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Chemistry and bioactivities of natural steroidal alkaloids

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Abstract

Steroidal alkaloids possess the basic steroidal skeleton with a nitrogen atom in rings or side chains incorporated as an integral part of the molecule. They have demonstrated a wide range of biological activities, and some of them have even been developed as therapeutic drugs, such as abiraterone acetate (Zytiga®), a blockbuster drug, which has been used for the treatment of prostate cancer. Structurally diverse natural steroidal alkaloids present a wide spectrum of biological activities, which are attractive for natural product chemistry and medicinal chemistry communities. This review comprehensively covers the structural classification, isolation and various biological activities of 697 natural steroidal alkaloids discovered from 1926 to October 2021, with 363 references being cited.

Keywords: Steroidal alkaloids, Chemistry, Bioactivities, Solanaceae, Liliaceae, Apocynaceae, Buxaceae

1 Introduction

Steroidal alkaloids are nitrogenous derivatives of natural steroids. They are an important class of alkaloids and conventional secondary metabolites that occur in plants including Solanaceae, Liliaceae, Apocynaceae, Buxaceae, amphibians and marine organisms. Previous research results exhibited that steroidal alkaloids possess potential anticancer, anticholinergic, antimicrobial, anti-inflammatory and analgesic, anti-myocardial ischemia, anti-giogenesis effects and other activities.

Steroidal alkaloids are already launched as drugs, such as abiraterone acetate, marketed as Zytiga® by Janssen Biotech (a subsidiary of Johnson & Johnson), is a steroidal antiandrogen medication approved by the Food and Drug Administration (FDA) for the treatment of metastatic castration resistant prostate cancer (mCRPC) in 2011 and metastatic high-risk castration-sensitive prostate cancer (mCSPC) in 2018 [1]. Zytiga® is a blockbuster drug on the prostate cancer market, and in 2020, it generated almost $2.4 billion in sales from the Johnson & Johnson annual report, with ongoing research into its application for additional indications. Natural steroidal alkaloid cyclovirobuxine D (**203**) is the main active component of oral drug "huangyangning" tablets listed in the Chinese pharmacopeia 2015. This drug, discovered from a folk prescription in the treatment of rheumatic disease, was approved by the China Food and Drug Administration (CFDA) in 2009 to treat cardiovascular and cerebrovascular diseases, such as coronary heart disease, angina pectoris, arrhythmia, heart failure, hypertension and cardiac neurosis [2]. Several steroidal glycoalkaloids from the local plant *Solanum linnaeanum* possess activity of slowing skin cancer growth in horses and cattle, in which *α*-solamargine (**500**) and *α*-solasonine (**501**) were identified. These two active compounds were subsequently developed into a topical treatment for keratoses, basal cell carcinomas, and squamous cell carcinomas, which were marketed in Australia signed Curaderm [3].

Sheep ranchers experienced outbreaks of cyclopic lambs, leading to the discovery of cyclopamine (**432**) as a plant derived teratogen [4]. Cyclopamine was the

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first compound found to antagonize the Hedgehog (Hh) signaling pathway, the constitutive activation of which is intimately implicated in many human malignancies [5]. Vismodegib and sonidegib, cyclopamine derivatives and Hh pathway inhibitors, were FDA-approved for the treatment of basal cell carcinoma and acute myeloid leukemia, respectively [6]. In 2016 cyclopamine was identified as a potent inhibitor of human respiratory syncytial virus (hRSV) replication [7].

Phyllobates terribilis frogs, made into poison darts by Central American indigenous people, advertise their lethal armament with their gaudy colors. Batrachotoxin (**615**) is a potent neurotoxin in the skin secretions of these frogs and as a tool to study voltage-sensitive sodium channels of excitable membranes [8, 9]. Toxicity is widespread among living organisms and how these frogs avoid poisoning themselves remains a mystery. A study addressed that a single rat muscle Na^+ channel mutation confers batrachotoxin autoresistance [10].

Some reviews related to steroidal alkaloids have been presented since 1953. For example, the chemistry of these alkaloids from the Liliaceae and Solanaceae [11–15], the Apocynaceaethe [16], the Buxaceae [17, 18], the marine organisms [19], synthesis of cephalostatins and ritterazines [20], biosynthesis of Buxaceae alkaloids [21], and biological activities [22, 23]. A comprehensive review was published in 1998 concerning the developments in the field of steroidal alkaloids [24]. In consideration of these reviews providing little information about recent research, we provide an updated review in a concise form, covering comprehensive structure classification, resources, biosynthesis and bioactivities of natural steroid alkaloids reported from 1926 to October 2021.

This review will help the scientific community understand natural steroidal alkaloids overall and compactly. We comprehensively summarize 16 structural subtypes of steroidal alkaloids along with their bioactivities and toxicity. In addition, steroidal alkaloids (**362–365**, **381**) whose names were not proposed by authors were presented only with numbers in the tables.

2 Basic skeletal classification

Steroidal alkaloids possess the basic steroidal skeleton with a nitrogen atom in rings or side chains incorporated as an integral part of the molecule [24]. In general, steroidal alkaloids can be classified into monomeric and dimeric on the basis of the carbon framework. Monomeric steroidal alkaloids, possessing a pregnane (C_{21}), cyclopregnane (C_{24}), cholestane (C_{27}) and other carbon heterocyclic skeletons, were isolated from plants, amphibians and some marine sponges. Dimeric steroidal alkaloids, a class of bis-steroidal pyrazine alkaloids, were only found in marine organisms. Figure 1 lists the different types of natural steroidal alkaloids.

2.1 Monomeric steroidal alkaloids

2.1.1 Pregnane alkaloids

The occurrence of 177 pregnane alkaloids (**1–177**), however, is not restricted to the Apocynaceae family, which is also found in Buxaceae, such as *Sarcococca* and *Pachysandra*.

2.1.1.1 Conanine type Conanine type alkaloids are characteristic of an 18,20-epimino five-membered E ring, and most of them contain an amino or oxygen at C-3 (Fig. 2). Alkaloids (**1–36**) were isolated from various plants of the family Apocynaceae, such as *Holarrhena*, *Funtumia*, *Malouetia*, and *Wrightia* (Table 1).

Conessine (**1**) was the first and most common conanine type alkaloid isolated from the seeds of *Holarrhena antidysenterica* [25]. Rings A and B of the pregnane moiety were dehydrogenated to form a conjugated system comprising two double bonds in regholarrhenine C (**28**), funtudienine (**29**), mokluangin D (**35**). Compounds **14–16** and **20–27** have secondary and tertiary amino group of the nitrogen in the heterocyclic ring, respectively, but both of them lack the C-3 amino function and possess a 1,4-dien-3-one system in ring A. Mokluangin B (**32**) contains a novel structure with the amide carbonyl group instead of the methyl group at C-20, whose structure was elucidated by analysis of NMR and MS spectroscopic data [26].

2.1.1.2 Paravallarine type Paravallarine type alkaloids bear a pregnane-(18 → 20)-lactone skeleton (Fig. 3) [42]. Currently, eight compounds (**37–44**) of this type have been found only in Apocynaceae family, including *Kibatalia* and *Paravallaris* (Table 2).

The structure of 20-*epi*-kibataline (**37**) contains a rare configuration 20*R*, while the configuration 20*S* is proposed for all remaining compounds [43]. Compounds **38–40** differ from others possessing an opposite orientation at C-3. The structure of kibalaurifoline (**44**) was carefully established from 2D NMR analyses, in which the conjugated system of the two double bonds $\Delta^{4(5)}$ and $\Delta^{6(7)}$ was determined from the HMBC spectrum [42].

2.1.1.3 Pregnane type Nearly all the reported pregnane type alkaloids, share the 5α-pregnane steroidal skeleton with varying functionalities such as an amino function at C-3 and C-20 that may be modified by methyl, benzoyl and aliphatic groups (Fig. 4). A total of 133 new alkaloids (**45–177**) were isolated from *Sarcococca* and *Pachysandra* of the Buxaceae family and *Holarrhena* of the Apocynaceae family (Table 3).

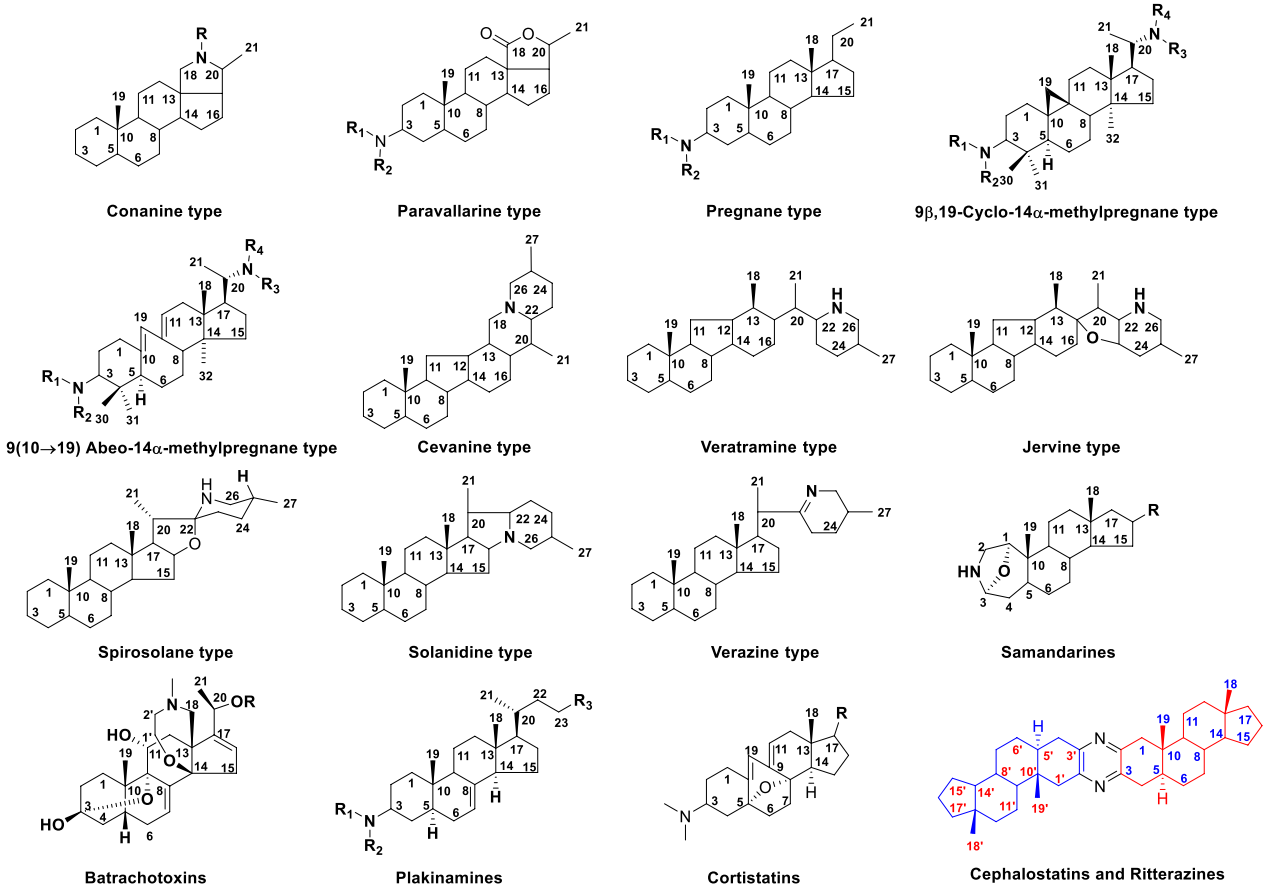


Fig. 1 Classification of steroidal alkaloids

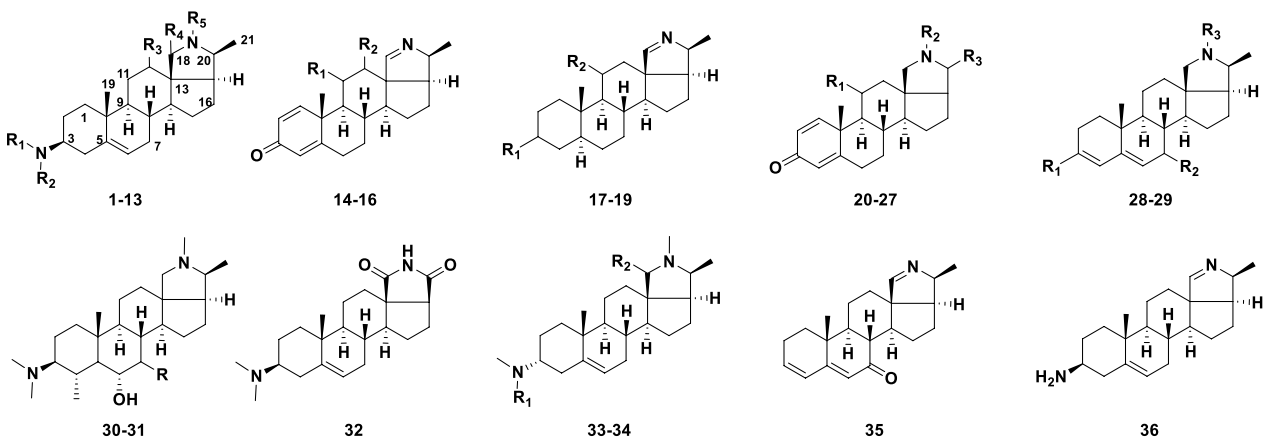
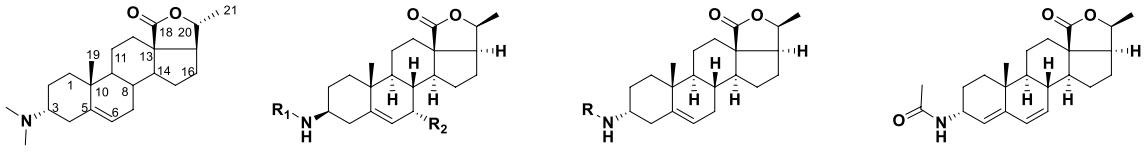


Fig. 2 Structures of conanine type steroidal alkaloids **1–36**

For alkaloids with nitrogen substituents at C-3, only **53–62** and **172–176** bear 3*α* substituents, whereas most compounds possess the 3*β* configuration. All of them except **143–154** contain nitrogen substituents at C-20, which is a common feature of pregnane type alkaloids. Salignarine A **(167)** has a novel structure with an epoxide functionality at C-5–C-6 [44]. Two compounds, pachysanone **(148)** and pachysanonin **(149)**

Table 1 Structures and sources of conanine type steroidal alkaloids **1–36**

No	Compounds	Substitution groups and others	Sources	References
1	Conessine	$R_1=R_2=R_5=CH_3$; $R_3=R_4=H$	*Holarrhena antidysenterica*	[25]
2	7*α*-Hydroxy-conessine	$R_1=R_2=R_5=CH_3$; $R_3=R_4=H$; 7-*α*-OH	*H. antidysenterica*	[27]
3	Regholarrhenine D	$R_1=R_2=CH_3$; $R_3=R_4=H$; $R_5=OH$	*H. antidysenterica*	[28]
4	Antidysentericine	$R_1=R_2=CH_3$; $R_3=R_5=H$; $R_4=O$	*H. antidysenterica*	[29]
5	Isoconessimine	$R_1=R_5=CH_3$; $R_2=R_3=R_4=H$	*Funtumia elastica*	[30]
6	Holarrhetine	$R_1=R_2=R_5=CH_3$; $R_3=\beta$-$(CH_3)_2C=CHCH_2COO$; $R_4=H$	*F. elastica*	[30]
7	Holarrhesine	$R_1=R_4=H$; $R_2=R_5=CH_3$; $R_3=\beta$-$(CH_3)_2C=CHCH_2COO$	*F. elastica*	[30]
8	Conessimin	$R_1=R_2=CH_3$; $R_3=R_4=R_5=H$	*Holarrhena antidysenterica*	[31]
9	Conarrhimin	$R_1=R_2=R_3=R_4=R_5=H$	*H. antidysenterica*	[31]
10	Conimin	$R_1=CH_3$; $R_2=R_3=R_4=R_5=H$	*H. antidysenterica*	[31]
11	Mokluangin A	$R_1=R_3=R_5=H$; $R_2=CH_3$; $R_4=O$	*H. pubescens*	[26]
12	Mokluangin C	$R_1=R_2=R_3=R_5=H$; $R_4=O$	*H. pubescens*	[26]
13	*N*-Formylconessimine	$R_1=R_2=CH_3$; $R_3=R_4=H$; $R_5=CHO$	*H. antidysenterica*	[32]
14	Holonamine	$R_1=\alpha$-OH; $R_2=H$	*H. antidysenterica*	[27]
15	12*α*-Hydroxynorcona-*N*(18),1,4-trienin-3-one	$R_1=H$; $R_2=\alpha$-OH	*Funtumia africana*	[33]
16	11*α*,l2*α*-Dihydroxynorcona-*N*(18),1,4-trienin-3-one	$R_1=R_2=\alpha$-OH	*F. africana*	[33]
17	Conkurchine	$R_1=\beta$-NH_2; $R_2=H$; $\triangle^{5,6}$	*Holarrhena antidysenterica*	[34]
18	Malouetafrine	$R_1=O$; $R_2=H$; $\triangle^{4,5}$	*Malouetia brachyloba*	[35]
19	Wrightiamine A	$R_1=\beta$-NH_2; $R_2=\alpha$-OAc	*Wrightia javanica*	[36]
20	Regholarrhenine A	$R_1=\alpha$-OH; $R_2=CH_3$; $R_3=\beta$-CH_3	*Holarrhena antidysenterica*	[37]
21	Regholarrhenine B	$R_1=\alpha$-OH; $R_2=H$; $R_3=\beta$-CH_3	*H. antidysenterica*	[37]
22	Holadiene	$R_1=H$; $R_2=R_3=CH_3$	*H. pubescens*	[38]
23	Kurchinidine	$R_1=R_2=H$; $R_3=CH_3$	*H. pubescens*	[38]
24	Kurchilidine (I)	$R_1=R_2=H$; $R_3=\beta$-Et	*H. antidysenterica*	[39]
25	Kuchamide (II)	$R_1=OH$; $R_2=H$; $R_3=O$	*H. antidysenterica*	[39]
26	Holamide	$R_1=H$; $R_2=CONHCH_3$; $R_3=CH_3$	*H. antidysenterica*	[40]
27	Pubescinine	$R_1=\alpha$-OAc; $R_2=H$; $R_3=CH_3$; $\triangle^{17,20}$	*H. antidysenterica*	[40]
28	Regholarrhenine C	$R_1=NHCH_3$; $R_2=R_3=H$	*H. antidysenterica*	[37]
29	Funtudienine	$R_1=H$; $R_2=O$; $R_3=CH_3$	*H. antidysenterica*	[32]
30	Kurcholessine	$R=\beta$-OH	*H. antidysenterica*	[28]
31	Regholarrhenine E	$R=\alpha$-OH	*H. antidysenterica*	[28]
32	Mokluangin B		*H. pubescens*	[26]
33	Isoconkuressine	$R_1=R_2=H$	*H. antidysenterica*	[32]
34	Conkuressine	$R_1=CH_3$; $R_2=H$	*H. antidysenterica*	[32]
35	Mokluangin D		*H. pubescens*	[41]
36	Irehline		*H. pubescens*	[41]



37 **38-40** **41-43** **44**

Fig. 3 Structures of paravallarine type steroidal alkaloids **37–44**

Table 2 Structures and sources of paravallarine type steroidal alkaloids **37–44**

No	Compounds	Substitution groups and others	Sources	References
37	20-*Epi*-kibataline		*Paravallaris macrophylla*	[43]
38	3-*Epi*-gitingensine	$R_1 = R_2 = H$	*Kibatalia laurifolia*	[42]
39	Paravallarine	$R_1 = CH_3$; $R_2 = H$	*K. laurifolia*	[42]
40	7*α*-Hydroxyparavallarine	$R_1 = CH_3$; $R_2 = OH$	*K. laurifolia*	[42]
41	Gitingensine	R = H	*K. laurifolia*	[42]
42	*N*-Methylgitingensine	$R = CH_3$	*K. laurifolia*	[42]
43	*N*-Acetylgitingensine	R = Ac	*K. laurifolia*	[42]
44	Kibalaurifoline		*K. laurifolia*	[42]

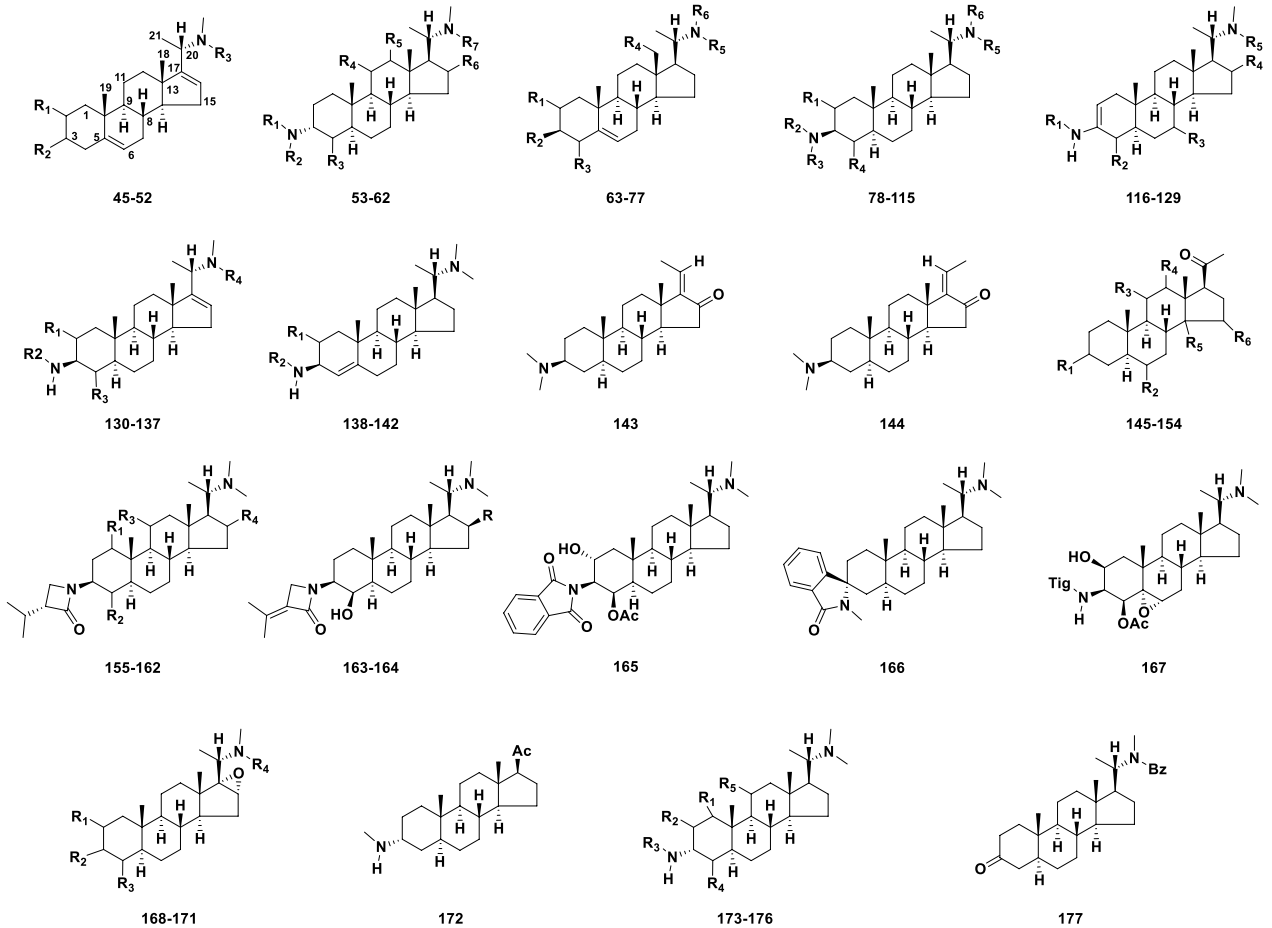


Fig. 4 Structures of pregnane type steroidal alkaloids **45–177**

bear a 3,4-dimethylpent-3-enoyloxy substituent at C-11, a rare functional group in natural products [45]. Compounds **155–164**, bear a (3′sopropyl)-*β*-lactam ring at the C-3 position, whereas compound **165** bears a phthalimido moiety at the same position [46]. Spiropachysine **(166)** possesses a five membered-ring spiro-lactam and a disubstituted benzene ring at C-3 [46]. Compounds **168–171** display a structural modification that has not been reported from this genus, viz. the epoxy ring at C-16/C-17. *N*-methylfuntumafrine **(172)** shows a novel structure with an acetyl group at C-17 [47].

