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An overview of the chemical constituents from the genus *Delphinium* reported in the last four decades†

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Species of the genus *Delphinium* have been extensively used for different purposes by various civilizations worldwide since antiquity. Phytochemical investigations on *Delphinium* plants in the last four decades (1980–2019) have afforded a total of 453 new compounds, most of which are diterpenoid alkaloids. These constituents are of great research significance due to their novel structures and broad bioactivities. This review addresses, for the first time, the chemical constituents of *Delphinium* plants and the biological properties of these compounds to facilitate future research.

1. Introduction

The genus *Delphinium* (Larkspur), an important member of the family Ranunculaceae, comprises approximately 365 species, which are distributed mainly in northern temperate regions, including in Asia, Europe, and North America.[1] There are also a few species growing in North Africa, such as *D. cossonianum* and *D. staphisagria* in Morocco,[2,3] *D. macrocentrum* in Kenya,[4] and *D. leroyi* in Ethiopia.[5] Notably, among the 365 *Delphinium* species, 232 (200 endemic) have been found in China.[6] *Delphinium* plants prefer cool and moist conditions and mainly grow in alpine-cold regions, such as the Hengduan Mountains region in Southwest China, which is the most important centre of diversity and speciation of this genus, as at least 167 *Delphinium* species have been found in this region.

Delphinium plants have been extensively used for different purposes by various civilizations worldwide since antiquity. *Delphinium* plants feature various coloured flowers ranging from white, yellow, and red to blue, and they have been cultivated as horticultural plants in Europe since the 17th century. Currently, *Delphinium* plants are one of the most famous and popular horticultural plants around the world, and thousands of ornamental varieties of *Delphinium* have been cultivated and applied widely in bonsai, gardens, and greenbelts. *Delphinium* flowers are also an important source of natural dyes; for example, yellow dye for silk has been extracted from *D. zalil* flowers for a long period of time in Iran and India.[7] In addition, *Delphinium* plants are traditionally used as herbal pesticides against lice and scorpions since the time of Dioscorides (in the 1st century A.D.), approximately two thousand years ago.[8] During the battle at Waterloo, the British army also used the powders of *D. staphisagra* and *D. peregrinum* to prevent and kill lice.[9] In China, there are five *Delphinium* species, namely, *D. grandiflorum*, *D. albocoeruleum* var. *przewalskii*, *D. chefoense*, *D. korshinskyanum*, and *D. likiangense*, that have been used to kill the larvae of mosquito, lice, and flies.[6] Most importantly, for centuries, plants of this genus, mainly their tubers and roots, have been extensively used as herbal medicines—in Turkey to treat epilepsy, tetanus, rabies, and emesis; in Iran to treat disorders of the spleen, jaundice, a nd dropsy; and in Nepal to treat fever and wounds.[7,8] In China, *Delphinium* plants have a long history as folk medicines for the treatment of many kinds of diseases, such as traumatic injury, rheumatism, enteritis, influenza, oedema, asthma, ringworm, scabies and other skin diseases, as well as stomach ache, migraine, tooth ache, neuralgia, and other kinds of pain. At least 18 species of *Delphinium* have been used medically in Chinese traditional medicine (TCM) because of their unique and proven therapeutic effects.[6]

Since the end of the 18th century, the chemical constituents in *Delphinium* plants have been investigated. Several earlier studies have attempted to isolate anthocyanin pigments from *Delphinium* flowers, and the first anthocyanin (delphinin) was identified from *D. consolida* in 1915 by Willstätter *et al.*[10] At almost the same time, research on *Delphinium* alkaloids, mainly the diterpenoid alkaloid (DA) components, was also conducted.[11] The DAs in *Delphinium* plants have attracted the attention of scientists for a long time, and most studies on these plants have been devoted to the DA components. In addition, the non-alkaloidal constituents of *Delphinium* plants have also been

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studied. To date, thousands of components with diverse chemical structures, including alkaloids, flavonoids and other phenolic compounds, fatty acids, terpenoids and steroids, have been isolated from *Delphinium* plants. These constituents offer novel structures and broad and impressive biological activities, including antioxidant, antiparasitic, antiphlogistic, antineoplastic, and immunoregulatory effects.

Several review articles and monographs regarding the distribution and physiological and NMR spectroscopic data of naturally occurring DAs, which have mainly been isolated from *Delphinium* and its sibling genera *Aconitum* and *Consolida*, have been published.[12–15] However, to date, there has been no individual and comprehensive review of the chemical constituents of the *Delphinium* genus. Therefore, this review was prepared to summarize the structural features and biological activities of the chemical constituents from *Delphinium* species for the first time. The aim of this review is to provide a complete overview of the chemical constituents of the *Delphinium* genus reported in the last four decades (from 1980 to 2019), which will facilitate further research and exploitation of this genus.

2. Alkaloids

In addition to the genera *Aconitum* and *Consolida*, *Delphinium* is a genus in the Ranunculaceae family that is well known for its characteristic DA components.[16,17] DAs are clearly the major constituents of *Delphinium* plants, and most of the published articles are devoted to DA components. In the past forty years, a large number of biologically active and structurally complex DAs have been isolated from various species of *Delphinium*. Table 1S† lists the names, plant sources, types, and the references of the new DAs isolated from *Delphinium* plants in the last four decades. Structurally, DAs are usually classified as C_{18}-, C_{19}-, or C_{20}-DAs, which can be further divided into several to dozens of subtypes. Fig. 1 shows the fourteen subtypes of DAs that have been found in *Delphinium* plants in the last four decades. Herein, the new DAs as well as other alkaloids isolated from *Delphinium* plants are summarized by category.

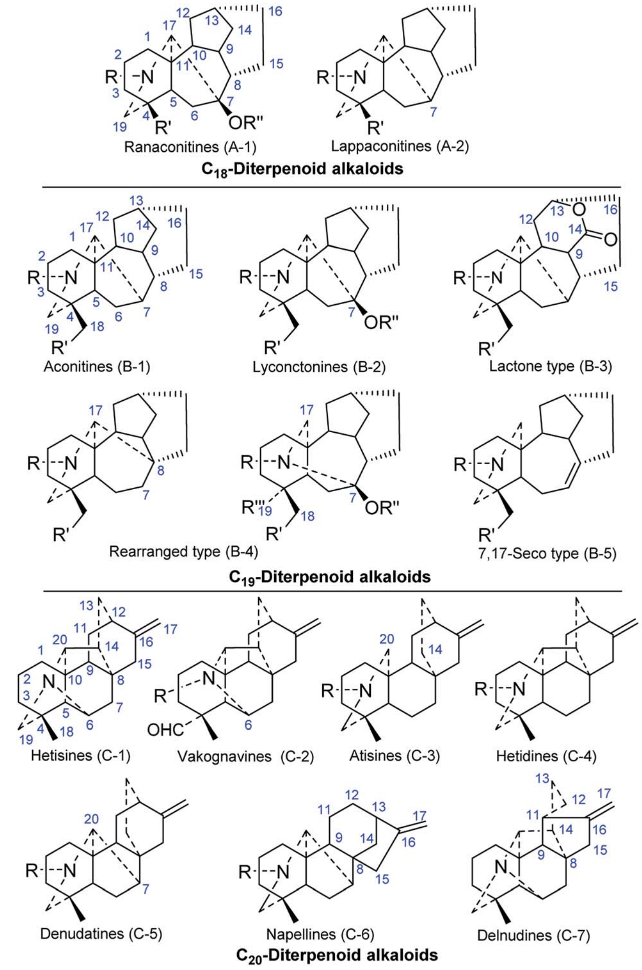


Fig. 1 Subtypes of DAs covered in this review.

2.1 C_{18}-Diterpenoid alkaloids

The C_{18}-DAs, also called "bisnorditerpenoid alkaloids", are a small sub-group of DAs.[18] Compared with C_{19}-DAs, C_{18}-DAs are distinguished by the absence of C-18, and their C-4 moiety is a methine or an oxygenated quaternary carbon. C_{18}-DAs can be classified into two subtypes based on whether an oxygen-containing functionality is attached at C-7, namely, lappaconitine-type compounds (A-2), which do not possess an oxygen-containing functionality at C-7, and ranaconitine-type compounds (A-1), which do have an oxygen-containing functionality at this position.

To the best of our knowledge, only 23 new C_{18}-DAs from *Delphinium* plant have been reported in the last four decades, and they were obtained from 7 different species (Fig. 2). Most of these compounds are ranaconitine-type C_{18}-DAs, with the exception of giraldine I (**21**) from *D. giraldii*,[19] delphicrispuline (**22**) from *D. crispulum*,[20] and naviconine (**23**) from *D. naviculare* var. *lasiocarpum*,[21] which are lappaconitine-type compounds. Sixteen ranaconitine-type C_{18}-DAs possessing a 7,8-methylenedioxy group were reported, and these compounds are anthriscifolcones A and B (**1** and **2**) and anthriscifoltines A–G (**3–9**) from *D. anthriscifolium* var. *majus*,[22–24] and anthriscifolcines A–G (**10–16**) from *D. anthriscifolium* var. *savatieri*.[25,26] Most of them contain a 10-OH substituent, and the exceptions are alkaloids **10–11** and **16**. Three of the ranaconitine-type C_{18}-DAs, namely, delboxine (**18**) from *D. bonvalotii*,[27] 14-demethyltuguaconitine (**19**) from *D. stapeliosum*,[28] and tiantaishansine (**20**) from *D. tiantaishanense*,[29] contain a 3,4-epoxide unit. Giraldine I (**21**) was characterized by the lack of an oxygenated substituent at C-16.[19] Alkaloids delphicrispuline (**22**) and naviconine (**23**) possess an anthranoyl group at C-18,[20] and **23** features an *N*–CHO formamide group instead of an *N*-ethyl group.[21]

2.2 C_{19}-Diterpenoid alkaloids

The majority of naturally occurring DAs are C_{19}-DAs, and they are usually regarded as the representative type of DAs. In-depth investigations of C_{19}-DAs in chemical and pharmacological fields have been carried, and more information is available on

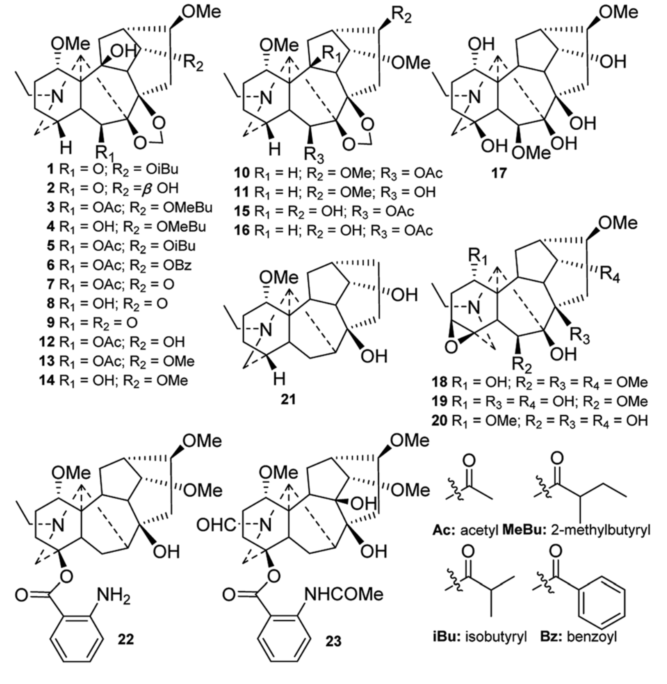


Fig. 2 C_{18}-DAs from *Delphinium* plants.

these compounds than on C_{18}- or C_{20}-DAs. According to their molecular skeletons, C_{19}-DAs can be divided into six types, namely, lycaconitines (B-1), aconitines (B-2), lactones (B-3), 7,17-seco derivatives (B-4), rearranged compounds (B-5), and pyro derivatives. In the last four decades, a total of 299 new C_{19}-DAs belonging to these five types have been isolated from *Delphinium* plants.

