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Review

Quinolizidine-Type Alkaloids: Chemodiversity, Occurrence, and Bioactivity

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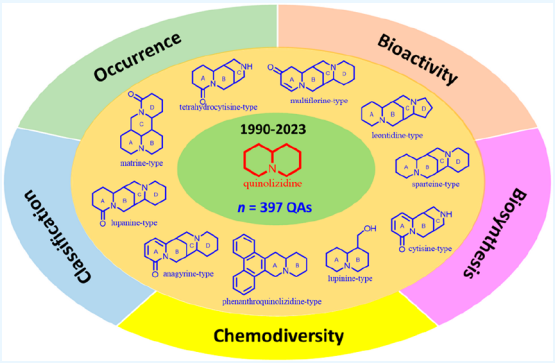
ABSTRACT: Quinolizidine alkaloids (QAs) are nitrogen-containing compounds produced naturally as specialized metabolites distributed in plants and animals (e.g., frogs, sponges). The present review compiles the available information on the chemical diversity and biological activity of QAs reported during the last three decades. So far, 397 QAs have been isolated, gathering 20 different representative classes, including the most common such as matrine (13.6%), lupanine (9.8%), anagyrine (4.0%), sparteine (5.3%), cytisine (6.5%), tetrahydrocytisine (4.3%), lupinine (12.1%), macrocyclic bisquinolizidine (9.3%), biphenylquinolizidine lactone (7.1%), dimeric (7.1%), and other less known QAs (20.9%), which include several structural patterns of QAs. A detailed survey of the reported information about the bioactivities of these compounds indicated their potential as cytotoxic, antiviral, antimicrobial, insecticidal, anti-inflammatory, antimalarial, and antiacetylcholinesterase compounds, involving favorable putative drug-likeness scores. In this regard, research progress on the structural and biological/pharmacological diversity of QAs requires further studies oriented on expanding the chemical space to find bioactive scaffolds based on QAs for pharmacological and agrochemical applications.



INTRODUCTION

The quinolizidine alkaloids (QAs) are nitrogenous heterocycles with a 1-azabicyclo[4.4.0]decane moiety obtained from natural sources.[1] QAs are specialized metabolites biosynthesized from the amino acid L-lysine.[2] Their core structure can be built from one or two quinolizidines, differentiating them from other alkaloids derived from the L-lysine pathway, such as piperidine, indolizidine, and lycopodium alkaloids.[3] QAs have been reported to possess various pharmacological effects such as sedative,[4] anticonvulsant,[5] anti-inflammatory,[6] antiviral,[7] antitumor,[8] antipyretic,[9,10] antihepatitis B,[11] antifibrotic, antiallergic, antidiarrheal, analgesic,[6] and antimicrobial.[12,13] Sparteine and lupinine were the first QAs to be isolated from *Lupinus luteus* leaves and stems at the onset of the 20th century.[14] With the development of chromatographic and spectroscopic techniques, many naturally occurring QAs have been isolated and identified, and they still attract widespread attention for their plausible applications. In this sense, there are different natural sources for which QAs have been reported, whose structural variability is highlighted. Consequently, they can be classified according to the different QA moieties depending on the number of cycles and cyclic arrangement. The seven most-known structural QA types can be globally gathered (Figure 1), characterized by one quinolizidine moiety, as in the case of the substituted, fused bicycle quinolizidines (i.e., lupinine-type). Bridged tricycles, such as cytisine and tetrahydrocytisine, are also characteristic quinolizidine classes. Finally, the tetracyclic quinolizidines are divided into two

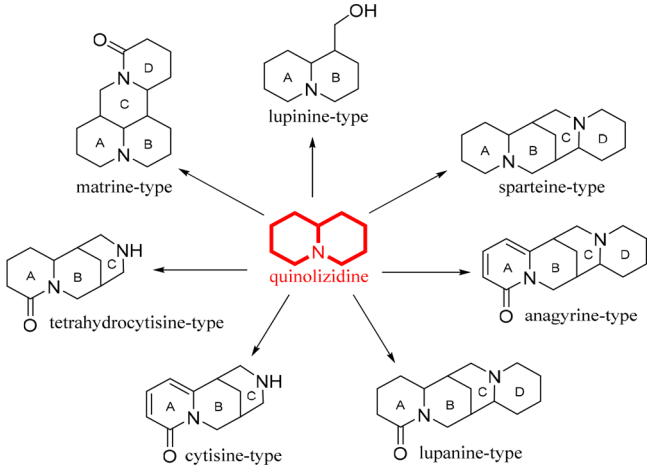


Figure 1. Structural types of the most common quinolizidine alkaloids.

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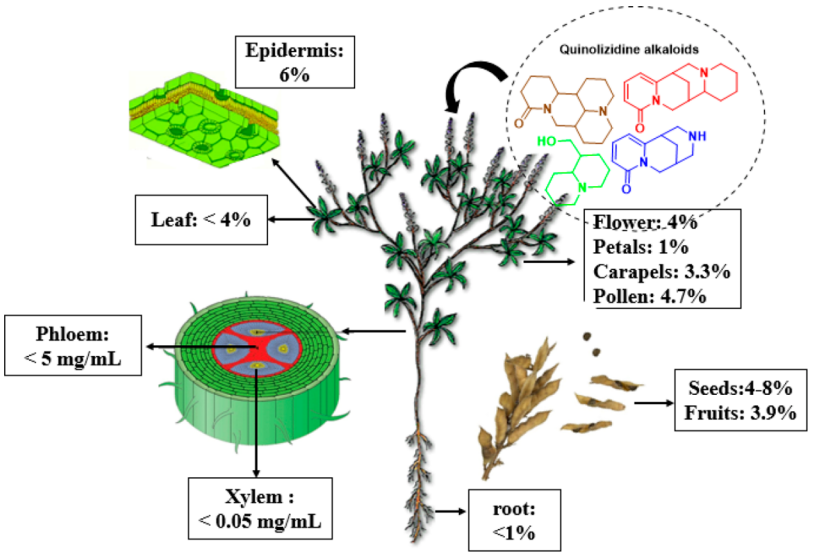

Figure 2. General distribution of quinolizidines in different plant parts of QA-producing legumes.

groups, such as fused (i.e., matrine-type) and bridged (i.e., lupanine, anagyrine, and sparteine) heterocycles.

Considering that these most-known QA types are mainly associated with Fabaceae-related taxa, the present compilation was organized on the basis of three motivations: (1) lack of exclusive and comprehensive information on QAs reported to date from diversified sources, even incorporating animal sources such as sponges and frogs,[15] since the available reviews on QAs are emphasized on occurrence in particular taxa, e.g., *Sophora*,[8,16,17] their bioactivities,[18] biosynthesis,[19−21] and diversity;[22−24] (2) classification of QA structures beyond the plant-derived QAs; and (3) recognition of structural diversity and substituent variations within common QA skeletons to be described in light of their chemodiversity. Hence, this review provides comprehensive background information on the chemodiversity of QAs, focusing on their structural variants, substitutions, occurrences, and reported biological activities, harmonizing previous reviews.

Roles for Natural Producers. One of the leading chemical functions of alkaloids in plants is the defense against predators and herbivores.[25] QAs have antimicrobial properties but have also been reported to be teratogenic to some ruminants.[26] However, the importance of quinolizidine function in plants is essential. For instance, *Lupinus* plants use compounds such as QAs in periods of biotic stress as a repellent strategy against insects.[27] Likewise, humans have also used these QAs in mixtures with carotenoids and tannins for crop bioremediation purposes, taking advantage of the direct influence and allelopathic properties of the tannins and the toxicity of the alkaloids.[28,29]

Another relevant function of these QAs is the chemical similarity to some molecules participating in signal transmission from the nervous system. Hence, they can block neuroreceptors, intermediaries of neuronal signal transduction, and ion channels in vertebrates and insects.[1] Additionally, they can serve as plant growth regulators since, in some cases, cadaverine- and putrescine-derived alkaloids increase significantly during germination.[30] Finally, the alkaloids are associated with fatty acids facilitating translocation within the plant since they can serve as storage products or transportation of nonmetabolized nitrogen. Indeed, QAs in Fabaceae can serve as nitrogen storage, especially the atmospherically fixed N_2.[31−33]

General Distribution. Although QAs have predominantly been isolated from the Fabaceae family,[25] it is worth noting that other plant families, such as Saururaceae,[23] Acanthaceae,[34] Phyllanthaceae,[35] Rubiaceae,[36] Lycopodiaceae,[37] Lycopodiaceae,[38−41] Urticaceae,[42] Ericaceae,[43] Euphorbiaceae,[44] and Connaraceae,[23] have also been investigated for the presence of relevant QAs. Additionally, QAs have been reported in families of terrestrial and marine animal species such as Dendrobatidae,[45,46] Mantellidae,[47,48] Formicidae,[49] Clavelinidae,[50] and Petrosiidae.[15] Particularly, a series of petrosins, xestospongins, and araguspongines have also been identified from marine sponges belonging to the genera *Petrosia*, *Xestospongia*, and *Oceanapia*[15,51−54] but have also been identified in frog skins, specifically in the families Dendrobatidae and Mantellidae, highlighting species such as *Phyllobates aurotaenia*, *Melanophryniscus moreirae*, *Melanophryniscus toads*,[45] *Epipedobates tricolor*,[46] *Mantella baroni*,[48] and *Mantella basileo*.[47] These alkaloids constitute a unique type of macrocyclic QAs, formed by the union of two quinolizidines (precisely two 1-oxaquinolizidine fragments), called bisquinolizidines.[15] They have exhibited biological activities such as cytotoxicity,[55] anti-inflammatory,[56] selective inhibition of the IP3 receptor, and HIV-1 RT inhibitory activity.[7]

The Fabaceae family, one of the world's largest flowering plants (Angiosperms), is the primary source of QAs. It has cosmopolitan distribution but is also well-represented in the flora of the Andes.[57] It is the third largest family worldwide among the Angiosperms, surpassed by the Asteraceae and Orchidaceae families.[58] Remarkably, the QAs are biosynthesized and accumulated in the so-called primitive legumes of the tribes *Genisteae*, *Lupinus*, *Sophoreae*, *Dalbergieae*, *Euchresteae*, *Thermopsidae*, *Bossiaeae*, *Brongniartieae*, *Podalyrieae*, *Liparieae*, and *Crotalarieae*.[1] The previous tribes include the six most relevant genera due to the highest occurrence of QAs, such as *Lupinus*, *Ulex*, *Cytisus*, *Sophora*, *Genista*, and *Orphanodendron*.[1,19,59]

The peripheral part of the seeds, bark, root, fruit, and leaf epidermis can majorly accumulate QAs.[60] Previous studies suggest that QAs play an essential role in plant defense against

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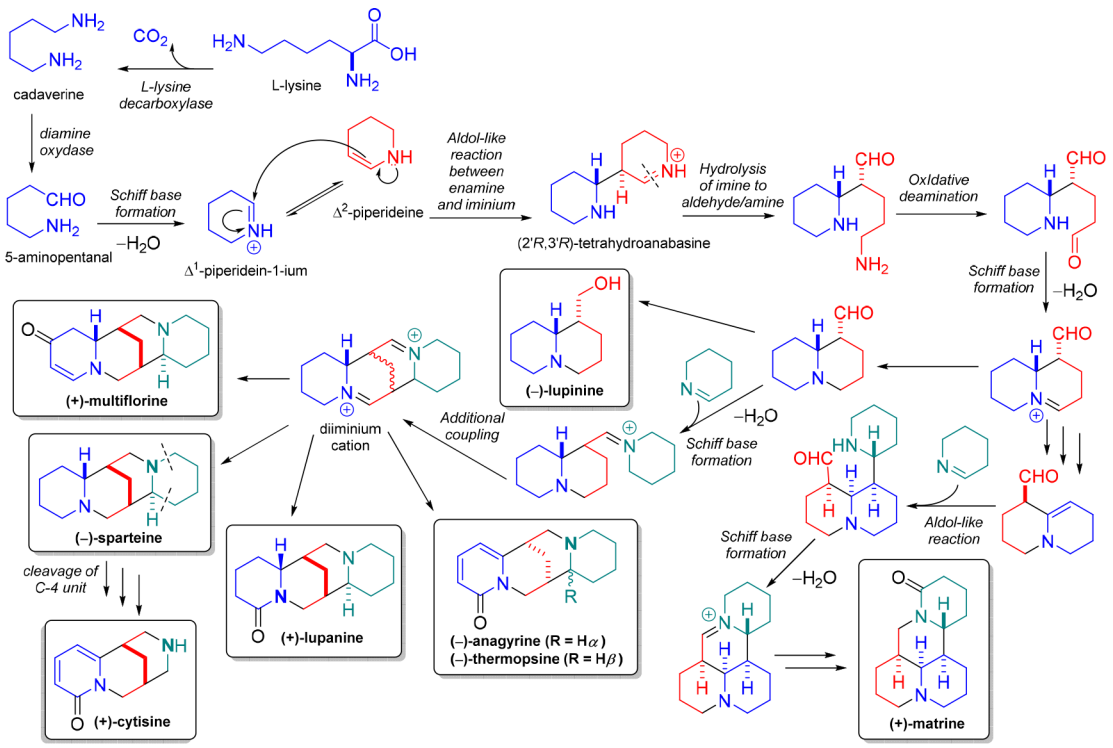

Figure 3. Biosynthesis of the most common quinolizidine alkaloids produced by legume plants.

insects due to the bitter taste and toxicity conferred by QAs, especially in the seeds, where their most significant accumulation occurs.[1] The biosynthesis of most Fabaceae alkaloids (quinolizidines) is carried out in the green aerial parts of the plant, specifically in the chloroplast. These alkaloids are transported by the phloem to other plant organs and tissues and are predominantly accumulated in subepidermal cellular structures.[61,62] The organs necessary for survival and reproduction, such as flowers and seeds, store exceptionally high amounts of defensive alkaloids.[1] The seeds of Fabaceae plants are rich in alkaloids and can reach up to 3−4%, as they are moved from the senescent leaves during the growing season. In general, QAs are widely distributed in different plant parts/organs of QA-producing legumes, so there is an estimate of the alkaloid percentage gathered in each plant part, as depicted in Figure 2.

Relevant Biosynthetic Remarks. QAs are biosynthesized from the amino acid L-lysine (Figure 3). This amino acid undergoes oxidative decarboxylation due to the action of the lysine decarboxylase (LDC), a pyridoxal phosphate (PLP)-dependent enzyme.[3] This enzymatic process results in cadaverine, a precursor and intermediary between L-lysine and QAs. Thus, the nitrogen atoms of the quinolizidine skeleton ($C_{15}N_2$) are derived from L-lysine-derived cadaverine.[19] However, despite the relevant abundance and distribution of QAs, there is a lack of knowledge of QA biosynthesis, although several hypotheses and proposals have been raised in recent decades. For more information, a recent review carefully discussed the mechanistic insights into the QA biosynthesis, particularly the pathway related to the sparteine formation based on the often-ignored precursor feeding studies.[20]

The preferred hypothesis of the QA biosynthetic pathway starts with the copper amine oxidase (CAO)-catalyzed oxidative deamination of the precursor cadaverine and its subsequent cyclization to form the next important intermediary (i.e, Δ^1-piperidein-1-ium cation), whose step involves an aldol-like coupling between the two piperideine-related tautomers.[20] This dimerization occurs under plant physiological pH (pH = 6.5−7.0), forming two stereocenters having four potential stereochemical variants but being stereoselective to the product (2′*R*,3′*R*)-tetrahydroanabasine (THA) and, in turn, to the bicyclic (−)-lupinine.[63,64] In this transformation, the imine-containing ring of THA is hydrolyzed, and another oxidative deamination proceeds (Figure 3), forming the basic quinolizidine core, achieved through a Schiff base formation.[19] Although the experimental evidence remains to be generated, it has been proposed that incorporating another Δ^1-piperideine molecule could produce the additional diazatetra(tri)cyclic moieties.[65,66] In addition, the cleavage of the fourth ring and the oxidation to a 2-pyridone system offer a potential route to cytisine, considering that any of the outermost rings could be cleaved to produce the same product.[3,67] Once the bicyclic, tricyclic, and tetracyclic structures are assembled, they can be modified by dehydrogenation, oxygenation, hydroxylation, glycosylation, or esterification (Figure 3). These transformations can afford a wide variety of structurally related quinolizidines.[68] For instance, acetylated products of 13α-hydroxylupanine/13α-hydroxymultiflorine and lupinine/epilupinine are produced by acyltransferases (e.g., HMT/HLT and ECT/EFT-LCT/LFT).[69] So far, only two enzymes have been identified in the QA pathway. Therefore, the discovery of biosynthetic genes remains as an opportunity for understanding the attractive chemistry and biology involved in QA biosynthesis.[19,21]

STRUCTURAL VARIATIONS AND OCCURRENCE OF QUINOLIZIDINE ALKALOIDS

This review aimed to gather the chemical structures of naturally occurring QAs, reported between 1990 and 2023, to disclose the available QA-related chemical space. The presence

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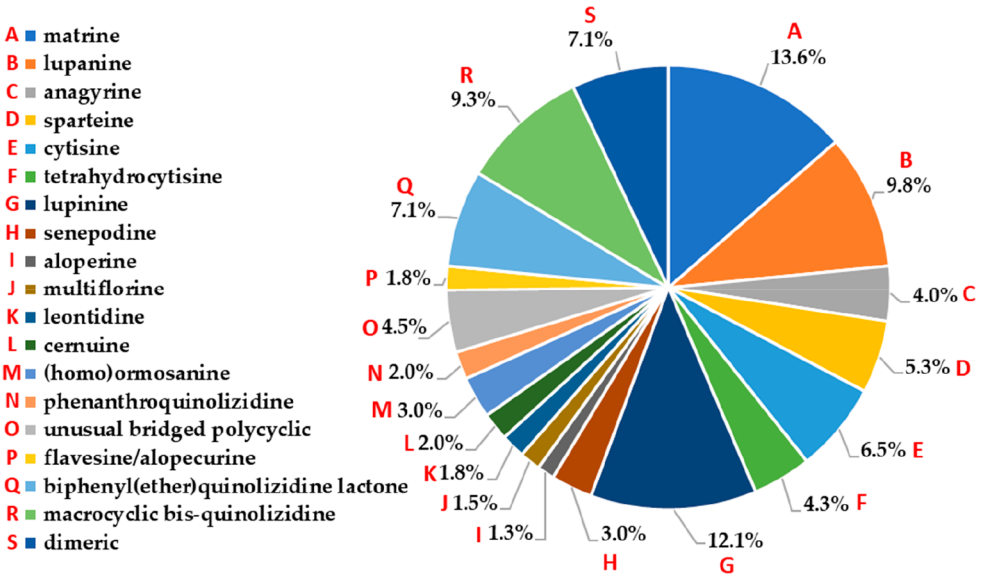

Figure 4. Distribution of the compiled quinolizidines (n = 397) according to the structural type.

of intriguing QA diversity and complexity has broadened our understanding of their structural characteristics, including their varied natural sources (plants and animals). Thus, the compiled compounds (n = 397) were mainly related to bridged or fused polycyclic QAs, including the most known QA types such as matrine, lupanine, anagyrine, sparteine, cytisine, tetrahydrocytisine, and lupinine-type compounds,[18,20,66] as depicted in Figure 1. In addition, other QAs with a more complex structure were also found, such as macrocyclic bisquinolizidine and biphenyl quinolizidine lactones, and widely reported as marine natural products[51] and from frog skins.[46] In this context, Figure 4 shows the percentage of alkaloids subdivided into classified QA types. Matrine-type QAs are the most frequently isolated (13.6%), followed by lupinine (12.1%), lupanine-type (9.8%), macrocyclic bisquinolizidines (9.3%), and biphenyl(ether)-quinolizidine lactones (7.1%). The remaining QA types encompass 48.1% of the total representatives and comprise 15 distinct structural variants (Figure 4). To disclose the QAs' chemical diversity, the reported structural variants for each QA type and the global features of the compiled chemical space are expanded on below. To support such an expansion, the names and codified structural information on QAs (**1**−**397**) in the simplified molecular input line entry specification (SMILES) are presented in Table S1, and their structures are depicted in Figures S1−S22 (Supporting Information).

Matrine-Type QAs. The matrine-type QAs are significant representatives and abundant in species of the *Sophora* genus.[16] This QA type and its sources have been used in traditional Chinese medicine for many years. Matrine-type QAs contain two condensed quinolizidine units, having a 6/6/6/6 diazatetracyclic building block and forming a fused, nonlinear bisquinolizidine. More than 50 matrine alkaloids have been isolated and described thus far, and they are disclosed in compounds **1**−**54** (Figure 5, Figure S1). The basic structure of this type of QA is the matrine alkaloid (**7**), having the mentioned tetracyclic moiety formed by two quinolizidine moieties and four contiguous stereogenic centers. The relative configurations of these chiral centers in matrine-related QAs have α- (at C-5, C-6, and C-7) and β-oriented (at C-11) hydrogens. Other basic structures have β-oriented hydrogens at C-6 (**14**) and C-7 (e.g., **15**).

