-2 (FP-2), have been recognized as novel promising targets for the treatment of HAT and malaria respectively, because of their key roles for parasite survival. The importance of rhodesain, a cysteine protease of *T. brucei*, is due to its several functions, such as its role in crossing the blood brain barrier, thus inducing the neurological stage of HAT; other functions include the turnover of variant surface glycoproteins that coat trypanosomes, degradation of host immunoglobulins to reduce the host immune response, and degradation of parasite and imported host proteins within lysosomes. On the other hand, FP-2, the main cysteine protease of *P. falciparum*, hydrolyzes hemoglobin to provide amino acids that are essential to the parasite for protein synthesis. FP-2 may also be responsible for the cleavage of the cytoskeletal proteins ankyrin and band-4.1 to facilitate rupture of the red-cell membrane. Thus, the development of novel rhodesain and FP-2 inhibitors is a promising challenge to obtain new effective agents for the treatment of HAT and malaria.

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