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Oral presentation

Dynamic pharmacophores of the 5-HT1B receptor

RC Glen* and J Bell

Address: Unilever Centre for Molecular Sciences Informatics, Department of Chemistry, Lensfield Road, Cambridge, CB21EW, UK
* Corresponding author

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Proteins are dynamic entities, with significant motions of both the main chain and side chains. When ligands bind, they bind in an ensemble of conformations, some of which are stable enough to be observed through x-ray crystallography or by NMR. In many cases, the bound state cannot be determined as there are no structural data available. Until very recently, this has been the case for GPCR's with covalently bound ligands. However, it has often been possible to propose common binding conformations and interactions through pharmacophore analysis, and this approach can be useful in understanding the requirements for binding and in proposing alternative scaffolds or substituents.

With the recent publication of a number of GPCR structures with bound ligands, it is interesting to compare and contrast these approaches using homology modeling and molecular dynamics to gain a deeper understanding of how these two methods can be combined. In particular, do the overlays and molecular interactions deduced from pharmacophore analysis have a physical meaning, and how may they be improved? What lessons can we learn from a combined approach and how does this help with compound optimization?

We will look in detail at a system we have studied for a number of years, the 5-HT1B receptor, for which pharmacophore analysis and the dynamics of homology models are compared.