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

Novel δ-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 cytokinres 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 d-Lactam base Histone Deacetylase Inhibitors; synthesis and biological evaluation for anti-inflamatory activities as well as anti-proliferative activity.

[PD1-41] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Epoxidation and reduction of cholesterol, 1,4,6-cholestatrien-3-one, and 4,6-cholestadien-3?-ol

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Many naturally occurring polyhydroxylated sterols and oxysterols exhibit potent biologic activities. The role of oxycholesterol 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 chown 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 oxidize with 2,3-dichloro-5,6-dicyano-1,4- benzoquinone to yield 1,4,6-cholestatrien-3-one, which was reduced with $NaBH_4$ in absolute ethanol to produce 4,6-cholestadien-3?-ol. 30% H_2O_2 and m-chloroperoxybenzoic acid were used as epoxidizing agents and $NaBH_4$ 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-β-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^+-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-β-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

compare biological activities with the normal ribonucleoside. An amino group serves as a bioisostere of a hydroxyl group and 2'-hydroxyl substituted 3'-aminonucleosides apparently have a higher population of N-type nucleoside conformations. Here, we report the synthesis of the azido- and amino-substituted tiazofurin derivatives, starting from 1,2;5,6-di-O-isopropylidene-D-glucose.

[PD1-43] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Cytotoxic activity of 1-phenyl-2-alkylsulfonylamido propanol derivatives

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The 20 alkylsulfonylamido propanol derivatives had been investigated for their cytotoxic activity against HT-29 colon cancer, Caki-2 renal cancer, A549 lung cancer, PC-3 prostate cancer, HL-60 leukemia cell using MTT assay. Cytotoxic activity was strongly influenced by the substituted alkyl chain length and the optimal alkyl chain length for cytotoxicity was C11. Some of alkylsulfonylamido propanol derivatives showed stronger activity than reference compound, B13.

[PD1-44] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

The docking and searching approach to hit COX-2 inhibitors

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The typical approach of virtual screening is to prepare a 3D database and dock each member to the receptor, and carry out a post-analysis to make a final selection of compounds to be tested. The biological test of these compounds leads to 'hit'. The size of the 3D database is rate-determining factor because the docking process is still time-consuming method. The number of compounds for biological testing is cost-determining factor because the materials used in the test are cost-consuming. The use of the representative subsets derived from the entire database help reduce runtime of docking procedure. The representative subset was made by the method of chemistry space selection. The flexible docking was applied to 3D subset database for the screening of COX-2 inhibitor. The compounds derived from this docking study were sent for the COX-2 inhibition test. Three compounds were hit. Several substructure queries from three compounds were searched into the entire database. The compounds derived from substructure searching were sent for the COX-2 inhibition test. We obtained more hits. Such strategies, that use the docking to subset and the substructure-searching, possibly reduce the runtime of the docking and the number of total compounds sent for biological test.

[PD1-45] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Antifungal activities of juglone and naphthazarine derivatives

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Juglone and naphthazarine derivatives were newly systhesized for the evaluation of antifungal activities. These derivatives were prepared by methylation of juglone and 2,3-dichloro-5,8-dihydroxy-1,4-naphthoquinone, and by regioselective nucleophilic subsitution with arylthiols. All compounds were tested in vitro for their growth inhibitory activities against pathogenic fungi by the standard method. The MIC values were determined by comparison to flucytosine as a standard agent. In general, most juglone derivatives shows in vitro antifungal activities. Among them, 2-arylthio-5-methoxy-juglones showed the most potent antifungal activities against all pathogenic fungi.