Table 3 Structures and sources of pregnane type steroidal alkaloids **45–177**

No	Compounds	Substitution groups and others	Sources	References
45	Saracocinaene	$R_1=H$; $R_2=\alpha$-$N(CH_3)_2$; $R_3=Ac$	*Sarcococca saligna*	[48]
46	Sarconidine	$R_1=H$; $R_2=\beta$-$NHCH_3$; $R_3=CH_3$	*S. saligna*	[49]
47	Salonine B	$R_1=H$; $R_2=\beta$-OCH_3; $R_3=CH_3$	*S. saligna*	[50]
48	Salignamine	$R_1=R_3=H$; $R_2=\beta$-OCH_3	*S. saligna*	[51]
49	2-Hydroxysalignamine	$R_1=\beta$-OH; $R_2=\beta$-OCH_3; $R_3=CH_3$	*S. saligna*	[51]
50	*N*-[Formyl(methyl)amino]salonine B	$R_1=H$; $R_2=\beta$-OCH_3; $R_3=CHO$	*S. saligna*	[51]
51	Wallichimine A	$R_1=H$; $R_2=\beta$-$N(CH_3)_2$; $R_3=CH_3$	*S. wallichii*	[52]
52	Wallichimine B	$R_1=R_3=H$; $R_2=\beta$-$N(CH_3)_2$	*S. wallichii*	[52]
53	Sarcodine	$R_1=R_2=CH_3$; $R_3=R_4=R_5=R_6=H$; $R_7=Ac$	*S. saligna*	[48]
54	Paxillarine A	$R_1=Bz$; $R_2=R_7=CH_3$; $R_3=\beta$-OAc; $R_4=R_5=H$; $R_6=\beta$-OH	*Pachysandra axillaris*	[53]
55	Paxillarine B	$R_1=Bz$; $R_2=R_7=CH_3$; $R_3=\beta$-OAc; $R_4=R_6=H$; $R_5=\beta$-OH	*P. axillaris*	[53]
56	Pachysamine B	$R_1=Sen$; $R_2=R_7=CH_3$; $R_3=R_4=R_5=R_6=H$	*P. procumbens*	[46]
57	Pachysamine E	$R_1=Sen$; $R_2=R_3=R_4=R_5=R_6=H$; $R_7=CH_3$	*P. terminalis*	[54]
58	(+)-(20*S*)-20-(Dimethylamino)-3*α*-(methylbenzoylamino)-11-methylene-5*α*-pregnane	$R_1=Bz$; $R_2=R_3=R_5=R_6=H$; $R_4=CH_2$; $R_7=CH_3$	*P. procumbens*	[55]
59	(+)-(20*S*)-20-(Dimethylamino)-3*α*-(methylbenzoylamino)-5*α*-pregn-12*β*-yl acetate	$R_1=Bz$; $R_2=R_3=R_4=R_6=H$; $R_5=\beta$-OAc; $R_7=CH_3$	*P. procumbens*	[55]
60	(+)-(20*S*)-20-(Dimethylamino)-3*α*-(methylsenecioylamino)-5*α*-pregn-12*β*-ol	$R_1=Sen$; $R_2=R_3=R_4=R_6=H$; $R_5=\beta$-OH; $R_7=CH_3$	*P. procumbens*	[55]
61	Hookerianine A	$R_1=CO$-Bn; $R_2=R_3=R_4=R_5=R_6=H$; $R_7=CH_3$	*Sarcococca hookeriana*	[56]
62	Sarchookloide C	$R_1=Tig$; $R_2=R_3=R_4=R_5=R_6=H$; $R_7=CH_3$	*S. hookeriana*	[57]
63	Pachyaximine A	$R_1=R_3=R_4=H$; $R_2=OCH_3$; $R_5=R_6=CH_3$	*S. saligna*; *P. procumbens*	[46, 48]
64	Sarsalignone	$R_1=R_4=H$; $R_2=NH$-Tig; $R_3=O$; $R_5=R_6=CH_3$	*S. saligna*	[58]
65	Sarsaligenone	$R_1=R_4=H$; $R_2=NH$-Tig; $R_3=O$; $R_5=R_6=CH_3$; $\triangle^{14,15}$	*S. saligna*	[58]
66	Epipachysamine-*E*-5-en-4-one	$R_1=R_4=H$; $R_2=NH$-Sen; $R_3=O$; $R_5=R_6=CH_3$	*S.brevifolia*	[59]
67	N_b-Demethylepipachysamine-*E*-5-ene-4-one	$R_1=R_4=R_5=H$; $R_2=NH$-Sen; $R_3=O$; $R_6=CH_3$	*S. brevifolia*	[59]
68	Salignarine B	$R_1=\beta$-OH; $R_2=NH$-Tig; $R_3=R_4=H$; $R_5=R_6=CH_3$	*S. saligna*	[44]
69	Salignarine C	$R_1=\beta$-OH; $R_2=NH$-Sen; $R_3=R_4=H$; $R_5=R_6=CH_3$	*S. saligna*	[44]
70	Iso-*N*-formylchonemorphin-5-ene	$R_1=R_3=R_4=R_5=H$; $R_2=N(CH_3)_2$; $R_6=CHO$	*S. zeylanica*	[60]
71	Alkaloid C	$R_1=R_3=R_4=H$; $R_2=OCH_3$; $R_5=R_6=CH_3$	*S. saligna*	[50]
72	Salignarine F	$R_1=R_4=H$; $R_2=NH$-Tig; $R_3=\beta$-OH; $R_5=R_6=CH_3$	*S. saligna*	[51]
73	Saracosine	$R_1=R_3=R_4=H$; $R_2=N(CH_3)_2$; $R_5=Ac$; $R_6=CHO$	*S. saligna*	[51]
74	Sarcodinine	$R_1=R_3=R_4=H$; $R_2=N(CH_3)_2$; $R_5=R_6=CH_3$	*S. saligna*	[51]
75	5,14-Dehydro-N_a-demethylsaracodine	$R_1=R_3=R_4=H$; $R_2=NHCH_3$; $R_5=Ac$; $R_6=CH_3$; $\triangle^{14,15}$	*S. saligna*	[61]
76	Holadysenterine	$R_1=R_3=H$; $R_2=NH_2$; $R_4=R_5=OH$; $R_6=Ac$	*Holarrhena antidysenterica*	[62]
77	(20*S*)-20*α*-Cinnamoylamino-3*β*-dimethylamino-5-en-pregnane	$R_1=R_3=R_4=R_5=H$; $R_2=N(CH_3)_2$; $R_6=COCH=CHph$	*Pachysandra terminalis*	[63]
78	SarcovagineA	$R_1=R_4=\beta$-OH; $R_2=Tig$; $R_3=H$; $R_5=R_6=CH_3$	*Sarcococca vegans*	[64]
79	Sarcovagine B	$R_1=\alpha$-OH; $R_2=Tig$; $R_3=H$; $R_4=\beta$-OAc; $R_5=R_6=CH_3$	*S. vegans*	[64]
80	Sarcovagine C	$R_1=R_3=H$; $R_2=Tig$; $R_4=\beta$-OAc; $R_5=R_6=CH_3$	*S. vegans*; *S. hookeriana*	[64, 65]
81	*N*-Formylchonemorphine	$R_1=R_2=R_4=H$; $R_3=CHO$; $R_5=R_6=CH_3$	*S. saligna*	[58]
82	Vaganine A	$R_1=R_2=H$; $R_3=Sen$; $R_4=\beta$-OAc; $R_5=R_6=CH_3$	*S. saligna*	[58]
83	Sarcorine	$R_1=R_2=R_4=H$; $R_3=Ac$; $R_5=R_6=CH_3$	*S. saligna*	[49]
84	N_a-Demethylsaracodine	$R_1=R_2=R_4=H$; $R_3=R_6=CH_3$; $R_5=Ac$	*S. saligna*	[66]
85	Saligcinnamide	$R_1=R_4=H$; $R_2=R_5=R_6=CH_3$; $R_3=Cin$	*S. saligna*	[67]
86	N_a-Methyl epipachysamine D	$R_1=R_4=H$; $R_2=R_5=R_6=CH_3$; $R_3=Bz$	*S. saligna*; *S. hookeriana*	[65, 67]

Table 3 (continued)

No	Compounds	Substitution groups and others	Sources	References
87	Epipachysamine D	$R_1=R_2=R_4=H$; $R_3=Bz$; $R_5=R_6=CH_3$	*S. saligna*	[67]
88	Salignenamide A	$R_1=R_2=R_4=H$; $R_3=COCHC(CH_3)CH(CH_3)CH_3$; $R_5=R_6=CH_3$	*S. saligna*; *S. hookeriana*	[65, 68]
89	2,4-Diacetoxyepipachysamine D	$R_1=\beta$-OAc; $R_2=H$; $R_3=Bz$; $R_4=\beta$-OAc; $R_5=R_6=CH_3$	*S. saligna*	[68]
90	Iso-*N*-formylchonemorphine	$R_1=R_4=R_5=H$; $R_2=R_3=CH_3$; $R_6=CHO$	*S. brevifolia*	[59]
91	Epipachysamine E	$R_1=R_3=R_4=H$; $R_2=Sen$; $R_5=R_6=CH_3$	*Pachysandra terminalis*	[54]
92	11-Hydroxyepipachysamine E	$R_1=R_2=R_4=H$; $R_3=Sen$; $R_5=R_6=CH_3$; 11-OH	*Sarcococca brevifolia*	[69]
93	Saligenamide C	$R_1=\beta$-OH; $R_2=H$; $R_3=Tig$; $R_4=\beta$-OAc; $R_5=R_6=CH_3$; $\triangle^{14,15}$	*S. saligna*	[70]
94	Saligenamide F	$R_1=R_4=H$; $R_2=CH_3$; $R_3=COCHC(CH_3)CH(CH_3)CH_3$; $R_5=R_6=CH_3$	*S. saligna*	[70]
95	2β-Hydroxyepipachysamine D	$R_1=\beta$-OH; $R_2=R_4=R_5=H$; $R_3=Bz$; $R_6=CH_3$	*S. saligna*	[70]
96	Axillarine C	$R_1=\beta$-OH; $R_2=H$; $R_3=Bz$; $R_4=\beta$-OAc; $R_5=R_6=CH_3$	*S. saligna*	[70]
97	Axillarine F	$R_1=\beta$-OH; $R_2=H$; $R_3=Tig$; $R_4=\beta$-OAc; $R_5=R_6=CH_3$	*S. saligna*	[70]
98	Salonine A	$R_1=\beta$-OH; $R_2=H$; $R_3=Tig$; $R_4=\beta$-OH; $R_5=R_6=CH_3$; $\triangle^{14,15}$	*S. saligna*	[50]
99	Dictyophlebine	$R_1=R_2=R_4=H$; $R_3=R_5=R_6=CH_3$	*S. saligna*; *S. hookeriana*	[51, 65]
100	Hookerianamine A	$R_1=R_2=R_4=H$; $R_3=R_5=R_6=CH_3$; $\triangle^{14,15}$	*S. hookeriana*	[71]
101	Isosarcodine	$R_1=R_4=H$; $R_2=R_5=R_6=CH_3$; $R_3=Ac$	*S. saligna*	[72]
102	Hookerianamide B	$R_1=\alpha$-OH; $R_2=H$; $R_3=Sen$; $R_4=\beta$-OH; $R_5=R_6=CH_3$	*S. hookeriana*	[71]
103	Hookerianamide C	$R_1=\beta$-OAc; $R_2=R_4=H$; $R_3=Sen$; $R_5=R_6=CH_3$	*S. hookeriana*	[71]
104	Hookerianamide D	$R_1=R_4=H$; $R_2=R_5=CH_3$; $R_3=COCHC(CH_3)CH(CH_3)CH_3$; $R_6=CHO$	*S. hookeriana*	[73]
105	Hookerianamide E	$R_1=\beta$-OAc; $R_3=R_4=H$; $R_2=Sen$; $R_5=R_6=CH_3$; $\triangle^{14,15}$	*S. hookeriana*	[73]
106	Hookerianamide G	$R_1=H$; $R_2=R_5=R_6=CH_3$; $R_3=Bz$; $R_4=\beta$-OAc	*S. hookeriana*	[73]
107	Hookerianamide I	$R_1=R_4=R_5=H$; $R_2=R_6=CH_3$; $R_3=Bz$	*S. hookeriana*	[74]
108	Chonemorphine	$R_1=R_2=R_3=R_4=H$; $R_5=R_6=CH_3$	*S. hookeriana*	[65]
109	*N*-Methypachysamine A	$R_1=R_4=H$; $R_2=R_3=R_5=R_6=CH_3$	*S. hookeriana*	[65]
110	Pachysamine J	$R_1=\alpha$-OH; $R_2=R_4=H$; $R_3=Sen$; $R_5=R_6=CH_3$	*Pachysandra axillaris*	[75]
111	Pachysamine O	$R_1=R_2=R_4=H$; $R_3=Cin$; $R_5=R_6=CH_3$	*P. axillaris*	[75]
112	Pachysamine P	$R_1=R_2=H$; $R_3=COCH_2C(CH_3)C(CH_3)CH_3$; $R_4=\beta$-OH; $R_5=R_6=CH_3$	*P. axillaris*	[75]
113	(20*S*)-2α,4β-Bis(acetoxy)-20-(*N*,*N*-dimethylamino)-3β-tigloylamino-5α-pregnane	$R_1=\alpha$-OAc; $R_2=H$; $R_3=Tig$; $R_4=\beta$-OAc; $R_5=R_6=CH_3$	*Sarcococca hookeriana*	[76]
114	(20*S*)-20α-Cinnamoylamino-3β-dimethylamino-pregnane	$R_1=R_4=R_5=H$; $R_2=R_3=CH_3$; $R_6=COCH=CHph$	*Pachysandra terminalis*	[63]
115	(20*S*)-(Bennzamido)-3β-(*N*,*N*-dimethyamino)-pregnane	$R_1=R_4=H$; $R_2=R_3=R_6=CH_3$; $R_5=Bz$	*Sarcococca. saligna*	[77]
116	Sarcovagine D	$R_1=Tig$; $R_2=O$; $R_3=R_4=H$; $R_5=CH_3$	*S. vegans*; *S. hookeriana*	[64, 65]
117	Sarcovagenine C	$R_1=Tig$; $R_2=O$;$R_3=R_4=H$; $R_5=CH_3$; $\triangle^{16,17}$	*S. vegans*; *S. hookeriana*	[65, 78]
118	Axillaridine A	$R_1=Bz$; $R_2=O$; $R_3=R_4=H$; $R_5=CH_3$	*S. saligna*; *P. procumbens*	[46, 69]
119	2,3-Dehydrosarsalignone	$R_1=Tig$; $R_2=O$; $R_3=R_4=H$; $R_5=CH_3$; $\triangle^{5,6}$	*S. saligna*	[61]
120	14,15-Dehydrosarcovagine D	$R_1=Tig$; $R_2=O$; $R_3=R_4=H$; $R_5=CH_3$; $\triangle^{14,15}$	*S. saligna*	[61]
121	Phulchowkiamide A	$R_1=Tig$; $R_2=O$; $R_3=R_4=R_5=H$	*S. hookeriana*	[72]
122	Hookerianamide F	$R_1=Tig$; $R_2=O$; $R_3=R_4=R_5=H$; $\triangle^{14,15}$	*S. hookeriana*	[71]
123	Hookerianamide H	$R_1=CHO$; $R_2=O$; $R_3=R_4=H$; $R_5=CH_3$	*S. hookeriana*	[73]
124	(+)-(20*S*)-3-(Benzoylamino)-20-(dimethylamino)-5α-pregn-2-en-4β-yl acetate	$R_1=Bz$; $R_2=\beta$-OAc; $R_3=R_4=H$; $R_5=CH_3$	*Pachysandra procumbens*	[46]

Table 3 (continued)

No	Compounds	Substitution groups and others	Sources	References
125	Pachysamine L	R_1 = Tig; R_2 = β-OAc; R_3 = R_4 = H; R_5 = CH_3	*P. axillaris*	[75]
126	Pachysamine M	R_1 = Sen; R_2 = O; R_3 = R_4 = H; R_5 = CH_3	*P. axillaris*	[75]
127	Pachysamine N	R_1 = Sen; R_2 = O; R_3 = H; R_4 = β-OH; R_5 = CH_3	*P. axillaris*	[75]
128	Sarsaligenine A	R_1 = Sen; R_2 = O; R_3 = R_4 = H; R_5 = CH_3; $\triangle^{16,17}$	*Sarcococca saligna*	[79]
129	Sarsaligenine B	R_1 = Sen; R_2 = O; R_3 = α-OH; R_4 = H; R_5 = CH_3	*S. saligna*	[79]
130	Sarcovagenines A	R_1 = R_3 = β-OH; R_2 = Tig; R_4 = CH_3	*S. vegans*	[78]
131	Sarcovagenines B	R_1 = α-OH; R_2 = Tig; R_3 = β-OAc; R_4 = CH_3	*S. vegans*	[78]
132	Salignarine D	R_1 = R_3 = H; R_2 = Sen; R_4 = CH_3	*S. saligna*	[44]
133	(−)-Vaganine D	R_1 = H; R_2 = Sen; R_3 = β-OAc; R_4 = CH_3	*S. coriacea*	[80]
134	(+)-Nepapakistamine A	R_1 = R_3 = β-OAc; R_2 = Tig; R_4 = H	*S. coriacea*	[80]
135	5,6-Dihydrosarconidine	R_1 = R_3 = H; R_2 = R_4 = CH_3	*S. saligna*	[51]
136	16-Dehydrosarcorine	R_1 = R_3 = H; R_3 = Ac; R_4 = CH_3	*S. saligna*	[61]
137	Hookerianamide A	R_1 = R_3 = β-OH; R_2 = Sen; R_4 = CH_3	*S..hookeriana*	[72]
138	Saligenamide B	R_1 = β-OH; R_2 = Sen; $\triangle^{14,15}$	*S. saligna*	[67]
139	Salignarine E	R_1 = H; R_2 = Tig	*S. saligna*	[44]
140	Saligenamide D	R_1 = α-OH; R_2 = Tig; $\triangle^{16,17}$	*S. saligna*	[69]
141	2-Hydroxysalignarine E	R_1 = β-OH; R_2 = Tig	*S. saligna*	[51]
142	Salonine C	R_1 = H; R_2 = Tig; $\triangle^{14,15}$	*S. saligna*	[51]
143	*E*-salignone		*S. saligna*	[65]
144	*Z*-salignone		*S. saligna*	[65]
145	Holamine	R_1 = α-NH_2; R_2 = R_3 = R_4 = H; R_5 = R_6 = α-H; $\triangle^{5,6}$	*Holarrhena curtisii*	[81]
146	3α-Amino-14β-hydroxypregnan-20-one	R_1 = α-NH_2; R_2 = R_3 = R_4 = R_6 = H; R_5 = β-OH	*H. curtisii*	[81]
147	15α-Hydroxyholamine	R_1 = α-NH_2; R_2 = R_3 = R_4 = H; R_5 = α-H; R_6 = α-OH; $\triangle^{5,6}$	*H. curtisii*	[81]
148	Pachysanone	R_1 = O; R_2 = H; R_3 = α-$OCOCH_2C(CH_3)C(CH_3)CH_3$; R_4 = β-OAc; R_5 = R_6 = H	*Pachysandra axillaris*	[45]
149	Pachysanonin	R_1 = β-$N(CH_3)_2$; R_2 = H; R_3 = α-$OCOCH_2C(CH_3)C(CH_3)CH_3$; R_4 = β-OAc; R_5 = R_6 = H	*P. axillaris*	[45]
150	Pachysamine Q	R_1 = β-$N(CH_3)_2$; R_2 = R_4 = β-OAc; R_3 = α-OCO-Bn; R_5 = R_6 = H	*P. axillaris*	[75]
151	Pachysamine R	R_1 = β-$N(CH_3)_2$; R_2 = R_4 = β-OAc; R_3 = α-$OCOCH_2C(CH_3)C(CH_3)CH_3$; R_5 = R_6 = H	*P. axillaris*	[75]
152	Terminamine F	R_1 = α-NCH_3-Sen; R_2 = R_3 = R_4 = R_5 = R_6 = H	*P. terminalis*	[82]
153	Terminamine G	R_1 = α-NCH_3-Bz; R_2 = R_3 = R_4 = R_5 = R_6 = H	*P. terminalis*	[82]
154	Funtumine	R_1 = α-NH_2; R_2 = R_3 = R_4 = R_5 = R_6 = H	*Holarrhena floribunda*	[83]
155	(+)-(20*S*)-20-(Dimethylamino)-3-(3′α-isopropyl)-lactam-5α-pregn-2-en-4-one	R_1 = R_3 = R_4 = H; R_2 = O; $\triangle^{1,2}$	*Pachysandra procumbens*	[46]
156	(+)-(20*S*)-20-(Dimethylamino)-16α-hydroxy-3-(3′α-isopropyl)-lactam-5α-pregn-2-en-4-one	R_1 = R_3 = H; R_2 = O; R_4 = α-OH; $\triangle^{1,2}$	*P. procumbens*	[46]
157	Pachystermine A	R_1 = R_3 = R_4 = H; R_2 = O	*P. terminalis*	[54]
158	(+)-(20*S*)-20-(Dimethylamino)-16α-hydroxy-3β-(3′α-isopropyl)-lactam-5α-pregn-4-one	R_1 = R_3 = H; R_2 = O; R_4 = α-OH	*P. procumbens*	[55]
159	Terminamine A	R_1 = R_3 = H; R_2 = O; R_4 = β-OH	*P. terminalis*	[82]
160	Terminamine B	R_1 = β-OAc; R_2 = R_4 = β-OH; R_3 = α-OAc	*P. terminalis*	[82]
161	Terminamine C	R_1 = β-OAc; R_2 = R_4 = β-OH; R_3 = val	*P. terminalis*	[82]
162	Pachystermine B	R_1 = R_3 = R_4 = H; R_2 = β-OH	*P. terminalis*	[82]
163	Terminamine D	R = OH	*P. terminalis*	[82]
164	Terminamine E	R = H	*P. terminalis*	[82]
165	(+)-(20*S*)-2α-Hydroxy-20-(dimethylamino)-3β-phthalimido-5α-pregnan-4β-yl acetate		*P. procumbens*	[46]
166	Spiropachysine		*P. procumbens*	[46]
167	Salignarine A		*Sarcococca saligna*	[44]

Table 3 (continued)

No	Compounds	Substitution groups and others	Sources	References
168	Epoxynepapakistamin A	$R_1=R_3=\beta$-OAc; $R_2=\beta$-NH-Tig; $R_4=H$	*S. coriacea*	[47]
169	Epoxysarcovagenine D	$R_1=R_4=H$; $R_2=\beta$-NH-Tig; $R_3=O$; $\triangle^{2,3}$	*S. coriacea*	[47]
170	(*S*)-20-(*N*,*N*-Dimethylamino)-16α,17α-epoxy-3β-methoxy-pregn-5-ene	$R_1=R_3=R_4=H$; $R_2=\beta$-OCH_3; $\triangle^{5,6}$	*S. hookeriana*	[76]
171	Hookerianine B	$R_1=R_3=H$; $R_2=\alpha$-NH-Bz; $R_4=CH_3$	*S. hookeriana*	[56]
172	*N*-methylfuntumafrine		*S. coriacea*	[47]
173	Pachysamines K	$R_1=R_4=H$; $R_2=\alpha$-OH; $R_3=$Bz; $R_5=\alpha$-OH	*Pachysandra axillaris*	[75]
174	Archosokloide A	$R_1=R_5=H$; $R_2=\beta$-OH; $R_3=$Tig; $R_4=\beta$-OH	*Sarcococca hookeriana*	[57]
175	Sarchookloide B	$R_1=R_4=R_5=H$; $R_2=\beta$-OH; $R_3=$Tig	*S. hookeriana*	[57]
176	4-Dehydroxyepisarcovagine A	$R_1=\beta$-OH; $R_2=R_4=R_5=H$; $R_3=$Tig; $\triangle^{14,15}$	*S. pruniformis*	[84]
177	(20*S*)-(Bennzamido)-pregnane-3-one		*S. saligna*	[77]

2.1.2 Cyclopregnane alkaloids

The *Buxus* genus of the Buxaceae family is a rich source of cyclopregnane alkaloids, and 116 cyclopregnane alkaloids (**178–293**) have been reported from *B. sempervirens, B. longifolia, B. hildebrandtii, B. bodinieri, B. hyrcana, B. microphylla, B. papillosa, B. wallichiana*, *B. rugulosa, B. natalensis,* and *B. macowanii.*

Cyclopregnane alkaloids, also known as triterpenoid alkaloids, possess a unique pregnane type structure with C-4 methyl groups, a 9β,10β-cycloartenol system, and a degraded C-20 side chain. All alkaloids possess a nitrogen function at C-3 and/or C-20, which may be unmethylated, partially methylated, or fully methylated. Structurally, the majority of these alkaloids contain either a 9β,19-cyclo-14α-methylpregnane type or a 9(10 → 19) abeo-14α-methylpregnane type, having a characteristic substituent pattern at C-4.

2.1.2.1 9β,19-Cyclo-14α-methylpregnane type Out of the 116 cyclopregnane alkaloids, 50 (**178–227**) belong to this type, which are characteristic of the genus *Buxus* (Table 4). This type of compound is characterized by a pentacyclic 4,4,14-trimethyl-9,19-cyclopregnane skeleton (Fig. 5).

Cyclobuxine D **(178)** was the first steroidal alkaloid from *Buxus* bearing a C-4 methylene substituent [85]. Later, cyclobuxamidine **(179)** and trans-cyclosuffrobuxinine **(213)** of this type were isolated from *B. longifolia* [86]. Buxbodine A **(181)** has a unique structure due to the lack of a keto or an amino functionality at the C-3 position [87]. Typically, all alkaloids of this type have a C-3 amino or carbonyl group, except for buxmicrophylline K **(186)**, which has a hydroxyl group substituted at C-3 [88]. In compounds *trans*-cyclosuffrobuxinine **(213)** and sempervirone **(215),** the methylamino group at C-20 is eliminated and the secondary alcohol at C-16 is oxidized [86, 89]. Buxozine C **(214)** with a tetrahydro-oxazine ring joining the C-16α and the C-20 nitrogen has been isolated from *B. papillosa.* The mass spectra of compound **214** exhibit the ions at m/z 127 and 113 due to cleavage of ring D, and these ions serve as diagnostic features to determine the presence of a tetrahydro-oxazine ring in ring D [90].

2.1.2.2 9(10 → 19)Abeo-14α-methylpregnane alkaloids This type contains a tetracyclic system in which 9,19 bond fission has occurred to give seven-membered ring B (Fig. 6). Sixty-six alkaloids (**228–293)** were isolated from the genus *Buxus* (Table 5).

Alkaloids **248–254** and **290–291** are members of the class having a tetrahydro-oxazine moiety incorporated in ring A, while in compound **288** an oxazine ring is attached to ring D [89]. The presence of this ring can be easily recognized by the ^{1}H NMR spectrum exhibiting the presence of two pairs of AB doublets at δ 3.20–4.50 [91]. Compounds **255–258** belong to a unique class having a conjugated triene system at $\triangle^{1,2}$, $\triangle^{10,19}$ and $\triangle^{9,11}$. Compounds **259–264**, **282–284** and **292** belong to the rarely occurring class having an additional tetrahydrofuran ring incorporated in their structures through the ether linkage between C-10, C-2, or C-10 and C-23. Buxalongifolamidine (**268**) and **270–272** containing a hydroxyl group at C-10 may support the plausible biosynthesis of the ether linkage in these alkaloids [107]. Compounds **285–287** and **292** are rare cyclopregnane alkaloids featuring an epoxy motif [108]. Sempervirooxazolidine (**289**) also represents a novel structure having an oxazolidine moiety incorporated in its structure at C-2 and C-3 [96]. The compound 17-Oxo-3-benzoylbuxadine (**293**) having a carbonyl group at C-17 has been isolated from *B. hyrcana* [94].

Table 4 Structures and sources of 9*β*,19-Cyclo-14*α*-methylpregnane type steroidal alkaloids **178–227**

No	Compounds	Substitution groups and others	Sources	References
178	Cyclobuxine	$R_1=H$; $R_2=\alpha$-OH	*Buxus sempervirens*	[85]
179	Cyclobuxamidine	$R_1=Ac$; $R_2=H$	*B. longifolia*	[86]
180	Cyclobuxoviridine	$R_1=O$; $R_2=R_4=CH_3$; $R_3=H$; $\triangle^{1,2}$	*B. hildebrandtii*	[91]
181	Buxbodine A	$R_1=R_3=H$; $R_2=R_4=CH_3$	*B. bodinieri*	[87]
182	Buxbodine B	$R_1=O$; $R_2=R_4=CH_3$; $R_3=\beta$-OH; $\triangle^{1,2}$	*B. bodinieri*	[87]
183	N_b-Demethylcyclomikurane	$R_1=O$; $R_2=CH_3$; $R_3=R_4=H$	*B. sempervirens*	[92]
184	Cyclimikuranine	$R_1=O$; $R_2=R_4=CH_3$; $R_3=H$	*B. sempervirens*	[92]
185	N_b-Demethylcyclobuxoviricine	$R_1=O$; $R_2=R_4=CH_3$; $R_3=\alpha$-OH; $\triangle^{1,2}$	*B. hyrcana*	[93]
186	Buxmicrophylline K	$R_1=\beta$-OH; $R_2=CH_3$; $R_3=\alpha$-OH; $R_4=H$	*B. microphylla*	[88]
187	*N*-Demethylcyclomikuranine	$R_1=O$; $R_2=CH_3$; $R_3=\alpha$-OH; $R_4=H$	*B. microphylla*	[88]
188	31-Demethylcyclobuxoviridine	$R_1=O$; $R_2=H$; $R_3=H$; $R_4=CH_3$; $\triangle^{1,2}$	*B. hyrcana*	[94]
189	Cyclomicrobuxamine	$R_1=R_3=H$; $R_2=CH_2$	*B. hildebrandtii*	[91]
190	Cyclomicrobuxeine	$R_1=R_3=H$; $R_2=CH_2$; $\triangle^{16,17}$	*B. sempervirens*	[95]
191	30-Hydroxycyclomicobuxene	$R_1=R_3=H$; $R_2=CH_2OH$; $\triangle^{4,5}$	*B. sempervirens*	[96]
192	Buxippine K	$R_1=CH_3$; $R_2=CH_2$; $R_3=\alpha$-OH	*B. hyrcana*	[93]
193	Cyclorolfeine		*B. hildebrandtii*	[91]
194	Cyclobuxomicreinine		*B. longifolia*	[97]
195	Isodihydrocyclomicrophylline A	$R_1=R_2=R_5=R_6=CH_3$; $R_3=CH_2OH$; $R_4=\alpha$ -OH	*B. sempervirens*	[98]
196	Buxasamarine	$R_1=R_2=R_3=CH_3$; $R_4=\alpha$-OH; $R_5=H$; $R_6=CH_3$; $\triangle^{1,2}$	*B. longifolia*	[86]
197	Buxmicrophylline C	$R_1=H$; $R_2=$Isobu; $R_3=CH_2OH$; $R_4=\alpha$-OH; $R_5=R_6=CH_3$; $\triangle^{6,7}$	*B. microphylla*	[99]
198	Buxbodine D	$R_1=R_2=R_3=CH_3$; $R_4=R_5=H$; $R_6=Ac$; $\triangle^{6,7}$	*B. bodinieri*	[87]
199	Buxbodine E	$R_1=R_2=R_3=CH_3$; $R_4=R_5=R_6=H$; $\triangle^{6,7}$	*B. bodinieri*	[87]
200	Buxakashmiramine	$R_1=$Syr; $R_2=R_5=R_6=CH_3$; $R_3=CH_2OH$; $R_4=H$	*B. papillosa*	[100]
201	Cycloprotobuxine C	$R_1=R_2=R_3=R_5=R_6=CH_3$; $R_4=H$; $\triangle^{6,7}$	*B. papillosa*	[100]
202	Cyclovirobuxeine A	$R_1=R_2=R_3=R_5=R_6=CH_3$; $R_4=\alpha$-OH; $\triangle^{6,7}$	*B. papillosa*	[100]
203	Cyclovirobuxine D	$R_1=R_5=H$; $R_2=R_3=R_6=CH_3$; $R_4=\alpha$-OH	*B. wallichiana*	[101]
204	Hyrcamine	$R_1=H$ $R_2=$Tig; $R_3=CH_2OH$; $R_4=\alpha$ -OAc; $R_5=R_6=CH_3$	*B. hyrcana*	[93]
205	Buxidine	$R_1=H$ $R_2=$Bz; $R_3=CH_2OH$; $R_4=\alpha$-OH; $R_5=R_6=CH_3$; $\triangle^{6,7}$	*B. hyrcana*	[93]
206	Buxandrine	$R_1=H$ $R_2=$Bz; $R_3=CH_2OH$; $R_4=\alpha$ -OAc; $R_5=R_6=CH_3$; $\triangle^{6,7}$	*B. hyrcana*	[93]
207	Buxrugulosamine	$R_1=H$; $R_2=Ac$; $R_3=CH_3$; $R_4=H$; $R_5=H$; $R_6=CH_3$	*B.rugulosa*	[102]
208	Buxmicrophylline E	$R_1=H$; $R_2=$Bz; $R_3=CH_2OH$; $R_4=$O-Bz; $R_5=R_6=CH_3$	*B. microphylla*	[103]
209	Buxmicrophylline F	$R_1=H$; $R_2=$Isobu; $R_3=CH_2OH$; $R_4=$O-Bz; $R_5=R_6=CH_3$; $\triangle^{6,7}$	*B. microphylla*	[103]
210	Buxmicrophylline G	$R_1=H$; $R_2=$Isofer; $R_3=CH_2OH$; $R_4=\alpha$ -OH; $R_5=R_6=CH_3$	*B. microphylla*	[103]
211	Buxmicrophylline H	$R_1=H$; $R_2=$Syr; $R_3=CH_2OH$; $R_4=\alpha$ -OH; $R_5=R_6=CH_3$	*B. microphylla*	[103]
212	Cyclonataminol	$R_1=R_2=R_3=R_5=R_6=CH_3$; $R_4=\alpha$-OH; 2-α-OH; $\triangle^{6,7}$	*B. natalensis*	[104]
213	*trans*-Cyclosuffrobuxinine		*B. longifolia*	[86]
214	Buxozine C		*B. papillosa*	[90]
215	Sempervirone		*B. papillosa*	[89]
216	Buxmicrophylline D	$R_1=R_2=CH_3$; $R_3=R_4=H$	*B. microphylla*	[99]
217	Buxmicrophylline I	$R_1=R_2=R_3=H$; $R_4=$Syr	*B. microphylla*	[103]
218	Buxmicrophylline J	$R_1=H$; $R_2=R_3=CH_3$; $R_4=$Bz	*B. microphylla*	[88]
219	Buxmicrophylline P	$R_1=R_2=H$; $R_3=\beta$-CH_3; $R_4=H$	*B. microphylla*	[105]
220	Buxmicrophylline Q	$R_1=R_2=H$; $R_3=\beta$-CH_3; $R_4=$Syr	*B. microphylla*	[105]
221	Buxmicrophylline R	$R_1=R_2=H$; $R_3=\beta$-CH_3; $R_4=$Van	*B. microphylla*	[105]
222	Buxmicrophylline B	$R_1=R_3=H$; $R_2=CH_3$	*B. microphylla*	[99]
223	*E*-cyclobuxaphylamine	$R_1=R_3=H$; $R_2=CH_3$; $\triangle^{7,8}$	*B. sempervirens*	[95]
224	*Z*-cyclobuxaphylamine	$R_1=R_2=H$; $R_3=CH_3$; $\triangle^{7,8}$	*B. sempervirens*	[95]
225	Buxbodine C	$R_1=R_2=CH_3$; $R_3=H$; $\triangle^{6,7}$	*B. bodinieri*	[87]
226	Cyclobuxaphylline	$R_1=R_2=CH_3$; $R_3=H$	*B. sempervirens*	[92]