In addition, the matrine-type QAs are sometimes found in the *N*-oxide form (e.g., **1**, **2**, **17**, **18**, and **37**), with N-1 being the most common point for such oxidation. The matrine-type QAs **1**−**54** differ mainly in their substitution patterns and stereochemistry.[70] They contain structural variations associated with double bonds (specifically in the D-ring) and α- or β-oriented substitutions around each tetracycle, such as hydroxyl (e.g., **1**, **3**, **4**, **8**, **18**, **19**, **21**, **29**, **30**−**43**, **45**, **47**, **49**, **50**, **53**, and **54**), acetyl (e.g., **33**, **35**, **39**, **51**, and **52**), epoxy (e.g., **40** and **41**), (methylthio)methoxy (e.g., **34** and **36**), methoxy (e.g., **38**), and indolyl (e.g., **22**) groups.[71] Thus, nine different positions for matrine substitutions (R^1 to R^9) were evidenced, the structural distribution of which is outlined in Figure 5.

The matrine-type compounds (**1**−**54**) have been extensively obtained from *Sophora* plants (96% of records) and mostly isolated from seeds and aerial parts from *S. flavescens*,[16] *S. alopecuroides*,[72] *S. tonkinensis*,[73] *S. leachiana*,[74] *S. velutina*,[75] and *Oxytropis* plants, e.g., *O. ochrocephala*,[76,77] and even widely reported from seeds and leaves of *Genista* plants.[27] Additionally, according to Table 1, these compounds have been mainly isolated from the aerial parts, roots, and seeds, which comprise the plant parts where the QAs accumulate the most.[1]

Lupanine-Type QAs. Two condensed quinolizidine units constitute lupanine-type QAs. However, they differ from other QA types, e.g., sparteine-type, by the presence of a carbonyl group at C-2, forming a lactam moiety with N-1 as ring A. Lupanines also differ from the matrine-type compounds because they involve a 6/6/6/6 diazatetracyclic building block to form a bridged bisquinolizidine.[95] So far, almost 40 lupanine-like QAs have been reported, comprising a chemical diversification illustrated by compounds **55**−**93** (Figure 6, Figure S2). The central structural core agrees with the alkaloid lupanine (levo or dextrorotatory, i.e., **56** or **61**, respectively), which is mostly substituted in rings A and D.[85] Compounds **55**−**93** exhibited C-3, C-4, and C-5 as preferred substitution positions in ring A, while the most substituted positions in ring D are associated with C-12, C-13, and C-15. In general, the most common substitutions are hydroxyl groups, affording alkaloids such as 5α-hydroxylupanine (**57**) or 13α-hydrox-

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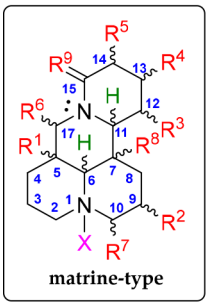

(1) R^1=β-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=β-OH, R^7=H, R^8=α-H, R^9=O, X=O^-, H6α, H11β
(2) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X=O^-, H6α, H11β
(3) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X=O^-, $\Delta^{13(14)}$, H6α, H11β
(4) R^1=α-OH, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β
(5) R^1=β-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=β-OH, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β
(6) R^1=β-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β
(7) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β
(8) R^1=α-H, R^2=α-OH, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β
(9) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X = : , $\Delta^{13(14)}$, H6α, H11β
(10) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^9=O, X = : , $\Delta^{7(8),\ 11(12),\ 13(14)}$, H6α
(11) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=H_2, X = : , H6α, H11β
(12) R^1=β-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X = : , H6α, H11α
(13) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X = : , H6β, H11α
(14) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X = : , $\Delta^{11(12),\ 13(14)}$, H6α
(15) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X = :, $\Delta^{12(13)}$, H6α, H11β
(16) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^9=O, X = : , $\Delta^{7(11)}$, H6α
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(18) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=β-OH, R^6=H, R^7=H, R^8=α-H, R^9=O, X= O^-, H6α, H11β
(19) R^1=α-OH, R^2=H, R^3=H, R^4=H, R^5=β-OH, R^6=H, R^7=H, R^8=α-H, R^9=O, X = : , H6α, H11β
(20) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=ethyl, R^6=H, R^7=H, R^8=β-H, R^9=O, X= : , $\Delta^{11(12),\ 13(14)}$, H6α
(21) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=β-OH, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β
(22) R^1=β-H, R^2=α-2-(1*H*-indol-3-yl)-2-oxoethyl, R^3=H, R^4=H, R^5=H, R^6=H, R^7=O=, R^8=β-H, R^9=O, X = : , $\Delta^{8(9)}$, H6α, H11β
(23) R^1=α-H, R^2=H, R^3=H, R^4=β-*O*-butoxy, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β
(24) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=β-ethyl, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β
(25) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X = : , $\Delta^{9(10),\ 13(14)}$, H6α, H11β
(26) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X = : , $\Delta^{2(3),\ 3(14)}$, H6α, H11β
(27) R^1=β-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=β-H, R^9=O, X= : , H6β, H11β
(28) R^1=β-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^9=O, X= : , $\Delta^{7(11)}$, H6α
(29) R^1=α-H, R^2=α-OH, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^9=O, X= : , $\Delta^{7(11)}$, H6α
(30) R^1=α-H, R^2=α-OH, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , $\Delta^{13(14)}$, H6α, H11β
(31) R^1=α-H, R^2=α-OH, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X = : , $\Delta^{11(12),\ 13(14)}$, H6α
(32) R^1=α-OH, R^2=α-OH, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , $\Delta^{13(14)}$, H6α, H11β
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(35) R^1=α-OH, R^2=α-OAc, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β
(36) R^1=α-OH, R^2=α-OCH_2SCH_3, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β
(37) R^1=α-H, R^2=α-OH, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X= O^-, H6α, H11β
(38) R^1=α-OH, R^2=α-OCH_3, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β
(39) R^1=α-OH, R^2=α-OAc, R^3–H, R^4–H, R^5–H, R^6–H, R^7–H, R^9=O, X= : , $\Delta^{6(7)}$, H11β
(40) R^1=α-OH, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^9=O, X= : , α-6,7-epoxide, $\Delta^{13(14)}$, H11β
(41) R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-OH, R^9=O, X= : , α-5,6,-epoxide, $\Delta^{13(14)}$, H11β
(42) R^1=α-OH, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , $\Delta^{13(14)}$, H6α, H11β
(43) R^1=α-OH, R^2=α-OH, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β
(44) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^9=O, X= : , $\Delta^{6(7)}$, H11β
(45) R^1=α-OH, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^9=O, X= : , $\Delta^{6(7)}$, H11β
(46) R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , $\Delta^{5(6)}$, H11β
(47) R^1=α-H, R^2=H, R^3=α-OH, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X = : , $\Delta^{13(14)}$, H6α, H11β
(48) R^1=β-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , $\Delta^{13(14)}$, H6α, H11β
(49) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-OH, R^9=O, X = : , $\Delta^{11(12),\ 13(14)}$, H6α
(50) R^1=α-H, R^2=H, R^3=β-OH, R^4=H, R^5=H, R^6=H, R^7=H, R^8=α-H, R^9=O, X = : , $\Delta^{13(14)}$, H6α, H11β
(51) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=α-OAc, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β
(52) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=β-OAc, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β
(53) R^1=α-H, R^2=H, R^3=H, R^4=H, R^5=α-OH, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β
(54) R^1=β-H, R^2=H, R^3=H, R^4=H, R^5=β-OH, R^6=H, R^7=H, R^8=α-H, R^9=O, X= : , H6α, H11β

Figure 5. Matrine-type quinolizidine alkaloids **1**–**54**.

ylupanine (**63**) but also ester moieties such as angeloyl (**91**), tigloyl (**75**), cinnamoyl (**70**), or pyrroyl (**90**). Common unsaturations are also present at positions $\Delta^{5(6)}$ (**55**) or $\Delta^{7(17)}$ (**77**), forming dehydrolupanines. Furthermore, the *N*-oxide derivatives at N-16 are also very common in these QA types. Ten distinct positions for lupanine substitutions (R^1 to R^{10}) were then revealed, the structural distribution of which is depicted in Figure 6.

On the other hand, compounds **55**–**93** (lupanine-type) show their most significant occurrence in the genus *Lupinus*, followed by *Sophora* and other genera such as *Genista*, *Acosmium*, *Ormosine*, *Thermopsis*, and *Cytisus* (Table 1). Thus, lupanine-type QAs are abundant mainly in the *Lupinus* genus and distributed in the aerial parts, leaves, seeds, bark, and root,[25] according to the gathered information in Table 1. More than 170 QAs have been identified in different species of the genus *Lupinus*.[95] Some species, such as *L. argenteus*,[96] *L. exaltatus*,[97] *L. angustifolius*,[98] *L. albus*,[67] *L. mexicanus*,[99] and *L. lanatus*,[89] are important representatives, where the QA diversity related to lupanine-type compounds has been widely investigated.

Anagyrine-Type QAs. Anagyrine-type alkaloids are structurally very similar to lupanine-type alkaloids since they have the 6/6/6/6 diazatetracyclic building block, forming a bridged bisquinolizidine, but differ in the 2-pyridone moiety in ring A as the typical feature of these QAs. There are currently 19 anagyrines reported as natural QAs, as represented by compounds **94**–**109** (Figure 7, Figure S3). The alkaloids

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Table 1. Sources of Isolated Matrine-Type (1−54) and Lupanine-Type (55−93) Quinolizidine Alkaloids (QAs)

QAs	Species	Plant part	Ref
1−11	*Sophora flavescens*	roots	16
12−16	*Sophora alopecuroides*	roots	17
17−21	*Sophora tonkinensis*	roots	73
22	*Sophora alopecuroides*	seed	78
23−24	*Oxytropis ochrocephala* Bunge	whole plants	76,77
25−26	*Sophora flavescens* Ait., *Subprostrate sophora*	roots	79
27−28	*Sophora flavescens*	roots	9
29−31	*Sophora flavescens* Ait.	chipped roots	80
32−46	*Sophora tonkinensis* Gagnep	seeds	71
47−48	*Sophora flavescens*	roots	11
49−50	*Sophora alopecuroides*	aerial parts	4
51−54	*Sophora alopecuroides, S. tonkinensis, S. viciifolia, Thermopsis lanceolata*	fresh leaves	81
55−56	*Sophora flavescens* Ait.	roots	16
57−59	*Sophora flavescens*	roots	78
60	*Lupinus albus* L.	seeds	67
61	*Cytisus purgans*	aerial parts	82
62−64	*Lupinus angustifolius*	aerial parts	83
65	*Sophora velutina* subsp. *zimbabweensis*	fruits and pods	75
66−67	*Lupinus lanatus*	aerial parts	84
68	*Lupinus albus, L. angustifolius*	seeds	85
69	*Lupinus* sp.	leaves	23
70	*Gonocytisus pterocladus*	whole plant	86
71−73	*Acosmium panamense*	bark	87
74−75	*Cytisus scoparius*	seeeds	88
76	*Lupinus lanatus*	seeds	89
77−82	*Genus pearsonia*	aerial parts	88
83	*Ormosia krugii*	seeds	90
84	*Lupinus polyphyllus*	leaves	91
85	*Lygos raetam*	aerial parts	92
86−87	*Lupinus* sp.	aerial parts	93
88−93	*Personia cajanifolia* subsp. *Cryptantha, P. sessilifolia* subsp. *marginata*	aerial parts	94

anagyrine (**94**) and thermopsine (**95**) are the representatives of this QA type, which are epimerically related and differentiated by the relative configuration of C-11 (i.e., β-H for **94** and α-H for **95**). Compounds **94−109** exhibit various substitutions on ring D at C-15, C-14, and C-12, while ring C appeared to be substituted at C-17 with a methoxyoxoethyl moiety (**102**). In addition, the C-7−C-8−C-9 bridge is mostly α-oriented. Like lupanines, an *N*-oxide thermopsine derivative at N-16 was also isolated (**108**), and other common substitutions, such as hydroxyl, epoxy, acetyl, alkanoyl, and indolyl, are also found in these QAs. An isolated alkaloid exhibited a double bond in $\Delta^{13(14)}$ (**104**), whereas other QA molecules exhibited an additional nitrogen instead of C-13 (**100**). Six substitution points in anagyrine-type QAs (R^1 to R^6) are evidenced, as illustrated in Figure 7. These 2-pyridone-containing QAs (**94−109**) are typical alkaloids of many *Papilionoideae* subfamily-belonging genera,[95] such as *Anagyris*, *Thermopsis*, *Genista*, *Clathrotropis*, and *Sophora* (Table 2), and generally absent in *Lupinus*, excepting *L. arboreus* and *L. argenteus*.[96]

Sparteine-Type QAs. (+)- or (−)-Sparteine (**110** or **111**, respectively) constitutes the basic structure of this type of QA. They are also constituted by a bridged tetracyclic formed by two quinolizidine units, having a 6/6/6/6 building block similar to the lupanine moiety,[95] but differentiated by the absence of the carbonyl group at C-2 in ring A, mentioned above. Sparteine-type QAs appeared to have fewer reported chemical variants than lupanine-type QAs. Over 20 sparteine alkaloids have been currently reported, and their structural variations are represented by compounds **110−130** (Figure 8, Figure S4). Most of these sparteine-like compounds are characterized by an α-H at C-6 and a β-H at C-11. Generally, an α-orientation for C-7−C-8−C-9 is usually presented, with some β-oriented exceptions (**121−124**). Furthermore, some sparteines have substitutions at C-10 and C-17, specifically oxygenated groups (carbonyl and hydroxyl), and the presence of bulkier substitutions, such as piperidine derivatives. The substitution pattern (R^1 to R^{11}) of these QAs is depicted in Figure 8. Finally, unsaturations have also been observed, specifically at $\Delta^{2(3)}$ and $\Delta^{5(6)}$ in ring A and at $\Delta^{11(12)}$, affording dehydrosparteine-like QAs (e.g., **114−116**, **121**, **123**, **124**, and **130**).

Regarding sparteine-type alkaloids (**110−130**), *Lupinus* plants produce and accumulate this QA type in seeds and leaves[112] and other genera such as *Acosmium*, *Lygos*, and *Houttuynia* (Saururaceae) (Table 2). Additionally, this QA type has also been isolated from seeds, leaves, flowers, and aerial parts of species belonging to the genera *Cytisus*,[113] *Ormosia*,[114] *Ulex*,[115] *Genista*,[116] *Lupinus*,[25] and *Sophora*,[117] which contain structurally related sparteine-type compounds.

Cytisine-Type QAs. The cytisine-type QA is a class of bridged tricycle alkaloids containing a 2-pyridone moiety in ring A and mainly isolated from plants of the Faboideae subfamily.[118] These QAs are characterized by having a 6/6/6 diazatricyclic building block, forming the base structure of 1,5-methanopyrido[1,2-*a*][1,5]diazocine, whose C-7−C-8−C-9 bridge has an α-orientation. Twenty-five cytisine-like alkaloids have been currently described, whose structural variations are represented by compounds **131−155** (Figure 9, Figure S5). Such variations comprise a particular substitution pattern on ring C, as shown as R^1 to R^3 in Figure 9. In general, the different derivatives of cytisine (**132**) are mostly substituted at N-12, specifically with oxide, carbonyl, hydroxyl, alkanoyl, and alk(en)yl groups. Additionally, cytisine-like QAs can be hydroxylated at C-9 (**140**), while other cytisines have a carbonyl group at C-11 (e.g., **148−150**) or an allyl group (**137**), which is generated if a sparteine-like tetracycle undergoes a ring D cleavage.[119] The alkaloid 3-hydroxy-11-norcytisine (**156**) is a cytisine-like QA isolated from *Laburnum anagyroides* green pods,[120] having an unusual 7,11-diazatricyclo[7,2,1,$0^{2,7}$]dodeca-2,4-dien-6-one (6/6/5) moiety formed by the C-13 loss (Figure 9).

Cytisine-type QAs (**131−156**) are also characteristic of the Fabaceae family plant species, and their distribution is widespread in various Fabaceae genera, widely distributed in the genera *Sophora*, *Genista*, *Cytisus*, *Osyris*, *Spartium*, *Petteria*, *Euchresta*, *Dermatophyllum*, and *Styphnolobium* and isolated from leaves, aerial parts, roots, seeds, and flowers (Table 3). Notably, these compounds accumulate mainly in the seeds and leaves and are obtained on a commercial scale from *Laburnum anagyroides* (=*Cytisus laburnum*),[121] *Sophora alopecuroides*,[4]

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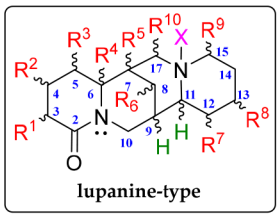

(55) R^1= H, R^2= H, R^3= H, R^5= α-H, R^6= H, R^7= H, R^8= H, R^9= H, R^{10}= H, X= : , $\Delta^{5(6)}$, H9α, H11α
(56) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= α-H, R^6= H, R^7= H, R^8= H, R^9= H, R^{10}= H, X= : , H9α, H11α
(57) R^1= H, R^2= H, R^3= α-OH, R^4= β-H, R^5= α-H, R^6= H, R^7= H, R^8= H, R^9= H, R^{10}= H, X= : , H9α, H11α
(58) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= β-OH, R^6= H, R^7= H, R^8= H, R^9= H, R^{10}= H, X= : , H9β, H11α
(59) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= α-H, R^6= H, R^7= H, R^8= H, R^9= H, R^{10}= H, X= $-O^-$, H9α, H11α
(60) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= H, R^9= H, R^{10}= β-OH, X= : , H9β, H11α
(61) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= H, R^9= H, R^{10}= H, X= : , H9β, H11α
(62) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= α-H, R^6= H, R^7= H, R^8= H, R^9= H, R^{10}= H, X= : , H9α, H11β
(63) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= α-H, R^6= H, R^7= H, R^8= α-OH, R^9= H, R^{10}= H, X= : , H9α, H11α
(64) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= α-H, R^6= H, R^7= H, R^8= α-*O*-tygloyl, R^9= H, R^{10}= H, X= : , H9α, H11α
(65) R^1= H, R^2= H, R^3= H, R^4= β-OH, R^5= α-OH, R^6= H, R^7= H, R^8= H, R^9= H, R^{10}= H, X= : , H9α, H11α
(66) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= α-*O*-anthranoyl, R^9= H, R^{10}= H, X= : , H9β, H11α
(67) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= α-*O*-(*E*)-cinnamoyl, R^9= H, R^{10}= H, X= : , H9β, H11α
(68) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= α-*O*-angeloyl, R^9= H, R^{10}= H, X= : , H9β, H11α
(69) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= H, R^9= H, R^{10}= =O, X= : , H9β, H11α
(70) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= α-*O*-(*Z*)-cinnamoyl, R^9= H, R^{10}= H, X= : , H9β, H11α
(71) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8=β-OCH_3, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
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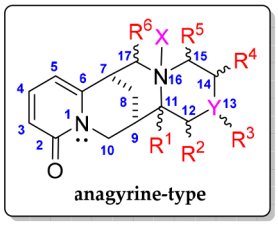
(73) R^1= β-OH, R^2= α-OH, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8=β-OCH_3, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(74) R^1= β-OH, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8=β-OH, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(75) R^1= β-OH, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8=α-*O*-tigloyl,, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(76) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= O=, R^9=β-OH, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(77) R^1= H, R^2= H, R^3= α-OH, R^4= β-H, R^6= H, R^7= H, R^8=H, R^9=H, R^{11}=H, X= : , $\Delta^{7(17)}$, H9β, H11α
(78) R^1= α-OH, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= H, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(79) R^1= β-OH, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= H, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(80) R^1= β-OH, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= α-OH, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(81) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6=α-OH H, R^7= H, R^8= α-OH, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(82) R^1= β-OH, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6=α-OH H, R^7= H, R^8= α-OH, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(83) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8=α-*O*-4-hydroxytigloyl, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(84) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8=α-OCH_3 , R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(85) R^1= H, R^2= H, R^3= H, R^4= α-H, R^5= α-H, R^6= H, R^7= α-OH, R^8=H , R^9=H, R^{10}=H, R^{11}=H, X= : , H9α, H11β
(86) R^1= β-OH, R^2= α-OH, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= H, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(87) R^1= β-OH, R^2= α-OH, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= α-*O*-tigloyl, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(88) R^1= β-OH, R^2= α-*O*-angeloyl, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= H, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(89) R^1= β-OH, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= β-OH, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(90) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= OH, R^8= α-(2-1*H*-pyrroyl)-carboxyl, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(91) R^1= H, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= α-OH, R^7= H, R^8= α-*O*-angeloyl, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(92) R^1= H, R^2= β-OH, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= H, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α
(93) R^1= β-OH, R^2= H, R^3= H, R^4= β-H, R^5= β-H, R^6= H, R^7= H, R^8= α-*O*-angeloyl, R^9=H, R^{10}=H, R^{11}=H, X= : , H9β, H11α

Figure 6. Lupanine-type quinolizidine alkaloids **55**−**93**.



