Nature stands as an inexhaustible source of novel chemotypes and pharmacophores, and has been a source of medicinal agents for thousands of years, and an impressive number of modern drugs find their origin in natural products. Natural product chemistry has experienced explosive and diversified growth, making natural products the subject of much interest and promise in the present day research directed towards drug design and discovery. It is noteworthy that natural products are a source of new compounds with diversified structural arrangements possessing interesting biological activities. Natural products, thus, have played and continue to play an invaluable role in the drug discovery process. Recently, there has been a renewed interest in natural products research due to the failure of alternative drug discovery methods to deliver many lead compounds in key therapeutic areas such as immunosuppression, anti-infective, and metabolic diseases. However, continuing improvements in natural products research are needed to continue to be competitive with other drug discovery methods, and also to keep pace with the ongoing changes in the drug discovery process. Faithful drives are needed in a more intensified fashion to explore “Nature” as a source of novel and active agents that may serve as the leads and scaffolds for elaboration into urgently needed efficacious drugs for a multitude of disease indications.

Natural products have provided considerable value to the pharmaceutical industry over the past half century. In particular, the therapeutic

* Corresponding author. E-mail: brahmg2001@yahoo.co.in; brahmg2001@gmail.com
areas of infectious diseases and oncology have benefited much from numerous drug classes derived from the natural form and as templates for synthetic modification. About 40 new drugs launched on the market between 2000 and 2010, originating from terrestrial plants, terrestrial microorganisms, marine organisms, and terrestrial vertebrates and invertebrates are reported, and summarized categorically (as per disease area) in this article. In addition, this review incorporates natural products and natural product-derived compounds that are being presently evaluated in clinical trials or are in registration highlighting their mechanism of action. These drugs substances, representative of very wide chemical diversity, thus continue to demonstrate the importance of compounds from natural sources in modern drug discovery efforts. Hence, the proven natural product drug discovery track record, coupled with the continuing threat to biodiversity through the destruction of terrestrial and marine ecosystems, provides a compelling challenge for the global scientific community to undertake expanded exploration of “Nature” as a source of novel leads for the development of drugs and other valuable bioactive agents. A huge number of natural product-derived compounds in various stages of clinical development highlight the existing viability and significance of the use of natural products as sources of new drug candidates.

“Organic chemistry just now is enough to drive one mad. It gives the impression of a primeval tropic forest, full of the most remarkable things, a monstrous and boundless thicket, with no way to escape, into which one may well dread to enter.”

Wöhler (1835)

1. Introduction

Almost two centuries had elapsed after Wöhler’s historical comment cited in his letter to Berzelius in the year 1835 on the ongoing development of organic chemistry; his “monstrous and boundless thicket” is now sufficiently more dense and complex than ever and quite forbidding to strangers! Natural products chemistry, a vital section of organic chemistry,
has also undergone an explosive growth in its own course and has already established itself as a distinct discipline. Mother Nature now stands as an inexhaustible source of novel chemotypes and pharmacophores.¹

Nature’s terrestrial flora and fauna have formed the basis of sophisticated traditional medicine systems that have been in existence for thousands of years — such an intrinsic dependence of human beings on Nature has invoked tremendous interest in the scientific world, which ultimately led to the isolation of a vast number of chemical agents with the potential for multipurpose uses.²⁻⁹ Natural product chemists took up the challenge of determining the structures of ever more complicated natural products. From the late 19th century until today, generations of natural product chemists have applied their skills and intellect to many tens of thousands of molecules of natural origin, encouraged by a society that values many natural products for their life-giving or life-enhancing properties. Although ~200 000 natural compounds derived from natural sources such as plants, animals or microorganisms are currently known, this figure is with small variety regards to the widen of natural resources; only about 5–15% of nearly 250 000 higher plants and less than 1% of the microbial world have been explored so far chemically — the vast majority of these sources remains untapped.¹⁰⁻¹² The future of natural products in drug discovery, thus, appears to be a tale of justifiable hope. The pragmatic optimism currently placed on natural products in search of new drugs and lead molecules has recently been aptly expressed as “The world of plants, and indeed all natural sources, represent a virtually untapped reservoir of novel drugs awaiting imaginative and progressive organizations”.¹

By the 20th century, natural products began to provoke some biochemists interested in understanding the way in which compounds were made that eventually initiated the concepts of biosynthetic pathways for different kinds of natural products. In the early 20th century, very few researchers associated with the emerging departments of clinical biochemistry, pharmacology, toxicology, microbiology and cell biology became motivated to work with some specific natural products, but the study of natural products as a group was still largely confined to chemistry departments. By the mid 20th century, some cell biologists and physiologists screened a few natural products (viz. colchicine, atropine, nicotine, digoxin, etc.) as experimental tools that influenced or disrupted cell functions in specific
ways. However, it was the discovery of antibiotics that offered the study of natural products a great boost in microbiology departments and ensured that natural products remained central to growing pharmaceutical companies.\textsuperscript{13,14} Due to multidirectional promising aspects, the interest in natural products continues to this very day.\textsuperscript{15–30} The last decade has seen a greater use of botanical products among members of the general public through self-medication than never before. The use of herbal drugs is once more escalating in the form of complementary and alternative medicine (CAM).\textsuperscript{31,32} This phenomenon has been mirrored by an increasing attention to phytomedicines as a form of alternative therapy by the health professions; in many developing countries of the world, there is still a major reliance on crude drug preparation of plants used in traditional medicines for their primary healthcare.\textsuperscript{33–36} The World Health Organization (WHO) estimates that approximately 80\% of the world’s population relies mainly on traditional medicine, predominantly originated from plants, for their primary health care.\textsuperscript{37,38} The worldwide economic impact of herbal remedies is noteworthy; in the US alone, in 1997, it was estimated that 12.1\% of the population spent $5.1 billion on herbal remedies.\textsuperscript{39} In the UK, sales of herbal remedies were worth of £75 million in 2002, an increase of 57\% over the previous 5 years of herbal medicines.\textsuperscript{40} Studies carried out in other countries, such as Australia and Italy, also suggest an increasing prevalence of use of herbal medicines among the adult population.\textsuperscript{40,41} In India and China, the Ayurvedic and Chinese traditional medicine systems respectively are particularly well developed, and both have provided potential for the development of Western medicine. Throughout our evolution, the importance of natural products for medicine and health has been enormous; the past few years have seen a renewed interest in the use of natural compounds and, more importantly, their role as a basis for drug discovery. The modern tools of chemistry and biology — in particular, the various “-omics” technologies — now allow scientists to detail the exact nature of the biological effects of natural compounds on the human body, as well as to uncover possible synergies, which holds much promise for the discovery of new therapies against many devastating diseases.\textsuperscript{42–49} Natural products, thus, have been the major sources of chemical diversity as starting materials for driving pharmaceutical discovery over the past century.\textsuperscript{1,50,51} Many natural products and synthetically modified
natural product derivatives have been successfully developed for clinical use to treat human diseases in almost all therapeutic areas.\(^{52}\) Natural product medicines have come from various source materials including terrestrial plants, terrestrial microorganisms, marine organisms, and terrestrial vertebrates and invertebrates.\(^{4,8,41,42}\) The importance of natural products in modern medicine has been described in a number of earlier reviews and reports.\(^{8,30,53–60}\)

A comprehensive review of natural products in clinical trials, “Recent Natural Products Based Drug Development: A Pharmaceutical Industry Perspective”, was published in 1998 by Shu.\(^{61}\) Since then, a good number of discussions have been published that describe natural product-derived compounds in clinical trials by organism type, compound class and/or therapeutic area.\(^{48,53–71}\) In addition, there have been a number of reviews detailing marine-derived natural products in clinical trials.\(^{47,57,72–80}\) This present chapter is aimed, particularly, to highlight the impact and opportunities of natural products in modern drug discovery programs delineating the approved natural product-based drugs launched during the period 2000 to 2010, and also natural product-based drug candidates undergoing clinical evaluation.

2. Natural Products in Traditional Medicine:
A Historical Perspective in Brief

Natural products (including plants, animals and minerals) have been the basis of treatment of human diseases. History of medicine dates back practically to the existence of human civilization. Modern medicine system has gradually developed over the years by scientific and observational efforts of scientists; however, the basis of its development remains rooted in traditional medicine and therapies, prevailing throughout the world for thousands of years, which continue to provide mankind with new remedies. Plant-based medicines initially dispensed in the form of crude drugs such as tinctures, teas, poultices, powders, and other herbal formulations,\(^{6}\) now serve as the basis of novel drug discovery. The plant-based indigenous knowledge was passed down from generation to generation in various parts of the world throughout its history and has significantly contributed to the development of different traditional systems of medicine.
The history of traditional medicine in India can be traced to the remote past. Multidirectional therapeutic uses of various plants in traditional way are known in India since the Vedic times as Ayurvedic and Unani systems of medicine. The lore of any country man is built upon the experience of generations, often of centuries and the data upon which it is based have often been obtained at a price in human lives which no modern research worker would ever dream of considering. The earliest mention of the medicinal use of plants is found in the Rig Veda, perhaps the oldest repository of human knowledge, having been written between 4500 and 1600 BC. “Susruta Samhita” which was written not later than 1000 BC contains a comprehensive chapter on therapeutics and “Charaka Samhita”, written about the same period, gives a remarkable description of the materia medica as it was known to the ancient Hindus. During the centuries that have gone by, the materia medica of the indigenous system of medicine has become explosive and heterogeneous.

The “Nei Ching” is also one of the earliest health science anthologies, which dates back to 1300 BC. Some of the first records on the use of natural products in medicine were written in cuneiform in Mesopotamia on clay tablets and date to approximately 2600 BC. Indeed, many of these agents continue to exist in one form or another to this day as treatments for various ailments. Chinese herb guides document the use of herbaceous plants as far back in times as 2000 BC; in fact, “The Chinese Materia Medica” has been repeatedly documented over centuries starting at about 1100 BC. Li Shih-Chen produced a Chinese drug encyclopedia during the Ming Dynasty entitled “Pen-ts’as kang mu” in AD 1596, which records 1898 herbal drugs and 8160 prescriptions. Egyptians have been found to have documented uses of various herbs in 1500 BC; the best known of these documents is the Ebers Papyrus, which documents nearly 1000 different substances and formulations, most of which are plant-based medicines. The Greek Botanist, Pedanius Dioscorides compiled a work entitled “De Materia Medica” in approximately AD 100, and this is still a very well-known European document on the use of herbs in medicine. However, it should not go unrecognized that it was the Arabs who were responsible for maintaining the documentation of much of the Greek and Roman knowledge of herbs and natural products and expanding that information with their own knowledge of Chinese and Indian herbal medicine.
Besides, various types of societies and botanical clubs held meetings and published different types of communications to educate the general people with regard to the availability of natural products and how they could be helpful to an individual’s health. Samuel Thompson’s “Thompson’s New Guide to Health” was also one very popular publication. For a variety of reasons, the interest in natural products continues to this very day.\textsuperscript{16,17,19,20,22,83,84}

In many developing countries of the world, there is still a major reliance on crude drug preparation of plants used in traditional medicines for their primary health care.\textsuperscript{33–36} Pharmacognosists employed in the different institutions are aware of the changing trends of herbal medications and a number of useful texts on the analysis, uses, and potential toxicities of herbal remedies have appeared recently, which serves as useful guides in pharmacy practice. The history of medicine includes many ludicrous therapies. Nevertheless, ancient wisdom has been the basis of modern medicine and will remain as one important source of future medicine and therapeutics. The future of natural products drug discovery will be more holistic, personalized and involve the wise use of ancient and modern therapeutic skills in a complementary manner so that maximum benefits can be accrued to the patients and the community.\textsuperscript{85}

The use of natural products as medicine has invoked the isolation of active compounds; the first commercial pure natural product introduced for therapeutic use is generally considered to be the narcotic morphine (1), marketed by Merck in 1826,\textsuperscript{8} and the first semi-synthetic pure drug aspirin (2), based on a natural product salicin (3) isolated from \textit{Salix alba}, was introduced by Bayer in 1899. This success subsequently led to the isolation of early drugs such as cocaine, codeine, digitoxin (4), quinine (5), and pilocarpine (6), of which some are still in use.\textsuperscript{7,8,86–88}
The most striking feature of natural products in connection to their long-lasting importance in drug discovery is their structural diversity that is still largely untapped. Most natural products are not only sterically more complex than synthetic compounds, but differ also with regards to the statistical distribution of functionalities.\textsuperscript{89} They occupy a much larger volume of the chemical space and display a broader dispersion of structural and physicochemical properties than compounds issued from combinatorial synthesis.\textsuperscript{90} It needs to be mentioned that in spite of massive endeavors adopted in recent times for synthesizing complex structures following “diversity oriented synthesis” (DOS) strategy,\textsuperscript{91} about 40\% of the chemical scaffolds found in natural products are still absent in today’s medicinal chemistry.\textsuperscript{92} The chemical diversity and unique biological

\begin{align*}
\text{Digitoxin (4)}
\end{align*}
activities of a wide variety of natural products have propelled many discoveries in chemical and biological sciences, and provided therapeutic agents to treat various diseases as well as offered leads for the development of valuable medicines.

The history of pharmacognosy is, in part, defined by the ever-expanding catalog of naturally occurring, biologically active compounds that have been discovered and characterized. It has been estimated that about 40% of medicines have their origin in these natural products. The chemical potential of plants is however, still largely unexplored. Chemical diversity has only been analyzed in about 5–15% of all land plants, and even here only the most abundant compounds have been well characterized. Hence, there remains an unprecedented possibility for the discovery of novel chemicals that may find diverse uses from pharmaceuticals through fine chemicals. Natural products, thus, continue to be a major source of biologically active compounds that may serve as commercially significant entities themselves or may provide lead structures for the development of modified derivatives possessing enhanced activity and/or reduced toxicity.

Even though combinatorial synthesis is now producing molecules that are drug-like in terms of size and property, these molecules, in contrast to natural products, have not evolved to interact with biomolecules. Natural compounds such as brefeldin A, camptothecin, forskolin and immunophilins often interfere with protein–protein interaction sites. Analysis of the properties of synthetic and natural compounds compared to drugs revealed the distinctiveness of natural compounds, especially concerning the diversity of scaffolds and the large number of chiral centres. This may be one reason why ~50% of the drugs introduced to the market during the last 20 years are derived directly or indirectly from natural compounds.

In chemical biology, natural products play an important role to elucidate complex cellular mechanisms, including signal transduction and cell cycle regulation, leading to the identification of important targets for therapeutic intervention. There has been an increasing demand for new natural products, or new natural product-like small molecules in the fields of genomic and proteomics for the rapid identification of large numbers of gene products for which the small molecule modulators will
be of both biological and medicinal interest.\textsuperscript{99–103} Besides, the combination of cell biology and high throughput technology has led to the development of various cellular assays in which small molecule libraries can be used to identify and study previously known targets.\textsuperscript{104}

The reason for the lack of lead compounds from synthetic libraries in some therapeutic areas such as anti-infectives, immunosuppression, oncology, and metabolic diseases may be due to the different chemical space occupied by natural products and synthetic compounds.\textsuperscript{89,90,92,105} This difference in chemical space makes natural products an attractive alternative to synthetic libraries, especially in therapeutic areas that have a dearth of lead compounds. Natural products have been used also as starting templates in the synthesis of combinatorial libraries.\textsuperscript{92,106–110} Natural product pharmacophores are well represented in lists of “privileged structures”, which make them ideal candidates for building blocks for biologically relevant chemical libraries.\textsuperscript{111,112} Natural products still constitute a prolific source of novel lead compounds or pharmacophores for medicinal chemistry, and hence, natural products should be incorporated into a well-balanced drug discovery program. Besides their potential as lead structures in drug discovery, natural products also provide attractive scaffolds for combinatorial synthesis and act as indispensable tools for the validation of new drug targets.\textsuperscript{113}

4. Natural Products in Drug Discovery: Success, Constrains and New Approaches for Remedies

4.1. A Success Story

Mother Nature still continues to be a resource of novel chemotypes and pharmacophores, and an impressive number of modern drugs have been isolated from natural sources, many based on their uses in traditional medicine systems.\textsuperscript{33–35,114} To a large extent, the use of natural products in drug design represents the natural evolution of this old tradition. It has been extensively documented that the traditional medicine systems of many cultures worldwide are based on plants,\textsuperscript{38,113,115–118} for example in countries like China\textsuperscript{33} and India\textsuperscript{35} where plants have formed the basis for traditional systems of medicines. According to Kim and Park,\textsuperscript{119} natural
products have been regarded as important sources that could produce potential chemotherapeutic agents. A comprehensive review of the history of medicine may be consulted, in this regard, on the homepage of the National Library of Medicine (NLM), History of Medicine at www.nlm.nih.gov/hmd/hmd.html.