Table 4 (continued)

No	Compounds	Substitution groups and others	Sources	References
227	17-Oxocycloprotobuxine		*B. sempervirens*	[106]

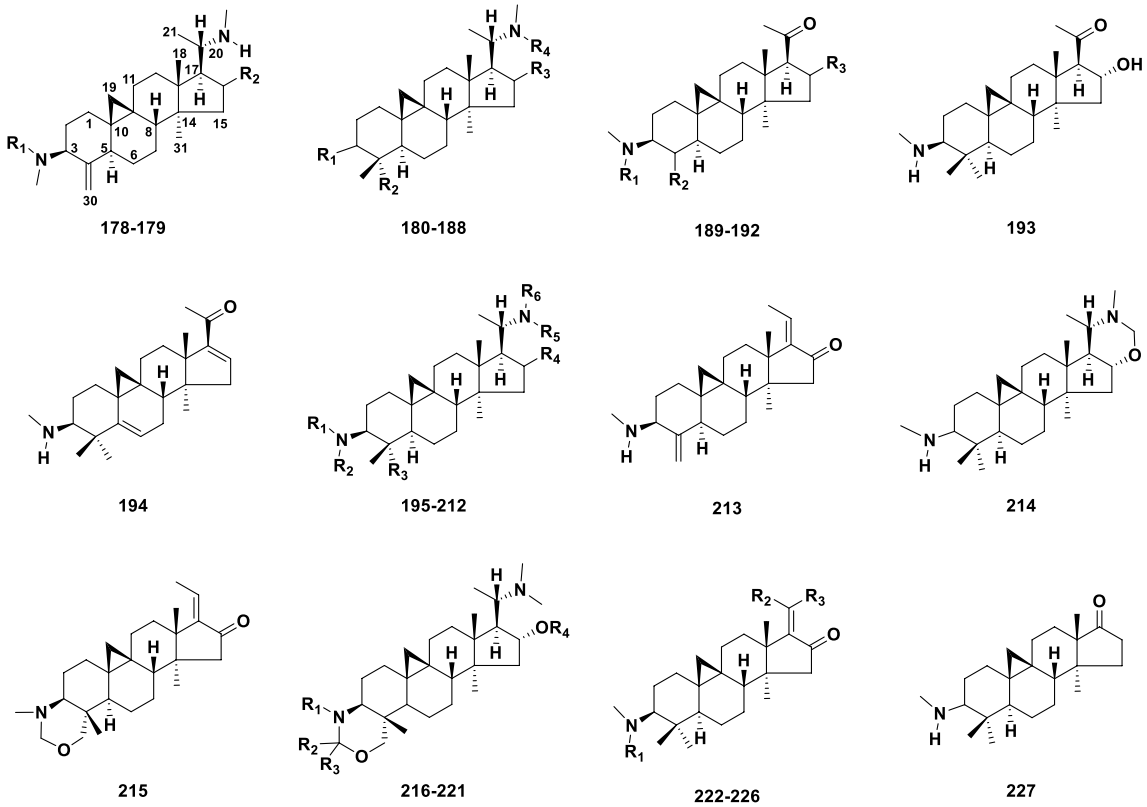


Fig. 5 Structures of 9*β*,19-cyclo-14*α*-methylpregnane type steroidal alkaloids **178–227**

2.1.3 Cholestane alkaloids

Based on the carbon framework, C_{27} alkaloids can be divided into two types: C-nor-D-homosteroidal alkaloids and cholestane alkaloids. The former, usually referred to as *Veratrum* steroidal alkaloids, characterised by a five-membered C-ring and six-membered D-ring system, can be further divided into cevanine, veratramine, and jervine types. The latter, usually named *Solanum* steroidal alkaloids, containing the common ABCD steroid skeleton, generally occurring as glycosides, can be grouped into spirosolane, solanidine and verazine types.

A total of 310 new members (**294–603)** were derived mainly from the genus *Solanum* in the Solanaceae family, and the genera *Veratrum* and *Fritillaria* in Liliaceae family.

2.1.3.1 Cevanine type Members of the cevanine type are characterized by the hexacyclic benzo [7, 8] fluoreno[2,1-*β*]quinolizine nucleus (Fig. 7) [15]. This type is the largest representative group of C-nor-D-homosteroidal alkaloids, and currently comprises 91 new members (**294–384)** from *Veratrum* and *Fritillaria* genera in the Liliaceae family (Table 6).

Veratrenone (**294**), the first alkaloid with a cevanine skeleton from *V. album*, was investigated in 1974 [118]. The structure of isobaimonidine (**301**), the C-6 epimer of baimonidine (**299**), was deduced by chemical transformation [119]. Eleven glycoalkaloids (**302**, **317**, **326**, **329–331, 333, 337, 341**, **343** and **384**) have been isolated from various *Fritillaria* species in cevanine-type alkaloids. Alkaloid pingbeinone (**372**) has a unique structure with a lack of a C-18 methylene unit, and its structure could be unequivocally established by X-ray diffraction of its corresponding hydroiodide salt [120]. Alkaloids **349–368** belong to the rarely occurring class of cholestane alkaloids having a tetrahydrofuran

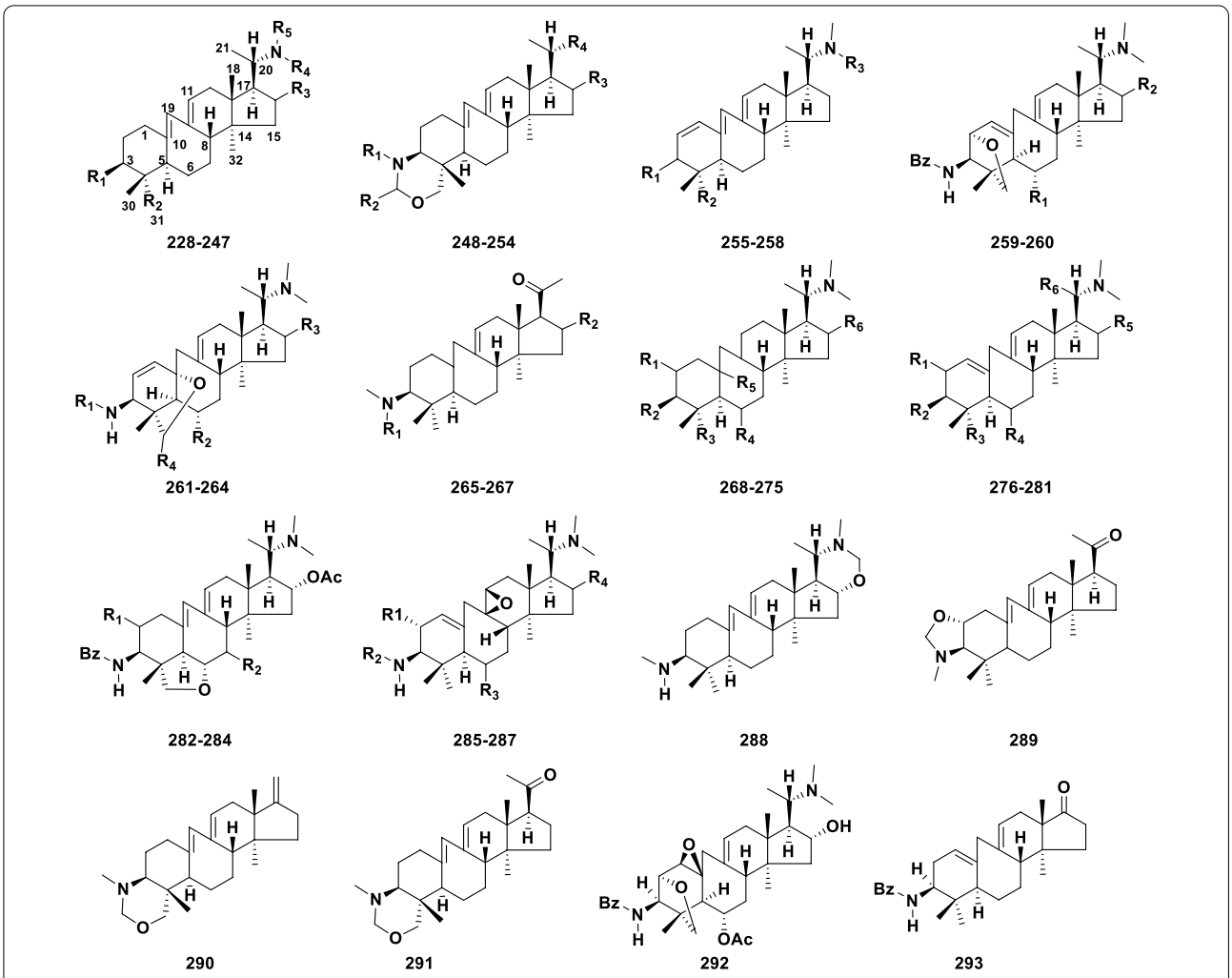


Fig. 6 Structures of 9(10 → 19)abeo-14*α*-methylpregnane type steroidal alkaloids **228–293**

ring incorporated in their structures. Heilonine (**371**), the first example with an aromatic D-ring in the group of cevanine alkaloids, was isolated from *Fritillaria ussuriensis* in the group of Kaneko [121]. Compounds **373–376** are four unique steroidal alkaloids with a seven-membered G-ring formed by a connection between C-18 and C-27. Taipaienine (**377**) [122] and yibeisine (**378**) [123], which are unique in bearing a C-25 hydroxyl moiety as of a cevanine system, have been isolated from *Fritillaria taipaiensis* and *Fritillaria pallidiflora*, respectively. Compounds **318–321** and frititorine B (**384**) [124] are steroidal alkaloid *N*-oxide derivatives. Neoverataline A (**379**) and neoverataline B (**380**), having a novel 3,4-secocevane-4,9-olid-3-oic acid skeleton, were obtained from the genus *Veratrum* [125]. Compound **381** possesses a rare 9-hydroxy moiety within cevanine-type alkaloids [126].

2.1.3.2 Veratramine type The veratramine type of steroidal alkaloids, in which ring E of cevane has been opened at C-18 (Fig. 8). Compounds **385–411**, a total of 27 veratramine alkaloids, have been found in *Veratrum* and *Fritillaria* (Table 7).

Thirteen alkaloids, **387**, **390–394**, **402–408** containing an aromatic D-ring are unusual in C_{27} steroidal alkaloids, and concurrently **387** is a steroidal alkaloid *N*-oxide derivative. A chemical investigation of the hypogeal parts of *Fritillaria imperialis* furnished two unique bases, impranine (**398**) and dihydroimpranine (**399**), which have a methyl group at C-12. This is the first time the novel "impranane" class derived from the veratramine skeleton has been found in the genus *Fritillaria* [179]. Veratravine A (**405**) and zhebeisine (**411**) contain a new oxazinane ring F forming a rare 6/6/5/6/6/6 fused-ring system.

Table 5 Structures and sources of 9(10 → 19)abeo-14α-methylpregnane type steroidal alkaloids **228–293**

No	Compounds	Substitution groups and others	Sources	References
228	Buxamine A	$R_1=N(CH_3)_2$; $R_2=R_4=R_5=CH_3$; $R_3=H$	*Buxus hildebrandtii*; *B. natalensis*	[91, 104]
229	Buxamine C	$R_1=NHCH_3$; $R_2=R_4=R_5=CH_3$; $R_3=H$	*B. hildebrandtii*	[91]
230	30-*O*-benzoyl-16-deoxybuxidienine C	$R_1=H$; $R_2=CH_2O$-Bz; $R_3=H$; $R_4=R_5=CH_3$	*B. hildebrandtii*	[91]
231	30-Hydroxybuxamine A	$R_1=R_4=R_5=CH_3$; $R_2=CH_2OH$; $R_3=H$	*B.hildebrandtii*	[91]
232	30-Norbuxamine A	$R_1=R_4=R_5=CH_3$; $R_2=R_3=H$	*B.hildebrandtii*	[91]
233	*N*-benzoyl-*O*-acetylbuxalongifoline	$R_1=$NH-Bz; $R_2=$COH; $R_3=\alpha$-OH; $R_4=R_5=CH_3$	*B. longifolia*	[86]
234	16α-Acetoxy-buxabenzamidienine	$R_1=$NH-Bz; $R_2=R_4=R_5=CH_3$; $R_3=\alpha$-OAc	*B. longifolia*	[86]
235	Buxaminol C	$R_1=NHCH_3$; $R_2=R_4=R_5=CH_3$; $R_3=\alpha$-OH	*B. sempervirens*	[95]
236	Papilamine	$R_1=NHCH_3$; $R_2=R_5=CH_3$; $R_3=R_4=H$	*B. sempervirens*	[95]
237	16α-Hydro-xypapillamidine	$R_1=$NH-Ac; $R_2=R_4=R_5=CH_3$; $R_3=\alpha$-OH	*B. papillosa*	[109]
238	(+)-Benzoylbuxidienine	$R_1=$NH-Bz; $R_2=R_4=R_5=CH_3$; $R_3=\alpha$-OH	*B. hyrcana*	[110]
239	Buxamine F	$R_1=NH_2$; $R_2=R_4=R_5=CH_3$; $R_3=H$	*B. sempervirens*	[106]
240	N_{20}-Formylbuxaminol E	$R_1=N(CH_3)_2$; $R_2=CH_3$; $R_3=\alpha$-OH; $R_4=H$; $R_5=$COH	*B. sempervirens*	[111]
241	O_{16}-syringylbuxaminol E	$R_1=N(CH_3)_2$; $R_2=CH_3$; $R_3=\alpha$-O-Syr; $R_4=R_5=H$	*B. sempervirens*	[111]
242	N_{20}-acetylbuxamine G	$R_1=NHCH_3$; $R_2=CH_3$; $R_3=H$; $R_4=H$; $R_5=$Ac	*B. sempervirens*	[111]
243	N_{20}-acetylbuxamine E	$R_1=N(CH_3)_2$; $R_2=CH_3$; $R_3=H$; $R_4=H$; $R_5=$Ac	*B. sempervirens*	[111]
244	Buxakarachiamine	$R_1=$NH-COCH(OH)CH$(CH_3)_2$; $R_2=CH_2OH$; $R_3=H$; $R_4=R_5=CH_3$	*B. papillosa*	[100]
245	Buxahejramine	$R_1=$NH-COCH(OH)CH$(CH_3)CH_2CH$; $R_2=CH_2OH$; $R_3=H$; $R_4=R_5=CH_3$	*B. papillosa*	[100]
246	31-Demethylbuxaminol A	$R_1=N(CH_3)_2$; $R_2=H$; $R_3=\alpha$-OH; $R_4=R_5=CH_3$	*B. natalensis*	[104]
247	Buxaminol A	$R_1=N(CH_3)_2$; $R_2=R_4=R_5=CH_3$; $R_3=\alpha$-OH	*B. natalensis*	[104]
248	Moenjodarmine	$R_1=CH_3$; $R_2=R_3=H$; $R_4=N(CH_3)_2$	*B. hildebrandtii*; *B. hyrcana*	[91, 112]
249	N_b-Demethylharapamine	$R_1=CH_3$; $R_2=R_3=H$; $R_4=NH_2$	*B. papillosa*	[113]
250	Homomoenjodaramine	$R_1=R_2=CH_3$; $R_3=H$; $R_4=N(CH_3)_2$	*B. hyrcana*	[112]
251	Buxhyrcamine	$R_1=R_2=R_3=H$; $R_4=N(CH_3)_2$	*B. hyrcana*	[94]
252	Macowanioxazine	$R_1=CH_3$; $R_2=H$; $R_3=\alpha$-OH; $R_4=N(CH_3)_2$	*B. macowanii*	[114]
253	16α-Hydroxymacowanitriene	$R_1=CH_3$; $R_2=H$; $R_3=\alpha$-OH; $R_4=N(CH_3)_2$; $\triangle^{1,2}$	*B. macowanii*	[114]
254	Macowanitriene	$R_1=CH_3$; $R_2=R_3=H$; $R_4=N(CH_3)_2$; $\triangle^{1,2}$	*B. macowanii*	[114]
255	Papillotrienine	$R_1=\beta$-$NHCH_3$; $R_2=R_3=CH_3$	*B. papillosa*	[113]
256	N_b-Demethylpapilliotrienine	$R_1=\beta$-$NHCH_3$; $R_2=CH_3$; $R_3=H$	*B. papillosa*	[113]
257	Hyrcatrienine	$R_1=\beta$-NH-Bz; $R_2=R_3=CH_3$	*B. hyrcana*	[93]
258	31-Hydroxybuxatrienone	$R_1=O$; $R_2=CH_2OH$; $R_3=CH_3$	*B. macowanii*	[114]
259	O^2-Buxafuranamine	$R_1=H$; $R_2=H$	*B. hildebrandtii*	[115]
260	6-Hydroxy-O^2-buxafuranamine	$R_1=OH$; $R_2=H$	*B. hildebrandtii*	[115]
261	O^{10}-Buxafurana-mine	$R_1=$Bz; $R_2=OH$; $R_3=R_4=H$	*B. hildebrandtii*	[115]
262	O^{10}-Natafuranamine	$R_1=$Bz; $R_2=OH$; $R_3=\alpha$-OH; $R_4=H$	*B. natalensis*	[104]
263	Buxusemine B	$R_1=$Bz; $R_2=OH$; $R_3=\alpha$-OH; $R_4=O$	*B. sempervirens*	[108]
264	Buxusemine C	$R_1=$Bz; $R_2=R_3=R_4=H$	*B. sempervirens*	[108]
265	(−)-16-Hydroxybuxaminone	$R_1=CH_3$; $R_2=\alpha$-OH; $\triangle^{10,19}$	*B. sempervirens*	[97]
266	Semperviraminone	$R_1=CH_3$; $R_2=H$; $\triangle^{1,10}$; $\triangle^{16,17}$	*B. sempervirens*	[95]
267	N_a-Demethylsemperviraminone	$R_1=R_2=H$; $\triangle^{1,10}$; $\triangle^{16,17}$	*B. sempervirens*	[95]
268	Buxalongifolamidine	$R_1=R_4=H$; $R_2=$NH-Bz; $R_3=CH_2OH$; $R_5=\alpha$-OH; $R_6=\alpha$-OAc; $\triangle^{1,2}$; $\triangle^{9,11}$	*B. longifolia*	[107]
269	Semperviraminol	$R_1=\alpha$-OH; $R_2=$NH-Bz; $R_3=CH_3$; $R_4=\beta$-OAc; $R_5=/$; $R_6=H$; $\triangle^{1,10}$	*B. sempervirens*; *B. papillosa*	[100, 106]
270	*N*-Benzoylbuxahyrcanine	$R_1=R_4=R_6=H$; $R_2=$NH-Bz; $R_5=\beta$-OH; $R_3=CH_3$; $\triangle^{9,11}$	*B. hyrcana*	[116]
271	*N*-Tigloylbuxahyrcanine	$R_1=R_4=R_6=H$; $R_2=$NH-Tig; $R_3=CH_3$; $R_5=\beta$-OH; $\triangle^{9,11}$	*B. hyrcana*	[116]

Table 5 (continued)

No	Compounds	Substitution groups and others	Sources	References
272	*N*-Isobutyroyl-buxahyrcanine	$R_1=R_4=R_6=H$; $R_2=$Isobu; $R_3=CH_3$; $R_5=\beta$-OH; $\triangle^{9,11}$	*B. hyrcana*	[116]
273	Hyrcanone	$R_1=R_4=R_6=H$; $R_2=$NH-Bz; $R_3=CH_3$; $R_5=/$; 11-O; $\triangle^{1,10}$	*B. hyrcana*	[93]
274	2*α*,16*α*,31-Triacetyl-9,11-dihydrobuxiran	$R_1=R_6=\alpha$-OAc; $R_2=$NH-Bz; $R_3=CH_2$ OAc; $R_4=H$; $R_5=/$; $\triangle^{1,10}$	*B. hyrcana*	[117]
275	Macowamine	$R_1=R_4=R_5=R_6=H$; $R_2=NCH_3$-Van; $R_3=CH_2OH$; $\triangle^{9,11}$	*B. macowanii*	[114]
276	16*α*-Hydroxy-N_a-benzoylbuxadine	$R_1=R_4=H$; $R_2=$NH-Bz; $R_3=CH_3$; $R_5=\alpha$-OH; $R_6=$OH	*B. sempervirens*	[95]
277	N_b-Dimethylbuxupapine	$R_1=R_4=R_5=H$; $R_2=N(CH_3)_2$; $R_3=R_6=CH_3$	*B. papillosa*	[109]
278	(+)-16*α*,31-Diacetylbuxadine	$R_1=R_4=H$; $R_2=$NH-Bz; $R_3=CH_2OAc$; $R_5=\alpha$-OAc; $R_6=CH_3$	*B. sempervirens*	[92]
279	Hyrcanol	$R_1=\beta$-OH; $R_2=$NH-Bz; $R_3=R_6=CH_3$; $R_4=\alpha$-OAc; $R_5=H$	*B. hyrcana*	[93]
280	Buxabenzacinine	$R_1=R_3=H$; $R_2=$NH-Bz; $R_4=CH_2OAc$; $R_5=\alpha$-OH; $R_6=CH_3$	*B. hyrcana*	[93]
281	2*α*,16*α*,31-Triacetylbuxiran	$R_1=\alpha$-OAc; $R_2=$NH-Bz; $R_3=H$; $R_4=CH_2OAc$; $R_5=\alpha$-OAc; $R_6=CH_3$	*B. hyrcana*	[117]
282	Cyclovirobuxeine F	$R_1=R_2=H$	*B. longifolia*	[86]
283	(+)-O^6-Buxafurandiene	$R_1=\alpha$-OH; $R_2=\beta$-OH	*B. hyrcana*	[110]
284	(+)-7-deoxy-O^6-Buxafurandiene	$R_1=\alpha$-OH; $R_2=\beta$-H	*B. hyrcana*	[110]
285	2*α*,16*α*-Diacetoxy-9*β*,11b-epoxybuxamidine	$R_1=$OAc; $R_2=$Bz; $R_3=H$; $R_4=\alpha$-OAc	*B. papillosa*	[89]
286	Buxapapillinine	$R_1=$OAc; $R_2=$Bz; $R_3=\alpha$-OAc; $R_4=H$	*B. sempervirens*; *B. hyrcana*	[106, 110]
287	Buxusemine D	$R_1=R_4=H$; $R_2=$Bz; $R_3=\alpha$-OAc	*B. sempervirens*	[108]
288	Papillozine C		*B. papillosa*	[89]
289	Sempervirooxazolidine		*B. sempervirens*	[96]
290	Hyrcanine		*B. hyrcana*	[112]
291	Buxaquamarine		*B. hyrcana*	[110]
292	O^2-Natafuranamine		*B. natalensis*	[104]
293	17-Oxo-3-benzoylbuxadine		*B. hyrcana*	[94]

2.1.3.3 Jervine type The steroidal alkaloids of the jervine subgroup are hexacyclic compounds that have the tetrahydrofuran E ring fused onto a methylpiperidine F ring system forming an ether bridge between carbon atoms C_{17} and C_{23} (Fig. 9) [15]. The jervine type currently consists of 29 new members (**412—440**) from *Veratrum* and *Fritillaria* (Table 8).

Verdine (**412**) was first separated from the bulbs of *Veratrum dahuricum* in 1980 [191], and its structure was finally elucidated in 1984 by X-ray diffraction [192]. Two new steroidal alkaloids, kuroyurinidine (**417**) [193] and 23-isokuroyurinidine (**418**) [194], bearing C-2*β*, C-3*α*, and C-6*β* hydroxyl groups, were found in the genus *Fritillaria*. Whole plants of *Veratrum taliense* have yielded a novel steroidal alkaloid, 6,7-epoxyverdine (**437**), whose structure with an epoxide functionality at C-5/C-6 was determined by 2D NMR spectroscopic analysis [195]. Yibeinone A (**439**) features a jervine skeleton with a rare 12*α*,13*α*-epoxy ring [156].

2.1.3.4 Spirosolane type Spirosolane alkaloids (**441–526**) have a unique 1-oxa-6-azaspiro[4.5] decane ring system in ring E, which can form a spirosolane 22-*α* N type and 22-*β* N type (Fig. 10) [205]. They were reported from *Solanum* and *Lycopersicon* in the Solanaceae family, *Fritillaria meleagris* and *Lilium longiflorum* in the Liliaceae family (Table 9).

