

Review Article

Phytochemical and Pharmacological Properties of the Genus *Melodinus* – A Review

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Abstract

Melodinus is an important genus comprising of approximately 53 species of medicinal plants (Apocynaceae). Some species have been used in Chinese folk medicine for the treatment of meningitis in children, rheumatic heart diseases, and diuresis, as well as a decongestive against migraine and sinusitis. This paper is a review of the literature up to May 2015 and describes 263 compounds from 69 articles, and includes chemical constituents isolated from *Melodinus*, mainly indole alkaloids, quinoline alkaloids, dimeric alkaloids, terpenoids and other compounds. It is also hoped that an overview of their cytotoxic characteristics will further the development of new anti-cancer agents.

Keywords: *Melodinus*, Indole alkaloids, Dimeric alkaloids, Cytotoxicity, Medicinal plants

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INTRODUCTION

Melodinus is a genus of ca. 53 species in the family Apocynaceae, mainly distributed in tropical and subtropical Asia and from Oceania to the Pacific coast. Among them, ca. 11 species occur in South China, Southwest China and Taiwan [1]. Some species, such as *M. suaveolens* and *M. henryi* have been used in Chinese folk medicine for the treatment of meningitis in children, rheumatic heart diseases, diuresis, bone fracture and so on [2,3]. *M. scandens* is used as a decongestive, against migraines, sinusitis and otitis [4]. In Australia, an aq extract of *M. australis*, when injected into a dog, produced a sharp drop in blood pressure, accompanied by an increase in the depth of respiration and decrease in rate [5]. Current crude alkaloid mixtures and purified alkaloids from some *Melodinus* species have demonstrated antitumor

and antibacterial activities [6,7]. Many characteristic melodinus alkaloids, such as meloscine, epimeloscine, scandine and vincadifformine, had for a long time attracted great interest of synthetic organic chemists as challenging targets due to their marked diversity and complicated architectures [8,9,10] And more than twenty alkaloids were reviewed from the genus *Melodinus* by Sevenet *et al* [11]. About 14 alkaloids can be classified into the melodan skeleton and its rearranged version and derived from 18, 19-didehydrotabersonine as parent compound in the plant family Apocynaceae [12] Recently, much attention has been paid to *Melodinus* plants to search active melodinus alkaloids. Extensive studies of the *Melodinus* genus have led to the identification of several novel alkaloids. Only 22 species of the genus have been chemically investigated and provided an array of structurally interesting indole

alkaloids, quinoline alkaloids, dimeric indole alkaloids, diterpenoids, triterpenes and others compounds over the past few decades. Some compounds show cytotoxic and anti-inflammatory activities. In this paper, we summarize phytochemistry and pharmacological activities of the *Melodinus* species so as to collate the existent information on this plant.

PHYTOCHEMICAL CONSTITUENTS

By the deadline of MAY 2015, phytochemical studies on this genus led to the isolation of 263 compounds. Their structures are shown below and their names, the corresponding plant sources are collected. As can be seen, indole alkaloids are the dominant constituents within this genus.

Alkaloids

Plants of the genus *Melodinus* (Apocynaceae) have been proven to be good sources of alkaloids. This genus has been regarded as a rich source of monoterpene indole alkaloids, which originated from the condensation of tryptophan with secologanin. We now list 252 alkaloids which were obtained from the genus *Melodinus*. The structural characters and relationships of the major *Melodinus* alkaloid groups are discussed.

Monoterpene indole alkaloids

Kopsinine-type

In this paper, indole alkaloids could be classified into ten groups from some *Melodinus* plants. This first type included nineteen alkaloids (1-19) (Table 1, Figure 1) [13-35]. The common characteristic compounds, venalstonine (3) and venalstonine (7) were produced by more than fifteen *Melodinus* species. Three aspidofractinine oxo-derivatives (9-11) were obtained from *M. reticulates* and *M. guillauminii* [13,14]. Melodinine L (12) was new alkaloid identified as venalstonine-N (4)-oxide from *M. tenuicaudatus* and *M. yunnanensis* [27,34]. Methoxyl substitution at C (15), a rare phenomenon, were present in pyrifoline (13) and refractidine (14) obtained from *M. australis* [33]. Melodinine Q (17) was venalstonine derivative with a CH₃-CO-CH-unit [29]. 14, 15-Seco-3-oxo-kopsinal (16) originated a further oxidation of bond C (14)-C (15) of venalstonine was identified by comparison of their spectral and physical properties from *M. guillauminii* [14]. 10, 22 - Dioxokopsane was a known alkaloids but was isolated obtained from this genus for the first time [35].

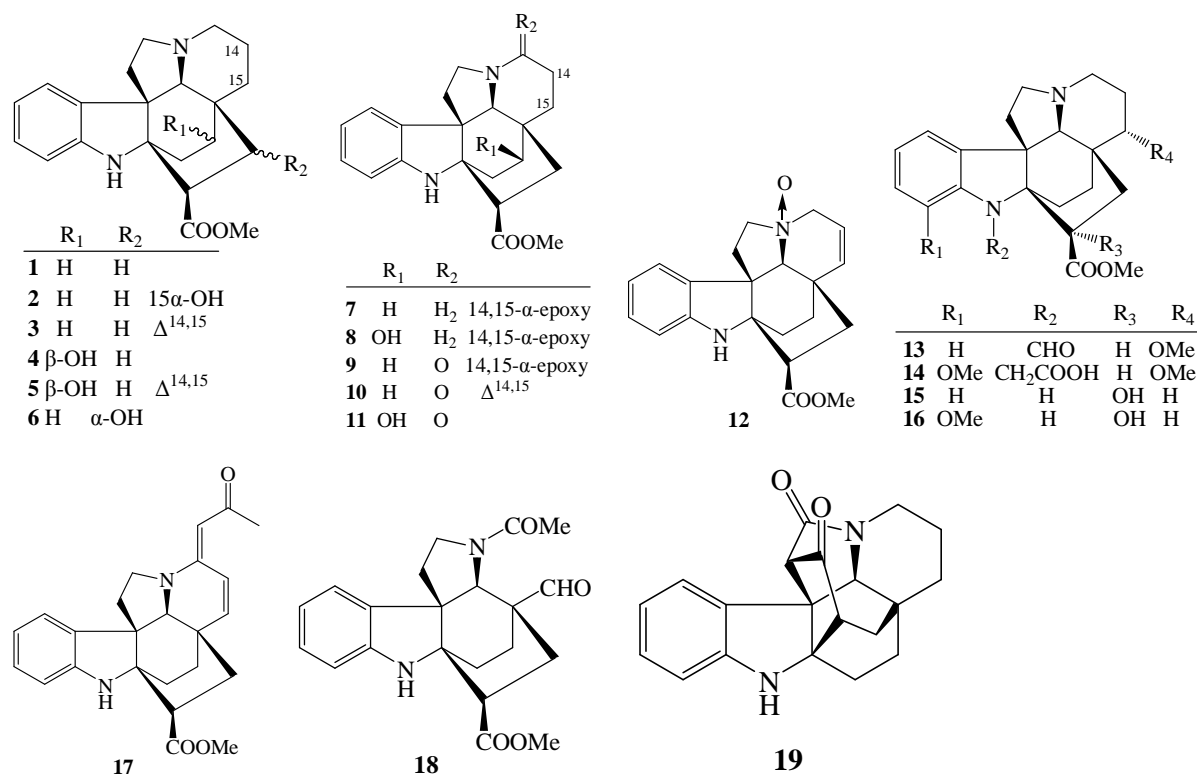


Figure 1: Structures of kopsinine-type alkaloids from *Melodinus* spp

Nomenclature:A= aerial parts
B= stem barkR= root
S= stems

F= fruit

T= twigs

L= leaves

Tr= trunk

N= not mentioned

Table 1: Kopsinine-type alkaloids from genus *Melodinus*

No.	Compound name	Species	Ref.
1	Kopsinine	<i>M. fusiformis</i> (R & S), <i>M. guillauminii</i> (A & B), <i>M. morsei</i> (N), <i>M. reticulatus</i> (L & S)	[13-16]
2	15 α -Hydroxykopsinine	<i>M. fusiformis</i> (R & S), <i>M. guillauminii</i> (A & B), <i>M. hemsleyanus</i> (R), <i>M. morsei</i> (N)	[14-17]
3	Venalstonine= Δ^6 -Kopsinine	<i>M. australis</i> (N), <i>M. balansae</i> (L), <i>M. fusiformis</i> (L, R & S), <i>M. guillauminii</i> (A & B), <i>M. hemsleyanus</i> (A), <i>M. insulae-pinorum</i> (A & B), <i>M. oblongus</i> (L), <i>M. polyadenus</i> (L& S), <i>M. phylliraeoides</i> (L), <i>M. reticulatus</i> (L & S), <i>M. scandens</i> (N), <i>M. suaveolens</i> (N), <i>M. tenuicaudatus</i> (N)	[13-15,18-29]
4	19 β -Hydroxykopsinine	<i>M. insulae-pinorum</i> (A & B)	[24]
5	19 β -Hydroxyvenalstonine	<i>M. guillauminii</i> (A & B), <i>M. oblongus</i> (S), <i>M. reticulatus</i> (S & L)	[13,14,30]
6	17 α -Hydroxyvenalstonine	<i>M. tenuicaudatus</i> (N)	[27]
7	Venalstonidine= $\Delta^6,7\xi$ -Epoxy-kopsinine	<i>M. australis</i> (N), <i>M. balansae</i> (L), <i>M. celastroides</i> (A), <i>M. fusiformis</i> (L & S), <i>M. guillauminii</i> (A & B), <i>M. hemsleyanus</i> (A), <i>M. insulae-pinorum</i> (A & B), <i>M. morsei</i> (L & S), <i>M. polyadenus</i> (L& S), <i>M. phylliraeoides</i> (L), <i>M. reticulatus</i> (L & S), <i>M. scandens</i> (N), <i>M. yunnanensis</i> (L & T)	[13,14,18-25,28,31,32]
8	19- β -Hydroxyvenalstonidine	<i>M. insulae-pinorum</i> (A & B), <i>M. reticulatus</i> (L & S)	[13,24]
9	3-Oxovenalstonidine	<i>M. reticulatus</i> (L & S)	[13]
10	3-Oxovenalstonine	<i>M. guillauminii</i> (A & B), <i>M. reticulatus</i> (L & S)	[13,14]
11	3-Oxohydroxykopsinine	<i>M. guillauminii</i> (A & B)	[14]
12	Melodinine L	<i>M. tenuicaudatus</i> (N), <i>M. yunnanensis</i>	[27,32]
13	Refractidine	<i>M. australis</i> (N)	[33]
14	Pyrifoline	<i>M. australis</i> (N)	[33]
15	Kopsinine B	<i>M. henryi</i> (L & S)	[34]
16	12-Methoxykopsinaline	<i>M. henryi</i> (L & S)	[34]
17	Melodinine Q	<i>M. suaveolens</i> (N)	[29]
18	14,15-Seco-3-oxokopsinal	<i>M. guillauminii</i> (A & B)	[14]
19	10,22-Dioxokopsane	<i>M. henryi</i> (L)	[35]

Tabersonine-group

This stereochemical series was more commonly encountered in the tabersonine group, as indicated in structures 20-55 (Table 2, Figure 2), respectively. The simple tabersonine derivatives (20-47) were identified from sixteen *Melodinus* species. Compounds 30- 36, in which C (14)-C (15) were epoxidized, were also isolated from *M. aeneus*, *M. fusiformis*, *M. hemsleyanus*, *M. henryi*, *M. morsei*, *M. oblongus*, *M. suaveolens* and *M. tenuicaudatus* [15,25-29,37,38,42,43]. Continuation of study on the genus *Melodinus*

had led to the isolation of six new monoterpenoid indole alkaloids, melodinines M- S (47-52, resp.), as well as seven known tabersonine derivatives (25, 26, 29, 31, 45, 53) from *M. suaveolens* by Liu *et al.* The structure difference of 11-hydroxytabersonine and melodinine A (47), melodinine A was that the benzene ring A was oxidized to a dienone system. Alkaloids (51 - 53) were identified as an acetyl derivative of tabersonine by the NMR from *M. tenuicaudatus* [29]. And melotinine A (55), an unprecedented skeleton with a 6/5/5/6/7 pentacyclic rearranged

ring system, which have been derived from tabersonine, was also isolated [41].

