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SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS DERIVED FROM NATURAL PRODUCTS

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Abstract

Natural products and their structural analogues have historically made a major contribution to pharmacotherapy, especially for cancer and infectious diseases. Nevertheless, natural products also present challenges for drug discovery, such as technical barriers to screening, isolation, characterization and optimization, which contributed to a decline in their pursuit by the pharmaceutical industry from the 1990s onwards. In recent years, several technological and scientific developments including improved analytical tools, genome mining and engineering strategies, and microbial culturing advances are addressing such challenges and opening up new opportunities. Consequently, interest in natural products as drug leads is being revitalized, particularly for tackling antimicrobial resistance. Here, we summarize recent technological developments that are enabling natural product-based drug discovery, highlight selected applications and discuss key opportunities.The first total synthesis and development of a variety of bioactive natural products have been accomplished by using carbohydrates as a chiral source. In addition, practically useful intermediates have been created, analogs of natural products have been prepared, their structure-activity relationships studied, and the large-scale preparations of medicinally useful compounds established.

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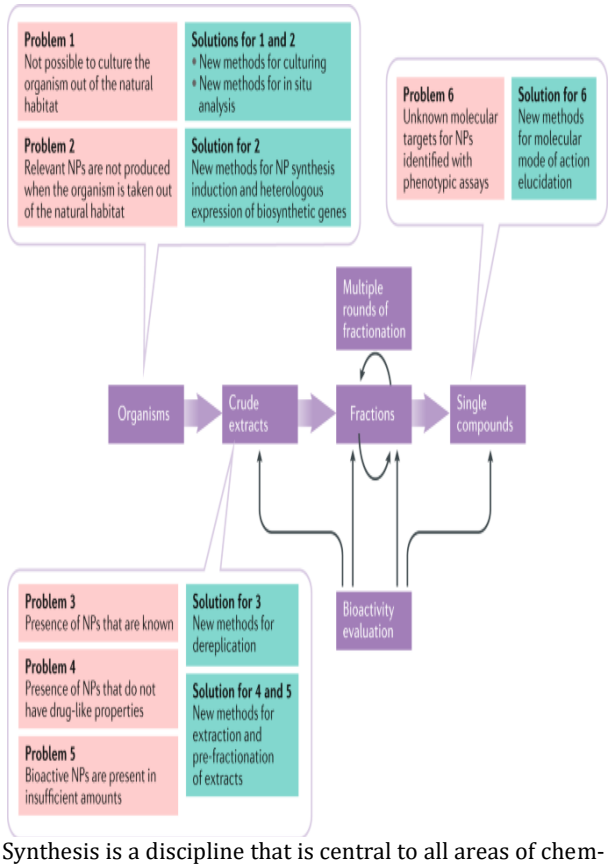
Introduction

Historically, natural products (NPs) have played a key role in drug discovery, especially for cancer and infectious diseases [1,2], but also in other therapeutic areas, including cardiovascular diseases (for example, statins) and multiple sclerosis (for example, fingolimod) [3,4,5]. NPs offer special features in comparison with conventional synthetic molecules, which confer both advantages and challenges for the drug discovery process. NPs are characterized by enormous scaffold diversity and structural complexity. They typically have a higher molecular mass, a larger number of sp3 carbon atomsand oxygen atoms but fewer nitrogen and halogen atoms, higher numbers of H-bond acceptors and donors, lower calculated octanol water partition coefficients and greater molecular rigidity compared with synthetic compound libraries [6,7]. These differences can be advantageous; for example, the higher rigidity of NPs can be valuable in drug discovery tackling protein–protein interactions. Indeed, NPs are a major source of oral drugs 'beyond Lipinski's rule of five. The increasing significance of drugs not conforming to this rule is illustrated by the increase in molecular mass of approved oral drugs over the past 20 years. NPs are structurally 'optimized' by evolution to serve particular biological functions, including the regulation of endogenous defence mechanisms and the interaction (often competition) with other organisms, which explains their high relevance for infectious diseases and cancer [8,9,10]. Furthermore, their use in traditional medicine may provide insights regarding efficacy and safety. Overall, the NP pool is enriched with

