



Cite this: *RSC Adv.*, 2025, **15**, 38281

## Ten years of advances in the chemistry and bioactivities of natural C<sub>19</sub>-diterpenoid alkaloids

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C<sub>19</sub>-diterpenoid alkaloids (DAs) constitute the most representative and largest class of DAs and have long been a popular focus of natural product research. In the past ten years (2015–2024), approximately 354 new C<sub>19</sub>-DAs have been reported, composing eight structural subtypes, among which aconitine-type DAs are the most common, followed by lycocotonine-type DAs. In addition, several rare substituents and novel skeletons have been reported, demonstrating the rich structural diversity of this class. C<sub>19</sub>-DAs are distributed only among *Aconitum* and *Delphinium* plants in the Ranunculaceae family, with a highly regular distribution pattern within these groups. Natural C<sub>19</sub>-DAs exhibit various physiological activities, including antitumor, anti-inflammatory, analgesic, and antimicrobial activities. In summary, the diverse structures and biological activities of C<sub>19</sub>-DAs highlight the great potential of this type of compound as lead compounds in drug discovery; in particular, the antitumor and anti-inflammatory effects of C<sub>19</sub>-DAs merit further in-depth study.

Received 31st March 2025  
 Accepted 24th September 2025  
 DOI: 10.1039/d5ra02226f  
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### 1. Introduction

DAs (diterpenoid alkaloids) are heterocyclic compounds in which the C-19 or C-20 of a tetracyclic or pentacyclic diterpene is linked to the nitrogen atom of β-aminoethanol, methylamine or ethylamine.<sup>1</sup> DAs can be divided into four main types according to the number of carbon atoms in the parent nucleus, namely, C<sub>18</sub>-, C<sub>19</sub>-, C<sub>20</sub>-, and bis-DAs. C<sub>19</sub>-DAs, once known as norditerpenoid alkaloids, are the most representative type of DA structure; they were the first type of DA to be discovered, and the greatest number of reported DA compounds are in this group.<sup>2</sup> Aconitine, which was isolated from *Aconitum napellus* by Geiger PL in 1833, was the first reported DA and is the best-known

compound of this class. The discovery of aconitine not only marked the beginning of the study of DAs but also played an important role in the history of natural medicinal chemistry. C<sub>19</sub>-DAs have a polycyclic fused cage skeleton with abundant substituents at multiple positions. The complex chemical structures of these materials have long attracted the persistent and intense research interest of chemists in the fields of natural products and organic synthesis.<sup>3,4</sup> In the approximately two centuries since the discovery of aconitine, more than 900 natural C<sub>19</sub>-DAs have been reported, including eight structural subtypes with rich structural diversity.

The distribution of C<sub>19</sub>-DAs is limited to plants from the genera *Aconitum* and *Delphinium* in the family Ranunculaceae. Many plants from these two genera have a long history of medicinal use worldwide, such as the famous traditional Chinese medicines (TCMs) Fuzi (processed lateral roots of *A. carmichaelii*), Chuanwu (processed mother roots of *A. carmichaelii*), Caowu (processed roots of *A. kusnezoffii*), and Xue-shangyizhishao (*A. brachypodium*).<sup>5,6</sup> *Delphinium* plants are also widely used medicinally to treat bruises, rheumatism, toothache, and enteritis.<sup>7</sup> C<sub>19</sub>-DAs are recognized as characteristic active components of these medicinal plants. C<sub>19</sub>-DAs have various pharmacological activities, in particular, significant anti-inflammatory and analgesic effects. In China, two C<sub>19</sub>-DAs have been used clinically as analgesics, namely, 3-acetylaconitine, discovered in *A. flavum*, and crassicauline A, discovered in *A. crassicaule*. The successful development and wide application of these C<sub>19</sub>-DA drugs originating from traditional medicines have encouraged researchers to conduct further and in-depth chemical and pharmaceutical research on these types of compounds.<sup>8–10</sup> In the past ten years (2015–2024),

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approximately 354 new natural C<sub>19</sub>-DAs have been discovered that exhibit significant physiological activities, including anti-tumor, anti-inflammatory, analgesic, antimicrobial, and cholinesterase inhibition. To better promote the development and application of C<sub>19</sub>-DAs and their related medicinal plant resources, in this paper, we have specifically investigated the chemical structural characteristics, distribution, and biological characteristics of C<sub>19</sub>-DAs from natural sources reported in the past ten years.

## 2. Structure and classification

C<sub>19</sub>-DAs can be divided into eight subtypes according to their parent core structure and substituent groups (Fig. 1). Aconitine-

type (**A**) and lycocotonine-type (**B**) C<sub>19</sub>-DAs are the two most important subtypes, accounting for approximately 70% of the total number of C<sub>19</sub>-DAs. These two structure subtypes differ in the presence of a 7-oxygenated substituent; aconitine-type DAs (**A**) do not contain this substituent, whereas lycocotonine-type DAs (**B**) do. Pyro-type (**C**) refers to molecules with  $\Delta^{8,15}$  or 15-keto groups, which are obtained from aconitine-type DAs by eliminating 8-OAc or 15-oxygenated substituents. Lactone-type (**D**) refer to C<sub>19</sub>-DAs with a six-membered lactone C ring, which are obtained through Baeyer–Villiger oxidation of aconitine-type DAs. Typically, franchetine-type DAs (**E**) have a *N*-C-17-O-C-6 *N,O*-mixed acetal group. Recently, franchetine-type DAs with *N*-C-17-O-C-7 or *N*-C-19-O-C-6 *N,O*-mixed acetal groups have also been reported. Seco-type DAs (**F**)

