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(Conception by Stephen Hanessian)

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Preface

The Ebers Papyrus, originating from about 1500 BC, is one of the oldest documents that describe the use of natural products for healing diseases. Several herbs are described in its about 700 remedies and magical formulas, for example, the squill (*Urginea maritima*) against dropsy (edema caused by cardiac insufficiency). Indeed, this plant contains cardiac glycosides that are beneficial in such a condition. Another important document, from the first century AD, is the book De Materia Medica of the Greek physician Dioscurides. It lists about 600 medicinal plants, 35 animal products, and 90 minerals. Obviously, these collections of remedies resulted from the accumulated experience of earlier millennia. Not all contained information is reliable; in later centuries, the wheat had to be separated from the chaff, a task that still today is not completely accomplished if we consider so many marketed herbal preparations without proven therapeutic value. On the other hand, opium, the fever-lowering bark of the Cinchona tree, the foxglove (*Digitalis purpurea*), and many other herbal drugs remained in therapy, later being replaced by the isolated active principles morphine, quinine, digitoxin, and others.

The main sources of drugs from nature or lead structures for such drugs are plants, microorganisms, animals, and humans. Plants provide drugs and lead structures for the treatment of a large variety of different diseases. Microorganisms yield mainly antibiotics but also other therapeutic principles, for example, the important statins. Animal toxins almost exclusively serve as pharmacological tools, but human neurotransmitters and hormones were, and still are, valuable leads for more potent and selective analogs, sometimes even with inverse pharmacological activities. The main advantage of many natural products is their three-dimensional structure, avoiding the “flatness” of so many synthetic compounds, and their high degree of chemical diversity, going far beyond the creativity of organic chemists. However, this is also their main disadvantage, besides the problems of accessibility (consider the early problems in taxol supply); due to the complexity of their structures, chemical variation is often so difficult and costly that pharma companies hesitate to invest in their optimization. On the other hand, natural products, whether resulting from plants or from microorganisms, are excellent lead structures, from the viewpoint of ligand–target interactions. In their biosynthesis, all plant secondary metabolites have already “seen” the binding site of a protein; thus, their structural features and properties mediate the interaction with proteins. In addition, many of these compounds serve a certain purpose; they protect a plant that cannot run away in sight of a predator, because they are bitter, sharp, or slightly toxic (only bad experience trains the predator to avoid a certain plant – a dead animal cannot learn anymore!). Correspondingly, in evolution, the plants producing such compounds had a better chance to survive and to reproduce. Microorganisms need antibiotics to compete with other microorganisms. Last but not least, animal and human active principles are perfect lead structures because they act at endogenous receptors and other therapeutically relevant targets.

There are already numerous books on the role of natural products in drug research – therefore, why present another one? The simple reason is that natural products were not only important in the past. Taxol, the statins, artemisinin, and epothilone are just a few examples of natural products that recently yielded important and successful new drugs and many more are under active investigation. A recent publication analyzed the origin of 1073 new chemical entities (small molecules, excluding biologicals) of the years 1981–2010 [1]: 6% of these drugs were natural products themselves, 28% were derivatives of natural products, 14% were characterized as mimics of natural products, and 16% as synthetics whose pharmacophore was derived from a natural product. In total, almost 2/3 of the newly introduced drugs originated in some manner from a natural product! This predominance of natural products is even more pronounced in the area of anticancer drugs and in the field of antibiotics.

We are very grateful to Stephen Hanessian, a world-leading expert in the field of natural product chemistry, for undertaking the task to edit this book with so many chapters on recent developments and success stories. In addition, we are grateful to all chapter authors for their excellent work, which provides a comprehensive overview of current research on new drugs from natural products. Finally, we would like to thank Frank Weinreich and Heike Nöthe of Wiley-VCH Verlag GmbH for their ongoing commitment to our book series Methods and Principles in Medicinal Chemistry.

October 2013
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Reference

1 Newman, D.J. and Cragg, G.M. (2012) Natural products as sources of new drugs over the 30 years from 1981 to 2010. *Journal of Natural Products*, **75**, 311–335.

Personal Foreword

Nature has been an abundant source of bioactive compounds for millennia. Modern science has unraveled the complex molecular architectures of natural products often possessing an unusual assortment of functional groups that would have defied all odds only a few decades ago.