'bioactive' compounds covering a wider area of chemical space compared with typical synthetic small-molecule libraries [11, 12]. Despite these advantages and multiple successful drug discovery examples, several drawbacks of NPs have led pharmaceutical companies to reduce NP-based drug discovery programmes. NP screens typically involve a library of extracts from natural sources, which may not be compatible with traditional target-based assays [13,14,15]. Identifying the bioactive compounds of interest can be challenging, and dereplication tools have to be applied to avoid rediscovery of known compounds. Accessing sufficient biological material to isolate and characterize a bioactive NP may also be challenging. Furthermore, gaining intellectual property (IP) rights for (unmodified) NPs exhibiting relevant bioactivities can be a hurdle, since naturally occurring compounds in their original form may not always be patented (legal frameworks vary between countries and are evolving), although simple derivatives can be patent-protected. An additional layer of complexity relates to the regulations defining the need for benefit sharing with countries of origin of the biological material, framed in the United Nations 1992 Convention on Biological Diversity and the Nagoya Protocol, which entered into force in 2014 , as well as recent developments concerning benefit sharing linked to use of marine genetic resources. NPs have evolved over millions of years and acquired a unique chemical diversity, which consequently results in the diversity of their biological activities and drug-like properties. Therefore, even before the rise of the modern chemical pharmacology, NPs have been used for centuries as components of traditional medicines, in particular as active components of herbal remedies. Nowadays, some of the traditional healing practices, such as Indian Ayurveda, traditional Chinese medicine or African herbal medicines, remain the primary treatment option for many people across the world, due to economic reasons, to personal beliefs or to the difficulty in accessing pharmaceutical products. In modern pharmacology too, NPs have become one of the most important resources for developing new lead compounds and scaffolds. Every week, scientific articles in peer-reviewed journals are published describing the positive effects of NPs on the healing process of various human and animal diseases. Major classes of antibiotics and antifungals are based on NPs isolated from microorganisms. Drugs used in the treatment of various cancers, cardiovascular diseases, diabetes, and more are often NPs or their derivatives. For instance, between 1981 and 2014 over 50% of newly developed drugs were developed from NPs. NPs and their derivatives are also actively studied in food, cosmetic industries and in agriculture, with natural pesticides development. This growing interest over NPs and their application resolved in uncontrollable growth of the number of published open and commercial databases, industrial catalogues, books of NPs and collections of structures provided in supplementary materials or research articles, compiling NPs from various organisms, geographical locations, targeted diseases and traditional uses. It became, therefore, a real challenge to find a complete and comprehensive open database for NPs. One other major problem is the publication of structures only in graphical format, such as in the annual reviews of Marine Natural Products: these are not easily retrievable to be computationally analysed and they are not automatically integrated into public molecular databases. Virtual NP collections are therefore required for virtual screening, which is the first step in all exploratory molecular analyses and to some extent, in the discovery of NP-based drug or other types of active components. For example, the prior virtual screening of known NPs can prevent loss of time with extracting and purifying samples, postponing the wet lab step to the moment of theoretical identification of best candidates. In this way, the usage of modern cheminformatics technologies allows to accelerate research and save time and money for better results. The previous reviews on NPs databases are either outdated and do not reference the actual state of NP resources, either focus on one particular type of application for such databases, in particular databases that can be used for dereplication, a particular geographic origin of NPs or simply do not refer a significant part of NP resources.

Steps in the process are shown in purple boxes, with associated key limitations shown in red boxes and advances that are helping to address these limitations in modern natural product (NP)-based drug discovery shown in green boxes. The process begins with extraction of NPs from organisms such as bacteria. The choice of extraction method determines which compound classes will be present in the extract (for example, the use of more polar solvents will result in a higher abundance of polar compounds in the crude extract). To maximize the diversity of the extracted NPs, the biological material can be subjected to extraction with several solvents of different polarity. Although the complexity of NP structures can be advantageous, the generation of structural analogues to explore structure–activity relationships and to optimize NP leads can be challenging, particularly if synthetic routes are difficult.NP-based drug leads are often identified by phenotypic assays, and deconvolution of their molecular mechanisms of action can be time-consuming. Here, we discuss recent technological and scientific advances that may help to overcome challenges in NP-based drug discovery, with an emphasis on three areas: analytical techniques, genome mining and engineering, and cultivation systems. In the concluding section, we highlight promising future directions for NP drug discovery.



Synthesis is a discipline that is central to all areas of chemistry. It encompasses the unique ability of chemists to develop new reactions and to design molecules or molecular systems with a desired (or anticipated) set of properties be they enzyme inhibitors, receptor agonists, fluorescent dyes, transition metal catalysts, molecular devices, nanotubes, modified surfaces, solid-state compositions, or novel polymers. The proactive and creative nature of the science of chemical synthesis is unique among all of the physical sciences. This is especially true of research in natural products synthesis.

