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Choline kinase (ChoK) catalyzes the ATP-dependent phosphorylation of choline, the first committed step in the CDP-choline pathway for the biosynthesis of phosphatidylcholine. Overexpression and increased activity of one of the human ChoK isoforms, ChoK alpha have been constitutively reported in malignant cells and tumour tissues. This suggests that the enzyme plays a relevant role in tumorigenesis. Some sets of in vitro and in vivo experiments confirmed that ChoK inhibition is one of the potential novel strateges for the development of new antiproliferative and anticancer drugs. The importance of ChoK for the regulation of cell proliferation has been studied by using an inhibitor hemicholinium-3 (HC-3), which was initially characterized as a lethal, respiratory paralytic agent. Most of the ChoK inhibitors introduced so far are the chemically modified derivatives based on the structure of HC-3. Crystal structures of HC-3 bound human ChoK alpha were determinded with and without ADP. In the crystal structures, HC-3 molecule was well accommodated between the N and C-terminal lobes of ChoK protein, and its one end was placed on the same binding site as a substrate choline, while the other end partially exposed to the solvent. The inhibitor molecule was stabilized mainly through the hydrophobic interactions contributed by the C-terminal lobe. These 3D information provides the first molecular detailed view concerning the mode of inhibitory action and expand our understanding of the factors governing selectivity.

Keywords: tumorigenesis, antiproliferative and anticancer drug, inhibitor

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Fragment screening and structure-based design of adrenaline synthesis inhibitors

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The enzyme phenylethanolamine N-methyltransferase (PNMT) catalyses the biosynthesis of adrenaline, a neurotransmitter linked to the central control of blood pressure. As part of an ongoing international collaboration to develop PNMT inhibitors, we found that the enzyme conceals a cryptic binding site (1-2). This site is revealed upon binding inhibitors that are double the size of the physiological substrate. The changes in active site size and shape are brought about by unfavourable side-chain conformations and rigid-body helix motions, at a modest estimated energetic cost of 2-3 kcal/mol. Our findings further underline the importance of incorporating protein flexibility in structure-based inhibitor design studies, and raise the question of whether such sites are accessible through moderate affinity fragment screening approaches. To address this question, we implemented fragment-based screening by X-ray crystallography for PNMT. We used the ActiveSight library of 384 compounds and found that a number of fragments bind to the PNMT active site. These will now be elaborated to develop potent and selective PNMT inhibitors.

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Keywords: enzyme inhibitor drug design, structure-based drug design, binding enzyme inhibitors

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Design of anti-allergic inhibitors for human hematopoietic prostaglandin D synthase

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Structure-based drug design (SBDD) is not certainly major process in the pharmaceutical company, however, the cost for drug discovery is huge and gradually increased, therefore, the importance of SBDD is thought to be greater and greater. The novel in-silico screening methods of Multiple Target Screening1 (MTS) and Docking score index2 (DSI) using the matrix on the interaction between the protein structures and chemical compounds were developed. To examine the effect of these methods, we selected human hematopoietic prostaglandin D synthase (H-PGDS) as a target. H-PGDS catalyzes the isomerization of PGH2, a common intermediate of various prostanoids, to PGD2, an inflammatory mediator, in the presence of glutathione (GSH). Oral administration of the H-PGDS inhibitor of HQL-79 suppressed antigen-induced eosinophilic accumulation in the lung of wild-type mice and human H-PGDS-overexpressing mice, gliosis and demyelination in twitcher mice, and musclar distrophy in mdx mice4. The optimizing of the known inhibitor4 as well as the screening of a novel lead compound for human H-PGDS by using in silico method are now in progress.
References

Keywords: complex compounds crystal structure, structure-based drug design, antiallergic drugs

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Structure-based drug design in HIV protease- and tRNA-guanine transglycosylase inhibitor development

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