(94) R^1=β-H, R^2=R^3=R^4=R^5=R^6=H, Y= C, X= :
(95) R^1=α-H, R^2=R^3=R^4=R^5=R^6=H, Y= C, X= :
(96) R^1=β-H, R^2= H, R^3=β-OH, R^4=H, R^5=α-(3-1*H*-indolyl)carbonyl, R^6=H, Y= C, X= :
(97) R^1=β-H, R^2=H, R^3=α-OH, R^4=H, R^5=α-(1-hydroxy)ethyl, R^6=H, Y= C, X= :
(98) R^1=β-H, R^2=H, R^3=α-OH, R^4=R^5=R^6=H, Y= C, X= :
(99) R^1=β-H, R^2=H, R^3=β-OH, R^4=R^5=R^6=H, Y= C, X= :
(100) R^1=α-H, R^2=H, R^3=α-pent-4-enoyl, R^4=R^5=R^6=H, Y= N, X= :
(101) R^1=β-H, R^2=H, R^3=α-*O*-acetyl, R^4=R^5=R^6=H, Y= C, X= :
(102) R^1=α-H, R^2=R^3=R^4=R^5=H, R^6=α-2-methoxy-2-oxoethyl, Y= C, X= :
(103) R^1=β-H, R^2=H, R^3=α-OH, R^3=R^4=H, R^5=α-methoxycarbonyl, R^6=H, Y= C, X= :
(104) R^1=β-H, R^2=β-OH, R^3=R^4=R^5=R^6=H, $\Delta^{13(14)}$, Y= C, X= :
(105) R^1=α-H, R^2,R^3=α-epoxy, R^4=R^5=R^6=H, Y= C, X= :
(106) R^1=α-H, R^2=R^3=R^4=R^5=H, R^6= O=, Y= C, X= :
(107) R^1=α-H, R^2=R^3=H, R^4=β-OH, R^5=R^6=H, Y= C, X= :
(108) R^1=α-H, R^2=R^3=R^4=R^5=R^6=H, Y= C, X=O^-
(109) R^1=β-H, R^2=H, R^3= O=, R^4=R^5=R^6=H, Y= C, X= :

Figure 7. Anagyrine-type quinolizidine alkaloids **94**−**109**.

Thermopsis alterniflora,[122] *Thermopsis lanceolata*,[123] and *Caragana sinica*.[124]

Tetrahydrocytisine-Type QAs. The tetrahydrocytisine-type QAs are also characterized to be tricycles and differ from those of the cytisine type by the absence of a 2-pyridone moiety in the A ring. They also have a 6/6/6 building block, forming the base structure of a 1,5-methanopyrido[1,2-*a*][1,5]diazocine. The C-7−C-8−C-9 bridge can be α- or β-oriented (e.g., **158** and **157**, respectively). Despite the fact that fewer chemical variants are reported for tetrahydrocytisine-type than for cytisine-type QAs, more substitutions were evidenced for the 17 alkaloids belonging to this QA class, illustrated by the structures of compounds **157**−**173** (Figure 10, Figure S6). Seven positions were observed to be substituted in tetrahydrocytisine-type QAs (R^1 to R^9, Figure 10). Tetrahydrocytisine (**158**) has chemical variants commonly substituted at N-12, such as cytisine-like QAs. In addition, C-13 is also substituted with an allyl group, affording angustifoline (**161**) derivatives. On the carbonyl group, the position can occur at C-2 in this QA type as cytisine derivatives but also at C-4 in ring A, forming a cyclohexenone moiety,

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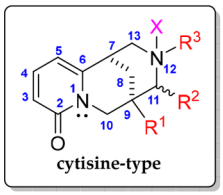
Table 2. Sources of Isolated Anagyrine-Type (94−109) and Sparteine-Type (110−130) Quinolizidine Alkaloids (QAs)

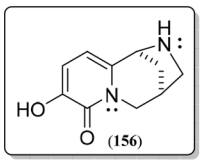
QAs	Species	Plant Part	Ref
94	*Anagyris fetida*	aerial parts	100
95	*Thermopsis rhombifolia, Genista sessilifolia, G. tinctoria* L.	leaves	101
96	*Sophora alopecuroides*	seed	78
97−99	*Clathrotropis glaucophylla*	bark	102
100	*Sophora grzfithii.*	leafy shoots	88
101	*Thermopsis chinensis*	seeds	93
102−109	*Thermopsis lanceolata*	seeds	103
110	*Lupinus* sp.	aerial parts	104
111−113	*Thermopsis chinensis, Laburnum watereri*	leaves	93
114	*Lupinus angustifolius*	aerial parts	83
115−119	*Lupinus* sp.	aerial parts	105
120	*Acosmium dasycarpum* (Vog.)	root bark	106
121−124	*Cytisus monspessulanus*	leaves	107
125	*Lupinus sericeus* Purshl	aerial parts	108
126	*Lygos ruetam* var. *surcocurpa*	aerial part	109
127	*Genista sesslifolia DC*	aerial parts	110
128	*Laburnum watereri*	leaves	93
129−130	*Lupinus varius*	seeds	111

typical for albine (**168**) derivatives. Particularly, compound **167**, a Δ^5-dehydroalbine, exhibited a 4-pyridone moiety.

These tetrahydrocytisine-type alkaloids (**157−173**) appear as the main QA in some lupin species such as *L. angustifolius*.[19,28] Very often, these alkaloids (such as **169**) are considered minor components in Old World species (*L. micranthus, L. albus*), in South American species (*L. gibertianus, L. mutabilis*), and in North American plants (*L. perennis, L. elegans, L. leucophyllus*).[141] The most significant accumulation of this QA type has been reported in leaves and flowers of *Templetonia*[134] and *Lupinus*[142] plants (Table 3).

Lupinine-Type QAs. Lupinine-type QAs represent the most basic quinolizidine unit, whose building block is a 6/6, forming the 1-azabicyclo[4.4.0]decane moiety, to comprise the

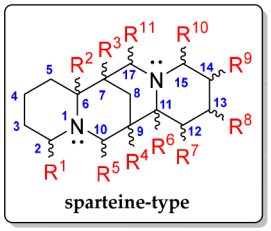




(**131**) R^1=α-H, R^2=H, R^3=methyl, X=O$^-$
(**132**) R^1=α-H, R^2=H, R^3=H, X= :
(**133**) R^1=α-H, R^2=H, R^3=methyl, X= :
(**134**) R^1=α-H, R^2=H, R^3=butyl, X= :
(**135**) R^1=α-H, R^2=H, R^3=but-3-en-1-yl, X= :
(**136**) R^1=α-H, R^2=H, R^3=ethoxycarbonyl, X= :
(**137**) R^1=α-H, R^2=α-allyl, R^3=H, X= :
(**138**) R^1=α-H, R^2=H, R^3=methylhydroxy, X= :
(**139**) R^1=α-H, R^2=H, R^3=formyl, X= :
(**140**) R^1=α-OH, R^2=H, R^3=methyl, X= :
(**141**) R^1=α-H, R^2=H, R^3=*O*-acetyl, X= :
(**142**) R^1=α-H, R^2=H, R^3=carboxymethylene, X= :
(**143**) R^1=α-H, R^2=H, R^3=2-amino-2-oxoethyl, X= :
(**144**) R^1=α-H, R^2=H, R^3=OH, X= :
(**145**) R^1=α-H, R^2=H, R^3=3β-hydroxy-2-oxobutyl, X= :
(**146**) R^1=α-H, R^2=H, R^3=3α-hydroxy-2-oxobutyl, X= :
(**147**) R^1=α-H, R^2=H, R^3=methoxycarbonyl, X= :
(**148**) R^1=α-H, R^2=O=, R^3=propyl, X= :
(**149**) R^1=α-H, R^2=O=, R^3=3-hydroxypropyl, X= :
(**150**) R^1=α-H, R^2=O=, R^3=(4-diethylamino)-4-oxobutyl, X= :
(**151**) R^1=α-H, R^2=H, R^3=2-oxo-2,5-dihydrofuran-3-yl, X= :
(**152**) R^1=α-H, R^2=H, R^3=6-(hydroxymethyl)pyridin-3-yl, X= :
(**153**) R^1=α-H, R^2=H, R^3=2-(1*H*-indol-3-yl)-2-oxoethyl, X= :
(**154**) R^1=α-H, R^2=H, R^3=glucose, X= :
(**155**) R^1=α-H, R^2=O=, R^3=4-oxopentyl, X= :

Figure 9. Cytisine-type quinolizidine alkaloids **131−156**.

quinolizidine core.[143] From this basic structure, based on (−)-lupinine and (+)-epilupinine (**174** and **175**, respectively), many substituted homologues have been identified in different plant and animal sources.[22] Hence, more than 40 lupinine-like compounds have been reported, with structural variations illustrated with the reported compounds **174−220** (Figure 11, Figure S7). They are characterized by having oxygenated substitutions such as hydroxyl (**177−178**), hydroxyalkyl (**183**), acetyl (**187** and **189**), (substituted) benzoyl (**207−209**, **215**), (substituted) cinnamoyl (**210−212**), furan-3-yl (**216−220**), and other substitutions associated with alk(en/in)yl (**187−197**, typically found in frog skins), phenyl (**205−206**), pyridyl (**201−204**), and (substituted) piperidin-1-yl (**199−200**, **213−214**). These substitutions can be found in the different positions of the quinolizidine ring, comprising a substitution pattern represented by nine different positions (R^1 to R^9, Figure 11). However, substitutions at C-6 have not yet been reported but involve chemical variants with α- or β-oriented hydrogens. In addition, two iminium salts between C-2 and N-1 have also been reported (**182−183**) as structural



(**110**) R^1=H, R^2=α-H, R^3=R^4=α-H, R^5=H, R^6=β-H, R^7=R^8=R^9=R^{10}=R^{11}=H
(**111**) R^1=H, R^2=β-H, R^3=R^4=α-H, R^5=H, R^6=α-H, R^7=R^8=R^9=R^{10}=R^{11}=H
(**112**) R^1=H, R^2=α-H, R^3=R^4=β-H, R^5=H, R^6=α-H, R^7=R^8=R^9=R^{10}=R^{11}=H
(**113**) R^1=H, R^2=α-H, R^3=R^4=α-H, R^5=H, R^6=α-H, R^7=R^8=R^9=R^{10}=R^{11}=H
(**114**) R^1=H, R^2=α-H, R^3=R^4=α-H, R^5=R^7=R^8=R^9=R^{10}=R^{11}=H, $\Delta^{11(12)}$
(**115**) R^1=phenyl, R^2=α-H, R^3=R^4=α-H, R^5=H, R^6=β-H, R^7=R^8=R^9=R^{10}=R^{11}=H, $\Delta^{2(3)}$
(**116**) R^1=phenyl, R^2=β-H, R^3=R^4=α-H, R^5=H, R^6=α-H, R^7=R^8=R^9=R^{10}=R^{11}=H, $\Delta^{2(3)}$
(**117**) R^1=α-carbonitrile, R^1=β-methyl, R^2=α-H, R^3=R^4=α-H, R^5=H, R^6=β-H, R^7=R^8=R^9=R^{10}=R^{11}=H
(**118**) R^1=β-methyl, R^2=α-H, R^3=R^4=α-H, R^5=H, R^6=β-H, R^7=R^8=R^9=R^{10}=H, R^{11}=β-methyl
(**119**) R^1=β-methyl, R^2=α-H, R^3=R^4=α-H, R^5=H, R^6=β-H, R^7=R^8=R^9=R^{10}=H, R^{11}=O=
(**120**) R^1=H, R^2=α-H, R^3=R^4=α-H, R^5=β-1-acetyl-1,4,5,6-tetrahydropyridin-3-yl, R^6=β-H, R^7=H, R^8=α-OH, R^9=R^{10}=R^{11}=H
(**121**) R^1=H, R^3=R^4=β-H, R^5=O=, R^6=α-H, R^7=R^8=R^9=R^{10}=R^{11}=H, $\Delta^{5(6)}$
(**122**) R^1=H, R^2=β-H, R^3=R^4=β-H, R^5=O=, R^6=α-H, R^7=R^8=R^9=R^{10}=R^{11}=H
(**123**) R^1=H, R^3=R^4=β-H, R^5=O=, R^6=β-H, R^7=R^8=R^9=R^{10}=R^{11}=H, $\Delta^{5(6)}$
(**124**) R^1=H, R^2=β-H, R^3=R^4=β-H, R^5=O=, R^6=β-H, R^7=R^8=R^9=R^{10}=R^{11}=H, $\Delta^{2(3)}$
(**125**) R^1=H, R^2=β-H, R^3=R^4=α-H, R^5=O=, R^6=β-H, R^7=α-OH, R^8=R^9=R^{10}=R^{11}=H
(**126**) R^1=H, R^2=α-H, R^3=R^4=α-H, R^5=H, R^6=b-H, R^7=α-OH, R^8=R^9=R^{10}=R^{11}=H
(**127**) R^1=H, R^2=β-H, R^3=R^4=α-H, R^5=α-CH_2OH, R^6=α-H, R^7=R^8=R^9=R^{10}=R^{11}=H
(**128**) R^1=H, R^2=α-H, R^3=R^4=α-H, R^5=H, R^6=β-H, R^7=R^8=H, R^9=α-OH, R^{10}=R^{11}=H
(**129**) R^1=β-OH, R^2=α-H, R^3=R^4=α-H, R^5=O=, R^6=β-H, R^7=R^8=R^9=R^{10}=R^{11}=H
(**130**) R^1=H, R^3=R^4=α-H, R^5=O=, R^6=β-H, R^7=H, R^8=α-OH, R^9=R^{10}=R^{11}=H, $\Delta^{5(6)}$

Figure 8. Sparteine-type quinolizidine alkaloids **110−130**.

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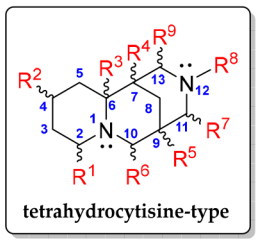
Table 3. Sources of Isolated Cytisine-Type (131−156) and Tetrahydrocytisine-Type (157−173) Quinolizidine Alkaloids (QAs)

QAs	Species	Part	Ref
131−133	*Sophora flavescens*	roots	16
134	*Sophora flavescens*	roots	125
135	*Genista quadriflora* Munby	roots and aerial parts	126
136−137	*Dermatophyllum arizonicum, Dermatophyllum gypsophilum, Dermatophyllum secundiflorum, Styphnolobium affine, Styphnolobium japonicum*	leaf tissue	119
138	*Sophora velutina* subsp. *zimbabweensis*	fruits and pods	75
139	*Spartium junceum*	fresh flowers	127
140	*Osyris alba* L.	aerial parts	128
141	*Euchresta tubulosa* Dunn	stem	129
142−144	*Sophora exigua*	aerial parts	88
145−146	*Sophora griffithii*	leaves	130
147	*Petteria ramentacea*	buds, leaves, and flowers	131
148−155	*Thermopsis lanceolata*	seeds	103,132
156	*Laburnum anagyroides*	green pods	120
157	*Sophora flavescens*	roots	125
158	*Genista quadriflora*	roots and aerial parts	126
159	*Guianodendron praeclarum*	leaves	133
160−161	*Lupinus angustifolius*	aerial parts	83
162	*Lupinus* sp.	leaves	23
163−164	*Templetonia biloba*	leaves	134
165	*Lupinus termis*	seeds	135
166	*Thermopsis mongolica*	aerial parts	136
167	*Lupinus termis*	seeds	137
168	*Lupinus angustifolius*	seeds	85
169	*Lupinus angustifolius, L. campestris*	aerial parts	23
170−171	*Virgilia diuaricata, V. oroboides*	left	138
172	*Lupinus albus*	aerial parts	139
173	*Lupirnus polyphyllus*	stems, leaves, and pods	140



(**157**) R^1=O=, R^2=H, R^3=β-H, R^4=R^5=β-H, R^6=H, R^7=H, R^8=CH_3, R^9=H
(**158**) R^1=O=, R^2=H, R^3=β-H, R^4=R^5=α-H, R^6=H, R^7=H, R^8=H, R^9=H
(**159**) R^1=O=, R^2=H, R^3=β-H, R^4=R^5=β-H, R^6=β-(1-acetyl)-1,4,5,6-tetrahydropyridin-3-yl, R^7=β-allyl, R^8=CH_3, R^9=H
(**160**) R^1=O=, R^2=H, R^3=β-H, R^4=R^5=β-H, R^6=H, R^7=H, R^8=but-3-en-1-yl, R^9=H
(**161**) R^1=O=, R^2=H, R^3=β-H, R^4=R^5=β-H, R^6=H, R^7=β-allyl, R^8=H, R^9=H
(**162**) R^1=H, R^2=H, R^3=α-H, R^4=R^5=α-H, R^6=H, R^7=H, R^8=CH_3, R^9=H
(**163**) R^1=O=, R^2=H, R^3=β-H, R^4=R^5=α-H, R^6=H, R^7=H, R^8=CHO, R^9=H
(**164**) R^1=O=, R^2=H, R^3=α-H, R^4=R^5=α-H, R^6=H, R^7=H, R^8=CH_3, R^9=H
(**165**) R^1=O=, R^2=H, R^3=α-H, R^4=R^5=β-H, R^6=H, R^7=α-3-carboxypropyl, R^8=CH_2OH, R^9=H
(**166**) R^1=O=, R^2=H, R^3=β-H, R^4=R^5=β-H, R^6=H, R^7=β-allyl, R^8=H, R^9=H
(**167**) R^1=H, R^2=O=, R^4=α-H, R^5=R^6=β-H,R^7=H, R^8=H, R^9=β-allyl, $\Delta^{2(3),\,5(6)}$
(**168**) R^1=H, R^2=O=, R^3=β-H, R^4=R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=β-allyl, $\Delta^{2(3)}$
(**169**) R^1=H, R^2=O=, R^3=β-H, R^4=R^5=β-H, R^6=H, R^7=H, R^8=but-3-en-1-yl, R^9=H, $\Delta^{2(3)}$
(**170**) R^1=H, R^2=H, R^3=β-H, R^4=R^5=β-H, R^6=O=, R^7=H, R^8=CH_3, R^9=H
(**171**) R^1=H, R^2=H, R^3=β-H, R^4=R^5=β-H, R^6=O=, R^7=H, R^8=but-3-en-1-yl, R^9=H
(**172**) R^1=H, R^2=O=, R^3=β-H, R^4=R^5=α-H, R^6=H, R^7=H, R^8=CH_3, R^9=β-allyl, $\Delta^{2(3)}$
(**173**) R^1=O=, R^2=H, R^3=β-H, R^4=R^5=α-H, R^6=H, R^7=β-allyl, R^8=CH_3, R^9=H

Figure 10. Tetrahydrocytisine-type quinolizidine alkaloids **157−173**.

variations of this type of QAs. Finally, thermlanseedline A (**221**) is an alkaloid containing the quinolizidine moiety coupled with an acetylpiperidyl fragment, which was proposed to be derived from thermopsine after oxidative ring D cleavage/demethylation/acetylation biosynthetic steps.[132]

This type of alkaloid (**174−221**) is the most abundant in the Fabaceae family, and they generally occur in the genera *Lupinus, Baptisia, Thermopsis, Maackia, Genista, Lycopodium, Ulex, Prosopis, Cytisus,* and *Sophora*.[21] The first reported structure of lupinine was carried out in 1938, isolated from the leaves of the *Lupinus luteus*,[144] and different *Lupinus* genotypes have shown the presence of lupinine-type compounds.[145] In addition, furan-3-yl-containing lupinine-type QAs were isolated from *Nuphar* plants. Additionally, 26% of records correspond to other genera of other families that can also biosynthesize QAs, such as *Hypoestes* (Acanthaceae), *Flueggea* (Phyllanthaceae), *Myrioneuron* (Rubiaceae), *Huperzia* (Lycopodiaceae), *Heimia* (Lythraceae), *Boehmeria* (Urticales), *Vaccinium* (Ericaceae), *Croton* (Euphorbiaceae), and *Clavelina* (Clavelinidae), whereas the other 16% of records correspond to animal species such as *Solenopsis picea*[49] and frog skin of the *Dendrobates*,[146] *Mantella*,[48] and *Epipedobates*[46] genera (Table 4).