Spirosolane alkaloids generally occur as glycosides. Compounds **441– 451** have no double bond between C-5 and C-6, and the nitrogen atom in the F ring is always in the *α*-orientation (22-*α* N). Ring F can contain other moieties, such as hydroxyl or acetyl groups. Most glycosidic units are attached to the aglycone at the hydroxyl group at C-3, but some of them may be attached at other locations, such as C-6, C-7, C-23, C-25, and C-27. For example, esculeoside A (**448**) and lycotetraose G (**449**) have one glucose linked to ring-F at C-25 and C-23, respectively [206]. Compounds **474–515** are the largest members in spirosolane alkaloids, with 22-*β* N and double bonds between C-5 and C-6. Almost all spirosolane

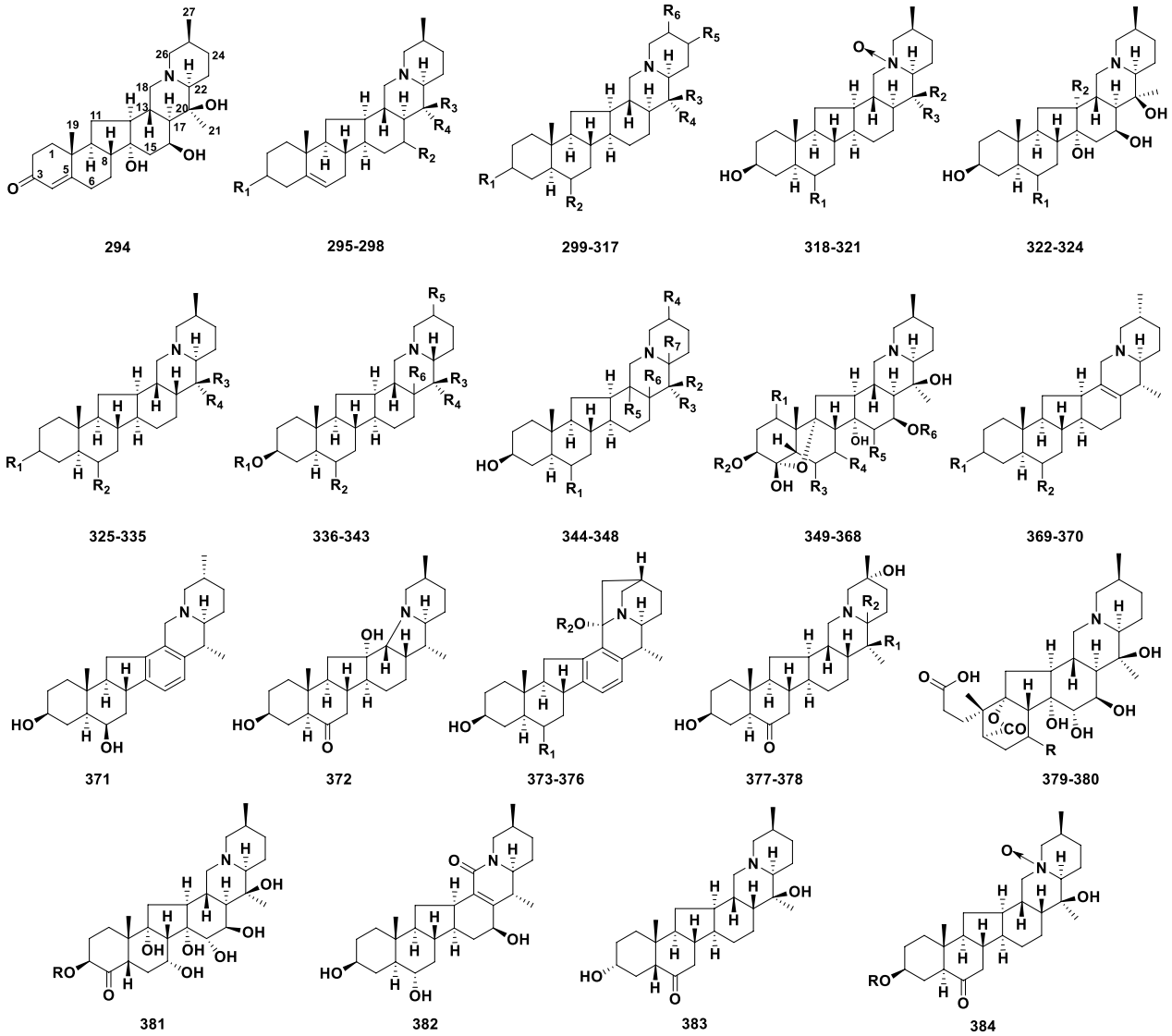


Fig. 7 Structures of cevanine type steroidal alkaloids **294–384**

alkaloids at C-16 are in the β-orientation, however, **504** is an exception since it possesses a 16 β-H in its E ring [207]. There are many substitutions and changes in these compounds, such as **475**, **478** and **498** have a hydroxy group on C-27 in the F ring, and **486**, **497**, **499** and **507** have a hydroxy group on C-12 in the C ring. Five rare C-3 amino spirosolane alkaloids, **517–521** [208, 209] were isolated from aerial parts of the genus *Solanum.*

2.1.3.5 Solanidine type In the solanidine type, the side-chain of a C_{27} steroid has been converted into an indolizidine ring (Fig. 11). Solanidine alkaloids (**527–555**) currently include 29 novel members from *Veratrum*, *Fritillaria* and *Solanum* (Table 10).

α-Solanine (**528**) was found mainly in the tuber of potato (*Solanum tuberosum* L.) and in the whole plant of the nightshade (*Solanum nigrum* Linn.) of the Solanaceae family [255]. The bulbs of *F. delavayi* yielded (22*R*,25*S*)-solanid-5-enine-3β,5α,6β-triol (**550**) [133], the first example with a glycol moiety at the A- and B-rings in the group of solanidine alkaloids. An investigation of *V. dahuricum* furnished unusual glycoalkaloid **552** [194], which represents the first member of a new class with a 15,16-secosolanida-5,14-diene skeleton. The two novel compounds, **553** [256] and **554** [257], bearing a methylene substituent at C-20 and C-7, respectively, were structurally elucidated by extensive 2D NMR analysis.

Table 6 Structures and sources of cevanine type steroidal alkaloids **294–384**

No	Compounds	Substitution groups and others	Sources	References
294	Veratrenone		*Veratrum album*	[118]
295	Shinonomenine	$R_1=\beta$-OH; $R_2=R_4=H$; $R_3=CH_3$	*V. grandiflorum*	[127]
296	Veraflorizine	$R_1=\beta$-OH; $R_2=H$; $R_3=OH$; $R_4=CH_3$	*V. grandiflorum*	[127]
297	Fritillarizine	$R_1=\alpha$-OH; $R_2=H$; $R_3=OH$; $R_4=CH_3$	*Fritillaria verticillata*	[128]
298	Veramarine-3-yl formate	$R_1=\beta$-OCOH; $R_2=\beta$-OH; $R_3=OH$; $R_4=CH_3$	*Veratrum nigrum*	[129]
299	Baimonidine:	$R_1=\alpha$-OH; $R_2=\beta$-OH; $R_3=OH$; $R_4=CH_3$; $R_5=H$; $R_6=\beta$-CH_3	*Fritillaria verticillata*	[130]
300	Isoverticine	$R_1=R_2=\beta$-OH; $R_3=OH$; $R_4=CH_3$; $R_5=H$; $R_6=\beta$-CH_3	*F. verticillata*	[130]
301	Isobaimonidine	$R_1=R_2=\alpha$-OH; $R_3=OH$; $R_4=CH_3$; $R_5=H$; $R_6=\beta$-CH_3	*F. verticillata*	[119]
302	3-β-D-Petilinineglucoside	$R_1=$D-Glc; $R_2=\alpha$-OH; $R_3=H$; $R_4=CH_3$; $R_5=H$; $R_6=\alpha$-CH_3	*Fritillaria ussuriensis*	[131]
303	Ebeiedinone	$R_1=\beta$-OH; $R_2=O$; $R_3=H$; $R_4=CH_3$; $R_5=H$; $R_6=\beta$-CH_3	*F. ebeiensis*	[132]
304	Delafrine	$R_1=R_2=\beta$-OH; $R_3=CH_3$; $R_4=H$; $R_5=H$; $R_6=\beta$-CH_3	*F. delavayi*	[133]
305	Delafrinone	$R_1=\beta$-OH; $R_2=O$; $R_3=CH_3$; $R_4=H$; $R_5=H$; $R_6=\beta$-CH_3	*F. delavayi*	[133]
306	Zhebeinine	$R_1=\beta$-OH; $R_2=\alpha$-OH; $R_3=OH$; $R_4=CH_3$; $R_5=H$; $R_6=\alpha$-CH_3	*F. thunbergii*	[134]
307	Puqiedinone	$R_1=\beta$-OH; $R_2=O$; $R_3=H$; $R_4=CH_3$; $R_5=H$; $R_6=\alpha$-CH_3	*F. puqiensis*	[135]
308	Zhebeinone	$R_1=\beta$-OH; $R_2=O$; $R_3=OH$; $R_4=CH_3$; $R_5=H$; $R_6=\alpha$-CH_3	*F. thunbergii*	[136]
309	Dongbeinine	$R_1=\beta$-OH; $R_2=O$; $R_3=CH_3$; $R_4=H$; $R_5=H$; $R_6=\beta$-CH_3	*F. thunbergii*	[137]
310	Dongbeirine	$R_1=\beta$-OH; $R_2=O$; $R_3=CH_3$; $R_4=H$; $R_5=H$; $R_6=\alpha$-CH_3	*F. thunbergii*	[137]
311	Ebeiedine	$R_1=R_2=\beta$-OH; $R_3=H$; $R_4=CH_3$; $R_5=H$; $R_6=\beta$-CH_3	*F. ebeiensis*	[138]
312	Impericine	$R_1=R_2=\beta$-OH; $R_3=CH_3$; $R_4=H$; $R_5=H$; $R_6=\beta$-CH_3; $\triangle^{23,24}$	*F. imperialis*	[139]
313	Forticine	$R_1=R_2=\beta$-OH; $R_3=CH_3$; $R_4=H$; $R_5=H$; $R_6=\beta$-CH_3	*F. imperialis*	[139]
314	Lichuanine	$R_1=R_2=\beta$-OH; $R_3=CH_3$; $R_4=H$; $R_5=H$; $R_6=\alpha$-CH_3	*F. lichuanensis*	[140]
315	Puqiedine	$R_1=R_2=\beta$-OH; $R_3=H$; $R_4=CH_3$; $R_5=H$; $R_6=\alpha$-CH_3	*F. puqiensis*	[141]
316	3α-Puqiedin-7-ol	$R_1=R_3=\alpha$-OH; $R_2=\beta$-OH; $R_4=H$; $R_5=H$; $R_6=\beta$-CH_3	*F. puqiensis*	[141]
317	Yibeinone F	$R_1=O$-β-D-Glc; $R_2=\alpha$-OH; $R_3=H$; $R_4=CH_3$; $R_5=\alpha$-OH; $R_6=\beta$-CH_3	*F. pallidiflora*	[142]
318	Verticine *N*-oxide	$R_1=\alpha$-OH; $R_2=OH$; $R_3=CH_3$	*F. thunbergii*	[143]
319	Verticinone *N*-oxide	$R_1=O$; $R_2=OH$; $R_3=CH_3$	*F. thunbergii*	[143]
320	Isoverticine-β-*N*-oxide	$R_1=\beta$-OH; $R_2=OH$; $R_3=CH_3$	*F. wabuensia*	[144]
321	Lichuanisinine	$R_1=\beta$-OH; $R_2=CH_3$; $R_3=H$	*F. lichuanensis*	[140]
322	Pingbeimine A	$R_1=\alpha$-OH; $R_2=H$	*F. ussuriensis*	[145]
323	Pingbeimine B	$R_1=\alpha$-OH; $R_2=OH$	*F. ussuriensis*	[146]
324	Pingbeimine C	$R_1=O$; $R_2=H$	*F. ussuriensis*	[147]
325	Delavine	$R_1=R_2=\beta$-OH; $R_3=H$; $R_4=CH_3$	*F. delavayi*	[148]
326	Hupeheninoside	$R_1=\beta$-D-Glc; $R_2=\beta$-OH; $R_3=H$; $R_4=CH_3$	*F. hupehensis*	[149]
327	Delavinone	$R_1=R_3=H$; $R_2=O$; $R_4=CH_3$	*F. delavayi*	[148]
328	Hupehenirine	$R_1=O$; $R_2=\beta$-OH; $R_3=H$; $R_4=CH_3$	*F. hupehensis*	[150]
329	Yibeinoside A	$R_1=O$-β-D-Glc; $R_2=O$; $R_3=H$; $R_4=CH_3$	*F. pallidiflora*	[151]
330	Hupehemonoside	$R_1=\beta$-D-Glc; $R_2=O$; $R_3=OH$; $R_4=CH_3$	*F. delavayi*	[152]
331	Delavine-3-*O*-β-D-Glucopyranoside	$R_1=O$-β-D-Glc; $R_2=\beta$-OH; $R_3=H$; $R_4=CH_3$	*F. persica*	[153]
332	Yubeinine	$R_1=\alpha$-OH; $R_2=O$; $R_3=OH$; $R_4=CH_3$	*F. yuminensis*	[154]
333	Yubeiside	$R_1=O$; $R_2=\beta$-*O*-β-D-Glc; $R_3=R_4=H$	*F. yuminensis*	[154]
334	Hupeheninate	$R_1=Ac$; $R_2=\beta$-OH; $R_3=H$; $R_4=CH_3$	*F. delavayi*	[155]
335	Imperialine	$R_1=\beta$-OH; $R_2=O$; $R_3=OH$; $R_4=CH_3$	*F. pallidiflora*	[156]
336	Chuanbeinone	$R_1=R_3=H$; $R_2=O$; $R_4=CH_3$; $R_5=\beta$-CH_3; $R_6=\beta$-H	*F. delavayi*	[157]
337	Hareperminside	$R_1=$D-Glc; $R_2=\beta$-OH; $R_3=H$; $R_4=CH_3$; $R_5=\alpha$-CH_3; $R_6=\beta$-H	*F. karelinii*	[158]
338	Tortifoline	$R_1=R_4=H$; $R_2=\beta$-OH; $R_3=CH_3$; $R_5=\beta$-CH_3; $R_6=\beta$-H	*F. tortifolia*	[159]
339	Siechuansine	$R_1=H$; $R_2=\alpha$-OH; $R_3=OH$; $R_4=CH_3$; $R_5=\alpha$-CH_3; $R_6=\beta$-H	*F. siechuanica*	[160]
340	Songbeinone	$R_1=R_4=H$; $R_2=O$; $R_3=CH_3$; $R_5=\beta$-CH_3; $R_6=\beta$-H	*F. unibracteata*	[161]
341	Yibeinoside B	$R_1=$D-Glc; $R_2=O$; $R_3=H$; $R_4=CH_3$; $R_5=\beta$-CH_3; $R_6=\beta$-H	*F. pallidiflora*	[151]
342	Persicanidine B/Harepermine	$R_1=R_3=H$; $R_2=\beta$-OH; $R_4=CH_3$; $R_5=\alpha$-CH_3; $R_6=\beta$-H	*F. karelinii*; *F. persica*	[158, 162]

Table 6 (continued)

No	Compounds	Substitution groups and others	Sources	References
343	Yibeinone D	R_1 = D-Glc; R_2 = O; R_3 = CH_3; R_4 = OH; R_5 = β-CH_3; R_6 = α-H	*F. pallidiflora*	[156]
344	Wanpeinine A	R_1 = α-OH; R_2 = OH; R_3 = CH_3; R_4 = β-CH_3; R_5 = α-H; R_6 = R_7 = β-H	*F. anhuiensis*	[163]
345	Persicanidine A	R_1 = β-OH; R_2 = H; R_3 = CH_3; R_4 = α-CH_3; R_5 = R_7 = α-H; R_6 = β-H	*F. persica*	[164]
346	Yibeirine	R_1 = β-OH; R_2 = OH; R_3 = CH_3; R_4 = β-CH_3; R_5 = R_7 = β-H; R_6 = α-H	*F. pallidiflora*	[123]
347	Yibeinone C	R_1 = O; R_2 = OH; R_3 = CH_3; R_4 = α-CH_3; R_5 = R_7 = β-H; R_6 = α-H	*F. pallidiflora*	[156]
348	Yibeinone E	R_1 = O; R_2 = CH_3; R_3 = H; R_4 = α-CH_3; R_5 = R_6 = α-H; R_7 = H	*F. pallidiflora*	[165]
349	Germaline	R_1 = R_3 = R_6 = H; R_2 = COC(OH)(CH_3)CH(OAc)CH_3; R_4 = α-OH; R_5 = α-*O*-2-methylbutyroyl	*Veratrum. lobelianum*	[166]
350	Germatetrine	R_1 = R_3 = R_6 = H; R_2 = COC(OH)(CH_3)CH(OAc)CH_3; R_4 = α-OAc; R_5 = α-*O*-2-methylbutyroyl	*V. lobelianum*	[166]
351	Stenophylline A	R_1 = R_3 = R_6 = H; R_2 = Ang; R_4 = α-OH; R_5 = α-O-Ang	*V. stenophyllum*	[167]
352	Maackinine	R_1 = R_3 = R_6 = H; R_2 = Ang; R_4 = α-OAc; R_5 = α-O-Ang	*V. maackii*	[168]
353	Verussurinine	R_1 = R_2 = R_3 = H; R_4 = R_5 = α-OH; R_6 = 2-methylbutyroyl	*V. nigrum var. ussuriense*	[169]
354	Verussurine	R_1 = R_3 = R_6 = H; R_2 = Ver; R_4 = α-OAc; R_5 = α-OCOCH(CH_3)CH_2CH_3	*V. nigrum var. ussuriense*	[170]
355	Verabenzoamine	R_1 = R_3 = R_6 = H; R_2 = Ver; R_4 = α-OH; R_5 = α-OCOCH(CH_3)CH_2CH_3	*V. nigrum var. ussuriense*	[170]
356	Angeloylzygadenine	R_1 = R_3 = R_4 = R_6 = H; R_2 = Ang; R_5 = α-OH	*V. viride*	[171]
357	Zygadenine	R_1 = R_2 = R_3 = R_4 = R_6 = H; R_5 = α-OH	*V. viride*	[171]
358	Germine	R_1 = R_2 = R_3 = R_6 = H; R_4 = β-OH; R_5 = α-OH	*V. viride*	[171]
359	15-*O*-Methylbutyroylgermine	R_1 = R_2 = R_3 = R_6 = H; R_4 = β-OH; R_5 = α-O-Methylbutyroyl	*V. viride*	[171]
360	Neojerminalanine	R_1 = α-OAc; R_2 = R_3 = R_6 = H; R_4 = α-OH; R_5 = α-OOCOCH(CH_3)CH_2CH_3	*V. album*	[172]
361	15-Angeloylgermine	R_1 = R_2 = R_3 = R_6 = H; R_4 = α-OH; R_5 = Ang	*V. taliense*	[173]
362		R_1 = R_3 = R_6 = H; R_2 = Ac; R_4 = α-OAc; R_5 = Ang	*V. dahuricum*	[174]
363		R_1 = R_3 = R_5 = R_6 = H; R_2 = Ver; R_4 = α-OH	*V. dahuricum*	[174]
364		R_1 = R_3 = R_6 = H; R_2 = Ac; R_4 = α-OH; R_5 = Ang	*V. dahuricum*	[174]
365		R_1 = R_3 = R_6 = H; R_2 = Ver; R_4 = α-OH; R_5 = Ang	*V. dahuricum*	[174]
366	15-*O*-(2-Methylbutanoyl)-3-*O*-veratroylprotoverine	R_1 = R_6 = H; R_2 = Ver; R_3 = R_4 = α-OH; R_5 = α-OCOCH(CH_3)CH_2CH_3	*V. nigrum*	[175]
367	Veramadine A	R_1 = R_3 = R_5 = R_6 = H; R_2 = Ver; R_4 = α-OH	*V. maackii var. japonicum*	[176]
368	Veramadine B	R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H	*V. maackii var. japonicum*	[176]
369	Ebeienine	R_1 = R_2 = β-OH	*Fritillaria ebeiensis*	[138]
370	Ziebeimine	R_1 = α-OH; R_2 = β-OH	*F. ebeiensis*	[132]
371	Heilonine		*F. ussuriensis*	[121]
372	Pingbeinone		*F. ussuriensis*	[120]
373	Ussuriedine	R_1 = β-OH; R_2 = H	*F. ussuriensis*	[177]
374	Ussuriedinone	R_1 = O; R_2 = H	*F. ussuriensis*	[177]
375	Ussurienine	R_1 = β-OH; R_2 = CH_3	*F. ussuriensis*	[177]
376	Ussurienone	R_1 = O; R_2 = CH_3	*F. ussuriensis*	[177]
377	Taipaienine	R_1 = H; R_2 = β-H	*F. taipaiensis*	[122]
378	Yibeisine	R_1 = OH; R_2 = α-H	*F. pallidiflora*	[123]
379	Neoverataline A	R = H	*Veratrum taliense*	[125]
380	Neoverataline B	R = α-OH	*V. taliense*	[125]
381		R = Ver	*V. nigrum*	[126]
382	Frithunbol A		*Fritillaria thunbergii*	[178]
383	Frititorine A		*F. tortifolia*	[124]
384	Frititorine B	R = D-Glc	*F. tortifolia*	[124]

2.1.3.6 Verazine type Members of the verazine type, having a 22/23,26-epiminocholestane skeleton, are characterized by the absence of ring E and the presence of a piperidine ring D and consist of 46 new members (**556–601**) (Fig. 12). They were obtained from *Veratrum*, *Fritillaria*, *Allium victorialis* and *Zygadenus sibiricus* in the

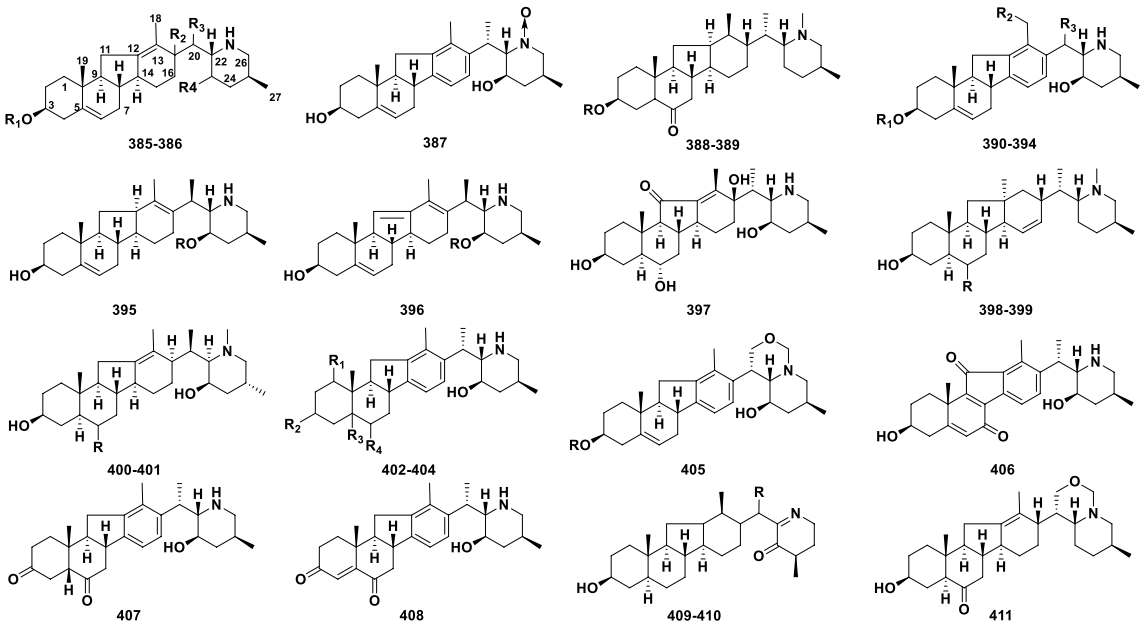


Fig. 8 Structures of veratramine type steroidal alkaloids **385–411**

Liliaceae family, and only one *Solanum* species, *Solanum Hypomalacophyllum* (Table 11).

The alkaloidal fraction of *Veratrum stenophyllum* gave a new 3*β*,20*β*-dihydroxy-$\triangle^5$–22,26-epiminocholestane alkaloid, Stenophylline B (**564**). Its structure was established on the basis of spectroscopic comparisons with known verazine-type alkaloids [268]. Rhamnoveracintine (**576**), having a five-membered heterocyclic ring and L-rhamnose as structural features, is the first example of a C_{26} steroidal alkaloid from the aerial parts of a *Veratrum* species [269]. Ebeietinone (**586**), the first example of a verazine type alkaloid with a 5*β*-hydroxyl group, was structurally assigned based on MS and NMR and confirmed by X-ray crystallography [270]. Verdinine (**587**) [271], fetisinine (**588**) [179] and isoecliptalbine (**597**) [203], exhibiting a pyridine ring as a structural feature, were pyridyl-pregnane-type steroidal alkaloids, and their structural assignment was performed by extensive spectroscopic techniques and some chemical transformations.

2.1.3.7 Others Two distinctive alkaloids, veragranine A (**602**) and veragranine B (**603**), featuring a 6/6/6/5/6/6 polycyclic structure (Fig. 13), in which a previously unidentified linkage of C-12/23 generates a rigid skeleton, resulting in a new subtype of cholestane steroidal alkaloid, were isolated from *Veratrum grandiflorum* [290].

2.1.4 Miscellaneous monomeric steroidal alkaloids

2.1.4.1 Samandarines Approximately 11 samandarines (**604–614**) are a unique class of steroidal alkaloids isolated and characterized from terrestrial salamanders of the genus *Salamandra* (Table 12). They differ from other types since they are built by a seven-membered A-ring with nitrogen at position 3. Therefore, they belong to the uncommon group of 3-aza-A-homo-5*α*,10*α*-androstans, an androstane with an N-enlarged A-ring (Fig. 14) [291].

Samandarines can be further grouped according to their constitution. The first group consists of molecules with an oxazolidine system present, including **604–607**, **608** and **610–612**. Members of the second group, e.g. cycloneosamandion (**609**), lack an intact oxazolidine system, whereas they share a carbinolamine function [292]. A third group consists of samandarines in which both the oxazolidine system and the carbinolamine group are missing, and only samanine (**613**) and samanone (**614**) were described from this group.

2.1.4.2 Batrachotoxins Only 7 batrachotoxins (**615–621**) were isolated in minute quantities from the skins of poison arrow frogs (*Phyllobates aurotaenia*) as well as from the skins and feathers of New Guinea birds (genus *Pitohui* and *Iflita*) (Table 13). They exhibit novel structural features, including a steroid-based pentacyclic core skeleton, an intramolecular 3-hemiketal, and a seven-membered oxazapane ring (Fig. 15) [301].

