【Grant-in-Aid for Scientific Research (S)】

Broad Section E

Title of Project : Development of new catalysts and precise synthetic reactions directed for peptide drug synthesis

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Keyword : Peptide drug, Design of catalysts, Precise synthesis, Amino acid, Maruoka Catalyst

【Purpose and Background of the Research】

With the current situation where new development of small-molecule drugs and high-molecule drugs is at a standstill, the importance of peptide drug development as a medium-molecule drug can be easily seen from the recent trends of domestic and overseas pharmaceutical companies, and its future potential has many expectations from both industry and academia. On the other hand, peptide synthesis has been undertaken for a long time, and although various synthetic methods including solid-phase peptide synthesis have been developed so far, it is still insufficient for precise synthesis of peptide drugs in recent years. Although it has been clarified that the pharmacological effect of a peptide containing a bulky amino acid is significantly sustained, it is difficult to selectively introduce a bulky amino acid by a conventional approach. In this research, we will focus on the development of new synthetic methodologies based on the precise design of new metal and organocatalyst, thereby enabling the efficient synthesis of peptide drugs that make use of radical chemistry in addition to anionic and cationic chemistry. By using such approaches, we would like to solve some intrinsic problem that cannot be realized by conventional methodologies.

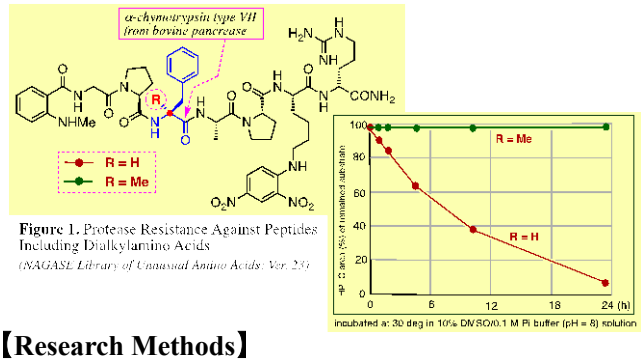

Figure 1. Protease Resistance Against Peptides Including Dialkylamino Acids

(NAGASE Library of Unnatural Amino Acids: Ver. 2.0)

【Research Methods】

In this research, we will create various high-performance catalysts and develop new synthetic reactions by utilizing such high-performance catalysts for peptide drug synthesis. In addition to various natural and unnatural amino acids that are the starting materials for peptide drug synthesis required for this research, various bulky α,α-dialkyl amino acids can be easily prepared from commercially available amino acid derivatives using "Maruoka Catalyst®" and "Simplified Maruoka Catalyst®". Utilizing these various amino acids, we carry out (1) the development of highly difficult amide condensation reaction based on the selective activation of amino esters; (2) the development of selective peptide cleavage reaction based on the activation of amide bond; (3) the development of a novel functionalization reaction based on the selective activation of the inactive C-H group of amino acid derivatives; (4) the development of site- and chemoselective N-C bond formation from a specific amide N-H group. Next, we would like to apply these new synthetic reactions to amino acids and oligopeptides, and clarify the superiority of radical reactions in comparison with anionic and cationic reactions. By aiming at both basic and practical research, we would like to strongly promote the rational design of new catalysts and the development of new synthetic reactions for peptide drug synthesis, thereby producing many fruitful results on this project.

【Expected Research Achievements and Scientific Significance】

It has been considered that it is extremely difficult to selectively introduce bulky amino acids and *N*-alkyl amino acids into peptide chains by conventional peptide synthesis. By applying a new peptide synthesis utilizing the high-performance molecular catalysts designed and created in this research, the hitherto highly difficult peptide synthesis will be realized. The series of basic research results obtained from this research are expected to enable the efficient synthesis of peptides that were previously difficult to synthesize and new peptides with significantly sustainable pharmacological effects. It is expected that great progress will be made by our new strategies, and that it will have a great spillover effect in the field of peptide drug.

【Publications Relevant to the Project】

・ S. Sakurai, A. Matsumoto, T. Kano, K. Maruoka, Cu-Catalyzed Enantioselective Alkylarylation of Vinylarenes Enabled by Chiral Binaphthyl-BOX Hybrid Ligands. *J. Am. Chem. Soc.*, **142**, 19017-19022 (2020).

・ Z. Wang, A. Matsumoto, K. Maruoka, Efficient Cleavage of Tertiary Amide Bonds via Radical-Polar Crossover Using a Copper(II) Bromide/Selectfluor Hybrid System. *Chem. Sci.*, **11**, 12323-12328 (2020).

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