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Artificial Glutamate Analogs as a Ligand for Neuronal Receptors

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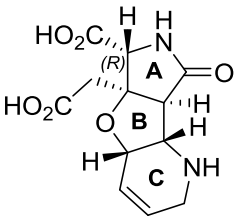
Ionotropic glutamate receptors (iGluRs) play a pivotal role in learning and memory by mediating the majority of fast excitatory neurotransmission in the mammalian central nervous system (CNS). We have previously studied construction of a molecular library of artificial glutamate analogs by diversity-oriented synthesis (DOS) for discovery of selective ligands for iGluRs. Further synthetic study based on the structure of the hit compounds successfully led us to identify IKM–159 as an antagonist selective to (*S*)–2–amino–3–(3–hydroxy–5–methyl–4–isoxazolyl)propionic acid (AMPA) type iGluRs.

IKM–159 selectively inhibits GluA2- and GluA4-containing subtype of AMPA type iGluR. Furthermore, the interactions of IKM–159 with GluA2 ligand-binding domain (LBD) have been clarified by crystallographic study.

To improve the potency and selectivity of IKM–159 toward AMPA type iGluRs, in the present work, we further study the structure–activity relationships of IKM–159 analogs. Here, we report our synthetic studies along this line of research based on the second generation diversity-oriented synthesis of C-ring analogs of the artificial glutamate (IKM–159) starting from 7–oxanorbornene prepared by tandem Ugi / Diels–Alder reaction of 2–furaldehyde. Synthesis and the preliminary data on the biological activity will be discussed.



(*R*)-IKM-159