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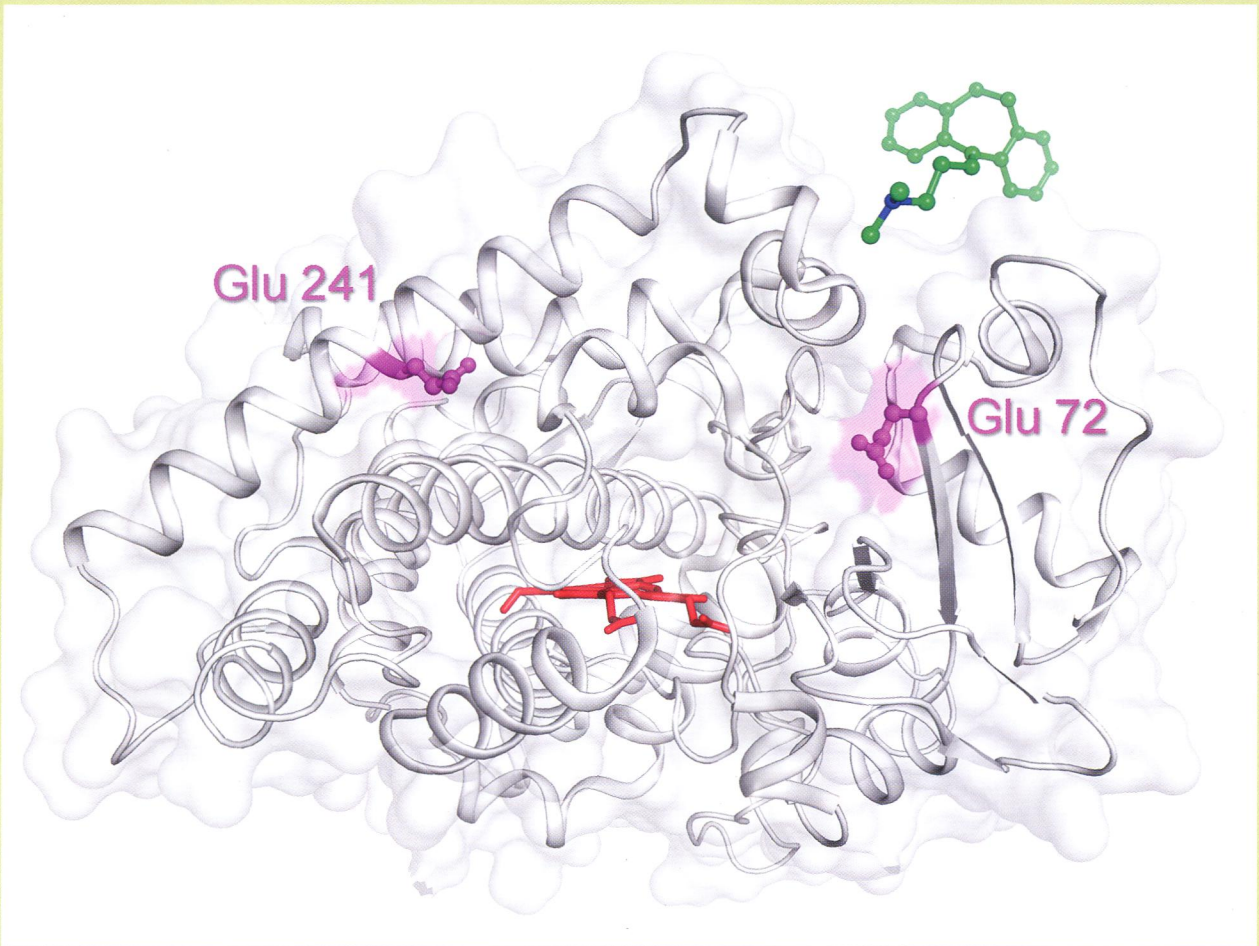

Effect of Cytochrome P450 2C19 and 2C9 Amino Acid Residues 72 and 241 on Metabolism of Tricyclic Antidepressant Drugs

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About the cover: Cytochrome P450s (CYPs) comprise a superfamily of heme-containing enzymes that are mainly responsible for oxidative transformation of xenobiotics in human, animals, plants, and bacteria. CYP2C9 and 2C19 are well conserved and metabolize numerous clinically important drugs. Although distinct substrate specificities have been reported between CYP2C9 and 2C19, the isoforms share 91% amino acid to be identical in a total of 490 residues. Here, we show a crystal structure of CYP2C19 (pdb: 4gqs). Two investigated residues (magenta) and a heme (red) are represented as a stick model. One of the investigated drugs, amitriptyline, is also depicted as a ball-and-stick model, and carbon and nitrogen atoms are colored in green and blue, respectively. Reciprocal mutants for both CYP2C19 and 2C9 were produced, and their metabolic activities and spectroscopic properties were examined using three tricyclic antidepressant (TCA) drugs. Consequently, we concluded that amino acid residue 72 plays a key role in TCA drug metabolism by limiting the binding affinities of CYP2C19 and CYP2C9. See the article by Attia *et al.* on page 176 of this issue.