

Comparison of CYP 3A4 metabolism between DA-8159 and Sildenafil in vitro and in vivo

Park KyungJin^o, Youn HaeSun, Shim Hyunjoo, Kim SoonHoe, Yoo MooHi, Kim WonBae

Research Laboratories, Dong-A Pharmaceutical Co.,Ltd.

DA-8159 is a new PDEV inhibitor, synthesized by Dong-A Pharm., as an oral agent to treat male erectile dysfunction. DA-8159 and sildenafil are mainly metabolized by cytochrome P450 enzyme CYP 3A4. In this study, we compared the metabolism of DA-8159 with sildenafil in vitro and in vivo. First, we quantified the remaining ratio of original compound, DA-8159 and sildenafil, after we incubated drugs for 30 minutes with human liver microsome cytochrome P450 3A4. The remaining ratio of DA-8159 is higher than sildenafil (Sildenafil : 19.76% ,DA-8159 : 50.67%). In vivo experiment, we examined changes in the drugs metabolism when we inhibited CYP 3A4 by the ketoconazole administration in rats. When CYP 3A4 is inhibited, AUC₀₋₈ of sildenafil was increased by 352.75% .On the hand, AUC₀₋₈ of DA-8159 was increased by only 44.10%. It means that sildenafil is more metabolized than DA-8159 by CYP 3A4. Therefore, it is considered that the drug interaction of DA-8159 is less than that of sildenafil.

[PA1-28] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Synthesis and Evaluation of Biological activities of New Imine Derivatives of Apicidin

Jin ChengHua^o, Kim HyungKyo, Han JeongWhan, Lee HyangWoo, Lee YinWon, Zee OkPyo, Jung YoungHoon

College of Pharmacy, Sungkyunkwan University, Suwon 440-746

Apicidin, a natural product HDAC inhibitor, is recently isolated from *Fusarium* sp, at Merk Research Laboratories, induces therapeutic applications as a broad spectrum antiprotozoal agent to multi-drug resistant malaria and a potential antitumor agent. The biological activity of apicidin appears to be apicocomplexan HDAC at low nanomolar concentrations.

In since, we have worked about the synthesis and the evaluation of biological activities of various derivatives of apicidin, we have discovered that apicidin and some derivatives have mild antitumor activity, which change the morphology of tumor cells to the one of normal cells.

As part of our program toward the development of new antitumor agents, we synthesized its derivatives systemically, and then studied their structure-activity relationships. At present, we modified the ketone moiety of apicidin to obtain various imine derivatives in consideration of interaction with HDAC

[PA1-29] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Revers phase HPLC Separation of D-Amygdalin and Neoamygdalin and Optimum Conditions for Inhibition of Racemization of Amygdalin

Hwang Eun Young^o, Kim DongMin, Koh Jung A, Lee SangSoo, Lee JeHyun, Lee YongMoon, Hong SeonPyo

Department of Oriental Pharmaceutical Sciences, Kyung Hee University, College of Pharmacy, Chungbuk National University

In boiling aqueous solution, D-amygdalin usually begins to convert into neoamygdalin in 3 min and more than 30% of the initial D-amygdalin is found as neoamygdalin after 30 min. In this report, we establish methods for simple HPLC analysis and the inhibition of D-amygdalin conversion. D-Amygdalin and its conversion product, neoamygdalin, were clearly separated on reverse-phase column chromatography by an optimized eluent of 10 mM sodium phosphate buffer (pH 3.8) containing 6% acetonitrile. Linearity for analyzing D-amygdalin and neoamygdalin was observed in the range from 0.05 to 0.5 mM. The detection limits for D-amygdalin and neoamygdalin were ca. 5 μ M per injected amount. We found that D-amygdalin conversion was completely inhibited by adding 0.05% citric acid to the aqueous solution before boiling. To prevent the loss of pharmaceutical potency of Tonin, we applied this method to measure the conversion rate of D-amygdalin. We confirmed that D-amygdalin conversion in Tonin is effectively inhibited by acidic boiling solution with 0.1% citric acid.

[PA1-30] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Effects of Aporphine Compounds on Dopamine Biosynthesis in PC12 Cells

Jin ChunMei⁰¹, Lee JaeJoon¹, Shouyu Yin¹, Kim YuMi¹, Ryu SiYong², Lee MyungKoo¹

¹College of Pharmacy, Chungbuk National University; ²대전시 유성구 화학연구소

The effects of aporphine isoquinoline alkaloids such as liriodenine, anonaine and asimilobine on dopamine biosynthesis in PC12 cells were investigated. Treatment of PC12 cells with liriodenine (10 μ M), anonaine (0.05 μ M) and asimilobine (0.15 μ M) showed 33.6%, 37.7% and 35.1% inhibition of dopamine content for 12 h. The IC_{50} values of liriodenine, anonaine and asimilobine were 8.4 μ M, 0.05 μ M and 0.13 μ M, respectively. Dopamine content decreased at 3 h and reached minimal level at 12 h after the exposure to aporphine isoquinoline alkaloids described above. Under these conditions, tyrosine hydroxylase (TH) and aromatic amino acid decarboxylase (AADC) activities were also inhibited by aporphine alkaloids. These compounds did not show cytotoxic effects, which were examined by MTT test assay. These results suggest that aporphine isoquinoline alkaloids contribute partially to the decrease in dopamine content by the inhibition of TH and AADC activities in PC12 cells. Intracellular mechanisms of aporphine alkaloids need further studies.

*Supported by Korea Research Foundation

[PA1-31] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Inhibitory effect of Lonicera Japonica on trypsin-induced inflammatory mediator secretion from human leukemic mast cells

Kang OkHwa⁰, Kim JinAh, Baek OkSeon, Lee YoungMi

Department of Oriental Pharmacy, College of Pharmacy, Wonkwang University, Iksan, Korea

Mast cells play an important role in inflammation by functioning as a source of histamine, tryptase, and proinflammatory cytokines. *Lonicera Japonica* (Caprifoliaceae, Lc) has been used to treat inflammation. We investigated whether the water extract of *Lonicera Japonica*(Lc) inhibit production of inflammatory mediators such as tryptase and tumor-necrosis factor (TNF)- α , and phosphorylation of extracellular signal-regulated kinase(ERK) in trypsin-stimulated HMC-1. Lc (0.01 mg/ml-1.0 mg/ml) significantly inhibited tryptase and TNF- α production in a dose-dependent manner. Moreover, Lc inhibited ERK phosphorylation in trypsin-stimulated HMC-1. Our results suggest that Lc may inhibit tryptase and TNF- α production via ERK pathway.