Chapter 2
Drug Discovery From Natural Sources

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Abstract Organic compounds from terrestrial and marine organisms have extensive past and present use in the treatment of many diseases and serve as compounds of interest both in their natural form and as templates for synthetic modification. Over 20 new drugs launched on the market between 2000 and 2005, originating from terrestrial plants, terrestrial microorganisms, marine organisms, and terrestrial vertebrates and invertebrates, are described. These approved substances, representative of very wide chemical diversity, together with several other natural products or their analogs undergoing clinical trials, continue to demonstrate the importance of compounds from natural sources in modern drug discovery efforts.

Keywords natural products, drug discovery, terrestrial plants, terrestrial microorganisms, marine organisms, terrestrial vertebrates, terrestrial invertebrates, chemical diversity

Introduction

For thousands of years, natural products have played an important role throughout the world in treating and preventing human diseases. Natural product medicines have come from various source materials including terrestrial plants, terrestrial microorganisms, marine organisms, and terrestrial vertebrates and invertebrates.1 The importance of natural products in modern medicine has been discussed in recent reviews and reports.1-6 The value of natural products in this regard can be
assessed using 3 criteria: (1) the rate of introduction of new chemical entities of wide structural diversity, including serving as templates for semisynthetic and total synthetic modification, (2) the number of diseases treated or prevented by these substances, and (3) their frequency of use in the treatment of disease. An analysis of the origin of the drugs developed between 1981 and 2002 showed that natural products or natural product-derived drugs comprised 28% of all new chemical entities (NCEs) launched onto the market. In addition, 24% of these NCEs were synthetic or natural mimic compounds, based on the study of pharmacophores related to natural products. This combined percentage (52% of all NCEs) suggests that natural products are important sources for new drugs and are also good lead compounds suitable for further modification during drug development. The large proportion of natural products in drug discovery has stemmed from the diverse structures and the intricate carbon skeletons of natural products. Since secondary metabolites from natural sources have been elaborated within living systems, they are often perceived as showing more “drug-likeness and biological friendliness than totally synthetic molecules,” making them good candidates for further drug development. Scrutiny of medical indications by source of compounds has demonstrated that natural products and related drugs are used to treat 87% of all categorized human diseases (48/55), including as antibacterial, anticancer, anticoagulant, antiparasitic, and immunosuppressant agents, among others. There was no introduction of any natural products or related drugs for 7 drug categories (anesthetic, antianginal, antihistamine, anxiolytic, chelator and antidote, diuretic, and hypnotic) during 1981 to 2002. In the case of antibacterial agents, natural products have made significant contributions as either direct treatments or templates for synthetic modification. Of the 90 drugs of that type that became commercially available in the United States or were approved worldwide from 1982 to 2002, ~79% can be traced to a natural product origin. Frequency of use of natural products in the treatment and/or prevention of disease can be measured by the number and/or economic value of prescriptions, from which the extent of preference and/or effectiveness of drugs can be estimated indirectly. According to a study by Grifo and colleagues, 84 of a representative 150 prescription drugs in the United States fell into the category of natural products and related drugs. They were prescribed predominantly as anti-allergy/pulmonary/respiratory agents, analgesics, cardiovascular drugs, and for infectious diseases. Another study found that natural products or related substances accounted for 40%, 24%, and 26%, respectively, of the top 35 worldwide ethical drug sales from 2000, 2001, and 2002. Of these natural product-based drugs, paclitaxel (ranked at 25 in 2000), a plant-derived anticancer drug, had sales of $1.6 billion in 2000. The sales of 2 categories of plant-derived cancer chemotherapeutic agents were responsible for approximately one third of the total anticancer drug sales worldwide, or just under $3 billion dollars in 2002; namely, the taxanes, paclitaxel and docetaxel, and the camptothecin derivatives, irinotecan and topotecan. This short review covers new drugs derived from natural sources launched in the 6-year period from 2000 to 2005, and drug candidates from natural sources in clinical