Vindolinine-type

This type was a small group with eleven alkaloids, **56-66** (Table 3, Fig 3), which contained a C (2)-C (19) bond in an aspido-spermine ring from *Melodinus* spp. All of them expect compound **66** belong to the five pair of epimers and their names, the corresponding plant sources and the reference are collected in Table 3.

Aspidospermidine-type

Aspidospermidine alkaloids, **67-73** (Fig 4), may be derived from vincadifformine by deformylation. Eburenine (1,2-dehydroaspido-spermidine) (**67**) and (-)-aspido-spermidine (**68**) were isolated from air-dried leaves, twigs and aerial parts of *M. morsei* (L & T), *M. henryi* and air-dried leaves of *M. celastroides* [28,44,48,49]. Previous pharmacological investigations on leaves of *M. celastroides*, epi-20, 21(+)-aspido-spermidine (**69**), Nb-oxyepi-20, 21(+)-aspido-spermidine (**70**), melocelinine (**71**) and meloceline (**72**) were

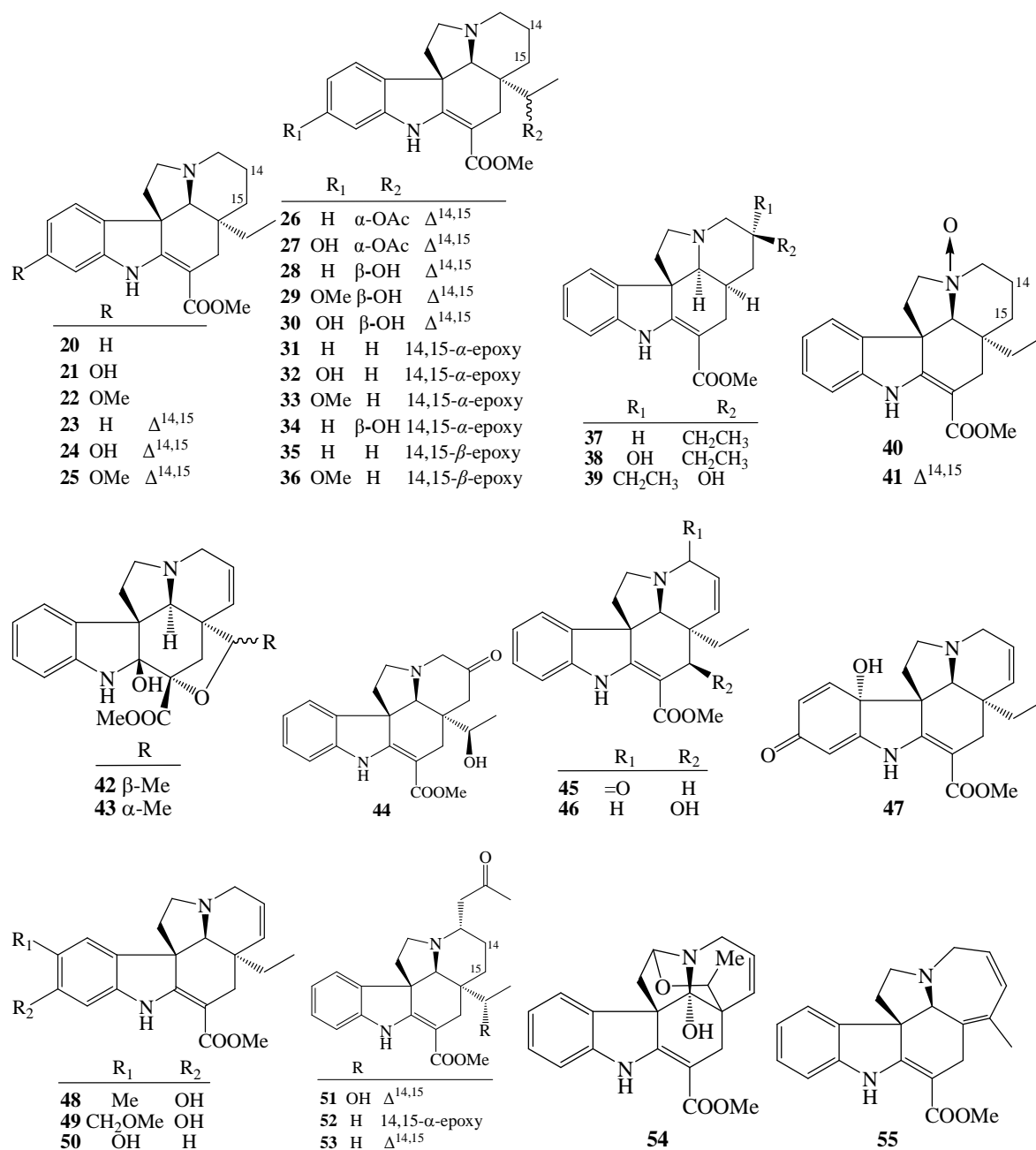


Figure 2: Structures of tabersonine-group alkaloids from *Melodinus* spp

Table 2: Tabersonine-group alkaloids from genus *Melodinus*

No.	Compound name	Species	Ref.
20	Vincadifformine	<i>M. aeneus</i> (L), <i>M. morsei</i> (L & S)), <i>M. polyadenus</i> (L & S), <i>M. scandens</i> (N), <i>M. suaveolens</i> (Tr)	[16,19,22,28,36-38]
21	11-Hydroxyvincadifformine	<i>M. hemsleyanus</i> (A), <i>M. morsei</i> (L & S)	[25,28]
22	11-Methoxyvincadifformine	<i>M. suaveolens</i> (Tr)	[37]
23	Tabersonine	<i>M. aeneus</i> (L), <i>M. balansae</i> (L), <i>M. elastroides</i> (L), <i>M. fusiformis</i> (L, R & S), <i>M. hemsleyanus</i> (A), <i>M. henryi</i> (F & R), <i>M. morsei</i> (L & S), <i>M. oblongus</i> (S), <i>M. polyadenus</i> (L & S), <i>M. reticulatus</i> (F), <i>M. scandens</i> (N), <i>M. suaveolens</i> (Tr), <i>M. tenuicaudatus</i> (N), <i>M. yunnanensis</i> (L & T)	[13,15,19,20,22,25,28-32,37-42]
24	11-Hydroxytabersonine	<i>M. axillaris</i> (R), <i>M. balansae</i> (L), <i>M. fusiformis</i> (R & S), <i>M. guillauminii</i> (A & B), <i>M. hemsleyanus</i> (A & R), <i>M. morsei</i> (L & S), <i>M. oblongus</i> (L), <i>M. tenuicaudatus</i> (B), <i>M. suaveolens</i> (Tr, L & T)	[14,15,17,20,25-29,37,43-46]
25	11-Methoxytabersonine	<i>M. aeneus</i> (L), <i>M. fusiformis</i> (R & S), <i>M. guillauminii</i> (A & B), <i>M. hemsleyanus</i> (A), <i>M. henryi</i> (F & R), <i>M. polyadenus</i> (L & S), <i>M. reticulatus</i> (F), <i>M. suaveolens</i> (Tr), <i>M. tenuicaudatus</i> (B), <i>M. yunnanensis</i> (L & T)	[13-15,22,25,27,29,32,37,38,42,43]
26	19-Acetyltabersonine	<i>M. morsei</i> (L & S), <i>M. suaveolens</i> (N)	[28,29]
27	11-Hydroxy-19-acetyltabersonine	<i>M. tenuicaudatus</i> (N), <i>M. morsei</i> (L & S)	[27,28]
28	19 <i>R</i> -Hydroxytabersonine	<i>M. suaveolens</i> (Tr)	[37]
29	11-Methoxy-19 <i>R</i> -hydroxytabersonine	<i>M. suaveolens</i> (Tr)	[29,37]
30	11,19 <i>R</i> -Dihydroxytabersonine	<i>M. fusiformis</i> (R & S), <i>M. hemsleyanus</i> (A), <i>M. suaveolens</i> (Tr)	[15,25,37]
31	Lochnericine	<i>M. aeneus</i> (L), <i>M. morsei</i> (L & S), <i>M. suaveolens</i> (N), <i>M. yunnanensis</i> (L & T)	[28,29,32,38]
32	11-Hydroxy-14,15 α -Epoxytabersonine	<i>M. fusiformis</i> (R & S), <i>M. hemsleyanus</i> (A), <i>M. morsei</i> (L & S), <i>M. tenuicaudatus</i> (N)	[15,25,27,28]
33	Hazuntine	<i>M. suaveolens</i> (Tr), <i>M. tenuicaudatus</i> (B)	[37,43]
34	Cathovalinine	<i>M. suaveolens</i> (Tr)	[37]
35	β -Epoxytabersonine	<i>M. oblongus</i> (L)	[26]
36	Lochnerinine	<i>M. aeneus</i> (L), <i>M. henryi</i> (F & R)	[38,42]
37	(+)-20- <i>R</i> -Pseudovincadifformine	<i>M. polyadenus</i> (L & S)	[22]
38	(+)-20- <i>R</i> -Pandoline	<i>M. polyadenus</i> (L & S)	[22]
39	(+)-20- <i>S</i> -Pandoline	<i>M. polyadenus</i> (L & S)	[22]
40	Vincadifformine N _b -oxide	<i>M. morsei</i> (L & S), <i>M. yunnanensis</i> (L & T)	[28,32]
41	Tabersonine N ₄ -oxide	<i>M. yunnanensis</i> (L & T)	[32]
42	Melobaline	<i>M. balansae</i> (L)	[20]
43	Vincoline	<i>M. hemsleyanus</i> (R), <i>M. morsei</i> (A), <i>M. suaveolens</i> (Tr)	[17,36,37,44]
44	Baloxine	<i>M. balansae</i> (L)	[20]
45	3-Oxotabersonine	<i>M. suaveolens</i> , <i>M. yunnanensis</i> (L & T)	[29,32]
46	17-Hydroxy-14,15-dihydroxytabersonine	<i>M. yunnanensis</i> (L & T)	[32]
47	Melodinine M	<i>M. suaveolens</i> (N)	[29]
48	Melodinine N	<i>M. suaveolens</i> (N)	[29]
49	Melodinine O	<i>M. suaveolens</i> (N)	[29]
50	Melodinine P	<i>M. suaveolens</i> (N)	[29]
51	Melodinine R	<i>M. suaveolens</i> (N)	[29]
52	Melodinine S	<i>M. suaveolens</i> (N)	[29]
53	3 α -Acetonyltabersonine	<i>M. suaveolens</i> (N)	[29]
54	Buxomeline	<i>M. celastroides</i> (L)	[40]
55	Melotenine A	<i>M. tenuicaudatus</i> (N)	[41]

