TERPENES

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Medicinal Chemistry Lessons From Nature

(Volume 2)

Terpenes

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FOREWORD

From the dawn of time, men resorted to Nature for all they need. No exception was made for health and, especially, pain. WHO estimated that almost 80% of people count on medicinal plants to take care of their "well-being" and here is the justification for the growing interest in the study of natural products and the development of their derivatives.

Among the wide range of molecules in the rich repository that Nature offers, we need to mention the terpene class, to which a whole volume of this book has been dedicated.

This volume aims to provide the readers with a brief and focused collection of some of the latest advances in the field with particular insight into the development of synthetic derivatives from a parent natural compound with highly promising bioactivity and the design of innovative formulations for possible administration.

Indeed, by scrolling through the volume index, the readers can find exciting novelty on terpenes-related topics in four well-organized chapters, including (1) a detailed overview of the sesquiterpenes polypharmacology; (2) an interesting journey around the cannabinoids world towards the development of new synthetic Δ9-THC derivatives; (3) the design of specific formulations to overcome the volatility issue of small sized terpenes-based essential oils; and (4) an update on the newest generations of endoperoxides endowed with antimalarial activity. Also, the interested audience is strongly encouraged to get more deepen understanding of the presented topics by a large number of selected references present in each chapter.

Notably, every topic dealt with in this volume, and in general in the whole book, fully describes the selected terpene scaffold in all the investigated MedChem and pharmaceutical points of view. Thus, detailed information on the design and synthesis of the compounds, their bioactivity and pharmacokinetics data, along with computational and formulation studies are provided.

The authors, also, discuss how the chemical modification of parent compounds affects biological or enzymatic activity and ADME profile, suggesting how to justify the changes in the activity/ADME data in MedChem terms.

Through the several examples of MedChem strategies to fix the most common issues on terpene derivatives, *e.g*. low potency and poor solubility, the authors drive the young researcher audience to derive general rules that could be useful in different experiments and studies they will perform. For these reasons, I strongly believe the book is addressed to a heterogeneous audience, comprising both expert and beginner MedChem scientists and pharmaceutical technologists and anyone who wants to update their knowledge on this broader and broader field of terpene research under the kind and helpful guidance of the authors, which are widely recognized scientists in Academia.

In the next chapters, the readers will find recurrent concepts that we could summarize with the following keywords: #terpenes; #sesquiterpenes; #medicinalchemistry; #pain; #malaria; #naturalproducts; #optimization; #drugdesign; #bioactivity; #synthesis; #computationalchemistry; #biology; #chemistry; #formulation; and so on.

Good reading and taking notes.

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PREFACE

Natural products are often used in drug development due to their ability to provide unique and chemically diverse structures unmatched by any synthetic chemical collection. Medicinal Chemists have always been inspired by nature because natural products are often perceived as safer and for their capability to interact with biological targets. Indeed, in recent years, there has been emerging research on traditional herbal medicines based on their efficacy in the treatment of diseases for which they have been traditionally applied.

Conversely, natural compounds suffer from several issues such as scarce availability and seasonality, high differences in the production/extraction/isolation, low purity in commercial products from worldwide suppliers, and side effects. Moreover, due to their chemical complexity and the optional presence of different chiral centers, the total synthesis of a natural compound can be also challenging and expensive.

This book series would propose the latest discoveries in the field of compounds inspired by nature and obtained by chemical/enzymatic modification of a natural compound in the search for biologically active molecules for the treatment of human/animal ailments and permit the disposal of a wider arsenal for clinicians. The natural compounds are grouped into three clusters. The chapters are built in the following format: • General background on the (phyto)chemistry of the scaffold; • General background on the pharmacological profile of the scaffold; • Description of the proposed derivatives and their potentialities with respect to the parent compounds (with a particular emphasis on the synthetic approaches and structure-activity relationships); • *In silico* analysis of the crucial interactions with the biological target, when available; • Clinical studies and patent surveys (if available) on the new and proposed structures.