Nature has also been the provider, the enticer, and the healer. Indeed, some of the most impressive contributions to the field of organic chemistry have been associated with the design and total synthesis of natural products. The same could be said of their biological activities, mode of action, and therapeutic value. These major advances at the interface between the chemistry and biology of natural products have showcased the courage, resolve, and, above all, the passion of dedicated scientists.

As the title itself reflects, this book is dedicated to the importance of natural products in medicinal chemistry. Structured into five thematic parts, the book consists of 16 chapters, each contributed by experts in the field, who have admirably written about their seminal contributions over the years to address diverse aspects of natural products in chemistry and biology. The five themes cover principally the importance of natural products as drugs, platforms for both chemical and genetic modifications to create newer entities, unique collections of biogenetically diverse compounds, and inspiration points for the design and synthesis of surrogates, mimics, hybrids, and chimeras.

I thank all the contributors for their efforts and collegiality in making this a very special volume that will be pedagogically and practically informative to students and professionals alike.

October 16, 2013 *Stephen Hanessian*

Part One
Natural Products as Sources of Potential Drugs and Systematic Compound Collections

Natural Products in Medicinal Chemistry, First Edition. Edited by Stephen Hanessian.

1

Natural Products as Drugs and Leads to Drugs: An Introduction and Perspective as of the End of 2012[1)]

David J. Newman and Gordon M. Cragg

1.1

Introduction

Two very frequent comments (together or separately) that have been made, in writing and verbally, over the last 15–20 years can be summarized as follows:

- The use (or pursuit) of natural products as either drugs or as leads to new chemistry that will lead to drugs is now passé, and that what is needed is the use of very high-throughput screens, coupled to large numbers of novel molecules produced by combinatorial chemistry.
- The clever use of computational methods to fit compounds into the active sites of the enzyme (or receptor) of interest will permit the derivation of large numbers of drugs to be discovered and then commercialized rapidly as a result.

We think that perhaps the best answer to comments such as these can be seen in two simple graphical models shown in Figures 1.1 and 1.2. In Figure 1.1, we have plotted the number of small *ie* meaning up to roughly 45 amino acid residues, with Byetta® being the upper limit, against the number of "N" and "S*" classifications as defined in Ref. [1] from January 1, 1981 through December 31, 2012. In Figure 1.2, we have taken the total number of "N-related" approved drugs over the same time frame as a percentage of the approved drugs for that year. The mean percentage per year of "N-derived drugs" ± the standard deviation over this time frame is 33.4 ± 8.9%, and in 2010, 50% of the 18 approved small-molecule drugs were in this category.

What must be borne in mind is that these are the most conservative figures as we only count a drug once, in the United States if it was first approved by the FDA (Food and Drug Administration) or the approving country's equivalent of the FDA. Thus, compounds that are subsequently approved for another disease either in the same or in a different country, or whose pharmaceutical properties are extended by slow release or by combination with other agents, are not counted again. There are a few exceptions to this general rule such as the use of nanoparticle-associated

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1) The opinions expressed in this chapter are those of authors, and not of the US Government.

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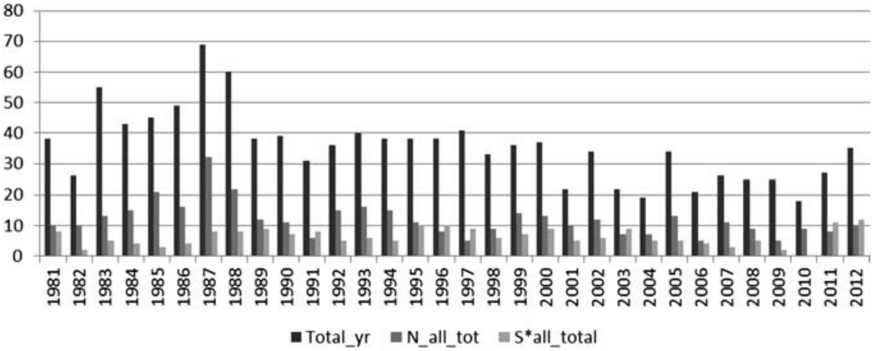


Figure 1.1 Numbers of natural product-related (N plus S*) small molecules per year (1981–2012).

albumins in the case of some versions of Taxol® and combinations of different modified insulins, but these, however, account for less than 0.3% of about 1500 compounds (small and large) approved in the last 32 years.

