針對新藥開發研究者、結構生物學家的 Structure Based Drug Design (SBDD) 應用實例

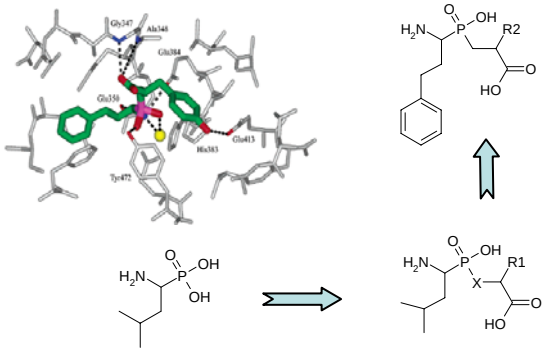
最強力的Leucine Aminopeptidase有機磷抑制劑：以結構為本之設計，其化學和活性

A new class of very potent inhibitors of cytosol leucine aminopeptidase (LAP), a member of matalloprotease family, is described. The X-ray structure of bovine lens leucine aminopeptidase comoplexed with the phosphonic acied analogue of leucine (LeuP) usa used for structure-based design of novel LAP inhibitors and for the analysis of their interactions with the enzyme binding site. The inhibitors were designed by modification of phosphonic group in the LeupP structure toward finding the substituents bound at the S' side of the enzyme. This resulted in two classes of compounds, the phosphonamidate and phosphinate dipeptide analogues, which were synthesized and evaluated as inhibitors of the enzyme. The binding affinities of these inhibitors toward the enzyme are the highest, if considering all compounds containing a phosphorus atom that mimick the transition state of the reaction catalyzed by LAP. The key feature, which determines their selectivity, is structure at the P1' position. Aromatic and aliphatic substituents placed at this position strongly interact with the LAP S1' binding pocket, while a significant increase in binding affinity toward aminopeptidase N (APN) was observed for compounds containing aromatic versus leucine side chains at the P1' position. The most promising LAP inhibitors designed by computeraided approach, the phosphonamidate depeptide analogues, were unstable at pH below 12, because of the P-N bond decomposition, which excluded the possibility of determinations of their binding affinities toward LAP.

The Most Potent Organophosphorus Inhibitors of Leucine Aminopeptidase. Structure-Based Design, Chemistry, and Activity

Reference: **Jolanta Grembecka et al, *J. Med. Chem.* 2003, 46, 2641;**

Used Module: **Ludi**



DT-Diaphorase活性點殘基的綜合探討：作為DT-Diaphorase 受質的Benzimidazolediones的合理設計

A series of quinone substrates were modeled into the active site of human Dt-diaphorase and minimized. Correlation of these models with the substrate specificity Kcat/Km provided insights into the structural requirements of quinone substrates. The W105, F106, and H194 residues can influence the position of the quinone substrate in the active site resulting in formation of one of the two possible Mechael anions resulting from hydride transfer from FADH2. Electron withdrawing groups on the substrate can stabilized these anions resulting in excellent substrate specificity. Inspection of models indicted that the W-1-5 and F-106 residues form parallel walls that will accommodate large polycyclic substrates. Thus excellent polycyclic substrates of DT-diaphorase were designed. However, the placement of tetrahedral centers on these polycyclic substrates interfered with the W105 and the F106 residues resulting in their exclusion from the active site. The histidine (H194) residue permits recognition of substrate enantiomers as a result of hydrogen bonding interactions. As a result of this study, it will be possible to design poor to excellent substrates of DT-diaphorase and take advantage of varying levels of this enzyme in histologically different cancers.

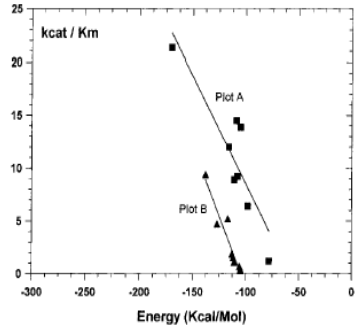
A Comprehensive Study of the Active Site Residues of DT-Diaphorase: Rational Design of Benzimidazolediones as DT-Diaphorase Substrates