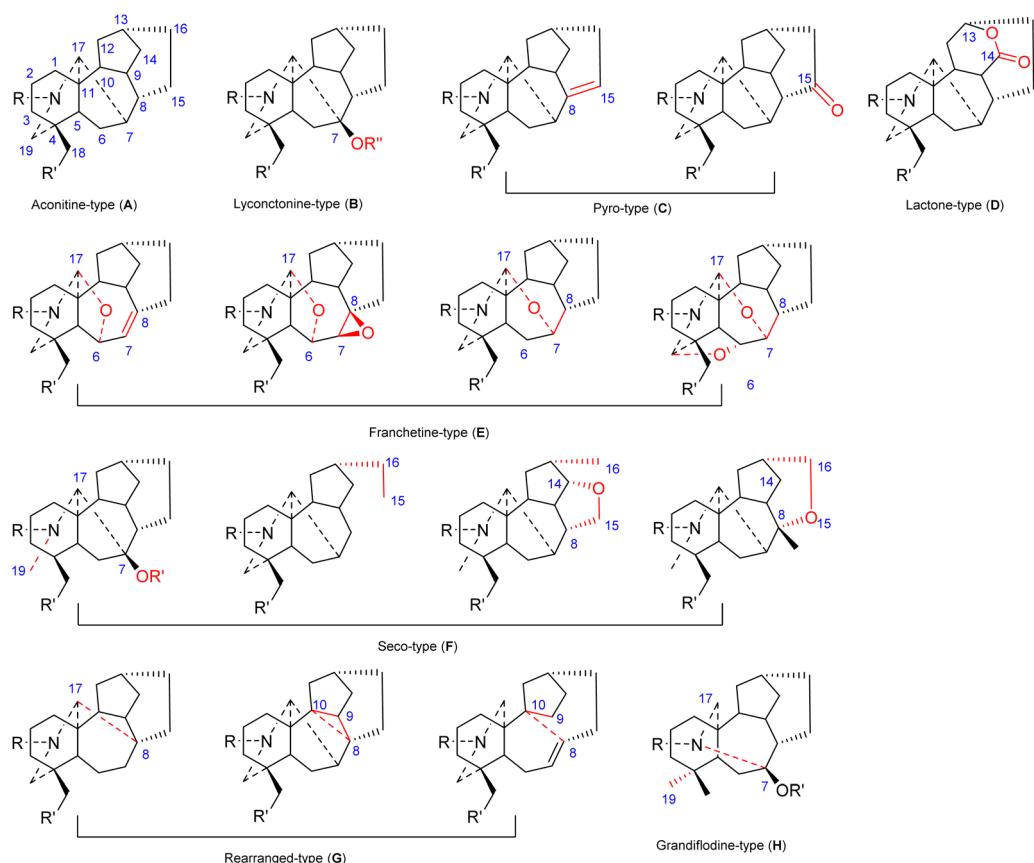


Fig. 1 Structure types of C<sub>19</sub>-DAs.

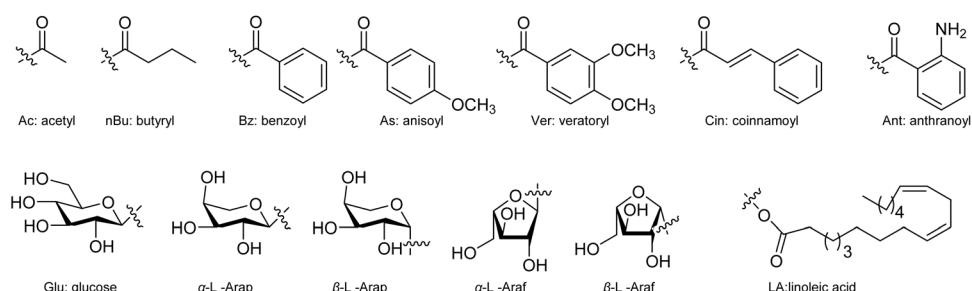


Fig. 2 Structures of common substituents in C<sub>19</sub>-DAs.



include 7,17-seco-type, 4,19-seco-type, 8,15-seco-type, and 15,16-seco-type C<sub>19</sub>-DAs. The rearranged-type DAs (G) mainly include acetone-type, vilmoraconitine-type and vilmorine A-type DAs. Grandiflodian-type C<sub>19</sub>-DAs (H) are a newly reported type of C<sub>19</sub>-DA scaffold. The names, subtypes, plant sources and references of 354 natural C<sub>19</sub>-DAs reported in the past ten years (2015.01–2024.12) are listed in Table S1. Herein, the structural features of C<sub>19</sub>-DAs are discussed by category.

## 2.1. Aconitine-type C<sub>19</sub>-DAs (A)

Aconitine-type DAs are the most important type of C<sub>19</sub>-DAs, with the largest number of reported compounds (192) in the past 10 years. Aconitine-type DAs are reported mainly from the genus *Aconitum*, with only approximately 10 DAs isolated from the genus *Delphinium* (**A17**, **A23**, **A25**, **A75**, **A76**, **A85**, **A86**, **A126**, **A145**, and **A147**). According to the form of the N atom, natural aconitine-type C<sub>19</sub>-DAs can be further divided into 162 amines (**A1**–**A162**), one N,O-mixed acetal compound (**A163**), two N-oxide derivatives (**A164**–**A165**), seven amide/lactam compounds (**A166**–**A172**), 17 imines (**A173**–**A191**), and one quaternary ammonium salt (**A192**) (Fig. 3). Specifically, uncinatine D (**A76**), isolated from *D. uncinatum*, has a N-ethanol substituent,<sup>11</sup> and szechenyianine E (**A168**) from *A. szechenyianum* has a N-hexyl group.<sup>12</sup> The degree of oxidation of aconitine-type C<sub>19</sub>-DAs is generally lower than that of lycocotonine-type C<sub>19</sub>-DAs; aconitine-type DAs usually have oxygenated substituents at C-1, C-8, C-14, and C-16, followed by C-18, C-6, C-3, C-10, C-13 and C-15. Rarely, pseudostapine B (**A74**) from *A. pseudostapfianum*<sup>13</sup> and refractines D–K (**A89**–**A96**) from *A. refractum*<sup>14</sup> feature an OH-5 group, whereas villosudine B (**A121**) from *A. franchetii* has an OH-2 group.<sup>15</sup> In addition, sepaconitine (**A122**) and lappaconidine (**A123**) from *A. barbatum*<sup>16</sup> have an OH-9 group. Typically, C<sub>19</sub>-DAs possess an oxygenated substituent at C-16, most often a methoxy group. However, in austroyunnanine B (**A124**)<sup>17</sup> and apetaldine E (**A148**),<sup>18</sup> the oxygenated substituents at C-16 were eliminated, generating a  $\Delta^{15,16}$  group. In addition, 8-dehydroxyl-bikhaconine (**A32**), isolated from *A. ouvrierianum*, is characterized by the lack of an oxygenated substituent at C-8.<sup>19</sup>

The most common substituents in  $C_{19}$ -DAs are  $OCH_3$ ,  $OH$  and its esters, including Ac (acetyl), Bz (benzoyl), As (anisoyl), Vr (veratroyl), Cin (cinnamoyl), and anthranoyl groups and their derivatives (Fig. 2). In general, the OAc and aroyl groups are located mainly at C-8 and C-14, whereas anthranoyl groups and their derivatives are commonly placed at C-18. A series of compounds including brevicanines A-D (**A151-A154**), isolated from *A. brevicalcaratum*,<sup>20</sup> and novolunines A-B (**A155-A156**), isolated from *A. novoluridum*,<sup>21</sup> have a 2-(2-methyl-4-oxoquinazolin-3-yl)benzoate group linked to C-18.