The readership of this book is represented primarily by Academies, Researchers, Specialists in the pharmaceutical field, Industry sector, Contract Research Organizations and hospitals dealing with clinical research.

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CHAPTER 1

Sesquiterpenes: A Terpene Subclass with Multifaceted Bioactivities

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Abstract: Sesquiterpenes are terpene compounds, containing three isoprene units rearranged in a wide variety of structures. They occur widely in nature, not only in plants but also in fungi and marine environments. Owing to peculiar structures and diverse biological activities, they attracted great attention in pharmaceutical, medicinal chemistry and nutraceutical fields. The present chapter collects novel insights into chemistry, distribution in nature and pharmacological properties of sesquiterpenes, focusing especially on caryophyllane, lactone-type, and eremophilane subgroups, due to the growing pharmacological interest. Novel structures and alternative natural sources to be further investigated and exploited have been highlighted too. Moreover, some issues regarding toxicity risk and bioavailability of sesquiterpenes, which can limit their application in practice, have been discussed.

Keywords: Artemisinin, Alantolactone, Arglabin, Anticancer, Antimalarial, Antiinflammatory, Antimigraine, β-Caryophyllene, Capsidiol, Chemopreventive, Eremophilane, α-Humulene, Helenalin, Isopetasin, Parthenolide, Petasin, Terpenes.

INTRODUCTION

Terpenes are a large class of structurally diverse and widely distributed secondary metabolites, derived from a common basic building block, namely five-carbon isoprene unit (C_5H_8), assembled in linear chains or cyclic structures Table **1**. More complex and functionalized terpenes, namely terpenoids, can also occur in nature [1].

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Table 1. Classification of terpene subclasses

Terpene Subclass	Isoprene Units	Number of Carbons
Monoterpenes	2	C10
Sesquiterpenes	3	C15
Diterpenes	4	C20
Sestertepenes	5	C25
Triterpenes	6	C30
Tetraterpenes	8	C40

Two major biosynthetic routes, namely the mevalonate (MVA) pathway and 2C-methyl-D-erythritol-4-phosphate (MEP) pathway (or Rohmer pathway), have been reported to be the terpene sources [2, 3]. The MVA pathway leads to the formation of the terpenoid C5 precursors isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP): three molecules of acetyl-CoA are condensed to a 3-hydroxy-3-methylglutaryl-CoA, which is subsequently reduced to MVA, whose phosphorylation and further rearrangements lead to IPP and DMAPP (Fig. **1**) In the MEP (or Rohmer) pathway, 1-deoxy-D-xylulose 5-phosphate, obtained by condensation of pyruvate and glyceraldehyde 3-phosphate, is converted into MEP which further leads to IPP and DMAPP, the basic building blocks of all terpene (Fig. **1**).

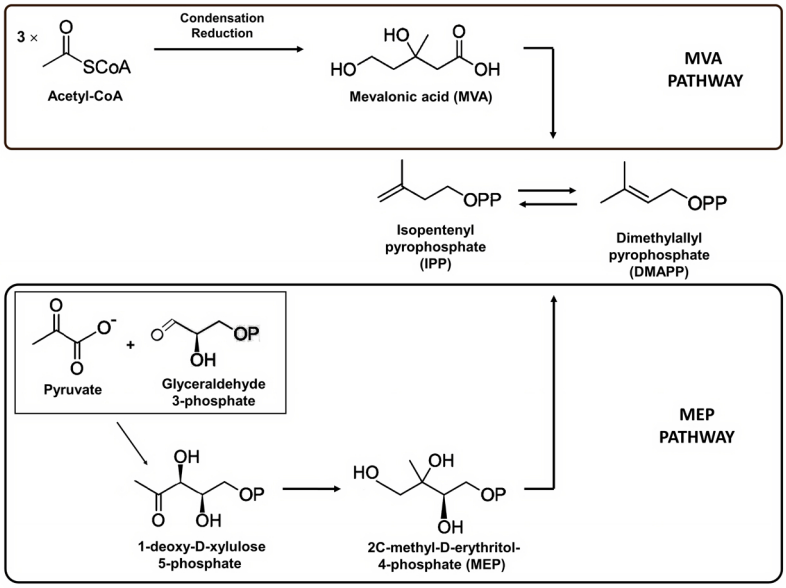

Fig. (1). Biosynthetic pathways of terpenes: MVA or mevalonate pathway and MEP (2C-methyl-D-erythritol-4-phosphate) or Rohmer pathway.

