of fat synthesis and inhibited insulin secretion and declined the glucose and triglycerides levels in plasma.

[PA1-16] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

OST-5440, A Small Molecule Inhibitor of Human Cathepsin K, Inhibits Bone Resorption *In Vivo* as well as *In Vitro*

Kim HD, Park JH, Lee SS, Son MH, Kwak WY, Yang JS, Lim JI, Kim SH, Kim WB, Lee CH, Lee BY

Research Laboratories, Dong-A Pharmaceutical Co., Ltd., 47-5 Sangkal-Ri, Kiheung-Up, Yongin-Si, Kyungki-Do, #449-905, and †Yuhan Research Institute, 27-3 Tangjeong-Dong, Kunpo-Si, Kyungki-Do, #435-715, Korea

Cathepsin K (CK) is a cysteine protease that plays a major and essential role in osteoclast-mediated degradation of collagen matrix of bone. Its tissue-limited distribution and pivotal contribution to bone resorption meet the requirements as the potential therapeutic target of the disease with excessive bone loss such as osteoporosis. In a search for potent CK inhibitors, we found OST-5440 that effectively inhibited bone resorption *in vivo* as well as *in vitro*.
OST-5440 is a synthetic compound that efficiently and selectively inhibits human CK compared with SB357114 as the reference compound. OST-5440 was demonstrated to be superior to SB357114 in selectivity against especially human cathepsin L and bovine cathepsin S which are highly active and closely related to CK, as well as with the comparable IC_{50} value of 2.7 nM against human CK. Moreover OST-5440 efficiently suppressed osteoclast-mediated bone resorption with IC_{50} value of 30 nM in the *in vitro* culture system using unfractionated bone cell isolated from neonatal rabbits.
For the evaluation of *in vivo* efficacy, in the thyroparathyroidectomized (TPTX) rats as an animal model exhibiting the acute bone resorption, orally administered OST-5440 suppressed PTH-induced hypercalcemia as a dose-dependent manner with ED_{50} value of 29 mg/kg, whereas SB357114 showed no significant effect up to 10 mg/kg.
Conclusively, OST-5440 as a potent and selective inhibitor of human CK effectively suppressed bone resorption *in vitro* and *in vivo*, and may propose the therapeutic potential in diseases caused by the excessive bone resorption, such as osteoporosis.

[This study was supported by a grant of the Korea Health 21 R&D Project, Republic of Korea (01-PJ1-PG4-01PT01-0027)]

[PA1-17] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

In vivo metabolism of 2-methylaminoethyl-4,4'-dimethoxy-5,6,5',6'-dimethylenedioxybiphenyl-2'-carboxy-2-carboxylate (DDB-S) in rats using deutrium labeled compound

Lee Eunyoung°, Shin Myoungyoup, Lee Mijin, Jung Hayoun, Son Junghyun, Kim Dong-Hyun

Bioanalysis and Biotransformation Research Center, Korea Institute of Science and Technology

2-Methylaminoethyl-4,4'-dimethoxy-5,5',6,6'-dimethylenedioxybiphenyl-2'-carboxy-2-carboxylate (DDB-S), a synthetic compound derived from DDB, has been known to protect liver against carbon tetrachloride-, D-galactosamine-, thioacetamide-, and prednisolone- induced hepatic injury in experimental animals. The metabolism of this compound has been assessed in