INDOLE AND BISINDOLE ALKALOIDS FROM *Tabernaemontana corymbosa*

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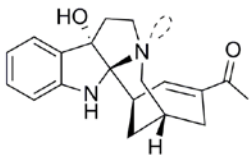
ABSTRACT

A total of 59 alkaloids (**1**–**59**) were isolated and characterized from the leaf and stem-bark extracts of the Malayan *Tabernaemontana corymbosa* Roxb. ex Wall.. Of these, 25 are new alkaloids. Among the new alkaloids, the pentacyclic alkaloids, voatinggine (**1**) and tabertinggine (**2**), which are postulated to derive from a common cleavamine-type precursor, the hexacyclic iboga-derived indole, cononuridine **3**, the pentacyclic indoles, criofolinine (**4**) and vernavosine (**5**) incorporating pyrroloazepine and pyridopyrimidine moieties, respectively, are notable for incorporating novel or intriguing molecular skeletons. Other new alkaloids isolated from this study include a *seco*-yohimbine (taberisidine, **7**), five iboga (conodusines A–E, **8**–**12**), seven *Aspidosperma* (apocidines A–G, **20**–**26**), three vincamine (conoduzidines A–C, **30**–**32**), one heteroyohimbine [16α-methoxycarbonyl-16,17-dihydro-19-*epi*-ajmalicine, **34**], two iboga-vobasinyl bisindoles, tabernamidines A and B (**55**, **56**) and one *Aspidosperma-Aspidosperma* bisindole alkaloid (conofolidine, **59**). Two of the iboga alkaloids, conodusines B and C (**9**, **10**) and the iboga containing bisindole (tabernamidine B, **56**) are notable for the presence of an α-substituted acetyl group at C-20 of the iboga carbon skeleton (naturally-occurring iboga alkaloids with C-20 substitution by ethyl, hydroxyethyl, or acetyl groups, are usually β-oriented). Conofolidine (**59**) showed pronounced cytotoxicity toward human KB/S, KB/VJ300(–), KB/VJ300(+), PC-3, LNCaP, MCF7, MDA-MB-231, HT-29, and HCT 116 cancer cells (IC_{50} 0.2–5.9 μg/mL).



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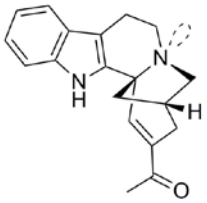

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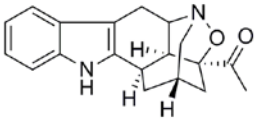

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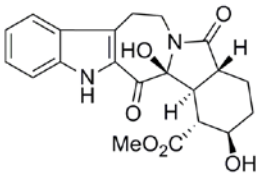

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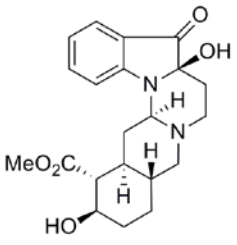

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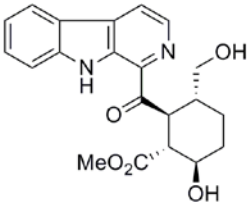

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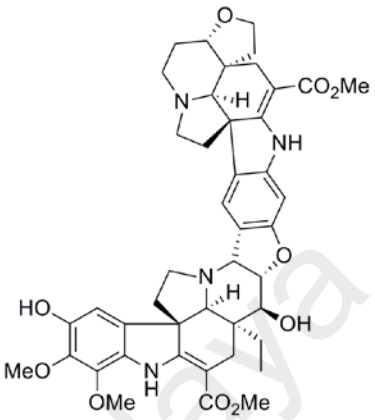

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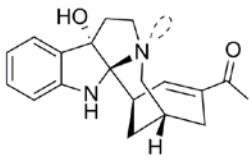
ABSTRAK

Dalam kajian ini, sebanyak 59 alkaloid (**1**–**59**) telah diasingkan dan dicirikan dari ekstrak daun dan kulit-batang pokok *T. corymbosa* Roxb. ex Wall.. Daripada jumlah tersebut, 25 alkaloid merupakan alkaloid baru. Di antaranya ada beberapa alkaloid yang mempunyai rangka molekul yang 'novel' dan menarik. Misalnya, voatinggine (**1**) dan tabertinggine (**2**), merupakan alkaloid pentasiklik yang dicadangkan berasal dari precursor jenis 'cleavamine' yang sama, conodurinine (**3**) adalah alkaloid hexasiklik yang berasal dari alkaloid iboga, criofolinine (**4**) dan vernavosine (**5**) merupakan alkaloid indol pentasiklik yang masing-masing mengandungi unit pyrroloazepine dan pyridopyrimidine. Selain daripada itu, alkaloid-alkaloid baru lain yang diasingkan dalam kajian ini termasuk satu alkaloid *seco*-yohimbine (taberisidine, **7**), lima alkaloid iboga (conodusine A–E, **8**–**12**), tujuh alkaloid *Aspidosperma* (apocidine A–G, **20**–**26**), tiga alkaloid vincamine (conoduzidine A–C, **30**–**32**), satu alkaloid heteroyohimbine [16α-methoxycarbonyl-16,17-dihydro-19-*epi*-ajmalicine, **34**], dua alkaloid bisindol iboga-vobasine (tabernamidine A dan B, **55**–**56**) dan satu alkaloid bisindol *Aspidosperma-Aspidosperma* (conofolidine, **59**). Di antara kalangan alkaloid iboga, conodusine B dan C (**9**, **10**) dan tabernamidine B (**56**, alkaloid bisindol yang mangandungi unit iboga) merupakan alkaloid yang mempunyai penggantian α-asetil di C-20 dalam rangka iboga (alkaloid iboga yang terdapat secara semula jadi yang mempunyai penukarganti etil, hidroksietil atau asetil pada C-20 biasanya berorientasi β). Conofolidine (**59**) menunjukkan kesan sitotoksik yang kuat terhadap sel-sel kanser manusia KB/S, KB/VJ300(–), KB/VJ300(+), PC-3, LNCaP, MCF7, MDA-MB-231, HT-29, dan HCT 116 (IC_{50} 0.2–5.9 μg/mL).



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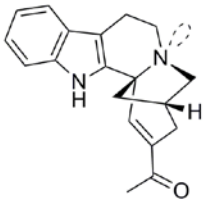

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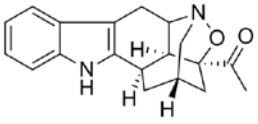

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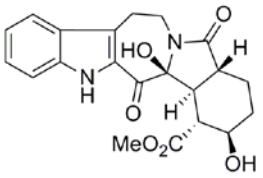

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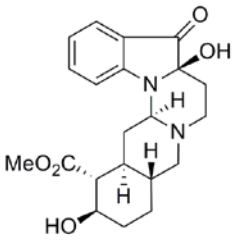

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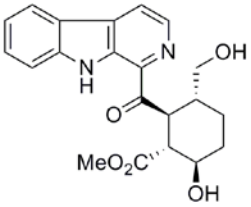

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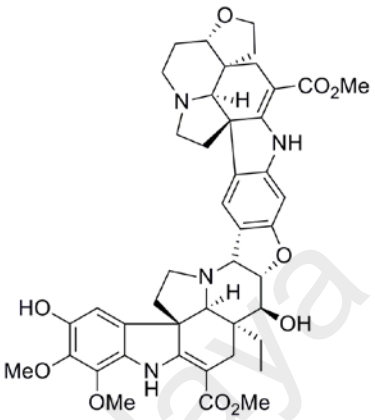

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LIST OF ABBREVIATIONS

α	Alpha
β	Beta
γ	Gamma
δ	Delta
λ	Lambda
Å	Angstrom
$[\alpha]_D$	Specific rotation
°C	Degree Celsius
K	Kelvin
mL	Milliliter
kg	Kilogram
mg	Milligram
μg	Microgram
cm^{-1}	Wavenumber
nm	Nanometer
MHz	Megahertz
J	Coupling constant
m/z	Mass-to-charge ratio
IC_{50}	Half maximal inhibitory concentration
EC_{50}	Half maximal effective concentration
DBE	Degree of unsaturation
dec	Decomposed
ppm	Parts per million
mp	Melting point
UV	Ultraviolet
IR	Infrared
MS	Mass spectrometry
HRESIMS	High resolution electrospray ionization mass spectrometry
HRDARTMS	High resolution direct analysis in real time mass spectrometry
ECD	Electronic circular dichroism
TDDFT	Time-dependent density functional theory
PCM	Polarizable continuum model
NMR	Nuclear magnetic resonance
2D NMR	Two-dimensional nuclear magnetic resonance
^{1}H NMR	Proton nuclear magnetic resonance
^{13}C NMR	Carbon-13 nuclear magnetic resonance
COSY	Correlation Spectroscopy
HMQC	Heteronuclear Multiple Quantum Coherence
HSQC	Heteronuclear Single Quantum Coherence
H2BC	Heteronuclear 2-Bond Correlation
HMBC	Heteronuclear Multiple Bond Correlation
NOESY	Nuclear Overhauser Effect Spectroscopy
NOE	Nuclear Overhauser Effect

CCDC	Cambridge Crystallographic Data Centre
$CDCl_3$	Deuterated chloroform
CD_3OD	Deuterated methanol
C_6D_6	Benzene-d_6
DMSO-d_6	Dimethyl sulfoxide-d_6
Me	Methyl
OMe	Methoxy
NaOMe	Sodium methoxide
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
MeOH	Methanol
PTSA	*p*-toluenesulfonic acid
AcOH	Acetic acid
SiO_2	Silica
s	Singlet
d	Doublet
t	Triplet
q	Quartet
m	Multiplet
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
dddd	Doublet of doublet of doublet of doublets
dt	Doublet of triplets
dq	Doublet of quartets
td	Triplet of doublets
qd	Quartet of doublet

CHAPTER 1: INTRODUCTION

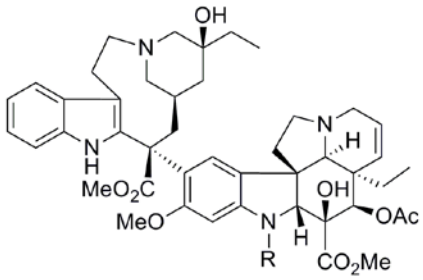
1.1 General

Natural products (or secondary metabolites) from plants, microbes, marine and terrestrial organisms, constitute productive sources of active compounds and chemical lead structures for the discovery and development of new medicines.[1–7] Although these naturally derived organic compounds may not necessarily represent active ingredients in their final form, the majority of drugs in the market have their origin in nature.[3,4,7] For example, with reference to cancer chemotherapeutic agents, plant-derived natural products or their derivatives which have been in clinical use include the *Catharanthus roseus* bisindole alkaloids and their derivatives (vincristine, vinblastine,[8–11] vindesine,[10,12] vinorelbine[10,11,13]), the campothecins,[10,14–16] the epipodophyllotoxins,[17–19] and the taxanes.[20–22] Similarly, antitumor antibiotics from microbes in clinical use include doxorubicin,[23–25] bleomycin,[10,26–32] dactinomycin (actinomycin D),[10,32–36] and mitomycin C.[10,32,37] Furthermore, examples of natural product-derived anticancer agents, recently approved, or in advanced clinical development, include: combretastatin,[10] vinflunine,[4,38–40] and cabazitaxel[4] from plants, romidepsin[4,41,42] and epothilones[10,43] from microbes, and, bryostatins[10] and trabectedin[10,44–48] from marine organisms, to cite a few examples (Figure 1.1).

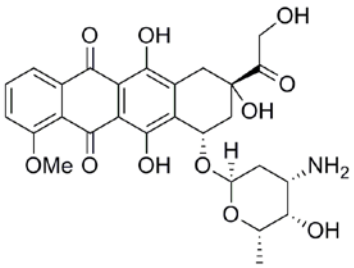
Plants, in particular higher plants, have a long history of use for medical purposes in treating and preventing diseases.[1] Many of them are still in use today as ingredients of official drugs or as herbal preparations used in traditional medicines.[7,49] Rational drug discovery from plants started at the beginning of the 19th century, when the German pharmacist Sertürner succeeded in isolating morphine from the opium poppy. This in turn stimulated the interest of organic chemists who initiated extensive

investigations of other medicinal plants for their chemical constituents. The plant kingdom comprises a large number of species, which produces a large number of bioactive compounds with a vast diversity of chemical scaffolds. It has been estimated that approximately 25% of all drugs prescribed today originated from plants.[3,50,51] Since only about 15% of existing plants have been chemically and pharmacologically investigated in a systematic manner,[1,3,6,52] it is not inconceivable that there remains a potentially large number of plant compounds that are yet to be investigated.[1] Plant-derived natural products therefore remain as a key source of new chemical entities for active pharmaceutical ingredients and lead compounds.[1,6]

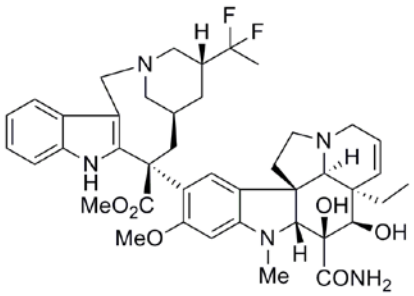
Malaysia being one of the world's biodiversity rich countries, continues to provide opportunities for the discovery of new natural products with novel chemical scaffolds and useful biological activity. In this context, the Malayan *Tabernaemontana corymbosa* (Apocynaceae) was chosen for investigation with emphasis on the following aspects: the discovery and structure elucidation of new natural products, the documentation of the alkaloid composition, investigation of reactivity of the new compounds, and, the evaluation of biological activity.



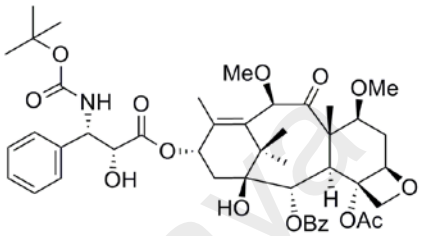
R = CHO Vincristine
R = Me Vinblastine



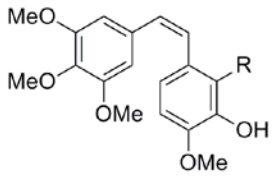
Doxorubicin



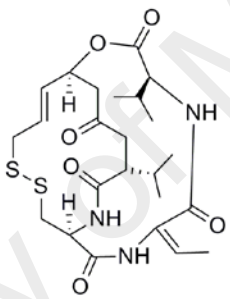
Vinflunine



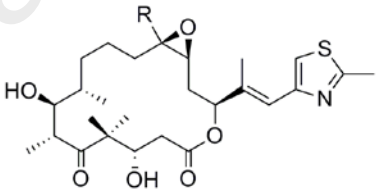
Cabazitaxel



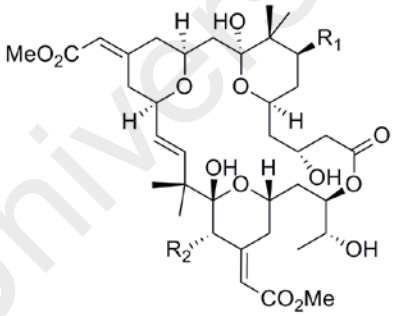
R = OH Combrestatins A-1
R = H Combrestatins A-4



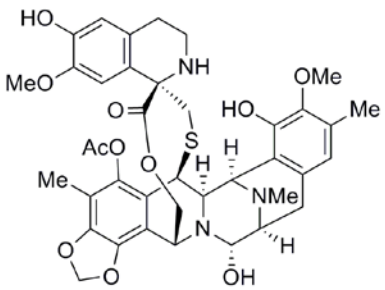
Romidepsin



R = H Epothilone A
R = Me Epothilone B



R_1 = OAc, R_2 = OCO(CH)$_4$*n*-Pr Bryostatin 1
R_1 = OH, R_2 = OCO(CH)$_4$*n*-Pr Bryostatin 2



Trabectedin

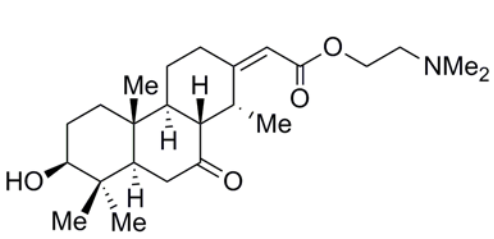
Figure 1.1: Examples of bioactive natural products

1.2 The Alkaloids

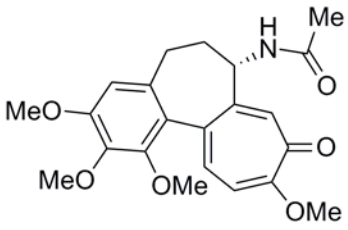
Alkaloids constitute one of the major classes of natural products. Plant extracts containing alkaloids have been widely used as ingredients in potions, medicines, poultices, and poisons as early as 4000 years ago. The isolation of morphine in 1805 by the German pharmacist, Friedrich Sertürner, marked the beginning of alkaloid chemistry. The term 'alkaloid' was first mentioned in 1819 by W. Meissner to describe substances of plant origin with an alkali-like or basic character.[53–55] Over the years, the definition of an alkaloid has changed significantly as more alkaloids from various natural sources have been isolated and their structures elucidated. Hesse has presented a more general definition of alkaloids: Alkaloids are nitrogen-containing organic substances of natural origin with a greater or lesser degree of basic character.[53] To date, there is no precise definition of an alkaloid. The term may generally apply to naturally occurring nitrogen-containing compounds, excluding the amino acids of primary metabolism, complex peptides and proteins constructed from those amino acids, and nucleic acids.[55]

The total number of alkaloids thus far isolated from various sources (plants, fungi, bacteria, marine organisms, *etc.*) is enormous (ca. 50, 000).[53,56] These alkaloids can be classified into five distinct alkaloid classes, according to the position of the N-atom in the main structural element (Figure 1.2):[53,57,58]

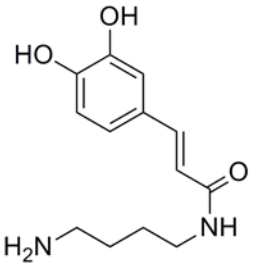
i. Heterocyclic alkaloids
ii. Alkaloids with exocyclic N-atoms and aliphatic amines (*e.g.*, (–)-cassaine, colchicine)
iii. Putrescine, spermidine, and spermine alkaloids (*e.g.*, paucine, inandenin-12-one, chaenorhin)
iv. Peptide alkaloids (*e.g.*, integerrine, mucronine A)
v. Terpene and steroid alkaloids (*e.g.*, aconitine, samandarine)



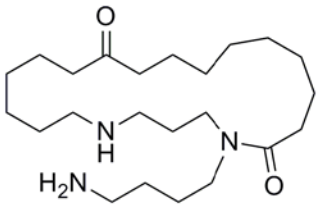
(–)-Cassaine



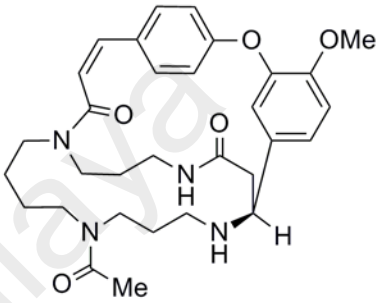
(+)-Colchicine



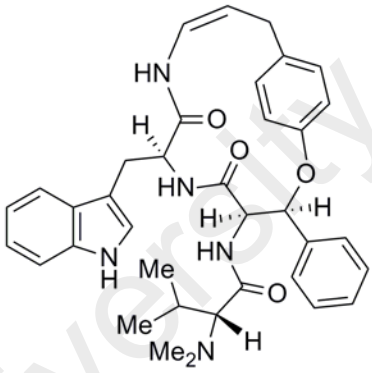
Paucine



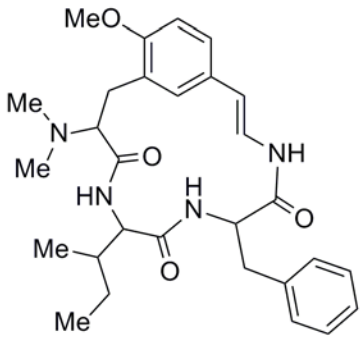
Inandenin-12-one



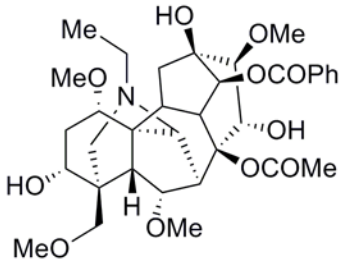
(+)-Chaenorhin



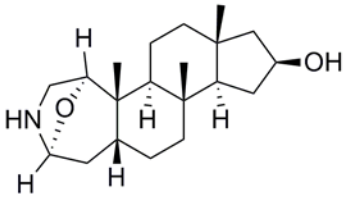
Integerrine



Mucronine A



(+)-Aconitine



Samandarine

Figure 1.2: Examples of alkaloids from the five alkaloid classes

Among the five classes, the heterocyclic alkaloids constitute the largest group and in common usage the term alkaloids usually refer to the heterocyclic alkaloids. These can be further divided into 15 subclasses based on the carbon-nitrogen skeleton as shown below (Figure 1.3):[53,57,58]

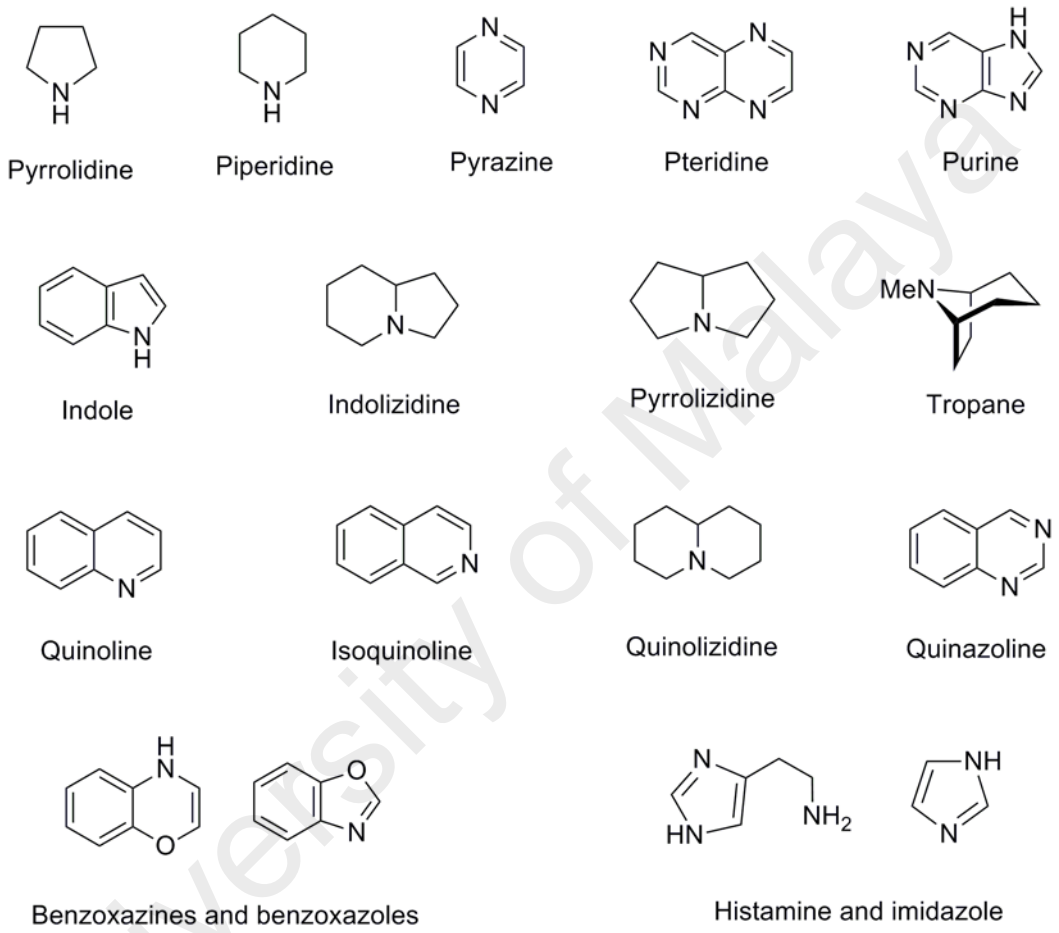


Figure 1.3: Subclasses (15) of the heterocyclic alkaloids

1.3 Indole Alkaloids of the Apocynaceae

1.3.1 General

The indole alkaloids constitute the biggest single class of the alkaloids and account for about 20% of all known alkaloids.[53,56–58] This figure includes both those compounds that incorporate the actual indole chromophore and those containing its derivatives: namely indoline (also known as dihydroindole), indolenine, hydroxyindolenine, α-methylideneindoline, pseudoindoxyl, and oxindole (Figure 1.4). Also members of this group are alkaloids in which the nucleus incorporates an additional benzene or pyridine ring, for instance, carbazole, or β- and γ-carbolines, and their derivatives (Figure 1.4).[53,57,58]

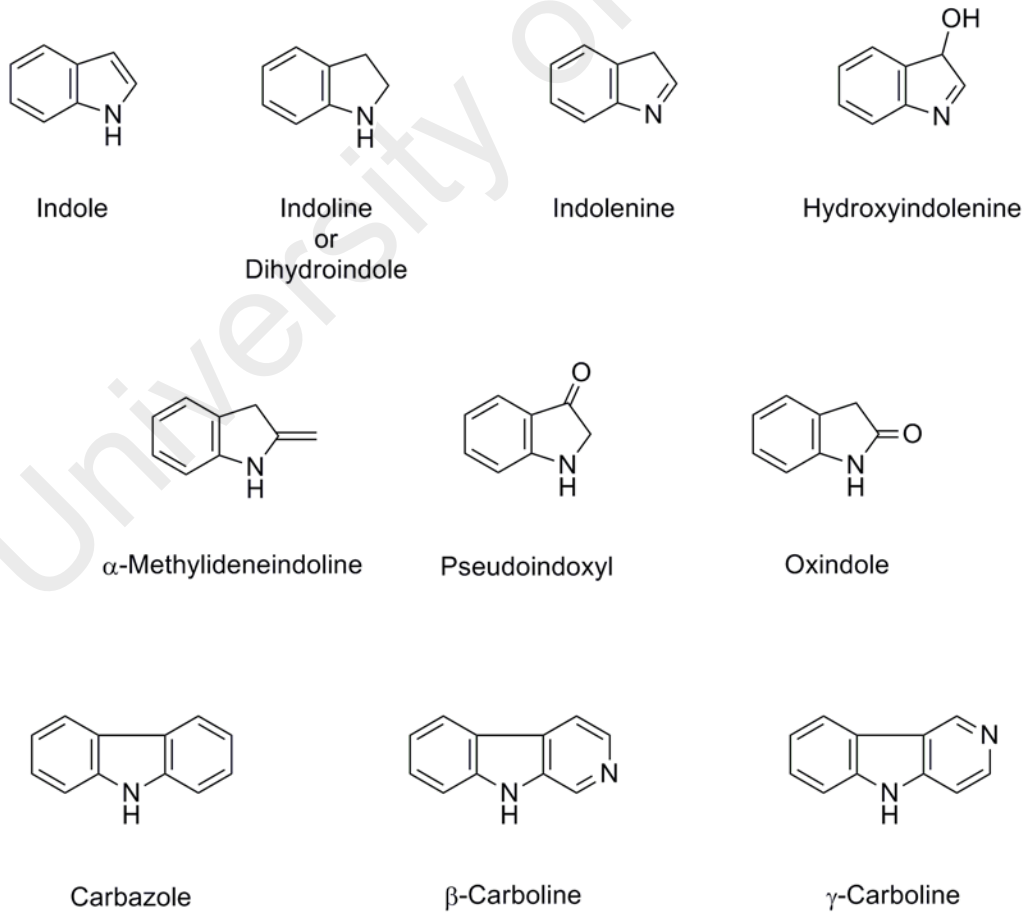


Figure 1.4: Indole and its derivatives

1.3.2 Classification of the Indole Alkaloids

Indole alkaloids can be further subclassified based on structural and biogenetic criteria. In general, the indole alkaloids can be divided into two main classes with respect to their structural features. The first comprises the simple indole alkaloids, which do not present a structural uniformity, having only the indole nucleus or a direct derivative of it as a common feature (*e.g.*, harmane). Indole alkaloids of the second class, which are known as the monoterpene indole alkaloids, contain two structural units, *viz.*, tryptamine (or tryptophan) with the indole nucleus and a C_9- or C_{10}-monoterpene moiety derived from secologanin (Figure 1.5). The majority of the indole alkaloids from plants are from this category.[53,57,58]

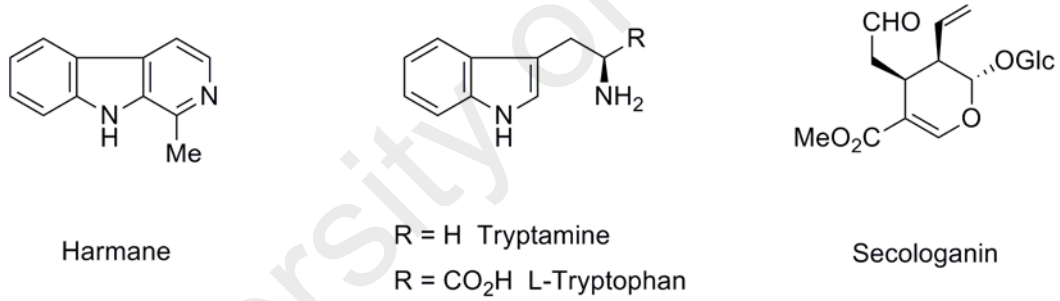


Figure 1.5: Harmane, tryptamine/L-tryptophan, and secologanin

The monoterpene indole alkaloids share a common biogenetic origin, namely strictosidine, which is a condensation product of secologanin and tryptamine.[59–61] On the basis of their biogenesis they have been structurally grouped into ten main skeletal types: corynanthean (C), vincosan (D), vallesiachotaman (V), strychnan (S), aspidospermatan (A), eburnan (E), plumeran (P), heynean (H), capuronan (K), and tacaman (T) (Figure 1.6).[62–102] Indole alkaloids of the C-, D-, V-, S-, and A-types contain skeletons with a non-rearranged secologanin moiety, while alkaloids of E-, P-, H-, and J-types contain skeletons with a rearranged secologanin moiety. The plausible

biogenetic relationships among these alkaloids are shown in Scheme 1.1.[53,57,58,62–65] The ten main skeletal types can be further subdivided according to the increasing complexity of their basic carbon skeletons.

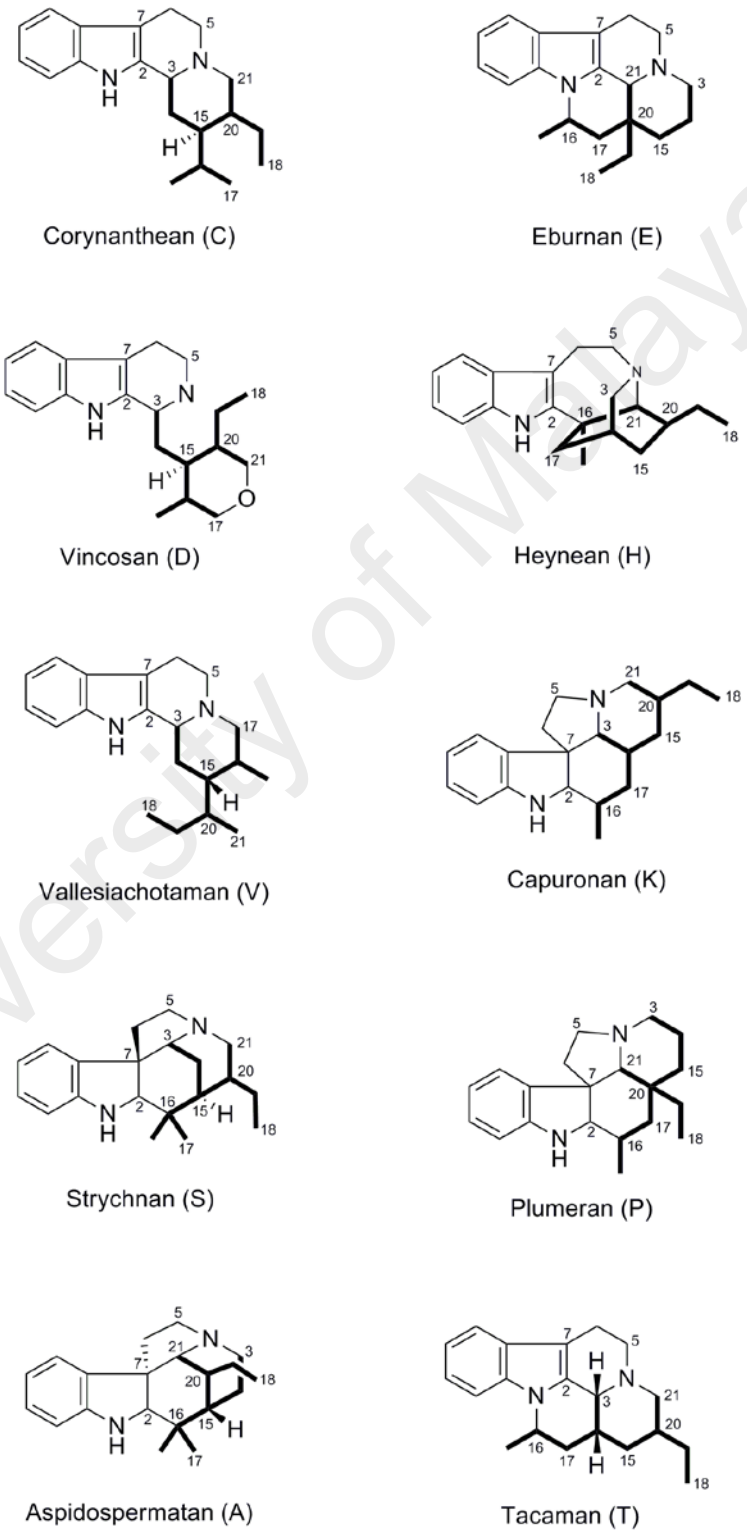
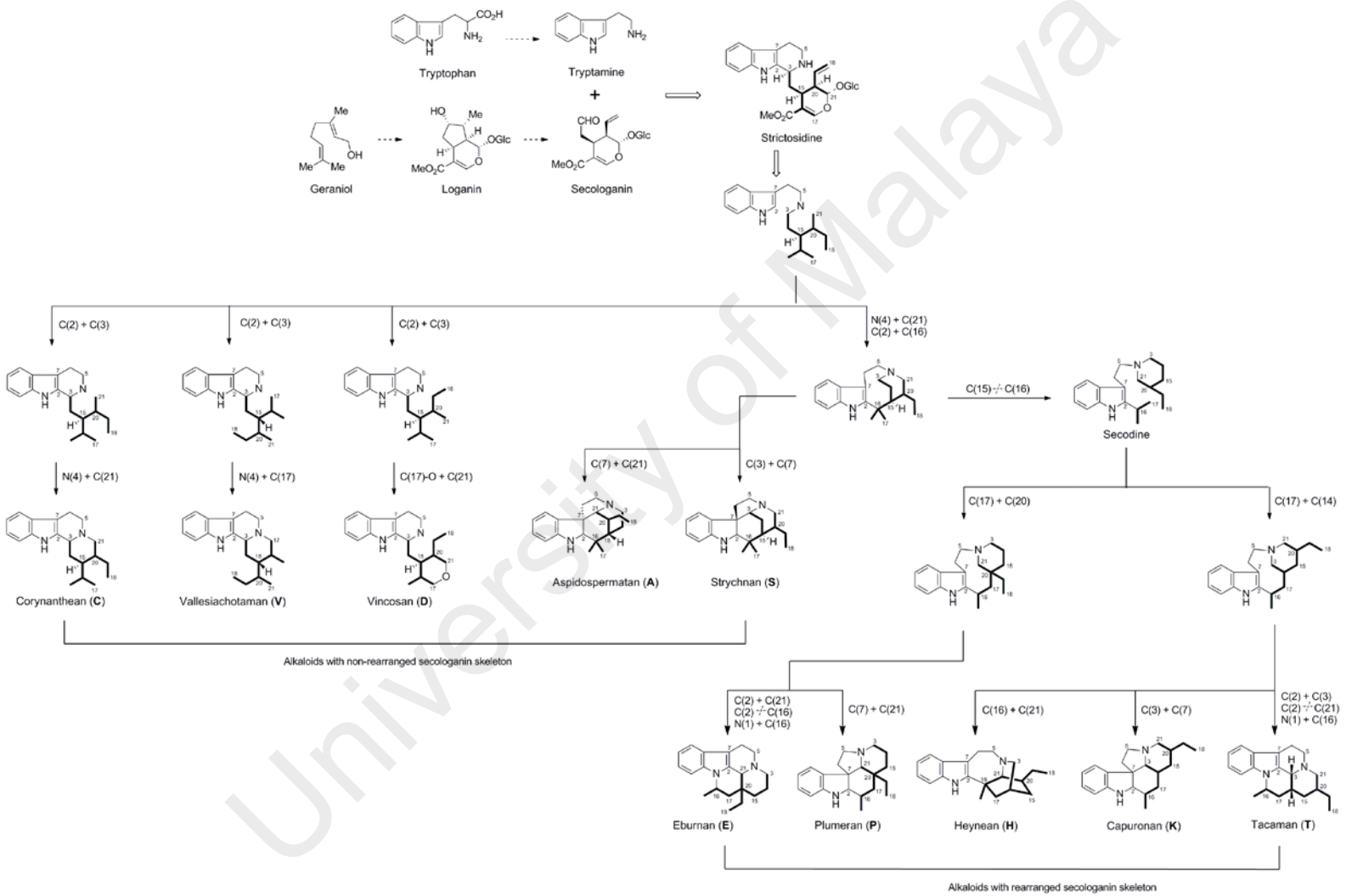


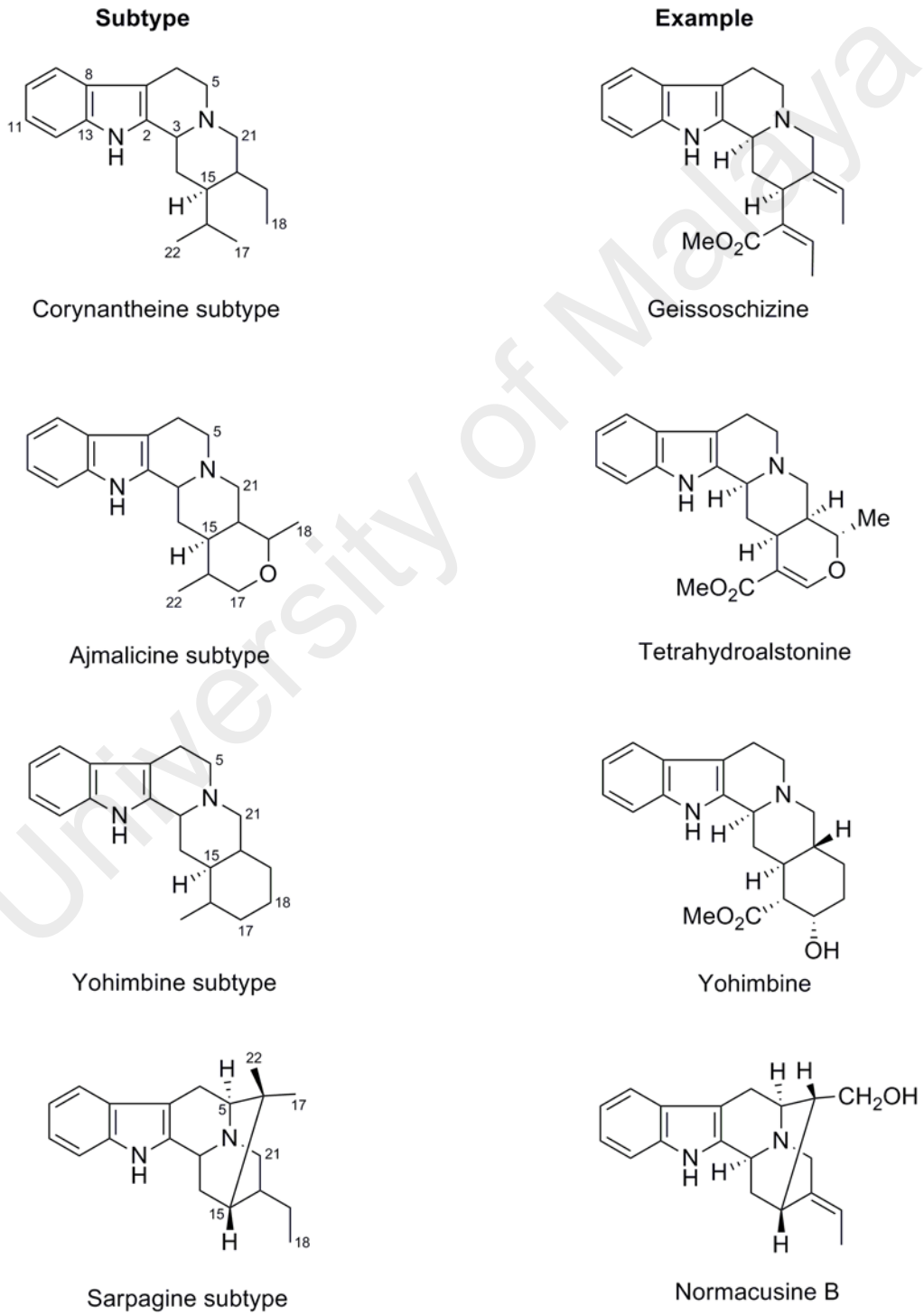
Figure 1.6: Classification of the monoterpenoid indole alkaloids

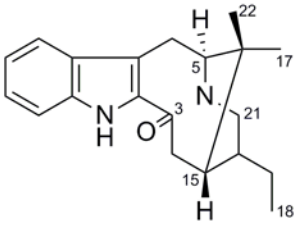
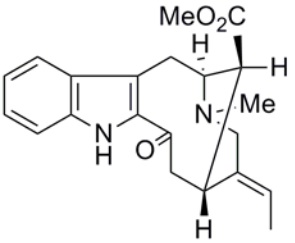
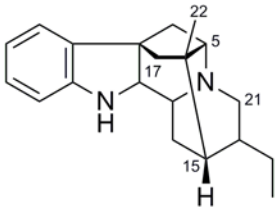
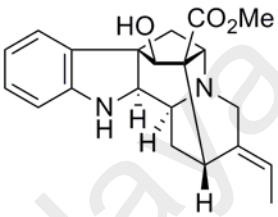
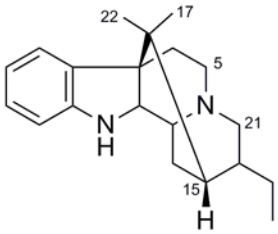
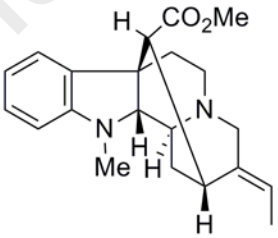
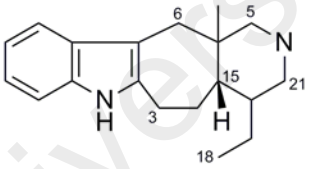
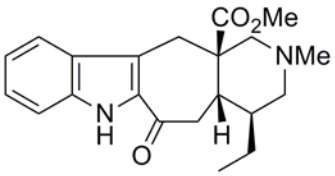
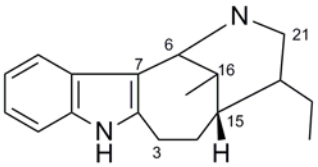
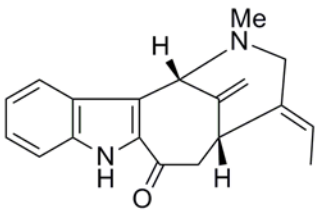


Scheme 1.1: Biogenetic inter-relationship of the ten main skeletal types of indole alkaloids with C_9- or C_{10}-monoterpene components

1.3.3 Alkaloids of the Corynanthean (C) Type

The corynanthean group of alkaloids is the largest group of indole alkaloids found in the Apocynaceae.[62–64,66,103–106] The main subtypes and their respective examples are given in Figure 1.7.



Subtype	Example
 Vobasine subtype	 Vobasine
 Ajmaline subtype	 Quebrachidine
 Akuammiline subtype	 Cathafoline
 Ervatamine subtype	 Ervatamine
 Ervitisine subtype	 Ervitisine

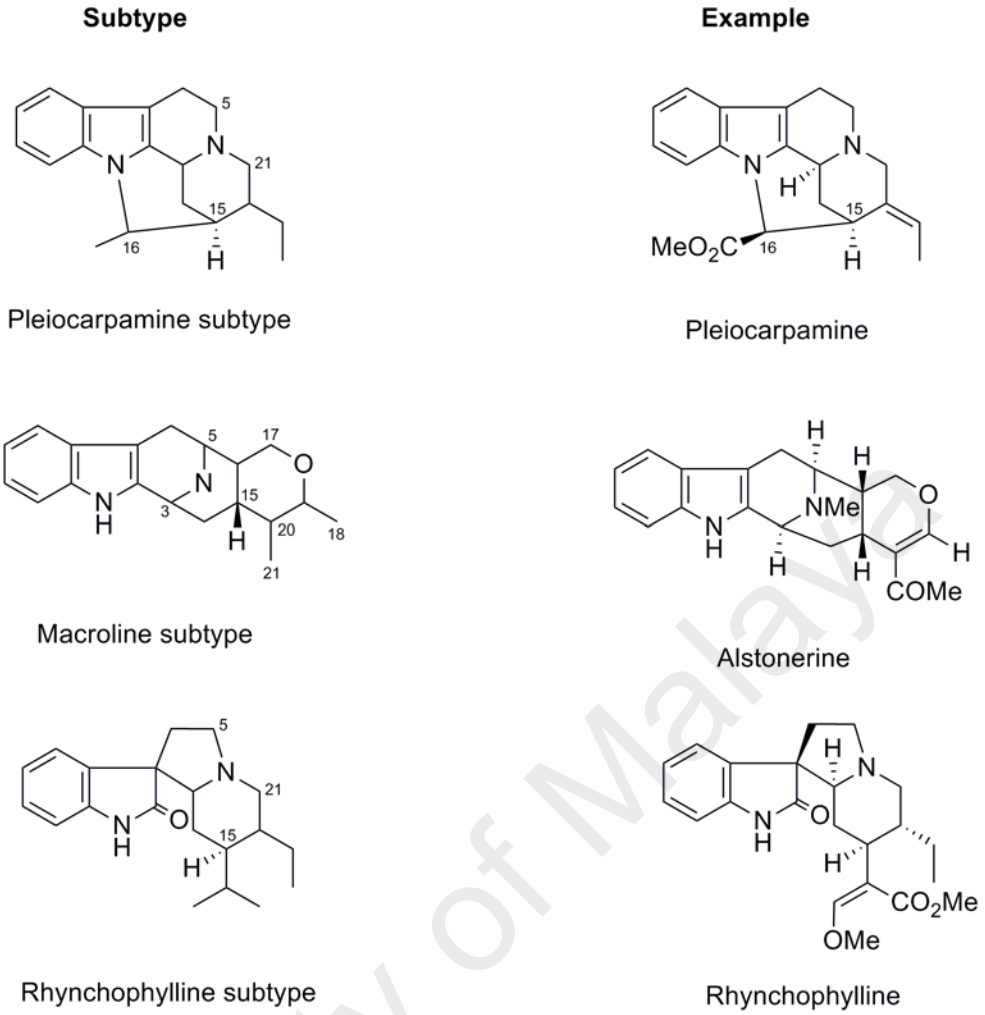


Figure 1.7: Main skeletal subtypes of the corynanthean alkaloids

1.3.4 Alkaloids of the Vallesiachotaman (V) Type

The vallesiachotaman alkaloids are small group of indole alkaloids which share a common precursor with the corynanthean alkaloids.[62–64,66,103–106] Alkaloids of this group can be further classified into three main subtypes, namely, vallesiachotamine, angustine, and camptothecin as shown in Figure 1.8.

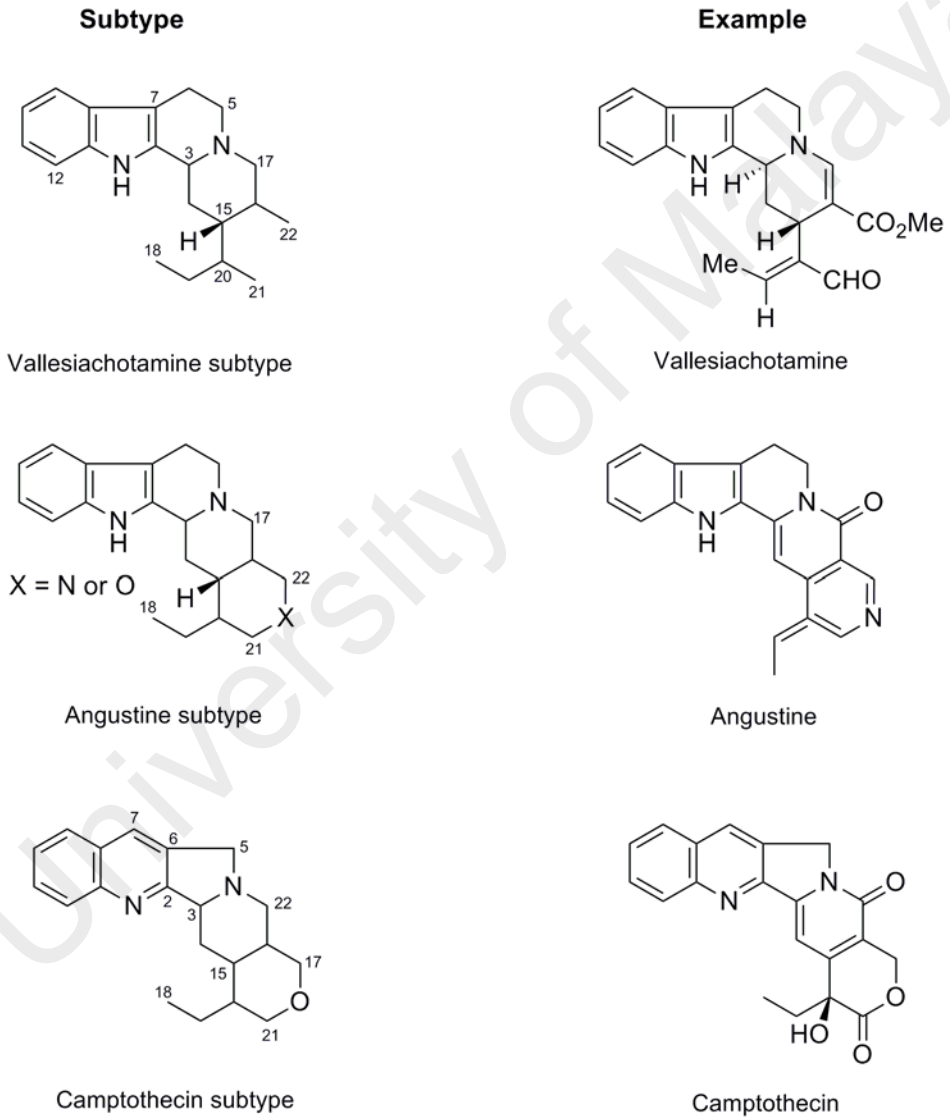
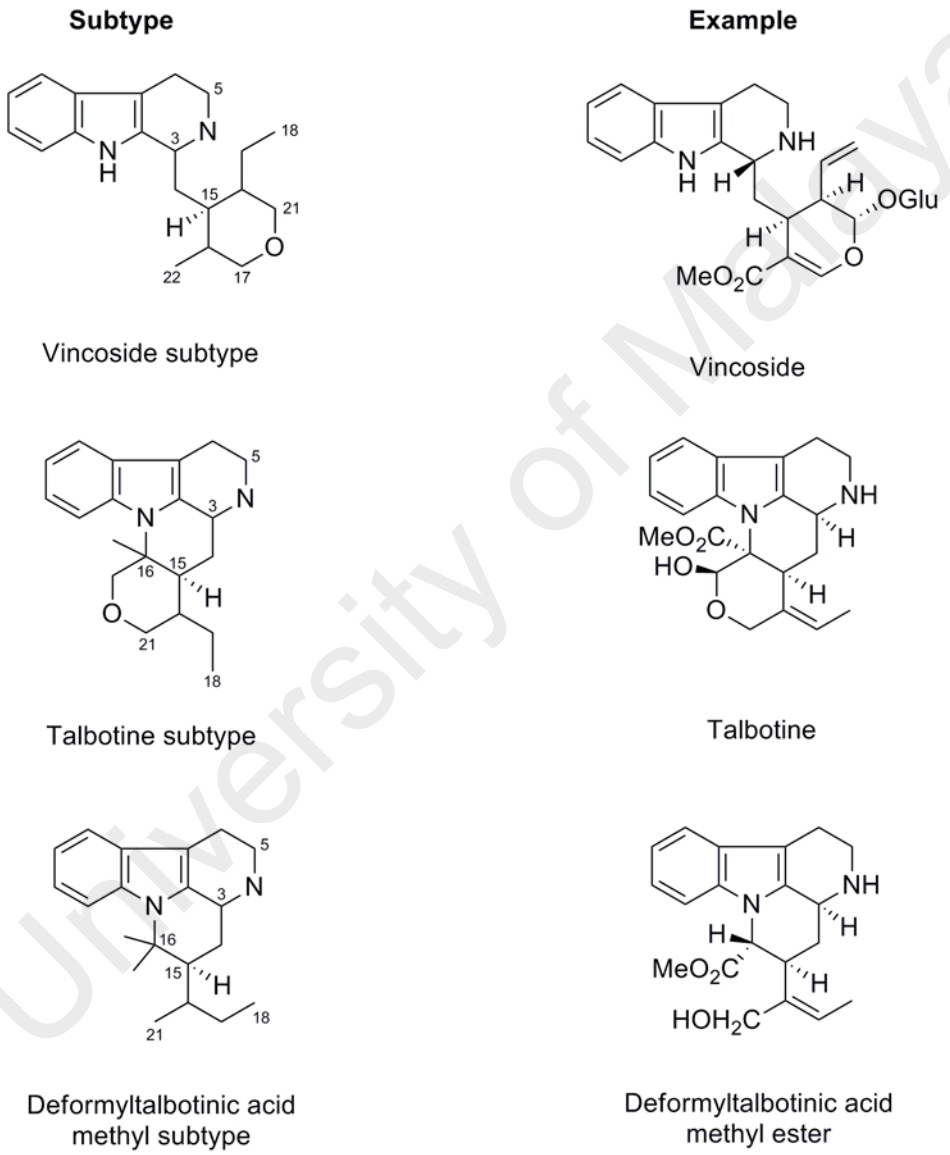


Figure 1.8: Main skeletal subtypes of the vallesiachotaman alkaloids

1.3.5 Alkaloids of the Vincosan (D) Type

There are only a small number of vincosan alkaloids[62–64,66,103–106] which were isolated from the Apocynaceae and are subdivided into five subtypes, namely, vincoside, talbotine, deformyltalbotinic acid methyl ester, perakine, and peraksine (Figure 1.9).



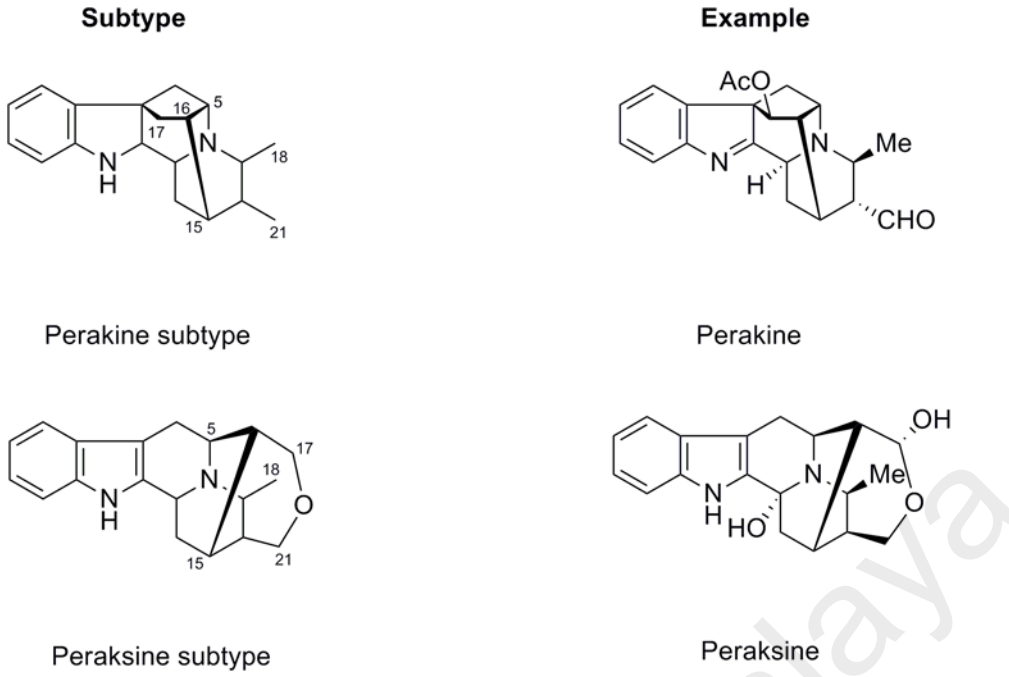


Figure 1.9: Main skeletal subtypes of the vincosan alkaloids

1.3.6 Alkaloids of the Strychnan (S) Type

The strychnan alkaloids, which occur predominantly in the *Strychnos* species of the Loganiaceae family, show considerable variation in the skeletal framework.[62,63] However, the majority of the alkaloids isolated from the Apocynaceae are of the akuammicine subtype, which is also the simplest skeletal subtype of this group (Figure 1.10).[107]

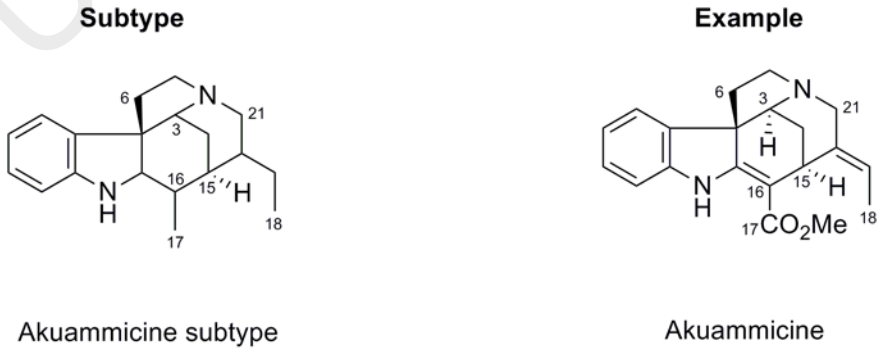
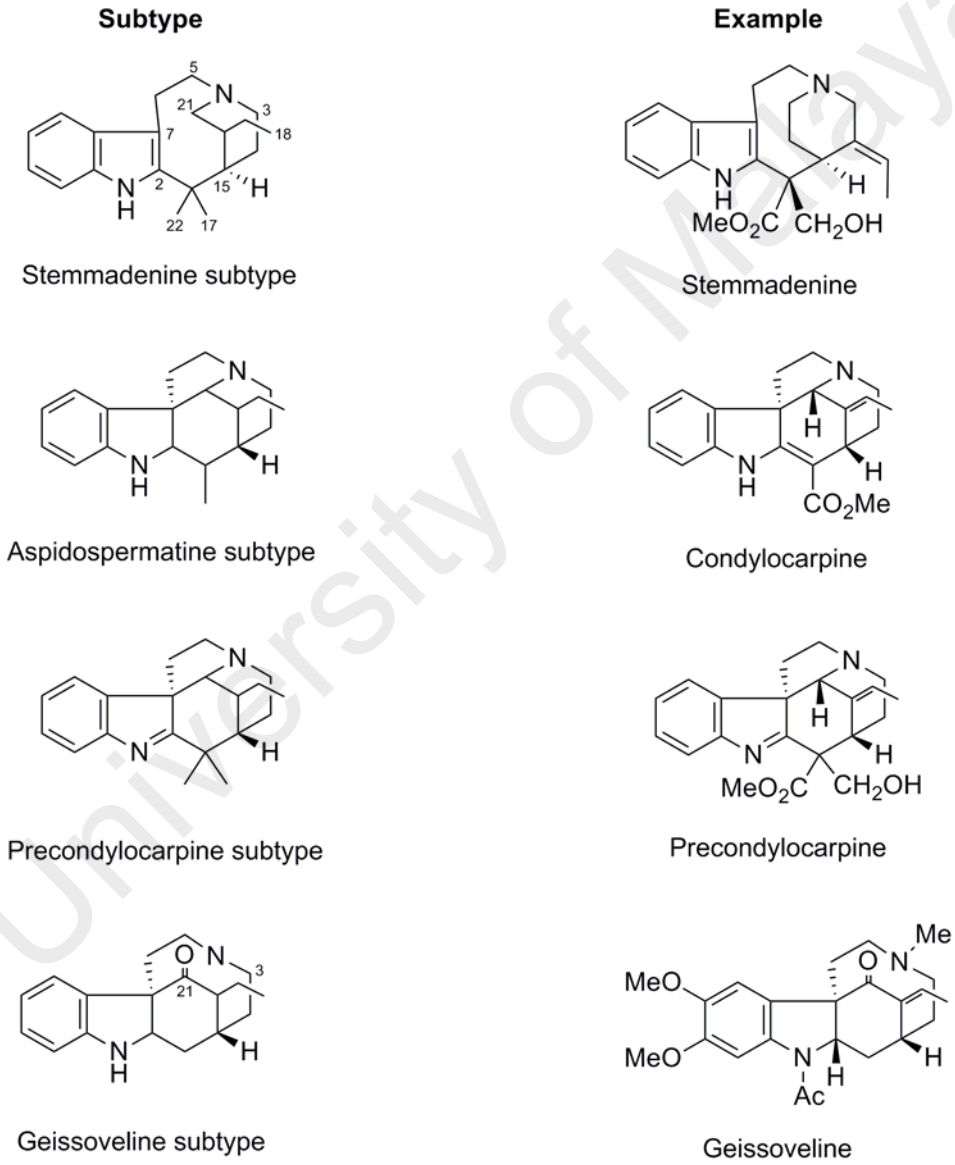


Figure 1.10: Main skeletal subtypes of the strychnan alkaloids

1.3.7 Alkaloids of the Aspidospermatan (A) Type

The aspidospermatan alkaloids[62–64,66,103–106] are further divided into seven main subtypes based on the variations in the carbon skeleton, namely, stemmadenine, aspidospermatine, precondylocarpine, geissovelline, dichotine, ellipticine, and olivacine (Figure 1.11).



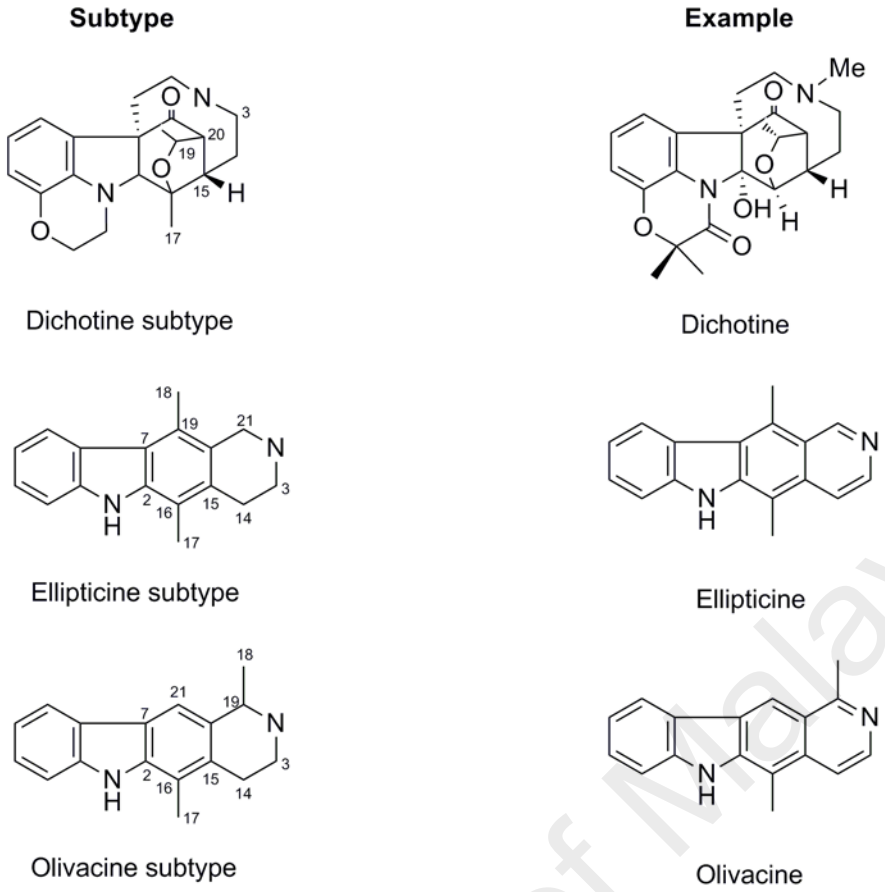


Figure 1.11: Main skeletal subtypes of the aspidospermatan alkaloids

1.3.8 Alkaloids of the Eburnan (E) Type

The eburnan group of alkaloids can be divided into three subgroups.[108] Two of these subgroups, namely, eburnamine and vincamine originate from the α condensation of tryptamine with the rearranged secologanin skeleton, followed by cyclization onto N-1. The third group is represented by the schizogamine subtype. The structures of these skeletal subtypes are shown in Figure 1.12.[62–64,66,103–106]

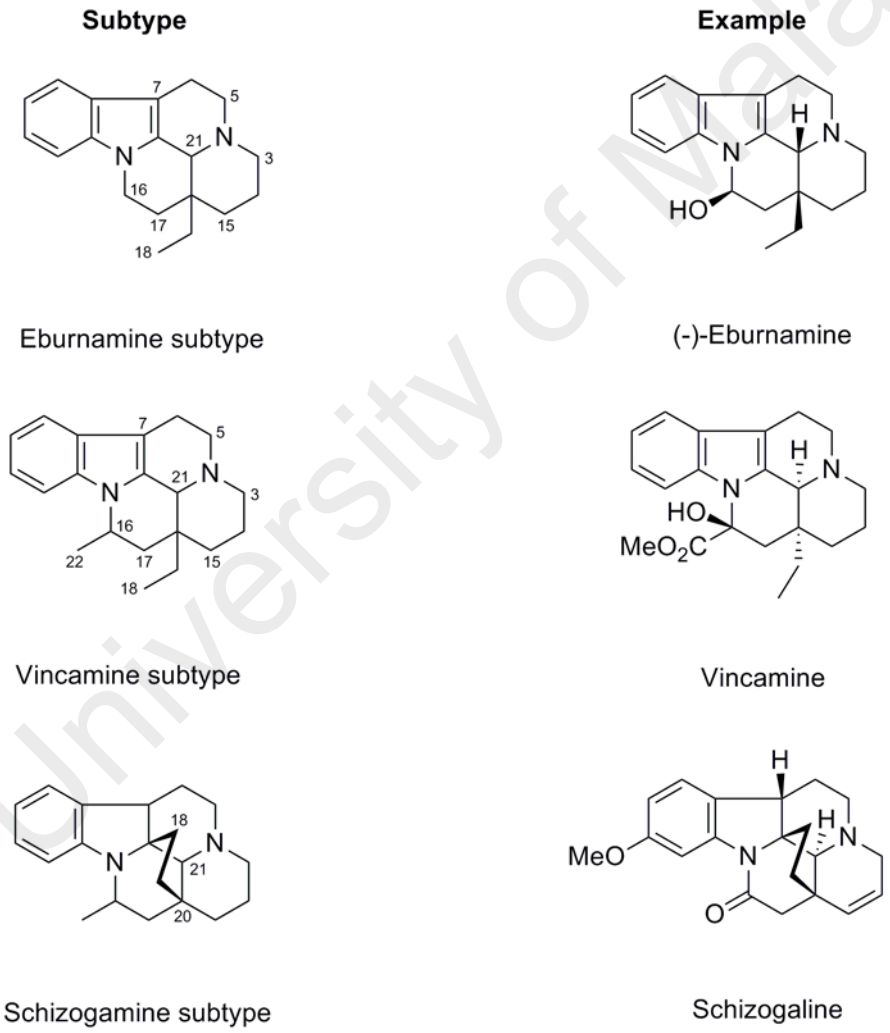
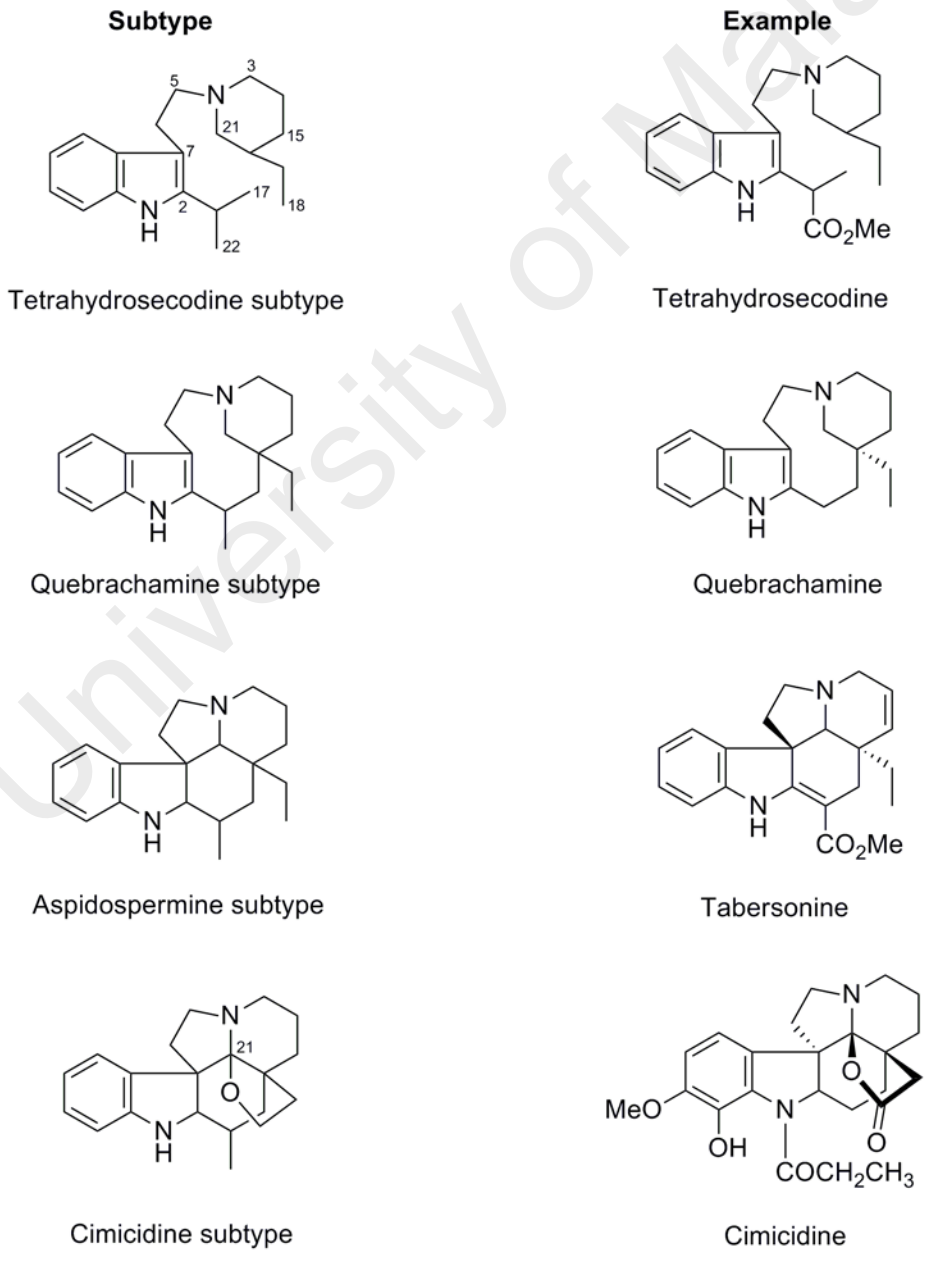
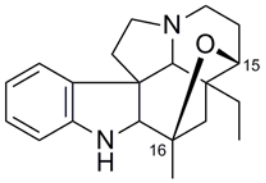
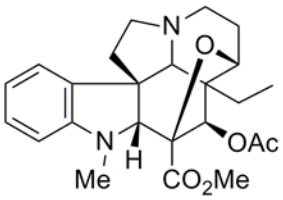
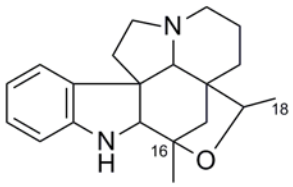
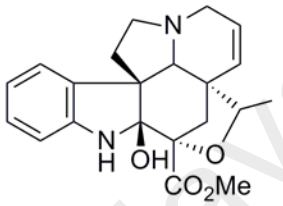
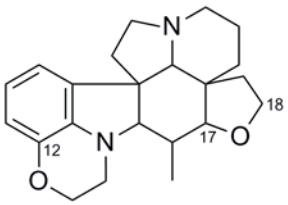
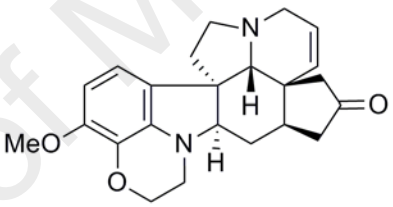
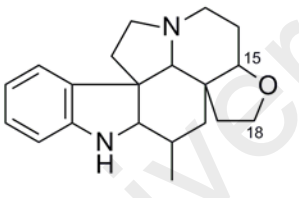
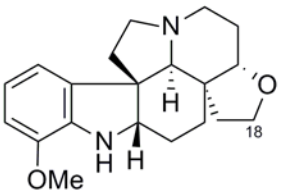
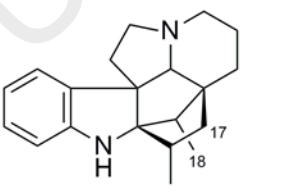
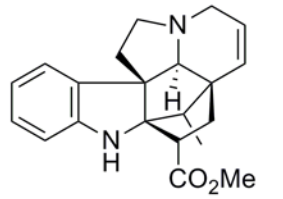


Figure 1.12: Main skeletal subtypes of the eburnan alkaloids

1.3.9 Alkaloids of the Plumeran (P) Type

The plumeran alkaloids constitute the second largest group of the indole alkaloids after the corynanthean group and are characterized by a rich variation of the carbon skeleton.[62–64,66,103–106,109,110] The alkaloids of the plumeran type are found exclusively from the subfamily Plumerioideae of the Apocynaceae which accounts for the name given to this group of alkaloids.[62,63] The plumeran alkaloids can be further grouped into 13 subtypes and are shown in Figure 1.13.



Subtype	Example
	
Cathovaline subtype	Cathanneine
	
Vincoline subtype	Vincoline
	
Neblinine subtype	Neblinine
	
Beninine subtype	Beninine
	
Vindolinine subtype	Vindolinine

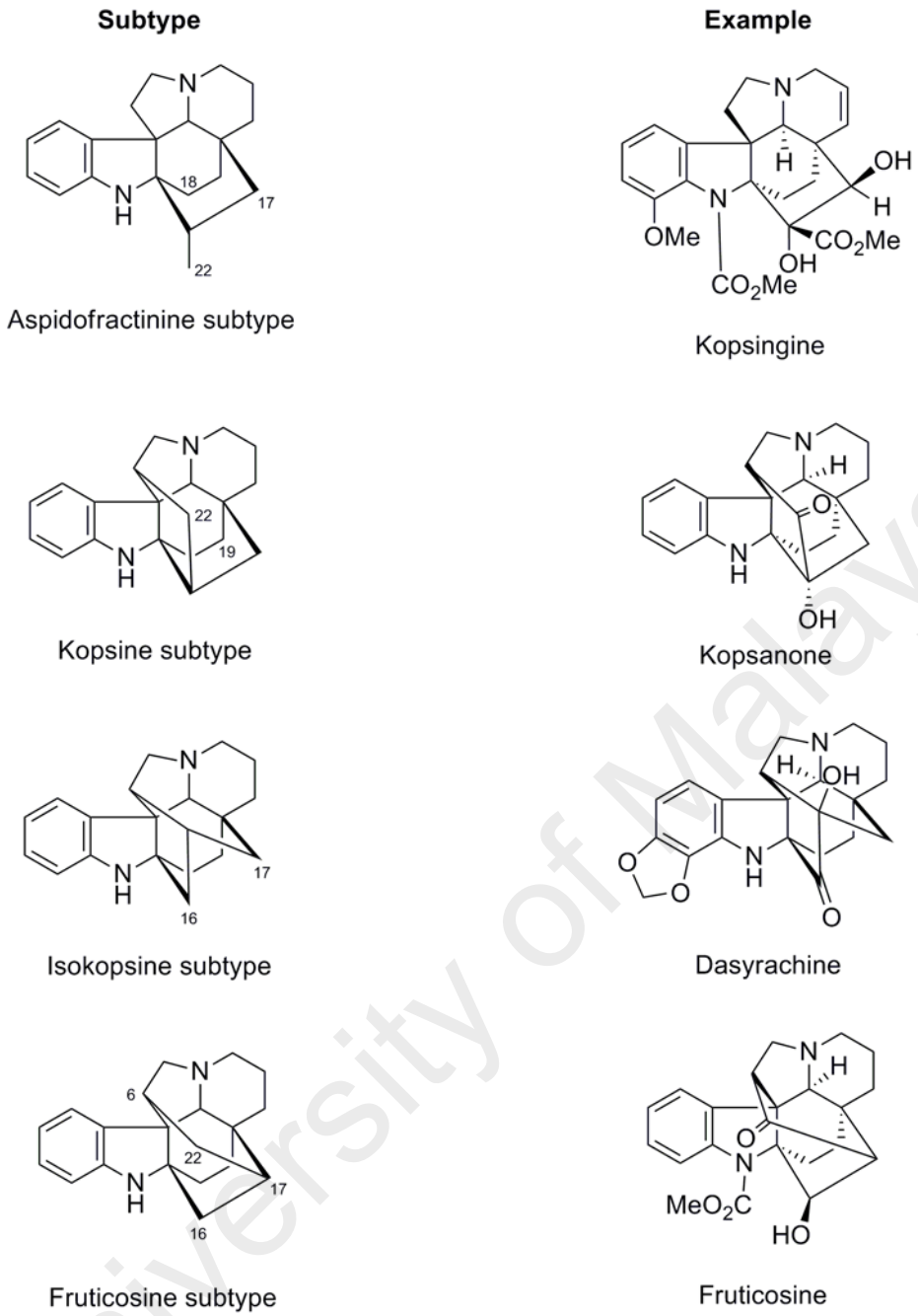


Figure 1.13: Main skeletal subtypes of the plumeran alkaloids

1.3.10 Alkaloids of the Heynean (H) Type

Hesse has further divided the ibogan or (J) group into two new main groups, namely, heynean (H) and capuronan (K), based on the structure types found as well as from biogenetic considerations. The heynean alkaloids can be further subdivided into four structure subtypes as shown in Figure 1.14.[62–64,66,103–106,109,111]

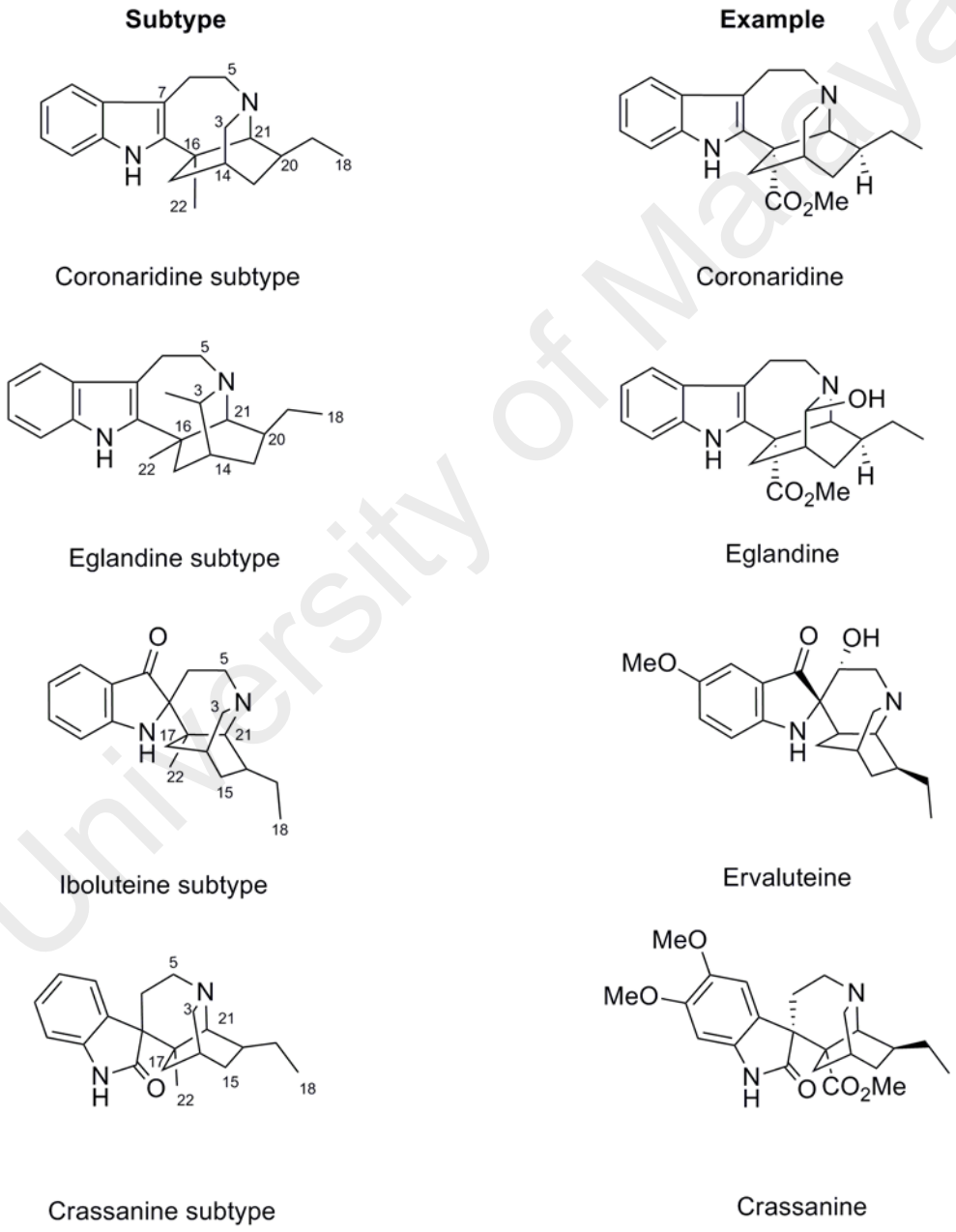


Figure 1.14: Main skeletal subtypes of the heynean alkaloids

1.3.11 Alkaloids of the Capuronan (K) Type

The capuronan alkaloids are distinguished from the heynean type alkaloids by the absence of the C-16–C-21 linkage. The main subtypes of capuronan alkaloids are as shown in Figure 1.15.[62–64,66,103–106,109,111]

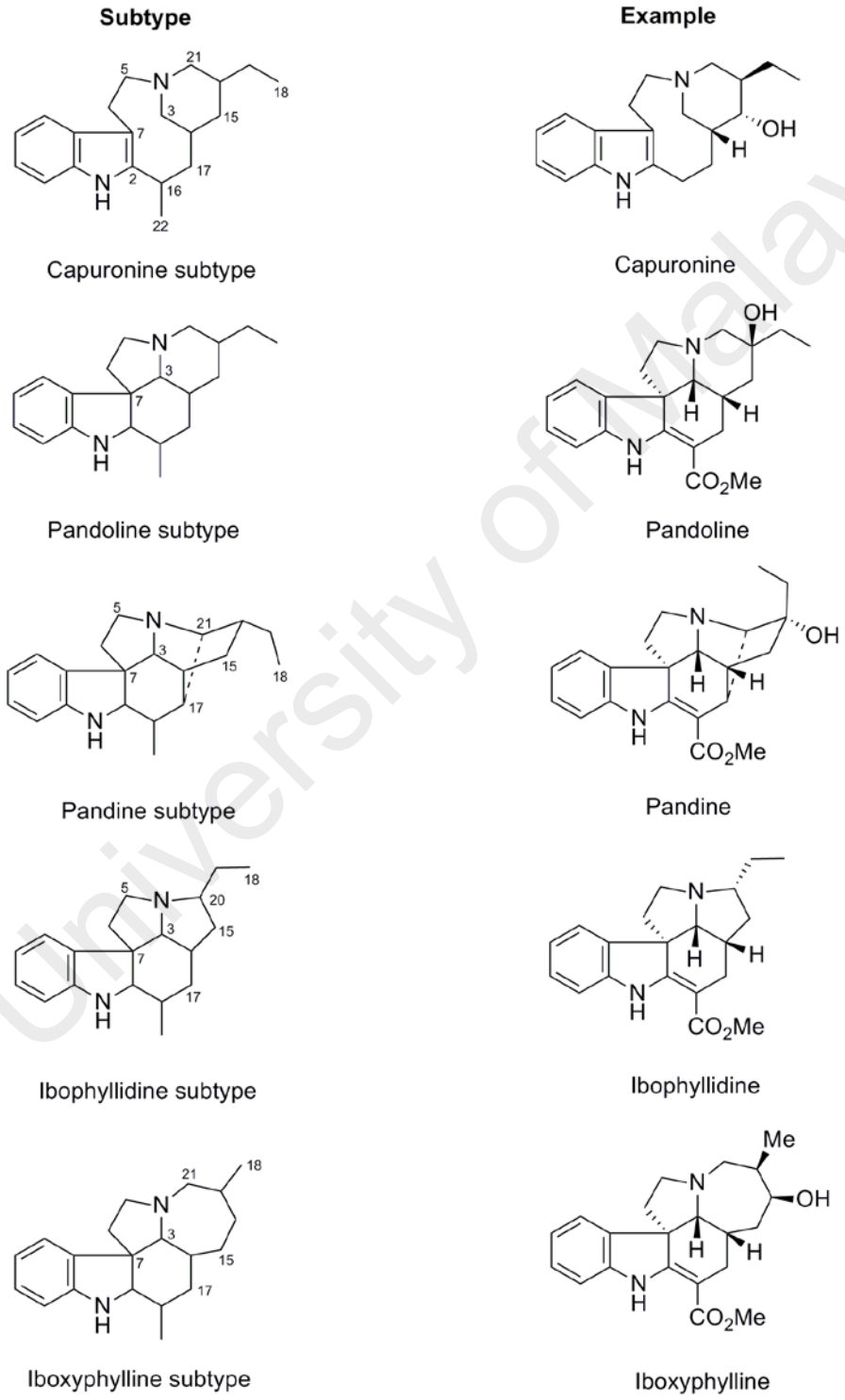


Figure 1.15: Main skeletal subtypes of the capuronan alkaloids

1.3.12 Alkaloids of the Tacaman (T) Type

The tacaman group of alkaloids was added by Verpoorte and Van Beek (1984) as one of the main skeletal groups to account for the isolation of several tacamines from *Tecoma* species.[64,65] To date, the tacaman group of alkaloids are limited to only one skeletal type as shown in Figure 1.16. [62–64,66,103–106,109]

Figure 1.16: Main skeletal subtype of the tacaman alkaloids

1.4 The Genus *Tabernaemontana*

1.4.1 General

The genus *Tabernaemontana* L. (tribe Tabernaemontaneae of the subfamily Rauvolfioideae (or Plumerioideae) of the family Apocynaceae)[112,113] is a large genus with about 110 species, which are distributed throughout the tropical and some subtropical parts of the world (18 in Africa, 15 in Madagascar, one in the Mascarene Island, 55 in America, and 21 in Asia, Oceania and Australia), as well as the only genus that is distributed over the whole tropical part of the world.[113] The species abundance, coupled with the wide geographical distribution and the large number of synonyms of this genus, have in the past given rise to considerable confusion regarding their taxonomic classification. These difficulties have been resolved to a considerable extent by the comprehensive review of this genus (the Old World species) by Leeuwenberg, based on the examination of herbarium (mainly) as well as living specimens in the wild.[65,113] This has resulted in a significant reduction in the number of species as well as the realization that many genera are more closely related to the genus than previously thought. A list of the synonyms of the genus *Tabernaemontana* is given in Table 1.1.[64,65,113]

Plants of the genus *Tabernaemontana* are usually shrubs or trees of primary dry-land forest below 3000 m, and are repeatedly dichotomously branched from low down. The trunk is terete, rarely with buttresses on large trees, and the bark is pale to dark-grey or brown, smooth or rough with large lenticels and white latex. The leaves are opposite to each other and petiolate or sometimes sessile. The flowers have 5-merous, actinomorphic except for the subequal sepals and are sweet-scented. The fruits are

composed of two separate or less often basally united mericarps, one of which sometimes remains small or not developed.[113]

Table 1.1: Synonyms of the Genus *Tabernaemontana*

Anacampta	*Hazunta*	*Phrissocarpus*
Anartia	*Leptopharyngia*	*Protogabunia*
Bonafousia	*Merizadenia*	*Pterotaberna*
Camerunia	*Muntafara*	*Quadricasaea*
Capuronetta	*Ochronerium*	*Rejoua*
Codonemma	*Oisthanthera*	*Sarcopharyngia*
Conopharyngia	*Pagiantha*	*Stenosolen*
Domkeocarpa	*Pandaca*	*Taberna*
Ervatamia	*Pandacastrum*	*Testupides*
Gabunia	*Peschiera*	

The *Tabernaemontana* species found in Malaysia are listed below.[113,114]

I. *T. antheonycta* Leeuwenberg
II. *T. corymbosa* Roxb. ex Wall.
III. *T. crispa* Roxb. ex Wall.
IV. *T. dichotoma* Roxb. ex Wall.
V. *T. divaricata* (L) R. Br. ex Roem. & Schult.
VI. *T. hirta* Hook. f.
VII. *T. macrocarpa* Jack
VIII. *T. malaccensis* Hook. f.
IX. *T. pandacaqui* Lam.
X. *T. pauciflora* Bl.
XI. *T. peduncularis* Wall.
XII. *T. polyneura* (King & Gamble) D. J. Middleton
XIII. *T. polysperma* Merr.

Plants of this genus are widely used in traditional medicine, ranging from decoctions for washing wounds to steam-baths for curing syphilis. In addition, they also have other non-medicinal applications, such as the use of root extracts as ingredients in arrow poisons and latex as birdlime.[64,65] In the chemical screening of *Tabernaemontana* species, alkaloids are usually found as the major active components, while other important secondary metabolites are only found occasionally. In recent studies, plants of this genus have been found to be prodigious producers of alkaloids, in particular indole and bisindole alkaloids with many structurally novel skeletons and useful biological activities.

1.4.2 Alkaloids of the Genus *Tabernaemontana*

Plants of the genus *Tabernaemontana* produce a vast variety of indole alkaloids. The major alkaloids found in *Tabernaemontana* species are mainly of the corynanthean (C), plumeran (P), and heynean (H) [or iboga] types. The H-type seems to be characteristic of all *Tabernaemontana* plants, being found in almost all species. No vincosan (D) alkaloids were found in *Tabernaemontana* species thus far, and only a few examples of vallesiachotaman (V), strychnan (S), aspidospermatan (A), eburnan (E), and tacaman (T) type alkaloids have been detected. In addition to monomeric compounds, many bisindole alkaloids with useful bioactivities were also obtained from plants of this genus.[64,65,105,115,116]

1.4.3 Occurrence and Distribution of Alkaloids in the Genus *Tabernaemontana*

The occurrence of alkaloids in *Tabernaemontana* as reported in the literature (up to Dec. 2015) is summarized in Table 1.2.

Table 1.2: Occurence of Alkaloids in *Tabernaemontana*

Plant	Plant part	Alkaloids	References
T. accedens Müll. Arg. (*Peschiera accedens*)	Root-bark	Accedine (**171**)	117,118
		Accedinine (**588**)	119
		Accedinisine (**586**)	119
		Affinisine (**136**)	119
		N(1)-Demethyl-16-*epi*-accedine (**172**)	120
		N(4)-Demethylvoacamine (**489**)	119
		N(1)-Methyl-16-*epi*-affinine (**165**)	117
		Voacamidine (**442**)	119
		Voacamine(**485**)	119
		Voacamine *N*-oxide (**486**)	119
T. affinis Müll. Arg. (*P. affinis*)	Root-bark	Affinine (**164**)	121,122
		Affinisine (**136**)	121–123
		Coronaridine (**16**)	123
		Coronaridine pseudoindoxyl (**405**)	123
		19-*Epi*-heyneanine (**321**)	123
		Heyneanine (**17**)	123
		19(*R*)-Hydroxyibogamine (**15**)	124
		Iboxygaine (**362**)	124
		Olivacine (**65**)	123,125
		Vobasine (**48**)	121
		Voacangine (**18**)	124
		Voacristine (= Voacangarine) (**19**)	124
	Roots, stems	Affinisine (**136**)	126
		Coronaridine (**16**)	126
		Iboxygaine (**362**)	126
		Voacangine (**18**)	126
		Voacristine (= Voacangarine) (**19**)	126
		Voacristine hydroxyindolenine (**393**)	126
T. alba Mill.	Seeds	Coronaridine (**16**)	127
		Tabersonine (**216**)	127
T. albiflora (Miq.) Pulle	Stem-bark	(–)-Albifloranine (**331**)	128
		Coronaridine (**16**)	129
		(+)-20(*R*)-18,19-Dihydroxy-pseudovincadifformine (**262**)	130
		Desethylibophyllidine (**278**)	129
		20-*Epi*-ibophyllidine (**274**)	129
		18-Hydroxy-20-*epi*-ibophyllidine (**275**)	131
		19(*R*)-Hydroxy-20-*epi*-ibophyllidine (**276**)	131
		19(*S*)-Hydroxy-20-*epi*-ibophyllidine (**277**)	131

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		19-Hydroxyibophyllidine (**281**)	131
		(+)-19-Hydroxy-20-*epi*-pandoline (**263**)	130
		Ibophyllidine (**279**)	129
T. amblyocarpa Urb.	Stems	(+)-Tubotaiwine (**213**)	132
		Vallesamine (**103**)	132
		Voacristine (= Voacangarine) (**19**)	132
	Leaves, stems, flowers	19-Oxovoacangine (**367**)	133–136
		Heyneanine (**17**)	133,134,136
		Ibogamine (**13**)	132–134,136
	Stems, flowers	Iboxygaine (**362**)	134,135
		Voacangine (**18**)	132,133,137
	Leaves, flowers	Coronaridine (**16**)	132,133,137
		Isovoacristine (**368**)	132,137
	Leaves, stems	Isovoacangine (**318**)	132,135
	Leaves	Akuammidine (**144**)	132
	Flowers	Tabersonine (**216**)	134
T. amygdalifolia Jacq.	Roots	Coronaridine (**16**)	138
		Cylindrocarpidine (**236**)	138
		12-Demethylaspidospermine (**235**)	138
		12-Demethoxycylindrocarpidine (**237**)	139
		O-Demethylpalosine (**240**)	140
		Homocylindrocarpidine (**238**)	139
		5-Oxocylindrocarpidine (**239**)	138
		Voacangine (**18**)	138
T. angulata Mart. (*Anacampta angulata*)	Bark	Voacristine-7-hydroxyindolenine (**393**)	141
	Stem	Coronaridine (**16**)	142
		Voacangine (**18**)	142
T. apoda Wr. ex Sauv. (*T. armeniaca*, *Peschiera apoda*)	Leaves, flowers	Apodine (**244**)	143,144
		Voacristine (= Voacangarine) (**19**)	145,146
		Voacristine-7-hydroxyindolenine (**393**)	145,146
	Leaves, roots, flowers	Coronaridine (**16**)	144,147,148
		Ibogamine (**13**)	147–149
		Voacangine (**18**)	147–150
	Root-bark, flowers	Voacangine-7-hydroxyindolenine (**390**)	145,151
		Voacangine pseudoindoxyl (= Voaluteine) (**406**)	150,152
	Fruits	Ibogaine-7-hydroxyindolenine (**396**)	150
		Iboluteine (= Ibogaine pseudoindoxyl) (**411**)	150
		Voacristine pseudoindoxyl (**407**)	145

Table 1.2, continued

Plant	Plant part	Alkaloids	References
	Leaves	Apodinine (**245**)	151
		Deoxoapodine (**28**)	144
	Root-bark	Heyneanine (**17**)	152
	Leaves, roots	Isovoacangine (**318**)	148,149
T. arborea Rose	Seeds	Isovoacangine (**318**)	153
		Tabersonine (**216**)	153
	Latex, trunk	19-*Epi*-voacristine (= 19-*Epi*-voacangarine) (**366**)	154,155
		Vobasine (**48**)	154,155
		19(*R*)-Hydroxyconopharyngine (**369**)	154,155
	Twigs	Conopharyngine (**319**)	155
	Latex, trunk	19-*Epi*-voacorine (**491**)	155,156
	Latex, leaves	Voacamine (**485**)	154,156
	Seeds, latex, twigs	Voacangine (**18**)	153,155,156
T. attenuata (Miers) Urb. (*A. meyeri*)	Leaves	16-*Epi*-pleiocarpamine (**129**)	157
		11-Hydroxycoronaridine (**317**)	157
		10-Hydroxyheyneanine (**349**)	157
		11-Hydroxyheyneanine (**350**)	157
	Stem-bark, root-bark	Angustine (**134**)	157
		Conopharyngine (**319**)	157
		Coronaridine (**16**)	157
		Coronaridine-7-hydroxyindolenine (**388**)	157
		Eglandine (**336**)	157
		19-*Epi*-heyneanine (**321**)	157
		Heyneanine (**17**)	157
		Ibophyllidine (**279**)	157
		Isovoacangine (**318**)	157
		Jollyanine (= Conopharyngine-7-hydroxyindolenine) (**391**)	157
		6(*R*)-3,6-Oxidocoronaridine (**400**)	157
		(+)-Tubotaiwine (**213**)	157
		Voacangine (**18**)	157
T. aurantiaca Gaudich. (*Rejouna aurantiaca*, *E. aurantiaca*)	Bark, leaves, flowers	Iboluteine (= Ibogaine pseudoindoxyl) (**411**)	158,159
		Voaluteine (= Voacangine pseudoindoxyl) (**406**)	158,159
		Vobtusine (**544**)	158,160
	Bark	Voacangine (**18**)	158

Table 1.2, continued

Plant	Plant part	Alkaloids	References
T. australis Müll. Arg. (*P. australis*)	Stems	Voacangine (**18**)	161
		Voacamine (**485**)	161
	Seeds	Tabersonine (**216**)	162
		Coronaridine-7-hydroxyindolenine (**388**)	162
	Roots	16'-Decarbomethoxyvoacamine (**58**)	162
		Tabernamine (**57**)	162
	Leaves	Catharinensine (**127**)	162
	Leaves, root-bark	Olivacine (**65**)	162
	Seeds, root-bark	Coronaridine (**16**)	162
T. bovina Lour.	Leaves, stems	14α,15β-Dihydroxy-*N*(1)-methylaspidospermine (**243**)	163
		19(*R*)-*Epi*-voacristine (**366**)	163
		Hecubine (= *N*(1)-Methylvoaphylline) (**283**)	163
		20-Hydroxyconopharyngine (**320**)	163
		Ibogaine (**360**)	163
		Ibogaline (**385**)	163
		Isovoacristine (**368**)	164
		(–)-Mehranine (**241**)	163
		Methylene-bis-mehranine (**542**)	164
		3-Oxomehranine (**242**)	163
		Pedunculine (= Conofoline) (**540**)	163
		Tabernaebovine (**543**)	164
	Seeds	Tabernaemontabovine (**561**)	165
		Tabernaemontavine (**565**)	165
T. brachyantha Stapf. (*Conopharyngia brachyantha*)	Stem-bark	Anhydrovobasindiol (= Taberpsychine) (**191**)	166
		Normacusine B (**51**)	166
		Voacorine (**490**)	166
T. buchtieni H. Winkler (*P. buchtieni*)	Stem-bark	Affinisine (**136**)	167
		Buchtienine (**584**)	167
		Ceridimine (**579**)	167
		Chloromethylene-affinisinium (**152**)	167
		Coronaridine (**16**)	167
		Coronaridine-7-hydroxyindolenine (**388**)	167
		N(4)-Demethylaccedinisine (**587**)	167
		N(4)-Demethylceridimine (**580**)	167
		N(4)-Demethyltabernamine (**475**)	167
		19-*Epi*-heyneanine (**321**)	167
		19-*Epi*-voacorine (**491**)	167
		18,19(*R*)-Dihydroxycoronaridine (**330**)	167
		3,14-Dihydroolivacine (**68**)	167
		4',17(β)-Dihydrotchibangensine (**583**)	167
		Eglandine (**336**)	167

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		Eglandulosine (= 3-oxocoronaridine) (**335**)	167
		Heyneanine (**17**)	167
		18-Hydroxyaffinisine (**153**)	167
		3'(*R*/*S*)-Hydroxy-*N*(4)-demethyltabernamine (**477**)	167
		3-Hydroxytetrahydroolivacine (**67**)	167
		Ibogamine (**13**)	167
		Isositsirikine (**119**)	167
		Janetine (**66**)	167
		N(1)-Methylpericyclivine (**142**)	167
		Normacusine B (**51**)	167
		Ochropamine (**168**)	167
		Affinisine *N*(4)-oxide (= *N*(4)-Oxyaffinisine) (**139**)	167
		Vallesamine (**103**)	167
		Voachalotine (**137**)	167
		Voaphylline (= Conoflorine) (**282**)	167
		Voaphylline-7-hydroxyindolenine (**291**)	167
	Leaves	Apodine (**244**)	167
		Voacristine (= Voacangarine) (**19**)	167
		Voacristine-7-hydroxyindolenine (**393**)	167
	Stem-bark, leaves	Olivacine (**65**)	167
T. bufalina Lour. (*Ervatamia hainanensis*)	Roots	Coronaridine (**16**)	168
		Coronaridine-7-hydroxyindolenine (**388**)	168
		Ervahanine A (**480**)	169
		Ervahanine B (**454**)	169
		Ervahanine C (**498**)	169
		Ervahaimine A (**482**)	170
		Ervahaimine B (**463**)	170
		Ervahaimidine A (**483**)	170
		Ervahaimidine B (**464**)	170
		Geissoschizol (**116**)	168
		Heyneanine (**17**)	168
		3(*S*)-3-(β-Hydroxyethyl)-coronaridine (**345**)	168
		10-Hydroxygeissoscchizol (**117**)	168
		10-Hydroxyheyneanine (**349**)	168
		Ibogamine (**13**)	168
		3-Oxocoronaridine (= Eglandulosine) (**335**)	168
		Perivine (**170**)	168
		Vobasine (**48**)	168
	Stems	Coronaridine (**16**)	171
		Coronaridine-7-hydroxyindolenine (**388**)	171
		19(*R*)-Heyneanine (**321**)	171
		19(*S*)-Heyneanine (**17**)	171
		Heyneanine-7-hydroxyindolenine (**392**)	171
		10-Hydroxycoronaridine (**316**)	171
		Voacangine (**18**)	171
		Vobasine (**48**)	171
	Twigs, Leaves	Coronaridine (**16**)	172
		Coronaridine hydroxyindolenine (**388**)	172
		19-*Epi*-heyneanine (**321**)	172
		Ervahainine A (**414**)	173

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		Heyneanine (**17**)	172
		Vobasine (**48**)	172
	Aerial parts	Ervatamine A (**438**)	174
		Ervatamine B (**109**)	174
		Ervatamine C (**110**)	174
		Ervatamine D (**111**)	174
		Ervatamine E (**112**)	174
		Ervatamine F (**413**)	174
		Ervatamine G (= Taberdivarine G) (**328**)	174
		Ervatamine H (**357**)	174
		Ervatamine I (**421**)	174
		Coronaridine (**16**)	174
		Heyneanine (**17**)	174
		3-(2'-Oxopropyl)-19-*epi*-heyneanine (**329**)	174
		Pandine (**270**)	174
T. calcarea Pichon (*Pandaca calcarea, P. caducifolia*)	Leaves	Apparicine (**105**)	175
		Dregamine (**156**)	175
		20-*Epi*-pandoline (**261**)	176
		16-*Epi*-silicine (**93**)	177
		Pandine (**270**)	175,176
		Pandoline (**260**)	175,176
		Pseudotabersonine (**258**)	176
		(+)-20(*R*)-Pseudovincadifformine (**259**)	176
		Silicine (**91**)	176,177
	Leaves, flowers	Coronaridine (**16**)	178
		19-*Epi*-heyneanine (**321**)	178
		3(*R/S*)-Hydroxytabernanthine (**386**)	178
		19-*Epi*-voacristine (= 19-*Epi*-voacangarine) (**366**)	178
		19-*Epi*-voacristine-7-hydroxyindolenine (**394**)	178
		Heyneanine (**17**)	178
		11-Hydroxycoronaridine (**317**)	178
		Ibogamine (**13**)	178
		Isovoacangine (**318**)	178
		Isovoacristine (**368**)	178
		10-Methoxyibogamine (**360**)	178
		11-Methoxyibogamine (**384**)	178
		19-*Epi*-3-oxo-voacristine (**352**)	178
		Voacangine (**18**)	178
		Voacristine (= Voacangarine) (**19**)	178
T. campestris (*P. campestris* (Rizz.) Rizz.)	Leaves, bark, roots	Coronaridine (**16**)	179
		Heyneanine (**17**)	179
		Isovoacangine (**318**)	179
		Isovoacristine (**368**)	179
		12-Methoxy-*N*(4)-methylvoachalotine (**147**)	179
		Voacamine (**485**)	179
		Voacangine (**18**)	179
		Voacangine-7-hydroxyindolenine (**390**)	179
		Voachalotine (**137**)	179
		Vobasine (**48**)	179

Table 1.2, continued

Plant	Plant part	Alkaloids	References
T. capuronii Leeuwenberg (*Capuronetta elegans*)	Leaves, stem-bark	14,15-Anhydrocapuronidine (**265**)	180
		14,15-Anhydro-1,2-dihydrocapuronidine (**264**)	180
		Capuronidine (**268**)	181
		Capuronine (**257**)	181
		20'(*R*)-Capuvosidine (**562**)	180,182
		Capuvosine (**578**)	181,182
		20'(*R*)-Dehydroxycapuvosine (**576**)	180,182
		N(4)-Demethylcapuvosine (**577**)	180
		20'(*R*)-1,2-Dihydrocapuvosidine (**563**)	182
T. catharinensis A. DC. (*P. catharinensis*)	Root-bark	Catharinensine (**127**)	183
		Conodurine (**500**)	183
		Coronaridine (**16**)	183–185
		Coronaridine-7-hydroxyindolenine (**388**)	184
		16'-Decarbomethoxyvoacamine (**58**)	183
		16-*Epi*-affinine (**49**)	183
		Heyneanine (**17**)	183–185
		Isovoacangine (**318**)	183
		12-Methoxy-*N*(4)-methylvoachalotine (**147**)	184,186
		Voacangine (**18**)	185
		Voacangine-7-hydroxyindolenine (**390**)	184
		Vobasine (**48**)	184
	Roots	12-Methoxy-*N*(4)-methylvoachalotine (**147**)	187
		Voachalotine (**137**)	187
T. cerifera Panch. & Seb. (*Pagiantha cerifera*)	Leaves	Apparicine (**105**)	188
		Ibogaine (**360**)	189
		Olivacine (**65**)	188
		Voacangine (**18**)	189
		Voacangine-7-hydroxyindolenine (**390**)	189
		Vobasine (**48**)	188
	Stem-bark	Pagicerine (**190**)	190,191
		Pagisulfine (**176**)	190,192
	Bark	Ceridimine (**579**)	190,193
T. chippii Pichon	Root-bark	Akuammiline (**182**)	194
		Anhydrovobasindiol (= Taberpsychine) (**191**)	194
		Apparicine (**105**)	194
		Chippiine (**424**)	194
		Conoduramine (**457**)	194
		Conodurine (**500**)	194
		Conopharyngine (**319**)	194
		Conopharyngine-7-hydroxyindolenine (**391**)	194
		Coronaridine (**16**)	194
		Deacetylakuammiline (**181**)	194
		16-*Epi*-affinisine (**140**)	194
		16-*Epi*-isositsirikine (**118**)	194
		12-Hydroxyakuammicine (**206**)	194
		3'(*R*/*S*)-Hydroxyconoduramine (**461**)	194
		3'(*R*/*S*)-Hydroxyconodurine (**504**)	194
		3(*R*/*S*)-Hydroxyconopharyngine (**344**)	194
		3'(*R*/*S*)-Hydroxy-16'-decarbomethoxyconodurine (**506**)	194

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		3'(*R*/*S*)-Hydroxyvoacamine (**488**)	194
		Ibogaline (**385**)	194
		Isositsirikine (**119**)	194
		Isovoacangine (**318**)	194
		Normacusine B (**51**)	194
		Monogagaine (**573**)	194
		3-Oxoconopharyngine (**343**)	194
		Pericyclivine (**138**)	194
		Picraline (**187**)	194
		Pleiocarpamine (**128**)	194
		(+)-Tubotaiwine (**213**)	194
		Voaphylline (= Conoflorine) (**282**)	194,195
		Vobasine (**48**)	194
		Vobasinol (**180**)	194
		Vobparicine (**570**)	194,196
		Vobparicine *N*-oxide (**571**)	194
T. ciliata Pichon	Leaves	Pandicine (**591**)	197
T. citrifolia L. (*T. oppositifolia*)	Leaves	Akuammidine (**144**)	198
		Apparicine (**105**)	198–200
		12,12'-Bis(11-hydroxycoronaridinyl) (**567**)	200
		Conoflorine (= Voaphylline) (**282**)	200
		14,15-Dehydrotetrastachyne (**558**)	200,201
		14,15-Dehydrotetrastachynine (**560**)	200
		16-*Epi*-isositsirikine (**118**)	200
		20-*Epi*-pandoline (**261**)	200
		Fluorocarpamine (**130**)	200
		10-Hydroxycoronaridine (**316**)	200
		11-Hydroxycoronaridine (**317**)	200
		Ibogaine (**360**)	200
		Iboxygaine (**362**)	198
		Lochnericine (**219**)	198
		3-Oxovoacangine (**340**)	198
		3-Oxovoacristine (**351**)	198
		Pandine (**270**)	200
		Pleiocarpamine (**128**)	200
		Sitsirikine (**121**)	200
		Tabersonine (**216**)	127,198,200
		(+)-Tubotaiwine (**213**)	200
		Vallesamine (**103**)	198,200
		Voacamine (**485**)	161
		Voacangine-7-hydroxyindolenine (**390**)	198
		Voacristine (= Voacangarine) (**19**)	198
	Leaves, roots	Coronaridine (**16**)	127,161,198,199
		Ibogamine (**13**)	161,198,200
		Voacangine (**18**)	161,198–200
T. coffeoides Boj. Ex A. DC. (*T. modesta, T. membranacea, Hazunta angustifolia,*	Leaves	Akuammidine (**144**)	202
		Deoxoapodine (**28**)	203
		14,15-Dihydroxyvincadifformine (**220**)	203
		Heyneanine (**17**)	202
		10-Hydroxy-11-methoxytabersonine (= Jerantinine A) (**226**)	202

Table 1.2, continued

Plant	Plant part	Alkaloids	References
H. coffeoides, *H. membranacea*, *H. modesta*, *H. modesta methuenii*, *H. silicola*, *H. velutina*)		Lochnericine (**219**)	203
		Methuenine (**82**)	203
		3-Oxotabersonine (**221**)	203
		Pericyclivine (**138**)	203
		Polyneuridine (**143**)	202
		Stemmadenine (**99**)	204
		Tabersonine (**216**)	203
		Vallesamine (**103**)	203
		Vincanidine (**207**)	204
		Voaphylline (= Conoflorine) (**282**)	202
	Stem-bark	19'(*R*)-Hydroxytabernaelegantine A (**514**)	204,205
		Isoreserpiline (**115**)	204
		6-Oxomethuenine (**86**)	204
		Reserpiline (**114**)	204
		Tetraphyllicine (**199**)	204
		Tetraphyllicine dimethoxybenzoate (**200**)	204
		Tetraphyllicine monomethoxybenzoate (**201**)	204
		Tetraphyllicine trimethoxybenzoate (**202**)	204
	Roots	Coronaridine (**16**)	206
		Ibogamine (**13**)	202–204,207
		Voacangine (**18**)	206
	Root-bark	20'(*S*)-19',20'-Dihydrotabernamine (**472**)	205
		20-*Epi*-silicine (**92**)	204
		Tabernaelegantine A (**512**)	204,205
	Stem-bark, root-bark	3,14-Dihydroellipticine (**64**)	202–204
		Isomethuenine (**85**)	202,204
		6-Oxo-16-*epi*-silicine (**95**)	203
	Leaves, twigs	Hazuntine (**224**)	208
		Hazuntinine (**225**)	208
		Tabernaemontanine (**50**)	208
	Leaves, stem-bark, root-bark	Apparicine (**105**)	203
		Isovoacangine (**318**)	204
		Silicine (**91**)	203,204
	Root-bark, roots	6-Oxosilicine (**94**)	202–204,206
	Leaves, roots	19-*Epi*-heyneanine (**321**)	202
	Leaves, stem-bark	Normacusine B (**51**)	204
	Leaves, twigs, stem-bark	Voacarpine (**173**)	208