Isoprene directly originates from IPP or DMAPP, while monoterpenes are synthesized from a geranyl pyrophosphate (GPP) precursor (also known as geranyl diphosphate or GDP), produced by the condensation of IPP and DMAPP (Fig. **2**) [4]. GPP and one molecule of IPP can be condensed to farnesyl diphosphate (FPP), which can be further converted into different sesquiterpenes and triterpenes; furthermore, the addition of IPP to FPP leads to geranyl geranyldiphosphate (GGPP), from which diterpenes and tetraterpenes (or carotenoids) arise [4].

Terpenes are produced by a wide variety of plants, fungi and some animals, mediating antagonistic and beneficial interactions among organisms [2]. Particularly, high terpene levels have been found in plant reproductive structures and foliage, where they can act as allelopathic compounds, mediating plant biotic and abiotic interactions [1]. Indeed, some of them, especially volatile compounds, have been exploited by plants as a weapon against herbivores and pathogens; moreover, other compounds can mediate plant metabolic adaptation to climate changes and regulate cell membrane permeability due to their lipophilic nature [5]. For instance, in response to root feeding by caterpillars, corn (*Zea mais* L.) roots release the sesquiterpene β-caryophyllene, which is attractive to entomopathogenic nematodes and stimulates their killing ability against herbivore larvae [6].

The monoterpene ketone pulegone has been reported to be the main environmental defense released by *Mentha pulegium* L., while helivypolides, annuolides and helibisabonols are the most significant allelochemicals produced by sunflower (*Helianthus annuus* L.) [7, 8]. Similarly, monoterpenes and sesquiterpenes contained in the essential oil from *Cinnamomum septentrionale* Hand.-Mazz. produced phytotoxic effects against several species, such as *Taraxacum officinale* L. and *Eucalyptus grandis* L [8].

Another example of allelopathic interaction is the *"Salvia phenomenon"*, characterized by the ability of some *Salvia* species (i.e. *Salvia leucophylla* and *S. apiana*) to form a typical vegetation patterning in the soil in its vicinity, due to the production of monoterpenoids (i.e. camphor, 1,8-cineol, β-pinene, α-pinene and camphene) which hinder the growth of other plants [8]. The phytotoxic effects of *Salvia* spp. have been also ascribed to the presence of di- and triterpene compounds, which include clerodane and neo-clerodane diterpenoids [9]; moreover, a number of phytotoxic diterpenes have been found in both plant and microorganisms [10].

Terpenes have attracted great scientific attention due to their multiple biological properties, thus strengthening the industrial interest in their application as

CHAPTER 2

From Δ^9-THC to Synthetic Cannabinoids: Multi-Faceted Therapeutic Agents and Versatile Scaffolds for Drug Discovery

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Abstract: *Cannabis sativa* L. has been used for millennia by humans for medicinal, ritual and recreational uses. Commonly known under its dried form (flowers and leaves) as marijuana, this plant produces hundreds of phytomolecules, including phytocannabinoids, terpenes and flavonoids. Over the past decades, it is most abundant and most therapeutically relevant component, (-)-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC) has generated considerable interest due to its various therapeutic properties. Most of them result from the interaction with two G-protein coupled receptors named cannabinoid receptors (CB1 and CB2). This chapter gives a broad overview of the main structural investigations performed on the natural scaffold of Δ^9-THC in order to modulate the affinity for the cannabinoid receptors and, potentially, its therapeutic properties. The design of several synthetic cannabinoid derivatives will be presented, and their structure-activity relationships will be analysed.