Senepodine-Type QAs. A group of alkaloids, also known for being part of the*Lycopodium* QAs, comprise the $C_{22}N_2$

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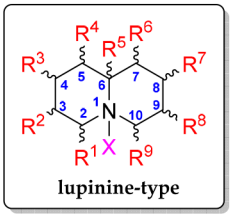

(**174**) R^1=H, R^2=H, R^3=H, R^4=H, R^5=β-H, R^6=α-CH_2OH, R^7=H, R^8=H, R^9=H, X= :
(**175**) R^1=H, R^2=H, R^3=H, R^4=H, R^5=β-H, R^6=β-CH_2OH, R^7=H, R^8=H, R^9=H, X= :
(**176**) R^1=H, R^2=H, R^3=H, R^4=H, R^5=β-H, R^6=acetamidomethylene, R^7=H, R^8=H, R^9=H, X= :
(**177**) R^1=H, R^2=H, R^3=H, R^4=H, R^5=β-H, R^6=β-CH_2OH, R^7=β-OH, R^8=H, R^9=H, X= :
(**178**) R^1=β-CH_3, R^2=H, R^3=β-CH_3, R^3=α-OH, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=H, X= :
(**179**) R^1=β-CH_3, R^2=H, R^3=β-CH_3, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=H, X= :
(**180**) R^1=β-(piperidin-2-yl)methyl, R^2=H, R^3=β-methyl, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=H, X= :
(**181**) R^1=β-(piperidin-2-yl)methyl, R^2=H, R^3=β-methyl, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=H, X=O^-
(**182**) R^1=CH_3, R^2=H, R^3=β-CH_3, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=H, $\Delta^{1(2)}$, N^+, X= :
(**183**) R^1=CH_3, R^2=H, R^3=β-CH_3, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=β-2-hydroxypropyl, $\Delta^{1(2)}$, N^+, X= :
(**184**) R^1=H, R^2=H, R^3=H, R^4=H, R^5=β-H, R^6=H, R^7=O=, R^8=H, R^9=β-CH_3, X= :
(**185**) R^1=H, R^2=H, R^3=H, R^4=H, R^5=α-H, R^6=H, R^7=O=, R^8=H, R^9=β-CH_3, X= :
(**186**) R^1=H, R^2=H, R^3=H, R^4=H, R^5=β-H, R^6=β-carboxyamino, R^7=H, R^8=H, R^9=H, X= :
(**187**) R^1=α-(deca-1,3-dien-1-yl), R^2=H, R^3=H, R^4=H, R^5=α-H, R^6=H, R^7=H, R^8=β-acetyl, R^9=α-CH_3, X= :
(**188**) R^1=α-(deca-1,3-dien-1-yl), R^2=H, R^3=H, R^4=H, R^5=α-H, R^6=H, R^7=H, R^8=β-OH, R^9=α-CH_3, X= :
(**189**) R^1=β-CH_3, R^2=α-acetyl, R^3=H, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=β-(1*Z*,3*E*)-octa-1,3-dien-1-yl, X= :
(**190**) R^1=β-pent-4-en-1-yl, R^2=H, R^3=H, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=β-pent-4-en-1-yl, X= :
(**191**) R^1=H, R^2=hex-2-en-1-ylidene, R^3=H, R^4=α-OH, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=H, X= :
(**192**) R^1=β-pent-2-en-4-yn-1-yl, R^2=H, R^3=H, R^4=β-CH_3, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=H, X= :
(**193**) R^1=β-CH_3, R^2=H, R^3=H, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=β-propyl, X= :
(**194**) R^1=α-allyl, R^2=H, R^3=H, R^4=α-ethyl, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=H, X= :
(**195**) R^1=α-pent-2-en-4-yn-1-yl, R^2=H, R^3=H, R^4=α-ethyl, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=H, X= :
(**196**) R^1=α-pent-2-en-4-yn-1-yl, R^2=H, R^3=H, R^4=β-ethyl, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=H, X= :
(**197**) R^1=α-hex-5-en-1-yl, R^2=H, R^3=H, R^4=α-methyl, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=H, X= :
(**198**) R^1=β-6-(dimethylamino)hexyl, R^2=H, R^3=β-CH_3, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=H, X= :
(**199**) R^1=H, R^2=H, R^3=H, R^4=H, R^5=β-H, R^6=β-CH_2OH, R^7=H, R^8=6-oxo-1,6-dihydropyridin-2-yl, R^9=H, X= :
(**200**) R^1=H, R^2=H, R^3=H, R^4=H, R^5=β-H, R^6=β-CH_2OH, R^7=H, R^8=6-oxopiperidin-2-yl, R^9=H, X= :
(**201**) R^1=H, R^2=H, R^3=H, R^4=H, R^5=β-H, R^6=β-CH_2OH, R^7=H, R^8=β-6-methoxypiridin-2-yl, R^9=H, X= :
(**202**) R^1=H, R^2=H, R^3=β-OH, R^4=H, R^5=β-H, R^6=β-CH_2OH, R^7=H, R^8=β-6-methoxypiridin-2-yl, R^9=H, X= :
(**203**) R^1=H, R^2=β-OH, R^3=H, R^4=H, R^5=β-H, R^6=β-CH_2OH, R^7=H, R^8=β-6-methoxypiridin-2-yl, R^9=H, X= :
(**204**) R^1=H, R^2=H, R^3=β-OH, R^4=H, R^5=β-H, R^6=β-CH_2OH, R^7=H, R^8=β-6-oxo-1,6-dihydropyridin-2-yl, R^9=H, X= :
(**205**) R^1=H, R^2=H, R^3=H, R^4=H, R^5=β-H, R^6=H, R^7=α-acetyl, R^8=H, R^9=β-4-hydroxy-3-methoxyphenyl, X= :
(**206**) R^1=H, R^2=4-methoxyphenyl, R^3=3,4-dimethoxyphenyl, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=H, $\Delta^{3(4)}$, X= :
(**207**) R^1=β-CH_3, R^2=α-benzoyloxy, R^3=H, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=α-carboxymethyl, X= :
(**208**) R^1=β-CH_3, R^2=α-3,4-dimethoxybenzoyloxy, R^3=H, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=α-carboxymethyl, X= :
(**209**) R^1=β-CH_3, R^2=α-2,4-dimethoxybenzoyloxy, R^3=H, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=α-carboxymethyl, X= :
(**210**) R^1=β-CH_3, R^2=α-(*Z*)-cinnamoyloxy, R^3=H, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=α-carboxymethyl, X= :
(**211**) R^1=β-CH_3, R^2=α-(*Z*)-4-methoxycinnamoyloxy, R^3=H, R^4=H, R^5=β-H, R^6=H, R^7=H, R^8=H, R^9=α-carboxymethyl, X= :
(**212**) R^1=H, R^2=H, R^3=H, R^4=H, R^5=β-(3-methoxy-4-α-rhamnosyloxycinnamoyloxy)methyl, R^6=, R^7=H, R^8=H, R^9=H, X= :
(**213**) R^1=H, R^2=H, R^3=H, R^4=H, R^5=α-H, R^6=β-(2,6-dioxopiperidin-1-yl)methyl, R^7=H, R^8=H, R^9=H, X= :
(**214**) R^1=H, R^2=H, R^3=H, R^4=H, R^5=α-H, R^6=β-(2-oxopiperidin-1-yl)methyl, R^7=H, R^8=H, R^9=H, X= :
(**215**) R^1=H, R^2=H, R^3=H, R^4=H, R^5=β-H, R^6=β-(benzoyloxy)methyl, R^7=H, R^8=H, R^9=H, X= :
(**216**) R^1=furan-3-yl, R^2=H, R^3=H, R^4=β-CH_3, R^5=β-H, R^6=H, R^7=H, R^8=α-CH_3, R^9=H, X=O^-
(**217**) R^1=furan-3-yl, R^2=H, R^3=H, R^4=β-CH_3, R^5=β-H, R^6=H, R^7=H, R^8=α-CH_3, R^9=H, X= :
(**218**) R^1=furan-3-yl, R^2=H, R^3=H, R^4=β-CH_3, R^5=β-H, R^6=H, R^7=H, R^8=β-CH_3, R^9=H, X= :
(**219**) R^1=furan-3-yl, R^2=H, R^3=H, R^4=β-CH_3, R^5=β-H, R^6=H, R^7=H, R^8=α-CH_3, R^8=β-OH, R^9=H, X= :
(**220**) R^1=4-carboxy-1-oxobut-3-en-2-yl, R^2=H, R^3=H, R^4=β-CH_3, R^5=β-H, R^6=H, R^7=H, R^8=α-CH_3, R^9=H, X= :
(**221**) R^1=O=, R^2=H, R^3=H, R^4=H, R^6=O=, R^7=H, R^8=β-1-acetylpiperidin-2-yl, R^9=H, $\Delta^{3(4),5(6)}$, X= :

Figure 11. Lupinine-type quinolizidine alkaloids **174**−**221**.

adduct formed between a lupinine-like moiety with an α- or β-oriented (1,7-dimethyldecahydroquinolin-5-yl)methyl moiety at C-10.[38] (+)- and (−)-Senepodine (**222** and **223**, respectively) can be considered the basic structure of this QA type.[165] Eleven senepodine-related compounds have been reported, having structural variations at six different positions (R^1 to R^6, Figure 12), involving three variations for the lupinine moiety and the other three for the decahydroquinoline substitution. The four substituting positions involved α- or β-oriented methyl groups at C-2, C-4, N-1′, and C-8′ (**224**−**225**), formyl and acetyl groups at N-1′ (**226**−**227**, **229**), and piperidin-2-yl at C-2 (**230**−**232**). Iminium salts between C-2 and N-1 have also been reported (**224**). In addition, α- or β-oriented hydrogens can be found at C-6 and C-10′ in the lupinine and decahydroquinoline moieties, respectively (Figure 12, Figure S8). Finally, a particular senepodine-like alkaloid, consisting of a fastigiatine-quinolizidine adduct ($C_{27}N_3$), himeradine A (**233**), was isolated from *Lycopodium chinense* (Table 4), having the fastigiatine moiety attached to C-2 through a methylene bridge.[164]

Uncommon Diazatetracyclic QAs (Aloperine, Multiflorine, Leontidine, and Cernuine Types). These QA types (**234**−**259**) have structural similarities to sparteine or lupanine since they contain a diazatetracyclic moiety (Figure 13). However, they did not fall into the above-described QA types, but they can be gathered into four subclasses due to their structural similarities, such as aloperine, multiflorine, leontidine, and cernuine types. The first uncommon diazatetracyclic QA, i.e., aloperine type, have been isolated from *Sophora* and *Oxytropis* plants (Table 5). Thus, aloperine (**234**) is the base structure of this QA variant (**234**−**237**), sharing a sparteine-like structure but differing by the nitrogen position, i.e., N-12 in ring D. Aloperines have exclusively been reported with an α-oriented C-7−C-8−C-9 bridge. The other two related alkaloids have been isolated with formyl and oxide substitutions at N-12 (**235** and **236**, respectively)[166] and have a carbonyl at C-10 and an aromatic D ring (**237**) (Figure 13). Ochrocephalamine D (**238**) is an aloperine-like QA, isolated from *Oxytropis ochrocephala*,[166] having an additional pyrrolidin-2-one moiety

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Table 4. Sources of Isolated Lupinine- (174-221) and Senepodine-Type (222−233) Quinolizidine Alkaloids (QAs)

QAs	Species	Part	Ref
174−175	*Lupinus* sp.	aerial parts	147
176	*Maackia amurensis* var. *Buergeri, M. tashiroi*	fresh stems	148
177	*Virgilia divaricata, V. oroboides*	leaves	93
178	*Lycopodium cernuum* var. *sikkimense*	whole plants	149
179−183	*Lycopodium cernuum, L. chinense*	club moss	150
184−185	*Vaccinium myrtillus*	aerial parts	43
186	*Epipedobates tricolor*	skin	151
187−189	*Clavelina picta*	leaves and aerial part	93,152
190−191	*Melanophryniscus klappenbachi, M. cupreuscapularis*	skin of poison frogs	45
192−193	*Mantella basileo*	skin	47
194−197	*Mantella baroni*	skin	48
198	*Huperzia phlegmaria*	club moss	37
199−200	*Sophora chrysophylla*	bark	153
201−203	*Ulex jussiaei*	aerial parts	154
204	*Maackia amurensis* var. *buergeri*	leaves	155
205	*Heimia salicifolia*	leaves	41
206	*Pilea* aff. *martinii*	aerial parts	156
207−211	*Cylicomorpha solmsii*	leaves	157
212	*Lupinus varius* ssp. *orientalis*	leaves	81
213	*Sophora nuttalliana, S. stenophylla*	leaf and stem tissue	158
214	*Bongardia Chrysogonum*	tubers	159
215	*Lupinus varius* ssp. *orientalis*	aerial parts	81
216−219	*Nuphar pumilum*	rhizomes	160
220	*Nuphar japonicum*	rhizomes	161
221	*Thermopsis lanceolata*	seeds	132
222−233	*Lycopodium chinense*	club moss	23,38,150,162−164

formed by a further carbonyl group linked to N-12 and C-10 (Figure 13, Figure S9).

On the other hand, (−)-multiflorine (**239**) comprises the basic structure of another related QA type, with a particularly high occurrence in the genus *Lupinus*[167] (Table 5), differing from lupanine by the C-4 carbonyl group, a nitrogen position at the D-ring (i.e., N-16), and a characteristic double bond at C-2. The β-oriented C-7−C-8−C-9 bridge has exclusively been reported for these QAs. Five additional multiflorine-like alkaloids have also been isolated (**239−244**), representing the structural variations of this QA type, which involve a further double bond at C-5 (**240**), a hydroxyl group at C-13 (**241−242**), an oxide at N-16 (**243**) or *O*-tigloyl ester (**244**) (Figure 13, Figure S10).

Another type of lupanine-like diazatetracyclic QA is related to leontidine (**245**), widely distributed in the genera *Camoensia*, *Guianodendron*, and *Orphanodendron* (Table 5), which differs from lupanine by the presence of a five-membered D-ring instead of a six-membered one, forming a quinolizidine/indolizidine adduct.[59] This type of QA exhibits an α- or β-oriented C-7−C-8−C-9 bridge and a carbonyl group at C-2 (e.g., **245−247**, **250**) but also at C-10 (e.g., **248−249**). In addition, unsaturations at C-2 (**248−249**), C-3 and C-5 (**245−246**), and the oxide group at N-15 (**250**) can also be found. In addition, velutinine (**251**) is a highly unsaturated leontidine-like alkaloid isolated from *Sophora velutina* subsp. *Zimbabweensis* stem bark,[75] having a hydroxyl at C-8, an α-pyridone moiety at ring A, and a methylenedioxy group at C-13/C-14 (Figure 13, Figure S11).

Finally, cernuine (**254**) is the representative alkaloid of a QA type constituted by a tetradecahydro-2*H*-pyrido[1′,2′:3,4]-pyrimido[2,1,6-*de*]quinolizine moiety, which is also known to be part of the *Lycopodium* alkaloids[168] (Table 5). Eight cernuine-type QAs (**252−259**) have been reported, characterized by having a carbonyl group at C-1 and can involve an α-oriented hydroxyl or acetyl group at C-12 (**252**, **256−259**) or an α-hydroxyl at C-2 (**255**). They also have a $\Delta^{C14(15)}$ unsaturation (**258−259**) and an *N*-oxide at N-8 (**252−253**) (Figure 13, Figure S12).

Triazapolycyclic QAs (Ormosanine- and Homoormosanine-Type). An interesting QA type involves those compounds having triazapolycyclic moieties (**260−271**) being related to (+)- or (−)-ormosanine (**260** or **264**, respectively) and homoormosanine (**267**) as the basic structures (Figure 14). The ormosanine-type alkaloids (**260−266**) have a diazatetracycle moiety bonded with a piperidine unit at C-9, commonly distributed in the *Podopetalum*[176] and *Bowdichia*[177] genera (Table 6). The other four ormosanine-like diastereomers have been reported due to the configuration of six chiral carbons (i.e., C-5, C-7, C-9, C-10, C-17, and C-18) (**261**, **263**, **265**, and **266**). Finally, a $\Delta^{5(6)}$-containing structural variant of **264** was also reported ((−)-podopetaline, **262**).[24] On the other hand, the homoormosanine-type QAs are based on a singular triazahexacyclic structure (**267−271**) involving an aloperine moiety fused with an additional azabicyclic fragment bonded at N-1 and C-9 of the aloperine moiety (Figure 14, Figure S13). The additional azabicyclic moiety can

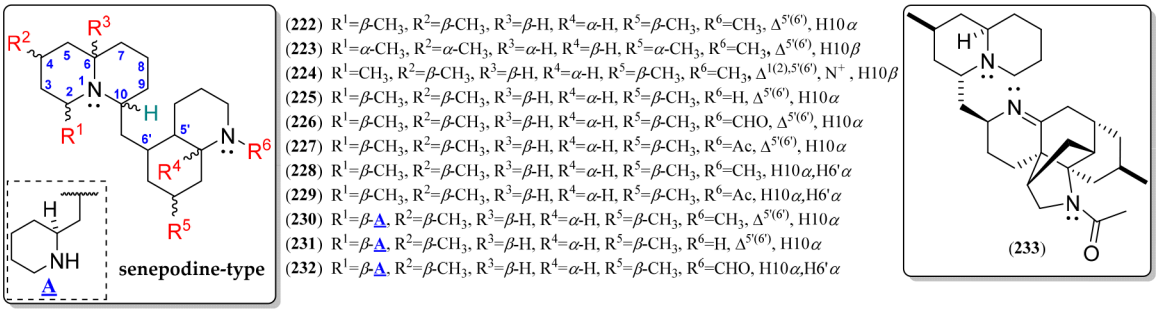

Figure 12. Senepodine-type quinolizidine alkaloids **222−233**.

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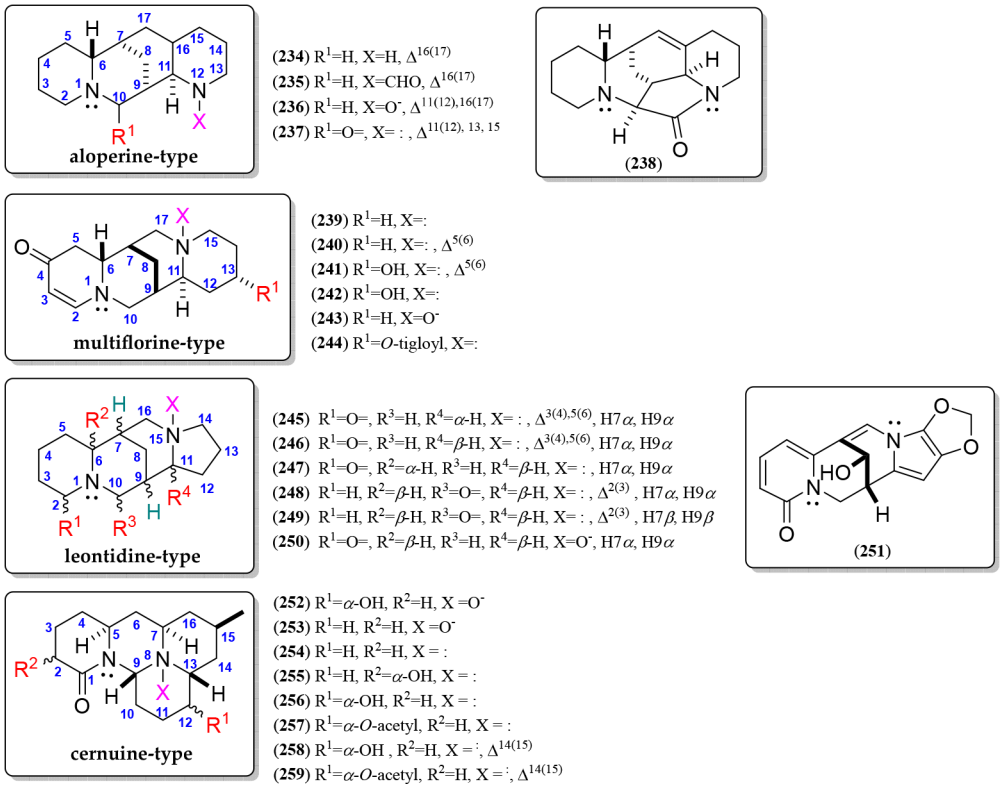

Figure 13. Aloperine, multiflorine, leontidine, and cernuine-type quinolizidine alkaloids **234**−**259**.

