Looking for a New Type of CK2 Ligands: Combined Crystallographic and STD Examination of an Allosteric Binding Pocket

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CK2, an eukaryotic protein kinase (EPK), is involved in the regulative mechanism of signaling pathways and plays, amongst others, a role for apoptosis and tumor genesis. Small molecular inhibitors are therefore of high interest. However, most of them are - due to structural similarities of EPKs - of low selectivity.

The quarternary structure of the CK2 holoenzyme is very important for its selectivity and activity. From a recently solved crystal structure[1] and by studying inhibition kinetics, it was deduced, that small molecules can bind at the interface between two parts of the holoenzyme, CK2α and CK2β. This new allosteric binding pocket, located at CK2α, could be the starting point for the development of a new type of inhibitors, which would interfere with the protein-protein interaction and therefore selectively deactivate CK2.

In this work, saturation transfer difference spectroscopy (STD) was applied for a preselection of possible ligands for the allosteric binding pocket. To evaluate the binding of different types of small organic inhibitors, a combined study including STD experiments and analysis of available X-ray structures was used. The complementary information obtained from this approach allowed the elaboration of a protocol for the search of lead structures.

[1] Raaf, J.; Brunstein, E.; Issinger, O.-G.; Niefind, K., *Chem. & Biol.*, **2008**, *15*, 111-117.