Keywords: Cannabinoids, Cannabinoid Receptors, Structure-Activity Relationship, Synthesis, Δ^9-THC, Δ^8-THC, Therapeutic Application.

INTRODUCTION

HISTORY OF CANNABIS SATIVA L.

Cannabis sativa L. is considered a very unique plant due to its history, chemistry, pharmacology, toxicology, and deep social impact. *Cannabis sativa* L. belongs to the family of Cannabaceæ which includes only two genera (*Cannabis* and *Humulus*). The various subspecies of *C. sativa* L. identified so far mostly reflect the chemotype or geographical variants of a single taxonomic entity rather than distinct species [1]. It is one of the best characterized plant varieties with an

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inventory of at least 489 natural compounds identified so far [2], comprising many different chemical classes, such as mono- and sesquiterpenes, sugars, steroids, flavonoids, hydrocarbons, nitrogen compounds, and especially cannabinoids, which are terpenophenolic compounds. Marijuana, a drug derived from *Cannabis sativa* L., is an illicit substance made mainly of the dried flowers and leaves of the plant which is sold in the illegal market. Despite the prohibitions, marijuana is the most cultivated, trafficked, and consumed drug in the world. This versatile crop has been used for millennia by humans, not only for recreational or ritual purposes but also for medicinal uses. Whereas its medicinal and psychoactive properties were well known for thousands of years, the elucidation of the mechanisms of actions of cannabis was only established in the late 19th century. Indeed, in 1843 Sir William B. O'Shaughnessy, an Irish physician, was the first to report on the medical use of cannabis, noting that hemp: "*possesses, in small doses, an extraordinary power of stimulating the digestive organs, exciting the cerebral system, of acting also on the generative apparatus*" [3]. The report also noted the ability of hemp oil to alleviate pain and to reduce seizures in infants. Cannabinol **1** was the first compound isolated in 1896 [4] and was initially considered as the active constituent of cannabis. Its chemical structure was fully elucidated only in 1940 (Fig. (**1**) [5, 6] together with the isolation of several other non-cannabinoid natural products, including cannabidiol **2** (CBD) [7]. Finally, the active component of cannabis, (–)-Δ^9-tetrahydrocannabinol **3** (Δ^9-THC), was discovered in 1964 by Gaoni and Mechoulam, who reported its structure elucidation and its partial synthesis [8].

Biogenesis of Phytocannabinoids

More than 100 natural products were isolated from *Cannabis sativa* L. and characterized mostly in the 1960s and 1970s [2, 9 - 11]. These compounds have been divided according to their structure into different classes, including the two predominant Δ^9-THC **3** and CBD **2**, Cannabinol **1** (CBN), but also Δ^8-*trans*-tetrahydrocannabinol **4** (Δ^8-THC), Cannabigerol **5** (CBG) and Cannabichromene **6** (CBC) among others (Fig. **1**).

