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Lauraceae alkaloids

Dayana Lacerda Custódio and Valdir Florêncio da Veiga Junior

Covering up to the beginning of 2013

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Lauraceae is one of the most representative botanical families, presenting 67 genera with over 2,500 species, and more than 300 different alkaloids reported, mainly isoquinolines. Its diversity and relevance to chemosystematic relationships is presented and discussed.

1 Introduction

The Lauraceae botanical family has a tropical and subtropical distribution, concentrated in Asian and American rain forests, including about 67 genera with over 2,500 species. It is found particularly in countries with biodiversity hot spots. Brazil, for example, has a great representative number of species, with approximately 25 genera and 400 Lauraceae species. Lauraceae is considered one of the most important families in the floristic composition in some of its forest ecosystems.^{1,2}

Several Lauraceae species have been used in the manufacture of various products with great economic value, in areas such as the food and wood industries, for example *Ocotea porosa*, the popular “Imbuia” and *Ocotea odorifera*, known as “Sassafras”. Additional, natural products found in species such as *Aniba rosaeodora*, with an essential oil rich in linalool, an excellent perfume fixative, possess high economic value in international markets.³⁻⁶

However, some species have their use restricted to traditional communities, who have empirical knowledge about the use of these plants.⁷ Many neolignans have been described in this family, and these substances have been used as lead compounds for new drug development.⁸ Together with neolignans and essential oils, this family presents several alkaloids, with isoquinolines as the main class reported in the literature.^{9, 10}

The isoquinoline alkaloids are formed from the amino acid tyrosine by consecutive reactions forming the tetrahydroisoquinoline core (**1**, **Fig. 1**) and have a great importance due several pharmacological activities described to the benziltetrahydroisoquinoline (**2**), aporphine (**3**), and pavine (**4**) skeletons. Another alkaloid group present in Lauraceae are the indole alkaloids, which have benzopyrrolic structures where the indole (**5**) core is formed by the fusion

of benzene and pyrrole rings at positions 2 and 3. When this link occurs at positions 3 and 4 of the pyrrole ring, the formation of the isoindole (**6**) core occurs. The structure numbering starts at the atom near the pyrrole ring junction, followed by other atoms around the indolic core.¹¹ The pyridine alkaloids, also found in this family, present a pyridine (**7**) ring that originates from nicotinic acid.¹²

2 Isoquinoline alkaloids

The isoquinoline alkaloids represent the majority of the alkaloids described in the Lauraceae family, and have been reported in various genera. They stand out in Lauraceae due their detection in several species and in various plant parts (Table 1).

The most frequently detected alkaloids in Lauraceae belong to the aporphinic group, with only one benzyltetrahydroisoquinoline. With methoxyls and only a few hydroxyl groups located at positions 1, 2, 8, 10 or 11, these alkaloids have similar structures and polarities: actinodaphnine (**8**), dicentrine (**9**), isoboldine (**10**), laurolitsine (norbaldine) (**11**), boldine (**12**), laurotetanine (**13**) and N-methylaurotetanine (**14**). The alkaloids actinodaphnine (**8**) and dicentrine (**9**) present a dioxymethylene at C-1 and C-2, while reticuline (**15**), a benzyltetrahydroisoquinoline alkaloid, also has two hydroxyls at C-7 and C-11, two methoxyls at C-6 and C-10 and a methyl at the nitrogen atom. Among the aporphine structures, actinodaphnine (**8**), laurolitsine (**11**), boldine (**12**), laurotetanine (**13**) and N-methylaurotetanine (**14**) present a hydroxyl at C-9. Laurolitsine (**11**) has a methyl at C-10, while laurotetanine (**13**), boldine (**12**), laurotetanine (**13**), N-methylaurotetanine (**14**) and isocorydine (**16**) have a

methoxyl at C-1. Laurolitsine (**11**) and boldine (**12**) have a hydroxyl at C-2, and laurotetanine (**13**), N-methylaurotetanine (**14**) and isocorydine (**16**) have a methoxyl at C-2.

Stem bark is the most common plant part where these alkaloids can be found in Lauraceae, together with leaves. Several studies have found these alkaloids in roots as well. Taking into account that almost all of these species are trees and not shrubs, it is important to note that the preference of performing a phytochemical study on roots indicates an objective approach based on a characteristic of the family.

Some of these alkaloids have been pharmacologically studied with promising activities for use in different health areas. High cytotoxicity was observed for actinodaphnine (**8**) using the Mel-5 and HL-60 cell lines.¹⁶ This alkaloid also induced apoptosis in human hepatoma cells Mahvalu by increasing nitric oxide, reactive oxygen species and modulating NF- κ B signalling.¹⁸

Dicentrine (**9**) showed cytotoxic activity in the HCE-6, Molt-4, CESS, HL60, K562 and MS-G2 cell lines.²⁵ Hoet et al.⁶² observed that dicentrine (**9**) presented activity against *Trypanosoma brucei* using *in vitro* assays. Recently, it was observed that this alkaloid has an antinociceptive effect following a pain stimulus (acetic acid) in experiments with mice.³⁰ This alkaloid also presented potent vasorelaxation in experiments conducted in mice, where the IC₅₀ ranged from 0.08 to 2.48 μ M.¹⁷

Laurolitsine (**11**) showed cytotoxic activity against the Hep-2 cell line.⁴⁶ This substance also presented significant inhibitory activity against type I HIV integrase with an IC₅₀ of 16.3 μ M.⁴⁴ Antiplasmodial activity against *Plasmodium falciparum* (clone 3D7) was also reported for this substance with an IC₅₀ of 1.49 mg/mL.⁶³

Boldine (**12**) showed antiinflammatory activity using a model of the oedema induced by carrageenan, in addition to antinociceptive activity.^{64,65} This compound has also shown cytotoxic

activity against HEP-2 tumour cells with total inhibition of the cell culture at a concentration of 0.3 mg/mL.⁶⁶

Morais et al.⁶⁷ performed neuropharmacological studies carried out with reticuline (**15**) in mice, observing that this alkaloid caused changes in sleep behaviour, motor coordination and conditioned avoidance responses in these animals, suggesting that this alkaloid possesses potent central nervous system depressant effects. Dias et al.⁶⁸ observed a blood pressure lowering effect in rats, and Medeiros and coworkers⁵⁸ observed that this molecule induces vasorelaxation through the blockade of L-type Ca²⁺ channels.

The similarity of these substances and their pharmacological activities strongly indicates that further studies must be performed. These alkaloids are commonly obtained in very small quantities. Isolation on the gram scale would allow additional pharmacological experiments.

In addition to these substances, the most common alkaloids found in Lauraceae, there have been many other isoquinoline alkaloids described, with more restricted distribution. The genus *Ocotea* is one of the most studied in Lauraceae, with several alkaloids found, predominantly aporphines. In *Ocotea macropoda*, dicentrine (**9**), together with predicentrine (**17**, **Fig. 2**), ocopodine (**18**), nordicentrine (**19**), dehydrodicentrine (**20**), dehydroocopodine (**21**) and dicentrinone (**22**) were identified.^{69,70} In *O. macrophylla*, isocorydine (**16**), (+)-natenine (**23**), glaucine (**24**) and dehydronantenine (**25**) were identified.⁶¹

In recent studies performed on *O. macrophylla* leaves, the alkaloids dicentrine (**9**), (+)-nantenine (**23**), dehydronantenine (**25**), (+)-neolitsine (**26**, **Fig. 3**), (+)-N-acetyl-nornantenine (**27**), (+)-cassythidine (**28**) and didehydroocotein (**29**)²⁸ were isolated. From the stem, the alkaloids (S)-3-methoxynordomesticine (**30**), (S)-N-ethoxycarbonyl-3-methoxynordomesticine (**31**), (S)-N-formyl-3-methoxynordomesticine (**32**) and (S)-N-methoxycarbonyl-3-

methoxynordomesticine (**33**) were also detected and identified. The alkaloid (S)-3-methoxynordomesticine (**30**) showed moderate antifungal activity against *Fusarium oxysporum* f. sp. *lycopersici* and antimicrobial activity towards *Staphylococcus aureus* 6538 and *Enterococcus faecalis* 29212⁷¹. (+)-nantenine (**23**) has also presented a reversible effect in muscle contraction and Ca²⁺ transients in experiments using rats.⁷²

Extracts from the leaves of *O. brachybotra* yielded the alkaloids dicentrine (**9**), predicentrine (**17**), ocopodine (**18**), (±)-glaziovine (**34**, **Fig. 4**), cassythicine (**35**), leucoxine (**36**) and sinacutine (**37**). In the same study, the authors isolated morphinone derivatives such as pallidine (**38**), ocobitrine (**39**) and 14-episiomenine (**40**). Their structures were elucidated by the usual spectroscopy methods and chemical correlations.²⁶

A great number of isoquinoline alkaloids has been reported in other species of *Ocotea*, including (+)-isoboldine (**10**), (-)-zenkerine (**41**, **Fig. 5**), (+)-laurelliptine (**42**), (-)-pulcine (**43**) and nororientidine (**44**), observed in *O. caesia* stems³⁷, and 1-(p-methoxybenzoyl)-6,7-methylenedioxyisoquinoline (**45**), 1-(hydroxy-p-methoxybenzyl)-6,7-methylenedioxyisoquinoline (**46**), 1,2-dihydro-1-(p-methoxybenzoyl)-6,7-methylenedioxyisoquinoline (**47**) and 1,2-dihydro-1-(hydroxy-p-methoxybenzyl)-6,7-methylenedioxyisoquinoline (**48**), obtained from *O. pulchella* stem bark.⁷³

In *Ocotea vellosiana*, the alkaloids predicentrine (**17**), nordicentrine (**19**), ocoteine (**49**, **Fig. 6**), O-methylcassyfiline (**50**), leucoxyllonine (**51**), ocotominarine (**52**) and reticuline (**15**) were detected in the branches; ocopodine (**18**) and ocominarine (**53**) in the leaves; glaucine (**24**), isocorydine (**16**) and corydine (**54**) in fruits; dicentrine (**9**) were identified in all plant parts studied.³¹ In *Ocotea duckei* were isolated the benzyloisoquinoline alkaloids reticuline (**15**) from the leaves and stem bark^{58,67} and coclaurine (**55**) from the stem.⁷⁴ Several aporphine structures

were isolated from *O. minarum* leaves, which were identified as dicentrine (**9**), predicentrine (**17**), ocopodine (**18**), dicentrinone (**22**), leucoxine (**36**), ocoteine (**49**), leucoxilonine (**51**), ocotominarine (**52**), ocominarine (**53**), thalicminine (**56**), norleucoxilonine (**57**), isoconovine (**58**), 4-hydroxydicentrine (**59**) and ocominarone (**60**). Structure identification was performed by spectroscopy methods and chemical correlations.²⁷

Investigations on *O. glaziovii* leaves have afforded assimilobine (**61**, **Fig. 7**), caaverine (**62**), liridinine (**63**) and glaziovine (**34**),⁷⁵ these compounds were also observed in *O. variabilis*.⁷⁶ This species has also shown the presence of nantenine (**23**), apoglaziovine (**64**) and variabiline (**65**).⁷⁶ In the species *O. sinuata*, nordomesticine (**66**) was found, while isocorydine (**16**), taliporfine (**67**), oconovine (**68**), ococriptine (**69**), ocoxilonine (**70**) and hernandonine (**71**) were identified in *Ocotea*, but without species recognition.^{69,77,78}

A number of alkaloid structures have been elucidated in *O. puberula*: dicentrine (**9**), N-methyllaurotetanine (**14**), predicentrine (**17**), leucoxine (**36**), ocoteine (**49**), thalicminine (**56**), isodomesticine (**72**, **Fig. 8**), dicentrine N-oxide (**73**), dehydroocoteine (**74**), didehydroocoteine (**75**) and 3-hydroxydicentrine (**76**).^{69,79-81} Further studies on the seedling leaves of *Ocotea puberula* have yielded dicentrine (**9**), boldine (**12**), leucoxine (**36**) and isodomesticine (**72**), in concentrations higher than those observed in the leaves of adult individuals.²⁹ The methanolic extract of *O. leucoxyton* yielded dicentrinone (**22**) as the major alkaloid besides dicentrine (**9**) and leucoxytonine (**51**).⁸² In the leaves of *O. holdridgeana*, isocorydine (**16**), O,O-dimethylcorituberine (**77**), 3-hydroxynuciferine (**78**) and 3-methoxynuciferine (**79**) were identified.⁸³

López and coworkers⁸⁴ obtained the alkaloids isocorydine (**16**), 3-hydroxynuciferine (**78**) and 3-hydroxy-6a,7-dihydronuciferine (**80**, **Fig. 9**) from ethanolic extracts of *O. brenesii* leaves.

Studies performed with *O. acutangula* leaves led to the identification of (S)-(-)-pallidine (**38**), its derivative (S)-(-)-O-methylpallidine (**81**), as well as the alkaloids (S)-(-)-pallidine (**82**) and (S)-(-)-O-methylpallidine (**83**).⁸⁵

From *O. rodiaei* stem bark, the structures of the alkaloids rodiasine (**84**, **Fig. 10**), ocotamine (**85**), demerarine (**86**), norrodiasine, dirosine, otocamine and ocodemerine were elucidated.⁸⁶ Other alkaloids found in the genus *Ocotea* are talbaicalidine (**87**) in *O. bucherii*,⁸⁷ talictuberine (**88**) and 3-O-dimethyltalictuberine (**89**) in *O. insularis*.⁸⁸

Most of these references on the *Ocotea* genus addressed is mentioned in the review about *Ocotea* aporphine alkaloids performed by Zanin and Lordello,³ in which the authors reported the occurrence of 54 aporphine alkaloids distributed in 17 species, including 39 aporphines, four oxoaporphines, five 6a,7dehydroaporphines, one didehydroaporphine, one C-3-O-aporphine, one C-4-O-aporphine, two fenantrenes and one proaporphine.

Recently, the alkaloids (+)-neolitsine (**26**), (+)-6S-ocoteine-N-oxide (**90**, **Fig. 11**), (+)-norocoxilonine (**91**) and (+)-talicsimidine (**92**) were isolated from the leaves and stem bark of *Ocotea acutifolia*.⁸⁹

In *Cryptocarya*, several isoquinoline alkaloids have also been described. However, this genus presents several unusual pavine alkaloids. Among the exceptions are armepavine (**93**, **Fig. 12**), a benzyloquinoline alkaloid obtained from *Cryptocarya archboldiana* leaves that represents 70% of the alkaloidal fraction obtained.⁹⁰ Other alkaloids present in the genus are (+)-orientaline (**94**) and laudanidine (**95**) in the stem bark of *C. amygdalina*,⁹¹ ateroline (**96**) and velucryptine (**97**) in *C. velutinosa* leaves⁹² and (+) - (1R, 1Ra)-1a-hydroxymagnocumarine (**98**) from *C. konishii*.⁹³ Lisicamine (**99**) was isolated from the stem bark of *Cryptocarya strictifolia*.⁹⁴ In *C. odorata* stem bark, laurotetanine (**13**), N-methyl-laurotetanine (**14**), reticuline (**15**),

isocorydine (**16**) and cryptodrine (**100**) were found.⁵¹ From *C. phyllostemom* stem bark, two tetrahybenzylisoquinoline alkaloids, (+)-phyllocryptine (**101**) and (+)-phyllocryptonine (**102**) were obtained.⁹⁵

The study of *C. ferrea* stems led to the isolation of three aporphine alkaloids, (-)-O-methylisopiline (**103**, **Fig. 13**), (+)-lirioferine (**104**) and (+)-norlirioferine (**105**).⁹⁶ Seven benzylisoquinoline alkaloids were obtained from *C. rugulosa* stem bark: (+)-reticuline (**15**), papraline (**106**), (+)-norcinnamolaurine (**107**), (+)-codamine (**108**), (+)-6-methoxy-1-(3'-methoxybenzyl)-N-methyl-7-isoquinolinol (**109**), (-)-N-methylisococlaurine (**110**) and (+)-reticuline N-oxide (**111**).⁹⁷

Cryptocarya chinensis is one of the most studied in this genus, with several alkaloids identified: isoboldine (**10**), (\pm)-romneine (**112**, **Fig. 14**), (-)-eschscholtzine (**113**), (+)-eschscholtzidine (**114**),⁹⁸ (-)-isocaryachine-N-oxide (**115**), isoboldine- β -N-oxide (**116**), 1-hydroxycryprochine (**117**), (+)-isocaryachine (**118**), (+)-caryachine (**119**), (-)-caryachine (**120**), (-)-isocaryachine (**121**), (-)-munitagine (**122**), bisnorargemine (**123**),³⁴ all of them isolated from the leaves of this species.

