Identification of potential inhibitors of malarial aspartyl protease, Plasmepsin II, via three-dimensional database search

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Pasmodium falciparum is one of the causative agents of malaria, a disease of word-wide importance. The malaria parasite encodes two aspartic proteases, Plasmepsin I and II, which are essential enzymes of its hemoglobin degradation pathway. The World Health Organization has recognized the plasmepsins as attractive targets for the design of novel chemotherapeutic compounds for the treatment of malaria. A computational three-dimensional (3D) database search was used to identify potential inhibitors of Plasmepsin II. Starting from the X-ray crystal structure of the pepstatin bound to the Plasmepsin II, preliminary docking of all compounds in the Maybridge Chemical Database into the active site was carried out. Based on the interaction energy score between docked compounds and the active site 5430 compounds were selected. A pharmacophore (Figure), defined using two catalytic aspartates (Asp34 and Asp214) and a hydrogen bond forming atoms (O or N) from the database compounds, was used to re-screen the 5430 compounds against Plasmepsin II. Based on the hydrogen bond distances between active site residues and docked compounds 15 compounds were selected. The structural details between the binding motif of Plasmempsin II and inhibitors identified in the present work will be discussed. The compounds identified in the present study may contribute to the future development of inhibitors for Plasmepsin II.

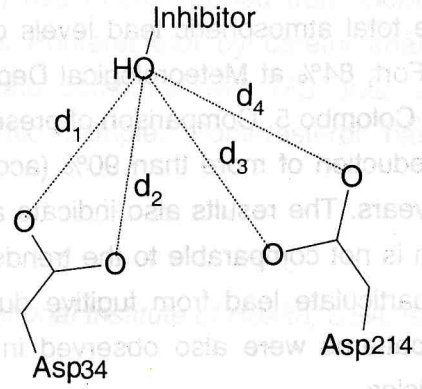

Figure: Pharmacophore used to re-screen selected compounds. $2.5 \leq d_1, d_2, d_3, d_4 \leq 3.5$ Å

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