Ligand-receptor interactions

The ligands possessing the potential for development to new therapeutic agents are usually molecules of low-molecular weight with differing intrinsic flexibilities, which can affect their binding interactions with receptors. Motions between thermally accessible receptor conformational states can modify ligand binding sites, giving distinct chemical interactions between the ligand and the receptor and thus affecting the ligand biological profile. With the aim to introduce a dynamic aspect in the understanding of ligand-receptor binding we have investigated ligand-receptor interactions in aqueous solution using the combination of spectroscopic and computational methods. For the first time the ligand-receptor interactions of an intrinsically flexible inhibitor with antifungal activity and different structure scaffold from azoles were determined at the atomic level (**1**). The key binding interactions of this novel type of inhibitors responsible for the selective inhibition of fungal CYP51 enzyme over the human ortholog were revealed and provided novel insight into the understanding of the mechanism of selective binding to fungal CYP51, which is the main drug target for the treatment of fungal infections. Studies of binding of ligands with various structure scaffolds to MurD ligase, an attractive drug target for design of novel antibiotics, led us to the discovery of complex dynamic processes that are the result of internal flexibility of ligands and the receptor. Effects of these processes on the conformation of the bound ligands, the stability of the ligand-receptor interactions and the binding site adaptability were determined and explained. The structural and dynamic insight into the observed differences in the biological activity of novel ligands as well as novel directions for the design of potent MurD inhibitors was provided (**2-4**).

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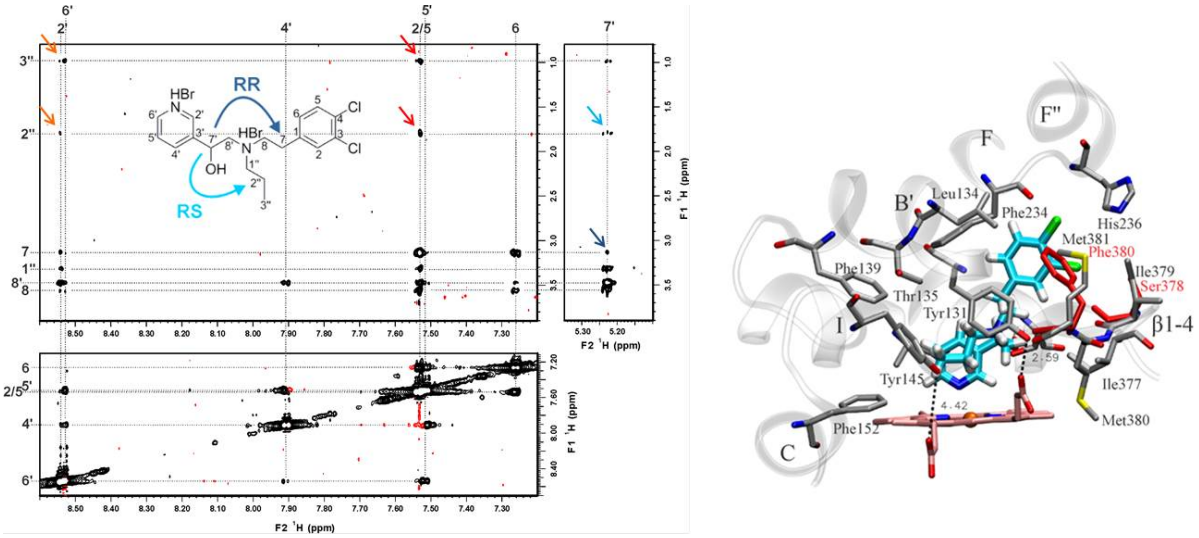

The energetically most favourable binding pose of new inhibitor in the CYP51 active site (right), which is consistent with measured NOE connectivities (left). The interactions of halogenated phenyl ring with unconserved residues Ile379 and Met381 (Ser378 and Phe380 in fungal CYP51) are crucial for selective binding.