Research focusing on the synthesis of natural products has its origin in structure determination, which in decades prior to the advent of modern physical and spectroscopic methods was accomplished by degradation and partial synthesis of fragments or, in some cases, by the relay and/or total synthesis of the natural product itself. However, in spite of the remarkable techniques that are now available to the natural product isolation chemist, it is not always possible to assign the complete stereochemistry on the basis of spectroscopic methods. In such cases, chemical synthesis continues to play a significant role in structure determination. Interest in natural products synthesis has also been fueled by the recognition that many classes of important pharmaceutical agents derive from natural productss-lactam antibiotics, macrolide antibiotics, and steroid hormones are three illustrative classes of natural products that have given rise to important medicinal agents. Fascination with the role that secondary metabolites play in regulating cellular and other biological processes continues to provide the stimulus for natural products synthesis, as well as research on the development of small-molecule libraries and ultimately drug candidates based on natural product leads. In many cases, the quantities of natural products available from natural sources are so limited that total synthesis is required in order to provide material for further biological characterization, a necessary step to determine if the natural product warrants further exploration as a lead structure for drug development. Importantly, interest in natural products synthesis has stimulated incredible advances in the development of new synthetic methods and new strategies for synthesis of structurally and stereochemically complex molecules. Even a cursory examination of the workhorse bondforming reactions in use todays ranging from the multitude of palladium(0)- and nickel(0)- catalyzed coupling reactions, to ruthenium-mediated olefin metathesis and other transition metalmediated C-C bond-forming reactions, to C-H activation, to the many important and newly emerging methods for asymmetric synthesis and asymmetric catalysis, among many others reveals that most were not available to the practicing organic or medicinal chemist even two decades ago. Natural products synthesis provides an important forum for testing and demonstrating the synthetic utility of newly developed methods and strategies, as the unique and often complex arrangements of functionality and stereochemistry in natural product targets provide stringent tests. In essence, efforts to apply new methods to complex natural product targets provide a Darwinian selection pressure that ensures that the methodology platforms available to the bench chemist continue to evolve in a highly productive direction.

Isolation of natural products

Isolation of new structures (e.g. secondary metabolites like macrolides, alkaloids, terpenes) represents a fundamental research topic. Only a few research teams focusing on isolation techniques are active in Europe. A major aim of this action will be to emphasise new research directions in this very important area. Especially actinomyceten and soil fungi based on European sources will be of interest. Ethnopharmacologically plants applied for the treatment of specified diseases will be studied. Invertebrates from the Mediterranean Sea (e.g. sponges, molluses, tunicates, bryozoans) could offer an enormous basis of compounds. Finally, rare bacteria, e.g. the gliding myxobacteria provided already a great variety of new structures (ratjadones, sorangicins, soraphenes, epothilones). The epothilone case (discovered at the Gesellschaft f_r Biotechnologische Forschung, Braunschweig, Germany) could be a story of success, because epothilone B and some analogues are currently in clinical trials.

Discovery of new leads

A very important step will be the discovery of a new lead structure based on natural products. Again, the epothilones, secondary metabolites from myxobacteria, are one of the most important leads in cancer therapy today. Special attention will be focused on test systems provided by industry. High throughput screening and target-

orientated assays will provide quick access to interesting structures.

Structure determination

Structure elucidation of new complex molecules requires considerable knowledge on new analytical techniques, like HPLC, GC, MS, and NMR. Especially, high field NMR combined with novel pulse sequences will be of great importance and allow several groups to benefit from exchanging data and samples. In addition, solid phase NMR will be important to study interactions of small molecules with proteins (rational design of drugs), which finally could lead to a receptor model.

New Strategies for total synthesis of biologically active natural products

This sub-topic represents an extremely important aspect in the new action. The development of new strategies for total synthesis combines in ideal form different areas in organic synthesis. Research collaboration will create a flexible access to interesting and novel routes to synthesise new molecules. Stereochemistry (dia- and enantioselective reagents) will be a major aspect and will train students to get a more detailed insight of this important issue. Furthermore, domino reactions play an important role in the synthesis of complex natural products, because in a sequence of events several strategic bonds can be formed stereo selectively in one-pot.

Applications of analytical techniques

Classical NP-based drug research starts with biological screening of 'crude' extracts to identify a bioactive 'hit' extract, which is further fractionated to isolate the active NPs. Bioactivity-guided isolation is a laborious process with a number of limitations, but various strategies and technologies can be used to address some of them. For example, to create libraries that are compatible with high-throughput screening, crude extracts can be pre-fractionated into sub-fractions that are more suitable for automated liquid handling systems. In addition, fractionation methods can be adjusted so that sub-fractions preferentially contain compounds with drug-like properties (typically moderate hydrophilicity). Such approaches can increase the number of hits compared with using crude extracts, as well as enabling more efficient follow-up of promising hits.Analytical advances that enable the profiling of responses to bioactive molecules at the single-cell level can also accelerate NP-based drug discovery.

