Structural and Ligand Binding Properties Studies of the IKK2 Molecular Target

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The control of NFkB release through IKK complex inhibition represents a potential target for the modulation of immune function in treatment of autoimmune diseases. The subunit IKK2 is the major inhibitory of the IKK complex activity and consequently the inhibition of IKK2 is considered a promising approach for the treatment of chronic inflammation and cancer. In this work, we used the technique of comparative modeling to obtain a three-dimensional structure of IKK2 and performed molecular docking studies to achieve a better understanding of the molecular properties that may confer potency and selectivity to some small molecule inhibitors. The molecular model was constructed with Modeller v.8 through multiple templates approach. The molecular docking studies of the cofactor ATP and 20 inhibitors, described in the literature, with different potency and selectivity, were performed with Glide software. The molecular docking results indicated that (i) the potency of the stronger inhibitors can be associated to the formation of one or more hydrogen bonds between the ligand and the hinge region, mainly with the residue Cys85; (ii) the inhibitors selectivity probably can be associated with the presence of aromatic groups at the final part of the hinge region. As concluding remarks, the molecular model built for IKK2 together with the docking methodology employed were able to provide important and consistent informations with respect to structural and chemical inhibitor characteristics that may confer potency and selectivity. These features could assist future developments and optimizations of IKK2 new inhibitors.

Word Keys: NFkB, IKK2, molecular docking, comparative modeling.
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