[PA1-1] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Determination of Optical Purity of a-Arylmethylpropionic acds by Normal Phase Liquid Chromatography

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A variety of 2-arylmethylpropionic acds(profens) have been widely used as non-steroidal anti-inflammatory drugs for the relief of acute and chronic rheumatoid arthritis and osteoarthritis, as well as for other connective tissue disorders and pains. Example are fenoprofen, ibuprofen, ketoprofen, and naproxen. All are chiral and, except for naproxen, are marketed in racemic form. Enantioseparations of profens have been of considerable interest because their anti-inflammatory and analgesic effecs have been attributed almost exclusively to their S-enantiomer.
A simple method for determination of (+) and (-) - a-arylmethylpropionc acids has been developed . By means of EEDQ, a-arylmethylpropinic acids is coupled to (s)-napthylethylamide, a reaction which is complete in 3 hr at room temperature . The diasteoisomeric derivatves are then separated by normal-phase high-performance liquid chromatography.

[PA1-2] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

Effect of cationic homopolypeptide on the mucin release from airway goblet cells in vitro and in vivo.

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In this study, we tried to investigate whether poly-L-arginine(PLA)(MW 10,800) significantly affect mucin release from cultured hamster airway goblet cells and the mucosubstances of hypersecretory airway goblet cells of rats. Confluent primary hamster tracheal surface epithelial(HTSE) cells were metabolically radiolabeled with 3H-glucosamine for 24 hr and chased for 30 min in the presence of varying concentrations of PLA to assess the effects on 3H-mucin release. Possible cytotoxicities of PLA were assessed by measuring both Lactate Dehydrogenase(LDH) release and by checking the possible changes on the morphology of HTSE cells during treatment. For in vivo experiment, hyperplasia of rat airway goblet cells and increase in intraepithelial mucosubstances were induced by exposing rats to SO2 for 3 weeks and varying concentrations of PLA were administered inhalationally to assess the effects on the mucosubstances of airway goblet cells of rats. The results were as follows : (1) PLA significantly inhibited mucin release from cultured HTSE cells in a dose-dependent manner , (2) there was no significant release of LDH and no significant change on the morphology of cultured HTSE cells during treatment, (3) PLA also affected the intraepithelial mucosubstances of hypersecretory rats and restored them to the levels of control animals. We conclude that PLA inhibit mucin release from airway goblet cells without significant cytotoxicity and possibly normalize the hypersecretion of airway mucosubstances in vivo. This finding suggests that PLA might function as an airway mucoregulative agent.

[PA1-3] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

High-Throughput Fluorometric Assay for HCV NS3 Protease Inhibitors

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The proteolysis of HCV non-structural protein is reported to be the most essential process for HCV virus replication. This proteolytic processing is catalyzed by a chymotrypsin-like serine protease which is located in the N-terminal region of non-structural protein 3(NS3). The cDNA of HCV NS3 (1-180) protease was cloned into expression vector. The fusion protein with the N-terminal six histidine was over-expressed in Escherichia coli. In order to discover NS3 protease inhibitors, we have established a high throughput screening(HTS) system based upon a fluorogenic assay in a 96-well format. Over 4,000 compounds in-house library were evaluated for their inhibitory activities on HCV NS3 protease with newly developed HTS method. Among these compounds, 35 compounds were founded with IC50 values of less than 5 uM and one compound with less than 1 uM. The advantages of this fluorogenic NS3 protease assay system are fast, accurate and reproducible.
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[PA1-4] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

INFLUENCE OF DOXORUBICIN ON CATECHOLAMINE SECRETION FROM THE PERFUSED RAT ADRENAL GLAND

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Doxorubicin (DX, adriamycin) is an anthracycline that is a highly effective chemotherapeutic agent used largely in the treatment of solid tumors (Singal and Iliskovic, 1998, Feldman et al., 2000, Slamon et al., 2001). Bounias and his coworkers (1997) have shown that catecholamines (CA) including epinephrine, norepinephrine and dopamine, and DOPA enhance the generation of hydroxyl radicals by chemotherapeutic antibiotics (DX, farnorubicin and mitomycin C). It has been also found that in closed-chest pure-bred beagles infused with DX into coronary artery, the plasma norepinephrine concentration as well as plasma natriuretic peptide levels were greatly increased. Increased circulating and heart CA levels have been reported in experimental animals treated with DX or daunorubicin, a closely related anthracycline (Bristow et al., 1979, Bristow et al., 1981, Soldani et al., 1981). Moreover, at a lower concentration (3 x 10-6 M), DX facilitated CA secretion induced by acetylcholine and 51mM K+ from the bovine adrenal medulla (Pinto et al., 1987). In contrast with these results, Robison and Girl (1987) have reported that plasma CA and myocardial guanylate cyclase activity examined at 14 weeks after treatment with DX in rats were unchanged throughout the course of the study. In acute and chronic studies treated with DX, in rabbits, myocardial CA levels were also unchanged (Jackson et al., 1984). On the other hand, it has been shown that chronic adriamycin treatment rather inhibits the neuronal exocytotic release of CA at the cardiac sympathetic nerve terminals of the rabbits (Kawada et al, 2000). Therefore, the present study was attempted to investigate the effect of doxorubicin on secretion of catecholamines (CA) evoked by ACh, high K+, DMPP and McN-A-343 from the isolated perfused rat adrenal gland and to establish the mechanism of its action. Doxorubicin (10-7 ~ 10-6 M) perfused into an adrenal vein for 60 min produced dose- and time-dependent inhibition in CA secretory responses evoked by ACh (5.32 x 10-3 M), DMPP (10-4 M for 2 min) and McN-A-343 (10-4 M for 2 min). However, doxorubicin did not affect CA secretion by high K+ (5.6 x 10-2 M). Doxorubicin itself did also fail to affect basal catecholamine output. Furthermore, in adrenal glands loaded with doxorubicin (3 x 10-7 M), CA secretory responses evoked by Bay-K-8644, an activator of L-type Ca2+ channels and cyclopiazonic acid, an inhibitor of cytoplasmic Ca2+-ATPase were time-dependently inhibited. However, daunorubicin (3 x 10-7 M), given into the adrenal gland for 60 min, attenuated CA secretory responses evoked by ACh (5.32 x 10-3 M), DMPP (10-4 M for 2 min) and McN-A-343 (10-4 M for 2 min), not that by high K+ (5.6 x 10-2 M). Taken together, these results suggest that doxorubicin inhibits greatly CA secretion evoked by stimulation of cholinergic (both nicotinic and muscarinic) receptors, but does not affect that by membrane depolarization. It is thought that this inhibitory effect of doxorubicin may be mediated by blocking the calcium influx into the rat adrenal medullary chromaffin cells as well as by the inhibition of Ca2+ release from the cytoplasmic calcium store. It also seems that there is no difference in the mode of action between doxorubicin and daunorubicin in rat adrenomedullary CA secretion.

[PA1-5] [04/18/2002 (Thr) 14:00 - 17:00 / Hall E]

In Vitro Anti-tumor Activity of Novel Farnesyltransferase Inhibitor