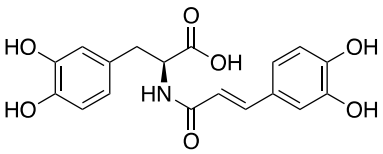
Synthesis and evaluation of catechol derivatives as an amyloid-beta aggregation inhibitor

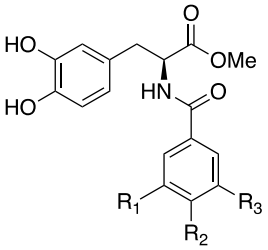
Department of Biochemical Engineering, Graduate School of Science and Engineering, Yamagata University, Yonezawa, Yamagata 992-8510, Japan
○Fusheng Xu, Miyu Okada, Misato Tajiri, Koki Makabe, Hiroyuki Konno
Keywords: *Alzheimer's disease, Amyloid beta, catechol derivatives, Aggregation inhibition*

Amyloid β (Aβ) is peptide consisting of 36-43 amino acid residues generated from amyloid β precursor protein (APP) [1]. Aβ fibrils exhibit self-propagating and its aggregations may lead to variations in clinical and pathological characteristics of Alzheimer's disease (AD). Therefore, inhibition of Aβ aggregation is considered to be an important means to effectively treat and inhibit Alzheimer's disease [2].

Clovamide (**1**) is a natural polyphenol product isolated from red clover. As a catechol derivative, clovamide (**1**) has anti-inflammatory and anti-oxidant effects. Dr. Tsunoda from the University of Tsukuba has demonstrated that the natural product clovamide has some activity to inhibit Aβ aggregation [3]. However, we think that the presence of the L-dopa structure is the key to the activity of clovamide (**1**). After the synthesis of clovamide (**1**), we appropriately changed the structure of clovamide (**1**) to synthesize a series of catechol derivatives. We tested all the synthesized compounds for inhibition of Aβ aggregation and found that five compounds showed potent inhibitory activity. These small molecules not only have excellent water solubility, but also have low or near-absence of cytotoxicity. We also proved our idea by transmission electron microscopy, particle radius, and other experiments, which are described in this paper.



clovamide (**1**)



catechol derivatives

1) M. Walsh, D. J. Selkoe, *J. Neurochem.* 101 (**2007**) 1172-1184.
2) M. Tajiri, R. Yamada, M. Hotsumi, K. Makabe, H. Konno, *Eur J Med Chem.* 215 (**2021**) 113289.
3) T. Tsunoda, M. Takase, H. Shigemori, Bioorg. Med. Chem. 26 (**2018**) 32-2-3209.