[S1-2] [10/17/2002 (Thurs) 11:10~11:30/Hall A]

Rapid Analysis of Metabolic Stability and Structure of Metabolites in New Drug Development

Dong-Hyun Kim

Bioanalysis and Biotransformation Research Center, KIST, Seoul 136-791, Korea

Recent technological innovations in the drug discovery process such as combinatorial synthesis and high throughput screening have led to the identification of an increasingly large number of compounds at the hits-to-leads stage. Therefore, rapid and precise pharmacokinetic/ metabolic screening is essential to enhance the tractability of selected leads and to minimize the risk of failure in the later stages of drug development. In this presentation, role of drug metabolism and pharmacokinetics in the drug discovery stage will be reviewed. In addition, simple and rapid methods to evaluate metabolic stability and structure of metabolites developed in our lab will be presented. Dopamine receptor antagonists were incubated with liver microsomes and their metabolites were by LC/MS. The incubated samples were either individually analyzed or pooled into the designed cassette groups prior to analysis by HPLC/electrospray (ESI) ITMS in full-scan mode. The metabolic stability of the drugs was determined by comparing their signals after incubation. The quantitative results from the cassette analysis procedure agreed well with those obtained from conventional discrete analysis. The metabolic stability of examined dopamine receptor antagonists was in the range of 15.6-93.1%. In addition, present cassette analysis allowed simultaneous detection of metabolites formed during the same incubation without having to reanalyze the samples. The metabolites were first characterized by nominal mass measurement of the corresponding protonated molecules. Subsequent multi-stage tandem spectrometry (MS^n) on the ion trap instrument allowed characterization of structure of the detected metabolites. *N,O*-dealkylation and ring hydroxylation reaction were identified to be major metabolic reaction in piperazinylalkylisoxazole derivatives. These results suggested that present approach is useful

for rapid evaluation of metabolic stability and structural characterization of metabolites within a short period in new drug discovery.

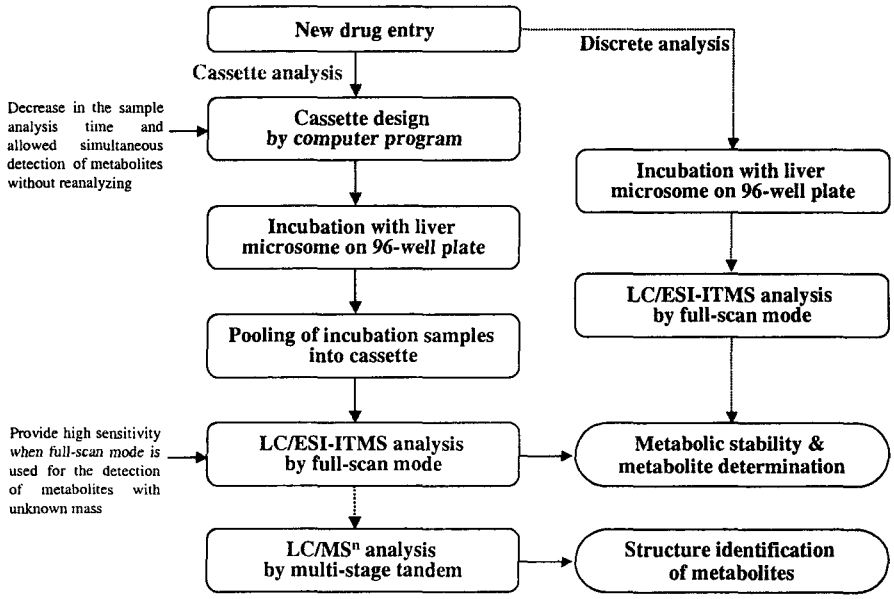

Figure. Strategy for rapid metabolic screening