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NEW SELECTIVE AND POTENT INHIBITORS OF HUMAN CYTOCHROM P450 1A FAMILY ENZYMES

F. Peter Guengerich[1], Young-Jin Chun[2], Sanghee Kim[3], Donghak Kim, Sang-Kwang Lee[1], Mi-Sook Dong[4], and Yune-Fang Ueng[5]

[1]Department of Biochemistry and Center in Molecular Toxicology, Vanderbilt University, Nashville, TN 37232-0146, U.S.A.; [2]College of Pharmacy, Chungang University, Seoul 156-756, Korea; [3]Natural Product Research Institute, Seoul National University, Seoul 110-460, [4]Korea Graduate School of Biotechnology, Korea University Seoul 136-071, Korea, and [5]National Research Institute of Chinese Medicine, Taipei, Taiwan, Republic of China

The cytochrome P450 (P450) 1 family (1A1, 1A2, 1B1) is involved in the activation of many pro-carcinogens. Previously we characterized a number of synthetic bi- and polycyclic hydrocarbon acetylenes as selective-mechanism-based inhibitors of recombinent P450s 1A1, 1A2, 1B1 (Shimada et al., *Chem. Res. Toxicol.*, 11, 1048-1056, 1998). We reported that the drug oltipraz is a mechanism-based indicator of P450 1A2 (Lagouet et al. *Chem. Res. Toxicol.*, 13, 245-252, 2000). We also found that the grape natural product resverastrol is a "mixed" inhibitor of P450 1A1 (Chun et al., *Biochem. Biophys. Res. Commun.*, 262, 20-24, 1999).

Further work has demonstrated that resveratrol is a non-competitive inhibitor of P450 1B1(K_i 10-30 μM). Analysis of series of resveratrol derivatives yielded one with strong P450 1B1 inhibition, 2,4,3',5'-tetramethoxystilbene (TMS), with all resveratrol phenols methylated and an *O*-methoxy group added to the 4-OH-substituted phenyl ring. The 7-ethoxyresorufin *O*-deethtlation (EROD) activity of recombinant P450 1B1 was inhibited with IC_{50} ~ 6nM (IC_{50} = 300nM for 1A1 and =300nM for 1A2). Estradiol 2- and 4-hyoxylation by P450 1B1 were competitively inhibited by TMS with Ki 3 nM.

The P450 1B1-catalyzed activation of 2-amino-3,5-dimethylimidazo[4,5-*f*]quinoline (MeIQ) in an *Escherichia coli lac* (2-frameshift) test was inhibited with an IC_{50} ~ 0.5μM. These properties and resistance of TMS to oxidation suggest its potential in cancer inhibition.

The natural product rutaecarpaine, isolated from a Chinese medicinal plant, inhibits P450 1A2 in mouse and human liver. Mouse 7-methoxyresorufin *O*-demethylation (MROD) was inhibited with Ki 39nM, and 1μM rutaecarpain inhibited MROD, EROD, and phenacetin O-deethylation (P450 1A2 activites) in human liver microsomes by 77-98%

These natural compound and derivatives have potential in the inhibition of tumor inhibition. (Supported in part by USPHS grants R35 CA44353, R01 CA90426, P30 ES00267).