The technological advances discussed above have the potential to reinvigorate NP-based drug discovery in both established and emerging areas. NPs have long been the key source of new drugs against infectious diseases, especially antibiotics. Selected NPs with antimicrobial properties discovered by leveraging advances discussed in the sections above, including strategies to exploit the human microbiome for novel NPs. Along with the search for new NPs with antimicrobial activities, researchers are continuing to develop and optimize already known NP classes, making use of advances in biosynthetic engineering, total synthesis or semi-synthetic strategies. NPs remain a promising pool for the discovery of scaffolds with high structural diversity and various bioactivities that can be directly developed or used as starting points for optimization into novel drugs.

The complex regulation of NP biosynthesis in response to the environment means that the conditions under which producing organisms are cultivated can have a major impact on the chance to identify novel NPs. Several strategies have been developed to improve the likelihood of identifying novel NPs compared with monoculture under standard laboratory conditions and to make "uncultured" microorganisms grow in a simulated natural environment. One well-established approach to promote the identification of novel NPs is the modulation of culture conditions such as temperature, pH and nutrient sources. This strategy may lead to activation of silent gene clusters, thereby promoting production of different NPs. The term "One Strain Many Compounds" (OSMAC) was coined for this approach about 20 years ago, but the concept has a longer history, with its use being routine in industrial microbiology since the 1960s. While OSMAC is still widely used for the identification of new bioactive compounds for recent examples), this approach has limited capacity to mimic the complexities of the natural habitats. It is difficult to predict the combination of cues (which might also involve metabolites secreted by other members of the microbial community) to which the microorganism has evolved to respond by switching metabolic programs. To account for such kind of interactions, co-culturing using "helper" strains can be applied. This can enable the production and identification of new NPs, as illustrated by recent studies in which particular fungi were co-cultured with Streptomcyes species. Study of the molecular mechanisms underlying the ability of "helper" strains to increase the cultivability of previously uncultured microbes can lead to the identification of specific growth factors, allowing expansion of the number of species that can be successfully cultured. The siderophore-assisted growth is based on the property of these compounds to provide iron for microbes unable to autonomously produce siderophores themselves, and the application of this approach led to the isolation of previously uncultivated microorganisms. The development of strategies to cultivate microbial symbionts that produce NPs only upon interaction with their hosts can promote access to new NPs. Microbial symbionts interacting with insects or other organisms are a highly promising reservoir for the discovery of novel bioactive NPs produced in a unique ecological context. To stimulate NP production, culturing strategies can be developed that better mimic the native environment of microbial symbionts of insects, including the use of media either containing lyophilized dead insects or L-proline, a major constituent of insect hemolymph.

Advances in knowledge on biosynthetic pathways for NPs and in developing tools for analysing and manipulating genomes are further key drivers for modern NP based drug discovery. Two key characteristics enable the identi-

fication of biosynthetic genes in the genomes of the producing organisms. First, these genes are clustered in the genomes of bacteria and filamentous fungi. Second, many NPs are based on polyketide or peptide cores, and their biosynthetic pathways involve enzymes — polyketide synthases and non-ribosomal peptide synthetases, respectively — that are encoded by large genes with highly conserved modules.

Genome mining and engineering

"Genome mining" is based on searches for genes that are likely to govern biosynthesis of scaffold structures, and can be used to identify NP biosynthetic gene clusters. Prioritizing gene clusters for further work is facilitated by advances in biosynthetic knowledge and predictive bioinformatics tools, which can provide hints about whether the metabolic products of the clusters have chemical scaffolds that are new or known, thereby supporting dereplication . Such predictive tools for gene cluster analysis can be applied in combination with spectroscopic techniques to accelerate the identification of NPs and determine the stereochemistry of metabolic products. Furthermore, to extend genome mining from a single genome to entire genera, microbiomes or strain collections, computational tools have been developed, such as BiG-SCAPE, which enables sequence similarity analysis of biosynthetic gene clusters, and CORASON, which uses a phylogenomic approach to elucidate evolutionary relationships between gene clusters.

Conclusion

Recent progress in the total syntheses and development of selected bioactive natural products is reviewed. Most of the total syntheses that have been completed in our laboratories have been the first ever accomplished. Establishment of the total syntheses by use of carbohydrates as chiral sources created a comprehensive method to investigate a variety of bioactive natural products. The achievement of successful results in research is, of course, of prime importance. Yet, prior to undertaking research, it is essential that the objectives of the research are clearly understood and defined. Hence, it may be no exaggeration to say that the selection of target molecules decides, above all, the value of the research itself, particularly with respect to bioactive natural product synthesis.

Conflict of Interest

Authors are declared that no conflict of Interest

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