Poster Presentation

MS04.P01

Structural and thermal analyses of a hydrolysis compound of thalidomide

K. Otogawa[1], Y. Ogino[1], K. Ishikawa[1], M. Tanaka[2], M. Shiro[3], T. Osaka[1], T. Asahi[1]

[1]Waseda University, Advanved Science and Engneering, Tokyo, Japan, [2]AIST, Ibaraki, Japan, [3]ASMeW, Tokyo, Japan

Thalidomide (TD) is a historically famous chiral drug. After prescription as a safe hypnotic, TD was suspected of contributing to teratogenicity, resulting in prohibition of the use of TD. TD and its derivatives, however, have attracted a renewed attention since their therapeutic effects for Hansen's disease and multiple myeloma were demonstrated. Meanwhile TD has been known to suffer from spontaneous hydrolysis with complicated pathways, leading to the production of various metabolites of TD. Therefore, we are now facing the difficulty in specifying the compounds which cause desired and/or adverse effects in the drug mechanism of TD. In a previous study, pure hydrolytic products of TD were synthesized and assayed for production-inhibitory activity of TNF-α, a kind of cytokine that induces inflammation. This study has showed that some products, especially α-(2-carboxybenzamido)glutarimide (CBG), exhibit high potency for the inhibition of TNF-α production compared to original TD. The hydrolytic products of TD thus are found to greatly attribute to the pharmacological effect of TD. For comprehending effects of the hydrolytic products, it is much significant to perform physicochemical analysis of them because their properties are deeply related to molecular stability and interaction with receptor proteins. In this study, we thus aim to investigate the physicochemical properties of CBG employing X-ray crystal structural analysis and thermal analyses. Single crystals of racemic and enantiomeric CBG were grown by solvent evaporation methods. On the crystallization, we chose alcoholic solvents such as methanol and ethanol. Surprisingly, crystals grown from the CBG solutions have indicated the same crystal structure of TD with high reproducibility. This unique result is likely to represent dehydration of CBG in non-aqueous solvents, which has not been reported so far. The detailed mechanism is under investigation.

[1] *G. Blaschke, HP. Ktaft, K. Fickentscher, et al, (1979). Arzneimittel-Forschung, 29, 1640-1642,* ***[2]*** *Nakamura T., Noguchi T., Miyachi H., et al, (2007). Chem. Pharm. Bull , 55, 651-654,* ***[3]*** *Suzuki. T., Tanaka M., Shiro motoo., et al, (2010). Phase Transition, 83, 223-234*

Keywords: thalidomide, α-(2-carboxybenzamido)glutarimide, crystal analysis