Ketoconazole is well known for CYP3A4 inhibition. Recently, a number of reports described that ketoconazole not only inhibits CYP3A4 enzyme activity, but also inhibits expression of CYP3A4 as well as P-glycoprotein. The inhibition may be at the transcriptional protein complex of PXR and SRC-1. Previously, we reported a Chinese SNP of PXR at Q158. Transfection of K158-PXR mutant into HepG2 or LS174T cells diminished the induction of CYP3A4 by refampicin. Mammalian two-hybrid studies indicated the Q158K mutation of PXR de-couples the interaction between PXR and SRC-1. Our studies using K159-PXR supported the results of inhibition of ketoconazole on PXR-SRC-1 complex. Our experimental model however indicated that there are other components of transcriptional inhibition. Additional studies indicated that HNF4α and its interaction is also inhibited by ketoconazole dose-dependently. The inhibition is not limited to ketoconazole. Other azole antifungalics such as miconazole, econazole, sulconazole, bifonazole, itraconazole, and voriconazole inhibit CYP3A4 activity at enzyme level and transcriptional level at various concentrations. In our experimental conditions, fluconazole seems to be the only exception. The inhibition on CYP3A4 transcription by fluconazole is limited at drug concentrations up to 50 µM.

In current drug development, ketoconazole inhibition studies are often required for CYP3A4 substrates. Our studies suggest that ketoconazole inhibition is mediated by many pathways. For example, the in vivo inhibition of ketoconazole can be through the inhibition on P-glycoprotein no less than CYP3A4, so is the inhibition on interplay between the two. With more azole antifungalics developed, ketoconazole is less clinically important. The use of ketoconazole in drug-drug interaction study is often as a model drug. However, ketoconazole inhibition in vivo is over-complicated as a model drug. If influence of CYP3A4 enzyme inhibition is evaluated, a specific CYP3A4 inhibitor without transcriptional inhibition is suggested. When the inhibition on protein expression of PXR-related enzyme or transporter is a concern, and in other cases the inhibition on expression is desired, a PXR-SRC-1-HNF4α inhibitor without direct enzyme or transporter inhibition is recommended. Furthermore, the study also suggests that transcriptional protein complex can be a novel drug target or toxicity mechanism.

References:
4) Lim, Y. P. and Huang, J. D.: Inhibition of CYP3A4 expression by ketoconazole is mediated by disruption of pregnane X-receptor (PXR), steroid receptor coactivator-1 (SRC-1), and hepatic nuclear factor 4α (HNF4α) interaction. Pharmacogenet. Genom. In press.