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Interaction of Antimigraine Agents With Cytochrome P450 3A4: Modelling Biotransformation Reactions by Combined QM/MM methods

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[**Introduction**]

The cytochrome P450 enzymes play a central role in drug metabolism by catalyzing the biotransformation of a wide variety of xenobiotics. CYP3A4 is a major CYP450 isoform with broad substrate specificity and is estimated to be involved in the metabolism of approximately 50% drugs used in humans.

[**Computational Methods**]

Docking studies were carried out using LigandFit module in Cerius2. Accurate DFT calculations were carried out using DMol^3 in Material Studio using DNP basis set. Molecular dynamics/Quantum Mechanics calculations were also carried out using hybrid accelerated quantum molecular dynamics software 'Hybrid-Colors'.

[**Results and Discussion**]

We have studied the mechanism and selectivity of CYP3A4 mediated hydroxylation of (S)-N-[1-(3-morpholin-4-yl phenyl)ethyl]-3-phenylacrylamide and suppression of metabolism through fluoro substitution. Our studies indicate that ligand forms weakly bound complex and then next step is the formation of the bond between aromatic ring carbon and oxyferryl oxygen (Fig.1). This step requires activation and involves charge transfer from the ligand to the active site, which indicates that hydroxylation may proceeds predominantly through an electrophilic pathway via a cation-like σ complex. Our results may help to explain and predict electronic factors contributing to reactivity in this enzymatic process.

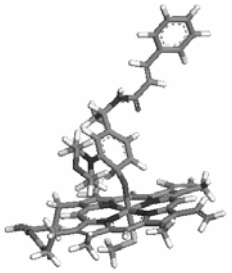

Fig.1:Intermediate structure in ligand hydroxylation by Compound I