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

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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 recombinant 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 μ M). 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*-deethyltation (EROD) activity of recombinant P450 1B1 was inhibited with $IC_{50} \sim 6$ nM ($IC_{50} = 300$ nM for 1A1 and =300nM for 1A2). Estradiol 2- and 4-hydroxylation by P450 1B1 were competitively inhibited by TMS with K_i 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 $IC_{50} \sim 0.5$ μ M. 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 1 μ M rutaecarpain inhibited MROD, EROD, and phenacetin *O*-deethylation (P450 1A2 activities) 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).