[PD1-46] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

The 3D-QSAR study of non-peptide bradykinin antagonists by CoMFA

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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. Some active compounds such as FR 173657, LF 160687, and bradyzide were reported very recently. In our search for the new bradykinin antagonists, we designed and synthesized the iminodiacetic acid derivatives having two or three amide bonds and lipophilic ring system in each molecule. Liquid phase combinatorial synthesis using the iminodiacetic acid template gave diverse individual compounds rapidly and efficiently on a 10-50 mg scale.To understand the structural basis for the antibradykinin activity and to guide the design of more potent compounds we performed three-dimensional quantitative activity relationship (3D-QSAR) studies for this series using comparative molecular field analysis (CoMFA) The bradykinin inhibition activity (%) at 0.1 M concentration on the guinea-pig ileum contraction exhibited a strong correlation with steric and electrostatic factors of the molecules. The statistical results of the traning set, cross-validated q2 (0.703) and conventional r2 (0.997) values, gave reliability to the prediction of the antibradykinin activities of this series. The relative contribution of steric and electrostatic field were 33.8% and 47.9% respectively.

[PD1-47] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Synthesis of TZD Analogs as PPARγ Specific Ligands

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PPARs (peroxisome proliferator activated receptors) are member of nuclear hormone receptors superfamily. Activations of PPARs upon binding with ligands modulate glucose metabolite, differentiation of adipocyte, inflammation response, and so on. Thiazolidinedione analog is one of the potential antidiabetic drug that binds and activates PPAR selectively and enhances insulin sensitivity. In an effort to develop novel and effective antidiabetic thiazolidindione analogs, we have synthesized tetrahydroquinoline and para-substituted benzene-linked thiazolidinedione analogs by coupling reaction of the hydrophobic segments with hydroxybenzylthiazolidinedione.

[PD1-48] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

The 3D-QSAR Studies on the Indolinones Derivatives of PTKIs: CoMFA& CoMSIA

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The three-dimensional quantitative structure-activity relationship (3D-QSAR) study using the comparative molecular field analysis (CoMFA) was performed on indolinones derivatives as an inhibitor of the protein tyrosine kinase of fibroblast growth factor receptor (FGFR). In the training set, twenty-four indolinone derivatives were aligned based on the indole fragment and the steric and electrostatic fields were included in the analysis. The best predicted model showed the cross-validated coefficient (r^2_{cv}) of 0.804 and non-cross validated coefficient (r^2) of 0.942. The CoMFA study can be used to predict several new inhibitors of the FGFR.

[PD1-49] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Approach to the Total Synthesis of Acanthoside-D

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Acanthoside-D, one of major components of Acanthopanacis Cortex, is known as a ginseng-like substance. it has been known to possess diverse biological effects. Acanthoside-D has a furofuran lignan structure and the synthesis of which poses interesting and often unsolved proplems of stereocontrol. Although a few interesting syntheses providing this natural product have been reported, an intermolecular McMurry coupling - intramolecular Mitsunobu cyclization route has not yet been explored. We report here a short and efficient synthetic pathway to the total synthesis of Acanthoside-D from aryl aldehydes and methyl acrylates via Baylis-Hillman reaction, intermolecular McMurry coupling and intramolecular Mitsunobu cyclization as key reactions.

[PD1-50] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Synthesis and biological activity of novel substituted pyridines and purines containing 2,4-thiazolidinedione

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Type 2 diabetes is characterized by high level of blood glucose and insulin and impaired action. In recent years, the treatment of type 2 diabetes has been revolutionized with the advent of thiazolidinedione (TZD) class of molecules that ameliorate insulin resistance and thereby normalize elevated blood glucose levels. These TZDs are synthetic, high-affinity ligands of peroxisome proliferator activated receptor-gamma (PPARγ); a member of the nuclear receptor family that controls the expression of genes in the target tissues of insulin action. Shortly after the launch of the TZDs, several reports of treatment-related toxicity have been published. Rosiglitazone, the second launched TZD is a potent ligand of PPARγ and shows efficient insulin sensitization in type 2 diabetes patients. Even though, rosiglitazone has been associated with liver, cardiovascular and hematological toxicity. In order to synthesize novel TZDs with better safety and efficacy, we designed and prepared a series of novel TZD compound containing substituted pyridines and purines group using LUDI program and molecular modeling study. Based on these results, we modified the substituted pyridines and purines with TZD moiety (Entry No. 6a-d, 12a-e, 18a-d, 23a-c). We evaluated their effect on triglyceride accumulation in 3T3-L1 cells and their hypoglycemic activity in genetically diabetic KKA_y mice in vivo. On the basis of their biological activities, 5-(4-{2-[N-methyl-(5-phenyl-pyridin-2-yl)amino}ethoxy]benzyl}thiazolidine-2,4-dione (6d) was selected for further evaluation and is presently under further pharmacological studies.

[PD1-51] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Synthesis and Anti-cancer Activity of Indirubin Derivatives as the CDK Inhibitors

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The cyclin-dependent kinases (CDKs), a group of serine/threonine kinases that form active heterodimeric complexes binding to cyclins, are key regulators of the cell cycle. The role of cyclin dependent kinases(CDKs) in cell cycle regulation has stimulated an interest in them as potential targets for proliferative diseases such as cancer, psoriasis, and chemotherapeutic agent-induced alopecia. Indirubin, an active ingredient of a traditional Chinese recipe Danggui Longhui Wan, are potent CDK inhibitors competing with ATP for binding to the catalytic site of the CDKs. In this study, we synthesized several indirubin analogs and evaluated them for their inhibitory activities. Among the induribin derivatives tested in cytotoxic activities against several human cancer cell lines compared to Ellipticine, AGM 011 displayed equally high cytotoxic activity with an IC_{50} value of 1.2 mM against human stomach cancer cell line.

[PD1-52] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Synthesis and Biological Evaluation of Allylamine Type Antimycotics