Modulation of carcinogen-activating enzymes by synthetic trans-stilbene analogs

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Previous studies have demonstrated that 2,3',4,5'-tetramethoxystilbene (TMS) and 3,3',4',5,5'-pentamethoxystilbene (PMS) showed selective inhibition of human cytochrome P450 1B1 and 1A1 in vitro, respectively. In the present study, the effects of synthetic stilbene analogs on the expression of cytochrome P450 1A1 or 1B1 were investigated in human tumor cell lines such as HepG2, MCF-7 and MCF-10A. TCDD caused a dramatic increase in the amount of P450 1A1 or 1B1 proteins and mRNA levels. TMS suppressed TCDD-induced P450 1B1 expression in MCF-7 and MCF-10A cells in a dose-dependent manner. PMS also showed a dose-dependent decrease in P450 1A1 protein and mRNA levels induced by TCDD in HepG2 cells. The cytotoxic effects of these analogs were determined in these cell lines. Taken together, our results indicate that PMS and TMS are strong modulators of P450s gene expression as well as potent and selective inhibitors of P450 1A1 or 1B1, respectively. The detailed mechanisms of suppression of P450s gene expression needs to be determined.

[PC1-2] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Submicrosecond dynamics of nucleic acids studied with a long-lifetime metal-ligand complex

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The metal-ligand complex, $[Ru(phen)_2(dppz)]^{2+}$ (phen = 1,10-phenanthroline, dppz = dipyrido[3,2-a:2',3'-c] phenazine) (RuPD), was used as a spectroscopic probe for studying nucleic acid dynamics. The RuPD complex displays a long lifetime and a molecular light switch property upon DNA binding due to shielding of its dppz ligand from water. To show the usefulness of this luminophore (RuPD) for probing nucleic acid dynamics, we examined its intensity and anisotropy decays when intercalated into $tRNA^{val}$ and pBlueScript SK(+) plasmids using frequency-domain fluorometry with a blue light-emitting diode (LED) as the modulated light source. The mean lifetime for the $tRNA^{val}$ was much shorter than that for the pBlueScript SK(+) plasmids, suggesting a more efficient shielding from water by the plasmids. Because of their size difference, the anisotropy decay data also showed a much shorter slow rotational correlation time for the $tRNA^{val}$ than for the pBlueScript SK(+) plasmids. These results indicate that RuPD can be useful for studying nucleic acid dynamics.

[PC1-3] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

POTENT INHIBITION OF HUMAN CYTOCHROME P450 1 ENZYMES BY DIMETHOXYPHENYL VINYL THIOPHENE

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Recently we have reported that various hydroxystilbenes show strong inhibition of human P450 1 activity. A series of synthetic trans-stilbene derivatives were prepared and their inhibitory potentials were evaluated with the bacterial membrane of recombinant human P450 1A1, 1A2 or 1B1 coexpressed with human NADPH-P450 reductase to find new candidates for cancer chemoprevention. Of the compounds tested, SY-021 (3,5-dimethoxyphenyl vinyl thiophene) exhibited a potent inhibition of human P450 1B1 with an IC_{50} value of 2 nM. SY-021 also showed the inhibition of P450 1A1 with IC_{50} value of 61 nM and P450 1A2 with IC_{50} value of 11 nM. SY-021 showed 31-fold selectivity for P450 1B1 over P450 1A1 and 6-fold selectivity for P450 1B1 over 1A2. We have further investigated the inhibition kinetics of P450 1A1, 1A2 and 1B1 by SY-021. The modes of inhibition by SY-021 were non-competitive for all three P450 1 enzymes. Effect of preincubation with NADPH on inhibition of