

Study on the natural products as drug leads

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We carry out two projects, “Isolation, structure determination and study on the mechanism of the biological activity of natural products” and “Biosynthetic pathway of alkaloids isolated from the marine-derived fungus”. We use marine invertebrates and microorganisms collected in Indonesia. We tested various biological activities and among them focus on the ubiquitin-proteasome system (UPS).

1. Search for inhibitors of the UPS from natural sources for drug development

The UPS plays a major role in selective protein degradation and regulates various cellular events. In 2003, a proteasome inhibitor, bortezomib, was approved by FDA for the treatment of patients with multiple myeloma, therefore validating the proteasome as an anticancer target. On the other hand, polyubiquitination of proteins requires three enzymes, ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2) and ubiquitin-protein ligase (E3), and is prerequisite to proteasome-mediated protein degradation, which leads to the idea that inhibitors against E1, E2, and E3 are drug candidates for treatments of diseases related to polyubiquitination. We succeeded in isolating himeic acid A as an E1 enzyme, leucettamol A as an inhibitor of Ubc13 (E2)-Uev1A interaction, and (-)-hexylitaconic acid as an inhibitor of p53-HDM2 (E3) interaction.

2. Biosynthetic pathway of alkaloids isolated from the marine-derived fungus

We isolated new alkaloids, notoamides, from a marine-derived *Aspergillus* sp. Among them, notoamide B and stephacidin A contain a bicyclo[2.2.2]diazaoctane ring, which is proposed to be constructed from notoamide E by the intra-molecular Diels-Alder (IMDA) reaction. Williams and Gloer *et al.* reported the isolation of antipodes of our alkaloids from the terrestrial *Aspergillus*. With regard to the generation of both enantiomers, the IMDA reaction would occur in a face-selective manner in both *Aspergillus* sp. The biosynthetic pathway of notoamide congeners is an interesting subject of current investigation.