ALKALOIDS AND OTHER NITROGEN-CONTAINING DERIVATIVES

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Simone Carradori

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(Volume 3)

Alkaloids and Other Nitrogen-Containing Derivatives

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CONTENTS

FOREWORD

Heteroatoms can be found in a number of naturally occurring substances, active pharmaceutical ingredients as well as excipients, substituting isosterically/bioisosterically carbon atoms. Many nitrogen-containing heterocycles can be considered as privileged scaffolds due to statistics describing as more than 85% of all biologically-active chemical entities are endowed with a heterocycle and that approximately 60% of FDA-approved drugs contain a nitrogen heterocycle in their structure. This volume reflects the pivotal role of nitrogen-containing heterocycles in modern drug design from natural compounds and their utilization in the scaffold-hopping strategy. Moreover, the presence of these heterocycles could provide the improvement of solubility, lipophilicity, polarity and hydrogen bonding capacity to biologically active agents, as well as the optimization of their ADME/Tox properties.

Nitrogen-containing compounds were shown to exhibit a very wide range of biological activities mimicking natural compounds or endogenous metabolites. A large chemical diversity can be obtained by different and innovative synthetic methodologies to expand/explore the available drug-like chemical space and to obtain robust Structure-Activity Relationships (SARs) within the scaffold.

KEY FEATURES

1. Updated information on natural compounds and their semi-synthetic derivatives;
2. In-depth analysis of novel findings and promising applications;
3. Use of organic reactions as a powerful tool in drug discovery to enhance the biological potential or give new chemical and biological properties to the parent molecules;
4. Investigation of the molecular mechanisms.

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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 to 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 also be 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

Alkaloids: A Brief Overview of Botanical and Pharmacological Properties

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Abstract: The classical definition of alkaloids describes this class of secondary metabolites as chemical structures containing nitrogen as part of a heterocyclic, with alkaline character, characterized by complex structure and limited distribution, mainly in the plant kingdom. The modern history of alkaloids starts in the early nineteenth century as figured by two milestone dates, 1803 when Derosne described the isolation of a mixture containing narcotin and morphine from opium, and 1819 when the chemist Meissner delivered an operative definition of the term alkaloid. They have been observed with sporadic distribution in bacteria, fungi, Pteridophytae and Gymnophytae, while they are mainly represented in higher plants and within Angiosperms, particularly in selected families, such as Annonaceae, Lauraceae, Loganaceae, Menispermaceae, Papaveraceae, Ranuncolaceae, Rubiaceae, Rutaceae, Solanaceae and others. Frequently, a plant activates selectively a metabolic pathway that produces a mixture of multiple but structure-related alkaloids. Sometimes, dozens may be with a restricted number representing the majority of the total content. The latter parameter could change significantly as a result of a plethora of many factors, including the plant organ, seasonal variations, phenological status and others. As general rules, the alkaloids are segregated in the form of salt inside cell vacuole or sometimes in laticifer, mainly through the superficial tissues, supporting the hypothesis of their biological involvement in plant-environment interactions.

Keywords: Alkaloids, Network pharmacology, Phytochemistry, Plant secondary metabolites.

INTRODUCTION

The alkaloids, whose name was coined by the German chemist Carl Friedrich Wilhelm Meissner, in 1819, constitute a heterogeneous group of plant secondary metabolites, which are generally characterized by one or more nitrogen atoms

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placed in an amino acid-deriving heterocycle. Basically, the alkaloids are organic compounds whose elementary analysis yields quaternary composition (C,H,O,N), although it is also possible to find ternary molecules (C, H, N), and more rarely they can be formed by five elements (C, H, N, O, S), as well. Ternary alkaloids are generally volatile compounds, whereas quaternary molecules are non-volatile and crystallizable molecules. They are also characterized by variability in the saturation of nitrogen atoms and overall have low solubility in water. By contrast, they are largely soluble in organic solvents. Noteworthy, a relevant number of alkaloids are also produced by amphibians, including potent neurotoxins [1]. According to their chemical-physical properties, many analytical methods have been developed for the extraction and quali-quantitative determination of the alkaloids. A classical extraction procedure for alkaloid extraction starts with diluted acid extraction (i.e., 5% sulfuric acid in water/hydroalcoholic solution) and subsequent organic extraction to remove pigments and other impurities. The subsequent alkalinization (ammonia or sodium bicarbonate) induces the precipitation of alkaloids as free bases that can be recovered by filtration or by liquid-liquid extraction in organic solvents. Ultrasound- and microwave-assisted methods proved to be very efficacious for extracting phytocomplexes containing alkaloids from different plant materials, whereas liquid and gas chromatography methods are now routinely employed, especially if hyphenated with mass spectrometry and nuclear magnetic resonance detection [2]. However, radio-immuno- and ELISA assays are also diffuse. Different qualitative tests are described to define the presence of alkaloids in plant extracts, such as Dragendorff's reagent (bismuth potassium iodide solution) that results positive with an orange precipitate, but a multiple test approach is required to discriminate among the different alkaloid subclasses [3, 4]. Basically, alkaloids are small molecules with numerous bio-pharmacological effects, including antibiotic, narcotic, stimulant, antiproliferative/anticancer. Among natural compounds, about 15-20% are alkaloids, and up to now, more than 12,000 alkaloids have been identified in numerous plants, especially in the angiosperm clade, whereas they are almost absent in the gymnosperms and other lower plants (considering some exceptions such as taxine alkaloids, lycopodine or ergot alkaloids from fungi). The alkaloids investigation started in the early nineteenth century with an exponential increase of structure isolation and characterization only in the second half of 1900. This delay could be related to the technological development of phytochemical techniques, but also to the frequent presence in natural sources in low amounts (in a free state, as salt or as N-oxide) and not related to vexillary effects, as confirmed by mainly (but not exclusive, i.e., the reddish sanguinarine) colorless feature. In the past, these phytocompounds were suggested to be a reservoir, defence substances, phytohormones or also waste products. The diverse nature and physical-chemical characteristics reflect in a wide range of biological

