Structure-Based Drug Discovery from NMR Chemical Shift Perturbations

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Over the past decade, NMR spectroscopy has provided versatile tools to study protein-ligand interactions that are useful for structure-based drug design. A prominent example is SAR by NMR[1], which takes advantage of the fact that significant chemical shift perturbations (CSP) can be measured upon ligand binding. Since chemical shifts are exquisitely sensitive on the chemical environment of molecules, a comparison of theoretical calculation of CSP upon protein-ligand complexation with experiment can provide insights into protein-ligand interactions at the molecular level. Recently, we have developed an accurate and fast approach to calculate NMR chemical shifts using quantum mechanics.[2] We have applied this approach to study FKBP-GPI[3] and cellular retinol-binding protein (CRBP)[4] complexes. By comparing with experimental CSP values, we were able to select the native state of the ligand from a collection of decoy poses and evaluate the quality of NMR structures for the binding pocket. Our results suggest that the combination of experimental and theoretical NMR chemical shift perturbations can provide a new approach for structure-based drug discovery.

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