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PRESENTATION TYPE: Contributed Paper : Poster

CURRENT SUBJECT AREA: Organic (4)

CURRENT SYMPOSIA: Molecular Function of Natural Products: Advances towards Chemical Biology (# 237)

Abstract

TITLE: Natural product-inspired glutamate analogs; The diverted synthesis and the neuronal activity

Abstract Body: iGluRs play an important role in higher brain functions such as learning and memory by mediating the majority of fast excitatory neurotransmission in the mammalian CNS. iGluRs are also thought to be fully or partly involved in nociception and closely related to several brain diseases. Development of selective ligands for iGluRs is thus important for understanding higher brain functions and treatment of neuronal diseases.

The artificial glutamate analog IKM-159, designed from marine-derived natural products, kainic acid and dysiherbaine, was discovered as a selective inhibitor for AMPA-type iGluR in the CNS by our previous study employing DOS. IKM-159 binds to the subunit protein GluA2 of the AMPA receptor with only a weak potency, which, however, depends on the C-ring structure interestingly. For better understanding of the biological functions of AMPA receptor, we planned to study diverted synthesis of the C-ring analogs that would allow us to generate structurally diverse analogs with improved potency of the activity.

For the efficient diverted synthesis, we established the advanced intermediate¹ placed at the late stage in the synthesis as a branching point for each analog. Prepared in 28% yield over 8 steps starting from Ugi/Diels-Alder reaction employing 2-furaldehyde, the intermediate possesses a common heterobicyclic core as the AB-ring, and homoallylic alcohol part as a scaffold for construction of structurally diverse C-ring. We then successfully applied some diverse mode of cyclizations to this homoallylic alcohol. Each protected analog was finally treated with hydrochloric acid for deprotection of carboxyl groups.

More than ten analogs have been accomplished using these procedures, and subjected to *in vivo* assay by intracerebroventricular injection on mice. The design, synthesis, and *in vivo* assay of these novel glutamate analogs will be presented.

Reference

1) Chiba, M. *et al.*, published online (DOI:10.1016/j.bmcl.2015.03.037).

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Invited Paper :

Invited Paper Confirmation:

Student Poster Competition: Yes

Visa: No