C. chinensis stems have yielded the pavine alkaloids (+)-eschscholtzidine (**114**), (+)-caryachine (**119**), (+)-escholtzidine-N-oxide (**124**, **Fig. 15**), (-)-12-hydroxyeschscholtzidine (**125**), (-)-12-hydroxycrychine (**126**), (-)-N-demethylcrychine (**127**), neocaryachine (**128**), crychine (**129**), (-)-argemonine (**130**), dorianine (**131**), (-)-N-demethyl-phelocryptine (**132**), in addition to the proaporphines cryprochine (**133**), isocryprochine (**134**), prooxocryptochine (**135**), isoamuronine (**136**) and (+) - 8,9-dihydroestepharine (**137**).⁹⁹

From the stem bark, (-)-eschscholtzidine (**114**), 1-hydroxycryprochine (**117**), (+)-caryachine (**119**), (-)-caryachine (**120**), (-)-isocaryachine (**121**), (-)-neocaryachine (**128**), (+)-

cryprochine (**133**), (-)-isocaryachine-N-oxide B (**138**, Fig. 16), (-)-caryachine-N-oxide (**139**), 6,7-methylenedioxy-N-methylisoquinoline (**140**), (+)-isocaryachine-N-oxide (**141**), (+)-cinnamolaurine (**142**), (-)-mutagenine, 4-(6,7)-dimethoxyisoquinoline-1-ylmethylphenol, (-)-2-O-norargemonine and (-)-N,N-dimethylcaryachine were isolated,^{98,100,101} as well as three quaternary pavine alkaloids as N-methoxy salts of caryachine (**143**), neocaryachine (**144**) and crychine (**145**) from *C. chinensis* callus culture.¹⁰² Caryachine was also obtained as an N-methoxy salt (**143**) by Chen et al.¹⁰³ from the stem bark of *C. chinensis*.

A number of isoquinoline alkaloids have been reported in the genus *Cassytha*; the most studied species is *Cassytha filiformis*. Several alkaloids have been described to this species, including neolitsine (**26**), cassythidine (**28**), O-methylcassyfiline (= O-methylcassytine) (**50**), cassyfiline (= cassytine) (**146**, Fig. 17), lisicamine (**99**), cassamedine (**147**), cassameridine (**148**), launobine (**149**), bulbocapnine (**150**), (+)-nornuciferine (**151**), (+)-nuciferine (**152**), aterospermidine (**153**), liriodenine (**154**), O-methylateroline (**155**), catafiline (**156**), cataformine (**157**), isofiliformine (**158**), cassythic acid (**159**), norpredicentrine (**160**), (-)-O-methylflavinatine (= sebiferine) (**161**), (-)-salutaridine (**162**) and 1,7-methylenedioxy-3,10,11-trimethoxyaporphine (**163**).¹⁴⁻¹⁷

In *Cassytha pubescens*, the aporphine alkaloids isoboldine (**10**), nantenine (**23**), laurelliptine (**42**), nordomesticine (**66**), domesticine (**164**, Fig. 18) and sinoacutine (**165**) were identified.³³ Tsai and coworkers¹⁷ observed in this species dicentrine (**9**), neolitsine (**26**), cassytine (**146**) and cassythic acid (**159**). The cassytine (**146**) showed high activity against the cell lines Mel-5 (IC₅₀ of 24.3 μM) and HL-60 (IC₅₀ of 19.9 μM), and was also active in *in vitro* assays with *Trypanosoma brucei*.^{16,62} Cytotoxic activity of neolitsine (**26**) was also observed in the cancer cell lines HeLa and 3T3 with an IC₅₀ of 21.6 μM and 21.4 μM, respectively.¹⁶

Investigations into *Aniba* species afforded (R)-(+)-noranicanine (**166**, **Fig. 19**), a benzyloisoquinoline trioxygenated alkaloid that was isolated from the stem bark of *Aniba canellila*.¹⁰⁴ Eleven other benzyltetrahydroisoquinoline alkaloids were also reported in this species, including four compounds monosubstituted on ring C with a hydroxyl at C-11, i.e. (-)-norcanelliline (**167**), (+)-canelliline (**168**), anicanine (**169**) and canellinoxine (**170**); two compounds monosubstituted at C-9 in ring D, i.e. (-)-anibacanine (**171**) and (+)-manibacanine (**172**); two compounds monosubstituted at C-11 in ring D, i.e. (-)-pseudoanibacanine (**173**) and (+)-pseudoanibacanine (**174**); and three alkaloids with the same substitution pattern on rings A and B with a methyl group at positions 8 α and 8 β , i.e. (-)- α -8-methylpseudoanibacanine (**175**), (-)- β -8-methylpseudoanibacanine (**176**) and (-)- α -8-methylanibacanine (**177**).¹⁰⁵ Additionally, isoboldine (**10**), reticuline (**15**) and N-methylcoclaurine (**178**) were isolated from *Aniba muca* stem bark.³² Reticuline (**15**) was also found in *Aniba rosaeodora*.⁵⁶

In the genus *Lindera*, lindecarpine (**179**, **Fig. 20**) and N-methylindecarpine (**180**) have been reported in *L. pipericarpa* roots,¹⁰⁶ and N-methylaurotetanine (**14**), isocoridine (**16**) and norisocoridine (**181**) in the stem bark.⁵⁴ The bisbenzyloisoquinoline dimer lindoldhamine (**182**) was isolated from leaves of *L. oldhamii*.¹⁰⁷ D-dicentrine (**9**) was observed in *L. megaphylla* roots,²⁵ while laurotetanine (**13**) was obtained from *L. benzoin* branches.⁵² The alkaloids laurolitsine (**11**), hernandine (**183**), hernangerine (**184**), N-methylhernangerine (**185**), ocokryptine (N-methylhernandine) (**186**), hernandonine (**187**), 7-oxohernangerine (**188**), lindechunine A (**189**), lindechunine B (**190**) and 7-oxohernagine (**191**) were isolated from the roots of *Lindera chunii*.⁴⁴ Among the alkaloids found in *Lindera chunii* significant inhibitory activity against type I HIV integrase was observed for hernandonine (**187**), 7-oxohernangerine (**188**) and lindechunine A (**189**) with IC₅₀ of 7.7 μ M, 18.2 μ M and 21.1 μ M, respectively.⁴⁴

More recently, some common aporphine alkaloids were observed in *Lindera angustifolia* roots, such as isoboldine (**10**), norboldine (**11**), boldine (**12**), laurotetanine (**13**), N-methylaurotetanine (**14**), reticuline (**15**), norisocoridine (**181**), and N-ethoxycarbonyllaurotetanine (**192**, **Fig. 21**), in addition to the magnocurarine (**193**).³⁵ In *Lindera aggregata*, the alkaloids laurilitine (**11**), boldine (**12**), reticuline (**15**), (-)-pallidine (**38**), norisocoridine (**181**), linderaline (**194**), protosinomenine (**195**), laudanosoline 3',4'-dimethylether (**196**), norisoboldine (**197**) and pronuciferine (**198**), together with the bisbenzylisoquinoline linderegatine (**199**) were isolated from the ethanolic extract of the roots.^{43,108} Among these alkaloids, norisoboldine (**197**) has been reported to inhibit the production of proinflammatory cytokines in experiments with the mouse macrophage cell lineage RAW 264.7.^{43,109} For norisocoridine (**181**), antinociceptive activity and a high capacity for sequestering free radicals with an SC₅₀ of 14.1 mg/mL have been found.⁶⁵

A number of structures are related to the genus *Litsea*, among them litebamine (**200**, **Fig. 22**), a phenanthrene alkaloid observed in *L. cubeba* stems, with the structure 3,7-dihydroxy-4,6-dimethoxy-N-methyl-tetrahydropyridine [4,3-a]phenanthrene,¹¹⁰ N-methylaurotetanine (**14**) and the quaternary alkaloids (-)-magnocurarine (**193**), (-)-oblongine (**201**), (-)-8-O-methyloblongine (**202**) and xantoplanine (**203**).^{55,93} *L. cubeba* stem bark yielded five new isoquinoline alkaloids, i.e. (+)-N-(methoxycarbonyl)-N-nordicentrin (**204**), (+)-N-(methoxycarbonyl)-N-norpredicentrine (**205**), (+)-N-(methoxycarbonyl)-N-norglaucine (**206**), (+)-N-(methoxycarbonyl)-N-norbulbodione (**207**), (+)-N-(methoxycarbonyl)-N-norisocorydione (**208**) and (+)-8-methoxyisolaurenine-N oxide (**209**), all obtained from the 70% ethanolic extract.¹¹¹ The alkaloids (+)-N-(methoxycarbonyl)-N-nordicentrin (**204**), (+)-N-(methoxycarbonyl)-N-norpredicentrine (**205**) and (+)-N-(methoxycarbonyl)-N-norglaucine (**206**) showed antimicrobial

activity against the bacteria *S. aureus* and two fungi, *A. alternata* and *C. nicotianae*, while (+)-*N*-(methoxycarbonyl)-*N*-norbulbodione (**207**) and (+)-*N*-(methoxycarbonyl)-*N*-norisocorydione (**208**) exhibited significant cytotoxicity against six tested tumour cell lines.¹¹¹ Other alkaloids found in the stem bark of this species were (+)-laurotetanine (**13**), *N*-methyllaurotetanine (**14**) and isocorydine (**16**).⁵³

Some well-known alkaloids were also found in species of *Litsea*, such as isoboldine (**10**), laurelliptine (**42**) and liriodenine (**154**) in *L. glutinosa* leaves,¹¹² actinodaphnine (**8**), boldine (**12**), laurotetanine (**13**) and *N*-methyllaurotetanine (**14**) in *L. sebifera* leaves and branches, norboldine (laurohitsine) (**11**) and boldine (**12**) in *L. wightiana* stem bark¹³ and laurohitsine (**11**), boldine (**12**) and (+)-reticuline (**15**) in *L. leefeana* leaves.⁴⁵

A study on *Litsea laurifolia* led to the isolation of laurohitsine (**11**) from the bark and actinodaphnine (**8**), reticuline (**15**) and glaziovine (**34**) from the leaves.²⁰ From *Litsea laeta* stem bark, the alkaloids glaucine (**24**), laetanine (**210**, **Fig. 23**), laetine (**211**) and *N*,*O*-dimethylharnovine (**212**) were isolated.^{113,114} In the same study, the authors isolated nordicentrine (**19**) and dicentrinone (**22**) from the leaves of *Litsea salicifolia*. Barbosa-Filho et al.⁶⁴ listed several alkaloids with anti-inflammatory activity, including glaucine (**24**). Recently, a new bisbenzylisoquinoline alkaloid was isolated from the stem bark of *Litsea lancifolia*, the lancifoliaine (**213**), plus seven other known alkaloids: actinodaphnine (**8**), norboldine (**11**), boldine (**12**), reticuline (**15**), cassythicine (**35**), pallidine (**38**) and *N*-allyllaurohitsine (**214**).¹¹⁵ The alkaloids isoboldine (**10**), reticuline (**15**) and thalifoline (**215**) were isolated from *L. petiolata* bark.³⁶

In the genus *Neolitsea*, the alkaloids actinodaphnine (**8**), isoboldine (**10**), laurohitsine (**11**), boldine (**12**), reticuline (**15**), (-)-talicsimidine (**92**), (+)-cassythine (**146**), liriodenine (**154**), (+)-

O-methylflavinatine (= sebiferine) (**161**), neolitacumonine (**216**, **Fig. 24**), (-)-norushinsunine (**217**), N-methylactinodaphnine (**218**), (-)-anonaine (**219**) and oxogalucine (**220**) were isolated from the stem bark of *N. acuminatissima*.²³ In *Neolitsea sericea* stems and leaves, actinodaphnine (**8**), isoboldine (**10**), laurilitine (**11**), boldine (**12**), laurotetanine (**13**), N-methylaurotetanine (**14**), reticuline (**15**), N-oxides of reticuline (**111**), norisocoridine (**181**), N-methylactinodaphnine (**218**), L-roemerine (**221**), litsericine (**222**), N-oxides of pallidine (**223**), boldine (**224**), juziphine (**225**) and N-methylaurotetanine (**226**) were found as well as (+)-corituberine (**227**).^{21,22,116-120} In the stem bark of *Neolitsea variabilissima*, L-hernovine (**228**), L-nandigerine (**229**) and L-N-methylhernovine (**230**) were found.¹²¹

Among the isoquinoline alkaloids described in the genus *Phoebe*, laurilitine (**11**), liriiodenine (oxoushinsunine) (**154**), roemerine (**221**), ushinsunine (**231**, **Fig. 25**) and laurodionine (**232**) were isolated from the bark and stem of *Phoebe formosana*,^{47,122} and some pentasubstituted aporphines were found in the bark of *Phoebe mollicella*, i.e. norpurpleine (**233**), purpleine (**234**), preocoteine (**235**) and norpreocoteine (**236**).¹²³ From the leaves of *Phoebe pittieri*, the alkaloids liriioferine (**104**) and norliriioferine (**105**) were obtained.¹²⁴ Reticuline (**15**), norliriioferine (**105**), norpurpleine (**233**) and 1,2,3-trimethoxy-9,10-methylenedioxiaporphine (**237**) were isolated in the bark of the same species.⁵⁹ In *P. chinensis*, several compounds with aporphine skeletons were obtained from the stem bark, including laurilitine (**11**) and laurotetanine (**13**), very common structures in Lauraceae, as well as caaverine (**62**), liriiodenine (**154**), sebiferine (=O-methylflavinatine) (**161**), anonaine (**219**) and roemerine (**221**).⁴⁶

In *Phoebe grandis*, the phoebegrandines A (**238**, **Fig. 26**) and B (**239**), as well as phoebegrandine C, D and E were isolated from the leaves, while norboldine (**11**), boldine (**12**),

laurotetanine (**13**), lindecarpine (**179**), (-)-grandine A (**240**), (-)-8, 9-dihydrolinearisine (**241**), scortechiniines A and B (**242**) and lauroformine (**243**) were obtained from the stem bark.^{48,125-127} In *P. lanceolata* stem bark, the alkaloids laurodionine (**232**) and nordelporphine (**244**) were identified, and were also observed in *P. formosana* stem bark.^{122,128,129} In *Phoebe scortechinii* leaves, the dimer tryptamine proaporphine, (-)-phoebescortechiniine and phoebegrandines A (**238**) and B (**239**) were found,¹³⁰ while in the stem the aporphine norboldine (**11**), as well as the proaporphine alkaloids (+)-scortechiniine A and B (**242**), (-)-hexahydromecambrine A (**245**) and (-)-norhexahydromecambrine A (**246**) were identified.⁴⁹ Antiplasmodial activity against *Plasmodium falciparum* (clone 3D7) was reported for the alkaloids isolated from the stem bark of *P. tavoyana*, i.e. sebiferine (**161**) and roemerine (**221**), with IC₅₀ values of 2.76 mg/mL and 0.89 mg/mL, respectively.⁶³

Investigations into *Dehaasia triandra* afforded isocorydine (**16**) in the leaves, and some bisbenzylisoquinoline structures, including obaberine (**247**, **Fig. 27**), norobaberine (**248**), 3',4'-dihydrostafasubine (**249**) and norisotetrandrine (**250**) were detected in stems of *D. triandra*.^{60,131,132} Mukhtar et al.¹³³ studied the leaves of *Dehaasia longipedicellata* and isolated five morfinandienone alkaloids, including (-)-pallidine (**38**), (+)-pallidinine (**82**), (-)-sinoacutine (**165**), (+)-milonine (**251**) and (-)-8,4-dehydrosalutaridine (**252**).