activities when administered to animals, mainly related to the evidence of strong pharmacological activities (due to a reduced therapeutic index) rather than a common biological target. More probably, the alkaloids can be regarded as intermediates of plant secondary metabolism with a different and often unknown role for the plant. Different hypotheses on their functions are proposed and supported by evidence, but for everyone, a number of exceptions are always available. Therefore, no general rule can be extrapolated for their function in plants. Alkaloids contain nitrogen, but frequently they are present in a low amount to be considered an efficient storage system [5]. In some cases, the alkaline nature is associated with the presence of specific acids, but this was evidenced in a limited number of cases, such as for quinine and quinic or chinchotannic acids in *Cinchona* species. It is not clear if they are necessary for the same alkaloid producing plant; indeed, they actively participate in plant metabolism, as highlighted by daily and long-term qualitative and quantitative variations. However, it was also demonstrated that plant producing alkaloids can lose this peculiarity after grafting, with no evident physiological effects. At the same time, alkaloids are not generally toxic for the producer and are well tolerated and metabolized by other plants (the mitostatic effect of *Colchicum autumnalis* alkaloid could be considered as an exception). The origin from common and ubiquitous precursors coupled with no negative effect on plant metabolism also suggests the hypothesis that the synthesis is due to either fortuitous or relictual biosynthetic pathways still not affected by metabolism evolution. More widely plausible results the interpretation of alkaloids as products of specialized plant metabolism useful for interactions with other living organisms and abiotic factors. In this sense, the bitter taste or the strong pharmacological effects (even when toxic) should be an easily decodable deterrent message for herbivores, for example, as well as the protective diurnal variation of alkaloids could be related to the protective effects exerted by selected alkaloids against oxidative stress induced by both solar irradiation and light metabolism reactions. The interactions are more complex in the presence of parasite/hemiparasite plants. Some plants, such as *Castilleja integra* can accumulate selectively different classes of alkaloids depending on the host plant metabolism, while an exception can be the hemiparasite *Osyris alba* that has a concomitant presence of quinolizidine and pyrrolizidine alkaloids, probably related to a concomitant parasitism of multiple hosts, that could represent an evolved strategy to enhance the defense effect attributed to both sub-classes of secondary metabolites [6]. However, alkaloids are also found in bacteria, fungi and animals (Fig. **1**)

Both terrestrial (insects, amphibians, reptiles, birds, mammals) and marine (sponges, asteroids, tunicates, scleractinians, dogfish sharks) animals synthesize and release alkaloids for protecting against infections and predators. Considering the heterogeneity of this group of natural compounds, different classification

CHAPTER 2

Synthesis of Natural Morphinans and Development of Related Alkaloids

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Abstract: Morphine, an alkaloid isolated from the opium poppy, has been widely used as an analgesic, and has been a fascinating synthetic target of organic chemists. All these opioid drugs produce their biological actions through three receptor types, μ, δ, and κ, belonging to the G-protein-coupled receptor family. Currently, used opioid analgesics also share a number of severe side effects, limiting their clinical usefulness. The chemically highly versatile structure of morphine and its related natural alkaloids has continuously engaged the interest of pharmaceutical and medicinal chemistry research, aiming for the synthesis and identification of numerous semi- and synthetic opioid ligands as safer therapeutic agents or with novel therapeutic properties and with lesser unwanted side effects with the final goal to reduce complications and to improve patient compliance. This review provides the first total synthesis reported in 1952 and focuses on representative examples of various derivatives and interesting approaches for the development of structurally correlated molecules with substitutions at different rings position leading to preclinical and clinically valuable opioids.

Keywords: Alkaloid, Morphine, Codeine, Thebaine, Codeinone.

INTRODUCTION

The existence of bioactive compounds in plants and other natural sources has been known for millennia. Among these, alkaloids are characterized by great structural diversity, and one of the oldest used in medicine by humans has been morphine. Some controversy persists regarding the exact date of the first discovery of morphine [1, 2]. The first reports of the extraction and isolation of morphine from *P. somniferum* were made by German pharmacist Friedrich Wilhelm Adam Sertürner in the early 1800s [2, 3], and after less than 20 years, Heinrich Emmanuel Merck commercialized the substance. Despite the limited

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understanding of its structure and mechanism of action, pure morphine became a standard treatment of pain in the 19th Century [4]; from the same plant in the next years, a number of structurally related alkaloids, such as codeine, thebaine and codeinone, were discovered and characterized Fig. (**1**).

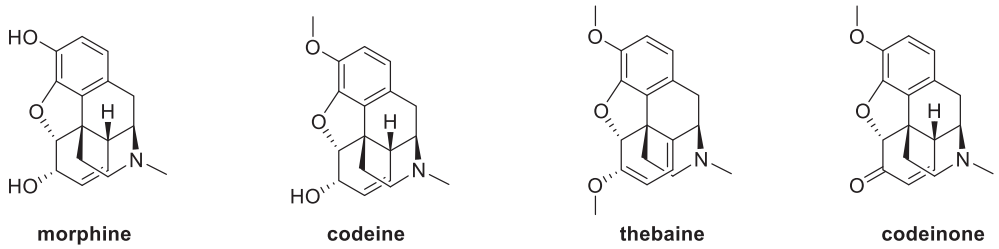

Fig. (1). Structures of natural alkaloids: morphine, codeine, thebaine and codeinone.

Morphine and codeine are the main active opioid alkaloids in opium. In humans, they act on the central nervous system to produce a wide range of effects, including analgesia, euphoria, sedation, respiratory depression, cough suppression and peripheral effects such as constipation [5]. The principal target for the majority of the effects of opioid alkaloids, whether beneficial or adverse, is the μ opioid receptor (μ-OR) [6] despite the two closely related members known as δ- and κ-ORs [7]. They are G protein-coupled receptor (GPCR) and are widely distributed in the central and peripheral nervous system [8 - 10], exerting critical functions not only in the modulation of pain but also in other physiological and pathophysiological processes [11 - 19]. It has been proven that activation of different types of opioid receptors can pose various biological effects [20 - 24]. The μ-OR constitutes the main opioid target for the management of pain, acute pulmonary oedema, cough, diarrhoea and shivering [5]. Substantial efforts have been invested in the separation of their analgesic actions from their liability for notorious effects based on the understanding of the pharmacological action of μ opioids and opioid receptors [17]. Unlike μ opioid agonists, κ opioid agonists can potentially promote potent analgesia without producing typical opioid-like adverse effects, providing a basis for the development of selective κ opioid agonists as potential analgesics [25 - 28]. However, opioid drugs are highly addictive and, because of this, the clinical efficacy of opioid drugs is often limited by the development of tolerance and dependence [29]. To date, no synthetic drug or naturally occurring compound has been found which can rival the broad spectrum analgesic properties of the opium alkaloids and, for this reason, many efforts from researchers are made in the synthesis of semi- or total synthetic compounds to obviate this issue. To understand the complicated structure-activity relationship (SAR) of these compounds, Portoghese introduced for the first time the message−address concept to explain and design selective opioid ligands from

