

COMPUTATIONAL DESIGN STRATEGIES FOR THE IDENTIFICATION OF NOVEL INHIBITORS OF THYMIDINE KINASES

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Human thymidine kinase 1 (hTK1) is a deoxynucleoside kinase that is responsible for the activation of the antiviral prodrugs AZT and d4T¹. The expression of hTK1 is cell cycle regulated and the active enzyme is only found in S-phase cells.² Therefore, inhibitors of hTK1 may also be useful as anticancer drugs. In addition, TKs from pathologic bacteria could be attractive targets for novel antibiotics. Two crystal structures of hTK1 were published recently with the feedback inhibitor thymidine triphosphate (TTP) in the active site^{1, 3}. Most computational docking applications study the binding modes of ligands by utilizing prior knowledge of binding sites. Therefore the docking area is usually limited to a specific protein region. Recently, the concept of “blind docking” has been explored to scan entire proteins for potential drug binding sites⁴. This application is in particular useful in cases where the drug binding site of the protein (target pocket) is unknown or in cases where the search is focusing on alternative drug binding sites (similar pockets)⁵. Blind docking of 592 molecules (many having protein kinase inhibitor capacity) into hTK1 using the FlexX module of Sybyl 7.1 identified three major binding sites: The substrate (thymidine) binding site, the ATP-binding site, and a third binding site in some distance from the previous two, which maybe be associated with the formation of the tetrameric active form of hTK1. Potential candidate compounds for biological studies are currently being identified.

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