An approach for producing a CK2alpha inhibitor using X-ray, calculation and ITC


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Protein kinase CK2alpha is a highly pleiotropic serine/threonine protein kinase. CK2alpha plays important roles in cell growth, proliferation, and survival, while it is highly expressed in a wide variety of tumors.(1) Furthermore, CK2alpha is a target protein for glomerulo nephritis (GN) therapy, because an administration of either antisense oligodeoxynucleotide against CK2alpha or low molecular weight CK2alpha-specific inhibitors effectively prevents the progression of renal pathology in the rat GN models.(2)

To design a novel and potent CK2alpha inhibitor, we determined four X-ray crystal structures of CK2alpha-inhibitor complexes (cc-04791, cc-04820, apigenin, ellagic acid), and measured enzyme kinetic parameters using ITC (Isothermal Titration Calorimetry) for the respective inhibitors. Thermodynamic data, specifically enthalpy (ΔH) and entropy (ΔS), reveal the forces that drive complex formation. Furthermore, binding affinity - Kd in range of millimolar to nanomolar is a powerful information for drug design targeting highly homologous kinases. Supported with computational analysis, these data show the specific contributions of some important residues in ligand-binding, and lead to design a potent inhibitor.

Fig.1 CK2 alpha inhibitors


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