Large numbers of promising lead molecules have come out of Ayurvedic experimental base including Rauwolfia alkaloids for hypertension, psoralens in vitiligo, guggulsterons as hypolipidemic agents, Mucuna pruriens for Parkinson’s disease, bacosides in mental retention, phyllanthus as antivirals, picrosides in hepatic protection, curcumines in inflammations, withanolides and many others steroidal lactones and glycosides as immunomodulators,24,120 plants have thus, always been a rich source of natural product leads — a few more examples are: morphine, cocaine, digitalis, quinine, tubocurarine, nicotine, muscarine, paclitaxel (Taxol™) and artemisinin. There are growing evidences where the old molecules are finding new applications through better understanding of traditional knowledge and clinical observations. For instance, the alkaloid, forskolin isolated by Hoechst and coleonol by Central Drug Research Institute (CDRI), Lucknow, India a few decades ago from Coleus forskohlii121 and phytochemicals from Stephania glabra, which were shelved for a considerable time are now being rediscovered as adenylate cyclase and nitric oxide activators, which may help in preventing conditions including obesity and atherosclerosis.122 Natural products also provide a vast pool of pancreatic lipase inhibitors as potential candidates, which can be developed into new drugs for the treatment of conditions like obesity.123 A large number of promising leads for the development of newer anti-inflammatory drugs are also available in medicinal plants.124

The blossoming of natural product discovery efforts occurred after the large scale production of penicillin during World War II, when the pharmaceutical companies that contributed to the war-time efforts to build stocks of penicillin refocused their programs on the search for new antibiotics from microorganisms.50 Mining of the bacterial genome and identification of crucial targets followed by study of new bacterial or fungal strains have resulted in the discovery of significant antibacterial agents such as cephalosporins, streptomycin, gentamicin, tetracycline, chloramphenicol,
aminoglycosides, rifamycins and many others that spurred the industry to develop large research and development programs around natural product discovery, particularly microbial fermentation-based technologies.\textsuperscript{125,126} All of the major pharmaceutical companies had programs on natural product discovery, and these programs focused not only on anti-bacterial and anti-fungal targets, but also on targets other than infectious diseases. In the 1970s for example, the discovery of cholesterol biosynthesis-inhibiting drugs compactin\textsuperscript{127,128} and mevinolin (a fungal metabolite isolated from cultures of \textit{Aspergillus terreus})\textsuperscript{129,130} led to the development of the hugely successful statin therapeutics, which even today represent successes in both medical treatment and in pharmaceutical business fortunes.\textsuperscript{131–134} Since the past five decades, marine sources (viz. coral, sponges, fish and marine microorganisms) have attracted scientists from different disciplines leading to the discovery of several marine natural products with promising biological activities; a few of them include curacin A, eleutherobin, discodermolide, bryostatins, dolostatins, and cephalostatins.\textsuperscript{78,135} Venoms and toxins (peptides and non-peptides) found in snakes, spiders, scorpions, insects, and other microorganisms are also significant in drug discovery due to their specific interactions with macromolecular targets in the body, and have been proven crucial while studying receptors, ion channels, and enzymes. Toxins like $\alpha$-bungarotoxin (from the venom of the elapid snake Taiwanese banded krait (\textit{Bungarus multicinctus})),\textsuperscript{136,137} tetrodotoxin (from puffer fish and many other widely varying animals including certain bacteria)\textsuperscript{138–143} and teprotide (from Brazilian viper)\textsuperscript{144} etc. are in clinical trials for drug development. Similarly, neurotoxins obtained from \textit{Clostridium botulinum} (responsible for botulism, a serious food poisoning), were been found to be significant in preventing muscle spasm.\textsuperscript{145}

The impact of natural products on drug discovery has, thus, been enormous; natural products originating from microorganism, plant and animal sources have been the single most productive source of leads for the development of drugs to treat human diseases.\textsuperscript{9,48,52} More than 80% of drug substances involved in drug discovery programs in “olden times” (i.e. before the advent of high-throughput screening (HTS) and the post-genomic era) were reported to be natural products or inspired by natural product structures.\textsuperscript{87,113} It is arguably still true; comparisons of the information
presented on sources of new drugs from 1981 to 2007 indicate that almost half of the drugs approved since 1994 are based on natural products. In the areas of cancer and infectious diseases, 60% and 75% of new drugs, respectively, originated from natural sources between 1981 and 2002. Between 2001 and 2005, 23 new drugs derived from natural products were introduced for the treatment of disorders such as bacterial and fungal infections, cancer, diabetes, dyslipidemia, atopic dermatitis, Alzheimer’s disease and genetic diseases such as tyrosinaemia and Gaucher disease; two drugs have been approved as immunosuppressive agents and one for pain management. Thirteen natural product-related drugs were approved from 2005 to 2007 and, as pointed out by Butler, five of these represented the first members of new classes of drugs: the peptides exenatide and ziconotide, and the small molecules ixabepilone, retapamulin and trabectedin. Of the 90 antibacterial drugs that became commercially available in the US or were approved worldwide from 1982 to 2002, ~79% can be traced to a natural product origin. According to a study by Grifo and his colleagues, 84 of a representative 150 prescription drugs (prescribed mainly as anti-allergy/pulmonary/respiratory agents, analgesics, cardiovascular drugs, and for infectious diseases) in the US were natural products and related drugs. Another study found that natural products or related substances accounted for 40%, 24%, and 26% of the top 35 worldwide ethical drug sales in 2000, 2001, and 2002 respectively. 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 two 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. In addition to this historical success in drug discovery, natural products are likely to continue to be sources of new commercially viable drug leads. Combined with pharmacological screening, the chemistry of natural products has always provided highly useful leads for drug discovery. The search for new biologically active compounds are most often based on hints from ethnobotany but there are still a large number of unstudied plants, mushrooms, marine organisms, insects, and microorganisms. There is a wealth of molecular diversity out there, waiting to be discovered and utilized.
4.2. Lacunae/Constrains

After very successful drug discovery and development programs based on natural products, the pharmaceutical industry, in particular the large pharmaceutical companies, de-emphasized natural product discovery research in the 1990s and early 2000s.\textsuperscript{27,60,146,150,151} This was caused by the advent of alternative drug discovery methods such as rational drug design involving automated high-throughput screening (HTS) technology in combination with combinatorial chemistry\textsuperscript{152–159} with the belief and hope that newly developed technologies would result in the development of drugs within a short and affordable time scale of the so-called “blitz” screen (start to finish in 3 months). Thus, the promise of a ready supply of large synthetic compound libraries led many companies to eliminate or considerably scale down their natural product operations.\textsuperscript{160–164} The major causative points that directed the downfall of natural products in the pharmaceutical industry in the 1990s include difficulties in access and supply, complexities of natural product chemistry, the inherent slowness of working with natural products, and concerns about intellectual property rights. Rediscovery of known compounds is a major problem when screening natural product libraries. This is caused by a lack of efficient dereplication methodologies for both natural product sourcing and compounds in the natural product libraries. The time-consuming processes of dereplication and purification are not compatible with the present regime of “blitz” screening campaigns in which assay support is only available for a limited duration (3 months). Besides, natural products are often structurally complex; modification of complex natural products using organic chemistry is frequently challenging. Medicinal and combinatorial chemists prefer not to work with natural products because of the large size and complexity of the compounds, which have too many functional groups to protect. It is difficult to prepare as many natural product analogs as synthetic chemicals in the same amount of time.\textsuperscript{47} However, despite the promise of these alternative drug discovery methods, there is still a shortage of lead compounds progressing into clinical trials. This is especially the case in therapeutic areas such as oncology, immunosuppression and metabolic diseases where natural products have played a central role in lead discovery. Marketed drugs derived from natural products still account for significant revenues in many of the major pharmaceutical companies.\textsuperscript{165} Lipitor, zocor and pravachol, the cholesterol-regulating
therapeutic agents derived from the natural product statin class of compounds, continue to generate multi-billion dollar revenues. Antibiotics, like zithromax and the generic penicillins, continue to be essential in medical care, however they contribute less to pharmaceutical revenues than non-antibiotics due to their relatively limited dosing intervals.

### 4.3. New Approaches for Possible Remedies

Recent technological advances and the development of new methods have revolutionized the screening of natural products and offer a unique opportunity to re-establish natural products as major source of drug leads. The new methods and technologies can address the aforementioned limitations of the screening of natural products. Examples of recent advances in the application of these technologies that have immediate impact on the discovery of novel drugs are: (i) development of a streamlined screening process for natural products, (ii) improved natural product sourcing, (iii) advances in organic synthetic methodologies, (iv) combinatorial biosynthesis, and (v) microbial genomics. Each of these technologies was discussed in details by Kin S. Lam in his article “New aspects of natural products in drug discovery”.

Approaches based on reverse pharmacology may also offer efficient platforms for herbal formulations; the impact of such approaches has recently been elaborately reviewed by Patwardhan and Vaidya. All these technologies at large have already shown an impact on the development of natural product leads arising out of varying natural sources inducing microbial and marine environments. The biosynthesis of natural products themselves can also be manipulated with the understanding of the genetics and biosynthesis pathways to yield new derivatives with possibly superior qualities and quantities. In addition to identifying new natural products, genome mining would certainly have an impact on the understanding and manipulation of the production of natural products.

Natural product compounds not only serve as drugs or templates for drugs, but in many instances lead to the discovery and better understanding of targets and pathways involved in the disease process. Elucidation of the anti-inflammatory mechanism of aspirin action led to the discovery of the cyclooxygenase isozymes COX-1 and -2, which are being used in the development of novel anti-inflammatory drugs. Again natural products
that interact with some other novel targets, such as the protein–protein complexes B-catenin in the WNT pathway and HIF-1/p300,\textsuperscript{169} have validated these anticancer targets and pathways. Natural products also create opportunities for additional drug targets to be identified and exploited in these pathways. Whereas synthetic drugs are typically the result of numerous structural modifications over the course of an extensive drug discovery program, a natural product can go straight from “hit” to drug in many situations. Microbial natural products are notable not only for their potential therapeutic activities, but also for the fact that they frequently have the desirable pharmacokinetic properties required for clinical development. Antibacterial agents erythromycin A, vancomycin, penicillin G, streptomycin and tetracycline, antifungal agents amphotericin B and griseofulvin, the cholesterol-lowering agent lovastatin, anticancer agents daunorubicin, mitomycin C and bleomycin, and immunosuppressants rapamycin, mycophenolic acid and cyclosporine A are just a few of the many microbial natural products that reached the market without requiring any chemical modifications. These examples clearly demonstrate the remarkable ability of microorganisms to produce drug-like small molecules.\textsuperscript{47}

5. Drug Discovery, Development and Approval Processes

The final launching of a natural product (NP)-based drug in the market is a multi-step phenomena starting from its discovery stage.\textsuperscript{170} Bioactivity-guided screening followed by isolation and characterization of a NP-lead molecule is the first step; after that the NP-lead enters into the drug discovery stage involving target identification and lead optimization. Lead optimization is an outcome of various steps including analysis (also involves QSAR and molecular modeling), design, synthesis and screening. In the drug discovery and development stages, the pharmacokinetics and pharmacodynamics including absorption, distribution, metabolism, excretion, and toxicity (ADMET) for the test drug molecule are thoroughly investigated. After analyzing all these data, the drug molecule may enter into the final development stage for drug delivery that involves proper production formulation, which is eventually considered for clinical trials. The whole process may be summarized in the flowchart (Fig. 1).\textsuperscript{170} Lead identification and optimization (involving medicinal and combinatorial chemistry), lead
Natural Products in Drug Discovery

Fig. 1. Flowchart for drug discovery, development and approval of a natural product-based drug.

development (including pharmacology, toxicology, pharmacokinetics, absorption, distribution, metabolism, and excretion (ADME) and drug delivery), and clinical trials all take considerable time. It has been estimated that the process of drug discovery usually takes an average period of 10 years and costs more than $800 million. Much of this time and money is spent on the numerous leads that are discarded during the drug discovery process. It is also estimated that only 1 in 5000 lead compounds will successfully advance through clinical trials and be approved for use.

For approval and marketing of a new drug, certain processes are to be followed: first, the Investigational New Drug (IND) application is submitted to the US Food and Drug Administration (FDA) or European Medicines Agency (EMEA) before commencement of clinical trials. Once clinical trials are successfully completed, the applicant files for a New Drug Application (NDA) in the US or Marketing Authorization Application (MAA) in Europe seeking the drug’s approval for marketing, to which the agency replies in the form of an “approval letter”, “non-approval letter” or “approvable letter”. An “approval letter” allows the applicant to begin marketing of product, while a “non-approval letter” rejects the application. An “approvable letter” informs the applicants that the agency have completed their scientific review and determined that the application can be approved pending resolution of minor deficiencies identified in the letter or during an inspection of the manufacturing facilities.
6. Natural Product-Based Drugs Approved During 2000–2010

A total of about 38 natural product-based drugs were approved and launched in the market during the period 2000 to 2010. This section deals with these approved drugs as per categorized diseases areas such as infectious disease area (15 drugs), oncology (7 drugs), neurological disease area (7 drugs), cardiovascular and metabolic disease area (4 drugs), diabetes (1 drug), and some other diseases areas (4 drugs). In addition, all these approved drugs are summarized in Table 1.

6.1. Infectious Disease Area

6.1.1. Arteether

Arteether (7; Artemotil®, Artecef®), the semi-synthetic derivative of artemisinin (8), is a potent antimalarial drug. Artemisinin, a natural endoperoxide sesquiterpene lactone, is the active chemical constituent of Artemisia annua L. (Asteraceae), a plant used in traditional Chinese medicine. Arteether belongs to the first-generation of artemisinin analogs obtained by derivatization at C-10, and such semi-synthetic derivatives were proved to be extremely active and more potent than the parent compound, acting rapidly as blood schizontocidal agent against the parasite’s (Plasmodium falciparum) asexual erythrocytic (red blood cell) stage as well as against the parasite blood-stage gametocytes (sexual stage), which can potentially help to reduce the rate of malaria transmission. Other derivatives of artemisinin are in various stages of clinical development as antimalarial drugs in Europe.
Table 1. Natural product (NP)-derived drugs launched since 2000 by year with reference to their lead compound, classification, therapeutic area and mechanism of action.

<table>
<thead>
<tr>
<th>Year</th>
<th>Generic name (Str. No.; trade name)</th>
<th>Lead compound (Str. No.)</th>
<th>Compound class</th>
<th>Classification</th>
<th>Producing organism/Origin</th>
<th>Disease area/Indication</th>
<th>Mechanism of action</th>
<th>Reference</th>
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<tr>
<td>2000</td>
<td>Arteether (7; Artemotil®, Artecef®, E-Mal®)</td>
<td>Artemisinin (8)</td>
<td>Endoperoxide sesquiterpene lactone</td>
<td>Semi-synthetic NP</td>
<td>Plant</td>
<td>Antimalarial</td>
<td>Acts as blood schizontocidal agent against the parasite’s asexual erythrocytic (red blood cell) stage and also against the parasite blood-stage gametocytes (sexual stage)</td>
<td>54, 171–179</td>
</tr>
<tr>
<td>2000</td>
<td>Gemtuzumab ozogamicin (30; Mylotarg®)</td>
<td>Calicheamicin (31)</td>
<td>Enediyne-type antibiotic</td>
<td>NP-derived Microbial</td>
<td>Anticancer</td>
<td>DNA-cleaving</td>
<td>319–331</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Bivalirudin (55; Angiomax®)</td>
<td>Hirudin</td>
<td>Peptide</td>
<td>Synthetic congener</td>
<td>Animal</td>
<td>Antithrombotic</td>
<td>Specific and reversible direct thrombin inhibitor (DTI)</td>
<td>479–491</td>
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<tr>
<td>2001</td>
<td>Caspofungin acetate (9; Cancidas®)</td>
<td>Pneumocandin B0</td>
<td>Lipopeptide</td>
<td>Semi-synthetic NP</td>
<td>Microbial</td>
<td>Antifungal</td>
<td>Inhibits fungal cell wall synthesis</td>
<td>180–186</td>
</tr>
<tr>
<td>2001</td>
<td>Ertapenem (10; Invanz®)</td>
<td>Thienamycin (11)</td>
<td>Carbapenem antibiotic</td>
<td>NP-derived Microbial</td>
<td>Antibacterial</td>
<td>Inhibits bacterial cell wall synthesis</td>
<td>187–197</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Cefditoren pivoxil (12; Spectracel®)</td>
<td>Cephalosporin</td>
<td>β-Lactum antibiotic</td>
<td>NP-derived Microbial</td>
<td>Antibacterial</td>
<td>Inhibits bacterial cell wall synthesis</td>
<td>198–200</td>
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Table 1. (Continued)

