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Quinolines, Isoquinolines, Angustureine, and Congeneric Alkaloids — Occurrence, Chemistry, and Biological Activity

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1. Introduction

The alkaloids are a family of compounds widely found in nature. Therefore, they are nitrogenous secondary metabolites heterocyclic derivatives of amino acids or by the transamination process, which confers basic character [1].

The term alkaloid, linguistically derived from the Arabic *al-quali* (ash plants), is used to designate pharmacologically active nitrogen compounds found predominantly in Angiosperms [2]. Their distribution is not uniform in that division. It is estimated that approximately 40% of all plant families have at least one plant species that contains alkaloids. They are easily found in Fabaceae and Solanaceae but are rare in Gymnosperms and Pteridophytes such as ferns and monocots [3]. Although most occur in plants, alkaloids have also been isolated from algae, insects, marine and land animals, microorganisms, and fungi [4].

Since the dawn of civilization, there are reports of the use of plant extracts containing alkaloids for various purposes. The death of Socrates in 399 BC, for example, was attributed to the consumption of the extract of *Conium maculatum* containing the alkaloid coniine. There are also reports that during the last century BC, Cleopatra employed extracts of *Hyoscyamus muticus* containing the alkaloid atropine to dilate the pupils to look more attractive. It is known that medieval European women employed extract from *Atropa belladonna* with the same goal. Moreover, 25% of contemporary medicines are plant-derived. For example, morphine is extracted from the poppy. It is a narcotic drug used as analgesic and marketed since 1827 by Merck [2].

Several alkaloids (papaverine, morphine, and cocaine) can cause different stimuli in the nervous system of an animal; a common phenomenon in ecological relationships may constitute, for example, a defense mechanism by plants against herbivores [1].

The importance of alkaloids in the development of medicine is unquestionable since several advances made in the battle against diseases like malaria, leukemia, cancer, and neurodegenerative diseases would not have occurred without the use of these substances [1].

This chapter focuses on the occurrence occurring, chemistry, and biological activity of the quinoline and isoquinoline alkaloids, including the angustureine and congeneric alkaloids.

2. Quinoline and isoquinoline alkaloids

Among the various classes of alkaloid compounds, this section highlights the quinoline and isoquinoline alkaloids. They were originally obtained from natural sources, whose remarkable biological activities and relatively simple structures have attracted great interest in the scientific community, especially researchers involved in the chemistry of natural products. However, these compounds have also attracted the interest of synthetic organic chemists due to the need to obtain increased amounts aimed at additional biological research, as well as in developing efficient synthetic routes for these alkaloids and their derivatives, whose chemical and biological properties could become greatly enhanced by the design of new structures from these modifications.

2.1. Methods of extraction of quinoline and isoquinoline alkaloids

The general method for extracting and isolating alkaloids from plants consists of an acid-base extraction. The dried and pulverized plant is extracted with organic solvents or with acidified water. When the extraction is carried out with organic solvents immiscible with water, the plant sample is alkalized prior to being extracted. For this, the sample is wrapped in filter paper, as a cartridge, humidified with dilute basic solution, e.g., ammonium hydroxide, and extracted under heating using Soxhlet apparatus with organic solvent such as ethyl ether, chloroform, or dichloromethane. After extraction, the solvent volume is reduced by half in rotary evaporator under reduced pressure. The remaining volume of the solvent containing the alkaloid residue is transferred to a separatory funnel and extracted with aqueous phosphoric acid solution (pH 1 to 2) or hydrochloric acid. The wetting of the plant sample with basic solution allows the alkaloids are released from organic acids, thus facilitating its extraction by organic solvents. Meanwhile, when using an acidified solution, alkaloids tend to form salts with these strong acids, facilitating their removal from the two-phase system, water-solvent for the separation of these into the aqueous phase [5].

Another extraction technique uses polar solvent such as ethanol, for example. However, if a plant contains a high amount of lipids, a preextraction with a nonpolar solvent such as hexanes or petroleum ether is necessary for removing these lipids. Next, the organic solvent is concentrated under reduced pressure and the residue solubilized in water [6]. As most alkaloids are

basic or are found in salt form, aqueous solutions of phosphoric acid (pH 1 to 2) or hydrochloric acid are used for their removal. Neutral amide alkaloids, such as colchicine and piperine (Figure 1), remain in the organic phase when treated with an organic solvent (usually ethyl acetate) during the extraction process, while most of the other alkaloids may be extracted using an organic solvent only after neutralization of the aqueous phase with a base [4].

