Review Article

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Glycoalkaloids: Structural diversity and pharmacological activities

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Abstract

Glycoalkaloids (GAs) are a class of special secondary metabolites found in plants. Studies have found that they have a wide range of pharmacological activities, such as antiviral, antifungal, and anticancer properties, with significant potential for development and utilization value. At present, alkaloid glucosides mainly fall into 2 categories: indole alkaloid glucosides and steroid alkaloid glucosides. In addition, there are small amounts of quinolines, isoquinolines, isoguanines, and other alkaloids. At present, only a few of the GAs have been found, which is inconsistent with the diversity of alkaloids. In addition, only a few GAs have been isolated and identified. This paper reviews the natural alkaloid glycosides from the perspectives of structural classification and pharmacological activity. It analyzes the reasons for the limited number of isolated components and proposes a rational separation method based on the literature. To provide references for the separation, identification, and bioactivity of glycoalkaloids.

Keywords glycoalkaloids, water-soluble extract, separation methods

Introduction

Natural products have consistently played a pivotal role in pharmaceutical research, exerting profound impacts on the treatment of human diseases[1]. Glycoalkaloids (GAs), a special class of alkaloids, are water-soluble natural products that take alkaloids as aglycans and are connected with monosaccharides or oligosaccharides through C-O, C-C, or N-C bonds. They are weakly alkaline and are present in many plants. GAs have a wide range of pharmacological activities, including anticancer, antiviral, antifungal, and anti-inflammatory properties. In addition, GAs are natural defense-active substances, which belong to a class of secondary metabolites synthesized by plants during genetic evolution to protect against the invasion of microorganisms, animals, and insects. As a result, some of these substances exhibit certain levels of toxicity. Consequently, GAs have received a lot of attention due to their beneficial or detrimental factors.

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In this paper, 200 types of natural alkaloid glycosides were reviewed. The data was collected from SciFinder, PubMed and Web of Science from 2000 to 2024 using "alkaloid glycosides and glycoalkaloid" as keywords. These natural products are classified according to their structural framework, and their biological activities are summarized (**Table 1**). The paper examines the structural classification and pharmacological activity of GAs while also briefly outlining separation methods to provide a reference for related research.

Indole alkaloid glycoside

The fundamental structure of monoterpenoid indole alkaloids, also known as riboid iridoid alkaloids, is formed by the condensation of a riboid strychnoside molecule and a tryptamine molecule through the Mannich reaction. Simple monoterpene indoles can be subdivided into cardambinoid, pentacyclic monoterpene indoles, pentacyclic monoterpene oxidized indoles, tetracyclic monoterpene indoles, tetracyclic monoterpene oxidized indoles and other alkaloids based on their skeleton types and oxidation states (**Fig. 1**).

Monoterpene indole alkaloside

Cardambin-type indole alkaloid glycosides

Cardambine-type indole alkaloids are an important part of monoterpene indole alkaloids, accounting for about 3% of the total. At present, 14 natural cardambine-type indole alkaloides (1-14) have been identified (**Fig. 2**). Among them, compounds 1-3 are typical cardambine-type indole alkalosides. Compound 1 was discovered by Nakashima et al[2] in the Chinese medicine plant Adina rubescens, and its total synthesis from tryptophan derivatives was realized according to the biogenic pathway. Brown et al[3] isolated 2 and 3 from the polar components of *Neolamarckia cadamba* (Roxb.) Bosser of

Table 1

Information table of natural alkaloid glycosides.

No.	English name	Source	CAS registry number	References
1	Secorubenine	*Adina rubescens* Hemsl.	2762850-16-6	[2]
2	3α-dihydrocadambine	*Uncaria rhynchophylla*	54483-84-0	[3]
3	Cadambine	*Uncaria rhynchophylla*	54422-49-0	[3]
4	5-carboxystrictosidine	*Adina rubescens* Hemsl.	34371-47-6	[2]
5	Palicoside	*Palicourea marcgravii* (Rubiaceae)	123828-68-2	[4]
6	Ophiorrhiside A	*Ophiorrhiza pumila*	1464719-38-7	[5]
7	Ophiorrhiside B	*Ophiorrhiza pumila*	1464719-39-8	[5]
8	Ophiorrhiside C	*Ophiorrhiza pumila*	1464719-40-1	[5]
9	Ophiorrhiside D	*Ophiorrhiza pumila*	1464719-41-2	[5]
10	Ophiorrhiside E	*Ophiorrhiza pumila*	1464719-42-3	[5]
11	Ophiorrhiside F	*Ophiorrhiza pumila*	1464719-43-4	[5]
12	Dolichantoside	*Strychnos gossweileri*	68727-52-6	[6]
13	Lyaloside	*Palicourea adusta*	56021-85-3	[7]
14	3,4,5,6-tetradehydrodolichantoside	*Strychnos mellodora*	245041-39-8	[8]
15	Vincoside lactam	*Camptotheca acuminata* Decne	23141-27-7	[9]
16	Strictosamide	*Camptotheca acuminata* Decne; *Nauclea orientalis*	23141-25-5	[9,10]
17	Rhynchophine	*Uncaria rhynchophylla*	84638-29-9	[11]
18	Nauclecoside	*Nauclea officinalis* Pierre ex Pitard	121880-11-3	[12]
19	Nauclecosidine	*Nauclea officinalis* Pierre ex Pitard	121880-13-5	[12]
20	10-hydroxystrictosamide	*Nauclea orientalis*	135531-63-4	[10]
21	6'-*O*-acetylstrictosamide	*Nauclea orientalis*	135531-64-5	[10]
22	2'-*O*-β-D-glucopyranosyl-11-hydroxyvincoside lactam	*Uncaria rhynchophylla*	1190085-36-9	[13]
23	2'-*O*-[β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl]-11-hydroxyvincosamide	*Uncaria rhynchophylla*	2215872-24-3	[14]
24	Neonaucleoside B	*Neonauclea sessilifolia*	539825-81-5	[15]
25	Neonaucleoside C	*Neonauclea sessilifolia*	539825-82-6	[15]
26	(3*S*,7*R*)-javaniside	*Nauclea officinalis*	2254737-84-1	[16]
27	Javaniside epimers	*Tabernaemontana peduncularis*, *Tabernaemontana divaricate*	–	—
28	Javaniside epimers	*Tabernaemontana peduncularis*, *Tabernaemontana divaricate*	–	[17]
29	Nauclealomide A	*Nauclea officinalis*	2191454-07-4	[17]
30	Javanuronic acid	*Tabernaemontana peduncularis*, *Tabernaemontana divaricate*	–	[17]
31	Glabratine	*Uncaria glabrata*	142750-47-8	[18]
32	Naucleamide A-10-*O*-β-D-glucopyranoside	*Nauclea officinalis* Pierre ex Pitard	958002-12-5	[19]
33	10-hydroxycathafoline 10-*O*-α-L-arabinopyranoside	*Catharanthus roseus*	1419802-33-7	[20]
34	10-hydroxydeformodihydropseudoa kuammigine 10-O-α-L-arabinopyranoside	*Catharanthus roseus*	1419802-37-1	[20]
35	Nutanoside A	*Gardneria nutans* Siebold & Zuccarini	–	[21]
36	Nutanoside B	*Gardneria nutans* Siebold & Zuccarini	–	[21]
37	22-*O*-demethyl-22-*O*-β-D-glucopyranosylisocorynoxeine	*Uncaria rhynchophylla*	1190085-37-0	[13]
38	Nauclealomide A	*Nauclea officinalis*	552333-60-5	[16]
39	Umbellatine	*Psychotria umbellata*	141433-60-5	[22]
40	Aspidospermidose	*Rhazya stricta*	110325-67-2	[23]
41	Cryptospirosanguines A	*Cryptolepis sanguinolenta* (Lindl.) Schltr	–	[24]
42	Cryptospirosanguines B	*Cryptolepis sanguinolenta* (Lindl.) Schltr	–	[24]
43	Ternatoside C	*Ranunculus ternatus*	1023629-54-0	[25]
44	Rutaecarpine-10-*O*-β-D-glucopyranoside	*Evodia rutaecarpa* (Juss.) Benth.	1435946-00-1	[26]
45	1-*O*-β-D-glucopyranosylrutaecarpine	*Evodia rutaecarpa*	1884364-62-8	[27]
46	Ternatoside D	*Ranunculus ternatus*	1023629-56-2	[25]
47	Rutaecarpine-10-*O*-rutinoside	*Euodia rutaecarpa* (Juss.) Benth.	1435946-01-2	[28]
48	Bruceacanthinoside	*Brucea javanica* (Simaroubaceae)	159194-91-9	[29]
49	Glucodichotomine B	*Stellaria dichotoma* L. var. *lanceolata*	845673-16-7	[30]
50	Ailantcanthinoside A	*Ailanthus altissima*	960002-00-0	[31]
51	Ailantcanthinoside B	*Ailanthus altissima*	960002-01-1	[31]
52	(6-*O*-β-D-glucopyranosyl-1*H*-indol-3-yl) carboxylic acid methyl ester	*Clematis terniflora* DC	1460326-26-4	[32]

Table 1

(*Continued*)

