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Interaction of Human Cytochrome P450 3A4 with Hydrophobicity Probe Nile Red Shows Heterogeneous, Strong Binding JENNIFER HANSEN, F. GUENGERICH, MARTHA MARTIN, GLENN MARSCH, PHYSICS DEPARTMENT, GROVE CITY COLLEGE, GROVE CITY PA 16127 TEAM, CENTER IN MOLECULAR TOXICOLOGY, VANDERBILT UNIVERSITY, NASHVILLE, TN, 37232 TEAM — Human cytochrome P450 3A4 (CYP 3A4) binds an unusually wide variety of substrates, and metabolizes about 50% of all drugs. Steady-state fluorescence spectra were acquired for complexes of CYP 3A4 and the fluorescence probe Nile Red. Difference fluorescence spectra and Hill plots were generated, and Hill coefficients were determined. The fluorescence from multiple Nile Red bound states was observed, with all bound states having higher emission energies than the fluorescence from free Nile Red. Nile Red was titrated into 150nM CYP 3A4, and fluorescence difference spectra showed the quenching of CYP 3A4 tryptophan fluorescence by Nile Red. CYP 3A4 was also added to Nile Red, and changes in the Nile Red fluorescence spectra were monitored. The dissociation constant showed tight binding, with $K_d = 44\text{n}M$. Good fits to the Hill plots were obtained with $n = 1$, suggesting non-cooperative binding. This study revealed strong, heterogeneous, non-cooperative binding of Nile Red to CYP 3A4.

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