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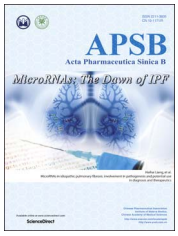

REVIEW

The modification of natural products for medical use

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KEY WORDS

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Synthesis;
Multi-dimensional optimization;
Structure–acitivity reactivity;
Artemisinin;
Indirubin

Abstract Drug innovation is characterized by painstaking molecular-level syntheses and modifications as the basic components of research and development. Similarly, natural products are chemically tailored and modified based upon their structural and biological properties. To some extent, the modification of natural products is quite different from *de novo* structure-based drug discovery. This review describes the general strategies and principles for the modification of natural products to drugs, as illustrated by several successful medicines that originated from natural products.

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1. Introduction

The species diversity of plants, animals, microorganisms, and marine organisms results in a multitude of secondary metabolites with diverse chemical structures, which have played, and will continue to play, a vital role in the drug discovery and development process. Indeed, the diversity of plant-based systems has provided an enormous number of lead compounds in healthcare. Similarly, the application of microorganismal metabolites as chemotherapeutics has created the field of antibiotics for anti-infectious and anti-cancer therapies. Many scaffolds of compounds obtained from marine microorganisms and phytoplankton, algae sponges for example, similarly have provided more recent leads for drug discovery and development. And finally, endogenous neurotransmitters and active peptides from human beings and animals constitute an important source for drug research.

From the standpoint of drug innovation, it is necessary to modify natural product structures, because the aim in generation of secondary metabolites by organisms is to protect themselves from natural enemies as well as the environment. Natural product–based drug discovery is characterized with a starting-point of an active compound that necessitates "tailor-made" or individualized manipulation of the structure so as to reach a drug criterion. In this context, the molecular modification of natural products is quite different from the strategy of structure-based drug discovery. This article describes some aspects and principles of modifying natural compounds to lead to successful medicines.

2. The general features of natural products

Natural products, from simple salicylic acid to complex vancomycin, encompass compounds with various molecular sizes, chemotypes, and structural features that can be summarized as follows.

2.1. *Structural diversity and complexity*

Natural products are characterized by their structural diversity, much of which is even unexpected by chemists. For example in Fig. 1A, anti-malarial artemisinin (**1**) is composed of a fused trioxene system with peroxy, lactone, cyclic acetal and ketal moieties. The individual scaffold of artemisinin maintains both the oxidative potential as well as chemical stability. The well-known anti-cancer drug paclitaxel (**2**) possesses a 6,8,6,4-tetracycle-fused skeleton linking functional groups at special positions that ensures binding to tubulin. The non-peptide cholecystokinin (CCK) antagonist asperlicin (**3**), originated from extracts of *Aspergillus alliaceus*, is a chemically-complex molecule with a quinazolinone-fused benzodiazepine core.

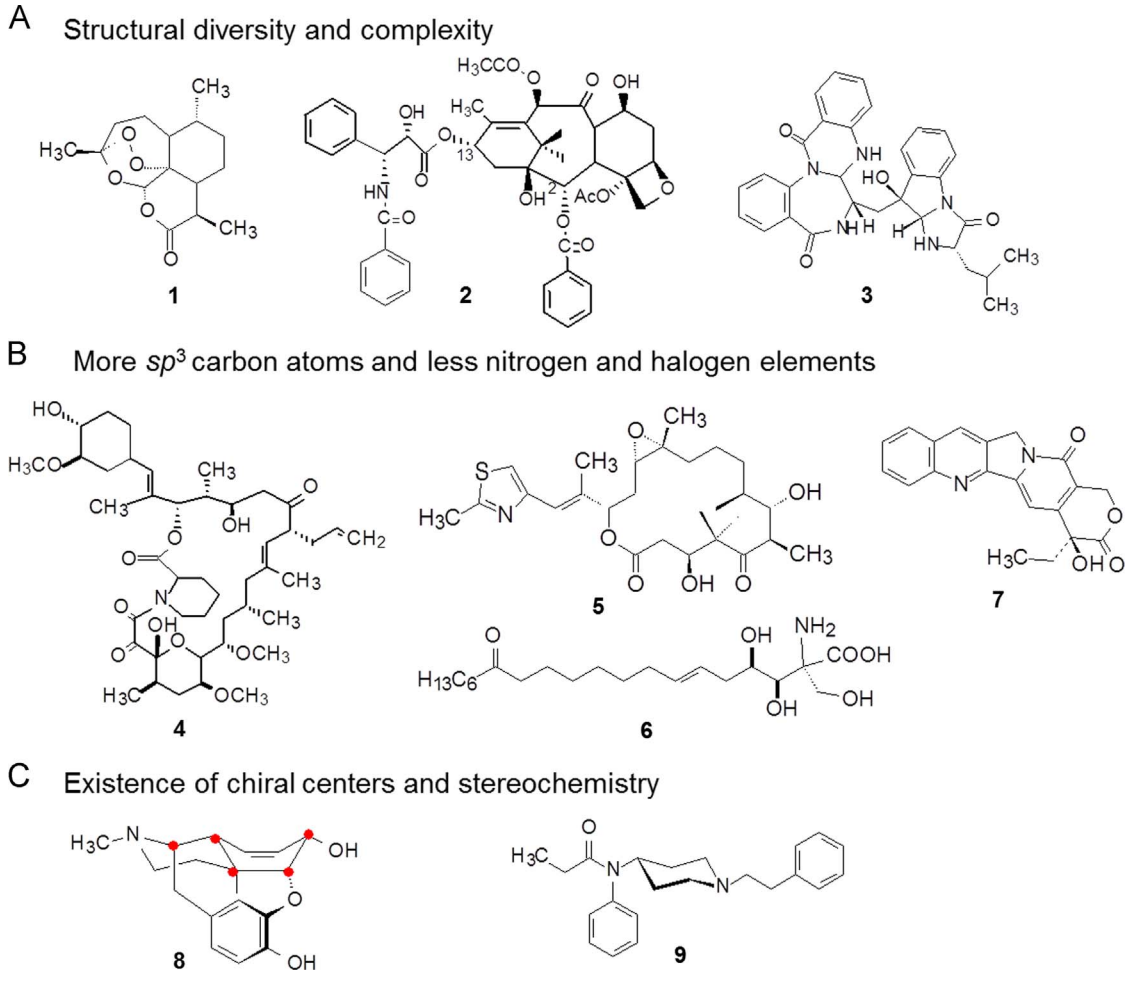

Figure 1 The general features of natural products.

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