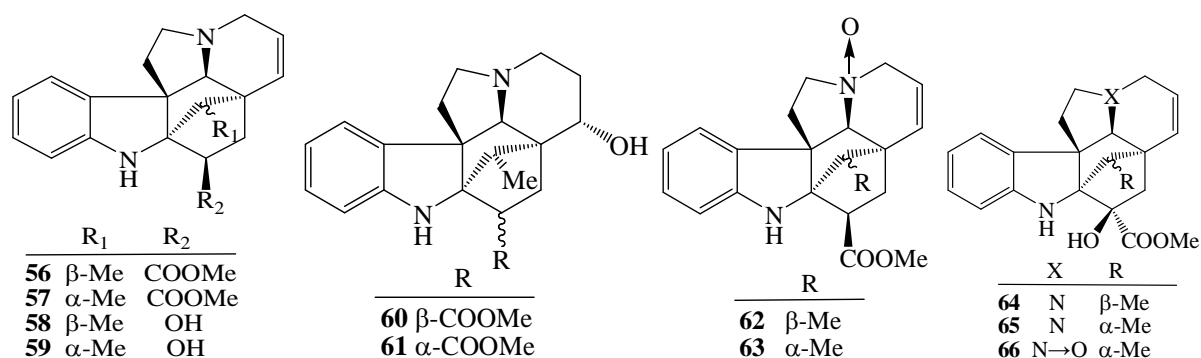


Figure 3: Structures of vindolinine-type alkaloids from *Melodinus* spp

Table 3: Vindolinine-type alkaloids from genus *Melodinus*

No.	Compound name	Species	Ref
56	19 <i>S</i> -Vindolinine = Vindolinine	<i>M. balansae</i> (L), <i>M. fusiformis</i> (R & S), <i>M. hemsleyanus</i> , <i>M. morsei</i> (N,), <i>M. Oblongus</i> (S), <i>M. hylliraeoides</i> (L), <i>M. Suaveolens</i> (Tr), <i>M. tenuicaudatus</i> (B)	[15,16,20, 23,27,28,3 0,37,43]
57	19 <i>R</i> -Vindolinine = Epivindoline	<i>M. celastroides</i> (L), <i>M. hemsleyanus</i> (A), <i>M. morsei</i> (L & S), <i>M. phylliraeoides</i> (L), <i>M. oblongus</i> (S)	[16,23,25, 28,30,40]
58	16-Hydroxyvindolinine	<i>M. oblongus</i> (S)	[30]
59	16-Hydroxyepivindolinine	<i>M. oblongus</i> (S)	[30]
60	15α-Hydroxy-14,15- dihydrovindolinine	<i>M. Morsei</i> (N)	[16,47]
61	15α-Hydroxy-14,15-dihydro- 16-epivindolinine	<i>M. morsei</i> (N)	[16,47]
62	Vindolinine N _β -oxide	<i>M. balansae</i> (L), <i>M. hemsleyanus</i> (R), <i>M. morsei</i> (N), <i>M. phylliraeoides</i> (L), <i>M. tenuicaudatus</i> (B)	[16,17,20, 23,43]
63	Epivindolinine N _β -oxide	<i>M. balansae</i> (L), <i>M. morsei</i> (N), <i>M.</i> <i>phylliraeoides</i> (L), <i>M. tenuicaudatus</i> (B)	[16,20,23, 43]
64	16β-Hydroxy-19 <i>R</i> -vindolinine	<i>M. hemsleyanus</i> (R & A)	[17,25]
65	16β-Hydroxy-19 <i>S</i> -vindolinine	<i>M. hemsleyanus</i> (A)	[25]
66	16β-Hydroxy-19 <i>S</i> -vindolinine N-oxide	<i>M. hemsleyanus</i> (R)	[17]

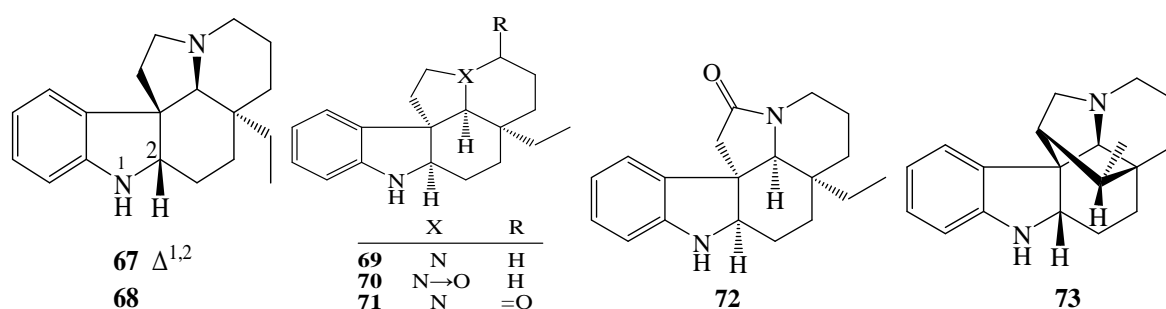


Figure 4: Structures of aspidospermidine-type alkaloids from *Melodinus* spp

isolated [50]. 6,7-Didehydroisotuboxenine (**73**) was only aspidospermidine alkaloid isolated from leaves and twigs of *M. yunnanensis* [32].

Aspidospermidine-type

Aspidospermidine alkaloids, **67-73** (Fig 4), may be derived from vincadifformine by deformylation.

Eburenine (1,2-dehydroaspidospermidine) (**67**) and (-)-aspidospermidine (**68**) were isolated from air-dried leaves, twigs and aerial parts of *M. morsei* (L & T), *M. henryi* and air-dried leaves of *M. celastroides* [28,44,48,49]. Previous pharmacological investigations on leaves of *M. celastroides*, epi-20, 21(+)-aspidospermidine (**69**), Nb-oxyepi-20, 21(+)-aspidospermidine (**70**),

Table 4: Eburnamine-type and derivatives alkaloids from genus *Melodinus*

No.	Compound name	Species	Ref.
87	O-methyl- Δ^{14} -vincanol	<i>M. tenuicaudatus</i> (N), <i>M. yunnanensis</i> (L & T)	[27,32]
88	16-Epi- O-methyl- Δ^{14} -vincanol	<i>M. khasianus</i> (B), <i>M. yunnanensis</i> (L & T) <i>M. celastroides</i> (L), <i>M. henryi</i> (F & R), <i>M. insulae-pinorum</i> (B & A),	[24,30,32,39,42,43,49,51]
89	Δ^{14} -Vincanol= Δ^{14} -Eburnamine	<i>M. khasianus</i> (B), <i>M. oblongus</i> (S), <i>M. tenuicaudatus</i> (B), <i>M. yunnanensis</i> (L & T)	[24,30,49]
90	16-Epi- Δ^{14} -vincanol	<i>M. celastroides</i> (L), <i>M. insulae-pinorum</i> (B & A), <i>M. oblongus</i> (S)	[24,30,49]
91	Δ^{14} -Vincine=14,15-Dehydrovincamine	<i>M. henryi</i> (F & R), <i>M. polyadenus</i> (L & S), <i>M. suaveolens</i> (Tr), <i>M. tenuicaudatus</i> (B), <i>M. yunnanensis</i> (L & T)	[2,22,32,37,43]
92	Epi-16-dehydro-14,15-vincine	<i>M. aeneus</i> (L)	[38]
93	Δ^{14} -Vincamine	<i>M. henryi</i> (F & R), <i>M. yunnanensis</i> (L & T)	[32,42,52]
94	Epi-16- Δ^{14} -vincamine (+)-16-epi- Δ^{14} -vincamine	<i>M. aeneus</i> (L), <i>M. henryi</i> (R), <i>M. yunnanensis</i> (L & T)	[32,38,52]
95	14-Epieburnamine = (-)-Isoeburnamine; (3 α ,14 β ,16 α)	<i>M. henryi</i> (L)	[35,48]
96	(+)-Eburnamine = (+)-Vincanol	<i>M. celastroides</i> (L), <i>M. henryi</i> (L)	[35,39]
97	Melodinine F	<i>M. henryi</i> (N)	[48]
98	Melodinine G	<i>M. henryi</i> (N)	[48]
99	Δ^{14} -Vincamenine N ₄ -oxide	<i>M. yunnanensis</i> (L & T)	[32]
100	O-Methylepivincanol	<i>M. henryi</i> (N)	[48]
101	(-)-Eburnamenine = Vincamenine	<i>M. henryi</i> (L)	[35,48]
102	11-Methoxy- Δ^{14} -vincamenine	<i>M. guillauminii</i> (B & A)	[14]
103	11-Methoxy- Δ^{14} -vincanol	<i>M. guillauminii</i> (B & A)	[14]
104	Δ^{14} -Vincamenine	<i>M. yunnanensis</i> (L & T)	[53]
105	Δ^{14} -Isoeburnamine	<i>M. celastroides</i> (L), <i>M. henryi</i> (F & R), <i>M. oblongus</i> (S)	[30,40,42]
106	(+)-Isoeburnamine	<i>M. henryi</i> (R)	[52]
107	20-Oxo-eburnamine	<i>M. henryi</i> (L& S)	[34]
108	19-Oxoeburnamine	<i>M. henryi</i> (L& S)	[34]
109	Meloyunine	<i>M. yunnanensis</i> (L & T)	[32]
110	14 β -Hydroxymeloyunine	<i>M. yunnanensis</i> (L & T)	[32]
111	16-Decarbomethoxy-vincapsine	<i>M. yunnanensis</i> (L & T)	[32]
112	16,19-Epoxy- Δ^{14} -vincanol	<i>M. yunnanensis</i> (L & T)	[32]
113	14,17-Epoxy-eburnamine	<i>M. henryi</i> (F, R & S)	[54]

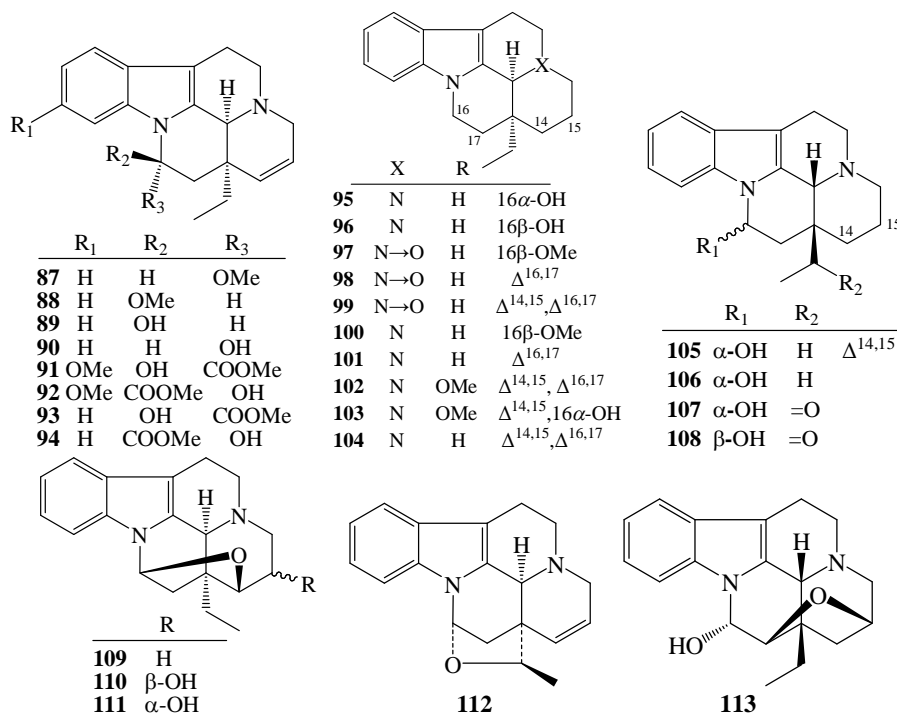


Figure 6: Structures of eburnamine-type alkaloids from *Melodinus* spp

M. tenuicaudatus, *M. suaveolens* (L & T) and *M. yunnanensis* (L & T) [26,32,35,43,45,46].

Geissoschizine-type and derivatives (Table 5(a) and (b), Figure 9)

Twenty-five constituents, 133- 157, were isolated from *M. acutiflorus*, *M. australis*, *M. fusiformis*, *M. hemsleyanus*, *M. khasianus*, *M. oblongus* and *M. tenuicaudatus* [15,20,27,28,32,43,50,54].

Picaline-type (**133-139**) and anhydrojmaline-type alkaloids (**140-141**) are biogenetically considered to be derived from geissoschizine (**144**) with its derivative by ring closure between the C(7) and C(16) positions and between the C(5) and C(16). As a common intermediate, geissoschizine (**144**) would also provide the mavacurine-type alkaloids (**149-150**) and tetrahydroalstonin (**151**).