Figure 1. Structure of the neutral amide alkaloids colchicine and piperine.

Distillation methods are rarely employed for isolating alkaloids. This is possible only in cases of low molecular weight alkaloids like coniine and sparteine (Figure 2) [4].

Figure 2. Structure of the alkaloids coniine and sparteine.

Generally, the crude extract is purified by column chromatography (CC), employing silica gel or alumina as the stationary phase and a mixture of appropriate solvents as the mobile phase, following an appropriate choice made via thin layer chromatography (TLC). Often, alkaloids still need additional purification by recrystallization, employing solvent systems such as ethanol/water, methanol/chloroform, or acetone/methanol [4].

While these techniques are successful to extract and to isolate most alkaloids, for those highly water soluble and, therefore, partially or totally insoluble in organic solvents, these methods are not appropriate [6].

Although generally higher solubility in aqueous solutions involves greater bioactivities [6], the employment of more suitable methods for the extraction of highly water-soluble alkaloids is very useful.

In the case of quaternary alkaloids, the residual aqueous solution should be tested with a reagent suitable for the detection of alkaloids (Dragendorff reagent, for example) after completion of conventional partition methods. If it is positive, one should employ methods such as direct crystallization, precipitation as insoluble salts, extraction with polar

solvent water-immiscible, or formation of pseudobases to extract the alkaloids from the aqueous phase [6].

Alkaloids *N*-oxides can be isolated by indirect methods or chemical derivatization, through a reaction of reduction to the corresponding tertiary basis and extracted using the conventional method, and subsequently regenerated by an oxidation reaction, using oxidizing agents such as peroxide hydrogen or *m*-chloroperbenzoic acid. In some cases, the *N*-oxides containing higher aliphatic chains can be almost completely extracted by increasing the basicity of the aqueous phase, but for those who have high levels of hydroxylation, it is infeasible [6].

The methods employed to extract most common polyhydroxylated alkaloids are the direct extraction and ion exchange chromatography [6].

After extraction of alkaloids, a quantitative analysis that may be performed by traditional methods such as simple weighing or base titration after dilution under acidic conditions is recommended. Other widely used techniques for the quantification of alkaloids are by employing the HPLC apparatus with UV detection and by testing the refractive index depending on the structure of the isolated compound(s) [5].

2.2. Occurrence in nature of quinoline and isoquinoline alkaloids

The quinoline and isoquinoline alkaloids were initially extracted from coal tar in 1834 and 1835, respectively. Quinoline, which has high boiling temperature, is commonly employed in organic synthesis as a solvent. Isoquinoline has a low melting temperature and both have moderate basicity ($pK_a = 4.9$ and 5.1 , respectively) [7].

Although the vast majority of quinoline and isoquinoline alkaloids derived from flowered plants, they can also be isolated from animals and microorganisms, some representative examples are given in Table 1 [7].

Structure	Usual name	Source	Biological activity
Argemonine	<i>Argemone</i> sp.	-
Berberine	Family of <i>Berberidaceae</i>	Antiprotozoal Antimalarial Antibacterial Antidiarrheal
Berlambine	<i>Thalictrum foliolosum</i>	-
Camptothecin	<i>Camptotheca acuminata</i>	Topoisomerase inhibitor (anticancer agent)

Structure	Usual name	Source	Biological activity
Canadine	Family of <i>Berberidaceae</i>	-
Cinchonine	<i>Cinchona</i> (tropical species belonging to the family Rubiaceae)	Antimalarial
Codeine	<i>Opium</i>	Analgesic Antitexpectorant
Dictamnine	<i>Dictamnus albus</i>	hepatotoxicity (cytotoxicity to HepG2 cells)
Emetine	Family of Rubiaceae	Emetic Antiamoebic
Erysotramidine	<i>Erythrina genus</i>	Antifeedant
Erythraline	<i>Erythrina genus</i>	Antifeedant
Glaucine	<i>Glaucium genus</i>	Antitexpectorant
Haemanthamine	<i>Narcissus confusus</i>	-
Hydrastine	<i>Hydrastis canadensis</i>	Uterine hemostatic Antiseptic
Hydroquinine	<i>Cinchona</i> (tropical species belonging to the family Rubiaceae)	Depigmenting