No.	English name	Source	CAS registry number	References
53	Indican	*Calanthe discolor*	487-60-5	[33]
54	Isatindigoside A	*Isatis tinctoria*	2377567-80-9	[34]
55	Isatindigoside B	*Isatis tinctoria*	2377567-81-0	[34]
56	3*E*,11*E*-(3-methyl-2-butenylidene acid)-2-indolinone-1-*O*-β-D-glucopyranoside	*Actaea dahurica* (syn. *Cimicifuga dahurica*)	2691938-51-7	[35]
57	Isatindigoside D	*Isatis tinctoria*	1989648-04-5	[36]
58	4-(β-glucopyranosyloxy)-1*H*-indole-3-acetamide	*Capparis tenera*	1014977-26-4	[37]
59	4-(β-glucopyranosyloxy)-1*H*-indole-3-carbaldehyde	*Capparis tenera*	1014977-27-5	[37]
60	3-(2-hydroxyethyl)-1*H*-indole-5-*O*-β-D-glucopyranoside	*Tetracentron sinense*	888030-67-9	[38]
61	Liliumtide B	*Lilium davidii* var. *unicolor*	–	[39]
62	*N*-(1-deoxy-α-D-fructofuranos-1-yl)-L-tryptophan	*Lilium davidii* var. *unicolor*	87251-66-9	[39]
63	Isatindigoside L	*Isatis indigotica*	–	[40]
64	Stixilenin	*Stixis scandens*	–	[41]
65	6'-*O*-β-D-apiofuranosylindican	*Calanthe discolor*	1175698-40-4	[33]
66	Glucoindican	*Calanthe discolor*	209465-67-8	[33]
67	Isatigotindoledioside A	*Isatis indigotica*	2270844-24-9	[42]
68	Isatigotindoledioside B	*Isatis indigotica*	2270844-25-0	[42]
69	Isatigotindoledioside C	*Isatis indigotica*	2270844-26-1	[42]
70	Isatigotindoledioside D	*Isatis indigotica*	2270844-27-2	[42]
71	Isatindigodiphindoside	*Isatis indigotica*	2138868-72-9	[42]
72	Isatigotindoledioside E	*Isatis indigotica*	2270844-28-3	[42]
73	Isatigotindoledioside F	*Isatis indigotica*	2270844-29-4	[42]
74	Calanthoside	*Calanthe discolor*	209465-66-7	[33]
75	(-)-(2′*R*)-isatindigoside K	*Isatis indigotica*	–	[40]
76	(+)-(2′*S*)-isatindigoside K	*Isatis indigotica*	–	[40]
77	Glycohaplopine	*Haplophyllum perforatum*	74201-15-3	[43]
78	Glycoperine	*Haplophyllum perforatum* (M. B.) Kar. et Kir.	55740-45-9	[44]
79	1-methyl-4-methoxy-8-(β-D-glucopyranosyloxy)-2(1*H*)-quinolinone	*Echinops gmelinii* (Compositae)	780825-79-8	[45]
80	4-methoxy-8-(β-D-glucopyranosyloxy)-2(1*H*)-quinolinone	*Echinops gmelinii* (Compositae)	780825-80-1	[45]
81	β-D-glu-4,5-dimethoxy-1,6-dihydroxy-10-methyl-acridone	*Atalantia buxifolia*	2374232-13-8	[46]
82	3,4-dihydroxyquinoline 4-*O*-β-D-glucopyranoside	*Glycyrrhiza uralensis*	–	[47]
83	Zanthonitiside A	*Zanthoxylum nitidum*	–	[48]
84	Zanthonitiside **B**	*Zanthoxylum nitidum*	–	[48]
85	Fordianoside	*Aristolochia fordiana*	1600489-69-7	[49]
86	(*S*) -7-hydroxy-1-(*p*-hydroxybenzyl) -2, 2-*N*, *N*-dimethyl-1,2,3, 4-tetrahydroisoquinoline-6-*O*-β-D-glucopyranoside	*Coptis chinensis* Franch.	–	[50]
87	(1*R*)-(4-hydroxybenzyl)-7-hydroxyl-8-*O*-β-D-glucopyranosyl-1,2,3,4-tetrahydroisoquinoline	*Corydalis humosa*	1572928-84-7	[51]
88	Phellodendronoside A	*Phellodendron chinense* Schneid. (Rutaceae)	2765404-44-0	[52]
89	Manshurienine C	*Stephania succifera*	–	[53]
90	*N*-formyl-asimilobine-2-*O*-β-D-glucoside	*Stephania succifera*	1346007-92-8	[54]
91	Erythraline-11β-*O*-glucopyranoside	*Erythrina crista-galli*	–	[55]
92	(+)-16β-D-glucoerysopine	*Erythrina crista-galli*	–	[55]
93	1-*N*-monomethylcarbamate-argentinine-3-*O*-β-D-glucoside	*Stephania succifera*	1623791-36-5	[54]
94	(-)-1-*O*-β-D-glucoside-8-oxo-tetrahydropalmatine	*Stephania succifera*	1623791-35-4	[54]
95	8-oxotetrahy-corydalmine-1-*O*-β-D-glucopyranoside	*Stephania succifera*	–	[53]
96	(*S*) -*N*-methyltetrahydropalmatubine-9-*O*-β-D-glucopyranoside	*Coptis chinensis* Franch.	–	[50]
97	Locustoside A disulfate	*Bruchidius dorsalis* pupal case	–	[56]
98	Locustoside B disulfate	*Bruchidius dorsalis* pupal case	2244792-66-1	[57]
99	Saikachinoside A monosulfate	*Bruchidius dorsalis* pupal case	2244792-64-9	[57]
100	Saikachinoside A disulfate	*Bruchidius dorsalis* pupal case	2244792-65-0	[57]
101	Saikachinoside A trisulfate	*Bruchidius dorsalis* pupal case	–	[56]
102	Saikachinoside B disulfate	*Bruchidius dorsalis* pupal case	–	[56]
103	Hordenine-*O*-[(6"-*O*-*trans*-cinnamoyl)-4'-*O*-β-D-glucopyranosyl-α-L-rhamnopyranoside	*Selaginella doederleinii* Hieron. (Selaginellaceae)	–	[58]
104	Hordenine-*O*-α-L-rhamnopyranoside	*Selaginella doederleinii* Hieron. (Selaginellaceae)	–	[58,59]
105	*N*-methyltyramine-O-α-L-Rhamnopyranoside	*Selaginella doederleinii* Hieron. (Selaginellaceae)	–	[58]
106	Scandemide	*Stixis scandens*	—	[41]
107	Codonopiloside A	*Codonopsis pilosula*	1702285-14-0	[60]
108	Arabinothalictoside	*Aristolochia fordiana*	153287-94-6	[49]

Table 1

(***Continued***)

No.	English name	Source	CAS registry number	References
109	Dissitumine	*Zanthoxylum dissitum* Hemsl.	–	[61]
110	Zanthonitiside C	*Zanthoxylum nitidum*	–	[48]
111	Zanthonitiside D	*Zanthoxylum nitidum*	–	[48]
112	6-hydroxy-5,6-*seco*-stemocurtisinoside	Stemona curtisii Hook.f.	2695587-42-7	[62]
113	Xylostosidine	*Lonicera Xylosteum* L.	74518-57-3	[63]
114	Bakankoside	*Strychnos vacacoua* Baill.	1398-17-0	[64]
115	Grandifoline	*Malaxis grandifolia*	34426-04-5	[65]
116	Liparisalkaloid A	*Liparis odorata*	2081956-72-9	[66]
117	Liparisalkaloid B	*Liparis odorata*	2081956-73-0	[66]
118	Liparisalkaloid C	*Liparis odorata*	1777823-31-0	[66]
119	Unibrasolanosides A	*Fritillaria unibracteata* P. K. Hsiao & K. C. Hsia	101009-59-0	[67]
120	Unibrasolanosides B	*Fritillaria unibracteata* P. K. Hsiao & K. C. Hsia	–	[67]
121	Unibrasolanosides C	*Fritillaria unibracteata* P. K. Hsiao & K. C. Hsia	–	[67]
122	Unibrasolanosides D	*Fritillaria unibracteata* P. K. Hsiao & K. C. Hsia	–	[67]
123	Unibrasolanosides E	*Fritillaria unibracteata* P. K. Hsiao & K. C. Hsia	–	[67]
124	Unibrasolanosides F	*Fritillaria unibracteata* P. K. Hsiao & K. C. Hsia	–	[67]
125	Unibraverazosides A	*Fritillaria unibracteata* P. K. Hsiao & K. C. Hsia	–	[67]
126	Unibraverazosides B	*Fritillaria unibracteata* P. K. Hsiao & K. C. Hsia	–	[67]
127	Unibratomatoside A	*Fritillaria unibracteata* P. K. Hsiao & K. C. Hsia	–	[67]
128	Yibeiglycoalkaloid A	*Fritillaria pallidiflora* Schrenk (Liliaceae)	–	[68]
129	Yibeiglycoalkaloid B	*Fritillaria pallidiflora* Schrenk (Liliaceae)	–	[68]
130	Yibeiglycoalkaloid C	*Fritillaria pallidiflora* Schrenk (Liliaceae)	–	[68]
131	Yibeiglycoalkaloid D	*Fritillaria pallidiflora* Schrenk (Liliaceae)	–	[68]
132	Yibeiglycoalkaloid E	*Fritillaria pallidiflora* Schrenk (Liliaceae)	–	[68]
133	Solanigrinoside A	*Solanum nigrum*	–	[69]
134	Solanigrinoside B	*Solanum nigrum*	–	[69]
135	Solanigrinoside C	*Solanum nigrum*	–	[69]
136	Erianosides A	*Solanum erianthum.*	–	[70]
137	Erianosides B	*Solanum erianthum.*	–	[70]
138	Sinisolanoside A	*Fritillaria sinica*	–	[71]
139	Sinisolanoside C	*Fritillaria sinica*	–	[71]
140	Sinisolanoside B	*Fritillaria sinica*	–	[71]
141	Solanindioside A	*Solanum violaceum*	3026289-33-5	[72]
142	Solanindioside B	*Solanum violaceum*	3026289-34-6	[72]
143	Solanindioside C	*Solanum violaceum*	3026289-35-7	[72]
144	Peimisine-3-*O*-β-D-glucoside	*wabuensis*	1407161-78-7	[73]
145	Verticinoside-β-N-oxide	*Fritillaria sinica*	–	[73]
146	Verticinonoside N-oxide	*Fritillaria sinica*	–	[73]
147	Wabuensin F	*Fritillaria unibracteata* var.	–	[73]
148	Hupehenizioside	*wabuensis*	934279-30-8	[73]
149	Puqiedinone-3-O-β-D-glucoside	*Fritillaria unibracteata* var.	1407162-45-1	[73]
150	Zhebeinone-3-O-β-D-glucoside	*wabuensis*	1258605-31-0	[73]
151	Verticillinoid A	*Fritillaria unibracteata* var.	–	[73]
152	Edpetiline	*wabuensis*	32685-93-1	[73]
153	Imperialine-3-O-β-D-glucoside	*Fritillaria unibracteata* var.	67968-40-5	[73]
154	Wabuensin E	*wabuensis*	–	[73]
155	Wabuensin C	*Fritillaria unibracteata* var. *wabuensis*	–	[73]
156	Wabuensin D	*Fritillaria unibracteata* var.	–	[73]

