NEW ALKALOIDS FROM SELECTED MALAYSIAN *ALSTONIA* AND *LYCOPODIUM* SPECIES AND THEIR BIOLOGICAL ACTIVITY

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NEW ALKALOIDS FROM SELECTED MALAYSIAN *ALSTONIA* AND *LYCOPODIUM* SPECIES AND THEIR BIOLOGICAL ACTIVITY

ABSTRACT

Two Malaysian plants, *Alstonia penangiana* Sidiyasa (family: Apocynaceae) and *Lycopodium platyrhizoma* J.H.Wilce (family: Lycopodiaceae), were investigated for their alkaloidal composition. This project represents the first reported phytochemical study on these two plant species. A total of 94 alkaloids (**1**–**94**) were isolated and characterized from the leaf and stem-bark extracts of *Alstonia penangiana*, a plant endemic to Penang Island, Malaysia. Of these, 32 are new alkaloids. The leaf extract of *A. penangiana* yielded a total of 15 new alkaloids, including a pair of type-A and type-B macroline isomers (**1**, **2**), four macroline oxindoles (**20**–**23**), three talpinine-type oxindoles (**41**–**43**), two ajmaline alkaloids (**57**–**58**), as well as four macroline-akuammiline bisindoles (**76**–**79**). The stem-bark extract of *A. penangiana* gave a total of 19 new alkaloids. These include seven sarpagine alkaloids (**32**–**38**), an akuammiline alkaloid **39**, a C_{14} methylene-bridged indolizidine derivative (**40**), seven macroline-sarpagine bisindoles (**80**–**86**), and a macroline-pleiocarpamine bisindole **88**. Evaluation of the *in vitro* growth inhibitory activity of the new alkaloids against a panel of human cancer cell lines, including KB/S, KB/VJ300(–), KB/VJ300(+), PC-3, LNCaP, MCF7, MDA-MB-231, HT-29, and HCT 116 cancer cells showed strong cytotoxicity for the bisindole alkaloids (**76**–**77**, IC_{50} 0.3–8.3 μM; **80**–**86**, IC_{50} 0.02–9.7 μM). A total of 19 alkaloids (**95**–**113**) were isolated and characterized from the whole plant of *Lycopodium platyrhizoma*. Of these, three are new alkaloids, including two lycodine alkaloids (**95**–**96**) and one fawcettimine alkaloid (**110**). Lycoplatyrine A (**95**) is an uncommon lycodine alkaloid having C-2 substituted with a C_5N (piperidine) moiety. The alkaloid compositions of the two plants are summarized in Table 2.1 and Table 2.61.

Keywords: *Alstonia*, *Lycopodium*, alkaloids, indole, bisindole.

ALKALOID BARU DARIPADA SPESIES TERPILIH *ALSTONIA* DAN *LYCOPODIUM* DI MALAYSIA DAN KEAKTIFAN BIOLOGINYA

ABSTRAK

Dua jenis tumbuhan tempatan (Malaysia) iaitu *Alstonia penangiana* Sidiyasa (keluarga: Apocynaceae) dan *Lycopodium platyrhizoma* J.H.Wilce (keluarga: Lycopodiaceae), telah dikaji dari segi kandungan alkaloidnya. Kajian ini merupakan laporan pertama mengenai kandungan sebatian fitokimia bagi dua tumbuhan tersebut. Sebanyak 94 alkaloid (**1**–**94**) telah diasingkan dan dikenalpastikan daripada ekstrak daun dan kulit-batang pokok *A. penangiana*, spesies yang hanya dijumpai di Pulau Pinang, Malaysia. Daripada jumlah ini, 32 sebatian merupakan alkaloid baru. Kajian kimia terhadap ekstrak daun *A. penangiana* telah memberikan 15 alkaloid baru, termasuk sepasang isomer macroline jenis A dan B (**1**, **2**), empat macroline oxindola (**20**–**23**), tiga talpinine oxindola (**41**–**43**), dua ajmaline (**57**–**58**), dan empat bisindola macroline-akuammiline (angustilongines A–D, **76**–**79**). Sebanyak 19 alkaloid baru telah dijumpai daripada ekstrak kulit-batang *A. penangiana*, termasuk tujuh sarpagine (**32**–**38**), satu akuammiline (**39**), satu terbitan indolizidin (**40**), tujuh bisindola macroline-sarpagine (**80**–**86**), dan satu bisindola macroline-pleiocarpamine (**88**). Penilaian aktiviti perencatan secara *in vitro* oleh alkaloid baru terhadap pertumbuhan pelbagai sel kanser manusia, termasuk KB/S, KB/VJ300(–), KB/VJ300(+), PC-3, LNCaP, MCF7, MDA-MB-231, HT-29, dan HCT 116, menunjukkan aktiviti sitotoksik yang kuat bagi bisindola (**76**–**77**, IC_{50} 0.3–8.3 μM; **80**–**86**, IC_{50} 0.02–9.7 μM). Sejumlah 19 alkaloid (**95**–**113**) telah diasing dan dicirikan daripada seluruh tumbuhan *L. platyrhizoma*. Daripada jumlah ini, tiga merupakan alkaloid baru, termasuk dua lycodine (**95**–**96**) dan satu fawcettimine (**110**). Lycoplatyrine A (**95**) merupakan alkaloid jenis lycodine yang luar biasa di mana C-2 telah digantikan dengan moieti C_5N (piperidina). Kandungan alkaloid bagi dua tumbuhan tersebut telah dirumuskan dalam Jadual 2.1 dan 2.61.

Kata kunci: *Alstonia*, *Lycopodium*, alkaloid, indola, bisindola.

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LIST OF SYMBOLS AND ABBREVIATIONS

J	:	Coupling constant (in Hertz)
ε	:	Epsilon
λ	:	Lambda
m/z	:	Mass-to-charge ratio
A	:	Ampere
Å	:	Angstrom
Ac	:	Acetyl
Ac_2O	:	Acetic anhydride
B3LYP	:	Becke, three-parameter, Lee-Yang-Parr
br	:	Broad
CCDC	:	Cambridge Crystallographic Data Centre
$CDCl_3$	:	Deuterated chloroform
CD_2Cl_2	:	Deuterated dichloromethane
$CHCl_3$	:	Chloroform
cm^{-1}	:	Wavenumber
^{13}C NMR	:	Carbon-13 nuclear magnetic resonance
COSY	:	Correlation spectroscopy
°C	:	Degree Celsius
d	:	Doublet
2D	:	Two-dimensional
DART	:	Direct analysis in real time
DBE	:	Degree of unsaturation
dd	:	Doublet of doublets
ddd	:	Doublet of doublet of doublets

dec	:	Decomposed
DFT	:	Density functional theory
dq	:	Doublet of quartets
dt	:	Doublet of triplets
ECD	:	Electronic circular dichroism
ESI	:	Electrospray ionization
Et	:	Ethyl
EtOAc	:	Ethyl acetate
h	:	Hour
HMBC	:	Heteronuclear Multiple Bond Correlation
^{1}H NMR	:	Proton nuclear magnetic resonance
HPLC	:	High Performance Liquid Chromatography
HRMS	:	High Resolution Mass Spectrometry
HSQC	:	Heteronuclear Single Quantum Coherence
IC_{50}	:	Half maximal inhibitory concentration
IPNI		International Plant Names Index
IR	:	Infrared
m	:	Multiplet
Me	:	Methyl
MeCN	:	Acetonitrile
MeOD-d_4	:	Deuterated methanol
MeOH	:	Methanol
mg	:	Milligram
MHz	:	Megahertz
min	:	Minute
mL	:	Millilitre

mp	:	Melting point
MS	:	Mass Spectrometry
NMR	:	Nuclear Magnetic Resonance
NOE	:	Nuclear Overhauser Effect
NOESY	:	Nuclear Overhauser Effect Spectroscopy
ppm	:	Parts per million
q	:	Quartet
qd	:	Quartet of doublets
rt	:	Room temperature
s	:	Singlet
SiO_2	:	Silica gel
t	:	Triplet
td	:	Triplet of doublets
TDDFT	:	Time-Dependent Density Functional Theory
TLC	:	Thin Layer Chromatography
TMS	:	Tetramethylsilane
TOF	:	Time-of-Flight
UV	:	Ultraviolet

LIST OF FIGURES IN APPENDIX

CHAPTER 1: INTRODUCTION

1.1 Natural Products

Nature produces a myriad of natural products or secondary metabolites which are present in most living organisms including plants, microbes, and marine and terrestrial organisms.[1-5] Since ancient days, humans have been exploring their surrounding environment in search of plants which can be used for the treatment and prevention of diseases, with the earliest use of crude drugs dating as far back as 3000–2500 BCE.[6] The first isolation of a natural product from medicinal plant was reported in 1805 by the German pharmacist, Sertürner, who successfully isolated morphine from the opium poppy, work which represents the foundation of natural product chemistry and which initiated the extensive chemical investigations of chemical constituents in plants.[7,8] Plants encompassing a large variety of species distributed across the globe, are fertile sources of bioactive phytochemicals, many characterized by complex structures of great diversity.[9] It has been estimated that only about 15% of plant species on Earth have been systematically investigated for their phytochemical constituents, thus it is not surprising that a significant portion of secondary metabolites in plants remain undiscovered.[10] It has also been recently estimated that about 35% of the new approved drugs for the past 30 years (1981–2014) were either natural products or directly derived therefrom.[11]

Some examples of plant-derived natural products that have been developed into anticancer drugs which are currently in clinical use include the *Catharanthus* bisindole alkaloids and their analogues (vincristine, vinblastine,[12-14] vindesine,[12,15] vinorelbine[16,17]), the taxanes (paclitaxel or Taxol,[18-20] docetaxel[21]), and the camptothecins (topotecan,[22-24] irinotecan[25,26]) to name a few. Those derived from

microbes which are in clinical use include dactinomycin,[27] the anthracyclines (doxorubicin,[28-30] daunorubicin[31,32], epirubicin[33]), and the epothilones[34,35] (lactam analog of epothilone B, ixabepilone, approved in 2007, others in development) (Figure 1.1). The discovery of the anti-malarial compound artemisinin from the Chinese medicinal plant *Artemisia annua*, and its subsequent introduction into clinical use has been recently recognized by the award of the 2015 Nobel Prize in Physiology or Medicine.[36] Some natural products of plant origin are potent acetylcholinesterase (AChE) inhibitors, such as galanthamine which is used for the treatment of Alzheimer's disease[37,38] and physostigmine in the treatment of glaucoma.[39] Natural products therefore remain as a fertile and promising source for the discovery of new bioactive organic molecules which may act as useful templates for drug development.[11,40-43]

Malaysia is a country with great biodiversity and is home to a wealth of diverse flora species.[44] These tremendous bioresources present a great opportunity for the discovery of natural products with novel structures and/or useful biological activity, and the intensive chemical investigation of these plants would very likely be rewarding.[45] Plants of the genus *Alstonia* have a pantropical distribution[46,47] and are usually rich in alkaloids, and were therefore chosen as part of our explorations in alkaloid chemistry.[48-53] *Alstonia penangiana*, a rare and previously uninvestigated *Alstonia* species found only on Penang Hill, Penang, was chosen for investigation in the present study with the emphasis on the discovery and structure elucidation of new natural products, as well as the evaluation of biological activity of the alkaloids obtained. Another group of plants that have received attention are plants of the genus *Lycopodium*. These plants have been reported to provide structurally interesting alkaloids,[54-59] and a detailed chemical study was carried out for the previously uninvestigated species *L. platyrhizoma* collected from the Genting Highlands.

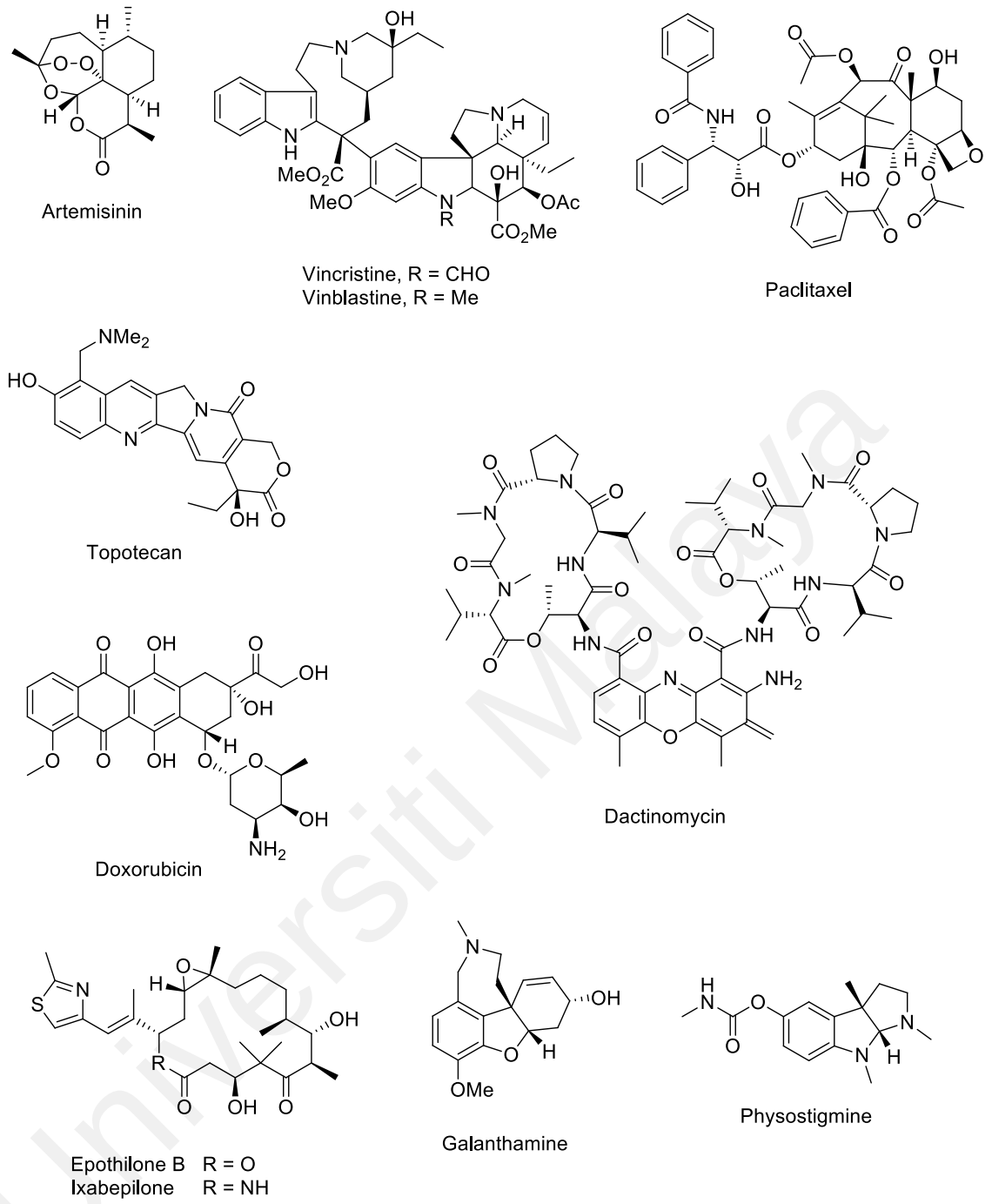


Figure 1.1: Examples of bioactive natural products and semisynthetic derivatives

1.2 The Alkaloids

Alkaloids constitute one of the prominent classes of natural products. The term 'alkaloid' was first introduced in 1819 by Meissner to define compounds of plant origin with an alkali-like or basic property. As more alkaloids were discovered and their structures established, the definition of an alkaloid has also changed significantly.[7,60,61] In 1910, Winterstein and Trier proposed that alkaloids are plant-derived, basic, and physiologically active compounds with limited distribution in nature. According to this definition, alkaloids possess complex structures with the heterocyclic nitrogen originating from amino acids (or their derivatives).

Hesse presented a more general definition of alkaloids as follows: Alkaloids are nitrogen-containing organic substances of natural origin with a greater or lesser degree of basic character. This represented a rather convenient approach to classify a vast group of naturally-occurring, nitrogen-containing organic substances of great structural diversity.[60,62] Most of the known alkaloids can be classified into five distinct classes based on the position of the N-atom in the main structural element (Figure 1.2):[61,63,64]

i. Heterocyclic alkaloids
ii. Alkaloids with exocyclic nitrogen and aliphatic amines (e.g., (−)-ephedrine (−)-cassaine, mescaline)
iii. Putrescine, spermidine, and spermine alkaloids (e.g., agleptine, inandenin-12-one, homaline)
iv. Peptide alkaloids (e.g., celenamide E)
v. Terpene and steroid alkaloids (e.g., aconitine, solanidine, conessine)

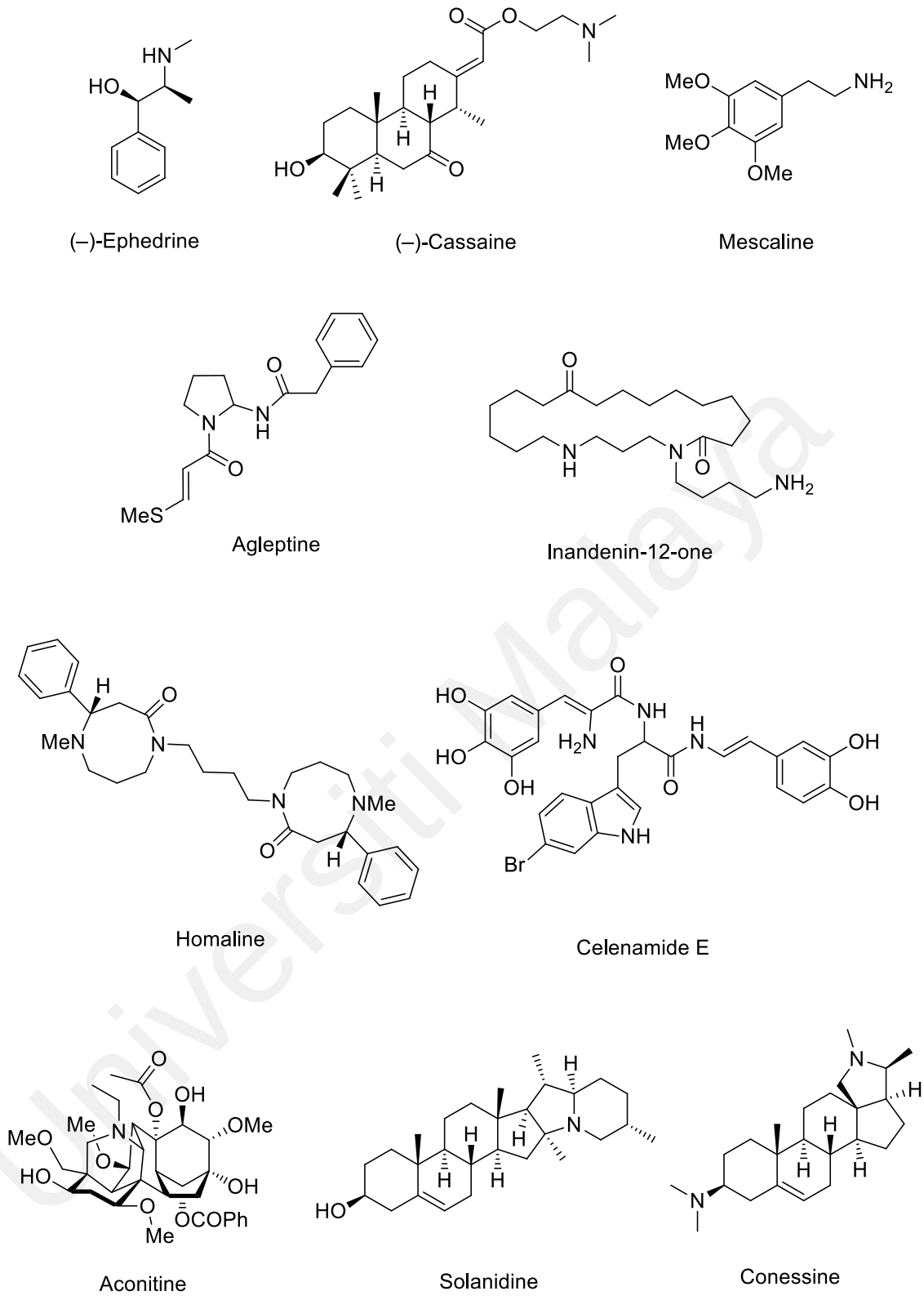


Figure 1.2: Examples of alkaloids from the five alkaloid classes

A significant number of the existing alkaloids belong to the class of heterocyclic alkaloids, which can be further divided into 15 subclasses based on the structure of the heterocyclic moiety (Figure 1.3).[61,63,64]

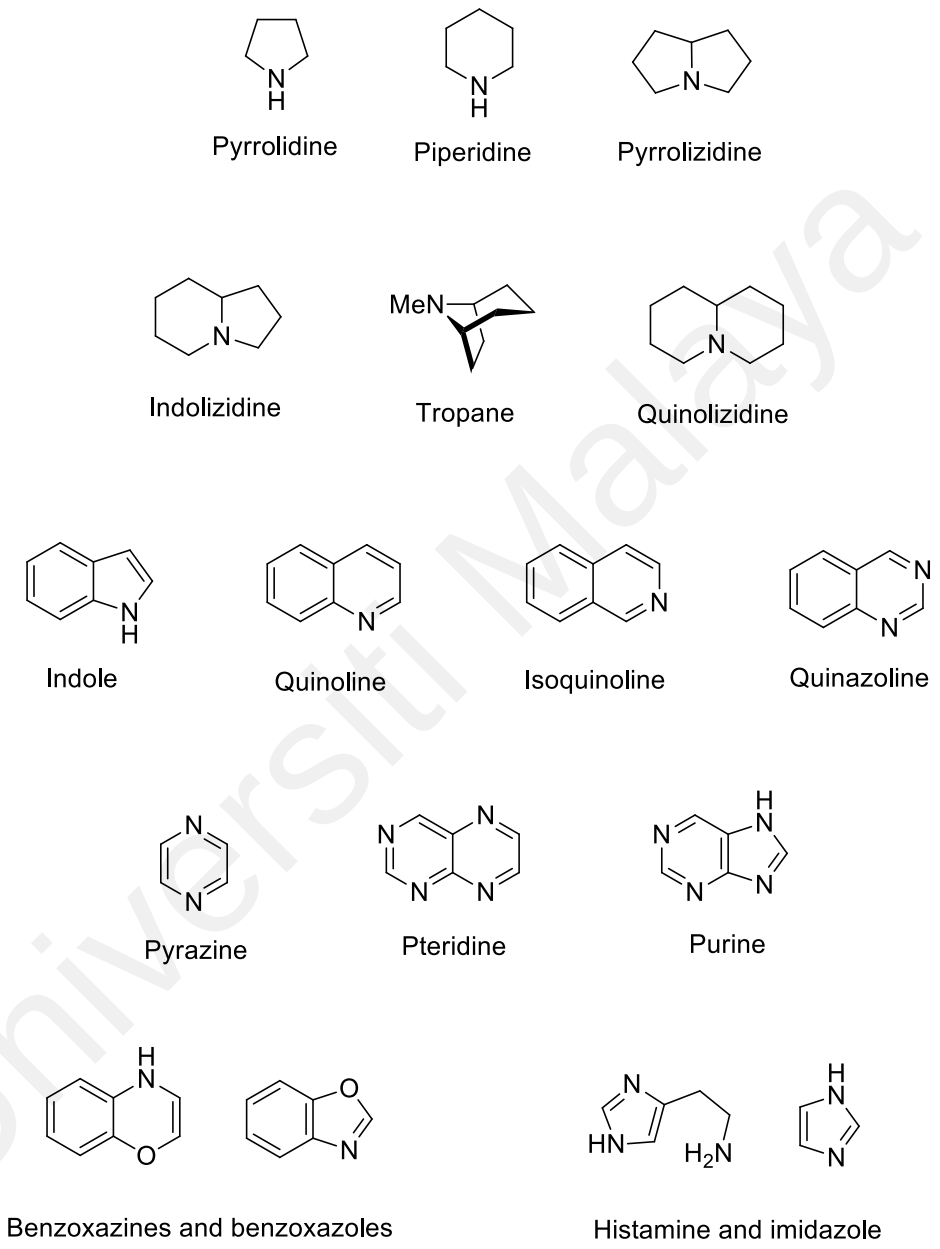


Figure 1.3: Subclasses of heterocyclic alkaloids

1.3 Indole Alkaloids

Indole alkaloids constitute the largest class of the alkaloids and account for about 20% of all known alkaloids.[61,63-65] Indole alkaloids include both those compounds that incorporate the actual indole chromophore and those containing its derivatives, such as indoline (dihydroindole), indolenine, hydroxyindolenine, α-methylideneindoline, pseudoindoxyl, and oxindole (Figure 1.4). Other indole alkaloids are those in which the nucleus incorporates an additional benzene or pyridine ring, for example, carbazole, or β- and γ-carbolines, and their derivatives (Figure 1.4).[61,63,64]

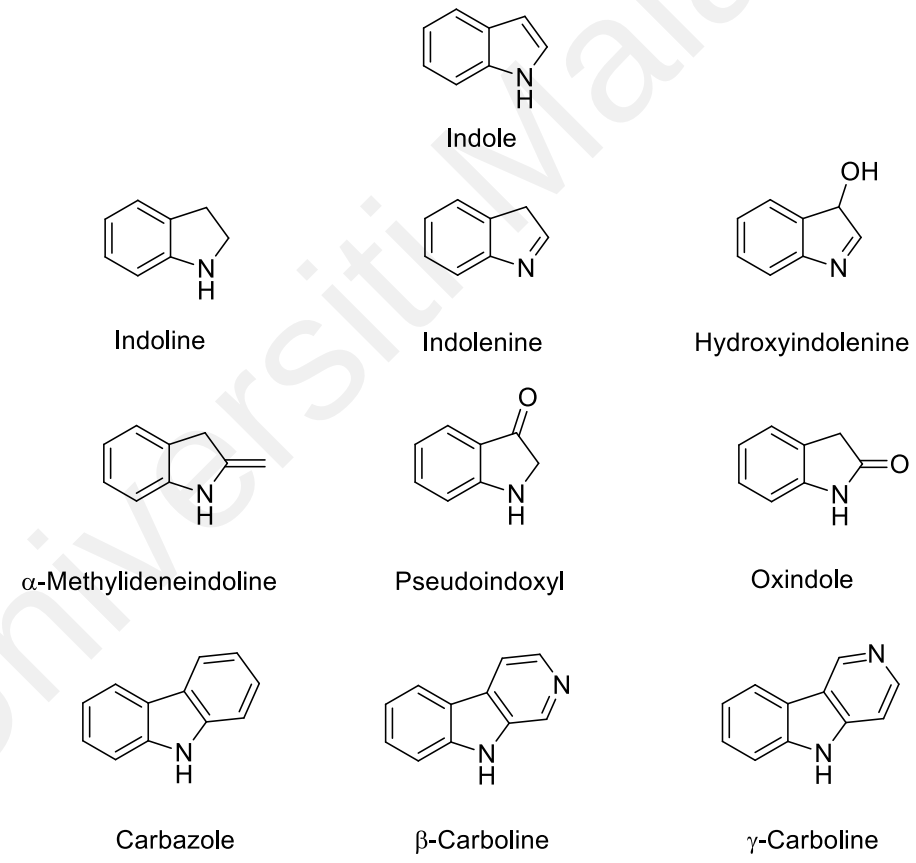
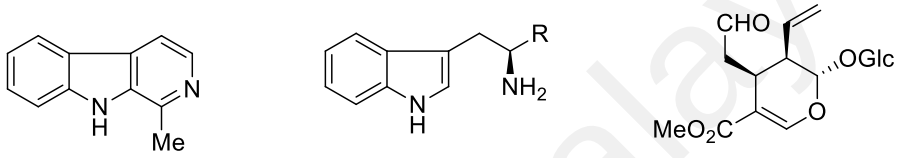


Figure 1.4: Indole and its derivatives

From a structural viewpoint, indole alkaloids can be divided into two general categories. The first consists of simple indole alkaloids (e.g., harmane), which do not possess a structural uniformity, other than the commonly present indole nucleus or its direct derivative. The other class of indole alkaloids comprises the monoterpene indole alkaloids which consist of two structural units, viz., tryptamine (or tryptophan) bearing the indole nucleus and a C_9- or C_{10}-monoterpene unit derived from secologanin (Figure 1.5). The majority of plant-derived indole alkaloids belong to this class.[61,63,64]



Harmane

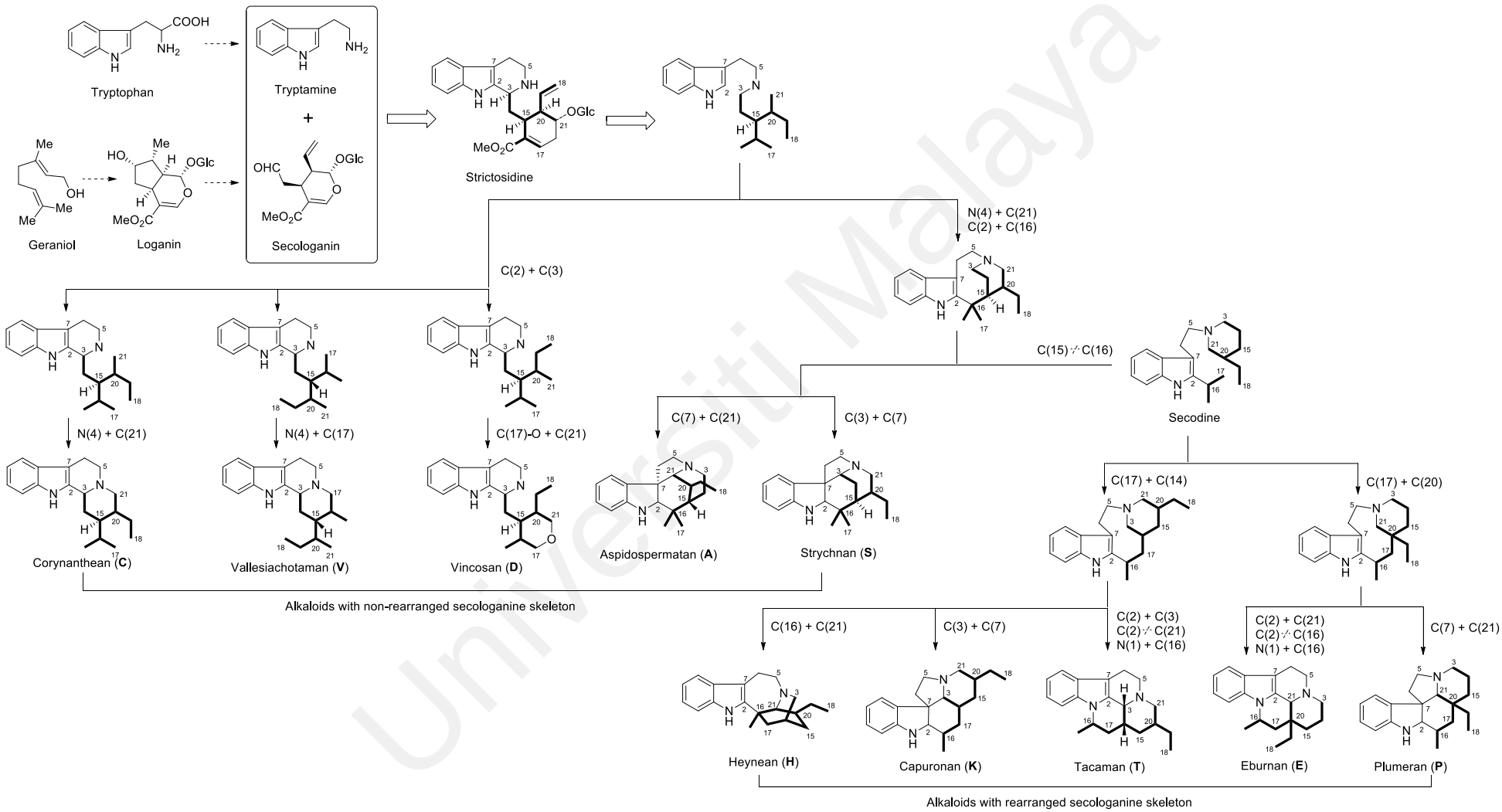
Tryptamine; R = H
L-Tryptophan; R = CO_2H

Secologanin

Figure 1.5: Harmane, tryptamine/L-tryptophan, and secologanin

1.4 Monoterpene Indole Alkaloids

Monoterpene indole alkaloids share a common biogenetic precursor, namely strictosidine, which is the enzymatic condensation product of secologanin and tryptamine.[66-68] Based on their biogenesis, these alkaloids could be structurally grouped into ten major skeletal types: corynanthean (C), vincosan (D), vallesiachotaman (V), strychnan (S), aspidospermatan (A), eburnan (E), plumeran (P), heynean (H), capuronan (K), and tacaman (T).[69-109] Indole alkaloids belonging to the C-, D-, V-, S-, and A-types possess skeletal structures with a non-rearranged secologanin moiety, whereas alkaloids of E-, P-, H-, K-, and T-types possess skeletal structures with a rearranged secologanin moiety. Monoterpenoid indole alkaloids are numbered according to the biogenetic numbering system developed by Le Men and Taylor.[110] The plausible biogenetic relationships between these alkaloids are shown in Scheme 1.1.[61,63,64,106-109] The ten major skeletal types can be further divided into subtypes based on the increasing structural complexity of their basic carbon skeleton (Figure 1.6).[105-118]



Scheme 1.1: Biogenetic inter-relationships of the ten major skeletal types of the monoterpene indole alkaloids

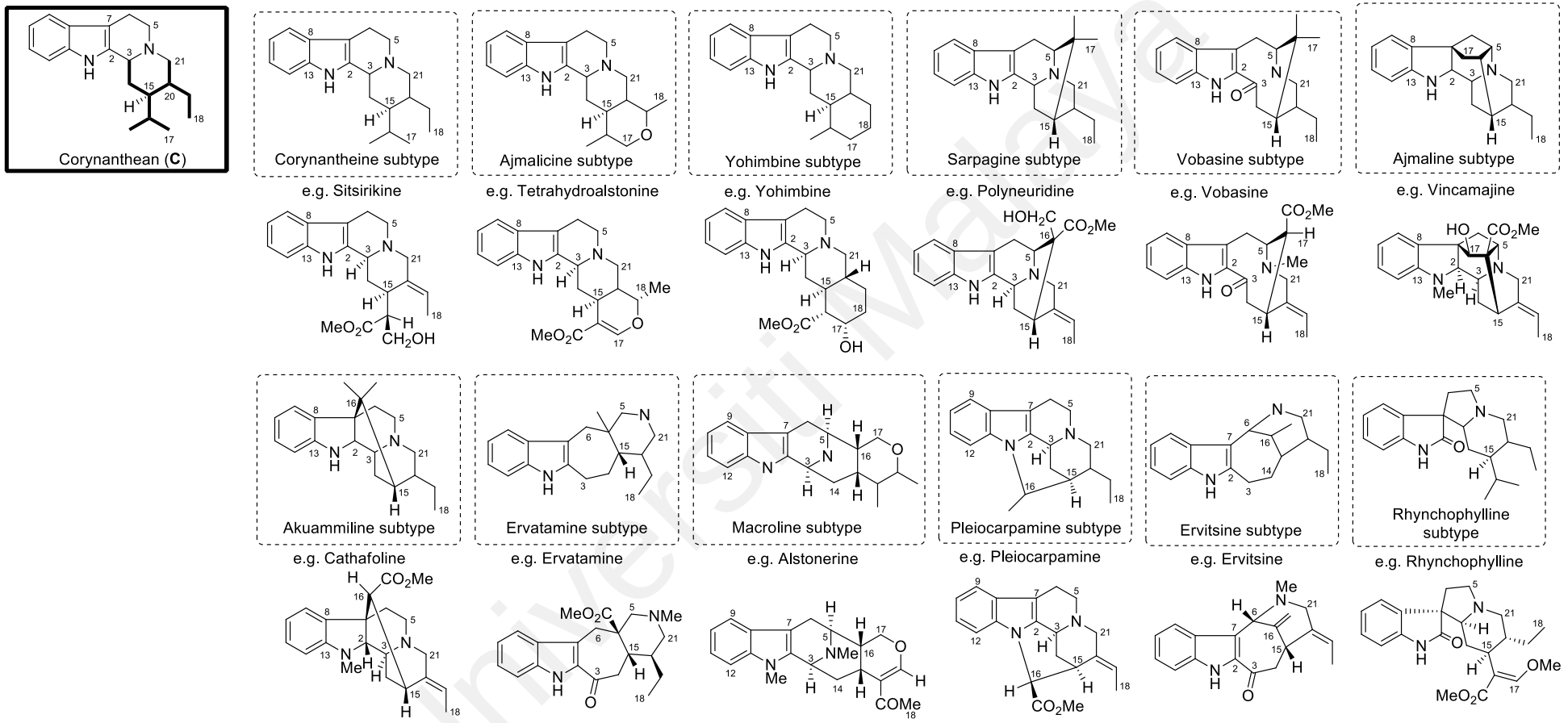


Figure 1.6: Main skeletal subtypes of the monoterpenoid indole alkaloids

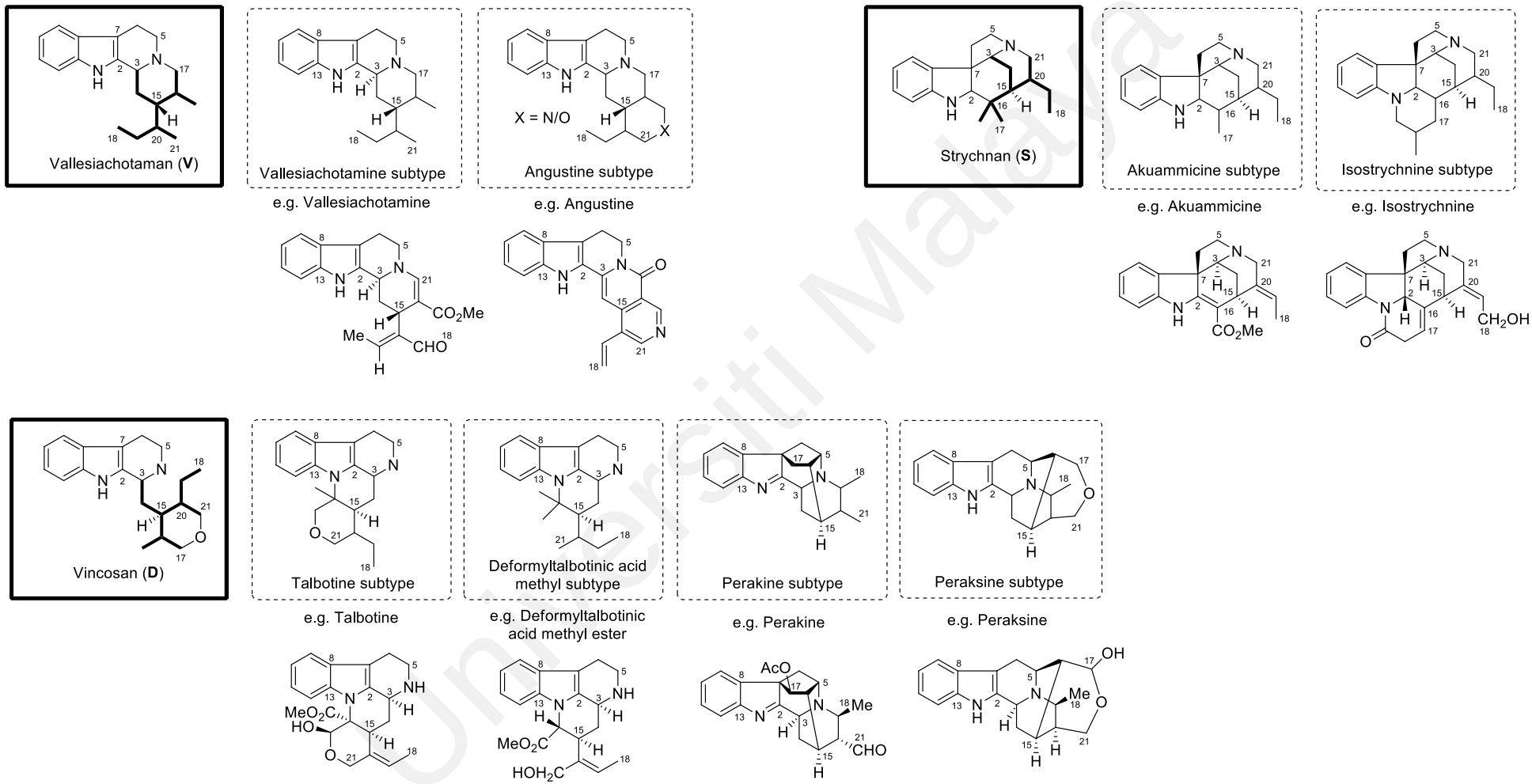
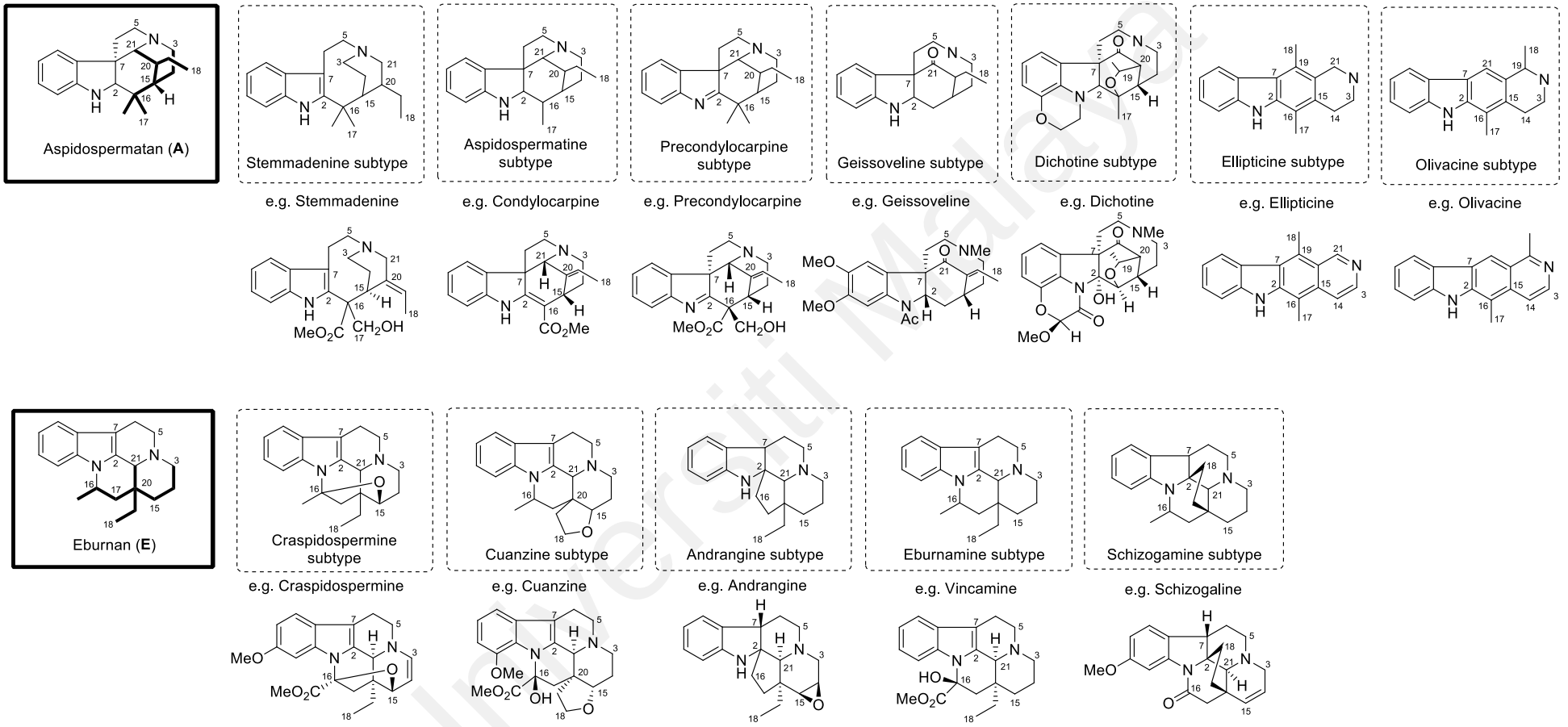


Figure 1.6, continued



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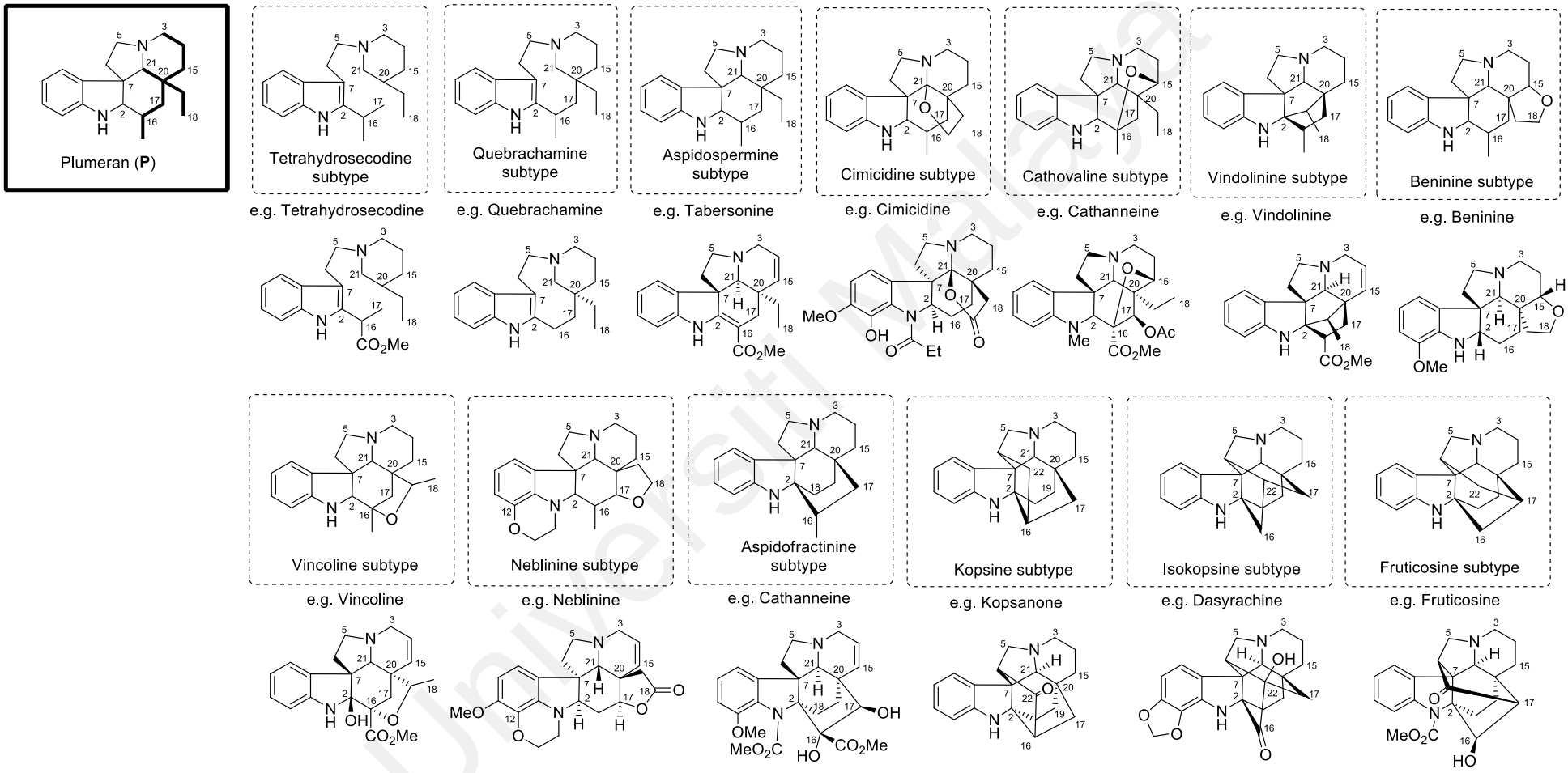

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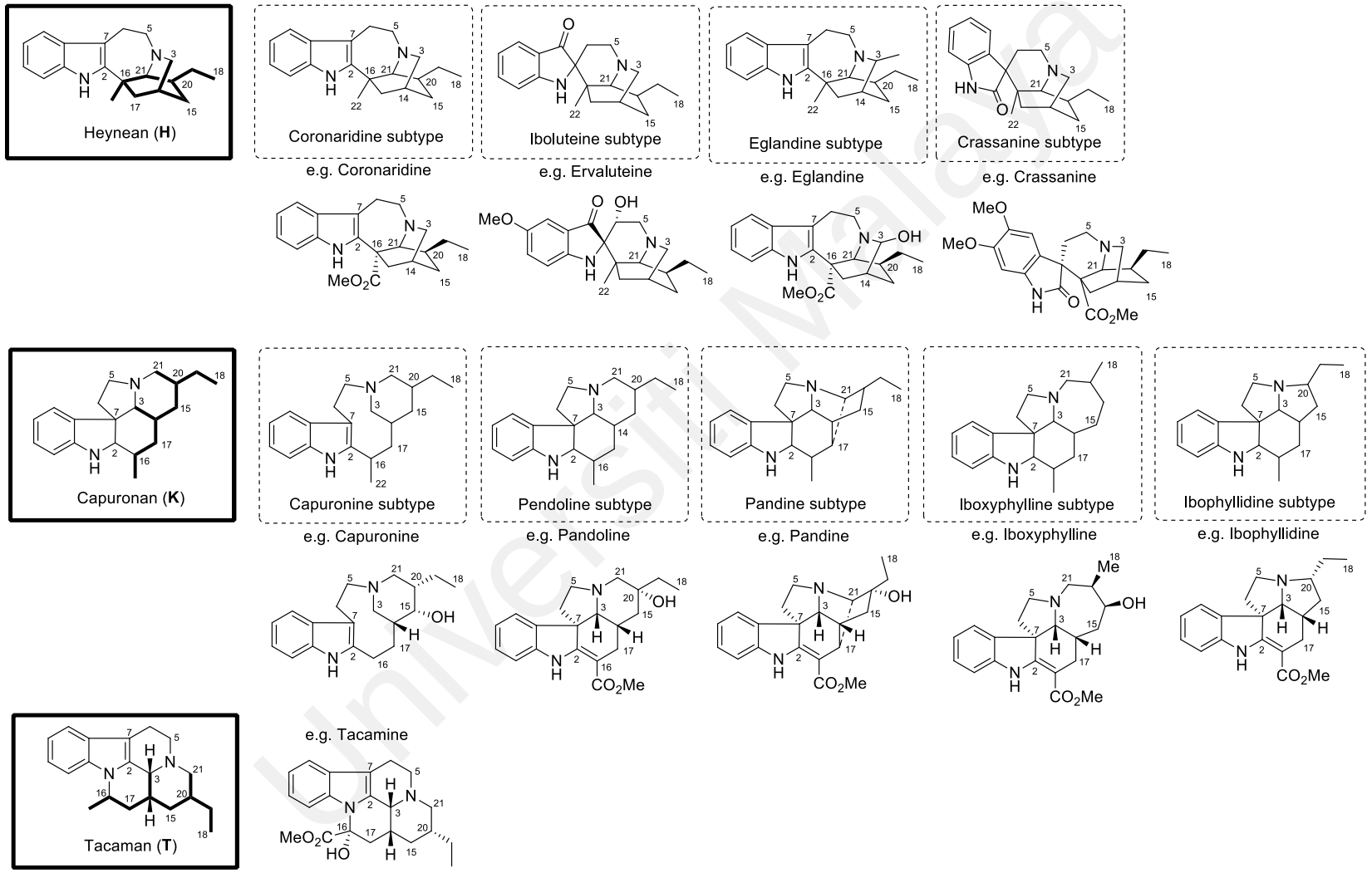


Figure 1.6, continued

1.5 The Genus *Alstonia*

The genus *Alstonia*, comprising trees and shrubs, is the largest and most widespread genus in the subtribe Alstoniinae of the tribe Plumerieae (family: Apocynaceae). More than 40 species are reported to be distributed over the tropical and subtropical parts of the world (Central America, Africa and Asia). The diversity of *Alstonia* plants is centralized in the Malesian region (Malaysia, Singapore, Indonesia, Brunei, Philippines, and Papua New Guinea).[46,47,119] Of a total of 19 species reported from this region, eight can be found in Peninsular Malaysia. *Alstonia* plants are known by the local name '*Pulai*' in Malaysia. Among the eight Malayan species, five are grouped under the sect. *Alstonia* (*A. scholaris* (L.) R.Br., *A. angustiloba* Miq., *A. pneumatophora* Backer ex Den Berger, *A. rostrata* C.E.C.Fisch., and *A. spatulata* Blume), while the other three are in the sect. Monuraspermum (*A. angustifolia* Wall. ex A.DC., *A. macrophylla* Wall. ex G.Don, and *A. penangiana* Sidiyasa).[46]

Plants of the genus *Alstonia* may grow up to 60 m in height and more than 200 cm in diameter. The young trees (Sect. *Alstonia*) have pagoda-shape crowns which appear monopodial, while older trees possess sympodial crowns. The trunks of larger trees usually have evolved buttress roots which are small to large in size. The bark is smooth to rough (sometimes corky) and the leaves vary in their arrangement, shape, size, and ornamentation, which are important diagnostic characters of the species or sections of the genus. The flowers are small and narrow, measuring up to 2.5 mm in diameter and may grow up to 40 mm long in mature buds.[46] Plants of this genus have been used to treat malaria and dysentery throughout Southeast Asia. They have long been regarded as one of the important medicinal plants and are widely used in traditional medicine; some examples are listed in Table 1.1.[120]

Table 1.1: Uses of *Alstonia* plants in Traditional Medicine

Species	Distribution	Traditional uses
A. angustifolia Wall. ex A.DC.	Malaysia, Singapore, Sumatra etc.	-The leaves are heated and boiled, then externally applied to the spleen area to treat fever. -The bark is used in treatment of malaria.
A. angustiloba Miq.	Thailand, Malaysia, Singapore, Sumatra etc.	-The latex is used to treat boils and abscesses -The latex is used to alleviate toothache
A. macrophylla Wall. ex G.Don.	Thailand, Cambodia, Malaysia, Sumatra, Philippines etc.	-The bark is used to treat fever, fatigue, irregular menses, liver disease, dysentery, malaria, diabetes, and to expel worms from the intestines. -The leaf decoction is used to treat lung and ear infections
A. spectabilis R.Br.	Indonesia, Philippines, Northern Australia, New Guinea etc.	-The bark and leaves (decoction) are used to treat cough and sore throat. -The leaf decoction is used to relieve asthma.
A. spatulata Blume	Thailand, Malaysia, Myanmar, New Guinea etc.	-The bark (aqueous extract) is used to treat diabetes mellitus. -The latex is used for skin diseases
A.scholaris Linn. R. Br.	India, Southern China, Malesia, Northern Australia	-The bark is used to reduce fever, to treat colds, bronchitis, diarrhea, and dysentery. -The leaf poultice is used to treat skin diseases. -The latex is used for rheumatic pains and also to treat ulcers

The *Alstonia* plant chosen for the present study, *A. penangiana* (Figure 1.7), is a species endemic to Peninsular Malaysia. It is known to occur only on Bukit Bendera, Penang Island and was first described by Sidiyasa in 1998 as a new species. The vegetative specimens of *A. penangiana* cannot be distinguished from those of *A. angustifolia* and *A. macrophylla* since these plants are very similar in terms of leaf shape and leaf arrangement. *A. penangiana* differs from *A. angustifolia* in its longer corolla bud, longer corolla tube, and longer corolla lobes, and from *A. macrophylla* mainly in its sepals which are pubescent instead of glabrous or puberulous outside and on the free part of them inside, and in the corolla lobes which are entirely pilose instead of basally pilose inside.[46] Definitive identification of *A. penangiana* (including

differentiation from *A. macrophylla* and *A. angustifolia*) therefore requires careful examination of flower specimens.

Figure 1.7: *Alstonia penangiana* Sidiyasa (Bukit Bendera, Penang)

1.5.1 Occurrence and Distribution of Alkaloids in the Genus *Alstonia*

Plants of the genus *Alstonia* are rich sources of indole and bisindole alkaloids. An important feature of *Alstonia* alkaloids is the predominance of macroline units.[52,121-123] The occurrence of alkaloids in *Alstonia* as reported in the literature (up to April 2019) is summarized in Table 1.2 (botanical authority of species in accordance with IPNI).

Table 1.2: Occurrence of Alkaloids in *Alstonia*

Species	Plant part	Alkaloids	References
A. actinophylla K.Schum. (Australia)	Leaves	Actinophyllic acid (**534**)	124
A. angustifolia Wall. ex A.DC. (Peninsular Malaysia)	Leaves	*O*-Acetylyohimbine (yohimbine-17-*O*-acetate)(**454**)	125,126
		Affinisine (**44**)	125,126
		Akuammicine (**179**)	125,126
		Alstocraline (**604**)	125,126
		Alstonerine (**3**)	125,126
		Alstonisine (**24**)	125,126
		Angusticraline (**603**)	125,126
		Antirhine (**443**)	125,126
		Cathafoline (**52**)	125,126
		19,20-Dehydro-*O*-acetylyohimbine (**467**)	125,126
		19,20-Dehydro-10-methoxytalcarpine (**151**)	125,126
		Fluorocarpamine (**70**)	125,126
		Foliacraline (**602**)	125,126
		16-Hydroxystrictamine (**352**)	125,126
		Lochnerine (**47**)	125,126
		11-Methoxyakuammicine (**71**)	125,126
		10-Methoxymacrocarpamine (**594**)	125,126
		10-Methoxymacrocarpamine *N*-oxide (**595**)	125,126
		10-Methoxyvillalstonine (**596**)	125,126
		10-Methoxyvillalstonine *N*-oxide (**597**)	125,126
		Normacusine B (**410**)	125,126
		Norquaternine (10,11-dimethoxypicrinine, volkensine) (**316**)	125,126
		Pleiocarpamine (**67**)	125,126
		Tetrahydrocantleyine (**118**)	125,126
		Vincamajine (**62**)	125,126
		Yohimbine (**453**)	125,126
	Stem bark	Affinisine (**44**)	125,126
		Alstonerine (**3**)	125,126
		Alstonisine (**24**)	125,126
		Alstophylline (**9**)	125,126
		Angustimaline (**139**)	125,126

Table 1.2, continued

Species	Plant part	Alkaloids	References
		Fluorocarpamine (**70**)	125,126
		Macralstonine (**585**)	125,126
		11-Methoxyakuammicine (**71**)	125,126
		Villalstonine (**90**)	125,126
		Villalstonine *N*-oxide (**91**)	125,126
	Root	Alstonerine (**3**)	123,127
		Alstophylline (**9**)	123,127
		4'-Hydroxy-3',5'-dimethoxybenzoyl-vincamajine (**59**)	123,127
		Macralstonine (**585**)	123,127
		Macrocarpamine (**89**)	123,127
		11-Methoxyakuammicine (**71**)	123,127
		Nor-C-fluorocurarine (**219**)	123,127
		Pleiocarpamine (**67**)	123,127
		Villalstonine (**90**)	123,127
		Vincamajine (**62**)	123,127
A. angustifolia Wall. ex A.DC. (Peninsular Malaysia)	Stem bark	*O*-Acetyltalpinine (**421**)	128,129
		Affinisine (**44**)	128,129
		Affinisine oxindole (**431**)	128,129
		Alstofonidine (**155**)	128
		Alstohentine (**17**)	128
		Alstomicine (**19**)	128
		Alstonal (**25**)	128
		Alstonerinal (**4**)	128,129
		Alstonerine (**3**)	128,129
		Alstonisine (**24**)	128
		Alstonoxine B (**172**)	128
		Alstopirocine (**165**)	128
		Alstoumerine (**48**)	128
		Alstoumerine oxindole (**432**)	128,129
		Angustimaline (**139**)	130
		Angustimaline A (**140**)	130
		Angustimaline B (**141**)	130
		Angustimaline C (**142**)	130
		Angustimaline D (**136**)	130
		Angustimaline E (**137**)	130
		Anhydromacralstonine (**580**)	128
		Antirhine (**443**)	128
		Bipleiophylline (**576**)	51
		N(1)-Demethylalstonerinal (**6**)	128,129
		N(1)-Demethylalstonerine (**5**)	128,129
		20,21-Dihydroalstonerine (**149**)	128,129
		Dihydrocorynantheol (**440**)	128
		19-Epitalcarpine (**148**)	128,129
		Fluorocarpamine (**70**)	128

Table 1.2, continued

Species	Plant part	Alkaloids	References
		7-Hydroxypleiocarpamine (**470**)	128,129
		16*R*,19,20*E*-Isositsirikine (**65**)	128
		16*R*,19,20*Z*-Isositsirikine (**435**)	128
		Lochnerine (**47**)	128
		Macrocarpamine (**89**)	128
		Macrocarpine B (**146**)	128,129
		Macrocarpine C (**147**)	128,129
		Macrocarpine D (**15**)	128,129
		Macrocarpine E (**16**)	127
		Macrocarpine F (**143**)	128,129
		Macrocarpine G (**144**)	128,129
		Macrodasine A (**157**)	131
		Macrodasine B (**158**)	131
		Macrodasine C (**156**)	131
		Macrodasine D (**162**)	131
		Macrodasine E (**163**)	131
		Macrodasine F (**160**)	131
		Macrodasine G (**159**)	131
		N(4)-Methyl-19-epitalpinine (**422**)	128,129
		N(4)-Methyl-*N*(4),21-secotalpinine (**14**)	128,129
		Normacusine B (**410**)	128
		Normacusine B-2(*S*)-pseudoindoxyl (**430**)	128,129
		Perhentidine A (**583**)	128
		Perhentidine C (**582**)	128
		Perhentinine (**94**)	128
		Perhentisine A (**606**)	132
		Perhentisine B (**607**)	132
		Perhentisine C (**605**)	132
		Picramicine (**446**)	128
		Pleiocarpamine (**67**)	128
		Pleiomaltinine (**69**)	128
		Pleiomalicine (**473**)	128
		Talcarpine (**13**)	128
		Talpinine (**423**)	128
		Talpinine oxindole (**429**)	128,129
		Villalstonidine A (**592**)	132
		Villalstonidine B (**598**)	132
		Villalstonidine C (**599**)	132
		Villalstonidine D (**600**)	132
		Villalstonidine E (**601**)	132
		Villalstonidine F (**593**)	132
		Villalstonine (**90**)	132
		Villalstonine *N*-oxide (**91**)	132
	Leaves	Affinisine (**44**)	128
		Affinisine oxindole (**431**)	128
		Alstolactone A (**154**)	128

Table 1.2, continued

Species	Plant part	Alkaloids	References
		Alstonal (**25**)	128
		Alstonisine (**24**)	128
		Alstonoxine A (**31**)	128
		Alstonoxine B (**172**)	128
		Alstonoxine E (**171**)	128
		Alstophylline (**9**)	128
		19,20-Dehydro-10-methoxytalcarpine (**151**)	128
		N(1)-Demethylmacrocarpine B (macrocarpine D) (**15**)	128
		18,19-Dihydroisositsirikine (**64**)	128
		10,11-Dimethoxynareline (**516**)	128
		Fluorocarpamine (**70**)	128
		11-Hydroxystrictamine (**50**)	128
		Isoalstonoxine B (**176**)	128
		16*R*,19,20*Z*-Isositsirikine (**435**)	128
		Macrocarpine B (**146**)	128
		Macrogentine A (**177**)	128
		10-Methoxyaffinisine (**45**)	128
		11-Methoxystrictamine (**49**)	51
		N(1)-Methylsarpagine (**412**)	128
		Normacusine B (**410**)	128
		6-Oxopleiocarpamine (**468**)	128
		Pleiocarpamine (**67**)	128
		Strictamine (**347**)	128
		Yohimbine (**453**)	128
A. angustifolia Wall. ex A.DC. (Indonesia)	Stem bark	Akuammicine (**179**)	133
		Akuammicine *N*-oxide (**184**)	133
		Alstogustine (**204**)	134
		Echitamine (**336**)	133
		19-Epialstogustine (**201**)	134
		N(4)-Demethylalstogustine (**203**)	133
		N(4)-Demethylalstogustine *N*-oxide (**205**)	133
		N(4)-Demethylechitamine (**334**)	133
		N(4)-Methylakuammidine (**417**)	133
		N(4)-β-Methylantirhine (**444**)	133
		Tubotaiwine (**249**)	133
A. angustifolia Wall. ex A.DC. (Vietnam)		Affinisine (**44**)	135
		Alstonerinal (**4**)	135
		Macrocarpine B (**146**)	135
		N(4)-Methyltalpinine (**424**)	135
		N(4)-Methyl-*N*(4),21-secotalpinine (**14**)	135
		Villalstonidine D (**600**)	135
		Villalstonidine E (**601**)	135
		Villalstonine (**90**)	135
		Villalstonine *N*(4)-oxide (**91**)	135

Table 1.2, continued

Species	Plant part	Alkaloids	References
A. angustifolia Wall. ex A.DC. (Peninsular Malaysia)	Leaves	Affinisine (**44**)	53
		Affinisine oxindole (**431**)	53
		Alstofoline (**30**)	53
		Alstolactone (**18**)	53
		Alstolagumine (**73**)	53
		Alstonal (**25**)	53
		Alstonerinal (**4**)	53
		Alstonerine (**3**)	53
		Alstonisine (**24**)	53
		Alstonoxine A (**31**)	53
		Alstonoxine B (**172**)	53
		Alstophylline (**9**)	53
		Alstoumerine (**48**)	53
		Alstovine (**74**)	53
		Cathafoline (**52**)	53
		Cathafoline *N*-oxide (**53**)	53
		N(1)-Demethylalstonal (**27**)	53
		N(4)-Demethylalstonerinal (**8**)	53
		N(4)-Demethylalstonerine (**7**)	53
		N(1)-Demethylalstonisine (**26**)	53
		11-Hydroxystrictamine (**50**)	53
		16*R*,19,20*E*-Isositsirikine (**65**)	53
		Isoalstonisine (**170**)	53
		Lagumicine (**231**)	53
		Lagumidine (**75**)	53
		Lochnerine (**47**)	53
		Macrogentine (**178**)	53
		11-Methoxyakuammicine (**71**)	53
		10-Methoxyaffinisine (**45**)	53
		10-Methoxycathafoline (**355**)	53
		10-Methoxycathafoline *N*-oxide (**356**)	53
		11-Methoxystrictamine (**49**)	53
		10-Methoxyvincamajine (**385**)	53
		N(4)-Methyl-*N*(4),21-secotalpinine (**14**)	53
		Nor-*C*-fluorocurarine (**219**)	53
		Normacusine B (**410**)	53
		Quebrachidine (**63**)	53
		Sitsirikine (**437**)	53
		Strictamine (**347**)	53
		Talcarpine (**13**)	53
		Vincamajine (**62**)	53
		Vincorine (**54**)	53
	Stem bark	Alstonal (**25**)	136
		Alstonerinal (**4**)	53,136
		Alstonerine (**3**)	136
		Alstonisine (**24**)	136
		Alstophylline (**9**)	136

Table 1.2, continued

Species	Plant part	Alkaloids	References
		Cathafoline (**52**)	136
		Lochnerine (**47**)	136
		10-Methoxyaffinisine (**45**)	53,136
		10-Methoxycathafoline (**355**)	53,136
		Vincamajine (**62**)	136
A. angustiloba Miq. (Indonesia)	Whole plant	*O*-Acetylvallesamine (**487**)	137
		Angustilobine A (**498**)	137
		Angustilobine B (**503**)	137
		Cantleyine (**117**)	138
		Echitamidine (**196**)	139
		15-Hydroxy-angustilobine A (**497**)	137
		Nor-6,7-secoangustilobine A (**500**)	137
		4,6-Secoangustilobinal A (**499**)	137
		6,7-Secoangustilobine B (**508**)	137
		6,7-Seco-6-cyanostemmadenine (**494**)	137
		6,7-Seco-19,20α-epoxyangustilobine B (**513**)	137
		19,20-*E*-Vallesamine (**485**)	137
		Venoterpine (**116**)	138
A. angustiloba Miq. (Peninsular Malaysia)	Leaves	*O*-Acetylvallesamine (**487**)	140
		Alstolucine B (**209**)	140
		Andransinine (**556**)	140
		Angustilobine A (**498**)	140
		Angustilobine B (**503**)	140,141
		Angustilobine C (**515**)	140
		Angustilocine (**512**)	141
		Angustilodine (**474**)	141
		Condylocarpine (**247**)	140
		Echitamidine (**196**)	141
		16-Epivincamine (**555**)	140
		16*R*,19,20*E*-Isositsirikine (**65**)	140
		Leuconoxine (**537**)	141
		Losbanine (**511**)	141
		Picraline (**296**)	141
		Picrinine (**313**)	141
		Scholaricine (**190**)	141
		6,7-Secoangustilobine B (**508**)	140,141
		6,7-Seco-19,20α-epoxyangustilobine B (**513**)	141
		20*S*-Tubotaiwine (**249**)	140
		19,20-*E*-Vallesamine (**485**)	140,141
	Bark	17-*O*-Acetyl-*N*(4)-demethylechitamine (**341**)	140
		Ajmalicine (**451**)	141
		Akuammicine (**179**)	141
		Angustilobine B (**503**)	140,141

Table 1.2, continued

Species	Plant part	Alkaloids	References
		Angustiphylline (**568**)	140
		Cantleyine (**117**)	140,141
		N(4)-Demethylechitamine (**334**)	140,141
		6,7-Secoangustilobine B (**508**)	140
		6,7-Seco-19,20α-epoxyangustilobine B (**513**)	141
		20*S*-Tubotaiwine (**249**)	140
		Undulifoline (**481**)	140
		19,20-*E*-Vallesamine (**485**)	140,141
		Venoterpine (**116**)	140,141
		Yunnanensine (**493**)	140
A. angustiloba Miq. (Peninsular Malaysia)	Leaves	Alstilobanine A (**479**)	142
		Alstilobanine B (**484**)	142
		Alstilobanine C (**482**)	142
		Alstilobanine D (**509**)	142
		Alstilobanine E (**475**)	142
		Alstonamic acid (angustilobine B acid) (**505**)	142
		6,7-Secoangustilobine B (**508**)	142
		Undulifoline (**481**)	142
A. boonei De Wild. (Africa)	Stem bark	Alstiboonine (**324**)	143
		Echitamidine (**196**)	144
		N(1)-Formylechitamidine (**206**)	144
A. congensis Engl. (Africa)	Leaves	17-*O*-Acetyl-norechitamine (**341**)	145
		Angustilobine A (**498**)	145
		12-Methoxytubotaiwine (**251**)	145
		6,7-Secoangustilobine A (**502**)	145
		6,7-Secoangustilobine B (**508**)	145
	Stem bark	Akuammidine (**416**)	145
		Angustilobine A (**498**)	145
		Angustilobine B (**503**)	145
		Angustilobine B *N*-oxide (**506**)	145
		Echitamidine (**196**)	145
		Echitamine (**336**)	145
		12-Methoxyakuammicine (**181**)	145
	Root bark	17-*O*-Acetyl-norechitamine (**341**)	145
		Akuammicine (**179**)	145
		Echitamidine (**196**)	145
		Echitamine (**336**)	145
		12-Methoxyakuammicine (**181**)	145

Table 1.2, continued

Species	Plant part	Alkaloids	References
		12-Methoxy-*N*(4)-methylakuammicine (**182**)	145
		Norechitamine (*N*(4)-demethylechitamine) (**334**)	145
		6,7-Secoangustilobine B (**508**)	145
		Tubotaiwine (**249**)	145
A. constricta F.Muell. (Australia)	Stem bark	Alstonidine (**130**)	146
		Alstonilidine (**128**)	146
		1-Carbomethoxycarboline (**127**)	146
		14-Ketoalstonidine (**129**)	146
		Quebrachidine (**63**)	146
		O-3',4',5'-Trimethoxybenzoylquebrachidine (**60**)	146
		Vincamedine (**382**)	146
	Root bark	Alstonidine (**130**)	147
		Alstonilidine (**128**)	147
		Reserpine (**466**)	147
		O-3,4,5-Trimethoxybenzoylquebrachidine (**60**)	147
		O-3,4,5-Trimethoxycinnamoylvincamajine (**375**)	147
		Vincamajine (**62**)	147
A. coriacea Pancher ex S.Moore (New Caledonia)	Stem bark	Cabucraline (**358**)	148
		Corialstonine (**122**)	148
		Desmethylquaternine (norquaternine) (**316**)	148
		Gentianine (**119**)	148
		10-Methoxydeplancheine (**441**)	148
		10-Methoxy-3-epi-α-yohimbine (**456**)	148
		Vincamajine (**62**)	148
A. deplanchei Van Heurck & Müll.Arg. (New Caledonia)	Leaves	Pleiocorine (**578**)	149
		Pleiocraline (**579**)	150
		Vincorine (**54**)	149
	Stem bark	Deplancheine (**442**)	151
A. glabriflora Markgr. (New Guinea)	Bark	Alstophylline (**9**)	152
		Macralstonine (**585**)	152
		Pleiocarpamine (**67**)	152
		Villalstonine (**90**)	152

Table 1.2, continued

Species	Plant part	Alkaloids	References
A. glaucescens Monach. (Thailand)	Stem bark	17-*O*-Acetyl-*N*(4)-demethylechitamine (**341**)	[153]
		N(4)-Demethylechitamine (**334**)	[153]
		N(4)-Demethylechitamine *N*-oxide (**338**)	[153]
		Echitamidine (**196**)	[153]
		Echitamidine *N*-oxide (**198**)	[153]
		Echitamine (**336**)	[153]
		Echitaminic acid (**337**)	[153]
		20-Epi-19ξ-echitamidine (**202**)	[153]
A. lanceolata Van Heurck & Müll.Arg. (New Caledonia)	Stem bark	Akuammicine (**179**)	[154]
		ψ-Akuammigine (**372**)	[154]
		Cathafoline (**52**)	[154]
		Compactinervine (**218**)	[154]
		10,11-Dimethoxy-1-methyldeacetylpicraline (**300**)	[154]
		10,11-Dimethoxy-1-methyldeacetylpicraline-3',4',5'-trimethoxybenzoate (**303**)	[154]
		10,11-Dimethoxy-1-methylpicraline (**302**)	[154]
		Gentianine (**119**)	[154]
		Lanceomigine (**532**)	[154]
		Lanceomigine *N*-oxide (**533**)	[154]
		Lochnericine (**264**)	[154]
		10-Methoxycompactinervine (**216**)	[154]
		Picraline (**296**)	[154]
A. lanceolifera S.Moore (New Caledonia)	Leaves	10,11-Dimethoxy-1-methyldeacetylpicraline benzoate (**301**)	[155]
		10,11-Dimethoxy-1-methyldeacetylpicraline (**300**)	[155]
		10,11-Dimethoxy-1-methyldeacetylpicraline-3',4',5'-trimethoxybenzoate (**303**)	[155]
		10-Methoxydeplancheine (**441**)	[155]
	Stem bark	Akuammiline (**344**)	[156]
		10,11-Dimethoxy-1-methyldeacetylpicraline-3',4',5'-trimethoxybenzoate (**303**)	[156]
		10,11-Dimethoxy-1-methylpicraline (**302**)	[156]
		Lochnericine (**264**)	[156]
		11-Methoxyakuammicine (**71**)	[156]
		10-Methoxycompactinervine (**216**)	[156]
		11-Methoxycompactinervine (alstovine) (**74**)	[156]
		10-Methoxy-nor-C-fluorocurarine (**220**)	[156]
		10-Methoxyvincamajine (**385**)	[157]
		N(1)-Methyl-10-methoxyakuammidine (**420**)	[157]
		Picraline (**296**)	[156]
		O-Trimethoxybenzoylhydroxyvincamajine (**383**)	[157]
		O-Trimethoxycinnamoyl-10-hydroxy-vincamajine (**384**)	[157]
		O-Trimethoxycinnamoyl-10-methoxy-vincamajine (**386**)	[157]

Table 1.2, continued

Species	Plant part	Alkaloids	References
		O-3',4',5'-Trimethoxycinnamoylvincamajine (**375**)	[157]
A. lenormandii Van Heurck & Müll.Arg. (New Caledonia)	Leaves	10,11-Dimethoxy-1-methyldeacetylpicraline benzoate (**301**)	[158]
		10,11-Dimethoxy-1-methyldeacetylpicraline-3',4',5'-trimethoxybenzoate (**303**)	[158]
		Gentianine (**119**)	[158]
		12-Methoxycompactinervine (**217**)	[158]
		12-Methoxy-19,20-α-epoxyakuammicine (**215**)	[158]
	Bark	Akuammiline (**344**)	[158]
		10,11-Dimethoxy-1-methyldeacetylpicraline (**300**)	[158]
		10,11-Dimethoxy-1-methylpicraline (**302**)	[158]
		Lochnericine (**264**)	[158]
		11-Methoxyakuammicine (**71**)	[158]
		11-Methoxycompactinervine (alstovine) (**74**)	[158]
		12-Methoxycompactinervine (**217**)	[158]
		Picraline (**296**)	[158]
A. lenormandii var. *minutifolia* Boiteau (New Caledonia)	Leaves	10,11-Dimethoxy-1-methyldeacetylpicraline-3',4',5'-trimethoxybenzoate (**303**)	[158]
		Gentianine (**119**)	[158]
		12-Methoxycompactinervine (**217**)	[158]
A. macrophylla Wall. ex G.Don. (Sabah, Malaysian Borneo)	Bark	Alstonal (**25**)	[125,159]
		Alstonisine (**24**)	[125,159]
		N(4)-Demethylalstophyllal oxindole (**168**)	[125,159]
		N(4)-Demethylalstophylline oxindole (**169**)	[125,159]
		Talcarpine (**13**)	[125,159]
A. macrophylla Wall. ex G.Don. (Sri Lanka)	Leaves	Alstomacrocine (**150**)	[160]
		Alstonamide (**327**)	[161]
		Alstophylline (**9**)	[162]
		Alstopicralamine (quaternine) (**319**)	[163]
		Alstoumerine (**48**)	[161]
		Cabucraline (**358**)	[162]
		Demethoxyalstonamide (**56**)	[161]
		N(4)-Demethylalstophylline oxindole (**169**)	[164]
		16-Hydroxy-*N*(4)-demethylalstophylline oxindole (**167**)	[165]
		10-Hydroxystrictamine (**351**)	[160]
		19-Hydroxyvincamajine (**390**)	[162]
		Macroxine (**175**)	[166]
		Cathafoline (**52**)	[165]
		Strictaminolamine (**360**)	[167]

Table 1.2, continued

Species	Plant part	Alkaloids	References
		Vincamajine (**62**)	162,163
		Vincorine (**54**)	162
	Bark	Alstonerine (**3**)	162
		Anhydromacralstonine (**580**)	162
		Macralstonine (**585**)	162
		Talcarpine (**13**)	162
A. macrophylla Wall. ex G.Don. (Thailand)	Leaves	Alstophylline (**9**)	168
		Cathafoline (**52**)	168
		Cathafoline *N*-oxide (**53**)	168
		N(4)-Demethylalstophylline oxindole (**169**)	168
		11-Methoxyakuammicine (**71**)	168
		11-Methoxyakuammicine *N*-oxide (**72**)	168
		Vincamajine (**62**)	168
		Vincamajine-17-*O*-veratrate (**378**)	168
		Vincamajine-*N*(1)-tri-*O*-methylgallate (**61**)	168
		Vincorine (**54**)	168
	Stem	Macralstonine (**585**)	169
		Thungfaine (lumusidine D) (**589**)	169
	Root bark	Alstomacroline (**575**)	170
		Alstomacrophylline (**587**)	170
		Alstonerine (**3**)	170
		Alstophylline (**9**)	170
		Alstoumerine (**48**)	170
		20-Epiantirhine (**445**)	170
		Macralstonine (**585**)	171
		Macrocarpamine (**89**)	170
		O-Methylmacralstonine (**586**)	171
		Pleiocarpamine (**67**)	171
		Talcarpine (**13**)	171
		Villalstonine (**90**)	171
		Villalstonine *N*-oxide (**91**)	170
A. macrophylla Wall. ex G.Don. (Phillipines)	Leaves	Cathafoline (**52**)	172
		10,11-Dimethoxy-*N*(1)-methylpicrinine (quaternine) (**319**)	172
		11-Methoxy-19,20α-epoxyakuammicine (alstolagumine) (**73**)	172
		10-Methoxy-*N*(1)-methylburnamine-17-*O*-benzoate (**298**)	172
		10-Methoxy-*N*(1)-methylburnamine-17-*O*-veratrate (**299**)	172

Table 1.2, continued

Species	Plant part	Alkaloids	References
		11-Methoxy-19-oxo-20α-hydroxyakuammicine (lagumidine) (**75**)	172
		Norquaternine (10,11-dimethoxypicrinine, volkensine) (**316**)	172
		Strictamine (**347**)	172
		5α,10,11-Trimethoxystrictamine (**350**)	172
	Root	Affinisine (**44**)	173
		Alstophylline (**9**)	173
		O-Benzoylvincamajine (**380**)	173
		Macralstonidine (**87**)	173
		Macralstonine (5**85**)	173
		Macrocarpamine (**89**)	173
		Macrosalhine (**428**)	173
		N(1)-Methyl-2,16-dihydroakuammicine (**229**)	173
		Picralstonine (**322**)	173
		Picrinine (**313**)	173
		Pleiocarpamine (**67**)	173
		Villalstonine (**90**)	173
A. macrophylla Wall. ex G.Don. (India)	Leave	Affinisine (**44**)	174
		Picralstonine (**322**)	174
		Picrinine (**313**)	174
A. macrophylla Wall. ex G.Don. (Terengganu, Peninsular Malaysia)	Leaves	Alstohentine (**17**)	175
		Alstomaline (**333**)	175
		Alstomicine (**19**)	175
		Alstonal (**25**)	175
		Alstonerinal (**4**)	175
		Alstonerine (**3**)	175
		Alstonisine (**24**)	175
		Alstonoxine B (**172**)	175
		Alstophyllal (**10**)	175
		Alstophylline (**9**)	175
		Demethylalstonamide (**56**)	175
		N(4)-Demethylalstophyllal oxindole (**168**)	175
		N(4)-Demethylalstophylline oxindole (**169**)	175
		10,11-Dimethoxy-1-methyldeacetylpicraline-3',4',5'-trimethoxybenzoate (**303**)	175
		10,11-Dimethoxynareline (**516**)	175
		16-Hydroxyalstonal (**29**)	175
		16-Hydroxyalstonisine (**28**)	175
		16-Hydroxy-*N*(4)-demethylalstophyllal oxindole (**166**)	175
		16-Hydroxy-*N*(4)-demethylalstophylline oxindole (**167**)	175

Table 1.2, continued

Species	Plant part	Alkaloids	References
		Macrocarpine A (**145**)	175
		Macrocarpine B (**146**)	175
		6-Methoxy-4-methylquinoline (**114**)	175
		6-Methoxy-α-methyl-4-quinoline methanol (**115**)	175
		N(4)-Methyl-*N*(4),21-secotalpinine (**14**)	175
		Norquaternine (10,11-dimethoxypicrinine, volkensine) (**316**)	175
		6-Oxoalstophyllal (**153**)	175
		6-Oxoalstophylline (**152**)	175
		Quaternine (**319**)	175
		Talcarpine (**13**)	175
		Vincoridine (**332**)	175
		Vincorine (**54**)	175
	Stem bark	Alstonal (**25**)	176
		Alstonisine (**24**)	176
		Alstophyllal (**10**)	176
		Alstophylline (**9**)	176
		Angustimalal (**138**)	176
		N(1)-Demethylalstophyllal (**12**)	176
		N(4)-Demethylalstophyllal oxindole (**168**)	176
		N(1)-Demethylalstophylline (**11**)	176
		N(4)-Demethylalstophylline oxindole (**169**)	176
		Fluorocarpamine (**70**)	176
		16*R*,19,20*E*-Isositsirikine (**65**)	176
		Macrocarpine A (**145**)	176
		Macrocarpine B (**146**)	176
		Macrocarpine C (**147**)	176
		Macrodasine A (**157**)	176
		Macrodasine B (**158**)	176
		11-Methoxyakuammicine (**71**)	176
		N(4)-Methyl-*N*(4),21-secotalpinine (**14**)	176
		Perhentinine (**94**)	176
		Pleiocarpamine (**67**)	176
		Talcarpine (**13**)	176
		Villalstonine (**90**)	176
A. macrophylla Wall. ex G.Don. (Indonesia)	Leaves	Alstiphyllanine A (**401**)	177-179
		Alstiphyllanine B (**304**)	178,179
		Alstiphyllanine C (**305**)	178,179
		Alstiphyllanine D (**306**)	178,179
		Alstiphyllanine E (**307**)	179
		Alstiphyllanine F (**308**)	179
		Alstiphyllanine G (**297**)	179
		Alstiphyllanine H (**402**)	177,179
		Alstiphyllanine I (**403**)	177

Table 1.2, continued

Species	Plant part	Alkaloids	References
		Alstiphyllanine J (**404**)	177
		Alstiphyllanine K (**405**)	177
		Alstiphyllanine L (**406**)	177
		Alstiphyllanine M (**407**)	177
		Alstiphyllanine N (**408**)	177
		Alstiphyllanine O (**61**)	177
		Alstonal (**25**)	179
		Alstonerine (**3**)	179
		Burnamine (*O*-deacetylpicraline) (**311**)	179
		19*Z*-Burnamine-17-*O*-3',4',5'-trimethoxybenzoate (**309**)	178,179
		10,11-Dimethoxy-*N*(1)-methylpicrinine (quaternine) (**319**)	179
		10-Methoxy-*N*(1)-methylburnamine-17-*O*-veratrate (**299**)	178,179
		Picralinal (**321**)	179
		Picrinine (**313**)	179
		Vincamajine (**62**)	177,179
		Vincamajine-17-*O*-3',4',5'-trimethoxybenzoate (**376**)	177,179
		Vincamajine-17-*O*-veratrate (**378**)	177,179
		Vincamedine (**382**)	177-179
A. macrophylla Wall. ex G.Don. (Peninsular Malaya)	Leaves	19,20-*Z*-Affinisine (**413**)	180,181
		Alstofolinine A (**164**)	180,181
		Alstomaline (**333**)	181
		Alstonal (**25**)	181
		Alstonamide (**327**)	181
		Alstonerinal (**4**)	181
		Alstonerine (**3**)	181
		Alstonisine (**24**)	181
		Alstophyllal (**10**)	181
		Alstophylline (**9**)	181
		Alstonoxine A (**31**)	181
		Alstonoxine B (**172**)	181
		Alstonoxine C (**174**)	180,181
		Alstoumerine (**48**)	181
		Cathafoline (**52**)	181
		Cathafoline *N*-oxide (**53**)	181
		2(*S*)-Cathafoline (**362**)	180,181
		Demethoxyalstonamide (**56**)	181
		11-Demethoxyquaternine (**320**)	180,181
		10-Demethoxyvincorine (**329**)	180,181
		10-Demethoxyvincorine *N*(4)-oxide (**330**)	180,181
		11-Demethoxyvolkensine (12-demethoxytabernulosine) (**317**)	181
		N(4)-Demethylalstophyllal oxindole (**168**)	181
		N(4)-Demethylalstophylline oxindole (**169**)	181

Table 1.2, continued

Species	Plant part	Alkaloids	References
		18,19-Dihydroisositsirikine (**64**)	181
		10,11-Dimethoxynareline (**516**)	181
		Fluorocarpamine (**70**)	181
		2(*R*)-3-Hydroxycathafoline (**361**)	180,181
		11-Hydroxystrictamine (**50**)	181
		16*R*,19,20*E*-Isositsirikine (**65**)	181
		Macrocarpine B (**146**)	181
		11-Methoxyakuammicine (**71**)	181
		11-Methoxyakuammicine *N*(4)-oxide (**72**)	181
		10-Methoxycathafoline (**355**)	181
		2(*S*)-10-Methoxycathafoline (**363**)	180,181
		11-Methoxystrictamine (**49**)	181
		11-Methoxyvincorine (**328**)	180,181
		N(4)-Methyl-*N*(4),21-secotalpinine (**14**)	181
		Normacusine B (**410**)	181
		Norvincorine (**55**)	181
		Picrinine (**313**)	181
		Pleiocarpamine (**67**)	181
		Quebrachidine (**63**)	181
		Quaternine (**319**)	181
		Sitsirikine (**437**)	181
		Strictamine (**347**)	181
		Talcarpine (**13**)	181
		Talpinine (**423**)	181
		Vincamajine (**62**)	181
		Vincamajine *N*(4)-oxide (**381**)	180,181
		Vincamajine 17-*O*-veratrate (**378**)	181
		Vincamajine 17-*O*-veratrate *N*(4)-oxide (**379**)	180,181
		Vincorine (**54**)	181
		Vincorine *N*(4)-oxide (**326**)	180,181
		Yohimbine (**453**)	181
	Bark	19,20-*Z*-Affinisine (**413**)	180,181
		Affinisine (**44**)	181
		Affinisine oxindole (**431**)	181
		Alstoumerine (**48**)	181
		Alstonerine (**3**)	181
		Alstonerinal (**4**)	181
		Alstophylline (**9**)	181
		Alstophyllal (**10**)	181
		Alstonoxine B (**172**)	181
		Alstonoxine D (**173**)	180,181
		Anhydromacralstonine (**580**)	181
		Antirhine (**443**)	181
		Cathafoline (**52**)	181
		Cathafoline *N*(4)-oxide (**53**)	181
		2*S*-Cathafoline (**362**)	180,181

Table 1.2, continued

Species	Plant part	Alkaloids	References
		20,21-Dihydroalstonerine (**149**)	180,181
		Fluorocarpamine (**70**)	181
		16-Hydroxymethylpleiocarpamine (**68**)	181
		16*R*,19,20*E*-Isositsirikine (**65**)	181
		Lumusidine A (**588**)	181,182
		Lumusidine B (**93**)	181,182
		Lumusidine C (**590**)	181,182
		Lumusidine D (**589**)	181,182
		Lumutinine A (**591**)	52,181
		Lumutinine B (**92**)	52,181
		Lumutinine C (**609**)	52,181
		Lumutinine D (**608**)	52,181
		Lumutinine E (**510**)	181
		Macralstonine (**585**)	122,181
		Macralstonidine (**87**)	181
		Macrocarpamine (**89**)	181
		Macrocarpine A (**145**)	181
		Macrocarpine B (**146**)	181
		Macrocarpine C (**147**)	181
		Macrocarpine D (**15**)	180,181
		Macrodasine A (**157**)	181
		Macrodasine G (**159**)	181
		Macrodasine H (**161**)	180,181
		11-Methoxyakuammicine (**71**)	181
		N(4)-Methyl-*N*(4),21-secotalpinine (**14**)	181
		Normacusine B (**410**)	181
		Perhentidine A (**583**)	122,181
		Perhentidine B (**584**)	122,181
		Perhentinine (**94**)	122,181
		Picramicine (**446**)	181
		Pleiocarpamine (**67**)	181
		Pleiomaltinine (**69**)	181
		Talcarpine (**13**)	181
		Talpinine (**423**)	181
		1,2,3,4-Tetrahydro-1-oxo-β-carboline (**126**)	181
		Villalstonidine B (**598**)	181
		Villalstonidine F (**593**)	181,182
		Villalstonine (**90**)	181
		Villalstonine *N*-oxide (**91**)	181
		Vincamajine (**62**)	181
		Vincorine (**54**)	181
A. mairei H.Lév. (China)	Leaves	Alpneumine A (**234**)	183
		Alstomairine A (**233**)	183
		Alstomairine B (**235**)	183
		Alstomairine C (**236**)	183

Table 1.2, continued

Species	Plant part	Alkaloids	References
A. muelleriana Domin (Australia)	Bark	Alstonerine (**3**)	184,185
		Alstonisidine (**573**)	185
		Alstonisine (**24**)	185
		Des-*N*'(1)-methylanhydromacralstonine (**581**)	186
		2,7-Dihydropleiocarpamine (**469**)	186
		Macralstonine (**585**)	187
		11-Methoxyakuammicine (**71**)	188
		Pleiocarpamine (**67**)	186
		Quebrachidine (**63**)	186
		Villalstonine (**90**)	185
		Vinervinine (12-methoxyakuammicine) (**181**)	186
A. odontophora Boiteau (New Caledonia)	Leaves and stem	Antirhine (**443**)	189
		N(1)-Demethylpleiocorine (**577**)	189
		11-Methoxyakuammicine (**71**)	189
		Pleiocarpamine (**67**)	189
		Pleiocorine (**578**)	189
		Pleiocraline (**579**)	189
		Quebrachidine (**63**)	189
		Vincamajine (**62**)	189
A. plumosa Labill. (New Caledonia)	Stem bark	Caberine (**364**)	190
		Caberoline (**370**)	190
		Cabucraline (**358**)	190
		Cabucraline *N*-oxide (**359**)	190
		10-Carboaldehydecabucraline (**357**)	190
		Cathafoline (**52**)	190
		Desoxycabufiline (**571**)	190
		2,7-Dihydroxypleiocarpamine (**471**)	190
		Fluorocarpamine (**70**)	190
		11-Methoxycompactinervine (alstovine) (**74**)	190
		Nordesoxycabufiline (**572**)	190
		Pleiocarpamine (**67**)	190
		Pleiocorine (**578**)	190
		Pleiocraline (**579**)	190
		Quaternoline (**371**)	190
		Quaternoxine (**365**)	190
		Strictamine (**347**)	190
	Root	Cabucraline (**358**)	190
		Cabucraline *N*-oxide (**359**)	190
		Fluorocarpamine (**70**)	190
		11-Methoxycompactinervine (alstovine) (**74**)	190
		Pleiocarpamine (**67**)	190
		Plumocraline (**574**)	190
		3,4-Seco-3,14-dehydrocabucraline (**561**)	190

Table 1.2, continued

Species	Plant part	Alkaloids	References
A. pneumatophora Backer ex Den Berger (Peninsular Malaysia)	Leaves	Actinophyllic acid (**534**)	191
		Akuammidine (**416**)	191
		Alpneumine A (**234**)	191
		Alpneumine B (**237**)	191
		Alpneumine C (**238**)	191
		Alpneumine D (**239**)	191
		Alpneumine E (**240**)	191
		Alpneumine F (**535**)	191
		Alpneumine G (**554**)	191
		Alpneumine H (**483**)	191
		Alsmaphorazine A (**241**)	192
		Alsmaphorazine B (**242**)	192
		Alsmaphorazine C (**562**)	193
		Alsmaphorazine D (**563**)	193
		Alsmaphorazine E (**564**)	193
		Alstilobanine B (**484**)	191
		Apovincamine (**552**)	191
		Echitamidine (**196**)	191
		Scholarine (12-methoxyechitamidine) (**187**)	191
		Vincamine (**553**)	191
	Bark	Akuammicine (**179**)	50
		Alstilobanine C (**482**)	50
		Angustilobine B (**503**)	50
		Cantleyine (**117**)	50
		16-Decarbomethoxy-6,7-secoangustilobine B (**510**)	50
		N(4)-Demethylalstogustine (**203**)	50
		N(4)-Demethylalstogustine *N*(4)-oxide (**205**)	50
		N(4)-Demethylechitamine (**334**)	50
		19-Epi-echitamidine (**200**)	50
		16-Epivincamine (**555**)	50
		15-Hydroxy-angustilobine A (**497**)	50
		16*R*,19,20*E*-Isositsirikine (**65**)	50
		Neozeylanicine (**120**)	50
		Nor-6,7-secoangustilobine A (**500**)	50
		Pneumatophorine (**495**)	50
		Rhazimol (**346**)	50
		4,6-Secoangustilobinal A (**499**)	50
		6,7-Secoangustilobine B (**508**)	50
		Strictamine (**347**)	50
		20*S*-Tubotaiwine (**249**)	50
		19,20-*E*-Vallesamine (**485**)	50
		Venoterpine (**116**)	50
		Yunnanensine (**493**)	50

Table 1.2, continued

Species	Plant part	Alkaloids	References
A. quaternata Van Heurck & Müll.Arg. (New Caledonia)	Whole plant	Cathafoline (**52**)	[194]
		10,11-Dimethoxy-*N*(1)-methylpicrinine (quaternine) (**319**)	[194]
		Pseudoyohimbine (**458**)	[194]
		Quaternatine (**457**)	[194]
		Quaternidine (**312**)	[194]
		Quaternoline (**371**)	[194]
		Quaternoxine (**365**)	[194]
		20(*R*)-Tubotaiwine (**248**)	[194]
		Vincamajine (**62**)	[194]
		Yohimbine (**453**)	[194]
A. rostrata C.E.C.Fisch. (China)	Leaves and Twigs	17-*O*-Acetyl-norechitamine (**341**)	[195]
		Akuammidine (**416**)	[195]
		Alstrostine A (**565**)	[196]
		Alstrostine B (**566**)	[196]
		Alstrostine C (**244**)	[195]
		Alstrostine D (**245**)	[195]
		Alstrostine E (**246**)	[195]
		Alstrostine F (**567**)	[195]
		Deacetylakuammiline (**346**)	[195]
		N(4)-Demethylechitamine (**334**)	[195]
		19,20-Dihydroakuammicine (**207**)	[195]
		Echitamidine (**196**)	[195]
		Isovallesiachotamine (*Z*-vallesiachotamine) (**439**)	[195]
		12-Methoxyechitamidine (scholarine) (**187**)	[195]
		19-Oxo-12-methoxyechitamidine (**214**)	[195]
		6,7-Secoangustilobine	[195]
		Tabersonine (**261**)	[195]
		Undulifoline (**481**)	[195]
		Vallesiachotamine (*E*-vallesiachotamine) (**438**)	[195]
A. rostrata C.E.C.Fisch. (China)	Twigs	17-*O*-Acetyl-norechitamine (**341**)	[197]
		N(4)-Demethylalstogustine (**203**)	[197]
		N(4)-Demethylechitamine (**334**)	[197]
		12-Methoxyechitamidine (**187**)	[197]
		Winphylline A (**340**)	[197]
		Winphylline B (**195**)	[197]
	Bark	17-*O*-Acetyl-*N*(4)-demethylechitamine (**341**)	[198]
		Alstrostine G (**558**)	[198]
		Alstrostine H (**243**)	[198]
		Alstrostine I (**189**)	[198]
		Alstrostine J (**133**)	[198]
		Alstrostine K (**480**)	[198]
		Antirhine (**443**)	[198]

Table 1.2, continued

Species	Plant part	Alkaloids	References
		N(4)-Demethylalstogustine (**203**)	198
		N(4)-Demethylalstogustine *N*(4)-oxide (**205**)	198
		N(4)-Demethylechitamine (**334**)	198
		N(4)-Demethyl-12-methoxyalstogustine	198
		N(4)-Demethyl-12-methoxyalstogustine *N*(4)-oxide (**186**)	198
		Eburenine (**267**)	198
		Echitamidine (**196**)	198
		16-Epivincamine (**555**)	198
		12-Methoxyechitamidine (**187**)	198
		N(4)-Methyl-aspidodasycarpine (**288**)	198
		Picraline (**296**)	198
		6,7-Secoangustilobine B (**508**)	198
		Vallesamine (19,20-*E*-vallesamine) (**485**)	198
A. rostrata C.E.C. Fisch. (Peninsular Malaysia)	Bark	Akuammicine (**179**)	50
		(-)-Alstolucine B (**209**)	50
		Cantleyine (**117**)	50
		N(4)-Chloromethylechitamidine chloride (**197**)	50
		N(4)-Demethylechitamine (**334**)	50
		Epi-leuconolam (revised to 6,7-dehydroleuconoxine) (**539**)	50
		Echitamidine (**196**)	50
		Leuconolam (**542**)	50
		Leuconoxine (**537**)	50
		Mersicarpine (**559**)	50
		O-Methylleuconolam (**543**)	50
		Neozeylanicine (**120**)	50
		Rhazinicine (**541**)	50
		Rostracine (**121**)	50
		Tetrahydroalstonine (**450**)	50
		20(*S*)-Tubotaiwine (**249**)	50
		Undulifoline (**481**)	50
		19,20-*E*-Vallesamine (**485**)	50
		E-Vallesiachotamine (**438**) and *Z*-Vallesiachotamine (**439**)	50
		Venoterpine (**116**)	50
A. rupestris Kerr (China)	Aerial parts	11-Acetyl-6,7-epoxy-8-oxo-vincadifformine (**258**)	199
		14-chloro-11,15-dihydroxy-vincadifformine (**262**)	199
		6,7-Epoxy-11-hydroxy-8-oxovincadifformine (**259**)	199
		6,7-Epoxy-8-oxo-vincadifformine (**257**)	199
		Perakine *N*(1),*N*(4)-dioxide (**396**)	199
		Vinorine *N*(1),*N*(4)-dioxide (**392**)	199

Table 1.2, continued

Species	Plant part	Alkaloids	References
A. scholaris (L.) R.Br. (Thailand)	Leaves	Alschomine (**280**)	200
		Isoalschomine (**281**)	200
		Nareline (**517**)	200
		Picrinine (**313**)	200
		Scholaricine (**190**)	200
		Tubotaiwine (**249**)	200
		19,20-*E*-Vallesamine (**485**)	200
	Stem bark	*N*(4)-Demethylechitamine (**334**)	201
		Echitamine (**336**)	201
		18(or19)-Hydroxy-19,20-dihydroakuammicine (**208**)	201
		Picrinine (**313**)	201
		Tubotaiwine (**249**)	201
	Root bark	Akuammicine (**179**)	201,202
		Akuammicine *N*(4)-methiodide (**183**)	201,202
		Akuammicine *N*(4)-oxide (**184**)	201,202
		ψ-Akuammigine (**372**)	201,202
		N(4)-Demethylechitamine (**334**)	201,202
		Echitamidine (**196**)	201,202
		Echitamine (**336**)	201,202
		Tubotaiwine (**249**)	201,202
A. scholaris (L.) R.Br. (Peninsular Malaysia, east coast)	Leaves	5-Epinareline ethyl ether (**521**)	125,203
		Nareline ethyl ether (**519**)	125,203
		Nareline methyl ether (**520**)	125,203
		Picrinine (**313**)	125,203
		Scholaricine (**190**)	125,203
		Scholarine *N*-oxide (**188**)	125,203
A. scholaris (L.) R.Br. (Peninsular Malaysia, west coast)		Alstobrogaline (**279**)	204
		Alstolaxepine (**514**)	49
		Alstoscholactine (**477**)	49
		6,7-Secoangustilobine B (**508**)	49
		19,20-*E*-Vallesamine (**485**)	49
A. scholaris (L.) R.Br. (India)	Leave	Akuammidine (**416**)	205
		Echitamidine (**196**)	206
		Echitamine (**336**)	206
		Nareline (**517**)	205
		Picralinal (**321**)	205
		Picrinine (**313**)	205,206
		Pseudoakuammigine (**372**)	205

Table 1.2, continued

Species	Plant part	Alkaloids	References
		Scholarine (12-methoxyechitamidine) (**187**)	207
	Fruit pods	*N*-Formylscholarine (**230**)	208
		Nareline (**517**)	208
		Picrinine (**313**)	208
		Strictamine (**347**)	208
A. scholaris (L.) R.Br. (The Phillipines)	Leaves	Angustilobine B acid (**505**)	200,209
		Angustilobine B *N*(4)-oxide (**506**)	210
		Lagunamine (19-hydroxytubotaiwine) (**252**)	200,209
		Losbanine (**511**)	200,209
		Manilamine (**496**)	210
		N(4)-Methylangustilobine B (**507**)	210
		6,7-Secoangustilobine B (**508**)	200,209,210
		20*S*-Tubotaiwine (**249**)	200,209,210
		20*S*-Tubotaiwine *N*-oxide (**250**)	200
		19,20-*E*-Vallesamine (**485**)	210
	Bark	17-*O*-Acetylechitamine (**335**)	209
		N(4)-Demethylechitamie (**334**)	209
		Echitamine (**336**)	209
		Losbanine (**511**)	209
		6,7-Secoangustilobine B (**508**)	209
		20*S*-Tubotaiwine (**249**)	209
		Tubotaiwine *N*-oxide (**250**)	209
A. scholaris (L.) R.Br. (Taiwan)	Leaves	Alschomine (**280**)	200
		19-Epischolaricine (**192**)	200
		Isoalschomine (**281**)	200
		Nareline (**517**)	200
		Picralinal (**321**)	200
		Picrinine (**313**)	200
		6,7-Secoangustilobine B (**508**)	200
		19,20-*E*-Vallesamine (**485**)	200
A. scholaris (L.) R.Br. (Indonesia)	Leaves	Akuammidine (**416**)	200,211
		Akuammidine *N*-oxide (**418**)	211
		ψ-Akuammigine (**372**)	200
		ψ-Akuammigine *N*-oxide (**373**)	200
		Leuconolam (**542**)	200
		N(1)-Methylburnamine (**295**)	200
		N(4)-Methylscholaricine (**191**)	200
		Picraline (**296**)	200
		Scholaricine (**190**)	200

Table 1.2, continued

Species	Plant part	Alkaloids	References
		6,7-Secoangustilobine B (**508**)	200
		6,7-Seco-19,20α-epoxyangustilobine B (**513**)	200
		19,20-*E*-Vallesamine (**485**)	200
		19,20-*E*-Vallesamine *N*-oxide (**486**)	200
	Bark	Akuammicine *N*-oxide (**184**)	212
		Akuammiginone (**374**)	212
		N(4)-Demethylalstogustine (**203**)	212
		N(4)-Demethylalstogustine *N*-oxide (**205**)	212
		Echitamidine *N*-oxide (**198**)	212
		Echitamidine-*N*-oxide 19-*O*-β-D-glucopyranoside (**199**)	212
		Echitaminic acid (**337**)	212
A. scholaris (L.) R.Br. (Pakistan)	Leaves	Alstonamine (**504**)	213
		Rhazimanine (**433**)	213
		19,20-*E*-Vallesamine (**485**)	214
		19,20-*Z*-Vallesamine (**488**)	214
A. scholaris (L.) R.Br. (China)	Leaves	Akuammidine (**416**)	215-217
		Alstonitrine A (**275**)	218
		Alstolactine A (**289**)	219
		Alstolactine B (**290**)	219
		Alstolactine C (**291**)	219
		Alstolucine D (**212**)	220
		Alstoniascholarine A (**490**)	221
		Alstoniascholarine B (**491**)	221
		Alstoniascholarine C (**492**)	221
		Alstoniascholarine D (**134**)	221
		Alstoniascholarine E (**536**)	221
		Alstoniascholarine F (**221**)	221
		Alstoniascholarine G (**222**)	221
		Alstoniascholarine H (**223**)	221
		Alstoniascholarine I (**224**)	221
		Alstoniascholarine J (**226**)	221
		Alstoniascholarine K (**227**)	221
		Alstoniascholarine L (**292**)	220
		Alstoniascholarine M (**293**)	220
		Alstoniascholarine N (**294**)	220
		Alstoniascholarine O (**193**)	220
		Alstoniascholarine P (**194**)	220
		Alstoniascholarine Q (**186**)	220
		Alstorisine A (**540**)	216
		19,20-*E*-Alstoscholarine (**530**)	222
		19,20-*Z*-Alstoscholarine (**531**)	222
		Alstoscholarisine A (**544**)	223

Table 1.2, continued

Species	Plant part	Alkaloids	References
		Alstoscholarisine B (**545**)	223
		Alstoscholarisine C (**546**)	223
		Alstoscholarisine D (**547**)	223
		Alstoscholarisine E (**548**)	223
		Alstoscholarisine F (**125**)	224
		Alstoscholarisine G (**135**)	224
		Alstoscholarisine H (**549**)	48
		Alstoscholarisine I (**550**)	48
		Alstoscholarisine J (**551**)	48
		Burnamine (**311**)	216,220
		1-[2-[2-(Carboxymethyl)indole-3-yl]ethyl]-3-ethylpyridinium hydroxide inner salt (**132**)	225
		10-Demethoxyvincorine *N*(4)-oxide (**330**)	226
		N(4)-Demethylalstogustine (**203**)	217
		N(4)-Demethylalstogustine *N*-oxide (**205**)	220
		N(4)-Demethylechitamine (**334**)	215
		Echitamidine (**196**)	220
		Epi-leuconolam (revised to 6,7-dehydroleuconoxine) (**539**)	217
		19-Epischolaricine (**192**)	215,217,220,222
		17-Formyl-10-demethoxyvincorine *N*(4)-oxide (**331**)	226
		(*Z*)-16-Formyl-5α-methoxylstrictamine	216,227
		(+)-Geissoschizine (**434**)	216
		5-Hydroxy-19,20-*E*-alschomine (**282**)	228
		5-Hydroxy-19,20-*Z*-alschomine (**283**)	228
		Isoalschomine (**281**)	220
		Isovallesiachotamine (**439**)	216,222
		Leuconolam (**542**)	217,229
		Melosline A (**478**)	225
		Melosline B (**131**)	225
		10-Methoxyalstiphyllanine H (**389**)	226
		12-Methoxyechitamidine (**187**)	222
		N(1)-Methoxymethyl picrinine (**318**)	229
		5α-Methoxystrictamine (**353**)	215-217,222,227,229
		N(1)-Methylburnamine (**295**)	215
		Methyl (2*β*,16*R*,19*E*)-4,5-didehydro-1,2-dihydro-2-hydroxy-16-(hydroxymethyl)akuammilan-4-ium-17-oate chloride (**367**)	215
		Nareline (**517**)	220,222,227
		17-Nor-excelsinidine (**557**)	217,230
		Normavacurine-21-one (**472**)	228
		5-Oxo-17-deacetyl-1,2-dihydroakuammiline (**366**)	215
		Picralinal (**321**)	215-217,220,229
		Picrinine (**313**)	215-217,220,222,227,229
		Polyneuridine (**414**)	220
		Pseudoakuammigine *N*(4)-oxide (**373**)	220
		Rhazimanine (**433**)	215

Table 1.2, continued

Species	Plant part	Alkaloids	References
		Scholaricine (**190**)	215-217,220,222,229
		Scholarine (12-methoxyechitamidine) (**187**)	216
		Scholarisine A (**526**)	231,232
		Scholarisine H (**560**)	227
		Scholarisine I (**524**)	220,227,232
		Scholarisine J (**525**)	227
		Scholarisine K (**285**)	227
		Scholarisine L (**286**)	227
		Scholarisine M (**287**)	227
		Scholarisine N (**489**)	227
		Scholarisine O (**123**)	227
		Scholarisine P (**522**)	217
		Scholarisine Q (different structure as **284**) (**368**)	217
		Scholarisine R (different structure as **315**) (**436**)	217
		Scholarisine S (**518**)	217
		Scholarisine T (**528**)	232
		Scholarisine U (**523**)	232
		Scholarisine V (**527**)	232
		Scholarisine W (**529**)	232
		Strictamine (**347**)	216,220,222,227,230
		Strictamine *N*(4)-oxide (**348**)	222
		Strictosamide (**465**)	217
		Tubotaiwine (**249**)	216,220
		Tubotaiwine *N*-oxide (**250**)	216,220
		19,20-*E*-Vallesamine (**485**)	215-217,220,222,227,229
		19,20-*Z*-Vallesamine (**488**)	220
		Vallesamine *N*(4)-oxide (**486**)	220,222
		Vallesiachotamine (*E*-vallesiachotamine) (**438**)	216,221
		(+)-Vincadifformine (**253**)	216
	Fruits	Scholarisine Q (**284**) (same name as **368**)	233
		Scholarisine R (**315**) (same name as **436**)	233
	Bark	Akuammidine (**416**)	234
		Alstonlarsine A (**476**)	235
		Alstonlarsine B (**447**)	235
		Alstonlarsine C (**448**)	235
		Alstonlarsine D (**449**)	235
		N(4)-Demethylechitamine (**334**)	234
		Echitamidine (**196**)	234
		Echitamine (**336**)	234
		19-Epi-ajmalicine (**452**)	234
		3-Epi-dihydrocorymine (**339**)	234
		20-Epi-19-oxodihydroakuammicine (alstolucine F) (**211**)	234

Table 1.2, continued

Species	Plant part	Alkaloids	References
		19-Epischolaricine (**192**)	234
		19*Z*-16-Formyl-5α-methoxystrictamine (**354**)	234
		Leuconoxine (**537**)	234
		5-Methoxystrictamine (**353**)	234
		Nareline (**517**)	234
		Picralinal (**321**)	234
		Picrinine (**313**)	234
		Scholarisine B (**325**)	234
		Scholarisine C (**276**)	234
		Scholarisine D (**277**)	234
		Scholarisine E (**278**)	234
		Scholarisine F (**314**)	234
		Scholarisine G (**538**)	234
		19,20-*E*-Vallesamine (**485**)	234
A. spatulata Blume (Peninsular Malaysia)	Leaves	Akuammicine (**179**)	236
		Alstolobine A (**501**)	236
		(-)-Alstolucine A (**232**)	236
		(-)-Alstolucine B (**209**)	236
		(-)-Alstolucine C (**210**)	236
		(-)-Alstolucine D (**212**)	236
		(-)-Alstolucine E (**213**)	236
		(-)-Alstolucine F (**211**)	236
		N(4)-Demethyl-12-methoxyalstogustine (**185**)	236
		16-Epivincamine (**555**)	236
		16*R*,19,20*E*-Isositsirikine (**65**)	236
		Nor-6,7-secoangustilobine A (**500**)	236
		Picrinine (**313**)	236
		4,6-Secoangustilobinal A (**499**)	236
		20(*R*)-Tubotaiwine (**248**)	236
		Undulifoline (**481**)	236
		Vincadifformine (**253**)	236
		Vincamine (**553**)	236
		Vinervine/12-Hydroxyakuammicine (**180**)	236
	Stem Bark	Akuammicine (**179**)	236
		(±)-Angustilobine B (**503**)	236
		N(4)-Demethylechitamine (**334**)	236
		N(4)-Demethyl-12-methoxyalstogustine (**185**)	236
		15-Hydroxy-angustilobine A (**497**)	236
		Leuconoxine (**537**)	236
		20*R*-Tubotaiwine (**248**)	236
		20*S*-Tubotaiwine (**249**)	236
		Undulifoline (**481**)	236
		19,20-*E*-Vallesamine (**485**)	236
		Vinervine/12-Hydroxyakuammicine (**180**)	236

Table 1.2, continued

Species	Plant part	Alkaloids	References
A. spectabilis R.Br. (New Guinea)	Bark	Macralstonine (**585**)	152
		N(1)-Methylsarpagine (**412**)	152
		Pleiocarpamine (**67**)	152
		Quebrachidine (**63**)	152
		Villalstonine (**90**)	152
		Vincamajine (**62**)	152
A. sphaerocapitata Boiteau (New Caledonia)	Leaves	Akuammicine (**179**)	237
		Caberoline (**370**)	237
		Cabucraline (**358**)	237
		Cathafoline (**52**)	237
		Desoxycabufiline (**571**)	237
		Z-Isositsirikine (**435**)	237
		11-Methoxyakuammicine (**71**)	237
		10-Methoxyvincamedine (**387**)	237
		10-Methoxyvincamedine *N*-oxide (**388**)	237
		Quaternoline (**371**)	237
		20(*S*)-Tubotaiwine (**249**)	237
		Vincamedine (**382**)	237
	Stem bark	Akuammicine (**179**)	237
		Cabucraline (**358**)	237
		Cathafoline (**52**)	237
		Desoxycabufiline (**571**)	237
		11-Methoxyakuammicine (**71**)	237
		10-Methoxyvincamedine (**387**)	237
		10-Methoxyvincamedine *N*-oxide (**388**)	237
		Nor-C-fluorocurarine (**219**)	237
		Nordesoxycabufiline (**572**)	237
		Undulatine (**569**)	237
		Vincamedine (**382**)	237
	Fruit	Akuammicine (**179**)	237
		Cabucraline (**358**)	237
		Cathafoline (**52**)	237
		Desoxycabufiline (**571**)	237
		10-Methoxyvincamedine (**387**)	237
		10-Methoxyvincamedine *N*-oxide (**388**)	237
		11-Methoxyakuammicine (**71**)	237
		Quaternoxine (**365**)	237
		Quebrachidine (**63**)	237
		Vincamedine (**382**)	237
		Vincoridine (**332**)	237

Table 1.2, continued

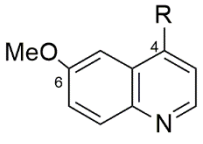
Species	Plant part	Alkaloids	References
A. undulata Guillaumin (New Caledonia)	Leaves	Cabucraline (**358**)	238
		Cathafoline (**52**)	238
		Deformylundulatine (**570**)	238
		Pericyclivine (**419**)	238
		Tetrahydroalstonine (**450**)	238
		Vincorine (**54**)	238
	Root bark	Alstonisidine (**573**)	238
		Cabucraline (**358**)	238
		Cabucraline *N*-oxide (**359**)	238
		Deplancheine (**442**)	238
		Desoxycabufiline (**571**)	238
		Fluorocarpamine (**70**)	238
		Gentiacraline (**369**)	238
		11-Methoxyakuammicine (**71**)	238
		11-Methoxyakuammicine *N*-oxide (**72**)	238
		Pleiocarpamine (**67**)	238
		Plumocraline (**574**)	238
		Tetrahydroalstonine (**450**)	238
		Vincamedine (**382**)	238
A. undulifolia Kochummen & K.M.Wong (Peninsular Malaysia)	Stem bark	Akuammicine (**179**)	125,239
		Cantleyine (**117**)	125,239
		N(4)-Demethylechitamine (**334**)	125,239
		Echitamidine (**196**)	125,239
		Echitamine (**336**)	125,239
		20-Epi-19ξ-echitamidine (**202**)	125,239
		Pleiocarpamine (**67**)	125,239
		Tetrahydrocantleyine (**118**)	125,239
		Undulifoline (**481**)	125,239
A. venenata R.Br. (India)	Leaves	Alstolenine (**345**)	240
		Deacetylakuammiline (rhazimol) (**346**)	240
		19,20-Dihydropolyneuridine (**415**)	240
		Echitoveniline (**273**)	241
		11-Methoxyechitovenedine (**268**)	241
		11-Methoxyechitoveniline (**272**)	241
		Polyneuridine (**414**)	240
		Raucaffrinoline (**397**)	240
	Fruit	Echitoserpidine (**271**)	242
		Echitoserpine (**270**)	243
		Echitovenedine (**269**)	244
		Echitoveniline (**273**)	241
		11-Methoxyechitovenedine (**268**)	241

Table 1.2, continued

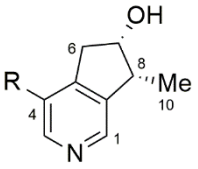
Species	Plant part	Alkaloids	References
		11-Methoxyechitoveniline (**272**)	[241]
		(+)-Minovincinine (**266**)	[244]
		Venoterpine (**116**)	[245]
	Root bark	Alstovenine (**461**)	[246]
		5,22-Dioxokopsane (**274**)	[246]
		16-Epialstovenine (**460**)	[246]
		16-Epivenenatine (**462**)	[246]
		Isovenenatine (**459**)	[246]
		Venenatine (**463**)	[246]
		Venoxidine (**464**)	[246]
A. villosa Blume (Indonesia)	Leaves	19*Z*-Burnamine-17-*O*-3',4',5'-trimethoxybenzoate (**309**)	[247]
		17-Deacetyl-5α,10-dimethoxyakuammiline-17-*O*-benzoate (**343**)	[247]
		17-Deacetyl-5α,10-dimethoxyakuammiline-17-*O*-3',4',5'-trimethoxybenzoate (**342**)	[247]
		5α,10-Dimethoxystrictamine (**349**)	[247]
		19*Z*-16-Formyl-5α-methoxystrictamine (**354**)	[247]
		11-Methoxy-19,20α-epoxyakuammicine (alstolagumine) (**73**)	[247]
		10-Methoxy-*N*(1)-methylburnamine-17-*O*-benzoate (**298**)	[247]
		10-Methoxy-*N*(1)-methylburnamine-17-*O*-veratrate (**299**)	[247]
		19*Z*-5α-Methoxyrhazimine (**124**)	[247]
		Norquaternine (10,11-dimethoxypicrinine, volkensine) (**316**)	[247]
		19*Z*-Picralinal (**310**)	[247]
		Quaternine (10,11-dimethoxy-*N*(1)-methyl-picrinine) (**319**)	[247]
		5α,10,11-Trimethoxystrictamine (**350**)	[247]
		Vincamajine (**62**)	[247]
		Vincamajine-17-*O*-3',4',5'-trimethoxybenzoate (**376**)	[247]
		Vincamajine-17-*O*-3',4',5'-trimethoxybenzoate *N*-oxide (**377**)	[247]
		Yohimbine-17-*O*-acetate (*O*-acetylyohimbine) (**454**)	[247]
A. vitiensis Seem. (New Caledonia)	Stem	Cabucraline (**358**)	[248]
		11-Methoxycompactinervine (alstovine) (**74**)	[248]
		Pleiocarpamine (**67**)	[248]
		Quaternoxine (**365**)	[248]
		Vincorine (**54**)	[248]

