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Protein crystallography is a versatile technique in the investigation of detailed protein-ligand interactions, and hence, an important tool in structure-based drug design. Here, we will focus on two recent examples in structure-based drug design from our laboratory: HIV-1 protease and tRNA-guanine transglycosylase. The design and structural investigation of HIV-1 protease inhibitors using linear achiral oligoamines is a starting point for the development of non-peptidic inhibitors. Interestingly, initial compounds showed affinity in the low micromolar range not only for HIV-1 protease but also to other aspartic proteases such as plasmepsins and renin. Therefore, a compound series was generated that forms the basis to a general route for lead structure identification of aspartic proteases. tRNA- guanine transglycosylase (TGT) is an essential enzyme in the infection pathway of Shigella. The enzyme catalyzes the exchange of guanine in the wobble position of tRNAHis,Tyr,Asn,Asp against the modified base preQ1. Z. mobilis TGT is used for structural studies of potent ligands which are based on the lin-benzoguanine scaffold. Here, a series of different side chains leading to the modified 2-amino-lin-benzoguanines resulted in effective inhibitors in the low nanomolar range. The gain of affinity is achieved by additional charge-assisted hydrogen bonds for the protein-ligand complex.

Keywords: crystal structures, anti-HIV drug design, TGT complexes

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Crystal structure of complexes of peptidoglycan recognition protein with carbohydrates

Punit Kaur, Pradeep Sharma, Nagendra Singh, Mau Sinha, Rishi Jain, Vikram Gopalakrishnapillai, Amandeep Kaur, Sujata Sharma, Srinivasan Alagiri, Tej P. Singh
All India Institute of Medical Sciences, Biophysics, Ansari Nagar, New Delhi, Delhi, 110029, India, E-mail：kaurpunit@gmail.com

Peptidoglycan Recognition Protein (PGRP) is a pattern recognition molecule which interacts with pathogen associated molecular patterns which are expressed by the pathogenic bacteria. The PGRP-S kill the bacteria by interacting with their cell walls and interfering with the peptidoglycan (PGN) biosynthesis of both gram positive and gram negative bacteria. The PGNs are essential components of bacteria which are absent in mammals. Thus, PGRP contributes to the host defense against bacterial infections. The first PGRP protein was isolated from mammary gland secretions from animals infected by mastitis. It was crystallized in the native state as well as with the carbohydrates, n-acetyl glucosamine, n-acetyl galactosamine, disaccharide and rhamnose. The isomorphous crystals of these complexes belong to space group *I*222 with cell dimensions, $a = 89.3$ Å, $b = 102.6$ Å and $c = 164.0$ Å. There were four crystallographically independent molecules in the asymmetric unit which form two types of dimers. The single PGRP has two binding sites, one for binding to PGN and the second for binding to non-PGN molecules. In one dimer, there are two exposed PGN binding sites while in the second the two non-PGN binding sites are exposed. In all the complexes, the carbohydrates bind at the PGN binding sites of one complex. The PGRP-S residues, His37, Thr152 and Ser154 are involved in the recognition of carbohydrate with side chains of all these residues involved in the formation of hydrogen bonds with carbohydrate residue/residues. The non-PGN binding site was empty in the second complex indicating a different preference for the ligand binding.

Keywords: peptidoglycan recognition protein, carbohydrate, antibacterial

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Crystal structure of human CK2 alpha in complex with ellagic acid

Yusuke Sekiguchi[1], Tetsuko Nakaniwa[1], Takayoshi Kinoshita[1], Isao Nakanishi[2], Kazuo Kitaura[2], Akira Hirasawa[2], Gozoh Tsujimoto[2], Toshiji Tada[1]
[1]osaka prefecture univ., science, nakai gakuencho1-1, sakai, osaka, 599-8531, Japan, [2]Graduate school of Pharmaceutical sciences, Kyoto University, E-mail：sekiguchi07@b.s.osakafu-u.ac.jp

Casein kinase 2 (CK2) is a highly pleiotropic serine/threonine protein kinase, composed of two catalytic (CK2alpha) and two regulatory (CK2beta) subunits. CK2 is a target protein for glomerulonephritis therapy. We have determined the crystal structure, at 2.35Å resolutions, of human CK2alpha in complex with ellagic acid, which is an ATP-competitive inhibitor. The structure reveals that ellagic acid binds to the active residue Lys68. Ellagic acid interestingly binds to the hinge region connecting the N- and C-lobes through a water molecule. The structural information of the complex including the indirect interaction would be a great help to design unique and potent CK2 inhibitor.

Keywords: X-ray, ck2, inhibitor

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Rapid and precise protein 3D-model preparation for SBDD

Takao Matsuzaki[1], Isao Ishizaka[2]
[1]Independent Drug Design Advisor, 2007-1-404 Uchikoshimachi, Hachioji, Tokyo, 192-0911, Japan, [2]Autofact Inc., 4-1-14 Higashikoigakubo, Kokubunjishi, Tokyo, 185-0014, Japan, E-mail：tak-matsuzaki-45@cb3.so-net.ne.jp

Though protein 3D-models have been very useful in SBDD (Structure Based Drug Design), there was no simple and practical method to make them. Light solidification of acrylic polymers and simple mechanical movements have enabled a protein of 50 Å to be shaped in 1.5 hours into a model of ca.10 cm with a precision of 0.05Å. The left photo is a 3D-model builder with a control PC. Protein 3D-models become very important when our drug target is a PPI (Protein-Protein Interaction) system. Drug target sites are not obvious in a PPI system, unlike enzyme cases where catalytic sites or substrate binding sites are mostly drug target sites. Protein 3D-models can tell potential drug target sites at a glance, making them a 'Must' tool for drug designers. The right photo shows the complicated PPI model of hexameric assembly of IL-6, receptor alpha and gp-130. Enlarged models with 1 Å = 4 mm scale for protein and ligand can show atomic level interactions and stimulate medicinal chemists how to optimize ligand structures.

Keywords: model, protein, SBDD