

# DRUG METABOLISM AND DISPOSITION

A Publication of the American Society for Pharmacology and Experimental Therapeutics

June 2009

Vol. 37, No. 6

## CONTENTS

### SHORT COMMUNICATIONS

Comparative Levels of *O*<sup>6</sup>-Methylguanine, Pyridyl-oxobutyl-, and Pyridylhydroxybutyl-DNA Adducts in Lung and Liver of Rats Treated Chronically with the Tobacco-Specific Carcinogen 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone. *Pramod Upadhyaya, Bruce R. Lindgren, and Stephen S. Hecht* . . . . . **1147**

□ The Role of Human Hepatic Cytochrome P450 Isozymes in the Metabolism of Racemic 3,4-Methylenedioxyethylamphetamine and Its Single Enantiomers. *Markus R. Meyer, Frank T. Peters, and Hans H. Maurer* . . . . . **1152**

### ARTICLES

□ Fenofibrate Metabolism in the Cynomolgus Monkey using Ultraperformance Liquid Chromatography-Quadrupole Time-of-Flight Mass Spectrometry-Based Metabolomics. *Aiming Liu, Andrew D. Patterson, Zongtao Yang, Xinying Zhang, Wei Liu, Fayang Qiu, He Sun, Kristopher W. Krausz, Jeffrey R. Idle, Frank J. Gonzalez, and Renke Dai* . . . . . **1157**

Pharmacokinetics of the Dipeptidyl Peptidase 4 Inhibitor Saxagliptin in Rats, Dogs, and Monkeys and Clinical Projections. *Aberra Fura, Ashish Khanna, Viral Vyas, Barry Koplowitz, Shu-Ying Chang, Christian Caporuscio, David W. Boulton, Lisa J. Christopher, Kristina D. Chadwick, Lawrence G. Hamann, W. Griffith Humphreys, and Mark Kirby* . . . . . **1164**

Long-Lasting Inhibition of the Transporter-Mediated Hepatic Uptake of Sulfobromophthalein by Cyclosporin A in Rats. *Yoshihisa Shitara, Yoshiko Nagamatsu, Satomi Wada, Yuichi Sugiyama, and Toshiharu Horie* . . . . . **1172**

□ Impact of Gut Microbiota on Intestinal and Hepatic Levels of Phase 2 Xenobiotic-Metabolizing Enzymes in the Rat. *Walter Meinl, Silke Sczesny, Regina Brigelius-Flohé, Michael Blaut, and Hansruedi Glatt* . . . . . **1179**

Oxidized Metabolites of Oltipraz Exert Cytoprotective Effects against Arachidonic Acid through AMP-Activated Protein Kinase-Dependent Cellular Antioxidant Effect and Mitochondrial Protection. *Young Nam Kwon, Sang Mi Shin, Il Je Cho, and Sang Geon Kim* . . . . . **1187**

Interactions of Olomoucine II with Human Liver Mitochondrial Cytochromes P450. *Michal Siller, Pavel Anzenbacher, Eva Anzenbacherova, Karel Dolezal, Igor Popa, and Miroslav Strnad* . . . . . **1198**

Novobiocin Is a Potent Inhibitor for Human Organic Anion Transporters. *Peng Duan and Guofeng You* . . . . . **1203**

Protein Electrophile-Binding Motifs: Lysine-Rich Proteins Are Preferential Targets of Quinones. *Matthew T. Labenski, Ashley A. Fisher, Heng-Hsiang Lo, Terrence J. Monks, and Serrine S. Lau* . . . . . **1211**

Metabolic Disposition of [<sup>14</sup>C]Bazedoxifene in Healthy Postmenopausal Women. *Appavu Chandrasekaran, William E. McKeand, Pamela Sullivan, William DeMaio, Randall Stoltz, and JoAnn Scatina* . . . . . **1219**

□ Development of a High-Throughput Brain Slice Method for Studying Drug Distribution in the Central Nervous System. *Markus Fridén, Fredric Ducrozet, Brian Middleton, Madeleine Antonsson, Ulf Bredberg, and Margareta Hammarlund-Udenaes* . . . . . **1226**