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<th>Year</th>
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<th>Mechanism of action</th>
<th>Reference</th>
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<tbody>
<tr>
<td>2001</td>
<td>Pimecrolimus (58; Elidel®)</td>
<td>Ascomycin</td>
<td>Macrolactum antibiotic</td>
<td>Semi-synthetic NP</td>
<td>Microbial</td>
<td>Inflammatory skin diseases and atopic dermatitis</td>
<td>Blocks T-cell activation</td>
<td>505–517</td>
</tr>
<tr>
<td>2002</td>
<td>Biapenem (14; Omegacin®)</td>
<td>Thienamycin (11)</td>
<td>Carbapenem-type β-lactum</td>
<td>NP-derived</td>
<td>Microbial</td>
<td>Antibacterial</td>
<td>Inhibits bacterial cell wall synthesis</td>
<td>201–210</td>
</tr>
<tr>
<td>2002</td>
<td>Amrubicin hydrochloride (32; Calsed®)</td>
<td>Doxorubicin (33)</td>
<td>Anthraquinone</td>
<td>NP-derived</td>
<td>Microbial</td>
<td>Anticancer</td>
<td>Inhibits topoisomerase II</td>
<td>208–210, 332–336</td>
</tr>
<tr>
<td>2002</td>
<td>Nitisinone (59; Orfadin®)</td>
<td>Leptospermine</td>
<td>2-[2-Nitro-4-(trifluoromethyl)benzoyl] cyclohexane-1,3-dione</td>
<td>NP-derived</td>
<td>Plant</td>
<td>Antityrosinaemia</td>
<td>Inhibits p-hydroxyphenyl-pyruvate dioxygenase (HPPD) activity</td>
<td>208–210, 518–524</td>
</tr>
<tr>
<td>2002</td>
<td>Galantamine hydrobromide (43; Reminyl®)</td>
<td>Galantamine (42)</td>
<td>Alkaloid</td>
<td>NP</td>
<td>Plant</td>
<td>Alzheimer’s disease</td>
<td>Inhibits the activity of acetylcholinesterase (AChE)</td>
<td>393–402</td>
</tr>
<tr>
<td>2003</td>
<td>Daptomycin (15; Cubicin™)</td>
<td>Daptomycin (15)</td>
<td>Lipopeptide</td>
<td>NP</td>
<td>Microbial</td>
<td>Antibacterial</td>
<td>Disrupts multiple aspects of bacterial cell membrane function</td>
<td>211–225</td>
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<tr>
<th>Year</th>
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<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Miglustat (60; Zavesca&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>1-Deoxynojirimycin (DNJ)</td>
<td>Iminosugar</td>
<td>Semi-synthetic</td>
<td>Microbial</td>
<td>Type 1 Gaucher disease (GD1)</td>
<td>Inhibits glucosylceramide synthase activity</td>
<td>215–217, 525–531</td>
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<tr>
<td>2003</td>
<td>Mycophenolate sodium (62; Myfortic&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Mycophenolic acid (61)</td>
<td>Fatty acid antibiotic</td>
<td>NP</td>
<td>Microbial</td>
<td>Immuno-suppression</td>
<td>Inhibits inosine monophosphate dehydrogenase (IMPDH) activity</td>
<td>215–217, 532–560</td>
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<tr>
<td>2003</td>
<td>Rosuvastatin calcium (56; Crestor&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Mevastatin</td>
<td>Statin</td>
<td>NP-derived</td>
<td>Microbial</td>
<td>Dyslipidemia</td>
<td>Inhibits the rate-limiting step in the formation of endogenous cholesterol by HMG-CoA reductase</td>
<td>215–217, 492–495</td>
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<td>2004</td>
<td>Telithromycin (16; Ketek&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Erythromycin A</td>
<td>14-Membered macrolide</td>
<td>Semi-synthetic</td>
<td>Microbial</td>
<td>Antibacterial</td>
<td>Blocks bacterial polypeptide chain growth</td>
<td>181, 182, 183, 226–230</td>
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<tr>
<td>2004</td>
<td>Apomorphine hydrochloride (44; Apokyn&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Morphine (43)</td>
<td>Alkaloid</td>
<td>Semi-synthetic</td>
<td>Plant</td>
<td>Parkinson’s disease</td>
<td>Potent dopamine receptor agonist</td>
<td>403–416</td>
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<tr>
<td>2004</td>
<td>Ziconotide (45; Prialt&lt;sup&gt;™&lt;/sup&gt;)</td>
<td>Ziconotide (45)</td>
<td>Peptide</td>
<td>NP</td>
<td>Animal</td>
<td>Pain</td>
<td>Acts as a selective N-type voltage-gated calcium channel blocker</td>
<td>417–428</td>
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<tr>
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<th>Disease area/ Indication</th>
<th>Mechanism of action</th>
<th>Reference</th>
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<tr>
<td>2004</td>
<td>Tiotropium bromide (54; Spiriva&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Atropine</td>
<td>Alkaloid</td>
<td>Semi-synthetic</td>
<td>Plant</td>
<td>Chronic obstructive pulmonary disease (COPD)</td>
<td>Inhibits M&lt;sub&gt;3&lt;/sub&gt; muscarinic receptors</td>
<td>475–478</td>
</tr>
<tr>
<td>2005</td>
<td>Tigecycline (19; Tygacil&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Tetracycline (17)</td>
<td>Tetracyclines</td>
<td>Semi-synthetic</td>
<td>Microbial</td>
<td>Antibacterial</td>
<td>Inhibits bacterial protein translation</td>
<td>231–238</td>
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<tr>
<td>2005</td>
<td>Doripenem (20; Fimibax&lt;sup&gt;®&lt;/sup&gt;; Doribax&lt;sup&gt;TM&lt;/sup&gt;)</td>
<td>Thienamycin (11)</td>
<td>Carbapenem-type β-lactam</td>
<td>NP-derived</td>
<td>Microbial</td>
<td>Antibacterial</td>
<td>Inhibits bacterial cell wall growth</td>
<td>239–247</td>
</tr>
<tr>
<td>2005</td>
<td>Micafungin (21; Mycamine&lt;sup&gt;®&lt;/sup&gt;; Funguard&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>FR901379</td>
<td>Macrocyclic lipopeptide-lactone</td>
<td>Semi-synthetic</td>
<td>Microbial</td>
<td>Antifungal</td>
<td>Inhibits fungal cell wall synthesis</td>
<td>186, 208–210, 248–260</td>
</tr>
<tr>
<td>2005</td>
<td>Fumagillin (22; Flisint&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Fumagillin (22)</td>
<td>Antibiotic</td>
<td>NP</td>
<td>Microbial</td>
<td>Antiparasitic</td>
<td>Inhibits intestinal microsporidiosis</td>
<td>261–278</td>
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<tr>
<td>2005</td>
<td>Dronabinol (46; Cannabidiol (47) (Sativex&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Dronabinol (46)</td>
<td>Cannabinoids</td>
<td>NPs</td>
<td>Plant</td>
<td>Pain</td>
<td>Suppresses neurotransmitter release</td>
<td>429–438</td>
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<tr>
<td>2005</td>
<td>Zotarolimus (53; Endeavor&lt;sup&gt;TM&lt;/sup&gt; stent)</td>
<td>Sirolimus (33)</td>
<td>Macrolide antibiotic</td>
<td>Semi-synthetic</td>
<td>Microbial</td>
<td>Cardiovascular surgery</td>
<td>Inhibits cell proliferation, preventing scar tissue formation and minimizes restenosis in angioplasty patients</td>
<td>467–474</td>
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<tr>
<td>Year</td>
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<td>Producing organism/Origin</td>
<td>Disease area/Indication</td>
<td>Mechanism of action</td>
<td>Reference</td>
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<tr>
<td>2006</td>
<td>Anidulafungin (23; Eraxis™/Ecalta™)</td>
<td>Echinocandin B (24)</td>
<td>Lipopeptide antibiotic</td>
<td>Semi-synthetic NP</td>
<td>Microbial</td>
<td>Antifungal</td>
<td>Inhibits fungal cell wall synthesis</td>
<td>279–293</td>
</tr>
<tr>
<td>2006</td>
<td>Exenatide (57; Byetta™)</td>
<td>Exenatide-4 (57)</td>
<td>A 39-amino-acid peptide</td>
<td>NP</td>
<td>Animal</td>
<td>Diabetes</td>
<td>Enhances glucose-dependent insulin secretion by the pancreatic β-cells, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying</td>
<td>496–504</td>
</tr>
<tr>
<td>2007</td>
<td>Temsirolimus (35; Torisel™)</td>
<td>Sirolimus (34)</td>
<td>Macrolide antibiotic</td>
<td>Semi-synthetic NP</td>
<td>Microbial</td>
<td>Anticancer</td>
<td>Leads to cell cycle arrest in the G1 phase, and inhibits tumor angiogenesis by reducing synthesis of vascular endothelial growth factor (VEGF)</td>
<td>337–350</td>
</tr>
</tbody>
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Table 1. (Continued)

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<th>Disease area/Indication</th>
<th>Mechanism of action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>Trabectedin (36; Yondelis™)</td>
<td>Trabectedin (36)</td>
<td>Tetrahydro-isoquinoline alkaloid</td>
<td>NP</td>
<td>Ascidian (marine animal)</td>
<td>Anticancer</td>
<td>Inhibits cell proliferation by disrupting the cell cycle</td>
<td>351–362</td>
</tr>
<tr>
<td>2007</td>
<td>Ixabepilone (40; Ixempra™)</td>
<td>Epothilone B (38)</td>
<td>Macrolide antibiotic</td>
<td>NP-derived</td>
<td>Microbial</td>
<td>Anticancer</td>
<td>Binds directly to β-tubulin subunits on microtubules, ultimately leading to cell death</td>
<td>363–374</td>
</tr>
<tr>
<td>2007</td>
<td>Lisdexamfetamine (48; Vyvanse®)</td>
<td>Amphetamine (49)</td>
<td>Amine</td>
<td>NP-derived</td>
<td>Plant</td>
<td>Attention deficit hyperactivity disorder (ADHD)</td>
<td>Increases the release of amphetamine-type monoamines into the extraneuronal space, thereby improving the effect of ADHD</td>
<td>439–448</td>
</tr>
<tr>
<td>2008</td>
<td>Methylaltrexone (50; Relistor®)</td>
<td>Naltrexone (51)</td>
<td>Alkaloid</td>
<td>NP-derived</td>
<td>Plant</td>
<td>Opioid-induced constipation and pain</td>
<td>Blocks peripheral opioid receptors, and acts as an antagonist</td>
<td>449–459</td>
</tr>
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<th>Mechanism of action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Capsaicin (52; Qutenza®)</td>
<td>Capsaicin (52)</td>
<td>Vanilloid</td>
<td>NP</td>
<td>Plant/Pain</td>
<td>Binds to the ion channel receptor vanilloid receptor subtype 1 (VR 1)</td>
<td>460–466</td>
</tr>
<tr>
<td>2009</td>
<td>Telavancin (28; Vibativ™)</td>
<td>Vancomycin (27)</td>
<td>Antibiotic</td>
<td>Semi-synthetic Microbial</td>
<td>Antibacterial</td>
<td>Inhibits bacterial cell wall synthesis</td>
<td>304–311</td>
</tr>
<tr>
<td>2009</td>
<td>Everolimus (40; Afinitor®)</td>
<td>Sirolimus (34)</td>
<td>Macrolide antibiotic</td>
<td>Semi-synthetic NP</td>
<td>Microbial</td>
<td>Anticancer</td>
<td>Inhibits mTOR kinase activity</td>
</tr>
<tr>
<td>2009</td>
<td>Romidepsin (41; Istodax®)</td>
<td>Romidepsin (41)</td>
<td>Depsipeptide</td>
<td>NP</td>
<td>Microbial</td>
<td>Anticancer</td>
<td>Inhibits histone deacetylase (HDAC)</td>
</tr>
<tr>
<td>2010</td>
<td>Aztreonam lysine (29; Cayston™)</td>
<td>Aztreonam (29)</td>
<td>Monobactam antibiotic</td>
<td>NP-derived</td>
<td>Microbial</td>
<td>Antibacterial</td>
<td>Inhibits bacterial cell wall synthesis</td>
</tr>
</tbody>
</table>
The central Drug Research Institute (CDRI) in collaboration with CIMAP (Central Institute of Medicinal and Aromatic Plants), Lucknow, India have also conducted extensive clinical trials with arteether that was found not only to be very safe but also proved to be a fast-acting blood schizontocidal agent. CDRI has licensed the drug to Themis Chemicals Ltd., Mumbai which is marketing it under the trade name “E-Mal®” as an injectable formulation. The Drugs Controller General (India) has allowed the use of the drug exclusively in hospitals and nursing homes. The drug is indicated for use only in severe \textit{P. falciparum}-induced-malaria including cerebral malaria as a second-line treatment for chloroquine-resistant cases. It is not recommended to be used as a first-line treatment against malaria to avoid against overuse, which may lead to the emergence of resistance against this drug once again.\cite{179}

6.1.2. Caspofungin acetate

Caspofungin acetate (9; Cancidas®, Merck, 2001) is a semi-synthetic antifungal lipopeptide compound derived from pneumocandin B\textsubscript{0}, a fermentation product of \textit{Glarea lozoyensis}. The drug inhibits the synthesis of the glucose homopolymer $\beta$-(1,3)-D-glucan, an essential component...
of the cell wall of many fungi but absent in mammals. The noncompetitive inhibition of β-(1,3)-D-glucan synthase by caspofungin interferes with fungal cell wall synthesis, leading to osmotic instability and death of the fungal cell.\textsuperscript{180–184}

6.1.3. Ertapenem

Ertapenem (10; Invanz\textsuperscript{TM}, Merck, 2001) is a new 1β-methylcarbapenem antibiotic derived from thienamycin (11), isolated from \textit{Streptomyces cattleya}.\textsuperscript{181,187–191} The drug shows promising broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria, such as clinically relevant Enterobacteriaceae including \textit{Escherichia coli}, \textit{Klebsiella} species, \textit{Citrobacter} species, \textit{Enterobacter} species, \textit{Morganella morganii}, \textit{Proteus} species, and \textit{Serratia marcescens}.\textsuperscript{190,192–195} Ertapenam is licensed for use in adults and has been marketed by Merck as “Invanz\textsuperscript{TM}” since 2001; later in 2005, it was licensed for use in children of more than 3 months of age. The antibiotic inhibits bacterial cell wall synthesis by binding to specific penicillin-binding proteins (PBPs). It is highly stable against most β-lactamases including AmpC β-lactamases and extended-spectrum β-lactamases with the exception of metallo-β-lactamases.\textsuperscript{190,195–197}

6.1.4. Cefditoren pivoxil

Cefditoren pivoxil (12; Spectracef\textsuperscript{®}; TAP Pharmaceuticals, 2001) is an oral prodrug of cefditoren (13), a derivative of cephalosporin isolated from \textit{Cephalosporium} species. The prodrug is readily hydrolyzed by intestinal esterases to the microbiologically active cephalosporin cefditoren (13)
Cefditoren pivoxil (Spectracef\textsuperscript{TM}) (12)

\[ \text{Esterase (hydrolysis)} \]

\[ \begin{align*}
\text{Cefditoren pivoxil (Spectracef\textsuperscript{TM}) (12)} \\
\text{Cefditoren (13)}
\end{align*} \]
exhibiting a broad spectrum of activity against both Gram-positive and
Gram-negative bacteria, and is stable to hydrolysis in the presence of a
variety of β-lactamases. Cefditoren pivoxil is approved for use in the
treatment of acute exacerbations of chronic bronchitis (AECB), mild-to-
moderate community-acquired pneumonia (CAP), acute maxillary
sinusitis, acute pharyngitis/tonsillitis, and uncomplicated skin and skin
structure infections in adult and adolescent patients. Thus, cefditoren
pivoxil is a good option for the treatment of adult and adolescent patients
with specific respiratory tract or skin infections, particularly if there is
concern about *Streptococcus pneumoniae* with decreased susceptibility to
penicillin, or β-lactamase-mediated resistance among the common com-
community-acquired pathogens.\textsuperscript{198–200}

Cefditoren bears a 2-aminothiazole methoxime ring that has been found
to be responsible for its Gram-negative activity, while the methylthiazole-
substituted vinyl group at C-3 offers antibacterial activity against
Gram-positive bacteria. It has been observed that the hydrophilic carboxyl
group of the parent drug makes cefditoren orally inactive due to poor per-
meation across the intestinal mucosa; hence, esterification of the polar
carboxyl group increases lipophilicity and allows intestinal absorption to
occur. That is, cefditoren pivaloyl methyl ester (12) is not biologically
active, but after absorption, esterases readily hydrolyze the prodrug to the
biologically active cefditoren (13).\textsuperscript{200}

6.1.5. Biapenem

Biapenem (14; Omegacin\textsuperscript{®}; Wyeth Lederle Japan, 2002) is a new ana-
log of carbapenem based on thienamycin, isolated from *Streptomyces
cattleya*; the antibacterial drug is found to be effective against both
Gram-negative and Gram-positive bacteria including the species that
produce β-lactamases. The early carbapenems (e.g. imipenem) are
unstable to hydrolysis by human renal dihydropeptidase (DHP)-I
and require co-administration with a DHP-I inhibitor (e.g. cilastatin).
On the contrary, biapenem (14) is found to be more stable to hydroly-
sis by human renal DHP-I than imipenem, meropenem, and panipenem,
and can thus be administered as a single agent without a DHP-I
inhibitor.\textsuperscript{201–210}
6.1.6. Daptomycin

Daptomycin (15; Cubicin™; Cubist Pharmaceuticals, 2003), a cyclic lipopeptide antibacterial agent derived from *Streptomyces roseosporus*, was approved for the treatment of complicated skin and skin structure infections (cSSSIs) caused by Gram-positive pathogens, including vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus* and right-sided *S. aureus* endocarditis. Daptomycin has a unique mechanism of action that results in the disruption of multiple aspects of bacterial cell membrane function. It appears to bind to the membrane and cause rapid depolarization, resulting in a loss of membrane potential, leading
to the inhibition of protein, DNA and RNA synthesis, which results in bacterial cell death. The rapid bactericidal activity of daptomycin makes it an attractive antibiotic for serious Gram-positive infections.211–225

6.1.7. Telithromycin

Telithromycin (16; Ketek®, Aventis, 2004) is a semi-synthetic derivative of the 14-membered macrolide, erythromycin A, isolated from Saccharopolyspora erythraea, and retains the macrolactone ring as well as a D-desosamine sugar moiety. It is the first approved ketolide, developed by Sanofi-Aventis in Phases II/III trials in 1998, that received approval from the FDA in April 2004 against respiratory infections. The drug exhibits an antibacterial effect on respiratory tract pathogens resistant to other macrolides. Telithromycin (16) displays bactericidal activity by blocking the progression of the growing polypeptide chain by binding with the peptidyltransferase site of the bacterial 50S ribosomal subunit.180,181,183,226–230

6.1.8. Tigecycline

Tigecycline (19, Tygacil®; Wyeth, 2005) is the 9-tert-butyl-glycylamido derivative of minocycline (18), which is in turn semi-synthetically derived
from the natural product tetracycline (17) isolated from *Streptomyces aureofaciens*. It is among one of the new generation antibiotics known as glycyclines; it contains a centralized four-ring carbocyclic skeleton substituted at the D-9 position, thus conferring broad spectrum activity. Tigecycline exhibited antibacterial activity typical of other tetracyclines, but with more potent activity against tetracycline-resistant organisms. Tigecycline is only utilized in an injectable formulation for clinical use, unlike currently marketed tetracyclines that are available in oral dosage forms. The drug (19) connects with 30S ribosome and hinders amino-acyl tRNA molecules moving to the A site of the ribosome, thus inhibiting protein translation. Tigecycline (19) was developed by Wyeth and was approved in June 2005 by the FDA for use against intra-abdominal and complicated skin and skin structure infections (cSSSIs). Since May 2006, tigecycline (19) has been approved in Europe and later in October 2007, a supplemental NDA for community-acquired pneumonia (CAP) to the FDA was submitted.