Structure	Usual name	Source	Biological activity
Jamine	<i>Cocculus hirsutus</i>	Anti-hyperglycemic
Lavendamycin	<i>Streptomyces leventulae</i>	Antitumor antibiotic
Lephocereine	<i>Lephocereus schotti</i>	-
Lycorine	<i>Lycoris radiata</i>	hypotensive
Maritidine	-	-
Morphine	<i>Opium</i>	Analgesic
Nandinine	<i>Nandina domestica</i>	-
Nantenine	<i>Nandina domestica</i>	α 1 Adrenergic and serotonin antagonist 5-HT _{2A}
Nitidine	<i>Zanthoxylum nitidum</i>	Topoisomerase inhibitor (anticancer agent)
N-norlaudanosine	-	-
Palmitine	<i>Jateorhiza palmate</i>	-

Structure	Usual name	Source	Biological activity
Papaverine	<i>Opium</i>	Vasodilator
Pellotine	<i>Lophophora williamsii</i>	-
Protoemetine	<i>Alangium lamarckii</i>	-
Protoemetinol	<i>Alangium lamarckii</i>	Emetic Antiamebic Anticancer
Psychotrine	<i>Uragoga ipecacuanha</i>	Inhibitor of HIV-1 transcriptase
Quinidine	<i>Cinchona</i> (tropical species belonging to the family Rubiaceae)	Antiarrhythmic Antimalarial
Quinine	<i>Cinchona</i> (tropical species belonging to the family Rubiaceae)	Antimalarial Muscle relaxant
d-Quinotoxine	-	-
Reticuline	<i>Anona reticulate</i> <i>Opium</i>	-
Sandramycin	<i>Norcardioides</i> sp. (microorganism)	Antitumor antibiotic

Structure	Usual name	Source	Biological activity
Skimmianine	<i>Skimmia japonica</i>	Sedative Anticonvulsant
Sanguinarine	<i>Sanguinaria</i>	Antibacterial
Stepholidine	<i>Stephania intermedia</i>	D ₁ receptor agonist D ₂ receptor antagonist
Streptonigrin	<i>Streptomyces flocculus</i>	Antitumor antibiotic
Tetrahydropa-Imitine	<i>Corydalis family</i>	Analgesic
Thalictricavine	<i>Corydalis tuberosa</i>	-
Tubocurarin	<i>Chododendron tomentosum</i>	Neuromuscular blocking agent

Table 1. Quinoline and isoquinoline alkaloids: natural sources and biological activities.

2.3. Biosynthetic origin of quinoline and isoquinoline alkaloids

The most One of the systems used for the classification of alkaloids is based on the kind of nitrogen heterocycle in the structure and its botanical origin (plant family which is extracted); thus, the name given to an alkaloid derived from the genus or species of organism produced, including the term "ine." Another commonly used system takes into account its precursor amino acid. Thus, alkaloid derivatives of tryptophan and tyrosine are biosynthetically classified as quinoline and isoquinoline, respectively (Figure 3) [3].

Thus, quinoline alkaloids are derived from 3-hydroxyanthranilic acid, a metabolite formed from tryptophan through a sequence of enzymatic reactions (Figure 4). The condensation between 3-hydroxyanthranilic acid and malonyl-SCoA, followed by cyclization, produces quinoline alkaloid (Figure 4) [8-10].

Figure 3. Structure of quinoline and isoquinoline alkaloids.

Figure 4. Biosynthesis of quinoline alkaloids.

In the case of isoquinoline systems, the biosynthesis proceeds from the cyclization of the Schiff base formed between the dopamine and an aliphatic aldehyde [8]. Dopamine is obtained from the hydroxylation and decarboxylation of tyrosine. A second intermediate, *p*-hydroxyphenyl acetaldehyde, can also be formed by transamination, decarboxylation, and hydroxylation of tyrosine. The condensation of these intermediates followed by a sequence of steps (cyclization, hydroxylation, and methylation) produces the (*S*)-reticuline, a biosynthetic intermediate of all isoquinoline alkaloids (Figure 5) [11].