A series of C<sub>19</sub>-DAs containing sugar substituents have been reported, including refractine L (**A105**), isolated from *A. ouvrardianum*,<sup>19</sup> aconicarmichosides E-L isolated from *A. carmichaelii* (**A106–A108**, **A110–A114**, **A114**, **A116**)<sup>22</sup> and aconicarmichosides A–C (**A109**, **A113**, **A115**).<sup>23</sup> The glycosyl types include  $\beta$ -D-Glu,  $\alpha$ -L-Arap,  $\beta$ -L-Arap,  $\alpha$ -L-Araf, and  $\beta$ -L-Arap. The substitution position is typically at C-14,<sup>23,24</sup> although aconicarmichoside E (**A106**), isolated from *A. carmichaelii*,<sup>24</sup> is linked with  $\beta$ -L-Araf at C-1. In

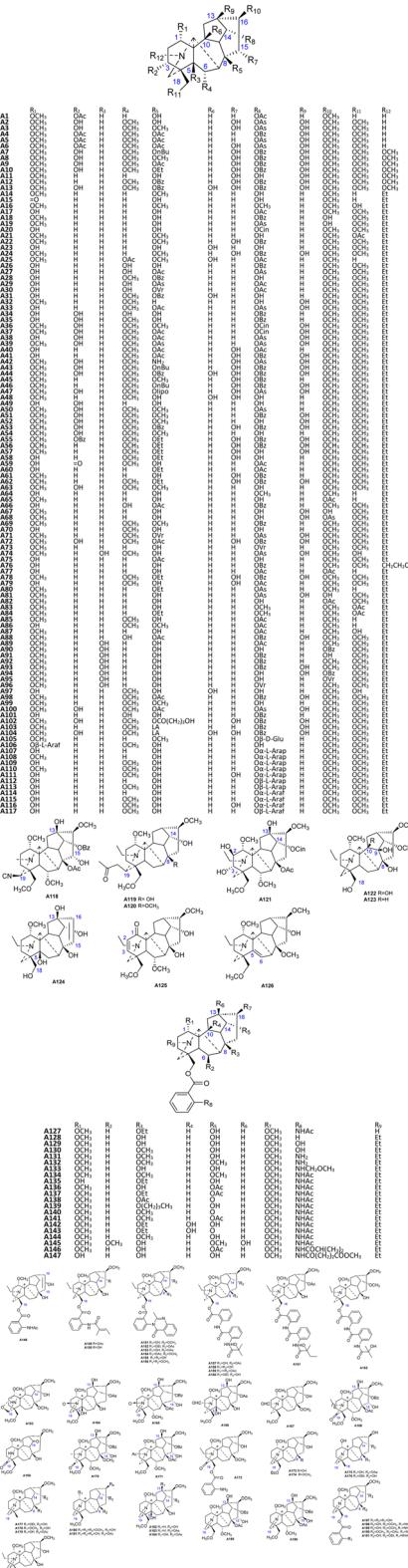


Fig. 3 The structures of aconitine-type C<sub>12</sub>-DAs (A1–A192)

addition, carmichasine A (**A118**), which was isolated from *A. carmichaelii*,<sup>25</sup> possesses a rare cyano group at C-19. 19R-Acetonyltalatisamine (**A119**), isolated from *A. ouvrierianum*,<sup>19</sup> and hemanconitine D (**A120**), isolated from *A. hemsleyanum*,<sup>26</sup> have an

acetonyl ( $\text{CH}_2\text{COCH}_3$ ) at C-19, which may be artifacts. A few components containing double bonds have also been reported; for example, lasiandroline (**A125**), isolated from *A. nagarum*, contains an  $\alpha,\beta$ -unsaturated ketone,<sup>27</sup> and jadwarine B (**A126**),

isolated from *D. denudatum*,<sup>28</sup> contains a  $\Delta 5,6$  group. In addition, two compounds, namely, sinchiangensine A (**A104**), isolated from *A. sinchiangense*,<sup>29</sup> and refractine L (**A105**), isolated from *A. refractum*, are esterified by a long-chain fatty acid at C-8.<sup>14</sup>

