2 H-1,2,3-Triazole-based dipeptidyl nitriles : potent, selective, and Trypanocidal rhodesain inhibitors by structure-based design

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Macrocyclic inhibitors of rhodesain (RD), a parasitic cysteine protease and drug target for the treatment of human African trypanosomiasis, have shown low metabolic stability at the macrocyclic ether bridge. A series of acyclic dipeptidyl nitriles was developed using structure-based design (PDB ID: 6EX8). The selectivity against the closely related cysteine protease human cathepsin L (hCatL) was substantially improved, up to 507-fold. In the S2 pocket, 3,4-dichlorophenylalanine residues provided high trypanocidal activities. In the S3 pocket, aromatic residues provided enhanced selectivity against hCatL. RD inhibition (K; i; values) and in vitro cell-growth of Trypanosoma brucei rhodesiense (IC; 50; values) were measured in the nanomolar range. Triazole-based ligands, obtained by a safe, gram-scale flow production of ethyl 1 H-1,2,3-triazole-4-carboxylate, showed excellent metabolic stability in human liver microsomes and in vivo half-lives of up to 1.53 h in mice. When orally administered to infected mice, parasitaemia was reduced but without complete removal of the parasites.
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