6.1.9. *Doripenem*

*Doripenem* (20; Finibax®/Doribax®; Shionogi Co. Ltd., 2005; Johnson & Johnson, 2007), a synthetic carbapenem-type β-lactam, has appeared to be an ultra-broad spectrum injectable antibiotic. It was launched in Japan by Shionogi Co. Ltd. in the year 2005 as a broad antibacterial spectrum. In October 2007, Johnson & Johnson (J&J) (formerly Peninsula Pharmaceuticals) obtained formal FDA approval for the use of doripenem
intra-abdominal and urinary tract infections, including pyelonephritis.\textsuperscript{244,245} When doripenem is absorbed into the body, the drug takes effect by eliminating the initial bacteria causing the infection. Primarily, doripenem decreases the process of cell wall growth, which eventually leads to elimination of the infectious cell bacteria altogether. The use of doripenem (20) for treatment of hospital-acquired (nosocomial) pneumonia (HAP) is under FDA review, while in Europe, treatment of HAP and complicated urinary tract infections are under review.\textsuperscript{72,246,247}

6.1.10. \textit{Micafungin}

Micafungin (21; Mycamine\textsuperscript{®}/Funguard\textsuperscript{®}; Astellas Pharma/Fujisawa, Japan, 2002, 2005), is a semi-synthetic derivative of FR901379 that was first launched by Fujisawa in Japan in 2002 as a potent antifungal agent.\textsuperscript{208–210} This echinocandin-type compound exhibited good antifungal activity against a broad range of \textit{Candida} species, including azole-resistant strains, and \textit{Aspergillus} species, during \textit{in vitro} and animal studies.\textsuperscript{186} Micafungin is indicated for the treatment of candidemia, acute disseminated candidiasis, candida peritonitis, abscesses and esophageal candidiasis.\textsuperscript{248–251} It received final approval from the US Food and Drug Administration on March 2005 and gained approval in the European Union on April 25, 2008. The drug (21) inhibits the production of 1,3-β-D-glucan, an essential polysaccharide component of fungal cell wall; this decreased glucan production leads to osmotic instability and thus cellular lysis;\textsuperscript{248–260} since January 2008, micafungin has been approved for the prophylaxis of \textit{Candida} infections in patients undergoing hematopoietic stem cell transplantation.
6.1.11. Fumagillin

Fumagillin (22; Flisint®; Sanofi-Aventis, 2005) was first isolated in 1949 from Aspergillus fumigatus261 and used shortly thereafter to treat intestinal amoebiasis;262–264 this antimicrobial agent is capable of inhibiting the proliferation of endothelial cells. In September 2005, France approved the use of fumagillin (22) as a potent antibiotic against intestinal microsporidiosis; this is a disease caused by the spore-forming unicellular parasite Enterocytozoon bieneusi, which is of major concern to immunocompromised patients as it can cause chronic diarrhea.265–273 In addition, semi-synthetic derivatives of fumagillin (22) with anti-angiogenic activity have undergone clinical evaluation for the treatment of cancer.72 Fumagillin can block blood vessel formation by binding to an enzyme called methionine aminopeptidase-2 (MetAP-2), and for this reason, the compound, together with semi-synthetic derivatives, are investigated as
an angiogenesis inhibitor in the treatment of cancer and related disease areas.\textsuperscript{274–278}

6.1.12. Anidulafungin

Anidulafungin (23; Eraxis\textsuperscript{TM} in US/Ecalta\textsuperscript{TM} in Europe, Pfizer, 2006), finds use against invasive and esophageal candidiasis and candidemia;\textsuperscript{279–281} the drug is a semi-synthetic derivative of the fungal metabolite echinocandin B (24).\textsuperscript{282} The drug was originally developed by Eli Lilly and licensed to Vicuron Pharmaceuticals, which was further purchased by
Pfizer in June 2005; Pfizer gained FDA approval in February 21, 2006 (Eraxis™ in the US) and EMEA approval (Ecalta™ in Europe) in July 2007. Anidulafungin inhibits enzyme complex 1,3-β-D-glucan synthase, thereby inhibiting fungal 1,3-β-D-glucan synthesis; this leads to the lysis of the fungal cell wall, and cell death. Glucan synthase is not present in mammalian cell walls and therefore is an attractive target for antifungal activity.

6.1.13. Retapamulin

Retapamulin (26; Altabax™ in the US and Altargo™ in Europe; GlaxoSmithKline, 2007) received FDA approval in April 2007 and the European Medicines Agency (EMEA) approval in June 2007 for its topical use as 1% retapamulin ointment against bacterial infections. The drug is a semi-synthetic derivative of the fungal metabolite pleuromutilin (25), the first among pleuromutilin antibiotics developed by GlaxoSmithKline for topical treatment of impetigo caused by Gram-positive Staphylococcus aureus or Streptococcus pyogenes. Pleuromutilin (25) was found to bind to peptidyl transferase and exhibits antibacterial activity by inhibiting protein synthesis in bacteria. Retapamulin (26) also exerts its antibacterial potential specifically as a protein synthesis inhibitor. The medication selectively inhibits bacterial protein synthesis by interacting at
a site on the 50S subunit of the bacterial ribosome through an interaction that differs from other antibiotics.\textsuperscript{296,297,301}

6.1.14. Telavancin

Telavancin (28; Vibativ\textsuperscript{TM}; Theravance/Astellas Pharmaceuticals, 2009), was discovered by Theravance as an antibacterial agent, and was developed in partnership with Astellas.\textsuperscript{304–307} Telavancin (28), a semi-synthetic derivative of vancomycin (27), inhibits bacterial growth by binding to
bacterial peptidoglycan precursors termini, D-Ala-D-Ala; it shows dual mode of action though disruption of plasma barrier membrane functions by depolarization in addition to inhibition of cell wall synthesis.\textsuperscript{308} Theravance submitted an NDA in December 2006 and an MAA in May 2007 for the use of telavancin (28) against Gram-positive complicated skin and skin structure infections (cSSSIs) and methicillin-resistant \textit{Staphylococcus aureus} (MRSA) that was approved in September 2009 by the FDA.\textsuperscript{309–311} Theravance also submitted telavancin (28) to the FDA in a second indication against nosocomial pneumonia or hospital-acquired pneumonia (HAP). In November 2009, the FDA released a complete response letter to Theravance for telavancin (28) NDA against nosocomial pneumonia.\textsuperscript{311}

6.1.15. \textit{Aztreonam lysine}

\textit{Aztreonam lysine} (29; Cayston\textsuperscript{TM}; Gilead Sciences, 2010), an inhaled lysine salt formulation of monobactam aztreonam, has been evaluated by Gilead in various Phase III trials against cystic fibrosis (CF) patients having a pulmonary infection of the Gram-negative bacteria \textit{Pseudomonas aeruginosa}.\textsuperscript{312–317} In February 2010, the FDA approved the use of Temsirolimus (35) in CF patients, however its safety and efficacy is yet to be established in pediatric patients or \textit{Burkholderia cepacia} colonized

\begin{center}
\includegraphics[width=0.5\textwidth]{Aztreonam.png}
\end{center}

\textit{Aztreonam (29)
patients. Aztreonam binds to penicillin-binding proteins of susceptible bacteria, leading to the inhibition of bacterial cell wall synthesis and cell death.

6.2. **Oncology**

6.2.1. *Gemtuzumab ozogamicin*

Gemtuzumab ozogamicin (30; Mylotarg®; Wyeth, 2000), the first and approved antibody–anticancer conjugate, was co-developed by Wyeth and UCB Pharma and launched in 2000 for the treatment of refractory acute myeloid leukaemia. Gemtuzumab ozogamicin (30) consists of N-acetyl-calicheamicin dimethyl hydrazide (CalichDMH), a derivative of the enediyne natural product calicheamicin (31), linked through a pH-labile hydrazone moiety to a recombinant humanized IgG4 k antibody. Mylotarg®, a prodrug of calicheamicin bound to the anti-CD33 monoclonal antibody, is cleaved by lysosomes in the cells to release calicheamicin. Calicheamicin is a hydrophobic member of the enediyne family of DNA-cleaving antibiotics and is effective in the treatment of...
patients with acute myeloid lymphoma. The calicheamicins (also known as the LL-E3328 antibiotics) were discovered from fermentation products produced by *Micromonospora echinospora* ssp. *calichensis*; calicheamicin (32) is an extremely potent cytotoxin that binds in the minor groove of DNA causing double strand DNA breakage. In the US, the drug was approved by the FDA in 2001 for use in patients over the age of 60 with relapsed acute myelogenous leukemia (AML), or those who are not considered candidates for standard chemotherapy.

6.2.2. *Amrubcin hydrochloride*

Amrubcin hydrochloride (33; Calsed®, Sumitomo Pharmaceuticals Co, 2002, Japan), a derivative of doxorubicin (34), isolated from *Streptomyces peucetius* var *caesius*, showed activity comparable to that of doxorubicin on transplantable animal tumors, including P388 leukemia, sarcoma 180, and Lewis lung carcinoma, and exhibited more potent antitumor activity against human tumor xenografts of breast, lung, and gastric cancer. The drug converts to its active form in the body and acts as an inhibitor of topoisomerase II, thereby finding an application in the treatment of lung cancer. It has been marketed in Japan since 2002 by Sumitomo Pharmaceuticals under the brand name Calsed®.
6.2.3. Temsirolimus

Temsirolimus (35; Torisel™, CCI-779; Wyeth, 2007), a semi-synthetic derivative of sirolimus (34), is an intravenous drug for the treatment of renal cell carcinoma (RCC)\(^{337-340}\) developed by Wyeth Pharmaceuticals.
and approved by the US Food and Drug Administration (FDA) in May 2007, and was also approved by the European Medicines Agency (EMEA) in November 2007. Sirolimus (34), a macrolide antibiotic, was first discovered as a product of the bacterium *Streptomyces hygroscopicus* in a soil sample from Easter Island.341 Temsirolimus (35) has been found to be a specific inhibitor of mTOR (mammalian target of rapamycin) and interferes with the synthesis of proteins that regulate proliferation, growth, and survival of tumor cells.342–345 Treatment with temsirolimus leads to cell cycle arrest in the G1 phase, and also inhibits tumor angiogenesis by reducing synthesis of vascular endothelial growth factor (VEGF).346–350

6.2.4. *Trabectedin*

Trabectedin (36; Yondelis™, ecteinasidin-743, ET-743; Zeltia and Johnson and Johnson, 2007), a tetrahydroisoquinoline alkaloid produced by the ascidian *Ecteinascidia turbinata*,351–356 received approval for its sale in Europe, Russia and South Korea by Zeltia and Johnson and Johnson under the brand name Yondelis™ for the treatment of advanced soft tissue sarcoma (STS).357–358 Trabectedin (36) binds to the minor groove of DNA and inhibits cell proliferation by disrupting the cell cycle.359,360 The biological mechanism of action is believed to involve the production of superoxides near the DNA strand, resulting in DNA backbone cleavage and cell apoptosis. The actual mechanism is not yet known, but is believed to proceed from the reduction of molecular oxygen into superoxide via an unusual auto-redox reaction on a hydroxyquinone moiety of the compound following. There is also some speculation the compound becomes “activated” into its reactive oxazolidine form.

In September 2007, the EMEA approved the use of trabectedin against ovarian cancer (OC) and STS. In November 2009, Yondelis™ received its second marketing authorization from the European Commission for its administration in combination with pegylated liposomal doxorubicin (Doxil, Caelyx) for the treatment of women with relapsed ovarian cancer; presently, trabectedin (36) is under Phase II trials for the treatment of paediatric sarcomas as well as breast and prostate cancers.72 The European Commission and the US Food and Drug Administration (FDA) have granted orphan drug status to trabectedin for soft tissue sarcomas and
ovarian cancer. Trabectedin (36) is produced commercially semi-synthetically from the eubacterium-derived cyanosafacin B (37).361,362

6.2.5. Ixabepilone

Ixabepilone (38; Ixempra™, BMS-247550; Bristol-Myers Squibb, 2007), a semi-synthetic derivative of epothilone B (39) produced by Sorangium cellulosum, was developed by Bristol-Myers Squibb (BMS) as an anti-cancer drug (administered through injection) that binds directly to β-tubulin subunits on microtubules, leading to suppression of microtubule dynamics, blocking of cells in the mitotic phase and ultimately leading to
cell death. In October 2007, the FDA approved ixabepilone, for the treatment of aggressive metastatic or locally advanced breast cancers that no longer respond to currently available chemotherapies, to be used as a monotherapy and as combination therapy with Xeloda against breast cancer patients who are resistant to standard therapy.

6.2.6. Everolimus

Everolimus (40; Afinitor®, Novartis, 2009), a rapamycin analog, is the 42-O-(2-hydroxyethyl) derivative of sirolimus (34), and is marketed as an immunosuppressant by Novartis under the tradename Afinitor® for use in advanced renal cell carcinoma. In March 2009, the FDA approved everolimus (40) for use against advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. The drug works similarly to sirolimus as an inhibitor of mTOR (mammalian target of rapamycin), a serine–threonine kinase, downstream of the PI3K/AKT pathway. Everolimus (40) binds to an intracellular protein, FKBP-12, resulting in an inhibitory
complex formation and inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP), downstream effectors of mTOR, involved in protein synthesis. In addition, everolimus inhibited the expression of hypoxia-inducible factor (e.g. HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by the drug has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in vitro and/or in vivo studies. The spectrum of kinase inhibition, therefore its mechanism of anticancer activity, is different from that of Pfizer’s Sutent (sunitinib malate) or Onyx Pharmaceuticals’ Nexavar (sorafenib).

Much research has also been conducted on everolimus and other mTOR inhibitors for use in a number of cancers. The FDA has recently approved everolimus for organ rejection prophylaxis on April 22, 2010. A Phase II trial reports it is effective in the treatment of subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis. In Oct 2010, the FDA approved its use in SEGA unsuitable for surgery. As of Oct 2010 Phase III trials are under way in breast cancer, gastric cancer, hepatocellular carcinoma, pancreatic neuroendocrine tumors (NET), and lymphoma.

6.2.7. Romidepsin

Romidepsin (41; Istodax®, Gloucester Pharmaceuticals, 2009), a naturally occurring histone deacetylase (HDAC) inhibitor obtained from the bacteria Chromobacterium violaceum, was developed and evaluated by Gloucester Pharmaceuticals in various Phase I/II trials sponsored by the National Cancer Institute (NCI) to use against cutaneous and peripheral T-cell lymphoma (TCL). In November 2009, romidepsin (41) was approved by the FDA under the trade name Istodax® against selective cutaneous TCL patients that have received a minimum of one prior systemic therapy, while three Phase II trials for multiple myeloma and peripheral TCL are still recruiting patients. Romidepsin acts as a histone deacetylase (HDAC) inhibitor; HDACs catalyze the removal of acetyl groups from acetylated lysine residues in histones, resulting in the modulation of gene expression. HDACs also deacetylate non-histone proteins,
such as transcription factors. *In vitro*, romidepsin causes the accumulation of acetylated histones, and induces cell cycle arrest and apoptosis of some cancer cell lines with IC$_{50}$ values in the nanomolar range. The mechanism of the antineoplastic effect of romidepsin observed in nonclinical and clinical studies has not been fully characterized.$^{383-391}$ In January 2010, Celgene Pharmaceuticals completed the acquisition of Gloucester Pharmaceuticals.$^{392}$

### 6.3. Neurological Diseases

#### 6.3.1. Galantamine hydrobromide

Galantamine hydrobromide (42; Reminyl®, Janssen, 2002), is used for the treatment of mild to moderate Alzheimer’s disease and various other memory impairments, particularly those of vascular origin.$^{208-210,393-397}$ It is an Amaryllidaceae alkaloid obtained from *Galanthus nivalis* that has been used traditionally in Bulgaria and Turkey for neurological conditions.$^{398,399}$ Galantamine (42) is a competitive, reversible cholinesterase inhibitor. It reduces the action of acetylcholinesterase (AChE) and therefore tends to increase the concentration of acetylcholine in the brain. It is hypothesized that this action might relieve some of the symptoms of Alzheimer’s. It was launched onto the market as a selective acetylcholinesterase inhibitor for Alzheimer’s disease treatment, slowing the process of neurological degeneration by inhibiting acetylcholinesterase
as well as binding to and modulating the nicotinic acetylcholine receptor.\textsuperscript{54,401,402} Approximately 75\% of a dose of galantamine is metabolized in the liver. \textit{In vitro} studies have shown that hepatic CYP2D6 and CYP3A4 are involved in galantamine metabolism. Galantamine was launched in Austria as Nivalin\textsuperscript{®} in 1996 and as Reminyl\textsuperscript{®} in the rest of Europe and the US in 2002.\textsuperscript{72}

6.3.2. \textit{Apomorphine hydrochloride}

Apomorphine hydrochloride (44; Apokyn\textsuperscript{®}; Bertek, 2004), is a semi-synthetic derivative of opium alkaloid morphine (43) isolated from poppy (\textit{Papaver somniferum}), and it has long been known for its erectile activity at the effective dose of 2–6 mg; physicians discovered the effect over 100 years ago, but found the drug, at a much higher dose (ca. 200 mg), to be more suitable for poison victims as an emetic because it also causes serious nausea and vomiting.\textsuperscript{61} Apomorphine exerts its erectile effect at the central nervous system; the drug has been found to be a non-selective dopamine agonist which activates both D\textsubscript{1}-like and D\textsubscript{2}-like
receptors, with some preference for the latter subtypes. This potent dopamine receptor agonist is used to treat Parkinson’s disease, a chronic neurodegenerative disease caused by the loss of pigmented mesostriatal dopaminergic neurons linking the substantia nigra (pars compacta) to the neostriatum (caudate nucleus and putamen); subcutaneous apomorphine is currently used for the management of sudden, unexpected and refractory levodopa-induced off states in fluctuating Parkinson’s disease. Apomorphine has been reported to be an inhibitor of β-amyloid fibril formation, and may thus have potential as a therapeutic for Alzheimer’s disease.

### 6.3.3. Ziconotide

Ziconotide (45; Prialt™; Elan, 2004), is a non-opioid and non-NSAID analgesic agent used for the amelioration of severe and chronic pain. It is a synthetic version of the N-type calcium channel blocker ω-conotoxin MVIIA, a peptide first isolated from the venom of cone snail (Conus magus) venom. In December 2004, the Food and Drug Administration approved ziconotide (45) when delivered as an infusion into the cerebrospinal fluid using an intrathecal pump system for the treatment of severe chronic pain, and is currently used in pain management. Ziconotide (45), the synthetic form of peptide ω-conotoxin, acts as a selective N-type voltage-gated calcium channel blocker. This action inhibits the release of pro-nociceptive neurochemicals like glutamate, calcitonin gene-related peptide (CGRP), and substance P in the brain and spinal cord, resulting in pain relief. In 2005, Elan launched ziconotide (45) in US and Europe for the treatment of patients suffering from chronic pain. Rights for marketing ziconotide (Prialt™) in Europe was obtained by Eisai in March 2006.

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\text{H}_2\text{N-CKKGAKCSRLMYDCCTGSCRSGKC-CONH}_2
\]

Ziconotide (45)
6.3.4. Dronabinol and Cannabidol

Dronabinol (46) and cannabidol (47) (Sativex®; GW Pharmaceuticals, 2005), as a mixture formulation named as Sativex (tradename), the world’s first pharmaceutical prescription medicine derived from the cannabis plant (*Cannabis sativa* L.). The drug (a mixture of dronabinol (46) and cannabidol (47)), was launched in Canada in April 2005 for neuropathic pain relief in multiple sclerosis, and was also approved by Health Canada in August 2007 as an adjunctive analgesic for severe pain in advanced cancer patients by reducing the use of breakthrough opioid medications. Sativex® has also been found to reduce pain efficiently in patients with advanced cancer, and has been recommended by FDA to enter directly in Phase III trials. In November 2009, GW Pharmaceuticals disclosed that recruitment for Phase II/III cancer pain trial of Sativex® has been completed. In March 2010, GW Pharmaceuticals provided an update on the progress of regulatory submission for Sativex® oromucosal spray for the treatment of the symptoms of spasticity due to multiple sclerosis.