2.2.1 Lycaconitines.

In *Delphinium* plants, lycaconitines are the most common type of C_{19}-DAs. A total of 232 new lycaconitine-type C_{19}-DAs were isolated from *Delphinium* plants in the last four decades. The lycaconitine-type C_{19}-DAs are characterized by the presence of an oxygenated group at C-7, and it is usually a 7-OH or a 7,8-methylenedioxy group. Based on the state of the *N*-atom, lycaconitine-type C_{19}-DAs can be further divided into four subtypes, namely, the *N*,*O*-mixed acetal sub-type, the amide sub-type, the imine and quaternary ammonium sub-type, and the amine sub-type.[14]

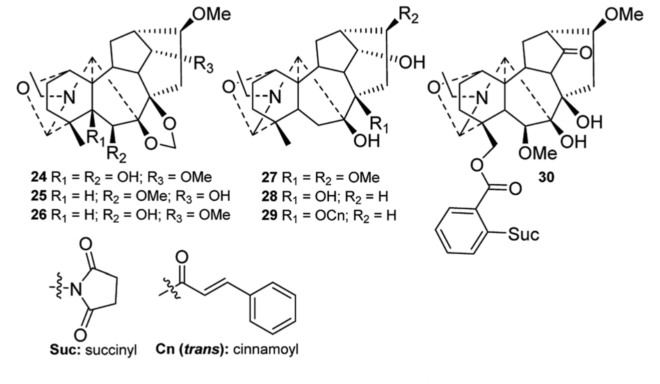


Fig. 3 Lycaconitines with mixed acetal unit from *Delphinium* plants.

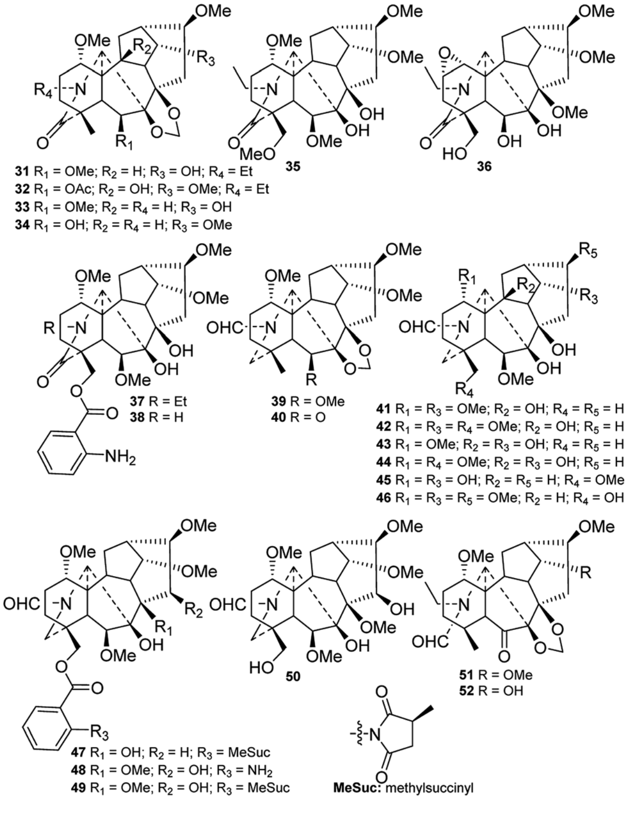


Fig. 4 Amide lycaconitines from *Delphinium* plants.

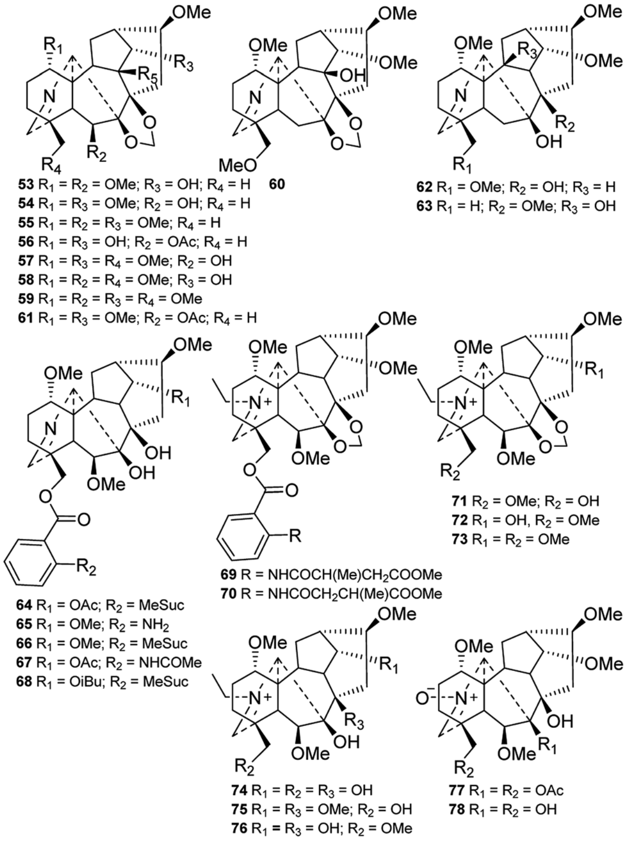
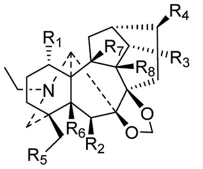
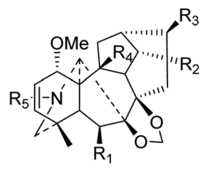


Fig. 5 Imine lycaconitines from *Delphinium* plants.

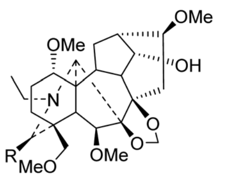


	R₁	R₂	R₃	R₄	R₅	R₆	R₇	R₈
91	OMe	OMe	OH	OMe	H	H	H	H
92	OMe	O	OMe	OMe	H	H	H	H
93	OMe	O	OH	OMe	H	H	H	H
94	OMe	OH	OMe	OH	H	H	H	H
95	OH	H	OMe	OMe	OMe	H	OH	OH
96	OMe	H	OMe	OMe	OMe	H	H	OH
97	OMe	H	OMe	OMe	OMe	H	OH	OH
98	OAc	H	OMe	OMe	OMe	H	OH	OH
99	OH	H	OMe	OMe	OMe	H	H	OH
100	OMe	H	OMe	OH	OMe	H	H	OH
101	OH	H	OH	OMe	H	H	H	OH
102	OMe	H	OH	OMe	OMe	H	H	H
103	OH	OH	OH	OMe	H	H	H	H
104	OMe	OMe	OH	OMe	OMe	H	H	H
105	OMe	H	O	OMe	OMe	H	H	H
106	OMe	H	OAc	OMe	OMe	H	OH	H
107	OMe	OH	OAc	OMe	OMe	H	OH	H
108	OMe	OAc	O	OMe	OMe	H	OH	H
109	OMe	H	OAc	OMe	OH	H	OH	H
110	OMe	H	OMe	OMe	OH	H	OH	H
111	OMe	H	OH	OMe	OMe	H	H	H
112	OH	OH	OMe	OH	OMe	H	H	H
113	OMe	H	OMe	OMe	H	OH	H	H
114	OH	OMe	OH	OMe	OMe	H	H	H
115	OMe	O	OMe	OH	H	H	H	H
116	OH	H	OH	OMe	H	H	H	H
117	OMe	OAc	OMe	OH	H	H	H	H
118	OMe	O	OMe	OMe	H	OH	H	H
119	OMe	H	OH	OMe	OMe	H	OH	H
120	OMe	H	OAc	OMe	OMe	H	H	H
121	OH	OH	OH	OMe	OMe	H	H	H
122	OH	OH	OH	OMe	H	H	H	H
123	OMe	OH	OH	OMe	OMe	H	H	H
124	OMe	OH	OMe	OMe	OMe	H	OH	H
125	OMe	OH	OH	OMe	H	H	OH	H
126	OMe	O	OMe	OMe	H	H	OH	H
127	OH	OMe	OH	OMe	H	H	H	H
128	OMe	O	OMe	OH	OMe	H	H	H
129	OMe	H	OMe	OH	OMe	H	H	H
130	OMe	OH	OMe	OH	H	H	H	H
131	OH	OH	OMe	OMe	H	OH	H	H
132	OH	OAc	OMe	OMe	H	H	H	H
133	OH	OMe	OH	OMe	OH	H	H	H
134	OMe	OAc	OMe	OH	H	H	OH	H
135	OMe	OAc	OMe	OH	H	OH	H	H
136	OMe	OAc	OMe	OMe	H	OH	H	H
137	OMe	OH	OMe	OMe	H	OH	H	H
138	OMe	OMe	OMe	OMe	OMe	H	H	H
139	OMe	OMe	OH	OMe	OH	H	OH	H
140	OMe	O	OAc	OMe	H	H	H	H
141	OMe	OAc	OMeBu	OMe	H	H	OH	H
142	OMe	OAc	OiBu	OMe	H	H	OH	H
143	OMe	OAc	OBz	OMe	H	H	OH	H
144	OMe	OAc	OMe	OMe	H	H	H	H
145	OMe	OMe	OMe	OMe	H	H	H	H
146	OMe	OAc	OMe	OAc	H	H	OH	H
147	OMe	OH	OMe	OMe	H	H	H	H
148	OMe	O	O	OMe	H	H	H	H
149	OMe	H	OMe	OMe	H	H	H	H
150	OMe	OAc	OMe	OMe	H	H	H	H
151	OMe	H	OMe	OMe	H	H	H	H
152	OMe	OMe	OMe	OMe	H	H	OMe	H
153	O	O	OH	OMe	H	H	H	H

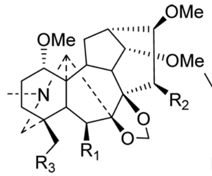
Fig. 6 Amine lycaconitines with 7,8-methylenedioxy group from *Delphinium* plants.