From the stem bark of *Actinodaphne pruinosa* a new alkaloid was isolated, (+)-N-(2-hydroxypropyl)lindecarpine (**253**, **Fig. 28**), which showed cytotoxicity against P-388 leukaemia cells with an IC₅₀ of 3.9 µg/mL.⁴⁰ Additionally, the alkaloids (+)-norboldine (**11**), (+)-boldine (**12**), (+)-lindecarpine (**179**) and (+)-methyllindecarpine (**180**) were obtained.⁴⁰ In *A. sesquipedalis*, the presence of dicentrine (**9**) was reported in the stem bark,²⁴ while in *A. nitida* laurolitsine (**11**) and boldine (**12**) were found in the stem bark and leaves.³⁹

Two morphinandienone structures were obtained from *Beilschmiedia oreophila* stems and bark, i.e. oreobiline (**254**, **Fig. 29**) and 6-epioreobiline.¹³⁴ From *B. brevipes* leaves, the benzylisoquinoline alkaloids (6,7-dimethoxy-4-methylisoquinolinyl)-(4'-methoxyphenyl)-metanone (**255**) and *O,O*-dimethylannoherine (**256**) were obtained.¹³⁵ Recently, in *Beilschmiedia kunstleri*, the alkaloids (+)-norboldine (**11**), (-)-pallidine (**38**) and (+)-*N*-methylisococlaurine (**257**) from leaves; (-)-isocaryachine (**121**), (+)-normuciferine (**151**), noraterosperminine (**258**) and (+)-*N*-demethylphyllocaryptine (**259**) were isolated from stem bark; (+)-boldine (**12**), (+)-laurotetanine (**13**) and (+)-cassythicine (**35**) were obtained from vegetal parts.^{50,136}

In the genus *Machilus*, the alkaloid (+)-*L*-reticuline (**15**) was found in *M. thumbergii*, *D,L*-coclaurine (**55**) in *M. kusanoi* and *M. macranta*; (+)-*L*-laudanidine (**95**) in *M. obovatifolia* and *M. arisanensis*; (-)-*L-N*-noramepavine (**260**, **Fig. 30**) in *M. kusanoi*, *M. pseudolongifolia*, *M. thumbergii*, *M. obovatifolia*, *M. arisanensis* and *M. zuihoensis*; *D,L-N*-norarmepavine (**261**) in *M. pseudolongifolia*, *M. thumbergii*, *M. obovatifolia*, *M. arisanensis* and *M. zuihoensis*.¹³⁷⁻¹⁴² From *M. glauscescens* leaves, the oxoaporphine alkaloids machigline (1,2-methylenedioxy-9-hydroxy-10-methoxyoxoaporphine) (**262**) and ateroline (**96**) were obtained.¹⁴³

Studies performed on *Alseodaphne* species led to the identification of (+)-reticuline (**15**), a mixture of coclaurine (**55**) isomers in a proportion of 3:1 ((+)-coclaurine: (-)-coclaurine) and (-)-*N*-norarmepavine (**261**) in *A. archboldiana*,¹⁴⁴ while in *A. semicarpifolia*, the C-4 hydroxylated aporphine srilankine (**263**, **Fig. 31**) was obtained.¹⁴⁵ In *A. corneri* stem bark, a new bisbenzylisoquinoline alkaloid, 3',4'-dihydronorstephasubine (**264**), together with two known structures, norstephasubine (**265**) and girolidine (**266**) we found; moderate vasorelaxation effects were identified for **264** and **266** in rat aorta assays.¹⁴⁶ From the roots of the same species, the

bisbenzylisoquinoline alkaloids norstephasubine (**265**), (-)-girolidine (**266**), (+)-norlimacusine (**267**) and (+)-stephasubine (**268**) were isolated.¹⁴⁷

Among the alkaloids described in *Alseodaphne perakensis*, N-methyl-2,3,6-trimethoxymorphinandien-7-one (**269**, **Fig. 32**) has been described as the main alkaloid in leaves, along with a mixture of other alkaloids in small quantities, including N-methyl-2,3,6-trimethoxymorphinandien-7-one N-oxide (**270**).^{148,149} From the stem bark of the same species, the alkaloids α' -oxoperakensimines A (**271**), B (**272**) and C (**273**) were isolated. In the same study, vasorelaxation activity was also reported for both substances using rat aorta assays.¹⁵⁰ Recently, a new alkaloid in this species was observed, also present in the stem bark, i.e. N-cyanomethylnorboldine (**274**), in addition to the known structures, N-methylaurotetanine (**14**) and norboldine (**11**).⁴¹

Some genera of Lauraceae have had few reports regarding the occurrence of alkaloids in their species. For example in, *Sassafras albidum* root bark, structures common in Lauraceae, such as isoboldine (**10**), norboldine (**11**), boldine (**12**) and reticuline (**15**) have been described, as well as norcinnamolaurine (**107**) and cinnamolaurine (**142**).³⁸ Coclaurine (**55**), norcinnamolaurine (**107**) and corituberine (**227**) were isolated from the stems of *Mezilaurus synandra*.¹⁵¹ Le Quesne et al.¹⁵² obtained laurelliptine (**42**), an aporphine alkaloid, from the leaves and branches of *Nectandra rigida*. In *Ravensara aromatica* stem bark, the quaternary chloride base of N-methylisocorydine (**275**, **Fig. 33**) was observed.¹⁵³ From the ethanolic extract of *Pleurothyrium cinereum* leaves, the oxoaporphines thalicminine (**56**) and pleurotirine (**276**) were isolated.¹⁵⁴

A number of common Lauraceae alkaloids have been found in *Laurus nobilis*, such as (+)-actinodaphinine (**8**), (+)-boldine (**12**), (+)-reticuline (**15**), (+)-neolitsine (**26**), (+)-

isodomeesticine (**72**), (+)-cryptodorine (**100**), (+)-launobine (**149**), (+)-N-methylactinodaphnine (**218**), (+)-nandigerine (**229**), (+)-norisodomeesticine (**277**, **Fig. 34**) from the leaves; actinodaphnine (**8**), reticuline (**15**) and launobine (**149**) from the branches; and actinodaphnine (**8**), (+)-reticuline (**15**), (+)-launobine (**149**) and (+)-nandigerine (**229**) from the roots.¹⁹

Three related alkaloids were found in *Licaria arminiaca* stem bark, i.e. bracteoline (**278**, **Fig. 35**), O-methylbracteoline and α -dehydroreticuline (**279**); this was the first report of these structures in this genus.¹⁵⁵

3 Indole alkaloids

The indole substances reported in Lauraceae include cecilin (**280**, **Fig. 36**), a β -carboline alkaloid isolated from the trunk of *Aniba santalodora*¹⁵⁶ and triptophol-5-O- β -D-glycopyranoside (**281**), obtained from *Ocotea minarum* fruits.¹⁵⁷

In *L. petiolata*, two indole alkaloids were isolated from the bark, identified as aribine (= harmine) (**282**, **Fig. 37**) and norharmine (**283**).³⁶ Other β -carboline structures, i.e. the daibucarboline A (**284**), B (**285**) and C (**286**), were obtained from *Neolitsea daibuensis* roots. In the same study, moderate antiinflammatory activity of daibucarboline A (**284**) was observed due to the inhibition of nitrite-producing cell lines, with an IC₅₀ of 18.41 μ M.¹⁵⁸

4 Pyridine alkaloids

Pyridine type alkaloids have been observed in Lauraceae, but with less frequency, as well as some indole alkaloids. In *Aniba rosaeodora*, the presence of two tertiary structures, anibine (**287**, **Fig. 38**)¹⁵⁹ and duckein (**288**)¹⁶⁰ has been reported, both obtained from the stem. Anibine

(287) was also found in *Aniba fragrans* stems;¹⁶¹ this alkaloid was reported to possess analeptic activity.¹⁶²

5 Other classes of alkaloids

Besides isoquinoline, indole and pyridine alkaloids, the Lauraceae family also presents some other less common skeletons. Criptopleurine (289, Fig. 39), a phenanthroquinolizidine, was observed in *C. laevigata*, and showed good activity against human nasopharyngeal epidermoid carcinoma (KB) cells with an IC₅₀ of 5.10 mg/mL.¹⁶³ The indolizidine quaternary alkaloid anibamine, elucidated as 6,8-didec-(1*Z*)-eni-5,7-dimethyl-2,3-dihydro-1*H*-indolizidine (290), was obtained from *Aniba panurensis* as a salt of trifluoroacetic acid,¹⁶⁴ and from another *Aniba* species.¹⁶⁵

The dibenzopyrrolidine alkaloids cryptowoline (291, Fig. 40), O-methyl-cryptowoline (292), cryptowolinol (293) and cryptowolidine (294) were observed in *Cryptocarya phyllostemon* stem bark, while cryptaustoline (295) and cryptowolinol (293) were obtained from *Cryptocarya oubatchensis* stem bark and leaves.¹⁶⁶ In *Litsea cubeba*, two dibenzopyrrolidine structures, i.e. (-)-litcubine (296) and (-)-litcubinine (297) were isolated.¹⁶⁷

Andrianaivoravelona et al.¹⁶⁸ isolated a tryptamine-derived alkaloid in a methanolic extract from the stem bark of *Ravensara anisata*, *N*-(*p*-coumaroyl)-tryptamine (298, Fig. 41).

In *Aniba riparia*, the *N*-benzoyltyramines riparin I (299, Fig. 42), riparin II (300) and riparin III (301) were isolated.¹⁶⁹ Antimicrobial activity was reported for all three substances,¹⁷⁰ as well as antinociceptive activity for riparin I (299),¹⁷¹ anxiolytic activity for riparin II (300) and III (301), and antidepressant activity for riparin III (301), dependent on its interaction with

serotonergic, noradrenergic and dopaminergic systems.¹⁷²⁻¹⁷⁵ Castelo-Branco et al.¹⁷⁶ observed in pharmacological studies that the riparins I (**299**), II (**300**) and III (**301**) induced relaxation of contractions in guinea pig ileum and rat uterus produced by acetylcholine and histamine and oxytocin and bradykinin, respectively.

In study performed in *Machilus yaoshansis* stem bark, two triterpene glycosylated alkaloids were isolated, machilaminoside A (**302**, Fig. 43) and machilaminoside B (**303**), as new substances in this species.¹⁷⁷

The alkaloids receive great attention in research on natural products due to the variety of pharmacological activities that have, which makes them indispensable ingredients for new drugs.¹⁷⁸ However, obtaining these substances from their natural sources, it is often infeasible due to the low yields observed in extractions.¹⁷⁹ Even when it is possible to obtain them on a large scale from natural sources, high solvent consumption and time impracticable the process.¹⁷⁹ Thus the synthesis of alkaloids has been a promising alternative for obtaining, with several established routes, including procedures of metabolic engineering and biocatalysis.¹⁸⁰⁻¹⁸³

Among the alkaloids observed in Lauraceae family, some structures already have their synthesis described in the literature, such as actinodaphnine, boldine and isocorydine.¹⁸⁴⁻¹⁸⁶ Techniques employing microorganisms to obtain molecules of interest are also reported as obtaining the reticuline from simple carbon sources employing *Escherichia coli* and by fermentation of dopamine using *Saccharomyces cerevisiae*.¹⁸⁷⁻¹⁸⁹ Some of these alkaloids are still used in the semi-synthesis of more complex alkaloids like litebamine and glaucine from boldine.¹⁹⁰⁻¹⁹¹

The combined molecular modelling and synthesis is an important tool in achieving most active alkaloids and derivatives in bulk. Studies of isoquinoline alkaloids, often reported in

Lauraceae, showed that some structural characteristics favor the presence of pharmacological activity. Among them was observed that the replacement of hydroxyl by methoxyl groups, aromatization of the ring C in protoberberine alkaloids and the quaternary nitrogen contribute to the increase of antipoliiovirus, antiviral and acetylcholinesterase inhibitory activities of the alkaloids.¹⁹²⁻¹⁹³ Moreover, the presence of 1,2-methylenedioxy groups and substituted groups in nitrogen appear to contribute to the reduced of alkaloid activity.¹⁹²⁻¹⁹³

6 Conclusion

According to the data presented here, it can be seen that the Lauraceae family presents a great number of alkaloids with wide variety, with over 300 structures in 21 genera described in the literature. Isoquinoline alkaloids are reported as the major class with about 287 compounds, as well as seven indoles, seven dibenzopyrrolidines, three pyridines, three benzoyltyramines, two glycoside triterpene alkaloids, one phenanthroquinolizidine, one indolizidine and one tryptamine derivative. The isoquinoline alkaloids are present in all genera reported in this review, and represent the major class in Lauraceae. However, other classes are reported in this family, some of them with only a few structures restricted to a specific genus.

Concerning the indole alkaloids, one structure has been mentioned in *Aniba santalodora*, one in *Ocotea minarum*, two in *Litsea petiolata* and three in *Neolitsea daibuensis*. Another class present in Lauraceae is the pyridine alkaloids, represented by three structures restricted to *Aniba rosaeodora*. Among the dibenzopyrrolidines, five structures are present in *Cryptocarya oubatchensis* and *Cryptocarya phyllostemon* and two have been reported in *Litsea cubeba*. Other alkaloid classes are also present in Lauraceae, such as the N-benzoyltyramines riparins I, II and

III, observed in *Aniba riparia*, an indolizidine in *Aniba panurensis*, a quinolizidine in *Cryptocarya laevigata*, a tryptamine derivative in *Ravensara anisata* and two glycoside triterpene alkaloids in *Machilus yaoshansis*.

In order to evaluate a possible grouping taxonomic effect on the alkaloid composition, Hierarchical Cluster Analysis (HCA) was performed using R software, version 3.0.1. The alkaloid frequency was analysed in the species according to data in the literature. In the HCA analysis, classes were separated into two groups. The first group was formed by *Ocotea* grouping with the other genera that present major isoquinoline alkaloids, including *Cassytha*, *Lindera* and *Phoebe* (**Fig. 44**). These genera have only isoquinoline alkaloids of different subclasses, is soon expected to be grouped. The genus *Ocotea* is not in this group, but very close to it since this genus also presents an indole structure and several isoquinolines.

The second largest group is formed by the genera that present other classes besides isoquinolines in their composition, such as *Ravensara*, which presents a glycoside tryptamine derivative. *Litsea* and *Cryptocarya* are grouped together due to the presence of dibenzopyrrolidine structures found in both genera. *Aniba* and *Machilus* are grouped together due the presence of exclusive alkaloid classes in their composition, since *Aniba* presents pyridine and benzoyltyramine structures, and *Machilus* contains glycoside triterpene alkaloids.

The structures reported in this review predominantly belong to the isoquinoline class, which is composed of 287 structures distributed in all genera mentioned. The isoquinoline alkaloids were separated into subclasses with 148 aporphines, 47 benzyloisoquinolines, 23 pavines, 21 proaporphines, 21 bisbenzyloisoquinolines, 18 morphinandienones, five simple isoquinolines and four phenathrenes (**Fig. 45**). There are eight common isoquinoline structures, i.e. aporphine actinodaphnine (**8**), dicentrine (**9**), isoboldine (**10**), laurolitsine (norbaldine) (**11**),

boldine (**12**), laurotetanine (**13**), N-methylaurotetanine (**14**) and isocorydine (**16**), and one benzyloisoquinoline, reticuline (**15**), that are present in several species of Lauraceae (Fig. 2).

The genus *Ocotea* is the most studied, with 87 alkaloids described, including 86 isoquinolines and one indole. *Ocotea minarum* is the species with largest number of described isoquinoline structures, with 14 aporphine alkaloids. The *Ocotea* alkaloids are mostly aporphines, including 62 structures. Other genera rich in aporphine alkaloids are *Cassytha*, *Lindera*, *Litsea*, *Neolitsea* and *Phoebe* with 27, 22, 23 and 19 structures, respectively.

Another genus with many reported structures is *Cryptocarya*, with 68 alkaloids, including 62 isoquinolines, five dibenzopyrrolidines and one quinolizidine. *Cryptocarya chinensis* is the most studied species in this genus, with 39 structures described, among them 23 pavine skeletons, a subgroup of isoquinoline alkaloids almost restricted to the genus *Cryptocarya*. The pavine structure (-)-isocaryachine (**121**) has also been observed in *Beilschmiedia kunstleri*.

Benzyloisoquinoline alkaloids have been reported mainly in *Aniba* with 14 substances. This subclass is also present in *Cryptocarya* species with 15 alkaloids reported, while the proaporphines are mostly found in *Phoebe*, with 12 structures present in *Phoebe grandis* and *Phoebe scortechinii*. The morphidiane structures are observed in more quantity in *Ocotea* and *Dehaasia* with eight and five structures, respectively, while the bisbenzyloisoquinolines are described mainly in *Alseodaphne* and *Ocotea*, with seven structures in each genus. Small quantities of others isoquinoline subclasses have also been observed, among them four phenanthrenes, one in *Beilschmiedia*, one in *Litsea* and two in *Ocotea*. Simple isoquinolines have been detected in *Cryptocarya* and *Litsea* with four and one, respectively.

The pavine structures were observed in *Cryptocarya* and *Beilschmiedia*, while *Dehhasia* and *Alseodaphne* present bisbenzyloisoquinoline alkaloids in high proportions when compared

with the other genera that possess this type of alkaloid. The genera *Aniba*, *Machilus* and *Mezilaurus* contain a number of benzyloisoquinoline structures. On the other hand, the genus *Phoebe* presents a great quantity of proaporphine alkaloids. Other genera with small quantities of proaporphine alkaloids are *Ocotea*, *Neolitsea* and *Lindera* with one structure each, and *Cryptocarya*, with six proaporphine alkaloids.

The genera *Ravensara*, *Pleurothyrium* and *Nectandra* have few aporphine alkaloids, while *Cassytha* and *Laurus* have mainly aporphines and a few structures belonging to the morphinandienone and benzyloisoquinoline subclasses.

There are some genera with few alkaloids described, such as *Cinnamomum*, *Mezilaurus*, *Nectandra*, *Pleurothyrium* and *Ravensara*, which have one to three alkaloids each. Perhaps these genera do not possess the biosynthetic routes to alkaloids in their secondary metabolism, or are just less studied than other genera.

Some of these substances have restricted distribution, showing the possibility of their use as chemical markers, and thereby may play an important role in chemotaxonomy. Pharmacological properties have been observed, such as the cytotoxicity of actinodaphnine (**8**), dicentrine (**9**) and boldine (**12**) and the antiinflammatory effect of the latter, in addition to the potent central nervous system depressant effect observed for reticuline (**15**).

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Fig. 1. Classes of Lauraceae alkaloids.