In Figure 1.3, we have shown the breakdown by category, again using the classifications used previously [1] of all drugs and small drugs approved over the last 32 years from January 1, 1981 through December 31, 2012, which should be studied by the interested reader. Again, if one looks at these diagrams, the role of natural product structures as leads (N- and S*-linked materials) is still very significant and even in 2011–2012, 41 of the 62 small-molecule drugs fell into these categories (data not shown but available from the authors on request).

In addition, in Figure 1.4, as befits authors from the US National Cancer Institute (NCI), we have shown the breakdown for all antitumor drugs from the beginning of chemotherapy treatments in the mid-1930s, using variations on the mustard gas used in warfare in World War I, through to the large number of tyrosine protein kinase inhibitors approved in the last few years, with almost all being isosteres of ATP and binding at the ATP site. As already mentioned, in the 2011–2012 N to S* breakdown, 16 of the 18 small-molecule antitumor drugs fell into these classifications. The isostere link was reconfirmed by an excellent presentation given by Fabbro [2] of Novartis at the recent NAD 2012 Meeting in Olomouc, the Czech Republic in July

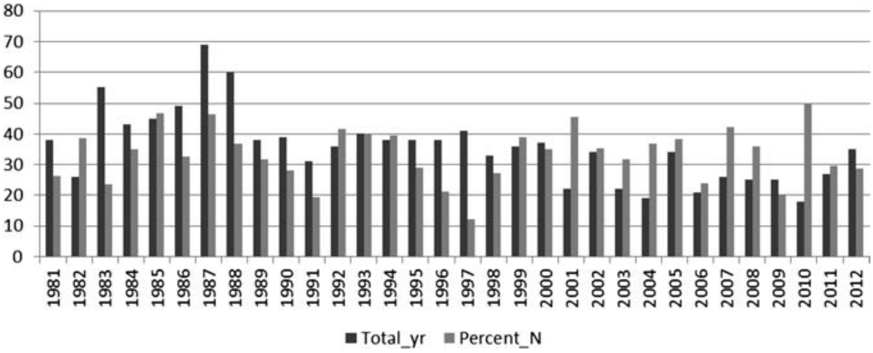
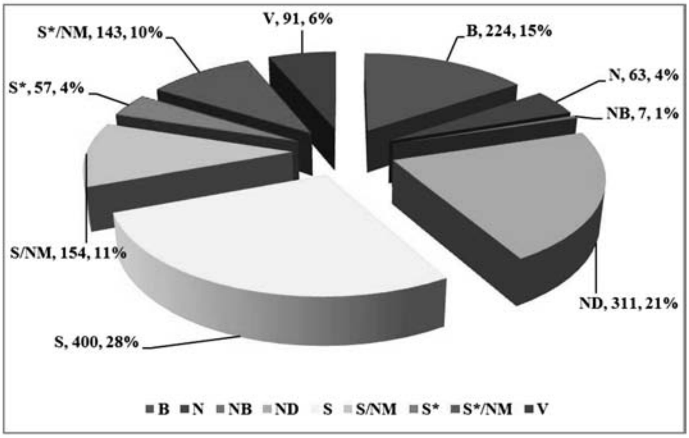


Figure 1.2 Percentage of natural product related (N) small molecules per year (1981–2012).

All drugs January 1, 1981 – December 31, 2012; N = 1450



Small drugs January 1, 1981 – December 31, 2012; N = 1135

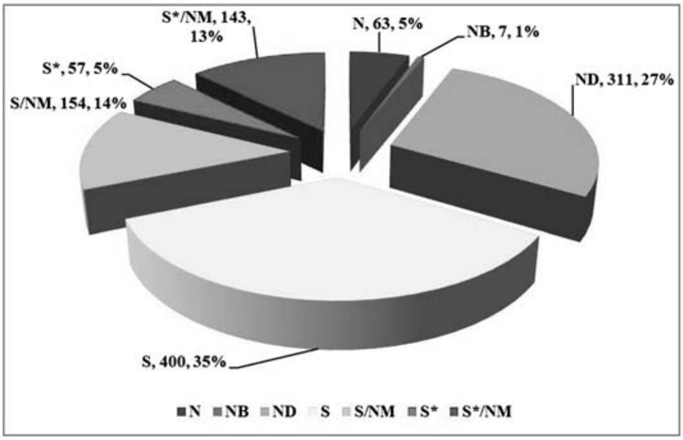


Figure 1.3 Sources of all approved drugs 1981–2012.

