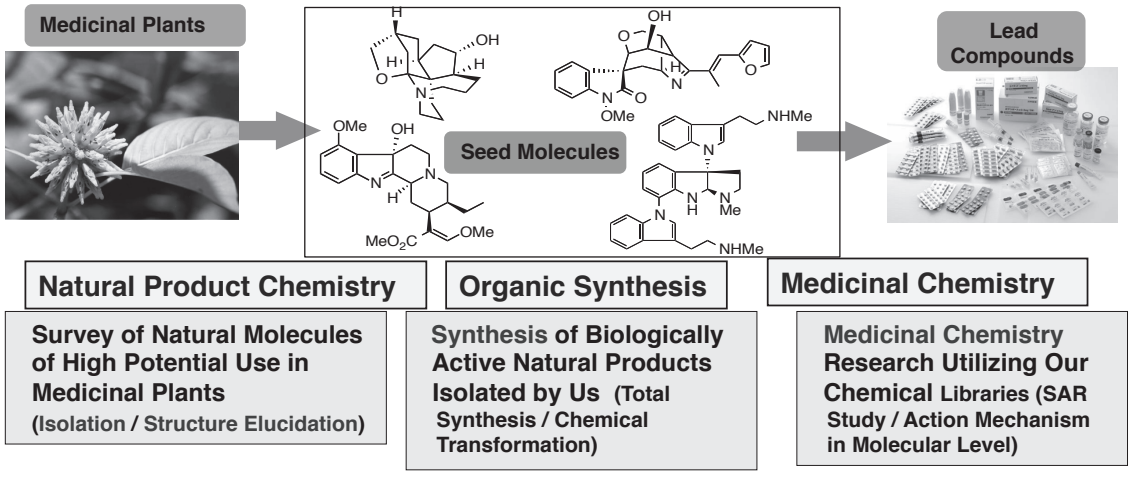
AL01 Survey, Synthesis and Medicinal Chemistry Research on Bioactive Alkaloids

Hiromitsu TAKAYAMA
Graduate School of Pharmaceutical Sciences, Chiba University

We have been carrying out the investigation of biologically active alkaloids from medicinal plants and development of lead-compounds for medicines. Our basic research strategy is starting with survey of natural alkaloids of high potential use in the medicinal plants, synthesis of biologically active alkaloids isolated by our hands, and medicinal chemistry research using our chemical libraries. In this lecture, I will present our recent research results on alkaloids acting on nervous system and exhibiting antitumor activities.

Comprehensive Studies on Drug Development from Alkaloids in Medicinal Plants



We have focused on the opiate-like effects of a rubiaceous plant, *Mitragyna speciosa*, growing in the Malay Peninsula and started elucidation of active principle in this herbal medicine. As a result, we found a minor new indole alkaloid, 7-hydroxymitragynine, exhibiting potent analgesic activity acting on mu-opioid receptors, which are more potent than that of morphine. Subsequently, aiming at the creation of more potent compounds, a number of derivatives were synthesized, and we succeeded in finding a promising drug-lead compound showing strong antinociceptive activity even in oral administration. From an African *Voacanga* plant, which is known as a herbal drug, we also found a number of Iboga-type indole alkaloids acting on cannabinoid receptors (CB1) or capsaicin receptors (TRPV1). In order to develop drug discovery research using these as seed molecules, we developed a route for comprehensive total synthesis of Iboga-type alkaloids. In the study of *Lycopodium* alkaloids showing potent acetylcholinesterase inhibitory activity, we discovered numerous alkaloids with diverse skeletons and achieved asymmetric total syntheses of those alkaloids.

Regarding natural products having antitumor activity, we have investigated alkaloids in plant genera, such as *Kopsia, Gelsemium, Ophiorrhiza, Pandunus*, and others. Among them, in the study of *Gelsemium*, which was know as toxic plant, we discovered a wide variety of novel alkaloids, found potent tumor cytotoxic effects on gelsedine-type alkaloids, and developed synthetic route of these alkaloids.

One of the strategic features in the above-mentioned total synthesis of alkaloids is “Bioinspired Synthesis”, which incorporates hypothetical biosynthetic-pathway into the key step of total synthesis. Using this approach, we have achieved efficient total synthesis of various kinds of alkaloids, including the shortest total synthesis of a representative *Lycopodium* alkaloid, lycodine.