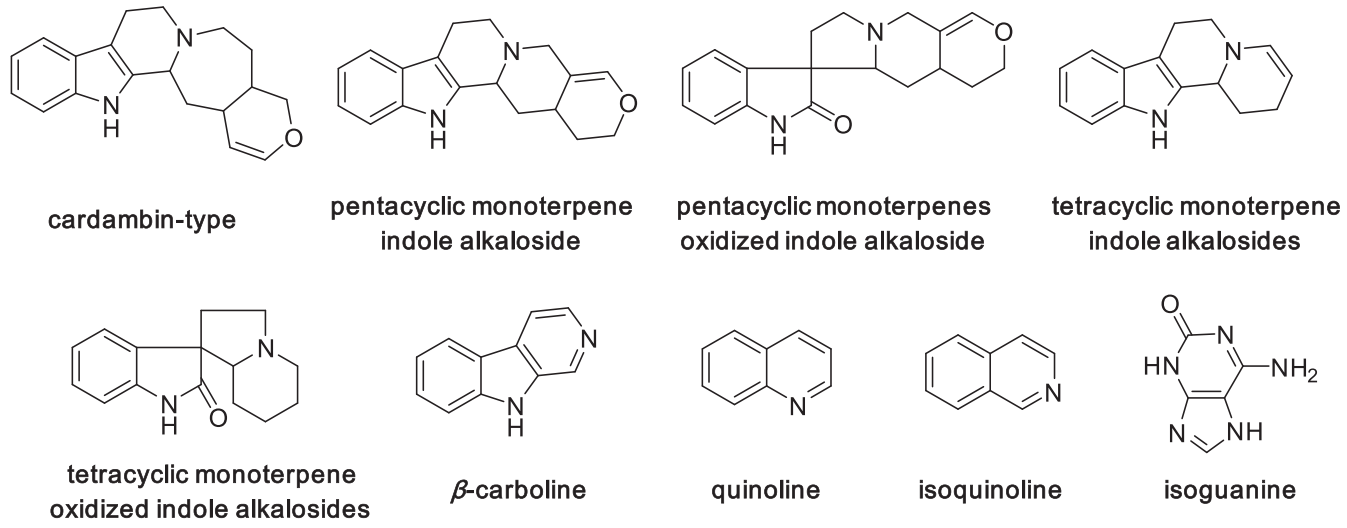


Figure 1. Skeleton types of indole alkaloid glucoside.

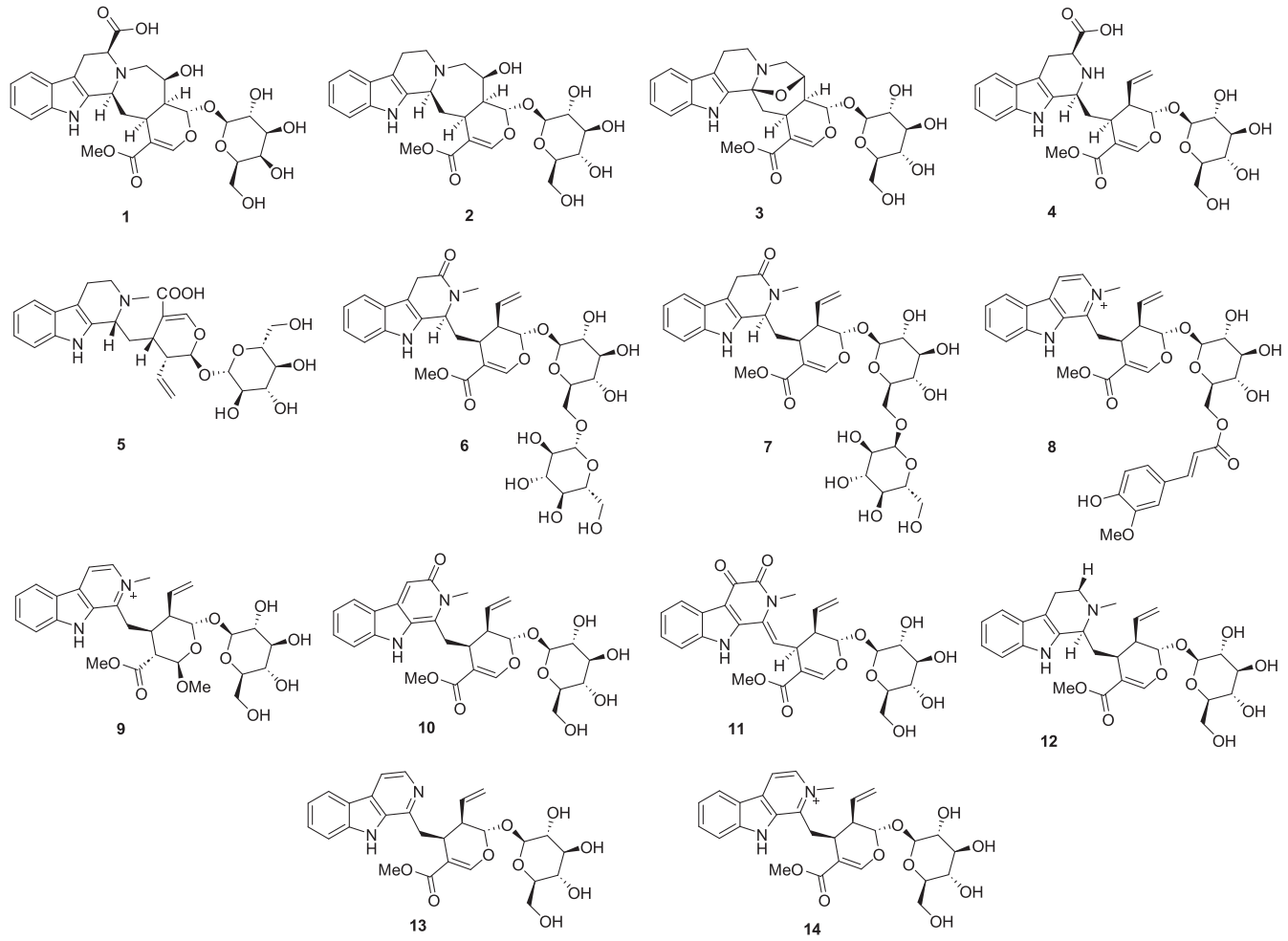


Figure 2. Cadambine type indole alkaloid glycosides.

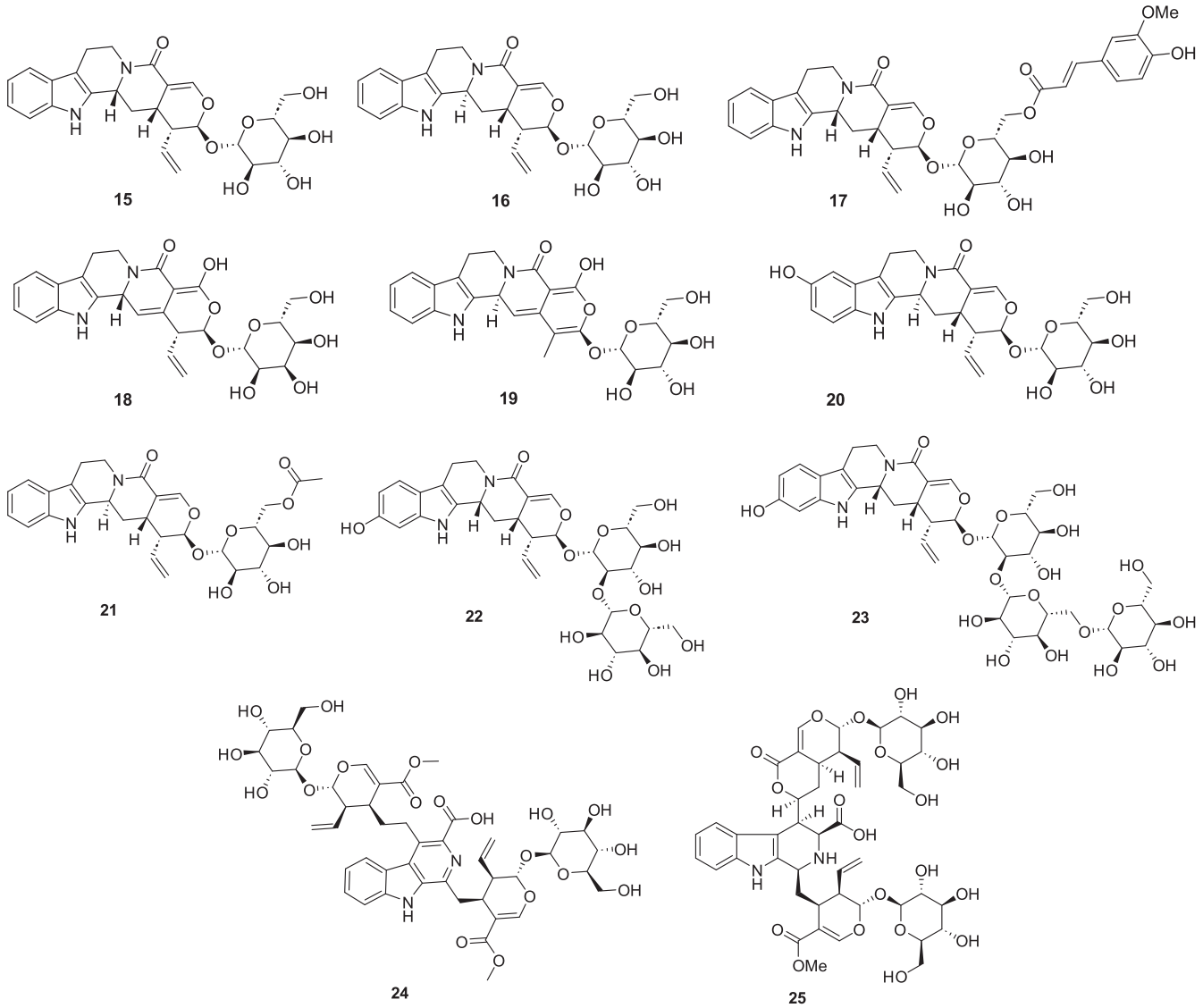


Figure 3. Pentacyclic monoterpene indole alkaloid glycosides.

Rubiaceae Juss. in 1974 using gel permeation and ion exchange chromography. Compounds 4-14 are derivatives of cardamine indole alkaloid glycoside formed by D ring cleavage of cardamine indole alkaloid. They were isolated from *Adina rubescens* Hemsl.[2], *Palicourea marcgravii*[4], *Ophiorrhiza pumila*[5], *Strychnos gossweileri*[6,8], and *Palicourea adusta*[7]. Compounds 6 and 7 have lactam structure fragments in the C ring, and the C-5 and C-6 positions of compound 11 have 1,2-dicarbonyl functional groups, forming a highly oxidized C ring.