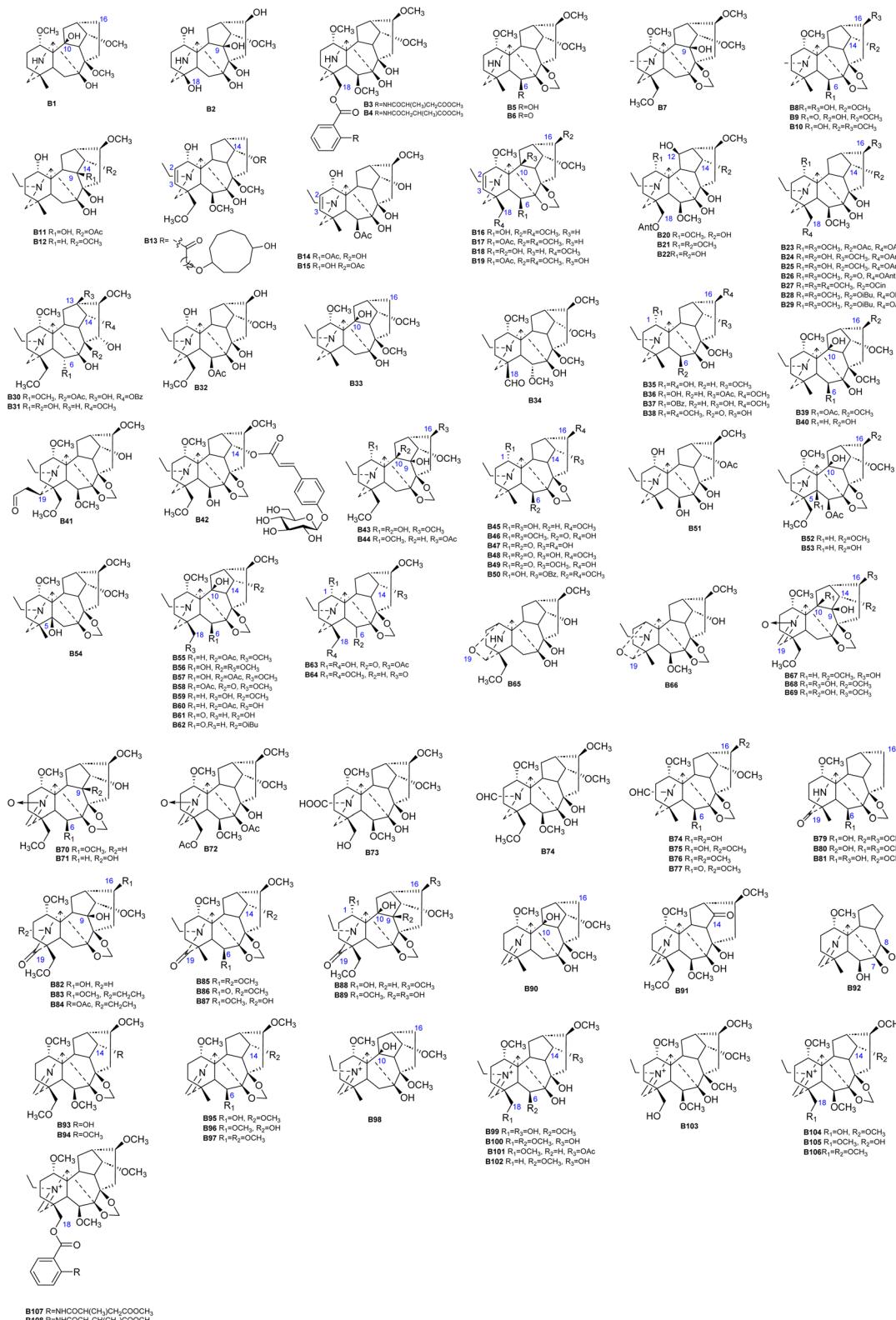


Fig. 4 Structures of lycocotonine-type C<sub>19</sub>-DAs (B1–B108).



## 2.2. Lycocotonine-type C<sub>19</sub>-DAs (B)

The number of lycocotonine-type DAs is second only to that of aconitine-type DAs, with 108 published in the past ten years (Fig. 4). Lycocotonine-type DAs have been isolated mainly from *Delphinium*, with only approximately 9 compounds reported from *Aconitum*. In terms of the form of the N atom, the reported lycocotonine-type C<sub>19</sub>-DAs included 64 amines (**B1–B64**), two N,O-mixed acetal compounds (**B65–B66**), 6 N-oxide derivatives (**B67–B72**), 17 amide/lactam compounds (**B73–B89**), 8 imines (**B90–B97**), and 11 quaternary ammonium salts (**B98–B108**). Seven lycocotonine-type DAs (**B13–B19**) containing a  $\Delta^{2,3}$  group have been reported. The degree of oxidation of lycocotonine-type DAs is generally greater than that of aconitine-type DAs, whose C-1, C-6, C-7, C-8, C-10, C-14, C-16, and C-18 carbons often undergo oxidative substitution. Rarely, ajacisine A (**B20**),

isolated from *D. ajacis*,<sup>30</sup> and ajacisine B (**B21**),<sup>30</sup> ajacisine G (**B22**),<sup>31</sup> and grandifoline D (**B52**), isolated from *D. grandiflorum*, have an OH-12 substitution,<sup>32</sup> whereas grandifoline F (**B53**)<sup>32</sup> and elapaciline (**B54**), isolated from *D. elatum* cv. Pacific Giant,<sup>33</sup> have an OH-5 group.

A series of C<sub>19</sub>-DAs isolated from *D. pachycentrum* by our group, pachycentine B (**B33**) and pachycentine C (**B1**),<sup>10</sup> are characterized by the lack of an oxygenated substituent at C-16. Lycocotonine-type DAs have fewer kinds of substituents, and the most common substitutions are OCH<sub>3</sub>, OH, and OCH<sub>2</sub>O, whereas 7,8-OCH<sub>2</sub>O can be considered a characteristic substituent of lycocotonine-type C<sub>19</sub>-DAs. Except for the anthranoyl group and its derivatives, aryl groups are rare in lycocotonine-type C<sub>19</sub>-DAs. Iliensine A (**B42**), from *D. iliense*, possesses a rare *E*-*p*-hydroxy cinnamoyl group.<sup>34</sup> In addition, majusine D (**B13**), whose C-14 is esterified by 3-((5-hydroxycyclononyloxy) propanoic acid, was discovered in *D. majus*.<sup>35</sup> Pseudonidine B (**B41**), isolated from *D. pseudoaemulans*,<sup>36</sup> has an acetyl group linked to C-19, which may be an artificial product.

## 2.3. Pyro-type C<sub>19</sub>-DAs (C)

Pyro-type DAs are C<sub>19</sub>-DAs containing a  $\Delta^{8,15}$  or a 15-keto group. These DAs were originally isolated from processed aconite and are considered thermal decomposition products of aconitine-type C<sub>19</sub>-DAs containing an OH-15 group.<sup>37</sup> In recent years, only two alkaloids of this type have been reported, namely, nagaconitine B (**C1**)<sup>38</sup> and nagarumine D (**C2**),<sup>17</sup> both of which were isolated from *A. nagarum* and have a 15-keto group (Fig. 5).

## 2.4. Lactone-type C<sub>19</sub>-DAs (D)

Lactone-type C<sub>19</sub>-DAs are a highly specific class of compounds among C<sub>19</sub>-DAs featuring a  $\delta$ -lactonized C ring. In recent years, only four lactone-type C<sub>19</sub>-DAs have been reported (Fig. 5), that

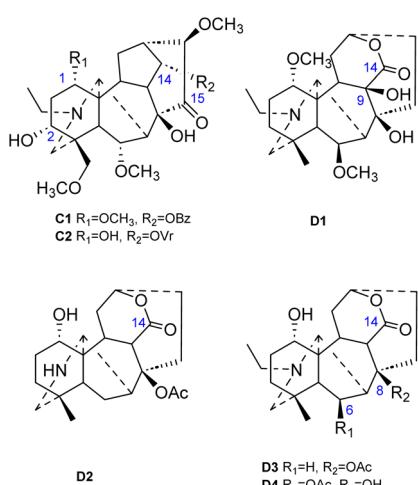


Fig. 5 Structures of pyro- and lactone-type C<sub>19</sub>-DAs.