Table 1.2, continued

Plant	Plant part	Alkaloids	References
	Leaves, twigs, stem-bark, roots	Dregamine (**156**)	208
	Leaves, twigs, stem-bark, root-bark	Vobasine (**48**)	202–204,208
T. contorta Stapf	Stem-bark	Conopharyngine (**319**)	209
		Coronaridine (**16**)	209
		Ibogaine (**360**)	209
		Voacangine (**18**)	209
		Voacristine (= Voacangarine) (**19**)	209
T. corymbosa Roxb. ex Wall. (*E. corymbosa*, *E. officinalis*, *E. chinensis* (Merr.) Tsiang, *E. yunnanensis* Tsiang)	Leaves	Apparicine (**105**)	210
		Bistabercarpamine A (**524**)	211
		Bistabercarpamine B (**525**)	211
		Conodiparine A (**451**)	212
		Conodiparine B (**495**)	212
		Conodiparine C (**452**)	212
		Conodiparine D (**496**)	212
		Conodiparine E (**453**)	212
		Conodiparine F (**497**)	212
		Conodirinine A (**528**)	213
		Conodirinine B (**529**)	213
		Conodurine (**500**)	214
		Conodutarine A (**508**)	212
		Conodutarine B (**509**)	212
		Cononitarine A (**510**)	212
		Cononitarine B (**511**)	212
		Coronaridine (**16**)	214
		19,20-Dehydroervatamine (**81**)	215
		14,15-Didehydro-10-hydroxy-11-methoxyvincamine (**299**)	216
		Dippinine A (**422**)	217,218
		Dippinine D (**427**)	218
		Heyneanine (**17**)	214
		19-*Epi*-isovoacristine (**372**)	214
		Ervachinine C (**443**)	214
		7(*S*)-16(*R*)-19,20-*E*-Isositsirikine oxindole (**124**)	219
		Ibogaine (**360**)	220
		Ibogamine (**13**)	214
		Isovoacangine (**318**)	214
		Isovoacristine (**368**)	221
		Jerantinine A (**226**)	222
		Jerantinine B (**227**)	222
		Jerantinine C (**228**)	222
		Jerantinine D (**229**)	222
		Jerantinine E (**230**)	222
		Jerantinine F (**246**)	222
		Jerantinine G (**247**)	222
		Jerantinine H (**248**)	216
		Jerantiphylline A (**249**)	216

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		Jerantiphylline B (**250**)	216
		11-Methoxytronocarpine (**74**)	210
		Methuenine (**82**)	215
		N(1)-Methoxy-19,20-dehydroervatamine (**84**)	215
		Modestanine (= Deoxoapodine) (**28**)	223
		Norfluorocurarine (**52**)	210
		Normacusine B (**51**)	223
		3-(2'-Oxopropyl)-19-*epi*-heyneanine (**329**)	224
		3-(2'-Oxopropyl)-coronaridine (**327**)	224
		5-Oxo-19,20-dehydroervatamine (**83**)	215
		Tabercarpamine A (**526**)	214
		Tabercarpamine B (**527**)	214
		Tabercarpamine C (**251**)	214
		Tabercarpamine D (**252**)	214
		Tabercarpamine E (**253**)	214
		Tabercarpamine F (**254**)	214
		Tabercarpamine G (**428**)	214
		Tabercarpamine H (**429**)	214
		Tabercarpamine I (**430**)	214
		Tabercarpamine J (**431**)	214
		Tabernaecorymbosine A (**518**)	214
		Voacangine (**18**)	214
		Yohimbine (**39**)	223
		β-Yohimbine (**38**)	223
		β-Yohimbine oxindole (**113**)	223
		β-Yohimbine pseudoindoxyl (**46**)	223
		Vandrikine (**29**)	223
	Leaves, twigs	17-Acetyl-tabernaecorymbosine A (**519**)	225
		19-Acetonylvoacangine (**347**)	226
		Apparicine (**105**)	226
		Conodurine (**500**)	225
		Conofoline (**540**)	226
		Conopharyngine (**319**)	227
		Coronaridine (**16**)	226
		Coronaridine hydroxyindolenine (**388**)	226
		16'-Decarbomethoxyvoacamine (**58**)	225
		19,20-Dehydroervatamine (**81**)	226
		2α,7α-Dihydrodihydroxyvoaphylline (**293**)	226
		19,20-Dihydroervahanine A (**471**)	226
		Dregamine (**156**)	226
		Eglandine (**336**)	226
		20-*Epi*-ervatarnine (**89**)	226
		19-*Epi*-5-oxovoacristine (**356**)	227
		Ervadivaricatine A (**469**)	226
		Ervadivaricatine B (**470**)	226
		Ervaoffine A (**415**)	227
		Ervaoffine B (= Ervaluteine) (**404**)	227
		Ervaoffine C (**416**)	227
		Ervaoffine D (**437**)	227
		Ervatamine (**88**)	226
		Heyneanine (**17**)	226,227
		19(*S*)-Hydroxyibogamine (**14**)	227
		Ibogaline (**385**)	227
		Ibogaine (**360**)	227
		Ibogamine (**13**)	226
		Ibogaine-5,6-dione (**380**)	227
		7(*S*)-Ibogaine hydroxyindolenine (**396**)	227
		Ibogaine *N*(4)-oxide (**361**)	227

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		Iboluteine (= Ibogaine pseudoindoxyl) (**411**)	227
		Isovoacangine (**318**)	226
		Isovoacristine (**368**)	226
		3-Oxocoronaridine (**335**)	226
		3-(2'-Oxopropyl) coronaridine (**327**)	226
		3-(2'-Oxopropyl) coronaridine hydroxyindolenine (**389**)	226
		7(*S*)-3-Oxoibogaine hydroxyindolenine (**397**)	227
		Tabercorine A (**533**)	225
		Tabercorine B (**534**)	225
		Tabercorine C (**535**)	225
		Tabernaelegantine D (**448**)	226
		Tabernaemontanine (**50**)	226
		Taberdivarine A (**568**)	226
		Taberdivarine B (**569**)	226
		Taberdivarine C (**520**)	226
		Taberdivarine D (**521**)	226
		Taberdivarine E (**522**)	226
		Taberdivarine F (**523**)	226
		Taberdivarine G (= Ervatamine G) (**328**)	226
		Taberdivarine H (**315**)	226
		Tabernaricatine A (**536**)	225
		Tabernaricatine B (**537**)	225
		Tabernaricatine D (**532**)	225
		Voacangine (**18**)	227
		Voacristine (**19**)	227
		Voaphylline-7-hydroxyindolenine (**291**)	226
		Vobasine (**48**)	226
	Leaves, stem-bark	Conodurinine (**507**)	228
		Coronaridine (**16**)	220,221
		19-*Epi*-heyneanine (**321**)	220,221
		Heyneanine (**17**)	220,221
		19'(*S*)-Hydroxyconoduramine (**462**)	228
		Ibogamine (**13**)	220,221
		Isovoacryptine (**371**)	221
		Vobasonidine (**589**)	229
	Stems	Coronaridine (**16**)	230
		Coronaridine-7-hydroxyindolenine (**388**)	230
		Ervataine (**419**)	230
		Heyneanine (**17**)	230
		Ibogaine (**360**)	230
		Dregamine (**156**)	231
		20-*Epi*-ervatamine (**89**)	231
		Ervatamine (**88**)	231
		Tabernaemontanine (**50**)	231
		Voacangine (**18**)	221,231
		Voacristine (= Voacangarine) (**19**)	231
	Stem-bark	Affinisine (**136**)	210,232
		Antirhine (**122**)	232
		N(4)-Chloromethylnorfluorocurarine chloride (**210**)	232
		Conodurine (**500**)	228
		Conomicidine A (**434a**)	232,233
		Conomicidine B (**435a**)	232,233
		Coronaridine (**16**)	232
		Coronaridine-7-hydroxyindolenine (**388**)	221
		Conolutinine (**76**)	232,234

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		Conoliferine (**433a**)	232,235
		Cononusine (**432**)	232
		Criofolinine (**4**)	236
		16'-Decarbomethoxyvoacamine (**58**)	232
		16'-Decarbomethoxyvoacamine pseudoindoxyl (**530**)	232
		Dippinine B (**423**)	218
		Dippinine C (**426**)	218,237
		19-*Epi*-isovoacristine (**372**)	221
		16-*Epi*-normacusine B (**135**)	210
		16-*Epi*-vobasenal (**162**)	238
		16-*Epi*-vobasine (**163**)	238
		Ervahanine A (**480**)	228
		Ervaluteine (= Ervaoffine B) (**404**)	232
		Ervatensine A (= Ervachinine B) (**467**)	232
		Ervatensine B (**468**)	232
		3(*R*/*S*)-Ethoxycoronaridine (**334**)	221
		3(*R*/*S*)-Ethoxy-19-*epi*-heyneanine (**326**)	221
		3(*R*/*S*)-Ethoxyheyneanine (**325**)	221
		16-Ethoxytronocarpine (**75**)	210
		7(*R*)-Geissoschizol oxindole (**125**)	219,232
		7(*S*)-Geissoschizol oxindole (**123**)	219,232
		Heyneanine (**17**)	232
		19-*Epi*-heyneanine (**321**)	232
		19'(*S*)-Hydroxyconodurine (**505**)	228
		20(*S*)-Hydroxy-1,2-dehydropseudoaspidospermidine (**269**)	232
		19'(*S*)-Hydroxyervahanine A (**481**)	228
		19(*S*)-Hydroxyibogamine (**14**)	221
		12-Hydroxynorfluorocurarine (**209**)	210
		3-Hydroxy-3,4-*seco*-coronaridine (**436**)	221
		19'(*R*)-Hydroxytabernamine (**478**)	239
		19'(*S*)-Hydroxytabernamine (**479**)	239
		Ibogaine (**360**)	232
		Ibogaine-7-hydroxyindolenine (**396**)	232
		Ibogamine (**13**)	232
		Iboluteine (= Ibogaine pseudoindoxyl) (**411**)	232
		Iboxygaine (**362**)	232
		Isoconoliferine (**433b**)	235
		Isoconomicidine A (**434b**)	233
		Isoconomicidine B (**435b**)	233
		7(*R*)-16(*R*)-19,20-*E*-Isositsirikine oxindole (**126**)	219,232
		Isovoacangine (**318**)	221
		Lirofoline A (**439**)	232,240
		N(4)-Demethyltaberpsychine (**192)**	219
		Modestanine (= Deoxoapodine) (**28**)	224
		Norfluorocurarine (**52**)	232
		Norfluorocurarine *N*(4)-oxide (**208**)	210
		Normacusine B (**51**)	224
		3-Oxocoronaridine (**335**)	221
		3-Oxo-19-*epi*-heyneanine (**323**)	221
		6-Oxoibogaine (**378**)	232
		19'-Oxotabernamine (**56**)	239
		Pericyclivine (**138**)	210
		Strictamine (**184**)	210
		Tabernaemontanine (**50**)	238
		Tabernamine (**57**)	210
		Taberpsychine (= Anhydrovobasindiol) (**191**)	210
		Tabertinggine (**2**)	241
		Tacamine-*N*-oxide (**310**)	238

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		Tacamodinine (**314**)	232
		Tacamonine-*N*-oxide (**307**)	238
		Taipinisine (**585**)	238
		Tronocarpine (**73**)	242
		Tronoharine (**80**)	243
		Tronoharine (**80a**, revised structure)	238
		Velbanamine (**54**)	232
		Vernavosine (**5**)	236
		Vernavosine ethyl ether (**6**)	236
		Vincamajicine (**203**)	232
		Voastrictine (**77**)	244
		Vobasidine A (**158**)	238
		Vobasidine B (**159**)	238
		Vobasidine C (**155**)	238
		Vobasidine D (**160**)	238
		Vobasenal (**161**)	238
		Vobasine (**48**)	238
		Vobatricine (**574**)	229
		Voachalotine (**137**)	232
		Voatinggine (**1**)	241
		β-Yohimbine (**38**)	224
		β-Yohimbine oxindole (**113**)	224
		β-Yohimbine pseudoindoxyl (**46**)	224
	Whole plant	19-Acetonylisovoacangine (**348**)	245
		Coronaridine (**16**)	245
		Conophyllidine (**60**)	246
		16'-Decarbomethoxy-19,20-dihydro-20-*epi*-voacamine (**474**)	246
		16'-Decarbomethoxyvoacamine (**58**)	245,246
		10-Demethoxynorvincorine (**189**)	246
		Difforlemenine (**196**)	245
		14,15-Didehydro-10,11-dimethoxyvincamine (**302**)	246
		14,15-Didehydro-10,11-dimethoxy-16-*epi*vincamine (**300**)	246
		14,15-Didehydro-10-hydroxy-11-methoxy-16-*epi*vincamine (**301**)	246
		14,15-Didehydro-10-hydroxy-11-methoxyvincamine (**299**)	246
		Dihydroevocarpine (**70**)	247
		Ervachinine A (**466**)	245
		Ervachinine B (= Ervatensine A) (**467**)	245
		Ervachinine C (**443**)	245
		Ervachinine D (**444**)	245
		Ervachinine E (**441**)	247
		Evocarpine (**69**)	247
		(+)-Hecubine (= *N*(1)-Methylvoaphylline) (**283**)	245
		Heyneanine (**17**)	245
		19(*S*)-Hydroxyconopharyngine (**370**)	246
		20(*S*)-Hydroxy-1,2-dehydropseudoaspidospermidine (**269**)	246
		Ibogaine (**360**)	246
		Ibogaine-7-hydroxyindolenine (**396**)	246
		Isovoacangine (**318**)	245
		1-Methyl-2-nonyl-4(1*H*)-quinolone (**71**)	247
		1-Methyl-2-[(*Z*)-6-undecenyl]-4(1*H*)-quinolone (**72**)	247
		12-Methoxyvoaphylline (**284**)	246
		3-(2'-Oxopropyl)-voacangine (**347**)	245
		Picrinine (**188**)	246

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		Rhazinaline (= Rhazimal) (**183**)	246
		Rutaecarpine (**133**)	247
		Strictamine (**184**)	246
		Tabernaecorymbosine A (**518**)	245
		(–)-Velbanamine (**54**)	246
		Vincadiffine (**167**)	245
		Voacangine (**18**)	246
		Voachalotine (**137**)	246
		Voacristine (**19**)	246
		Voaphylline (= Conoflorine) (**282**)	245,246
		Vobasine (**48**)	245
T. crassa Benth. (*T. durissima*, *Conopharyngia crassa*, *C. durissima*, *C. jollyana*, *Gabunia odoratissima*)	Stem-bark	Akuammiline (**182**)	248
		Anhydrovobasindiol (= Taberpsychine) (**191**)	248
		Conopharyngine (**319**)	249,250
		Conopharyngine-7-hydroxyindolenine (**391**)	251
		Coronaridine (**16**)	252,253
		Heyneanine (**17**)	251
		Ibogaine (**360**)	250
		Ibogamine (**13**)	253
		Isovoacangine (**318**)	249,253
		3-Oxocoronaridine (**335**)	254
		5-Oxocoronaridine (**373**)	252
		3-Oxoheyneanine (**322**)	254
		3-Oxoconopharyngine (**343**)	254
		Voacristine (= Voacangarine) (**19**)	251
		O-Acetylpolyneuridine (**145**)	251
		Conoduramine (**457**)	249,253
		Crassanine (**418**)	255
		Gabunine (**499**)	253
		19(*S*)-Hydroxyconopharyngine (**370**)	251,255,256
		Pericyclivine (**138**)	253
		Perivine (**170**)	251
		Vobasine (**48**)	253
T. crassifolia Pichon	Stem-bark	Ibogamine (**13**)	257
		Tabernanthine (= 11-Methoxyibogamine) (**384**)	257
T. cymosa Jacq.	Leaves	Angustine (**134**)	258
		14,15-Dehydrotetrastachyne (**558**)	258
		16-*Epi*-isositsirikine (**118**)	258
		19-*Epi*-voacristine (= 19-*Epi*-voacangarine) (**366**)	258
		(+)-Tubotaiwine (**213**)	258
		10-Hydroxyheyneanine (**349**)	258
	Stem-bark	Ibogaine-7-hydroxyindolenine (**396**)	258
		10-Methoxyeglandine (**346**)	258
		Voacangine pseudoindoxyl (= Voaluteine) (**406**)	258
	Seeds	(+)-Condylocarpine (**212**)	259
		(+)-14,15-Dehydro-16-*epi*-vincamine (**33**)	259
		Heyneanine (**17**)	259
		Isositsirikine (**119**)	259
		3-Oxotabersonine (**221**)	259
		Stemmadenine (**99**)	259
		Stemmadenine *N*-oxide (**100**)	259

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		Tabersonine (**216**)	259
		Tabersonine *N*-oxide (**217**)	259
		Tetrahydroalstonine (**35**)	259
	Stem-bark, root-bark	16'-Decarbomethoxyvoacamine (**58**)	258
		N(4)-Demethylvoacamine (**489**)	258
		Ibogaine (**360**)	258
		Olivacine (**65**)	258
		Voacamidine (**442**)	258
		Voacamine (**485**)	258
	Seeds, leaves	10-Hydroxycoronaridine (**316**)	258,259
		Voacristine (= Voacangarine) (**19**)	258,259
	Seeds, stem-bark	3-Oxovoacangine (**340**)	258,259
		Coronaridine (**16**)	258,259
	Leaves, root-bark	Vobasine (**48**)	258
	Leaves, stem-bark	Pleiocarpamine (**128**)	258
	Leaves, stem-bark, root-bark	Voacangine-7-hydroxyindolenine (**390**)	258
	Seeds, leaves, stem-bark, root-bark	Voacangine (**18**)	258,259
T. debrayi (Mgf.) Leeuwenberg (*Pandaca debrayi*)	Leaves	Pandine (**270**)	175
		Pandoline (**260**)	175
	Leaves, stem-bark, root-bark	Dregamine (**156**)	175
T. dichotoma Roxb. ex Wall (*Ervatamia dichotoma*, *Pagiantha dichotoma*, *Rejuoa dichotoma*)	Leaves	19-*Epi*-iboxygaine (**363**)	260
		19-*Epi*-voacristine (= 19-*Epi*-voacangarine) (**366**)	260
		16-Hydroxy-16,22-dihydroapparicine (**102**)	261
		Perivine (**170**)	260
		Voaphylline-7-hydroxyindolenine (**291**)	261
	Flowers	*O*-Acetylvallesamine (**104**)	262
		Dichomine (**271**)	262
		19-*Epi*-heyneanine (**321**)	262
		Voaphylline (= Conoflorine) (**282**)	262
		Vobasine (**48**)	262

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Plant	Plant part	Alkaloids	References
	Stem-bark	Monogagaine (**573**)	263
	Stem-bark, roots	*N*(4)-Demethyltabernamine (**475**)	264
		Heyneanine (**17**)	264
		3'(R/S)-Hydroxy-*N*(4)-demethylervahanine A (**484**)	264
		3'(R/S)-Hydroxy-*N*(4)-demethylervahanine B (**459**)	264
		3'(R/S)-Hydroxy-*N*(4)-demethyltabernamine (**477**)	264
		3'(*R*/*S*)-Hydroxytabernamine (**476**)	264
		3'(*R*/*S*)-Hydroxyvoacamine (**488**)	264
		Ibogamine (**13**)	264
		Isomethuenine (**85**)	264
		3-Ketopropyl-19(*R*)-heyneanine (**324**)	264
		3,19(*R*)-Oxidocoronaridine (**359**)	264
		3-Oxocoronaridine (**335**)	264
		Perivine (**170**)	264
		Tabernamine (**57**)	264
		Voacamine (**485**)	264
	Leaves, flowers	12-Methoxyvoaphylline (**284**)	260,262
		Vallesamine (**103**)	261,262
	Stem-bark, flowers	3-Ketopropylcoronaridine (**337**)	262,264
	Leaves, stem-bark	Vobasine (**48**)	260,264
	Leaves, stems, roots, flowers	Apparicine (**105**)	260,262,264
	Stem-bark, flowers, roots	Coronaridine (**16**)	262,264
T. divaricata (L.) R. Br. (*T. coronaria*, *Ervatamia coronaria*, *E. divaricata*)	Leaves	Apparicine (**105**)	265–267
		Conofoline (= Pedunculine) (**540**)	266
		Conophyllidine (**60**)	268
		Conophylline (**538**)	268,269
		Conophyllinine (**539**)	267
		19-*Epi*-heyneanine (**321**)	270
		16-Hydroxy-16, 22-dihydroapparicine (**102**)	267
		Ibogaine (**360**)	267
		Ibogamine (**13**)	267
		16(*R*)-19,20-*E*-Isositsirikine (**119**)	267
		16(*R*)-19,20-*E*-Isositsirikine oxindole (**124**)	267
		Isovoacristine (**368**)	270,271
		(–)-Mehranine (**241**)	266,267
		Lochnericine (**219**)	272,273
		N(1)-Methylvoafinine (**286**)	267
		N(1)-Methylvoaphylline (= Hecubine) (**283**)	266,267
		Pachysiphine (**218**)	266,267
		Peduncularidine (**541**)	267

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		Taberhanine (**231**)	267
		Voacangine (**18**)	267
		Voacristine (**19**)	267
		Voafinidine (**289**)	267
		Voafinine (**285**)	267
		Voaharine (**294**)	266,269
		Voalenine (**292**)	267
		Voaphylline (**282**)	266,267
		Voastrictine (**77**)	267
	Root-bark	Coronaridine-7-hydroxyindolenine (**388**)	274
		5-Hydroxy-6-oxocoronaridine (**375**)	274
		3-Oxocoronaridine (**335**)	274,275
		5-Oxocoronaridine (**373**)	274
		6-Oxocoronaridine (**374**)	274
		Pseudovobparicine (**572**)	276
	Stems	16'-Decarbomethoxyvoacamine (**58**)	277
		19,20-Dihydroervahanine A (**471**)	277
		3'(*R*/*S*)-Hydroxyvoacamine (**488**)	233
		3-(2'-Oxopropyl)-coronaridine (**327**)	275
	Flowers	Tabersonine (**216**)	265
		3,14;4,19-Tetrahydroolivacine (= Janetine) (**66**)	278
	Leaves, stems	Akuammicine (**204**)	246
		Apparicine (**105**)	246
		Coronaridine (**16**)	161,270,272,273,277,279
		Coronaridine-7-hydroxyindolenine (**388**)	246
		Dregamine (**156**)	161,270,272,273
		Dehydroxyervataminol (**98**)	246
		19,20-Didehydro-6α-hydroxyervatamine (**97**)	246
		19,20-Dihydrotabernamine (**472**)	246
		20-*Epi*-ervatamine (**89**)	246
		14,15-β-Epoxytabersonine (= Pachysiphine) (**218**)	246
		Ervadivaricatine A (**469**)	246
		Ervadivaricatine B (**470**)	246
		Ervatamine (**88**)	246
		Ibogamine (**13**)	246
		(–)-Mehranine (**241**)	246
		11-Methoxy-*N*(1)-methyldihydropericyclivine (**154**)	270
		Tabernaemontanine (**50**)	246
		Tabersonine (**216**)	246
		Tubotaiwine (**213**)	246
		Voacangine (**18**)	246
		Voacangine-7-hydroxyindolenine (**390**)	246
		Voaphylline (**282**)	246
	Root-bark, stems	Heyneanine (**17**)	274,277
		Voacamine (**485**)	271,274,277
		Voacristine (= Voacangarine) (**19**)	270,272,273,277
	Leaves, flowers	*N*(1)-Methylvoaphylline (= Hecubine) (**283**)	265,278,280
		Voaphylline (= Conoflorine) (**282**)	265,272,273,280
	Leaves, stem-bark	Voacangine (**18**)	270–273,279

Table 1.2, continued

Plant	Plant part	Alkaloids	References
	Root-bark, stem-bark	Ibogamine (**13**)	274,279
	Stem-bark	*O*-Acetylvallesamine (**104**)	281
		Apparicine (**105**)	281
		Conodusarine (**487**)	282
		Conofoline (**540**)	281
		Conolobine A (**107**)	281
		Conolobine B (**108**)	281
		Conolodine (**106**)	281
		Coronaridine (**16**)	281
		3(*S*)-Cyanocoronaridine (**381**)	281
		3(*S*)-Cyanoisovoacangine (**383**)	281
		3(*S*)-Cyanovoacangine (**382**)	281
		10,11-Demethoxychippiine (**425**)	281
		19,20-Dehydroervatamine (**81**)	281
		3(*R*/*S*)-Ethoxycoronaridine (**334**)	281
		3(*R*/*S*)-Ethoxyvoacangine (**354**)	281
		Heyneanine (**17**)	281
		10-Hydroxycoronaridine (**316**)	281
		16(*S*)-Hydroxy-16,22-dihydroapparicine (**102**)	281
		19(*S*)-Hydroxyibogamine (**14**)	281
		Ibogaine (**360**)	281
		Ibogamine (**13**)	281
		Iboxygaine (**362**)	281
		(16*R*,19*E*)-Isositsirikine (**119**)	281
		Isovoacangine (**318**)	270,279,281
		Lirofoline B (**440**)	240
		(–)-Mehranine (**241**)	281
		Methuenine (**82**)	281
		3-Oxocoronaridine (**335**)	281
		3-Oxovoacangine (**340**)	281
		Pachysiphine (**218**)	281
		Pericyclivine (**138**)	281
		Tubotaiwine (**213**)	281
		Vallesamine (**103**)	281
		Voacamine (**485**)	281
		Voacangine (**18**)	281
		Voacangine-7-hydroxyindolenine (**390**)	281
		Voacristine (**19**)	281
		Voafinidine (**289**)	281
		Voafinine (**285**)	281
		Voalenine (**292**)	281
		Voaphylline (**282**)	281
		Voastrictine (**77**)	281
		Vobasine (**48**)	281
	Leaves, stems, roots	Vobasine (**48**)	270,271
	Leaves, stems, roots, flowers	Tabernaemontanine (**50**)	161,270–273

Table 1.2, continued

Plant	Plant part	Alkaloids	References
	Whole plant	Conofoline (**540**)	283
		Cononitarine B (**511**)	283
		Conophylline (**538**)	283
		Ervachinine A (**466**)	283
		Ervachinine B (= Ervatensine A) (**467**)	283
		Ervachinine C (**443**)	283
		19-*Epi*-isovoacristine (**372**)	283
		Heyneanine (**17**)	283
		Ibogaine (**360**)	283
		Isovoacangine (**318**)	283
		N(1)-Methylvoaphylline (**283**)	283
		Picrinine (**188**)	283
		Tabernaecorymbosine A (**518**)	283
		Tabernanthine (**384**)	283
		Tabernaricatine A (**536**)	283
		Tabernaricatine B (**537**)	283
		Tabernaricatine C (**531**)	283
		Tabernaricatine D (**532**)	283
		Tabernaricatine E (**445**)	283
		Tabernaricatine F (**399**)	283
		Tabernaricatine G (**387**)	283
		3-(2'-Oxopropyl)-voacangine (**347**)	283
		19,20-*E*-Vallesamine (**103**)	283
		Voacangine-7-hydroxyindolenine (**390**)	283
		Voacristine (**19**)	283
		Voacristine-7-hydroxyindolenine (**393**)	283
		Voaphyllinediol (**290**)	283
T. eglandulosa Stapf (*T. chartacea, Gabunia eglandulosa, G. longifera*)	Leaves, twigs	16,17-Anhydrotacamine (**304**)	284
		(+)-20(*R*)-1,2-Dehydropseudoaspidospermidine (**266**)	284
		16(*R*)-Descarbomethoxytacamine (**312**)	284
		16(*S*)-Descarbomethoxytacamine (**313**)	284
		(+)-20(*R*)-15,20-Dihydrocleavamine (**255**)	284
		(−)-20(*S*)-15,20-Dihydrocleavamine (**256**)	284
		16-*Epi*-tacamine (**309**)	284
		11-Hydroxycoronaridine (**317**)	284
		(+)-20(*S*)-Hydroxy-1,2-dehydropseudo-aspidospermidine (**269**)	284
		19(*S*)-Hydroxytacaine (**311**)	284
		17-Hydroxytacamonine (**306**)	284
		Ibogamine (**13**)	284
		Norfluorocurarine (**52**)	284
		20(*R*)-Pseudovincadifformine (**259**)	284
		Tacamine (**308**)	284
		Tacamonine (**305**)	284
		(+)-Tubotaiwine (**213**)	284
		Voaphylline (= Conoflorine) (**282**)	284
	Root-bark	Isovoacangine (**318**)	285
		Perivine (**170**)	285
		Voacamine (**485**)	285
	Root-bark	3(*R*/*S*)-Hydroxycoronaridine (**333**)	285
		3(*R*/S)-Hydroxyisovoacangine (**339**)	285
	Stem-bark	Conopharyngine (**319**)	209

Table 1.2, continued

Plant	Plant part	Alkaloids	References
	Roots, stems	Eglandine (**336**)	286
		Eglandulosine (= 3-Oxocoronaridine) (**335**)	286
	Leaves, twigs, stem-bark	Coronaridine (**16**)	284,287
T. elegans Stapf (*Conopharyngia elegans*)	Leaves	Alasmontanine A (**548**)	288
		Eleganine A (**174**)	289
		Dregamine (**156**)	289
		Tabernaemontanine (**50**)	289
		Tabernine A (**61**)	290
		Tabernine B (**62**)	290
		Tabernine C (**63**)	290
		Vobasine (**48**)	289
	Whole plant	Appariciné (**105**)	291
		Dregaminol (**178**)	291
		Dregaminol methyl ether (**179**)	291
		3'(*R*/S)-Hydroxyconodurine (**504**)	291
		16(*S*)-Hydroxy-16,22-dihydroappariciné (**102**)	291
		3'(*R*/*S*)-Hydroxytabernaelegantine B (**447**)	291
		Isovoacangine (**318**)	291
		3'-Methoxytabernaeelegantine C (**515**)	291
		Tabernaemontaninol (**177**)	291
		(+)-Tubotaiwine (**213**)	291
		Vobasine (**48**)	291
		Vobasinol (**180**)	291
	Roots	Dregamine (**156**)	292
		16-*Epi*-dregamine (**157**)	292
		Tabernaelegantine B **(446**)	292
		Tabernaelegantine C (**513**)	292
		Tabernaemontanine (**50**)	292
		Voacangine (**18**)	292
	Root-bark	Conoduramine (**457**)	293
		Tabernaelegantinine A (**517**)	294
		Tabernaelegantinine B (**450**)	294
		Tabernaelegantinine C (**516**)	294
		Tabernaelegantinine D (**449**)	294
	Whole plant, root-bark	Dregamine (**156**)	291,293
		Tabernaelegantine A (**512**)	291,293,294
		Tabernaelegantine B (**446**)	291,293,294
		Tabernaelegantine C (**513**)	291,293,294
		Tabernaelegantine D (**448**)	291,293,294
		Tabernaemontanine (**50**)	291,293
T. eusepala Aug. DC. (*Pandaca eusepala*)	Stem-bark	Appariciné (**105**)	295
		(+)-20(*S*)-1,2-Dehydropseudoaspidospermidine (**267**)	295
		(+)-20(*R*)-15,20-Dihydrocleavamine (**255**)	295
		(−)-20(*S*)-15,20-Dihydrocleavamine (**256**)	295
		19-*Epi*-voacristine (= 19-*Epi*-voacangarine) (**366**)	295
		Ibogaine (**360**)	295
		Ibogaine-7-hydroxyindolenine (**396**)	295

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		Vobasine (**48**)	295
T. flavicans Willd. Ex Roem. & Schult. (*Anartia flavicans*)	Stems	Ibophyllidine (**279**)	118,296
		Ibophyllidine *N*(4)-oxide (**280**)	118,296
T. fuchsiaefolia A. DC. (*Peschiera fuchsiaefolia*)	Stem-bark	Affinisine (**136**)	297
		16'-Decarbomethoxyvoacamine (**58**)	298,299
		N(4)-Demethylvoacamine (**489**)	298,299
		Ervahanine A (**480**)	299
		Euchsiaefoline (**149**)	299,300
		Heyneanine (**17**)	299
		3(*R*/*S*)-Hydroxycoronaridine (**333**)	299
		Ibogamine (**13**)	299
		12-Methoxy-*N*(4)-methylvoachalotine (**147**)	300
		12-Methoxy-*N*(4)-methylvoachalotine ethyl ester (**148**)	300
		Perivine (**170**)	298,299
		Tabernamine (**57**)	299
		Voacamidine (**442**)	298,299
		Voacamine (**485**)	301
		Voacangine (**18**)	301
		Voachalotine (**137**)	297,301
		Voacristine (= Voacangarine) (**19**)	299
		Vobasinol (**180**)	299
T. glandulosa (Stapf) Pichon	Leaves, stems	Conophylline (**538**)	302
		Coronaridine (**16**)	302
		12-Demethoxytabernulosine (**186**)	303
		Difforlemenine (**196**)	302
		Difforlemenitine (**194**)	302
		10,12-Dimethoxynareline (**197**)	302
		19-*Epi*-difforlemenitine (**195**)	302
		3(*R*/*S*)-Ethoxycoronaridine (**334**)	304
		3(*R*/*S*)-Hydroxycoronaridine (**333**)	305
		Tabernulosine (**185**)	302
		Vincadiffine (**167**)	302
		Voacangine (**18**)	302
		Vobasine (**48**)	302
T. grandiflora L.	Stem-bark	Coronaridine-7-hydroxyindolenine (**388**)	306
		3(*R*/*S*)-Hydroxyvoacangine (**341**)	306
		Heyneanine (**17**)	306
		3-Hydroxyvoacangarine (**353**)	306
		Voacangarine (= Voacristine) (**19**)	306
		Voacangine (**18**)	306
		Voacangine-7-hydroxyindolenine (**390**)	306
	Seeds	Conoflorine (= Voaphylline) (**282**)	307
		14,15-Dehydrotetrastachynine (**558**)	307
		11-Hydroxycoronaridine (**317**)	307
		14β-Hydroxyquebrachamine (**288**)	307
		3-Oxotabersonine (**221**)	307

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		3-Oxovincadifformine (**222**)	307
		Pachysiphine (**218**)	307
		Quebrachamine (**287**)	307
		Tabersonine (**216**)	307
	Seeds, stem-bark	Coronaridine (**16**)	306,307
T. heterophylla Vahl (*T. tenuiflora, Peschiera heterophylla, P. diversifolia, P. tenuifolia, Stenosolen heterophyllus*)	Leaves	Affinisine (**136**)	308
		Apparicine (**105**)	308
		Coronaridine (**16**)	308
		16'-Decarbomethoxyvoacamine (**58**)	308
		3-*Epi*-ervafolidine (**550**)	309
		Ervafolene (**555**)	309,310
		Ervafolidine (**549**)	309
		Ervafoline (**553**)	309,310
		19'(*S*)-Hydroxy-3-*epi*-ervafolidine (**552**)	309
		19'(*R*)-Hydroxyervafolidine (**551**)	309
		19'-Hydroxyervafolene (**556**)	309,310
		19'-Hydroxyervafoline (**554**)	309,310
		Ibogaine (**360**)	308
		Ibogamine (**13**)	308
		Olivacine (**65**)	308
		Pandine (**270**)	308,310
		Pandoline (**260**)	308,310
		Tabernamine (**57**)	308
		3,14;4,19-Tetrahydroolivacine (**66**)	308
		Vallesamine (**103**)	308
		Voacamine (**485**)	308
		Voacangine (**18**)	310
		Voacangine-7-hydroxyindolenine (**390**)	310
		Voaphylline (= Conoflorine) (**282**)	308,310
		Vobasine (**48**)	308
T. heyneana Wall. (*Ervatamia heyneana, Pagiantha heyneana*)	Flowers	Coronaridine-7-hydroxyindolenine (**388**)	311
		Ervatine (**409**)	311
		15β-Stemmadenine (**101**)	312
		Tabersonine (**216**)	311
		Voacristine-7-hydroxyindolenine (**393**)	311
	Stem-bark	*O*-Acetylvallesamine (**104**)	313
		Apparicine (**105**)	313
		Camptothecin (**78**)	314
		10-Hydroxycoronaridine (**316**)	313
		9-Methoxycamptothecin (**79**)	314
		19(*S*)-3,19-Oxidovoacangine (**358**)	313
		6(*R*)-3,6-Oxidovoacangine *N*(4)-oxide (**403**)	313
		19-Oxovoacangine (= Voacryptine) (**367**)	313
		(+)-Tubotaiwine (**213**)	313
		Voacangine-7-hydroxyindolenine (**390**)	313
	Roots	Ibogamine (**13**)	315
		3-Oxocoronaridine (**335**)	315
		Voacangine pseudoindoxyl (= Voaluteine) (**406**)	315
	Leaves	Isovoacristine (**368**)	316

Table 1.2, continued

Plant	Plant part	Alkaloids	References
	Stem-bark, flowers	Heyneanine (**17**)	311,313,317,318
		Voacristine (= Voacangarine) (**19**)	311,313
	Stem-bark, leaves	Tabernoxidine (**417**)	319
	Stem-bark, roots	Voacangine (**18**)	313,315
	Stem-bark, flowers, seeds, roots	Coronaridine (**16**)	311,313,315,317,319,320
T. hilariana Müll. Arg.	Root-bark	Catharanthine (**420**)	321
		Coronaridine (**16**)	321
		Coronaridine pseudoindoxyl (**405**)	321
		3(*R*/*S*)-Hydroxycoronaridine (**333**)	321
		3(*R*/*S*)-Hydroxyvoacangine (**341**)	321
		Ibogamine (**13**)	321
		Isovoacangine (**318**)	321
		3-Oxocoronaridine (**335**)	321
		3-(2'-Oxopropyl)-coronaridine (**327**)	321
		Tabernanthine (**384**)	321
		Tetraphyllicine (**199**)	321
		Voacangine (**18**)	321
		Voacangine pseudoindoxyl (= Voaluteine) (**406**)	321
		Voacangine-7-hydroxyindolenine (**390**)	321
T. hirta Hook. f. (*E. hirta*)	Leaves, root-bark	*O*-Acetyl-16-*epi*-affinisine (**141**)	322
		Affinisine (**136**)	322
		Affinisine *N*(4)-oxide (**139**)	322
		Apparicine (**105**)	322
		16'-Decarbomethoxy-19,20-dihydrovoacamine (**473**)	322
		16'-Decarbomethoxyvoacamine (**58**)	322
		16'-Decarbomethoxyvoacamine pseudoindoxyl (**530**)	322
		Dehydro-16-*epi*-affinisine (**193**)	322
		19,20-Dehydro-β-yohimbine (**42**)	322
		4',17(β)-Dihydrotchibangensine (**583**)	322
		Dregamine (**156**)	322
		16-*Epi*-affinisine (**140**)	322
		16-*Epi*-normacusine B (**135**)	322
		12-Hydroxynorfluorocurarine (**209**)	322
		Ibogaine (**360**)	322
		Iboxygaine (**362**)	322
		Iboxygaine-7-hydroxyindolenine (**398**)	322
		Isositsirikine (**119**)	322
		Norfluorocurarine (**52**)	322
		Norfluorocurarine *N*(4)-oxide (**208**)	322
		Normacusine B (**51**)	322
		Tabernaemontanine (**50**)	322
		Voacristine (= Voacangarine) (**19**)	322
		Vobasine (**48**)	322

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		Yohimbine (**39**)	322
		β-Yohimbine (**38**)	322
		β-Yohimbine oxindole (**113**)	322
		β-Yohimbine pseudoindoxyl (**46**)	322
T. humblotii (Baill.) Pichon (*T. ochrascens*, *Pandaca ochrascens*, *P. speciosa*)	Leaves	Akuammicine (**204**)	323
		Akuammidine (**144**)	323
		Apparicine (**105**)	323
		(+)-14,15-Dehydro-16-*epi*-vincamine (**33**)	323
		19-*Epi*-iboxygaine (**363**)	323
		19-*Epi*-iboxygaline (**364**)	323
		Ibogaine (**360**)	323
		Iboxygaline (**365)**	323
	Leaves, stem-bark	Voacangine (**18**)	324
		Voacristine (= Voacangarine) (**19**)	324
T. hystrix Steud. (*T. echinata* Vell., *Peschiera echinata*)	Root-bark	Affinine (**164**)	325
		Affinisine (**136**)	325
		Coronaridine (**16**)	326
		Coronaridine hydroxyindolenine (**388**)	326
		Hystrixnine (**169**)	325
		Ibogamine (**13**)	325
		Ibogamine-7,8-dione (**379**)	326
		12-Methoxyvoachalotine (**146**)	326
		N(4)-Methylaffinisine (**151**)	325
		Olivacine (**65**)	325,326
		3-Oxocoronaridine (**335**)	326
		5-Oxocoronaridine (**373**)	326
		3-Oxocoronaridine hydroxyindolenine (**395**)	326
		Vobasine (**48**)	326
	Leaves, stem, root-bark	Augustine (**134**)	258
		Coronaridine (**16**)	258
		16'-Decarbomethoxyvoacamine (**58**)	258
		N(4)-Demethylvoacamine (**489**)	258
		10-Hydroxycoronaridine (**316**)	258
		10-Hydroxyheyneanine (**349**)	258
		Ibogaine (**360**)	258
		Ibogaine-7-hydroxyindolenine (**396**)	258
		16-*Epi*-isositsirikine (**118**)	258
		Olivacine (**65**)	258
		6(*R*)-3,6-Oxidovoacangine (**402**)	258
		3-Oxovoacangine (**340**)	258
		Pleiocarpamine (**128**)	258
		Tubotaiwine (**213**)	258
		Voacamine (**485**)	258
		Voacangine (**18**)	258
		Voacangine-7-hydroxyindolenine (**390**)	258
		Voacangine pseudoindoxyl (**406**)	258
		Voacristine (**19**)	258
		Vobasine (**48**)	258
T. laeta Mart.	Root-bark	Coronaridine (**16**)	327
		Heyneanine (**17**)	327

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		N(4)-Methylvoachalotine (**150**)	327
		Tabernamine (**57**)	327
		Voacangine (**18**)	327
	Leaves, stems	Affinine (**164**)	328,329
		Akuammidine (**144**)	328
		Conodurine (**500**)	329
		Geissoschizol (**116**)	328,329
		Normacusine B (**51**)	328
		Voacamine (**485**)	329
		Vobasine (**48**)	328,329
	Leaves, stems, root-bark	Conodurine (**500**)	327,328
		Voacamine (**485**)	327,328
T. longipes Donn. Sm.	Seeds	Tabersonine (**216**)	330
		Voacangine (**18**)	330
	Seeds, leaves	Coronaridine (**16**)	330,331
T. lundii A. DC. (*Peschiera lundii*)	Leaves, stem-bark	Coronaridine (**16**)	332
		19-*Epi*-voacristine (= 19-*Epi*-voacangarine) (**366**)	332
		Ibogaine (**360**)	332
		Iboxygaine (**362**)	332
		Iboxygaine-7-hydroxyindolenine (**398**)	332
		Voacangine (**18**)	332
		Voacristine (= Voacangarine) (**19**)	332
		Voacristine pseudoindoxyl (**407**)	332
		Vobasine (**48**)	332
T. macrocalyx Müll. Arg. (*Anacampta macrocalix*)	Stem-bark	Coronaridine-7-hydroxyindolenine (**388**)	333
		19-*Epi*-voacangarine (= 19-*Epi*-voacristine) (**366**)	333
		Heyneanine (**17**)	333
		3-Oxocoronaridine-7-hydroxyindolenine (**395**)	333
		Voacangarine-7-hydroxyindolenine (**393**)	333
		Voacangine-7-hydroxyindolenine (**390**)	333
	Leaves	10-Hydroxycoronaridine (**316**)	333
	Seeds	Tabersonine (**216**)	334
	Stem-bark, leaves	Voacangarine (= Voacristine) (**19**)	333
		Voacangine (**18**)	333
	Seeds, stem-bark	Coronaridine (**16**)	333,334
T. macrocarpa Jack (*Ervatamia macrocarpa,*	Roots	Coronaridine pseudoindoxyl (**405**)	335
		19-*Epi*-heyneanine (**321**)	335
		3-Oxocoronaridine (**335**)	335
		Voacangine pseudoindoxyl (= Voaluteine) (**406**)	335

Table 1.2, continued

Plant	Plant part	Alkaloids	References
Pagiantha macrocarpa)	Seeds	Voacangine (**18**)	336
		Voaphylline (= Conoflorine) (**282**)	336
	Seeds, roots	Coronaridine (**16**)	335,336
		Voacangine-7-hydroxyindolenine (**390**)	335,336
T. malaccensis Hook. f.	Leaves, root-bark	19,20-Dehydroervatamine (**81**)	337
		16-*Epi*-ervatamine (**90**)	337
		16-*Epi*-methuenine (= Isomethuenine) (**85**)	337
		Dregamine (**156**)	337
		N(1)-Methoxy-19,20-dehydroervatamine (**84**)	337
		N(1)-Methoxymethuenine (**87**)	337
		Methuenine (**82**)	337
		6-Oxomethuenine (**86**)	337
T. markgrafiana J. F. Macbr.	Bark	*O*-Acetylvallesamine (**104**)	338
		Akuammidine (**144**)	338
		Coronaridine (**16**)	338
		Coronaridine-7-hydroxyindolenine (**388**)	338
		5,6-Dehydrocoronaridine (**355**)	338
		10,11-Demethoxychippiine (**425**)	338
		16(*R*)-19,20-(*E*)-*Epi*-isositsirikine (**118**)	338
		Heyneanine (**17**)	338
		Heyneanine-7-hydroxyindolenine (**392**)	338
		3(*R*/*S*)-Hydroxycoronaridine (**333**)	338
		Ibogaine (**360**)	338
		Ibogamine (**13**)	338
		3(*R*)-Methoxycoronaridine (**338**)	338
		3(*R*)-Methoxyvoacangine (**342**)	338
		3-Oxocoronaridine (**335**)	338
		3-Oxovoacangine (**340**)	338
		Vallesamine (**103**)	338
		Voacangine (**18**)	338
		Voacristine (= Voacangarine) (**19**)	338
T. mauritiana Poir. (*Pandaca mauritiana*)	Roots, stem-bark	Dregamine (**156**)	336
		Vobasine (**48**)	336
	Roots, stem-bark, leaves	(+)-Tubotaiwine (**213**)	336
T. minutiflora Pichon (*Pandaca minutiflora*)	Leaves	(+)-Condylocarpine (**212**)	339
		Coronaridine (**16**)	339
		Stemmadenine (**99**)	339
		Stereoisomer of 15,20; 15',20'-tetrahydro-presecamine (**590**)	339
		(+)-Tubotaiwine (**213**)	339
		(+)-Vincadifformine (**232**)	339
		Vobasine (**48**)	339

Table 1.2, continued

Plant	Plant part	Alkaloids	References
T. mocquerysii Aug. DC. (*T. boiteaui*, *Pandaca boiteaui*, *P. callosa*, *P. mocquerysii*)	Stem-bark	20'(*R*)-Capuvosidine (**562**)	182,340
		16'-Decarbomethoxyvoacamine (**58**)	340
		19,20-Dehydroervatamine (**81**)	340
		20(*S*)-1,2-Dehydropseudoaspidospermidine (**267**)	340
		20'(*R*)-Dehydroxycapuvosine (**576**)	340
		20'(*R*)-Dehydroxyisocapuvosine (**575**)	340
		20'(*R*)-1,2-Dihydrocapuvosidine (**563**)	340
		20'(*S*)-1,2-Dihydrocapuvosidine (**564**)	340
		(+)-20(*R*)-15,20-Dihydrocleavamine (**255**)	340
		(−)-20(*S*)-15,20-Dihydrocleavamine (**256**)	340
		20(*R*)-Pseudoaspidospermidine (**272**)	340
		20(*S*)-Pseudoaspidospermidine (**273**)	340
		(+)-Tubotaiwine (**213**)	340
		Voacamine (**485**)	340
	Root-bark	Coronaridine (**16**)	341
		19-*Epi*-heyneanine (**321**)	341
		19-*Epi*-voacristine (= 19-*Epi*-voacangarine) (**366**)	341
		Heyneanine (**17**)	341
		Voacangine (**18**)	341
		Voacristine (= Voacangarine) (**19**)	341
	Root-bark, stem-bark	Ervitsine (**96**)	340,342
		Methuenine (**82**)	340,342
T. mucronata Merr. (*Ervatamia mucronata*)	Bark	Coronaridine (**16**)	343
		Tabernaemontanine (**50**)	343
T. olivacea Müll. Arg.	Stems	Akuammidine (**144**)	344
		Condylocarpine *N*(4)-oxide (**214**)	344
		Coronaridine (**16**)	344
		Coronaridine-7-hydroxyindolenine (**388**)	344
		Coronaridine pseudoindoxyl (**405**)	344
		Heyneanine (**17**)	344
		Ibogaine (**360**)	344
		Ibogamine (**13**)	344
		Voacangine (**18**)	344
		Voacangine-7-hydroxyindolenine (**390**)	344
		Voacangine pseudoindoxyl (= Voaluteine) (**406**)	344
		Voacristine (= Voacangarine) (**19**)	344
T. orientalis R. Br. (*Ervatamia lifuana*, *E. daemeliana*)	Bark	16'-Decarbomethoxy-19,20-dihydro-20-*epi*-voacamine (**474**)	345
		16'-Decarbomethoxy-19,20-dihydrovoacamine (**473**)	345
		16'-Decarbomethoxyvoacamine (**58**)	345
		Dregamine (**156**)	345
		Voacamine (**485**)	345
		Voacristine (= Voacangarine) (**19**)	345
	Leaves	Apparicine (**105**)	345
		Ibogaine (**360**)	345
		Iboxygaine (**362**)	345

Table 1.2, continued

Plant	Plant part	Alkaloids	References
	Leaves, twigs	Conopharyngine (**319**)	346
		Coronaridine (**16**)	346
		20-*Epi*-pandoline (**261**)	346
		Ervatamine (**88**)	346
		Pandine (**270**)	346
		Pandoline (**260**)	345
	Leaves, stem-bark	19,20-Dehydroervatamine (**81**)	345
	Bark, leaves, twigs	Tabernaemontanine (**50**)	345,346
	Leaves, twigs, bark	Dregamine (**156**)	345
	Leaves, twigs, stem-bark	20-*Epi*-ervatamine (**89**)	345
T. pachysiphon Stapf. (*T. cumminsii*, *T. holstii*)	Leaves	Conopharyngine-7-hydroxyindolenine (**391**)	347
		Conopharyngine pseudoindoxyl (**408**)	348
		19(*S*)-Hydroxyconopharyngine (**370**)	348
	Seeds	Pachysiphine (**218**)	349
		Voacangine (**18**)	349
	Root-bark, stem-bark	Affinine (**164**)	350
		Anhydrovobasindiol (= Taberpsychine) (**191**)	350
		Conoduramine (**457**)	350
		Conodurine (**500**)	350
		Coronaridine (**16**)	350
		11'-Demethylconoduramine (**456**)	350
		16-*Epi*-affinisine (**140**)	350
		16-*Epi*-isositsirikine (**118**)	350
		Gabunine (**499**)	350
		3(*R*/*S*)-Hydroxyconopharyngine (**344**)	350
		Ibogaline (**385**)	350
		Isositsirikine (**119**)	350
		Lochnericine (**219**)	350
		Normacusine B (**51**)	350
		3'-Oxoconodurine (**501**)	350
		3-Oxocoronaridine (**335**)	350
		3'-(2-Oxopropyl)-conodurine (**502**)	350
		Pericyclivine (**138**)	350
		Perivine (**170**)	350
	Leaves, stem-bark, root-bark	Apparicine (**105**)	350,351
		Conopharyngine (**319**)	350,352
		(+)-Tubotaiwine (**213**)	349,353,354
		(+)-Tubotaiwine *N*(4)-oxide (**215**)	350,354
		Isovoacangine (**318**)	350,354

Table 1.2, continued

Plant	Plant part	Alkaloids	References
T. pandacaqui Poir. (*T. laurifolia, Ervatamia pandacaqui*)	Leaves	*O*-Acetylvallesamine (**104**)	355
		Akuammicine (**204**)	355
		3-*Epi*-ervafolidine (**550**)	356
		(+)-20-*Epi*-lochneridine (**211**)	357
		Ervafolidine (**549**)	356
		Ervafoline (**553**)	356
		Pericyclivine (**138**)	356
		Vallesamine (**103**)	355
	Bark	Coronaridine (**16**)	358,359
		Ibogamine (**13**)	358
		Iboxygaine (**362**)	358
		Isovoacangine (**318**)	358
		Isovoacristine (**368**)	358
		Tabernanthine (**384**)	358
	Stems	Ervatamine (**88**)	355
		Voaluteine (= Voacangine pseudoindoxyl) (**406**)	355
	Leaves, stems	Pandine (**270**)	355
		Tabernaemontanine (**50**)	355,356
		Voacangine (**18**)	355,360
		Voacristine (= Voacangarine) (**19**)	355
T. peduncularis Wall. (*E. peduncularis*)	Leaves, stem-bark	Coronaridine (**16**)	361
		Heyneanine (**17**)	361
		Heyneanine-7-hydroxyindolenine (**392**)	361
		Pedunculine (= Conofoline) (**540**)	361
		Peduncularidine (**541**)	361
T. peduliflora K. Schum. (*Conopharyngia penduliflora*)	Stem-bark	Conopharyngine (**319**)	209
		Coronaridine (**16**)	209,362
		10-Hydroxycoronaridine (**316**)	363
		Voacangine (**18**)	209,363
T. psorocarpa (Pierre ex Stapf) Pichon	Stem-bark	Coronaridine (**16**)	364
		16-*Epi*-isositsirikine (**118**)	364
		Isovallesiachotamine (**132**)	364
		12-Methoxy-14,15-dehydrovincamine (**298**)	364
		Tetrahydroalstonine (**35**)	364
		Vallesiachotamine (**131**)	364
		Voacangine (**18**)	364
T. psychotriifolia H. B. K.	Leaves	16-*Epi*-isositsirikine (**118**)	258
		19-*Epi*-voacristine (= 19-*Epi*-voacangarine) (**366**)	258
		10-Hydroxycoronaridine (**316**)	258
		10-Hydroxyheyneanine (**349**)	258
		(+)-Tubotaiwine (**213**)	258
		Voacristine (= Voacangarine) (**19**)	258
	Stem-bark	Anhydrovobasindiol (= Taberpsychine) (**191**)	365
		16-*Epi*-vobasinic acid (**166**)	365
		Ibogaine-7-hydroxyindolenine (**396**)	258
		6(*R*)-3,6-Oxidovoacangine (**402**)	258
		3-Oxovoacangine (**340**)	258

Table 1.2, continued

Plant	Plant part	Alkaloids	References
	Roots	Voacamine (**485**)	258
	Root-bark	Voacamidine (**442**)	258
	Leaves, root-bark	Vobasine (**48**)	258
		Pleiocarpamine (**128**)	258
	Stem-bark, root-bark	16'-Decarbomethoxyvoacamine (**58**)	258
		Ibogaine (**360**)	258
		N(4)-Demethylvoacamine (**489**)	258
	Roots, stem-bark	Coronaridine (**16**)	258
	Root-bark, stem-bark	Affinine (**164**)	365
	Leaves, stem-bark, root-bark	Voacangine (**18**)	258
T. quadrangularis	Roots	Coronaridine (**16**)	366
		19-*Epi*-heyneanine (**321**)	366
		Heyneanine (**17**)	366
		19(*R*)-Hydroxyibogamine (**15**)	366
		19(*R*)-Hydroxyibogamine pseudoindoxyl (**412**)	366
		Ibogaine (**360**)	366
		Ibogamine (**13**)	366
		Ibogamine pseudoindoxyl (**410**)	366
		3-Oxocoronaridine (**335**)	366
		3-Oxovoacangine (**340**)	366
		Voacangine (**18**)	366
		Voacangine-7-hydroxyindolenine (**390**)	366
T. retusa (Lam.) Pichon (*T. noronhiana*, *Conopharyngia retusa*, *Pandaca retusa*, *Plumeria retusa*)	Leaves	Coronaridine (**16**)	367
		Heyneanine (**17**)	367
		3-Oxovoacangine (**340**)	367
		Voacangine (**18**)	367
		Voacristine (= Voacangarine) (**19**)	367
	Seeds	Pachysiphine (**218**)	368
		Tabersonine (**216**)	368
		Voaphylline (= Conoflorine) (**282**)	368
T. riedlii Müll. Arg.	Leaves, seeds	(+)-Minovincine (**233**)	369
		3-Oxominovincine (**234**)	369
		(+)-Vincadifformine (**232**)	369
		rac-vincadifformine (*rac*-**232**)[a]	369

Table 1.2, continued

Plant	Plant part	Alkaloids	References
T. rigida (Miers) Leeuwenberg (*T. macrophylla, Anacampta rigida, Phrissocarpus rigidus*)	Stem-bark	(+)-Apovincamine (**303**)	369
		(–)-16-*Epi*-vincamine (**296**)	369
		(+)-21-*Epi*-vincamine (**297**)	369
		(+)-Vincamine (**295**)	369
		rac-16-*Epi*-vincamine (*rac*-**296**)[a]	369
		rac-21-*Epi*-vincamine (*rac*-**297**)[a]	369
		rac-Vincamine (*rac*-**295**)[a]	369
T. rupicola Benth. (*Anacampta rupicola*)	Leaves, twigs	Voacangine pseudoindoxyl (= Voaluteine) (**406**)	370
		Voacristine pseudoindoxyl (**407**)	370
T. salzmannii (A. DC.) Miers (*P. salzmannii*)	Leaves	3(*S*)-Hydroxyisovoacangine (**339**)	371
		Isovoacangine (**318**)	371
		Isovoacristine (**368**)	371
	Root-bark	Coronaridine (**16**)	371
		Heyneanine (**17**)	371
		Olivacine (**65**)	371
		3-Oxocoronaridine (**335**)	371
		Voacangine (**18**)	371
		Voachalotine (**137**)	371
T. sananho Ruíz & Pav.	Bark	Coronaridine (**16**)	372
		Heyneanine (**17**)	372
		3(*R*/*S*)-Hydroxycoronaridine (**333**)	372
		Ibogamine (**13**)	372
		Voacangine (**18**)	372
T. sessilifolia Bak. (*Muntafara sessilifolia*)	Leaves, stem-bark	Apparicine (**105**)	373
		Coronaridine (**16**)	373
		Dregamine (**156**)	373
		6-Hydroxy-3-oxocoronaridine (**376**)	373
		6-Hydroxy-3-oxoisovaocangine (**377**)	373
		Isovoacangine (**318**)	373
		6(*R*)-3,6-Oxidocoronaridine (**400**)	373
		6(*R*)-3,6-Oxidoisovoacangine (**401**)	373
		Tabernaemontanine (**50**)	373
	Stem-bark	Coronaridine (**16**)	374
		19,20α-Dihydroeleganine A (**175**)	374
		3(*R*/*S*)-Hydroxycoronaridine (= Eglandine) (**333**)	374
		3'(*R*/*S*)-Hydroxytabernaelegantine A (**493**)	374
		3'(*S*)-Hydroxytabernaelegantine C (**494**)	374
		3-Oxocoronaridine (= Eglandulosine) (**335**)	374
		3-Oxocoronaridine hydroxyindolenine (**395**)	374
		3'-Oxotabernaelegantine A (**492**)	374
		3'-Oxotabernaelegantine B (**465**)	374
		Tabernaelegantine A (**512**)	374
		Tabernaelegantine D (**448**)	374
		Tabernaemontanine (**50**)	374

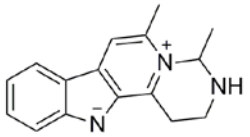
Table 1.2, continued

Plant	Plant part	Alkaloids	References
T. siphilitica Leeuwenberg (*T. tetratachia, Bonafousia tetrastachia, Echites siphilitica*)	Leaves	Apparicine (**105**)	375
		12,12'-Bis(11-hydroxycoronaridinyl) (**567**)	376
		Bonafousine (**581**)	377,378
		Coronaridine (**16**)	376
		Geissoschizine (**120**)	379
		12-Hydroxyvincadifformine (**223**)	375
		Isobonafousine (**582**)	378
		Isovoacangine (**318**)	375,376
		Pleiocarpamine (**128**)	375
		Tetrahydroalstonine (**35**)	375
		Tetrastachyne (**557**)	375
		Tetrastachynine (**559**)	375
		(+)-Tubotaiwine (**213**)	375
		(+)-Vincadifformine (**232**)	375
		Voacangine (**18**)	375,376
T. sphaerocarpa Bl. (*Pagiantha sphaerocarpa*)	Leaves, seeds	Dregamine (**156**)	380
		Tabernaemontanine (**50**)	380
	Stem	Biscarpamontanine A (**566**)	381
		Biscarpamontanine B (**545**)	381
		3-Hydroxyvoacangine (**341**)	381
		3-Hydroxyvobtusine (**547**)	381
		Ibogamine (**13**)	381
		Voacangine (**18**)	381
		Vobasine (**48**)	381
		Vobtusine (**544**)	381
		Vobtusine lactone (**546**)	381
T. stapfiana Britten (*T. johnstonii* (Stapf) Pichon, *Conopharyngia johnstonii*)	Stem-bark	Conoduramine (**457**)	382
		Conodurine (**500**)	382
		19',20'-Epoxyconoduramine (**458**)	382
		Gabunamine (**455**)	382
		Gabunine (**499**)	382
		Ibogamine (**13**)	382
		Pericyclivine (**138**)	382
		Perivine (**170**)	382
		Tabernamine (**57**)	383
	Root-bark	Ibogamine (**13**)	383
		Tabernamine (**57**)	383
		Tubotaiwine (**213**)	384
		Tubotaiwine *N*-oxide (**215**)	384
T. stellata Pichon (*Pandaca stellata*)	Root-bark	Coronaridine (**16**)	367
T. subglobosa Merr.	Twigs	Ervatamine (**88**)	385
		Vobasine (**48**)	385
	Leaves, roots	Conoduramine (**457**)	386
		Conodurine (**500**)	386
		Coronaridine (**16**)	386

Table 1.2, continued

Plant	Plant part	Alkaloids	References
		Heyneanine (**17**)	386
		19'(*R*)-Hydroxyconoduramine (**460**)	386
		19'(*R*)-Hydroxyconodurine (**503**)	386
		Isovoacangine (**318**)	386
		Tabernaelegantine A (**512**)	386
		Tabernaelegantine B (**446**)	386
		Tabernamine (**57**)	386
	Leaves, roots, twigs	Dregamine (**156**)	385,386
		Tabernaemontanine (**50**)	385,386
T. undulata Vahl (*Bonafusia undulata*)	Seeds, stem-bark	Coronaridine (**16**)	367,387
		Voaphylline (= Conoflorine) (**282**)	334
	Stem-bark	19-*Epi*-heyneanine (**321**)	334,387
		19-*Epi*-voacristine (= 19-*Epi*-voacangarine) (**366**)	387
		18-Hydroxycoronaridine (**331**)	387
		18-Hydroxyvoacangine (**332**)	387
		Quebrachidine (**198**)	334
		Voacangine (**18**)	333,387
T. ventricosa Hochst. ex A. DC.	Whole plant	Akuammicine (**204**)	388
		Akuammicine *N*-oxide (**205**)	388
		Apparicine (**105**)	388
		16-*Epi*-isositsirikine (**118**)	388
		10-Hydroxycoronaridine (**316**)	388
		10-Hydroxyheyneanine (**349**)	388
		Norfluorocurarine (**52**)	388
		(+)-Tubotaiwine (**213**)	388
T. wallichiana Steud.	Leaves	Isovoacangine (**318**)	389
	Leaves, stem-bark	Coronaridine (**16**)	389
		Voacangine (**18**)	389
		Voacristine (= Voacangarine) (**19**)	389

[a] *rac* = racemic.



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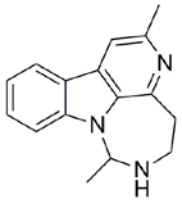

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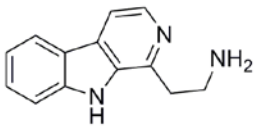

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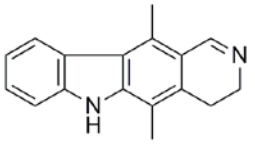

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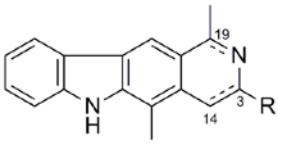
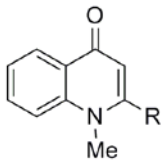
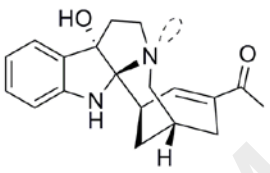


65 R = H, $\Delta^{3,14;4,19}$
66 R = H
67 R = OH
68 R = H, $\Delta^{4,19}$



69 R =
70 R =
71 R =
72 R =



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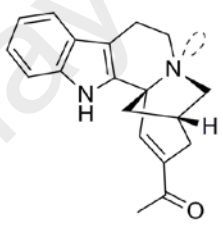

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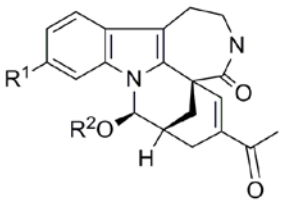
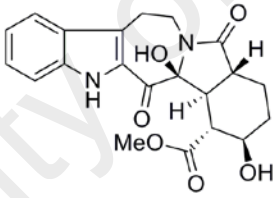


73 $R^1 = R^2 = H$
74 R^1 = OMe, R^2 = H
75 R^1 = H, R^2 = Et



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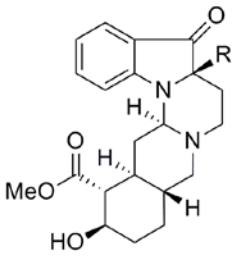
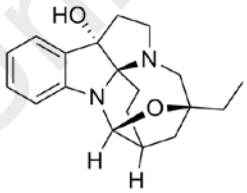


5 R = OH
6 R = OEt



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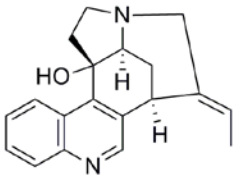

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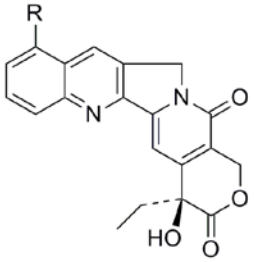
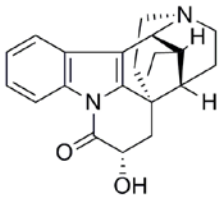
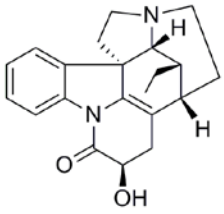


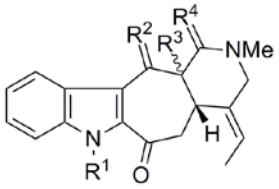
78 R = H
79 R = OMe



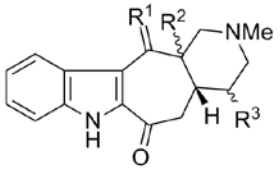
80



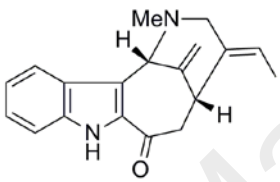
80a (revised)



81 R^1 = H, R^2 = R^4 = H,H, R^3 = β-CO_2Me
82 R^1 = H, R^2 = R^4 = H,H, R^3 = β-H
83 R^1 = H, R^2 = H,H, R^3 = β-CO_2Me, R^4 = O
84 R^1 = OMe, R^2 = R^4 = H,H, R^3 = β-CO_2Me
85 R^1 = H, R^2 = R^4 = H,H, R^3 = α-H
86 R^1 = H, R^2 = O, R^3 = β-H, R^4 = H,H
87 R^1 = OMe, R^2 = R^4 = H,H, R^3 = β-H



88 R^1 = H,H, R^2 = β-CO_2Me, R^3 = β-Et
89 R^1 = H,H, R^2 = β-CO_2Me, R^3 = α-Et
90 R^1 = H,H, R^2 = α-CO_2Me, R^3 = β-Et
91 R^1 = H,H, R^2 = β-H, R^3 = α-Et
92 R^1 = H,H, R^2 = β-H, R^3 = β-Et
93 R^1 = H,H, R^2 = α-H, R^3 = α-Et
94 R^1 = O, R^2 = β-H, R^3 = α-Et
95 R^1 = O, R^2 = α-H, R^3 = α-Et



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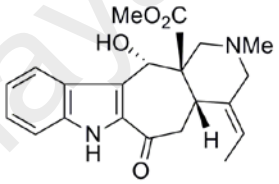

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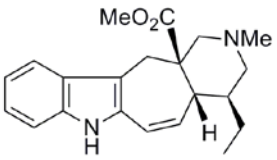
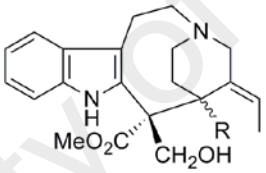
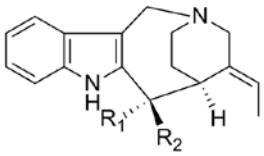


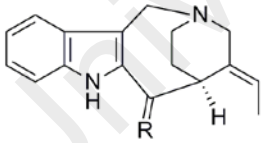
98



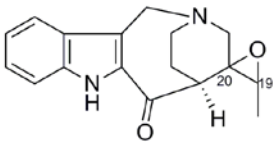
99 R = α-H
100 R = α-H, N(4)→O
101 R = β-H



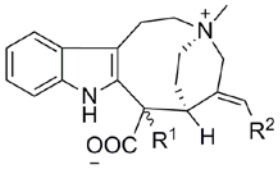
102 R^1 = OH, R^2 = Me
103 R^1 = CH_2OH, R^2 = CO_2Me
104 R^1 = CH_2OAc, R^2 = CO_2Me



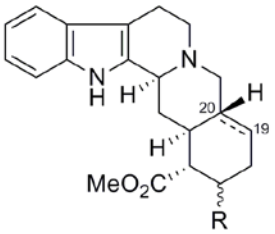
105 R = CH_2
106 R = O



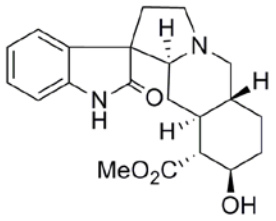
107 R = 19(*R*),20(*R*)
108 R = 19(*S*),20(*R*)



109 R^1 = β-H, R^2 = Me
110 R^1 = α-H, R^2 = Me
111 R^1 = α-CH_2OH, R^2 = Me
112 R^1 = α-CH_2OH, R^2 = CH_2OH



38 R = β-OH
39 R = α-OH
42 R = β-OH, $\Delta^{19,20}$



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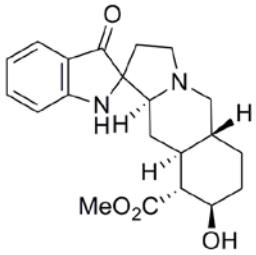

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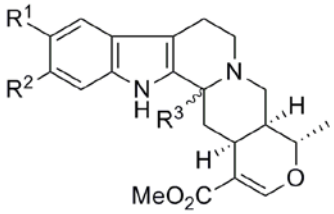
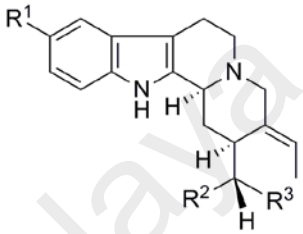
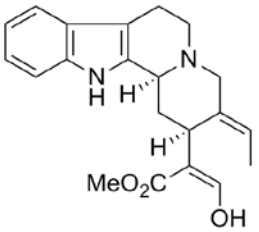


35 $R^1 = R^2 = H$, R^3 = α-H
114 $R^1 = R^2$ = OMe, R^3 = β-H
115 $R^1 = R^2$ = OMe, R^3 = α-H



116 $R^1 = R^3 = H$, $R^2 = CH_2OH$
117 R^1 = OH, $R^2 = CH_2OH$, $R^3 = H$
118 $R^1 = H$, $R^2 = CH_2OH$, $R^3 = CO_2Me$
119 $R^1 = H$, $R^2 = CO_2Me$, $R^3 = CH_2OH$



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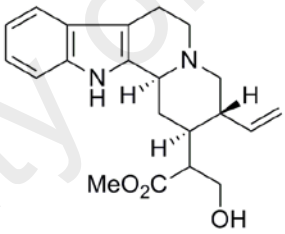

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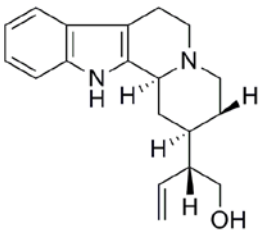

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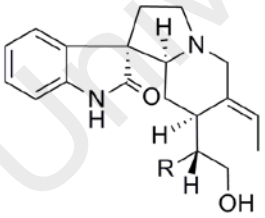
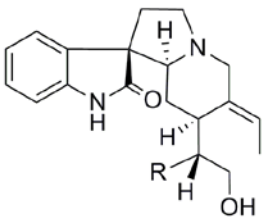
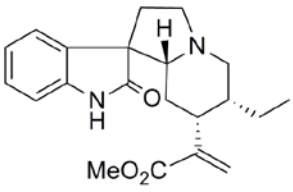


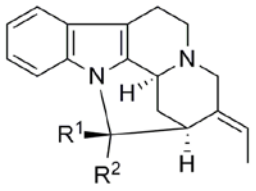
123 R = H
124 R = CO_2Me



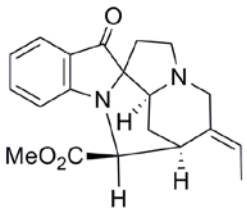
125 R = H
126 R = CO_2Me



127



128 $R^1 = CO_2Me$, $R^2 = H$
129 $R^1 = H$, $R^2 = CO_2Me$



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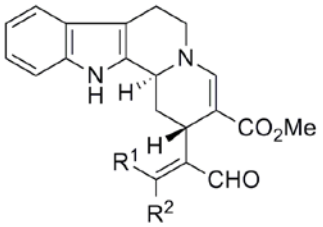
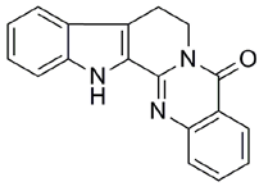


131 $R^1 = H$, $R^2 = Me$
132 $R^1 = Me$, $R^2 = H$



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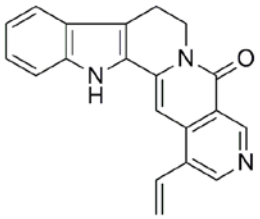

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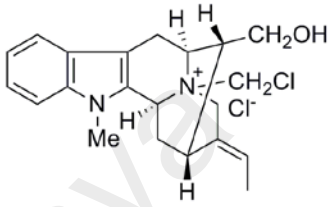

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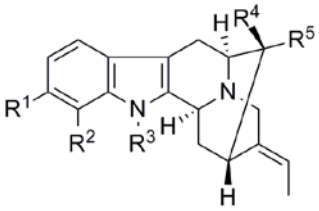
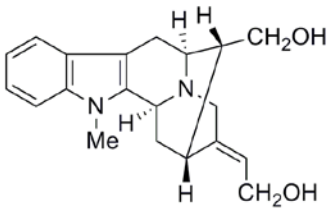


51 $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = CH_2OH$
135 $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = CH_2OH$
136 $R^1 = R^2 = R^4 = H$, $R^3 = Me$, $R^5 = CH_2OH$
137 $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = CH_2OH$, $R^5 = CO_2Me$
138 $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = CO_2Me$
139 $R^1 = R^2 = R^4 = H$, $R^3 = Me$, $R^5 = CH_2OH$, N(4)→O
140 $R^1 = R^2 = R^5 = H$, $R^3 = Me$, $R^4 = CH_2OH$
141 $R^1 = R^2 = R^5 = H$, $R^3 = Me$, $R^4 = CH_2OAc$
142 $R^1 = R^2 = R^5 = H$, $R^3 = Me$, $R^4 = CO_2Me$
143 $R^1 = R^2 = R^3 = H$, $R^4 = CH_2OH$, $R^5 = CO_2Me$
144 $R^1 = R^2 = R^3 = H$, $R^4 = CO_2Me$, $R^5 = CH_2OH$
145 $R^1 = R^2 = R^3 = H$, $R^4 = CH_2OAc$, $R^5 = CO_2Me$
146 $R^1 = H$, $R^2 = OMe$, $R^3 = Me$, $R^4 = CH_2OH$, $R^5 = CO_2Me$
147 $R^1 = H$, $R^2 = OMe$, $R^3 = Me$, $R^4 = CH_2OH$, $R^5 = CO_2Me$, $MeN(4)^+$
148 $R^1 = H$, $R^2 = OMe$, $R^3 = Me$, $R^4 = CH_2OH$, $R^5 = CO_2Et$, $MeN(4)^+$
149 $R^1 = R^4 = H$, $R^2 = OMe$, $R^3 = Me$, $R^5 = CO_2Et$, $MeN(4)^+$
150 $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = CH_2OH$, $R^5 = CO_2Me$, $MeN(4)^+$
151 $R^1 = R^2 = R^5 = H$, $R^3 = Me$, $R^4 = CH_2OH$, $MeN(4)^+$



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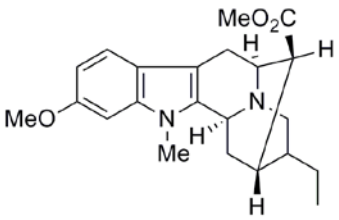

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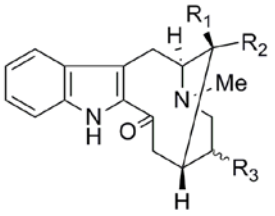
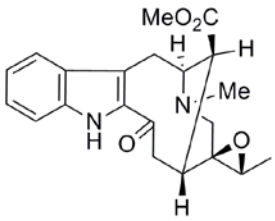


50 $R^1 = CO_2Me$, $R^2 = H$, $R^3 = \beta$-Et
155 $R^1 = H$, $R^2 = CO_2Me$, $R^3 = \beta$-Et
156 $R^1 = CO_2Me$, $R^2 = H$, $R^3 = \alpha$-Et
157 $R^1 = H$, $R^2 = CO_2Me$, $R^3 = \alpha$-Et



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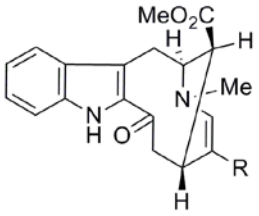
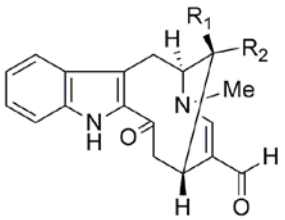
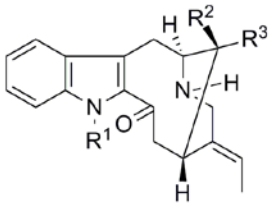


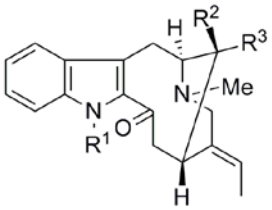
159 R = Et
160 R = Ac



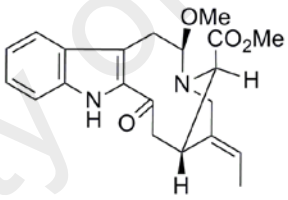
161 $R^1 = CO_2Me$, $R^2 = H$
162 $R^1 = H$, $R^2 = CO_2Me$



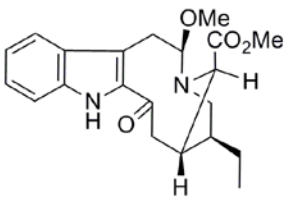
170 $R^1 = H$, $R^2 = CO_2Me$, $R^3 = H$
171 $R^1 = Me$, $R^2 = H$, $R^3 = CH_2OH$
172 $R^1 = R^3 = H$, $R^2 = CH_2OH$
173 $R^1 = H$, $R^2 = CO_2Me$, $R^3 = CH_2OH$



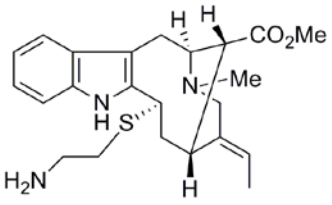
48 $R^1 = R^3 = H$, $R^2 = CO_2Me$
49 $R^1 = R^2 = H$, $R^3 = CH_2OH$
163 $R^1 = R^2 = H$, $R^3 = CO_2Me$
164 $R^1 = R^3 = H$, $R^2 = CH_2OH$
165 $R^1 = Me$, $R^2 = H$, $R^3 = CH_2OH$
166 $R^1 = R^2 = H$, $R^3 = COOH$
167 $R^1 = H$, $R^2 = CO_2Me$, $R^3 = CH_2OH$
168 $R^1 = Me$, $R^2 = CO_2Me$, $R^3 = H$
169 $R^1 = R^2 = H$, $R^3 = CH_2OMe$



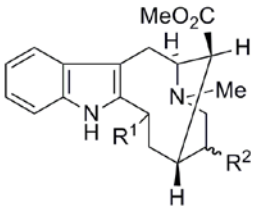
174



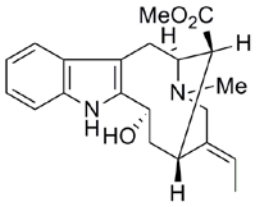
175



176



177 R^1 = α-OH, R^2 = β-Et
178 R^1 = α-OH, R^2 = α-Et
179 R^1 = OMe, R^2 = α-Et



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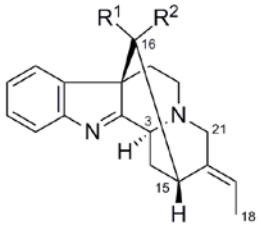
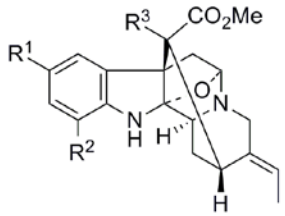
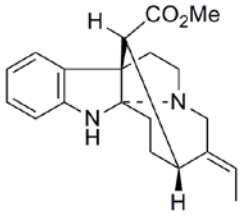


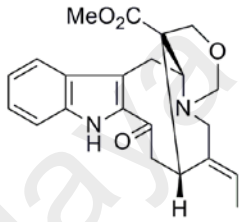
181 R^1 = CH_2OH, R^2 = CO_2Me
182 R^1 = CH_2OAc, R^2 = CO_2Me
183 R^1 = CO_2Me, R^2 = CHO
184 R^1 = H, R^2 = CO_2Me



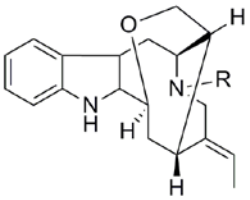
185 R^1 = R^2 = OMe, R^3 = H
186 R^1 = OMe, R^2 = R^3 = H
187 R^1 = R^2 = H, R^3 = CH_2OAc
188 R^1 = R^2 = R^3 = H



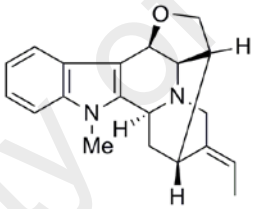
189



190



191 R = Me
192 R = H



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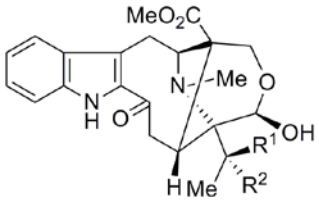
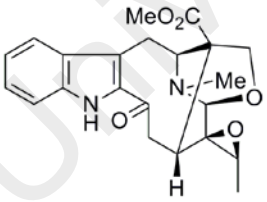


194 R^1 = OH, R^2 = H
195 R^1 = H, R^2 = OH



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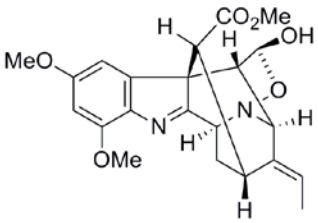

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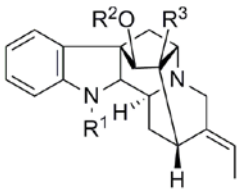
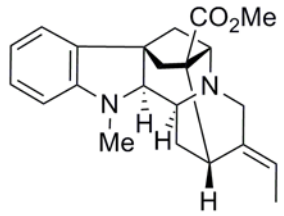
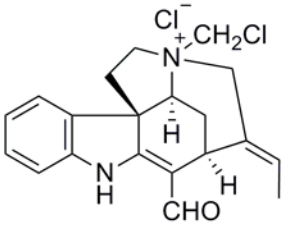


198 R^1 = R^2 = H, R^3 = CO_2Me
199 R^1 = Me, R^2 = R^3 = H
200 R^1 = Me, R^2 = $COC_6H_4(OMe)$, R^3 = H
201 R^1 = Me, R^2 = $COC_6H_3(OMe)_2$, R^3 = H
202 R^1 = Me, R^2 = $COC_6H_2(OMe)_3$, R^3 = H



203



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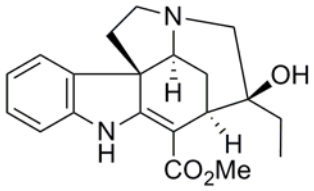

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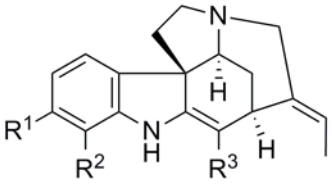


52 $R^1 = R^2 = H$, $R^3 = CHO$

204 $R^1 = R^2 = H$, $R^3 = CO_2Me$

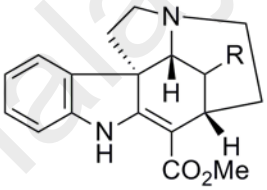
205 $R^1 = R^2 = H$, $R^3 = CO_2Me$, N(4)→O

206 $R^1 = H$, $R^2 = OH$, $R^3 = CO_2Me$

207 $R^1 = OH$, $R^2 = H$, $R^3 = CHO$

208 $R^1 = R^2 = H$, $R^3 = CHO$, N(4)→O

209 $R^1 = H$, $R^2 = OH$, $R^3 = CHO$

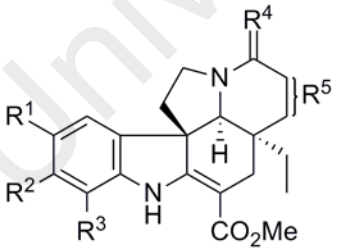


212 R = =CHMe

213 R = α-Et,

214 R = =CHMe, N(4)→O

215 R = α-Et, N(4)→O



216 $R^1 = R^2 = R^3 = H$, $R^4 = H,H$, $R^5 = \Delta^{14,15}$

217 $R^1 = R^2 = R^3 = H$, $R^4 = H,H$, $R^5 = \Delta^{14,15}$, N(4)→O

218 $R^1 = R^2 = R^3 = H$, $R^4 = H,H$, R^5 = 14,15-β-O

219 $R^1 = R^2 = R^3 = H$, $R^4 = H,H$, R^5 = 14,15-α-O

220 $R^1 = R^2 = R^3 = H$, $R^4 = H,H$, R^5 = 14,15-diol

221 $R^1 = R^2 = R^3 = H$, $R^4 = O$, $R^5 = \Delta^{14,15}$

222 $R^1 = R^2 = R^3 = H$, $R^4 = O$, R^5 = nil

223 $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = H,H$, R^5 = nil

224 $R^1 = R^3 = H$, $R^2 = OMe$, $R^4 = H,H$, R^5 = 14,15-O

225 $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = H,H$, R^5 = 14,15-β-O

226 $R^1 = OH$, $R^2 = OMe$, $R^3 = H$, $R^4 = H,H$, $R^5 = \Delta^{14,15}$

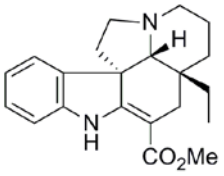
227 $R^1 = OH$, $R^2 = OMe$, $R^3 = H$, $R^4 = H,H$, R^5 = 14,15-α-O

228 $R^1 = OH$, $R^2 = OMe$, $R^3 = H$, $R^4 = O$, $R^5 = \Delta^{14,15}$

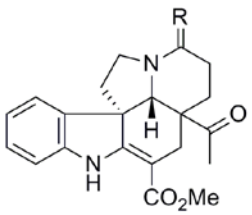
229 $R^1 = OH$, $R^2 = OMe$, $R^3 = H$, $R^4 = O$, R^5 = 14,15-α-O

230 $R^1 = OH$, $R^2 = OMe$, $R^3 = H$, $R^4 = H,H$, R^5 = nil

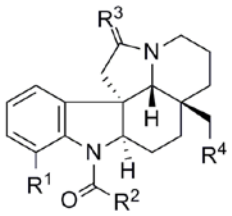
231 $R^1 = OH$, $R^2 = R^3 = OMe$, $R^4 = H,H$, R^5 = 14,15-β-O



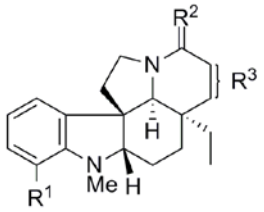
232



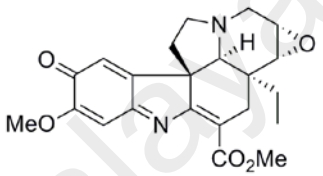
233 R = H,H
234 R = O



235 R^1 = OH, R^2 = R^4 = Me, R^3 = H,H
236 R^1 = OMe, R^2 = Me, R^3 = H,H, R^4 = CO_2Me
237 R^1 = H, R^2 = Me, R^3 = H,H, R^4 = CO_2Me
238 R^1 = OMe, R^2 = Et, R^3 = H,H, R^4 = CO_2Me
239 R^1 = OMe, R^2 = Me, R^3 = O, R^4 = CO_2Me
240 R^1 = OH, R^2 = Et, R^3 = H,H R^4 = Me



241 R^1 = H, R^2 = H,H, R^3 = 14,15-β-O
242 R^1 = H, R^2 = O, R^3 = 14,15-β-O
243 R^1 = OH, R^2 = H,H, R^3 = 14-αOH,15-βOH



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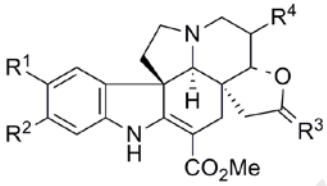
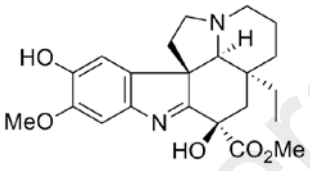


28 R^1 = R^2 = R^4 = H, R^3 = H,H
29 R^1 = H, R^4 = H, R^2 = OMe, R^3 = H,H
244 R^1 = R^2 = R^4 = H, R^3 = O
245 R^1 = R^2 = H, R^3 = O, R^4 = OH
246 R^1 = OH, R^2 = OMe, R^3 = H,H, R^4 = H



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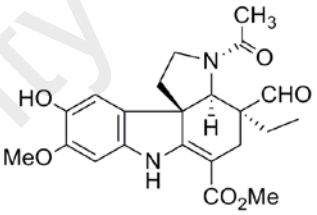

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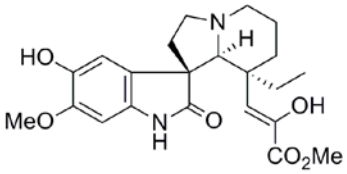

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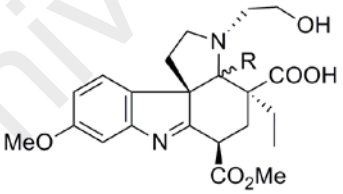
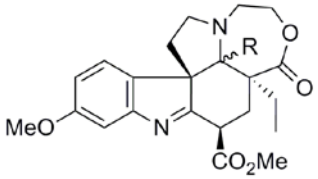
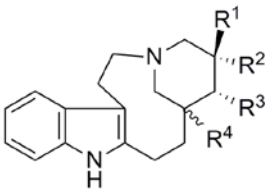


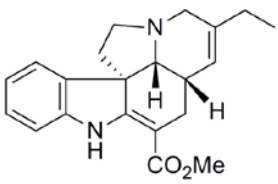
251 R = α-H
252 R = β-H



253 R = α-H
254 R = β-H



54 R^1 = OH, R^2 = Et, R^3 = H, R^4 = α-H
255 R^1 = R^3 = H, R^2 = Et, R^4 = β-H
256 R^1 = Et, R^2 = R^3 = H, R^4 = β-H
257 R^1 = H, R^2 = Et, R^3 = OH, R^4 = β-H



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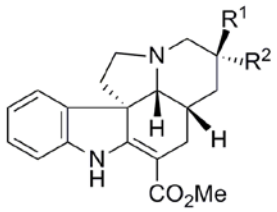
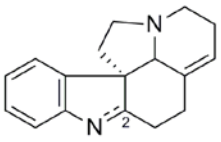
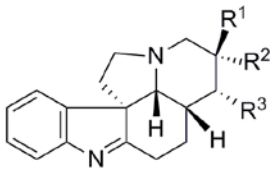


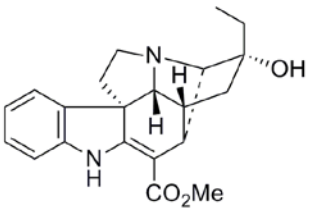
259 R^1 = H, R^2 = Et
260 R^1 = Et, R^2 = OH
261 R^1 = OH, R^2 = Et
262 R^1 = H, R^2 = $CH(OH)CH_2OH$
263 R^1 = OH, R^2 = CH(OH)Me



264
265 $\Delta^{1,2}$



266 R^1 = R^3 = H, R^2 = Et
267 R^1 = Et, R^2 = R^3 = H
268 R^1 = H, R^2 = Et, R^3 = OH
269 R^1 = OH, R^2 = Et, R^2 = H



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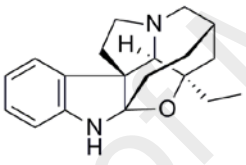

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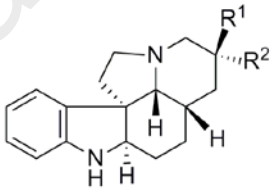
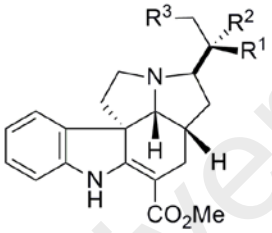
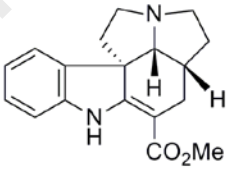


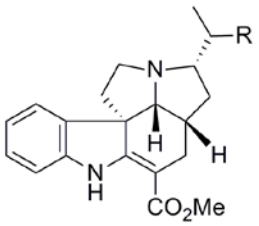
272 R^1 = H, R^2 = Et
273 R^1 = Et, R^2 = H



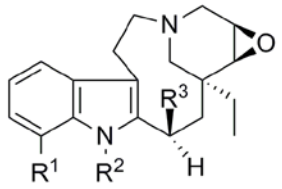
274 R^1 = R^2 = R^3 = H
275 R^1 = R^2 = H, R^3 = OH
276 R^1 = OH, R^2 = R^3 = H
277 R^1 = R^3 = H, R^2 = OH



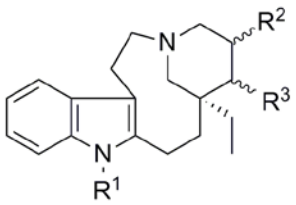
278



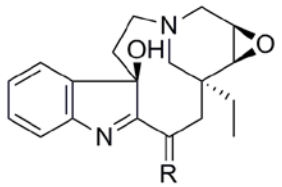
279 R = H
280 R = H, N(4)→O
281 R = OH



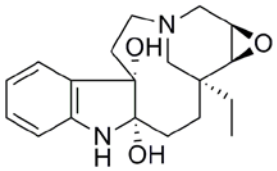
282 $R^1 = R^2 = R^3 = H$
283 $R^1 = R^3 = H$, $R^2 = Me$
284 $R^1 = OMe$, $R^2 = R^3 = H$
285 $R^1 = R^2 = H$, $R^3 = OH$
286 $R^1 = H$, $R^2 = Me$, $R^3 = OH$



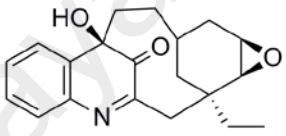
287 $R^1 = R^2 = R^3 = H$
288 $R^1 = R^3 = H$, $R^2 = \beta$-OH
289 $R^1 = Me$, $R^2 = \alpha$-OH, $R^3 = \beta$-OH
290 $R^1 = H$, $R^2 = R^3 = OH$



291 R = H,H
292 R = O



293



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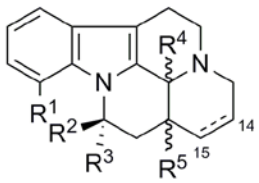
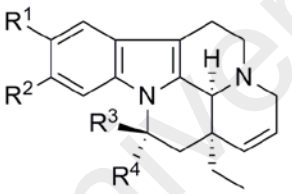
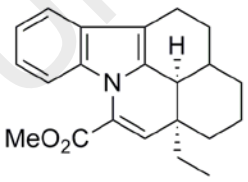


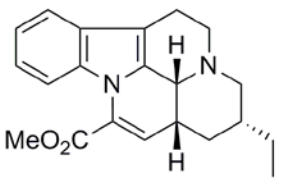
33 $R^1 = H$, $R^2 = CO_2Me$, $R^3 = OH$, $R^4 = \alpha$-H, $R^5 = \alpha$-Et, $\Delta^{14,15}$
295 $R^1 = H$, $R^2 = OH$, $R^3 = CO_2Me$, $R^4 = \alpha$-H, $R^5 = \beta$-Et
296 $R^1 = H$, $R^2 = CO_2Me$, $R^3 = OH$, $R^4 = \alpha$-H, $R^5 = \alpha$-Et
297 $R^1 = H$, $R^2 = OH$, $R^3 = CO_2Me$, $R^4 = \beta$-H, $R^5 = \alpha$-Et
298 $R^1 = OMe$, $R^2 = OH$, $R^3 = CO_2Me$, $R^4 = \alpha$-H, $R^5 = \alpha$-Et, $\Delta^{14,15}$



299 $R^1 = OH$, $R^2 = OMe$, $R^3 = OH$, $R^4 = CO_2Me$
300 $R^1 = R^2 = OMe$, $R^3 = CO_2Me$, $R^4 = OH$
301 $R^1 = OH$, $R^2 = OMe$, $R^3 = CO_2Me$, $R^4 = OH$
302 $R^1 = R^2 = OMe$, $R^3 = OH$, $R^4 = CO_2Me$



303



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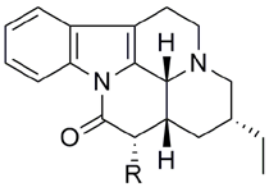
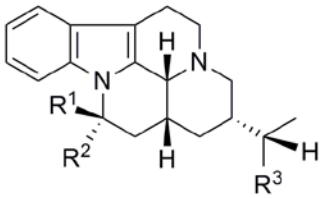


305 R = H
306 R = OH
307 R = H, N(4)→O



308 $R^1 = CO_2Me$, $R^2 = OH$, $R^3 = H$

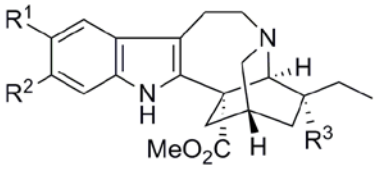
309 $R^1 = OH$, $R^2 = CO_2Me$, $R^3 = H$

310 $R^1 = OH$, $R^2 = CO_2Me$, $R^3 = H$, $N(4)\rightarrow O$

311 $R^1 = CO_2Me$, $R^2 = R^3 = OH$

312 $R^1 = OH$, $R^2 = R^3 = H$

313 $R^1 = R^3 = H$, $R^2 = OH$



18 $R^1 = OMe$, $R^2 = R^3 = H$

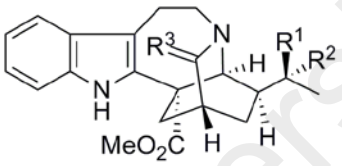
316 $R^1 = OH$, $R^2 = R^3 = H$

317 $R^1 = R^3 = H$, $R^2 = OH$

318 $R^1 = R^3 = H$, $R^2 = OMe$

319 $R^1 = R^2 = OMe$, $R^3 = H$

320 $R^1 = R^2 = OMe$, $R^3 = OH$



16 $R^1 = R^2 = H$, $R^3 = H,H$

17 $R^1 = OH$, $R^2 = H$, $R^3 = H,H$

321 $R^1 = H$, $R^2 = OH$, $R^3 = H,H$

322 $R^1 = OH$, $R^2 = H$, $R^3 = O$

323 $R^1 = H$, $R^2 = OH$, $R^3 = O$

324 $R^1 = H$, $R^2 = OH$, $R^3 = H,CH_2Ac,(R/S)$

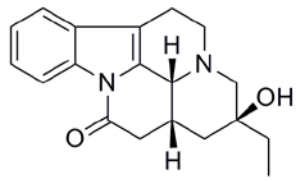
325 $R^1 = OH$, $R^2 = H$, $R^3 = H,OEt,(R/S)$

326 $R^1 = H$, $R^2 = OH$, $R^3 = H,OEt,(R/S)$

327 $R^1 = R^2 = H$, $R^3 = H,CH_2Ac,(R/S)$

328 $R^1 = R^2 = H$, $R^3 = H,CH_2OH(S)$

329 $R^1 = H$, $R^2 = OH$, $R^3 = H,CH_2Ac,(R/S)$



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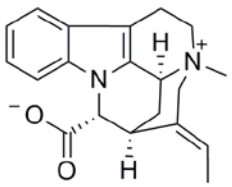

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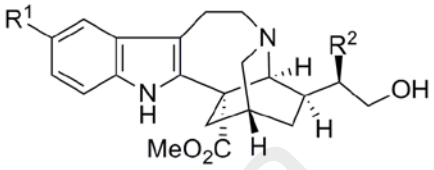
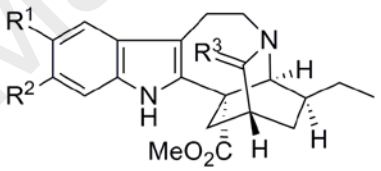


330 $R^1 = H$, $R^2 = OH$

331 $R^1 = R^2 = H$

332 $R^1 = OMe$, $R^2 = H$



333 $R^1 = R^2 = H$, $R^3 = H,OH,(R/S)$

334 $R^1 = R^2 = H$, $R^3 = H,OEt,(R/S)$

335 $R^1 = R^2 = H$, $R^3 = O$

336 $R^1 = R^2 = H$, $R^3 = H,OH,(R)$

337 $R^1 = R^2 = H$, $R^3 = H,CH_2Ac,(R/S)$

338 $R^1 = R^2 = H$, $R^3 = H,OMe,(R)$

339 $R^1 = H$, $R^2 = OMe$, $R^3 = H,OH,(R/S)$

340 $R^1 = OMe$, $R^2 = H$, $R^3 = O$

341 $R^1 = OMe$, $R^2 = H$, $R^3 = H,OH,(R/S)$

342 $R^1 = OMe$, $R^2 = H$, $R^3 = H,OMe,(R)$

343 $R^1 = R^2 = OMe$, $R^3 = O$

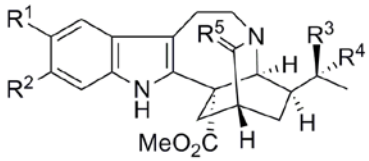
344 $R^1 = R^2 = OMe$, $R^3 = H,OH,(R/S)$

345 $R^1 = R^2 = H$, $R^3 = H,CH(OH)Me,(S)$

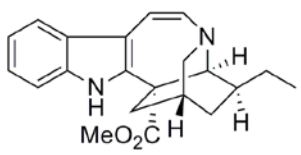
346 $R^1 = OMe$, $R^2 = H$, $R^3 = H,OH,(R)$

347 $R^1 = OMe$, $R^2 = H$, $R^3 = H,CH_2Ac$

348 $R^1 = H$, $R^2 = OMe$, $R^3 = H,CH_2Ac$



349 $R^1 = R^3 = OH$, $R^2 = R^4 = H$, $R^5 = H,H$
350 $R^1 = R^4 = H$, $R^2 = R^3 = OH$, $R^5 = H,H$
351 $R^1 = OMe$, $R^2 = R^4 = H$, $R^3 = OH$, $R^5 = O$
352 $R^1 = OMe$, $R^2 = R^3 = H$, $R^4 = OH$, $R^5 = O$
353 $R^1 = OMe$, $R^2 = R^4 = H$, $R^3 = OH$, $R^5 = H,OH,(R/S)$
354 $R^1 = OMe$, $R^2 = R^3 = R^4 = H$, $R^5 = H,OEt,(R/S)$



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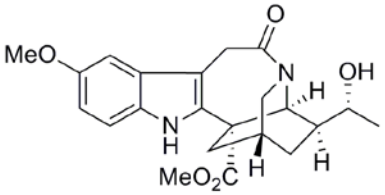

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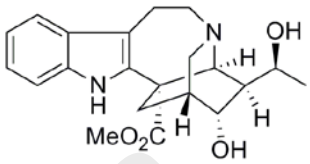

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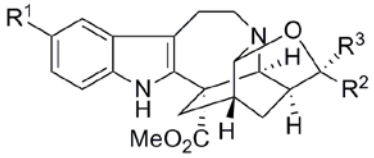
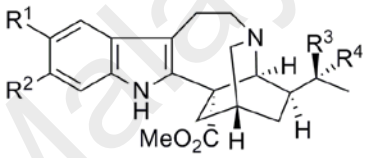
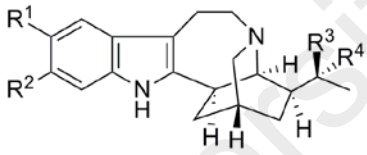


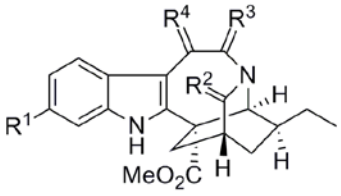
358 $R^1 = OMe$, $R^2 = Me$, $R^3 = H$
359 $R^1 = R^2 = H$, $R^3 = Me$



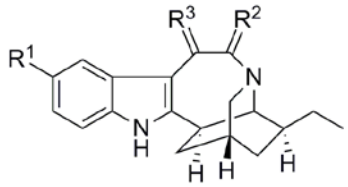
19 $R^1 = OMe$, $R^2 = R^4 = H$, $R^3 = OH$
366 $R^1 = OMe$, $R^2 = R^3 = H$, $R^4 = OH$
367 $R^1 = OMe$, $R^2 = H$, $R^3,R^4 = O$
368 $R^1 = R^4 = H$, $R^2 = OMe$, $R^3 = OH$
369 $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = OH$
370 $R^1 = R^2 = OMe$, $R^3 = OH$, $R^4 = H$
371 $R^1 = H$, $R^2 = OMe$, $R^3,R^4 = O$
372 $R^1 = R^3 = H$, $R^2 = OMe$, $R^4 = OH$



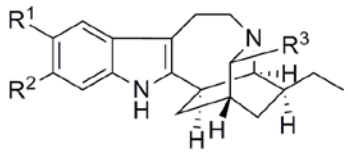
13 $R^1 = R^2 = R^3 = R^4 = H$
14 $R^1 = R^2 = R^4 = H$, $R^3 = OH$
15 $R^1 = R^2 = R^3 = H$, $R^4 = OH$
360 $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
361 $R^1 = OMe$, $R^2 = R^3 = R^4 = H$, $N(4)\rightarrow O$
362 $R^1 = OMe$, $R^2 = R^4 = H$, $R^3 = OH$
363 $R^1 = OMe$, $R^2 = R^3 = H$, $R^4 = OH$
364 $R^1 = R^2 = OMe$, $R^3 = OH$, $R^4 = H$
365 $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = OH$



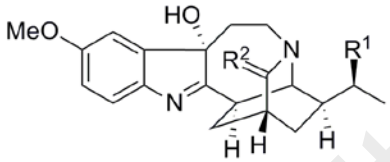
373 $R^1 = H$, $R^2 = R^4 = H,H$, $R^3 = O$
374 $R^1 = H$, $R^2 = R^3 = H,H$, $R^4 = O$
375 $R^1 = H$, $R^2 = H,H$, $R^3 = H,OH$, $R^4 = O$
376 $R^1 = H$, $R^2 = O$, $R^3 = H,H$, $R^4 = H,OH$
377 $R^1 = OMe$, $R^2 = O$, $R^3 = H,H$, $R^4 = H,OH$



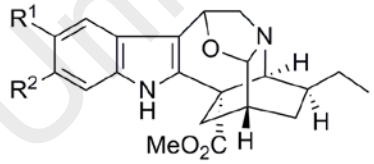
378 R^1 = OMe, R^2 = H,H, R^3 = O
379 R^1 = H, R^2 = R^3 = O
380 R^1 = OMe, R^2 = R^3 = O



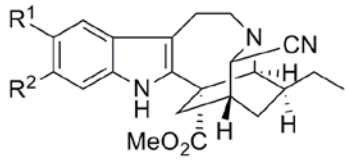
384 R^1 = R^3 = H, R^2 = OMe
385 R^1 = R^2 = OMe, R^3 = H
386 R^1 = H, R^2 = OMe, R^3 = OH,(*R*/*S*)
387 R^1 = OMe, R^2 = H, R^3 = CH_2Ac



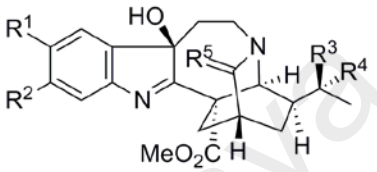
396 R^1 = H, R^2 = H,H
397 R^1 = H, R^2 = O
398 R^1 = OH, R^1 = H,H
399 R^1 = H, R^2 = CH_2COMe



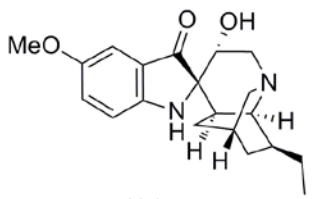
400 R^1 = R^2 = H
401 R^1 = H, R^2 = OMe
402 R^1 = OMe, R^2 = H
403 R^1 = OMe, R^2 = H, N(4)→O



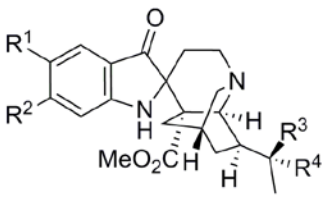
381 R^1 = R^2 = H
382 R^1 = H, R^2 = OMe
383 R^1 = OMe, R^2 = H



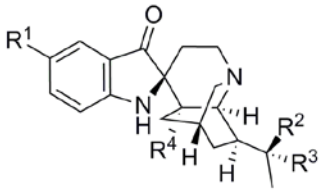
388 R^1 = R^2 = R^3 = R^4 = H, R^5 = H,CH_2Ac
389 R^1 = R^2 = R^3 = R^4 = H, R^5 = H,H
390 R^1 = OMe, R^2 = R^3 = R^4 = H, R^5 = H,H
391 R^1 = OMe, R^2 = R^3 = R^4 = H, R^5 = H,H
392 R^1 = R^2 = R^4 = H, R^5 = H,H, R^3 = OH
393 R^1 = OMe, R^2 = R^4 = H, R^5 = H,H, R^3 = OH
394 R^1 = R^2 = OMe, R^3 = H, R^4 = OH, R^5 = H,H
395 R^1 = R^2 = R^3 = R^4 = H, R^5 = O



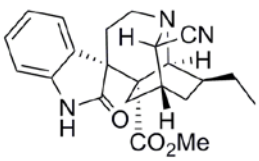
404



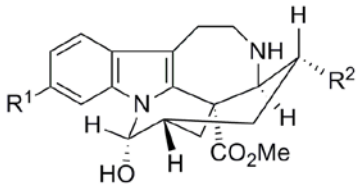
405 R_1 = R_2 = R_3 = R_4 = H
406 R^1 = OMe, R^2 = R^3 = R^4 = H
407 R^1 = OMe, R^2 = R^3 = H, R^4 = OH
408 R^1 = R^2 = OMe, R^3 = R^4 = H
409 R^1 = R^4 = H, R^2 = OMe, R^3 = OH



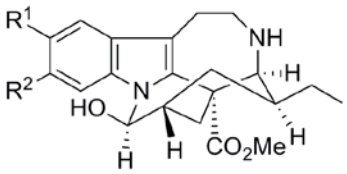
410 $R^1 = R^2 = R^3 = R^4 = H$
411 $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
412 $R^1 = R^2 = R^4 = H$, $R^3 = OH$
413 $R^1 = R^3 = H$, $R^2 = OH$, $R^4 = CO_2Me$



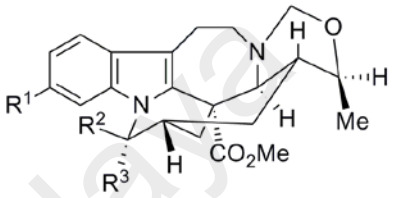
414



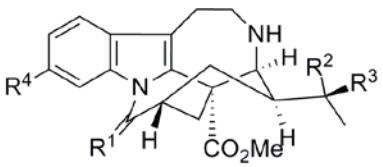
422 $R^1 = OMe$, $R^2 = CH_3CH(OH)$
423 $R^1 = H$, $R^2 = CH_3CO$



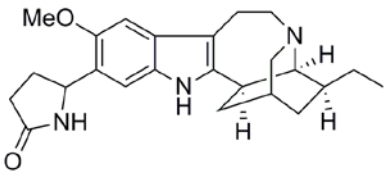
424 $R^1 = R^2 = OMe$
425 $R^1 = R^2 = H$