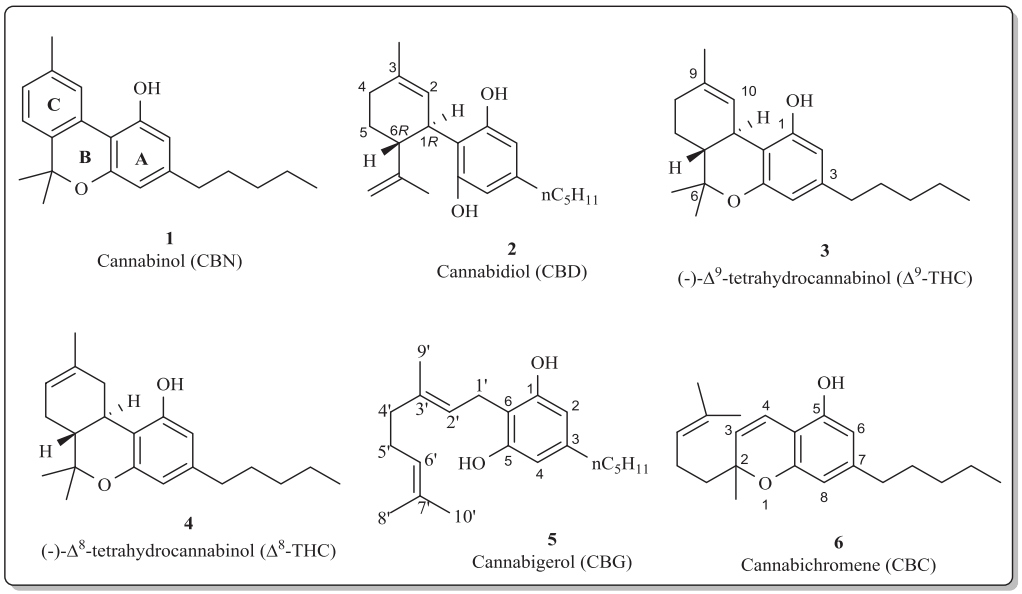

Fig. (1). Main phytocannabinoids isolated in *Cannabis sativa* L.

The biogenesis of phytocannabinoids is summarized in Scheme **(1)** [12, 13]. The natural precursor *n*-hexanoylCoA **7** is transformed into olivetolic acid **9** through the tri-fold addition of malonyl-acetate derived units **8**, followed by cyclization and aromatization. A specific prenyltransferase catalyzes the condensation of **9** and geranyl phosphate (GPP, **10**) [14 - 16] to afford cannabigerolic acid (CBGA, **11**) which gives, after decarboxylation, cannabigerol **5**. It is nowadays generally accepted that the decarboxylation step for CBGA **11** and all the other cannabinoids is non-enzymatic and occurs spontaneously during either the storage, the extraction or the purification of the compounds. The oxidative intramolecular cyclization of **11** leads to the formation of cannabichromenic acid (CBCA, **12**) and, by decarboxylation, cannabichromene **6**. Moreover, the oxidation of CBGA **11** is also leading to the formation of a link between C-1 and C-6 of the prenyl unit, affording cannabidiol **2**, the main constituent of the fiber-type (non-psychotropic) varieties of *C. sativa.* This stereospecific intramolecular cyclization occurs through the cationic intermediate **13** and is catalysed by *CBDA synthase* [17], which has been isolated and characterized [18]. Another enzyme, *THCA synthase*, promotes the attachment of the phenolic oxygen leading to the formation of the tricyclic system of tetrahydrocannabinolic acid (THCA) **14**. As mentioned above, its decarboxylated analog Δ^9-THC **3** is considered as an artifact since its concentration in extracts increases during storage, while simultaneously, the concentration of THCA **14** decreases. Numerous analogues sharing this terpenoid structural framework have been identified: Δ^8-THC **4** shows

CHAPTER 3

Encapsulation of Essential Oils within Lipid-Based Formulations for Enhanced Antimicrobial Activity

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Abstract: Aromatic plants have been used since ancient times for their medicinal properties, including potent antimicrobial activity. Strong evidence indicates that plant extracts, in general, and essential oils (EOs), in particular, can act as effective antimicrobial agents against a wide spectrum of pathogenic microorganisms. However, their poor water solubility and stability, as well as their high volatility, make the administration of EOs to achieve the desired therapeutic effects particularly challenging. Therefore, these features severely limit the application of EOs in the pharmaceutical field. In this context, nanotechnology-based strategies for developing nano-scaled carriers for the efficient delivery of EOs might offer potential solutions. In particular, considering the lipophilic nature of EOs, lipid-based nanocarriers represent the most suitable vehicles for the effective encapsulation and delivery of EOs. This chapter provides an overview of the different chemical compositions due to various endogenous and/or exogenous factors of a selection of oils and the most recent lipid-based encapsulation strategies to enhance their antimicrobial activity and promote their pharmaceutical application.