Table 5. Sources of Isolated Aloperine- (234−238), Multiflorine- (239−244), Leontidine- (245−251), and Cernuine-Type (252−259) Quinolizidine Alkaloids (QAs)

QAs	Species	Part	Ref
234	*Sophora alopecuroides*	seeds and leaves	169
235−238	*Oxytropis ochrocephala* Bunge	whole plant	166,170
239	*Lupinus lanatus*	aerial parts	84
240−242	*Lupinus albus*	seeds	171
243	*Lupinus hirsutus* Linn	seedlings	172
244	*L. albus, L. varius, L. orientalis, L. hartwegii, L. densiflorus*	whole plant	173
245	*Leontice ewersmannii*	leaves	174
246−248	*Orphanodendron bernalii, O. grandiflorum*	leaves	133
249	*Guianodendron praeclarum*	leaves	133
250	*Maackia tashiroi*	stems	175
251	*Sophora velutina* subsp. *zimbabweensis*	fruits and pods	75
252−253	*Lycopodium cernuum, L. chinense*	club moss	150
254−259	*Lycopodium cernuum* var. *Sikkimense*	club moss	149

be formed through a methylenediaza bridge (**267**−**270**) or an N-1−C-20 linking (**271**). Homoormosanine (**267**) has these three epimeric variants (**268**−**270**) differentiated by the α/β-oriented hydrogen patterns at five chiral carbons, i.e., C-5, C-6, C-8, C-21, and C-22 (R^1 to R^5, Figure 14, Figure S14).

Phenanthroquinolizidine QAs. This QA type has a phenanthrene moiety fused with a quinolizidine, sharing the carbons C-3−C-4 of the quionolizidine fragments (**272**−**279**). The alkaloids (+)- or (−)-cryptopleurine (**275** or **277**, respectively) can be considered to be the basic structure of this QA type (Figure 15, Figure S15). Apart from **275**/**277**, six phenanthroquinolizidine QAs have been additionally reported (**272**−**274**, **276**, **278**−**279**), varying by six different substitutions (R^1 to R^6, Figure 15) involving hydroxyl or methoxyl groups and the α- or β-orientation of H-6. A representative of this QA type was first isolated in 1935 from the species *Tylophora indica*. In addition, the genus *Tylophora*, *Pilea*, *Boehmeria*, and *Hypoestes* are the reported plant sources of these particular QAs (Table 7).

Unusual Bridged Polycyclic QAs. Other QA types can be gathered into unique alkaloids containing unusually bridged polycycles (**280**−**297**). In this group, the N^1,N^{12}-diazaadamantane alkaloids are included (**280**−**283**), highly isolated from the genus *Acosmium*; therefore, acosmine (**280**) is the basic structure for this kind of alkaloid[106] (Figure 16, Figure S17). Few structural variants have been reported for the acosmine-type QAs, involving a substitution at C-6 (R^1), which comprises esterified 4-hydroxybutyl chains (**282**−**282**) or an allyl group (**283**). In addition, panacosmine (**284**) is a special diaza-adamantane alkaloid since it involves a 1-acetyl-1,4,5,6-tetrahydropyridin-3-yl substitution (**284**) instead of an acetamidomethylene (**280**) in the absence of the 4-hydroxybutyl substitution (Figure 16). On the other hand, neosecurinan (**285**) is an interesting hexahydro-2*H*,7*H*-5,10b-ethanofuro[2,3-*a*]quinolizine-containing QA, which was isolated for the first time in 1956 from the genus *Securinegaen* (Phyllanthaceae).[35] Eight securinol-type stereoisomers have been isolated (**286**−**293**) (Figure 16, Figure S17) from twigs and leaves of *Flueggea virosa* (Phyllanthaceae).[35] These stereoisomers differed from **285** by the presence of a carbonyl group at C-12, forming a furan-2(5*H*)-one moiety, whose differences between them are related to the absolute configuration of C-2, the C-7−C-15−C-14−C-10 bridge, and the carbinol carbon at C-8[35] (Figure 16). Finally, myrifabral-

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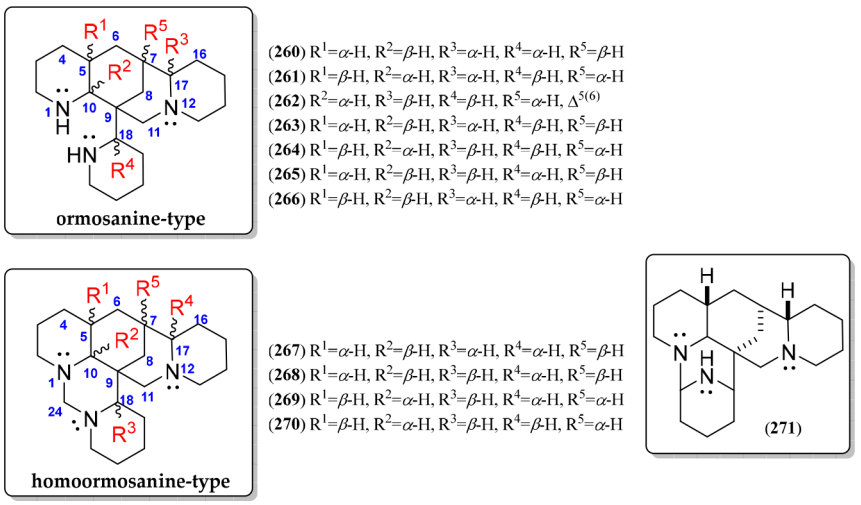


(260) R^1=α-H, R^2=β-H, R^3=α-H, R^4=α-H, R^5=β-H
(261) R^1=β-H, R^2=α-H, R^3=α-H, R^4=β-H, R^5=α-H
(262) R^2=α-H, R^3=β-H, R^4=β-H, R^5=α-H, $\Delta^{5(6)}$
(263) R^1=α-H, R^2=β-H, R^3=α-H, R^4=β-H, R^5=β-H
(264) R^1=β-H, R^2=α-H, R^3=β-H, R^4=β-H, R^5=α-H
(265) R^1=α-H, R^2=β-H, R^3=β-H, R^4=α-H, R^5=β-H
(266) R^1=β-H, R^2=β-H, R^3=α-H, R^4=β-H, R^5=α-H

(267) R^1=α-H, R^2=β-H, R^3=α-H, R^4=α-H, R^5=β-H
(268) R^1=α-H, R^2=β-H, R^3=β-H, R^4=α-H, R^5=β-H
(269) R^1=β-H, R^2=α-H, R^3=β-H, R^4=α-H, R^5=α-H
(270) R^1=β-H, R^2=α-H, R^3=β-H, R^4=β-H, R^5=α-H

Figure 14. Ormosanine- and homoormosanine-type quinolizidine alkaloids **260**−**271**.

Table 6. Sources of Isolated Ormosanine- (260−266) and Homoormosanine-Type (267−271) Quinolizidine Alkaloids (QAs)

QAs	Species	Part	Ref
260−261	*Bowdichia uirgiloides*	stem bark	177
262−263	*Podopetalum ormondii* F. Muell	leaves	176
264−266	*Templetonia retusa*	aerial parts	24
267−269	*Bowdichia virgiloides*	stem bark	177
270	*Podopetalum ormondii* F. Muell	leaves	176
271	*Dasyprocta leporina*	seeds	178

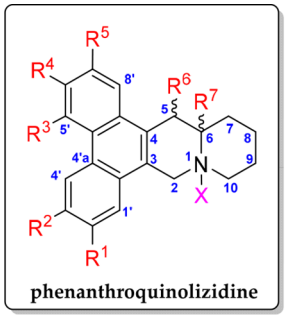
type QAs (**294**−**297**) are an uncommon group of QAs possessing a particular cyclohexane-bridged, tetrahydro-2*H*-pyran-fused quinolizidine skeleton (Figure 16, Figure S18), involving two pairs of epimers at C-13 (α- or β-OH as R^2) and an α-oriented (diethylamino)methyl group at C-14 (R^1) (**296**−**297**). These QAs represent the first quinolizidine alkaloids of the genus *Myrioneuron*.[36]

Modified Matrine-Related QAs (Flavesine- And Alopecurine-Type). Flavesine-type QAs (**298**−**301**) represent a particular group of modified alkaloids isolated from *Sophora* and *Oxytropis* plants (Table 7). They have a matrine-like structure with an open-loop ring D, forming a 3-carboxypropyl moiety and having structural variations related to the unsaturation pattern in ring C (**298**−**300**) and a piperidine amide (**301**) (Figure 17, Figure S19).[183] Other modified matrine-related QAs involve alopecurine A (**302**) or B (**303**), which constitutes the first reported example of a matrine-type alkaloid with C-5−C-6 and C-6−C-7 bond fragmentations,[183] respectively, and the ochrocephalamine E (**304**), which was identified as a 14-*nor* methylene matrine with a unique 6/6/6/5 ring system[170] (Figure 17, Figure S19).

Table 7. Sources of Isolated Phenanthroquinolizidines (272−279), Unusual Bridged Polycycles (280−297), Flavesine (298−301), and Alopecurine-Type (302−304) Quinolizidine Alkaloids (QAs)

QAs	Species	Part	Ref
272	*Hypoestes forskaolii*	aerial part	34
273−275	*Pilea* aff. *martinii*	leaves	179
276	*Tylophora indica*	aerial parts	180
277	*Tylophora indica*	leaves	181
278−279	*Boehmeria siamensis*	whole plants	42
280	*Acosmium dasycarpum* (Vog.) Yakovlev	root bark	106
281−282	*Acosmium panamense*	seed	182
283	*Acosmium dasycarpum* (Vog.) Yakovlev	root bark	106
284	*Guianodendron praeclarum*	leaves	133
285−293	*Flueggea virosa*	twigs and leaves	35
294−297	*Myrioneuron faberi*	aerial parts	36
298−303	*Sophora flavescens*	roots	183
304	*Oxytropis ochrocephala* Bunge	whole plant	170

Biphenyl and Phenyl Ether Quinolizidine Lactones. This QA type corresponds to a complex alkaloid class particularly occurring in Lythraceae plants,[41] typified by having biphenyl or phenyl ether quinolizidine lactone skeletons. The



(272) R^1=H, R^2=OCH_3, R^3=H, R^4=R^5=OCH_3, R^6=β-OH, R^7=α-H, X=O^-
(273) R^1=H, R^2=OCH_3, R^3=R^4=OCH_3, R^5=H, R^6=H, R^7=β-H, X= :
(274) R^1=H, R^2=OCH_3, R^3=H, R^4=OH, R^5=OCH_3, R^6=H, R^7=β-H, X= :
(275) R^1=H, R^2=OCH_3, R^3=H, R^4=R^5=OCH_3, R^6=H, R^7=β-H, X= :
(276) R^1=H, R^2=OH, R^3=H, R^4=R^5=OCH_3, R^6=H, R^7=α-H, X= :
(277) R^1=H, R^2=OCH_3, R^3=H, R^4=R^5=OCH_3, R^6=H, R^7=α-H, X= :
(278) R^1=R^2=OCH_3, R^3=H, R^4=OCH_3, R^5=H, R^6=H, R^7=α-H, X= :
(279) R^1=R^2=OH, R^3=H, R^4=OCH_3, R^5=H, R^6=H, R^7=α-H, X= :

Figure 15. Phenanthroquinolizidine alkaloids **272**−**279**.

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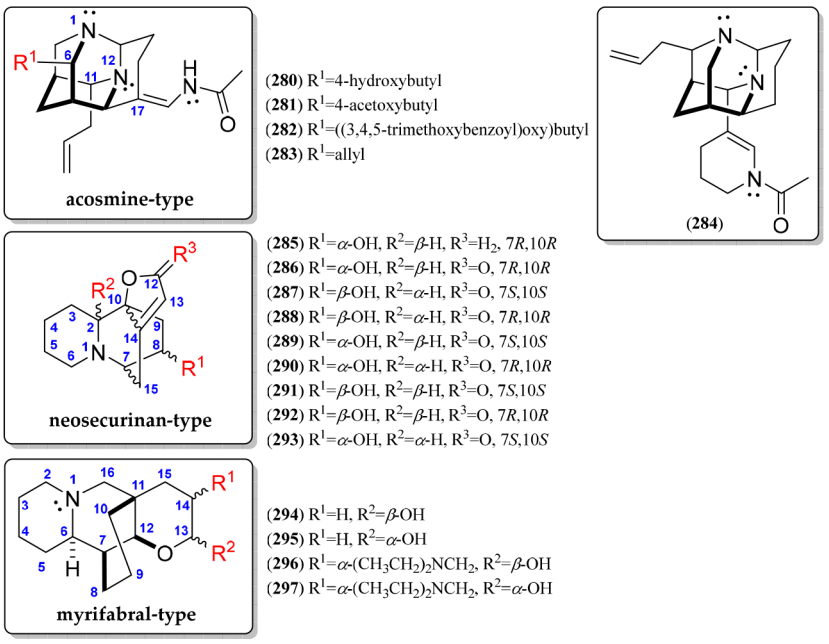

Figure 16. Unusual bridged polycyclic quinolizidine alkaloids **280**−**297**.

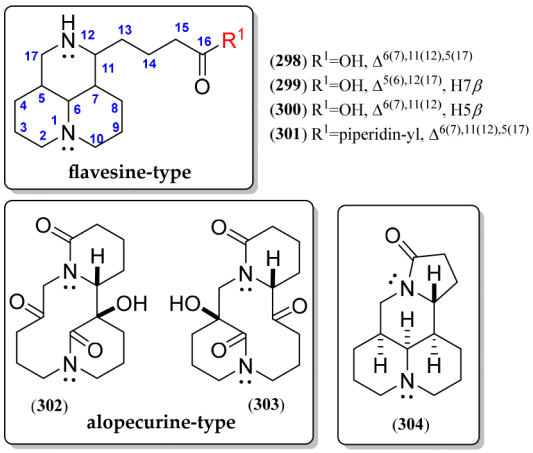

Figure 17. Flavesine and alopecurine quinolizidine alkaloids **298**−**304**.

structure contains quinolizidine (rings A and B) and biphenyl or phenyl ether (rings C and D), connected by C-4−C-2″ and C-2−O−C-12 bonds for both skeletons and the C1′−C1″ or C1′−O−C1″ bond for biphenyl or phenyl ether, respectively, forming the typical dodecano-12-lactone or 7-oxatridecane-13-lactone moiety, respectively. The basic structural core is represented by the alkaloid lythrine (**319**) or lagerine (**331**), although some of them are characterized by a hydroxyl group at C-14, involving those QAs related to lythridine (**321**).[39,40] In this regard, various phytochemical studies have led to the isolation of 21 biphenyl-containing (**305**−**325**) and seven phenyl-ether-bearing (**326**−**332**) QAs, whose structural variations are depicted in Figures 18 and S20, implying seven substituting positions (R^1 to R^7) for biphenyl and four substituting positions (R^1 to R^4) for phenyl ether quinolizidine lactones. Such variations comprise hydroxyl or methoxyl groups at C-2′, C-4″, C-5″, and C-6″ as the distinctive substitution pattern on biphenyl and phenyl ether substructures. In addition, hydroxyl substitutions at C-9 (e.g., **308**) or C-10 (e.g., **326**), having α- and β-orientation, respectively, also occurred. Some variants include an *N*-oxide group at N-5 (**309**−**310**, **315**, **317**, **329**), which was reported for the first time from *Lagerstroemia indica* (Lyrthraceae).[184] Finally, reported quinolizidine lactones (90%) include α-hydrogen at C-10. In addition, these lactones have also been isolated from *Heimia* (Lythraceae) plants (Table 8).

Macrocyclic Bisquinolizidines. Macrocycle-containing QAs are a class of marine natural products found mainly in sponges, which are considered to be biogenetically derived from bis-3-alkylpyridine units.[185] Araguspongins/xestospongins and petrosins are the two distinct macrocyclic QA subtypes, chemically characterized by possessing bis-1-oxaquinolizidine (6/6) and bisquinolizidine-2-one (6/6) moieties, respectively.[55] Thus, the bis-1-oxaquinolizidine units are connected by two six-carbon chains at C-2 and C-9 of each quinolizidine unit (i.e., C-2−$(CH_2)_6$−C-9′ and C-9−$(CH_2)_6$−C-2′), while the two bisquinolizidine-2-one units have the C-1−$(CH_2)_5$−C-9′ and C-9−$(CH_2)_5$−C-1′ connectivity, which comprise the respective macrocyclic substructure.[54] Thirty-seven chemical variants are reported for macrocyclic QAs, and the bis-1-oxaquinolizidine-containing QAs (n = 31) are more abundant than bis-quinolizidine-2-one-containing QAs (n = 6), the structures of which are depicted in Figures 19 and S21. In the case of araguspongins/xestospongins (**333**−**363**), the chemical diversity is mainly represented by stereochemical variations in six positions (R^1 to R^6, Figure 19). Hence, hydroxyl groups at C-9(9′) (R^1 and R^4), methyl groups at C-3(3′) (R^2 and R^3), hydrogens at C-10(10′) (R^5 and R^6), and the connecting six-carbon chains can exhibit α- or β-orientation. A similar case is found for petrosins (**364**−**369**), having stereochemical variations at C-1(1′), C-9(9′), C-10(10′) (having α- or β-oriented hydrogens), and C-3(3′) (having α- or β-oriented methyl groups; Figure 19, Figure S21). These marine-origin macrocycles are mainly found in the genera *Xestospongia*, *Neopetrosia*, and *Petrosia*, belonging to the Petrosiidae family, but also from *Haliclona* (Chalinidae) and *Oceanapia* (Phloeodictyidae) (Table 8).

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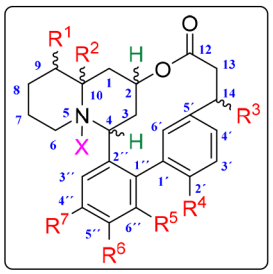
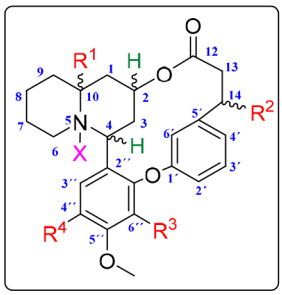


(305) R^1=H, R^2=α-H, R^3=α-OH, R^4=OH; R^5=OH, R^6=OCH_3, R^7=H, X= : , H2β, H4α
(306) R^1=H, R^2=α-H, R^3=β-OH, R^4=OH; R^5=OH, R^6=OCH_3, R^7=H, X= : , H2β, H4α
(307) R^1=H, R^2=β-H, R^3=α-OH, R^4=OH; R^5=H, R^6=OCH_3, R^7=OH, X= : , H2β, H4α
(308) R^1=β-OH, R^2=β-H, R^3=H, R^4=OH; R^5=H, R^6=OCH_3, R^7=OH, $\Delta^{13(14)}$, X= : , H2β, H4α
(309) R^1=H, R^2=β-H, R^3=H, R^4=OH, R^5=H, R^6=OCH_3, R^7=OH, $\Delta^{13(14)}$, X=O^- , H2β, H4α
(310) R^1=H, R^2=β-H, R^3=H, R^4=OH, R^5=H, R^6=OCH_3, R^7=OCH_3, $\Delta^{13(14)}$, X=O^- , H2β, H4α
(311) R^1=H, R^2=α-H, R^3=α-OH, R^4=OH; R^5=H, R^6=OCH_3, R^7=OH, X= : , H2β, H4α
(312) R^1=H, R^2=α-H, R^3=α-OH, R^4=OH; R^5=H, R^6=OCH_3, R^7=OH, X= : , H2β, H4α
(313) R^1=H, R^2=α-H, R^3=β-OH, R^4=OH; R^5=H, R^6=OCH_3, R^7=OH, X= : , H2β, H4α
(314) R^1=H, R^2=α-H, R^3=β-OCH_3, R^4=OH; R^5=H, R^6=OCH_3, R^7=OH, X= : , H2β, H4α
(315) R^1=H, R^2=α-H, R^3=H, R^4=OH; R^5=H, R^6=OCH_3, R^7=OH, X=O^- , H2α, H4β
(316) R^1=H, R^2=α-H, R^3=H, R^4=OH; R^5=H, R^6=OCH_3, R^7=OH, X= : , H2α, H4β
(317) R^1=H, R^2=α-H, R^3=H, R^4=OH; R^5=OCH_3, R^6=OCH_3, R^7=H, X=O^- , H2α, H4β
(318) R^1=β-OH, R^2=β-H, R^3=H, R^4=OH; R^5=H, R^6=OCH_3, R^7=OCH_3, $\Delta^{13(14)}$, X= : , H2β, H4α
(319) R^1=H, R^2=α-H, R^3=H, R^4=OH; R^5=H, R^6=OCH_3, R^7=OCH_3, $\Delta^{13(14)}$, X= : , H2β, H4α
(320) R^1=H, R^2=α-H, R^3=H, R^4=OH; R^5=OH, R^6=OCH_3, R^7=H, $\Delta^{13(14)}$, X= : , H2β, H4α
(321) R^1=H, R^2=α-H, R^3=α-OH, R^4=OH; R^5=H, R^6=OCH_3, R^7=OCH_3, X= : , H2β, H4α
(322) R^1=H, R^2=β-H, R^3=H, R^4=OH; R^5=H, R^6=OCH_3, R^7=OCH_3, $\Delta^{13(14)}$, X= : , H2β, H4α
(323) R^1=H, R^2=β-H, R^3=α-OH, R^4=OH; R^5=H, R^6=OCH_3, R^7=OCH_3, X= : , H2β, H4α
(324) R^1=H, R^2=α-H, R^3=H, R^4=OH; R^5=H, R^6=OCH_3, R^7=OH, $\Delta^{13(14)}$, X= : , H2β, H4α
(325) R^1=H, R^2=β-H, R^3=H, R^4=OH; R^5=H, R^6=OCH_3, R^7=OH, $\Delta^{13(14)}$, X= : , H2β, H4α



(326) R^1=β-H, R^2=α-OH, R^3=H, R^4=OH, X= : , H2β, H4α
(327) R^1=β-H, R^2=α-OH, R^3=OH, R^4=H, X= : , H2β, H4α
(328) R^1=α-H, R^2=α-OH, R^3=H, R^4=OH, X= : , H2β, H4α
(329) R^1=α-H, R^2=H, R^3=OH, R^4=H, X=O^- , H2α, H4β
(330) R^1=β-H, R^2=H, R^3=H, R^4=OCH_3, X= : , H2β, H4α
(331) R^1=β-H, R^2=H, R^3=OH, R^4=H, X= : , H2β, H4α
(332) R^1=α-H, R^2=H, R^3=H, R^4=OCH_3, X= : , H2β, H4α

Figure 18. Biphenyl (**305**−**325**) and phenyl ether (**326**−**332**) quinolizidine lactones.