Table 1.2, continued

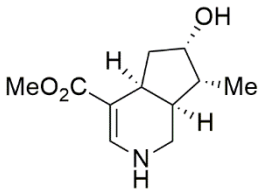
Species	Plant part	Alkaloids	References
A. yunnanensis Diels (China)	Whole plant	19-Acetoxy-11-methoxytabersonine (**255**)	249
		Alloyohimbine (**455**)	249
		Alstoyunine A (**425**)	249
		Alstoyunine B (**427**)	249
		Alstoyunine C (**399**)	249
		Alstoyunine D (**400**)	249
		Alstoyunine E (vinorine *N*-oxide) (**393**)	249
		Alstoyunine F (**409**)	249
		Alstoyunine G (**256**)	249
		Alstoyunine H (**260**)	249
		19*Z*-Burnamine-17-*O*-3',4',5'-trimethoxybenzoate (**309**)	249
		14-Chloro-15-hydroxy-vincadifformine (**263**)	250
		Compactinervine (**218**)	249
		Echitoserpidine (**271**)	249
		(-)-Echitoveniline (**273**)	249
		19-Epi-ajmalicine (**452**)	249
		11-Hydroxy-6,7-epoxy-8-oxovincadifformine (**259**)	250
		Lochnerinine (**265**)	249
		11-Methoxytabersonine (**254**)	249
		Perakine (**394**)	249
		Perakine *N*(4)-oxide (**395**)	250
		Picraline (**296**)	249
		Picrinine (**313**)	249
		Raucaffrinoline (**397**)	249
		Raucaffrinoline *N*(4)-oxide (**398**)	250
		Tabersonine (**261**)	249
		Vellosimine (**411**)	249
		Vellosiminol (normacusine B) (**410**)	249
		Vinorine (**391**)	249
		Vinorine *N*(1),*N*(4)-dioxide (**392**)	250
	Aerial parts	Alstiyunnanenine A (**426**)	251
		Alstiyunnanenine B (**323**)	251
		Alstiyunnanenine C (cathafoline *N*-oxide) (**53**)	251
		Alstiyunnanenine D (**225**)	251
		Alstiyunnanenine E (**228**)	251
		Alstoniascholarine I (**224**)	251



114 R = Me
115 R = CH(Me)OH



116 α-10-Me, R = H
117 α-10-Me, R = CO_2Me



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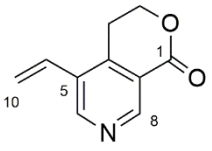

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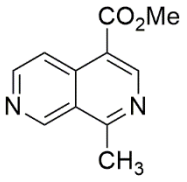

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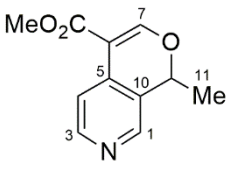

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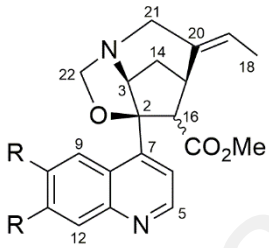
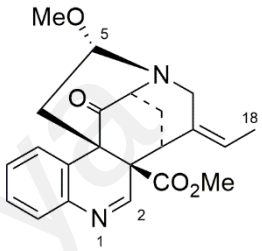
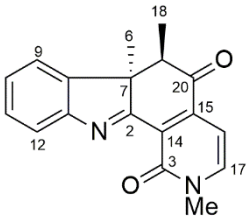


122 R = OMe
123 R = H, β-CO_2Me



124



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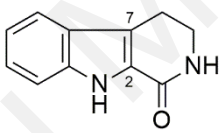

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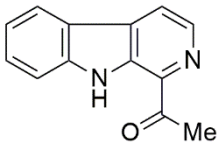

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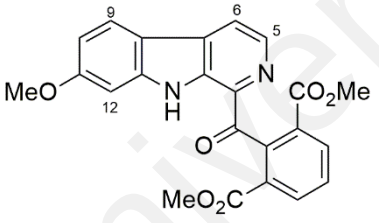

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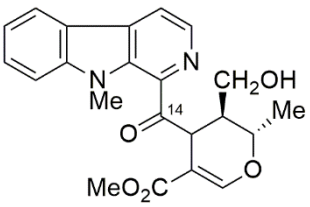

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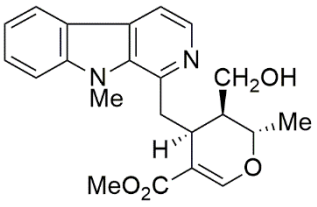
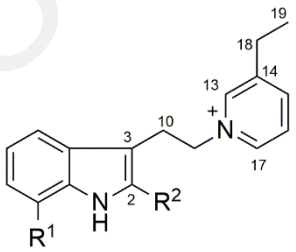
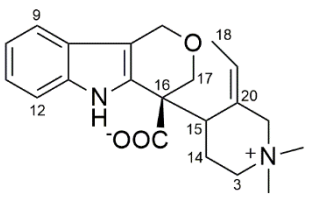


130



131 R^1 = H, R^2 = COO^-
132 R^1 = H, R^2 = CH_2COO^-
133 R^1 = OMe, R^2 = CH_2COO^-



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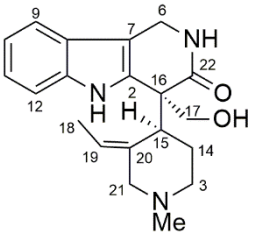

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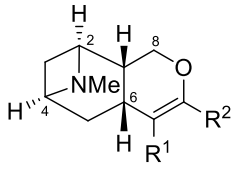
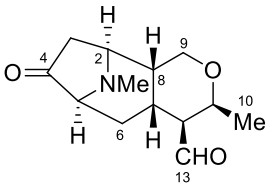


136 R^1 = CHO, R^2 = Me
137 R^1 = COMe, R^2 = H



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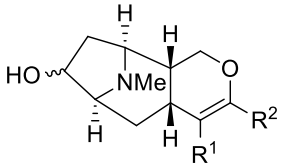
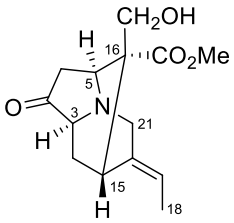


139 α-OH, R^1 = COMe, R^2 = H
140 α-OH, R^1 = CHO, R^2 = Me
141 β-OH, R^1 = CHO, R^2 = Me
142 β-OH, R^1 = COMe, R^2 = H



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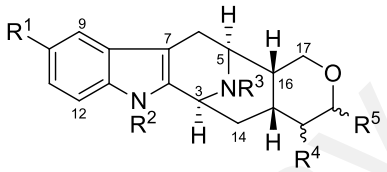
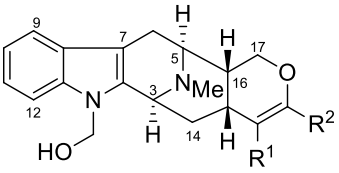
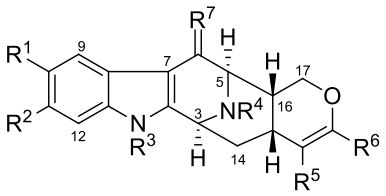


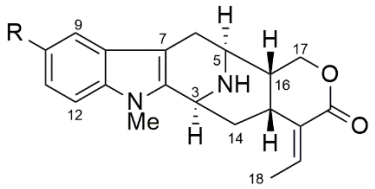
15 R^1 = H, R^2 = H, R^3 = Me, R^4 = α-CH_2OH, R^5 = 18-β-Me
16 R^1 = H, R^2 = H, R^3 = Me, R^4 = β-CH_2OH, R^5 = 18-β-Me
143 R^1 = H, R^2 = Me, R^3 = H, R^4 = β-CH_2OH, R^5 = 18-β-Me
144 R^1 = H, R^2 = Me, R^3 = H, R^4 = α-CH_2OH, R^5 = 18-β-Me
145 R^1 = H, R^2 = Me, R^3 = Me, R^4 = β-CH_2OH, R^5 = 18-β-Me
146 R^1 = H, R^2 = Me, R^3 = Me, R^4 = α-CH_2OH, R^5 = 18-β-Me
147 R^1 = H, R^2 = Me, R^3 = Me, R^4 = α-CH_2OAc, R^5 = 18-β-Me
17 R^1 = H, R^2 = Me, R^3 = Me, R^4 = β-CH_2OH α-OH, R^5 = 18-β-Me
13 R^1 = H, R^2 = Me, R^3 = Me, R^4 = β-CHO, R^5 = 18-β-Me
148 R^1 = H, R^2 = Me, R^3 = Me, R^4 = β-CHO, R^5 = 18-α-Me
14 R^1 = H, R^2 = Me, R^3 = Me, R^4 = α-CHO, R^5 = 18-β-Me
149 R^1 = H, R^2 = Me, R^3 = Me, R^4 = β-COMe, R^5 = H
150 R^1 = H, R^2 = Me, R^3 = Me, R^4 = β-CH(OH)Me, R^5 = H



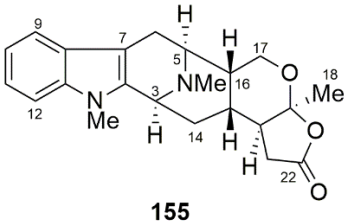
1 R^1 = COMe, R^2 = H
2 R^1 = CHO, R^2 = Me



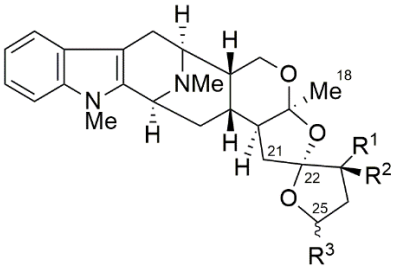
3 R^1 = H, R^2 = H, R^3 = Me, R^4 = Me, R^5 = COMe, R^6 = H, R^7 = H,H
4 R^1 = H, R^2 = H, R^3 = Me, R^4 = Me, R^5 = CHO, R^6 = Me, R^7 = H,H
7 R^1 = H, R^2 = H, R^3 = Me, R^4 = H, R^5 = COMe, R^6 = H, R^7 = H,H
8 R^1 = H, R^2 = H, R^3 = Me, R^4 = H, R^5 = CHO, R^6 = Me, R^7 = H,H
5 R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = CHO, R^6 = Me, R^7 = H,H
6 R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = COMe, R^6 = H, R^7 = H,H
151 R^1 = OMe, R^2 = H, R^3 = Me, R^4 = Me, R^5 = CHO, R^6 = Me, R^7 = H,H
11 R^1 = H, R^2 = OMe, R^3 = H, R^4 = Me, R^5 = COMe, R^6 = H, R^7 = H,H
12 R^1 = H, R^2 = OMe, R^3 = H, R^4 = Me, R^5 = CHO, R^6 = Me, R^7 = H,H
9 R^1 = H, R^2 = OMe, R^3 = Me, R^4 = Me, R^5 = COMe, R^6 = H, R^7 = H,H
10 R^1 = H, R^2 = OMe, R^3 = Me, R^4 = Me, R^5 = CHO, R^6 = Me, R^7 = H,H
152 R^1 = H, R^2 = OMe, R^3 = Me, R^4 = Me, R^5 = COMe, R^6 = H, R^7 = O
153 R^1 = H, R^2 = OMe, R^3 = Me, R^4 = Me, R^5 = CHO, R^6 = Me, R^7 = O



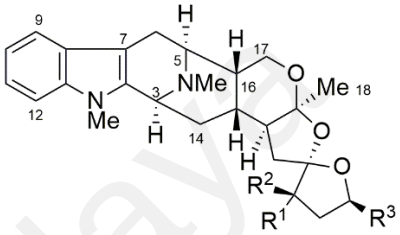
18 R = H
154 R = OMe



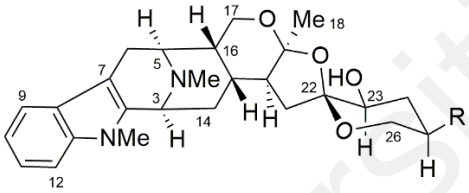
155



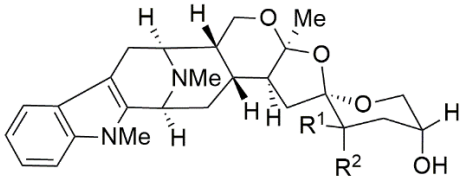
156 R^1,R^2 = O (oxo), R^3 = β-CH_2OH
157 R^1 = H, R^2 = OH, R^3 = α-CH_2OH



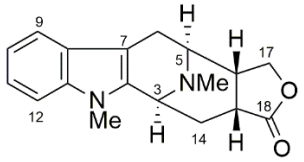
158 R^1,R^2 = O (oxo), R^3 = CH_2OH
159 R^1 = OH, R^2 = H, R^3 = CH_2OH



160 R = OH
161 R = H



162 R^1 = OH, R^2 = H
163 R^1 = H, R^2 = OH



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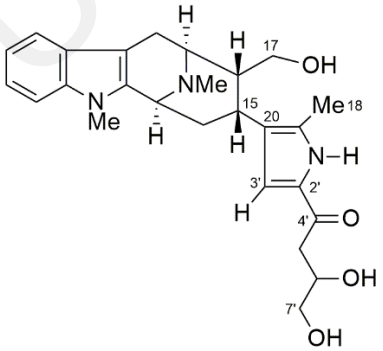
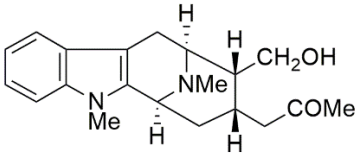


165



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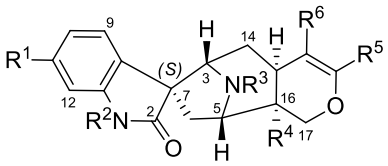
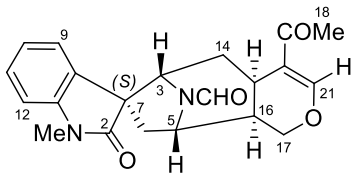
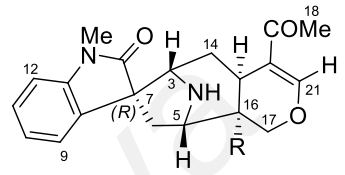


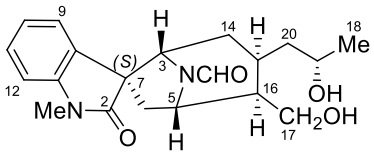


30

20 R^1 = H, R^2 = H, R^3 = H, R^4 = OH, R^5 = Me, R^6 = CHO
21 R^1 = H, R^2 = H, R^3 = H, R^4 = OH, R^5 = H, R^6 = COMe
24 R^1 = H, R^2 = Me, R^3 = H, R^4 = H, R^5 = H, R^6 = COMe
25 R^1 = H, R^2 = Me, R^3 = H, R^4 = H, R^5 = Me, R^6 = CHO
26 R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = H, R^6 = COMe
27 R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = Me, R^6 = CHO
28 R^1 = H, R^2 = Me, R^3 = H, R^4 = OH, R^5 = H, R^6 = COMe
29 R^1 = H, R^2 = Me, R^3 = H, R^4 = OH, R^5 = Me, R^6 = CHO
166 R^1 = OMe, R^2 = Me, R^3 = H, R^4 = OH, R^5 = Me, R^6 = CHO
167 R^1 = OMe, R^2 = Me, R^3 = H, R^4 = OH, R^5 = H, R^6 = COMe
168 R^1 = OMe, R^2 = Me, R^3 = H, R^4 = H, R^5 = Me, R^6 = CHO
169 R^1 = OMe, R^2 = Me, R^3 = H, R^4 = H, R^5 = H, R^6 = COMe



22 R = OH
170 R = H



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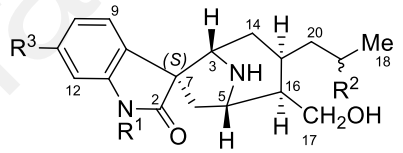
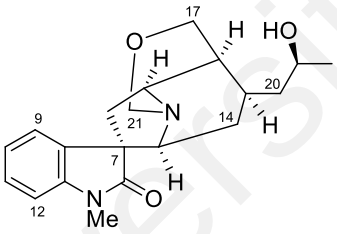


31 R^1 = H, R^2 = O (19-oxo), R^3 = H
171 R^1 = H, R^2 = 19-α-OH, R^3 = H
172 R^1 = Me, R^2 = 19-α-OH, R^3 = H
173 R^1 = Me, R^2 = 19-α-OH, R^3 = OMe
174 R^1 = Me, R^2 = O (19-oxo), R^3 = OMe



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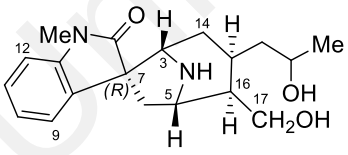
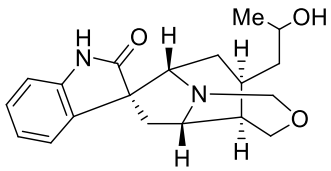
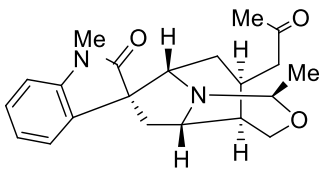


176



177



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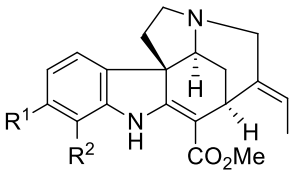
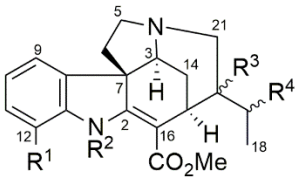
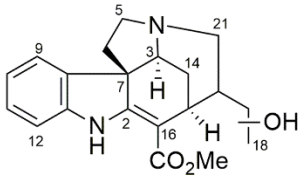


71 R^1 = OMe, R^2 = H
72 R^1 = OMe, R^2 = H, N(4)→O
179 R^1 = H, R^2 = H
180 R^1 = H, R^2 = OH
181 R^1 = H, R^2 = OMe
182 R^1 = H, R^2 = OMe, N(4)-Me
183 R^1 = H, R^2 = H, N(4)→MeI
184 R^1 = H, R^2 = H, N(4)→O



185 R^1 = OMe, R^2 = H, R^3 = β-H, R^4 = α-OH
186 R^1 = OMe, R^2 = H, R^3 = β-H, R^4 = α-OH, N(4)→O
187 R^1 = OMe, R^2 = H, R^3 = α-H, R^4 = β-OH
188 R^1 = OMe, R^2 = H, R^3 = α-H, R^4 = β-OH, N(4)→O
189 R^1 = OMe, R^2 = H, R^3 = α-H, R^4 = nil
190 R^1 = OH, R^2 = H, R^3 = α-H, R^4 = β-OH
191 R^1 = OH, R^2 = H, R^3 = α-H, R^4 = β-OH, N(4)-Me
192 R^1 = OH, R^2 = H, R^3 = α-H, R^4 = α-OH
193 R^1 = OH, R^2 = H, R^3 = β-H, R^4 = α-OH
194 R^1 = OH, R^2 = H, R^3 = β-H, R^4 = α-OH, N(4)→O
195 R^1 = OH, R^2 = H, R^3 = β-H, R^4 = β-OH, N(4)→O
196 R^1 = H, R^2 = H, R^3 = α-H, R^4 = β-OH
197 R^1 = H, R^2 = H, R^3 = α-H, R^4 = β-OH, N(4)→$CH_2Cl^+Cl^-$
198 R^1 = H, R^2 = H, R^3 = α-H, R^4 = β-OH, N(4)→O
199 R^1 = H, R^2 = H, R^3 = α-H, R^4 = β-O-D-glucopyranoside, N(4)→O
200 R^1 = H, R^2 = H, R^3 = α-H, R^4 = α-OH
201 R^1 = H, R^2 = H, R^3 = β-H, R^4 = β-OH, N(4)-Me
202 R^1 = H, R^2 = H, R^3 = β-H, R^4 = β-OH
203 R^1 = H, R^2 = H, R^3 = β-H, R^4 = α-OH
204 R^1 = H, R^2 = H, R^3 = β-H, R^4 = α-OH, N(4)-Me
205 R^1 = H, R^2 = H, R^3 = β-H, R^4 = α-OH, N(4)→O
206 R^1 = H, R^2 = CHO, R^3 = α-H, R^4 = β-OH
207 R^1 = H, R^2 = H, R^3 = H, R^4 = H,H



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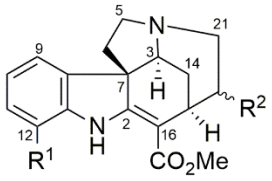
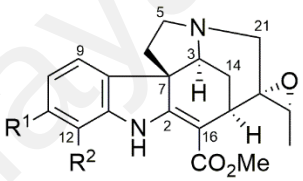
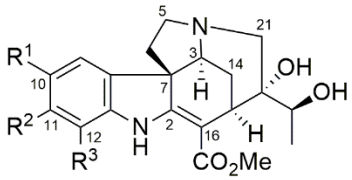


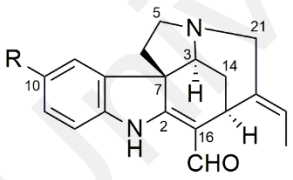
209 R^1 = H, R^2 = β-COMe
210 R^1 = H, R^2 = β-COMe, N(4)→O
211 R^1 = H, R^2 = α-COMe
212 R^1 = OH, R^2 = β-COMe
213 R^1 = OH, R^2 = α-COMe
214 R^1 = OMe, R^2 = β-COMe



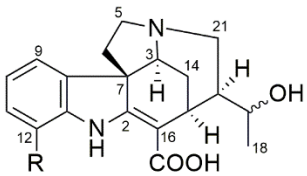
73 R^1 = OMe, R^2 = H
215 R^1 = H, R^2 = OMe



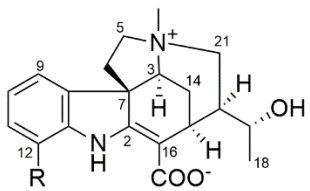
74 R^1 = H, R^2 = OMe, R^3 = H
216 R^1 = OMe, R^2 = H, R^3 = H
217 R^1 = H, R^2 = H, R^3 = OMe
218 R^1 = H, R^2 = H, R^3 = H



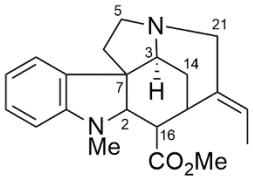
219 R = H
220 R = OMe



221 β-19-OH, R = H
222 β-19-OH, R = OH
223 β-19-OH, R = OMe
224 α-19-OH, R = OMe, N(4)→O
225 α-19-OH, R = OH, N(4)→O



226 R = OMe
227 R = H
228 R = OH



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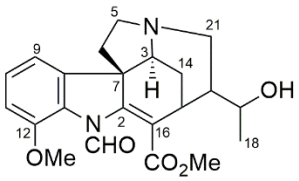

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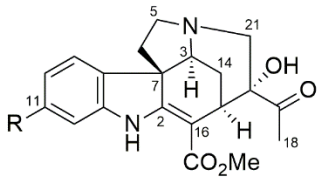
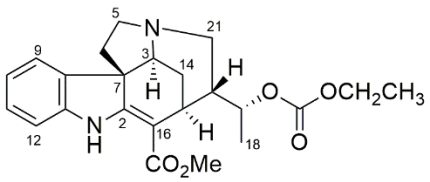


231 R = H
75 R = OMe



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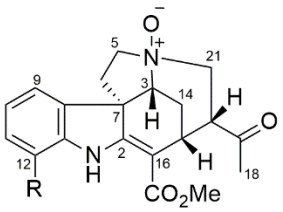
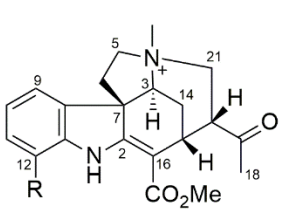
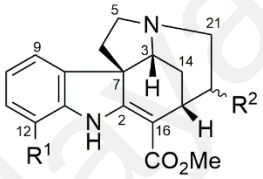


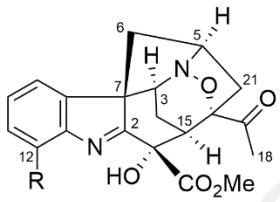
233 R = OMe
234 R = OH



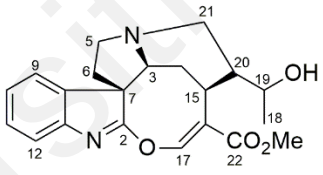
235 R = OMe
236 R = OH



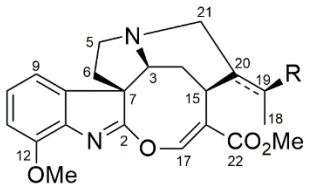
237 R^1 = OH, R^2 = α-COMe
238 R^1 = H, R^2 = α-COMe, N(4)→O
239 R^1 = OH, R^2 = β-COMe
240 R^1 = H, R^2 = β-COMe



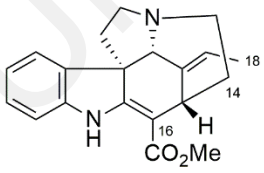
241 R = OH
242 R = H



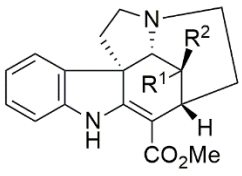
243



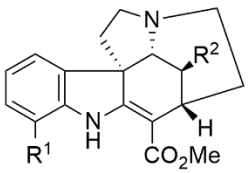
244 R = OH
245 R = O
246 R = H, $\Delta^{19,20}$



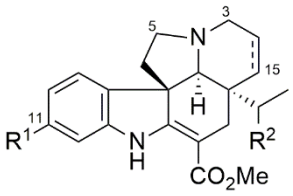
247



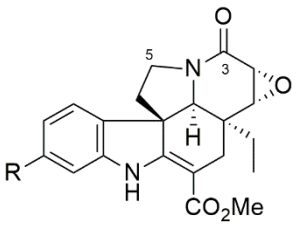
248 R^1 = Et, R^2 = H
249 R^1 = H, R^2 = Et
250 R^1 = H, R^2 = Et, N(4)→O



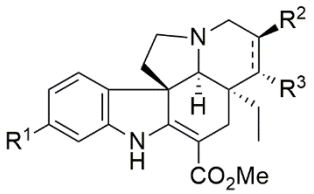
251 R^1 = OMe, R^2 = Et
252 R^1 = H, R^2 = CH(α-OH)Me



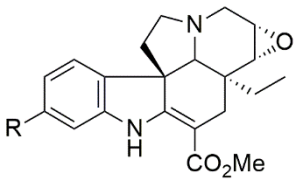
253 R^1 = H, R^2 = nil
254 R^1 = OMe, R^2 = nil, $\Delta^{14,15}$
255 R^1 = OMe, R^2 = OAc, $\Delta^{14,15}$



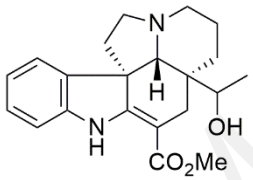
256 R = OMe
257 R = H
258 R = OAc
259 R = OH



260 R^1 = OMe, R^2 = Cl, R^3 = OH
261 R^1 = H, R^2 = H, R^3 = H, $\Delta^{14,15}$
262 R^1 = OH, R^2 = Cl, R^3 = OH
263 R^1 = H, R^2 = Cl, R^3 = OH



264 R = H
265 R = OMe



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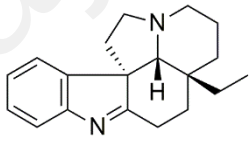

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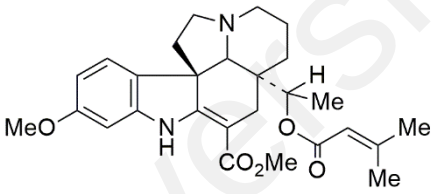

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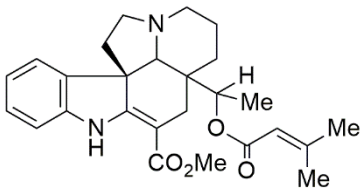

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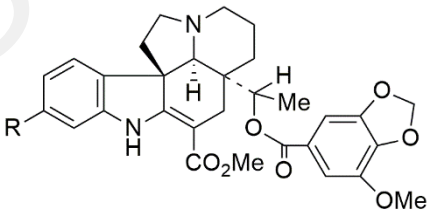
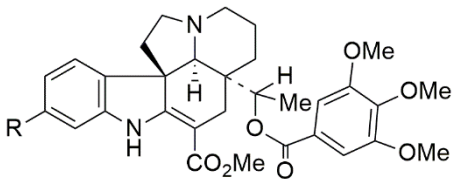
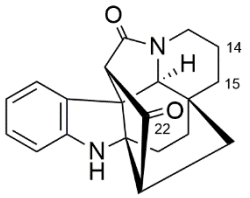


270 R = OMe
271 R = H



272 R = OMe
273 R = H



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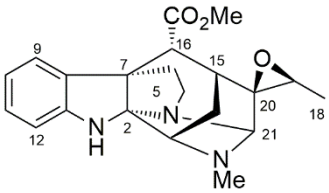

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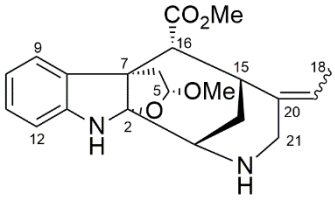
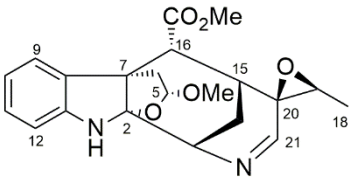


276 19,20 *E*, 5-α-OMe
277 19,20 *Z*, 5-β-OMe



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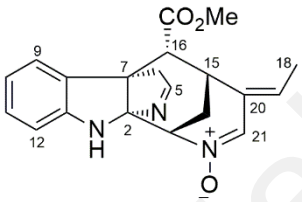

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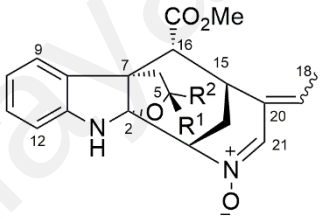
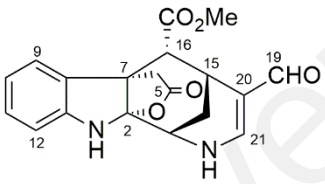


280 R^1 = H, R^2 = OMe, 19,20 *E*
281 R^1 = OMe, R^2 = H, 19,20 *E*
282 R^1 = H, R^2 = OH, 19,20 *E*
283 R^1 = H, R^2 = OH, 19,20 *Z*



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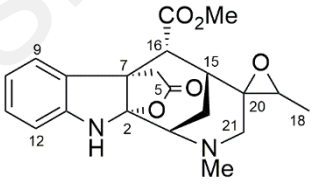
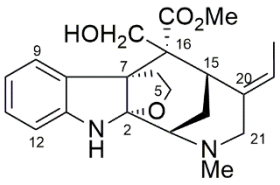


285 19*S*, 20*S*
286 19*R*, 20*S*
287 19*S*, 20*R*



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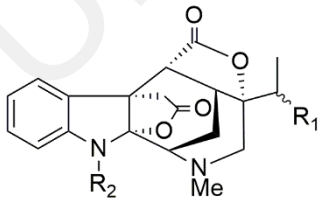
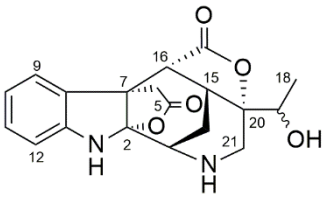
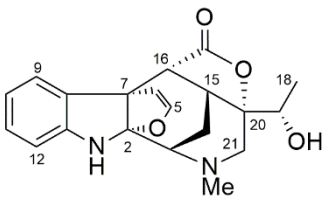


289 R^1 = OH, 19*R*; R^2 = H
290 R^1 = OH, 19*S*; R^2 = H
291 R^1 = OH, 19*R*; R^2 = CH_2OCH_3



292 19*R*
293 19*S*



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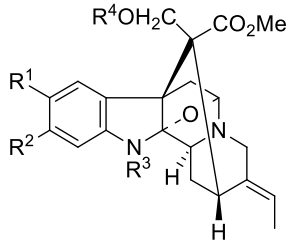
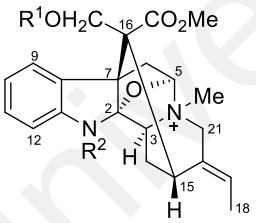
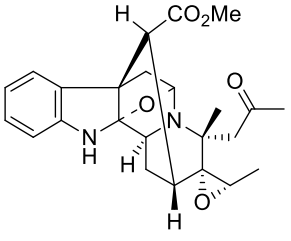


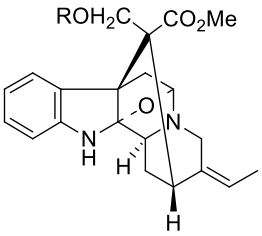
295 R^1 = H, R^2 = H, R^3 = Me, R^4 = H
296 R^1 = H, R^2 = H, R^3 = H, R^4 = acetyl
297 R^1 = OMe, R^2 = H, R^3 = Me, R^4 = H
298 R^1 = OMe, R^2 = H, R^3 = Me, R^4 = benzoate
299 R^1 = OMe, R^2 = H, R^3 = Me, R^4 = veratrate
300 R^1 = OMe, R^2 = OMe, R^3 = Me, R^4 = H
301 R^1 = OMe, R^2 = OMe, R^3 = Me, R^4 = benzoate
302 R^1 = OMe, R^2 = OMe, R^3 = Me, R^4 = acetyl
303 R^1 = OMe, R^2 = OMe, R^3 = Me,
R^4 = 3',4',5'-trimethoxybenzoate
304 R^1 = OMe, R^2 = H, R^3 = Me, N(4)-Me,
R^4 = 3',4'-dimethoxybenzoate
305 R^1 = OMe, R^2 = H, R^3 = Me, N(4)-Me,
R^4 = 3',4',5'-trimethoxybenzoate
306 R^1 = OMe, R^2 = H, R^3 = Me,
R^4 = 3',4',5'-trimethoxybenzoate
307 R^1 = H, R^2 = H, R^3 = H,
R^4 = 3',4'-dimethoxybenzoate
308 R^1 = OMe, R^2 = H, R^3 = H,
R^4 = 3',4',5'-trimethoxybenzoate



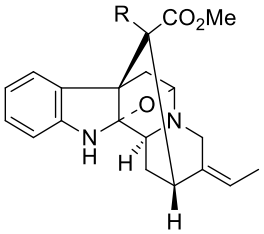
323 R^1 = 3',4'-dimethoxybenzoate, R^2 = Me
324 R^1 = H, R^2 = H



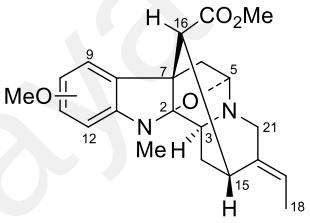
325



309
R = 3',4',5'-trimethoxybenzoate



310 R = CHO
311 R = CH_2OH



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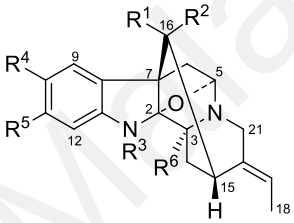
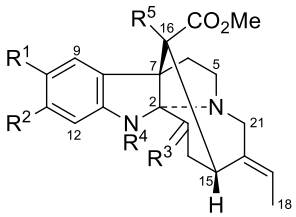
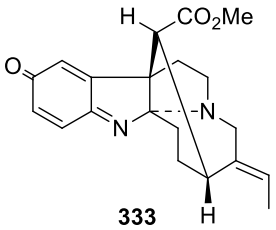


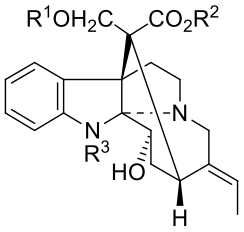
313 R^1 = H, R^2 = CO_2Me, R^3 = H, R^4 = H, R^5 = H, R^6 = H
314 R^1 = H, R^2 = CO_2Me, R^3 = H, R^4 = H, R^5 = H, R^6 = OMe
315 R^1 = H, R^2 = CO_2Me, R^3 = H, R^4 = H, R^5 = H, R_6 = OH
316 R^1 = H, R^2 = CO_2Me, R^3 = H, R^4 = OMe, R^5 = OMe, R^6 = H
317 R^1 = H, R^2 = CO_2Me, R^3 = H, R^4 = OMe, R^5 = H, R^6 = H
318 R^1 = H, R^2 = CO_2Me, R^3 = CH_2OMe, R^4 = H, R^5 = H, R^6 = H
319 R^1 = H, R^2 = CO_2Me, R^3 = Me, R^4 = OMe, R^5 = OMe, R^6 = H
320 R^1 = H, R^2 = CO_2Me, R^3 = Me, R^4 = OMe, R^5 = H, R^6 = H
321 R^1 = CHO, R^2 = CO_2Me, R^3 = H, R^4 = H, R^5 = H, R^6 = H
322 R^1 = CO_2Me, R^2 = H, R^3 = H, R^4 = H, R^5 = H, R^6 = H



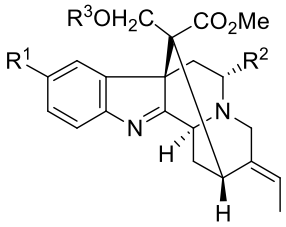
54 R^1 = OMe, R^2 = H, R^3 = H,H, R^4 = Me, R^5 = H
326 R^1 = OMe, R^2 = H, R^3 = H,H, R^4 = Me, R^5 = H, N(4)→O
56 R^1 = OMe, R^2 = H, R^3 = H,H, R^4 = CHO, R^5 = H
55 R^1 = OMe, R^2 = H, R^3 = H,H, R^4 = H, R^5 = H
327 R^1 = OMe, R^2 = OMe, R^3 = H,H, R^4 = CHO, R^5 = H
328 R^1 = OMe, R^2 = OMe, R^3 = H,H, R^4 = Me, R^5 = H
329 R^1 = H, R^2 = H, R^3 = H,H, R^4 = Me, R^5 = H
330 R^1 = H, R^2 = H, R^3 = H,H, R^4 = Me, R^5 = H, N(4)→O
331 R^1 = H, R^2 = H, R^3 = H,H, R^4 = Me, R^5 = CHO, N(4)→O
332 R^1 = H, R^2 = H, R^3 = O, R^4 = Me, R^5 = H



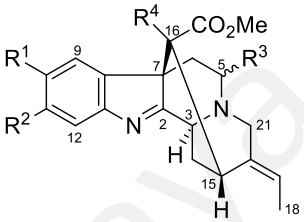
333



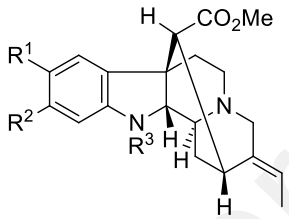
334 R^1 = H, R^2 = Me, R^3 = H
335 R^1 = Ac, R^2 = Me, R^3 = H, N(4)-Me
336 R^1 = H, R^2 = Me, R^3 = H, N(4)-Me
337 R^1 = H, R^2 = H, R^3 = H, N(4)-Me
338 R^1 = H, R^2 = Me, R^3 = H, N(4)→O
339 R^1 = H, R^2 = Me, R^3 = Me
340 R^1 = H, R^2 = Me, R^3 = CHO
341 R^1 = Ac, R^2 = Me, R^3 = H



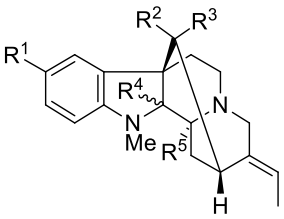
342 R^1 = OMe, R^2 = OMe,
R^3 = 3',4',5'-trimethoxybenzoate
343 R^1 = OMe, R^2 = OMe, R^3 = benzoate
344 R^1 = H, R^2 = H, R^3 = acetyl
345 R^1 = H, R^2 = H,
R^3 = 3',4',5'-trimethoxybenzoate
346 R^1 = H, R^2 = H, R^3 = H



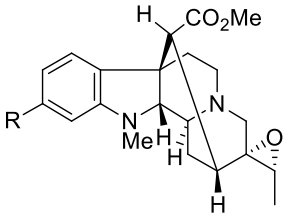
347 R^1 = H, R^2 = H, R^3 = H, R^4 = H
348 R^1 = H, R^2 = H, R^3 = H, R^4 = H, N(4)→O
39 R^1 = H, R^2 = OMe, R^3 = H, R^4 = H, N(4)→O
49 R^1 = H, R^2 = OMe, R^3 = H, R^4 = H
50 R^1 = H, R^2 = OH, R^3 = H, R^4 = H
51 R^1 = OMe, R^2 = H, R^3 = H, R^4 = H
349 R^1 = OMe, R^2 = H, R^3 = α-OMe, R^4 = H
350 R^1 = OMe, R^2 = OMe, R^3 = α-OMe, R^4 = H
351 R^1 = OH, R^2 = H, R^3 = H, R^4 = H
352 R^1 = H, R^2 = H, R^3 = H, R^4 = OH
353 R^1 = H, R^2 = H, R^3 = β-OMe, R^4 = H
354 R^1 = H, R^2 = H, R^3 = α-OMe, R^4 = CHO



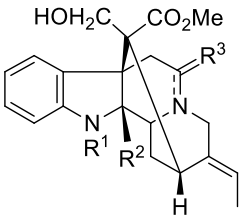
355 R^1 = OMe, R^2 = H, R^3 = Me
356 R^1 = OMe, R^2 = H, R^3 = Me, N(4)→O
357 R^1 = CHO, R^2 = OMe, R^3 = Me
358 R^1 = H, R^2 = OMe, R^3 = Me
359 R^1 = H, R^2 = OMe, R^3 = Me, N(4)→O
52 R^1 = H, R^2 = H, R^3 = Me
53 R^1 = H, R^2 = H, R^3 = Me, N(4)→O



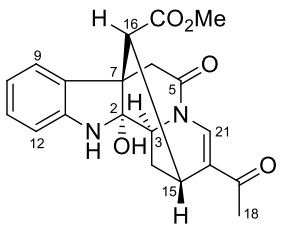
360 R^1 = H, R^2 = CO_2Me, R^3 = H, R^4 = α-OH, R^5 = H
361 R^1 = H, R^2 = H, R^3 = CO_2Me, R^4 = β-H, R^5 = OH
362 R^1 = H, R^2 = H, R^3 = CO_2Me, R^4 = α-H, R^5 = H
363 R^1 = OMe, R^2 = H, R^3 = CO_2Me, R^4 = α-H, R^5 = H



364 R = OMe
365 R = H



366 R^1 = H, R^2 = H, R^3 = O
367 R^1 = Me, R^2 = OH, R^3 = H,nil,
$\Delta^{4,5}$, N(4)-Cl



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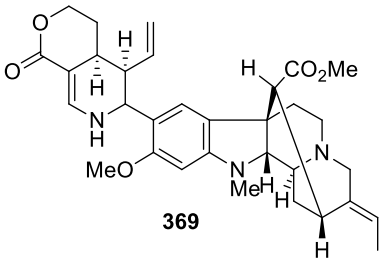

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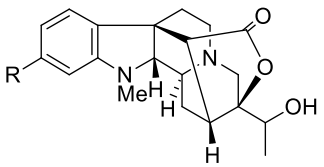
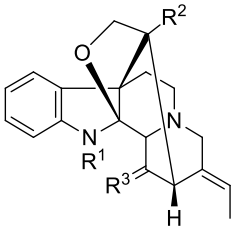
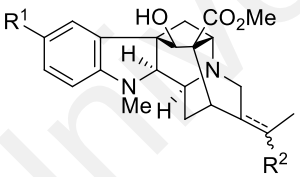


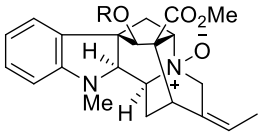
370 R = OMe
371 R = H



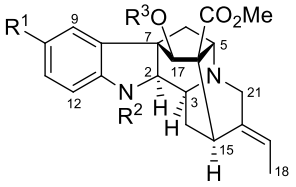
372 R^1 = Me, R^2 = CO_2Me, R^3 = nil
373 R^1 = Me, R^2 = CO_2Me, R^3 = nil, N(4)→O
374 R^1 = H, R^2 = COO^-, R^3 = O, N(4)-Me



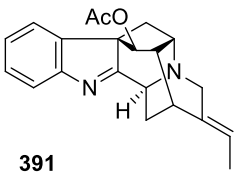
389 R^1 = OMe, R^2 = H, $\Delta^{19,20}$, N(4)→O
390 R^1 = H, R^2 = OH



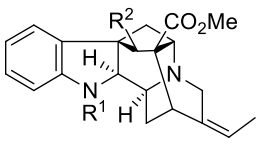
401 R = Ac
402 R = H



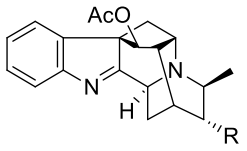
63 R^1 = H, R^2 = H, R^3 = H
60 R^1 = H, R^2 = H, R^3 = 3',4',5'-trimethoxybenzoyl
57 R^1 = H, R^2 = 3',4',5'-trimethoxybenzoyl, R^3 = 3',4',5'-trimethoxybenzoyl
58 R^1 = H, R^2 = 3',4',5'-trimethoxybenzoyl, R^3 = 4'-OH-3',5'-dimethoxybenzoyl
61 R^1 = H, R^2 = tri-*O*-methylgallate, R^3 = H
59 R^1 = H, R^2 = Me, R^3 = 4'-OH-3',5'-dimethoxybenzoyl
375 R^1 = H, R^2 = Me, R^3 = 3',4',5'-trimethoxycinnamoyl
376 R^1 = H, R^2 = Me, R^3 = 3',4',5'-trimethoxybenzoate
377 R^1 = H, R^2 = Me, R^3 = 3',4',5'-trimethoxybenzoate, N(4)→O
378 R^1 = H, R^2 = Me, R^3 = veratrate
379 R^1 = H, R^2 = Me, R^3 = veratrate, N(4)→O
380 R^1 = H, R^2 = Me, R^3 = Benzoyl
62 R^1 = H, R^2 = Me, R^3 = H
381 R^1 = H, R^2 = Me, R^3 = H, N(4)→O
382 R^1 = H, R^2 = Me, R^3 = Ac
383 R^1 = OH, R^2 = Me, R^3 = 3',4',5'-trimethoxybenzoyl
384 R^1 = OH, R^2 = Me, R^3 = 3',4',5'-trimethoxycinnamoyl
385 R^1 = OMe, R^2 = Me, R^3 = H
386 R^1 = OMe, R^2 = Me, R^3 = 3',4',5'-trimethoxycinnamoyl
387 R^1 = OMe, R^2 = Me, R^3 = Ac
388 R^1 = OMe, R^2 = Me, R^3 = Ac, N(4)→O



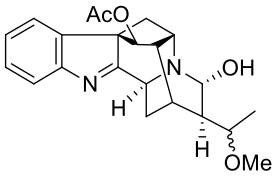
391
392 N(1)→O, N(4)→O
393 N(4)→O



403 R^1 = veratroyl, R^2 = OAc
404 R^1 = eudesmoyl, R^2 = OAc
405 R^1 = benzoyl, R^2 = OAc
406 R^1 = veratroyl, R^2 = OH
407 R^1 = eudesmoyl, R^2 = OH
408 R^1 = benzoyl, R^2 = OH



394 R = CHO
395 R = CHO, N(4)→O
396 R = CHO, N(1)→O, N(4)→O
397 R = CH_2OH
398 R = CH_2OH, N(4)→O
399 R = COOH, N(4)→O
400 R = COOH, N(1)→O, N(4)→O



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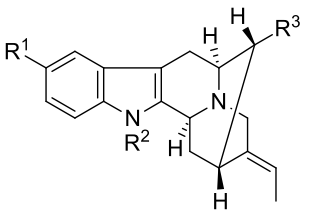
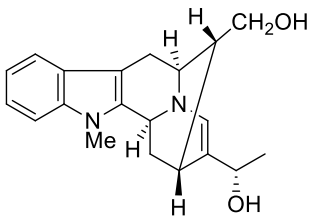


410 R^1 = H, R^2 = H, R^3 = CH_2OH
411 R^1 = H, R^2 = H, R^3 = CHO
44 R^1 = H, R^2 = Me, R^3 = CH_2OH
412 R^1 = OH, R^2 = H, R^3 = CH_2OH
45 R^1 = OMe, R^2 = Me, R^3 = CH_2OH
46 R^1 = OMe, R^2 = Me, R^3 = CH_2OH, N(4)→O
47 R^1 = OMe, R^2 = H, R^3 = CH_2OH



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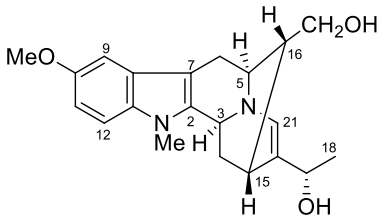
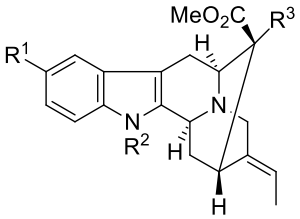
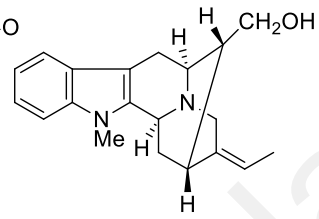


32



416 R^1 = H, R^2 = H, R^3 = CH_2OH
417 R^1 = H, R^2 = H, R^3 = CH_2OH, N(4)→Me
418 R^1 = H, R^2 = H, R^3 = CH_2OH, N(4)→O
419 R^1 = H, R^2 = H, R^3 = H
420 R^1 = OMe, R^2 = Me, R^3 = CH_2OH



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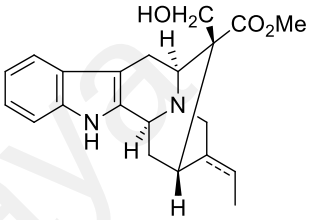
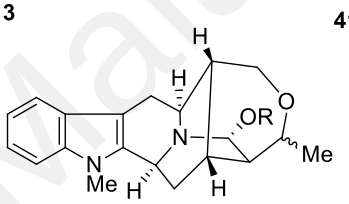
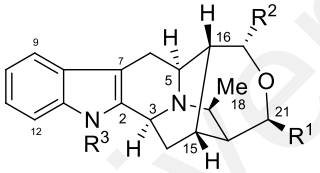


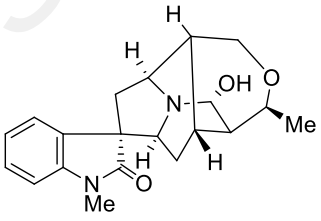
414 $\Delta^{19,20}$
415



421 R = Ac, 19-β-Me
422 R = H, 19-α-Me, N(4)→Me
423 R = H, 19-β-Me
424 R = H, 19-β-Me, N(4)→Me



425 R^1 = OMe, R^2 = OH, R^3 = H
426 R^1 = OMe, R^2 = OH, R^3 = Me
427 R^1 = OH, R^2 = OMe, R^3 = H
428 R^1 = OH, R^2 = H, R^3 = H, N(4)-Me



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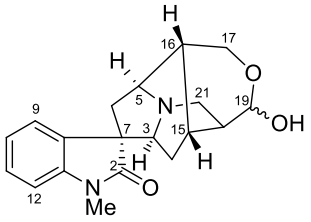
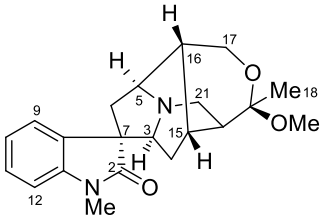


41 19-β-OH
42 19-α-OH



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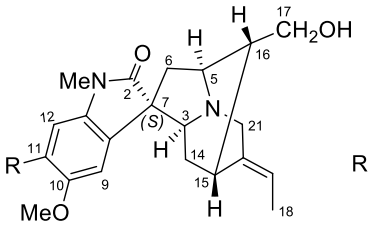
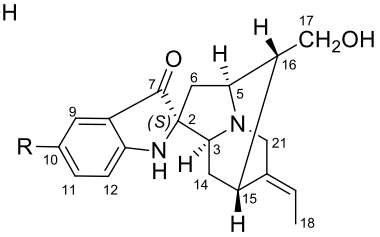
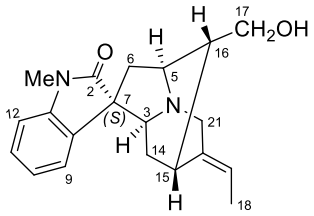


34 R = H
35 R = OMe
36 R = OMe, N(4)→O



430 R = H
33 R = OMe



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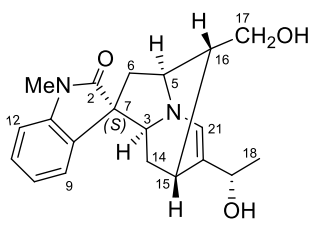

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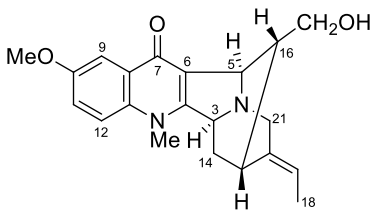
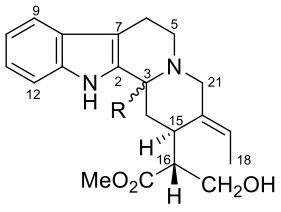
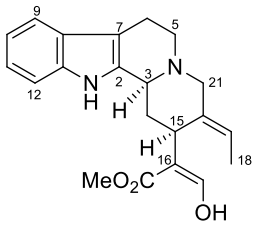


37
38 N(4)→O



65 R = α-H
433 R = β-H



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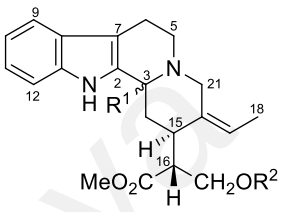
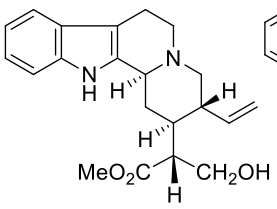


435 R^1 = α-H, R^2 = H
436 R^1 = β-H, R^2 = Glu



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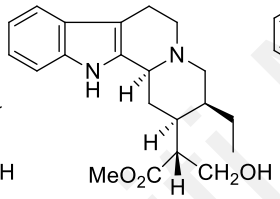

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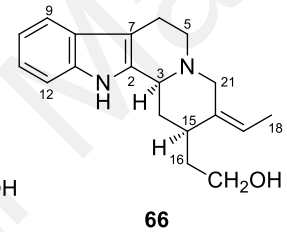

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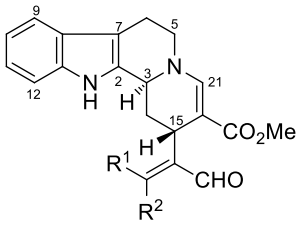
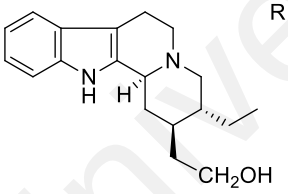


438 R^1 = Me, R^2 = H
439 R^1 = H, R^2 = Me



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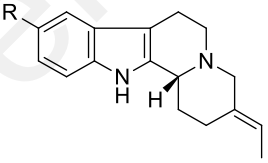
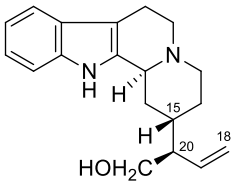
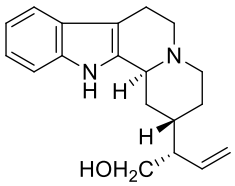


441 R = OMe
442 R = H



443
444 N(4)-Me



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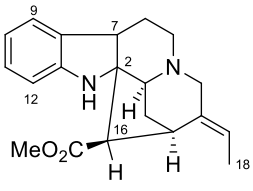

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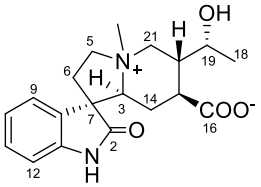

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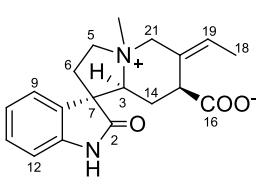

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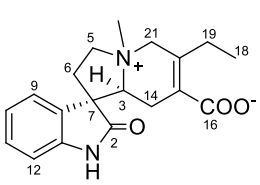

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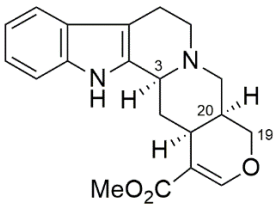

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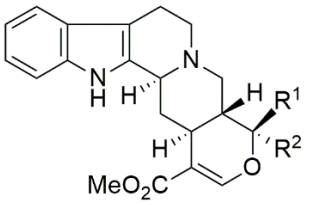
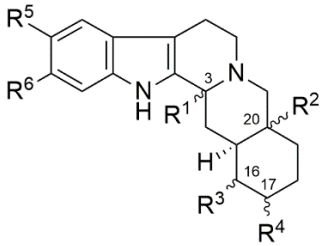
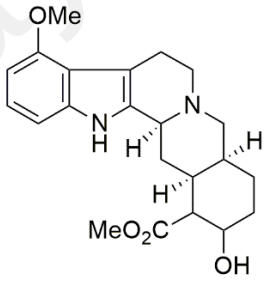


451 R^1 = H, R^2 = Me
452 R^1 = Me, R^2 = H



453 R^1 = α-H, R^2 = β-H, R^3 = α-CO_2Me, R^4 = α-OH, R^5 = H, R^6 = H
454 R^1 = α-H, R^2 = β-H, R^3 = α-CO_2Me, R^4 = α-OAc, R^5 = H, R^6 = H
455 R^1 = α-H, R^2 = α-H, R^3 = α-CO_2Me, R^4 = α-OH, R^5 = H, R^6 = H
456 R^1 = β-H, R^2 = α-H, R^3 = β-CO_2Me, R^4 = α-OH, R^5 = OMe, R^6 = H
457 R^1 = β-H, R^2 = α-H, R^3 = β-CO_2Me, R^4 = α-OH, R^5 = H, R^6 = OMe
458 R^1 = β-H, R^2 = β-H, R^3 = α-CO_2Me, R^4 = α-OH, R^5 = H, R^6 = H



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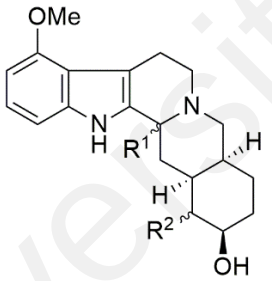
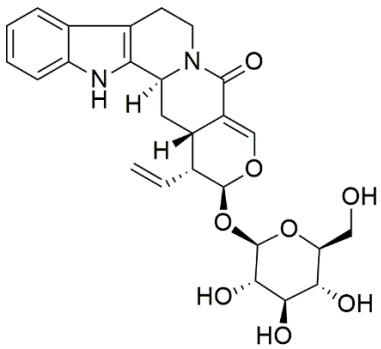


460 R^1 = α-H, R^2 = α-CO_2Me
461 R^1 = α-H, R^2 = β-CO_2Me
462 R^1 = β-H, R^2 = α-CO_2Me
463 R^1 = β-H, R_2 = β-CO_2Me
464 R^1 = β-H, R^2 = β-CO_2Me, N(4)→O



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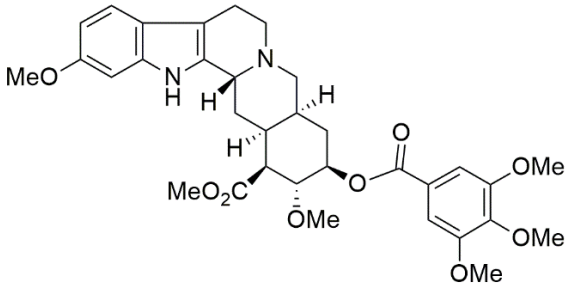

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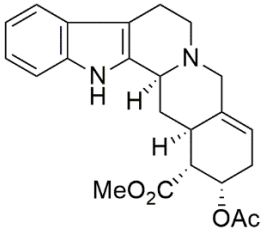

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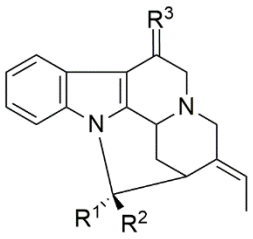
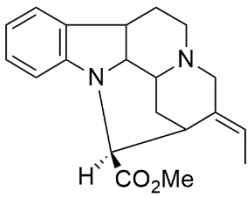


67 R^1 = H, R^2 = CO_2Me, R^3 = H,H
468 R^1 = H, R^2 = CO_2Me, R^3 = O



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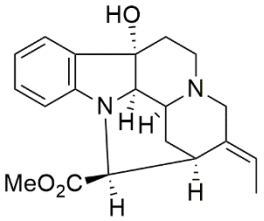

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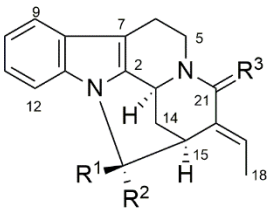
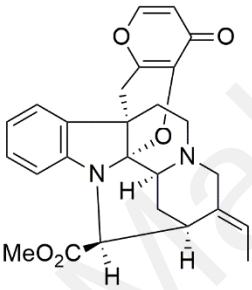


472 R^1 = CH_2OH, R^2 = H, R^3 = O
68 R^1 = CO_2Me, R^2 = CH_2OH, R^3 = H,H



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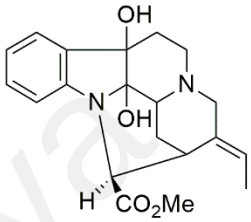

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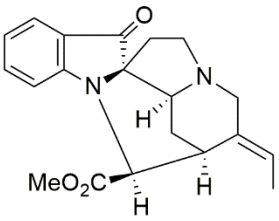
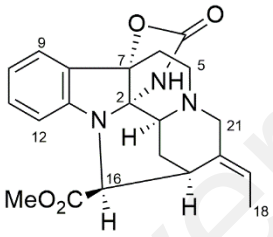
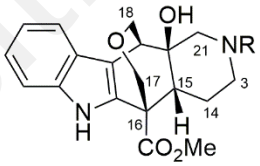


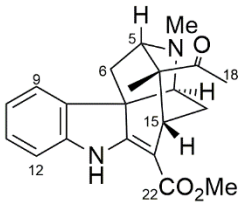
70



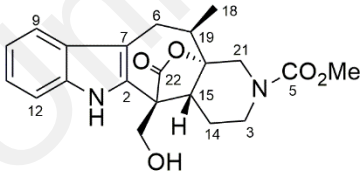
473



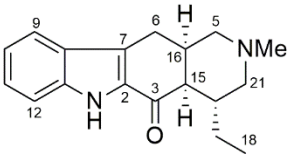
474 R = Me
475 R = H



476



477



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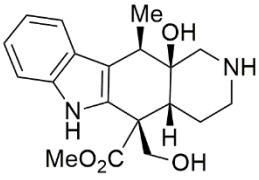
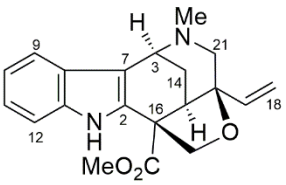


479



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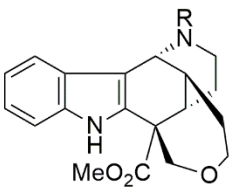
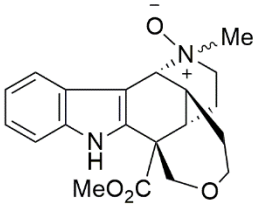
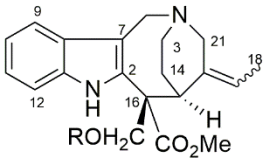


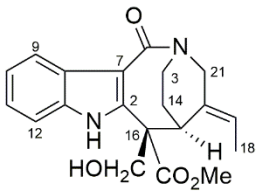
481 R = Me
482 R = H



483 R = α-Me
484 R = β-Me



485 R = H, 19,20 *E*
486 R = H, 19,20 *E*,N(4)→O
487 R = Ac, 19,20 *E*
488 R = H, 19,20 *Z*



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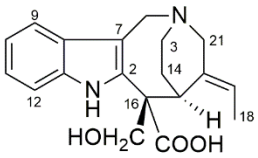
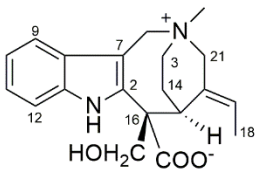


490
491 N(4)→O



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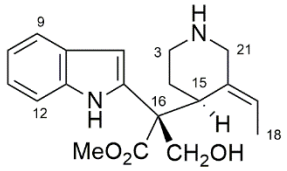
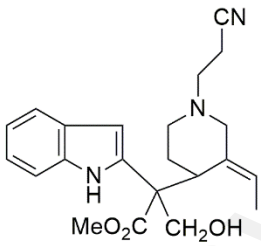


493



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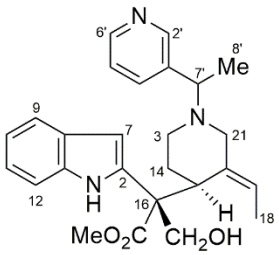

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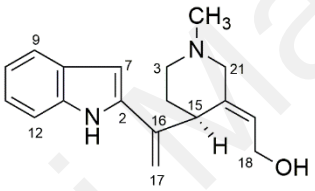

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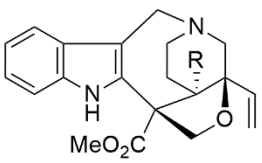
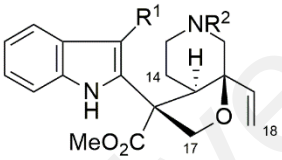
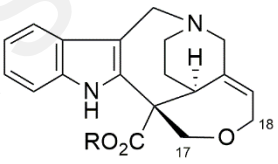


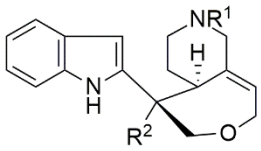
497 R = OH
498 R = H



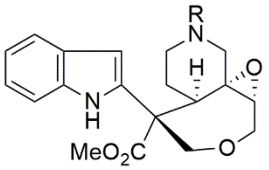
499 R^1 = CHO, R^2 = H
500 R^1 = H, R^2 = H
501 R^1 = H, R^2 = CO_2Et
502 R^1 = H, R_2 = Me



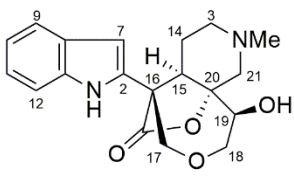
503 (–), R = Me
504 (+), R = Me
505 R = H
506 R = Me, N(4)→O
507 R = Me, N(4)→Me



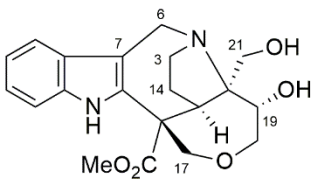
508 R^1 = Me, R^2 = CO_2Me
509 R^1 = Me, R^2 = CO_2Me, N(4)→O
510 R^1 = Me, R^2 = H
511 R^1 = H, R^2 = CO_2Me



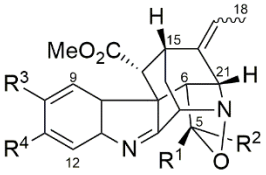
512 R = H
513 R = Me



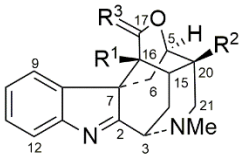
514



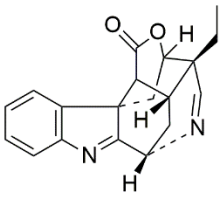
515



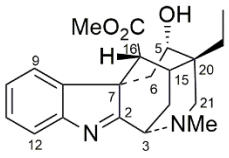
516 R^1 = OH, R^2 = H, R^3 = OMe, R^4 = OMe, 19,20 *E*
517 R^1 = OH, R^2 = H, R^3 = H, R^4 = H,19,20 *E*
518 R^1 = OH, R^2 = H, R^3 = H, R^4 = H,19,20 *Z*
519 R^1 = OEt, R^2 = H, R^3 = H, R^4 = H, 19,20 *E*
520 R^1 = OMe, R^2 = H, R^3 = H, R^4 = H, 19,20 *E*
521 R^1 = H, R^2 = OEt, R^3 = H, R^4 = H,19,20 *E*



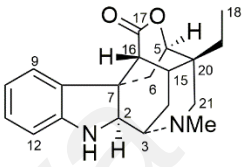
522 R^1 = CH_2OH, R^2 = CH_2CH_3, R^3 = O
523 R^1 = H, R^2 = H, R^3 = O
524 R^1 = H, R^2 = CH_2CH_3, R^3 = O
525 R^1 = H, R^2 = CH_2CH_3, R^3 = OH(β),H



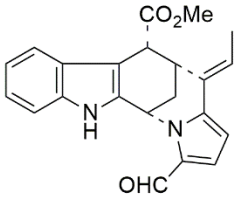
526



527



528
529 $\Delta^{N(4),21}$



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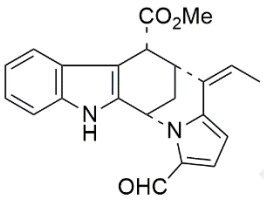
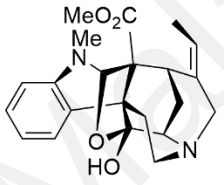
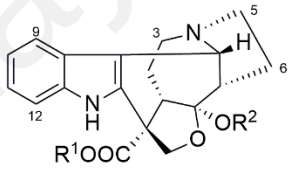


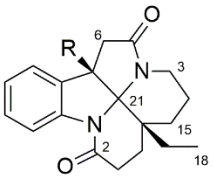
531



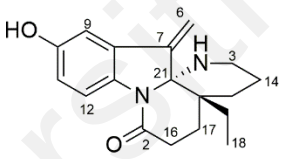
532
533 N(4)→O



534 R^1 = H, R^2 = H
535 R^1 = Me, R^2 = H
536 R^1 = H, R^2 = Et



537 R = H
538 R = OH
539 $\Delta^{6,7}$, R = nil



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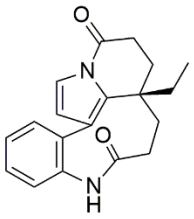
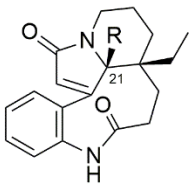
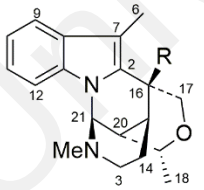


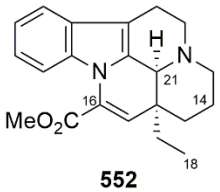
541



542 R = OH
543 R = OMe



544 α-18-Me, R = H
545 α-18-Me, R = CO_2Me
546 β-18-Me, R = CO_2Me
547 β-18-Me, R = CO_2H
548 β-18-Me, R = H



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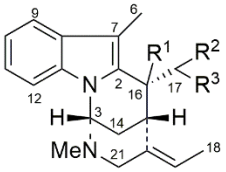
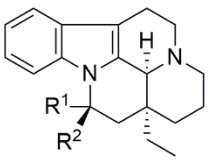
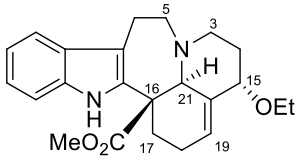


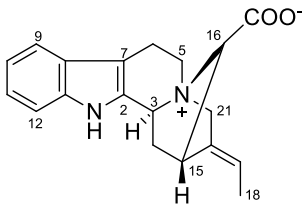
549 R^1 = H, R^2 = H, R^3 = OH
550 R^1 = CO_2Me, R^2 = H, R^3 = OH
551 R^1 = OH, R^2 = OMe, R^3 = OMe



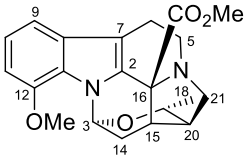
553 R^1 = CO_2Me, R^2 = OH
554 R^1 = CO_2Me, R^2 = OH, N(4)→O
555 R^1 = OH, R^2 = CO_2Me



556



557



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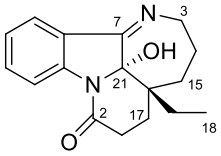
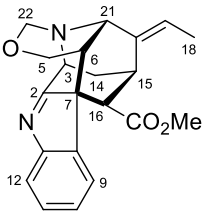


559



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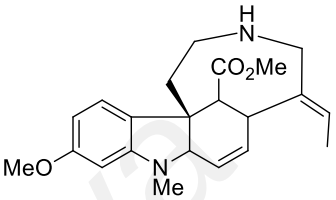

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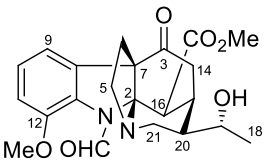

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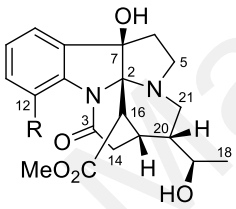
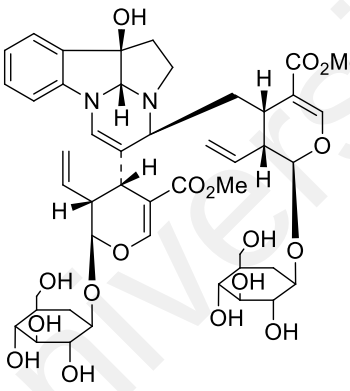


563 R = H
564 R = OMe



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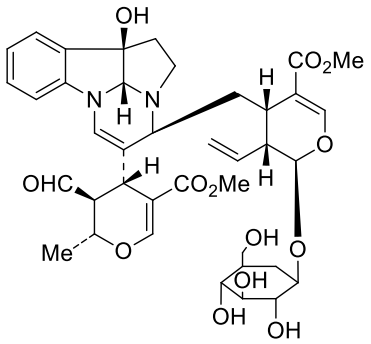

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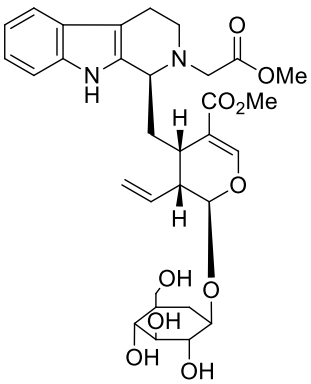

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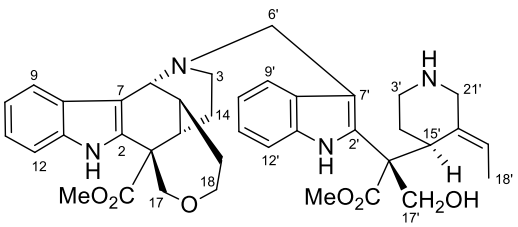

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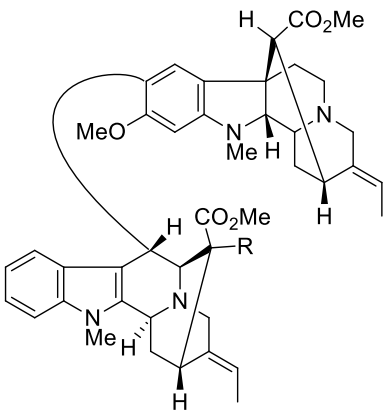
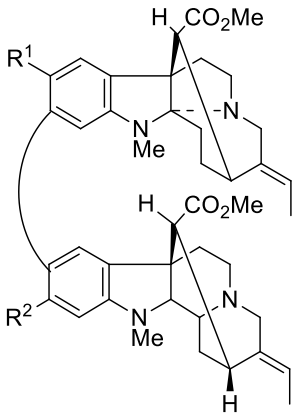
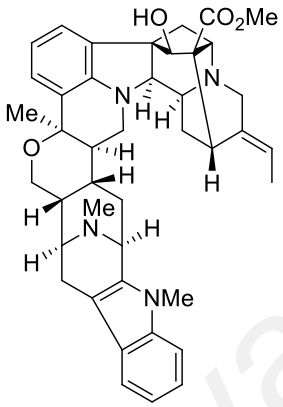


569 R = CH_2OH
570 R = H



571 R^1 = OMe, R^2 = OMe
572 R^1 = OMe, R^2 = H, or
R^1 = H, R^2 = OMe



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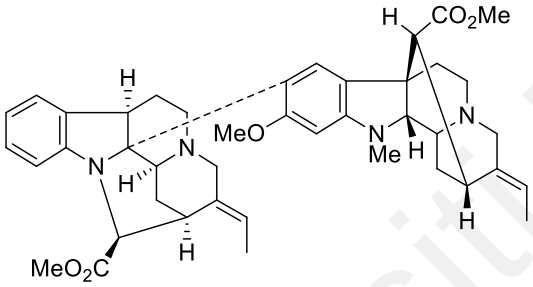

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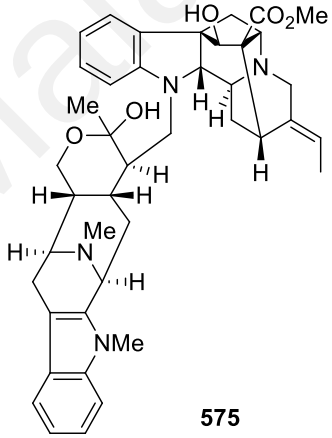

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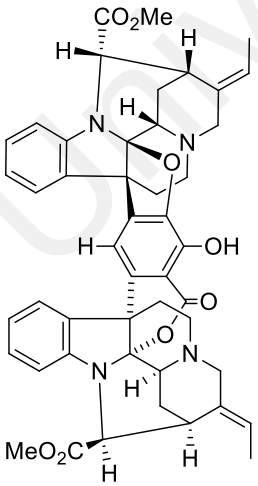

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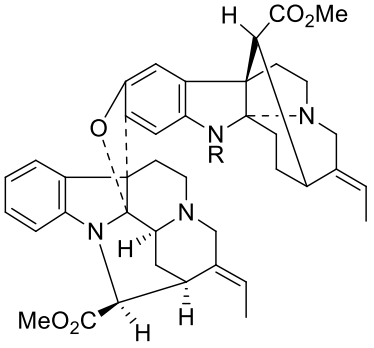
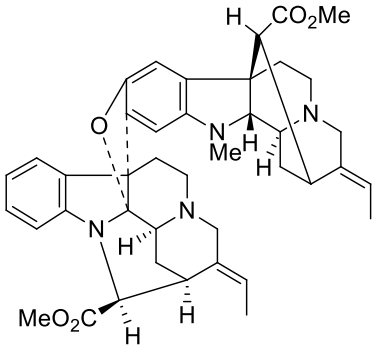


577 R = H
578 R = Me



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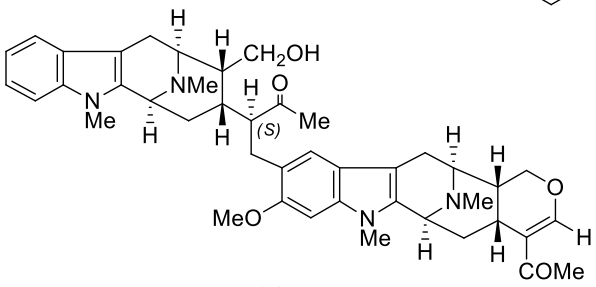

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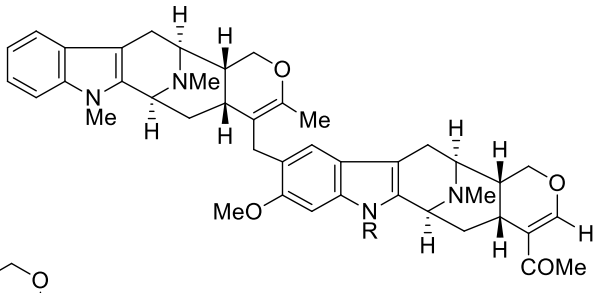
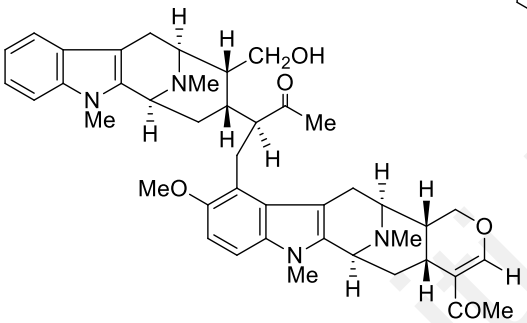


580 R = Me
581 R = H



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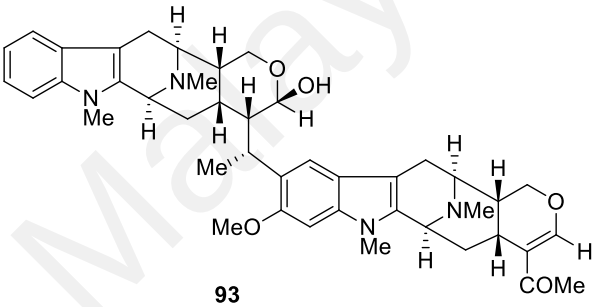

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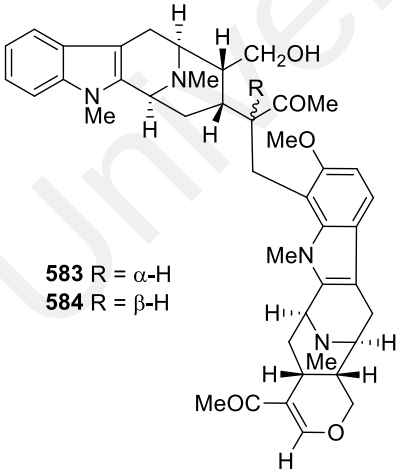
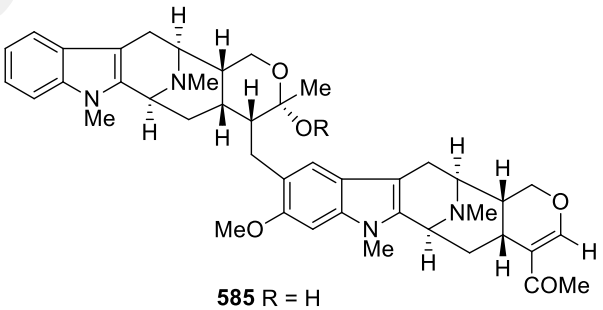
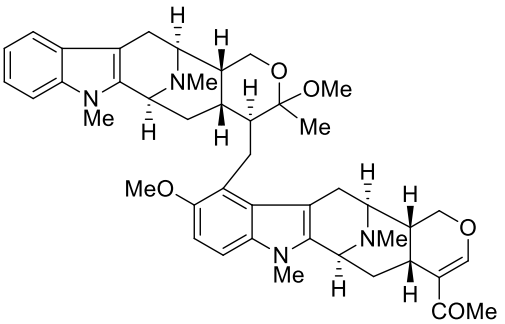


583 R = α-H
584 R = β-H



585 R = H
586 R = Me



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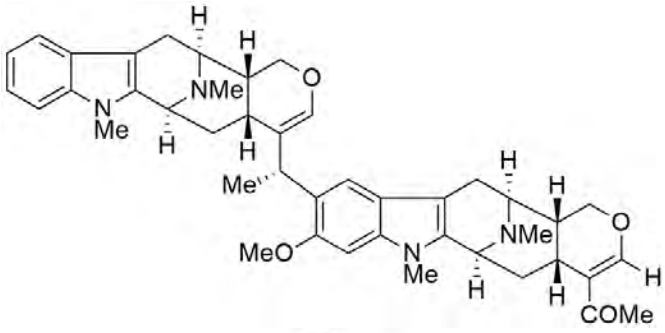

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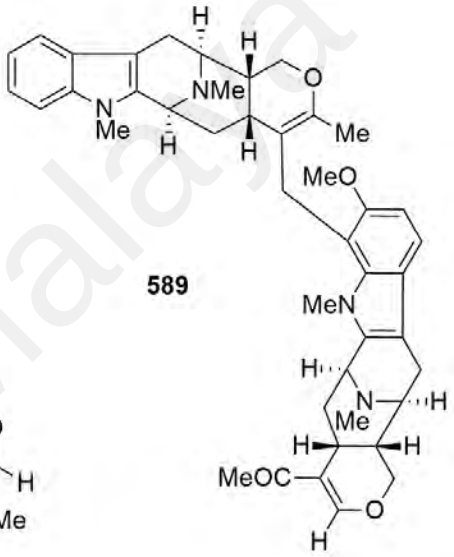

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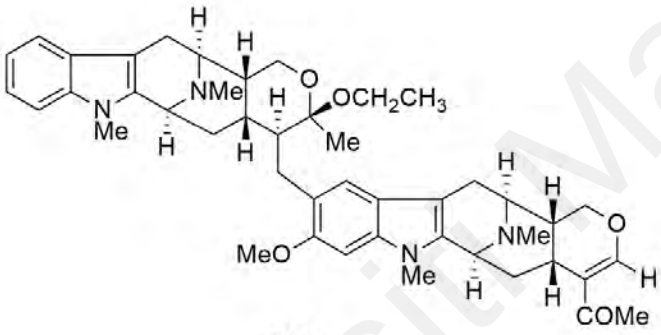

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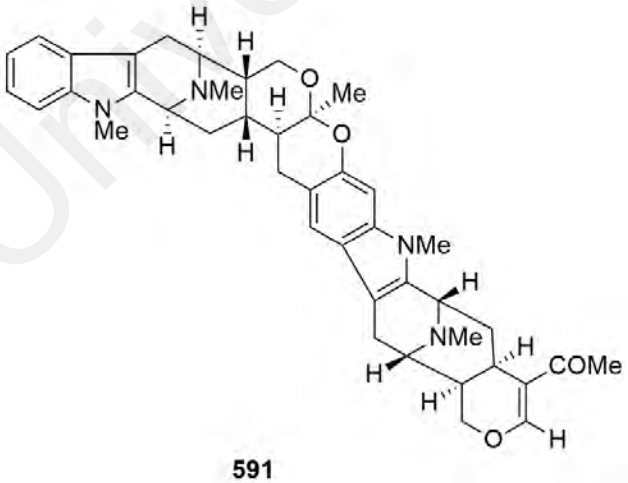

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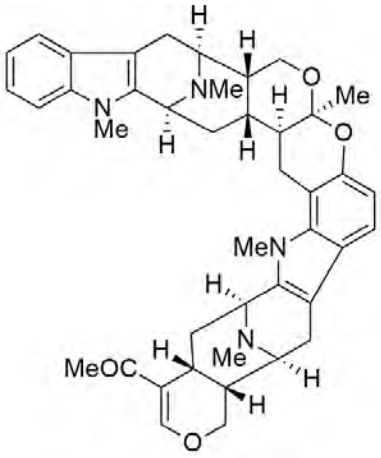

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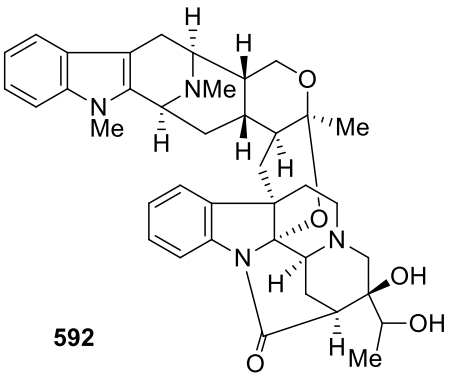

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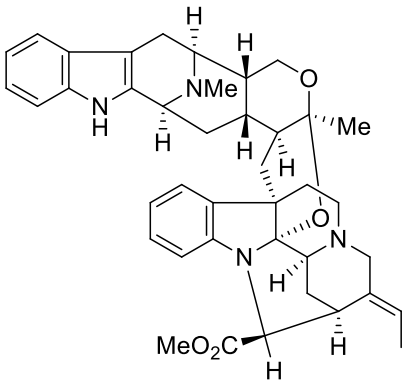

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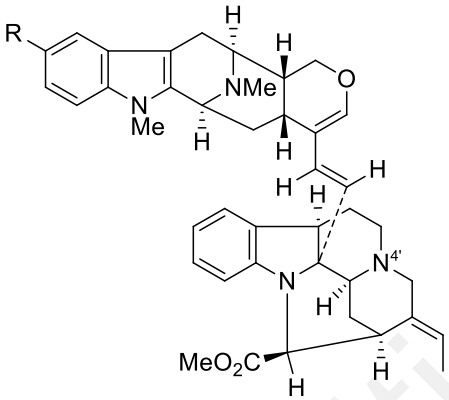
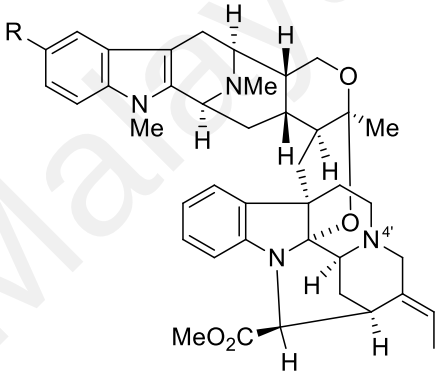
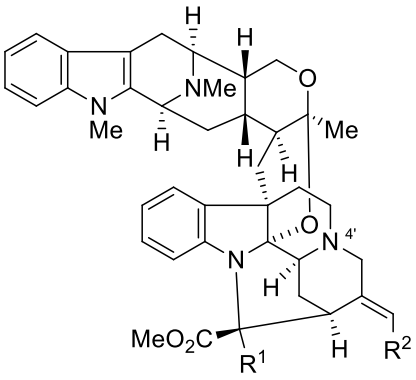


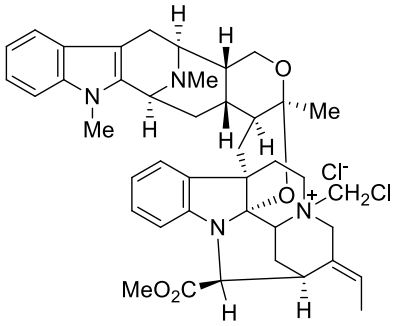
88 R = H, N(4')→O
89 R = H
594 R = OMe
595 R = OMe, N(4')→O



596 R = OMe
597 R = OMe, N(4')→O



598 R^1 = CH_2OH, R^2 = Me
599 R^1 = H, R^2 = CH_2OH
90 R^1 = H, R^2 = Me
91 R^1 = H, R^2 = Me, N(4')→O
600 R^1 = H, R^2 = Me, N(4')→Me



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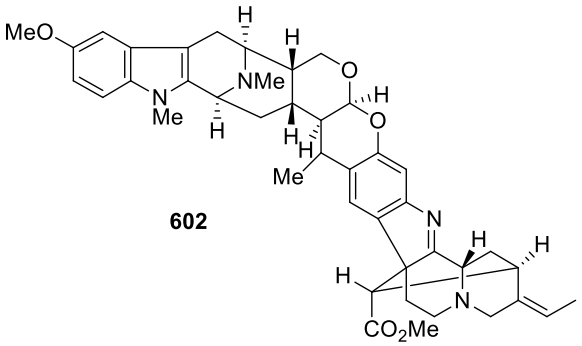

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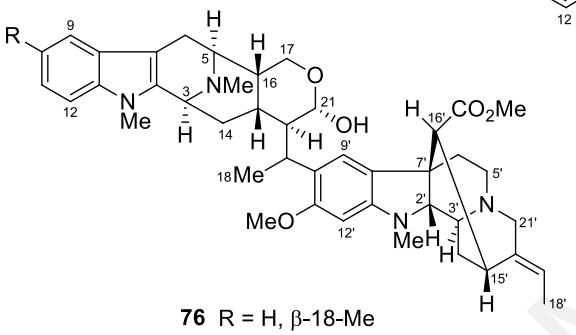
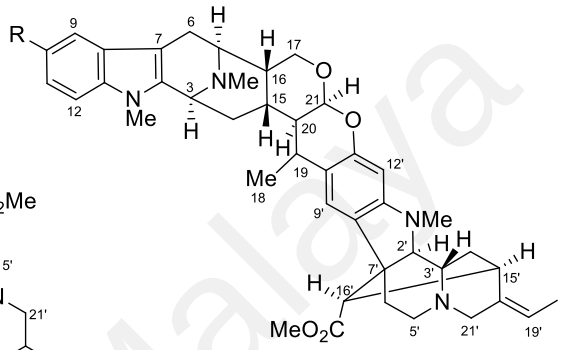
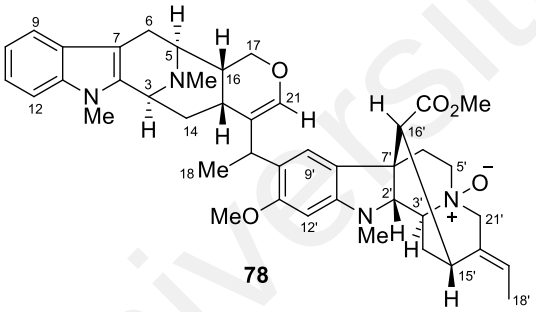


76 R = H, β-18-Me
603 R = OMe



77 R = H, β-18-Me
604 R = OMe, α-18-Me



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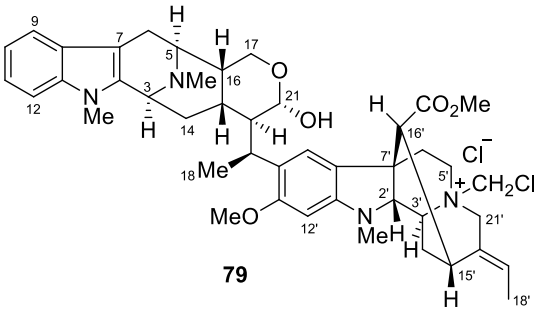

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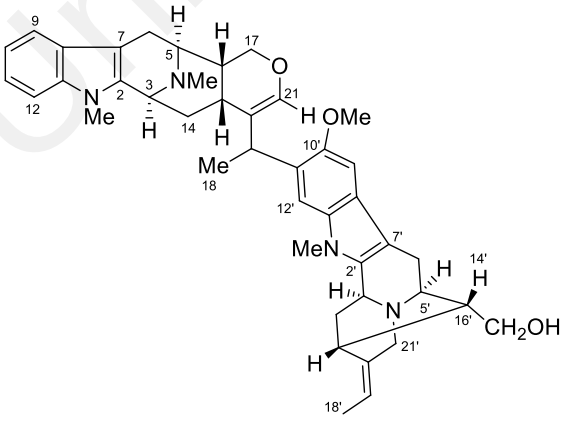

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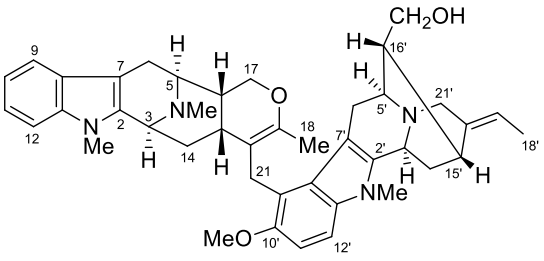

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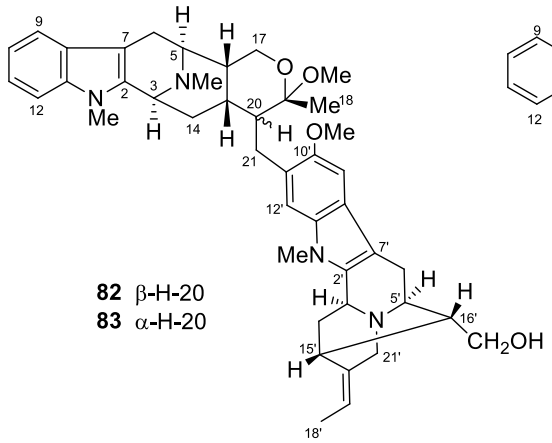
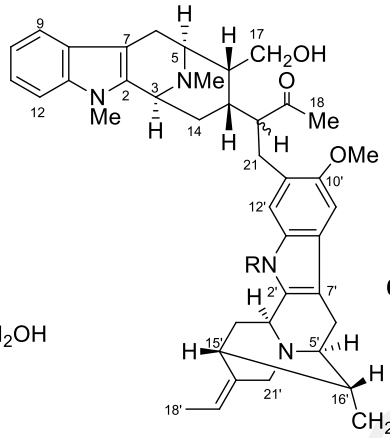
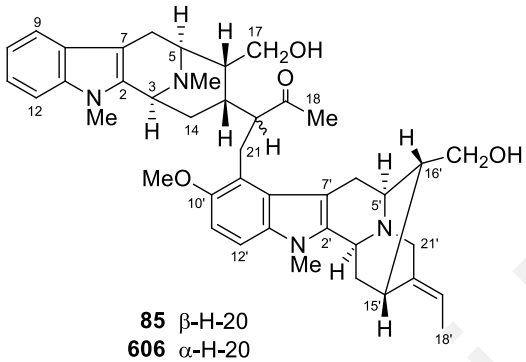


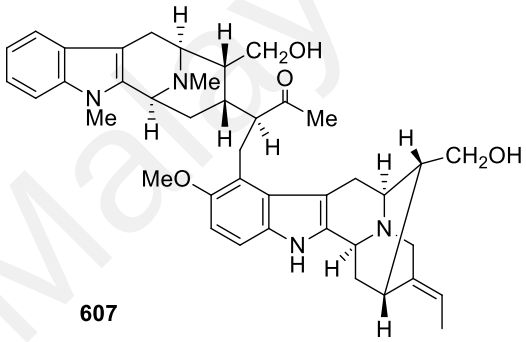
82 β-H-20
83 α-H-20



84 β-H-20, R = Me
605 α-H-20, R = H



85 β-H-20
606 α-H-20



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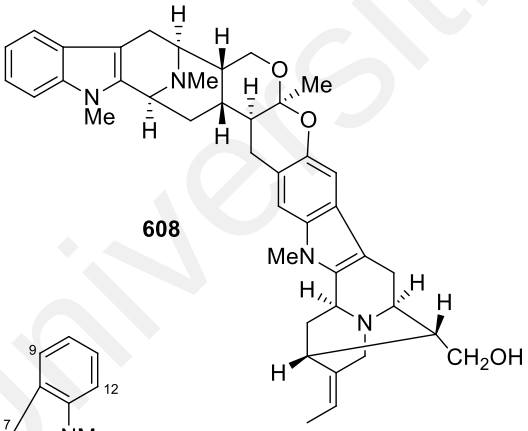

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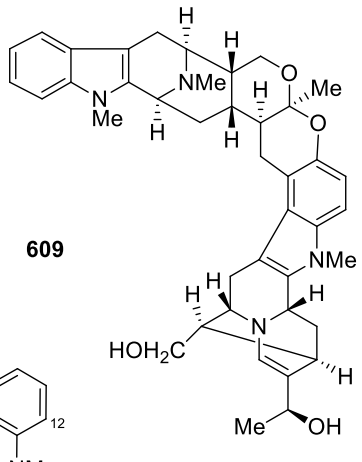

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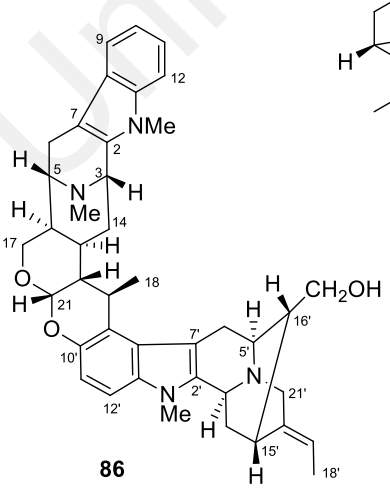
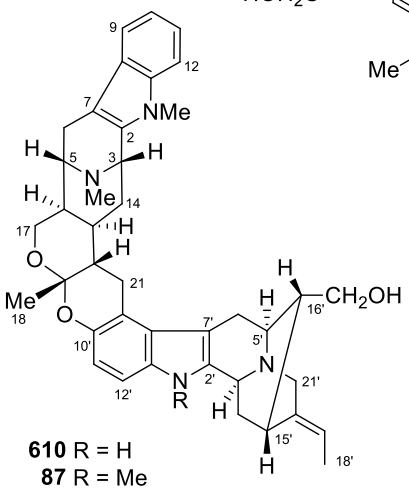


86



610 R = H
87 R = Me

1.6 *Lycopodium* Alkaloids

Plants from the family Lycopodiaceae have been shown to produce *Lycopodium* alkaloids as early as 1881 when lycopodine was isolated from *Lycopodium complanatum*.[252] *Lycopodium* alkaloids are defined based on their botanical occurrence and are notable for their unique ring systems and structural diversity, which have attracted numerous chemical studies.[61,253-256]

Lycopodium alkaloids can be classified into four main groups, viz., lycopodine, lycodine, fawcettimine, and a miscellaneous group. The first group (lycopodine-type) possessing the lycopodane skeleton, is the most widespread and largest group among the four classes. The second group (lycodine-type) is characterized by the presence of pyridine or pyridone ring as part of their structural framework. Unlike lycopodine- and lycodine-type alkaloids, in fawcettimine-type alkaloids, C-4 is bonded to C-12 instead of C-13. The other alkaloids which do not belong to the three classes above are classified under the miscellaneous group represented by phlegmarine, which was regarded as the precursor of all *Lycopodium* alkaloids.[253,257,258] The major classes of the *Lycopodium* alkaloids and their representative examples are given in Figure 1.8. The plausible biogenetic relationships among the main groups of *Lycopodium* alkaloids are shown in Scheme 1.2.

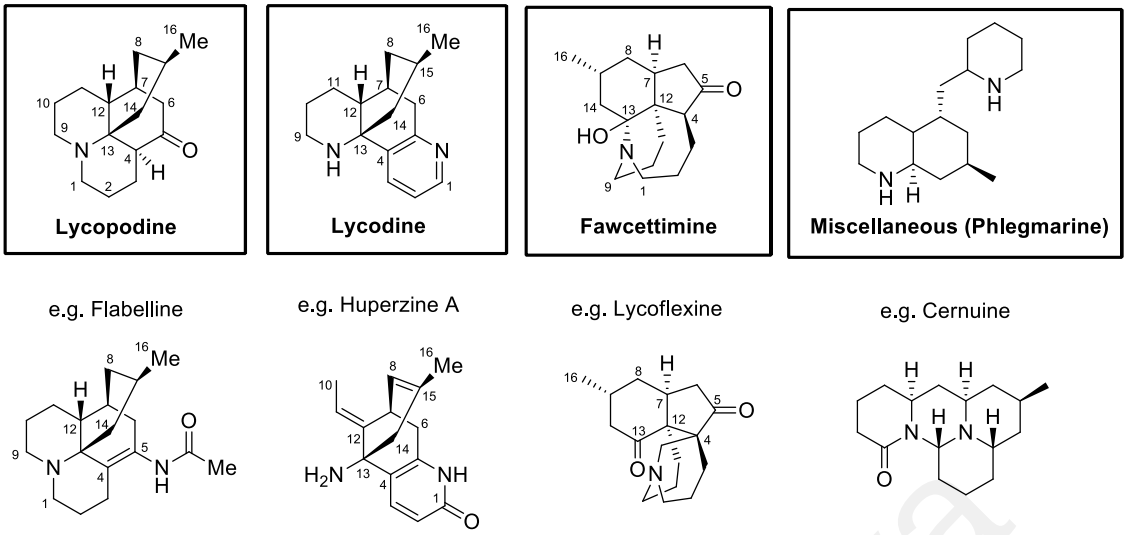
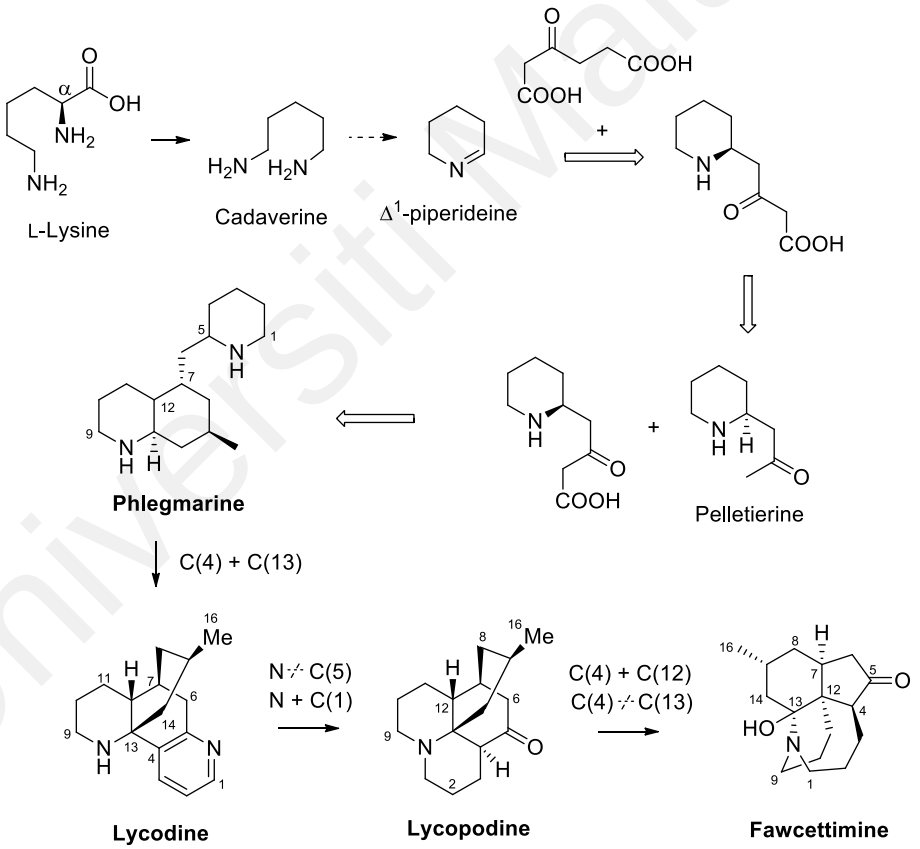


Figure 1.8: Main structural types of *Lycopodium* alkaloids



Scheme 1.2: Biogenetic inter-relationships of the four main classes of *Lycopodium* alkaloids

1.7 The Genus *Lycopodium*

The family Lycopodiaceae was initially divided into two large genera, *Lycopodium* and *Phylloglossum*, according to an old classification system reported by Baker.[259] In the succeeding years, more taxonomical studies have been conducted. At present, the taxonomic classification of Lycopodiaceae species, as regards the genus (genera) and family (families) remains a matter of debate. The most widely accepted system is the branching out of the Lycopodiaceae family into four main genera (*Lycopodium*, *Diphasiastrum*, *Huperzia*, and *Lycopodiella*) as reported by Øllgaard (1987).[260-262] Based on this classification, the nomenclature system for plants in the family Lycopodiaceae was revised accordingly (e.g., *Lycopodium serratum* was revised to *Huperzia serrata*).[263]

Plants of the genus *Lycopodium*, one of the fern allies,[264] are mainly distributed in the temperate and tropical regions throughout the world. These plants occur in diverse environments including coniferous forests, mountainous regions, and marshlands.[258,265] *Lycopodium* plants, one of the oldest plants on our planet,[264] comprise about 40 different species.[261] They are low, evergreen, and non-flowering plants that reproduce via spores instead of seeds. These plants are called clubmosses due to the appearance of their strobili (spore-bearing bodies) as club-shaped growths at the tip of the moss-like branches.[255] *Lycopodium* plants are terrestrial or epiphytic plants with small leaves (needle- or scale-like) scattered along the stem and branches.[258] In Malaysia, most of these plants only thrive in moist regions,[266] and about six species are reported to occur at varying altitudes and in diverse vegetation types. These are *Lycopodium casuarinoides* Spring, *Lycopodium clavatum* L., *Lycopodium platyrhizoma* J.H.Wilce, *Lycopodium volubile* Sw., *Lycopodium* sp., and *Lycopodium cernuum* L..[267] In the past, *Lycopodium* plants were also utilized in folklore medicines due to their therapeutic properties in treating wounds, dysentery, neuralgia, and hypertension.[268]

The *Lycopodium* plant chosen in the present study, *L. platyrhizoma* J.H.Wilce (Figure 1.9), is the only member of the genus *Lycopodium* section *Complanata*, occurring in Malaysia.[267] In terms of its distribution, *L. platyrhizoma* is a warm area species and has only been found in Malaysia, Sumatra, and Java. The species is strictly terrestrial and occurs in areas with elevation from 1300 m and above. The species is also characterized by its extreme flattening rhizome, the absence of leaf bases on the lower side of the branchlets, and the many strobili per peduncle.[267,269] This species has not been previously investigated.

Figure 1.9: *Lycopodium platyrhizoma* J.H.Wilce (Genting Highlands, Malaysia)

1.7.1 Occurrence and Distribution of Alkaloids in the Genus *Lycopodium*

Plants of the genus *Lycopodium* are rich sources of alkaloids with incredible structural variety. It has fascinated scientists for the ability of these simple plants to produce an outstanding number of structurally-diverse alkaloids.[57,253,255,257,258,270-275] While monomeric alkaloids constitute the major portion of the known *Lycopodium* alkaloids, dimeric alkaloids have also been isolated on multiple occasions.[258] The occurrence of alkaloids in *Lycopodium* as reported in the literature (up to April 2019) is summarized in Table 1.3 (botanical authority of species in accordance with IPNI).

