プロテアソーム阻害剤ベラクトシン A シス型異性体の構造活性相関研究

Structure-Activity Relationship Study of Unnatural *cis*-Isomer of Belactosin A, a Potent Proteasome Inhibitor

Shuhei Kawamura[1], Yuka Unno[2], Anja List[3], Kaori Itagaki[1], Akira Mizuno[1], Motohiro Tanaka[4], Takuma Sasaki[4], Michael Groll[3], Akira Asai[2], Mitsuhiro Arisawa[1], and Satoshi Shuto[1].

1. Hokkaido University, Sapporo, 060-0812, Japan. 2. University of Shizuoka, Shizuoka, 422-8526, Japan. 3. Center for Integrated Protein Science at the Department Chemie, Lehrstuhl für Biochemie, Technische Universität München, Garching D-85747, Germany. 4. Aichi Gakuin University, Nagoya, 464-8650, Japan

Proteasome is a multicatalytic proteinase complex which works on the turnover of large portion of intracellular proteins. In 2003, for the first time as a proteasome inhibitor, bortezomib was approved by FDA for the treatment of patients with relapsed or refractory multiple myeloma, and many proteasome inhibitors have been studied as potent anti-cancer drug candidates so far.

Belactosin A is a natural product isolated from *Streptomyces Sp.* [1] which has anti-proliferative activity in human cancer cell lines due to the proteasome inhibition [2]. Previously, we synthesized stereo- and regioisomers of Belactosin A and found that *cis*-isomer **1** of belactosin A has somewhat greater proteasome inhibitory activity than belactosin A itself [3] and their synthetic precursors **2**, having hydrophobic substituents, are much more potent [4]. (Fig. 1)

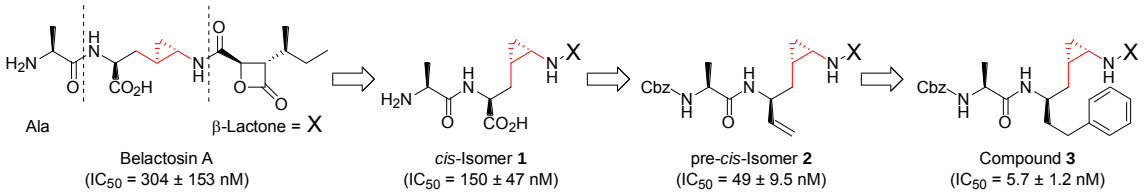

Figure 1. Structure of belactosin A and its derivatives.

We have newly designed and synthesized a series of *cis*-belactosin A derivatives and found a highly potent proteasome inhibitor **3**, which inhibits the chymotrypsin-like activity of proteasome as strong as bortezomib (IC_{50} = 4.5 nM). We will present the details of these results.

＜参考文献＞

[1] Asai, A *et al. J. Antibiot.* **2000**, *53*, 81. [2] Asai, A. *et al. Biochem. Pharmacol.* **2004**, *67*, 227. [3] Shuto, S. *et al. Org. Lett.* **2008**, *10*, 3571. [4] Shuto, S. *et al. Org. Biomol. Chem.* **2009**, *7*, 1868.

発表者紹介

氏名　　川村　周平

所属　　北海道大学生命科学院生命医薬科学コース

学年　　D2

研究室　創薬有機化学研究室