the morphinan structure [30 - 32]. According to this hypothesis, subtype-selective opioid ligands have been proposed to contain two chemical motifs, one for efficacy (message) and the other for subtype selectivity (address) [33]. While the message motif is very similar or invariant, the address motif is variable [32]. This concept has been widely adopted to study opioid ligands and their pharmacology. Indeed, small modifications to the structure of GPCR ligands can lead to major changes in functional activity, switching agonists to antagonists or vice versa. In many cases, these dramatic shifts in functional activity are accompanied by only minor variations in binding affinity [34]. In this chapter, a brief overview of the state of the art of total synthesis of morphine is provided and focuses on the synthesis of morphinan derivatives resulting from manipulation of the natural products themselves.

TOTAL SYNTHESIS OF MORPHINE

The total synthesis of morphine proved to be an arduous task, occupying the attention of several research groups in the last 70 years and, despite several ingenious approaches, the synthesis fails, in terms of cost, to compete favourably with the isolation from the plant, remaining morphine on the list of goals of synthetic chemists. Structurally, morphine has a strained pentacyclic skeleton bearing a densely functionalized cis-hydro-dibenzofuran core and five continuous chiral centers, which include a critical all-carbon quaternary stereocenter Fig. (**2**)., making its molecular architecture and indispensable role in the clinical application an attractive scaffold for the chemists.

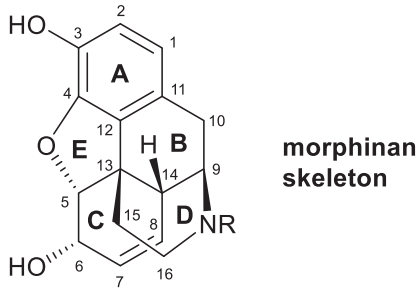

Fig. (2). Morphine skeleton and atoms numbering.

Gates's group reported the first total synthesis of morphine in 1952 [35, 36]. The pioneering approach started from a naphthalene diol **1** and after several steps which involved Michael-type addition of ethyl cyanoacetate, oxidation, hydrolysis, decarboxylation and intermolecular Diels-Alder reaction afforded the complete construction of ring **C** (**2**) as outlined in Scheme (**1**).

CHAPTER 3

Caffeine-based Compounds for the Treatment of Neurodegenerative Disorders

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Abstract: Neurodegenerative disorders, such as Alzheimer's and Parkinson's, are very complex diseases, whose treatment and prevention are still very problematic to date. The search for new potential treatments is always a current topic. In this context, the discovery of molecules with a dual-targeting action against both MAO-B enzyme and A_{2A} receptor has been largely pursued in recent years, considering their involvement in the etiological process of these diseases. In particular, caffeine, an alkaloid largely present in beverages and foods, has been shown to possess beneficial effects in the prevention/treatment of neurodegenerative disorders. Moreover, *in vitro* assays have confirmed its interaction with the MAO-B enzyme and A_{2A} receptor, stimulating the synthesis of caffeine chemical derivatives that can strongly act against these two targets. In this chapter, several classes of caffeine derivatives have been discussed, with particular attention on their synthesis and (dual) biological activity of MAO-B enzyme and A_{2A} receptor.

Keywords: Adenosine receptor, Caffeine derivatives, MAO-B, Neurodegenerative disorders, Xanthine.

INTRODUCTION

Alzheimer's (AD) and Parkinson's (PD) diseases represent two of the most widespread neurodegenerative diseases in the world, characterized by common physiological events, such as oxidative stress, misfolded proteins, protein aggregation, excitotoxicity, neuroinflammation and neuronal loss [1]. The neuropathological features of AD and PD are directly correlated with dysfunctions of the cholinergic and dopaminergic systems, respectively, and thus, the therapies for the treatment of these pathologies are focused on improving these dysfunctions [2, 3]. In particular, AD therapy is based on three strategies: cholinesterases (ChEs) and monoamine oxidases (MAOs) inhibition, providing

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neuroprotection by using an antioxidant approach, and reduction of Aβ peptide aggregation. Also in the case of PD therapy, three strategies are mainly applied: the use of L-dopa and dopamine agonists, the inhibition of monoamine oxidase-B (MAO-B) and catechol-*O*-methyltransferase (COMT), and the use of cholinergic and glutamate antagonists. In particular, both AD and PD pathogeneses are characterized by alterations of MAO and adenosine receptors (AR) activity. MAOs (MAO-A and MAO-B) are a class of enzymes involved in the oxidative deamination of biogenic and xenobiotic amines, including neurotransmitters released by neurons and glia cells. In AD, alteration of MAOs activity has been shown to promote the formation of amyloid plaques and neurofibrillary tangles, and the cognitive impairment via the destruction of cholinergic neurons and disorder of the cholinergic system [4, 5]. In PD, the altered activity of MAO-B promotes a faster depletion of dopamine and causes neuron damage due to the formation of oxidative agents [6 - 8]. ARs are a class of four G protein-coupled receptors (A_1, A_{2A}, A_{2B}, A_3) largely distributed in the human organism. Among these receptors, A_{2A} subtypes are mainly localized in the central nervous system and are involved in the release of neurotransmitters (acetylcholine, dopamine, glutamate) [9, 10]. An altered activity and expression of these two receptors have been associated with neurodegenerative disorders such as AD and PD, and the use of antagonists can be useful in improving the health status [9, 11 - 14].

Drug design is the process of finding new molecules based on the knowledge of the biological target. The concept of 'one molecule – one target – one disease' has been a well-developed approach in the pharmaceutical field. The main idea of this approach is the treatment of a considered disease through the modulation of a single target. However, some phenomena of resistance and robustness in many biological pathways depict that inhibiting a single target might fall short of producing the desired therapeutic effect [15 - 17]. Since the simultaneous intervention of two or multiple targets relevant to one disease has shown improved therapeutic efficacy, there has been a move toward multiple target drugs [18]. Multitarget therapeutic strategy can be accomplished by one of these approaches: acting upon different targets in order to obtain a combination effect, altering the ability of another to reach the target, and binding the different sites on the same target to create a combination effect [19, 20].