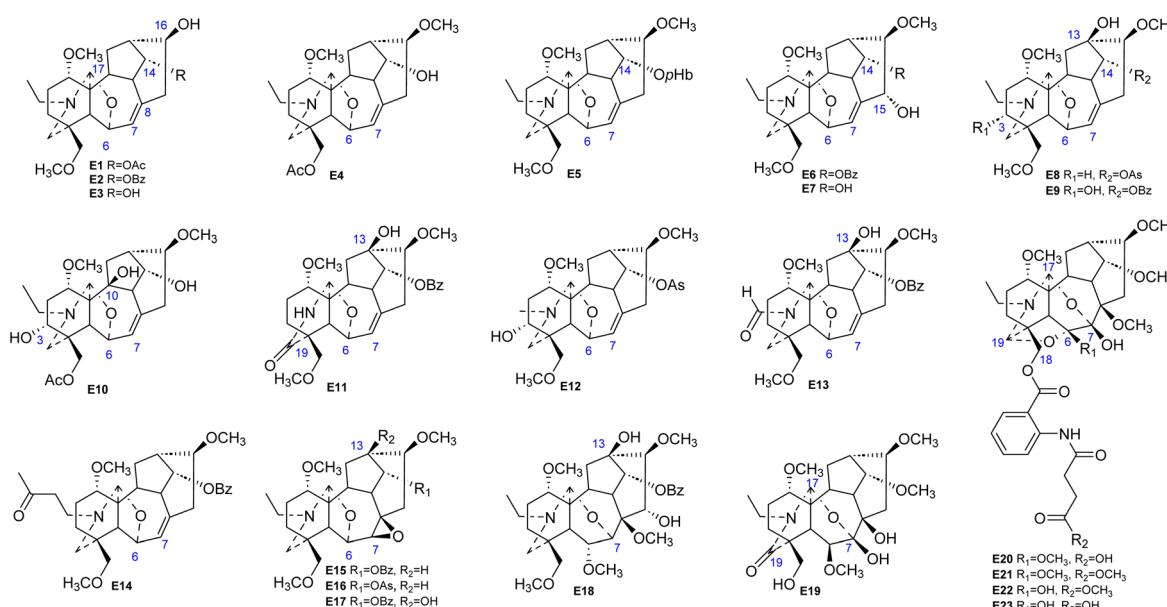


Fig. 6 Structures of franchetine-type C<sub>19</sub>-DAs.



is, 6 $\beta$ -methoxy,9 $\beta$ -dihydroxylheteratisine (**D1**), isolated from *A. heterophyllum*,<sup>39</sup> and rotundifosines A-C (**D2-D4**), isolated from *A. rotundifolium*.<sup>40</sup>

## 2.5. Franchetine-type C<sub>19</sub>-DAs (E)

In the last ten years, 23 new franchetine-type DAs (**E1-E23**) have been reported. All DAs of this type were isolated from *Aconitum* plants, except grandifline B (**E19**), which was isolated from *D. grandiflorum*.<sup>41</sup> Typically, franchetine-type DAs are defined as DAs with a *N*-C-17-O-C-6 *N*,*O*-mixed acetal group, and these DAs generally have a  $\Delta^{7,8}$  group (Fig. 6).<sup>19,25,42-48</sup> Three compounds, namely, 7,8-epoxy-franchetine (**E15**), acotarine B (**E16**), and flavumoline (**E17**), have a 7,8-epoxy group<sup>42,45,48</sup> and are likely derived from lycocotonine-type C<sub>19</sub>-DAs. In addition, szechenyianine D (**E18**)<sup>12</sup> and grandifline B (**E19**)<sup>41</sup> possess *N*-C-17-O-C-7 *N*,*O*-mixed acetal groups, and aconicumines A-D (**E20-E23**) have *N*-C-17-O-C-7 and *N*-C-19-O-C-6 *N*,*O*-mixed acetal groups, but these two types of structures remain to be further confirmed by single-crystal X-ray diffraction experiments.<sup>49</sup>

## 2.6. Seco-type C<sub>19</sub>-DAs (F)

Seco-type DAs (**F**) refer to 7,17-seco-type, 4,19-seco-type, 8,15-seco-type, and 15,16-seco-type C<sub>19</sub>-DAs. Four 7,17-seco-type DAs, namely, hemaconitine A (**F1**) from *A. hemisleyanum* var. *circinatum*,<sup>26</sup> szechenyianine C (**F2**) from *A. szechenyianum*,<sup>50</sup> brunodelphinine D (**F3**) from *D. brunonianum*,<sup>51</sup> and brunodelphinine B (**F4**) from *D. brunonianum*,<sup>51</sup> have been reported in recent years (Fig. 7). Brunodelphinine B (**F4**) also possesses an open C ring, whose C-13-C-14 bond is also broken, forming an extra COOH-14 group, representing a novel class of seco-type DAs. Reported in 2015,<sup>52</sup> *N*-formyl-4,19-secopacanine (**F5**) from *D. elatum* is a 4,19-seco-type DA whose C-4-C-19 bond is broken to form a new aldehyde group, CHO-19, which might be formed by Grob cleavage of a lycocotonine-type C<sub>19</sub>-DA with an OH-3 group. An analog, *N*-formyl-4,19-secoyunnadelphinine (**F6**), was also isolated from *D. elatum*.<sup>53</sup> The 8,15-seco-type C<sub>19</sub>-DAs nagaraines A (**F7**) and B (**F8**) were isolated from *A. nagarum* by our group and possess an open D ring formed by breaking the C-8-C-15 bond.<sup>54</sup> These two compounds are also characterized by a lack of an oxygenated substituent at C-14. Stylosines A (**F9**) and B

(**F10**) from *A. stylosum* are novel 15,16-seco-type C<sub>19</sub>-DAs reported in 2020. These DAs are formed by cleaving the C-15-C-16 bond, and a new  $\gamma$ -lactone group is formed. Notably, nagarine A (**F7**) was also isolated from *A. stylosum*, suggesting that these two types of compounds may share similar biosynthetic pathways.<sup>55</sup> Kusnezosines A-C (**F11-F13**) are novel 15,16-seco-type C<sub>19</sub>-DAs isolated from *A. kusnezoffii* var. *gibbiferum*. Their C-15-C-16 bond was opened, forming a new six-membered inner ester D ring.<sup>56</sup> The analog austroyunnanine D (**F14**) was isolated from *A. austroyunnanense*.<sup>46</sup>

