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Development of small-molecule antagonists for PAC1 receptor aimed at drug discovery of novel analgesics

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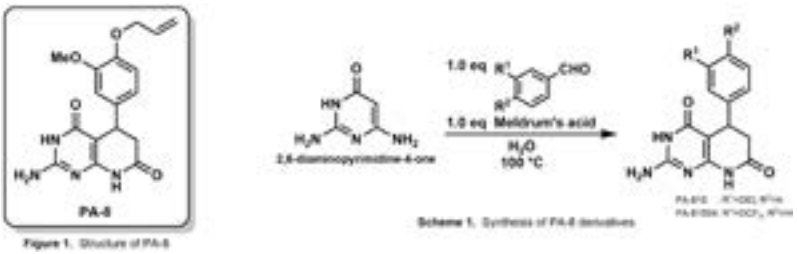
Neuropathic pain such as postherpetic neuralgia is a chronic pain characterized by severe spontaneous pain and allodynia. However, the mechanisms of such a pain are unclear. Previously, our research group has demonstrated that stimulation of PAC1 receptor elicits long-lasting mechanical allodynia in mice, suggesting the important roles of the PAC1 receptor and its ligand PACAP in chronic pain. Currently, there are no small-molecule antagonists for PAC1 receptor aimed at developing an oral drug. Recently, we have discovered a novel small-molecule antagonist of the PAC1 receptor (named PA-8) by *in silico* screening followed by *in vitro/vivo* pharmacological assays. On the basis of the structure of PA-8, we aimed at synthesizing novel compounds having more potent antagonistic activity. We synthesized over twenty derivatives and evaluated their antagonistic activities for the PAC1 receptor. Among them, two more potently derivatives (PA-810 and PA-81004) inhibited PACAP-induced phosphorylation of CREB in the PAC1 receptor-expressing CHO cells than PA-8. Intrathecal injection of both derivatives inhibited PACAP-induced nociceptive behavior and mechanical allodynia in mice. Further, the oral administration of these compounds inhibited nociceptive behavior in neuropathic pain model mice.



Biography

Takuya Okada have completed master of Graduate School of Science and Engineering, University of Toyama in 2016. Then, he entered Graduate School of Innovative Life Science, University of Toyama, and going to get PhD in 2019.