

P450 1B1 by SY-021 was determined. These results suggest that SY-021 is one of the most potent inhibitor of human P450 1 enzymes and may be considered as a good candidate for a cancer chemopreventive agent in human

[PC1-4] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Ceramide analogs inhibit inducible nitric oxide synthase expression and nitric oxide production in interferon-gamma and lipopolysaccharide-stimulated RAW 264.7 macrophages.

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Nitric oxide (NO) production through the inducible nitric-oxide synthase (iNOS) pathway has been implicated in inflammatory diseases and cellular injury. Inhibition of various genes related to inflammation, including iNOS is one of the major roles of well-known anti-inflammatory drugs. In the present study, the effects of ceramide analogs on iNOS expression and NO production were evaluated to investigate how ceramide and its structurally related analogs modulate NO-mediated cellular signals and inflammation. Of ten compounds tested, KY3336 and KY3436 significantly inhibited the NO production in RAW 264.7 murine macrophage cells stimulated with lipopolysaccharides (LPS) and interferon (IFN)-gamma in a dose-dependent manner. Expression of iNOS was also significantly suppressed by these analogs. In conclusion, synthetic ceramide analogs decrease iNOS-dependent NO production in LPS and IFN gamma-stimulated RAW 264.7 macrophages, prompting investigation of its potential use as anti-inflammatory drugs.

[PC1-5] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Environmentally benign, Background-free protein staining in SDS-polyacrylamide gels using an counter ion-dye complex solution.

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Environmentally benign protein staining method in sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) using both an acidic dye, zincon (ZC) and a basic dye, ethyl violet (EV) is described. It is based on a counter ion-dye staining technique that employs oppositely charged two dyes to form an ion-pair complex. The selective binding of the free dye molecules to proteins in an acidic solution produces bluish violet colored bands. It is a rapid procedure, involving only fixing and staining steps that are completed in 45 min. The sensitivity of this method is 5-10 ng of protein which is four-fold better than that of the conventional Coomassie brilliant blue R-250 (CBBR) staining and is comparable to the sensitivities of the colloidal Coomassie brilliant blue G (CBBG) staining, rapid silver staining and SYPRO fluorescence staining procedures. This staining method can be applied to detect for the trace amount of protein in 2D-PAGE. Compatibility of the counter ion-dye stain with MALDI-TOF MS has been demonstrated. Due to the use of nontoxic solvent, ethanol, high sensitivity and rapidity, this stain may be more practical than any other dye-based stains for routine laboratory purposes.

[PC1-6] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

ROLES OF PGE₂ AND 15-DEOXY-Δ^{12, 14} PROSTAGLANDIN J₂ IN ET-18-O-CH₃-INDUCED INFLAMMATORY CELL DEATH

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Cyclooxygenase-2 (COX-2) is an inducible enzyme expressed in response to a variety of cytokines and other proinflammatory stimuli. It has been known that aberrant up-regulation of COX-2 is associated with resistance to apoptosis. Contrary to the above notion, treatment of MCF10A-*ras* cells with the anti-tumor agent ET-18-O-CH₃ caused increased expression of COX-2 and its mRNA transcript, while inducing apoptosis as revealed by proteolytic cleavage of poly(ADP-ribose)polymerase, caspase-3 activation, and positive TUNEL staining. To determine whether the ET-18-O-CH₃-induced apoptosis is associated with up-regulation of COX-2 expression, the selective COX-2 inhibitor celecoxib was used. Celecoxib treatment attenuated ET-18-O-CH₃-induced apoptosis as well as COX-2 expression and PGE₂ production, suggesting that induction of COX-2 by ET-18-O-CH₃ is causally linked to the induction of apoptosis. In another study, PGE₂ and 15-deoxy- $\Delta^{12,14}$ prostaglandin J₂ (15d-PGJ₂) induced apoptosis in MCF10A-*ras* cells. ET-18-O-CH₃ induced expression of EP2 receptor and peroxisome proliferator-activated receptor γ (PPAR γ). GW9662, an antagonist of PPAR γ , suppressed the ET-18-O-CH₃-induced COX-2 expression. These findings suggest that ET-18-O-CH₃ induces COX-2 expression through interaction with PPAR γ that PGE₂ and 15d-PGJ₂ accumulated as a consequence of COX-2 up-regulation may mediate apoptosis in ET-18-O-CH₃-treated MCF10A-*ras* cells.

[PC1-7] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Flexible docking of stereoisomers of allyl substituted penam sulfones into metallo- β -lactamase with QXP

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Bacterial β -lactamases provide resistance to β -lactams by hydrolyzing the β -lactam bond. On the basis of their catalytic mechanisms, β -lactamases are divided into two major groups. Class A, C and D which belong to the first group require serine in the active site and class B which is the second group require Zn(II) for their activity. Among class B enzymes, *Bacteroides fragilis* β -lactamase (CcrA enzyme) require two Zn(II) ions per monomer for maximal enzymatic activities. Using the computer docking program, QXP, one known β -lactamase inhibitors, sulbactam, and two sets of α and β isomers of novel allyl substituted derivatives of sulbactam were docked into the *Bacteroides fragilis* β -lactamase. The docking results demonstrated that isomers having β configuration at C-6 with high biological activity proven experimentally docked well into the active site but those with little or no activities - sulbactam and isomers having α configuration at C-6 - were not docked. The docking results also provided potential binding modes for each isomer. These results suggest that not only the stereoisomers can be selected but also the effect of metal ion in a protein could be elucidated by the docking study.

[PC1-8] [10/17/2002 (Thr) 13:30 - 16:30 / Hall C]

Flexible docking of novel antitumor agents into human topoisomerase I-DNA complex with FlexiDock

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DNA topoisomerases catalyze changes in DNA topology through cycles of transient DNA strand breakage and religation. During this process, the active site tyrosine in human DNA topoisomerase I (Top I) becomes covalently linked to the 3'-ends of a single-stranded nick in the DNA duplex. Stabilization of the Top I-DNA cleavable complex is the common initial event leading to the cytotoxicity of top I inhibitors. Using the flexible docking program FlexiDock, novel antitumor agents with benzoin-dione structure were docked into the human Top I-DNA complex. Among 16 agents tested, five with IC₅₀ between 0.1 and 5 μ M were docked well, intercalating DNA and forming up to 5 H-bonding to Top I-DNA complex. Out of four agents with moderate activity with IC₅₀ below 20 μ M, three were docked while one was not. The remaining seven agents with IC₅₀ over 20 μ M were either not docked or docked with different binding modes. The well docked structures showed similar intercalative binding modes with the known Top I inhibitors, such as camptothecin and topotecan. These results suggest that benzoin-dione series of antitumor agents probably inhibit Top I by trapping reversible Top I-DNA cleavable complex, presenting the mechanism of its activity.