The structure of pseudobatrachotoxin (**616**) is the 20*α*-p-bromobenzoate of batrachotoxinin A (**615**) [302]. Batrachotoxin (**617**) is the 20*α* ester of **615** with 2,4-dimethylpyrrole-3-carboxylic acid [302], while homobatrachotoxin (**618**) is the 20*α* ester of **615** with

Table 7 Structures and sources of veratramine type steroidal alkaloids **385–411**

No	Compounds	Substitution groups and others	Sources	References
385	Hosukinidine	$R_1=R_2=R_4=H$; $R_3=\beta$-CH_3	*Veratrum grandiflorum*	[180]
386	Veratramanol A	$R_1=X$; $R_2=\beta$-H; $R_3=\alpha$-CH_3; $R_2=\beta$-OAc	*Veratrum maackii var. japonicum*	[181]
387	Veratramine-*N*-oxide		*V. mentzeanum*	[182]
388	Ningpeisine	R=H	*Fritillaria ningguoensis*	[183]
389	Ningpeisinoside	R=D-Glc	*F. ningguoensis*	[183]
390	20-Isoveratramine	$R_1=H$; $R_2=H$; $R_3=\beta$-CH_3	*Veratrum patulum*	[184]
391	Veratramine-3-yl acetate	$R_1=Ac$; $R_2=H$; $R_3=\alpha$-CH_3	*V. nigrum*	[129]
392	Veratramine	$R_1=H$; $R_2=H$; $R_3=\alpha$-CH_3	*V. dahuricum*	[185]
393	Veratrosine	$R_1=$D-Glc; $R_2=H$; $R_3=\alpha$-CH_3	*V. dahuricum*	[185]
394	Veratravine E	$R_1=H$; $R_2=OH$; $R_3=\alpha$-CH_3	*Veratrum taliense*	[186]
395	23-*O*-β-D-Glucopyranosyl-20-isoveratramine	R=D-Glc	*V. patulum*	[187]
396	(22*S*,23*R*,25*S*)-23-*O*-β-D-glucopyranosyl-5,11,13-veratratriene-3b,23-diol	R=D-Glc	*V. patulum*	[187]
397	Veramarine		*V. album*	[172]
398	Impranine	R=O	*Fritillaria imperialis*	[179]
399	Dihydroimpranine	R=β-OH	*F. imperialis*	[179]
400	Puqienine A	R=β-OH	*F. puqiensis*	[188]
401	Puqienine B	R=O	*F. puqiensis*	[188]
402	Yibeinone B	$R_1=H$; $R_2=\beta$-OH; $R_3=\alpha$-H; $R_4=O$	*F. pallidiflora*	[156]
403	Veratravine F	$R_1=\alpha$-OH; $R_2=\alpha$-OH; $R_3=\beta$-H; $R_4=H$	*Veratrum taliense*	[186]
404	Veratravine G	$R_1=\alpha$-OH; $R_2=\beta$-OH; $R_3=\beta$-H; $R_4=H$	*Veratrum taliense*	[186]
405	Veratravine A	R=D-Glc	*Veratrum taliense*	[186]
406	Veratravine B		*Veratrum taliense*	[186]
407	Veratravine C		*Veratrum taliense*	[186]
408	Veratravine D		*Veratrum taliense*	[186]
409	$\triangle^5$(20*R*,24*R*)23-oxo-24-methylsolacongetidine	R=β- CH_3	*Veratrum grandiflorum*	[189]
410	$\triangle^5$(20*S*,24*R*)23-oxo-24-methylsolacongetidine	R=α-CH_3	*V. grandiflorum*	[189]
411	Zhebeisine		*Fritillaria thunbergii*	[190]

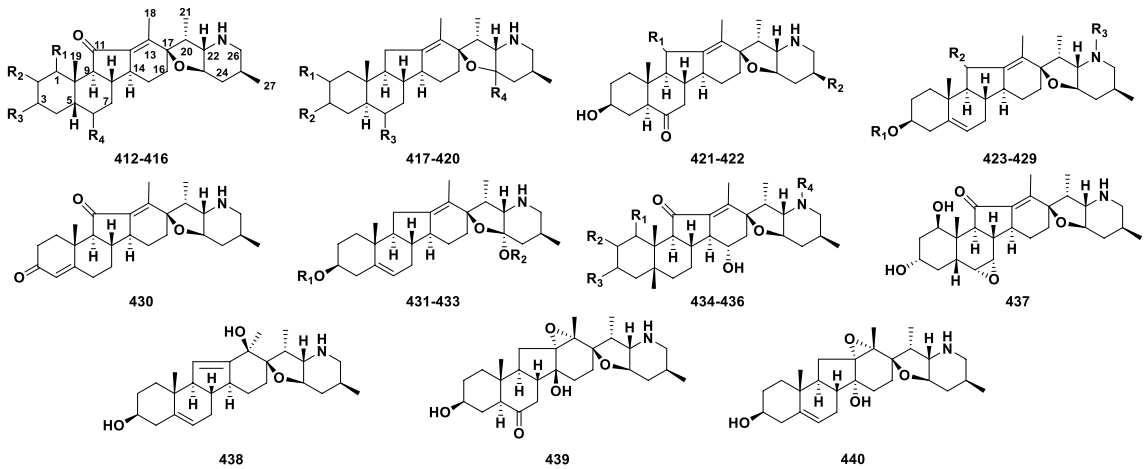


Fig. 9 Structures of jervine type steroidal alkaloids **412–440**

Table 8 Structures and sources of jervine type steroidal alkaloids **412–440**

No	Compounds	Substitution groups and others	Sources	References
412	Verdine	R_1 = β-OH; R_2 = H; R_3 = R_4 = α-OH	*Veratrum dahuricum*	[191]
413	1-Hydroxy-5,6-dihydrojervine	R_1 = α-OH; R_2 = R_4 = H; R_3 = β-OH	*V. album*	[196]
414	2β-Hydroxyverdine	R_1 = R_2 = β-OH; R_3 = R_4 = α-OH	*V. dahuricum*	[197]
415	(1β,3α,5β)-1,3-Dihydroxyjervanin-12-en-11- one	R_1 = β-OH; R_2 = R_4 = H; R_3 = α-OH	*V. nigrum*	[198]
416	Veratraline C	R_1 = R_3 = α-OH; R_2 = R_4 = H	*V. taliense*	[199]
417	Kuroyurinidine	R_1 = β-OH; R_2 = α-OH; R_3 = β-OH; R_4 = α-H	*Fritillaria camtschatcensis*	[193]
418	23-Isokuroyurinidine	R_1 = β-OH; R_2 = α-OH; R_3 = β-OH; R_4 = β-H	*F. maximowiczii*	[194]
419	Frithunbol B	R_1 = H; R_2 = β-OH; R_3 = O; R_4 = β-H	*F. thunbergii*	[178]
420	Frititorinec	R_1 = H; R_2 = α-OH; R_3 = O; R_4 = α-H	*Fritillaria tortifolia*	[124]
421	Yibeissine	R_1 = β-OH; R_2 = β-CH_3	*F. pallidiflora*	[200]
422	Tortifolisine	R_1 = H; R_2 = α-CH_3	*F. tortifolia*	[201]
423	Verapatulin	R_1 = H; R_2 = O; R_3 = $COOCH_3$	*Veratrum patulum*	[184]
424	*O*-Acetyljervine	R_1 = Ac; R_2 = O; R_3 = H	*V. album*	[202]
425	Methyljervine-*N*-3′-propanoate	R_1 = H; R_2 = O; R_3 = $(CH_2)_2COOCH_3$	*V. album*	[202]
426	Neoverapatuline	R_1 = H; R_2 = α-OH; R_3 = $COOCH_3$	*V. nigrum*	[198]
427	Jervine	R_1 = R_3 = H; R_2 = O	*V. dahuricum*	[185]
428	Jervine-3-yl formate	R_1 = COH; R_2 = O; R_3 = H	*V. nigrum*	[129]
429	Veratraline A	R_1 = H; R_2 = O; R_3 = CH_2NHAc	*V. taliense*	[199]
430	Jervinone		*V. album*	[196]
431	23-Methoxycyclopamine	R_1 = H; R_2 = CH_3	*V. nigrum*	[175]
432	Cyclopamine	R_1 = R_2 = H	*V. californicum*	[4]
433	23-methoxycyclopamine 3-*O*-β-D-glucopyranoside	R_1 = D-Glc; R_2 = CH_3	*V. maackii*	[203]
434	Veraussine A	R_1 = R_3 = α-OH; R_2 = β-OH; R_4 = COOEt	*V. nigrum var. ussuriense*	[204]
435	Veraussine B	R_1 = R_3 = α-OH; R_2 = β-OH; R_4 = $COOCH_3$	*V. nigrum var. ussuriense*	[204]
436	(1β,3β,5β)-1,3-Dihydroxyjervanin-12(13)-en-11-one	R_1 = R_3 = β-OH; R_2 = R_4 = H	*V. nigrum*	[129]
437	6,7-Epoxyverdine		*V. taliense*	[195]
438	Jerv-5,11-diene-3β,13β-diol		*V. nigrum*	[129]
439	Yibeinone A		*Fritillaria pallidiflora*	[156]
440	Veratraline B		*Veratrum taliense*	[199]

2-ethyl-4-methylpyrrole-3-carboxylic acid [303]. These structures were confirmed by partial synthesis of batrachotoxin selective acylation.

2.1.4.3 Plakinamines Considerable research effort has been focused on the discovery of new bioactive natural products from marine animals. A number of new steroidal alkaloids have been isolated in the process, mostly from marine invertebrates. A marine sponge of the genus *Plakina* and *Corticium* sp. yielded nineteen new steroidal alkaloids (**622–640**), namely, plakinamine (Table 14). Plakinamines have modified ergostane-type steroidal cores, as they possess nitrogen substitution at C-3 in the A ring and linear or cyclized nitrogenous side chains (Fig. 16) [305].

Plakinamine G (**630**) bearing a rare side chain with an α,β-unsaturated γ-lactam ring was structurally assigned by 2D NMR spectroscopy and accurate mass measurements (HR-EIMS) [306]. Most plakinamines contain a substituted pyrrolidine ring in the steroidal side chain, only in plakinamine I (**633**) the pyrrolidine nitrogen forms an additional fused piperidine ring system [307]. The first natural representative of steroidal alkaloids with a double bond at C-2 and an amine substituent at C-4 was plakinamine J (**634**) [307]. Three new steroidal alkaloids, plakinamine L, M and P (**638–640**), have unprecedented acyclic side chains, while other compounds contain cyclized nitrogenous side chains.

2.1.4.4 Cortistatins Kobayashi et al. isolated a new family of abeo-9(10-19)-androstane-type steroidal alkaloids with oxabicyclo[3.2.1]octane called cortistatins, from the Indonesian marine sponge *Corticium simplex* (Fig. 17, Table 15) [314]. Up to now, this family has 11 members (**641–651**), with the B and C rings connected through an interesting and characteristic oxo-bridge.

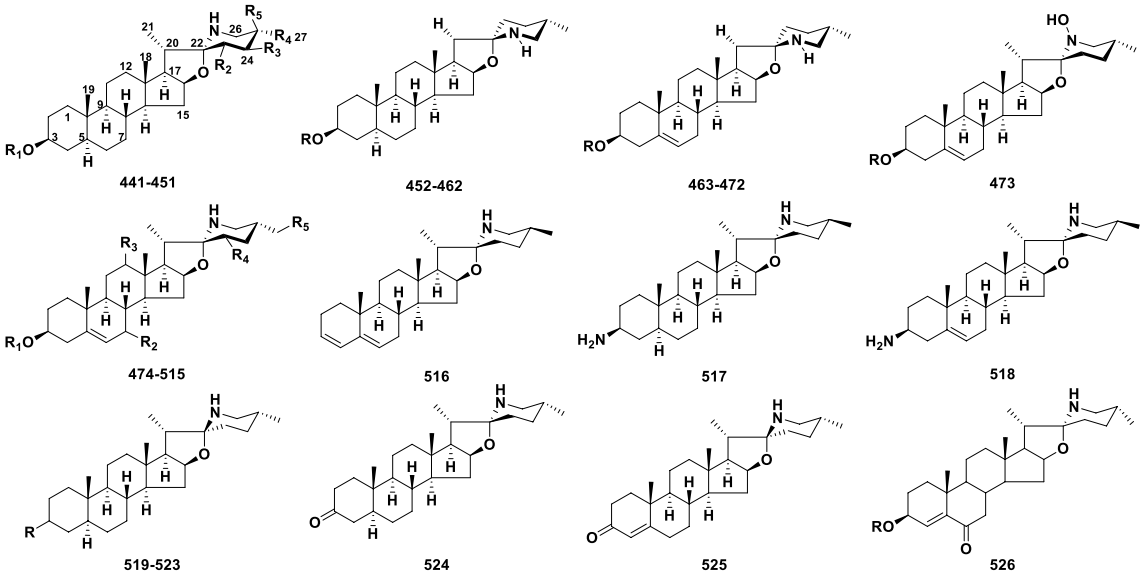


Fig. 10 Structures of spirosolane type steroidal alkaloids **441–526**

Cortistatins A–D (**641–644**) and J–L (**651, 648–649**) have a 5-membered E-ring decorated with a unique isoquinoline moiety at C-17.

2.2 Dimeric steroidal alkaloids

2.2.1 Cephalostatins

The 20 cephalostatins (**652–671**) have been isolated only in one marine organism: *Cephalodiscus gilchristi*, a tiny marine worm predominantly found in shallow and temperate waters (Table 16). The structure of cephalostatins, characterized by an adissymmetric bis-steroidal pyrazine framework, consisting of 13 rings is quite unusual (Fig. 18) [20].

The atypical C-22′ spiroketals involving C-18′ in most cephalostatins 1–4 (**652–654**, **659**), 9–11 (**664**, **655–656**), 14–19 (**668–671**, **657–658**) and C-12′ in cephalostatins 5 (**660**) and cephalostatins 6 (**661**) are also noteworthy. Cephalostatins 10 (**655**), 11 (**656**) [318], and 13 (**667**) [319] with an oxygen substituent (OMe or OH) at the 1α- or 1′α-positions, close to the central pyrazine ring, are rare in this type alkaloids. Both cephalostatins 5 (**660**) and 6 (**661**) contain an aromatic C′ ring that is rather unusual in naturally occurring steroids [320]. The only symmetric cephalostatin 12 (**666**) containing two identical steroid units is unique [319]. Cephalostatin 16 (**670**), the only compound contains the [4.5] spiroketal system with the unusual 22*S* configuration (not yet confirmed by synthesis) in the right side steroid unit, whereas other cephalostatins have a common [4.4] spiroketal system in the right steroidal unit [321].

2.2.2 Ritterazines

The ritterazine class of steroidal alkaloids comprises 26 compounds (**672–697**), all of which were found in the lipophilic extract of the tunicate *Ritterella tokioka* collected off the Izu Peninsula by Fusetani and colleagues (Table 17). They are spiroketal-containing steroidal heterodimers (Fig. 19). Ritterazines and cephalostatins share common structural features, in which two highly oxygenated hexacyclic steroidal units are fused via a pyrazine ring at C-2 and C-3 and both side chains of the steroidal units form either [4.4] or [4.5] spiroketals [20].

The hydroxyl groups of cephalostatins at C-12, C-17, C-23, and C-26 are more oxygenated in the right side hemispheres than in ritterazines, which is hydroxylated only at C-12, while the left side hemisphere ritterazines are more oxygenated, with C-7′, C-12′, C-17′ and C-25′ being hydroxylated. All cephalostatins contain β-hydroxyl oxygen substituents at the C-12 position, while some ritterazines bear carbonyl groups at this position. In the original paper, the configuration of ritterazine B (**674**) at the spiro carbon atom was mistaken for the same as in cephalostatin 1 in 1995 [328]. However, this has been recently revised by Phillips and Shair, who synthesized the right half of ritterazine B in 2007 [329]. Ritterazines J–M (**683–686**), exhibited the presence of the [4.5] spiroketal system on both sides of the alkaloid molecule, but only one of them, ritterazine K (**684**), was symmetrical [330]. In the original paper ritterazine M (**686**) was erroneously assigned as the *S* configuration at C-22, along with an incorrect configuration at C-12 [330]. A chemical synthesis of this compound by Fuchs

Table 9 Structures and sources of spirosolane type steroidal alkaloids **441–526**

No	Compounds	Substitution groups and others	Sources	References
441	*β*-Soladulcine	R_1 = Solatriose; R_2 = R_3 = R_5 = H; R_4 = CH_3	*Solanum dulcamara*	[210]
442	Soladulcidine	R_1 = R_2 = R_3 = R_4 = R_5 = H	*S. dulcamara*	[211]
443	Soladulcine A	R_1 = Chacotriose; R_2 = R_3 = R_5 = H; R_4 = CH_3	*S. dulcamara*	[212]
444	Soladulcine B	R_1 = Lycotetraose; R_2 = R_3 = R_5 = H; R_4 = CH_3	*S. dulcamara*	[212]
445	Dihydrosolasuaveoline	R_1 = L-Rha-(1 → 2)-[D-Glc-(1 → 2)-D-Glc-(1 → 4)]-D-Gal; R_2 = R_3 = R_5 = H; R_4 = CH_3	*S. suaveolens*	[213]
446	Solalyratine A	R_1 = D-Xyl-(1 → 3)-D-Gal; R_2 = R_3 = R_5 = H; R_4 = CH_3	*S. lyratum*	[214]
447	Solalyratine B	R_1 = [D-Xyl-(1 → 2)-D-Glc-(1 → 4)-D-Gal]; R_2 = R_3 = R_5 = H; R_4 = CH_3	*S. lyratum*	[214]
448	Esculeoside A	R_1 = Lycotetraose; R_2 = OAc; R_3 = R_4 = H; R_5 = CH_2-*O*-D-Glc	*Lycopersicon esculentum* var. *cerasiforme*	[206]
449	Lycotetraose G	R_1 = Lycotetraose; R_2 = OAc; R_3 = *O*-D-Glc; R_4 = CH_3; R_5 = H	*Lycopersicon esculentum* var. *cerasiforme*	[206]
450	22-Imido-3-[4′-(6″-deoxy-*α*-L-mannoside)-*β*-D-glucoside]-5-dehydro spirostane	R_1 = L-Rha-(1 → 4)-D-Glc; R_2 = R_3 = R_4 = H; R_5 = CH_3	*Solanum xanthocarpum*	[215]
451	Neorickiioside B	R_1 = Lycotetraose; R_2 = OH; R_3 = R_5 = H; R_4 = CH_3	*S. neorickii*	[216]
452	β_2-Tomatine	R = D-Xyl-(1 → 3)-D-Glc-(1 → 4)-D-Gal	*Lycopersicon esculentum*	[217]
453	Dihydro-*β*-Solamarine	R = Chacotriose	*Solanum dulcamara*	[218]
454	Polyanine	R = D-Xyl-(1 → 2)-D-Xyl-(1 → 3)-D-Glc	*S. polyadenium*	[219]
455	Sisunine	R = Commertetraose	*S. ajanhuiri*	[220]
456	Tomatidine-3-*O*-*β*-D-glucopyranoside	R = D-Glc	*S. arboreum*	[221]
457	Tomatidine-3-*O*-*β*-[D-xylopyranosyl-(1 → 6)]-*β*-D-glucopyranoside	R = D-Xyl-(1 → 6)-D-Glc	*S. arboreum*	[221]
458	Tomatidine	R = H	*Lycopersicon esculentum*	[222]
459	*α*-Tomatine	R = Lycotetraose	L. *esculentum*	[216]
460	*β*-Tomatine	R = D-Glc-(1 → 2)-D-Glc-(1 → 4)-D-Gal	*Solanum nigrum*	[223]
461	*γ*-Tomatine	R = D-Glc-(1 → 4)-D-Gal	*S. tuberosum*	[223]
462	*Δ*-Tomatine	R = D-Gal	*Lycopersicon esculentum*	[223]
463	*γ*-Solamarine	R = L-Rha-(1 → 4)-D-Glc	*Solanum dulcamara*	[224]
464	γ_1-Solamarine	R = L-Rha-(1 → 2)-D-Glc	*S. dulcamara*	[225]
465	*δ*-Solamarine	R = D-Glc-(1 → 3)-D-Gal	*S. dulcamara*	[225]
466	22,25-Diepisycophantine	R = [D-Xyl-(1 → 2)-L-Rha-(1 → 4)]-L-Rha-(1 → 2)-D-Glc	*S. sycophanta*	[226]
467	Solaculine A	R = [D-Xyl-(1 → 2)-L-Rha-(1 → 4)]-L-Rha-(1 → 2)-D-Glc	*S. aculeastrum*	[227]
468	Tomatidenol	R = H	*S. auiculare*	[228]
469	(22*S*, 25*S*)-spirosol-5-en-3*β*-yl *O*-*β*-D-glucopyranosyl-(1 → 4)-*O*-[*α*-L-rhamnopyranosyl-(1 → 2)]-*β*-D-glucopyranoside	R = D-Glc-(1 → 4)-[L-Rha-(1 → 2)]-D-Glc	*Fritillaria meleagris*	[229]
470	*β*-Solamarine	R = D-Glc-(1 → 4)-[L-Rha-(1 → 2)]-D-Glc	*S. nigrum*	[223]
471	*α*-Solamarine	R = Solatriose	*Solanum nigrum*	[223]
472	Dehydrotomatine	R = Lycotetraose	*Lycopersicon esculentum*	[223]
473	*N*-hydroxysolamargine	R = Chacotriose	*S. robustum*	[230]
474	3-*O*-*β*-lycotetraoside of solasodine	R_1 = Lycotetraose; R_2 = R_3 = R_4 = R_5 = H	*S. japonense*	[231]
475	Spirosolane *β*-D-glucopyranoside deriv	R_1 = Chacotriose; R_2 = R_4 = H; R_3 = *β*-OH; R_5 = OH	*S. nigrum*	[232]
476	Solaverine I	R_1 = Chacotriose; R_2 = R_3 = R_5 = H; R_4 = OH	*S. toxicarium*; *S. verbascifolium*	[233]
477	Solaverine II	R_1 = D-Glc-(1 → 3)-[L-Rha-(1 → 2)]-D-Gal; R_2 = R_3 = R_5 = H; R_4 = OH	*S. toxicarium*; *S. verbascifolium*	[233]
478	Solaverine III	R_1 = Chacotriose;R_2 = R_3 = H; R_4 = R_5 = OH	*S. toxicarium*; *S. verbascifolium*	[233]

Table 9 (continued)

No	Compounds	Substitution groups and others	Sources	References
479	Incanumine	R_1 = [D-Xyl-(1 → 4)-L-Rha-(1 → 4)]-D-Xyl-(1 → 3)-D-Glc; $R_2 = R_3 = R_4 = R_5 = H$	*S. incanum*	[234]
480	(23*S*)-23-Hydroxyanguivine	R_1 = D-Xyl-(1 → 3)-[L-Rha-(1 → 2)]-D-Glc; $R_2 = R_3 = R_5 = H$; $R_4 = OH$	*S. uporo*	[233]
481	β_1-Solamargine	R_1 = L-Rha-(1 → 2)-D-Glc; $R_2 = R_3 = R_4 = R_5 = H$	*S. robustum*	[235]
482	Anguivine	R_1 = [D-Xyl-(1 → 3)-L-Rha-(1 → 2)]-D-Glc; $R_2 = R_3 = R_4 = R_5 = H$	*S. anguivi*	[236]
483	Robustine	R_1 = L-Ara-(1 → 3)-[L-Rha-(1 2)]-[L-Rha-(1 → 4)]-D-Glc; $R_2 = R_3 = R_4 = R_5 = H$	*S. robustum*	[235]
484	Ravifoline	R_1 = L-Rha-(1 → 4)-[L-Rha-(1 → 2)]-D-Xyl; $R_2 = R_3 = R_4 = R_5 = H$	*S. platanifolium*	[237]
485	(3*β*,22*α*,25R)-Spirosol-5-en-3-yl 6-deoxy-*α*-L-mannopyranoside	R_1 = L-Rha; $R_2 = R_3 = R_4 = R_5 = H$	*S. unguiculatum*	[238]
486	Robeneoside A	R_1 = Chacotriose; $R_2 = R_4 = R_5 = H$; $R_3 = \alpha$-OH	*S. lycocarpum*	[238]
487	3-*O*-*α*-L-rhamnopyranosyl-(1 → 2)-*α*-L-rhamnopyranosyl-(1 → 4)-*β*-D-galactopyranosyl solasodine	R_1 = L-Rha-(1 → 4)-[L-Rha-(1 → 2)]-D-Gal; $R_2 = R_3 = R_4 = R_5 = H$	*S. unguiculatum*	[238]
488	Sycophantine	R_1 = [D-Xyl-(1 → 2)-L-Rha-(1 → 4)]-L-Rha-(1 → 2)-D-Glc; $R_2 = R_3 = R_4 = R_5 = H$	*S. coccineum*	[239]
489	Solanelagnin	R_1 = L-Rha-(1 → 4)-[L-Rha-(1 → 3)]-D-Glc; $R_2 = R_3 = R_4 = R_5 = H$	*S. elaeagnifolium*	[240]
490	12-Hydroxysolasonine	R_1 = Solatriose; $R_2 = R_4 = R_5 = H$; $R_3 = \beta$-OH	*S. uporo*	[241]
491	Isoanguivine	R_1 = D-Xyl-(1 → 3)-[L-Rha-(1 → 2)]-D-Gal; $R_2 = R_3 = R_4 = R_5 = H$	*S. uporo*	[241]
492	Solashabanine	R_1 = [D-Glc-(1 → 6)-D-Glc-(1 → 3)]-L-Rha-(1 → 2)-D-Gal; $R_2 = R_3 = R_4 = R_5 = H$	*S. suaveolens*	[213]
493	(23*S*)-23-Hydroxyisoanguivine	R_1 = D-Xyl-(1 → 3)-[L-Rha-(1 → 2)]-D-Gal; $R_2 = R_3 = R_5 = H$; $R_4 = OH$	*S. uporo*	[241]
494	Solasuaveoline	R_1 = L-Rha-(1 → 2)-[D-Glc-(1 → 2)-D-Glc-(1 → 4)-D-Gal; $R_2 = R_3 = R_4 = R_5 = H$	*S. suaveolens*	[213]
495	(25*R*)-3*β*-[*O*-*α*-L-Rhamnopyranosyl-(1 → 2)-[*O*-*β*-D-glucopyranosyl-(1 → 4)-*O*-*α*-L-rhamnopyranosyl-(1 → 4)]-*β*-D-glucopyranosyl]-22*α*-spirosol-5-ene	R_1 = [D-Glc-(1 → 4)-L-Rha-(1 → 4)]vRha-(1 → 2)-D-Glc; $R_2 = R_3 = R_4 = R_5 = H$	*S. aculeastrum*	[242]
496	Arudoine	R_1 = D-Xyl-(1 → 3)-[L-Rha-(1 → 2)]-[L-Rha-(1 → 4)]-D-Glc; $R_2 = R_3 = R_4 = R_5 = H$	*S. arundo*	[243]
497	Robeneoside B	R_1 = Solatriose; $R_2 = R_4 = R_5 = H$; $R_3 = \alpha$-OH	*S. lycocarpum*	[244]
498	27-Hydroxysolamargine	R_1 = Chacotriose; $R_2 = R_3 = R_4 = H$; $R_5 = OH$	*S. asperum*	[244]
499	12-Hydroxysolamargine	R_1 = Chacotriose; $R_2 = R_4 = R_5 = H$; $R_3 = \beta$-OH	*S. lycocarpum*	[245]
500	*α*-Solamargine	R_1 = Chacotriose; $R_2 = R_3 = R_4 = R_5 = H$	*S. macrocarpon; S. aethiopicum*	[246]
501	*α*-Solasonine	R_1 = Solatriose; $R_2 = R_3 = R_4 = R_5 = H$	*S. macrocarpon; S. aethiopicum*	[246]
502	(22*R*,25*R*)-spirosol-5-en-3*β*-yl	R_1 = D-Glc-(1 → 4)-[L-Rha-(1 → 2)]-D-Glc; $R_2 = R_3 = R_4 = R_5 = H$	*Lilium longiflorum*	[247]
503	*O*-L-rhamnopyranosyl-(1 → 2)-[6-O-acetyl-*β*-D-glucopyranosyl-(1 → 4)]-*β*-D-glucopyranoside	R_1 = 6-Ac-D-Glc-(1 → 4)-[L-Rha-(1 → 2)]-D-Glc; $R_2 = R_3 = R_4 = R_5 = H$	L *longiflorum*	[247]
504	(22*R*,25*R*)-16*β*-H-22*α*-N-spirosol-3*β*-ol-5-ene-3-*O*-*α*-L-rhamnopyranosyl-(1 → 2)-[*α*-L-rhamnopyranosyl-(1 → 4)]-*β*-D-glucopyranoside	R_1 = Chacotriose; $R_2 = R_3 = R_4 = R_5 = H$; C_{16} = *R* configuration	*Solanum surattense*	[207]
505	*γ*-Solamargine	R_1 = D-Glc; $R_2 = R_3 = R_4 = R_5 = H$	*S. nigrum*	[248]
506	β_1-Solasonine	R_1 = L-Rha-(1 → 2)-D-Gal; $R_2 = R_3 = R_4 = R_5 = H$	*S. nigrum*	[248]

Table 9 (continued)