Table 1.3: Occurrence of Alkaloids in *Lycopodium*

Species	Alkaloids	References
L. alpinum L.	Clavolonine (**705**)	276
	Des-*N*-methyl-α-obscurine (**100**)	276
	Lycoclavine (**728**)	276
	Lycopodine (**700**)	276
L. annotinum L.	Acetylfawcettiine (**714**)	277
	Acetyllofoline (**718**)	278,279
	O-Acetylacrifoline (**726**)	279,280
	Acrifoline (**725**)	280-283
	Acrifolinol (**744**)	280
	Annofoline (**720**)	284
	Annopodine (**779**)	285

Table 1.3, continued

Species	Alkaloids	References
	Annotine (**763**)	279-282
	Annotinine (**766**)	279-283
	Annotinolide A (**770**)	286
	Annotinolide B (**771**)	286
	Annotinolide C (**769**)	286
	Annotinolide D (**764**)	287
	Annotinolide E (**765**)	287
	Annotinolide F (**773**)	287
	Annotoxine (acrifoline **725** + annotine **763**)	280-282
	Fawcettiine (β-lofoline) (**711**)	284
	Isolycopodine (lycopodine **700** + acrifoline **725**)	281
	Lannotinidine A (**781**)	288,289
	Lannotinidine B (**789**)	289
	Lannotinidine C (**734**)	288,289
	Lannotinidine D (**735**)	289
	Lannotinidine E (**767**)	289
	Lannotinidine F (**768**)	289
	Lannotinidine G (**772**)	289
	Lannotinidine H (**748**)	288
	Lannotinidine I (**733**)	288
	Lannotinidine J (**780**)	288
	Lofoline (α-lofoline) (**717**)	284
	Lycoannotine A (**777**)	287
	Lycoannotine B (**778**)	287
	Lycoannotine C (**774**)	287
	Lycoannotine D (**741**)	287
	Lycoannotine E (**758**)	287
	Lycoannotine F (**755**)	287
	Lycoannotine G (**98**)	287
	Lycoannotine H (**676**)	287
	Lycoannotine I (**808**)	287
	Lycodine (**97**)	290
	Lycodoline (**106**)	279-281,283,291
	Lycofoline (**722**)	284
	Lycopodine (**700**)	279,281-283
	Lyconnotine (**776**)	292
	Nicotine (**852**)	293
	α-Obscurine (**638**)	279,281,294
	β-Obscurine (**637**)	279,281,294
	5,15-Oxidolycopodane (**762**)	283,295

Table 1.3, continued

Species	Alkaloids	References
L. casuarinoides Spring	Carinatumin B (**644**)	296,297
	Casuarine A (**837**)	298
	Casuarine B (casuarinine A) (**643**)	298
	Casuarinine A (casuarine B) (**643**)	296,297,299,300
	Casuarinine B (**645**)	296,300
	Casuarinine C (**647**)	296
	Casuarinine D (**639**)	296
	Casuarinine E (**616**)	296,297,299
	Casuarinine F (**629**)	296
	Casuarinine G (**631**)	296
	Casuarinine H (**102**)	296
	Casuarinine I (**660**)	296
	Casuarinine J (**670**)	296
	Casuarinoside A (**666**)	301
	Casuarinoside B (**633**)	301
	Casuarinoside C (**623**)	301
	Casuarinoside D (**627**)	301
	Casuarinoside E (**649**)	301
	Casuarinoside F (**650**)	301
	Casuarinoside G (**651**)	301
	Casuarinoside H (**652**)	301
	N-Demethylhuperzinine (**615**)	296-299,302,303
	N-Demethyl-β-obscurine (**99**)	296
	8,15-Dihydrohuperzinine (**628**)	303
	8,15-Dihydrolycoparin A (**632**)	297
	Huperzine B (**642**)	296-298,300,303,304
	Huperzine C (**611**)	296,297,299,304,305
	Huperzine D (**612**)	296-300,303-305
	(7*S*,12*S*,13*R*)-Huperzine D-16-*O*-β-D-glucopyranoside (**621**)	297
	Huperzinine (**613**)	296-300,302,303,305
	Huperzinine *N*-oxide (**614**)	296,300,303
	16-Hydroxyhuperzine B (**656**)	297
	Lycocasuarine A (**634**)	306
	Lycocasuarine B (**635**)	306
	Lycocasuarine C (**659**)	306
	Lycocasuarine D (**661**)	301
	Lycocasuarine E (**663**)	301
	Lycocasuarine F (**658**)	301
	Lycocasuarine G (**664**)	301
	Lycocasuarine H (**665**)	301
	Lycocasuarine I (**626**)	271
	Lycocasuarine J (**636**)	271
	Lycocasuarine K (**630**)	271
	Lycocasuarine L (**657**)	271
	Lycocasuarine M (**653**)	271

Table 1.3, continued

Species	Alkaloids	References
	Lycocasuarine N (**654**)	271
	Lycocasuarine O (**640**)	271
	Lycocasuarine P (**641**)	271
	Lycocasuarine Q (**655**)	271
	Lycocasuarinine A (**622**)	299
	Lycocasuarinine B (**624**)	299
	Lycocasuarinine C (**625**)	299
	Lycocasuarinine D (**662**)	299
	Lycoparin A (**617**)	297,304
	Lycoparin B (**619**)	304
	Lycoparin C (**620**)	297,304
	11β-Methoxyhuperzine B (**646**)	300
	N-Methyl-11-acetoxyhuperzine B (**648**)	297
	N-Methyllycodine (**669**)	300
	β-Obscurine (**637**)	303
	16-Oxohuperzinine (**618**)	300
L. clavatum L.	Acetyldihydrolycopodine (**731**)	307,308
	Acetylfawcettiine (**714**)	309
	Acetyllycoclavine (**719**)	310
	N_{α}-Acetyl-N_{β}-methylphlegmarine (**850**)	308
	Anhydrolycodoline (**736**)	308
	Clavatine (flabelliformine) (**702**)	311
	Clavatoxine (lycodoline **106** + flabelliformine **702**)	311
	Clavolonine (**705**)	307,310
	Deacetylfawcettiine (**716**)	307
	Deacetyllycoclavine (**729**)	310
	8-Deoxyserratinine (**828**)	312
	Des-*N*-methyl-α-obscurine (**100**)	294,313
	Dihydrolycopodine (complanatine)(**730**)	307,308,310,313,314
	8β,11α-Dihydroxylycopodine (**686**)	315
	Fawcettiine (β-lofoline) (**711**)	307,309,316
	Fawcettimine (**829**)	307,314
	Flabelliformine (**702**)	310
	6α-Hydroxylycopodine (**105**)	317
	Lucidioline (**721**)	318
	Lycoclavatumide (**832**)	315
	Lycoclavine (**728**)	310
	Lycodine (**97**)	294
	Lycodoline (**106**)	308,313,314,319
	Lycoflexine (lycobergine) (**820**)	308,314
	Lycopodine (**700**)	307-311,313,314,319,320
	Nicotine (**852**)	320
	α-Obscurine (**638**)	294,313

Table 1.3, continued

Species	Alkaloids	References
L. complanatum L.	Acetylfawcettiine (**714**)	321
	Clavolonine (**705**)	321
	Complanadine A (**104**)	322
	Complanadine B (**680**)	323
	Complanadine C (**681**)	324
	Complanadine D (**682**)	324
	Complanadine E (**683**)	325
	Dehydroisofawcettiine (**703**)	321
	Dehydroisofawcettiine *N*-oxide (**704**)	321
	12-Deoxyhuperzine O (**109**)	321,326
	Des-*N*-methyl-α-obscurine (**100**)	327
	Des-*N*-methyl-β-obscurine (**99**)	327
	Diphaladine A (**698**)	327
	6-Epi-8β-acetoxylycoclavine (**727**)	321
	Fawcettidine (**830**)	328
	Fawcettimine (**829**)	328
	Flabelliformine (**702**)	321
	11-Hydroxylycodine (**671**)	329
	6α-Hydroxylycopodine (**105**)	321,327
	Lycoclavine (**728**)	321
	Lycodine (**97**)	321
	Lycoflexine (**820**)	327
	Lycogladine A (**788**)	330
	Lycogladine B (**793**)	330
	Lycogladine C (**785**)	330
	Lycogladine D (**786**)	330
	Lycogladine E (**787**)	330
	Lycogladine F (**782**)	330
	Lycogladine G (**111**)	330
	Lycogladine H (**112**)	330
	Lycopladine A (**677**)	331
	Lycopladine B (**783**)	330,332
	Lycopladine C (**784**)	332
	Lycopladine D (**794**)	332
	Lycopladine E (**732**)	333
	Lycopladine F (**672**)	334
	Lycopladine G (**673**)	334
	Lycopladine H (**842**)	335
	Lycoplanine A (**843**)	336
	Lycoplanine B (**739**)	328
	Lycoplanine C (**742**)	328
	Lycoplanine D (hydroxy-des-*N*-methyl-α-obscurine) (**101**)	328
	Lycopoclavamine B (**792**)	328
	Lycopodine (**700**)	309,321,337
	Lycopodine *N*-oxide (**107**)	321
	Lycoposerramine K (**737**)	327
	Lyconadin A (**844**)	329,338

Table 1.3, continued

Species	Alkaloids	References
	Lyconadin B (**845**)	332
	Lyconadin C (**846**)	338,339
	Lyconadin D (**836**)	325,338
	Lyconadin E (**113**)	325,338
	Lyconadin F (**847**)	339
	Lyconadin G (**667**)	338
	Lyconadin H (**668**)	338
	Lycospidine A (**838**)	326
	N-Methyllycodine (**669**)	294
	Obscurumine A (**701**)	327
	Phlegmariurine B (**818**)	327
L. confertum Willd.	Deacetylpaniculine (**710**)	340,341
	Paniculine (**709**)	341
L. contiguum Klotzsch	Acetyldihydrolycopodine (**731**)	309
	Acetylfawcettiine (**714**)	309,342
	Clavolonine (**705**)	342
	Deacetylfawcettiine (**716**)	309
	Dihydrolycopodine (**730**)	309
	Fawcettiine (**711**)	342
	Lycopodine (**700**)	309,342
L. densum Labill.	Clavolonine (**705**)	343
	Flabelliformine (**702**)	295,343
	Lycodoline (**106**)	295,343
	Lycopodine (**700**)	343
L. deuterodensum Herter	Anhydrolycodoline (**736**)	317
	Clavolonine (**705**)	317
	Flabelliformine (**702**)	317
	Flabelline (**749**)	317
	Lycodine (**97**)	317
	Lycodoline (**106**)	317
	Lycoflexine (**820**)	317
	Lycopodine (**700**)	317,344

Table 1.3, continued

Species	Alkaloids	References
L. fastigiatum R.Br.	Acetyldihydrolycopodine (**731**)	317
	Anhydrolycodoline (**736**)	317
	Clavolonine (**705**)	317
	Des-*N*-methylfastigiatine (**679**)	317
	Dihydrolycopodine (**730**)	317
	Fastigiatine (**678**)	317
	Flabelliformine (**702**)	317
	Flabelline (**749**)	317
	Lycodine (**97**)	317
	Lycodoline (**106**)	317
	Lycoflexine (**820**)	317
	Lycopodine (**700**)	317
	α-Obscurine (**638**)	317
L. fawcettii F.E.Lloyd & Underw.	Acetylfawcettiine (**714**)	316
	Acetyllycofawcine (8-acetoxy-lycofawcine) (**761**)	316
	Acetyllycofoline (5-acetoxy-lycofoline)(**723**)	316
	Deacetylfawcettiine (**716**)	345
	Des-*N*-methyl-α-obscurine (**100**)	346
	Diacetyllycofoline (**724**)	316
	Fawcettidine (**830**)	345,346
	Fawcettiine (**711**)	309,342,345
	Fawcettimine (**829**)	345
	Lycodine (**97**)	346
	Lycodoline (**106**)	345
	Lycofawcine (**760**)	346
	Lycofoline (**722**)	316
L. flabelliforme Blanch.	Acetyldihydrolycopodine (**731**)	337
	Annotinine (**766**)	347
	Clavolonine (**705**)	347
	Des-*N*-methyl-α-obscurine (**100**)	347
	Dihydrolycopodine (complanatine) (**730**)	337,348-350
	Flabellidine (**103**)	337,347
	Flabelliformine (**702**)	349,350
	Flabelline (**749**)	350
	Hydroxy-des-*N*-methyl-α-obscurine (lycoplanine D) (**101**)	347
	Lycodine (**97**)	347
	Lycopodine (**700**)	337,348,349
	Nicotine (**852**)	337
	α-Obscurine (**638**)	350
	β-Obscurine (**637**)	337
L. issleri (Rouy) Domin	Lycopodine (**700**)	309

Table 1.3, continued

Species	Alkaloids	References
L. japonicum Thunb.	8β-Acetoxy-11α-hydroxylycopodine (**694**)	351
	8β-Acetoxy-12β-hydroxylycopodine (**693**)	351,352
	Acetylfawcettiine (**714**)	351-353
	Acetylfawcettiine *N*-oxide (**715**)	353
	Acetyllycofawcine (**761**)	352
	Acetyllycoposerramine M (**696**)	354
	Anhydrolycodoline (**736**)	352
	Clavolonine (**705**)	351-353
	Deacetylfawcettiine (**716**)	352
	14,15-Dehydrolycoflexine (**821**)	355,356
	8-Deoxy-13-dehydroserratinine (**827**)	355
	Des-*N*-methyl-α-obscurine (**100**)	351,356,357
	Diacetyllycofoline (**724**)	353
	(15*R*)-14,15-Dihydroepilobscurinol (**805**)	355,356
	4α,8β-Dihydroxylycopodine (**685**)	352
	6α,8β-Dihydroxylycopodine (**684**)	352
	Diphaladine A (**698**)	354
	15-Epi-6-hydroxy-6,7-dehydro-8-deoxy-13-dehydroserratinine (**826**)	353
	Fawcettiine (**711**)	352-354
	Fawcettiine *N*-oxide (**712**)	353
	Fawcettimine (**829**)	351,353,358,359
	Huperzinine (**613**)	357
	8β-Hydroxy-11α-acetoxylycopodine (**689**)	352
	11α-Hydroxyacetylfawcettiine (**706**)	352
	12β-Hydroxy-acetylfawcettiine (**707**)	351
	12β-Hydroxy-acetylfawcettiine *N*-oxide (**708**)	354
	11β-Hydroxy-12-epilycodoline (**699**)	352,354
	8β-Hydroxyhuperzine E (**747**)	352
	6-Hydroxyl-6,7-dehydro-8-deoxy-13-dehydroserratinine (**825**)	353,355
	6-Hydroxyl-6,7-dehydrolycoflexine (**823**)	355,356
	8β-Hydroxylycodoline (**687**)	352
	8β-Hydroxylycoposerramine K (**738**)	352
	5α-Hydroxy-6-oxodihydrophlegmariurine A (**819**)	353
	Isoobscurinine (**814**)	353
	Isopalhinine A (**809**)	356
	α-Lofoline (**717**)	351,352
	Lucidioline (**721**)	360
	Lycocernuine (**851**)	356
	Lycoclavine (**728**)	354
	Lycodine (**97**)	352,356
	Lycodoline (**106**)	360
	Lycofawcine (**760**)	352
	Lycoflexine (**820**)	351,355,356,358
	Lycojapodine A (**841**)	353,358
	Lycojaponicumin A (**834**)	359
	Lycojaponicumin B (**835**)	359

Table 1.3, continued

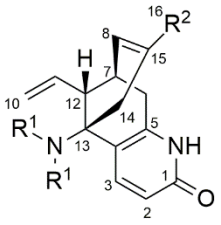
Species	Alkaloids	References
	Lycojaponicumin C (**839**)	353,359
	Lycojaponicumin D (**840**)	361
	Lycojaponicumin E (**831**)	356,361
	Lycopladine H (**842**)	356
	Lycopoclavamine A (**791**)	351,356
	Lycopodine (**700**)	352-354,358
	Lycoposerramine G (**690**)	352
	Lycoposerramine K (**737**)	354
	Lycoposerramine M (**695**)	351,352
	N-Methylhydroxypropyllycodine (**674**)	357
	N-Methyllycodine (**669**)	357
	17α-Methyllycoflexine (**822**)	356
	Miyoshianine A (**692**)	360
	Miyoshianine C (**691**)	360
	α-Obscurine (**638**)	351,356,357,360
	β-Obscurine (**637**)	357
	Obscurinine (**813**)	351,353
	Palcernine A (**824**)	356
	Palhinine A (**799**)	353,355,356
	Palhinine D (previously named as palhinine B) (**798**)	355,362
	Phlegmariurine B (**818**)	353
	4α,8β,12β-Trihydroxylycopodine (**688**)	352
L. magellanicum (P.Beauv.) Sw.	Acetyldihydrolycopodine (**731**)	363
	Acetylfawcettiine (**714**)	363
	Clavolonine (**705**)	364
	Deacetylfawcettiine (**716**)	364
	Fawcettiine (**711**)	364
	Lycodine (**97**)	363
	Lycopodine (**700**)	363,364
	Magellanine (**817**)	363,364
	Magellaninone (5-dehydro-magellanine) (**816**)	363,364
	N-Methyllycodine (**669**)	363
	α-Obscurine (**638**)	364
	β-Obscurine (**637**)	364
L. obscurum L.	Acetylacrifoline (**726**)	295,365-367
	Acetylannofoline (**754**)	295,365,367
	Acetyldihydrolycopodine (*O*-acetyldihydrolycopodine) (**731**)	367-369
	5*R*,8*R*-*O*-Acetylfawcettiine (acetylfawcettiine) (**714**)	366
	Acetylfawcettiine (**714**)	56,367,368
	Acetyllobscurinol (**806**)	369
	5-Acetyllycofoline (acetyllycofoline) (**723**)	366
	(8β)-8-(Acetyloxy)obscurumine A (**697**)	370
	Acrifoline (**725**)	366

Table 1.3, continued

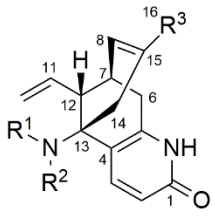
Species	Alkaloids	References
	Acrifolinol (**744**)	369
	Anhydrodihydrolycopodine (**745**)	295,365
	Anhydrolycodoline (**736**)	366,368
	Annotinine (**766**)	371
	Cermizine D (**849**)	370
	Cermizine D *N*-oxide (**848**)	370
	Clavolonine (**705**)	366,369,370
	Deacetylfawcettiine (**716**)	56,366,372
	Deacetyllycofawcine (**759**)	370
	Dehydroisofawcettiine (**703**)	372
	Des-*N*-methyl-α-obscurine (**100**)	56,366-369
	Des-*N*-methyl-β-obscurine (**99**)	56,368,369,372
	Dihydrolycopodine (**730**)	366,369
	Epilobscurinol (**803**)	369
	Fawcettiine (**711**)	366,367
	Flabellidine (**103**)	369
	Flabelliformine (**702**)	56,366,367,369
	Hydroxypropyllycodine (**675**)	369
	Isofawcettiine (**713**)	366,370
	Isoobscurinine (**814**)	56
	Lobscurinol (**804**)	369
	β-Lofoline (fawcettiine) (**711**)	369
	Lycobscurine A (**801**)	372
	Lycobscurine B (**802**)	372
	Lycobscurine C (**807**)	372
	Lycodine (**97**)	369-371
	Lycodoline (**106**)	56,366,367
	Lycoflexine (**820**)	367,368
	Lycofoline (**722**)	366,369
	Lycopodine (**700**)	56,365-369,371
	Lyconnotinol (**775**)	369
	Nicotine (**852**)	365
	α-Obscurine (**638**)	365
	β-Obscurine (**637**)	365
	Obscurinine (**813**)	56,368,373
	Obscurumine A (**701**)	323
	Obscurumine B (**753**)	56,323,366-368
	Obscurumine C (**740**)	368
	Obscurumine D (**795**)	368
	Obscurumine E (**800**)	368
	Obscurumine F (**751**)	366,367
	Obscurumine G (**752**)	366,367
	Obscurumine H (**810**)	56
	Obscurumine I (**811**)	56
	Obscurumine J (**812**)	56
	Obscurumine K (**833**)	56
	Obscurumine L (**796**)	56

Table 1.3, continued

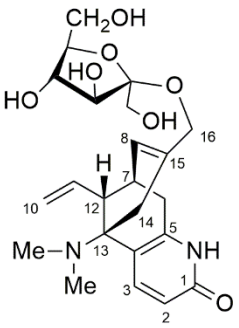
Species	Alkaloids	References
	Obscurumine M (**797**)	56
	Obscurumine N (**790**)	56
	Obscurumine O (**743**)	56
	Obscurumine P (**750**)	56
	Strictumine A (**756**)	366
	Strictumine B (**757**)	366
L. paniculatum Rosenst. ex Nessel	Acetyldihydrolycopodine (**731**)	374,375
	Anhydrodeacetylpaniculine (**746**)	374,376
	Deacetyllycoclavine (**729**)	374,376
	Deacetylpaniculine (**710**)	376
	Dihydrolycopodine (**730**)	374,375
	Flabellidine (**103**)	376
	Lycoclavine (**728**)	376
	Lycopaniculatine (paniculatine) (**815**)	374,375
	Lycopodine (**700**)	374,375
	Paniculine (**709**)	374,376
L. sabinifolium Willd.	Dihydrolycopodine (**730**)	295,377
	Lycopodine (**700**)	377
	Nicotine (**852**)	377
L. sitchense Rupr.	Clavolonine (**705**)	309
	Lycopodine (**700**)	309
	α-Obscurine (**638**)	309
L. thyoides Willd.	Acetyldihydrolycopodine (**731**)	342,374
	Acetylfawcettiine (**714**)	309,342
	Fawcettiine (**711**)	309,342
	Flabellidine (**103**)	309
	Lycopodine (**700**)	309,342
L. tristachyum Pursh	Anhydrodihydrolycopodine (**745**)	378
	Flabelliformine (**702**)	295,378
	Lycodine (**97**)	309
	Lycopodine (**700**)	378
	Nicotine (**852**)	378
L. volubile Sw.	Dihydrolycopodine (**730**)	379
	Lycopodine (**700**)	379



611 R^1 = H, R^2 = Me
612 R^1 = Me, R^2 = CH_2OH
613 R^1, R^2 = Me
614 R^1, R^2 = Me, N→O
615 R^1 = H,Me, R^2 = Me
616 R^1 = H,Me, R^2 = CH_2OH



617 R^1 = R^2 = Me, R^3 = CO_2H
618 R^1 = Me, R^2 = Me, R^3 = CHO
619 R^1 = Me, R^2 = H, R^3 = CO_2H
620 R^1 = H, R^2 = H, R^3 = CH_2OH
621 R^1 = Me, R^2 = Me, R^3 = CH_2OGlu
622 R^1 = Me, R^2 = Me, R^3 = CH_2OH, N→O



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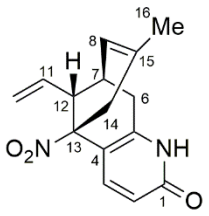

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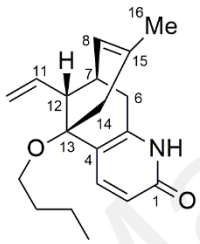

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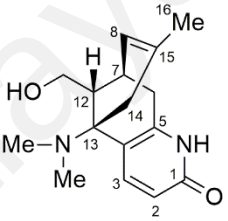

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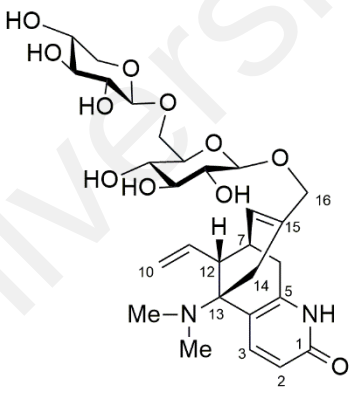

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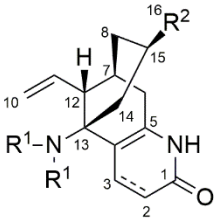
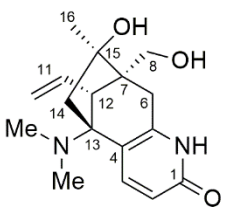


96 R^1 = H, R^2 = Me
102 R^1 = H, $\Delta^{2,3}$, R^2 = Me
628 R^1 = Me, $\Delta^{2,3}$
629 $\Delta^{2,3}$, R^1 = Me, R^2 = CH_2OH
630 $\Delta^{2,3}$, R^1 = H, R^2 = CH_2OH
631 $\Delta^{2,3}$, R^1 = Me,H, R^2 = Me
632 $\Delta^{2,3}$, R^1 = Me, R^2 = COOH
633, $\Delta^{2,3}$, R^1 = Me, R^2 = CH_2OGlu



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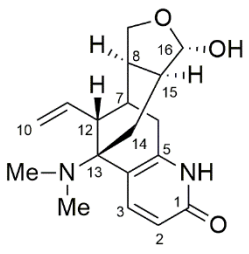

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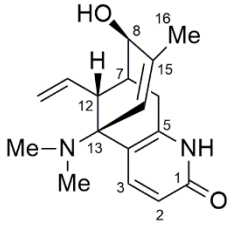

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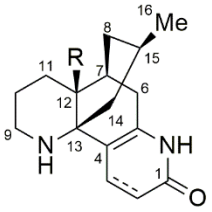
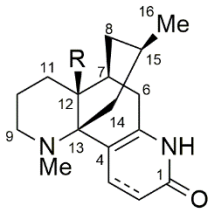
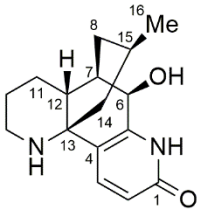


99 R=H, $\Delta^{2,3}$
100 R=H
101 R=OH



637 R=H, $\Delta^{2,3}$
638 R=H



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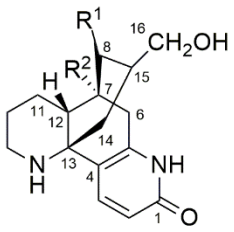
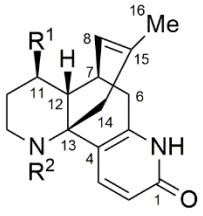
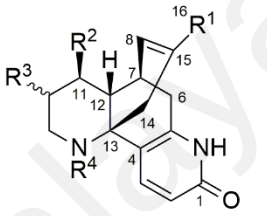


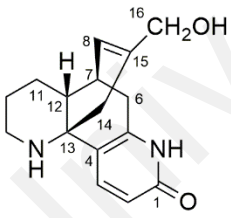
640 R^1 = α-OH, R^2 = H
641 R^1 = H, R^2 = OH



642 R^1 = nil, R^2 = H
643 R^1 = OH, R^2 = Me
644 R^1 = OH, R^2 = H
645 R^1 = OMe , R^2 = Me
646 R^1 = OMe, R^2 = H
647 R^1 = Cl, R^2 = Me
648 R^1 = OAc, R^2 = Me



649 R^1 = OGlu, R^2 = nil, R^3 = nil, R^4 = Me
650 R^1 = Me, R^2 = α-OGlu, R^3 = nil, R^4 = Me
651 R^1 = Me, R^2 = nil, R^3 = α-OGlu, R^4 = Me
652 R^1 = Me, R^2 = OH, R^3 = α-OGlu, R^4 = Me
653 R^1 = Me, R^2 = nil, R^3 = β-OH, R^4 = H
654 R^1 = Me, R^2 = α-OH, R^3 = nil, R^4 = H
655 R^1 = CH_2OH, R^2 = β-OH, R^3 = nil, R^4 = Me



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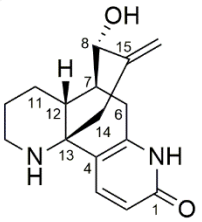

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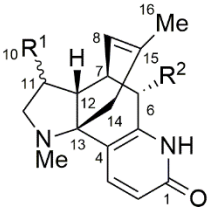
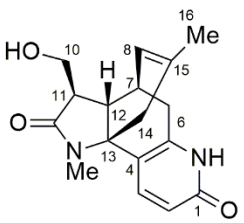


660 R^1 = β-Me, R^2 = nil
661 R^1 = β-CH_2OH, R^2 = nil
662 R^1 = β-CH_2OH, R^2 = nil, N→O
663 R^1 = β-CH_2OH, R^2 = OH
664 R^1 = α-OH, R^2 = nil
665 R^1 = β-OH, R^2 = nil
666 R^1 = β-OGlu, R^2 = nil



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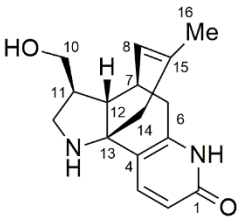

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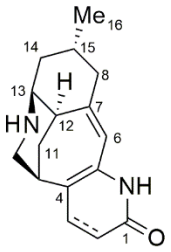
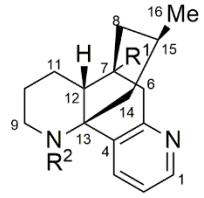
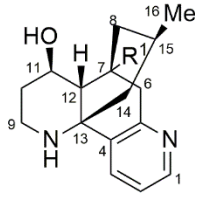


668
667 $\Delta^{2,3}$



97 R^1 = H, R^2 = H
669 R^1 = H, R^2 = Me
670 R^1 = OH, R^2 = H



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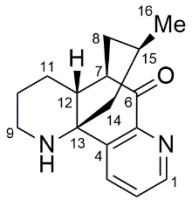

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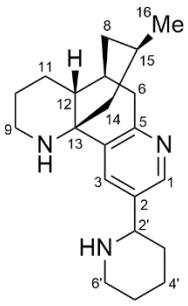

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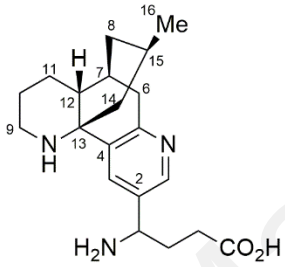

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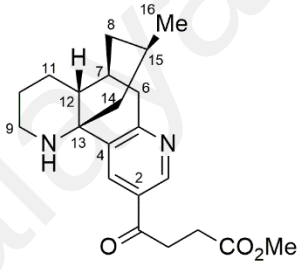

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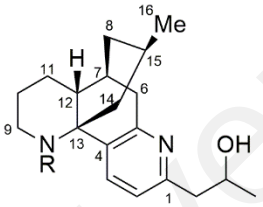
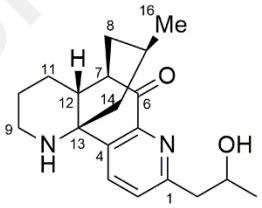


674 R = Me
675 R = H



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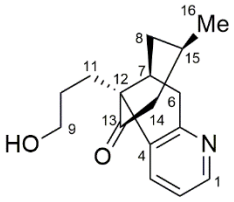

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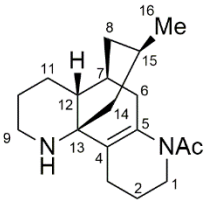

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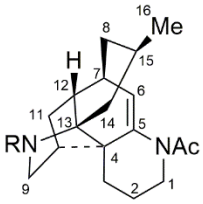
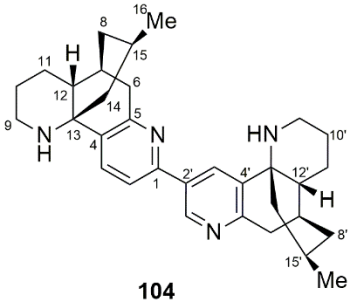


678 R = Me
679 R = H



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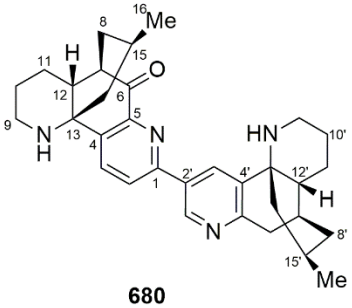

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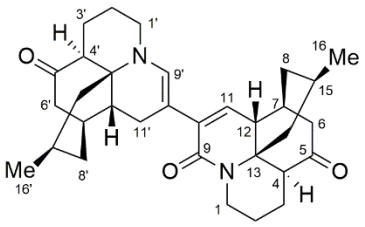

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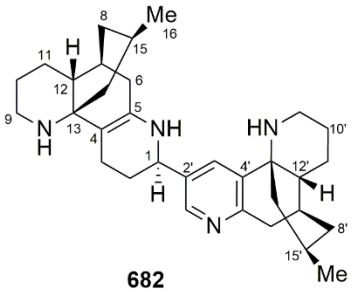

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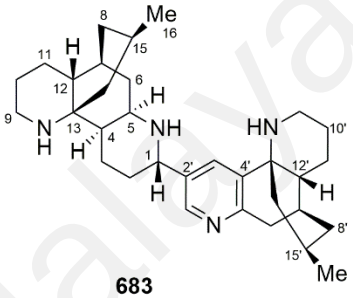
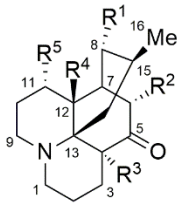
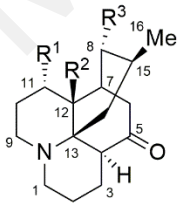


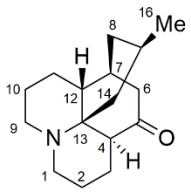
683



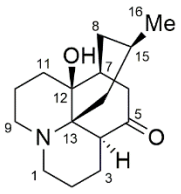
684 $R^1 = R^2 = OH$, $R^3 = R^4 = R^5 = H$
685 $R^1 = R^3 = OH$, $R^2 = R^4 = R^5 = H$
686 $R^1 = OH$, $R^3 = R^2 = nil$, $R^4 = H$, $R^5 = OH$
687 $R^1 = R^4 = OH$, $R^2 = R^3 = R^5 = H$
688 $R^1 = R^3 = R^4 = OH$, $R^2 = R^5 = H$
689 $R^1 = OH$, $R^2 = R^3 = R^4 = H$, $R^5 = OAc$
690 R^1, R^2, $R^5 = H$, R^3, $R^4 = OH$
691 $R^1 = OH$, $R^2 = nil$, $R^3 = H$, $R^4 = OH$, $R^5 = nil$, N→O
692 $R^1 = H$, $R^2 = nil$, $R^3 = OH$, $R^4 = OH$, $R^5 = nil$, N®O



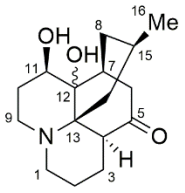
693 $R^1 = H$, $R^2 = OH$, $R^3 = OAc$
694 $R^1 = OH$, $R^2 = H$, $R^3 = OAc$
695 $R^1 = OH$, $R^2 = H$, $R^3 = nil$
696 $R^1 = OAc$, $R^2 = H$, $R^3 = nil$
697 $R^1 = nil$, $R^2 = OH$, $R^3 = OAc$, N→O



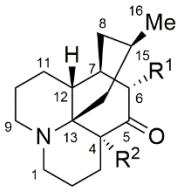
700
107 N→O



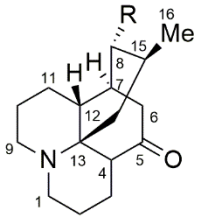
106
701 N→O



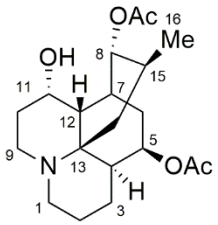
698 β-12-OH, N→O
699 α-12-OH



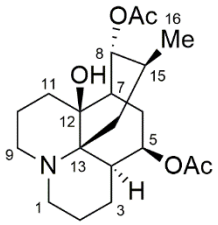
105 $R^1 = OH$, $R^2 = H$
702 $R^1 = H$, $R^2 = OH$



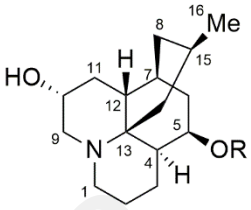
703 R = OAc
704 R = OAc, N→O
705 R = OH



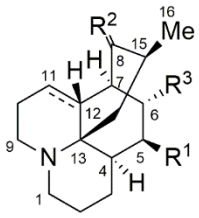
706



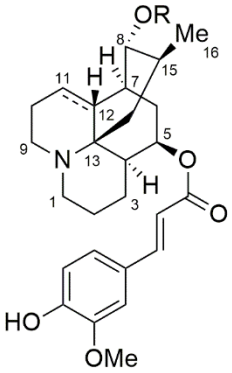
707
708 N→O



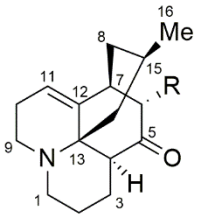
709 R = Ac
710 R = H



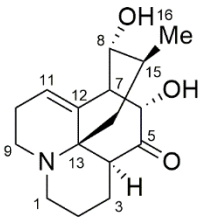
711 R^1 = OAc, R^2 = α-OH,H, R^3 = nil
712 R^1 = OAc, R^2 = α-OH,H, R^3 = nil, N→O
713 R^1 = OH , R^2 = α-OAc,H, R^3 = nil
714 R^1 = OAc, R^2 = α-OAc,H, R^3 = nil
715 R^1 = OAc, R^2 = α-OAc,H, R^3 = nil, N→O
716 R^1 = OH, R^2 = α-OH,H, R^3 = nil
717 R^1 = OAc, R^2 = β-OH,H, R^3 = nil
718 R^1 = OAc, R^2 = β-OAc,H, R^3 = nil
719 R^1 = OAc, R^2 = nil, R^3 = OAc
720 R^1 = OH, R^2 = O, R^3 = nil
721 $\Delta^{11,12}$, R^1 = OH, R^2 = nil, R^3 = OH
722 $\Delta^{11,12}$, R^1 = OH, R^2 = α-OH,H, R^3 = nil
723 $\Delta^{11,12}$, R^1 = OAc, R^2 = α-OH,H, R^3 = nil
724 $\Delta^{11,12}$, R^1 = OAc, R^2 = α-OAc,H, R^3 = nil
725 $\Delta^{11,12}$, R^1 = OH, R^2 = O, R^3 = nil
726 $\Delta^{11,12}$, R^1 = OAc, R^2 = O, R^3 = nil
727 R^1 = OAc, R^2 = α-OAc,H, R^3 = OH
728 R^1 = OAc, R^2 = nil , R^3 = OH
729 R^1 = OH, R^2 = nil , R^3 = OH
730 R^1 = OH, R^2 = nil , R^3 = nil
731 R^1 = OAc, R^2 = nil , R^3 = nil
732 R^1 = OAc, R^2 = nil , R^3 = nil, N→O



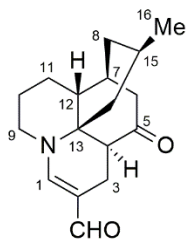
733 R = Ac
734 R = H
735 $\Delta^{11,12}$, R = H



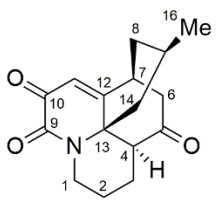
736 R = nil
737 R = OH



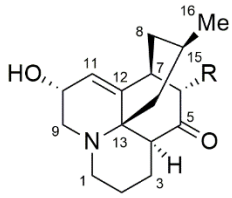
738



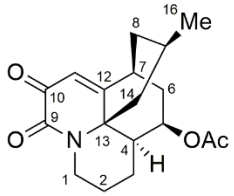
739



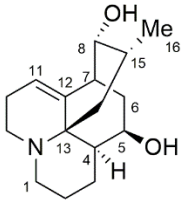
740



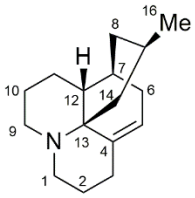
741 R = nil
742 R = OH



743



744



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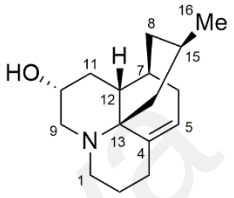
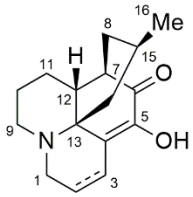
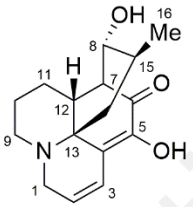


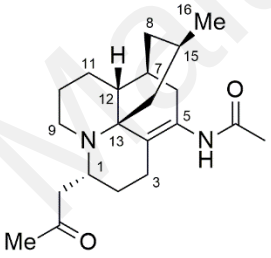
746



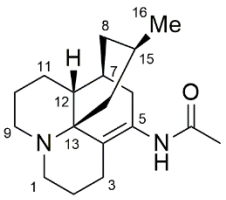
108 $\Delta^{2,3}$
109



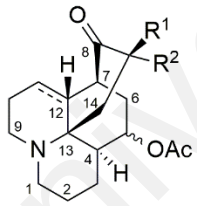
747



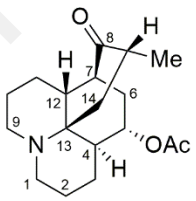
748



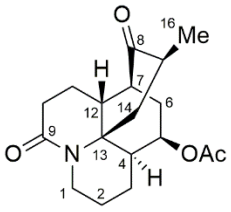
749



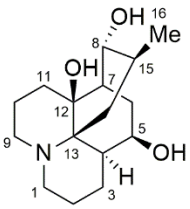
750 α-OAc,
R^1 = OH, R^2 = Me, $\Delta^{11,12}$
751 β-OAc,
R^1 = Me, R^2 = H, $\Delta^{11,12}$
752 β-OAc,
R^1 = Me, R^2 = OH
753 β-OAc,
R^1 = Me, R^2 = H
754 β-OAc,
R^1 = H, R^2 = Me
755 β-OAc,
R^1 = OH, R^2 = Me, $\Delta^{11,12}$



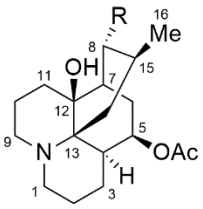
756
757 N→O



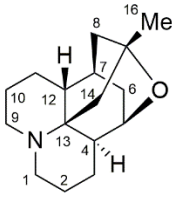
758



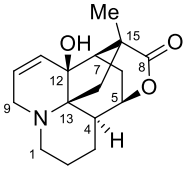
759



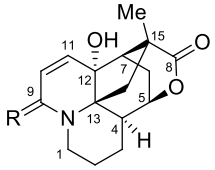
760 R = OH
761 R = OAc



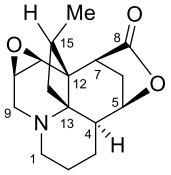
762



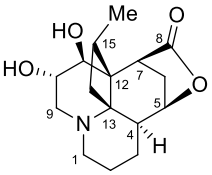
763



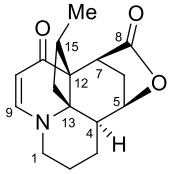
764 R = nil
765 R = O



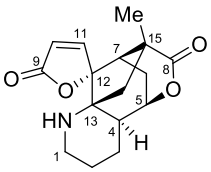
766



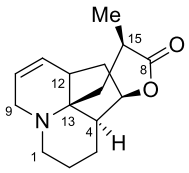
767



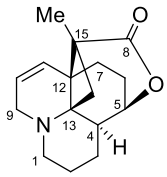
768



769



770



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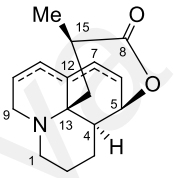
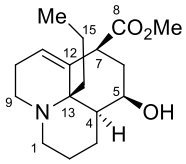
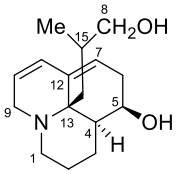


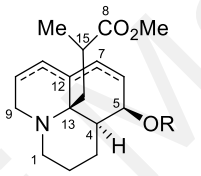
772 $\Delta^{7,12;10,11}$
773 $\Delta^{6,7;12,11}$



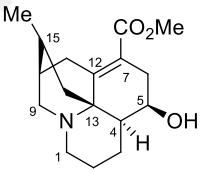
774



775



776 R = H, $\Delta^{7,12;10,11}$
777 R = Ac, $\Delta^{7,12;10,11}$
778 R = Ac, $\Delta^{6,7;12,11}$



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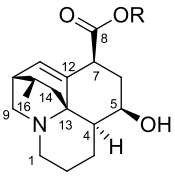
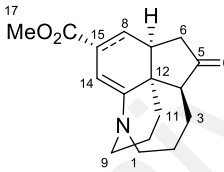
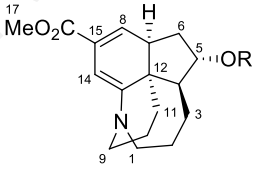


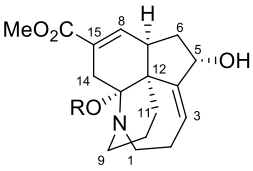
780 R = H
781 R = Me



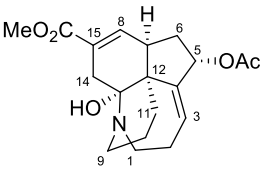
111 α-CO_2Me
112 β-CO_2Me
782 $\Delta^{8,15}$



783 R = H
784 R = Ac



785 R = H
786 R = Me



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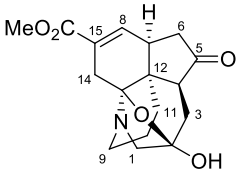

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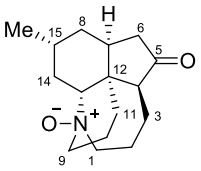

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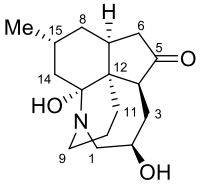

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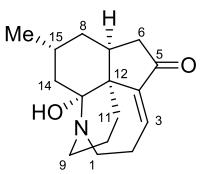

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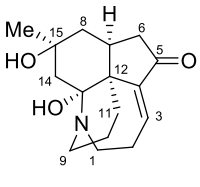

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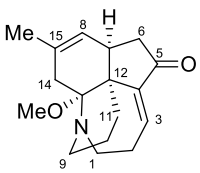

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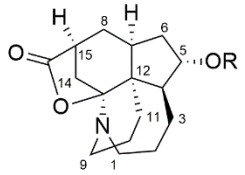

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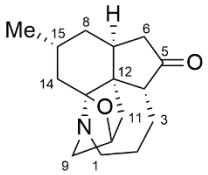

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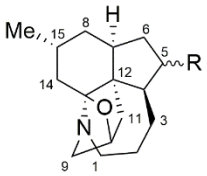
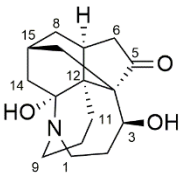


796 R = α-OH
797 R = β-OH



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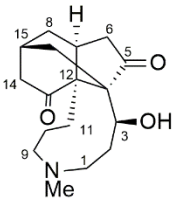

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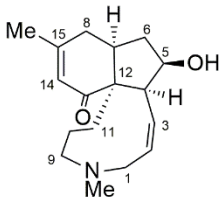

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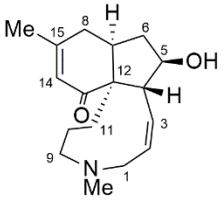

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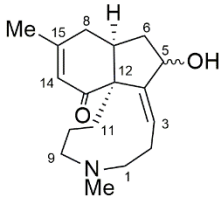
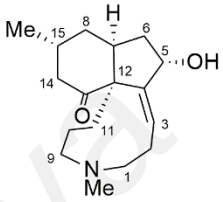
802 N→O



803 R = β-OH
804 R = α-OH



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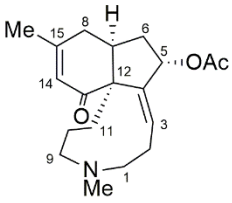

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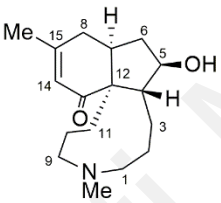

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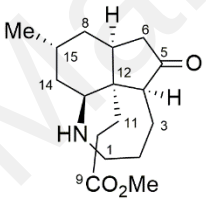

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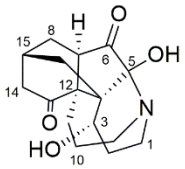

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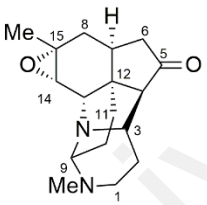

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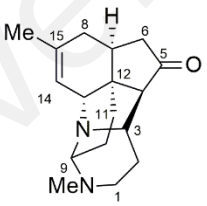

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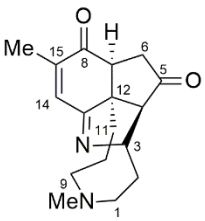

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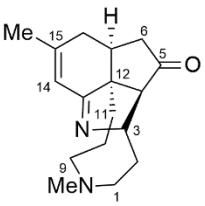

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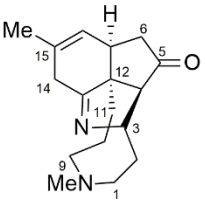

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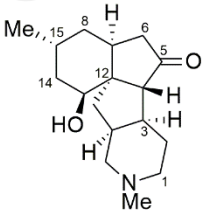

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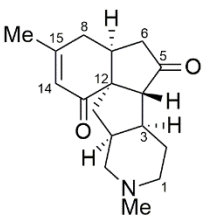

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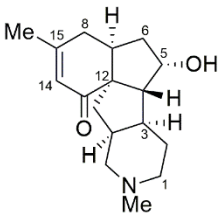

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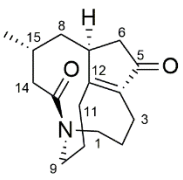

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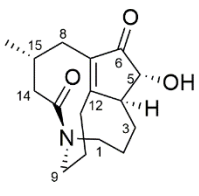

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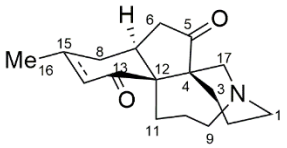

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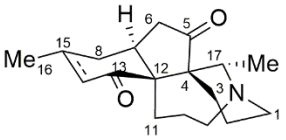

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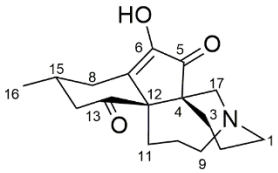

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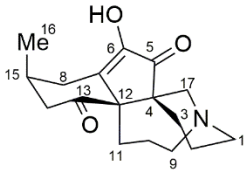

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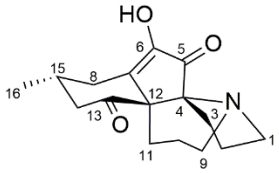

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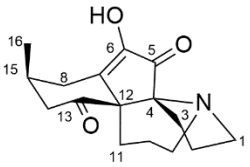

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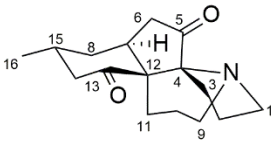

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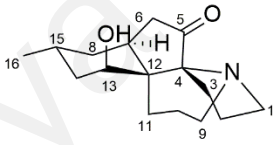

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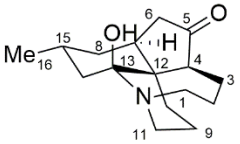

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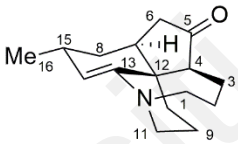

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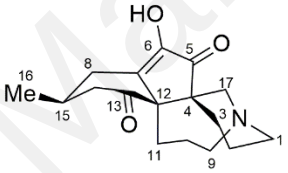

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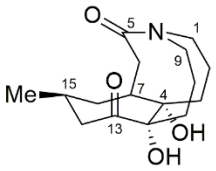

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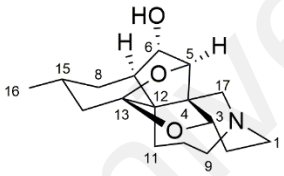

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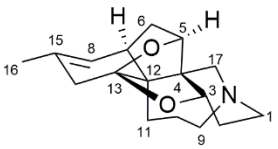

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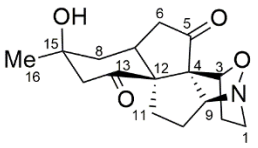

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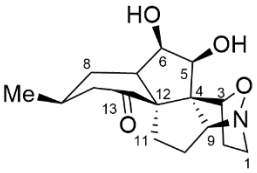

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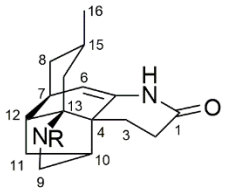
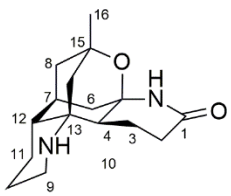


113 R = H
836 R = Me



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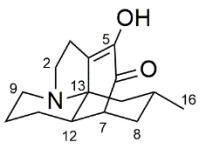

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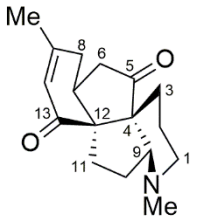

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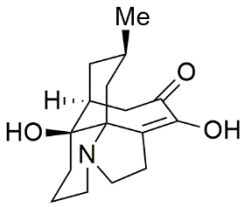

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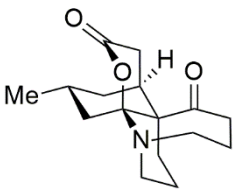

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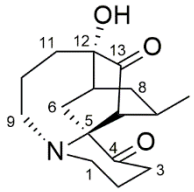

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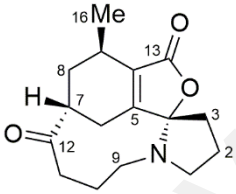

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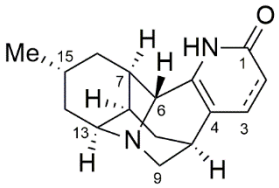
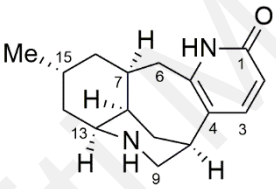


844 $\Delta^{2,3}$

845



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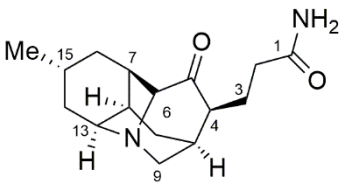

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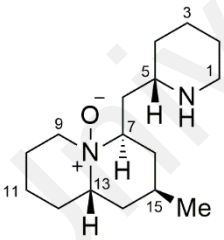

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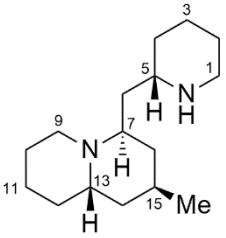

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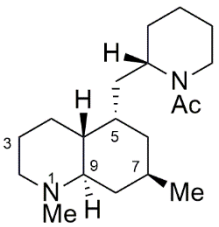

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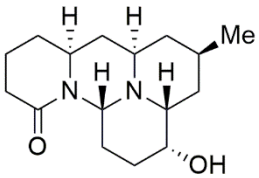

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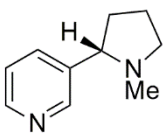

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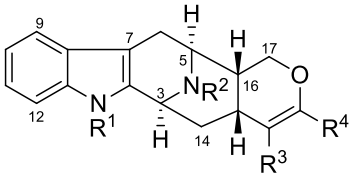
1.8 Objectives of the Present Research

The aim of the present study is to investigate the alkaloid composition of two previously uninvestigated Malaysian plants, *Alstonia penangiana* (collected in Bukit Bendera) and *Lycopodium platyrhizoma* (collected in Genting Highlands), with emphasis on the following aspects: the discovery and structure elucidation of the new alkaloids, the documentation of the alkaloid composition in these plants, and, the evaluation of the biological activity of new alkaloids.

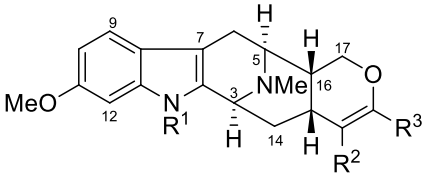
CHAPTER 2: RESULTS AND DISCUSSION

2.1 Alkaloids from *Alstonia penangiana*

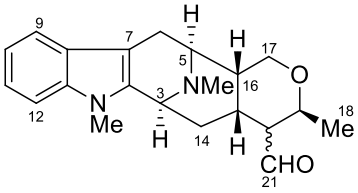
A total of 94 alkaloids (**1**–**94**, Figure 2.1) were isolated and characterized from the leaves and stem-bark extracts of the Malayan *Alstonia penangiana* (Bukit Bendera, Penang) and the results are summarized in Table 2.1. Of these, 32 are new alkaloids. The leaf extract of *A. penangiana* yielded a total of 15 new alkaloids, including a pair of type-A and type-B macroline isomers (compounds **1** and **2**, respectively), four macroline-type oxindoles (alstonisinines A–C, **20**–**22**; alstonoxine F, **23**), three talpinine-type oxindoles (**41**–**43**), two ajmaline alkaloids (vincamaginines A–B, **57**–**58**), as well as four macroline-akuammiline bisindoles (angustilongines A–D, **76**–**79**). The stem-bark extract of *A. penangiana* gave a total of 19 new alkaloids. These include seven sarpagine alkaloids (**32**–**38**), an akuammiline alkaloid **39**, a C_{14} methylene-bridged indolizidine derivative (**40**), seven macroline-sarpagine bisindoles (angustilongines E–H, **80**–**83**; angustilongines J–K, **84**–**85**; angustilongine M, **86**), and a macroline-pleiocarpamine bisindole **88**.



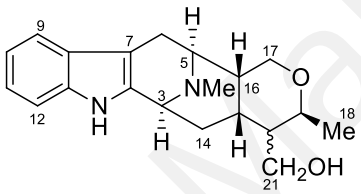
1 $R^1 = CH_2OH$, $R^2 = Me$, $R^3 = COMe$, $R^4 = H$
2 $R^1 = CH_2OH$, $R^2 = Me$, $R^3 = CHO$, $R^4 = Me$
3 $R^1 = Me$, $R^2 = Me$, $R^3 = COMe$, $R^4 = H$
4 $R^1 = Me$, $R^2 = Me$, $R^3 = CHO$, $R^4 = Me$
5 $R^1 = H$, $R^2 = Me$, $R^3 = COMe$, $R^4 = H$
6 $R^1 = H$, $R^2 = Me$, $R^3 = CHO$, $R^4 = Me$
7 $R^1 = Me$, $R^2 = H$, $R^3 = COMe$, $R^4 = H$
8 $R^1 = Me$, $R^2 = H$, $R^3 = CHO$, $R^4 = Me$



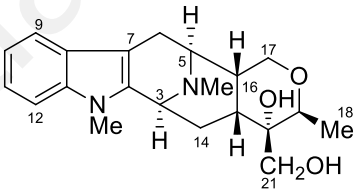
9 $R^1 = Me$, $R^2 = COMe$, $R^3 = H$
10 $R^1 = Me$, $R^2 = CHO$, $R^3 = Me$
11 $R^1 = H$, $R^2 = COMe$, $R^3 = H$
12 $R^1 = H$, $R^2 = CHO$, $R^3 = Me$



13 β-CHO
14 α-CHO



15 α-CH_2OH
16 β-CH_2OH



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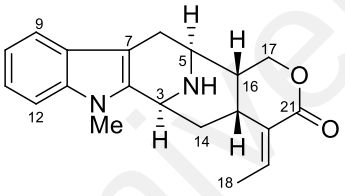

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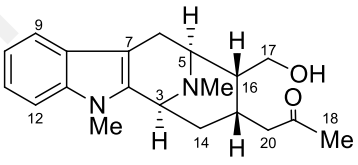

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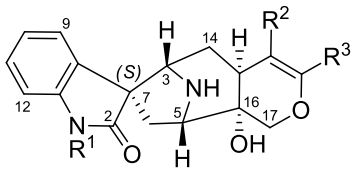
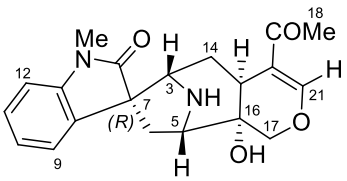


20 $R^1 = H$, $R^2 = CHO$, $R^3 = Me$
21 $R^1 = H$, $R^2 = COMe$, $R^3 = H$
28 $R^1 = Me$, $R^2 = COMe$, $R^3 = H$
29 $R^1 = Me$, $R^2 = CHO$, $R^3 = Me$



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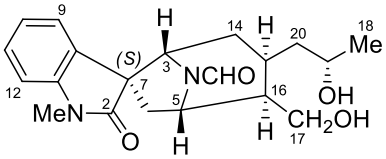

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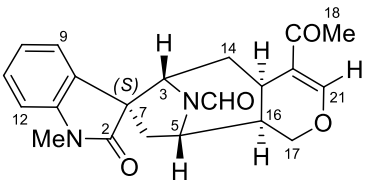
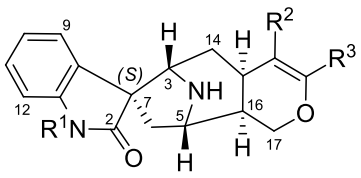
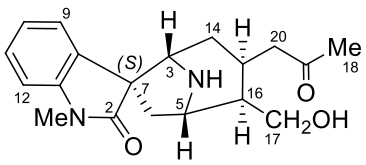


30

Figure 2.1: Alkaloids from *Alstonia penangiana*



24 R^1 = Me, R^2 = COMe, R^3 = H
25 R^1 = Me, R^2 = CHO, R^3 = Me
26 R^1 = H, R^2 = COMe, R^3 = H
27 R^1 = H, R^2 = CHO, R^3 = Me



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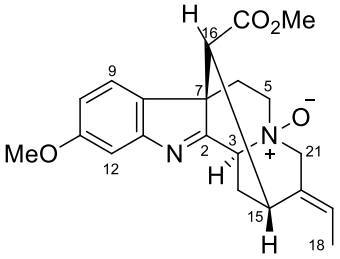

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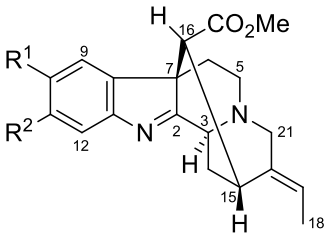
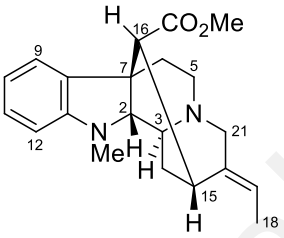
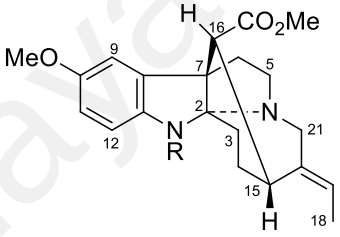


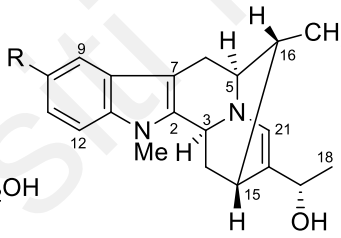
49 R^1 = H, R^2 = OMe
50 R^1 = H, R^2 = OH
51 R^1 = OMe, R^2 = H



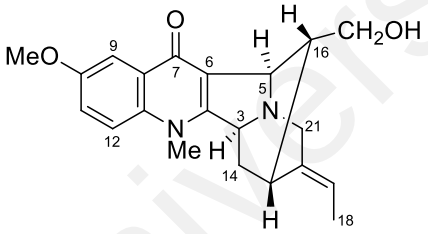
52
53 N(4)→O



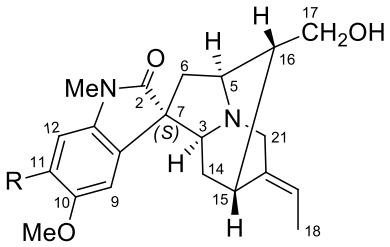
54 R = Me
55 R = H
56 R = CHO



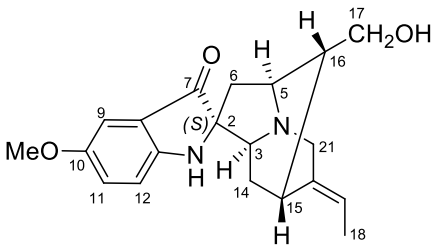
32 R = OMe
48 R = H



37
38 N(4)→O



34 R = H
35 R = OMe
36 R = OMe, N(4)→O



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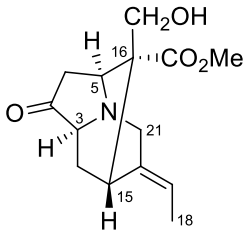

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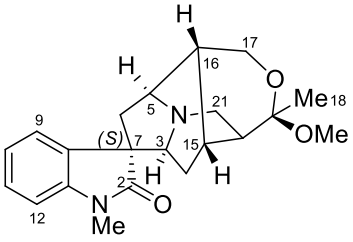
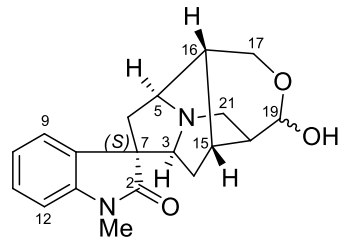
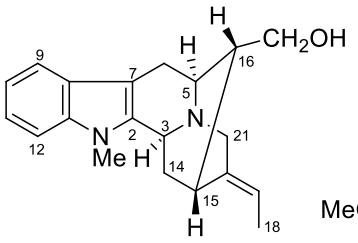


41

Figure 2.1, continued



42 19-β-OH
43 19-α-OH



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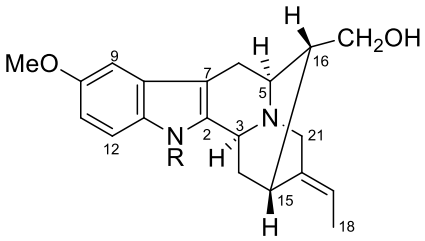
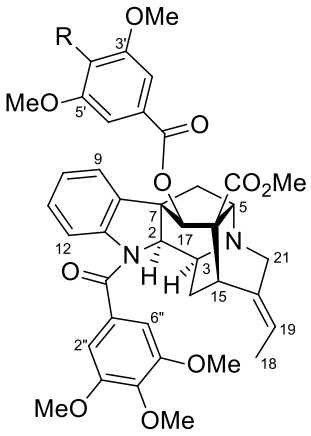
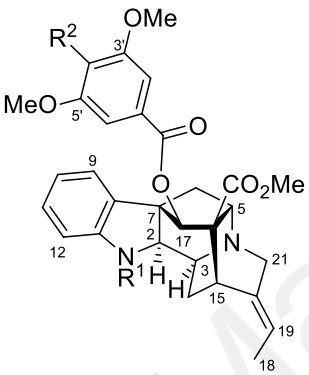


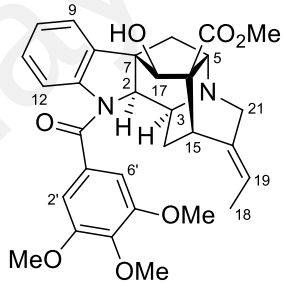
45 R = Me
46 R = Me, N(4)→O
47 R = H



57 R = OMe
58 R = OH



59 R^1 = Me, R^2 = OH
60 R^1 = H, R^2 = OMe



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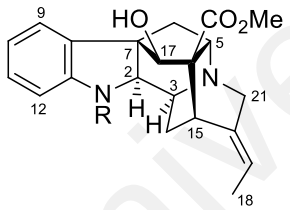
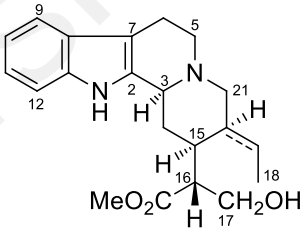
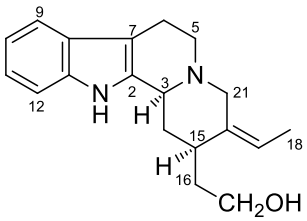


62 R = Me
63 R = H



64
65 $\Delta^{19,20}$



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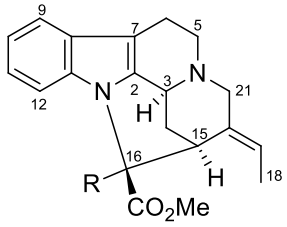
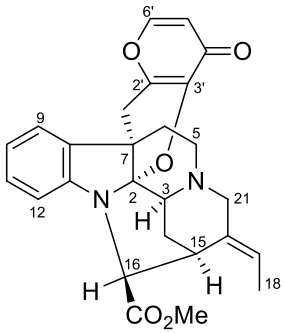


67 R = H
68 R = CH_2OH



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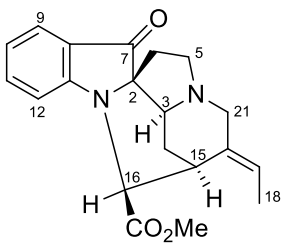

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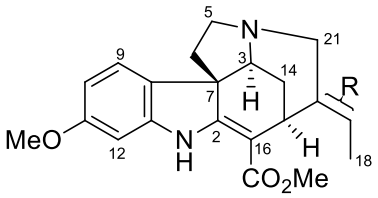
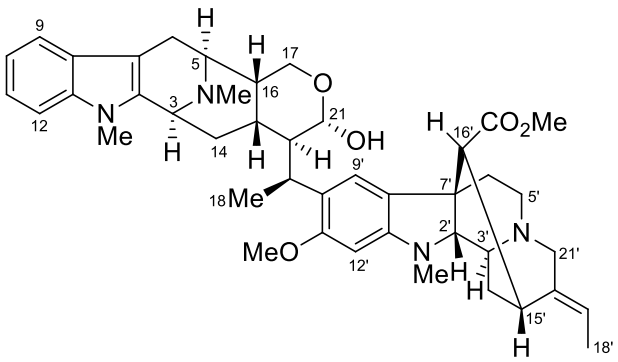
Figure 2.1, continued



71 R = $\Delta^{19,20}$
72 R = $\Delta^{19,20}$, N(4)→O
73 R = 19,20-epoxy (α)
74 R = diol (19-β-OH, 20-α-OH)
75 R = 19-oxo, 20-α-OH



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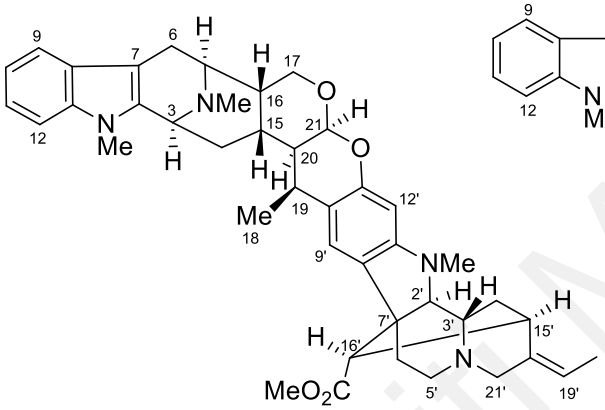

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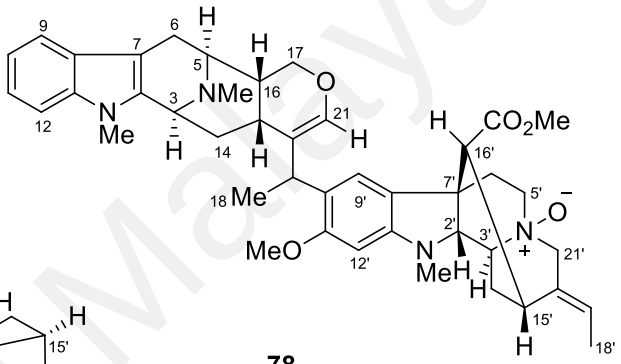

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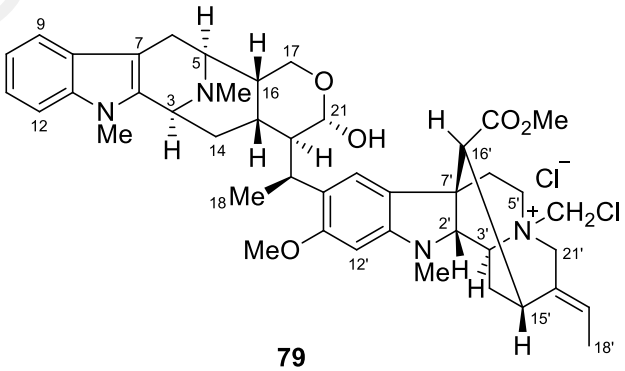

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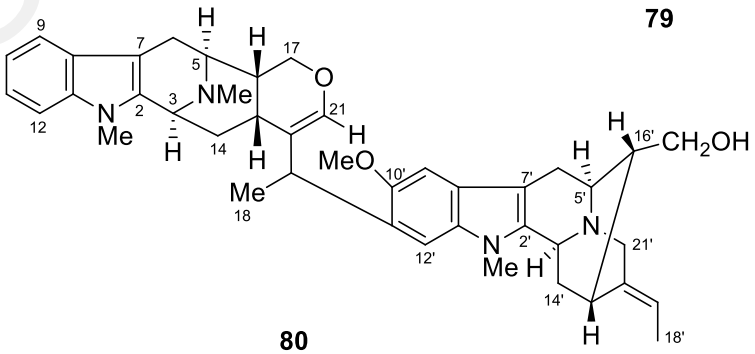

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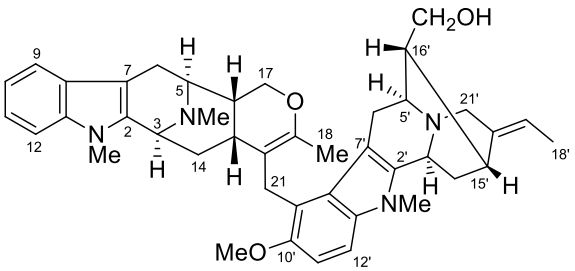
Figure 2.1, continued



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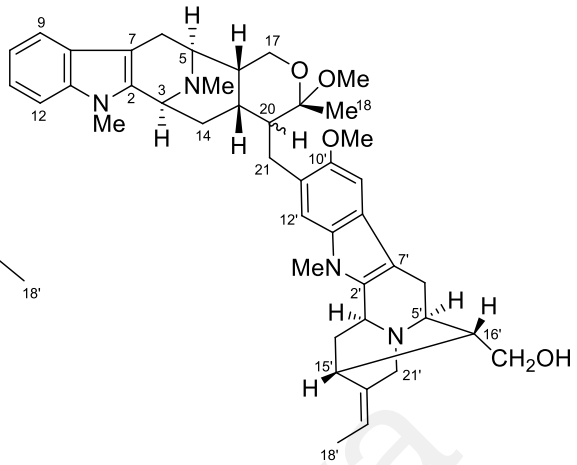
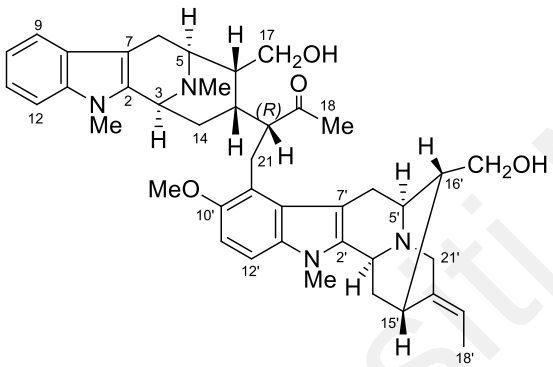


82 20-β-H
83 20-α-H



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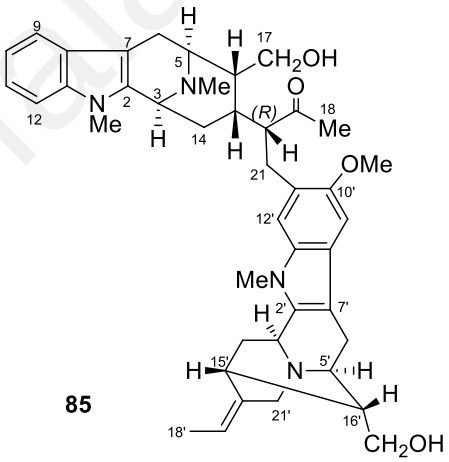

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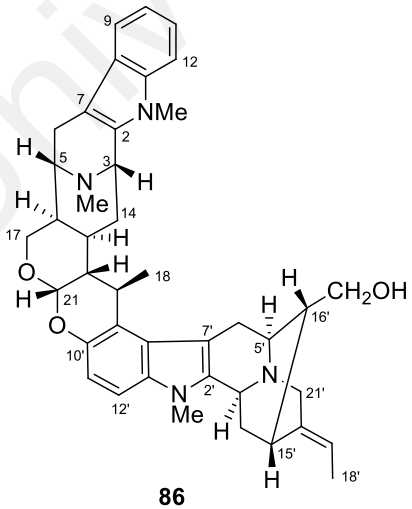

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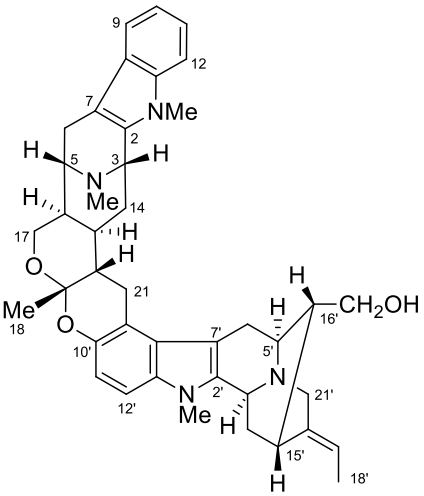

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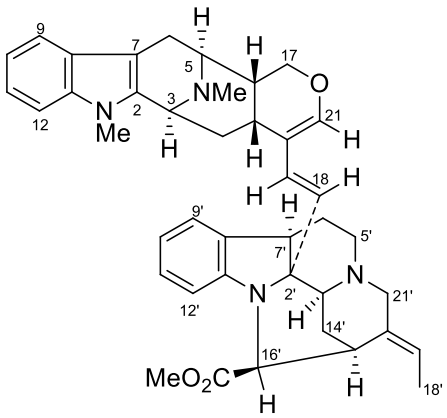
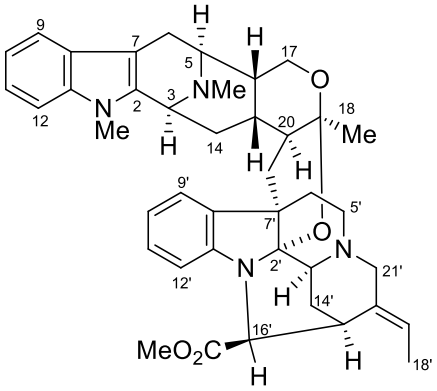
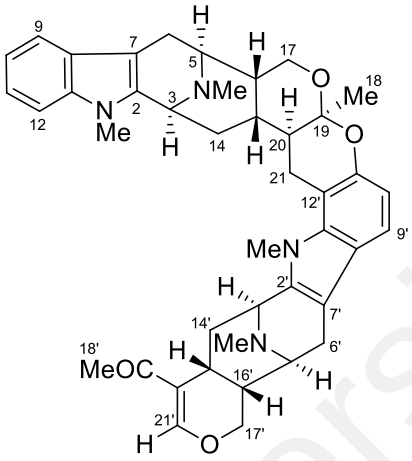
Figure 2.1, continued



88 N(4')→O
89



90
91 N(4')→O



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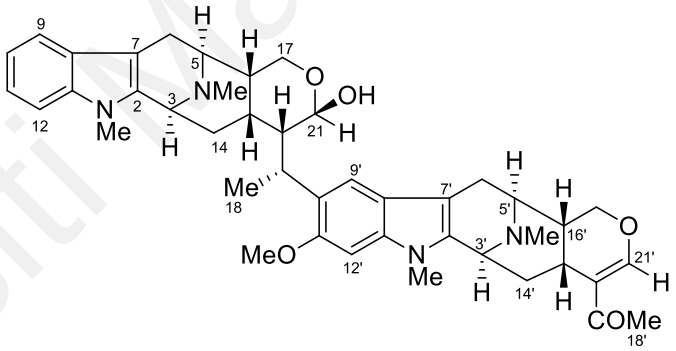

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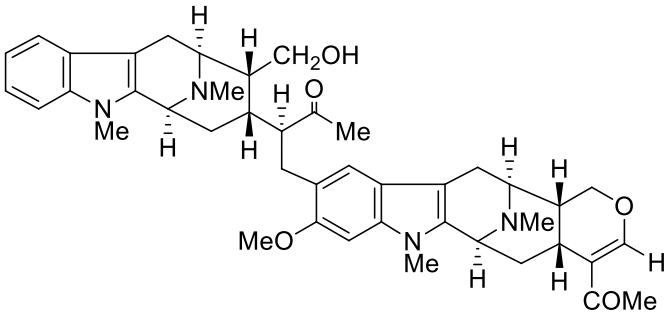


94

Figure 2.1, continued

Table 2.1: Alkaloid Composition of *A. penangiana*

Plant part	Alkaloid	Yield (mg kg^{-1})
Sample A Leaves (3.0 kg)	Alstonerine (**3**), Alstonerinal (**4**)	234
	N(4)-Demethylalstonerine (**7**), *N*(4)-Demethylalstonerinal (**8**)	4.20
	Alstophylline (**9**), Alstophyllal (**10**)	4.27
	Talcarpine (**13**)	9.20
	N(4)-Methyl-*N*(4),21-secotalpinine (**14**)	4.57
	Macrocarpine D (**15**)	6.77
	Alstohentine (**17**)	4.60
	Alstolactone (**18**)	2.23
	Alstonoxine F (**23**) [new]	11.1
	Alstonisine (**24**), Alstonal (**25**)	1021
	N(1)-Demethylalstonisine (**26**), *N*(1)-Demethylalstonal (**27**)	4.77
	Alstofoline (**30**)	1.47
	Alstonoxine A (**31**)	0.73
	Alstomutinines D (**42**) and E (**43**) [new]	1.17
	Affinisine (**44**)	1.57
	10-Methoxyaffinisine (**45**)	13.5
	Alstoumerine (**48**)	9.27
	11-Methoxystrictamine (**49**)	33.1
	11-Hydroxystrictamine (**50**)	5.83
	Cathafoline (**52**)	50.2
	Cathafoline *N*(4)-oxide (**53**)	118
	Vincorine (**54**)	98.7
	Norvincorine (**55**)	7.17
	Demethoxyalstonamide (**56**)	7.67
	Vincamaginine A (**57**) [new]	1.53
	Vincamaginine B (**58**) [new]	1.03
	4'-Hydroxy-3',5'-dimethoxybenzoylvincamajine (**59**)	8.13
	O-3,4,5-Trimethoxybenzoylquebrachidine (**60**)	7.23
	Vincamajine *N*(1)-tri-*O*-methylgallate (**61**)	3.50
	Vincamajine (**62**)	11.2
	Quebrachidine (**63**)	23
	Pleiocarpamine (**67**)	1.40
	Fluorocarpamine (**70**)	0.47
	11-Methoxyakuammicine (**71**)	7.97
	Alstolagumine (**73**)	4.37
	Alstovine (**74**)	4.03
	Lagumidine (**75**)	10.6
	Angustilongine A (**76**) [new]	22.8
	Angustilongine B (**77**) [new]	0.80
	Angustilongine C (**78**) [new]	0.47

Table 2.1, continued

Plant part	Alkaloid	Yield (mg kg^{-1})
	Angustilongine D (**79**) [new]	1.8
	Perhentinine (**94**)	1.33
Sample B	Alstomutinine A (**1**) [new]	1.79
Leaves	Alstomutinine B (**2**) [new]	1.54
(2.4 kg)	Alstonerine (**3**), Alstonerinal (**4**)	4167
	N(1)-Demethylalstonerine (**5**), *N*(1)-Demethylalstonerinal (**6**)	38.2
	N(4)-Demethylalstonerine (**7**), *N*(4)-Demethylalstonerinal (**8**)	46.7
	Talcarpine (**13**)	11.9
	N(4)-Methyl-*N*(4),21-secotalpinine (**14**)	7.79
	Alstohentine (**17**)	3.42
	Alstomicine (**19**)	62.6
	Alstonisinine A (**20**) [new]	1.29
	Alstonisinine B (**21**) [new]	6.13
	Alstonisinine C (**22**) [new]	2.88
	Alstonoxine F (**23**) [new]	121
	Alstonisine (**24**), Alstonal (**25**)	103
	N(1)-Demethylalstonisine (**26**), *N*(1)-Demethylalstonal (**27**)	37.7
	16-Hydroxyalstonisine (**28**)	114
	16-Hydroxyalstonisine (**28**), 16-Hydroxyalstonal (**29**)	1194
	Alstomutinine C (**41**) [new]	5.38
	Affinisine (**44**)	1.17
	10-Methoxyvincamidine (10-Methoxystrictamine) (**51**)	0.75
	18,19-Dihydroisositsirikine (**64**)	1.67
	Alstolagumine (**73**)	3.33
Stem-bark	Alstonerine (**3**), Alstonerinal (**4**)	1037
(2.7 kg)	*N*(1)-Demethylalstonerine (**5**), *N*(1)-Demethylalstonerinal (**6**)	1.37
	Alstophylline (**9**), Alstophyllal (**10**)	1088
	N(1)-Demethylalstophylline (**11**), *N*(1)-Demethylalstophyllal (**12**)	1.04
	Talcarpine (**13**)	39
	N(4)-Methyl-*N*(4),21-secotalpinine (**14**)	77.6
	Macrocarpine E (**16**)	3.44
	Alstomicine (**19**)	5.11
	Alstonisine (**24**), Alstonal (**25**)	4.33

Table 2.1, continued

Plant part	Alkaloid	Yield (mg kg^{-1})
	16-Hydroxyalstonisine (**28**), 16-Hydroxyalstonal (**29**)	40.4
	Alstopenidine A (**32**) [new]	24.3
	Alstopenidine B (**33**) [new]	10.5
	Alstopenidine C (**34**) [new]	27.1
	Alstopenidine D (**35**) [new]	2.07
	Alstopenidine E (**36**) [new]	5.85
	Alstopenidine F (**37**) [new]	4.30
	Alstopenidine G (**38**) [new]	1.44
	Alstopenidine H (**39**) [new]	2.56
	Alstochalotine (**40**) [new]	1.44
	Affinisine (**44**)	10.1
	10-Methoxyaffinisine (**45**)	19599
	10-Methoxyaffinisine *N*(4)-oxide (**46**)	6.15
	Lochnerine (**47**)	394
	Alstoumerine (**48**)	13.6
	Cathafoline (**52**)	84.2
	Cathafoline *N*(4)-oxide (**53**)	13.6
	Vincamajine (**62**)	172
	Quebrachidine (**63**)	31
	16(*R*),19(*E*)-Isositsirikine (**65**)	2.41
	Z-Geissoschizol (**66**)	1.89
	Pleiocarpamine (**67**)	245
	16-Hydroxymethylpleiocarpamine (**68**)	4.15
	Pleiomaltinine (**69**)	1.85
	11-Methoxyakuammicine *N*(4)-oxide (**72**)	0.48
	Alstovine (**74**)	22.2
	Angustilongine E (**80**) [new]	4.74
	Angustilongine F (**81**) [new]	8.67
	Angustilongine G (**82**) [new]	2.41
	Angustilongine H (**83**) [new]	0.63
	Angustilongine J (**84**) [new]	1.89
	Angustilongine K (**85**) [new]	87.8
	Angustilongine M (**86**) [new]	15.0
	Macralstonidine (**87**)	20.7
	Angustilongine L (**88**) [new]	0.93
	Macrocarpamine (**89**)	43
	Villalstonine (**90**)	72.7
	Villalstonine *N*(4')-oxide (**91**)	2.41
	Lumutinine B (**92**)	0.59
	Lumusidine B (**93**)	1.04

2.1.1 Macroline Alkaloids

2.1.1.1 Alstomutinines A (1) and B (2)

Alstomutinines A (**1**) and B (**2**) were initially isolated as a mixture which co-eluted in column chromatography (SiO_2) and which proved resistant to further resolution by column chromatography (SiO_2, RP-18, Sephadex LH-20), preparative radial chromatography, reverse-phase HPLC, and fractional crystallization. The mixture was eventually resolved by chiral-phase HPLC to give pure **1** and **2**.

Compound **1** (alstomutinine A) was obtained as a light yellowish oil with $[\alpha]^{25}_{D}$ –179 (*c* 0.10, $CHCl_3$). The IR spectrum showed absorption bands at 3389 and 1615 cm^{-1} which were assigned to hydroxy and conjugated ketocarbonyl functionalities, respectively, while the UV spectrum (229, 262 nm) was characteristic of an indole chromophore. The HRMS data ($[M + H]^+$ *m/z* 353.1860) was in agreement with the molecular formula $C_{21}H_{24}N_2O_3$. The ^1H NMR data of **1** (Table 2.2) showed the presence of four aromatic H of an unsubstituted indole moiety (δ 7.15–7.50), an N-4-Me (δ 2.37, s), an olefinic hydrogen associated with an enol ether (δ 7.55, s), a methyl ketone (δ 2.09, s), an oxymethylene corresponding to OCH_2-17 (δ 4.18, 4.39), and a deshielded methylene resonance at δ_H 5.48, 5.62 (δ_C 66.6). The latter deshielded methylene (CH_2-22) suggested bonding to both an oxygen and a nitrogen atom. The ^{13}C NMR data (Table 2.2) showed the presence of all 21 carbon atoms, comprising two methyl, four methylene, nine methine, two tertiary carbons attached to N-1, one ketocarbonyl, and three quaternary carbon atoms. The COSY data (Figure 2.2) showed the presence of $CHCH_2$ and $CHCH_2CHCHCH_2$ partial structures, suggestive of macroline indoles and corresponding respectively to the C-5–C-6 and C-3–C-14–C-15–C-16–C-17 units present in macroline type alkaloids. The three-bond methylene H-22 to C-2 and C-13

correlations (Figure 2.2) in the HMBC spectrum confirmed attachment of a hydroxymethyl unit to the indolic N-1.

Alstomutinine B (**2**) is an isomer of **1** as shown by HRMS data (*m/z* 353.1861 [M + H]$^+$). The ^{1}H NMR data (Table 2.2) showed a general similarity to that of **1** except for the presence of a methyl singlet at δ 2.16 (Me-18) and an aldehyde-H resonance at δ 9.58 (H-21), in place of the acetyl methyl resonance at δ 2.09 (Me-18) and the olefinic singlet at δ 7.55 (H-21), respectively. The same was true of the ^{13}C NMR data (Table 2.2) which also showed a general similarity to that of **1** except for the methyl resonance at δ 16.6 (Me-18), the olefinic resonance at δ 171.7 (C-19), and the conjugated aldehyde carbonyl resonance at δ 189.0 (C-21), in place of the acetyl methyl resonance at δ 24.8 (Me-18), the conjugated ketocarbonyl resonance at δ 196.2 (C-19), and the olefinic resonance at δ 158.0 (C-21). These compounds therefore correspond to the type A (**2**) and type B (**1**) macroline alkaloids.[126] These alkaloids have been previously encountered in the genus *Alstonia* and were in a number of instances obtained as mixtures which were resistant to further resolution by chromatography or fractional crystallization.[129,130,176] In the present instance, the *N*-1-hydroxymethyl-substituted macrolines **1** and **2** were eventually separated by chiral-phase HPLC (Figure 2.3). This is also the first isolation of indole alkaloids substituted at the indolic nitrogen by a hydroxymethyl group. Compounds **1** and **2** can be considered as the *N*-1-hydroxymethyl derivatives of alstonerine (**3**) and alstonerinal (**4**), respectively. The structure and relative configuration are in complete agreement with the HMBC (Figure 2.2) and NOESY (Figure 2.4) data, respectively. The ^{1}H NMR spectra of **1** and **2** are shown in Figures 2.5 and 2.6, respectively.

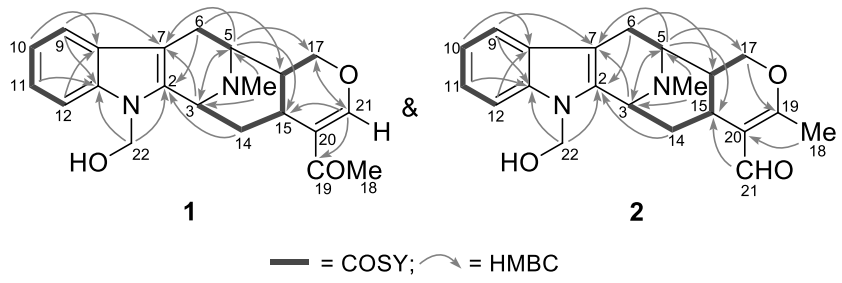


Figure 2.2: COSY and selected HMBCs of **1** and **2**

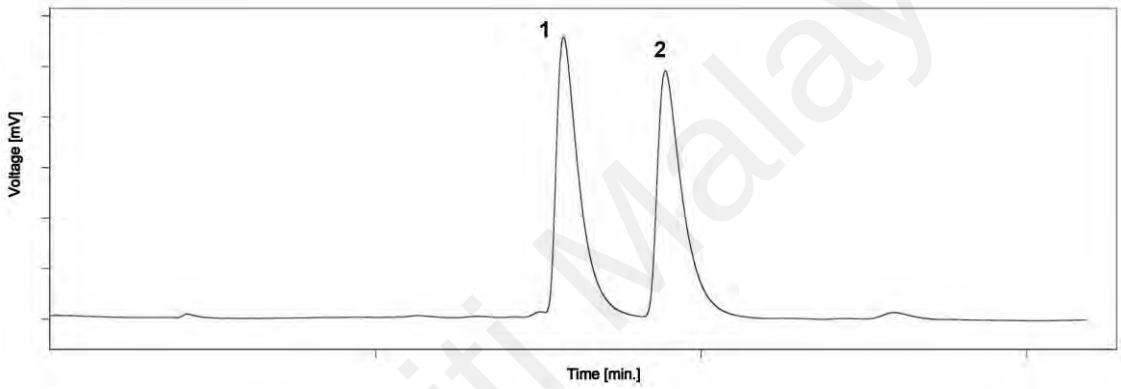


Figure 2.3: HPLC chromatogram of **1** and **2**

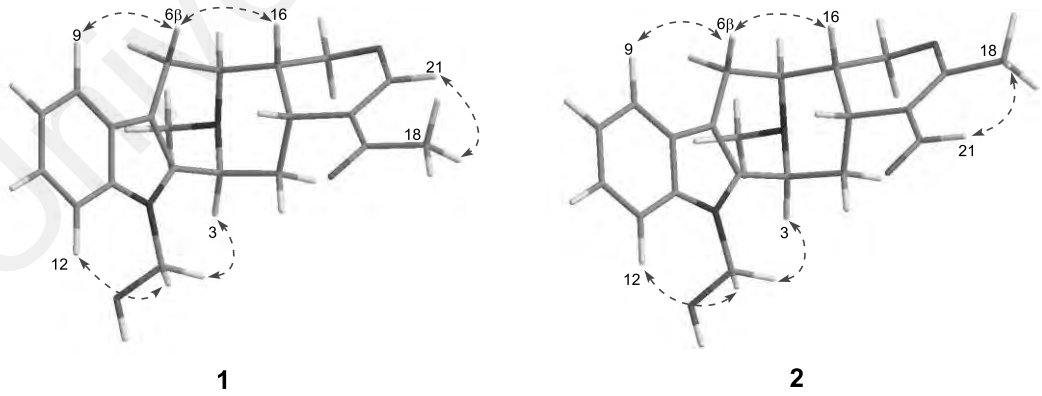


Figure 2.4: Selected NOEs of **1** and **2**

Table 2.2: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Alstomutinine A (**1**) and Alstomutinine B (**2**)[a]

H/C	1		2	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	132.7	-	132.6	-
3	54.0	3.95 br t (4.0)	53.8	3.93 br t (4.0)
5	54.7	3.11 d (7.0)	54.7	3.09 d (7.0)
6β	22.9	2.49 d (17.0)	22.8	2.48 d (17.0)
6α		3.34 dd (17.0, 7.0)		3.33 dd (17.0, 7.0)
7	108.5	-	108.4	-
8	127.7	-	127.7	-
9	118.1	7.48 d (8.0)	118.0	7.48 d (8.0)
10	120.1	7.14 td (8.0, 1.0)	120.0	7.14 td (8.0, 1.0)
11	121.8	7.23 td (8.0, 1.0)	121.8	7.23 td (8.0, 1.0)
12	109.9	7.50 d (8.0)	109.9	7.50 d (8.0)
13	136.6	-	136.5	-
14α	32.8	1.84 td (13.0, 4.0)	32.2	1.82 td (13.0, 4.0)
14β		2.20 dt (13.0, 4.0)		2.19 dt (13.0, 4.0)
15	23.7	2.54 m	23.2	2.52 m
16	38.3	1.90 dt (12.0, 4.0)	38.2	1.89 dt (12.0, 4.0)
17β	67.7	4.18 ddd (12.0, 4.0, 2.0)	68.0	4.21 ddd (12.0, 4.0, 2.0)
17α		4.39 t (12.0)		4.44 t (12.0)
18	24.8	2.09 s	16.5	2.16 s
19	196.2	-	171.5	-
20	120.8	-	117.1	-
21	158.0	7.55 s	188.9	9.59 s
N(4)-Me	41.7	2.37 s	41.5	2.37 s
$\underline{CH_2}OH$	66.6	5.48 d (12.0)	66.5	5.50 d (12.0)
		5.62 d (12.0)		5.61 d (12.0)

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY.

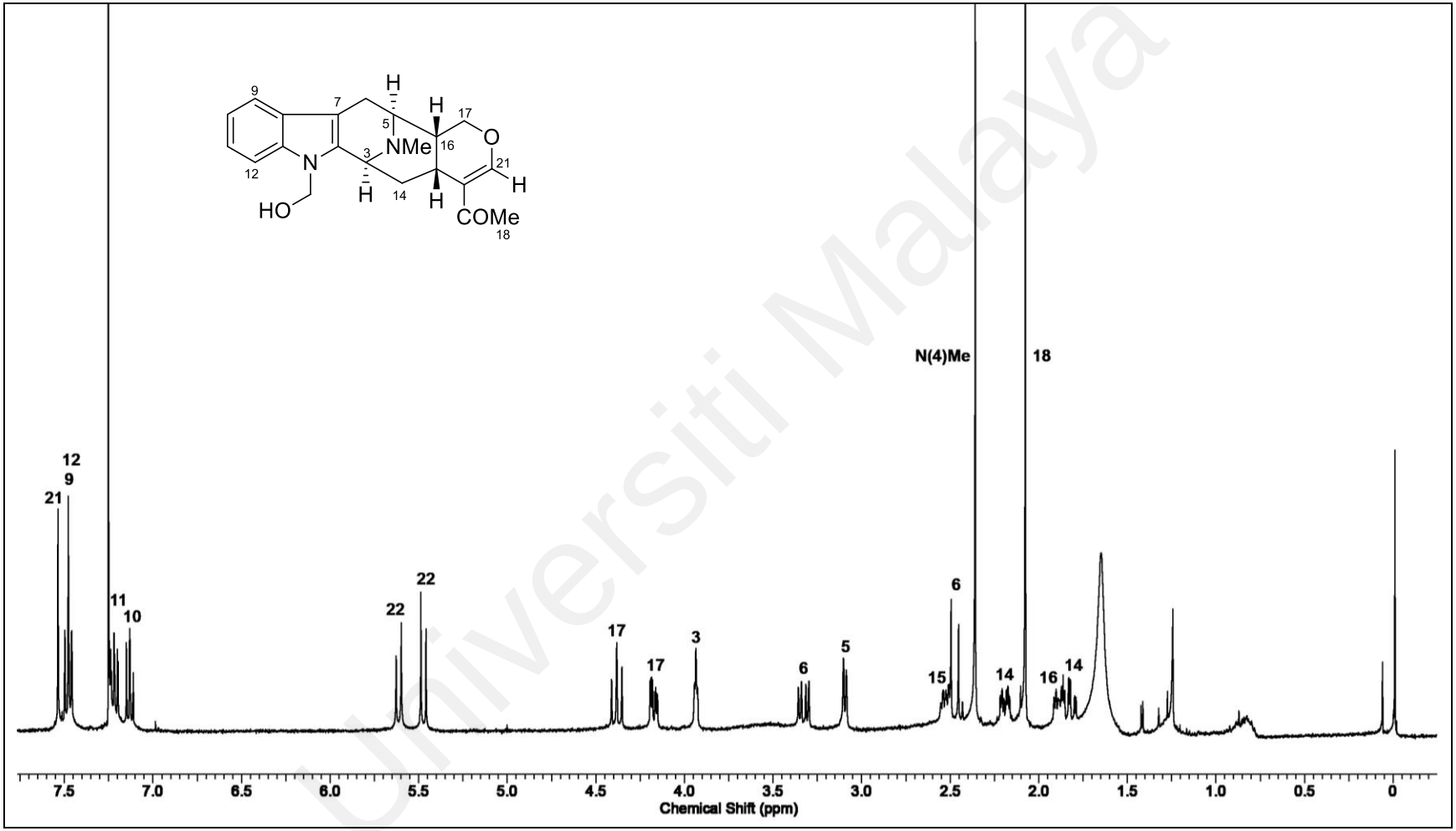


Figure 2.5: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstomutinine A (**1**)

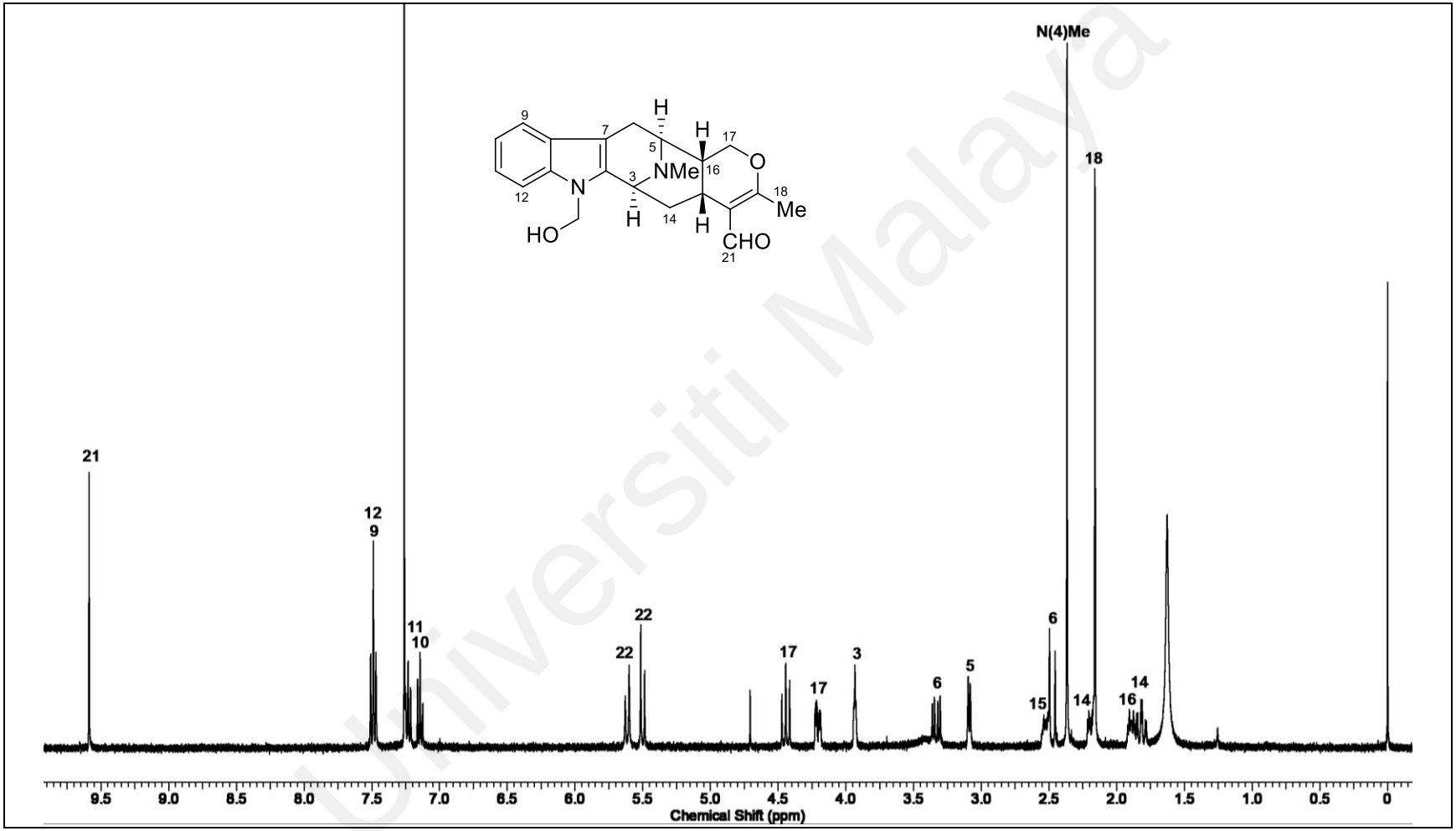


Figure 2.6: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstomutinine B (**2**)

2.1.1.2 Alstonerine (3), Alstonerinal (4), *N*(1)-Demethylalstonerine (5), *N*(1)-Demethylalstonerinal (6), *N*(4)-Demethylalstonerine (7), *N*(4)-Demethylalstonerinal (8), Alstophylline (9), Alstophyllal (10), *N*(1)-Demethylalstophylline (11), *N*(1)-Demethylalstophyllal (12), Talcarpine (13), *N*(4)-Methyl-*N*(4),21-secotalpinine (14), Macrocarpine D (15), Macrocarpine E (16), Alstohentine (17), Alstolactone (18), and Alstomicine (19)

Thirteen known macroline alkaloids including alstonerine (**3**),[126,136,162,185] alstonerinal (**4**),[136] *N*(1)-demethylalstonerine (**5**),[129] *N*(1)-demethylalstonerinal (**6**),[129] *N*(4)-demethylalstonerine (**7**),[53] *N*(4)-demethylalstonerinal (**8**),[53] alstophylline (**9**),[126,168,170] alstophyllal (**10**),[175] *N*(1)-demethylalstophylline (**11**),[176] *N*(1)-demethylalstophyllal (**12**),[6] talcarpine (**13**),[159,380,381] *N*(4)-methyl-*N*(4),21-secotalpinine (**14**),[176,380] macrocarpine D (**15**),[180] macrocarpine E (**16**),[129] alstohentine (**17**),[175] alstolactone (**18**),[53] and alstomicine (**19**)[175] were also isolated in the present study. The ^{1}H and ^{13}C NMR data of these compounds are summarized in Tables 2.3–2.11, and their ^{1}H NMR spectra are shown in Figures A1–A12 (see Appendix). Other data are given in the Experimental Section.

Table 2.3: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Alstonerine (**3**) and Alstonerinal (**4**)[a]

H/C	3		4	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	137.1	-	137.1	-
3	54.6	3.87 t (3.0)	54.6	3.86 t (3.0)
5	53.7	3.07 br d (7.0)	53.6	3.07 br d (7.0)
6	22.8	2.49 d (16.0)	22.3	2.48 d (16.0)
6		3.32 dd (16.0, 7.0)		3.31 dd (16.0, 7.0)
7	105.8	-	105.8	-
8	126.5	-	126.5	-
9	117.7	7.49 br d (8.0)	117.3	7.44 br d (8.0)
10	120.7	7.08 td (8.0, 1.0)	121.0	7.08 td (8.0, 1.0)
11	118.6	7.19 td (8.0, 1.0)	118.6	7.19 td (8.0, 1.0)
12	108.6	7.31 br d (8.0)	108.6	7.31 br d (8.0)
13	137.1	-	137.1	-
14	38.5	1.81 td (12.0, 3.0)	38.5	1.79 td (12.0, 3.0)
14		2.12 ddd (12.0, 5.0, 3.0)		2.12 ddd (12.0, 5.0, 3.0)
15	32.3	2.61 dt (12.0, 5.0)	31.8	2.61 dt (12.0, 5.0)
16	41.7	1.89 m	41.7	1.89 m
17	67.7	4.16 ddd (11.0, 4.0, 2.0)	68.0	4.18 ddd (11.0, 4.0, 2.0)
17		4.40 t (11.0)		4.46 t (11.0)
18	22.7	2.07 s	16.5	2.15 s
19	195.7	-	170.6	-
20	126.5	-	126.5	-
21	157.4	7.52 s	188.6	9.65 s
N(1)-Me	29.0	3.64 s	29.0	3.63 s
N(4)-Me	24.9	2.31 s	24.9	2.31 s

[a] $CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C).

Table 2.4: ^{1}H NMR Spectroscopic Data (δ) of *N*(1)-Demethylalstonerine (**5**), *N*(1)-Demethylalstonerinal (**6**), *N*(4)-Demethylalstonerine (**7**), and *N*(4)-Demethylalstonerinal (**8**)[a]

H	5 (*J*/Hz)	6 (*J*/Hz)	7 (*J*/Hz)	8 (*J*/Hz)
3	4.14 m	4.14 m	4.23 br s	4.22 br s
5	3.32 m	3.32 m	3.48 br d (7.0)	3.47 br d (7.0)
6	2.70 br d (16.0)	2.70 br d (16.0)	2.70 d (16.0)	2.70 d (16.0)
6	3.37 dd (16.0, 6.0)	3.37 dd (16.0, 6.0)	3.26 dd (16.0, 7.0)	3.26 dd (16.0, 7.0)
9	7.67 d (7.0)	7.67 d (7.0)	7.44 br d (8.0)	7.44 br d (8.0)
10	7.09 t (7.0)	7.09 t (7.0)	7.09 td (8.0, 1.0)	7.09 td (8.0, 1.0)
11	7.15 t (7.0)	7.15 t (7.0)	7.20 td (8.0, 1.0)	7.20 td (8.0, 1.0)
12	7.87 d (7.0)	7.87 d (7.0)	7.33 br d (8.0)	7.33 br d (8.0)
14	2.04 m	2.04 m	1.80 m	1.80 m
14	2.22 dt (13.0, 3.0)	2.22 dt (13.0, 3.0)	2.10 ddd (12.0, 5.0, 3.0)	2.10 ddd (12.0, 5.0, 3.0)
15	2.65 dd (12.0, 5.0)	2.65 dd (12.0, 5.0)	2.73 m	2.73 m
16	2.04 m	2.04 m	1.91 m	1.91 m
17	4.22 dd (11.0, 4.0)	4.22 dd (11.0, 4.0)	4.21 ddd (11.0, 4.0, 2.0)	4.24 ddd (11.0, 4.0, 2.0)
17	4.70 m	4.70 m	4.46 t (11.0)	4.51 t (11.0)
18	2.09 s	2.19 s	2.09 s	2.17 s
21	7.56 s	9.63 s	7.54 s	9.66 s
N(1)-H	9.01 br s	9.01 br s	-	-
N(1)-Me	-	-	3.64 s	3.63 s
N(4)-Me	2.48 br s	2.48 br s	-	-

[a]$CDCl_3$, 400 MHz.

Table 2.5: ^{13}C NMR Spectroscopic Data (δ) of *N*(1)-Demethylalstonerine (**5**), *N*(1)-Demethylalstonerinal (**6**), *N*(4)-Demethylalstonerine (**7**), and *N*(4)-Demethylalstonerinal (**8**)[a]

C	5	6	7	8
2	129.8	129.8	136.5	136.5
3	55.8	55.8	46.5	46.4
5	55.2	55.2	48.4	48.3
6	23.2	23.2	28.8	28.8
7	105.6	105.6	107.0	107.0
8	126.4	126.8	126.7	126.7
9	117.8	117.8	117.7	117.7
10	119.4	119.4	118.9	118.9
11	121.8	121.8	121.1	121.1
12	111.5	111.5	109.0	109.0
13	136.2	136.2	136.9	136.9
14	31.9	31.9	31.0	31.0
15	22.7	22.7	23.6	23.1
16	38.6	38.6	37.4	37.4
17	67.0	67.0	67.4	67.8
18	25.0	16.6	25.0	16.6
19	195.8	171.8	195.4	170.8
20	119.9	116.3	121.3	117.5
21	158.0	188.8	150.9	188.6
N(1)-Me	-	-	29.0	29.0
N(4)-Me	41.1	41.1	-	-

[a]$CDCl_3$, 100 MHz.

Table 2.6: ^{1}H NMR Spectroscopic Data (δ) of Alstophylline (**9**), Alstophyllal (**10**), *N*(1)-Demethylalstophylline (**11**), and *N*(1)-Demethylalstophyllal (**12**)[a]

H	9 (*J*/Hz)	10 (*J*/Hz)	11 (*J*/Hz)	12 (*J*/Hz)
3	3.86 m	3.84 m	3.82 br s	3.82 br s
5	3.09 d (7.0)	3.06 d (7.0)	3.10 d (6.0)	3.10 d (6.0)
6	2.48 d (16.0)	2.45 d (16.0)	2.48 d (16.0)	2.48 d (16.0)
6	3.30 dd (16.0, 7.0)	3.29 dd (16.0, 7.0)	3.30 dd (16.0, 6.0)	3.30 dd (16.0, 6.0)
9	7.34 d (8.0)	7.34 d (8.0)	7.33 d (8.0)	7.33 d (8.0)
10	6.76 dd (8.0, 1.0)	6.76 dd (8.0, 2.0)	6.76 dd (8.0, 2.0)	6.76 dd (8.0, 2.0)
12	6.81 d (1.0)	6.81 d (2.0)	6.84 d (2.0)	6.84 d (2.0)
14	1.80 td (12.0, 3.0)	1.77 td (12.0, 4.0)	1.81 m	1.81 m
14	2.11 m	2.14 m	2.13 m	2.13 m
15	2.62 m	2.61 m	2.64 dt (11.0, 5.0)	2.64 dt (11.0, 5.0)
16	1.90 m	1.89 m	1.92 m	1.92 m
17	4.18 ddd (11.0, 4.0, 2.0)	4.19 ddd (11.0, 4.0, 2.0)	4.17 ddd (11.0, 4.0, 2.0)	4.19 ddd (11.0, 4.0, 2.0)
17	4.42 t (11.0)	4.46 t (11.0)	4.45 t (11.0)	4.50 t (11.0)
18	2.09 s	2.17 s	2.09 s	2.17 s
21	7.53 s	9.66 s	7.54 s	9.66 s
N(1)-Me	3.60 s	3.60 s	-	-
N(4)-Me	2.34 s	2.32 s	2.36 s	2.36 s
11-OMe	3.89 s	3.89 s	3.84 s	3.84 s

[a]$CDCl_3$, 400 MHz.

Table 2.7: ^{13}C NMR Spectroscopic Data (δ) of Alstophylline (**9**), Alstophyllal (**10**), *N*(1)-Demethylalstophylline (**11**), and *N*(1)-Demethylalstophyllal (**12**)[a]

C	9	10	11	12
2	131.8	132.6	129.2	129.2
3	53.6	53.9	54.8	54.8
5	54.6	54.8	55.1	55.1
6	22.3	25.0	22.9	22.5
7	105.8	105.7	106.4	106.4
8	121.0	121.0	121.6	121.6
9	118.2	118.3	118.2	118.2
10	108.1	108.3	108.8	108.8
11	155.9	155.8	156.2	156.2
12	93.2	93.4	95.4	95.4
13	137.9	137.9	136.8	136.8
14	31.8	32.3	32.9	32.9
15	24.9	25.0	23.0	23.0
16	38.4	38.5	38.6	38.6
17	67.7	67.7	67.7	68.1
18	16.5	22.9	25.0	16.5
19	170.0	195.5	195.6	170.0
20	121.0	121.0	121.6	121.6
21	188.8	157.0	157.5	188.8
N(1)-Me	29.0	29.1	-	-
N(4)-Me	41.6	41.7	41.5	41.5
11-OMe	55.8	56.1	55.8	55.8

[a]$CDCl_3$, 100 MHz.

Table 2.8: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Talcarpine (**13**) and *N*(4)-Methyl-*N*(4),21-secotalpinine (**14**)[a]

H/C	13		14	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	132.8	-	132.8	-
3	53.5	3.98 m	53.1	3.93 m
5	54.5	2.90 d (7.0)	54.9	2.96 d (7.0)
6	22.5	2.45 d (16.0)	22.4	2.49 d (16.0)
6		3.27 dd (16.0, 7.0)		3.30 dd (16.0, 7.0)
7	106.6	-	106.6	-
8	126.2	-	126.2	-
9	118.1	7.49 br d (8.0)	117.9	7.52 br d (8.0)
10	118.9	7.10 td (8.0, 1.0)	118.9	7.13 td (8.0, 1.0)
11	121.0	7.19 td (8.0, 1.0)	121.0	7.21 td (8.0, 1.0)
12	108.7	7.29 br d (8.0)	108.9	7.31 br d (8.0)
13	137.2	-	137.0	-
14	30.1	1.45 ddd (12.0, 4.0, 3.0)	26.7	1.28 m
14		2.50 td (12.0, 4.0)		2.37 m
15	27.0	2.20 m	26.1	2.37 m
16	39.4	2.06 dt (11.0, 5.0)	42.5	1.93 m
17	68.8	3.89 dd (12.0, 5.0)	67.1	3.75 dd (12.0, 5.0)
17		4.14 t (12.0)		4.06 t (12.0)
18	19.2	1.30 d (7.0)	20.2	1.20 d (7.0)
19	69.4	3.98 m	67.8	3.93 m
20	54.6	1.79 br s	57.7	2.37 m
21	204.7	9.95 d (3.0)	203.0	9.41 br s
N(1)-Me	29.1	3.62 s	29.0	3.58 s
N(4)-Me	41.8	2.32 s	41.6	2.31 s

[a] $CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C).

Table 2.9: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Macrocarpine D (**15**) and Macrocarpine E (**16**)[a]

H/C	15		16	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	132.2	-	132.1	-
3	55.0	3.95 m	54.9	3.85 br t (3.0)
5	55.1	2.94 d (7.0)	54.5	2.82 d (7.0)
6	22.5	2.46 d (16.0)	22.5	2.43 d (17.0)
6		3.27 dd (16.0, 7.0)		3.23 dd (17.0, 7.0)
7	107.7	-	107.4	-
8	127.1	-	126.9	-
9	118.0	7.49 d (7.5)	118.0	7.48 dd (7.0, 1.0)
10	119.4	7.11 t (7.5)	119.3	7.10 td (7.0, 1.0)
11	121.3	7.15 t (7.5)	121.2	7.14 td (7.0, 1.0)
12	110.9	7.32 d (7.5)	110.8	7.31 dd (7.0, 1.0)
13	135.5	-	135.7	-
14	26.1	1.62 dt (13.0, 4.0)	31.3	1.44 ddd (13.0, 5.0, 3.0)
14		2.28 td (13.0, 4.0)		2.43 td (13.0, 4.0)
15	27.1	2.01 m	28.6	1.98 dt (13.0, 5.0)
16	43.6	1.89 dt (12.0, 4.0)	39.2	2.08 dd (12.0, 5.0)
17	67.7	3.74 dd (12.0, 5.0)	68.9	3.76 dd (12.0, 5.0)
17		4.08 t (12.0)		4.04 t (12.0)
18	20.3	1.16 d (6.0)	18.7	1.21 d (6.7)
19	70.5	3.50 m	71.1	3.93 (6.7, 2.6)
20	46.9	1.50 m	43.5	1.06 m
21	61.7	3.34 dd (11.0, 8.0)	62.8	3.64 dd (11.0, 4.0)
21	-	3.50 dd (11.0, 5.0)		3.71 dd (11.0, 6.0)
N(1)-Me	-	-	-	-
N(4)-Me	41.6	2.34 s	41.5	2.30 s
N(1)-H	-	7.89 br s	-	8.14 br s

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C).

Table 2.10: ^{1}H NMR Spectroscopic Data (δ) of Alstohentine (**17**), Alstolactone (**18**), and Alstomicine (**19**)[a]

H	17 (*J*/Hz)	18 (*J*/Hz)	19 (*J*/Hz)
3	3.83 d (10.0)	4.46 br s	4.01 br s
5	3.31 m	3.50 d (7.0)	3.49 d (7.0)
6	2.37 d (16.0)	2.73 d (16.0)	2.56 d (17.0)
6	2.95 dd (16.0, 4.0)	3.38 dd (16.0, 7.0)	3.31 dd (17.0, 7.0)
9	7.41 br d (8.0)	7.52 br d (8.0)	7.50 d (8.0)
10	7.04 td (8.0, 1.0)	7.15 td (8.0, 1.0)	7.11 t (8.0)
11	7.14 td (8.0, 1.0)	7.24 td (8.0, 1.0)	7.20 t (8.0)
12	7.24 br d (8.0)	7.33 br d (8.0)	7.31 d (8.0)
14	1.77 dd (14.0, 10.0)	1.68 ddd (14.0, 5.0, 3.0)	1.61 m
14	2.73 dd (14.0, 10.0)	2.21 m	2.27 m
15	1.90 dd (10.0, 6.0)	2.90 m	2.27 m
16	1.61 td (6.0, 3.0)	2.21 m	1.69 br s
17	3.44 dd (12.0, 3.0)	4.32 ddd (12.0, 5.0, 2.0)	3.90 br d (11.0)
17	3.70 br d (12.0)	5.04 t (12.0)	3.98 br d (11.0)
18	1.21 d (6.0)	1.45 d (7.0)	2.04 s
19	3.31 q (6.0)	7.11 qd (7.0, 1.0)	-
20	-	-	2.43 dd (17.0, 7.0)
20	-	-	2.64 dd (17.0, 7.0)
21	3.34 s	-	-
21	3.34 s	-	-
N(1)-Me	3.57 s	3.62 s	3.63 s
N(4)-Me	2.37 s	-	2.37 s
OH	9.01 br s	-	-

[a]$CDCl_3$, 400 MHz.

Table 2.11: ^{13}C NMR Spectroscopic Data (δ) of Alstohentine (**17**), Alstolactone (**18**), and Alstomicine (**19**)[a]

C	17	18	19
2	135.9	136.1	132.5
3	49.4	46.0	53.2
5	54.7	47.9	59.1
6	20.8	28.3	22.2
7	103.3	107.7	105.9
8	127.0	126.7	126.3
9	118.0	118.0	118.1
10	119.2	119.2	119.0
11	121.4	121.4	121.0
12	108.9	109.0	108.9
13	137.3	139.9	137.2
14	28.6	29.8	34.3
15	34.9	27.1	25.1
16	38.5	38.7	43.6
17	70.8	68.6	66.0
18	15.0	13.8	30.5
19	79.1	142.3	207.5
20	68.9	128.9	46.2
21	64.7	165.7	-
N(1)-Me	29.5	29.0	28.9
N(4)-Me	38.7	-	41.4

[a]$CDCl_3$, 100 MHz.

2.1.2 Macroline Oxindoles

2.1.2.1 Alstonisinine A (20)

Alstonisinine A (**20**)[382] was obtained as a white amorphous solid, with $[\alpha]^{25}_{D}$ +183 (*c* 0.2, MeOH). The IR spectrum showed absorption bands at 3210, 1682, and 1605 cm^{-1} due to OH/NH, conjugated formyl carbonyl (δc 190.5), and lactam carbonyl (oxindole, δc 185.0) functionalities, respectively, while the UV spectrum (225 and 261 nm) was characteristic of an oxindole chromophore. HRMS measurements ($[M + H]^+$ *m/z* 341.1511) provided the molecular formula $C_{19}H_{20}N_2O_4$.

The ^{1}H NMR data (Table 2.12) of **20** indicated the presence of an unsubstituted indole moiety (four aromatic H, δ 6.85−8.07), a formyl hydrogen (δ 9.81), a pair of geminal hydrogens due to an oxymethylene OCH_2-17 (δ 3.98, 4.67), and a methyl singlet (δ 2.24) due to Me-18 bound to a trisubstituted double bond. The ^{13}C NMR data (Table 2.12) accounted for all 19 carbon signals including one methyl, three methylene, eight methine, one tertiary carbon bonded to an indolic nitrogen, two oxygenated tertiary carbon atoms, one lactam carbonyl (oxindole), and three quaternary carbons. The COSY and HSQC data (Figure 2.7) revealed the following partial structures: $NCHCH_2$ and $NCHCH_2CH$, corresponding to N-4–C-5–C-6 and N-4–C-3–C-14–C-15, respectively, of a macroline oxindole skeleton. The presence of the oxymethylene OCH_2-17 and the olefinic moiety (C-19=C-20), to which the methyl (C-18) and formyl (C-21) groups are attached, allowed completion of the six-membered ring E which is fused to ring D at C-15 and C-16.

The signal corresponding to H-16 in macroline oxindoles (usually seen at ca. δ 1.98),[383] was however not observed in the ^{1}H NMR spectrum of **20** and furthermore, the resonance due to C-16 was observed at δ_C 67.6, indicative of an oxygenated tertiary carbon.

This suggests that in **20**, C-16 is a tertiary carbon bearing a hydroxy group, as in the case of 16-hydroxyalstonal (**29**). Analysis of 2D NMR data allowed the identification of compound **20** as the *N*(1)-demethyl derivative of 16-hydroxyalstonal (Figure 2.7). The relative configurations at the various stereogenic centers are similar to those in 16-hydroxyalstonal (**29**) from the similarity of their ^{1}H and ^{13}C NMR data (chemical shifts and coupling behavior), as well as the NOESY data. The configuration of the spirocyclic center (C-7) was assigned as *S* from the diagnostic C-2 (δ 185.0) and C-8 (δ 129.5) chemical shifts which was further confirmed by the observed H-9/H-15 NOEs. The α-orientation of the C-16 hydroxy group was indicated by the H-17β/H-14β NOEs (Figure 2.8).

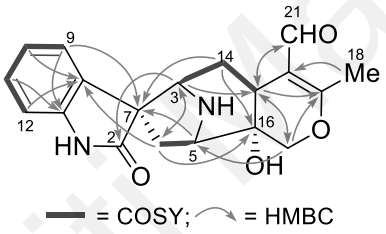


Figure 2.7: COSY and selected HMBCs of **20**

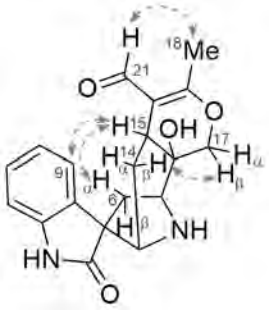


Figure 2.8: Selected NOEs of **20**

2.1.2.2 Alstonisinine B (21)

Alstonisinine B (**21**)[382] was obtained as a white amorphous solid, with $[\alpha]^{25}_{D}$ +113 (*c* 0.1, MeOH). The UV spectrum showed absorption maxima (210 and 253 nm) characteristic of an oxindole chromophore, while the IR spectrum indicated the presence of NH/OH (3295 cm^{-1}), conjugated ketocarbonyl (1702 cm^{-1}, δc 197.1), and lactam carbonyl (1609 cm^{-1}, oxindole δc 184.4) functionalities. The HRMS data showed an $[M + H]^+$ ion at *m/z* 341.1500 consistent with the molecular formula $C_{19}H_{20}N_2O_4$, indicating that **21** is isomeric with **20**.

As in compound **20**, the ^{1}H NMR data of **21** (Table 2.12) also indicated a macroline oxindole alkaloid with an unsubstituted indole moiety (4 aromatic H at δ 6.89−8.14). However, resonances due to formyl (δ 9.81, CHO-21) and methyl (δ 2.24, Me-18) groups seen in **20** were not observed in **21**. Instead resonances due to an olefinic H (δ 7.67, H-21) and an acetyl methyl (δ 2.27, COMe) were seen in **20**. Thus, it is apparent that the difference between **20** and **21** is confined to the ring E moiety. Corresponding changes were observed for the signals of C-18, C-19, and C-21 (δ_C 25.0, 197.1, and 156.9, respectively) in the ^{13}C NMR spectrum of **21**. These observations suggest that **21** is the type-B macroline isomer of **20** (a type-A macroline). As in the case of **20**, C-16 in **21** is also linked to a hydroxy group (δ_C 67.9). The *S* configuration of the spirocyclic C-7 is consistent with the observed C-2 (δ 184.4) and C-8 (δ 129.4) shifts as well as the observed H-9/H-15 NOEs (Figure 2.9). Alstonisinines A (**20**) and B (**21**) can also be considered as the *N*(1)-demethyl analogues of 16-hydroxyalstonal (**29**) and 16-hydroxyalstonisine (**28**), respectively.

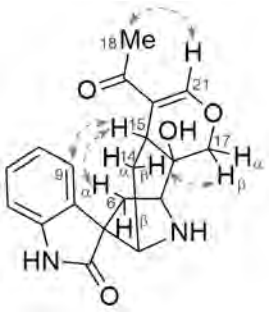


Figure 2.9: Selected NOEs of **21**

2.1.2.3 Alstonisinine C (22)

Alstonisinine C (**22**)[382] was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ +180 (*c* 0.4, $CHCl_3$). The IR absorption bands at 3403, 1708, and 1616 cm^{-1}, indicated the presence of NH/OH, lactam carbonyl, and conjugated ketocarbonyl functions, respectively. The UV spectrum is characteristic of an oxindole chromophore (225 and 256 nm). The molecular formula $C_{20}H_{22}N_2O_4$ was determined by HRMS measurements ($[M + H]^+$ *m/z* 355.1666).

The ^{1}H NMR data (Table 2.12) of **22** displayed resonances due to an unsubstituted indole unit (4H at δ 6.82−7.28), an olefinic H (δ 7.59), an *N*-methyl singlet (δ 3.25), and an acetyl group (a 3-H singlet at δ 2.26). The ^{13}C NMR data (Table 2.12) showed a total of 20 carbon resonances, including two methyl, three methylene, eight methine, a tertiary carbon linked to an indolic nitrogen, a lactam carbonyl (oxindole), a conjugated ketone, a tertiary carbon bonded to an oxygen atom, and three quaternary carbons.

The ^{1}H and ^{13}C NMR data of **22** were similar to those of 16-hydroxyalstonisine (**28**), with the exception of the resonances due to C-2 and C-8, which were found at δ_C 177.5 and 137.2 in **22**, compared to δ_C 182.2 and 128.9, respectively, in 16-hydroxyalstonisine (**28**). These chemical shift values are of diagnostic significance for the assignment of the spirocyclic C-7 configuration in unsubstituted macroline oxindoles[129,383] and in this case, led to the identification of **22** as the (7*R*)-diastereomer of (7*S*)-16-hydroxyalstonisine (**28**).[175] The assignment of 7*R* configuration was further supported

by the observed H-9/H-6β NOEs (Figure 2.10), as well as by the observed upfield shift of H-9 by ca. 1 ppm to δ 7.14 in **22**, in contrast to that of 7*S* diastereomers (δ H-9 ≈ 8.1, e.g., **20** and **21**).

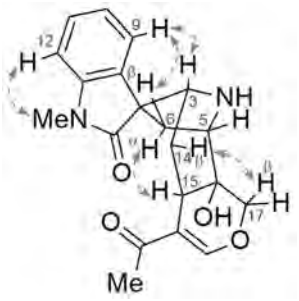


Figure 2.10: Selected NOEs of **22**

The deshielding of H-9 in the 7*S* oxindoles (e.g., compounds **20** and **21**) is due to the anisotropic effect of the proximate C-20–C-21 double bond. Such an effect is not seen in the 7*R* counterpart as the change in configuration at the spirocenter results in the double bond being located away from the aromatic ring and hence unable to exert any anisotropy on H-9.[383] The proposed structure is entirely consistent with the HMBC data (Figure 2.11).

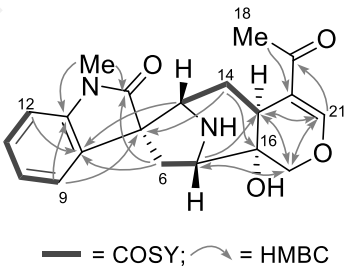


Figure 2.11: COSY and selected HMBCs of **22**

The ^{1}H NMR spectra of the three new pentacyclic macroline oxindoles (**20**, **21**, and **22**), described in the preceding sections, are shown in Figures 2.12, 2.13, and 2.14, respectively.

Table 2.12: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Alstonisinine A (**20**), Alstonisinine B (**21**), and Alstonisinine C (**22**)[a]

H/C	20[b]		21[b]		22[c]	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	185.0	-	184.4	-	177.5	-
3	63.4	3.15 m	63.5	3.22 m	66.7	3.15 m
5	61.3	3.42 br d (7.0)	61.2	3.50 br d (7.0)	61.7	3.62 br d (7.5)
6β	37.4	2.30 dd (14.5, 7.0)	37.5	2.39 m	38.3	2.19 dd (14.0, 7.5)
6α		2.47 d (14.5)		2.52 dd (14.0, 1.0)		2.92 dd (14.0, 1.0)
7	57.8	-	57.7	-	58.0	-
8	129.5	-	129.4	-	137.2	-
9	125.8	8.07 m	125.8	8.14 m	120.8	7.14 dd (8.0, 1.0)
10	123.2	7.14 m	123.3	7.25 m	122.4	7.02 td (8.0, 1.0)
11	128.2	7.15 m	128.1	7.25 m	128.0	7.28 td (8.0, 1.0)
12	109.9	6.85 m	109.6	6.89 m	107.9	6.82 d (8.0)
13	141.6	-	141.2	-	142.4	-
14β	32.9	1.32 ddd (15.0, 12.0, 4.0)	33.3	1.39 ddd (15.0, 12.0, 3.0)	34.6	1.33 ddd (14.0, 11.0, 3.0)
14α		2.35 ddd (15.0, 7.0, 2.0)		2.39 m		2.44 ddd (14.0, 7.0, 3.0)
15	32.2	3.00 m	32.9	3.09 ddd (12.0, 7.0, 2.0)	33.3	3.75 ddd (11.0, 7.0, 2.0)
16	67.6	-	67.9	-	68.8	-
17α	71.6	3.98 dd (12.0, 2.0)	71.4	4.01 dd (12.0, 2.0)	71.0	3.94 dd (11.0, 2.0)
17β		4.67 d (12.0)		4.67 d (12.0)		4.52 d (11.0)
18	16.6	2.24 s	25.0	2.27 s	25.8	2.26 s
19	171.4	-	197.1	-	197.0	-
20	116.0	-	119.6	-	119.6	-
21	190.5	9.81 s	156.9	7.67 s	155.2	7.59 s
N(1)Me	-	-	-	-	26.6	3.25 s

[a]Assignments based on DEPT, COSY, HSQC, HMBC, and NOESY. [b]$CDCl_3$ (with a drop of MeOD-d_4), 400 (^{1}H) and 100 MHz (^{13}C). [c]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C).

