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Review

# Insights into drug discovery from natural products through structural modification

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ABSTRACT

Natural products (NPs) have played a key role in drug discovery and are still a prolific source of novel lead compounds or pharmacophores for medicinal chemistry. Pharmacological activity and druggability are two indispensable components advancing NPs from leads to drugs. Although naturally active substances are usually good lead compounds, most of them can hardly satisfy the demands for druggability. Hence, these structural phenotypes have to be modified and optimized to overcome existing deficiencies and shortcomings. This review illustrates druggability optimization of NPs through structural modification with some successful examples.



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## 1. Introduction

Over the past century, a number of natural compounds extracted from animals, plants, microbes and marine organisms have been used to treat human diseases [1,2]. The endeavor involved well-known drugs such as penicillin (antibacterial), morphine (analgesic), artemisinin (antimalarial) and paclitaxel (anticancer). Review of natural products (NPs) over the 30 years from 1981 to 2010 revealed that approximately 40% of the developed therapeutic agents approved by FDA were NPs, their derivatives, or synthetic mimetics related to NPs [3]. Despite increasing competition from combinatorial and classical compound libraries, there has been a steady introduction of NP-derived drugs in the last years. A total of 19 NPs-based drugs were approved for marketing worldwide between 2005 and 2010, covering infectious (bacterial, fungal, parasitic and viral), immunological, cardiovascular, neurological, inflammatory and related diseases, and oncology [4].

### 1.1. Potential of natural products

Structural diversity is a striking feature of NPs accounting for their lasting importance in drug discovery [5,6]. With increasing druggable targets in the postgenomic era, chemical diversity of screening libraries plays a major role in the fierce competition among pharmaceutical companies. In this respect, NPs are a rather indispensable complement to synthetic compound collections [7,8]. NPs are also featured by steric complexity and differ from synthetic compounds with respect to the statistical distribution of functionalities [8]. They interrogate a different and wider chemical space, and possess a broader dispersion of structural and physicochemical properties than synthetic compounds [9–11]. Some academic groups and companies have made their attempts to synthesize increasingly complex structures to match the chemical space occupied by NPs, however, about 83% of core ring scaffolds present in NPs are still absent from commercially available molecules and screening libraries [12]. In addition, most NPs show more favorable ADME/T properties compared to synthetic molecules, although they often deviate from "drug-likeness" criteria, such as Lipinskis Rule of Five [13,14]. Moreover, NPs recognized as 'privileged structures' also provide attractive scaffolds for combinatorial synthesis and library design [15–17], and serve as chemical probes for the validation of new drug targets [18].

### 1.2. Challenges with natural product research

Despite the proven track record of natural products in drug discovery and their uncontested unique structural diversity, there are still several problems associated with NPs. Typical limitations of NP leads are low solubility or chemical instability, which especially hamper the development of parenteral drugs [19]. Furthermore, many natural products are complex structures with high molecular weight. "Heavy" structures break Lipinski's rules and will most likely exhibit no absorption from the gut into the blood, therefore impeding oral formulation [20]. Additionally, the intellectual property situation is often less clear in unmodified NPs. Although naturally active substances are usually good lead compounds, most of them can hardly satisfy the demands for druggability. NP leads are frequently optimized through structural modification to achieve the final candidate. Of the 58 NP drugs launched in the period of 1981–2011, 31 are structural analogues of the native NP leads [21].

## 2. General principles for structural modification of natural products

The ultimate goal of structural modification of NPs is to obtain new drugs. Pharmacological activity and druggability are two essential factors for drug innovation. Pharmacological activity is definitely indispensable, and druggability is destined by physico-chemical, biochemical, pharmacokinetic and safety properties of drugs. Structural modification of NPs should, therefore, be involved in all the contents of the above two aspects. It is necessary to perform selective modification of NPs according to the deficiency or shortcomings of the structure, the activity, and physico-chemical and pharmacokinetic properties. Generally, the following principles should be followed: increasing potency and selectivity, improving physico-chemical properties such as solubility, distribution, ionizability, etc., enhancing the chemical and metabolic stability, improving biochemical properties, improving pharmacokinetic properties including absorption, distribution, metabolism and excretion, eliminating or reducing side-effects, and attaining intellectual properties. Some successful examples of NPs through structural modification are illustrated as follows.

### 2.1. Examples for structural modification of natural products

#### 2.1.1. Improvement of physico-chemical properties

*2.1.1.1. Increase of low solubility.* Low water solubility limits absorption and causes poor oral bioavailability. Although many cutting-edge technologies have been developed to formulate insoluble compounds over the years, medicinal chemists would like to solve drug delivery problems with "covalent bonds" [22], to improve solubility through structural modifications including adding ionizable or polar groups. Typically, a basic amine or a carboxylic acid is introduced to the structure.

Artemisinin (**1**), a sesquiterpene lactone peroxide originally isolated from Chinese traditional medicine qinghao (*Artemisia annua* L.) [23], has shown potent activity in a variety of diseases, most notably malaria and, more recently, several types of cancers [24] and cytomegalovirus [25]. However, its poor solubility in water or oil caused difficulty in its rescue of severe malaria patients. To address this, oil-soluble artemether (**2**) and water-soluble sodium artesunate (**3**) were approved in China in 1987. The sodium salt of a carboxylic acid analogue achieved higher solubility, yet in this case the compound was unstable, resulting from the facile hydrolysis of the ester linkage. Although the carboxylic group in compound **4** was linked to the artemisinin nucleus via a more stable ethereal linkage, their antimalarial activity was much less active than that of sodium artesunate [26]. Ultimately, the amine analogues (maleates or oxlates of **5**) attained better solubility and stability and were active after oral dosing [27]. Despite immense efforts, no new artemisinin derivative has been developed. Artemisone (**6**) was a 10-alkylaminoartemisinin analogue whose preparation entailed chemistry distinct to that leading to other derivatives and which extended the efficacy limit beyond