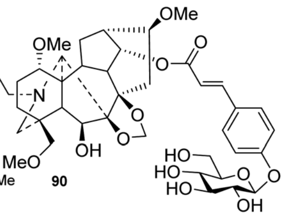
79 R_1 = OAc; R_4 = OH; R_2 = R_3 = OMe; R_5 = Et
80 R_1 = OAc; R_3 = R_4 = OH; R_2 = OMe; R_5 = Et
81 R_1 = OAc; R_4 = OH; R_2 = R_3 = OMe; R_5 = Me
82 R_1 = OAc; R_3 = R_4 = OH; R_2 = OMe; R_5 = Me
83 R_1 = R_3 = OAc; R_2 = OMe; R_4 = OH; R_5 = Et
84 R_1 = OAc; R_2 = R_4 = OH; R_3 = OMe; R_5 = Et
85 R_1 = R_4 = OH; R_2 = R_3 = OMe; R_5 = Et
86 R_1 = OAc; R_4 = H; R_2 = R_3 = OMe; R_5 = Et



87 R = CH_2COCH_3



88 R_1 = OAc; R_2 = OH; R_3 = OMe
89 R_1 = OH; R_2 = R_3 = H



90

Fig. 6 (*contd.*)

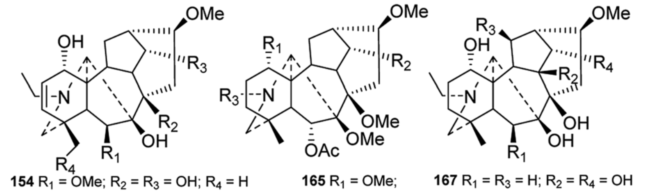
In the last four decades, only seven lycaconitine-type DAs (**24–30**) with an N–$C_{(19)}$–O–$C_{(1)}$ mixed acetal unit were found (Fig. 3). Among them, graciline (**28**) and 8-*O*-cinnamoylgraciline (**29**) are characterized by the absence of an oxygenated group at C-16,[30] and alkaloid **29** features a cinnamoyl unit at C-8.[2] In addition, laxicymine (**24**) from *D. laxicymosum* var. *pilostachyum* has a rare 5-OH group,[31] and grandifloricine (**30**) from *D. grandiflorum* contains a ketone carbonyl at C-14 along with an *N*-(succinimido)anthranoyl group at C-18.[32]

Twenty new amide lycaconitines were reported in the studied period (Fig. 4). Alkaloids **31–38** contain an N–$C_{(19)}$=O lactam group, which might be formed by the carbonylation of 19-OH.[33–37] Budelphine (**36**) from *D. buschianum* possesses a rare 1,2-epoxy group.[36] There are 12 alkaloids (**39–50**) with an *N*–CHO formamide group formed from a C-21 aldehyde.[4,38–45] Among these compounds, alkaloids **41–45** are DAs that have no oxygen-containing group at C-16.[4,39–41] *N*-Formyl-4,19-secopacinine (**51**)[45] and *N*-formyl-4,19-secoyunnadelphinine (**52**)[38] from *D. elatum* contain another kind of formamide, which is formed from C-19 aldehydes.

Sixteen lycaconitine-type DAs with an imine group at C-19 were isolated from *Delphinium* plants (Fig. 5). Nine of these DAs (**53–61**) contain a 7,8-methylenedioxy group,[29,45–51] and of these, caerunine (**60**) from *D. caeruleum* possesses a 9-OH group.[50] Another five imine DAs (**64–68**) contain a 7,8-diol group along with an anthranoyl group at C-18.[7,37,52–54] In addition, orthocentrine (**63**) from *D. orthocentrum* possesses an 8-OMe moiety along with a 10-OH group.[55] Eight quaternary ammonium bases, including pseudorenines A and B (**69** and **70**), and pseudophnines A–D (**71**, **73–74**, and **76**) from *D. pseudoaemulans*,[48] and sharwuphinine B (**72**) from *D. shawurense*,[56] naviculine (**75**) from *D. naviculare* var. *lasiocarpum*[21] were reported, although these might be artefacts of the extraction and isolation procedure. Sharwuphinine A (**76**) from *D. shawurense*[57] and chrysotrichumine A (**77**) from *D. chrysotrichum*[58] are both alkaloids with a nitrone group between C-17 and C-19.

A total of 177 new amine lycaconitine-type C_{19}-DAs have been reported, and they can be subdivided into three groups according to their oxygenated substituents at C-7 and C-18, namely, the 7,8-methylenedioxy group, the 7-OH group, and the 7-OH/18-anthranoyl group.

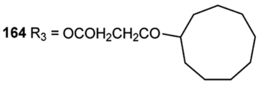
Seventy-six new lycaconitine-type alkaloids with a 7,8-methylenedioxy unit have been reported in the last four decades (Fig. 6). Among these alkaloids, eight (**79–86**) contain a $\Delta^{2,3}$ group, including siwanines A–D (**79–82**) from *D. siwanense* var. *leptogen*,[59] siwanine E and F (**82** and **83**) from *D. siwanense*,[60] deacetylswinanine A (**85**) from *D. orthocentrum*,[55] and tatsiensine (**86**) from *D. tatsienense*.[61] Notably, iliensine A (**90**) from *D. iliense* features a 4-*O*-β-D-glucose-cinnamate ester, making it the first example of a natural DA containing a glucose moiety.[62] Pseudouridine B (**87**) from *D. pseudoaemulans* possesses a rare acetonyl group at C-19.[48] The remaining alkaloids contain only common oxygenated groups, such as OH, =O, OMe, and OAc groups, while OMeBu (2-methylbutyryl) and OiBu (isobutyryl) groups are less common. In most cases, these oxygenated groups are located at C-1, C-6, C-14, and C-18. There are also a small number of alkaloids with oxygenated groups at C-5, C-9, and C-10. Most of them possess a 16-OMe group, and some have a 16-OH substituent; delretine (**146**) from *D. retropilosum* has a rare 16-OAc.[63]



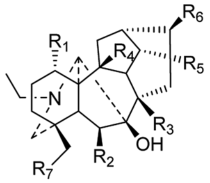
154 R_1 = OMe; R_2 = R_3 = OH; R_4 = H
155 R_1 = OMe; R_2 = OH; R_3 = OAc; R_4 = H
156 R_1 = OMe; R_2 = OH; R_3 = OBz; R_4 = H
157 R_1 = R_2 = OMe; R_3 = OH; R_4 = H
158 R_1 = R_3 = R_4 = OMe; R_2 = OH
159 R_1 = OMe; R_3 = O; R_4 = H; R_2 = OH
160 R_1 = R_2 = R_3 = OH; R_4 = H
161 R_1 = OH; R_3 = OAc; R_4 = H; R_2 = OMe
162 R_1 = OH; R_2 = OMe; R_3 = OAc; R_4 = H
163 R_1 = ¦ÁOAc; R_2 = OH; R_3 = OAc; R_4 = H
164 R_1 = R_2 = R_4 = OMe

165 R_1 = OMe;
R_2 = OBz; R_3 = Et
166 R_1 = O;
R_2 = OAc; R_3 = H

167 R_1 = R_3 = H; R_2 = R_4 = OH
168 R_1 = OMe; R_2 = H;
R_3 = OH; R_4 = OBz



164 R_3 = $OCOH_2CH_2CO$–



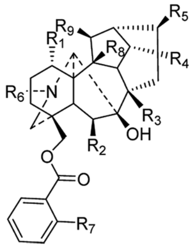
	R_1	R_2	R_3	R_4	R_5	R_6	R_7
169	OH	OMe	OMe	H	OH	OMe	OMe
170	OH	OH	OMe	H	OAc	OMe	OMe
171	OMe	OMe	OH	H	OMe	OMe	OH
172	OH	OMe	OMe	H	OH	OMe	OH
173	OMe	O	OH	H	OMe	OMe	H
174	OBz	H	OMe	H	OH	OMe	H
175	OH	H	OMe	H	OMe	OH	H
176	OH	H	OMe	H	OAc	OMe	H
177	OH	H	OMe	H	OH	OMe	H
178	OMe	OAc	OMe	OH	OMe	OMe	H
179	OH	OMe	OMe	H	OAc	OMe	OMe
180	OH	OMe	OMe	H	OMe	OMe	OMe
181	OMe	H	OMe	OH	OH	OMe	H
182	OH	H	OH	H	OH	OMe	H
183	OH	OMe	OH	H	OH	OMe	H
184	OH	H	OH	H	OH	H	H
185	OMe	OMe	OH	H	OMe	OMe	OH
186	OMe	OMe	OH	H	OH	OMe	H
187	OH	H	OH	H	OAc	OMe	H
188	OH	OMe	OH	H	OMe	H	OMe
189	OMe	OMe	OH	H	OBz	OMe	H
190	OMe	OMe	OH	H	OiBu	OMe	H
191	OMe	OMe	OH	H	OMeBu	OMe	H
192	OMe	OMe	OH	H	*cis*-OCn	OMe	H
193	OMe	OMe	OH	H	OCn	OMe	H
194	OMe	OMe	OH	H	OMeBu	OMe	OMe
195	OH	OMe	OH	H	OAc	OMe	H
196	OH	OH	OMe	H	OH	OMe	OMe
197	OMe	OMe	OH	H	OAc	OMe	OH
198	OMe	OMe	OH	H	OAc	OMe	H
199	OMe	OMe	OH	H	OMe	OMe	H
200	OMe	OH	OH	H	OMe	OMe	H
201	OMe	OMe	OH	H	OiBu	OMe	OMe
202	OMe	OMe	OH	H	OH	OMe	OMe
203	OH	αOMe	OH	H	OH	OMe	OMe

Fig. 7 Amine lycaconitines with 7-OH group from *Delphinium* plants.

Fifty new amine lycaconitines possessing a 7-OH group were reported in the past forty years (Fig. 7). Eleven alkaloids (**154–164**) containing a $\Delta^{2,3}$ group were reported,[26,64–68] and among these, majusine D (**164**) from *D. majus* possesses a novel 3-(cyclononyloxy)propanoate ester group at C-14.[69] Alkaloids **192** and **193**, a pair of isomers from *D. cardiopetalum*, possess *cis*- and *trans*-cinnamoyl groups at C-14, respectively.[70] Gracinine (**168**) from *D. gracile* has a hydroxyl group at C-10, which is an infrequently substituted position.[71] Pergilone (**166**) and delphiperegrine (**165**) from *D. peregrinum* uniquely feature a methoxy group at C-7.[72]

Fifty-two new DAs belonging to the 7-OH/18-anthranoyl group were reported (Fig. 8). These alkaloids are substituted with anthranilic acid derivatives at C-18. Amidogens are usually substituted by succinyl or methyl-succinyl groups or other amide side chains, which might be formed by the breakage of succinyl or methyl-succinyl groups. Ajanine (**208**) from *D. ajacis* possesses a 2-hydroxyl-2-methylbutyroyle ester chain at C-14,[73] and alpinine (**219**) from *D. alpinum* possesses a propionyl group at C-14.[74]

2.2.2 Aconitines. Although aconitine-type C_{19}-DAs represent the most common naturally occurring DAs, the number of these DAs reported from *Delphinium* plants is much lower than the number of lycaconitine-type compounds. In the last four decades, only 62 new aconitine-type C_{19}-DAs from *Delphinium* plants were reported (Fig. 9). Several alkaloids possessed at least one uncommon substituent. For example, alkaloids **262**, **263** and **264** possess $\Delta^{1,2}$, $\Delta^{2,3}$ and $\Delta^{5,6}$ groups,[75–77] respectively, and alkaloids **256–260** possess an N–$C_{(19)}$–O–$C_{(1)}$ mixed acetal unit.[78–82] Staphisadrine (**267**) from *D. staphisagria* features an aldehyde at C-18,[83] and peregrinine (**261**) from *D. peregrinum* var. *elongatum* has an $N{=}C_{(19)}$ imine.[82] Alkaloids **261** and **262** contain a β-oriented OAc group at C-6.[75,82] The other alkaloids mainly vary in the quantity, position and orientation of common oxygenated substituents, including OH, OMe and OAc. Most of the oxygenated substituents are located at C-1, C-6, C-8, C-16, and C-19. Alkaloids **269–270** and **266** have a hydroxyl group at C-10,[75,84,85] which is a rare substitution pattern. Generally, aconitine-type DAs have a 16-OMe moiety, but cardiopetaline (**290**) from *D. cardiopetalum* and souline (**297**) from *D. souliei* are exceptions to this statement, as they lack this



