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

Upgrading architecturally complex natural products: innovations in total synthesis and high-throughput generation of analogues and functional molecules

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Purpose and Background of the Research

●Outline of the Research

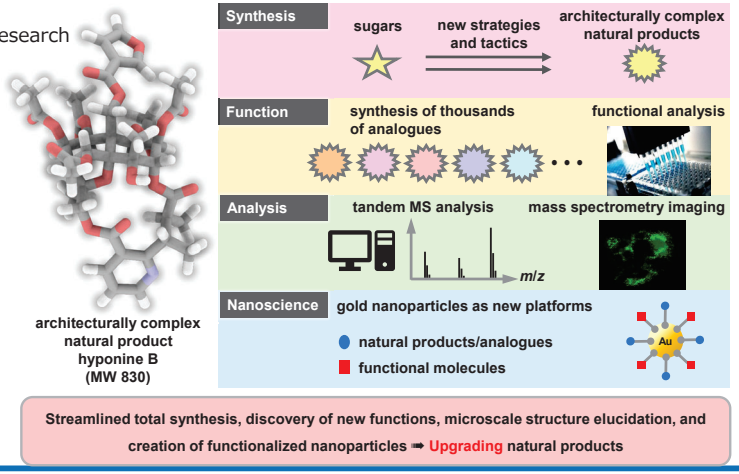
Architecturally complex natural products with multiple functional groups and molecular weights over 500 often exhibit more potent bioactivities than common drugs, thus representing untapped resources for privileged structures for developing new pharmaceuticals. Applications of these molecules are hampered, however, due to the difficulty associated with their isolation from nature, biosynthesis or total synthesis. In this project, we will cultivate new molecular science by integrating natural product synthesis, analytical chemistry, and nanoscience. We will construct thousands of natural product analogues, upgrade activities of the natural products, and endow them with new functions using nanoparticles. The achievements will accelerate and transform the drug discovery process based on natural products.

●Research Background

The development of new pharmaceuticals is urgently needed to treat cancer, neurodegenerative diseases, autoimmune diseases, and lifestyle-related diseases, and to fight the endless battle against viruses such as SARS-CoV-2 and pathogenic bacteria such as multidrug-resistant strains.

There are three molecular categories that are currently available as drug candidates. Proteins such as antibodies are used as large-molecule drugs, and peptides and nucleic acids have received increasing attention as middle-molecule drugs. Compared with these biopolymer-based molecules, the molecular weights of common natural products are smaller, yet they have the longest history of being used as small-molecule drugs. In fact, more than 30% of recently approved drugs are natural products or their analogues, exemplifying the superiority of bioactive natural products to other molecular species as drug seed/lead compounds.

Figure 1. Research Overview



Among the underexplored groups of natural products, we are particularly focused on architecturally complex natural products with molecular weights larger than those of common pharmaceutical molecules (500–2000, Fig. 1). Their chemical structures comprise multiple cyclic structures and possess many polar functional groups. As the number of functional groups increases, the binding of natural products to target proteins becomes stronger and more specific through a greater number of hydrogen bonds. Thus, architecturally complex natural products often exhibit potent biological activities through specific recognition of target receptors and are expected to be seed/lead compounds for drug discovery, but their biological activities have not been investigated for pharmaceutical research because of the scarcity of materials obtained from nature and the difficult fermentation production processes. Under these circumstances, total synthesis is the only practical solution to generate a sufficient amount of samples. An efficient synthetic route to natural products will allow us to prepare a large number of synthetic analogues for the optimization of natural products as new drugs and to create new molecular platforms that combine synthetic natural products with different functional molecules. Developing a practical synthetic supply of architecturally complex natural products is an extremely challenging task, however, which presents a bottleneck for research.

●Research Aim

This project integrates synthetic chemistry, analytical chemistry, and nanoscience. The project is designed on the basis of architecturally complex natural products that are not currently considered drug candidates due to their structural complexity. First, we will realize the total syntheses by developing new strategies and tactics, and prepare thousands of analogues by applying the realized synthetic routes. Next, we will develop an efficient high-throughput method for determining the structure of thousands of analogues. Furthermore, we will efficiently create molecules with novel functions using gold nanoparticles as a molecular platform.

Expected Research Achievements

We will upgrade these evolutionarily selected natural products into compounds with even more potent activities and nanoparticles with novel functions (Fig. 1). To achieve these objectives, we will formulate four subprojects, namely, synthesis, function, analysis, and nanoscience.

(1) Synthesis: We selected the architecturally complex terpenoids, which have never been chemically constructed before, as targets for total synthesis. We will develop new strategies and tactics using radical reactions. The achievements here will greatly simplify the synthesis of a variety of architecturally complex natural products.

(2) Function: We will realize chemical generation and biological evaluation of thousands of analogues in a high-throughput fashion. The thousands of analogues will be subjected to a high-throughput evaluation of their bioactivities.

(3) Analysis: We will utilize tandem mass spectrometry to elucidate the structures of the analogues, and directly analyze the molecular behavior of architecturally complex natural products in cells and tissues by mass spectrometry imaging.

(4) Nanoscience: We will realize novel functions that are not possible with the use of organic molecules or proteins alone by exploiting gold nanoparticles. The creation of such novel functionalized molecules will enable temporal, spatial, and environmental control of biological activity, which has not been feasible before.

This research will innovate the many factors of the drug discovery process, thereby accelerating pharmaceutical research and generating a new foundation for molecular science and technology. Therefore, this research will positively influence a wide range of scientific, technological, and public health fields, and will effectively provide treatment solutions for serious diseases.

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