Table 8. Sources of Isolated Biphenyl (305−325), Phenyl Ether (326−332), and Macrocyclic (305−332) QAs

QAs	Species	Part	Ref
305−314	*Heimia salicifolia*	leaves	39,40
315−317	*Lagerstroemia indica*	aerial parts	184
318−328	*Heimia salicifolia*	leaves	41
329	*Lagerstroemia indica*	aerial parts	184
330−332	*Heimia salicifolia*	leaves	40
333	*Xestospongia muta*	sponges	15
334	*Neopetrosia chaliniformis*	sponges	185
335	*Xestospongia muta*	sponges	15
336	*Neopetrosia chaliniformis*	sponges	185
337	*Xestospongia muta*	sponges	15
338	*Neopetrosia chaliniformis*	sponges	185
339−342	*Xestospongia* sp.	sponges	186
343−344	*Xestospongia exigua*	sponges	187
345	*Neopetrosia exigua*	sponges	55
346−349	*Xestospongia muta*	sponges	15
350	*Haliclona exigua*	sponges	188
351−354	*Xestospongia exigua*	sponges	189
355−359	*Oceanapia* sp.	sponges	190
360−362	*Xestospongia* sp.	sponges	191,192
363	*Neopetrosia exigua*	sponges	193
364−365	*Xestospongia muta*	sponges	15
366	*Petrosia seriata*	sponges	51
367	*Xestospongia exigua*	sponges	194
368−369	*Neopetrosia chaliniformis*	sponges	185

Dimeric QAs. Within this group are gathered those QAs that have unusual patterns to afford dimers or form interesting two-pair quinolizidine adducts (Figure 20, Figure S22), isolated from plants of the genera *Thermopsis*, *Sophora*, *Oxytropis*, and *Nuphar* (Table 9). In this sense, a series of QA adducts (**370**−**376**), namely, thermlanseedlines B−F and thermseedlines F−G, were isolated from *Thermopsis lanceolata*,[103,132] involving thermopsine or cytisine dimers or thermopsine/cytisine adducts. In this regard, a thermopsine dimer involved linking through an additional tetrahydrofuran ring (**370**), whereas the thermopsine/cytisine adducts (**371**−**372**) comprised an alkenyl chain between C-12 and N-12 of the 12-hydroxythermopsine and 11-oxocytisine moieties, respectively. In addition, the cytisine dimers contained an N^{12},$N^{12'}$-oxoalkyl (**373**−**375**) or N^{12},$N^{12'}$-alkoxyoxoalkyl (**376**) bridge between two 11-oxocytisine units. On the other hand, matrine-type dimers have also been discovered, mostly isolated from *Sophora alopecuroides*, which include different dimerization patterns, e.g., C-9−C-2′ (**377**, **379**), C-10−C-3′ (**378**, **380**), C-13−C-14′ (**382**), C-10−C-14′ (**383**), and C-11/C-12−C-13′/C-14′ (**384**−**386**), involving various substituted matrine units. Furthermore, other matrine adducts also involved *nor*-matrine derivatives, which contain loops formed by ring cleavage, such as ring A of the second matrine unit attached at C-3 of the first matrine unit (**381**) or ring B in the first unit linked to C-9 of a julolidine unit, representing rare epimeric *nor*-matrine/julolidine alkaloids (**387**−**388**) isolated from seeds.[78] Finally, the dimeric thiospirane quinolizidines (**389**−**397**), particularly isolated from *Nuphar* plants and known consequently as *Nuphar* alkaloids,[160] are composed of two lupinine-type units (usually substituted by α/β-methyl, α/β-furan-3-yl, and α/β-hydroxyl groups at C-6, C-3, and C-10, respectively) and connected by a spirocyclic tetrahydrothiophene ring. In addition, the sulfur can be oxygenated, forming a sulfoxide group (**390**, **394**, and **396**), or unfunctionalized (**389**, **391**−**393**, **395**, and **397**).

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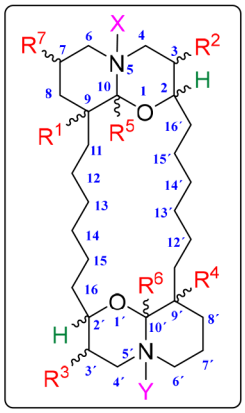
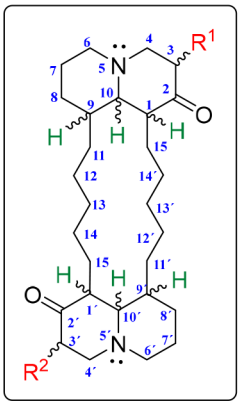


(333) R^1=α-OH, R^2=H, R^3=H, R^4=α-H, R^5=α-H, R^6=α-H, R^7=H, X=Y= : , H2α, H2′α
(334) R^1=β-H, R^2=H, R^3=H, R^4=β-H, R^5=β-H, R^6=β-H, R^7=H, X=Y= : , H2β, H2′β
(335) R^1=α-OH, R^2=H, R^3=H, R^4=α-OH, R^5=α-H, R^6=α-H, R^7=H, X=Y= : , H2α, H2′α
(336) R^1=α-H, R^2=H, R^3=H, R^4=α-H, R^5=β-H, R^6=β-H, R^7=H, X=Y= : , H2β, H2′β
(337) R^1=α-H, R^2=H, R^3=H, R^4=α-H, R^5=α-H, R^6=α-H, R^7=H, X=Y= : , H2α, H2′α
(338) R^1=β-H, R^2=H, R^3=H, R^4=α-H, R^5=β-H, R^6=β-H, R^7=H, X=Y= : , H2β, H2′β
(339) R^1=β-H, R^2=α-CH_3, R^3=H, R^4=β-H, R^5=α-H, R^6=α-H, R^7=H, X=Y= : , H2α, H2′α
(340) R^1=β-H, R^2=β-CH_3, R^3=H, R^4=β-H, R^5=α-H, R^6=α-H, R^7=H, X=Y= : , H2α, H2′α
(341) R^1=β-H, R^2=β-CH_3, R^3=α-CH_3, R^4=β-H, R^5=α-H, R^6=α-H, R^7=H, X=Y= : , H2α, H2′α
(342) R^1=β-H, R^2=β-CH_3, R^3=α-CH_3, R^4=β-H, R^5=α-H, R^6=α-H, R^7=H, X=Y= : , H2α, H2′α
(343) R^1=α-OH, R^2=H, R^3=H, R^4=β-H, R^5=α-H, R^6=α-H, R^7=H, X=O^- , Y= : , H2α, H2′α
(344) R^1=α-OH, R^2=H, R^3=H, R^4=α-OH, R^5=α-H, R^6=α-H, R^7=H, X=O^-, Y= : , H2α, H2′α
(345) R^1=β-H, R^2=H, R^3=H, R^4=β-H, R^5=α-H, R^6=α-H, R^7=H, X=Y= : , H2β, H2′β
(346) R^1=α-OH, R^2=α-CH_3, R^3=α-CH_3, R^4=α-OH, R^5=α-H, R^6=α-H, R^7=H, X=Y= : , H2α, H2′α
(347) R^1=α-OH, R^2=α-CH_3, R^3=α-CH_3, R^4=α-H, R^5=α-H, R^6=α-H, R^7=H, X=Y= : , H2α, H2′α
(348) R^1=α-OH, R^2=H, R^3=α-CH_3, R^4=α-OH, R^5=α-H, R^6=α-H, R^7=H, X=Y= : , H2α, H2′α
(349) R^1=α-OH, R^2=H, R^3=H, R^4=β-OH, R^5=α-H, R^6=β-H, R^7=H, X=Y= : , H2β, H2′α
(350) R^1=α-OH, R^2=α-CH_3, R^3=H, R^4=α-OH, R^5=α-H, R^6=α-H, R^7=H, X=Y= : , H2α, H2′α
(351) R^1=α-H, R^2=H, R^3=H, R^4=α-H, R^5=β-H, R^6=β-H, R^7=H, X=Y= : , H2β, H2′β
(352) R^1=β-OH, R^2=H, R^3=β-CH_3, R^4=β-H, R^5=β-H, R^6=β-H, R^7=H, X=Y= : , H2β, H2′β
(353) R^1=β-H, R^2=H, R^3=H, R^4=α-H, R^5=β-H, R^6=β-H, R^7=H, X=Y= : , H2β, H2′β
(354) R^1=β-OH, R^2=H, R^3=H, R^4=α-H, R^5=β-H, R^6=β-H, R^7=H, X=Y= : , H2β, H2′β
(355) R^1=α-OH, R^2=H, R^3=H, R^4=α-H, R^5=β-H, R^6=β-H, R^7=H, X=Y= : , H2α, H2′α
(356) R^1=α-OH, R^2=H, R^3=H, R^4=α-H, R^5=β-H, R^6=β-H, R^7=H, X= : , Y=O^- , H2α, H2′α
(357) R^1=α-OH, R^2=H, R^3=H, R^4=α-H, R^5=β-H, R^6=β-H, R^7=H, X=Y=O^- , H2α, H2′α
(358) R^1=α-H, R^2=α-CH_3, R^3=H, R^4=α-H, R^5=β-H, R^6=β-H, R^7=H,X=Y= : , H2α, H2′α
(359) R^1=α-H, R^2=α-CH_3, R^3=H, R^4=α-OH, R^5=β-H, R^6=β-H, R^7=H,X=Y= : , H2α, H2′α
(360) R^1=β-H, R^2=H, R^3=H, R^4=β-H, R^5=α-H, R^6=α-H, R^7=α-OH, X=Y= : , H2α, H2′α
(361) R^1=β-OH, R^2=H, R^3=H, R^4=β-H, R^5=β-H, R^6=β-H, R^7=H, X=Y= : , H2β, H2′β
(362) R^1=β-H, R^2=β-CH_3, R^3=β-CH_3, R^4=α-H, R^5=α-H, R^6=α-H, R^7=H, X=Y= : , H2β, H2′β
(363) R^1=β-H, R^2=β-CH_3, R^3=β-CH_3, R^4=β-H, R^5=α-H, R^6=α-H, R^7=H, X=Y= : , H2β, H2′β



(364) R^1=α-CH_3, R^2=α-CH_3, H1α, H9β, H10α, H1′α, H9′β, H10′α
(365) R^1=β-CH_3, R^2=α-CH_3, H1β, H9α, H10β, H1′α, H9′β, H10′α
(366) R^1=β-CH_3, R^2=α-CH_3, H1β, H9α, H10β, H1′β, H9′α, H10′α
(367) R^1=β-CH_3, R^2=β-CH_3, H1α, H9β, H10α, H1′α, H9′α, H10′β
(368) R^1=α-CH_3, R^2=β-CH_3, H1β, H9α, H10α, H1′α, H9′α, H10′β
(369) R^1=α-CH_3, R^2=α-CH_3, H1β, H9α, H10α, H1′α, H9′α, H10′β

Figure 19. Macrocyclic bisquinolizidines **333**−**369**.

BIOACTIVITY OF QUINOLIZIDINE ALKALOIDS: AN OVERVIEW

There is relevant chemical QA variability and a wide distribution in animal and plant sources, as described above (Figures 1−20, Tables 1−9). Apart from this generous chemodiversity and origin, these QA groups have great importance due to their biological activity[18] but are also recognized as toxic agents.[199] For instance, the QAs present in seeds, pods, leaves, aerial parts, and roots of some genistoid plants have been broadly studied, and the alkaloids causing the lupin bittering contain mostly lupanine, lupinine, and hydroxylupanine.[53] Such bitter-related QAs have an excitatory effect on the CNS, depressing the respiratory and vasomotor centers, mainly observed in sheep,[200] and exhibiting acute anticholinergic toxicity. These facts promoted lupin seed debittering or the research on low QA-containing lupin varieties since lupin seeds are good food options due to their protein content and quality.[201] Likewise, "twisted calf disease" cases have been reported in cattle due to the anagyrine presence in some herbaceous plants, which is responsible for teratogenic effects.[202,203] However, QAs have other relevant biological activities that can be exploited for several applications. In general, matrine-type QAs are mostly cytotoxic and anticancer bioactive (e.g., **7**), whereas lupanine-type (e.g., **57**−**59**) and sparteine-type (e.g., **110**−**113**) QAs have potential against insects and microorganisms. Likewise, the cytisine and tetrahydrocytisine-type QAs have effects as cytotoxic and antiviral agents (e.g., **132**−**133**, and **157**), and in the case of the lupinine and macrocycle types, they exhibited relevant antiviral and anticancer properties. In this context, the bioactivities of the most abundant QAs, such as matrine, lupanine, sparteine, cytisine, lupinine, and other QA types, are described below and summarized in Table 10, focusing specifically on the most promising results of the alkaloid types.

The matrine-type alkaloids have been reported as the most biologically active QAs,[6] exhibiting a wide spectrum of biological properties, including antitumor,[204] antiviral,[205] and anti-inflammatory[10] activities. In addition, they have attracted

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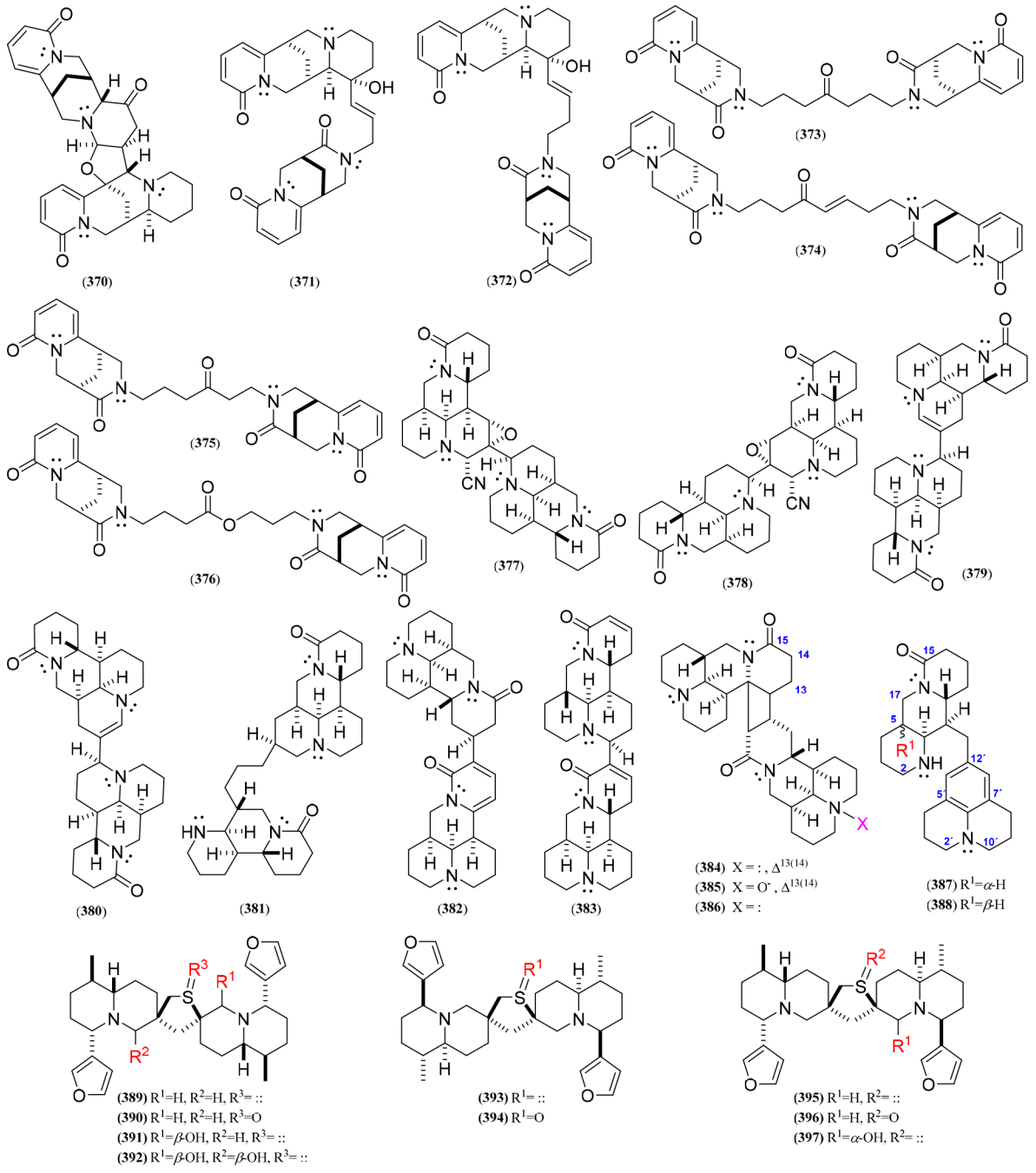

Figure 20. Dimeric quinolizidine alkaloids **370**−**397**.

