Our long-term research goals involve the SARs study and the synthetic procedure development of wogonin and its analogs. We investigated efficient synthetic pathways of wogonin and its bioisosteres in a large quantity to decipher the structural requirements for anti-inflammatory activities. We plan to serially delete or modify the 5,7-dihydroxyl groups of wogonin to observe the effects of the hydroxyl groups on anti-inflammatory activity. Also we modofied the 8- methoxy group on a ring since it is known to be necessary for biological activity. In this presentation, we will report the synthesis and biological activity of wogonin bioisosteres with biologically equivalent functional groups of the 8-methoxy groups.

[PD1-15] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Developing a pharmacophore model for nonpeptide bradykinin antagonists

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Bradykinin is an autocoid related to acute and chronic pain and inflammation. The non-peptide bradykinin antagonists are of interest as novel anti-inflammatory therapeutics. To understand the structural basis for the bradykinin antagonistic activity and to guide the design of more potent compounds we analysed the three dimensional pharmacophore model. Seven active compounds very recently reported such as FR 167344, FR 173657, LF 160687, and bradyzide were used as our pharmacophore model analysis. The Catalyst softwares from Accelrys gave two pharmarcophore models as a result. Our pharmacophore model 1 contained four features: (1) aromatic ring (2) H-bond acceptor (3) H-bond acceptor and (4) H-bond acceptor lipid. The pharmacophore model 2 was similar to model 1 with only difference in feature 1 as hydrophobic side chain instead of aromatic ring.Three compounds synthesized were fit to the pharmacophore model by 2-3 features. These compounds are less active than the seven compounds used for the model analysis. Compounds that fit better to the pharmacophore model in all four features will be suggested for structural optimization of synthesized compounds.

[PD1-16] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Studies on Biochemical Mechanism of DNA Alkylating Agents Tethered to Ligands for Retinoic acid Receptor

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Transcription factors (TF) can bind tightly to specific DNA lesions formed by some anticancer agents. The formation these TF:(drug-modified DNA) complex may disrupt expression of genes critical for cell survival, and it was proved to be one of biochemical mechanisms of anticancer activity. Based on this model, we have designed programmable DNA Alkylating agents that can also attract TF, especially nuclear receptors. As a model compound, we designed drug molecules, RA-mustard and Am580-mustard, that enable to bind both retinoic acid receptor (RAR) and DNA by using molecular modeling techniques, and synthesized them by connecting chlorambucil and ligand for RAR with a linker unit. We conducted thermal DNA strand breakage assay on drug-modified DNA, and confirmed the DNA adduct formation by drug. The interaction of drug with RAR was also identified by binding assay using RAR-overexpressed cell extract. To examine the effect of drug on gene expression, we tranfected the drug-modified plasmid DNA into the RAR-dependent luciferase reporter cell line. The presence of drug-DNA adduct diminished RAR-dependent luciferase expression in a dose dependent manner. The results revealed that our rationally designed agents follow the target mechanism in which the drug-DNA adduct can hijack RAR and disrupt the gene expression in RAR-abundant cell. The concept proved in this study would be applied to design other agents that selectively target cells abundant with specific disease-related TF.

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