Mammalian tissues contain at least two types of cannabinoid receptors, CB₁ and CB₂. The active cannabinoid ingredients of Sativex® react with the cannabinoid receptors. A receptor on a brain cell can stick or “bind” certain substances for a while. If this happens, it has an effect on the cell and the nerve impulses it produces, which causes a “dimming down” of the symptoms of spasticity. In patients who respond to Sativex®, it is this effect that helps to improve their symptoms of spasticity and to help them cope better with their usual daily activities. It has been hypothesised that these endogenous cannabinoids function in the CNS as “retrograde synaptic messengers” being released from postsynaptic
neurons and traveling backwards across synapses to activate presynaptic CB₁ receptors and to suppress neurotransmitter release. The mechanisms, by which the biological actions of endogenous cannabinoids are terminated, have not been fully evaluated. However, it appears likely that they are removed from the extracellular space by tissue uptake and that intracellular metabolism via an enzyme system, fatty acid amide hydrolase (FAAH), is also involved.⁴³⁶–⁴³⁸

### 6.3.5. Lisdexamfetamine

Lisdexamfetamine (48; L-lysine-D-amphetamine, NRP104; Vyvanse®; New River and Shire Pharmaceuticals, 2007), a psychostimulant prodrug (sold under the tradename Vyvanse®) of the phenethylamine and amphetamine chemical classes, consists of dextroamphetamine coupled with the essential amino acid L-lysine. Lisdexamfetamine (48) is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children 6–12 years and in adults (April 2008) as an integral part of a total treatment program that may include other measures (i.e. psychological, educational, and social). Attention-deficit hyperactivity disorder (ADHD), a neurodevelopmental disorder in which dopaminergic and noradrenergic neurotransmission are supposed to be dysregulated, is primarily characterized by the co-existence of attentional problems and hyperactivity.⁴³⁹–⁴⁴¹

Methylphenidate and amphetamines have been used for ADHD management for many years but due to abuse potentials, these drugs are controlled substances.⁴⁴² Lisdexamfetamine itself is inactive and acts as a prodrug to dextroamphetamine upon cleavage of the lysine portion of the molecule. It was developed for the intention of creating a longer-lasting and more-difficult-to-abuse version of dextroamphetamine, as the requirement
of conversion into dextroamphetamine in the gastrointestinal tract increases its duration and renders it ineffective upon any other ingestion routes than the oral route. Intravenously administered lisdexamfetamine initially produced effects similar to placebo, and therefore intravenous abuse is completely ineffective; there is no increased onset or effect as occurs with intravenous administration of dextroamphetamine compared to oral use of the same. In February 2007, New River and Shire Pharmaceuticals obtained FDA approval for use of lisdexamfetamine (48) to help ADHD, and in April 2007, Shire bought New River.

Vyvanse®, the prodrug of dextroamphetamine, is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of such monoamines into the extra-neuronal space. Norepinephrine and dopamine contribute to maintaining alertness, increasing focus, and sustaining thought, effort, and motivation. However, the exact therapeutic action in ADHD is not known.

6.3.6. Methylnaltrexone

Methylnaltrexone (50: Relistor®, Wyeth, 2008), an N-methyl derivative of naltrexone (51), contains a charged tetravalent nitrogen atom and remains unable to cross the blood–brain barrier (BBB), and so has antagonist effects throughout the body. Methylnaltrexone (50) binds to the same receptors as opioid analgesics such as morphine, but it acts as an antagonist, blocking the effects of those analgesics, specifically the constipating effects on the gastrointestinal tract. Furthermore, as methylnaltrexone cannot cross the blood–brain barrier, it does not reverse...
the pain-killing properties of opioid agonists or cause withdrawal symptoms. This is the primary difference that makes methylnaltrexone behave differently from naltrexone (51), an approved drug used in management of alcohol and opioid dependence.452–459

Methylnaltrexone (50), thus, blocks peripheral opioid receptors activated by opioids administered for pain relief that cause side effects such as constipation, urinary retention and severe itching. In May 2007, Wyeth and Progenics filed an NDA for subcutaneous doses of methylnaltrexone (50) for the treatment of opioid-induced constipation (OIC) and other pain indications. In March 2008, Wyeth and Progenics reported that methylnaltrexone (50) failed in two Phase III trials for intravenous use in the treatment of post-operative ileus. In April 2008, Progenics and Wyeth announced that Health Canada and the FDA have approved methylnaltrexone (50) for the treatment of OIC. Since May 2009, an oral formulation of methylnaltrexone (50) is under Phase II trials against OIC in chronic pain. After acquisition of Wyeth by Pfizer in October 2009, both decided for joint operations.

6.3.7. Capsaicin

Capsaicin (52; Qutenza®, NeurogesX, 2009), an active component of chili peppers belonging to genus Capsicum, was first isolated in pure and crystalline form by John Clough Thresh in 1876.460 Capsaicin is currently used in topical ointments to relieve the pain of peripheral neuropathy; the burning and painful sensations associated with capsaicin (capsaicin does not actually cause a chemical burn, or any direct tissue damage at all) result from its chemical interaction with sensory neurons.461–463 Capsaicin, being a member of the vanilloid family, binds to the ion channel receptor vanilloid

![Capsaicin (52)](image-url)
receptor subtype 1 (VR 1), thereby permitting cations to pass through the cell membrane and into the cell when activated. The resulting depolarization of the neuron stimulates it to signal the brain. In November 2009, NeurogesX gained FDA approval for Qutenza® (a transdermal 8% patch of capsaicin (52)) against neuropathic pain combined with postherpetic neuralgia. In April 2010, NeurogesX launched Qutenza in US and is planning to market it in Europe by Astellas Pharma Europe Ltd.

6.4. Cardiovascular and Metabolic Disease Area

6.4.1. Zotarolimus

Zotarolimus (53; Endeavor™ stent; ABT-578; Medtronic, 2005), a semi-synthetic derivative of sirolimus (34), was designed for use in stents with phosphorylcholine as a carrier; coronary stents reduce early complications
and improve late clinical outcomes in patients needing interventional cardio-
diology. Sirolimus (34; Rapamune, Wyeth) was originally discovered from
bacterium Steptomyces hygroscopicus with promising antifungal activ-
ity\(^\text{467,468}\) and is being used along with other coronary stents against
restenosis of coronary arteries due to balloon angioplastysis. Zotarolimus
(53) is an active principle of Endeavor\(^\text{TM}\) (tradename) stent that inhibits
cell proliferation, preventing scar tissue formation and minimizes resteno-
sis in angioplasty patients \(\text{[469]}\). In July 2005, Medtronic received
European approval for the sale of the Endeavor drug-eluting coronary stent
that consists of a cobalt-based alloy integrated with a biomimetic phos-
phorylcholine polymer\(^\text{470–472}\). In February 2008, Medtronic received FDA
approval for the use of Endeavor\(^\text{®}\) against coronary artery disease\(^\text{,473}\) while
Cypher\(^\text{®}\) is being marketed by Cordis (Johnson & Johnson)\(^\text{474}\).

6.4.2. Tiotropium bromide

Tiotropium bromide (54; Spiriva\(^\text{®}\); Boehringer-Ingelheim/Pfizer, 2004) has been approved by the US Food and Drug Administration (FDA) for the
treatment of bronchospasm associated with chronic obstructive pulmonary
disease (COPD)\(^\text{475}\). Tiotropium, a derivative of atropine from Atropa
belladonna (Solanaceae), is a potent reversible nonselective inhibitor of

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\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{Me} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\text{S} & \quad \text{S} \\
\text{Br} & \quad \text{Br} \\
\end{align*}
\]

Tiotropium bromide (54)
muscarinic receptors. Tiotropium is structurally analogous to ipratropium, a commonly prescribed drug for COPD, but this anticholinergic bronchodilator has shown longer-lasting effects (24 hours). Although the drug does not display selectivity for specific muscarinic receptors, on topical application it acts mainly on M₃ muscarinic receptors located on smooth muscle cells and submucosal glands not to produce smooth muscle contraction and mucus secretion, thus producing a bronchodilatory effect. Tiotropium bromide (54) capsules for inhalation are co-promoted by Boehringer-Ingelheim and Pfizer under the trade name Spiriva®.

6.4.3. Bivalirudin

Bivalirudin (55; Angiomax®, The Medicines Company [MDCO], 2000) is a leech antiplatelet protein that is an inhibitor of collagen-induced platelet aggregation. Chemically, it is a synthetic congener of the naturally occurring drug hirudin (found in the saliva of the medicinal leech Hirudo medicinalis). Bivalirudin (55) is a new, genetically engineered form of hirudin, the substance in the saliva of the leech (Haementeria officinalis), and stops blood clotting, acting as a specific and reversible direct thrombin inhibitor (DTI). Bivalirudin is used to reduce the risk of blood clotting in adults with severe chest pain (unstable angina) who are undergoing a procedure to open blocked arteries in the heart. Bivalirudin overcomes many limitations seen with indirect thrombin inhibitors, such as heparin; bivalirudin is a short, synthetic peptide that is potent, highly specific, and a reversible inhibitor of thrombin. It inhibits both circulating and clot-bound thrombin, while also inhibiting thrombin-mediated platelet activation and aggregation. Bivalirudin has a quick onset of action and a short half-life, and does not bind to plasma proteins (other than thrombin) or to red blood cells, thereby offering a predictable antithrombotic response.

Bivalirudin (55)

Bivalirudin directly inhibits thrombin by specifically binding both to the catalytic site and to the anion-binding exosite of circulating and clot-bound thrombin. Thrombin is a serine proteinase that plays a central
role in the thrombotic process. It cleaves fibrinogen into fibrin monomers, and activates Factors V, VIII, and XIII, allowing fibrin to develop a covalently cross-linked framework which stabilizes the thrombus. Thrombin also promotes further thrombin generation, and activates platelets, stimulating aggregation and granule release. The binding of bivalirudin to thrombin is reversible as thrombin slowly cleaves the bivalirudin-Arg3-Pro4 bond, resulting in the recovery of thrombin active site functions.480–491

6.4.4. Rosuvastatin calcium

Rosuvastatin calcium (56; Crestor®; AstraZeneca, 2003), an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and a derivative of mevastatin isolated from Penicillium citrinum and P. brevicompactum, is an effective lipid-lowering agent approved internationally (in most of Europe, the US, and Canada) for the management of dyslipidemias.215–217,492,493 Like other available HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin), rosuvastatin competitively inhibits the rate-limiting step in the formation of endogenous cholesterol by HMG-CoA reductase. Consequently, hepatic intracellular stores of cholesterol are reduced, which results in reduced serum levels of low-density lipoprotein-cholesterol (LDL-C) and triglycerides, and increased serum levels of high-density lipoprotein-cholesterol (HDL-C), and thus improves the overall lipid profile of patients.494 Pitavastatin (Livalo,
Sankyo/Kowa, 2003), an analog of mevastatin-like rosuvastatin, has been approved for the treatment of dyslipidemia in Japan.495

6.5. Diabetes

6.5.1. Exenatide

Exenatide (57; Byetta™; Amylin and Eli Lilly, 2005), originally named exenatide-4, is a 39-amino acid peptide isolated from the oral secretions of the Gila monster (Heloderma suspectum), a poisonous lizard found in the southwestern US and northern Mexico, and the first insulin mimetic found to improve glycemic control.496–498 Subcutaneous exenatide (57) was launched in the US for use in patients with type 2 diabetes who have failed in glycemic control by treatment with metformin and/or a sulfonylurea.499,500 Exenatide (57) has a structure similar to glucagon-like peptide-1 (GLP-1), a human hormone that helps the pancreas to regulate glucose-induced insulin secretion when the blood glucose levels are elevated, and is the first compound in a new class of drugs called “incretin mimetics”;501,502 it enhances glucose-dependent insulin secretion by the pancreatic β-cells, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying, although the mechanism of action is still under study. Eli Lilly obtained FDA in April 2005 while Amylin Pharmaceuticals gained EMEA approval in November 2006 for the use of a synthetic version of exenatide (57) as an adjunctive therapy in type 2 diabetes mellitus.503,504 Amylin Pharmaceuticals, Eli Lilly and Alkermes in May 2009 submitted a NDA for subcutaneous dosing of exenatide (57) once weekly to the FDA, which was accepted in July 2009.


Exenatide (57)

6.6. Few Other Disease Areas

6.6.1. Pimecrolimus

Pimecrolimus (58; Elidel®; Novartis, 2001) is a novel macrolactum derivative of ascomycin, isolated as a fermentation product of Streptomyces.
Pimecrolimus (58) is an immunomodulating agent used in the treatment of atopic dermatitis (eczema). It is currently available as a topical cream, once marketed by Novartis (however Galderma Pharmaceuticals is promoting the compound in Canada since early 2007) under the tradename Elidel®. Its mechanism of action involves blocking T cell activation via the pimecrolimus–macrophilin complex that prevents the dephosphorylation of the cytoplasmic component of the nuclear factor of activated T cells (NF-AT). Pimecrolimus also prevents the release of inflammatory cytokines and mediators from mast cells. This drug was approved for the treatment of inflammatory skin diseases such as allergic contact dermatitis and atopic dermatitis.180,181,505–517

6.6.2. Nitisinone

Nitisinone (59; Orfadin®, Swedish Orphan, 2002) is a derivative of leptospermone,518 an important new class of herbicides from the bottlebrush plant (Callistemon citrinus), and exerts an inhibitory effect for p-hydroxyphenylpyruvate dioxygenase (HPPD) involved in plastoquinone synthesis; the
drug (59) originally developed as an herbicide is now used successfully in the treatment of hereditary tyrosinemia type 1 (HT-1), a severe inherited disease of humans caused by a deficiency of fumaryl acetoacetate hydrolase (FAH), leading to accumulation of fumaryl and maleyl acetoacetate, and progressive liver and kidney damage.\textsuperscript{208–210,519–522} The mechanism of action of nitrisinone involves reversible inhibition of 4-hydroxyphenylpyruvate oxidase,\textsuperscript{519,523} thus preventing the formation of maleylacetoacetic acid and fumarylacetoacetic acid, which have the potential to be converted to succinyl acetone, a toxin that damages the liver and kidneys.\textsuperscript{524}

6.6.3. Miglustat

Miglustat (60; Zavesca\textsuperscript{®}; Actelion, 2003) has been approved for patients unable to receive enzyme replacement therapy as a therapeutic drug for type 1 Gaucher disease (GD1). Miglustat (OGT 918, N-butyl-1-deoxynojirimycin), a semi-synthetic derivative of 1-deoxynojirimycin isolated from the broth filtrate of \textit{Streptomyces lavendulae}, is an analog of D-glucose and a white to off-white crystalline solid that has a bitter taste. Type 1 Gaucher disease is an autosomal recessive disorder one gets from both parents. Gaucher disease is a progressive lysosomal storage disorder associated with pathological accumulation of glucosylceramide in cells of the monocyte/macrophage lineage. People with type 1 Gaucher have a defect in the enzyme called glucocerebrosidase (also known as glucosylceramide synthase) that acts on a fatty substance glucocerebroside (also known as glucosylceramide). Accumulation of glucosylceramide causes liver and spleen enlargement, changes in the bone marrow and blood, and bone disease. Miglustat (60) reversibly inhibits the activity of glucosylceramide synthase, the ceramide-specific glucosyltransferase that catalyzes the formation of glucocerebroside (i.e. glycosphingolipids) and thereby decreases
tissue storage of glucosylceramide. Miglustat is, thus, a glucosylceramide synthase inhibitor.\textsuperscript{215–217,525–527}

Treatment with miglustat (60) is known as substrate reduction therapy (SRT). Unlike enzyme replacement therapy (ERT), which has a direct effect on the breakdown of glycosphingolipids, the concept of SRT in Gaucher disease involves reduction of the delivery of potential storage material to the macrophage system. Patients treated with miglustat for 3 years show significant improvements in organ volumes and haematological parameters. Miglustat was effective over time and showed acceptable tolerability in patients who continued with treatment for 3 years. Miglustat was effective in adults with mild to moderate type 1 Gaucher disease and it is the first treatment to be approved for patients with Niemann-Pick type C disease. Miglustat may only be used in the treatment of type 1 Gaucher patients for whom enzyme replacement therapy is unsuitable; it has been approved by both the European Union and FDA for the treatment of progressive neurological manifestations in adult or pediatric patients with Niemann-Pick type C disease (NPC). It has also been approved for NPC treatment in Canada, Switzerland, Brazil, Australia, Turkey and Israel.\textsuperscript{528–531}

6.6.4. \textit{Mycophenolate sodium}

Mycophenolate sodium (62; Myfortic\textsuperscript{®}; Norvatis, 2003) is an immunosuppressant drug used to prevent rejection in organ transplantation. It is a selective, noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), the rate-limiting enzyme in the \textit{de novo} pathway of guanosine nucleotide synthesis. Thus, mycophenolic acid (61), originally
purified from *Penicillium brevicompactum*, has a selective antiproliferative effect on B- and T-lymphocytes that rely on the *de novo* synthesis of purine, and is used for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants treated with cyclosporin (cyclosporin A) and corticosteroids. Mycophenolate sodium is particularly indicated for the prevention of renal transplant rejection in adults; besides, the drug has also been used to prevent rejection in liver, heart, and/or lung transplants in children over 2 years. Mycophenolic acid was initially marketed as the prodrug mycophenolate mofetil (63; MMF) to improve oral bioavailability. More recently, the salt mycophenolate sodium has been introduced. Mycophenolic acid (63) is commonly marketed under the tradenames CellCept® (63; mycophenolate mofetil; Roche) and Myfortic® (62; mycophenolate sodium; Novartis).215–217,532–560

7. Natural Product-Based Drugs in Clinical Developments

Natural products (NP) or natural product-derived compounds undergoing clinical developments in various disease areas are summarized in this section. Drug candidates are categorized (Tables 2–5) according to the natural sources of their corresponding leads, viz. plant (Table 2 and Fig. 2), microorganism (Table 3 and Fig. 3), marine (Table 4 and Fig. 4) and animal (Table 5 and Fig. 5) sources. Each drug candidate is also supplemented with its structure, code name, disease indication, mechanism of action, development status and name of the developer including respective references.
Table 2. Plant-derived natural product-based drug candidates under clinical evaluation.