## 2.7. Rearranged-type C<sub>19</sub>-DAs (G)

Acoseptine-type DAs, whose C-17-C-7 bond is rearranged to a C-17-C-8 bond, was first discovered in *A. septentrionale* in 1999 by Usmanova *et al.* Acoseptine-type DAs usually contain a 7-keto substitution.<sup>57</sup> To date, only 10 acoseptine-type DAs have been reported. Pachycentine A (**G1**),<sup>10</sup> an acoseptine-type DA that lacks an oxygenated substituent at C-16 (Fig. 8), was isolated from *D. pachycentrum* by our group. In addition, two acoseptine-type compounds containing an *o*-aminobenzene moiety at C-18 DAs acosinomonines A-B (**G2-G3**) were isolated from *A. sinomontanum*.<sup>58</sup> The first vilmoraconitine-type DA, vilmoraconitine, which possesses a high-strain cyclopropane ring formed by the linkage of the C-8-C-10 bond, was isolated from *A. vilmorinianum* by Tan *et al.* Two analogs, vilmorines B (**G4**) and C (**G5**, vilmorriantine E<sup>59</sup>), were isolated from the same plant by our group.<sup>60</sup> A *N*-oxide derivative, episcopine A (**G6**), was isolated from *A. episcopale*.<sup>61</sup> Vilmotenitine-type DA was established by our group and is formed by the breakage of the C-8-C-9 bond on the basis of vilmoraconitine-type DA, thus generating a 6/6/6 framework. Thus far, only three vilmoraconitine-type DAs have been reported, namely, vilmotenitines A (**G7**) and B (**G8**), which were isolated from *A. vilmorinianum* var. *patentipilum*,<sup>62</sup> and nagarumine C (**G9**), which was isolated from *A. nagarum*.<sup>63</sup>

## 2.8. Grandiflodine-type C<sub>19</sub>-DAs (H)

Grandiflodine B (**H1**), in which the *N*-C-19 bond is broken and a *N*-C-7 bond is formed, was isolated from *D. grandiflorum* by Chen *et al.*<sup>64</sup> Its structure suggests that it may be formed by Grob

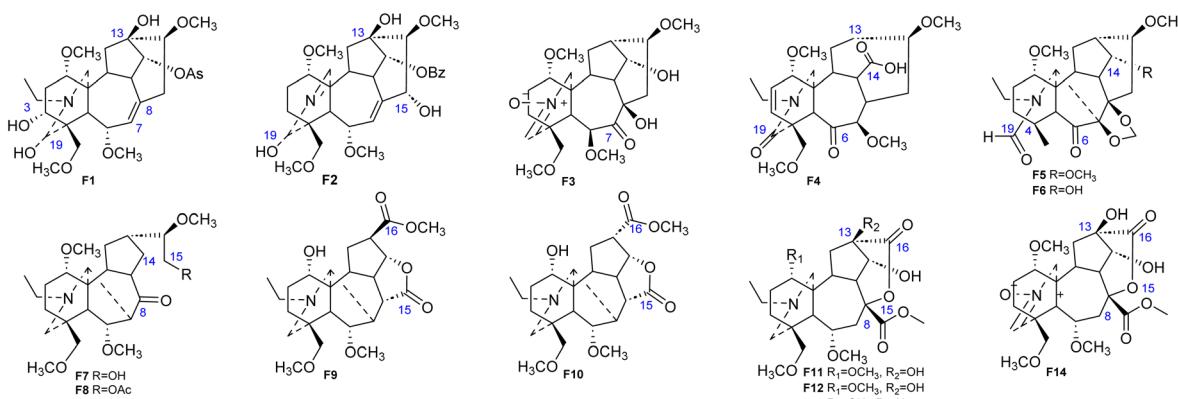
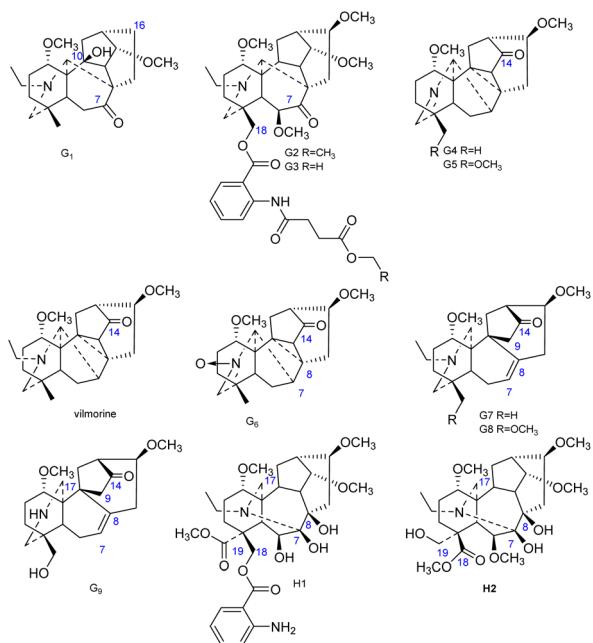


Fig. 7 The structures of seco-type C<sub>19</sub>-DAs.



Fig. 8 Structures of rearranged-type and grandiflodine-type C<sub>19</sub>-DAs.

cleavage of lycocotonine-type C<sub>19</sub>-DAs with OH-19 substitution, resulting in the cleavage of N-C-19 and C-17-C-7 bonds, followed by oxidation and acetalization. An analog, gyalianutine A (H2), was isolated from *D. gyalianum*.<sup>65</sup>

### 3. Distribution

As shown in Table 1, the distribution of C<sub>19</sub>-DAs is highly concentrated, in that all of the reported C<sub>19</sub>-DAs were isolated from plants of the genera *Aconitum* and *Delphinium* in the Ranunculaceae family. In general, alkaloids with more complex and specialized structures have a narrower distribution in higher plants. Consistent with this pattern, C<sub>19</sub>-DAs have a more complex skeletal ring system and also a narrower distribution than C<sub>20</sub>-DAs do.<sup>66</sup>

The distributions of various subtypes of C<sub>19</sub>-DAs exhibit strong regularity. Aconitine-type C<sub>19</sub>-DAs have been reported mainly from *Aconitum* plants only approximately 10 aconitine-type DAs have been obtained from *Delphinium* plants. Conversely, lycocotonine-type C<sub>19</sub>-DAs have been reported mainly from the genus *Delphinium*, and only approximately nine lycocotonine-type C<sub>19</sub>-DAs have been isolated from the genus *Aconitum*. Therefore, aconitine-type and lycocotonine-type C<sub>19</sub>-DAs can be considered characteristic DA components of *Aconitum* and *Delphinium*, respectively. According to systematic taxonomy and molecular biology, *Delphinium* plants are more

evolved than *Aconitum* plants are.<sup>67</sup> In general, among metabolites with identical chemical structural skeletons, those with a higher the degree of oxidation are considered more evolved. The degree of oxidation of the lycocotonine-type C<sub>19</sub>-DAs was greater than that of the aconitine-type compounds. The distribution of these two kinds of compounds supported the view that *Delphinium* plants are more evolved than *Aconitum* plants in terms of taxonomy. The number of other types of C<sub>19</sub>-DAs was relatively small, but the regularity of their distribution was still apparent. In general, pyro-type, lactone-type, franchetine-type and seco-type C<sub>19</sub>-DAs are distributed mainly in *Aconitum* plants and rarely in *Delphinium* plants. Currently, only two grandiflodine-type DAs are known, both isolated from *Delphinium*.