No	Compounds	Substitution groups and others	Sources	References
507	Solanigroside P	R_1 = L-Rha-(1 → 4)-D-Glc; $R_2 = R_4 = R_5$ = H; R_3 = *α*-OH	*S. nigrum*	[248]
508	Khasianine	R_1 = L-Rha-(1 → 4)-D-Glc; $R_2 = R_3 = R_4 = R_5$ = H	*S. nigrum*	[249]
509	β_2-Solasonine	R_1 = D-Glc-(1 → 4)-D-Gal; $R_2 = R_3 = R_4 = R_5$ = H	*S. nigrum*	[250]
510	7*α*-Hydroxy-khasianine	R_1 = L-Rha-(1 → 4)-D-Glc; R_2 = *α*-OH; $R_3 = R_4 = R_5$ = H	*S. nigrum*	[250]
511	7*α*-Hydroxy-solamargine	R_1 = Chacotriose; R_2 = *α*-OH; $R_3 = R_4 = R_5$ = H	*S. nigrum*	[250]
512	7*α*-Hydroxy-solasonine	R_1 = Solatriose; R_2 = *α*-OH; $R_3 = R_4 = R_5$ = H	*S. nigrum*	[250]
513	Solasodine	$R_1 = R_2 = R_3 = R_4 = R_5$ = H	*Lycopersicon esculentum; Solanum nigrum; S.dulcamara*	[223]
514	*γ*-Solasonine	R_1 = D-Gal; $R_2 = R_3 = R_4 = R_5$ = H	*S. nigrum*	[223]
515	(25*R*)-22*a*N-spirosol-5(6)-en-3*β*-ol-7-oxo-3-*O*-*α*-Lrhamnopyranosyl-(1 → 2)-[*α*-L-rhamnopyranosyl-(1 → 4)]-*β*-D-glucopyranoside	R_1 = Chacotriose; R_2 = O; $R_3 = R_4 = R_5$ = H	*S. nigrum*	[251]
516	Solasodiene		*S. torvum*	[252]
517	(22*R*,25*R*)3*β*-amino-5*α*-spirosolane		*S. triste*	[208]
518	(22*R*,25*R*)3*β*-amino-5-spirosolene		*S. triste*	[208]
519	(22*S*,25*S*)-3*β*-aminospirosol-5-ene	R = *β*-NH_2; $\triangle^{5,6}$	*S. arboreum*	[209]
520	Soladunalinidine	R = *β*-NH_2	*S. arboreum*	[209]
521	3-*Epi*-soladunalinidine	R = *α*-NH_2	*S. arboreum*	[209]
522	Caavuranamide	R = *β*-NHCHO	*S. caavurana*	[253]
523	5-Tomatidan-3-one	R = O	*S. caavurana*	[253]
524	5*β*-solasodan-3-one		*S. avicccculare*	[254]
525	4-Tomatiden-3-one		*S. caavurana*	[253]
526	(25*R*)-22*aN*-spirosol-4(5)-en-3*β*-ol-6-oxo-3-*O*-*α*-Lrhamnopyranosyl-(1 → 2)-[*α*-L-rhamnopyranosyl-(1 → 4)]-*β*-D-glucopyranoside	R = Chacotriose	*S. nigrum*	[251]

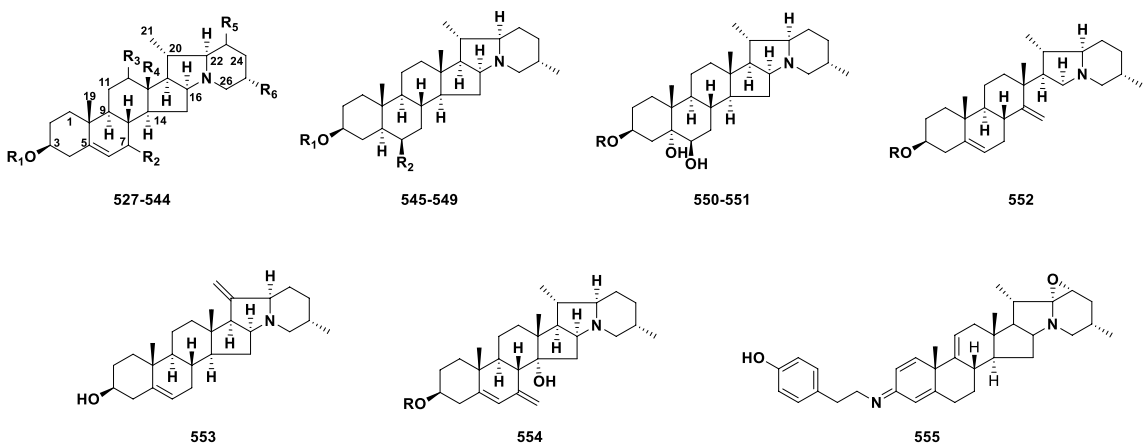


Fig. 11 Structures of solanidine type steroidal alkaloids **527–555**

Table 10 Structures and sources of solanidine type steroidal alkaloids **527–555**

No	Compounds	Substitution groups and others	Sources	References
527	*α*-Chaconine	R_1 = Chacotriose; R_2 = R_3 = R_5 = H; R_4 = R_6 = CH_3	*Solanum chacoense*	[224]
528	*α*-Solanine	R_1 = Solatriose; R_2 = R_3 = R_5 = H; R_4 = R_6 = CH_3	*S. tuberosum*; *S. nigrum*	[255]
529	Leptine I	R_1 = Chacotriose; R_2 = R_3 = H; R_4 = R_6 = CH_3; R_5 = OAc	*S. chacoense*	[224]
530	Leptinine I	R_1 = Chacotriose; R_2 = R_3 = H; R_4 = R_6 = CH_3; R_5 = OH	*S. orbignianum*	[258]
531	Leptine II	R_1 = Solatriose; R_2 = R_3 = H; R_4 = R_6 = CH_3; R_5 = OAc	*S. chacoense*	[224]
532	Leptinine II	R_1 = Solatriose; R_2 = R_3 = H; R_4 = R_6 = CH_3; R_5 = OH	*S. orbignianum*	[258]
533	Dehydrodemissine	R_1 = Lycotetraose; R_2 = R_3 = R_5 = H; R_4 = R_6 = CH_3	*S. commersonii*	[259]
534	Dehydrocommersonine	R_1 = Commertetraose; R_2 = R_3 = R_5 = H; R_4 = R_6 = CH_3	*S. chacoense*	[224]
535	Solanidine	R_1 = R_2 = R_3 = R_5 = H; R_4 = R_6 = CH_3	*S. tuberosum*	[260]
536	Epirubijervin	R_1 = R_2 = R_5 = H; R_3 = *β*-OH; R_4 = R_6 = CH_3	*Veratrum grandiflorum*	[180]
537	Camtschatcanidine	R_1 = R_2 = R_3 = R_5 = H; R_4 = CH_3; R_6 = CH_2OH	*Fritillaria camtschatcensis*	[261]
538	Oligoglycoside	R_1 = [L-Rha-(1 → 2)][D-Glc-(1 → 4)]-D-Glc; R_2 = R_3 = R_5 = H; R_4 = R_6 = CH_3	*F. thunbergii*	[262]
539	(22*S*,25*S*)-solanid-5-en-3*β*-ol	R_1 = R_2 = R_3 = R_5 = H; R_4 = R_6 = CH_3	*Fritillaria anhuiensis*	[256]
540	(3*β*,7*β*)-7-Hydroxysolanid-5-en-3-yl 6-deoxy-*α*-L-mannopyranosyl-(1 → 2)-[6-deoxy-*α*-L-mannopyranosyl-(1 → 4)]-*β*-D-glucopyranoside	R_1 = 6-deoxy-L-Man-(1 → 2)-[6-deoxy-L-Man-(1 → 4)]-D-Glu; R_2 = *β*-OH; R_3 = R_5 = H; R_4 = R_6 = CH_3	*Solanum tuberosum*	[257]
541	(3*β*)-7-Oxosolanid-5-en-3-yl 6-deoxy-*α*-L-mannopyranosyl-(1 → 2)-[6-deoxy-*α*-L-mannopyranosyl-(1 → 4)]-*β*-D-glucopyranoside	R_1 = 6-deoxy-L-Man-(1 → 2)-[6-deoxy-L-Man-(1 → 4)]-D-Glc; R_2 = O; R_3 = R_5 = H; R_4 = R_6 = CH_3	*S. tuberosum*	[257]
542	(3*β*)-7-Oxosolanid-5-en-3-yl 6-Deoxy-*α*-L-mannopyranosyl-(1 → 2)-[*β*-D-glucopyranosyl-(1 → 3)]-*β*-D-galactopyranoside	R_1 = 6-deoxy-L-Man-(1 → 2)-[D-Glc-(1 → 3)]-D-Gal; R_2 = O; R_3 = R_5 = H; R_4 = R_6 = CH_3	*S. tuberosum*	[257]
543	Isorubijervine	R_1 = R_2 = R_3 = R_5 = H; R_4 = CH_2OH; R_6 = CH_3	*Veratrum viride*	[263]
544	Rubijervine	R_1 = R_2 = R_5 = H; R_3 = *β*-OH; R_4 = R_6 = CH_3	*V. taliense*	[263]
545	Demissine	R_1 = Lycotetraose; R_2 = H	*Solanum chacoense*; *S. commersonii*	[264]
546	Commersonine	R_1 = Commertetraose; R_2 = H	*S. chacoense*; *S. commersonii*	[264]
547	Demissidine	R_1 = R_2 = H	*S. tuberosum*	[265]
548	Dihydro-β_1-Chaconine	R_1 = L-Rha-(1 → 2)-D-Glc; R_2 = H	*S. juzepczukii*; *S. curtilobum*	[266]
549	Dihydrosolanine	R_1 = Solatriose; R_2 = H	*S. juzepczukii*; *S. curtilobum*	[266]
550	(22*R*,25*S*)-solanid-5-enine-3*β*,5*α*,6*β*-triol	R = H	*Fritillaria delavayi*	[133]
551	(3*β*,5*α*,6*β*)-5,6-Dihydroxysolanidan-3-yl 6-Deoxy-*α*-L-mannopyranosyl-(1 → 2)-[6-deoxy-*α*-L-mannopyranosyl-(1 → 4)]-*β*-D-glucopyranoside	R = 6-deoxy-L-Man-(1 → 2)-[6-deoxy-L-Man-(1 → 4)]-D-Glc	*Solanum tuberosum*	[257]
552	15,16-Seco-22*α*H,25*β*H-solanida-5,14-dien-3*β*-ol-*O*-*β*-D-glucopyranosyl-(1 → 4)-*β*-D-xylopyranoside	R = D-Glc-(1 → 4)]-D-Xyl	*Fritillaria maximowiczii*	[194]
553	(22*S*,25*S*)-Solanid-5,20(21)-dien-3*β*-ol		*F. anhuiensis*	[256]

Table 10 (continued)

No	Compounds	Substitution groups and others	Sources	References
554	(3*β*)-14-Hydroxysolanid-5-en-3-yl 4-*O*-(6-Deoxy-*α*-L-mannopyranosyl)-*β*-D-glucopyranoside	R = 4-*O*-(6-deoxy-L-Man)-D-Glc	*Solanum tuberosum*	[257]
555	(*E*)-*N*-[80(4-hydroxyphenyl)ethyl]-22*α*,23*α*-epoxy-solanida-1,4,9-trien-3-imine		*S. campaniform*	[267]

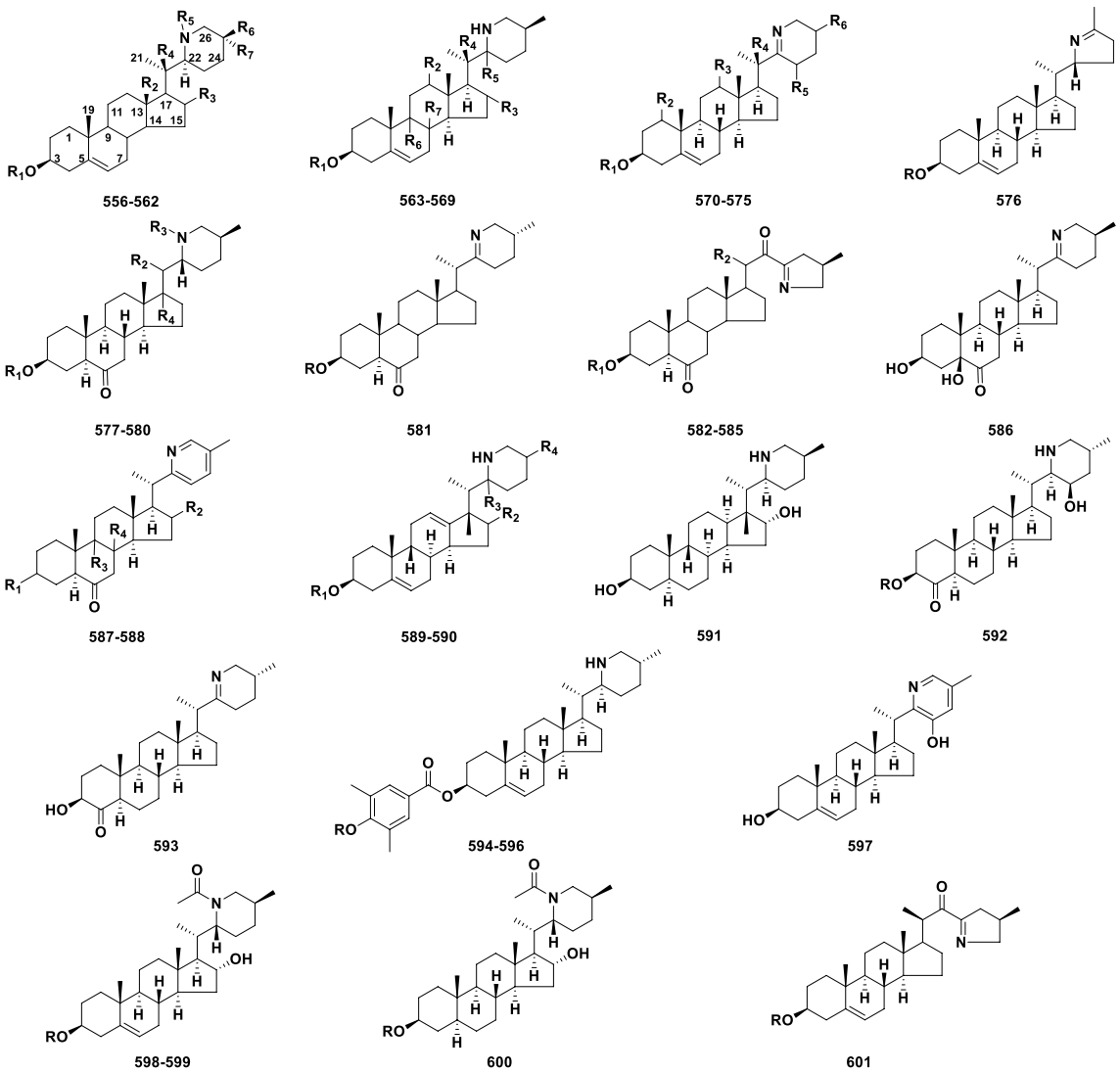


Fig. 12 Structures of verazine type steroidal alkaloids **556–601**

et al. allowed correcting the structure [331]. Ritterazines A (**672**), T (**673**), D (**676**), E (**677**), N (**687**), O (**688**), U-X (**693–696**), and Z (**697**) have a unique five-membered C ring on their right side, which is a rearranged steroid nucleus, the same as *Veratrum* alkaloids. Structural abbreviations used in this review are illustrated in Fig. 20.

3 Biological activities

3.1 Anticancer effects

Most steroidal alkaloids showed anticancer activity as cytotoxicity with the IC_{50} values listed in Table 18. Among the seven human cancer cell lines SMMC-772, A-549, SK-BR-3, PANC-1, K562, SGC7901 and HL-60, the most sensitive cell line according to sarcovagine D (**116**) was SK-BR-3, which had an IC_{50} value of 2.25 μM. [79]. Holamine (**145**) and funtumine (**154**) exhibited anticancer activity against human colon adenocarcinoma (HT-29) with IC_{50} values of 31.06 and 22.36 μM, respectively. The study demonstrated that **145** and **154** induced cytotoxicity through the induction of apoptosis in HeLa, MCF-7, and HT-29 cancer cells [83]. Then, they induced apoptosis through the elevation of reactive oxygen species (ROS), mitochondrial function modulation, the perturbation of F-actin polymerization, and caspase-3 induction, which were all more prominent in HeLa cells [334].

Cyclopamine (**432**), a Hedgehog (Hh) signaling pathway antagonist, was first identified as a potent teratogen in animals. Among the nine human pancreatic cell lines examined, the IC_{50} values of cyclopamine ranged from

Table 11 Structures and sources of verazine type steroidal alkaloids **556–601**

No	Compounds	Substitution groups and others	Sources	References
556	Hapepunine	$R_1=R_4=R_5=R_7=H$; $R_2=R_6=CH_3$; $R_3=\beta$-OH	*Fritillaria camtschatcensis*	[272]
557	Anrakorinine	$R_1=R_4=R_5=R_7=H$; $R_2=CH_2OH$; $R_3=\beta$-OH; $R_6=CH_3$	*F. camtschatcensis*	[272]
558	Hapepunine 3-*O*-*α*-L-rhamnopyranosyl-(1 → 2)-*β*-D-glucopyranoside	$R_1=$ D-Glc(2 → 1)-L-Rha; $R_2=R_6=CH_3$; $R_3=\beta$-OH; $R_4=R_5=R_7=H$	*F. thunbergii*	[262]
559	Pingbeidinoside	$R_1=H$; $R_2=R_5=R_7=CH_3$; $R_3=\alpha$-OH; $R_4=OH$; $R_6=O$-D-Glc	*F. ussuriensis*	[273]
560	Pingbeinine	$R_1=R_4=H$; $R_2=R_5=CH_3$; $R_3=\beta$-OH; $R_6=OH$; $R_7=CH_3$	*F. ussuriensis*	[274]
561	Pingbeininoside	$R_1=$ D-Glc; $R_2=R_5=CH_3$; $R_3=\beta$-OH; $R_4=H$; $R_6=OH$; $R_7=CH_3$	*F. ussuriensis*	[274]
562	Hapepunine 3-*O*-*β*-cellobioside	$R_1=$ D-Glc(4 → 1)-D-Glc; $R_2=R_6=CH_3$; $R_3=\beta$-OH; $R_4=R_5=R_7=H$	*F. maximowiczii*	[193]
563	Muldamine	$R_1=R_2=R_4=H$; $R_3=\alpha$-OAc; $R_5=R_6=\alpha$-H; $R_7=\beta$-H	*Veratrum californicum*	[275]
564	Stenophylline B	$R_1=R_2=R_3=H$; $R_4=OH$; $R_5=R_6=\beta$-H; $R_7=\alpha$-H	*V. stenophyllum*	[268]
565	Vertaline B	$R_1=R_2=H$; $R_3=\beta$-OH; $R_4=OH$; $R_5=R_7=\beta$-H; $R_6=\alpha$-H	*V. taliense*	[276]
566	Veramiline-3-*O*-*β*-D-glucopyranoside	$R_1=$ D-Glc; $R_2=R_3=R_4=H$; $R_5=R_6=\beta$-H; $R_7=\alpha$-H	*V. taliense*	[277]
567	Stenophylline-*β*-3-*O*-*β*-D-glucopyranoside	$R_1=$ D-Glc; $R_2=R_3=H$; $R_4=OH$; $R_5=R_6=\beta$-H; $R_7=\alpha$-H	*V. taliense*	[277]
568	Veramivirine	$R_1=R_3=R_4=H$; $R_2=\beta$-OH; $R_5=R_7=\beta$-H; $R_6=\alpha$-H	*V. viride*	[278]
569	Oblonginine	$R_1=R_2=R_4=H$; $R_3=\beta$-OH; $R_5=R_7=\beta$-H; $R_6=\alpha$-H	*V. oblongum*	[279]
570	Verazinine	$R_1=$ D-Glc; $R_2=R_3=R_4=R_5=H$; $R_6=\beta$-CH_3	*Zygadenus sibiricus*	[280]
571	Veranigrine	$R_1=R_3=R_4=R_5=H$; $R_2=\beta$-OH; $R_6=\beta$-CH_3	*Veratrum nigrum*	[281]
572	Veramitaline	$R_1=R_2=R_4=R_5=H$; $R_3=\alpha$-OH; $R_6=\beta$-CH_3	*V. nigrum*	[281]
573	(20*R*,25*R*)-12*β*-*O*-acetyl-20*β*-hydroxyisoverazine	$R_1=R_2=R_5=H$; $R_3=\beta$-OAc; $R_4=OH$; $R_6=\alpha$-CH_3	*V. grandiflorum*	[282]
574	(20*R*,25*R*)-12*β*-*O*-acetyl-20*β*-hydroxyisoverazine-3-*O*-*β*-D-glucopyranoside	$R_1=$ D-Glc; $R_2=R_5=H$; $R_3=\beta$-OAc; $R_4=OH$; $R_6=\alpha$-CH_3	*V. grandiflorum*	[282]
575	(20*R*,25*R*)-isoveralodinine	$R_1=$ D-Glc; $R_2=R_4=H$; $R_3=\beta$-OAc; $R_5=O$; $R_6=\alpha$-CH_3	*V. grandiflorum*	[282]
576	Rhamnoveracintine	R = L-Rha	*V. album*	[269]
577	Puqietinone	$R_1=H$; $R_2=\alpha$-CH_3; $R_3=CH_3$; $R_4=\alpha$-H	*Fritillaria puqiensis*	[188]
578	Yibeinoside C	$R_1=$ D-Glc(1 → 4)-D-Gal; $R_2=\beta$-CH_3; $R_3=H$; $R_4=\beta$-H	*F. pallidiflora*	[283]
579	*N*-Demethylpuqietinone	$R_1=R_3=H$; $R_2=\alpha$-CH_3; $R_4=\alpha$-H	*F. puqiensis*	[188]
580	Puqietinonoside	$R_1=$ D-Glc; $R_2=\alpha$-CH_3; $R_3=CH_3$; $R_4=\alpha$-H	*F. puqiensis*	[188]
581	(25*R*)-22,26-Epimino-3*β*-hydroxy-5*α*-cholest-22(*N*)-en-6-one 3-*O*-*β*-D-glucopyranoside	R = D-Glc	*F. persica*	[284]
582	(25*R*)-23,26-Epimino-3*β*-hydroxy-5*α*-cholest-23(*N*)-en-6,22-dione	$R_1=H$; $R_2=\alpha$-CH_3	*F. persica*	[284]
583	(25*R*)-23,26-Epimino-3b-hydroxy-5*α*-cholest-23(*N*)-en-6,22-dione 3-*O*-*β*-D-glucopyranoside	$R_1=$ D-Glc; $R_2=\alpha$-CH_3	*F. persica*	[284]
584	(20*R*,25*R*)-23,26-Epimino-3b-hydroxy-5*α*-cholest-23(*N*)-en-6,22-dione	$R_1=H$; $R_2=\beta$-CH_3	*F. persica*	[284]
585	(20*R*,25*R*)-23,26-Epimino-3b-hydroxy-5a-cholest-23(*N*)-en-6,22-dione 3-*O*-*β*-D-glucopyranoside	$R_1=$ D-Glc; $R_2=\beta$-CH_3	*F. persica*	[284]
586	Ebeietinone		*F. ebeiensis*	[270]
587	Verdinine	$R_1=\beta$-OAc; $R_2=\beta$-OH; $R_3=\beta$-H; $R_4=\alpha$-H	*Veratrum lobelianum*	[271]
588	Fetisinine	$R_1=\alpha$-OH; $R_2=H$; $R_3=\alpha$-H; $R_4=\beta$-H	*Fritillaria imperialis*	[179]
589	Diacetylveralkamine	$R_1=$ Ac; $R_2=\alpha$-OAc; $R_3=\alpha$-H; $R_4=\beta$-CH_3	*Veratrum lobelianum*	[285]

Table 11 (continued)

No	Compounds	Substitution groups and others	Sources	References
590	veralinine 3-*O*-*α*-L-rhamnopyranosyl-(1 → 2)-*β*-D-glucopyranoside	R_1 = L-Rha-(1 → 2)-D-Glc; R_2 = H; R_3 = *β*-H; R_4 = *α*-CH_3	*V. grandiflorum*	[189]
591	Tetrahydroveralkamine		*V. lobelianum*	[285]
592	Deacetoxysolaphyllidine 3-*O*-*β*-D-glucopyranoside		*Solanum hypomalacophyllum*	[286]
593	4-Keto-5,6-dihydro-(20*S*)-verazine		*S. hypomalacophyllum*	[286]
594	Allumine A	R = H	*Allium victorialis*	[287]
595	Allumine B	R = D-Glc	*A. victorialis*	[287]
596	Allumine C	R = D-Glc-$CH_2OCO(CH_2)_{10}CH_3$	*A. victorialis*	[288]
597	Isoecliptalbine		*Veratrum maackii*	[203]
598	Spiraloside A	R = L-Rha-(1 → 4)-D-Glc	*Solanum spirale*	[289]
599	Spiraloside B	R = D-Glc	*Solanum spirale*	[289]
600	Spiraloside C	R = D-Glc	*Solanum spirale*	[289]
601	Tomatillidine 3-*O*-*β*-D-glucopyranoside Veratrum dahuricum	R = X	*V. dahuricum*	[197]

8.79 to more than 30 μM [335]. In addition, **432** also showed prominent anticancer effects, including small-cell lung cancer (SCLC) [336], oral squamous cell carcinoma (OSCC) [337], breast cancer [338], pancreatic cancer [339], hepatocellular carcinoma (HCC) [340] and human erythroleukemia cells [341]. Furthermore, **432** induced apoptosis in HCC cells through inhibition of the Sonic Hh signaling pathway by downregulating Bcl-2 [340]. In addition, **432** could induce apoptosis and upregulate cyclooxygenase-2 (COX-2) expression which plays a crucial role in the proliferation and differentiation of leukemia cells [341].

Tomatidine (**458**) and solasodine (**513**), important alkaloids found in a large number of *Solanum* species, exerted cytotoxic activity against HBL-100 cells [342]. They had a weak inhibitory effect on MCF-7, HT-29 and HeLa cells by blocking the cell cycle in the G_0/G_1 phase [343]. *α*-Solamargine (**500**) and *α*-solasonine (**501**), the two glycosides of **513**, differed only in their carbohydrate moieties, which are used in the treatment of keratoses, basal cell carcinomas, and squamous cell carcinomas [344]. Moreover, **500** was significantly

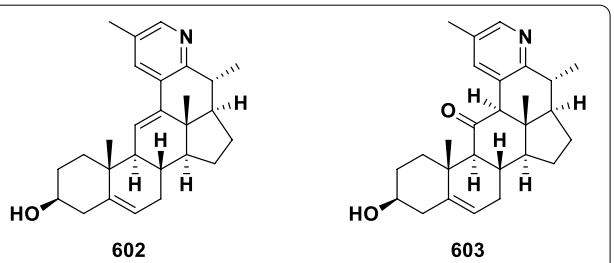


Fig. 13 Structures of others cholestane steroidal alkaloids **602–603**

Table 12 Structures and sources of samandarines **604–614**

No	Compounds	Substitution groups and others	Sources	References
604	Samandarine	R = *β*-OH	*Salamandra maculosa*	[293]
605	Samandarone	R = O	*S. maculosa*	[294]
606	*O*-acetylsamandarine	R = *β*-OAc	*S. maculosa*	[295]
607	*O*-(*S*)-3-hydroxybutanoylsamandarine	R = *β*-$OCOCH_2CH(\alpha\text{-}OH)CH_3$	*S. salamandra*	[296]
608	Samandaridine		*S. maculosa*	[294]
609	Cycloneosamandione		*S. maculosa*	[292]
610	Cycloneosamandaridin		*S. maculosa*	[297]
611	Samandenone		*S. maculosa*	[298]
612	Samandinine		*S. maculosa*	[299]
613	Samanine	R = *β*-OH	*S. maculosa*	[300]
614	Samanone	R = O	*S. salamandra*	[296]

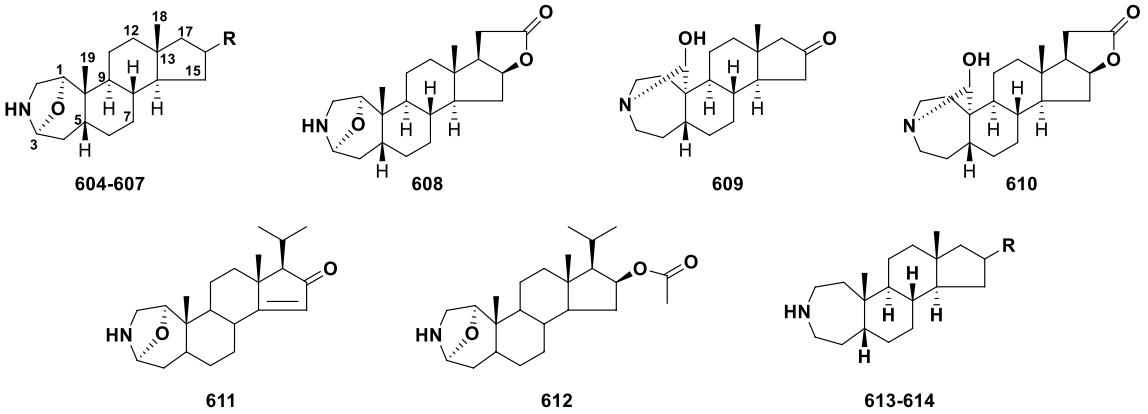


Fig. 14 Structures of samandarines **604–614**

Table 13 Structures and sources of batrachotoxins **615–621**

No	Compounds	Substitution groups and others	Sources	References
615	Batrachotoxinin A	R = H	*Phyllobates aurotaenia*	[302]
616	Pseudobatrachotoxin	R = X_1	*P. aurotaenia*	[302]
617	Batrachotoxin	R = X_2	*P. aurotaenia*	[302]
618	Homobatrachotoxin	R = X_3	*P. aurotaenia; Pitohui dichrous*	[302, 303]
619	Batrachotoxinin A-20*R*-*cis*-crotonate	R = $COCHCHCH_3$	*Ifrita kowaldi*	[304]
620	Batrachotoxinin A-20*R*-3′-hydroxypentanoate	R = $COCH_2CH(OH)CH_2CH_3$	*I. kowaldi*	[304]
621	Batrachotoxinin A-20*R*-acetate	R = Ac	*I. kowaldi*	[304]

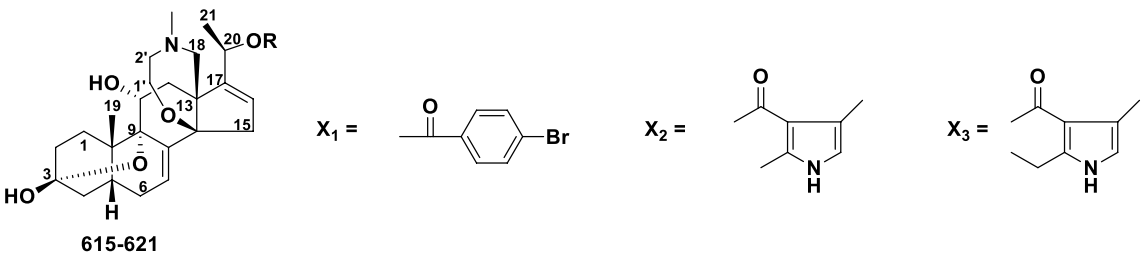


Fig. 15 Structures of batrachotoxins **615–621**

cytotoxic to the human tumor cell lines H441, H520, H661, H69, HeLa, A549, MCF-7, K562, HCT116, U87 and HepG2 with IC_{50} values from 2.1 to 8.0 μM [345, 346]. The cellular and molecular mechanism of **500** anti-human breast cancer cells HBL-100, ZR-75-1 and SK-BR-3 were investigated, and it was concluded that this compound could activate apoptotic proteins and inhibite anti-apoptotic, so it has great potential as an anti-human breast cancer candidate drug [347]. The target of *α*-solanine (**528**) inducing apoptosis in $HepG_2$ cells seemed to be mediated by the inhibition of the expression of Bcl-2 protein [255].