2.4. Biological activities of quinoline and isoquinoline alkaloids

In addition to the biological activities shown in Table 1, many quinoline alkaloids and their analogues represent the most important drugs currently used to combat malaria, with chloroquine, amodiaquine, piperazine, primaquine, quinine, and mefloquine (Figure 6)

Figure 5. Biosynthesis of isoquinoline alkaloids.

being the most representative drugs of this group [12]. Even today, many studies are still being conducted to increase the efficiency of quinoline derivatives such as AZT-chloro-quinoline, quinine-dihydroartemisinin, and MEFAS, a salt derived from mefloquine and artesunate [13] (Figure 7).

Figure 6. Structure of some quinoline alkaloids and their analogues.

Figure 7. Structure of other quinoline derivatives.

On the other hand, the quinoline nucleus has also demonstrated a critical role in the development of new anticancer drugs. Some of its derivatives showed excellent results on various types of cancer cells, through different mechanisms of action. Recently, three protein kinase inhibitors (Bosutinib, Lenvatinib, and Cabozantinib) and an inhibitor of farnesyltransferase (Tipifarnib) (Figure 8), considered as potential anticancer agents, entered into phase of clinical trials [14].

Figure 8. Structure of bosutinib, lenvatinib, cabozantinib, and tipifarnib quinoline nucleus.

Knowing that functionalized quinolines have also shown high anti-carcinogenic potential, in addition to acting as anti-angiogenic agents, and inhibitors of telomerase in various human tumor cells, Muñoz and coworkers [15] selected the DM8 and DM12 tetrahydroquinolines (Figure 9) for testing cytotoxic activity. They observed that individually these compounds significantly inhibited cell growth of breast cancer, and when tested concomitantly with other two anticancer drugs, they work synergistically to increase their cytotoxic activities. The results obtained for the DM12 quinoline made this compound a promising candidate as a new adjunctive anticancer agent.

Figure 9. Structure of the DM8 and DM12 tetrahydroquinoline alkaloids.

Furthermore, Villemagne and Okamura [16] obtained promising results with other quinoline derivatives used as selective ligands for Tau proteins, associated with brain damage, which represent a risk factor for diseases such as Alzheimer's, which allowed the investigation of the causes, diagnosis, and treatment of neurodegenerative diseases, encephalopathy, and traumatic brain injury.

Biological activities of hundreds of other substituted quinolines have been reported, many of which are promising in terms of their potential as pharmaceutical agents. 2-Methyl-5-hydroxy-1,2,3,4-tetrahydroquinoline exhibits analgesic activity with a potency one-eighth that of morphine [17]. 1,2,3,4-Tetrahydroquinoline-4-carboxylic acid is used in tissue-irrigating solutions [18]. A wide array of other biological activities have been reported, including *inter alia* inhibition of (H⁺/K⁺)-ATPase [19], blood serum monoamine oxidase [20], angiotensin I converting enzyme [21], lipoxygenase [22], lipid peroxidation [23], bone resorption [24], leukotriene synthesis [25, 26], and bacterial dihydrofolate reductase [27]. Relevance to many other indications has also been noted [28-54].

In addition to the numerous utilities in the pharmacological area, studies are being performed in order to investigate the potential activities of these alkaloids as agrochemical agents. Sanguinarine and chelerythrine (Figure 10), for example, have shown high activity against fungi and phytopathogenic bacteria *in vitro*, with sanguinarine being the most effective against *Rhizoctonia solani* fungus, which has a wide range of hosts, which causes disease in most plants grown in the world [55].

Figure 10. Structure of the sanguinarine and chelerythrine agrochemical agents.

3. Tetrahydroquinoline alkaloids angustureine, galipeine, galipinine, and cuspareine

Among the simplest natural alkaloids that contain the 1,2,3,4-tetrahydroquinoline core are angustureine and its congeners, galipeine, cuspareine, and galipinine (Figure 11). The structures are more narrowly described as 2-alkyl-1-methyl-1,2,3,4-tetrahydroquinolines. They are chiral by virtue of the stereogenic center at position 2. There is an excellent review of the chemistry and synthesis of 1,2,3,4-tetrahydroquinolines by Diaz and Dudley [56].