Table 9. Sources of Isolated Dimeric (370−397) Quinolizidine Alkaloids (QAs)

QAs	Species	Part	Ref
370−**376**	*Thermopsis lanceolata*	seeds	103,132
377−**381**	*Sophora alopecuroides* L.	aerial parts	195
382	*Oxytropis ochrocephala* Bunge	whole plant	196
383	*Sophora alopecuroides* L.	seeds	78
384−**386**	*Sophora alopecuroides*	leaves	197
387−**388**	*Sophora alopecuroides* L.	seeds	78
389−**394**	*Nuphar pumilum*	rhizomes	160
395	*Nuphar Alkaloids*	rhizomes	198
396−**397**	*Nuphar pumilum*	rhizomes	160

attention due to their capacity to reduce hand and foot diseases caused by enterovirus (EV-71), which does not have an available vaccine. Hence, therapeutics based on derivatives of **1** have shown relevant results that could lead to the management and control of EV-71 (e.g., **34**−**35**) in the future.[205] Moreover, matrine derivatives (e.g., **3**) have reduced disease symptoms by compensating for the decreased T-cell levels.[206] It has also been suggested that **12** can inhibit and suppress the expression of TLR4, a pattern recognition receptor whose activation produces pro-inflammatory cytokines.[207] Compounds **1**−**17** have been reported to inhibit the growth of malignant cells and tumors with promising results (IC_{50} < 20 μM against different cancer cell lines) through proliferation inhibition and apoptosis induction, whose

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Table 10. Overview of Biological Activities of Quinolizidine Alkaloids (QAs)

QAs	Activity tested	Outcome	Ref
4, 131−133	NO production in LPS-stimulated RAW 264.7 cells	IC_{50} = 22.1 μM	16
4−5, 27−28	Effect against HL-60, A-549, and SW480 cell lines	IC_{50} < 50 μM	9
7	Inhibition of *Botryosphaeria dothidea* mycelial growth	MIC = 1.682 mg/mL	218
7	Acaricidal (*Tetranychus cinnabarinus*) and aphicidal (*Aphis citricola*) activities	LC_{50} < 2 mg/mL	217
12−13	Cytotoxic activity (endothelial cells)	IC_{50} = 15.2 μM	16,214
12−16	Cytotoxic activity	IC_{50} = 57.8 μM (HepG-2) and 83.1 μM (CNE-2) for 12	242
17−21	*In vivo* anti-inflammatory activity	Significant inflammation reduction of 17 and 19	73
22	Antiviral activity against the hepatitis B virus	53.8% inhibition under the noncytotoxic concentration of 0.035 mM	78
23	Cytotoxic activity	IC_{50} = 20 μM (A-549)	76
32−46	Insecticidal activity	LC_{50} < 50 mg/mL	71
47−48	Antiviral activity against the hepatitis B virus	48.3−79.3% inhibition	11
47−48	Antiviral activity against the hepatitis B virus	41.3% inhibition	11
55−56	Cytotoxic activity	56 inhibit the growth of GSC-3# at 20 μg/mL	16
56	Glucose homeostasis	Improved glycemic control at 1 mM	222
57	Antiviral activity against the hepatitis B virus	53.8% inhibition	125
57−59, 134, 157	Antibacterial activities against *Staphylococcus aureus* and *Escherichia coli*	8 μg/mL < MIC < 32 μg/mL	125
65	Antibacterial activity against *Pseudomonas aeruginosa* and *Enterococcus faecalis*	10.9 μg/mL < MIC < 20.8 μg/mL	75
66−67, 239	Antibacterial activity against: *Staphylococcus aureus*, *S. epidermides*, *S. saprophyticum*, and *Streptococcus pyogenes*	25 μg/mL < MIC < 100 μg/mL	84
110−113	Insecticidal activity against *Spodoptera frugiperda*	Mortality = 83% at day 7 for 110	82,223,243,244
132	Cytotoxic activity	IC_{50} = 5.36 μM, inducing apoptosis.	229,231
132	Antiviral activity against human influenza virus A	IC_{50} < 200 μM	235
132	Cytotoxic activity	Cell percentage in the G2/M phase at 24 h increased from 21.1 to 50.0% (HEK293, Hep-G2, and Jurkat cell lines)	229
138	Antibacterial activity against *E. faecalis*	MIC = 208.3 μg/mL	75
148−155	Insecticidal activity against *Aphis fabae*	LC_{50} < 50 μg/mL	103,132
148−155	Inhibition against tomato spotted wilt virus	Protective effect >70%	103,132
161	Cytotoxic activity	IC_{50} = 10 μM (COLO-205)	245
179−183	Cytotoxic activity and acetylcholinesterase inhibition	IC_{50} < 330 μM (AChE) IC_{50} < 5.5 μg/mL (L1210)	150
189	Neuronal nicotinic acetylcholine receptors	IC_{50} = 1.5 μM ($\alpha4\beta2$-nAChRs) and 1.3 μM ($\alpha7$-nAChRs)	152
198	Cytotoxic activity HL-60 cells	IC_{50} = 39 μM (HL-60)	37
205, 311−314	Antimalarial activity	IC_{50} < 5 μg/mL (*P. falciparum*)	40
333−337	Cytotoxic activity	IC_{50} < 1.02 μM against all tested cancer cell lines	15
234	Cell growth and *in vitro* tumorigenesis of human thyroid cancer cells	IC_{50} < 161.7 μM (IHH-4)	246
234	Inhibition of human immunodeficiency virus 1	EC_{50} = 1.2 and 1.6 μM (NL4-3 and YU2)	240
234−237	Anticonvulsant effect	234 exhibited a better anticonvulsant effect	17,240
272	Antimalarial activity	IC_{50} < 6.11 nM (*P. falciparum*)	34
276	Cytotoxic activity	IC_{50} = 1.6 nM (A375), 2.5 nM (A549), 1.4 nM (HCT116) and 4.1 nM (Namalwa−Burkitt's lymphoma)	180
278−279	Cytotoxic activity	0.2 ng/mL < IC_{50} < 100 ng/mL	42
294−297	Inhibition of hepatitis C virus replication	0.9 μM < IC_{50} < 4.7 μM	36
303	Antiviral activity against the hepatitis B virus	46.0−14.1% inhibition	183
311−314	Antimalarial activity	IC_{50} = 4.76 μg/mL (*P. falciparum*)	40
333, 335, 337	Cytotoxic activity	IC_{50} < 1.02 μM against all tested cancer cell lines	15
337−339	Cytotoxic activity	ED_{50} > 20 μM	166

advances were compiled in a comprehensive review recently published on the anticancer properties of **1** and its derivatives.[208] However, matrine and some naturally occurring derivatives are limited by various factors (i.e., toxicity, bioavailability, and low water solubility), and different matrine-inspired compounds have been synthesized to improve the inhibitory action against cancer cells.[208] Compound **15** can improve the clinical signs of experimental autoimmune encephalomyelitis (EAE).[209,210] These studies have reported that **15** delays the disease progress, attenuates the clinical severity of EAE when tested in rats, decreases inflammation and demyelination generated in the brain, and suppresses apoptosis of oligodendrocytes (OLG) in the rat central nervous system.[211]

Compounds **1−11** exhibited cytotoxic, anti-inflammatory, and antianaphylactic activities. Recent studies have examined the expression of the hypoxia-inducible 1-alpha factor (HIF-1a) and endothelial vascular growth factor in different phases of human hemangioma (HA). At different concentrations (0−2 μg/μL) of **2**, it was demonstrated that the HIF-1a expression

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increases significantly in the proliferation phase of HA but decreases in the involuntary phase of HA.[212] On the other hand, alkaloid **9** has been widely studied for its anti-inflammatory properties. Recent studies have shown its excellent effects against lupus nephritis (LN) and lupus erythematosus (SLE) since it reduces the inflammatory response and inhibits the activation of the inflammatory NLRP3.[213,214] Additionally, compound **2** has also been reported to inhibit epidermal growth factor receptor (EGFR) related signaling pathways from suppressing the proliferation and invasion of malignant cells responsible for gastric cancer.[215] Alkaloid **2** significantly inhibited migration and invasion of human gastric cancer cells by decreasing phospho-cofilin (Ser3) and phospho-LIMK1 (Thr508) without changing the total expression of cofilin and LIMK1.[216] In addition, alkaloid **7** showed acaricidal and aphicidal effects on *Tetranychus cinnabarinus* and *Aphis citricola*,[217] respectively, and antifungal activity against *Botryosphaeria dothidea*[218] and *Fusarium oxysporum*.[219]

It has been reported that the consumption of seeds from *Lupinus* plants containing alkaloid **62** has led to intoxication events in humans due to the acute anticholinergic toxicity of some lupanine-type QAs. The most common symptoms are blurred vision, dry mouth, easy flushing, and confusion.[201] Such symptoms are reported in a human who consumed 0.5 L of bitter water from *Lupinus* seeds. The immediate symptoms were weakness, accelerated palpitations, extrasystoles, and different anticholinergic symptoms.[220] According to the antecedents, the lethal dose in rats for alkaloids **62** and **63** was investigated, determining a DL_{50} = 1664 mg/kg.[221] However, other lupanines, e.g., **56**, positively influenced pancreatic cells in an animal model of type-2 diabetes mellitus.[222] In the presence of glucose at 15 mM, insulin secretion was significantly elevated by compound **56** (0.5 mM). At the same time, the alkaloid did not stimulate insulin release with lower glucose concentrations, suggesting that **56** improved glycemic control in response to an oral glucose tolerance test in streptozotocin-diabetic rats.[222] In this context, the effect on insulin secretion of three alkaloids isolated from *Lupinus* has recently been studied, such as compounds **56**, **59**, and **70**, along with a synthetic derivative involving *in vitro* evidence of an increase in glucose-induced insulin release, whose effect intensity depended on glucose concentration and ATP-sensitive K channel blocking.[32] Also, various lupanine-type QAs have shown cytotoxic activities, such as **56** and **61** against human glioma stem cells GSC-3#,[16] human breast cancer (MDA-MB-231), and human lung cancer (A549).[82] Furthermore, esterified lupanines, such as **64** and **67**, exhibited high deterrent effects against coleopteran and lepidopteran insects such as *Spodoptera frugiperda*[223] and *Choristoneura fumiferana*,[224] as well as antibacterial activity by **65** and **66** against *Pseudomonas aeruginosa*, *Enterococcus faecalis*,[75] *Staphylococcus aureus*, *S. epidermides*, *S. saprophyticum*, and *Streptococcus pyogenes*.[84]

Sparteine-type alkaloids are relevant QAs since studies report their neuroprotective effects against cellular diseases associated with Alzheimer's.[225] Sparteine-type compounds, such as **110**, may inhibit protein synthesis and acetylcholine receptors,[226] while **125** presented nematicidal activity against *Hemonchus contortus* and *Teladorsagia circumcincta*.[227] Similarly, **110** has toxic effects by inhibiting K^+ channels and the tDNA synthesis and formation.[95] In addition, compound **110** and analogs have shown that subcutaneous administration of 25 mg/kg in neonatal rats decreases the mRNA levels of muscarinic acetylcholine receptors, specifically of M1−M3 subtypes, and generates an increase of M7 mRNA between 7 and 14 days after administration.[228] Furthermore, the anticonvulsant effects of **110** on the behavior and electroencephalic activity were studied in three states of epilepsy (SE) models.[5]

Some studies have investigated the effect of some cytisine-type QAs (e.g., **131** and **132**) on human lung and breast cancer. Results showed that **132** (i.e., cytisine) inhibited the growth of lung cancer cell lines, including A549 (IC_{50} = 26.83 μM), NCI-H23 (IC_{50} = 49.79 μM), and NCI-H460 (IC_{50} = 32.45 μM) cells using the CCK-8 assay.[229] Alkaloid **132** was influential in suppressing lung cancer cells through cell cycle arrest and the induction of mitochondrial-mediated apoptosis, suggesting that compound **132** may be a promising candidate for developing lung cancer treatments.[229] In addition, compound **132** and homologues induce apoptosis of tumor cells via the endoplasmic reticulum (ER) pathway.[230] The information suggested that calcium overload promotes ER stress-induced apoptosis in cytisine-induced HepG2 cells, modulating the CHOP/GADD153, JNK, and caspase-4 pathways.[231] Finally, the caspase cascade is activated to induce apoptosis of HepG2 cells, through the mitochondrial pathway, according to the reduction in the mitochondrial membrane potential.[231] Following cytisine treatment, mitochondrial permeability may increase, leading to mitochondrial matrix expansion, outer membrane rupture, and a cytochrome C release.[231]

Alkaloid **132** and structurally related compounds (**131**−**155**) have been shown to have a high affinity for the neuronal nicotinic acetylcholine receptors (nAChR) and are essential probes in the investigation of central nervous system disorders.[232] Particularly, cytisine showed affinity to nAChRs and can activate α7-nAChR expression.[230] Moreover, some synthetic derivatives (e.g., cytisine-12-carbamide and *N*-allylcytisine-12-carbamide) are acetylcholinesterase inhibitors and are toxic against *Artemia salina* at concentrations below 1000 ppm.[233] Additionally, the antiviral activity of **132** was also evaluated against the human influenza A (H1N1) virus, the human parainfluenza virus type-3 (HPIV-3), and SARS-CoV-2 virus.[234] **132**−**136** showed remarkable activity against HPIV-3 with a selectivity index (SI) of 58, calculated as the ratio of CC_{50}/IC_{50}.[235] Compounds **148**−**155** isolated from seeds of *Thermopsis lanceolata* had moderate insecticidal activity against *Aphis fabae* (LC_{50} = 43.15 and 46.47 mg/L, respectively),[123] and compound **132** showed antifungal activity against *Fusarium oxysporum*.[219] On the other hand, compounds **150**−**151** isolated from the rhizomes of the Chinese plant known as "*Shan-Dou-Gen*" (*Sophora tonkinensis*) were evaluated against the cancer lines T24 (human bladder cancer cell line), SPC-A2 (human lung adenocarcinoma), and A549 (human lung adenocarcinoma). The best results were obtained for **150** against the A549 cancer line, with an IC_{50} = 10.36 μM.[236]

Alkaloid **174** is one of the most representative alkaloids of the genus *Lupinus* and can be considered the basic form of QAs, i.e., the 6/6 azabicycle quinolizidine moiety.[95] This QA type has had several biological activity records in recent years.[8] In this regard, **179**−**180** inhibited acetylcholinesterase at IC_{50} = 330 and 220 μM and cytotoxicity against murine lymphoma L1210 cells (IC_{50} = 4.9 and 5.5 μg/mL),[150] while QA **189** was a potent blocker of $\alpha4\beta2$- and α7-nAChRs (IC_{50} = 1.5 and 1.3

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μM, respectively). Alkaloid **199** was tested against HL-60 (human myeloid leukemia cell line), SMMC-7721 (human hepatocarcinoma cell line), and SW480 (human colon carcinoma), and the results were found to be promising (IC_{50} < 10 μM).[9] Compounds **206** and **207** displayed lower cytotoxicity compared with the commercial standard, being potent antiangiogenic agents.[156] Senepodines **222** and **227** showed moderate cytotoxicity against human blood promyelocytic leukemia (HL-60, 46% inhibition at 100 μM), whereas **224** and **225** did not show activity.[38]

Those compounds structurally related to **234** (aloperine-type) show excellent anticancer, anti-inflammatory, antifibrotic, antiviral, and antiarrhythmic activities.[17] In this regard, alkaloid **234** has been explored as an anti-inflammatory and antitumor agent.[237] Recent studies have demonstrated that **234** generates protection against acute renal injury induced by ischemia-reperfusion.[238] Additionally, studies have shown that **234** and its derivatives selectively repress IL-1β and IFN-α expression, regulating PI3K/Akt/mTOR signaling and NF-ob transcriptional activity.[8,239] In addition, **234** has also been one of the most important compounds because it inhibits HIV infection by blocking HIV-1 entry.[240] This compound responded well by inhibiting cell−cell fusion mediated by the HIV envelope at low concentrations. This study demonstrated that the naturally occurring **234** and synthetic derivatives are key bioactives for inhibiting this globally problematic infection.[240] Additionally, alkaloids **235**−**237** demonstrated potent antihepatitis B virus activities (HBV) and are more potent against the hepatitis B e-antigen (HBeAg) secretion than the hepatitis B surface antigen (HBsAg).[166] On the other hand, the antimicrobial activity of **239** against four Gram-positive bacteria (i.e., *Staphylococcus aureus*, *S. epidermides*, *S. saprophyticum*, and *S. pyogenes*), three Gram-negative bacteria (i.e., *Escherichia coli*, *Klebsiela pneumonia*, and *Shigella sonei*), and three yeasts (i.e., *Candida albicans*, *Sacharomyes cerevisae*, and *Criptococcus neoformans*) was evaluated, demonstrating moderate to good results (MIC < 50.0 μg/mL).[84] Regarding (homo)ormosanine-type QAs, compounds **260** and **267** showed good *in vitro* activity against chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* (IC_{50} = 0.5 μg/mL).[241] Alkaloid **276** (a phenanthroquinolizidine QA) was evaluated against a panel of 30 cancer cell lines and found to inhibit the proliferation of all tested cell lines, including three multidrug-resistant cell lines (average IC_{50} value of 2.1 nM), which is much lower than that of those previously reported for commercial standards.[180] Phenanthroquinolizidines **278** and **279** show cytotoxic activity against six cancer lines, including colon, lung, breast, prostate, kidney, and leukemia, with IC_{50} between 0.2 and 100 ng/mL,[42] whereas **272** exhibited high activity against malaria.[34] The myrifabrals **294**−**297** inhibited hepatitis C virus replication (HCV, IC_{50} 0.9−4.7 μM) with cytotoxicity lower than reference standards.[36]

COMPENDIUM OF BIOLOGICAL ACTIVITIES REPORTED FOR QUINOLIZIDINE ALKALOIDS

The studies conducted have primarily centered on investigating the biological properties of QAs, which can be categorized into eight classes, including cytotoxic, antiviral, antimicrobial, insecticidal, anti-inflammatory, antimalarial, antiacetylcholinesterase, and miscellaneous activities. A comprehensive compilation of each QA (**1**−**397**) can be found in Table S2 (Supporting Information), and the subsequent description highlights the most pertinent findings.

Cytotoxic Activity. Tumor cells are characterized by uncontrolled growth and unlimited proliferation. The primary function of many anticancer drugs is to damage these tumor cells directly. In the case of quinolizidine treatments, they have demonstrated the ability to inhibit the proliferation of tumor cells in various cancer types, including HL-60 (human promyelocytic leukemia cells), SMMC-7721 (hepatocellular carcinoma), human glioma stem cells (GSC), A-549 (adenocarcinomic human alveolar basal epithelial), MCF-7, and SW-480 (human colon adenocarcinoma). Considering the above, alkaloids have shown bioactivity against these specific cell lines depending on their respective types. For instance, matrine-type compounds (**5**,[9] **6**,[247] **7**,[248,249] **23**,[77] **27**,[9] and **55**[250]) have demonstrated cytotoxic activity with average IC_{50} values greater than 50 μM against SMMC-7721, A549, HepG2, HL-60, MCF-7, and SW480 lines. Furthermore, lupanine- and cytisine-type compounds have also exhibited promising results in terms of cytotoxicity. Specifically, compounds **56**,[16] **94**,[251] **135**, and **139**[236] have shown cytotoxic activity against GSC-3#, GSC-12#, GSC-18#, MCF-7, and HEPG-2 lines, with IC_{50} values ranging between 117 and 20 μM.

In addition, an important group of lupinine-type quinolizidines, specifically compounds **179**−**184** (IC_{50} > 8.2 μg/mL), demonstrated activity against murine lymphoma cells L1210.[150] Compound **186** exhibited activity against TE-671, SH-SY5Y, IMR-32, and K-177 with IC_{50} values greater than 55 μM,[46] while **187**−**188** showed activity against P-388, A-549, U-251, and SNl2KI with IC_{50} values above 24.7 μg/mL.[252] QA **198** was evaluated against HL-60 (IC_{50} = 39 μM),[37] while **298** was evaluated against five cancer lines with IC_{50} values below 100 μM.[9] Compounds **206**−**211** were assessed against the HCT-116 line, demonstrating IC_{50} > 80.2 μM.[157] On the other hand, compounds **216**−**219** were evaluated against B16 melanoma cells, resulting in inhibitions of less than or equal to 50%.[160] Regarding compounds **222**−**236**, they were tested against L1210 lymphoma cells, exhibiting IC_{50} values below 7.5 μg/mL.[163] Furthermore, QAs **230**−**236** were tested against various cancer lines, including MG-63, U2OS-OS, HepG2 2.2.15, papillary thyroid carcinoma (IHH-4), and anaplastic thyroid carcinoma (8505c and KMH-2), showing IC_{50} values above 100 μM (inactive),[38,246,253] except for the L1210 line, which demonstrated IC_{50} values below 10 μg/mL.[164] Compounds **244** and **245** displayed moderate activity (IC_{50} > 50 μM) against U-87 (glioblastoma), 518-A2 (melanoma), and HCT-116 (colon cancer).[174] Finally, compounds **272**−**276** were successfully evaluated against KB (mouth epidermal carcinoma cells, CCL-17), HepG-2 (human liver hepatocellular carcinoma cells, HB-8065), LU-1 (human lung adenocarcinoma cells, HTB-57), and MCF-7 (human breast cancer cells, HTB-22), with IC_{50} values above 1 μM, demonstrating promising potential.[179] QA **277** was evaluated against human gastric cancer AGS (hypoxia-inducible factor-1) with an IC_{50} of 8.7 nM,[254,255] while **285** and **288** were evaluated against the P388 cell line; however, no promising activity was obtained.[256] These results indicate that matrine- and lupinine-type quinolizidines show the most promising activity against the investigated cancer cell lines. Therefore, it is crucial to continue expanding the experimental knowledge regarding the biological activity of these QA types.