Fig. 2. *Ocotea* isoquinoline alkaloids.

Fig. 3. *Ocotea* isoquinoline alkaloids.

Fig. 4. *Ocotea* isoquinoline alkaloids.

Fig. 5. *Ocotea* isoquinoline alkaloids.

Fig. 6. *Ocotea* isoquinoline alkaloids.

Fig. 7. *Ocotea* isoquinoline alkaloids.

Fig. 8. *Ocotea* isoquinoline alkaloids.

Fig. 9. *Ocotea* isoquinoline alkaloids.

Fig. 10. *Ocotea* isoquinoline alkaloids.

Fig. 11. *Ocotea* isoquinoline alkaloids.

- Fig. 12.** *Cryptocarya* isoquinoline alkaloids.
- Fig. 13.** *Cryptocarya* isoquinoline alkaloids.
- Fig. 14.** *Cryptocarya* isoquinoline alkaloids.
- Fig. 15.** *Cryptocarya* isoquinoline alkaloids.
- Fig. 16.** *Cryptocarya* isoquinoline alkaloids.
- Fig. 17.** *Cassytha* isoquinoline alkaloids.
- Fig. 18.** *Cassytha* isoquinoline alkaloids.
- Fig. 19.** *Aniba* isoquinoline alkaloids.
- Fig. 20.** *Lindera* isoquinoline alkaloids.
- Fig. 21.** *Lindera* isoquinoline alkaloids.
- Fig. 22.** *Litsea* isoquinoline alkaloids.
- Fig. 23.** *Litsea* isoquinoline alkaloids.
- Fig. 24.** *Neolitsea* isoquinoline alkaloids.
- Fig. 25.** *Phoebe* isoquinoline alkaloids.
- Fig. 26.** *Phoebe* isoquinoline alkaloids.
- Fig. 27.** *Dehaasia* isoquinoline alkaloids.
- Fig. 28.** *Actinodaphne* isoquinoline alkaloids.
- Fig. 29.** *Beilschmiedia* isoquinoline alkaloids.
- Fig. 30.** *Machilus* isoquinoline alkaloids.
- Fig. 31.** *Alseodaphne* isoquinoline alkaloids.
- Fig. 32.** *Alseodaphne* isoquinoline alkaloids.
- Fig. 33.** *Ravensara* isoquinoline alkaloids.
- Fig. 34.** *Laurus* isoquinoline alkaloids.
- Fig. 35.** *Licaria* isoquinoline alkaloids.
- Fig. 36.** *Aniba* and *Ocotea* indole alkaloids.
- Fig. 37.** *Litsea* and *Neolitsea* indole alkaloids.
- Fig. 38.** *Aniba* pyridine alkaloids.

Fig. 39. *Cryptocarya* phenanthroquinolizidine and *Litsea* indolizidine alkaloids.

Fig. 40. *Cryptocarya* and *Litsea* dibenzopyrrolidine alkaloids.

Fig. 41. *Ravensara* tryptamine-derived alkaloid.

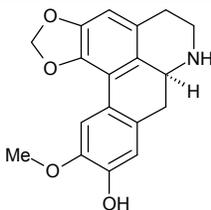
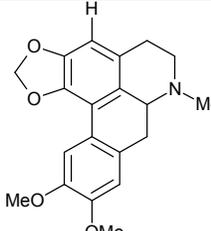
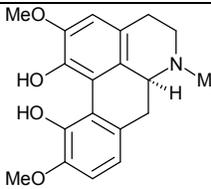
Fig. 42. *Aniba* N-benzoyltyramines alkaloids.

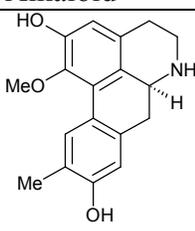
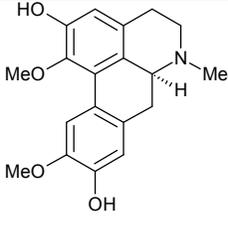
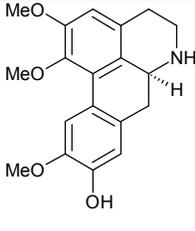
Fig. 43. *Machilus* triterpene glycosylated alkaloids.

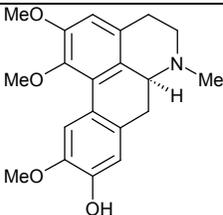
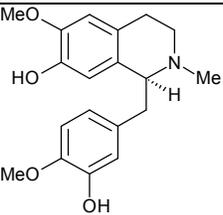
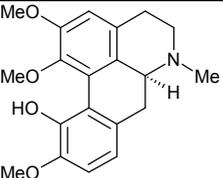
Fig. 44. HCA analysis of Lauraceae alkaloid classes.

Fig. 45. Isoquinoline groups of alkaloids present in Lauraceae genera.

Table 1: Distribution of the most common isoquinoline alkaloids from Lauraceae.

| Alkaloid | Genus | Species | Part of the plant | Reference |
|---|-------------------------|-------------------------|----------------------|-----------|
|  <p>actinodaphnine (8)</p> | <i>Actinodaphne</i> | <i>obovata</i> | leaves and branches | 13 |
| | <i>Cassytha</i> | <i>filiformis</i> | aerial part | 14 |
| | | | 15 | |
| | | | 16 | |
| | | | 17 | |
| | <i>Cinnamomum</i> | <i>insularimontanum</i> | roots | 18 |
| | <i>Laurus</i> | <i>nobilis</i> | aerial part and root | 19 |
| | <i>Litsea</i> | <i>sebifera</i> | leaves and branches | 13 |
| <i>laurifolia</i> | | leaves | 20 | |
| <i>Neolitsea</i> | <i>sericea</i> | leaves and stem bark | 21 | |
| | | 22 | | |
| | <i>acuminatissima</i> | stem bark | 23 | |
|  <p>dicentrine (9)</p> | <i>Actinodaphne</i> | <i>sesquipedalis</i> | stem bark | 24 |
| | <i>Cassytha</i> | <i>filiformis</i> | aerial part | 14 |
| | | | 16 | |
| | 17 | | | |
| | <i>Lindera</i> | <i>megaphylla</i> | roots | 25 |
| | <i>Ocotea</i> | <i>brachybotra</i> | leaves | 26 |
| | | <i>macropoda</i> | | 14 |
| | | <i>minarum</i> | leaves | 27 |
| | | <i>macrophylla</i> | leaves | 28 |
| | | <i>puberula</i> | leaves | 29 |
| fruits | | | 30 | |
| <i>vellosiana</i> | stem, leaves and fruits | 31 | | |
|  <p>isoboldine (10)</p> | <i>Aniba</i> | <i>muca</i> | stem bark | 32 |
| | <i>Cassytha</i> | <i>filiformis</i> | aerial part | 15 |
| | | <i>pubescens</i> | | 33 |
| | <i>Cryptocarya</i> | <i>chinensis</i> | leaves | 34 |
| | <i>Lindera</i> | <i>angustifolia</i> | roots | 35 |
| | <i>Litsea</i> | <i>petiolata</i> | stem bark | 36 |
| | <i>Neolitsea</i> | <i>acuminatissima</i> | stem bark | 23 |
| | <i>Ocotea</i> | <i>caesia</i> | stem | 37 |
| | <i>Sassafras</i> | <i>albidum</i> | root bark | 38 |

| Alkaloid | Genus | Species | Part of the plant | Reference |
|---|----------------------|-----------------------|----------------------|-----------|
|  <p>lauroilsine (11)</p> | <i>Actinodaphne</i> | <i>nitida</i> | leaves | 39 |
| | | <i>pruinosa</i> | stem bark | 40 |
| | <i>Alseodaphne</i> | <i>perakensis</i> | stem bark | 41 |
| | <i>Cinnamomum</i> | <i>camphora</i> | roots | 42 |
| | <i>Lindera</i> | <i>aggregata</i> | roots | 43 |
| | | <i>angustifolia</i> | roots | 35 |
| | | <i>chunii</i> | roots | 44 |
| | <i>Litsea</i> | <i>laurifolia</i> | stem bark | 20 |
| | | <i>wightiana</i> | stem bark | 13 |
| | | <i>leefeana</i> | leaves | 45 |
| | <i>Neolitsea</i> | <i>acuminatissima</i> | stem bark | 23 |
| | | <i>sericea</i> | stem bark and leaves | 22 |
| | | | | 21 |
| | <i>Phoebe</i> | <i>chinensis</i> | stem bark | 46 |
| | | <i>formosana</i> | stem bark | 47 |
| | <i>grandis</i> | stem bark | 48 | |
| | <i>scortechinii</i> | stem bark | 49 | |
| <i>Sassafras</i> | <i>albidum</i> | root bark | 38 | |
|  <p>boldine (12)</p> | <i>Actinodaphne</i> | <i>nitida</i> | stem bark | 39 |
| | | <i>pruinosa</i> | stem bark | 40 |
| | <i>Beilschmiedia</i> | <i>kunstleri</i> | stem bark | 50 |
| | <i>Laurus</i> | <i>nobilis</i> | leaves | 19 |
| | <i>Lindera</i> | <i>aggregata</i> | roots | 43 |
| | | <i>angustifolia</i> | roots | 35 |
| | <i>Litsea</i> | <i>leefeana</i> | leaves | 45 |
| | | <i>sebifera</i> | leaves and branches | 13 |
| | | <i>wightiana</i> | stem bark | 13 |
| | <i>Neolitsea</i> | <i>acuminatissima</i> | stem bark | 23 |
| | | <i>sericea</i> | stem bark and leaves | 22 |
| | | | | 21 |
| | <i>Ocotea</i> | <i>puberula</i> | leaves | 29 |
| | <i>Phoebe</i> | <i>grandis</i> | stem bark | 48 |
| | <i>Sassafras</i> | <i>albidum</i> | root bark | 38 |
|  <p>laurotetanine (13)</p> | <i>Actinodaphne</i> | <i>obovata</i> | leaves and branches | 13 |
| | <i>Beilschmiedia</i> | <i>kunstleri</i> | stem bark | 50 |
| | <i>Cryptocarya</i> | <i>odorata</i> | stem bark | 51 |
| | <i>Lindera</i> | <i>angustifolia</i> | roots | 35 |
| | | <i>benzoin</i> | branches | 52 |
| | <i>Litsea</i> | <i>cubeba</i> | stem bark | 53 |
| | | <i>sebifera</i> | leaves and branches | 13 |
| | <i>Neolitsea</i> | <i>sericea</i> | stem bark and leaves | 22 |
| | | | | 21 |
| | <i>Phoebe</i> | <i>chinensis</i> | stem bark | 46 |
| | <i>grandis</i> | stem bark | 48 | |

| Alkaloid | Genus | Species | Part of the plant | Reference |
|---|---------------------|-----------------------|-----------------------|-----------|
|  <p>N-methyllaurotetanine (14)</p> | <i>Actinodaphne</i> | <i>obovata</i> | leaves and branches | 13 |
| | <i>Alseodaphne</i> | <i>perakensis</i> | stem bark | 41 |
| | <i>Cryptocarya</i> | <i>odorata</i> | stem bark | 51 |
| | <i>Lindera</i> | <i>angustifolia</i> | roots | 35 |
| | | <i>pipericarpa</i> | stem bark | 54 |
| | <i>Litsea</i> | <i>cubeba</i> | | 55 |
| | | <i>cubeba</i> | stem bark | 53 |
| | | <i>sebifera</i> | leaves and branches | 13 |
| <i>Neolitsea</i> | <i>sericea</i> | stem bark and leaves | 22 | |
| | | 21 | | |
|  <p>reticuline (15)</p> | <i>Aniba</i> | <i>muca</i> | stem bark | 32 |
| | | <i>rosaeodora</i> | stem | 56 |
| | <i>Cinnamomum</i> | <i>camphora</i> | roots | 42 |
| | <i>Cryptocarya</i> | <i>odorata</i> | stem bark | 51 |
| | <i>Laurus</i> | <i>nobilis</i> | roots and aerial part | 19 |
| | <i>Lindera</i> | <i>aggregata</i> | roots | 43 |
| | <i>Litsea</i> | <i>laurifolia</i> | leaves | 20 |
| | | <i>leefeana</i> | leaves | 45 |
| | | <i>petiolata</i> | stem bark | 36 |
| | <i>Neolitsea</i> | <i>acuminatissima</i> | stem bark | 23 |
| | | <i>sericea</i> | leaves | 22 |
| | <i>Ocotea</i> | <i>duckei</i> | stem bark and leaves | 57, 58 |
| | | <i>vellosiana</i> | fruits | 31 |
| | <i>Phoebe</i> | <i>pittieri</i> | stem bark | 59 |
| <i>Sassafras</i> | <i>albidum</i> | root bark | 38 | |
|  <p>isocorydine (16)</p> | <i>Cryptocarya</i> | <i>odorata</i> | stem bark | 51 |
| | <i>Dehaasia</i> | <i>triandra</i> | leaves | 60 |
| | <i>Lindera</i> | <i>pipericarpa</i> | stem bark | 54 |
| | <i>Litsea</i> | <i>cubeba</i> | stem bark | 53 |
| | <i>Ocotea</i> | <i>macrophylla</i> | stem | 61 |
| | <i>Ocotea</i> | <i>vellosiana</i> | fruits | 31 |

Valdir Florencio Veiga Junior completed masters and PhD degrees in Natural Products Chemistry at Rio de Janeiro Federal University (UFRJ), Brazil, in 2004 under the supervision of Professor Angelo Pinto. He is currently associate professor of Biological Chemistry at the Amazonas Federal University (UFAM) and his research is focused on understanding the Chemiodiversity produced by Lauraceae, Burseraceae and Fabaceae botanical families. He is the leader of Q-BiomA, a research group on Chemistry of Amazonian Biomolecules.

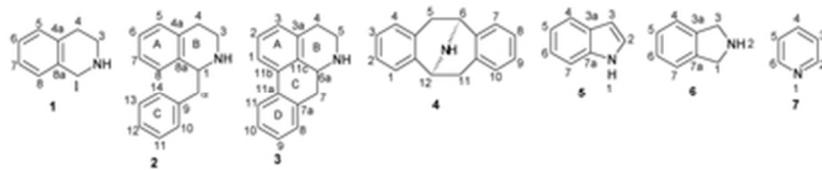


Valdir Veiga Picture
66x100mm (96 x 96 DPI)

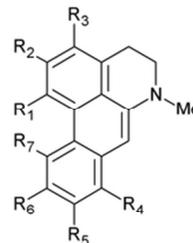
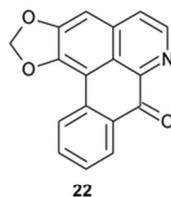
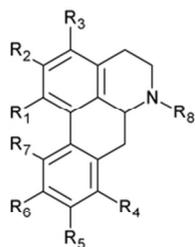
Dayana Lacerda Custódio obtained her BSc degree in Biological Sciences in 2006 from Universidade Estadual de Londrina, Brazil. In 2013 she received her PhD degree in Biotechnology, with the alkaloids from *Aniba rosaeodora* essential oil extraction byproducts at the Universidade Federal do Amazonas. Actually she is a visiting researcher with fellowship from Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro at the Instituto Politécnico of Universidade do Estado do Rio de Janeiro.