Cephalostatin 1–20 (**652–671**) were significantly cytotoxic to the human tumor cell lines BXPC-3, MCF-7, SF-268, NCI-H460, KM20L2 and DU-145. Of these compounds, cephalostatin 2 (**653**) was the most active compound, with GI_{50} (growth inhibition of 50%) values in the range of 0.0056–0.11 nM. Importantly, compared with the cephalostatins 9 (**664**) and 20 (**665**), the inhibitory effects of **653** and cephalostatin 1 (**652**) were significantly increased by 100–1000 times. From this evidence, it was clear that the spirostanol structure must be intact and was the critical center for antineoplastic activities. The opening of the left-side spiro-ring significantly reduced

Table 14 Structures and sources of plakinamines **622–640**

No	Compounds	Substitution groups and others	Sources	References
622	Plakinamine A	$R_1=R_2=R_3=H$	*Plakina* sp.	[308]
623	Plakinamine F	$R_1=R_2=CH_3$; $R_3=O$	*Corticium* sp.	[309]
624	Plakinamine B	$R_1=\alpha$-$NHCH_3$; $R_2=H$; $R_3=CH_3$	*Plakina* sp.	[308]
625	Plakinamine H	$R_1=\beta$-$N(CH_3)_2$; $R_2=O$; $R_3=H$	*Corticium* sp.	[306]
626	4α-Hydroxydemethylplakinamine B	$R_1=\alpha$-NH_2; $R_2=\beta$-OH; $R_3=CH_3$	*Corticium* sp.	[306]
627	Plakinamines C		*Corticium* sp.	[310]
628	Plakinamines D		*Corticium* sp.	[310]
629	Plakinamine E		*Corticium* sp.	[309]
630	Plakinamine G		*Corticium* sp.	[306]
631	Tetrahydroplakinamine A	$R_1=\alpha$-NH_2; $R_2=H$	*Corticium* sp.	[306]
632	Dihydroplakinamine K	$R_1=\beta$-NH_2; $R_2=\beta$-OAc	*Corticium niger*	[307]
633	Plakinamine I		*C. niger*	[307]
634	Plakinamine J		*C. niger*	[307]
635	Plakinamine K	$R_1=CH_3$; $R_2=\beta$-OAc	*C. niger*	[307]
636	Plakinamine N	$R_1=R_2=H$	*C. niger*	[311]
637	Plakinamine O	$R_1=H$; $R_2=\beta$-OAc	*C.niger*	[311]
638	Plakinamine L	R=H	*Corticium* sp.	[305]
639	Plakinamine M	R=β-OH	*Corticium* sp.	[312]
640	Plakinamine P		*Plakina* sp.	[313]

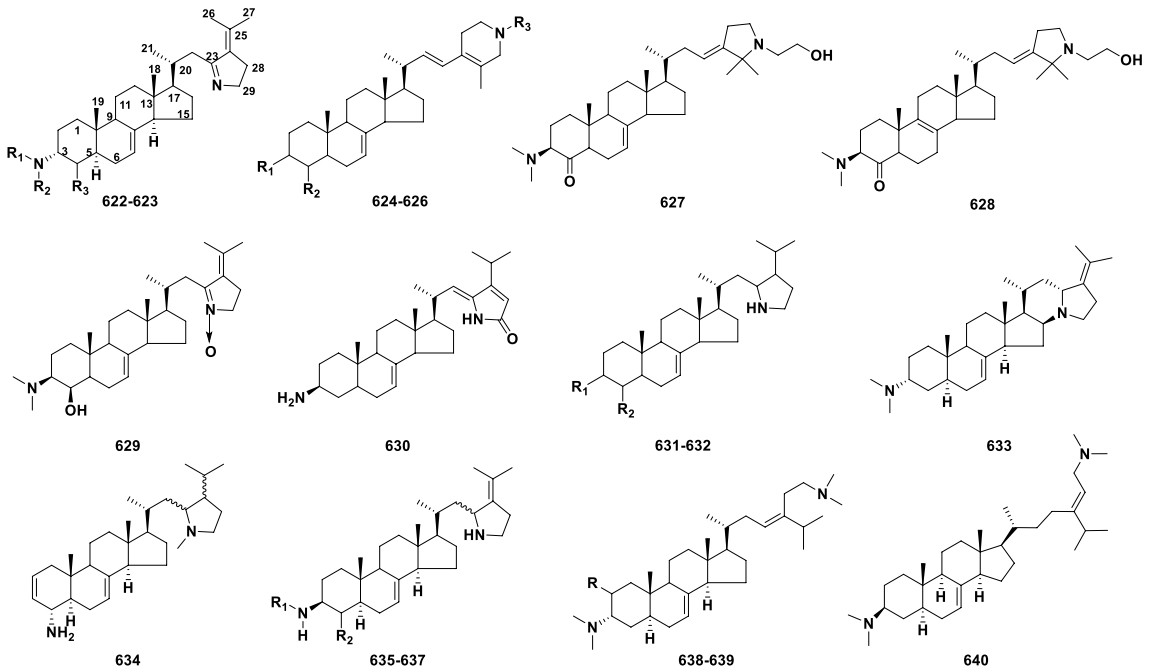


Fig. 16 Structures of plakinamines **622–640**

the inhibition of these carcinoma cells. A significant contribution of the presence of a hydroxy group at C-8′ to antineoplastic potency was evident by comparing the activity of cephalostatins 2 (**653**) and 1 (**652**), which was further supported by the cancer growth inhibitory activity of cephalostatins 20 (**665**) and 9 (**664**). Compounds **653** and **665**, in which the hydroxy substitution at C-8′,

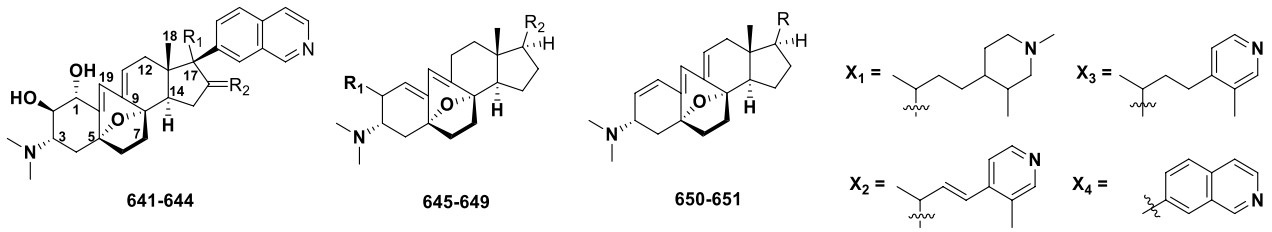


Fig. 17 Structures of cortistatins **641–651**

Table 15 Structures and sources of cortistatins **641–651**

No	Compounds	Substitution groups and others	Sources	References
641	Cortistatin A	$R_1=H$; $R_2=H$; H	*Corticium simplex*	[315]
642	Cortistatin B	$R_1=H$; $R_2=\alpha$-H; β-OH	*C. simplex*	[315]
643	Cortistatin C	$R_1=H$; $R_2=O$	*C. simplex*	[315]
644	Cortistatin D	$R_1=OH$; $R_2=O$	*C. simplex*	[315]
645	Cortistatin E	$R_1=H$; $R_2=X_1$	*C. simplex*	[316]
646	Cortistatin G	$R_1=H$; $R_2=X_2$	*C. simplex*	[316]
647	Cortistatin H	$R_1=H$; $R_2=X_3$	*C. simplex*	[316]
648	Cortistatin K	$R_1=H$; $R_2=X_4$	*C. simplex*	[317]
649	Cortistatin L	$R_1=\beta$-OH; $R_2=X_4$	*C. simplex*	[317]
650	Cortistatin F	$R=X_1$	*C. simplex*	[316]
651	Cortistatin J	$R=X_4$	*C. simplex*	[317]

Table 16 Structures and sources of cephalostatins **652–671**

No	Compounds	Substitution groups and others	Sources	References
652	Cephalostatin 1	$R_1=R_2=R_3=R_4=H$	*Cephalodiscus gilchristi*	[322]
653	Cephalostatin 2	$R_1=R_2=R_3=H$; $R_4=OH$	*C. gilchristi*	[323]
654	Cephalostatin 3	$R_1=CH_3$; $R_2=R_3=H$; $R_4=OH$	*C. gilchristi*	[323]
655	Cephalostatin 10	$R_1=R_2=H$; $R_3=OCH_3$; $R_4=OH$	*C. gilchristi*	[318]
656	Cephalostatin 11	$R_1=R_3=H$; $R_2=OCH_3$; $R_4=OH$	*C. gilchristi*	[318]
657	Cephalostatin 18	$R_1=R_2=R_4=H$; $R_3=OCH_3$	*C. gilchristi*	[324]
658	Cephalostatin 19	$R_1=R_3=R_4=H$; $R_2=OCH_3$	*C. gilchristi*	[324]
659	Cephalostatin 4		*C. gilchristi*	[323]
660	Cephalostatin 5	$R=CH_3$	*C. gilchristi*	[320]
661	Cephalostatin 6	$R=H$	*C. gilchristi*	[320]
662	Cephalostatin 7		*C. gilchristi*	[325]
663	Cephalostatin 8		*C. gilchristi*	[325]
664	Cephalostatin 9	$R=H$	*C. gilchristi*	[325]
665	Cephalostatin 20	$R=OH$	*C. gilchristi*	[326]
666	Cephalostatin 12	$R=H$	*C. gilchristi*	[319]
667	Cephalostatin 13	$R=OH$	*C. gilchristi*	[319]
668	Cephalostatin 14	$R=H$	*C. gilchristi*	[327]
669	Cephalostatin 15	$R=CH_3$	*C. gilchristi*	[327]
670	Cephalostatin 16		*C. gilchristi*	[321]
671	Cephalostatin 17		*C. gilchristi*	[321]

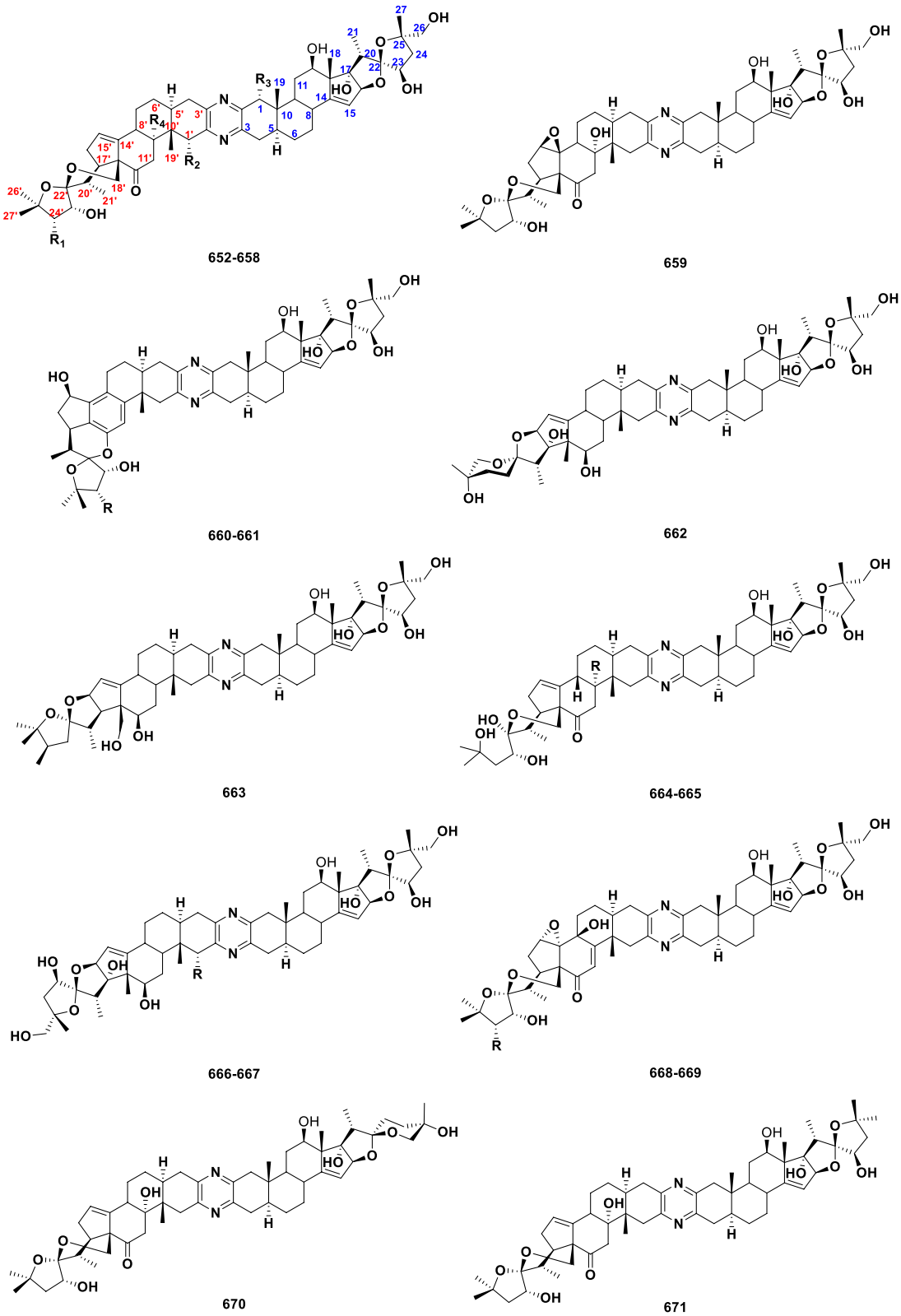


Fig. 18 Structures of cephalostatins **652–671**

Table 17 Structures and sources of ritterazines **672–697**

No	Compounds	Substitution groups and others	Sources	References
672	Ritterazine A	$R_1=R_2=OH$	*Ritterella tokioka*	[332]
673	Ritterazine T	$R_1=R_2=H$	*R. tokioka*	[333]
674	Ritterazine B		*R. tokioka*	[328, 329]
675	Ritterazine C		*R. tokioka*	[328]
676	Ritterazine D	R=H	*R. tokioka*	[330]
677	Ritterazine E	$R=CH_3$	*R. tokioka*	[330]
678	Ritterazine F	R=*β*-OH	*R. tokioka*	[330]
679	Ritterazine H	R=O	*R. tokioka*	[330]
680	Ritterazine G	$R_1=R_2=\beta$-OH; $R_3=\alpha$-OH; $\triangle^{14,15}$	*R. tokioka*	[330]
681	Ritterazine I	$R_1=\beta$-OH; R_2=O; $R_3=\alpha$-OH	*R. tokioka*	[330]
682	Ritterazine Y	$R_1=R_3=H$; $R_2=\beta$-OH	*R. tokioka*	[333]
683	Ritterazine J	$R_1=R_3=OH$; $R_2=\beta$-OH	*R. tokioka*	[330]
684	Ritterazine K	$R_1=H$; $R_2=\beta$-OH; $R_3=OH$	*R. tokioka*	[330]
685	Ritterazine L	$R_1=R_3=H$; $R_2=\beta$-OH	*R. tokioka*	[330]
686	Ritterazine M	$R_1=R_3=H$; $R_2=\alpha$-OH	*R. tokioka*	[330, 331]
687	Ritterazine N		*R. tokioka*	[333]
688	Ritterazine O		*R. tokioka*	[333]
689	Ritterazine P		*R. tokioka*	[333]
690	Ritterazine Q		*R. tokioka*	[333]
691	Ritterazine R		*R. tokioka*	[333]
692	Ritterazine S		*R. tokioka*	[333]
693	Ritterazine U		*R. tokioka*	[333]
694	Ritterazine V		*R. tokioka*	[333]
695	Ritterazine W		*R. tokioka*	[333]
696	Ritterazine X		*R. tokioka*	[333]
697	Ritterazine Z		*R. tokioka*	[333]

had considerably increased activity compared with compounds **652** and **664**, respectively [326].

Ritterazines A–Z (**672–697**) were all significantly cytotoxic to the human tumor cell lines of P388 murine leukemia cells. Of these compounds, ritterazine B (**674**) was the most active with an IC_{50} value of 0.00015 μg/mL. The presence of both the terminal 5/6 spiroketal and the hydroxyl groups was found to be especially important for pronounced inhibition of P388 cells. Ritterazines B (**674**) and F (**678**), which have terminal 5/6 spiroketal, showed high cytotoxicity against P388 cells, whereas ritterazine C, possessing 5/5 spiroketal structure, showed a lower significant level of cytotoxicity [333].

3.2 Anticholinergic effects

Some pregnane and cyclopregnane type alkaloids are distributed in many genera of Apocynaceae and display significant anticholinergic activity. Cholinesterase (ChE), divided into two enzymes acetylcholinesterase (AChE) and butyrylcholinestarase (BChE), have been identified as potential targets in the treatment of AD, myasthenia gravis and glaucoma. The IC_{50} values of AChE and BchE inhibited by most steroidal alkaloids are listed in Table 19.

Phulchowkiamide A (**121**), containing a carbonyl group at C-4 along with the tigloylamino moiety at position C-3, was found to be the most potent inhibitor of AChE and BChE among these alkaloids with IC_{50} values of 0.5 and 0.4 μM, respectively [71]. Similarly, compounds such as sarsalignone (**64**) [68], sarsaligenone (**65**) [70], sarcovagine D (**116**), sarcovagenine C (**117**) [71], and hookerianamide F (**122**) [73], which have in common with **121**, displayed higher inhibitory activity than other compounds. In general, the *α*,*β*-unsaturated carbonyl group and tigloylamino moiety might be considered to be important factors to increase the activity.

From the list, we found that some alkaloids, including axillarine C (**96**), hookerianamide B (**102**), hookerianamide C (**103**), saligenamide D (**140**), cyclovirobuxeine A (**202**), hyrcanone (**273**), impericine (**312**), delavine (**325**), and persicanidine A (**345**), appeared to be more selective inhibitors of BChE. The presence of a C-2*β* hydroxy group, as in 2-hydroxysalignamine (**49**), saligenamide C

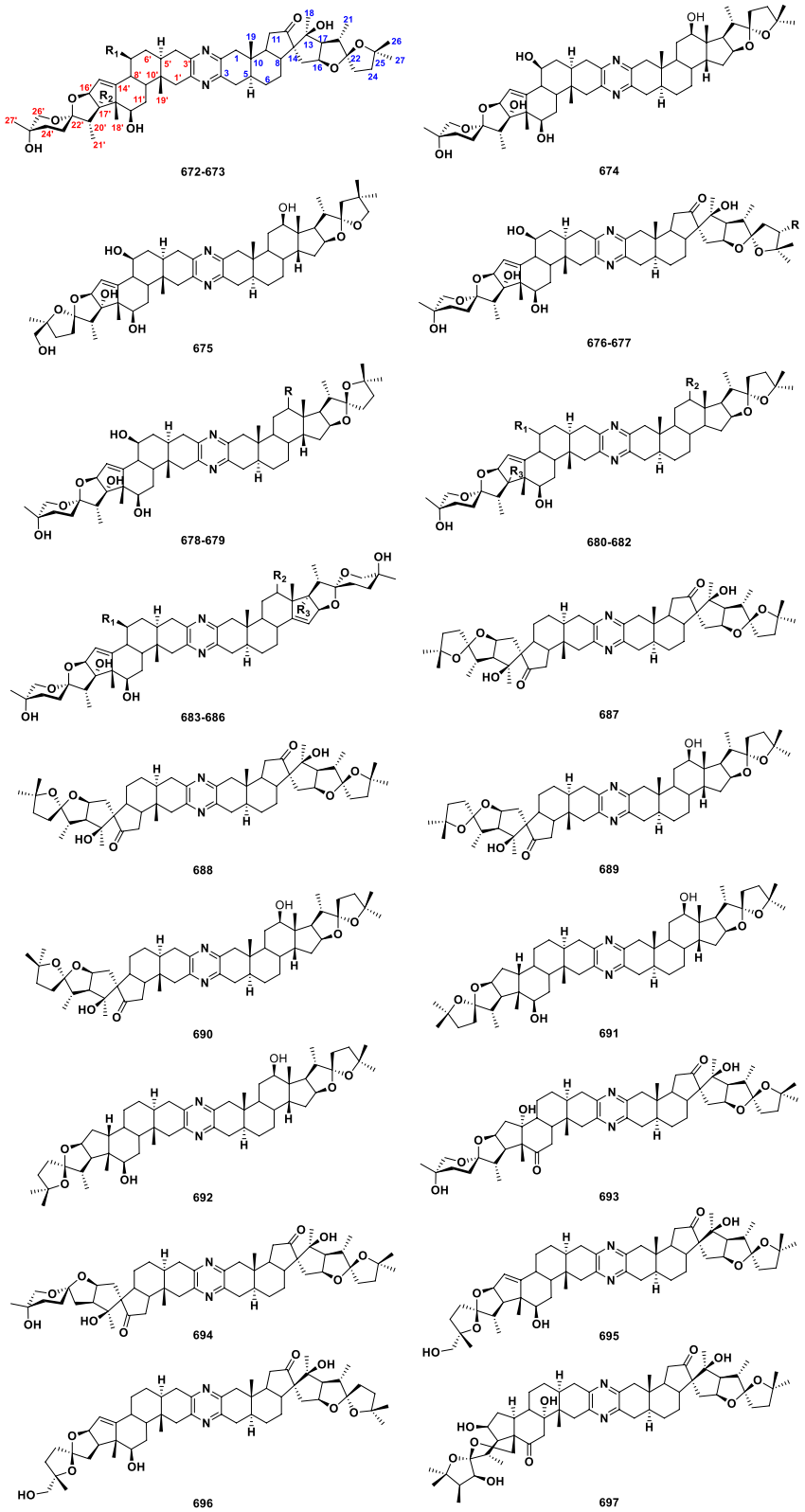


Fig. 19 Structures of ritterazines **672–697**

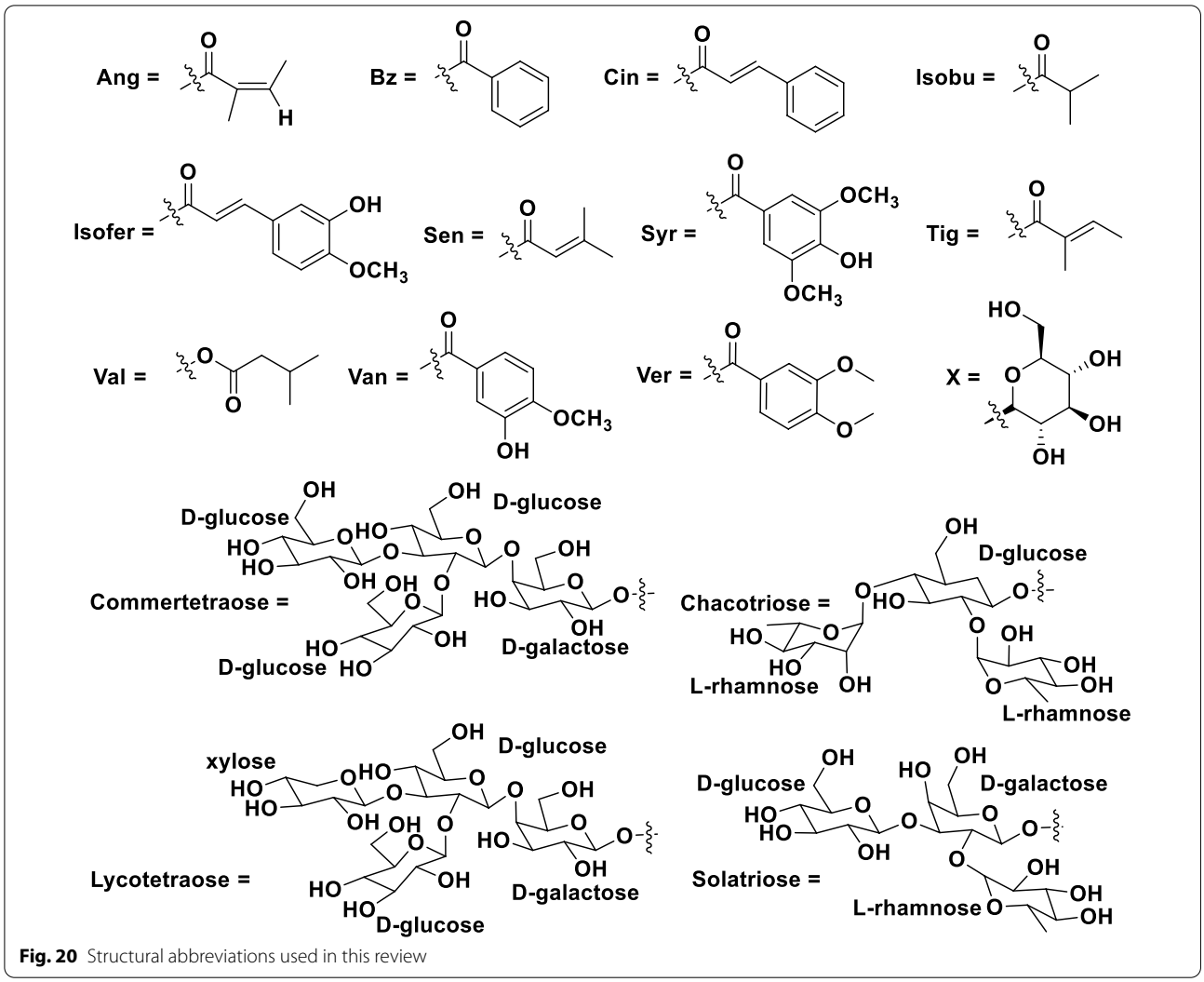


Fig. 20 Structural abbreviations used in this review

(**93**), axillarine C (**96**), axillarine F (**97**), salonine A (**98**), and hookerianamide A (**137**) caused a negative effect on the inhibitory activity towards both AChE and BChE. In general, pregnane alkaloids were more selective than cyclopregnane alkaloids towards AChE and BChE. This might be due to the effect of the C-4 methyl groups and the cyclopropane ring in cyclopregnane alkaloids that decreased the activity.

