

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

Biological Sciences (Medicine, dentistry, and pharmacy)



Title of Project : **Synthetic Studies on Biologically Functional Molecules Aiming to Supply Rare Compounds and to Modify Useful Compounds**

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Research Area : Synthetic Organic Chemistry, Natural Product Chemistry

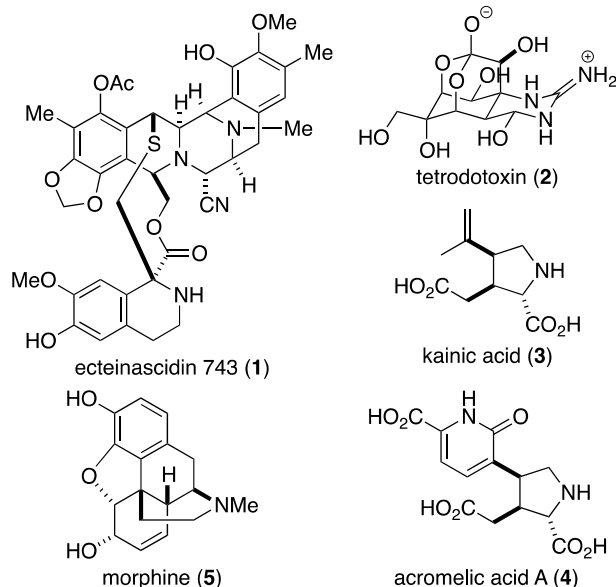
Keyword : total synthesis, biologically functional molecules, natural products

【Purpose and Background of the Research】

Molecules isolated from natural sources exhibit a variety of bioactivities. Such compounds with low molecular weights are called natural products, and have been used as medicines as well as important seeds for developing novel medicines. Synthetic studies of natural products and accomplishment of their robust synthesis would lead to providing molecules useful for human beings in necessary amounts. In this project we will carry out synthetic studies on biologically functional molecules aiming to supply rare compounds and to modify useful compounds.

【Research Methods】

This project deals with synthesis of natural products such as ecteinascidin 743 (1), tetrodotoxin (2), kainic acid (3), acromelic acid A (4), morphine (5), and so on.



Ecteinascidin 743 (Et-743), isolated from the Caribbean tunicate *Ecteinascidia turbinata*, has been shown to display a highly potent cytotoxicity against a variety of tumor cell lines at very low concentrations. Because of the unique mechanism of action against the tumor cell lines, Et-743 was considered as a potential anticancer drug.

Extensive clinical trials resulted in the approval of

Et-743 in 2007 for the treatment of advanced soft tissue sarcoma and in 2009 for relapsed platinum-sensitive ovarian cancer in combination with liposomal doxorubicin. Et-743 is currently in clinical trials for the treatment of breast, lung, pancreas, and prostate cancers.

The structural complexity and the limited availability of Et-743 from nature have made it a very attractive synthetic target. Indeed, a variety of total synthesis and synthetic studies of Et-743, which include ours, have been reported. Despite considerable effort, the clinical supply of Et-743 is relying solely on a long-step semisynthesis from cyanosafracin B produced by bacterial fermentation. A practical and scalable synthesis of Et-743 is therefore eagerly sought after. In this project, a novel and efficient synthetic route toward ET-743 will be developed, based on the knowledge of the previous synthetic studies.

【Expected Research Achievements and Scientific Significance】

This project will contribute to the development of medicinal chemistry by establishment of the synthetic route toward the rare compounds. During the investigations, a variety of knowledge on synthetic organic chemistry will be obtained, which would directly or indirectly influence development of novel drugs.

【Publications Relevant to the Project】

- Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.*, 124, 6552 (2002)
- Imai, T.; Nakata, H.; Yokoshima, S.; Fukuyama, T. *Synthesis*, 44, 2743 (2012)

【Term of Project】

FY2013-2017

【Budget Allocation】

165, 600 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.ps.nagoya-u.ac.jp/lab_pages/natural_products/index.html