In this context, the development of molecules that can act on both MAO-B and A_{2A} receptor represents an innovative approach for the treatment of AD and PD, and in the last years, the use of caffeine derivatives has shown to be a potentially effective approach for this aim.

CAFFEINE ACTIVITY AND SYNTHESIS

Caffeine, 1,3,7-trimethylxanthine Fig. (**1**)., is a purine alkaloid discovered in the 1820s [21] in coffee (*Coffea arabica*) and tea (*Camellia sinensis*). It is also largely present in maté (*Ilex paraguariensis*) and cacao (*Theobroma cacao*) [22, 23].

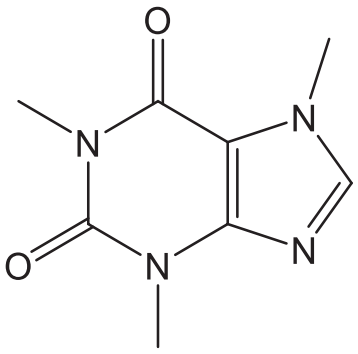

Fig. (1). Chemical structure of caffeine.

The consumption of caffeine-rich beverages and foods has been very widespread since ancient times, and controversies regarding the risks and the benefits of caffeine on human health have always been a strong topic of debate. However, mainly in the last two decades, several studies have evidenced the beneficial roles of caffeine in some diseases, such as type II diabetes mellitus, hepatitis C, hepatocellular carcinoma, and non-alcoholic fatty liver disease and neurodegenerative diseases [24 - 27]. In particular, several studies on animal models have shown the preventive/protective effect of caffeine against AD and PD [28, 29], although its mechanism of action is not properly clear, and several hypotheses have been formulated. Among these hypotheses, the MAO-B inhibition activity and the antagonism on A_2 receptor were also explored through *in vitro* assays, confirming the activity of caffeine against these two targets. In particular, K_i values of 3.83 mM for the anti-MAO-B activity [30] and 43-50 μM for the antagonism on the A_{2A} receptor [31, 32] have been measured. These results led to consider caffeine as a lead compound to obtain derivatives with an enhanced activity on MAO-B and A_{2A} receptor targets.

From a chemical point of view, pure caffeine is generally obtained as a by-product of the decaffeination process [33, 34], where caffeine is extracted by using three different processes that use water, organic solvents or supercritical fluids (CO_2) [35 - 37]. However, scientific literature also reports the total synthesis of this molecule, although this process is not very used.

CHAPTER 4

Piperine Derivatives: New Trends in Medicinal Chemistry

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Abstract: The alkaloid piperine has always attracted the interest of pharmaceutical botanists for its biological activities and pharmacokinetics-modulating properties. It is currently used in combination with other compounds for the treatment of several diseases. Starting from its peculiar structure, medicinal chemists have explored the chemical space around the amide portion, the conjugated double bond chain and the benzodioxole ring. This approach led to a large plethora of derivatives, which diversified the properties of the parent compound or improved its potency against specific targets or biological systems. In this chapter, several classes of piperine derivatives have been discussed and classified according to the proposed therapeutic use, with a particular attention on their structure-activity relationships and biological activity values.

Keywords: Acaricidal, Antimicrobial activity, Anti-cancer activity, Anti-protozoal, Insecticidal, MAO-B inhibitor, Natural compounds, Neuroinflammation, Piperine, PPAR, SAR analysis, Vitiligo.

INTRODUCTION

Piperine, (2*E*,4*E*)-5-(1,3-benzodioxol-5-yl)-1-piperidin-1-ylpenta-2,4-dien-1-one ($C_{17}H_{19}NO_3$), is the major alkaloid (5-9%) of black pepper (*Piper nigrum* L., Piperaceae) and is responsible for its characteristic pungent flavor [1, 2]. Piperine was first isolated in 1819 by the Danish chemist Hans Christian Ørstedt and its structure is composed of an amide moiety (piperidine with an α,β-unsaturated carbonyl group) linked by a butadiene chain to an aromatic moiety (1,3-benzodioxole or piperonal) Fig. (**1**) [3].

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Piperine has four isomeric forms: *trans-trans* isomer (piperine), *cis-trans* isomer (isopiperine), *cis-cis* isomer (chavicine), and *trans-cis* isomer (isochavicine) Fig. (**1**). Compared to piperine, its geometrical isomers have no pungency and do not display significant pharmacological properties [4, 5]. In general, piperine can be extracted from plant material using polar organic solvents by means of different techniques, such as Soxhlet extraction, supercritical fluid extraction, ultrasound and microwave-assisted extraction, and ion liquid ultrasound-assisted extraction [5, 6].

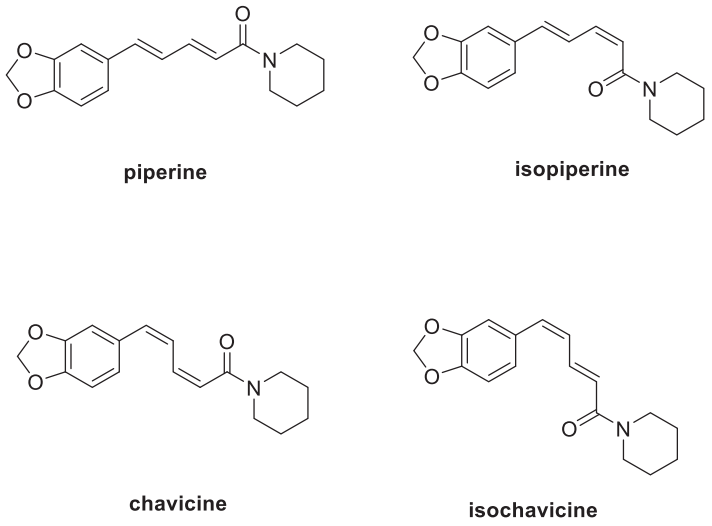

Fig. (1). Piperine – structural isomers.