Keywords: Antimicrobial Activity, Chemical Composition, Essential Oils, Encapsulation, Liposomes, Microemulsions, Nanoemulsions, Nanostructured Lipid Carriers, Solid Lipid Nanoparticles.

INTRODUCTION

Essential oils (EOs) are very complex natural mixtures that can contain around 60 components at quite different concentrations. These volatile compounds extracted from plants or plant organs like flowers, seeds, buds, leaves, fruits, wood, roots, barks and twigs are responsible for the characteristic flavour and aroma. There are several methods for extracting EOs: by use of liquid carbon dioxide or microwaves, by distillation (*via* steam and/or water) or mechanical methods, such

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as cold pressing. The aromatic chemicals that give the typical essence to each oil are extracted and combined with carrier oil.

EOs can be applied in various cases, including pharmaceutical and health industries but are most commonly used in the practice of aromatherapy; they are also used in a wide range of consumer goods, such as soaps, detergents, toilet products and cosmetics. EOs are obtained from aromatic flora or plants bearing many Angiospermic families, such as Rutaceae, Lamiaceae, Myrtaceae, Asteraceae and Zingiberaceae [1]. All EOs have their own unique smell and potential health benefits, such as for treating insomnia (lavender oil), as an antibiotic and antimicrobial (peppermint and tea tree oils) or as an anti-inflammatory (cumin and rosemary oils). The presence of a variety of diverse constituents in EOs could be responsible for wide spectrum of biological activities of the plant.

EOs are products of an unregulated sector, and the quality and their chemical composition can vary greatly. In this regard, it is very important that an EO is pure and of high quality, that it is free of synthetic additives and that has not been modified during the extraction process from the plant.

The main volatile constituents of EOs are terpenes, organic compounds consisting of multiples of isoprene units (containing five carbon atoms) and linear-chain, aromatic or heterocyclic compounds. Different combinations of the isoprene units originate structurally and functionally different classes of terpenes [2]. When a terpene contains oxygen, it is called a terpenoid.

Generally, hydrocarbons and oxygenated compounds such as alcohols, aldehydes, ketones, acids, esters, and oxides are responsible for odors and the characteristic aroma. The analytical technique useful for determining the chemical composition of EOs is gas chromatography. There are many reports in the literature that have contained useful information about the composition of different EOs [3 - 5]. EOs are complex materials and multi-component systems classified into non-volatile, semi-volatile, and volatile compounds according to their nature. Furthermore, the chemical composition of EOs depends on the place of origin, climatic conditions, and plant species [6]. By the analysis of EO, the following compounds are found in varying proportions, and they are the main groups [7]:

TERPENE HYDROCARBONS

-Monoterpene hydrocarbons: found in almost all EOs and have a structure of 10 carbon atoms and at least one double bond. The 10 carbon atoms are derived from two isoprene units.

-Sesquiterpenes: they consist of 15 carbon atoms and have complex pharmacological actions.
Monoterpenes, diterpenes, and sesquiterpenes are the main groups of terpenes found in spices and herbs; they have notable biological activities such as antimicrobial effects on different pathogens [8, 9].

Oxygenated Compounds

• Phenols: some examples are thymol, eugenol and carvacrol. These components have great antiseptic, antibacterial and disinfectant qualities.
• Alcohols: they are divided into monoterpene and sesquiterpene alcohols, such as linalool, citronellol, terpineol and bisabolol.
• Aldehydes: they have antifungal, anti-inflammatory, disinfectant, and sedative therapeutic properties.
• Ketones: they can be toxic, but they also have some great therapeutic benefits.
• Esters: like linalyl acetate, they are normally very fragrant and tend to be fruity and their therapeutic effects include sedative and antispasmodic activities.
• Ethers: the most common are the phenolic ones, such as the anethole present in anise.
• Oxides: the main therapeutic effect of oxides is that of expectorant, with 1,8-cineole, commonly known as eucalyptol, the best known.

