

Title:

**Assessment and Confirmation of Species Difference in Nonlinear
Pharmacokinetics of Atipamezole with Physiologically Based
Pharmacokinetic Modeling**

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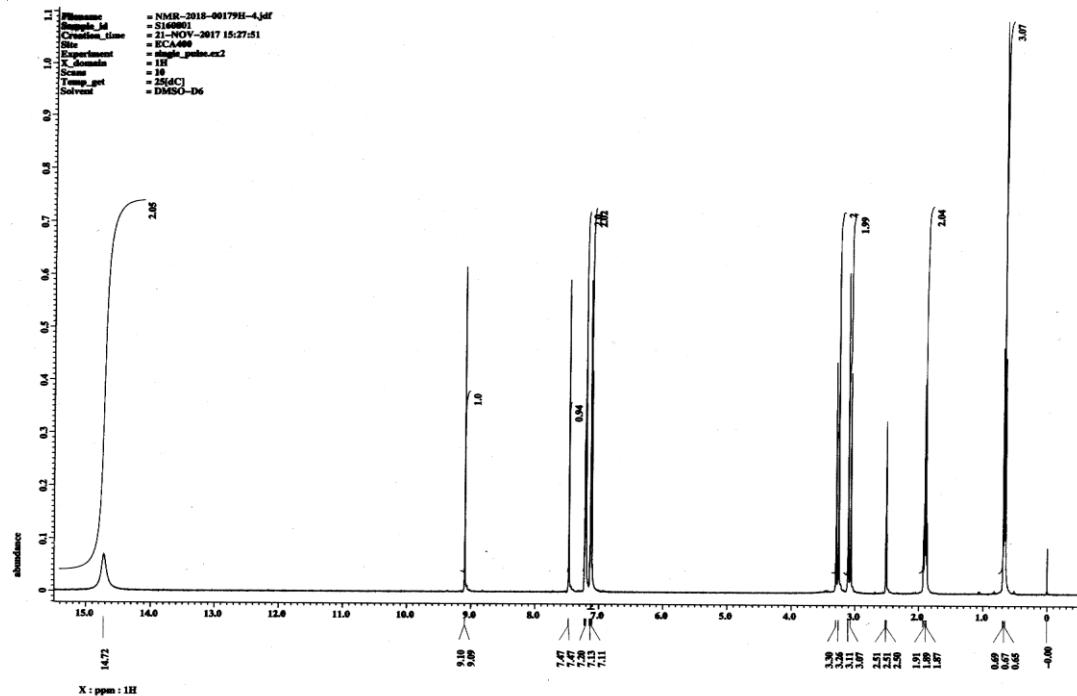