	R_1	R_2	R_3	R_4	R_5	R_6	R_8	R_9	R_7
204	OMe	OMe	OH	OMe	OMe	Et	H	H	$\mathrm{NHCOCH_2CH(Me)COOMe}$
205	OMe	OMe	OH	OMe	OMe	Et	H	H	NHCOCH(Me)Et
206	OMe	OMe	OH	OMe	OMe	Et	H	H	$\mathrm{NHCOCH(Me)_2}$
207	OMe	OMe	OH	OAc	OMe	Et	H	H	NHCOCH(Me)Et
208	OMe	OMe	OH	OCOC(Me)(OH)Et	OMe	Et	H	H	NHCOMe
209	OMe	OMe	OH	OMe	OMe	Et	H	H	$\mathrm{NHCOCH(Me)CH_2COOH}$
210	OMe	OMe	OH	OH	OMe	Et	H	OH	$\mathrm{NH_2}$
211	OMe	OMe	OH	OMe	OMe	Et	H	OH	$\mathrm{NH_2}$
212	OMe	OMe	OH	O	OMe	Et	H	H	$\mathrm{NH_2}$
213	OH	OMe	OH	OH	OMe	Et	H	H	$\mathrm{NH_2}$
214	OH	OMe	OH	OMe	OH	Et	H	H	$\mathrm{NH_2}$
215	OH	OMe	OH	OMe	OMe	Et	H	H	$\mathrm{NH_2}$
216	OMe	OMe	OH	OMe	OMe	Et	H	H	$\mathrm{NHCOCH(Me)CH_2CONH_2}$
217	OMe	OMe	OH	OMe	OMe	Et	H	H	$\mathrm{NHCOCH_2CH(Me)CONH_2}$
218	OH	OMe	OH	OH	OMe	Et	H	H	$\mathrm{NHCOCH_3}$
219	OMe	OMe	OEt	OCOEt	OMe	Et	H	H	MeSuc
220	OMe	OMe	OH	OiBu	OMe	Et	H	H	Suc
221	OMe	OMe	OH	OiBu	OMe	Et	H	H	$\mathrm{NHCOCH_3}$
222	OMe	OMe	OH	OAc	OMe	Et	H	H	Suc
223	OMe	OMe	OH	OMe	H	Et	H	H	MeSuc
224	OMe	OMe	OH	OMeBu	OMe	Et	H	H	$\mathrm{NH_2}$
225	OMe	OMe	OH	OMe	OMe	H	H	H	$\mathrm{NH_2}$
226	OMe	OMe	OMe	OMe	OMe	Et	H	H	MeSuc
227	OMe	OMe	OMe	OMe	OMe	Et	H	H	$\mathrm{NHCOCH_2CH(Me)CONH_2}$
228	OMe	OMe	OH	OiBu	OMe	Et	H	H	$\mathrm{NHCOCH(Me)CH_2CONH_2}$
229	OMe	OMe	OH	OMeBu	OMe	Et	H	H	$\mathrm{NHCOCH(Me)CH_2CONH_2}$
230	OMe	OMe	OH	OiBu	OMe	Et	H	H	$\mathrm{NH_2}$
231	OMe	OMe	OH	OH	OMe	Et	H	H	$\mathrm{NHCOCH_2CH(Me)CONH_2}$
232	OMe	OMe	OH	OiBu	OMe	Et	H	H	$\mathrm{NHCOCH_2CH(Me)CONH_2}$
233	OMe	OMe	OH	OMe	OAc	Et	H	H	MeSuc
234	OMe	OMe	OH	OMe	OMe	Et	OH	H	MeSuc
235	OH	OMe	OH	OMe	OMe	Et	H	H	MeSuc
236	OMe	OMe	OH	OH	OAc	Et	H	H	MeSuc
237	OMe	OMe	OH	OAc	OAc	Et	H	H	MeSuc
238	OMe	OMe	OH	OMe	OH	Et	H	H	MeSuc
239	OMe	OMe	OH	OMe	H	Et	H	H	$\mathrm{NHCOCH(Me)CH_2COOMe}$
240	OMe	OMe	OH	OMe	H	Et	H	H	$\mathrm{NHCOCH_2CH(Me)COOMe}$
241	OMe	OMe	OH	OAc	OAc	Et	H	H	$\mathrm{NHCOCH_2CH(Me)CONH_2}$
242	OMe	OMe	OH	OAc	OAc	Et	H	H	$\mathrm{NHCOCH(Me)CH_2CONH_2}$
243	OMe	OMe	OH	OAc	OAc	Et	H	H	$\mathrm{NHCOCH_2CH(Me)COOH}$
244	OMe	OMe	OH	OH	OMe	Et	H	H	NHCOMe
245	OMe	OMe	OH	OMe	OMe	Et	H	H	$\mathrm{NHCOCH(Me)CH_2COO(CH_2)_3Me}$
246	OMe	OH	OAc	OMe	OMe	Et	H	H	Suc
247	OH	OMe	OMe	O	OMe	Et	H	H	MeSuc
248	OMe	OMe	OH	OMe	OMe	Et	H	H	$\mathrm{NHCOCH_2CH_2COOMe}$
249	OMe	OMe	OH	O	OMe	Et	H	H	MeSuc
250	OH	OMe	OMe	OMe	OMe	Et	H	H	$\mathrm{NH_2}$
251	OMe	OMe	OMe	OMe	OMe	Et	H	H	$\mathrm{NH_2}$
252	OMe	OMe	OH	OAc	OMe	Et	H	H	$\mathrm{NHCOCH_2(Me)COOMe}$
253	OMe	OMe	OH	OH	OMe	Et	H	H	MeSuc
254	OMe	OMe	OH	OMe	OMe	Et	H	H	$\mathrm{NHCOCH(Me)CH_2COOMe}$
255	OMe	OMe	OH	OMe	OMe	H	H	H	$\mathrm{NH_2}$

Fig. 8 Lycaconitines with 7-OH/18-anthranoyl group from *Delphinium* plants.

group at C-16.[81,86] Moreover, delstaphisine (**309**) from *D. staphisagria* has a 16-OH group,[87] and staphisadrinine (**291**) from *D. staphisagria* features a ketone carbonyl at C-16.[83]

2.2.3 Lactone-, rearranged- and 7,17-seco-type compounds. The other types of C_{19}-DAs are rare (Fig. 10). Two new lactone-type C_{19}-DAs, namely, 8-acetylheterophyllisine (**319**) from *D.*

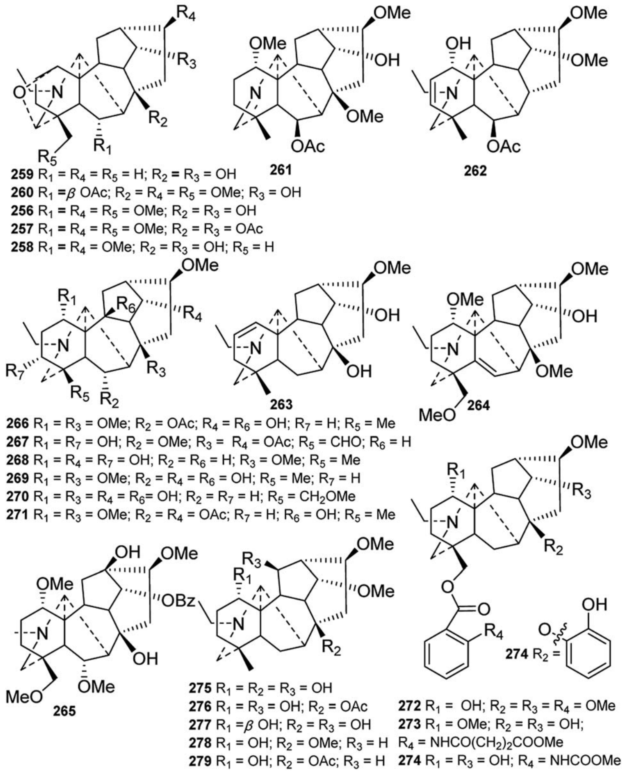


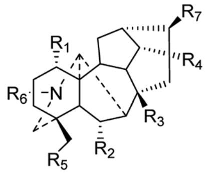
Fig. 9 Aconitines from *Delphinium* plants.

denudatum[88] and souline B (**318**) from *D. souliei*,[89] both featuring a hexanolactone C ring, were reported. In addition, two rearranged C_{19}-DAs, grandiflodine B (**320**) and yunnanenseine A (**321**), were isolated from *D. grandiflorum* and *D. yunnanense*, respectively.[90,91] Yunnanenseine A (**321**) is a typical acoseptine-type rearranged C_{19}-DA in which its $C_{(7)}$–$C_{(17)}$ bond was rearranged to a $C_{(8)}$–$C_{(17)}$ bond, forming an additional ketone at C-7. Grandiflodine B (**320**) features an unusual lycoctonine-type C_{19}-DA skeleton generated *via* cleavage of the N–$C_{(19)}$ and $C_{(7)}$–$C_{(17)}$ bonds and the construction of a N–$C_{(7)}$ bond. Leueandine (**322**) is the only 7,17-seco-type C_{19}-DA from a *Delphinium* plant, and it possesses a franchetine-type skeleton with a cinnamoyl group at C-14.[92]

2.3 C_{20}-Diterpenoid alkaloids

Although C_{20}-type DAs account for a relatively small proportion of DAs in terms of quantity, they are much more structurally diverse than C_{19}-type DAs. The skeletons of C_{20}-DAs are fairly complex, and more than 20 subtypes have been defined.[93] As listed in Table 1S,† approximately 89 new alkaloids belonging to seven of the subtypes of C_{20}-DAs were isolated from *Delphinium* plants in the last four decades.