Finally, lactones and coumarins can also be found.

The chemical profile of an EO, even obtained from the same species, may differ according to the geographical source and the harvest season of a particular plant species and also for the same species from different regions [10 - 13]. Genotype, interaction with the environment and agronomic conditions, such as the age of the plant, the degree of maturity of the plant, the harvest time and the composition of the soil, can influence the quali-quantitative composition of EO [11, 14]. Furthermore, the extraction product can vary in quality and/or quantity depending on the type of extraction method chosen [15].

In this regard, Table **1** shows different chemical compositions of a selection of EOs endowed with antimicrobial properties. They have been selected on the base of the formulation studies reported in the following paragraphs.

NANOENCAPSULATION OF ESSENTIAL OILS

EOs represent an important part of the traditional Pharmacopeia [115]. Nowadays, a large number of biological activities have been reported for EOs to prevent and treat human diseases, and, in particular, a lot of evidence exists on their antimicrobial properties [116, 117].

CHAPTER 4

Antimalarial Endoperoxides: from Natural Sesquiterpene Drugs to a Rising Generation of Synthetic Congeners

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Abstract: Malaria is a vector-borne tropical disease caused by protozoans belonging to the genus *Plasmodium*, which has been scourging mankind for hundreds of millions of years. Despite the masterful progress in preventing disease transmission and reducing morbidity and fatal outcomes, malaria is on the rise again. Global concerns are focused on the spread of resistance to current drugs in the management of severe or ultimately lethal *P. falciparum* infection. To fully exploit the potential of existing agents and overcome their critical drawbacks, novel synthetic and formulation approaches have been explored. In this field, the clinical value of the natural drug artemisinin (ART) and its derivatives have been firmly established, and ART combination therapies (ACTs) have been recommended as first-line treatment against infection caused by chloroquine-resistant (CQR) *P. falciparum* strains. Over time, however, ART treatment options have become inadequate, and strict demand for new and effective agents has emerged. In this chapter, the medicinal chemistry aspects of artemisinins will be discussed, covering their unique mode of action and their structural features in relation to stability, pharmacokinetic profile, and antiplasmodial activity. Beyond ACT strategies, significant classes of compounds obtained through both ART covalent bitherapy and dimerization approaches will be presented as well. Furthermore, a special section will focus on the most recent endoperoxide-based synthetic antimalarials as new powerful and cost-effective alternatives to the "golden drug". It is expected that reported results will provide a strong incentive for further studies, and that unceasing research efforts will succeed in reaching the eventual eradication of this endemic plague.

Keywords: Antimalarial drugs, Artemisinin (ART), Artemisinin combination therapy (ACT), Chloroquine (CQ), Covalent bitherapy, Endoperoxides, Iron(II)protoporphyrin IX, Malaria, Molecular hybridization, Multidrug-resistant, Ozonides, Protozoan, *Plasmodium* spp., Sesquiterpene, 1,2,4,5-tetraoxanes, 1,2,4-trioxanes, 1,2,4-trioxolanes, World Health Organization (WHO).

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INTRODUCTION

Malaria is a devasting, vector-borne parasitosis caused by ancient unicellular protozoans of the genus *Plasmodium,* members of the large Apicomplexa taxon. This plague is endemic in tropical and sub-tropical regions, affecting approximately 40% of the world's population. Although malaria ranks fourth among the major human infectious diseases, after pneumococcal acute respiratory infections, acquired immunodeficiency syndrome (AIDS) and tuberculosis (TBC), it is recognized that *Plasmodium* spp. represent the deadliest parasite species throughout the history of mankind [1]. The reasons for parasite survival and continued infection in the human race are the results of an intricate evolutive interplay between hosts, pathogens, and infected vectors, deeply connected with climatic and socio-economic variables.

