Synthetic investigation of selective ligands for synaptic receptors based on natural product privileged structures

Masato Oikawa, Koichi Fukushima, Kenji Morokuma, Hiyori Itagaki, Yuichi Ishikawa

Yokohama City University
Seto 22-2, Kanazawa-ku, Yokohama 236-0027, Japan
E-mail address: moikawa@yokohama-cu.ac.jp

Ionotropic glutamate receptors (iGluRs) are key synaptic receptors for central neurotransmission in mammals, and involved not only in fast neurotransmission but also in higher brain function such as learning and memory formation. A total of eighteen iGluRs with different functions and distribution in brain are known, and they are largely divided into three types, N-methyl-D-aspartic acid (NMDA) type, (S)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA) type, and kainic acid (KA) type.

We have been working on the development of subtype-selective ligands for iGluR, based on natural product privileged structures such as dysiherbaine, kainic acid, and lycoperdic acid. Previously, we have successfully developed IKM-159 as an AMPA receptor-selective inhibitor (Juknaite et al, *J. Med. Chem.* **2013**, *56*, 2283). Quite recently, a novel monocyclic analog of dysiherbaine has been designed and synthesized (Fukushima et al, manuscript in preparation).

We have also finished synthesis of all four diastereomers of mushroom toxin lycoperdic acid. Mice in vivo assay has suggested the structure-activity relationships of natural and unnatural diastereomers, to show the major important role of the five-membered oxacycle (Morokuma et al, manuscript in preparation).

Synthesis, biological evaluation, and molecular interactions with iGluR ligand binding domain, of the artificial and novel ligands inspired by privileged natural products, will be discussed.