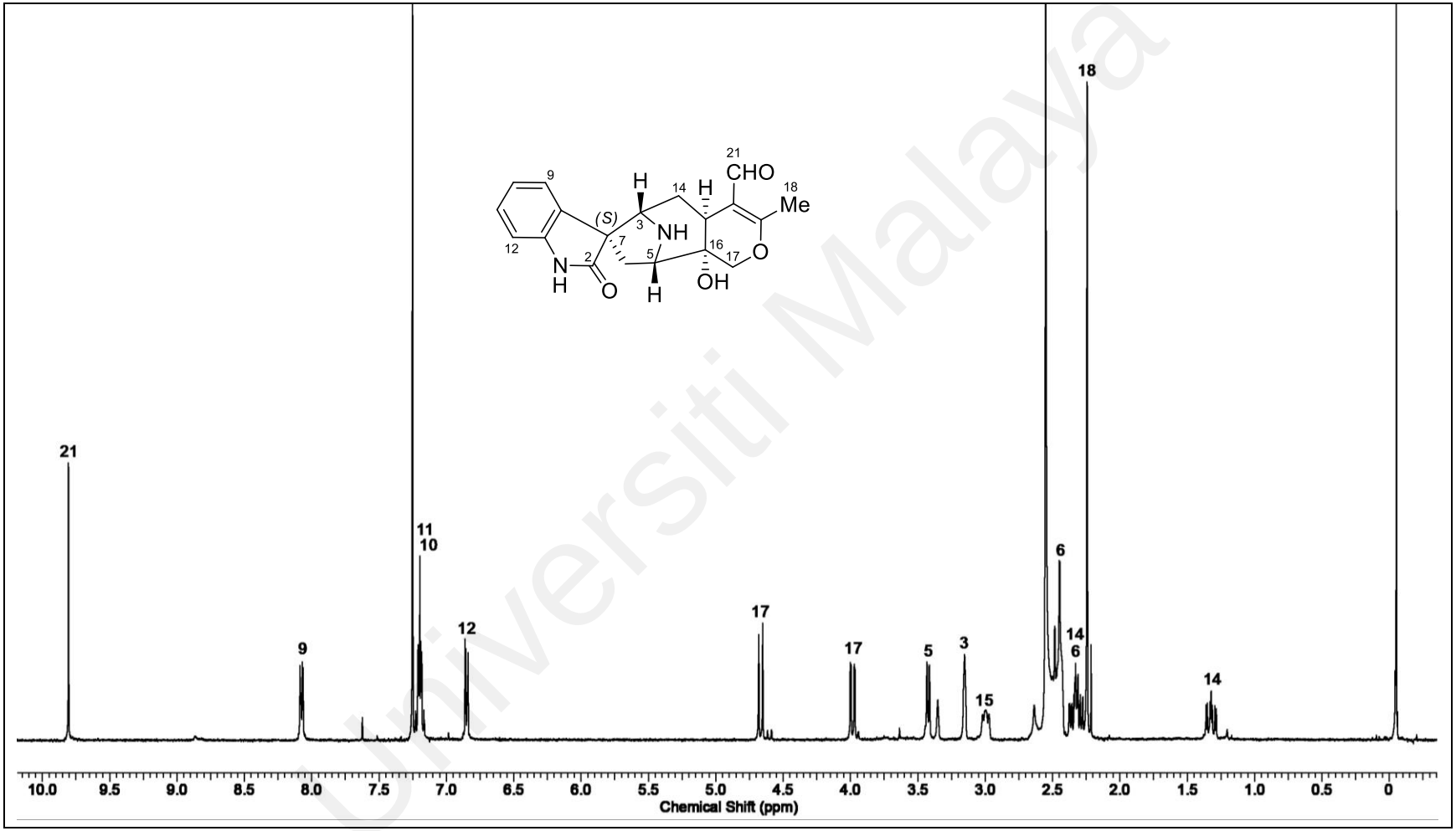


Figure 2.12: ^{1}H NMR Spectrum ($CDCl_3$ with a drop of MeOD-d_4, 400 MHz) of Alstonisinine A (**20**)

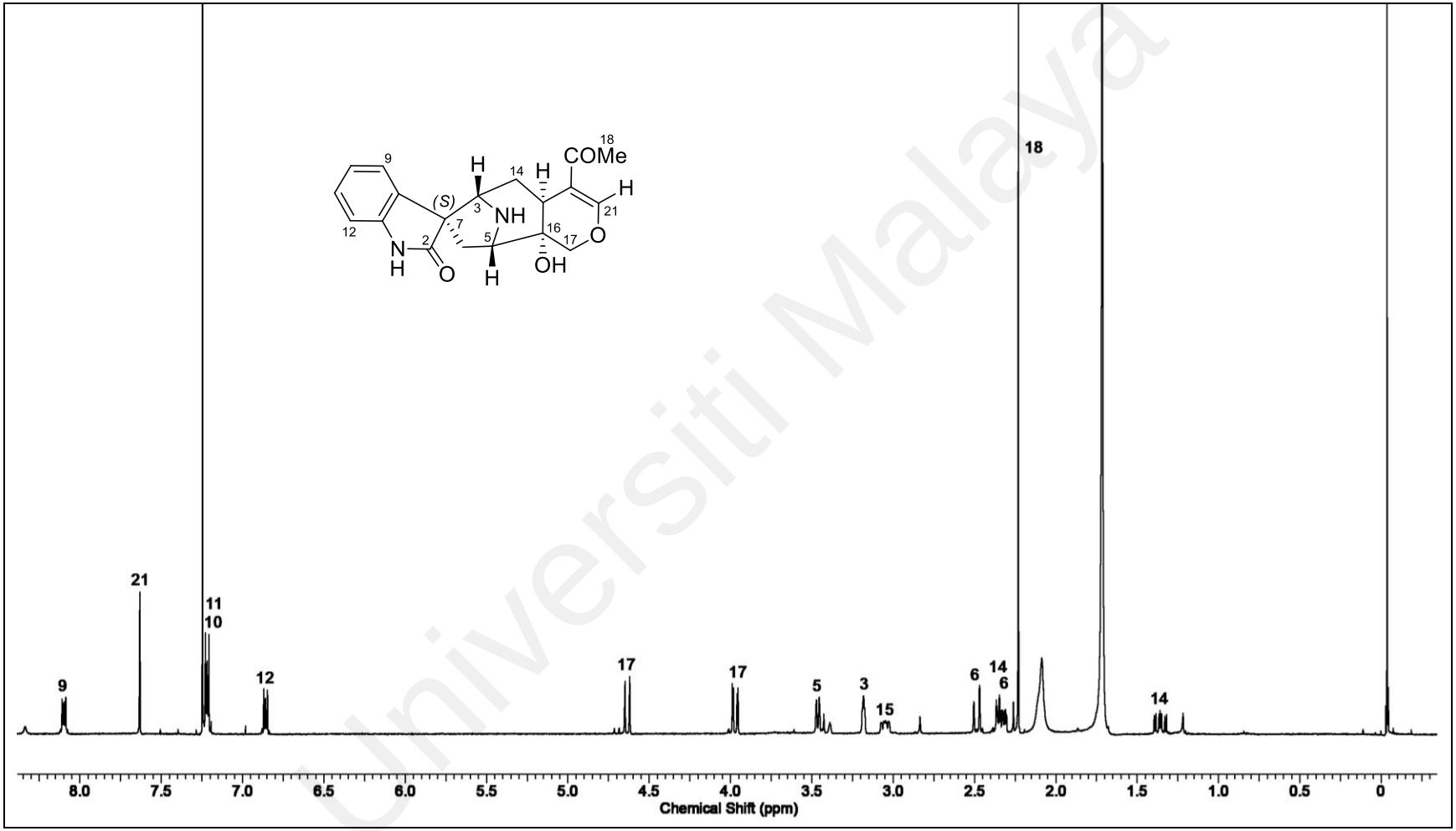


Figure 2.13: ^{1}H NMR Spectrum ($CDCl_3$ with a drop of MeOD-d_4, 400 MHz) of Alstonisinine B (**21**)

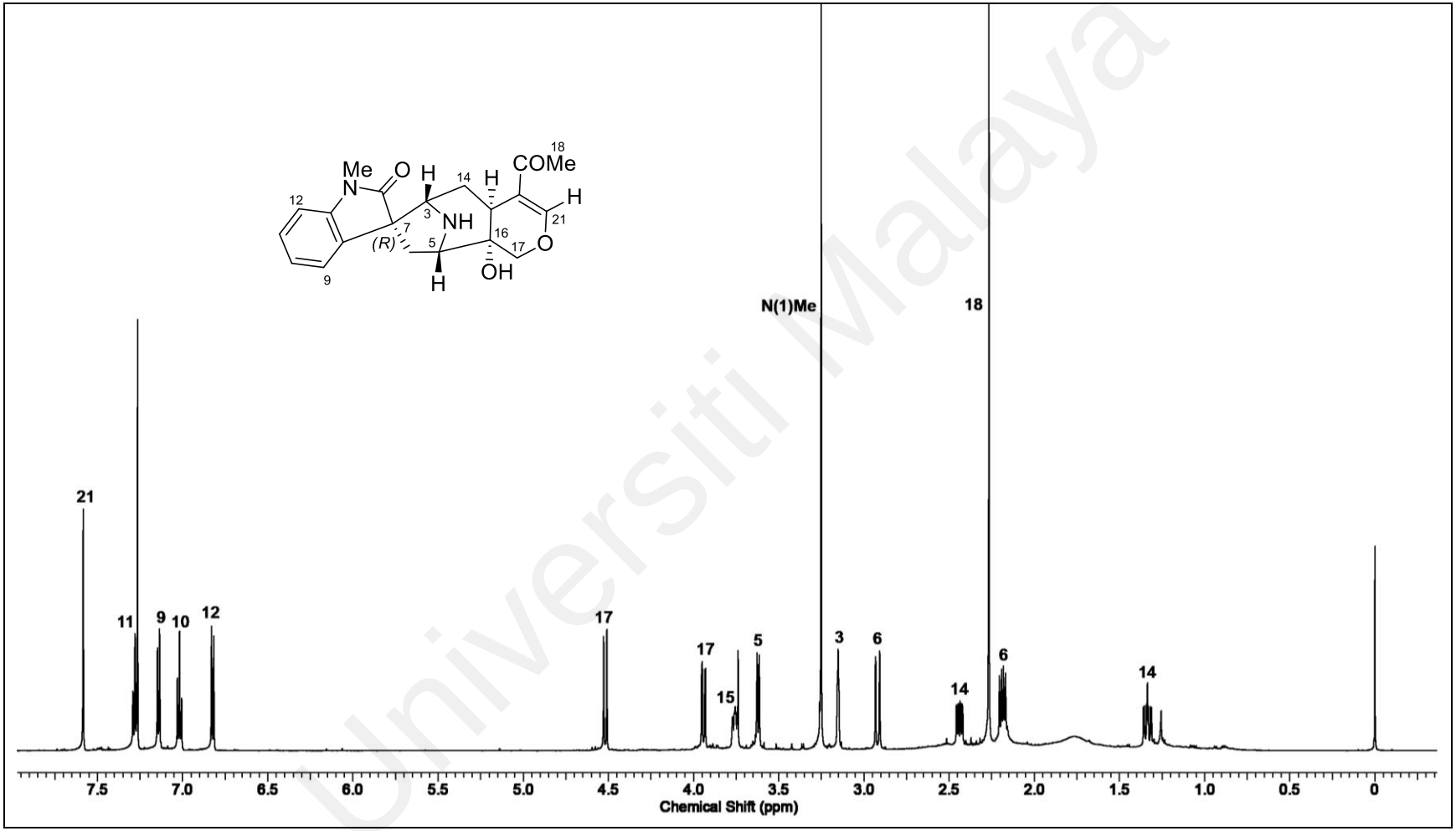


Figure 2.14: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Alstonisinine C (**22**)

2.1.2.4 Alstonoxine F (23)

Alstonoxine F (**23**)[382] was isolated as a light yellowish amorphous solid, with $[\alpha]^{25}_{D}$ −20 (*c* 0.3, $CHCl_3$). The UV spectrum showed absorption maxima at 214, 255, and 289 nm, characteristic of an oxindole chromophore. The IR spectrum indicated the presence of OH (3392 cm^{-1}), lactam carbonyl (1705 cm^{-1}), and formamide (1646 cm^{-1}) functions. The molecular formula $C_{20}H_{26}N_2O_4$ was established from the HRESIMS data ([M + H]$^+$ *m/z* 359.1971).

The ^{1}H NMR data (Table 2.13, **23a**) showed resonances due to the presence of an unsubstituted indole unit (δ 6.88−7.56), an N-1−methyl (δ 3.19), a formamide H (δ 8.14), an oxymethylene corresponding to $HOCH_2$-17 (δ 3.50, 3.67), an oxymethine (δ_H 4.0, δ_C 64.8), and a methyl group (δ 1.28, Me-18). The latter two groups constitute part of the 2-hydroxypropyl side chain. The ^{13}C NMR data (Table 2.13, **23a**) accounted for all 20 carbon resonances, including two methyl, four methylene, ten methine, one tertiary carbon atom bonded to an indolic nitrogen, one lactam carbonyl (oxindole), and two quaternary carbons. The observed carbon resonance at δ 159.4 in the ^{13}C NMR spectrum is consistent with the presence of the formamide group. The COSY data (Figure 2.15) disclosed the following partial structures: $HOCH_2CHCHCH_2$ and $CH_3CH(OH)CH_2CHCH_2CH$, corresponding to HO−C-17−C-16−C-5−C-6 and C-18−C-19−C-20−C-15−C-14−C-3 fragments, respectively, of an E-seco macroline alkaloid. Examination of the HMBC data (Figure 2.15) allowed assembly of the molecule, viz., an E-ring-seco macroline oxindole belonging to the alstonoxine series.[129,180,383] The configuration of the spirocenter C-7 was assigned as *S* based on the observed H-9/H-15 NOEs (Figure 2.16).

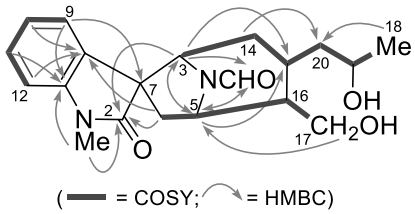


Figure 2.15: COSY and selected HMBCs of **23**

In the ^{1}H and ^{13}C NMR spectra of **23**, two distinct sets of resonances with different intensity were observed, which are attributed to the existence of a pair of rotamers due to the presence of formamide group, a feature previously noted in alstofoline (**30**).[383] Formamide groups experience restricted rotation about the C-N axis due to the partial double bond character of the C-N bond. As was previously noted in the case of alstofoline (**30**), although two distinct bands are observed during preparative radial chromatography, equilibration is rapid in solution at room temperature, leading to an equilibrium mixture of two rotamers, with one form predominating. Thus, the ^{1}H NMR spectra recorded for the collected fractions were generally identical. The ^{1}H NMR data (Table 2.13) showed two sets of signals assignable to the two rotamers with a ten-fold predominance of the major rotamer (**23a**). Other than the nine overlapping ^{1}H resonances, the signals for the remaining eleven resonances, while close, are clearly discernible. This phenomenon was also evident in the ^{13}C NMR spectrum of **23** (Table 2.13), in which most of the carbon resonances appeared in pairs with one set clearly predominant, and only two carbon signals coincident. The major difference in the NMR data between the two rotamers are the resonances corresponding to H-3 and H-5 (in the ^{1}H NMR spectrum), as well as those due to C-3 and C-5 (in the ^{13}C NMR spectrum) of the two rotamers. It was previously suggested that the major rotamer **23a** was one having the carbonyl C=O and H-5 in an approximately *syn*-coplanar orientation resulting in the deshielding of H-5, whereas the minor rotamer **23b** was one having the carbonyl C=O and H-3 in an approximately *syn*-coplanar orientation, resulting in the

deshielding of H-3.[383] This proposal was consistent with the NOEs observed for NCHO/H-3 in **23a** (major rotamer) and NCHO/H-5 in **23b** (minor rotamer) (Figure 2.16). The proposed major and minor rotamers are also in agreement with the DFT (Density Functional Theory) calculations which estimated the major rotamer to be more stable than the minor rotamer by about 4.4 kcal mol^{-1} (18.3 kJ mol^{-1}) (Figure 2.16).

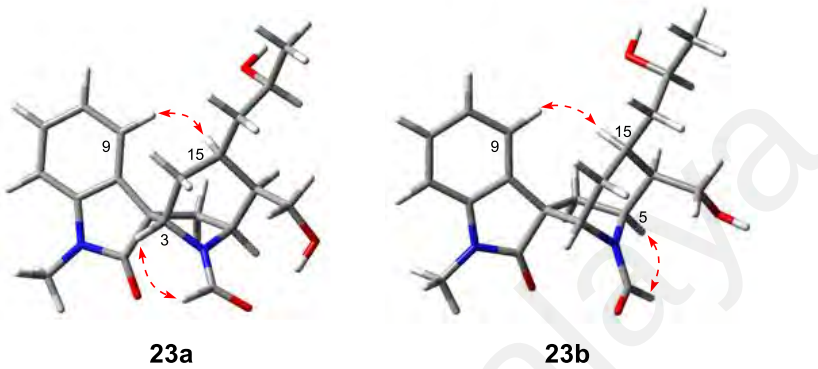


Figure 2.16: Optimized geometries of major (**23a**) and minor (**23b**) conformers of **23** at the B3LYP/6-31G(d) level and their key NOEs

As repeated attempts at crystallization only afforded amorphous solids, the absolute configuration was determined by ECD measurements in conjunction with TDDFT calculations (Figure 2.17).

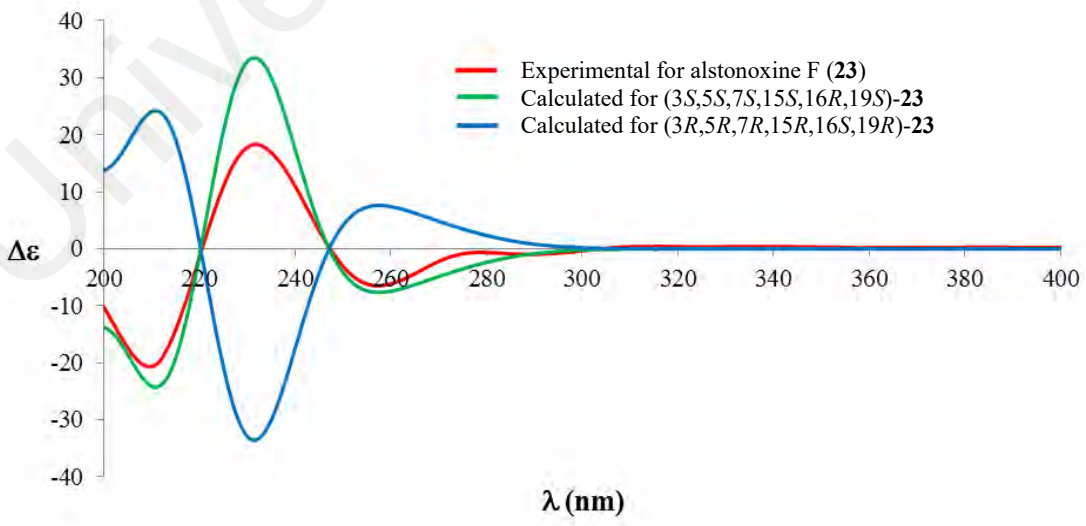


Figure 2.17: Experimental ECD and calculated ECD spectra of **23**

However, a crystal was eventually found among the amorphous solids formed during crystallization from MeCN-MeOH, which was suitable for X-ray diffraction analysis. The X-ray crystal structure (Figure 2.18) provided confirmation for the proposed structure, as well as facilitating assignment of the (19*S*) configuration and establishment of the absolute configuration. The ^{1}H NMR spectrum of **23** is shown in Figure 2.19.

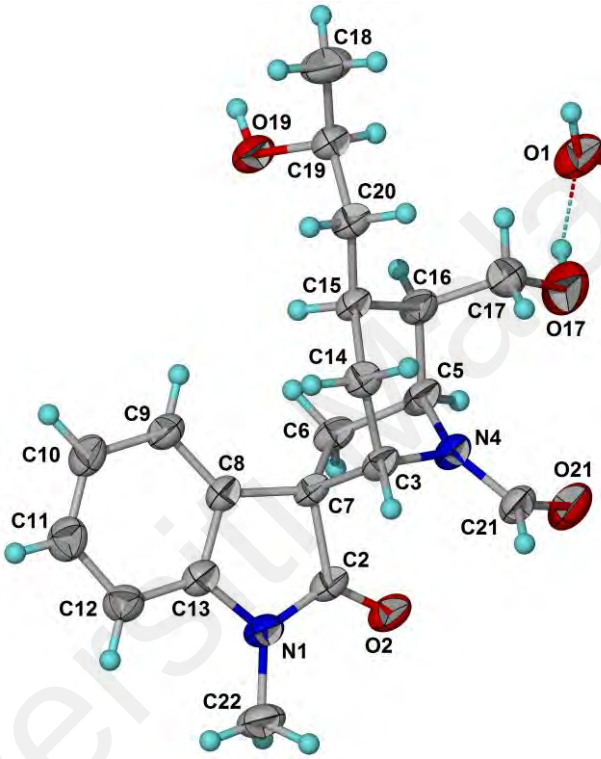


Figure 2.18: X-Ray crystal structure of **23**

Table 2.13: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Alstonoxine F (**23**)[a]

H/C	23a		23b	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	179.6	-	179.8	-
3	61.7	3.83 m	56.8	4.46 m
5	51.0	5.05 br d (8.0)	55.3	4.65 br d (8.0)
6α	37.3	2.21 d (14.0)	37.1	2.21 d (14.0)
6β		2.62 dd (14.0, 8.0)		2.66 dd (14.0, 8.0)
7	53.9	-	54.1	-
8	127.3	-	127.6	-
9	124.7	7.56 d (8.0)	124.6	7.56 d (8.0)
10	123.0	7.12 t (8.0)	122.6	7.09 t (8.0)
11	129.0	7.35 t (8.0)	128.8	7.33 t (8.0)
12	108.4	6.88 d (8.0)	108.3	6.85 d (8.0)
13	144.5	-	144.7	-
14β	33.8	1.53 td (14.0, 4.0)	32.0	1.57 td (14.0, 4.0)
14α		1.87 ddd (14.0, 6.0,1.0)		1.87 ddd (14.0, 6.0, 1.0)
15	27.6	2.98 m	27.2	2.98 m
16	42.1	2.26 m	43.0	2.26 m
17	59.7	3.50 t (12.0)	59.7	3.61 t (10.0)
17		3.67 m		3.79 dd (10.0, 5.0)
18	25.0	1.28 d (6.0)	24.7	1.28 d (6.0)
19	64.8	4.00 m	64.8	4.00 m
20	40.8	1.30 m	41.1	1.30 m
20		1.42 ddd (14.0, 10.0, 3.0)		1.42 ddd (14.0, 10.0, 3.0)
N(1)-Me	26.3	3.19 s	26.4	3.16 s
N(4)-C<u>H</u>O	159.4	8.14 s	159.6	8.22 s

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); assignments based on DEPT, COSY, HSQC, HMBC, and NOESY.

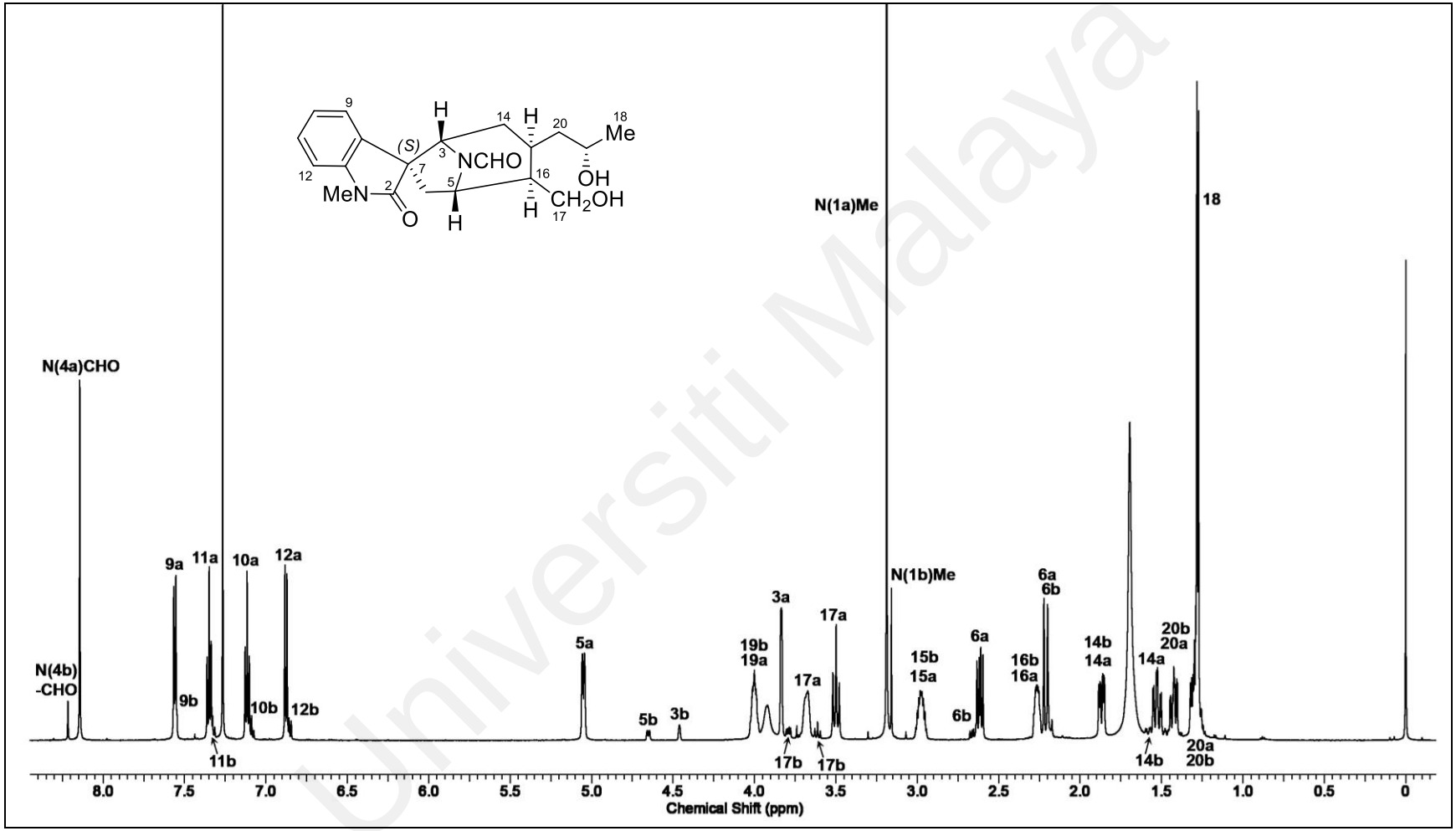


Figure 2.19: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Alstonoxine F (**23**)

2.1.2.5 Alstonisine (24), Alstonal (25), *N*(1)-Demethylalstonisine (26), *N*(1)-Demethylalstonal (27), 16-Hydroxyalstonisine (28), 16-Hydroxyalstonal (29), Alstofoline (30), and Alstonoxine A (31)

Eight known macroline-type oxindole alkaloids including alstonisine (**24**),[125,126,159,185,384] alstonal (**25**),[53,159] *N*(1)-demethylalstonisine (**26**),[383] *N*(1)-demethylalstonal (**27**),[383] 16-hydroxyalstonisine (**28**),[175] 16-hydroxyalstonal (**29**),[175] alstofoline (**30**),[383,385] and alstonoxine A (**31**),[383,385] were also isolated in the present study. The ^{1}H and ^{13}C NMR data of these compounds are summarized in Tables 2.14–2.17, and their ^{1}H NMR spectra are shown in Figures A13–A18 (see Appendix). Other data are given in the Experimental Section.

Table 2.14: ^{1}H NMR Spectroscopic Data (δ) of Alstonisine (**24**), Alstonal (**25**), *N*(1)-Demethylalstonisine (**26**), and *N*(1)-Demethylalstonal (**27**)[a]

H	24 (*J*/Hz)	25 (*J*/Hz)	26 (*J*/Hz)	27 (*J*/Hz)
3	3.18 br s	3.18 br s	3.27 br s	3.27 br s
5	3.68 br d (7.0)	3.67 dd (7.0, 2.0)	3.69 br d (7.0)	3.69 br d (7.0)
6	2.19 br d (13.0)	2.18 br d (13.0)	2.20 br d (13.0)	2.19 br d (13.0)
6	2.52 dd (13.0, 7.0)	2.51 dd (13.0, 2.0)	2.57 dd (13.0, 7.0)	2.56 dd (13.0, 7.0)
9	8.25 br d (8.0)	8.24 br d (8.0)	8.22 br d (8.0)	8.22 br d (8.0)
10	7.30 td (8.0, 1.0)	7.30 td (8.0, 1.0)	7.25 m	7.25 m
11	7.33 td (8.0, 1.0)	7.34 td (8.0, 1.0)	7.20 m	7.20 m
12	6.88 br d (8.0)	6.87 br d (8.0)	6.91 br d (8.0)	6.91 br d (8.0)
14	1.55 ddd (14.0, 12.0, 3.0)	1.54 ddd (14.0, 12.0, 3.0)	1.57 ddd (14.0, 12.0, 2.0)	1.55 ddd (14.0, 12.0, 2.0)
14	2.25 ddd (14.0, 6.0, 3.0)	2.29 ddd (14.0, 6.0, 3.0)	2.26 ddd (14.0, 6.0, 2.0)	2.30 ddd (14.0, 6.0, 2.0)
15	3.40 dt (12.0, 6.0)	3.36 dt (12.0, 6.0)	3.39 dt (12.0, 6.0)	3.35 dt (12.0, 6.0)
16	1.96 m	1.97 m	1.98 m	1.98 m
17	4.26 ddd (11.0, 4.0, 2.0)	4.28 ddd (11.0, 4.0, 2.0)	4.26 ddd (11.0, 4.0, 2.0)	4.28 ddd (11.0, 4.0, 2.0)
17	4.45 t (11.0)	4.51 t (11.0)	4.46 t (11.0)	4.52 t (11.0)
18	2.24 s	2.24 s	2.24 s	2.24 s
21	7.62 s	9.86 s	7.63 s	9.86 s
N(1)-Me	3.20 s	3.20 s	-	-
N-H	-	-	8.54 br s	8.57 br s

[a]$CDCl_3$, 400 MHz.

Table 2.15: ^{13}C NMR Spectroscopic Data (δ) of Alstonisine (**24**), Alstonal (**25**), *N*(1)-Demethylalstonisine (**26**), and *N*(1)-Demethylalstonal (**27**)[a]

C	24	25	26	27
2	181.9	181.9	184.2	184.2
3	63.4	63.4	64.0	64.0
5	55.9	55.9	56.4	56.4
6	41.5	41.5	41.9	41.9
7	56.5	56.5	57.3	57.3
8	128.7	128.7	129.6	129.6
9	125.1	125.1	126.1	126.0
10	122.8	122.8	123.4	123.3
11	127.5	127.5	128.0	128.0
12	107.5	107.5	109.4	109.4
13	143.6	143.6	140.8	140.8
14	30.6	30.3	31.0	30.7
15	23.8	23.5	24.2	23.9
16	36.5	36.5	37.1	37.1
17	68.2	67.9	68.6	68.4
18	24.5	16.2	24.9	16.6
19	196.0	170.5	196.6	171.1
20	121.3	117.7	121.8	118.1
21	157.2	189.0	157.6	189.5
N(1)-Me	25.8	25.8	-	-

[a]$CDCl_3$, 100 MHz.

Table 2.16: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of 16-Hydroxyalstonisine (**28**) and 16-Hydroxyalstonal (**29**)[a]

H/C	28		29	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	182.2	-	182.2	-
3	63.5	3.16 t (3.0)	63.5	3.16 br s
5	61.2	3.53 d (7.0)	61.2	3.52 d (7.0)
6	37.8	2.35 m	37.8	2.35 dd (14.0, 7.0)
6		2.51 dd (14.0, 1.0)		2.49 dd (14.0, 1.0)
7	57.3	-	57.3	-
8	128.9	-	128.9	-
9	125.4	8.17 dd (8.0, 1.0)	125.4	8.16 dd (8.0, 1.0)
10	123.4	7.29 td (8.0, 1.0)	123.4	7.28 td (8.0, 1.0)
11	128.1	7.33 td (8.0, 1.0)	128.0	7.33 td (8.0, 1.0)
12	108.0	6.87 dd (8.0, 1.0)	108.0	6.87 dd (8.0, 1.0)
13	143.9	-	143.9	-
14	33.4	1.39 ddd (15.0, 12.0, 3.0)	33.1	1.38 ddd (15.0, 11.0, 3.0)
14		2.35 m		2.40 ddd (15.0, 7.0, 3.0)
15	33.1	3.10 ddd (12.0, 7.0, 2.0)	32.7	3.06 m
16	68.2	-	68.1	-
17	71.5	4.01 dd (12.0, 2.0)	71.8	4.03 dd (12.0, 2.0)
17		4.70 d (12.0)		4.76 d (12.0)
18	25.0	2.26 s	16.5	2.30 s
19	196.7	-	170.2	-
20	119.6	-	115.8	-
21	156.5	7.66 s	189.8	9.89 s
N(1)-Me	26.2	3.20 s	26.2	3.20 s

[a] $CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C).

Table 2.17: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Alstofoline (**30**) and Alstonoxine A (**31**)[a]

H/C	30a[b]		30b[c]		31	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	179.7	-	179.5	-	182.3	-
3	60.9	3.82 br s	56.3	4.49 br s	63.1	3.25 br s
5	50.3	4.91 br d (7.0)	55.1	4.31 br d (7.0)	61.7	3.90 br d (8.0)
6	39.4	2.22 m	38.6	2.22 m	40.7	2.15 dd (13.0, 2.0)
6		2.68 dd (13.0, 7.0)		2.77 dd (13.0, 7.0)		2.43 dd (13.0, 8.0)
7	53.2	-	53.0	-	57.2	-
8	129.0	-	129.0	-	129.0	-
9	125.8	8.28 dd (8.0, 1.0)	125.8	8.25 dd (8.0, 1.0)	125.0	7.84 br d (8.0)
10	123.5	7.39 td (8.0, 1.0)	123.2	7.39 td (8.0, 1.0)	123.1	7.20 td (8.0, 1.0)
11	127.0	7.32 td (8.0, 1.0)	126.8	7.32 td (8.0, 1.0)	128.1	7.32 td (8.0, 1.0)
12	108.1	6.88 dd (8.0, 1.0)	108.1	6.87 br d (8.0)	108.1	6.87 br d (8.0)
13	144.1	-	144.3	-	144.1	-
14	32.3	1.57 ddd (14.0, 12.0, 2.0)	31.9	1.56 m	33.0	1.71 m
14		2.53 ddd (14.0, 6.0, 2.0)		2.42 ddd (14.0, 6.0, 2.0)		1.87 ddd (14.0, 6.0, 2.0)
15	24.5	3.59 dt (12.0, 6.0)	24.4	3.59 dt (12.0, 6.0)	26.1	3.05 m
16	37.1	2.22 m	37.0	2.22 m	41.4	1.71 m
17	66.5	3.90 t (11.0)	66.1	3.96 t (11.0)	65.8	3.80 dd (12.0, 2.0)
17		4.42 ddd (11.0, 4.0, 2.0)		4.27 ddd (11.0, 4.0, 2.0)		4.02 dd (12.0, 1.0)
18	24.9	2.26 s	25.0	2.26 s	30.8	2.21 s
19	196.3	-	196.3	-	208.4	-
20	120.6	-	120.9	-	47.0	2.72 dd (18.0, 6.0)
		-		-		2.79 dd (18.0, 7.0)
21	157.5	7.63 s	157.1	7.61 s	-	-
N(1)-Me	26.2	3.18 s	26.4	3.17 s	26.2	3.20 s
N(4)-CHO	160.1	8.10 s	158.8	8.10 s	-	-

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C). [b]Major rotamer. [c]Minor rotamer.

2.1.3 Sarpagine, Akuammiline, and Talpinine Alkaloids

2.1.3.1 Alstopenidine A (32)

Alstopenidine A (**32**) was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ +6.4 (*c* 0.43, CH_3OH), and subsequently as light yellowish prisms from $CHCl_3$–hexane (mp 119.3–119.6 °C). The UV spectrum (283, 229 nm) is characteristic of an indole chromophore, while the IR spectrum showed a broad band at 3274 cm^{-1} due to the presence of hydroxy groups. The HRESIMS data ($[M + H]^+$ *m/z* 355.2027) established the molecular formula as $C_{21}H_{26}N_2O_3$ (DBE = 10).

The ^1H NMR data (Table 2.18) showed the presence of three aromatic resonances due to a substituted indole moiety (δ 6.84–7.17), a deshielded singlet corresponding to an isolated olefinic hydrogen (δ 6.49, H-21), an *N*-methyl singlet (δ 3.56, N-1–Me), an aromatic methoxy singlet (δ 3.86), resonances due to the geminal hydrogens of an oxymethylene group (δ 3.45, 3.58, $HOCH_2$-17), an oxymethine quartet (δ 4.49, H-19), and a methyl doublet (δ 1.35, Me-18). The aromatic resonances (*δ* 6.95 s; 6.84, d, *J* = 9 Hz; 7.17 d, *J* = 9 Hz) indicated 10- or 11-methoxy substitution. Confirmation of 10-methoxy substitution was provided by the three-bond MeO/C-10 correlation in the HMBC spectrum, as well as the NOEs observed between MeO-10 and H-9, H-11, and between H-12 and N-1–Me (Figure 2.20). The COSY data indicated the presence of a $NCHCH_2CHCH(CH_2)CHCH_2$ fragment in addition to a CH_3CHOH unit due to the C-18–C-19 hydroxyethyl side chain. The former corresponds to the N–C-3–C-14–C-15–C-16(C-17)–C-5–C-6 fragment of a sarpagine-type alkaloid, which was confirmed by the HMBC data (Figure 2.20). The attachment of the 2-hydroxyethyl side chain at C-20 was indicated by the observed H-18/C-20 and H-19/C-15 three-bond correlations in the HMBC spectrum (Figure 2.20).

The ^{13}C NMR spectrum displayed a total of 21 carbon resonances (Table 2.18), comprising three methyl, three methylene, nine methine, an oxygenated tertiary carbon atom (δ 153.8), two tertiary carbon atoms bonded to the indolic nitrogen, and three quaternary carbon atoms, in agreement with the molecular formula. The carbon resonances resonating downfield at δ 135.5 and 149.5 were readily assigned to the olefinic methine C-21 and the quaternary sp^2 carbon C-20, respectively. The resonance due to H-16 was unusually shielded at δ 1.62 suggesting location of H-16 in the shielding zone of the indole moiety, while the H-17 resonances were seen at δ 3.45 and 3.58, which were expected for hydroxymethyl hydrogens. This observation coupled with the observed H-16/H-6β NOE (Figure 2.20) allowed the configuration at C-16 to be assigned as *R*. This assignment was confirmed by X-ray diffraction analysis, which also established the C-19 configuration (*S*), as well as the absolute configuration of compound **32** (Figure 2.21). Compound **32** is therefore the 10-methoxy derivative of alstoumerine (**48**). Alstoumerine was first isolated from *A. macrophylla* from Sri Lanka,[161] but the structure (configurations at C-16 and C-19) was subsequently revised based on X-ray analysis.[52] The ^{1}H NMR spectrum of **32** is shown in Figure 2.22.

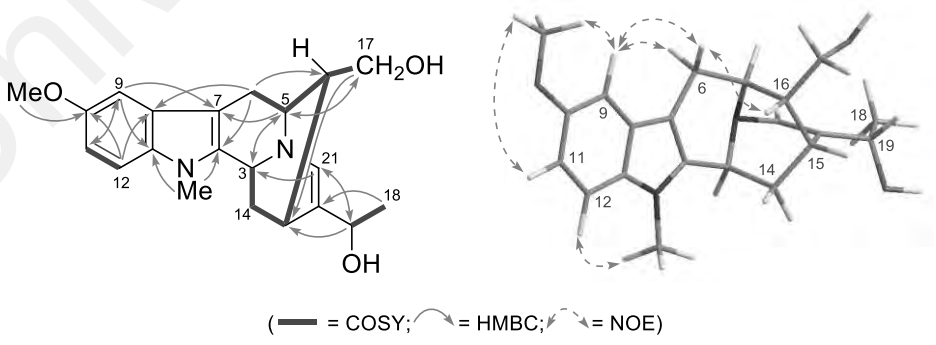


Figure 2.20: COSY, selected HMBCs, and selected NOEs of **32**

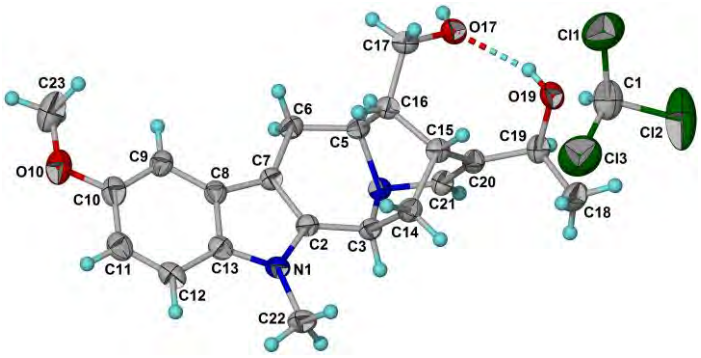


Figure 2.21: X-Ray crystal structure of **32**

Table 2.18: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Alstopenidine A (**32**)[a]

H/C	δ_C	δ_H (*J*/Hz)
2	139.8	-
3	48.6	3.87 m
5	56.4	3.01 m
6β	25.2	2.68 d (15.5)
6α		3.10 dd (15.5, 5.0)
7	102.0	-
8	127.4	-
9	100.6	6.95 br s
10	153.8	-
11	110.7	6.84 br d (9.0)
12	109.4	7.17 d (9.0)
13	132.8	-
14β	38.4	1.63 m
14α		1.89 ddd (12.0, 10.0, 2.0)
15	29.5[b]	2.79 m
16	44.3	1.62 m
17a	64.2	3.45 dd (12.0, 5.0)
17b		3.58 m
18	21.9	1.35 d (6.4)
19	66.9	4.49 q (6.4)
20	149.5	-
21	135.5	6.49 br s
N(1)-Me	29.3[b]	3.56 s
10-OMe	56.0	3.86 s

[a]$CDCl_3$ (with a drop of methanol-d_4), 400 (^{1}H) and 100 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY. [b]Interchangeable.

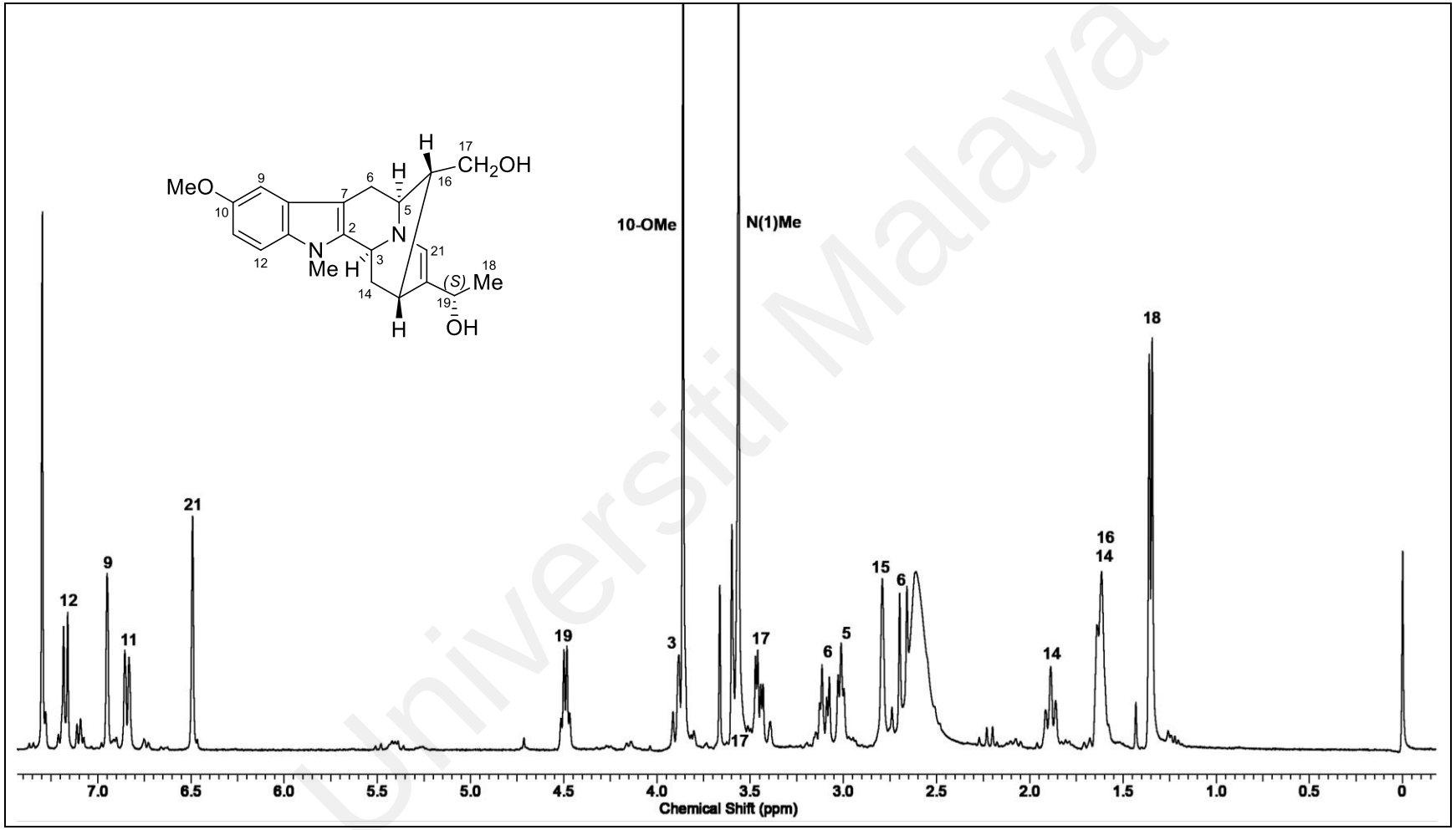


Figure 2.22: ^{1}H NMR Spectrum ($CDCl_3$ with a drop of MeOD-d_4, 400 MHz) of Alstopenidine A (**32**)

2.1.3.2 Alstopenidine B (33)

Alstopenidine B (**33**) was isolated as a green-yellow fluorescent oil, with $[\alpha]^{25}_{D}$ −58.3 (*c* 0.06, $CHCl_3$). The IR spectrum indicated the presence of OH/NH and carbonyl groups at 3401 and 1685 cm^{-1}, respectively, while the UV spectrum indicated the presence of a pseudoindoxyl chromophore (λ_{max} 228, 259 sh, 286 nm). The HRMS data of **33** ([M + H]$^+$ *m/z* 341.1856) gave the molecular formula $C_{20}H_{24}N_2O_3$.

The ^{1}H NMR data (Table 2.19) showed the presence of three aromatic hydrogens (δ 6.82–7.12) due to a substituted indole moiety, an N-H singlet (δ 4.43), an ethylidene side chain seen as a methyl doublet of triplets (δ 1.61, dt, *J* = 6.8, 2.0 Hz; Me-18) coupled with an olefinic quartet (δ 5.30, q, *J* = 6.8 Hz; H-19), an aromatic methoxy singlet at δ 3.77 (10-OCH_3), and two oxymethylene hydrogens due to a hydroxymethyl group (δ 3.56, 2H, $HOCH_2$-17).

The ^{13}C NMR spectrum (Table 2.19) showed a total of 20 carbon resonances, including two methyl, four methylene, eight methine, an oxygenated tertiary carbon (δ 153.8), two tertiary carbon atoms bonded to the indolic nitrogen, a ketocarbonyl (δ 205.1, C-7), and two quaternary carbon atoms. The methylene resonance at δ 65.6 corresponds to the hydroxymethyl $HOCH_2$-17, while the presence of a spirocyclic carbon at δ 73.8 (C-2) and a ketocarbonyl at δ 205.1 (C-7), indicated an alkaloid with a pseudoindoxyl chromophore. This conclusion was supported by the three-bond correlations from NH to C-7 and C-8, as well as from H-6 to C-7 (Figure 2.23) in the HMBC spectrum. The presence of a low-field resonance due to an oxygenated tertiary carbon (δ 153.8), along with the resonance due to an aromatic methoxy group (δ 55.9) is consistent with the presence of a methoxy-substituted indole moiety. The assignment of the methoxy group to C-10 was in accordance with the coupling pattern of the three aromatic hydrogens (δ 6.82 d, *J* = 9.0 Hz, H-12; 7.08 d, *J* = 2.7 Hz, H-9; 7.12 dd, *J* =

9.0, 2.7 Hz, H-11) and the observed H-12/N-H, H-9/10-OMe, H-11/10-OMe NOEs (Figure 2.24).

The COSY data (Figure 2.23) showed, in addition to the ethylidene C=CHCH$_3$ (C-20–C-19–C-18) unit, the same NCHCH$_2$CHCH(CH$_2$)CHCH$_2$ (C-3–C-14–C-15–C-16(–C-17)–C-5–C-6) fragment present in the previous compound **32**, suggesting a sarpagine-type alkaloid. Examination of the ^{1}H (Figure 2.25), ^{13}C, and 2D (COSY, HSQC, HMBC) NMR data led to the structure shown in **33**. The configuration at the spirocyclic C-2 was assigned as *S* based on the NOE observed between H-14β and NH, while the configuration at C-16 was assigned as *R* from the NOE observed between H-16 and H-14β. The geometry of the C-19, C-20 double bond was assigned as *E*, based on the observed H-15/CH$_3$-18 and H-19/H-21 NOEs (Figure 2.24). Compound **33** is related to normacusine B pseudoindoxyl (10-methoxy derivative),[129] or alternatively, to lochnerine[386] (pseudoindoxyl derivative).

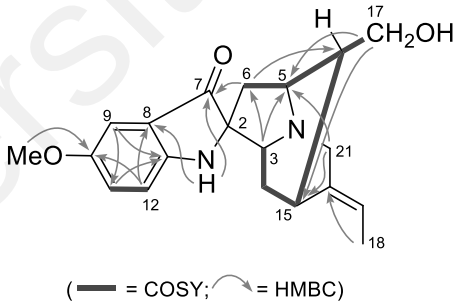


Figure 2.23: COSY and selected HMBCs of **33**

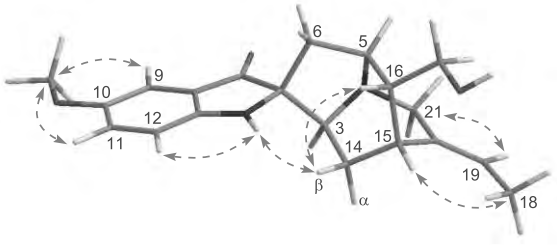


Figure 2.24: Selected NOEs of **33**

Table 2.19: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Alstopenidine B (**33**)[a]

H/C	δ_C	δ_H (*J*/Hz)
2	73.8	-
3	61.3	3.25 dd (10.0, 2.0)
5	58.9	2.98 dd (6.0, 3.4)
6β	47.0	1.58 d (13.0)
6α		2.70 dd (13.0, 6.0)
7	205.1	-
8	120.4	-
9	105.2	7.08 d (2.7)
10	153.8	-
11	127.2	7.12 dd (9.0, 2.7)
12	113.7	6.82 d (9.0)
13	155.4	-
14α	29.9	1.77 ddd (14.0, 10.0, 2.0)
14β		2.09 ddd (14.0, 4.0, 2.0)
15	26.8	2.82 m
16	48.5	1.71 m
17	65.6	3.56 m
17		3.56 m
18	12.5	1.61 dt (6.8, 2.0)
19	114.9	5.30 q (6.8)
20	136.7	-
21	49.2	3.58 m
		3.58 m
N-H	-	4.43 s
10-OMe	55.9	3.77 s

[a] $CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY.

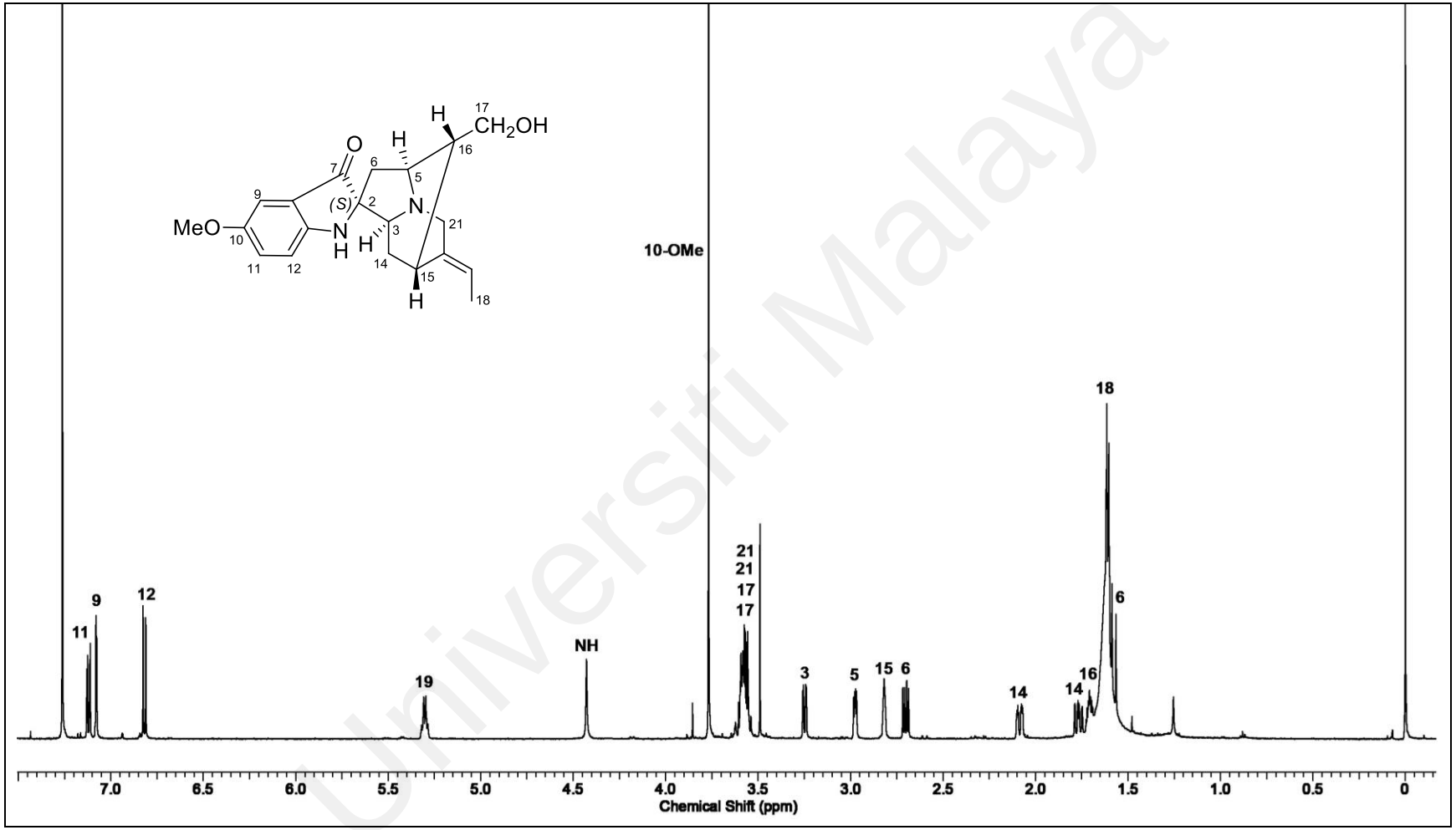


Figure 2.25: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Alstopenidine B (**33**)

2.1.3.3 Alstopenidine C (34)

Alstopenidine C (**34**) was isolated as a yellowish oil, with $[\alpha]^{25}_{D}$ −11 (*c* 0.2, $CHCl_3$). The UV spectrum (222, 263, and 307 nm) showed the presence of an oxindole chromophore, while the IR spectrum showed the presence of OH (3378 cm^{-1}) and lactam carbonyl (1708 cm^{-1}) functions. HRMS measurements ($[M + H]^+$ *m/z* 355.2036) yielded the molecular formula $C_{21}H_{26}N_2O_3$.

The ^1H NMR data (Table 2.20) of **34** showed the presence of three aromatic hydrogens (δ 6.70–6.95) due to a substituted indole moiety, resonances due to an ethylidene side chain (δ 1.59, 5.27), two aminomethylene hydrogens (δ 3.63, 2H; NCH_2-21), two hydroxymethyl hydrogens (δ 3.60, 2H; $HOCH_2$-17), an N-1-methyl singlet (δ 3.16), and an aromatic methoxy group (δ 3.81). The presence of only three aromatic hydrogens and the similarity of the coupling pattern (δ 6.95, d, *J* = 2.4 Hz; δ 6.80, dd, *J* = 8.4, 2.4 Hz; 6.70, d, *J* = 8.4 Hz) with that of **32** indicated 10-methoxy substitution, which was also confirmed by the HMBC (Figure 2.26) and NOE (NOEs for H-12/N-1–Me, H-9/OCH_3, H-11/OCH_3, Figure 2.27) data. The ^{13}C NMR data (Table 2.21) of **34** accounted for all 21 carbon resonances, including three methyl, four methylene, eight methine, an oxygenated tertiary carbon (δ 155.3, C-10), one tertiary carbon linked to the indolic nitrogen, a lactam carbonyl, and three quaternary carbon atoms. The methyl resonances at δ_C 56.1, 26.8, and 12.6, are readily assigned to MeO-10, N-1–Me, and CH_3-18, respectively, while the lactam carbonyl resonance at δ 181.5 is assigned to C-2, which was supported by the H-6 to C-2 and N-1-Me to C-2 correlations (Figure 2.26) in the HMBC spectrum. The COSY data indicated the presence of $NCHCH_2CHCH(CH_2)CHCH_2$ and CH_3CH partial structures corresponding to C-3–C-14–C-15–C-16(C-17)–C-5–C-6 fragment and the ethylidene side chain (C-18–C-19) of a sarpagine-type alkaloid (Figure 2.26).

Examination of the 1D (^{1}H and ^{13}C) and 2D (COSY, HSQC, HMBC) NMR data allowed the identification of **34** as the oxindole derivative of 10-methoxyaffinisine (**45**). The ^{1}H and ^{13}C NMR data (Tables 2.20 and 2.21) of **34** were generally similar to those of affinisine oxindole,[53,180] with the exception of some differences due to the substitution of a methoxy group at C-10 in **34**. The relative configuration of **34** was similar to that of affinisine oxindole as shown by the NOESY data (Figure 2.27). The configuration at the spirocyclic C-7 was assigned as *S*, based on the observed H-9/H-6β, H-14β, H-16 NOEs (Figure 2.27).

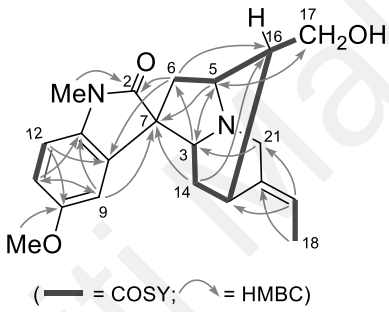


Figure 2.26: COSY and selected HMBCs of **34**

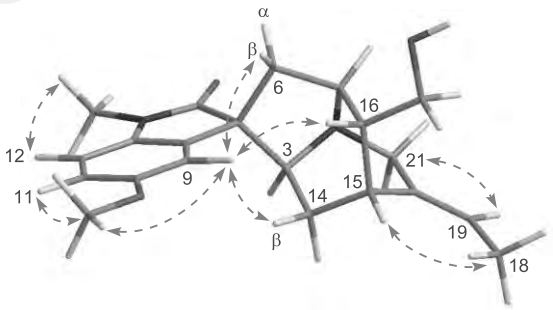


Figure 2.27: Selected NOEs of **34**

2.1.3.4 Alstopenidine D (35)

Alstopenidine D (**35**) was isolated as a yellowish oil, with $[\alpha]^{25}_{D}$ –20.7 (*c* 0.28, $CHCl_3$). The UV (223, 267, and 306 nm; oxindole chromophore) and IR (1707 cm^{-1}, lactam carbonyl; 3409 cm^{-1}, hydroxy) spectra of **35** showed a general similarity with those of **34**, indicating the presence of a similar oxindole chromophore as well as hydroxy and lactam carbonyl functional groups. HRMS measurements ($[M + H]^+$ *m/z* 385.2137) established the molecular formula of **35** as $C_{22}H_{28}N_2O_4$, differing from **34** by an additional 30 mass units.

The ^1H NMR spectrum of **35** (Table 2.20) shared many features in common with **34** such as the presence of resonances due to an ethylidene side chain (δ 1.59, 5.27), two aminomethylene hydrogens (δ 3.62, 2H; NCH_2-21), two hydroxymethyl hydrogens (δ 3.61, 2H, $HOCH_2$-17), as well as an N-1-methyl group (δ 3.17). However, in compound **35**, the aromatic hydrogen resonances were observed as two singlets at δ 6.44 and 6.93, while two aromatic methoxy singlets were also observed at δ 3.89 and 3.92, indicating 10,11-dimethoxy-substitution. The ^{13}C NMR data of **35** (Table 2.21) accounted for all 22 carbon resonances, including four methyl, four methylene, seven methine, two oxygenated tertiary carbons, one tertiary carbon linked to the indolic nitrogen, a lactam carbonyl (δ 182.2), and three quaternary carbon atoms. Comparison of the ^{13}C NMR data with those of **34** also indicated a general similarity, except for the presence of an additional OMe substituent at C-11 (OMe-11, δ 56.4; C-11, δ 150.2) in the case of **35**. As in the case of **34**, the COSY data of **35** (Figure 2.28) also indicated the presence of $NCHCH_2CHCH(CH_2)CHCH_2$ and CH_3CH partial structures corresponding to C-3–C-14–C-15–C-16(C-17)–C-5–C-6 and C-18–C-19 (ethylidene side chain) fragments of a sarpagine-type alkaloid.

The aromatic resonances at δ 6.44 and 6.93 were assigned to H-12 and H-9, respectively, from the observed H-12/N-1–Me, H-9/OCH_3-10, H-12/OCH_3-11, and H-9/H-6β NOEs (Figure 2.29), which was also consistent with the HMBC data (^3J from OMe-10 to C-10 and OMe-11 to C-11, Figure 2.28). The configuration at the spirocyclic C-7 was deduced to be *S*, based on the NOEs observed for H-9/H-6β, H-14β, H-16 (Figure 2.29). Compound **35** is therefore, the 11-methoxy derivative of alstopenidine C (**34**).

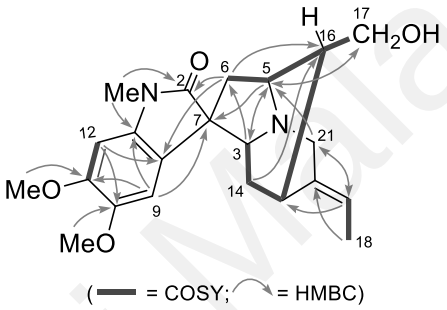


Figure 2.28: COSY and selected HMBCs of **35**

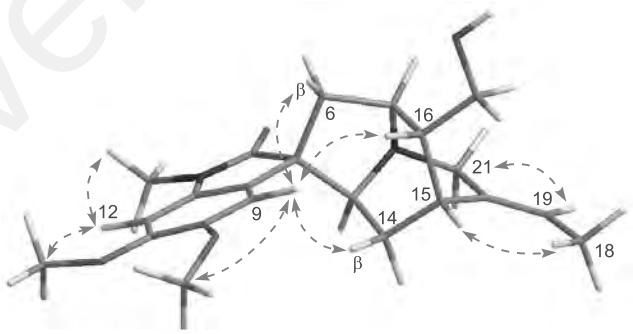


Figure 2.29: Selected NOEs of **35**

2.1.3.5 Alstopenidine E (36)

Alstopenidine E (**36**) was obtained as a light yellowish oil, with $[\alpha]^{25}_{D}$ –26 (*c* 0.12, $CHCl_3$). The UV (223, 281, 303 nm) and IR (1717, 3341 cm^{-1}) spectra of **36** showed a general similarity with those of **35**, indicating the presence of a similar oxindole chromophore, as well as OH and lactam carbonyl functional groups. The ^{13}C resonance at δ 178.9 was also consistent with presence of a lactam/oxindole function. The HRESIMS data showed an $[M + H]^+$ peak at *m/z* 401.2086 which yielded the molecular formula $C_{22}H_{28}N_2O_5$, 16 mass units higher than that of **35**.

Comparison of the NMR data of **36** (Tables 2.20 and 2.21) with those of **35** revealed a close correspondence, such as the presence of two aromatic singlets (δ_H 6.40, 7.05), an N-1-Me singlet (δ_H 3.11), two aromatic methoxy groups (δ_H 3.91, 3.94; δ_C 58.2, 56.4), a hydroxymethyl $HOCH_2$-17 (δ_H 3.67 m, 2H; δ_C 64.1), and an ethylidene side chain (δ_H 1.60 br d, 5.32 br q, J = 6.8 Hz). However, the resonances due to H-3 (δ 3.93), H-5 (δ 4.12), and H-21 (δ 4.43, 4.56) in **36** were significantly deshielded when compared to those of **35** (H-3: 3.23, H-5: 3.08, H-21: 3.62). Similarly, the corresponding C-3, C-5, and C-21 were also shifted downfield from δ_C 62.9, 59.2, and 49.0 in **35** to 75.5, 74.7, and 64.1 in **36**, respectively. Compound **36** is therefore the N-4 oxide of alstopenidine D (**35**).

The ^1H NMR spectra of **34–36** are shown in Figures 2.30–2.32.

Table 2.20: ^{1}H NMR Spectroscopic Data (δ) of Alstopenidine C (**34**), Alstopenidine D (**35**), and Alstopenidine E (**36**)[a]

H	34 (*J*/Hz)	35 (*J*/Hz)	36 (*J*/Hz)
3	3.26 br d (10.0)	3.23 dd (10.0, 2.0)	3.93 m
5	3.10 dd (6.0, 3.0)	3.08 dd (6.0, 3.0)	4.12 m
6β	1.70 d (12.8)	1.68 d (12.8)	2.20 d (13.0)
6α	2.73 dd (12.8, 6.0)	2.72 dd (12.8, 6.0)	3.44 dd (13.0, 6.0)
9	6.95 d (2.4)	6.93 s	7.05 s
11	6.80 dd (8.4, 2.4)	-	-
12	6.70 d (8.4)	6.44 s	6.40 s
14α	1.50 ddd (14.5, 10.0, 2.0)	1.51 ddd (14.4, 10.0, 2.0)	1.92 dd (15.0, 10.4)
14β	2.14 ddd (14.5, 4.0, 2.0)	2.10 ddd (14.4, 4.0, 2.0)	2.53 dd (15.0, 5.2)
15	2.84 m	2.85 m	2.91 m
16	1.95 m	1.92 m	2.72 m
17	3.60 m	3.61 m	3.67 m
17	3.60 m	3.61 m	3.67 m
18	1.59 dt (6.8, 2.0)	1.59 dt (6.8, 2.0)	1.60 br d (6.8)
19	5.27 q (6.8)	5.27 q (6.8)	5.32 br q (6.8)
21	3.63 m	3.62 m	4.43 d (16.0)
	3.63 m	3.62 m	4.56 d (16.0)
N(1)-Me	3.16 s	3.17 s	3.11 s
10-OMe	3.81 s	3.89 s	3.94 s
11-OMe	-	3.92 s	3.91 s

[a]$CDCl_3$, 400 MHz; assignments based on COSY, HSQC, and NOESY.

Table 2.21: ^{13}C NMR Spectroscopic Data (δ) of Alstopenidine C (**34**), Alstopenidine D (**35**), and Alstopenidine E (**36**)[a]

C	34	35	36
2	181.5	182.2	178.9
3	63.1	62.9	75.5
5	59.2	59.2	74.7
6	44.8	44.7	41.2
7	57.1	57.0[b]	56.8
8	132.0	121.0	118.5
9	115.6	113.6	114.6
10	155.3	144.3	144.7
11	111.3	150.2	150.9
12	107.9	94.1	94.2
13	138.2	138.9	138.4
14	28.7	29.1	29.3
15	26.5	26.6[c]	25.4
16	48.2	48.4	46.5
17	65.9	66.0	64.1
18	12.6	12.6	12.6
19	114.7	114.6	117.1
20	136.9	137.0	130.5
21	49.0	49.0	64.1
N(1)-Me	26.8	26.8[c]	27.1
10-OMe	56.1	58.0	58.2
11-OMe	-	56.4[b]	56.4

[a]$CDCl_3$, 100 MHz; assignments based on HSQC and HMBC. [b,c]Interchangeable.

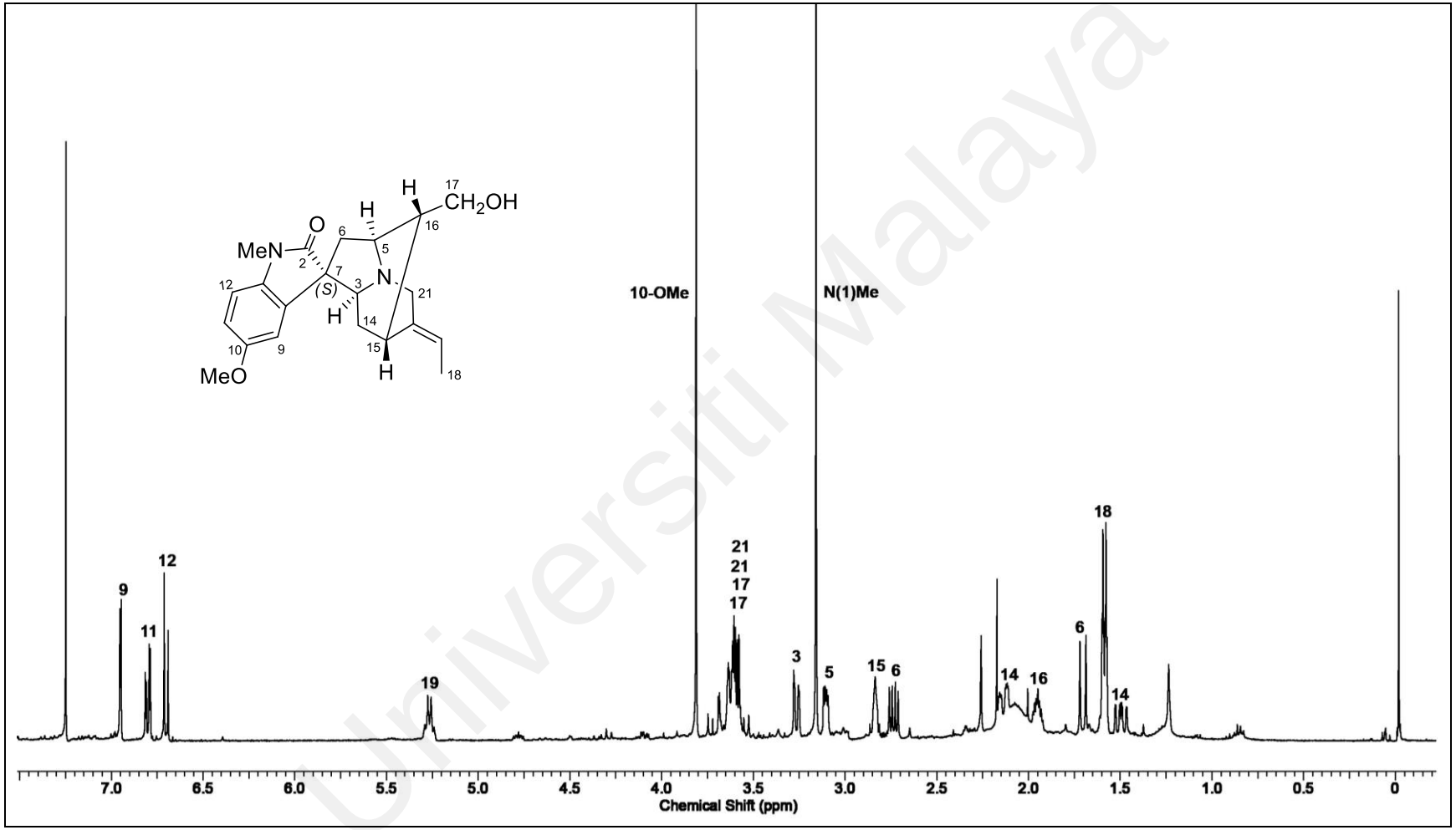


Figure 2.30: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstopenidine C (**34**)

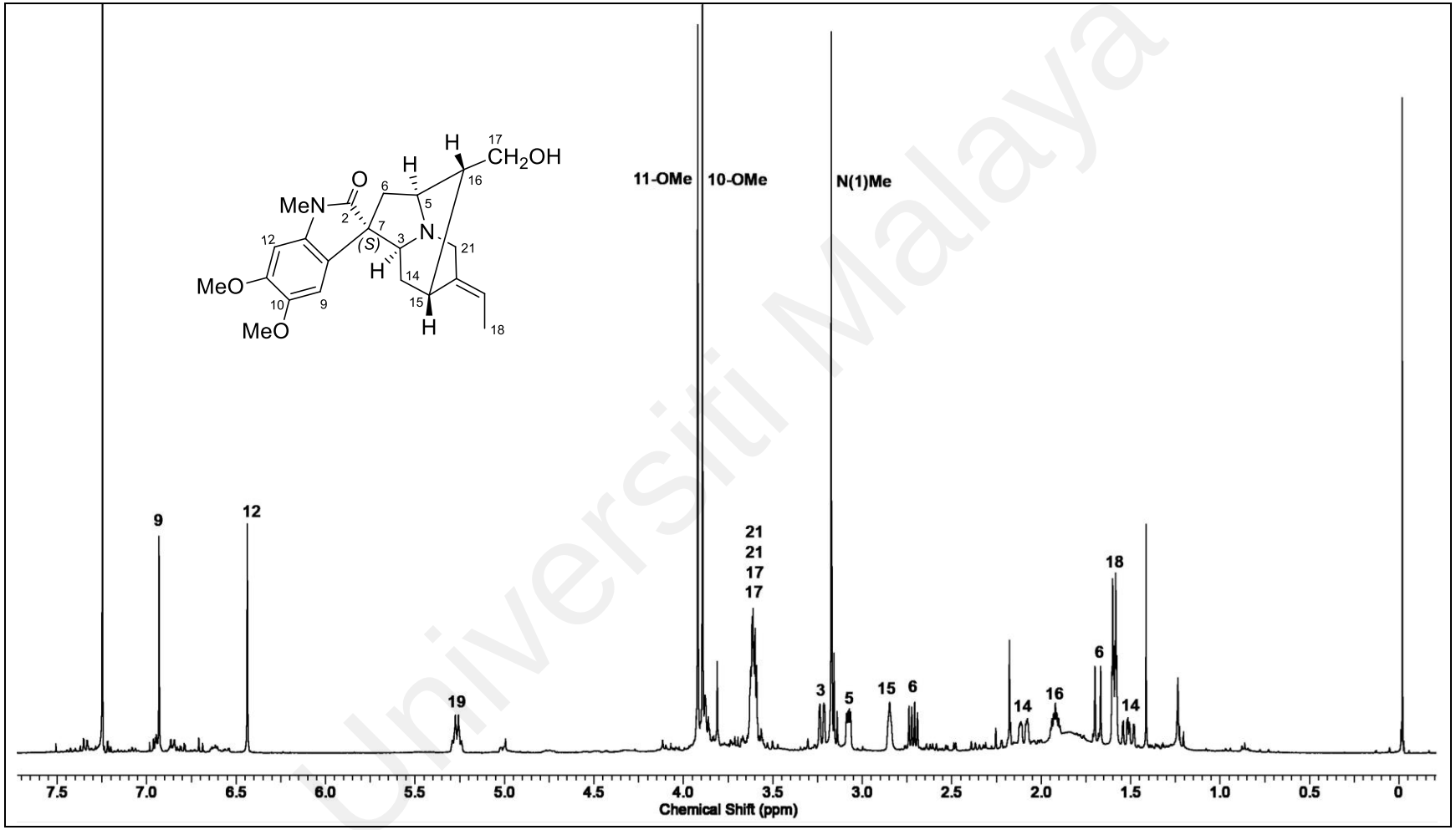


Figure 2.31: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstopenidine D (**35**)

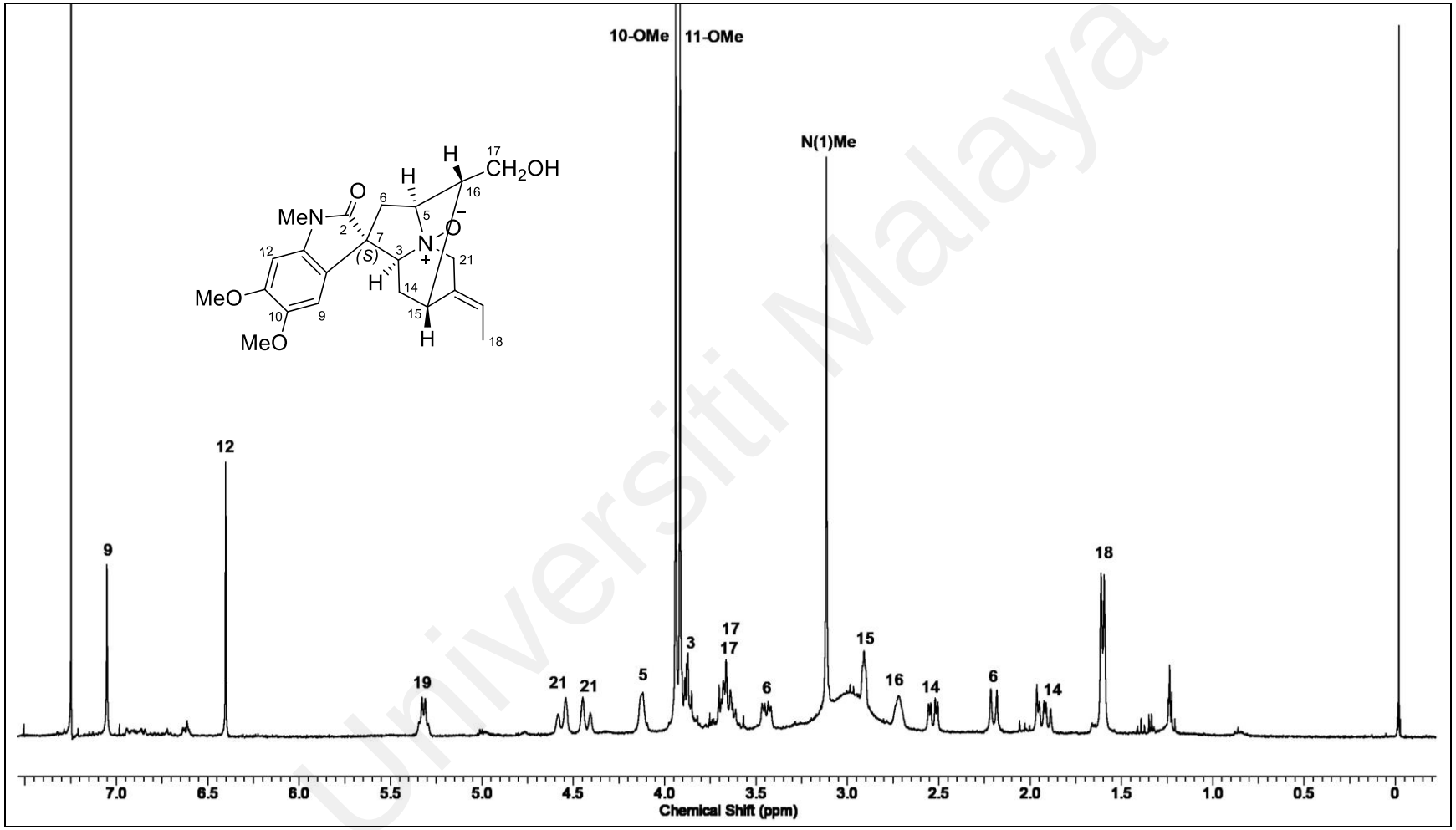


Figure 2.32: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstopenidine E (**36**)

2.1.3.6 Alstopenidine F (37)

Alstopenidine F (**37**) was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ +73 (*c* 0.09, $CHCl_3$). The UV spectrum showed absorption maxima at 215, 226, 251, 260, 333, and 346 nm, suggestive of a 4-quinolone chromophore.[387] The IR spectrum showed absorption bands at 1579 and 3347 cm^{-1} due to carbonyl and hydroxy functions, respectively. HRMS measurements ($[M + H]^+$ *m/z* 353.1869) yielded the molecular formula $C_{21}H_{24}N_2O_3$ (DBE = 11).

The ^1H NMR data (Table 2.22) showed the presence of three aromatic hydrogens (δ 7.29–7.89), an ethylidene side chain (δ 1.59, 5.36), an aminomethylene group (δ 3.78, 2H; CH_2-21), a hydroxymethyl group (δ 3.49, 3.69; $HOCH_2$-17), an N-1-Me singlet (δ 3.76), as well as an aromatic methoxy singlet (δ 3.93, OCH_3-10). The ^{13}C NMR data (Table 2.22) showed a total of 21 carbon resonances, comprising three methyl, three methylene, eight methine, a conjugated ketocarbonyl group (δ 171.5), an oxygenated tertiary carbon (δ 156.5), two tertiary carbons bonded to the indolic nitrogen, and three quaternary carbons. The COSY data showed the presence of the $NCHCH_2CHCH(CH_2)CH$ partial structure which corresponds to the N-4–C-3–C-14–C-15–C-16(C-17)–C-5 fragment present in sarpagine alkaloids (Figure 2.33).

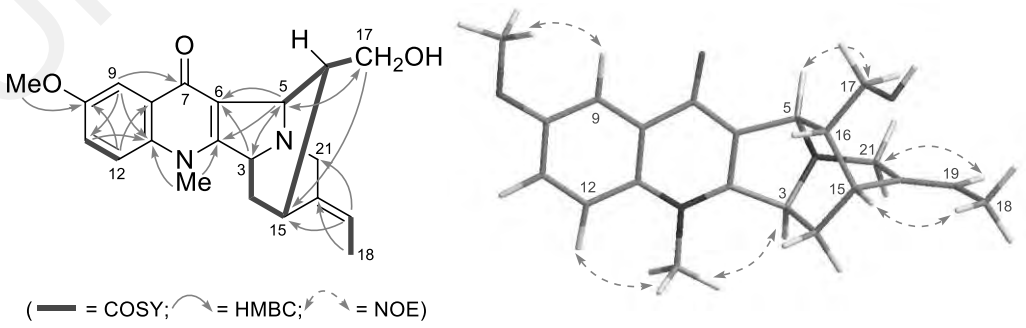


Figure 2.33: COSY, selected HMBCs, and selected NOEs of **37**

However, the terminal CH_2 fragment corresponding to C-6 in sarpagine compounds has been excised from the main fragment and the ^1H resonances due to H-6 were also not observed in the ^1H NMR spectrum of **37** (Figure 2.34). Another notable difference in the ^1H NMR data of **37** when compared to those of the other sarpagine-type compounds (e.g., 10-methoxyaffinisine **45**) is the observation that the aromatic H-9 resonance in **37** (δ 7.89, Table 2.22) was significantly deshielded compared to H-9 of sarpagine compounds (e.g., δ 6.92 in **45**), suggestive of the effect of anisotropy exerted by some proximate group. The conjugated ketocarbonyl resonance observed at δ 171.5 was assigned to C-7 from the three-bond correlations (Figure 2.33) observed from H-9 to the carbonyl C-7 in the HMBC spectrum, while C-6 is a quaternary sp^2 carbon linked to C-7 and C-2, forging a 4-quinolone (instead of indole) chromophore. These conclusions are supported by the observed H-5 to C-2 and H-3 to C-6 three-bond correlations in the HMBC spectrum. The significant deshielding of H-9 in **37** is likely due to anisotropy exerted by the π-electrons of the proximate carbonyl group. The HMBC and NOESY data were entirely consistent with the proposed structure and the relative configuration. Alkaloid **37** is likely derived from 10-methoxyaffinisine (**45**) via oxidative cleavage of the indole α,β-bond, followed by intramolecular ring closure.[387,388]

2.1.3.7 Alstopenidine G (38)

Alstopenidine G (**38**) was obtained as a yellowish oil, with $[\alpha]^{25}_D$ +34 (*c* 0.20, $CHCl_3$). The UV spectrum showed similar absorption maxima as the previous compound **37** (204, 215, 224, 253, 261, 332, 347 nm), indicating the presence of the similar quinolone chromophore while the IR spectrum showed the presence of carbonyl (1589 cm^{-1}) and hydroxy (3363 cm^{-1}) functions. The HRESIMS data ($[M + H]^+$ *m/z* 369.1824) yielded the molecular formula $C_{21}H_{24}N_2O_4$, 16 mass units higher than that of **37**, suggestive of

an *N*-oxide. Further support for this inference was provided by the NMR data which were similar to those of **37** except for the deshielding of H-3, H-5, and H-21 in the ^{1}H NMR spectrum, and of C-3, C-5, and C-21 in the ^{13}C NMR spectrum of **38** compared to those of **37** (Table 2.22; Figures 2.34–2.35). Compound **38** is therefore, the N-4-oxide of alstopenidine F (**37**).

Table 2.22: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Alstopenidine F (**37**) and Alstopenidine G (**38**)[a]

H/C	**37**		**38**	
	δ_C	**δ_H (*J*/Hz)**	**δ_C**	**δ_H (*J*/Hz)**
2	160.4	-	155.6	-
3	59.3	4.35 dd (8.8, 2.3)	75.3	4.98 d (9.2)
5	60.5	4.14 d (1.6)	78.3	4.76 br s
6	125.7	-	119.5	-
7	171.5	-	171.9	-
8	129.4	-	129.6	-
9	105.9	7.89 d (3.0)	106.0	7.83 d (3.0)
10	156.5	-	156.9	-
11	122.1	7.29 dd (9.0, 3.0)	122.3	7.30 dd (9.3, 3.0)
12	116.8	7.44 d (9.0)	117.1	7.45 d (9.3)
13	135.3	-	135.5	-
14β	29.9	1.85 m	30.9	2.20 m
14α		1.96 ddd (13.0, 8.8, 2.4)		2.41 m
15	31.5	3.07 m	30.6	3.18 m
16	43.7	2.06 m	45.0	2.49 m
17a	65.7	3.49 dd (10.5, 6.6)	63.9	3.51 dd (11.0, 7.0)
17b		3.69 dd (10.5, 8.5)		3.77 m
18	12.4	1.59 dt (6.8, 2.0)	12.5	1.63 d (6.8)
19	115.3	5.36 q (6.8)	118.0	5.40 br q (6.8)
20	135.3	-	130.4	-
21	49.1	3.78 m	64.6	4.49 m
		3.78 m		4.49 m
N(1)-Me	36.0	3.76 s	36.5	3.80 s
10-OMe	55.8	3.93 s	55.8	3.91 s

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY.

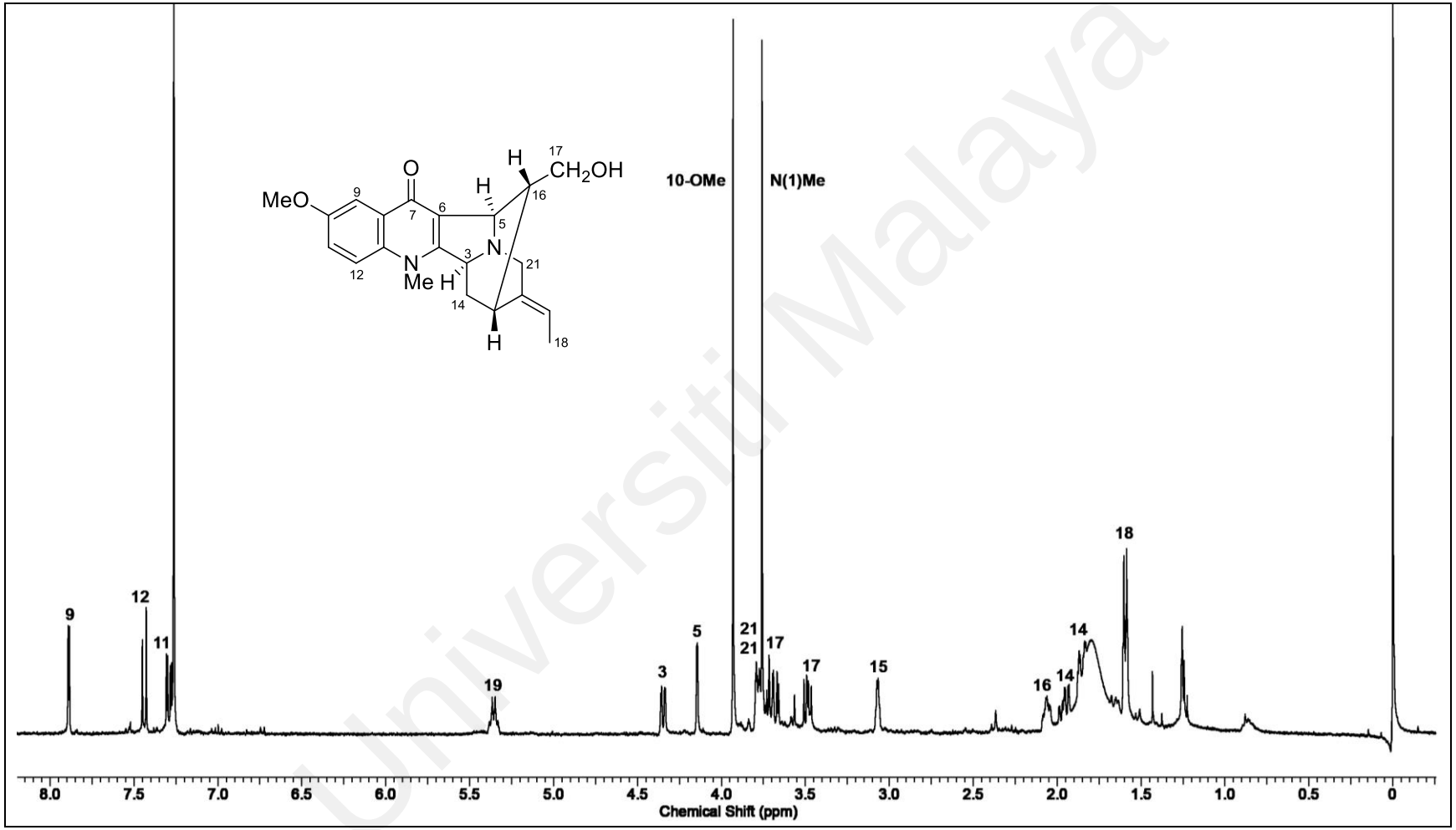


Figure 2.34: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstopenidine F (**37**)

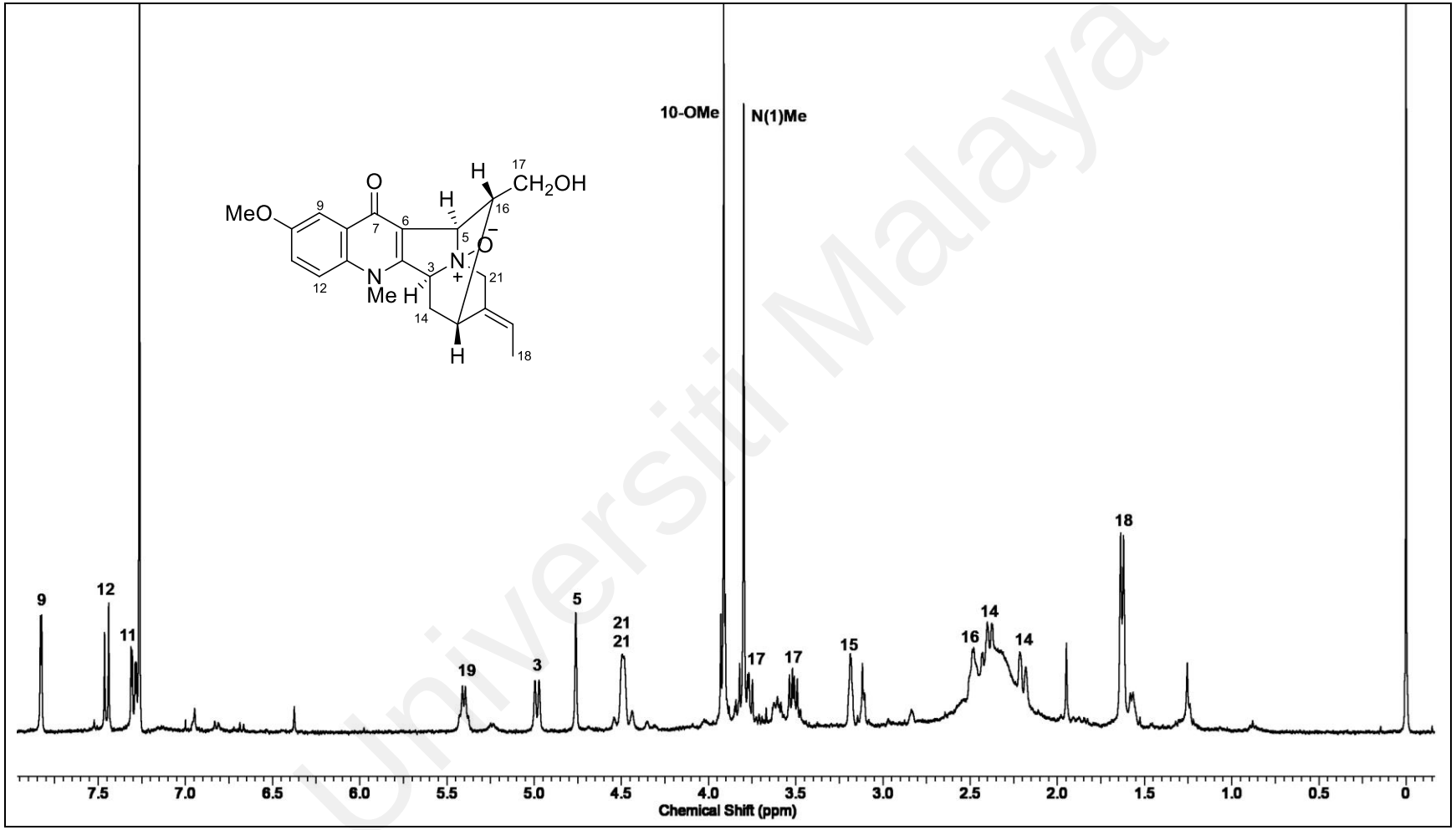


Figure 2.35: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstopenidine G (**38**)

2.1.3.8 Alstopenidine H (39)

Alstopenidine H (**39**) was obtained as a light yellowish oil, with $[\alpha]^{25}_{D}$ −107 (*c* 0.07, $CHCl_3$). The UV spectrum showed presence of an indolenine chromophore (204, 232, and 279 nm) while the IR spectrum showed the presence of an ester carbonyl (1736 cm^{-1}) function. The HRESIMS data showed an $[M + H]^+$ peak at *m/z* 369.1825, which analyzed for $C_{21}H_{24}N_2O_4$ + H. The NMR spectroscopic data (Tables 2.23, Figure 2.36) indicated an akuammiline-type alkaloid and were very similar to those of 11-methoxystrictamine (**49**). However, the resonances of H-3, H-5, and H-21 (in the ^1H NMR spectrum), as well as of the corresponding C-3, C-5, and C-21 (in the ^{13}C NMR spectrum), were significantly deshielded compared to those of **49**. This observation coupled with the fact that the M^+ of **39** is 16 mass units higher than that of 11-methoxystrictamine (**49**), allowed the identification of compound **39** as the N-4-oxide of 11-methoxystrictamine.

Table 2.23: ^1H and ^{13}C NMR Spectroscopic Data (δ) of Alstopenidine H (11-Methoxystrictamine *N*(4)-oxide) (**39**)[a]

H/C	δ_C	δ_H (*J*/Hz)	H/C	δ_C	δ_H (*J*/Hz)
2	182.0		14	33.9	1.98 m
3	78.0	5.10 d (4.5)	14		3.09 m
5	69.4	3.15 m	15	30.3	3.56 m
5		3.47 m	16	54.5	2.15 d (3.1)
6	24.8	2.00 m	18	13.4	1.62 dd (6.7, 2.0)
6		3.47 m	19	125.0	5.75 br q (6.7)
7	53.2		20	128.9	
8	136.5		21	72.1	4.04 d (16.0)
9	123.9	7.30 d (8.3)	21		4.52 br d (16.0)
10	112.7	6.77 br d (8.3)	11-OMe	55.7	3.84 s
11	160.8	-	$\underline{C}O_2Me$	170.8	
12	107.6	7.25 br s	$CO_2\underline{Me}$	52.0	3.74 s
13	156.5	-			

[a]$CDCl_3$, 400 (^1H) and 100 MHz (^{13}C); assignments based on COSY, HSQC, HMBC.

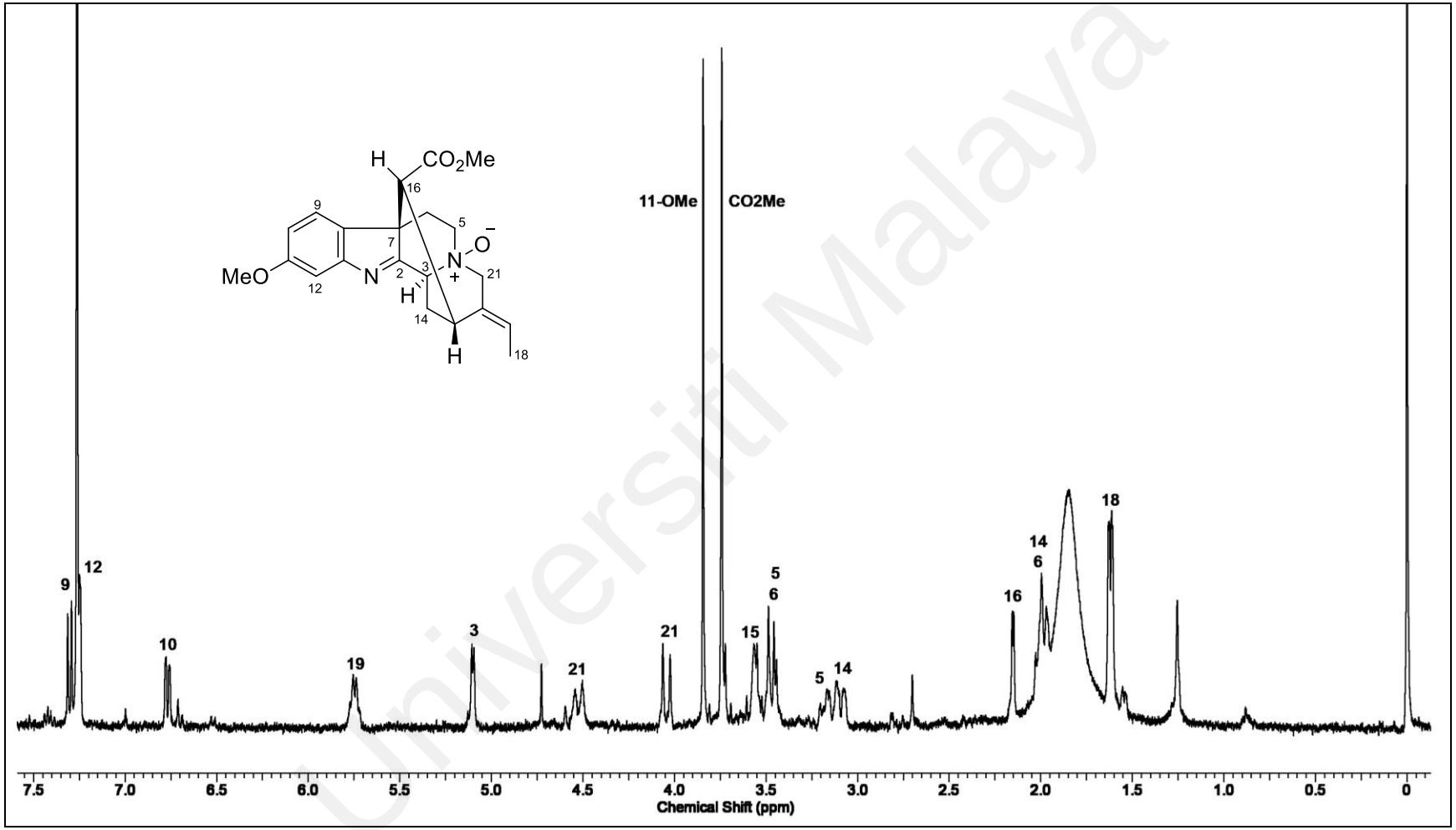


Figure 2.36: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstopenidine H (**39**)

2.1.3.9 Alstochalotine (40)

Alstochalotine (**40**) was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ +11.3 (*c* 0.2, $CHCl_3$). The UV spectrum of **40** did not exhibit any significant absorption maximum, while the IR spectrum indicated the presence of hydroxy (3430 cm^{-1}) and various carbonyl (1757, 1734 cm^{-1}) functions. The HRESIMS data ($[M + H]^+$ *m/z* 266.1398) yielded the molecular formula $C_{14}H_{19}NO_4$.

The ^1H NMR data (Table 2.24) showed the presence of an ethylidene side chain (δ 1.55 br d, 5.22 q; *J* = 6.8 Hz), an aminomethylene (δ 3.61, 2H, CH_2-21), a hydroxymethyl (δ 3.77, 3.98, $HOCH_2$-17), and a methyl ester group (δ 3.70, CO_2Me). The ^{13}C NMR data of **40** showed the presence of a ketocarbonyl (δ 216.8), an ester carbonyl (δ 175.1), two methyl, four methylene, four methine, and two quaternary carbon atoms, for a total of 14 carbon resonances. The COSY and HSQC data (Figure 2.37) revealed three spin systems with partial structures $NCHCH_2CH$, $NCHCH_2$, and CH_3CH, the latter fragment corresponding to the ethylidene side chain. Consideration of the HMBC data (Figure 2.37) allowed assembly of the molecule, a 3,7-methano-bridged indolizidine derivative as shown in structure **40**. A search of the literature revealed that a compound with a similar carbon skeleton, gelsochalotine, has been recently reported from *Gelsemium elegans*.[389]

The ^1H NMR data (Table 2.24) of **40** and gelsochalotine showed a general similarity except for the downfield shift of H-5 to δ 4.61 in compound **40** from δ 3.27 in gelsochalotine. Likewise, the ^{13}C NMR data (Table 2.24) were also similar, except for the resonances of C-15 and C-17, which in **40** were shifted upfield to δ 31.7 and 64.4, respectively, compared to δ 36.4 and 68.6, in gelsochalotine.[389] These differences are likely due to a change in the configuration at C-16. The absolute configuration of gelsochalotine (16*S*) was previously established by X-ray diffraction. In the case of **40**, the NOESY data indicated a change in the C-16 configuration to 16*R*. Thus, for

compound **40**, NOEs were observed between H-17 and H-6β, H-17 and H-14β, as well as between Me-18 and CO_2Me (Figure 2.38). This is only possible in the 16*R* compound **40**, since in the case of the 16*S* gelsochalotine, the hydroxymethyl ($HOCH_2$-17) group will be oriented away and in the opposite direction from the C-6 and C-14 hydrogens. The same is true for the Me-18 and CO_2Me groups, which will be oriented in opposite directions in the 16*S* gelsochalotine. Another difference between the two compounds has to do with the configuration of the 19,20-double bond. In gelsochalotine, the configuration of the 19,20-double bond is *Z* as shown by X-ray diffraction, as well as by the NOESY data (NOEs for H-19/H-15, Me-18/H-21).[389] In the case of the present compound **40**, NOEs were observed for H-19/H-21 and Me-18/H-15, indicating that in **40**, the ethylidene side chain is *E*-configured. Alstochalotine (**40**) therefore differs from gelsochalotine in the configuration at C-16 as well as the configuration of the 19,20-double bond. Compound **40** is likely a degradation product from a sarpagine oxindole precursor.[389] The ^{1}H NMR spectrum of **40** is shown in Figure 2.39.

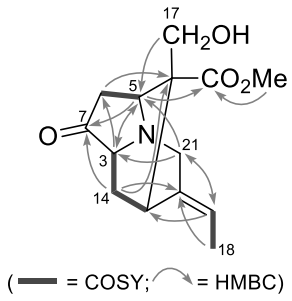


Figure 2.37: COSY and selected HMBCs of **40**

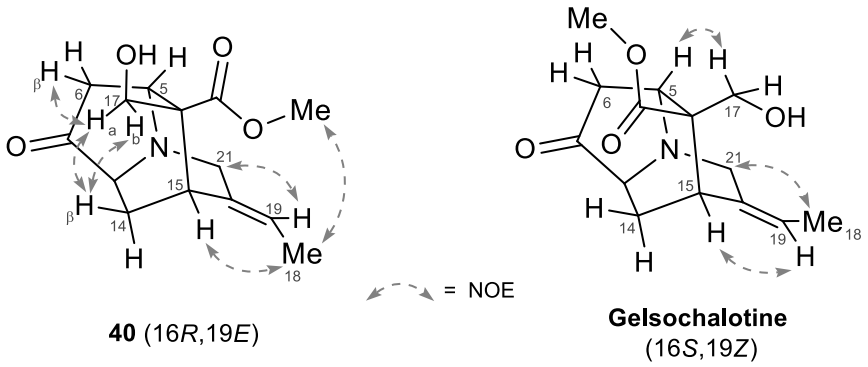


Figure 2.38: Selected NOEs of **40** and gelsochalotine

Table 2.24: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Alstochalotine (**40**)[a]

H/C	δ_C	δ_H (*J*/Hz)	H/C	δ_C	δ_H (*J*/Hz)
3	60.5	3.28 dd (10.0, 2.0)	17a	64.4	3.77 d (10.8)
5	57.1	4.61 d (7.0)	17b		3.98 d (10.8)
6β	40.8	2.59 d (18.4)	18	12.4	1.55 br d (6.8)
6α		2.70 dd (18.4, 7.0)	19	115.4	5.22 q (6.8)
7	216.8	-	20	136.2	-
14β	26.4	1.73 ddd (14.5, 4.0, 2.0)	21	48.3	3.61 m
14α		1.82 ddd (14.5, 10.0, 2.0)	21		3.61 m
15	31.7	2.96 m	$\underline{C}O_2Me$	175.1	-
16	52.5	-	$CO_2\underline{Me}$	52.3	3.70 s

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY.

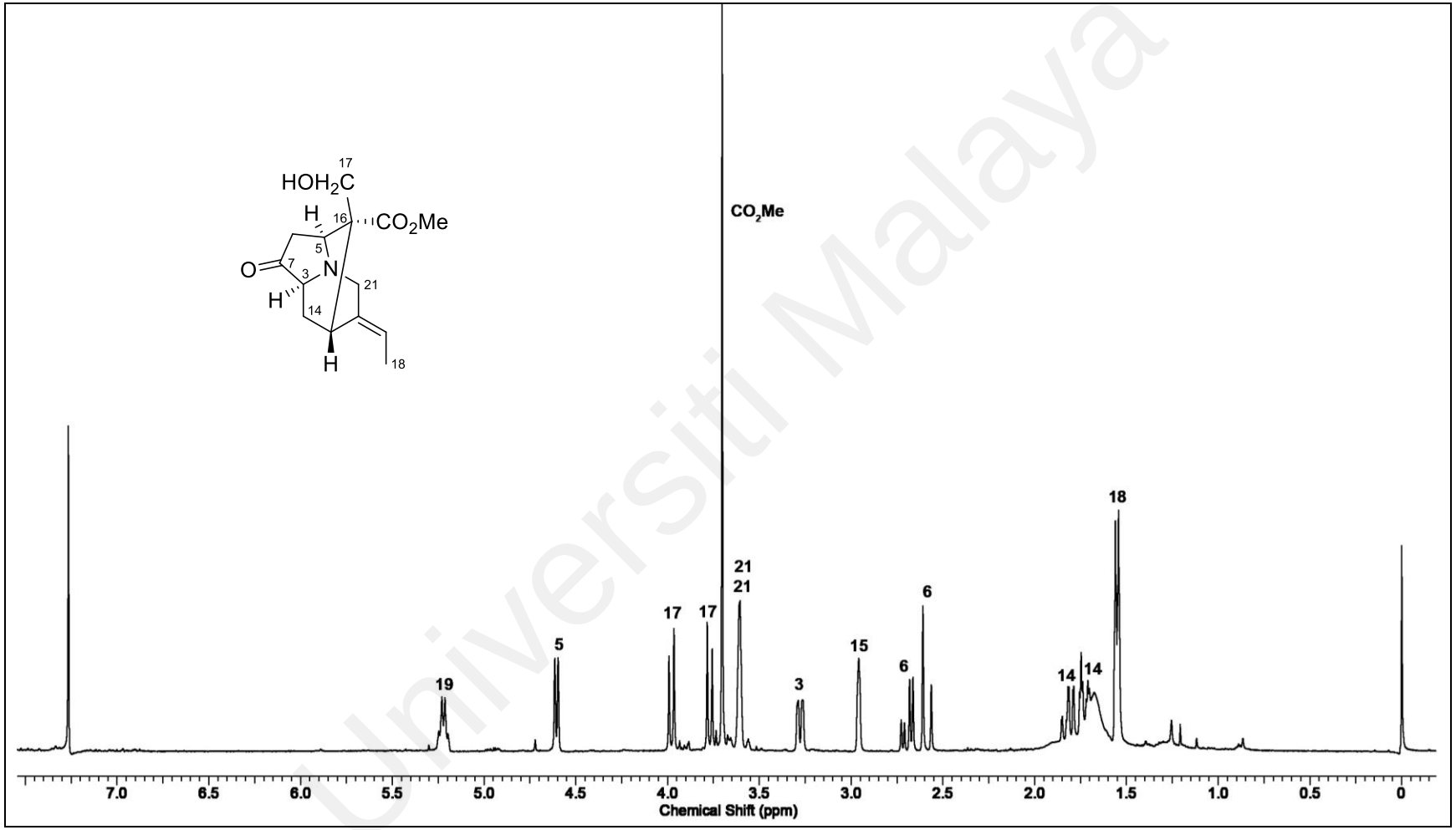


Figure 2.39: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstochalotine (**40**)

2.1.3.10 Alstomutinine C (41)

Alstomutinine C (**41**) was isolated as a yellowish oil, with $[\alpha]^{25}_{D}$ −134 (*c* 0.32, $CHCl_3$). HRMS measurements showed an $[M + H]^+$ ion at *m/z* 355.2011, from which the molecular formula, $C_{21}H_{26}N_2O_3$ was derived. The IR spectrum showed an absorption band at 1717 cm^{-1} due to a γ-lactam carbonyl function, while the UV spectrum (234, 256, and 285 nm) indicated an oxindole alkaloid.

The ^{1}H NMR data (Table 2.25) showed the presence of four aromatic resonances of an unsubstituted indole moiety (δ 6.81–7.29), an N-1 methyl singlet (δ 3.20), a methoxy singlet (δ 3.26), and another singlet due to an isolated methyl (δ 1.24, Me-18). The ^{13}C NMR data (Table 2.25) showed a total of 21 carbon resonances including three methyl, four methylene, nine methine, one tertiary carbon linked to the indolic nitrogen, one lactam carbonyl (δ 181.9), one acetal carbon (δ 100.2), and two quaternary carbon atoms.

The COSY data (Figure 2.40) showed the presence of a $CH_2CHCH(CH_2)CH(CHCH_2)CH_2CH$ fragment which corresponds to C-6–C-5–C-16(–C-17)–C-15(–C-20–C-21)–C-14–C-3 of a talpinine-type alkaloid. Further support for this was provided by the observed H-17, H-21/C-19, H-14, H-5/C-7, and H-6/C-2, C-8 three-bond correlations (Figure 2.40) in the HMBC spectrum.

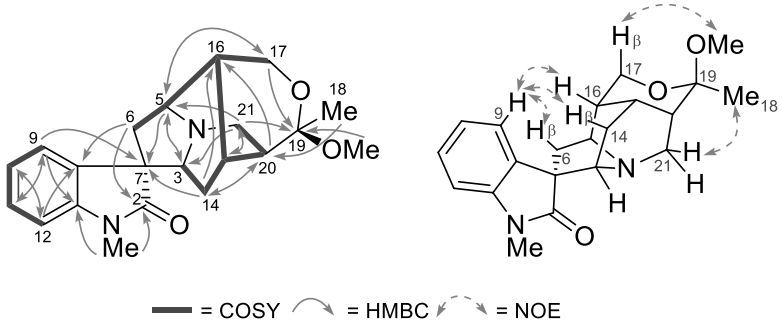


Figure 2.40: COSY, selected HMBCs, and selected NOEs of **41**

The NMR data were very similar to those of talpinine oxindole (**429**),[129] except for the presence of an aminomethylene (δ_H 3.08, 3.15, H-21; δ_C 44.5, C-21) in **41** in place of the hydroxymethine (δ_H 5.06, H-21; δ_C 84.4, C-21) in talpinine oxindole (**429**), and the presence of an additional methoxy group (δ_H 3.26; δ_C 48.3) in **41**, in place of the H-19 oxymethine (δ_H 4.07, H-19; δ_C 72.1, C-19) in talpinine oxindole. The methoxy group in **41** was linked to the acetal C-19 (δ 100.2) from the observed CH_3O to C-19 three-bond correlation (Figure 2.40) in the HMBC spectrum. In contrast to talpinine oxindole, Me-18 in **41** was observed as an isolated singlet instead of a doublet, indicating tetrasubstitution of the adjacent acetal C-19.

The relative configuration at C-7 was assigned as *S* based on the NOEs observed for H-9/H-6β, H-14β and H-16, while the orientations of Me-18 and MeO-19 were deduced to be α and β, respectively, from the observed Me-18/H-21 and MeO-19/H-17β NOEs (Figure 2.40). The ^{1}H NMR spectrum of **41** is shown in Figure 2.41.

Table 2.25: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Alstomutinine C (**41**)[a]

H/C	δ_C	δ_H (*J*/Hz)	H/C	δ_C	δ_H (*J*/Hz)
2	181.9	-	14β		1.99 ddd (15.0, 5.0, 2.0)
3	62.1	3.17 d (9.0)	15	21.3	2.31 m
5	60.8	3.42 dd (7.0, 2.0)	16	38.4	1.51 br s
6β	44.6	1.63 d (13.0)	17β	65.3	3.81 dd (11.0, 2.0)
6α		2.77 dd (13.0, 7.0)	17α		3.51 d (11.0)
7	56.7	-	18	19.8	1.24 s
8	130.7	-	19	100.2	-
9	126.6	7.20 d (8.0)	20	38.3	1.45 m
10	121.5	7.06 t (8.0)	21α	44.5	3.08 dd (15.0, 10.0)
11	128.1	7.29 t (8.0)	21β		3.15 dd (15.0, 4.0)
12	107.8	6.81 d (8.0)	N(1)-Me	26.6	3.20 s
13	144.5	-	OMe-19	48.3	3.26 s
14α	27.8	1.23 m			

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY.

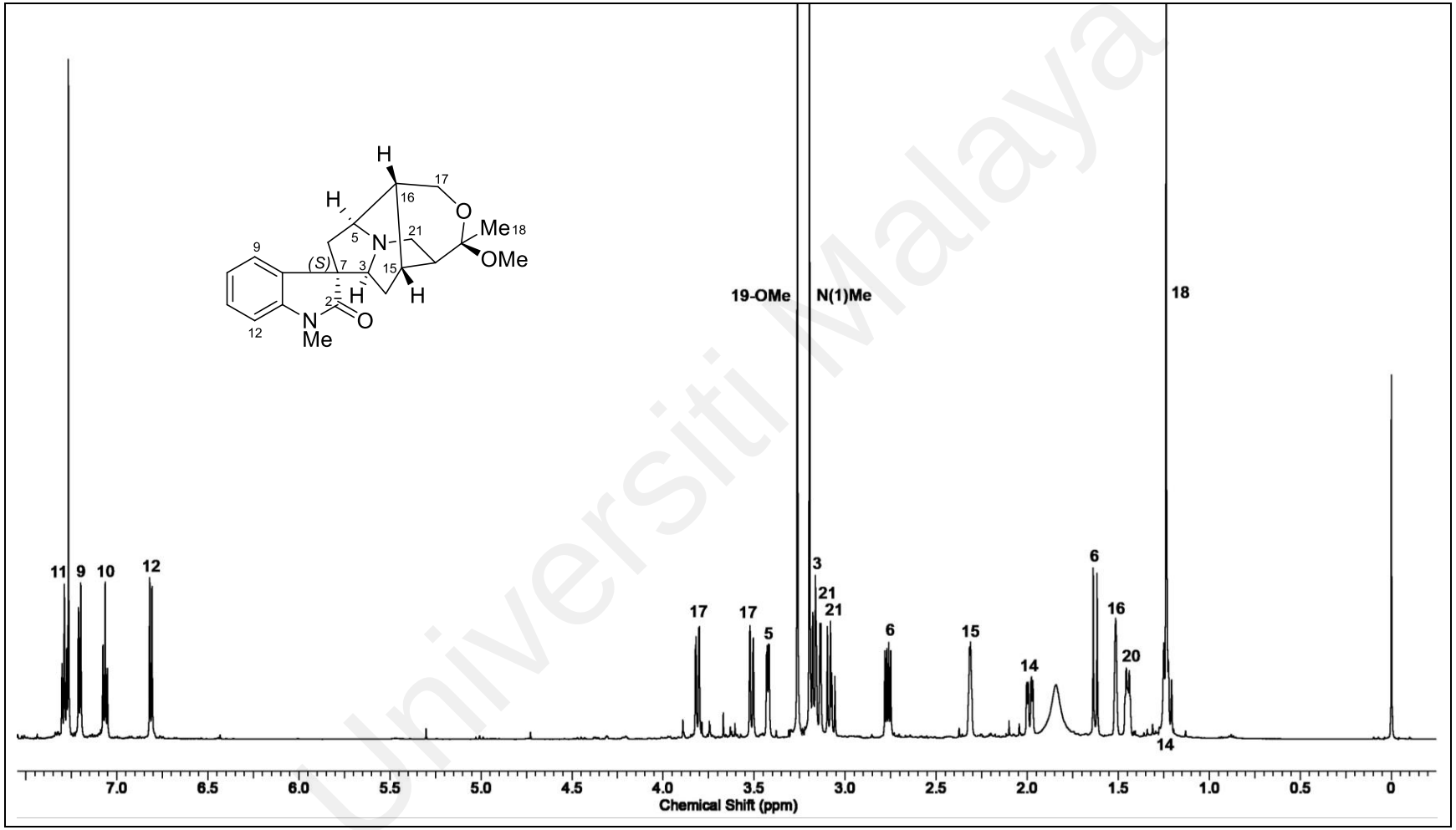


Figure 2.41: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Alstomutinine C (**41**)

2.1.3.11 Alstomutinines D (42) and E (43)

Compounds **42** (alstomutinine D, major epimer) and **43** (alstomutinine E, minor epimer) co-eluted in column chromatography and were obtained as an inseparable mixture (ratio: 2:1), which resisted all further attempts at chromatographic resolution, including resort to chiral-phase HPLC (see Figure 2.42). As it turned out these compounds exist as a mixture due to a property of the molecule, which results in the rapid establishment of a dynamic equilibrium of the two forms under ambient conditions (*vide infra*).

The **42**/**43** mixture was obtained as a light yellowish oil. The IR spectrum showed the presence of lactam carbonyl (1709 cm^{-1}) and OH (3390 cm^{-1}) functionalities, while the UV spectrum showed the presence of oxindole chromophores (211, 255, and 285 nm). The ESIMS showed the presence of only one $[M + H]^+$ peak at *m/z* 327 and HRMS measurements (*m/z* 327.1707) yielded the molecular formula $C_{19}H_{22}N_2O_3$.

The ^1H and ^{13}C NMR data (Table 2.26) showed two sets of resonances corresponding to the two isomers present (ratio: ca. 2:1). In the ^{13}C NMR spectrum of the mixture, nearly all the resonances were duplicated, occurring in pairs (17) with very close chemical shifts and with several resonances (2) coincident (Table 2.26). A similar situation was observed in the ^1H NMR spectrum, with five out of a total of 19 resonances coincident/overlapped (Table 2.26). Furthermore, each of the two sets of ^1H resonances accounted for the presence of four aromatic hydrogens of an unsubstituted indole moiety, an N-1–methyl, an oxymethylene (OCH_2-17), and a methine (H-19) linked to two oxygen atoms and associated with a hemiacetal group.

The NMR data showed many features which were also present in talpinine oxindole (**429**)[129] and the previous compound **41**, suggesting the presence of a similar talpinine-type oxindole alkaloid. Comparison of the ^1H and ^{13}C NMR data (Table 2.26) with that of talpinine oxindole showed the following differences: first, the methyl doublet (δ_H 1.33, Me-18) linked to the oxymethine C-19 (δ_C 72.1) was absent and was replaced by

OH, since C-19 was a hemiacetal (δ_C 95.3, 97.0) in **42**/**43**; second, the hydroxymethine C-21 (δ_C 84.8) in talpinine oxindole was a methylene in **42**/**43** (δ_C 45.2, 40.9). The 2D NMR data (COSY and HMBC, Figure 2.43) were consistent with the talpinine-type oxindole hemiacetal structures **42** and **43**. In the ^{13}C NMR spectrum, marked differences between the two isomers were observed for the resonances for C-15 and C-17 (**42**: δ 20.1, 63.4, respectively; **43**: *δ* 26.9, 69.3, respectively). This suggests that **42** and **43** are C-19 epimers since C-15 and C-17 are γ relative to the OH substituted α carbon, C-19, in the same tetrahydropyran ring. As such, the shift differences could therefore be explained by the γ-*gauche* effect.[390,391] In the case of epimer **42** with an axially-oriented OH at C-19 (C-19–βOH), C-15 and C-17 (with 1,3-diaxially substituted hydrogens in the six-membered ring) will experience shielding due to the γ-*gauche* effect. These considerations allow the assignment of the major C-19–βOH epimer **42** and the minor C-19–αOH epimer **43**. Consideration of the NOESY data (NOE observed for H-19/H-21β in **42** and for H-19/H-15, H-17β in **43**, Figure 2.44) led to similar conclusions. Under ambient conditions, the epimers **42** and **43** undergo rapid interconversion (Figure 2.45) via intermediacy of an open chain form, with the equilibrium favoring the C-19–βOH epimer. The ^{1}H NMR spectrum of **42**/**43** is shown in Figure 2.46.

