【Grant-in-Aid for Specially Promoted Research】

Revolutional Peptide Synthesis and Logical Molecular Design

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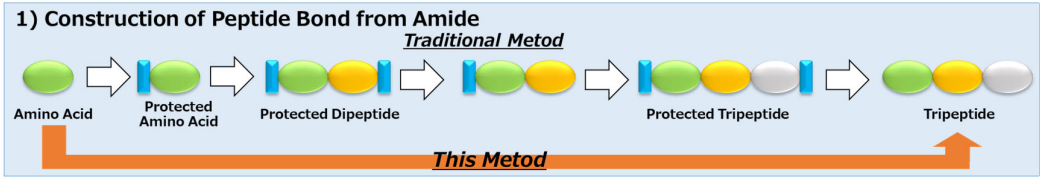
Purpose and Background of the Research

●Outline of the Research

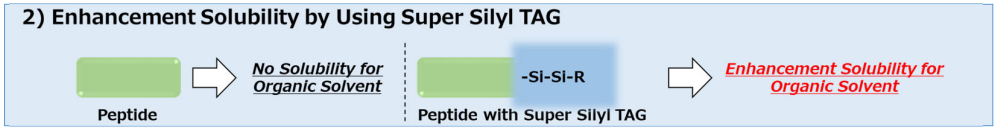
Since the first example of chemical peptide synthesis was reported in the 1960s, half a century has passed without any improvement such as low reactivity, purity of product, and escalating the price of products due to multi-steps of purification. We will be a complete game changer in the area of peptide synthesis. The applied research will completely change the peptide part of conventional organic chemistry textbooks. We believe that this is a once-in-a-decade achievement in the field of drug discovery.

The research is consist from three parts.

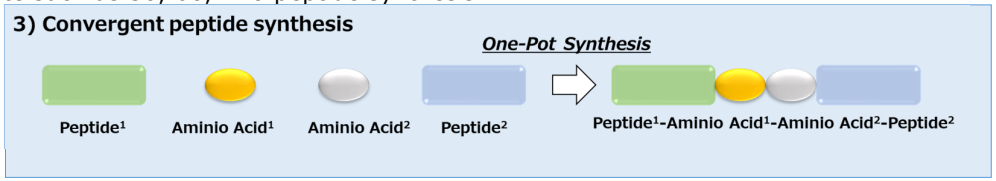
1) In traditional method, we have to repeat multi-steps such as protection, activation, peptide bond formation, and deprotection. However, we have succeeded the construction of peptide bond from amide bond in single step. Based on this achievement, we will synthesize a variety of bioactive peptide.



2) The longer peptide have less solubility for organic solvent. Although this drawback has conventionally been addressed by attaching a long-chain alkyl group as TAG, this is not sufficient for practical use. Therefore, we will try to obtain complete liposolubilization by attaching TAG with super silyl group.



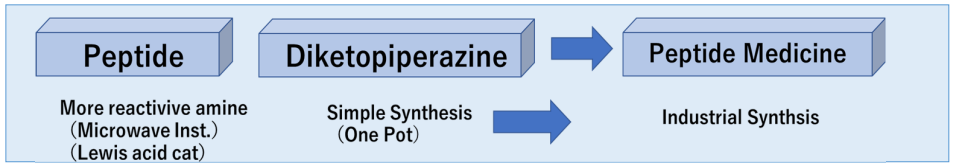
3) This is an effective convergent peptide elongation. After synthesizing 10-15 peptides, elongation of between peptide chains will be performed with exponential rate such as 30, 60, 120 peptide synthesis.



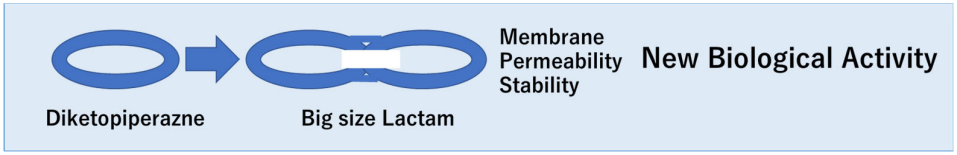
Finally, we have plan not only for synthesizing peptides but exploring what kind of peptide shows bioactivity. To achieve this area, we have begun peptide mixed synthesis, which multiple peptides are formed at once in a single reaction vessel.

Expected Research Achievements

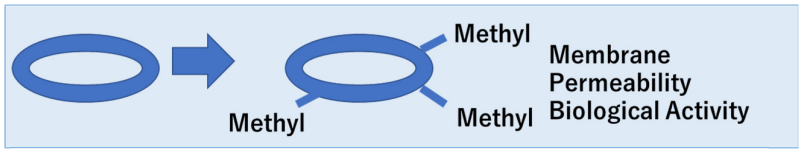
The construction of peptide bond from amide bond is performed by using diketopiperadine (DKP) as substrate. In order to obtain DKPs at a low cost in the future, we se our goal for synthesizing DKPs in a single step first. It will be able to quickly respond to production orders.



Furthermore, we also plan to proceed a ring-expansion reaction to afford macrolactams by reacting with another peptide chain to a DKP. Since macrolactams have excellent membrane permeability and stability in vivo, a simple method for their synthesis has been desired.



N-methylated peptides have great advantage in drug discovery because they are expected to improve membrane permeability by enhance lipophilicity. This methylated peptide synthesis would be achieved simply methylation for NH of DKP. We have already succeeded in synthesizing N-methylated DKP with model-substrate. Then, we will check scope of substrate and apply for N-methyl peptide synthesis.



In the synthesis of natural products, we sill start with the synthesis of insulin. At first, we will need the preparation of A chain and B chain , which are 21 peptides and 30 peptide respectively. We believe that the preparation will realize in short step by using our convergent strategy. Despite of the high price of insulin, there are large number of patients who need them. Therefore, the contribution of a successful of this synthesis would be extremely large.

As mentioned above, the peptide synthesis invented in this study will be a game-changing, which is completely surpasses conventional method as disruptive innovation. Furthermore, the goal of our research is not limited to the simple synthesis of target peptides, but also including the development of industrial mass synthesis technique using the new method as construction of basis for social implementation.

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