Hetisine-type C_{20}-DAs (C-1), which are characterized by a heptacyclic system with an N–$C_{(6)}$ bond, constitute the majority of the new C_{20}-DAs from *Delphinium* plants. A total of 56 new hetisines were obtained from the *Delphinium* species (Fig. 11 and 12). These alkaloids vary mainly in the variety, quantity, position and orientation of their oxygenated substituents, including hydroxyl, acetyl, benzoyl, isobutyryl, 2-methylbutyryl, ketone and carbonyl groups. Anthriscifolmine J (**330**) from *D. anthriscifolium* var. *savatieri* features a unique 2-hydroxy-2-methylpropanoyloxy group at C-3 along with a formyloxy group at C-13,[94] and grandiflodine A (**324**) from *D. grandiflorum* has a rare cyano group at C-18.[90] 14-Hydroxyhetisinone N-oxide (**327**) from *D. gracile* is a rare hetisine-type N-oxide,[95] and delatisine (**326**) from *D. elatum* possesses an N–$C_{(19)}$–O–$C_{(2)}$ mixed acetal unit.[96] In addition, several structurally novel hetisine-type C_{20}-DAs were reported. Anthriscifolsine A (**325**) from *D. anthriscifolium* var. *majus* features a seco C ring generated through unprecedented $C_{(11)}$–$C_{(12)}$ bond cleavage in the hetisine skeleton.[97] The N–$C_{(17)}$ bond in grandiflodine A (**324**) can be cleaved, forming an additional ketone carbonyl at C-17.[90] Leptanine (**323**), which was isolated from *D. leptocarpum*, is a dimeric alkaloid consisting of a hetisine-type C_{20}-DA part and an indolinonepyrrole fragment. According to X-ray



	R_1	R_2	R_3	R_4	R_5	R_6	R_7
280	OMe	OAc	OMe	OH	H	Et	OMe
281	OH	βOH	OMe	OAc	OMe	Et	OMe
282	OH	OMe	OMe	OH	OH	Et	OMe
283	OH	H	OMe	OH	H	Et	OMe
284	OMe	OAc	OMe	OAc	H	Et	OMe
285	OMe	OAc	OMe	OMe	H	Et	OMe
286	OH	H	H	OH	H	Et	OMe
287	OMe	OMe	OH	OH	H	Et	OMe
288	OAc	βOH	OAc	OH	H	Et	OMe
289	OH	H	OAc	OAc	OMe	Et	OMe
290	OH	H	OH	OH	H	Et	H
291	OH	OMe	OH	OH	OMe	Et	O
292	OMe	OAc	OMe	OBz	H	Et	OMe
293	OMe	O	OMe	OH	H	Et	OMe
294	OMe	OH	OH	OH	H	Et	OMe
295	OH	βOH	OMe	OH	H	Et	OMe
296	OMe	H	OMe	OH	H	Et	OMe
297	OMe	H	OH	OH	H	Et	H
298	OH	H	OH	OAc	H	Et	OMe
299	OMe	OAc	OMe	OMe	H	H	OMe
300	OMe	OAc	OMe	OH	H	Et	OMe
301	OH	βOAc	OH	OH	H	Et	OMe
302	OH	βOMe	OH	OAc	OH	Et	OMe
303	OH	βOMe	OH	OH	OH	Et	OMe
304	OMe	βOMe	OH	OH	OH	Et	OMe
305	OH	βOH	OH	OAc	H	Et	OMe
306	OH	H	OH	OMe	OMe	Et	OMe
307	OH	βOH	OAc	OAc	OMe	Et	OMe
308	OAc	βOMe	OAc	OAc	OMe	Et	OMe
309	OH	OMe	OAc	OAc	OMe	Et	OH
310	OH	OMe	OAc	OAc	OH	Et	OMe
311	OH	OMe	OH	OAc	OMe	Et	OMe
312	OH	OMe	OH	OH	OH	Et	OMe
313	OH	βOMe	OAc	OAc	OMe	Me	OMe
314	OMe	OMe	OAc	OBz	H	Me	OMe
315	OH	H	OH	OAc	H	Et	OMe
316	OMe	OMe	OH	OAc	OMe	Et	OMe
317	βOH	H	OH	βOAc	OMe	Et	OMe

Fig. 9 (*contd.*)

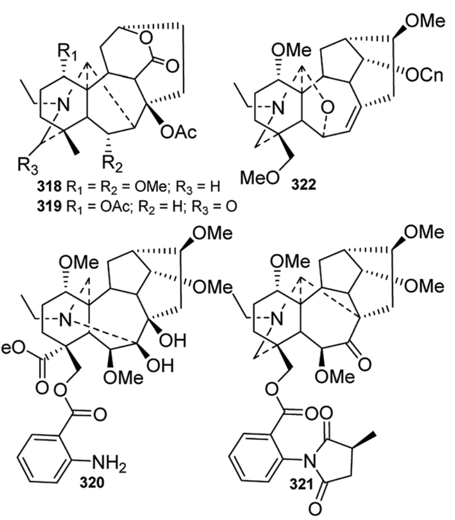


Fig. 10 Lactone-, 7,17-seco-, and rearranged-type DAs from *Delphinium* plants.

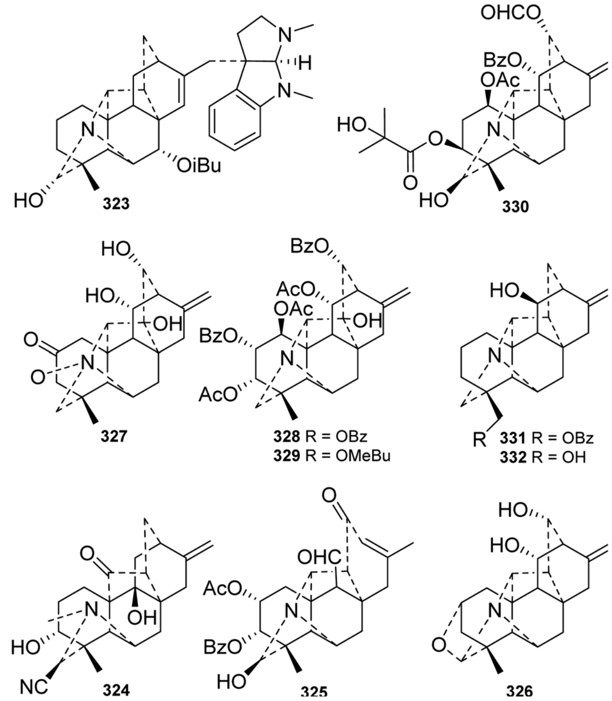


Fig. 11 Hetisine type C_{20}-DAs from *Delphinium* plants.

crystal structure analysis, the indolinonepyrrole fragment was bound to the hetisine-type C_{20}-DA part through an α-directed (relative to the indoline core) $C_{(17)}$–$C_{(3')}$ covalent bond.[98]

Vakognavine-type C_{20}-DAs (C-2) have an *N*–$C_{(19)}$ seco hetisine skeleton in addition to a formyl group at C-4. During the past forty years, 17 new vakognavines were isolated from 6 *Delphinium* species (Fig. 13). Generally, vakognavine-type C_{20}-DAs seldom have a $C_{(15)}{=}C_{(16)}$ bond, but anthriscifolmines G (**393**) and H (**392**) from *D. anthriscifolium* var. *savatieri* are exceptions to this statement.[99] In addition, anthriscifolmines E–H (**390–393**) feature a rare formyloxy group at C-11 along with a unique 2-hydroxy-2-methylpropanoyloxy group or a 2-methylpropanoyloxy group at C-13.[99]

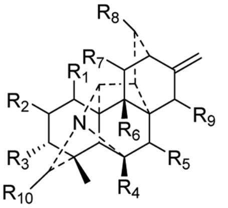
Atisine-type C_{20}-DAs (C-4) have always been regarded as the biosynthetic precursors of the other C_{20}-DAs, possess a relatively simple pentacyclic framework. Twelve atisines from seven *Delphinium* species were reported (Fig. 13). Structurally, isoazitine (**404**) and 13-(2-methylbutyryl)azitine (**406**) each possess an azomethine between *N* and C-19 or C-17.[3,100] Uncinatine (**414**) from *D. uncinatum* bears an uncommon *N*–CH=CHOH group.[101] Delphatisine A (**412**)[102] and delphatisine D (**413**)[58] possess oxazolidine rings formed by a carbinolamine ether linkage between C-20 and C-17 or C-19, respectively. Delphatisines B (**411**) and C (**410**) feature a γ-lactone-fused oxazolidine ring.[103] The γ-lactone ring in honatisine (**403**) was open, forming an extra carboxylic acid group at C-22. In addition, a unique 1′,3′,5′-trimethyl-4′-oxocyclohexyloxy unit was substituted at C-24.[104]

Other subtypes of C_{20}-DAs were also reported. Six new hetidine-type C_{20}-DAs (C-3), including anthriscifolmine I (**396**) from *D. anthriscifolium* var. *savatieri*,[94] carduchoron (**398**) and delcarduchol (**399**) from *D. carduchorum*,[105] macrocentrine (**401**) from *D. macrocentrum*,[4] cardionidine (**402**) from *D. cardiopetalum*,[106] and 2-dehydrodeacetylheterophylloidine (**400**) from *D. pentagynum*,[52] were acquired. Among these alkaloids, cardionidine (**402**) features an anhydride function in its B ring.[106] Three denudatine-type DAs (C-5), including anthriscifolmines A (**416**) and B (**415**) from *D. anthriscifolium* var. *savatieri*, which possess a 16,17-epoxy group and a butyryl group at C-13,[107] and cordizine (**417**) from *D. corymbosum*, which possesses a CH_3-17β angular methyl group, were reported.[108] Moreover, a napelline-type C_{20}-DA (C-6), norsongoramine (**418**), with an *N*–$C_{(19)}$–*O*–$C_{(1)}$ mixed acetal unit was obtained from *D. tamarae*,[109] and a delnudine-type C_{20}-DA (C-7), trichodelphinine F (**419**), possessing a rare phenylacetyl group at C-2, was isolated from *D. trichophorum*.[110]

2.4 Other alkaloids

In addition to DAs, other types of alkaloids have also been isolated from *Delphinium* plants (Fig. 14). Several amide alkaloids from *Delphinium* plants have been reported. Five new acyl anilines, delamides A–E (**420–424**), which possessed an *O*-ester aniline bearing an amide side chain, were isolated from *D. brunonianum* by Zou *et al.*[111] Diaz *et al.* reported the isolation of three new anthranilic acid derivatives (**425–427**), also called dianthramides, from tissue cell cultures of *D. staphisagria*.[112] In addition, a novel lactam (**428**) possessing a 2-azabicyclo[2.2.1]heptane unit bearing a trimethoxy naphthalene ring, was isolated from *D. caeruleum*.[113]

Tetrahydroisoquinoline alkaloids are widely distributed in the Ranunculaceae family. While little attention has been paid to the isoquinoline alkaloids in *Delphinium* plants, a new benzyltetrahydrobenzylisoquinoline alkaloid, *O*-methylroefractine *N*-oxide (**429**), was found in *D. fangshanense*.[114]