Pentacyclic monoterpene indole alkaloside

Pentacyclic monoterpene indole alkaloids accounted for 20% of the total monoterpene indole alkaloids, but only 11 glycosides (15-25) have been found (**Fig. 3**). Compound 15 is the first pentacyclic monoterpene indole alkaloid isolated from *Camptotheca acuminata* Decne[9]. *Uncaria rhynchophylla* contains a large number of pentacyclic monoterpene indole alkaloids, from which 3 glycosides have been found, rhynchophine (17), 2'-*O*-*β*-D-glucopyranosyl-11-hydroxyvincoside lactam (22), and 2'-*O*-[*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranosyl]-11-hydroxyvincosamide (23). Compound 23 was extracted by Zhang et al using alcohol lifting and water precipitation methods[14], and it was the first indole alkaloid triglycoside isolated from the genus. Compound 17 was synthesized using 15 as the starting material[11,13,14]. In addition, indole alkaloids of pentacyclic monoterpenes have also been found in Bilium (*Nauclea officinalis* Pierre ex Pitard)[12] and Rosewood (*Nauclea orientalis*)[10] (18-21). Itoh et al isolated 2 pentacyclic monoterpene indole alkaloids, neophenoside B

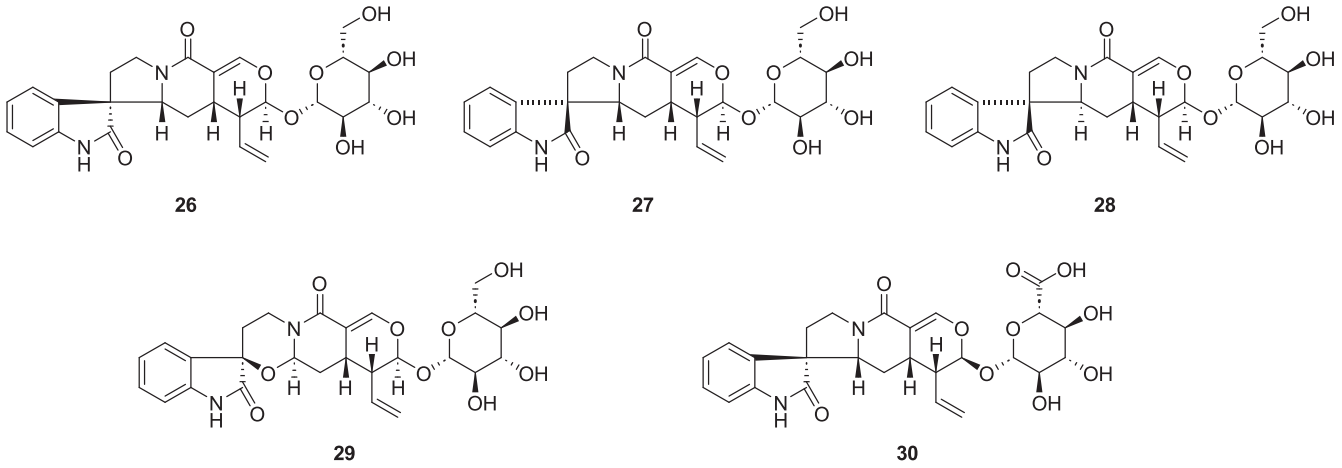


Figure 4. Oxidation of indole alkaloid glycosides by pentacyclic monoterpenes.

and C (24 and 25), from the dried roots of *Neonauclea sessilifolia* in the Rubiaceae family[15].

Oxidation of indole alkaloside by pentacyclic monoterpenes

Pentacyclic monoterpene oxidized indole alkaloids accounted for 24% of the total indole alkaloids of monoterpenes, 5 glycosides were found (**Fig. 4**). Compounds 26-28 were epimers to each other, which were isolated from *Tabernaemontana peduncularis*, *Tabernaemontana divaricate*, and *Nauclea officinalis*[16,17]. Their structures and absolute configurations were determined by NMR, HRESIMS, X-ray diffraction, and ECD calculations. Nauclealomide A (29) is a monoterpenoid indole alkaloid with a rare tetrahydro-2*H*-1,3-oxazine ring. Javanuronic acid (30) is a rare monoterpenoid indole alkaloid with a glucuronic acid moiety[17].

Tetracyclic monoterpene indole alkalosides

Tetracyclic monoterpene indole alkaloids accounted for 28% of the total monoterpene indole alkaloids. At present, 6 tetracyclic monoterpene indole alkaloside glycosides (31-36) have been found in *Uncaria glabrata*[18], Nauclea officinalis[19], *Catharanthus roseus*[20], and *Gardneria nutans* Siebold & Zuccarini[21] (**Fig. 5**). Among them, compounds 35 and 36, 2 rare monoterpene indole alkalosides with glucose group at C-12, were discovered from the ethanol extract of *Gardneria nutans* Siebold & Zuccarini[21].

Oxidized indole alkalosides with tetracyclic monoterpene skeleton

The oxidized indole alkaloids with tetracyclic monoterpene skeleton accounted for 17% of the total monoterpene indole alkaloids. Compound 37 (**Fig. 6**) was found in the ethanol extract of *Uncaria rhynchophylla* leaves prepared by percolation method, and is also the only tetracyclic monoterpene oxidized indole alkaloside discovered so far[13].

Other monoterpene indole alkalosides

In addition to the above types of monoterpene indole alkalosides, compounds 38[15] and 39[22], 2 monoterpene indole alkalosides, were found from *Neonauclea sessilifolia* and *Psychotria umbellate*, respectively. (**Fig. 7**). A novel dihydroindole alkaloside, aspidospermidose (40), was discovered by gradient pH extraction from *Rhazya stricta*, and its N was linked with an oxidized sugar[23]. Two novel indoloquinoline alkaloid glycosides, cryptospirosanguines A (41) and B (42), were isolated from an ethanolic extract of the root of *Cryptolepis sanguinolenta* (Lindl.) Schltr[24].

β-carboline alkaloid glycosides

Carboline alkaloids are a class of compounds with a tricyclic skeleton structure of indolpyridine, belonging to the indole class of tryptamine alkaloids. *β*-carboline alkaloids exist widely in nature, and more than 300 *β*-carboline alkaloids have been isolated and identified[74]. A total of 9 *β*-carboline alkalosides have been identified (43-47) (**Fig. 8**), of which compounds 43-47 are indole quinazoline alkalosides isolated from the plants *Ranunculus ternatus* and *Evodia rutaecarpa*[25–28]. Compound 48, a new *β*-carboline alkaloside, was isolated from the aqueous phase prepared with methanol extract from the stem of *Brucea javanica*, a medicinal drug used to treat malaria[29]. Compound 49 is a water layer extracted by Morikawa et al[30] from the *n*-butanol of the root of the Chinese herbal herb *Stellaria dichotoma* L. var. *lanceolata*. A *β*-carboline alkaloid monoglycoside was isolated by HPLC using the YMC-Pack ODS-A column. Compounds 50 and 51 were discovered from the root bark of *Ailanthus altissima* by using n-butanol to extract the water layer[31].

Simple indole alkaloid glycosides

At present, 24 simple indole alkaloid glycosides (52-76) have been found (**Fig. 9**), which is a kind of component found more frequently in indole alkaloid glycosides. 12

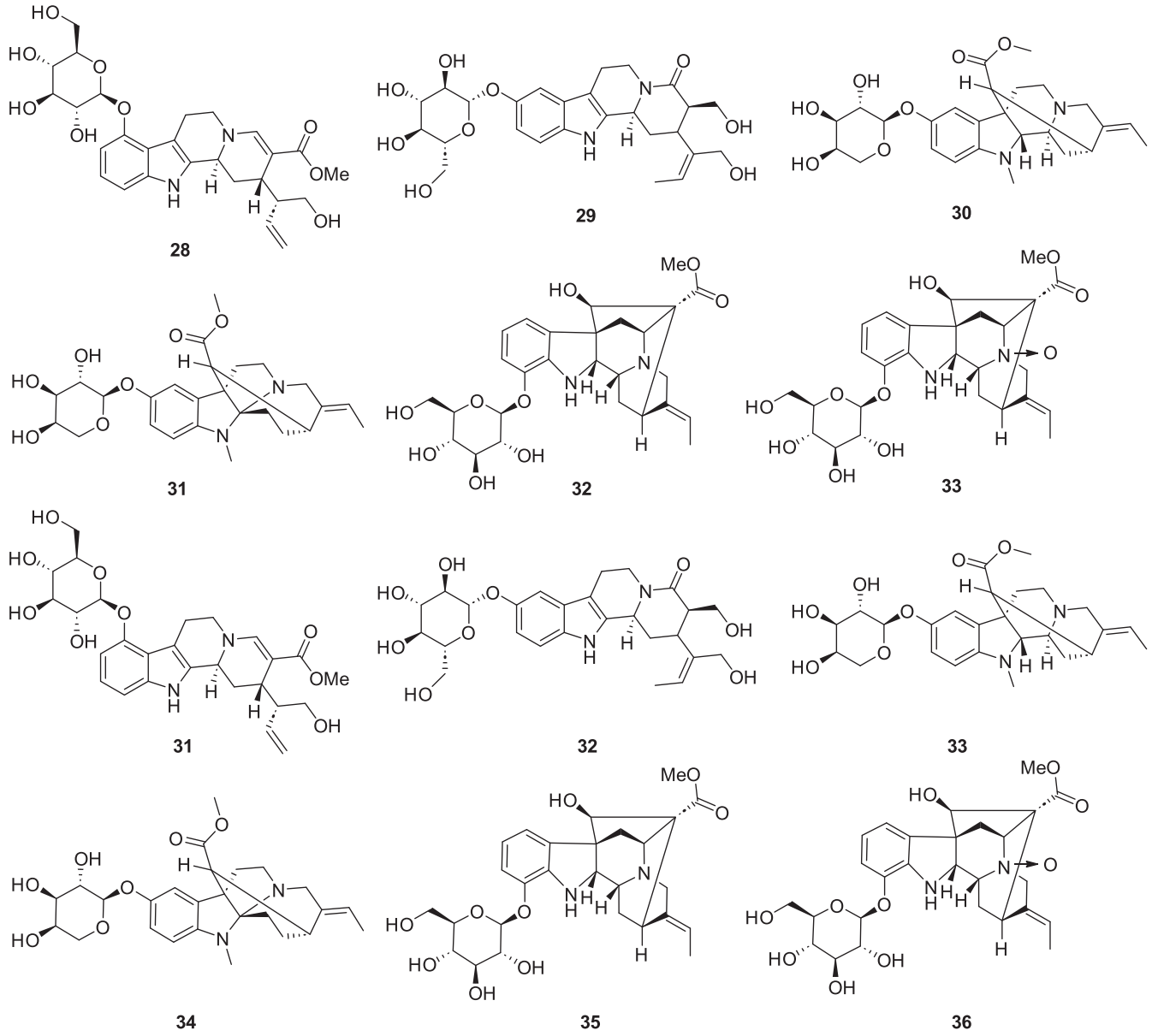


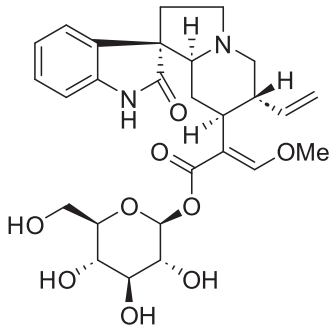
Figure 5. Tetracyclic monoterpene indole alkalosides.

simple indole alkaloid glycosides (54,55,57,63,67-73,75 and 76) were found in the *n*-butanol layer of *Isatis tinctoria*[34,36,40,42]. Compounds 58 and 59 are large polar components extracted from the *n*-butanol site of *Capparis tenera*, and compounds 72-76 are C-S-linked indole alkaloid glucosides. In addition to the simple indole alkaloid glycosides found in *Isatis tinctoria*, they could also be found in *Stixis scandens*[41], *Clematis terniflora* DC[32], *Calanthe discolor*[33], *Actaea dahurica* (syn.Cimicifuga dahurica)[35], *Tetracentron sinense*[38], and *Lilium davidii* var. unicolor[39].

