

Inhibition of cytochrome P450 3A4 isoform by macrolides – structural insight, mentor: Sanja Koštrun

The cytochrome P450s (CYPs) constitute a superfamily of isoforms that play an important role in the oxidative metabolism of drugs.¹ Each CYP isoform possesses a characteristic broad spectrum of catalytic activities of substrates. Whenever 2 or more drugs are administered concurrently, the possibility of drug interactions exists. The ability of a single CYP to metabolise multiple substrates is responsible for a large number of documented drug interactions associated with CYP inhibition. From the viewpoint of drug therapy, to avoid potential drug-drug interactions, it is desirable to develop a new drug candidate that is not a potent CYP inhibitor or inducer and the metabolism of which is not readily inhibited by other drugs.²

It is well known that standard macrolides are moderate to potent CYP 3A4 inhibitors.³ Because human liver samples and recombinant human CYPs are now readily available, *in vitro* systems have been used as screening tools to predict the potential for *in vivo* drug interaction.⁴ Approaches using *in vitro*, *in silico* and *in vivo* models⁵ will be used to study CYP3A4 inactivation by diverse set of macrolide derivatives. Influence of the 3D structure of these complex natural compounds and their possible interaction with CYP enzymes will be studied based on the available protein crystal structures.

References:

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