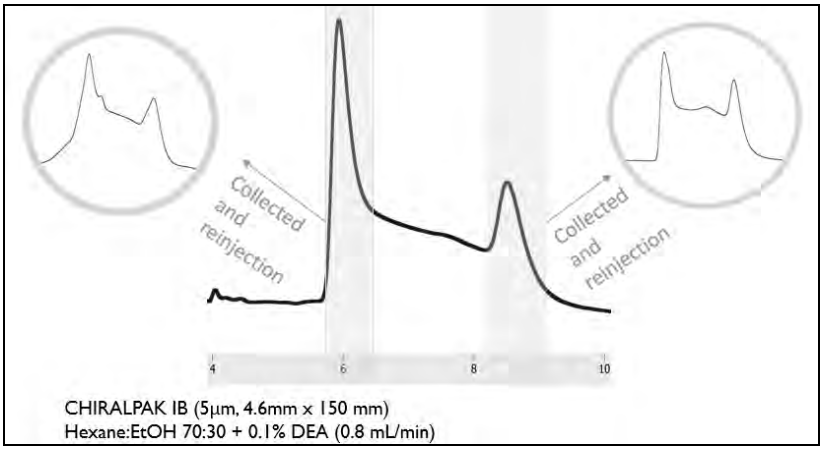


Figure 2.42: HPLC chromatogram of the mixture **42** and **43**

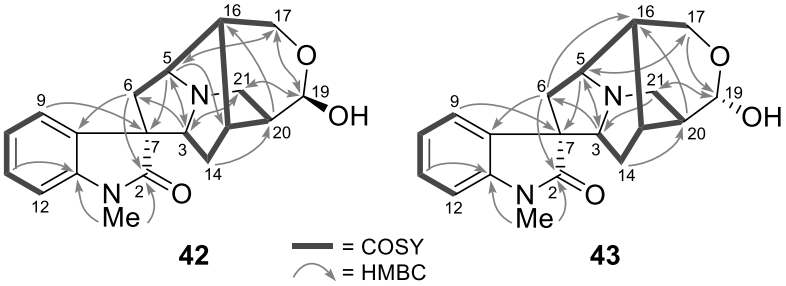


Figure 2.43: COSY and selected HMBCs of **42** and **43**

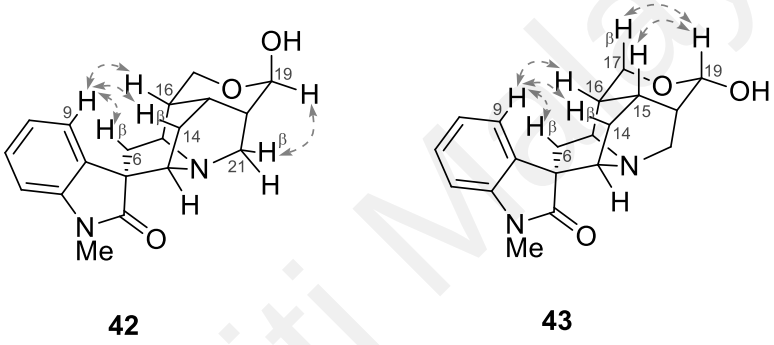


Figure 2.44: Selected NOEs of **42** and **43**

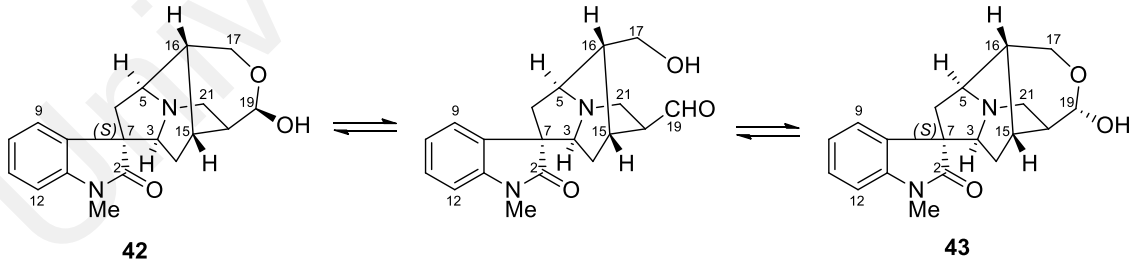


Figure 2.45: Interconversion of **42** and **43** via an open chain hydroxyaldehyde intermediate

Table 2.26: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Alstomutinine D (**42**) and Alstomutinine E (**43**)[a]

H/C	42		43	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	181.98	-	181.88	-
3	62.65	3.19 m	62.54	3.19 m
5	60.14	3.48 m	60.65	3.44 dd (6.0, 2.0)
6β	44.83	1.63 d (13.0)	44.57	1.63 d (13.0)
6α		2.75 dd (13.0, 6.0)		2.77 dd (13.0, 6.0)
7	56.62	-	56.57	-
8	130.73	-	130.67	-
9	126.73	7.20 d (8.0)	126.58	7.18 d (8.0)
10	121.67	7.06 t (8.0)	121.63	7.05 t (8.0)
11	128.21	7.28 t (8.0)	128.26	7.28 t (8.0)
12	107.99	6.80 d (8.0)	108.03	6.80 d (8.0)
13	144.56	-	144.56	-
14α	27.63	1.25 m	28.16	1.30 dd (15.0, 10.0)
14β		1.98 br dd (15.0, 5.0)		2.02 ddd (15.0, 5.0, 2.0)
15	20.05	2.21 m	26.94	1.76 m
16	39.18	1.56 br s	38.41	1.49 br s
17α	63.44	3.48 m	69.31	3.84 dd (11.0, 1.0)
17β		4.17 dd (11.0, 1.0)		3.59 dd (11.0, 1.0)
19	95.33	4.98 s	96.97	4.69 s
20	34.21	1.64 m	35.73	1.68 m
21β	45.18	3.04 dd (15.0, 4.0)	40.91	3.39 dd (15.0, 3.0)
21α		3.11 dd (15.0, 10.0)		2.95 dd (15.0, 10.0)
N(1)-Me	26.64	3.19 s	26.64	3.19 s

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY.

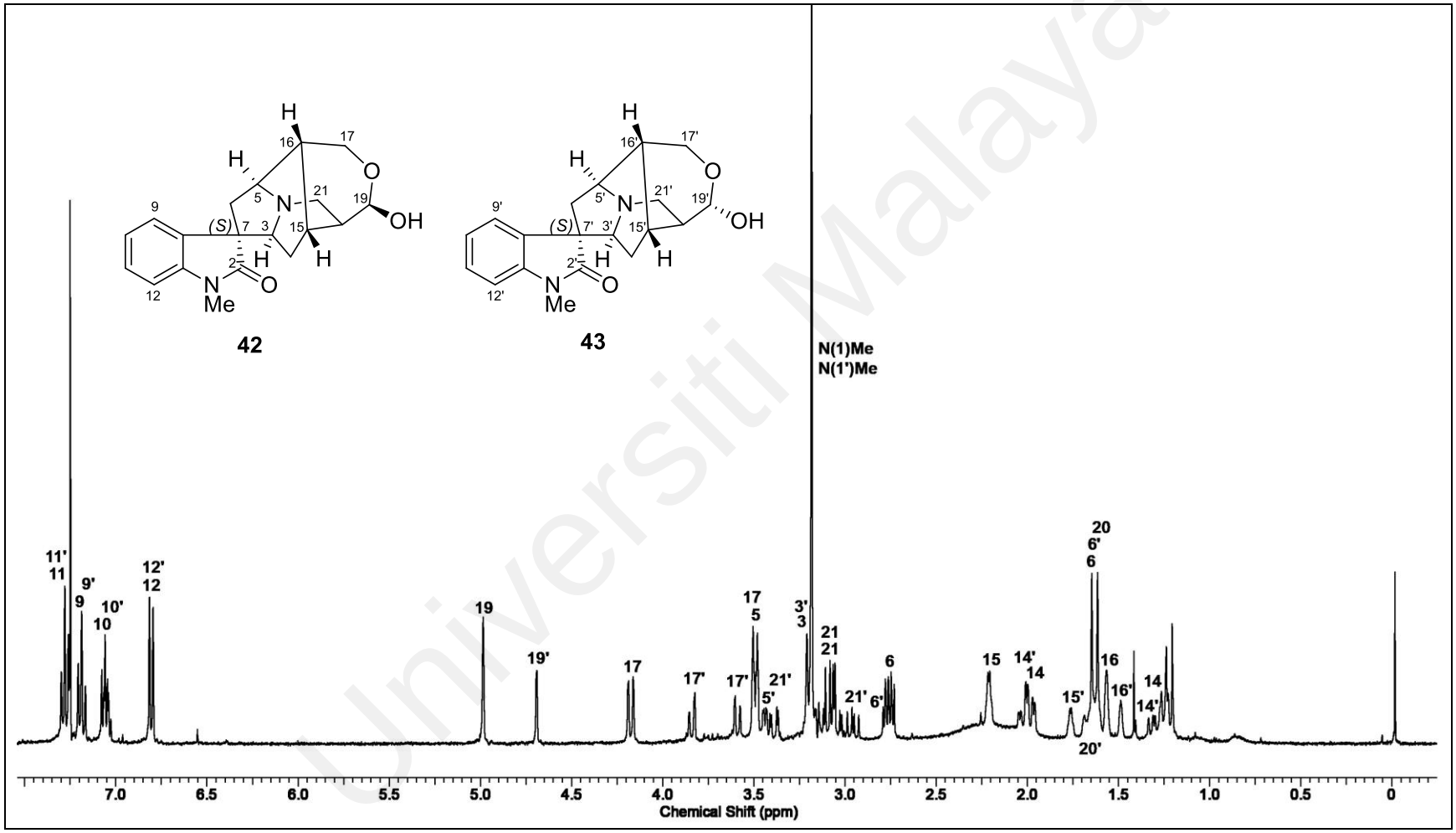


Figure 2.46: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstomutinine D (**42**) and Alstomutinine E (**43**)

2.1.3.12 Affinisine (44), 10-Methoxyaffinisine (45), 10-Methoxyaffinisine *N*(4)-oxide (46), Lochnerine (47), and Alstoumerine (48)

Five known sarpagine-type alkaloids including affinisine (**44**),[174,392-394] 10-methoxyaffinisine (**45**),[136] 10-methoxyaffinisine *N*(4)-oxide (**46**),[395] lochnerine (**47**),[386,396] and alstoumerine (**48**) [52,161] were also isolated in the present study. The ^{1}H and ^{13}C NMR data of these compounds are summarized in Tables 2.27–2.29, and their ^{1}H NMR spectra are shown in Figures A19–A23 (see Appendix). Other data are given in the Experimental Section.

Table 2.27: ^{1}H NMR Spectroscopic Data (δ) of Affinisine (**44**), 10-Methoxyaffinisine (**45**), 10-Methoxyaffinisine *N*(4)-oxide (**46**), and Lochnerine (**47**)[a]

H	44 (*J*/Hz)	45 (*J*/Hz)	46 (*J*/Hz)[b]	47 (*J*/Hz)
3	4.17 dd (10.0, 2.0)	4.20 dd (10.0, 2.0)	4.52 br d (10.0)	4.06 dd (10.0, 2.0)
5	2.24 m	2.79 m	3.15 m	2.76 m
6	2.60 dd (15.0, 1.0)	2.59 dd (15.0, 1.0)	2.69 d (15.7) (β)	2.62 dd (15.0, 1.0)
	3.01 dd (15.0, 5.0)	3.04 dd (15.0, 5.0)	3.62 m (α)	3.00 dd (15.0, 5.0)
9	7.42 br d (8.0)	6.92 d (1.0)	6.92 d (2.0)	6.91 d (1.0)
10	7.07 td (8.0, 1.0)	-	-	-
11	7.18 td (8.0, 1.0)	6.83 dd (8.0, 1.0)	6.86 dd (9.0, 2.0)	6.78 dd (8.0, 1.0)
12	7.28 br d (8.0)	7.17 d (8.0)	7.17 d (9.0)	7.19 d (8.0)
14	1.60 ddd (12.0, 4.0, 2.0)	1.67 ddd (12.0, 4.0, 2.0)	1.96 br d (12.4) (β)	1.71 ddd (12.0, 4.0, 2.0)
	2.03 ddd (12.0, 10.0, 2.0)	2.01 ddd (12.0, 10.0, 2.0)	2.44 br dd (12.4, 10.0) (α)	2.01 ddd (12.0, 10.0, 2.0)
15	2.74 m	2.79 m	2.87 m	2.76 m
16	1.75 tdd (8.0, 6.0, 2.0)	1.81 tdd (8.0, 6.0, 1.0)	2.18 br td (8.0, 6.0)	1.83 tdd (8.0, 6.0, 1.0)
17	3.47 m	3.54 m	3.50 m	3.42 m
	3.47 m	3.54 m	3.54 m	3.42 m
18	1.61 dt (7.0, 2.0)	1.63 dt (7.0, 2.0)	1.65 d (6.8)	1.61 dt (7.0, 2.0)
19	5.36 br q (7.0)	5.40 br q (7.0)	5.46 br q (6.8)	5.36 br q (7.0)
21	3.55 m	3.54 m	4.05 br d (16.0) (β)	3.42 m
	3.55 m	3.54 m	4.35 br d (16.0) (α)	3.42 m
N(1)-Me	3.61 s	3.59 s	3.60 s	-
NH	-	-	-	8.02 br s
10-OMe	-	3.85 s	3.85 s	3.85 s

[a]$CDCl_3$, 400 MHz. [b]Assignments based on COSY, HSQC, and NOESY.

Table 2.28: ^{13}C NMR Spectroscopic Data (δ) of Affinisine (**44**), 10-Methoxyaffinisine (**45**), 10-Methoxyaffinisine *N*(4)-oxide (**46**), and Lochnerine (**47**)[a]

C	44	45	46[b]	47
2	139.4	140.2	135.3	138.7
3	49.2	49.2	65.8	50.8
5	54.5	54.4	68.8	54.9
6	27.2	27.4	24.1	27.1
7	103.4	103.1	101.7	104.1
8	127.2	127.6	127.0	127.6
9	118.0	100.6	100.8	100.5
10	118.6	153.7	154.2	153.8
11	120.6	110.5	111.6	111.9
12	108.5	109.3	109.7	110.0
13	137.1	132.6	133.1	131.6
14	32.5	32.8	33.1	33.4
15	27.0	27.1	26.2	27.6
16	44.0	44.2	44.2	44.2
17	64.6	64.9	63.5	65.0
18	12.6	12.7	12.8	12.8
19	116.2	116.5	119.4	116.8
20	135.6	135.8	131.1	135.1
21	55.9	56.2	71.6	55.7
N(1)-Me	29.1	29.6	29.7	-
10-OMe	-	56.0	56.0	56.0

[a]$CDCl_3$, 100 MHz. [b]Assignments based on HSQC and HMBC.

Table 2.29: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Alstoumerine (**48**)[a]

H/C	δ_C	δ_H (*J*/Hz)
2	139.4	-
3	48.6	3.88 dd (10.0, 2.0)
5	56.4	3.03 t (6.0)
6	29.6	2.69 d (15.0)
6		3.12 dd (15.0, 6.0)
7	102.5	-
8	127.2	-
9	118.1	7.48 br d (8.0)
10	118.9	7.10 td (8.0, 1.0)
11	121.0	7.19 td (8.0, 1.0)
12	108.7	7.28 br d (8.0)
13	137.4	-
14	38.7	1.61 m
14		1.88 ddd (12.0, 10.0, 2.0)
15	29.2	2.78 br s
16	44.4	1.61 m
17	64.6	3.46 dd (12.0, 5.0)
17		3.62 dd (12.0, 4.0)
18	22.3	1.36 d (7.0)
19	67.3	4.52 d (7.0)
20	149.3	-
21	136.4	6.54 d (1.0)
N(1)-Me	25.4	3.58 s

[a] $CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C).

2.1.3.13 11-Methoxystrictamine (49), 11-Hydroxystrictamine (50), 10-Methoxyvincamidine (51), Cathafoline (52), Cathafoline *N*(4)-oxide (53), Vincorine (54), Norvincorine (55), and Demethoxyalstonamide (56)

Eight known akuammiline-type alkaloids including 11-methoxystrictamine (**49**),[397] 11-hydroxystrictamine (**50**),[126] 10-methoxyvincamidine (**51**),[398] cathafoline (**52**),[136,399] cathafoline *N*(4)-oxide (**53**),[168,399] vincorine (**54**),[380,400,401] norvincorine (**55**),[400] and demethoxyalstonamide (**56**)[161] were also isolated in the present study. The ^{1}H and ^{13}C NMR data of these compounds are summarized in Tables 2.30–2.33, and their ^{1}H NMR spectra are shown in Figures A24–A31 (see Appendix). Other data are given in the Experimental Section.

Table 2.30: ^{1}H NMR Spectroscopic Data (δ) of 11-Methoxystrictamine (**49**), 11-Hydroxystrictamine (**50**), and 10-Methoxyvincamidine (**51**)[a]

H	49 (*J*/Hz)	50 (*J*/Hz)	51 (*J*/Hz)[b]
3	4.71 d (5.0)	4.68 d (5.0)	4.67 d (5.0)
5	2.60 td (14.0, 5.0)	2.58 td (14.0, 5.0)	2.63 m
5	2.75 dd (14.0, 6.0)	2.72 dd (14.0, 6.0)	2.73 dd (15.0, 6.0)
6	1.99 dd (14.0, 5.0)	1.98 dd (14.0, 5.0)	1.98 dd (15.0, 5.0)
6	3.67 td (14.0, 6.0)	3.67 td (14.0, 6.0)	3.70 m
9	7.31 d (8.0)	7.23 d (8.0)	7.01 d (1.5)
10	6.72 dd (8.0, 2.0)	6.64 dd (8.0, 2.0)	-
11	-	-	6.86 dd (8.0, 1.5)
12	7.20 d (2.0)	7.14 d (2.0)	7.52 d (8.0)
14	1.75 dd (14.0, 3.0)	1.74 dd (14.0, 3.0)	1.75 dd (14.0, 3.0)
14	2.69 ddd (14.0, 5.0, 3.0)	2.67 ddd (14.0, 5.0, 3.0)	2.67 m
15	3.52 br s	3.50 br s	3.51 br s
16	2.07 d (3.0)	2.09 d (3.0)	2.10 d (4.0)
18	1.55 dd (7.0, 2.0)	1.54 dd (7.0, 2.0)	1.55 dd (7.0, 2.0)
19	5.53 br q (7.0)	5.50 br q (7.0)	5.50 br q (7.0)
21	3.17 d (17.0)	3.12 d (17.0)	3.13 d (17.0)
	4.07 br d (17.0)	4.04 br d (17.0)	4.06 br d (17.0)
10-OMe	-	-	3.80 s
11-OMe	3.79 s	-	-
CO_2Me	3.72 s	3.72 s	3.72 s

[a]$CDCl_3$, 400 MHz. [b]Assignments based on COSY, HSQC, and HMBC.

Table 2.31: ^{13}C NMR Spectroscopic Data (δ) of 11-Methoxystrictamine (**49**), 11-Hydroxystrictamine (**50**), and 10-Methoxyvincamidine (**51**)[a]

C	49	50	51[b]
2	189.5	191.9	188.4
3	55.1	54.6	55.0
5	51.6	51.7	51.8
6	32.0	33.4	33.2
7	55.3	55.4	56.2
8	138.0	137.0	147.7
9	123.6	123.8	110.3
10	111.7	113.0	158.1
11	160.3	157.6	112.8
12	107.0	108.4	121.2
13	156.8	156.0	149.1
14	35.5	35.9	35.9
15	32.0	32.2	32.5
16	55.5	55.7	55.2
18	13.0	12.9	13.0
19	121.5	120.2	120.2
20	135.5	137.3	138.0
21	53.4	53.3	53.6
10-OMe	-	-	55.7
11-OMe	55.6	-	-
$\underline{C}O_2Me$	171.4	171.5	171.6
$CO_2\underline{Me}$	51.7	51.5	51.6

[a]$CDCl_3$, 100 MHz. [b]Assignments based on HSQC and HMBC.

Table 2.32: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Cathafoline (**52**) and Cathafoline *N*(4)-oxide (**53**)[a]

H/C	52		53	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	79.3	2.50 s	78.6	2.88 s
3	47.4	4.10 d (5.0)	69.8	4.64 d (5.0)
5	50.8	2.62 dd (14.0, 5.0)	66.8	3.36 dd (14.0, 6.0)
5		3.82 td (14.0, 5.0)		4.47 m
6	31.2	1.41 dd (15.0, 5.0)	29.3	1.73 dd (16.0, 6.0)
6		3.07 ddd (15.0, 14.0, 5.0)		3.21 ddd (16.0, 14.0, 6.0)
7	43.1	-	41.2	-
8	140.5	-	138.3	-
9	121.0	6.94 dd (8.0, 1.0)	121.2	6.69 br d (8.0)
10	119.4	6.69 td (8.0, 1.0)	120.1	6.75 td (8.0, 1.0)
11	127.2	7.09 td (8.0, 1.0)	128.0	7.15 td (8.0, 1.0)
12	109.4	6.60 dd (8.0, 1.0)	110.2	6.66 br d (8.0)
13	153.2	-	151.3	-
14	33.9	1.59 dd (14.0, 3.0)	31.5	1.87 dd (14.0, 2.0)
14		2.37 ddd (14.0, 5.0, 3.0)		2.82 m
15	34.4	3.59 br s	32.3	3.65 br s
16	52.9	2.96 d (3.0)	51.5	3.03 d (3.0)
18	13.0	1.50 dd (7.0, 3.0)	13.3	1.57 dd (7.0, 2.0)
19	119.2	5.38 br q (7.0)	124.1	5.62 br q (7.0)
20	139.3	-	129.8	-
21	54.9	2.90 d (16.0)	72.4	3.82 m
21		3.91 br d (16.0)		4.45 br d (13.0)
N(1)-Me	34.0	2.63 s	34.3	2.82 s
$\underline{C}O_2Me$	172.9	-	171.9	-
$CO_2\underline{Me}$	51.5	3.79 s	51.8	3.82 s

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C).

Table 2.33: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Vincorine (**54**), Norvincorine (**55**), and Demethoxyalstonamide (**56**)[a]

H/C	54		55		56	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	97.7	-	94.8	-	94.7	-
3	20.4	1.66 m	26.2	1.77 m	26.3	1.83 m
3		2.29 m		2.45 ddd (15.0, 11.0, 2.0)		2.37 ddd (16.0, 11.0, 2.0)
5	55.0	2.73 ddd (11.0, 9.0, 2.0)	54.3	2.80 ddd (12.0, 9.0, 1.0)	54.3	2.79 dd (12.0, 9.0)
5		3.38 td (11.0, 9.0)		3.62 m		3.21 ddd (12.0, 11.0, 8.0)
6	40.9	1.99 ddd (14.0, 9.0, 2.0)	40.5	2.07 m	41.3	2.02 m
6		2.47 ddd (14.0, 11.0, 9.0)		2.56 ddd (14.0, 11.0, 9.0)		2.56 ddd (14.0, 11.0, 9.0)
7	57.2	-	57.5	-	58.4	-
8	138.5	-	137.4	-	139.8	-
9	112.2	6.95 d (2.0)	112.4	6.93 d (2.0)	112.0	7.01 d (3.0)
10	152.0	-	153.4	-	157.0	-
11	111.3	6.63 dd (8.0, 2.0)	111.8	6.60 dd (8.0, 2.0)	110.0	6.74 dd (9.0, 3.0)
12	105.0	6.19 d (8.0)	109.6	6.48 d (8.0)	117.0	8.01 d (9.0)
13	143.7	-	141.4	-	132.3	-
14	26.3	1.77 m	26.3	1.86 m	27.7	1.83 m
14		1.77 m		1.86 m		2.02 m
15	34.7	3.60 d (4.0)	35.2	3.67 d (5.0)	35.4	3.71 br d (5.0)
16	50.7	2.80 d (2.0)	50.3	2.85 br s	49.9	2.83 br s
18	13.5	1.59 dd (7.0, 2.0)	13.6	1.60 dd (7.0, 2.0)	13.5	1.60 dd (7.0, 2.0)
19	122.3	5.40 br q (7.0)	124.0	5.46 br q (7.0)	123.2	5.44 br q (7.0)
20	139.0	-	137.9	-	138.9	-
21	58.3	3.00 d (15.0)	57.6	3.04 br d (15.0)	58.0	3.01 d (16.0)
21		3.80 br d (15.0)		3.93 br d (15.0)		3.91 br d (16.0)
N(1)-Me	27.9	2.58 s	-	-	-	-
10-OMe	56.0	3.73 s	55.9	3.73 s	55.6	3.78 s
$\underline{C}O_2Me$	173.6	-	173.3	-	173.0	-
$CO_2\underline{Me}$	51.6	3.79 s	51.7	3.80 s	51.8	3.82 s
N(1)-CHO	-	-	-	-	160.0	8.50 s

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C).

2.1.4 Ajmaline Alkaloids

2.1.4.1 Vincamaginine A (57)

Vincamaginine A (**57**) was obtained as a light yellowish oil, with $[\alpha]^{25}_{D}$ −172 (*c* 0.2, $CHCl_3$). The UV spectrum (215, 275, 298 nm) showed the presence of *N*-acyl dihydroindole and trimethoxybenzoyl chromophores. The IR spectrum displayed absorption bands at 1733 and 1652 cm^{-1}, due to the ester carbonyl and amide carbonyl groups, respectively. The molecular formula of **57** ($C_{41}H_{44}N_2O_{11}$) was established by HRESIMS measurements ($[M + H]^+$ *m/z* 741.3027), and corresponds to 21 degrees of unsaturation.

The ^1H NMR data of **57** (Table 2.34) indicated the presence of four aromatic resonances due to an unsubstituted indole unit (δ 6.25–6.92, 4H), another two singlets, each accounting for two aromatic hydrogens (δ 7.07, 2H; 7.09, 2H), six aromatic methoxy groups (δ 3.89–3.94), an ethylidene side chain (δ 1.56, 5.32), and a methyl ester (δ 3.49). The presence of the additional nonindole aromatic hydrogens indicated the incorporation of additional aromatic units and corresponds to the presence of two trimethoxy-substituted aromatic moieties. The two aromatic moieties are identical and are attributed to two 3,4,5-trimethoxy-substituted rings based on the presence of six aromatic methoxy groups as well as the observation of two sets of aromatic 2H singlets. The ^{13}C NMR spectrum (Table 2.34) accounted for all 41 carbon resonances including eight methyl, three methylene, 14 methine, an ester carbonyl (δ 172.0), a conjugated amide carbonyl (δ 169.3), a conjugated ester carbonyl (δ 163.7), a tertiary carbon bonded to the indole nitrogen (C-13), six tertiary carbon atoms bonded to oxygen, and six quaternary carbons. The oxymethine resonance seen at δ_H 6.18 (δ_C 75.7) is reminiscent of H-17/C-17 in a vincamajine ester derivative. This is consistent with the 2D NMR data (Figure 2.47) which confirmed a vincamajine-type core skeleton with the C-17 oxygen bonded to one of the trimethoxybenzoyl (or eudesmoyl) unit to form an

ester linkage (^3J from H-17 to the ester carbonyl, Figure 2.47). The second trimethoxybenzoyl moiety must be connected to the indolic nitrogen (N-1), in view of the absence of an indolic N-H or an N-1–Me in the ^{1}H NMR spectrum, as well as the presence of an amide carbonyl in the ^{13}C NMR spectrum of **57**. The relative configuration of **57** follows those in vincamajine and its derivatives, as indicated by the NOESY data (Figure 2.48). The α-orientation of H-17 is evident from the observed H-17/H-14β, H-15 NOEs, while the geometry of the 19,20-double bond is *E* from the observed H-18/H-15 and H-19/H-21 NOEs (Figure 2.48).

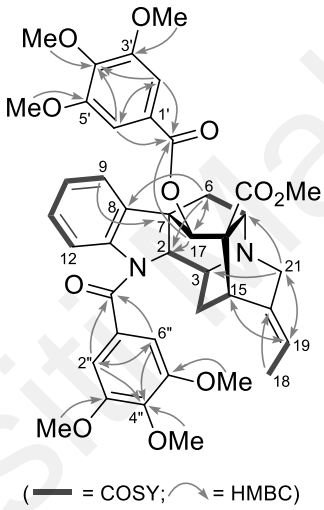
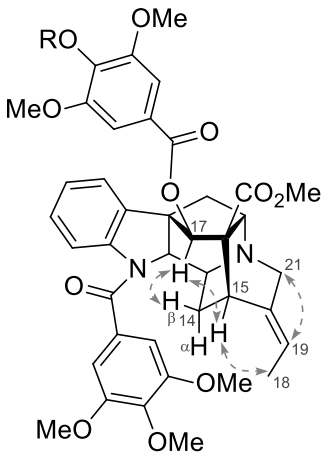


Figure 2.47: COSY and selected HMBCs of **57**



57 R = OMe
58 R = OH

Figure 2.48: Selected NOEs (ROEs) of **57** and **58**

2.1.4.2 Vincamaginine B (58)

Vincamaginine B (**58**) was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ –379 (*c* 0.2, $CHCl_3$). The similarity of the UV spectrum (214, 280, 297 nm) with that of **57** indicated the presence of *N*-acyldihydroindole and trimethoxybenzoyl chromophores. The IR spectrum was also similar, showing the presence of ester carbonyl (1733 cm^{-1}) and amide carbonyl (1651 cm^{-1}) functionalities. The HRESIMS data ($[M + H]^+$ *m/z* 727.2873) yielded the molecular formula $C_{40}H_{42}N_2O_{11}$, which is 14 mass units less than that of **57**, suggesting the replacement of CH_3 in **57** with H in **58**.

The ^{1}H NMR data (Table 2.34) of **58** resembles that of **57** with nearly identical chemical shifts, although a notable difference is the loss of an aromatic methoxy group in **58** (5 x OMe groups) when compared to **57** (6 x OMe groups). These observations (MS and ^{1}H NMR) indicated the replacement of an aromatic OMe substituent by OH in **58**, which was confirmed by the observed base-induced bathochromic shift in the UV spectrum. Another significant difference is in the resonances due to the aromatic OMe groups in the ^{1}H NMR spectrum. In compound **57**, three distinct aromatic methoxy resonances were observed (a 12H singlet at δ 3.89 due to 4 x OMe groups; two 3H singlets at δ 3.92 and 3.94 due to 2 x OMe groups), while in **58**, only one overlapped aromatic methoxy resonance was observed (a 15H singlet at δ 3.93 due to 5 x OMe groups) (Table 2.33). Comparison of the ^{13}C NMR data of **58** with those of **57** also showed similarity except for changes in the carbon shifts of some of the aromatic carbons (1', 3', 4', 5') of the 'upper' syringoyl moiety in **58** (Table 2.34). The acid residue in the C-17 ester group in **58** was identified as syringoyl (or 4'-hydroxy-3',5'-dimethoxybenzoyl) instead of eudesmoyl (or 3',4',5'-trimethoxybenzoyl) from the observed ^3J correlations from H-2'/H-6' to the ester carbonyl in the HMBC spectrum (Figure 2.49).

These observations (MS, UV, ^{1}H and ^{13}C NMR, HMBC) enabled the identification of vincamaginine B (**58**) as 17-*O*-4'-hydroxy-3',5'-dimethoxybenzoyl-*N*(1)-3",4",5"-trimethoxybenzoylvincamajine. The relative configuration of **58** was presumed to follow that of **57** from the similarity of their NMR and NOESY data (Figure 2.48). The ^{1}H NMR spectra of **57** and **58** are shown in Figure 2.50 and Figure 2.51, respectively.

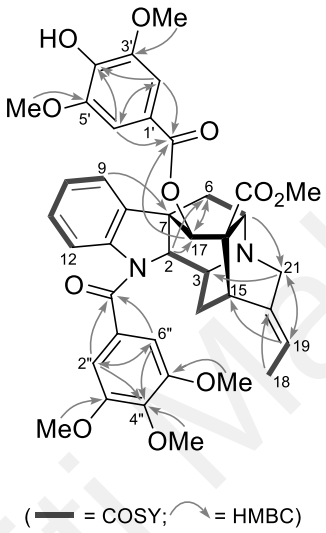


Figure 2.49: COSY and selected HMBCs of **58**

Table 2.34: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Vincamaginine A (**57**) and Vincamaginine B (**58**)[a]

H/C	57		58	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	70.6	4.33 d (5.0)	70.5	4.34 d (5.0)
3	52.9	4.56 dd (10.0, 5.0)	52.9	4.57 dd (10.0, 5.0)
5	61.6	3.73 d (5.0)	61.6	3.74 d (5.0)
6α	35.5	1.95 d (12.0)	35.5	1.96 d (12.0)
6β		2.72 dd (12.0, 5.0)		2.73 dd (12.0, 5.0)
7	57.0	-	57.0	-
8	130.4	-	130.5	-
9	123.7	6.92 dd (7.5, 1.0)	123.7	6.92 dd (7.5, 1.0)
10	123.0	6.71 t (7.5)	123.0	6.70 td (7.5, 1.0)
11	127.8	6.89 td (7.5, 1.0)	127.8	6.88 td (7.5, 1.0)
12	116.0	6.25 d (7.5)	116.0	6.25 d (7.5)
13	144.8	-	144.8	-
14α	23.1	1.72 dd (14.5, 10.0)	23.1	1.72 dd (14.5, 10.0)
14β		2.40 dd (14.5, 5.0)		2.40 dd (14.5, 5.0)
15	30.0	3.58 d (5.0)	30.0	3.58 d (5.0)
16	59.0	-	59.0	-
17	75.7	6.18 s	75.6	6.17 s
18	12.7	1.56 d (7.0)	12.7	1.55 d (7.0)
19	117.3	5.32 q (7.0)	117.3	5.31 q (7.0)
20	136.2	-	136.2	-
21	55.4	3.51 m	55.4	3.51 m
21		3.51 m		3.51 m
$CO_2\underline{Me}$	51.8	3.49 s	51.8	3.47 s
$\underline{C}O_2Me$	172.0	-	172.1	-
1′	124.3	-	120.2	-
1″	130.3	-	130.3	-
2′, 6′	106.6	7.07 s	106.4	7.10 s
2″, 6″	106.6	7.09 s	106.4	7.09 s
3′, 3″, 5′, 5″	153.0	-	146.8	-
3′-OMe, 5′-OMe, 3″-OMe, 5″-OMe	56.0	3.89 s	56.5	3.93 s
4′	142.6	-	139.7	-
4″	141.3	-	141.3	-
4′-OMe	61.0	3.92 s		-
4″-OMe	60.9	3.94 s	61.0	3.93 s
O-C=O	163.7	-	163.8	-
N-C=O	169.3	-	169.4	-

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); assignments based on DEPT, COSY, HSQC, HMBC, and NOESY/ROESY.

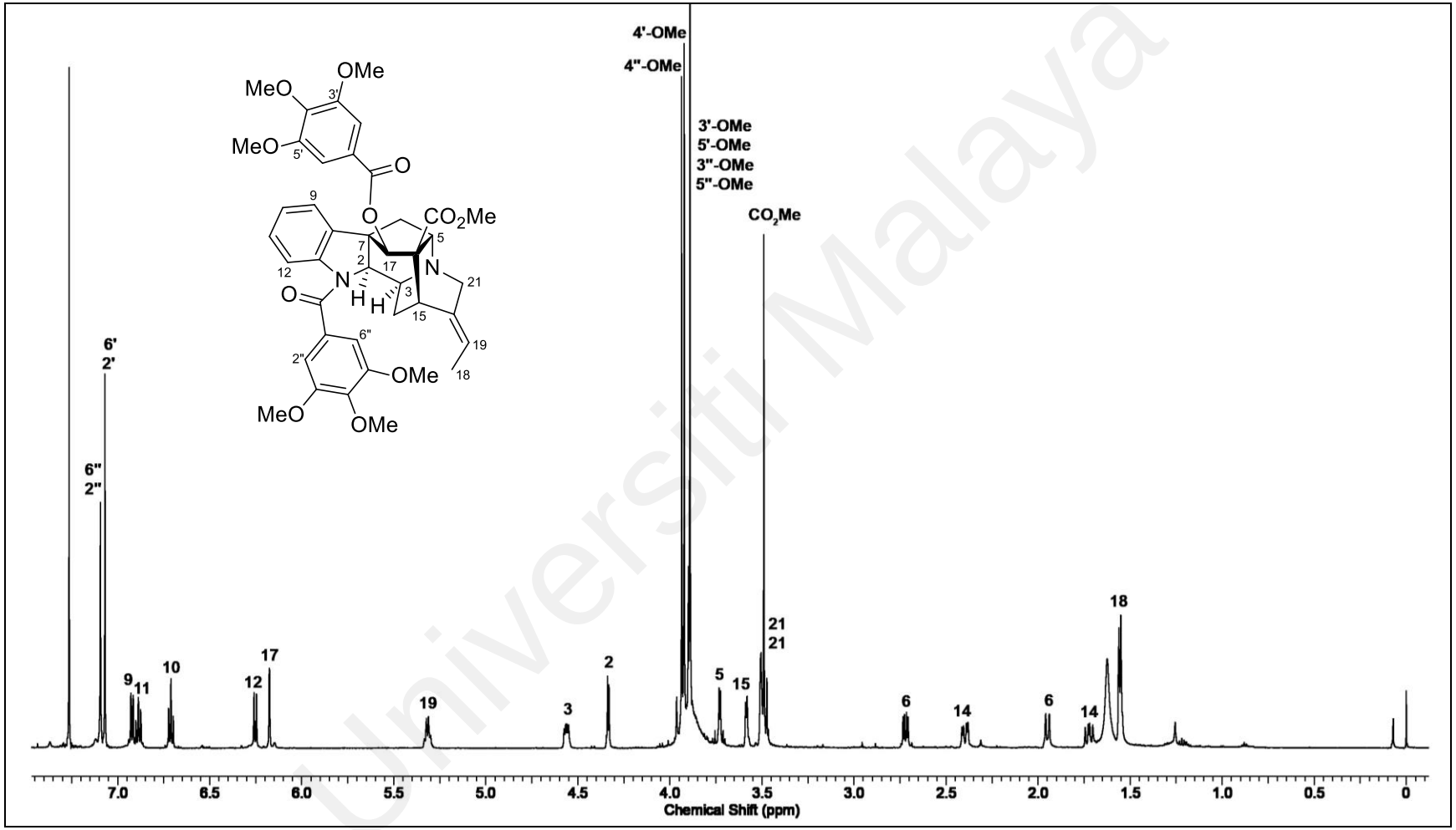


Figure 2.50: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Vincamaginine A (**57**)

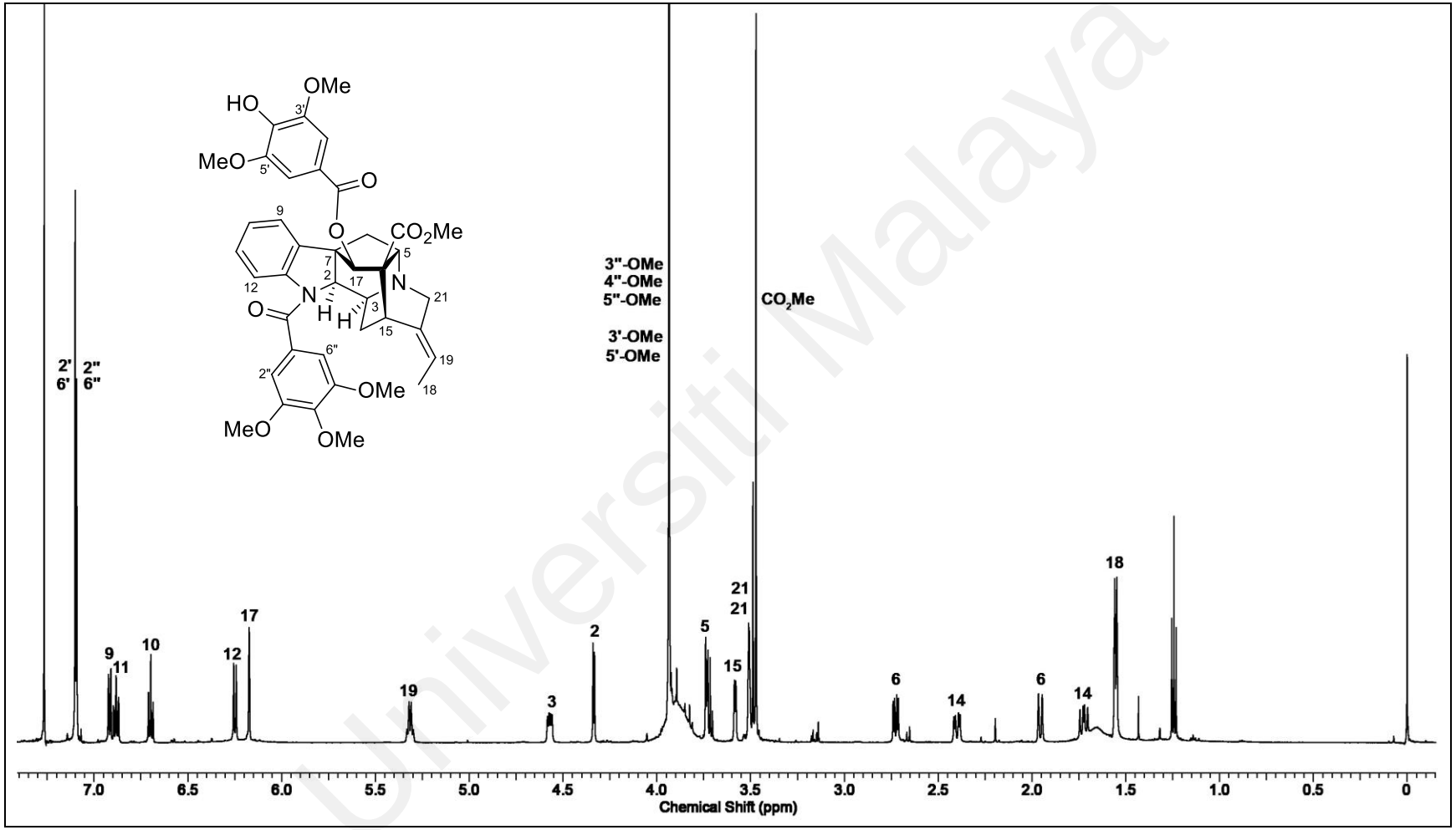


Figure 2.51: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Vincamaginine B (**58**)

2.1.4.3 4′-Hydroxy-3′,5′-dimethoxybenzoylvincamajine (59), *O*-3,4,5-Trimethoxybenzoylquebrachidine (60), Vincamajine *N*(1)-tri-*O*-methylgallate (61), Vincamajine (62), and Quebrachidine (63)

Five known ajmaline-type alkaloids including 4′-hydroxy-3′,5′-dimethoxybenzoylvincamajine (**59**),[127] *O*-3,4,5-trimethoxybenzoylquebrachidine (**60**),[147] vincamajine *N*(1)-tri-*O*-methylgallate (**61**),[402] vincamajine (**62**),[147,148] and quebrachidine (**63**)[403,404] were also isolated in the present study. The ^{1}H and ^{13}C NMR data of these compounds are summarized in Tables 2.35–2.36, and their ^{1}H NMR spectra are shown in Figures A32–A36 (see Appendix). Other data are given in the Experimental Section.

Table 2.35: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of 4′-Hydroxy-3′,5′-dimethoxybenzoylvincamajine (**59**), *O*-3,4,5-Trimethoxybenzoylquebrachidine (**60**), and Vincamajine *N*(1)-tri-*O*-methylgallate (**61**)[a]

H/C	59		60		61	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	75.0	3.27 d (5.0)	68.7	3.90 m	70.5	4.29 d (4.7)
3	53.2	3.60 dd (10.0, 5.0)	54.7	3.55 m	52.9	4.35 m
5	61.7	3.68 d (4.7)	61.6	3.67 d (4.8)	61.4	3.61 d (5.0)
6α	36.8	1.88 d (11.7)	36.9	1.91 d (11.8)	34.7	1.78 d (11.7)
6β		2.71 m		2.72 dd (11.8, 4.8)		2.67 dd (11.7, 5.0)
7	56.4	-	57.1	-	57.2	-
8	128.7	-	128.2	-	131.3	-
9	123.5	6.86 dd (7.5, 1.0)	124.0	6.88 d (7.5)	124.8	7.24 m
10	119.1	6.55 td (7.5, 1.0)	119.6	6.58 t (7.5)	123.2	6.99 m
11	128.6	7.12 td (7.5, 1.0)	128.5	7.05 t (7.5)	128.0	7.00 m
12	109.2	6.67 d (7.5)	111.0	6.78 d (7.5)	115.6	6.43 m
13	154.3	-	151.5	-	144.5	-
14α	21.9	1.59 dd (14.0, 10.0)	22.3	1.58 dd (14.0, 9.8)	22.8	1.56 dd (14.0, 10.0)
14β		2.72 m		2.82 dd (14.0, 5.0)		2.19 dd (14.0, 5.0)
15	30.2	3.55 d (5.0)	30.4	3.55 m	30.1	3.52 d (5.0)
16	59.2	-	59.1	-	59.7	-
17	76.2	5.89 s	76.0	5.92 s	75.7	4.40 s
18	12.7	1.55 d (6.8)	12.7	1.55 d (6.8)	12.9	1.59 d (6.8)
19	116.9	5.29 q (6.8)	116.8	5.28 q (6.8)	116.9	5.28 q (6.8)
20	136.5	-	136.6	-	136.4	-
21	55.6	3.47 dt (16.0, 2.3)	55.4	3.46 m	55.2	3.42 ABq (16.0, 2H)
		3.52 br d (16.0)		3.46 m		
N(1)Me	34.2	2.67 s	-	-	-	-
$CO_2\underline{Me}$	51.7	3.40 s	51.7	3.42 s	51.8	3.73 s
$\underline{C}O_2Me$	172.3	-	172.3	-	173.0	-
1′	139.4	-	124.7	-	131.0	-
2′, 6′	106.5	7.17 s (2H)	106.7	7.14, s (2H)	106.0	6.90 br s (2H)
3′, 5′	146.7	-	152.9	-	56.5	-
4′	120.6	-	142.3	-	141.5	-
3′-OMe, 5′-OMe	56.4	3.92 s (6H)	56.2	3.89 s (6H)	56.5	3.83 br s (6H)
4′-OMe	-	-	60.9	3.92 s	61.1	3.93 s
O-C=O	163.8	-	163.7	-	169.8	-

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); assignments based on COSY, HSQC, and HMBC.

Table 2.36: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Vincamajine (**62**) and Quebrachidine (**63**)[a]

H/C	62		63	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	74.4	3.23 d (5.0)	68.5	3.82 br s
3	53.1	3.55 dd (10.0, 5.0)	54.6	3.45 m
5	61.6	3.57 d (5.0)	61.6	3.54 d (5.0)
6	35.2	1.76 d (12.0)	35.6	1.73 d (12.0)
		2.58 dd (12.0, 5.0)		2.63 dd (12.0, 5.0)
7	57.0	-	57.8	-
8	130.1	-	129.6	-
9	128.2	7.12 dd (8.0, 1.0)	124.8	7.18 br d (8.0)
10	119.1	6.77 td (8.0, 1.0)	119.6	6.81 td (8.0, 1.0)
11	124.4	7.14 td (8.0, 1.0)	128.2	7.12 td (8.0, 1.0)
12	109.0	6.63 dd (8.0, 1.0)	110.9	6.78 br d (8.0)
13	154.4	-	151.7	-
14	21.8	1.49 dd (14.0, 10.0)	22.3	1.44 dd (14.0, 10.0)
		2.42 dd (14.0, 5.0)		2.56 dd (14.0, 5.0)
15	30.0	3.46 d (5.0)	30.3	3.45 m
16	59.4	-	59.6	-
17	74.5	4.02 s	74.3	4.29 s
18	12.8	1.57 br d (7.0)	12.8	1.59 dt (7.0, 2.0)
19	116.5	5.26 br q (7.0)	116.4	5.26 br q (7.0)
20	136.5	-	136.8	-
21	55.2	3.44 m	55.3	3.45 m
		3.44 m		3.45 m
N(1)Me	34.2	2.61 s	-	-
$CO_2\underline{Me}$	51.5	3.67 s	51.6	3.70 s
$\underline{C}O_2Me$	173.0	-	173.3	-

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C).

2.1.5 Corynantheine Alkaloids

2.1.5.1 18,19-Dihydroisositsirikine (64), 16(*R*),19(*E*)-Isositsirikine (65), *Z*-Geissoschizol (66), Pleiocarpamine (67), 16-Hydroxymethylpleiocarpamine (68), Pleiomaltinine (69), and Fluorocarpamine (70)

Seven known corynantheine-type alkaloids including 18,19-dihydroisositsirikine (**64**),[405] 16(*R*),19(*E*)-isositsirikine (**65**),[405,406] *Z*-geissoschizol (**66**),[407,408] pleiocarpamine (**67**),[409,410] 16-hydroxymethylpleiocarpamine (**68**),[411] pleiomaltinine (**69**),[412,413] and fluorocarpamine (**70**)[190] were also isolated in the present study. The ^{1}H and ^{13}C NMR data of these compounds are summarized in Tables 2.37–2.41, and their ^{1}H NMR spectra are shown in Figures A37–A43 (see Appendix). Other data are given in the Experimental Section.

Table 2.37: ^{1}H NMR Spectroscopic Data (δ) of 18,19-Dihydroisositsirikine (**64**), 16(*R*),19(*E*)-Isositsirikine (**65**), and *Z*-Geissoschizol (**66**)[a]

H	64 (*J*/Hz)	65 (*J*/Hz)	66 (*J*/Hz)[b]
3	2.98 m	4.33 br s	3.50 d (11.4)
5	2.44 m	3.15 m	2.68 m
5	2.98 m	3.27 ddd (13.0, 6.0, 2.0)	3.15 m
6	2.69 dd (14.0, 5.0)	2.67 dd (16.0, 6.0)	2.76 m
6	2.98 m	2.99 m	3.01 m
9	7.45 br d (8.0)	7.47 br d (8.0)	7.46 d (7.5)
10	7.07 td (8.0, 1.0)	7.10 td (8.0, 1.0)	7.08 t (7.5)
11	7.12 br t (8.0)	7.16 td (8.0, 1.0)	7.13 t (7.5)
12	7.27 br d (8.0)	7.39 br d (8.0)	7.31 d (7.5)
14	1.36 m	2.24 m	1.34 m
14	2.13 br d (12.5)	2.24 m	2.27 br d (12.3)
15	1.56 m	3.15 m	2.36 m
16	2.98 m	2.52 ddd (11.0, 8.0, 5.0)	1.56 m
16	-	-	2.04 m
17	3.69 dd (11.0, 6.0)	3.54 m	3.82 br t (6.3)
17	3.96 dd (11.0, 7.0)	3.54 m	3.82 br t (6.3)
18	0.90 t (8.0)	1.66 dd (7.0, 2.0)	1.71 d (6.5)
19	1.15 m	5.65 br q (7.0)	5.33 br q (6.5)
19	1.68 m	-	-
20	1.68 m	-	-
21	1.78 t (11.0)	2.98 d (13.0)	2.75 m
21	2.98 m	3.54 m	3.88 d (12.2)
$CO_2\underline{Me}$	3.61 s	3.81 s	-
NH	8.42 br s	8.81 br s	8.03 br s

[a]$CDCl_3$, 400 MHz. [b]Assignments based on COSY, HSQC, and HMBC.

Table 2.38: ^{13}C NMR Spectroscopic Data (δ) of 18,19-Dihydroisositsirikine (**64**), 16(*R*),19(*E*)-Isositsirikine (**65**), and *Z*-Geissoschizol (**66**)[a]

C	64	65	66[b]
2	134.5	133.8	134.6
3	59.9	52.8	59.8
5	53.1	51.3	52.6
6	21.6	17.7	21.6
7	108.0	107.7	108.0
8	127.4	127.6	127.3
9	118.2	118.0	118.1
10	119.4	119.5	119.3
11	121.4	121.6	121.3
12	111.0	111.3	110.8
13	136.2	136.2	136.0
14	32.2	30.2	36.5
15	40.5	32.6	37.8
16	47.6	49.6	34.2
17	62.1	62.1	60.6
18	10.8	13.3	13.1
19	23.2	123.7	116.6
20	39.6	133.7	136.7
21	60.2	52.5	55.6
$CO_2\underline{Me}$	51.9	52.2	-
$\underline{C}O_2Me$	174.4	175.4	-

[a]$CDCl_3$, 100 MHz. [b]Assignments based on HSQC and HMBC.

Table 2.39: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Pleiocarpamine (**67**) and 16-Hydroxymethylpleiocarpamine (**68**)[a]

H/C	67		68	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	136.8	-	137.1	-
3	50.5	3.84 t (3.0)	50.4	3.77 m
5	49.8	2.28 m	49.5	2.25 ddd (13.3, 8.5, 6.5)
5		3.35 ddd (13.0, 10.0, 3.0)		3.35 ddd (13.3, 10.0, 2.8)
6	20.6	2.66 ddd (16.0, 10.0, 6.0)	20.5	2.63 ddd (15.5, 10.0, 6.5)
6		3.14 ddd (16.0, 9.0, 3.0)		3.15 ddd (15.5, 8.5, 2.8)
7	107.9	-	108.7	-
8	128.5		128.7	
9	118.2	7.53 m	118.3	7.54 m
10	119.8	7.09 m	120.2	7.10 m
11	120.5	7.09 m	121.0	7.10 m
12	112.2	6.94 m	112.0	7.10 m
13	137.4		139.0	
14	28.4	2.19 ddd (13.0, 3.0, 2.0)	25.4	2.03 ddd (13.5, 4.0, 2.2)
14		2.49 ddd (13.0, 3.0, 2.0)		2.62 m
15	33.6	3.51 br s	33.3	3.74 t (3.5)
16	61.1	5.21 d (4.0)	68.5	-
18	12.4	1.47 dd (7.0, 2.0)	12.5	1.52 dd (7.0, 2.0)
19	122.7	5.30 qd (7.0, 2.0)	122.2	5.29 qd (7.0, 2.0)
20	133.1	-	134.5	-
21	56.4	1.73 br d (13.0)	56.5	1.85 dt (13.0, 2.0)
21		2.59 d (13.0)		2.61 d (13.0)
22	-	-	66.0	4.24 d (12.0)
22	-	-		4.52 d (12.0)
$CO_2\underline{Me}$	51.8	3.56 s	51.5	3.32 s
$\underline{C}O_2Me$	169.0	-	173.1	-

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C).

Table 2.40: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Pleiomaltinine (**69**)[a]

H/C	δ_C	δ_H (*J*/Hz)
2	95.7	-
3	50.3	3.19 m
5	47.4	2.86 m
5		3.15 m
6	31.6	1.45 dt (14.4, 2.0)
6		2.32 td (14.4, 4.0)
7	44.9	-
8	134.1	-
9	120.5	7.08 br d (7.8)
10	119.8	6.82 td (7.8, 1.0)
11	127.6	7.06 td (7.8, 1.0)
12	110.6	6.30 br d (7.8)
13	146.7	-
14	27.2	1.74 dt (13.0, 3.6)
14		2.83 m
15	31.6	3.37 q (3.6)
16	57.3	4.79 d (3.6)
17	170.0	-
18	12.2	1.59 dd (6.8, 2.0)
19	119.1	5.42 qd (6.8, 2.0)
20	134.9	-
21	52.9	3.04 d (12.4)
21		4.27 dt (12.4, 2.0)
CO_2Me	51.8	3.73 s
2'	146.3	-
3'	142.5	-
4'	171.6	-
5'	115.8	6.20 d (5.6)
6'	152.6	7.53 d (5.6)
7'	26.6	3.20 m
7'		3.20 m

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY.

Table 2.41: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Fluorocarpamine (**70**)[a]

H/C	δ_C	δ_H (*J*/Hz)
2	76.0	-
3	61.8	3.51 br s
5	55.0	2.99 m
5		2.99 m
6	39.0	2.21 dd (12.0, 6.0)
6		2.99 m
7	205.2	-
8	120.4	-
9	124.1	7.62 br d (8.0)
10	119.5	6.90 br t (8.0)
11	137.2	7.51 br t (8.0)
12	111.1	6.70 br d (8.0)
13	163.6	-
14	24.9	1.37 dt (13.0, 3.0)
14		1.91 dt (13.0, 3.0)
15	30.5	3.64 br d (9.0)
16	63.0	4.56 d (9.0)
18	12.3	1.63 d (6.0)
19	121.0	5.50 br q (6.0)
20	133.9	-
21	53.4	3.31 d (14.0)
21		3.38 br d (14.0)
CO_2Me	51.8	3.72 s
CO_2Me	172.5	-

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C).

2.1.6 Strychnan Alkaloids

2.1.6.1 11-Methoxyakuammicine (71), 11-Methoxyakuammicine *N*(4)-oxide (72), Alstolagumine (73), Alstovine (74), and Lagumidine (75)

Five known strychnan-type alkaloids including 11-methoxyakuammicine (**71**),[188,402] 11-methoxyakuammicine *N*(4)-oxide (**72**),[402] alstolagumine (**73**),[172] alstovine (**74**),[154] and lagumidine (**75**)[53,172] were also isolated in the present study. The ^{1}H and ^{13}C NMR data of these compounds are summarized in Tables 2.42–2.44, and their ^{1}H NMR spectra are shown in Figures A44–A48 (see Appendix). Other data are given in the Experimental Section.

Table 2.42: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of 11-Methoxyakuammicine (**71**) and 11-Methoxyakuammicine *N*(4)-oxide (**72**)[a]

H/C	71		72	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
2	167.5	-	164.7	-
3	61.8	4.12 br s	78.3	4.29 br s
5	55.7	3.06 dd (12.0, 6.0)	69.9	3.71 m
		3.37 td (12.0, 6.0)		3.99 m
6	45.6	1.87 dd (12.0, 6.0)	41.7	1.93 dd (14.0, 7.0)
		2.53 td (12.0, 6.0)		2.47 td (14.0, 7.0)
7	56.5	-	54.1	-
8	128.8	-	126.8	-
9	121.2	7.14 d (8.0)	121.9	7.41 d (8.5)
10	105.5	6.43 dd (8.0, 2.0)	106.0	6.40 dd (8.5, 2.0)
11	160.3	-	160.9	-
12	97.0	6.43 d (2.0)	97.5	6.37 d (2.0)
13	144.5	-	144.1	-
14	29.4	1.34 dt (14.0, 3.0)	27.9	1.37 br d (14.0)
		2.44 ddd (14.0, 3.0, 2.0)		2.75 br d (14.0)
15	30.5	3.96 br s	28.5	3.97 br s
16	101.6	-	102.0	-
18	13.0	1.67 dt (7.0, 1.0)	13.6	1.58 d (6.8)
19	122.4	5.42 br q (7.0)	127.1	5.55 br q (6.9)
20	137.4	-	133.3	-
21	56.4	3.03 d (14.0)	74.0	3.99 d (14.5)
		3.98 br d (14.0)		4.19 d (14.5)
N-H	-	8.95 s	-	8.85 s
$CO_2\underline{Me}$	51.1	3.81 s	51.4	3.75 s
$\underline{C}O_2Me$	167.7	-	167.2	-
11-OMe	55.5	3.78 s	55.6	3.70 s

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C).

Table 2.43: ^{1}H NMR Spectroscopic Data (δ) of Alstolagumine (**73**), Alstovine (**74**), and Lagumidine (**75**)[a]

H	73 (*J*/Hz)	74 (*J*/Hz)	75 (*J*/Hz)
3	3.98 t (3.0)	3.87 t (3.0)	3.93 t (3.0)
5	2.85 dd (12.0, 7.0)	2.77 m	2.79 dd (11.0, 7.0)
	3.15 td (12.0, 6.0)	3.08 td (13.0, 6.0)	3.07 ddd (13.0, 11.0, 6.0)
6	1.88 dd (12.0, 6.0)	1.82 dd (13.0, 6.0)	1.91 dd (13.0, 6.0)
	2.65 td (12.0, 7.0)	2.77 m	2.96 ddd (13.0, 11.0, 7.0)
9	7.09 d (8.0)	7.08 d (8.0)	7.07 d (8.0)
10	6.44 dd (8.0, 2.0)	6.46 dd (8.0, 2.0)	6.44 dd (8.0, 2.0)
12	6.43 d (2.0)	6.45 d (2.0)	6.43 d (2.0)
14	1.38 dt (13.0, 3.0)	1.15 dt (13.0, 3.0)	1.26 ddd (13.0, 3.0, 2.0)
	2.52 dt (13.0, 3.0)	2.77 m	2.86 dt (13.0, 3.0)
15	2.98 t (3.0)	2.96 br s	3.07 br s
18	1.41 d (6.0)	1.10 d (6.0)	2.37 s
19	2.92 q (6.0)	3.51 q (6.0)	-
21	2.71 d (13.0)	2.06 d (12.0)	2.65 dd (13.0, 1.0)
	2.98 d (13.0)	2.77 m	3.17 d (13.0)
N-H	9.05 br s	8.55 br s	8.93 br s
CO_2Me	3.74 s	3.88 s	3.78 s
11-OMe	3.79 s	3.79 s	3.69 s

[a]$CDCl_3$, 400 MHz.

Table 2.44: ^{13}C NMR Spectroscopic Data (δ) of Alstolagumine (**73**), Alstovine (**74**), and Lagumidine (**75**)[a]

C	73	74	75
2	171.2	172.8	171.4
3	60.7	60.5	60.2
5	54.5	53.9	53.1
6	44.3	43.2	42.3
7	56.6	56.9	55.6
8	128.0	127.9	126.6
9	120.6	120.3	120.2
10	105.7	105.9	105.9
11	160.1	159.9	160.2
12	97.2	97.2	97.4
13	145.0	144.6	145.4
14	29.0	25.6	24.7
15	30.8	35.0	35.1
16	98.9	98.7	99.0
18	14.5	14.6	25.2
19	61.4	69.8	211.8
20	62.0	72.5	76.9
21	54.1	51.6	50.2
$\underline{C}O_2Me$	168.1	168.9	167.8
$CO_2\underline{Me}$	50.9	51.9	51.0
11-OMe	55.5	55.5	55.5

[a]$CDCl_3$, 100 MHz.

2.1.7 Macroline-Akuammiline Bisindole Alkaloids

2.1.7.1 Angustilongine A (76)

Angustilongine A (**76**)[382] was initially isolated as an amorphous solid and subsequently as light yellowish block crystals from CH_2Cl_2–hexanes, with mp >199 °C (dec) and $[\alpha]^{25}_D$ +3 (*c* 0.4, $CHCl_3$). The UV spectrum (212, 232, 255, 295 nm) showed a composite of indole and dihydroindole chromophores. The IR spectrum showed absorption bands at 3360 and 1741 cm^{-1} due to OH and ester functionalities, respectively. HRESIMS measurements ($[M + H]^+$ *m/z* 707.4180) gave the molecular formula $C_{43}H_{54}N_4O_5$.

Examination of the ^1H (Table 2.45) and ^{13}C (Table 2.46) NMR data indicated a bisindole alkaloid constituted from the union of macroline and akuammiline moieties. The ^1H NMR data indicated the presence of resonances due to an unsubstituted indole unit (δ 7.04−7.37, macroline), two isolated aromatic singlets of another indole ring substituted at C-10' and C-11' (δ 6.40, 5.29; akuammiline), an aromatic methoxy singlet (δ 3.62, akuammiline), a methyl ester group (δ 3.74, akuammiline), an ethylidene side chain (δ 5.38, 1.48, akuammiline), three methyl singlets due to two N-1–Me (δ 3.37, macroline; 2.29, akuammiline) and an N-4–Me (δ 2.27, macroline), an oxymethylene due to C-17 (δ 3.45, 4.45; macroline), and a methyl doublet (δ 1.09) that is part of a CH_3CHCH fragment of the macroline unit. A low-field singlet at δ 5.36 (δ_C 93.7) was reminiscent of a methine of a hemiacetal group. The observed NOE (Figure 2.52) between the aromatic singlet at δ 5.29 and N-1'–Me (δ 2.29) allowed the assignment of this aromatic resonance to H-12' (akuammiline) and the other aromatic singlet at δ 6.40 to H-9'.

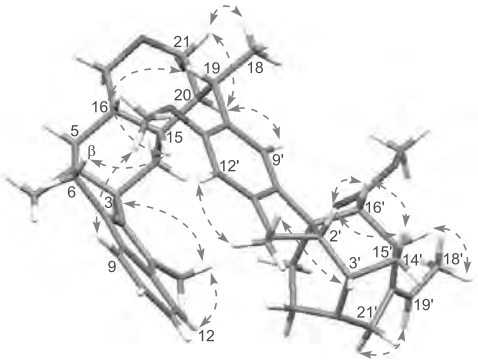


Figure 2.52: Selected NOEs of **76**

The ^{13}C NMR data (Table 2.46) showed the presence of 43 carbon atoms including seven methyl, seven methylene, 18 methine, one tertiary carbon linked to oxygen, three tertiary carbons bonded to indolic nitrogen, an ester carbonyl, and six quaternary carbons. Of these, the deshielded resonance at δ 156.2 was due to a methoxy-substituted aromatic carbon, which was assigned to C-11' from the three-bond H-9'/C-11' correlation in the HMBC spectrum (Figure 2.53), while the oxymethylene carbon signal at δ 59.6 (C-17) along with another deshielded resonance at δ 93.7 (C-21) were consistent with the presence of an hemiacetal function in ring E of the macroline unit. The substitution of the aromatic OMe group at C-11' indicated the branching of the bisindole from C-10' of the akuammiline half. The olefinic carbon signals seen at δ 140.0 (C-20') and 118.6 (C-19') are in accord with the presence of the ethylidene side chain in the akuammiline unit. Examination of the 2D NMR data (COSY, HMBC) allowed the complete assignment of the NMR resonances and in turn led to the identification of the macroline ($NCHCH_2$, $NCHCH_2CHCHCH_2O$, CH_3CHCH, OCHOH) and akuammiline (NCH_2CH_2, $CHCH_2CHCH$, $CH_3CH{=}C$, NCH_2) units linked by the methine C-19 as shown in Figure 2.53. The connection from C-19 of the macroline unit to C-10' of the akuammiline unit was supported by the three-bond correlations from CH_3-18 to C-20 and C-10'. The resonance of the methyl ester bonded to C-16' was

observed at δ 3.74 in the ^{1}H NMR spectrum, the lack of unusual shielding indicating the orientation of the carbomethoxy group away from the indole ring.

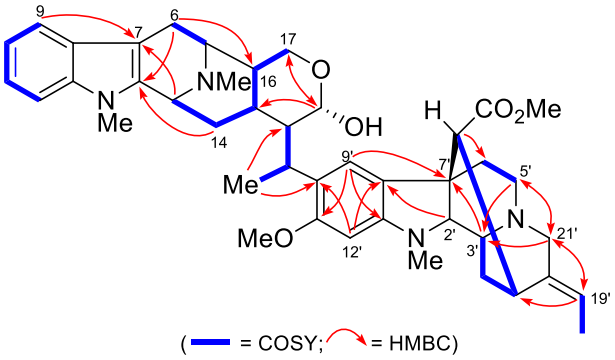


Figure 2.53: COSY and selected HMBCs of **76**

The observed NOE for H-14β/H-20α, which requires both these hydrogens to be equatorially oriented, indicated the substitution at C-20 to be β. Furthermore, the signal of H-21 was a singlet ($J_{20\text{-}21}$ = 0 Hz), requiring H-21 to be also equatorial (or β-oriented) and the 21-OH to be axial (or α-oriented). Determination of the configuration at C-19 by NMR however, was not possible, due to free rotation about the C-19–C-20 bond. The configuration at C-19 (*S*) as well as the absolute configuration of **76** was eventually established by X-ray diffraction analysis (Figure 2.54).

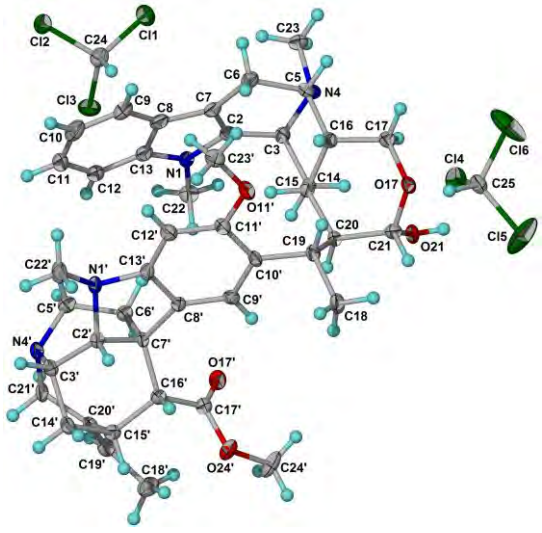


Figure 2.54: X-Ray crystal structure of **76**

2.1.7.2 Angustilongine B (77)

Angustilongine B (**77**)[382] was obtained as a light yellowish oil, with $[\alpha]^{25}_{D}$ −33 (*c* 0.1, $CHCl_3$). The IR spectrum indicated the presence of an ester carbonyl function (1736 cm^{-1}) but did not show any OH absorption band, which was seen in **76**, while the UV spectrum (229, 250, 294 nm) was similar to that of **76**, indicating a composite of indole and dihydroindole chromophores. HRMS measurements ($[M + H]^+$ *m/z* 675.3932) gave the molecular formula $C_{42}H_{50}N_4O_4$.

The ^1H (Table 2.45) and ^{13}C (Table 2.46) NMR data of **77** showed a general similarity to those of compound **76**, indicating a bisindole constituted from similar monomeric halves (macroline and akuammiline). In common with **76**, the ^1H NMR data showed the presence of an unsubstituted indole unit (δ 7.11–7.50, macroline), a 10',11'-disubstituted indole moiety (δ 6.45, 6.13; akuammiline), a methyl ester group (δ 3.67, akuammiline), an ethylidene side chain (δ 5.47, 1.48; akuammiline), three methyl groups due to two N-1–Me (δ 3.62, macroline; 2.62, akuammiline) and one N-4–Me (δ 2.32, macroline), a methyl doublet (δ 1.24, Me-18, macroline) that is part of a $CH_3CHCHCH(O)–O$ fragment, an oxymethylene due to OCH_2-17 (δ 3.97, 4.18; macroline), and a deshielded hydrogen (δ 5.44) corresponding to an acetal function (macroline).

The ^{13}C NMR data accounted for all 42 carbon resonances, including six methyl, seven methylene, 18 methine, a tertiary carbon bonded to oxygen, three tertiary carbons bonded to indolic N, an ester carbonyl (δ 172.5), and six quaternary carbons. A distinctly deshielded signal at δ_C 97.5 (δ_H 5.44) corresponds to the carbon of an acetal function. As in the case of **76**, bisindole **77** also showed an oxymethylene carbon signal at δ 67.5 due to C-17 of the macroline half, and olefinic carbon signals (δ 137.1, 120.9) due to the ethylidene side chain in the 'lower' akuammiline unit.

The NMR data of **77** differ from that of **76** in the absence of resonances due to the C-11' methoxy group in **76**, although the oxygen substitution at C-11' (δ 151.0) remains (^3J H-9'/C-11' in the HMBC spectrum; Figure 2.55). In addition, the molecular formula of **77** is less than that of **76** by 32 mass units (or loss of CH_3 and OH compared to **76**) as well as requiring the presence of an additional ring. Bond formation between the oxygen at C-11' and the hemiacetal C-21 in **76** (demethylation followed by elimination of water) forges an additional ring F, which incorporates an acetal function as a result of fusion of two tetrahydropyran units as shown in **77**. The structure is in full agreement with the HMBC (Figure 2.55) and NOESY (Figure 2.56) data.

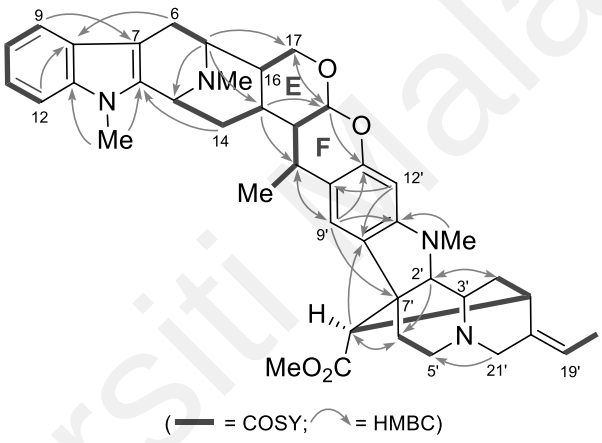


Figure 2.55: COSY and selected HMBCs of **77**

Since additional ring formation has led to the incorporation of the methyl bearing C-19 as part of a new tetrahydropyran ring, determination of the relative configuration at C-19 is now possible based on the NMR data. The *cis* fusion of rings E and F was evident from the observed $J_{20\text{-}21}$ coupling of 2.9 Hz in the ^{1}H NMR spectrum. The α-orientation (or equatorial disposition) of H-19 (19*S*) was deduced from the observed H-18/H-16, H-9' and H-9'/H-19 NOEs (Figure 2.56). The assignment of the configuration of C-19 in **77** as *S* by NMR data is also consistent with its likely origin from **76** (for which the absolute configuration has been confirmed by X-ray analysis, 19*S*) since the configurational integrity of C-19 is unaffected by the transformation from **76** to **77**.

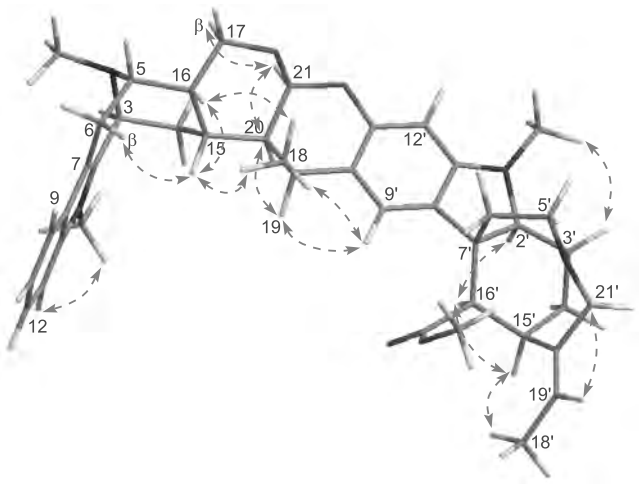


Figure 2.56: Selected NOEs of **77**

2.1.7.3 Angustilongine C (78)

Angustilongine C (**78**)[382] was isolated as a yellowish oil, with $[\alpha]^{25}_{D}$ +16 (*c* 0.1, $CHCl_3$). HRESIMS measurements ($[M + H]^+$ *m/z* 705.4041) yielded the molecular formula $C_{43}H_{52}N_4O_5$. The UV spectrum (230, 252, 295 nm) resembled those of **76** and **77**, indicating the presence of similar chromophores, while the presence of an ester carbonyl function was evident from the IR spectrum (1741 cm^{-1}).

Analysis of the ^1H, ^{13}C, and 2D NMR data indicated a macroline-akuammiline bisindole with a close resemblance to **76**. Thus, the ^1H NMR data (Table 2.45) also indicated the presence of four aromatic hydrogens due to an unsubstituted indole moiety (δ 7.10–7.48, macroline), two isolated aromatic singlets due to a 10',11'-disubstituted indole unit (δ 6.14, 6.80, akuammiline), an aromatic methoxy singlet (δ 3.61, akuammiline), a methyl ester group (δ 3.79, akuammiline), three methyl singlets due to two N-1–methyl (δ 3.52, 2.79) and an N-4–methyl (δ 2.26), a methyl doublet that is part of a CH_3CH fragment (δ 1.03, Me-18, macroline), geminal hydrogens of an oxymethylene OCH_2-17 (δ 3.94, 4.24; macroline), and an ethylidene side chain (δ 5.63, 1.57, akuammiline). The ^{13}C NMR data (Table 2.46) accounted for all 43 carbon resonances including seven methyl, seven methylene, 17 methine, a tertiary carbon

bonded to oxygen, three tertiary carbons linked to indolic N, an ester carbonyl (δ 172.0), and seven quaternary carbons. There are, however, several notable changes in the NMR data of **78** when compared to those of **76**. First, the signal due to H-20 was not seen in the ^{1}H NMR spectrum of **78**, while H-21 (δ 6.19) is an olefinic H. In the ^{13}C NMR spectrum, C-20 of **78** is a quaternary olefinic carbon (δ 119.4), while C-21 is an oxygenated olefinic methine (δ 140.1). These changes indicated that in **78**, a trisubstituted double bond involving C-20 and C-21, constituting part of an enol ether function was present in ring E of the macroline half. Another notable observation is that resonances due to H-3', H-5', and H-21', as well as the respective C-3', C-5', and C-21', of **78** were significantly deshielded when compared to those of **76**. Compound **78** is therefore the *N*(4')-oxide of the parent bisindole, **78a**, which is as yet unknown and which was not isolated in the current study. The proposed structure of **78** is entirely consistent with the HMBC (Figure 2.57) and NOESY (Figure 2.58) data.

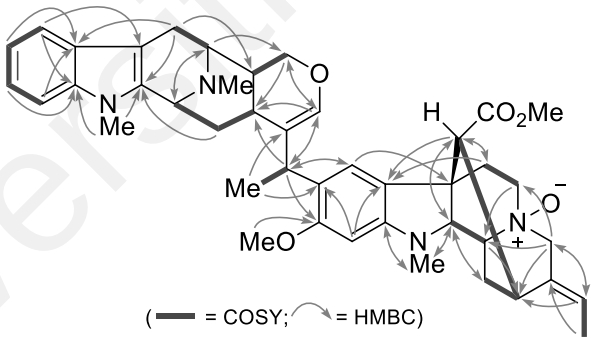


Figure 2.57: COSY and selected HMBCs of **78**

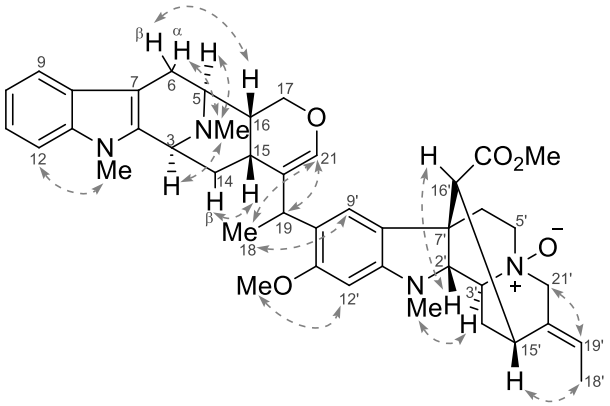
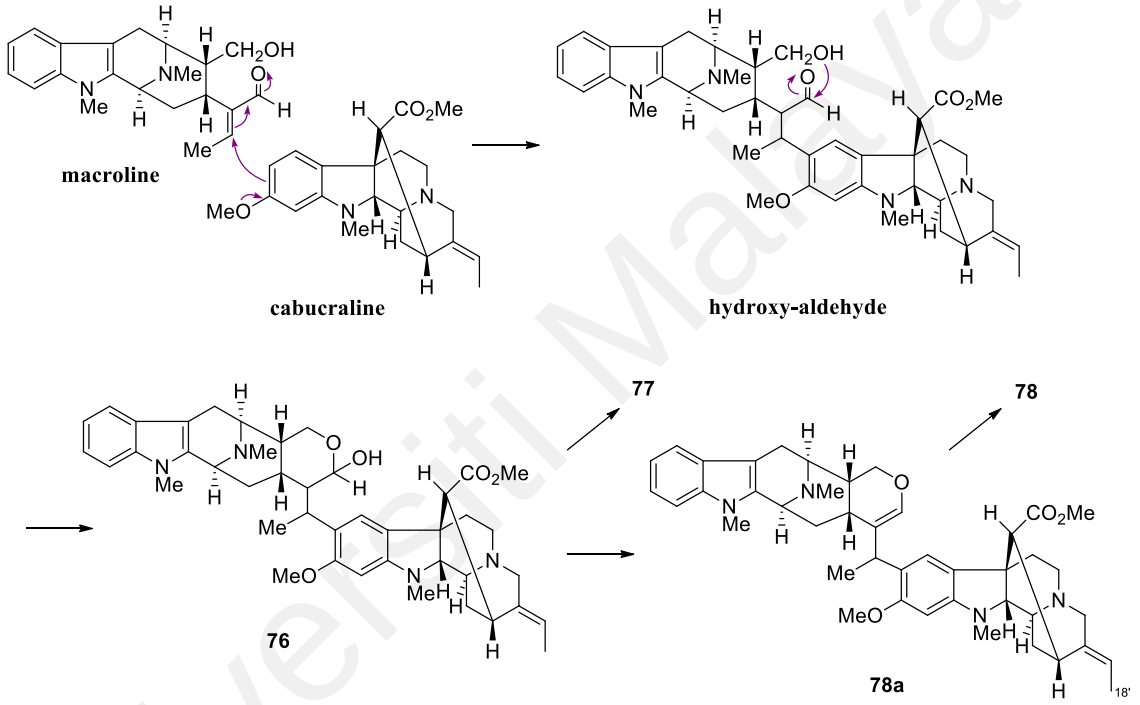


Figure 2.58: Selected NOEs of **78**

The bisindoles **76**–**78** possess a similar mode of connection of the constituent units as that in lumutinines C–D[52] and perhentisine A[132]. A possible biogenetic route to these alkaloids is summarized in Scheme 2.1, involving conjugate addition of cabucraline via its nucleophilic C-10' onto the hypothetical macroline (an E-seco-talcarpine) to afford a hydroxy-aldehyde intermediate. Subsequent ring closure to the hemiacetal **76** followed by ketalization furnishes **77**. Dehydration of **76** on the other hand gives rise to **78a**.



Scheme 2.1: Putative biogenetic pathway to **76–78**

2.1.7.4 Angustilongine D (79)

Angustilongine D (**79**)[382] was isolated as a light yellowish amorphous solid, with $[\alpha]^{25}_{D}$ +12 (*c* 0.3, $CHCl_3$). The HRESIMS showed an M^+ peak at *m/z* 755.3949, corresponding to molecular formula $C_{44}H_{56}N_4O_5Cl$, which differs from **76** by the addition of CH_2Cl. The similarity of the UV and IR spectra with those of **76**, indicated the incorporation of the similar monomeric halves and the presence of similar functionalities.

The ^{1}H NMR (Table 2.45) and ^{13}C NMR (Table 2.46) data showed a general correspondence with those of **79**, except for the presence of two additional resonances due to a pair of geminal hydrogens (δ 5.89 and 6.36, J = 9 Hz; δ_C 72.6) of a CH_2Cl group linked to N-4', which were absent in the ^{1}H NMR spectrum of **76**. In addition, the downfield shift of the resonances for C-3', C-5', and C-21' (δ 58.7, 57.2, and 63.5, respectively) of the akuammiline unit in **79** is consistent with the quaternization of the adjacent nitrogen (N-4') due to the formation of CH_2Cl_2 adduct. Formation of **79** is likely a result of the use of solvent mixtures containing dichloromethane during the crystallization of **76**. The proposed structure for **79** is in agreement with the HMBC data (Figure 2.59). The ^{1}H NMR spectra of compounds **76**–**79** are shown in Figures 2.60–2.63.

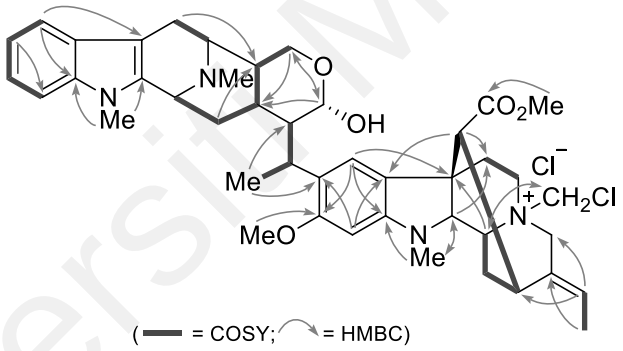


Figure 2.59: COSY and selected HMBCs of **79**

Table 2.45: ^{1}H NMR Spectroscopic Data (δ) of Angustilongines A–D (**76**–**79**)[a]

H	76 (*J*/Hz)	77 (*J*/Hz)	78 (*J*/Hz)	79 (*J*/Hz)
3	3.75 m	3.91 m	3.73 m	3.93 m
5	2.84 br d (7.0)	2.91 d (7.0)	3.05 m	2.96 m
6	2.19 br d (16.0) (β)	2.41 d (16.0) (β)	2.46 d (16.0) (β)	2.16 m
6	3.13 dd (16.0, 7.0) (α)	3.28 dd (16.0, 7.0) (α)	3.25 dd (16.0, 7.0) (α)	3.14 dd (16.0, 7.0)
9	7.37 d (7.5)	7.50 d (8.0)	7.48 d (7.5)	7.35 d (7.7)
10	7.04 t (7.5)	7.11 td (8.0, 1.0)	7.10 td (7.5, 1.0)	7.06 m
11	7.09 m	7.20 td (8.0, 1.0)	7.19 td (7.5, 1.0)	7.18 m
12	7.08 m	7.30 d (8.0)	7.28 d (7.5)	7.18 m
14	1.13 m (β)	1.53 m (β)	1.41 m (β)	1.27 br d (13.0)
14	2.84 m (α)	2.35 m (α)	1.72 td (13.0, 4.0) (α)	3.10 m
15	1.27 m	1.90 m	1.89 m	1.37 m
16	2.08 m	2.32 m	1.92 m	2.09 m
17	3.45 dd (11.5, 5.0) (β)	3.97 dd (12.0, 5.0) (β)	3.94 dd (11.0, 3.4) (β)	3.48 dd (11.0, 4.0)
17	4.45 t (11.5) (α)	4.18 t (12.0) (α)	4.24 t (11.0) (α)	4.59 br t (11.0)
18	1.09 d (7.0)	1.24 d (7.0)	1.03 d (7.0)	1.08 d (7.0)
19	3.17 m	2.61 m	3.39 q (7.0)	3.24 m
20	1.33 m	1.65 m	-	1.33 m
21	5.36 s	5.44 d (2.9)	6.19 s	5.40 s
N(1)-Me	3.37 s	3.62 s	3.52 s	3.37 s
N(4)-Me	2.27 s	2.32 s	2.26 s	2.30 br s
2'	2.24 br s	2.48 s	2.82 s	2.54 br s
3'	3.96 br d (5.0)	4.27 m	4.61 br d (5.0)	4.57 br d (5.0)
5'	2.56 dd (13.0, 6.5)	2.71 m	3.27 dd (12.0, 6.0)	3.27 m
5'	3.63 m	3.91 m	4.39 m	4.13 br t (12.0)
6'	0.86 br d (13.0)	1.26 m	1.37 dd (16.0, 6.0)	0.85 m
6'	2.91 m	3.03 m	3.03 m	3.13 m
9'	6.40 s	6.45 s	6.80 s	6.38 s
12'	5.29 s	6.13 s	6.14 s	5.67 s
14'	1.54 br d (13.0) (β)	1.64 m (β)	1.81 dd (15.0, 2.0) (β)	1.91 br d (14.0)
14'	2.32 m (α)	2.35 m (α)	2.78 m (α)	3.35 br d (14.0)
15'	3.51 m	3.58 m	3.60 m	3.65 m
16'	2.78 d (3.6)	2.85 d (4.0)	2.93 d (3.6)	2.83 d (3.0)
18'	1.48 dd (7.0, 2.0)	1.48 dd (7.0, 2.0)	1.57 dd (7.0, 2.0)	1.56 dd (7.0, 2.0)
19'	5.38 br q (7.0)	5.47 br q (7.0)	5.63 br q (7.0)	5.79 br q (7.0)
21'	2.90 m (β)	3.03 m (β)	3.80 m (β)	4.21 br d (14.0)
21'	3.89 br d (16.0) (α)	4.00 m (α)	4.44 br d (14.0) (α)	5.06 br d (14.0)
N(1')-Me	2.29 s	2.62 s	2.79 s	2.41 br s
CO_2Me'	3.74 s	3.67 s	3.79 s	3.79 s
11'-OMe	3.62 s	-	3.61 s	3.72 br s
CH_2Cl	-	-	-	5.89 d (9.0) 6.36 d (9.0)

[a]$CDCl_3$, 600 MHz; assignments based on COSY, HSQC, and NOESY.

Table 2.46: ^{13}C NMR Spectroscopic Data (δ) of Angustilongines A–D (**76**–**79**)[a]

C	76	77	78	79
2	132.9	133.0	133.5	132.3
3	54.2	53.5	53.6	54.4
5	55.3	54.4	55.2	55.5
6	22.2	23.0	22.9	22.4
7	106.5	106.5	106.2	106.2
8	126.3	126.5	126.6	126.1
9	117.6	118.0	118.0	117.8
10	118.2	118.2	118.7	118.5
11	120.4	120.9	120.6	129.8
12	108.6	108.8	108.8	108.6
13	136.8	137.1	137.0	136.9
14	32.5	32.9	33.5	31.7
15	25.3	27.7	28.6	25.1
16	38.2	39.4	40.6	38.2
17	59.6	67.5	66.4	59.2
18	19.5	20.7	20.4	20.2
19	ND[b]	32.9	34.1	ND[b]
20	48.2	39.1	119.4	46.9
21	93.7	97.5	140.1	93.3
N(1)-Me	28.6	29.0	29.0	28.9
N(4)-Me	41.8	41.7	41.7	41.6
2'	78.9	68.0	79.1	76.7
3'	47.4	47.6	70.1	58.7
5'	51.0	50.1	66.8	57.2
6'	31.7	30.0	29.9	28.0
7'	42.4	42.3	40.8	40.3
8'	132.3	133.0	130.0	129.9
9'	118.6	120.4	120.3	119.1
10'	124.3	118.2	126.0	126.1
11'	156.2	151.0	156.5	156.9
12'	92.9	98.6	94.7	94.8
13'	151.6	152.5	151.0	150.2
14'	33.9	32.9	31.7	31.7
15'	34.4	33.8	32.2	32.2
16'	52.9	52.7	51.9	51.4
18'	13.0	13.1	13.5	13.5
19'	118.6	120.9	124.0	126.1
20'	140.0	137.1	130.0	128.2
21'	54.9	54.4	72.5	63.5
N(1')-Me	33.2	34.3	34.7	35.3
CO_2Me'	51.4	51.5	52.0	52.0
CO_2Me'	173.0	172.5	172.0	171.6
11'-OMe	55.2	-	55.6	55.6
CH_2Cl	-	-	-	72.6

[a]$CDCl_3$, 150 MHz; assignments based on DEPT, HSQC, and HMBC.[b]Not detected.

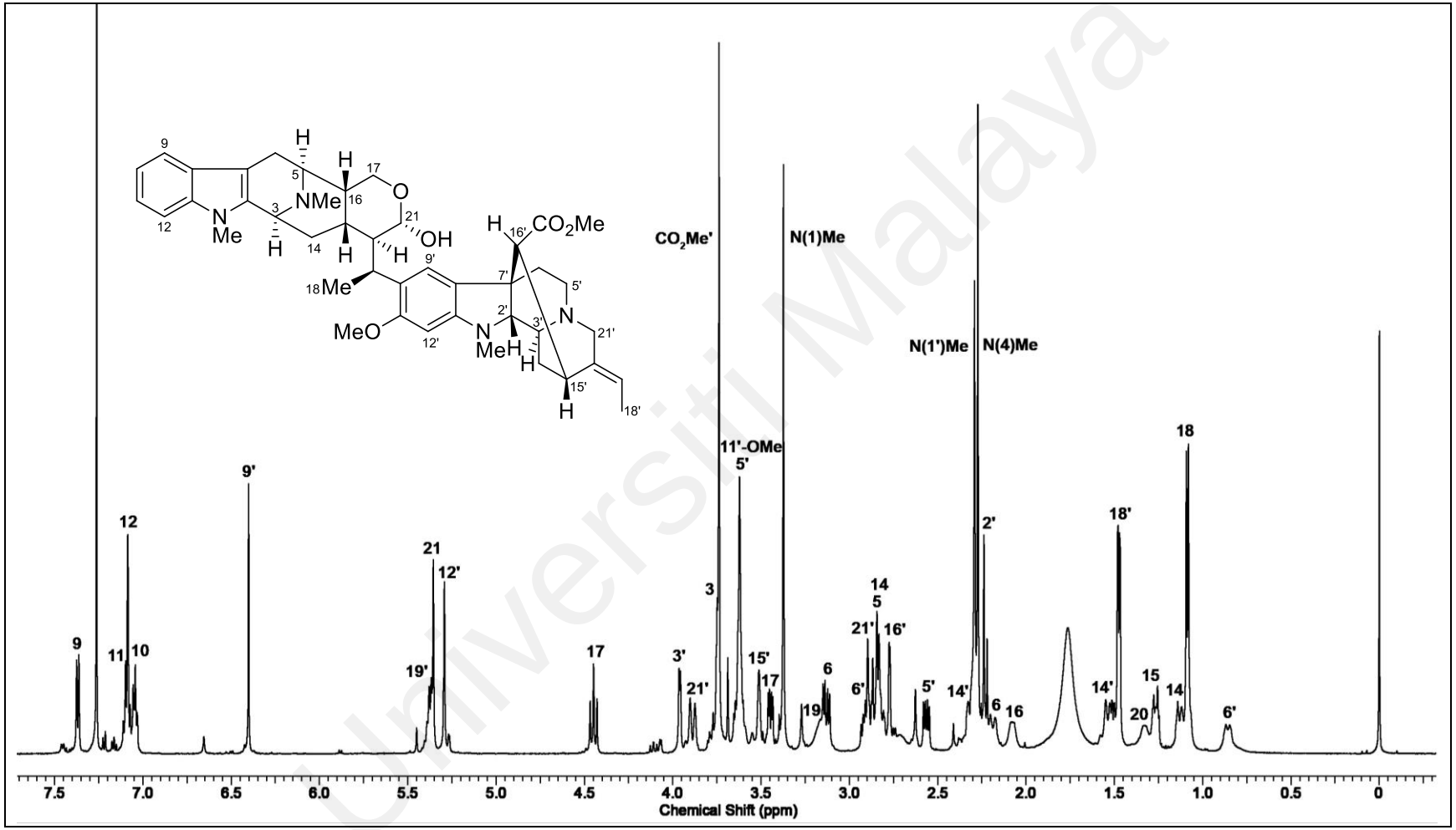


Figure 2.60: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Angustilongine A (**76**)

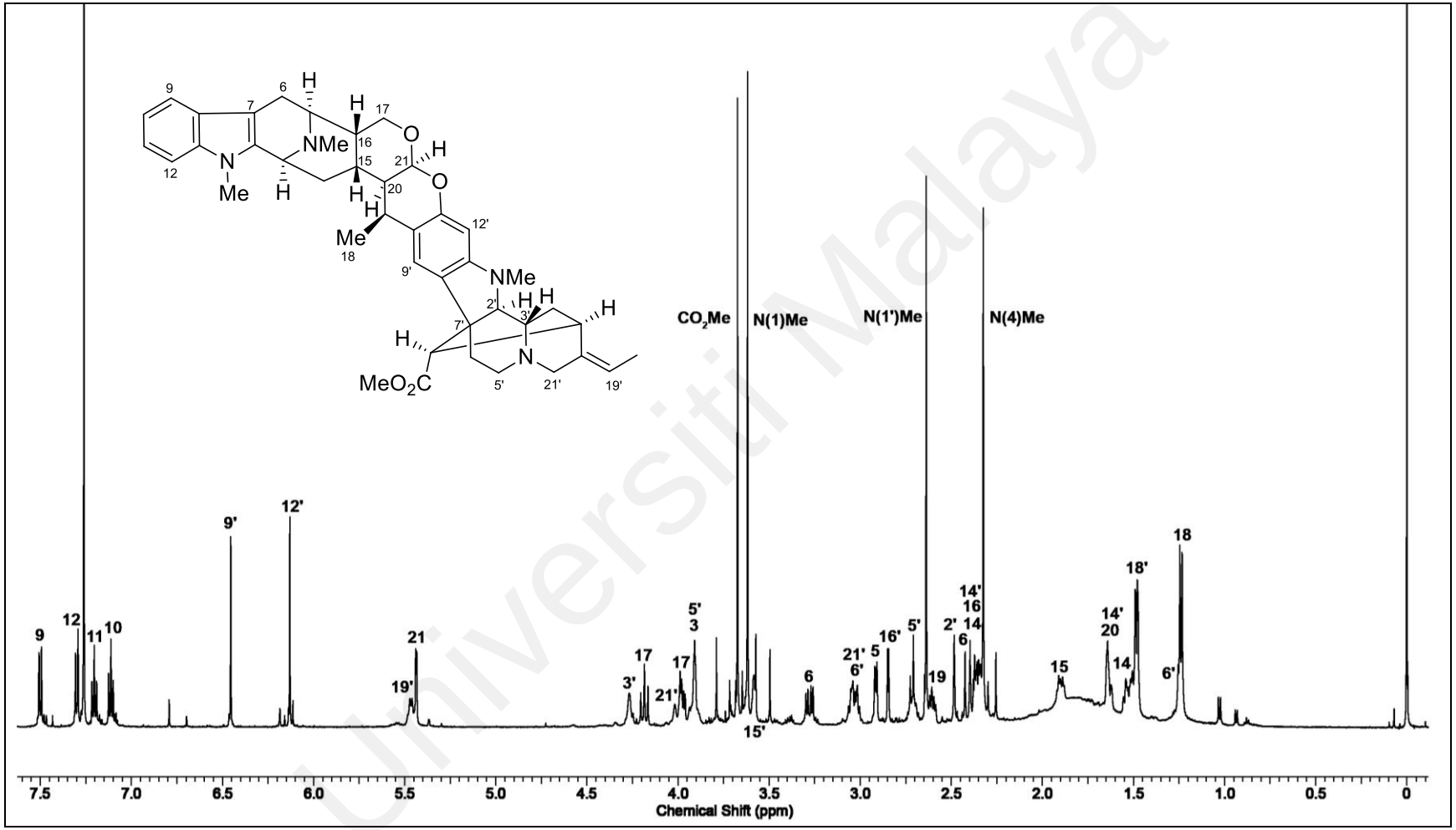


Figure 2.61: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Angustilongine B (**77**)

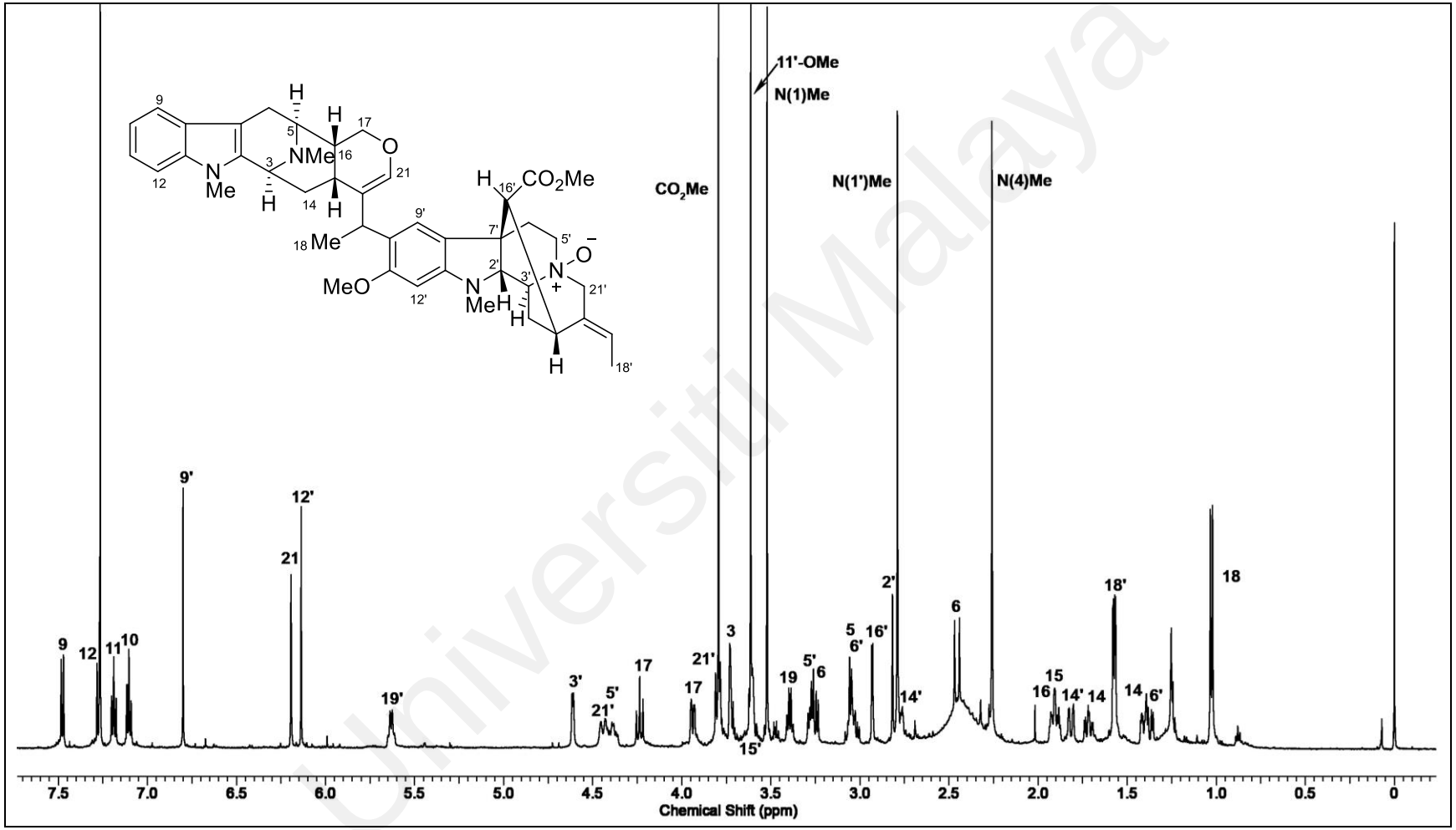


Figure 2.62: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Angustilongine C (**78**)

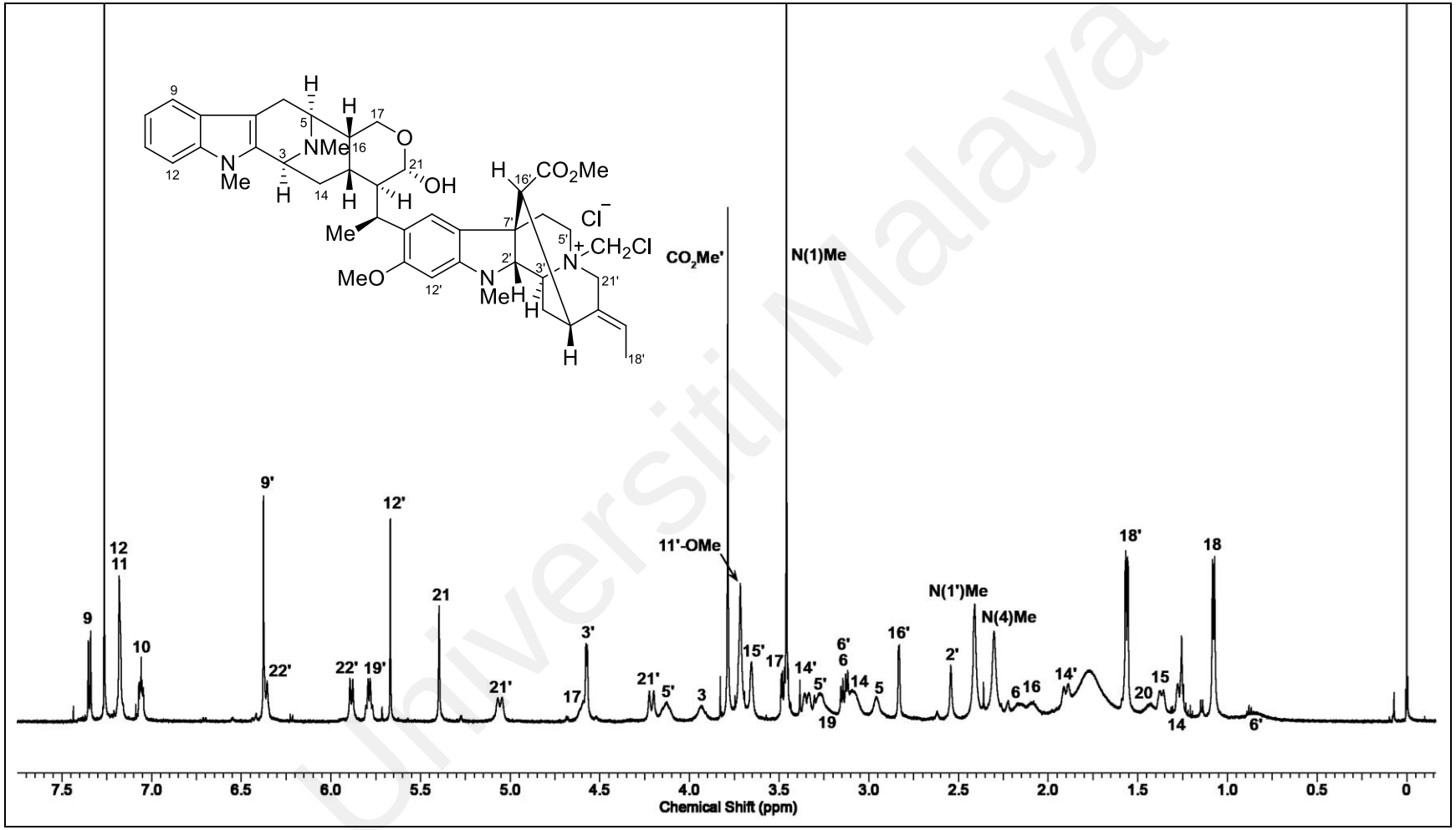


Figure 2.63: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Angustilongine D (**79**)

2.1.8 Macroline-Sarpagine Bisindole Alkaloids

2.1.8.1 Angustilongine E (80)

Angustilongine E (**80**)[414] was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ −74.4 (*c* 0.43, $CHCl_3$). The UV spectrum (229, 286 nm) showed the presence of an indole chromophore, while the IR spectrum (3395 cm^{-1}) indicated the presence of a hydroxy function. HRMS measurements ($[M + H]^+$ *m/z* 659.3951) yielded the molecular formula $C_{42}H_{50}N_4O_3$. Examination of the ^1H, ^{13}C, and 2D NMR data (COSY, HSQC, HMBC; Figure 2.64) of **80** indicated a bisindole constituted from the union of macroline ($NCHCH_2$, $NCHCH_2CHCHCH_2O$, CH_3CH) and sarpagine ($NCHCH_2CH$, $CH_2CHCHCH_2O$, CH_3CH) units.

The ^1H NMR data (Table 2.47) indicated the presence of four aromatic hydrogens due to an unsubstituted indole unit (δ 7.03–7.39, macroline), two isolated aromatic singlets due to another indole ring substituted at C-10' and C-11' (δ 6.62, 6.72; sarpagine), three *N*-methyl singlets (δ 3.20, 2.23, macroline; δ 3.24, sarpagine), an aromatic methoxy singlet (δ 3.54, OMe-10', sarpagine), a deshielded olefinic singlet associated with a trisubstituted double bond and indicative of oxygen substitution (δ 6.42, H-21, macroline), a methyl group (δ 1.62, doublet, Me-18') and an olefinic hydrogen (δ 5.41, br q, H-19') associated with an ethylidene side chain (sarpagine), an oxymethylene due to OCH_2-17 (δ 3.93, 4.29; macroline), another oxymethylene due to $HOCH_2$-17' (δ 3.50, 3.55; sarpagine), and, a methyl doublet (δ 1.24) linked to a CH quartet (δ 3.83) due to a CH_3CH fragment (C-18–C-19, macroline). The ^{13}C NMR data (Table 2.48) accounted for all 42 carbon resonances, including six methyl, seven methylene, 17 methine, a tertiary carbon bonded to oxygen, four tertiary carbons bonded to the two indole nitrogens, and seven quaternary carbons. The deshielded aromatic signal at δ 152.0 is attributed to the methoxy-substituted C-10', while the deshielded methine signal at δ 139.1 is due to an oxygenated olefinic carbon (C-21)

reminiscent of an enol ether. The carbon resonances seen at δ 66.0 and 65.2 in the ^{13}C NMR spectrum were assigned to the oxymethylene OCH_2-17 (macroline) and the hydroxymethyl $HOCH_2$-17' (sarpagine), respectively. The ethylidene side chain resonances of the sarpagine half were observed at δ 12.8, 116.5, and 136.7, corresponding to C-18', C-19', and C-20', respectively. The resonances due to the CH_3CH fragment of the macroline half were seen at δ 21.3 (C-18) and 32.6 (C-19).

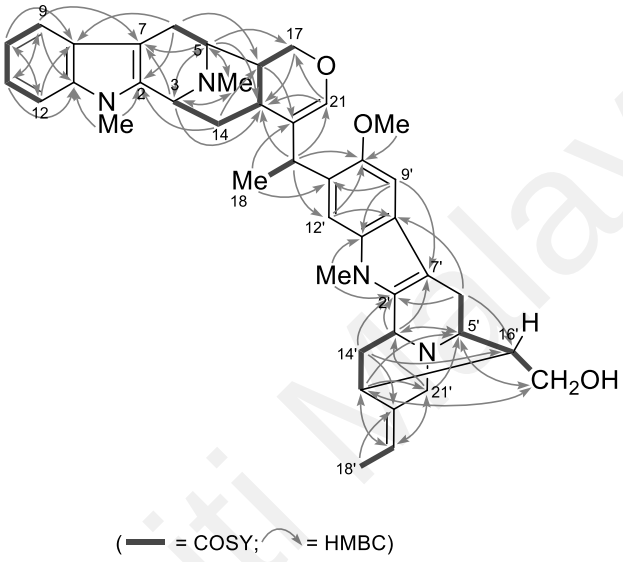


Figure 2.64: COSY and selected HMBCs of **80**

Since both indole nitrogens are methyl-substituted and only six aromatic hydrogens are accounted for, the bisindole must be branched from an aromatic carbon of the methoxy-substituted sarpagine half. The observed NOEs for H-9'/H-6'β and H-12'/N-1'–Me allowed the assignment of the aromatic ^1H resonances at δ 6.62 and 6.72 to H-9' and H-12' of the sarpagine half, respectively, while the NOE between H-9' and the aromatic methoxy signal (δ 3.54) indicated methoxy substitution at C-10' (Figure 2.65), leaving C-11' as the branching point of the bisindole from the 'lower' sarpagine unit.

The aromatic C-11' (sarpagine) and the quaternary olefinic C-20 (macroline) is connected via the two-carbon MeCH bridge at the methine C-19, as indicated by the

three-bond correlations for H-18/C-11', H-19/C-10', C-12', and H-12'/C-19 in the HMBC spectrum (Figure 2.64).

The structure and relative configuration of **80** were found to be consistent with the NOESY data (Figure 2.65), although the configuration at C-19 could not be determined due to the lack of suitable crystals for X-ray diffraction. The sarpagine half corresponds to a 10-methoxyaffinisine (**45**), which is also the sarpagine unit present in the remaining bisindoles (**81**–**85**). The configuration at C-16' is similar to that in methoxyaffinisine and is also consistent with the observation of H-16' upfield at δ 1.75 as a result of shielding by the indole moiety of the sarpagine unit. This was also evident from the observed H-16'/H-6'β NOE (Figure 2.65).

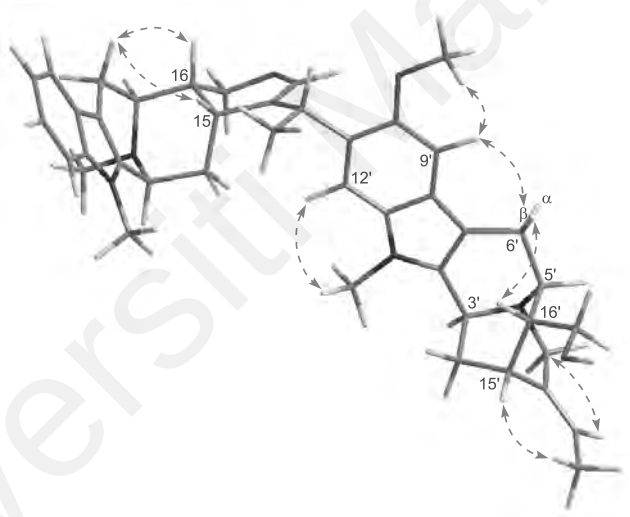


Figure 2.65: Selected NOEs of **80**

2.1.8.2 Angustilongine F (81)

Angustilongine F (**81**)[414] was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ –65 (*c* 0.4, $CHCl_3$). The UV spectrum (230, 286 nm) showed the presence of an indole chromophore, while the IR spectrum indicated the presence of an OH function (3403 cm^{-1}). HRMS measurements ($[M + H]^+$ *m/z* 659.3950) established the molecular formula as $C_{42}H_{50}N_4O_3$.

Examination of the ^{1}H and ^{13}C NMR data as well as 2D NMR data (COSY, HSQC, HMBC; Figure 2.66) indicated a constitution from the union of macroline and sarpagine monomeric units. However, while the sarpagine half remains as 10-methoxyaffinisine, there was a change in the macroline half, as well as in the mode of branching of the two monomeric units when compared to **80**.

The ^{1}H NMR data (Table 2.47) showed the resonances due to the presence of a 10-methoxyaffinisine unit: an N-1'–Me singlet (δ 3.14), an aromatic methoxy singlet (δ 3.60, OMe-10'), an ethylidene side chain (δ 1.67, 5.36), a hydroxymethyl $HOCH_2$-17' (δ 3.51, 2H), and a pair of aromatic AB doublets (δ 6.56, 6.69, *J*= 8.7 Hz) corresponding to a vicinally-substituted indole ring. The signal at δ 6.69 was assigned to H-12' based on the observed NOE between this hydrogen and N-1'–Me (Figure 2.67), which in turn allowed the assignment of the signal at δ 6.56 to H-11', leaving C-9' as the branching point of the bisindole from the 'lower' sarpagine unit. The remaining resonances, after discounting the sarpagine half, belong to the 'upper' macroline unit. These include four aromatic resonances of an unsubstituted indole moiety (δ 6.99–7.28), two methyl singlets due to an N-1–Me (δ 3.12) and an N-4–Me (δ 2.18), a singlet due to an isolated methyl (δ 1.83, C-18), geminal hydrogens of an oxymethylene OCH_2-17 (δ 3.89, 4.25), and a pair of AB doublets due to the isolated methylene CH_2-21 (δ 3.40, 3.75).

The ^{13}C NMR data (Table 2.48) accounted for all 42 carbon resonances, comprising six methyl, eight methylene, 15 methine, two tertiary carbon atoms linked to oxygen, four tertiary carbons linked to the indole N, and seven quaternary carbons. The resonances of the methoxyaffinisine moiety included the methoxy-substituted C-10' resonance at δ 151.1, the oxymethylene resonance due to the hydroxymethyl C-17' at δ 65.2, and the ethylidene side chain resonances at δ 12.8, 116.3, and 136.4, due to C-18', C-19', and C-20', respectively. The resonances of the macroline half included the oxymethylene resonance at δ 66.1 due to OCH_2-17, and the resonances of a

tetrasubstituted double bond associated with an enol ether function at δ 108.4 (C-20), and δ 144.2 (C-19). Examination of the 2D NMR data (Figure 2.66) indicated that the 'upper' macroline unit in **81** is a type-A macroline instead of the type-B macroline present in bisindole **80**. Thus, the olefinic H-21 singlet and the H-19 quartet seen in the ^{1}H NMR spectrum of **80** were absent in the ^{1}H NMR spectrum of **81**, while the CH_3-18 doublet present in **80** was replaced by a methyl singlet at δ 1.83 in the ^{1}H NMR spectrum of **81**.

Corresponding changes also occurred in the resonances due to C-19, C-20, and C-21. These changes were supported by the three-bond correlations for H-17/C-19 and H-18/C-20 in the HMBC spectrum (Figure 2.66). The branching of the bisindole from C-9' of the affinisine half via the C-21 methylene bridge to C-20 of the macroline half was confirmed by the three-bond correlations from H-21 to C-15, C-19, C-8', and C-10' in the HMBC spectrum (Figure 2.66). The relative configuration of **81** followed that of the constituent monomeric moieties as shown by the NOESY data (Figure 2.67).

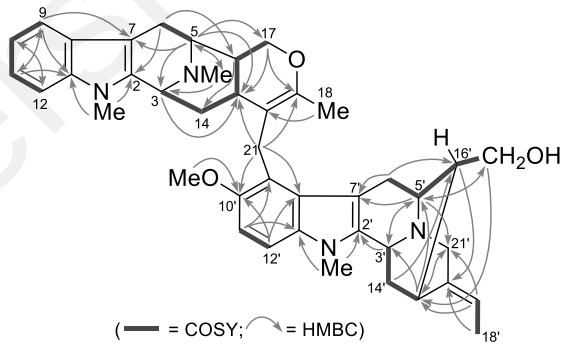


Figure 2.66: COSY and selected HMBCs of **81**

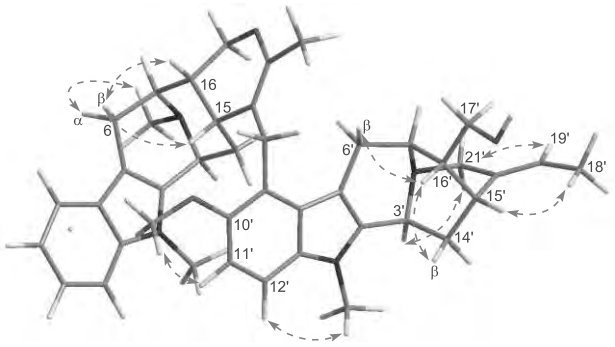


Figure 2.67: Selected NOEs of **81**

2.1.8.3 Angustilongine G (82)

Angustilongine G (**82**)[414] was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ +12.4 (*c* 0.15, $CHCl_3$). The presence of indole and OH groups was evident from the UV (227, 286 nm) and IR (3403 cm^{-1}) spectra, respectively. HRMS measurements ($[M + H]^+$ *m/z* 691.4199) established the molecular formula as $C_{43}H_{54}N_4O_4$.

As with the previous compounds **80** and **81**, the 2D NMR data of **82** (Figure 2.68) indicated a bisindole alkaloid constituted from the union of macroline and sarpagine (10-methoxyaffinisine) moieties. The ^{1}H NMR data (Table 2.47) of the sarpagine unit were similar to those of compound **80**, in particular the observation of two isolated aromatic singlets corresponding to H-9' (δ 6.69) and H-12' (δ 6.41) of the methoxyaffinisine moiety, indicating branching of the bisindole from C-11' of the sarpagine half, as is the case in **80**.

The resonances corresponding to the 'upper' macroline half included the four aromatic resonances of an unsubstituted indole moiety (δ 6.99–7.33), an isolated methyl singlet (δ 1.40, CH_3-18), two *N*-methyl singlets (δ 3.45, N-1–Me; δ 2.28, N-4–Me), another 3H singlet due to a methoxy group (δ 3.29, ketal), resonances due to an oxymethylene OCH_2-17 (δ 3.46, 4.20), and a one-H multiplet due to H-20 at δ 1.84 (overlapped with H-15). In addition, the 2D NMR data (HMBC: ^3J H-21/C-15, C-19, C-10', C-12'; Figure 2.68) also indicated that branching of the bisindole from C-20 of the macroline half to C-11' of the other unit is mediated by the C-21 methylene bridge. The ^{13}C NMR data (Table 2.48) showed the presence of seven methyl, eight methylene, 16 methine, a ketal (δ 101.3), one oxygenated tertiary carbon, four tertiary carbons linked to indole N, and six quaternary carbons, for a total of 43 carbon resonances.

The resonances due to the 10-methoxyaffinisine moiety could be assigned readily based on comparison with the data of **80**. The resonances of the 'upper' macroline unit were generally similar to those in **80** and **81**, except for those in ring E. Since the macroline unit in **82** is type A, the appropriate comparison of the ring E NMR data should be with **81**. Compound **82** differs from **81** by 32 mass units, or addition of H and OMe. The notable changes in the ^{13}C NMR data of **82** compared with **81** were in the resonances for C-19 and C-20, which are at δ 101.3 and 46.9 for **82**, respectively, from δ 144.2 and 108.4, respectively, in compound **81**, suggesting addition of OMe and H across the C-19–C-20 double bond of **81**. This was consistent with the upfield shift of C-19 to δ 101.3 in **82**, suggesting attachment of two oxygen atoms to a sp^3 carbon as well as the observation of the ketal OMe at δ 47.9 and the methine C-20 at δ 46.9. The C-21 methylene was observed at δ 27.5.

The NOEs observed for H-17α/OCH_3-19 allowed the assignment of the relative configuration at C-19 (β-CH_3, α-OCH_3) while the β-orientation of H-20 was deduced from the NOE observed for H-20/CH_3-18 (Figure 2.69). The possibility that **82** is artifact arising from the use of methanol during extraction of alkaloids (albeit under mild conditions) cannot be completely ruled out.