Dayana Custodio picture
225x300mm (300 x 300 DPI)



35x7mm (300 x 300 DPI)



17: R₁=R₅=R₆=OCH₃; R₂=OH; R₃=R₄=R₇=H; R₈=CH₃

20: R₁+R₂=OCH₂O; R₃=R₄=R₇=H; R₅=R₆=OCH₃

18: R₁+R₂=OCH₂O; R₃=R₇=H; R₄=R₅=R₆=OCH₃; R₈=CH₃

21: R₁+R₂=OCH₂O; R₃=R₇=H; R₄=R₅=R₆=OCH₃

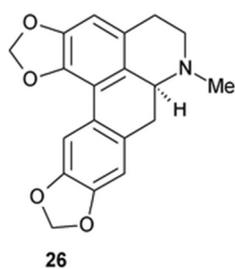
19: R₁+R₂=OCH₂O; R₃=R₄=R₇=R₈=H; R₅=R₆=OCH₃

25: R₁+R₂=OCH₃; R₃=R₄=R₇=H; R₅+R₆=OCH₂O

23: R₁=R₂=OCH₃; R₃=R₄=R₇=H; R₅+R₆=OCH₂O; R₈=CH₃

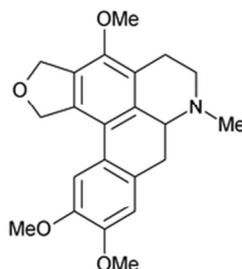
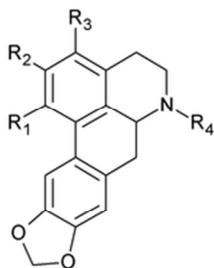
24: R₁=R₂=R₅=R₆=OCH₃; R₃=R₄=R₇=H; R₈=CH₃

71x37mm (300 x 300 DPI)

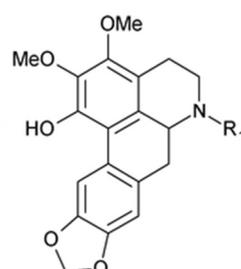


27: $R_1=R_2=OCH_3$; $R_4=COCH_3$

28: $R_1+R_2=OCH_2O$; $R_3=OCH_3$; $R_4=H$



29



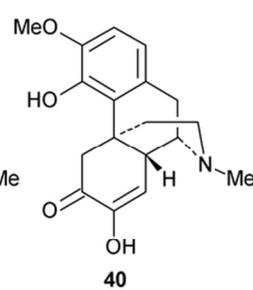
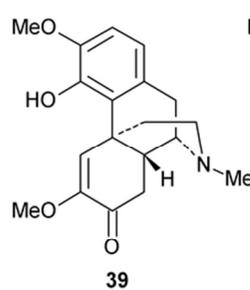
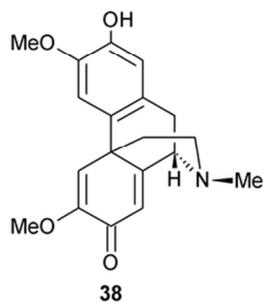
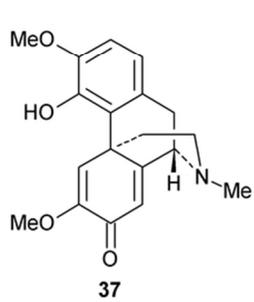
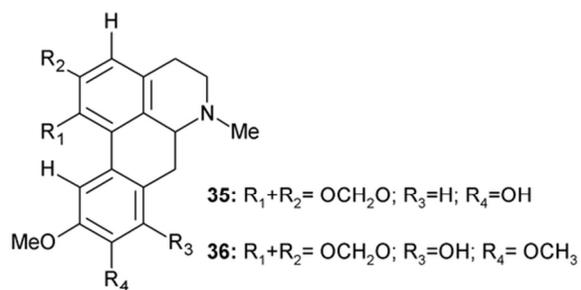
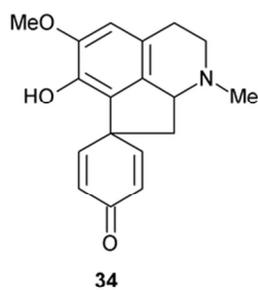
30: $R_1=H$

31: $R_1=COOCH_2CH_3$

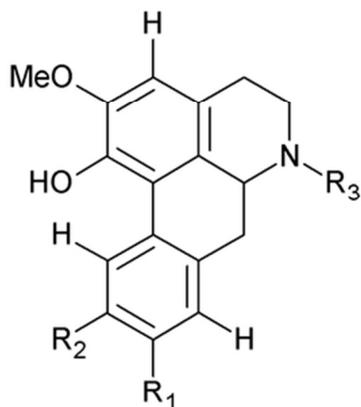
32: $R_1=COH$

33: $R_1=COOCH_3$

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75x49mm (300 x 300 DPI)

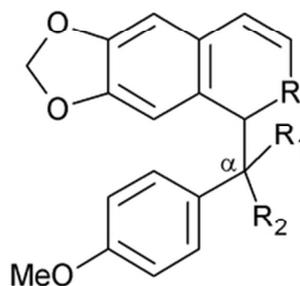


41: $R_1=R_3=H$; $R_2=OCH_3$

42: $R_1=OH$; $R_2=OCH_3$; $R_3=H$

43: $R_1=H$; $R_2=OCH_3$; $R_3=CH_3$

44: $R_1=OCH_3$; $R_2=R_3=H$



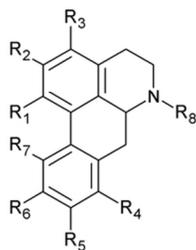
45: $R_1=O$; $R_2=O$, $\Delta 1,2$; $R=N$

46: $R_1=H$; $R_2=OH$, $\Delta 1,2$; $R=N$

47: $R_1=R_2=OH$; $R=NH$

48: $R_1=H$; $R_2=OH$; $R=NH$

62x47mm (300 x 300 DPI)



49: $R_1+R_2=OCH_2O$; $R_3=R_5=R_6=OCH_3$; $R_4=R_7=H$; $R_8=CH_3$

50: $R_1+R_2=OCH_2O$; $R_3=R_5=R_6=OCH_3$; $R_4=R_7=H$; $R_8=H$

51: $R_1+R_2=OCH_2O$; $R_3=R_4=R_5=R_6=OCH_3$; $R_7=H$; $R_8=CH_3$

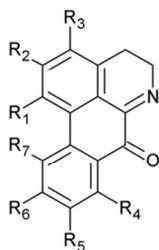
52: $R_1+R_2=OCH_2O$; $R_3=R_5=OCH_3$; $R_4=OCH_2O$; $R_6=H$; $R_7=CH_3$

53: $R_1+R_2=OCH_2O$; $R_3=R_6=H$; $R_4=OCH_2O$; $R_5=OCH_3$; $R_7=CH_3$

54: $R_1=OH$; $R_2=R_6=R_7=OCH_3$; $R_3=R_4=R_5=H$; $R_8=CH_3$

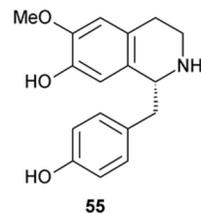
57: $R_1+R_2=OCH_2O$; $R_3=R_4=R_5=R_6=OCH_3$; $R_7=R_8=H$

58: $R_1=OH$; $R_2=R_3=R_6=R_7=OCH_3$; $R_4=R_5=H$; $R_8=CH_3$

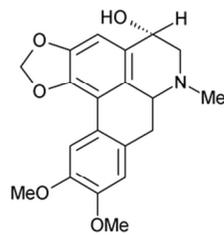


56: $R_1+R_2=OCH_2O$; $R_3=R_5=R_6=OCH_3$; $R_4=R_7=H$

60: $R_1+R_2=OCH_2O$; $R_3=R_4=R_5=R_6=OCH_3$; $R_7=H$

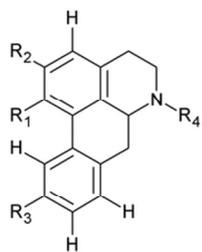


55



59

88x58mm (300 x 300 DPI)

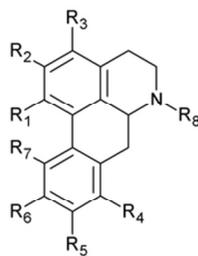


61: $R_1=\text{OCH}_3$; $R_2=\text{OH}$; $R_3=R_4=\text{H}$

62: $R_1=\text{OH}$; $R_2=\text{OCH}_3$; $R_3=R_4=\text{H}$

63: $R_1=\text{OH}$; $R_2=\text{OCH}_3$; $R_3=\text{H}$; $R_4=\text{CH}_3$

64: $R_1=R_3=\text{OH}$; $R_2=\text{OCH}_3$; $R_4=\text{CH}_3$



65: $R_1=\text{OH}$; $R_2=\text{OCH}_3$; $R_3=R_4=R_5=R_7=\text{H}$; $R_6=\text{N}(\text{CH}_2\text{Ph})_2$; $R_8=\text{CH}_3$

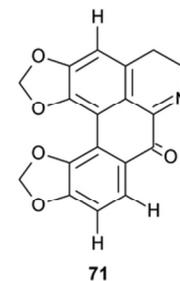
66: $R_1=\text{OH}$; $R_2=\text{OCH}_3$; $R_3=R_4=R_7=R_8=\text{H}$; $R_5+R_6=\text{OCH}_2\text{O}$

67: $R_1=\text{OH}$; $R_2=R_5=R_6=\text{OCH}_3$; $R_3=R_4=R_7=\text{H}$; $R_8=\text{CH}_3$

68: $R_1=R_2=R_3=R_6=\text{OCH}_3$; $R_4=R_5=\text{H}$; $R_7=\text{OH}$; $R_8=\text{CH}_3$

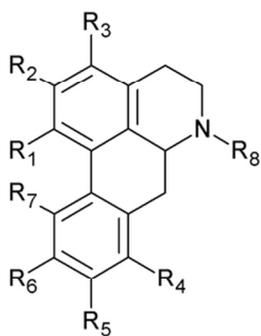
69: $R_1=R_6=\text{OCH}_3$; $R_2+R_3=\text{OCH}_2\text{O}$; $R_4=R_5=\text{H}$; $R_7=\text{OH}$; $R_8=\text{CH}_3$

70: $R_1+R_2=\text{OCH}_2\text{O}$; $R_3=R_5=R_6=\text{OCH}_3$; $R_4=\text{OH}$; $R_7=\text{H}$; $R_8=\text{CH}_3$



71

77x45mm (300 x 300 DPI)



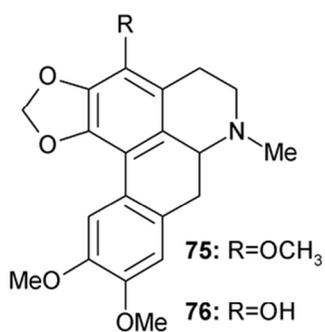
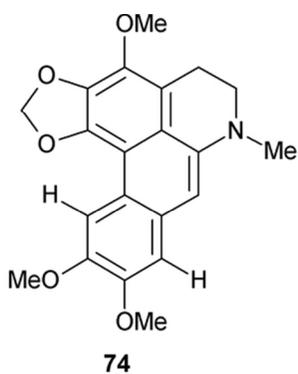
72: R₁=OCH₃; R₂=OH; R₃=R₄=R₇=H; R₅+R₆=OCH₂O; R₈=CH₃

73: R₁+R₂=OCH₂O; R₃=R₇=H; R₄=R₅+R₆=OCH₃=R₈=NOCH₃

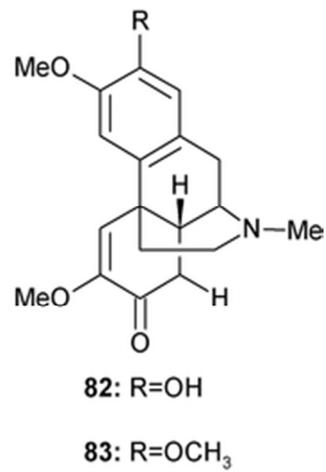
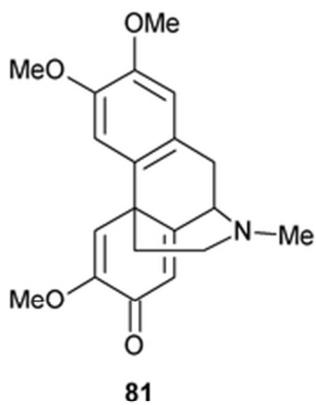
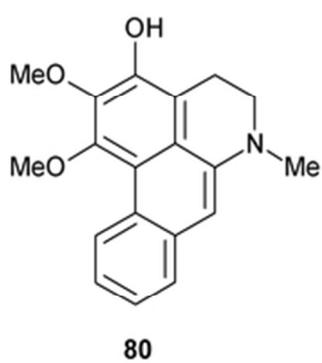
77: R₁=R₂=R₆=R₇=OCH₃; R₃=R₄=R₅=H; R₈=CH₃

78: R₁=R₂=OCH₃; R₃=H; R₄=R₅=R₆=R₇=H; R₈=CH₃

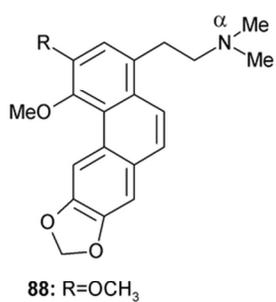
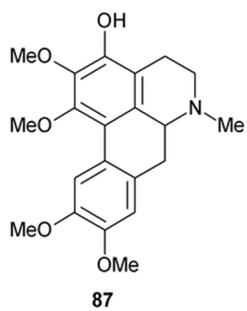
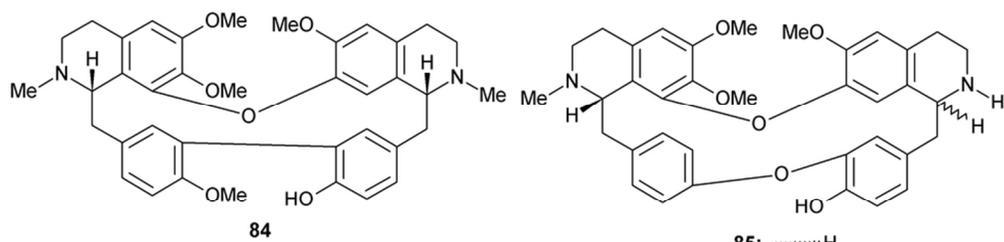
79: R₁=R₂=R₃=OCH₃; R₄=R₅=R₆=R₇=H; R₈=CH₃



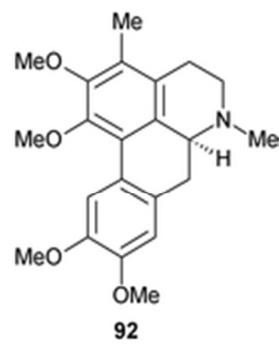
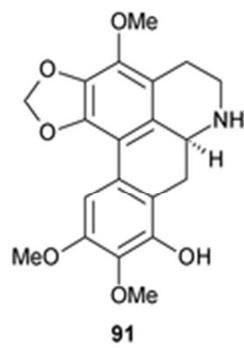
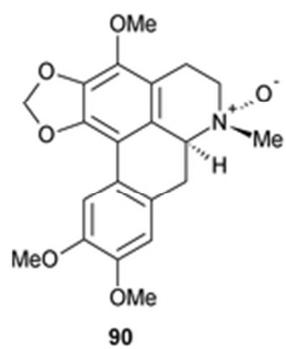
79x62mm (300 x 300 DPI)



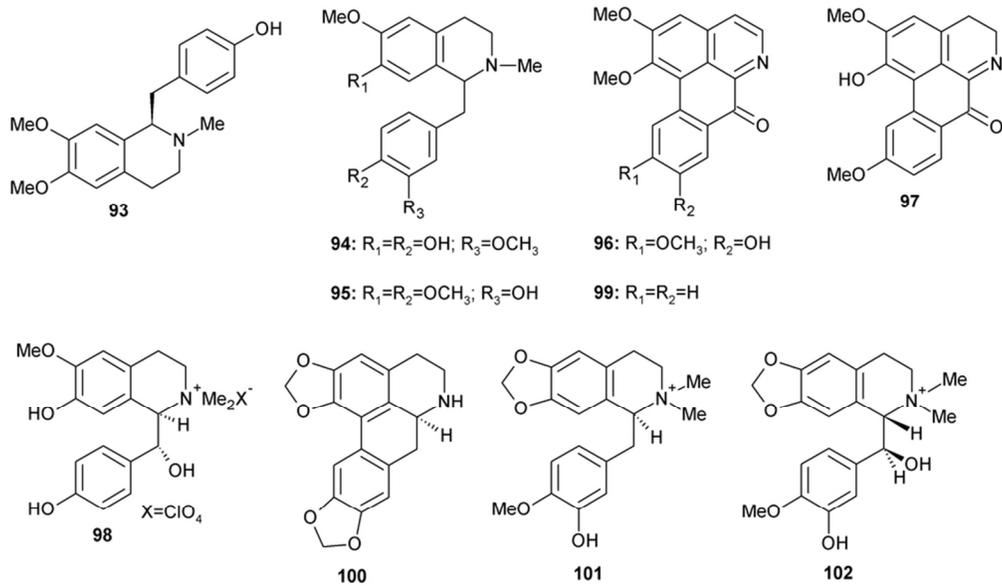
46x23mm (300 x 300 DPI)



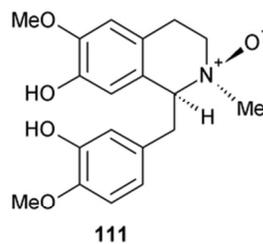
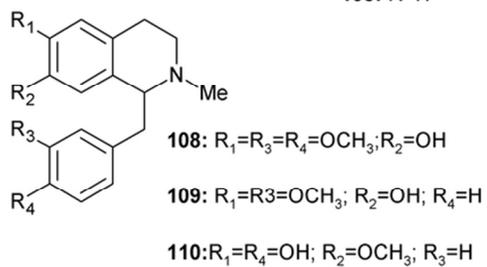
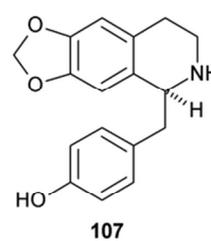
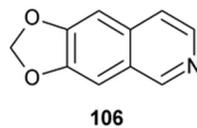
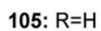
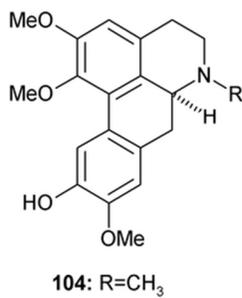
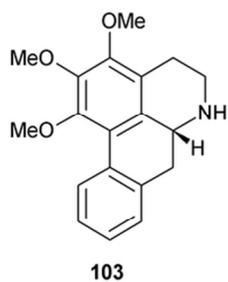
82x55mm (300 x 300 DPI)