Quinoline and isoquinoline alkaloid glycosides

Quinoline alkaloid glycosides

Quinoline alkaloids are a class of alkaloids derived from the quinoline ring as the basic parent nucleus and derived from the aminobenzoic acid pathway. Quinine, which has anti-malarial activity, and camptothecin, which has anti-tumor activity, are the representative components of this class. Currently, 8 quinoline alkaloid glycosides (77-84) were found from the water-soluble extract layers of *Haplophyllum perforatum*[43,44], *Zanthoxylum nitidum* Roxb.[48], and the water



37

Figure 6. Oxidation of indole alkaloid glycosides by tetracyclic monoterpenes.

layer of the *n*-butanol extracts of *Echinops gmelinii*[45], *Bougaina buxifolia* (Atalantia buxifolia)[46], and Glycyrrhiza uralensis[47](**Fig. 10**), all of which are monoglycosides except 78, which is a diglycoside. The parent nucleus of 81 is a relatively rare acridone.

Isoquinoline alkaloid glycosides

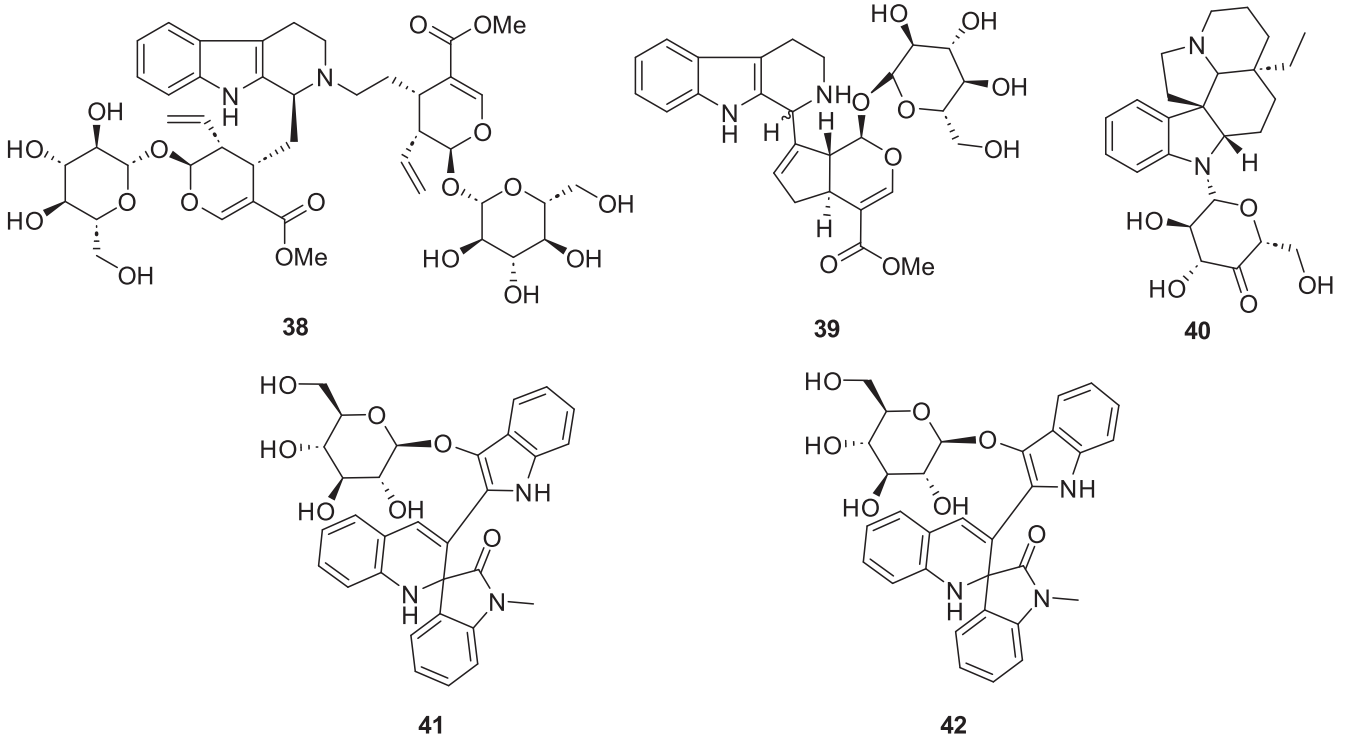
Isoquinoline alkaloids are derived from phenylalanine and tyrosine series and have the basic parent nucleus of isoquinoline or tetrahydroisoquinoline. They are widely distributed in plants and have many biological activities. At present, 10 isoquinoline alkaloid glycosides and their derivatives have been found (85-96) (**Fig. 11**).[49–55] Among them, 85-88 benzyl isoquinoline alkalosides, which were isolated from the methanol extraction of *Aristolochia fordiana*[49], and the water layer of the acetone extracts of *Corydalis humosa*[51] and *Phellodendron chinense Schneid*[52]. 94 and 95 were 2 proberberine alkalosides, which were found in *Stephania succifera*[54].

Isoguanine alkaloside

Six sulfonated isoguanine alkalosides (97-102) were found (**Fig. 12**), all of which were found from the water extraction site of the pupal case built by the bruchid beetle *Bruchidius dorsalis* inside the seed of *Gleditsia japonica*[56,57].

Other alkaloid glycosides

In addition to the above GAs, 15 other types of GAs (103-109) were also found (**Fig. 13**)[48,49,58–64,66], including 3 phenethylamine alkalosides (103-118) isolated from the methanol extracts of *Selaginella doederleinii* Hieron, which were treated with hydrochloric acid and alkalization with concentrated ammonia water[58,59]. Codonopsis pilosula A (107)[60] was isolated from *Codonopsis pilosula* by the same method. Two naphthylamine alkalosides (110 and 111) were isolated from the water layer of *Zanthoxylum nitidum* Roxb.[48]. Compounds 113 and 114 were 2 monoterpene alkalosides, which were isolated from *Loniceru xylosteum* L.[63] and *Strychnos vacacoua* Baill.[64], respectively.



38 39 40 41 42

Figure 7. Other monoterpene indole alkaloid glycosides.

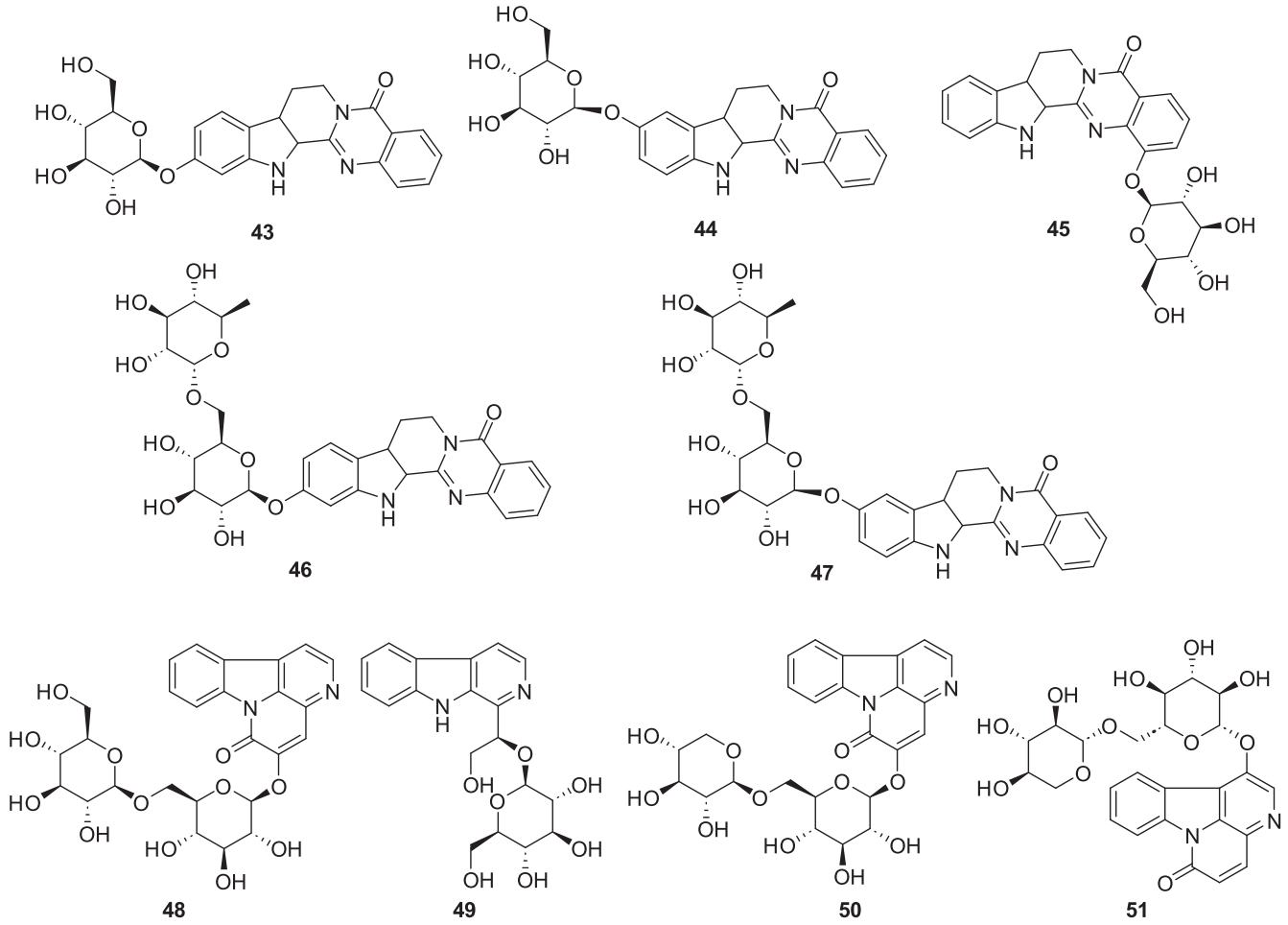


Figure 8. β-carboline alkaloid glycosides.