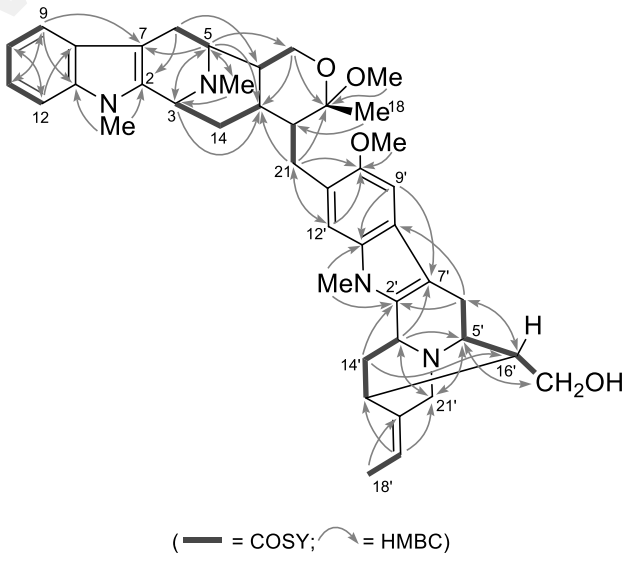


Figure 2.68: COSY and selected HMBCs of **82**

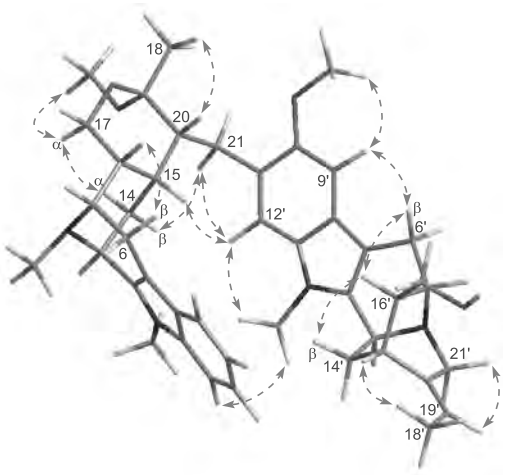


Figure 2.69: Selected NOEs of **82**

2.1.8.4 Angustilongine H (83)

Angustilongine H (**83**)[414] is an isomer of compound **82** as shown by the HRMS data ($[M + H]^+$ *m/z* 691.4217; $C_{43}H_{54}N_4O_4$). It was obtained as a light yellowish oil, with $[\alpha]^{25}_D$ +42.4 (*c* 0.09, $CHCl_3$). The UV (228, 286 nm) and IR (3403 cm^{-1}) data were similar to those of **82** (indole chromophore and OH), as were the 2D NMR data (COSY and HMBC; Figure 2.70).

The ^1H NMR data of **83** (Table 2.47) showed a close similarity with those of **82** while the ^{13}C NMR data (Table 2.48) were also essentially similar, except for notable differences in the resonances due to C-14, C-15, C-16, and C-21. These observations indicated an epimeric relationship, with C-20 likely to be the epimeric center, which was confirmed by the NOESY data. Comparison of the NOESY data showed that for compound **83** (with H-20α), NOE was observed between H-20 and H-14β (Figure 2.71), which was not seen in **82** (Figure 2.69). On the other hand, a NOE was observed between H-21a and H-14β for compound **82** (with H-20β, Figure 2.69), but was not seen in **83** (Figure 2.71). The configuration at C-19 was identical to that in compound **82** from the observed H-17α/OMe-19 NOEs. Compound **83** is therefore the 20*S* epimer of **82**. The ^1H NMR spectra of **80**–**83** are shown in Figures 2.72–2.75.

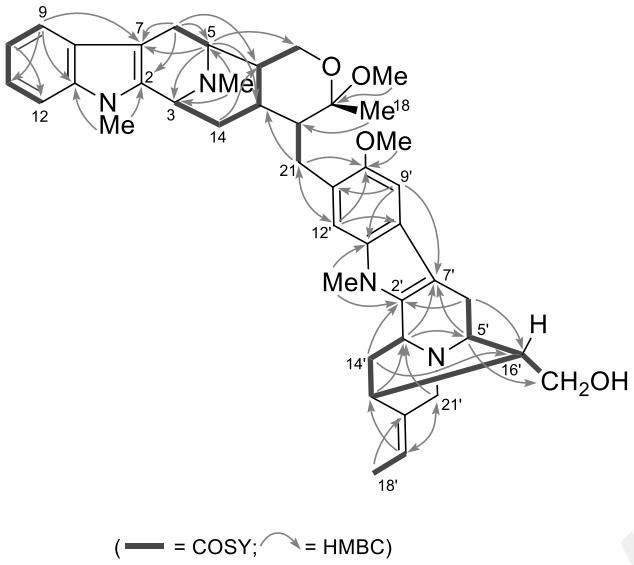


Figure 2.70: COSY and selected HMBCs of **83**

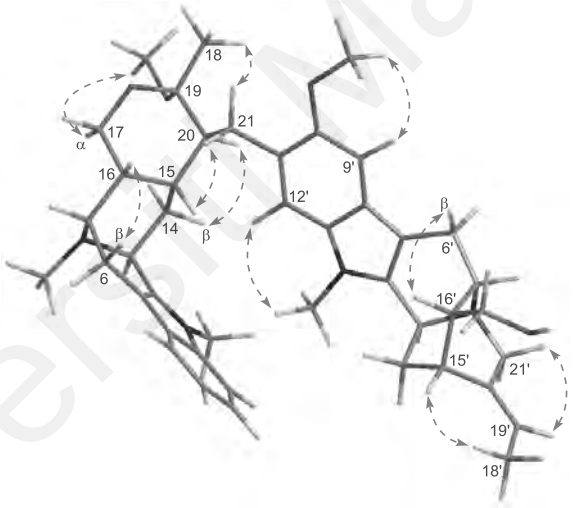


Figure 2.71: Selected NOEs of **83**

Table 2.47: ^{1}H NMR Spectroscopic Data (δ) of Angustilongines E–H (**80**–**83**)[a]

H	80 (*J*/Hz)[b]	81 (*J*/Hz)[c]	82 (*J*/Hz)[b]	83 (*J*/Hz)[b]
3	3.68 m	3.50 m	3.93 m	3.79 m
5	2.99 d (7.0)	2.94 m	2.93 m	2.98 d (7.0)
6β	2.34 d (16.0)	2.29 d (16.0)	2.33 d (16.0)	2.41 m
6α	3.19 dd (16.0, 7.0)	3.06 dd (16.0, 7.0)	3.16 dd (16.0, 7.0)	3.25 dd (16.0, 7.0)
9	7.39 d (7.0)	7.28 d (7.8)	7.33 d (7.7)	7.40 d (7.7)
10	7.03 t (7.0)	6.99 m	6.99 m	7.05 m
11	7.15 m	7.13 m	7.08 m	7.10 m
12	7.16 m	7.13 m	7.08 m	7.11 m
14β	1.30 br d (10.0)	1.22 m	1.73 m	1.21 ddd (12.5, 5.0, 3.0)
14α	1.83 m	1.69 m	2.80 m	2.97 m
15	1.84 m	1.45 m	1.84 m	1.84 m
16	1.84 m	1.80 m	1.79 m	2.17 m
17β	3.93 br d (11.0)	3.89 m	3.46 m	3.53 m
17α	4.29 t (11.0)	4.25 t (11.0)	4.20 t (11.5)	4.14 t (11.5)
18	1.24 d (7.2)	1.83 s	1.40 s	1.40 s
19	3.83 q (7.2)	-	-	-
20	-	-	1.84 m	1.53 m
21a	6.42 s	3.40 d (16.5)	2.50 m	2.37 m
21b	-	3.75 d (16.5)	2.93 m	3.05 dd (13.5, 3.0)
N(1)-Me	3.20 s	3.12 s	3.45 s	3.38 s
N(4)-Me	2.23 s	2.18 s	2.28 s	2.28 s
19-O<u>Me</u>	-	-	3.29 s	3.29 s
3'	4.16 br d (10.0)	3.92 m	4.02 br d (10.0)	4.02 br d (10.0)
5'	2.78 m	2.60 m	2.77 m	2.75 m
6'β	2.51 d (15.0)	2.60 m	2.50 m	2.44 d (15.0)
6'α	2.96 dd (15.0, 5.0)	2.97 m	2.95 m	2.90 dd (15.0, 5.0)
9'	6.62 s	-	6.69 s	6.44 s
11'	-	6.56 d (8.70)	-	-
12'	6.72 s	6.69 d (8.70)	6.41 s	6.54 s
14'β	1.56 ddd (12.0, 4.0, 2.0)	1.20 m	1.32 ddd (12.5, 4.0, 2.0)	1.55 m
14'α	2.02 m	1.84 m	1.94 m	2.01 ddd (12.0, 10.0, 2.0)
15'	2.78 m	2.77 m	2.78 m	2.80 m
16'	1.75 m	1.57 m	1.73 m	1.75 m
17'	3.50 m	3.51 m	3.49 m	3.52 m
17'	3.55 m	3.51 m	3.55 m	3.58 m
18'	1.62 d (6.8)	1.67 d (6.8)	1.66 d (7.0)	1.64 d (6.8)
19'	5.41 br q (6.8)	5.36 br q (6.8)	5.41 br q (7.0)	5.41 br q (6.8)
21'	3.60 m	3.49 m	3.59 m	3.60 m
21'	3.64 m	3.57 m	3.59 m	3.60 m
N(1')-Me	3.24 s	3.14 s	2.84 s	2.94 s
10'-OMe	3.54 s	3.60 s	3.71 s	3.62 s

[a]Assignments based on COSY, HSQC, and NOESY. [b]$CDCl_3$, 600 MHz.[c]$CDCl_3$, 400 MHz.

Table 2.48: ^{13}C NMR Spectroscopic Data (δ) of Angustilongines E–H (**80**–**83**)[a]

C	**80**[b]	**81**[c]	**82**[b]	**83**[b]
2	133.4	133.1	133.4	133.3
3	53.8	53.8	54.1	54.6
5	55.1	55.5	55.5	55.3
6	22.7	22.5	22.5	22.8
7	105.9	105.4	106.6	106.3
8	126.4	126.1	126.4	126.4
9	118.0	117.5	117.9	117.7
10	118.4	118.1	118.4	118.5
11	120.4	120.0	120.2	120.3
12	108.4	108.4	108.6	108.7
13	136.7	136.6[d]	136.7	136.9
14	32.8	32.5	27.0[f]	32.5
15	25.2	26.1	25.7	27.5[g]
16	40.3	40.9	43.8	37.4
17	66.0	66.1	61.3	61.8
18	21.3	16.8	22.7	21.2
19	32.6	144.2	101.3	101.7
20	120.3	108.4	46.9	45.7
21	139.1	26.4	27.5	31.6
N(1)-Me	28.3	28.8	28.6[e]	28.8
N(4)-Me	41.8	41.6	41.7	41.8
19-OMe	-	-	47.9	47.5
2'	139.1	140.0	139.2	138.8
3'	49.7	49.3	49.4	49.4
5'	54.3	54.3	54.2	54.2
6'	27.2	28.4	26.9[f]	27.0
7'	102.8	102.5	102.5	102.6
8'	125.3	128.0	123.5	125.6
9'	99.3	118.6	98.7	98.4
10'	152.0	151.1	151.9	151.9
11'	128.6	107.2	125.1	124.3
12'	106.9	106.7	109.6	110.0
13'	132.1	132.4	131.5	131.7
14'	33.0	32.5	32.8	33.0
15'	27.6	27.5	27.6	27.6[g]
16'	44.2	43.8	44.2	44.2
17'	65.2	65.2	65.2	65.1
18'	12.8	12.8	12.8	12.8
19'	116.5	116.3	116.5	116.5
20'	136.7	136.4[d]	136.4	136.9
21'	56.4	56.1	56.3	56.4
N(1')-Me	29.2	28.6	28.7[e]	28.6
10'-OMe	56.1	57.5	55.6	55.3

[a]Assignments based on DEPT, HSQC, and HMBC. [b]$CDCl_3$, 150 MHz. [c]$CDCl_3$, 100 MHz. [d-g]Interchangeable.

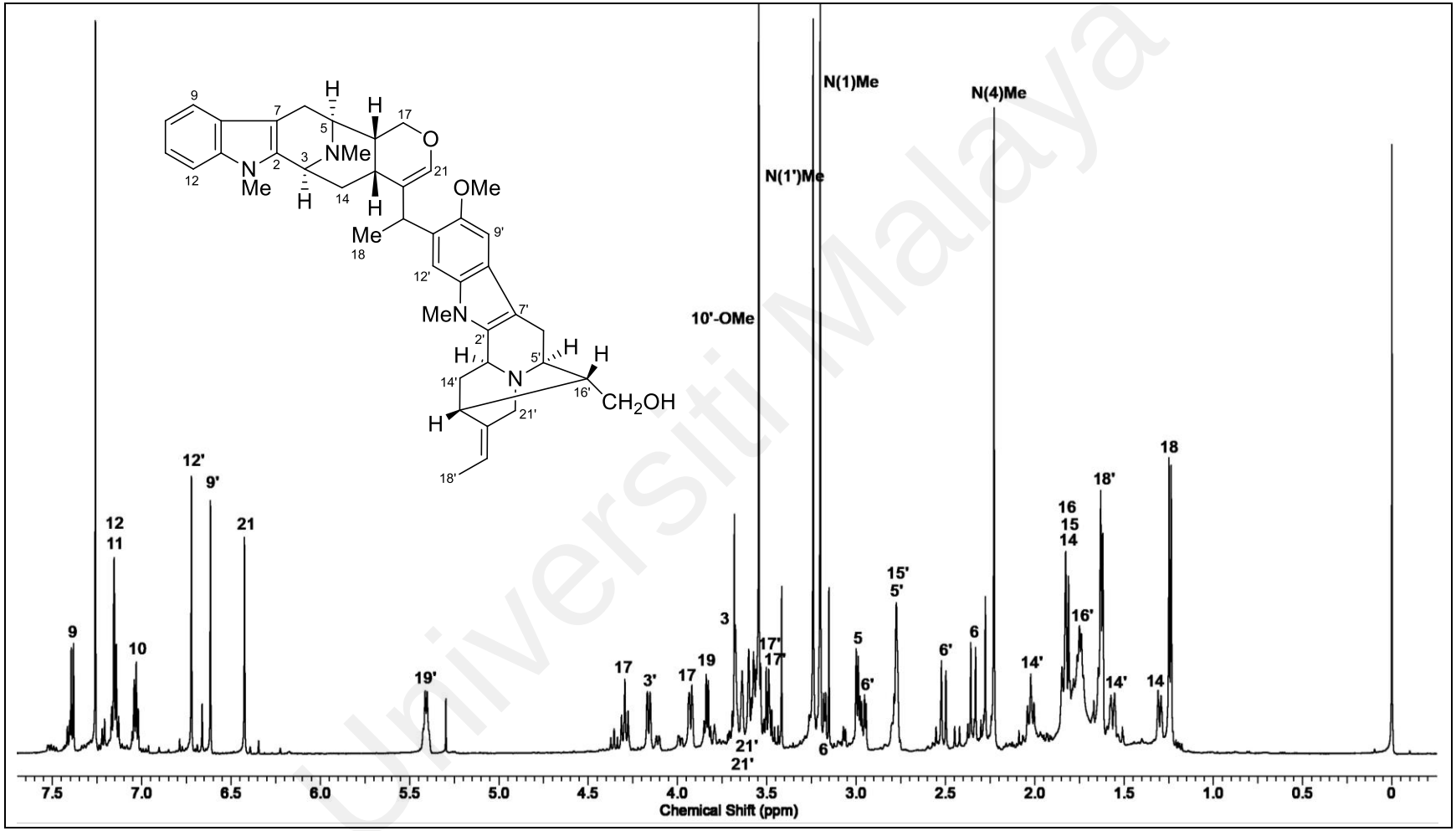


Figure 2.72: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Angustilongine E (**80**)

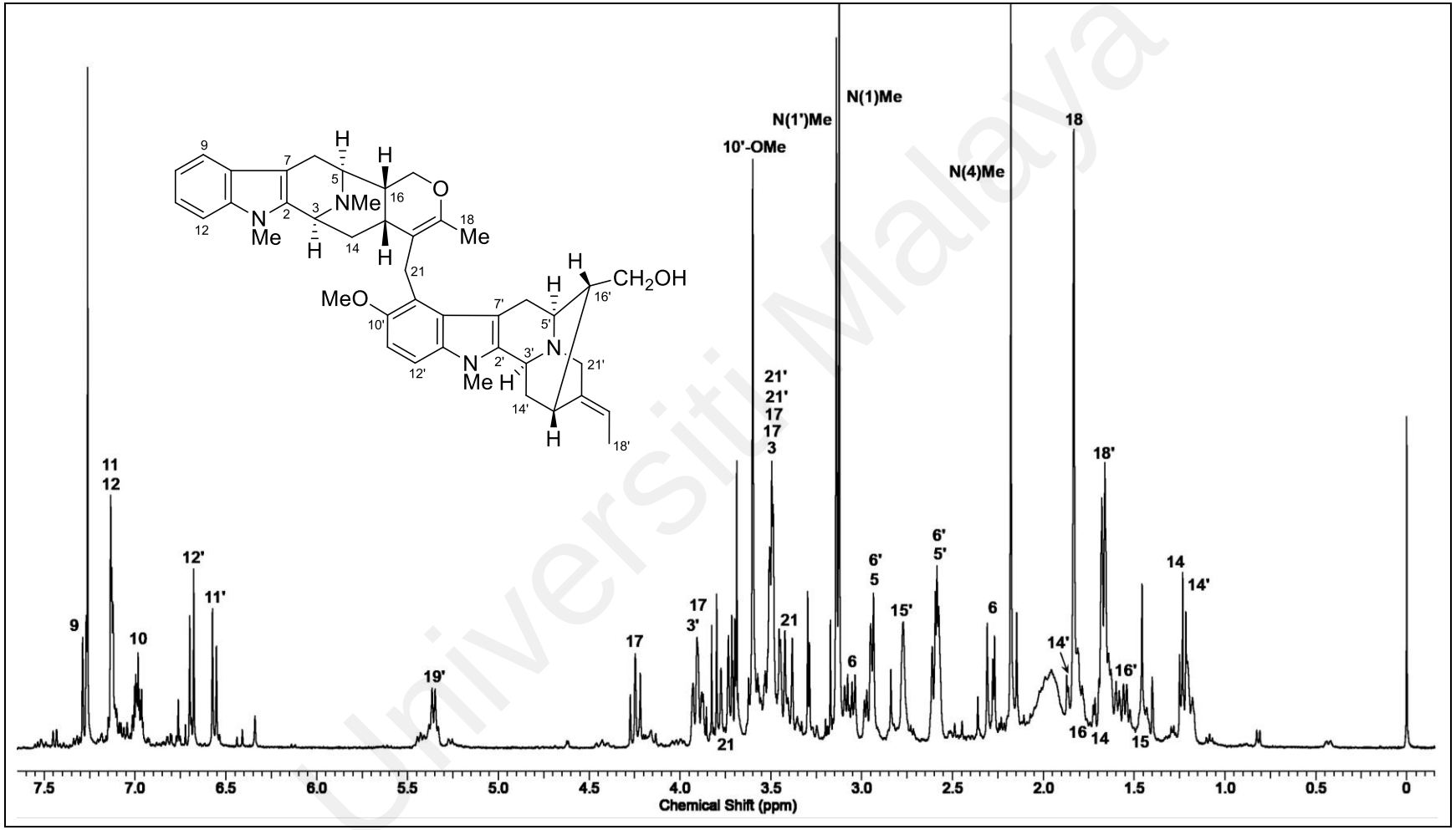


Figure 2.73: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Angustilongine F (**81**)

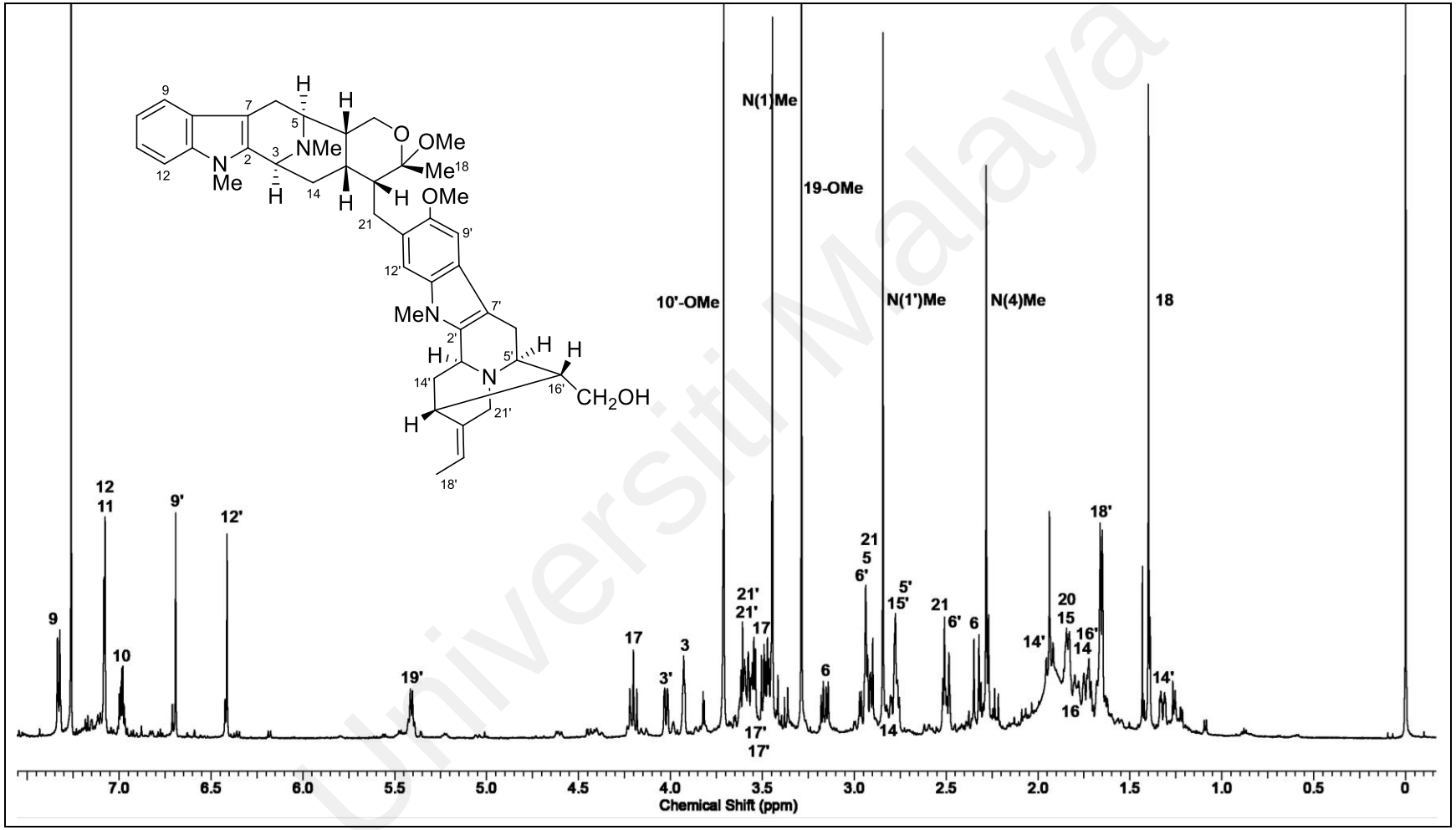


Figure 2.74: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Angustilongine G (**82**)

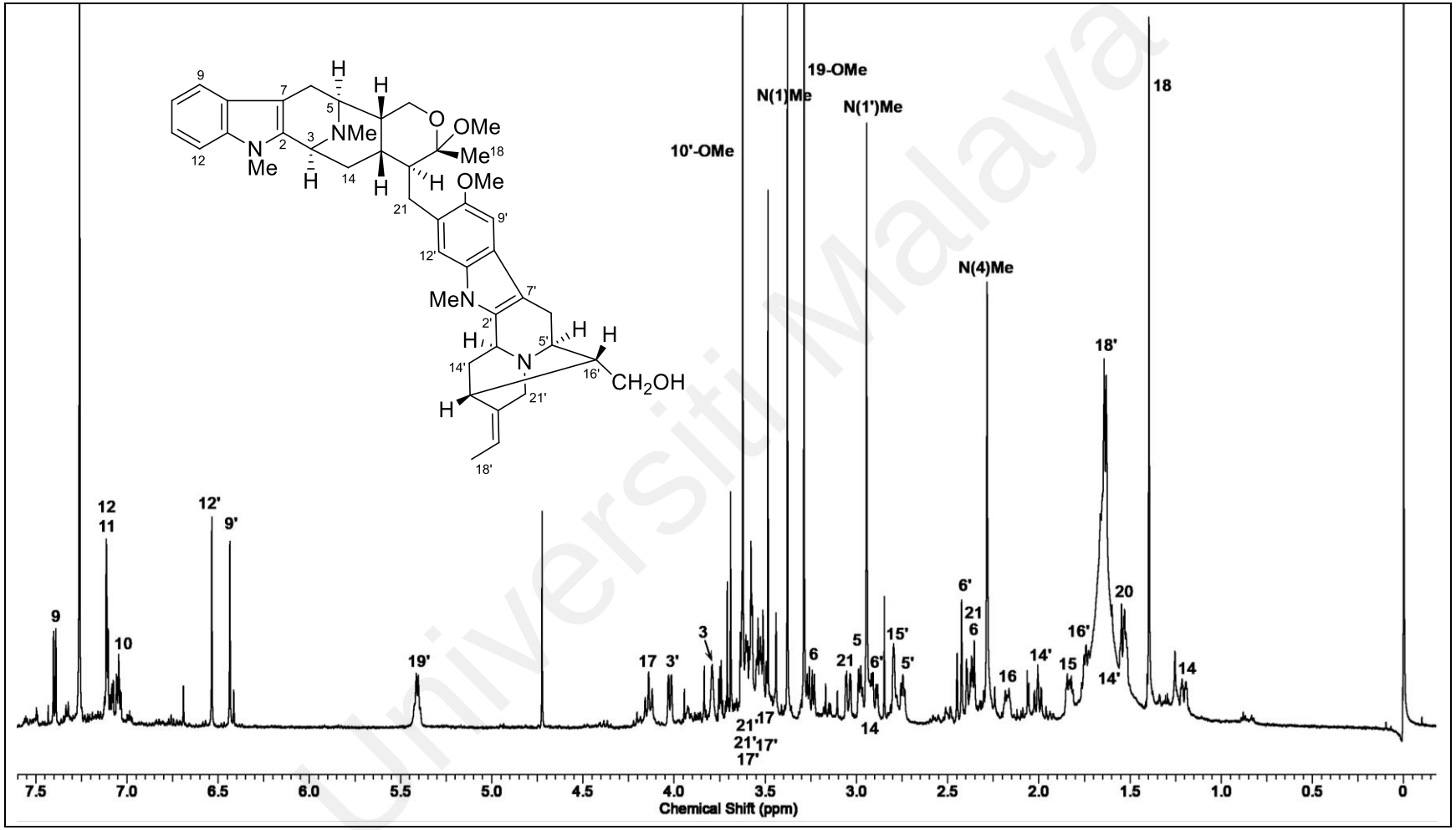


Figure 2.75: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Angustilongine H (**83**)

2.1.8.5 Angustilongine J (84)

Angustilongine J (**84**)[414] was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ +119.0 (*c* 0.26, $CHCl_3$). The UV spectrum showed absorption maxima (230 and 284 nm) characteristic of an indole chromophore, while the IR spectrum (3392 cm^{-1}) indicated the presence of an OH function. HRESIMS measurements ($[M + H]^+$ *m/z* 677.4087) gave the molecular formula $C_{42}H_{52}N_4O_4$.

As in the previous bisindole alkaloids (**80**–**83**), the ^1H (Table 2.49) and ^{13}C (Table 2.50) NMR data of **84** indicated constitution from macroline and sarpagine monomeric units. The resonances due to the lower methoxyaffinisine moiety could be readily assigned by comparison with the NMR data of **80**–**83**. The aromatic resonances resembled those of compound **81**, with the observation of a pair of aromatic AB doublets at δ 6.82 and 7.04, *J* = 8.8 Hz, (Table 2.49) indicating branching of the bisindole from C-9' of the sarpagine half.

The ^1H NMR data (Table 2.49) of the macroline half showed the presence of four aromatic hydrogens of an unsubstituted indole moiety (δ 7.14 –7.55), three methyl singlets, corresponding to N-1–Me (δ 3.58), N-4–Me (δ 2.35), and an acetyl methyl (δ 1.41, CH_3-18), geminal hydrogens of a hydroxymethyl due to $HOCH_2$-17 (δ 4.06, 4.52), and a methylene due to CH_2-21 (δ 2.74, 3.11). The ^{13}C NMR data (Table 2.50) of the ring E carbons, such as C-15, C-16, and the hydroxymethyl C-17 of the 'upper' macroline unit, showed a general similarity to those of compound **81**. However, notable differences were observed for the resonances due to C-18, C-19, and C-20, which were observed at δ 34.4, 214.6, and 52.9, respectively, in compound **84**, compared to δ 16.8, 144.2, and 108.4, respectively, in compound **81**. These changes, in particular that of C-19, were consistent with a ring-opened ring E where C-18, C-19, C-20 corresponds to a 2-oxo-propyl fragment linked to C-15 and C-21 from the methine C-20, as indicated by the HMBC data (^3J H-14/C-20, H-21/C-19, H-18/C-20; Figure 2.76).

The opened E ring in **84** renders the assignment of the relative configuration of C-20 to be not as straightforward compared to the ring closed alkaloids such as **82** and **83**, where stereochemical assignments are possible from the NOESY data. Analysis of the ^{1}H NMR data of **84** indicated that, although H-20 is a multiplet (δ 3.53), both of the C-21 hydrogens are well resolved (δ 2.74, dd, J = 13.0, 11.0 Hz, H-21a; δ 3.11, dd, J = 13.0, 5.0 Hz, H-21b). The large $J_{20–21}$ coupling of 11 Hz indicated that **84** adopts a preferred conformation about the C-20–C-21 bond which results in H-20 and H-21a being oriented *anti* to each another, presumably to minimize interactions due to the presence of three bulky groups bonded to these carbons. In view of this, as well as the observed H-20/H-14α, H-21a/H-15, and H-21b/H-16 NOEs (Figure 2.77), the configuration at C-20 could be assigned as *R*. A useful NMR-based method for the assignment of the C-20 configuration in the related bisindoles (e.g., perhentinine,[122] E-seco-macralstonine,[122] perhentisines A–C,[132] and perhentidines A–C[122]) was described previously. This approach is based on examination of the resonances of the hydroxymethyl C-17 hydrogens of the 'upper' macroline unit, which have been shown to be of diagnostic significance for the assignment of C-20 configuration in these compounds. These resonances are well separated in the 20*R* bisindoles ($\Delta\delta = \delta_{17b} - \delta_{17a} \sim 0.3–0.4$), but are close in the 20*S* bisindoles ($\Delta\delta = \delta_{17b} - \delta_{17a} \sim 0–0.1$). This trend reverses in the case of the *O*-acetyl derivatives. In the case of **84**, where the resonances of the OCH_2-17 hydrogens are well separated ($\delta_{17b} - \delta_{17a} = 0.46$), the C-20 configuration can be accordingly assigned as *R*.

Another interesting feature present in **84** is that this alkaloid behaves like macralstonine in that, in solution, it exists as an equilibrium mixture of ring-opened (ketone, **84**) and cyclized (hemiketal, **84a**) forms with the ring-opened form predominating in $CDCl_3$ solution, but exists essentially as the hemiketal in the solid state (as shown by the X-ray structure of macralstonine and the absence of the ketone

carbonyl IR band in macralstonine and **84**).[122,415] Thus, for compound **84** in $CDCl_3$ solution, the ratio of the acyclic (**84**) to the cyclized form (**84a**) was 3.79:1, while in CD_2Cl_2, it was 3.52:1, and in methanol-d_4, it was 1:2.16. The NMR signals for indole hydrogens and H-17 were used to monitor the ratios of these forms in various solvents.

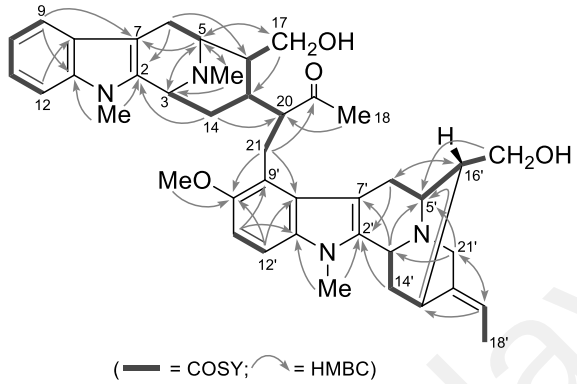


Figure 2.76: COSY and selected HMBCs of **84**

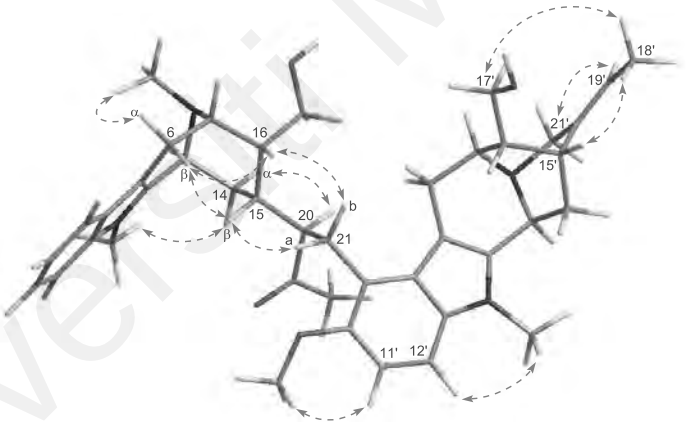


Figure 2.77: Selected NOEs of **84**

2.1.8.6 Angustilongine K (85)

Angustilongine K (**85**)[414] was isolated as a light yellowish oil, with $[\alpha]^{25}_D$ +61.0 (*c* 0.26, $CHCl_3$). The UV (228 and 286 nm) and IR (3383 cm^{-1}) spectra were similar to those of **84**, indicating the presence of similar chromophore (indole) and functional group (OH). The molecular formula, $C_{42}H_{52}N_4O_4$, from the HRESIMS data ($[M + H]^+$ *m/z* 677.4085) indicated that it is isomeric with **84**.

The NMR data (Tables 2.49–2.50) showed similarities with those of **84**, except for the aromatic resonances of the 10-methoxyaffinisine unit, which in **85** was observed as two singlets at δ 6.72 and 6.83, compared to a pair of AB doublets at δ 6.82 and 7.04 (*J* ~ 9 Hz) in **84**. Apart from this major difference, the NMR data (including the 2D NMR data; Figure 2.78) of **85** were essentially similar to those of **84**, indicating a similar structure, except for branching of the bisindole from C-11' in **85**, which was also supported by the observed three-bond correlations H-21/C-19,C-10',C-12' in the HMBC spectrum (Figure 2.78). The NOEs observed for H-9'/10'-OMe and H-12'/N-1'-Me (Figure 2.79) were also consistent with the presence of a 10',11'-disubstituted sarpagine moiety.

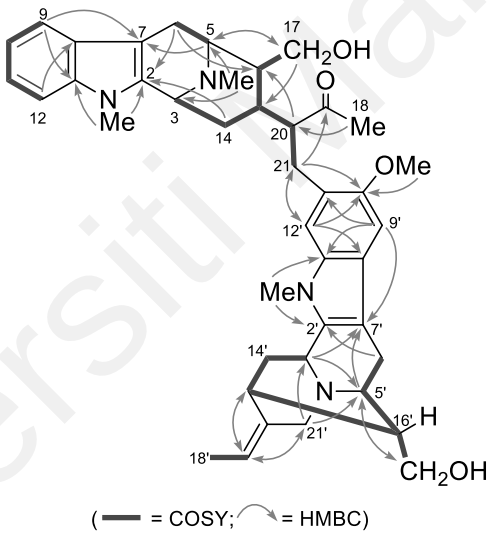


Figure 2.78: COSY and selected HMBCs of **85**

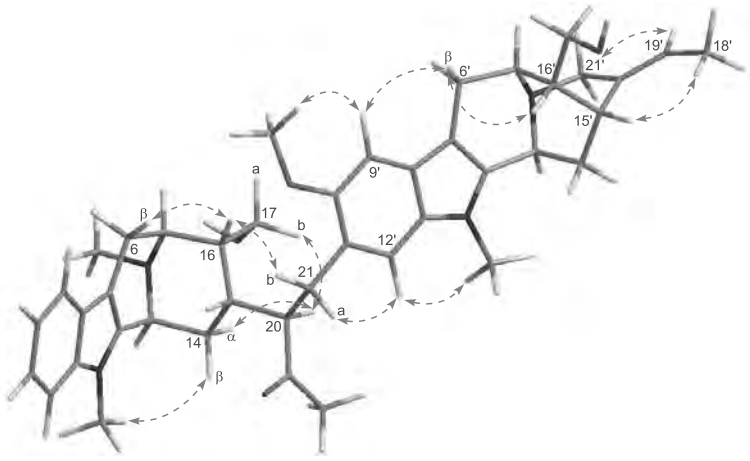


Figure 2.79: Selected NOEs of **85**

Since, in contrast to **84**, the H-20 and H-21 resonances were poorly resolved in **85**, acetylation (Ac_2O/pyr) was carried out, which gave the di-*O*-acetyl derivative **85b**, which, unlike the parent alkaloid, showed well-resolved H-20 and H-21 resonances in the ^1H NMR spectrum (Table 2.51). Thus, for **85b**, H-20 was clearly observed at δ 3.02 as a td with J = 11.0 and 3.7 Hz, while the C-21 hydrogens were observed at δ 2.38 (H-21a, dd, J = 13.0, 11.0 Hz) and 3.23 (H-21b, dd, J = 13.0, 3.7 Hz). As in the case of **84**, the large $J_{20\text{-}21}$ coupling of 11 Hz coupled with the observed H-20/H-14α, H-17 and H-21b/H-17 NOEs (Figure 2.79), allowed the assignment of the 20*R* configuration for **85b** and hence the parent alkaloid **85**.

Furthermore, as discussed above in the case of **84**, the resonances of the hydroxymethyl C-17 hydrogens in **85** are well separated ($\delta_{17b} - \delta_{17a} = 0.30$), allowing the assignment of the C-20 configuration in **85** as *R*. In the *O*-acetyl derivative **85b**, this trend reverses and the resonances due to the C-17 hydrogens were found to be coincident ($\Delta\delta = \delta_{17b} - \delta_{17a} \sim 0$), consistent with the assignment of a 20*R* configuration.

In addition, compound **85** also behaves like **84** in that the open-chain (**85**) and cyclic (**85a**) forms coexist in equilibrium in $CDCl_3$ solution (**85**:**85a**; ratio 2.80:1). The ratio of the acyclic hydroxyketone form to the cyclized hemiketal form was 2.38:1 in CD_2Cl_2, 1:2.89 in MeOD-d_4, and 1:2.50 in MeCN-d_3. The NMR signals for indole hydrogens and H-17 were used to monitor the ratios of these forms in various solvents. The NMR spectra of **84**, **85**, and **85b** are shown in Figure 2.80–2.82.

Table 2.49: ^{1}H NMR Spectroscopic Data (δ) of Angustilongines J–K (**84**–**85**)[a]

H	84 (*J*/Hz)	84a (*J*/Hz)	85 (*J*/Hz)	85a (*J*/Hz)
3	3.96 m	3.82 m	3.99 m	3.94 m
5	3.56 m	2.93 d (6.8)	3.59 m	2.94 m
6	2.57 d (16.7) (β)	2.40 d (16.3) (β)	2.55 m (β)	2.34 m (β)
6	3.33 m (α)	3.22 dd (16.3, 6.8) (α)	3.34 m (α)	3.17 dd (16.3, 7.1) (α)
9	7.55 d (8.0)	7.45 d (8.0)	7.51 d (8.0)	7.34 d (8.0)
10	7.14 t (8.0)	7.07 t (8.0)	7.13 t (8.0)	7.00 m
11	7.23 t (8.0)	7.16 m	7.21 td (8.0, 1.0)	7.09 m
12	7.34 d (8.0)	7.19 d (8.0)	7.30 d (8.0)	7.09 m
14	1.51 br d (12.0) (β)	1.47 m	1.42 br d (12.0) (β)	1.75 m
14	2.23 td (12.0, 4.5) (α)	2.75 m	2.33 m (α)	2.83 m
15	2.08 m	1.68 m	2.03 m	1.89 m
16	1.85 m	1.88 m	1.88 m	1.80 m
17	4.06 dd (11.0, 2.0) (a)	3.46 m (β)	4.12 m (a)	3.50 m (β)
17	4.52 d (11.0) (b)	4.45 t (11.6) (α)	4.42 dd (11.0, 1.5) (b)	4.51 t (11.6) (α)
18	1.41 s	1.05 s	1.52 s	1.47 s
20	3.53 m	2.32 m	3.38 m	1.85 m
21a	2.74 dd (13.0, 11.0)	2.65 m	2.36 m	2.36 m
21b	3.11 dd (13.0, 5.0)	3.12 m	3.10 dd (13.0, 4.0)	3.10 m
N(1)-Me	3.58 s	3.24 s	3.58 s	3.44 s
N(4)-Me	2.35 s	2.30 s	2.38 s	2.29 s
3'	4.10 d (10.0)	4.16 br d (9.6)	4.12 m	4.02 br d (9.4)
5'	2.58 m	2.60 m	2.77 m	2.77 m
6'	2.69 m (β)	3.01 m	2.56 m (β)	2.50 d (14.5) (β)
6'	2.78 dd (15.0, 4.7) (α)	3.09 m	2.99 dd (15.0, 5.0) (α)	2.99 m (α)
9'	-	-	6.83 s	6.71 s
11'	6.82 d (8.8)	6.85 d (8.8)	-	-
12'	7.04 d (8.8)	6.41 d (8.8)	6.72 s	6.45 s
14'	1.56 br d (12.0) (β)	1.61 m	1.62 m (β/a)	1.35 br d (12.1)
14'	1.98 ddd (12.0, 10.0, 1.4) (α)	2.03 m	2.04 m (α/b)	1.94 m
15'	2.70 m	2.70 m	2.79 m	2.79 m
16'	1.60 m	1.72 m	1.79 m	1.85 m
17'	3.32 m	3.38 m	3.51 m	3.51 m
17'	3.32 m	3.27 m	3.57 m	3.57 m
18'	1.60 d (6.7)	1.60 m	1.62 d (6.7)	1.65 d (6.7)
19'	5.35 br q (6.7)	5.35 m	5.39 br q (6.7)	5.41 m
21'	3.50 m	3.50 m	3.58 m	3.58 m
	3.55 m	3.55 m	3.58 m	3.58 m
N(1')-Me	3.52 s	3.52 s	3.47 s	2.87 s
10'-OMe	3.92 s	3.92 s	3.89 s	3.72 s

[a]Assignments based on COSY, HSQC, and NOESY. $CDCl_3$, 600 MHz.

Table 2.50: ^{13}C NMR Spectroscopic Data (δ) of Angustilongines J–K (**84**–**85**)[a]

C	84	84a	85	85a
2	132.9	133.1	132.6	133.8
3	53.2	54.1	53.1	54.0
5	59.8	55.4	59.7	55.5
6	22.4	22.6	22.4	22.4
7	106.0	106.3	105.9	106.6
8	126.4	126.4	126.1[b]	126.1
9	118.0	117.7	118.0	117.9
10	118.8	118.4	118.9	118.5
11	121.0	120.1	121.0	120.3
12	109.2	108.7	109.0	108.6
13	137.3	136.8	137.3	136.8
14	32.5	26.3	32.9	26.8
15	31.9	29.2	32.3	26.0
16	42.1	44.6	42.1	43.9
17	66.3	61.1	66.2	61.3
18	34.4	29.3	33.7	29.5
19	214.6	98.5	214.6	98.9
20	52.9	44.8	53.7	45.5
21	27.6	27.2	33.0	27.8
N(1)-Me	29.0	28.5	29.4[c]	28.7
N(4)-Me	41.3	41.8	41.4	41.7
2'	140.8	140.8	139.7	139.5
3'	49.7	49.7	49.5	49.5
5'	54.8	55.3	54.2	54.2
6'	28.8	29.5	27.2	27.1
7'	103.4	103.2	103.0	102.6
8'	127.0	127.3	126.4[b]	126.4
9'	117.7	117.7	98.6	98.8
10'	151.3	151.5	151.8	152.0
11'	105.9	106.3	121.3	125.2
12'	106.8	106.9	110.7	109.6
13'	133.2	133.3	132.0	131.6
14'	33.1	33.1	33.0	32.8
15'	27.8	27.6	27.7	27.7
16'	44.6	43.6	44.4	44.2
17'	65.2	65.5	65.2	65.2
18'	12.7	12.7	12.8	12.8
19'	116.3	116.3	116.4	116.4
20'	136.1	136.1	136.4	136.4
21'	56.2	56.2	56.4	56.4
N(1')-Me	29.3	29.3	29.0[c]	28.7
10'-OMe	56.4	56.5	55.6	55.6

[a]$CDCl_3$, 150 MHz; assignments based on DEPT, HSQC, and HMBC. [b-c]Interchangeable.

Table 2.51: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Di-*O*-acetylangustilongine K (**85b**)[a]

H/C	δ_C	δ_H (*J*/Hz)	H/C	δ_C	δ_H (*J*/Hz)
2	133.4	-	2'	139.5	-
3	53.1	3.89 m	3'	49.4	4.12 br d (10.0)
5	53.6	3.41 br d (7.0)	5'	54.3	2.76 m
6	22.1	2.47 d (16.5) (β)	6'	27.0	2.55 d (15.0) (β)
6		3.33 dd (16.5, 7.0) (α)	6'		2.98 dd (15.0, 5.0) (α)
7	106.7	-	7'	102.8	-
8	126.6	-	8'	126.1	-
9	118.0	7.53 d (8.0)	9'	98.8	6.83 s
10	118.7	7.12 t (8.0)	10'	151.8	-
11	120.8	7.20 t (8.0)	11'	121.3	-
12	108.9	7.29 d (8.0)	12'	110.5	6.74 s
13	137.2	-	13'	132.0	-
14	31.6[b]	1.26 br d (13.0) (β)	14'	32.5	1.64 m
14		1.85 td (13.0, 4.0) (α)	14'		2.06 m
15	31.5[b]	2.05 m	15'	27.5	2.75 m
16	42.1[c]	2.21 m	16'	40.8	1.96 m
17	62.5	4.57 m	17'	66.1	3.86 m
17		4.57 m	17'		4.02 dd (11.0, 6.0)
18	32.5	1.46 s	18'	12.7	1.57 d (6.8)
19	213.9	-	19'	117.1	5.42 q (6.8)
20	54.0	3.02 td (11.0, 3.7)	20'	135.3	-
21a	32.2	2.38 dd (13.0, 11.0)	21'	56.4	3.60 m
21b		3.23 dd (13.0, 3.7)	21'		3.60 m
N(1)-Me	29.0	3.56 s	N(1')-Me	29.4	3.47 s
N(4)-Me	41.9[c]	2.30 s	10'-OMe	55.5	3.87 s
O<u>C</u>OMe	171.4	-	O<u>C</u>OMe'	171.1	-
OCO<u>Me</u>	21.3	2.14 s	OCO<u>Me</u>'	20.9	2.00 s

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C). [b-c]Interchangeable.

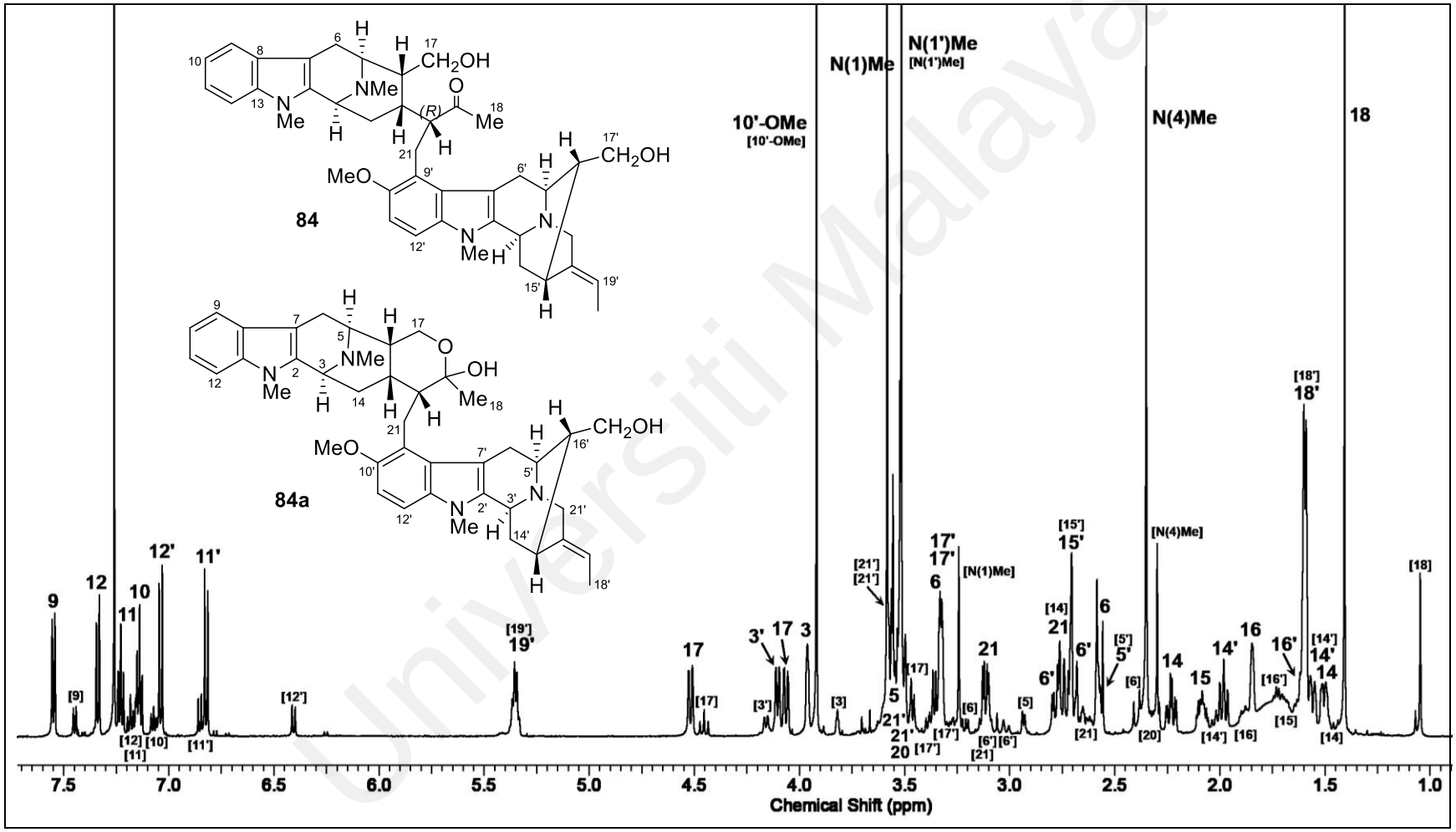


Figure 2.80: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Angustilongine J (**84**) and E-Seco angustilongine J [**84a**]

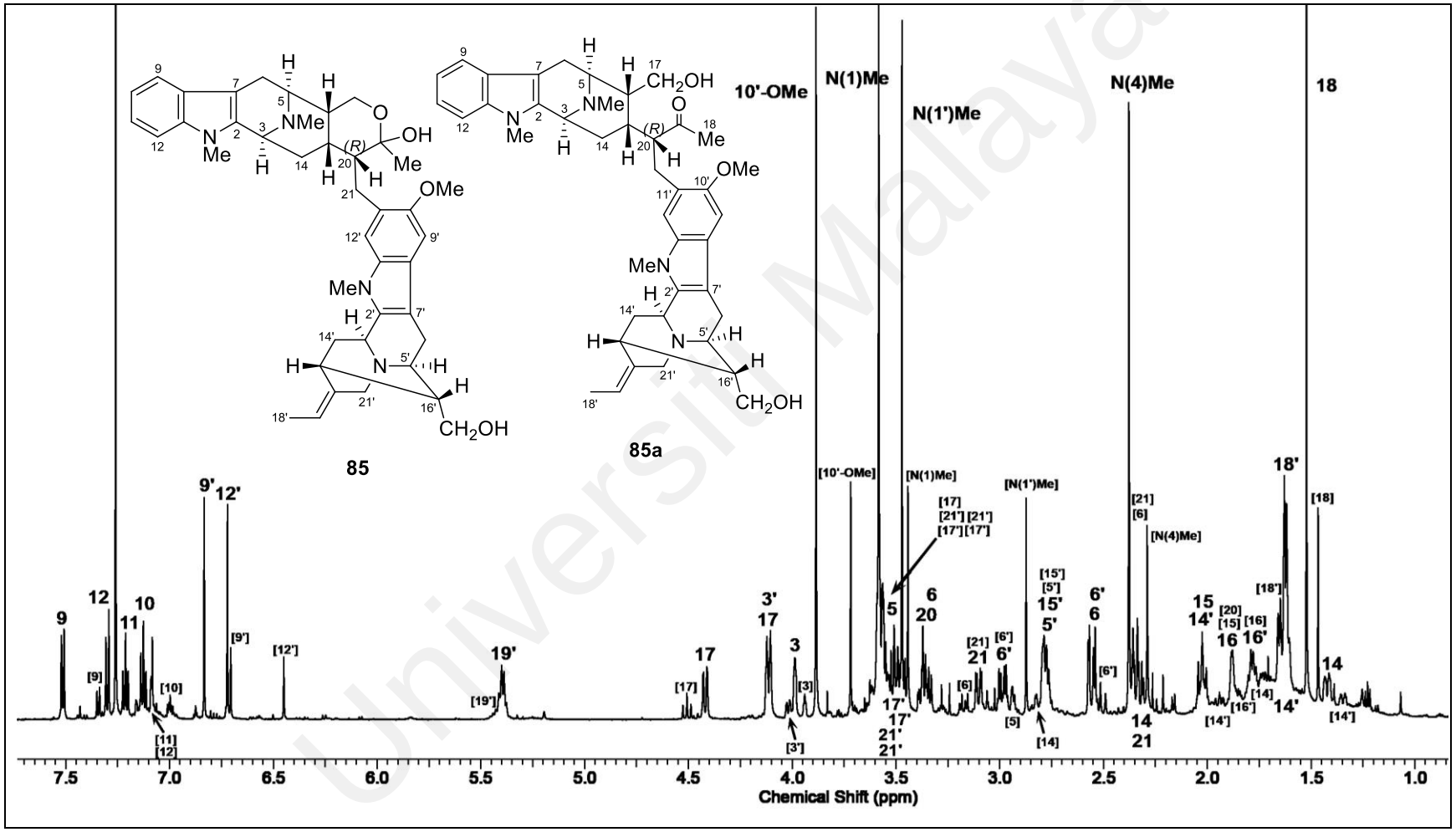


Figure 2.81: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Angustilongine K (**85**) and E-Seco angustilongine K [**85a**]

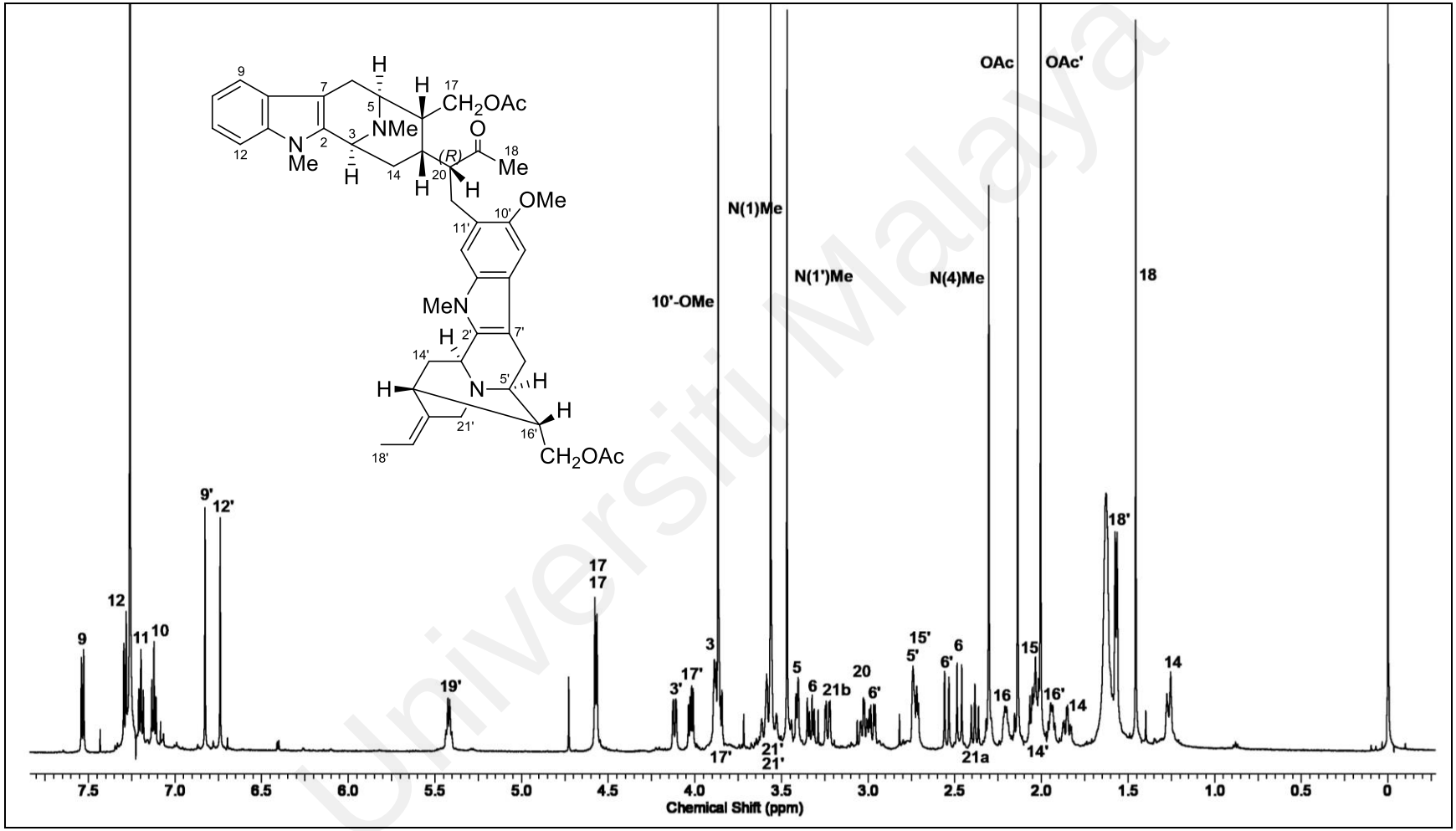


Figure 2.82: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Di-*O*-acetylangustilongine K (**85b**)

2.1.8.7 Angustilongine M (86)

Angustilongine M (**86**) was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ +5.2 (*c* 0.23, $CHCl_3$). The UV spectrum (229 and 285 nm) showed the presence of an indole chromophore, while the IR spectrum (3427 cm^{-1}) indicated the presence of an OH group. HRMS measurements ($[M + H]^+$ *m/z* 645.3804) gave the molecular formula $C_{41}H_{48}N_4O_3$.

The ^1H (Table 2.52) and ^{13}C (Table 2.53) NMR data showed resonances similar to bisindoles **80**–**85**, suggesting the presence of a macroline-sarpagine bisindole. The 2D NMR data (Figure 2.83) were also consistent with the constitution from macroline ($NCHCH_2$, $NCHCH_2CHCHCH_2O$, CH_3CH) and sarpagine ($NCHCH_2CH$, $NCH(CH_2)CHCH_2O$, CH_3CH) units. The ^1H NMR data (Table 2.52) indicated the presence of four aromatic hydrogens of an unsubstituted indole moiety (δ 7.12–7.53; macroline), a pair of aromatic AB doublets at δ 6.78 and δ 7.00 (*J* = 8.5 Hz) corresponding to a vicinally-substituted indole moiety (sarpagine), a deshielded hydrogen at δ 5.46 due to an acetal function (macroline), an ethylidene side chain (δ 1.64, 5.42; sarpagine), a methyl doublet at δ 1.23 (CH_3-18; macroline), an oxymethylene due to OCH_2-17 (δ 3.87, 4.10; macroline), a hydroxymethyl due to $HOCH_2$-17' (δ 3.52, 3.61; sarpagine), and three NMe groups (δ 3.64, 2.29, macroline; δ 3.54, sarpagine). The ^{13}C NMR data (Table 2.53) showed a total of 41 carbon resonances, including five methyl, seven methylene, 18 methine, an oxygenated tertiary sp^2 carbon (δ 144.6), four tertiary carbon atoms bonded to the two indolic nitrogen atoms, and six quaternary carbon atoms. The presence of an acetal group was indicated by the deshielded methine resonance at δ_C 94.3 suggestive of attachment to two oxygen atoms (C-21), while the methylene signals at δ_C 65.3 and 65.0 are consistent with the presence of the oxymethylene C-17 and the hydroxymethyl C-17', respectively. The

olefinic resonances at δ_C 117.0 and 135.4 correspond to C-19' and C-20', respectively of the ethylidene side chain (sarpagine).

The NOE observed between N-1'–Me of the sarpagine half at δ 3.54 and the aromatic doublet at δ 7.00, allowed the assignment of this resonance to H-12' and the other aromatic doublet at δ 6.78 to H-11' (Figure 2.84). In addition, the three-bond correlation observed from H-12' to the oxygenated aromatic carbon at δ 144.6 in the HMBC spectrum indicated oxygen substitution at C-10', leaving C-9' as the branching point of the bisindole from the 'lower' sarpagine half (Figure 2.83). Since only three oxygen atoms are indicated by the MS data and there was no evidence for the presence of an aromatic methoxy group, the other branching point from the sarpagine half must be via the oxygen linked to C-10'. The presence of a MeCHCHCH–O unit corresponding to C-18–C19–C-20–C-21 indicated that the 'upper' unit corresponds to a type B macroline. The presence of an acetal function indicated bonding of C-21 (δ_C 94.3) to two oxygen atoms, one of which was linked to C-17 from the H-17 to C-21 three bond correlation (Figure 2.83). The other oxygen was linked to C-10' of the sarpagine half from the three bond H-21 to the C-10' correlation. Likewise, the observed Me-18 to C-9' correlation (Figure 2.83), indicated that the bisindole is linked from C-19 of the macroline half to C-9' of the sarpagine unit. This mode of fusion of the two halves has resulted in the formation of an additional ring (F) between the two indole units.

The α-orientation of H-21 was indicated by the NOEs observed for H-21/H-17α and H-21/H-14α (Figure 2.84), while the rings E/F *cis* fusion requires the adjacent H-20 to be also α-oriented. This inference was also supported by the observed small vicinal $J_{20\text{-}21}$ coupling of 2.5 Hz in the ^{1}H NMR spectrum (Figure 2.85). The orientation of Me-18 was assigned as α from the NOEs observed for H-18/H-20 and H-19/H-16. Angustilongine M is related to macralstonidine[149] in that the former incorporates a type

B, while the latter a type A macroline half. Other linearly-fused bisindoles reported previously include lumutinines A–B (macroline-macroline),[52] macralstonidine[149] and lumutinines C–E (macroline-sarpagine),[52,132] and angustilongine B, foliacraline and alstocraline (macroline-akuammiline).[126,382] A plausible biogenetic pathway to alkaloids **80**–**86** is shown in Scheme 2.2.

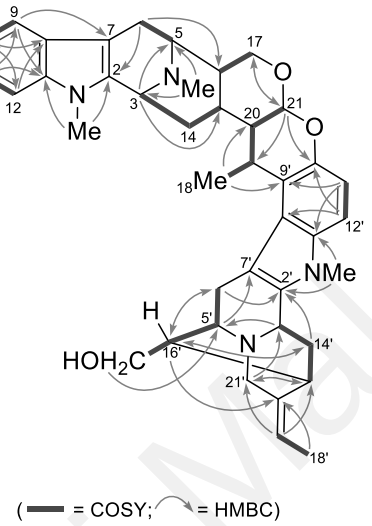


Figure 2.83: COSY and selected HMBCs of **86**

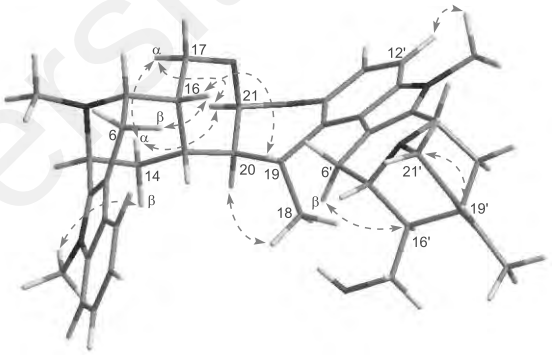
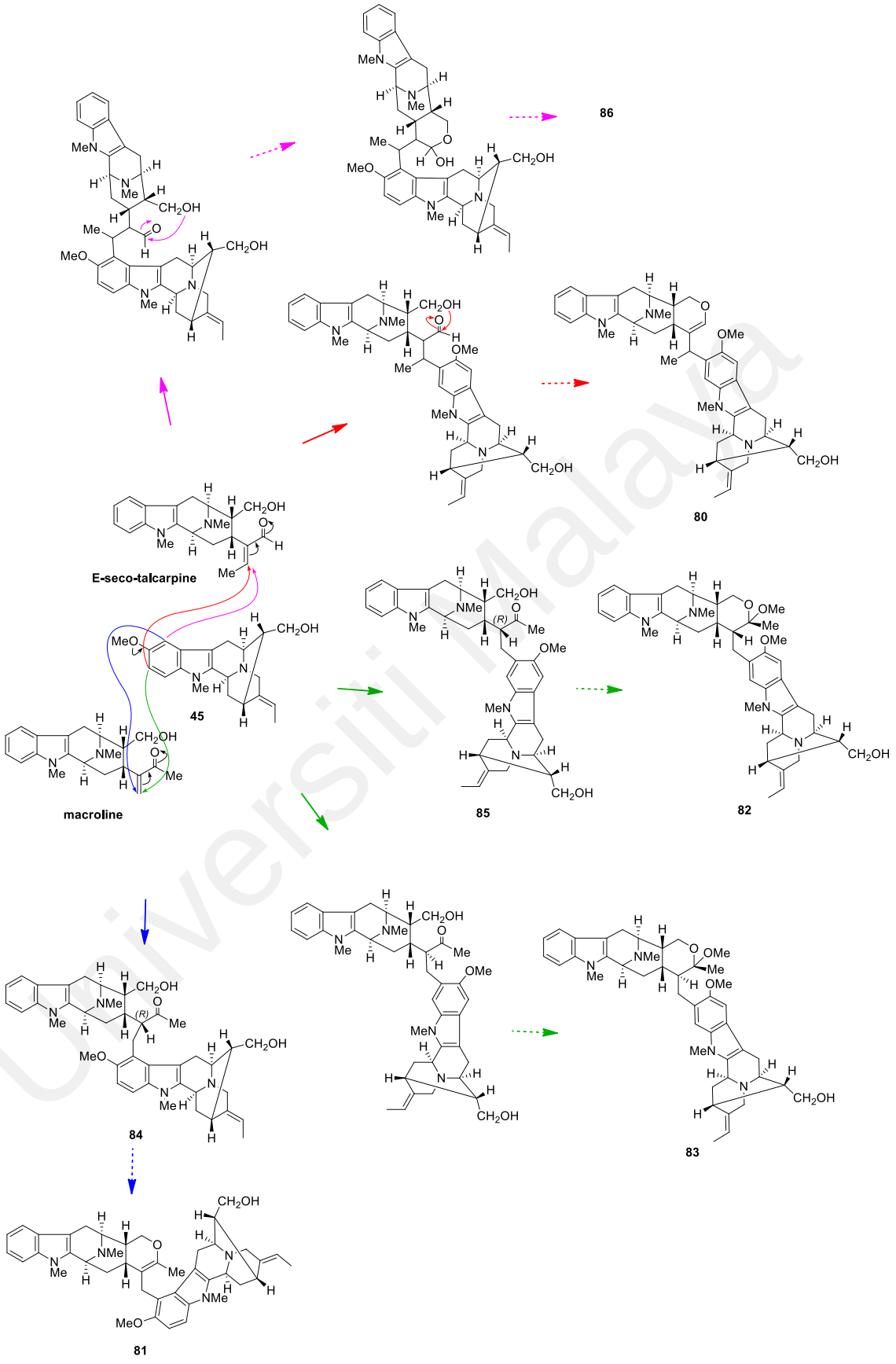


Figure 2.84: Selected NOEs of **86**

2.1.8.8 Macralstonidine (87)

A known macroline-sarpagine bisindole, namely macralstonidine (**87**)[149] was also isolated in the present study. The ^{1}H and ^{13}C NMR data of **87** are summarized in Tables 2.52–2.53, and the ^{1}H NMR spectrum is shown in Figure A49 (see Appendix). Other data are given in the Experimental Section.



Scheme 2.2: Possible biogenetic pathway to **80**–**86**

Table 2.52: ^{1}H NMR Spectroscopic Data (δ) of Angustilongine M (**86**)[a] and Macralstonidine (**87**)[b]

H	86 (*J*/Hz)	87 (*J*/Hz)	H	86 (*J*/Hz)	87 (*J*/Hz)
3	3.93 m	3.75 m	3'	4.19 br d (9.5)	4.16 br d (10.0)
5	3.03 m	3.00 d (7.0)	5'	2.79 m	2.64 d (5.0)
6	2.37 d (16.0) (β)	2.45 br d (16.0)	6'	2.80 m (β)	2.67 br d (15.0)
6	3.23 dd (16.0, 6.4) (α)	3.27 dd (16.0, 7.0)	6'	3.13 br dd (15.0, 4.3) (α)	3.17 dd (15.0, 5.0)
9	7.53 d (8.0)	7.51 br d (7.5)	9'	-	-
10	7.12 t (8.0)	7.11 td (7.5, 1.0)	11'	6.78 d (8.7)	6.72 d (9.0)
11	7.21 t (8.0)	7.18 td (7.5, 1.0)	12'	7.00 d (8.7)	7.04 d (9.0)
12	7.31 d (8.0)	7.27 br d (7.5)	14'	1.74 m (β)	1.74 m
14	1.66 m (β)	1.21 m	14'	2.09 m (α)	2.10 m
14	2.46 m (α)	2.33 td (13.0, 4.0)	15'	2.86 m	2.87 m
15	1.78 m	1.86 m	16'	1.96 m	1.79 m
16	1.94 m	2.01 m	17'	3.52 m	3.53 m
17	3.87 br dd (11.5, 4.1) (β)	3.68 dd (11.5, 4.0)	17'	3.61 m	3.53 m
17	4.10 m (α)	4.62 t (11.5)	18'	1.64 d (6.6)	1.65 d (6.8)
18	1.23 d (6.7)	1.37 s	19'	5.42 br q (6.6)	5.41 q (6.8)
19	3.01 m		21'	3.61 m	3.53 m
20	1.88 m	1.96 m	21'	3.61 m	3.60 m
21	5.46 br d (2.5)	2.77 br d (17.5)	N(1')-Me	3.54 s	3.57 s
21	-	3.23 m			
N(1)-Me	3.64 s	3.45 s			
N(4)-Me	2.29 s	2.28 s			

[a]$CDCl_3$, 600 MHz; assignment based on COSY, HSQC and NOESY. [b]$CDCl_3$, 400 MHz.

Table 2.53: ^{13}C NMR Spectroscopic Data (δ) of Angustilongine M (**86**)[a] and Macralstonidine (**87**)[b]

C	86	87	C	86	87
2	133.8	133.3	2'	139.9	139.4
3	52.8	53.9	3'	49.4	49.4
5	54.2	55.0	5'	54.5	54.2
6	22.4	22.6	6'	29.3	29.3
7	106.1	106.8	7'	102.3	103.1
8	126.8	126.3	8'	124.8	124.9
9	118.1	117.8	9'	118.9	111.2
10	118.7	118.7	10'	144.6	147.4
11	120.8	120.6	11'	111.9	112.3
12	109.0	108.8	12'	107.6	107.5
13	137.1	136.8	13'	133.3	132.3
14	31.2	26.7	14'	32.9	32.8
15	30.1	30.3	15'	27.5	27.4
16	37.9	43.3	16'	44.0	44.1
17	65.3	62.2	17'	65.0	64.7
18	26.5	25.4	18'	12.8	12.8
19	30.0	98.8	19'	117.0	116.8
20	44.5	36.9	20'	135.4	135.5
21	94.3	26.5	21'	56.1	55.9
N(1)-Me	29.3	29.3	N(1')-Me	29.1	29.0
N(4)-Me	41.3	41.6			

[a]$CDCl_3$, 150 MHz; assignments based on DEPT, HSQC, and HMBC. [b]$CDCl_3$, 100 MHz.

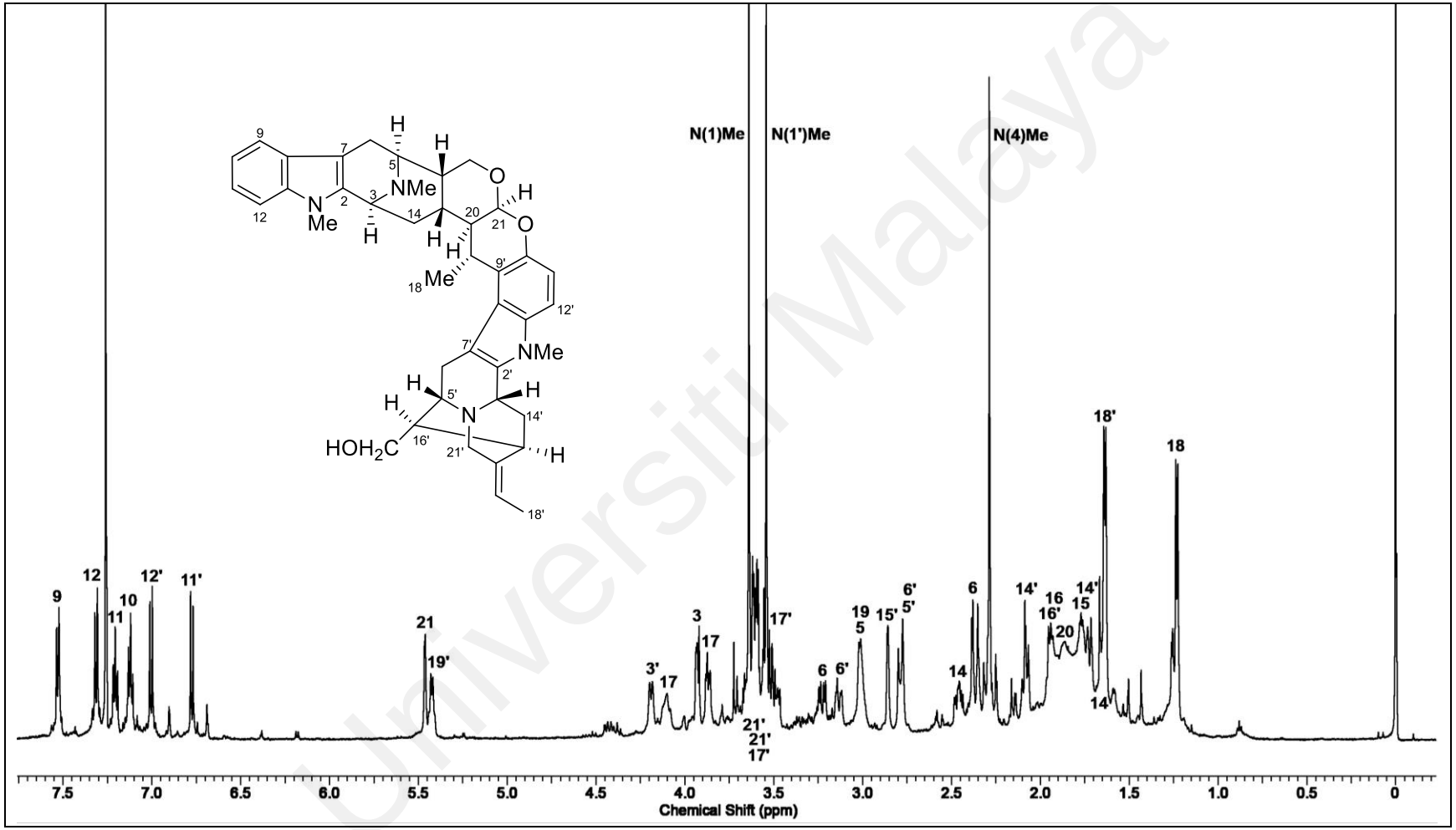


Figure 2.85: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Angustilongine M (**86**)

2.1.9 Macroline-Pleiocarpamine Bisindole Alkaloids

2.1.9.1 Angustilongine L (88)

Angustilongine L (**88**)[414] was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ −18 (*c* 0.13, $CHCl_3$). The UV spectrum showed absorption maxima (205, 231, 255, 293 nm) corresponding to the indole and dihydroindole chromophores. The HRESIMS data ([M + H]$^+$ *m/z* 659.3611) established the molecular formula $C_{41}H_{46}N_4O_4$, which is 16 mass units higher than that of a known bisindole, macrocarpamine (**89**). Compound **88** was readily identified as the *N*(4')-oxide of macrocarpamine (**89**) from the ^{1}H and ^{13}C NMR data (Figure 2.86, Tables 2.54–2.55), in which the resonances for H-3', H-5', and H-21', as well as the corresponding C-3', C-5', and C-21', are notably deshielded when compared to those of **89**.

2.1.9.2 Macrocarpamine (89), Villalstonine (90), Villalstonine *N*(4)-oxide (91), Lumutinine B (92), Lumusidine B (93), and Perhentinine (94)

Three known macroline-pleiocarpamine bisindoles including macrocarpamine (**89**),[127,170,173] villalstonine (**90**),[126,416] and villalstonine *N*(4)-oxide (**91**),[126,170] as well as three known macroline-macroline bisindoles including lumutinine B (**92**),[52] lumusidine B (**93**),[182] and perhentinine (**94**),[122,176] were also isolated in the present study. The ^{1}H and ^{13}C NMR data of these compounds are summarized in Tables 2.54–2.60, and their ^{1}H NMR spectra are shown in Figures A50−A55 (see Appendix). Other data are given in the Experimental Section.

Table 2.54: ^{1}H NMR Spectroscopic Data (δ) of Angustilongine L (**88**) and Macrocarpamine (**89**)[a]

H	88 (*J*/Hz)	89 (*J*/Hz)	H	88 (*J*/Hz)	89 (*J*/Hz)
3	3.86 br t (3.0)	3.79 br t (3.4)	3'	3.41 m	2.86 m
5	3.05 d (7.0)	2.97 d (7.0)	5'	3.45 m	2.86 m
6β	2.45 d (16.5)	2.39 d (16.4)	5'	3.45 m	2.86 m
6α	3.27 dd (16.5, 7.0)	3.20 dd (16.4, 7.0)	6'	1.81 m	1.39 m
9	7.43 d (8.0)	7.37 br d (7.5)	6'	2.11 m	1.71 m
10	7.10 t (8.0)	7.03 td (7.5, 1.0)	7'	2.75 dd (10.7, 7.7)	2.53 dd (10.7, 7.7)
11	7.23 t (8.0)	7.15 td (7.5, 1.0)	9'	6.92 d (7.5)	6.83 br d (7.5)
12	7.37 d (8.0)	7.29 br d (7.5)	10'	6.57 t (7.5)	6.44 td (7.5, 1.0)
14	1.79 m	1.79 m	11'	6.82 td (7.5, 1.0)	6.72 td (7.5, 1.0)
14	1.87 m	1.79 m	12'	5.86 d (7.5)	5.77 br d (7.5)
15	2.02 m	1.98 m	14'	1.96 m	1.62 dt (13.5, 3.6)
16	1.90 m	1.84 dt (12.0, 4.0)	14'	2.91 dt (14.0, 3.5)	2.02 dt (13.5, 3.0)
17β	3.98 dd (11.0, 3.0)	3.88 dd (11.0, 3.0)	15'	3.20 m	3.07 m
17α	4.29 t (11.0)	4.19 t (11.0)	16'	4.12 d (3.8)	4.10 br d (3.6)
18	4.52 d (16.0)	4.50 d (16.0)	18'	1.62 dd (6.8, 1.6)	1.48 dd (7.0, 2.0)
19	5.57 d (16.0)	5.37 d (16.0)	19'	5.54 br q (6.8)	5.29 qd (7.0, 2.0)
21	6.30 s	6.19 s	21'	5.12 br d (13.0)	4.25 dt (12.6, 2.0)
N(1)-Me	3.67 s	3.61 s	21'	3.31 d (13.0)	2.86 m
N(4)-Me	2.33 s	2.25 s	$CO_2\underline{Me}$'	3.74 s	3.63 s

[a]$CDCl_3$, 400 MHz; assignment based on COSY, HSQC and NOESY.

Table 2.55: ^{13}C NMR Spectroscopic Data (δ) of Angustilongine L (**88**) and Macrocarpamine (**89**)[a]

C	88	89	C	88	89
2	132.7	132.9	2'	70.2	66.7
3	53.7	53.8	3'	69.0	54.3
5	54.8	54.9	5'	66.1	49.9
6	22.7	22.6	6'	28.2	21.4
7	106.7	106.6	7'	44.2	45.6
8	126.4	126.4	8'	131.2	133.6
9	118.0	117.9	9'	123.9	123.2
10	119.0	118.9	10'	119.0	117.6
11	121.1	120.9	11'	127.6	126.6
12	109.0	108.8	12'	108.6	107.8
13	137.2	137.1	13'	145.9	147.2
14	32.3	32.3	14'	23.5	29.3
15	23.7	23.7	15'	31.0	32.0
16	38.8	38.9	16'	57.9	58.1
17	66.9	66.8	17'	169.7	170.5
18	122.0	125.5	18'	12.7	12.2
19	129.7	127.3	19'	125.1	118.5
20	115.1	115.6	20'	129.7	135.7
21	146.1	144.5	21'	67.2	52.8
N(1)-Me	29.2	29.1	CO_2Me'	52.1	51.7
N(4)-Me	41.8	41.8			

[a]$CDCl_3$, 100 MHz; assignments based on DEPT, HSQC, and HMBC.

Table 2.56: ^{1}H NMR Spectroscopic Data (δ) of Villalstonine (**90**) and Villalstonine *N*(4)-oxide (**91**)[a]

H	90 (*J*/Hz)	91 (*J*/Hz)	H	90 (*J*/Hz)	91 (*J*/Hz)
3	3.86 t (3.0)	3.86 m	3'	3.73 m	4.26 m
5	2.91 br d (7.0)	2.91 d (7.0)	5'	2.69 m	3.35 m
6	2.47 d (16.0)	2.41 m	5'	3.12 td (14.0, 2.0)	3.62 m
6	3.29 dd (16.0, 7.0)	3.30 m	6'	1.11 br d (14.0)	1.64 m
9	7.55 br d (8.0)	7.55 br d (8.0)	6'	2.03 td (14.0, 4.0)	1.88 td (16.0, 5.0)
10	7.15 br t (8.0)	7.15 br t (8.0)	9'	6.88 br d (8.0)	6.92 d (8.0)
11	7.23 br t (8.0)	7.23 td (8.0, 1.0)	10'	6.99 br t (8.0)	6.77 t (8.0)
12	7.34 br d (8.0)	7.33 br d (8.0)	11'	6.70 br t (8.0)	7.04 dt (8.0, 1.0)
14	1.44 dt (13.0, 3.0)	1.43 m	12'	6.15 br d (8.0)	6.17 d (8.0)
14	2.42 m	2.41 m	14'	1.68 dt (12.0, 3.0)	2.57 br d (13.7)
15	1.60 m	1.60 m	14'	2.69 m	2.82 dt (13.7, 3.0)
16	2.09 m	2.08 dt (12.0, 5.0)	15'	3.22 br d (3.0)	3.27 br d (3.0)
17	3.73 m	3.75 dd (12.0, 5.0)	16'	4.44 d (3.0)	4.44 d (3.7)
17	4.00 t (11.0)	3.96 t (12)	18'	1.55 d (7.0)	1.62 dd (7.0, 2.0)
18	1.25 s	1.27 s	19'	5.36 q (7.0)	5.49 q (7.0)
20	1.16 dd (12.0, 3.0)	1.20 dd (13.7, 5.0)	21'	2.92 d (12.0)	3.30 m
21	1.60 m	1.64 m	21'	4.19 br d (12.0)	5.01 br d (13.3)
21	2.42 m	2.37 m	$CO_2\underline{Me}$'	3.68 s	3.70 s
N(1)-Me	3.62 s	3.61 s			
N(4)-Me	2.31 s	2.31 s			

[a]$CDCl_3$, 400 MHz.

Table 2.57: ^{13}C NMR Spectroscopic Data (δ) of Villalstonine (**90**)[a] and Villalstonine *N*(4)-oxide (**91**)[b]

C	90	91	C	90	91
2	135.8	132.7	2'	92.1	93.1
3	53.4	53.4	3'	51.7	67.1
5	54.4	54.3	5'	47.4	64.2
6	22.8	23.1	6'	31.2	34.5
7	106.6	106.8	7'	44.1	42.9
8	126.4	126.5	8'	132.8	133.6
9	118.3	118.4	9'	120.7	121.5
10	120.8	119.0	10'	118.1	119.8
11	118.8	121.1	11'	126.4	127.5
12	108.7	108.8	12'	109.2	110.2
13	136.9	137.0	13'	146.9	146.0
14	32.4	32.6	14'	27.4	21.7
15	32.3	31.8	15'	31.7	31.4
16	37.8	37.6	16'	57.7	57.7
17	65.6	65.6	18'	12.4	12.8
18	26.5	26.4	19'	118.2	125.0
19	98.5	99.1	20'	136.1	130.1
20	36.7	36.5	21'	52.9	67.8
21	28.4	28.0	$CO_2\underline{Me}$'	51.6	52.1
N(1)-Me	29.0	29.1	$\underline{C}O_2Me$'	171.3	170.3
N(4)-Me	41.7	41.9			

[a]$CDCl_3$, 100 MHz.

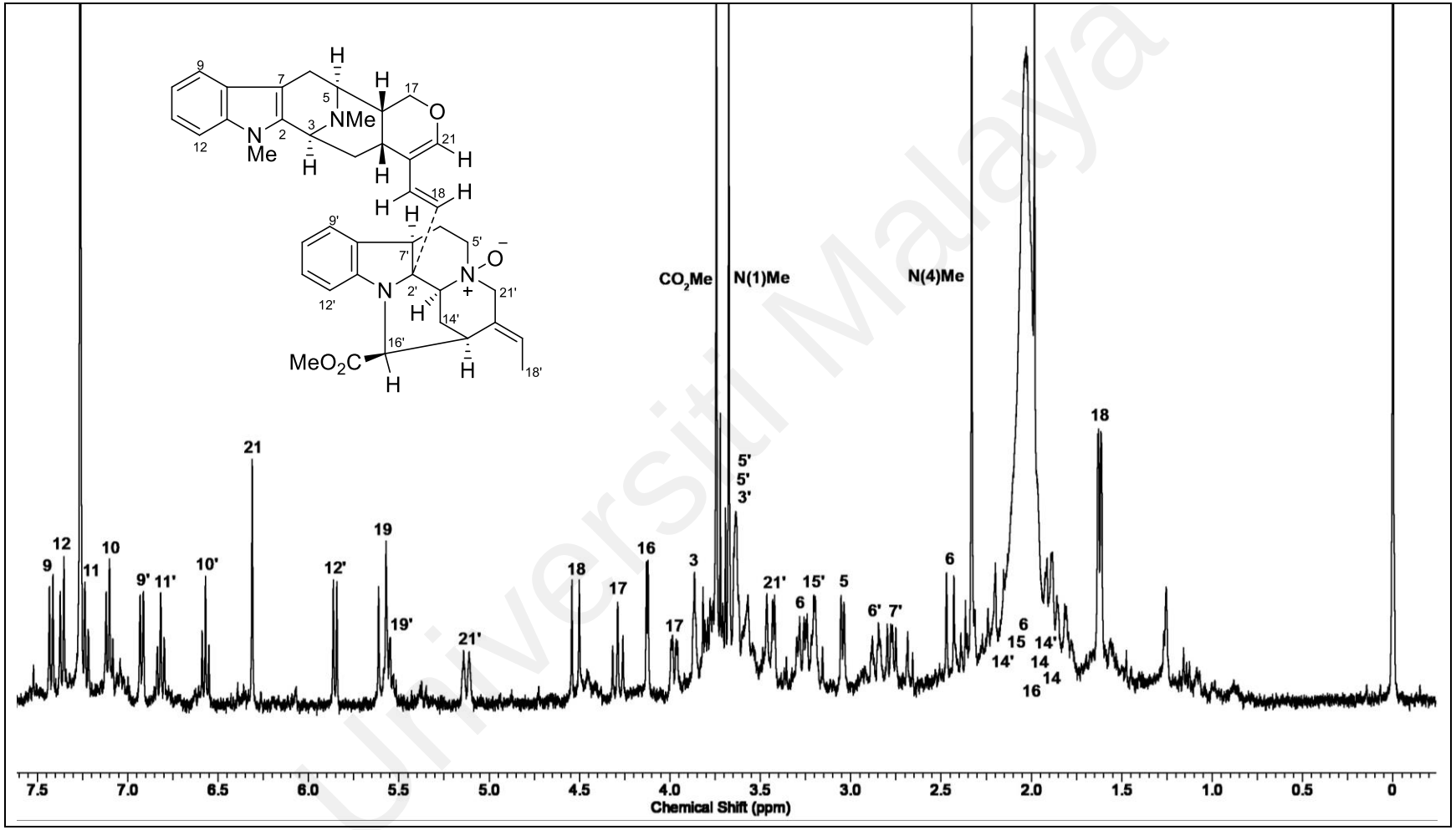


Figure 2.86: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Angustilongine L (**88**)

Table 2.58: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Lumutinine B (**92**)[a]

H/C	δ_C	δ_H (*J*/Hz)	H/C	δ_C	δ_H (*J*/Hz)
2	136.8[b]	-	2'	132.1	-
3	51.3	3.93 d (8.0)	3'	53.9	3.81 m
5	54.1	3.37 m	5'	54.7	3.06 d (7.0)
6	21.6	2.35 m	6'	22.8	2.41 m
6		3.12 dd (16.0, 5.0)	6'		3.22 dd (16.5, 7.0)
7	104.7	-	7'	106.3	-
8	127.5	-	8'	121.8	-
9	118.1	7.49 br d (7.5)	9'	116.7	7.16 d (8.0)
10	118.9	7.09 td (7.5, 1.0)	10'	110.6	6.66 d (8.0)
11	120.8	7.17 m	11'	149.6	-
12	108.9	7.28 br d (7.5)	12'	103.2	-
13	137.1[b]	-	13'	135.7	-
14	31.0	2.52 m	14'	32.5	2.15 m
14		1.78 m	14'		1.79 m
15	28.3	1.78 m	15'	23.0	2.66 m
16	37.3	1.75 m	16'	38.6	1.88 m
17	65.0	4.22 dd (11.0, 3.0)	17'	68.0	4.41 t (11.0)
17		3.75 m	17'		4.16 dd (11.0, 3.0)
18	25.6	1.54 s	18'	25.3	2.12 s
19	99.4	-	19'	195.9	-
20	38.0	2.68 m	20'	121.3	-
21	24.2	3.33 m	21'	157.9	7.55 s
21		3.54 m	N(1')-Me	32.5	3.86 s
N(1)-Me	29.6	3.65 s	N(4')-Me	41.9	2.29 s
N(4)-Me	40.2	2.39 s			

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C). [b]Interchangeable.

Table 2.59: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Lumusidine B (**93**)[a]

H/C	δ_C	δ_H (*J*/Hz)	H/C	δ_C	δ_H (*J*/Hz)
2	132.4	-	2'	131.1	-
3	54.3	3.63 m	3'	54.1	3.98 m
5	55.5	2.90 d (7.0)	5'	54.9	3.11 m
6	22.9	2.31 m	6'	22.8	2.51 m
6		3.17 m	6'		3.13 m
7	106.0	-	7'	105.1	-
8	125.9	-	8'	120.2	-
9	117.3	7.33 d (7.0)	9'	119.6	7.01 s
10	118.3	7.03 m	10'	124.8	-
11	119.8	7.05 m	11'	154.4	-
12	108.1	6.51 d (7.0)	12'	91.8	5.63 s
13	136.4	-	13'	136.5	-
14	26.9	1.38 m	14'	32.4	1.79 m
14		2.57 m	14'		2.11 m
15	26.2	1.30 m	15'	23.0	2.48 m
16	44.5	1.84 m	16'	38.6	1.87 m
17	59.8	3.48 dd (12.0, 4.0)	17'	67.9	4.17 dd (11.5, 3.0)
17		4.47 t (12.0)	17'		4.41 t (11.5)
18	19.5	1.18 d (6.8)	18'	25.1	2.06 s
19	40.3	2.87 m	19'	195.6	-
20	44.9	2.46 m	20'	121.2	-
21	93.4	5.39 d (3.2)	21'	157.6	7.51 s
N(1)-Me	27.6	2.57 s	N(1')-Me	29.4	3.44 s
N(4)-Me	41.9	2.29 s	N(4')-Me	41.8	2.51 s
			11'-OMe	54.7	3.21 s

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C).

Table 2.60: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Perhentinine (**94**)[a]

H/C	δ_C	δ_H (*J*/Hz)	H/C	δ_C	δ_H (*J*/Hz)
2	131.3	-	2'	132.9	-
3	53.1	4.09 dd (4.0, 2.0)	3'	53.7	3.79 t (3.0)
5	59.2	3.46 d (7.0)	5'	54.7	2.99 d (7.0)
6	22.6	2.54 m	6'	22.0	2.28 m
6		3.32 m	6'		3.08 m
7	105.9	-	7'	105.4	-
8	126.3	-	8'	120.1	-
9	118.2	7.52 br d (8.0)	9'	118.7	6.90 s
10	119.0	7.13 td (8.0, 1.0)	10'	119.1	-
11	120.9	7.22 td (8.0, 1.0)	11'	153.6	-
12	108.7	7.32 br d (8.0)	12'	91.3	6.69 s
13	137.0	-	13'	136.5	-
14	32.3	1.98 m	14'	32.4	1.75 td (12.0, 3.0)
14		2.41 m	14'		2.04 m
15	31.5	2.14 m	15'	22.8	2.54 m
16	43.1	1.57 m	16'	38.3	1.84 dt (11.0, 4.0)
17	66.5	3.95 dd (11.0, 3.0)	17'	67.7	4.13 ddd (11.0, 4.0, 1.0)
17		4.01 dd (11.0, 2.0)	17'		4.37 t (11.0)
18	31.1	1.72 s	18'	24.9	2.05 s
19	213.2	-	19'	195.4	-
20	54.5	3.32 m	20'	120.8	-
21	32.0	2.41 m	21'	157.4	7.51 s
21		3.08 m	N(1')-Me	28.9	3.55 s
N(1)-Me	29.0	3.65 s	N(4')-Me	41.2	2.25 s
N(4)-Me	41.7	2.34 s	11'-OMe	55.5	3.87 s

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C).

2.2 An NMR-based method for differentiating between *A. penangiana* and *A. macrophylla*

A. penangiana is endemic to Penang Island, Malaysia and occurs in a narrow band (approximately defined by the partially degraded Moniot Road/Trail) at about 1000 ft. elevation on Bukit Bendera.[46] *A. macrophylla* on the other hand is found abundantly on Penang Island, particularly on the foothills surrounding the main central hills of the island. In the case of Bukit Bendera, *A. macrophylla* can be found in the foothills as well as up to about 1000 ft. There is therefore an overlap zone where *A. penangiana* and *A. macrophylla* coexist. Since the vegetative specimens of *A. penangiana* are very similar to those of *A. macrophylla* (and *A. angustifolia*), and differentiation between these requires careful examination of flower specimens,[46] this presents a problem since identification of the plant is only possible during the flowering season. It is known from this and earlier studies that the major alkaloid present in the stem-bark extract of *A. macrophylla* is the bisindole villalstonine (**90**),[181,417] while 10-methoxyaffinisine (**45**) is the major alkaloid present in the stem-bark extract of *A. penangiana*. Although this can be seen to some extent by comparing TLC chromatograms of the crude basic fractions from the two plants, similarity of the R_f values ($\Delta R_f \sim 0.07$; SiO_2, 10% MeOH/$CHCl_3$) and overlap of multiple component alkaloids, adversely affect the reliability of this approach. In this regard, a ^{1}H NMR-based method was developed which permits clear differentiation between these two species without requiring examination of flower specimens. Crude basic stem-bark fractions of verified samples of *A. macrophylla* and *A. penangiana* from Bukit Bendera were dissolved in $CDCl_3$ and the respective ^{1}H NMR spectra were obtained and compared with those of 10-methoxyaffinisine (**45**) and villalstonine (**90**). It is evident from Figure 2.87 that the samples can be distinguished based on the major alkaloid present (*A. penangiana*: 10-methoxyaffinisine; *A. macrophylla*: villalstonine) as shown by the respective ^{1}H NMR spectrum. This

approach therefore provides an additional and invaluable chemotaxonomic tool for differentiation of the two species in addition to comparison of TLCs of extracts and examination of vegetative specimens.

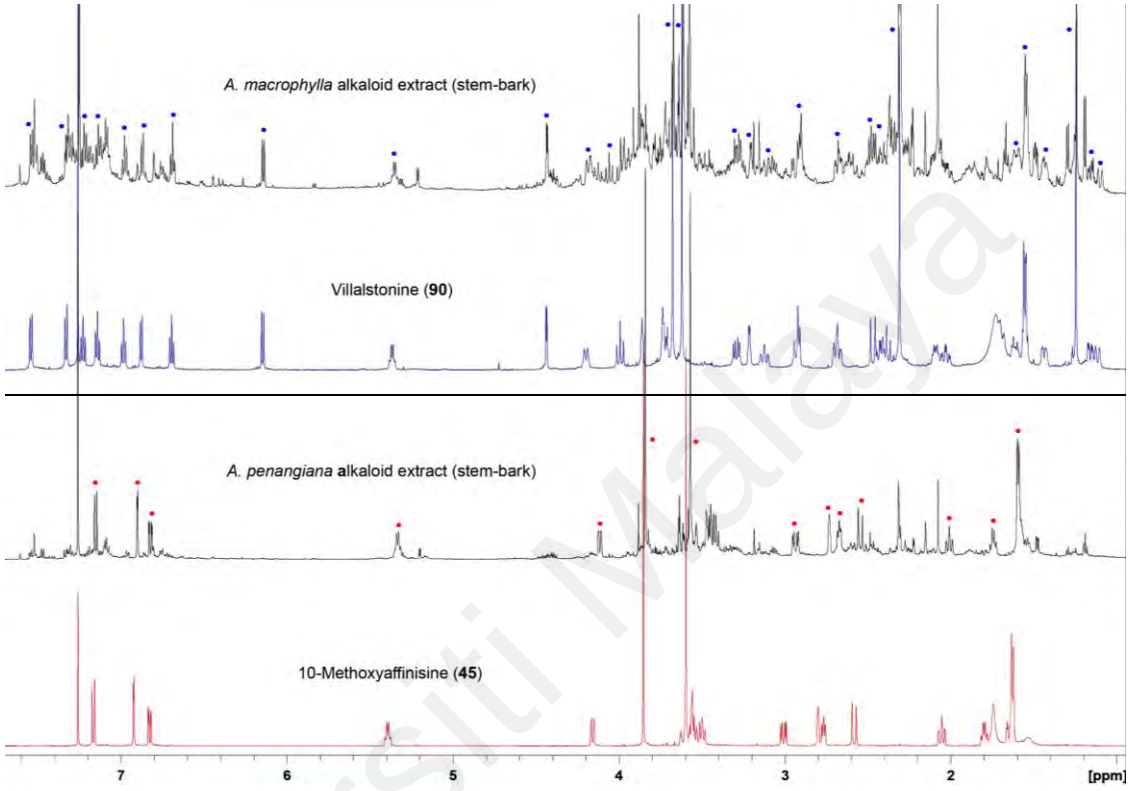


Figure 2.87: Comparison of ^{1}H-NMR spectra (600 MHz) of alkaloid extracts (stem-bark) from *A. penangiana* and *A. macrophylla*

2.3 Alkaloids from *Lycopodium platyrhizoma*

A total of 19 alkaloids (**95**–**113**, Figure 2.88, Table 2.61) were isolated and characterized from the whole plant of the Malayan *Lycopodium platyrhizoma* (Genting Highlands, Pahang) and the results are summarized in Table 2.61. Of these, three are new alkaloids, including two lycodine-type alkaloids, lycoplatyrines A and B (**95**–**96**), and one fawcettimine-type alkaloid, lycoplatyrine C (**110**). Lycoplatyrine A (**95**) is an uncommon lycodine-type alkaloid in which C-2 of ring A is substituted with a piperidine moiety. The structures and absolute configurations of lycoplanine D (**101**) and lycogladine H (**112**) were confirmed by X-ray diffraction analysis.

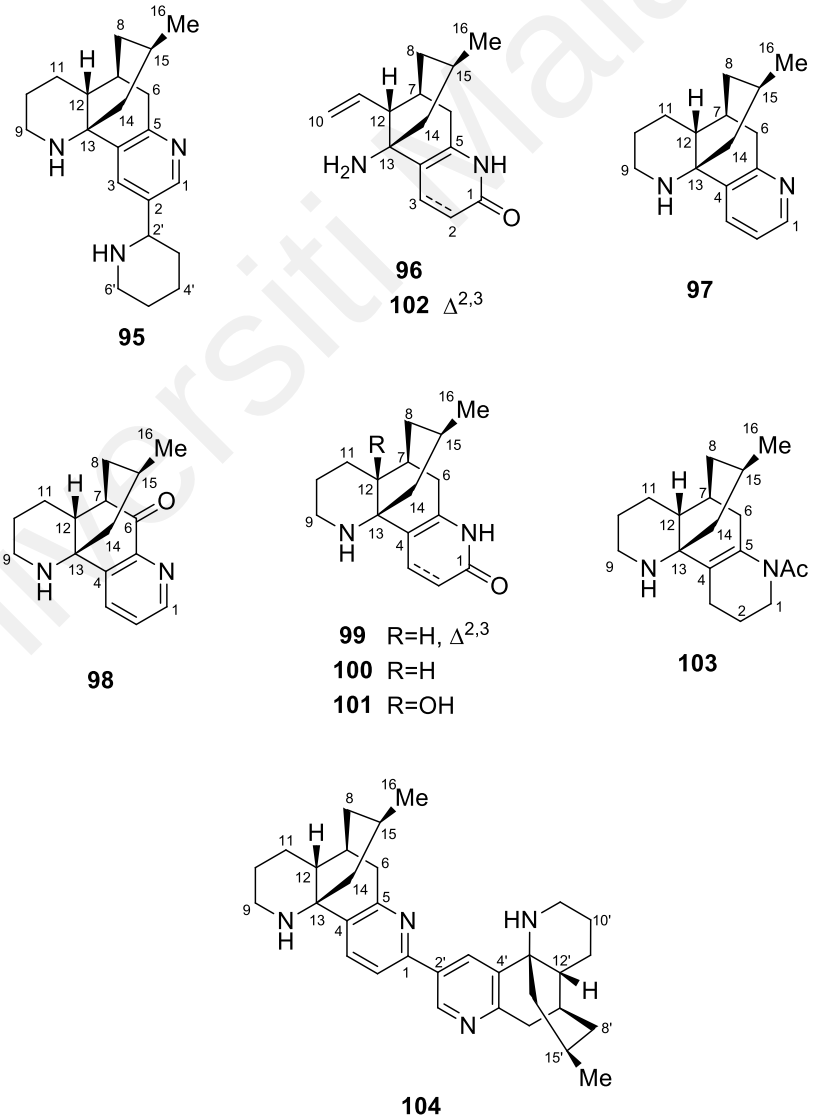


Figure 2.88: Alkaloids from *Lycopodium platyrhizoma*

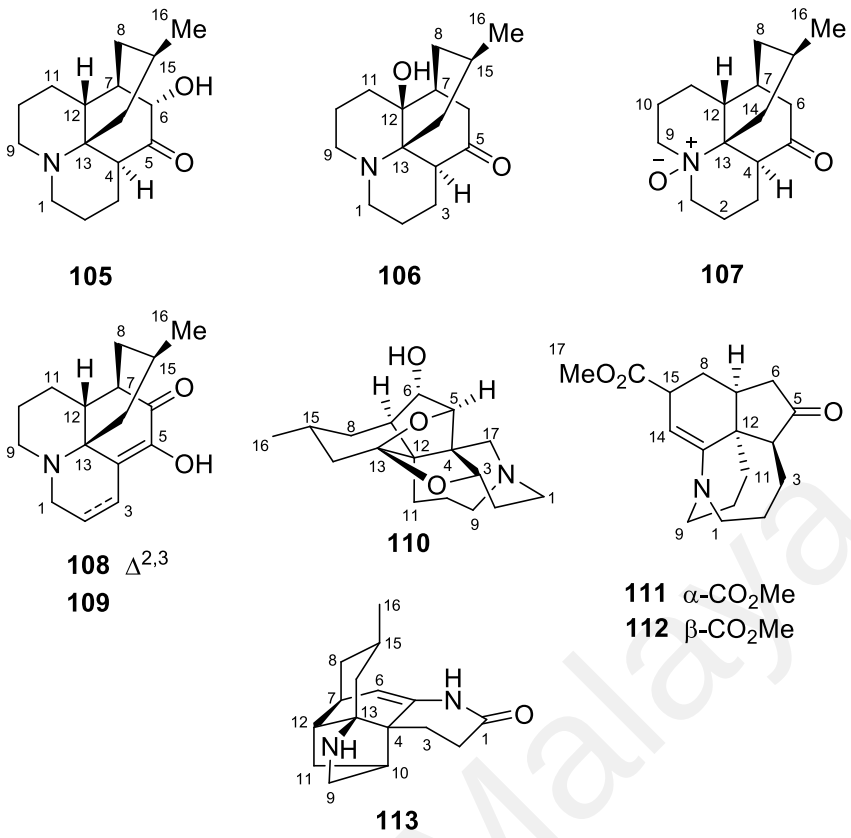


Figure 2.88, continued

Table 2.61: Alkaloid Composition of *Lycopodium platyrhizoma*

Plant part	Alkaloid	Yield (mg kg^{-1})
Whole plant (14.0 kg)	Lycoplatyrine A (**95**) [new]	0.35
	Lycoplatyrine B (**96**) [new]	4.30
	Lycodine (**97**)	54.6
	Lycoannotine G (**98**)	0.29
	Des-*N*-methyl-β-obscurine (**99**)	10.5
	Des-*N*-methyl-α-obscurine (**100**)	10.5
	Lycoplanine D (**101**)	4.66
	Casuarinine H (**102**)	2.16
	Flabellidine (**103**)	1.27
	Complanadine A (**104**)	0.71
	6α-Hydroxylycopodine (**105**)	2.51
	Lycodoline (**106**)	0.14
	Lycopodine *N*-oxide (**107**)	0.06
	Huperzine E (**108**)	0.32
	12-Deoxyhuperzine O (**109**)	0.31
	Lycoplatyrine C (**110**) [new]	0.24
	Lycogladine G (**111**)	0.14
	Lycogladine H (**112**)	0.51
	Lycogladines G (**111**), H (**112**)	3.46
	Lyconadin E (**113**)	0.44

2.3.1 Lycodine Alkaloids

2.3.1.1 Lycoplatyrine A (95)

Lycoplatyrine A (**95**)[418] was obtained as a yellowish oil, with $[\alpha]^{25}_{D}$ −19 (*c* 0.16, $CHCl_3$). The UV spectrum (231, 273, and 280 nm) was similar with those of lycodine (**97**), while the IR spectrum indicated the presence of NH groups (3389 and 3281 cm^{-1}). The odd nominal mass given by the HRESIMS data (*m/z* 326.2597 $[M + H]^+$) indicated the presence of an odd number of nitrogen atoms and established the molecular formula as $C_{21}H_{31}N_3$.

The ^1H and ^{13}C NMR data (Table 2.62) showed the presence of two sets of resonances with nearly coincident chemical shifts, due to the presence of a pair of unresolvable compounds with nearly identical structures. Attempted resolution of the two compounds using conventional column chromatography (SiO_2), preparative radial chromatography (Chromatotron, SiO_2), passage over Sephadex LH-20, and HPLC (reverse- and chiral-phase) were unsuccessful. The ratio of the two compounds was determined to be 1.3:1 (**95a**:**95b** in $CDCl_3$), which was invariant even when the spectra were recorded in different solvents ($CDCl_3$, benzene-d_6, toluene-d_8), suggesting that **95** was obtained as a mixture of two diastereomers.

The ^{13}C NMR data (Table 2.62) showed 21 carbon resonances, of which 18 appeared as pairs with very similar chemical shifts (the average $\Delta\nu$ for all paired signals was 0.08 ppm) and were therefore indistinguishable, while three resonances were overlapped. The ^1H and ^{13}C NMR resonances could be assigned into the two respective sets with the aid of the DEPT and HSQC data. The ^1H NMR showed close similarities with those of lycodine (**97**), which was the major alkaloid isolated in the present study. Whereas additional proton resonances were present in the upfield region in the ^1H NMR spectrum of **95** compared to that in **97**, in the downfield region only two pairs of *meta*-coupled aromatic proton signals were observed for **95** (Table 2.62, **95a**, δ_H 8.33, d, J = 2

Hz, H-1; δ_H 7.76, d, J = 2 Hz, H-3), compared to three aromatic proton signals for **97** (due to H-1, H-2, and H-3). These observations suggest that **95** is a pair of C-2 substituted derivatives of **97**. Subtraction of the lycodine fragment from the molecular formula of **95** revealed the presence of a $C_5H_{10}N$ moiety at C-2. Analysis of the ^{13}C, DEPT and HSQC data revealed the $C_5H_{10}N$ moiety to contain one sp^3 methine (Table 2.62, **95a**, δ_C 59.82) and four sp^3 methylenes (δ_C 47.73, 34.92, 25.27, 25.71), suggestive of a piperidinyl substituent. The presence of a 2-piperidinyl moiety was revealed by the COSY data, which showed a $CHCH_2CH_2CH_2CH_2$ partial structure, in addition to the partial structures present in the lycodine unit (Figure 2.89). The attachment from C-2 to the piperidinyl moiety at C-2′ was also confirmed by the observed three-bond HMBC correlations from H-1 and H-3 to C-2′, and from H-2′ to C-1 and C-3 (Figure 2.89).

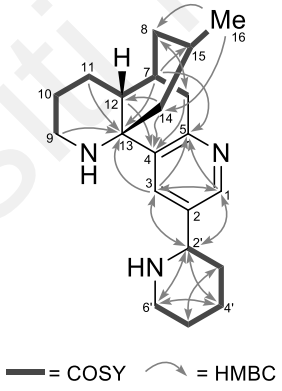


Figure 2.89: COSY and selected HMBCs of **95**

The relative configuration of the lycodine unit was assumed to follow that of lycodine (**97**), based on the similarity of the NMR data including NOESY, as well as from the X-ray structures of **101** (*vide infra*) and other alkaloids incorporating the core lycodine unit.[298,419] The NOEs observed for the axially-oriented hydrogens of rings C and D showed that these rings adopt a chair conformation and are *trans*-fused. The orientation of the methyl group at C-15 was deduced to be β (equatorial) from the NOE

observed for H-15/H-6a (Figure 2.90). In addition, the observed $J_{8\text{-}15}$ coupling constant of 12.4 Hz provided further support for the α-orientation of H-15 (H-8β and H-15α *trans*-diaxial). This left C-2′ as the epimeric center.

The 2-(2′-piperidinyl)pyridine substructure present in **95** was previously encountered in the simple nicotine-related alkaloids, anabasine and anatabine, which were also isolated as racemic mixtures with C-2′ being the enantiomeric center.[420-422] In fact, the ^{1}H (Figure 2.91) and ^{13}C NMR due to the piperidinyl units in **95** and anabasine showed a close resemblance to each other.[423,424]

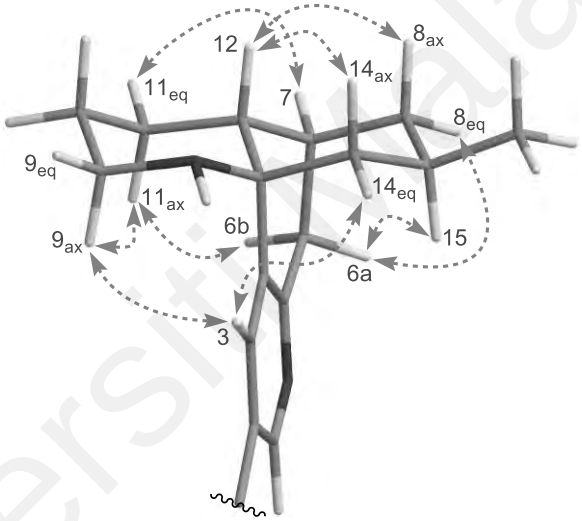
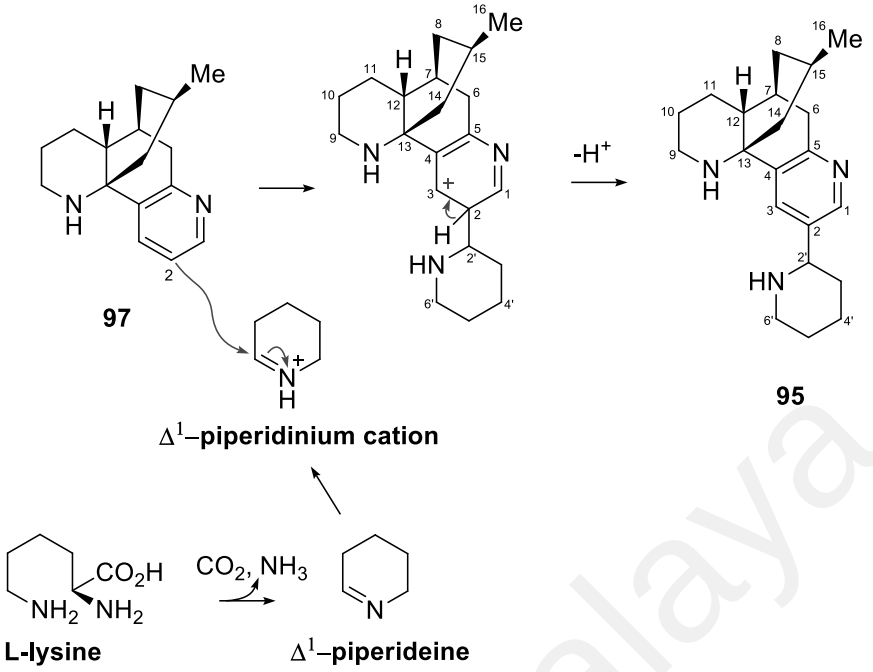


Figure 2.90: Selected NOEs of **95**

Compound **95** is possibly derived from electrophilic substitution at C-2 of lycodine (**97**) by the Δ^{1}-piperidinium cation, in turn derived from L-lysine (Scheme 2.3).[118,421,422] Substitution at C-2 in lycodine-type alkaloids is uncommon. Among the known examples are lycopladines F and G (C-2 substitution by a C_4N amino acid residue).[334] Lycoplatyrine A (**95**) represents the first lycodine-type alkaloid that is substituted with a piperidine moiety at C-2.



Scheme 2.3: Possible biogenetic pathway to **95**

Table 2.62: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Lycoplatyrine A (**95**)[a]

H/C	95a		95b	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
1	145.54[b]	8.33, d (2.0)	145.72[b]	8.36, d (2.0)
2	138.54[c]	-	138.59[c]	-
3	131.10[d]	7.77, d (2.0)	131.33[d]	7.76, d (2.0)
4	135.68[e]	-	135.56[e]	-
5	157.40[f]	-	157.55[f]	-
6	35.01[g]	2.70, d (18.6) (a)	35.05[g]	2.70, d (18.6) (a)
6		3.14, dd (18.6, 7.2) (b)		3.14, dd (18.6, 7.2) (b)
7	33.71[h]	2.09, m	33.74[h]	2.09, m
8	43.80[i]	1.34, td (12.4, 3.8) (ax)	43.81[i]	1.34, td (12.4, 3.8) (ax)
8		1.77, m (eq)		1.77, m (eq)
9	41.34[j]	2.43, m (ax)	41.44[j]	2.43, m (ax)
9		2.79, m (eq)		2.79, m (eq)
10	27.72[k]	1.56, m	27.67[k]	1.56, m
10		1.56, m		1.56, m
11	26.15	1.19, m (ax)	26.15	1.19, m (ax)
11		1.53, m (eq)		1.53, m (eq)
12	44.49[l]	1.61, m	44.55[l]	1.61, m
13	56.29[m]	-	56.33[m]	-
14	51.25[n]	1.19, m (ax)	51.37[n]	1.19, m (ax)
14		1.46, d (10.2) (eq)		1.46, d (10.2) (eq)
15	25.80[o]	1.22, m	25.81[o]	1.22, m
16	22.05[p]	0.77, d (5.9)	22.07[p]	0.78, d (5.9)
2′	59.82[q]	3.63, d (9.2)	59.94[q]	3.63, d (9.2)
3′	34.92	1.53, m	34.92	1.53, m
3′		1.81, m		1.81, m
4′	25.27[r]	1.53, m	25.29[r]	1.53, m
4′		1.91, m		1.91, m
5′	25.71[s]	1.55, m	25.74[s]	1.55, m
5′		1.67, m		1.67, m
6′	47.73	2.80, m	47.73	2.80, m
6′		3.21, dd (11.6, 1.6)		3.21, dd (11.6, 1.6)

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY. ax (axial) and eq (equatorial) descriptors used with reference to Figure 2.90.[b-s]Interchangeable

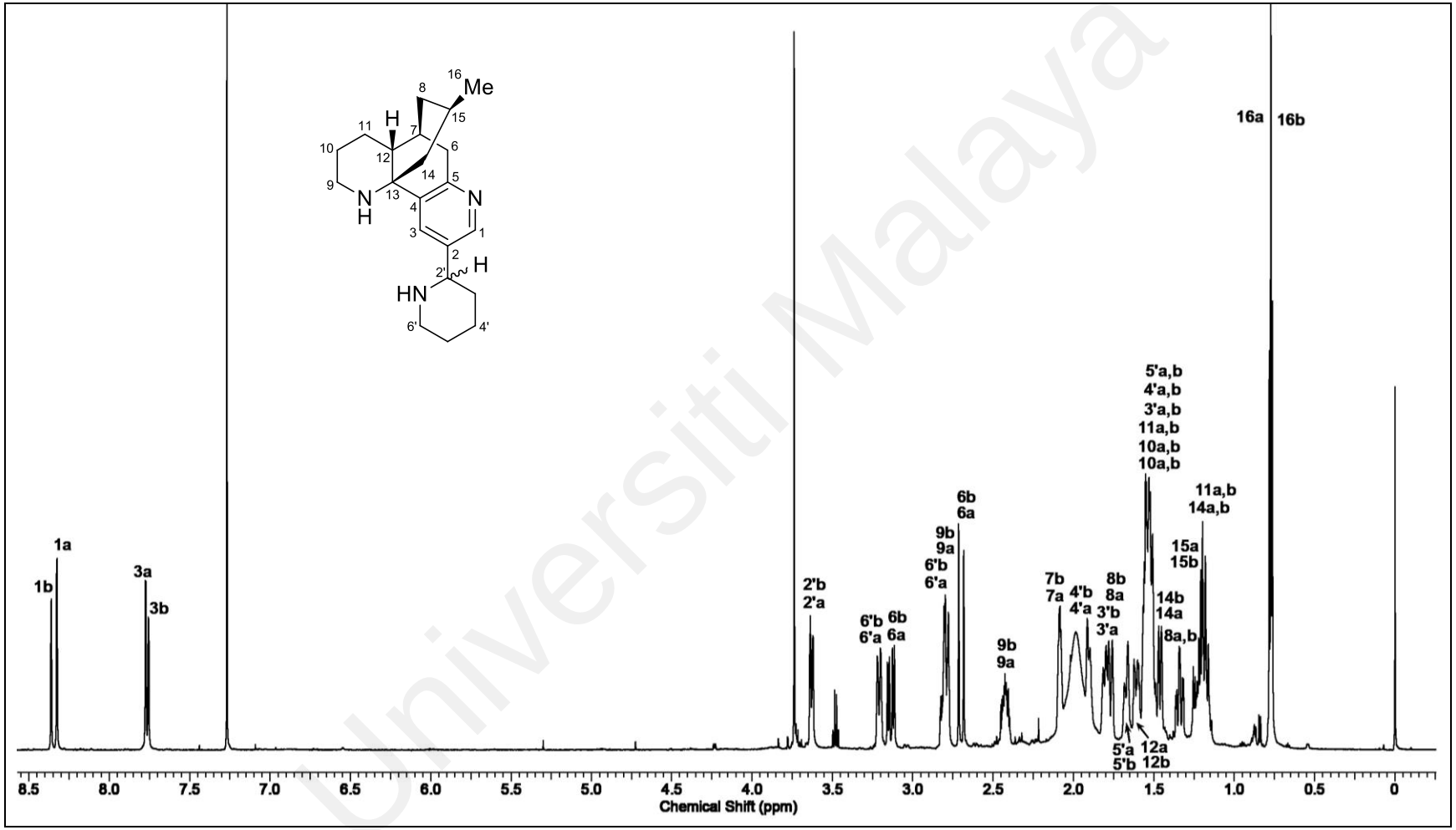


Figure 2.91: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Lycoplatyrine A (**95**)

2.3.1.2 Lycoplatyrine B (96)

Lycoplatyrine B (**96**)[418] was isolated as a yellowish oil, with $[\alpha]^{25}_{D}$ +64 (*c* 0.61, $CHCl_3$). The UV spectrum (λ_{max} 251 nm) was characteristic of a dihydropyridone chromophore, while the IR spectrum indicated the presence of lactam carbonyl (1654 cm^{-1}), primary amine, and lactam NH (3356 and 3275 cm^{-1}) functionalities. HRMS measurements ([M + H]$^+$ peak at *m/z* 247.1815) established the molecular formula as $C_{15}H_{22}N_2O$.

