

P019 Exploiting Protein Flexibility in the Structure-Based Design of Selective Kinase Inhibitors

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The pathological characteristics of Alzheimer's Disease (AD) have recently been linked to glycogen synthase kinase 3 β (GSK-3 β). It has been shown that inhibiting this kinase with ATP-competitive small molecules results in reduced tau phosphorylation (a hallmark of AD). However, the design of selective, potent and drug-like inhibitors is still an on-going challenge. Most the small molecule GSK-3 β inhibitors described to date target the highly conserved kinase ATP-binding pocket. Current structure-based design methods do not adequately take into account protein flexibility but rely on static crystal structures. We present an application of a new computational drug design methodology, Active Site Pressurization (ASP), which is used to examine the intrinsic flexibility of the ATP-binding pocket which differs significantly between different kinases. A 3D quantitative structure-activity relationship (QSAR) model is then generated to predict the activity of potential kinase inhibitors using both ligand- and receptor-based design strategies.

The model we present demonstrates how structurally diverse ligands can potentially interact with the recognition site in such a way that static crystal structure are unable to reveal. The effects of induced protein conformational change resulting from ASP on GSK-3 β and the subsequent 3D QSAR model will be presented.