Piperine was reported to exhibit a wide spectrum of biological activities, including antioxidant, chemopreventive, antimicrobial, immune-modulatory, anti-inflammatory, cardioprotective, hepatoprotective, antidiabetic, and anti-allergic effects, alongside a bioavailability enhancing potential by inhibition of xenobiotics metabolism [7 - 11]. Table **1** presents the main documented bioactivities of piperine. A plethora of reviews dealing with the therapeutic effects and health promoting perspectives of piperine have been published in recent years. Thus, Haq *et al*. [9] and Shityakov *et al*. [6] reviewed the chemistry, pharmacokinetics, safety issues, and multifaceted biological potential of piperine. Quijia *et al*. [3] and Stojanovic-Radic *et al*. [12] discussed the extraction methods of piperine and the development of analytical methods for its qualitative and quantitative characterization from plant matrices, and biological fluids, and drug delivery systems. Lee *et al*. [13] and Gorgani *et al*. [14] analyzed the *in vivo* implications of piperine-drug interactions, with emphasis on its putative use as a bioenhancer, but also featured novel formulations designed to optimize the delivery of piperine. In addition, reviews dealing with the anti-tubercular [15],

chemopreventive and anticancer [16, 17], and antidiabetic [18] effects of piperine, alongside their mechanisms of action, have also been published.

Table 1. Piperine – main biological activities.

Biological Activity	Main Outcome of the Study	References
NorA Efflux Pump Inhibitory Activity	MEC 50 µg/mL determined a four-fold reduction in MIC of ciprofloxacin against *Staphylococcus aureus* ATCC 29213 MEC 50 µg/mL determined a two-fold reduction in MIC of ciprofloxacin against *S. aureus* MRSA 15187 clinical isolate	[22]
	MEC 50 µg/mL determined a two-fold reduction in MIC of ciprofloxacin against *S. aureus* 1199 and NorA overexpressing *S. aureus* 1199B bacteria	[23, 24]
Anti-Mycobacterial activity	MIC > 100 µg/mL against *Mycobacterium tuberculosis* H37Rv (ATCC 27294), rifampicin-resistant *M. tuberculosis*, and MDR *M. tuberculosis* clinical isolate	[25]
	MIC 128 µg/mL against *M. smegmatis* mc2 155 ATCC 700084	[26]
	MIC 39 µg/mL against MDR *M. tuberculosis* GN/mt-75 MIC 3000 µg/mL against MDR *M. smegmatis* GN/ms-43	[27]
	MIC 50 µg/mL against ofloxacin-resistant *M. tuberculosis* isolates	[28]
Anti-Leishmanial Activity	IC_{50} 0.752 mM against amastigotes of *Leishmania donovani* IC_{50} 2.558 mM against promastigotes of *L. donovani*	[29]
	IC_{50} 28 µM against amastigotes of *L. amazonensis* IC_{50} 14.2 µM against promastigotes of *L. amazonensis*	[30]
	IC_{50} 3.03 µg/mL against promastigotes of *L. infantum* IC_{50} 23.98 µg/mL against amastigotes of *L. infantum*	[31]
Anti-Trypanosomal Activity	IC_{50} 7.36 µM against epimastigotes of *Trypanosoma cruzi* IC_{50} 4.91 µM against amastigotes of *T. cruzi*	[32]
	IC_{50} 72.40 µM against *T. brucei* ssp. *brucei*	[33]
	IC_{50} 14.45 µM against *T. evansi*	[34]
Anti-Plasmodial Activity	IC_{50} >200 µM against *P. falciparum* W2 strain	[35]
Anti-Filarial activity	MIC 3.09 µg/mL, IC_{50} 8.19 µg/mL, LC_{50} 16.47 µg/mL against *Setaria cervi* microfilariae MIC 5.09 µg/mL, IC_{50} 16.38 µg/mL, LC_{50} 31.08 µg/mL against *Setaria cervi* adults	[36]

CHAPTER 5

Designing Noscapine-based Anti-Cancer Agents

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Abstract: Cancer is the second leading cause of death globally, in which factors, such as tobacco, radiation, and obesity contribute to this alarming data. Among the available pharmacotherapy, natural products, such as noscapine, have historical evidence in treating this disease, showing promising results aimed at inhibiting tubulin. In this context, this remarkable molecule has been tested as a conjugated drug in treating the COVID-19 pandemic. In this chapter, we demonstrate noscapine structurally-related compounds, analyzing them based on SAR studies, and discuss the most promising results reported so far.

Keywords: Anti-cancer, Drug discovery, Noscapine-based, SAR analysis.

INTRODUCTION

Epidemiological aspects, economic burden, and natural anti-cancer products dated in ancient history on Egyptian mummies over 3,000 years B.C., cancer refers to a large set of diseases belonging to the group of non-communicable diseases (NCDs) [1, 2], which also include heart attacks, stroke, chronic respiratory diseases, diabetes, and mental disorders where, together, these are responsible for about 70% of deaths in the world [3]. Currently, cancer is the second leading cause of death in the world (1 among 6 deaths), with about 18.1 million cases and 9.6 million deaths reported in 2018 [4]. The most common types of cancer are lung (2.09 million), breast (2.09 million), and colorectal (1.8 million) cancers [5, 6], with global economic impact measured in 2010 at approximately US$ 1.16 trillion [7]. In this sense, estimates show an increase in 29.5 million cases until 2040 [8].

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This disease can start in almost any organ or tissue from the body so that abnormal cells proliferate uncontrollably, resulting from the dysregulation of homeostasis processes due to epigenetic mutations or modifications in the genes that control the stages of multiplication and apoptosis [9 - 11]. The invasion occurs in other organs and adjacent regions, where the latter process, called metastasis, is a significant cause of death Fig. (**1**) [12 - 14].