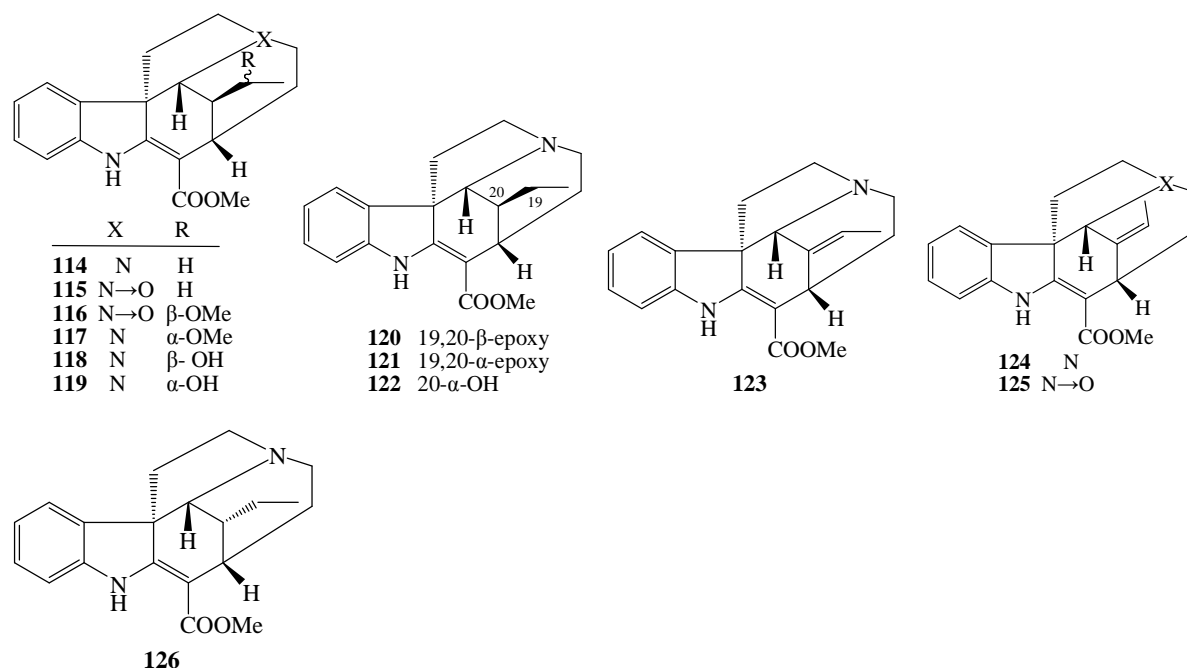


Figure 7: Structures of tubotaiwine -type alkaloids from *Melodinus* spp

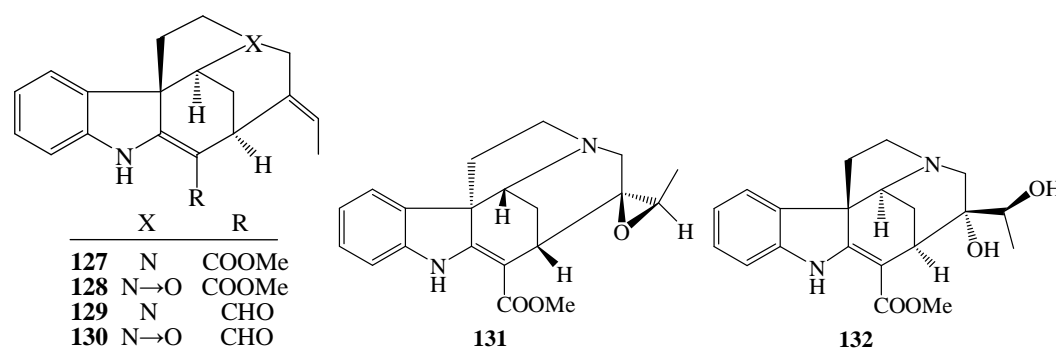


Figure 8: Structures of akuammicine-type alkaloids from *Melodinus* spp

Leuconotis alkaloid 376 and its analogues (Figure 10)

Melodinines A-C (**158-160**, resp.), together with leuconotis alkaloid 376 (**161**), possessed 22 skeletal carbons arranged compactly in six rings, were isolated from *M. henryi* by RP-18 gel and Sephadex LH-20 [48].

Axillarisine (**162**) was found from dry root powder of *M. axillaris* by Yan et al [45]. Three other novel

alkaloids, melohenine A (**163**), an unusual C24 monoterpene indole alkaloid with additional skeletal carbons arranged compactly in eight rings, and henrycinols A- B (**164-165**) with an a cinnamoyl group system were also isolated from roots of *M. henryi* [52,57]. The relative configuration of henrycinols A and B was determined by NOESY analysis.

Table 5: Geissoschizine-type and derivatives alkaloids from genus *Melodinus*

No.	Compound name	Species	Ref
133	Picaline	<i>M. oblongus</i> (S)	[30]
134	Picalinal	<i>M. hemsleyanus</i> (A), <i>M. oblongus</i> (L)	[25,26]
135	Picrinine	<i>M. hemsleyanus</i> (A), <i>M. oblongus</i> (L)	[25,26]
136	Deacetylpicaline	<i>M. fusiformis</i> , <i>M. oblongus</i> (S)	[15,30]
137	Deacetylakuammiline= rhazimol	<i>M. acutiflorus</i> , <i>M. oblongus</i> (S), <i>M. yunnanensis</i> (L & T)	[30,32,56]
138	16-Epirhazinaline=rhazinaline	<i>M. acutiflorus</i> (L), <i>M. yunnanensis</i> (L & T)	[32,56]
139	Akuammiline	, <i>M. khasianus</i> (B), <i>M. oblongus</i> (S)	[30,51]
140	Akuamidine	<i>M. australis</i> (N), <i>M. hemsleyanus</i> (A)	[18,25]
141	Normacusine B	<i>M. tenuicaudatus</i> (B)	[43]
142	Polyneuridine	<i>M. suaveolens</i> (L & T)	[55]
143	Isositsirikine	<i>M. henryi</i> , <i>M. insulae-pinorum</i> (B & A), <i>M. phylliraeoides</i> (L), <i>M. yunnanensis</i> (L & T)	[23,24,32,48]
144	(+)-Geissoschizine	<i>M. phylliraeoides</i> (L)	[23]
145	Geissoschizol	<i>M. morsei</i> (A)	[36,44]
146	Nortetraphyllicine	<i>M. henryi</i> (L& S)	[34]
147	Nb-Methylnortetraphyllicine	<i>M. henryi</i> (L& S)	[34]
148	(+)-Ajmaline	<i>M. Balansae</i> (L)	[21]
149	Pleiocarpamine	<i>M. guillauminii</i> (B & AP), <i>M. oblongus</i> (S)	[14,26,30]
150	16-Hydroxymethyl pleocarpamine	<i>M. oblongus</i> (L)	[26]
151	Tetrahydroalstonin	<i>M. oblongus</i> (L)	[26]
152	Strictosamide	<i>M. axillaris</i> (R)	[45]
153	Demethylstrictosidine	<i>M. axillaris</i> (R)	[45]
154	Vallesiachotamine	<i>M. axillaris</i> (R), <i>M. henryi</i> (N)	[45,48]
155	(-)-Antirhine	<i>M. celastroides</i> (A)	[31]
156	Descarbomethoxydihydrogambirtannine	<i>M. henryi</i> (N)	[48]
157	Renoxidine = Reserpine N-oxide	<i>M. balansae</i> (L)	[20]

Other indole alkaloids, 166-178 (Figure 11)

Two known compounds, stemmadenine (**166**) and its N-oxide (**167**), were isolated from *M. henryi* [18,35,48]. N-acyl-indolinine (**168**) and a new diazaspindoindole alkaloid, melodinine E (**169**) were structural type seldom reported from *M. morsei* and *M. henryi*, resp. [28,48]. 6/7-Seco rearranged spiro-indolone alkaloids, meloyunines A (**170**) and B (**171**) were elucidated from leaves and twigs of *M. yunnanensis*. These structures were elucidated based on NMR, FTIR, UV, and MS spectroscopic data [53]. Mehri *et al* reported melonine (**172**) and Nb-oxy-melonine (**173**) from *M. celastroides* possibly artifacts due to the use of CH₂Cl₂ or HCl as an extraction solvent [40,49]. In 1978, Baassou *et al* found (-)-ibogamine (**174**) from *M. aeneus* [38]. Two novel alkaloids arbophylline (**175**) and 15-β-methoxy-14, 15-dihydroandraginine (**176**) were isolated from leaves and twigs of *M. yunnanensis* [32]. Melodinoxanine (**177**), which derived from an oxygenated derivative of isocarapanaubine (**178**), was a unique oxindole alkaloid with an extra oxygen atom in the C-ring of a heteroyohimbine skeleton from the stems and leaves of *M. henryi* growing in Yunnan, China [34].

Monoterpenoid quinoline alkaloids**Scandine derivatives, 179-183 (Figure 12)**

In 1969, Bernauer *et al* identified scandine (**179**), which was a naturally occurring biologically active product derived from plants, was important as a possible starting material for the syntheses of valuable pharmaceuticals, from *M. scandens* first time [58]. Then, this compound and 10-hydroxyscandine (**180**) were isolated from the other seven plants of *M. fusiformis*, *M. hemsleyanus*, *M. henryi*, *M. khasianus*, *M. oblongus*, *M. tenuicaudatus*, *M. scandens*, *M. suaveolens* [2,15,17,19,25,27,28,29,30,43,46,55,59]. And the absolute configuration has aroused the great concern [60]. The crystal structure and absolute configuration of (+)-scandine have been determined by X-ray diffraction [61,62]. Some fo scandine derivatives, 10-methoxyscandine (**181**), scandine Nb-oxide (**182**), melodinine U (**183**) and T (**184**), melodinhene C-D (**185-186**) obtained from *M. tenuicaudatus*, *M. fusiformis*, *M. henryi*, *M. suaveolens* [15,27,29,55,63]. The interesting chemical significance of the *Melodinus* plants prompted researchers to initiate a phytochemical study on the twigs and leaves of *M. suaveolens*, which led to the isolation of two new quinoline alkaloids, 14, 15-dihydroscandine (**187**) and 15β-

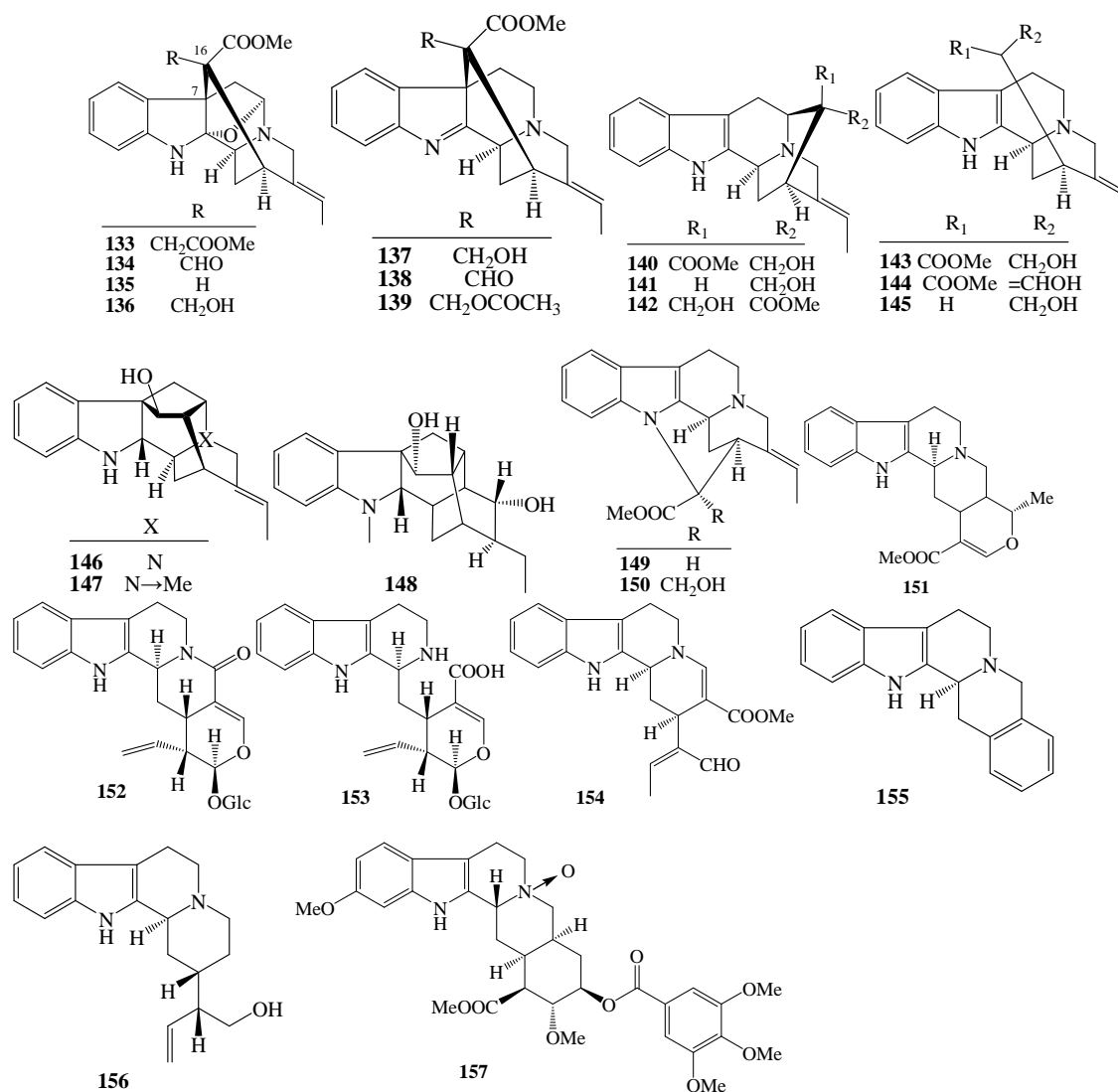


Figure 9: Structures of geissoschizine-type and derivatives alkaloids from *Melodinus* spp