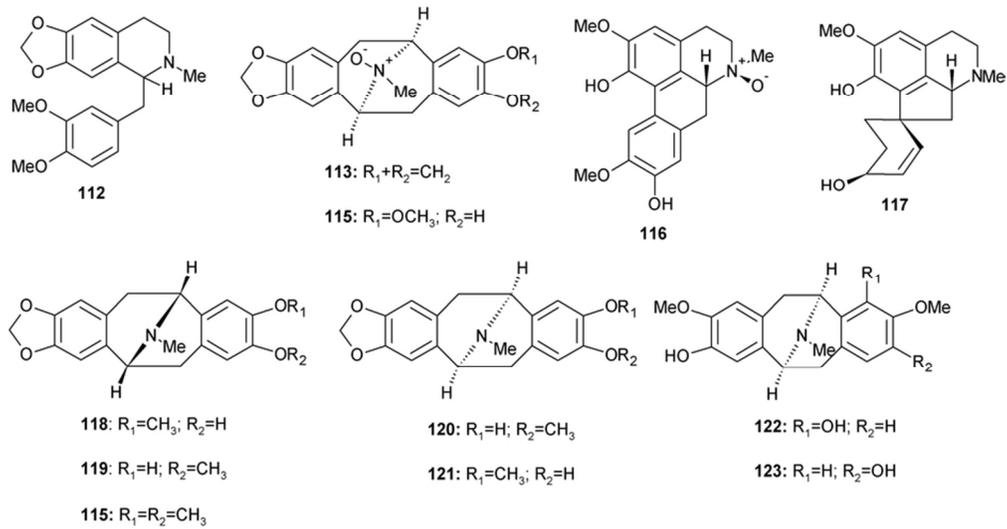
40x15mm (300 x 300 DPI)



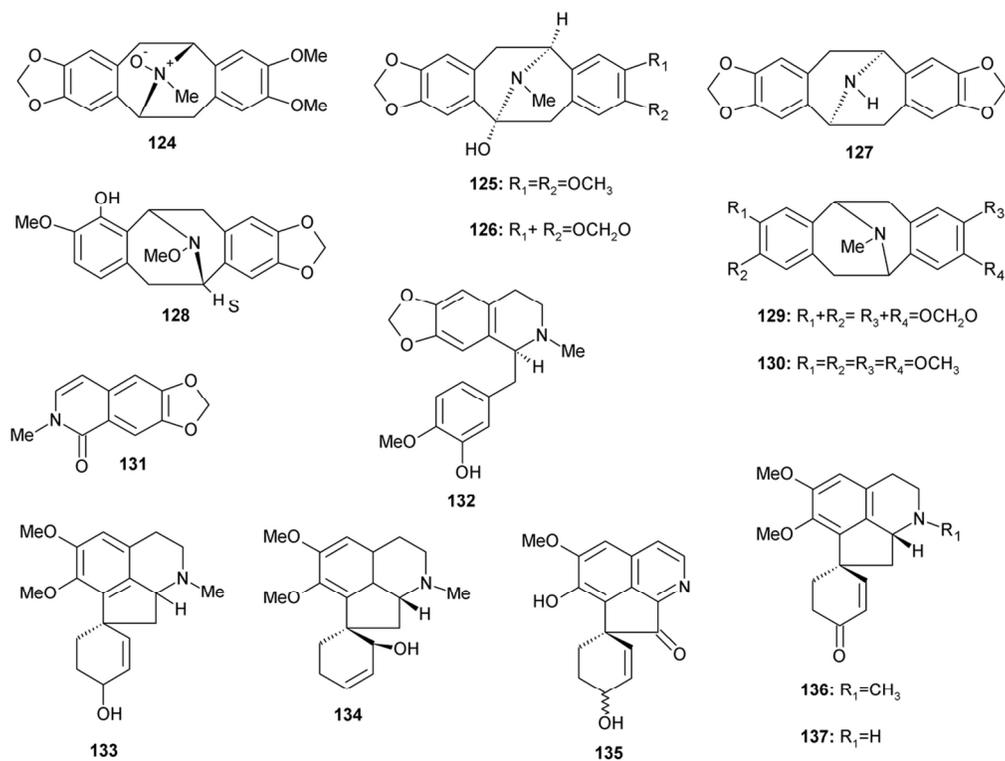
82x49mm (300 x 300 DPI)



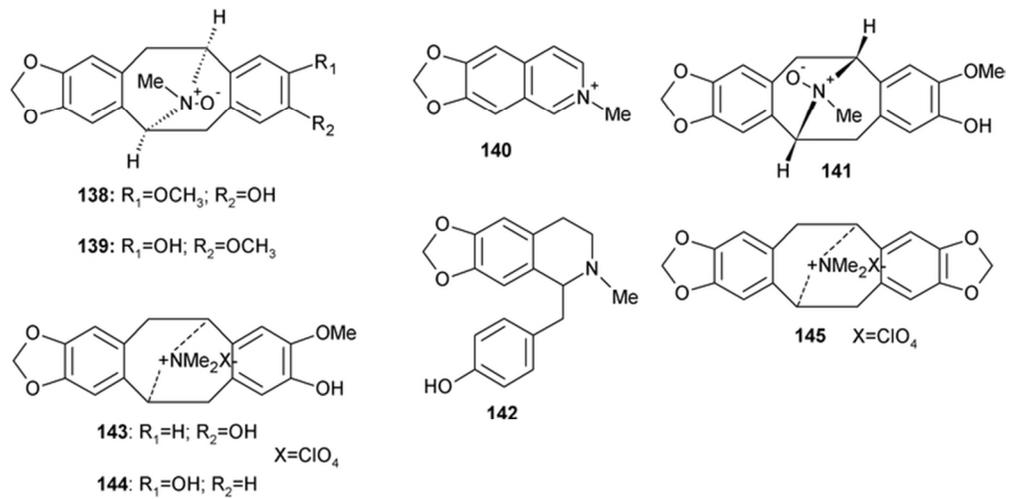
74x46mm (300 x 300 DPI)



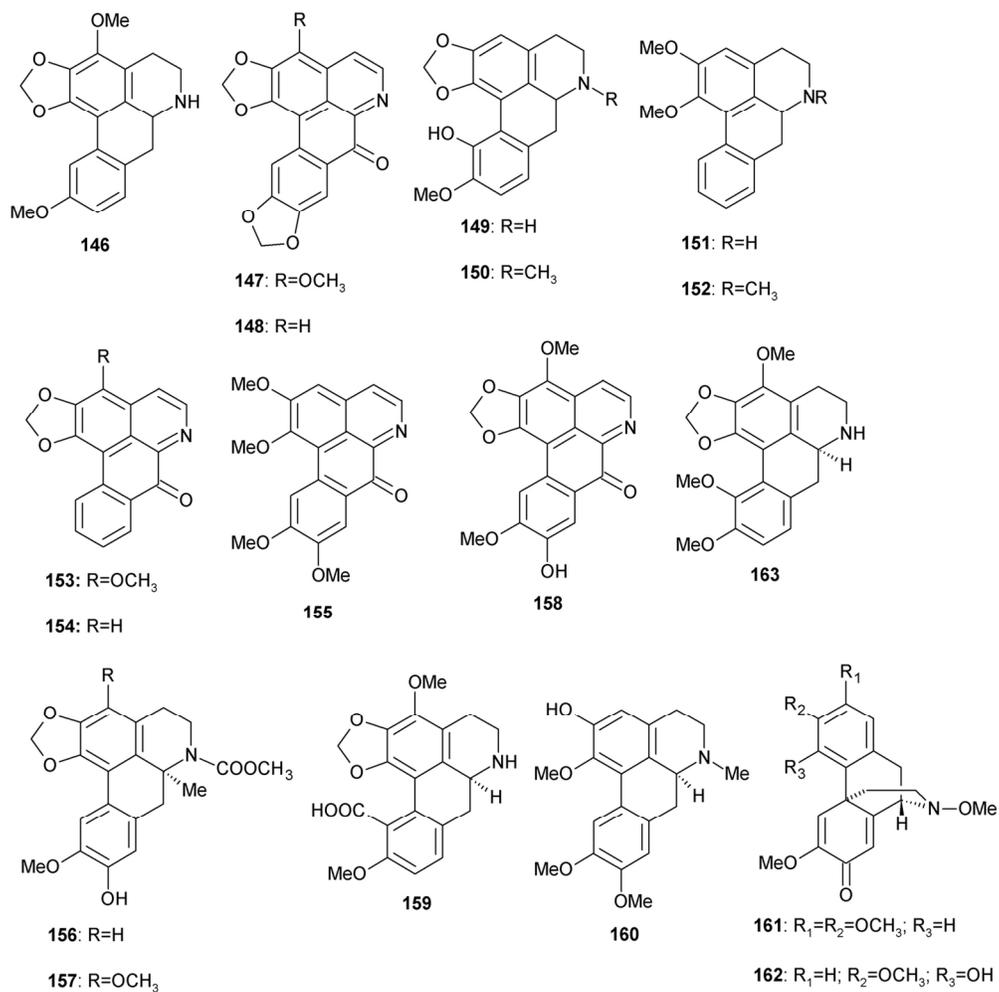
79x43mm (300 x 300 DPI)



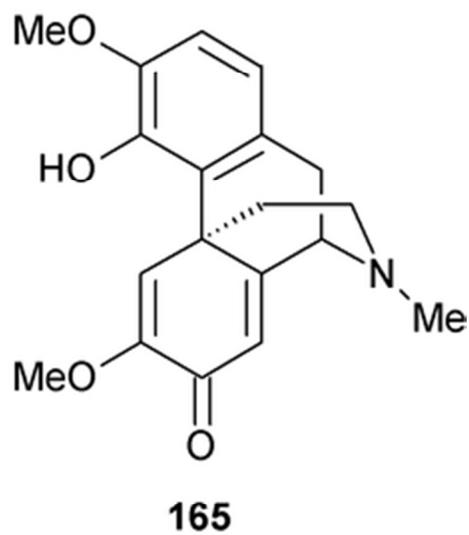
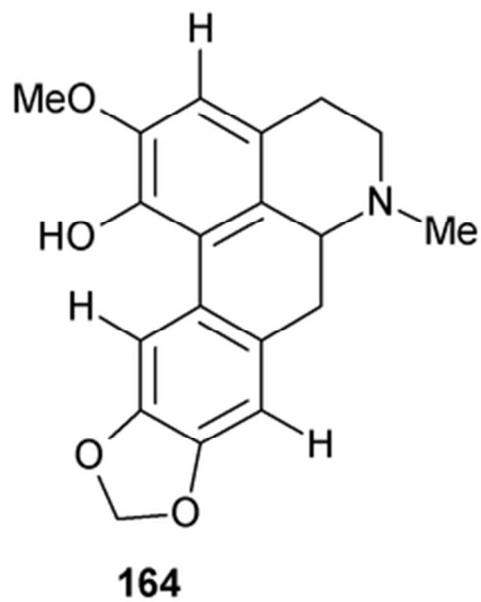
109x85mm (300 x 300 DPI)



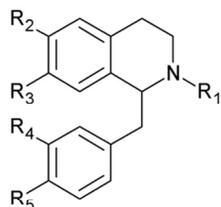
65x34mm (300 x 300 DPI)



136x137mm (300 x 300 DPI)



40x27mm (300 x 300 DPI)

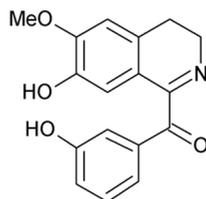


166: $R_1=R_5=H$; $R_2=R_3=OCH_3$; $R_4=OH$ 1R

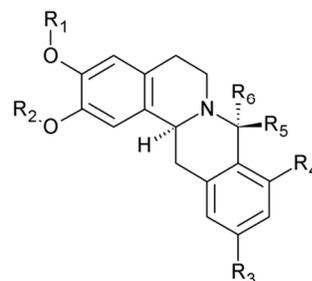
167: $R_1=R_3=R_5=H$; $R_2=OCH_3$; $R_4=OH$ 1S

168: $R_1=CH_3$; $R_2=OCH_3$; $R_3=R_4=OH$; $R_5=H$ 1S

169: $R_1=R_5=H$; $R_2=R_3=R_4=OH$



170



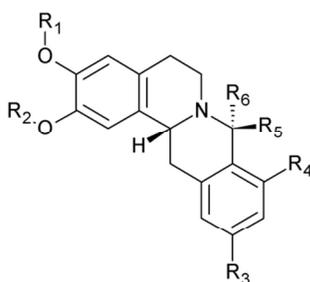
171: $R_1=CH_3$; $R_2=R_3=R_5=R_6=H$; $R_4=OH$

173: $R_1=CH_3$; $R_2=R_4=R_5=R_6=H$; $R_3=OH$

175: $R_1=R_6=CH_3$; $R_2=R_4=R_5=H$; $R_3=OH$

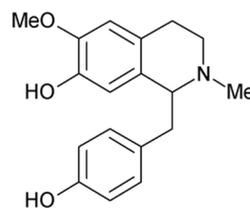
176: $R_1=R_5=CH_3$; $R_2=R_6=R_4=H$; $R_3=OH$

177: $R_1=R_6=CH_3$; $R_2=R_3=R_5=H$; $R_4=OH$



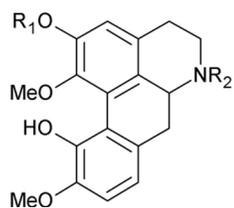
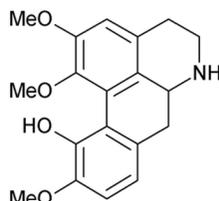
172: $R_1=R_2=CH_3$; $R_3=R_5=R_6=H$; $R_4=OH$

174: $R_1=R_2=CH_3$; $R_6=R_5=R_4=H$; $R_3=OH$

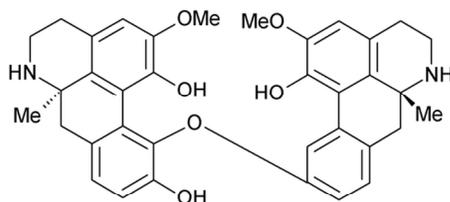


178

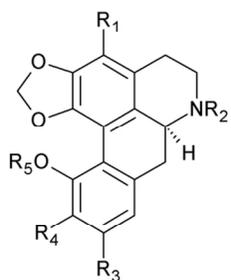
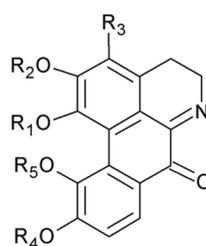
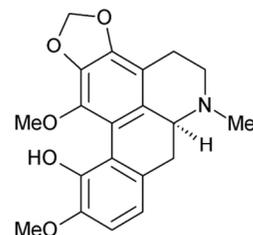
104x91mm (300 x 300 DPI)