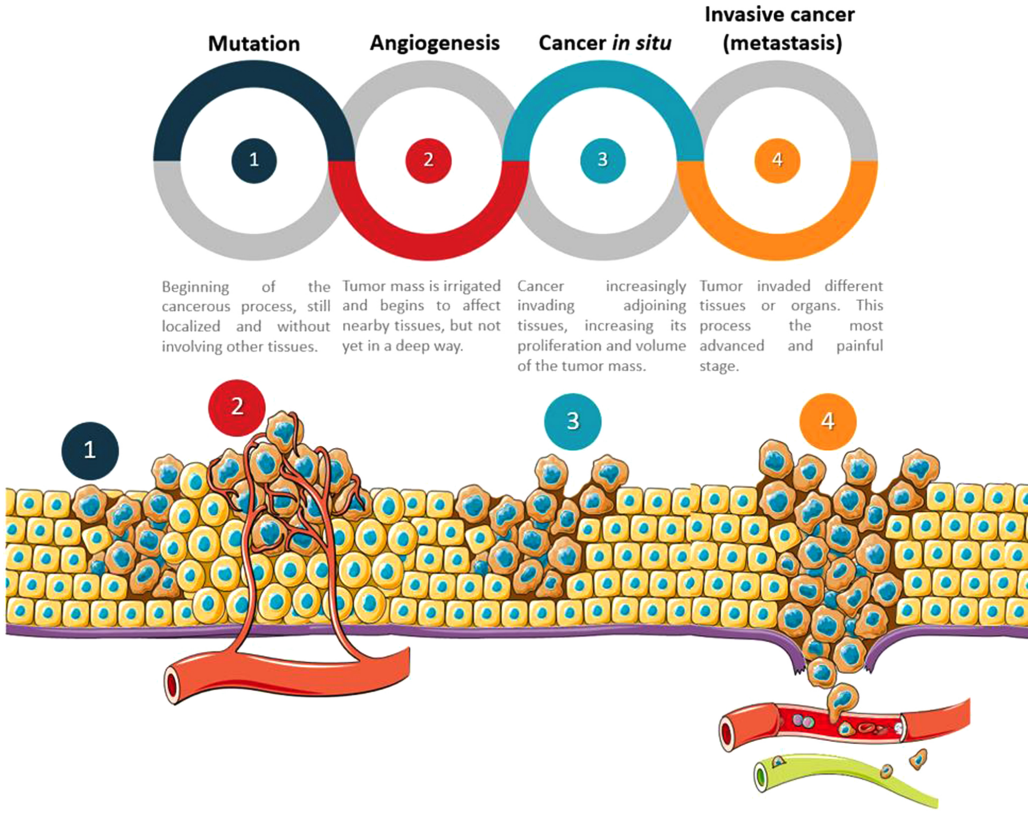

Fig. (1). Schematic representation of the cancer process evolution.

Natural products derived from animals, plants, and microorganisms have had a prominent place in the treatment of several pathologies since the beginning of humankind, being used by approximately 50,000–80,000 flowering plants in different therapeutic approaches worldwide [15]. Among these, plant alkaloids are rich materials for the development of pharmaceutical products, in which the alkaloid isolate corresponds to a secondary alkaline nitrogen-containing metabolite found in heterocyclic compounds, where about 27,000 substances of this class have already been identified [16, 17]. Such structures are found in

families *Asteraceae, Apocynaceae, Berberidaceae, Boraginaceae, Buxaceae, Chenopodiaceae, Euphorbiaceae, Fabaceae, Fumariaceae, Lauraceae, Loganiaceae, Magnoliaceae, Menispermaceae, Papaveraceae, Rubiaceae, Rutaceae*, and *Solanaceae*, with rare occurrence in monocots and gymnosperms [18].

Concerning cancer therapy, natural products obtained from different sources have been applied throughout history, starting with the development of vinca alkaloids, vinblastine **(1)** and vincristine (**2**) Fig. (**2**)., isolated from *Catharanthus roseus* (Apocynaceae) by Canadian scientists Robert Noble and Charles Beer in the 1950s [19 - 21]. The use of at least 3,000 plants is reported for treating cancers. Still, more than 60% of the anti-cancer agents used have been obtained from natural sources, such as plants and microorganisms [22].

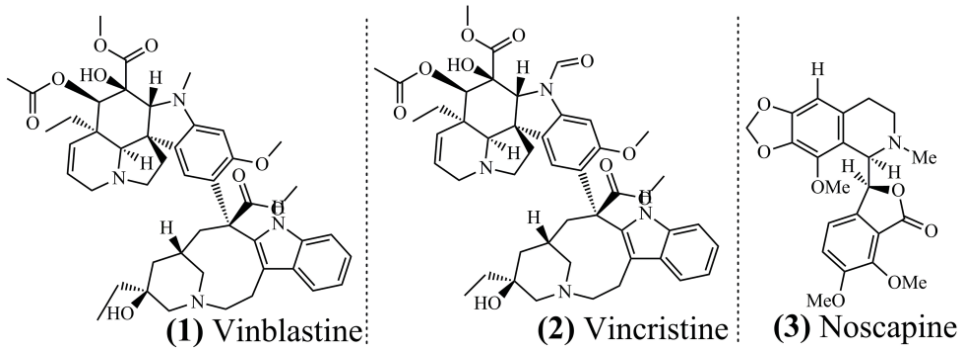

Fig. (2). Alkaloid structures of relevance in anti-cancer pharmacotherapy.

Among this class, noscapine **(3)** refers to phthalideisoquinoline alkaloid found in opium poppy (*Papaver somniferum*) Fig. (**2**)., non-sedative, and used in the development of anti-cancer and anti-stroke compounds [23, 24], in addition to being used as a cough suppressant agent [25, 26]. Additionally, in clinical trials involving cancer patients, tolerance by 80% was observed even in large doses, demonstrating a safety profile [27]. Recently, noscapine **(3)** has been investigated against the pandemic SARS-CoV-2 (COVID-19) for attenuation of cytokine-mediated by bradykinin via ACE2 inhibition [28]. This fact could minimize the tissue damage in the lungs and reduce the patients' recovery time [29, 30].

In this chapter, we will demonstrate all strategies that have been related to the discovery and design of anti-cancer noscapine-based drugs, emphasizing the primary SAR study strategies for obtaining these compounds. Thus, we aim to provide valuable information addressed to design new useful, safe, selective, and low-cost compounds against this severe disease.