Steroid alkaloid glycosides

Since Zhao et al have made a detailed review of steroid alkaloids, this article will not introduce too much[75]. From then on, 37 SGAs were reported (**Fig. 14**). Wang et al isolated 119-127, from the *n*-butanol extraction layer of the bulbs of *Fritillaria unibracteata* P. K. Hsiao & K. C. Hsia[67]. 128-132 were isolated from the *n*-butanol extraction layer of *Fritillaria pallidiflora Schrenk*[68]. Solanigrinoside A–C (133-135) were isolated from the methanol extract of *Solanum nigrum*[69]. 136-137 were isolated from the leaves of *Solanum erianthum*[70]. SGAs (144, 147-156) were obtained from the bulbs of *Fritillaria sinica*. Verticinoside-*β*-*N*-oxide (145) and verticinonoside N-oxide (146) were 2 rare *N* oxide glycosides[71]. Three pyridinyl SGAs (141-143) were isolated from the fruit of *Solanum violaceum*[72].

Pharmacological activities of alkaloid glycosides

GAs are naturally active substances with a variety of physiological effects and have an inhibitory effects on asthma, inflammation, high cholesterol, hypertension, tumors, and other common diseases. Therefore, it is of great significance to study its pharmacological activity for its potential utilization value. SGAs have a wide range of pharmacological activities, and their mechanisms of action have been continuously discovered. Bishal Nepal et al introduced the biological characteristics of SGAs. In addition, its effects on model membrane systems have been reviewed[76]. After the review by Zhao et al, SGAs continued to be found to have potential pharmacological activity. For example, in a $CuSO_4$-induced transgenic zebrafish model, compounds 120-127 were found to reduce macrophage migration and the number of macrophages around the neural matrix of zebrafish, with moderate anti-inflammatory activity, using indometaxine as a positive control[67]. In addition to SGAs, other alkaloids also showed certain biological activities, such as anti-inflammatory, cytotoxic, antibacterial, analgesic, hypolipidemia, antiviral, melatonin receptor activation, and so on.

Anti-inflammatory activity

In the LPS-induced nitric oxide (NO) release model of RAW264.7 macrophages, indole alkaloid glycosides 15[21], 45[34], and 109[61] were found to inhibit NO production, with IC_{50} values of 6.36 μM, 27.6 μM, and 26.12 ± 0.81 μM,

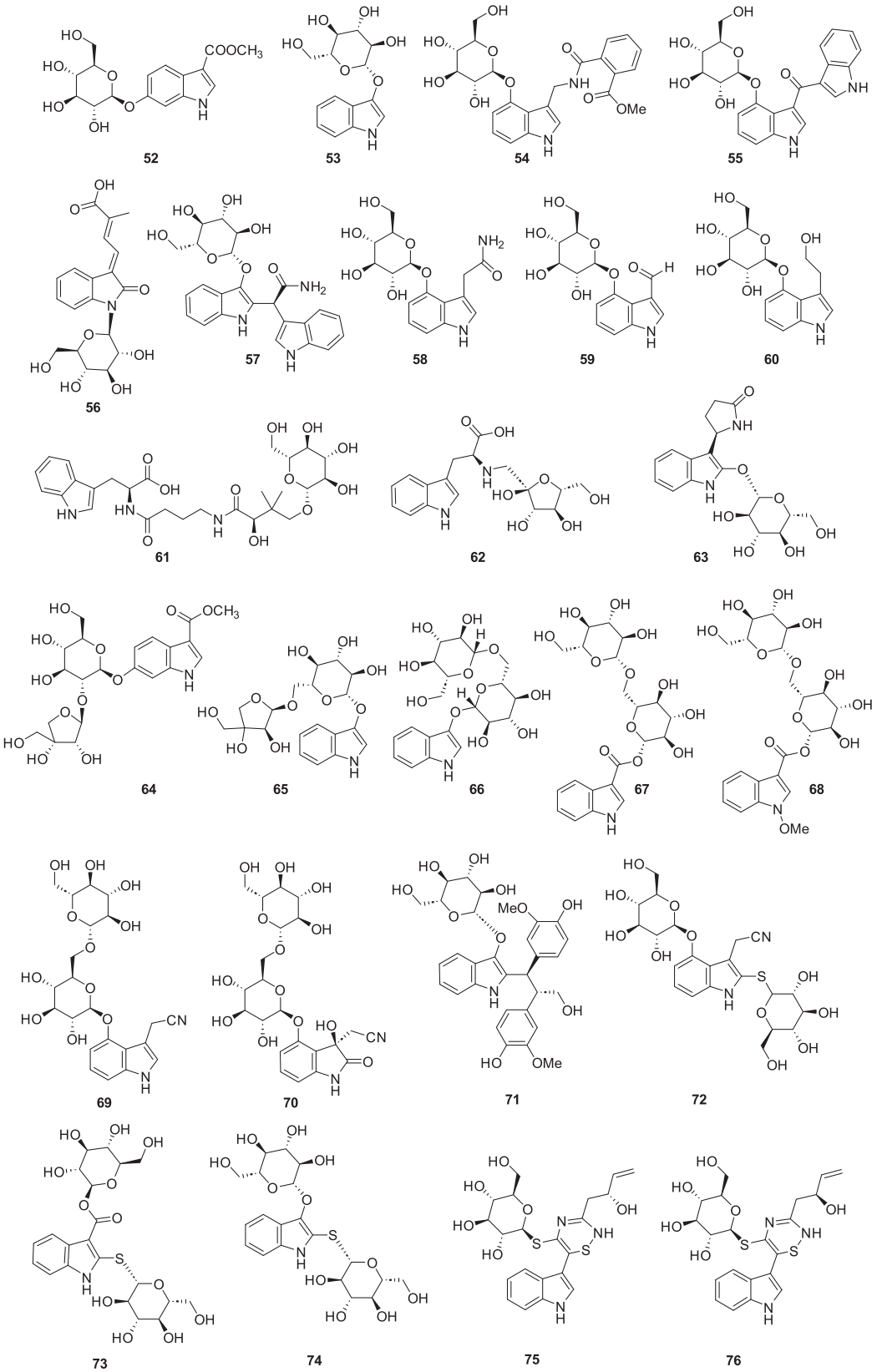


Figure 9. Simple indole alkaloid glycosides.

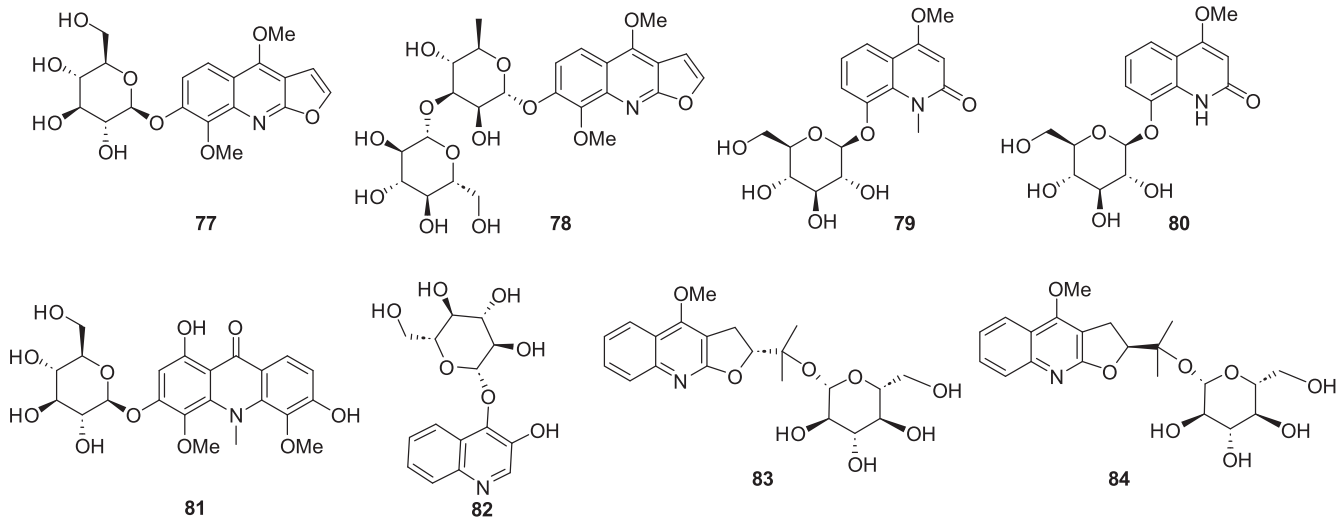


Figure 10. Quinoline alkaloid glycosides.

respectively. In addition, compounds 16 and 32 can significantly inhibit the mRNA expression of LPS-induced inflammatory factors TNF-α and IL-6 in BV2 microglia, with potential anti-inflammatory activity[21].

Si et al[52] found that benzyl isoquinoline alkaloside 88 binds stably to inflammatory proteins such as extracellular signal-regulated kinase, stress-activated protein kinase, and p38 mitogen-activated protein kinase through molecular docking technology. Therefore, the anti-inflammatory activity of LPS-induced RAW264.7 macrophages was evaluated in the model of NO release. It was found that 88 could effectively reduce the levels of NO, TNF-α, IL-1β, and IL-6 and reduce the expression of iNOS and COX-2 protein.