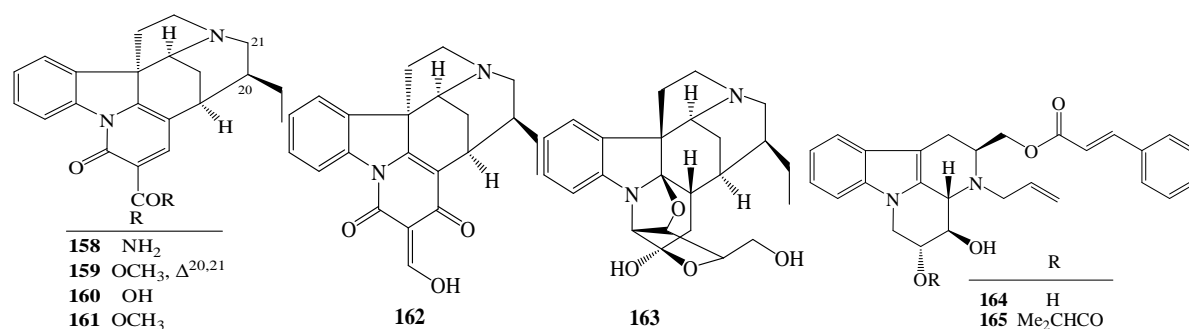


Figure 10: Structures of leuconotis alkaloid 376 and its analogues alkaloids from *Melodinus* spp

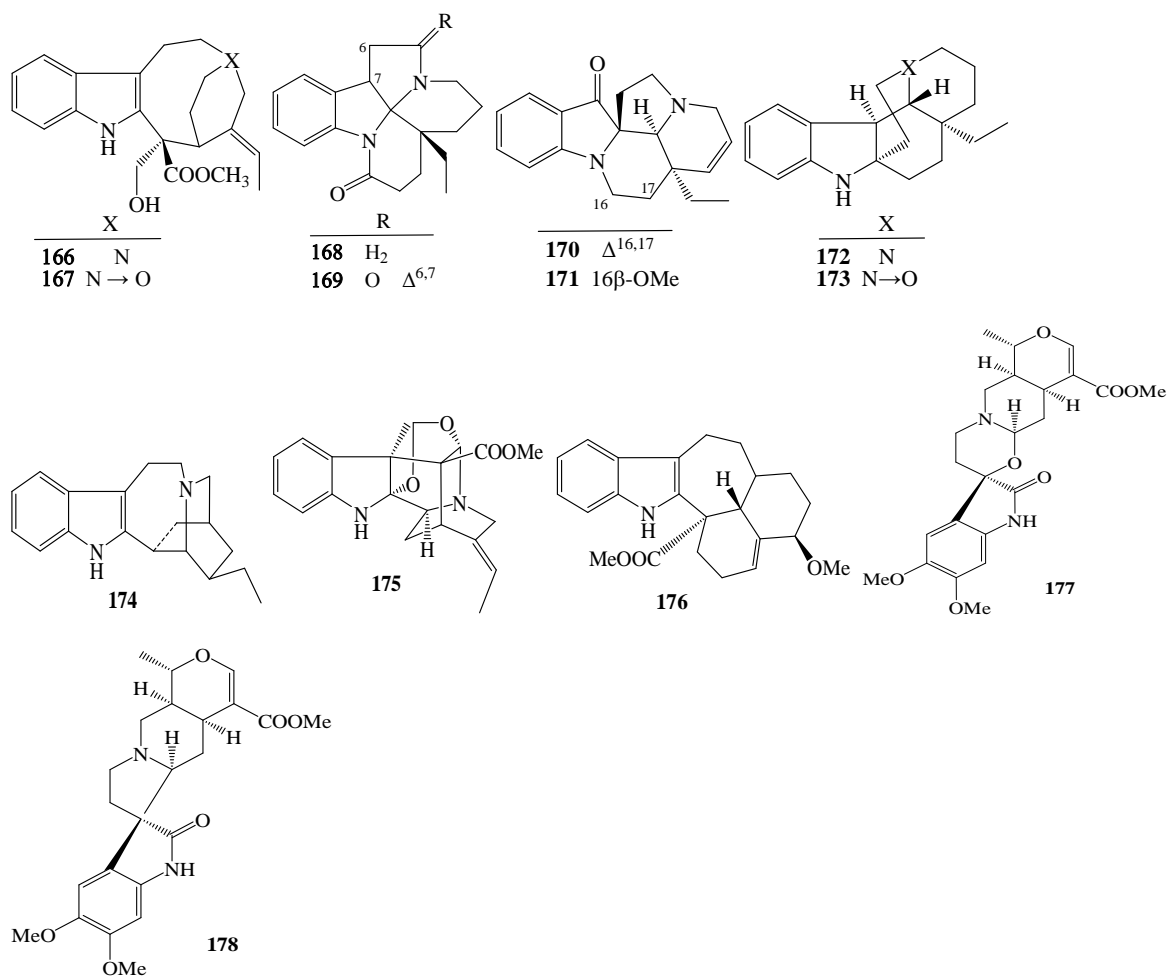


Figure 11: Structures of other indole alkaloids from *Melodinus* spp

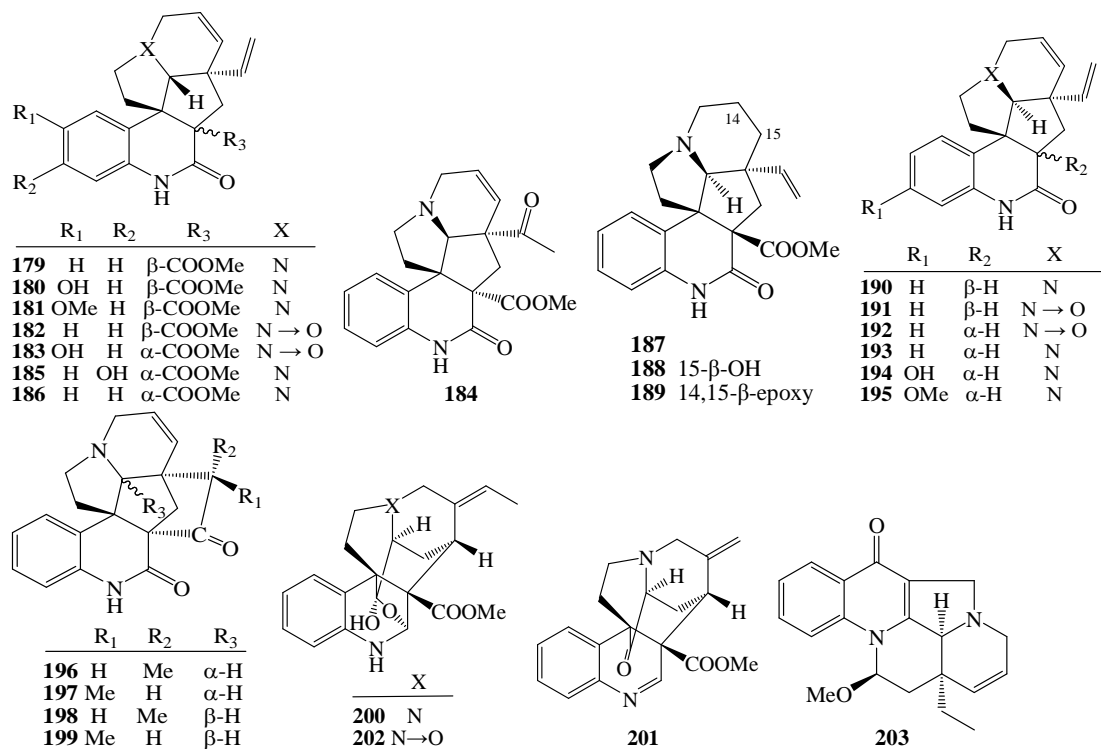


Figure 12: Structures of scandine derivatives quinoline alkaloids from *Melodinus* spp

hydroxy- 14,15-dihydroscandine (**188**), along with a known alkaloids 14, 15- β -epoxy-scandine (**189**) [46,55].

Meloscine derivatives, 190-195 (Figure 12)

Meloscine (**190**) and its Nb-oxide (**191**) were isolated from *M. hemsleyanus*, *M. oblongus*, *M. scandens*, *M. suaveolens* [25,30,55,59]. Four epi-meloscine compounds, N-oxyepimeloscine (**192**), epimeloscine (**193**), 9-hydroxyepimeloscine (**194**) and 9-methoxyepimeloscine (**195**), were isolated from *M. scandens* [19,58,60,61,64]. Meloscandonine (**196**) was isolated from *M. fusiformis*, *M. hemsleyanus*, *M. khasianus*, *M. scandens*, *M. oblongus*, *M. tenuicaudatus* [15,19,25-28,55,58,61]. And the structure of stereochemistry by UV, IR, NMR and X-ray [65,66]. 19-Epimeloscandonine (**197**) and melodinhenine E-F (**198, 199**) obtained from *M. fusiformis*, *M. hemsleyanus*, *M. henryi* and *M. oblongus* [25,28,63]. On the structure elucidation of the main alkaloids of *M. acutiflorus*, which led to a revision of the structures of rhazicine (**200**) and rhazimine (**201**), were first isolated. Further investigation of the extract of leaves of *M. acutiflorus* gave a new alkaloid, rhazicine N-oxide (**202**) [56,67]. To our knowledge, the first report of the co-occurrence of monoterpene indoles meloyunine C (**203**) and precursor Δ 14-vincamenine (**104**) in same plant, supporting the biosynthesis of quinoline from *M. yunnanensis* and concurring with previous *in vivo* tracer experiments in the literature [53].

Other monomeric alkaloids, 204-210 (Figure 13)

(-)-Rhazinilam (**204**) was a natural compound isolated from *M. australis* and *M. henryi*, whose tetracyclic structure possesses an axially chiral phenyl-pyrrole subunit bridged by a nine-membered lactam ring [18,35,48,68]. Melohenine B (**205**), 14, 15-dehydromelohenine B (**206**) and

14-O-ethyl-substituted (3 α ,14 α ,16 α)-2,7-secoeburnamine derivative (**207**) with an unprecedented 6/9/6/6 tetracyclic ring system, regarded as a key intermediate from indole to quinoline alkaloids were obtained from *M. henryi* and *M. yunnanensis* [35,52,55]. Three simple alkaloids, venoterpine (**208**), (\square)-R/S-1-(3-pyridyl)ethanol (**209**) and 2, 5-diphenyloxazole (**210**), were also isolated from *M. aeneus*, *M. axillaris* and *M. celastroides* [33,38,45].

Bisindole alkaloids

Eburnamine derivative dimeric alkaloids (Figure 14)

Fifteen bisindole alkaloids, melonines C-D (**211-212**), having an eburnamine-aspido-spermidine linkage, guillauminiine (**213**), paucivenine (**214**), tenuicausine (**215**), demethylteuicausine (**216**) and melodinine J (**217**), possessing an eburnamine-tabersonine skeleton, melodinine H-I (**218-219**), melodinhenine A-B (**220-221**) of the eburnamine-vindolinine type, and melonine A (**222**), melaxillarinine (**223**) and melaxillaridine (**224**) with an eburnamine-quebrachamine derivatives, were isolated from eight *Melodinus* species by column chromatography (CC), TLC, RP-18 gel, Sephadex LH-20 [6,14,21,27,42,43,45,65,68-71]. The absolute configuration of **220** and **221** was determined using ECD exciton chirality method. *M. insulaepinorum* furnished an eburnamine-kopsinine bisalkaloid, insulopinine (**225**) [24]. From *M. celastroides*, celastromeline (**226**) and celastromelidine (**227**) were the tertiary analogues of Le chlorure de chloromethyl celastromelinium (**228**) and Le chlorure de chloromethyl celastromelidinium (**229**), and their quasi-dimeric structures were not likely to be artifacts [49]. The later eburnamine-diazaspiroindole bisindole alkaloids, melonine B (**230**) was isolated as a pale-red powder from *M. henryi* [71].

