CHAPTER 2

Natural Products in Drug Discovery:
Present Status and Perspectives

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Abstract

Natural products and their derivatives have been and continue to be rich sources for drug discovery. However, natural products are not drugs. They are produce in nature and through biological assays they are identified as leads, which become candidates for drug development. More than 60% of the drugs that are in the market derive from natural sources. During the last two decades, research aimed at exploiting natural products as a resource has seriously declined. This is in part due to the development of new technologies such as combinatorial chemistry, metagenomics and high-throughput screening. However, the new drug discovery approaches did not fulfilled the initial expectations. This has lead to a renewed interest in natural products, determined by the urgent need for new drugs, in particular to fight against infections caused by multi-resistant pathogens.

Introduction

Historically, chemical substances, derived from animals, plants and microbes have been used to treat diseases. Plants and microorganisms produce unique bioactive substances, providing access to very different types of lead compounds, the natural products.

Natural products have played and continue to play an invaluable role in the drug discovery process, particularly in the areas of cancer and infectious diseases. In fact, more than 60% of the approved drugs are of natural origin. In the modern drug discovery era there are three major sources of new compounds: original natural products, structures derived semi-synthetically from natural products and combinatorial synthetic compounds based on natural products models.[1-3] Bioactive natural products are mostly low-molecular weight organic compounds known as secondary metabolites.[4] The producer organisms can growth without synthesizing these metabolites and produce them in response to environmental cues. These compounds could be produced in nature as "weapons" that organisms use to fight each other.[5,6]

In this chapter will be described the role of natural products in the evolution of drug discovery, giving emphasis to the natural products which provide candidates to be used in infectious disease therapy: the antibiotics. Antibiotics are biologically active molecules with different structures and mode of action made by microorganisms, which are active against other microorganisms at low concentrations. Many antibiotics are made chemically by modification of natural products through a process called semi-synthesis and the effective compound is a semi-synthetic derivative. In Table 1 are summarized different antibiotics from natural origin actually used in the clinic. The majority of antibiotics inhibit targets involved in essential microbial functions: protein synthesis (30S and 50S subunits of the ribosome and RNA polymerase), DNA replication (DNA gyrase) and cell

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Table 1. Microbial secondary metabolites or derivatives used as antibiotics

Antibiotic	Class	Target	Derived From	Produced By
Amikacin	Semisynthetic aminoglycoside	Protein synthesis: binding to the 30S ribosomal subunit	Kanamycin	-
Amoxycillin	Semisynthetic hydroxyampicillin	Cell-wall synthesis: penicillin-binding protein (PBP)	Ampicillin	-
Amphotericin B	Natural polyene macrolide	Fungal membrane	-	*Streptomyces nodosus*
Ampicillin	Semisynthetic aminobenzylpenicillin	Cell-wall synthesis: PBPs	Peniciflin	-
Azithromycin	Semisynthetic 15 membered azalide	Protein synthesis: binding to the 50S ribosomal subunit	Erythromycin	-
Aztreonam	Semisynthetic monocyclic ß-lactam	Cell-wall synthesis: PBP3	SQ-26180	*Chomobacterium violaceum*
Bacitracin	Natural thiazolpeptide	Peptidoglycan synthesis: lipid pyrophosphorylase inhibitor	-	*Bacillus licheniformis*
Caspofungin	Semisynthetic lipopeptide	Fungal wall: glucan synthesis	Pneumocandin B	*Clarea lozoyensis*
Cephalosporin	Natural cephem	Cell-wall synthesis: PBPs	-	*Cephalosporium acremonium*
Chloramphenicol	Natural phenicol	Protein synthesis: binding to the 50S ribosomal subunit	-	*Streptomyces venezuelae*
Clavulanic acid	Natural oxa-1-penem	ß lactamase inhibitor	-	*Streptomyces clavuligerus*
Clindamycin	Semisynthetic thiooctopyranoside	Protein synthesis: binding to the 50S ribosomal subunit	Lincosamine	*Streptomyces lincolnensis*

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