	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}
333	βOH	H	H	H	H	H	H	H	βOH	H
334	H	αOiBu	H	H	αOAc	H	αOAc	αOBz	H	βOMe
335	H	αOiBu	H	H	H	H	αOAc	αOAc	H	αOH
336	H	αOiBu	H	H	H	H	αOH	αOAc	H	αOH
337	H	αOiBu	H	H	H	H	αOH	αOH	H	αOH
338	H	αOAc	OAc	H	H	OH	βOH	βOH	βOH	H
339	H	αOiBu	H	OH	H	OH	βOH	H	βOiBu	αOH
340	H	αOH	H	H	H	H	αOH	βOAc	H	H
341	H	αOAc	OBz	H	H	H	βOH	O	H	βOH
342	H	H	H	H	αOiBu	H	βOAc	αOAc	H	βOH
343	H	H	H	H	αOiBu	H	βOAc	αOH	H	βOH
344	H	H	O	OH	H	H	H	αOiBu	H	H
345	H	H	O	H	H	H	H	αOiBu	H	H
346	H	H	O	OH	H	H	H	αOiBu	H	H
347	H	H	O	H	H	H	αOH	αOMeBu	H	H
348	H	H	H	H	αOBz	H	αOAc	H	αOH	H
349	H	βOH	H	H	βOH	H	βOH	H	H	H
350	H	αOH	H	H	H	H	αOAc	αOiBu	H	H
351	H	αOH	H	H	H	H	αOH	αOiBu	H	H
352	H	αOH	H	H	H	H	αOAc	αOMeBu	H	H
353	H	αOAc	H	H	H	H	αOH	αOAc	H	H
354	H	O	H	H	H	H	αOAc	αOiBu	H	H
355	αOH	αOBz	H	H	H	H	αOH	βOH	H	αOH
356	H	H	H	H	αOiBu	H	αOH	H	βOH	βOH
357	βOAc	αOMeBu	OH	H	H	H	αOAc	αOBz	H	H
358	βOAc	αOiBu	OH	H	H	H	αOAc	αOBz	H	H
359	βOAc	αOH	OiBu	H	H	H	αOAc	αOBz	H	H
360	βOAc	αOH	OMeBu	H	H	H	αOAc	αOBz	H	H
361	H	βOBz	OAc	H	H	H	αOH	αOAc	H	H
362	H	O	H	H	H	H	αOBz	βOH	βOH	H
363	H	O	H	H	H	H	αOBz	βOH	βOAc	H
364	H	O	H	H	H	OAc	H	αOH	H	H
365	H	H	H	H	αOH	H	α-OH	αOH	H	H
366	H	H	OH	H	H	H	H	H	βOAc	βOH
367	H	O	H	OH	H	H	αOH	βOH	H	H
368	H	H	H	OH	H	H	αOH	H	H	H
369	H	O	H	H	H	H	αOH	αOH	βOH	H
370	H	O	H	OH	H	H	αOMeBu	βOH	H	H
371	H	O	H	OH	H	H	αOH	βOAc	H	H
372	H	O	βOAc	OH	H	H	αOMeBu	βOH	H	H
373	H	O	H	H	H	OAc	αOH	αOAc	H	H
374	H	OH	H	OH	H	H	H	βOH	H	H
375	H	O	H	OH	H	OH	H	βOAc	H	H
376	H	O	H	OH	H	H	H	βOH	H	H
377	H	H	H	H	αOH	H	αOAc	H	βOH	H
378	βOAc	βOAc	H	H	H	H	H	βOAc	H	H

Fig. 12 The hetisine type C_{20}-DAs from *Delphinium* plants.

3. Flavonoids

Delphinium, the flowers of which have petals of various colours, *i.e.*, white, red, violet and blue, are widely cultivated as one of the most famous horticultural plants in the world. The anthocyanidin pigments in the *Delphinium* flowers have attracted considerable attention for a long time. As early as 1915, Willstitter isolated the first anthocyanidin pigment, delphinin, from the reddish-purple petals of *D. consolida*.[10,115] During the last four decades, eight new anthocyanidins were reported from different cultivated varieties of *D. hybridum* (Fig. 14). Two new delphinin glycosides, violdelphin (**450**)[116] and cyanodelphin (**443**),[117] were isolated from the violet petals of *D. hybridum* cv "Blue Night" and the blue petals of *D. hybridum* cv "Blue Springs", respectively. Structurally, violdelphin (**450**) contains two *p*-hydroxybenzoic acid units and four hexose substituents in addition to the delphinin core, and cyanodelphin (**443**) contains four *p*-hydroxybenzoic acid units and seven glucose units in its

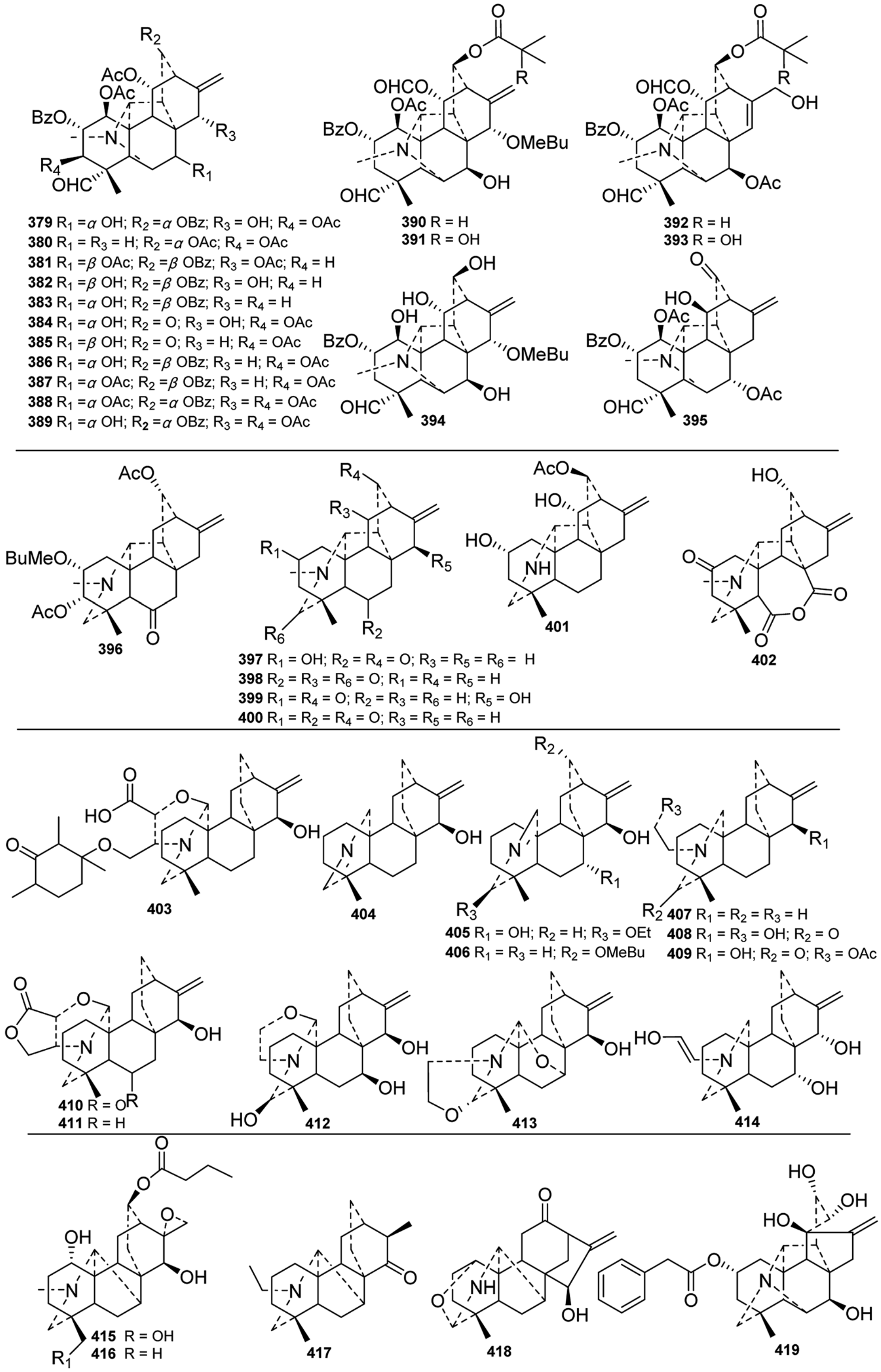


Fig. 13 The vakognavine-type, hetidine-type, atisine-type, denudatine-type C_{20}-DAs from *Delphinium* plants.

structure. In addition, six new acylated pelargonidin 3,7-glycosides (**444–449**) were isolated from the red petals of *D. hybridum* cv "Princess Caroline".[118] These pelargonidin glycosides possess various acylated glucoses and rhamnoses at C-3 and C-7. Characteristically, glycosides **447** and **449** are acylated at the 3-glucose residue with malonic acid.

In addition to anthocyanidins, *Delphinium* plants are also rich in flavonol glycosides. In 1973, Arazashvili *et al.* first reported the identification of two known flavonol glycosides from the leaves of *D. flexiosum* and *D. elisabethae*.[119] Dozens of flavonols and their glycosides were isolated from *Delphinium* plants during the next forty years, including some common and widespread constituents, such as rutin, quercetin, kaempferol, and luteolin as well as

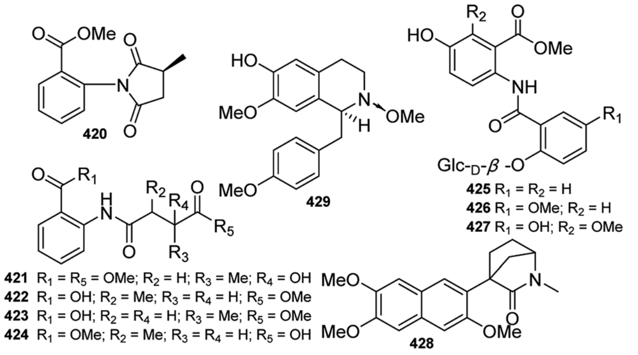
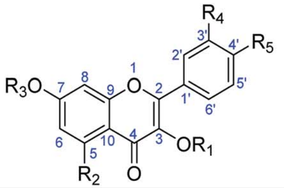


Fig. 14 The other alkaloids from *Delphinium* plants.

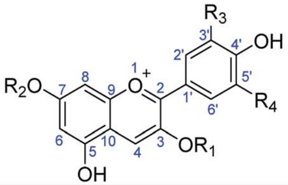
their glycosides.[120] Eleven new compounds have been reported from four *Delphinium* species, with the aglycones being kaempferol (**434–437** and **440**) and quercetin derivatives (**430–433** and **438–439**) (Fig. 15). The novelty of these flavonol glycosides is mainly determined by the type and position of the acyl groups on the carbohydrate chains. Structurally, flavonol glycosides **436–439** from *D. staphisagria* possess a 2-*O*-acetyl glucosyl group at C-7,[121] while flavonol glycoside **440** from *D. formosum* has a 4,6-*O*-diacetyl glucosyl group.[122] Compound **430**, a benzoylated quercetin glycoside, was isolated from *D. carolinianum*,[123] and compounds **431–435** are a series of tetraglycosides acylated by caffeic acid and cumaric acid.[124]

4. Phenolics

A certain number of phenolic compounds, such as benzoic and phenylacetic acid derivatives, have been identified from *Delphinium* plants.[125–127] However, most of these phenolic compounds are common, structurally simple and widely distributed in the plant kingdom; new structures are rarely discovered.