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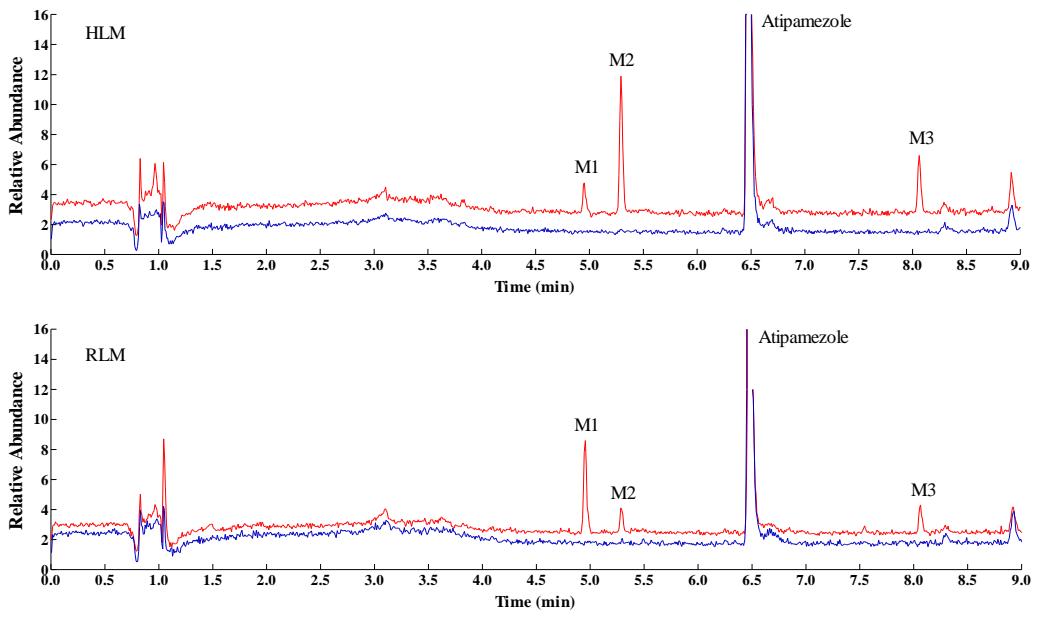
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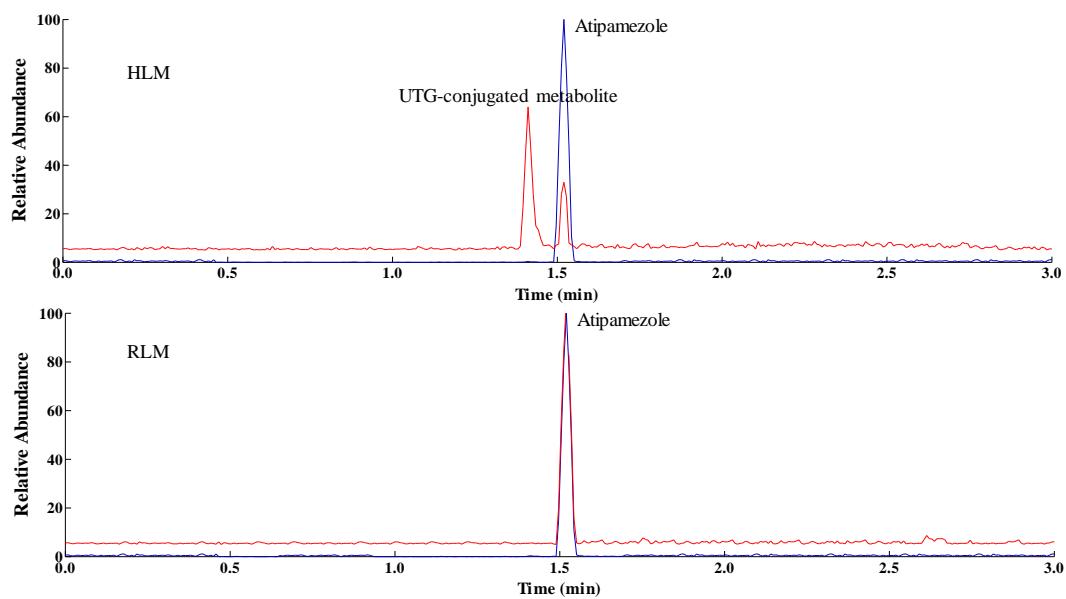
Drug Metabolism and Disposition



