P450 1A1, 1A2, or 1B1 by SY-081. The modes of inhibition by SY-081 were mixed-type for all three cytochrome P450 1 enzymes. The K_i values of SY-081 for P450 1A1, 1A2, or 1B1 inhibition were 15.1, 29.6, or 1.4 nM, respectively. Effect of preincubation with NADPH on inhibition of cytochrome P450 1A1, 1A2, 1B1 by SY-081 was determined. Taken together, the data suggest that SY-081 is a new potently selective inhibitor of cytochrome P450 1B1 and understanding of the detailed mechanism of SY-081 action will be helpful to elucidate how cytochrome P450 1B1 is involved in the metabolism of procarcinogens such as benzo[a]pyrene or DMBA.

[PC1-20] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Induction of cell death by 2,4,3',5'-tetramethoxystilbene in human acute promyelocytic leukemia (HL-60) cells and its mechanism.

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We have previously shown that 2,4,3',5'-tetramethoxystilbene (TMS), a synthetic trans-stilbene analogue, is one of the most potently selective inhibitor of human cytochrome P450 1B1 in vitro and in vivo. In the present studies, the apoptotic effects of TMS were investigated in HL-60 cells. The effects of TMS on the proliferation of HL-60 cells were determined with MTT assay. TMS exhibited cytotoxicity with an IC_{50} value of 37 nM. Cotreatment with TMS and etoposide, a well-known anticancer drug significantly enhanced the cytotoxicity. We have investigated the detailed mechanism of cell death by TMS. We have determined that the cytotoxic effect of TMS was due to the induction of apoptosis, which was confirmed by Annexin V staining, poly(ADP-ribose) polymerase (PARP) cleavage, and cytochrome c release. TMS also induced DNA fragmentation in a dose-dependent manner. Taken together, we suggest that the apoptosis-inducing activity and inhibitory activity of cytochrome P450 1B1 of TMS make this compound be useful for anticancer strategies of hormone-mediated carcinogenesis.

[PC1-21] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Inhibitory mechanism of cyclohexylimminobenzoxathiol LYR-64 compound on LPS-induced NO production

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Nitric oxide (NO) is known to work as an important signaling molecule involved in regulating a wide range of biological activities in the neuronal, vascular, and immune system. NO and its metabolites mediate a number of host defence functions and are also implicated in the pathogenesis of tissue damage associated with inflammation. Cyclohexylimminobenzoxathiol LYR-64 compound inhibited LPS-induced NO production in murine macrophages Raw264.7 with an IC50 value of 0.7 uM with 95.9% inhibition at 3 uM, 63.5% at 1 uM and 30.2% at 1 uM. Moreover, iNOS mRNA and its protein expressions were abrogated by the cyclohexylimminobenzoxathiol LYR-64 compound in LPS-stimulated Raw264.7 cells. To further investigate the mechanism responsible for the inhibition of iNOS gene expression by cyclohexylimminobenzoxathiol LYR-64 compound, we examined the effect of the compound on NF-kB signaling. We found that cyclohexylimminobenzoxathiol LYR-64 compound inhibited NF-kB DNA binding activity as well as nuclear translocation, but did not inhibit IkB degradation.

[PC1-22] [2003-10-10 09:00 - 13:00 / Grand Ballroom Pre-function]

Inhibitory effects of [6]-gingerol on phorbol ester-induced cox-2 expression in mouse skin: p38 mapk and p65/rela as possible molecular targets

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