Antiviral Activity. Viral infections significantly threaten humans, animals, and economically important crops worldwide, leading to substantial mortality and disease-related losses. In order to mitigate the detrimental effects caused by various

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viruses, natural targets have been investigated, yielding noteworthy outcomes in both *in vitro* and *in vivo* studies. Several QAs have been examined for their ability to affect specific viruses, including the hepatitis B virus, hepatitis C, nonhuman influenza virus (H3N2), enterovirus EV-71, coxsackie B virus, human herpesvirus-6 (HHV-6), tobacco mosaic virus (TMV), tomato spotted wilt virus (TSWV), and others. In this regard, QAs **2**,[257] **7**,[78] **13**,[183] **15**,[11] **21**,[258] **22**,[78] **28**,[183] **48**,[11] **96**,[78] **132**,[258] **235**,[166] **237**,[170] **238**,[166] **298**,[183] **304**,[170] **383**,[78] **387**,[78] and **388**[78] showed promising results against the hepatitis B virus, with inhibition percentages between 10 and 60% for the serologic marker (HBsAg) and between 10 and 40.5% for the antigen (HBeAg). On the other hand, compounds **294**−**297** were active against the hepatitis C virus with CC_{50} values between 119 and 170 μM and EC_{50} between 2 and 5 μM.[36] The importance of the effect of QAs **3**, **14**, **47**, and **50** against the nonhuman influenza virus (H3N2) has also been reported, with mean inhibitory concentrations between 60 and 400 μM.[259,260] In addition, the matrine-type compounds **32**−**46** showed valuable results against the tobacco mosaic virus (TMV) with a protective effect above 50% and a curative effect between 20 and 65%. In another study, the effect of quinolizidines **4**, **8**, **21**, and **202** against the Coxsackie B virus (pathogenic enterovirus) was evaluated, and the best result was obtained for compound **202** (IC_{50} = 4.66 μM).[261] Finally, the inhibitory effect of **9** against the human herpes virus 6 (HHV-6) exhibited an IC_{50} = 3.9 μM,[262] while compounds **150**−**155**, **221**, and **370**−**376** were evaluated against the tomato spotted wilt virus (TSWV) in *Nicotiana tabacum* cv.K326, whose results showed protective and curative effects between 16 and 60% and 18−50%, respectively.[132]

Antimicrobial Activity. The antimicrobial effect of QAs has been evaluated against several microorganisms such as bacteria and fungi. Recent studies have evaluated the antifungal activity of compounds **2**, **7**, **15**, **56**, **59**, **62**, **63**, **92**, **94**, **110**, **132**, **133**, **139**, **160**, **161**, **174**, and **239** against the phytopathogen *Fusarium oxysporum*, involving IC_{50} values between 10 and 400 μM.[219] On the other hand, some studies were performed on the effect of quinolizidines **351**−**354** against *Candida albicans* ATCC 14503, *C. albicans* UCD-FR1, *C. glabrata*, and *C. krusei*, with MIC values between 30 and 100 μg/mL.[191] Other studies have evaluated the antibacterial activity of compounds **65**, **133**, **138**, and **251** against *Enterococcus faecalis*, with MIC values between 20 and 200 μg/mL.[75] In addition, alkaloids **57**−**59**, **66**−**67**, **134**, **157**, and **202** were evaluated against two Gram-positive bacteria, i.e., *Staphylococcus aureus* and *Escherichia coli*, including a broad MIC range between 25 and 200 μg/mL,[84,125,261] whose best outcome was obtained for compound **202** (MIC = 8 μg/mL for *S. aureus* and MIC = 0.8 μg/mL for *E. coli*).[261] Finally, the antibacterial activity of **214** was evaluated against *Proteus mirabilis*, *P. vulgaris*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Shigellu dysenteriue*, with MIC values between 100 and 150 μg/mL.[159]

Insecticidal Activity. Insecticidal studies of QAs have also been investigated to counteract the problems caused by some insects on economically important crops, such as the black aphid (*Aphis fabae*), the common house mosquito (*Culex pipiens*), the red spider mite (*Tetranychus urticae*), and the brown leafhopper (*Nilaparvata lugens*). According to these studies, compounds **37**, **103**, **105**−**109**, **148**−**155**, **221**, and **370**−**376** showed insecticidal activity with LC_{50} between 25 and 32 ppm and inhibitions between 35 and 80%, demonstrating their promising protective capacity for *Vicia faba* crops.[71,103,132] Another study examined quinolizidines **94** and **133** against *Culex pipiens*, involving LC_{50} ranging between 3.42 and 8.26 ppm and LC_{90} between 43.83 and 154.18 ppm.[251] Insecticidal activity studies have also been conducted with the QAs **102**−**109**, **103**−**108**, and **375**−**376**, involving an LC_{50} between 49 and 65 ppm and inhibitions greater than 50% against *Nilaparvata lugens* and *Tetranychus urticae*.[103,132]

Anti-inflammatory Activity. The anti-inflammatory activity of QAs on the tumor necrosis factor (TNF-α), associated with inflammation, apoptosis, and joint destruction, and the interleukin-6 factor (IL-6), associated with endothelial cells and fibroblasts, has also been evaluated. These studies have shown that compounds **1**, **7**, **17**, **94**, **133**, and **377**−**381** could positively inhibit the TNF-α with values greater than 50%. The best result was obtained with compound **377**, which showed an inhibition of 96.64%. In the case of the IL-6 factor, the studies reported 40−68% inhibitions.[78,195,263−265]

Antimalarial Activity. Significant research efforts have been focused on exploring active compounds against tropical diseases with malaria being one of the primary targets. In this regard, the investigation of QAs against the parasitic protozoan *Plasmodium falciparum* has been conducted. Thus, QAs have shown promising results comparable to commercial standards, highlighting the promising activity of **260** (IC_{50} = 5 μg/mL),[241] **267** (IC_{50} < 20 μg/mL),[241] and **268** (IC_{50} = 6.11 nM for KI strain and 5.13 nM for FCR3 strain of *P. falciparum*).[34] **318**−**325** were also active against D6 and W2 *P. falciparum* clones, and the best results were obtained with **322** and **325** with IC_{50}s between 2.80 and 4.76 μg/mL.[41] Finally, compound **335** was also tested against the African clone D6 (IC_{50} = 670 ng/mL) and Indochinese clone W2 (IC_{50} = 280 ng/mL) of *P. falciparum*.[187]

Antiacetylcholinesterase Activity. The antiacetylcholinesterase activity is a significant and medically relevant biological effect. This activity is particularly important because it has the potential to inhibit the degradation of acetylcholine, a neurotransmitter released in the synaptic clefts. Natural substances, including QAs, that possess the ability to inhibit the enzyme responsible for acetylcholine breakdown can enhance cholinergic neurotransmission by slowing acetylcholine degradation. With the aforementioned benefits in mind, studies were conducted to assess the inhibitory effects of compounds **110**, **111**, **126**, **189**, and **253**−**259** on acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). These compounds exhibited inhibitions ranging from 15% to 73.9%, and their mean inhibitory concentrations ranged from 21 to 331 μM.[5,150,266] Finally, compound **189** blocked neuronal nicotinic acetylcholine receptors ($\alpha4\beta2$ and $\alpha7$) with IC_{50} between 1.3 and 1.5 μM.[152]

Miscellaneous Activities. Finally, some of the compiled QAs have undergone testing for specific types of biological activity that are less commonly observed. Despite their particularity, these reports provide valuable information regarding the bioactivity of these diverse and structurally intriguing compounds. Among these activities, the antiarrhythmic effect of QA **7** was tested on mice, whose lethal dose (LD_{50}) was 72.1 mg/kg,[267] and the same compound was effective as a biopesticide against *Diaphorina citri* (LC_{50} = 1247 ppm and LC_{90} = 5712 ppm), *Panonychus citri* (LC_{50} = 42 ppm and LC_{90} = 73.7 ppm), *Sitophilus zeamais* (LC_{50}= 463.9 ppm and LC_{90} = 1121 ppm), and *Spodoptera frugiperda* (LC_{50} = 384.3 and LC_{90} = 1034 ppm).[195] In the case of compound **174**,

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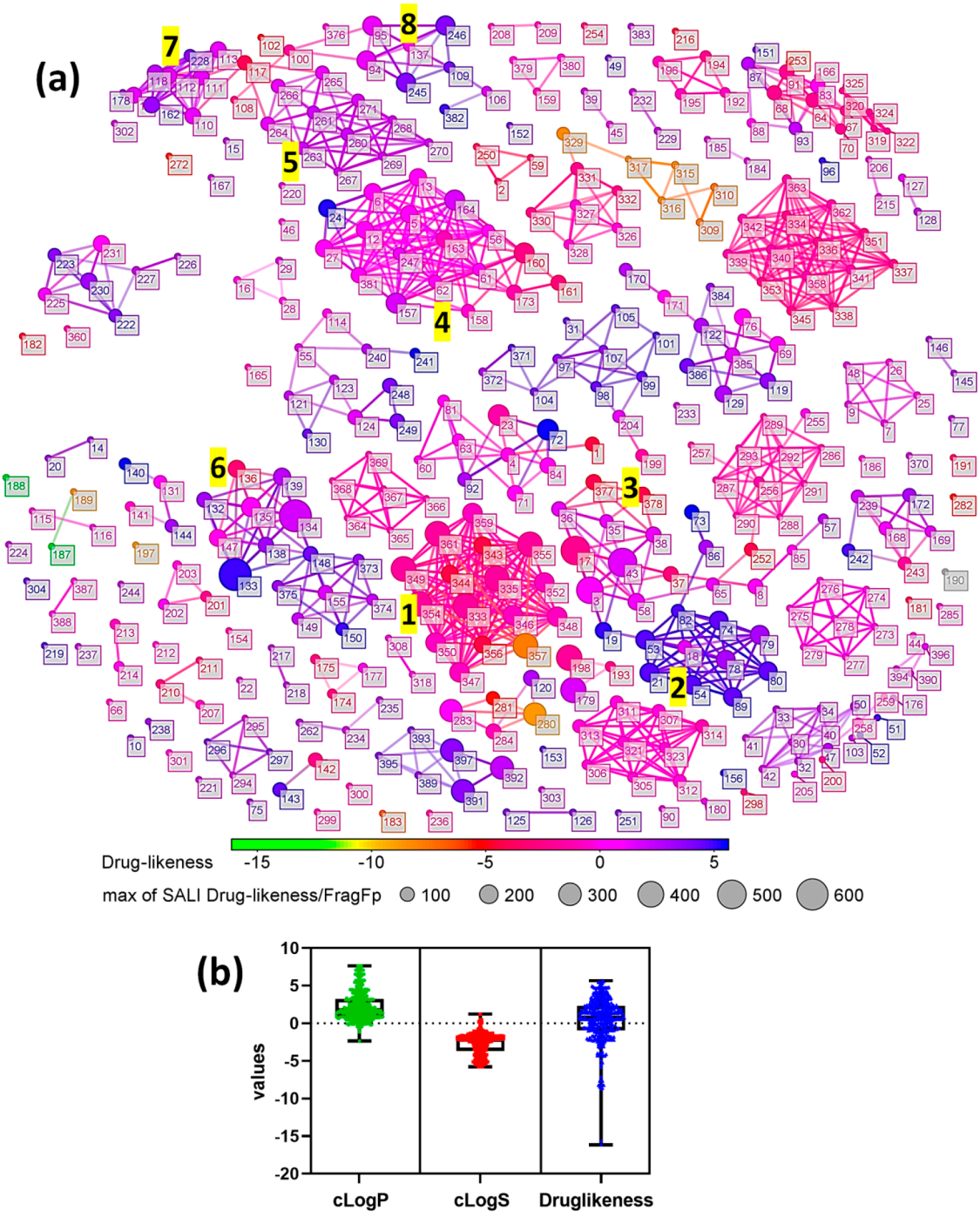

Figure 21. (a) Similarity plot combining the *Frag*FP descriptor and drug-likeness. Colors were determined according to the drug-likeness score (*d*). Numbers in small boxes are related to QA numbering **1**−**397**. Ball size is related to the structure−activity landscape index (SALI) of *d*/*Frag*Fp. Numbers in yellow rectangles are related to the relevant clusters **1**−**8**. (b) Box plots of calculated values of *c* Log *P*, *c* Log *S*, and drug-likeness (*d*) values of QAs **1**−**397**.

dietary activity was investigated in rainbow trout, and no toxic effects were observed at a recommended dietary dose of 500 mg/kg.[268] In addition, the inhibitory activity against hPTP1B (human protein tyrosine phosphatase 1B) of compounds **286**−**287** and the vasodilatory activity of compounds **339**−**342** have been documented. However, in both cases, these compounds were found to be inactive.[186,269] On the other hand, compound **352** was evaluated as a possible inhibitor of somatostatin and vasoactive intestinal peptide, and the results were very promising with IC_{50} = 12 μM.[270] Furthermore, a compound of the same QA type, i.e., **353**, was a potent inhibitor of the inositol 1,4,5-trisphosphate receptor and endoplasmic reticulum Ca^{2+} pumps with an inhibition of 78%.[271] Finally, the RLAR (rat lens aldose reductase) activity of compounds **315**−**317** and **329** was evaluated with inhibitions between 25 and 32%[184] and the antimetastatic activity of compounds **389**−**397**, whose best result was obtained for QAs **391**−**392** with inhibitions of 86.6% and 86.8%, respectively, classifying them as potent antimetastatic agents.[160]

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STRUCTURAL AND DRUG-LIKENESS COMPARISON OF COMPILED QUINOLIZIDINE ALKALOIDS

The compiled information shows that QAs, a category of natural compounds, have garnered considerable attention in drug discovery research due to their wide range of pharmacological activities (Table 10, Table S2). QAs possess intricate structural complexity and distinctive properties, which position them as potential candidates for creating innovative therapeutics. However, an essential aspect to consider for this purpose, beyond biological properties, pertains to the physicochemical characteristics required for a compound to be suitable for drug development.[272] This aspect can be rationalized under the drug-likeness concept, which refers to a set of physicochemical properties that a compound should possess to effectively access body cells and perform physiological or pharmacological functions while maintaining safety within the host organism.[273] Therefore, it can be considered a qualitative measure that aims to strike a balance between molecular and structural features, indicating how closely a substance resembles a potential drug regarding bioavailability.[274] In this regard, structural factors come into consideration when evaluating the drug-likeness of QAs, considering that they exhibit a complexity with multiple stereocenters, which provides numerous variations and expands the range of potential drug-like properties that can be attributed to them. To explore such factors, the custom-made QA-based library (n = 397) was structurally compared using the similarity analysis module included in the DataWarrior ver. 5.5.0 program[275] to visualize plausible structural relationships and patterns to define interesting QA-based scaffolds. Thus, the similarity plot (Figure 21a) on associating the *Frag*FP descriptor (i.e., a substructure fragment dictionary-based binary fingerprint similar to the MDL keys) and the DataWarrior-based drug-likeness approach[275] led to finding eight main clusters having similar fingerprints and positive drug-likeness score (d) (calculated values in Table S3). In this regard, the cluster with the best drug-likeness profile (d > 3, clusters 2 and 5) involved matrine and lupanine-type compounds having a 3-hydroxypiperidin-2-one moiety (related to **53** and **78**, respectively) and the (homo)ormosanine-type QAs (e.g., **260**−**272**), which seem to exhibit more drug-like properties. Compounds **53** and **78** have no reported activity, but they are related to **18** and **21**, which exhibited promising anti-HBV activity.[258] Other important clusters (i.e., **1**, **3**, and **5**−**8**) involved bismacrocyclic (e.g., related to **355** and **336**), piperidin-2-one-containing (e.g., related to darvasamine (**12**), camoensidine (**247**), *N*-formyltetrahydrocytisine (**163**), alopecuroide E (**381**)), cytisine-type (e.g., **132** and **133**), and leontidine-type (e.g., **247**) QAs with positive drug-likeness scores (d > 0).

The d/*Frag*Fp ratio, which serves as the structure−activity landscape index (SALI), demonstrated values exceeding 200 (represented by the size of the balls in Figure 21a) for approximately 26% of the compiled QAs (SALI > 200). This enabled the prediction of the drug-like potential of these QAs based on their chemical structure, utilizing the principle of molecular similarity to known drugs. In essence, drug-likeness refers to the inherent characteristics of a chemical compound that are necessary to attain the desired optimal pharmacological properties.[272] Generally, QAs exhibited a favorable drug-likeness profile, with a positive d score observed for 62.7% of QAs (Figure 21a,b, Table S3). These facts suggested that most QAs contained fragments that are commonly found in commercially available drugs. However, some QAs were part of the exception (d < −5) with bad drug-like profiles, such as alkenyl-substituted lupinines (e.g., **188** and **189**), biphenylquinolizidine lactones (e.g., **315**−**317**), acosmine-type (e.g., **280**), and dimeric quinolizidines (e.g., **377**). In addition, most QAs also exhibited reasonable hydrophilicity, involving medians within the range of commercial drugs (c Log P > 0; 0 > c Log S > −4) (Figure 21b), rationalized by the presence of various H-acceptors (ca. four on average) (Table S3).

These findings indicated that the biological activities of QAs might be of paramount importance in drug discovery since their drug-like properties place QAs as attractive starting points for the development of drug candidates targeting various diseases and conditions. Although QAs present challenges and advantages due to their structural complexity, several offer immense potential as drug candidates. Continued research efforts focused on improving their drug-likeness through expanding the chemical space by isolation of more variants or synthetic modifications and computational modeling, and optimization strategies will pave the way for the development of novel therapeutics based on QAs.[276]

PERSPECTIVES

QAs have emerged as a fascinating class of naturally occurring compounds with diverse chemical structures and significant biological activities. The chemistry and biological activities of QAs have been the subject of extensive research, and their perspectives hold great promise for various scientific disciplines. From a chemical perspective, QAs exhibit remarkable structural complexity and diversity. Multiple substituted variants and stereocenters within the quinolizidine scaffold add to their structural intricacy. This complexity provides a fertile ground for studying stereochemistry, synthetic methodologies, and structure−activity relationships (SARs) in the context of drug discovery and natural product chemistry.[18] In addition, the biological activity of QAs is another intriguing aspect that has attracted significant attention. These alkaloids have demonstrated a wide range of pharmacological properties, making them promising candidates for the development of therapeutics (Table 2). QAs have exhibited antimicrobial activity against various bacterial and fungal strains, including multidrug-resistant pathogens. Their cytotoxicity against cancer cells has also been investigated, showing potential as anticancer agents. Moreover, QAs have shown antiviral activity against several viral infections, such as hepatitis B and C viruses, and have been explored for their insecticidal and insect-repellent properties.

Understanding the mechanisms underlying the biological activities of QAs is crucial for their further development and utilization.[17] Further studies can reveal that their bioactivities are often mediated through the modulation of specific molecular targets and cellular pathways, interacting with enzymes, receptors, ion channels, and signaling pathways, leading to their diverse pharmacological effects.[277] However, several of them remain to be examined, and consequently, elucidating the molecular mechanisms of action can provide valuable insights into the design and optimization of QA-based therapeutics.

In recent years, advancements in analytical techniques, synthetic methodologies, and medicinal chemistry techniques have facilitated the obtention of diverse QA derivatives and

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analogs. These efforts to expand QA-related chemical space have contributed to SAR studies and structure-based drug design, enabling the development of potent and selective QA-based compounds.[278,279] Moreover, the discovery of natural sources of QAs, including plants, marine organisms, and animals, continues to expand the chemical space and offers new prospects for exploring QA chemistry and biological activity. In this context, the research perspectives on the chemistry, occurrence, and biological activity of QAs are multifaceted and hold immense potential. They provide opportunities for the discovery of novel drugs, exploration of natural product chemistry, and development of sustainable insecticides and antimicrobial agents. Furthermore, the unique structural features and diverse biological activities of QAs make them interesting subjects for interdisciplinary research, encompassing fields such as synthetic chemistry, pharmacology, biochemistry, and molecular biology.

CONCLUDING REMARKS

The present review encompasses a compilation of 397 quinolizidine alkaloids (QAs) representing the chemical diversity of these specialized metabolites isolated and reported over the past three decades. This compilation was organized into various QA types; as such, categorization had not been previously undertaken but was necessary. These QA types exhibit a high degree of structural complexity, characterized by intricate stereoisomerism, which renders them attractive as leads and scaffolds for various purposes. Most of these compounds have been isolated from the seeds, leaves, and aerial parts of Fabaceae plants, although other families, such as Lythraceae, also contain an intriguing group of macrocycle-type QAs. Additionally, macrocycle-type QAs have been identified in marine sponges (*Petrosia*, *Xestospongia*, and *Oceanapia*), frogs (Dendrobatidae), and ants (Formicidae). Despite initially being recognized for their natural defensive properties, various types of QAs have attracted considerable attention for research and utilization due to their wide range of biological activities. These activities include cytotoxic, antiviral, antimicrobial, insecticidal, anti-inflammatory, antimalarial, and antiacetylcholinesterase effects. Importantly, these QAs also exhibit a favorable putative drug-likeness profile, making them promising candidates to be considered in drug discovery endeavors. Accordingly, the chemistry, occurrence, and biological activity perspectives of QAs offer a rich landscape for scientific exploration and innovation. Continued research efforts, including synthetic studies, structure−activity relationship investigations, and mechanistic studies, will undoubtedly contribute to unlocking the full potential of QAs as valuable chemical entities with significant therapeutic applications.

Thus, the information gathered in this review underscores the need for further research to expand the chemodiversity and identify more potent bioactive compounds based on QAs as valuable scaffolds for pharmacological and agrochemical applications.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c02179.

Names and SMILES of **397** compiled quinolizidine alkaloids (QAs) (Table S1), individual structures of quinolizidine alkaloids **1**−**397** (Figures S1 to S22), compendium of reported biological activity of the 397 quinolizidine alkaloids (Table S2), and calculated properties of compiled QAs **1**−**397** (Table S3) (PDF)

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