## 4. Biological activity

### 4.1. Anti-tumor activity

A series of natural C<sub>19</sub>-DAs exhibit significant antitumor effects. Three recently characterized C<sub>19</sub>-DAs, brunonianines D–F (A85, A86, and B102), discovered in the Chinese Tibetan medicine *D. brunonianum*, exhibited significant inhibitory effects on the proliferation of the ovarian cancer cell line Skov-3,<sup>68</sup> with IC<sub>50</sub> values of 2.57, 8.05, and 5.85 μM, respectively. Among these DAs, brunonianine D (A85) had stronger activity than the positive control drug HCPT (IC<sub>50</sub> = 3.06 μM) and also significantly inhibited tumor growth in a Skov-3 tumor load mouse model with little negative impact on healthy tissues. Studies have shown that brunonianine D (A85) exerts its antitumor effects by inhibiting cell migration, invasion and proliferation and by inducing cell apoptosis by activating the Bax/Bcl-2/caspase-3 signaling pathway.<sup>68</sup> The pyro-type DA nagaconitine C (A40) discovered in the medicinal plant *A. nagarum* var. *heterotrichum* in Yunnan, China, was also able to significantly inhibit the growth of Skov-3, with an IC<sub>50</sub> value of 43.78 μM, whereas the IC<sub>50</sub> value of cisplatin as the positive control drug was 11.58 μM.<sup>38</sup>

Several lipo class of C<sub>19</sub>-DAs, which are defined as C<sub>19</sub>-DAs that contain fatty acid ester groups (such as oleic acid and linoleic acid), have shown broad-spectrum tumor cytotoxicity *in vitro*.<sup>69</sup> Lipojesaconitine (A47) from *A. japonicum* subsp. *subcuneatum* in Japan<sup>33</sup> significantly inhibited the growth of four human tumor cell lines (A549, MDA-MB-231, MCF-7, and KB) (Table 2), with IC<sub>50</sub> values between 6.0 and 7.3 μM. However, its cytotoxicity against the multidrug-resistant KB-VIN cell line was relatively weak (IC<sub>50</sub> = 18.6 μM), indicating that lipojesaconitine was likely exported by P-glycoprotein. Similarly, the lipoalkaloid sinchiangensin A (A104), obtained from *A. sinchiangense*, and the known compound lipodeoxyaconitine also exhibited significant inhibitory activity against various tumor cell lines, with IC<sub>50</sub> values comparable to that of cisplatin. Lipo DAs may be selective inhibitors of topoisomerase II $\alpha$ .<sup>70</sup> Notably, compared with other ester C<sub>19</sub>-DAs, lipoalkaloids are less toxic;<sup>71</sup> thus, they have unique advantages and great potential as antitumor drug lead compounds.<sup>72,73</sup>

Three aconitine-type C<sub>19</sub>-DAs, 6-demethoxyhypaconitine (A11), carmichaeline K (A61) and 8-O-ethyloyldeoxyaconitine

Table 1 The distributions of C<sub>19</sub>-DAs

Family	Genus	A	B	C	D	E	F	G	H
Ranunculaceae	<i>Aconitum</i>	182	9	2	4	22	10	8	0
	<i>Delphinium</i>	10	99	0	0	1	4	1	2



Table 2  $IC_{50}$  values ( $\mu M$ ) of  $C_{19}$ -DAs against tumor cells

Name	A-549	MDA-MB-231	H460	HeLa	HepG2	HL-60	SMCC-7721	MCF-7	KB	KB-VIN	SW480	Ref.
Lipojesaconitine (A47)	7.3	6.0						6.7	6.0	18.6		33
Sinchiangensine A (A104)	12.8				9.2	9.6	11.8			18.8	29	
Lipodeoxyaconitine	10.1				3.2	12.4	9.7			7.4	29	
6-O-Acetyl-16-demethyldelsolin (B32)						37.4	33.1				75	
6-Demethoxyhypaconine (A11)	18.2		22.8								74	
Carmichaeline K (A61)	21.3		22.3								74	
8-O-Ethy-benzoyldeoxyaconine (A62)	12.6		12.8								74	
14 $\alpha$ -Benzoyloxy-13 $\beta$ ,15 $\alpha$ -dihydroxy-1 $\alpha$ ,6 $\alpha$ ,8 $\beta$ ,16 $\beta$ ,18-pentamethoxy-19-oxoaconitan (A170)	18.7			19.7	17.6						76	

(A62), which were isolated from the TCM *A. carmichaelii*, moderately inhibited the proliferation of A549 and H460 tumor cells, with  $IC_{50}$  values ranging from 12.6 to 22.8  $\mu M$ .<sup>74</sup> Network pharmacology analysis revealed that these DAs may inhibit tumor cell growth and promote apoptosis by regulating the PI3K-AKT signaling pathway, interleukin signaling pathway and MAPK signaling pathway. The  $IC_{50}$  values of 6-O-acetyl-16-demethyldelsolin (B32), isolated from *D. grandiflorum*, for the inhibition of SMCC-7721 and MCF-7 cell proliferation were 37.4 and 33.1  $\mu M$ , respectively.<sup>75</sup> The aconitine-type DA A170, isolated from *A. austroyunnanense*, also inhibited the proliferation of A49, HeLa and HepG2 cells.<sup>76</sup>

In addition, Hu *et al.* reported that nagarumine E (E12) found in *A. nagarum*<sup>47</sup> exhibited cytotoxicity against five gastric cancer cell lines (GES-1, AGS, HGC-27, MKN-45 and MGC-803), with  $IC_{50}$  values of 16.1, 15.2, 14.7, 14.3 and 13.8  $\mu M$ , respectively. Austroyunnanine D (F14), isolated from *A. austroyunnanense*, showed cytotoxicity against three gastric cancer cell lines, with  $IC_{50}$  values of 17.6  $\mu M$  (MGC-803), 14.3  $\mu M$  (BGC-823) and 15.8  $\mu M$  (SGC-7901).<sup>46</sup>

#### 4.2. Anti-inflammatory activity

The medicinal plants of the genera *Aconitum* and *Delphinium* are widely used in TCMs to treat inflammatory diseases, suggesting that they may be rich in active anti-inflammatory components. Some recently discovered  $C_{19}$ -DAs have shown significant anti-inflammatory activity *in vitro*. For example, two aconitine-type DAs, szechenyianines A (A185) and B (A165), and one seco-type DA, szechenyianine C (F2) discovered in the medicinal plant *A. szechenyianum*, which is widely distributed in western

China, effectively reduced NO production in polysaccharide (LPS)-induced RAW 264.7 cells, with  $IC_{50}$  values of 36.6  $\mu M$ , 3.3  $\mu M$  and 7.5  $\mu M$ , respectively (Table 3).<sup>50</sup> Notably, the activities of A165 and F2 were greater than that of the positive control dexamethasone ( $IC_{50}$ , 8.3  $\mu M$ ). The results showed that the presence of the N → O group might enhance anti-inflammatory activity.