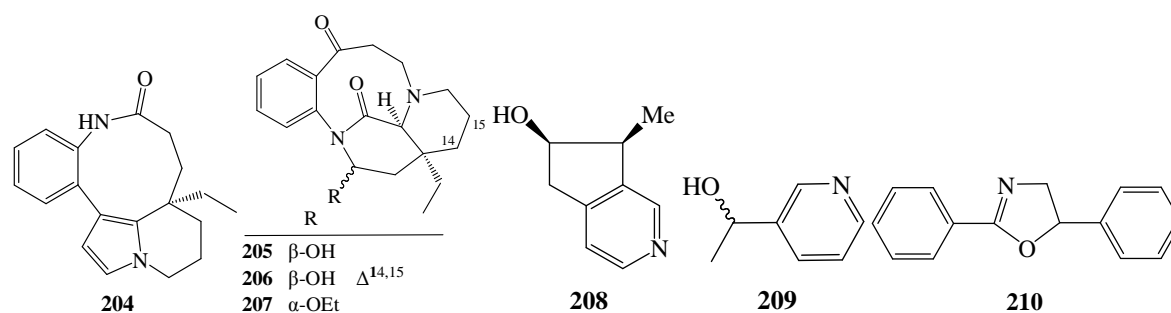


Figure 13: Structures of other monomeric alkaloids alkaloids from *Melodinus* spp

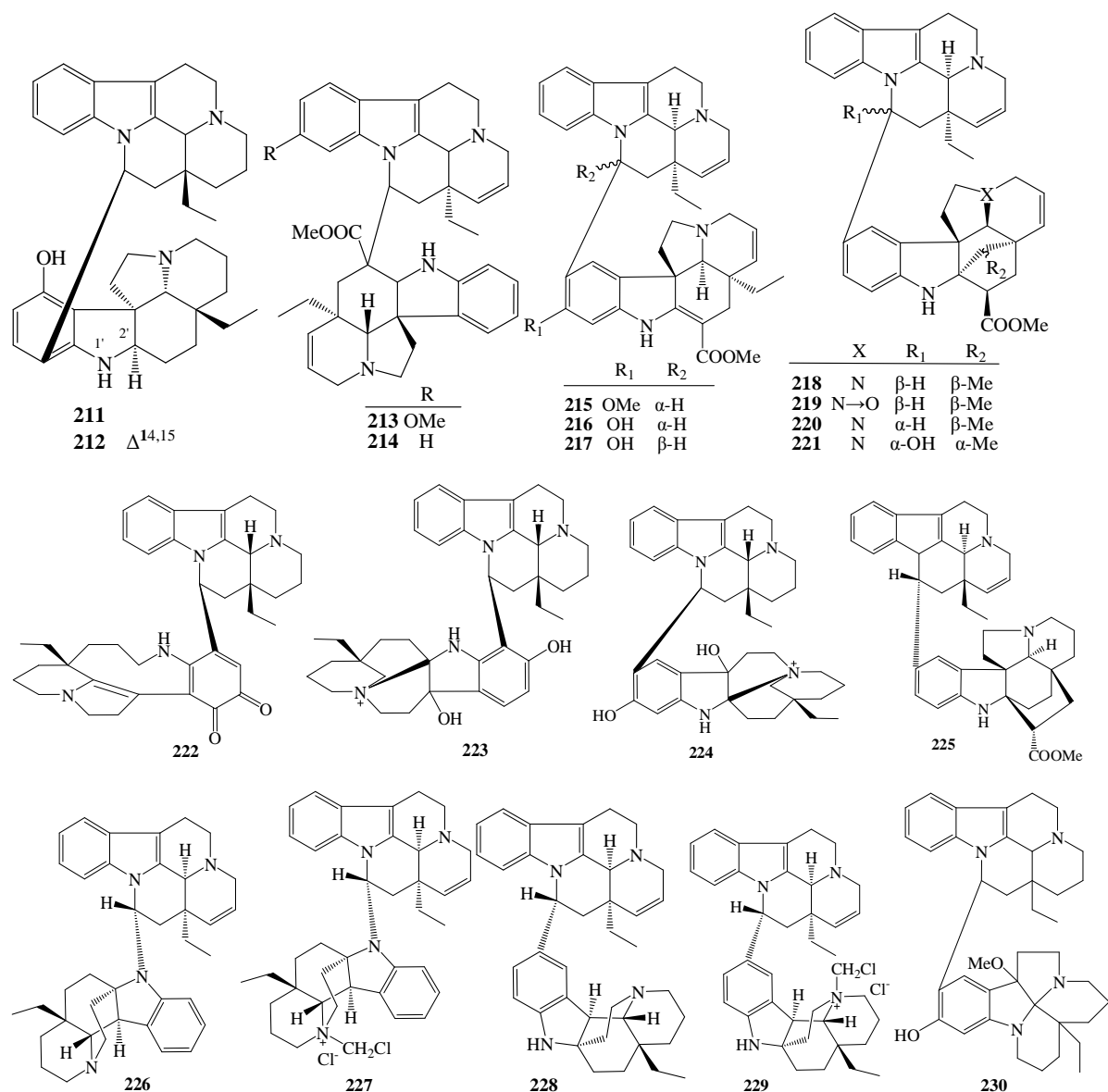


Figure 14: Structures of eburnamine-type dimeric alkaloids from *Melodinus* spp

Tabersonine derivative dimeric alkaloids, 231-247 (Figure 15)

In this part, we list all tabersonine derivative dimeric alkaloids except eburnamine-tabersonine type. Tabersonine-tabersonine skeleton, melodinine K (**231**) and melomorsine I (**232**) were isolated from *M. tenuicaudatus* and *M. fusiformis*, resp. [27,28]. In 2013, melosuavine D-F (**233-235**) were identified by Liu *et al* from twigs and leaves of *M. suaveolens* [69]. From *M. suaveolens* and *M. scandens*, three tabersonine-scandine, melosuavine A-C (**236-238**), and three tabersonine-vindolinine type, melosuavine G-H (**239-240**) and scandomelidine (**241**) were obtained [69,72]. The isolation and structural determination of lochnericine-kopsinine derivatives from *M. yunnanensis* and *M. morsei*,

meloyine (**242**) and melomorsine (**243**), were studied [32,44]. Four 18, 19-dehydrotabersonin-vincadifformine derivatives, scandomelonine (**244**) and its epimer (**245**), scandomeline (**246**) and its epimer (**247**), were isolated from *M. scandens* [72,73].

Other dimeric alkaloids (248-252), (Figure 15)

Melaxilline (**248**) and melaxilline (**249**) were obtained from *M. axillaris* [45]. To investigate antitumor indole alkaloids from the leaves and twigs of *M. morsei*, melofusine I (**250**) was subjected to RP-18 silica gel CC on eluting with 70 % - 75 % aq. MeOH [28]. *M. celastroides* contained two other dimeric alkaloids, Dichlorure de methylene Nb,Nb' [bis-(+)-meloninium] (**251**) and methylene 10,10'-bis-(+)-Na-norvallesami-

