

W0535

Structure of the Catalytic Domain of Human Protein Kinase C-beta II Complexed with a Bisindolylmaleimide Inhibitor. Neil Grodsky, Ying Li, Djamal Bouzida, Robert Love, Jordan Jensen, Beverly Nodes, Jim Nonomiya, Stephan Grant, Pfizer Global Research & Development, San Diego, CA 92121 USA.

The conventional protein kinase C isoform, PKC β II, is a signaling kinase activated during the hyperglycemic state that has been identified as a therapeutic target for the treatment of microvascular-related diabetic complications. In this report, we describe the protein crystal structure of the catalytic kinase domain of PKC β II complexed with an ATP-competitive inhibitor, 2-methyl-1*H*-indol-3-yl-BIM-1, at 2.6 Å resolution. The kinase domain of PKC β II was cleaved and purified from full-length PKC β II expressed in baculovirus-infected insect cells. The overall kinase domain structure followed the classical bilobal fold and was in its fully activated conformation with three well-defined phosphorylated residues: Thr-500, Thr-641, and Ser-660. Different from the crystal structures of other PKC-isoforms, the PKC β II catalytic domain had a novel α -helix in the turn motif located near the ATP-binding site. The bound inhibitor adopted a nonplanar conformation within the ATP binding site. This PKC β II–inhibitor complex represents the first structural description of any conventional PKC kinase domain and may serve as a template for the rational design of conventional PKC inhibitors.