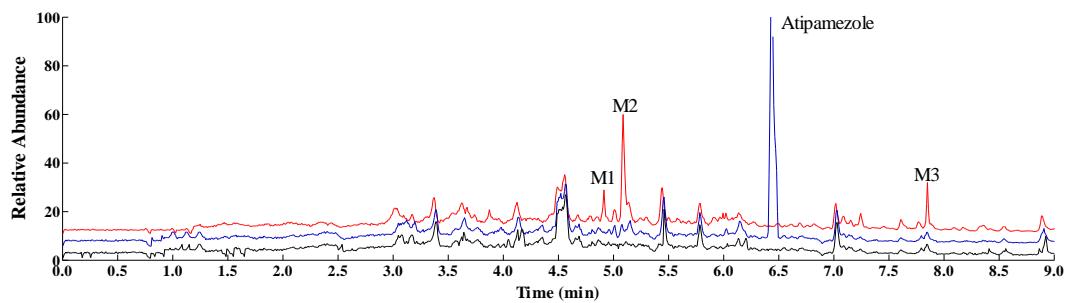
Supplemental Figure 1. NMR spectrum of atipamezole



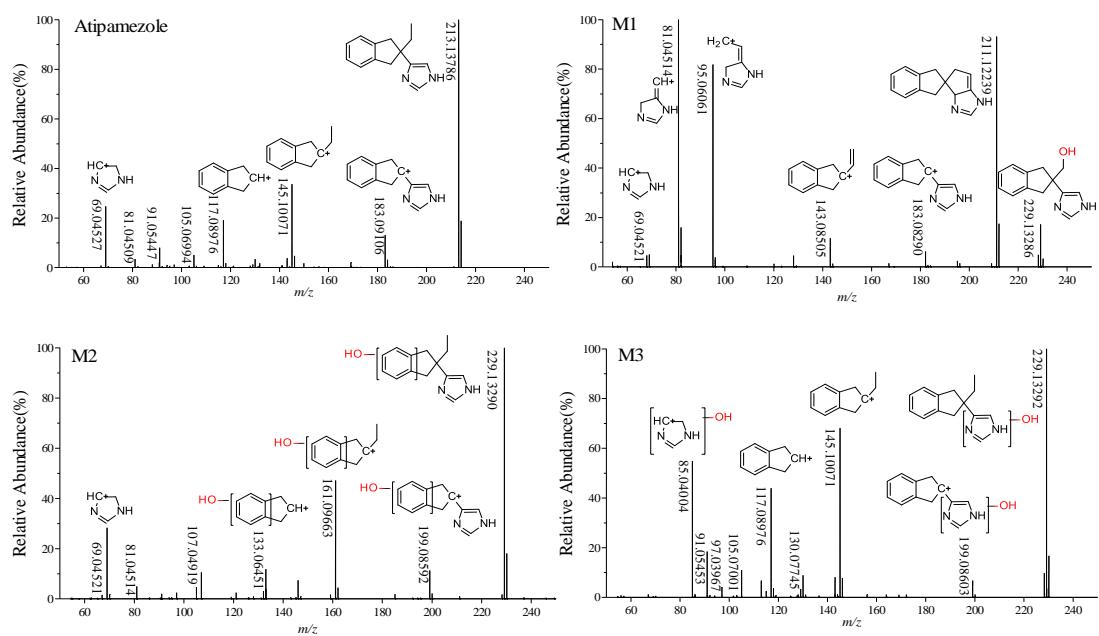
Supplemental Figure 2. Comparative TICs of atipamezole and its metabolites obtained from rat and human liver microsomes before and after incubation with NADPH. (Blue curves represent sample at 0min, red curves represent sample at 60min).



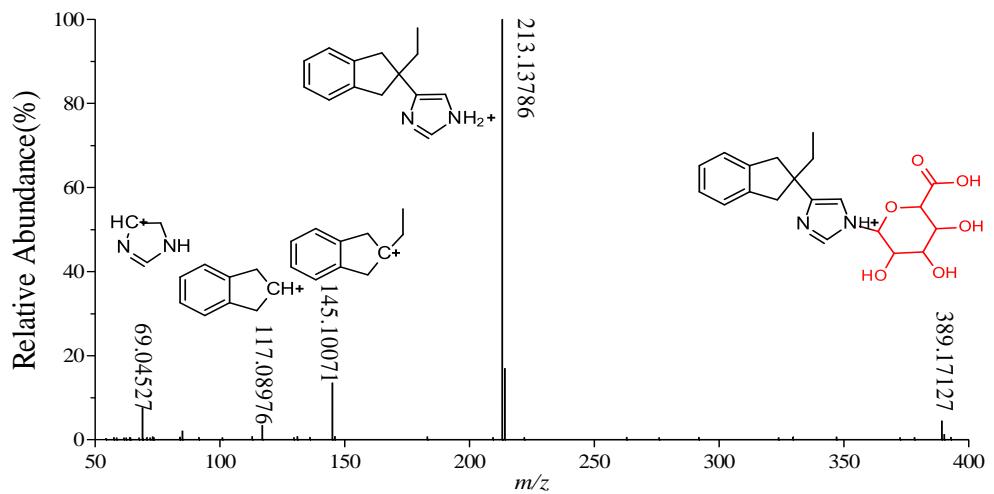
Supplemental Figure 3. Comparative TICs of atipamezole and its metabolites obtained from rat and human liver microsomes before and after incubation with UDPGA. (Blue curves represent sample at 0min, red curves represent sample at 60min).



Supplemental Figure 4. Comparative TICs of atipamezole and its metabolites obtained from bile of BDC rat before and after administration of atipamezole. (Blue curve represents blank bile spiked with atipamezole, green curve represents blank bile before dosing of atipamezole, red curve represents bile sample after dosing of atipamezole @2h).



Supplemental Figure 5. MS /MS spectra of oxidized metabolites of atipamezole



Supplemental Figure 6. MS /MS spectra of UGT-conjugated metabolite of atipamezole in HLM