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NMR-assisted studies of ligand-protein interactions in solution

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Nuclear Magnetic Resonance (NMR) spectroscopy in solution can effectively recognize and characterize protein state heterogeneity and can simultaneously probe the structures and dynamics of proteins and their complexes with atomic resolution. It can also detect sparsely populated, high-energy conformational states of proteins with population fractions close to 1% and lifetimes from μs to ms. The method is non-invasive and non-destructive and can study biomolecules under near physiological conditions even in living cells. In addition, new hardware, software, isotope labelling strategies, and pulse sequences have helped to move the main limitation of solution NMR spectroscopy, namely the molecular weight, to the order of 1 MDa. Solution NMR spectroscopy can detect ligand binding over a wide range of binding affinities and is uniquely suited for characterizing protein weak binders. Regardless of the thermodynamic nature of the interactions, the heteronuclear single quantum coherence NMR method is capable of quantitatively determining the residue-specific parameters for very weak binding events (KD > 10 mM) for which other traditional biophysical methods are not reliable.
The potential of ligand-based and protein-based NMR methods for the identification and characterization of ligand-protein interactions will be presented using the results of our studies of ligand binding to the protein targets for the development of antimicrobial agents such as muramyl ligase D and sterol 14-alpha; demethylase [1], including studies of transient interactions of endogenous modulators with nerve growth factor [2].

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