*Continued on next page*

<p>Quantitative Prediction of in Vivo Profiles of CYP3A4 Induction in Humans from in Vitro Results with a Reporter Gene Assay. <i>Masanari Kozawa, Masashi Honma, and Hiroshi Suzuki</i> . . . <b>1234</b></p>	<p><i>S. Thelingwani, Simbarashe P. Zvada, Hugues Dolgos, Anna-Lena B. Ungell, and Collen M. Masimirembwa</i> . . . . . <b>1286</b></p>
<p>Characterization of Dasatinib and Its Structural Analogs as CYP3A4 Mechanism-Based Inactivators and the Proposed Bioactivation Pathways. <i>Xiaohai Li, Yuanjun He, Claudia H. Ruiz, Marcel Koenig, and Michael D. Cameron</i> . . . . . <b>1242</b></p>	<p>The Major Human Pregnane X Receptor (PXR) Splice Variant, PXR.2, Exhibits Significantly Diminished Ligand-Activated Transcriptional Regulation. <i>Yvonne S. Lin, Kazuto Yasuda, Mahfoud Assem, Cynthia Cline, Joe Barber, Chia-Wei Li, Vladyslav Kholodovych, Ni Ai, J. Don Chen, William J. Welsh, Sean Ekins, and Erin G. Schuetz</i> . . . <b>1295</b></p>
<p>Breast Cancer Resistance Protein Interacts with Various Compounds in Vitro, but Plays a Minor Role in Substrate Efflux at the Blood-Brain Barrier. <i>Rong Zhao, Thomas J. Raub, Geri A. Sawada, Steven C. Kasper, James A. Bacon, Arlene S. Bridges, and Gary M. Pollack</i> . . . . . <b>1251</b></p>	<p>Assessing the Metabolic Competence of Sandwich-Cultured Mouse Primary Hepatocytes. <i>Karen Mathijs, Anne S. Kienhuis, Karen J. J. Brauers, Danyel G. J. Jennen, Agustin Lahoz, Jos C. S. Kleinjans, and Joost H. M. van Delft</i> . . . . . <b>1305</b></p>
<p>Evaluation of Multiple in Vitro Systems for Assessment of CYP3A4 Induction in Drug Discovery: Human Hepatocytes, Pregnane X Receptor Reporter Gene, and Fa2N-4 and HepaRG Cells. <i>Dermot F. McGinnity, George Zhang, Jane R. Kenny, Geraldine A. Hamilton, Sara Otmani, Karen R. Stams, Suzette Haney, Patrick Brassil, David M. Stresser, and Robert J. Riley</i> . . . . . <b>1259</b></p>	<p>Functional Characterization of the Human Organic Cation Transporter 2 Variant p.270Ala&gt;Ser. <i>Oliver Zolk, Thomas F. Solbach, Jörg König, and Martin F. Fromm</i> . . . . . <b>1312</b></p>
<p>Expression Quantitative Trait Loci Mapping Identifies New Genetic Models of Glutathione S-Transferase Variation. <i>Kevin R. Hayes, Brandon M. Young, and Mathew T. Pletcher</i> . . . . . <b>1269</b></p>	<p>Key Residues Controlling Binding of Diverse Ligands to Human Cytochrome P450 2A Enzymes. <i>N. M. DeVore, B. D. Smith, J. L. Wang, G. H. Lushington, and E. E. Scott</i> . . . . . <b>1319</b></p>
<p>Regulation of Expression and Activity of Rat Intestinal Multidrug Resistance-Associated Protein 2 by Cholestatic Estrogens. <i>Agostina Arias, Silvina S. M. Villanueva, María L. Ruiz, Marcelo G. Luquita, Luis M. Veggi, José M. Pellegrino, Mary Vore, Viviana A. Catania, and Aldo D. Mottino</i> . . . . . <b>1277</b></p>	<p>Ligand Diversity of Human and Chimpanzee CYP3A4: Activation of Human CYP3A4 by Lithocholic Acid Results from Positive Selection. <i>Santosh Kumar, Huan Qiu, Numan Oezguen, Holger Herlyn, James R. Halpert, and Leszek Wojnowski</i> . . . . . <b>1328</b></p>
<p>In Vitro and in Silico Identification and Characterization of Thiabendazole as a Mechanism-Based Inhibitor of CYP1A2 and Simulation of Possible Pharmacokinetic Drug-Drug Interactions. <i>Roslyn</i></p>	<p><b>ACCELERATED COMMUNICATION</b></p> <p>Intestinal Perfusion with Mesenteric Blood Sampling in Wild-Type and Knockout Mice: Evaluation of a Novel Tool in Biopharmaceutical Drug Profiling. <i>Raf Mols, Joachim Brouwers, Alfred H. Schinkel, Pieter Annaert, and Patrick Augustijns</i> . . . . . <b>1334</b></p>

Supplemental material is available online at <http://dmd.aspetjournals.org>.

About the cover: Binding of thiabendazole into the active site of CYP1A2 (PDB 2HI4). See article by Thelingwani et al. on page 1286 of this issue.