Cytotoxic activity

Compound 52 showed significant cytotoxicity to human ECA-109 with an IC_{50} value of 1.85 μM/mL, and paclitaxel ($IC_{50} = 0.19$ μM/mL) was used as the standard for determination[32]. Compound 111 showed significant cytotoxic activity against MKN-45 cancer cells with an IC_{50} of 7.4 ± 1.0 μM[48], and the anticancer agent mitoxantrone (MX) was used as the positive agent ($IC_{50} = 7.8 \pm 0.9$ μM). Solasonine has a similar inhibitory effect to cisplatin on the proliferation of human cancer SGC-7901 cells, and induces the apoptosis of SGC-7901 cells by triggering the endoplasmic reticulum stress pathway and mitochondrial pathway[77]. It has also been found to inhibit osteosarcoma cancer metastasis by regulating glucose metabolism through the Wnt/β-Catenin/Snail pathway[78]. Solasodine has significant cytotoxic effects on human colorectal cancer cells HT-29 and osteosarcoma cells MG-63, while very low toxicity on normal cells (fibroblast L-929), suggesting its use as a novel targeted therapeutic agent for colon and bone cancer[79].

Antibacterial and antiplasmodial activities

Zeng et al[54] found in the activity screening that compound 94 had a stronger growth inhibition effect on *Staphylococcus aureus* and compound 93 had a moderate inhibition effect on both *Staphylococcus aureus* and MRSA strains compared with kanamycin sulfate, a positive control drug. In addition, compound 48 inhibited the growth of chloroquine-resistant strains of *Plasmodium falciparum* K1 in culture[29].

Analgesic activity

Compound 39 produced a dose-dependent (100 to 300 mg/kg) central analgesic effect in mouse tail-dumping and hot-plate models, and the analgesic effect was reversed by naloxone, suggesting that its central analgesic effect was related to at least partial activation of opioid receptors. In the mouse formalin and capsaicin-induced pain model, 39 dose-dependent (100 to 300 mg/kg) can produce neuropathic analgesia, and when administered in combination with NMDA antagonists, there is a synergistic effect, indicating that NMDA receptors are involved in its analgesic mechanism[22].

Antilipidemic activity

Through in vitro determination of triglyceride content in HepG2 cells, it was found that liparisalkaloid A (116), liparisalkaloid B (117), and liparisalkaloid C (118) all showed the effect of lowering blood lipids[66]. The main feature of its cholesterol-lowering effect is that it closely binds with 3β-hydroxy-sterol (such as cholesterol) to form a complex, thus significantly disturbing the cell membrane structure.

Antiviral activity

Compound 91 was found to significantly inhibit the replication of tobacco Mosaic virus by leaf disk method[55]. In addition, isatigotindolediosides C (69) and isatigotindolediosides E (72) found in Isatis root showed inhibitory activity against Coxsackie B3 virus[42].

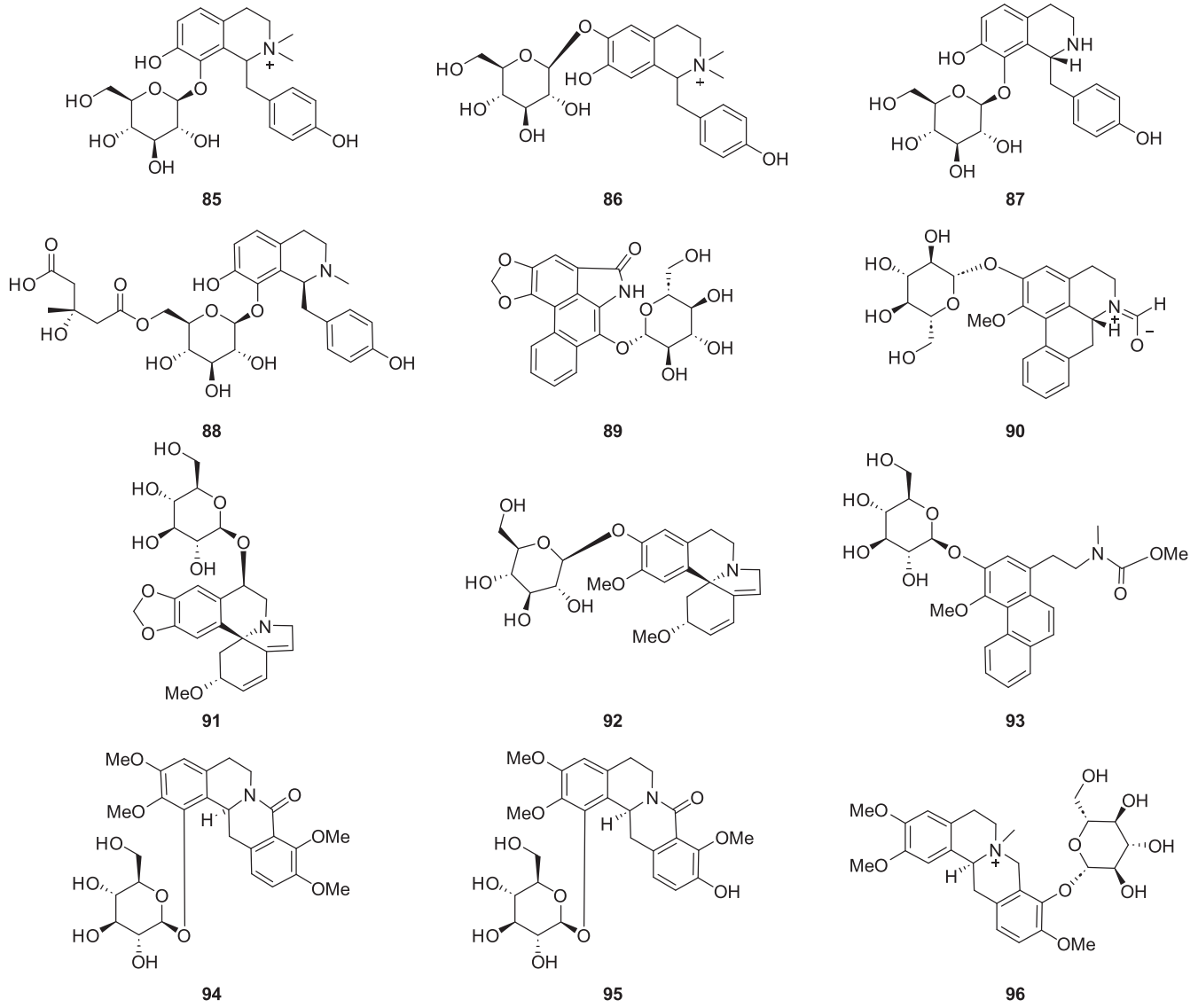


Figure 11. Isoquinoline alkaloid glycosides.

Melatonin receptor agonist activity

Compounds 2, 3, and 23 found in *Uncaria rhynchophylla* showed melatonin receptor activation activity in HEK293 cells, among which 2 and 3 showed moderate activity against MT_1 and MT_2 receptors, with activation rates of 36.6% and 21.4%, 24.2% and 8.5%, respectively. Twenty-three has the strongest activity against MT_1 and MT_2 melatonin receptors at a concentration of 1 mM, with activation rates of 79.6% and 46.3%, respectively, which provides a new candidate drug for antidepression[14].

Summary and discussion

At present, the GAs mainly fall into 2 categories. SGAs are nitrogen-containing steroid glycosides and oligosaccharide chains. They are commonly found in Solanum plants and serve as the primary active components of this genus. In all, 107 SGAs containing 6 skeletons have been isolated and identified from more than 350 species of plants in this genus[75]. In addition, small amounts of SGAs were also found in Liliaceae plants. Indole alkaloid glycosides, another type, form aglycones from indole and other structures. They are primarily found in *Nauclea* (Rubiaceae) plants. Approximately 70 indole alkaloid glycosides have been identified. In addition to the 2 types of GAs, the current isolation and identification also involve a small amount of quinoline, isoquinoline, isoguanine alkaloid glycosides, and some simple alkaloid glycosides. From the above perspective, the types and the number of alkaloid glycosides found so far are limited, which is inconsistent with the diversity of alkaloids. It is worth exploring these components in depth.

According to a comprehensive chemoinformatics analysis of the properties of natural glycosides included in the Dictionary of

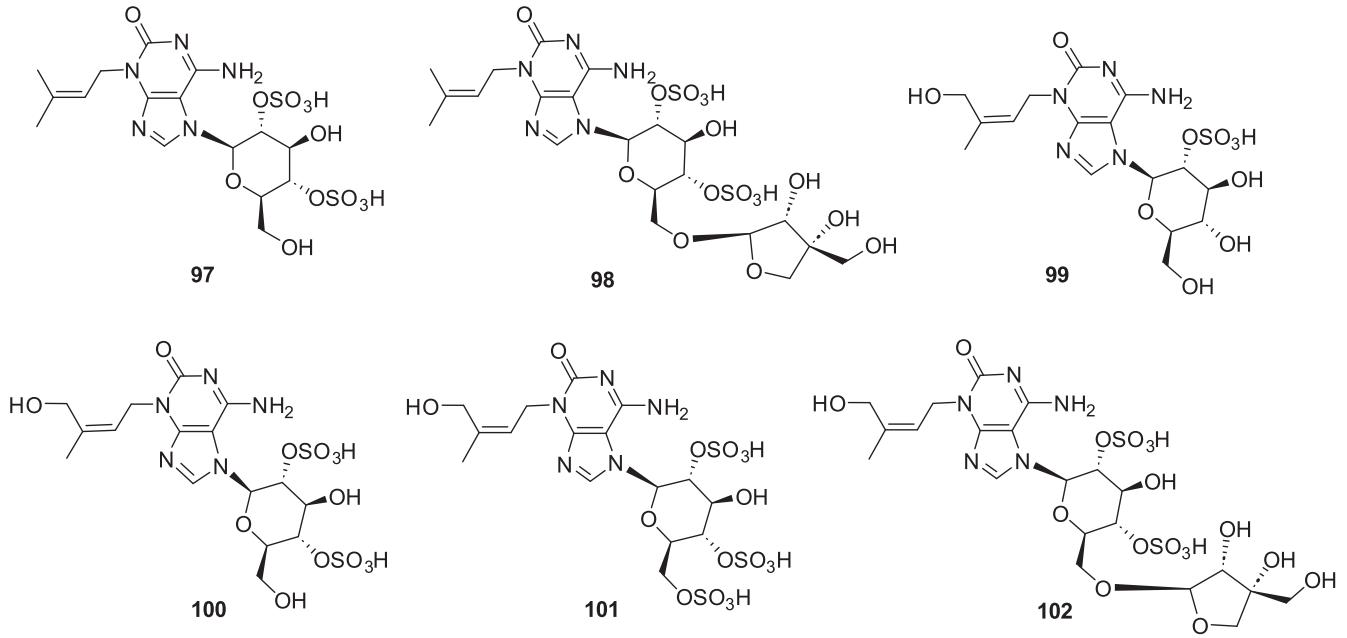


Figure 12. Isoguanine alkaloid glycosides.