In addition to the presence of a lactam NH at δ_H 7.66 and a methyl group at δ_H 0.87, the ^{1}H NMR data (Table 2.63) showed the presence of three olefinic protons with an ABX spin system that is characteristic of a vinyl side chain (δ_H 5.79, dt, *J* = 17.0, 10.0 Hz; δ_H 5.19, dd, *J* = 17.0, 2.0 Hz; and δ_H 5.11, dd, *J* = 10.0, 2.0 Hz). The ^{13}C NMR data (Table 2.63) accounted for all 15 carbon resonances, including one methyl, six methylene (including a vinyl methylene at δ_C 118.3), four methine (including one vinyl methine at δ_C 138.3), two tertiary carbons linked to nitrogen atoms (δ_C 129.8 and 53.1), a lactam carbonyl (δ_C 171.5), and a quaternary carbon atom, in agreement with the molecular formula. The presence of the characteristic vinyl side chain suggested that **96** may be related to huperzinine and casuarinine H (**102**), which are ring C-opened lycodine alkaloids.[296,302] Comparison of the ^{1}H and ^{13}C NMR data of **96** with those of casuarinine H (**102**) indicated that they are virtually similar except for replacement of the C-2–C-3 double bond in **102** by a single bond in **96**. The presence of the ethylene unit due to the C-2–C-3 fragment was also shown by the COSY data (Figure 2.92). The branching of the vinyl side chain from C-12 was confirmed by the three-bond HMBC correlations from H-12 to C-10 and from H-10 to C-12 (Figure 2.92). The relative configurations at the various stereogenic centers (C-7, C-12, C-13, and C-15) were similar to those in compound **102** as shown by the NOE data (Figure 2.93). Compound

96 is therefore the 2,3-dihydro derivative of casuarinine H (**102**). The ^{1}H NMR spectrum of **96** is shown in Figure 2.94.

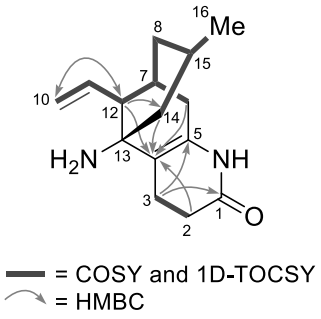


Figure 2.92: COSY, 1D-TOCSY, and selected HMBCs of **96**

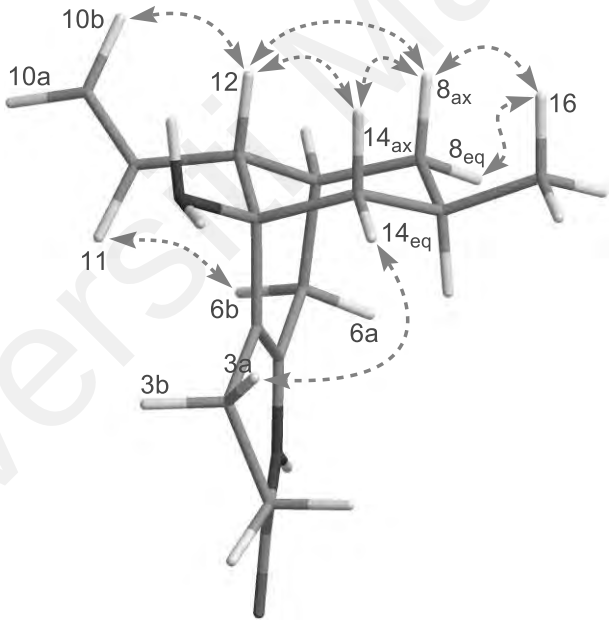


Figure 2.93: Selected NOEs of **96**

Table 2.63: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Lycoplatyrine B (**96**)[a]

H/C	δ_C	δ_H (*J*/Hz)
1	171.5	-
2	31.1	2.43, m
2		2.43, m
3	19.8	2.26, m (a)
4	113.9	2.42, m (b)
5	129.8	-
6	30.1	1.72, d (18.0) (a)
6		2.43, m (b)
7	34.4	2.11, m
8	42.8	1.21, br t (14.0)[b] (ax)
8		1.68, m (eq)
10	118.3	5.11, dd (10.0, 2.0) (a)
10		5.19, dd (17.0, 2.0) (b)
11	138.3	5.79, dt (17.0, 10.0)
11		-
12	54.8	2.03, dd (10.0, 2.8)
13	53.1	-
14	46.9	0.89, m (ax)
14		1.68, m (eq)
15	26.9	1.66, m
16	21.9	0.87, d (6.0)
NH	-	7.66, br s

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY. ax (axial) and eq (equatorial) descriptors used with reference to Figure 2.93. [b]*J* determined from homonuclear decoupling experiments.

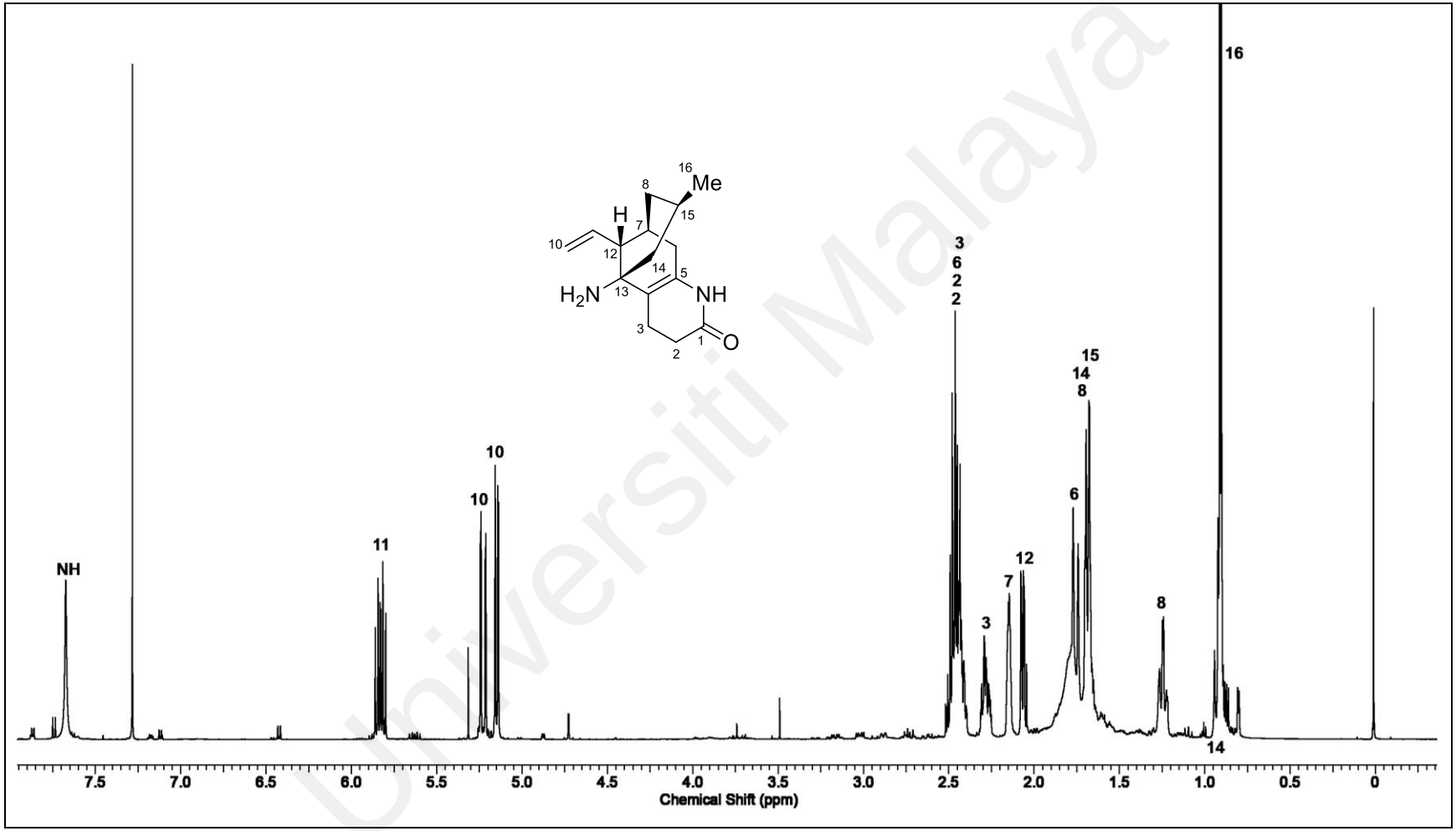


Figure 2.94: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Lycoplatyrine B (**96**)

2.3.1.3 Lycodine (97), Lycoannotine G (98), Des-*N*-methyl-β-obscurine (99), Des-*N*-methyl-α-obscurine (100), Lycoplanine D (101), Casuarinine H (102), Flabellidine (103), and Complanadine A (104)

Seven known lycodine-type alkaloids including lycodine (**97**),[290,371] lycoannotine G (**98**),[287] des-*N*-methyl-β-obscurine (**99**),[294,369] des-*N*-methyl-α-obscurine (**100**),[369] lycoplanine D (**101**),[328,347] casuarinine H (**102**),[296] flabellidine (**103**),[347] as well as one known lycodine-lycodine dimer, complanadine A (**104**)[322] were also isolated in the present study. The absolute configuration of lycoplanine D (**101**) was confirmed for the first time by X-ray diffraction analysis (Figure 2.95). The ^{1}H and ^{13}C NMR data of these compounds are summarized in Tables 2.64–2.67, and their ^{1}H NMR spectra are shown in Figures A56–A63 (see Appendix). Other data are given in the Experimental Section.

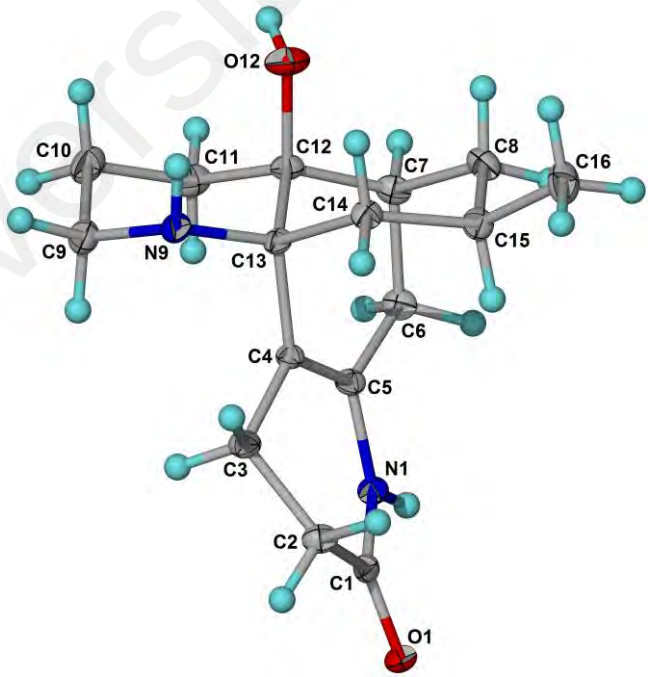


Figure 2.95: X-Ray crystal structure of alkaloid **101**

Table 2.64: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Lycodine (**97**) and Lycoannotine G (**98**)[a]

H/C	97		98	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
1	146.9	8.38 d (4.7)	149.0	8.74 dd (4.5, 1.5)
2	121.6	7.14 dd (7.7, 4.7)	128.2	7.54 dd (8.0, 4.5)
3	133.3	7.80 d (7.7)	135.6	8.10 br d (8.0)
4	136.1	-	142.8	-
5	158.8	-	149.5	-
6	35.3	2.72 d (18.7)	199.7	-
6		3.17 dd (18.7, 7.2)		-
7	33.8	2.10 m	51.3	2.82 dt (4.5, 2.5)
8	43.8	1.35 td (12.7, 3.8)	38.6	1.49 td (13.0, 4.5)
8		1.79 br d (12.7)		2.00 br d (13.0)
9	41.4	2.44 td (13.1, 2.7)	41.2	2.44 td (13.0, 3.6)
9		2.78 br d (13.1)		2.88 br d (13.0)
10	28.0	1.56 m	27.3	1.56 m
10		1.56 m		1.56 m
11	26.2	1.20 m	26.4	1.25 m
11		1.55 m		1.66 m
12	44.7	1.60 m	48.2	1.93 br d (11.5)
13	56.1	-	56.8	-
14	51.5	1.16 t (12.1)	48.7	1.38 m
14		1.47 br d (12.1)		1.68 m
15	25.9	1.19 m	26.3	1.31 m
16	18.5	0.78 d (6.2)	21.8	0.84 d (6.3)

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY.

Table 2.65: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Des-*N*-methyl-β-obscurine (**99**) and Des-*N*-methyl-α-obscurine (**100**)[a]

H/C	99		100	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
1	164.9	-	171.3	-
2	117.4	6.47 d (9.3)	31.1	2.48 m
2		-		2.48 m
3	139.9	7.61 d (9.3)	18.8	2.23 m
3		-		2.32 m
4	118.0	-	111.8	-
5	144.9	-	131.2	-
6	29.8	2.46 d (18.7)	30.1	1.69 m
6		2.95 dd (18.7, 7.0)		2.38 br d (17.4)
7	33.3	2.03 m	33.4	1.89 br s
8	43.1	1.28 m	43.4	1.23 td (13.7, 3.7)
8		1.73 br d (13.1)		1.66 m
9	41.4	2.44 td (12.2, 2.9)	42.6	2.45 m
9		2.79 br d (12.2)		2.85 br d (11.9)
10	25.8	1.24 m	27.0	1.52 m
10		1.51 m		1.62 m
11	27.8	1.48 m	25.9	1.43 m
11		1.58 m		1.43 m
12	44.5	1.51 m	44.4	1.44 m
13	54.6	-	55.8	-
14	49.6	1.06 t (11.9)	45.9	0.89 t (11.9)
14		1.48 m		1.51 m
15	25.9	1.39 m	26.5	1.64 m
16	21.8	0.82 d (6.4)	22.0	0.87 d (6.2)

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY.

Table 2.66: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Lycoplanine D (**101**), Casuarinine H (**102**), and Flabellidine (**103**)

H/C	**101**[a]		**102**[b]		**103**[b]	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
1	171.1	-	164.8	-	ND[c]	3.09 m
1		-		-		3.79 m
2	30.8	2.48 m	119.2	6.41 d (9.6)	24.3	1.85 m
2		2.48 m		-		1.85 m
3	19.3	2.20 m	140.4	7.73 d (9.6)	20.8	2.01 m
3		2.20 m		-		2.01 m
4	112.7	-	120.6	-	ND[c]	-
5	131.1	-	143.8	-	137.1	-
6	32.4	1.87 m	29.9	2.47 d (19.1)	31.6	ND[c]
6		2.45 m		3.03 dd (19.1, 7.0)		ND[c]
7	37.4	1.91 m	34.2	2.27 m	44.0	1.44 m
8	37.2	1.32 br d (13.3)	42.5	1.28 td (13.0, 3.6)	43.6	1.19 td (13.0, 4.0)
8		1.81 m		1.72 br d (13.0)		1.65 m
9	42.0	2.50 m	-	-	42.5	2.47 td (12.0, 3.0)
9		2.77 dd (13.9, 3.9)		-		2.82 dd (12.0, 3.0)
10	22.0	1.45 m	117.2	5.12 dd (9.8, 1.9)	26.6	1.64 m
10		1.82 m		5.21 dd (17.3, 1.9)		1.64 m
11	31.6	1.38 m	137.2	5.59 dt (17.3, 9.8)	26.0	1.45 m
11		1.84 m		-		1.45 m
12	69.0	-	49.8	2.13 dd (9.8, 3.0)	26.4	1.54 m
13	58.9	-	54.7	-	56.9	-
14	39.1	1.05 dd (12.5, 4.3)	52.3	1.08 t (12.3)	45.6	0.90 t (12.4)
14		1.37 m		1.62 br d (12.3)		1.57 m
15	25.6	1.65 m	26.4	1.36 m	33.9	1.84 m
16	21.7	0.88 d (6.5)	21.8	0.83 d (6.8)	22.1	0.84 d (6.8)
N<u>H</u>(amide)	-	7.27 s	-	-		-
12-O<u>H</u>	-	2.82 br s	-	-		-
$CH_3\underline{C}$=O	-	-	-	-	169.6	-
$\underline{C}H_3C$=O	-	-	-	-	23.8	2.10 s

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); [b]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY. [c]Not detected.

Table 2.67: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Complanadine A (**104**)[a]

H/C	δ_C	δ_H (*J*/Hz)	H/C	δ_C	δ_H (*J*/Hz)
1	152.68	-	1'	145.58	8.95 d (2.0)
2	118.75	7.60 d (8.4)	2'	133.46	-
3	134.15	7.89 d (8.4)	3'	131.61	8.36 br s
4	133.46	-	4'	133.46	-
5	158.86	-	5'	159.14	-
6	35.19	2.84 d (19.0)	6'	35.50	2.78 d (19.0)
6		3.24 dd (19.0, 7.4)	6'		3.22 dd (19.0, 7.2)
7	33.74	2.14 m	7'	33.88	2.14 m
8	43.73	1.32 m	8'	43.73	1.32 m
8		1.78 br d (11.2)	8'		1.78 br d (11.2)
9	41.42	2.49 m	9'	41.45	2.49 m
9		2.81 m	9'		2.81 m
10	26.2	1.25 m	10'	26.2	1.25 m
10		1.25 m	10'		1.25 m
11	27.80	1.55 m	11'	27.94	1.55 m
11		1.55 m	11'		1.55 m
12	44.61	1.63 m	12'	44.61	1.63 m
13	56.32	-	13'	56.44	-
14	51.20	1.19 m	14'	51.33	1.19 m
14		1.53 m	14'		1.53 m
15	25.84	1.55 m	15'	25.94	1.55 m
16	22.00	0.79 d (5.6)	16'	22.04	0.79 d (5.6)

[a]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C); assignments based on COSY, HSQC, and HMBC.

2.3.2 Lycopodine Alkaloids

2.3.2.1 6α-Hydroxylycopodine (105), Lycodoline (106), Lycopodine *N*-oxide (107), Huperzine E (108), and 12-Deoxyhuperzine O (109)

Five known lycopodine-type alkaloids including 6α-hydroxylycopodine (**105**),[310] lycodoline (**106**),[425,426] lycopodine *N*-oxide (**107**),[427] huperzine E (**108**),[428] and 12-deoxyhuperzine O (**109**)[429] were also isolated in the present study. The ^{1}H and ^{13}C NMR data of these compounds are summarized in Tables 2.68–2.70, and their ^{1}H NMR spectra are shown in Figures A64–A68 (see Appendix). Other data are given in the Experimental Section.

Table 2.68: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of 6α-Hydroxylycopodine (**105**)[a]

H/C	δ_C	δ_H (*J*/Hz)
1	46.6	2.52 dd (14.0, 4.8)
1		3.34 m
2	18.6	1.37 br d (14.0)
2		1.90 qt (14.0, 4.8)
3	19.5	1.61 m
3		2.04 br d (14.0)
4	39.2	3.37 m
5	213.6	-
6	78.1	3.80 s
7	42.4	2.16 s
8	39.7	1.29 m
8		1.68 d (8.4)
9	47.6	2.61 m
9		3.15 td (12.3, 2.5)
10	26.8	1.63 m
10		1.81 m
11	26.4	1.59 m
11		2.22 qd (14.0, 7.0)
12	44.7	1.60 m
13	60.5	-
14	42.9	0.89 t (12.6)
14		2.62 m
15	26.1	1.29 m
16	23.2	0.85 d (5.5)

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY.

Table 2.69: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Lycodoline (**106**) and Lycopodine *N*-oxide (**107**)[a]

H/C	106		107	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
1	46.1	2.47 dd (14.5, 5.5)	63.1	3.34 m
1		3.25 m		3.70 td (14.1, 4.5)
2	17.7	1.37 m	21.3	1.86 m
2		1.89 m		1.93 m
3	19.5	1.64 m	17.3	1.67 m
3		2.09 m		2.21 m
4	43.3	2.93 dd (12.0, 3.5)	48.4	2.96 dd (12.2, 2.6)
5	212.1	-	207.8	-
6	44.3	2.34 dd (16.6, 1.9)	41.9	2.30 m
6		2.60 m		2.58 dd (16.7, 6.5)
7	40.7	2.09 m	37.5	2.66 br d (12.9)
8	35.6	1.37 m	34.7	2.10 dd (13.6, 4.3)
8		1.96 td (12.0, 4.0)		2.30 m
9	46.1	2.60 m	59.2	3.32 m
9		3.22 m		3.99 td (12.9, 2.8)
10	20.6	1.71 m	19.8	1.80 m
10		2.12 m		2.73 m
11	30.1	1.51br d (11.0)	23.2	1.67 m
11		2.13 m		1.86 m
12	69.5	-	36.0	2.24 m
13	61.5	-	75.4	-
14	35.8	1.51 m	41.2	1.37 td (12.7, 3.5)
14		2.25 d (9.0)		1.67 m
15	24.3	1.42 m	25.5	1.52 m
16	22.5	0.88 d (5.7)	22.6	0.93 d (6.2)

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY.

Table 2.70: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Huperzine E (**108**) and 12-Deoxyhuperzine O (**109**)

H/C	**108**[a]		**109**[b]	
	δ_C	δ_H (*J*/Hz)	δ_C	δ_H (*J*/Hz)
1	50.0	3.09 dd (19.9, 4.5)	46.3	2.75 br d (13.9)
1		4.02 dt (19.9, 2.3)		3.53 td (13.9, 3.9)
2	128.7	5.89 ddd (10.0, 4.5, 2.3)	16.7	1.40 m
2		-		2.13 m
3	119.7	6.74 dd (10.0, 2.3)	20.7	2.16 m
3		-		2.97 m
4	121.6	-	129.0	-
5	143.1	-	144.6	-
6	197.0	-	196.3	-
7	48.6	2.59 m	48.7	2.55 m
8	37.3	1.33 td (13.0, 4.6)	36.5	1.28 td (12.8, 4.4)
8		1.81 m		1.73 m
9	50.1	2.62 m	48.8	2.60 br d (11.4)
9		2.79 td (11.7, 3.7)		3.02 td (11.4, 4.0)
10	25.5	1.66 m	25.7	1.66 m
10		1.66 m		1.66 m
11	26.4	1.39 td (12.7, 4.7)	26.7	1.43 m
11		1.47 m		1.43 m
12	46.6	1.78 m	47.4	1.73 m
13	57.2	-	58.3	-
14	41.2	1.06 t (12.3)	41.0	1.00 t (12.5)
14		2.10 dd (12.3, 3.8)		2.45 dd (12.5, 4.2)
15	25.6	1.61 m	26.2	1.43 m
16	21.7	0.92 d (6.5)	21.8	0.94 d (6.8)

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); [b]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C); Assignments based on COSY, HSQC, HMBC, and NOESY.

2.3.3 Fawcettimine Alkaloids

2.3.3.1 Lycoplatyrine C (110)

Lycoplatyrine C (**110**)[418] was isolated as a yellowish oil with $[\alpha]^{25}_{D}$ –20 (*c* 0.18, $CHCl_3$). The IR spectrum showed bands due to a hydroxy group (3403 cm^{-1}), while HRMS measurements ($[M + H]^+$ *m/z* 292.1914) established the molecular formula as $C_{17}H_{25}NO_3$.

The ^1H NMR data (Table 2.71) showed the presence of three oxymethine hydrogens (δ_H 4.23, 3.94, and 3.75), three pairs of aminomethylene hydrogens (δ_H 3.27 and 3.14; δ_H 3.90 and 2.90; δ_H 4.06 and 3.34), and a methyl doublet (δ_H 0.95). The ^{13}C NMR spectrum accounted for a total of 17 carbon resonances, including one methyl, eight methylene (including three aminomethylene: δ_C 52.9, 50.3, 45.0), five methine (including three oxymethine: δ_C 84.3, 76.7, 71.8), a ketal function (δ_C 110.6), and two quaternary carbon atoms. Based on the partial structures obtained from the COSY and 1D-TOCSY data (Figure 2.96), as well as the presence of the characteristic ketal carbon (δ_C 110.6), the structure of **110** was deduced to be closely related to that of obscurumine K (**833**), a fawcettimine-type alkaloid recently isolated from *L. complanatum* and reported while the current study was in progress.[56] Furthermore, the ^1H and ^{13}C NMR data of **110** were essentially similar to those of obscurumine K (**833**), except for notable differences involving H/C-8, H/C-6, and H/C-15, in particular, the replacement of the C-8–C-15 double bond in obscurumine K by a single bond in **110**, and, the replacement of the methylene unit at C-6 in the former by a hydroxymethine in **110**. The presence of the CH_2CH partial structure due to the C-8–C-15 fragment in **110** was evident from the COSY and 1D-TOCSY data, while the presence of the C-6 hydroxymethine was supported by the observed three-bond correlations from H-8 to C-6 and from H-6 to C-4 and C-12 in the HMBC spectrum (Figure 2.96).

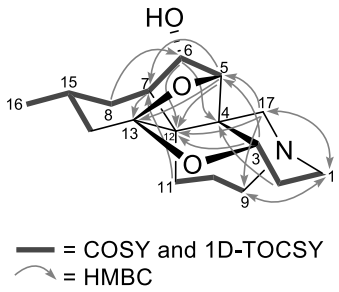


Figure 2.96: COSY, 1D-TOCSY, and selected HMBCs of **110**

The relative configurations at all stereocenters of **110**, with the exception of C-6 and C-15, were deduced to be similar to those of obscurumine K based on the NOESY data. The orientation of the OH group at C-6 was deduced to be α, from the observed NOEs for H-6/H-8β, H-15 (Figure 2.97). The observed $J_{8\text{-}15}$ and $J_{14\text{-}15}$ coupling constants of 15.0 and 13.0 Hz, respectively, were suggestive of their *trans*-diaxial disposition and consistent with an axially oriented H-15 and an equatorially-oriented methyl group at C-16. This was further supported by the NOEs observed for H-6/H-15 and H-8α/H-16 (Figure 2.97). The ^{1}H NMR spectrum of **110** is shown in Figure 2.98.

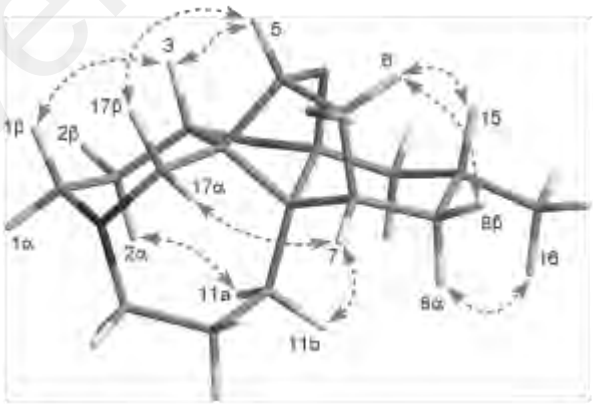


Figure 2.97: Selected NOEs of **110**

Table 2.71: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Lycoplatyrine C (**110**)[a]

H/C	δ_C	δ_H (*J*/Hz)
1	50.3	3.14, br d (14.0) (α)
1		3.27, td (14.0, 2.5) (β)
2	24.3	2.09, tdd (14.0, 9.4[b], 4.9) (α)
2		2.36, m (β)
3	71.8	4.23, dd (9.4, 7.5)[b]
4	53.6	-
5	84.3	3.94 s
6	76.7	3.75 s
7	45.8	2.21, m
8	31.2	1.24, td (15.0, 5.3) (α)
8		1.83, br d (15.0) (β)
9	52.9	2.90, br t (14.0)
9		3.90, br d (14.0)
10	21.3	1.92, m
10		2.15, m
11	24.8	1.69, t (13.4) (a)
11		1.94, m (b)
12	50.9	-
13	110.6	-
14	32.5	1.16, t (13.0)
14		1.81, dd (13.0, 4.6)
15	27.4	1.91, m
16	21.6	0.95, d (6.6)
17	45.0	3.34, d (15.0) (β)
17		4.06, d (15.0) (α)

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY.[b]*J* determined from homonuclear decoupling experiments.

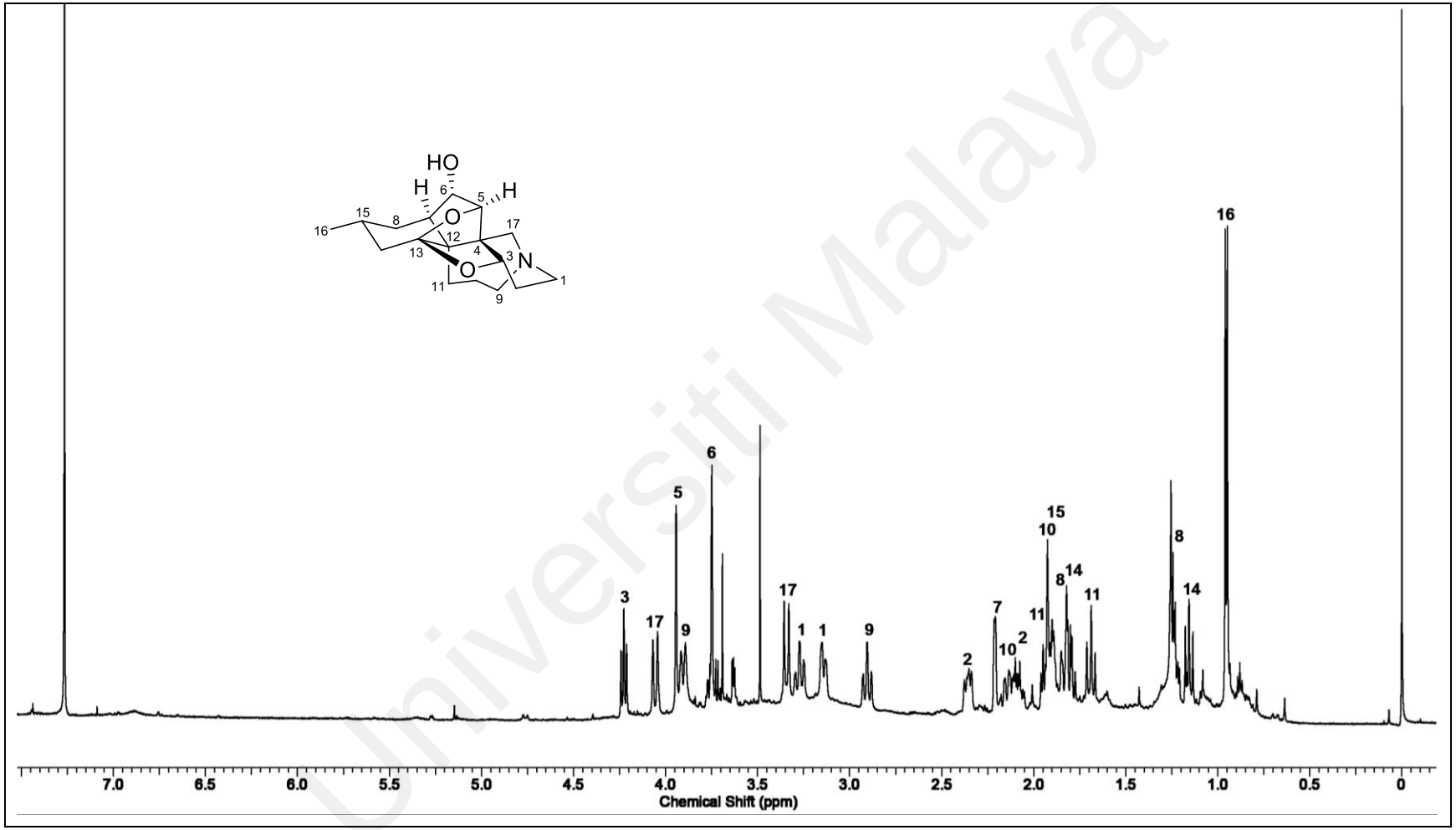


Figure 2.98: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Lycoplatyrine C (**110**)

2.3.3.2 Lycogladine G (111), Lycogladine H (112), and Lyconadin E (113)

Three known fawcettimine-type alkaloids including lycogladine G (**111**),[330] lycogladine H (**112**),[330] and lyconadin E (**113**)[325] were also isolated in the present study. The absolute configuration of lycogladine H (**112**) was established for the first time by X-ray diffraction analysis (Figure 2.99). The ^{1}H and ^{13}C NMR data of these compounds are summarized in Table 2.72, and their ^{1}H NMR spectra are shown in Figures A69–A71 (see Appendix). Other data are given in the Experimental Section.

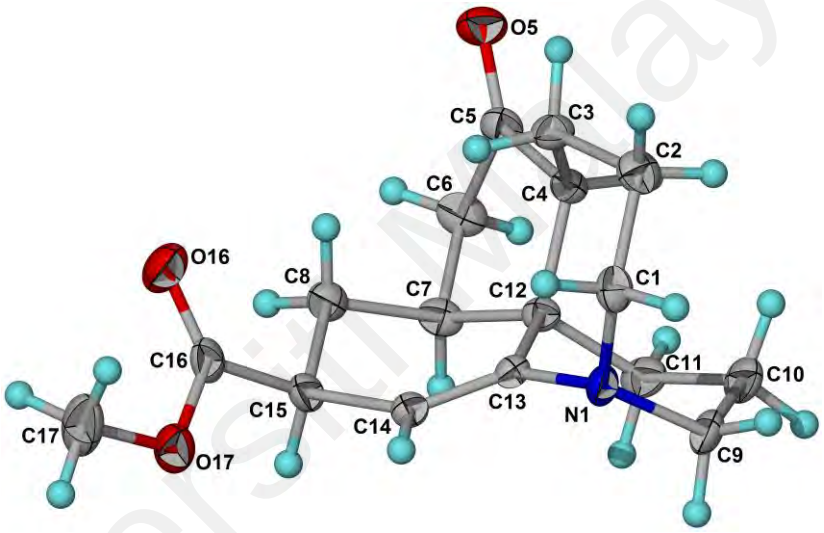


Figure 2.99: X-Ray crystal structure of lycogladine H (**112**)

Table 2.72: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Lycogladine G (**111**), Lycogladine H (**112**), and Lyconadin E (**113**)

H/C	**111**[a]		**112**[a]		**113**[b]	
	δ_C	**δ_H (*J*/Hz)**	**δ_C**	**δ_H (*J*/Hz)**	**δ_C**	**δ_H (*J*/Hz)**
1	60.5	3.03 td (12.9, 3.8)	60.3	3.05 td (14.0, 3.8)	169.7	
1		3.17 m		3.14 dd (14.0, 4.0)		
2	31.1	1.70 m	31.2	1.69 m	29.7	2.37 m
2		1.75 m		1.76 m		2.58 ddd (17.0, 4.5, 2.0)
3	28.9	1.27 tdd (14.0, 12.0, 1.8)	28.8	1.36 tdd (14.0, 12.0, 1.4)	19.4	1.70 m
3		2.30 dd (14.0, 5.6)		2.30 dd (14.0, 6.3)		1.81 m
4	55.8	2.14 d (12.0)	55.9	2.15 d (12.0)	48.4	
5	218.1	-	217.7	-	136.6	
6	44.3	2.11 d (17.0)	44.5	2.11 d (16.7)	103.5	4.63 d (5.5)
6		2.78 dd (17.0, 7.5)		2.82 dd (16.7, 7.5)		
7	37.9	2.34 ddd (13.0, 7.5, 4.8)	40.2	2.05 ddd (13.5, 7.5, 4.2)	46.7	1.82 m
8	29.0	1.13 td (13.0, 5.7)	30.6	1.17 td (13.5, 12.0)	37.9	1.04 ddd (13.5, 12.0, 3.0)
8		1.95 m		1.87 m		1.53 m
9	51.5	3.01 m	51.4	3.00 m	49.7	2.74 d (9.8)
9		3.08 td (13.0, 3.7)		3.08 td (13.0, 3.9)		3.06 dt (9.8, 3.0)
10	23.5	1.61 m	23.5	1.60 m	43.5	
10		1.89 qt (13.0, 4.5)		1.87 m		2.33 m
11	38.3	1.66 dd (13.0, 4.5)	38.3	1.62 m	33.3	1.59 m
11		1.98 m		2.01 m		1.59 m
12	46.1	-	46.3	-	39.4	2.31 m
13	149.6	-	148.6	-	63.0	
14	118.2	5.81 d (5.3)	118.9	5.79 s	36.9	1.12 t (13.0)
14		-		-		1.71 m
15	39.2	3.16 m	40.9	3.25 ddd (12.0, 4.8, 1.7)	24.9	1.92 m
16	174.0	-	174.1	-	22.2	
CO_2Me	51.9	3.70 s	52.0	3.69 s	-	
NH(amide)	-	-	-	-	-	7.65 s

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); [b]$CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C); assignments based on COSY, HSQC, HMBC, and NOESY.

2.4 Biological Activity

2.4.1 General

Alkaloids are important secondary metabolites owing to their broad spectrum of biological activities. Apart from the systematic chemical investigations, alkaloids isolated from the present study were screened for their biological properties. Indole alkaloids were tested for their cytotoxic effects, including their potential in reversing multidrug resistance (MDR) in vincristine-resistant KB cells, while *Lycopodium* alkaloids were tested for their acetylcholinesterase (AChE) inhibitory activity.

2.4.2 Cytotoxicity and Reversal of Multidrug Resistance (MDR)

Alkaloids obtained from *A. penangiana* in the present study were screened for their cytotoxic activity against several human cancer cell lines (KB, PC-3, LNCaP, MCF7, MDA-MB-231, HT-29, HCT 116, and A549), as well as for their potential in reversing multidrug resistance (MDR) in vincristine-resistant KB (VJ 300) cells. The alkaloids were tested at an initial concentration of 30μg/mL and the IC_{50} values were then determined for the more active compounds, and the results are summarized in Table 2.73.

Of the monomeric indole alkaloids tested, most were found to be ineffective against the cancer cell lines tested except for the ajmaline-type alkaloids (**57**, **58**) which showed strong cytotoxicity towards HCT 116 cancer cells. Alkaloids **57** and **58** were also found to reverse multidrug resistance in vincristine-resistant KB (VJ300) cells. Vincamaginine B (**58**, IC_{50}: 2.20 μM) showed higher potency than vincamaginine A (**57**, IC_{50}: 3.36 μM) against HCT-116 cells, while vincamaginine A (**57**, IC_{50}: 0.87 μM) showed better potency than vincamaginine B (**58**, IC_{50}: 3.00 μM) in the reversal of multidrug resistance in vincristine-resistant KB (VJ300) cells. These differences could

be attributed to the change in the substituent at C-4' of the benzoyl unit in **57** (CH_3O–C-4') and **58** (HO–C-4'). Both **57** and **58** showed only weak cytotoxicity against normal drug-sensitive KB cells (IC_{50}: 12.2–14.2 μM). The quinolone alkaloid (**37**) showed appreciable cytotoxicity against vincristine-resistant KB cells (IC_{50}: 9.2 μM), while the C_{14} indolizidine alkaloid (alstochalotine **40**) displayed appreciable cytotoxicity against HT-29 cancer cells (IC_{50}: 8.2 μM).

All the bisindoles tested displayed strong cytotoxicity against various human cancer cell lines, including KB, PC-3, LNCaP, MCF7, MDA-MB-231, HT-29, HCT 116, and A549. In general, the macroline-sarpagine bisindoles (**80**–**86**) displayed better cytotoxicity against the selected cancer cell lines compared to the macroline-akuammiline alkaloids. The macroline-sarpagine bisindoles (**81**–**85**) were the most active against HT-29 cancer cells at IC_{50} of 0.02–0.07 μM, compared to the macroline-akuammiline bisindoles (IC_{50}: 0.27–0.69 μM).

Among the macroline-sarpagine bisindoles tested, angustilongine M (**86**), which is the only linearly fused bisindole tested, showed the best cytotoxicity towards A549 cancer cells (IC_{50}: 2.1 μM). Of all the bisindole alkaloids tested, angustilongines J (**84**) and K (**85**), both having an E-seco macroline subunit, displayed the best cytotoxicity against HCT-116 cancer cells (IC_{50}: 1.5–2.1 μM). The cytotoxicity of macroline-derived bisindole alkaloids has only been previously reported for macroline-macroline and macroline-pleiocarpamine bisindoles which were found to be cytotoxic against a number of human cancer cell lines.[171,417] This study represents the first cytotoxicity investigation on macroline-akuammiline and macroline-sarpagine bisindole alkaloids.

Table 2.73: Cytotoxic Effects of Alkaloids Isolated from *Alstonia penangiana*

Compound	IC_{50}, µM						
	KB/S	KB/VJ300	KB/VJ300[a]	MCF7	MDA-MB-231	HT-29	HCT 116
Macroline							
Alstomutinine A (**1**)	>30	>30	>30	>30	>30	>30	>30
Alstomutinine B (**2**)	>30	>30	>30	-	-	>30	-
Macroline Oxindole							
Alstonisinine A (**20**)	>30	>30	>30	>30	>30	>30	>30
Alstonisinine B (**21**)	>30	>30	>30	-	-	>30	-
Alstonisinine C (**22**)	>30	>30	>30	>30	>30	>30	>30
Alstonoxine F (**23**)	>30	>30	>30	>30	>30	>30	>30
Sarpagine							
Alstopenidine A (**32**)	>30	>30	>30	>30	>30	>30	>30
Alstopenidine B (**33**)	>30	>30	>30	>30	>30	>30	>30
Alstopenidine C (**34**)	>30	>30	19.08	>30	>30	>30	>30
Talpinine							
Alstomutinine C (**41**)	>30	>30	>30	-	-	>30	-
Alstomutinines D (**42**) and E (**43**)	>30	>30	>30	-	-	>30	-
Ajmaline							
Vincamaginine A (**57**)	12.17	18.25	0.87	>30	20.27	>30	3.36
Vincamaginine B (**58**)	14.18	28.24	3.00	19.18	17.63	>30	2.20

[a]KB: Human oral epidermoid carcinoma; KB/S: vincristine-sensitive KB carcinoma; KB/VJ300: vincristine-resistant KB carcinoma; MCF7 and MDA-MB-231: human breast adenocarcinoma; HT-29 and HCT 116: human colorectal carcinoma. [b]Data expressed as mean ± SD of three independent experiments. [c]With added vincristine, 0.1 µM, which did not affect the growth of the KB/VJ300 cells.

Table 2.73, continued

Compound	IC_{50}, µg/mL											
	KB/S	**KB/ VJ300**	**KB/ VJ300[a]**	**PC-3**	**LNCaP**	**MCF7**	**MDA-MB-231**	**HT-29**	**HCT 116**	**A549**	**CCD-18Co**	**MRC-5**
Others												
Alstopenidine F (**37**)	>30	9.15	>30	-	-	>30	>30	>30	>30	-	-	-
Alstochalotine (**40**)	>30	>30	>30	-	-	>30	>30	8.21	>30	-	-	-
Macroline-Akuammiline Bisindoles												
Angustilongine A (**76**)	2.00	15.21	10.34	12.92	6.89	3.78	5.18	0.69	6.51	8.29	-	-
Angustilongine B (**77**)	0.70	6.68	0.86	7.16	3.88	3.82	3.25	0.27	5.19	6.49	-	-
Macroline-Sarpagine Bisindoles												
Angustilongine E (**80**)	0.64	6.66	0.18	8.15	6.22	4.48	4.49	0.27	12.60	7.02	-	7.89
Angustilongine F (**81**)	2.83	5.90	-	6.06	-	2.01	4.78	0.07	4.16	9.04	9.67	-
Angustilongine G (**82**)	0.75	16.99	3.87	12.48	3.73	5.34	4.84	0.07	14.53	10.99	-	12.35
Angustilongine H (**83**)	2.42	2.92	-	3.08	-	1.27	1.42	0.03	2.93	6.81	4.29	-
Angustilongine J (**84**)	2.52	5.48	8.75	13.50	-	7.74	4.13	0.03	1.48	3.91	4.07	-
Angustilongine K (**85**)	1.65	3.57	4.16	10.45	-	8.45	12.70	0.02	2.11	3.02	5.07	-
Angustilongine M (**86**)	4.96	7.55	-	6.10	-	9.98	5.91	0.16	4.73	2.05	12.76	-
Control												
Vincristine	0.75 ng/mL	0.78										
Cisplatin				11.13	7.12	6.42	3.03	10.14	4.05	13.29	4.42	5.34
Verapamil			0.39									

[a]KB: Human oral epidermoid carcinoma; KB/S: vincristine-sensitive KB carcinoma; KB/VJ300: vincristine-resistant KB carcinoma; PC-3 and LNCaP: human prostate carcinoma; MCF7 and MDA-MB-231: human breast adenocarcinoma; HT-29 and HCT 116: human colorectal carcinoma; A549: human lung carcinoma; CCD-18Co: human colon fibroblast; MRC-5: human fetal lung fibroblast. [b]Data expressed as mean ± SD of three independent experiments; [c]With added vincristine, 0.1 µM, which did not affect the growth of the KB/VJ300 cells.

2.4.3 Acetylcholinesterase (AChE) inhibitory activity

Since some *Lycopodium* alkaloids (e.g., huperzine A) have been reported to possess potent AChE (acetylcholinesterase) inhibition activity,[253,258,299] the new *Lycopodium* alkaloids isolated in this study (**95**, **96**, and **101**) were evaluated for their AChE inhibitory activity using a modified Ellman's method.[430] Unfortunately, none of the new alkaloids tested showed appreciable potency ($IC_{50} > 30$ μM).

CHAPTER 3: EXPERIMENTAL

3.1 Sources and Authentication of Plant Materials

Plant material (stem-bark and leaves) of *A. penangiana* was collected in Bukit Bendera, Penang Island, whereas the whole plant of *L. platyrhizoma* was collected in Genting Highlands, Pahang, and were identified by Dr. Yong (Institute of Biological Sciences, University of Malaya). Herbarium voucher specimens (Table 3.1) are deposited at the Herbarium, University of Malaya.

Table 3.1: Sources and Authentication of Plant Materials

Herbarium Specimen No.	Locality	Species	Collection month
KLU 49466	Penang	*A. penangiana* (Sample A)	April 2012
KLU 49468	Penang	*A. penangiana* (Sample B)	November 2014
KLU 48246	Pahang	*L. platyrhizoma*	January 2014

3.2 General

Melting points were determined on a Mel-Temp melting point apparatus or an Electrothermal IA9100 digital melting point apparatus and were uncorrected. Optical rotations were determined on a JASCO P-1020 automatic digital polarimeter. UV spectra were recorded on a Shimadzu UV-2600 spectrophotometer. ECD spectra were measured with a JASCO J-815 CD spectrometer in methanol. IR spectra were recorded on a PerkinElmer RX1 FT-IR or Spectrum 400 FT-IR/FT-FIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using tetramethylsilane (TMS) as internal standard on JEOL JNM (ECA or ECX 400 MHz) or Bruker Avance III spectrometers (400 or 600 MHz). Coupling constants (*J*) are reported in Hz and

chemical shift (δ) in ppm. ESIMS and HRESIMS were obtained on an Agilent 6530 Q-TOF or 6550 iFunnel Q-TOF spectrometer, and HRDARTMS were recorded on a JEOL Accu TOF-DART mass spectrometer. All solvents were distilled prior to use with the exception of diethyl ether.

3.3 X-Ray Diffraction Analysis

X-Ray diffraction analyses were carried out on a Rigaku Oxford (formerly Agilent Technologies) SuperNova Dual diffractometer with Cu Kα radiation (λ = 1.54184 Å) or Mo Kα (λ = 0.71073 Å) radiation at rt or 100 K or 160–170 K. The structures were solved by intrinsic phasing methods (SHELXT-2014) and refined with full-matrix least-squares on F^2 (SHELXL-2018). All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were placed in idealized positions and refined as riding atoms with the relative isotropic parameters. The absolute configuration was determined on the basis of the Flack[431-433] parameter [x = 0.03(7)], refined using 2364 Friedel pairs.

3.4 Computational Method

The conformations of compound **23** (3*S*, 5*S*, 7*S*, 15*S*, 16*R*, 19*S*) were obtained by Spartan'14 software using the MMFF94 force field.[382] Conformers occurring within a 10 kcal mol^{-1} energy window from the global minimum were imported into the Gaussian 09 software[434] for DFT-level geometry optimization and frequency calculation using the B3LYP functional with a basis set of 6-31G(d). TDDFT electronic circular dichroism (ECD) calculations were performed at the B3LYP/6-311++G(d,p) level with the optimized conformers using a PCM solvation model for MeOH. The ECD curve for each optimized conformer was weighted by Boltzmann distribution after UV correction, and the overall ECD curves were produced by SpecDis, version 1.64, software.

3.5 Chromatographic Methods

3.5.1 Column Chromatography (CC)

Flash chromatography was carried out using Merck silica gel 9385 (40–63 μm) as stationary phase. The ratio of silica gel to the sample was approximately 30:1 for crude samples and 100:1 for semi-pure fractions. The silica gel was made into a slurry with starting solvent before it was packed onto a glass column with sintered glass disc and was allowed to equilibrate for at least an hour before use. The solvent systems normally used as eluents were chloroform (or ethyl acetate) with increasing methanol gradient. Eluted fractions were monitored using thin layer chromatography (TLC) and appropriate fractions were combined and where necessary subjected to further separation by re-chromatography or preparative radial chromatography. Reverse phase silica gel (Merck LiChroprep RP-18, 40-63 μm) was also used by employing solvent system of water with increasing methanol (or acetonitrile) gradient. Other stationary phase in use included DIOL and NH_2 functionalized silica gel (Merck LiChroprep 40-63 μm).

3.5.2 Thin Layer Chromatography (TLC)

Thin layer chromatography (TLC) was routinely used to detect the presence of alkaloids, to scout for starting solvent system used for various chromatography separation, and to check for purity of sample. The crude alkaloid extracts, fractions from chromatography, and isolated pure alkaloids were examined by TLC using pre-coated 5 cm x 10 cm aluminium plates, 0.25 mm thickness, silica gel 60 F_{254} (Merck, Darmstadt, G.F.R.). The sample solution was spotted onto TLC plate using a piece of fine glass capillary tube and the TLC was then developed in saturated chromatographic tanks with various solvent systems at room temperature. The alkaloidal spots were visualized by

examination of the TLC plates under UV light (254 or 365 nm), followed by spraying with Dragendorff's reagent, which formed orange spots in the presence of alkaloids. The hR_f values of the alkaloids are tabulated in Tables 3.2 and 3.3.

Table 3.2: The hR_f Values of Alkaloids Isolated from *Alstonia penangiana*

Alkaloid	$CHCl_3$	EtOAc	Et_2O	$CHCl_3$: MeOH (10:1)	EtOAc: MeOH (10:1)
Alstomutinine A (**1**)	1	20	6	55	42
Alstomutinine B (**2**)	1	19	5	57	41
Alstonerine (**3**), Alstonerinal (**4**)	12	35	21	80	59
N(1)-Demethylalstonerine (**5**), *N*(1)-Demethylalstonerinal (**6**)	3	29	16	62	56
N(4)-Demethylalstonerine (**7**), *N*(4)-Demethylalstonerinal (**8**)	4	10	3	56	27
Alstophylline (**9**), Alstophyllal (**10**)	10	33	16	77	56
N(1)-Demethylalstophylline (**11**), *N*(1)-Demethylalstophyllal (**12**)	1	26	10	56	49
Talcarpine (**13**)	4	17	9	51	35
N(4)-Methyl-*N*(4),21-secotalpinine (**14**)	1	13	9	46	31
Macrocarpine D (**15**)	0	6	2	22	28
Macrocarpine E (**16**)	0	4	1	32	22
Alstohentine (**17**)	3	9	2	53	38
Alstolactone (**18**)	3	9	2	57	28
Alstomicine (**19**)	0	6	2	47	26
Alstonisinine A (**20**)	0	29	9	42	57
Alstonisinine B (**21**)	0	28	7	41	56
Alstonisinine C (**22**)	3	27	4	57	48
Alstonoxine F (**23a** or **23b**)	0	1	0	20	9
Alstonoxine F (**23a** or **23b**)	0	5	0	33	19
Alstonisine (**24**), Alstonal (**25**)	10	43	30	76	60
N(1)-Demethylalstonisine (**26**), *N*(1)-Demethylalstonal (**27**)	3	37	14	60	56

Table 3.2, continued

Alkaloid	$CHCl_3$	EtOAc	Et_2O	$CHCl_3$: MeOH (10:1)	EtOAc: MeOH (10:1)
16-Hydroxyalstonisine (**28**), 16-Hydroxyalstonal (**29**)	4	39	18	61	58
Alstofoline (**30**)	4	22	4	69	49
Alstonoxine A (**31**)	3	6	4	57	23
Alstopenidine A (**32**)	0	1	0	32	16
Alstopenidine B (**33**)	0	3	0	24	20
Alstopenidine C (**34**)	1	3	1	33	16
Alstopenidine D (**35**)	0	1	0	31	11
Alstopenidine E (**36**)	0	0	0	5	0
Alstopenidine F (**37**)	0	0	0	22	4
Alstopenidine G (**38**)	0	0	0	6	1
Alstopenidine H (**39**)	0	0	0	12	0
Alstochalotine (**40**)	0	34	15	58	60
Alstomutinine C (**41**)	0	4	3	56	21
Alstomutinines D (**42**) and E (**43**)	0	1	0	14	7
Affinisine (**44**)	4	13	6	44	33
10-Methoxyaffinisine (**45**)	4	11	4	44	30
10-Methoxyaffinisine *N*(4)-oxide (**46**)	0	0	0	15	0
Lochnerine (**47**)	0	6	1	22	18
Alstoumerine (**48**)	0	3	0	37	19
11-Methoxystrictamine (**49**)	4	5	2	58	16
11-Hydroxystrictamine (**50**)	0	4	3	34	13
10-Methoxyvincamidine (10-Methoxystrictamine) (**51**)	0	4	1	54	14
Cathafoline (**52**)	0	1	0	14	3
Cathafoline *N*(4)-oxide (**53**)	0	0	0	30	4
Vincorine (**54**)	9	44	43	74	59
Norvincorine (**55**)	4	5	4	44	17
Demethoxyalstonamide (**56**)	23	58	41	84	74
Vincamaginine A (**57**)	6	23	6	77	54
Vincamaginine B (**58**)	4	19	5	71	51
4'-Hydroxy-3',5'-dimethoxybenzoylvincamajine (**59**)	5	24	10	71	46

Table 3.2, continued

Alkaloid	$CHCl_3$	EtOAc	Et_2O	$CHCl_3$: MeOH (10:1)	EtOAc: MeOH (10:1)
O-3,4,5-Trimethoxybenzoylquebrachidine (**60**)	3	17	5	63	38
Vincamajine *N*(1)-tri-*O*-methylgallate (**61**)	8	23	8	68	49
Vincamajine (**62**)	6	27	18	66	46
Quebrachidine (**63**)	4	11	5	49	32
18,19-Dihydroisositsirikine (**64**)	3	30	17	41	55
16(*R*),19(*E*)-Isositsirikine (**65**)	0	7	3	28	20
Z-Geissoschizol (**66**)	0	11	6	27	34
Pleiocarpamine (**67**)	1	4	2	47	10
16-Hydroxymethylpleiocarpamine (**68**)	1	2	1	31	7
Pleiomaltinine (**69**)	0	1	0	44	7
Fluorocarpamine (**70**)	3	8	5	60	28
11-Methoxyakuammicine (**71**)	0	2	1	38	7
11-Methoxyakuammicine *N*(4)-oxide (**72**)	0	0	0	25	0
Alstolagumine (**73**)	4	6	2	64	25
Alstovine (**74**)	0	2	0	27	7
Lagumidine (**75**)	0	1	0	33	10
Angustilongine A (**76**)	0	0	0	13	3
Angustilongine B (**77**)	0	0	0	26	3
Angustilongine C (**78**)	0	0	0	19	0
Angustilongine D (**79**)	0	0	0	5	0
Angustilongine E (**80**)	0	2	0	43	18
Angustilongine F (**81**)	0	2	1	30	11
Angustilongine G (**82**)	0	2	1	36	14
Angustilongine H (**83**)	0	1	0	34	8
Angustilongine J (**84**)	0	0	0	13	3
Angustilongine K (**85**)	0	0	0	19	5
Angustilongine M (**86**)	0	2	0	49	16
Macralstonidine (**87**)	0	9	2	57	28
Angustilongine L (**88**)	0	0	0	20	0
Macrocarpamine (**89**)	0	1	0	42	7
Villalstonine (**90**)	3	6	4	52	17
Villalstonine *N*(4')-oxide (**91**)	0	0	0	30	0
Lumutinine B (**92**)	0	5	1	72	25
Lumusidine B (**93**)	0	1	0	30	12
Perhentinine (**94**)	0	5	1	57	22

Table 3.3: The hR_f Values of Alkaloids Isolated from *Lycopodium platyrhizoma*

Alkaloid	$CHCl_3$	EtOAc	Et_2O	$CHCl_3$: MeOH (10:1)	EtOAc: MeOH (10:1)
Lycoplatyrine A (**95**)	0	0	0	4	0
Lycoplatyrine B (**96**)	2	5	2	33	13
Lycodine (**97**)	1	6	4	46	24
Lycoannotine G (**98**)	5	6	2	58	21
Des-*N*-methyl-β-obscurine (**99**)	0	1	0	23	9
Des-*N*-methyl-α-obscurine (**100**)	0	2	2	21	9
Lycoplanine D (**101**)	0	1	0	6	4
Casuarinine H (**102**)	0	1	0	18	9
Flabellidine (**103**)	0	0	0	20	5
Complanadine A (**104**)	0	0	0	19	4
6α-Hydroxylycopodine (**105**)	3	5	8	30	14
Lycodoline (**106**)	0	1	4	13	4
Lycopodine *N*-oxide (**107**)	0	0	1	13	0
Huperzine E (**108**)	5	11	0	61	29
12-Deoxyhuperzine O (**109**)	3	5	5	44	14
Lycoplatyrine C (**110**)	0	0	0	4	0
Lycogladine G (**111**)	8	30	24	71	47
Lycogladine H (**112**)	10	30	24	71	47
Lyconadin E (**113**)	0	0	0	5	0

3.5.3 Preparative Radial Chromatography

Preparative radial chromatography (Chromatotron) was carried out using a circular chromatographic glass plate (diameter = 24 cm) coated with a layer of silica gel. To prepare the chromatographic plate, the perimeter of the plate is secured with cellophane tape to form a mold. Silica gel (Merck 7749 Kieselgel 60 PF_{254}, 50 g) is added to about 110 mL of cold distilled water to give a slurry. The slurry is shaken and then quickly poured onto the circular glass plate before the silica gel starts to set. The glass plate is rotated while the gel is being poured to obtain an even settling (silica gel layer with uniform thickness). The plate is then left to air-dry at room temperature for at least an hour before the overnight drying (about 12 hours) in oven at 80 °C. Sample to be purified was dissolved in a minimum volume of a suitable solvent and loaded at the

centre of the spinning plate to form a thin band. Elution of different fractions then proceeds with the progressive increase in solvent strength of the eluent introduced via an in-line solvent reservoir. The fractions are collected, concentrated by rotary-evaporation, examined by TLC, and combined accordingly. Solvent systems used for preparative radial chromatography were mostly ammonia-saturated. Some of the solvent systems used as eluents were chloroform, chloroform/methanol, dichloromethane, dichloromethane/methanol, diethyl ether, diethyl ether/methanol, ethyl acetate, ethyl acetate/hexanes, ethanol/hexanes.

3.5.4 Gel Permeation Chromatography

Dry powder of Sephadex LH-20 was allowed to swell in methanol overnight prior to packing into a glass column. The slurry was resuspended and poured onto the column and was allowed to equilibrate at room temperature. Before the sample solution was loaded into the column, it was first filtered with a 0.45 μm nylon membrane, as a precautionary step to extend the lifespan of the stationary phase. After each use, LH-20 material in the column was regenerated by washing step with 2-3 column volumes of methanol and subsequent re-equilibration.

3.5.5 High Performance Liquid Chromatography (HPLC)

The models of the HPLC instruments in use were Waters 600 equipped with UV/Visible Detector or Waters AutoPurification Systems equipped with Photodiode Array (PDA) Detector. Both reverse phase and normal phase HPLC columns were used in the current study. The reverse phase HPLC column used was Agilent Zorbax Eclipse Plus C18 (4.6 x 100 mm) and the solvent systems used were mixtures of water and acetonitrile. HPLC-grade methanol was also used for the cleaning or flushing of the reverse phase HPLC column. The normal phase HPLC column used was a chiral phase

HPLC column, Daicel CHIRALPAK IB (4.6 x 150 mm), and the solvent used for this separation was mixture of *n*-hexane and absolute ethanol. All solvents used were filtered with 0.45 µm nylon membrane and sonicated for at least an hour prior to HPLC separation. Samples were dissolved in ethanol (normal phase HPLC) or methanol (reverse phase HPLC) and filtered with 0.45 µm nylon membrane.

3.6 TLC Spray Reagent (Dragendorff's Reagent)

Solution A: 0.85 g of bismuth nitrate was dissolved in a mixture of 10 mL glacial acetic acid and 40 mL of distilled water.

Solution B: 8 g of potassium iodide was dissolved in 20 mL of distilled water.

A stock solution was prepared by mixing solution A and B in ratio of 1:1 (by volume). Dragendorff's reagent was prepared by mixing 1 mL of stock solution with 2 mL of glacial acetic acid and 10 mL of distilled water. Orange spots that appear on the TLC plate sprayed with this reagent indicated the presence of alkaloids.

3.7 Extraction of Alkaloids

The plant materials were air dried in wooden drying racks and ground, followed by extraction with distilled ethanol or methanol for 3 days at room temperature. The alcoholic extract was then filtered and the residue was then re-extracted with a fresh portion of distilled ethanol or methanol. This step was repeated 6 or 7 times. The combined extract was concentrated by evaporation under reduced pressure using a rotary evaporator to about a tenth of the original volume. The concentrated crude extract was then added slowly into 3% tartaric acid solution with constant stirring. The acidic solution was then filtered through kieselguhr to remove the non-alkaloidal substances.

The filtrate was then basified with saturated potassium carbonate solution until the pH of the solution reaches the scale of 10 and the liberated alkaloids were extracted exhaustively with chloroform. The chloroform extract was then washed with distilled water and dried over anhydrous sodium sulphate. Lastly, the solvent was removed using rotary evaporator to furnish the crude alkaloidal mixture.

3.8 Isolation of Alkaloids

3.8.1 General Procedure

The crude alkaloid mixture obtained from the extraction procedure described above was initially fractionated by column chromatography over silica gel. The column was eluted with chloroform, followed by a stepwise increase of methanol gradient. Based on TLC, the many fractions collected were combined into several major fractions, which were then subjected to further fractionation by flash chromatography, preparative radial chromatography, gel permeation chromatography (LH-20), and HPLC until pure alkaloids are obtained.

3.8.2 Isolation of Alkaloids from *Alstonia penangiana*

Extraction of 3 kg of dried leaves (sample A) yielded *ca.* 29 g of crude alkaloidal mixture. Additionally, the extraction of 2.7 kg of dried stem-bark and 2.4 kg of dried leaves (sample B) from another batch of collection yielded about 77 g and 21 g of crude alkaloidal mixture, respectively. These alkaloidal mixtures were then subjected to repeated chromatography, as summarized in the flow diagrams shown in Figures 3.1–3.3 to yield the pure alkaloids.

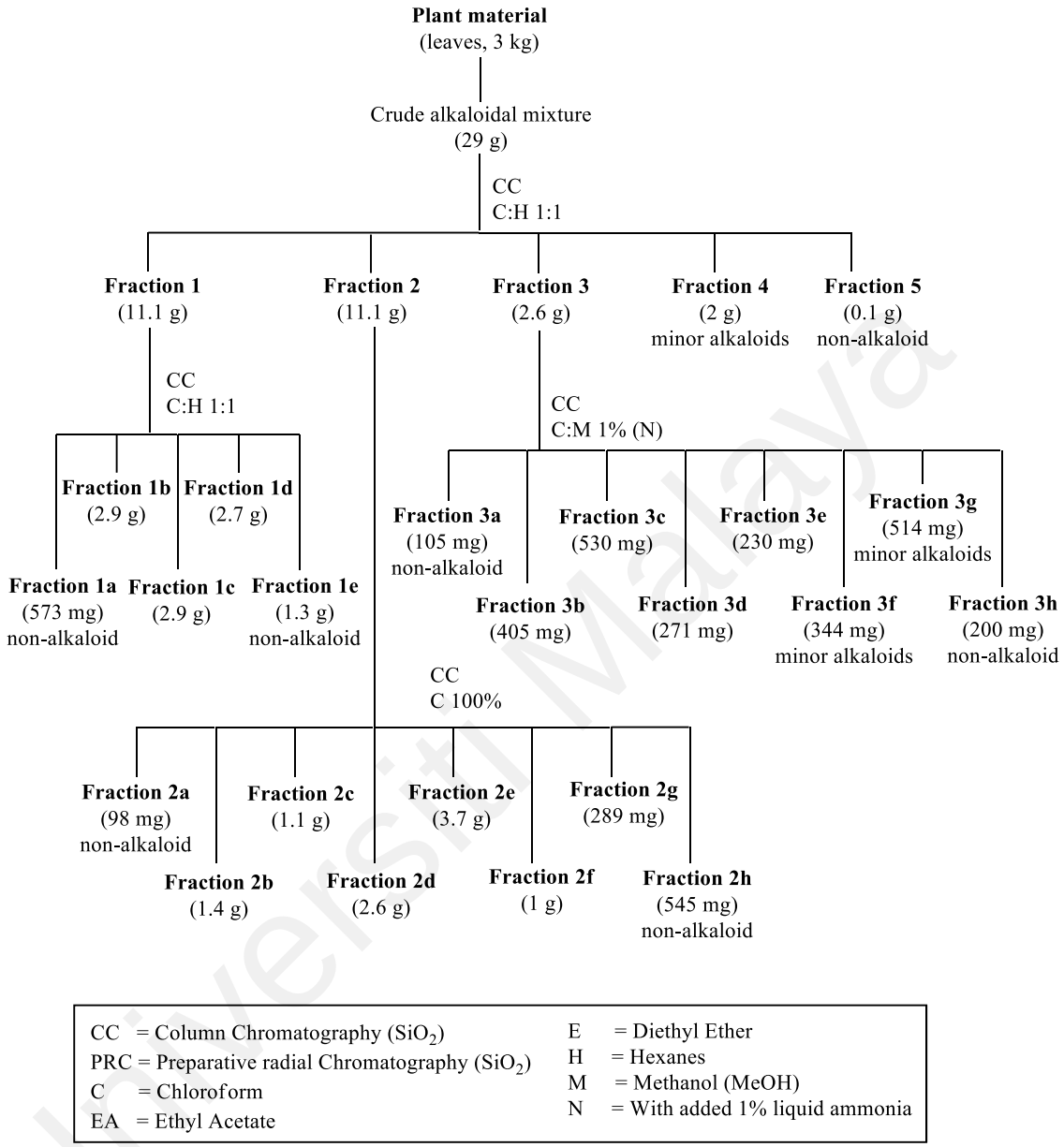


Figure 3.1: Isolation of alkaloids from the leaf extract (sample A) of *Alstonia penangiana*

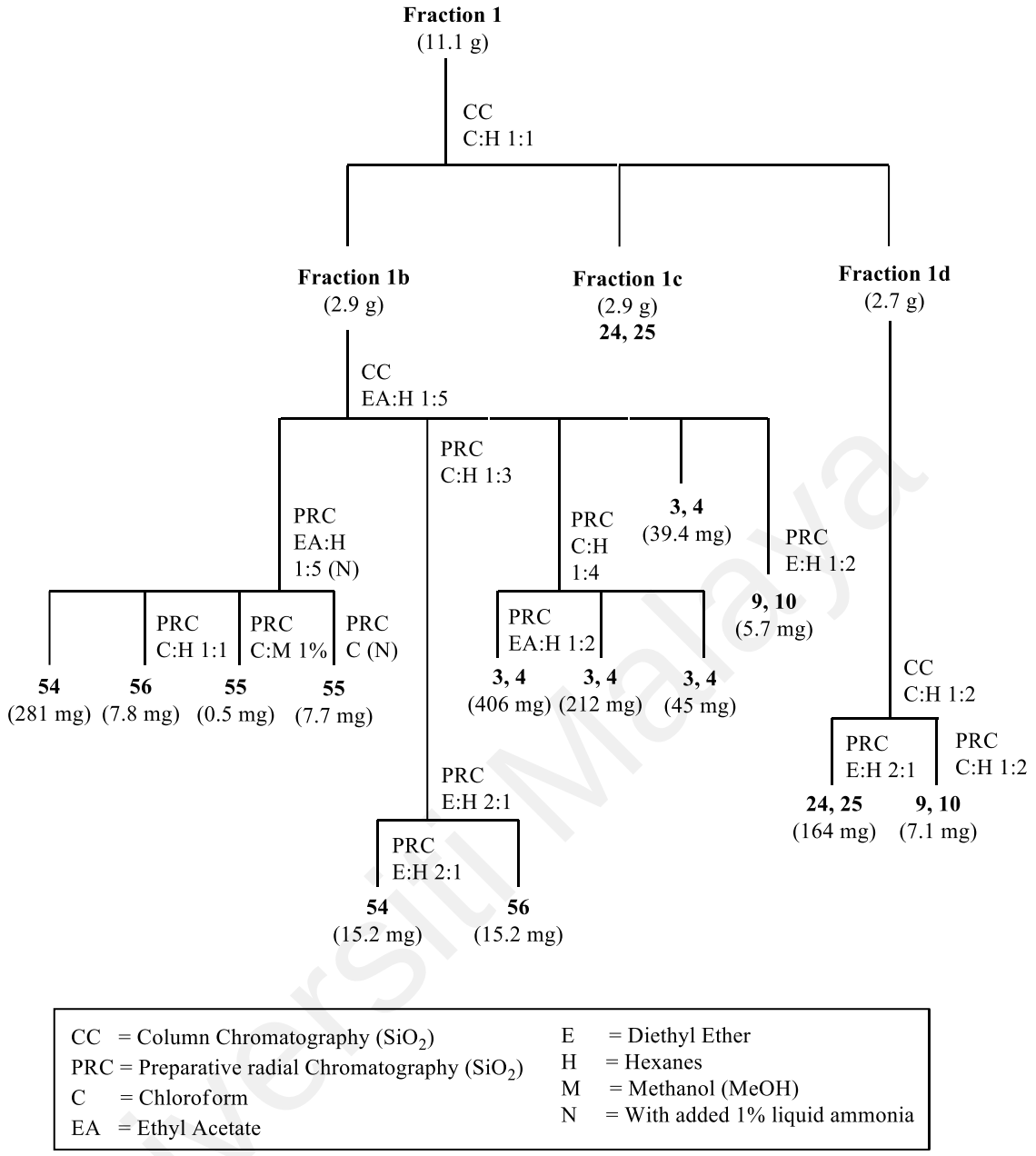


Figure 3.1, continued

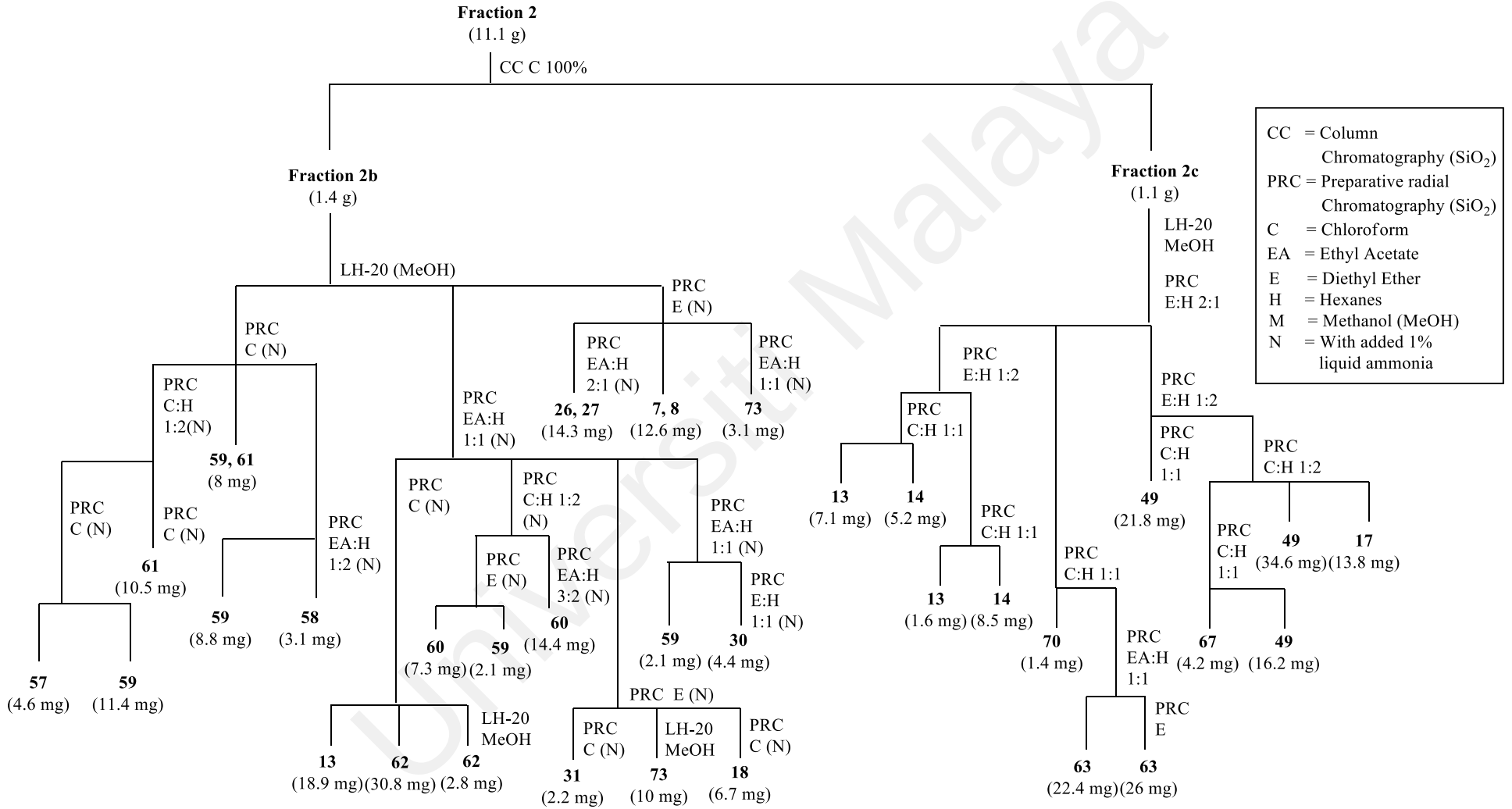


Figure 3.1, continued

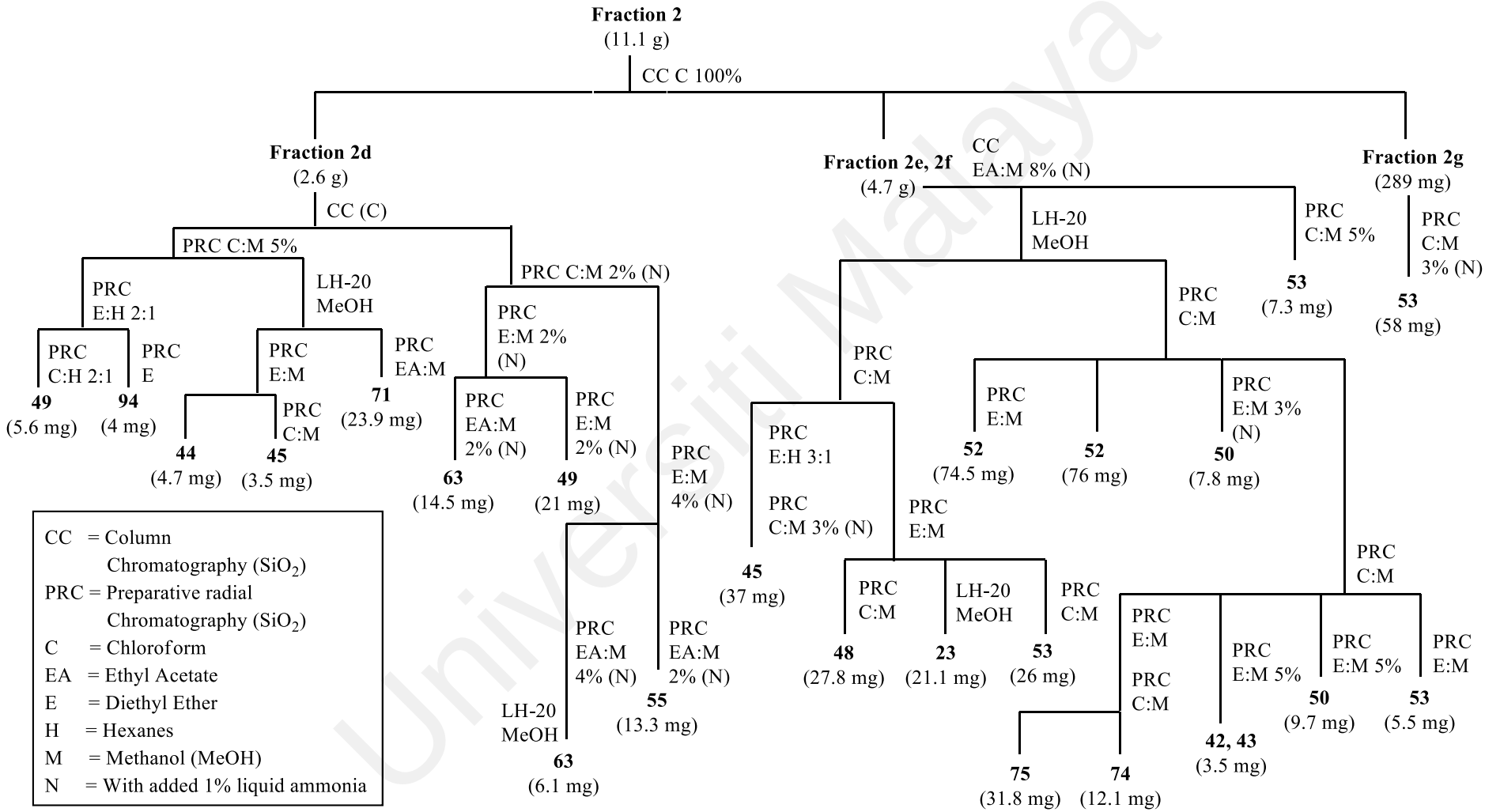


Figure 3.1, continued

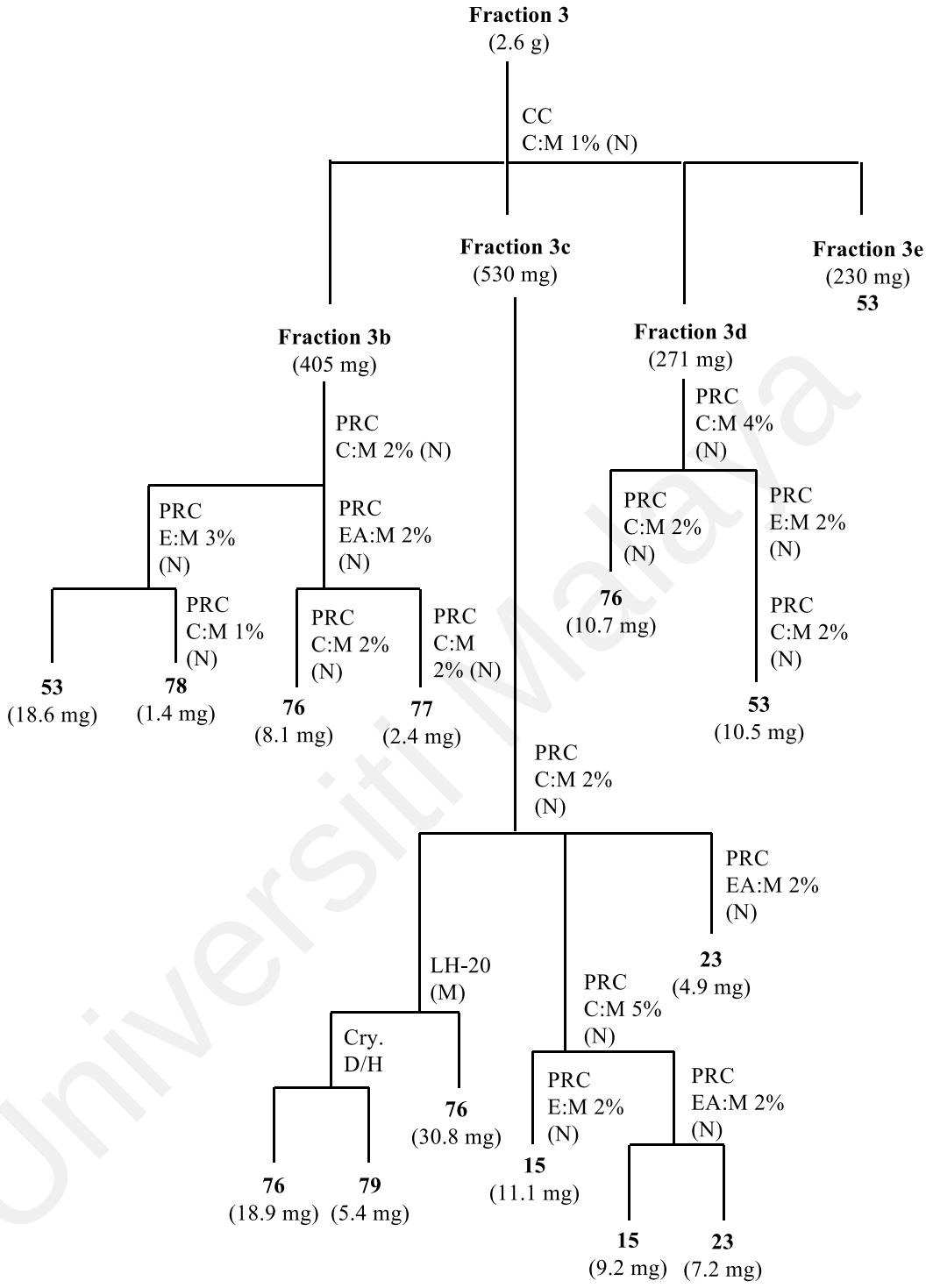


Figure 3.1, continued

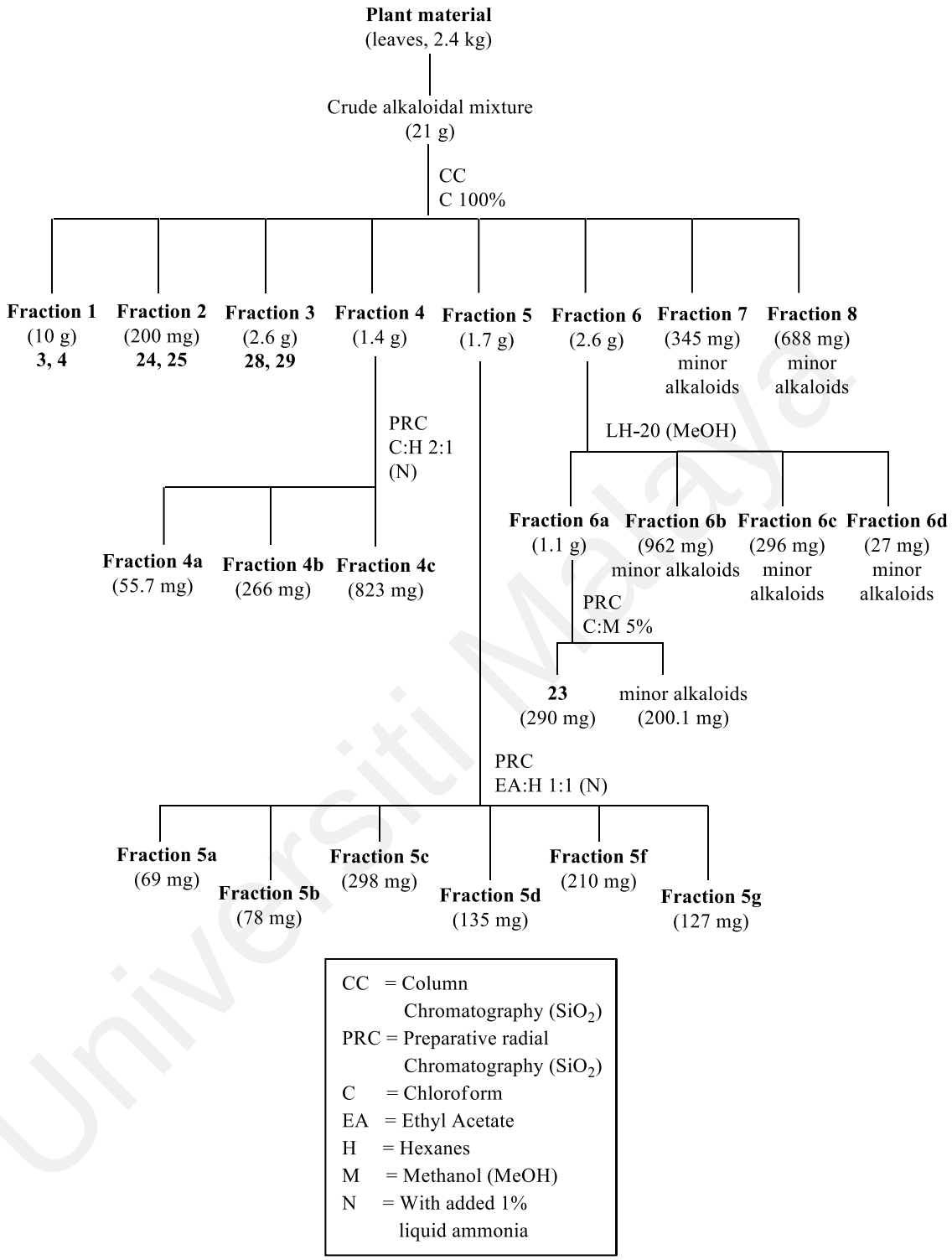


Figure 3.2: Isolation of alkaloids from the leaf extract (sample B) of *Alstonia penangiana*

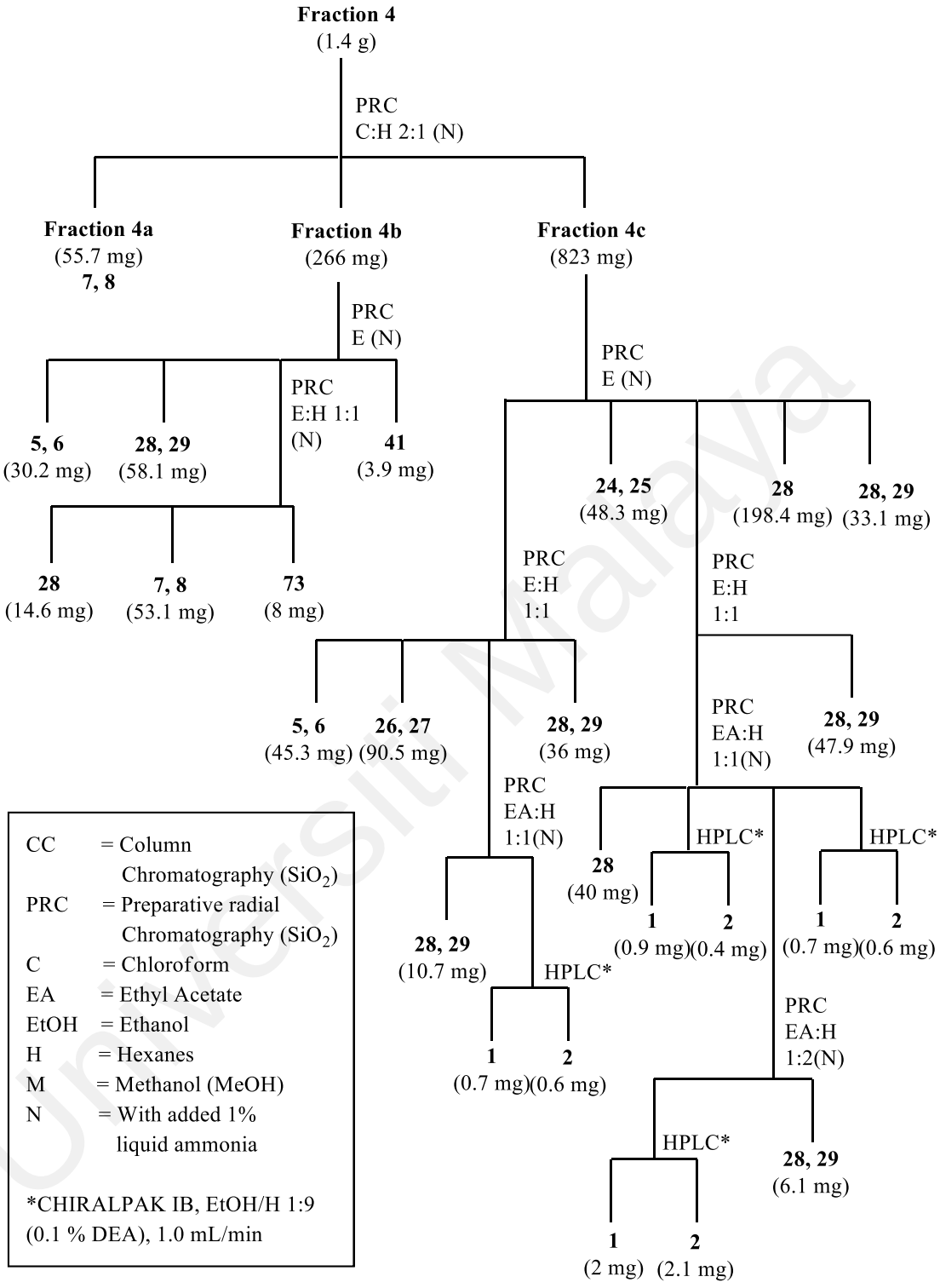


Figure 3.2, continued

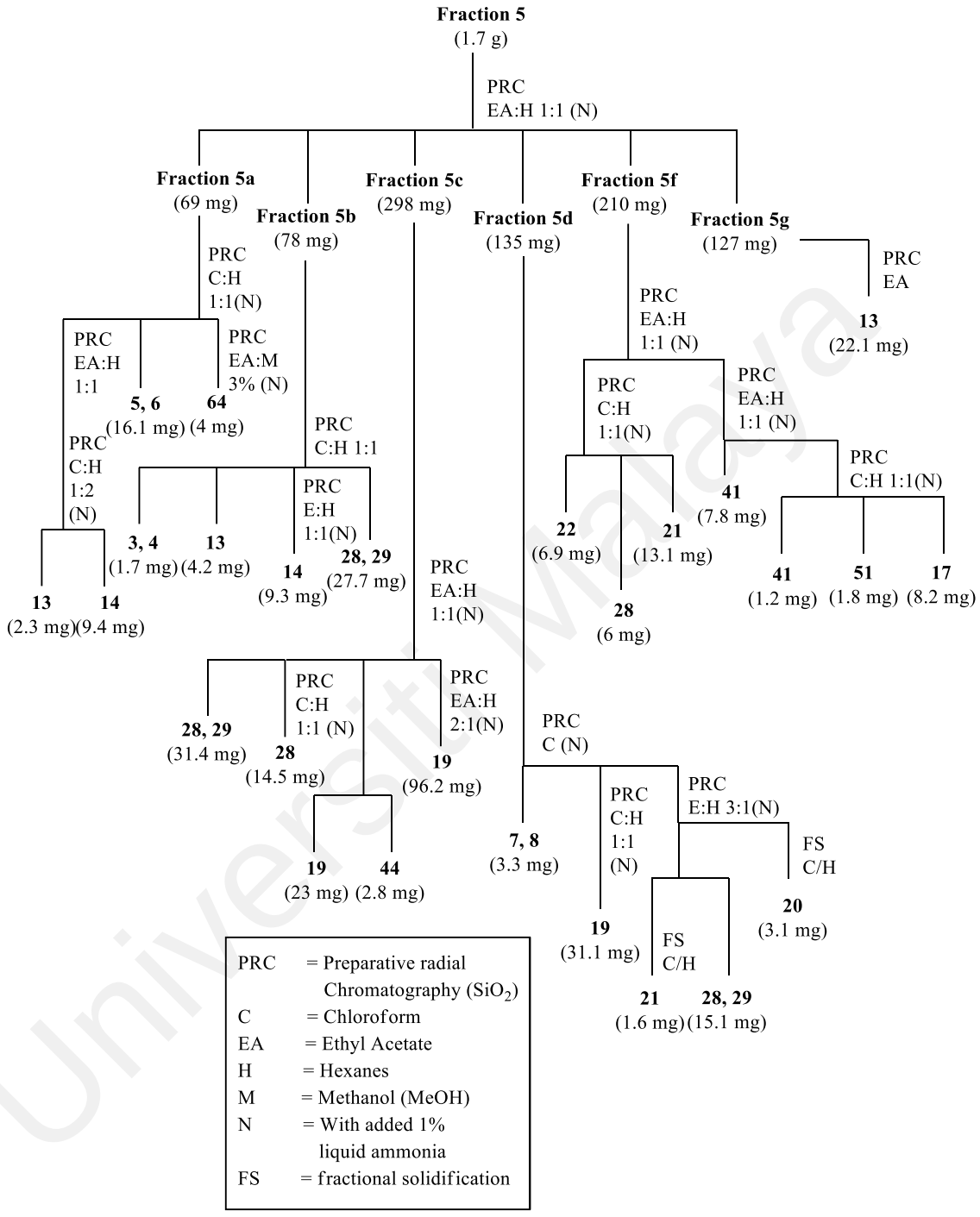


Figure 3.2, continued

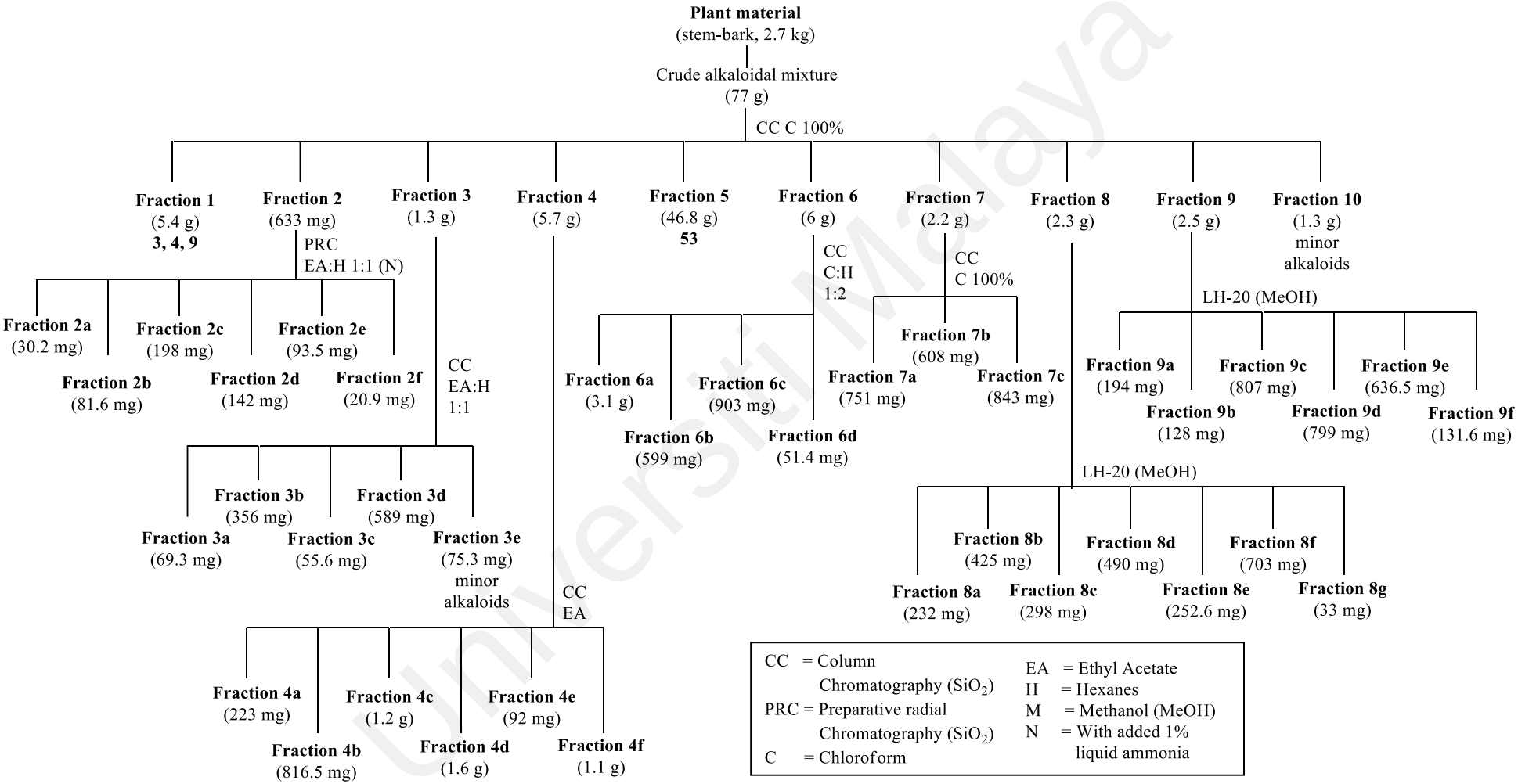


Figure 3.3: Isolation of alkaloids from the stem-bark extract of *Alstonia penangiana*

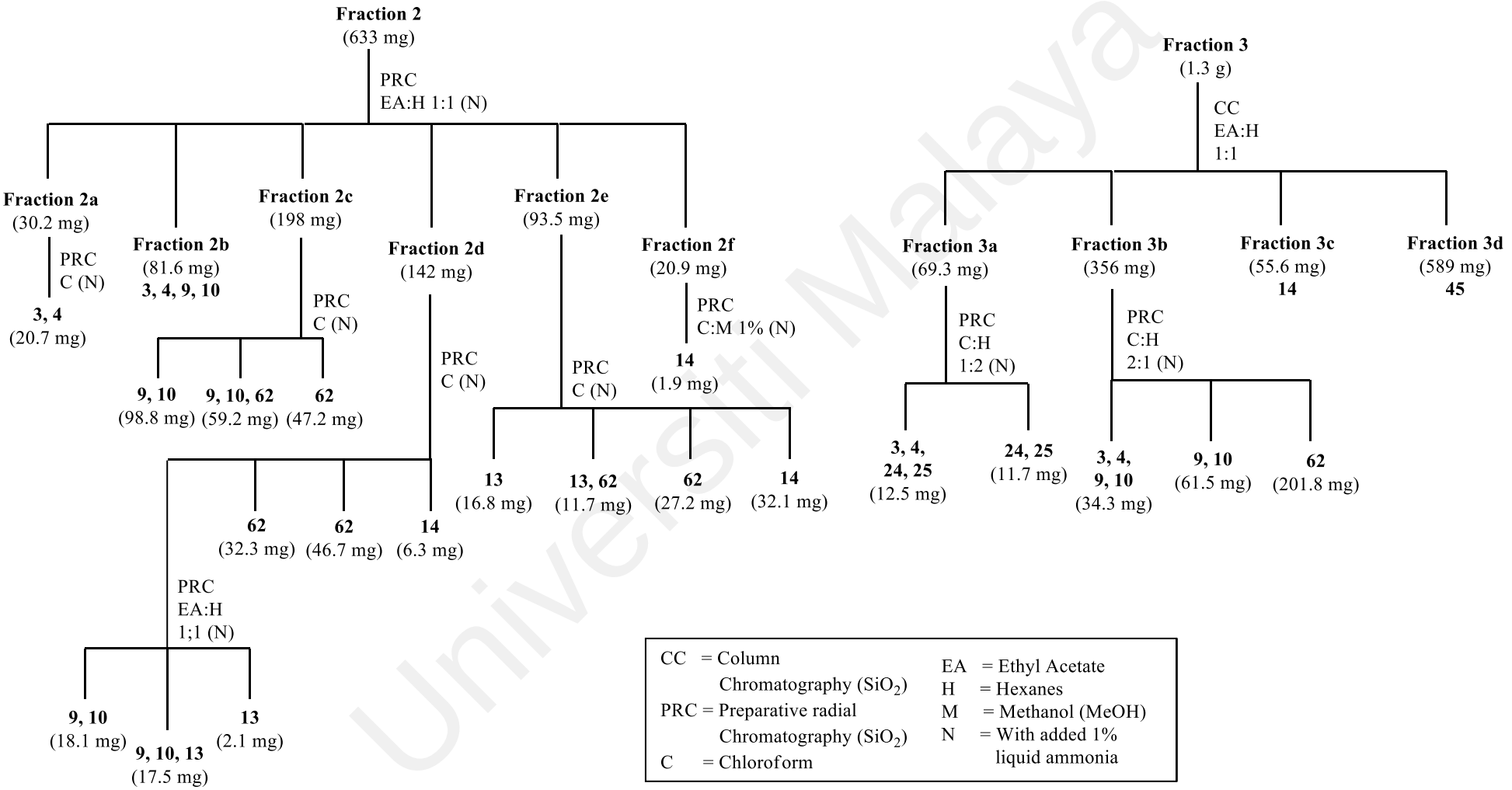


Figure 3.3, continued

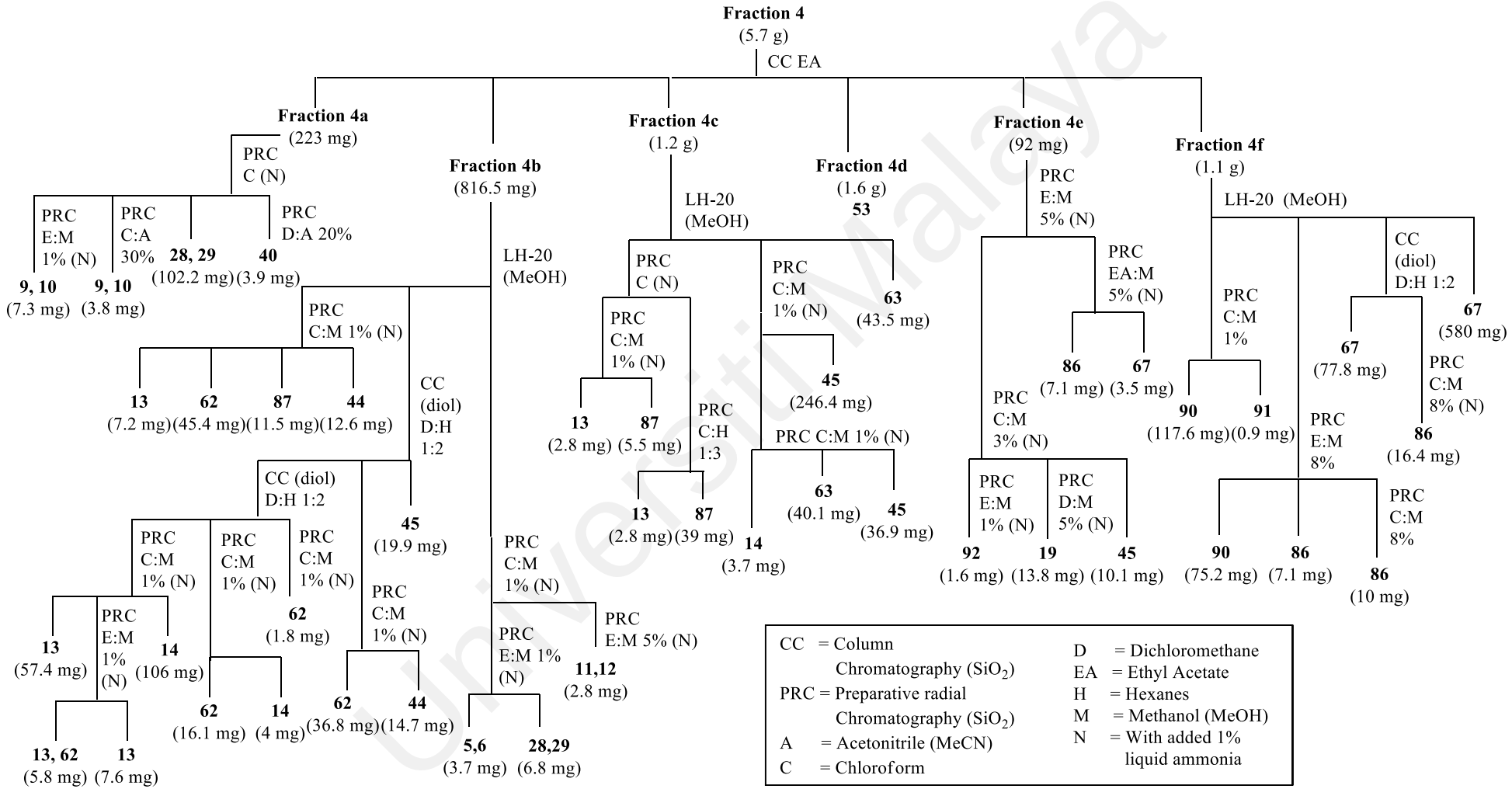


Figure 3.3, continued

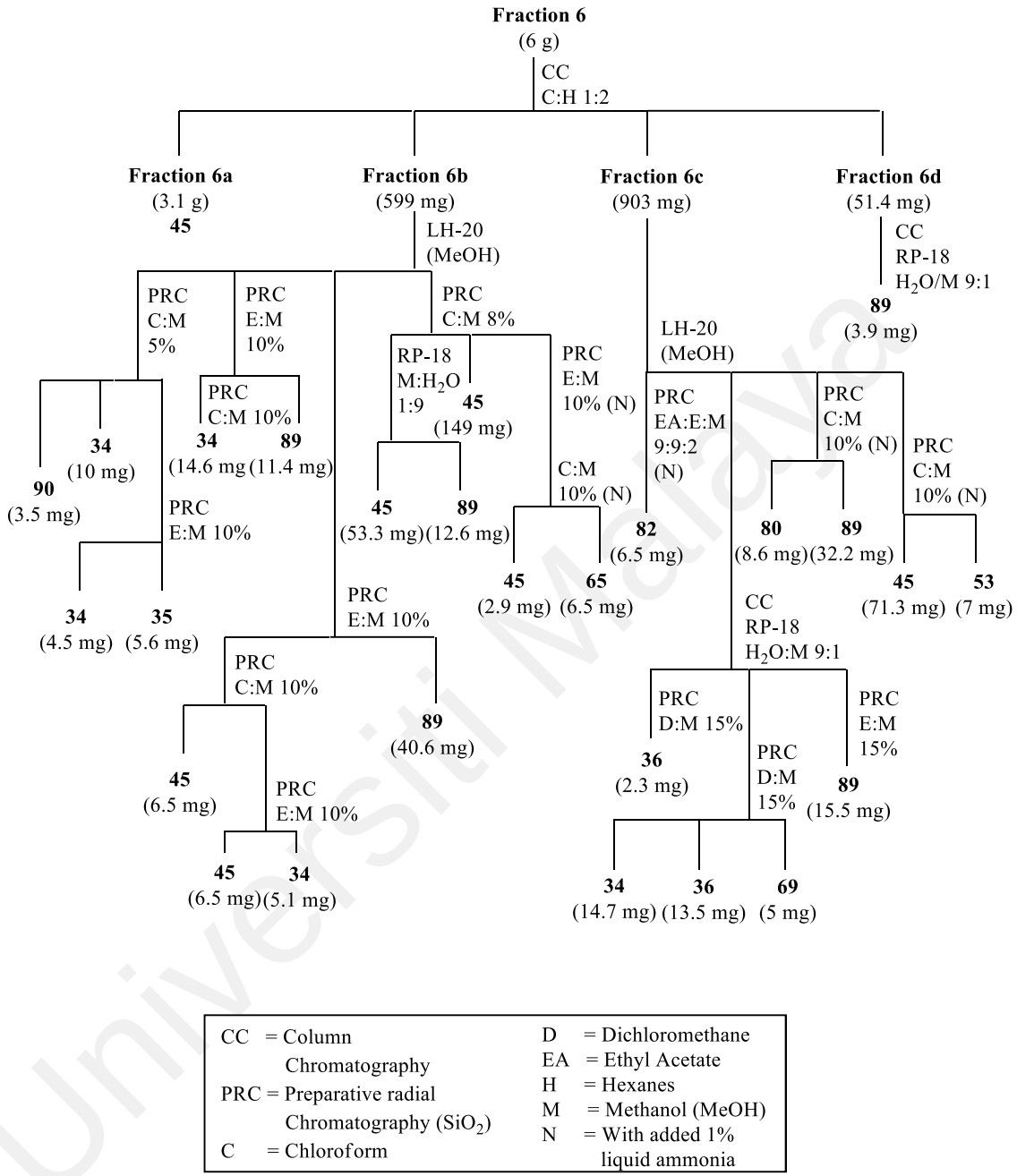


Figure 3.3, continued

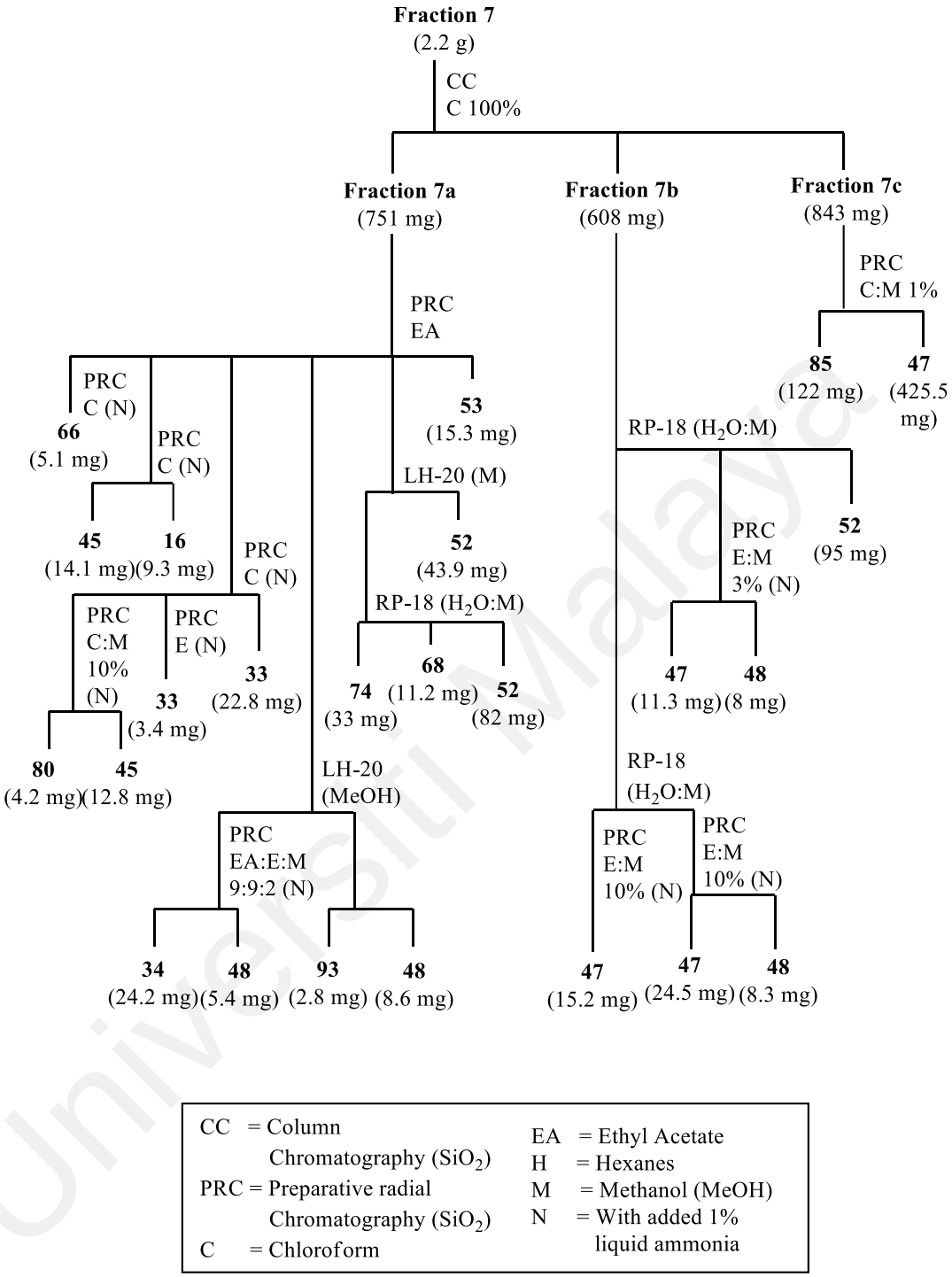


Figure 3.3, continued

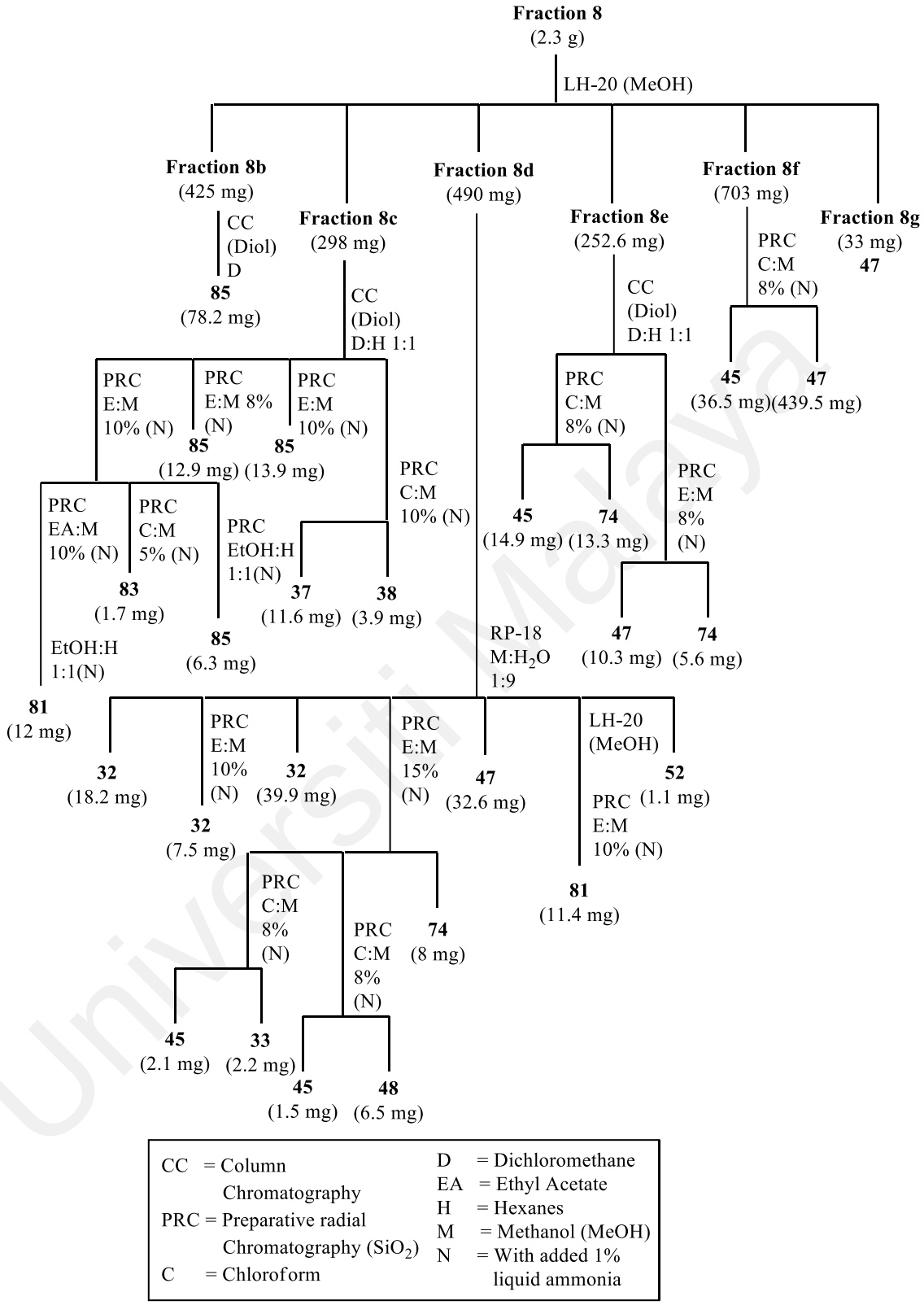


Figure 3.3, continued

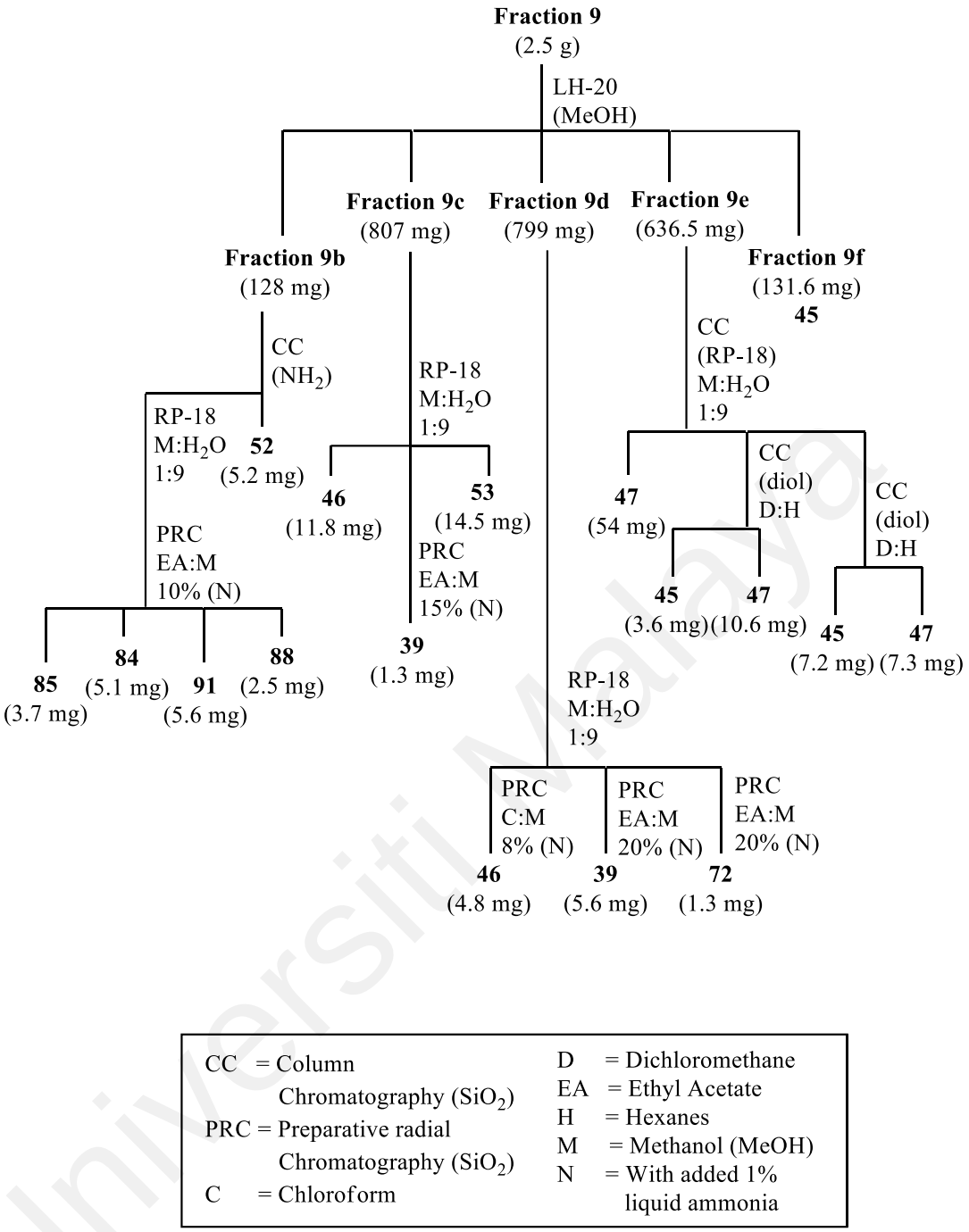


Figure 3.3, continued

3.8.3 Isolation of Alkaloids from *Lycopodium platyrhizoma*

Extraction of 14 kg of the dried whole plant of *Lycopodium platyrhizoma* yielded about 11 g of crude alkaloidal mixture. This alkaloidal mixture was then subjected to repeated chromatography, as summarized in the flow diagram shown in Figure 3.4 to yield 19 pure alkaloids.