CHAPTER 6

Biogenic Amine and Amino Acid Derivatives as Carbonic Anhydrase Modulators

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Abstract: Biogenic amines (BAs) and amino acids (AAs) are essential components of every living organism, being the precursors of vital compounds, such as hormones, alkaloids, nucleic acids and proteins, among others. They are directly involved in many metabolic processes, growth regulation, cellular transmission and diseases. A plethora of biological substrates yet to be fully identified are the targets of BAs and AAs. The Carbonic Anhydrases (CAs; EC 4.2.1.1) are listed among them. These metalloenzymes are virtually expressed in every living organism, with eight genetically distinct families described to date. CAs main biological function is represented by CO_2 hydration catalysis. Amino acids and amines are usually reported as efficient CA activators and are thus potentially useful for therapeutic purposes in aging and neurodegenerative diseases as well as tissue engineering. To date, polyamines are the only exception as they were identified to act as CA inhibitors. Here, we will review the main contributions in the field covering the effects of such crucial molecules on CAs expressed in various organisms (mammals, fungi, protozoan, bacteria and archaea). Synthetic analogues of amines and amino acids obtained from various drug design approaches, will also be considered.

Keywords: Amino Acids, Biogenic amines, Bone mineralization, Carbonic anhydrase activators (CAAs), Carbonic anhydrase inhibitors (CAIs), Drug design, Enhanced spatial learning, Pathogens CAs.

INTRODUCTION

Biogenic amines (BAs) and amino acids (AAs) are essential components of every living organism, directly involved in many metabolic processes. AAs are zwitterionic compounds consisting of an α-carbon atom covalently attached to a hydrogen atom (H), an amino group (NH_2), a carboxyl group (COOH), and a side-

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chain R group [1]. Of the over 300 naturally occurring amino acids, 22 constitute the monomer units of proteins, and they are therefore called "proteinogenic amino acids" [2]. Non-proteinogenic amino acids are amino acids not incorporated into proteins which, along with some proteinogenic amino acids, can interact directly with specific biological targets, such as receptors and transporters, acting as neurotransmitters or hormones (like GABA, L-DOPA, or triiodothyronine) [1, 2]. Decarboxylation of some AAs generates BAs such as histamine, tyramine, tryptamine and phenylethylamine. BAs account for a wide group of basic nitrogenous naturally occurring organic compounds endowed with biological activities that participate in the metabolism of microorganisms, plants and animals [3]. Other BAs such as spermine, spermidine, serotonin, dopamine, and norepinephrine are obtained from condensation and/or hydroxylation reactions. Reactions of amination and transamination of aldehydic and ketone substrates are also responsible for the biosynthesis of various BAs [3, 4]. From the chemical view point, BAs may be classified into monoamines, diamines and polyamines when the number of amine groups is considered, or as aliphatic, aromatic, and heterocyclic when the main chemical scaffold is considered [3, 4]. As for the physiological perspective, BAs are involved in the supply of energy through the generation of proton gradients, acid buffering, regulation of osmotic and oxidative stress, and DNA regulation as the main ones. In some bacteria, the expression of decarboxylases responsible for BA production has been considered a virulence factor. Histamine released from bacteria can cause host tissue damage, which in turn facilitates its colonization and invasion; tyramine is reported to enhance adhesion to mucosal tissues and colonization [3, 4]. In eukaryotic cells, BAs are implicated in cell division and differentiation events, synthesis of nucleic acids and proteins, and stabilization of membranes. In plants, the production of some BAs was related to defensive roles against insects and herbivores [3, 4].

It is clear that BAs, as well as their amino acid precursors, have wide implications in numerous patho/physiological events among all organisms. This implies that the biological targets involved are numerous and yet to be identified exhaustively. In this review, we specifically focus on BAs and natural amino acids as modulators of the Carbonic Anhydrases (CAs; EC 4.2.1.1) enzymes which are valuable targets for the development of new drugs.

CAs are a family of metalloenzymes listed among the most efficient catalysts in nature [5]. Their main physiological role consists in speeding up the reaction reported in **Equation 1**, allowing this transformation to occur fast enough to satisfy the metabolic needs of most cells/tissues [5].

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+ \quad \textbf{(1)}$$

CA biological meaning is not limited to pH regulation itself, as in superior organisms such as mammals, this enzyme is actively involved in the secretion of electrolytes, gluconeogenesis, urea biosynthesis and lipogenesis, and bone and cardiovascular remodelling [6]. In algae, cyanobacteria and plants, the expressed CAs are involved in the regulation of photosynthesis by means of the Carbon-Concentrating mechanisms (CCMs) [7]. In pathogenic microorganisms such as bacteria, fungi and protozoa, the reaction catalyzed by CAs has a crucial role in regulating the virulence and survival of microorganisms within the host environment [8 - 10]. It is clear the pre-eminent role of such a reaction and, therefore, the high value of agents able to modulate it through activation or inhibition, with important applications spanning from Medicinal Chemistry to the Biotechnological fields [6, 11, 12].

Up to now, eight distinct and genetically unrelated CA families are known and are reported with the Greek letters α−, β−, γ−, δ−, ζ−, η−, θ− and ι-CAs, with the latter being very recently discovered [5, 13, 14]. The CAs possessing catalytic activity bear a metal ion within their cavity site [5, 6]. The α-, β-, η− and θ− classes contain Zn(II), γ-class probably Fe(II), δ-class can also contain Co(II) under Zn-limited conditions, the ζ Cd(II) [5, 15]. The latest discovered ι-CAs has been identified in marine phytoplankton and is believed to be a Mn(II) protein [14]. The metal ion (II) is coordinated in a tetrahedral geometry, coordinated by three amino acidic residues and a water molecule/hydroxide ion in the coordination sphere [5]. CAs active sites are divided into hydrophilic and hydrophobic sections [16]. This peculiar structural feature creates preferential ways for the substrate (CO_2) to feed the enzyme and for the products (H^+, HCO_3^-) to be expelled, and thus contributes to the CA large efficiency [16, 17].

The CA catalytic mechanism for the hydration reaction of CO_2 is well known and evolves in a ping-pong fashion, according to the scheme reported below using the α-CA isoform II as a model enzyme [5, 16] Scheme (**1**).

CHAPTER 7

Design of Antimalarial Compounds on Quinoline Scaffold: From Plant to Drug

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Abstract: *Plasmodium* species are responsible for a high incidence of cases and resistance, even with several approved drugs. Quinoline derivatives are recognized as a source of active compounds, where tafenoquine has been recently approved. Cases of resistance and the indiscriminate use of anti-malarials against COVID-19 have negatively contributed to eradicating this disease. In this context, modifications at 2- or 4-amino positions from the quinoline scaffold or even its metal complexes have shown promising advances in the field, especially against resistant strains, such as 3D7, W2, D10, Dd2, K_1, and FCR-3. In this chapter, we discussed all aspects involving such compounds, presenting their results based on SAR analysis and recent contributions/advances involving this classic scaffold arising from nature.

