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Cytochrome P450-mediated biotransformation of the antitrypanosomal methamidoxime prodrug DB844 forms novel metabolites through intramolecular rearrangement

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Abstract

DB844 (CPD-594-12), N-methoxy-6-{5-[4-(N-methoxyamidino)phenyl]-furan-2-yl}-nicotinamidine, is an oral prodrug that has shown promising efficacy in both mouse and monkey models of second stage human African trypanosomiasis. However, gastrointestinal (GI) toxicity was observed with high doses in a vervet monkey safety study. In the current study, we compared the metabolism of DB844 by hepatic and extrahepatic cytochrome P450s to determine if differences in metabolite formation underlie the observed GI toxicity. DB844 undergoes sequential O-demethylation and N-dehydroxylation in the liver to form the active compound DB820 (CPD-593-12). However, extrahepatic CYP1A1 and CYP1B1 produced two new metabolites, MX and MY. Accurate mass and collision-induced dissociation mass spectrometry analyses of the metabolites supported proposed structures of MX and MY. In addition, MY was confirmed with a synthetic standard and detection of nitric oxide release when DB844 was incubated with CYP1A1. Taken altogether, we propose that MX is formed by insertion of an oxygen into the amidine C=N to form an oxaziridine, which is followed by intramolecular rearrangement of the adjacent O-methyl group and subsequent release of nitric oxide. The resulting imine ester, MX, is further hydrolyzed to form MY. These findings may contribute to furthering the understanding of toxicities associated with benzamidoxime- and benzmethamidoxime-containing molecules.

Biography

Michael Zhuo Wang has completed his Ph.D. in 2003 from Duke University and postdoctoral studies from the University of North Carolina at Chapel Hill. He is now Assistant Professor from the University of Kansas. He has published 25 papers in reputed journals in the fields of analytical chemistry, drug metabolism and drug discovery for protozoan infections.