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Synthesis of Poison-Frog Alkaloids and Their Pharmacological Effects at Neuronal Nicotinic Acetylcholine Receptors

Naoki Toyooka
(Faculty of Pharmaceutical Sciences, University of Toyama)

A diverse array of biologically active alkaloids has been discovered in amphibian skin, and now over 800 poison-frog alkaloids, representing 25 structural classes, have been detected in amphibian skin. We achieved the flexible chiral synthesis of 5,8-disubstituted indolizidine and 1,4-disubstituted quinolizidine type poison-frog alkaloids using the highly stereoselective Michael type conjugate addition reaction to the cyclic enaminoesters to afford the trisubstituted piperidine ring system as the key step. Thus, we synthesized about 10 natural products and its congeners according to the above strategy. We also succeeded in the first total synthesis of 5,6-8-trisubstituted indolizidine **223A** and unique tricyclic alkaloid **205B** by sequential use of the above key addition reaction. The proposed structure for natural **223A** was revised to the epimer at the 6-position, and the absolute stereochemistry of natural **205B** was determined by our total syntheses. Investigations of the inhibitory effects of synthetic poison-frog alkaloids on neuronal nicotinic acetylcholine receptors (nAChRs) have also been conducted, and we found that 5,8-disubstituted indolizidine **235B'** is a potent noncompetitive and selective blocker of $\alpha4\beta2$ nAChRs, and its specificity is comparable with that of the best characterized competitive antagonist of the above receptors, dihydro-β-erythroidine (DHβE). These result indicated that the **235B'** is a promising lead compound for the drug design to treat autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).