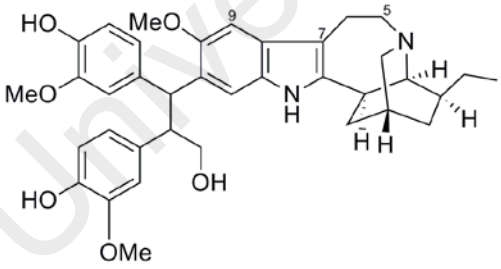
426 $R^1 = R^2 = H$, $R^3 = OH$
427 $R^1 = OMe$, R^2,$R^3 = O$



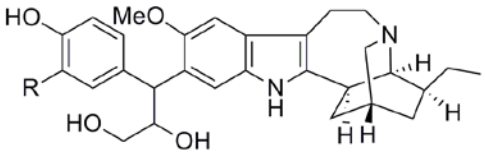
428 $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
429 $R^1 = OMe$, $R^2 = OH$, $R^3 = R^4 = H$
430 $R^1 = OMe$, $R^2 = R^3 = H$, $R^4 = O$
431 $R^1 = R^3 = R^4 = H$, $R^2 = OH$



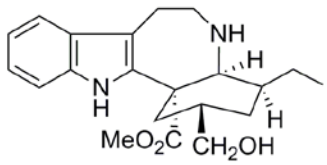
432



433a 1'(*S*),2'(*S*)
433b 1'(*R*),2'(*R*)



434a R = OMe, 1'(*S*),2'(*S*)
434b R = OMe, 1'(*R*),2'(*R*)
435a R = H, 1'(*S*),2'(*S*)
435b R = H, 1'(*R*),2'(*R*)



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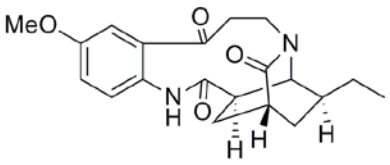

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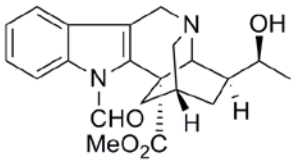

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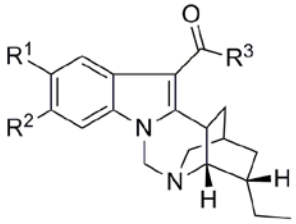
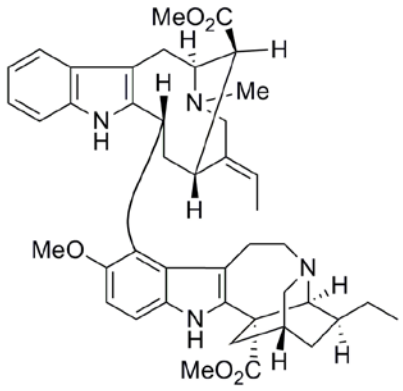


439 R^1 = OMe, R^2 = R^3 = H
440 R^1 = OMe, R^2 = H, R^3 = CH_2OH
441 R^1 = R^3 = H, R^2 = OMe,



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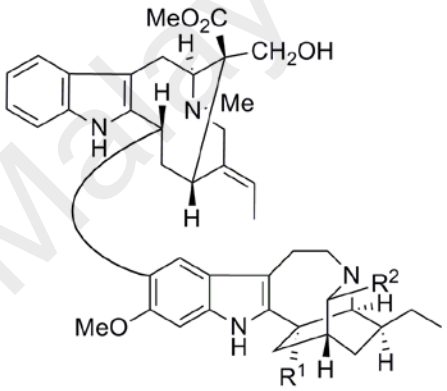
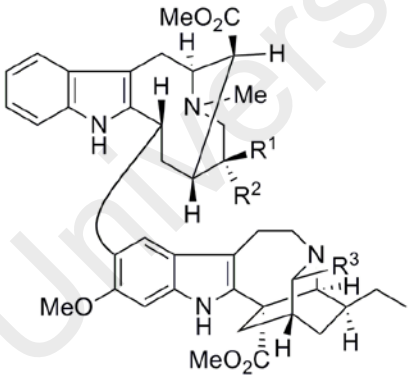
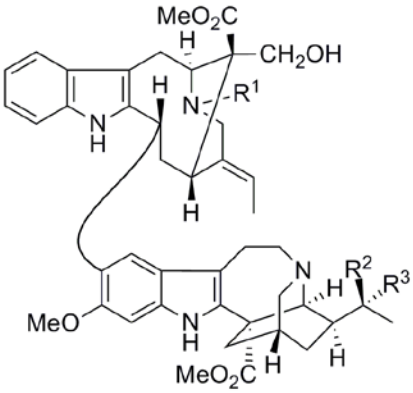


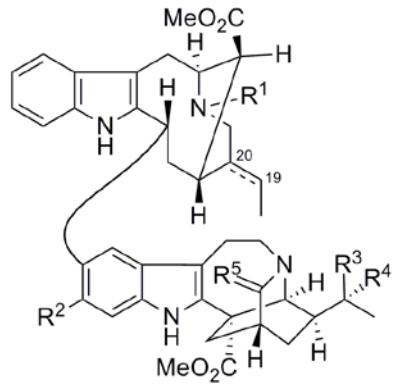
443 R^1 = CO_2Me, R^2 = H
444 R^1 = H, R^2 = H
445 R^1 = CO_2Me, R^2 = CH_2Ac



446 R^1 = Et, R^2 = R^3 = H
447 R^1 = Et, R^2 = H, R^3 = OH,(*R*/*S*)
448 R^1 = R^3 = H, R^2 = Et
449 R^1 = H, R^2 = Et, R^3 = CN
450 R^1 = Et, R^2 = H, R^3 = CH_2Ac



451 R^1 = Me, R^2 = OH, R^3 = H
452 R^1 = Me, R^2,R^3 = O
453 R^1 = R^3 = H, R^2 = OH



454 R^1 = Me, R^2 = R^4 = R^5 = H, R^3 = H,H, $\Delta^{19,20}$

455 R^1 = R^4 = R^5 = H, R^2 = OMe, R^3 = H,H, $\Delta^{19,20}$

456 R^1 = Me, R^2 = OH, R^3 = H,H, R^4 = R^5 = H, $\Delta^{19,20}$

457 R^1 = Me, R^2 = OMe, R^3 = H,H, R^4 = R^5 = H, $\Delta^{19,20}$

458 R^1 = Me, R^2 = OMe, R^3 = H,H, R^4 = R^5 = H, 19,20-epoxy

459 R^1 = R^2 = R^4 = R^5 = H, R^3 = H,OH,(*R*/*S*), $\Delta^{19,20}$

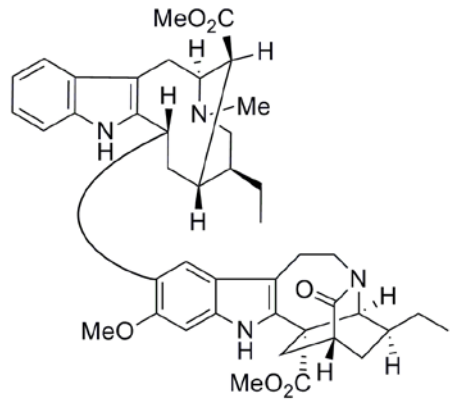
460 R^1 = Me, R^2 = OMe, R^3 = H,H, R^4 = H, R^5 = OH, $\Delta^{19,20}$

461 R^1 = Me, R^2 = OMe, R^3 = H,OH,(*R*/*S*), R^4 = R^5 = H, $\Delta^{19,20}$

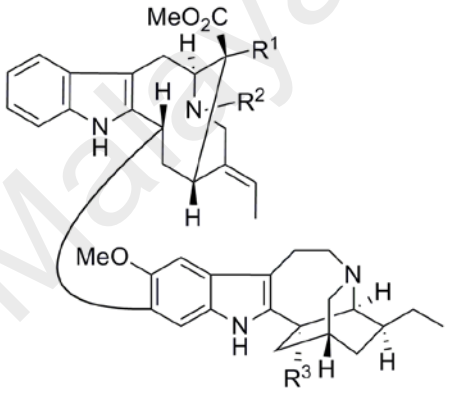
462 R^1 = Me, R^2 = OMe, R^3 = H,H, R^4 = OH, R^5 = H, $\Delta^{19,20}$

463 R^1 = Me, R^2 = H, R^3 = O, R^4 = R^5 = H, $\Delta^{19,20}$

464 R^1 = Me, R^2 = R^4 = R^5 = H, R^3 = H,CH(OH)Me, $\Delta^{19,20}$



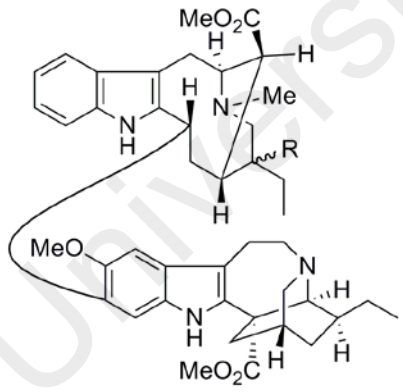
465



466 R^1 = CH_2OH, R^2 = Me, R^3= CO_2Me

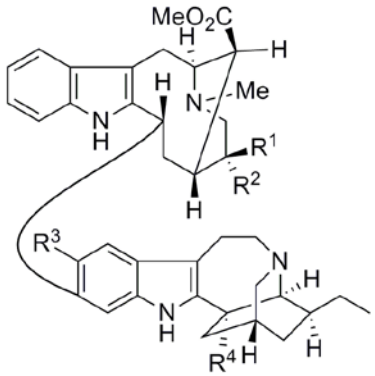
467 R^1 = CH_2OH, R^2 = R^3 = H

468 R^1 = R^2 = R^3 = H



469 R = β-H

470 R = α-H

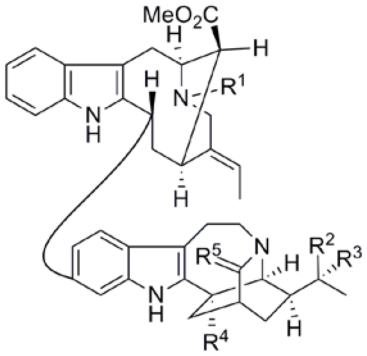


471 R^1 = Et, R^2 = R^3 = H, R^4 = CO_2Me

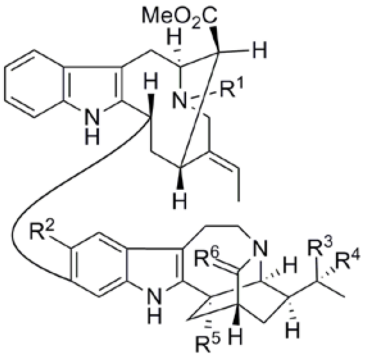
472 R^1 = Et, R^2 = R^3 = R^4 = H

473 R^1 = R^4 = H, R^2 = Et, R^3 = OMe

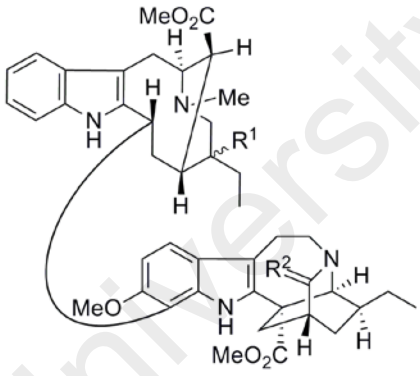
474 R^1 = Et, R^2 = R^4 = H, R^3 = OMe



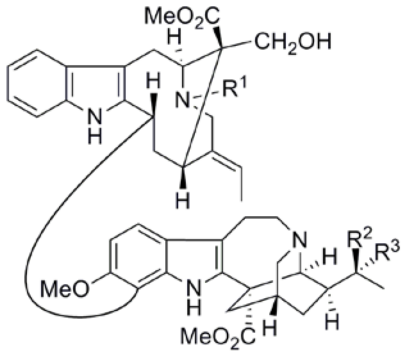
56 R^1 = Me, R^2,R^3 = O, R^4 = H, R^5 = H,H
57 R^1 = Me, R^2 = R^3 = R^4 = H, R^5 = H,H
475 R^1 = R^2 = R^3 = R^4 = H, R^5 = H,H
476 R^1 = Me, R^2 = R^3 = R^4 = H, R^5 = H,OH,(*R*/*S*)
477 R^1 = R^2 = R^3 = R^4 = H, R^5 = H,OH,(*R*/*S*)
478 R^1 = Me, R^2 = R^4 = H, R^3 = OH, R^5 = H,H
479 R^1 = Me, R^2 = OH, R^3 = R^4 = H, R^5 = H,H
480 R^1 = Me, R^2 = R^3 = H, R^4 = CO_2Me, R^5 = H,H
481 R^1 = Me, R^2 = OH, R^3 = H, R^4 = CO_2Me, R^5 = H,H
482 R^1 = Me, R^2 = R^3 = H, R^4 = CO_2Me, R^5 = O,
483 R^1 = Me, R^2 = R^3 = H, R^4 = CO_2Me, R^5 = H,CHOHMe



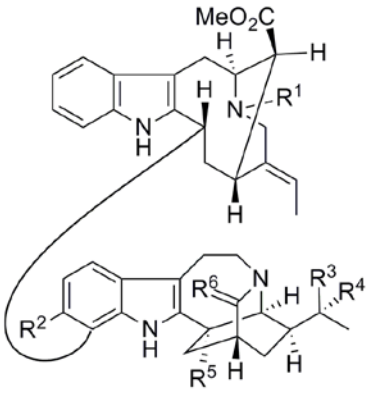
58 R^1 = Me, R^2 = OMe, R^3 = R^4 = R^5 = H, R^6 = H,H
484 R^1 = R^2 = R^3 = R^4 = H, R^5 = CO_2Me, R^6 = H,OH,(*R*/*S*)
485 R^1 = Me, R^2 = OMe, R^3 = R^4 = H, R^5 = CO_2Me, R^6 = H,H
486 R^1 = Me, R^2 = OMe, R^3 = R^4 = H, R^5 = CO_2Me, R^6 = H,H, N(4)→O
487 R^1 = Me, R^2 = OMe, R^3 = R^4 = H, R^5 = CO_2Me, R^6 = O
488 R^1 = Me, R^2 = OMe, R^3 = R^4 = H, R^5 = CO_2Me, R^6 = H,OH,(*R*/*S*)
489 R^1 = R^3 = R^4 = H, R^2 = OMe, R^5 = CO_2Me, R^6 = H,H
490 R^1 = Me, R^2 = OMe, R^3 = OH, R^4 = H, R^5 = CO_2Me, R^6 = H,H
491 R^1 = Me, R^2 = OMe, R^3 = H, R^4 = OH, R^5 = CO_2Me, R^6 = H,H



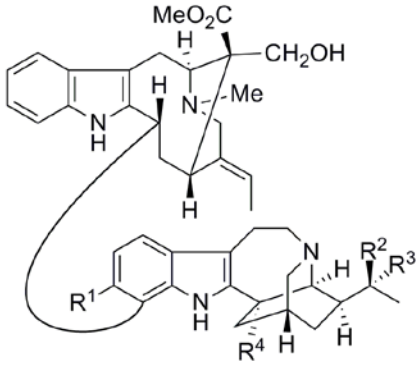
492 R^1 = α-H, R^2 = O
493 R^1= α-H, R^2 = H, OH, (*R*/*S*)
494 R^1= β-H, R^2 = H, OH (*S*)



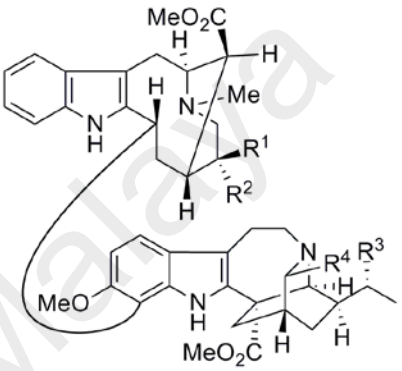
495 R^1 = Me, R^2 = OH, R^3 = H
496 R^1 = Me, R^2,R^3 = O
497 R^1 = R^3 = H, R^2 = OH



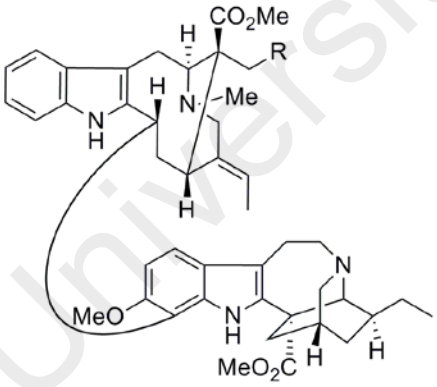
498 R^1 = Me, R^2 = R^3 = R^4 = H, R^5 = CO_2Me, R^6 = H,H
499 R^1 = R^3 = R^4 = H, R^2 = OMe, R^5 = CO_2Me, R^6 = H,H
500 R^1 = Me, R^2 = OMe, R^3 = R^4 = H, R^5 = CO_2Me, R^6 = H,H
501 R^1 = Me, R^2 = OMe, R^3 = R^4 = H, R^5 = CO_2Me, R^6 = O
502 R^1 = Me, R^2 = OMe, R^3 = R^4 = H, R^5 = CO_2Me, R^6 = H,CH_2Ac
503 R^1 = Me, R^2 = OMe, R^3 = H, R^4 = OH, R^5 = CO_2Me, R^6 = H,H
504 R^1 = Me, R^2 = OMe, R^3 = R^4 = H, R^5 = CO_2Me, R^6 = H,OH,(*R*/*S*)
505 R^1 = Me, R^2 = OMe, R^3 = OH, R^4 = H, R^5 = CO_2Me, R^6 = H,H
506 R^1 = Me, R^2 = OMe, R^3 = R^4 = R^5 = H, R^6 = H,OH,(*R*/*S*)
507 R^1 = R^4 = H, R^2 = OMe, R^3 = OH, R^5 = CO_2Me, R^6 = H,H



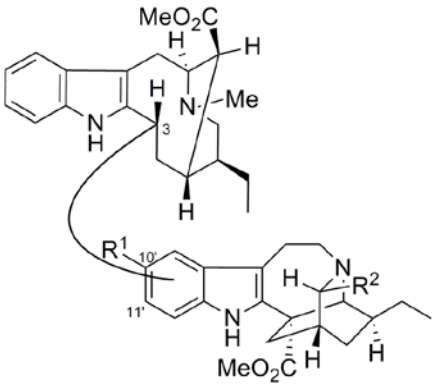
508 R^1 = OMe, R^2 = OH, R^3 = R^4 = H
509 R^1 = OMe, R^2,R^3 = O, R^4 = H
510 R^1 = OH, R^2 = OH, R^3 = H, R^4 = CO_2Me
511 R^1 = OH, R^2 = R^3 = H, R^4 = CO_2Me



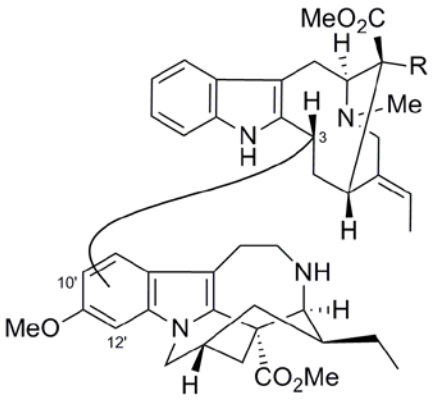
512 R^1 = Et, R^2 = R^3 = R^4 = H
513 R^1 = R^3 = R^4 = H, R^2 = Et
514 R^1 = Et, R^2 = R^4 = H, R^3 = OH
515 R^1 = R^3 = H, R^2 = Et, R^4 = OMe
516 R^1 = R^3 = H, R^2 = Et, R^4 = CN
517 R^1 = Et, R^2 = R^3 = H, R^4 = CH_2Ac



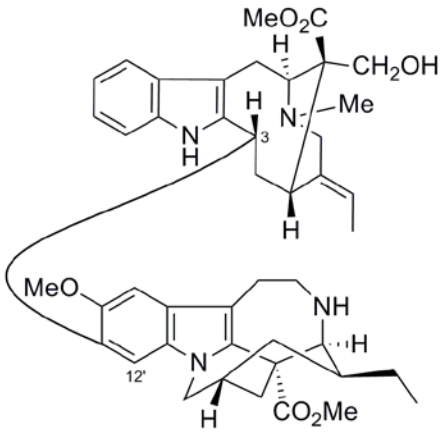
518 R = H
519 R = CH_2OAc



520 R^1 = R^2 = H, C(3)-C(10')
521 R^1 = H, R^2= CH_2Ac, C(3)-C(10')
522 R^1 = H, R^2= CH_2Ac, C(3)-C(11')
523 R^1 = OMe, R^2= CH_2Ac, C(3)-C(11')



524 R = CH_2OH, C(3)-C(12')
525 R = H, C(3)-C(10')
526 R = CH_2OH, C(3)-C(10')



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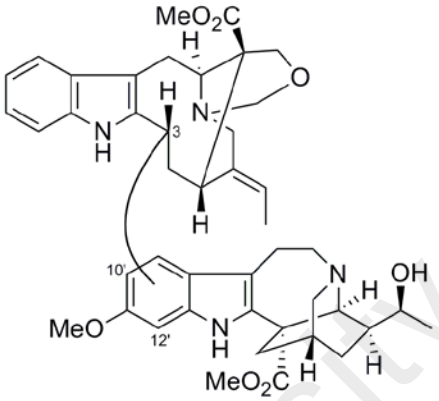
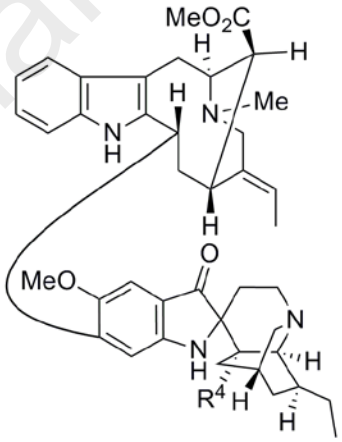


528 C(3)-C(10')
529 C(3)-C(12')



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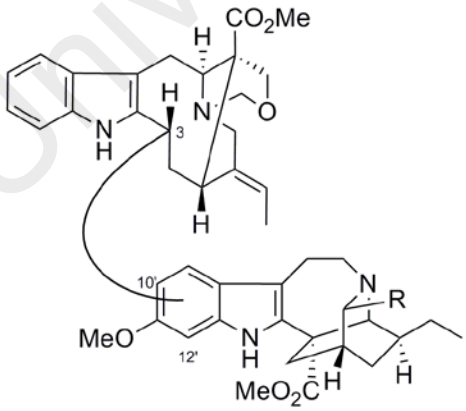
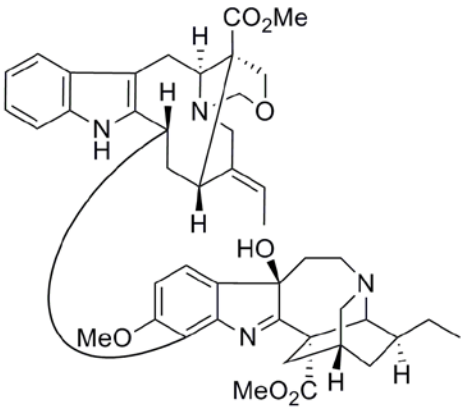


531 R = H, C(3)-C(10')
532 R = H, C(3)-C(12')
533 R = CH_2Ac, C(3)-C(12')



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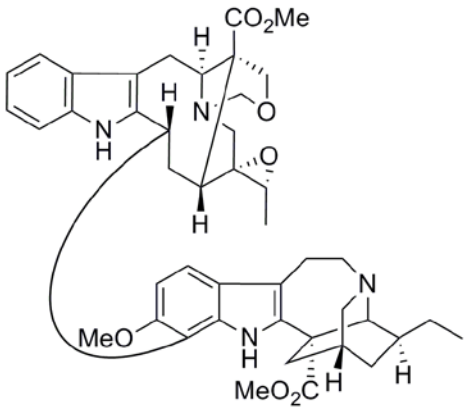

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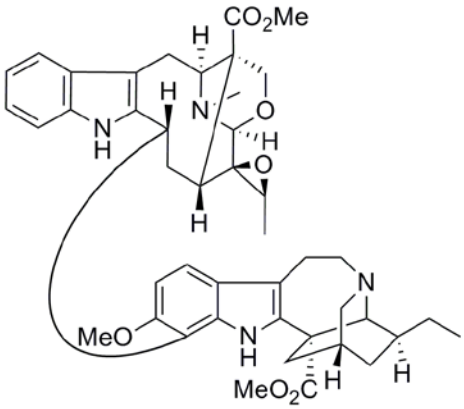

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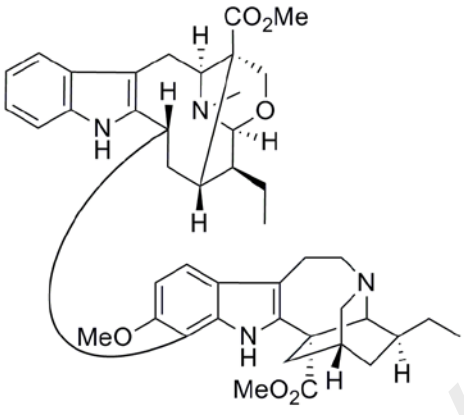

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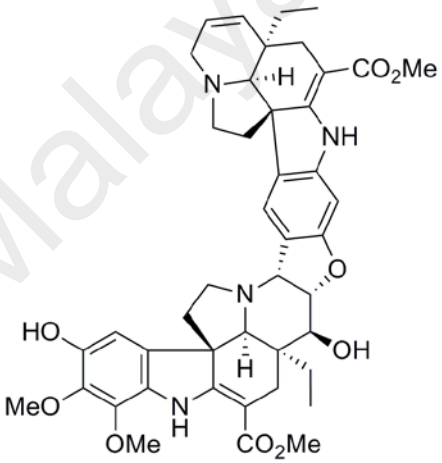

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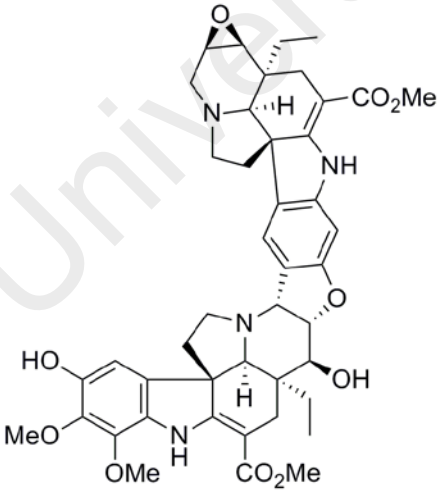

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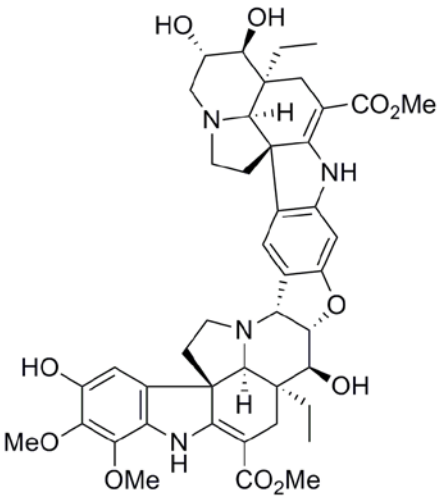

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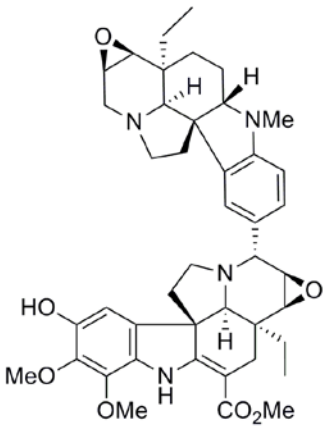

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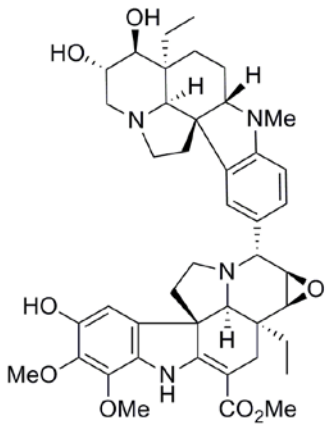

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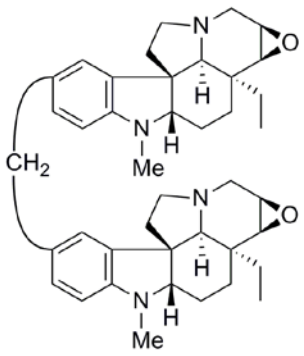

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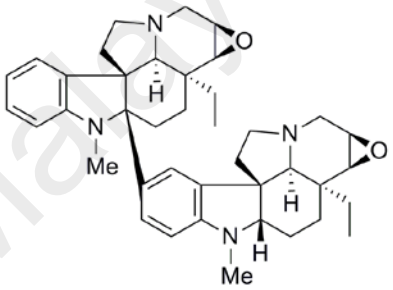

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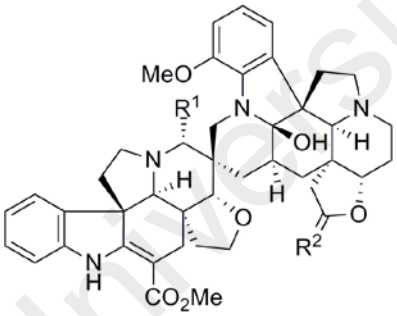
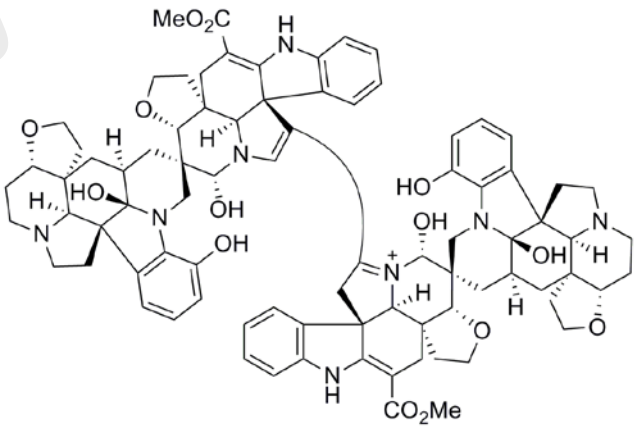


544 R^1 = H, R^2 = H,H
545 R^1 = OH, R^2 = O
546 R^1 = H, R^2 = O
547 R^1 = OH, R^2 = H,H



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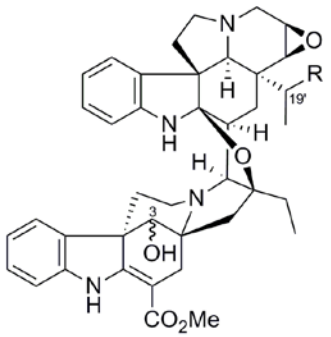
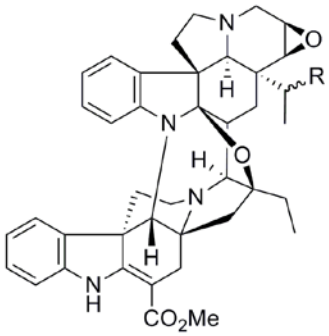
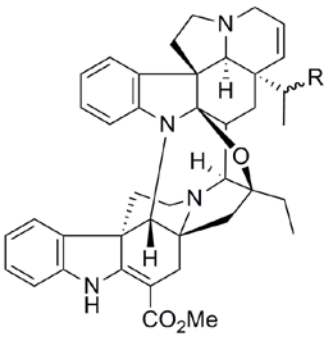


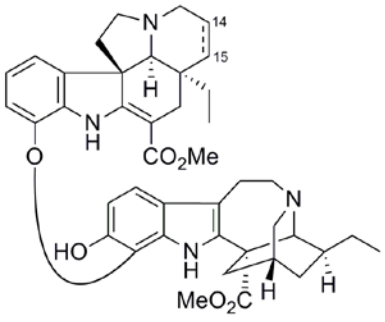
549 R = H, 3(*R*)
550 R = H, 3(*S*)
551 R = OH, 3(*S*), 19'(*R*)
552 R = OH, 3(*S*), 19'(*S*)



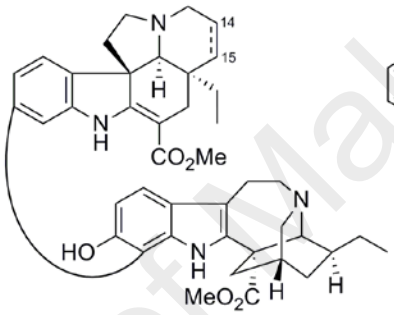
553 R = H
554 R = OH



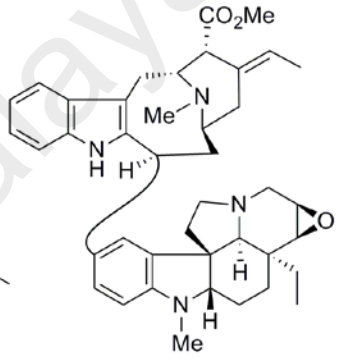
555 R = H
556 R = OH



557
558 $\Delta^{14,15}$



559
560 $\Delta^{14,15}$



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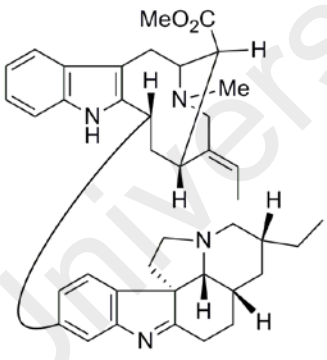

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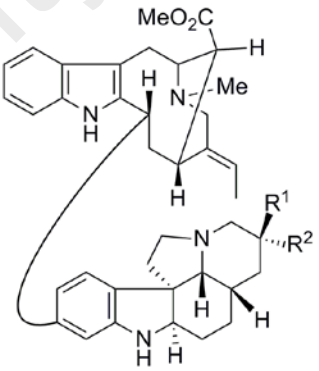
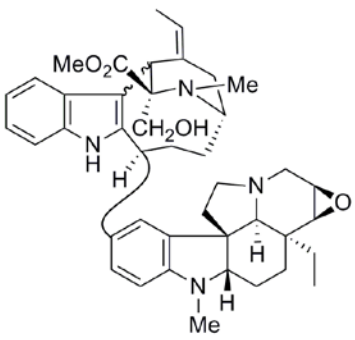


563 R^1 = H, R^2 = Et
564 R^1 = Et, R^2 = H



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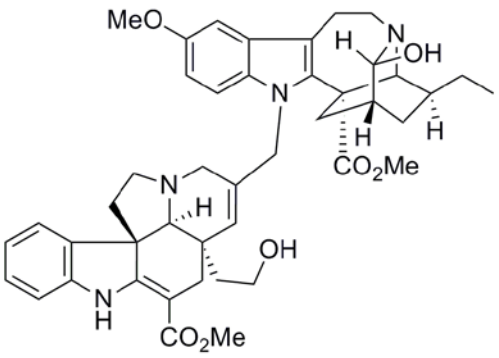

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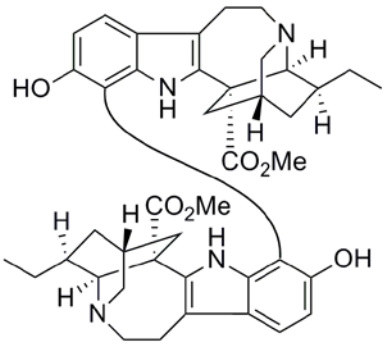

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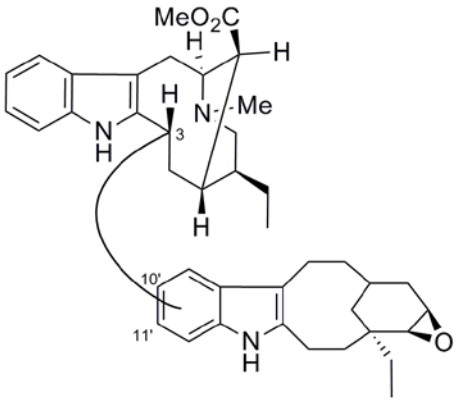
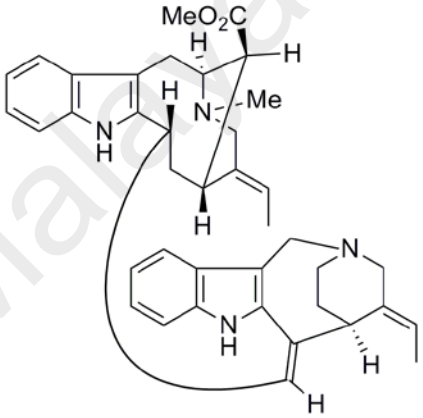
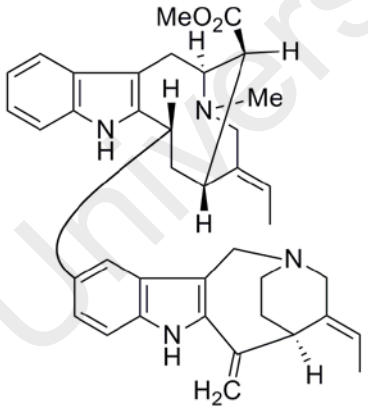


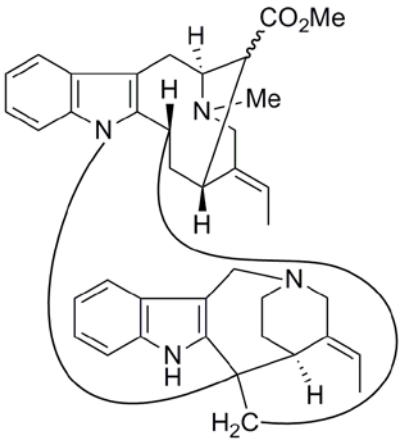
568 C(3)-C(11')
569 C(3)-C(10')



570
571 N(4')→O



572



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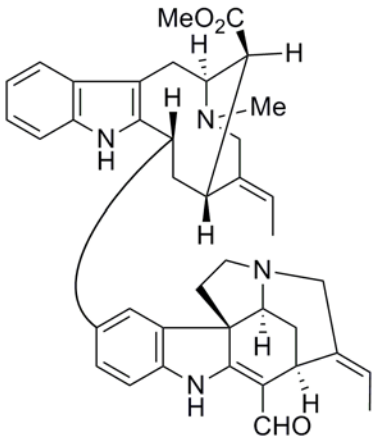

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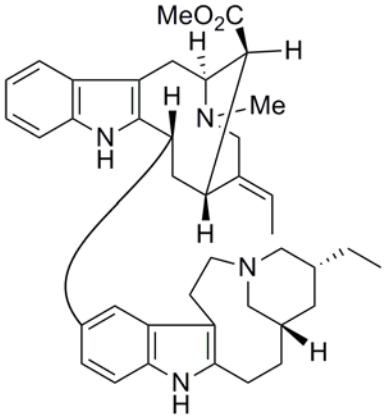

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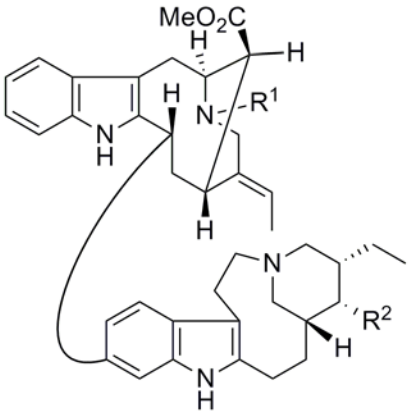
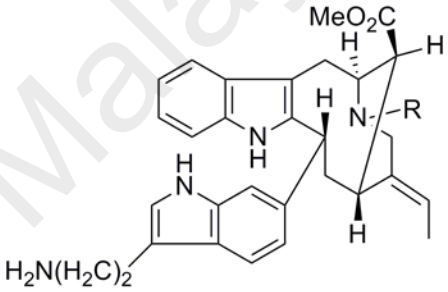
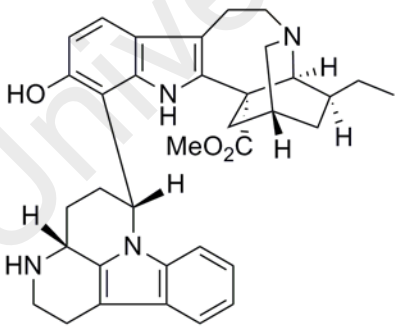


576 R^1 = H, R^2 = Me
577 R^1 = OH, R^2 = H
578 R^1 = OH, R^2 = Me



579 R = Me
580 R = H



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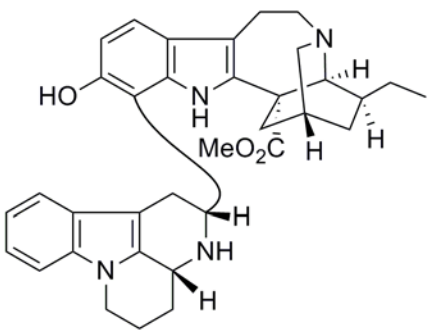

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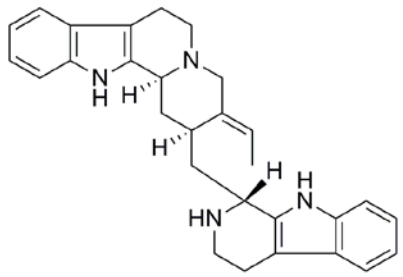

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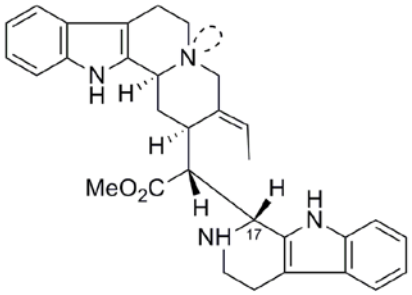

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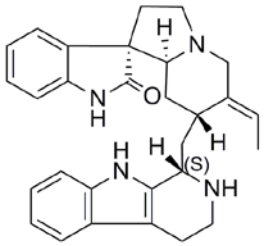

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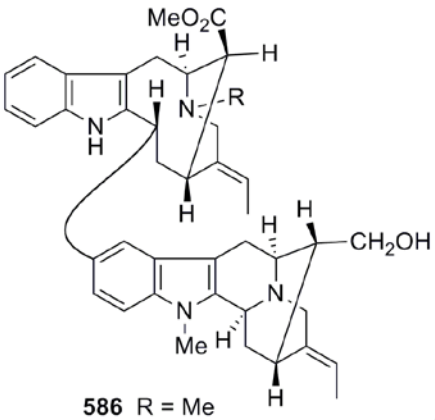
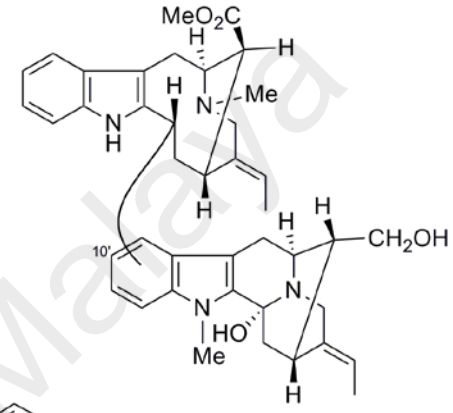


586 R = Me

587 R = H



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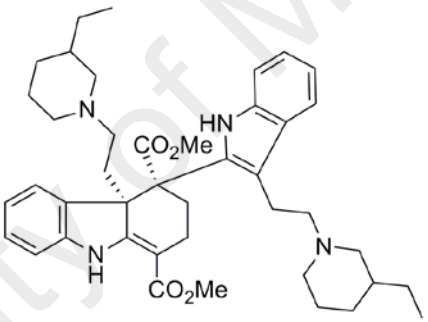

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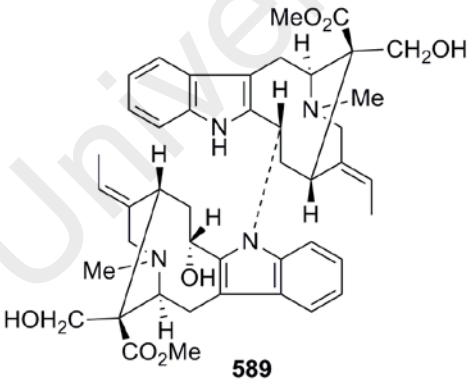

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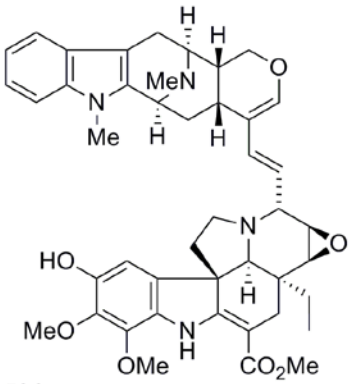


591

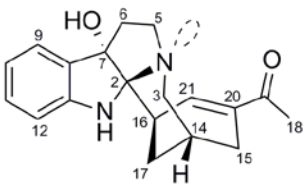
1.5 Objective of the Present Research

The aim of the present research is to carry out a detailed investigation of the alkaloid composition of *Tabernaemontana corymbosa*, collected near Panti Forest, Johor, Peninsular Malaysia, with particular emphasis on the following aspects: the discovery and structure elucidation of new natural products and their biogenetic significance, the documentation of the alkaloid composition, the investigation of reactivity of the new alkaloids, and, the evaluation of biological activity.

CHAPTER 2: RESULTS AND DISCUSSION

2.1 Alkaloids from *Tabernaemontana corymbosa*

A total of 59 alkaloids were isolated and characterized from the leaf and stem-bark extracts of the Malayan *Tabernaemontana corymbosa* Roxb. ex Wall. (occurring near Panti Forest, Johor) and the results are summarized in Table 2.1. Of these, 25 are new alkaloids. Among the new alkaloids are several which incorporate new molecular skeletons, such as the pentacyclic alkaloids, voatinggine (**1**) and tabertinggine (**2**), which are postulated to derive from a common cleavamine-type precursor, the hexacyclic iboga-derived indole, cononuridine (**3**), and, the pentacyclic indoles, criofolinine (**4**) and vernavosine (**5**), incorporating pyrroloazepine and pyridopyrimidine moieties, respectively. Other new alkaloids isolated from this study include a *seco*-yohimbine (taberisidine, **7**), five iboga (conodusines A–E, **8**–**12**), seven *Aspidosperma* (apocidines A–G, **20**–**26**), three vincamine (conoduzidines A–C, **30**–**32**), one heteroyohimbine [16α-methoxycarbonyl-16,17-dihydro-19-*epi*-ajmalicine, **34**], and three bisindole alkaloids (tabernamidines A **55** and B **56**, and conofolidine **59**). Two of the iboga alkaloids, conodusines B and C (**9**, **10**) and the iboga containing bisindole (tabernamidine B, **56**) are notable for the presence of an α-substituted acetyl group at C-20 of the iboga carbon skeleton (naturally-occurring iboga alkaloids with C-20 substitution by ethyl, hydroxyethyl, or acetyl groups, are usually β-oriented).



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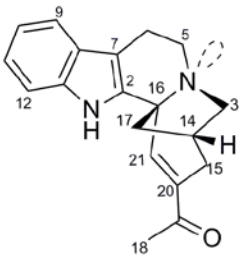

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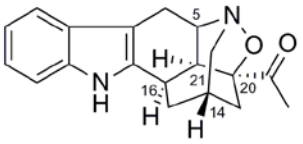

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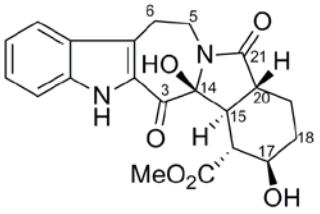

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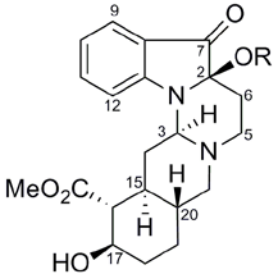

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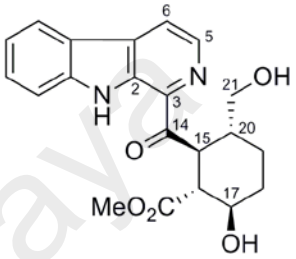

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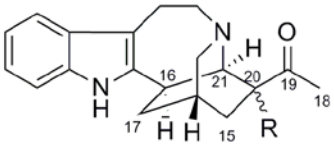

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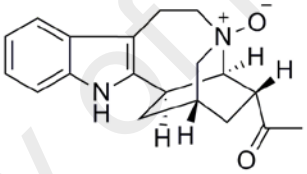
9 R = β-H



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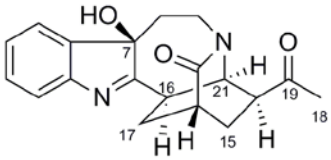

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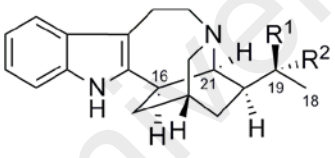

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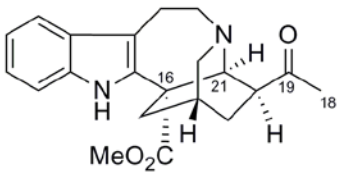
14 R^1 = OH, R^2 = H
15 R^1 = H, R^2 = OH



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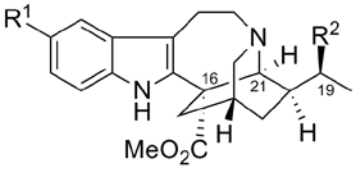

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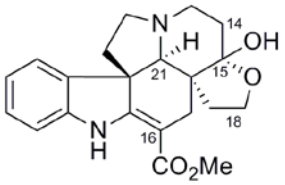
18 R^1 = OMe, R^2 = H
19 R^1 = OMe, R^2 = OH



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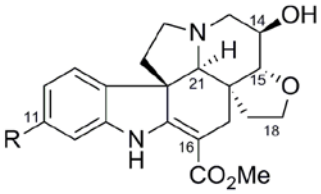

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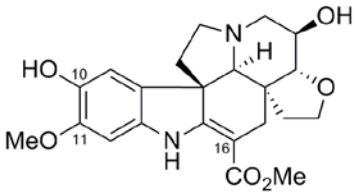

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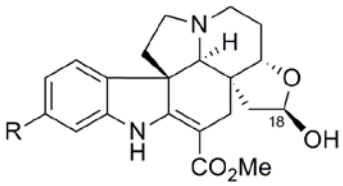

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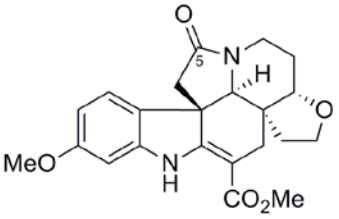

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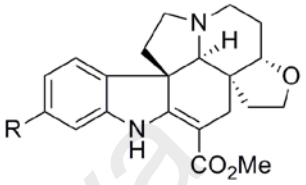

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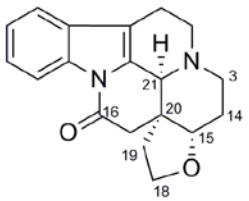

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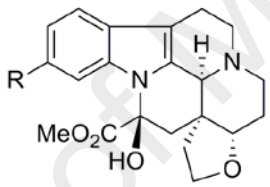

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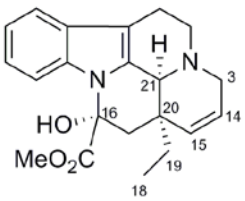

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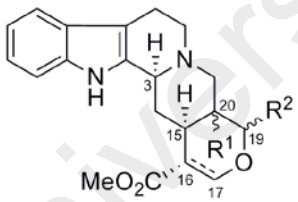
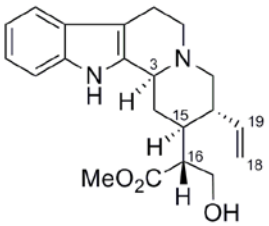


34 R^1 = β-H, R^2 = β-Me
35 R^1 = α-H, R^2 = α-Me, $\Delta^{16,17}$



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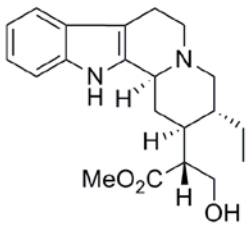

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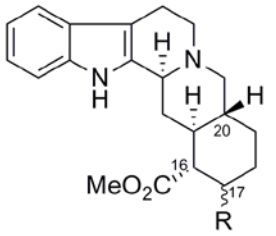

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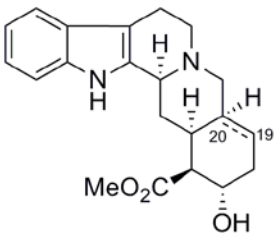
39 R = α-OH



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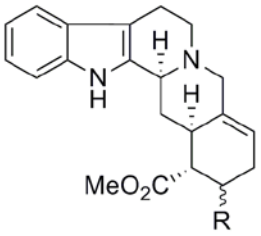
41 $\Delta^{19,20}$



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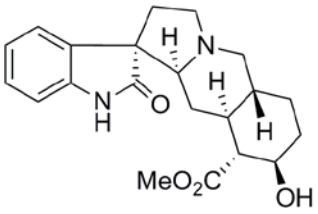

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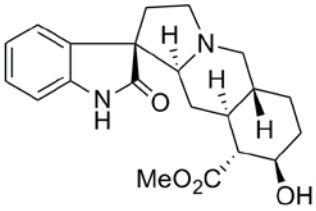

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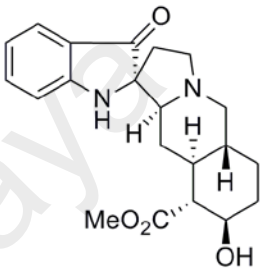
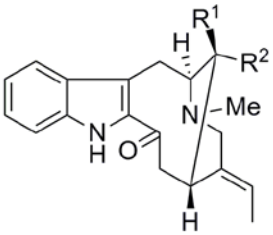
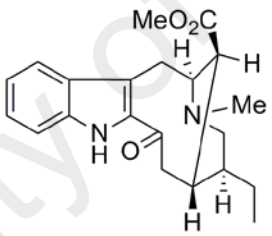


46
47 N(4)→O



48 $R^1 = CO_2Me$, $R^2 = H$
49 $R^1 = H$, $R^2 = CH_2OH$



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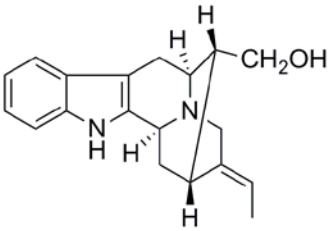

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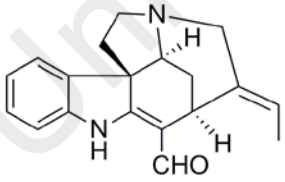

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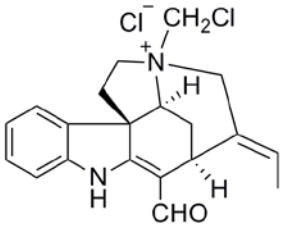

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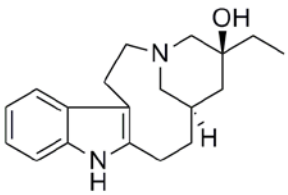

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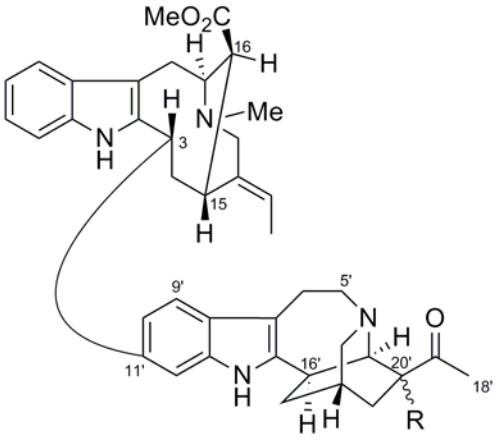
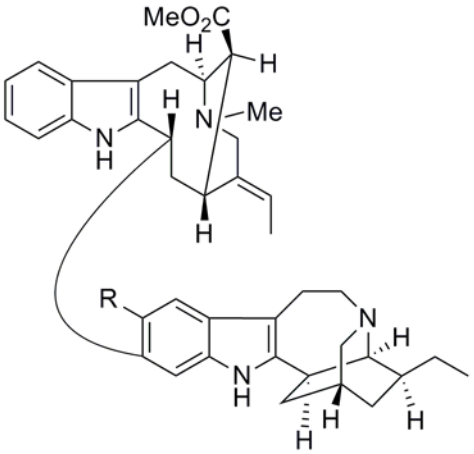
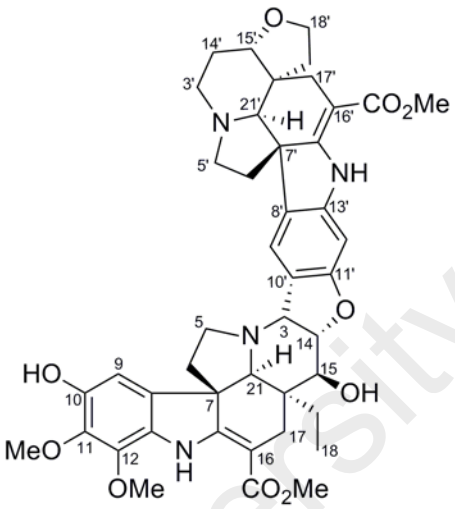


55 R = α-H
56 R = β-H



57 R = H
58 R = OMe



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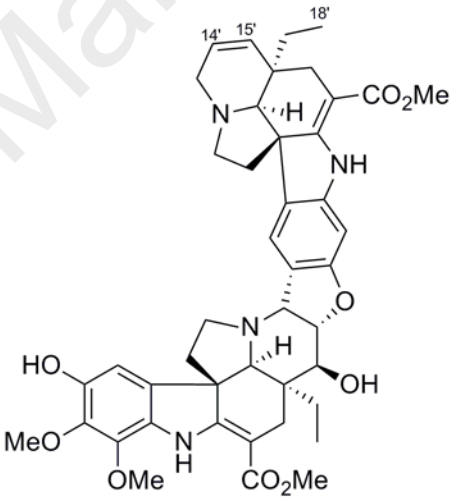

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Table 2.1: Alkaloid Composition of *T. corymbosa*

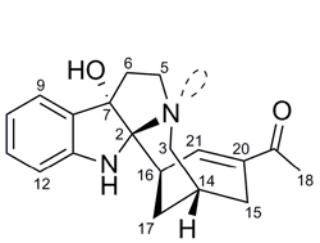
Plant part	**Alkaloid**	**Yield ($mgKg^{-1}$)**
Stem-bark	Voatinggine (**1**) [new]	1.58
	Tabertinggine (**2**) [new]	0.22
	Cononuridine (**3**) [new]	0.16
	Criofolinine (**4**) [new]	0.43
	Vernavosine ethyl ether (**6**) [new]	1.86
	Taberisidine (**7**) [new]	0.61
	Conodusine A (**8**) [new]	157
	Conodusine B (**9**) [new]	0.14
	Conodusines A, B (**8**, **9**)	107
	Conodusine C (**10**) [new]	0.29
	Conodusine D (**11**) [new]	0.14
	Conodusine E (**12**) [new]	1.07
	Ibogamine (**13**)	2.14
	19(*S*)-Hydroxyibogamine (**14**)	2.86
	19(*R*)-Hydroxyibogamine (**15**)	0.57
	Coronaridine (**16**)	6.43
	(–)-Heyneanine (**17**)	15.8
	Voacangine (**18**)	0.42
	Voacristine (**19**)	0.71
	Apocidine A (**20**) [new]	0.71
	Apocidine B (**21**) [new]	2.28
	Hedrantherine (**27**)	0.32
	Deoxoapodine (**28**)	3.57
	Vandrikine (**29**)	0.24
	Conoduzidine A (**30**) [new]	0.14
	16(*R*)-18,19-Dihydrositsirikine (**37**)	0.64
	β-Yohimbine (**38**)	257
	Yohimbine (**39**)	2.86
	19,20-Dehydro-α-yohimbine (**41**)	0.29
	19,20-Dehydroyohimbine (**43**)	0.29
	7(*S*)-β-Yohimbine oxindole (**44**)	0.21
	7(*R*)-β-yohimbine oxindole (**45**)	1.43
	β-Yohimbine pseudoindoxyl (**46**)	1.79
	β-Yohimbine pseudoindoxyl *N*(4)-oxide (**47**)	0.5
	Vobasine (**48**)	1.43
	16-*Epi*-affinine (**49**)	3.57
	Tabernaemontanine (**50**)	0.5
	Normacusine B (**51**)	0.93
	Norfluorocurarine (**52**)	0.14
	N(4)-Chloromethylnorfluorocurarine chloride (**53**)	1.43
	Velbanamine (**54**)	1.57

Table 2.1, continued

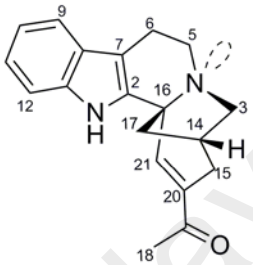
Plant part	Alkaloid	Yield ($mgKg^{-1}$)
	Tabernamidine A (**55**) [new]	0.14
	Tabernamidine B (=19'-Oxotabernamine) (**56**) [new]	0.11
	Tabernamidines A, B (**55**, **56**)	7.14
	Tabernamine (**57**)	0.07
	16'-Decarbomethoxyvoacamine (**58**)	0.29
Leaf	Vernavosine ethyl ether (**6**) [new]	3.08
	Taberisidine (**7**) [new]	1.00
	Apocidine A (**20**) [new]	1.00
	Apocidine C (**22**) [new]	0.42
	Apocidine D (**23**) [new]	0.38
	Apocidine E (**24**) [new]	2.31
	Apocidine F (**25**) [new]	0.23
	Apocidine G (**26**) [new]	2.31
	Deoxoapodine (**28**)	9.23
	Vandrikine (**29**)	3.85
	Conoduzidine B (**31**) [new]	0.77
	Conoduzidine C (**32**) [new]	1.00
	14,15-Dehydro-*epi*-vincamine (**33**)	0.31
	16α-Methoxycarbonyl-16,17-dihydro-19-*epi*-ajmalicine (**34**) [new]	0.15
	Tetrahydroalstonine (**35**)	0.12
	16(*R*)-Sitsirikine (**36**)	3.46
	β-Yohimbine (**38**)	0.54
	Yohimbine (**39**)	15.4
	α-Yohimbine (**40**)	0.85
	19,20-Dehydro-α-yohimbine (**41**)	3.85
	19,20-Dehydro-β-yohimbine (**42**)	0.77
	19,20-Dehydroyohimbine (**43**)	0.31
	7(*S*)-β-yohimbine oxindole (**44**)	3.15
	Conofolidine (**59**) [new]	3.85
	Conophyllidine (**60**)	0.12

2.1.1 Voatinggine (1) and Tabertinggine (2)

Voatinggine (**1**) and tabertinggine (**2**) are two new pentacyclic indole alkaloids isolated from the stem-bark extract in the present study and postulated to derive from an iboga precursor via a common cleavamine-type intermediate.



1



2

2.1.1.1 Voatinggine (1)

Voatinggine (**1**)[241] was initially obtained as a light yellowish oil, and subsequently crystallized from CH_2Cl_2–hexanes as colorless block crystals, mp 186–188 ^oC, with $[\alpha]^{25}_D$ +136 (*c* 0.49, $CHCl_3$). The IR spectrum showed bands due to NH/OH (3391 cm^{-1}) and conjugated ketone carbonyl (1650, 1611 cm^{-1}) functions, while the UV spectrum showed dihydroindole absorption maxima at 210, 239, and 297 nm.[390] The ESIMS showed an $[M + H]^+$ peak at *m/z* 311, and HRESIMS measurements ($[M + H]^+$ 311.1765) established the molecular formula as $C_{19}H_{22}N_2O_2$.

The ^1H NMR data (Table 2.2, Figure 2.7) showed the presence of an unsubstituted indoline chromophore from the presence of four aromatic resonances (δ 6.58–7.24), an indolic NH (δ 4.35), an olefinic hydrogen (δ 7.25, d, *J* = 6 Hz), and an acetyl side chain (δ_H 2.32, δ_C 25.5, 200.3). The ^{13}C NMR data (Table 2.2) showed a total of 19 carbon resonances, comprising one methyl, five methylenes, seven methines, one tertiary carbon bonded to the indolic nitrogen (δ 148.5, C-13), one tertiary carbon

linked to an oxygen (δ 89.7), one secondary carbon linked to two nitrogen atoms (δ 92.2), one ketone carbonyl (δ 200.3), and one quaternary carbon atom. The ^{13}C NMR spectrum confirmed the presence of the conjugated ketone carbonyl (δ_C 200.3) and a trisubstituted double bond associated with the olefinic hydrogen (δ_C 141.2, 144.0). The resonance at δ_C 89.7 was assigned to C-7 from the observed three-bond correlation from the aromatic doublet at δ 7.24 to this carbon in the HMBC spectrum. This doublet was in turn assigned to H-9 from its observed reciprocal NOE with H-6β (δ 2.10), while the other aromatic doublet at δ 6.58 was due to H-12 from its NOE with the indolic NH.

The COSY spectrum indicated, in addition to the presence of the four aromatic hydrogens, the presence of NCH_2CH_2 and $NCH_2CH(CH_2)CH_2CHCH=$ partial structures. The NCH_2CH_2 fragment corresponds to N-4–C-5–C-6 from the observed H-6 to C-8, C-2, and H-5 to C-2, C-3, three-bond correlations in the HMBC spectrum. This also confirmed the assignment of the low-field secondary resonance at δ_C 92.2 to C-2 which is linked to both the indolic N-1 and N-4, and indicated attachment of the C-5–C-6 fragment to the hydroxy-substituted C-7 at δ_C 89.7. These observations indicated fusion of the pyrrolidine ring unit to the indole moiety at C-2 and C-7. The $NCH_2CH(CH_2)CH_2CHCH=$ partial structure can be considered as the sum of two fragments sharing a common branching point (i.e. C-14). The NCH_2CHCH_2 fragment corresponds to N-4–C-3–C-14–C-15, while the $NCH_2CHCH_2CHCH=$ fragment corresponds to N-4–C-3–C-14–C-17–C-16–C-21. These assignments were supported by the observed H-3 to C-15, C-17, H-17 to C-15, and H-15 to C-3, three-bond correlations in the HMBC spectrum (Figure 2.1). The attachment of the C-18–C-19 acetyl side chain at the olefinic C-20 was indicated by the observed three-bond correlations from H-18 to C-20 and from H-21 to C-19, while the observed correlations from H-16 to C-14, C-20, and from H-21 to C-15, C-17, established the α,β-unsaturated cyclohexene ring moiety with acetyl side chain substitution at C-20. The linking of C-

16 to C-2 completes the assembly of the pentacyclic diazaspiro structure of voatinggine. The presence of the diazaspiro C-2 carbon was supported by its observed carbon shift at δ_C 92.2.[391]

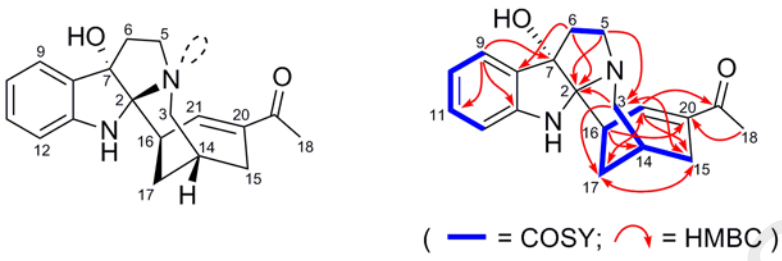


Figure 2.1: COSY and selected HMBCs of **1**

The proposed structure is in complete agreement with the HMBC data (Figure 2.1). The structure is also consistent with the NOE data (Figure 2.2), which also confirmed the relative configuration at the various stereogenic centers. Since suitable crystals were eventually obtained from dichloromethane-hexanes solution, the proposed structure and absolute configuration were also confirmed by an X-ray diffraction analysis (Figure 2.3).

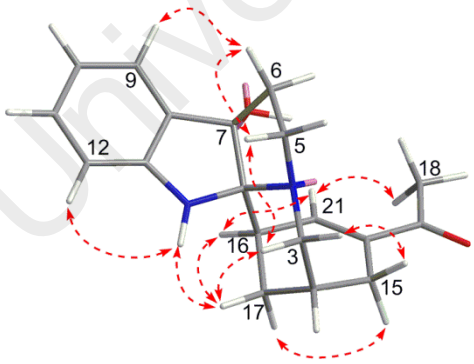


Figure 2.2: Selected NOEs of **1**

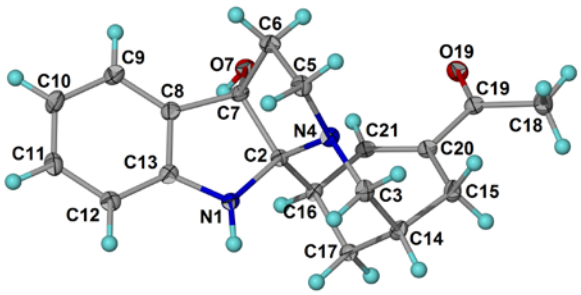


Figure 2.3: X-ray crystal structure of **1**

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

H/C	δ_C	δ_H (*J*/Hz)	HMBC		NOESY/1D NOE
			$^{2}J_{CH}$	$^{3}J_{CH}$	
2	92.2	-			
3α	53.9	2.77 d (11)	14	2, 15, 17	3β, 14, 15β
3β		2.91 dd (11, 2)			3α, 5β, 14, 17β
5β	49.3	2.50 td (8, 6)	6	2, 3	5α, 6β
5α		2.73 t (8)			5β, 6α
6α	42.4	1.94 td (12, 8)	5, 7	2, 8	5α, 6β
6β		2.10 dd (12, 6)			5α, 5β, 6α, 9
7	89.7	-			
8	132.2	-			
9	123.4	7.24 d (8)		7, 11, 13	6β, 10
10	118.8	6.77 t (8)		8, 12	9, 11
11	129.4	7.11 t (8)		9, 13	10, 12
12	109.3	6.58 d (8)		8, 10	11, NH
13	148.5	-			
14	26.8	2.15 m			3α, 3β, 15α, 15β, 17α, 17β
15β	30.9	2.26 d (19)	14, 20	3, 17, 21	3α, 15α
15α		2.56 dd (19, 7)			14, 15β, 17α
16	36.8	2.67 m		14, 20	17α, 17β, 21
17α	27.0	1.69 d (13)		3, 15, 21	14, 16, 17β
17β		1.86 d (13)			3β, 14, 16, 17α, NH
18	25.5	2.32 s	19	20	21
19	200.3	-			
20	141.2	-			
21	144.0	7.25 d (6)	16	15, 17, 19	16, 18
NH	-	4.35 br s			12, 17β

[a] $CDCl_3$, 600 (^{1}H) and 100 MHz (^{13}C); assignments based on COSY, HMQC, HMBC, and NOESY/1D NOE.

2.1.1.2 Tabertinggine (2)

Another alkaloid, tabertinggine (**2**)[241] with a new natural product skeleton and biogenetically related to voatinggine (**1**) was also isolated from the stem-bark extract. Tabertinggine (**2**) was initially obtained as an amorphous solid, which subsequently crystallized from chloroform as colorless needles, mp 113–115 ^{o}C, with $[\alpha]^{25}_{D}$ +107 (*c* 0.40, $CHCl_3$). The IR spectrum showed bands due to NH (3466 cm^{-1}) and conjugated ketone carbonyl (1667, 1628 cm^{-1}) functions. The UV spectrum showed characteristic indole absorption maxima at 225, 282 and 289 nm.[390] The ESIMS showed an $[M + H]^+$ peak at *m/z* 293, and HRESIMS measurements ($[M + H]^+$ 293.1653) established the molecular formula as $C_{19}H_{20}N_2O$.

The ^{1}H NMR data of **2** (Table 2.3, Figure 2.8) shared several features, which were also common in the spectrum of **1**, such as the presence of an unsubstituted indole chromophore from the presence of four aromatic resonances (δ 7.15–7.54), an indolic NH (δ 7.89), an isolated olefinic hydrogen (singlet at δ 6.85), and an acetyl side chain (δ_H 2.26, δ_C 25.3, 200.8). The ^{13}C NMR data (Table 2.3) showed a total of 19 carbon resonances, comprising one methyl, five methylene, six methine, three tertiary carbons bonded to nitrogen atoms, one ketone carbonyl, and three quaternary carbon atoms. In common with **1**, the ^{13}C NMR spectrum showed the presence of the conjugated ketone carbonyl (δ_C 200.8) and a trisubstituted double bond associated with the olefinic hydrogen (δ_C 138.7, 145.7). However, unlike **1**, the deshielded hydroxy-substituted tertiary resonance at δ_C 89.7 (C-7), and the downfield secondary carbon resonance at δ_C 92.2 (C-2) attributed in **1** to its attachment to two nitrogen atoms, were absent in the spectrum of **2**. These signals were replaced in the spectrum of **2** by sp^2 indole carbon resonances at δ_C 108.3 (C-7) and 135.6 (C-2) respectively. Comparison of the ^{1}H and ^{13}C NMR data of **1** and **2** showed that a methine in **1** has been replaced by a tertiary

carbon in **2**, which was eventually traced to C-16 (δ_H 2.67, δ_C 36.8 in **1**; δ_C 60.7 in **2**). Since C-16 is adjacent to the indole moiety, the low field resonance of this tertiary carbon suggested that it is also linked to a nitrogen atom, which turned out to be the case (*vide infra*).

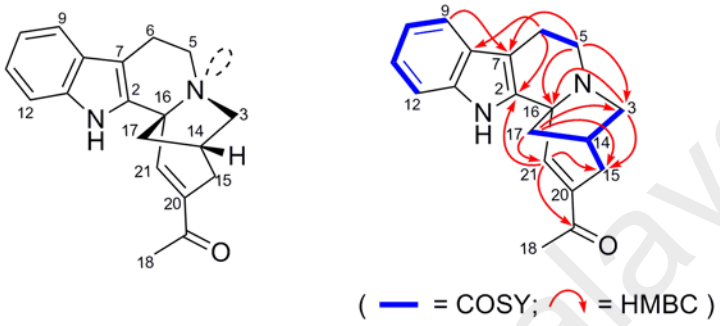


Figure 2.4: COSY and selected HMBCs of **2**

As in the case of **1**, the COSY spectrum also indicated in addition to the presence of the four aromatic hydrogens, the presence of NCH_2CH_2 which is attributed to N-4–C-5–C-6 from the observed H-6 to C-8, C-2, and H-5 to C-7, three-bond correlations in the HMBC spectrum, as well as the observed H-6β/H-9 NOE. However, unlike in the case of **1**, another partial structure shown from the COSY spectrum of **2**, was that of $NCH_2CH(CH_2)CH_2$, instead of $NCH_2CH(CH_2)CH_2CHCH$ in **1**. This corresponds to the N-4–C-3–C-14(C-17)–C-15 fragment in **2** as deduced from the HMBC data (^3J from H-17 to C-3; H-3 to C-15; Figure 2.4). The other observed correlations (Figure 2.4) established the acetyl substituted, conjugated cyclohexene ring (^3J from H-17 to C-15, C-21; H-21 to C-15, C-19), the branching from N-4 to the tertiary C-16 (^3J from H-5 to C-3, C-16; H-3 to C-16), and the branching from the tertiary C-16 to C-2, C-17, and C-21 (^3J from H-21 to C-2; H-17 to C-21).

The structure and relative configuration were also consistent with the NOE data (Figure 2.5). As for **1**, suitable crystals were obtained from chloroform solution and X-

ray diffraction analysis confirmed the structure proposed based on the spectroscopic data, in addition to providing the absolute configuration (Figure 2.6).

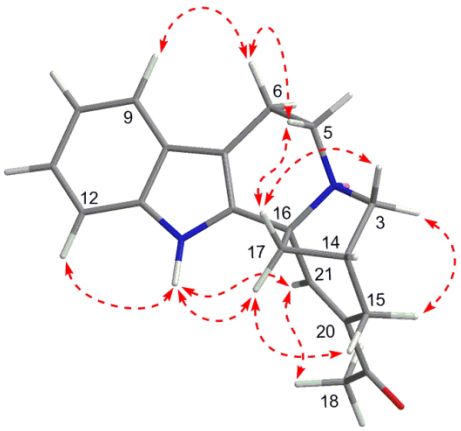


Figure 2.5: Selected NOEs of **2**

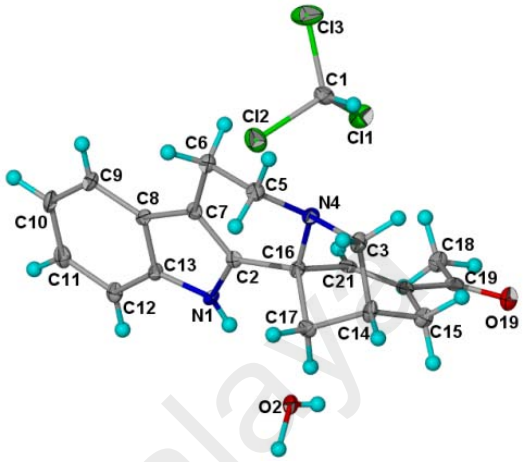
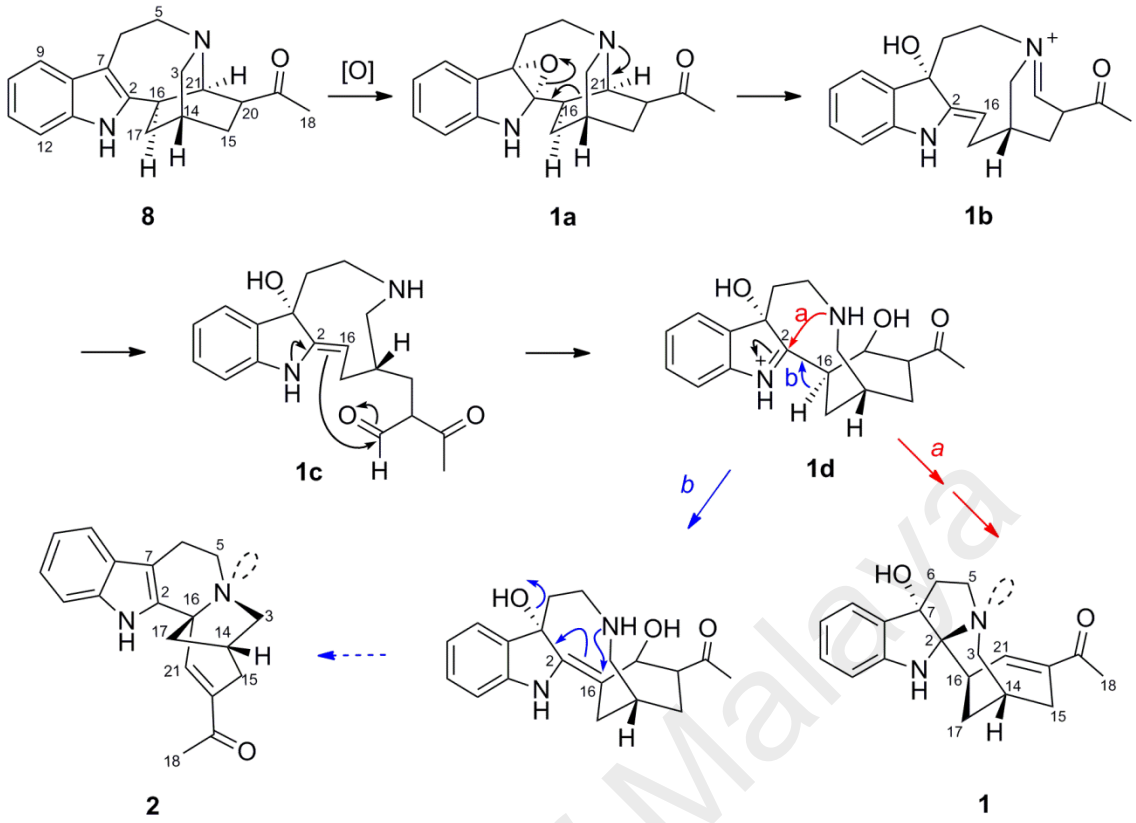


Figure 2.6: X-ray crystal structure of **2**

Although the basic ring systems of both the two new alkaloids have been encountered previously as intermediate compounds in synthesis (for instance, the pentacyclic ring skeleton of **2** was assembled by Büchi in his synthesis of ibogamine by reaction of β-indolylacetyl chloride with the salt from a nicotinamide-derived ethyl 2-azabicyclo[2.2.2]octan-6-one derivative, followed by treatment of the product with PTSA/AcOH,[392] while a pentacyclic ring system similar to **1**, but with different configuration and side-chain substitution, was obtained as a product from the oxidation of dehydroquebrachamine[393]), they are here isolated as optically active natural compounds for the first time, and represent two previously unencountered natural alkaloid skeletons.



Scheme 2.1: Possible biogenetic pathway to **1** and **2**

A possible pathway to these alkaloids from an iboga precursor via a common cleavamine-type intermediate is shown in Scheme 2.1. Oxidation of the keto-ibogamine [conodusine A (**8**), which also occurs in the stem-bark extract] yields the α-epoxide **1a**, which on a Grob-like fragmentation results in cleavage of the C-16–C-21 bond, yielding an iminium ion of a cleavamine-type compound, **1b**. Hydrolysis of this iminium ion **1b** gives the enamine of the ketone-aldehyde **1c**, which on an intramolecular enamine-aldehyde reaction gives the tetracyclic hydroxyindolenine **1d**. Closure of **1d** via path *a* (N-4 attack on imine carbon C-2, followed by dehydration) gives voatinggine (**1**), while the alternative closure via path *b* (deprotonation followed by N-4 attack on C-16, with concomitant aromatization and loss of OH) gives tabertinggine (**2**).

Table 2.3: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Tabertinggine (**2**)

H/C	δ_C [a]	δ_H [b] (*J*/Hz)	HMBC		NOESY/1D NOE
			$^{2}J_{CH}$	$^{3}J_{CH}$	
2	135.6	-			
3β	61.1	3.03 ddd (11, 7, 1)	14	5, 15, 16	14, 17β
3α		3.12 d (11)			15α
5β	51.2	2.89 td (10, 3)	6	3, 7, 16	3β, 5α, 17β
5α		3.09 m			5β
6β	22.2	2.80 dt (15, 3)	5, 7	2, 8	5β, 6α, 9
6α		2.95 m			
7	108.3	-			
8	126.5	-			
9	118.5	7.54 dd (8, 1)		7, 11, 13	6β, 10
10	119.5	7.15 ddd (8, 7, 1)		8, 12	9
11	121.8	7.21 ddd (8, 7, 1)		9, 13	12
12	111.2	7.36 dt (8, 1)		8, 10	11, NH
13	136.6	-			
14	33.6	2.84 m	3	-	3β, 15β, 15α, 17α, 17β
15α	33.1	2.37 d (18)	20	3, 17, 21	3α, 14, 15β
15β		2.50 d (18)			14, 15α, 17α
16	60.7	-			
17α	35.8	1.94 d (11)	16	3, 15, 21	14, 15β, 17β, NH
17β		2.07 dd (11, 5)			3β, 5β, 14, 17α
18	25.3	2.26 s	19		21
19	200.8	-			
20	138.7	-			
21	145.7	6.85 s	16	2, 15, 19	18, NH
NH	-	7.89 br s	2	7, 8	12, 17α, 21

[a] $CDCl_3/CD_3OD$, 100 MHz; [b] $CDCl_3$, 600 MHz; assignments based on COSY, HMQC, HMBC, and NOESY/1D NOE.

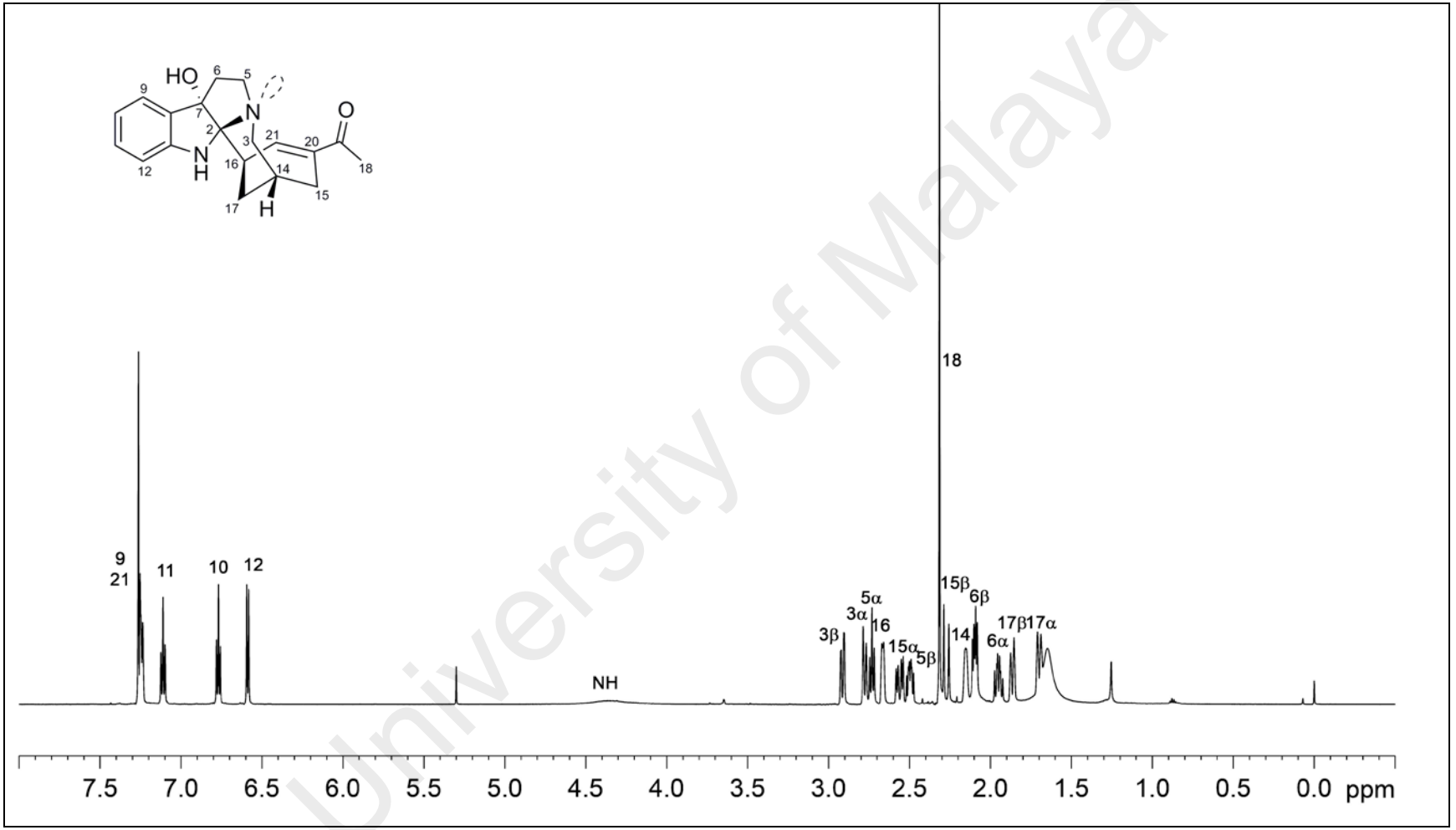


Figure 2.7: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Voatinggine (**1**)

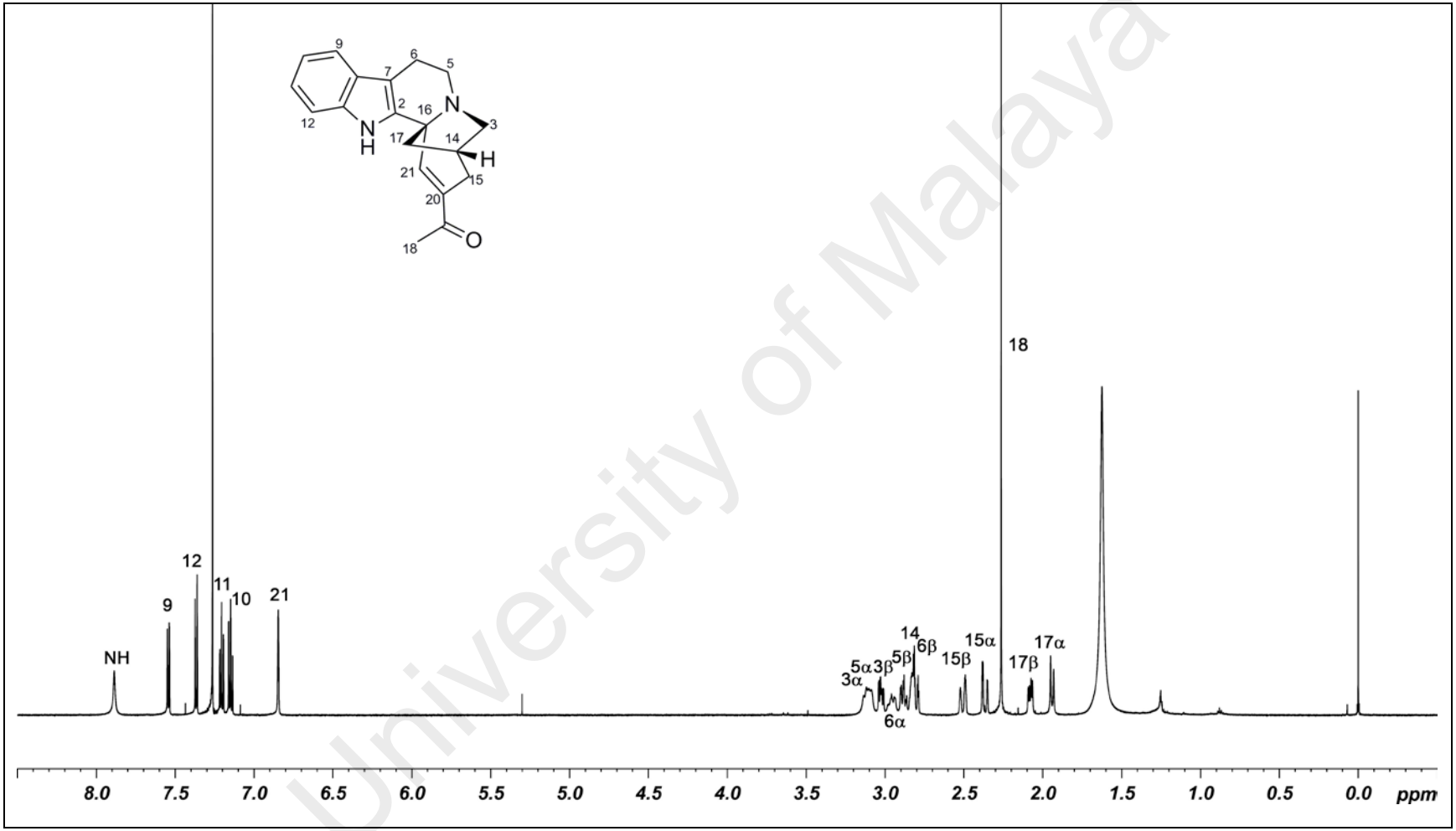


Figure 2.8: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Tabertinggine (**2**)

2.1.2 Cononuridine (3)

Compound **3** was isolated in minute amount as a light yellowish oil, with $[\alpha]^{25}_{D}$ –94 (*c* 0.05, $CHCl_3$). The UV spectrum showed characteristic indole chromophore absorptions at 226, 251 (sh), and 281 nm, while the IR spectrum showed absorption bands at 3396 and 1711 cm^{-1}, due to NH and ketone carbonyl functions, respectively. The ESIMS showed an $[M + H]^+$ peak at *m/z* 309, and HRESIMS measurements established the molecular formula as $C_{19}H_{20}N_2O_2$ (DBE = 11).

The ^{13}C NMR spectrum (Table 2.4) showed a total of 19 carbon resonances, comprising one methyl, four methylenes, eight methines, one ketone carbonyl, two tertiary carbons linked to the indolic nitrogen (corresponding to C-2 and C-13), one tertiary carbon linked to oxygen, and two quaternary carbon atoms. The ^1H NMR spectrum (Figure 2.12, Table 2.4) showed the presence of an indolic NH (δ 8.07), four aromatic resonances of an unsubstituted indole moiety (δ 7.12–7.50), and a methyl singlet of an acetyl side chain (δ_C 209.6, 25.3; δ_H 2.26). The remaining four methylenes and four methines were linked to give a $CH_2CHCHCHCH_2CH(CH_2)CH_2$ unit corresponding to C-6–C-5–C-21–C-16–C-17–C-14(C-3)–C-15, as deduced from the COSY, H2BC and HSQC data. The connection from C-6 to the indole moiety at C-7 was confirmed by the observed three-bond correlations from H-6 to C-8 and C-2, while the other end of this fragment (C-15) was linked to C-21 via C-20 from the observed H-15 to C-21 correlation in the HMBC spectrum. The three-bond correlation from H-17 to C-2 indicated the connection of C-16 to C-2. The carbon resonances at δ 55.3 (C-3) and δ 66.9 (C-5) suggested that these carbons are linked to a common nitrogen N-4 which was confirmed by the three-bond correlations observed from H-3 to C-5 and from H-5 to C-3 in the HMBC spectrum. The remaining acetyl group was branched from C-20 from the observed correlation from H-21 to C-19.

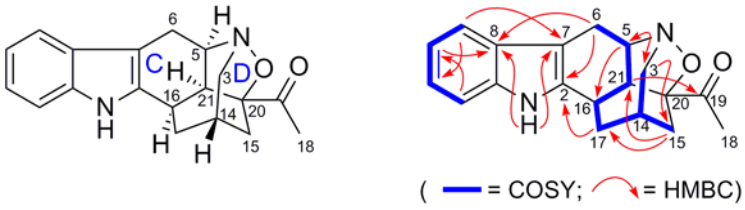


Figure 2.9: COSY and selected HMBCs of **3**

Based on the HRESIMS measurement, the molecular formula of compound **3** requires the presence of two oxygen atoms in the structure. Since one has been assigned to the ketone carbonyl (*vide supra*), another oxygen atom needs to be accounted for. The notable deshielding of C-20 at δ 87.2 suggested a tertiary carbon linked to a heteroatom, and hence C-20 as the site of oxygen substitution, which leads to insertion of the second oxygen between N-4 and C-20, resulting in formation of an isoxazolidine ring (ring D). The isoxazolidine ring D is *cis*-fused to the cyclohexene ring C, from the observed H-5/H-21 NOE. The structure deduced is consistent with the full HMBC (Figure 2.9) and NOESY/NOE (Figure 2.10) data. The absolute configuration of **3** was confirmed by X-ray diffraction analysis of its methyl iodide salt **3** (i.e. **3a**, Figure 2.11). Cononuridine (**3**) is therefore a hexacyclic alkaloid with an iboga-like skeleton, but differing from iboga by loss of a carbon atom in the tetrahydroazepine C ring, and incorporation of an additional isoxazolidine ring.

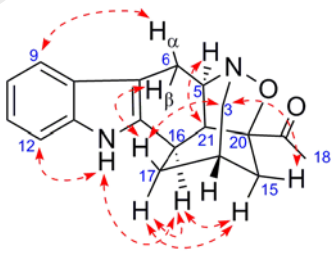


Figure 2.10: Selected NOEs of **3**

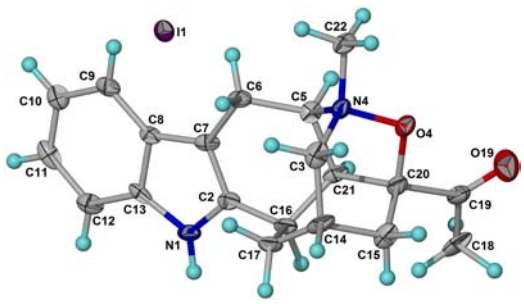
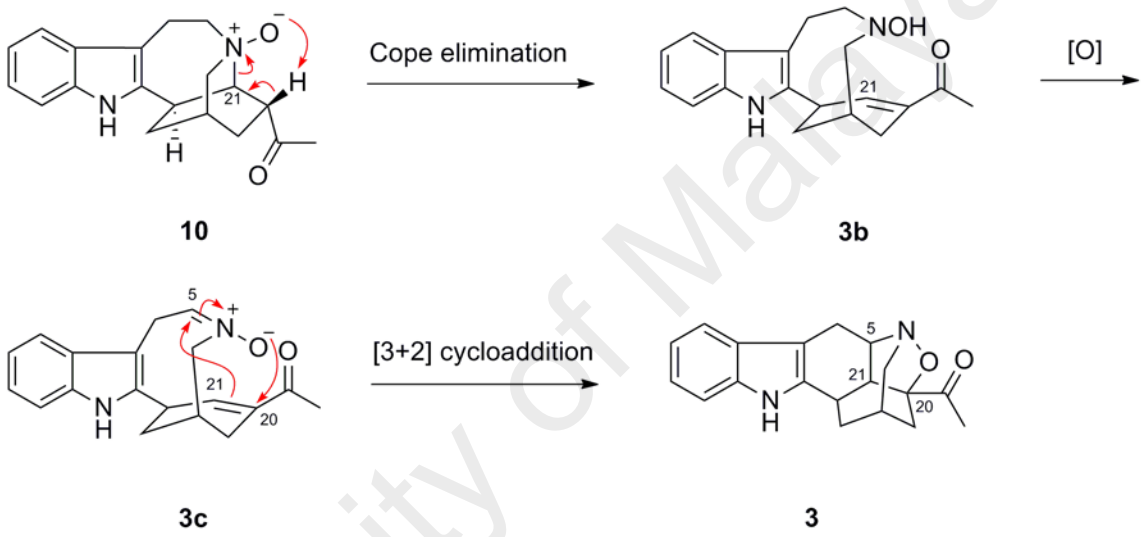


Figure 2.11: X-ray crystal structure of **3a**

A possible biogenetic pathway to **3** from an iboga *N*-oxide precursor **10** is shown in Scheme 2.2. An intramolecular Cope elimination of the *N*-oxide **10** leads to the hydroxylamine incorporating an α,β-unsaturated carbonyl function **3b**. Further oxidation of the hydroxylamine **3b** leads to the nitrone **3c** which then undergoes an intramolecular [3+2] cycloaddition to forge the hexacyclic ring system of cononuridine (**3**).



Scheme 2.2: A possible biogenetic pathway to **3**

Table 2.4: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Cononuridine (**3**)[a]

H/C	δ_C	δ_H (*J*/Hz)	HMBC		NOESY/1D NOE
			$^{2}J_{CH}$	$^{3}J_{CH}$	
2	142.1	-			
3a	55.3	3.05 d (15)		5, 15, 17	3b, 6β, 14, 17β
3b		3.71 dd (15, 4)			3a, 14, 15β
5	66.9	4.17 td (10.6, 8.6, 6.5)	6	3, 16	6α, 21
6β	20.6	2.43 dd (16.6, 6.5)	5	2, 8, 21	6α, 17β
6α		3.53 dd (16.6, 10.6)			5α, 6β, 9
7	105.8	-			
8	127.2	-			
9	117.4	7.50 dd (6.8, 1.6)		7, 11, 13	6α, 10
10	119.6	7.15 td (6.8, 1.6)		8	
11	121.1	7.12 td (6.8, 1.6)		9, 13	12
12	111.3	7.33 dd (6.8, 1.6)		8, 10	
13	135.4	-			
14	26.8	2.13 m			17β
15α	31.1	1.86 br d (13)	14, 20	3, 17	14, 15β, 16, 17α
15β		2.02 ddd (13, 4.4, 2)			15α
16	27.1	3.08 m		14	15α, 17α, 21
17β	37.9	1.38 dd (14, 7)	14, 16	2, 3, 15, 21	3a, 14, 17α
17α		2.43 m			14, 15α, 17β
18	25.3	2.26 s	19		
19	209.6	-			
20	87.2	-			
21	50.9	2.74 dd (8.6, 4.5)		17, 19	
NH		8.07 br s	2, 13	7, 8	12, 16

[a] $CDCl_3$, 400 (^{1}H) and 100 MHz (^{13}C); assignments based on COSY, H2BC, HSQC, HMBC, and NOESY/1D NOE.

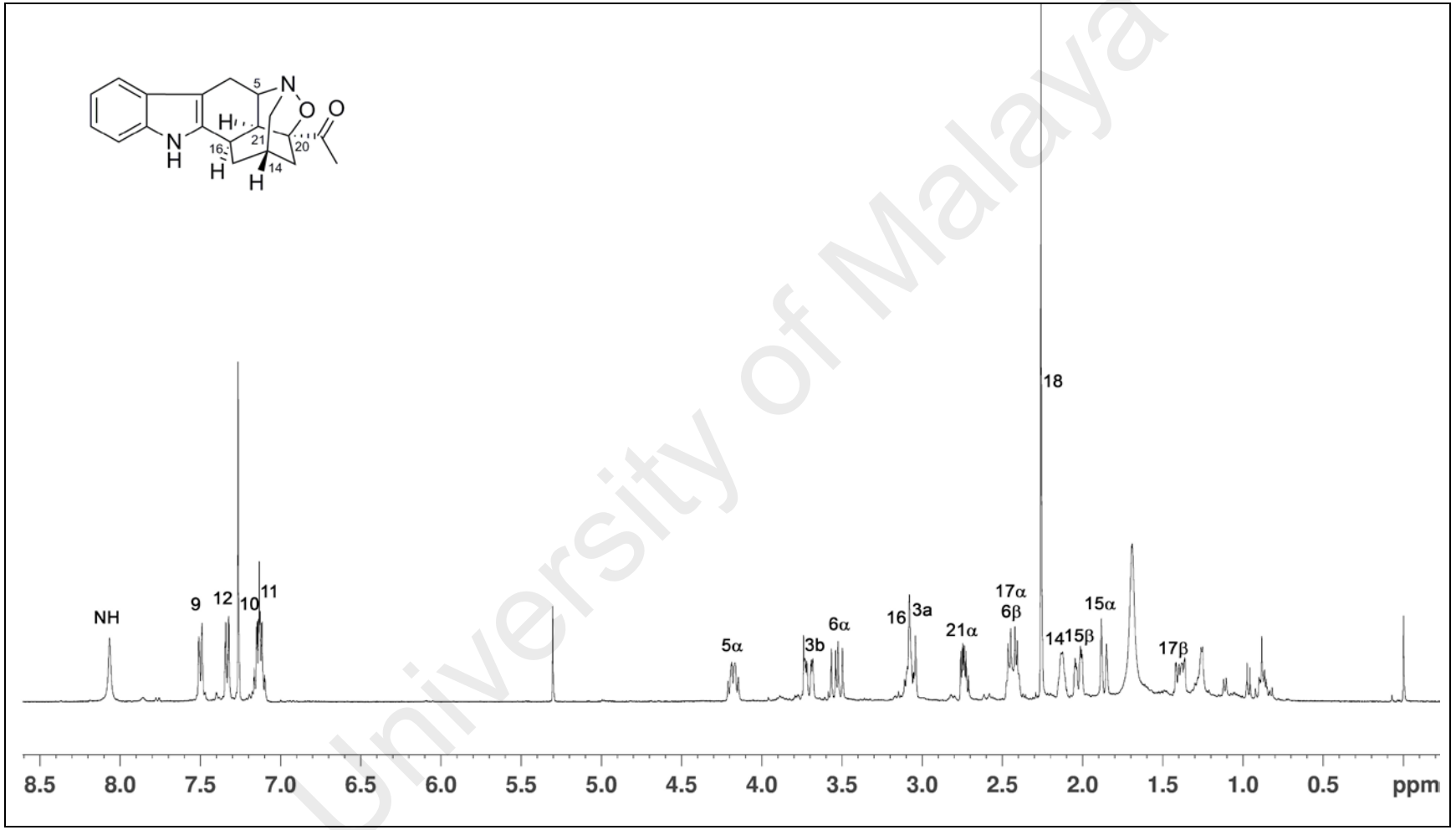
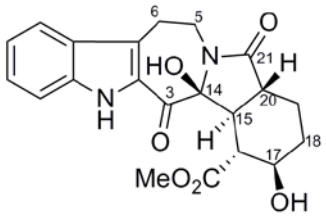


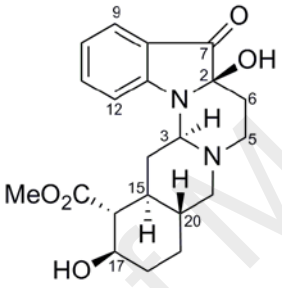
Figure 2.12: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Cononuridine (**3**)

2.1.3 Criofolinine (4), Vernavosine (5), and Vernavosine ethyl ether (6)

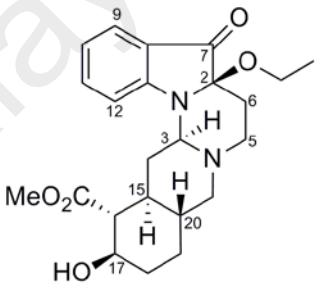
Criofolinine (**4**) and vernavosine (**5**) (isolated as its ethyl ether derivative, **6**) are pentacyclic alkaloids with previously unencountered natural product skeletons. Criofolinine (**4**), incorporating a pyrroloazepine motif within a pentacyclic ring system, while vernavosine (**5**) incorporating a pyridopyrimidine moiety embedded within the pentacyclic carbon framework.



4



5



6

2.1.3.1 Criofolinine (4)

Criofolinine (**4**)[236] was initially obtained as a light yellowish oil and subsequently crystallized from absolute ethanol as colorless block crystals, mp >190 °C (dec), with $[\alpha]^{25}_{D}$ +87 (*c* 0.3, $CHCl_3$). The IR spectrum showed bands due to NH/OH (3393 cm^{-1}) and various carbonyl (1699, 1648 cm^{-1}) functions, while the UV spectrum showed characteristic 2-acylindole absorption maxima at 205, 238, and 316 nm (log ε 4.67, 4.35, and 4.41, respectively).[281,390] The ESIMS showed an $[M + H]^+$ peak at *m/z* 399, and HRESIMS measurements ($[M + H]^+$ 399.1550) established the molecular formula as $C_{21}H_{22}N_2O_6$. The ^1H NMR data (Table 2.5, Figure 2.20) showed the presence of four aromatic resonances (δ 7.17–7.61), an indolic NH (δ 8.94), and a methoxy

corresponding to a methyl ester group (δ 3.88). The ^{13}C NMR data (Table 2.5) showed a total of 21 carbon resonances, comprising one methyl, four methylenes, eight methines, two tertiary carbons bonded to indolic nitrogen (corresponding to C-2, C-13), a secondary carbon bonded to two heteroatoms (δ 92.2), three carbonyl carbons (δ 173.5, 174.2, 191.8), and two quaternary carbon atoms. The resonance at δ 191.8 was due to a conjugated ketone carbonyl and can be readily assigned to C-3, as it is part of the acyl indole moiety. Two other carbonyl resonances were observed at δ 173.5 and 174.2, which were assigned to ester and lactam carbonyl functionalities, respectively. Assignment of the former resonance to the ester carbonyl was facilitated by the observed three-bond correlation from the ester methyl to the carbonyl resonance at δ 173.5 in the HMBC spectrum. The carbon resonances of the indole unit can be readily assigned based on analogy with other 2-acylindole alkaloids[281,394] and these assignments were readily corroborated by NOE and 2D NMR data. A downfield resonance at δ 92.2 was characteristic of a secondary carbon linked to a nitrogen and an oxygen atom,[391,395] while another resonance at δ 73.3 was due to an oxymethine.

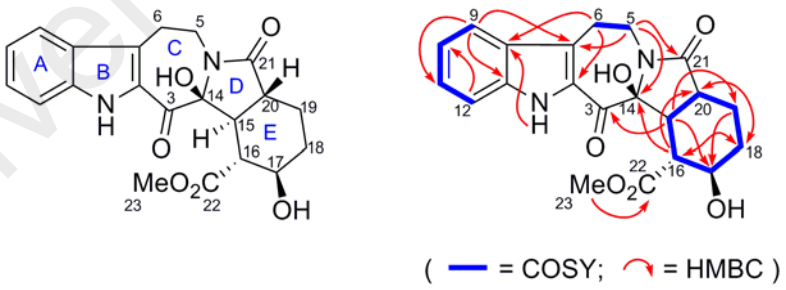


Figure 2.13: COSY and selected HMBCs of **4**

The COSY spectrum (Figure 2.13) showed two partial structures, an NCH_2CH_2 and a $CHCHCHCHCH_2CH_2$ fragment, the latter corresponding to a cyclohexane moiety. The assignment of the NCH_2CH_2 fragment to C-5–C-6 was supported by the three-bond correlations from H-6 to C-2, C-8, and from H-5 to C-7, in the HMBC

spectrum (Figure 2.13). The lactam carbonyl was deduced to be linked to N-4, from the observed H-5 to C-21 three-bond correlation. The same applies to the oxygen- and nitrogen-linked C-14 from the observed H-5 to C-14 correlation. The correlation from H-15 to the ketone carbonyl C-3, and from H-16 to C-14, indicated that the carbinol amine C-14 was linked to C-3. Examination of the ^{1}H and ^{13}C chemical shifts suggested substitution of the cyclohexane moiety by amide carbonyl, carbomethoxy, and hydroxy groups, corresponding to C-20–C-15–C-16–C-17–C-18–C-19. This six-membered ring E (with carbomethoxy and hydroxy substitution at C-16 and C-17, respectively) must therefore be linked to the lactam C-21 via C-20 and to the carbinol amine C-14 via C-15, which completes assembly of the 6/5/7/5/6 pentacyclic ring system of criofolinine (**4**).

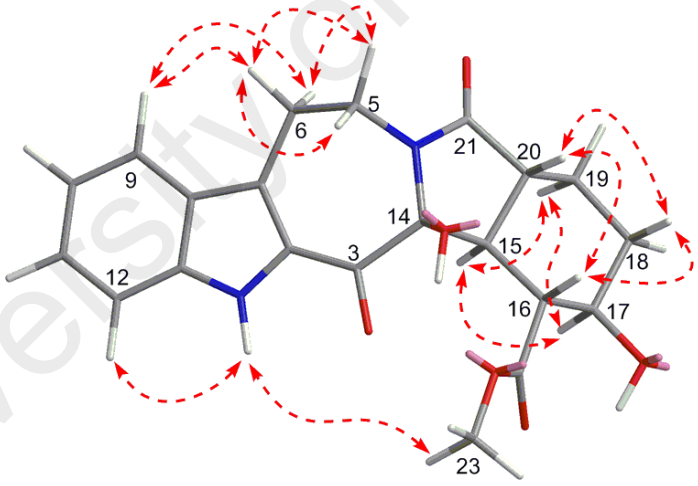


Figure 2.14: Selected NOEs of **4**

The relative configurations at the various stereogenic centers were established from the NOE data and the observed vicinal coupling constants. The D/E ring junction stereochemistry was deduced to be *trans* from the observed $J_{15–20}$ value of 12 Hz (H-15 and H-20 *trans*-diaxial). The reciprocal NOEs observed for H-16/H-18β, H-16/H-20, H-18β/H-20, and for H-15/H-17, H-15/H-19α, H-17/H-19α, indicated that these

hydrogens are axially oriented, which were consistent with a chair conformation adopted by the E-ring with the OH and CO_2Me substituents oriented equatorially (Figure 2.14). This was also in agreement with the observed $J_{15–16}$ and $J_{16–17}$ values of 12 and 10 Hz, respectively. The configuration at the carbinol amine C-14 could not be assigned with certainty based on the spectroscopic data alone but was nonetheless eventually established from X-ray analysis of **4**, which also provided confirmation of the structure (Figure 2.15, relative configuration) of this novel alkaloid deduced from the spectroscopic data. Criofolinine (**4**) represents a new monoterpenoid indole alkaloid skeleton, incorporating a pyrroloazepine motif within a pentacyclic ring system.