Reference: **Ali Suleman and Edward B. Skibo, *J. Med. Chem.* 2002, 45, 1211;**

Used Module: **DISCOVER, DOCKING, InsightII**

Table 1. DT-Diaphorase Kinetic Parameters and Calculated Active Site Energies

compd	k_{cat}/K_m (M^{-1} s^{-1}) $\times 10^5$	k_{cat} (s^{-1})	K_m (M) $\times 10^5$	active site energy (kcal/M)	plot
1a-(*S*)	13.9	2.64	0.19	−105	A
1a-(*R*)	6.4	3.26	0.51	−98.3	A
1b-(*R*)	8.9	2.7	0.3	−111	A
1b-(*S*)	12	2.4	0.2	−116	A
1c-(*R*)	9.2	1.47	0.16	−108	A
1c-(*S*)	5.2	1.87	0.36	−117	B
1d-(*R*)	21.3	9.56	0.45	−170	A
1d-(*S*)	9.4	3.955	0.42	−138	B
2-(*R*)	1.06	4.92	4.66	−115	B
2-(*S*)	1.88	2.972	1.58	−113	B
3a-(*R*)	1.54	3.81	1.79	−112	B
3a-(*S*)	4.72	3.85	0.59	−127	B
3b-(*R*)	0.4	4.845	12.2	−105	B
3b-(*S*)	0.69	1.735	2.5	−106	B
4c	1.18	3.811	1.18	−78	A
5	14.5	3.74	0.26	−109	A



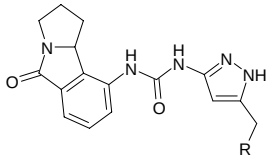
對Cdk4的選擇性抑制劑開發的新方法：根據Cdk4特定的胺基酸殘基的位置所作的資料庫設

Autors applied the following structure-based approach for designing selective Cdk4 inhibitors: (1) identification of specifically altererd amino acid residues around the ATP binding pocket in Cdk4 by comparison of 390 representative kinases, (2) prediction of appropriate positions to introduce substituents in lead compounds baed on the locations of the altered amino acid residues and the binding modes of lead compounds, and (3) library design to interact with the altered amino acid residues supported by denovo design programs. The results suggest that the hydrogen bond with the carboxyl group of Asp99 and hydrophobic van der Waals contact with the side chains of Thr102 and Gln98 are important.

A Novel Approach for the Development of Selective Cdk4 Inhibitors: Library Design Based on Locations of Cdk4 Specific Amino Acid Resides

Reference: **Teruki Honma et al *J. Med. Chem. 2001, 44, 4628;***

Used Module: **Ludi**



R Group	Inhibitory Activity (IC50, μM)		Selectivity
	Cdk4	Cdk2	Cdk2/Cdk4
	0.29	14	48
	0.13	17	130
	0.056	9.8	180
	0.72	20	27
	0.25	12	48
	0.0023	0.44	190

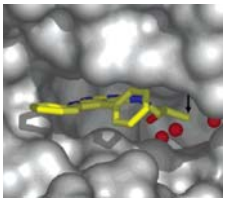
新的Chk1抑制劑的以結構為本之設計：氫鍵和蛋白質-配體間親合力的深入探討

They report the discovery, synthesis, and crystallographic binding mode of novel furanopyrimidine and pyrrolopyrimidine inhibitors of the Chk1 kinase, an oncology target. These inhibitors are synthetically tractable and inhibit Chk1 by competing for its ATP site. A chronological account allows an objective comoparison of modeled compound docking modes to the subsequently obtained crystal structures. The comparison provides insights regarding the interpretation of modeling results, in relationship to the multiple reasonable docking modes which may be obtained in a kinase-ATP site. The crystal structures were used to guide medicinal chemistry efforts. This led to a thorough characterization of a pair of ligand-protein complees which differ by a single hydrogen bond. An analysis indicates that this hydrogen bond is expected to contribute a fraction of the 10-fold change in binding affinity, adding a valuable observation to the debate about the energetic role of hydorgen bonding in molecular recognition.

Structure-Based design of Novel Chk1 Inhibitors: Insights into Hydrogen Bonding and Protein-Ligand Affinity

Reference: **Nicolas Foloppe, et al. *J. Med. Chem.* 2005, 48, 4332-4345**

Used Module: **CHARMm**



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