179: $R_1=R_2=H$ 180: $R_1=H$; $R_2=CH_3$ 

181

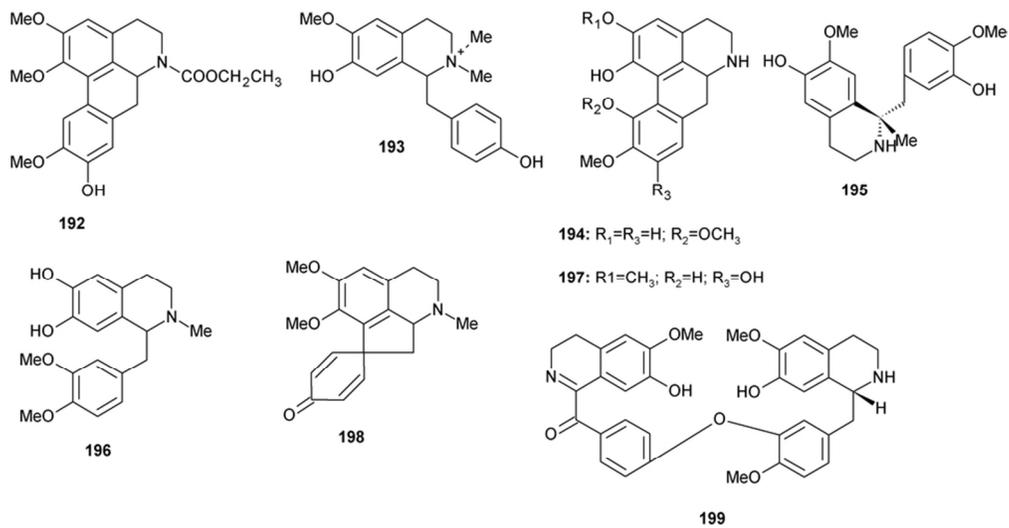


182

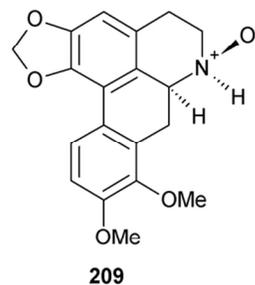
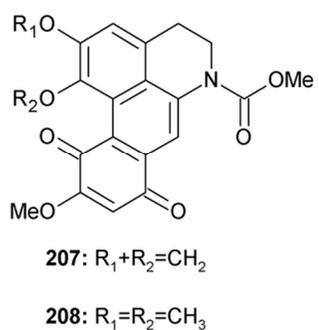
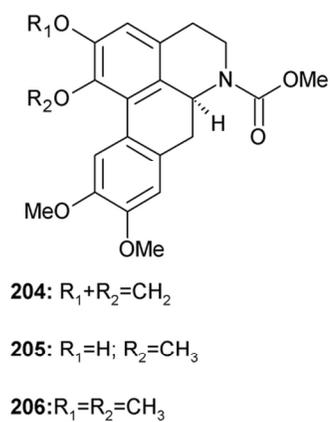
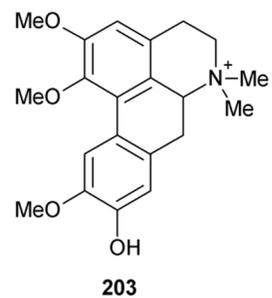
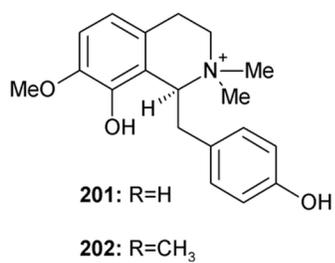
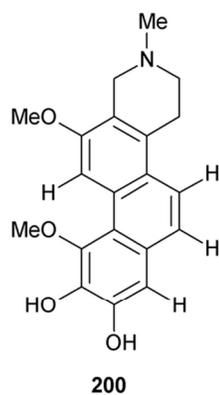
183: $R_1=OCH_3$; $R_2=R_3=H$; $R_4=OH$; $R_5=CH_3$ 184: $R_1=R_2=R_3=H$; $R_4=OH$; $R_5=CH_3$ 185: $R_1=R_3=H$; $R_2=R_5=CH_3$; $R_4=OH$ 190: $R_1=R_2=H$; $R_3+R_4=OCH_2O$; $R_5=H$ 187: $R_1+R_2=R_4+R_5=CH_2$; $R_3=H$ 188: $R_1+R_2=CH_2$; $R_3=R_4=H$; $R_5=CH_3$ 189: $R_1+R_2=CH_2$; $R_3=OCH_3$; $R_4=H$; $R_5=CH_3$ 191: $R_1=R_2=R_5=CH_3$; $R_3=R_4=H$ 

186

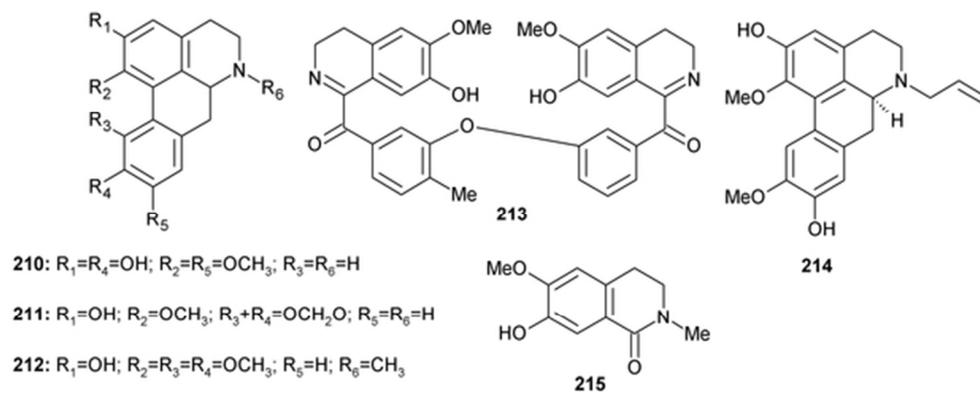
107x95mm (300 x 300 DPI)



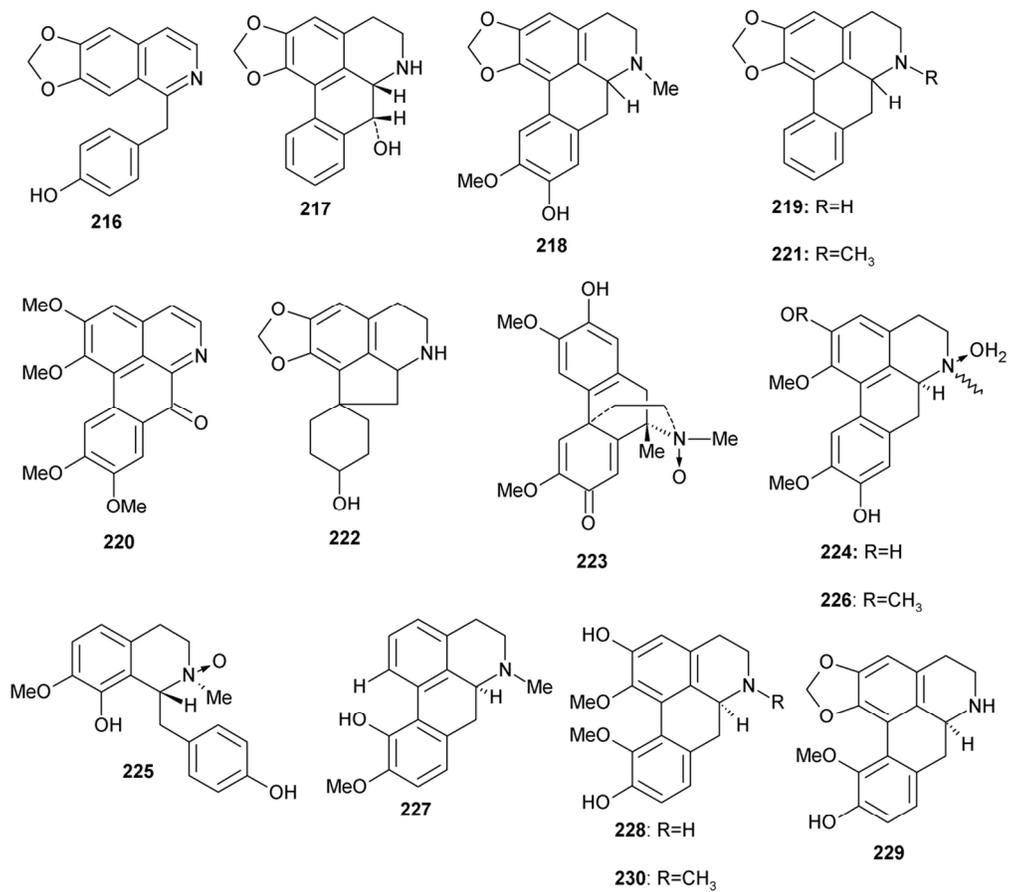
81x44mm (300 x 300 DPI)



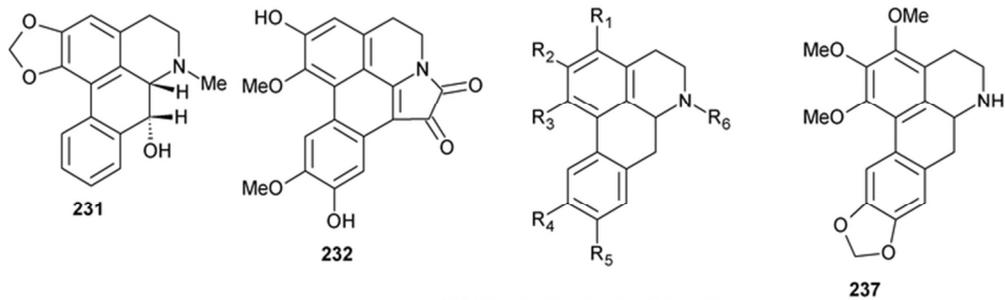
99x86mm (300 x 300 DPI)



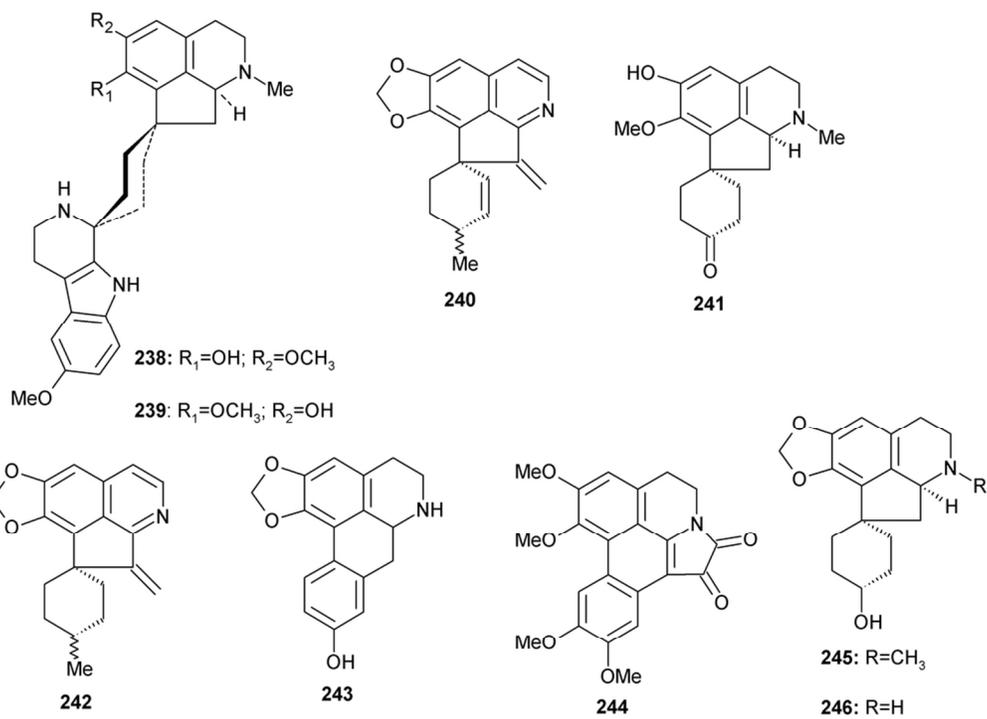
53x21mm (300 x 300 DPI)



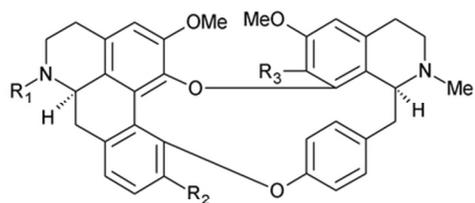
117x108mm (300 x 300 DPI)



63x31mm (300 x 300 DPI)

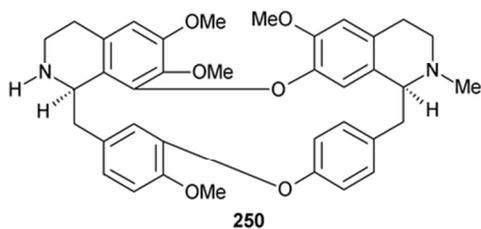


92x68mm (300 x 300 DPI)

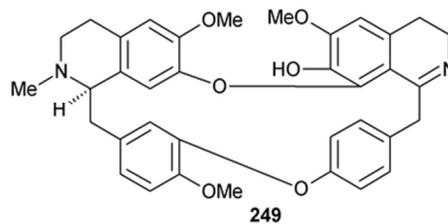


247: $R_1=CH_3$; $R_2=R_3=OCH_3$

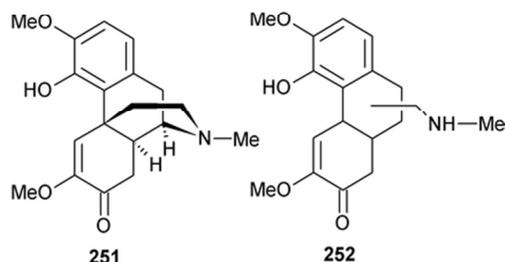
248: $R_1=H$; $R_2=R_3=OCH_3$



250



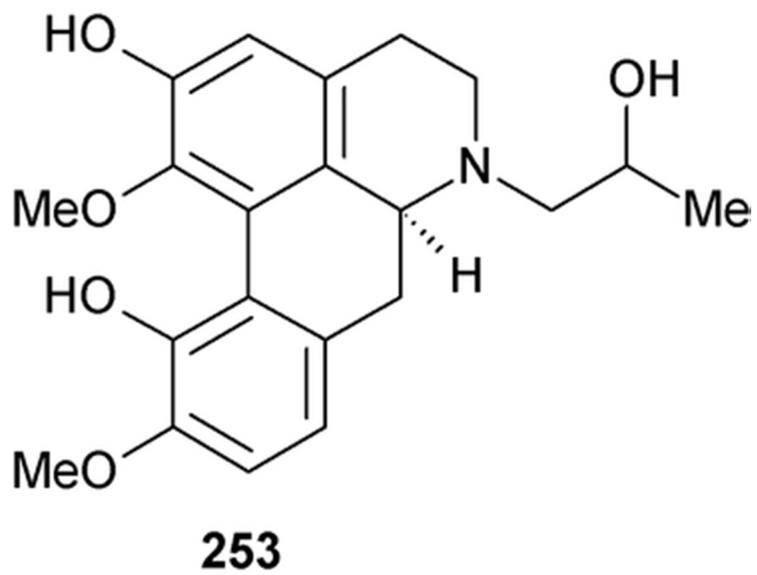
249



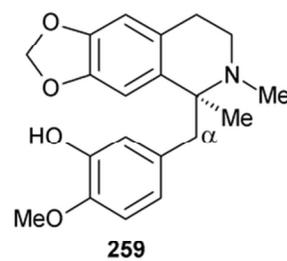
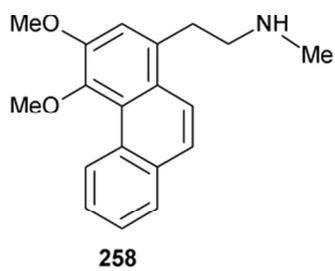
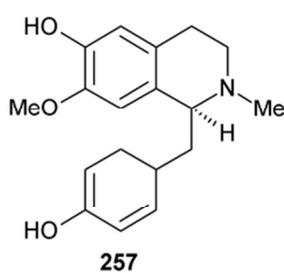
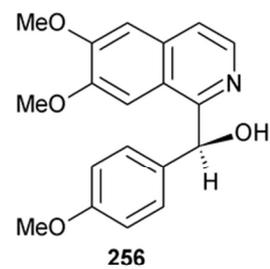
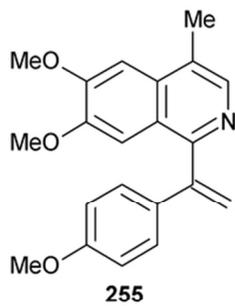
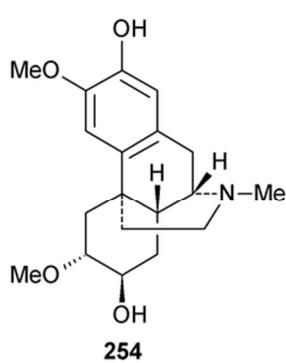
251

252

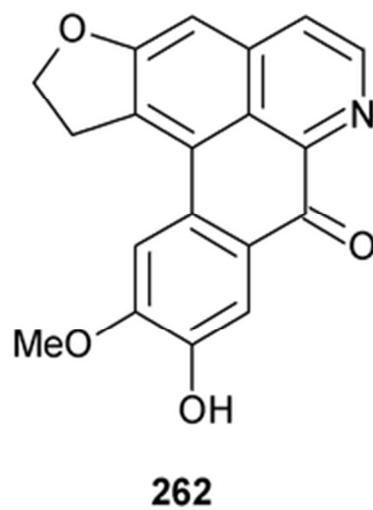
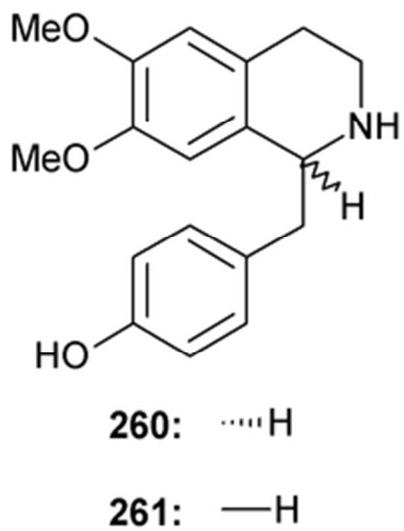
73x42mm (300 x 300 DPI)



