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

Integrated Disciplines (Complex Systems)

Title of Project : Expanding the medicinally relevant chemical space with architecturally complex natural products and their synthetic analogues

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Research Project Number : 17H06110 Researcher Number : 70322998
Research Area : Natural Product Synthesis, Bioorganic Chemistry
Keyword : Synthetic Chemistry, Total Synthesis, Natural Products, Drug Design, Biological Activity

【Purpose and Background of the Research】

Natural products provide a crucial foundation for novel drug discovery. Architecturally complex natural products with multiple functional groups and molecular weight over 500 often exhibit potent bioactivities, and represent privileged structures for the development of pharmaceuticals (Fig. 1). The biological profiles of most of these natural products are not well understood, because both practical isolation and synthetic preparation have been highly challenging. In this research, we will develop new synthetic routes to the complex natural products and their analogues, and expand the medicinally relevant chemical space.

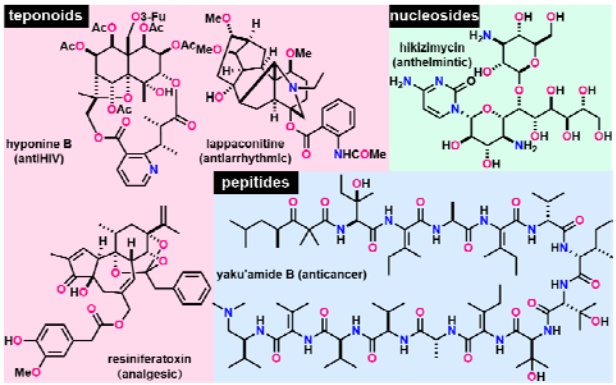

Figure 1 Architecturally complex natural products

【Research Methods】

First, the architecturally complex terpenes and nucleosides will be chemically constructed based on the radical-based convergent strategies (Fig. 2), and the peptides will be synthesized via a full solid-phase strategy. By employing the developed synthetic routes, a medicinally relevant chemical space will be expanded by preparation of 10 to 10,000 analogues of these natural products. Structure-activity relationship studies of these natural and artificial analogues will enable us to determine biologically significant structural features within their structures, and to elucidate their mode of actions. Thus obtained information will provide a chemical basis for the design of novel molecules with more potent and selective biological activities.

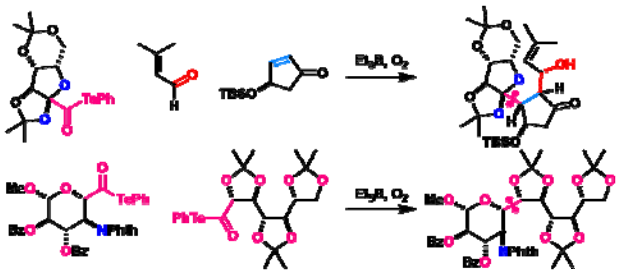

Figure 2 New radical-based convergent strategies

【Expected Research Achievements and Scientific Significance】

At the core of this research program is the development of new ideal strategies for assembling architecturally complex natural products. Efficient syntheses of these natural products will enable divergent syntheses of new analogues. These studies will expand a biologically relevant chemical space, and lead to the discovery of novel therapeutic agents based on the natural product templates. In this regard, this research will lead to a myriad of applications in future pharmaceutical and biological sciences.

【Publications Relevant to the Project】

· M. Koshimizu, M. Nagatomo, M. Inoue, "Unified Total Synthesis of 3-*epi*-Ryanodol, Cinnzeylanol, Cinncassiols A and B, and Structural Revision of Natural Ryanodol and Cinnacasol,"
Angew. Chem., Int. Ed. **2016**, *55*, 2493-2497.
· K. Masuda, M. Nagatomo, M. Inoue, "Direct Assembly of Multiply Oxygenated Carbon Chains by Decarbonylative Radical–Radical Coupling Reactions,"
Nature Chem. **2017**, *9*, 207-212.

【Term of Project】 FY2017-2021

【Budget Allocation】 157,800 Thousand Yen

【Homepage Address and Other Contact Information】

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