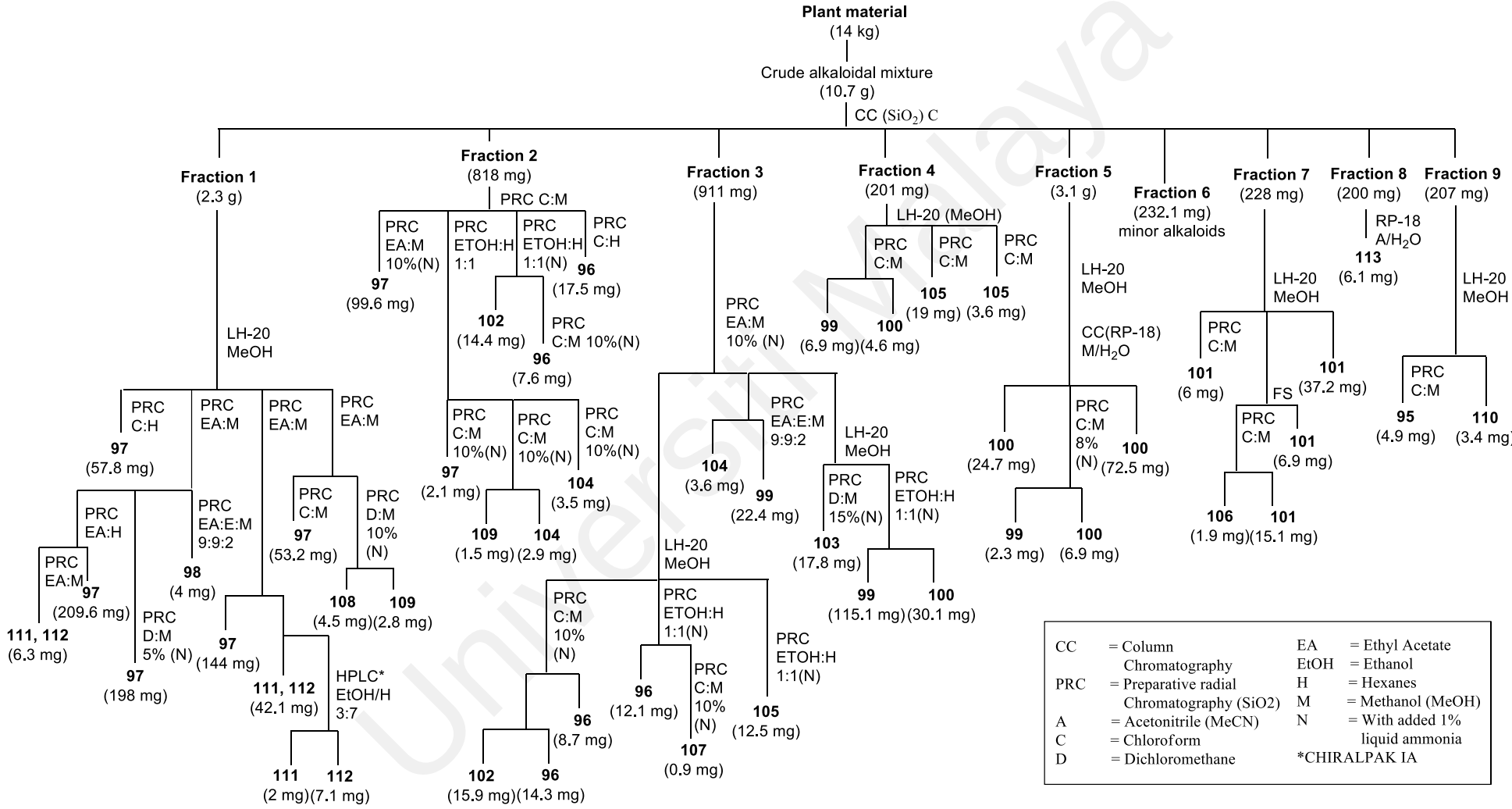


Figure 3.4: Isolation of alkaloids from the whole-plant extract of *Lycopodium platyrhizoma*

3.9 Compound Data

The following alkaloids were isolated from the stem-bark and leaf extracts of *A. penangiana*:

Alstomutinine A (1): light yellowish oil; $[\alpha]^{25}_{D}$ −179 (*c* 0.1, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 229 (4.14), 262 (3.75) nm; IR (dry film) ν_{max} 3389, 1615 cm^{-1}; HRDARTMS *m/z* 353.1860 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1865); ^1H and ^{13}C NMR data, see Table 2.2. HMBC: ^2J H-3 to C-2; H-5 to C-16; H-6 to C-5, C-7; H-17 to C-16; H-18 to C-19; H-21 to C-20. ^3J H-3 to C-5, C-7, C-15; H-5 to C-3, C-7, C-15, C-17; H-6 to C-2, C-8, C-16; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8; H-14 to C-2; H-17 to C-15, C-21; H-21 to C-15, C-17, C-19; C$\underline{H}_2$OH to C-2, C-13; N(4)-C$\underline{H}_3$ to C-3, C-5. NOESY: H-3/C$\underline{H}_2$OH, H-14α, H-14β, N(4)C$\underline{H}_3$; H-5/H-6α, H-6β, H-16, H-17β, N(4)C$\underline{H}_3$; H-6β/H-5, H-6α, H-9, H-16; H-6α/H-5, H-6β, N(4)C$\underline{H}_3$; H-9/H-6β, H-10; H-10/H-9; H-11/H-12; H-12/H-11, C$\underline{H}_2$OH; H-14α/H-3, H-14β, H-17α; H-14β/H-3, H-14α, H-15, C$\underline{H}_2$OH; H-15/H-14β, H-16; H-16/H-5, H-6β, H-15; H-17β/H-5, H-16, H-17α; H-17α/H-14α, H-17β; H-18/H-21; C$\underline{H}_2$OH/H-3, H-12, H-14β; N(4)C$\underline{H}_3$/H-3, H-5, H-6α.

Alstomutinine B (2): yellowish oil; $[\alpha]^{25}_{D}$ −123 (*c* 0.05, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 229 (4.35), 271 (4.09) nm; IR (dry film) ν_{max} 3384, 1615 cm^{-1}; HRDARTMS *m/z* 353.1861 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1865); ^1H and ^{13}C NMR data, see Table 2.2. HMBC: ^2J H-3 to C-2; H-5 to C-16; H-6 to C-5, C-7; H-17 to C-16; H-18 to C-19; H-21 to C-20. ^3J H-3 to C-5, C-7, C-15; H-5 to C-3, C-7, C-15, C-17; H-6 to C-2, C-8, C-16; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8; H-14 to C-2; H-17 to C-15, C-19; H-18 to C-20; H-21 to C-15; C$\underline{H}_2$OH to C-2, C-13;

N(4)-C<u>H</u>$_3$ to C-3, C-5. NOESY: H-3/C<u>H</u>$_2$OH, H-14α, H-14β, N(4)C<u>H</u>$_3$; H-5/H-6α, H-6β, H-16, H-17β, N(4)C<u>H</u>$_3$; H-6β/H-5, H-6α; H-9, H-16; H-6α/H-5, H-6β, N(4)C<u>H</u>$_3$; H-9/H-6β, H-10; H-10/H-9; H-11/H-12; H-12/H-11, C<u>H</u>$_2$OH; H-14α/H-3, H-14β, H-17α; H-14β/H-3, H-14α, H-15, C<u>H</u>$_2$OH; H-15/H-14β, H-16; H-16/H-5, H-6β, H-15, H-17β; H-17β/H-5, H-16, H-17α; H-17α/H-14α, H-17β; H-18/H-21; H-21/H-18; C<u>H</u>$_2$OH/H-3, H-12, H-14β; N(4)C<u>H</u>$_3$/H-3, H-5, H-6α.

Alstonerine (3), Alstonerinal (4): yellowish oil; $[\alpha]^{25}_{D}$ −55 (*c* 0.36, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 203 (3.96), 230 (4.12), 266 (3.70) nm; HRDARTMS *m/z* 337.1903 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_2$ + H, 337.1916); ^{1}H and ^{13}C NMR data, see Table 2.3.

***N*(1)-Demethylalstonerine (5), *N*(1)-Demethylalstonerinal (6)**: yellowish oil; $[\alpha]^{25}_{D}$ −58 (*c* 0.35, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 228 (4.36), 2.64 (3.93) nm; HRDARTMS *m/z* 323.1749 $[M + H]^+$ (calcd for $C_{20}H_{22}N_2O_2$ + H, 323.1760); ^{1}H and ^{13}C NMR data, see Tables 2.4 and 2.5, respectively.

***N*(4)-Demethylalstonerine (7), *N*(4)-Demethylalstonerinal (8)**: light yellowish oil; $[\alpha]^{25}_{D}$ −54 (*c* 0.56, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 231 (4.35), 2.60 (3.92) nm; HRESIMS *m/z* 323.1755 $[M + H]^+$ (calcd for $C_{20}H_{22}N_2O_2$ + H, 323.1760); ^{1}H and ^{13}C NMR data, see Tables 2.4 and 2.5, respectively.

Alstophylline (9), Alstophyllal (10): yellowish oil; $[\alpha]^{25}_{D}$ −98 (*c* 1.87, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 233 (4.36), 2.61 (3.89), 299 (3.53) nm; HRDARTMS *m/z* 367.2022 $[M + H]^+$ (calcd for $C_{22}H_{26}N_2O_3$ + H, 367.2022); ^{1}H and ^{13}C NMR data, see Tables 2.6 and 2.7, respectively.

***N*(1)-Demethylalstophylline (11), *N*(1)-Demethylalstophyllal (12)**: light yellowish oil; $[\alpha]^{25}_{D}$ –64 (*c* 0.14, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 204 (4.07), 230 (4.22), 259 (3.81), 298 (3.43) nm; HRDARTMS *m/z* 353.1848 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1865); ^1H and ^{13}C NMR data, see Tables 2.6 and 2.7, respectively.

Talcarpine (13): yellowish oil; $[\alpha]^{25}_{D}$ –10 (*c* 2.87, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (3.86), 226 (4.01), 277 (2.65), 285 (2.91), 294 (2.65) nm; HRDARTMS *m/z* 339.2071 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_2$ + H, 339.2073); ^1H and ^{13}C NMR data, see Table 2.8.

***N*(4)-Methyl-*N*(4),21-secotalpinine (14)**: light yellowish oil; $[\alpha]^{25}_{D}$ +36 (*c* 0.33, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (3.95), 228 (4.21), 280 (3.00), 285 (3.42), 300 (3.12) nm; HRDARTMS *m/z* 339.2073 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_2$ + H, 339.2073); ^1H and ^{13}C NMR data, see Table 2.8.

Macrocarpine D (15): yellowish oil; $[\alpha]^{25}_{D}$ –15 (*c* 0.15, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 231 (5.16), 286 (4.48) nm; IR (dry film) ν_{max} 3395, 3292 cm^{-1}; HRDARTMS *m/z* 327.2075 $[M + H]^+$ (calcd for $C_{20}H_{26}N_2O_2$ + H, 327.2073); ^1H and ^{13}C NMR data, see Table 2.9.

Macrocarpine E (16): yellowish oil; $[\alpha]^{25}_{D}$ +14 (*c* 0.47, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 227 (4.09), 282 (3.34) nm; IR (dry film) ν_{max} 3398, 3276 cm^{-1}; HRDARTMS *m/z* 327.2076 $[M + H]^+$ (calcd for $C_{20}H_{26}N_2O_2$ + H, 327.2073). ^1H and ^{13}C NMR data, see Table 2.9.

Alstohentine (17): yellowish oil; $[\alpha]^{25}_{D}$ –20 (*c* 0.41, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 228 (3.91), 289 (3.26) nm; IR (dry film) ν_{max} 3368 cm^{-1}; HRDARTMS *m/z* 357.2184

$[M + H]^+$ (calcd for $C_{21}H_{28}N_2O_3$ + H, 357.2178); ^1H and ^{13}C NMR data, see Tables 2.10 and 2.11, respectively.

Alstolactone (18): light yellowish oil; $[\alpha]^{25}_D$ +50 (*c* 0.34, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 216 (4.23), 228 (4.30), 284 (3.76), 293 (3.71) nm; IR (dry film) ν_{max} 3390, 1707 cm^{-1}; HRESIMS *m/z* 323.1755 $[M + H]^+$ (calcd for $C_{20}H_{22}N_2O_2$ + H, 323.1760); ^1H and ^{13}C NMR data, see Tables 2.10 and 2.11, respectively.

Alstomicine (19): yellowish oil; $[\alpha]^{25}_D$ –24 (*c* 0.14, $CHCl_3$). UV (EtOH) λ_{max} (log ε) 230 (3.80), 289 (3.11) nm; IR (dry film) ν_{max} 3400, 1711 cm^{-1}; HRDARTMS *m/z* 327.2067 $[M + H]^+$ (calcd for $C_{20}H_{26}N_2O_2$ + H, 327.2073). ^1H and ^{13}C NMR data, see Tables 2.10 and 2.11, respectively.

Alstonisinine A (20): white amorphous solid; $[\alpha]^{25}_D$ +183 (*c* 0.2, MeOH); UV (EtOH) λ_{max} (log ε) 225 (4.12), 261 (4.18) nm; IR (ATR) ν_{max} 3210, 1682, 1605 cm^{-1}; HRDARTMS *m/z* 341.1511 $[M + H]^+$ (calcd for $C_{19}H_{20}N_2O_4$ + H, 341.1501); ^1H and ^{13}C NMR data, see Table 2.12. HMBC: ^2J H-3 to C-14; H-5 to C-16; H-6 to C-5, C-7; H-14 to C-3, C-15; H-15 to C-14, C-16, C-20; H-17 to C-16; H-18 to C-19; H-21 to C-20. ^3J H-3 to C-2, C-5, C-6, C-15; H-5 to C-3, C-7, C-15, C-17; H-6 to C-2, C-3, C-8, C-16; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-7, C-16; H-15 to C-17, C-19, C-21; H-17 to C-5, C-15, C-19; H-18 to C-20; H-21 to C-15. NOESY: H-3/H-14α, H-14β; H-5/H-6β, H-17α; H-6β/H-5, H-6α; H-6α/H-6β, H-9, H-15; H-9/H-6α, H-10, H-14α, H-15; H-12/H-11; H-14β/H-3, H-14α, H-17β; H-14α/H-3, H-9, H-14β; H-15/H-6α, H-9, H-14α; H-17α/H-5, H-17β; H-17β/H-14β, H-17α; H-21/H-15, H-18.

Alstonisinine B (21): white amorphous solid; $[\alpha]^{25}_{D}$ +113 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 210 (4.19), 253 (3.99) nm; IR (ATR) ν_{max} 3295, 1702, 1609 cm^{-1}; HRDARTMS *m/z* 341.1500 $[M + H]^+$ (calcd for $C_{19}H_{20}N_2O_4$ + H, 341.1501); ^1H and ^{13}C NMR data, see Table 2.12. HMBC: ^2J H-5 to C-16; H-6 to C-5; H-14 to C-3, C-15; H-15 to C-14, C-16, C-20; H-17 to C-16; H-18 to C-19; H-21 to C-20. ^3J H-3 to C-15; H-5 to C-3, C-7, C-15, C-17; H-6 to C-2, C-3, C-8, C-16; H-9 to C-11, C-13; H-10 to C-12; H-11 to C-9; H-12 to C-8, C-10; H-14 to C-7, C-16; H-17 to C-15, C-21; H-21 to C-15, C-17, C-19. NOESY: H-3/H-14α, H-14β; H-5/H-6β, H-16; H-6β/H-5, H-6α; H-6α/H-6β, H-15; H-9/H-10, H-14α, H-15; H-12/H-11; H-10/H-9; H-11/H-12; H-14β/H-3, H-14α, H-17; H-14α/H-9, H-14β, H-15; H-15/H-6α, H-9, H-14α.

Alstonisinine C (22): light yellowish oil; $[\alpha]^{25}_{D}$ +180 (*c* 0.4, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 225 (3.99), 256 (4.09) nm; IR (dry film) ν_{max} 3403, 1708, 1616 cm^{-1}; HRDARTMS *m/z* 355.1666 $[M + H]^+$ (calcd for $C_{20}H_{22}N_2O_4$ + H, 355.1658); ^1H and ^{13}C NMR data, see Table 2.12. HMBC: ^2J H-5 to C-16; H-6 to C-5, C-7; H-9 to C-8, C-10; H-10 to C-9, C-11; H-11 to C-10, C-12; H-12 to C-13; H-14 to C-3, C-15; H-15 to C-14, C-16, C-20; H-17 to C-16; H-18 to C-19; H-21 to C-20. ^3J H-3 to C-5, C-6, C-8, C-15; H-5 to C-3, C-7, C-15, C-17; H-6 to C-2, C-3, C-8, C-16; H-9 to C-7, C-11, C-13; H-10 to C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-7, C-16, C-20; H-15 to C-17, C-19, C-21; H-17 to C-5, C-15, C-21; H-18 to C-20; H-21 to C-15, C-17, C-19; N(1)C$\underline{H}_3$ to C-2, C-13. NOESY: N(1)C$\underline{H}_3$/H-12; H-3/H-9, H-14α, H-14β; H-5/H-6β, H-17α; H-6β/H-5, H-6α, H-9; H-6α/H-6β, H-15; H-9/H-6β; H-12/N(1)C$\underline{H}_3$; H-14β/H-3, H-14α, H-17β; H-14α/H-3, H-14β, H-15; H-15/H-6α; H-17α/H-5, H-17β; H-17β/H-14β, H-17α; H-21/H-18.

Alstonoxine F (23): light yellowish amorphous solid and subsequently colorless needles (MeCN–MeOH); mp >169 °C (dec); $[\alpha]^{25}_{D}$ –20 (*c* 0.3, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 214 (4.34), 255 (3.69), 289 (3.30) nm; ECD (MeOH), λ_{max} ($\Delta\ \varepsilon$) 210 (–18.94), 232 (16.82), 257 (–5.95), 278 (–0.57), 290 (–0.90). IR (dry film) ν_{max} 3392, 1705, 1646 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 2.13; HRESIMS *m/z* 359.1971 $[M + H]^+$ (calcd for $C_{20}H_{26}N_2O_4$ + H, 359.1971). HMBC (**23a** and **23b**): ^{2}J H-6 to C-5, C-7; H-14 to C-3, C-15; H-17 to C-16; H-18 to C-19; H-20 to C-19. ^{3}J H-3 to C-2, C-5, C-6, C-15, NCHO; H-5 to C-3, C-7, C-15, NCHO; H-6 to C-2, C-3, C-8, C-16; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-7, C-16, C-20; H-17 to C-5, C-15; H-18 to C-20; H-19 to C-15; H-20 to C-16; N(1)CH_3 to C-2, C-13; NCHO to C-3, C-5. NOESY (**23a** and **23b**): N(1)CH_3/H-12; H-3/H-14α, H-14β; H-5/H-6β, H-16, H-17; H-6α/H-6β, H-9, H-15; H-6β/H-5, H-6α; H-9/H-6α, H-10, H-14α, H-15; H-12/N(1)CH_3, H-11; H-14β/H-3, H-14α, H-17a; H-14α/H-3, H-9, H-14β, H-15, H-20a; H-15/H-6α, H-9, H-16, H-20a; H-16/H-5, H-15, H-17b, H-19; H-17a/H-5, H-14β, H-16, H-17b, H-20b; H-17b/H-5, H-16, H-17a, H-20b; H-18/H-19; H-19/H-15, H-16, H-18, H-20b; H-20a/H-14α, H-15; H-20b/H-17b, H-17a, H-19; NCHO/H-3 (**23a**); NCHO/H-5 (**23b**).

Alstonisine (24), Alstonal (25): yellowish oil; $[\alpha]^{25}_{D}$ +104 (*c* 0.59, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 213 (4.24), 231 sh (4.09), 256 (4.02) nm; HRDARTMS *m/z* 339.1719 $[M + H]^+$ (calcd for $C_{20}H_{22}N_2O_3$ + H, 339.1709); ^{1}H and ^{13}C NMR data, see Tables 2.14 and 2.15, respectively.

***N*(1)-Demethylalstonisine (26), *N*(1)-Demethylalstonal (27)**: yellowish oil; $[\alpha]^{25}_{D}$ +96 (*c* 0.72, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (4.12), 254 (3.91) nm; HRESIMS *m/z*

325.1550 $[M + H]^+$ (calcd for $C_{19}H_{20}N_2O_3$ + H, 325.1552); ^1H and ^{13}C NMR data, see Tables 2.14 and 2.15, respectively.

16-Hydroxyalstonisine (28): light yellowish amorphous solid; $[\alpha]^{25}_D$ +132 (*c* 0.28, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (4.17), 256 (3.95) nm; IR (dry film) ν_{max} 3400, 1685, 1611 cm^{-1}; HRDARTMS *m/z* 355.1661 $[M + H]^+$ (calcd for $C_{20}H_{22}N_2O_4$ + H, 355.1658); ^1H and ^{13}C NMR data, see Table 2.16.

16-Hydroxyalstonisine (28), 16-Hydroxyalstonal (29): light yellowish amorphous solid; $[\alpha]^{25}_D$ +169 (*c* 0.54, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (4.16), 257 (3.95) nm; HRDARTMS *m/z* 355.1661 $[M + H]^+$ (calcd for $C_{20}H_{22}N_2O_4$ + H, 355.1658); ^1H and ^{13}C NMR data, see Table 2.16.

Alstofoline (30): light yellowish oil; $[\alpha]^{25}_D$ +45 (*c* 0.22, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 214 (4.02), 246 (4.01), 254 (4.05), 290 (3.13) nm; IR (dry film) ν_{max} 1706, 1662, 1613 cm^{-1}; HRESIMS *m/z* 367.1660 $[M + H]^+$ (calcd for $C_{21}H_{22}N_2O_4$ + H, 367.1658); ^1H and ^{13}C NMR data, see Table 2.17.

Alstonoxine A (31): light yellowish oil; $[\alpha]^{25}_D$ −19 (*c* 0.11, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 216 (3.89), 255 (3.70), 285 (3.18) nm; IR (dry film) ν_{max} 3390, 3288, 1694 (br) cm^{-1}; HRESIMS *m/z* 329.1861 $[M + H]^+$ (calcd for $C_{19}H_{24}N_2O_3$ + H, 329.1865); ^1H and ^{13}C NMR data, see Table 2.17.

Alstopenidine A (32): light yellowish oil and subsequently light yellowish prisms from $CHCl_3$–hexane; mp 119.3–119.6 °C; $[\alpha]^{25}_D$ +6.4 (*c* 0.43, CH_3OH); UV (EtOH) λ_{max} (log ε) 283 (3.57), 229 (4.11), 205 (4.03) nm; IR (ATR) ν_{max} 3274 cm^{-1}; HRESIMS *m/z*

355.2027 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2022); ^1H and ^{13}C NMR data, see Table 2.18. HMBC: ^2J H-3 to C-2; H-6 to C-5, C-7; H-9 to C-10; H-17 to C-16; H-18 to C-19; H-19 to C-20. ^3J H-3 to C-5; H-5 to C-3, C-7, C-17; N(1)C<u>H</u>$_3$ to C-2, C-13; H-6 to C-2, C-8, C-16; H-9 to C-7, C-11, C-13; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-16; H-17 to C-5, C-15; H-18 to C-20; H-19 to C-15, C-21; H-21 to C-3, C-5, C-19; 10-OC<u>H</u>$_3$ to C-10. NOESY: H-9/H-6α, H-6β, 10-OC<u>H</u>$_3$; H-11/10-OC<u>H</u>$_3$; N(1)C<u>H</u>$_3$/H-12, H-14; H-6β/H-16; H-14α/H-18; H-5/H-6, H-16; H-15/H-14, H-16, H-18, H-17b; H-17a/H-5, H-16; H-17b/H-5, H-15; H-19/H-18, H-15; H-21/H-3, H-5, H-18, H-19.

Crystallographic data of 32: Light yellowish prisms, $C_{21}H_{26}N_2O_3.CHCl_3$, *M*r = 473.80, orthorhombic, space group $P2_12_12_1$, a = 10.3523(4) Å, b = 10.5595(3) Å, c = 21.0751(6) Å, V = 2303.83(13) Å^3, Z = 4, D_{calcd} = 1.366 gcm^{-3}, crystal size 0.5 x 0.14 x 0.08 mm^3, $F(000)$ = 992, Cu Kα radiation (λ = 1.54184 Å), T = 293(2) K, 35956 reflections measured ($8.39° \leq 2\theta \leq 147.89°$), 4646 unique ($R_{int}$ = 0.0509, R_{sigma} = 0.0199) which were used in all calculations. The final R_1 value was 0.0668 [$I>2\sigma(I)$] and wR_2 was 0.2124. The absolute configuration was determined on the basis of Flack[1] parameter [x = 0.012 (9)]. CCDC number: 1969912

Alstopenidine B (33): yellow-green fluorescent oil; $[\alpha]^{25}_D$ −58.3 (*c* 0.06, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 286 (3.03), 259 sh (3.36), 228 (4.10) nm; IR (dry film) ν_{max} 3401, 1685 cm^{-1}; HRDARTMS *m/z* 341.1856 $[M + H]^+$ (calcd for $C_{20}H_{24}N_2O_3$ + H, 341.1865); ^1H and ^{13}C NMR data, see Table 2.19. HMBC: ^2J H-6 to C-2, C-5; H-14 to C-15; H-17 to C-16; H-18 to C-19. ^3J H-3 to C-5, C-6; H-6 to C-7, C-16; N(1)<u>H</u> to C-7, C-8; H-9 to C-11, C-13; H-11 to C-13; H-12 to C-8, C-10; H-14 to C-2; H-16 to C-6; H-17 to C-5, C-15; H-18 to C-20; H-21 to C-5, C-15; 10-OC<u>H</u>$_3$ to C-10. NOESY: H-3/H-14α, H-21;

H-5/H-6, H-17, H-21; H-9/10-OC<u>H</u>$_3$; H-11/10-OC<u>H</u>$_3$; N(1)H/H-12, H-14β; H-15/H-14, H-17, H-16, H-18; H-16/H-14β, H-17; H-19/H-18, H-21.

Alstopenidine C (34): yellowish oil; $[\alpha]^{25}_D$ −11 (*c* 0.2, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 307 (3.19), 263 (3.83), 233 sh (3.75), 222 (3.85) nm; IR (dry film) ν_{max} 3378, 1708 cm^{-1}; HRDARTMS *m/z* 355.2036 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2022); ^1H and ^{13}C NMR data, see Tables 2.20 and 2.21, respectively. HMBC: ^2J H-6 to C-5, C-7; H-9 to C-10; H-18 to C-19; H-19 to C-18. ^3J H-3 to C-5, C-6; H-5 to C-3, C-7, C-17; H-6 to C-2, C-8, C-16; N(1)C<u>H</u>$_3$ to C-2, C-13; H-9 to C-7, C-11, C-13; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-7, C-16; H-17 to C-5; H-18 to C-20; H-19 to C-15, C-21; H-21 to C-3; 10-OC<u>H</u>$_3$ to C-10. NOESY: H-3/H-14α; H-5/H-6α; H-6α/H-3; H-9/H-6β, H-14β, H-16, 10-OC<u>H</u>$_3$; H-11/10-OC<u>H</u>$_3$; H-12/N(1)C<u>H</u>$_3$; H-15/H-14β, H-16, H-18; H-16/H-6β; H-17/H-5, H-15, H-16; H-19/H-18, H-21; H-21/H-19.

Alstopenidine D (35): yellowish oil, $[\alpha]^{25}_D$ −20.7 (*c* 0.28, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 306 sh (3.16), 267 (3.49), 223 (4.08) nm; IR (dry film) ν_{max} 3409, 1707 cm^{-1}; HRDARTMS *m/z* 385.2137 $[M + H]^+$ (calcd for $C_{22}H_{28}N_2O_4$ + H, 385.2127); ^1H and ^{13}C NMR data, see Tables 2.20 and 2.21, respectively. HMBC: ^2J H-6 to C-5, C-7; H-9 to C-10; H-12 to C-11, C-13; H-18 to C-19; H-19 to C-18. ^3J H-3 to C-5, C-6; H-5 to C-3, C-7, C-17; H-6 to C-2, C-8, C-16; N(1)C<u>H</u>$_3$ to C-2, C-13; H-9 to C-7, C-11, C-13; H-12 to C-8, C-10; H-14 to C-7, C-16; H-17 to C-5, C-15; H-18 to C-20; H-19 to C-15, C-21; H-21 to C-3, C-5, C-19; 10-OC<u>H</u>$_3$ to C-10, 11-OC<u>H</u>$_3$ to C-11. NOESY: H-3/H-14α; H-5/H-17, H-21; H-9/H-6β, H-14β, H-16, 10-OC<u>H</u>$_3$; H-12/11-OC<u>H</u>$_3$, N(1)C<u>H</u>$_3$; H-15/H-14β, H-16, H-18; H-16/H-17; H-19/H-18, H-21.

Alstopenidine E (36): light yellowish oil; $[\alpha]^{25}_{D}$ −26 (*c* 0.12, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 303 sh (3.26), 281 (3.47), 223 sh (4.09), 205 (4.22) nm; IR (dry film) ν_{max} 3341, 1717 cm^{-1}; HRESIMS *m/z* 401.2086 $[M + H]^+$ (calcd for $C_{22}H_{28}N_2O_5$ +H, 401.2076); ^1H and ^{13}C NMR data, see Tables 2.20 and 2.21, respectively. HMBC: ^2J H-6 to C-7; H-9 to C-10; H-12 to C-11, C-13; H-18 to C-19; H-19 to C-18. ^3J H-6 to C-2, C-8, C-16; N(1)C$\underline{H}_3$ to C-2, C-13; H-9 to C-7, C-11, C-13; H-12 to C-8, C-10; H-14 to C-7, C-16, C-20; H-18 to C-20; H-19 to C-15, C-21; 10-OC$\underline{H}_3$ to C-10, 11-OC$\underline{H}_3$ to C-11. NOESY: H-3/N(1)C$\underline{H}_3$; H-9/H-14β, H-16, 10-OC$\underline{H}_3$; H-12/11-OC$\underline{H}_3$, N(1)C$\underline{H}_3$; H-15/H-18; H-19/H-18.

Alstopenidine F (37): light yellowish oil; $[\alpha]^{25}_{D}$ +73 (*c* 0.09, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 215 (4.18), 226 (4.19), 251 (4.21), 260 (4.16), 333 (3.71), 346 (3.75) nm; IR (dry film) ν_{max} 3347, 1579 cm^{-1}; HRESIMS *m/z* 353.1869, HRDARTMS *m/z* 353.1865 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1865); ^1H and ^{13}C NMR data, see Table 2.22. HMBC: ^2J H-5 to C-6; H-9 to C-10; H-17 to C-16; H-18 to C-19. ^3J H-3 to C-5, C-6; H-5 to C-2, C-3, C-17; N(1)C$\underline{H}_3$ to C-2, C-13; H-9 to C-7, C-11, C-13; H-11 to C-13; H-12 to C-8, C-10; H-17 to C-5, C-15; H-18 to C-20; H-19 to C-15, C-21; 10-OC$\underline{H}_3$ to C-10. NOESY: H-3/H-14α, H-21α; H-5/H-16, H-17b, H-21β; H-9/10-OC$\underline{H}_3$; H-12/N(1)C$\underline{H}_3$; N(1)C$\underline{H}_3$/H-3, H-14; H-15/H-16, H-14α, H-14β, H-18; H-16/H-17a, H17b; H-17b/H-16, H-17a; H-19/H-18, H-21; H-21/H-19.

Alstopenidine G (38): yellowish oil; $[\alpha]^{25}_{D}$ +34 (*c* 0.20, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 204 (4.17), 215 (4.19), 224 (4.17), 253 (4.21), 261 (4.23), 332 (3.69), 347 (3.73) nm; IR (dry film) ν_{max} 1589, 3363 cm^{-1}; HRESIMS *m/z* 369.1824 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_4$ + H, 369.1814); ^1H and ^{13}C NMR data, see Table 2.22. HMBC: ^2J H-9 to C-10; H-18 to C-19. ^3J H-5 to C-2, C-3, C-17; N(1)C$\underline{H}_3$ to C-2, C-13; H-9 to C-7, C-11,

C-13; H-11 to C-9, C-13; H-12 to C-8, C-10; H-17 to C-5; H-18 to C-20; H-19 to C-15; 10-OC<u>H</u>$_3$ to C-10. NOESY: H-3/H-14α, H-21α, N(1)C<u>H</u>$_3$; H-5/H-17b, H-21β; H-9/10-OC<u>H</u>$_3$; H-12/N(1)C<u>H</u>$_3$; H-14α/H-3; H-14β/H-15; H-16/H-15, H-17a; H-18/H-15, H-19; H-19/H-18, H-21; H-21β/H-5, H-19; H-21α/H-3, H-19.

Alstopenidine H (11-Methoxystrictamine *N*(4)-oxide) (39): light yellowish oil; $[\alpha]^{25}_{D}$ −107 (*c* 0.07, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 204 (4.10), 232 (4.06), 279 (3.51) nm; IR (dry film) ν_{max} 1736 cm^{-1}; HRESIMS *m/z* 369.1825 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_4$ + H, 369.1814); ^1H and ^{13}C NMR data, see Table 2.23.

Alstochalotine (40): light yellowish oil; $[\alpha]^{25}_{D}$ +11.3 (*c* 0.2, $CHCl_3$); IR (dry film) ν_{max} 3430, 1757, 1734 cm^{-1}; HRDARTMS *m/z* 266.1398 $[M + H]^+$ (calcd for $C_{14}H_{19}NO_4$ + H, 266.1392); ^1H and ^{13}C NMR data, see Table 2.24. HMBC: ^2J H-3 to C-7; H-5 to C-6, C-16; H-6 to C-5, C-7; H-14 to C-3, C-15; H-17 to C-16; H-18 to C-19; H-19 to C-18; H-21 to C-20. ^3J H-3 to C-5, C-6; H-5 to C-3, C-7, <u>C</u>O$_2$Me; H-6 to C-16; H-14 to C-7, C-16, C-20; H-15 to C-3; H-17 to C-5, C-15, <u>C</u>O$_2$Me; H-18 to C-20; H-19 to C-15, C-21; H-21 to C-3, C-5, C-19. NOESY: H-3/H-14α; H-5/H-6, H-21; H-15/H-14α, H-14β, H-18; H-17b/H-14β, H-15, H-17a; H-17a/H-6β, H-14β, H-17b; H-19/H-18, H-21.

Alstomutinine C (41): yellowish oil; $[\alpha]^{25}_{D}$ −134 (*c* 0.32, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 285 (3.15), 256 (3.73), 234 (3.56) nm; IR (dry film) ν_{max} 1717 cm^{-1}; HRDARTMS *m/z* 355.2011 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2022); ^1H and ^{13}C NMR data, see Table 2.25. HMBC: ^2J H-6 to C-5, C-7; H-11 to C-10, C-12; H-12 to C-13; H-14 to C-3, C-15; H-15 to C-14, C-16, C-20; H-17 to C-16; H-18 to C-19; H-20 to C-15, C-19, C-21; H-21 to C-20; ^3J H-3 to C-5, C-6, C-15, C-21; H-5 to C-3, C-7, C-17; H-6 to C-2, C-3, C-8, C-16; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to

C-8, C-10; H-14 to C-7, C-16, C-20; H-15 to C-5, C-21; H-16 to C-6, C-20; H-17 to C-5, C-15, C-19; H-20 to C-14, C-16; H-21 to C-3, C-5, C-15, C-19; OC$\underline{H}_3$ to C-19; N(1)C$\underline{H}_3$ to C-2, C-13. NOESY: N(1)C$\underline{H}_3$/H-12; H-3/H-14α; H-5/H-6α, H-6β, H-16, H-21β; H-6α/H-5, H-6β; H-6β/H-6α, H-9, H-16; H-9/H-6β, H-10, H-14β, H-16; H-10/H-9, H-11; H-11/H-10, H-12; H-12/N(1)C$\underline{H}_3$, H-11; H-14α/H-14β, H-20; H-14β/H-9, H-14α, H-15; H-15/H-14α, H-14β, H-16, H-17β, H-20; H-16/H-6β, H-9, H-14β, H-15, H-17α, H-17β; H-17β/H-15, H-16, H-17α, 19-OC$\underline{H}_3$; H-17α/H-16, H-17β; H-18/H-20, H-21α, 21β, 19-OC$\underline{H}_3$; H-20/H-14α, H-15, H-18, H-21α; 19-OC$\underline{H}_3$/H-17β, H-18; H-21α/H-14α, H-18, H-20, H-21β; H-21β/H-18, H-21α.

Alstomutinines D (42) and E (43): yellowish oil; $[\alpha]^{25}_{D}$ −71 (*c* 0.18, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 285 (3.45), 255 (3.83), 231 wk (3.74), 211 (4.36) nm; IR (dry film) ν_{max} 3390, 1709 cm^{-1}; HRESIMS *m/z* 327.1707 $[M + H]^+$ (calcd for $C_{19}H_{22}N_2O_3$ + H, 327.1709); ^1H and ^{13}C NMR data, see Table 2.26.

HMBC (**42**): ^2J H-5 to C-16; H-6 to C-5, C-7; H-10 to C-11; H-14 to C-3, C-15; H-17 to C-16. ^3J H-3 to C-5, C-6, C-21; H-5 to C-3, C-7, C-15, C-17; H-6 to C-2, C-8, C-16; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-7, C-16, C-20; H-17 to C-5, C-15, C-19; H-19 to C-15, C-17, C-21; H-20 to C-16; H-21 to C-3, C-5, C-19; N(1)C$\underline{H}_3$ to C-2, C-13. NOESY: H-3/H-14α; H-5/H-6α, H-21β; H-6α/H-6β; H-6β/H-6α, H-9; H-9/H-6β, H-10, H-14β, H-16; H-10/H-9, H-11; H-11/H-10, H-12; H-12/H-11, N(1)C$\underline{H}_3$; H-14α/H-14β, H-20; H-14β/H-5, H-9, H-14α, H-16; H-15/H-14α, H-16, H-17β, H-20; H-16/H-9, H-15, H-17; H-17α/H-16; H-17β/H-15, H-16, H-17α; H-19/H-20, H-21β; H-20/H-14α, H-15, H-19, H-21α; H-21β/H-5, H-19; H-21α/H-20.

HMBC (**43**): ^{2}J H-6 to C-5, C-7; H-10 to C-11; H-14 to C-3; H-19 to C-20. ^{3}J H-3 to C-5, C-6; H-5 to C-3, C-7, C-17; H-6 to C-2, C-8, C-16; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-7, C-16, C-20; H-17 to C-5, C-15, C-19; H-19 to C-21; H-20 to C-16; H-21 to C-3, C-5, C-15; N(1)C$\underline{H}_3$ to C-2, C-13. NOESY: H-5/H-6α, H-17α; H-6α/H-6β; H-6β/H-6α, H-9; H-9/H-6β, H-10, H-14β, H-16; H-10/H-9, H-11; H-11/H-10, H-12; H-12/H-11, N(1)C$\underline{H}_3$; H-14α/H-14β, H-20; H-14β/H-14α, H-16; H-15/H-17β, H-19; H-16/H-9, H-17α, H-17β; H-17β/H-15, H-16, H-17α, H-19; H-17α/H-5, H-16, H-17β; H-19/H-15, H-17β, H-20; H-20/H-14α, H-19, H-21α; H-21β/H-21α; H-21α/H-20, H-21β.

Affinisine (44): light yellowish oil; $[\alpha]^{25}_{D}$ +40 (*c* 0.63, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 225 (4.15), 288 (3.98), 302 (3.82) nm; HRDARTMS *m/z* 309.1955 $[M + H]^+$ (calcd for $C_{20}H_{24}N_2O$ + H, 309.1967); ^{1}H and ^{13}C NMR data, see Tables 2.27 and 2.28, respectively.

10-Methoxyaffinisine (45): yellowish oil; $[\alpha]^{25}_{D}$ +49 (*c* 0.51, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 223 (4.25), 283 (4.02), 300 (3.91) nm; IR (dry film) ν_{max} 3103 cm^{-1}; HRDARTMS *m/z* 339.2062 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_2$ + H, 339.2073); ^{1}H and ^{13}C NMR data, see Tables 2.27 and 2.28, respectively.

10-Methoxyaffinisine *N*(4)-oxide (46): yellowish oil, $[\alpha]^{25}_{D}$ +15 (*c* 0.17, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (4.25), 227 (4.12), 281 (3.58) nm; IR (dry film) ν_{max} 3368 cm^{-1}; HRESIMS *m/z* 355.2049 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2022); ^{1}H and ^{13}C NMR data, see Tables 2.27 and 2.28, respectively. HMBC: ^{2}J H-3 to C-2; H-6 to C-5, C-7; H-9 to C-10; H-11 to C-10; H-16 to C-5, C-17; H-18 to C-19; H-21 to C-20. ^{3}J N(1)C$\underline{H}_3$ to C-2, C-13; H-5 to C-3, C-7, C-17; H-6 to C-2, C-16; H-9 to C-7, C-11, C-13;

10-OC<u>H</u>$_3$ to C-10, H-11 to C-13; H-12 to C-8, C-10; H-14 to C-16; H-15 to C-5; H-16 to C-6, C-20; H-17 to C-15; H-18 to C-20; H-19 to C-15, C-21; H-21 to C-3. NOESY: H-3/N(1)C<u>H</u>$_3$, H-14α, H-21α; H-5/H-6β, H-16; H-6α/H-5, H-6β; N(1)C<u>H</u>$_3$/H-14β; H-6β/H-16; H-9/H-6β, 10-OC<u>H</u>$_3$; H-12/H-11, N(1)C<u>H</u>$_3$, H-14α/H-14β; H-15/H-14α, H-14β, H-16, H-18; H-16/H-14β; H-17/H-5, H-16; H-19/H-18, H-21β; H-21α/H-21β; H-21β/H-5.

Lochnerine (47): yellowish oil; $[\alpha]^{25}_{D}$ +57 (*c* 0.15, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 228 (4.27), 279 (3.93), 296 (3.35) nm; HRDARTMS *m/z* 325.1916 $[M + H]^+$ (calcd for $C_{20}H_{24}N_2O_2$ + H, 325.1916); ^1H and ^{13}C NMR data, see Tables 2.27 and 2.28, respectively.

Alstoumerine (48): light yellowish oil; $[\alpha]^{25}_{D}$ −8 (*c* 0.43, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 219 (3.89), 234 (3.93), 274 (3.73), 284 (3.77), 293 (3.71) nm; HRDARTMS *m/z* 325.1908 $[M + H]^+$ (calcd for $C_{20}H_{24}N_2O_2$ + H, 325.1916); ^1H and ^{13}C NMR data, see Table 2.29.

11-Methoxystrictamine (49): light yellowish oil; $[\alpha]^{25}_{D}$ +79 (*c* 1.09, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 214 (4.15), 250 (3.72), 282 (3.50), 299 (3.04) nm; HRDARTMS *m/z* 353.1870 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1865); ^1H and ^{13}C NMR data, see Tables 2.30 and 2.31, respectively.

11-Hydroxystrictamine (50): light yellowish oil; $[\alpha]^{25}_{D}$ +68 (*c* 0.49, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 215 (3.99), 265 (3.48), 280 (3.55), 296 (3.00) nm; HRDARTMS *m/z* 339.1718 $[M + H]^+$ (calcd for $C_{20}H_{22}N_2O_3$ + H, 339.1709); ^1H and ^{13}C NMR data, see Tables 2.30 and 2.31, respectively.

10-Methoxyvincamidine (10-Methoxystrictamine) (51): light yellowish oil; $[\alpha]^{25}_{D}$ +66 (*c* 0.09, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 204 (4.0), 221 (3.92), 280 (3.59) nm; IR (dry film) ν_{max} 1737 cm^{-1}; HRDARTMS *m/z* 353.1858 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1865); ^1H and ^{13}C NMR data, see Tables 2.30 and 2.31, respectively. HMBC: ^2J H-3 to C-2; H-6 to C-5; H-9 to C-10; H-16 to C-7, $\underline{C}O_2Me$; H-18 to C-19; H-21 to C-20. ^3J H-3 to C-7, C-15; H-5 to C-3; H-9 to C-13; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-2; H-16 to C-14, C-20; H-18 to C-20; H-19 to C-15; H-21 to C-3, C-5, C-19; $CO_2\underline{Me}$ to $\underline{C}O_2Me$; 10-O$\underline{CH_3}$ to C-10.

Cathafoline (52): light yellowish oil; $[\alpha]^{25}_{D}$ −34 (*c* 1.06, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 (3.22), 250 (3.62), 306 (4.18) nm; HRDARTMS *m/z* 339.2085 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_2$ + H, 339.2073); ^1H and ^{13}C NMR data, see Table 2.32.

Cathafoline *N*(4)-oxide (53): yellowish oil; $[\alpha]^{25}_{D}$ −29 (*c* 0.17, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 212 (3.98), 250 (3.81), 294 (3.31) nm; IR (dry film) ν_{max} 3392, 1736 cm^{-1}; HRESIMS *m/z* 355.2026 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2022); ^1H and ^{13}C NMR data, see Table 2.32.

Vincorine (54): yellowish oil; $[\alpha]^{25}_{D}$ −131 (*c* 14.05, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 255 (4.00), 326 (3.58) nm; HRDARTMS *m/z* 369.2184 $[M + H]^+$ (calcd for $C_{22}H_{28}N_2O_3$ + H, 369.2178); ^1H and ^{13}C NMR data, see Table 2.33.

Norvincorine (55): yellowish oil; $[\alpha]^{25}_{D}$ −137 (*c* 0.67, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 201 (4.46), 241 (3.94), 316 (3.52) nm; IR (dry film) ν_{max} 1734 cm^{-1}; HRDARTMS *m/z* 355.2007 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2022); ^1H and ^{13}C NMR data, see Table 2.33.

Demethoxyalstonamide (56): yellowish oil; $[\alpha]^{25}_{D}$ −61 (*c* 0.43, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (4.33), 264 (4.01), 291 (3.62), 361 (3.50) nm; IR (dry film) ν_{max} 1733, 1665 cm^{-1}; HRDARTMS *m/z* 383.1985 $[M + H]^+$ (calcd for $C_{22}H_{26}N_2O_4$ + H, 383.1971); ^1H and ^{13}C NMR data, see Table 2.33.

Vincamaginine A (57): light yellowish oil; $[\alpha]^{25}_{D}$ −172 (*c* 0.2, $CHCl_3$); UV (EtOH), λ_{max} (log ε) 215 (4.74), 275 (4.37), 298 sh (4.10) nm; IR (dry film) ν_{max} 1733, 1652 cm^{-1}; HRESIMS *m/z* 741.3027 $[M + H]^+$ (calcd for $C_{41}H_{44}N_2O_{11}$ + H, 741.3023); ^1H and ^{13}C NMR data, see Table 2.34. HMBC: ^2J H-3 to C-2; H-5 to C-6; H-6 to C-5, C-7; H-12 to C-13; H-14 to C-3, C-15; H-15 to C-14, C-20; H-18 to C-19; H-19 to C-18; H-21 to C-20; H-2" to C-1", C-3"; H-6" to C-1", C-5"; H-2' to C-1', C-3'; H-6' to C-1', C-5'. ^3J H-2 to C-6; H-3 to C-5, C-7, C-15; H-5 to C-3, C-7, $\underline{C}O_2Me$; H-6 to C-2, C-8, C-16, C-17; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-2, C-16, C-20; H-15 to C-3, C-19; H-17 to C-2, C-5, C-6, C-15, O$\underline{C}$=O; H-18 to C-20; H-19 to C-15, C-21; H-21 to C-3, C-5, C-15, C-19; H-2" to C-4", C-6", N$\underline{C}$=O; H-6" to C-2", C-4", N$\underline{C}$=O; 3"-OC$\underline{H}_3$ to C-3"; 5"-OC$\underline{H}_3$ to C-5"; 4"-OC$\underline{H}_3$ to C-4"; H-2' to C-4', C-6', O$\underline{C}$=O; H-6' to C-2', C-4', O$\underline{C}$=O; 3'-OC$\underline{H}_3$ to C-3'; 5'-OC$\underline{H}_3$ to C-5'; 4'-OC$\underline{H}_3$ to C-4'; $CO_2C\underline{H}_3$ to $\underline{C}O_2Me$. NOESY: H-2/H-3, H-6α; H-3/H-2, H-14α, H-21α; H-5/H-6α, H-6β, $CO_2C\underline{H}_3$; H-6α/H-2, H-5, H-6β; H-6β/H-5, H-6α, H-9; H-9/H-6β, H-10; H-10/H-9, H-11; H-11/H-10, H-12; H-12/H-11, H-2", H-6"; H-14α/H-3, H-14β, H-15; H-14β/H-14α, H-15, H-17; H-15/H-14α, H-14β, H-17, H-18; H-17/H-14β, H-15, H-2", H-6"; H-18/H-15, H-19, $CO_2C\underline{H}_3$; H-19/H-18, H-21; H-2"/3"-OC$\underline{H}_3$, H-12, H-17; H-6"/5"-OC$\underline{H}_3$, H-12, H-17; H-2'/3'-OC$\underline{H}_3$; H-6'/5'-OC$\underline{H}_3$.

Vincamaginine B (58): light yellowish oil; $[\alpha]^{25}_{D}$ −379 (*c* 0.2, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 214 (4.72), 280 (4.42), 297 sh (4.31) nm, addition of 0.1 M NaOH resulted in a

shift from 280 to 333 nm; IR (dry film) ν_{max} 1733, 1651 cm^{-1}; HRESIMS *m/z* 727.2873 $[M + H]^+$ (calcd for $C_{40}H_{42}N_2O_{11}$ + H, 727.2867); ^1H and ^{13}C NMR data, see Table 2.34. HMBC: ^2J H-10 to C-9; H-18 to C-19; H-21 to C-20; H-2" to C-1", C-3"; H-6" to C-1", C-5"; H-2' to C-1', C-3'; H-6' to C-1', C-5'. ^3J H-2 to C-6, C-14, C-17; H-5 to C-3, C-7, C-21; H-6 to C-16, C-17; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-2, C-16; H-17 to C-5, C-6, C-15, O<u>C</u>=O; H-18 to C-20; H-19 to C-15, C-21; H-21 to C-3, C-19; H-2" to C-4", C-6", N<u>C</u>=O; H-6" to C-2", C-4", N<u>C</u>=O; 3"-OC<u>H</u>$_3$ to C-3"; 5"-OC<u>H</u>$_3$ to C-5"; 4"-OC<u>H</u>$_3$ to C-4"; H-2' to C-4', C-6', O<u>C</u>=O; H-6' to C-2', C-4', O<u>C</u>=O; 3'-OC<u>H</u>$_3$ to C-3'; 5'-OC<u>H</u>$_3$ to C-5'; $CO_2C\underline{H}_3$ to <u>C</u>O_2Me. ROESY: H-2/H-3, H-6α; H-3/H-2, H-14α, H-21α; H-5/H-6α, H-6β, $CO_2C\underline{H}_3$; H-6α/H-2, H-5, H-6β; H-6β/H-5, H-6α, H-9; H-9/H-6β, H-10; H-10/H-9, H-11; H-11/H-10; H-12/H-2", H-6"; H-14α/H-3, H-14β, H-15, H-21α; H-14β/H-14α, H-15, H-17; H-15/H-14α, H-14β, H-17, H-18; H-17/H-14β, H-15, H-2", H-6"; H-18/H-15, H-19, $CO_2C\underline{H}_3$; H-19/H-18, H-21; H-21α/H-3; H-21/H-19; H-2"/3"-OC<u>H</u>$_3$, H-12, H-17; H-6"/5"-OC<u>H</u>$_3$, H-12, H-17; H-2'/3'-OC<u>H</u>$_3$; H-6'/5'-OC<u>H</u>$_3$.

4'-Hydroxy-3',5'-dimethoxybenzoylvincamajine (59): light yellowish oil; $[\alpha]^{25}_D$ −64 (*c* 0.11, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 250 (3.63), 287 (3.72) nm; IR (dry film) ν_{max} 3438, 1732, 1609 cm^{-1}; HRESIMS *m/z* 547.2387 $[M + H]^+$ (calcd for $C_{31}H_{34}N_2O_7$ + H, 547.2444); ^1H and ^{13}C NMR data, see Table 2.35. HMBC: ^2J H-2 to C-3; H-3 to C-2; H-5 to C-6; H-14 to C-15; H-15 to C-14, C-16; H-18 to C-19; H-19 to C-18; H-21 to C-20; H-2' to C-1', C-3'; H-6' to C-1', C-5'. ^3J N(1)C<u>H</u>$_3$ to C-2, C-13; H-2 to N(1)C<u>H</u>$_3$, C-14, C-17; H-3 to C-5, C-7, C-15, C-21; H-5 to C-3, C-7, C-17, <u>C</u>O_2Me; H-6 to C-2, C-16, C-17; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-2, C-16, C-20; H-15 to <u>C</u>O_2Me; H-17 to C-2, C-5, C-6, C-15, O<u>C</u>=O;

H-18 to C-20; H-19 to C-15, C-21; H-21 to C-3, C-5, C-19; H-2' to C-4', C-6', O<u>C</u>=O; H-6' to C-2', C-4', O<u>C</u>=O; 3'-OC<u>H</u>$_3$ to C-3'; 5'-OC<u>H</u>$_3$ to C-5'; $CO_2C\underline{H}_3$ to <u>C</u>O_2Me.

***O*-3,4,5-Trimethoxybenzoylquebrachidine (60)**: light yellowish oil; $[\alpha]^{25}_D$ −29 (*c* 0.34, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (4.36), 218 sh (4.10), 247 wk (3.56), 268 wk (3.60), 293 (3.45) nm; IR (dry film) ν_{max} 1720 (br) cm^{-1}; HRDARTMS *m/z* 547.2433 $[M + H]^+$ (calcd for $C_{31}H_{34}N_2O_7$ + H, 547.2444); ^{1}H and ^{13}C NMR data, see Table 2.35. HMBC: ^2J H-3 to C-2; H-6 to C-7; H-14 to C-3, C-15; H-18 to C-19; H-19 to C-18, H-2' to C-3', H-6' to C-5'. ^3J H-2 to C-6, C-14, C-17; H-5 to C-17, C-21; H-6 to C-2, C-16, C-17; H-9 to C-7, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-2, C-16; H-17 to C-5, C-6, C-15, O<u>C</u>=O; H-18 to C-20; H-19 to C-15, C-21; H-21 to C-3, C-5; H-2' to C-4', O<u>C</u>=O; H-6' to C-4', O<u>C</u>=O; 3'-OC<u>H</u>$_3$ to C-3'; 5'-OC<u>H</u>$_3$ to C-5'; 4'-OC<u>H</u>$_3$ to C-4'; $CO_2C\underline{H}_3$ to <u>C</u>O_2Me. NOESY: H-3/H-14α; H-5/H-6α, H-6β; H-9/H-6β; H-11/H-10; H-15/H-14α, H-14β, H-17/H-14β, H-15; H-19/H-18, H-21; H-2'/3'-OC<u>H</u>$_3$; H-6'/5'-OC<u>H</u>$_3$.

Vincamajine *N*(1)-tri-*O*-methylgallate (61): light yellowish oil; $[\alpha]^{25}_D$ −70 (*c* 0.53, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε) 211 (4.54), 276 (4.10) nm; IR (dry film) ν_{max} 3446, 1732, 1645 cm^{-1}; HRDARTMS *m/z* 547.2941 $[M + H]^+$ (calcd for $C_{31}H_{34}N_2O_7$ + H, 547.2444); ^{1}H and ^{13}C NMR data, see Table 2.35. HMBC: ^2J H-2 to C-3, C-7; H-5 to C-6, C-16; H-6 to C-5, C-7; H-9 to C-8; H-10 to C-11; H-11 to C-12; H-14 to C-3, C-15; H-15 to C-16, C-20; H-19 to C-18; H-21 to C-20. ^3J H-2 to N<u>C</u>=O, C-6, C-8, C-14, C-17; H-5 to C-3, C-7, C-17, C-21, <u>C</u>O_2Me; H-6 to C-2, C-8, C-16, C-17; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-10; H-14 to C-2, C-16, C-20; H-15 to C-3, C-5, C-19, C-21, <u>C</u>O_2Me; H-17 to C-2, C-5, C-6, C-15; H-19 to C-15, C-21; H-21 to C-19; $CO_2\underline{Me}$ to <u>C</u>O_2Me, 4'-OC<u>H</u>$_3$ to C-4'; NOESY: H-2/H-6α; H-3/H-

14α, H-14β, H-21α; H-5/H-6α, H-6β, H-21β; H-9/H-6α, H-6β; H-10; H-11/H-12; H-15/H-14α, H-14β, H-18; H-17/H-14β, H-15; H-19/H-18, H-21; H-2'/3'-OC<u>H</u>$_3$; H-6'/5'-OC<u>H</u>$_3$.

Vincamajine (62): light yellowish oil; $[\alpha]^{25}_D$ –20 (*c* 2.27, $CHC1_3$); UV (EtOH) λ_{max} (log ε) 204 (2.88), 249 (3.29), 292 (2.90) nm; HRDARTMS *m/z* 367.2017 $[M + H]^+$ (calcd for $C_{22}H_{26}N_2O_3$ + H, 367.2022); ^{1}H and ^{13}C NMR data, see Table 2.36.

Quebrachidine (63): light yellowish oil; $[\alpha]^{25}_D$ +38 (*c* 1.14, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 202 (3.82), 245 (4.19), 288 (3.92) nm; HRESIMS *m/z* 353.1889 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1865); ^{1}H and ^{13}C NMR data, see Table 2.36.

18,19-Dihydroisositsirikine (64): light yellowish oil; $[\alpha]^{25}_D$ –8 (*c* 0.2, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 225 (4.13), 280 (3.46) nm; IR (dry film) ν_{max} 3373, 2877, 1710 cm^{-1}; HRDARTMS *m/z* 357.2173 $[M + H]^+$ (calcd for $C_{21}H_{28}N_2O_3$ + H, 357.2178). ^{1}H and ^{13}C NMR data, see Tables 2.37 and 2.38, respectively.

16(*R*),19(*E*)-Isositsirikine (65): yellowish oil; $[\alpha]^{25}_D$ +10 (*c* 0.33, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 225 (4.27), 286 (3.96), 295 (3.65) nm; HRDARTMS *m/z* 355.2024 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2022); ^{1}H and ^{13}C NMR data, see Tables 2.37 and 2.38, respectively.

***Z*-Geissoschizol (66)**: light yellowish oil; $[\alpha]^{25}_D$ –21 (*c* 0.18, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (3.19), 224 (3.22), 281 (2.60) nm; IR (dry film) ν_{max} 3252 cm^{-1}; HRDARTMS *m/z* 297.1974 $[M + H]^+$ (calcd for $C_{19}H_{24}N_2O$ + H, 297.1967); ^{1}H and ^{13}C

NMR data, see Tables 2.37 and 2.38, respectively. HMBC: ^{2}J H-5 to C-6; H-14 to C-3, C-15; H-16 to C-15, C-17; H-17 to C-16; H-18 to C-19; H-19 to C-18; H-21 to C-20. ^{3}J H-5 to C-3, C-7, C-21; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-16 to C-14; H-18 to C-20; H-19 to C-15, C-21; H-21 to C-3, C-5, C-15, C-19.

Pleiocarpamine (67): light yellowish oil; $[\alpha]^{25}_{D}$ +99 (*c* 0.18, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (4.32), 284 (3.85) nm; IR (dry film) ν_{max} 1758 cm^{-1}; HRDARTMS *m/z* 323.1769 $[M + H]^+$ (calcd for $C_{20}H_{22}N_2O_2$ + H, 323.1760); ^{1}H NMR and ^{13}C NMR data, see Table 2.39.

16-Hydroxymethylpleiocarpamine (68): light yellowish oil; $[\alpha]^{25}_{D}$ +31 (*c* 0.56, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 227 (4.20), 284 (3.71) nm; IR (dry film) ν_{max} 3352, 1745 cm^{-1}; HRDARTMS *m/z* 353.1876 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1865); ^{1}H and ^{13}C NMR data, see Table 2.39.

Pleiomaltinine (69): yellowish oil; $[\alpha]^{25}_{D}$ +127 (*c* 0.23, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 214 (4.15), 240 (3.86), 284 (3.81) nm; IR (dry film) ν_{max} 1752, 1650, 1614, 1570 cm^{-1}; HRDARTMS *m/z* 447.1913 $[M + H]^+$ (calcd for $C_{26}H_{26}N_2O_5$ + H, 447.1920); ^{1}H and ^{13}C NMR data, see Table 2.40.

Fluorocarpamine (70): yellowish oil; $[\alpha]^{25}_{D}$ +163 (*c* 0.07, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 232 (4.15), 260 (3.59), 289 (3.20) nm; IR (dry film) ν_{max} 1748, 1696 cm^{-1}; HRDARTMS *m/z* 339.1693 $[M + H]^+$ (calcd for $C_{20}H_{22}N_2O_3$ + H, 339.1709); ^{1}H and ^{13}C NMR data, see Table 2.41.

11-Methoxyakuammicine (71): light yellowish oil; $[\alpha]^{25}_{D}$ −255 (*c* 1.20, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (4.05), 223 (4.06), 242 (3.94), 307 (3.88), 327 (4.01) nm; HRDARTMS *m/z* 353.1868 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1865); ^1H and ^{13}C NMR data, see Table 2.42.

11-Methoxyakuammicine *N*(4)-oxide (72): light yellowish oil; $[\alpha]^{25}_{D}$ −266 (*c* 0.07, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (4.49), 232 (4.27), 253 (4.16), 296 (3.98), 308 (4.04) nm; IR (dry film) ν_{max} 3201, 1737 cm^{-1}; HRESIMS *m/z* 369.1843 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_4$ + H, 369.1814); ^1H and ^{13}C NMR data, see Table 2.42.

Alstolagumine (73): yellowish oil; $[\alpha]^{25}_{D}$ −31 (*c* 0.16, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 211 (4.07), 235 (4.00), 251 (4.05), 309 (3.96), 322 (4.05) nm; HRESIMS *m/z* 369.1812 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_4$ + H, 369.1814); ^1H and ^{13}C NMR data, see Tables 2.43 and 2.44, respectively.

Alstovine (74): light yellowish oil; $[\alpha]^{25}_{D}$ −459 (*c* 0.4, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 223 (3.57), 248 (3.90), 302 (3.80), 325 (3.96) nm; HRDARTMS *m/z* 387.1925 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_5$ + H, 387.1920); ^1H and ^{13}C NMR data, see Tables 2.43 and 2.44, respectively.

Lagumidine (75): light yellowish oil; $[\alpha]^{25}_{D}$ −305 (*c* 0.12, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 226 (4.75), 250 (4.85), 308 (4.64), 330 (4.88) nm; HRDARTMS *m/z* 385.1767 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_5$ + H, 385.1763); ^1H and ^{13}C NMR data, see Tables 2.43 and 2.44, respectively.

Angustilongine A (76): light yellowish block crystals (CH_2Cl_2-hexanes); mp >199 °C (dec); $[\alpha]^{25}_D$ +3 (*c* 0.4, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 212 (4.64), 232 (4.54), 255 (3.90), 295 (3.99) nm; IR (dry film) ν_{max} 3360, 1741 cm^{-1}; HRESIMS *m/z* 707.4180 $[M + H]^+$ (calcd for $C_{43}H_{54}N_4O_5$ + H, 707.4172); ^1H and ^{13}C NMR data, see Tables 2.45 and 2.46, respectively. HMBC: ^2J H-3 to C-2, C-14; H-5 to C-16; H-6 to C-5, C-7; H-12 to C-13; H-14 to C-3, C-15; H-15 to C-14, C-16; H-17 to C-16; H-2' to C-3', C-7'; H-3' to C-2', C-14'; H-5' to C-6'; H-6' to C-5', C-7'; H-12' to C-11', C-13'; H-14' to C-3'; H-16' to $\underline{C}O_2Me$; H-18' to C-19'; H-21' to C-20'. ^3J H-3 to C-5, C-7, C-15; H-5 to C-3, C-7, C-15, C-17; H-6 to C-2, C-16; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-10; H-14 to C-2, C-16; H-15 to C-17; H-17 to C-15, C-21; H-18 to C-20, C-10'; H-20 to C-16; H-21 to C-15, C-17; N(1)C$\underline{H}_3$ to C-2, C-13; N(4)C$\underline{H}_3$ to C-3, C-5; H-2' to C-6', C-8'; H-3' to C-7', C-15'; H-5' to C-3', C-7', C-21'; H-9' to C-7', C-11', C-13'; H-12' to C-8', C-10'; H-14' to C-20'; H-15' to C-3', C-7'; H-16' to C-6', C-20'; H-18' to C-20'; H-19' to C-15', C-21'; H-21' to C-5', C-15', C-19'; N(1')C$\underline{H}_3$ to C-2', C-13'; $CO_2C\underline{H}_3$ to $\underline{C}O_2Me$; 11'-OC$\underline{H}_3$ to C-11'. NOESY: N(1)C$\underline{H}_3$/H-14β; H-3/N(1)C$\underline{H}_3$, N(4)C$\underline{H}_3$; H-5/N(4)C$\underline{H}_3$; H-6α/N(4)C$\underline{H}_3$; H-9/H-6β, 11'-OC$\underline{H}_3$; H-11/N(1')C$\underline{H}_3$; H-12/N(1)C$\underline{H}_3$; H-17α/H-14α; H-17β/H-5, H-16; H-19/H-16, H-18; H-20/H-14β, H-18; H-21/H-18, H-19, H-20; H-2'/H-14'β; H-3'/N(1')C$\underline{H}_3$; H-3'/N(1')C$\underline{H}_3$, H-2', H-14'α, H-14'β; H-9'/H-18, H-19, H-20, H-16', $CO_2C\underline{H}_3$; H-12'/11'-OC$\underline{H}_3$, N(1')C$\underline{H}_3$; H-15'/H-14', H-16', H-18'; H-16'/H-2', H-14'β; H-19'/H-18', H-21'β; H-21'α/H-14'α; $CO_2C\underline{H}_3$/H-18'.

Crystallographic data of 76: light yellowish block crystals, $C_{43}H_{54}N_4O_5.2CHCl_3$, *M*r = 945.63, monoclinic, space group $P2_1$, a = 9.4917(6) Å, b = 12.8453(9 Å, c = 18.5275(10) Å, β = 99.113(6)°, V = 2230.4(2) $Å^3$, Z = 2, D_{calcd} = 1.408 gcm^{-3}, crystal size 0.50 x 0.25 x 0.16 mm^3, F(000) = 992, Mo Kα radiation (λ = 0.71073 Å), T = 100(2) K. The final R_1 value is 0.0445 (wR_2 = 0.1216) for 7713 reflections [$I>2\sigma(I)$].

The absolute configuration of compound **76** was determined on the basis of Flack parameter [x = 0.03(7)], refined using 2364 Friedel pairs. CCDC number: 1822774.

Angustilongine B (77): light yellowish oil; $[\alpha]^{25}_{D}$ –33 (c 0.1, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 229 (4.48), 250 (3.87), 294 (3.92) nm; IR (dry film) ν_{max} 1736 cm^{-1}; HRDARTMS *m/z* 675.3932 $[M + H]^+$ (calcd for $C_{42}H_{50}N_4O_4$ + H, 675.3910); ^1H and ^{13}C NMR data, see Tables 2.45 and 2.46, respectively. HMBC: ^2J H-3 to C-2, C-14; H-5 to C-6, C-16; H-6 to C-5, C-7; H-9 to C-8; H-14 to C-3, C-15; H-15 to C-14, C-16, C-20; H-16 to C-15, C-17; H-17 to C-16; H-18 to C-19; H-19 to C-18, C-20, C-10'; H-21 to C-20; H-2' to C-7'; H-6' to C-5', C-7'; H-12' to C-11', C-13'; H-14' to C-3'; H-16' to C-7', C-15', $\underline{C}O_2Me$; H-18' to C-19'. ^3J H-3 to C-7, C-15, N(4)$\underline{C}H_3$; H-5 to C-3, C-15, C-17, N(4)$\underline{C}H_3$; H-6 to C-2, C-8, C-16; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-2, C-16, C-20; H-15 to C-17, C-19, C-21; H-16 to C-6, C-14, C-20; H-17 to C-15, C-21; H-18 to C-20, C-10'; H-19 to C-21, C-9', C-11'; H-21 to C-17, C-19, C-11'; N(1)C$\underline{H}_3$ to C-2, C-13; N(4)C$\underline{H}_3$ to C-3, C-5; H-2' to C-6', C-14', C-16', N(1')C$\underline{H}_3$; H-5' to C-3', C-7'; H-6' to C-16'; H-9' to C-7', C-11', C-13', C-19; H-12' to C-8', C-10'; H-14' to C-2'; H-15' to $\underline{C}O_2Me$; H-16' to C-2', C-6', C-8', C-14'; H-21' to C-5'; N(1')C$\underline{H}_3$ to C-2', C-13'; $CO_2C\underline{H}_3$ to $\underline{C}O_2Me$. NOESY: H-3/H-14β, N(1)C$\underline{H}_3$, N(4)C$\underline{H}_3$; H-5/N(4)C$\underline{H}_3$; H-6α/N(4)C$\underline{H}_3$; H-9/H-6β, H-10; H-11/H-12; H-12/N(1)C$\underline{H}_3$; H-14β/N(1)C$\underline{H}_3$; H-16/H-18; H-19/H-18, H-20; H-21/H-14α, H-17α, H-20; H-2'/N(1')C$\underline{H}_3$, H-14'β; H-3'/N(1')C$\underline{H}_3$; H-9'/H-18, H-19; H-12'/N(1')C$\underline{H}_3$; H-15'/H-16', H-18'; H-16'/H-2'; H-19'/H-18', H-21'; $CO_2C\underline{H}_3$/H-18'.

Angustilongine C (78): light yellowish oil; $[\alpha]^{25}_{D}$ +16 (c 0.1, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (4.58), 252 (4.03), 295 (4.03) nm; IR (dry film) ν_{max} 1741 cm^{-1}; HRESIMS *m/z* 705.4041 $[M + H]^+$ (calcd for $C_{43}H_{52}N_4O_5$ + H, 705.4016); ^1H and ^{13}C NMR data,

see Tables 2.45 and 2.46, respectively. HMBC: ^{2}J H-3 to C-2, C-14; H-5 to C-6, C-16; H-6 to C-5, C-7; H-9 to C-8; H-17 to C-16; H-18 to C-19; H-19 to C-18, C-20, C-10'; H-21 to C-20; H-2' to C-3', C-7'; H-3' to C-2', C-14'; H-6' to C-5', C-7'; H-12' to C-11', C-13'; H-16' to C-7', C-15', $\underline{C}O_2Me$; H-18' to C-19'. ^{3}J H-3 to C-5, C-7, C-15, N(4)$\underline{C}H_3$; H-5 to C-3, C-7, C-15, C-17; H-6 to C-2, C-8, C-16; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-2, C-16; H-15 to C-5; H-17 to C-15, C-21; H-18 to C-20, C-10'; H-19 to C-15, C-21, C-9', C-11'; H-21 to C-15, C-17, C-19; N(1)C$\underline{H}_3$ to C-2, C-13; N(4)C$\underline{H}_3$ to C-3, C-5; H-2' to C-6', C-14', C-16', N(1')C$\underline{H}_3$; H-3' to C-7', C-15'; H-5' to C-3', C-7'; H-6' to C-8', C-16'; H-9' to C-7', C-11', C-13', C-19; H-12' to C-8', C-10'; H-14' to C-2'; H-16' to C-2', C-6', C-8', C-14'; H-18' to C-20'; H-19' to C-15', C-21'; H-21' to C-3', C-5', C-15', C-19'; N(1')C$\underline{H}_3$ to C-2', C-13'; $CO_2C\underline{H}_3$ to $\underline{C}O_2Me$; 11'-OC$\underline{H}_3$ to C-11'. NOESY: H-3/N(1)C$\underline{H}_3$, N(4)C$\underline{H}_3$; H-5/N(4)C$\underline{H}_3$; H-6α/N(4)C$\underline{H}_3$; H-6β/H-16; H-9/H-6β; H-12/N(1)C$\underline{H}_3$; H-14β/N(1)C$\underline{H}_3$; H-17α/H-14α; H-17β/H-5; H-19/H-15, H-18; H-21/H-18, H-19; H-2'/H-3', H-14'β, H-16'; H-3'/N(1')C$\underline{H}_3$; H-9'/H-18, $CO_2C\underline{H}_3$; H-12'/11'-OC$\underline{H}_3$, N(1')C$\underline{H}_3$; H-15'/H-18'; H-16'/H-14'β; H-19'/H-18', H-21'β; H-21'α/H-14'α; $CO_2C\underline{H}_3$/H-18'.

Angustilongine D (79): light yellowish amorphous solid; $[\alpha]^{25}_{D}$ +12 (*c* 0.3, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 212 (4.70), 230 (4.55), 250 (3.96), 295 (4.04) nm; IR (dry film) ν_{max} 3392, 1739 cm^{-1}; HRESIMS *m/z* 755.3949 M^+ (calcd for $C_{44}H_{56}N_4O_5Cl$, 755.3939); ^{1}H and ^{13}C NMR data, see Tables 2.45 and 2.46, respectively. HMBC: ^{2}J H-6 to C-5, C-7; H-9 to C-8; H-14 to C-3, C-15; H-2' to C-3', C-7'; H-3' to C-2', C-14'; H-12' to C-11', C-13'; H-15' to C-16', C-20'; H-16' to C-7', C-15', $\underline{C}O_2Me$; H-18' to C-19'. ^{3}J H-6 to C-16; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-14 to C-16; H-17 to C-15, C-21; H-18 to C-20, C-10'; H-21 to C-15, C-17; N(1)C$\underline{H}_3$ to C-2, C-13; H-2' to N(1')C$\underline{H}_3$, C-6'; H-3' to C-7', C-15', $\underline{C}H_2Cl$; H-9' to C-7', C-11', C-13'; H-12' to C-8', C-10'; H-15' to C-3', C-7';

H-16' to C-6', C-8'; H-18' to C-20'; H-19' to C-15', C-21'; N(1')C<u>H</u>$_3$ to C-2', C-13'; $CO_2C\underline{H}_3$ to $\underline{C}O_2Me$; 11'-OC<u>H</u>$_3$ to C-11'.

Angustilongine E (80): light yellowish oil; $[\alpha]^{25}_D$ −74.4 (*c* 0.43, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 286 (3.91), 229 (4.51) nm; IR (dry film) ν_{max} 3395 cm^{-1}; HRDARTMS *m/z* 659.3951 $[M + H]^+$ (calcd for $C_{42}H_{50}N_4O_3$ + H, 659.3961); ^1H and ^{13}C NMR data, see Tables 2.47 and 2.48, respectively. HMBC: ^2J H-3 to C-2, C-14; H-5 to C-6, C-16; H-6 to C-5, C-7; H-9 to C-8; H-14 to C-3, C-15; H-17 to C-16; H-18 to C-19; H-19 to C-18, C-20, C-11'; H-21 to C-19; H-3' to C-2'; H-5' to C-6', C-16'; H-6' to C-5', C-7'; H-9' to C-10'; H-12' to C-11', C-13'; H-14' to C-3', C-15'; H-15' to C-16', C-20'; H-17' to C-16'; H-18' to C-19'; H-19' to C-18'; H-21' to C-20'. ^3J H-3 to C-5, C-7, C-15, N(4)$\underline{C}H_3$; N(4)C<u>H</u>$_3$ to C-3, C-5; H-5 to C-3, C-7, C-15, C-17, N(4)$\underline{C}H_3$; H-6 to C-2, C-8, C-16; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-2, C-16; H-16 to C-20; H-17 to C-15; H-18 to C-20, C-11'; H-19 to C-15, C-21, C-10', C-12'; H-21 to C-15, C-17, C-19; N(1)C<u>H</u>$_3$ to C-2, C-13; H-3' to C-5', C-7'; H-5' to C-3', C-17'; H-6' to C-2', C-8', C-16'; H-9' to C-7', C-11', C-13'; H-12' to C-19, C-8', C-10'; H-14' to C-2', C-16', C-20'; H-15' to C-3', C-5', C-17', C-21'; H-16' to C-20'; H-17' to C-5', C-15'; H-18' to C-20'; H-19' to C-15', C-21'; H-21' to C-3', C-5', C-19'; N(1')C<u>H</u>$_3$ to C-2', C-13'; 10'-OC<u>H</u>$_3$ to C-10'. NOESY: H-3/N(4)C<u>H</u>$_3$, H-14α, H-14β; H-5/N(4)C<u>H</u>$_3$; H-6β/H-15, H-16; H-9/H-6β, H-6α, H-10; H-12/N(1)C<u>H</u>$_3$; H-14β/N(1)C<u>H</u>$_3$; H-17β/H-5; H-17α/H-14α; H-19/H-18; H-21/H-19, H-18; H-3'/N(1')C<u>H</u>$_3$, H-14'α, H-21'α; H-6'α/H-5'; H-6'β/H-16'; H-9'/H-6'β, 10'-OC<u>H</u>$_3$; H-12'/H-18, N(1')C<u>H</u>$_3$; H-14'β/N(1')C<u>H</u>$_3$; H-15'/H-18'; H-17'/H-5', H-15', H-16'; H-19'/H-18', H-21'; H-21'/H-5'.

Angustilongine F (81): light yellowish oil; $[\alpha]^{25}_D$ −65 (*c* 0.4, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 286 (3.86), 230 (4.51) nm; IR (dry film) ν_{max} 3403 cm^{-1}; HRDARTMS *m/z*

659.3950 $[M + H]^+$ (calcd for $C_{42}H_{50}N_4O_3$ + H, 659.3961); ^1H and ^{13}C NMR data, see Tables 2.47 and 2.48, respectively. HMBC: ^2J H-5 to C-6; H-6 to C-5, C-7; H-9 to C-8; H-17 to C-16; H-18 to C-19; H-21 to C-20, C-9'; H-3' to C-2'; H-6' to C-5', C-7'; H-11' to C-10'; H-16' to C-5', C-17'; H-18' to C-19'; H-19' to C-18'. ^3J H-3 to C-15; N(4)C$\underline{H}_3$ to C-3, C-5; H-5 to C-3, C-7, C-15, C-17, N(4)$\underline{C}H_3$; H-6 to C-2, C-16; H-9 to C-7, C-11, C-13; H-10 to C-12; H-11 to C-9, C-13; H-12 to C-10; H-16 to C-14; H-17 to C-15, C-19; H-18 to C-20; H-21 to C-15, C-19, C-8', C-10'; N(1)C$\underline{H}_3$ to C-2, C-13; H-3' to C-5'; H-5' to C-3', C-7', C-17', C-21'; H-6' to C-2', C-16'; H-11' to C-9', C-13'; H-12' to C-8', C-10'; H-14' to C-16'; H-15' to C-3', C-5', C-21'; H-16' to C-20'; H-17' to C-5', C-15'; H-18' to C-20'; H-19' to C-15', C-21'; H-21' to C-3', C-15'; N(1')C$\underline{H}_3$ to C-2', C-13'; 10'-OC$\underline{H}_3$ to C-10'. NOESY: H-3/N(1)C$\underline{H}_3$, N(4)C$\underline{H}_3$, H-14α, H-14β; H-5/N(4)C$\underline{H}_3$; H-6α/N(4)C$\underline{H}_3$; H-6β/H-15, H-16; H-9/H-6β; H-12/N(1)C$\underline{H}_3$; H-14β/H-15, N(1)C$\underline{H}_3$; H-17β/H-5; H-17α/H-14α; H-21/H-18; H-3'/N(1')C$\underline{H}_3$, H-14'α, H-21'α; H-6'β/H-16'; H-11'/10'-OC$\underline{H}_3$; H-12'/N(1')C$\underline{H}_3$; H-14'β/N(1')C$\underline{H}_3$, H-15', H-16'; H-15'/H-14'α, H-16', H-18'; H-17'/H-5', H-15', H-16'; H-19'/H-18', H-21'; H-21'/H-5'.

Angustilongine G (82): light yellowish oil; $[\alpha]^{25}_D$ +12.4 (*c* 0.15, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 286 (3.84), 227 (4.46) nm; IR (dry film) ν_{max} 3403 cm^{-1}; HRDARTMS *m/z* 691.4199 $[M + H]^+$ (calcd for $C_{43}H_{54}N_4O_4$ + H, 691.4223); ^1H and ^{13}C NMR data, see Tables 2.47 and 2.48, respectively. HMBC: ^2J H-6 to C-5, C-7; H-9 to C-8; H-14 to C-15; H-17 to C-16; H-18 to C-19; H-21 to C-20; H-3' to C-2'; H-6' to C-5', C-7'; H-9' to C-8', C-10'; H-12' to C-11'; H-16' to C-17'; H-17' to C-16'; H-18' to C-19'; H-19' to C-18'. ^3J H-3 to C-5, C-15; N(4)C$\underline{H}_3$ to C-3, C-5; H-5 to C-3, C-7, C-15, C-17, N(4)$\underline{C}H_3$; H-6 to C-2, C-16; H-9 to C-7, C-11, C-13; H-10 to C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-17 to C-15, C-19; H-18 to C-20; 19-OC$\underline{H}_3$ to C-19; H-21 to C-15, C-19, C-10', C-12'; N(1)C$\underline{H}_3$ to C-2, C-13; H-3' to C-5', C-7', C-21'; H-5' to C-15', C-17', C-21';

H-6' to C-2', C-8', C-16'; H-9' to C-7', C-13'; H-12' to C-10', C-21; H-14' to C-2', C-16'; H-15' to C-5', C-17', C-21'; H-16' to C-6', C-14'; H-17' to C-5', C-15'; H-18' to C-20'; H-19' to C-15', C-21'; H-21' to C-3', C-5'; N(1')C$\underline{H}_3$ to C-2', C-13'; 10'-OC$\underline{H}_3$ to C-10'. NOESY: H-3/N(1)C$\underline{H}_3$, N(4)C$\underline{H}_3$, H-14α, H-14β; H-5/N(4)C$\underline{H}_3$; H-6α/N(4)C$\underline{H}_3$; H-6β/H-16; H-9/H-6β; H-12/N(1)C$\underline{H}_3$; H-14β/H-21a, N(1)C$\underline{H}_3$; H-17α/19-OC$\underline{H}_3$, H-14α; H-17β/H-5; 19-OC$\underline{H}_3$/H-18; H-20/H-18; H-21b/H-18; H-3'/N(1')C$\underline{H}_3$, H-14'α, H-21'α; H-6'β/H-16'; H-9'/H-6'β, 10'-OC$\underline{H}_3$; 10'-OC$\underline{H}_3$/H-18; H-12'/H-20, H-21a, N(1')C$\underline{H}_3$; H-14'β/N(1')C$\underline{H}_3$, H-15', H-16'; H-15'/H-14', H-18'; H-17'/H-5'; H-19'/H-18', H-21'.

Angustilongine H (83): light yellowish oil; $[\alpha]^{25}_{D}$ +42.4 (*c* 0.09, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 286 (3.82), 228 (4.46) nm; IR (dry film) ν_{max} 3403 cm^{-1}; HRDARTMS *m/z* 691.4217 $[M + H]^+$ (calcd for $C_{43}H_{54}N_4O_4$ + H, 691.4223); ^1H and ^{13}C NMR data, see Tables 2.47 and 2.48, respectively. HMBC: ^2J H-6 to C-5, C-7; H-18 to C-19; H-21 to C-20; H-3' to C-2'; H-6' to C-5', C-7'; H-9' to C-10'; H-16' to C-17'; H-18' to C-19'; H-19' to C-18'. ^3J N(4)C$\underline{H}_3$ to C-3, C-5; H-5 to C-3, C-7, C-15, C-17; H-6 to C-2, C-16; H-9 to C-7, C-11, C-13; H-10 to C-12; H-14 to C-16; H-18 to C-20; 19-OC$\underline{H}_3$ to C-19; H-21 to C-15, C-10', C-12'; N(1)C$\underline{H}_3$ to C-2, C-13; H-3' to C-5', C-7'; H-5' to C-7', C-17'; H-6' to C-2', C-16'; H-9' to C-7', C-11', C-13'; H-12' to C-8', C-10'; H-14' to C-2', C-16'; H-15' to C-3'; H-16' to C-20'; H-18' to C-20'; H-19' to C-15', C-21'; H-21' to C-3', C-19'; N(1')C$\underline{H}_3$ to C-2', C-13'; 10'-OC$\underline{H}_3$ to C-10'. NOESY: H-3/N(1)C$\underline{H}_3$, N(4)C$\underline{H}_3$, H-14α, H-14β; H-5/H-17β, N(4)C$\underline{H}_3$; H-6α/N(4)C$\underline{H}_3$; H-6β/H-16; H-9/H-6α, H-6β; H-12/N(1)C$\underline{H}_3$; H-14β/H-20, N(1)C$\underline{H}_3$; H-17α/19-OC$\underline{H}_3$, H-14α; 19-OC$\underline{H}_3$/H-18; H-21a/H-15; H-21b/H-18; H-3'/N(1')C$\underline{H}_3$, H-14'α, H-21'α; H-5'/H-6'β, H-21'β; H-6'β/H-16'; H-9'/10'-OC$\underline{H}_3$; H-12'/H-15, H-20, H-21, N(1')C$\underline{H}_3$; H-14'β/N(1')C$\underline{H}_3$, H-15'; H-15'/H-14'α, H-18'; H-17'/H-15'; H-19'/H-18', H-21'.

Angustilongine J (84): light yellowish oil; $[\alpha]^{25}_{D}$ +119 (*c* 0.26, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 284 (3.75), 230 (4.38) nm; IR (dry film) ν_{max} 3392 cm^{-1}; HRESIMS *m/z* 677.4087 $[M + H]^+$ (calcd for $C_{42}H_{52}N_4O_4$ + H, 677.4067); ^1H and ^{13}C NMR data, see Tables 2.49 and 2.50, respectively. HMBC: ^2J H-3 to C-2, C-14; H-5 to C-6; H-6 to C-5, C-7; H-14 to C-15; H-17 to C-16; H-18 to C-19; H-21 to C-9', C-20; H-3' to C-2'; H-6' to C-7'; H-11' to C-10'; H-14' to C-15'; H-16' to C-5', C-17'; H-18' to C-19'; H-19' to C-18'. ^3J H-3 to C-5, C-15; N(4)C$\underline{H}_3$ to C-3, C-5; H-5 to C-3, C-7, C-15, C-17, N(4)$\underline{C}H_3$; H-6 to C-2, C-16; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-2, C-20; H-17 to C-5, C-15; H-18 to C-20; H-21 to C-15, C-19, C-8', C-10'; N(1)C$\underline{H}_3$ to C-2, C-13; H-3' to C-5', C-7'; H-6' to C-2', C-16'; H-11' to C-9', C-13'; H-12' to C-8', C-10'; H-14' to C-2', C-16'; H-15' to C-3', C-5'; H-16' to C-6', C-14', C-20'; H-17' to C-5', C-15'; H-18' to C-20'; H-19' to C-15', C-21'; H-21' to C-3', C-5', C-19'; N(1')C$\underline{H}_3$ to C-2', C-13'; 10'-OC$\underline{H}_3$ to C-10'. NOESY: H-3/N(1)C$\underline{H}_3$, N(4)C$\underline{H}_3$, H-14α, H-14β; H-5/N(4)C$\underline{H}_3$; H-6α/N(4)C$\underline{H}_3$; H-6β/H-15, H-16; H-9/H-6α, H-6β, H-10; H-12/N(1)C$\underline{H}_3$; H-14α/H-20; H-14β/H-21a, N(1)C$\underline{H}_3$; H-17b/H-20, H-21b; H-20/H-18; H-21a/H-15; H-21b/H-16; H-3'/N(1')C$\underline{H}_3$, H-14'α, H-21'α; H-11'/10'-OC$\underline{H}_3$; H-12'/N(1')C$\underline{H}_3$; H-14'α/H-21'; H-15'/H-14'α, H-18'; H-17'/H-5', H-16'; H-19'/H-18', H-21'.

Angustilongine K (85): light yellowish oil; $[\alpha]^{25}_{D}$ +61 (*c* 0.26, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 286 (3.92), 228 (4.53) nm; IR (dry film) ν_{max} 3382 cm^{-1}; HRESIMS *m/z* 677.4085 $[M + H]^+$ (calcd for $C_{42}H_{52}N_4O_4$ + H, 677.4067); ^1H and ^{13}C NMR data, see Tables 2.49 and 2.50, respectively. HMBC: ^2J H-3 to C-2; H-5 to C-6, C-16; H-6 to C-5, C-7; H-9 to C-8; H-17 to C-16; H-18 to C-19; H-20 to C-19; H-21 to C-11', C-20; H-3' to C-2'; H-6' to C-5', C-7'; H-9' to C-10'; H-15' to C-20'; H-16' to C-5', C-17'; H-17' to C-16'; H-18' to C-19'; H-19' to C-18'. ^3J N(4)C$\underline{H}_3$ to C-3, C-5; H-3 to C-15; H-5 to C-7, C-15, C-17; H-6 to C-2, C-16; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9,

C-13; H-12 to C-8, C-10; H-14 to C-2; H-17 to C-5, C-15; H-18 to C-20; H-20 to C-16; H-21 to C-19, C-10', C-12'; N(1)C$\underline{H}_3$ to C-2, C-13; H-3' to C-5', C-7'; H-5' to C-7', C-15', C-17'; H-6' to C-2', C-8', C-16'; H-9' to C-7', C-11', C-13'; H-12' to C-21, C-8', C-10'; H-14' to C-20', C-2', C-16'; H-15' to C-3', C-19', C-21'; H-16' to C-6', C-14', C-20'; H-17' to C-5', C-15'; H-18' to C-20'; H-19' to C-15', C-21'; H-21' to C-3', C-5', C-15', C-19'; N(1')C$\underline{H}_3$ to C-2', C-13'; 10'-OC$\underline{H}_3$ to C-10'. NOESY: H-3/N(1)C$\underline{H}_3$, N(4)C$\underline{H}_3$; H-5/N(4)C$\underline{H}_3$; H-6α/N(4)C$\underline{H}_3$; H-6β/H-16; H-9/H-6α, H-6β; H-12/N(1)C$\underline{H}_3$; H-14β/N(1)C$\underline{H}_3$; H-17a/H-16; H-17b/H-20; H-18/H-20; H-21b/H-16; H-3'/N(1')C$\underline{H}_3$, H-14'α, H-21'α; H-5'/H-17', H-21'β; H-6'β/H-16'; H-9'/H-6'β, 10'-OC$\underline{H}_3$; H-12'/H-18, H-21a, N(1')C$\underline{H}_3$; H-15'/H-14'α, H-16', H-17', H-18'; H-19'/H-18', H-21'.

Acetylation of angustilongine K (85): To a stirred solution of **85** (11.9 mg, 0.018 mmol) in CH_2Cl_2 (3 mL) and pyridine (10 equiv.), was added Ac_2O (15 equiv.) and the mixture was stirred at room temperature with TLC monitoring. The reaction was stopped after about 95% conversion, by addition of 10% Na_2CO_3 solution (5 mL), after which the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The organic extract was dried (anhydrous Na_2SO_4), concentrated *in vacuo*, and then purified by preparative radial chromatography (SiO_2, $CHCl_3$–MeOH 5%) to give di-*O*-acetylangustilongine K (**85b**) (5.1 mg, 43%).

Di-*O*-acetylangustilongine K (85b): light yellowish oil; $[\alpha]^{25}_D$ +62 (*c* 0.08, $CHCl_3$); UV (EtOH), λ_{max} (log ε) 205 (4.42), 230 (4.54), 286 (3.95) nm; IR (dry film) ν_{max} 1717, 1740 cm^{-1}; ^1H and ^{13}C NMR data, see Table 2.51; HRESIMS *m/z* 761.4282 $[M + H]^+$ (calcd for $C_{46}H_{56}N_4O_6$ + H, 761.4278).

Angustilongine M (86): light yellowish oil; $[\alpha]^{25}_{D}$ +5.2 (*c* 0.23, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 285 (3.90), 229 (4.49) nm; IR (dry film) ν_{max} 3427 cm^{-1}; HRDARTMS *m/z* 645.3804 $[M + H]^+$ (calcd for $C_{41}H_{48}N_4O_3$ + H, 645.3805); ^1H and ^{13}C NMR data, see Tables 2.52 and 2.53, respectively. HMBC: ^2J H-3 to C-2; H-5 to C-6; H-6 to C-5, C-7; H-18 to C-19; H-3' to C-2'; H-6' to C-5', C-7'; H-11' to C-10'; H-16' to C-17'; H-17' to C-16'; H-18' to C-19'; H-19' to C-18'. ^3J H-3 to C-5, C-15; N(4)C<u>H</u>$_3$ to C-3, C-5; H-6 to C-16; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-17 to C-21; H-18 to C-9', C-20; H-21 to C-17, C-19, C-10'; N(1)C<u>H</u>$_3$ to C-2, C-13; H-3' to C-5'; H-5' to C-7'; H-6' to C-2', C-16'; H-11' to C-9', C-13'; H-12' to C-8', C-10'; H-14' to C-2', C-16'; H-15' to C-3', C-5', C-21'; H-16' to C-6', C-14', C-20'; H-17' to C-5', C-15'; H-18' to C-20'; H-19' to C-15', C-21'; H-21' to C-3', C-5', C-15'; N(1')C<u>H</u>$_3$ to C-2', C-13'. NOESY: H-3/N(1)C<u>H</u>$_3$, N(4)C<u>H</u>$_3$, H-14α, H-14β; H-5/N(4)C<u>H</u>$_3$; H-6α/N(4)C<u>H</u>$_3$; H-6β/H-16; H-9/H-6β; H-12/N(1)C<u>H</u>$_3$; H-14β/N(1)C<u>H</u>$_3$; H-15/H-19; H-16/H-5, H-19; H-17α/H-14α; H-17β/H-5; H-18/H-6'β, H-20; H-21/H-14α, H-17α, H-20; H-20/H-21; H-3'/N(1')C<u>H</u>$_3$, H-14'α, H-21'α; H-6'β/H-16'; H-12'/N(1')C<u>H</u>$_3$; H-15'/H-14'α, H-18'; H-17'b/H-5'; H-19'/H-18', H-21'.

Macralstonidine (87): light yellowish oil; $[\alpha]^{25}_{D}$ +94 (*c* 0.58, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 229 (4.20), 285 (3.67) nm; HRESIMS *m/z* 645.3821 $[M + H]^+$ (calcd for $C_{41}H_{48}N_4O_3$ + H, 645.3805); ^1H and ^{13}C NMR data, see Tables 2.52 and 2.53, respectively.

Angustilongine L (Macrocarpamine *N*(4')-oxide) (88): yellowish oil; $[\alpha]^{25}_{D}$ −18 (*c* 0.13, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (4.41), 231 (4.34), 255 (3.98), 293 (3.65) nm; IR (dry film) ν_{max} 1757 cm^{-1}; HRESIMS *m/z* 659.3611 $[M + H]^+$ (calcd for $C_{41}H_{46}N_4O_4$ + H, 659.3597); ^1H and ^{13}C NMR data, see Tables 2.54 and 2.55, respectively. HMBC:

^{2}J H-6 to C-7; H-5 to C-16; H-21 to C-20; H-18' to C-19'. ^{3}J H-5 to C-3, C-7, C-15, C-17; H-6 to C-2, C-16; H-9 to C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-10; H-19 to C-15, C-21, C-2'; H-18 to C-20; H-21 to C-15, C-17, C-19; N(1)C<u>H</u>$_3$ to C-2, C-13; H-9' to C-11', C-13'; H-10' to C-8', C-12'; H-11' to C-9', C-13'; H-12' to C-8', C-10'; H-18' to H-20'; $CO_2C\underline{H}_3$ to $\underline{C}O_2Me$.

Macrocarpamine (89): light yellowish oil; $[\alpha]^{25}_D$ –9 (*c* 0.39, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 207 (4.14), 231 (4.25), 255 (4.10), 290 (3.55) nm; IR (dry film) ν_{max} 1757 cm^{-1}; HRESIMS *m/z* 643.3661 $[M + H]^+$ (calcd for $C_{41}H_{46}N_4O_3$ + H, 643.3648); ^1H and ^{13}C NMR data, see Tables 2.54 and 2.55, respectively.

Villalstonine (90): yellowish oil; $[\alpha]^{25}_D$ +32 (*c* 3.76, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (5.80), 251 (5.83), 286 (5.90), 294 (5.91) nm; HRESIMS *m/z* 661.3771 $[M + H]^+$ (calcd for $C_{41}H_{48}N_4O_4$ + H, 661.3754); ^1H and ^{13}C NMR data, see Tables 2.56 and 2.57, respectively.

Villalstonine *N*(4')-oxide (91): yellowish oil; $[\alpha]^{25}_D$ +25 (*c* 0.11, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 203 (4.25), 229 (4.13), 286 (3.54) nm; HRESIMS *m/z* 677.3717 $[M + H]^+$ (calcd for $C_{41}H_{48}N_4O_5$ + H, 677.3703); ^1H and ^{13}C NMR data, see Tables 2.56 and 2.57, respectively.

Lumutinine B (92): yellowish oil; $[\alpha]^{25}_D$ –13 (*c* 0.08, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (5.71), 232 (5.64), 255 (5.35), 285 (4.95) nm; IR (dry film) ν_{max} 1616, 1651 cm^{-1}; HRESIMS *m/z* 673.3769 $[M + H]^+$ (calcd for $C_{42}H_{48}N_4O_4$ + H, 673.3754); ^1H and ^{13}C NMR data, see Table 2.58.

Lumusidine B (93): yellowish oil; $[\alpha]^{25}_{D}$ −29 (*c* 0.08, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 229 (5.48), 285 (4.84) nm; IR (dry film) ν_{max} 1615, 1652 cm^{-1}; HRESIMS *m/z* 705.4034 $[M + H]^+$ (calcd for $C_{43}H_{52}N_4O_5$ + H, 705.4016); ^1H and ^{13}C NMR data, see Table 2.59.

Perhentinine (94): yellowish oil; $[\alpha]^{25}_{D}$ −64 (*c* 0.2, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 231 (4.25), 298 (3.45) nm; IR (dry film) ν_{max} 3400, 1701, 1651, 1616 cm^{-1}; HRESIMS *m/z* 705.4024 $[M + H]^+$ (calcd for $C_{43}H_{52}N_4O_5$ + H, 705.4016); ^1H and ^{13}C NMR data, see Table 2.60.

The following alkaloids were isolated from *L. platyrhizoma*:

Lycoplatyrine A (95): yellowish oil; $[\alpha]^{25}_{D}$ −19 (*c* 0.16, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 231 (3.44), 273 (3.46), 280 (3.43) nm; IR (dry film) ν_{max} 3389, 3281 cm^{-1}; HRESIMS *m/z* 326.2597 $[M + H]^+$ (calcd for $C_{21}H_{31}N_3$ + H, 326.2591); ^1H and ^{13}C NMR data, see Table 2.62. HMBC: ^2J H-1 to C-2; H-6 to C-5, C-7; H-9 to C-10; H-10 to C-9, C-11; H-11 to C-10; H-12 to C-13; H-14 to C-13, C-15; H-16 to C-15; H-2' to C-2, C-3'; H-3' to C-2'; H-4' to C-3'. ^3J H-1 to C-3, C-5, C-2'; H-3 to C-1, C-5, C-13, C-2'; H-6 to C-4, C-8, C-12; H-7 to C-5, C-13, C-15; H-8 to C-6, C-12, C-14; H-9 to C-11, C-13; H-11 to C-9, C-13; H-12 to C-4, C-6; H-14 to C-4, C-8, C-12; H-16 to C-8, C-14; H-2' to C-1, C-3, C-4', C-6'; H-3' to C-5'; H-4' to C-2', C-6'; H-5' to C-3'; H-6' to C-2', C-4'. NOESY: H-1/H-2', H-3'; H-3/H-2', H-3', $H\text{-}9_{ax}$, $H\text{-}14_{eq}$; H-6a/H-7, $H\text{-}8_{eq}$, H-15; H-6b/H-7, $H\text{-}11_{ax}$; H-7/$H\text{-}8_{ax}$, $H\text{-}11_{eq}$, H-12; $H\text{-}8_{ax}$/H-12, H-16; $H\text{-}8_{eq}$/H-15, H-16; $H\text{-}9_{ax}$/$H\text{-}11_{ax}$; H-12/$H\text{-}14_{ax}$; $H\text{-}14_{ax}$/H-16; $H\text{-}14_{eq}$/H-15, H-16.

Lycoplatyrine B (96): yellowish oil; $[\alpha]^{25}_{D}$ +64 (*c* 0.61, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 251 (3.64) nm; IR (ATR) ν_{max} 3356, 3275, 1654 cm^{-1}; HRDARTMS *m/z* 247.1815 $[M + H]^+$ (calcd for $C_{15}H_{22}N_2O$ + H, 247.1810); ^1H and ^{13}C NMR data, see Table 2.63. HMBC: ^2J H-2 to C-1, C-3; H-3 to C-2, C-4; H-6 to C-5, C-7; H-8 to C-15; H-10 to C-11; H-11 to C-12; H-12 to C-7, C-11, C-13; H-14 to C-13, C-15; H-16 to C-15. ^3J H-2 to C-4; H-3 to C-1, C-5; H-6 to C-4, C-8; H-7 to C-5; H-8 to C-6, C-14; H-10 to C-12; H-12 to C-4, C-6, C-8, C-10, C-14; H-14 to C-4, C-8, C-16; H-15 to C-13; H-16 to C-8, C-14; C=ONH to C-2, C-4. NOE: H-3a/$H\text{-}14_{eq}$; H-6a/H-7; H-6b/H-7, H-11; $H\text{-}8_{ax}$/H-12, $H\text{-}14_{ax}$, H-16; $H\text{-}8_{eq}$/H-16; H-10a/H-11; H-10b/H-12; H-12/$H\text{-}8_{ax}$, $H\text{-}14_{ax}$; $H\text{-}14_{eq}$/H-16.

Lycodine (97): yellowish oil; $[\alpha]^{25}_{D}$ −13 (*c* 0.76, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 269 (3.86), 276 (3.76) nm; IR (ATR) ν_{max} 3354 cm^{-1}; HRESIMS *m/z* 243.1854 $[M + H]^+$ (calcd for $C_{16}H_{22}N_2$ + H, 243.1861); ^1H and ^{13}C NMR data, see Table 2.64. HMBC: ^2J H-1 to C-2; H-2 to C-1; H-6 to C-5, C-7; H-14 to C-13, C-15; H-16 to C-15. ^3J H-1 to C-3, C-5; H-2 to C-4; H-3 to C-5, C-13; H-6 to C-4, C-12; H-7 to C-11, C-15; H-8 to C-12, C-14; H-9 to C-11, C-13; H-14 to C-12, C-16; H-16 to C-8, C-14.

Lycoannotine G (98): light yellowish oil; $[\alpha]^{25}_{D}$ +13 (*c* 0.11, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 282 (3.42), 232 (3.66) nm; IR (dry film) ν_{max} 3309, 1698 cm^{-1}; HRDARTMS *m/z* 257.1642 $[M + H]^+$ (calcd for $C_{16}H_{20}N_2O$ + H, 257.1654); ^1H and ^{13}C NMR data, see Table 2.64. HMBC: ^2J H-1 to C-2; H-2 to C-1; H-7 to C-6, C-8, C-12; H-8 to C-7, C-15; H-11 to C-10, C-12; H-14 to C-13; H-15 to C-16; H-16 to C-15. ^3J H-1 to C-3, C-5; H-2 to C-4; H-7 to C-13; H-8 to C-6, C-12, C-14, C-16; H-11 to C-9; H-16 to C-8.

Des-*N*-methyl-β-obscurine (99): light yellowish amorphous solid; $[\alpha]^{25}_{D}$ −24 (*c* 0.33, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 314 (3.96), 231 (4.08) nm; IR (ATR) ν_{max} 3097, 1661

cm^{-1}; HRDARTMS *m/z* 259.1812 $[M + H]^+$ (calcd for $C_{16}H_{22}N_2O$ + H, 259.1810); ^{1}H and ^{13}C NMR data, see Table 2.65.

Des-*N*-methyl-α-obscurine (100): light yellowish amorphous solid; $[\alpha]^{25}_D$ −10 (*c* 0.39, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 254 (4.07) nm; IR (ATR) ν_{max} 3407, 3211, 1669 cm^{-1}; HRESIMS *m/z* 261.1961 $[M + H]^+$ (calcd for $C_{16}H_{24}N_2O$ + H, 261.1967); ^{1}H and ^{13}C NMR data, see Table 2.65. HMBC: ^2J H-2 to C-1, C-3; H-3 to C-2, C-4; H-6 to C-5, C-7; H-8 to C-7; H-16 to C-15. ^3J H-2 to C-4; H-3 to C-1; H-6 to C-4; H-7 to C-5, C-13; H-8 to C-6; H-9 to C-13; H-14 to C-4; H-16 to C-8, C-14.

Lycoplanine D (101): colorless block crystals ($CHCl_3$-MeOH); mp >186 °C (dec); $[\alpha]^{25}_D$ −18 (*c* 0.20, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 254 (3.98) nm; IR (ATR) ν_{max} 3491, 3214, 1652 cm^{-1}; HRDARTMS *m/z* 277.1907 $[M + H]^+$ (calcd for $C_{16}H_{24}N_2O_2$ + H, 277.1916); ^{1}H and ^{13}C NMR data, see Table 2.66. HMBC: ^2J H-2 to C-1, C-3; H-3 to C-2, C-4; H-6 to C-5, C-7; H-9 to C-10; H-11 to C-10; H-14 to C-13, C-15; H-16 to C-15. ^3J H-2 to C-4; H-3 to C-1, C-5, C-13; H-6 to C-4, C-8; H-7 to C-5; H-8 to C-6, C-14; H-9 to C-11, C-13; H-10 to C-12; H-14 to C-4, C-12, C-16; H-16 to C-8, C-14.

Crystallographic data of Lycoplanine D (101): $C_{16}H_{24}N_2O_2$, *M*r = 276.37, orthorhombic, space group $P2_12_12_1$, *a* = 7.3734(2) Å, *b* = 11.8187(3) Å, *c* = 15.8275(4) Å, *V* = 1379.27(6) Å^3, *Z* = 4, D_{calcd} = 1.331 g cm^{-3}, crystal size 0.4 x 0.2 x 0.2 mm^3, *F*(000) = 600, Cu Kα radiation (λ = 1.54184 Å), *T* = 168(1) K. The final R_1 value is 0.0343 (wR_2 = 0.0878) for 4890 reflections [$I>2\sigma(I)$]. The Flack, Hooft, and Parsons parameters were *x* = 0.07(13), *y* = 0.05(13), and *z* = 0.00(12), respectively. For the inverted structure, the Flack, Hooft, and Parsons parameters were *x* = 0.93(13), *y* = 0.95(13), and *z* = 1.00(12), respectively. CCDC number: 1865378.

Casuarinine H (102): yellowish oil; $[\alpha]^{25}_{D}$ –4 (*c* 0.8, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 313 (3.86), 230 (4.05) nm; IR (dry film) ν_{max} 3323, 1652 cm^{-1}; HRDARTMS *m/z* 245.1655 $[M + H]^+$ (calcd for $C_{15}H_{20}N_2O$ + H, 245.1654); ^1H and ^{13}C NMR data, see Table 2.66.

Flabellidine (103): yellowish oil; $[\alpha]^{25}_{D}$ +41 (*c* 0.89, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 235 (4.16) nm; IR (dry film) ν_{max} 3309, 1647 cm^{-1}; HRDARTMS *m/z* 289.2266 $[M + H]^+$ (calcd for $C_{18}H_{28}N_2O$ + H, 289.2280); ^1H and ^{13}C NMR data, see Table 2.66.

Complanadine A (104): yellowish oil; $[\alpha]^{25}_{D}$ –8 (*c* 0.18, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 294 (4.26), 242 (4.22) nm; IR (dry film) ν_{max} 3298 cm^{-1}; HRDARTMS *m/z* 483.3485 $[M + H]^+$ (calcd for $C_{32}H_{42}N_4$ + H, 483.3488); ^1H and ^{13}C NMR data, see Table 2.67. HMBC: ^2J H-1' to C-2'; H-2 to C-3; H-6 to C-5, C-7; H-8 to C-15; H-14 to C-15; H-16 to C-15; H-6' to C-5', C-7'; H-8' to C-15'; H-14' to C-15'; H-16' to C-15'. ^3J H-3 to C-1, C-5; H-6 to C-4, C-8; H-7 to C-5, C-13; H-8 to C-12, C-14; H-16 to C-8, C-14; H-1' to C-5'; H-3' to C-1', C-5'; H-6' to C-4', C-8'; H-7' to C-5', C-13'; H-8' to C-12', C-14'; H-16' to C-8', C-14'.

6α-Hydroxylycopodine (105): white amorphous solid; $[\alpha]^{25}_{D}$ –7 (*c* 0.91, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 298 wk (3.03), 219 (3.77) nm; IR (ATR) ν_{max} 2400–3200 (br), 1713 cm^{-1}; HRESIMS *m/z* 264.1956 $[M + H]^+$ (calcd for $C_{16}H_{25}NO_2$ + H, 264.1964); ^1H and ^{13}C NMR data, see Table 2.68.

Lycodoline (106): yellowish amorphous solid; $[\alpha]^{25}_{D}$ –47 (*c* 0.03, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 228 wk (3.43) nm; IR (ATR) ν_{max} 3210, 1700 cm^{-1}; HRESIMS *m/z* 264.1953 $[M + H]^+$ (calcd for $C_{16}H_{25}NO_2$ + H, 264.1964); ^1H and ^{13}C NMR data, see

Table 2.69. HMBC: ^{2}J H-2 to C-1; H-4 to C-3, C-13; H-6 to C-7; H-11 to C-12; H-16 to C-15. ^{3}J H-1 to C-3, C-13; H-6 to C-4, C-8, C-12; H-8 to C-14; H-9 to C-1, C-13; H-11 to C-9, C-13; H-14 to C-4, C-8, C-12; H-16 to C-8, C-14.

Lycopodine *N*-oxide (107): yellowish oil; $[\alpha]^{25}_{D}$ –33 (*c* 0.05, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 315 wk (3.20) nm; IR (dry film) ν_{max} 1705 cm^{-1}; HRESIMS *m/z* 264.2011 $[M + H]^+$ (calcd for $C_{16}H_{25}NO_2$ + H, 264.1964); ^{1}H and ^{13}C NMR data, see Table 2.69.

Huperzine E (108): yellowish oil; $[\alpha]^{25}_{D}$ +9 (*c* 0.23, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 317 (4.07), 225 (3.77) nm; IR (dry film) ν_{max} 3376, 1661 cm^{-1}; HRDARTMS *m/z* 260.1640 $[M + H]^+$ (calcd for $C_{16}H_{21}NO_2$ + H, 260.1651); ^{1}H and ^{13}C NMR data, see Table 2.70. HMBC: ^{2}J H-1 to C-2; H-2 to C-1; H-8 to C-7, C-15; H-11 to C-10, C-12; H-14 to C-13, C-15; H-15 to C-16; H-16 to C-15. ^{3}J H-1 to C-3, C-9, C-13; H-2 to C-4; H-3 to C-1, C-5, C-13; H-7 to C-15; H-8 to C-6, C-12, C-14, C-16; H-9 to C-1, C-11, C-13; H-11 to C-9; H-14 to C-4, C-8, C-12, C-16; H-16 to C-8, C-14.

12-Deoxyhuperzine O (109): yellowish oil; $[\alpha]^{25}_{D}$ –33 (*c* 0.08, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 282 (4.12) nm; IR (dry film) ν_{max} 3411 (br), 1664 cm^{-1}; HRDARTMS *m/z* 262.1801 $[M + H]^+$ (calcd for $C_{16}H_{23}NO_2$ + H, 262.1807); ^{1}H and ^{13}C NMR data, see Table 2.70. HMBC: ^{2}J H-2 to C-1, C-3; H-3 to C-2, C-4; H-8 to C-7, C-15; H-12 to C-13; H-14 to C-13, C-15; H-16 to C-15. ^{3}J H-1 to C-3, C-9, C-13; H-2 to C-4; H-3 to C-1, C-5, C-13; H-8 to C-6, C-12, C-14, C-16; H-9 to C-11, C-13; H-12 to C-4, C-14; H-14 to C-4, C-8, C-12, C-16; H-16 to C-8, C-14.

Lycoplatyrine C (110): yellowish oil; $[\alpha]^{25}_{D}$ –20 (*c* 0.18, $CHCl_3$); IR (dry film) ν_{max} 3403 cm^{-1}; HRDARTMS *m/z* 292.1914 $[M + H]^+$ (calcd for $C_{17}H_{25}NO_3$ + H, 292.1913);

^{1}H and ^{13}C NMR data, see Table 2.71. HMBC: ^{2}J H-2 to C-1, C-3; H-6 to C-5; H-7 to C-6, C-12; H-9 to C-10; H-11 to C-10, C-12; H-14 to C-13; H-16 to C-15. ^{3}J H-1 to C-3, C-9, C-17; H-2 to C-4; H-3 to C-5, C-12; H-5 to C-7, C-12, C-13; H-6 to C-4, C-8, C-12; H-7 to C-13, C-15; H-8 to C-6; H-9 to C-1, C-11; H-11 to C-7; H-16 to C-8; H-17 to C-1, C-5, C-9, C-12. NOESY: H-1β/H-3; H-1α/H-9a; H-2α/H-11a; H-2β/H-3; H-3/H-5, H-17β; H-5/H-6, H-17β; H-6/H-8β, H-15; H-7/H-8α, H-11b, H-17α; H-8β/H-16; H-8α/H-11b, H-16; H-14β/H-16; H-15/H-16; H-17α/H-10b.

Lycogladine G (111): yellowish oil; $[\alpha]^{25}_{D}$ +50 (*c* 0.03, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 281 wk (2.86), 272 wk (2.73), 231 (3.43) nm; IR (dry film) ν_{max} 1739 cm^{-1}; HRDARTMS *m/z* 290.1752 $[M + H]^+$ (calcd for $C_{17}H_{23}NO_3$ + H, 290.1756); ^{1}H and ^{13}C NMR data, see Table 2.72. HMBC: ^{2}J H-2 to C-1; H-3 to C-2, C-4; H-4 to C-3, C-5, C-12; H-6 to C-5, C-7; H-7 o C-6, C-8; H-8 to C-7, C-15; H-10 to C-9, C-11; H-11 to C-10, C-12; H-14 to C-13; H-15 to C-8, C-14, C-16. ^{3}J H-1 to C-9, C-3, C-13; H-3 to C-1, C-5, C-12; H-4 to C-2, C-6, C-7, C-11; H-6 to C-4, C-8; H-7 to C-4, C-5; H-8 to C-6, C-12, C-14, C-16; H-9 to C-1, C-11, C-13; H-10 to C-12; H-11 to C-4, C-7; H-14 to C-8, C-12, C-16; H-15 to C-7, C-13; H-17 to C-16.

Lycogladine H (112): colorless block crystals (EtOH), mp 155−157 ºC; $[\alpha]^{25}_{D}$ +44 (*c* 0.14, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 281 wk (2.64), 272 wk (2.39), 231 (3.33) nm; IR (dry film) ν_{max} 1738 cm^{-1}; HRDARTMS *m/z* 290.1757 $[M + H]^+$ (calcd for $C_{17}H_{23}NO_3$ + H, 290.1756); ^{1}H and ^{13}C NMR data, see Table 2.72. HMBC: ^{2}J H-2 to C-1; H-3 to C-2, C-4; H-4 to C-3, C-5, C-12; H-6 to C-5, C-7; H-8 to C-7, C-15; H-10 to C-9, C-11; H-11 to C-10, C-12; H-14 to C-13, C-15; H-15 to C-8, C-14. ^{3}J H-1 to C-9, C-3, C-13; H-3 to C-1, C-12; H-4 to C-11; H-6 to C-4, C-8; H-7 to C-5; H-8 to C-6, C-14, C-16; H-

9 to C-1, C-11, C-13; H-10 to C-12; H-11 to C-4, C-7, C-9, C-13; H-14 to C-8, C-12, C-16; H-15 to C-13; H-17 to C-16.

Crystallographic data of Lycogladine H (112): *M*r = 289.36, orthorhombic, space group $P2_12_12_1$, a = 6.80760(10) Å, b = 14.3592(2) Å, c = 15.3172(2) Å, V = 1497.28(4) Å^3, Z = 4, D_{calcd} = 1.284 gcm^{-3}, crystal size 0.4 x 0.3 x 0.1 mm^3, F(000) = 624, Cu Kα radiation (λ = 1.54184 Å), T = 160(2) K. The final R_1 value is 0.0399 (wR_2 = 0.1057) for 5378 reflections [$I>2\sigma(I)$]. The Flack, Hooft, and Parsons parameters were x = 0.2(2), y = 0.26(13), and z = 0.11(11), respectively. For the inverted structure, the Flack, Hooft, and Parsons parameters were x = 0.8(2), y = 0.74(13), and z = 0.89(11), respectively, from which it follows that the correct enantiomer is the one depicted in Figure 8. CCDC number: 1865379.

Lyconadin E (113): yellowish oil; $[\alpha]^{25}_D$ +6 (*c* 0.20, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 237 (3.35) nm; IR (dry film) ν_{max} 3282, 3202, 1673 cm^{-1}; HRDARTMS *m/z* 259.1799 $[M + H]^+$ (calcd for $C_{16}H_{22}N_2O$ + H, 259.1810); ^{1}H and ^{13}C NMR data, see Table 2.72. HMBC: ^2J H-2 to C-1, C-3; H-6 to C-5; H-9 to C-10; H-14 to C-13; H-16 to C-15. ^3J H-3 to C-1, C-5, C-13; H-6 to C-4, C-12; H-8 to C-12; H-9 to C-4, C-11, C-13; H-10 to C-3; H-11 to C-9; H-14 to C-4, C-16; H-16 to C-8, C-14.

3.10 Cytotoxicity Assays

Human cancer cell lines (MDA-MB-231, LNCaP, HCT 116, HT-29, PC-3, A549, and MCF7) were purchased from American Type Culture Collection (ATCC), USA. Human oral epidermoid carcinoma (KB) and vincristine-resistant KB cells (VJ 300) were obtained from Dr. Komiyama (Kitasato University, Japan). MCF7, LNCaP, PC-3, and A549 cells were maintained in RPMI 1650 medium. KB, KB (VJ 300), and MDA-MB-231 cells were maintained in Eagle's medium (DMEM). HT-29 and HCT 116 cells were cultured in McCoy's 5A medium. Cytotoxicity assays were performed following the similar procedure as described previously.[180] All media were supplemented with 10% fetal bovine serum and 2% penicillin/streptomycin. The cells were cultured at 37°C in 5% CO_2 atmosphere in a CO_2 incubator. The cells were then seeded in a 96-well microtiter plate (Nunc, Germany) at a concentration of 70,000 cells/mL, and incubated in a CO_2 incubator at 37°C for 24 h before the cells were treated with test samples. Seeded cells were treated with sample solution at six different concentrations (0.1, 0.3, 1, 3, 10 and 30 µg/mL) and incubated for 72 h. Wells containing untreated cells (without addition of sample) represented the negative control, whereas cells treated with vincristine, verapamil or cisplatin represented the positive control. DMSO was used to dilute the samples and the final concentration of DMSO in each well was no more than 0.5% (v/v). No adverse effect due to presence of DMSO was observed. At the end of the incubation period, 20 µL of MTT working solution (5 mg MTT in 1 mL phosphate-buffered saline) was added into each well and the 96-well microtiter plate was incubated for another three hours at 37°C. The medium was then gently aspirated from each well and 200 µL of DMSO were added to effect formazan solubilization. After the agitation of the microtiter plate for 15 min, the absorbance of each well was measured with a microplate reader (Emax, Molecular Devices or TECAN Infinite M200) at 540 nm with 650 nm.

The cytotoxic activity of each sample was expressed as the IC_{50} value, which is the concentration of the test sample that causes 50% inhibition of cell growth. All samples were assayed in three independent experiments.

3.11 Acetylcholinesterase (AChE) inhibition assays

Acetylcholinesterase (AChE) inhibitory activities were determined by modified Ellman's method.[430] The reaction mixture containing phosphate buffer (pH 8.0, 85 µL), test compound solution (15 µL), and AChE solution (50 µL, 0.2 U/mL) was incubated for 15 min at room temperature. All samples and positive control were dissolved in dimethyl sulfoxide (DMSO). The reaction was initiated by the addition of 50 µL of solution containing DTNB (Ellman's reagent, 0.4 mM) and acetylthiocholine (1 mM). The hydrolysis of acetylthiocholine was monitored at 410 nm every 60 s for 15 min. Huperzine A was used as positive control. All reactions were performed in triplicate. The percentage inhibition was calculated as follows: % inhibition = (E-S)/E ∗100 (E is the activity of the enzyme without test compound and S is the activity of enzyme with test compound).

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LIST OF PUBLICATIONS AND PAPERS PRESENTED

PUBLICATIONS:

(1) **Yeap, J. S. Y.**, Saad, H. M., Tan, C. H., Sim, K. S., Lim, S. H., Low, Y. Y., & Kam, T. S. (2019). Macroline-sarpagine bisindole alkaloids with antiproliferative activity from *Alstonia penangiana*. *Journal of Natural Products*, *82*, 3121–3132.

(2) **Yeap, J. S. Y.**, Lim, K. H., Yong, K. T., Lim, S. H., Kam, T. S., & Low, Y. Y. (2018). *Lycopodium* alkaloids: Lycoplatyrine A, an unusual lycodine-piperidine adduct from *Alstonia penangiana* and the absolute configurations of lycoplanine D and lycogladine H. *Journal of Natural Products*, *82*, 324–329.

(3) **Yeap, J. S. Y.**, Navanesan, S., Sim, K. S., Yong, K. T., Gurusamy, S., Lim, S. H., Low, Y. Y., & Kam, T. S. (2018). Ajmaline, oxindole, and cytotoxic macroline-akuammiline bisindole alkaloids from *Alstonia penangiana*. *Journal of Natural Products*, *81*, 1266–1277.

POSTER PRESENTATION IN SYMPOSIUM:

(1) **Yeap, J. S. Y.**, Lim, S. H., Low, Y. Y., & Kam, T. S. *Alkaloids from leaves extract of Alstonia penangiana*. Poster session presented at the 2018 Bilateral Symposium on Advanced Materials Between Universiti Malaya (UM)–National Taiwan University (NTU), 13th Aug 2018, Universiti Malaya, Kuala Lumpur, Malaysia.