The CYP79A1 catalyzed conversion of tyrosine to (E)-p-hydroxyphenylacetaldoxime unravelled using an improved method for homology modeling

The vast diversity and membrane-bound nature of plant P450s makes it challenging to study the structural characteristics of this class of enzymes especially with respect to accurate intermolecular enzyme-substrate interactions. To address this problem we here apply a modified hybrid structure strategy for homology modeling of plant P450s. This allows for structural elucidation based on conserved motifs in the protein sequence and secondary structure predictions. We modeled the well-studied Sorghum bicolor cytochrome P450 CYP79A1 catalyzing the first step in the biosynthesis of the cyanogenic glucoside dhurrin. Docking experiments identified key regions of the active site involved in binding of the substrate and facilitating catalysis. Arginine 152 and threonine 534 were identified as key residues interacting with the substrate. The model was validated experimentally using site-directed mutagenesis. The new CYP79A1 model provides detailed insights into the mechanism of the initial steps in cyanogenic glycoside biosynthesis. The approach could guide functional characterization of other membrane-bound P450s and provide structural guidelines for elucidation of key structure-function relationships of other plant P450s.

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