2012. Finally in this section, the influence of natural product structures on antitumor agents is such that if one sums the "N-related" then the answer is 89 or 47%, with the "S*-related" equaling 38 or 20% overall. Thus, one can see that natural product-related compounds in this disease category equal 67% of all approved small-molecule drug entities in this time frame. Although not shown, comparable figures are also seen for anti-infective agents over the 32-year time frame covered by Figure 1.3 (we have not gone back to the late 1930s for these data, but may well do so in time).

1.2
The Sponge-Derived Nucleoside Link to Drugs

Until about the 1960s, it was axiomatic that if you wished to make a biologically active nucleoside-derived molecule, you could modify the base including substitutions that

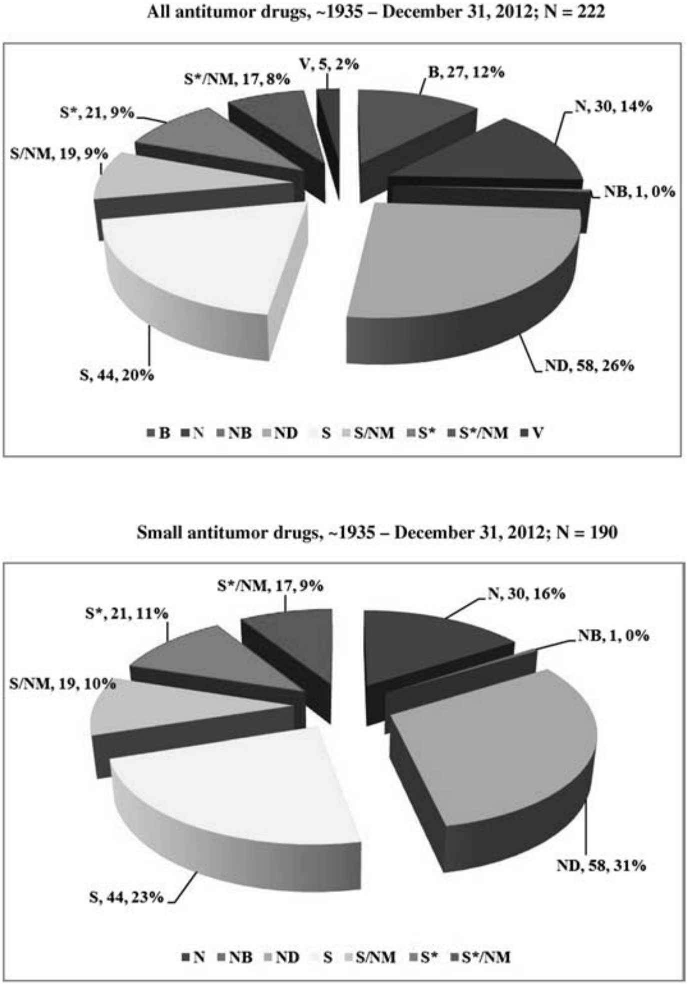


Figure 1.4 Sources of small molecule approved drugs 1981–2012 percentage of Na.

differed entirely from a pyrimidine or purine so that the base could comprise a multiplicity of heterocycles and even carbocycles. However, you had to use either ribose or deoxyribose as the sugar moiety, thus generating large numbers of molecules in pharmaceutical and academic laboratories that met these criteria; none, however, came to fruition as agents, aside from perhaps 5-fluorocytosine, first reported as being synthesized in 1957 [3] and launched as an antifungal agent in 1972.

However, these "conditions" changed as a result of the reports of Bergmann and coworkers [4–6] on the discovery and subsequent identification of spongothymidine (**1**) and spongouridine (**2**) in the early 1950s from the Caribbean sponge *Tethya crypta* as biologically active agents with arabinose instead of ribose or deoxyribose derivatives. These reports led to a complete reversal of the then current dogma