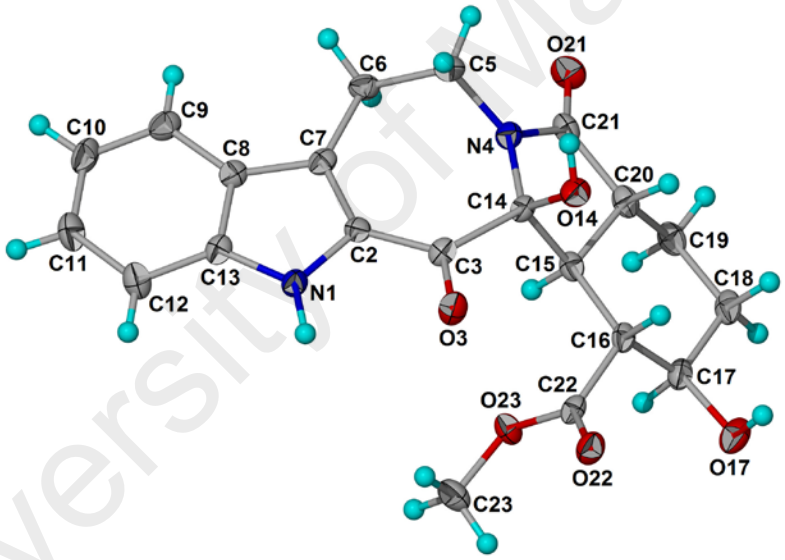


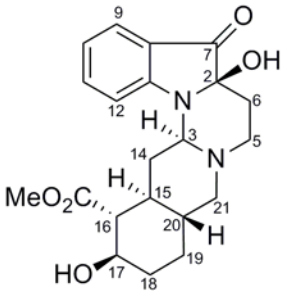
Figure 2.15: X-ray crystal structure of **4**

Table 2.5: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Criofolinine (**4**)[a]

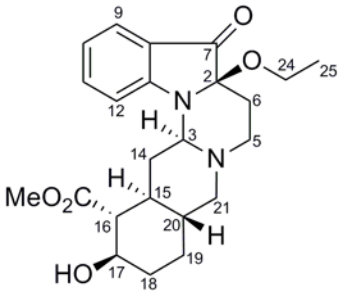
H/C	δ_C	δ_H (*J*/Hz)	HMBC		NOESY/1D NOE
			$^{2}J_{CH}$	$^{3}J_{CH}$	
2	128.5	-			
3	191.8	-			
5β	38.9	3.23 ddd (14, 12, 2)	6	7, 14, 21	5α
5α		4.31 ddd (14, 4, 2)			5β, 6α, 6β
6β	27.1	3.11 dt (18, 2)	7	2, 8	5α, 5β, 6α
6α		3.42 ddd (18, 12, 4)			5α, 6β
7	126.2	-			
8	127.4	-			
9	121.5	7.61 dd (8, 1)	8	7, 11, 13	6α, 6β, 10
10	121.1	7.17 ddd (8, 6, 2)		8, 12	
11	127.8	7.40 m		13	10
12	112.3	7.41 m		10	
13	137.7	-			
14	92.2	-			
15	50.2	2.01 t (12)	14, 16, 20	3, 17, 19, 22	17, 19α
16	50.8	2.68 dd (12, 10)	15, 17, 22	14, 18, 20	18β, 20
17	73.3	3.76 td (10, 3)			15, 16, 18α, 19α
18β	34.3	1.45 tdd (13, 10, 3)	17, 19	16, 20	16, 18α, 20
18α		2.14 dq (13, 3)			18β, 19α
19α	22.4	1.30 tdd (13, 12, 3)	18	17	
19β		2.20 dq (13, 3)			18β, 19α, 20
20	42.3	2.52 td (12, 3)	15, 19, 21	18	16, 18β, 19β
21	174.2	-			
CO_2Me	173.5	-			
CO_2*Me*	52.2	3.88 s		22	NH
NH		8.94 br s		8	12, 23

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); assignments based on COSY, H2BC, HMQC, HMBC, and NOESY/1D NOE

2.1.3.2 Vernavosine (5) and Vernavosine ethyl ether (6)



5



6

Vernavosine (**5**) was isolated as its ethyl ether derivative (**6**),[236] which was obtained as a yellow-green fluorescent oil, with $[\alpha]^{25}_{D}$ –49 (*c* 0.31, $CHCl_3$). The UV spectrum showed absorption maxima at 233, 257, and 396 nm, reminiscent of alkaloids possessing pseudoindoxyl chromophores,[390,396] while the IR spectrum showed bands due to OH (3416 cm^{-1}) and various carbonyl (1712 cm^{-1}) functions. The ESIMS showed an $[M + H]^+$ peak at *m/z* 415, and HRESIMS measurements ($[M + H]^+$ 415.2233) established the molecular formula as $C_{23}H_{30}N_2O_5$. The ^1H NMR spectrum of **6** (Figure 2.22, Table 2.6) showed the presence of four aromatic resonances associated with the indole moiety (δ 6.81–7.59), a methine linked to two nitrogen atoms (δ 4.55), an oxymethine (δ 3.87), a methyl singlet (δ 3.73) due to a methyl ester group (δ_C 51.7, 174.7), and an ethoxy side chain (δ_H 1.19, δ_C 14.7; δ_H 3.28, 3.32; δ_C 59.3). The absence of the characteristic indolic NH signal suggested substitution at the indolic nitrogen (N-1). The ^{13}C NMR data (Table 2.6) showed a total of 23 carbon resonances, comprising two methyls (δ 14.7, 51.7), seven methylenes, nine methines, two carbonyl carbons (δ 200.4, 174.7), one tertiary carbon bonded to indolic nitrogen, one secondary carbon bonded to two heteroatoms, and one quaternary carbon atom. Two carbonyl resonances were observed at δ 200.4 and 174.7, the former was due to a conjugated ketone, while the latter was assigned to the ester carbonyl. The ketone carbonyl was deduced to be at C-7 from the three-bond correlation from H-9 in the HMBC spectrum. In addition, an

oxymethine resonance was seen at δ 71.6, while the resonance at δ 89.3 was due to a secondary carbon linked to a nitrogen, and an oxygen atom.[391,395] This carbon corresponded to C-2 to which the ethoxy substituent is linked from the observed three-bond correlation from the ethoxy methylene hydrogens (H-24) to this carbon in the HMBC spectrum. The resonance at δ 69.4, which was associated with the ^{1}H resonance at δ 4.55, provided additional support for the presence of an aminal carbon.

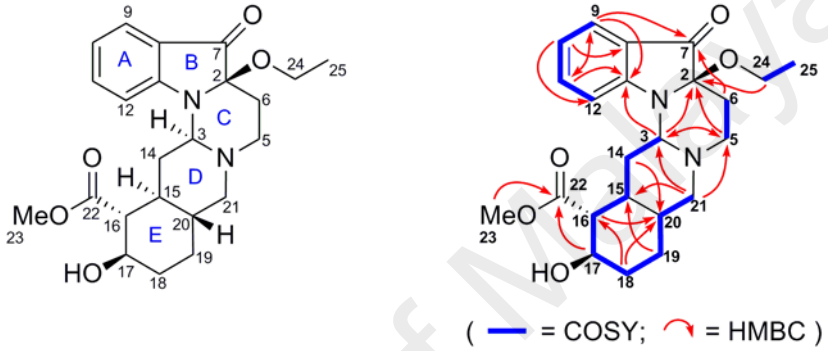


Figure 2.16: COSY and selected HMBCs of **6**

The COSY spectrum showed in addition to the aromatic and ethoxy moieties, two other partial structures, NCH_2CH_2 and $NCHCH_2CHCHCHCH_2CH_2CHCH_2$ (Figure 2.16). The former two-carbon fragment corresponded to C-5–C-6 from the three-bond correlation from H-5 to C-2 observed in the HMBC spectrum (Figure 2.16). The nine-carbon fragment corresponded to C-3–C-14–C-15–C-16–C-17–C-18–C-19–C-20–C-21. The aminal carbon, C-3 (δ_H 4.55; δ_C 69.4) was linked to both N-1 and N-4, while the assignments of the methyl ester substituted C-16 and hydroxy-substituted C-17, were consistent with the corresponding carbon resonances observed at δ 57.5 and 71.6, respectively. Similarly for C-21 (δ 59.3), which was linked to N-4. These assignments were in excellent agreement with the full HMBC data (Figure 2.16). The H-3 to C-13, C-2, and C-5 correlations were consistent with branching of C-3 from N-1 (and N-4),

while the H-21 to C-3 and C-5 correlations were consistent with the connection of C-21 to N-4.

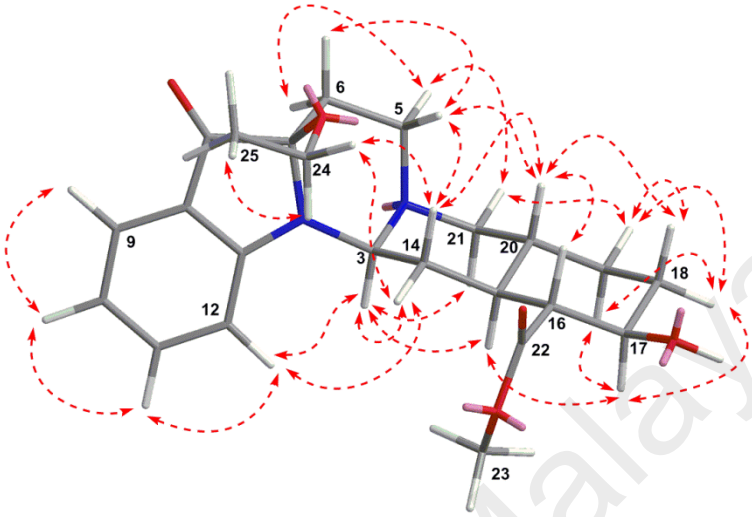


Figure 2.17: Selected NOEs of **6**

Examination of the vicinal coupling constants ($J_{5\beta-6\alpha}$, $J_{3\alpha-14\beta}$, $J_{14\beta-15\alpha}$, $J_{15\alpha-16\beta}$, $J_{16\beta-17\alpha}$, $J_{17\alpha-18\beta}$, $J_{18\beta-19\alpha}$, $J_{19\alpha-20\beta}$, $J_{20\beta-21\alpha} \sim$ 11–14 Hz) and the NOE data (Figure 2.17), indicated that the C, D, and E rings adopted the stable chair conformations, with *cis*-fused C/D and *trans*-fused D/E rings, and with the C-16 methyl ester and C-17–OH groups oriented equatorially. The C/D *cis*-ring fusion was also supported from the X-ray diffraction data of the methyl iodide salt of **6** (**6a**, Figure 2.18). The ethoxy group was deduced to be β-oriented from the observed H-24/H-14 NOEs and from its presumed origin, which required the alcohol nucleophile to approach the precursor iminium ion from the less hindered β-face (Scheme 2.3). Vernavosine (**5**) represents another novel monoterpenoid indole alkaloid skeleton, characterized by incorporation of a pyridopyrimidine moiety embedded within a pentacyclic ring system.

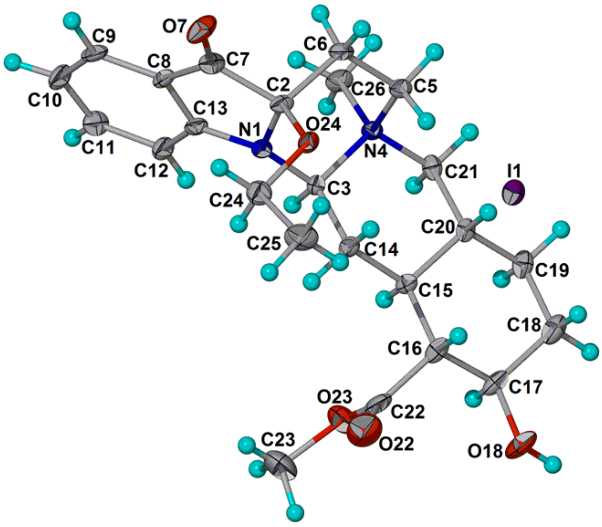


Figure 2.18: X-ray crystal structure of **6a**

We propose that both alkaloids originate from a common β-yohimbine precursor **38**, which was among the alkaloids present in the plant (Scheme 2.3). Thus, hydrolytic cleavage of the iminium ion **4a** derived from oxidation of the β-yohimbine precursor **38** gave the keto amine **4b**. Reduction of the ketone function, followed in succession by dehydration and oxidation, yielded the epoxide **4c**. Epoxide ring opening via transannular attack by the secondary amine nitrogen forged the pyrroloazepine ring system of the alcohol **4d**, which on selective oxidation of the benzylic alcohol moiety gave the conjugated ketone **4e**. Nucleophilic attack by water on the iminium ion derived from **4e** installed the tertiary alcohol functionality at C-14, and a final oxidation provided criofolinine (**4**).

Alternatively, oxidation of the same β-yohimbine precursor **38** gave the pseudoindoxyl alkaloid **46**. A further oxidation provided the N-4-oxide derivative **47**, which on a Grob-like fragmentation (Polonovski-like) yielded the imine-iminium ion intermediate **5b**. Ring closure via attack of the imine nitrogen (N-1) on the iminium ion yielded the pentacyclic ring system of vernavosine in the form of its iminium ion **5c**, which on reaction with water yields the carbinol amine **5**. In the presence of the stronger ethanol nucleophile (ethanol was used during extraction of alkaloids) the carbinol amine

5 will in all probability be readily converted to its ethanolysis product **6**, which was the final form of the alkaloid isolated. Hydrolysis of **6** (in two-phase medium with phase transfer catalysis) gave the putative precursor alkaloid, the carbinol amine **5**, while re-exposure of **5** to EtOH in the presence of a trace of acid gave **6**, providing additional confirmation for the origin of the ethyl ether derivative **6** from the original intact alkaloid **5**.

The ^{1}H (Figure 2.21) and ^{13}C NMR spectroscopic data of vernavosine (**5**) are reported in Table 2.6, while other data are presented in the Experimental Section. The absolute configuration of vernavosine (**5**) was also obtained by the X-ray diffraction analysis of its methyl iodide salt, **5a** (Figure 2.19).

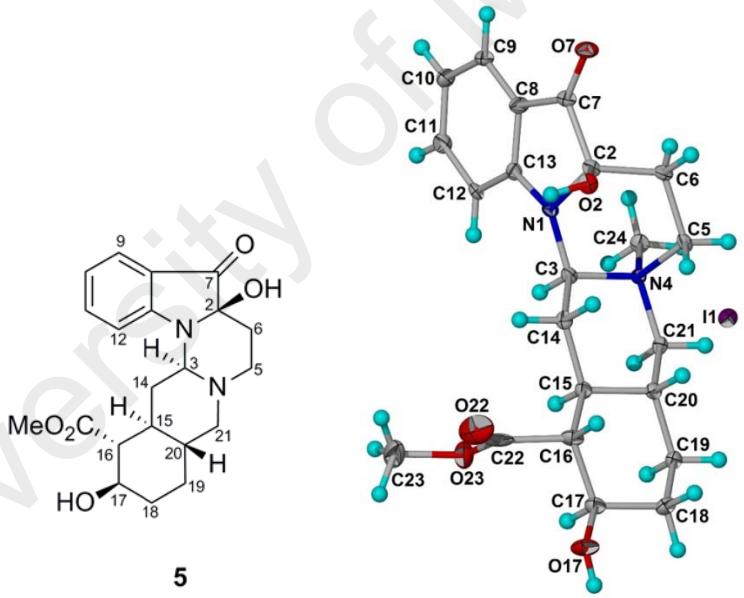
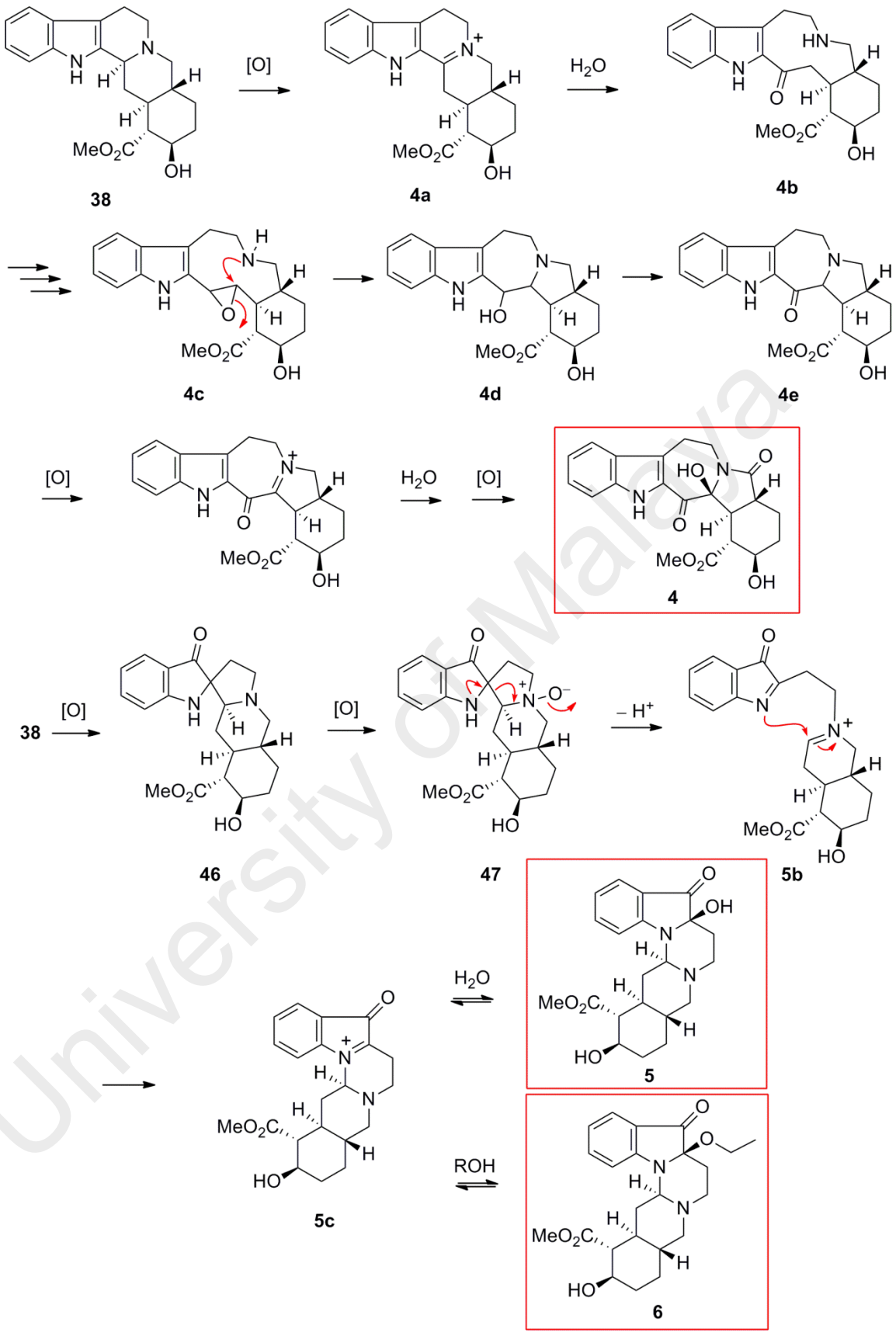


Figure 2.19: X-ray crystal structure of **5a**



Scheme 2.3: Possible biogenetic pathways to **4** and **5/6** from **38**

Table 2.6: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Vernavosine (**5**) and Vernavosine ethyl ether (**6**)

H/C		**5**[a]		**6**[b]
	δ_C	**δ_H (*J*/Hz)**	**δ_C**	**δ_H (*J*/Hz)**
2	85.7	-	89.3	-
3	71.7	4.22 dd (11, 3)	69.4	4.55 dd (12, 3)
5α	43.6	2.46 ddd (12, 7, 4)	41.3	2.48 ddd (12, 5, 3)
5β		3.32 ddd (12, 9, 6)		3.42 td (12, 3)
6α	31.3	1.79 ddd (14, 9, 7)	31.5	1.70 ddd (14, 12, 5)
6β		2.14 ddd (14, 6, 4)		2.06 dt (14, 3)
7	199.9	-	200.4	-
8	118.1	-	119.1	-
9	125.8	7.61 dd (8, 1)	125.3	7.59 dd (7, 1)
10	119.1	6.82 ddd (8, 7, 1)	119.1	6.81 t (7)
11	138.2	7.50 ddd (8, 7, 1)	138.3	7.51 ddd (8, 7, 1)
12	109.3	6.74 d (8)	109.8	6.86 d (8)
13	157.8	-	159.1	-
14α	32.9	1.70 dt (12, 3)	29.2	1.41 dt (12, 3)
14β		2.01 dt (12, 11)		2.26 q (12)
15	41.9	1.54 m	43.0	1.53 m
16	57.0	2.22 t (11)	57.5	2.22 t (11)
17	71.9	3.85 td (11, 4)	71.6	3.87 td (11, 4)
18β	34.0	1.42 tdd (13, 11, 4)	34.1	1.45 tdd (13, 11, 4)
18α		2.10 dq (13, 4)		2.12 dq (13, 4)
19α	27.5	1.09 qd (13, 4)	27.6	1.05 qd (13, 4)
19β		1.67 dq (13, 4)		1.62 dq (13, 4)
20	35.1	1.51 m	32.9	1.53 m
21α	59.4	2.40 dd (13, 11)	59.3	2.61 dd (14, 11)
21β		2.96 dd (13, 3)		2.92 dd (14, 3)
22	174.7	-	174.7	-
23	51.9	3.73 s	51.7	3.73 s
24	-	-	59.3	3.28 q (7)
24	-	-		3.32 q (7)
25	-	-	14.7	1.19 t (7)

[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); [b]$CDCl_3$, 600 (^{1}H) and 100 MHz (^{13}C); assignments based on COSY, H2BC, HMQC/HSQC, HMBC, and NOESY/1D NOE.

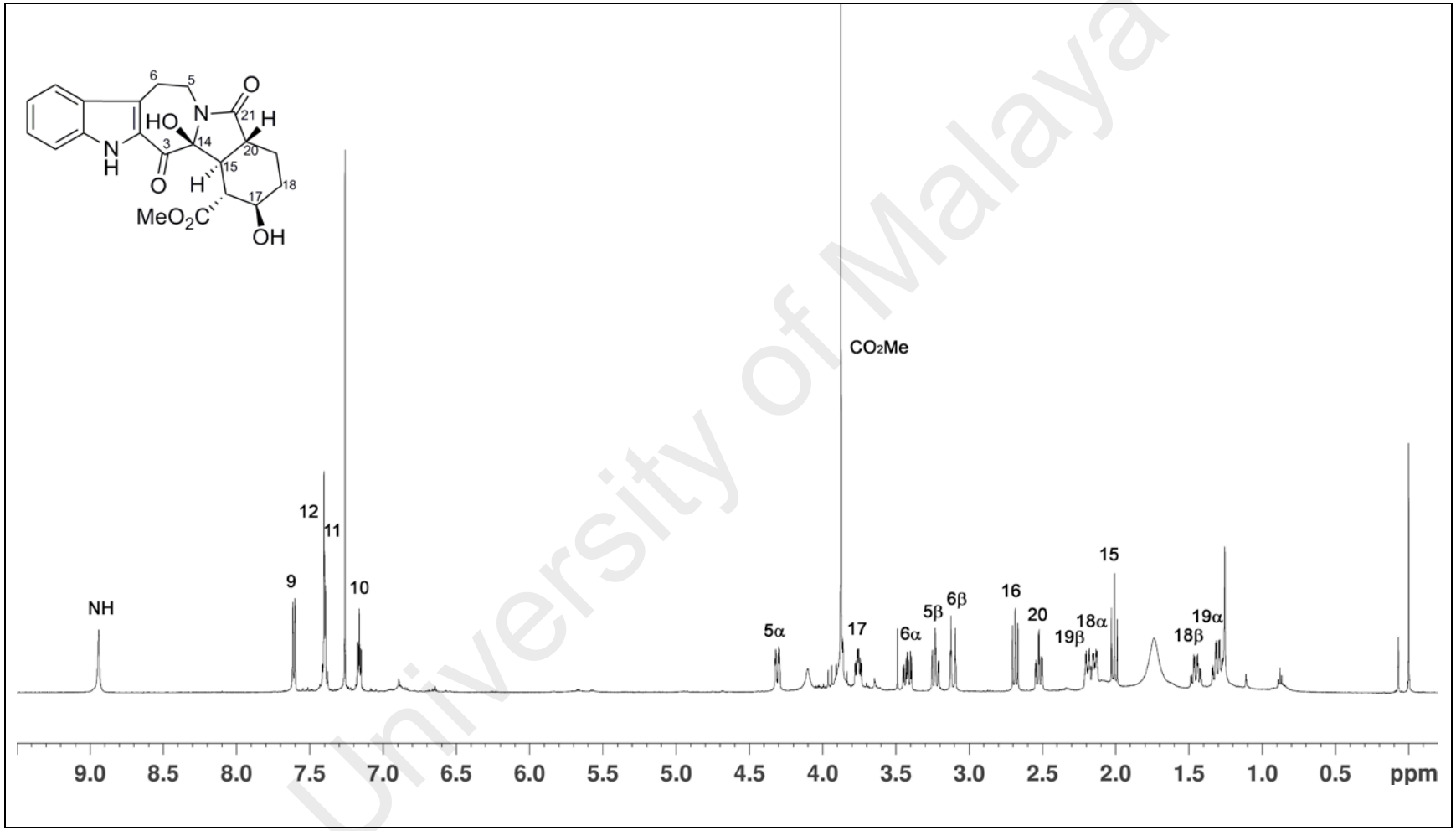


Figure 2.20: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Criofolinine (**4**)

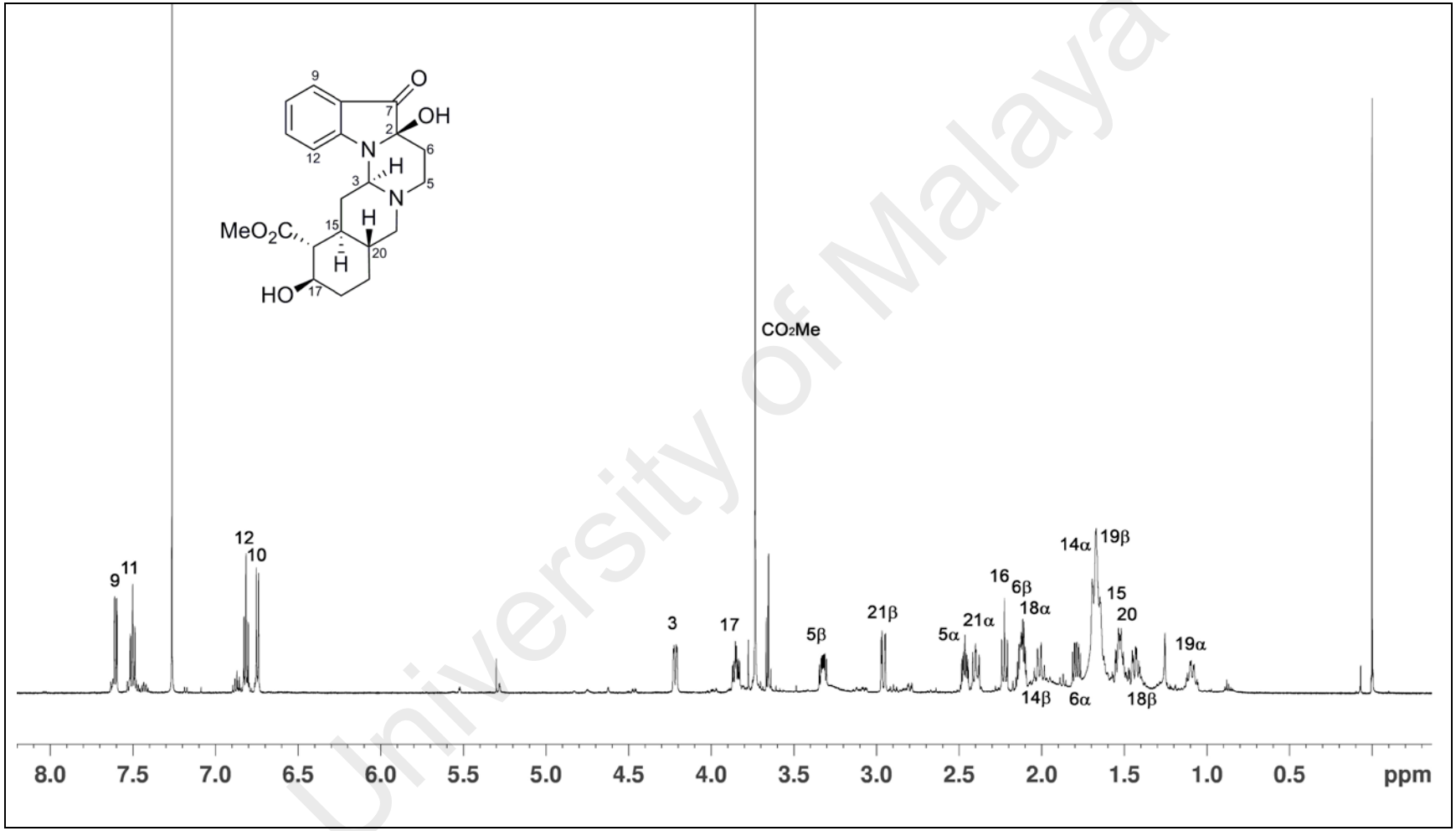


Figure 2.21: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Vernavosine (**5**)

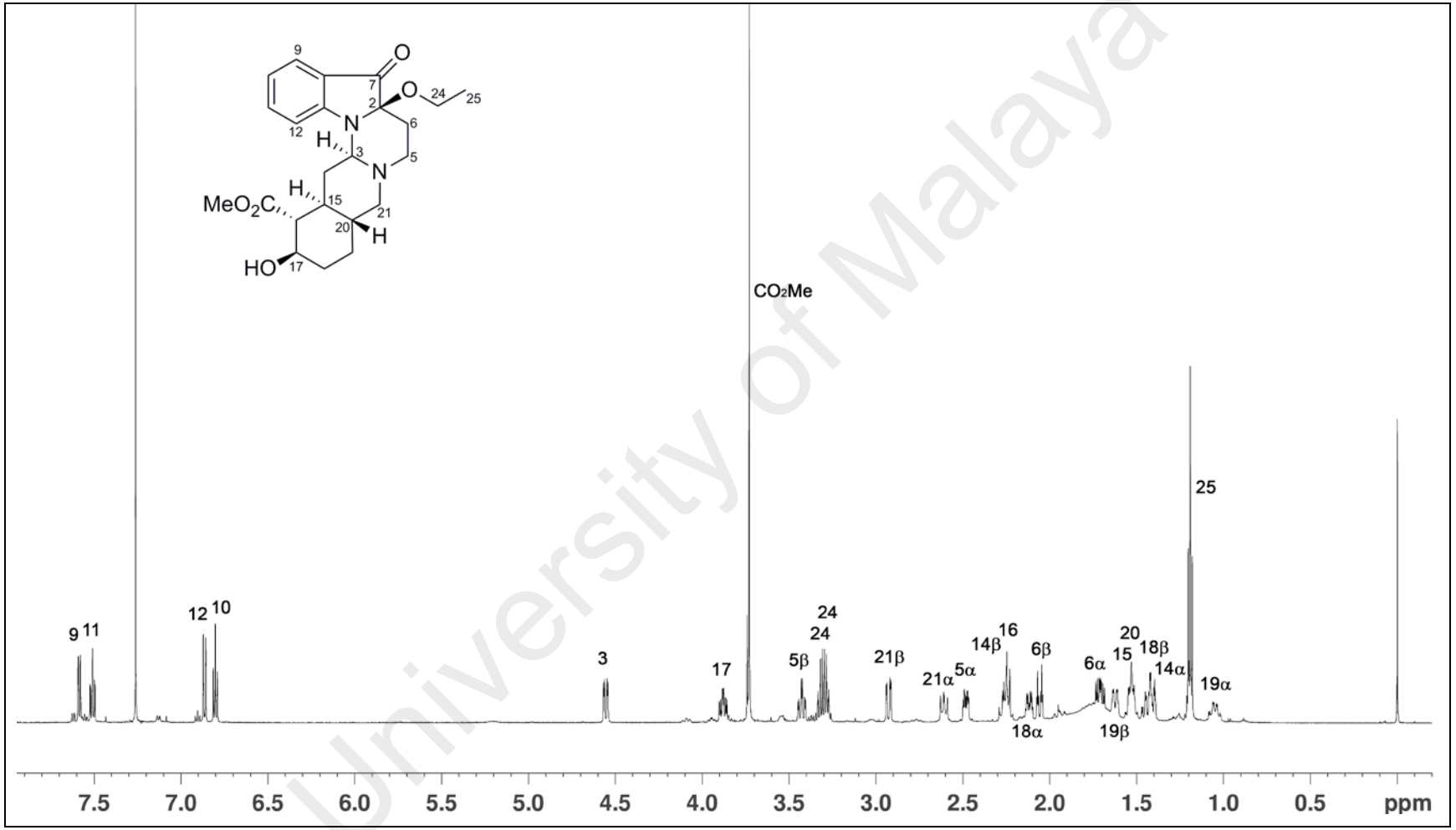


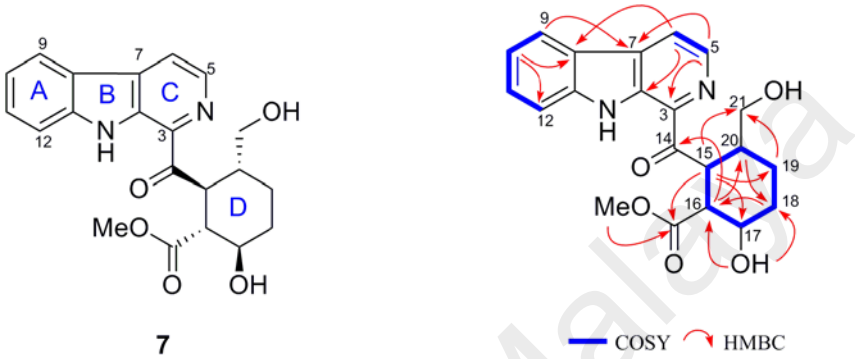
Figure 2.22: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Vernavosine ethyl ether (**6**)

2.1.4 Taberisidine (7)

Compound **7** was isolated as yellowish oil, $[\alpha]^{25}_{D}$ +42 (*c* 0.17, $CHCl_3$). The UV spectrum showed absorption maxima at 216, 287, 317 (sh), and 384 nm suggesting the presence of a β-carboline chromophore,[397,398] while the IR spectrum showed absorption bands due to NH, OH (3437, 3371 cm^{-1}) and various carbonyl (1726, 1666 cm^{-1}) functions. The ESIMS showed an $[M + H]^+$ peak at *m/z* 383, and HRESIMS measurement established the molecular formula as $C_{21}H_{22}N_2O_5$.

The ^{13}C NMR data (Table 2.7) accounted for all 21 carbon resonances, comprising one methyl, three methylenes, ten methines, three tertiary carbons linked to nitrogen (corresponding to C-2, C-13, and C-3), two carbonyl carbons, and two quaternary carbons. The resonance at δ 206.3 was assigned to the ketone carbonyl conjugated to the β-carboline moiety while the resonance at δ 174.4 was due to an ester carbonyl. The ^1H NMR spectrum (Figure 2.26, Table 2.7) showed in addition to the four aromatic hydrogens of an unsubstituted indole moiety (δ 8.18, dd, *J* = 7.8, 1 Hz, H-9; 7.37, ddd, *J* = 7.8, 7, 1 Hz, H-10; 7.64, ddd, *J* = 8.2, 7, 1 Hz, H-11; 7.59, d, *J* = 8.2 Hz, H-12) and the indolic NH (δ 10.31), two additional aromatic hydrogens which were seen as a pair of mutually-coupled AB doublets (δ 8.22, 8.52; *J* = 5 Hz) and which can be assigned to H-5 and H-6 of the β-carboline unit. The ^1H NMR spectrum also showed the presence of two OH resonances, a secondary OH at δ 3.21 and a primary OH at δ 4.99, with the corresponding oxymethine and hydroxymethyl resonances seen at δ 3.91 (H-17) and 3.39, 3.43 (H-21), respectively. A methyl singlet observed at δ 3.37 was assigned to the methyl ester group. It was also found that addition of a few drops of C_6D_6 to the sample (dissolved in $CDCl_3$), resulted in a better resolved spectrum, especially for several important signals in the non-aromatic region which were poorly resolved in $CDCl_3$. (Figures 2.26 and 2.27).

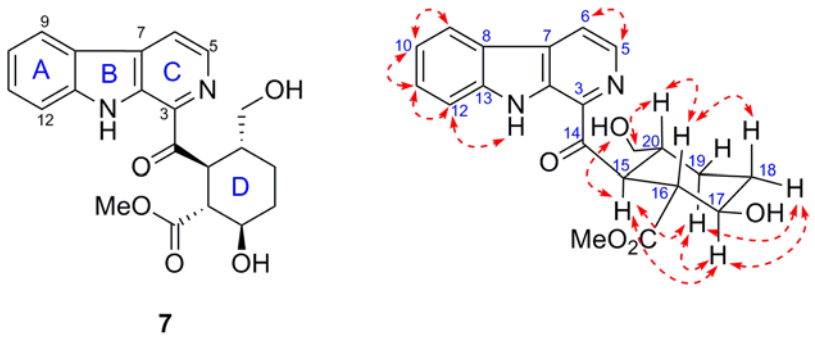
The COSY, H2BC and HSQC data (Figure 2.23) revealed the presence of a CHCHCHCH$_2$CH$_2$CH fragment in addition to NCH=CH corresponding to N–C-5–C-6 of the β-carboline unit. The CHCHCHCH$_2$CH$_2$CH fragment (constituting a substituted cyclohexane moiety) is linked to the β-carboline at the imine C-3 via a carbonyl bridge.



7

Figure 2.23: COSY and selected HMBCs of **7**

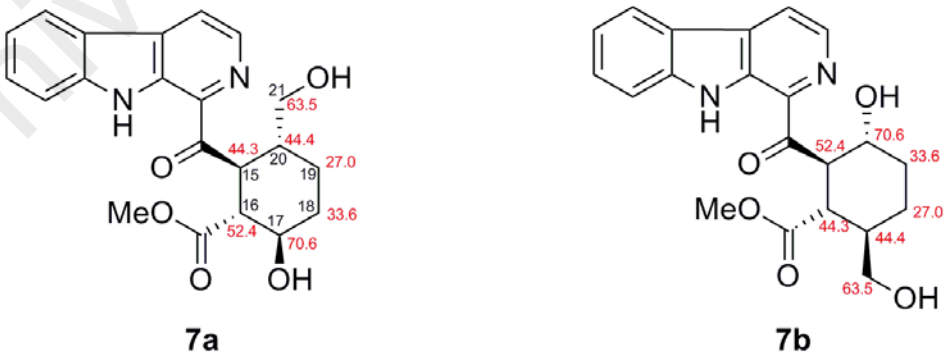
In addition to the carbonyl bridge, the cyclohexane unit is substituted by CO$_2$Me, OH, and CH$_2$OH groups. Consideration of the chemical shifts of the six-carbon fragment, and the HMBC data (Figure 2.23), facilitated complete assignment of the tetrasubstituted cyclohexane moiety and hence the overall structure of **7**. The ketone carbonyl and the carbomethoxy groups are linked at C-15 and C-16, respectively from the observed three-bond correlations from H-16 to the carbonyl resonance at δ 206.3 (C-14) and from H-15 to the ester carbonyl at δ 174.4. The observed three-bond correlation from H-15 to the oxymethine resonance at δ 70.6 indicated that the OH bearing secondary carbon corresponds to C-17. Attachment of the remaining hydroxymethyl side chain is at C-20 from the observed H-15 and H-19 to C-21 three-bond correlations in the HMBC spectrum (Figure 2.23).



7

Figure 2.24: Selected NOEs of **7**

Determination of the relative configuration at the various stereogenic centers is from analysis of the vicinal coupling and NOE data. H-15 and H-16 were observed as a triplet with J = 11.4 Hz (i.e., $J_{15\text{-}16} = J_{16\text{-}17} = J_{15\text{-}20}$ = 11.4 Hz). This observation requires a *trans*-diaxial relationship for H-15/H-16, H-16/H-17 and H-15/H-20. The observed NOEs (Figure 2.24) for H-15/H-17 and H-17/H-19α indicated that H-15, H-17, and H-19α are axially-oriented in the same direction, while H-16, H-18β and H-20 are axially-oriented in the opposite direction (NOEs observed for H-16/H-18β, H-20). This established a stable chair conformation for ring D with all the substituents oriented equatorially. The relative configuration of **7** is shown in Figure 2.24.

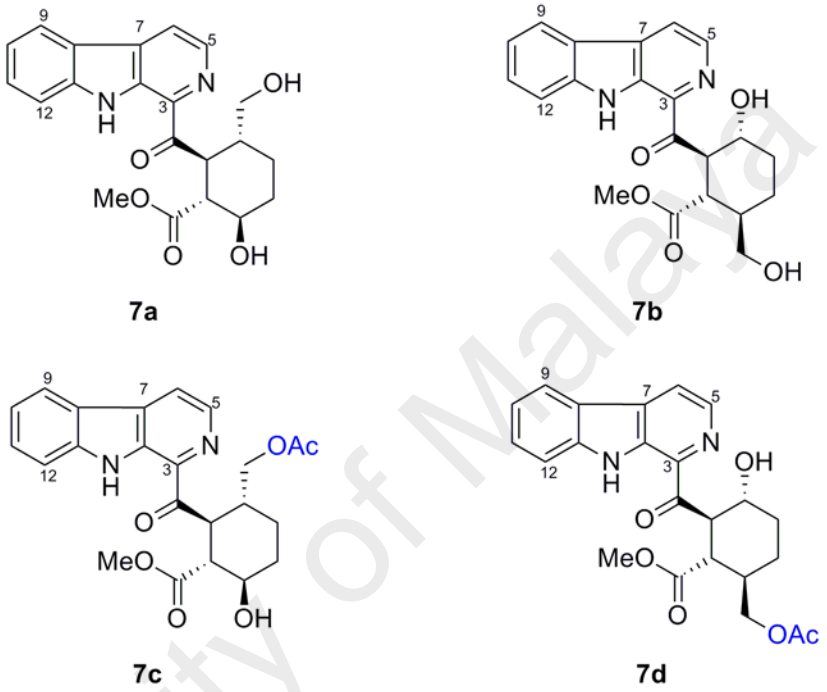


7a **7b**

Figure 2.25: Selected ^{13}C NMR data of **7a** and **7b**

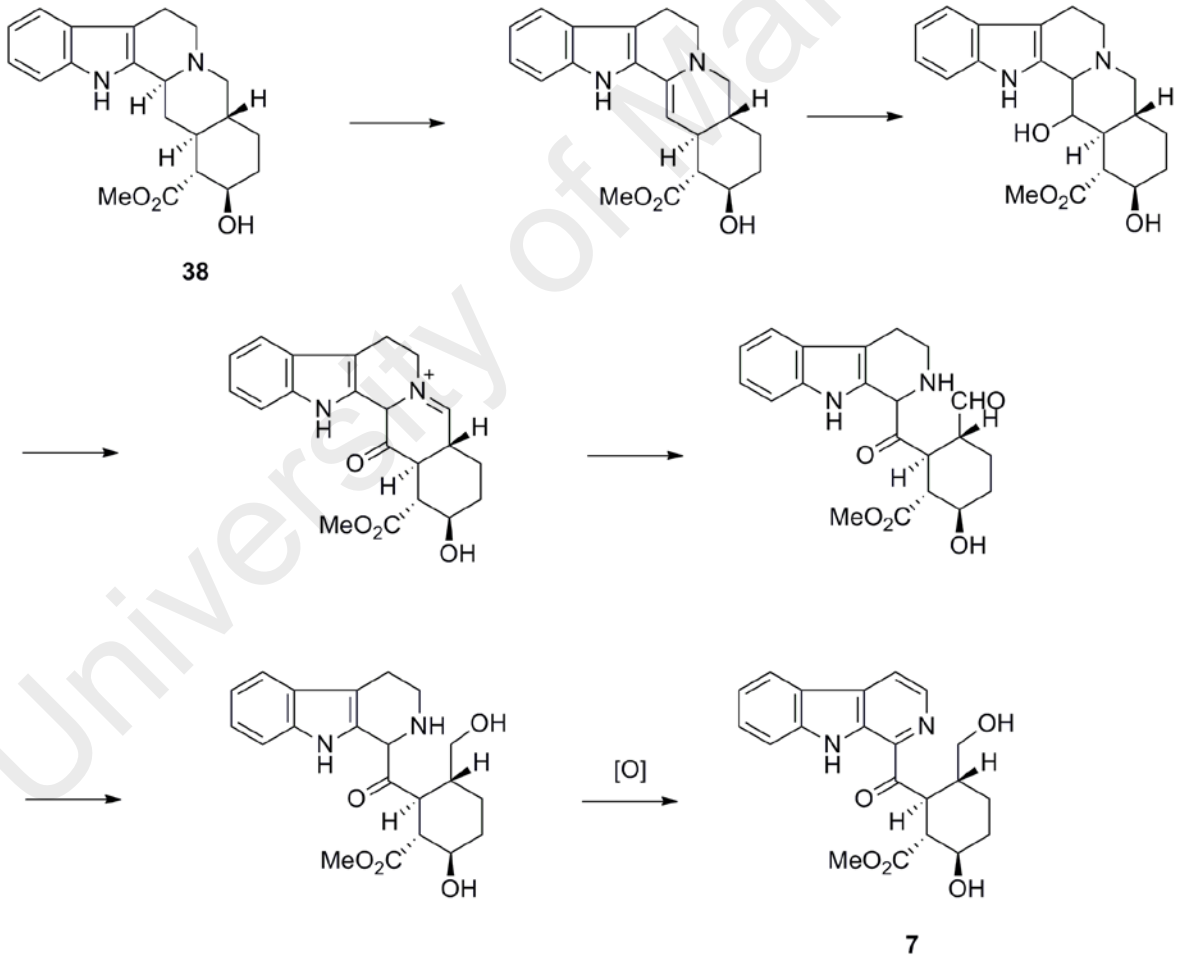
In principle, another possible structure, the regioisomeric **7b**, can be considered (Figure 2.25) if the assignments of the δ_C 52.4 and 44.3 resonances are interchanged to

C-15 and C-16, respectively, which lead in turn to corresponding changes in the assignments of the cyclohexane ring carbons in accordance with the COSY and HMBC data. Since HMBC and NOESY data (Figures 2.23 and 2.24) were unable to distinguish between the two regioisomers, an acetylation reaction was carried out.



Examination of the TLC, MS and NMR spectroscopic data of the acetylated product indicated that only the primary alcohol (hydroxymethyl group) undergo acetylation to give the *O*-acetyl derivative of **7** (i.e. **7c**). The ^{13}C NMR spectrum of **7c** showed a general similarity to **7** except for the presence of two additional carbon resonances at δ 170.3 and 20.1 due to the acetyl group. The same was observed in the ^{1}H NMR spectrum of **7c** versus **7**, with the major difference being the appearance of an additional methyl singlet at δ 1.44 due to the acetyl group. The observed shift of the acetyl methyl at δ 1.44 is significant as it is unusually upfield or shielded (c.f. δ ca. 2 in most *O*-acetyl derivatives).[399–401] This observation suggests that the shielding of these hydrogens is a result of anisotropy from the β-carboline ring system. Examination of models showed

that such a situation is possible in structure **7c** (Me of acetyl group located within shielding zone of β-carboline ring system) but not in structure **7d** (Me of acetyl group directed away from β-carboline moiety). Based on the above considerations as well as from a biogenetic viewpoint [**7a** can be considered as originating from β-yohimbine (**38**) by cleavage of the N-4–C-21 bond and adjustment of the oxidation states of the piperidine ring C, C-14, and C-21, Scheme 2.4], the structure and relative configuration of **7** is as shown in **7a**.



Scheme 2.4: A possible biogenetic pathway to **7**

Table 2.7: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Taberisidine (**7**) and *O*-Acetyltaberisidine (**7c**)

H/C	**7**[a]		**7**[b]		**7c**[c]	
	δ_C	**δ_H (*J*/Hz)**	**δ_C**	**δ_H (*J*/Hz)**	**δ_C**	**δ_H (*J*/Hz)**
2	135.1	-	135.0	-	135.3	-
3	136.0	-	136.3	-	136.1	-
5	138.1	8.52 d (5)	138.0	8.21 d (5)	138.3	8.53 d (5)
6	119.7	8.22 br d (5)	119.4	7.62 m	119.0	8.14 d (5)
7	132.5	-	132.2	-	131.5	-
8	120.6	-	120.6	-	120.6	-
9	122.1	8.18 dd (7.8, 1)	121.9	7.81 d (7.8)	121.9	8.16 d (8)
10	121.2	7.37 ddd (7.8, 7, 1)	120.9	7.11 td (7.8, 1)	120.9	7.35 td (8, 1.4)
11	129.8	7.64 ddd (8.2, 7, 1)	129.5	7.32 td (7.8, 1)	129.4	7.62 t (8)
12	112.2	7.59 d (8.2)	112.1	7.00 dd (7.8, 1)	112.0	7.59 d (8)
13	141.5	-	141.5	-	141.0	-
14	206.3	-	206.3	-	205.1	-
15	44.3	4.49 t (11.4)	44.7	4.57 td (11.5, 2)	45.3[d]	4.62 br t (11)
16	52.4	3.15 t (11.4)	52.9	3.23 ddd (11.5, 10.8, 2.7)	53.3	2.98 m
17	70.6	3.91 m	70.7	3.77 m	70.3	4.06 m
18β	33.6	1.59 m	33.8	1.44 qd (12.5, 3.5)	32.6	1.62 m
18α		2.24 dq (12.5, 3.3)		2.06 dq (12.5, 3.5)		2.20 dq (12.5, 3.5)
19β	27.0	1.80 m	27.1	1.55 dq (13.5, 3.5)	26.8	1.95 dq (13.5, 3.5)
19α		1.96 qd (13.5, 3.3)		1.90 dddd (13.5, 12.5, 12, 3.5)		1.45 m
20	44.4	1.78 m	44.7	1.65 ddd (12, 11.5, 3.5)	39.9	2.31 m
21	63.5	3.43 dd (12.5, 2)	63.6	3.30 m	67.0	3.94 dd (11.3, 5)
21		3.39 d (12.5)		3.39 m		3.85 dd (11.3, 7)
CO_2Me	174.4	-	174.2	-	173.6	-
CO_2*Me*	52.2	3.37 s	51.4	3.00 s	51.7	3.17 s
O*C*OMe	-	-	-	-	170.3	-
OCO*Me*	-	-	-	-	20.1	1.44 s
NH	-	10.31 br s	-	10.14 br s	-	10.38 br s
17-OH	-	3.21 br s	-	2.87 br s	-	2.98 br s
21-OH	-	4.99 br s	-	4.75 br s	-	-

[a]$CDCl_3$, 600 (^{1}H) and 100 MHz (^{13}C); [b]$CDCl_3/C_6D_6$, 600 (^{1}H) and 150 MHz (^{13}C); assignments based on COSY/H2BC, HSQC, HMBC, and NOESY/1D NOE; [c]$CDCl_3$, 400 (^{1}H) and 150 MHz (^{13}C); assignments based on HSQC and NOESY; [d]Not detected in ^{13}C NMR spectrum, assigned based on HSQC.

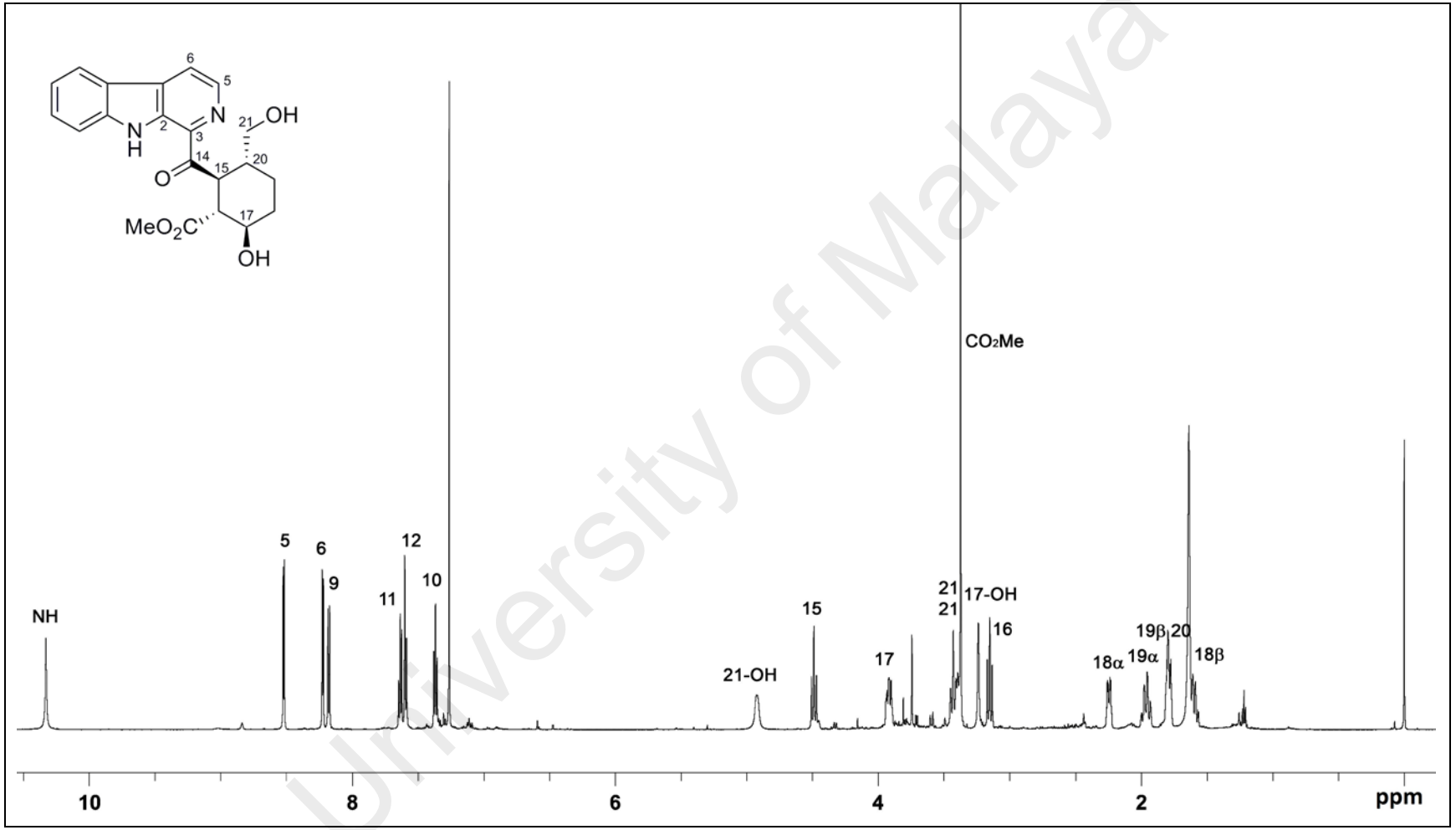


Figure 2.26: ^{1}H NMR spectrum ($CDCl_3$, 600 MHz) of Taberisidine (**7**)

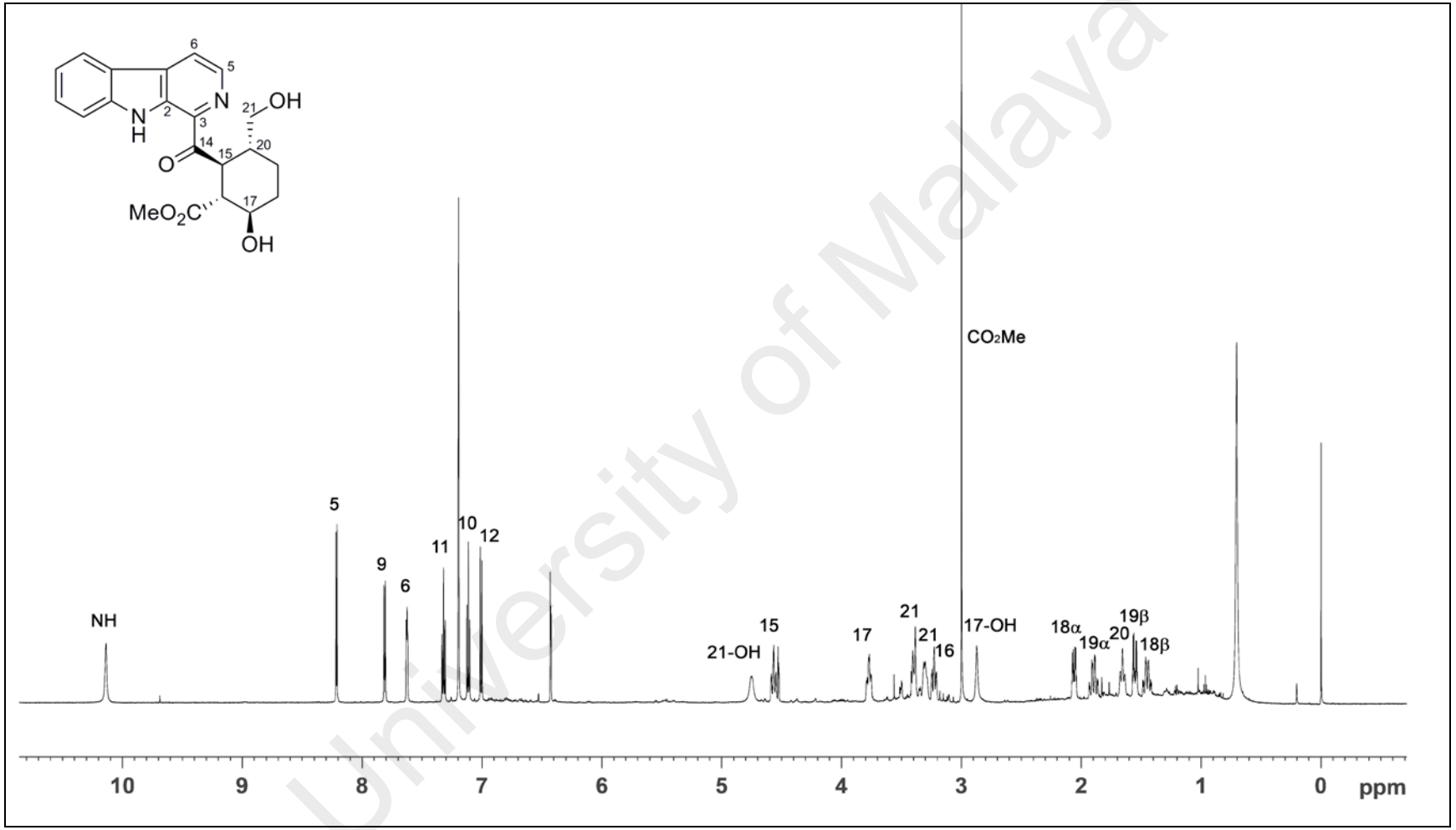


Figure 2.27: ^{1}H NMR spectrum ($CDCl_3/C_6D_6$, 600 MHz) of Taberisidine (**7**)

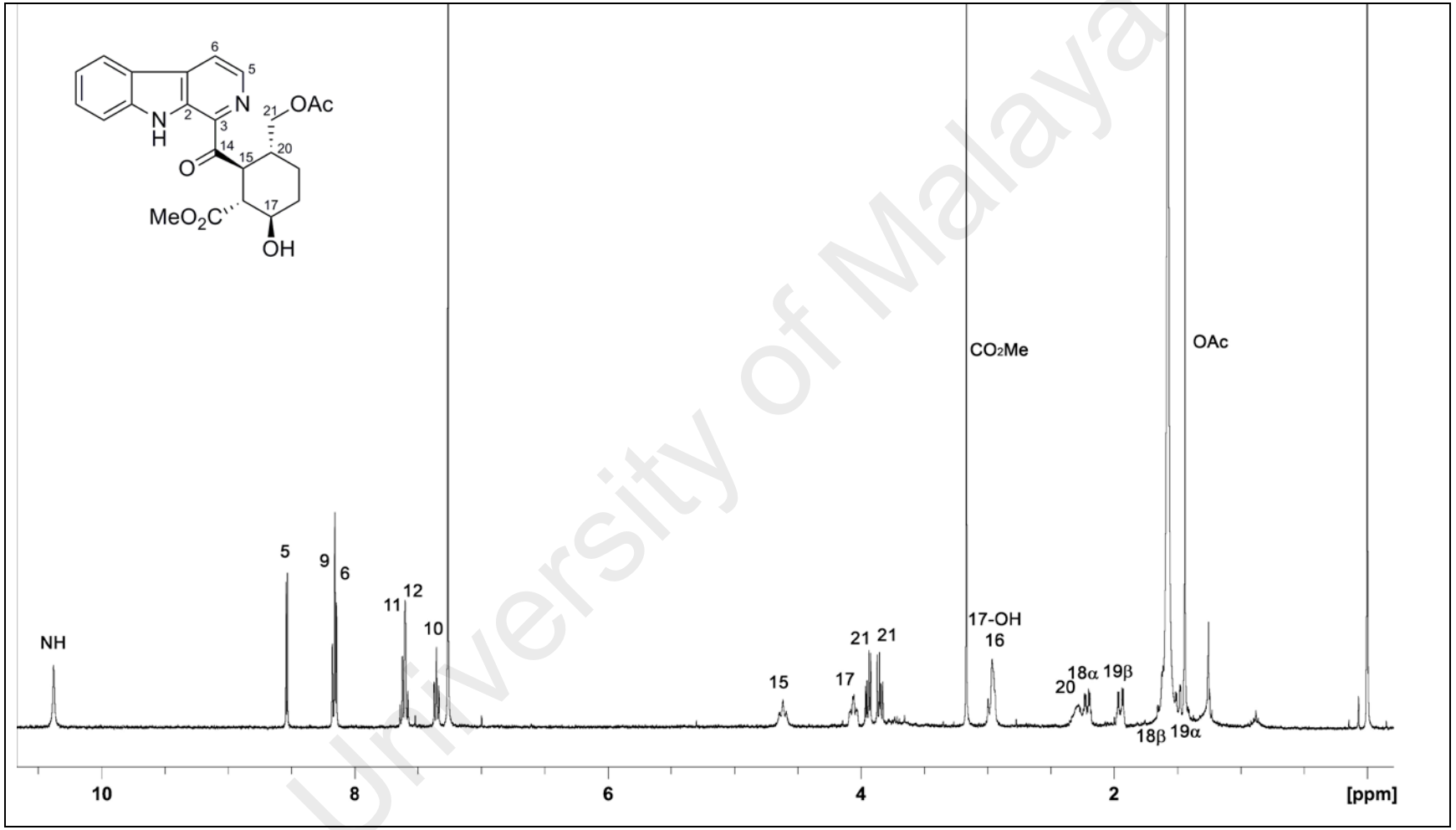


Figure 2.28: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of *O*-Acetyltaberisidine (**7c**)

2.1.5 Iboga alkaloids

2.1.5.1 Conodusine A (8)

Conodusine A (**8**)[402] was isolated by fractional crystallization from CH_2Cl_2–MeOH solutions containing mixtures of the two C-20 epimers **8** and **9** (with **8** as the major component) as colorless prisms with mp 196–199 ˚C and $[\alpha]^{25}_D$ +83 (*c* 1.00, $CHCl_3$). The UV spectrum showed absorption maxima at 227, 284, and 294 nm, characteristic of an indole chromophore, while IR spectrum showed bands due to NH (3396 cm^{-1}) and ketone carbonyl (1704 cm^{-1}) functions. The ESIMS showed an $[M + H]^+$ peak at *m/z* 295, and ^{13}C NMR and HRESIMS data established the molecular formula as $C_{19}H_{22}N_2O$.

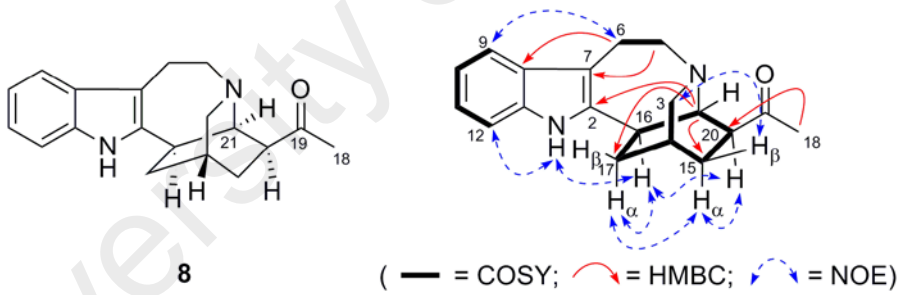


Figure 2.29: COSY, selected HMBCs and NOEs of **8**

The ^1H NMR spectrum of **8** (Figure 2.35, Table 2.8) showed the presence of an indolic NH (δ 7.78), four aromatic resonances of an unsubstituted indole moiety (δ 7.08–7.46), and a methyl singlet of an acetyl side chain (δ 2.20). The ^{13}C NMR spectrum (Table 2.9) showed a total of 19 carbon resonances comprising one methyl, five methylenes, eight methines, two tertiary carbons bonded to indolic nitrogen (corresponding to C-2 and C-13), one ketone carbonyl (δ 209.2), and two quaternary carbon atoms. The COSY spectrum showed the presence of NCH_2CH_2 and

$NCH_2CHCH_2CHCHCHCH_2$ partial structures, which are characteristic of iboga alkaloids. The ^{1}H and ^{13}C NMR data of **8** showed a general similarity to those of ibogamine (**13**), except for the absence of the H-19 resonances (δ 1.49, 1.55) and the appearance of a methyl singlet for H-18 (δ 2.20) instead of a triplet as in ibogamine. The presence of an acetyl side chain in place of an ethyl side chain was also supported by the carbon resonances at δ 209.2 and 27.9 in the ^{13}C NMR spectrum. The branching of the acetyl side chain from C-20 was indicated by the observed three-bond correlations from H-18 to C-20 in the HMBC spectrum, while the β-orientation of the acetyl substituent was indicated by the observed H-16/H-20 NOEs (Figure 2.29). In any case, the structure was also confirmed by an X-ray analysis (Figure 2.30) and the electronic circular dichroism (ECD) data (Figure 2.31) established the (14*S*, 16*R*, 20*S*, 21*R*) absolute configuration.

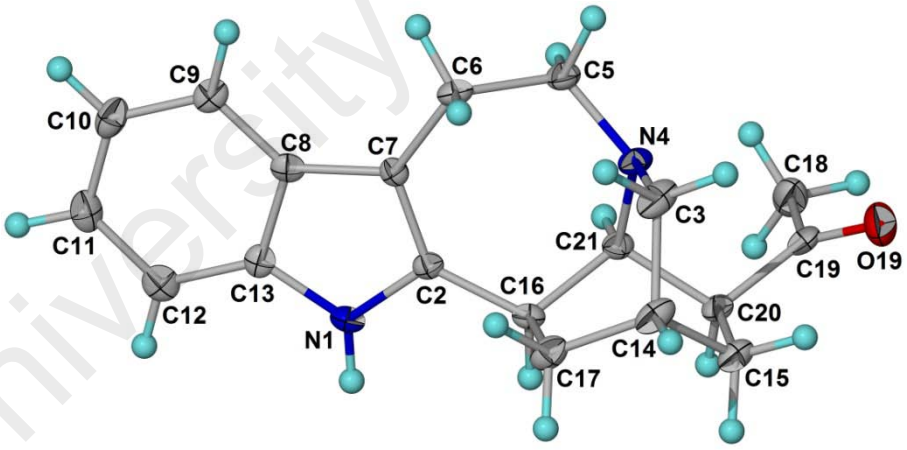


Figure 2.30: X-ray crystal structure of **8**

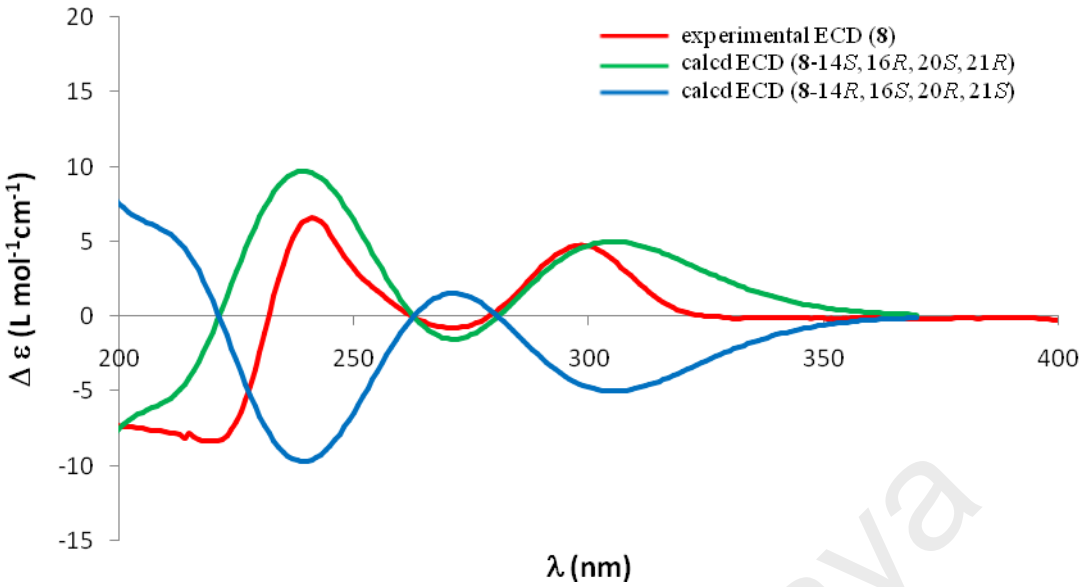
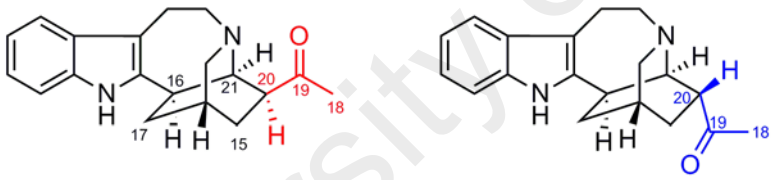


Figure 2.31: Experimental ECD spectrum of (+)-**8** and calculated ECD spectra of **8** (14*S*, 16*R*, 20*S*, 21*R*) and **8** (14*R*, 16*S*, 20*R*, 21*S*)

2.1.5.2 Conodusine B (9)



8 **9**

Compound **9** (conodusine B, the C-20 α-acetyl epimer of **8**)[402] co-eluted with **8** during column chromatography, but could be eventually purified by preparative radial chromatography after most of the epimer **8** has been removed by fractional crystallization, as a light yellowish oil, with $[\alpha]^{25}_{D}$ –101 (*c* 0.25, $CHCl_3$). The DART-TOF-MS showed an $[M + H]^+$ peak at *m/z* 295, which analyzed for $C_{19}H_{23}N_2O$ indicating that it is isomeric with **8**. The ^1H and ^{13}C NMR data (Tables 2.8 and 2.9, Figure 2.36) showed a close similarity to those of **8**, except for minor changes in the chemical shifts, with the more noticeable changes observed for H-15, H-16, H-20, and H-21, and C-16, C-18, and C-21, respectively. The observed H-15β/H-20 NOE (Figure

2.32) for compound **9**, instead of the H-16/H-20 NOE observed in the case of **8**, confirmed the assignment of **9** as the C-20 epimer of **8**.

The configurations at C-20 in compounds **8** and **9** as inferred above are also consistent with the observed coupling behavior of H-20 and H-15 in the ^{1}H NMR spectrum. In compound **8**, H-15β (δ 2.47) and H-15α (δ 1.52) can be distinguished by their respective NOEs with H-3 and H-17α (H-17α was in turned assigned by its NOE with H-16, Figure 2.29). The H-20 resonance in **8** was observed as a ddd, with J = 11, 4.3, and 2.6 Hz. The 11 Hz coupling must correspond to $J_{20\alpha\text{-}15\alpha}$ (H-20/H-15α dihedral angle ~ 0). In the case of **9**, H-20 was observed as a multiplet, but H-15β was observed as a ddt, with J = 13.8, 11, and 3 Hz, in which case the 11 Hz coupling must correspond to $J_{20\beta\text{-}15\beta}$. These observed coupling constants are only meaningful for an α-oriented H-20 in **8** and a β-oriented H-20 in **9**.

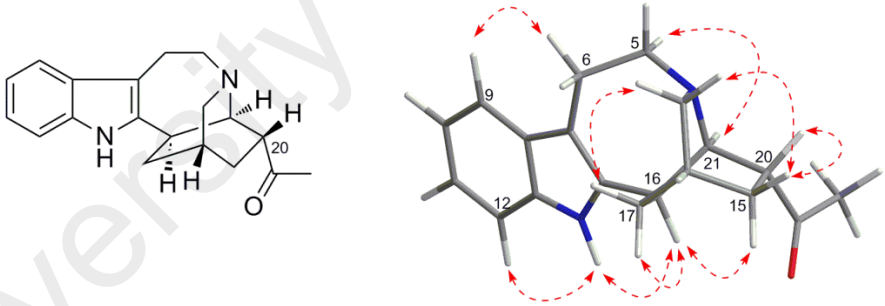
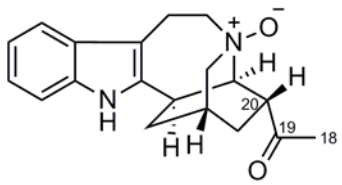
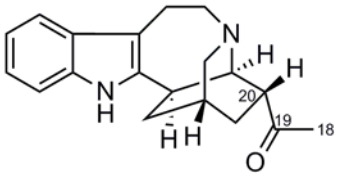


Figure 2.32: Selected NOEs of **9**

2.1.5.3 Conodusine C (10)

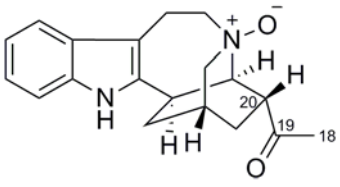


10



9

Conodusine C (**10**)[402] was obtained as colorless block crystals from MeOH, with mp > 188 °C (dec) and $[\alpha]^{25}_{D}$ −126 (*c* 0.13, MeOH). The UV and IR spectra were similar to those of **8** and **9**. The ESIMS showed an $[M+H]^+$ peak at *m/z* 311, consistent with the molecular formula $C_{19}H_{22}N_2O_2$, which was 16 mass units higher than those of **8** and **9**. The ^1H (Figure 2.37) and ^{13}C NMR spectra were generally similar to those of **8** and **9**, except for the resonances due to H-3, H-5, H-20, and H-21 in the ^1H NMR spectrum, and C-3, C-5 and C-21 in the ^{13}C NMR spectrum, which have been shifted downfield. These observations indicated that **10** is the N-4 oxide of **8** or **9**. The observed H-20/H-15β NOE (Figure 2.33) indicated that H-20 is β-oriented, which was also confirmed by X-ray analysis (Figure 2.34). Conodusine C (**10**) is therefore the N-4 oxide of **9**.



10

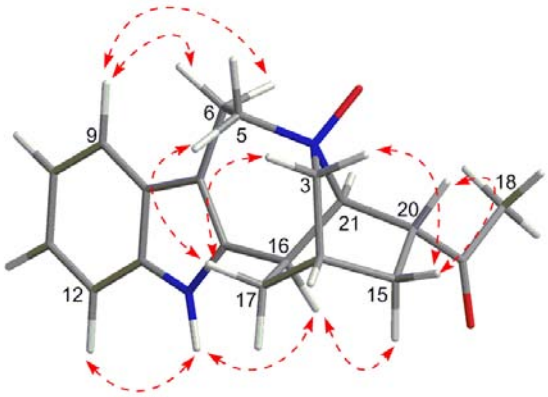


Figure 2.33: Selected NOEs of **10**

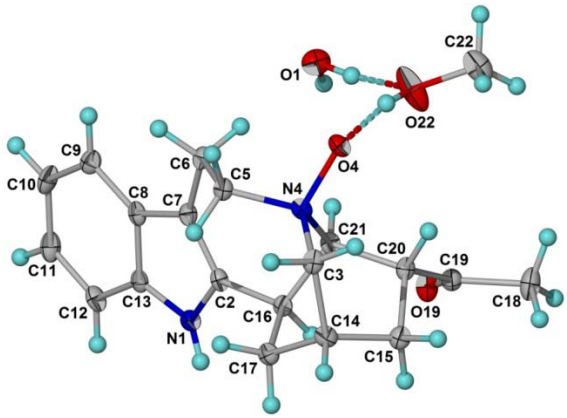


Figure 2.34: X-ray crystal structure of **10**

The possibility that **9** is an artifact formed from **8** under the conditions employed during isolation of the alkaloids cannot be completely discounted, since C-20 is α to a ketone carbonyl function, and epimerization via an enol or enolate intermediate is in principle possible. In addition, compound **8** although isolated as a natural product for the first time, has been previously encountered as an intermediate during the total synthesis of ibogamine, where it was observed that attempts to enrich the more polar C-20 epimer by treatment with NaOMe/MeOH resulted in a mixture comprising equal amounts of the epimers.[392] In the present instance, it was found that **8** could be readily separated since it crystallizes with great ease from solution, leaving eventually an approximately 1:1 mixture of the epimers, from which **9** can then be separated by preparative radial chromatography over SiO_2.

It is entirely possible that **9** was obtained as a true minor alkaloid from the plant, since the N-oxide of **9**, i.e., **10** was also isolated, although it is very likely that its further enrichment via epimerization from **8** during the isolation process also occurred as well. Conodusines B **9** and C **10** (and **56**, *vide infra*) represent rare instances of naturally-occurring iboga alkaloids with C-20 α-substitution, since naturally-occurring iboga alkaloids with ethyl, hydroxyethyl, or acetyl C-20 substituents, are to date always β.[115,403]

Table 2.8: ^{1}H NMR Spectroscopic Data (δ) of Conodusines A–C (**8**–**10**)[a]

H	**8**[a] **(*J*/Hz)**	**9**[a] **(*J*/Hz)**	**10**[b] **(*J*/Hz)**
3	2.98 dt (9.7, 2.6)	3.15 m	3.54 d (13)
3	3.00 dt (9.7, 2.4)	3.15 m	3.82 br d (13)
5	3.12 ddd (14.4, 13, 3)	3.33 m	3.93 dd (13, 8)
5	3.24 ddd (14.4, 4, 3)	3.38 m	4.00 dd (13, 8)
6	2.63 dt (16, 3)	2.70 m	3.05 dd (18, 8)
6	3.32 ddd (16, 13, 4)	3.35 m	3.36 dd (18, 8)
9	7.46 d (7.5)	7.46 d (7.4)	7.45 d (7.8)
10	7.08 td (7.5, 1.2)	7.07 t (7.4)	7.10 t (7.8)
11	7.12 td (7.5, 1.2)	7.11 t (7.4)	7.15 t (7.8)
12	7.26 d (7.5)	7.23 d (7.4)	7.29 d (7.8)
14	1.98 m	2.01 m	2.24 m
15α	1.52 ddt (13,11, 2.4)	2.12 m	1.95 d (13)
15β	2.47 ddt (13, 4.3, 3)	1.77 ddt (13.8, 11, 3)	2.08 d (13)
16	3.05 ddd (11.6, 5, 1.4)	2.87 dd (11.6, 5)	3.27 dd (11.3, 8)
17β	1.72 ddt (13, 5, 3)	1.63 ddt (13, 5, 3)	1.58 dd (11.6, 8)
17α	2.11 ddt (13, 11.6, 2.6)	2.08 m	2.21 m
18	2.20 s	2.20 s	2.28 s
20	2.68 ddd (11, 4.3, 2.6)	3.25 m	4.34 br t (9)
21	3.60 br s	3.40 br s	3.89 m
NH	7.78br s	7.76 br s	9.31 br s

[a]$CDCl_3$, 600 MHz; [b]$CDCl_3/CD_3OD$, 600 MHz; assignments based on COSY, HMQC/HSQC, and NOESY.

Table 2.9: ^{13}C NMR Spectroscopic Data (δ) of Conodusines A–C (**8**–**10**)

C	**8**[a]	**9**[b]	**10**[c]
2	141.3	140.9	138.0
3	49.3	49.5	72.9
5	54.4	54.6	76.9
6	20.3	20.1	19.8
7	109.9	109.8	110.2
8	129.7	129.4	127.2
9	118.0	117.8	117.6
10	119.4	119.3	119.6
11	121.2	121.2	121.7
12	110.3	110.4	110.9
13	134.5	134.3	134.8
14	26.2	25.9	28.6
15	24.0	24.7	24.8
16	39.9	35.3	29.6
17	34.7	34.3	31.4
18	27.9	29.0	26.5
19	209.2	209.3	208.9
20	53.9	54.4	44.6
21	56.8	55.4	69.7

[a]$CDCl_3$, 100 MHz; [b]$CDCl_3$, 150 MHz; [c]$CDCl_3/CD_3OD$, 150 MHz; assignments based on HMQC/HSQC, and HMBC.

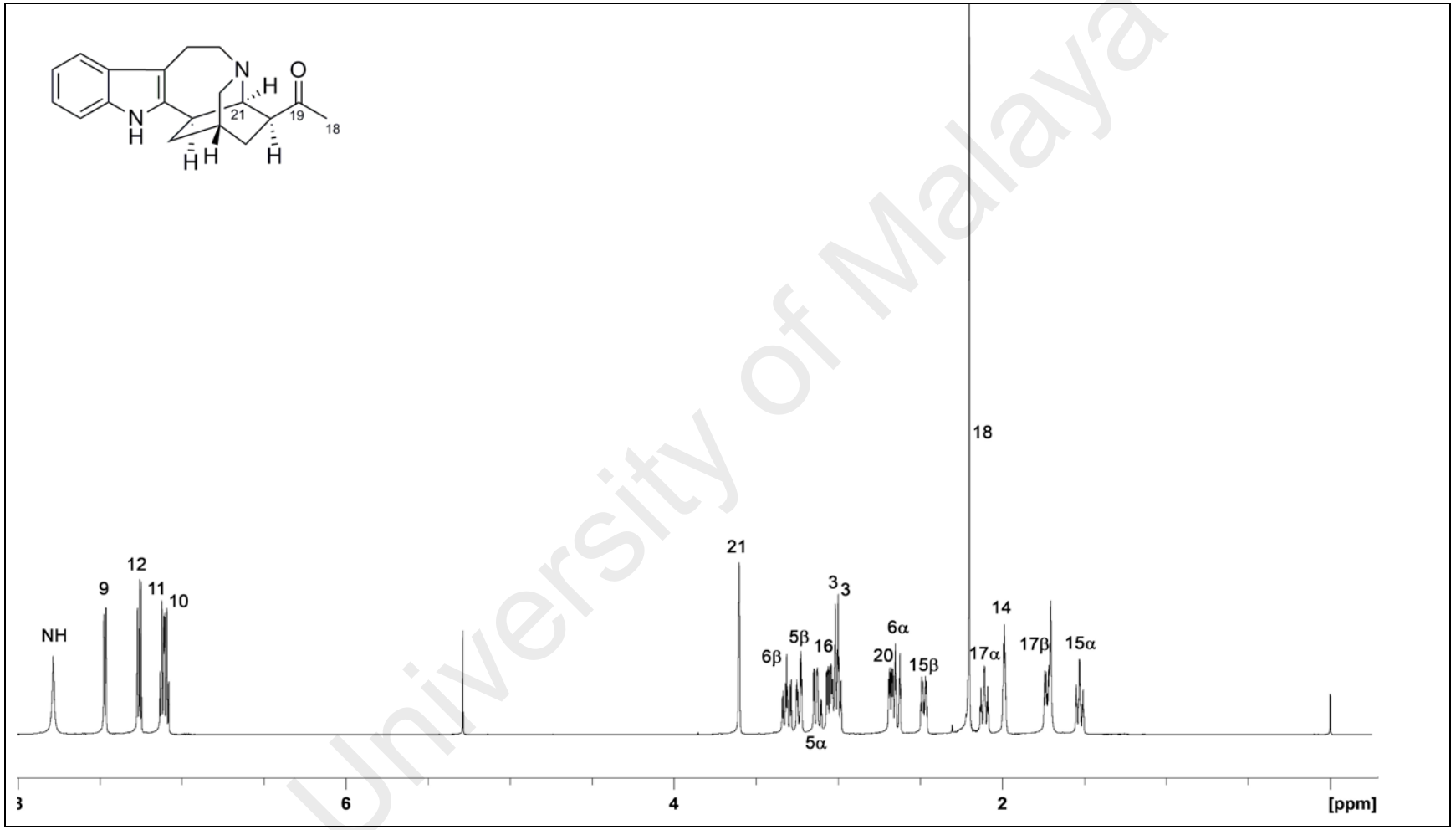


Figure 2.35: ^{1}H NMR spectrum ($CDCl_3$, 600 MHz) of Conodusine A (**8**)

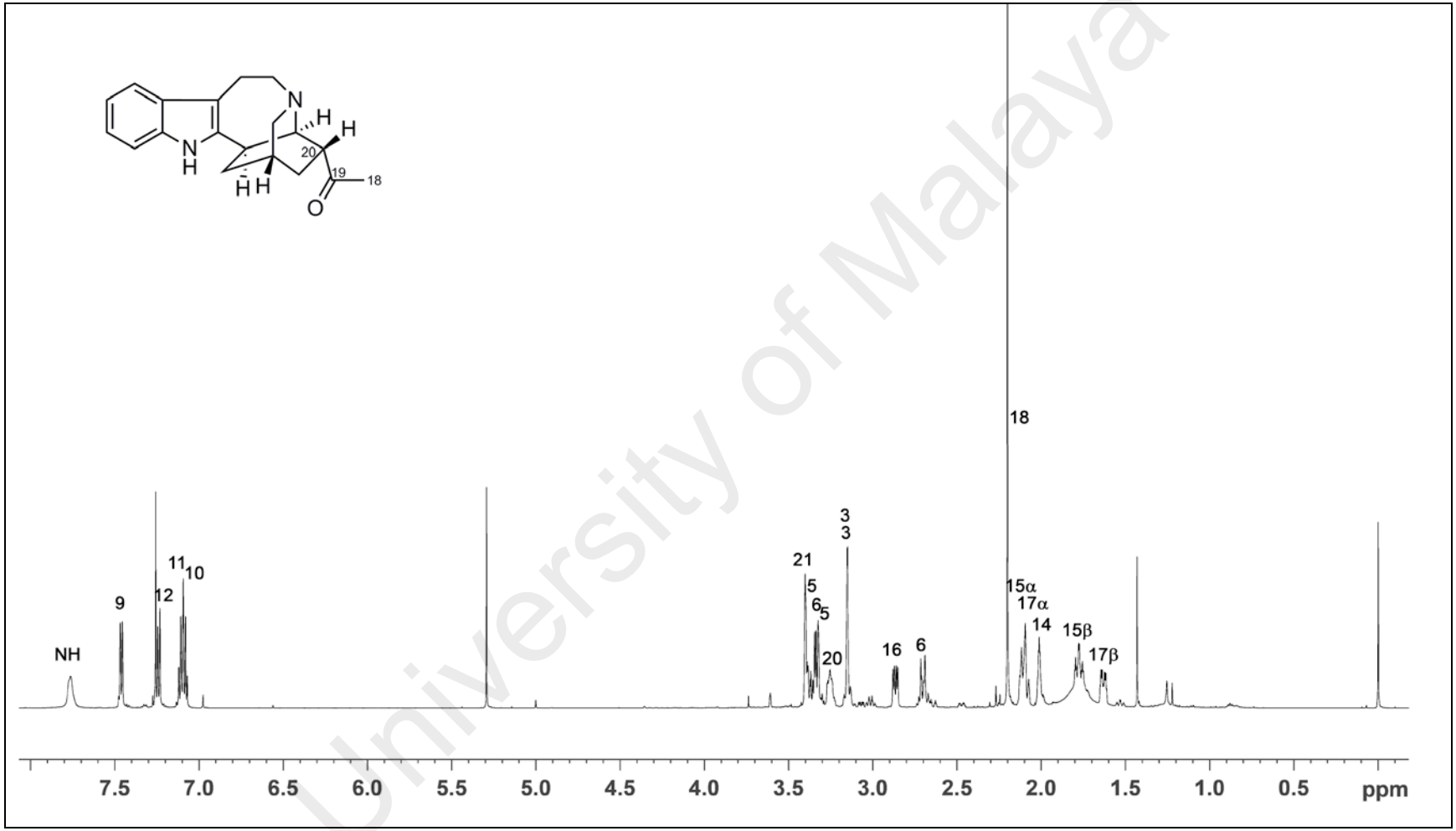


Figure 2.36: ^{1}H NMR spectrum ($CDCl_3$, 600 MHz) of Conodusine B (**9**)

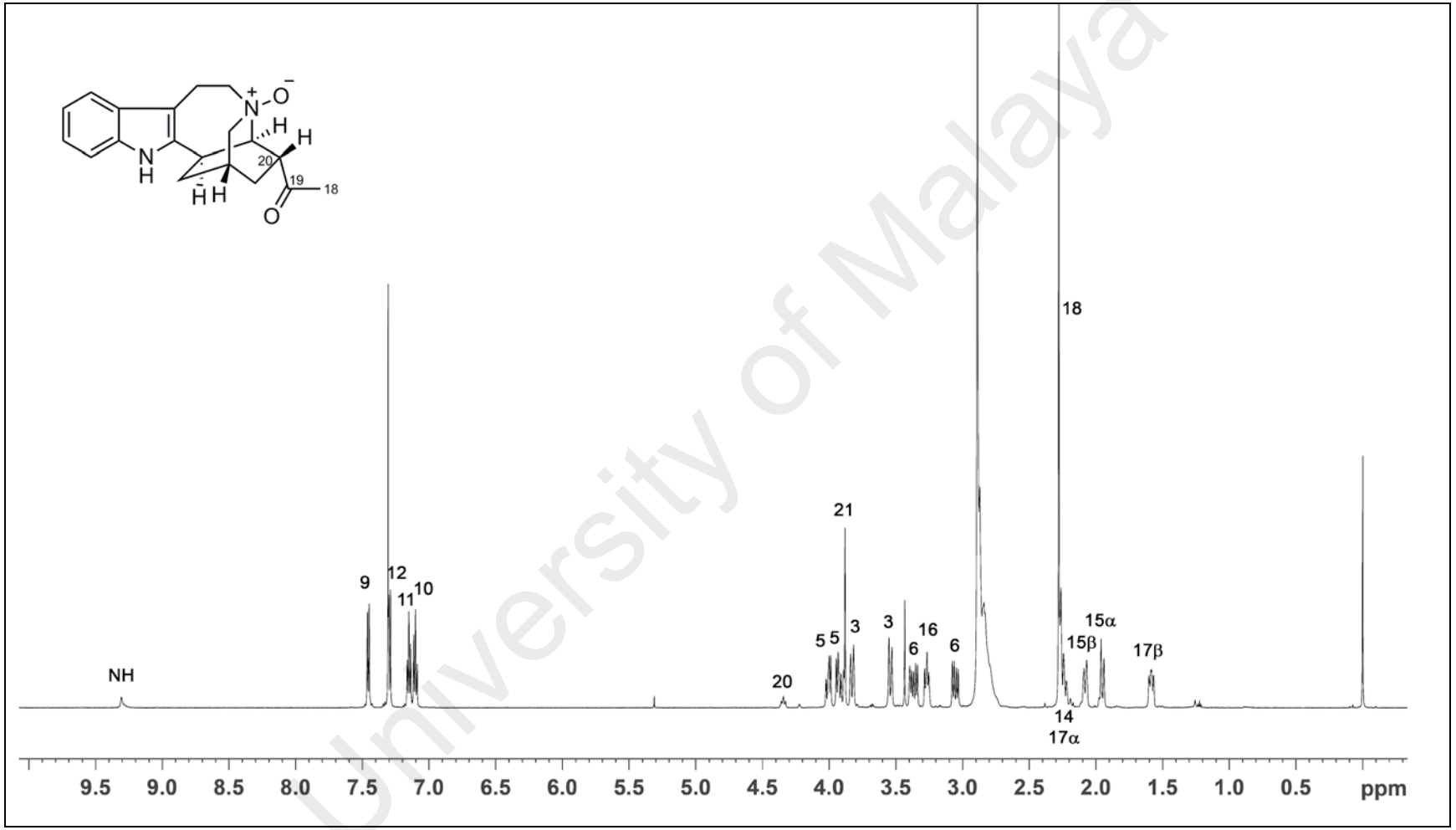


Figure 2.37: ^{1}H NMR spectrum ($CDCl_3/CD_3OD$, 600 MHz) of Conodusine C (**10**)

2.1.5.4 Conodusine D (11)

Conodusine D (**11**)[402] was obtained as a light yellowish oil, with $[\alpha]^{25}_{D}$ –26 (*c* 0.05, $CHCl_3$). The UV spectrum showed characteristic hydroxyindolenine absorption maxima at 221, 227 (sh), and 280 nm.[404] The ESIMS showed an $[M + H]^+$ peak at *m/z* 325, and HRESIMS measurements established the molecular formula as $C_{19}H_{20}N_2O_3$.

The ^{13}C NMR spectrum (Table 2.10) showed a total of 19 carbon resonances, comprising one methyl, four methylenes, eight methines, two carbonyl carbons, two tertiary carbons linked to the indolic nitrogen (corresponding to C-2 and C-13), one tertiary carbon linked to oxygen, and one quaternary carbon atom. Of the two carbonyls, one is a ketocarbonyl (δ 205.9, C-19) associated with the acetyl side chain (δ_H 2.19, H-18), while the other (δ 176.1) corresponds to an amide carbonyl. Since the NCH_2CH_2 partial structure, which corresponds to the N–C-5–C-6 unit, was present as shown by the COSY spectrum, the amide carbonyl must be at C-3, which was also confirmed by the H-5, H-15, and H-17 three-bond correlations to this amide resonance (δ 176.1) in the HMBC spectrum (Figure 2.38). Another deshielded resonance was observed at δ 184.8 (C-2), which together with the absence of an indolic NH in the ^1H NMR spectrum indicated the presence of an imine function.

The ^1H NMR spectrum (Figure 2.40, Table 2.10) showed the presence of four aromatic resonances of an unsubstituted indole moiety (δ 7.24–7.40), a methyl singlet of an acetyl side chain (δ 2.19), and a broad singlet at δ 3.10 due to OH, which was confirmed by a D_2O exchange experiment. The presence of an imine function and a hydroxy group linked to a tertiary carbon (δ_C 86.2) suggested that **11** is a hydroxyindolenine, with an amide carbonyl function at C-3. Analysis of the 2D NMR data led to the iboga alkaloid as shown in structure **11**, incorporating amide and hydroxyindolenine moieties. The attachment of the acetyl side chain is at C-20 from the

observed three-bond correlations from H-18 to C-20, and from H-21 to C-19 in the HMBC spectrum, while its orientation is β, from the observed H-20/H-16 NOE (Figure 2.38).

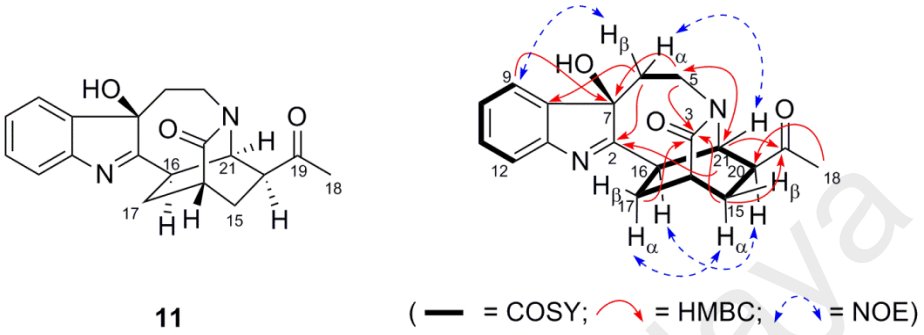
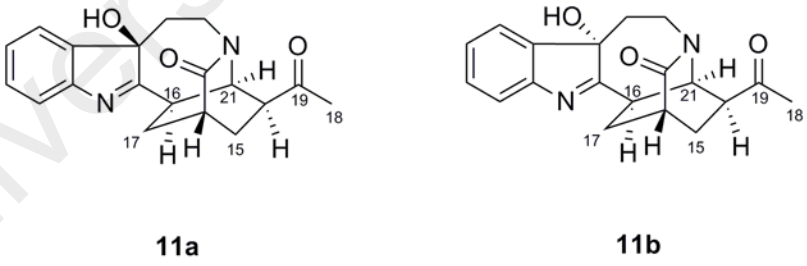


Figure 2.38: COSY, selected HMBCs and NOEs of **11**

It remains to establish the configuration at C-7, not a straightforward task, since C-7 is an oxygenated tertiary center. The preferred conformation adopted by the seven-membered tetrahydroazepine ring was indicated by the observed NOEs and coupling behavior of H-5 and H-6.



Assuming a β-oriented C-7–OH (**11a**), the observed NOE between H-6 (δ 1.89, *J* = 15.4, 11.7, 7.8 Hz) and H-21 (δ 4.20) allowed the assignment of H-6α. This hydrogen is *trans*-diaxial to H-5β (δ 4.79, *J* = 13.7, 11.7, 6.8 Hz). The notable deshielding of H-5β is a consequence of anisotropy from the proximate amide carbonyl; a similar effect was seen in 3-oxocoronaridine.[264] NOE was observed for H-9 and H-6β (δ 2.46, *J* = 15.4,

6.8 Hz). The same observations apply in the case of an α-oriented C-7–OH (**11b**). Since NMR in this case could not distinguish between the epimers, the ECD of compound **11** was recorded and compared with the DFT-calculated spectrum. The results are shown in Figure 2.39 where it can be seen that the experimental ECD is in agreement with structure **11a** (i.e., a β-oriented C-7–OH). Based on the above considerations, the structure of conodusine D is **11a**.

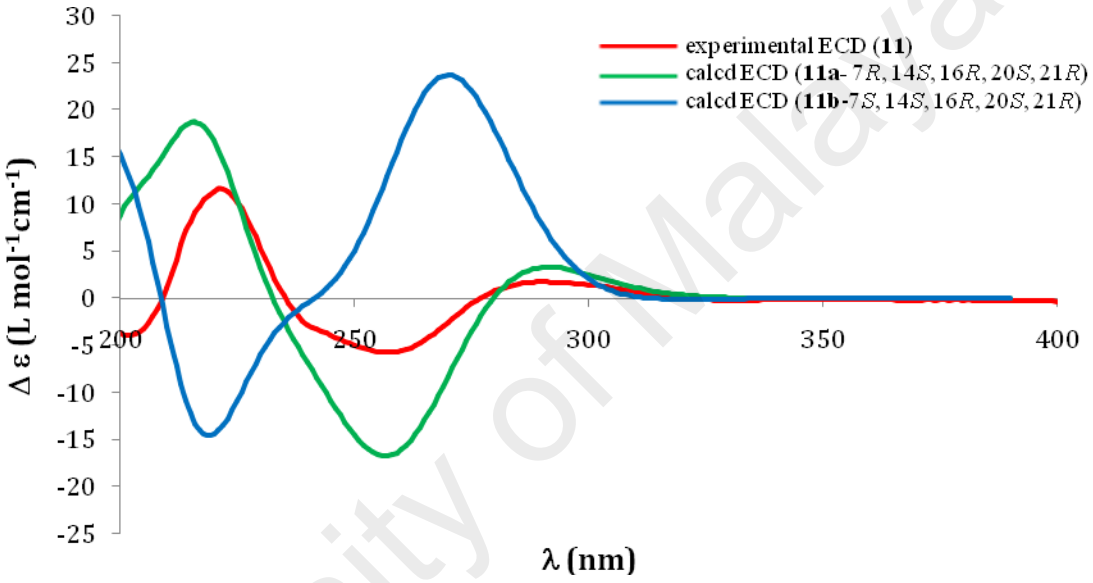


Figure 2.39: Experimental ECD spectrum of **11** and calculated ECD spectra of **11a** (7*R*, 14*S*, 16*R*, 20*S*, 21*R*) and **11b** (7*S*, 14*S*, 16*R*, 20*S*, 21*R*)

Table 2.10: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) for Conodusine D (**11**)[a]

H/C	**δ_C**	**δ_H (*J*/Hz)**
2	184.8	-
3	176.1	-
5α	39.1	3.21 dd (13.7, 7.8)
5β		4.79 ddd (13.7, 11.7, 6.8)
6α	33.3	1.89 ddd (15.4, 11.7, 7.8)
6β		2.46 dd (15.4, 6.8)
7	86.2	-
8	141.1	-
9	122.0	7.40 d (7.5)
10	127.1	7.24 m
11	130.0	7.33 m
12	120.7	7.35 m
13	151.3	-
14	38.2	2.84 m
15	26.1	2.16 m
15		2.23 m
16	44.2	3.40 ddd (10.7, 3.8, 1.6)
17	28.5	2.14 m
17		2.26 m
18	27.6	2.19 s
19	205.9	-
20	49.3	2.86 m
21	52.2	4.20 br t (1.6)
OH	-	3.10 br s

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

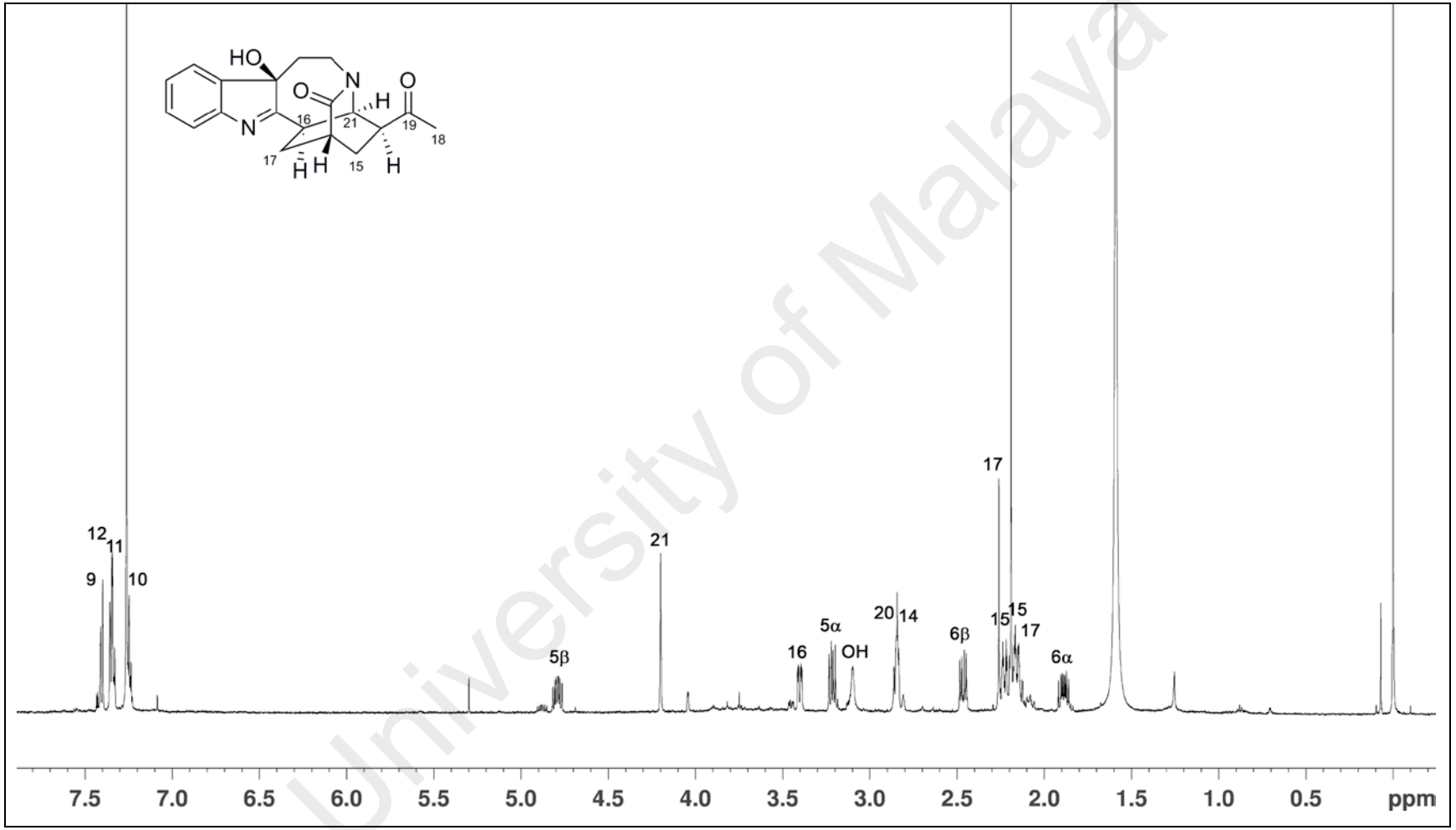
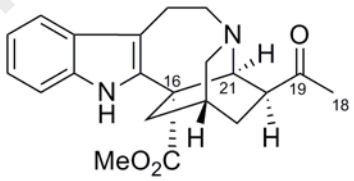


Figure 2.40: ^{1}H NMR spectrum ($CDCl_3$, 600 MHz) of Conodusine D (**11**)

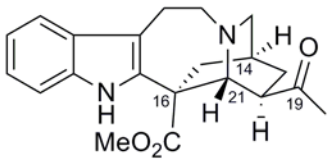
2.1.5.5 Conodusine E (12)

Conodusine E (**12**)[402] was obtained as colorless prisms from CH_2Cl_2–hexanes, with mp 192–195 ^oC and $[\alpha]^{25}_D$ +21 (*c* 0.53, $CHCl_3$). The UV spectrum showed indole chromophore absorption maxima at 227, 286, and 292 nm, while the IR spectrum showed absorption bands at 3350, 1724 and 1716 cm^{-1}, due to NH and various carbonyl functions. HRESIMS measurements established the molecular formula as $C_{21}H_{24}N_2O_3$.

The ^1H and ^{13}C NMR data (Table 2.11, Figure 2.44) indicated an iboga alkaloid with an unsubstituted indole moiety (δ 7.10–7.48), an indolic NH (δ 7.81), a methoxycarbonyl group at C-16 (δ_H 3.80, δ_C 53.1, 175.0), and a β-oriented acetyl side chain at C-20 [δ_H 2.25, δ_C 27.8, 208.3; NOE: H-15α/H-20 (Figure 2.41)], which leads to the structure shown in **12** (19-oxocoronaridine). However, an alkaloid with virtually identical MS and NMR data was very recently reported from *Ervatamia hainanensis*, and named ervatamine I. This alkaloid however had specific rotation ($[\alpha]^{20}_D$ –32 (*c* 0.6, $CHCl_3$)) opposite in sign to that of compound **12** {$[\alpha]^{25}_D$ +21 (*c* 0.53, $CHCl_3$)}.[174] These two compounds, (+)-conodusine E and (–)-ervatamine I, are therefore enantiomers. (Unfortunately, the ECD spectrum of ervatamine I was not reported in reference 175)



12a



12b

In order to establish the absolute configuration for **12** (**12a** or **12b**), two further experiments were carried out. First, **12** could be correlated with (–)-heyneanine (**17**) whose absolute configuration is known,[405] via oxidation of **17** with Dess-Martin

periodinane. Conodusine E (**12**) thus obtained had $[\alpha]^{25}_{D}$ +23 (*c* 0.18, $CHCl_3$){versus $[\alpha]^{25}_{D}$ +21 (*c* 0.53, $CHCl_3$) for natural **12**} and NMR data virtually identical to those of the natural product. Second, the ECD spectrum of **12** was recorded, and the results were compared with the calculated spectrum (Figure 2.42), which indicated that compound **12** belongs to the same enantiomeric series as exemplified by (–)-coronaridine (**16**), as opposed to (+)-catharanthine (**420**). In addition, the DFT-calculated specific rotation for structure **12a** was also in excellent agreement with that of the natural compound {$[\alpha]^{25}_{D\ (calcd)}$ +24; $[\alpha]^{25}_{D\ (obs)}$ +21 (*c* 0.53, $CHCl_3$)}. The absolute configuration of conodusine E is therefore represented by structure **12a**, which was subsequently confirmed by an X-ray (Cu Kα) analysis (Figure 2.43).

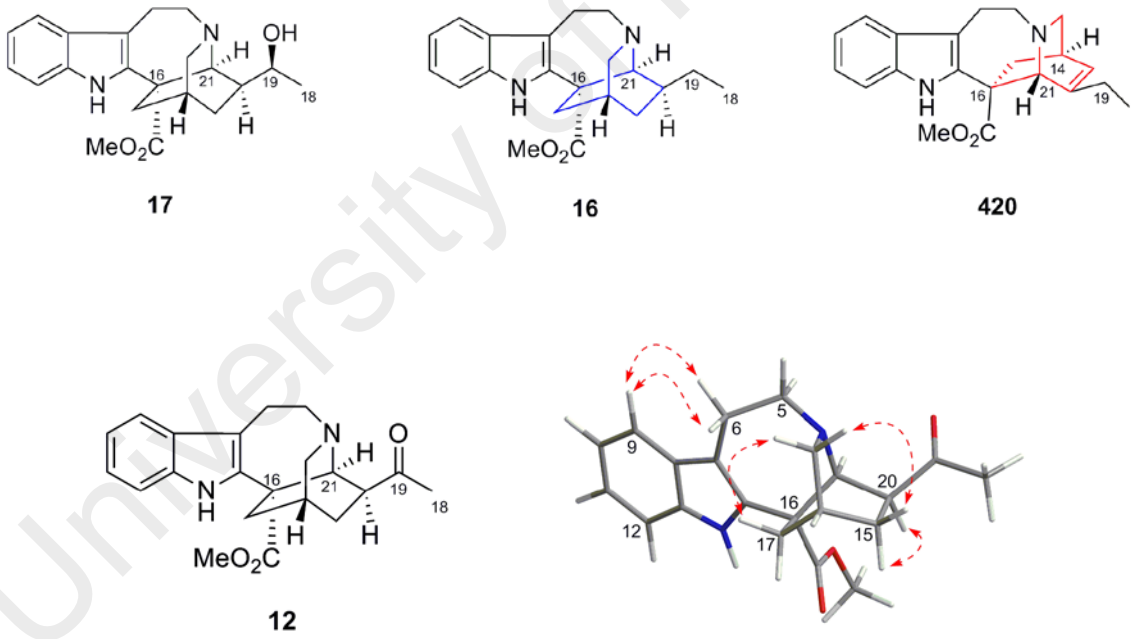


Figure 2.41: Selected NOEs of **12**

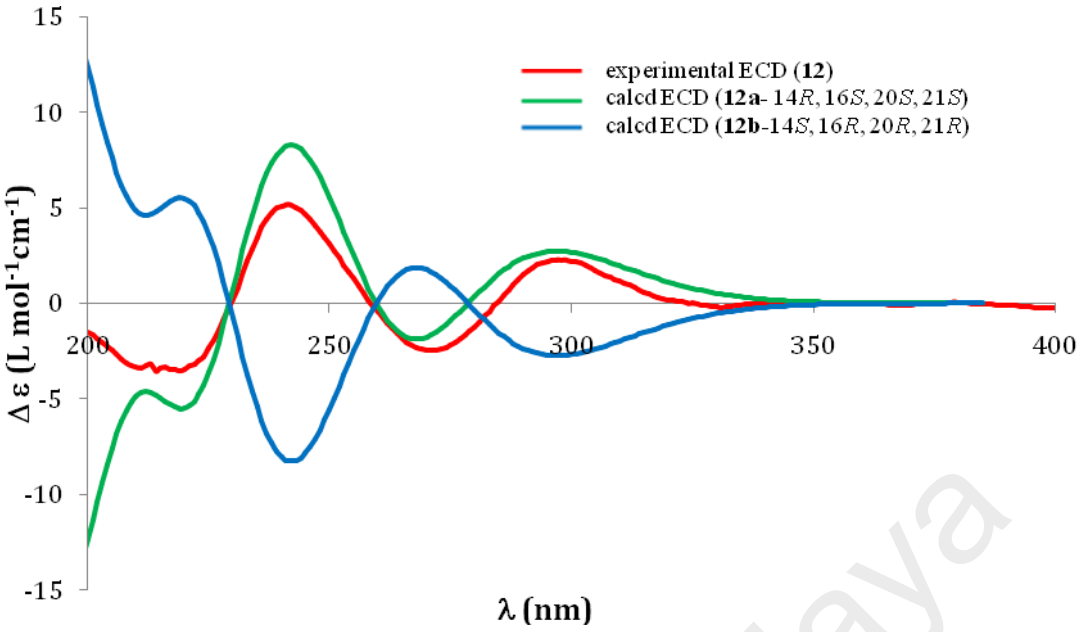


Figure 2.42: Experimental ECD spectrum of **12** and calculated ECD spectra of **12a** (14*R*, 16*S*, 20*S*, 21*S*) and **12b** (14*S*, 16*R*, 20*R*, 21*R*)

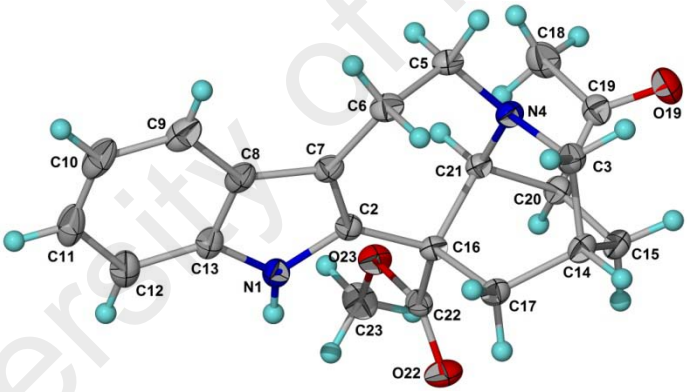


Figure 2.43: X-ray crystal structure of **12**

Table 2.11: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) for Conodusine E (**12**)[a]

H/C	**δ_C**	**δ_H (*J*/Hz)**
2	136.2	-
3b	51.0	2.78 dt (9, 2)
3a		2.96 m
5	53.4	3.10 dt (13.5, 5.4)
5		3.38 ddd (13.5, 8, 5.4)
6	21.8	3.00 m
6		3.18 m
7	110.7	-
8	128.8	-
9	118.5	7.48 d (7.8)
10	119.5	7.10 td (7.8, 1.2)
11	122.2	7.17 td (7.8, 1.2)
12	110.6	7.27 d (7.8)
13	135.4	-
14	26.9	2.02 m
15α	24.7	1.59 br t (11)
15β		2.25 m
16	54.2	-
17β	37.2	1.96 dt (13.5, 3)
17α		2.64 dt (13.5, 2)
18	27.8	2.25 s
19	208.3	-
20	51.0	2.45 ddd (10, 6, 1.5)
21	56.3	4.27 d (1.5)
CO_2Me	175.0	-
CO_2*Me*	53.1	3.80 s
NH	-	7.81 br s

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

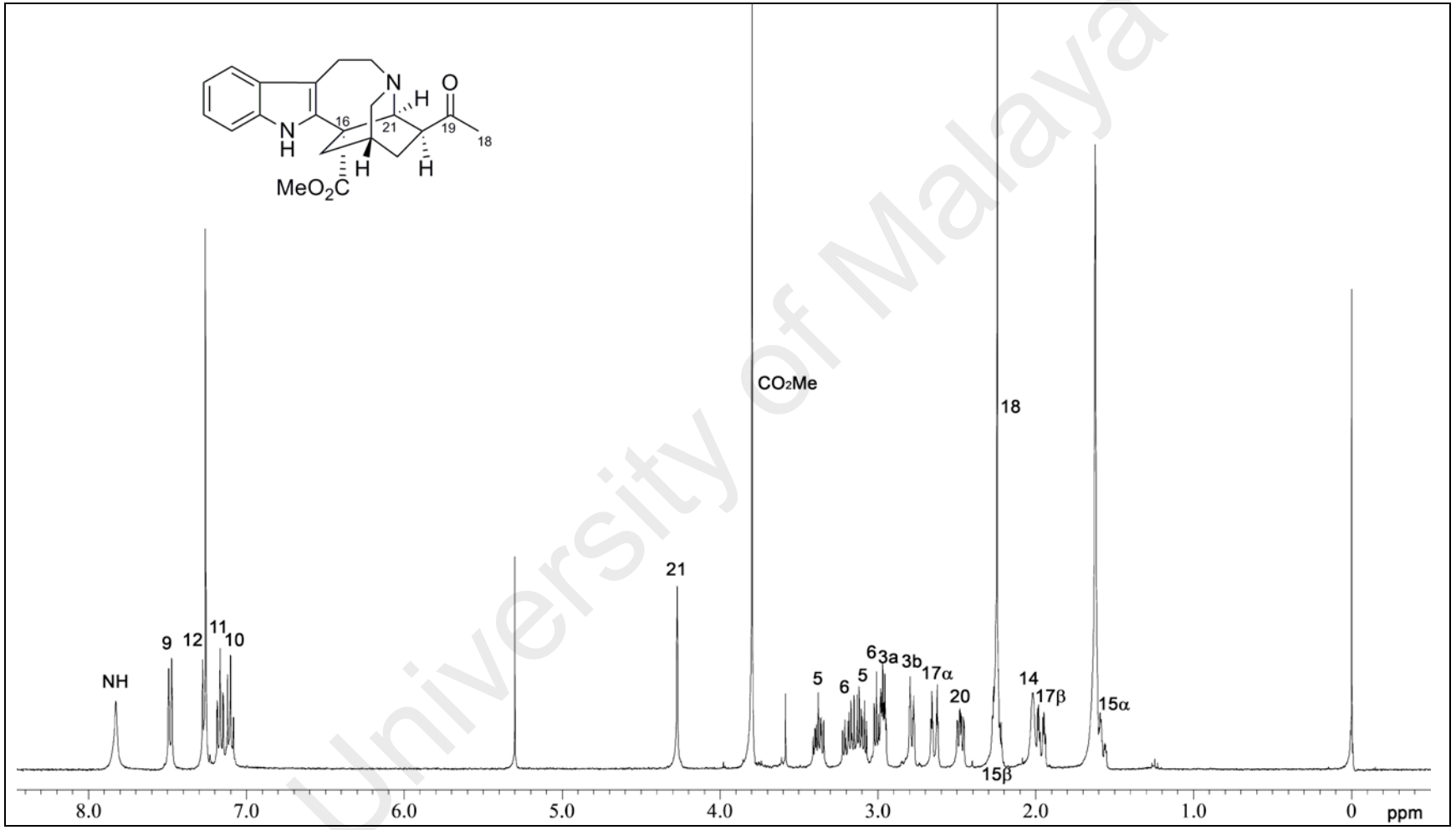
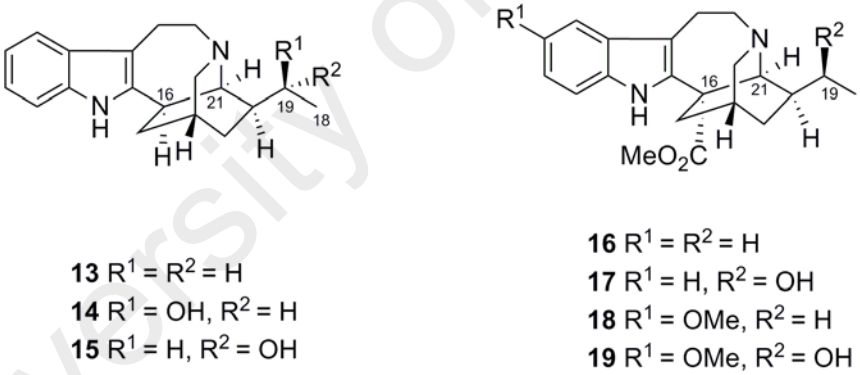


Figure 2.44: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of Conodusine E (**12**)

2.1.5.6 Ibogamine (13), 19(*S*)-Hydroxyibogamine (14), 19(*R*)-Hydroxyibogamine (15), Coronaridine (16), (–)-Heyneanine (17), Voacangine (18), and Voacristine (19)

Seven known iboga alkaloids including ibogamine (**13**),[161,376,406] 19(*S*)-hydroxyibogamine (**14**),[221,341,407] 19(*R*)-Hydroxyibogamine (**15**),[341,366,408] coronaridine (**16**),[126,161,313] (–)-heyneanine (**17**),[123,313,318] voacangine (1**8**),[126,157,161,313] and voacristine (**19**)[126,313] were also isolated in the present study. The absolute configuration of 19(*S*)-Hydroxyibogamine (**14**) was confirmed by the X-ray diffraction analysis (Figure 2.45). The ^{1}H NMR spectra of these compounds are shown in Figures 2.46–2.52, while the NMR spectroscopic data are summarized in Tables 2.12–2.15. Other data are given in the Experimental Section.



