[PD1-48] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Inhibition of prostaglandin E2 production by hydroxychalcone derivatives and the mechanism of action

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Effects of fifteen chalcone derivatives synthesized on prostaglandin E_2 production in rat peritoneal macrophages stimulated by 12-O-tetradecanoylphorbol-13-acetate (TPA), were examined to clarify the structure-activity relationship. Among chalcone derivatives tested, 2',4-dihydroxy-4'-methoxychalcone (compound 3), 2',4-dihydroxy-6'-methoxychalcone(compound 8) and 2'-hydroxy-4'-methoxychalcone (compound 9) were found to suppress significantly prostaglandin E_2 production, even at the concentration as low as 3 μM. Cyclooxygenase (COX)-1 isolated from sheep seminal vesicle was slightly inhibited by compound 9, although it showed no inhibition of COX-2 isolated from sheep placenta. At concentrations to inhibit prostaglandin E_2 production, compound 9 showed no effect on the release of radioactivity from [^{3}H]arachidonic acid-labeled macrophages stimulated by TPA. Western blot analysis revealed that the induction of COX-2 protein by TPA was inhibited by these three compounds in parallel with the inhibition of prostaglandin E_2 production. These findings suggest that the inhibition of prostaglandin E_2 production by these chalcone derivatives is due to the inhibition of TPA-induced COX-2 protein expression and 2-hydroxy, 4- or 6-methoxy and 4'-hydroxy or 4'-hydrogen groups are required for the expression of the inhibitory activity of prostaglandin E_2 production.

[PD1-49] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Novel Platinum(IV) compound, K101, having octahedral structure as Anticancer agent I - Synthesis and Evaluation of Anticancer activity

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Novel Pt(IV) compound, trans,cis-[Pt(acetato)2Cl2(1,4-butanediamine)] (K101) was synthesized for the purpose of development as new anticancer drug. The octahedal structure of trans,cis-[Pt(acetato)2Cl2 (1,4-butanediamine)] was determined by X-ray crystal diffraction method. Anticancer activity was examed using murine and human 12 cancer cell lines. Among them, K101 has shown excellent anticancer activity in human colon and breast cancer cell line realtive to cisplatin in vitro. In IC50 values, K101 is 1.95, 1.23μmol/mℓ and cisplatin is 7.89, 14.67μmol/mℓ in HCT116, HCT15 cell lines, K101 is 1.86, 1.25, 2.89μmol/mℓ and cisplatin is 10.33, 12.23, 17.51μmol/mℓ in SK-BR3, MCF7, MDA-MB231, respectively. In vivo activity against mouse B16 melanoma, antitumor activity of K101 is similar to cisplatin.

[PD1-50] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Selective cytotoxicity of a new platinum(II) complex on human ovarian cancer cell-lines and normal kidney cells

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Cisplatin is important antineoplastic agent, but dose-limiting nephrotoxicity prevents potential efficacy. There is interest in developing new platinum agents that have less toxicity. We have synthesizes a nove platinum (II) coordination complex containing cis-1,2-diaminocyclohexane as a carrier ligand, and glycolic acid as a leaving group. In this study, new platinum (II) complex compound [Pt(II)(cis-DACH)(GA)] was evaluated for cytotoxicity on cancer cell-lines and normal kidney cells. The new platinum complex has demonstrated high efficacy in the cytotoxicity against human ovarian adenocarcinoma cel lines (SKOV-3/NIH OVCAR-3). The cytotoxicity of this compound against rabbit proximal renal tubular cells and human renal cortical tissues was determined by MTT assay , the [3H]-thymidine uptake and glucose consumption test, and found to be quite less than those of cisplatin. Based on these results, this novel platinum compound appear to be a valuable lead compound with high efficacy and low nephrotoxicity.

[PD1-51] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Synthesis and Analgesic-antiinflammatory Activity of Cinmetacin Amides

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Five cinmetacin amides as potential nonsteroidal analgesic and antiinflammatory compounds were prepared and their analgesic-antiinflammatory activity was compared with cinmetacin. Cinmetacin and hydroxysuccinimide were reacted with dicyclohexyl carbodiimide to give cinmetacin active ester (4), which was treated with amines to yield cinmetacin amides (5-9). Compounds (5)and (9) showed stronger analgesic activity than cinmetacin, and compounds (5), (6), (9) showed comparable antiinflammatory activity to cinmetacin.

[PD1-52] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Total synthesis of (+)-Spectaline

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Functionalized piperidines are very important heterocycles because of their presence in numerous alkaloids, pharmaceuticals, and synthetic intermediates.
Recently, we have reported diastereoselective palladium(0)-catalyzed oxazoline formation reation from the acyclic allylic and homoallylic benzamide(Tetrahedron Lett. 1998, 39, 8129, J.Org. Chem. 1999, 64, 9450).
We envisioned that this method could be utilized to set the vicinal amino alcohol stereochemistry of (+)-spectaline. Also, we envisaged that hydrogenolysis of the oxazoline generated amino group, which condensed intramolecularly with the carbonyl group spontaneously to provide piperidine, which was in situ hydrogenated with hydrogen coming from the least hindered surface to provide the piperidine.
The key steps in our strategy are diastereoseletive oxazoline formation reaction catalyzed by Pd(O) and piperidine formation by hydrogenolysis of oxazoline using Pearlman's catalyst.

[PD1-53] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Total Syntheses of Sphingofungin F

Oh ChangYoung, Ham WonHun