Inspecting the Pharmacophore of Protein Kinase CK2 with Tetrabromobenzimidazoles

Roberto Battistutta[a,c], Marco Mazzorana[b,c], Stefania Sarno[b,c], Zygmunt Kazimierczuk[d], Giuseppe Zanotti[a,c], Lorenzo A. Pinna[b,c], *[a]Department of Chemistry, University of Padua, Italy. [b]Department of Biological Chemistry, University of Padua, Italy. [c]Venetian Institute for Molecular Medicine – VIMM, Padua, Italy. [d]Laboratory of Experimental Pharmacology, Polish Academy of Sciences Medical Research Center, Warsaw, Poland.* E-mail: roberto.battistutta @unipd.it

CK2 is a highly pleiotropic protein kinase whose high constitutive activity is suspected to cooperate to neoplasia. Here the crystal structures of the complexes between CK2 and three new selective tetrabromobenzimidazole derivatives inhibiting CK2 with K_i values between 40 and 400 nM are presented. The ligands bind to the CK2 active site in a different way with respect to the parent compound tetrabromobenzotriazole. They enter more deeply into the cavity establishing halogen bonds with the backbone of Asp114 and Val116 in the hinge region. A detailed analysis of the interactions highlights a major role of the hydrophobic effect in the binding of this class of inhibitors. In contrast polar interactions are responsible for the different orientation of the molecules in the active site which ultimately influences the extent of the accessible surface area buried to the solvent.

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