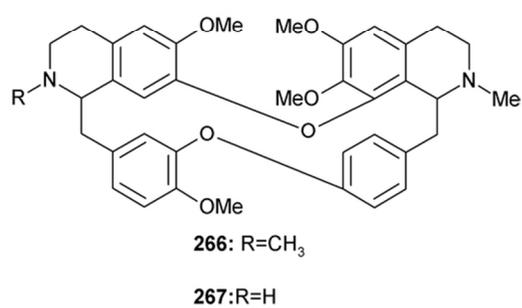
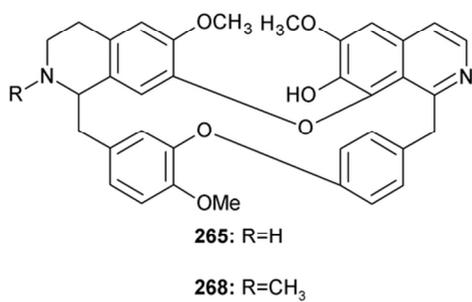
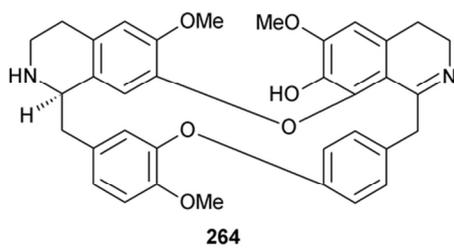
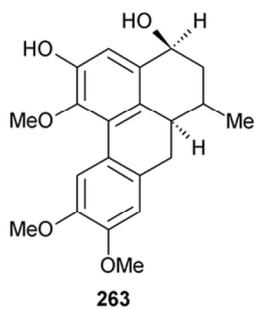
31x26mm (300 x 300 DPI)



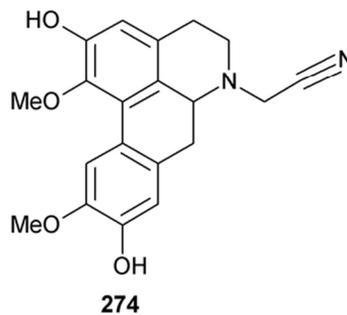
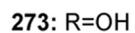
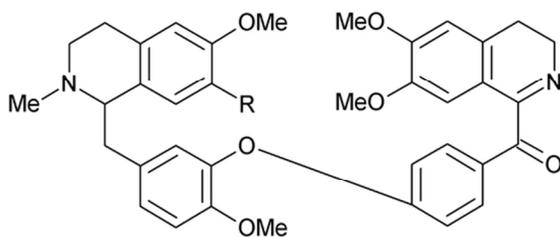
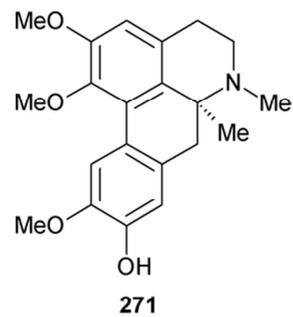
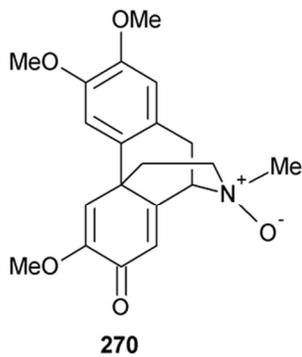
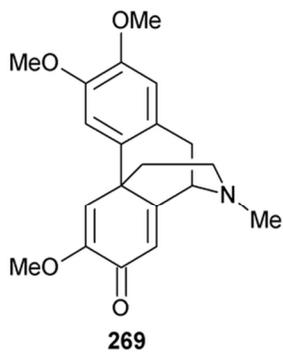
72x49mm (300 x 300 DPI)



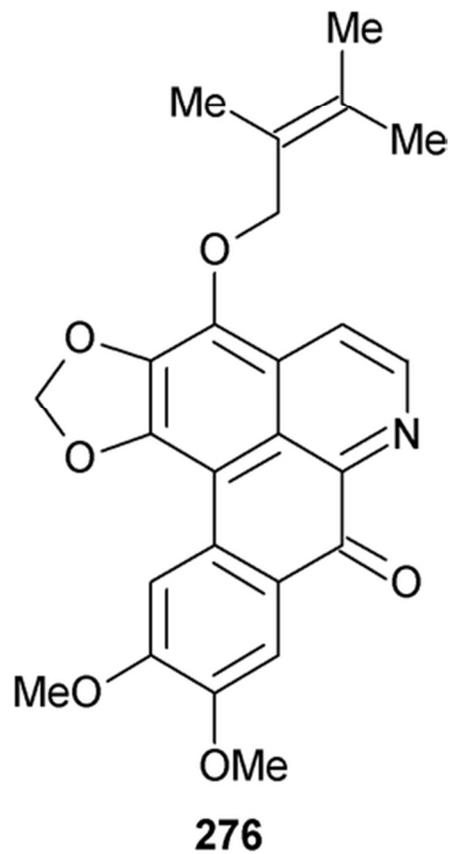
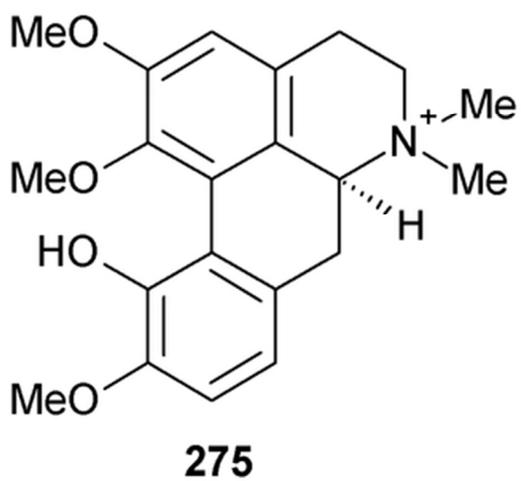
37x24mm (300 x 300 DPI)



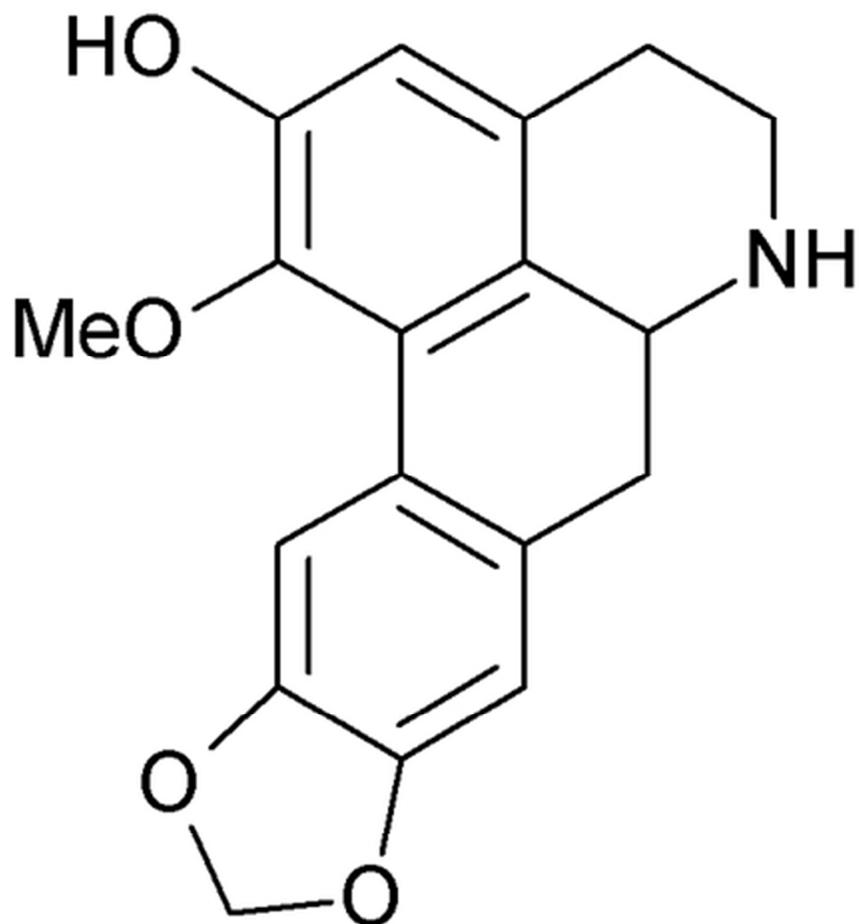
84x59mm (300 x 300 DPI)



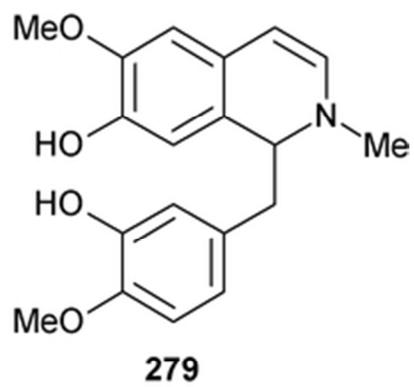
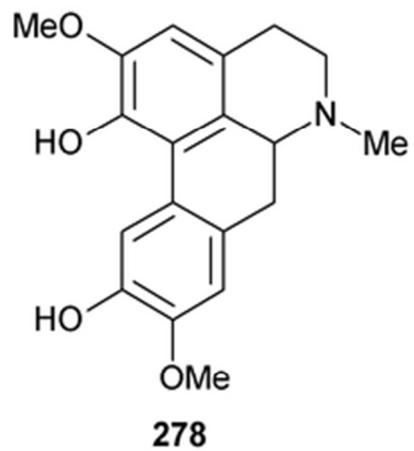
83x66mm (300 x 300 DPI)



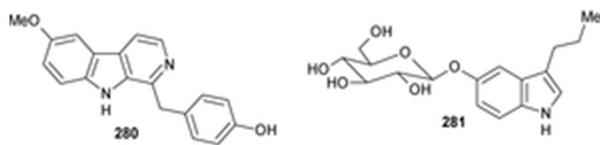
53x48mm (300 x 300 DPI)

**277**

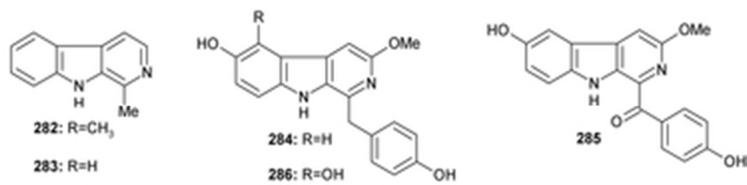
36x50mm (300 x 300 DPI)



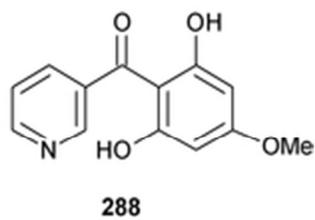
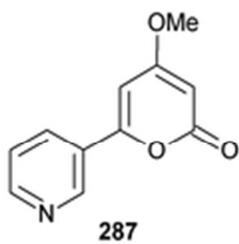
35x20mm (300 x 300 DPI)



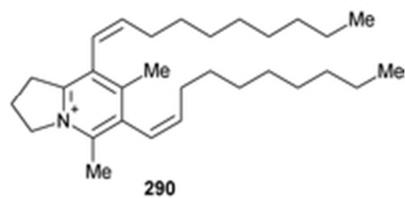
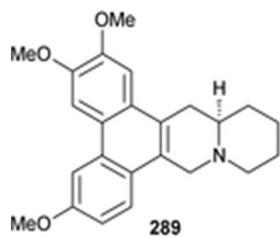
25x6mm (300 x 300 DPI)



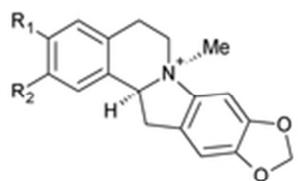
31x8mm (300 x 300 DPI)



26x11mm (300 x 300 DPI)



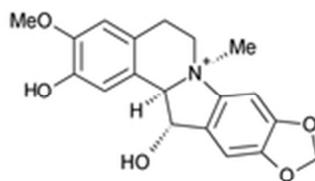
32x10mm (300 x 300 DPI)



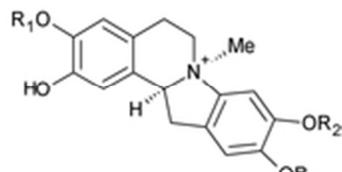
291: $R_1 = \text{OCH}_3$; $R_2 = \text{OH}$

292: $R_1 = R_2 = \text{OCH}_3$

294: $R_1 = \text{OH}$; $R_2 = \text{OCH}_3$



293

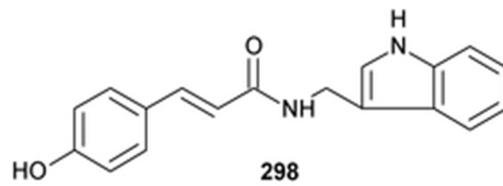


295: $R_1 = R_2 = R_3 = \text{CH}_3$

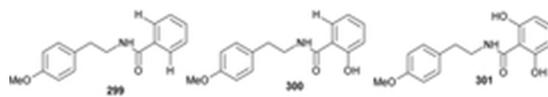
296: $R_1 = R_3 = \text{CH}_3$; $R_2 = \text{H}$

297: $R_1 = \text{CH}_3$; $R_2 = R_3 = \text{H}$

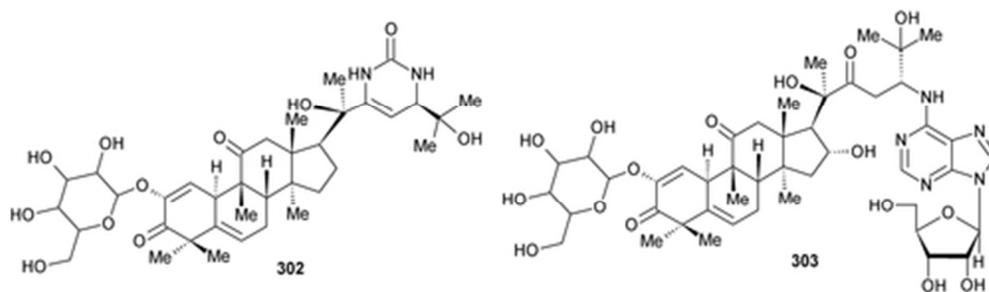
42x14mm (300 x 300 DPI)



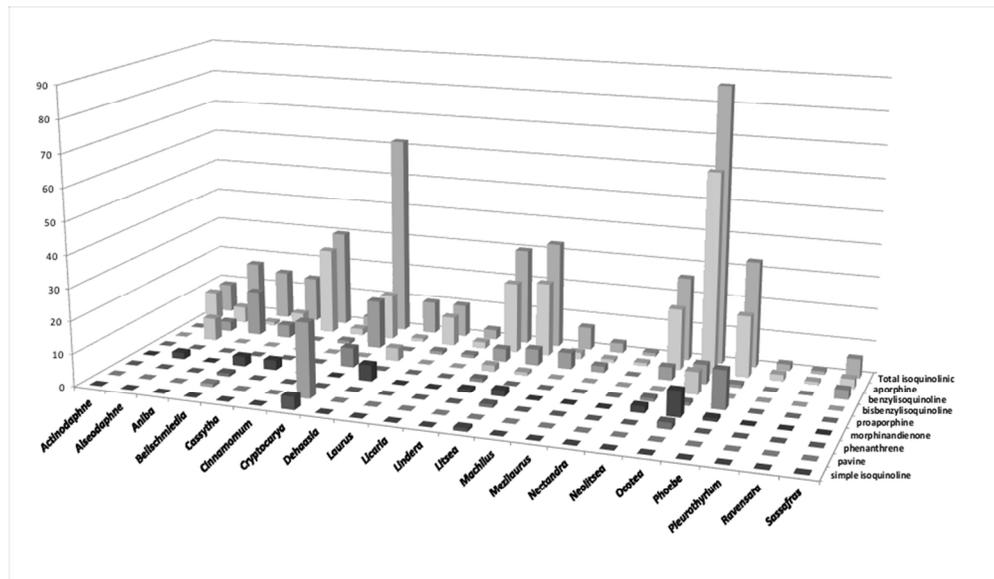
21x8mm (300 x 300 DPI)



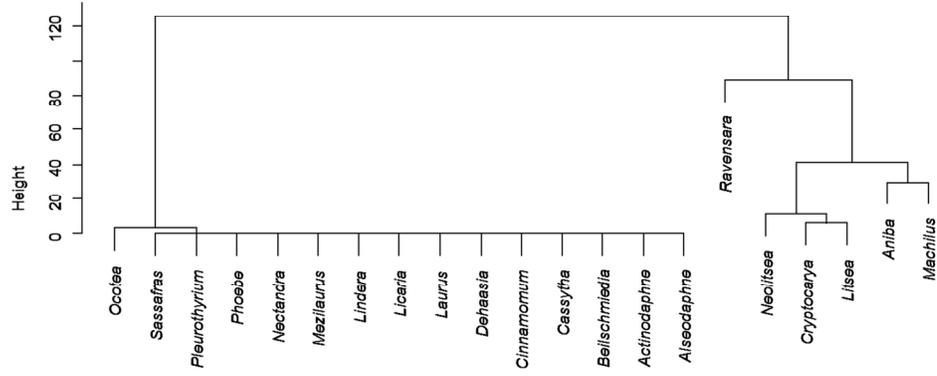
23x4mm (300 x 300 DPI)



42x12mm (300 x 300 DPI)



104x60mm (300 x 300 DPI)



146x79mm (300 x 300 DPI)