3.3 Antimicrobial effects

Steroidal alkaloids are considered a part of plant chemical defenses against various pathogens, namely, fungi, bacteria, and viruses. Epipachysamine-*E*-5-ene-4-one (**66**) and iso-*N*-formylchonemorphine (**90**) showed strong antibacterial activity against a wide range of pathogenic bacteria (*Bacillus cereus*, *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Pseudom aeruginosa*) with minimum inhibitory concentrations (MICs) of 0.0312–0.2500 (mg/mL), compared with the widely used antibiotics amoxicillin and ampicillin (0.0625–0.2500 mg/mL) [59]. The five pregnane alkaloids sarcovagine C (**80**), hookerianamide I (**107**), chonemorphine (**108**), *N*-methypachysamine A (**109**) and hookerianamide H (**123**), were all active in antibacterial properties against *Bacillus subtilis* with MIC values of lower than 20 μg/mL, and most of them displayed moderate to good antibacterial activities against *Micrococcus luteus*, *Streptococcus faecalis*, and *Pseudomonas pallida* [349]. As saligcinnamide (**85**), N_a-methyl epipachysamine D (**86**) and epipachysamine D (**87**) had the same skeleton, and possessed potent antibacterial activity against seven human pathogenic bacteria with inhibition zones ranging from 6 to 12 mm [67].

(+)-16*α*,31-Diacetylbuxadine (**278**) exhibited significant antibacterial activity with zones of inhibition (ZI) of 14–19 mm against *K. pneumoniae* and *Salmonella typhi* and moderate to weak activity (ZI = 4–12 mm) against other seven human pathogenic bacterias [92]. Neoverataline A (**379**), neoverataline B (**380**), stenophylline B

Table 18 Cytotoxic activity of steroidal alkaloids against tumor cell lines

Compounds	Cells	Activity	References
Mokluangin A (**10**)	Small cell lung cancer (NCI-H187)	IC_{50} = 30.6 μM	[41]
Irehline (**36**)	NCI-H187	IC_{50} = 27.7 μM	[41]
3-*Epi*-gitingensine (**38**)	Oral epidermoid carcinoma (KB)	IC_{50} = 21.2 μM	[42]
Paravallarine (**39**)	KB	IC_{50} = 12.8 μM	[42]
Pachysamine E (**57**)	Mouse lymphoid neoplasm (P388)	IC_{50} = 0.46 μg/mL	[54]
	Parental and the Adriamycin (doxorubicin)-resistant subline of mouse leukemia (P388/ADM)	IC_{50} = 0.45 μg/mL	[54]
Hookerianine A (**61**)	Colon cancer (SW480)	IC_{50} = 10.97 ± 1.36 μM	[56]
	Human prostate cancer (PC3)	IC_{50} = 32.97 ± 3.78 μM	[56]
	Breast adenocarcinoma (MCF-7)	IC_{50} = 37.70 ± 0.99 μM	[56]
	Human myelogenous leukemia (K562)	IC_{50} = 11.86 ± 0.82 μM	[56]
Vaganine A (**82**)	Breast cancer (MB-MDA-231)	IC_{50} = 0.18 μM	[82]
Epipachysamine D (**87**)	Human myeloid leukemia (HL-60)	IC_{50} = 2.96 μM; IC_{50} = 2.87 μM	[75, 79]
	Breast adenocarcinoma (MCF-7)	IC_{50} = 28.92 ± 1.22 μM	[56]
Epipachysamine E (**91**)	Human melanoma (B16)	IC_{50} = 2.5 μg/mL	[54]
	Shionogi carcinoma (SC115)	IC_{50} = 3.4 μg/mL	[54]
	Mouse lymphoid neoplasm (P388)	IC_{50} = 0.56 μg/mL	[54]
	Parental and the adriamycin (doxorubicin)-resistant subline of mouse leukemia (P388/ADM)	IC_{50} = 0.66 μg/mL	[54]
Sarcovagine D (**116**)	Hepatocellular carcinoma (SMMC-7721)	IC_{50} = 16.69 μM	[75]
	Lung cancer (A-549)	IC_{50} = 11.17 μM	[75]
	Breast cancer (SK-BR-3)	IC_{50} = 4.17 μM; IC_{50} = 2.25 μM	[75, 79]
	Pancreatic cancer (PANC-1)	IC_{50} = 10.76 μM; IC_{50} = 2.70 μM	[75, 79]
	Human myeloid leukemia (K562)	IC_{50} = 3.53 μM	[79]
	Gastric carcinoma (SGC7901)	IC_{50} = 4.87 μM	[79]
Sarsaligenine A (**128**)	Human myeloid leukemia (HL-60)	IC_{50} = 2.87 μM	[79]
	Human myeloid leukemia (K562)	IC_{50} = 8.48 μM	[79]
	Gastric carcinoma (SGC7901)	IC_{50} = 29.94 μM	[79]
	Breast cancer (SK-BR-3)	IC_{50} = 10.14 μM	[79]
	Pancreatic cancer (PANC-1)	IC_{50} = 12.34 μM	[79]
Sarsaligenine B (**129**)	Human myeloid leukemia (HL-60)	IC_{50} = 3.61 μM	[79]
	Human myeloid leukemia (K562)	IC_{50} = 17.10 μM	[79]
	Gastric carcinoma (SGC7901)	IC_{50} = 21.53 μM	[79]
	Breast cancer (SK-BR-3)	IC_{50} = 17.89 μM	[79]
	Pancreatic cancer (PANC-1)	IC_{50} = 32.84 μM	[79]
Holamine (**145**)	Human myeloid leukemia (HL-60)	IC_{50} = 24.22 μM	[75]
	Human colon adenocarcinoma (HT-29)	IC_{50} = 31.06 μM	[83]
	Human cervical cancer (HeLa)	IC_{50} = 51.42 μM	[83]
	Human breast adenocarcinoma (MCF-7)	IC_{50} = 42.82 μM	[83]
	Non-cancerous human fibroblast (KMST-6)	IC_{50} = 102.95 μM	[83]
Pachysanonin (**149**)	Lewis lung carcinoma (LLC)	IC_{50} = 2.0 ± 0.3 μg/mL	[83]
Funtumine (**154**)	Human colon adenocarcinoma (HT-29)	IC_{50} = 22.36 μM	[83]
	Human cervical cancer (HeLa)	IC_{50} = 46.17 μM	[83]
	Human breast adenocarcinoma (MCF-7)	IC_{50} = 52.69 μM	[83]
	Non-cancerous human fibroblast (KMST-6)	IC_{50} = 85.45 μM	[83]
Pachystermine A (**157**)	Human melanoma (B16)	IC_{50} = 6.3 μg/mL	[54]
	Breast cancer (MB-MDA-231)	IC_{50} = 0.32 μM	[82]
Terminamine A (**159**)	MB-MDA-231	IC_{50} = 0.18 μM	[82]
Terminamine B (**160**)	MB-MDA-231	IC_{50} = 0.20 μM	[82]
Terminamine C (**161**)	MB-MDA-231	IC_{50} = 0.08 μM	[82]

Table 18 (continued)

Compounds	Cells	Activity	References
Terminamine D (**163**)	MB-MDA-231	IC_{50} = 0.20 μM	[82]
Terminamine E (**164**)	MB-MDA-231	IC_{50} = 0.07 μM	[82]
Hookerianine B (**171**)	Colon cancer (SW480)	IC_{50} = 5.97 ± 0.13 μM	[56]
	Human hepatocarcinoma (SMMC-7721)	IC_{50} = 16.19 ± 0.56 μM	[56]
	Human prostate cancer (PC3)	IC_{50} = 11.57 ± 0.86 μM	[56]
	Breast adenocarcinoma (MCF-7)	IC_{50} = 19.44 ± 1.70 μM	[56]
	Human myelogenous leukemia (K562)	IC_{50} = 7.95 ± 0.02 μM	[56]
Veratramine (**392**)	Lung cancer (A549)	IC_{50} = 8.9 μmol/L	[185]
	Pancreatic cancer (PANC-1)	IC_{50} = 14.5 μmol/L	[185]
	Hh-dependent (SW1990)	IC_{50} = 26.1 μmol/L	[185]
	Hh-dependent (NCI-H249)	IC_{50} = 8.5 μmol/L	[185]
	Human glioma (SF188)	IC_{50} = 97.8 μmol/L	[198]
Germine (**358**)	Hh-dependent (SW1990)	IC_{50} = 47.2 μmol/L	[185]
	Hh-dependent (NCI-H249)	IC_{50} = 24.1 μmol/L	[185]
Cyclopamine (**432**)	Lung cancer (A549)	IC_{50} = 14.4 μmol/L	[185]
	pancreatic cancer (PANC-1)	IC_{50} = 29.3 μmol/L	[185]
	Hh-dependent (SW1990)	IC_{50} = 48.6 μmol/L	[185]
	Hh-dependent (NCI-H249)	IC_{50} = 4.4 μmol/L	[185]
	Human pancreatic adenocarcinoma (HPAF-2)	IC_{50} = 8.79 ± 0.94 μM	[335]
	Human pancreatic adenocarcinoma cell line Panc 10.05	IC_{50} = 11.33 ± 0.41 μM	[335]
	Human pancreatic adenocarcinoma cell line Panc 8.13	IC_{50} = 14.49 ± 0.85 μM	[335]
	Human pancreatic adenocarcinoma cell line Panc 2.03	IC_{50} = 16.57 ± 0.27 μM	[335]
	Human pancreatic adenocarcinoma cell line AsPC-1	IC_{50} = 16.74 ± 1.30 μM	[335]
	Human pancreatic adenocarcinoma cell line CFPAC-1	IC_{50} = 19.59 ± 0.32 μM	[335]
	Human pancreatic adenocarcinoma cell line BxPC-3	IC_{50} = 36.17 ± 0.31 μM	[335]
	Human pancreatic adenocarcinoma cell line S2013	IC_{50} = 45.09 ± 1.27 μM	[335]
α-Tomatine (**459**)	Breast cancer (MDA-MB-231)	IC_{50} = 26.4 ± 3.6 μg/mL	[348]
	Gastric adenocarcinoma (KATO-III)	IC_{50} = 16.4 ± 10.0 μg/mL	[348]
	Prostate cancer (PC3)	IC_{50} = 3.0 ± 0.3 μg/mL	[348]
α-Solamargine (**500**)	Human adenocarcinoma (H441)	IC_{50} = 3.0 μM	[345]
	Squamous cell lung carcinoma (H520)	IC_{50} = 6.7 μM	[345]
	Large cell lung cancer (H661)	IC_{50} = 7.2 μM	[345]
	Small cell lung cancer (H69)	IC_{50} = 5.8 μM	[345]
	Cervical carcinoma (HeLa)	IC_{50} = 6.0 μM	[346]
	Lung cancer (A549)	IC_{50} = 8.0 μM	[346]
	Breast adenocarcinoma (MCF-7)	IC_{50} = 2.1 μM	[346]
	Human myelogenous leukemia (K562)	IC_{50} = 5.2 μM	[346]
	Colon cancer cell line (HCT116)	IC_{50} = 3.8 μM	[346]
	Human primary glioblastoma (U87)	IC_{50} = 3.2 μM	[346]
	Liver cancer (HepG2)	IC_{50} = 2.5 μM	[346]
α-Solanine (**528**)	$HepG_2$	IC_{50} = 14.47 μg/mL	[255]
Plakinamine H (**625**)	Rat glioma (C6)	IC_{50} = 9.0 μg/mL	[306]
Plakinamine G (**630**)	C6	IC_{50} = 6.8 μg/Ml	[306]
Tetrahydroplakinamine A (**631**)	C6	IC_{50} = 1.4 μg/mL	[306]
Dihydroplakinamine K (**632**)	Human colon tumor (HCT-116)	IC_{50} = 1.4 μM	[307]
Plakinamine I (**633**)	HCT-116	IC_{50} = 5.2 μM	[307]
Plakinamine J (**634**)	HCT-116	IC_{50} = 10.6 μM	[307]
Plakinamine K (**635**)	HCT-116	IC_{50} = 6.1 μM	[307]
Cephalostatin 1 (**652**)	Pancreas adenocarcinoma (BXPC-3)	GI_{50} = 0.044 nM	[326]

Table 18 (continued)

Compounds	Cells	Activity	References
	Breast adenocarcinoma (MCF-7)	GI_{50} = 0.099 nM	[326]
	Glioblastoma (SF-268)	GI_{50} = 1.60 nM	[326]
	Human lung large cell carcinoma (NCI-H460)	GI_{50} = 0.044 nM	[326]
	Colon carcinoma (KM20L2)	GI_{50} = 0.066 nM	[326]
	Human prostate adenocarcinoma (DU-145)	GI_{50} = 0.11 nM	[326]
Cephalostatin 2 (**653**)	Pancreas adenocarcinoma (BXPC-3)	GI_{50} = 0.022 nM	[326]
	Breast adenocarcinoma (MCF-7)	GI_{50} = 0.022 nM	[326]
	Glioblastoma cells (SF-268)	GI_{50} = 0.12 nM	[326]
	Human lung large cell carcinoma (NCI-H460)	GI_{50} = 0.0056 nM	[326]
	Colon carcinoma (KM20L2)	GI_{50} = 0.0060 nM	[326]
	Human prostate adenocarcinoma (DU-145)	GI_{50} = 0.11 nM	[326]
Cephalostatin 9 (**664**)	Pancreas adenocarcinoma (BXPC-3)	GI_{50} = 14 nM	[326]
	Breast adenocarcinoma (MCF-7)	GI_{50} = 110 nM	[326]
	Glioblastoma (SF-268)	GI_{50} = 150 nM	[326]
	Human lung large cell carcinoma (NCI-H460)	GI_{50} = 39 nM	[326]
	Colon carcinoma (KM20L2)	GI_{50} = 58 nM	[326]
Cephalostatin 20 (**665**)	Pancreas adenocarcinoma (BXPC-3)	GI_{50} = 16 nM	[326]
	Breast adenocarcinoma (MCF-7)	GI_{50} = 22 nM	[326]
	Glioblastoma (SF-268)	GI_{50} = 36 nM	[326]
	Human lung large cell carcinoma (NCI-H460)	GI_{50} = 6.00 nM	[326]
	Colon carcinoma (KM20L2)	GI_{50} = 7.20 nM	[326]
	Human prostate adenocarcinoma (DU-145)	GI_{50} = 210 nM	[326]
Ritterazine A (**672**)	Murine leukemia (P388)	IC_{50} = 0.0035 μg/mL	[333]
Ritterazine T (**673**)	P388	IC_{50} = 0.46 μg/mL	[333]
Ritterazine B (**674**)	P388	IC_{50} = 0.00015 μg/mL	[333]
Ritterazine C (**675**)	P388	IC_{50} = 0.092 μg/mL	[333]
Ritterazine D (**676**)	P388	IC_{50} = 0.016 μg/mL	[333]
Ritterazine E (**677**)	P388	IC_{50} = 0.0035 μg/mL	[333]
Ritterazine F (**678**)	P388	IC_{50} = 0.00073 μg/mL	[333]
Ritterazine H (**679**)	P388	IC_{50} = 0.016 μg/mL	[333]
Ritterazine G (**680**)	P388	IC_{50} = 0.00073 μg/mL	[333]
Ritterazine I (**681**)	P388	IC_{50} = 0.014 μg/mL	[333]
Ritterazine Y (**682**)	P388	IC_{50} = 0.0035 μg/mL	[333]
Ritterazine J (**683**)	P388	IC_{50} = 0.013 μg/mL	[333]
Ritterazine K (**684**)	P388	IC_{50} = 0.0095 μg/mL	[333]
Ritterazine L (**685**)	P388	IC_{50} = 0.010 μg/mL	[333]
Ritterazine M (**686**)	P388	IC_{50} = 0.015 μg/mL	[333]
Ritterazine N (**687**)	P388	IC_{50} = 0.46 μg/mL	[333]
Ritterazine O (**688**)	P388	IC_{50} = 2.1 μg/mL	[333]
Ritterazine P (**689**)	P388	IC_{50} = 0.71 μg/mL	[333]
Ritterazine Q (**690**)	P388	IC_{50} = 0.57 μg/mL	[333]
Ritterazine R (**691**)	P388	IC_{50} = 2.1 μg/mL	[333]
Ritterazine S (**692**)	P388	IC_{50} = 0.46 μg/mL	[333]
Ritterazine U (**693**)	P388	IC_{50} = 2.1 μg/mL	[333]
Ritterazine V (**694**)	P388	IC_{50} = 2.1 μg/mL	[333]
Ritterazine W (**695**)	P388	IC_{50} = 3.2 μg/mL	[333]
Ritterazine X (**696**)	P388	IC_{50} = 3.0 μg/mL	[333]
Ritterazine Z (**697**)	P388	IC_{50} = 2.0 μg/mL	[333]

Table 19 Cholinesterase-inhibiting activities of steroidal alkaloids

Compounds	IC_{50}/μM		References
	AChE	BChE	
Salonine B (**47**)	n.a	4.5	[50]
2-Hydroxysalignamine (**49**)	82.5	20.9	[51]
N-[Formyl(methyl)amino]salonine B (**50**)	48.6	10.5	[51]
Sarsalignone (**64**)	7	2.2	[68]
Sarsaligenone (**65**)	5.8	4.3	[70]
Alkaloid C (**71**)	48.6	10.5	[50]
Salignarine F (**72**)	30.2	1.9	[51]
Saracosine (**73**)	20	3.8	[51]
Sarcodinine (**74**)	40	12.5	[51]
Sarcovagine C (**80**)	8	0.3	[74]
Vaganine A (**82**)	8.6	2.3	[70]
Sarcorine (**83**)	70	10.3	[70]
Saligcinnamide (**85**)	20	4.8	[70]
N_a-Methyl epipachysamine D (**86**)	10.1	3.2	[71]
Epipachysamine D (**87**)	28.9	2.8	[51]
Salignenamide A (**88**)	50.6	4.6	[70]
Iso-*N*-Formylchonemorphine (**90**)	6.3	4.07	[51]
Saligenamide C (**93**)	61.3	38.3	[70]
Saligenamide F (**94**)	6.3	4.1	[70]
2*β*-Hydroxyepipachysamine D (**95**)	78.2	28.9	[70]
Axillarine C (**96**)	227.9	18	[70]
Axillarine F (**97**)	182.4	18.2	[70]
Salonine A (**98**)	33.4	32.7	[50]
Dictyophlebine (**99**)	6.2	3.6	[51]
Hookerianamine A (**100**)	18.9	0.9	[71]
Isosarcodine (**101**)	10.3	1.9	[72]
Hookerianamide B (**102**)	26.4	0.7	[71]
Hookerianamide C (**103**)	23.2	0.6	[71]
Hookerianamide E (**105**)	15.9	6	[73]
Hookerianamide G (**106**)	11.4	1.5	[73]
Hookerianamide I (**107**)	34.1	0.3	[74]
Sarcovagine D (**116**)	2.2	2.3	[71]
Sarcovagenine C (**117**)	1.5	0.7	[71]
Axillaridine A (**118**)	5.21	2.5	[70]
2,3-Dehydrosarsalignone (**119**)	7	32.3	[61]
Phulchowkiamide A (**121**)	0.5	0.4	[71]
Hookerianamide F (**122**)	1.6	7.2	[73]
Hookerianamide H (**123**)	2.9	1.9	[74]
(−)-Vaganine D (**133**)	46.9	10	[80]
5,6-Dihydrosarconidine (**135**)	20.3	1.9	[51]
16-Dehydrosarcorine (**136**)	12.5	3.9	[61]
Hookerianamide A (**137**)	82.7	200	[71]
Saligenamide D (**140**)	185.2	23.7	[70]
2-Hydroxysalignarine E (**141**)	16	6.9	[51]
Salonine C (**142**)	7.8	32.3	[51]
Buxasamarine (**196**)	25.4	0.7	[100]
Cycloprotobuxine C (**201**)	38.8	2.7	[100]
Cyclovirobuxeine A (**202**)	105.7	2	[100]

Table 19 (continued)

Compounds	IC_{50}/μM		References
	AChE	BChE	
(+)-Benzoylbuxidienine (**238**)	35	No	[111]
Hyrcatrienine (**257**)	No	1.7	[93]
Hyrcanone (**273**)	145	20	[93]
(+)-O^6-Buxafurandiene (**283**)	17	No	[111]
(+)-7-Deoxy-O^6-buxafurandiene (**284**)	13	No	[111]
Impericine (**312**)	67.97 ± 2.46	1.607	[139]
Forticine (**313**)	> 500	100.5 ± 0.445	[139]
Delavine (**325**)	105.5 ± 1.45	1.706 ± 0.11	[139]
Persicanidine A (**345**)	352.2 ± 4.03	4.245 ± 0.079	[139]

n.t. not tested, *n.a.* not active

(**564**), veramiline-3-*O*-*β*-D-glucopyranoside (**566**) and jervine (**427**) were tested for antifungal properties against the phytopathogens *Phytophthora capisis* and *Rhizoctonia cerealis*, among which **380**, **564** and **566** displayed strong activity against *P. capisis* with MICs at 120, 80 and 80 μg/mL, respectively. The MIC of triadimefon, a positive control, against *P. capisis* was 80 μg/mL [125].

Tomatidine (**458**) potentiated the action of several aminoglycoside antibiotics (gentamicin, kanamycin, tobramycin, amikacin and streptomycin) against *S. aureus*, and the synergy between **458** and aminoglycosides could help reduce the incidence of resistance. Furthermore, **458** affected the haemolytic ability of *S. aureus* and repressed several agr-regulated virulence factors [350]. *α*-Chaconine (**527**), *α*-solanine (**528**), *α*-solamargine (**500**), *α*-solasonine (**501**), and *α*-tomatine (**459**) showed antimalarial activity, among which the most active compound **527** had no additive effect with **528**. When orally administered at 7.5 mg/kg/day for 4 days, **527** suppressed the parasitemia level by 71.38% [351]. Among the four mycobacterial species, *Mycobacterium tuberculosis*, *Mycobacterium avium*, *Mycobacterium intracellulare* and *Mycobacterium simiae*, plakinamine P (**640**) exhibited the strongest antibacterial effect against *M. tuberculosis*, giving a MIC of 1.8 μg/mL [313].

3.4 Anti-inflammatory and analgesic effects

Solasodine (**513**) significantly reduced the inflammatory reaction to carrageenan-induced rat paw oedema from 19.5 to 56.4% [352]. In addition, the antinociceptive activity of **513** was evaluated by a hot plate, formalin, and writhing tests. **513** caused a significant decrease in nociception at a dose of 8 mg/kg in acetic acid-induced mice abdominal constrictions, with a maximum inhibition of 61%, compared to indomethacin (74%). It could also significantly reduce the painful sensation caused by formalin and produce a significant increase in the pain threshold in the hot plate test. Overall, the results suggested that **513** may possess analgesic activity through both central and peripheral mechanisms [353].

The data provided by Chiu et al. suggested that tomatidine (**458**) inhibited NF-κB nuclear translocation and c-Jun N-terminal kinase activation, thereby decreasing the expression of COX-2 and inducible cytotoxic nitric oxide (NO) synthase, which might be beneficial for anti-inflammatory therapy. They also found **458** had a better anti-inflammatory effect than solasodine (**513**) in Lipopolysaccharide (LPS)-stimulated RAW 264.7 mouse macrophages [354].

α-Chaconine (**527**) and solanidine (**535**) were responsible for the anti-inflammatory effect, which was dependent on reducing the production of interleukin-2 and interleukin-8 induced by canidin A in Jurkat cells, and the induced NO production by LPS stimulated macrophages [355].

3.5 Anti-myocardial ischemia effects

Buxus microphylla is often used to treat cardiovascular and cerebrovascular diseases as *a* folk medicine in China. Cyclovirobuxine D (**203**) was the most potent component contributing to the anti-myocardial ischemia effects of the "huangyangning" tablet. This Chinese drug is used to treat cardiovascular and cerebrovascular diseases and has been developed successfully for more than 10 years in China. In the myocardial ischemia model induced by isoprenaline or pituitrin, 1.1 and 2.2 mg/kg cyclovirobuxine D could improve model rat plasma superoxide dismutase (SOD) activation, and reduce the plasma MDA, LDH, and phosphocreatine kinase (CPK) contents of model rats [356]. The main mechanism of **203** in treating acute myocardial ischemia may be attributed to inhibiting

blood stasis and thrombosis, enhancing NO release, and opening K_{ATP} channels [357]. In addition, data from a study of rats with congestive heart failure showed significant benefits after oral administration of **203**, indicating that it may be a promising and useful drug in the treatment of cardiac dysfunction [358].

3.6 Anti-giogenesis effects

Cortistatins, novel steroidal alkaloids extracted from *Corticium sponge*, showed highly selective anti-proliferative activity against human umbilical vein endothelial cells (HUVECs), which inhibited the formation of original capillaries, a process known as angiogenesis [314]. Among the eleven cortistatins A–J (**641**−**651**), cortistatins A (**641**) and J (**651**) showed the most strongest anti-proliferative action against HUVECs with IC_{50} values of 1.8 and 8 nM, which were 3000 and 300–1100 times more selective than normal human dermalfibroblast (NHDF) and tumor cell murine neuroblastoma cells (Neuro2A), respectively. [315].

3.7 Others

Among the four conanine-type alkaloids, conessine (**1**), conimin (**9**), mokluangin A (**10**), and irehline (**36**), **36** showed the most effective antimalarial activity (IC_{50} = 1.2 μM) against *Plasmodium falciparum,* comparable to that of the positive control dihydroartemisinine with an IC_{50} of 3.7 nM [41].

The anti-tussive activity of three steroidal alkaloids was also investigated. yibeinone C (**347**), imperialine (**335**), yibeinone B (**402**), and showed an apparent concentration-dependent relaxation of isolated tracheal preparation, amongst **347** and **335** showed significant effects with pA_2 values of 6.19 and 8.41, and EC_{50} values of 0.65 μmol/L and 4.40 nmol/L, respectively [156].

The five steroidal alkaloids puqienine A (**400**), puqienine B (**401**), puqietinone (**577**), *N*-demethylpuqietinone (**579**), and puqietinonoside (**580**) could significantly prolong the latent period and reduce the number of coughs in ammonia-induced mouse cough models at doses of 5 and 10 mg/kg, confirming their antitussive activity compared to the positive control codeine. The presence of these compounds may be responsible for the traditional use of *Fritillaria puqiensis* in cough remedies [188].

Plakinamines J (**634**), N (**636**), and O (**637**), containing a substituted pyrrolidine ring, showed potent antiproliferative activity against seven human colon carcinoma cell lines with mean GI_{50} values of 11.5, 2.4 and 1.4 μM, respectively, whereas plakinamine I (**633**) with the pyrrolidine nitrogen formed an additional fused piperidine ring system that exhibited relatively weak activity [311].

4 Toxicity

Jervine (**427**) and cyclopamine (**432**), veratrum alkaloids isolated from *Veratrum californicum*, had prominent teratogenic activity to produce synophthalmia and related cephalic malformations in sheep, cattle, goats and rabbits [359, 360]. In addition, the presence of C-5, C-6 olefinic linkages in the framework of jervanes was found to be a critical structural factor to enhance teratogenicity induction [361].

In both pregnant and nonpregnant mice, tomatidine (**458**), solasodine (**513**), and solanidine (**535**) induced an increase in liver weight after being fed a diet containing 2.4 mmol/kg of these aglycones for 14 days [362].

In terms of the LC_{50} and EC_{50} after 96 h of exposure, *α*-chaconine (**527**) was teratogenic and more embryotoxic than *α*-solanine (**528**) in frogs. The carbohydrate side chain attached to the 3-OH group of solanidine (**535**), the only difference between these two compounds, appeared to be an important factor in governing teratogenicity [363].

A pathophysiological study showed that isorubijervine (**543**) and rubijervine (**544**) were highly toxic compounds with LD_{50} values of 1.14 and 1.77 mg/kg in mice, respectively. They also exerted the strongest ability to inhibit the sodium channel $Na_V1.5$, which plays an essential role in cardiac physiological function [263].

5 Summary

Natural steroidal alkaloids with diverse bioactivities and high toxicity keep them one of the highlighted types of natural products. In this review, the structural diversity and biological activities of 697 natural steroidal alkaloids have been summarized and it is likely that many more steroidal alkaloids with novel structures will be discovered, especially rings E and F. Additionally, the high medicinal potential of cyclovirobuxine D, cyclopamine, *α*-solamargine, *α*-solasonine, cephalostatin 1 and many other members of this intriguing family of natural products is far from being exploited. Therefore, future research in this field will further contribute to understanding their full potential in drug development.

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Author contributions

M-LX searched the literature, collected the data, and drafted the manuscript; B-YH, Z-HQ, T-ZX and Z-JW provided corrective works of phytochemistry and biological activities; X-NW, D-YM and QZ revised the chemical structures. X-DL conceived the projects, revised manuscript and provided financial support. All authors read and approved the final manuscript.

Declarations

Competing interests
The authors declare that there are no conflicts of interest associated with this work.

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