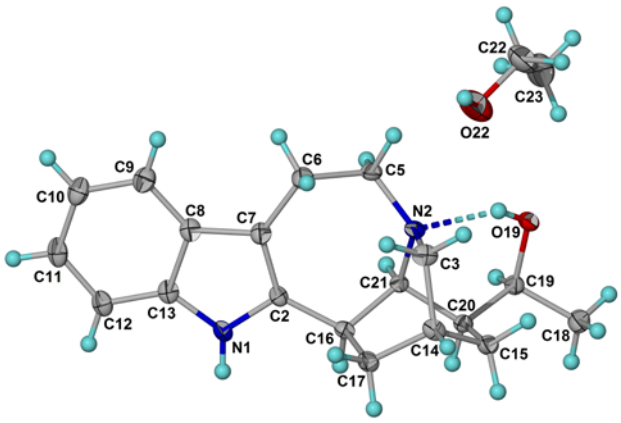


Figure 2.45: X-ray crystal structure of **14**

Table 2.12: ^{1}H NMR Spectroscopic Data (δ) of Ibogamine (**13**), 19(*S*)-Hydroxyibogamine (**14**), and 19(*R*)-Hydroxyibogamine (**15**)[a]

H	**13 (*J*/Hz)**	**14 (*J*/Hz)**	**15 (*J*/Hz)**
3	2.98 dt (9, 3)	3.00 dt (9.5, 2)	3.06 m
3	3.07 dt (9, 2)	3.08 dt (9.5, 2)	3.06 m
5	3.16 m	3.20 ddd (15, 4, 1)	3.17 m
5	3.39 m	3.34 dt (15, 4)	3.31 m
6	2.68 m	2.75 ddd (15.5, 4, 1)	2.76 ddd (16, 4, 2)
6	3.33 m	3.31 dt (15.5, 4)	3.26 m
9	7.47 ddd (7.5, 1.5, 0.5)	7.46 br dd (7.5, 1.3)	7.46 br d (7.3)
10	7.08 td (7.5, 1.5)	7.09 td (7.5, 1.3)	7.09 td (7.3, 1.4)
11	7.11 td (7.5, 1.5)	7.12 td (7.5, 1.3)	7.13 td (7.3, 1.4)
12	7.24 ddd (7.5, 1.5, 0.5)	7.25 ddd (7.5, 1.3, 0.7)	7.25 dd (7.3, 1.4)
14	1.84 m	2.00 m	1.99 m
15	1.22 ddt (13, 8, 3)	1.64 dddd (13, 11, 4, 2)	1.84 td (13, 3)
15	1.79 m	1.98 ddt (13, 8, 2.6)	1.91 m
16	2.92 ddd (11, 4, 2)	3.01 ddd (12, 3.5, 1.5)	2.93 ddd (12, 4, 2)
17	1.64 ddd (13, 7, 4)	1.67 ddd (13, 6.5, 3.5)	1.68 dq (13, 3)
17	2.04 ddt (13, 11, 2.5)	2.08 ddt (13, 12, 2.6)	2.07 br t (13)
18	0.90 t (7)	1.12 d (6.5)	1.28 d (6.5)
19	1.49 m	4.17 qd (6.5, 1.5)	3.91 qd (6.5, 2.2)
19	1.55 m	-	-
20	1.55 m	1.58 ddt (11, 4, 1.5)	1.62 m
21	2.96 br s	3.13 t (1.5)	3.39 br s
NH	7.64 br s	7.79 br s	8.04 br s

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

Table 2.13: ^{13}C NMR Spectroscopic Data (δ) of Ibogamine (**13**), 19(*S*)-Hydroxyibogamine (**14**), and 19(*R*)-Hydroxyibogamine (**15**)[a]

C	**13**	**14**	**15**
2	141.8	140.7	141.0
3	49.9	49.3	49.2
5	54.1	52.9	53.0
6	20.6	20.2	20.3
7	109.1	108.4	108.5
8	129.7	129.5	129.5
9	117.8	118.0	118.1
10	119.0	119.2	119.3
11	120.9	121.3	121.4
12	110.1	110.2	110.4
13	134.6	134.8	134.9
14	26.4	25.9	26.1
15	32.1	23.0	29.2
16	41.3	40.2	40.0
17	34.1	34.3	34.3
18	11.9	20.1	23.0
19	27.8	71.5	71.7
20	41.9	42.2	42.5
21	57.5	60.9	54.8

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

Table 2.14: ^{1}H NMR Spectroscopic Data (δ) of Coronaridine (**16**), (–)-Heyneanine (**17**), Voacangine (1**8**), and Voacristine (**19**)[a]

H	**16 (*J*/Hz)**	**17 (*J*/Hz)**	**18 (*J*/Hz)**	**19 (*J*/Hz)**
3	2.82 br d (9)	2.81 dt (9, 2)	2.81 dt (9, 2)	2.79 br d (9)
3	2.90 br dd (9, 3)	2.99 ddd (9, 4, 2.5)	2.91 m	2.98 ddd (9, 5, 2)
5	3.21 m	3.13 m	3.21 dt (13, 6)	3.10 m
5	3.39 m	3.46 m	3.37 dt (13, 5)	3.43 m
6	3.00 m	3.13 m	2.97 m	3.03 m
6	3.19 m	3.13 m	3.13 m	3.13 m
9	7.48 br d (7.5)	7.47 dd (7.5, 1)	6.92 d (2)	6.90 d (2)
10	7.08 td (7.5, 1)	7.10 td (7.5, 1)	-	-
11	7.15 td (7.5, 1)	7.17 td (7.5, 1)	6.80 dd (8.5, 2)	6.81 dd (8.5, 2)
12	7.25 dd (7.5, 1)	7.25 dd (7.5, 1)	7.13 d (8.5)	7.13 d (8.5)
14	1.88 m	2.03 m	1.87 m	2.00 m
15	1.13 br dd (12, 7.5)	1.56 dddd (13, 10, 4, 2)	1.10 m	1.54 br ddd (13, 10, 2)
15	1.74 br td (11, 3)	1.91 ddt (13, 6.5, 2)	1.73 dddd (12, 10, 4, 2)	1.89 ddt (13, 6.5, 2)
17	1.90 m	1.98 ddd (13, 4, 2.5)	1.89 ddd (14, 4, 2)	1.95 ddd (13, 4, 2)
17	2.58 br d (14)	2.16 dt (13, 2)	2.57 dt (14, 2)	2.59 br d (13)
18	0.90 t (7.5)	1.10 d (6.5)	0.90 t (7.5)	1.09 d (6.5)
19	1.44 m	4.17 qd (6.5, 1.5)	1.44 dqd (13, 7.5, 6.5)	4.15 q (6.5)
19	1.57 m	-	1.56 dqd (13, 7.5, 6.5)	-
20	1.33 m	1.46 ddt (10, 6.5, 1.5)	1.32 m	1.44 br dd (10, 6.5)
21	3.56 s	3.86 br s	3.55 br s	3.83 br s
CO_2*Me*	3.71 s	3.74 s	3.71 s	3.72 s
10-OMe	-	-	3.85 s	3.83 s
19-OH	-	6.42 br s	-	6.45 br s
NH	7.83 br s	7.89 br s	7.69 br s	7.83 br s

[a]$CDCl_3$, 400 MHz.

Table 2.15: ^{13}C NMR Spectroscopic Data (δ) of Coronaridine (**16**), (–)-Heyneanine (**17**), Voacangine (1**8**), and Voacristine (**19**)[a]

C	**16**	**17**	**18**	**19**
2	136.4	135.8	137.3	136.6
3	51.6	51.2	51.6	51.2
5	53.1	52.1	53.2	52.2
6	21.9	21.2	22.1	21.5
7	110.0	109.5	110.0	109.5
8	128.6	128.2	129.1	128.8
9	118.3	118.2	100.8	100.6
10	119.0	119.1	154.0	154.1
11	121.7	121.9	111.8	112.2
12	110.3	110.3	111.1	111.2
13	135.5	135.5	130.6	130.6
14	27.2	26.6	27.3	26.7
15	31.8	22.8	31.9	22.8
16	54.9	53.9	55.1	54.0
17	36.3	36.6	36.5	36.9
18	11.6	20.2	11.6	20.3
19	26.6	71.2	26.7	71.3
20	39.9	39.3	39.1	39.4
21	57.3	59.5	57.5	59.7
CO_2Me	175.6	174.6	175.8	174.8
CO_2*Me*	52.5	52.7	52.5	52.9
10-OMe	-	-	56.0	55.9

[a]$CDCl_3$, 100 MHz.

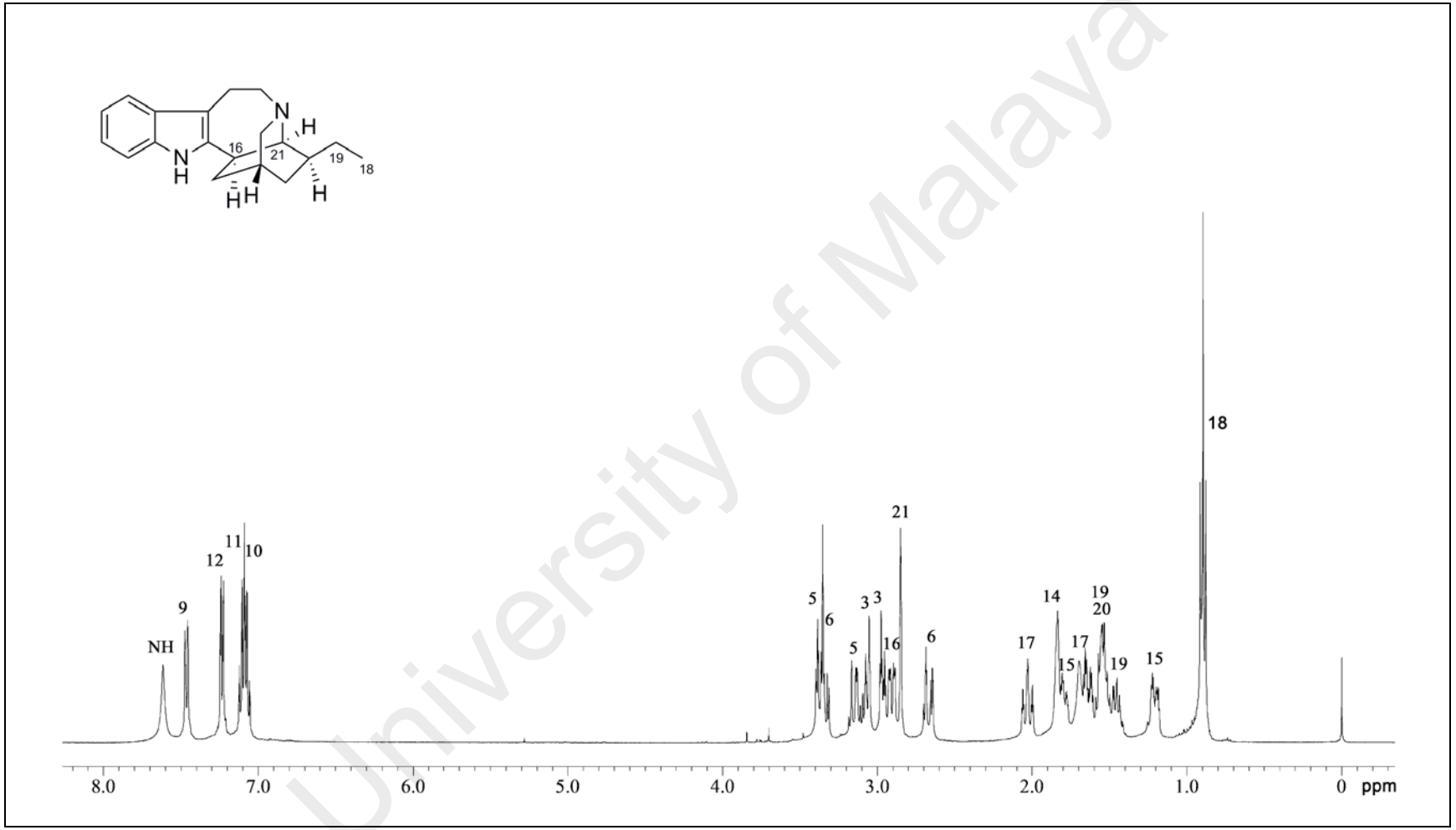


Figure 2.46: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of Ibogamine (**13**)

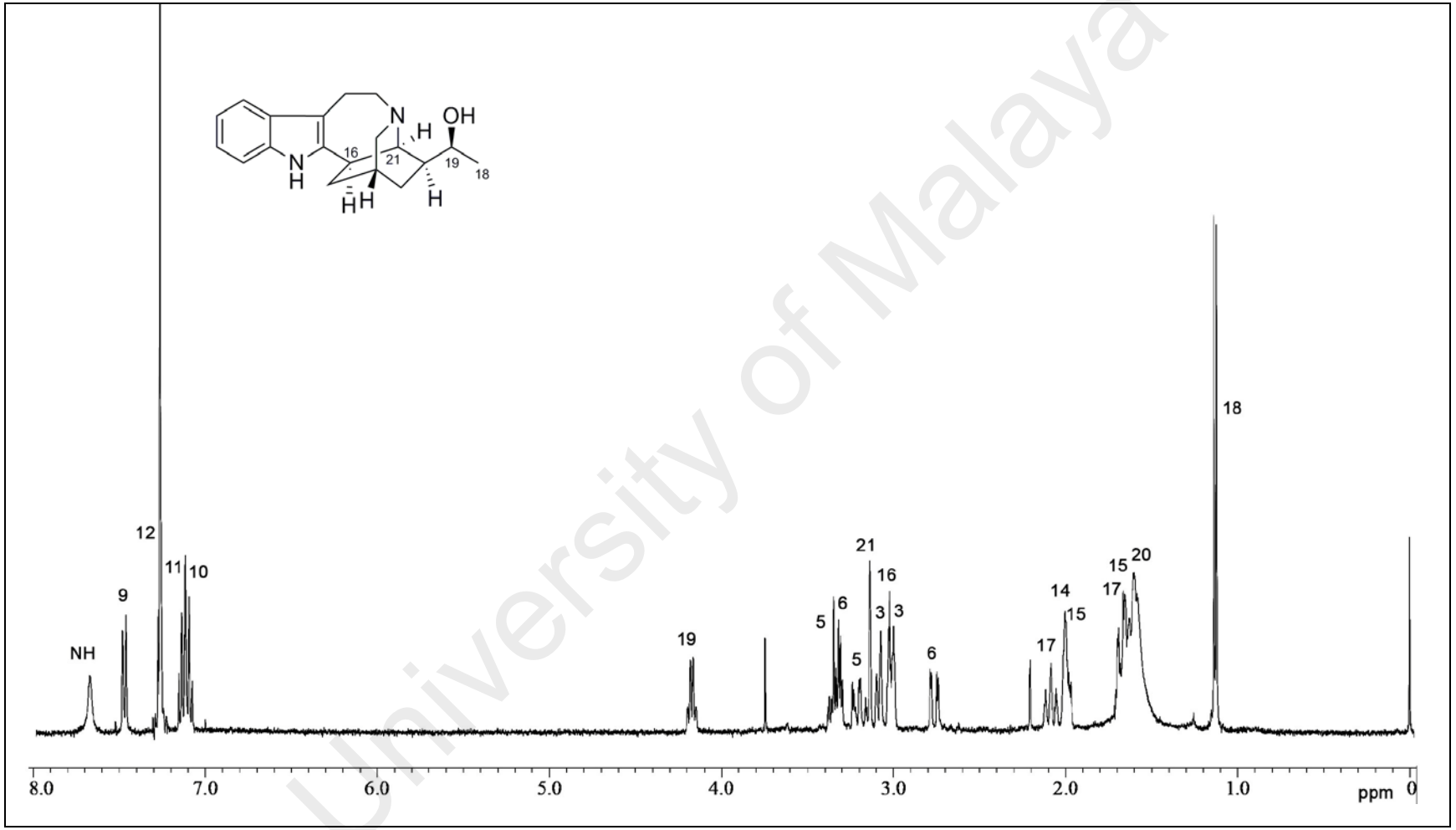


Figure 2.47: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 19(*S*)-Hydroxyibogamine (**14**)

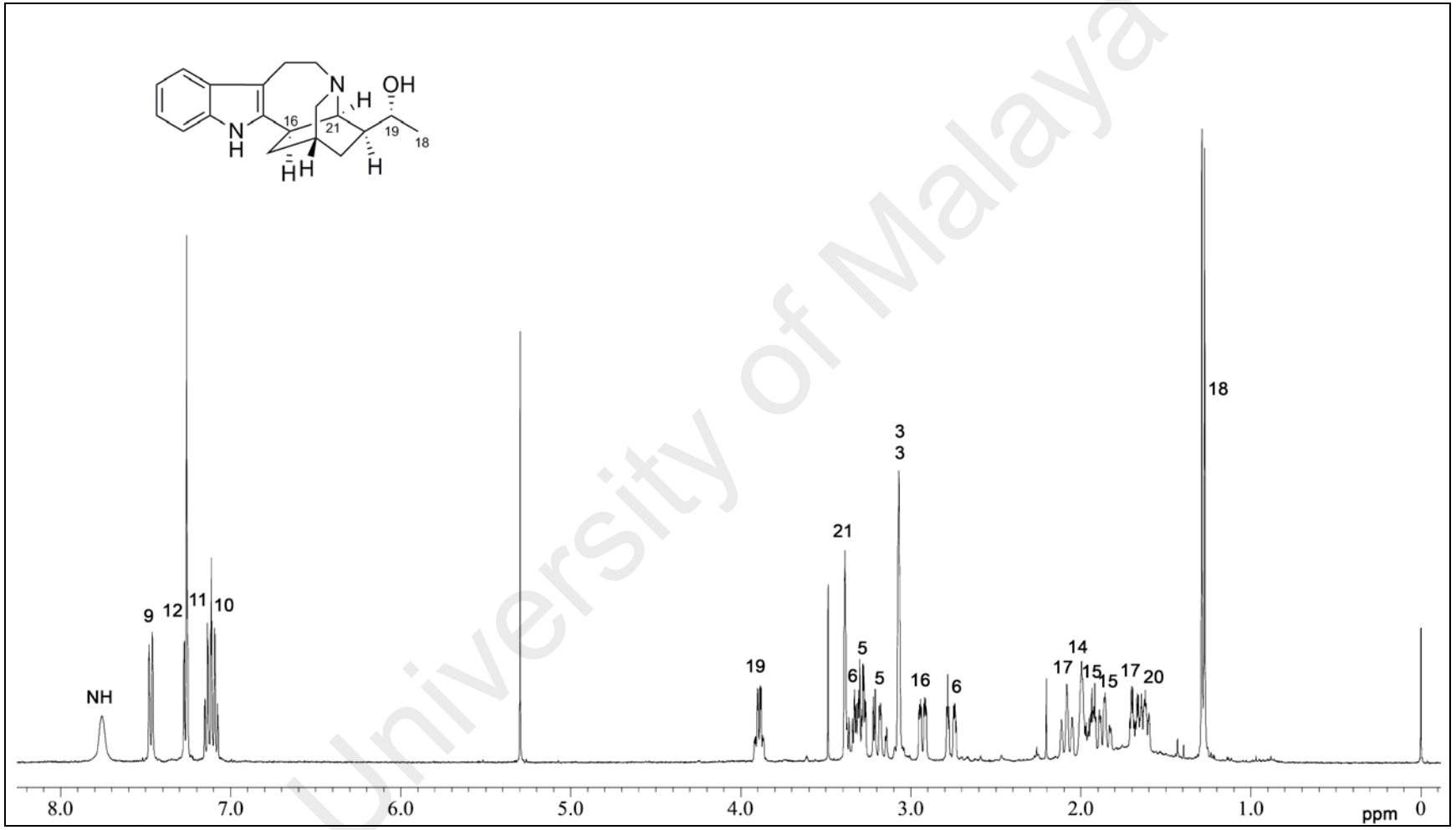


Figure 2.48: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 19(*R*)-Hydroxyibogamine **(15)**

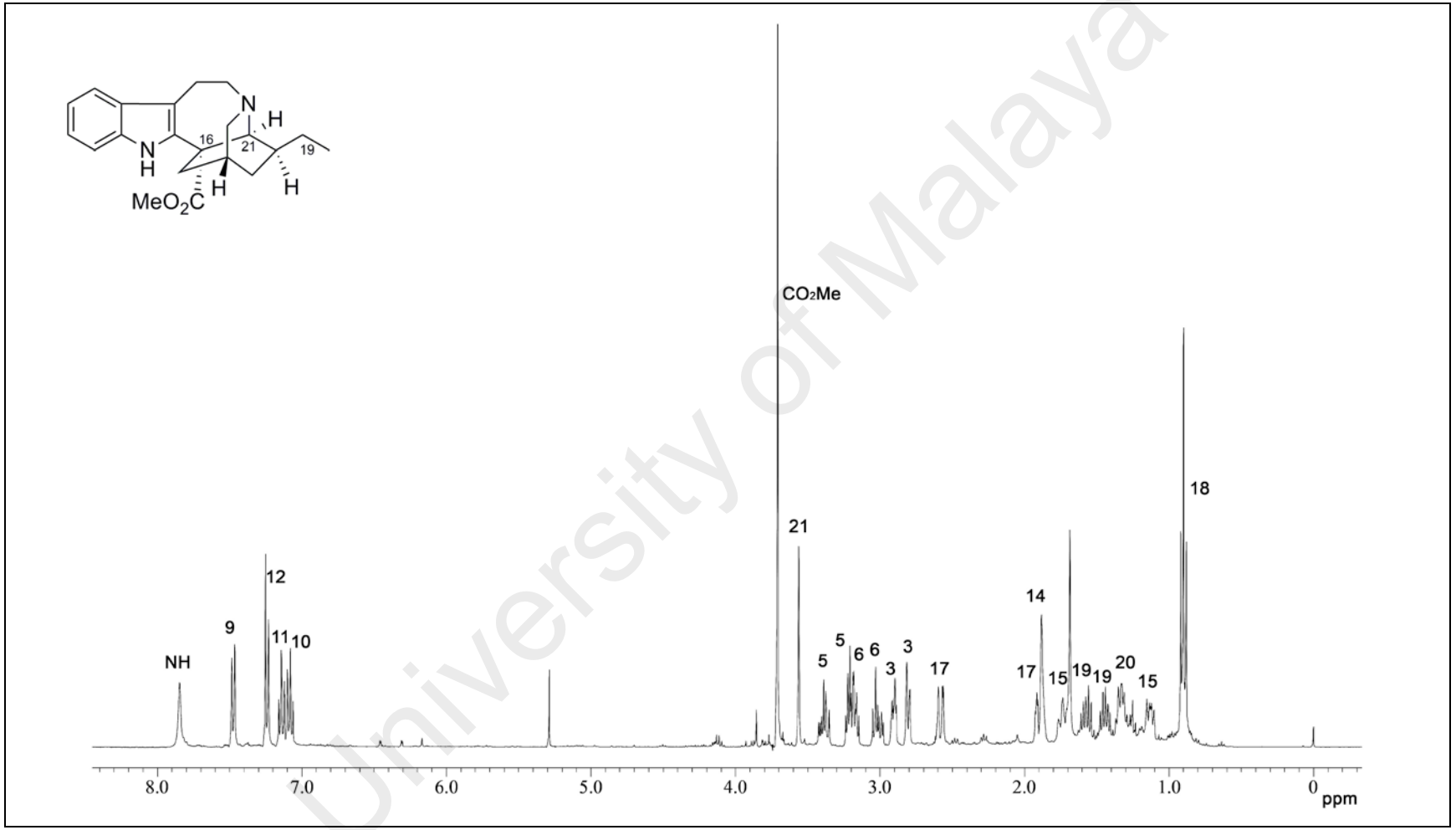


Figure 2.49: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of Coronaridine (**16**)

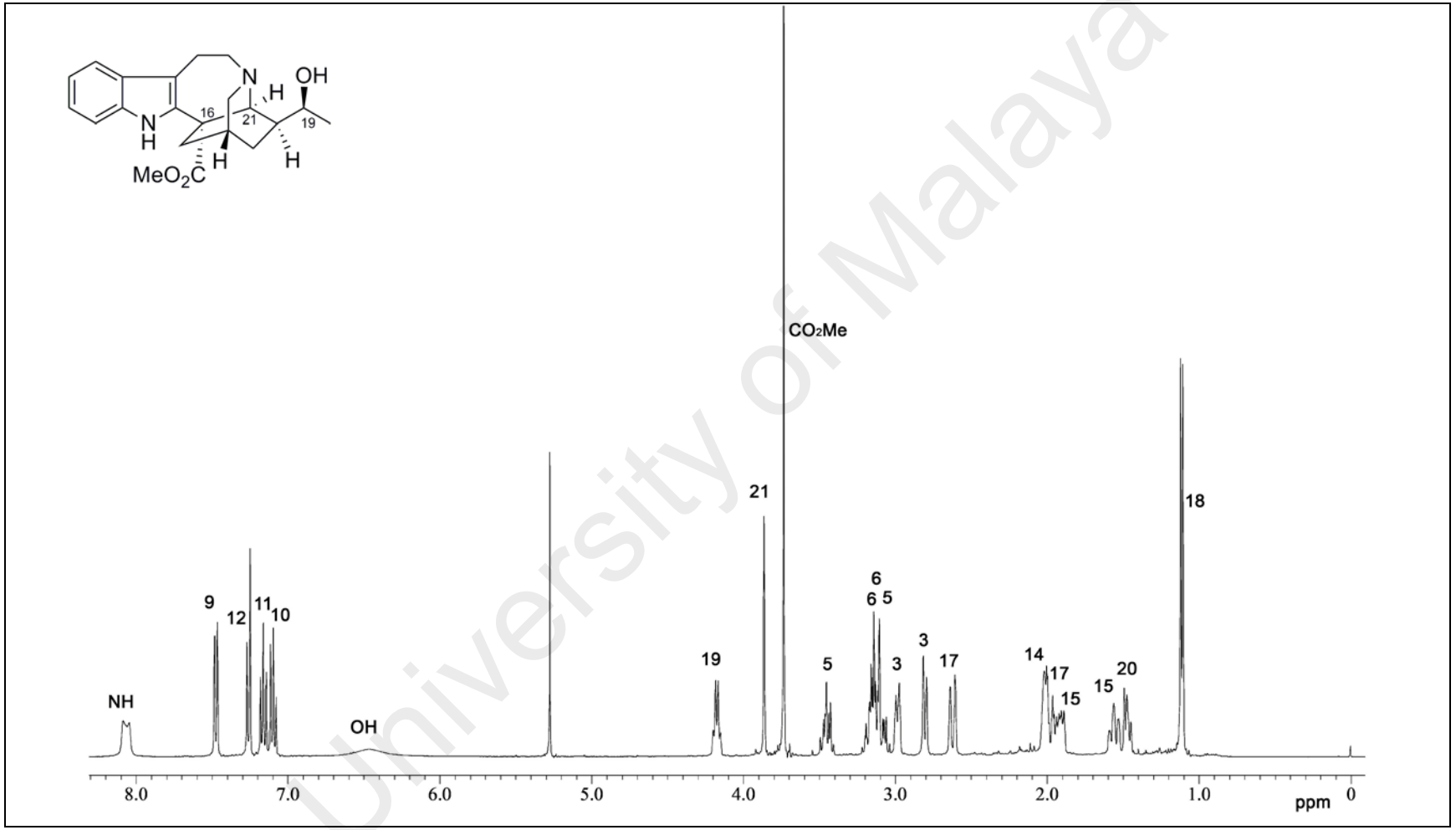


Figure 2.50: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of (–)-Heyneanine (**17**)

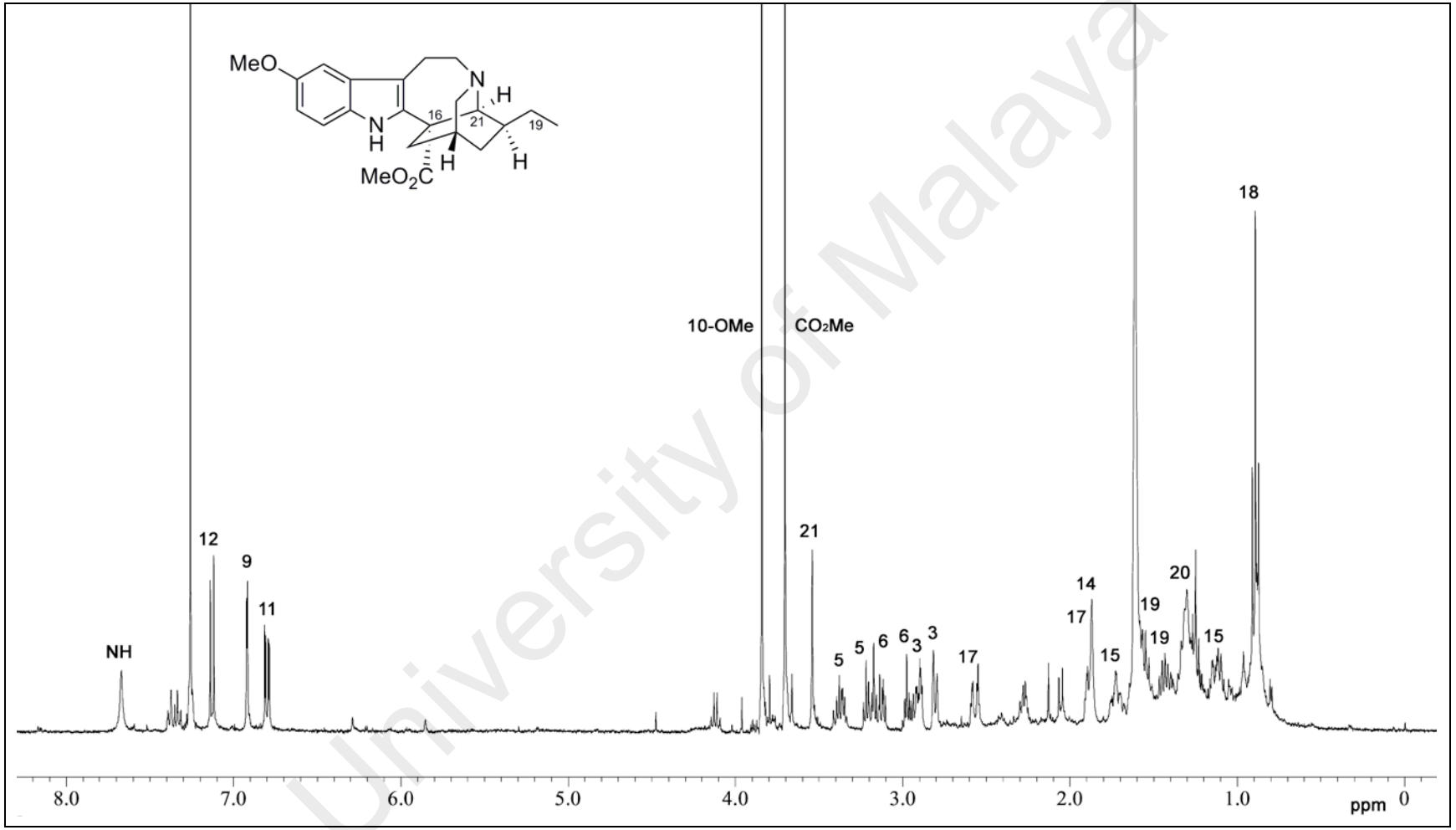


Figure 2.51: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of Voacangine (**18**)

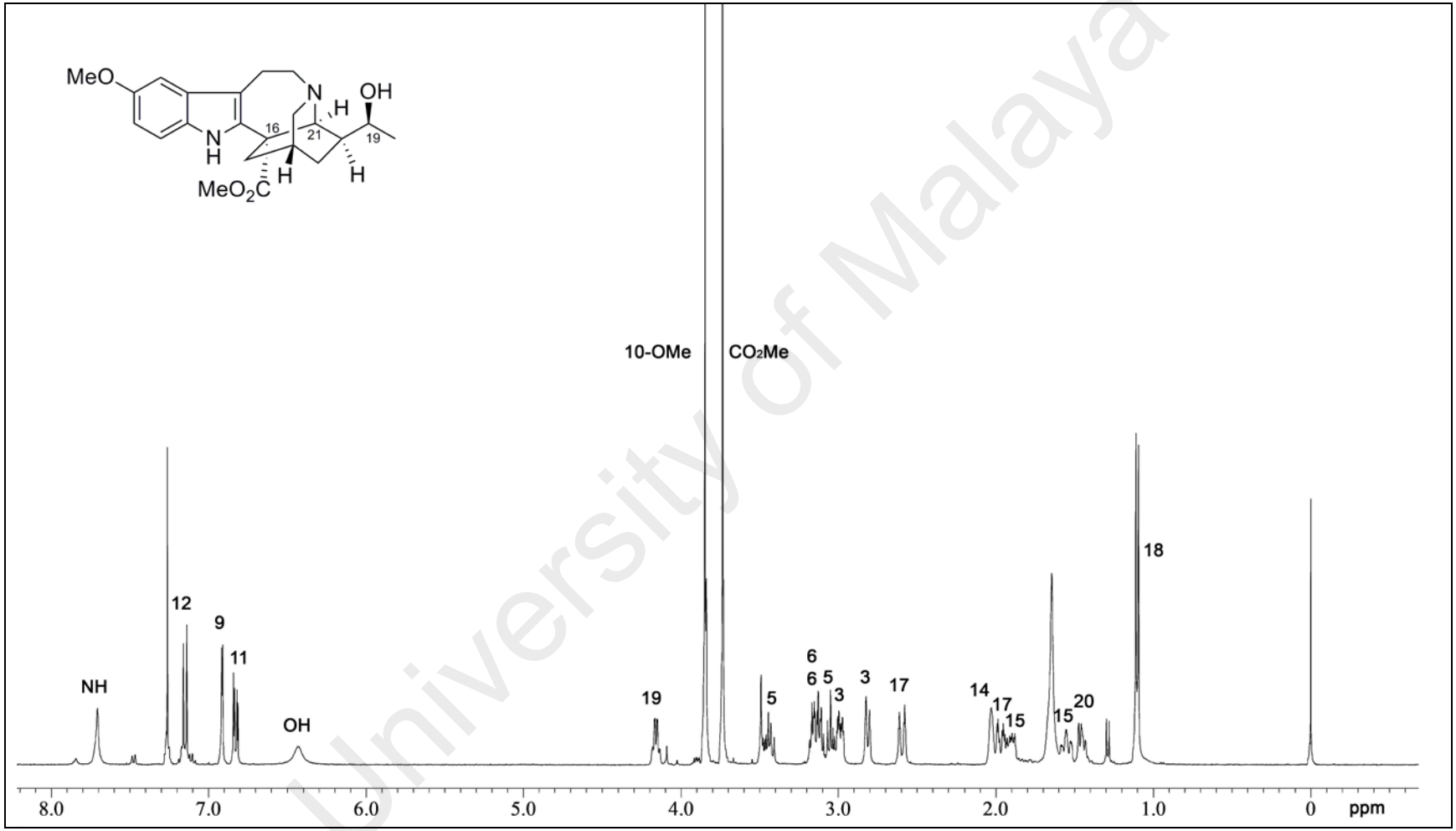
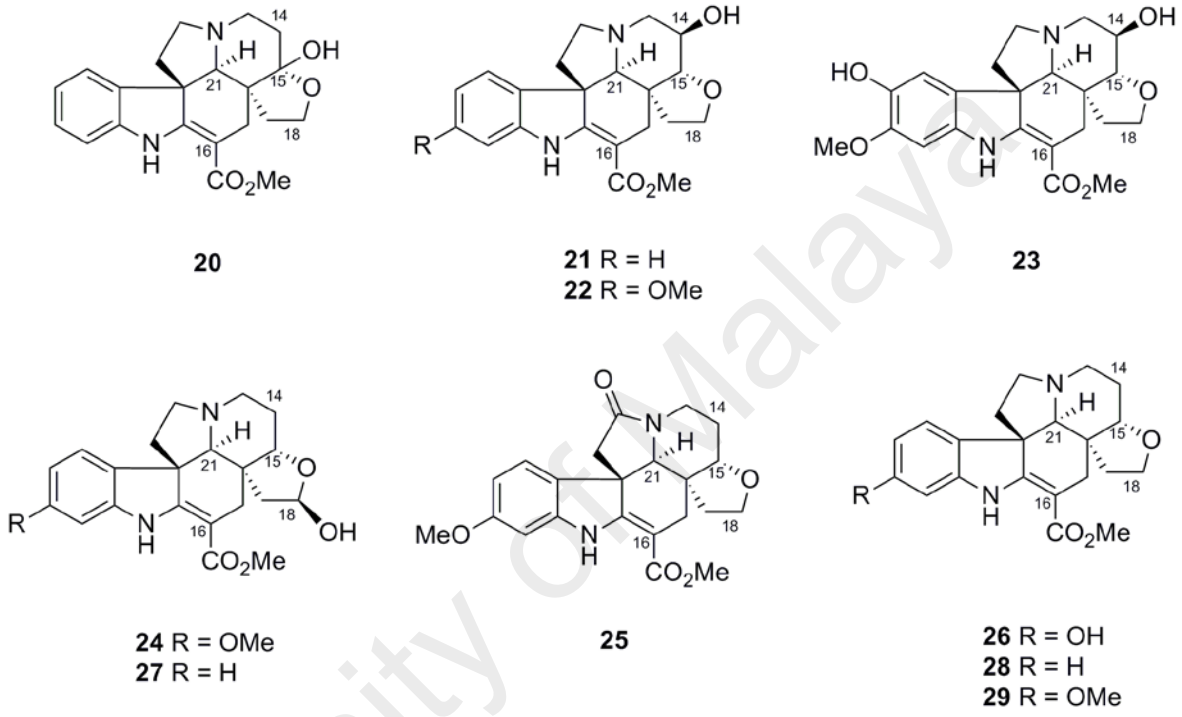


Figure 2.52: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of Voacristine (**19**)

2.1.6 *Aspidosperma* Alkaloids

Apocidines A–G (**20**–**26**) are new *Aspidosperma* alkaloids which are derivatives or analogues of hedrantherine (**27**), deoxoapodine (**28**), and vandrikine (**29**).



2.1.6.1 Apocidine A (20)

Apocidine A (**20**)[402] was initially isolated as a light yellowish oil which subsequently crystallized from CH_2Cl_2–MeOH as colorless plates, mp 214.5–215.5 °C, $[\alpha]^{25}_D$ –541 (*c* 0.19, $CHCl_3$). The UV spectrum showed absorption maxima at 224, 299, and 327 nm, characteristic of a β-anilinoacrylate chromophore. The IR spectrum showed absorption bands due to NH/OH (3380 cm^{-1}) and α,β-unsaturated carbonyl (1676 and 1609 cm^{-1}) functions. The ESIMS showed an $[M + H]^+$ peak at *m/z* 369, and HRESIMS measurements established the molecular formula as $C_{21}H_{24}N_2O_4$.

The ^{1}H NMR spectrum of **20** (Figure 2.65, Table 2.16) showed the presence of an indolic NH (δ 8.95), four aromatic resonances of an unsubstituted indole moiety (δ 6.80–7.22), a methyl ester (δ 3.77), and an isolated aminomethine corresponding to H-21 (δ 2.72). Another isolated methylene (δ 2.65, overlapped in the ^{1}H NMR spectrum) was indicated from the HSQC spectrum. The ^{13}C NMR spectrum (Table 2.18) showed a total of 21 carbon resonances comprising one methyl, seven methylenes, five methines, two tertiary carbons bonded to indolic nitrogen (δ 167.2, 143.3; corresponding to C-2, C-13, respectively), one hemiketal (δ 94.0, C-15), one ester carbonyl (δ 169.1), and four quaternary carbon atoms.

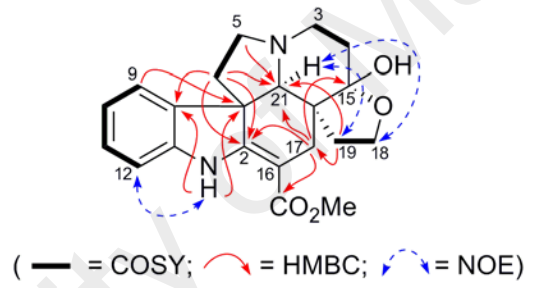


Figure 2.53: COSY, selected HMBCs and NOEs of **20**

The COSY spectrum of **20** showed the presence of OCH_2CH_2 and two NCH_2CH_2 partial structures. The two NCH_2CH_2 must be branched from N-4, and correspond to the N-4–C-5–C-6 and N-4–C-3–C-14 fragments. The isolated methylene (δ_H 2.65; δ_C 25.3) is linked to C-16 (δ 104.4) from the observed three-bond correlations from these methylene hydrogens to C-2 (δ_C 167.2) and to the ester carbonyl (δ_C 169.1) in the HMBC spectrum (Figure 2.53). The HMBC spectrum also showed three-bond correlations from the C-17 methylene hydrogens to the hemiketal carbon at δ_C 94.0 (C-15). Since branching of the oxyethylene side chain is from C-20 (from the observed three-bond correlations from H-19 to C-17 and C-21) and the molecular formula requires the presence of another ring, the oxyethylene fragment must be linked via its

oxygen atom to the hydroxy-substituted C-15 to form the tetrahydrofuranyl ring, fused to C-15 and C-20 of the pentacyclic aspidospermane moiety. The overall structure is entirely consistent with the HMBC data (Figure 2.53). The relative configurations at C-20 and C-15 are fixed by the *cis*-fusion of the tetrahydrofuranyl ring, and the observed H-21/H-19α, H-18α NOEs (Figure 2.53). In any case the structure of **20** was also confirmed by an X-ray analysis (Figure 2.54).

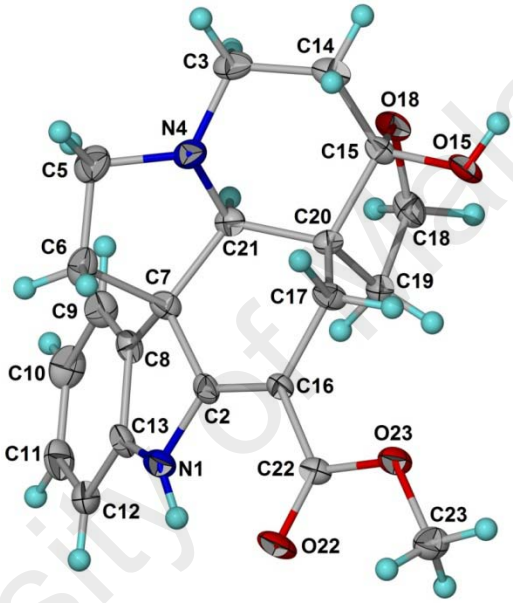
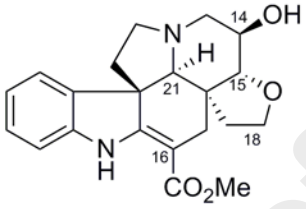


Figure 2.54: X-ray crystal structure of **20**

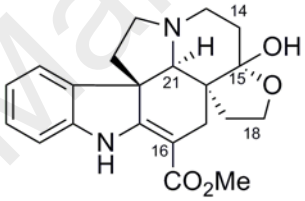
2.1.6.2 Apocidine B (21)

Apocidine B (**21**)[402] was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ –277 (*c* 0.37, $CHCl_3$). The UV (224, 297, and 328 nm) and IR (3380, 1676, and 1609 cm^{-1}) spectra showed the presence of a β-anilinoacrylate chromophore. The ESIMS showed an $[M + H]^+$ peak at *m/z* 369, and ^{13}C NMR and HRESIMS data established the molecular formula as $C_{21}H_{24}N_2O_4$ (i.e., similar to that of **20**). The similarity of the molecular formula, as well as the UV and IR data, with those of **20**, suggested that **21** and **20** are regioisomeric hexacyclic alkaloids.

The ^{13}C NMR spectrum (Table 2.18) showed a total of 21 carbon resonances, comprising one methyl, six methylenes, five methines, two oxygenated methines (δ 67.6, 83.7), two tertiary carbons linked to the indolic nitrogen (δ 166.4, C-2; 143.2, C-13), one ester carbonyl (δ 168.7), and four quaternary carbon atoms. The ^{1}H NMR spectrum (Figure 2.66, Table 2.16) showed the presence of four aromatic resonances of an unsubstituted indole moiety (δ 6.82–7.22), an indolic NH (δ 8.93), a methyl ester (δ 3.78), an isolated aminomethine corresponding to H-21 (δ 2.88), two oxymethines (δ 3.94, 3.68), and an isolated methylene (δ 2.54, 2.75).



21



20

The COSY and HMQC data (Figure 2.55) revealed the presence of three partial structures, i.e. NCH_2CH_2, NCH_2CHCH and OCH_2CH_2, corresponding to N–C-5–C-6, N–C-3–C-14–C-15 and O–C-18–C-19 fragments. Compared to **20**, where two NCH_2CH_2 fragments were present, one of these has been replaced by an NCH_2CHCH fragment (corresponding to N–C-3–C-14–C-15) in **21**. Oxygen substitutions at C-14 and C-15 were indicated by the respective carbon resonances at δ 67.6 and 83.7, respectively. As in the case of **20**, the isolated methylene at δ 2.54 and 2.75 was linked to C-16 and C-20, from the observed three-bond correlations from these methylene hydrogens (H_2-17) to C-2, C-21, and C-15. As in **20**, the remaining oxyethylene fragment was branched from C-15 and linked to C-20 via the ether oxygen to form the *c*is-fused tetrahydrofuranyl ring (^{3}J from H-18 to C-15, C-20 in the HMBC spectrum,

Figure 2.55). The relative configurations at C-20 and C-15 were also similar to those in **20** from the observed H-21/H-19α NOE. The OH group at C-14 is deduced to be axially- or β-oriented in a chair piperidine ring D (NOE for H-3α/H-21), since H-14 is equatorially-oriented from its NOE with both H-3 and H-15 (Figure 2.56), and from the observed coupling constants for H-3 ($J_{3\beta\text{-}14\alpha}$ = $J_{3\alpha\text{-}14\alpha}$ = 2 Hz) and H-15 ($J_{14\alpha\text{-}15\beta}$ = 2.7 Hz) (the signal for H-14 was seen as a broad singlet/multiplet).

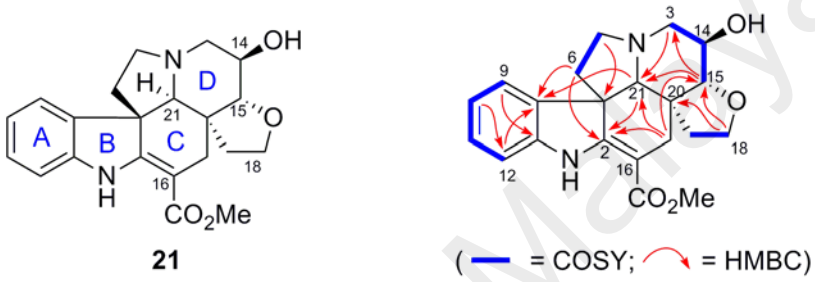


Figure 2.55: COSY and selected HMBCs of **21**

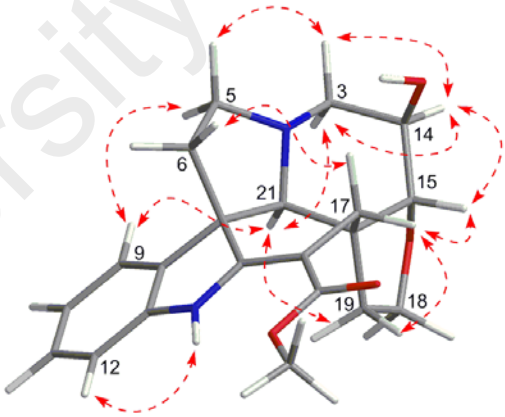
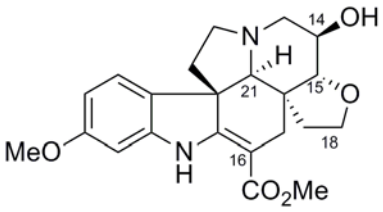


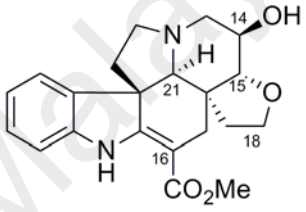
Figure 2.56: Selected NOEs of **21**

2.1.6.3 Apocidine C (22)

Apocidine C (**22**) was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ –44 (*c* 0.14, $CHCl_3$). The UV (226, 245, and 326 nm) and IR (3377, 1675, and 1615 cm^{-1}) spectra indicated the presence of a β-anilinoacrylate chromophore. The ESIMS showed an $[M + H]^+$ peak at *m/z* 399, which analyzed for $C_{22}H_{27}N_2O_5$, differing from apocidine B (**21**) by an addition of 30 mass units and consistent with the replacement of a H by an OMe group.



22



21

The ^{13}C NMR data (Table 2.18) showed a total of 22 carbon resonances, comprising two methyls, six methylenes, six methines, two tertiary carbons linked to the indolic nitrogen (C-2 and C-13), one methoxy-substituted aromatic carbon (δ 160.3), one ester carbonyl (δ 168.6), and four quaternary carbon atoms. The ^1H NMR spectrum (Figure 2.67, Table 2.16) showed the presence of three aromatic hydrogens (δ 6.40–7.10), an indolic NH (δ 8.90), an aromatic methoxy group (δ 3.79), a methyl ester (δ 3.78), an isolated aminomethine corresponding to H-21 (δ 2.82), two oxymethines (δ 3.67, 3.93) and an isolated methylene (δ 2.52, 2.72).

The COSY and HSQC data (Figure 2.57) revealed the presence of the same three partial structures as those present in apocidine B (**21**), i.e. NCH_2CH_2, NCH_2CHCH, and OCH_2CH_2, corresponding to N–C-5–C-6, N–C-3–C-14–C-15 and O–C-18–C-19. Furthermore, comparison of the ^1H and ^{13}C NMR data (Tables 2.16 and

2.18) of **22** with those of **21**, showed a general similarity except for the presence of only three aromatic hydrogen resonances and an additional aromatic methoxy resonance (δ_H 3.79, δ_C 55.5) in the NMR spectra of **22**. The substitution of the OMe group is deduced to be at C-11, which is consistent with the carbon resonance of C-11 at δ 160.3 and the observed NOEs for H-12/OMe and H-12/NH.

The relative configurations at C-20 and C-15 were also similar to those in apocidine B (**21**) from the observed H-21/H-19α and H-15/H-17 NOEs (Figure 2.57). The orientation of the 14-OH was deduced to be β as in **21**, from the observed H-3α/H-21 NOE, and from the observed coupling constants for H-3 ($J_{3\beta\text{-}14\alpha}$ = $J_{3\alpha\text{-}14\alpha}$ = 2.3 Hz) and H-15 ($J_{14\alpha\text{-}15\beta}$ = 2.7 Hz).

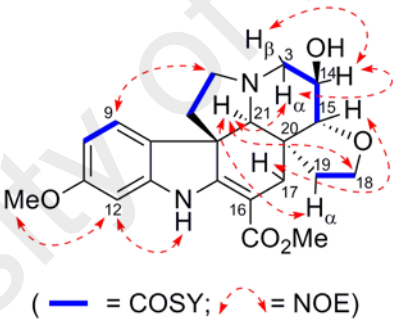
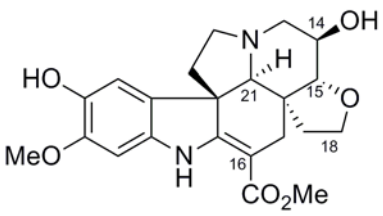


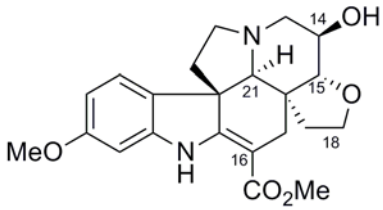
Figure 2.57: COSY and selected NOEs of **22**

2.1.6.4 Apocidine D (23)

Apocidine D (**23**) was isolated as a light yellowish oil, with $[\alpha]^{25}_D$ –179 (*c* 0.12, $CHCl_3$). The UV and IR spectra were similar to those of apocidine C (**22**). The ESIMS showed an $[M + H]^+$ peak at *m/z* 415, and HRESIMS measurement gave the molecular formula as $C_{22}H_{26}N_2O_6$, differing from that of **22** by 16 mass units (replacement of a H with an OH).



23



22

The ^{13}C NMR spectrum (Table 2.18) showed a total of 23 carbon resonances, comprising two methyls, six methylenes, five methines, two tertiary carbons linked to the indolic nitrogen (δ 167.4, C-2; 136.0, C-13), two tertiary carbons linked to oxygen (δ 140.1, 146.2), one ester carbonyl (δ 168.7), and four quaternary carbon atoms. The ^{1}H NMR spectrum (Figure 2.68, Table 2.16) showed the presence of two aromatic hydrogens (δ 6.45, 6.87), an indolic NH (δ 8.79), a methoxy group (δ 3.88), a methyl ester (δ 3.77), an isolated aminomethine corresponding to H-21 (δ 2.80), two oxymethines (δ 3.67, 3.92), and an isolated methylene (δ 2.52, 2.72).

The ^{1}H and ^{13}C NMR spectra of **23** (Tables 2.16 and 2.18) showed a general similarity to those of **22**, except for the absence of signal due to H-10, and the observation of the two aromatic hydrogens as sharp singlets. The two aromatic singlets (δ 6.87, H-9; 6.45, H-12) can be readily distinguished from the NOE interactions observed for H-9/H-5α and H-12/NH (Figure 2.58). This, and the NOE for H-12/11-MeO allowed the OH and OMe groups to be placed at C-10 and C-11, respectively. The relative configurations at various stereogenic centers were deduced to be similar to **22** from the NOESY data.

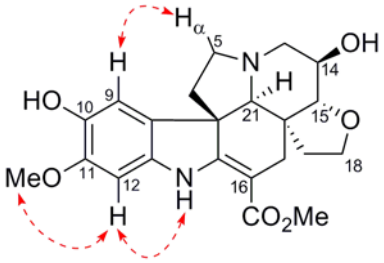
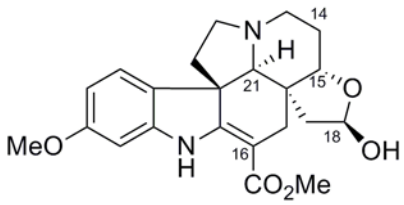


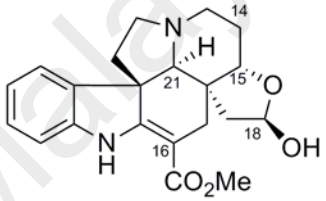
Figure 2.58: Selected NOEs of **23**

2.1.6.5 Apocidine E (24)

Apocidine E (**24**) was obtained as a light yellowish oil, with $[\alpha]^{25}_{D}$ –481 (*c* 0.32, $CHCl_3$). The UV and IR spectra of **24** were similar to those of apocidines A–D (**20**–**23**), indicating the presence of a β-anilinoacrylate chromophore. The ESIMS showed an $[M + H]^+$ peak at *m/z* 399, and ^{13}C NMR and HRESIMS data established the molecular formula as $C_{22}H_{26}N_2O_5$.



24

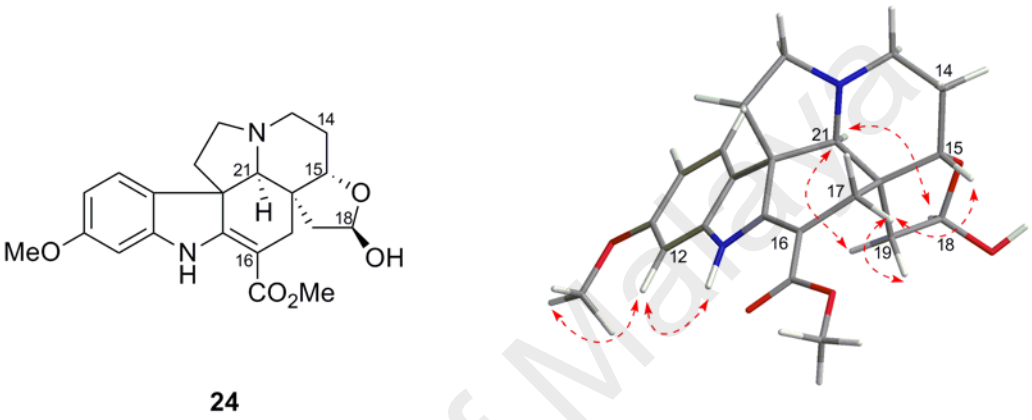


27

The ^{13}C NMR data (Table 2.18) showed a total of 22 carbon resonances [two methyls, six methylenes, five methines, one ester carbonyl (δ 168.7), one methoxy-substituted aromatic carbon (δ 160.1), two tertiary carbons linked to the indolic nitrogen (corresponding to C-2 and C-13), one hemiacetal (δ 96.5, C-18) and four quaternary carbon atoms], in agreement with the molecular formula. The ^1H NMR spectrum (Figure 2.69, Table 2.17) showed the presence of an indolic NH (δ 8.90), three aromatic hydrogens (δ 6.39, 6.41, 7.09), an aromatic methoxy group (δ 3.79), a methyl ester (δ 3.76), two oxymethines (δ 4.15, 5.35), and an isolated methylene (δ 2.40, 2.71).

The ^1H and ^{13}C NMR data of **24** were very similar to those of the known alkaloid, hedrantherine (**27**), except for the presence of the resonances due to an additional methoxy group (δ_H 3.79, δ_C 55.5) in place of one of the aromatic hydrogen resonances. The aromatic methoxy substituent is deduced to be at C-11 from the

observed carbon resonance of C-11 at δ 160.1 and the observed NOEs for H-12/OMe and H-12/NH. The OH group at C-18 is deduced to be β-oriented from the NOE observed for H-18/H-21, which requires H-18 to be α-oriented (C-18–βOH). The tetrahydrofuranyl ring is *cis*-fused to C-15 and C-20 with H-15 β-oriented from the NOE observed for H-15/H-17α (Figure 2.59).



24

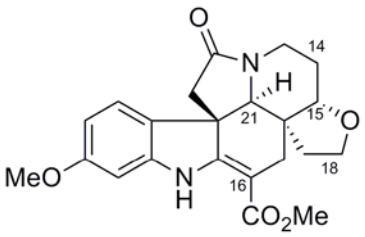
Figure 2.59: Selected NOEs of **24**

2.1.6.6 Apocidine F (25)

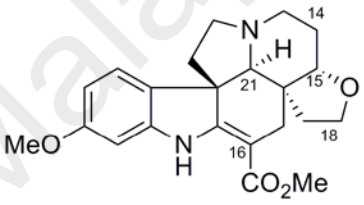
Apocidine F (**25**) was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ –208 (*c* 0.06, $CHCl_3$). The UV and IR spectra of **25** were similar to those of apocidines A–E (**20**–**24**), indicating the presence of a β-anilinoacrylate chromophore. The ESIMS showed an $[M + H]^+$ peak at *m/z* 397, and HRESIMS measurements established the molecular formula as $C_{22}H_{24}N_2O_5$.

The ^{1}H NMR spectrum (Figure 2.70, Table 2.17) showed the presence of an indolic NH (δ 8.91), three aromatic hydrogens (δ 6.46–7.13), two methyl groups (δ 3.80, 3.82), and two isolated methylenes from the observation of two pairs of AB doublets at δ 2.25, 2.43 (*J* = 15 Hz) and 2.63, 2.78 (*J* = 17.8 Hz). The ^{13}C NMR spectrum (Table 2.18) showed a total of 22 resonances, comprising two methyls, six

methylenes, five methines, two carbonyl carbons (δ 168.3, 170.4), one methoxy-substituted aromatic carbon (δ 160.8), two tertiary carbons linked to the indolic nitrogen (corresponding to C-2 and C-13), and four quaternary carbon atoms. The two carbonyl resonances observed at δ 168.3 and 170.4 were assigned to ester and lactam carbonyl functions, respectively. Assignment of the former resonance to the ester carbonyl was facilitated by the observed three-bond correlation from the ester methoxy (δ 3.80) to the carbonyl resonance at δ 168.3 in the HMBC spectrum.



25



29

The NMR data (Tables 2.17 and 2.18) of **25** were generally similar to those of vandrikine (**29**), except for the replacement of a methylene by a lactam carbonyl. The lactam carbonyl was deduced to be at position C-5 since the usual NCH_2CH_2 fragment corresponding to NC-5–C-6 has been replaced by a $NCOCH_2$ fragment in **25**. Another notable difference between the ^{1}H NMR of **25** and that of **29** is that the H-3β signal of **25** (δ 4.13) was significantly deshielded compared to that of **29** (δ 2.94). The deshielding of H-3β was due to the anisotropy from the proximate lactam carbonyl function located at C-5. This was further supported by the observed three-bond correlation from H-21 to this lactam carbonyl (δ 170.4) in the HMBC spectrum. The structure deduced is entirely consistent with the rest of the HMBC data (Figure 2.60). The relative configuration of **25** was similar to those of apocidines A–E (**20**–**24**) from the NOESY data (Figure 2.61).

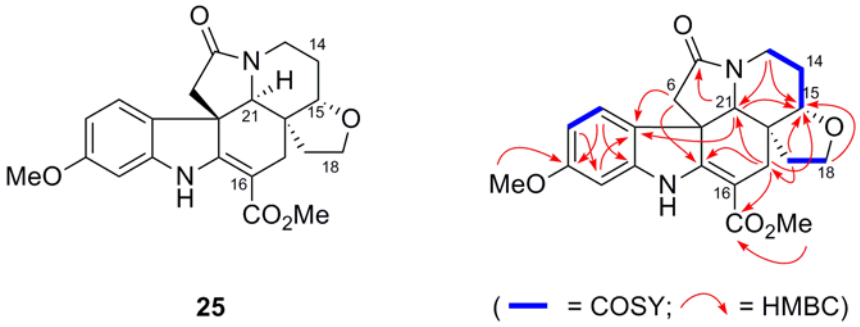


Figure 2.60: COSY and selected HMBCs of **25**

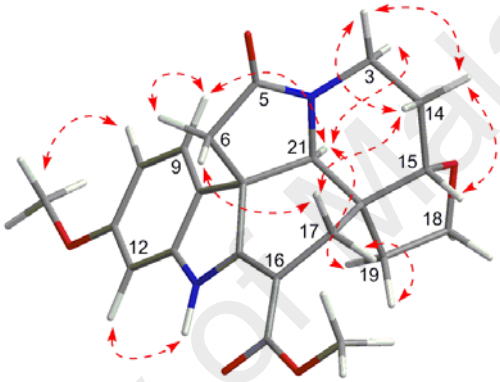
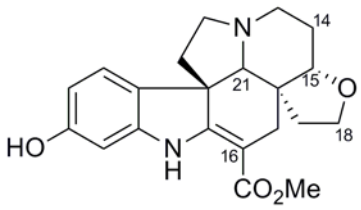


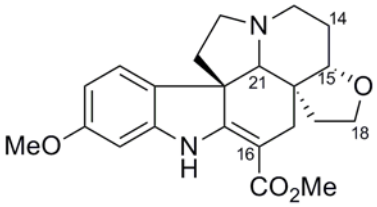
Figure 2.61: Selected NOEs of **25**

2.1.6.7 Apocidine G (26)

Apocidine G (**26**) was initially isolated as a light yellowish oil, which subsequently crystallized from chloroform as colorless block crystals, mp 141–143 ^{o}C, $[\alpha]^{25}_{D}$ –496 (*c* 0.29, $CHCl_3$). The UV and IR spectra of **26** were similar to those of vandrikine (**29**), indicating the presence of a β-anilinoacrylate chromophore. The ESIMS showed an $[M + H]^+$ peak at *m/z* 369, and HRMS measurements established the molecular formula as $C_{21}H_{24}N_2O_4$, 14 mass units lesser compared with vandrikine (**29**).



26



29

The ^{1}H NMR spectrum (Figure 2.71, Table 2.17) showed the presence of an indolic NH (δ 8.87), three aromatic resonances (δ 6.34, 6.36, 7.06), a methyl ester singlet (δ 3.78), and a pair of AB doublets (δ 2.29, 2.73) of an isolated methylene. The ^{13}C NMR spectrum (Table 2.18) showed a total of 21 carbon resonances comprising one methyl, seven methylenes, five methines, two tertiary carbons linked to indolic nitrogen (corresponding to C-2, C-13), one hydroxy-substituted aromatic carbon (δ 156.2), one ester carbonyl (δ 168.9) and four quaternary carbon atoms. The COSY and HSQC data revealed the presence of NCH_2CH_2, NCH_2CH_2CH and OCH_2CH_2 partial structures. Examination of the ^{1}H and ^{13}C NMR spectra showed similarity to those of vandrikine (**29**), except for the absence of the methoxy signal (δ_H 3.78, δ_C 55.6 in **29**) and the presence of an OH function (δ_H 5.63, exchanged with D_2O in **26**), which indicated that the OMe group in **29** has been replaced by an OH group in **26**. The position of OH substitution at C-11 was confirmed by the H-9 to C-7 and C-11 three-bond correlations, and the observed H-9/H-6α, H-10 and H-12/NH NOEs. Other correlations in the HMBC spectrum are shown in Figure 2.62, which are in complete agreement with the proposed structure. The relative configuration of **26** was similar to **29** as shown by the NOESY data (Figure 2.63). The structure and absolute configuration were also confirmed by X-ray diffraction analysis (Figure 2.64).

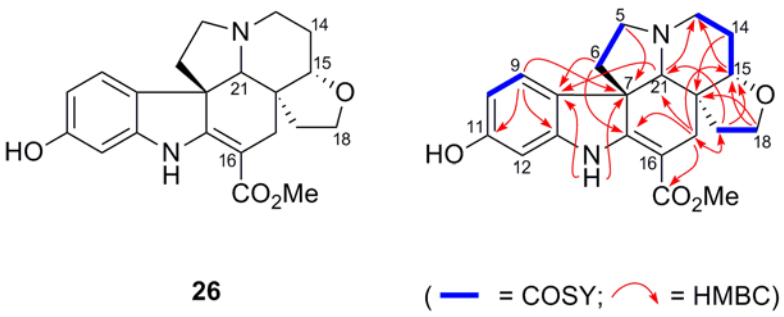


Figure 2.62: COSY and selected HMBCs of **26**

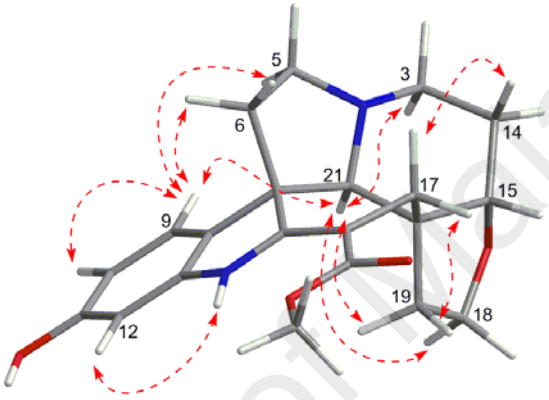


Figure 2.63: Selected NOEs of **26**

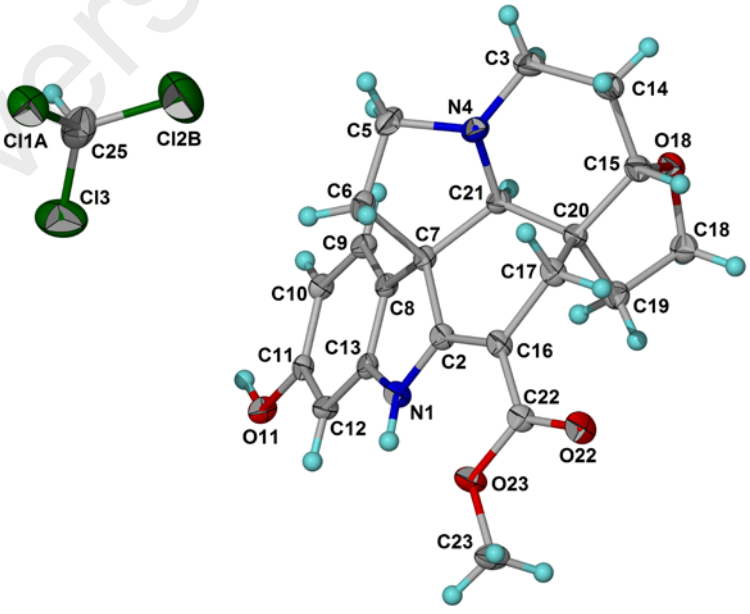


Figure 2.64: X-ray crystal structure of **26**

Table 2.16: ^{1}H NMR Spectroscopic Data (δ) of Apocidines A–D (**20**–**23**)[a]

H	**20 (*J*/Hz)**	**21 (*J*/Hz)**	**22 (*J*/Hz)**	**23 (*J*/Hz)**
3α	2.60 td (11, 4)	3.03 dd (11.5, 2)	3.01 dd (11.5, 2.3)	3.00 dd (11.6, 2.2)
3β	3.03 ddd (11, 5.2, 2)	3.11 dd (11.5, 2)	3.10 dd (11.5, 2.3)	3.09 dd (11.6, 2.2)
5α	2.70 m	2.80 ddd (12, 8.5, 4)	2.77 m	2.77 m
5β	2.98 dd (8.5, 6)	2.96 dd (8.5, 6)	2.95 dd (8.6, 6)	2.94 dd (8.5, 6)
6α	1.79 dd (11.6, 4)	1.79 dd (11.5, 4)	1.76 dd (11.5, 4)	1.76 dd (11.5, 4)
6β	2.10 td (11.6, 6)	2.07 td (11.5, 6)	2.04 td (11.5, 6)	2.05 td (11.5, 6)
9	7.22 d (7.7)	7.22 d (7.6)	7.10 d (8.8)	6.87 s
10	6.87 t (7.7)	6.90 t (7.6)	6.40 m	-
11	7.15 t (7.7)	7.17 t (7.6)	-	-
12	6.80 d (7.7)	6.82 d (7.6)	6.41 s	6.45 s
14	2.00 m	3.94 br s	3.93 m	3.92 m
14	2.00 m	-	-	-
15	-	3.68 d (2.7)	3.67 br d (2.7)	3.67 br d (2.7)
17α	2.65 br s	2.54 d (14.8)	2.52 dd (14.8, 1.7)	2.52 dd (14.8, 1.6)
17β	2.65 br s	2.75 d (14.8)	2.72 d (14.8)	2.72 d (14.8)
18	3.75 m	3.72 m	3.72 m	3.73 m
18	3.91 ddd (10, 8, 3)	3.73 m	3.75 m	3.77 m
19α	1.24 ddd (12.6, 8, 3)	1.34 ddd (12.8, 8, 4.8)	1.35 ddd (13, 7.8, 4.5)	1.33 ddd (13, 8, 4.6)
19β	1.73 ddd (12.6, 10, 2)	1.53 ddd (12.8, 10, 7.8)	1.53 ddd (13, 9.7, 7.8)	1.52 ddd (13, 9.7, 7.8)
21	2.72 s	2.88 s	2.82 s	2.80 s
CO_2*Me*	3.77 s	3.78 s	3.78 s	3.77 s
11-OMe	-	-	3.79 s	3.88 s
NH	8.95 br s	8.93 br s	8.90 br s	8.79 br s

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

Table 2.17: ^{1}H NMR Spectroscopic Data (δ) of Apocidines E–G (**24**–**26**)

H	**24**[a] **(*J*/Hz)**	**25**[b] **(*J*/Hz)**	**26**[b] **(*J*/Hz)**
3α	2.66 m	3.16 td (12.8, 2.8)	2.71 m
3β	2.95 m	4.13 dd (12.8, 5.5)	2.92 m
5α	2.62 m	-	2.63 ddd (11.5, 8, 4)
5β	2.93 m	-	2.94 m
6α	1.73 dd (11.4, 4)	2.63 d (17.8)	1.75 dd (11.5, 4)
6β	1.98 m	2.78 d (17.8)	2.01 td (11.5, 6.3)
9	7.09 d (8)	7.13 d (8.2)	7.06 d (8)
10	6.39 m	6.48 dd (8.2, 2)	6.34 dd (8, 2)
11	-	-	-
12	6.41 s	6.46 d (2)	6.36 d (2)
14	1.92 m	1.77 m	1.95 m
14	1.92 m	2.00 br d (14.5)	1.95 m
15	4.15 br s	3.83 br s	3.69 m
17α	2.40 d (14.5)	2.43 br d (15)	2.29 br d (14.5)
17β	2.71 d (14.5)	2.25 d (15)	2.73 d (14.5)
18	5.35 dd (6, 4)	3.86 m	3.71 m
18	-	3.86 m	3.79 m
19α	1.63 dd (14, 6)	1.45 ddd (13, 7.8, 4)	1.33 ddd (12.8, 8, 4.6)
19β	1.36 dd (14, 4)	1.58 ddd (13, 9.7, 8)	1.45 ddd (12.8, 10, 7.6)
21	2.68 s	3.88 s	2.78 s
CO_2*Me*	3.76 s	3.80 s	3.78 s
11-OMe	3.79 s	3.82 s	-
NH	8.90 br s	8.91 br s	8.87 br s
OH	-	-	5.63 br s

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

Table 2.18: ^{13}C NMR Spectroscopic Data (δ) of Apocidines A–G (**20**–**26**)[a]

C	**20**	**21**	**22**	**23**	**24**	**25**	**26**[b]
2	167.2	166.4	166.8	167.4	167.6	165.1	167.9
3	46.8	53.9	54.0	54.0	45.8	34.7	45.9
5	51.4	51.3	51.2	51.1	51.4	170.4	51.5
6	45.7	44.8	44.8	44.6	45.2	47.8	45.3
7	55.5	55.0	54.3	55.1	54.4	47.8	54.5
8	137.8	137.5	129.9	129.4	130.1	128.6	130.1
9	121.4	121.5	121.8	108.7	121.7	122.2	122.0
10	120.8	120.9	105.2	140.1	105.2	106.4	107.1
11	127.9	128.1	160.3	146.2	160.1	160.8	156.2
12	109.5	109.6	96.9	94.6	96.8	97.0	94.1
13	143.3	143.2	144.3	136.0	144.4	144.3	144.4
14	33.8	67.6	67.6	67.6	26.3	25.2	26.8
15	94.0	83.7	83.5	83.5	77.9	80.1	80.1
16	104.4	94.1	94.4	93.8	94.0	93.2	94.1
17	25.3	28.4	28.2	28.2	27.1	26.7	27.6
18	63.9	65.5	65.5	65.5	96.5	65.1	65.0
19	31.8	35.1	35.0	35.0	43.6	36.7	34.9
20	50.9	47.2	47.2	47.3	47.6	45.7	46.7
21	70.5	69.9	70.1	70.0	69.7	65.4	68.8
CO_2Me	169.1	168.7	168.6	168.7	168.7	168.3	168.9
CO_2*Me*	51.2	51.2	51.2	51.1	51.1	51.4	51.2
11-OMe	-	-	55.5	56.4	55.5	55.7	-

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

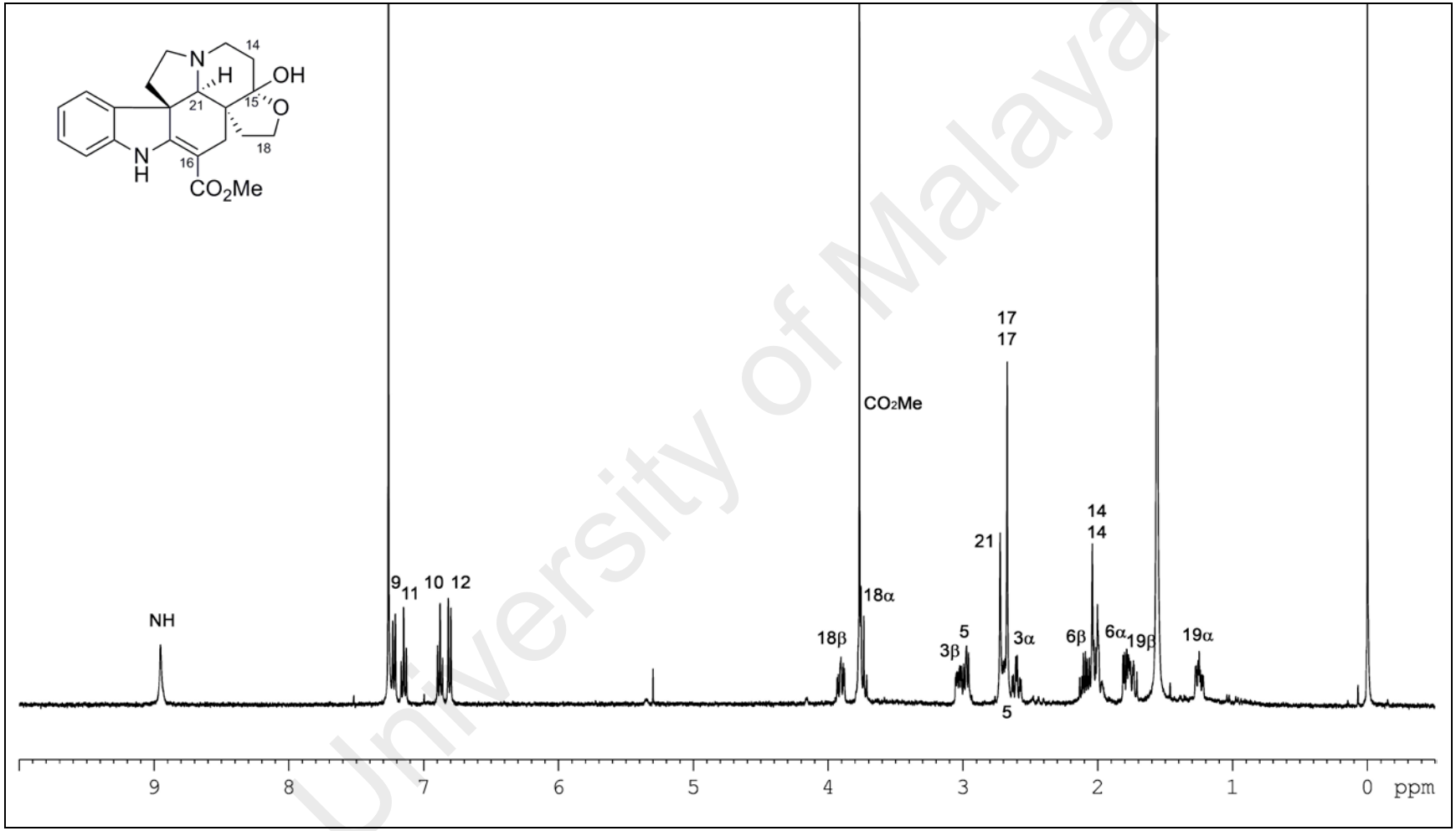


Figure 2.65: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of Apocidine A (**20**)

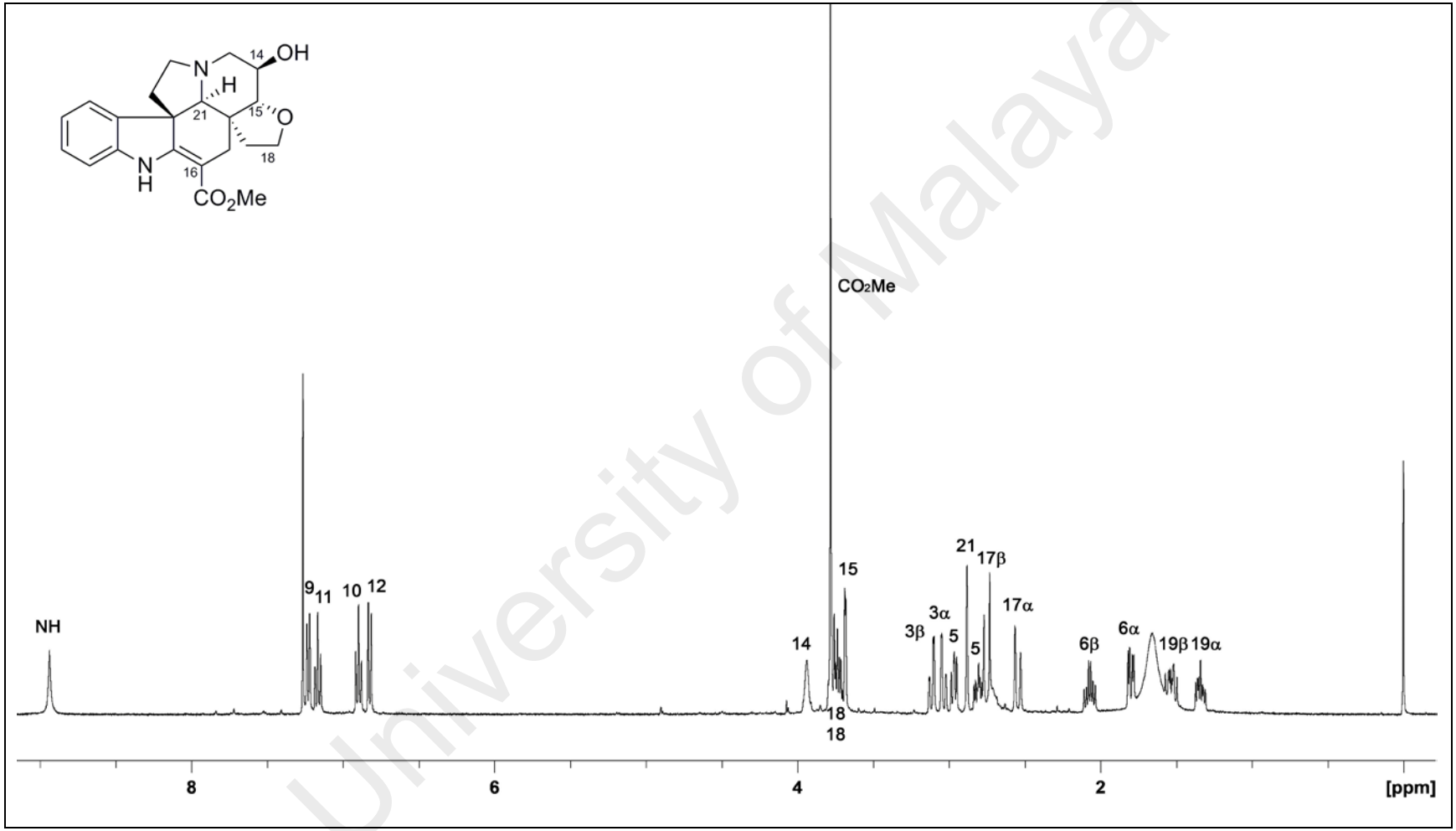


Figure 2.66: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of Apocidine B (**21**)

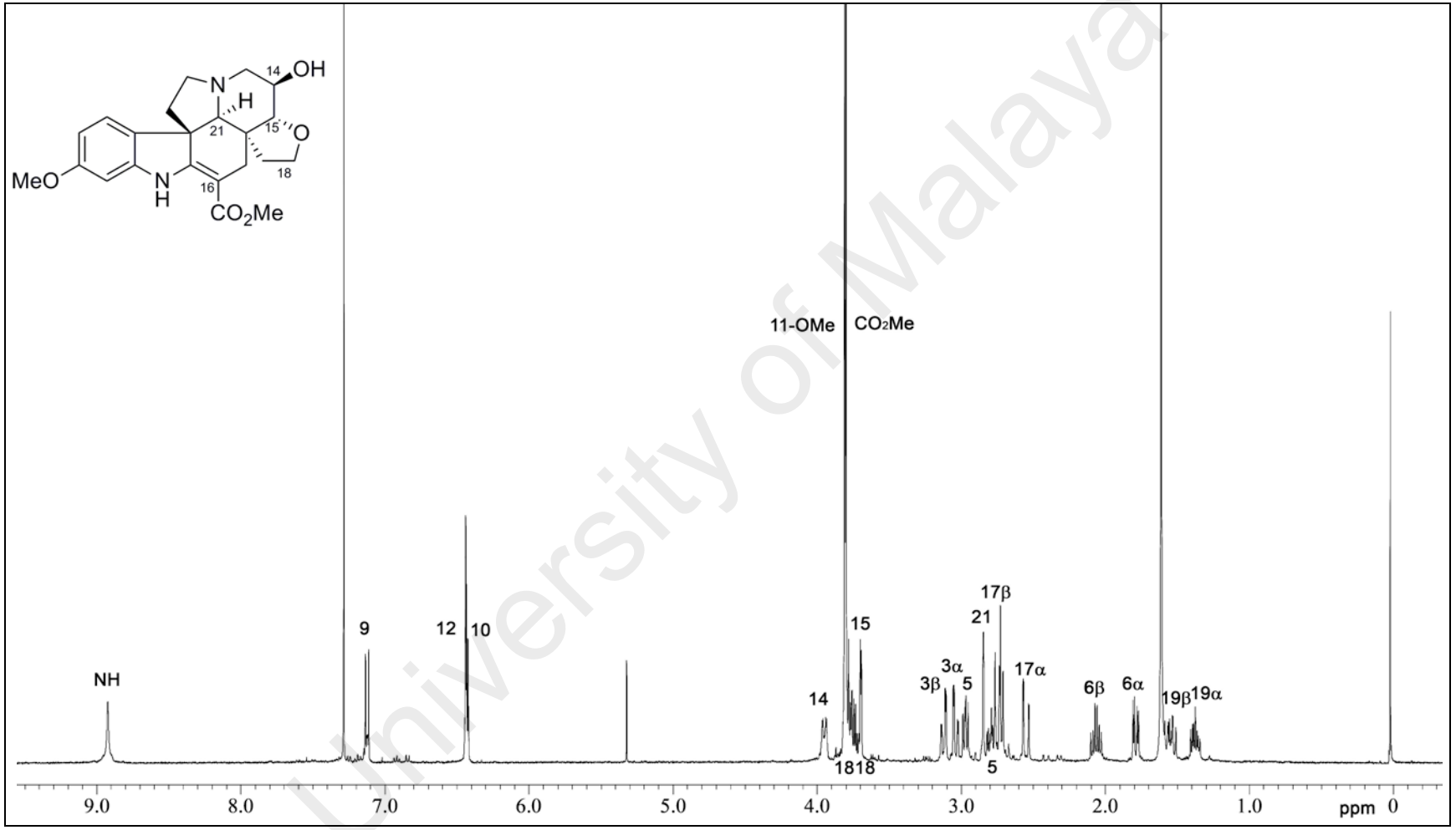


Figure 2.67: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of Apocidine C (**22**)

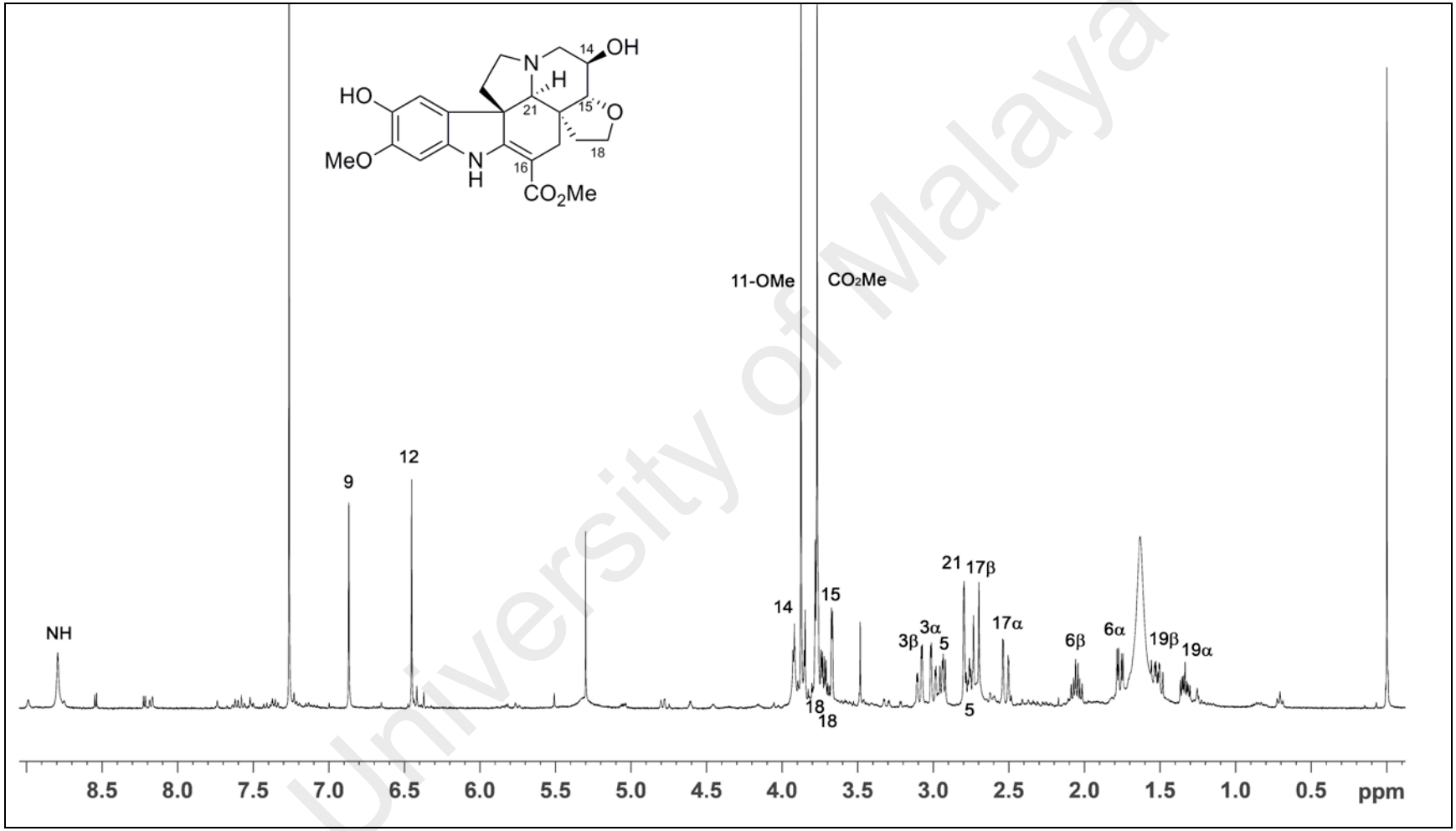


Figure 2.68: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of Apocidine D (**23**)

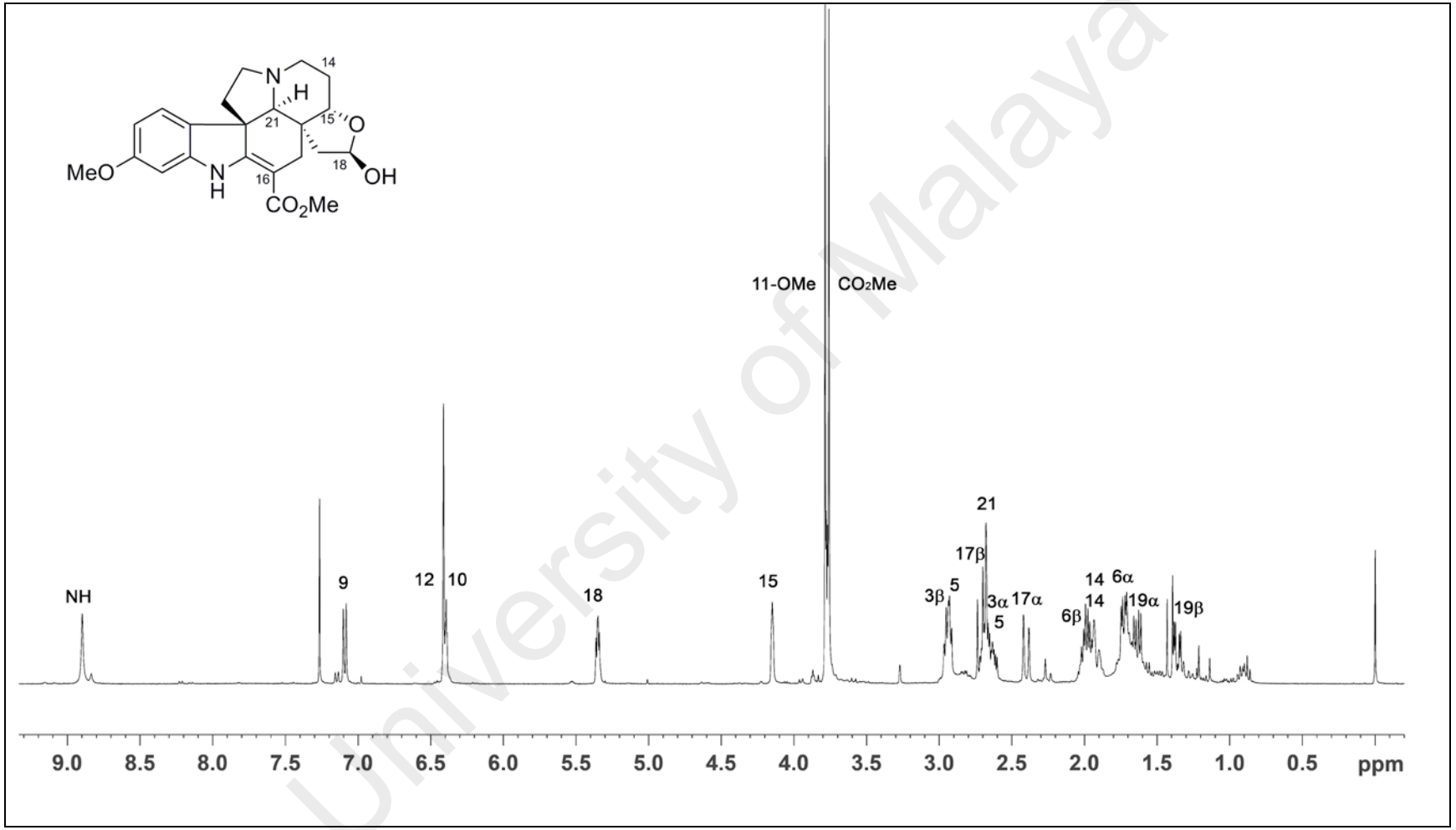


Figure 2.69: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of Apocidine E (**24**)

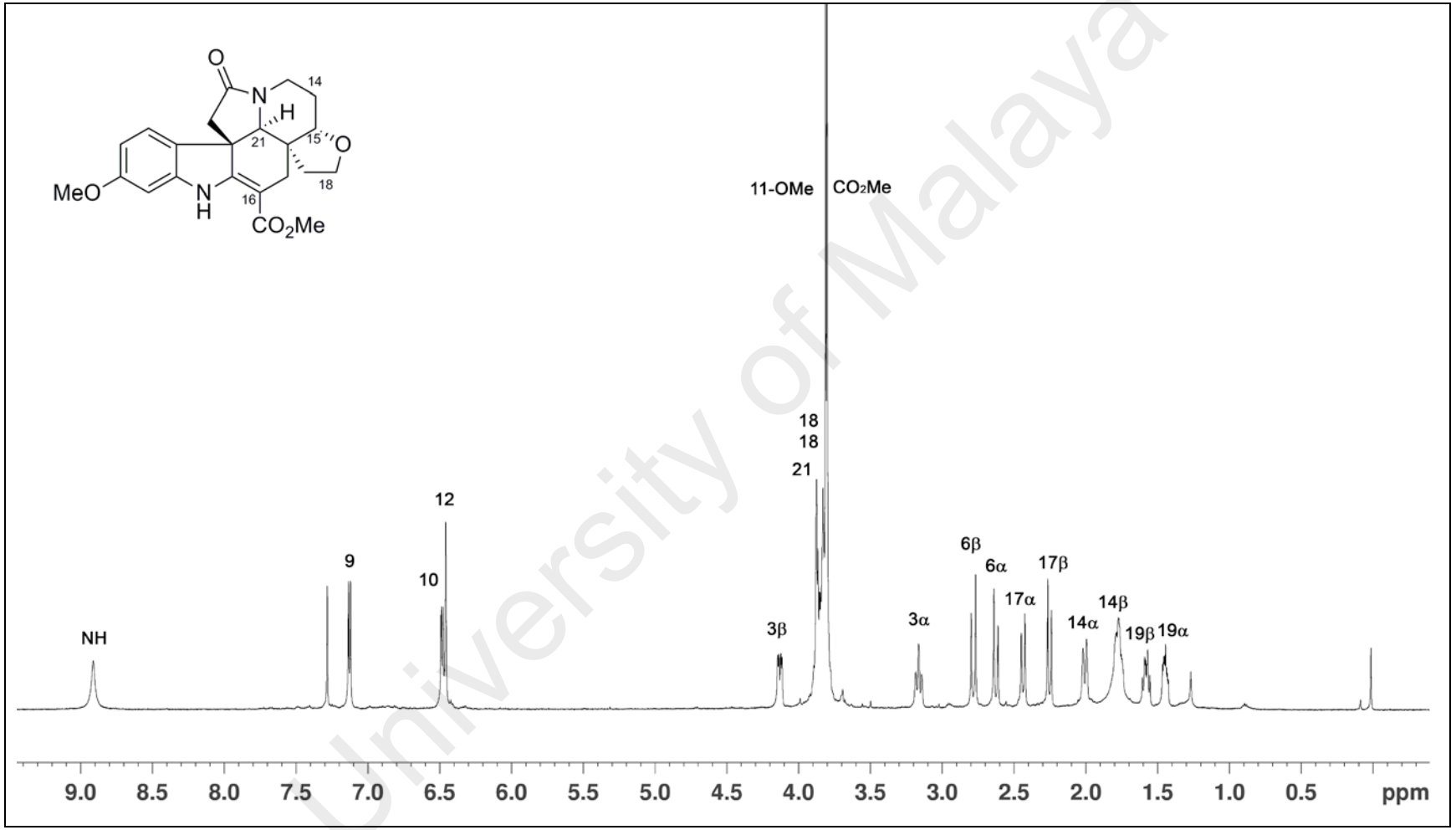


Figure 2.70: ^{1}H NMR spectrum ($CDCl_3$, 600 MHz) of Apocidine F (**25**)

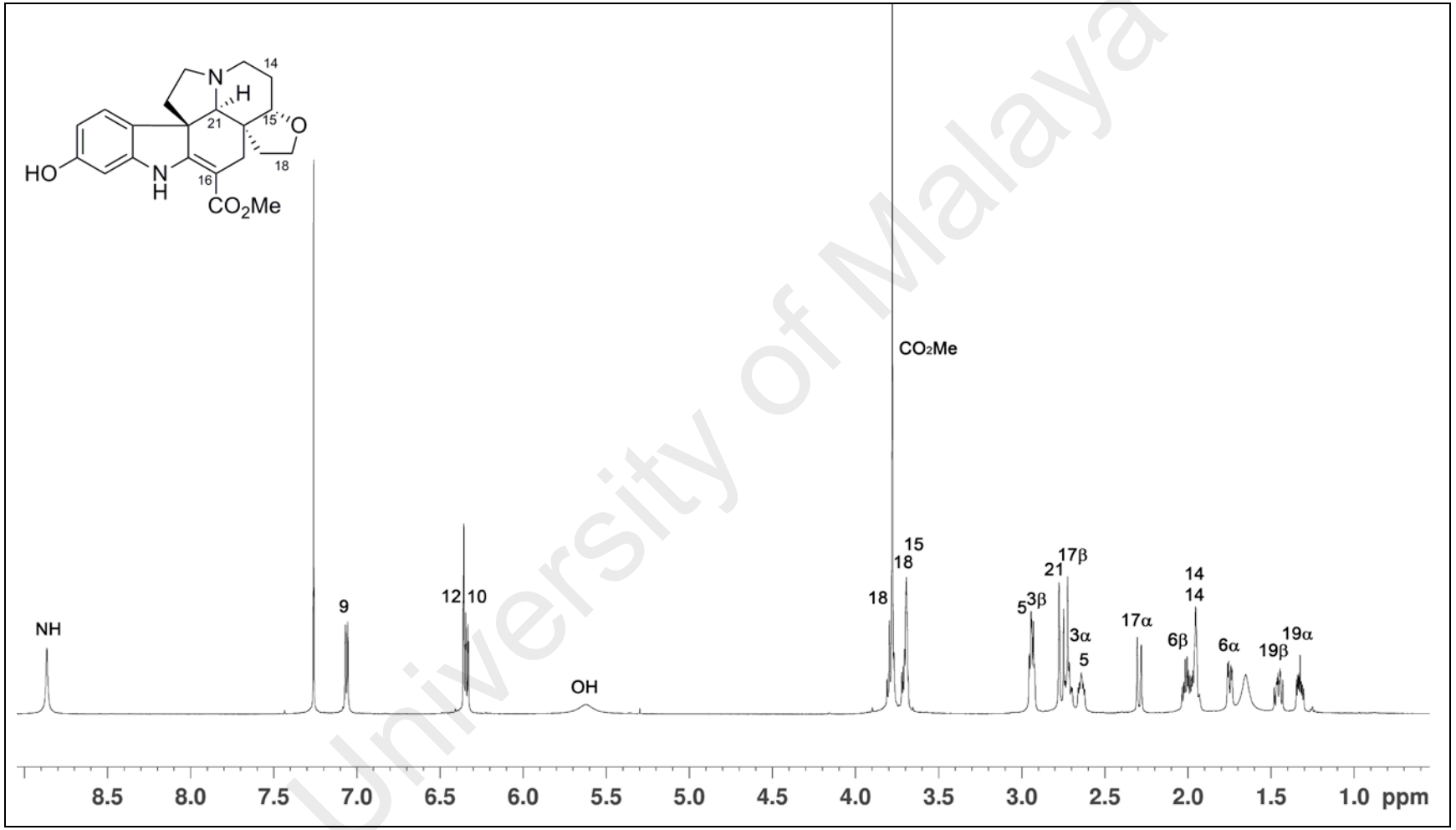


Figure 2.71: ^{1}H NMR spectrum ($CDCl_3$, 600 MHz) of Apocidine G (**26**)

2.1.6.8 Hedrantherine (27), Deoxoapodine (28), and Vandrikine (29)

Three known alkaloids belonging this group, *viz.*, hedrantherine (**27**),[409] deoxoapodine (**28**),[144,410–412] and vandrikine (**29**)[411,413,414] were also isolated in the present study. The ^{1}H NMR spectra of these compounds are shown in Figures 2.72–2.74, while the NMR spectroscopic data are summarized in Tables 2.19 and 2.20. Other data are given in the Experimental Section.