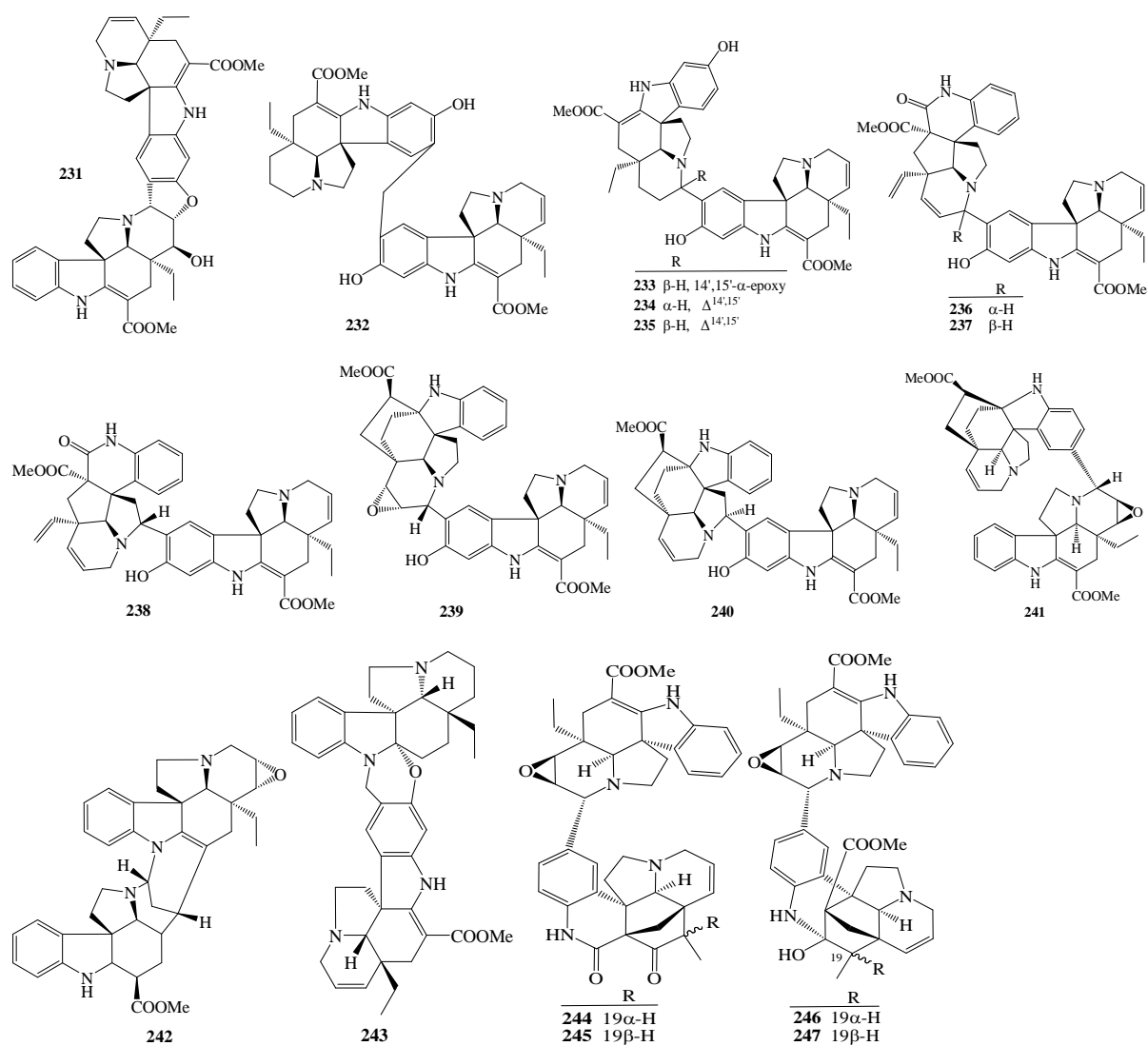


Figure 15: Structures of eburnamine-type dimeric alkaloids from *Melodinus* spp

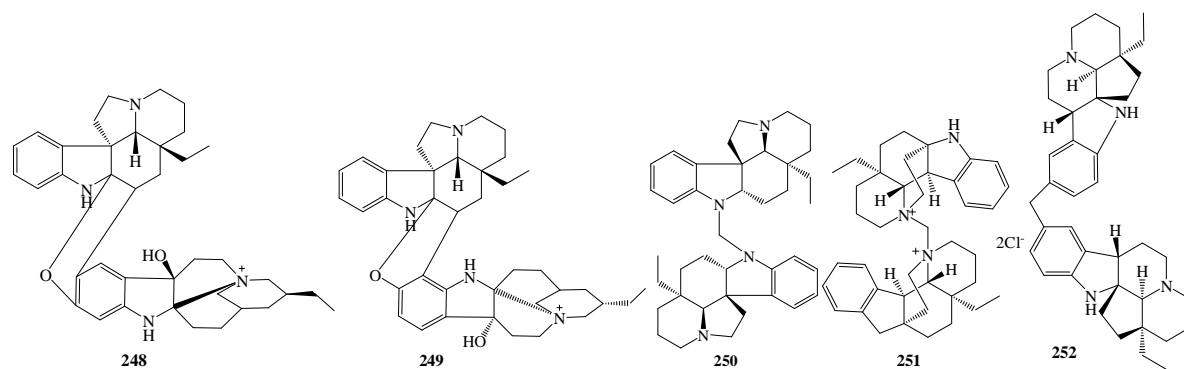


Figure 16: Structures of other dimeric alkaloids from *Melodinus* spp

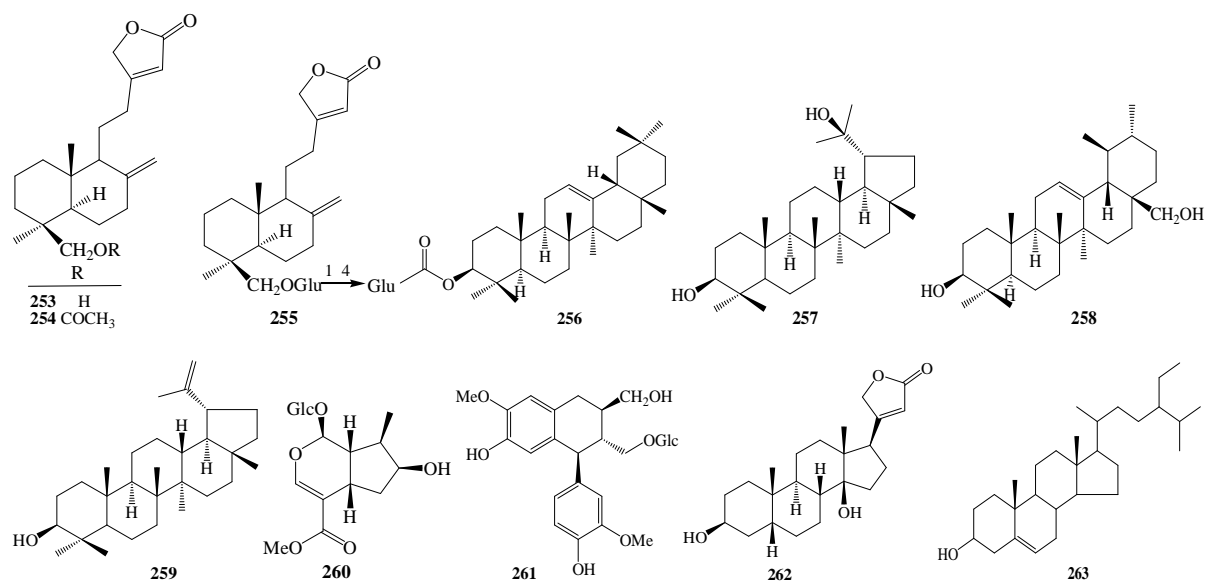


Figure 17: Structures of terpenoids and other compounds from *Melodinus* spp

dine (**252**). And alkaloid 251 was a quaternary ammonium and **252** possibly artifacts due to the use of CH_2Cl_2 as an extraction solvent [49].

Diterpenoids, triterpenes and others compounds (Figure 17)

A novel labdane diterpene, medigenin (**253**), O-acetyl-medigenin (**254**) and its glycoside, medinin (**255**), have been isolated from the ether extract of *M. monogynus* [74,75]. Four triterpenes, β -amyirin acetate (**256**), uvaol (**257**), monogynols A (**258**) and B (**259**), were isolated from *M. henryi*, *M. monogynus* and *M. reticulatus* [2,13,76-78]. One iridoid glycosides named loganin (**260**), a lignan glycoside, isolariciresinol-monoglucoside (**261**), two steroids, digitoxigenin (**262**) and β -sitosterol (**263**), were isolated from *M. henryi*, *M. monogynus* and *M. morsei* [2,36,78].

Extraction and isolation

Four methods were used for extraction and isolation. Firstly, the air-dried sample was extracted with EtOH or MeOH. The extract was partitioned between organic solvent and HCl solution. The acidic water-soluble materials, adjusted to pH 9 - 10 with ammonia solution, were extracted with EtOAc, MeOH or CHCl_3 to give an alkaloidal extract. Then, the extract was subjected to silica gel column chromatography (CC), TLC, MPLC with RP-18 gel CC, Sephadex LH-20 CC [27-29,32,34]. Secondly, *M. fusiformis* were extracted exhaustively with EtOH. After concentration, the material was obtained which was then dissolved in citric acid or tartaric acid,

filtered and the solution adjusted to pH 5 and 7 with NH_4OH , and then extracted with CHCl_3 , repeatedly. The extract was subjected to silica gel column chromatography (CC). Lastly, some dried *Melodinus* spp were ground and extracted with acetone or EtOH. The extract was filtered and concentrated and the residue extracted with similarity principle. The extract was subjected to silica gel column chromatography (CC), Et_2O , CHCl_3 and MeOH being used as eluents.

Pharmacological aspects

Cytotoxic activity

Continuous investigation of bioactive indole alkaloids from the genus *Melodinus*, include tests against seven human tumor cell lines, HL-60, SMMC-7721, A-549, MCF-7, SW480, SK-BR-3 and PANC-1. The results showed that these compounds exhibited stronger inhibitory activity with low IC_{50} than that of cisplatin (Table 6).

Pharmacological screening revealed 11-hydroxytabersonine (**24**) displayed antitumor activity [17].

Compound **32**, 11-hydroxy-14,15 α -epoxytabersonine, and rhazinilam (**204**) were the source of potent antitumor compounds against P-338 cell and KB cell line [15,79,80]. Evaluated for cytotoxicity by using the WT cell, compound **207** exhibited moderate cytotoxic activity [35]. Demethylteucausine (**216**), a new bisindole alkaloid was isolated from *M. hemsleyanus*, showed antitumor activities in pharmacological tests KB cell and HCT [6].

Table 6: Cytotoxicity of compounds (IC₅₀, μ M) from *Melodinus* spp

No.	HL-60	SMMC-7721	A-549	MCF-7	SW480	SK-BR-3	PANC-1	Ref
23	4.6	5.6	14.8	9.9	12.1	-	-	[28]
25	0.2	13.1	12.8	2.1	12.7	-	-	[27]
25	0.5	1.1	1.0	0.2	2.4	-	-	[29]
51	0.7	3.3	3.9	1.8	1.6	-	-	[29]
53	0.2	0.3	0.6	0.4	0.5	-	-	[29]
55	0.9	5.2	10.7	-	-	2.8	3.6	[41]
56	6.8	20.7	26.3	21.9	15.2	-	-	[28]
154	2.0	16.8	25.9	-	-	24.7	-	[48]
171	15.48	19.08	40.0	14.24	13.29	-	-	[53]
211	0.66	2.73	3.01	-	-	3.63	3.77	[71]
212	2.77	18.13	11.07	-	-	23.22	23.41	[71]
217	3.0	8.5	9.1	10.0	14.8	-	-	[27]
218	1.1	3.2	4.8	2.9	1.4	-	-	[27]
222	2.84	11.54	20.07	-	-	15.41	>40	[71]
230	2.53	7.40	14.70	-	-	7.78	14.45	[71]
231	0.1	3.0	5.0	2.7	5.7	-	-	[27]

Anti-inflammatory effects

Two new compounds **187-188** exhibited significant, dose-dependent inhibition of the production of lipopolysaccharide (LPS)-induced NO, IL-6 and IL-8 in mice macrophages. The results suggested that these new quinoline alkaloids could be new potential candidates for development as anti-inflammatory agents [46].

Other activities

11,19R-dihydroxytabersonine (**30**) had significant anti-fertility activity. The results of spermicidal effect *in vitro* showed that spermicidal concentration of 0.2 mg/ml [15]. Rhazinilam (**204**) evaluated against the disassembly of microtubules into tubulin with IC₅₀ value of 2 - 3 μ M [79,80]. Metabolism studies were conducted in order to investigate the reasons for the *in vivo* lack of activity of (-)-rhazinilam. The oxidative metabolism of (-)-rhazinilam were markedly less active than it *in vitro*, which might explain its *in vivo* inactivity [80].

CONCLUSION

Plants of the family Apocynaceae have been proven to be good sources of indole alkaloids, quinoline alkaloids, which originated from the condensation of tryptophan with secologanin. Some have been reported to display *in vitro* cytotoxicity against several human cancer cell lines, anti-inflammatory effects and antifertility activity. However, there still arise questions concerning the structure-activity relationships and elucidation of the action mechanism. There are 23 species of this genus whose isolation and activities have not previously been reported. Thus, much attention should be paid to the other

Melodinus species via further phytochemical, pharmacological and structure-activity relationship studies.

ACKNOWLEDGEMENT

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REFERENCES

1. *Florae Reipublicae Popularis Sinicae, Tomus 63, Delectis Florae Reipublicae Popularis Sinicae Edita, Science Press, Beijing, 1977, pp.17.*
2. Li CM, Wu SG, Tao GD, Zhong JY, You C, Zhou YL, Dong LY. Chemical constituents of *Simao Shanchen* (*Melodinus henryi*). *Zhongcaoyao* 1987; 18:52-53.
3. Zhong Hua Ben Cao, Shanghai Sentific & Technical Publishers, Shanghai, 1999; 16: 293.
4. Boiteau P, Allorge L, Sevenet T. *Adansonia* 1976; 15:397-407.
5. Raymond H. Physiological properties of an Australian apocynaceous plant, *Melodinus australis*. *Compt Rend* 1956; 243:2175-2178.
6. Yan KX, Hong SL, Feng XZ. Demethyltenuicausine, a new bisindole alkaloid from *Melodinus hemsleyanus*. *Acta Pharm Sin* 1998; 33:597-599.
7. Au KS, Gray DE. Alkaloids of *Melodinus suaveolens* and their excretion as a common end-product in the rat. *Biochem Pharmacol* 1969; 18:1553-1557.
8. Zhang HM, Curran DP. A short total synthesis of (\pm)-epimeloscine and (\pm)-meloscine enabled by a cascade radical annulation of a divinylcyclopropane. *J Am Chem Soc* 2011; 133:10376-10378.

