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Abstract:

The approach of exploiting highly conserved protein folds and structure in understanding protein function and in designing drugs leads to drugs that are less selective due to association with similar proteins. Over the years an open problem for researchers has been to develop drug design models based on non-conserved features to have higher selectivity. Recently a new structural feature, the dehydron, has been demonstrated to vary across proteins with conserved folds. Dehydrons are backbone hydrogen bonds that are not adequately protected from water. The importance of wrapping dehydrons in ligand binding and non-conservation of dehydrons across similar proteins makes them important candidates for markers in drug design. Investigation on a series of proteins – PDB entries: 1IA8, 1NVQ, 1NVS, 1NVR, 1OKZ, and 1PKD – revealed the potential impact of wrapping on binding affinity of the ligands. Unlike in 1NVS, 1NVR, 1OKZ, and 1PKD, inhibitor UCN in 1NVQ wrapped both the dehydrons in active site region of the checkpoint protein kinase, thereby indicating an increased potency and higher selectivity. On detailed analysis of 193 protein kinases, roughly 70% were found to have two or more dehydrons in the neighborhood of the bound ligand. Also, about 70% of proteins had dehydrons within the active site region. Only around 20% of ligands, however, actually wrapped two or more dehydrons. These statistics clearly illustrate the significance of dehydrons and their potential use as markers for drug design to enhance drug efficacy as well as selectivity, and to reduce side effects in the process.

Description:

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