Over time, an impressive advance in antiplasmodial prophylaxis, chemotherapy, and transmission control through national malaria campaigns has been made, culminating in a sensible decline in disease incidence and associated mortality in many areas of the world in the last decade [2]. According to the World Health Organization (WHO), in 2019, malaria affected 229 million people, with 22 million fewer cases than in 2010 [3]. Unfortunately, in recent years the decrease in malaria burden has stagnated, owing to the persistence of critical conditions in endemic regions that undermine the success of therapeutic/prophylactic protocols and vector containment programs. However, the main causative factor for this *debacle* resides in the great genetic variability of the etiologic agent, leading to a highly adaptive response under widespread drug pressure.

The case of parasite drug resistance is ideally exemplified by the first-line antimalarial agent chloroquine (CQ); introduced in 1950s, this very effective and remarkably cheap drug was the most widely used in the 4-aminoquinolines class for the treatment of uncomplicated *Plasmodium falciparum* malaria till the emergence, over the course of 30 years, of chloroquine-resistant *P. falciparum* (CRPF) strains. The main mechanism of resistance envisions subsequent mutations in the gene *Pfcrt*, which encodes for the parasite CQ resistance transporter (*Pf*CRT) protein, whose amplification leads to an enhancement in the extrusion of the xenobiotic from the digestive vacuole (DV) of the protozoan [4, 5]. Moreover, the degree of resistance can be modulated by polymorphisms in the *P. falciparum* multidrug resistance-1 (*Pf*MDR1) protein, an ABC transporter that also regulates the flux of CQ across the DV membrane [5, 6].

An important contributor to resistance is the elimination time of the dispensed agent from the body; by administering drugs with short half-lives, the window of selection (*i.e.*, the time during which antimalarial drugs persist at sub-therapeutic

concentrations) for drug tolerance and resistance are minimized. Accordingly, at least till 2008, there was no evidence for clinically relevant resistance of *Plasmodium* parasites to artemisinin, a superior drug for the treatment of multidrug-resistant *falciparum* malaria, possessing a very short half-life (~ 1-3 h). The approach of ART co-formulation with a second, longer-acting antimalarial, commonly termed artemisinin combination therapy (ACT), has emerged as a means to confer greater protection against the development of drug-resistant mutants, preserving the effectiveness of ART and the partner agent in the time.

Furthermore, present *Plasmodium* species are the result of a hundred million years of apicomplexan evolutionary adaptation to increasingly elaborate host innate and acquired immunity, and consequently display a high degree of antigen variability to escape such defenses, and to arrange alternative invasion pathways through the generation of functionally redundant ligands for human cell receptors [7, 8]. This scenario emphasizes the need to broaden the range of therapeutic targets and the variety of replacement agents in order to overcome the current protocols' drawbacks and delay antimalarial resistance for the longer-term goal of malaria elimination. Recent advances in our understanding of biology and genomics of malaria parasites may provide information for putative novel structures to be targeted, and help in designing new generations of anti-malarial drugs based on unexplored chemotypes and acting with different mechanisms. On these bases, plentiful strategies for anti-malarial drug discovery are currently inquired, and progress in high throughput screening and computer-aided technologies offers exciting opportunities for developing suited candidates.

A mention of the general aspects of the vector-borne disease could not be presented here for brevity's sake, and readers are then referred to the overwhelming literature existing on the topic [9 - 20]. However, a brief excursus on the antimalarial drugs currently in use will introduce the special focus on the ART "miracle molecule" and its congeners.

THE NATURE-DERIVED MAINSTAYS OF ANTIMALARIAL THERAPY

The existing antimalarial therapeutic arsenal owes a great tribute to nature since most of the curative molecules derive from medicinal plants, fungi, and microorganisms. The therapeutic effect of herbal medicines traditionally used by local communities was confirmed and defined by time, and natural agents such as quinine, artemisinin, febrifugine, and lapachol have been the cornerstone of antimalarial treatment for thousands of years. Again, antimalarial screening of natural products from fungal and microbial sources, of both terrestrial and marine provenience, has revealed a wide potential in view of their chemical diversity [21, 22].

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