9. Selig P, Bach T. Enantioselective total synthesis of the melodinus alkaloid (+)-meloscine. *Angew Chem Int Ed* 2008; 47:5082-5084.
10. Selig P, Herdtweck E, Bach T. Total synthesis of meloscine by a [2+2]-hotocycloaddition/ring-expansion route. *Chem Eur J* 2009; 15:3509-3525.
11. Sevenet T, Pusset J. *The alkaloids: chemistry and pharmacology*. Academic Press, New York, 1996; 48:34-38.
12. Szabo LF. Molecular interrelations in the melodinus alkaloids. *Arkiboc* 2007; vii:280-290.
13. Mehri H, Rochat C, Baassou S, Sevenet T, Plat M. Plant from new-caledonia. alkaloids of *Melodinus reticulatus*. *Planta Med* 1983; 48:72-76.
14. Zechis M, Lounkokobi J, Richard B, Plat M, Men-oliver LL, Sevenet T, Pusset J. Alkaloids of *Melodinus guillauminii*. *Phytochemistry* 1984; 23:171-174.
15. He X, Zhou Y, Huang ZH. Study on the alkaloids of *Melodinus fusiformis*. *Acta Chim Sinica* 1992; 50:96-101.
16. He YL, Chen WM, Feng XZ. The alkaloids of *Melodinus morsei*. *Phytochemistry* 1994;37: 1055-1057.
17. Yan KX, Feng XZ. Studies on the chemical constituents of hemsley *Melodinus* (*Melodinus shemsleyanus*). *Tradit Herb Drugs* 1998; 29:793-795.
18. Linde HHA. Die alkaloide aus *Melodinus australis* (F. Mueller) Pierre (Apocynaceae). *Helv Chim Acta* 1965; 48,1822-1842.
19. Mehri H, Plat M, Potier P. Apocynaceae of new caledonia, V. *Melodinus scandens*. Isolation of 10 momomeric alkaloids. description of two new alkaloids, N-oxyepimeloscine and meloscandonine. *Ann Pharm Fr* 1971; 29:291-296.
20. Mehri H, Koch M, Plat M, Potier P. Plants of new caledonia, XII. alkaloids of the leaves of *Melodinus balansae* (Apocynaceae). *Ann Pharm Fr* 1972; 30:643-650.
21. Mehri H, Rabaron A, Sevenet T, Plat M. Alcaloides de *Melodinus balansae* var. *paucivenosus*. *Phytochemistry* 1978; 17:1451-1452.
22. Le ML, Levy J, Sevenet T, Plat M. Plants of new caledonia, alkaloids from *Melodinus polyadenus* Baill. *Ann Pharm Fr* 1981; 39:369-373.
23. Mehri H, Sciamama S, Plat M, Sevenet T, Pusset J. Plants from new caledonia, alkaloids from *Melodinus phylliraeoides* Labill. *Ann Pharm Fr* 1984; 42:145-148.
24. Batchily F, Baassou S, Mehri H, Plat M, Sevenet T, Pusset J. Plants from new caledonia, part 90. alkaloids from *Melodinus insulae-pinorum* Boiteau. *Ann Pharm Fr* 1985; 43:359-364.
25. Guo LW, Zhou YL. Alkaloid from *Melodinus hemsleyanus*. *Phytochemistry* 1993; 34:563-566.
26. Lien LN, Dien PG, Pais M. Alkaloid from *Melodinus oblongus*(Apocynaceae). *Tap Chi Hoa Hoc* 2002; 40:47-51.
27. Feng T, Li Y, Wang YY, Cai XH, Liu YP, Luo XD. Cytotoxic indole alkaloids from *Melodinus tenuicaudatus*. *J Nat Prod* 2010; 73:1075-1079.
28. Cai XH, Jiang H, Li Y, Cheng GG, Liu YP, Feng T, Luo XD. Cytotoxic indole alkaloids from *Melodinus fusiformis* and *M. morsei*. *Chin J Nat Med* 2011; 9:259-263.
29. Liu YP, Li Y, Cai XH, Li XY, Kong LM, Cheng GG, Luo XD. Melodinines M-U, cytotoxic alkaloids from *Melodinus suaveolens*. *J Nat Prod* 2012; 75:220-224.
30. Lien LN, Dien PG, Pais M. Alkaloid from *Melodinus oblongus* (Apocynaceae). *Tap Chi Hoa Hoc* 2002; 40:79-85.
31. Baassou S, Mehri H, Rabaron A, Plat M, Sevenet T. Plants of new caledonia, alkaloids of *Melodinus celastroides* Baill. *Ann Pharm Fr* 1981; 39:167-170.
32. Cai XH, Li Y, Liu YP, Li XN, Bao MF, Luo XD. Alkaloids from *Melodinus yunnanensis*. *Phytochemistry* 2012; 83:116-124.
33. Linde HH. Alkaloid from *Melodinus australis*. 2. structure of refractidine and pyrifoline. *Pharm Acta Helv* 1970; 45:248-253.
34. Kitajima M, Ohara S, Kogure N, Wu YQ, Zhang RP, Takayama H. New indole alkaloids from *Melodinus henryi*. *Heterocycles* 2012; 85:1949-1959.
35. Zhou H, He HP, Wang YH, Hao XJ. A novel alkaloid from *Melodinus henryi*. *Helv Chim Acta* 2010; 93:2030-2032.
36. He YL, Chen WM, Feng XZ. Chemical constituent from *Melodinus morsei*. *Chin Tradit Herb Drugs* 1993; 24:623-265.
37. Ye JH, Zhou YL, Huang ZH, Picot F. Alkaloids from *Melodinus suaveolens*. *Phytochemistry* 1991; 30:3168-3170.
38. Baassou S, Mehri H, Plat M. Alcaloides de *Melodinus aeneus*. *Phytochemistry* 1978; 17:1449-1450.
39. Rabaron A, Plat M, Potier P. Isolement dela dehydro-14 isoeburnamine de *Melodinus celastroides*. *Phytochemistry* 1973; 12:2537-2539.
40. Rabaron A, Mehri H, Sevenet T, Plat M. Alcaloides de *Melodinus celastroides*. *Phytochemistry* 1978; 17:1452-1453.
41. Feng T, Li Y, Liu YP, Cai XH, Wang YY, Luo XD. Melotenine A, a cytotoxic monoterpene indole alkaloid from *Melodinus tenuicaudatus*. *Org Lett* 2010; 12:968-971.
42. Li CM, Tao GD, Wu SG, Zhou YL. Indole alkaloid of *Melodinus henryi* Craib. *Acta Botan Sin* 1989; 31:792-797.
43. Zhou YL, Ye JH, Li ZM, Huang ZH. Study on the alkaloids of *Melodinus tenuicaudatus*. *Planta Med* 1988; 54:315-317.
44. He YL, Chen WM, Feng XZ. Melomorsine, a new dimeric indoline from *Melodinus morsei*. *J Nat Prod* 1994; 57:411-414.
45. Yan KX. Chemical constituent from *Melodinus axillaris* and *M. Hemsleyanus* [dissertation]. [China]: Peking Union Medical College, 1997 May. 1- 58.

46. Lu F, Liu P, Yin SS, Zhang J, Wang J. Two new alkaloids from *Melodinus suaveolens*. *Nat Prod Commun* 2014; 9:1445-1447.
47. He YL, Chen WM, Feng XZ. Two new indole alkaloid of *Melodinus morsei*. *Chin Chem Lett* 1992; 3:715-718.
48. Feng T, Cai XH, Liu YP, Li Y, Wang YY, Luo XD. Melodinines A-G, monoterpene indole alkaloids from *Melodinus henryi*. *J Nat Prod* 2010; 73:22-26.
49. Mehri H, Baasou S, Flat M. Methylene-10,10'-bis[(+)-Nanorvallesamidine], methylene-Nb,Nb'[bis-(+)-meloninium] dichloride, and the chlorides of Nb'-chloromethyl celastromelinium and celastromelidinium: dimeric alkaloids and possible extraction artifacts from *Melodinus celastroides*. *J Nat Prod* 1991; 54:372-379.
50. Rabaron A, Plat M. Plants of new caledonia, XXVIII. alkaloids from *Melodinus celastroides*. *Planta Med* 1973; 7:319-324.
51. Li CM, Yang HC, Wu SG, Sun HD. Indole alkaloids from stem bark of *Melodinus khasianus*. *Acta Botan Yunnan* 1996; 18:356-358.
52. Zhang YW, Yang R, Cheng Q, Ofuji K. Henrycinols A and B, two novel indole alkaloids isolated from *Melodinus henryi*. *Helv Chim Acta* 2003, 86:415-419.
53. Cai XH, Li Y, Su J, Liu YP, Li XN, Luo XD. Novel indole and quinoline alkaloids from *Melodinus yunnanensis*. *Nat Prod Bioprospect* 2011; 1:25-28.
54. Li CM, Tao GD, Zhou YL. A new indole alkaloid from leaves of *Melodinus henryi*. *Acta Botan Yunnan* 1992; 14:32,66.
55. Zhang TT, Liu ZW, Wang WJ, Tong TB, Xu FF, Yuan JQ, Liu B, Zhang XQ, Ye WC. Alkaloids from *Melodinus suaveolens*. *Heterocycles* 2013, 87:2047-2052.
56. Hu WL, Hesse M. The alkaloids of *Melodinus acutiflorus*. rhyzicine N-Oxide. *Planta Med* 1988; 54:235-236.
57. Feng T, Cai XH, Li Y, Wang YY, Liu YP, Xie MJ, Luo XD. Melohenines A and B, two unprecedented alkaloids from *Melodinus henryi*. *Org Lett* 2009; 11:4834-4837.
58. Bernauer K, Englert G, Vetter W, Weiss E. Constitution of the melodinus alkaloids (+)-meloscine, (+)-epimeloscine, and (+)-scandine. *Helv Chim Acta* 1969; 52:1886-1905.
59. Li CM, Zhang HL, Wu SG, Sun HD. Quinolinic melodinus alkaloids from stem bark *Melodinus khasianus*. *Acta Botan Yunnan* 1994; 16:315-317.
60. Daudon M, Mehri H, Plat M, Hagaman EW, Schell FM, Wenkert E. Carbon-13 nuclear magnetic resonance spectroscopy of naturally occurring substances. XXXIV. monomeric quinolinic melodinus alkaloids. *J Org Chem* 1975; 40: 2838-2339.
61. Cannon JR, Croft KD, Matsuki Y, Patrick VA, Toia RT, White AH. Crystal structure and absolute configuration of (+)-scandine hydrobromide. *Aust J Chem* 1982; 35: 1655-1664.
62. Gu JM, Hu XR. Sandine: a catharanthus-derived alkaloid. *Acta Cryst* 2006; E62:4775-4777.
63. Ma K, Wang JS, Luo J, Kong LY. Six new alkaloids from *Melodinus henryi*. *Fitoterapia*, 2015, 100:133-138.
64. Mehri H, Diallo AO, Plat M. An alkaloid from leaves of *Melodinus scandens*. *Phytochemistry* 1995; 40:1005-1006.
65. Rodier N, Mauguen Y, Hachem-Mehri M, Plat M. Structure cristalline de la meloscandonine, C₂₀H₂₀N₂O₂: alcaloide du *Melodinus scandens* Forst. *Acta Cryst* 1978; B34:232-237.
66. Plat M, Hachem-Mehri M, Koch M, Scheidegger U, Potier P. Structure et stereochemie de la meloscandonine, alcaloide du *Melodinus scandens* Forst. *Tetrahedron Lett* 1970; 39:3395-3398.
67. Hu WL, Zhu JP, Umberto P, Roland P, Manfred H. Revision of the structures of rhyzicine and rhyzimine, two alkaloids from *Melodinus acutiflorus*. *Phytochemistry* 1987; 26:2625-2630.
68. Abraham DJ, Rosenstein RD, Lyon RL, Fong HHS. The structure elucidation of rhyznilam, a new class of alkaloids from the apocynaceae, by X-ray analysis. *Tetrahedron Lett* 1972; 13:909-912.
69. Liu YP, Zhao YL, Feng T, Cheng GG, Zhang BH, Li Y, Cai XH, Luo XD. Melosuavines A-H, cytotoxic bisindole alkaloid derivatives from *Melodinus suaveolens*. *J Nat Prod*, 2013; 76:2322-2329.
70. Yan KX, Feng XZ. Melaxillarinine, a new bisindole alkaloid from *Melodinus axillaris*. *Chin Chem Lett* 1997; 8:313-314.
71. Luo XD, Feng T, Li Y, Wang YY, Cai XH. Extraction method of melonine di-indole compounds from Chinese medicine *Melodinus* and their medical application as antitumor agents. *Faming Zhuanli Shenqing*. CN. Pat. 101, 704, 828 (Chem Abstr 2010, 153: 45657)
72. Mehri H, Flat M. The structure of scandomelidine, bisindole alkaloid from *Melodinus scandens*. *J Nat Prod* 1992; 55:241-244.
73. Daudon M, Mehri H, Plat M, Hagaman W, Wenkert E. Carbon-13 nuclear magnetic resonance spectroscopy of naturally occurring substances. 48. dimeric quinolinic melodinus alkaloids. *J Org Chem* 1976; 41:3275-3278.
74. Bhntnngar SOD, Khare MP. Herzwirksame glykoside aus *Melodinus monogynus* Roxb. *Chem Ber* 1968, 101:2084-2095.
75. Sethi A, Khare A, Khare MP. A labdane diterpene and its glycoside from *Melodinus monogynus*. *Phytochemistry* 1988; 27:2255-2259.
76. Chatterji SK, Sharma VN, Dhar ML. Chemical examination of the root bark of *Melodinus monogynus*. I. *J Sci Ind Research Inst(India)*, 1954; 13:546-549.
77. Chatterji SK, Anand N, Dhar ML. Chemical examination of *Melodinus monogynus*. II Identification of monogunol A and monogunol B. *J Sci Ind Research Inst(India)*, 1959; 18B:262-263.
78. Mitscher LA, Vorperian EN. Triterpenes from *Melodinus australis*. *Phytochemistry* 1971; 10:1687-1688.
79. Dupont C, Gueanard D, Tchertanov L, Thoret S, Gueritte F. D-ring substituted rhyznilam analogues:

- semisynthesis and evaluation of antitubulin activity.*
Bioorg Med Chem 1999; 7:2961-2969.
80. Decor A, Bellocq D, Thoison O, Lekieffre N, Chiaroni A, Ouazzani J, Cresteil T, Gueritte F and Baudoin O. *In vitro oxidative metabolism study of (-)-rhazinilam.*
Bioorg Med Chem 2006; 14:1558-1564.