

## Characterising induced-fit conformational changes in drug design

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As a method for elucidating the role of adrenaline in the central nervous system, Phenylethanolamine N-Methyltransferase (PNMT), the adrenaline synthesising enzyme, is an attractive target for structure-based inhibitor design. This research has integrated computational, kinetic and structural methods in a comprehensive approach that has resulted in the discovery of a cryptic binding cavity. Access to the cavity is achieved through dramatic induced-fit conformational changes undertaken by the enzyme in response to binding of particular inhibitors. Crystallographic structures of wild type and mutant PNMT complexed with a range of inhibitors has allowed detailed characterisation both of the extended binding pocket as well as the inhibitor chemical features that are required to induce the structural perturbations. The induced fit changes undertaken by the enzyme include movements of key active site residues and rigid body movements of nearby alpha helices, and result in a dramatic doubling in the volume of the binding pocket. Furthermore, additional kinetic and mutational analysis shows that these structural changes occur at relatively minor energetic cost. The research is now impacting on emerging techniques of drug design and development including virtual screening of compounds and fragment-based lead discovery.