	R_1~R_5	Plant
430	R_1 = 3-benzoyl-*β*-D-Glu-(1→2)-*β*-D-Glu; R_3 =*α*-L-Rha; $R_2 = R_4 = R_5$ = OH	*D. carolinianum* [123]
431	R_1 = [*β*-D-Xyl-(1→3)-4-*O*-*E*-*p*-caffeoyl-*α*-L-Rha-(1→6)][*β*-D-Glu-(1→2)]-*β*-D-Glu; R_3 = H; $R_2 = R_4 = R_5$ = OH	*D. gracile* [124]
432	R_1 = [*β*-D-Xyl-(1→3)-4-*O*-*E*-*p*-coumaroyl-*α*-L-Rha-(1→6)][*β*-D-Glu-(1→2)]-*β*-D-Glu; R_3 = H; $R_2 = R_4 = R_5$ = OH	
433	R_1 = [*β*-D-Xyl-(1→3)-4-*O*-*Z*-*p*-coumaroyl-*α*-L-Rha-(1→6)][*β*-D-Glu-(1→2)]-*β*-D-Glu; R_3 = H; $R_2 = R_4 = R_5$ = OH	
434	R_1 = *β*-D-Glu-(1→3)-4-*O*-*E*-*p*-coumaroyl-*α*-L-Rha-(1→6)-*β*-D-Glu; R_3 = 4-*O*-acetyl-*α*-L-Rha; $R_2 = R_5$ = OH; R_4 = H	
435	R_1 = *β*-D-Xyl-(1→3)-4-*O*-*E*-*p*-coumaroyl-*α*-L-Rha-(1→6)-*β*-D-Glu; R_3 = 4-*O*-acetyl-*α*-L-Rha; $R_2 = R_5$ = OH; R_4 = H	
436	R_1 = 2-*O*-acetyl-*β*-D-Glu; $R_3 = R_4$ =H; $R_2 = R_5$ = OH	*D. staphisagria* [121]
437	R_1 = 2-*O*-acetyl-*β*-D-Glu; R_3 = *β*-D-Glu; $R_2 = R_5$ = OH; R_4 = H	
438	R_1 = 2-*O*-acetyl-*β*-D-Glu; R_3 = *β*-D-Glu; $R_2 = R_4 = R_5$ = OH	
439	R_1 = 2-*O*-acetyl-*β*-D-Glu; R_3 = *α*-L-Rha; $R_2 = R_4 = R_5$ = OH	
440	R_1 = 4,6-*O*-diacetyl-*β*-D-Glu; R_3 = *α*-L-Rha; $R_2 = R_5$ = OH; R_4 = H	*D. formosum* [122]
441	R_1 = [2,3,4-*O*-triacetyl-*β*-D-Xyl-(1→3)-4-*O*-(*E*-*p*-*O*-acetyl-coumaroyl)-2-*O*-acetyl-*α*-L-Rha-(1→6) -3,4-diacetyl-*β*-D-Glu], R_3 = 2,3,4-triacetyl-*α*-L-Rha, $R_2 = R_4 = R_5$ = OAc	*D. gracile* [132]
442	R_1 = [2,3,4,5-*O*-tetraacetyl-*β*-D-Glu-(1→3)-4-*O*-(*E*-*p*-*O*-acetyl-coumaroyl)-2-*O*-acetyl-*α*-L-Rha-(1→6)-3,4-diacetyl-*β*-D-Glu], R_3 = 2,3,4-triaceyl-*α*-L-Rha, $R_2 = R_4 = R_5$ = OAc	



	R_1~R_4	Plant
443	R_1 = *α*-L-Rha-(1→6)-*β*-D-Glu; R_2 = [6-*O*-(6-*O*-*p*-hydroxybenzoyl-*β*-D-Glu)-*p*-hydroxybenzoyl][6-*O*-(6-*O*-*p*-hydroxybenzoyl-*β*-D-Glu)-*p*-hydroxybenzoyl]-*β*-D-Glu-(1→3)-*β*-D-Glu-(1→3)]-*β*-D-Glu; $R_3 = R_4$ = OH	*D. hybridum* [116-118]
444	R_1 = *α*-L-Rha-(1→6)-*β*-D-Glu; R_2 = *β*-D-Glu; $R_3 = R_4$ = H	
445	R_1 = *α*-L-Rha-(1→6)-*β*-D-Glu; R_2 = 6-*O*-*p*-hydroxybenzoyl-*β*-D-Glu; $R_3 = R_4$ = H	
446	R_1 = *α*-L-Rha-(1→6)-*β*-D-Glu; R_2 = 6-*O*-(4-*O*-*β*-D-Glu-*p*-hydroxybenzoyl)-*β*-D-Glu; $R_3 = R_4$ = H	
447	R_1 = 6-*O*-malonyl-*β*-D-Glu; R_2 = *β*-D-Glu; $R_3 = R_4$ = H	
448	R_1 = *β*-D-Glu; R_2 = 6-*O*-(4-*O*-*β*-D-Glu-*p*-hydroxybenzoyl)-*β*-D-Glu; $R_3 = R_4$ = H	
449	R_1 = 6-*O*-malonyl-*β*-D-Glu; R_2 = 6-*O*-(4-*O*-*β*-D-Glu-*p*-hydroxybenzoyl)-*β*-D-Glu; $R_3 = R_4$ = H	
450	R_1 = *α*-L-Glu-(1→6)-*β*-D-Glu; R_2 = [6-*O*-(4-*O*-*p*-hydroxybenzoyl-*β*-D-Glu)-*p*-hydroxybenzoyl]-*β*-D-Glu; $R_3 = R_4$ = OH	

Fig. 15 Flavonoid glycosides from *Delphinium* plants.

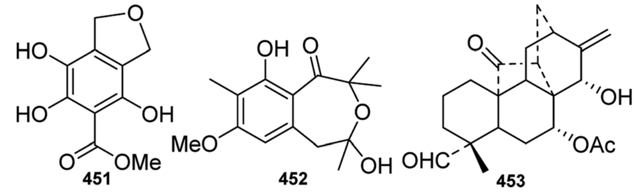


Fig. 16 Phenolics and diterpenoid from *Delphinium* plants.

Only two new phenolic compounds, namely, 2,5,6-trihydroxypiperonylic acid methyl ester (**451**) from *D. venulosum*[128] and oxformasine (**452**) from *D. formosum*,[129] were reported during the studied period (Fig. 16). Oxformasine (**452**) represents the first benzoxepine derivative from *Delphinium* species.

5. Terpenoids

In contrast to the wide variety of DAs present in *Delphinium* plants, terpenoids are rare. To date, only one new non-alkaloidal diterpenoid, campylopin (**453**) from *D. campylocentrum*, has been reported[130] (Fig. 15). Campylopin (**453**) is the first naturally occurring hetidane-type diterpenoid, and it has great significance for the biosynthesis of diterpenoid alkaloids, as it implies a new biosynthetic pathway from atisane or hetidane-type C_{20}-diterpenes to hetidine-type C_{20}-diterpenoid alkaloids.[131]

6. Bioactivities

In the past forty years, compounds isolated from *Delphinium* plants, mainly DAs and flavonols, have been screened for their multiple biological activities, including antineoplastic, antimicrobial, anti-inflammatory, and insecticidal and antifeedant activities, as well as cholinesterase inhibition effects. Some of the tested compounds showed considerable activities. Herein, the bioactivities of the compounds from the *Delphinium* plants are summarized.

Table 1 Cytotoxic activity of *Delphinium* alkaloids

			IC_{50} (μM)	
Plants	Alkaloids	Type	MCF-7	A549
D. chrysotrichum	Delphatisine C (**410**)	C-4	>50	2.36
	Delpheline	B-1	17.32	>50
	Delbrunine	B-1	16.50	10.63
	Etoposide	—	7.56	1.8
D. honanense	Honatisine (**403**)	C-4	3.16	>50
	Siwanine E	B-1	35.32	>50
	Delcorinine	B-1	18.60	31.63
	Uraphine	B-1	33.21	9.86
	Nordhagenine A	B-1	17.38	9.62
	Etoposide	—	7.53	1.82
D. trichophorum	Trichodelphinine A (**350**)	C-1	—	27.62
	Trichodelphinine B (**351**)	C-1	—	18.64
	Trichodelphinine C (**352**)	C-1	—	48.08
	Trichodelphinine D (**353**)	C-1	—	52.79
	Trichodelphinine E (**354**)	C-1	—	12.03
	Trichodelphinine F (**419**)	C-1	—	16.55
	Doxorubicin	—	—	0.60

6.1 Anticancer activity

A certain number of natural DAs have been reported to possess antiproliferative activities against various human cancer cell lines, indicating their great potential as new drugs for treating the corresponding cancers.[133] New DAs along with known DAs from *Delphinium* plants have also been reported to have *in vitro* anticancer activities (Table 1). The atisine-type DA delphatisine C (**410**) from *D. chrysotrichum* showed significant cytotoxic activity against A549 cells (IC_{50}, 2.36 μM),[103] and its analogue honatisine (**403**) from *D. honanense* also displayed impressive cytotoxic activity against MCF-7 cells with an IC_{50} value of 3.16 μM, making it more effective than the positive control etoposide (IC_{50}, 7.53 μM).[104] The cytotoxic activities of five hetisine-type C_{20}-DAs, trichodelphinines A–E (**350–354**), and one delnudine-type C_{20}-DA, trichodelphinine F (**419**), against A549 cells were tested.[110] The most active compounds (**351**, **354** and **419**) had low IC_{50} values (18.64, 12.03 and 16.55 μM, respectively), and the other compounds showed moderate cytotoxicities against A549 cells. In addition, known lycaconitine-type C_{19}-DAs, including delpheline, delbrunine, siwanine E, delcorinine, uraphine, nordhagenine A, and delbrunine from *D. chrysotrichum* and *D. honanense,* also showed certain anticancer activities against A549 and MCF-7 cells with IC_{50} values ranging from 9.62 to 35.32 μM.[104]

Although no detailed structure–activity relationship (SAR) study has yet been reported, it seems that C_{20}-DAs have shown more potential to be developed as antitumor drugs on account of their higher efficiency and lower toxicity.[13] Especially, the hetisine-type C_{20}-DAs, which have exhibited selective antiproliferative activity on human lung cancer cell A549, deserve further studies to identify more potent antitumor DAs. On the other hand, *Delphinium* plants have rarely been utilized for the treatment of cancer in TCM. The research presented above suggests that *Delphinium* plants with abundant DAs have great potential as herbal drugs for treating cancer, but more research is required to confirm this.

6.2 ChE inhibition effects

The discovery of natural ChE inhibitors is an active research area in natural medicinal chemistry due to the involvement of cholinesterases in Alzheimer's disease and related dementias.[134] In the early 1990s, methyllycaconitine, one of the principal active constituents of *Delphinium* species, was found to be an effective ligand for neuronal nicotinic acetylcholine receptor (nAChR) subtypes, which attracted the attention of scientists to the screening of natural cholinesterase inhibitors from *Delphinium* species. Several *Delphinium* alkaloids have been reported to exhibit considerable ChE inhibitory effects (Table 2). The aconitine-type C_{19}-DAs 1β-hydroxy, 14β-acetylcondelphine (**317**), jadwarine-A (**270**), jadwarine-B (**262**), and dihydropentagynine (**203**) from *D. denudatum* have been found to possess inhibitory effects of AChE and BChE with EC_{50} values ranging from 9.2 to 34.7 μM.[75] Ahmad *et al.* reported that an

Table 2 ChE inhibition effects of *Delphinium* alkaloids

Plants	Compounds	Type	EC_{50} (μM) AChE	EC_{50} (μM) BChE
D. denudatum	1β-hydroxy, 14β-acetyl condelphine (**317**)	B-2	19.8	31.5
	Jadwarine-A (**270**)	B-2	9.2	19.6
	Jadwarine-B (**262**)	B-2	16.8	34.7
	Isotalatizidine hydrate	B-2	12.1	21.4
	Dihydropentagynine (**203**)	B-1	11.2	22.2
	Allanzanthane A	—	8.2	18
	Galanthamine	—	10.1	20.6
D. brunonianum	Delamide A (**420**)	Amide	9.7	>50
	Rivastigmine	—	4.7	>10

isotalatazidine hydrate crystal isolated from *D. denudatum* showed competitive inhibition of both AChE and BChE with IC_{50} values of 12.13 μM and 21.41 μM, respectively.[135] In addition, the amide alkaloid delamide A (**420**) from *D. brunonianum* also showed highly selective AChE inhibitory activity (EC_{50}, 9.7 μM) and was shown to be a mixed-type reversible inhibitor of AChE by kinetic analysis.[111]

6.3 Insecticidal and antiparasitic activities

Delphinium plants have been used as natural insecticides since the time of Dioscorides. Previous studies have indicated that DAs might have evolved in nature to protect *Delphinium* and *Aconitum* plants against pests. Hence, searching for valuable natural insecticides from plants that are rich in DAs, which have been shown to be potent and selective ligands of the insect nicotinic receptor, is quite effective.[136,137] A series of DAs from *Delphinium* plants have been shown to possess insecticidal and antifeedant activities. Ulubelen *et al.* tested the repellency of 8 new alkaloids along with 12 known alkaloids belonging to three subtypes of DAs from Turkish *Delphinium* species against *Tribolium casteneum* (Table 3).[138] Most of the tested new alkaloids (**280**, **285**, **299**, **331**, **368–369**, and **378**) had repellency class III values (40.1–60%) for a short period, and venuluson (**369**) gave the highest level of repellency (59.37%), suggesting it is a promising candidate for insecticide development.