Table 2.19: ^{1}H NMR Spectroscopic Data (δ) of Hedrantherine (**27**), Deoxoapodine (**28**), and Vandrikine (**29**)[a]

H	27 (*J*/Hz)	28 (*J*/Hz)	29 (*J*/Hz)
3α	2.65 m	2.71 m	2.68 m
3β	2.95 m	2.92 m	2.94 m
5	2.65 m	2.65 m	2.64 m
5	2.93 m	2.92 m	2.95 m
6	1.75 dd (12, 4)	1.73 dd (11.4, 4)	1.73 dd (11.3, 4)
6	2.00 m	2.00 td (11.4, 6)	2.00 td (11.3, 6)
9	7.19 d (7.8)	7.21 d (7.8)	7.11 d (8.6)
10	6.86 td (7.8, 1)	6.85 td (7.8, 1)	6.39 m
11	7.13 td (7.8, 1)	7.11 td (7.8, 1)	-
12	6.79 d (7.8)	6.78 d (7.8)	6.40 s
14	1.94 m	1.93 m	1.94 m
14	1.94 m	1.93 m	1.94 m
15	4.14 br s	3.66 m	3.68 m
17α	2.39 dd (14.6, 1.6)	2.28 dd (14.6, 1.8)	2.28 d (14.5)
17β	2.72 d (14.6)	2.73 d (14.6)	2.73 d (14.5)
18	5.32 dd (5.9, 4)	3.66 m	3.68 m
18	-	3.73 m	3.76 m
19α	1.58 dd (14, 4)	1.26 ddd (12.7, 8, 4.5)	1.31 ddd (12.5, 8.3, 4.5)
19β	1.34 dd (14, 4)	1.42 ddd (12.7, 9.7, 7.5)	1.44 ddd (12.5, 10, 7.5)
21	2.70 s	2.80 s	2.77 s
CO_2*Me*	3.74 s	3.74 s	3.77 s
OMe	-	-	3.78 s
NH	8.92 br s	8.97 br s	8.86 br s

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

Table 2.20: ^{13}C NMR Spectroscopic Data (δ) of Hedrantherine (**27**), Deoxoapodine (**28**), and Vandrikine (**29**)[a]

C	**27**	**28**	**29**
2	167.2	167.4	167.8
3	45.9	46.1	46.1
5	51.5	51.6	51.5
6	45.2	45.3	45.4
7	55.1	55.2	54.6
8	137.8	137.9	130.4
9	121.4	121.4	121.8
10	120.8	120.8	105.2
11	127.9	127.8	160.2
12	109.5	109.5	96.9
13	143.2	143.2	144.4
14	26.4	26.1	27.0
15	77.9	80.0	80.1
16	93.8	94.0	94.2
17	27.2	27.7	27.7
18	96.5	65.1	65.1
19	43.7	35.0	34.9
20	47.6	46.7	46.8
21	69.6	68.8	68.9
CO_2Me	168.8	168.9	168.9
CO_2*Me*	51.2	51.2	51.2
11-OMe	-	-	55.6

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

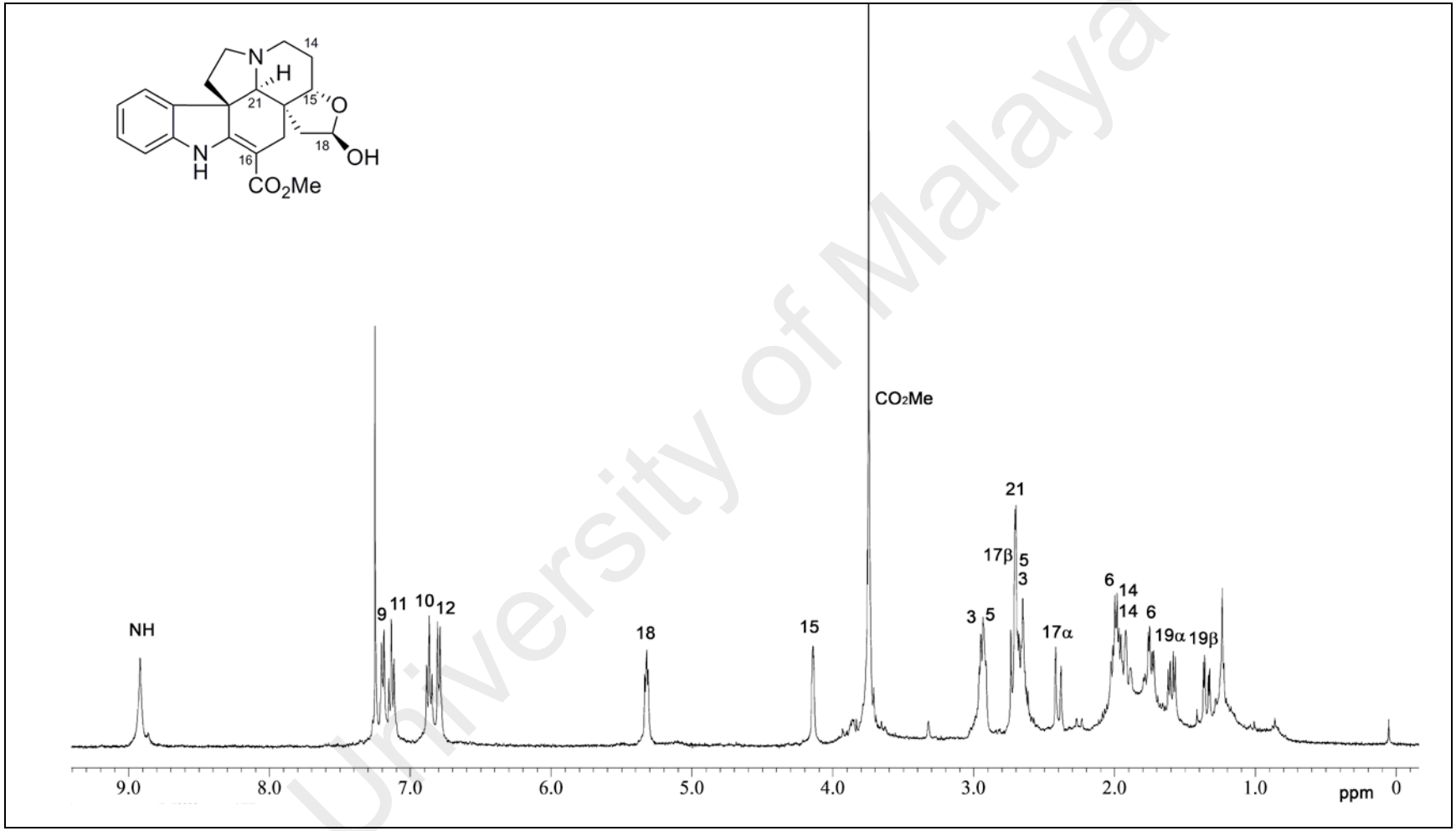


Figure 2.72: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of Hedrantherine (**27**)

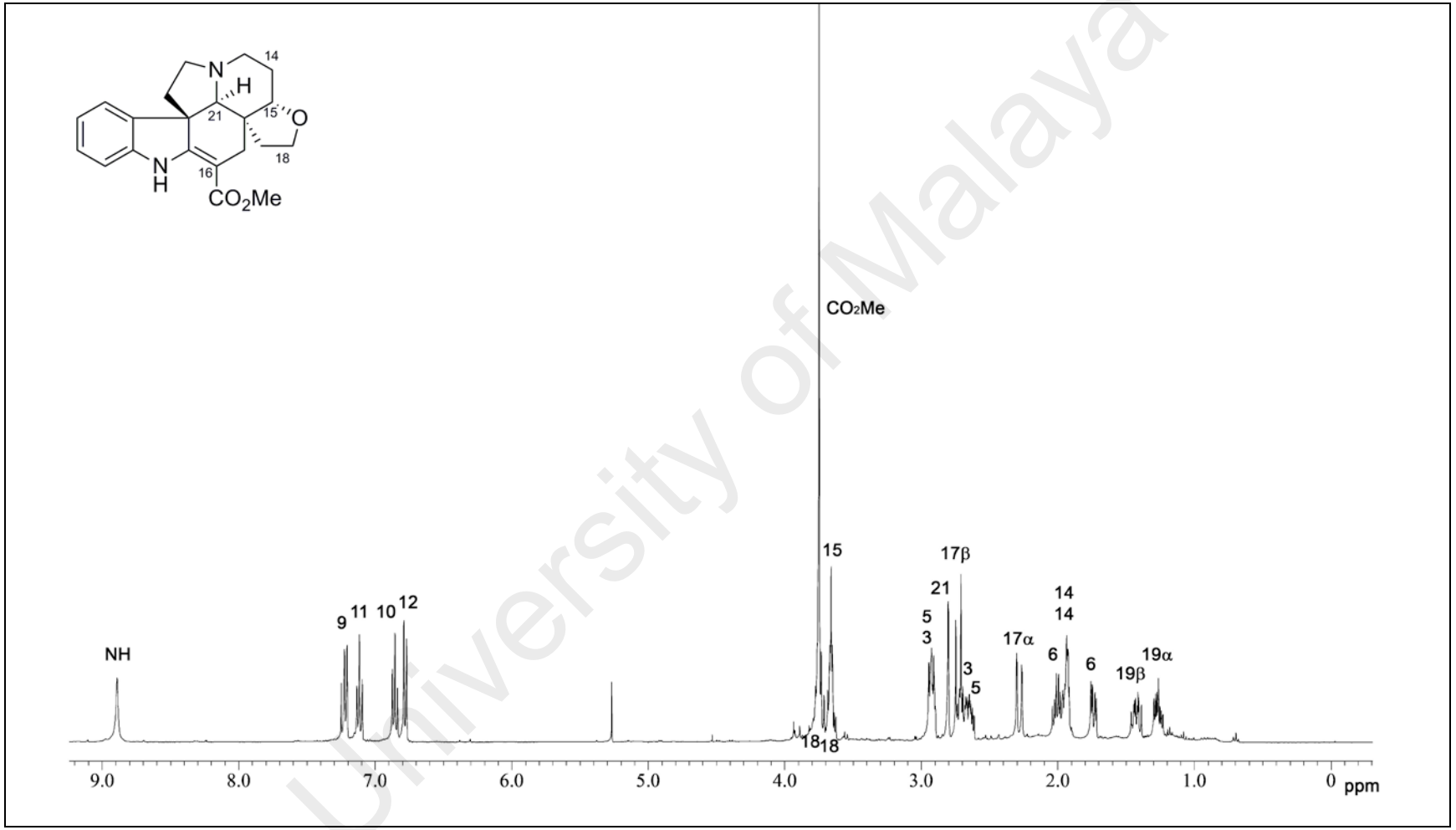


Figure 2.73: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of Deoxoapodine (**28**)

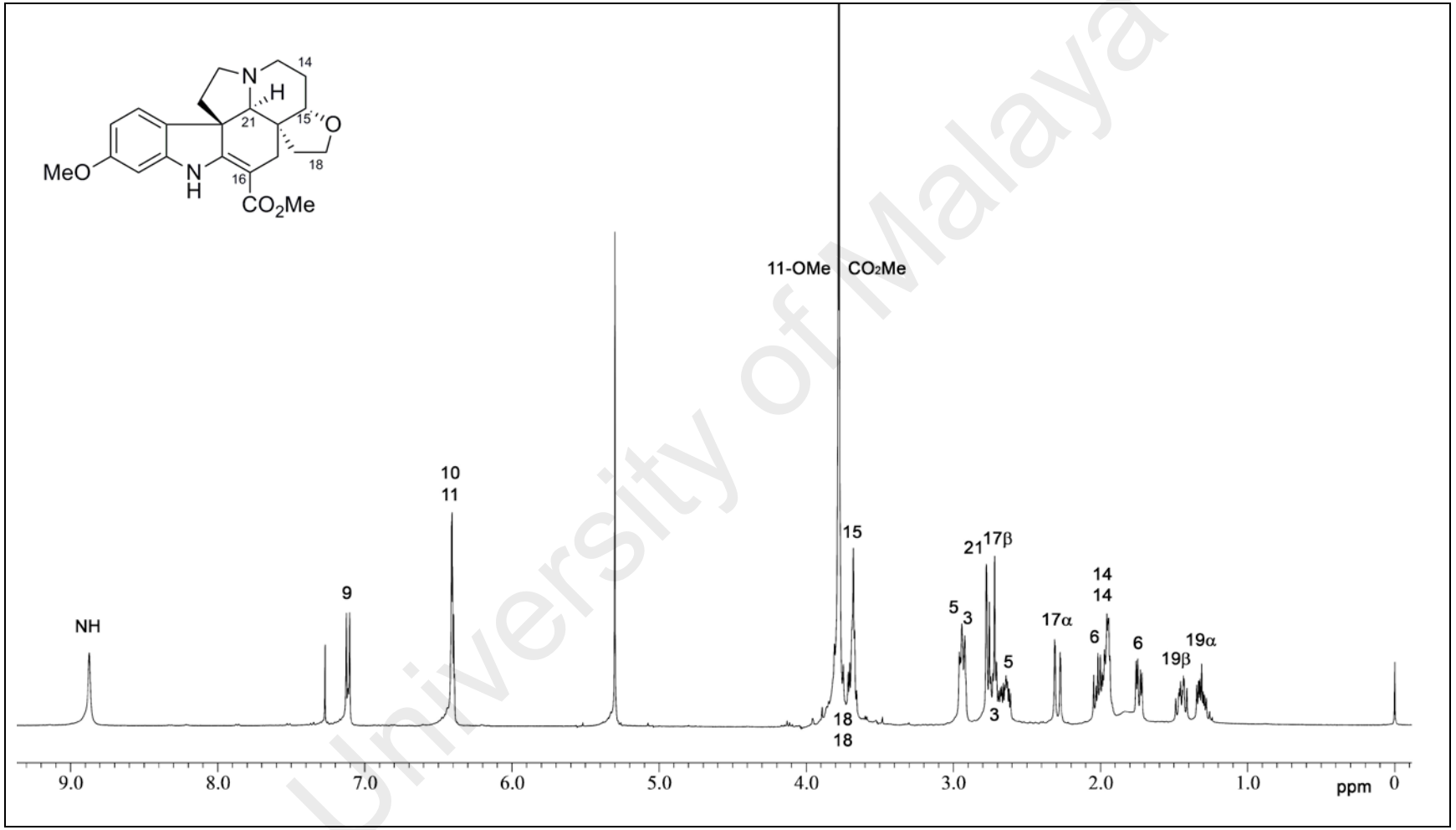
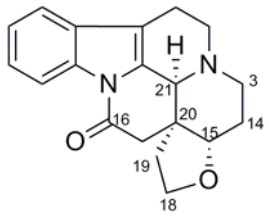


Figure 2.74: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of Vandrikine (**29**)

2.1.7 Eburnan/Vincamine Alkaloids

2.1.7.1 Conoduzidine A (30)



30

Conoduzidine A (**30**)[402] was initially obtained as a colorless oil, which subsequently crystallized from CH_2Cl_2–hexanes as colorless prisms, mp> 252 ^oC (dec) and $[\alpha]^{25}_D$ –31 (*c* 0.12, $CHCl_3$). The UV spectrum showed absorption maxima at 212, 242, 268, 294, and 303 nm indicative of an N-acylindole chromophore, similar to that of eburnamonine. The IR spectrum showed bands at 3428 and 1705 cm^{-1} due to NH and lactam functions, respectively. The ESIMS showed an $[M+H]^+$ peak at *m/z* 309, and HRESIMS measurements gave the molecular formula $C_{19}H_{20}N_2O_2$.

The ^{13}C NMR spectrum (Table 2.22) showed a total of 19 carbon resonances comprising seven methylenes, six methines, two tertiary carbons bonded to the indolic nitrogen (δ 131.7, 134.4), a lactam carbonyl (δ 166.2), and three quaternary carbon atoms. The observed carbon resonances of the methylene at δ 64.4, and the methine at δ 76.0, suggested that these carbons are linked to an oxygen atom. The ^1H NMR spectrum (Figure 2.80, Table 2.21) showed signals due to four aromatic hydrogens of an unsubstituted indole moiety (δ 7.30– 8.38), an isolated aminomethine at δ 4.45 corresponding to H-21, and a pair of AB doublets at δ 2.64 and 3.07 (*J* = 17 Hz) due to the geminally-coupled hydrogens of an isolated methylene (H-17).

The COSY and HMQC data showed the presence of the following partial structures: NCH_2CH_2, NCH_2CH_2CHO, and CH_2CH_2O. The isolated methylene was deduced to be linked to the lactam carbonyl function from the observed ^1H (δ 2.64, 3.07) and ^{13}C (δ 43.3) chemical shifts and the observed large coupling constant (17 Hz) for the geminal hydrogens. Since only two oxygen atoms are present as shown by the molecular formula, the other oxygen must be shared between the two oxygenated fragments in the form of an ether linkage to constitute a $NCH_2CH_2CHOCH_2CH_2$ partial structure. The NCH_2CH_2 fragment corresponds to N–C-5–C-6 from the observed H-5 to C-7 three-bond correlations in the HMBC spectrum (Figure 2.75) and from the H-9/H-6 NOEs (Figure 2.76). The observed three-bond correlations from H-21 to C-3 and C-15, and from H-5 and H-17 to C-21, permitted assembly of the pentacyclic vincamine/eburnan-like ring system. It remains to link the remaining $-OCH_2CH_2$ unit to C-20 to forge the tetrahydrofuran moiety fused to ring D at C-20 and C-15, to complete the hexacyclic ring system of conoduzidine A (**30**).

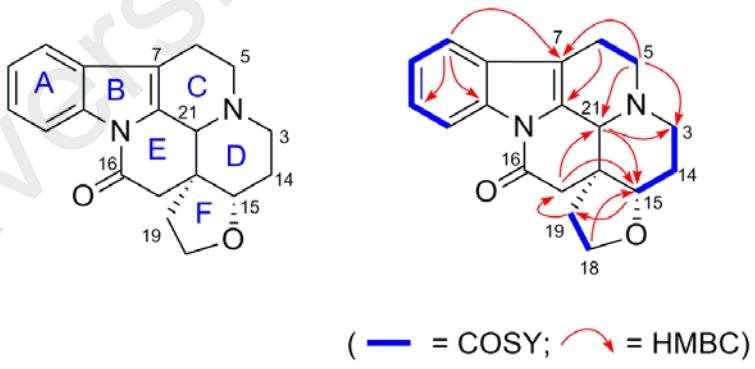
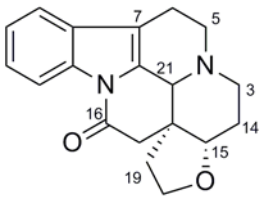
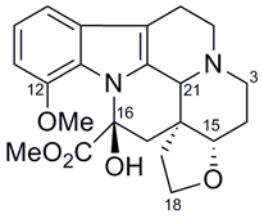


Figure 2.75: COSY and selected HMBCs of **30**



30



592

The absence of Wenkert Bohlmann bands[415,416] in the IR spectrum of **30** indicated a *cis* relationship between H-21 and the N-4 lone pair, in turn suggesting a *cis*-fused C/D ring. The relative configuration and preferred conformation are supported by the observed NOEs (Figure 2.76). The structure of **30** resembles that of the hexacyclic alkaloid cuanzine (**592**), except for the absence of the aromatic methoxy group and replacement of the C-16 methyl ester and hydroxy groups by oxygen, differences which are reflected in the ^{1}H and ^{13}C NMR spectra.[417] In view of the required *cis*-fusion of the tetrahydrofuranyl moiety, the configuration at C-20 and C-21 will determine the absolute configuration, which was provided by an X-ray (Cu Kα) diffraction analysis (Figure 2.77).

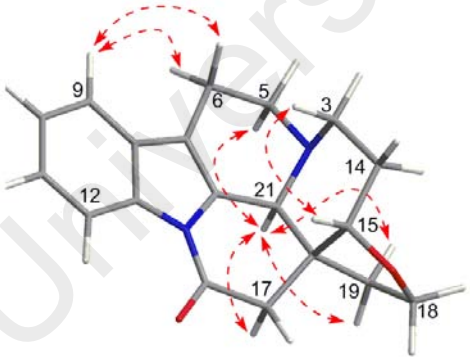


Figure 2.76: Selected NOEs of **30**

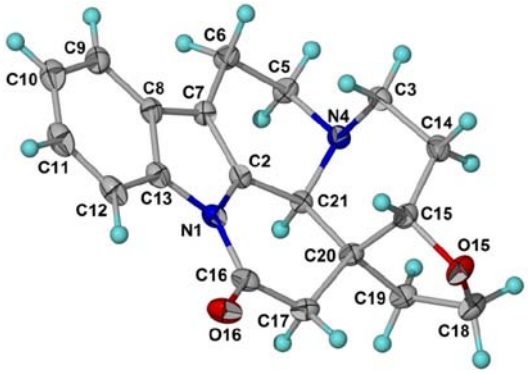
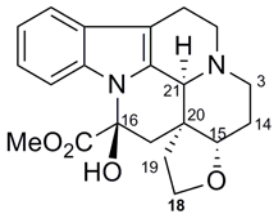
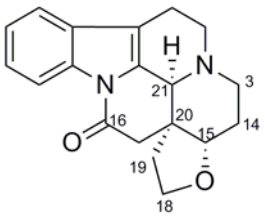


Figure 2.77: X-ray crystal structure of **30**

2.1.7.2 Conoduzidine B (31)



31



30

Conoduzidine B (**31**) was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ −16 (*c* 0.08, $CHCl_3$). The UV spectrum [227, 274 (sh), 282, and 290 nm] was typical of an indole chromophore. The IR spectrum showed bands at 3302 and 1746 cm^{-1} due to OH and ester carbonyl functions, respectively. The ESIMS showed an $[M + H]^+$ peak at *m/z* 369, and HRESIMS measurements gave the molecular formula $C_{21}H_{24}N_2O_4$.

The ^{13}C NMR data (Table 2.22) showed a total of 21 carbon resonances comprising one methyl, seven methylenes, six methines, two tertiary carbons bonded to the indolic nitrogen (δ 131.2, 134.5), a secondary carbon bonded to two heteroatoms (δ 82.0), an ester carbonyl (δ 173.9), and three quaternary carbon atoms. The ^1H NMR spectrum (Figure 2.81, Table 2.21) showed many features which were common with that of **30** such as the presence of four aromatic hydrogens (δ 7.08– δ 7.49), an isolated aminomethine at δ 4.42 corresponding to H-21, and a pair of AB doublets at δ 2.26 and 2.48 (*J* = 14 Hz, H-17). The COSY and HSQC data showed the presence of similar NCH_2CH_2, NCH_2CH_2CHO, and CH_2CH_2O partial structures (corresponding to N–C-5–C-6, N–C-3–C-14–C-15–O and O–C-18–C-19 units, respectively) similar to that of conoduzidine A (**30**), suggesting **31** possesses a similar eburnan/vincamine-like skeleton incorporating a tetrahydrofuranyl moiety.

The major differences shown by the NMR data of **31** compared to those of **30** are the absence of the C-16 lactam carbonyl resonance at δ 166.2 in the ^{13}C NMR spectrum of **31** and its replacement by a resonance at δ 82.0, and the appearance of signals due to a carbomethoxy group (δ_C 173.9, 54.4; δ_H 3.86) and an OH function (δ_H 4.62). These observations are consistent with hydroxy and carbomethoxy substitution at C-16.

In the case of **31**, the absence of a lactam function at C-16 has resulted in an upfield shift of H-12 from δ 8.38 in **30** to δ 7.08 in **31**, a consequence of loss of anisotropy exerted by the C-16 lactam carbonyl. The absence of an α-carbonyl in **31** has also resulted in a corresponding decrease in the H-17 geminal coupling constant (J = 14 Hz in **31** *vs* 17 Hz in **30**). The NOEs (Figure 2.78) observed for H-21/H-5α, H-17α, H-19 and H-3β/H-15 confirmed the relative configurations at C-15, C-20, and C-21. The β-orientation of the OH group at C-16 was indicated by the significant downfield shift observed for H-15 (δ 4.49) due to the spatially proximate OH group. Compound **31** (desmethoxy cuanzine) has been previously synthesized in racemic form[418,419] but is isolated as an optically active alkaloid for the first time in the present study.

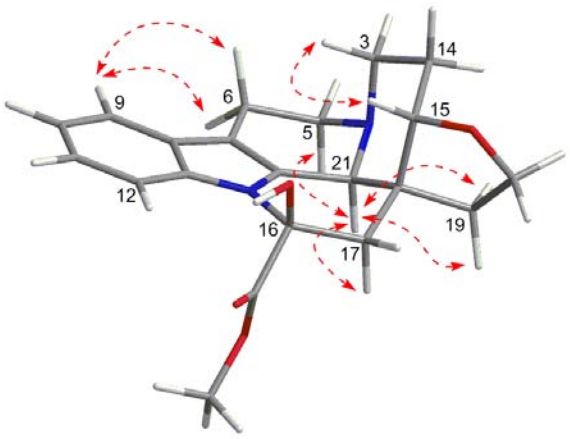
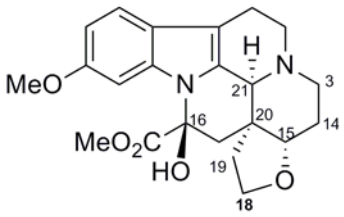
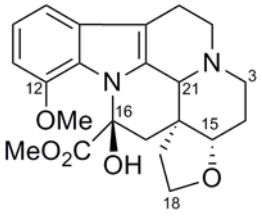


Figure 2.78: Selected NOEs of **31**

2.1.7.3 Conoduzidine C (32)



32

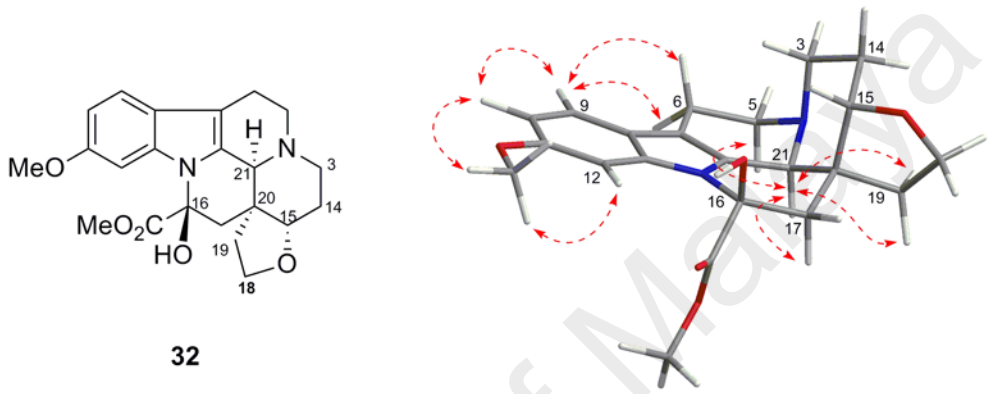


592

Conoduzidine C (**32**) was isolated as a yellowish oil, with $[\alpha]^{25}_{D}$ –19 (*c* 0.2, $CHCl_3$). The ESIMS showed an $[M + H]^+$ peak at *m/z* 399, and HRESIMS measurements gave the molecular formula $C_{22}H_{26}N_2O_5$ (i.e., isomeric with cuanzine **592**). The UV (229, 274, 297, 306 nm) and IR (3428, 1705 cm^{-1}) data were also similar to those of cuanzine (**592**).

The ^{13}C NMR data (Table 2.22) showed a total of 22 carbon resonances [two methyl, seven methylenes, five methines, two tertiary carbons bonded to the indolic nitrogen (δ 130.0, 135.2), a methoxy-substituted aromatic carbon (δ 156.4), a secondary carbon bonded to two heteroatoms (δ 82.1), an ester carbonyl (δ 174.0), and three quaternary carbon atoms]. The ^1H NMR spectrum (Figure 2.82, Table 2.21) showed signals due to three aromatic hydrogens (δ 6.59–7.34), two methoxy groups (δ 3.79, 3.85), an isolated aminomethine at δ 4.37 corresponding to H-21, and a pair of AB doublets at δ 2.23 and 2.45 (*J* = 14 Hz) due to the geminally-coupled hydrogens of an isolated methylene (H-17). The COSY and HSQC data disclosed partial structures that are characteristic of a cuanzine-type skeleton, i.e, NCH_2CH_2, NCH_2CH_2CHO, and CH_2CH_2O, corresponding to N–C-5–C-6, N–C-3–C-14–C-15–O and O–C-18–C-19 units, respectively. Examination of the NMR data of **32** showed a similarity to those of cuanzine (**592**)[417,420] except for the aromatic resonances (δ 7.34, d, *J* = 8 Hz, H-9; 6.79,

dd, *J* = 8, 2 Hz, H-10; 6.59, br d, *J* = 2 Hz, H-12) which indicated methoxy-substitution at C-11 in **32** instead of C-12 in cuanzine (**592**). The observed NOEs (H-9/H-6, 11-OMe/H-10, H-12) were also consistent with this assignment. The relative configurations at the various stereogenic centers were deduced to be similar to those of cuanzine (**592**) from the examination of the NOESY data (Figure 2.79).

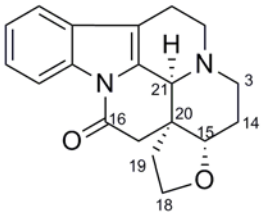


32

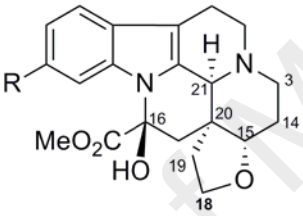
Figure 2.79: Selected NOEs of **32**

2.1.7.4 14,15-Dehydro-16-*epi*-vincamine (33)

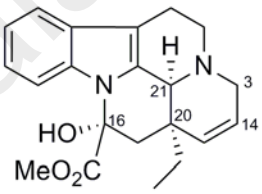
In addition to the three new vincamine-type alkaloids (conoduzidines A–C, **30**–**32**), a known vincamine-type alkaloid, *viz.*, 14,15-dehydro-16-*epi*-vincamine (**33**)[323,421–423] was also isolated in this study. The ^{1}H NMR spectra of these compounds are shown in Figures 2.80 and 2.93, and the NMR spectroscopic data are summarized in Tables 2.21 and 2.22. Other data are given in the Experimental Section.



30



31 R = H
32 R = OMe



33

Table 2.21: ^{1}H NMR Spectroscopic Data (δ) of Conoduzidine A (**30**), Conoduzidine B (**31**), Conoduzidine C (**32**), and 14,15-Dehydro-16-*epi*-vincamine (**33**)[a]

H	**30 (*J*/Hz)**	**31[b] (*J*/Hz)**	**32 (*J*/Hz)**	**33 (*J*/Hz)**
3	2.49 m	2.55 m	2.53 m	3.00 m
3	2.49 m	2.55 m	2.53 m	3.00 m
5	3.30 m	3.34 m	3.30 m	3.24 m
5	3.30 m	3.34 m	3.30 m	3.37 dd (13.7, 7)
6	2.55 m	2.59 m	2.57 m	2.51 ddd (16, 6, 1.5)
6	2.88 m	2.95 dddd (18, 10, 7.5, 2.5)	2.91 m	3.09 m
9	7.44 dd (7.3, 1.4)	7.49 m	7.34 d (8)	7.43 m
10	7.30 td (7.3, 1.4)	7.15 m	6.79 dd (8, 2)	7.10 m
11	7.34 td (7.3, 1.4)	7.14 m	-	7.09 m
12	8.38 d (7.3)	7.08 m	6.59 br d (2)	7.45 m
14	1.69 m	1.72 m	1.70 m	5.46 dt (10, 3)
14	1.69 m	1.72 m	1.70 m	-
15	3.59 dd (10, 7)	4.49 dd (10.7, 6.5)	4.48 dd (10.4, 6.5)	5.24 br d (10)
17α	2.64 d (17)	2.26 d (14)	2.23 d (14)	2.02 d (14)
17β	3.07 d (17)	2.48 d (14)	2.45 d (14)	2.56 d (14)
18	4.02 m	4.00 q (8.7)	3.98 q (8.6)	0.92 t (7.5)
18	4.02 m	4.05 m	4.03 m	-
19	1.74 m	1.63 m	1.60 m	1.45 dq (15, 7.5)
19	2.82 m	2.84 ddd (12.5, 10, 9)	2.82 m	1.78 dq (15, 7.5)
21	4.45 br t (2.5)	4.42 br s	4.37 br s	3.79 br s
CO_2*Me*	-	3.86 s	3.85 s	3.46 s
OMe	-	-	3.79 s	-
OH	-	4.62 br s	4.65	4.16 br s

[a]$CDCl_3$, 400 MHz; [b]$CDCl_3$, 600 MHz; assignments based on COSY, HMQC/HSQC, and NOESY/1D NOE.

Table 2.22: ^{13}C NMR Spectroscopic Data (δ) of Conoduzidine A (**30**), Conoduzidine B (**31**), Conoduzidine C (**32**), and 14,15-Dehydro-16-*epi*-vincamine (**33**)[a]

C	**30**	**31**[b]	**32**	**33**
2	131.7	131.2	130.0	132.8
3	42.4	42.6	42.6	43.9
5	50.5	50.7	50.8	49.8
6	17.0	17.3	17.4	16.7
7	112.6	106.2	106.0	106.5
8	129.9	128.9	123.2	129.0
9	118.4	118.7	119.2	118.1
10	124.2	120.6	109.6	120.3
11	124.7	122.1	156.4	121.7
12	116.4	110.4	95.3	112.7
13	134.4	134.5	135.2	136.7
14	27.9	27.7	27.8	125.8
15	76.0	74.3	74.4	126.8
16	166.2	82.0	82.1	83.9
17	43.3	42.8	42.9	46.0
18	64.4	64.0	64.0	8.5
19	33.8	34.4	34.4	35.4
20	46.6	43.7	43.7	38.5
21	55.5	56.3	56.4	57.1
CO_2Me	-	173.9	174.0	172.3
CO_2*Me*	-	54.4	54.4	52.7
OMe	-	-	55.9	-

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

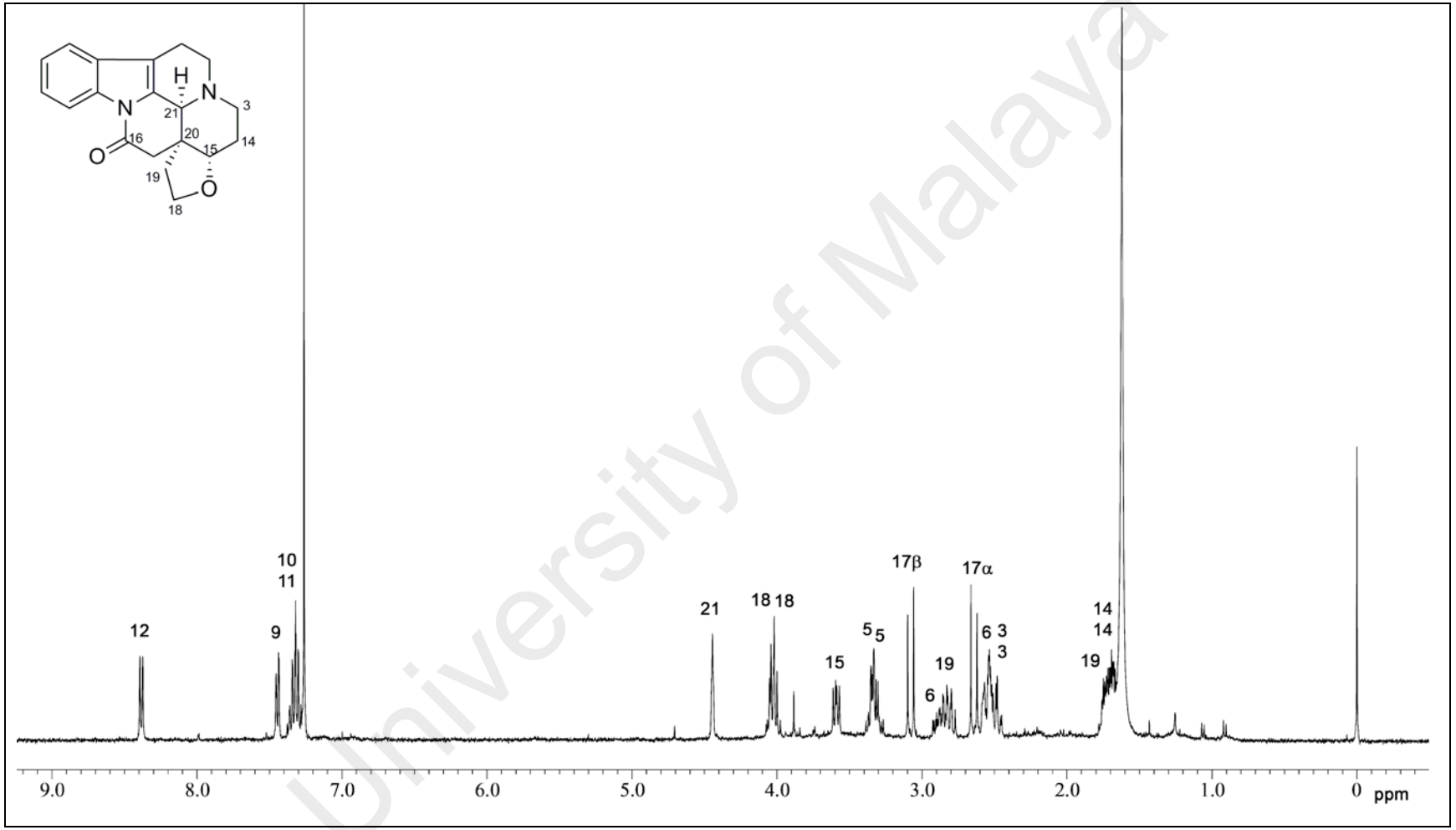


Figure 2.80: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of Conoduzidine A (**30**)

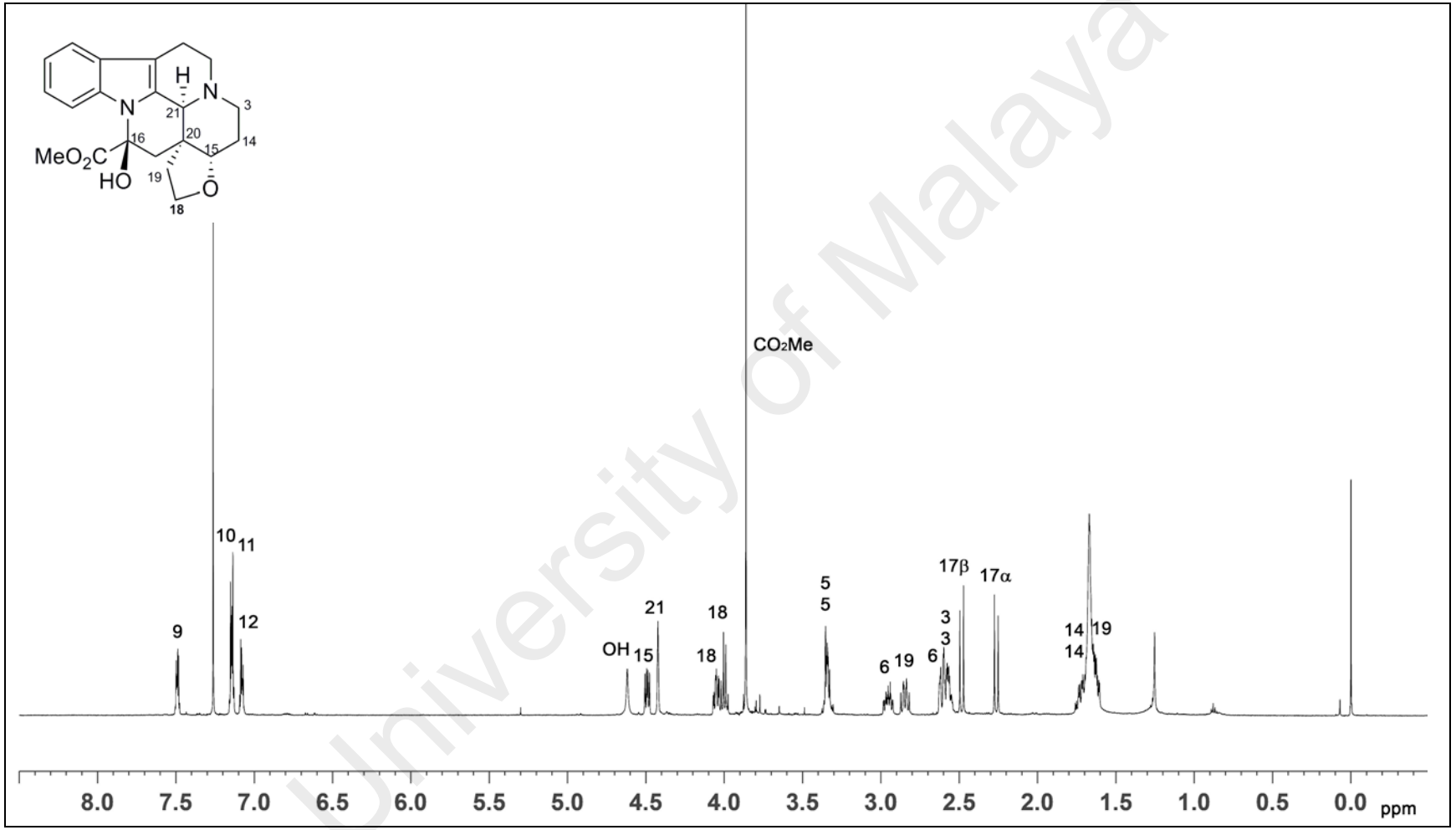


Figure 2.81: ^{1}H NMR spectrum ($CDCl_3$, 600 MHz) of Conoduzidine B (**31**)

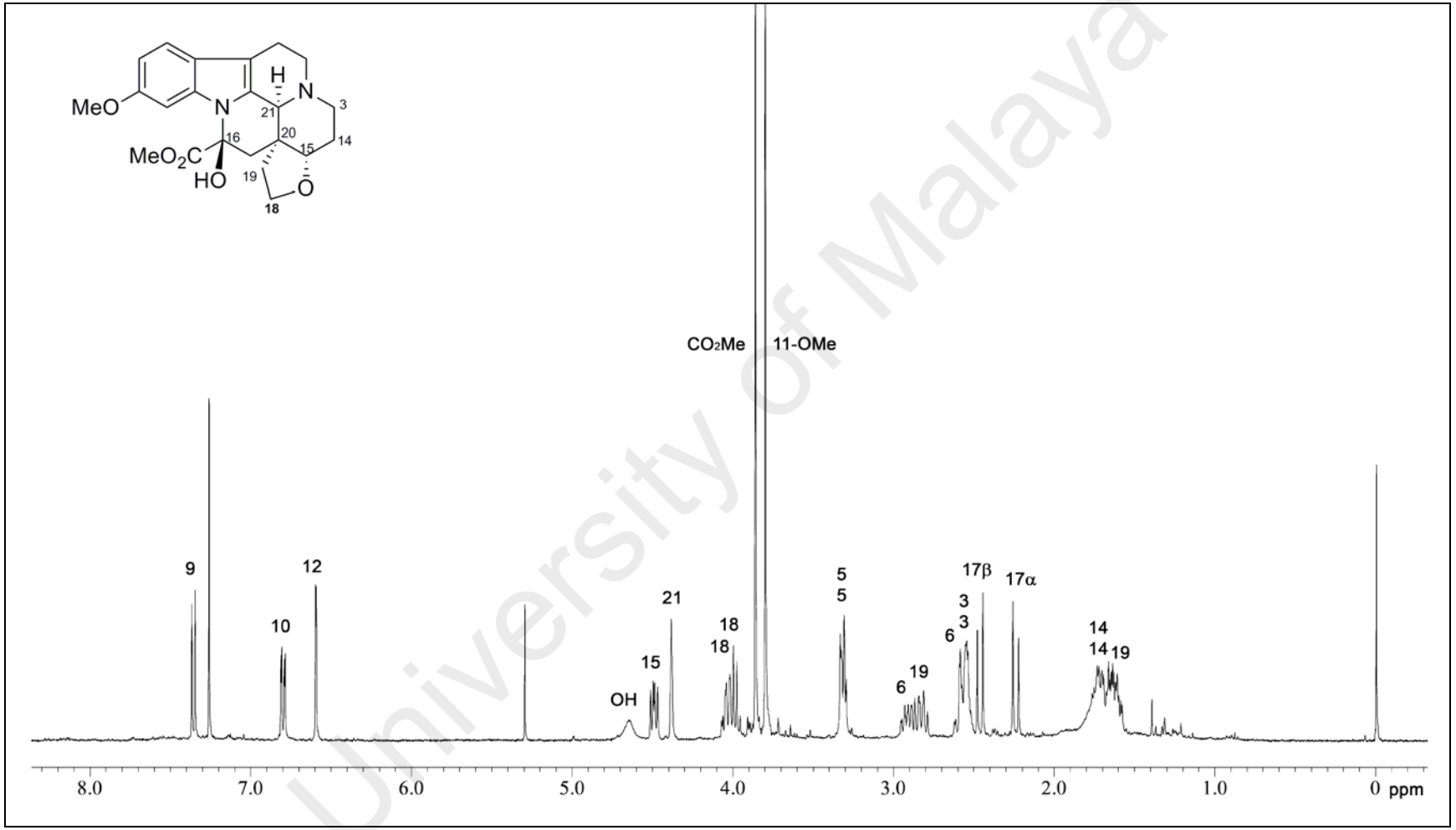


Figure 2.82: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of Conoduzidine C (**32**)

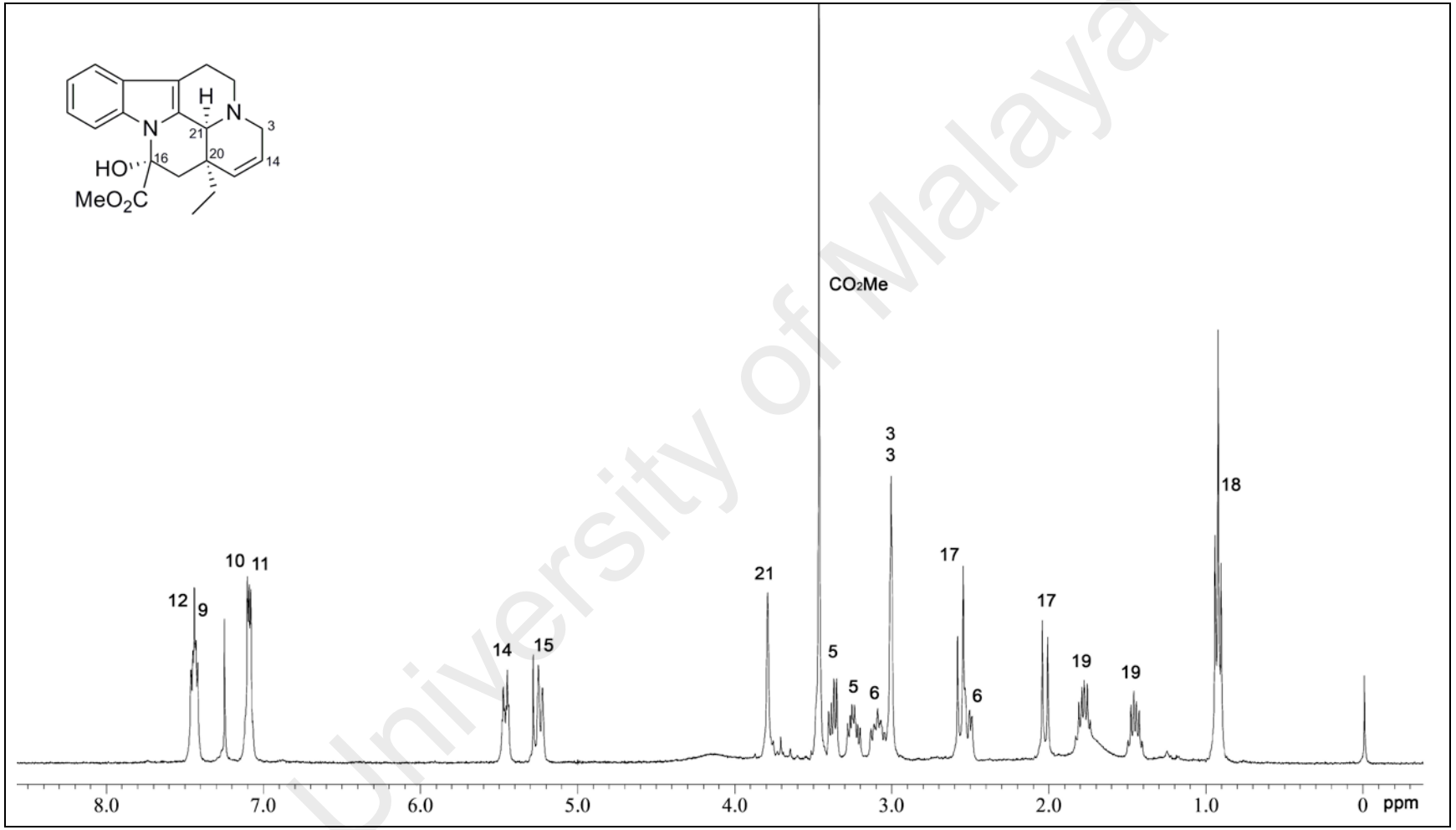


Figure 2.83: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of 14,15-Dehydro-16-*epi*-vincamine (**33**)

2.1.8 Corynanthean Alkaloids

2.1.8.1 16α-Methoxycarbonyl-16,17-dihydro-19-*epi*-ajmalicine (34)

Compound **34** was obtained as a light yellowish oil, with $[\alpha]^{25}_{D}$ +5 (*c* 0.16, $CHCl_3$). The UV spectrum showed absorption maxima at 226, 275 (sh), 283, and 291 nm, indicative of an indole chromophore. The IR spectrum indicated the presence of NH (3289 cm^{-1}) and ester carbonyl (1726 cm^{-1}) functions. In addition, Wenkert-Bohlmann bands were observed at 2817 and 2756 cm^{-1}.[415,416] The ESIMS showed an $[M + H]^+$ peak at *m/z* 355, and HRESIMS measurements established the molecular formula as $C_{21}H_{26}N_2O_3$.

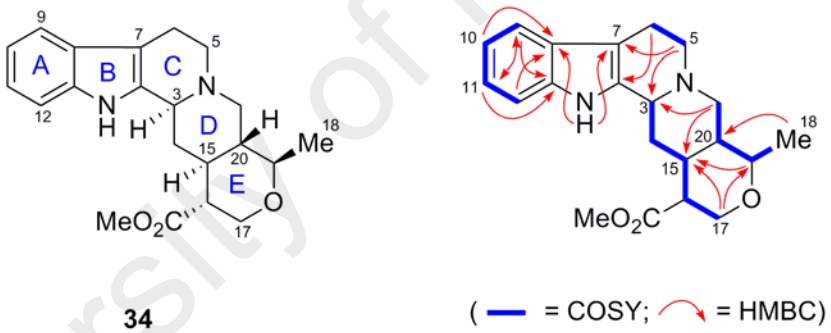
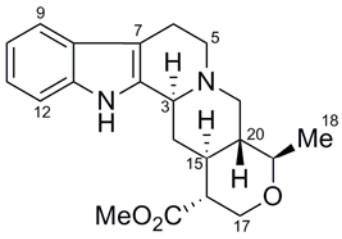


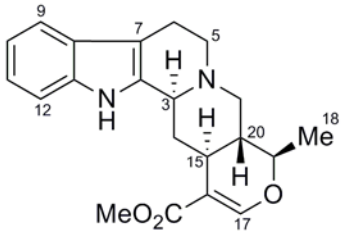
Figure 2.84: COSY and selected HMBCs of **34**

The ^{13}C NMR spectrum (Table 2.23) showed a total of 21 carbon resonances (two methyls, five methylenes, nine methines, one carbonyl carbon, two tertiary carbons linked to the indolic nitrogen, and two quaternary carbon atoms). The ^{1}H NMR spectrum (Figure 2.86, Table 2.23) showed the presence of four aromatic resonances of an unsubstituted indole moiety (δ 7.08–7.46), an indolic NH (δ 7.81), a methyl ester (δ 3.76), and a methyl doublet (δ 1.22). The COSY and HSQC data (Figure 2.84) revealed three partial structures, NCH_2CH_2, $NCHCH_2CHCHCH_2O$, and $NCH_2CHCH(CH_3)O$, corresponding to N–C-5–C-6, N–C-3–C-14–C-15–C-16–C-17–O–, and N–C-21–C-

20–C-19(C-18)–O–. These partial structures are characteristic of heteroyohimbine-type alkaloids (Figure 2.84).



34



593

The NMR data of **34** showed a close resemblance to those of 19-*epi*-ajmalicine (**593**),[424,425] except for the absence of signals associated with the trisubstituted C-16–C-17 double bond, such as the olefinic carbon resonances for C-16 (δ 107.8) and C-17 (δ 155.9) in the ^{13}C NMR spectrum and the signal due to the vinylic H-17 (δ 7.56) in the ^{1}H NMR spectrum. These resonances have in **34** been replaced by a methine at C-16 (δ_C 48.2, δ_H 2.56, td, J = 11, 4 Hz) and an oxymethylene at C-17 (δ_C 69.3; δ_H 3.57, t, J = 11 Hz, δ_H 4.13, dd, J = 11, 4 Hz) in **34**, consistent with saturation of the C-16–C-17 bond in **34**. Less substantial changes were observed for the signals of carbons β to C-16 and C-17 in the ^{13}C NMR spectrum.

The C/D ring junction stereochemistry was determined to be *trans* from the diagnostic Wenkert-Bohlmann bands (*vide supra*) in the IR spectrum, as well as from the H-3 coupling constant, which was observed as a broad doublet at δ 3.35 with the $J_{3-14\beta}$ value of 11 Hz, requiring H-3 and H-14β to be in *trans*-diaxial rearrangement. This was also supported by the observed NOEs for H-3/H-5α, H-15 and H-5α/H-21α. The D/E ring junction stereochemistry was deduced to be *trans* from the observed J_{15-20} value of 11 Hz (H-15 and H-20 *trans*-diaxial). The reciprocal NOEs observed for H-16/H-14β, H-16/H-20, H-15/H-17α, H-15/H-19α, and H-15/H-21α indicated that all

these hydrogens are axially oriented with the D- and E-rings adopting chair conformations and with the CO_2Me and Me substituents equatorially oriented (Figure 2.85). This was also in agreement with observed $J_{15\text{-}16}$ and $J_{19\alpha\text{-}20}$ values of 11 Hz.

Compound **34** is therefore the 16,17-dihydro derivative of 19-*epi*-ajmalicine. This compound has been previously obtained as a cyclized product (cyclositsirikine) derived from 16(*R*)-sitsirikine via oxymercuration-deoxymecuration,[426] but is isolated as a natural product for the first time in the present study.

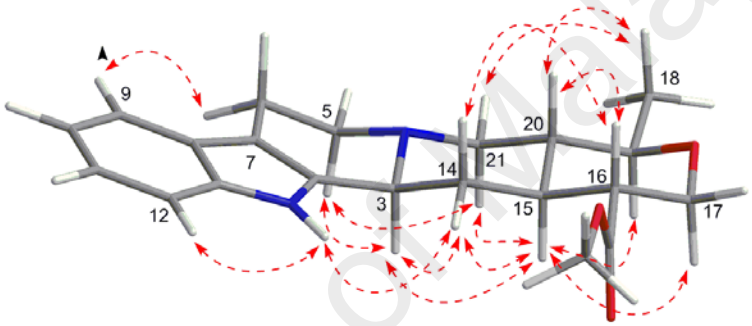


Figure 2.85: Selected NOEs of **34**

Table 2.23: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of 16α-Methoxycarbonyl-16,17-dihydro-19-*epi*-ajmalicine (**34**)[a]

H/C	**δ_C**	**δ_H (*J*/Hz)**
2	134.2	-
3	59.6	3.35 br d (11)
5α	53.3	2.66 td (11, 4)
5β		3.09 m
6α	21.8	2.70 br d (15.3)
6β		3.01 m
7	108.3	-
8	127.4	-
9	118.2	7.46 d (7.5)
10	119.5	7.08 t (7.5)
11	121.6	7.14 t (7.5)
12	110.9	7.29 d (7.5)
13	136.1	-
14β	33.8	1.40 dt (11.6, 11)
14α		2.15 m
15	41.2	1.86 qd (11, 3)
16	48.2	2.56 td (11, 4)
17α	69.3	3.57 t (11)
17β		4.13 dd (11, 4)
18	19.2	1.22 d (6)
19	75.8	3.27 dq (11, 6)
20	45.6	1.58 qd (11, 3.2)
21α	56.6	2.15 m
21β		3.02 dd (11, 3.2)
CO_2Me	173.0	-
CO_2*Me*	52.0	3.76 s
NH	-	7.81 br s

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

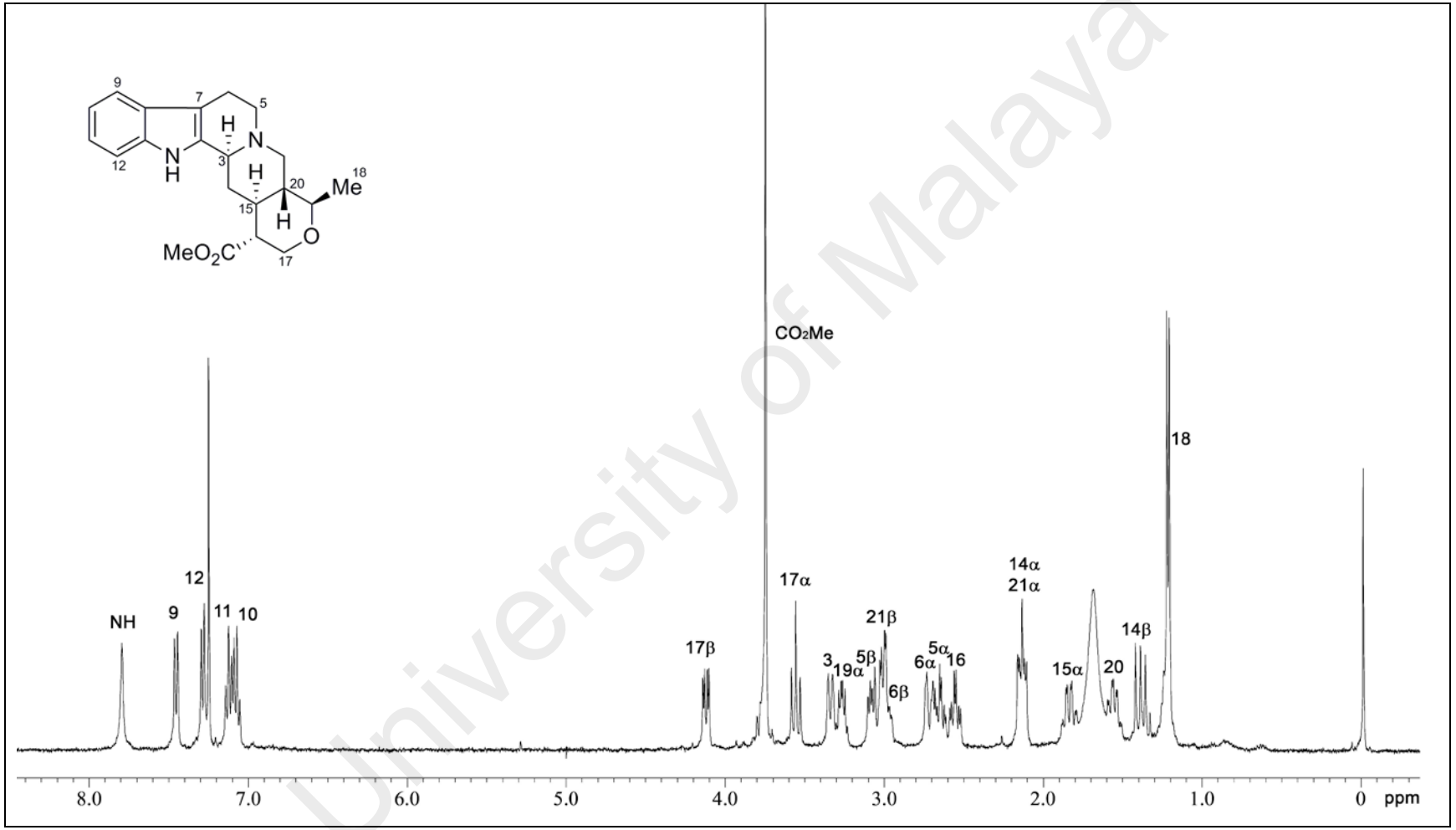
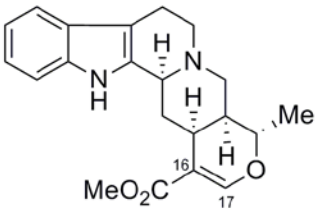


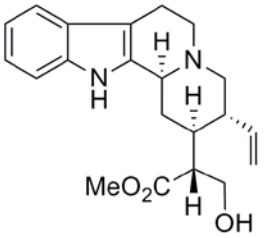
Figure 2.86: ^{1}H NMR spectrum ($CDCl_3$, 400MHz) of 16α-Methoxycarbonyl-16,17-dihydro-19-*epi*-ajmalicine (**34**)

2.1.8.2 Tetrahydroalstonine (35), 16(*R*)-Sitsirikine (36), 16(*R*)-18,19-Dihydrositsirikine (37), β-Yohimbine (38), Yohimbine (39), α-Yohimbine (40), 19,20-Dehydro-α-yohimbine (41), 19,20-Dehydro-β-yohimbine (42), 19,20-Dehydroyohimbine (43), 7(*S*)-β-Yohimbine oxindole (44), 7(*R*)-β-Yohimbine oxindole (45), β-Yohimbine pseudoindoxyl (46), and β-Yohimbine pseudoindoxyl *N*-oxide (47)

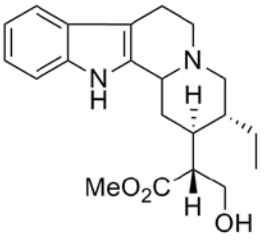
Thirteen known alkaloids belonging to this group, *viz.*, tetrahydroalstonine (**35**),[364,427,428] 16(*R*)-sitsirikine (**36**),[426,429,430] 16(*R*)-18,19-dihydrositsirikine (**37**),[322,429–431] β-yohimbine (**38**),[322,427,432] yohimbine (**39**),[322,427,429] α–yohimbine (**40**),[427,432] 19,20-dehydro-α-yohimbine (**41**),[432] 19,20-dehydro-β-yohimbine (**42**),[322,432] 19,20-dehydroyohimbine (**43**),[433] 7(*S*)-β-yohimbine oxindole (**44**),[322,432] 7(*R*)-β-yohimbine oxindole (**45**),[322,432] β-yohimbine pseudoindoxyl (**46**),[322,432,434] and β-yohimbine pseudoindoxyl *N*-oxide (**47**) were also isolated. β-Yohimbine (**38**) represents the major alkaloid present in both the bark and leaf extracts of this plant. The absolute configuration of 16(*R*)-18,19-dihydrositsirikine (**37**) was confirmed by X-ray analysis (Figure 2.87). The ^{1}H NMR spectra of these compounds are shown in Figures 2.88–2.100, while NMR spectroscopic data are summarized in Tables 2.24–2.30. Other data are given in the Experimental Section.



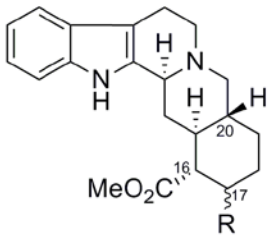
35



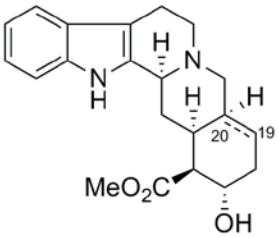
36



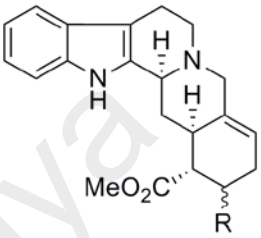
37



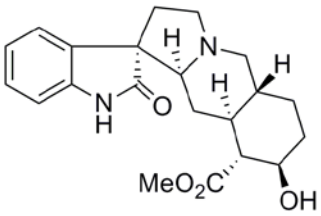
38 R = β-OH
39 R = α-OH



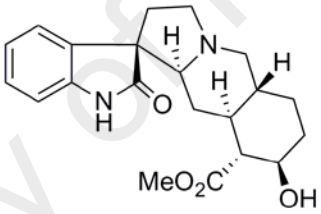
40
41 $\Delta^{19,20}$



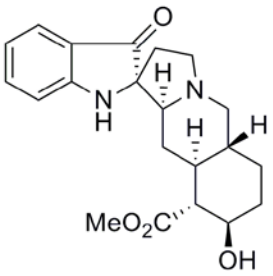
42 R = β-OH
43 R = α-OH



44



45



46
47 N(4)→O

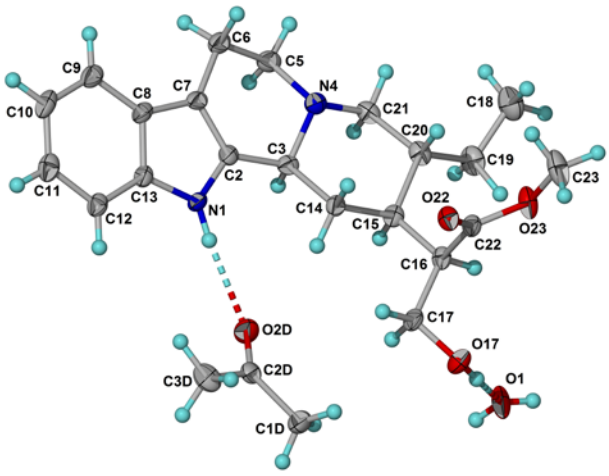


Figure 2.87: X-ray crystal structure of **37**

Table 2.24: ^{1}H NMR Spectroscopic Data (δ) of Tetrahydroalstonine (**35**), 16(*R*)-Sitsirikine (**36**), and 16(*R*)-18,19-Dihydrositsirikine (**37**)[a]

H	**35 (*J*/Hz)**	**36 (*J*/Hz)**	**37 (*J*/Hz)**
3	3.35 dd (12, 2)	3.14 br d (11)	1.47 m
5	2.55 m	2.51 m	2.32 td (11, 4)
5	2.93 m	2.99 m	2.89 m
6	2.69 m	2.68 dd (15, 4)	2.63 dd (16, 4)
6	2.93 m	2.99 m	2.94 m
9	7.27 d (7.5)	7.43 br d (8)	7.42 d (7.8)
10	7.07 td (7.5, 1.5)	7.03 td (7, 1)	7.05 t (7.8)
11	7.12 td (7.5, 1.5)	7.09 td (7, 1)	7.09 t (7.8)
12	7.45 d (7.5)	7.28 br d (8)	7.21 d (7.8)
14	1.53 q (12)	1.34 q (13)	1.23 m
14	2.50 m	2.23 dt (13, 3)	2.06 br d (12.4)
15	2.76 m	1.69 br t (11)	1.41 m
16	-	2.53 m	2.94 m
17	7.56 s	2.14 t (11)	3.59 dd (11, 6.8)
17	-	2.91 m	3.83 dd (11, 6.8)
18	1.40 d (6.2)	5.15 dd (10, 2)	0.84 t (7.5)
18	-	5.20 dd (17, 1)	
19	4.50 dq (10.3, 6.2)	5.52 dt (17, 10)	1.05 m
19	-	-	1.64 m
20	1.69 m	2.91 m	1.53 m
21	2.73 dd (12.3, 2)	3.70 dd (11, 6)	2.72 d (11)
21	3.10 dd (12.3, 3.5)	3.91 dd (11, 7)	2.82 m
CO_2*Me*	3.75 s	3.63 s	3.47 s
NH	7.87 s	8.80 br s	8.68 br s

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

Table 2.25: ^{13}C NMR Spectroscopic Data (δ) of Tetrahydroalstonine (**35**), 16(*R*)-Sitsirikine (**36**), and 16(*R*)-18,19-Dihydrositsirikine (**37**)[a]

C	**35**	**36**	**37**
2	134.5	134.2	134.5
3	59.8	59.8	59.6
5	53.5	52.8	52.8
6	21.7	21.6	21.4
7	108.0	107.7	107.8
8	127.2	127.2	127.3
9	118.0	118.1	118.3
10	114.4	119.3	119.4
11	121.4	121.4	121.4
12	110.8	111.0	111.2
13	136.0	136.2	136.2
14	34.2	31.6	31.6
15	31.3	40.4	39.9
16	109.5	44.6	47.6
17	155.7	61.1	61.1
18	18.5	118.3	10.8
19	72.5	138.4	23.0
20	38.4	48.2	39.4
21	36.3	62.0	59.6
CO_2Me	168.0	174.6	174.6
CO_2*Me*	51.1	51.8	51.8

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

Table 2.26: ^{1}H NMR Spectroscopic Data (δ) of β-Yohimbine (**38**), Yohimbine (**39**), and α-Yohimbine (**40**)[a]

H	**38 (*J*/Hz)**	**39 (*J*/Hz)**	**40 (*J*/Hz)**
3	3.19 br d (10)	3.26 br d (11)	3.15 br d (10.8)
5	2.58 td (11.6, 4)	2.56 td (11, 4)	2.53 m
5	3.05 m	3.05 m	2.97 m
6	2.68 dd (15.6, 4)	2.69 dd (15, 4)	2.68 m
6	2.95 m	2.95 m	2.92 m
9	7.44 d (7.8)	7.43 d (7.8)	7.45 d (7.5)
10	7.06 td (7.8, 1.4)	7.03 td (7.8, 1)	7.07 td (7.5, 1)
11	7.11 td (7.8, 1.4)	7.09 td (7.8, 1)	7.13 td (7.5, 1)
12	7.28 d (7.8)	7.26 d (7.8)	7.30 d (7.5)
14	2.39 m	1.27 td (12, 11)	1.59 m
14	1.91 dt (12, 2.4)	2.02 m	1.70 td (12.5, 10.8)
15	1.48 m	1.93 m	2.44 dq (12.5, 4.3)
16	2.10 t (10.4)	2.30 dd (11.5, 2)	2.55 m
17	3.80 m	4.19 br s	4.00 td (11, 4.3)
18	1.39 m	1.52 m	1.37 tdd (12.5, 11, 4)
18	2.05 m	1.93 m	2.05 m
19	1.12 qd (13, 3)	1.36 m	1.55 m
19	1.66 dq (13, 3)	1.52 m	2.11 m
20	1.48 m	1.52 m	1.82 m
21	2.05 m	2.16 t (11.4)	2.59 dd (11.4, 3)
21	2.96 m	2.88 dd (11.4, 2.3)	2.84 dd (11.4, 2)
CO_2*Me*	3.81 s	3.73 s	3.84 s
NH	7.99 br s	8.51 br s	7.75 br s
OH	-	2.43 br s	-

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

Table 2.27: ^{1}H NMR Spectroscopic Data (δ) of 19,20-Dehydro-α-yohimbine (**41**), 19,20-Dehydro-β-yohimbine (**42**), and 19,20-Dehydroyohimbine (**43**)[a]

H	**41 (*J*/Hz)**	**42 (*J*/Hz)**	**43 (*J*/Hz)**
3	3.43 br d (10.5)	3.39 br d (12)	3.45 br d (11)
5	2.62 td (11, 4)	2.62 td (11.5, 4.3)	2.62 td (11, 4)
5	3.08 m	3.09 ddd (11, 5.8, 1)	3.09 m
6	2.73 m	2.74 m	2.72 dd (14.5, 4)
6	2.97 m	3.00 m	2.99 m
9	7.42 d (7.8)	7.46 d (8)	7.45 d (7.8)
10	7.05 t (7.8)	7.08 ddd (8, 7, 1)	7.07 td (7.8, 1)
11	7.11 t (7.8)	7.14 ddd (8, 7, 1)	7.12 td (7.8, 1)
12	7.28 d (7.8)	7.31 d (8)	7.28 d (7.8)
14	1.54 dt (12.4, 10.5)	1.46 q (12)	1.37 dt (12, 11)
14	1.86 dt (12.4, 3.2)	2.23 ddd (12, 5, 2.5)	2.32 m
15	2.73 m	2.69 dd (12, 11)	2.86 dd (11, 10)
16	2.88 dd (11, 7)	2.43 dd (11, 10.5)	2.44 d (10)
17	4.08 td (11, 5.5)	4.06 td (10.5, 5.5)	4.34 br s
18	2.08 m	2.12 m	2.25 m
18	2.41 dt (13, 5.5)	2.46 m	2.40 m
19	5.57 d (5.5)	5.55 m	5.54 br s
21	2.98 m	2.98 m	3.08 m
21	3.35 d (11)	3.43 d (12.4)	3.42 d (12.8)
CO_2*Me*	3.83 s	3.85 s	3.81 s
NH	8.21 br s	7.81 br s	7.92 br s

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

Table 2.28: ^{13}C NMR Spectroscopic Data (δ) of β-Yohimbine (**38**), Yohimbine (**39**), α-Yohimbine (**40**), 19,20-Dehydro-α-yohimbine (**41**), 19,20-Dehydro-β-yohimbine (**42**), and 19,20-Dehydroyohimbine (**43**)[a]

C	**38**	**39**	**40**	**41**	**42**	**43**
2	134.3	134.4	134.5	133.8	133.7	133.7
3	59.6	60.2	60.3	60.1	59.0	59.5
5	53.0	53.0	53.3	52.6	52.6	52.7
6	21.8	21.6	21.7	21.7	21.6	21.7
7	108.3	107.6	108.5	108.4	108.6	108.5
8	127.4	127.2	127.3	127.3	127.3	127.3
9	118.2	118.1	118.1	118.3	118.2	118.2
10	119.5	119.2	119.5	119.5	119.5	119.5
11	121.5	121.3	121.5	121.6	121.6	121.5
12	110.9	109.9	110.8	111.0	110.8	110.9
13	136.1	136.2	136.0	136.1	136.1	136.2
14	34.2[b]	33.8	27.8	33.9	36.2	36.2
15	42.0	36.6	38.0	39.1	39.3	33.2
16	57.4	52.2	54.7	51.2	55.3	50.5
17	72.3	67.0	66.1	64.5	68.7	66.1
18	34.1[b]	31.6	33.1	32.4	33.9	32.7
19	28.0	23.3	24.6	119.9	119.5	118.2
20	39.9	40.3	36.6	135.1	133.7	134.1
21	61.1	61.3	60.6	62.1	61.2	61.8
CO_2Me	175.2	175.7	174.7	174.2	174.9	175.3
CO_2*Me*	52.1	52.0	52.0	52.1	52.2	52.3

[a]$CDCl_3$, 100 MHz; assignments based on HMQC and HMBC; [b]assignments are interchangeable.

Table 2.29: ^{1}H NMR Spectroscopic Data (δ) of 7(*S*)-β-Yohimbine oxindole (**44**), 7(*R*)-β-Yohimbine oxindole (**45**), β-Yohimbine pseudoindoxyl (**46**), and β-Yohimbine pseudoindoxyl *N*-oxide (**47**)[a]

H	**44 (*J*/Hz)**	**45[b] (*J*/Hz)**	**46 (*J*/Hz)**	**47[b] (*J*/Hz)**
3	2.45 m	2.22 br d (11.3)	2.46 br dd (11, 3)	3.22 dd (11, 2)
5	2.45 m	2.42 m	2.35 m	3.42 q (9.5)
5	3.25 t (9)	3.35 m	3.16 td (9, 2)	3.84 br t (9.5)
6	1.97 m	2.20 m	1.89 m	2.49 m
6	2.34 ddd (11.8, 9, 2)	2.47 m	2.30 m	2.58 m
9	7.35 d (7.5)	7.15 d (7.5)	7. 51 d (7.5)	7.52 d (8)
10	7.01 t (7.5)	7.03 td (7.5, 1)	6.73 td (7.5, 1)	6.74 t (8)
11	7.17 t (7.5)	7.18 td (7.5, 1)	7.40 td (7.5, 1)	7.43 t (8)
12	6.85 d (7.5)	6.86 d (7.5)	6.80 d (7.5)	6.81 d (8)
14	0.73 q (12)	1.19 m	1.08 m	1.02 br dt (13.5, 3)
14	0.99 d (12)	1.28 qd (11.3, 3)	1.16 m	2.02 dt (13.5, 11)
15	1.30 m	1.21 qd (11.3, 3)	1.26 m	1.41 qd (11,
16	1.92 m	2.19 t (11.3)	2.03 m	2.28 t (11)
17	3.73 m	3.72 td (11.3, 4)	3.73 td (11, 4)	3.76 td (11, 4)
18	1.33 m	1.40 m	1.35 qd (11, 4)	1.46 tdd (13, 11, 3.5)
18	2.02 m	2.20 m	2.00 m	2.10 m
19	1.13 m	1.18 m	1.12 m	1.34 qd (13, 3)
19	1.64 br d (12)	1.65 br d (13)	1.64 br d (13)	1.69 m
20	1.26 m	1.45 m	1.23 m	2.31 m
21	1.91 br t (10.5)	1.72 t (10.8)	1.80 t (10.5)	2.80 t (11.5)
21	3.12 d (10.5)	3.21 dd (10.8, 3)	3.05 dd (10.5, 3)	3.57 m
CO_2*Me*	3.57 s	3.56 s	3.51 s	3.58 s
NH	8.25 br s	8.76 br s	5.37 br s	6.66 br s

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

Table 2.30: ^{13}C NMR Spectroscopic Data (δ) of 7(*S*)-β-Yohimbine oxindole (**44**), 7(*R*)-β-Yohimbine oxindole (**45**), β-Yohimbine pseudoindoxyl (**46**), and β-Yohimbine pseudoindoxyl *N*-oxide (**47**)[a]

C	**44**[a]	**45**[b]	**46**[b]	**47**[b]
2	181.5	181.6	74.1	72.2
3	71.1	74.2	71.1	78.6
5	53.4	54.3	52.7	67.7
6	35.5	34.4	35.6	34.5
7	56.6	55.9	202.2	201.0
8	133.6	133.1	118.3	161.3
9	125.1	123.0	124.5	124.6
10	122.6	122.6	120.1	118.1
11	127.8	128.0	137.4	138.3
12	109.6	109.7	111.8	111.8
13	140.1	141.0	160.6	118.1
14	30.3	29.6	28.7	23.6
15	41.5	41.9	41.1	40.2
16	57.7	57.3	57.8	56.6
17	72.2	72.5	71.9	71.7
18	34.1	34.0	34.1	33.8
19	27.9	27.8	27.9	26.9
20	39.7	39.2	39.6	34.2
21	58.5	58.4	58.5	68.8
CO_2Me	174.5	174.9	174.1	173.8
CO_2*Me*	51.8	51.7	51.7	51.8

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

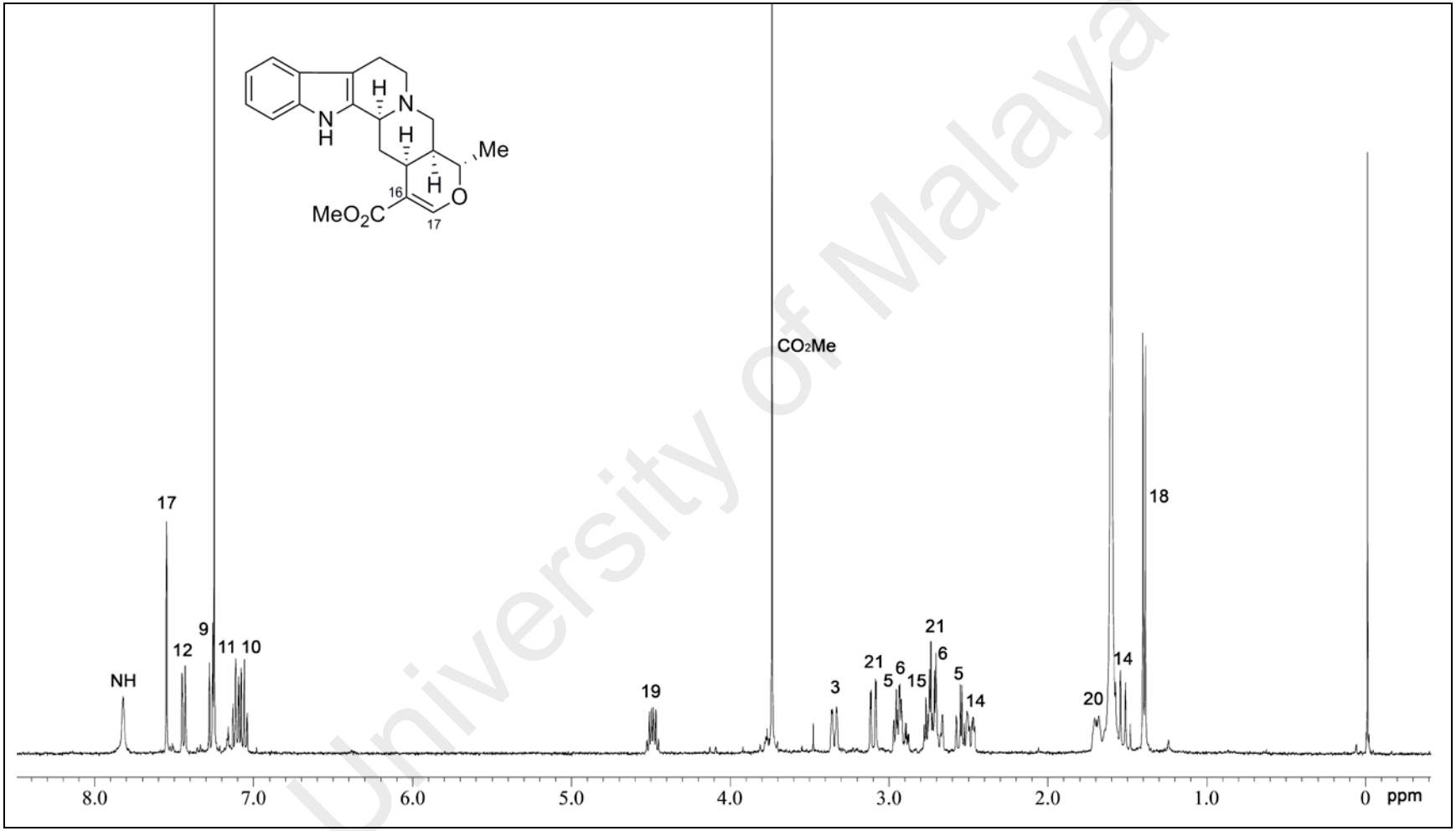


Figure 2.88: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of Tetrahydroalstonine (**35**)

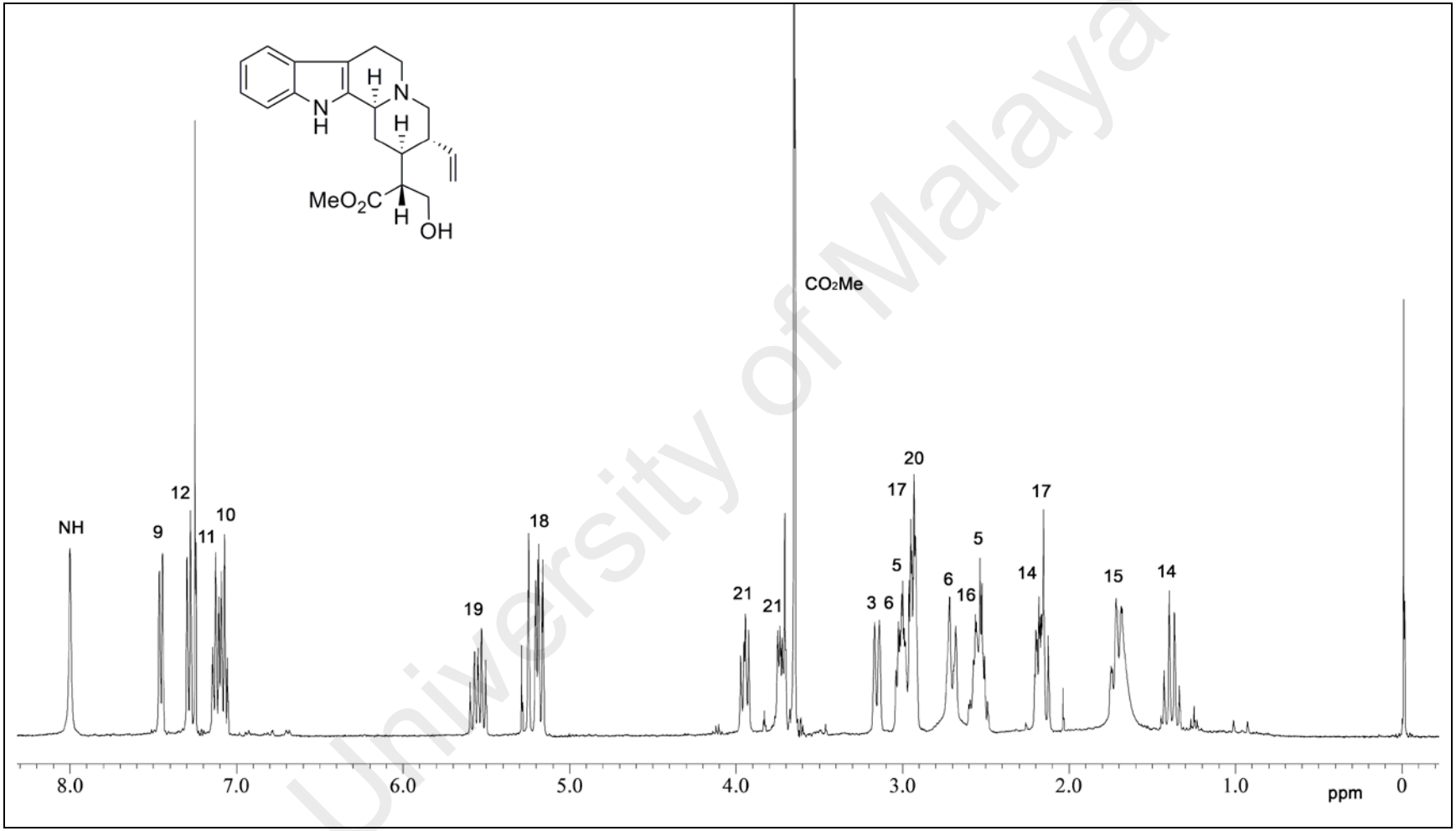


Figure 2.89: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of 16(*R*)-Sitsirikine (**36**)

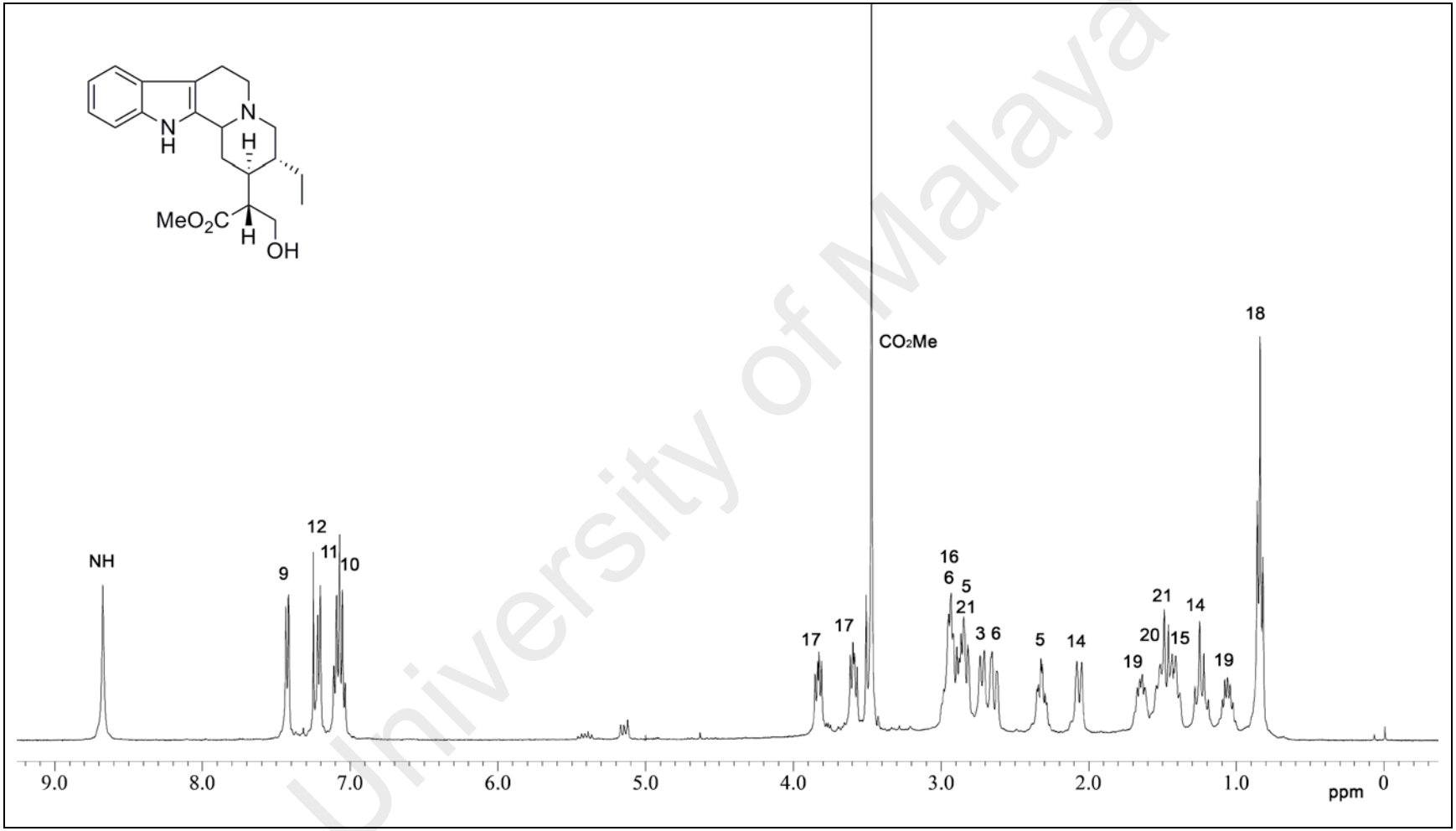


Figure 2.90: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of 19,20-Dihydroisositsirikine (**37**)

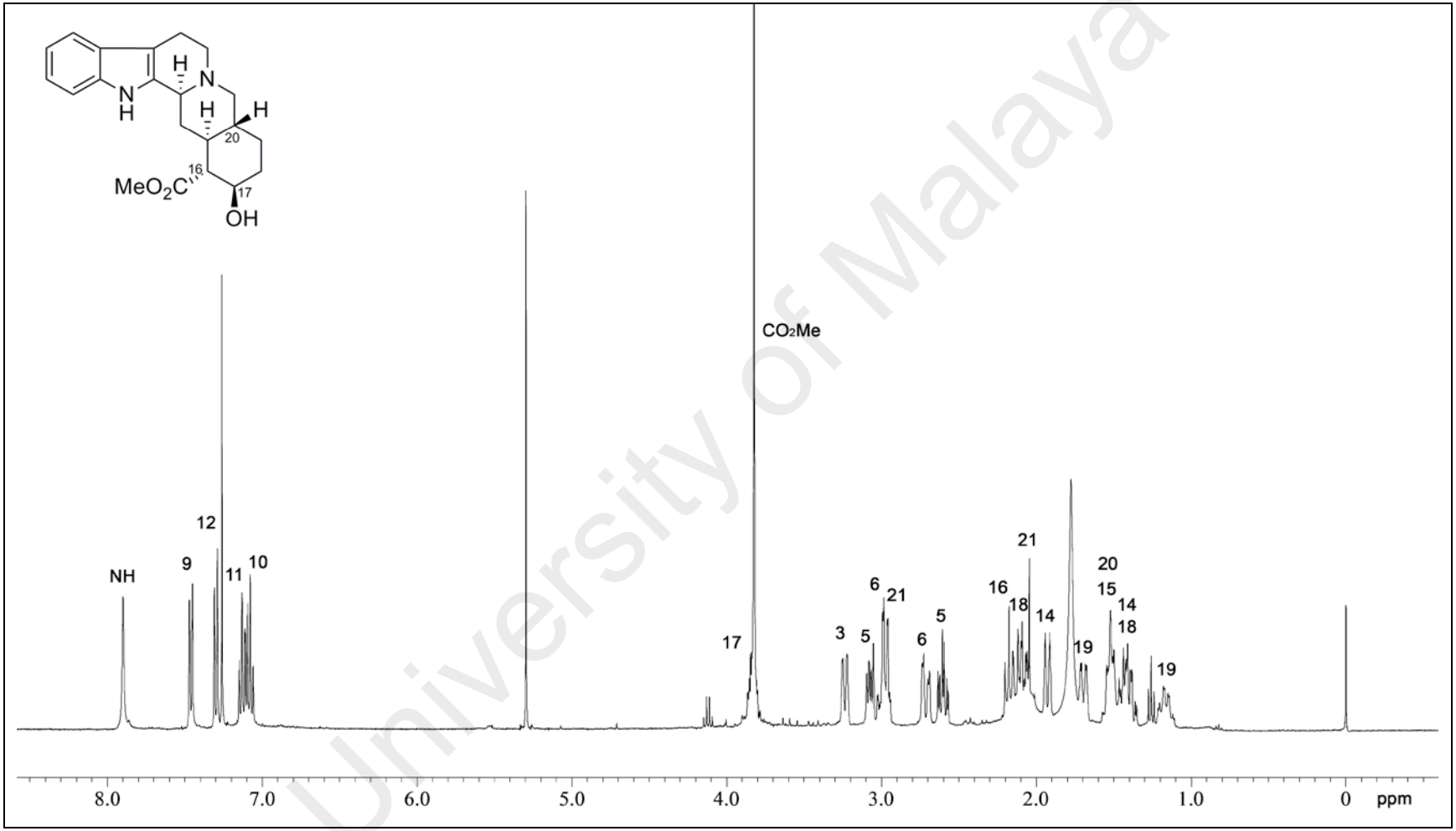


Figure 2.91: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of β-Yohimbine (**38**)

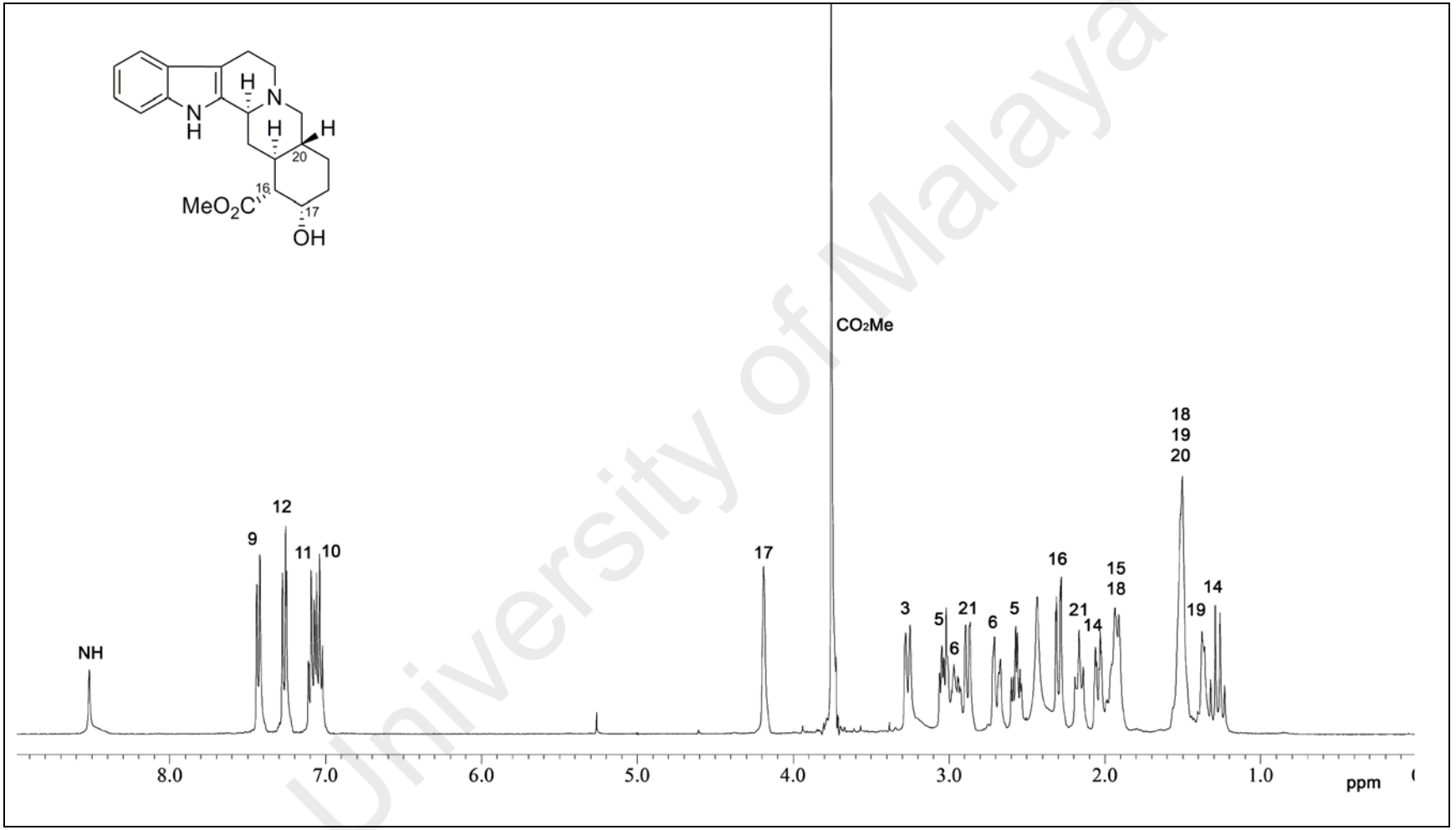


Figure 2.92: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of Yohimbine (**39**)

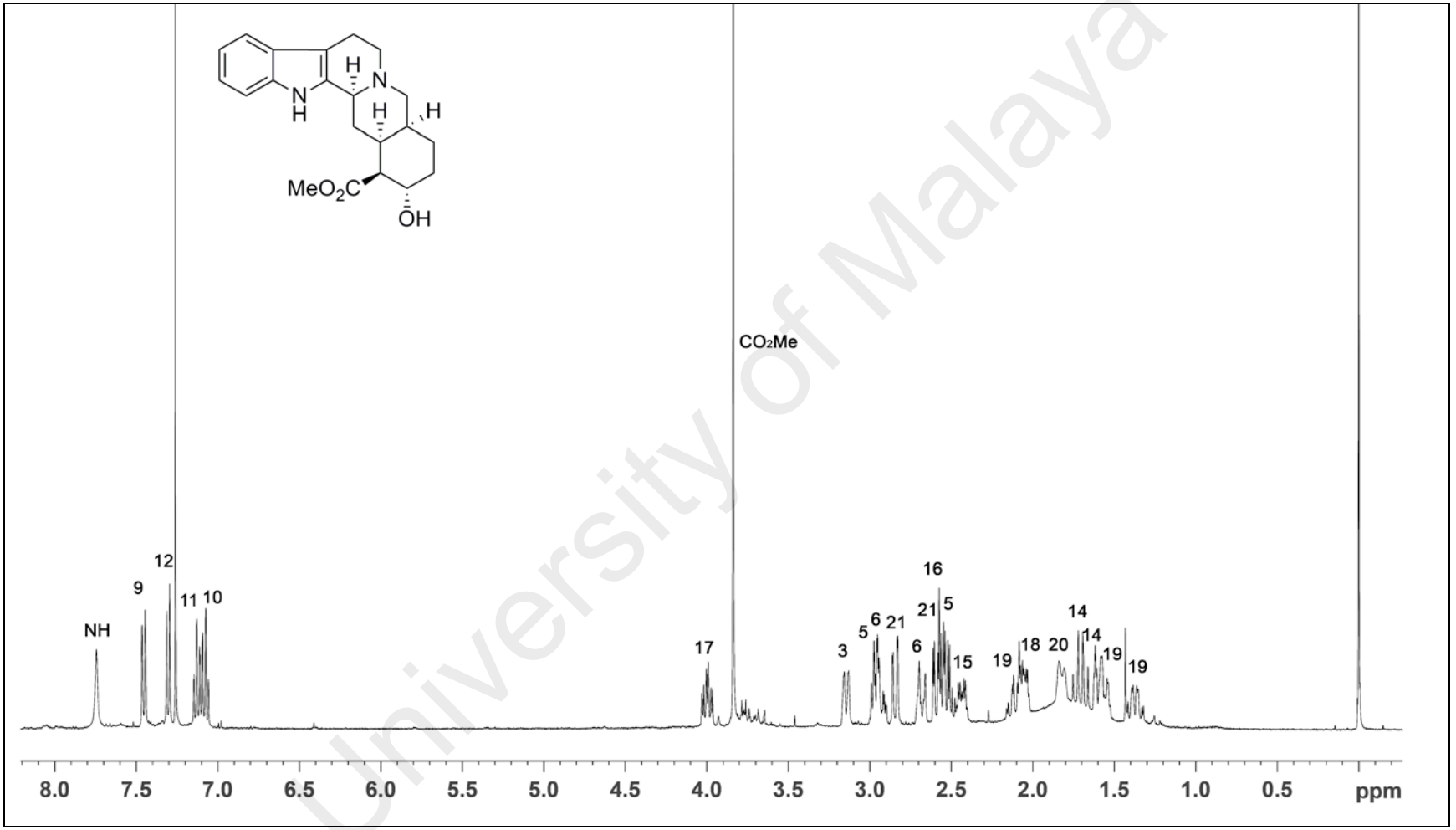


Figure 2.93: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of α-Yohimbine (**40**)

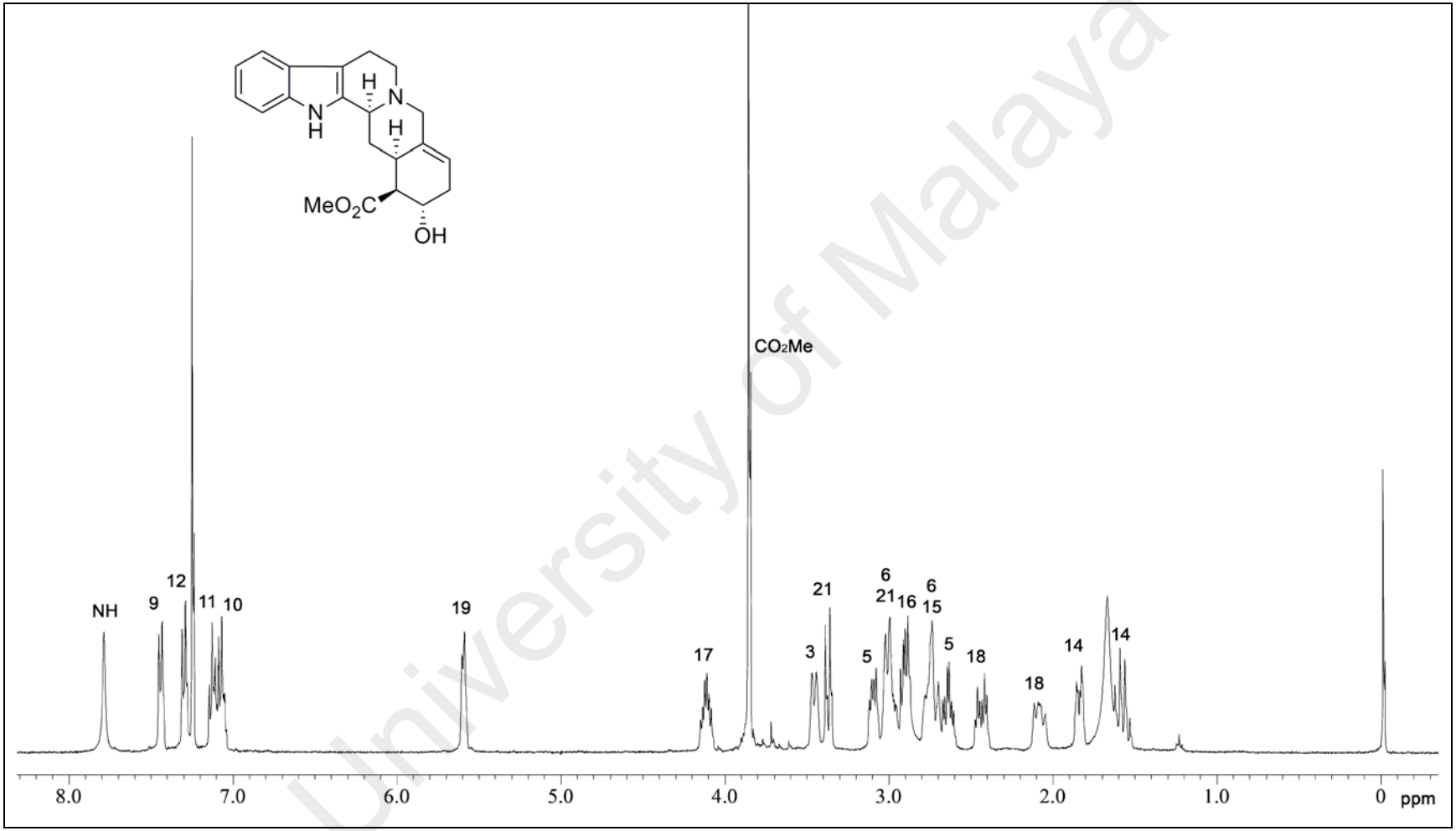


Figure 2.94: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of 19,20-Dehydro-α-yohimbine (**41**)

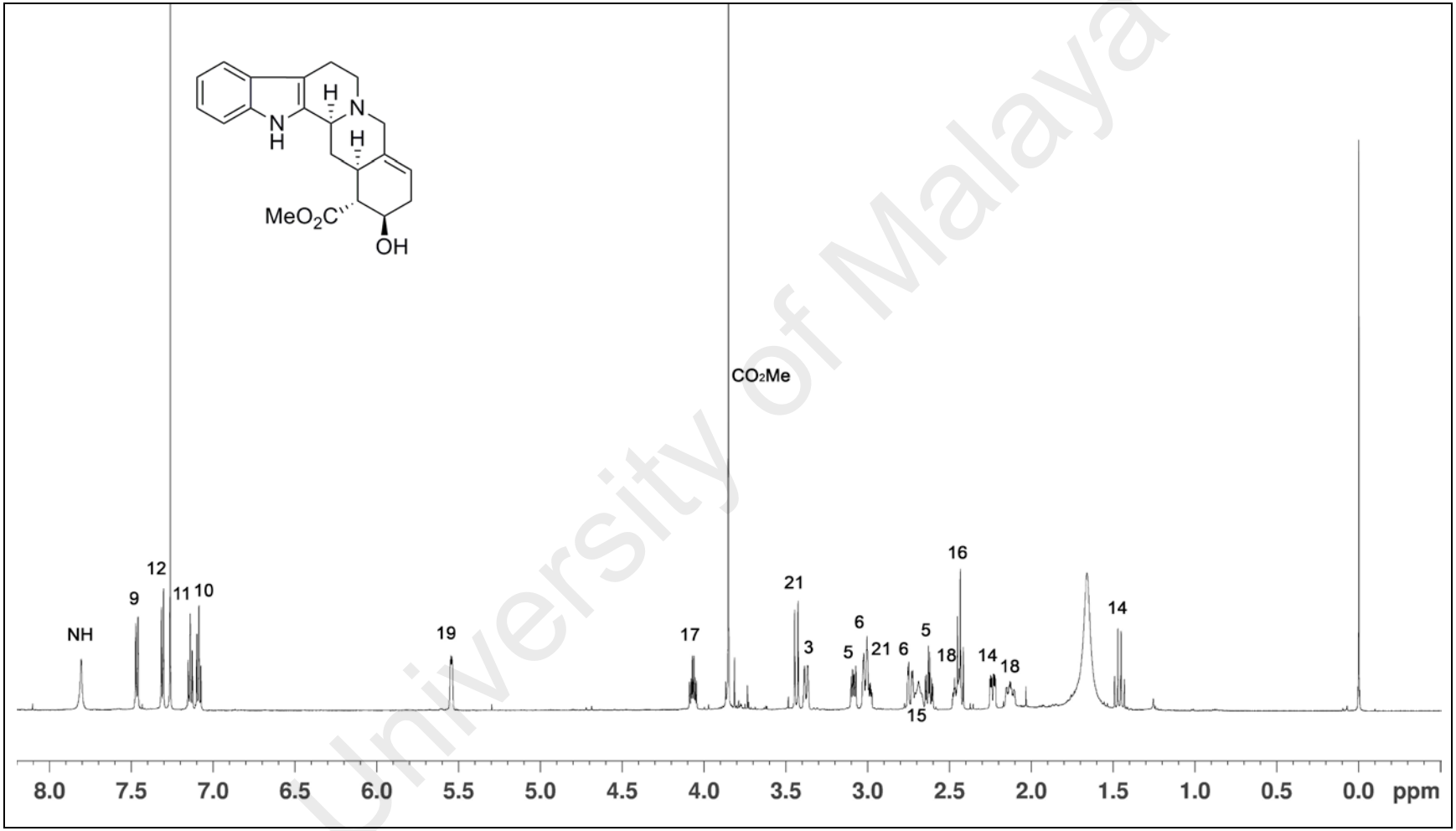


Figure 2.95: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of 19,20-Dehydro-β-yohimbine (**42**)

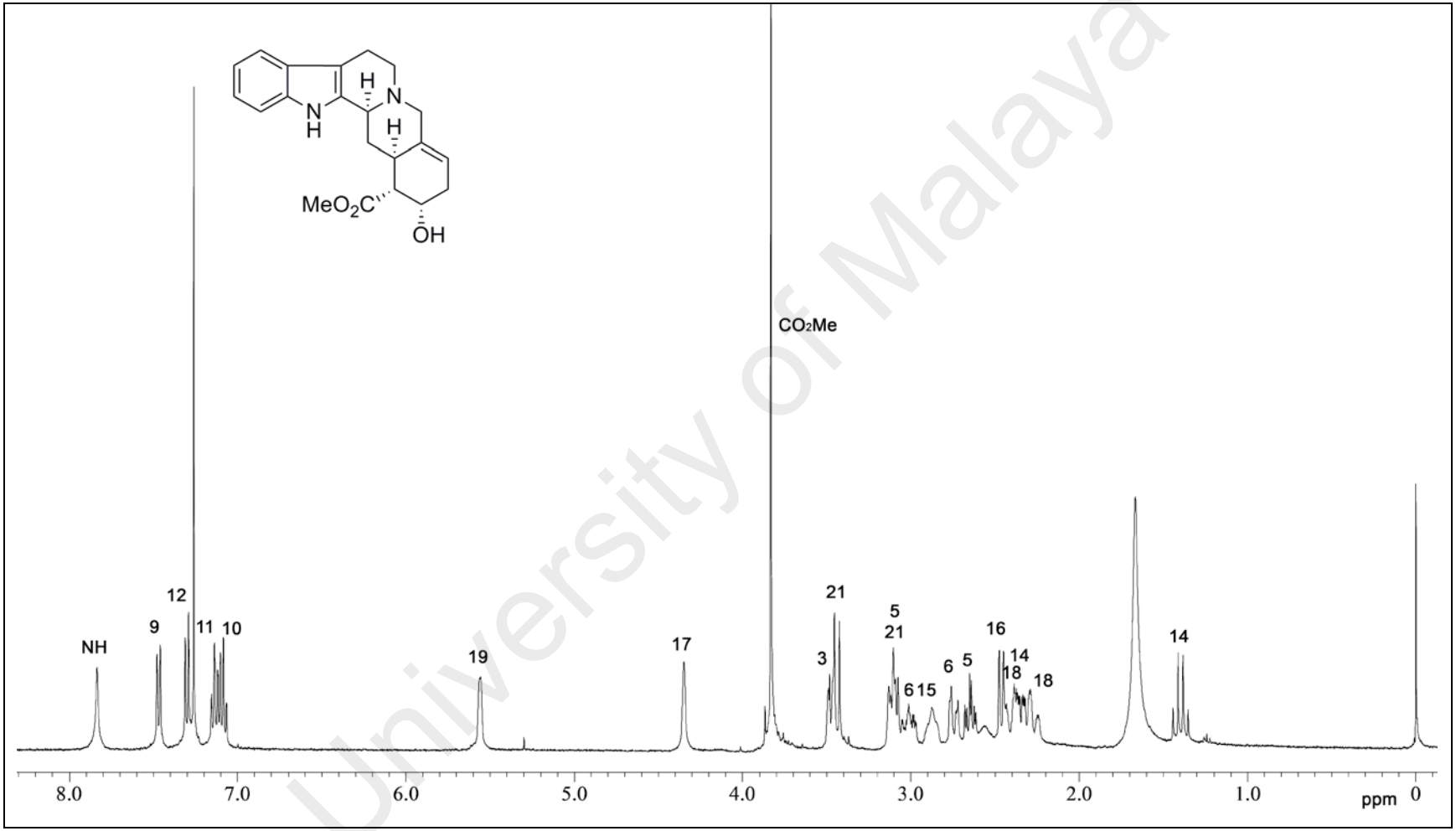


Figure 2.96: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of 19,20-Dehydroyohimbine (**43**)

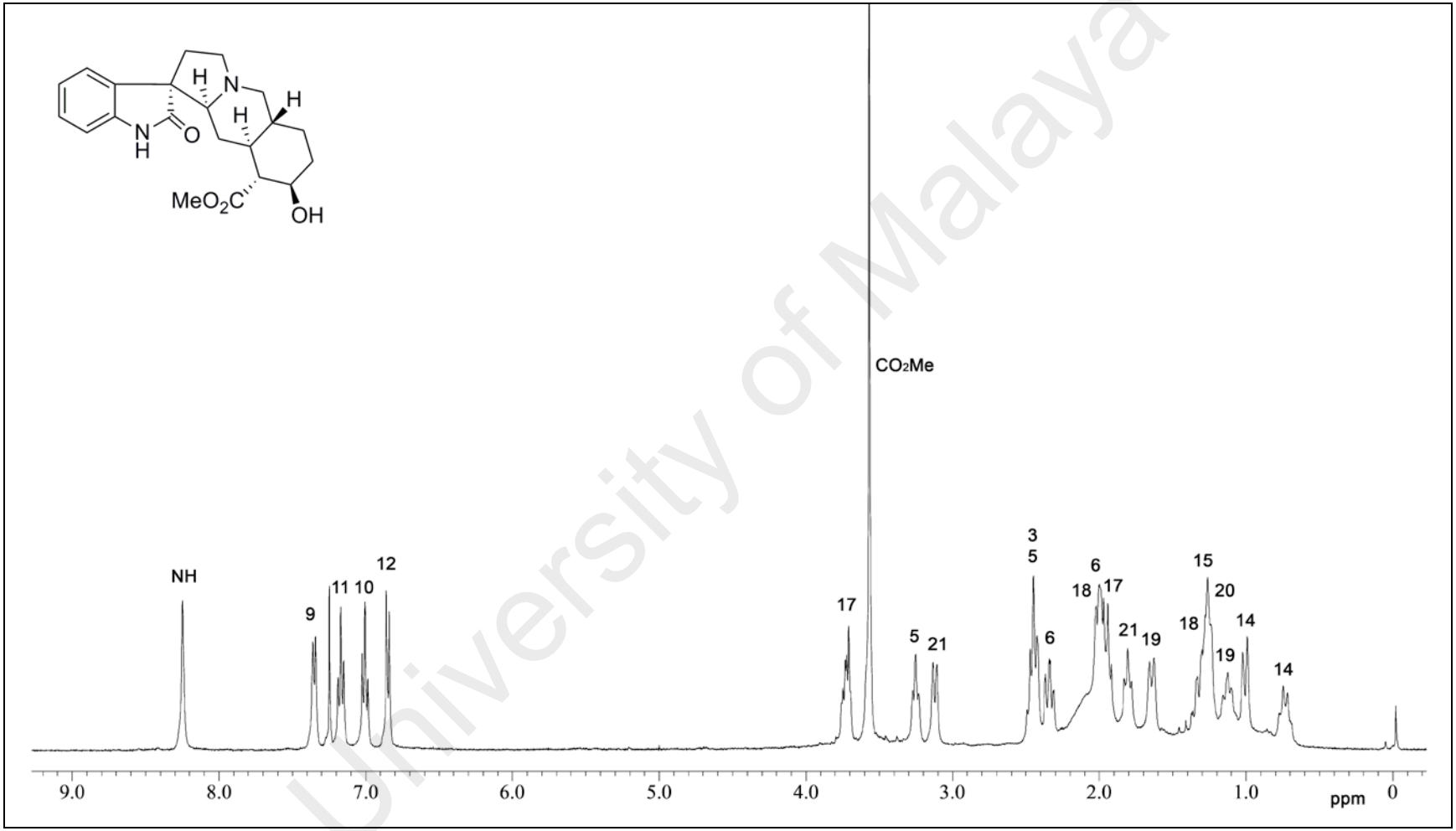


Figure 2.97: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of 7(*S*)-β-Yohimbine oxindole (**44**)

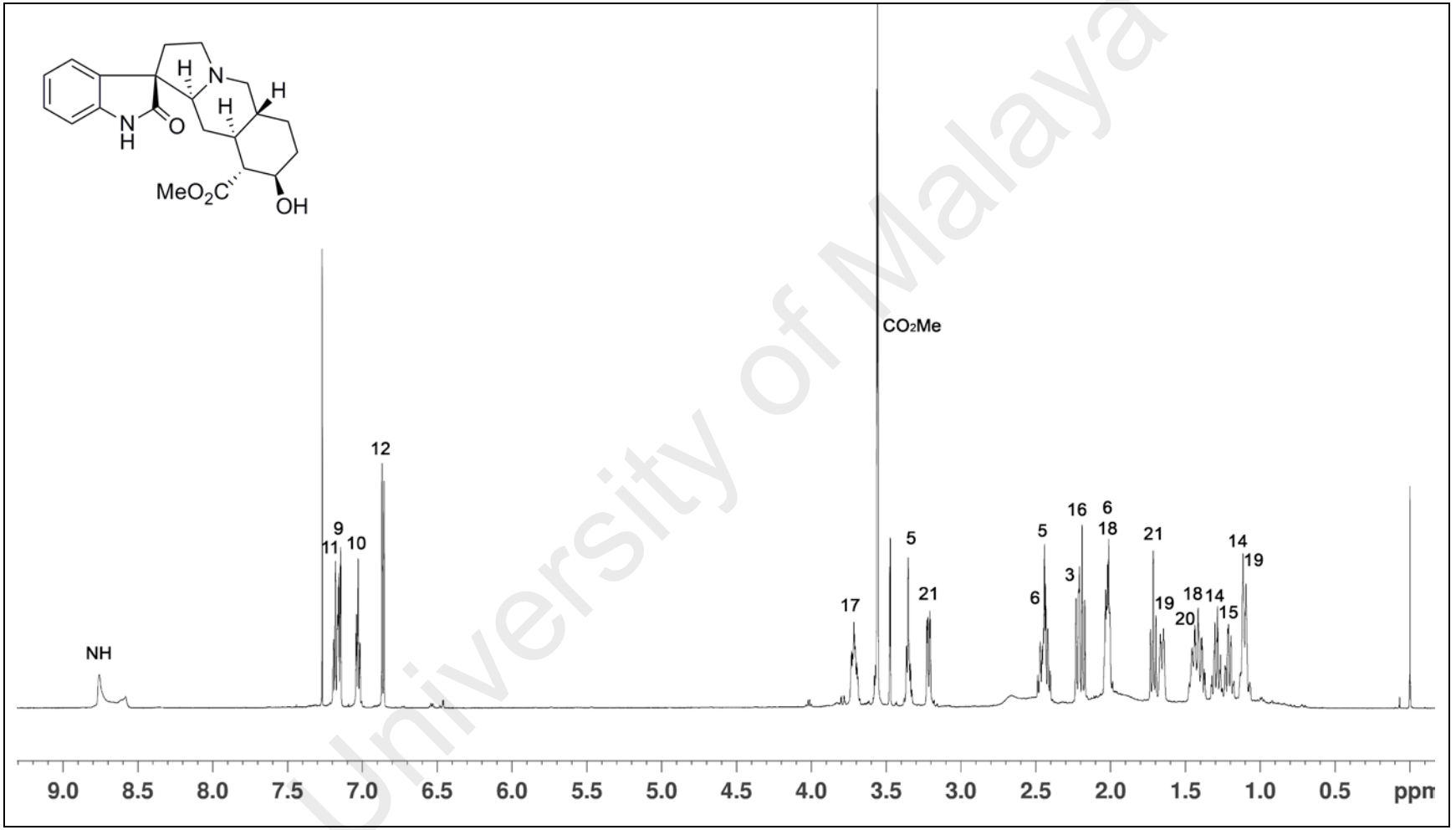


Figure 2.98: ^{1}H NMR Spectrum ($CDCl_3$, 600MHz) of 7(*R*)-β-Yohimbine oxindole (**45**)

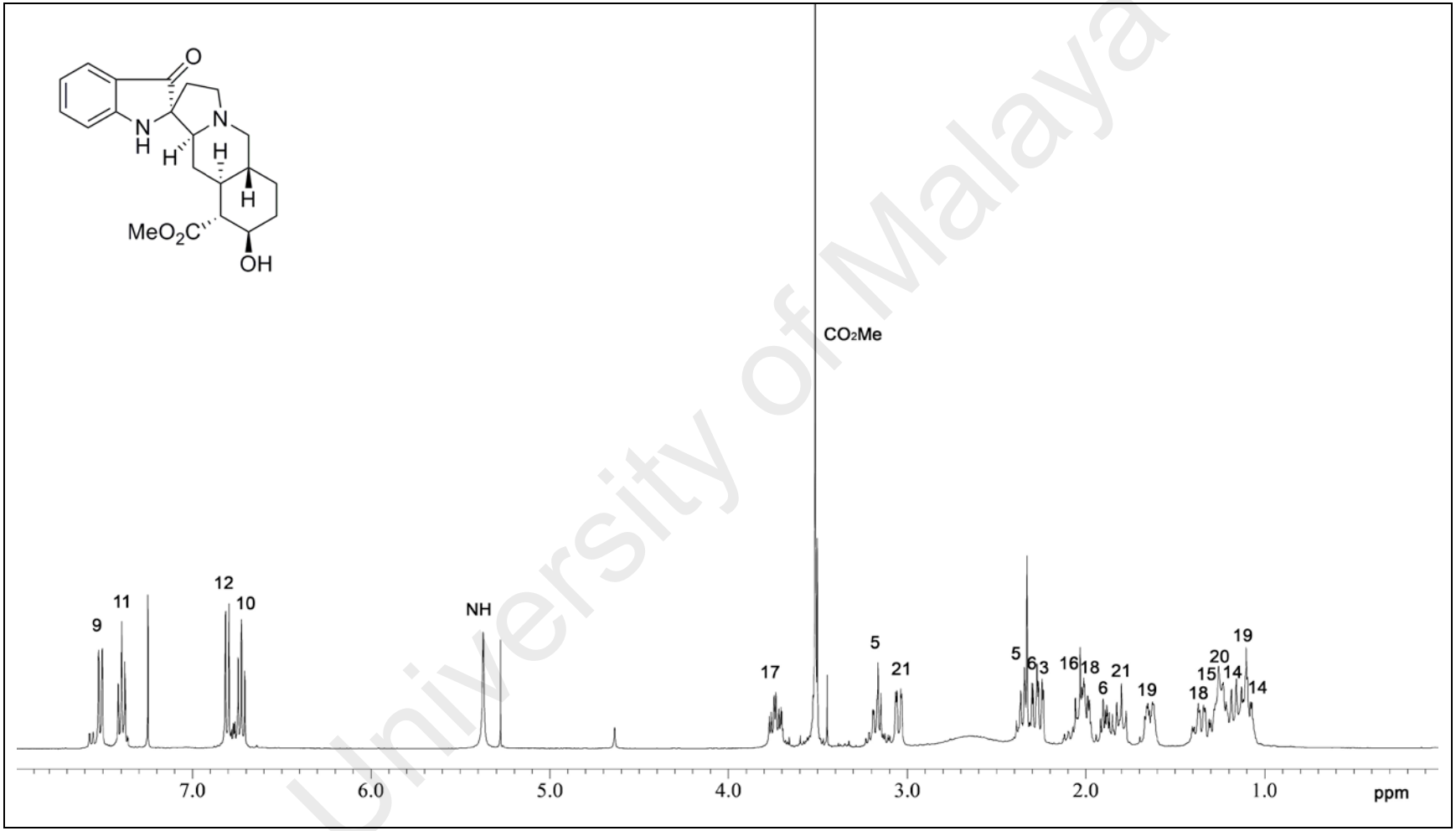


Figure 2.99: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of β-Yohimbine pseudoindoxyl (**46**)

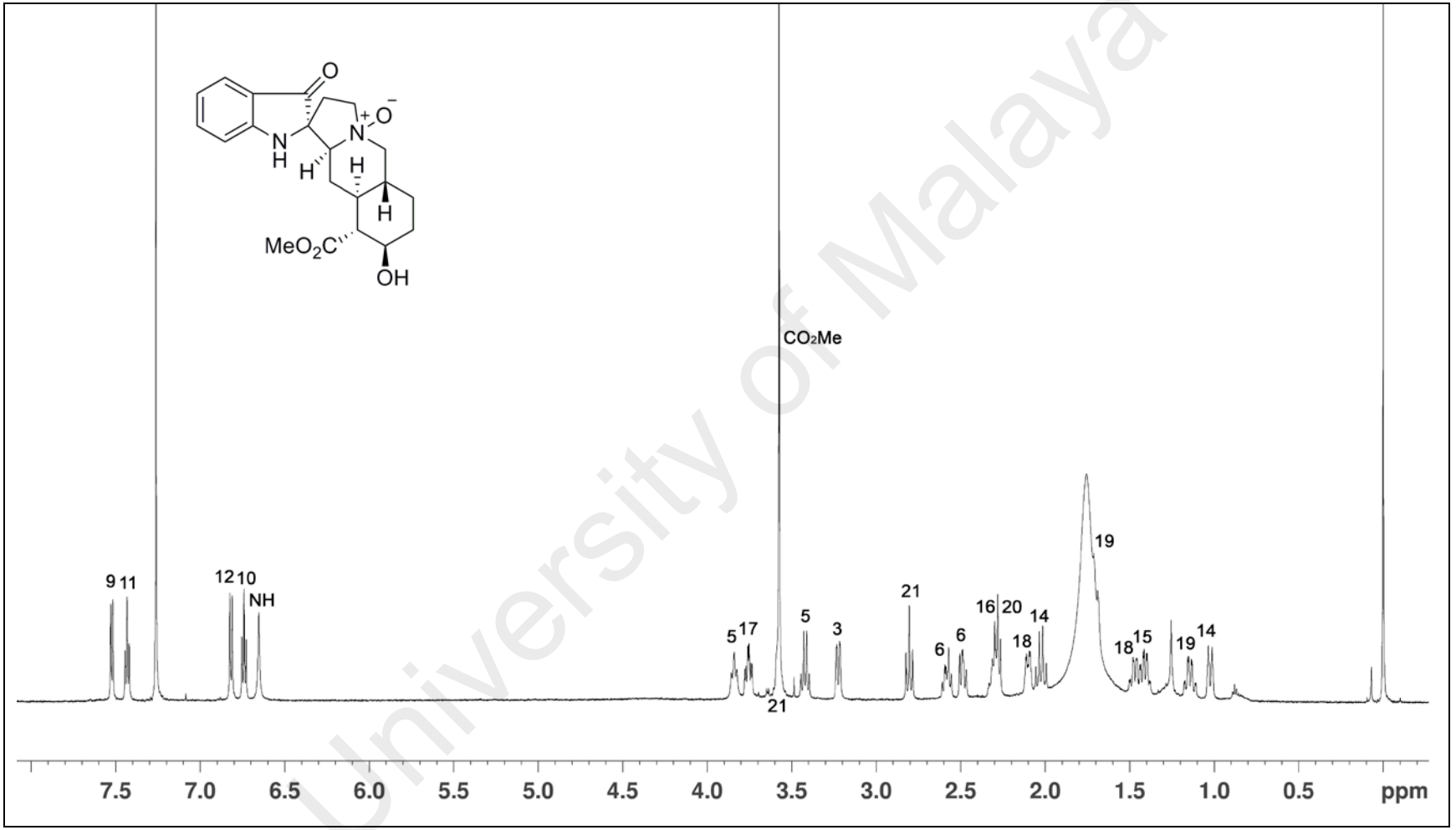
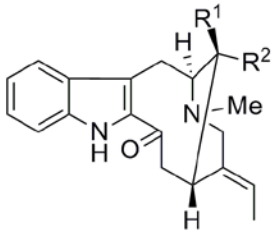


Figure 2.100: ^{1}H NMR Spectrum ($CDCl_3$, 600MHz) of β-Yohimbine pseudoindoxyl *N*-oxide (**47**)

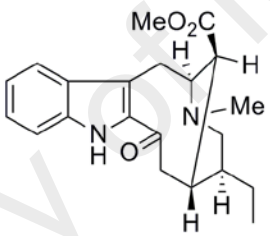
2.1.9 Vobasine and Sarpagine Alkaloids

2.1.9.1 Vobasine (48), 16-*Epi*-affinine (49), Tabernaemontanine (50), and Normacusine B (51)

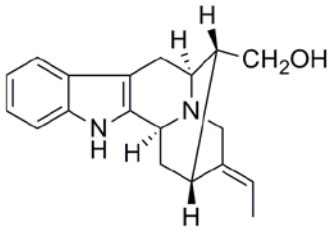
Four known alkaloids belonging to this group, *viz.*, vobasine (**48**),[350,435] 16-*epi*-affinine (**49**),[183,350,436,437] tabernaemontanine (**50**),[238,435,438] and normacusine B (**51**)[322,350] were also isolated in this study. The ^{1}H NMR spectra of these compounds are shown in Figures 2.101–2.104, while the NMR spectroscopic data are summarized in Tables 2.31 and 2.32. Other data are given in the Experimental Section.



