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Research

Research Interests

Computational Bio-organic Chemistry

Computational chemistry has an ever increasing role to play in the understanding of enzyme catalysis and in the design of highly selective, tight-binding inhibitors. The use of computers in chemistry has become widespread, whether as an aid to visualisation of 3-dimensional structures of large macromolecules, or in the interpretation of experimental data such as that obtained from X-ray crystallography or NMR. Alternatively computational chemistry can be used to predict reaction mechanisms or the 3-dimensional structures of molecules and their properties directly. At Birmingham, we utilise molecular orbital theory (MO) and molecular mechanics (MM) calculations, in collaboration with synthetic medicinal chemists, to gain insight into the catalytic mechanisms of selected enzymes and thereby design selective inhibitors for them.

Phosphatase enzymes are of particular interest as one, Inositol Monophosphatase, is the target for lithium therapy in manic depression and appears to make use of a mechanisms that differs from other phosphatase enzymes. Lithium itself is highly toxic and a far from ideal therapeutic agent, but the design of alternatives is particularly complex. As many phosphatases are involved in physiological control pathways, selectivity for Inositol Monophosphatase is essential and any therapeutic agent must be able to cross the blood-brain barrier whilst remaining sufficiently soluble to reach its target. We have made significant progress in refining our understanding of the catalytic mechanism and of the requirements for substrates and inhibitors so that we are currently in the process of designing inhibitors that can freely cross the blood-brain barrier.

The design process is greatly simplified when the 3-dimensional structure of the target enzyme is known, but unfortunately many enzymes of interest have not been crystallised. One such is Methyl Aspartase, a target for potential antibiotics. We have recently become involved in developing methods for the prediction of the three-dimensional structures of these enzymes. Where the structures of enzymes with similar sequences are known, it is relatively simple to build a 3-d structure for the target by homology modelling but becomes much harder as the degree of similarity declines. Though Methyl Aspartase catalyses very similar chemistry to the Enolase enzyme family and shares the same overall fold, sequence homology is rather low (approx. 30%) so conventional homology modelling techniques leave a great deal of uncertainty in the predicted structure. We are using experimental biochemical data, such as site-specific mutations, active site protection and cross-linking to locate the positions of specific amino acids thus providing a series of hooks on which to hang the sequence alignment. In this way we hope to provide a more reliable 3-D structure for this enzyme, which we can then use in the design of novel antibiotics.

As a counterpoint to our interest in ligand design, we are developing ideas in the design of mutations in enzyme active sites to change their substrate specificity. Enzymes make very efficient stereospecific catalysts and are therefore potentially very powerful tools in asymmetric synthesis, but all to often they are too selective in their choice of substrates and will not catalyse reactions of interest to synthetic chemists. By choosing appropriate mutations, the shape and properties of the binding pocket can be changed to accommodate the desired substrate.