Chapter Four

MACROLIDE AND POLYETHER POLYKETIDES
Biosynthesis and Molecular Diversity

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INTRODUCTION

Secondary Metabolites in Medicinal and Agricultural Chemistry

The healing and killing power of secondary metabolites has been explored by humans since prehistoric times. The very term "Pharmacology" was coined from the Greek word "Pharmakon" having the double meaning of both "Potion" and "Poison". Folklore references to such effects deal almost exclusively with plant extracts. Classic examples include the alkaloid metabolites atropine (**1**) and scopolamine (**2**) from *Atropa belladonna* (deadly nightshade), which are known to induce strong hallucinations, delirium, paralysis, and eventual death. Today, atropine is routinely used in ophthalmology for the dilation of the pupils during eye examinations, whereas scopolamine is used in the treatment of dizziness, gastrointestinal spasm, and motion sickness. Another striking example is that of tubocurarine (**3**), a metabolite of the Brazilian vine *Chondodendron tomentosum* and the key ingredient in *curare,* the extract used by South American Indians to poison their arrows. In modern medicine, tubocurarine is a useful clinical drug employed

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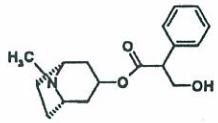
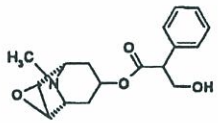
as a muscle relaxant during surgery.

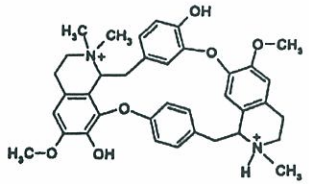
The existence of microorganisms was recognized only in the 17th century when the Dutch microscopist Anton van Leeuwenhoek turned a prototype microscope to the examination of water and decaying matter. However, the tremendous value of microbial metabolites was not realized until much after the



Atropine (1)

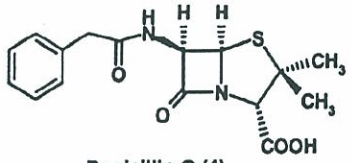


Scopolamine (2)



Tubocurarine (3)

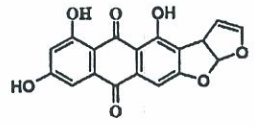
antagonistic effects of *Penicillium notatum* against *Staphylococcus aureus* had been recognized by Fleming and the isolation of penicillin G (**4**) had been achieved. This discovery launched a new era in medicine and the chemistry of natural products. In modern times, metabolites isolated from cultures of bacteria, fungi, or marine microorganisms play a pivotal role in the discovery of therapeutic agents. Recent reports indicate that secondary metabolites constitute approximately 60% of all the antitumor and antibiotic drugs on the market, as well as a significant portion of the new compounds undergoing clinical testing or development.[1]



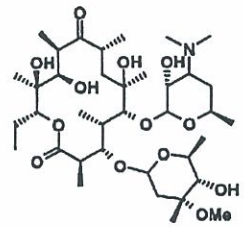
Penicillin G (4)

Polyketides constitute a special class of secondary metabolites, produced primarily by microorganisms and used in agriculture, food sciences, and especially as medicine for both humans and animals. Although these metabolites exhibit remarkable structural diversity, their biogenesis *in vivo* involves, primarily, the

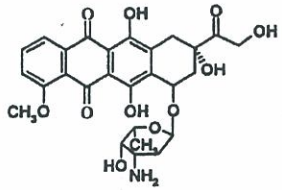
successive condensation of simple building blocks such as acetate, propionate, and butyrate. Examples of biologically important microbial poiyketides include the fungal aflatoxins, *e.g.* versicolorin A (**5**),[2] as well as numerous metabolites of filamentous bacteria, which include the antibiotics erythromycin A (**6**) and doxorubicin (**7**),[3,4] and the immunosuppressants FK506 (**8**),[5,6] and rapamycin (**9**).[7]



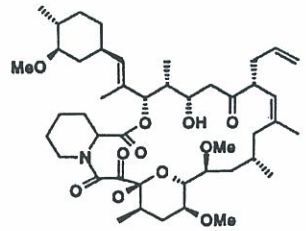
Versicolorin A (5)



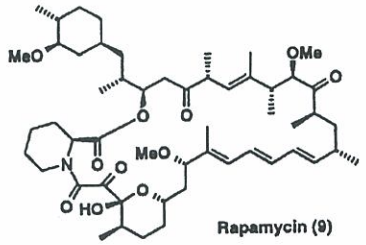
Erythromycin A (6)



Doxorubicin (7)



FK506 (8)



Rapamycin (9)

As with the plant alkaloids **1-3**, toxicity is also common among most clinically useful polyketides, thus compromising their therapeutic value. For example, the third most widely used class of antibiotics worldwide, the