48 R^1 = CO_2Me, R^2 = H
49 R^1 = H, R^2 = CH_2OH



50



51

Table 2.31: ^{1}H NMR Spectroscopic Data (δ) of Vobasine (**48**), 16-*Epi*-affinine (**49**), Tabernaemontanine (**50**), and Normacusine B (**51**)[a]

H	**48 (*J*/Hz)**	**49 (*J*/Hz)**	**50 (*J*/Hz)**	**51[b] (*J*/Hz)**
3	-	-	-	4.07 br d (10)
5	3.78 ddd (12, 7, 3)	3.28 t (10)	3.96 td (9, 3.5)	2.72 m
6	2.73 dd (13.5, 7)	3.44 (14.5, 7.6)	3.30 dd (15, 9)	2.63 d (15)
6	3.32 dd (13.5, 12)	3.54 dd (14.5, 10)	3.44 dd (15, 9)	3.02 dd (15, 5)
9	7.72 dd (8, 0.6)	7.71 d (8.4)	7.70 br d (8)	7.43 d (7.5)
10	7.16 dd (8, 5, 2.5)	7.17 ddd (8.4, 6.4, 1.6)	7.15 ddd (8, 5, 2)	7.07 t (7.5)
11	7.34 m	7.38 m	7.33 m	7.12 t (7.5)
12	7.34 m	7.37 m	7.33 m	7.30 d (7.5)
14	3.42 dd (15, 8)	2.67 dd (13, 8)	2.76 dd (12, 6.5)	1.69 br d (12)
14	3.52 dd (15, 10)	3.34 dd (13, 12)	3.40 t (12)	2.00 dd (12, 10)
15	3.98 ddd (10, 8, 3)	3.10 br dd (12, 8)	2.70 m	2.75 m
16	2.83 t (3)	1.96 m	3.03 t (3)	1.80 q (7)
17	-	3.60 dd (10.5, 4)	-	3.46 m
17	-	3.64 dd (10.5, 4)	-	3.46 m
18	1.72 dd (7, 1.5)	1.70 dd (6.8, 2)	0.97 t (7)	1.59 d (7)
19	5.47 qd (7, 1.5)	5.47 q (6.8)	1.54 m	5.33 q (7)
19	-	-	1.73 m	-
20	-	-	1.54 m	-
21	2.98 br d (14)	3.02 d (13)	2.50 d (13)	3.50 m
21	3.85 dt (14, 1.5)	3.70 br d (13)	3.19 dd (13, 3)	3.50 m
CO_2*Me*	2.61 s	-	2.61 s	-
NMe	2.66 s	2.56 s	2.57 s	-
NH	9.07 br s	9.19 br s	9.09 br s	8.81 br s

[a]$CDCl_3$, 400 MHz; [b]$CDCl_3/CD_3OD$, 600 MHz; assignments based on COSY and HMQC.

Table 2.32: ^{13}C NMR Spectroscopic Data (δ) of Vobasine (**48**), 16-*Epi*-affinine (**49**), Tabernaemontanine (**50**), and Normacusine B (**51**)[a]

C	**48**	**49**	**50**	**51**[b]
2	134.0	135.5	133.9	138.0
3	190.0	191.4	190.8	50.3
5	57.1	57.1	56.8	54.5
6	20.3	19.4	18.5	27.0
7	120.3	120.8	120.7	104.2
8	128.3	128.5	128.5	127.6
9	120.7	120.8	120.9	118.0
10	120.1	120.5	120.3	119.2
11	126.5	126.9	126.6	121.3
12	111.9	112.4	111.8	111.0
13	136.6	136.6	136.4	136.4
14	42.9	43.7	45.6	33.3
15	30.3	31.7	31.8	27.5
16	46.4	38.1	43.4	44.2
17	-	67.8	-	64.7
18	12.2	12.2	12.7	12.8
19	120.7	121.1	25.4	117.0
20	135.8	135.1	42.5	135.1
21	51.7	52.2	46.5	55.7
CO_2Me	50.3	-	50.2	-
CO_2*Me*	171.1	-	172.0	-
NMe	42.2	42.0	43.0	-

[a]$CDCl_3$, 100 MHz; [b]$CDCl_3$/CD_3OD, 100 MHz; assignments based on HMQC and HMBC.

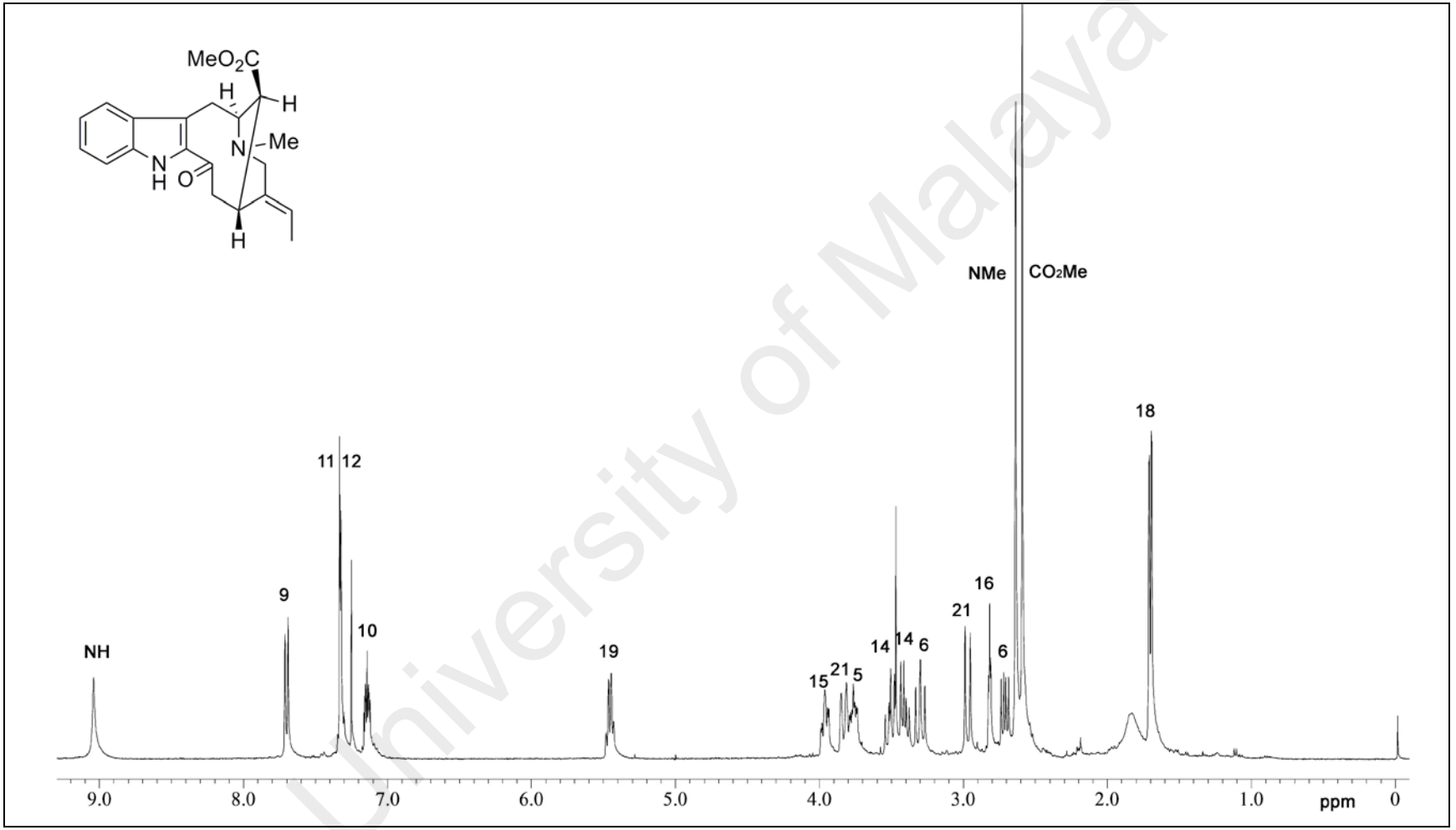


Figure 2.101: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of Vobasine (**48**)

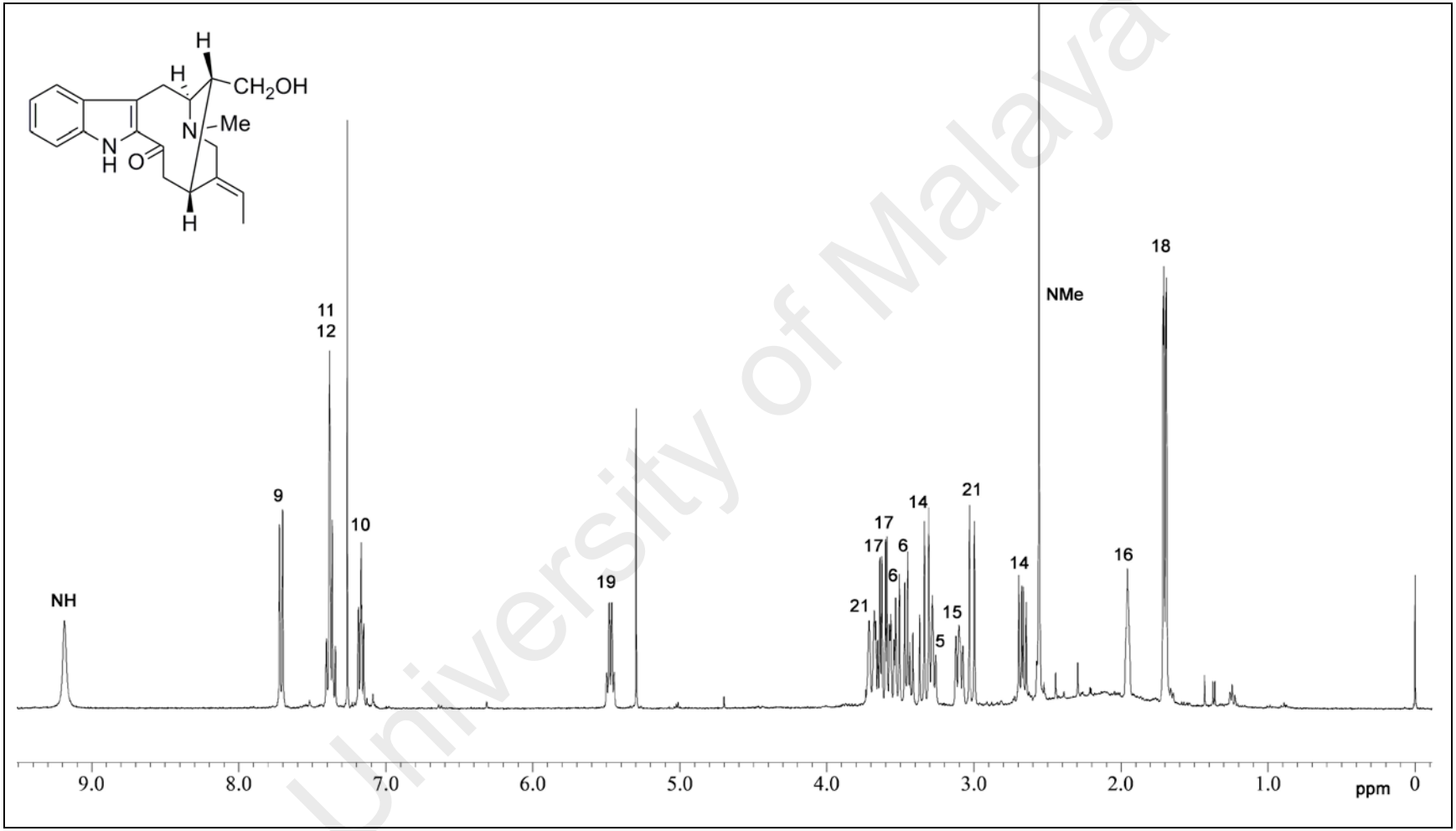


Figure 2.102: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of 16-*Epi*-affinine (**49**)

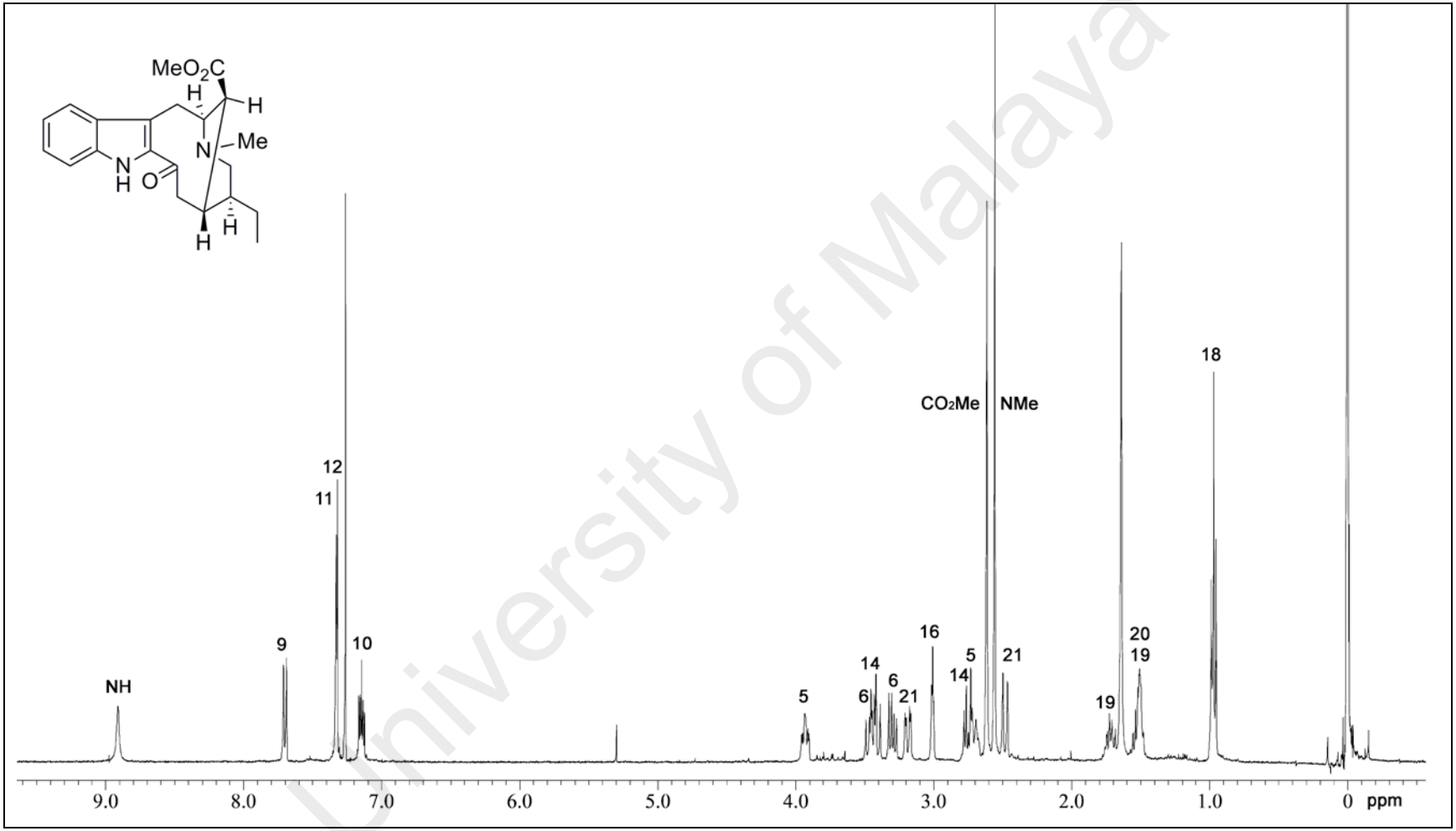


Figure 2.103: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of Tabernaemontanine (**50**)

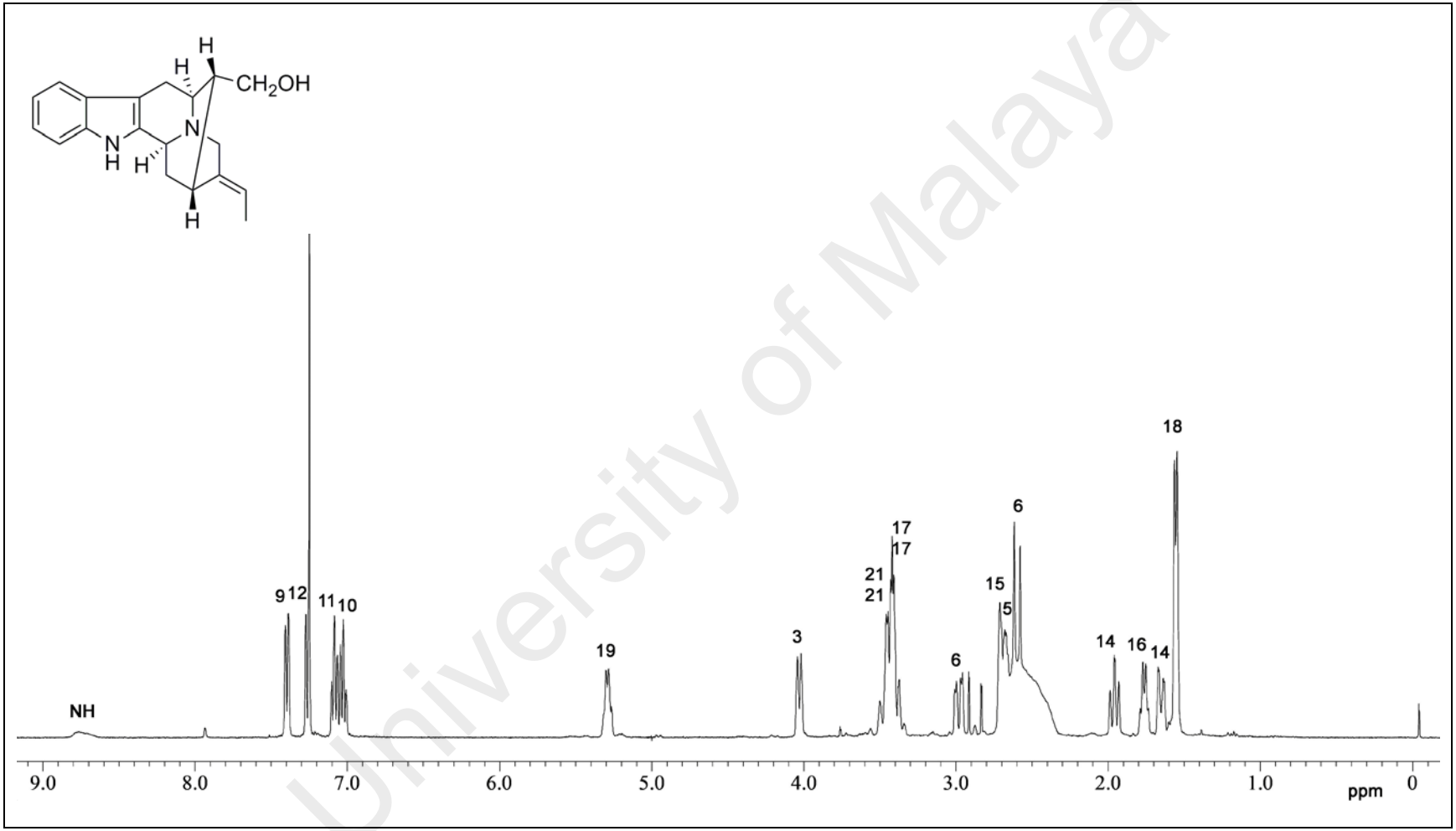
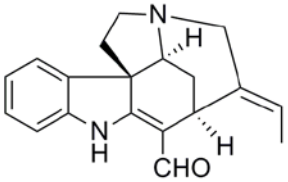


Figure 2.104: ^{1}H NMR Spectrum ($CDCl_3/CD_3OD$, 400MHz) of Normacusine B (**51**)

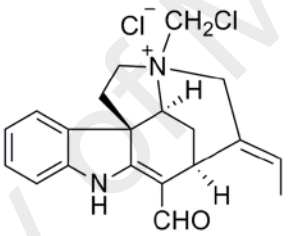
2.1.10 Strychnan and Other Alkaloids

2.1.10.1 Norfluorocurarine (52), *N*(4)-Chloromethylnorfluorocurarine chloride (53), and Velbanamine (54)

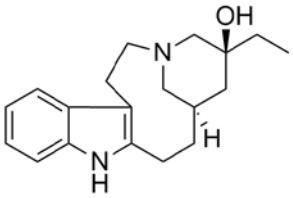
Three known monoterpenoid indole alkaloids belonging to this group isolated in this study are norfluorocurarine (**52**),[322] *N*(4)-chloromethylnorfluorocurarine chloride (**53**),[232] and velbanamine (**54**).[246] The ^{1}H NMR spectra of these compounds are shown in Figures 2.105–2.107, while the ^{1}H and ^{13}C NMR spectroscopic data are summarized in Tables 2.33 and 2.34. Other data are given in the Experimental Section.



52



53



54

Table 2.33: ^{1}H NMR Spectroscopic Data (δ) of Norfluorocurarine (**52**), *N*(4)-Chloromethylnorfluorocurarine chloride (**53**), and Velbanamine (**54**)[a]

H	**52 (*J*/Hz)**	**53[b] (*J*/Hz)**	**54 (*J*/Hz)**
3	4.10 td (4, 2)	4.77 s	1.98 dd (12, 2.9)
3	-	-	3.52 d (12)
5	3.07 ddd (12.4, 6.5, 1)	4.20 dd (11.7, 7)	2.28 m
5	3.31 td (12.4, 5.4)	4.11 dd (13.5, 11.7, 6)	2.66 dt (11, 3.6)
6	1.83 ddd (12.4, 5.4, 1)	2.09 dd (13.5, 6)	2.99 m
6	2.39 td (12.4, 6.5)	2.65 td (13.5, 7)	2.99 m
9	7.29 dd (7.5, 1)	7.88 d (7.6)	7.44 m
10	6.98 td (7.5, 1)	6.96 t (7.6)	7.05 m
11	7.20 td (7.5, 1)	7.24 t (7.6)	7.03 m
12	6.92 dd (7.5,1)	7.08 d (7.6)	7.12 m
14	1.29 ddd (13.5, 4, 2.2)	1.43 d (14.5)	1.94 m
14	2.58 ddd (13.5, 4, 2.2)	2.93 d (14.5)	-
15	3.71 m	3.98 s	1.37 dd (14, 5.9)
15	-	-	1.57 ddd (14, 3.6, 1.7)
16	-	-	2.82 m
16	-	-	2.82 m
17	9.36 s	9.76 s	2.18 m
17	-	-	2.35 m
18	1.60 ddd (6.9, 2.3, 1.6)	1.56 d (7)	0.77 t (7.5)
19	5.40 qt (6.9, 2.3)	5.83 q (7)	1.22 m
19	-	-	1.29 dt (14, 7.5)
21	2.94 br d (15.7)	4.37 d (14)	2.23 d (9)
21	4.00 qt (15.7, 2.3)	4.50 d (14)	2.31 m
CH_2Cl	-	5.88 d (9)	-
CH_2Cl	-	6.01 d(9)	-
NH	10.33 br s	11.30 br s	8.08 br s

[a]$CDCl_3$, 400 MHz; [b]DMSO-d_6, 400 MHz;

Table 2.34: ^{13}C NMR Spectroscopic Data (δ) of Norfluorocurarine (**52**), *N*(4)-Chloromethylnorfluorocurarine chloride (**53**), and Velbanamine (**54**)[a]

C	**52**	**53**[b]	**54**
2	168.8	164.8	138.7
3	61.7	71.8	50.8
5	56.6	61.6	52.5
6	46.4	42.8	22.8
7	58.2	56.0	108.2
8	136.9	133.7	127.6
9	120.8	122.1	117.0
10	121.9	121.3	118.6
11	127.7	129.0	120.6
12	110.3	110.7	110.8
13	142.8	143.1	135.3
14	30.8	27.9	30.2
15	31.2	26.5	40.5
16	111.0	112.0	23.0
17	188.4	185.2	31.6
18	12.8	13.7	7.0
19	120.4	128.7	32.5
20	139.5	131.9	71.7
21	56.7	63.4	66.0
CH_2Cl	-	70.0	-

[a]$CDCl_3$, 100 MHz; [b]DMSO- d_6, 100 MHz.

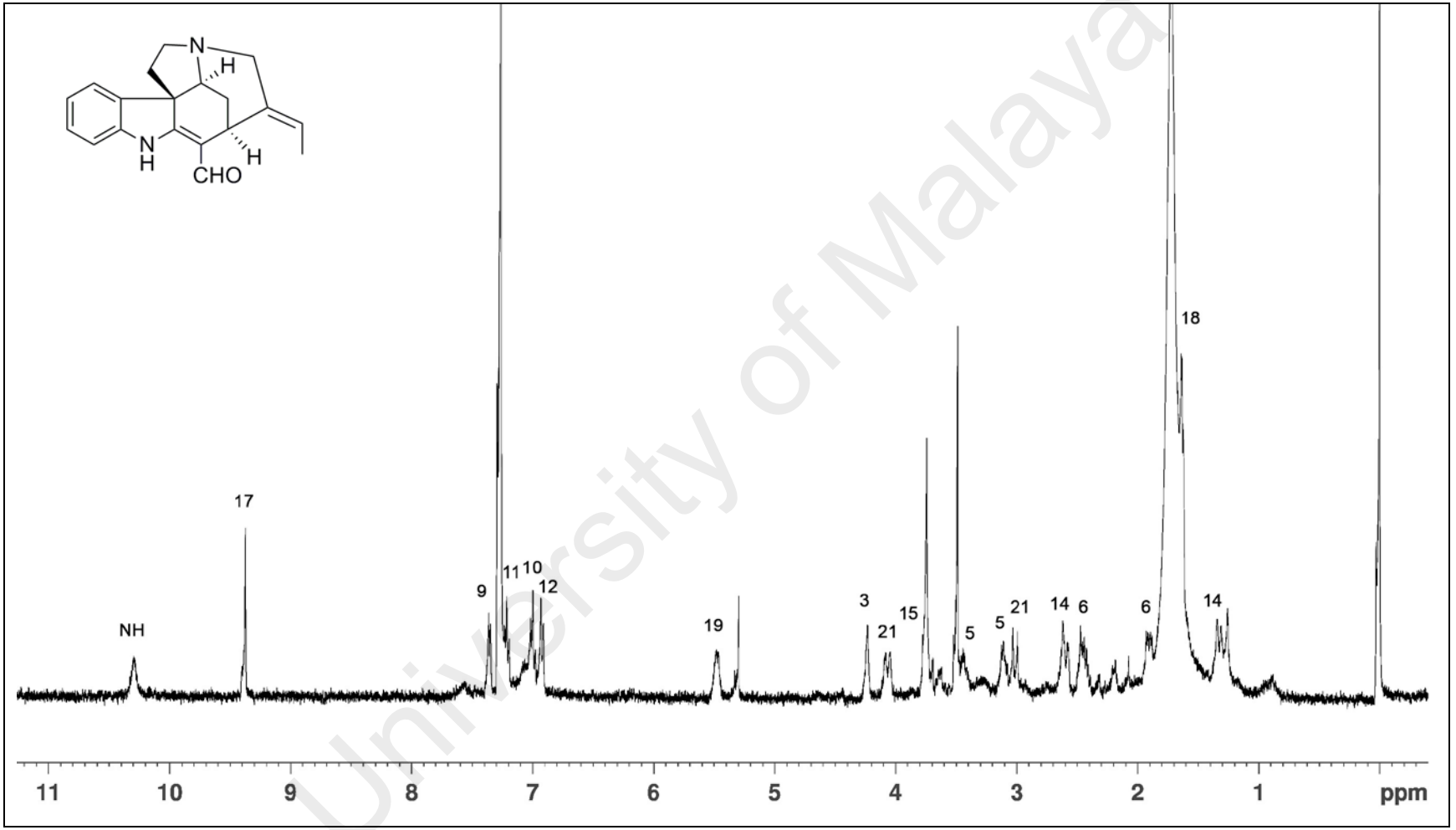


Figure 2.105: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of Norfluorocurarine (**52**)

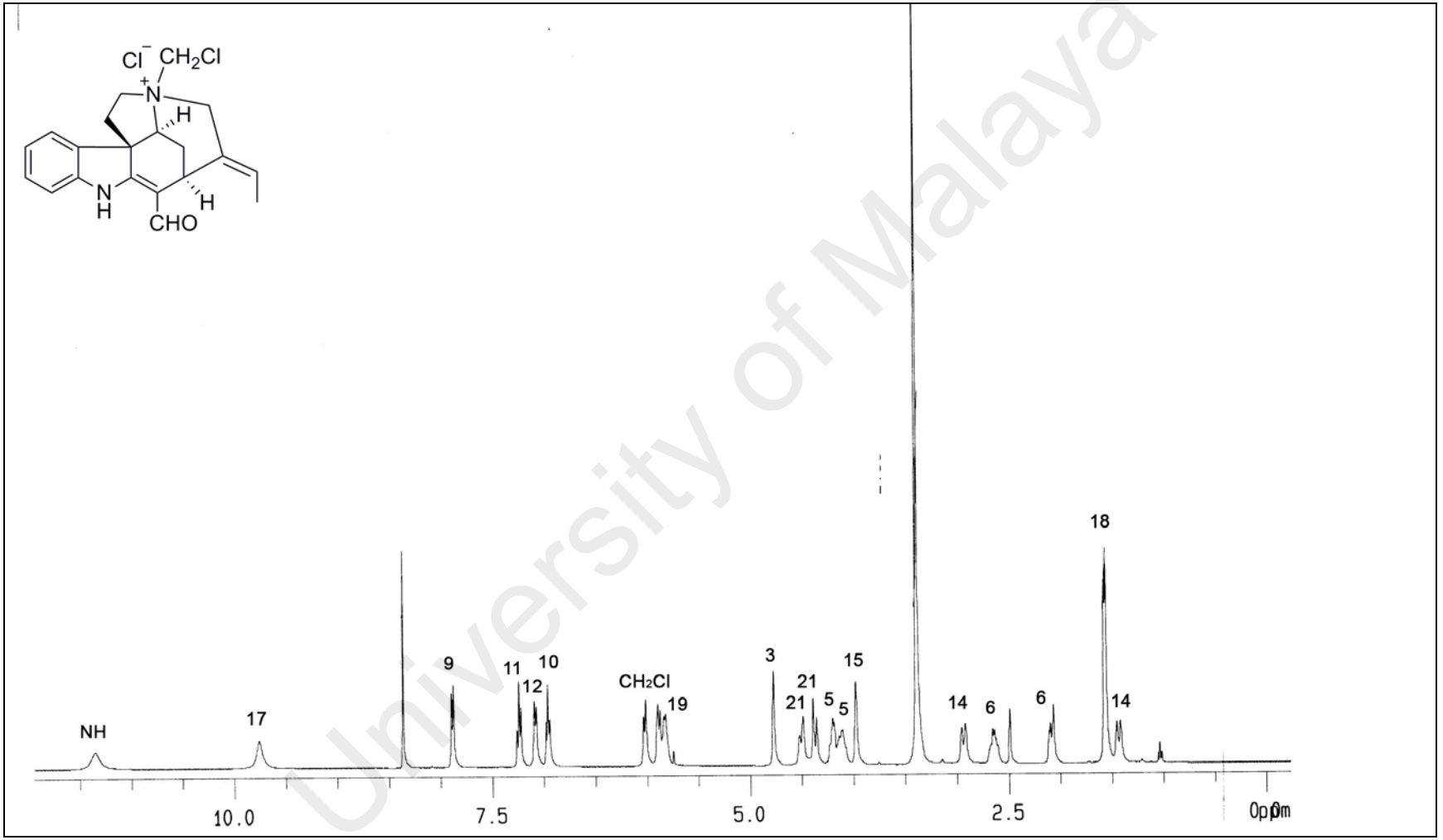


Figure 2.106: ^{1}H NMR Spectrum (DMSO-d_6, 400MHz) of *N*(4)-Chloromethylnorfluorocurarine chloride (**53**)

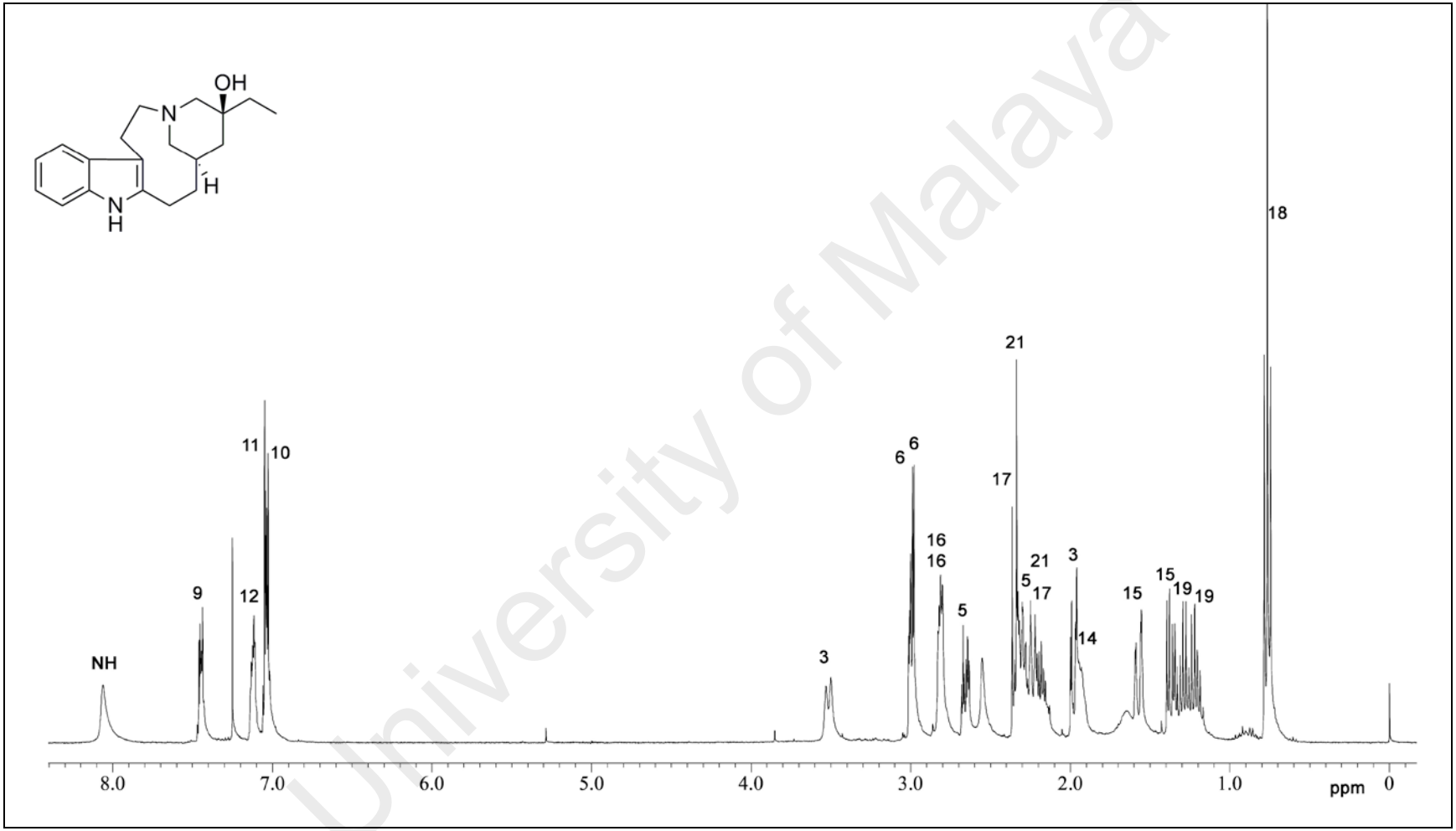
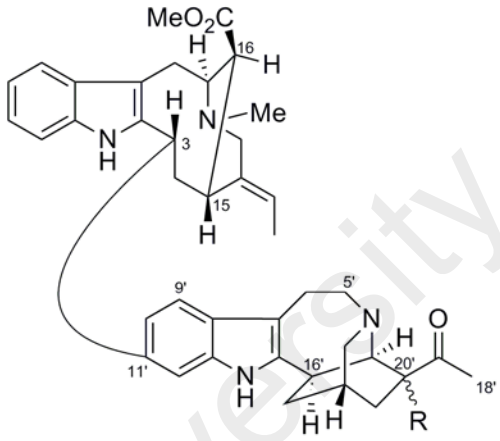


Figure 2.107: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of Velbanamine (**54**)

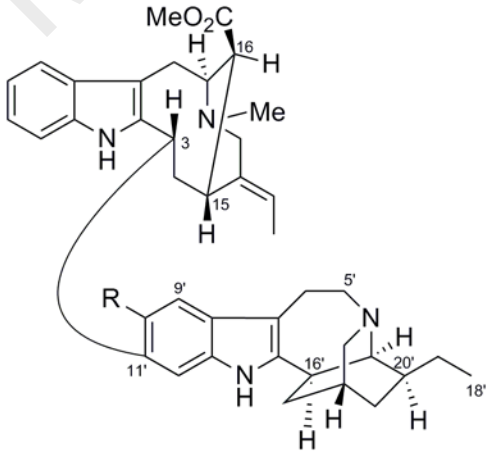
2.1.11 Bisindole Alkaloids

Iboga-Vobasinyl bisindoles

Four iboga-vobasinyl bisindoles were isolated from the stem-bark extract in the present study. Of these, two were new, *viz.*, tabernamidines A (**55**) and B (**56**). The other two known bisindole alkaloids are tabernamine (**57**) and 16'-decarbomethoxyvoacamine (**58**). The relative configuration at C-20' of the previously reported bisindole, 19'-oxotabernamine (C-20'-β-acetyl substitution) has been revised in the present study and renamed as tabernamidine B (C-20'-α-acetyl substitution).



55 R = α-H
56 R = β-H



57 R = H
58 R = OMe

2.1.11.1 Tabernamidines A and B (55, 56)

The two bisindoles **55** and **56**[402] co-eluted during column chromatography, but could be eventually purified by preparative radial chromatography and Sephadex LH-20. Tabernamidine A (**55**) was isolated as a light yellowish oil, with $[\alpha]^{25}_{D}$ –58 (*c* 0.13, $CHCl_3$). The UV spectrum showed characteristic indole chromophore absorption maxima at 234, 287, and 294 nm. The ESIMS showed an $[M + H]^+$ peak at *m/z* 631, and HRESIMS measurement established the molecular formula as $C_{40}H_{46}N_4O_3$.

Examination of the ^1H and ^{13}C NMR data of **55** (Tables 2.35 and 2.36) indicated a bisindole alkaloid constituted from the union of vobasine and iboga moieties. Thus the ^1H NMR spectrum showed the presence of two indolic NH (δ 7.47, 7.61), an unsubstituted indole moiety (δ 7.03–7.57, vobasinyl), an indole ring substituted at C-11' (δ 6.97–7.36, iboga), a methyl ester group (δ 2.46, vobasinyl), an N-methyl (δ 2.60, vobasinyl), an ethyledine side chain (δ 1.65, 5.32, vobasinyl), and an acetyl side chain (δ 2.17, iboga). The ^{13}C NMR spectrum showed a total of 40 resonances including resonances at δ 208.9 (ketone carbonyl, iboga), 171.9 (ester carbonyl, vobasinyl), and 118.9, 137.6 (olefinic C-19, C-20; vobasinyl). The methyl ester associated with the vobasinyl unit is notably shielded (δ 2.46) which places the ester function in the shielding zone of the aromatic ring. Only one H-3 resonance of the vobasinyl unit was observed as a one-H doublet of doublets at δ 4.64 (*J* = 13, 3 Hz), indicating the branching of the bisindole from C-3 of the vobasinyl moiety. The substitution at C-3 was deduced to be α (H-3β) from the observed H-3/N(1)-H, H-15 NOEs and the observed $J_{3\text{-}14\alpha}$ coupling of 13 Hz, while the geometry of the 19,20-double bond was deduced to be *E* from the observed H-18/H-15; H-19/H-21 NOEs.[232] The attachment to the iboga unit was deduced to be at C-11' from the observation of the three aromatic hydrogens of the iboga unit (a pair of AB doublets at δ 6.97, 7.36, *J* = 8 Hz; a broad

singlet at δ 7.01), the observed H-9'/H-6' and NH'/H-12' NOEs, and the observed carbon resonances which compared favorably to those of tabernamine (**57**). The ^{1}H and ^{13}C NMR data of **55** (and **56**) in fact showed a similarity to those of tabernamine except for replacement of the signals due to the ethyl side chain in **57**, by signals due to an acetyl group in **55** (δ_C 208.9, 27.7; δ_H 2.17).[239] Tabernamidine A (**55**) is therefore constituted from the union of a vobasinyl half (at C-3) and a conodusine A or conodusine B half (at C-11'). Comparison of the ^{1}H and ^{13}C NMR data of the iboga half of compound **55** (Tables 2.35 and 2.36) with those of conodusine A (**8**) and conodusine B (**9**) (Tables 2.8 and 2.9), clearly showed correspondence of the iboga half of bisindole **55** with conodusine A (**8**). Bisindole **55** is therefore 19'-oxotabernamine with C-20'-β-acetyl substitution. This conclusion was also supported by the observed H-20'/H-15'α, H-16' NOEs (Figure 2.108).

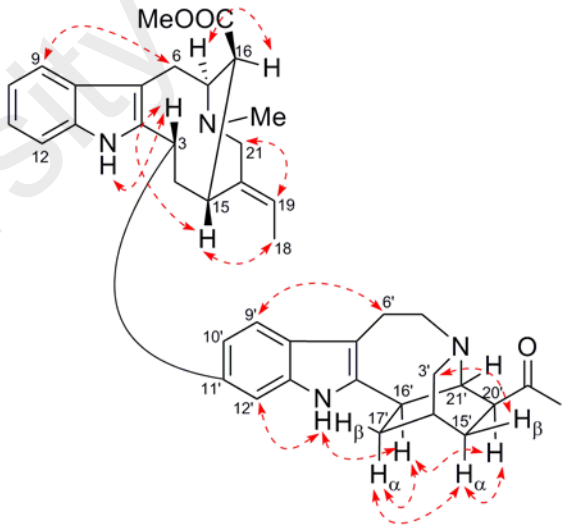


Figure 2.108: Selected NOEs of **55**

Tabernamidine B (**56**) was isolated from fractions containing **55** and **56** by preparative radial chromatography as a light yellowish oil, $[\alpha]^{25}_{D}$ −154 (*c* 0.05, $CHCl_3$). The UV spectrum was identical to that of **55**, and HRESIMS yielded the same molecular formula as **55** (i.e. $C_{40}H_{46}N_4O_3$). Examination of the ^{1}H and ^{13}C NMR data showed a general correspondence to those of **55**, except for notable changes in the chemical shifts of several ^{1}H and ^{13}C NMR resonances associated with the iboga unit. Thus, noticeable changes were observed for H-15', H-16', H-20', and H-21' in the ^{1}H NMR spectrum, and for C-16', C-18', and C-21' in the ^{13}C NMR spectrum, when compared to those of **55**. Comparison of the ^{1}H and ^{13}C NMR data of the iboga half of **56** (Tables 2.35 and 2.36) with those of conodusine A (**8**) and conodusine B (**9**) (Tables 2.8 and 2.9), showed correspondence of the iboga half of bisindole **56** with conodusine B (**9**). Bisindole **56** is therefore 19'-oxotabernamine with C-20'-α-acetyl substitution.

In a previous study of a different sample (variety) of *T. corymbosa* collected from a different location (Perak, Peninsular Malaysia), a bisindole alkaloid named 19'-oxotabernamine {$[\alpha]^{25}_{D}$ −158 (*c* 0.08, $CHCl_3$)}, in addition to tabernamine (**57**), 19'(*S*)-hydroxytabernamine (**479**), and 19'(*R*)-hydroxytabernamine (**478**), were isolated.[239] The structure then deduced for 19'-oxotabernamine had C-20'-β-acetyl substitution (corresponding to tabernamidine A, **55**), based on the assumption that the configuration at C-20' was similar to that in the parent alkaloid, tabernamine (**57**). This has now been shown to be incorrect since comparison of the NMR data (Tables 2.35 and 2.36 versus Tables 2.8 and 2.9) showed that the 19'-oxotabernamine isolated in the earlier study corresponds to tabernamidine B (**56**), and not tabernamidine A (**55**), as incorrectly assumed in the earlier disclosure.

Table 2.35: ^{1}H NMR Spectroscopic Data (δ) of Tabernamidines A (**55**) and B (**56**)[a]

H	**55 (*J*/Hz)**	**56 (*J*/Hz)**	**H**	**55 (*J*/Hz)**	**56 (*J*/Hz)**
3	4.64 dd (13, 3)	4.63 dd (13, 3)	3'	2.97 m	3.12 m
5	4.03 ddd (10, 8, 2.4)	4.05 td (10, 3)	3'	2.97 m	3.12 m
6	3.27 m	3.28 m	5'	3.08 m	3.25 m
6	3.49 m	3.51 dd (14, 11)	5'	3.21 m	3.35 m
9	7.57 d (8)	7.56 dd (8, 1.5)	6'	2.57 m	2.65 m
10	7.06 m	7.07 m	6'	3.26 m	3.28 m
11	7.04 m	7.04 m	9'	7.36 d (8)	7.36 d (8)
12	7.03 m	7.04 m	10'	6.97 br d (8)	6.96 br d (8)
14	1.96 m	1.97 m	12'	7.01 br s	6.99 br s
14	2.67 m	2.68 m	14'	1.96 m	1.97 m
15	3.76 m	3.77 m	15'	1.51 t (12)	1.77 t (12)
16	2.71 br t (3)	2.73 t (3)	15'	2.42 m	2.09 m
18	1.65 dd (6.5, 1.5)	1.65 dd (6.8, 1.2)	16'	3.01 dd (11.6, 3)	2.81 dd (11.5, 4)
19	5.32 q (6.5)	5.33 q (6.5)	17'	1.61 m	1.56 m
21	2.90 d (14)	2.92 d (14)	17'	2.07 t (12.5)	2.03 m
21	3.72 d (14)	3.73 m	18'	2.17 s	2.19 s
CO_2*Me*	2.46 s	2.47 s	20'	2.63 m	3.21 m
NMe	2.60 s	2.61 s	21'	3.55 br s	3.35 br s
NH	7.47 br s	7.47 br s	NH'	7.61 br s	7.62 br s

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

Table 2.36: ^{13}C NMR Spectroscopic Data (δ) of Tabernamidines A (**55**) and B (**56**)[a]

C	**55**	**56**	**C**	**55**	**56**
2	137.4	137.5	2'	141.5	141.3
3	45.3	45.3	3'	49.2	49.5
5	59.8	59.8	5'	54.3	54.6
6	19.4	19.4	6'	20.3	20.1
7	110.3	110.2	7'	109.8	109.8
8	129.8	129.8	8'	128.4	128.1
9	117.6	117.6	9'	118.2	118.1
10	119.0	119.0	10'	119.6	119.6
11	121.7	121.7	11'	139.1	139.1
12	109.9	109.9	12'	109.3	109.3
13	136.0	136.0	13'	134.6	134.4
14	39.0	38.9	14'	26.1	25.9
15	33.6	33.6	15'	24.0	24.7
16	47.0	47.0	16'	39.8	35.3
18	12.4	12.4	17'	34.5	34.3
19	118.9	119.0	18'	27.7	29.0
20	137.6	137.5	19'	208.9	209.3
21	52.4	52.4	20'	53.8	54.4
CO_2Me	171.9	171.8	21'	56.7	55.3
CO_2*Me*	50.0	50.0			
NMe	42.4	42.4			

[a]$CDCl_3$, 100 MHz.

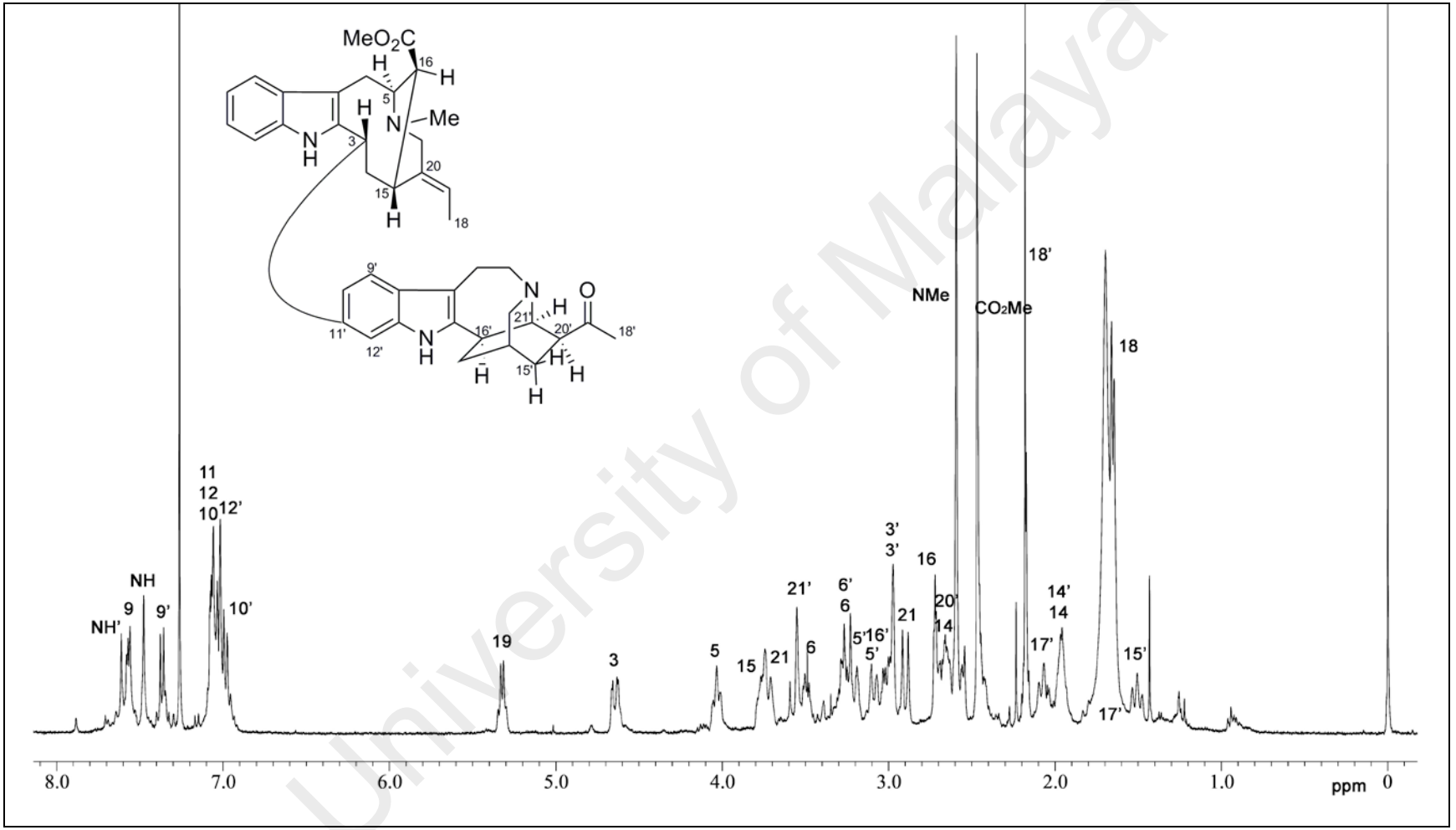


Figure 2.109: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of Tabernamidine A (**55**)

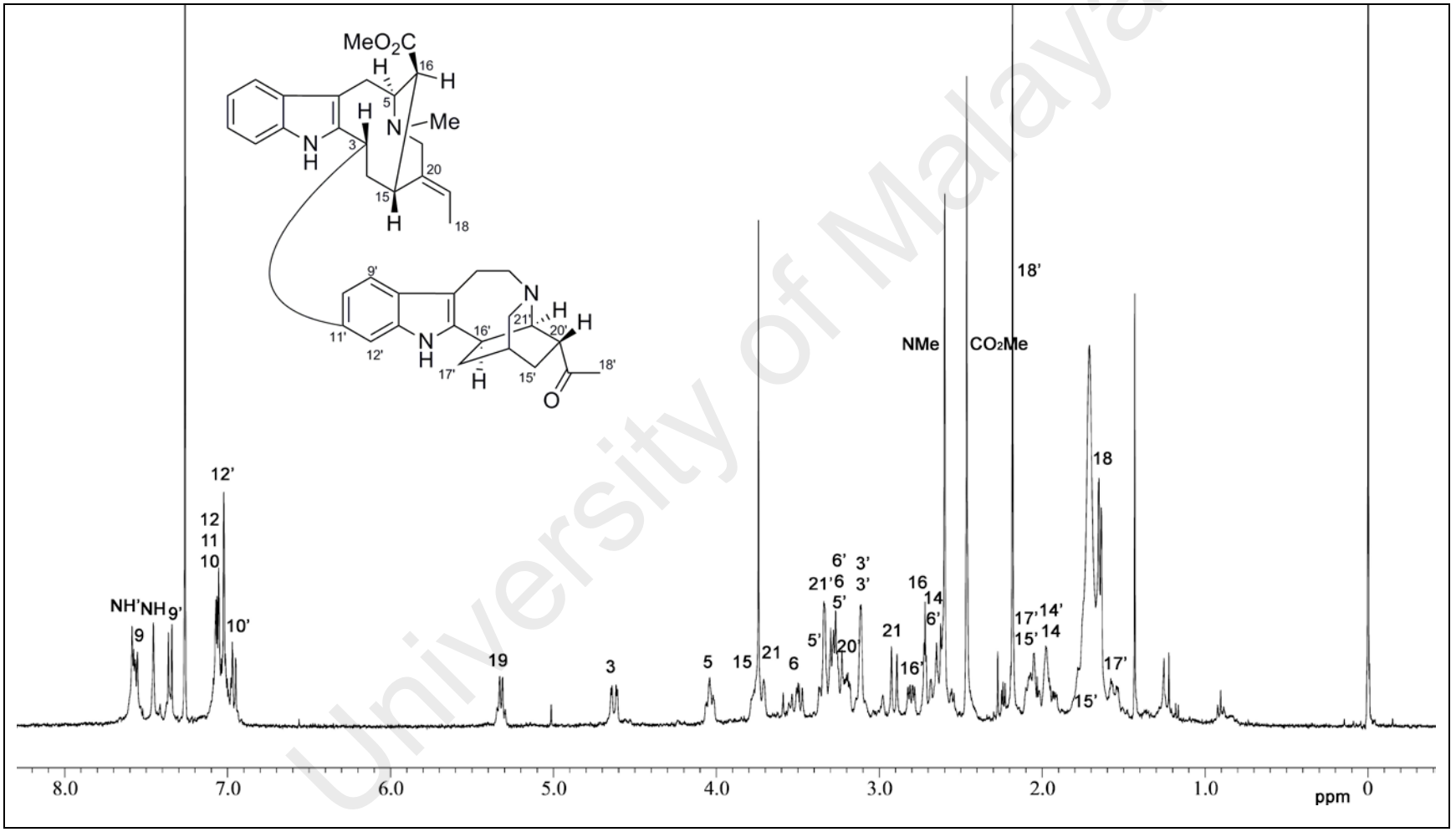
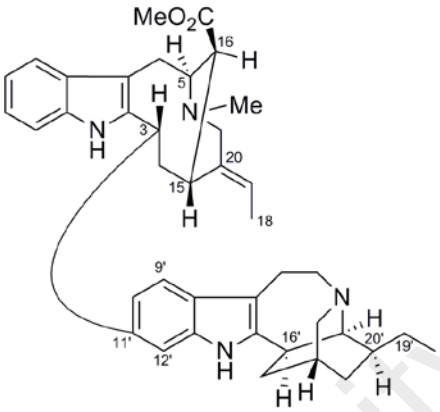


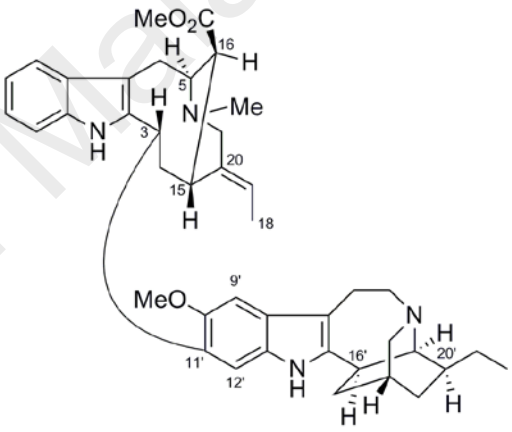
Figure 2.110: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of Tabernamidine B (**56**)

2.1.11.2 Tabernamine (57) and 16'-Decarbomethoxyvoacamine (58)

In addition to the two new tabernamidines A (**55**) and B (**56**), two known iboga-vobasinyl bisindoles, *viz.*, tabernamine (**57**)[239,264] and 16'-decarbomethoxyvoacamine (**58**)[322,436] were also isolated from this study. The ^{1}H NMR spectra of these compounds are shown in Figures 2.111 and 2.112, while the ^{1}H and ^{13}C NMR data are summarized in Tables 2.37 and 2.38. Other data are given in the Experimental Section.



57



58

Table 2.37: ^{1}H NMR Spectroscopic Data (δ) of Tabernamine (**57**) and 16'-Decarbomethoxyvoacamine (**58**)[a]

H	**57 (*J*/Hz)**	**58 (*J*/Hz)**	**H**	**57 (*J*/Hz)**	**58 (*J*/Hz)**
3	4.63 dd (13, 3)	5.12 d (10.2)	3'	2.93 dt (9, 3)	2.99 m
5	4.05 ddd (10, 8, 3)	4.02 m	3'	3.01 dt (9, 2)	2.99 m
6	3.25 dd (14.5, 8)	3.24 m	5'	3.09 m	3.10 t (13)
6	3.50 dd (14.5, 10)	3.38 d (14)	5'	3.33 m	3.46 t (13)
9	7.56 dd (7, 1)	7.54 d (7.1)	6'	2.64 m	2.60 m
10	7.05 m	7.04 m	6'	3.33 m	3.27 m
11	7.05 m	7.03 m	9'	7.35 d (7)	6.66 s
12	7.05 m	7.01 m	10'	6.96 dd (7, 1)	-
14	1.97 m	1.97 m	12'	7.01 d (1)	6.91 s
14	2.64 m	2.42 m	14'	1.80 m	1.78 m
15	3.77 dt (8, 3)	3.82 m	15'	1.18 tdd (11.8, 4, 1.5)	1.18 d (13)
16	2.71 t (3)	2.71 m	15'	1.76 m	1.74 m
18	1.65 dd (6.7, 1.5)	1.66 d (6.6)	16'	2.85 ddd (11.8, 4, 1.5)	2.79 m
19	5.31 qd (6.7, 1)	5.32 q (6.3)	17'	1.50 m	1.50 m
21	2.89 d (14)	2.90 d (13.7)	17'	1.97 m	1.94 m
21	3.72 dd (14, 1.5)	3.70 m	18'	0.88 d (7)	0.86 t (6.6)
CO_2*Me*	2.47 s	2.45 s	19'	1.5 m	1.50 m
NMe	2.59 s	2.58 s	19'	1.5 m	1.50 m
NH	7.51 br s	7.31 br s	20'	1.5 m	1.50 m
			21'	2.79 t (1.5)	2.79 m
			10'-OMe	-	3.99 s
			NH'	7.47 br s	7.69 br s

[a] $CDCl_3$, 400 MHz.

Table 2.38: ^{13}C NMR Spectroscopic Data (δ) of Tabernamine (**57**) and 16'-Decarbomethoxyvoacamine (**58**)[a]

C	57	58	C	57	58
2	137.4	138.1	2'	142.0	142.0
3	45.1	37.4	3'	49.7	49.9
5	59.6	59.9	5'	54.0	54.3
6	19.2	19.5	6'	20.5	20.5
7	110.1	110.1	7'	108.8	108.4
8	129.6	129.6	8'	128.2	128.7
9	117.4	117.2	9'	117.9	98.6
10	118.9	118.8	10'	119.2	150.8
11	121.6	121.5	11'	138.6	128.0
12	109.8	109.8	12'	109.1	110.2
13	135.9	135.7	13'	134.6	129.3
14	38.9	36.2	14'	26.3	26.1
15	33.5	33.5	15'	31.9	31.5
16	47.0	46.7	16'	41.2	40.6
18	12.2	12.3	17'	34.0	33.8
19	118.6	119.0	18'	11.8	11.8
20	137.6	137.4	19'	27.7	27.6
21	52.3	52.3	20'	41.8	41.6
CO_2Me	171.7	171.3	21'	57.5	57.9
CO_2*Me*	49.8	49.9	10'-OMe	-	56.0
NMe	42.2	42.2			

[a]$CDCl_3$, 100 MHz.

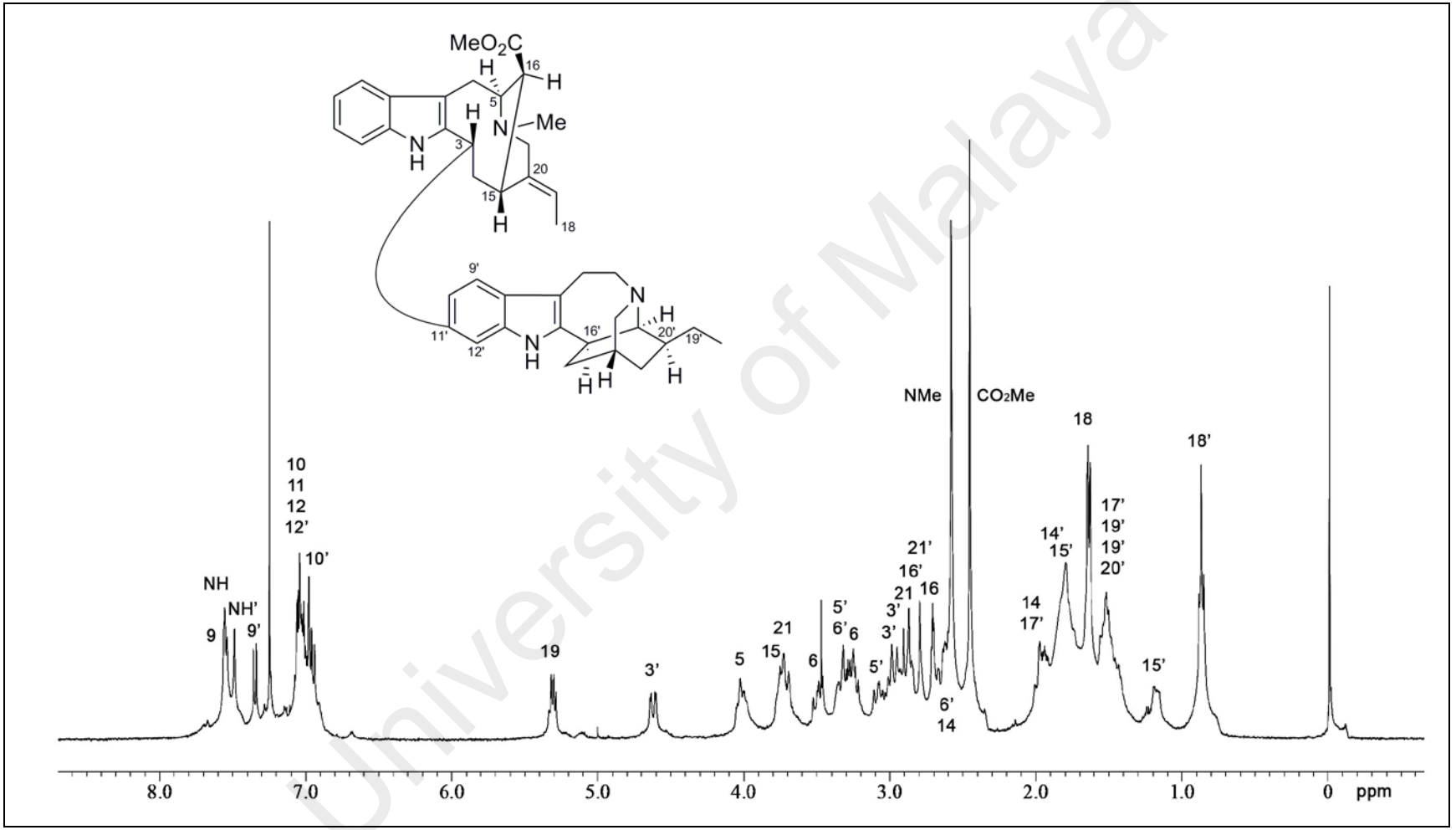


Figure 2.111: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of Tabernamine **(57)**

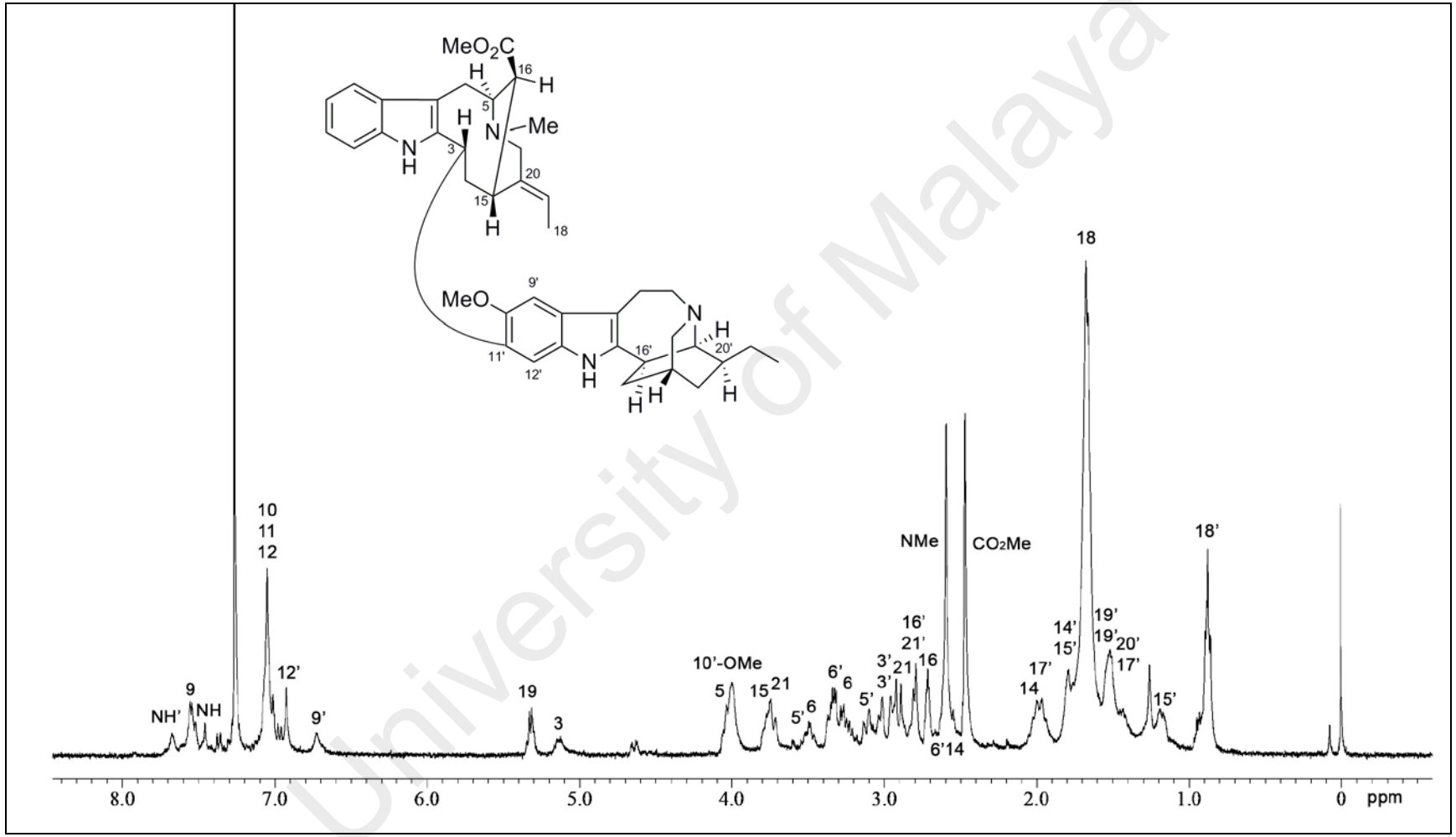


Figure 2.112: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of 16'-Decarbomethoxyvoacamine (**58**)

2.1.11.3 Conofolidine (59)

Conofolidine (**59**) was initially isolated as a light yellowish oil, which subsequently crystallized from MeOH as colorless crystals, mp >203 ^{o}C (dec), $[\alpha]^{25}_{D}$ –102 (*c* 0.45, MeOH). The UV spectrum showed absorption maxima at 210, 243, 310, and 334 nm, characteristic of a β-anilinoacrylate chromophore. The IR spectrum showed absorption bands due to NH/OH (3382 cm^{-1}) and α,β-unsaturated carbonyl (1674 and 1614 cm^{-1}) functions. The ESIMS showed an $[M + H]^+$ ion at *m/z* 795, and HRESIMS gave the molecular formula $C_{44}H_{50}N_4O_{10}$.

Examination of the ^{1}H and ^{13}C NMR data of **59**, indicated a bisindole alkaloid constituted from the union of two *Aspidosperma*-type monomeric units. The ^{13}C NMR spectrum (Table 2.39) showed a total of 44 carbon resonances comprising five methyls, 11 methylenes, nine methines, four tertiary carbons bonded to oxygen, four tertiary carbons linked to the indolic N-1 (corresponding to C-2, C-13, C-2', C-13'), two ester carbonyls (δ 168.7, 168.8), and nine quaternary carbon atoms. The ^{1}H NMR spectrum (Figure 2.116, Table 2.39) showed the presence of two indolic NH (δ 8.77, 8.88), three isolated aromatic hydrogens (δ 5.46, 6.35, and 7.19) one of which (δ 5.46) was significantly shielded, two hydroxy groups (δ 2.64 and 5.13), four methoxy groups (δ_H 3.77, 3.78, 3.79, and 3.86) of which two are associated with the presence of two carbomethoxy functions (δ_C 168.7, 168.8), an ethyl side chain (δ 0.70, 0.83 and 1.51), and two pairs of AB doublets (δ 2.39, 2.73; 2.33, 2.74). The presence of only three aromatic singlets indicated highly substituted indole rings where one indole ring was substituted at the position 10, 11, and 12 while the other is substituted at position 10' and 11'. This was confirmed by the NOEs observed for the indole NH (δ 8.77) and the

OMe signal (δ 3.86) at C-12, and for the NH' (δ 8.88) and the aromatic-H at δ 6.35 (H-12'). The other methoxy substituent is deduced to be at C-11 while the hydroxy group is at C-10 (δ_C 143.6, δ_H 5.13). This was supported by the observed HMBCs from 10–OH to C-9 and C-11, and from 11–OMe to C-11. Examination of the NMR data showed that one unit of the bisindole corresponds to the known alkaloid, taberhanine (**231**), while the other unit of the bisindole was readily deduced to be a 11-hydroxydeoxoapodine (or apocidine G (**26**) from the excellent agreement of the non-aromatic ^{13}C NMR resonances of this unit with those of **26**. The ^{1}H and ^{13}C NMR data of **59** showed a striking similarity to those of conophylline (**538**) and its congeners[267–269] except for the changes resulting from the change of the second monomer unit from 11-hydroxypachisyphine to apocidine G [i.e., the absence of the epoxide function and the presence of the tetrahydrofuranyl ring in **59** instead of an ethyl side chain in conophylline (**538**)].

The ethyl side chain is associated with the taberhanine unit from the three-bond correlations observed from H-18 to C-20 and from H-19 to C-17 and C-21 in the HMBC spectrum. The placement of the OH group at C-15 was based on the observed C-15 carbon shift at δ 69.5, as well as the coupling constant of H-15 (J = 11, 3.5 Hz), since on exchange with deuterium the H-15 doublet of doublets collapses to a doublet (J = 3.5 Hz).

The similarity of the H-3, H-14, and H-15 resonances of the piperidine ring D of the taberhanine unit of **59** with that of conophylline (**538**), indicated a similar mode of connection of the monomeric entities, i.e. via formation of a central dihydrofuran ring. This was also supported by the three-bond correlations from H-3 to H-9' and H-11' in the HMBC spectrum (Figure 2.113). The overall structure is consistent with the HMBC data. The relative configuration of **59** was deduced to be similar with that of conophylline (**538**) from examination of the NOE data (Figure 2.114). The structure and

absolute configuration were also confirmed by X-ray diffraction analysis (Figure 2.115).

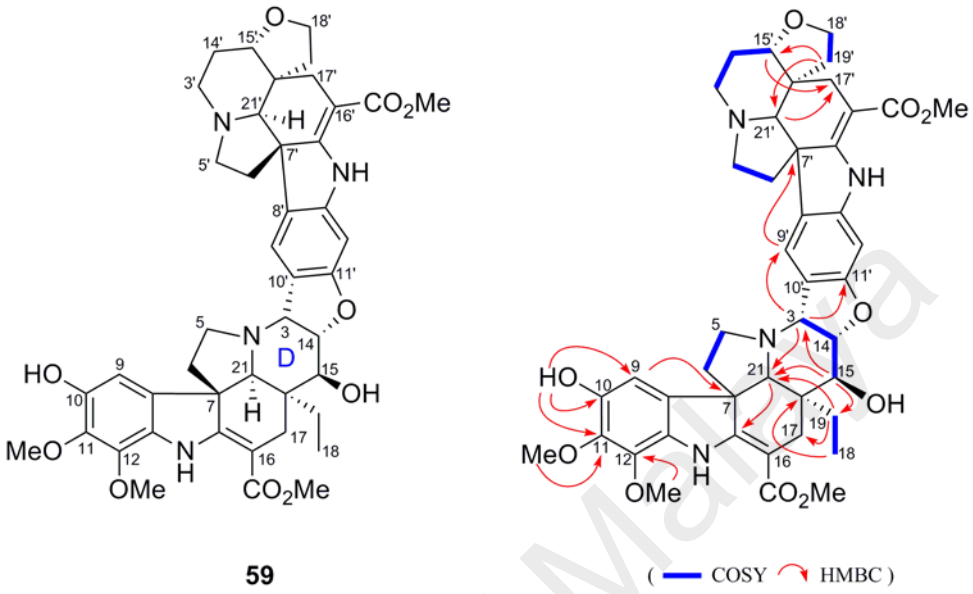


Figure 2.113: COSY and selected HMBCs of **59**

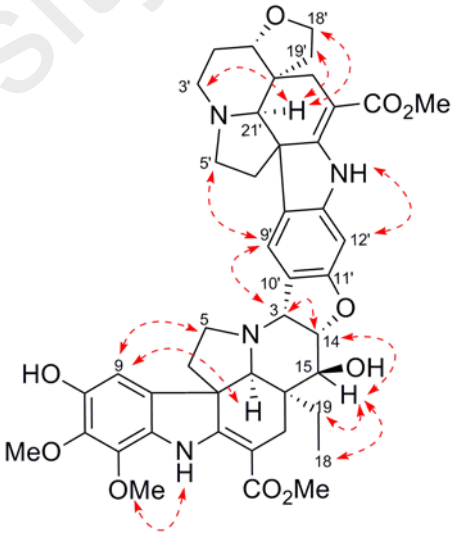


Figure 2.114: Selected NOEs of **59**

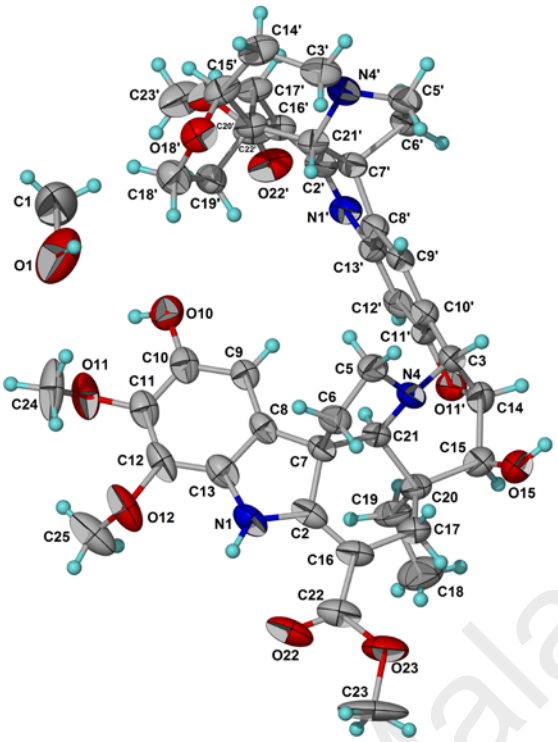


Figure 2.115: X-ray crystal structure of **59**

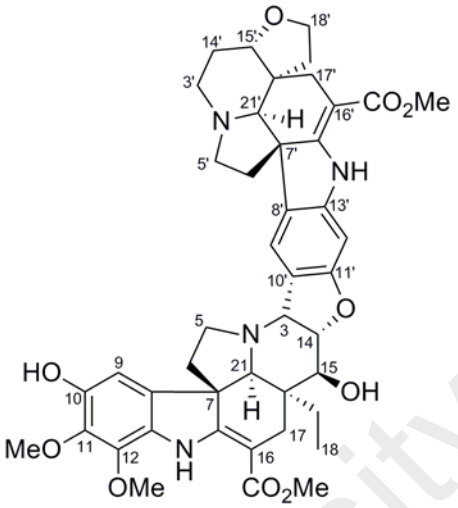
Table 2.39: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Conofolidine (**59**)[a]

H/C	δ_C	δ_H (*J*/Hz)	H/C	δ_C	δ_H (*J*/Hz)
2	164.7	-	2′	167.2	-
3	59.5	4.79 d (7.7)	3′	45.9	2.81 m
5	45.8	2.81 m	3′		2.95 m
5		2.97 m	5′	51.4	2.64 m
6	41.8	1.68 dd (11.5, 4)	5′		2.98 m
6		1.96 m	6′	45.7	1.76 dd (11.5, 4)
7	54.7	-	6′		2.06 td (11.5, 6.5)
8	133.6	-	7′	54.7	-
9	103.7	5.46 s	8′	130.9	-
10	143.6	-	9′	119.2	7.19 s
11	138.6	-	10′	113.7	-
12	136.7	-	11′	161.0	
13	128.8	-	12′	93.2	6.35 s
14	85.2	5.04 dd (7.7, 3.5)	13′	145.0	-
15	69.5	4.15 br dd (11, 3.5)	14′	26.5	1.98 m
16	90.7	-	14′		1.98 m
17	22.1	2.39 d (15.3)	15′	80.2	3.72 m
17		2.73 br d (15.3)	16′	94.3	-
18	7.4	0.70 t (7.3)	17′	27.9	2.33 br d (14.5)
19	26.4	0.83 dq (14.5, 7.3)	17′		2.74 d (14.5)
19		1.51 dq (14.5, 7.3)	18′	65.8	3.76 m
20	44.9	-	18′		3.87 m
21	65.3	2.57 br s	19′	35.8	1.55 ddd (13, 10, 7.8)
CO_2Me	168.7	-	19′		1.72 m
CO_2*Me*	51.1	3.77 s	20′	46.3	-
11-OMe	60.9	3.79 s	21′	68.8	2.93 br s
12-OMe	60.4	3.86 s	*C*O_2Me′	168.8	-
10-OH	-	5.13 br s	CO_2*Me*′	51.0	3.78 s
15-OH	-	2.64 br d (11)	NH′	-	8.88 br s
NH	-	8.77 br s			

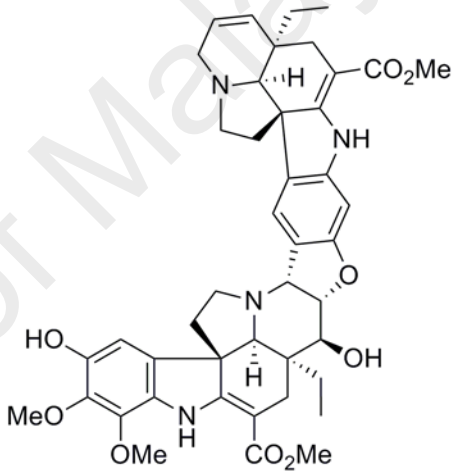
[a]$CDCl_3$, 600 (^{1}H) and 150 MHz (^{13}C); assignment based on COSY, HSQC, HMBC and NOESY.

2.1.11.4 Conophyllidine (60)

In addition to the above new bisindole (conofolidine **59**), the known bisindole conophyllidine (**60**)[268] was also isolated in this study. The ^{1}H NMR spectrum of **60** is shown in Figure 2.117, while the ^{1}H and ^{13}C NMR data are summarized in Table 2.40. Other data are given in the Experimental Section.



59



60

Table 2.40: ^{1}H and ^{13}C NMR Spectroscopic Data (δ) of Conophyllidine (**60**)[a]

H/C	δ_C	δ_H (*J*/Hz)	H/C	δ_C	δ_H (*J*/Hz)
2	164.6	-	2′	166.5	-
3	59.3	4.80 d (8)	3′	50.1	3.28 d (16)
3		-	3′		3.47 dd (16, 3)
5	45.8	2.85 ddd (11.5, 8.5, 4)	5′	50.7	2.77 m
5		2.97 dd (8.5, 6)	5′		3.07 t (6.5)
6	41.7	1.67 dd (11.5, 4)	6′	44.8	1.80 dd (11.5, 4)
6		1.99 td (11.5, 6)	6′		2.09 td (11.5, 6.5)
7	54.6	-	7′	54.7	-
8	133.4	-	8′	131.1	-
9	104.1	5.53 s	9′	119.2	7.21 s
10	143.6	-	10′	113.7	-
11	138.6	-	11′	160.8	-
12	136.6	-	12′	92.9	6.35 s
13	128.5	-	13′	144.9	-
14	85.0	5.05 dd (8, 4)	14′	124.2	5.79 br s
15	69.4	4.15 d (4)	15′	132.9	5.79 br s
16	90.4	-	16′	91.9	-
17	22.0	2.39 d (15.5)	17′	28.2	2.39 d (15.5)
17		2.73 dd (15.5, 1)	17′		2.61 d (15.5)
18	7.3	0.70 t (7.5)	18′	7.4	0.72 t (7.5)
19	26.3	0.84 dq (14, 7.5)	19′	27.2	1.10 dq (14, 7.5)
19		1.17 dq (14, 7.5)	19′		1.22 dq (14, 7.5)
20	44.6	-	20′	40.6	-
21	65.1	2.61 br s	21′	70.7	2.78 br s
CO_2Me	168.6	-	*C*O_2Me′	168.7	-
CO_2*Me*	50.8	3.77 s	CO_2*Me′*	50.7	3.77 s
11-OMe	60.7	3.81 s	NH′	-	9.00 br s
12-OMe	60.3	3.85 s			
10-OH	-	5.10 s			
NH	-	8.77 br s			

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

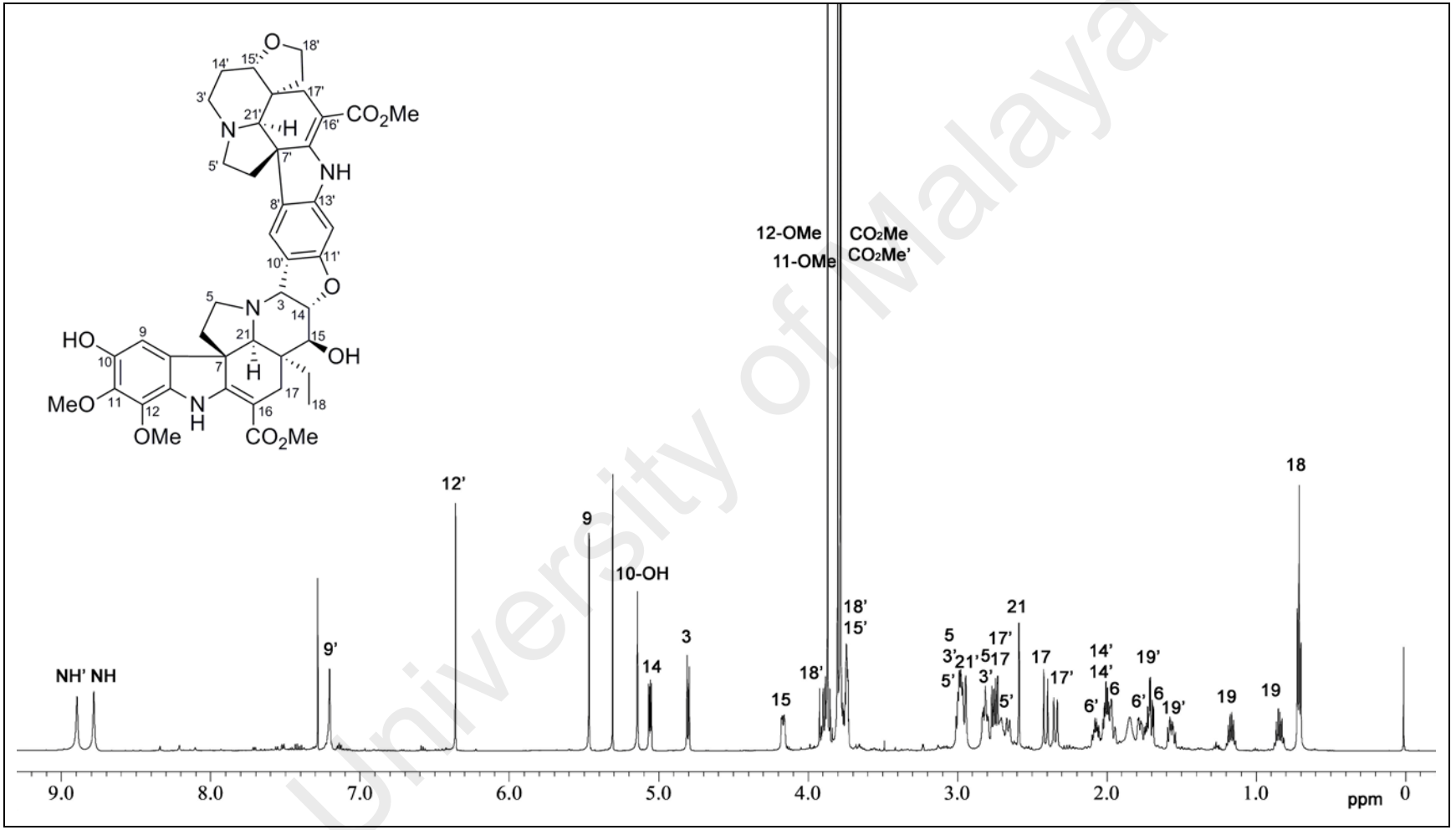


Figure 2.116: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of Conofolidine (**59**)

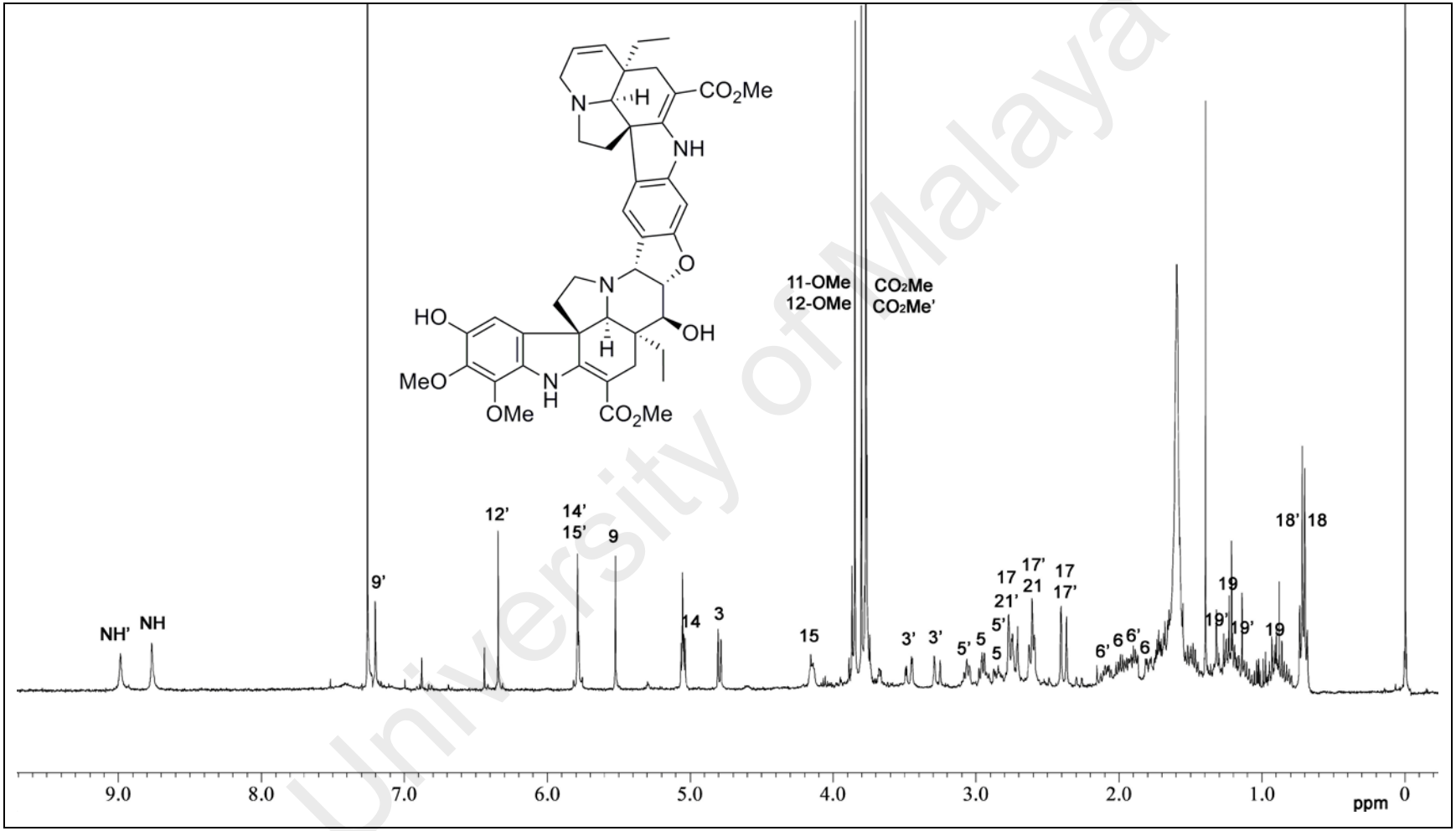


Figure 2.117: ^{1}H NMR Spectrum ($CDCl_3$, 400MHz) of Conophyllidine (**60**)

2.2 Biological Activity

2.2.1 General

Alkaloids are important active components due to their wide spectrum of pharmacological activities. In addition to our systematic chemical investigations, alkaloids isolated from the present study were screened for their biological activities, in particular for their cytotoxic effects, including their potential in reversing multidrug resistance (MDR) in vincristine-resistant KB cells, as well as vasorelaxation effects in isolated rat aorta rings.

2.2.2 Cytotoxicity and Reversal of Multidrug Resistance (MDR)

Cancer ranks among the leading causes of morbidity and mortality worldwide.[439] Cancers are diseases characterized by the growth of abnormal cells, which tend to proliferate in an uncontrolled way and, in some cases, to metastasize. The development of new anticancer drugs as well as more effective treatment strategies, are therefore of great importance in drug discovery and clinical therapy. Simultaneous resistance of cancer cells to multiple anticancer agents poses a major impediment in cancer chemotherapy which is commonly known as multidrug resistance (MDR).[440,441] MDR cells are usually characterized by the overexpression of an energy-dependent drug transport protein, P-gp. P-gp acts as drug efflux pump, actively extruding drugs from an intracellular environment, which results in reduced efficacy of drugs.[440] One of the approaches to overcome the MDR is to discover new chemosensitizing substances, which show low degree of toxicities but are effective against drug resistant resistant tumors.[442] There are several MDR-reversing agents that have been reported to overcome

MDR, including the calcium blockers (e.g. verapamil), antiarrhythmic agents (e.g. quinidine and reserpine), the immunosuppressant (e.g. cyclosporine A), and the antiestrogen anticancer drug (e.g. tamoxifen).[443] However, the mechanisms by which these drugs reverse MDR is not fully understood, and to date there are no MDR reversal agents available clinically (due to their toxicity), although several are currently undergoing clinical evaluation for the treatment of resistant tumors.[444,445]

As part of our group's ongoing search of new compounds from plants, alkaloids obtained from the present study were screened for their cytotoxic effects against several human cancer cell lines (KB, PC-3, LNCaP, MCF7, MDA-MB-231, HT-29, HCT 116, and A549), as well as 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 2.41.

The bisindole alkaloids, 16'-decarbomethoxyvoacamine (**58**) and conofolidine (**59**) displayed strong cytotoxic effects against a panel of human cancer cell lines, while vandrikine (**29**) displayed only moderate activity towards KB, MDA-MB-231, HT-29, and HCT 116 cancer cells. The cytotoxic effect of voacamine type alkaloids has been noted previously,[446,447] while conophylline (a congener of conofolidine) has been reported to be an inhibitor of the *ras* function.[448] Conophylline has also been reported to induce β-cell differentiation and to stimulate insulin production in rat pancreatic acinar carcinoma cells and in cultured fetal rat pancreatic tissue.[449,450] Tabertinggine (**2**) showed weak activity in reversing MDR in vincristine-resistant KB cell, while other tested compounds were inactive against various human cancer cell lines.

Table 2.41: Cytotoxic Effects of Alkaloids Isolated from *T. corymbosa*

Compound	**IC_{50}, μg/mL**									
	KB/S	**KB/VJ300**	**KB/VJ300[a]**	**PC-3**	**LNCaP**	**MCF7**	**MDA-MB-231**	**HT-29**	**HCT 116**	**A549**
Voatinggine (**1**)	>30	>30	>30							
Tabertinggine (**2**)	>30	>30	13.3							
Cononuridine (**3**)	>30	>30	>30							
Criofolinine (**4**)	>30	>30	>30	>30					>30	>30
Vernavosine ethyl ether (**6**)	>30	>30	>30	>30					>30	>30
Taberisidine (**7**)	>30	>30	>30							
Iboga										
Conodusine A (**8**)	>30	>30	>30							
Conodusine E (**12**)	>30	>30	>30							
19(*S*)-Hydroxyibogamine (**14**)	>30	>30	>30	>30			>30	>30	>30	>30
19(*R*)-Hydroxyibogamine (**15**)	>30	>30	>30							
Coronaridine (**16**)	16.9	18.9	7.7							
(–)-Heyneanine (**17**)	>30	>30	>30							
Voacristine (**19**)	>30	>30	>30							
Aspidosperma										
Apocidine A (**20**)	>30	>30	>30							
Apocidine B (**21**)	28.6	>30	>30	9.4			28.2	22	18.5	>30
Apocidine G (**26**)	>30	>30	>30							
Hedrantherine (**27**)	>30	>30	>30							
Deoxoapodine (**28**)	>30	>30	21.7	>30			>30	>30	>30	>30
Vandrikine (**29**)	4.6	>30	>30	19.4			5.3	7	7.7	>30

Table 2.41, 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**
Corynanthean										
β-Yohimbine (**38**)	>30	>30	>30							
Yohimbine (**39**)	>30	>30	>30							
β-Yohimbine pseudoindoxyl (**46**)	>30	>30	>30							
Bisindole										
16'-Decarbomethoxyvoacamine (**58**)	3.4	3.8	4.5	1.8	8.6	4	1.6	0.7	1	4.5
Conofolidine (**59**)	0.39	5.9	1.1	0.9	0.2	4.7	0.6	0.23	0.3	>30
Control										
Vincristine	2 ng/mL	5.4	5							
Cisplatin				0.6	2.4	0.7	1.1	4.8	4.3	1
Verapamil	>30	>30	6.4							

[a]With added vincristine 0.1 μg/mL, which did not affect the growth of the KB/VJ300 cells; 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.

2.2.3 Vasorelaxation Activity

Hypertension (also known as high blood pressure) remains a major public health problem and in particular as a major risk factor for strokes, cardiovascular diseases as well as renal disease.[451] Hypertensive disease is characterized by the abnormal vascular activity, including impaired endothelium-dependent relaxation and enhanced sensitivity to vasoconstrictors.[452,453] The mechanisms of action by antihypertensive drugs (vasodilators) are based on their dependence or independence on endothelium, the involvement of the NO/cGMP pathway, the blockage of voltage-dependent Ca^{2+} channels, and the activation of K^+ channels.[454,455] Although there is a large number of antihypertensive drugs available nowadays, their usefulness however is limited due to low efficacy, side effects, poor patient compliance and failure to reduce the cardiovascular risk to the level of the general population.[454,456,457] Therefore, it is important to discover new vasodilators from natural sources, as well as to study their mechanisms of action involving vasorelaxation.

In this study, several alkaloids from different structural groups (**6**, **8**, **28**, **38**, **39**, **44**, **45**, and **51**) were chosen to evaluate the vasorelaxation activity towards rat aortic rings. The results are summarized in Table 2.42 and Figure 2.118. Vernavosine ethyl ether (**6**), β-yohimbine (**38**), yohimbine (**39**),[458–460] and normacusine B (**51**),[461] were found to induce concentration-dependent relaxation in phenylephrine-precontracted rat aortic rings.

Table 2.42: Vasorelaxation effects of alkaloids (**6, 38, 39, 51**) on phenylephrine-induced contraction in isolated rat aortic rings

Compound	**EC_{50} (μM)**	**E_{max} (% relaxation)**
Vernavosine ethyl ether (**6**)	2.48	39.4 ± 4.4
β-Yohimbine (**38**)	0.1	7118.7 ± 2.6
Yohimbine (**39**)	0.04	121.1 ± 10.6
Normacusine B (**51**)	0.01	103.7 ± 9.5
Isoprenaline	0.08	79.7 ± 4.2

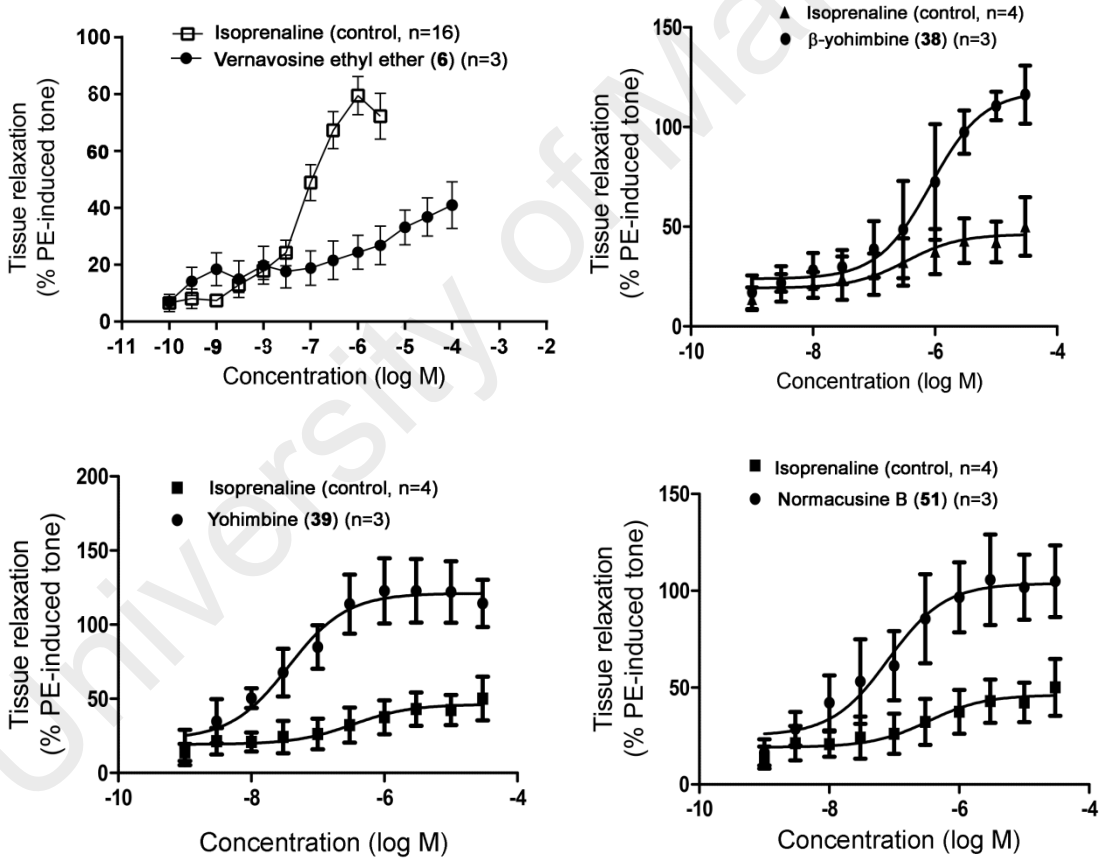


Figure 2.118: Vasorelaxation effects of alkaloids (**6**, **38**, **39**, **51**) on phenylephrine-induced contraction in isolated rat aortic rings

CHAPTER 3: EXPERIMENTAL

3.1 Source and Authentication of Plant Materials

Plant material (stem-bark and leaves) of *T. corymbosa* Roxb. ex Wall. was collected near Panti Forest, Johor, Malaysia, and identified by Dr. Richard C. K. Chung, Forest Research Institute, Malaysia (FRIM). Herbarium voucher specimens (K684, 685) are deposited at the Herbarium, University of Malaya. All plant materials were screened (TLC/dragendorff's reagent) for their alkaloidal constituents before any chemical analysis was carried out.

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 obtained on a Shimadzu UV-3101PC or a UV-2600 spectrophotometer in absolute ethanol. ECD spectra were measured using a JASCO J-815 CD spectrometer (Pharmaceutical Analysis Laboratory, Faculty of Pharmacy, UiTM, Puncak Alam Campus) in methanol. IR spectra were recorded on a PerkinElmer Spectrum 400 FT-IR/FT-FIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on JEOL JNM-ECA 400, or Bruker Avance III 400 and 600 spectrometers. Coupling constants (*J*) are reported in Hz and chemical shift (δ) in ppm. ESIMS and HRESIMS were obtained on an Agilent 6530 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, which was passed through activated neutral alumina before use.

3.3 X-ray Diffraction Analysis

X-ray diffraction analyses were carried out on a Bruker SMART APEX II CCD diffractometer with Mo Kα radiation (λ = 0.71073 Å) at 100–150 K, or 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. The structures were solved by direct methods (SHELXS-97) and refined with full-matrix least-squares on F^2 (SHELXL-2014/7). 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 structures were determined by refinement of the Flack parameter[462–464] and computational of the Hooft parameter.[465,466]

3.4 Computational Methods

Structures corresponding to compounds (+)-**8** (14*S*, 16*R*, 20*S*, 21*R*), (–)-**8** (14*R*, 16*S*, 20*R*, 21*S*), **11a** (7*R*, 14*S*, 16*R*, 20*S*, 21*R*), **11b** (7*S*, 14*S*, 16*R*, 20*S*, 21*R*), **12a** (14*R*, 16*S*, 20*S*, 21*S*), and **12b** (14*S*, 16*R*, 20*R*, 21*R*) were initially built using GaussView 5 and then optimized at the semi-empirical level of theory (AM1). These structures were then imported into the Gaussian 09software[467] for DFT-level geometry optimization using the B3LYP functional with basis set of 6-311++G(d,p) to obtain the energy minimized conformations. TDDFT ECD calculations were performed at the B3LYP/6-311++G(d,p) level with the optimized structures using a PCM solvation model for methanol. The ECD curves were produced by the SpecDis (version 1.64) software.[468] Optical rotation calculations at the wavelength of 589.3 nm were performed with the optimized structures at the B3LYP/6-311++G(d,p) computational level using a PCM solvation model for chloroform.

