S35-2 Process development of MX-68, anti-rheumatoid arthritis drug

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MX-68, a MTX derivative bearing dihydro-*2H*-1,4-benzothiazine moiety and L-homoglutamic acid moiety, was developed for treatment of rheumatoid arthritis. A large-scale preparation route of MX-68 was studied to supply the drug substance for the toxicity test and the clinical study. We focused on the solution of the original synthetic route that was a laboratory-scale synthesis for preclinical study because the problems for the large-scale preparation had been clear, for example purification by column chromatography using haloalkane solvent, low yield at the deprotection step and the formation of the major impurity at the final step. In order to solve these problems, we studied reaction and purification condition at each step. In these results, the improved process involved the following features: each step does not use haloalkane solvents and column chromatographic purification, and the formation of the major impurity at the final step was minimized. This improvement enabled us to supply sufficient quantities of MX-68, which was required for both the toxicity test and the clinical study.