Several investigations on the antifeedant activities of *Delphinium* alkaloids have been performed. The crude alkaloids of *D. cyphoplectrum* have slight antifeedant and insect repellent activities against the larvae of *Spodoptera littoralis*.[139] González-Coloma *et al.* tested the insect antifeedant activities of 21 DAs isolated from *Delphinium* species on *Spodoptera littoralis* and *Leptinotarsa decemlineata*. The antifeedant effects of the test compounds were structure- and species-dependent (EC_{50} values ranging between 0.42–22.5 and 0.1–17.77 μg cm^{-2} for *L. decemlineata* and *S. littoralis*, respectively). The most active antifeedants to *L. decemlineata* and *S. littoralis* were found be to

Table 3 Repellency of *Delphinium* alkaloids to *T. casteneum*

Plants	Alkaloids	Type	Repellency (%)	Class
D. venulosum	Venulol (**368**)	C-1	31.25	II
	Venuluson (**369**)	C-1	56.25	III
	Venudelphine (**378**)	C-1	40.62	III
	Hetisine	C-1	59.12	III
	Hetisinone	C-1	37.50	II
D. gueneri	14-Methyl peregrine (**285**)	B-2	46.87	III
	N-Deethyl-14-*O*-methylperegrine (**299**)	B-2	40.62	III
	Peregrine (**280**)	B-2	53.12	III
	Peregrine alcohol	B-2	37.50	II
	Talatisamine	B-2	34.37	II
	14-Acetyneoline	B-2	53.12	III
D. albiflorum	Lycoctonine	B-1	46.87	III
D. davisii	18-Benzoyldavisinol (**331**)	C-1	46.87	III
	Karakoline	B-2	37.50	II
D. uncinatum	14-Acetylvirescenine	B-1	43.75	III
	Condelphine	B-2	40.62	III
D. formosum	14-Demethylajacine (**244**)	B-1	40.62	III
	Delsemine B	B-1	37.50	II
	Delsoline	B-1	37.50	II
D. crispulum	Browniine	B-1	46.87	III
D. montanum	Gigactonine	B-1	43.75	III

Table 4 Antifeedant effects of *Delphinium* alkaloids to *L. decemlineata* and *S. littoralis*

Plants	Alkaloids	Type	EC_{50} (μg cm^{-2}) *L. decemlineata*	EC_{50} (μg cm^{-2}) *S. littoralis*
D. cardiopetalum	Hetisinone	C-1	13.1	>50
	Cardiopetamine (**362**)	C-1	22.5	5.5
	15-Acetyl-cardiopetamine (**363**)	C-1	12.9	>100
	Cardiodine (**329**)	C-1	2.2	4.4
D. gracile	Atisinium chloride	C-3	3.4	2.4
D. stenocarpa	Ajaconine	C-3	5.1	8.2
D. staphisagria	19-Oxodihydroatisine (**408**)	C-3	>50	0.1
	Azitine	C-3	>50	1.1
	Isoazitine (**404**)	C-3	6.9	4.1
D. cardiopetalum	Karakoline	B-2	0.44	>50
	Cardiopetaline (**259**)	B-2	0.42	≈50
	Cardiopetalidine (**184**)	B-1	>50	>50
	14-Benzoylgadesine	B-1	>50	13.61
D. montanum	8-*O*-Ethylaconine	B-2	>50	8.29
	Neoline	B-2	≈50	≈50
	Gigactonine	B-1	13.02	9.31
	Delcosine	B-1	1.11	3.53
	Methylicaconitine	B-1	2.78	17.77
D. pentagynum	Gadenine	B-1	11.93	>50

the cardiopetaline (**259**, EC_{50}, 0.42 μg cm^{-2}) and 19-oxodihydroatisine (**408**, EC_{50}, 0.1 μg cm^{-2}), respectively.[140,141] Shawurensine (**209**) from *D. naviculare* var. *lasiocarpum* also showed considerably potent antifeedant activity with EC_{50} values of 0.42 and 0.81 mg cm^{-2} against the larvae of *Spodoptera exigua* in a choice test and no choice test, respectively.[142] Generally, the antifeedant activities of C_{20}-DAs are lower than those of C_{19}-DAs, which might be attributed to the species- and structure-related differences in the taste receptor binding to these two classes of DAs,[143] and this result suggest that further investigations on the antifeedant effects of these compounds should be concentrated on C_{19}-DAs.

Among the new flavonol glycosides that have been isolated from *Delphinium* plants, a series of compounds (**431–437**, **439** and **441–442**) have demonstrated high antiparasitic activities.[132,144,145] In some cases, the antitrypanosomatid activities of these flavonol glycosides against *Trypanosoma cruzi* were more potent than that of the reference drug benznidazole. For example, compound **436** showed higher trypanocidal activity ($IC_{50} = 6.5$ μM) than benznidazole ($IC_{50} = 15.8$ μM) against the epimastigote form of *T. cruzi*, and compound **432** exhibited higher trypanocidal activity (IC_{50}, 21.2 μM) than benznidazole (IC_{50}, 23.3 μM) against the amastigote form of *T. cruzi*. These compounds also showed impressive leishmanicidal activities against both the extra- and intracellular forms of three *Leishmania* species (*Leishmania infantum*, *L. braziliensis* and *L. donovani*), and among these compounds, **439** presented the highest antileishmanial activity. Notably, all of these tested flavonol glycosides showed low toxicity to the corresponding host cells, resulting in higher selectivity indices than the reference drugs, which highlights their potential in the treatment of leishmaniasis and Chagas disease (Table 4).

6.4 Antifungal and antiviral activity

Delphinium species have been used for the treatment of itches and other skin eruptions in folk medicine, which indicates that the plants may possess constituents with antifungal activities. The new lactone-type C_{19}-DA 8-acetylheterophyllisine (**319**) from *D. denudatum* showed antifungal activity against a number of human pathogenic fungi, including *Allescheria boydii*,

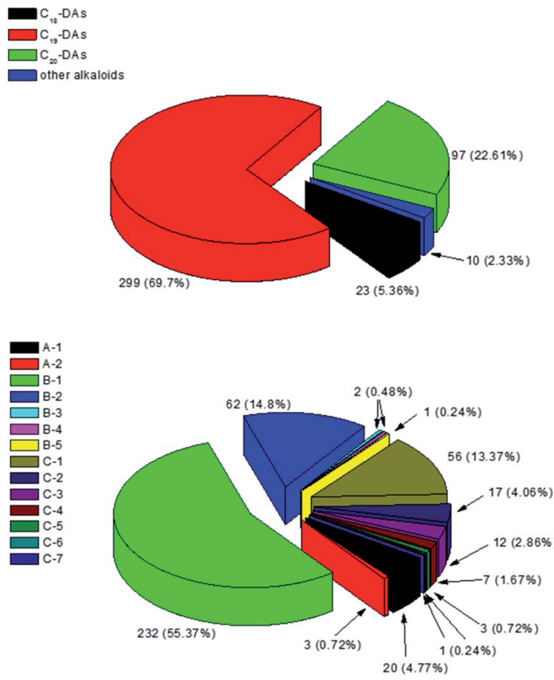


Fig. 17 The percentage of each type and sub-type of alkaloids from *Delphinium* species.

Aspergillus niger, *Epidermophyton floccosum*, and *Pleurotus ostreatus*, with MIC values of 100, 200, 250, and 150 μg mL^{-1}, respectively.[88]

Delphinium-derived DAs also showed antiviral activity. The new lycaconitine-type C_{19}-DAs ajacisines C–E (**212–214**), along with the known alkaloid isodelectine, which were isolated from *D. ajacis*, exhibited moderate to weak *in vitro* antiviral effects against respiratory syncytial virus (RSV) with IC_{50} values of 75.2, 35.1, 10.1, and 50.2 μM, respectively,[146] while the positive control (ribavirin) showed an IC_{50} value of 3.1 μM. The rearranged-type C_{19}-DA grandiflodine B (**21**), isolated from *D. grandiflorum*, also displayed a weak inhibitory effect on the growth of RSV with an IC_{50} value of 75.3 μM.[90]

7. Conclusions

To the best of our knowledge, investigations on the chemical constituents of *Delphinium* in the last four decades have reported a total of 453 new compounds, including 429 alkaloids, 21 flavonoids, two phenolic compounds, and one diterpenoid. Among the 429 new alkaloids, 419 are DAs, including 23 C_{18}-DAs, 299 C_{19}-DAs, and 97 C_{20}-DAs, which cover fourteen subtypes of DAs (Fig. 17). In view of the chemical diversity described, the lycaconitine sub-type of C_{19}-DAs (B-1), with 230 new members, are the most abundant DAs in the *Delphinium* plants, as they accounted for the largest proportion of new compounds (55.37%), followed by aconitine-type C_{19}-DAs (B-2) with 64 new members (14.8%) and hetisine-type C_{20}-DAs (C-1) with 56 new members (13.37%). The other subtypes only account for only a small portion of compounds (less than 20%). Obviously, DAs, especially lycaconitine-type C_{19}-DAs, are characteristic components of the genus *Delphinium*, which is distinguished from the genus *Aconitum* by the large number of aonitine-type C_{19}-DAs. Among these new compounds, several possess unprecedented structures, and their various biological activities, including anticancer activity, cholinesterase inhibition effects, insecticidal and antiparasitic activities, and antifungal and antiviral activities, have been reported. These findings underscore the large chemical and biological diversity among the chemical constituents of *Delphinium* plants, which could not only serve as a vast resource for drug discovery but also help elucidate the therapeutic effects of *Delphinium*-derived herbal drugs.

Although phytochemical and biological studies on the chemical constituents of *Delphinium* species have attracted considerable interest, some deficiencies remain. First, there are approximately 365 *Delphinium* species around the world, but the chemical constituents of only 87 species and 10 varietal have been studied in the last four decades. Among these species, *D. elatum*, *D. staphisagria*, *D. anthriscifolium* var. *savatieri*, *D. nuttallianum*, *D. anthriscifolium* var. *majus*, and *D. cardiopetalum* contributed relatively more new compounds than the other species. The biological constituents of other *Delphinium* species remain untapped. Hence, an extensive investigation of other species, especially species that are used medicinally, remains necessary. Second, all of the biological activities of the isolated compounds were investigated by using *in vitro* tests, namely, chemical and cellular models, and there is little research confirming the biological activities of *Delphinium* compounds using *in vivo* animal models or on their pharmacological mechanisms. It is necessary to evaluate the biological activities of *Delphinium*-derived constituents using both *in vitro* and *in vivo* models, which will facilitate further research and exploitation of this genus.

Conflicts of interest

There are no conflicts to declare.

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