

[PD1-40] [ 2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function ]

### **Novel $\delta$ -Lactam base Histone Deacetylase Inhibitors: Synthesis and Biological Evaluation I.**

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HDAC and HAT (histone acetyltransferase) are involved in co-regulation in chromatin remodeling and the functional regulation of gene transcription. Abnormal recruitment of HDAC is related to carcinogenesis. Thus, the identification of potent histone deacetylase (HDAC) inhibitor has been considered as very intriguing approach for development for cancer chemotherapy. More recently, anti-inflammatory activity of SAHA cytokines was reported via reduction of proinflammatory cytokines in vitro and in vivo. This may indicate HDAC inhibitors stimulate the expression of genes that control the synthesis of cytokines and HDAC could be a interesting target for anti-inflammatory disease. We, here, are addressing novel  $\delta$ -Lactam base Histone Deacetylase Inhibitors; synthesis and biological evaluation for anti-inflammatory activities as well as anti-proliferative activity.

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### **Epoxidation and reduction of cholesterol, 1,4,6-cholestatrien-3-one, and 4,6-cholestadien-3 $\alpha$ -ol**

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Many naturally occurring polyhydroxylated sterols and oxysterols exhibit potent biologic activities. The role of oxysterol including 2,5(R)-2,6-hydroxycholesterol is a potent inhibitor of cholesterol biosynthesis in vitro as it is an effective inhibitor of HMG-Coa reductase. Some new polyhydroxylated sterols were showed potent cytotoxicity to cancer cells. And it has also been shown to be an inhibitor of DNA synthesis. In order to synthesize the various oxy derivatives, we tried to positionselective and reagentselective epoxidation and reduction of cholesterol derivatives. Cholesterol was oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to yield 1,4,6-cholestatrien-3-one, which was reduced with NaBH<sub>4</sub> in absolute ethanol to produce 4,6-cholestadien-3 $\alpha$ -ol. 30% H<sub>2</sub>O<sub>2</sub> and m-chloroperoxybenzoic acid were used as epoxidizing agents and NaBH<sub>4</sub> and Li metal in ethanol/THF were used as reducing agent, respectively.

[PD1-42] [ 2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function ]

### **Synthesis of 2-(3'-azido- and 3'-amino-3'-deoxy- $\beta$ -D-ribofuranosyl)-thiazole-4-carboxamide**

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Inosine 5'-monophosphate dehydrogenase (IMPDH) is a critical enzyme in the regulation of cell proliferation and differentiation. This enzyme catalyzes the NAD<sup>+</sup>-dependent oxidation of IMP to XMP, the rate limiting step in de novo biosynthesis of guanine nucleotides. Therefore, the biochemical effect of IMPDH inhibition in sensitive cell types is decrease in intracellular guanine nucleotide levels, and the decrease in cellular GTP and deoxy GTP pool levels blocks DNA and RNA synthesis in rapidly proliferating tumor cells. Because of its critical role in purine biosynthesis, IMPDH is a drug design target for anticancer, antiviral, immunosuppressive and antimicrobial chemotherapy. Several compounds have been described as IMPDH inhibitors and among them, tiazofurin, 2- $\beta$ -D-ribofuranosylthiazole-4-carboxamide, is a C-nucleoside with potent inhibitory activity against IMPDH currently undergoing clinical trials as an antitumor agent. It was reported that aminosugar nucleosides possess antiviral and anticancer activities and 3'-azido-3'-deoxythymidine was converted to 3'-amino-3'-deoxy thymidine in some cells. One of the most important examples is puromycin, a derivative of 3'-amino-3'-deoxyadenosine. Based upon these findings, it was of interest to put an azido or amino group at the C-3' position of tiazofurin in order to