Enantioselective Synthesis and Neuroactivity-switching of Artificial Glutamate Analogs

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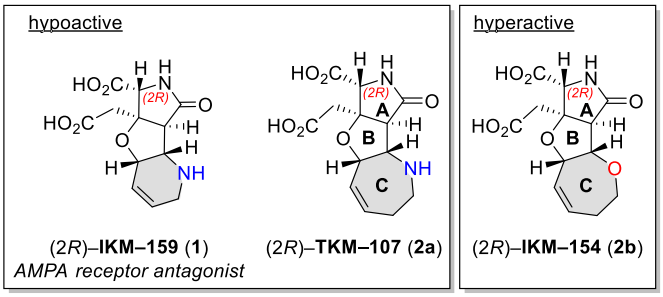
Abstract

Ionotropic glutamate receptors (iGluRs) play an important role in higher brain functions such as learning and memory in the mammalian central nervous system by mediating the majority of fast excitatory neurotransmission. iGluRs are also thought to be involved in nociception and closely related to several neuronal disorders such as epilepsy and Parkinson disease. To clarify the mechanism of action and to control the neurological function of iGluRs, subtype-selective ligands with diverse activities have been required.

IKM-159 (**1**) is an artificial glutamate analog developed in 2010[1] that selectively acts as an antagonist on AMPA-type iGluR. Upon intracerebroventricular injection, **1** inhibits the voluntary action of mice for several hours. Structure-activity relationships study has shown that the (2*R*)-enantiomer, but not the (2*S*)-counterpart, is neuroactive.[2] Interestingly, preliminary in vivo assay had shown that the neuroactivity is modulated by the structure of the lowest C-ring. Herein, we report enantioselective synthesis of the two homologs with different C-ring structures, TKM-107 (**2a**) and IKM-154 (**2b**), by employing chiral resolution strategy. In vivo assay on mice showed that (2*R*)-TKM-107 (**2a**) is hypoactive, whereas (2*R*)-IKM-154 (**2b**) is hyperactive. Thus we successfully developed a pair of iGluR ligand with opposite neurological activities useful for neurochemical research.

Keywords: central nervous system, enantioselective synthesis, ionotropic glutamate receptor, ligand, structure-activity relationships



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