<table>
<thead>
<tr>
<th>Lead compound (Str. No.)</th>
<th>Compound class</th>
<th>Name (synonym)</th>
<th>Disease area/Indication</th>
<th>Mechanism of action</th>
<th>Development status</th>
<th>Developer</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Artemisinin (8)</td>
<td>Endoperoxide sesquiterpene lactone</td>
<td>Arterolane (RBX11160, OZ-277) (64)</td>
<td>Antiparasitic (antimalarial)</td>
<td>Under study (on interaction of peroxide moiety with parasite targets)</td>
<td>Phase III</td>
<td>Ranbaxy</td>
<td>561–565</td>
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<tr>
<td>Betulinic acid (65)</td>
<td>Triterpenoid</td>
<td>Bevirimat (PA-457) (66)</td>
<td>Antiviral (anti-HIV)</td>
<td>Inhibits the final step of the HIV Gag protein processing and thus blocks HIV maturation</td>
<td>Phase IIb</td>
<td>Panacos Pharmaceuticals</td>
<td>566–573</td>
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<tr>
<td>Castanospermine (67)</td>
<td>Indolizine alkaloid</td>
<td>MX-3253 (formerly MBI-3253; Celgosivir; 6-O-butanoyl castanospermine) (68)</td>
<td>Antiviral [Hepatitis C virus (HCV)]</td>
<td>Inhibits α-glucosidase I</td>
<td>Phase II</td>
<td>MIGENIX</td>
<td>577–581</td>
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<tr>
<td>4-Methylumbelliferone (Hymecromone) (69)</td>
<td>Coumarin</td>
<td>Heparvit® (dietary supplement)</td>
<td>Antiviral (anti-HBV and anti-HCV)</td>
<td>Promotes bile discharge, and inhibits hyaluronan biosynthesis</td>
<td>Phase II</td>
<td>MTmedical Institute of Health and BioMonde</td>
<td>582</td>
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<tr>
<td>1,5-Di-caffeoylquinic acid (70)</td>
<td>Cyclic polyolic derivative</td>
<td>1,5-DCQA (70)</td>
<td>Antiviral (Anti-HIV/HIV/AIDS and hepatitis B)</td>
<td>Inhibits HIV-1 integrase</td>
<td>Phase I/II</td>
<td>Chinese Academy of Military Medical Sciences</td>
<td>583–585</td>
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<tr>
<td>Huperzine-A (71)</td>
<td>Sesquiterpene alkaloid</td>
<td>Huperzine-A (71)</td>
<td>Neurological (Alzheimer’s Disease)</td>
<td>Acetylcholinesterase (AChE) inhibitor</td>
<td>Clinical development Phase II</td>
<td>Chinese scientists</td>
<td>586–591</td>
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<tr>
<td>Morphine (43)</td>
<td>Alkaloid</td>
<td>Morphone-6-glucuronide (M6G) (72)</td>
<td>Neurological (pain; analgesic)</td>
<td>Mediates its effects by activating the micro-opioid receptor; it shows equivalent analgesia to morphine but to have a superior side-effect profile in terms of reduced liability to induce nausea and vomiting and respiratory depression.</td>
<td>Phase III</td>
<td>CeNeS Pharmaceuticals/ PAION Pharmaceuticals</td>
<td>592, 593</td>
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<tr>
<td>Lobeline (73)</td>
<td>Piperidine alkaloid</td>
<td>Lobeline (73)</td>
<td>Neurological (treatment of methamphetamine addiction and ADHD)</td>
<td>Reduces the methamphetamine induced dopamine release</td>
<td>Phase II</td>
<td>Yaupon Therapeutics and NIH</td>
<td>594–599</td>
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Table 2. (Continued)

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<tr>
<td>Capsaicin (52)</td>
<td>Capsaicinoid</td>
<td>Capsaicin (Coded 4975; ALGRX 4975; Adlea™ (52)) Civanex® (zucapsaicin cream 0.075%; WL-1001)</td>
<td>Neurological (pain indications such as severe post-surgical pain, posttraumatic neuropathic pain and musculoskeletal diseases)</td>
<td>Binds to vanilloid receptor subtype 1 (VR1)</td>
<td>Phase III</td>
<td>Anesiva</td>
<td>461, 600</td>
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<tr>
<td>Phlorizin (74)</td>
<td>Polyphenolic glycoside</td>
<td>Dapagliflozin (BMS-512148) (75)</td>
<td>Antidiabetic</td>
<td>Sodium glucose co-transporters (SGLTs) inhibitor that lowers glucose plasma level and improves insulin resistance.</td>
<td>Phase III</td>
<td>Winston Laboratories, Inc.</td>
<td>601</td>
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<tr>
<td>Resveratrol (76)</td>
<td>Triphenolic stilbene</td>
<td>SRT-501 (a formulation)</td>
<td>Against diabetes and obesity</td>
<td>Activates sirtuins by working indirectly, via the energy sensor AMP-activated protein kinase (AMPK)</td>
<td>Phase II</td>
<td>Sirtris Pharmaceuticals</td>
<td>608–614</td>
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<tbody>
<tr>
<td>Ajulemic acid (77)</td>
<td>Cannabinoid</td>
<td>CP 7075 (IP 751, ajulemic acid, CT-3) (synthetic version)</td>
<td>Neurological (neuropathic pain)</td>
<td>Suppresses IL-1β and matrix metalloproteinases (MMPs) through a peroxisome proliferator-activated receptor (PPAR) γ-mediated mechanism</td>
<td>Phase I</td>
<td>Cervelo Pharmaceuticals</td>
<td>615–618</td>
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<tr>
<td>1-Deoxynojirimycin (Moranoline; 78)</td>
<td>Aza-sugar-type</td>
<td>Isofagomine (PliceraTM, AT2101) (79)</td>
<td>Gaucher’s disease, a lysosomal storage disorder caused by β-glucocerebrosidase deficiency</td>
<td>Mimics the carbocation transition state used by glycosidases</td>
<td>Phase II</td>
<td>Amicus Therapeutics in collaboration with Shire Pharmaceuticals</td>
<td>619–622</td>
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<td>Himbacine (80)</td>
<td>Alkaloid</td>
<td>SCH 530348 (TRA) (81)</td>
<td>Cardiovascular diseases (antiplatelet agent)</td>
<td>Thrombin receptor antagonist</td>
<td>Phase III (acute coronary syndromes)</td>
<td>Schering-Plough</td>
<td>623–626</td>
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<tr>
<td>Eupatilin (82)</td>
<td>Flavone</td>
<td>DA-6034 (83)</td>
<td>Dry eye systems</td>
<td>Suppresses MMP-9 and inflammatory cytokines and activates MAPK Signaling pathway</td>
<td>Phase I</td>
<td>Dong-A Pharmaceuticals</td>
<td>627–629</td>
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<tr>
<td>Lead compound (Str. No.)</td>
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<td>Camptothecin (84)</td>
<td>Quinoline alkaloid</td>
<td>Karenitecin® (BNP-1350) (85)</td>
<td>Oncology (ovarian cancer)</td>
<td>Inhibits topoisomerase I</td>
<td>Phase III</td>
<td>BioNumerik and ASKA Pharmaceutical</td>
<td>630–634</td>
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<td>Diflomotecan (BN-80915) (86)</td>
<td>Oncology (advance metastatic cancers)</td>
<td>Inhibits topoisomerase I</td>
<td>Phase II</td>
<td>Ipsen</td>
<td>635, 636</td>
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<td>Gimatecan (ST-1481) (87)</td>
<td>Oncology (solid tumor)</td>
<td>Inhibits topoisomerase I</td>
<td>Phase II</td>
<td>Novartis/Sigma-Tau</td>
<td>637–639</td>
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<td>Elomotecan (BN-80927, LBQ707, R-1559) (88)</td>
<td>Oncology (advanced metastatic cancers)</td>
<td>Inhibits topoisomerase I</td>
<td>Phase I</td>
<td>Ipsen</td>
<td>640</td>
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<tr>
<td>DRF 1042 (89)</td>
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<td>Oncology</td>
<td>Inhibits topoisomerase I</td>
<td>Phase II/III</td>
<td>Dr Reddy/ClinTec International</td>
<td>641, 642</td>
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<td>Combretastatin A-4 (90)</td>
<td>Stilbenoid phenol</td>
<td>SN2310 141 (90)</td>
<td>Oncology</td>
<td>Inhibits topoisomerase I</td>
<td>Phase I</td>
<td>643</td>
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<td>Combretastatin A-4 phosphate (Zybrestat™, CA4P) (92)</td>
<td>Oncology (vascular disrupting agent)</td>
<td>Tubulin binding</td>
<td>Phase I/II/III</td>
<td>OXIGENE (Arizona State)</td>
<td>644–650</td>
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<td>Ombrabulin (AVE-8062; AC-7700) (93)</td>
<td>Oncology</td>
<td>Tubulin binding</td>
<td>Phase III</td>
<td>Sanofi-Aventis</td>
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<td>Combretastatin A-1 (94)</td>
<td>Stilbenoid phenol</td>
<td>OXi4503 (Combretastatin A-1 diphosphate) (95)</td>
<td>Oncology (advanced-stage solid tumors)</td>
<td>Tubulin binding</td>
<td>Phase I/II</td>
<td>OXiGENE (Arizona State)</td>
<td>652–657</td>
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<td>Paclitaxel (96)</td>
<td>Diterpene taxoid</td>
<td>Cabazitaxel (XRP-6258) (97)</td>
<td>Oncology (pancreatic and hormone-refractory prostate cancers)</td>
<td>Tubulin binding</td>
<td>Phase III</td>
<td>Sanofi-Aventis</td>
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<td>Larotaxel (XRP-9881) (98)</td>
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<td>Tubulin binding</td>
<td>Phase III</td>
<td>Sanofi-Aventis</td>
<td>658, 659, 661–664</td>
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<td>DHA-paclitaxel (Taxoprexin®) (99)</td>
<td>Oncology (metastatic melanoma)</td>
<td>Tubulin binding</td>
<td>Phase III</td>
<td>Luitpold Pharmaceuticals</td>
<td>665, 666</td>
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<td>Ortataxel (IDN-5109, BAY-59-8862) (100)</td>
<td>Oncology (solid tumors)</td>
<td>Tubulin binding</td>
<td>Phase I/II</td>
<td>Spectrum (Indena)</td>
<td>667–669</td>
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<td>Milataxel (MAC-321, TL-00139) (101)</td>
<td>Oncology (colorectal neoplasm)</td>
<td>Tubulin binding</td>
<td>Phase II</td>
<td>Wyeth Pharmaceuticals</td>
<td>670, 671</td>
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<td>Tesetaxel (DJ-927) (102)</td>
<td>Oncology</td>
<td>Tubulin binding</td>
<td>Phase I/II</td>
<td>Daiichi Sankyo/Genta</td>
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<td>TPI-287 (103)</td>
<td>Oncology</td>
<td>Tubulin binding</td>
<td>Phase II</td>
<td>Tapestry Pharmaceuticals</td>
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<td>BMS-188797 (104)</td>
<td>Oncology</td>
<td>Tubulin binding</td>
<td>Phase II</td>
<td>Bristol-Myers Squibb (BMS)</td>
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<td>Vinblastine (105) Vinca alkaloid</td>
<td>Vinflunine (Javlor®) (106)</td>
<td>Oncology (bladder cancer)</td>
<td>Tubulin binding</td>
<td>Phase III Pierre Fabre Laboratories</td>
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<tr>
<td>Noscapine (107) Benzyl-isoquinoline alkaloid</td>
<td>CB3304 (Noscapine) (107)</td>
<td>Oncology (multiple myeloma)</td>
<td>Tubulin binding</td>
<td>Phase I/II Cougar Biotechnology</td>
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<tr>
<td>Curcumin (108) Polyphenol</td>
<td>Curcumin (108)</td>
<td>Inflammation; oncology (matastatic colon cancer)</td>
<td>Various anti-inflammatory and antioxidative properties</td>
<td>Phase II Being conducted by various concerns worldwide</td>
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<tr>
<td>Oleanolic acid (109) Triterpenoid</td>
<td>RTA-402 (CDDO-Me) (110)</td>
<td>Oncology (prostate cancer)</td>
<td>Inhibits IκB alpha kinase activation</td>
<td>Phase I/II Reata Pharmaceuticals</td>
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<tr>
<td>β-Lapachone (111)</td>
<td>Naphthaquinone</td>
<td>β-Lapachone (ARQ-501) (111)</td>
<td>Oncology (pancreatic and ovarian cancer)</td>
<td>Increases pro-apoptotic protein E2F1, as well as induces expression of cyclin dependent kinase inhibitor 1A (CDKN1A or P21)</td>
<td>Phase II</td>
<td>ArQule</td>
<td>696–699</td>
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<tr>
<td>Rohitukine (112)</td>
<td>Flavone</td>
<td>Alvocidib (flavopiridol, HMR 1275) (113)</td>
<td>Oncology</td>
<td>Cyclin-dependent kinase inhibition</td>
<td>Phase III (NSCLC) Phase IIb (CLL)</td>
<td>Sanofi-Aventis</td>
<td>700–702</td>
</tr>
<tr>
<td>Daidzein (114)</td>
<td>Isoflavone</td>
<td>Phenoxodiol (115)</td>
<td>Oncology</td>
<td>NADH oxidase (tNOX) and sphingosine-1-phosphate inhibition</td>
<td>Phase III (ovarian cancer) Phase II (castrate and non-castrate prostate cancer)</td>
<td>Marshall Edwards (Novogen)</td>
<td>703–707</td>
</tr>
<tr>
<td>Genistein (116)</td>
<td>Isoflavone</td>
<td>Genistein (116)</td>
<td>Oncology (antitumor)</td>
<td>Protein-tyrosine kinase inhibition, antioxidative</td>
<td>Phase I/II</td>
<td>Astellas, Bausch &amp; Lomb</td>
<td>708</td>
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(Continued)
### Table 2. (Continued)

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<th>Lead compound (Str. No.)</th>
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<tbody>
<tr>
<td><strong>Flavone-8-acetic acid</strong>&lt;sup&gt;117&lt;/sup&gt;</td>
<td>Flavone derivative</td>
<td>ASA404 (DMXAA, ASA1404) &lt;sup&gt;118&lt;/sup&gt;</td>
<td>Oncology</td>
<td>Vascular targeting and angiogenesis inhibition</td>
<td>Phase III</td>
<td>Antisoma (University of Auckland)/Novartis</td>
<td>709–713</td>
</tr>
<tr>
<td><strong>Silybin</strong>&lt;sup&gt;119&lt;/sup&gt;</td>
<td>Flavonolignoid</td>
<td>IdB 1016 (Silipide; Silybin and phosphatidylcholine complex; Silophos&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Oncology</td>
<td>Antioxidant and anti-inflammatory</td>
<td>Phase II (cancer chemoprevention)</td>
<td>American College of Gastroenterology/Indena</td>
<td>714–719</td>
</tr>
<tr>
<td><strong>3′-O-Methyl nordihydroguaiaretic acid</strong> (NDGA; <strong>120</strong>&lt;sup&gt;121&lt;/sup&gt;)</td>
<td>Lignoid</td>
<td>Terameprocol (EM-1421, tetra-O-methyl nordihydroguaiaretic acid) &lt;sup&gt;121&lt;/sup&gt;</td>
<td>Oncology (solid tumors, glioma and leukemia)</td>
<td>Transcription inhibitor</td>
<td>Phase I/II</td>
<td>Erimos (John Hopkins)</td>
<td>720–726</td>
</tr>
<tr>
<td><strong>Epipodophyllotoxin</strong>&lt;sup&gt;122&lt;/sup&gt;</td>
<td>Alkaloid</td>
<td>Tafluposide &lt;sup&gt;123&lt;/sup&gt;</td>
<td>Oncology</td>
<td>Topoisomerase I and II inhibitor</td>
<td>Phase I</td>
<td>Pierre Fabre</td>
<td>727–729</td>
</tr>
<tr>
<td><strong>Ingenol</strong>&lt;sup&gt;124&lt;/sup&gt;</td>
<td>Tetracyclic diterpene</td>
<td>Ingenol 3-angelate (PEP005) &lt;sup&gt;125&lt;/sup&gt;/ Ingenol mebutate</td>
<td>Oncology</td>
<td>Protein kinase C activation</td>
<td>Phase II</td>
<td>Peplin</td>
<td>730–733</td>
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<tr>
<td><strong>Acronycin</strong>&lt;sup&gt;126&lt;/sup&gt;</td>
<td>Alkaloid</td>
<td>S23906-1 &lt;sup&gt;127&lt;/sup&gt;</td>
<td>Oncology (solid tumors)</td>
<td>DNA binding</td>
<td>Phase I</td>
<td>Laboratoires Servier (CNRS)</td>
<td>734–737</td>
</tr>
<tr>
<td><strong>Homoharringtonine</strong>&lt;sup&gt;128&lt;/sup&gt;</td>
<td>Alkaloid</td>
<td>Homoharringtonine (Omacetaxine mepesuccinate; Cellatlon&lt;sup&gt;®&lt;/sup&gt;) &lt;sup&gt;128&lt;/sup&gt;</td>
<td>Oncology</td>
<td>Protein synthesis inhibition</td>
<td>Phase II/III</td>
<td>ChemGenex</td>
<td>738, 739</td>
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Table 3. Microorganism-derived natural product-based drug candidates under clinical evaluation.