Natural Products by Chen et al[80], it was found that the proportion of glucosidation was higher in the slightly less polar structures such as steroids, tannins, and flavonoids, while the proportion of glucosidation was much lower in alkaloids. Through systematic investigation and analysis, the main reasons can be summarized into 2 aspects. In contrast, after the crude extraction of traditional Chinese medicine, the focus has primarily been on studying the organic layers, such as petroleum ether, chloroform, and ethyl acetate, while the water layers have been neglected. GAs are mostly ionic compounds that are easily soluble in water and acidic water. They are soluble in methanol, ethanol, *n*-butanol, and other organic solvents with higher polarity but are difficult to dissolve in lipophile organic solvents. This characteristic reduces the likelihood of detecting GAs from the beginning. In contrast, the classical method of water extraction and alcohol precipitation is used in the crude extraction of traditional Chinese medicine. GAs is highly likely to be removed along with hydrophilic impurities such as mucus, gelatinized starch, pectin, gum, and protein. This process causes a serious loss of the effective components of natural alkaloid glycosides, greatly reducing the possibility of discovery[81]. Most of the GAs mentioned in this paper are extracted from the water layer using *n*-butanol or directly separated from the water layer. Therefore, separating large polar components from the *n*-butanol extraction layer or the water extraction layer, with a focus on natural products, can enhance the efficiency of discovering natural GAs components.

In terms of pharmacological activity, most of the components of GAs summarized in this paper have not been evaluated for their activity. At present, the discovery of alkaloid-related components mainly focuses on the extraction layer of lipophilic compounds. However, most of the components of GAs have good hydrophilicity, which is often neglected. In contrast, it may be due to the fact that most GAs are removed as hydrophilic impurities in the early stage of sample treatment, resulting in a low content and an insufficient amount prepared for screening various pharmacological activities. Although many mechanisms of action of SGAs have been clarified, most biological studies focus on Solanaceae plants. Further research is needed for the discovery and evaluation of the components and activity of SGAs.

Future prospects

In summary, considering the unique structure of GAs, an in-depth study of their structural and activity relationships is critical to understanding their full potential in drug development. In addition, due to the difficulty in obtaining GAs naturally and their good biological activity, their synthesis or structural modification will significantly improve their utilization value.

Statement of ethics

This study did not involve human or animal subjects, and no ethical approval was required. The study protocol adhered to the guidelines established by the journal.

Conflict of interest statement

The author declares no competing interests.

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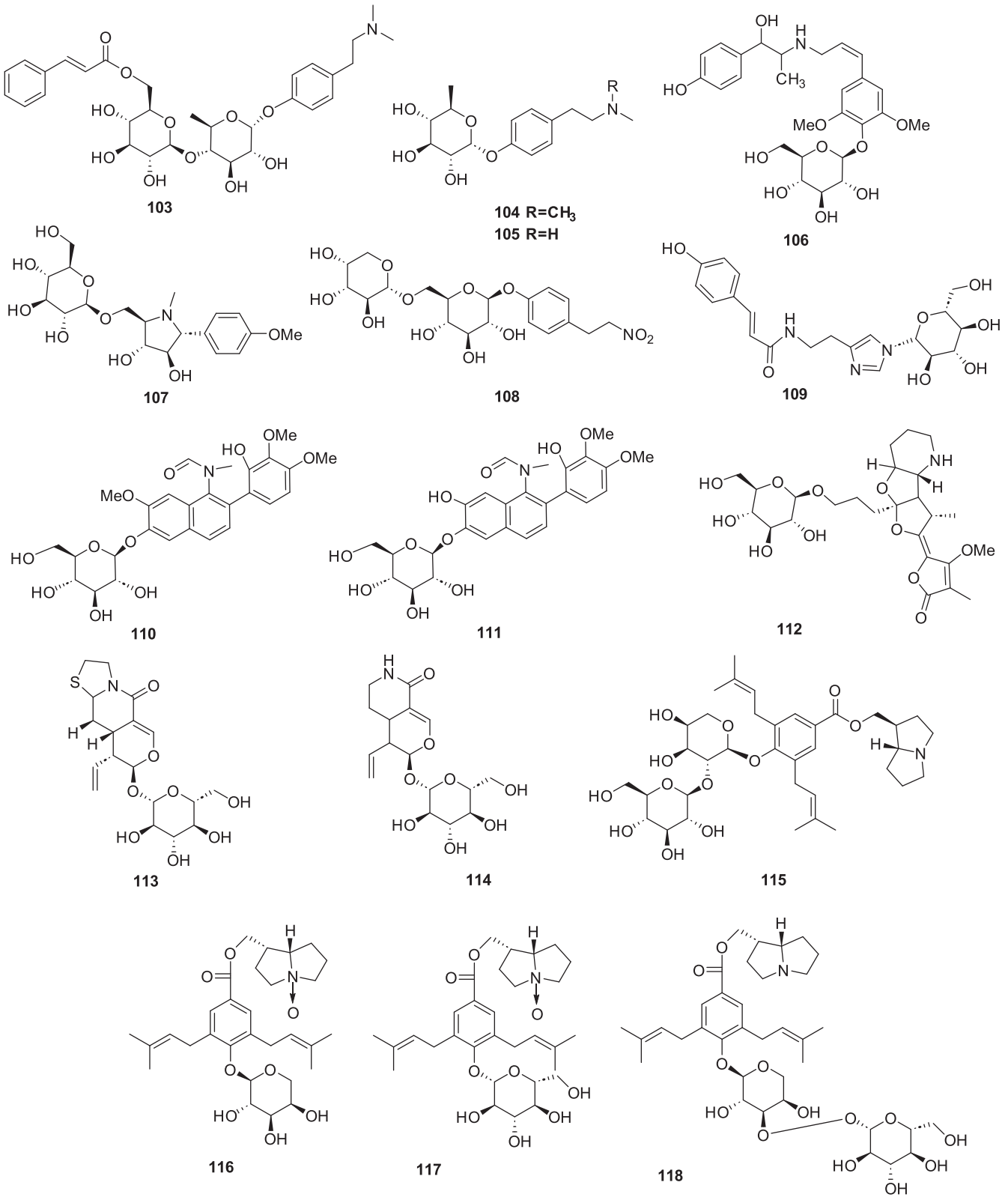

Figure 13. Other alkaloid glycosides.

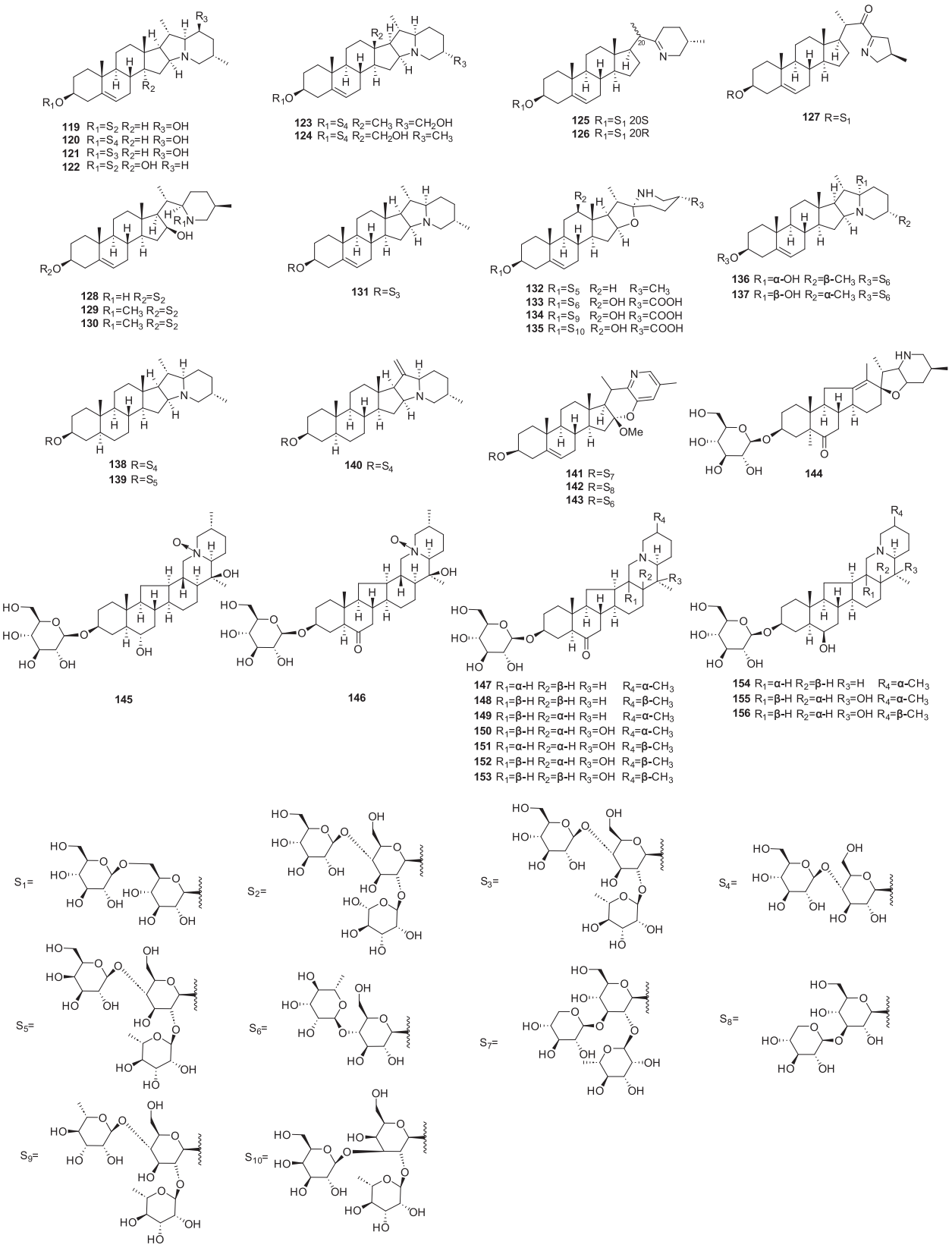

Figure 14. Steroid alkaloid glycosides.

Author contributions

Y.J. and G.X. wrote the original draft. L.W. and H.X. edited the manuscript. X.W. reviewed the manuscript. S.L. directed this article.

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