Figure 11. Structure of the 1,2,3,4-tetrahydroquinolin alkaloids angustureine, galipeine, cuspareine, and galipinine.

In 1999, Jacquemond-Collet and coworkers [57] isolated and characterized these four tetrahydroquinoline alkaloids (Figure 11) from the extract of the bark of *Galipea officinalis*, commonly known as “angostura” [58]. The genus *Galipea* comprises about 20 species that are found predominantly in the Northern of South America. *G. officinalis* is a shrub known by rural communities in the Venezuelan mountains for their pharmacological activities, and its extract is used in the control of dyspepsia, dysentery, and chronic diarrhea, in addition to presenting antimalarial, cytotoxic [59], molluscicidal activities, and antimicrobial properties, inhibiting the growth of *Mycobacterium tuberculosis*, the etiological agent of tuberculosis [60].

In later trials, galipinine and galipeine exhibited promising biological activities *in vitro* such as antimalarial (IC_{50} : 0.24-6.12 and 0.33-13.78 mM, respectively) for the protozoa species *Plasmodium falciparum*, one of the species causing malaria that is already resistant to chloroquine, one of the main drugs used to combat the disease [61].

Due to their structural simplicities associated with the promising pharmacological activities, these alkaloids, especially angustureine, have attracted the attention of the synthetic organic community. For this alkaloid alone, more than 24 different syntheses have already been described [62-85]. Some recent examples of the syntheses of these alkaloids are described below.

Diaz *et al.* [83] described the enantioselective synthesis of both alkaloids (*R*)-(-)- and (*S*)-(+)-angustureine with overall yields of 80% and 44%, respectively, and excellent enantiomeric excesses (95% and 96%, respectively), starting from the (*S*)- β -amino ester and (*R*)-sodium carboxylate, prepared following enzymatic resolution of the β -amino ester racemate [86, 87].

Foubelo *et al.* [85] described a second-generation synthesis of (-)-angustureine by way of 2-allyl-tetrahydroquinoline. A further sequence of three steps from this intermediate provided angustureine in 36% overall yield. However, 2-allyl-tetrahydroquinolines can serve as common precursors to various 2-substituted tetrahydroquinoline alkaloids by making use of the cross-metathesis reaction with the Hoveyda-Grubbs reagent (second-generation ruthenium catalyst) to achieve the appropriate side-chain homologation events.

In turn, Lam *et al.* [88] synthesized analogues of tetrahydroquinoline alkaloids employing asymmetric hydrogenation catalyzed by iridium. These compounds were tested *in vitro* for antitumor activities against lung cancer, breast cancer, hepatocellular carcinoma, and sarcoma cancer and have achieved remarkable results, as well as *in vivo*, using mice as animal models receiving hepatocellular tumor grafts, being that 1,2,3,4-tetrahydroquin-8-ol (Figure 12) revealed the highest toxicity to human cancer cells.

1,2,3,4-tetrahydroquin-8-ol

Figure 12. Structure of 1,2,3,4-tetrahydroquin-8-ol anticancer agent.

4. Concluding remarks

This chapter is an illustration of the fascinating world of chemistry of quinoline and isoquinoline alkaloids. The range of pharmacological and agrochemical activities, among others, associated with their biosynthetic routes and various natural sources demonstrates the creative universe of the nature of these alkaloids. This universe of compounds arouses interest to organic chemists in general, stimulated by the simplicity and its varied forms of exploitation throughout constant search for the discovery of novel pharmacological agents targeting the treatment of several diseases that affect society.

5. Future directions

In this chapter, we can verify the importance of quinoline and isoquinoline alkaloids due to their potent biological activities demonstrated by *in vitro* and *in vivo* assays, as well as

agrochemical agents reported throughout this chapter. Based on these facts, this family of compounds is presented as an inexhaustible source for research groups working with natural and synthetic products for the pharmaceutical area. In this context, our group intends to continue the study of these alkaloids with the synthesis of novel quinoline and isoquinoline derivatives, aimed at the discovery of new pharmacological agents.

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