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<tbody>
<tr>
<td>Cephalosporins</td>
<td>β-Lactum antibiotics</td>
<td>Cefotibipro medicaril (BAL-5788) (129)</td>
<td>Antibacterial</td>
<td>Inhibits bacterial cell wall synthesis</td>
<td>Phase III (cSSSIs)</td>
<td>Basilea Pharmaceutica and J&amp;J affiliated Cilag GmbH International</td>
<td>740–744</td>
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<tr>
<td></td>
<td></td>
<td>Ceftaroline acetate (PP-0903, TAK-599) (130)</td>
<td>Antibacterial</td>
<td>-do-</td>
<td>Phase II (cSSSIs; CAP)</td>
<td>Forest Laboratories</td>
<td>745–748</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>β-Lactum antibiotics</td>
<td>Tebipenem pivoxil (ME-1211, L-084) (131)</td>
<td>Antibacterial (otolaryngological/respiratory infections)</td>
<td>-do-</td>
<td>Phase III</td>
<td>Meiji Seika</td>
<td>749–751</td>
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<td></td>
<td></td>
<td>Tomopenem (CS-023, RO-408463, R1558) (132)</td>
<td>Antibacterial (common nosocomial infections)</td>
<td>-do-</td>
<td>Phase II</td>
<td>Daiichi Sankyo</td>
<td>752–754</td>
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<td></td>
<td>PZ601 (SM-216601) (133)</td>
<td>Antibacterial</td>
<td>-do-</td>
<td>Phase II</td>
<td>Protez, licensed from Dainippon Sumitomo</td>
<td>755, 756</td>
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<td>ME-1036 (CP5609) (134)</td>
<td>Antibacterial</td>
<td>-do-</td>
<td>Phase I</td>
<td>Forest and Meiji Seika</td>
<td>757, 758</td>
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<td></td>
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<td>Sulopenem (CP-70429) (135)</td>
<td>Antibacterial</td>
<td>-do-</td>
<td>Phase I</td>
<td>Pfizer</td>
<td>759–761</td>
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<tr>
<td></td>
<td></td>
<td>Faropenem daloxate (SUN-208, BAY-56-6824) (136)</td>
<td>Antibacterial</td>
<td>-do-</td>
<td>Phase III</td>
<td>Replidyne</td>
<td>762–764</td>
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Table 3.  (Continued)

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<tbody>
<tr>
<td>Teicoplanin analog A40926 (137)</td>
<td>Lipoglycopeptide antibiotic</td>
<td>Dalbavancin (Zeven®, BI-397) (138)</td>
<td>Antibacterial (cSSSIs)</td>
<td>Inhibits bacterial cell wall biosynthesis via formation of a complex with the C-terminal D-alanyl-D-alanine of growing peptidoglycan chains; in addition, it appears to have the unique ability to dimerise and anchor its lipophilic side chain in the bacterial membranes.</td>
<td>Phase III</td>
<td>Pfizer</td>
<td>765–769</td>
</tr>
<tr>
<td>Chloroeremomycin (139)</td>
<td>Glycopeptide antibiotic</td>
<td>Oritavancin (Nuvocid™, LY-333328) (140)</td>
<td>Antibacterial (cSSSIs including MRSA)</td>
<td>Inhibits bacterial cell wall biosynthesis</td>
<td>Phase III</td>
<td>Eli Lilly/Targanta</td>
<td>770</td>
</tr>
<tr>
<td>Vancomycin; Cephalosporin</td>
<td>Glycopeptide and β-lactum antibiotics</td>
<td>TD-1792 (a Vancomycin-Cephalosporin heterodimer) (141)</td>
<td>Antibacterial (cSSSIs including MRSA)</td>
<td>Inhibits bacterial cell wall synthesis</td>
<td>Phase II</td>
<td>Theravance</td>
<td>771</td>
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<tr>
<td>Ramoplanin (142)</td>
<td>Lipopeptide antibiotic</td>
<td>Ramoplanin factor A2 (Ramoplanin) (142)</td>
<td>Antibacterial [Clostridium difficile associated diarrhoea (CDAD)]</td>
<td>Inhibits bacterial cell wall synthesis</td>
<td>Phase II</td>
<td>Oscient Pharmaceuticals</td>
<td>772–777</td>
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<tr>
<td>Semi-synthetic Streptogramins</td>
<td>Macrolide peptide antibiotics</td>
<td>NXL-103 (XRP2868) — a 70:30 mixture of Flopristin (RPR132552A, Streptogramin A-type) (143) and Linopristin (RPR202698, Streptogramin B-type) (144)</td>
<td>Antibacterial (CAP and cSSSIs including MRSA)</td>
<td>Inhibits bacterial protein synthesis</td>
<td>Phase II</td>
<td>Sanofi-Aventis</td>
<td>778–783</td>
</tr>
<tr>
<td>Friulimicin B (145)</td>
<td>Lipopeptide antibiotic</td>
<td>Friulimicin B (145)</td>
<td>Antibacterial</td>
<td>Through complex formation with bactoprenol-phosphate, leading to the interruption of peptidoglycan and teichoic acid biosynthesis,</td>
<td>Phase I</td>
<td>MerLion Pharmaceuticals</td>
<td>224, 784–786</td>
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<tbody>
<tr>
<td>Duramycin (146)</td>
<td>Polycyclic peptide</td>
<td>Moli1901 (duramycin, 2262U90) (146)</td>
<td>Antibacterial (cystic fibrosis)</td>
<td>Increases chloride permeability in the nasal epithelium of healthy individuals and subjects with cystic fibrosis</td>
<td>Phase II</td>
<td>AOP Orphan in collaboration with Lantibio</td>
<td>787–789</td>
</tr>
<tr>
<td>Erythromycin (147)</td>
<td>Macrolide antibiotic</td>
<td>Cethromycin (Restanza™ (ABT-773) (148)</td>
<td>Antibacterial (CAP, other respiratory tract infections, and anthrax)</td>
<td>Inhibits bacterial protein synthesis by interacting close to the peptidyl transferase site of the 50S ribosomal subunit. The main binding sites are within domains II and V of the 23S rRNA.</td>
<td>Phase III</td>
<td>Advanced Life Sciences</td>
<td>790–795</td>
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<tbody>
<tr>
<td>BAL-19403 (150)</td>
<td>Antibacterial</td>
<td>(acne)</td>
<td>Shows strong suppression of the inflammatory response of human neutrophils, the white blood cells contributing to the inflammatory aspects of the disease.</td>
<td>Pre-clinical/Phase I</td>
<td>Basilea Pfizer AG</td>
<td>799–801</td>
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<tr>
<td>Telithromycin (Ketek®) (151)</td>
<td>Antibacterial (respiratory infections)</td>
<td>Inhibits bacterial protein synthesis by blocking the progression of the growing polypeptide chain through binding with the 50S subunit of ribosome</td>
<td>Phase II/III</td>
<td>Sanofi-Aventis</td>
<td>802</td>
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<tr>
<td>Tiacumicin B (152)</td>
<td>Macrolactone</td>
<td>Tiacumicin B</td>
<td>Antibacterial [Clostridium difficile-associated diarrhea (CDAD)]</td>
<td>Inhibits bacterial RNA synthesis</td>
<td>Phase III</td>
<td>Optimer Pharmaceuticals</td>
<td>803–809</td>
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<tr>
<td>Aminomethyl-cyclines</td>
<td>Aminomethyl-cycline</td>
<td>MK-2764 (PTK-0796; BAY 73-7388) (153)</td>
<td>Antibacterial (broad spectrum antibiotic against MRSA, MDR Streptococcus pneumoniae and vancomycin-resistant enterococci)</td>
<td>Inhibits bacterial protein synthesis</td>
<td>Phase III (treatment of hospital infections in both oral and i.v. injectable formulations)</td>
<td>Paratek/Novartis</td>
<td>810</td>
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<tr>
<td>Rs-DPLA (154) Lipid-A analog</td>
<td>Eritoran (E5564) (155)</td>
<td>Antibacterial (acts against sepsis by Gram-negative bacteria)</td>
<td>Inhibits endotoxin response through antagonism of the Toll-like receptor 4 (TLR4)</td>
<td>Phase III</td>
<td>Eisai</td>
<td>811–818</td>
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<tr>
<td>Rifamycin-quinolone heterodimer</td>
<td>Antibiotics</td>
<td>CBR-2092 (156)</td>
<td>Antibacterial</td>
<td>Exerts antimicrobial activity through combined effects on RNA polymerase, DNA topoisomerase IV and DNA gyrase</td>
<td>Phase Ila (treatment of infections caused by Gram-positive cocci)</td>
<td>Cumbre Pharmaceuticals</td>
<td>819, 820</td>
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<tbody>
<tr>
<td>WAP-8294A₂ (JA-002) (157)</td>
<td>Antibiotic</td>
<td>WAP-8294A₂ (157)</td>
<td>Antibacterial (MRSA infections and acne)</td>
<td>Interacts selectively to membrane phospholipids, causing severe damage to bacterial membrane</td>
<td>Various Phase I/II trials (gel, cream, injectable form)</td>
<td>aRigen Pharmaceuticals</td>
<td>821–824</td>
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<tr>
<td>Deoxymulundocandin (158)</td>
<td>Echinocandin-type antifungal antibiotic</td>
<td>Aminocandin (NXL-201, IP960, HMR-3270) (159)</td>
<td>Antifungal (Candida sp. infections)</td>
<td>Targets the glucan in fungal cell walls</td>
<td>Phase I</td>
<td>Novexel</td>
<td>825–827</td>
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<tr>
<td>Patrician A (160)</td>
<td>Polyene antibiotic</td>
<td>SPK-843 (161)</td>
<td>Antifungal (systemic mycosis)</td>
<td>Destabilizes fungal cell membrane</td>
<td>Phase II</td>
<td>Kaken Pharmaceuticals</td>
<td>828–834</td>
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<tr>
<td>Cyclosporin (162)</td>
<td>Cyclic peptide</td>
<td>NIM 811 (SDZ NIM 811, Cyclosporin 29, Melle cyclosporin) (163)</td>
<td>Antiviral (anti-HCV)</td>
<td>Inhibits mitochondrial permeability transition</td>
<td>Phase I</td>
<td>Sandoz (now Novartis)</td>
<td>835–840</td>
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<tr>
<td>Spicamycin (164)</td>
<td>Antibiotic</td>
<td>KRN5500</td>
<td>Neurology (neuropathic pain in cancer patients, in particular, chemotherapy-induced peripheral neuropathy)</td>
<td>Inhibits protein synthesis by interfering with endoplasmic reticulum and Golgi apparatus functions; it also induces cell differentiation and caspase-dependent apoptosis</td>
<td>Phase IIa</td>
<td>DARA Therapeutics, Inc.</td>
<td>841–844</td>
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<tr>
<td>Galactonojirimycin (165)</td>
<td>Aza-sugar type</td>
<td>Migalastat (AmigaTM, AT1001, 1-Deoxygalactonojirimycin, 1-Deoxygalactostatin) (166)</td>
<td>Fabry disease</td>
<td>Stabilizes protein structures and restores correct folding through binding with them</td>
<td>Phase III</td>
<td>Amicus Therapeutics in collaboration with Shire Pharmaceuticals</td>
<td>845, 846</td>
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<tr>
<td>Staurosporine (167)</td>
<td>Bis-indole alkaloid antibiotic</td>
<td>Ruboxistaurin (LY33531) (168)</td>
<td>Diabetes (diabetic peripheral retinopathy)</td>
<td>Protein kinase C (PKC) inhibitor</td>
<td>Phase III</td>
<td>Eli Lilly</td>
<td>847–853</td>
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<tr>
<td>Cyclosporine-A (162)</td>
<td>Macrocyclic peptide antibiotic</td>
<td>Vocllosporin (ISA-247, R1524) (169)</td>
<td>Immunosuppressive</td>
<td>Calcineurin inhibitor (prevention of the rejection of kidney graft)</td>
<td>Phase IIb</td>
<td>Lux Biosciences</td>
<td>854–856</td>
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<tr>
<td>Pladienolide D (170)</td>
<td>Macrolide antibiotic</td>
<td>E7107 (171)</td>
<td>Oncology</td>
<td>Binds with spliceosome-associated protein 130 (SAP130) and inhibits the splicing of pre-mRNA resulting in cell cycle arrest</td>
<td>Phase I</td>
<td>Eisai</td>
<td>857–860</td>
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<tr>
<td>Elsamicin A (172)</td>
<td>Antibiotic</td>
<td>Elsamicin A (Elsamitrucin) (172)</td>
<td>Oncology</td>
<td>Inhibits topoisomerase I</td>
<td>Phase II</td>
<td>Spectrum Pharmaceuticals</td>
<td>861</td>
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<tr>
<td>Doxorubicin (173)</td>
<td>Antibiotic</td>
<td>L-Annamycin (174)</td>
<td>Oncology</td>
<td>Inhibits topoisomerase II</td>
<td>Phase I/Ia</td>
<td>Callisto (M.D. Anderson Cancer Center)</td>
<td>862</td>
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<tr>
<td>Berubicin (RTA744, WP744) (175)</td>
<td>Oncology</td>
<td>Inhibits topoisomerase II</td>
<td>Phase II</td>
<td>Reata Pharmaceuticals</td>
<td>863, 864</td>
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<tr>
<td>Sabarubicin (MEN10755) (176)</td>
<td>Oncology</td>
<td>Inhibits topoisomerase II</td>
<td>Phase II (small-cell lung cancer; SCLC)</td>
<td>Menarini Pharmaceuticals</td>
<td>865–867</td>
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<tr>
<td>Nemorubicin (MMDX, PNU-152243A) (177)</td>
<td>Oncology</td>
<td>Inhibits topoisomerase II</td>
<td>Phase I/II</td>
<td>Nerviano Medical Sciences</td>
<td>868, 869</td>
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<tr>
<td>Distamycin A (178)</td>
<td>Antibiotic</td>
<td>Brostallicin (PNU-166196) (179)</td>
<td>Oncology</td>
<td>DNA minor groove binder</td>
<td>Phase II (monotherapy against STS of metastatic or advanced stage)</td>
<td>Cell Therapeutics (Nerviano Medical Sciences)</td>
<td>870–877</td>
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<tr>
<td>Geldanamycin (180)</td>
<td>Benzoquinone ansamycin antibiotic</td>
<td>Tanespimycin (17-AAG, KOS-953, NSC-330507) (181)</td>
<td>Oncology</td>
<td>Inhibits HSP90 and interrupts MAPK pathway</td>
<td>Phase II/III (anti-melanoma)</td>
<td>Kosan (NIH)</td>
<td>878–882</td>
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<td>Alvespimycin (17-DMAG, KOS-1022, NSC-707545) (182)</td>
<td>Oncology</td>
<td>HSP90 inhibitor</td>
<td>Phase I (solid tumors) Phase II (monotherapy against HER2-positive metastatic breast cancer)</td>
<td>Kosan (NIH)</td>
<td>88, 884</td>
</tr>
<tr>
<td>Retaspimycin (IPI-504, 17-AAG hydroquinone salt) (183)</td>
<td>Oncology</td>
<td>HSP90 inhibition</td>
<td>Phase I/II (breast cancer)</td>
<td>Infinity Pharmaceuticals</td>
<td>885, 886</td>
<td>(Continued)</td>
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Table 3. (Continued)

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<th>Mechanism of action</th>
<th>Development status</th>
<th>Developer</th>
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<tbody>
<tr>
<td>Sirolimus (34)</td>
<td>Macrolide antibiotic</td>
<td>Deforolimus (Ridaforolimus; MK-8669, AP-23573) (184)</td>
<td>Oncology</td>
<td>mTOR inhibition</td>
<td>Phase I/II/III (various tumor types including metastatic STS and bone sarcomas)</td>
<td>Merck and ARIAD</td>
<td>887–890</td>
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<td>Salinosporamide A (185)</td>
<td>Antibiotic</td>
<td>Salinosporamide A (NPI-0052) (185)</td>
<td>Oncology</td>
<td>Proteasome inhibition</td>
<td>Phase Ib (solid tumor malignancies)</td>
<td>Nereus</td>
<td>891–893</td>
</tr>
<tr>
<td>Staurosporine (167)</td>
<td>Bis-indole alkaloid antibiotic</td>
<td>Enzastaurin (LY317615) (186)</td>
<td>Oncology</td>
<td>Serine–threonine kinase inhibition</td>
<td>Phase II (NSCLC)</td>
<td>Eli Lilly</td>
<td>894–898</td>
</tr>
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<td></td>
<td></td>
<td>Midostaurin (PKC-412, CGP 41251, 4′-N-Benzoylstauroporine) (187)</td>
<td>Oncology</td>
<td>Inhibits protein kinases including FLT3 inhibition</td>
<td>Phase I/II</td>
<td>Novartis</td>
<td>899</td>
</tr>
<tr>
<td>K252a (Staurosporine analog) (188)</td>
<td>Alkaloidal antibiotic</td>
<td>Lestaurtinib (CEP-701, KT-5555) (189)</td>
<td>Oncology</td>
<td>Inhibition of FLT3 and tyrosine phosphorylation of TrkA</td>
<td>Phase II/III</td>
<td>Cephalon</td>
<td>900, 901</td>
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Table 3. (Continued)

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<th>Development status</th>
<th>Developer</th>
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<tr>
<td>UCN-01 201 (stauroporine analog) (190)</td>
<td>Alkaloidal antibiotic</td>
<td>KRX-0601 (UCN-01, KW-2401) (190)</td>
<td>Oncology</td>
<td>Inhibition of CDKs</td>
<td>Phase II (melanoma, TCL, SCLC)</td>
<td>Keryx (Kyowa Hakko/NCI)</td>
<td>902–905</td>
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<tr>
<td>Diazepinomicin (ECO-4601) (191)</td>
<td>Dibenzo-diazepine alkaloid</td>
<td>Diazepinomicin (ECO-4601) (191)</td>
<td>Oncology</td>
<td>RAS-mitogen-activated phosphokinase (MAPK) pathway inhibitor and inhibition of the peripheral benzodiazepine receptor</td>
<td>Phase I/II</td>
<td>Thallion (Ecopia)</td>
<td>906–910</td>
</tr>
<tr>
<td>Prodigiosin (Streptorubin B) (192)</td>
<td>Tri-pyrrole antibiotic</td>
<td>Obatoclax (GX15-070) (193)</td>
<td>Oncology</td>
<td>Bcl-2 inhibition</td>
<td>Phase I/II</td>
<td>Gemin X</td>
<td>911, 912</td>
</tr>
<tr>
<td>Epothilone B (38)</td>
<td>Polyketide macrolactone (with a methylthiazole group) antibiotic</td>
<td>Patupilone (Epothilone B, EPO-906) (38) Sagopilone (ZK-EPO, ZK-219477) (194)</td>
<td>Oncology</td>
<td>Microtubulin stabilization</td>
<td>Phase III (ovarian cancer)</td>
<td>Novartis</td>
<td>913, 914</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase II (lung, ovarian and prostate cancers)</td>
<td>Schering AG</td>
<td>368, 915–918</td>
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<th>Mechanism of action</th>
<th>Development status</th>
<th>Developer</th>
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<tr>
<td>Epothilone D (195)</td>
<td>-do-</td>
<td>9,10-Didehydro-epothilone D (KOS-1584) (196)</td>
<td>Oncology</td>
<td>Tubulin stabilization</td>
<td>Phase I/II</td>
<td>Kosan (Memorial Sloan-Kettering)</td>
<td>919</td>
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<tr>
<td>NPI-2350 (halimide, phenylahistin) (197)</td>
<td>Diketopiperazine</td>
<td>NPI-2358 (198)</td>
<td>Oncology</td>
<td>Tubulin binding</td>
<td>Phase II (NSCLC)</td>
<td>Nereus</td>
<td>920–922</td>
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<tr>
<td>Illudin S (199)</td>
<td>Sesquiterpenoid</td>
<td>Irofulven (MGI-114, HMAF) (200)</td>
<td>Oncology</td>
<td>DNA synthesis inhibition</td>
<td>Phase II/III (advanced-stage PC and advanced GI solid tumors)</td>
<td>Eisai (MGI Pharma)</td>
<td>923–926</td>
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**Table 4.** Marine-derived natural product-based drug candidates under clinical evaluation.

