Retrovirology

Poster presentation

Characterization of the In Vitro Human Liver Cytochrome P450 (CYP) Mediated Metabolism and Inhibition Potential of Vicriviroc

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Vicriviroc (formerly SCH 417690), a CCR5 receptor antagonist, is currently under investigation for the treatment of HIV infection. Human liver microsomes (HLM) metabolized vicriviroc via N-oxidation (M2/M3), O-demethylation (M15), N, N-dealkylation (M16), N-dealkylation (M41) and carboxylic acid formation (M35b/M37a). The metabolites generated under *in vitro* conditions were also detected in clinical studies after oral doses of vicriviroc. Incubation with recombinant human CYP3A4 formed all metabolites listed above, while CYP2C9 formed M15 and CYP3A5 formed M2/M3 and M41.

In clinical trials, vicriviroc co-administered with ≥100 mg QD ritonavir (RTV), a potent CYP 3A4 inhibitor, resulted in a Cmax 2 to 3 times higher and an AUC(0–12 hr) 4 to 5 times higher than vicriviroc alone. *In vitro* pre- or co-incubation inhibition studies with HLM demonstrated that vicriviroc does not significantly inhibit the activities of CYPs 1A2, 2A6, 2D6, 2C9, 3A4, or 2C19 at concentrations up to 26.7 μg/mL (100 X the expected human plasma Cmax following once daily oral doses of 10 mg + RTV), which suggests that vicriviroc is not an inhibitor of major CYP enzymes.

The results suggest that formation of the major vicriviroc metabolites in human liver microsomes is primarily mediated via CYP3A4, and that vicriviroc, at clinically relevant doses, is unlikely to inhibit other co-administered drugs metabolized by the major CYP 450 enzymes.