Keywords: Drug discovery, *Plasmodium* spp, Quinoline-based, SAR analysis.

INTRODUCTION

Epidemiological Aspects and Economic Burden

Neglected Tropical Diseases (NTDs) correspond to a set of 20 diseases that, according to the World Health Organization (WHO), affect about 1.5 billion people in 149 countries living in low-sanitization conditions and social vulnerability. Still, this group of diseases represents 11% of all global diseases [1 - 5]. Among NTDs, malaria is a significant and potentially fatal disease caused by

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five parasites from the genus *Plasmodium* (Fig. **1**)., transmitted by bites of infected female *Anopheles* mosquitoes [6 - 9]. Among these parasites, the most threatening is *P. vivax* (responsible for 75% of cases in the Americas) and *P. falciparum* (responsible for 99.7% of cases in African, 71% in the Eastern Mediterranean, 50% in South-East Asian, and 65% in Western Pacific Regions) [10, 11]. In 2019, malaria affected around 229 million individuals, culminating in 409,000 deaths, with 94% of these cases in the African continent. Children under six years old constitute the most vulnerable group, representing 67% of the total deaths in 2019 [10, 11].

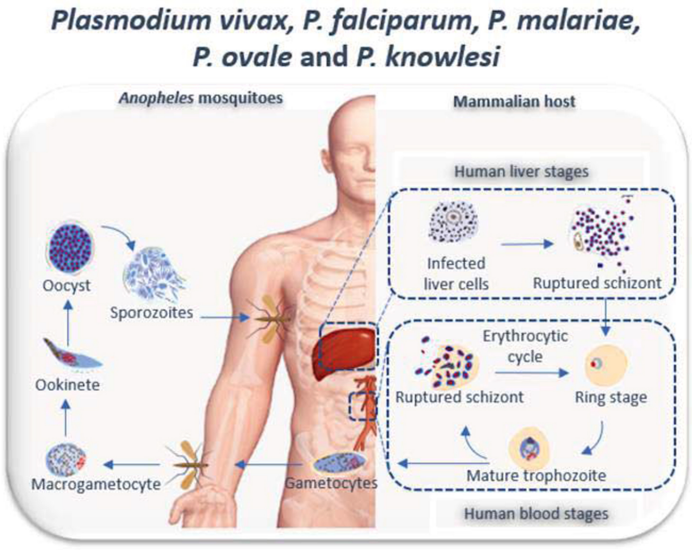

Fig. (1). The life cycle of infectious *Plasmodium* parasites. Sporozoites correspond to the infectious form of clinical relevance in the human host, constituting a relevant biological target for the design of anti-malarial drugs.

In 2018, malaria was the second largest investment, being behind only HIV/AIDS (US$ 7,351 million), where total costs with medicines, basic research, and vaccines represented around 87% of this budget [12]. This fact is part of a set of strategies designed by the WHO to reduce 90% of this disease's incidence and mortality rates and eliminate it from at least 35 countries until 2030 [13].

Natural Products and Anti-Malarial Activity: The Advent of Quinine and its Derivatives

Natural products from plants, animals, and microorganisms have been used to treat diseases since the beginning of humankind, constituting one of the primary sources of new medicines [14, 15]. Such importance is demonstrated in the 9th

Edition of International Pharmacopoeia (Ph. Int.), where more than 80 (out of 371) new drugs included were obtained from natural origin or derived from them. Besides, about 70% of 1,562 new approved drugs discovered between 1981 and 2014 came from natural origin [16 - 18]. In this scenario, natural products represent the main source of drugs for treating diverse parasitic diseases, where approximately 1,300 species of plants from 160 families have been used as therapy [19].

Two of the main compounds used in pharmacotherapy against malaria are natural products, where the treatment started with the advent of quinine **(1)** in 1817, obtained from the bark of *Cinchona* species (Rubiaceae) [20 - 22]. Based on the quinine **(1)**, other drugs have demonstrated efficacy against *Plasmodium* parasites. Among these, chloroquine **(2)**, primaquine **(3)**, hydroxychloroquine **(4)**, amodiaquine **(5)**, piperaquine **(6)**, and mefloquine **(7)** can be cited, justifying the drug design of bioactive compounds based on quinoline ring (Fig. **2**) [23 - 25]. In 2018, tafenoquine **(8)**, an orally-active 8-aminoquinoline analog, was approved by the Food and Drug Administration (FDA) in the USA. It was recommended for prophylaxis of malaria in adults since it could combat pre-erythrocytic (liver), erythrocytic (asexual), and gametocyte forms from both *P. falciparum* and *P. vivax* (Fig. **2**) [26, 27]. Other drug candidates based on quinoline scaffold are under investigation in clinical trials, such as AQ-13 **(9)**, a 4-aminoquinoline similar to chloroquine **(2)**, which is used in *P. falciparum* infections [28, 29], as well as DDD107498 **(10)**, a quinoline-4-carboxamide multistage compound (liver, blood, and transmission-blocking) active against, such *Plasmodium* species (Fig. **2**) [30, 31].

In 1972, artemisinin **(11)** was discovered from *Artemisia annua* plant [32 - 34], an herb used in traditional Chinese medicine for over 2,000 years, beginning the era of endoperoxide compounds against malaria (Fig. **2**) [35, 36].

Drug Resistance

Due to the irrational use of drugs, lack of diagnosis, and low therapeutic adherence, resistance cases to anti-malarial quinolines have been reported since the 1910s with quinine **(1)**, in addition to resistance to artemisinin **(11)** [37 - 39]. Due to the COVID-19 pandemic, anti-malarial drugs such as chloroquine **(2)** and hydroxychloroquine **(4)** have been widely used in a disorderly manner in several countries as a possible “cure” [40, 41]. Nonetheless, this resistance to chloroquine **(2)** has been reported since 1950-60 at the Cambodia-Thailand border [42]. In this context, the use of these drugs in the pandemic could increase resistance, causing an even more significant delay in the resurgence of sensitivity. It could also be a

SUBJECT INDEX

B

C

D

E

F

G

H

I

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Simone Carradori

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