<table>
<thead>
<tr>
<th>Lead compound (Str. No.)</th>
<th>Compound class</th>
<th>Name (synonym)</th>
<th>Disease area/Indication</th>
<th>Mechanism of action</th>
<th>Development status</th>
<th>Developer</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Anabaseine (201)</td>
<td>Tetrahydro-pyridinyl pyridine derivative (a nicotinic compound)</td>
<td>3-(2,4-Dimethoxy benzylidene)-anabaseine (DMXBA; GTS-21) (202)</td>
<td>Neurology (Alzheimer’s disease)</td>
<td>Enhances cognition; it acts as a partial agonist at neural nicotinic acetylcholine receptors. It binds to both the α4β2 and α7 subtypes, but activates only the α7 to a significant extent</td>
<td>Phase I/II</td>
<td>CoMentis</td>
<td>927–933</td>
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<tr>
<td>Plitidepsin (Aplidin) (203)</td>
<td>Cyclic depsipeptide</td>
<td>Plitidepsin (Aplidin®) (203)</td>
<td>Oncology</td>
<td>Inhibitor to VEGF, VEGFR1, and G1/G2 phase cell cycle</td>
<td>Phase II</td>
<td>PharmaMar</td>
<td>934–936</td>
</tr>
<tr>
<td>Halichondrin B (204)</td>
<td>Macro cyclic polyether</td>
<td>Eribulin (E7389, NSC-707389) (205)</td>
<td>Oncology</td>
<td>Tubulin assembly inhibition</td>
<td>Phase II/III (advanced or metastatic breast cancer)</td>
<td>Eisai</td>
<td>937–943</td>
</tr>
<tr>
<td>Hemiasterlin (206)</td>
<td>Oligopeptide</td>
<td>E7974 (207)</td>
<td>Oncology</td>
<td>Tubulin assembly inhibition</td>
<td>Phase I (against a variety of human tumor xenografts)</td>
<td>Eisai</td>
<td>944</td>
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(Continued)
<table>
<thead>
<tr>
<th>Lead compound (Str. No.)</th>
<th>Compound class</th>
<th>Name (synonym)</th>
<th>Disease area/Indication</th>
<th>Mechanism of action</th>
<th>Development status</th>
<th>Developer</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Psammaplin A (208)</td>
<td>Symmetrical bromotyrosine-derived disulfide</td>
<td>Panobinostat (LBH-589) (209)</td>
<td>Oncology</td>
<td>Inhibits histone deacetylase (HDAC)</td>
<td>Phase I/II/III</td>
<td>Novartis</td>
<td>945,946</td>
</tr>
<tr>
<td>Bryostatin 1 (210)</td>
<td>Macrolide lactone</td>
<td>Bryostatin 1 (210)</td>
<td>Oncology</td>
<td>Protein kinase C inhibition</td>
<td>Phase I/II</td>
<td>NCI</td>
<td>947–949</td>
</tr>
<tr>
<td>Jorumycin (211)</td>
<td>Dimeric isoquinoline alkaloid</td>
<td>Zalyps® (PM00104/50) (212)</td>
<td>Oncology</td>
<td>DNA binding and transcriptional activity</td>
<td>Phase I (solid tumors or lymphoma)</td>
<td>PharmaMar</td>
<td>950, 951</td>
</tr>
<tr>
<td>Dolastatin 15 (213)</td>
<td>Depsipeptide</td>
<td>Tasidotin (Synthadotin, ILX-651) (214)</td>
<td>Oncology</td>
<td>Induces G2/M phase cell cycle arrest by inhibiting tubulin assembly</td>
<td>Phase II</td>
<td>Genzyme</td>
<td>952–954</td>
</tr>
<tr>
<td>Dolastatin 10 (215)</td>
<td>Depsipeptide</td>
<td>Soblidotin (YHI-501, TZT-1027, Auristatin PE) (216)</td>
<td>Oncology</td>
<td>Tubulin assembly inhibition</td>
<td>Phase II</td>
<td>Yakult Honsha (ASKA Pharmaceutical)</td>
<td>955</td>
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<tr>
<td>Kahalalide F (217)</td>
<td>Depsipeptide</td>
<td>Kahalalide F (217)</td>
<td>Oncology</td>
<td>Alters lysosomal membrane function</td>
<td>Phase II</td>
<td>PharmaMar</td>
<td>956–961</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PM02734 (Irvalec®; 218)</td>
<td>Oncology</td>
<td>Alters lysosomal membrane function</td>
<td>Phase I</td>
<td>PharmaMar</td>
<td>962–965</td>
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Table 5. Animal-derived natural product-based drug candidates under clinical evaluation

<table>
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<tr>
<th>Lead compound (Str. No.)</th>
<th>Compound class</th>
<th>Name (synonym)</th>
<th>Disease area/Indication</th>
<th>Mechanism of action</th>
<th>Development status</th>
<th>Developer</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrodotoxin (TTX; isolated from Pufferfish) (219)</td>
<td>Quinazoline heterocycle</td>
<td>Tetrodotoxin (Tectin™/Tetrodin™) (219)</td>
<td>Neurology (Pain)</td>
<td>Blocks the action potentials in nerves through binding to sodium channels in cell membrane</td>
<td>Phase III (Tectin™ against neuropathic pain in cancer chemotherapy) Phase I (Tetrodin™ in the management of opiate withdrawal symptoms)</td>
<td>Wex Pharmaceuticals (in conjunction with Chinese Medical Institutes)</td>
<td>139, 966–969</td>
</tr>
<tr>
<td>Xen-2174 (220) (isolated from the snail Conus marmoreus)</td>
<td>13-Amino-acid peptide (a conotoxin)</td>
<td>Xen-2174 (220)</td>
<td>Neurology (Pain)</td>
<td>Inhibits norepinephrine transporter (NET)</td>
<td>Phase II (against acute post-operative pain and chronic pain in cancer patient)</td>
<td>Xenome</td>
<td>970–973</td>
</tr>
<tr>
<td>Trodusquemine (221) (isolated from the liver of the dogfish shark, Squalus acantbias)</td>
<td>Sulfated aminosterol</td>
<td>Trodusquemine (MSI-1436) (221)</td>
<td>Diabetes</td>
<td>Suppresses mammalian appetite through inhibition of protein tyrosine phosphatase 1B (PTP-1B)</td>
<td>Phase I (against type 2 diabetes and related symptoms)</td>
<td>Genaera Corporation</td>
<td>974–978</td>
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### Table 5. (Continued)

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<thead>
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<th>Lead compound (Str. No.)</th>
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<th>Developer</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indolicidin (222)</td>
<td>Peptide</td>
<td>Omiganan (223)</td>
<td>Antibacterial</td>
<td>Through bacterial cytoplasmic membrane interaction</td>
<td>Phase III</td>
<td>Developed by MIGENIX; licensed to Cadence Pharmaceuticals and Cutanea Life Sciences for catheter-related infections (coded Omigard™, CPI-226, MBI-226) and dermatological diseases (coded as CLS001, MX-594AN), respectively. Primary end point was not achieved in a Phase III trial and additional Phase III trials using a gel-based formulation by Cadence Pharmaceuticals are underway. Cutanea Life Sciences have successfully evaluated 222 in Phase II trials (2007) and the Phase III trials for treatment of rosacea, a chronic inflammatory skin disorder are underway.</td>
<td>979–983</td>
</tr>
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</table>
Fig. 2. Plant-derived drug candidates under clinical evaluation.
Fig. 2. (Continued)
Camptothecin (84): R = H
Karenitecin (85): R = \( \text{Si} \)
Gimatecan (87): R = \( \text{NO} \)

Diflomotecan (86)

Elomotecan (88)

DRF 1042 (89)

SN2310 (90)

Fig. 2. (Continued)
Combretastatin A-4 (91): \( R = \text{OH} \)
Combretastatin A-4 phosphate (92): \( R = \text{OPO}_3\text{Na}_2 \)
Ombrabulin (AVE-8062) (93): \( R = \text{H} \)
Combretastatin A-1 (94): \( R = \text{H} \)
OXi4503 (95): \( R = \text{PO}_3\text{Na}_2 \)

Pacitaxel (96): \( R_1 = \text{CH}_3, R_2 = \text{H} \)
BMS-188797 (104): \( R_1 = \text{OCH}_3, R_2 = \text{H} \)
DHA-paclitaxel (99): \( R_1 = \text{CH}_3, R_2 = \text{O} \)

Larotaxel (98)
Milataxel (101)

Fig. 2. (Continued)
Fig. 2. (Continued)
Fig. 2. (Continued)
Fig. 2. (Continued)
Fig. 3. Microorganism-derived drug evaluation.
Sulopenem (135)

Faropenem daloxate (136)

Teicoplanin analog (137): $R = OH$

Dalbavancin (138): $R = \text{NCH}_{3}$

Fig. 3. (Continued)
Chloroeremomycin (139): $R = H$

Oritavancin (140): $R = \text{Cl}$

TD-1792 (141)

Fig. 3. (Continued)
Ramoplanin factor A2 (142)

Flopristin (143)

Linopristin (144)

Fig. 3.  (Continued)
Friulimicin (145)

H-Ala-Lys-Gin-Ala-Ala-Phe-Gly-Pro-Phe-Abu-Phe-Val-Ala-HOAsp-Gly-Asn-Abu-LysOH

Duramycin (Moli 901) (146)

Erythromycin (147)

Cethromycin (148)

Fig. 3. (Continued)
Fig. 3. (Continued)
Fig. 3.  (Continued)
Fig. 3. (Continued)
Patrician A (160): $R_1 = OH$, $R_2 = H$

SPK-843 (161): $R_1 = \text{amino}$, $R_2 = \text{amino}$

Cyclosporin (162): $R = \text{alkyl}$

NIM-811 (163): $R = \text{alkyl}$

KRN5500 (164)

Fig. 3. (Continued)
Galactonojirimycin (165): $R = \text{OH}$
Migalastat (166): $R = \text{H}$

Staurosporine (167)

Ruboxistaurin (168)

Voclosporin (169)

Pladienolide D (170): $R = \text{Ac}$
E7107 (171): $R =$

Elsamicin A (172)

Fig. 3. (Continued)
Fig. 3. (Continued)
Brostatlicin (179)

Geldanamycin (180): R = OCH₃
Tanespimycin (181): R =
Alvespimycin (182): R =

Retaspimycin (183)

Sirolimus (34): R = H
Deforolimus (Ridaforolimus) (184): R =

Fig. 3. (Continued)
Salinosporamide A (185)

Enzastaurin (186)

Midostaurin (187)

K252a (188): R = COOCH₃

Lestaurtinib (KT-5555) (189): R = CH₂OH

KRX-0601 (190)

Diazepinomicin (191)

Prodigiosin (192)

Obatoclax (193)

Sagopilone (194)

Fig. 3. (Continued)
Fig. 3. (Continued)
Fig. 4. Marine-derived drug candidates under clinical evaluation.
**Fig. 4.** (Continued)
Natural Products in Drug Discovery

Jorumycin (211)

Zalypsis (212)

Dolastatin 15 (213): R =

Tasidotin (214): R =

Dolastatin 10 (215): R =

Soblidotin (216): R =

Fig. 4. (Continued)
Kahalalide F (217): $R = \begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \\ \text{CH}_3 \end{array}$

PM02734 (218): $R = \begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \\ \text{CH}_3 \end{array}$

Fig. 4. (Continued)
8. Concluding Remarks

Natural products continue to play a dominant role in the discovery of leads for the development of drugs to treat human diseases. Such chemical agents have traditionally also played a major role in drug discovery and still constitute a prolific source of novel chemotypes or pharmacophores for medicinal chemistry. Natural product-based scaffolds find key importance in drug discovery as well as in optimizing chemical diversity.
for human use. The impact of natural products on the development pipelines of the pharmaceutical industry is unabated. Despite increasing competition from combinatorial and classical compound libraries, there has been a steady introduction of natural product-derived drugs in the past years. Substances like taxol, cyclosporines and the “statins” are cornerstones of modern pharmacotherapy.

We should think of the real scenario that the vast majority of different natural sources remain virtually untapped. It is estimated that only 5–15% of the approximately 250,000 species of higher plants (terrestrial flora) have been investigated chemically and pharmacologically so far; hence, the large areas of tropical rainforests demands for thorough investigation that would unearth tremendous potential at large. The marine kingdom stands as an enormous resource for the discovery of potential chemotherapeutics, and is waiting for its proper exploration. Another vast unexplored area is the microbial world; it has been reported that “less than 1% of bacterial species and less than 5% of fungal species are currently known, and recent evidences indicate that millions of microbial species remain undiscovered. “Mother Nature” is thus, an inexhaustible source of drugs and lead molecules. The abundant scaffold diversity in natural products is coupled with “purposeful design” — usually to afford an advantage for survival in environments threatening growth and/or survival of producer organism. The quality of leads arising from natural product discovery is better and often more biologically friendly, due to their co-evolution with the target sites in biological systems.

Natural products, thus, still serve as an excellent source for modern drug discovery and development. The traditional strengths of natural products in oncology and infectious diseases are still ahead from the compounds under clinical trials against metabolic and other diseases. Through a medicinal chemistry approach, natural products with low bioactivity or known compounds can be modified synthetically to improve their pharmacological profiles. A good number of commercially approved drugs originated from natural products as well as the huge number of natural product-derived compounds in various stages of clinical development indicate that the use of natural product templates is still a viable source of new drug candidates.
Acknowledgements

Fruitful and valuable works of numerous researchers worldwide, upon which the present manuscript is based, are being acknowledged herein. The author is grateful to all of them regardless their names are enlisted in the reference section or not.

Abbreviations

- AChE: acetylcholinesterase
- AD: Alzheimer’s disease
- ADHD: attention deficit hyperactivity disorder
- ADMET: absorption, distribution, metabolism, excretion, and toxicity
- AECB: acute exacerbations of chronic bronchitis
- AIDS: acquired immune deficiency syndrome
- BBB: blood–brain barrier
- CAM: complementary and alternative medicine
- CAP: community-acquired pneumonia
- CDAD: Clostridium difficile-associated diarrhea
- CDKN1A: cyclin-dependent kinase inhibitor 1A
- CDRI: Central Drug Research Institute
- CF: cystic fibrosis
- CGRP: calcitonin gene-related peptide
- CIMAP: Central Institute of Medicinal and Aromatic Plants
- CKD: chronic kidney disease
- COPD: chronic obstructive pulmonary disease
- cSSSIs: complicated skin and skin structure infections
- DNA: deoxyribose nucleic acid
- DTI: direct thrombin inhibitor
- EMEA: European Medicines Agency
- ERT: enzyme replacement therapy
- FAAH: fatty acid amide hydrolase
- FAH: fumaryl acetoacetate hydrolase
- FDA: Food and Drug Administration (USA)
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>GLP-1</td>
<td>glucagon-like peptide-1</td>
</tr>
<tr>
<td>HAP</td>
<td>hospital-acquired pneumonia</td>
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<tr>
<td>HCT</td>
<td>human colon cancer</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HDAC</td>
<td>histone deacetylase</td>
</tr>
<tr>
<td>HDL-C</td>
<td>high-density lipoprotein-cholesterol</td>
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<tr>
<td>HIF-1</td>
<td>hypoxia-inducible factor</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HMG-CoA</td>
<td>3-hydroxy-3-methylglutaryl coenzyme A</td>
</tr>
<tr>
<td>HPPD</td>
<td>p-hydroxyphenylpyruvate dioxygenase</td>
</tr>
<tr>
<td>HT-1</td>
<td>hereditary tyrosinemia type 1</td>
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<tr>
<td>IMPDH</td>
<td>inosine monophosphate dehydrogenase</td>
</tr>
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<td>IND</td>
<td>investigational new drug</td>
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<td>LDL-C</td>
<td>low-density lipoprotein-cholesterol</td>
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<td>MAA</td>
<td>marketing authorization application</td>
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<td>MetAP-2</td>
<td>methionine aminopeptidase-2</td>
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<td>mTOR</td>
<td>mammalian target of rapamycin</td>
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<td>National Cancer Institute (USA)</td>
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<tr>
<td>NDA</td>
<td>new drug application (USA)</td>
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<td>NET</td>
<td>neuroendocrine tumor</td>
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<td>NF-AT</td>
<td>nuclear factor of activated T cells</td>
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<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
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<td>OC</td>
<td>ovarian cancer</td>
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<td>OIC</td>
<td>opioid-induced constipation</td>
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<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>PGE₂</td>
<td>prostaglandin E₂</td>
</tr>
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<td>PPAR</td>
<td>peroxisome proliferator-activated receptor</td>
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<tr>
<td>PTP-1B</td>
<td>protein tyrosine phosphatase 1B</td>
</tr>
<tr>
<td>QSAR</td>
<td>quantitative structure–activity relationship</td>
</tr>
<tr>
<td>RCC</td>
<td>renal cell carcinoma</td>
</tr>
<tr>
<td>RNA</td>
<td>ribose nucleic acid</td>
</tr>
<tr>
<td>S6K1</td>
<td>S6 ribosomal protein kinase</td>
</tr>
<tr>
<td>SEGA</td>
<td>subependymal giant cell astrocytoma</td>
</tr>
<tr>
<td>SGLT</td>
<td>sodium glucose co-transporter</td>
</tr>
<tr>
<td>SRT</td>
<td>substrate reduction therapy</td>
</tr>
<tr>
<td>STS</td>
<td>soft tissue sarcoma</td>
</tr>
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</table>
TCL  T-cell lymphoma
*tNOX  NADH oxidase
VEGF  vascular endothelial growth factor
VR 1  vanilloid receptor subtype 1
WHO  World Health Organization

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