3.5 Chromatographic Methods

3.5.1 Column Chromatography

Flash chromatography was performed using Merck silica gel 9385 (230-400 Mesh ASTM). The ratio of silica gel to the sample was approximately 30:1 for crude samples and 100:1 for semi-pure fractions. The gel was made into slurry with dichloromethane before it was packed onto the column and was allowed to equilibrate for at least an hour before use. When diethyl ether was used as an eluting solvent, the column was packed by the dry packing method. The solvent systems normally used as eluents were dichloromethane with increasing methanol gradient or diethyl ether with increasing ethyl acetate gradient. Fractions were monitored by thin layer chromatography (TLC) and appropriate fractions were combined and where necessary subjected to further separation by re-chromatography or preparative radial chromatography.

3.5.2 Thin Layer Chromatography

Thin layer chromatography (TLC) was routinely used to detect and separate the various alkaloids. The crude alkaloidal extracts, fractions from chromatography, and isolated pure alkaloids were examined by TLC using pre-coated 5 x 10 cm glass and aluminum plates, 0.25 mm thickness, silica gel 60 F_{254} (Merck, Darmstadt, G.F.R.). The TLC plates were spotted with a piece of fine glass capillary tube and 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. The hR_f values of the alkaloids are tabulated in Table 3.1.

Table 3.1: The hR_f Values of Alkaloids Isolated from *Tabernaemontana corymbosa*

Alkaloid	CH_2Cl_2:MeOH (99:1)	Et_2O	EtOAc	CH_2Cl_2:MeOH (10:1)	EtOAc:MeOH (20:1)
Voatinggine (**1**)	14	55	63	68	69
Tabertinggine (**2**)	1	8	8	50	19
Cononuridine (**3**)	27	43	56	79	66
Criofolinine (**4**)	2	4	24	43	46
Vernavosine ethyl ether (**6**)	3	8	19	55	37
Taberisidine (**7**)	6	13	42	56	54
Conodusine A (**8**)	9	22	35	38	48
Conodusine B (**9**)	4	4	32	17	10
Conodusine C (**10**)	1	0	0	14	0
Conodusine D (**11**)	0	0	4	41	11
Conodusine E (**12**)	26	59	66	83	72
Ibogamine (**13**)	8	59	45	62	57
19(*S*)-Hydroxyibogamine (**14**)	7	17	35	45	31
19(*R*)-Hydroxyibogamine (**15**)	6	18	19	40	28
Coronaridine (**16**)	57	83	75	87	79
Heyneanine (**17**)	20	43	53	77	64
Voacangine (**18**)	40	83	72	86	77
Voacristine (**19**)	19	26	49	74	60
Apocidine A (**20**)	10	46	54	67	62
Apocidine B (**21**)	27	43	56	73	66
Apocidine C (**22**)	10	27	52	77	61
Apocidine D (**23**)	3	12	41	66	55
Apocidine E (**24**)	6	38	52	71	61
Apocidine F (**25**)	9	14	40	77	55
Apocidine G (**26**)	5	48	56	66	65
Hedrantherine (**27**)	8	42	52	64	64
Deoxoapodine (**28**)	31	66	61	82	69
Vandrikine (**29**)	20	60	58	90	68
Conoduzidine A (**30**)	10	4	8	65	17
Conoduzidine B (**31**)	2	4	6	57	15
Conoduzidine C (**32**)	2	4	6	57	14
14,15-Dehydro-16-*epi*-vincamine (**33**)	5	32	40	65	48

Table 3.1, continued

Alkaloid	CH_2Cl_2:MeOH (99:1)	Et_2O	EtOAc	CH_2Cl_2:MeOH (10:1)	EtOAc:MeOH (20:1)
16α-Methoxycarbonyl-16,17-dihydro-19-*epi*-ajmalicine (**34**)	9	43	54	76	64
Tetrahydroalstonine (**35**)	48	75	73	85	77
16(*R*)-Sitsirikine (**36**)	4	26	49	58	60
16(*R*)-18,19-Dihydrositsirikine (**37**)	2	20	20	49	36
β-Yohimbine (**38**)	3	7	14	51	34
Yohimbine (**39**)	1	22	22	47	36
α-Yohimbine (**40**)	6	25	49	61	62
19,20-Dehydro-α-yohimbine (**41**)	2	20	20	49	36
19,20-Dehydro-β-yohimbine (**42**)	0	6	23	46	32
19,20-Dehydroyohimbine (**43**)	1	6.3	19	45	27
7(*S*)-β-Yohimbine oxindole (**44**)	3	9	30	46	44
7(*R*)-β-Yohimbine oxindole (**45**)	0	3	8	36	20
β-Yohimbine pseudoindoxyl (**46**)	1	2	5	41	12
β-Yohimbine pseudoindoxyl *N*-oxide (**47**)	0	0	0	9	0
Vobasine (**48**)	9	19	26	63	39
16-*Epi*-affinine (**49**)	4	23	17	48	29
Tabernaemontanine (**50**)	19	36	42	73	57
Normacusine B (**51**)	0	2.5	6.3	26	15
Norfluorocurarine (**52**)	3	3	3	47	4
N(4)-Chloromethylnorfluorocurarine chloride (**53**)	0	0	0	7	0
Velbanamine (**54**)	7	15	28	46	32
Tabernamidine A (**5**)	0	0	3	10	7
Tabernamidine B (**56**)	0	0	0	5	3
Tabernamine (**57**)	0	0	3	25	10
16'-Decarbomethoxyvoacamine (**58**)	0	4	6	32	15
Conofolidine (**59**)	0	6	34	73	55
Conophyllidine (**60**)	9	31	61	78	70

3.5.3 Preparative Radial Chromatography (Chromatotron)

Preparative radial chromatography (Chromatotron) was carried out using a round chromatographic plate measuring 24 cm in diameter. To prepare the chromatographic plate, the edge of the plate is secured with cellophane tape to form a mould. Silica gel (Merck 7749, 50 g) is added to about 110 mL of cold distilled water to give a slurry. The slurry is shaken and is then quickly poured onto the circular glass plate before setting commences. The circular glass plate is rotated while the gel is being poured to obtain an even setting. The plate is then left to air-dry for about an hour before being dried in an oven at 80 °C for about 12 hours. The sample was dissolved in a minimum volume of a suitable solvent and loaded at the centre of the plate while the plate is spinning to form a thin band. Elution is then carried with the appropriate solvent system. The fractions are collected, concentrated by rotary-evaporation, examined by TLC, and combined where appropriate. Some of the solvent systems used as eluents were:

Some of the solvent systems used as eluents were:

1. Dichloromethane
2. Dichloromethane: Methanol (with added 1% of liquid ammonia)
3. Diethyl ether
4. Diethyl ether (with added 1% of liquid ammonia)
5. Diethyl ether: Methanol
6. Diethyl ether: Methanol (with added 1% of liquid ammonia)
7. Ethyl acetate (with added 1% of liquid ammonia)
8. Ethyl acetate: Hexanes (with added 1% of liquid ammonia)
9. Acetone: Hexanes

3.5.4 Gel Permeation Chromatography

The dried powder of Sephadex LH-20 or G-75 was allowed to swell in methanol for an overnight before use. The slurry was poured onto the column and allowed to equilibrate to room temperature. The sample was filtered with a 0.45 μm nylon membrane before it was loaded into the column to ensure a longer column life. The column was regenerated by washing of the Sephadex LH-20 or G-75 gel with 2-3 column volumes of eluent, followed by re-equilibration.

3.6 Spray Reagents (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 equal volumes of solution A and B. 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 on the developed TLC plates indicate the presence of alkaloids.

3.7 Extraction of Alkaloids

The plant materials (stem-bark and leaves) were dried and ground before extracting with 95% ethanol for 2-3 days at room temperature. The ethanol extract was filtered and the residue was then re-extracted with a fresh portion of distilled ethanol. This procedure was repeated 5 or 6 times. The combined extract was then concentrated by distillation under reduced pressure using a rotary-evaporator to about a tenth of the original volume. The concentrated extract was then added slowly into 3% tartaric acid with constant stirring. The acidic solution was then filtered through kieselguhr to remove the non-alkaloidal substances. The filtrate was then basified with concentrated ammonia solution to about pH 10 with cooling and the liberated alkaloids were extracted exhaustively with dichloromethane. The dichloromethane extract was then washed with distilled water and dried over anhydrous sodium sulfate. Finally, the solvent was removed by evaporation under reduced pressure 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 vacuum chromatography over silica gel. The column was eluted with dichloromethane, followed by a stepwise increase of methanol gradient. Based on TLC, the many fractions collected were pooled into several major fractions, which were then subjected to further fractionation by flash chromatography, vacuum chromatography, gel permeation chromatography, or preparative radial chromatography until pure compounds are obtained.

3.8.2 Isolation of Alkaloids from the Stem-bark of *Tabernaemontana corymbosa*

Extraction of 14 kg of stem-bark material yielded *ca.* 38 g of crude alkaloidal mixture. This alkaloidal mixture was then subjected to repeated chromatography, as summarized in the flow diagram shown in Figure 3.1 to yield 44 pure alkaloids.

3.8.3 Isolation of Alkaloids from the Leaf of *Tabernaemontana corymbosa*

Extraction of 13 kg of leaf material yielded *ca.* 60 g of crude alkaloidal mixture. This alkaloidal mixture was then subjected to repeated chromatography, as summarized in the flow diagram shown in Figure 3.2 to yield 26 pure alkaloids.

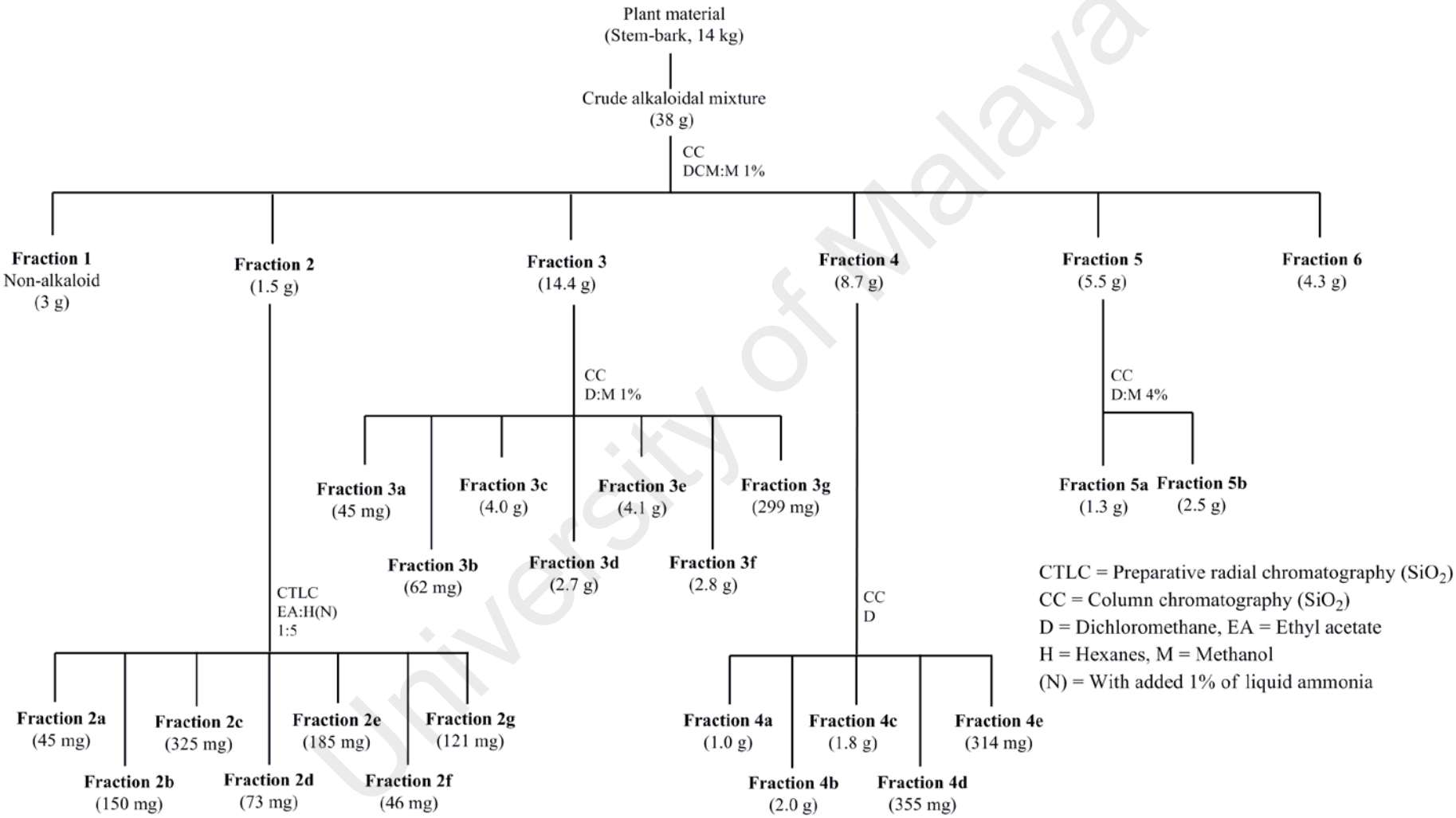


Figure 3.1: Isolation of alkaloids from the stem-bark extract of *Tabernaemontana corymbosa*

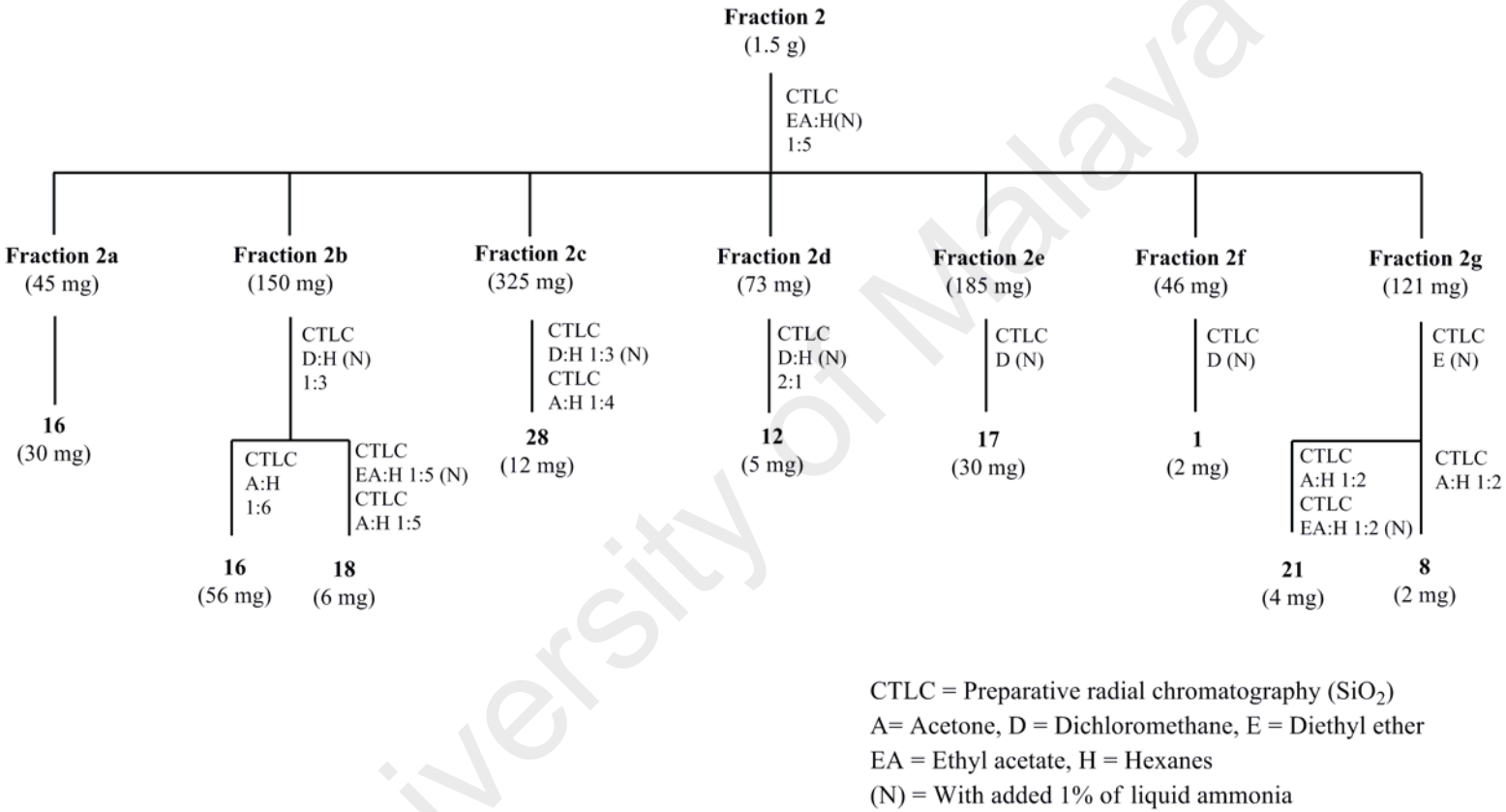


Figure 3.1, continued

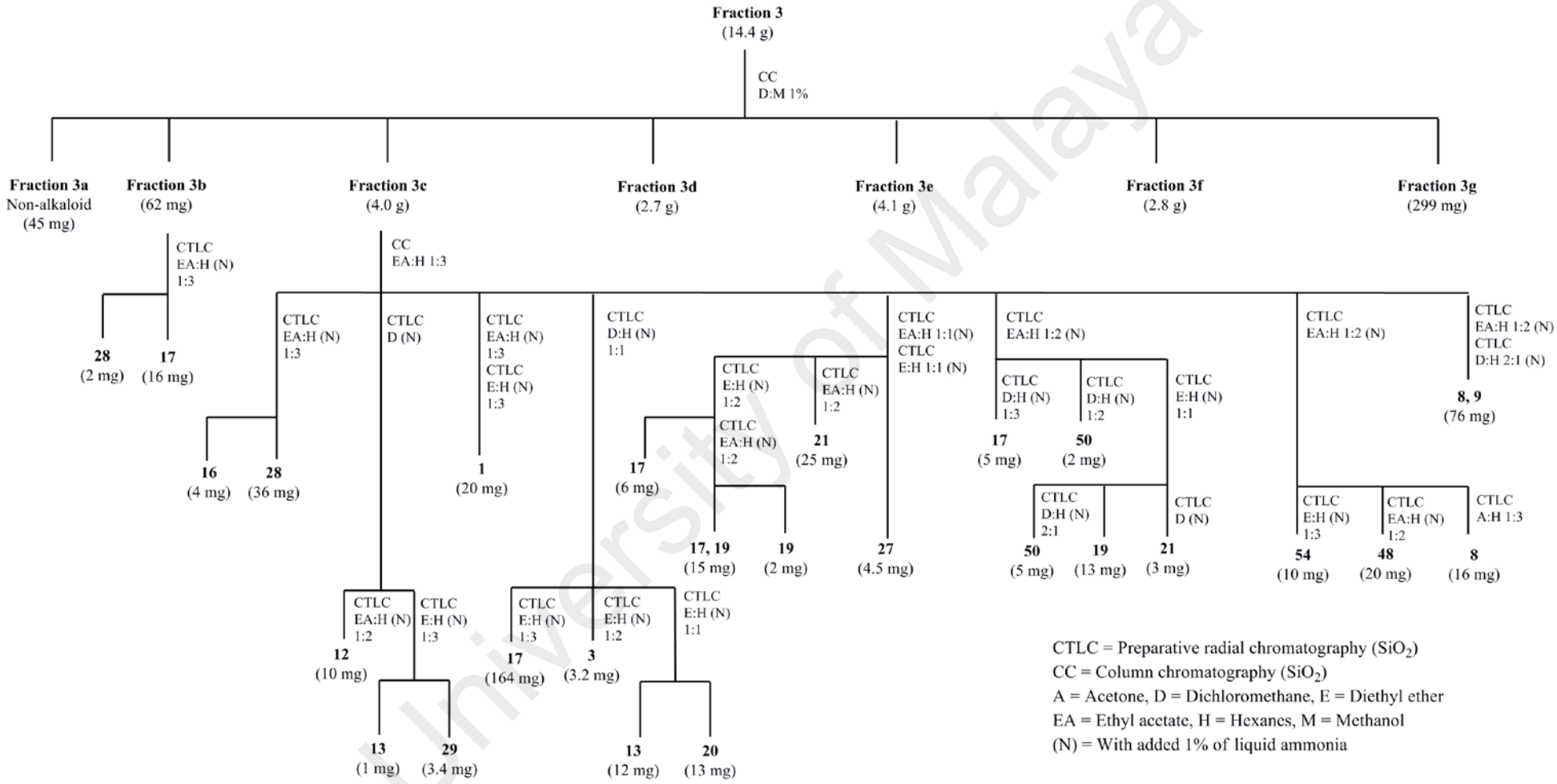


Figure 3.1, continued

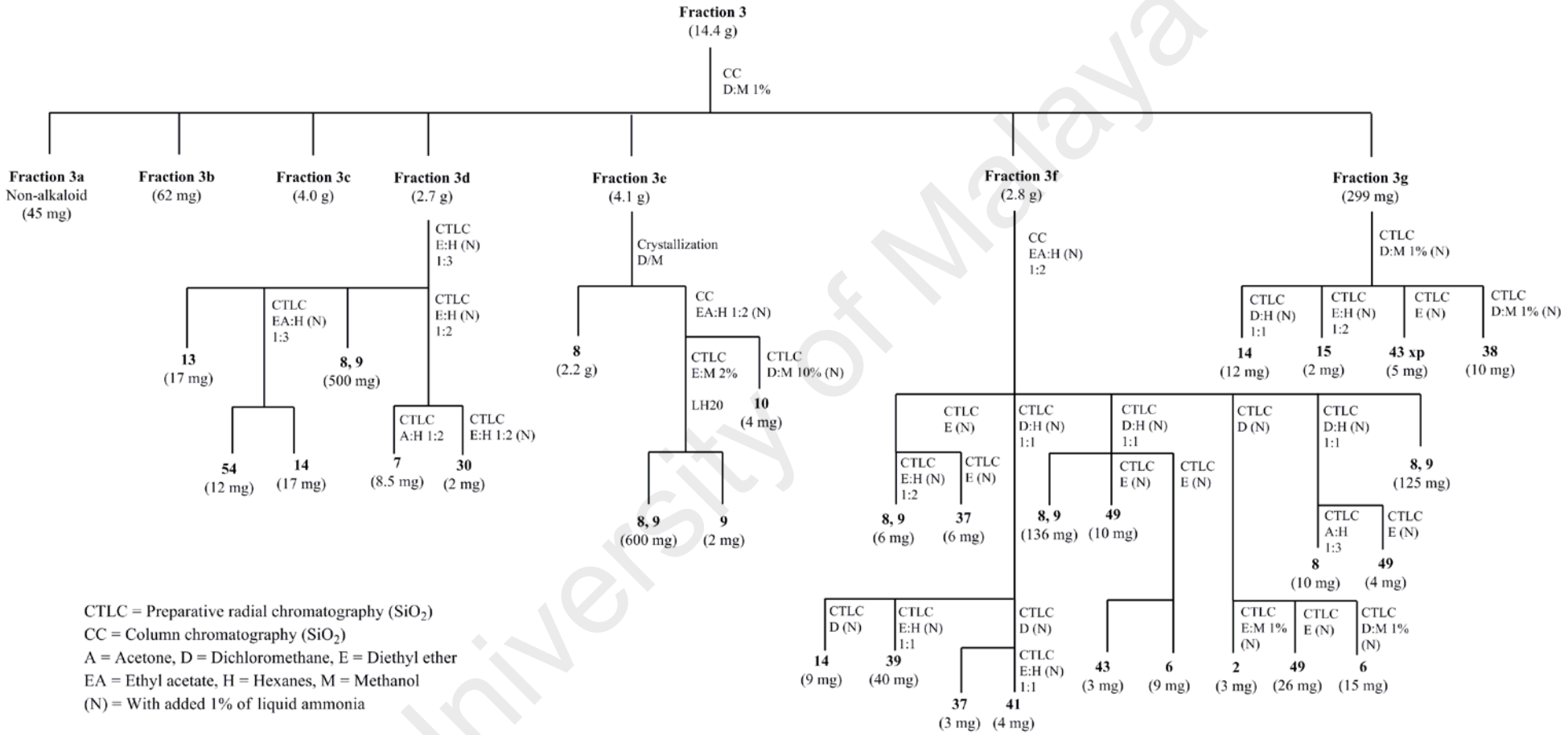


Figure 3.1, continued

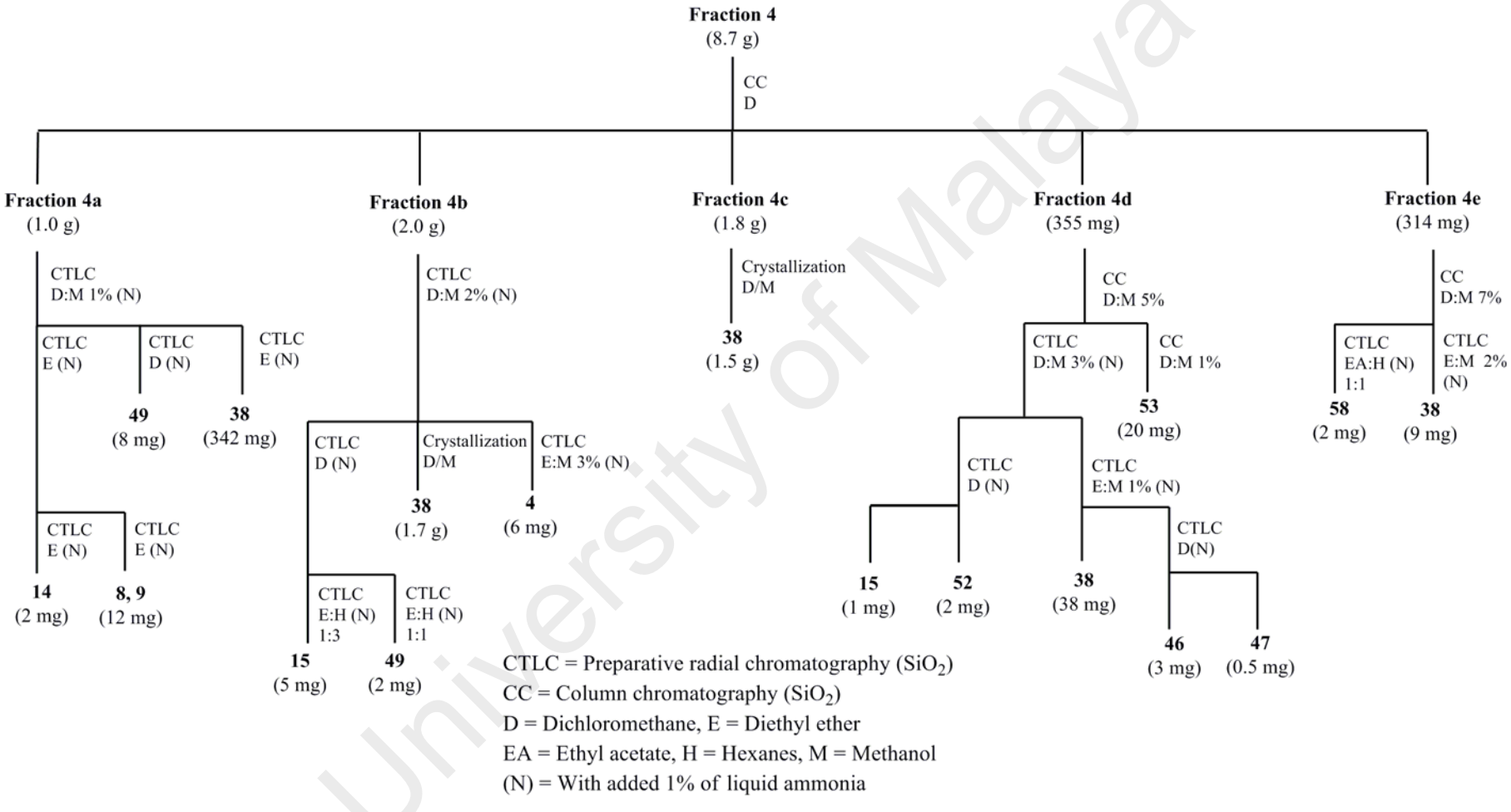


Figure 3.1, continued

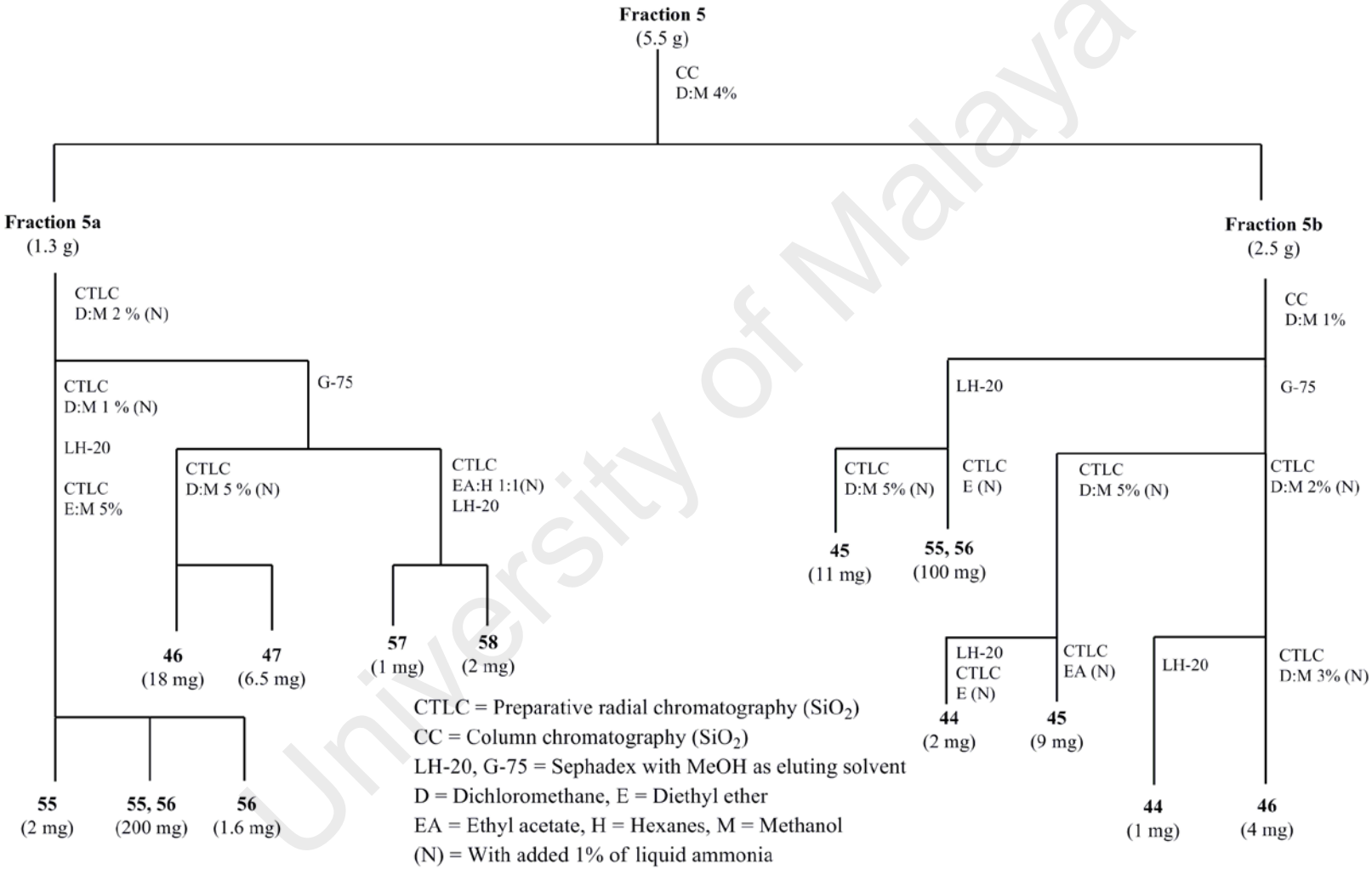


Figure 3.1, continued

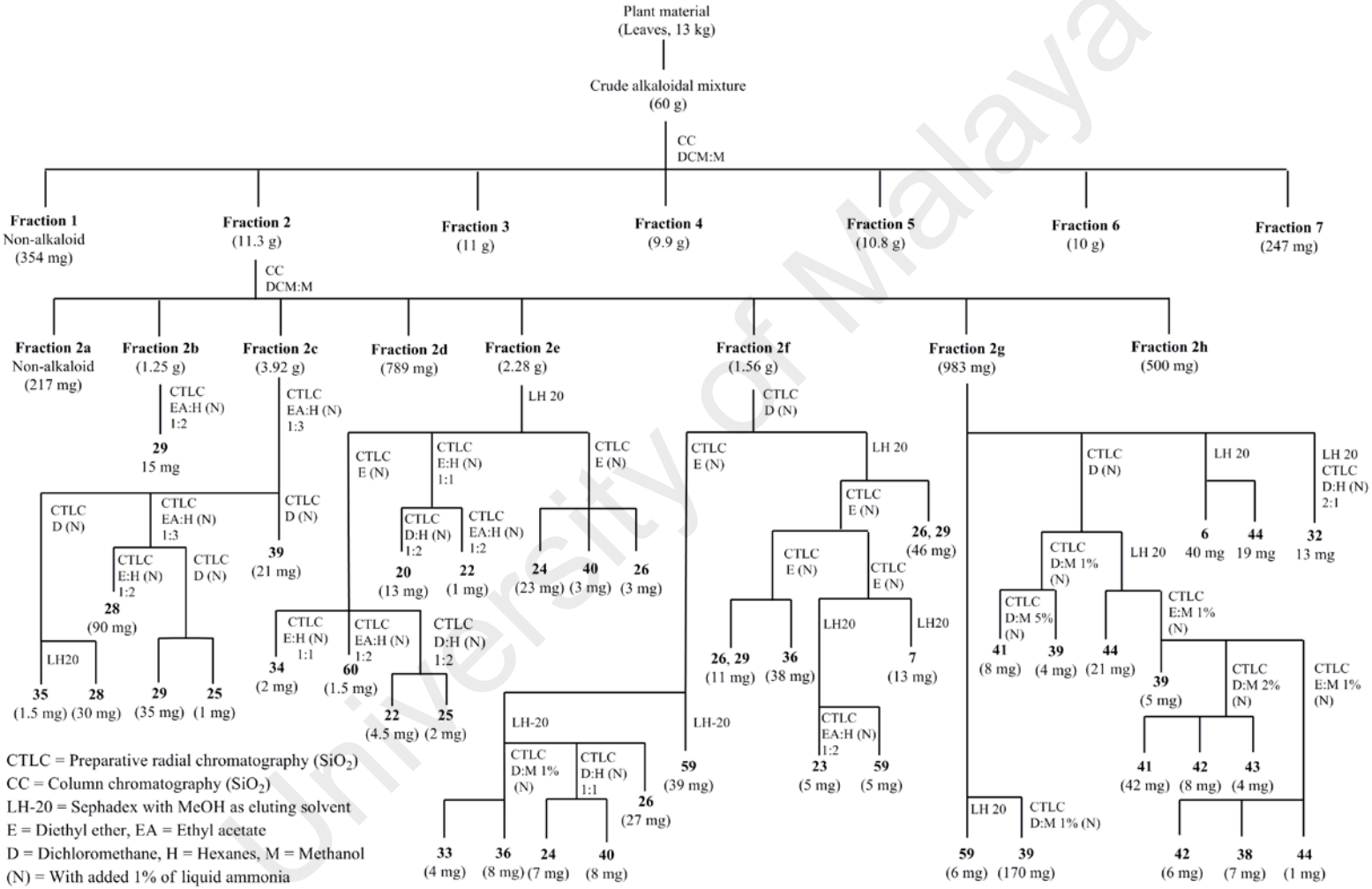


Figure 3.2: Isolation of alkaloids from the leaf extract of *Tabernaemontana corymbosa*

3.9 Compound Data

The following alkaloids were isolated from the stem-bark and leaf of *T. corymbosa*:

Voatinggine (1): colorless block crystals (CH_2Cl_2–hexanes); mp 186–188 ^oC; $[\alpha]^{25}_D$ +136 (*c* 0.49, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (4.05), 239 (3.99), 297 (3.47) nm; IR (dry film) ν_{max} 3391, 1650, 1611 cm^{-1}; HRESIMS *m/z* 311.1765 $[M + H]^+$ (calcd for $C_{19}H_{22}N_2O_2$ + H, 311.1754); ^1H and ^{13}C NMR data, see Table 2.2. HMBC: ^2J H-3 to C-14; H-5 to C-6; H-6 to C-5, C-7; H-15 to C-14, C-20; H-18 to C-19; H-21 to C-16. ^3J H-3 to C-2, C-15, C-17; H-5 to C-2, C-3; H-6 to C-2, C-8; 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-15 to C-3, C-17, C-21; H-16 to C-14, C-20; H-17 to C-3, C-15, C-21; H-18 to C-20; H-21 to C-15, C-17, C-19. NOESY: H-3α/H-3β, H-14, H-15β; H-3β/H-3α, H-5β H-14, H-17β; H-5β/H-5α, H-6β; H-5α/H-5β, H-6α; H-6α/H-5α, H-6β; H-6β/H-5α, H-5β, 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, NH; H-14/H-3α, H-3β, H-15α, H-15β, H-17α, H-17β; H-15β/H-3α, H-15α; H-15α/H-14, H-15β, H-17α; H-16/H-17α, H-17β, H-21; H-17α/H-14, H-16, H-17β; H-17β/H-3β, H-14, H-16, H-17α, NH; H-18/H-21; H-21/H-16, H-18; NH/H-12, H-17β.

Crystallographic data of 1: colorless block crystals, $C_{19}H_{22}N_2O_2$, *M*r = 310.39, monoclinic, belonging to space group $P2_1$, with *a* = 9.6564(3) Å, *b* = 8.3932(2) Å, *c* = 9.8414(3) Å, β =102.1833(3)º, *V* = 779.65(4) $Å^3$, D_{calcd} = 1.322 gcm^{-3}, *Z* = 2, crystal size 0.14 x 0.17 x 0.351 mm^3, *F*(000) = 332, Cu Kα radiation (λ = 1.54184 Å), T = 100K. The final R_1 value is 0.0373 (wR_2 = 0.1064) for 3040 reflections [$I>2\sigma(I)$]. Flack parameter [*x* = –0.17(19)], Hooft parameter [*y* = –0.10(4)]. CCDC number: 951763.

Tabertinggine (2): colorless needles ($CHCl_3$); mp 113–115 ^oC; $[\alpha]^{25}_D$ +107 (*c* 0.4, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 225 (4.78), 282 (4.43), and 289 (4.40) nm; IR ($CHCl_3$) ν_{max} 3466, 1667, 1628 cm^{-1}; HRESIMS *m/z* 293.1652 $[M + H]^+$ (calcd for $C_{19}H_{20}N_2O$ + H, 293.1648); ^1H and ^{13}C NMR data, see Table 2.3. HMBC: ^2J H-3 to C-14; H-5 to C-6; H-6 to C-5, C-7; H-14 to C-3; H-15 to C-20; H-17 to C-16; H-18 to C-19; H-21 to C-16; NH to C-2. ^3J H-3 to C-5, C-15, C-16; H-5 to C-3, C-7, C-16; H-6 to C-2, C-8; 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-15 to C-3, C-17, C-21; H-17 to C-3, C-15, C-21; H-21 to C-2, C-15, C-19; NH to C-7, C-8. NOESY/DNOE: H-3β/H-14, H-17β; H-3α/H-15α; H-5β/H-3β, H-5α, H-17β; H-5α/H-5β; H-6β/H-5β, H-6α, H-9; H-9/H-6β, H-10; H-10/H-9; H-11/H-12; H-12/H-11, NH; H-14/H-3β, H-15β, H-15α, H-17α, H-17β; H-15α/H-3α, H-14, H-15β; H-15β/H-14, H-15α, H-17α; H-17α/H-14, H-15β, H-17β, NH; H-18/H-21; H-21/H-18, NH; NH/H-12, H-17α, H-21.

Crystallographic data of 2: colorless needles, $C_{19}H_{20}N_2O.CHCl_3.H_2O$, *M*r = 429.77, orthorhombic, belonging to space group $P2_12_12_1$, with *a* = 6.7462(2) Å, *b* = 9.3007(3) Å, *c* = 32.0517(9) Å, *V* = 2011.06(11) $Å^3$, D_{calcd} = 1.419 gcm^{-3}, *Z* = 4, crystal size 0.36 x 0.12 x 0.02 mm^3, *F*(000) = 896, Mo Kα radiation (λ = 0.71073 Å), T = 100K. The final R_1 value is 0.0588 (wR_2 = 0.1228) for 3332 reflections [$I>2\ \sigma(I)$]. Flack parameter [*x* = 0.05(9)], Hooft parameter [*y* = 0.005(16)]. CCDC number: 951764.

Cononuridine (3): light yellowish oil; $[\alpha]^{25}_D$ –94 (*c* 0.05, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 226 (3.94), 251 sh (2.94), 281 (3.24) nm; IR (dry film) ν_{max} 3396, 1711, cm^{-1}; HRESIMS *m/z* 309.1600 $[M + H]^+$ (calcd for $C_{19}H_{20}N_2O_2$ + H, 309.1598); ^1H and ^{13}C NMR data, see Table 2.4. HMBC: ^2J H-5 to C-6; H-6 to C-5; H-15 to C-14, C-20; H-17 to C-14, C-16; H-18 to C-19; NH to C-2, C-13. ^3J H-3 to C-5, C-15, C-17; H-5 to C-3,

C-16; H-6 to C-2, C-8, C-21; H-9 to C-7, C-11, C-13; H-10 to C-8; H-11 to C-9, C-13; H-12 to C-8, C-10; H-15 to C-3, C-17; H-16 to C-14; H-17β to C-2, C-3, C-15, C-21; H-21 to C-17, C-19; NH to C-7, C-8. NOESY/DNOE: H-3a/H-3b, H-6β, H-14, H-17β; H-3b/H-3a, H-14, H-15β; H-5/H-6α, H-21; H-6β/H-6α, H-17β; H-6α/H-5α, H-6β, H-9; H-9/H-6α, H-10; H-11/H-12; H-14/H-17β; H-15α/H-14, H-15β, H-16, H-17α; H-15β/H-15α; H-16/H-15α, H-17α, H-21; H-17β/H-3a, H-14, H-17α; H-17α/H-14, H-15α, H-17β; NH/H-12, H-16.

Conversion of Cononuridine (3) to its Methyl Iodide Salt 3a: Iodomethane (0.5 mL, 8 mmol) was added to **3** (0.3 mg, 0.001 mmol), and the mixture allowed to stand for 24 h at rt. Excess iodomethane was then removed under reduced pressure to furnish a yellowish residue, which on recrystallization from MeOH gave the corresponding methyl iodide salt **3a**: light yellowish block crystals; mp 214–218 °C; HRDARTMS *m/z* 323.1773 $[M]^+$ (calcd for $C_{20}H_{23}N_2O_2$, 323.1760).

Crystallographic data of 3a: light yellowish block crystals, $C_{20}H_{23}N_2O_2^+I^-$, *M*r = 450.30, orthorhombic, space group $P2_12_12_1$, a = 7.6879(8) Å, b = 13.0251(14) Å, c = 18.905(2) Å, V = 1893.1(4) $Å^3$, Z = 4, D_{calcd} = 1.580 gcm^{-3}, crystal size 0.2 x 0.2 x 0.02 mm^3, $F(000)$ = 904, Mo Kα radiation (λ = 0.71073 Å), T = 100(2) K. The final R_1 value is 0.0439 (wR_2 = 0.1027) for 3636 reflections [$I>2\sigma(I)$]. The absolute configuration was determined on the basis of Flack parameter [x = –0.01(0.03)], refined using 1417 Friedel pairs. CCDC number: 1494344.

Criofolinine (4): colorless block crystals; mp > 190 °C (dec); $[\alpha]^{25}_D$ +87 (*c* 0.3, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (4.67), 2.38 (4.35), 316 (4.41) nm; IR (dry film)

ν_{max} 3393, 1699, 1648 cm^{-1}; HRESIMS *m/z* 399.1550 $[M + H]^+$ (calcd for $C_{21}H_{22}N_2O_6$ + H, 399.1551); ^1H and ^{13}C NMR data, see Table 2.5. HMBC: ^2J H-5 to C-6; H-6 to C-7; H-9 to C-8; H-15 to C-14, C-16, C-20; H-16 to C-15, C-17, C-22; H-18 to C-17, C-19; H-19 to C-18; H-20 to C-15, C-19, C-21. ^3J H-5 to C-7, C-14, C-21; H-6 to C-2, C-8; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-13; H-12 to C-10; H-15 to C-3, C-17, C-19, *C*CO_2Me; H-16 to C-14, C-18, C-20; H-18 to C-16, C-20; H-19 to C-17; H-20 to C-18; CO_2*Me* to *C*O_2Me, NH to C-8. NOESY/DNOE: H-5β/H-5α; H-5α/H-5β, H-6α, H-6β; H-6α/H-5α, H-6β; H-6β/ H-5α, H-5β, H-6α; H-9/H-6α, H-6β, H-10; H-11/H-10; H-15/H-17, H-19α; H-16/H-18β, H-20; H-17/H-15, H-16, H-18α, H-19α; H-18β/H-16, H-18α, H-20; H-18α/H-18β, H-19α; H-19β/H-18β, H-19α, H-20; H-20/H-16, H-18β, H-19β; CO_2*Me*/NH; NH/H-12, CO_2*Me*.

Crystallographic data of 4: colorless block crystals, $C_{21}H_{22}N_2O_6$, *M*r = 398.40, orthorhombic, belonging to space group $P2_12_12_1$, with *a* = 10.7249(5) Å, *b* = 12.1181(6) Å, *c* = 29.2040(13) Å, *V* = 3795.5(3) $Å^3$, D_{calcd} = 1.394 gcm^{-3}, *Z* = 4, crystal size 0.09 x 0.12 x 0.37 mm^3, *F*(000) = 1680, Mo Kα radiation (λ = 0.71073 Å), T = 150 K. The final R_1 value is 0.0492 (wR_2 = 0.1440) for 7804 reflections [$I > 2\sigma(I)$]. CCDC number: 1029243.

Vernavosine ethyl ether (6): yellow-green fluorescent oil; $[\alpha]^{25}_D$ –49 (*c* 0.31, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 233 (4.76), 2.57 (4.44), 396 (3.55) nm; IR (dry film) ν_{max} 3416, 1712, 1611 cm^{-1}; HRESIMS *m/z* 415.2233 $[M + H]^+$ (calcd for $C_{23}H_{30}N_2O_5$ + H, 415.2227); ^1H and ^{13}C NMR data, see Table 2.6. HMBC: ^2J H-3 to C-14; H-5 to C-6; H-6 to C-5; H-10 to C-11; H-14 to C-15; H-15 to C-20; H-16 to C-15, C-17, C-22; H-18 to C-19; H-21 to C-20; H-24 to C-25. ^3J H-3 to C-2, C-5, C-13; H-5 to C-2, C-3; H-6 to C-7; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-14 to C-20; H-

16 to C-20; H-17 to C-22; H-18 to C-16, C-20; H-19 to C-15; H-21 to C-3, C-5, C-15; H-23 to C-22; H-24 to C-2, C-7. NOESY/DNOE: H-3/H-12, H-14α, H-15, H-21α; H-5β/H-6β, H-14β, H-20; H-5α/H-6α, H-21β; H-6β/H-5β; H-6α/H-5α; H-9/H-10; H-10/H-9, H-11; H-11/H-10, H-12; H-14β/H-5β, H-20, H-24; H-14α/H-3, H-12, H-24; H-15/H-3, H-17; H-16/H-20; H-17/H-15, H-18α, H-19α; H-18β/H-19β, H-20; H-18α/H-17, H-19β, H-19α; H-19β/H-18β, H-18α, H-21β; H-19α/H-18α; H-20/H-5β, H-14β, H-16, H-18β; H-21β/H-5α, H-19β; H-21α/H-3; H-24/H-14β, H-14α, H-25.

Conversion of Vernavosine ethyl ether (6) to its Methyl Iodide Salt (6a): Iodomethane (0.5 mL, 8 mmol) was added to vernavosine ethyl ether (**6**) (1.1 mg, 0.001 mmol), and the mixture allowed to stand for 24 h at rt. Excess iodomethane was then removed under reduced pressure to furnish a yellowish residue, which on recrystallization from hot MeOH gave the corresponding methyl iodide salt **6a**: light yellowish block crystals ; mp > 218 °C (dec); HRDARTMS *m/z* 429.2397 $[M]^+$ (calcd for $C_{24}H_{33}N_2O_5$, 429.2389).

Crystallographic data of 6a: light yellowish block crystals, $C_{24}H_{33}N_2O_5^+I^-$, *M*r = 556.42, monoclinic, belonging to space group $P2_1$, with a = 10.4239(2) Å, b = 8.4186(2) Å, c = 14.8476(3) Å, V = 1273.54(5) Å^3, D_{calcd} = 1.451 gcm^{-3}, Z = 2, crystal size 0.2 x 0.2 x 0.3 mm^3, F(000) = 568, Mo Kα radiation (λ = 0.71073 Å), T = 150 K. The final R_1 value is 0.0382 (wR_2 = 0.1011) for 5866 reflections [$I > 2\sigma(I)$]. Flack parameter [x = 0.018(15)], Hooft parameter [y = 0.008(17)]. CCDC number: 1029244.

Hydrolysis of Vernavosine ethyl ether (6): Vernavosine ethyl ether (**6**) (5 mg, 0.012 mmol) was added to a two-phase system comprising 5% HCl (5 mL), CH_2Cl_2 (5 mL), and tetraethylammonium chloride (1.9 mg, 0.044 mmol). The mixture was stirred for 1

h at rt, after which 10% K_2CO_3 (10 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was washed with H_2O (3 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo, and the residue purified by preparative radial chromatography (SiO_2, 10% MeOH–CH_2Cl_2, NH_3-saturated) to give vernavosine (**5**) (2.8 mg, 60%).

Ethanolysis of Vernavosine (5): To a solution of vernavosine (**5**) (1 mg, 2.6 μmol) in 1 mL of absolute EtOH was added one drop of 5% HCl (ca. 20 μL). The mixture was stirred for 3 h at rt, basified with excess K_2CO_3, concentrated in vacuo, and the residue purified over a short pad of silica gel, eluting with 5% MeOH–CH_2Cl_2 to give a product corresponding to compound **6**.

Vernavosine (5): yellow fluorescent oil; $[\alpha]^{25}_D$ –62 (*c* 0.06, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 234 (3.48), 2.57 (2.91), 397 (2.59) nm; HRESIMS *m/z* 387.1914 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_5$ + H, 387.1914); ^1H and ^{13}C NMR data, see Table 2.6.

Conversion of Vernavosine (5) to its Methyl Iodide Salt (5a): Iodomethane (0.5 mL, 8 mmol) was added to vernavosine (**5**) (1 mg, 0.0025 mmol), and the mixture allowed to stand for 24 h at rt. Excess iodomethane was then removed under reduced pressure to furnish a yellowish residue, which on recrystallization from MeOH gave the corresponding methyl iodide salt **5a**: light yellowish needles; mp > 178 °C (dec); HRESIMS *m/z* 401.2075 $[M]^+$ (calcd for $C_{22}H_{29}N_2O_5$, 401.2075).

Crystallographic data of 5a: light yellowish needles, $C_{22}H_{29}N_2O_5^+I^-$, *M*r = 528.37, orthorhombic, space group $P2_12_12_1$, *a* = 8.4155(5) Å, *b* = 10.1342(6) Å, *c* = 25.9099 (15) Å, *V* = 2209.7(2) Å^3, *Z* = 4, D_{calcd} = 1.588 gcm^{-3}, crystal size 0.3 x 0.02 x 0.02

mm^3, F(000) = 1072, Mo Kα radiation (λ = 0.71073 Å), T = 100(2) K. The final R_1 value is 0.0381 (wR_2 = 0.0861) for 5813 reflections [$I>2\sigma(I)$]. The absolute configuration was determined on the basis of a Flack parameter [x = 0.008(0.017)], refined using 2378 Friedel pairs. CCDC number: 1494556.

Taberisidine (7): yellowish oil; $[\alpha]^{25}_{D}$ +42 (*c* 0.17, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 216 (4.52), 287 (4.13), 317 sh (3.70), 384 (3.68) nm; IR (dry film) ν_{max} 3437, 3371, 1726, 1666 cm^{-1}; HRESIMS *m/z* 383.1616 $[M + H]^+$ (calcd for $C_{21}H_{22}N_2O_5$ + H, 383.1601); ^{1}H and ^{13}C NMR data, see Table 2.7. HMBC: ^2J H-5 to C-6; H-6 to C-5; H-15 to C-14, C-16, C-20; H-16 to C-15, C-17, *C*O_2Me; H-18 to C-17, C-19; H-19 to C-18, C-20; NH to C-2, C-13; 17-OH to C-17. ^3J H-5 to C-3, C-7; H-6 to C-2, C-8; 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-15 to C-17, C-19, C-21, *C*O_2Me; H-16 to C-14, C-18, C-20; H-17 to *C*O_2Me; H-18 to C-16, C-20; H-19 to C-15, C-17, C-21; H-21 to C-15; NH to C-7, C-8; 17-OH to C-16, C-18; CO_2*Me* to *C*O_2Me. NOESY ($CDCl_3$/C_6D_6): H-5/H-6; H-9/H-10; H-11/H-10, H-12; H-15/H-17, H-19α; H-16/H-18β, H-20; H-17/H-15, H-18α, H-19α; H-18β/H-16, H-18α; H-18α/H-17, H-18α, H-19β, H-19α; H-19β/H-18α, H-19α; H-19α/H-15, H-17, H-19β; H-20/H-16, H-21; H-21/H-19β, H-20; NH/H-12.

Acetylation of Taberisidine (7): To a stirred solution of **7** (3.1 mg, 0.008 mmol) in CH_2Cl_2 (2 mL) and pyridine (5 μL, 0.062 mmol) was added Ac_2O (3 μL, 0.031 mmol), and the mixture was stirred at rt for 45 min. Na_2CO_3 solution (10%, 2 mL) was then added and the mixture extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried (Na_2SO_4), the solvent evaporated in vacuo, and the residue purified by preparative radial chromatography (SiO_2, CH_2Cl_2–MeOH 1%) to give the *O*-acetyl derivative **7c** (1.5 mg, 44%) as light yellowish oil; $[\alpha]^{25}_{D}$ –60 (*c* 0.3, $CHCl_3$); UV

(EtOH) λ_{max} (log ε) 222 (4.34), 286 (4.05), 311 (3.62), 383 (3.65) nm; HRESIMS *m/z* 425.1707 $[M + H]^+$ (calcd for $C_{23}H_{24}N_2O_6$ + H, 425.1707); ^1H and ^{13}C NMR data, see Table 2.7.

Conodusine A (8): colorless prisms (CH_2Cl_2–MeOH); mp 196–199 °C; $[\alpha]^{25}_D$ +83 (*c* 1.00, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 227 (4.59), 284 (3.95), 294 (3.89) nm; ECD (MeOH) λ_{max} (Δ ε) 221 (–8.33), 232 (0.18), 241 (6.58), 263 (–0.06), 271 (–0.78), 279 (0.08), 298 (4.75), 325 (0.02) nm; IR (dry film) ν_{max} 3396, 1704 cm^{-1}; HRESIMS *m/z* 295.1818 $[M + H]^+$ (calcd for $C_{19}H_{22}N_2O$ + H, 295.1805); ^1H and ^{13}C NMR data, see Tables 2.8 and 2.9, respectively. HMBC: ^2J H-5 to C-6; H-6 to C-7; H-18 to C-19; H-21 to C-20; NH to C-2, C-13. ^3J H-3 to C-5; H-5 to C-7, C-21; H-6 to C-2, C-8; H-9 to C-11, C-13; H-10 to C-8, C-12; H-11 to C-13; H-12 to C-8, C-10; H-15 to C-3; H-18 to C-20; H-21 to C-2, C-3, C-15, C-17; NH to C-7, C-8. NOESY: H-3a/H-14, H-17β; H-3b/H-14, H-15β; H-5α/H-5β, H-6α, H-21; H-6β/H-6α, H-17β; H-6α/H-5β, H-5α, H-6β, H-9; H-9/H-6α, H-6β, H-10; H-12/H-11, NH; H-15β/H-3b, H-14, H-15α; H-15α/H-14, H-15β, H-16, H-17α, H-20; H-16/H-15, H-17α, H-20, NH; H-17β/H-3a, H-17α; H-17α/H-16, H-15α; H-20/H-21; H-21/H-5α, H-18, H-20; NH/H-12, H-16.

Crystallographic data of 8: colorless prisms, $C_{19}H_{22}N_2O$, *M*r = 294.38, tetragonal, space group $P4_1$, *a* = 10.1845(18) Å, *b* = 10.1845(18) Å, *c* = 14.613(3) Å, *V* = 1515.7(6) $Å^3$, *Z* = 4, D_{calcd} = 1.290 gcm^{-3}, crystal size 0.52 x 0.13 x 0.02 mm^3, *F*(000) = 632, Mo Kα radiation (λ = 0.71073 Å), *T* = 100 K. The final R_1 value is 0.0402 (wR_2 = 0.0715) for 2421 reflections [$I>2\sigma(I)$]. CCDC number: 1448229.

Conodusine B (9): light yellowish oil; $[\alpha]^{25}_{D}$ −101 (*c* 0.25, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 227 (4.62), 284 (3.99), 291 (3.96) nm; HRDARTMS *m/z* 295.1815 $[M + H]^+$ (calcd for $C_{19}H_{22}N_2O$ + H, 295.1805); ^{1}H and ^{13}C NMR data, see Tables 2.8 and 2.9, respectively. HMBC: ^2J H-6 to C-5, C-7; H-9 to C-8; H-11 to C-12; H-15 to C-14; H-16 to C-2, C-17, C-21; H-18 to C-19; H-20 to C-19, C-21; NH to C-2, C-13. ^3J H-3 to C-5, C-15, C-17; H-5 to C-7, C-21; H-6 to C-2, C-8; H-9 to C-11, C-13; H-10 to C-8; H-11 to C-9, C-13; H-12 to C-8, C-10; H-14 to C-20; H-15 to C-17, C-19; H-16 to C-7; H-17 to C-2, C-15; H-18 to C-20; H-20 to C-16; H-21 to C-2, C-3, C-5, C-19; NH to C-7, C-8. NOESY: H-3/H-14, H-15β, H-17β; H-5α/H-21; H-6α/H-9; H-9/H-6β, H-6α, H-10; H-14/H-3, H-15β, H-17β; H-15β/H-15α, H-20; H-15α/H-15β, H-16; H-17β/H-3, H-6β, H-17α; H-17α/H-16, H-17β; H-18/H-20, H-21; H-20/H-15β, H-18; H-21/H-16, H-18; NH/H-12, H-16.

Conodusine C (10): colorless block crystals (MeOH); mp >188 °C (dec); $[\alpha]^{25}_{D}$ −126 (*c* 0.13, MeOH); UV (EtOH) λ_{max} (log ε) 222 (4.07), 284 (3.39), 291 (3.33) nm; IR (dry film) ν_{max} 3356, 1702 cm^{-1}; HRESIMS *m/z* 311.1759 $[M + H]^+$ (calcd for $C_{19}H_{22}N_2O_2$ + H, 311.1754). ^{1}H and ^{13}C NMR data, see Tables 2.8 and 2.9, respectively. HMBC: ^2J H-5 to C-6; H-6 to C-5, C-7; H-9 to C-8, C-10; H-15 to C-14, C-20; H-16 to C-2, C-17, C-21; H-17 to C-16; H-18 to C-19; H-20 to C-19; NH to C-2. ^3J H-3 to C-5, C-15, C-17; H-5 to C-7, C-21; H-6 to C-2, C-8; H-9 to C-7, C-11, C-13; H-10 to C-8; H-11 to C-9, C-13; H-12 to C-8, C-10; H-15 to C-3, C-17, C-19; H-16 to C-7, C-20; H-17 to C-2, C-3, C-15; H-20 to C-16; H-21 to C-2, C-3, C-15, C-17, C-19; NH to C-7, C-8. NOESY: H-3a/H-3b, H-14, H-6β, H-17β; H-3b/H-3a, H-14, H-15β; H-5β/H-17β; H-5α/H-5β, H-6β, H-6α; H-9/H-6β, H-6α, H-10; H-12/H-11; H-15β/H-3b, H-14, H-15α, H-20; H-

15α/H-14, H-15β, H-16; H-16/H-15α, H-17α, H-21; H-17β/H-3a, H-14, H-17α; H-20/H-15β, H-21; NH/H-12, H-16.

Crystallographic data of 10: colorless block crystals, $C_{19}H_{22}N_2O_2.CH_3OH.H_2O$, *M*r = 360.44, orthorhombic, space group $P2_12_12_1$, a = 6.5750(4) Å, b = 14.2730(8) Å, c = 19.3071(10) Å, V = 1811.87(18) Å^3, Z = 4, D_{calcd} = 1.321 gcm^{-3}, crystal size 0.52 x 0.26 x 0.12 mm^3, F(000) = 776, Mo Kα radiation (λ = 0.71073 Å), T = 100 K. The final R_1 value is 0.0498 (wR_2 = 0.1155) for 3710 reflections [$I>2\sigma(I)$]. CCDC number: 1448230.

Conodusine D (11): light yellowish oil; $[\alpha]^{25}_D$ –26 (*c* 0.05, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 221 (3.94), 227 sh (3.81), 280 (3.13) nm; ECD (MeOH) λ_{max} (Δ ε) 221 (11.64), 235 (0.32), 257 (–5.71), 277 (0.08), 289 (1.76) nm; HRESIMS *m/z* 325.1544 [M + H]$^+$ (calcd for $C_{19}H_{20}N_2O_3$ + H, 325.1547); ^{1}H and ^{13}C NMR data, see Table 2.10. HMBC: ^2J H-5 to C-6; H-6 to C-7; H-10 to C-9; H-14 to C-3; H-16 to C-2; H-18 to C-19; H-20 to C-15; H-21 to C-16, C-20. ^3J H-5 to C-3, C-7; H-6 to C-2, C-8; H-14 to C-20, C-21; H-15 to C-3, C-17, C-19; H-16 to C-7; H-17 to C-3, C-15; H-18 to C-20; H-20 to C-14, C-16; H-21 to C-2, C-3, C-5, C-15, C-19. NOESY: H-5β/H-5α, H-6β; H-5α/ H-5β, H-6β, H-6α, H-21; H-6β/H-5β, H-5α, H-6α, H-9; H-6α/H-5α, H-6β, H-21; H-9/H-6β; H-16/H-15α, H-17α, H-20, H-21; H-17α/H-15α; H-21/H-5α, H-6α, H-16, H-18, H-20.

Conodusine E (12): colorless prisms (CH_2Cl_2–hexanes); mp 192–195 °C; $[\alpha]^{25}_D$ +21 (*c* 0.53, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 227 (4.10), 286 (3.52), 292 (3.47) nm; ECD (MeOH) λ_{max} (Δ ε) 219 (–3.50), 230 (0.22), 241 (5.16), 259 (–0.15), 271 (–2.46), 285

(0.12), 297 (2.28), 324 (0.01) nm; IR (dry film) ν_{max} 3350, 1724, 1716 cm^{-1}; HRESIMS *m/z* 353.1876 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1860); ^1H and ^{13}C NMR data, see Table 2.11. HMBC ^2J H-5 to C-6; H-6 to C-7; H-14 to C-15; H-15 to C-20; H-17 to C-16; H-18 to C-19; H-20 to C-19; H-21 to C-20. ^3J H-3 to C-5, C-15, C-17, C-21; H-5 to C-3, C-7, C-21; H-6 to C-2, C-8; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-12 to C-8, C-10; H-15 to C-3, C-17; H-17 to C-2, *C*O_2Me; H-21 to C-2, C-3, C-5, C-15, C-17, C-19; CO_2*Me* to *C*O_2Me; NH to C-7, C-8, C-12. NOESY: H-3a/H-3b, H-14; H-3b/H-3a, H-14, H-15β; H-5β/H-5α, H-6β; H-5α/H-5β, H-21; H-9/H-6β, H-6α, H-10; H-15β/H-15α; H-15α/H-15β, H-17α, H-20; H-17β/H-3a, H-17α; H-17α/H-15α, H-17β; H-20/H-15α; H-21/H-5α, H-6α, H-20, CO_2*Me*; NH/H-12.

Crystallographic data of (12): colorless prisms, $C_{21}H_{24}N_2O_3$, *M*r = 352.42, orthorhombic, space group $P2_12_12_1$, *a* = 10.64511(16) Å, *b* = 10.65662(16) Å, *c* = 15.5709(2) Å, *V* = 1766.38(5) $Å^3$, *Z* = 4, D_{calcd} = 1.295 gcm^{-3}, crystal size 0.45 x 0.23 x 0.17 mm^3, *F*(000) = 728, Cu Kα radiation (λ = 1.54184 Å), *T* = 120 K. The final R_1 value is 0.0286 (wR_2 = 0.0780) for 3586 reflections [$I > 2\sigma(I)$]. The absolute configuration was determined on the basis of a Flack parameter of –0.05(4), refined using 1496 Friedel pairs. CCDC number: 1469917.

Oxidation of (–)-Heyneanine (17) to (+)-Conodusine E (12): To a solution of (–)-heyneanine (**17**) (14.7 mg, 0.042 mmol) in CH_2Cl_2 (5 mL) was added $NaHCO_3$ (0.052 g, 0.62 mmol), followed by the Dess-Martin periodinane reagent (0.3 M in CH_2Cl_2, 207 μL, 0.062 mmol). The resultant mixture was stirred for 30 min at rt. Ethyl acetate (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and 10% aqueous $Na_2S_2O_3$ (5 mL) were then added, and the mixture was stirred until the organic layer became clear. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phase was

washed with saturated aqueous NaCl (5 mL), dried with Na_2SO_4, filtered, the solvent removed *in vacuo*, and the residue purified by preparative radial chromatography (SiO_2, 5% MeOH–Et_2O, NH_3-saturated) to give (+)-conodusine E (**12**) (2.1 mg, 14%) as a colorless oil: $[\alpha]^{25}_D$ +23 (*c* 0.18, $CHCl_3$). The ^1H and ^{13}C NMR data were identical to that of the natural material.

Ibogamine (13): colorless oil; $[\alpha]^{25}_D$ –39 (*c* 0.85, $CHCl_3$). UV (EtOH) λ_{max} (log ε) 227 (4.28), 285 (3.68), 291 (3.67) nm; IR (dry film) ν_{max} 3399 cm^{-1}; HRESIMS *m/z* 281.2019 $[M + H]^+$ (calcd for $C_{19}H_{24}N_2$ + H, 281.2012). ^1H and ^{13}C NMR data, see Tables 2.12 and 2.13, respectively.

19(*S*)-Hydroxyibogamine (14): colorless block crystals (CH_2Cl_2–MeOH); mp 222–224 °C; $[\alpha]^{25}_D$ –12 (*c* 0.1, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 226 (4.54), 283 (3.90), 291 (3.85) nm; IR (dry film) ν_{max} 3399, 3227 cm^{-1}; HRESIMS *m/z* 297.1967 $[M + H]^+$ (calcd for $C_{19}H_{25}N_2O$ + H, 297.1961); ^1H and ^{13}C NMR data, see Tables 2.12 and 2.13, respectively.

Crystallographic data of 14: colorless block crystals, $2(C_{19}H_{24}N_2O).C_2H_6O$, *M*r = 638.87, orthorhombic, space group $P2_12_12_1$, *a* = 14.78248(9) Å, *b* = 17.53938(13) Å, *c* = 26.1840(2) Å, *V* = 6788.87(8) $Å^3$, *Z* = 8, D_{calcd} = 1.250 gcm^{-3}, crystal size 0.52 x 0.48 x 0.32 mm^3, *F*(000) = 2768, Cu Kα radiation (λ = 1.54178 Å), *T* = 136 K. The final R_1 value is 0.0375 (wR_2=0.1109) for 13153 reflections [$I>2\sigma(I)$]. Flack parameter [*x* = 0.01(0.03)], Hooft parameter [*y* = 0.01(0.03)].

19(*R*)-Hydroxyibogamine (15): light yellowish oil; $[\alpha]^{25}_D$ –22 (*c* 0.52, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 227 (4.30) and 283 (3.67) nm; IR (dry film) ν_{max} 3347 cm^{-1};

HRESIMS *m/z* 297.1967 $[M + H]^+$ (calcd for $C_{19}H_{24}N_2O$ + H, 297.1961); ^1H and ^{13}C NMR data, see Tables 2.12 and 2.13, respectively. HMBC: ^2J H-3 to C-14; H-5 to C-6; H-6 to C-7; H-16 to C-2; H-17 to C-14; H-18 to C-19; H-19 to C-20; H-21 to C-20; NH to C-2, C-13. ^3J H-3 to C-5, C-15, C-17; H-5 to C-7; H-6 to C-2, C-8; 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-15 to C-3, C-17; H-16 to C-7; H-17 to C-3, C-15; H-18 to C-20; H-19 to C-21; H-21 to C-19; H-21 to C-2, C-3, C-5, C-15, C-17; NH to C-7, C-8.

Coronaridine (16): colorless oil; $[\alpha]^{25}_D$ –32 (*c* 1.39, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 224 (3.90), 286 (4.24), 292 (4.21) nm; IR (dry film) ν_{max} 3380, 1719 cm^{-1}; HRESIMS *m/z* 339.2069 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_2$ + H, 339.2067); ^1H and ^{13}C NMR data, see Tables 2.14 and 2.15, respectively.

(–)-Heyneanine (17): white needle crystals (CH_2Cl_2–hexanes); mp 156–158 °C; $[\alpha]^{25}_D$ –24 (*c* 0.82, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 225 (4.51), 285 (3.89), 292 (3.81); IR (dry film) ν_{max} 3380, 3232 and 1725 cm^{-1}; HRESIMS *m/z* 355.2025 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2016); ^1H and ^{13}C NMR data, see Tables 2.14 and 2.15, respectively.

Voacangine (18): light yellow oil; $[\alpha]^{25}_D$ –33 (*c* 0.21, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 220 (4.38), 286 (3.93), and 299 sh (3.87) nm; IR (dry film) ν_{max} 3376, 1724, cm^{-1}; HRESIMS *m/z* 369.2180 $[M + H]^+$ (calcd for $C_{22}H_{28}N_2O_3$ + H, 369.2173); ^1H and ^{13}C NMR data, see Tables 2.14 and 2.15, respectively.

Voacristine (19): light yellowish oil; $[\alpha]^{25}_D$ –67 (*c* 0.02, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 223 (4.28), 283 (3.98), 300 (3.90) nm; IR (dry film) ν_{max} 3376, 3246, 1725 cm^{-1};

HRESIMS *m/z* 385.2130 $[M + H]^+$ (calcd for $C_{22}H_{29}N_2O_4$ + H, 385.2122); ^1H and ^{13}C NMR data, see Tables 2.14 and 2.15, respectively.

Apocidine A (20): colorless plates (CH_2Cl_2–MeOH); mp 214.5–215.5 ^oC; $[\alpha]^{25}_D$ –541 (*c* 0.19, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 224 (3.98), 299 (3.97), 327 (4.08) nm; IR (dry film) ν_{max} 3380, 1676, 1609 cm^{-1}; HRESIMS *m/z* 369.1818 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_4$ + H, 369.1809); ^1H and ^{13}C NMR data, see Tables 2.16 and 2.18, respectively. HMBC: ^2J H-5 to C-6; H-3 to C-14; H-18 to C-19; H-19 to C-20; NH to C-13. ^3J H-5 to C-7, C-21; H-6 to C-2, C-8, 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-17 to C-2, C-15, C-19, C-21, CO_2Me; H-18 to C-20; H-19 to C-17, C-21; H-21 to C-6, C-17, C-19; CO_2Me to CO_2Me; NH to C-7, C-8. NOESY: H-3β/H-3α, H-14; H-3α/H-3β, H-21; H-5β/H-6β; H-5α/H-5β, H-6α; H-6β/H-5β, H-6α; H-6α/H-5α, H-6β; H-9/H-21; H-14/H-3α, H-3β; H-17/H-14; H-18β/H-18α, H-19β, H-19α; H-18α/H-18β, H-19α, H-19β, H-21; H-19β/H-18β, H-19α; H-19α/H-18β, H-18α, H-19β, H-21; H-21/H-3α, H-5α, H-18α, H-19α; NH/H-12.

Crystallographic data of 20: colorless plates, $C_{21}H_{24}N_2O_4$, *M*r = 368.42, monoclinic, space group $P2_12_12_1$, *a* = 9.0098(6) Å, *b* = 7.1744(5) Å, *c* = 14.3213(10)Å, β = 92.200(5) Å, *V*=925.05(11) $Å^3$, *T* = 100 K, *Z* = 2, D_{calcd} = 1.323 gcm^{-3}, crystal size 0.21 x 0.15 x 0.02 mm^3, *F*(000) = 392, Mo Kα radiation (λ = 0.71073 Å), *T* = 100 K. The final R_1 value is 0.0495 (wR_2 = 0.1130) for 2480 reflections [$I>2\sigma(I)$]. CCDC number: 1448231.

Apocidine B (21): light yellowish oil; $[\alpha]^{25}_D$ –277 (*c* 0.37, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 224 (3.77), 297 (3.62), 328 (3.71) nm; IR (dry film) ν_{max} 3380, 1676, 1609

cm^{-1}; HRESIMS *m/z* 369.1820 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_4$ + H, 369.1809); ^1H and ^{13}C NMR data, see Tables 2.16 and 2.18, respectively. HMBC: ^2J H-6 to C-5; H-17 to C-16; H-18 to C-19; NH to C-13. ^3J H-3 to C-15, C-21; H-5 to C-7, C-21; H-6 to C-2, C-8; H-9 to C-13; H-10 to C-8, C-12; H-11 to C-9, C-13; H-12 to C-8, C-10; H-15 to C-3, C-21; H-17 to C-2, C-15, C-19, C-21, *C*O_2Me; H-18 to C-15, C-20; H-19 to C-15, C-21; H-21 to C-2, C-8, C-17; CO_2*Me* to *C*O_2Me; NH to C-7, C-8. NOESY: H-3α/H-14, H-21; H-3β/H-5β, H-14, H-21; H-5β/H-5α, H-6β, H-6α; H-5α/H-5β, H-6α; H-6β/H-5β, H-6α, H-17β; H-9/H-5α, H-10, H-21; H-11/H-12; H-14/H-3β, H-3α, H-15; H-15/H-17β, H-17α; H-17β/H-6β, H-15, H-17α; H-17α/H-15, H-17β, H-19β; H-18β/H-19β; H-18α/H-18β, H-19α, H-21; H-19β/H-17α, H-18β, H-19α; H-19α/H-18α, H-19β, H-21; H-21/H-3α, H-5α, H-19α; NH/H-12.

Apocidine C (22): light yellowish oil; $[\alpha]^{25}_D$ –44 (*c* 0.14, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 226 (3.97), 245 (4.02), 326 (4.13) nm; IR (dry film) ν_{max} 3377, 1675, 1615 cm^{-1}; HRESIMS *m/z* 399.1934 $[M + H]^+$ (calcd for $C_{22}H_{26}N_2O_5$ + H, 399.1915); ^1H and ^{13}C NMR data, see Tables 2.16 and 2.18, respectively. NOESY: H-3β/H-14; H-3α/H-14, H-21; H-5β/H-3β, H-5α, H-6β; H-5α/H-5β, H-6α; H-6β/H-5β, H-6α; H-6α/H-5α, H-6β; H-9/H-5α, H-10, H-21; H-12/11-OMe, NH; H-14/H-3β, H-3α; H-15/H-17β, H-17α, H-19β; H-18β/H-19β; H-18α/H-19α; H-19β/17α, H-18β, H-19α; H-19α/H-19β, H-21; H-21/ H-3α, H-18α, H-19α; NH/H-12.

Apocidine D (23): light yellowish oil; $[\alpha]^{25}_D$ –179 (*c* 0.12, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 224 (4.20), 248 (4.03), 313 (3.98), 342 (3.88) nm; IR (dry film) ν_{max} 3365, 1674, 1616 cm^{-1}; HRESIMS *m/z* 415.1855 $[M + H]^+$ (calcd for $C_{22}H_{26}N_2O_6$ + H, 415.1864); ^1H and ^{13}C NMR data, see Tables 2.16 and 2.18, respectively. HMBC: ^2J H-5 to C-6;

H-9 to C-10; H-12 to C-11, C-13; H-15 to C-14; H-17 to C-16, C-20; H-19 to C-20. ^{3}J H-3 to C-15, C-21; H-5 to C-7, C-21; H-6 to C-2, C-8, C-21; H-9 to C-7, C-11, C-13; H-12 to C-8, C-10; H-15 to C-3, C-21; H-17 to C-2, C-15, C-19; H-18 to C-15; H-19 to C-15, C-21; H-21 to C-8, C-17; 11-OMe to C-11; CO_2*Me* to *C*O_2Me. NOESY: H-3β/H-5β, H-14; H-3α/H-3β, H-14, H-21; H-5β/H-3β, H-5α, H-6β; H-5α/H-5β; H-6β/H-5β, H-6α; H-6α/H-6β; H-9/H-5α, H-21; H-12/11-OMe, NH; H-14/H-3β, H-3α, H-15; H-15/H-14, H-17β, H-17α; H-18β/H-19β; H-18α/H-19α; H-19β/H-17α, H-18β, H-19α; H-19α/H-18α, H-19β, H-21; NH/H-12.

Apocidine E (24): light yellowish oil; $[\alpha]^{25}_{D}$ –481 (*c* 0.32, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 225 (4.03), 247 (4.15), 306 sh (4.14), 325 (4.26) nm; IR (dry film) ν_{max} 3376, 1675 cm^{-1}; HRESIMS *m/z* 399.1922 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_5$ + H, 353.1914); ^{1}H and ^{13}C NMR data, see Tables 2.17 and 2.18, respectively. NOESY: H-3β/H-3α, H-14; H-6β/H-5β, H-6α, H-17β; H-6α/H-6β; H-9/H-5α, H-10, H-21; H-12/11-OMe, NH; H-14/H-15, H-17β; H-15/H-14, H-17β, H-17α, H-19β; H-18/H-19α, H-21; H-19β/H-17α, H-19α; NH/H-12.

Apocidine F (25): light yellowish oil; $[\alpha]^{25}_{D}$ –208 (*c* 0.06, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 224 sh (4.03), 247 (4.12), 307 sh (4.10), 326 (4.20) nm; IR (dry film) ν_{max} 3376, 1682, 1616 cm^{-1}; HRDARTMS *m/z* 397.1750 $[M + H]^+$ (calcd for $C_{22}H_{24}N_2O_5$ + H, 397.1759); ^{1}H and ^{13}C NMR data, see Tables 2.17 and 2.18, respectively. HMBC: ^{2}J H-6 to C-5, C-7; H-12 to C-11, C-13; H-17 to C-16, C-20; H-19 to C-20. ^{3}J H-3 to C-15, C-21; H-6 to C-2, C-8, C-21; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-12 to C-8, C-10; H-15 to C-3, C-17, C-18, C-21; H-17 to C-2, C-15, C-19, C-21, *C*O_2Me; H-18 to C-15; H-19 to C-15, C-17, C-21; H-21 to C-5, C-8, C-15, C-17; 11-OMe to C-11;

CO_2*Me* to *C*O_2Me. NOESY/DNOE: H-3β/H-3α, H-14β, H-14α; H-6β/H-6α, H-17β; H-6α/H-6β, H-9; H-9/H-6α, H-10, H-21; H-10/H-9, 11-OMe; H-12/NH; H-14β/H-3β, H-14α, H-15; H-17β/H-6β, H-14β, H-15, H-17α; H-17α/H-15, H-17β, H-19β; H-19β/H-17α, H-18, H-19α; H-19α/H-18, H-19β, H-21; NH/12.

Apocidine G (26): colorless block crystals ($CHCl_3$); mp 141–143 ^oC; $[\alpha]^{25}_D$ –496 (*c* 0.29, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 223 sh (4.11), 251 (4.24), 327 (4.37) nm; IR (dry film) ν_{max} 3359, 1672, 1601 cm^{-1}; HRDARTMS *m/z* 369.1799 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_4$ + H, 369.1809); ^1H and ^{13}C NMR data, see Tables 2.17 and 2.18, respectively. HMBC: ^2J H-5 to C-6; H-6 to C-7; H-10 to C-11; H-12 to C-11; H-17 to C-16, C-20; H-18 to C-19; H-19 to C-18; H-21 to C-7; NH to C-13. ^3J H-3 to C-15, C-21; H-5 to C-7, C-21; H-6 to C-2, C-8; H-9 to C-7, C-11, C-13; H-10 to C-8, C-12; H-12 to C-8, C-10; H-14 to C-20; H-15 to C-3, C-17, C-21; C-17 to C-2, C-15, C-19, C-21, *C*O_2Me; H-18 to C-15, C-20; H-19 to C-15, C-17, C-21; H-21 to C-3, C-8, C-17, C-19; CO_2*Me* to *C*O_2Me; NH to C-7, C-8. NOESY: H-3α/H-3β; H-5β/H-5α, H-6β; H-5α/H-5β, H-6α; H-6β/H-5β, H-6α, H-17β; H-6α/H-5α, H-6β; H-9/H-5α, H-6α, H-10, H-21; H-14/H-3β, H-15, H-17β; H-15/H-14, H-17β, H-17α; H-17β/H-6β, H-15, H-17α; H-17α/H-15, H-17β, H-19β; H-18β/H-18α, H-19β; H-18α/H-18β, H-19α, H-21; H-19β/H-17α, H-18β, H-19α; H-19α/H-18α, H-19β, H-21; NH/H-12, CO_2*Me*.

Crystallographic data of 26: colorless block crystals, $4C_{21}H_{28}N_2O_3.2C_3H_6O.H_2O$, *M*r = 1559.98, orthorhombic, space group $P2_12_12_1$, *a* = 16.0016(3) Å, *b* = 22.0616(4) Å, *c* = 24.2011(6) Å, *V* = 8543.5(3) $Å^3$, *Z* = 4, D_{calcd} = 1.213 gcm^{-3}, crystal size 0.50 x 0.03 x 0.02 mm^3, *F*(000) = 3368, Cu Kα radiation (λ = 1.54178 Å), *T* = 151(13) K. The final

R_1 value is 0.0688 (wR_2=0.1502) for 9743 reflections [$I>2\sigma(I)$]. Flack parameter [x = –0.09(0.16)], Hooft parameter [y = –0.15(0.18)].

Hedrantherine (27): light yellowish oil; $[\alpha]^{25}_{D}$ –496 (*c* 0.17, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 226 (3.72), 299 (3.70), 327 (3.83) nm; IR (dry film) ν_{max} 3389, 1673, 1608 cm^{-1}; HRESIMS *m/z* 369.1807 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_4$ + H, 369.1809); ^1H and ^{13}C NMR data, see Tables 2.19 and 2.20, respectively. HMBC: ^2J H-5 to C-6; H-6 to C-5, C-7; H-10 to C-11; H-17 to C-16, C-20; H-19 to C-18, C-20; H-21 to C-7; NH to C-13. ^3J H-3 to C-15, C-21; H-5 to C-7, C-21; H-6 to C-2, C-8; 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-15 to C-3, C-21; H-17 to C-2, C-19, C-21; H-18 to C-15; H-19 to C-15, C-21; H-21 to C-2, C-8, C-17, C-19; CO_2Me to CO_2Me; NH to C-7, C-8. NOESY/DNOE: H-9/H-10, H-21; H-15/H-14, H-17β, H-17α; H-17α/H-15, H-17β; H-18/H-19α, H-21; H-19β/H-17α, H-19α; H-19α/H-18, H-19β, H-21.

Desoxoapodine (28): light yellowish oil; $[\alpha]^{25}_{D}$ –486 (*c* 1.85, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 212 (4.21), 225 (4.23), 299 (4.19), 327 (4.31) nm; IR (dry film) ν_{max} 3373, 1675, and 1608 cm^{-1}; HRESIMS *m/z* 353.1863 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1860); ^1H and ^{13}C NMR data, see Tables 2.19 and 2.20, respectively. HMBC: ^2J H-5 to C-6; H-6 to C-5, C-7; H-17 to C-16, C-20; H-18 to C-19; H-19 to C-18; NH to C-13. ^3J H-3 to C-21; H-5 to C-7, C-21; H-6 to C-2, C-8; 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-15 to C-3; H-17 to C-2, C-17, C-19, C-21; H-18 to C-15; H-19 to C-15, C-17, C-21; H-21 to C-2, C-7; CO_2Me to CO_2Me; NH to C-7, C-8.

Vandrikine (29): light yellowish oil; $[\alpha]^{25}_{D}$ −505 (*c* 0.30, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 224 (3.88), 247 (3.77), 299 (3.69), 325 (4.08) nm; IR (dry film) ν_{max} 3373, 1674, and 1614 cm^{-1}; HRESIMS *m/z* 383.1980 $[M + H]^+$ (calcd for $C_{22}H_{26}N_2O_4$ + H, 383.1965); ^1H and ^{13}C NMR data, see Tables 2.19 and 2.20, respectively. HMBC: ^2J H-17 to C-16, C-21; H-18 to C-19; NH to C-13. ^3J H-5 to C-7; H-6 to C-2, C-8; H-9 to C-7, C-11, C-3; H-10 to C-8, C-12; H-12 to C-8, C-10; H-15 to C-3, C-21; H-17 to C-2, C-19, *C*O_2Me; H-19 to C-17, C-21; H-21 to C-2, C-17; 11-OMe to C-11; CO_2*Me* to *C*O_2Me; NH to C-7, C-8. NOESY: H-3α/H-3β; H-5α/H-5β, H-6α; H-6α/H-5α, H-6β; H-9/H-5α, H-6α, H-10, H-21; H-15/H-14, H-17β, H-17α; H-17β/H-6β, H-17α; H-17α/H-15, H-17β, H-19β; H-18β/H-18α, H-19β; H-18α/H-18β, H-19α, H-21; H-19β/H-17α, H-18β, H-19α; H-19α/H-19β, H-21; H-21/H-18α, H-19α; NH/H-12, CO_2*Me*.

Conoduzidine A (30): colorless prisms (CH_2Cl_2–hexanes); mp >252°C (dec); $[\alpha]^{25}_{D}$ −31 (*c* 0.12, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 212 (3.97), 242 (4.13), 268 (3.86), 294 (3.60), 303 (3.57) nm; IR (dry film) ν_{max} 3428, 1705 cm^{-1}; HRESIMS *m/z* 309.1598 $[M + H]^+$ (calcd for $C_{19}H_{20}N_2O_2$ + H, 309.1598); ^1H and ^{13}C NMR data, see Tables 2.21 and 2.22, respectively. HMBC: ^2J H-6 to C-5, C-7; H-14 to C-15; H-17 to C-16, C-20; H-18 to C-19; H-19 to C-18, C-20; H-21 to C-2, C-20. ^3J H-3 to C-21; H-5 to C-3, C-7, C-21; H-6 to C-2; 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-15 to C-17, C-18, C-19; H-17 to C-15, C-21; H-18 to C-15; H-19 to C-17, C-21; H-21 to C-3, C-15, C-19, C-20. NOESY: H-3/H-5, H-6β; H-5/H-6β, H-6α; H-12/H-11; H-14/H-3, H-15; H-17β/H-15, H-17α, H-18; H-17α/H-17β, H-19β; H-18/H-17β, H-17α, H-19β; H-19β/H-18, H-19α, H-21; H-19α/H-18, H-19β, H-21; H-21/H-5α, H-17α, H-19β, H-19α.

Crystallographic data of 30: colorless prisms, $C_{19}H_{20}N_2O_2$, *M*r = 308.37, orthorhombic, space group $P2_12_12_1$, a = 11.73280(10) Å, b = 13.07670(10) Å, c = 19.2454(2) Å, V = 2952.75(5) Å^3, Z = 8, D_{calcd} = 1.387 gcm^{-3}, crystal size 0.4 x 0.3 x 0.2 mm^3, F(000) = 1312, Cu Kα radiation (λ = 1.54184 Å), T = 100 K. The final R_1 value is 0.0354 (wR_2 = 0.0905) for 5866 reflections [$I>2\sigma(I)$]. The absolute configuration was determined on the basis of a Flack parameter of –0.06(8), refined using 2424 Friedel pairs. CCDC number: 1448232.

Conoduzidine B (31): light yellowish oil; $[\alpha]^{25}_D$ –16 (*c* 0.08, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 227 (4.44), 274 sh (3.84), 282 (3.84), 290 (3.73) nm; IR (dry film) ν_{max} 3302, 1746 cm^{-1}; HRESIMS *m/z* 369.1799 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_4$ + H, 369.1809); ^{1}H and ^{13}C NMR data, see Tables 2.21 and 2.22, respectively. NOESY: H-3/H-14; H-6/H-5; H-9/H-6β, H-6α, H-10; H-15/H-3, H-14, H-17β; H-17β/H-17α, H-18β; H-17α/H-17β, H-19β, H-21; H-18β/H-17β, H-19β; H-18α/H-19α; H-19β/H-18β, H-19α, H-21; H-19α/H-18α, H-19β, H-21; H-21/H-5α, H-17α, H-19β, H-19α.

Conoduzidine C (32): light yellowish oil; $[\alpha]^{25}_D$ –19 (*c* 0.2, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 229 (4.34), 274 (3.76), 297 (3.66), 306 sh (3.57) nm; IR (dry film) ν_{max} 3353, 1745 cm^{-1}; HRESIMS *m/z* 399.1906 $[M + H]^+$ (calcd for $C_{22}H_{26}N_2O_5$ + H, 369.1809); ^{1}H and ^{13}C NMR data, see Tables 2.21 and 2.22, respectively. NOESY: H-5/H-6; H-9/H-6β, H-6α, H-10; H-10/11-OMe; H-12/11-OMe; H-14/H-15; H-15/H-3, H-14, H-17β; H-17β/H-15, H-17α, H-18β; H-17α/H-17β, H-19β, H-21; H-18β/H-17β, H-18α, H-19β; H-18α/H-18β, H-19α; H-19β/H-17α, H-18β, H-19α, H-21; H-19α/H-18α, H-19β, H-21; H-21/H-5α, H-17α, H-19β, H-19α.

14,15-Dehydro-*epi*-vincamine (33): light yellowish oil; $[\alpha]^{25}_{D}$ +9 (*c* 0.13, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 226 (4.57), 275 (4.01), 282 (4.01), 291 (3.89) nm; IR (dry film) ν_{max} 3344, 1737 cm^{-1}; HRESIMS *m/z* 353.1866 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1860); ^1H and ^{13}C NMR data, see Tables 2.21 and 2.22, respectively.

16α-Methoxycarbonyl-16,17-dihydro-19-*epi*-ajmalicine (34): light yellowish oil; $[\alpha]^{25}_{D}$ +5 (*c* 0.16, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 226 (4.37), 275 sh (3.70), 283 (3.73), 291(3.67) nm; IR (dry film) ν_{max} 3289, 2817, 2756, 1726 cm^{-1}; HRESIMS *m/z* 355.2018 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2016); ^1H and ^{13}C NMR data, see Table 2.23. HMBC: ^2J H-3 to C-2; H-5 to C-6; H-14 to C-3, C-15; H-15 to C-14, C-20; H-16 to CO_2Me; H-17 to C-16; H-18 to C-19; H-20 to C-19, C-21; H-21 to C-20. ^3J H-5 to C-3, C-7; H-6 to C-2; 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-17 to C-15, C-19; H-18 to C-20; H-19 to C-15; H-21 to C-3, C-15; CO_2Me to CO_2Me; NH to C-7, C-8. NOESY: H-3/H-5α, H-14α, H-15, NH; H-5β/H-5α; H-5α/H-3, H-5β, H-21α; H-6β/H-6α, H-9; H-6α/H-6β, H-9; H-9/H-6β, H-6α, H-10; H-11/H-12; H-14β/H-14α, H-16; H-14α/H-3, H-14β, H-15, NH; H-15/H-3α, H-14α, H-17α, H-19, H-21α; H-16/H-14β, H-17β, H-20; H-17β/H-16, H-17α; H-17α/H-15, H-17β, H-19; H-18/H-19, H-20, H-21β; H-19/H-15, H-17α, H-18; H-20/H-14β, H-16, H-18, H-21β; H-21β/H-18, H-20, H-21α; NH/H-3, H-12, H-14α.

Tetrahydroalstonine (35): light yellowish oil; $[\alpha]^{25}_{D}$ −120 (*c* 0.08, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 227 (4.48), 251sh (2.94), 273sh (3.78), 283 (3.80), 290 (3.76) nm; IR (dry film) ν_{max} 3370, 1703 cm^{-1}; HRESIMS *m/z* 353.1868 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1860); ^1H and ^{13}C NMR data, see Tables 2.24 and 2.25, respectively.

16(*R*)-Sitsirikine (36): light yellowish oil; $[\alpha]^{25}_{D}$ –33 (*c* 0.14, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 226 (4.47), 272 (3.72), 283 (3.80), 290 (3.73) nm; IR (dry film) ν_{max} 3375, 2813, 2766, 1708 cm^{-1}; HRESIMS *m/z* 353.1868 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1860); ^1H and ^{13}C NMR data, see Tables 2.24 and 2.25, respectively.

16(*R*)-18,19-Dihydrositsirikine (37): colorless block crystals; mp > 165 °C (dec); $[\alpha]^{25}_{D}$ –30 (*c* 0.41, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 sh (4.17), 225 (4.30), 280 (3.66) nm; IR (dry film) ν_{max} 3372, 2823, 2776, 1709 cm^{-1}; HRESIMS *m/z* 357.2181 $[M + H]^+$ (calcd for $C_{21}H_{28}N_2O_3$ + H, 357.2173); ^1H and ^{13}C NMR data, see Tables 2.24 and 2.25, respectively.

Crystallographic data of 37: colorless block crystals, $4C_{21}H_{28}N_2O_3.2C_3H_6O.H_2O$, *M*r = 1559.98, orthorhombic, space group $P2_12_12_1$, *a* = 16.0016(3) Å, *b* = 22.0616(4) Å, *c* = 24.2011(6) Å, *V* = 8543.5(3) $Å^3$, *Z* = 4, D_{calcd} = 1.213 gcm^{-3}, crystal size 0.50 x 0.03 x 0.02 mm^3, *F*(000) = 3368, Cu Kα radiation (λ = 1.54178 Å), *T* = 151(13) K. The final R_1 value is 0.0688(wR_2=0.1502) for 9743 reflections [$I>2\sigma(I)$]. Flack parameter [*x* = –0.09(0.16)], Hooft parameter [*y* = –0.15(0.18)].

β-Yohimbine (38): colorless block crystals (CH_2Cl_2–MeOH); mp > 223 °C (dec); $[\alpha]^{25}_{D}$ –7 (*c* 0.17, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 226 (4.07), 283 (3.39), 291 (3.32) nm; IR (dry film) ν_{max} 3473, 3207, 2816, 2760, 1730 cm^{-1}; HRESIMS *m/z* 355.2018 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_3$ +H, 355.2016); ^1H and ^{13}C NMR data, see Tables 2.26 and 2.28, respectively.

Yohimbine (39): colorless needles (CH_2Cl_2–MeOH); mp > 223 °C (dec); $[\alpha]^{25}_D$ +14 (*c* 0.58, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 225 (4.42), 282 (4.16), 291 (4.15) nm; IR (dry film) ν_{max} 3363, 2813, 2759, 1723 cm^{-1}; HRESIMS *m/z* 355.2032 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2016); ^1H and ^{13}C NMR data, see Tables 2.26 and 2.28, respectively.

α-Yohimbine (40): light yellowish oil; $[\alpha]^{25}_D$ –57 (*c* 0.07, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 226 (4.26), 284 (3.71), 2.91 (3.68), 328 (3.32) nm; IR (dry film) ν_{max} 3358, 1719, 1686, 1618 cm^{-1}; HRESIMS *m/z* 355.2019 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2016); ^1H and ^{13}C NMR data, see Tables 2.26 and 2.28, respectively.

19,20-Dehydro-α-yohimbine (41): light yellowish oil; $[\alpha]^{25}_D$ +106 (*c* 0.22, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 223 (3.83), 282 (3.24), 340 (2.89) nm; IR (dry film) ν_{max} 3400, 2800, 2739, 1721, and 1644 cm^{-1}; HRESIMS *m/z* 353.1861 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1860); ^1H and ^{13}C NMR data, see Tables 2.27 and 2.28, respectively.

19,20-Dehydro-β-Yohimbine (42): light yellowish oil; $[\alpha]^{25}_D$ –4 (*c* 0.25, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 211 sh (3.83), 225 (4.03), 282 (3.36), 290 (3.30) nm; IR (dry film) ν_{max} 3362, 2749, 2814, 1722 cm^{-1}; HRESIMS *m/z* 355.1860 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 355.1860); ^1H and ^{13}C NMR data, see Tables 2.27 and 2.28, respectively.

19,20-Dehydroyohimbine (43): yellowish oil; $[\alpha]^{25}_D$ +29 (*c* 0.15, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 211 (4.15), 225 (4.36), 282 (3.69), 290 (3.63) nm; IR (dry film) ν_{max} 3314,

2747, 2813, 1726 cm^{-1}; HRESIMS *m/z* 353.1859 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1860); ^1H and ^{13}C NMR data, see Tables 2.27 and 2.28, respectively.

7(*S*)-β-Yohimbine oxindole (44): light yellowish oil; $[\alpha]^{25}_D$ +41 (*c* 1.20, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (4.25), 251 (3.70), 263 sh (3.54), 285 (3.06) nm; IR (dry film) ν_{max} 3259, 2757, 2805, 1709, 1621 cm^{-1}; HRESIMS *m/z* 371.1965 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_4$ + H, 371.1965); ^1H and ^{13}C NMR data, see Tables 2.29 and 2.30, respectively.

7(*R*)-β-Yohimbine oxindole (45): colorless needles (CH_2Cl_2–MeOH); mp 224–226 °C; $[\alpha]^{25}_D$ –28 (*c* 0.53, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (3.96), 252 (3.38), 264 (3.24), 287 (2.78) nm; IR (dry film) ν_{max} 3254, 2797, 2861, 1715, 1622 cm^{-1}; HRESIMS *m/z* 371.1976 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_4$ + H, 371.1965); ^1H and ^{13}C NMR data, see Tables 2.29 and 2.30, respectively.

β-Yohimbine pseudoindoxyl (46): yellow fluorescent oil; $[\alpha]^{25}_D$ –132 (*c* 1.50, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 216 sh (4.14), 234 (4.23), 256 (3.68), 401 (3.40) nm; IR (dry film) ν_{max} 3364, 2757, 2829, 1726, 1686, 1620 cm^{-1}; HRESIMS *m/z* 371.1965 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_4$ + H, 371.1965); ^1H and ^{13}C NMR data, see Tables 2.29 and 2.30, respectively.

β-Yohimbine pseudoindoxyl *N*-oxide (47): yellow fluorescent oil; $[\alpha]^{25}_D$ –37 (*c* 0.04, MeOH); UV (EtOH) λ_{max} (log ε) 232 (4.29), 259 (3.66), 401 (3.47) nm; IR (dry film) ν_{max} 3366, 1726, 1963, 1620 cm^{-1}; HRESIMS *m/z* 387.1919 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_4$ + H, 387.1915); ^1H and ^{13}C NMR data, see Tables 2.29 and 2.30, respectively.

Vobasine (48): colorless oil; $[\alpha]^{25}_{D}$ –139 (*c* 0.56, $CHCl_3$); UV (EtOH), λ_{max} (log ε) 208(4.17), 240 (4.04), 315 (4.10) nm; IR (dry film) ν_{max} 3313, 1727, 1641 cm^{-1}; HRESIMS *m/z* 353.1861 $[M + H]^+$ (calcd for $C_{21}H_{24}N_2O_3$ + H, 353.1860); ^1H and ^{13}C NMR data, see Tables 2.31 and 2.32, respectively.

16-*Epi*-affinine (49): light yellowish oil; $[\alpha]^{25}_{D}$ –231 (*c* 0.42, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (4.14), 228 sh (4.00), 239 sh (3.96), 319 (3.99) nm; IR (dry film) ν_{max} 3314, 1631 cm^{-1}; HRESIMS *m/z* 325.1912 $[M + H]^+$ (calcd for $C_{20}H_{24}N_2O_2$ + H, 325.1911); ^1H and ^{13}C NMR data, see Tables 2.31 and 2.32, respectively.

Tabernaemontanine (50): light yellowish oil; $[\alpha]^{25}_{D}$ –55 (*c* 0.33, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 228 (4.28), 311 (3.98) nm; IR (dry film) ν_{max} 3323, 1727, 1640 cm^{-1}; HRESIMS *m/z* 355.2021 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2016); ^1H and ^{13}C NMR data, see Tables 2.31 and 2.32, respectively.

Normacusine B (51): yellowish oil; $[\alpha]^{25}_{D}$ +25 (*c* 0.43, MeOH); UV (EtOH) λ_{max} (log ε) 212 sh (4.07), 226 (4.28), 280 (3.60), 291 (3.50) nm; IR (dry film) ν_{max} 3179 cm^{-1}; HRESIMS *m/z* 295.1803 $[M + H]^+$ (calcd for $C_{19}H_{22}N_2O$ + H, 295.1805); ^1H and ^{13}C NMR data, see Tables 2.31 and 2.32, respectively.

Norfluorocurarine (52): light yellowish oil; $[\alpha]^{25}_{D}$ –596 (*c* 0.03, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε) 232 (4.27), 296 (3.86), 364 (4.33); IR (dry film) ν_{max} 3298, 1643 cm^{-1}; HRESIMS *m/z* 293.1651 $[M + H]^+$ (calcd for $C_{19}H_{20}N_2O$ + H, 293.1648); ^1H and ^{13}C NMR data, see Tables 2.33 and 2.34, respectively.

***N*(4)-Chloromethylnorfluorocurarine chloride (53):** yellowish oil; $[\alpha]^{25}_{D}$ –218 (*c* 0.11, MeOH); UV (EtOH) λ_{max} (log ε) 202 (4.09), 242 (3.85), 298 (3.50), 361 (4.58) nm; IR (dry film) ν_{max} 3347 cm^{-1}; HRESIMS *m/z* 341.1421 $[M]^+$ (calcd for $C_{20}H_{22}ClN_2O^+$, 341.1415); ^1H and ^{13}C NMR data, see Tables 2.33 and 2.34, respectively.

Velbanamine (54): light yellowish oil; $[\alpha]^{25}_{D}$ –64 (*c* 0.19, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 229 (4.42), 285 (3.92), 292 (3.89) nm; IR (dry film) ν_{max} 3400, 3292 cm^{-1}; HRESIMS *m/z* 299.2116 $[M + H]^+$ (calcd for $C_{19}H_{26}N_2O$ + H, 299.2118); ^1H and ^{13}C NMR data, see Tables 2.33 and 2.34, respectively.

Tabernamidine A (55): light yellowish oil; $[\alpha]^{25}_{D}$ –58 (*c* 0.13, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 234 (4.44), 287 (3.93), 294 (3.91) nm; IR (dry film) ν_{max} 3387, 3281, 1708 cm^{-1}; HRESIMS *m/z* 631.3647 $[M + H]^+$ (calcd for $C_{40}H_{46}N_4O_3$ + H, 631.3643). ^1H and ^{13}C NMR data, see Tables 2.35 and 2.36, respectively. NOESY: H-3/H-14, H-15, NH; H-5/H-6β, H-16, NMe; H-6α/H-6β, H-14α, H-21α; H-9/H-5, H-6β, H-10; H-15/H-3, H-14, H-16, H-18; H-16/H-5, H-15; H-19/H-18, H-21; H-21α/H-21β, H-6α; H-21β/H-21α, NMe; NH/H-3, H-12; H-3'/H-6', H-14', H-15'β; H-5'β/H-3', H-5'α, H-6'; H-5'α/H-5'β, H-6', H-21'; H-9'/H-6', H-10'; H-10'/H-3, H-9'; H-15'β/H-3', H-14', H-15'α; H-15'α/H-14', H-15'β, H-17'α, H-20'; H-16'/H-17'α, H-20'; H-17'β/H-15'α, H-17'α; H-17'α/H-15'α, H-16', H-17'β; H-20'/ H-15'α, H-16', H-18', H-21'; H-21'/ H-5'α, H-16', H-18', H-20'; NH'/H-12', H-16'.

Tabernamidine B (56): light yellowish oil; $[\alpha]^{25}_{D}$ –154 (*c* 0.05, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 232 (5.21), 286 (4.72), 295 (4.68) nm; HRESIMS *m/z* 631.3652 $[M + H]^+$

(calcd for $C_{40}H_{46}N_4O_3$ + H, 631.3643); ^{1}H and ^{13}C NMR data, see Tables 2.35 and 2.36, respectively.

Tabernamine (57): light yellowish oil; $[\alpha]^{25}_D$ −20 (*c* 0.09, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 234 (4.56), 287 (4.01), 294 (4.00) nm; IR (dry film) ν_{max} 3396, 1720 cm^{-1}; HRESIMS *m/z* 617.3846 $[M + H]^+$ (calcd for $C_{40}H_{48}N_4O_2$ + H, 617.3851); ^{1}H and ^{13}C NMR data, see Tables 2.37 and 2.38, respectively.

16'-Decarbomethoxyvoacamine (58): light yellowish oil; $[\alpha]_D$ −61 (*c* 0.4, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 231 (4.86), 295 (4.42) nm; IR (dry film) ν_{max} 3378, 1741 cm^{-1}; HRESIMS *m/z* 647.3968 $[M + H]^+$ (calcd for $C_{41}H_{50}N_4O_3$ + H, 647.3956); ^{1}H NMR and ^{13}C NMR data, see Tables 2.37 and 2.38, respectively.

Conofolidine (59): colorless prisms (MeOH); mp > 203 ^oC (dec); $[\alpha]^{25}_D$ −102 (*c* 0.45, MeOH); UV (EtOH) λ_{max} (log ε) 210 (4.35), 243 (4.27), 310 (4.34), 334 (4.40) nm; IR (dry film) ν_{max} 3382, 1674, 1614 cm^{-1}; HRESIMS *m/z* 795.3600 $[M + H]^+$ (calcd for $C_{44}H_{50}N_4O_{10}$ + H, 795.3600); ^{1}H and ^{13}C NMR data, see Table 2.39. HMBC: ^{2}*J* H-3 to C-14; H-9 to C-10; H-14 to C-15; H- H-15 to C-14; H-17 to C-16, C-20; H-18 to C-19; H-19 to C-18, C-20; H-21 to C-7; 10-OH to C-10; NH to C-2, C-13; H-6' to C-5', C-7'; H-9' to C-10'; H-12' to C-11', C-13'; H-17' to C-16'; H-18' to C-19'; NH' to C-2', C-13'. ^{3}*J* H-3 to C-9', C-10', C-11', C-21; H-6 to C-2, C-8, C-21; H-9 to C-7, C-11, C-13; H-14 to C-20; H-15 to C-3, C-14, C-19, C-21; H-17 to C-15, C-19, C-21, *C*O_2Me; H-18 to C-20; H-19 to C-15, C-17, C-21; H-21 to C-2, C-3, C-8, C-17, C-19; 11-OMe to C-11; 12-OMe to C-12; CO_2*Me* to *C*O_2Me; 10-OH to C-9, C-10, C-11; NH to C-7, C-8; H-5' to C-7', C-21'; H-6' to C-2', C-8'; H-9' to C-3, C-7', C-11', C-13'; H-12' to C-8', C-10'; H-15' to C-17', C-21'; H-17' to C-2', C-15', C-16', C-19', C-21'; H-18' to C-15'; H-19' to C-

15', C-17', C-21'; H-21' to C-15', C-17', C-19'; CO_2Me' to CO_2Me'; NH' to C-7', C-8'. NOESY: H-9/H-5, H-6, H-21; H-14/H-3, H-15; H-15/H-14, H-18, H-19; H-17/H-6, H-18; H-18/H-17, H-19; H-19/H-18, H-21; H-3'/H-14'; H-6'/H-5', H-6'; H-9'/H-3, H-9, H-5', H-21'; H-15'/H-14', H-17'α, H-17'β; H-17'α/H-17'β, H-19'β; H-18'β/H-19'β; H-18'α/H-18'β, H-19'α, H-21'; H-21'/H-3'α, H-19'α; NH'/H-5'α, H-6'α, H-12', CO_2Me'.

Crystallographic data of 59: colorless prisms, $C_{44}H_{50}N_4O_{10}.CH_3OH$, *M*r = 826.92, tetragonal, space group $P4_32_12$, *a* = 16.2628(3) Å, *b* = 16.2628(3) Å, *c* = 35.9975(10) Å, *V* = 9520.6(5) Å^3, *Z* = 8, D_{calcd} = 1.154 gcm^{-3}, crystal size 0.4 x 0.4 x 0.2 mm^3, *F*(000) = 3520, Cu Kα radiation (λ = 1.54184 Å), *T* = 293(2) K. The final R_1 value is 0.0808 (wR_2 = 0.2397) for 9522 reflections [$I>2\sigma(I)$]. The absolute configuration was determined on the basis of Flack parameter [*x* = 0.05(0.09)], refined using 4069 Friedel pairs. CCDC number: 1494557.

Conophyllidine (60): light yellowish oil; $[\alpha]^{25}_D$ −147 (*c* 0.12, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (4.35), 243 (4.27), 310 (4.34), 334 (4.40) nm; IR (dry film) ν_{max} 3382, 1674, 1614 cm^{-1}; HRESIMS *m/z* 795.3600 $[M + H]^+$ (calcd for $C_{44}H_{50}N_4O_{10}$ + H, 795.3600); ^{1}H and ^{13}C NMR data, see Table 2.40.

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. K. Komiyama (Kitasato University, Japan). MCF7, LNCaP, PC-3, and A549 cells were cultured in RPMI 1650 medium. KB, KB (VJ 300), and MDA-MB-231 cells were cultured in Eagle's medium (DMEM). HT-29 and HCT 116 cells were cultured in McCoy's 5A medium. Cytotoxicity assays were carried out following essentially the same procedure as described previously.[469,470] All media were supplemented with 10% fetal bovine serum and 2% penicillin/streptomycin. The cells were cultured at 37°C under a humidified 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 prior to treatment with test samples. Seeded cells were treated with test samples 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) were regarded as negative control, while cells treated with vincristine, verapamil or cisplatin were served as positive control. DMSO was used to dilute the samples and the final concentration of DMSO in each well was not in excess of 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 200μL of DMSO were added to effect formazan solubilization. After agitation for 15 min, the absorbance of each well was measured with a microplate reader (Emax, Molecular Devices, USA) 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 Vasorelaxation Activity[471]

Male Sprague–Dawley rats (240–500 g) were used in all experiments (purchased from animal house, University Putra Malaysia, Malaysia). Ethics approval obtained from University of Nottingham's Animal Welfare Ethics Committee (UNMC#2kn). Rats were anaesthetised with Et_2O and sacrificed by cervical dislocation. The thoracic aorta was immediately excised and transferred into cold Krebs–Ringer bicarbonate solution. The Krebs–Ringer bicarbonate solution was freshly prepared daily following the composition (in mM): NaCl 120, KCl 5.4, $MgSO_4.7H_2O$ 2.4, KH_2PO_4 1.2, $NaHCO_3$ 25, Glucose 11.7, $CaCl_2$ 1.26. All connective tissues were removed from the aorta and cut into 4 mm rings. In a tissue bath, the aorta rings were suspended on metal wire triangles that were connected to a force transducer (MLTF050/ST, AD Instruments, US) via a long surgical suture thread. The measurement of tension was recorded by a PowerLab data acquisition system (LabChart v7.3.4). Aorta rings were maintained in 10 ml Krebs–Ringer bicarbonate solution at 37°C and aerated with 95% O_2, 5% CO_2. These rings were allowed to equilibrate for at least 30-min before the application of 2 g wt tension. The aorta rings were pre-contracted with 1×10^{-7} M of phenylephrine to achieve 70% of maximal contraction. Once a stable tone was established, cumulative concentration response curves to the compound (1×10^{-9} to 1×10^{-4} M) and isoprenaline (1×10^{-9} to 3×10^{-5} M) were determined. Compound was dissolved in DMSO to make 100 mM stock solutions; final bath concentration of DMSO was < 0.1% (v/v). (*R*)-(−)-Phenylephrine hydrochloride and isoproterenol hydrochloride

(isoprenaline) were purchased (Tocris Bioscience) and dissolved in distilled H_2O to make 10 mM stock solutions.

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