

**CRYSTAL STRUCTURE OF AN ALTERED CATALYTIC SUBUNIT
OF cAMP-DEPENDENT PROTEIN KINASE IN COMPLEX
WITH THE PKC-KINASE INHIBITOR BISINDOLYL-MALEIMIDE 2
IN TWO DIFFERENT CONFORMATIONS – IMPLICATIONS FOR
SELECTIVITY**

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Protein kinases are key enzymes in signal transduction controlling the majority of all regulatory events in the eukaryotic cell. The development of selective inhibitors for protein kinases therefore is a highly promising, and in some cases already has proven to be a successful approach in the treatment of human diseases. Protein kinase inhibitors are also highly important in biological research exploring signal transduction pathways. There selectivity is crucial for associating cellular events with an individual protein kinase. Various PKC inhibitors have been biochemically characterised, but not structurally. Due to the lack of a crystallisable PKC derivative, we used an altered PKA to crystallize the PKC-inhibitor bisindolyl-maleimide 2 (Bim2). The resulting orthorhombic crystal contains a dimer in the asymmetric unit with completely different conformations both of protein and inhibitor. The protein conformation of the molecule A is comparable to the staurosporine structure, whereas the molecule B is in the most open conformation of PKA crystallised up to now. The Bim2 within the half open conformation of molecule A fits very well in the structure and shows significant differences in binding in comparison to the planar staurosporine. Interestingly, the Bim2 in molecule B binds upside-down in the catalytic cleft of the wide open kinase. Modelling of the clinical phase III inhibitor LY333531 into the electron density of Bim2 reveals interesting features of the probable binding mechanism. They can be explained by the differences of the catalytic sites of PKC and PKA and by certain properties of the chemical structure of the inhibitor.