

INTEGRATED MEDICINAL CHEMICAL RESEARCH BASED ON PEPTIDE CHEMISTRY

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Peptides and natural peptide-like small molecules with biological activities are very important resources for the drug development. We have been focusing on these molecules for over a decade in the three fields of drugs. These are a fibrinogen receptor antagonist derived from a RGD peptide as a platelet aggregation inhibitor, a cyclic-dipeptidic tubulin polymerization inhibitor derived from natural phenylahistin as an anticancer drug, and a dipeptidic antibiotic negamycin as a potential genetic disease drug. Intensive modification of their chemical structures could enhance pharmacological activities that were valuable for the development of real drug candidates. In the presentation, medicinal chemistry on anticancer and genetic disease drugs will firstly be discussed.

Development of vascular disrupting agent NPI-2358/KPU-2 as an anticancer drug

Microtubule depolymerization agents with vascular disrupting activity have been drawing attention as a new anticancer agent that induces tumor-selective vascular collapse by targeting the vascular endothelial cells, thus preventing oxygen and nutrition supply to the tumor tissues, resulting in tumor regression. Therefore, we have been focusing on phenylahistin, a colchicine-like microtubule depolymerization agent. From structure-activity relationship studies, NPI-2358/KPU-2 with a highly potent cytotoxic activity was developed. This agent also exhibited strong vascular disrupting activity against human umbilical vein endothelial cells (HuVEC) and is undergoing Phase I clinical trials in the US. Moreover, we synthesized biotin-containing photoaffinity probe KPU-244-B2 from a potent derivative KPU-244 to investigate the tubulin-binding site of this type of compounds and understand the precise mechanism of their microtubule depolymerization.

Negamycin as a potential drug candidate for Duchenne muscular dystrophy

Our peptide-based medicinal chemistry has also focused on another intractable disease, i.e., genetic diseases. (+)-Negamycin, a hydrazine dipeptide, was found to restore dystrophin expression in skeletal and cardiac muscles of *mdx* mice, an animal model of Duchenne muscular dystrophy, with a read-through activity of premature termination codon (PTC). An efficient total synthesis of (+)-negamycin starting from achiral Boc-Gly-H with a total yield of 42% over only 8 steps was recently communicated and the medicinal chemistry of negamycin has been started.

Other projects based on an α -hydroxy- β -amino acid will also be discussed. The unique structure of this amino acid, in which three different functional groups are located on the two adjacent asymmetric carbon atoms, afforded interesting features to create new functional molecules useful in both organic and medicinal chemistry. By focusing on this amino acid, we developed 1) a new solid-supported Evans' chiral auxiliary for asymmetric synthesis, 2) an efficient method for the synthesis of difficult sequence-containing peptides, and 3) a water-soluble prodrug of paclitaxel by O-N intramolecular acyl migration of the *N*-benzoylphenylisoserine moiety. This prodrug research would contribute to "Chemical Pharmaceutics" that creates high-value added chemical structures with more appropriate physicochemical and drug delivery properties based on Organic Chemistry, contrary to conventional pharmaceutics that is focused on formulation techniques.