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Identifying the Binding Residues on CYP3A4 to Naringin using Protein Modeling and Docking

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3d molecular designs

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PDB File: 8DYC

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Description:

Cytochrome (CYP) enzymes are a superfamily of monooxygenase hemoprotein enzymes that are found throughout the body but are heavily concentrated in the endoplasmic reticulum and mitochondria of liver cells. These enzymes catalyze reactions that modify a wide range of substrates into more hydrophilic and, therefore, more readily excreted forms. CYP3A4 is one of the most abundant and important cytochrome p450 enzymes. This group of enzymes is heavily involved in the metabolism of foreign molecules, including many important drugs. The inhibition of CYP3A4 is of particular interest as it may affect the rate of breakdown of drugs, and therefore may affect the bioavailability of medications and the occurrence of drug-to-drugdrug interactions. Many chemicals can function as inhibitors of CYP3A4. Naringin, a flavonoid molecule associated with grapefruit is known to act as an inhibitor of CYP3A4. The exact binding of naringin and the mechanism by which it inhibits CYP3A4 is largely unknown. Our model showcases the potential sites of interaction between naringin and CYP3A4 that have been determined via molecular docking. It also shows the specific residues associated with the opening in the substrate channel and the areas of CYP3A4 that change conformation to allow for the binding of a wide range of substrates.

Specific Model Details:

***Opening of the Channel* (Cyan)**				
Specific Residues		Arg 372		Thr 224
Regions that Change the Shape of the Active Site (Royal Blue)				
Regions Forming the Active Site Cavity	48-58	202-260		464-496
Residues with Expected Interactions (Orchid)				
Glu 374	Arg 105	Arg 212	Ser 119	Ala 370
Arg 106	Phe 215	Phe 304	Leu 482	Ile 223

A model was created to show naringin, bound to protein CYP3A4 (derived from PDB 8DYC). This model also displays certain important regions and residues on the protein. The F-G helix linker region (202-260) and the N and C terminal loops that form the walls of the active site (48-58, 464-496) are colored blue and are involved in enabling the ability of CYP3A4 to adapt to a variety of substrates. The residues Arg 372, Thr 224, Glu 374, Arg 105, Arg 212, Ser 119, Ala 370, Phe 304, Arg 106, Phe 215, Ile 223, and Leu 482 were all found to be associated with the binding of naringin to CYP3A4. Of these residues, Arg 372 and Thr 224 also form the opening of the substrate binding cleft of CYP3A4. These are highlighted in cyan. The residues Glu 374, Arg 105, Arg 212, Ser 119, Ala 370, Phe 304, Arg 106, Phe 215, Ile 223, and Leu 482 are colored orchid. The prosthetic heme group of CYP3A4 is highlighted in red. Naringin, highlighted in green-yellow, is presented in the position determined by the molecular docking simulations.

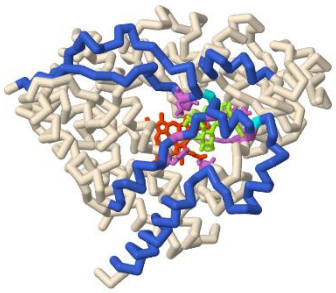

Figure 1: CYP3A4 (Derived from PDB 8DYC) with a Docked Naringin Molecule

Additional References:

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