Predicting Metabolism by Human Cytochromes P450117

Gabriele Cruciani

Laboratory for Chemometrics and Cheminformatics
Chemistry Department
University of Perugia
Via Elce di Sotto 10
I-06123 Perugia - Italy

A major requirement for a successful modern drug is its ability to establish an acceptable degree of bioavailability after oral administration. Incidence of low bioavailability can often be the result of decreased metabolic stability of the compound in particular by intervention of liver or gastrointestinal tract. The cytochrome P450 enzymes are involved in a significant fraction of events associated with drug metabolism. The action of these proteins is a common cause of adverse drug reactions and many failures in drug development have been attributed to this class of proteins. Adverse drug reactions rank as the 4^{th} commonest cause of death in the US costing the healthcare industry an estimated $ 136 billion per annum. Even though the reactions catalysed by cytochrome P450 enzymes is quite broad, P450 isozymes exhibit a strong regio- and stereospecificity toward their substrates. This is understood as the result of specific interactions between the enzyme and its substrate which orients the substrate in a position appropriate towards oxidation. The heme iron group which is a common structural motif in all cytochrome P450 enzymes is in this respect considered as crucial towards orienting as well as activating the substrate. The resultant metabolites are more polar than their parent molecules and have a greater likelihood to get excreted. In addition, the incorporated polar functionality can act as handle for drug conjugation metabolism which is further shortening the half-life time of the original parent molecule.

We have been actively involved in cytochrome P450 research working together with pharmaceutical companies since the year 2000. Our group was the first to successfully produce a computational procedure specifically designed to predict the likely site of oxidative metabolism for xenobiotics starting from the 3D structure of a compound. The site of metabolism is described by a probability function that is correlated to, and can be considered, the free energy of the Cyp-substrate recognition and reactivity process.

The aim of the present paper is to report a new method, fast, easy and computationally inexpensive for predicting CYP inhibition, substrate selectivity and site of metabolism, using human CYP X-ray structures and *ad hoc* developed 3D homology models. The methodology works for the most important human cytochromes, but can be applied automatically to all the cytochromes about which the 3D structure is known by X-ray or homology models. The methods thus appear as a valuable new tool in virtual screening and in early ADME-Tox field where potential drug-drug interaction and metabolic stability information must be evaluated to enhance drug design efforts.