Effect of DNA methylation on the reactivity of DNA alkylating agents

Yoo JaKyung, Park HyunJu

In mammalian species, CpG dinucleotides are highly methylated with 60–90% methylation at the 5-position of cytosine. The pattern of DNA methylation in a cell dramatically affects the function of the DNA by switching genes on or off. Abnormal methylation events occur during aging and in the development of many cancers. Methylated CpG was reported recently to affect the reactivity of agents (mitomycin C and benzo [a] pyrenedioleopside) that can form guanine adducts in DNA. It was suggested that the enhanced reactivity is attributed to either a local charge effect, making 2-amino group of guanine more nucleophilic, or to a local conformational change, rendering it more accessible.

In this study, we further examined the alklyation reactivity of various DNA alkylating agents at methylated DNA sites by using DNA strand breakage assay. The results suggest different mechanisms of adduct formation at methylated DNA depending upon which groove is attacked by those drug molecules.

[PD1–57] [ 10/17/2002 (Thr) 09:30 – 12:30 / Hall C ]

Anti-angiogenic and anti-tumor activity of 2′-hydroxy-4′-methoxychalcone

Jung SangHoon, Lee YeonSil, Lee Sanghyun, Lim SoonSung, Kim YeongShik, Shin KukHyun
Natural Products Research Institute, Seoul National University

In the previous study, we reported that 2′-hydroxy-4′-methoxychalcone, synthetic chalcone inhibited PGE2 production in TPA– stimulated rat peritoneal macrophages by inhibiting the induction of COX–2 protein.

The present study was carried out to clarify whether 2′-hydroxy-4′-methoxychalcone inhibit angiogenesis by the experimental methods in vitro and in vivo. 2′-Hydroxy-4′-methoxychalcone decreased angiogenesis of both chick embryos in the chorioallantoic membrane assay and basic fibroblast growth factor–induced vessel formation in the mouse Matrigel plug assay. 2′-Hydroxy-4′-methoxychalcone also reduced the proliferation of calf pulmonary arterial endothelial (CPAE) cells, and found to possess relatively weak gelatinase / collagenase inhibitory activity in vitro. 2′-Hydroxy-4′-methoxychalcone exhibited a strong anti-proliferative activity and was almost equipotent to that of genistein, a reference drug. 2′-Hydroxy-4′-methoxychalcone, when administered s.c. at a dose of 30 mg/kg for 20 days to mice implanted with murine Lewis lung carcinoma (LLC), caused a significant inhibition of tumor volume by 27.2%. 2′-Hydroxy-4′-methoxychalcone, when treated i. p. at the same dosage for 10 days to ICR mice bearing sarcoma 180, caused a significant suppression in tumor weight by 33.7%.

[PD1–58] [ 10/17/2002 (Thr) 09:30 – 12:30 / Hall C ]

Ligand-Based Virtual Screening for inhibitors of PTP-1B with Antihyperglycemic properties

Kim HeungJae, Yoo MooHi, Son MiWon, Kim SoonHoe
동아제약(주)연구소 신약연구부

Protein-tyrosine phosphatase 1B (PTP-1B), which plays a key role in insulin signaling, is rising as a fascinating target for type 2 diabetes and obesity. Many scientists in structural biology solved the three dimensional X-ray Crystal structure of this type of enzyme, so we could easily get the active site structure of PTP-1B or complex structure with ligand. Our virtual screening study for PTP-1B exactly based on these crystal strucutres from public database. We collected suitable complex structures and analyzed the critical properties of the binding interaction between active site and ligands. As a next step, we prepared some logical query set which possess above properties. Finally, we conducted the database search with our queries and have got a number of Hits and confirmed to be a potential skeleton of the lead through the enzyme assay.

[PD1–59] [ 10/17/2002 (Thr) 09:30 – 12:30 / Hall C ]
Stereocontrolled asymmetric synthesis of pancratistatin

Park Je-Eun, Kim Sanghee, Ko Hyojin
Natural Products Research Institute, College of Pharmacy, Seoul National University, 28 Yungun, Jongro, Seoul 110-460, Korea

Pancratistatin is a highly oxygenated phenanthridone alkaloid, exhibits a high level of in vitro and in vivo cancer cell growth in inhibitory activity, and antiviral activity. The asymmetric synthesis of this alkaloid has been accomplished from the commercially available (R)-(+) -3-Butyn-2-ol. We utilized the Claisen rearrangement and metathesis to install stereogenic centers in the cyclohexene ring that has absolute chemistry. Further functionalization of cyclohexene ring as described, previously by us led to the asymmetric total synthesis of (+)-Pancratistatin.

[PD1-60] [ 10/17/2002 (Thr) 09:30 - 12:30 / Hall C ]

Total synthesis of Antofine by using Intramolecular 1,3-dipolar cycloaddition of Azidealkene

Lee Jaekwang, Lee Taeho, Song Soyoung

Antofine belongs to the Phenanthroindolizidine group of alkaloids. This natural products exhibit interesting biological properties such as antitumor activity, and anti-inflammatory. Wittig reaction of phenanthrenealdehyde with the phosphonium salt provided the phenanthreneazidealkene in good yield. Intramolecular 1,3-dipolar cycloaddition of the resulting azidealkene in refluxing benzene proceeded the imine. It was reduced with cyanoborohydride or Noyori’s Asymmetric Hydrogenation. Then, completion of the total synthesis was achieved by using Pictet-Spengler cyclization.

[PD1-61] [ 10/17/2002 (Thr) 09:30 - 12:30 / Hall C ]

An Asymmetric Synthesis of (+)-Polyoxamic acid

Lee Kihun, Oh ChangYoung, Lee Keeyong, Kim YongHyun, Lee Yiusuk, Joo JaeEun, Ham WonHun
College of Pharmacy, Sungkyunkwan University

The Polyoxin complex is an antifungal antibiotics produced by Streptomyces caeoli var. ascosens that exhibit marked and selective activity against pytopathogenic fungi. They incorporate carbamoylated dipeptides attached to the sugar moiety. Controlled alkaline hydrolysis of polyoxins result in several products, one of which has been identified as (+)-(2S, 3S, 4S)-2-amino-3, 4, 5-trihydroxypentonic acid(polyoxamic acid). A variety of chemical syntheses of polyoxamic acid have been developed over several years. However, development of new method for synthesizing this polyhydroxy amino acid still remains challenging and worthwhile.

Recently, we have developed a new Pd(0)-catalyzed procedure for the stereoselective formation of an oxazine ring from an acyclic aliphatic and homoaliphatic amide having a benzoyl substituent as an N-protecting group. We would like to report here the stereoselective synthesis of oxazine ring from trans-oxazoline. The most significant point of this synthesis is that it is based on the oxazine ring formation in palladium(0) catalyzed condition.

After a few unsuccessful trial, we could find the right combination of reaction sequence and achieved (+)-polyoxamic acid from oxazine.

[PD1-62] [ 10/17/2002 (Thr) 09:30 - 12:30 / Hall C ]

Synthetic study of costunolide