The 11 novel lycaconitine-type  $C_{19}$ -DAs kamaonensines A–K (B44, B7, B88, B82, B83, B67, B84, B68, B71, B69, B89) isolated from *D. kamaonense* inhibited LPS-induced NO production, with  $IC_{50}$  values ranging from 0.9–85.5  $\mu M$ .<sup>77,78</sup> In particular, kamaonensine E (B83) exhibited a greater ability to inhibit NO production than did the positive control ( $IC_{50}$  = 0.9  $\mu M$ ). Network pharmacology analysis predicted that these compounds might exert anti-inflammatory effects by regulating related proteins in the MAPK signaling pathway, such as MAPK8, MAPK14 and HSP90 $\alpha$ . In addition, the molecular docking results revealed that compounds containing amide and methylenedioxy groups may have stronger anti-inflammatory effects. The novel franchetine-type DAs aconicumines A (E20) and C (E22), discovered in the medicinal plant *A. taipeicum* endemic to the Taibai Mountains in China,<sup>49</sup> and the novel scaffold compound grandiflodine B (H1), discovered in *D. grandiflorum*, also have NO production inhibitory effects.<sup>64</sup> Zhou *et al.* isolated four known franchetine-type DAs, *i.e.*, franchetine, kongboendine, leueandine and vilmorisine, from the roots of *A. sinoaxillare* and synthesized 14 analogs, all of which have been tested for their anti-inflammatory activities *in vitro*.<sup>79</sup> The results showed that franchetine, kongboendine and two of the analog compounds had stronger inhibitory effects on NO

Table 3 Inhibitory effect of  $C_{19}$ -DAs on NO production in LPS-stimulated RAW264.7 cell ( $IC_{50}$ ,  $\mu M$ )

Name	$IC_{50}$	Ref.	Name	$IC_{50}$	Ref.
Szechenyianine A (A185)	36.6	64	Kamaonensine H (B68)	16.0	78
Szechenyianine B (A165)	3.3	64	Kamaonensine J (B69)	18.1	78
Kamaonensine A (B44)	12.2	77	Kamaonensine I (B71)	17.4	78
Kamaonensine B (B7)	2.7	77	Kamaonensine K (B89)	2.2	78
Kamaonensine C (B88)	27.7	77	Aconicumine A (E20)	19.7	49
Kamaonensine D (B82)	12.2	77	Aconicumine C (E22)	97.4	49
Kamaonensine E (B83)	0.9	77	Szechenyianine C (F2)	7.5	64
Kamaonensine F (B84)	12.4	77	Grandiflodine B (H1)	72.7	81
Kamaonensine G (B67)	11.8	77			



production than did the positive control celecoxib. Structure-activity relationship studies revealed that the *in vitro* anti-inflammatory activity of franchetine-type DAs was closely related to their C-14 ester group: when this group was substituted with linear-chain fatty acids, the chain length was positively correlated with the anti-inflammatory activity of the resulting compound; aromatic acyl group substitution produced greater activity than heterocyclic ring and cycloparaffin moieties, and methoxy substitution on the aromatic ring enhanced the anti-inflammatory activity. Further studies revealed that franchetine inhibited the expression of the inflammatory proteins iNOS and COX-2. The anti-inflammatory effect of franchetine might be based on the inhibition of the TLR4-MyD88/NF- $\kappa$ B/MAPK signaling pathway, thereby inhibiting the expression of NO, ROS, TNF- $\alpha$ , and inflammatory factors or mediators such as IL-6, IL-1 $\beta$ , iNOS, and COX-2. In addition, franchetine has low toxicity in mice ( $LD_{50} > 20 \text{ mg kg}^{-1}$ ), indicating its potential for development as a drug.  $C_{19}$ -DAs also inhibit the production of other proinflammatory factors. For example, the 8,15-seco-type DAs nagarines A (F7) and B (F8), isolated from *A. nagarum*,<sup>54</sup> and the aconitine-type DAs taronenines A (A33), B (A30) and D (A27), isolated from *A. taronense*,<sup>80</sup> can inhibit LPS-induced IL-6 production in RAW 264.7 cells, with  $IC_{50}$  values ranging from 25.4–29.6  $\mu\text{g mL}^{-1}$ . The 15,16-seco-type DAs stylosines A (F9) and B (F10) significantly inhibited the LPS-induced inflammatory cytokines IL-1 $\beta$ , COX-2 and TNF- $\alpha$  in RAW 264.7 macrophages *in vitro*, and no cytotoxicity was detected at the test concentration (0.1  $\text{mg mL}^{-1}$ ).<sup>80</sup>

#### 4.3. Analgesic effects

The medicinal plants of the genus *Aconitum*, represented by Aconite Radix, are widely used in TCM to treat various types of pain, including rheumatic joint pain, neuralgia, and trauma.  $C_{19}$ -DAs are considered the main analgesic active component of *Aconitum* plants. The aconitine-type DA bulletaconitine A, discovered in *A. bulletanum*, has been used clinically in China for more than 30 years to treat common chronic pain, osteoarthritis and other diseases.<sup>82</sup> Some natural  $C_{19}$ -DAs reported recently also have significant analgesic effects. Shi *et al.* used a mouse acetic acid-induced writhing response model to screen the analgesic activity of a series of  $C_{19}$ -DA arabinosides isolated from Aconite Radix.<sup>24</sup> The results showed that at a dose of 1.0  $\text{mg kg}^{-1}$ , the aconicarmichosides E–F (A106–A107) and H–J (A114, A111, A116) exhibited significant analgesic effects compared with the blank control against the acetic acid-induced writhing response in mice, with an inhibition rate of more than 65.6%. In contrast, aconicarmichosides K (A108) and L (A110) only showed weak activity at high doses, with inhibition rates of less than 20%. Structure–activity relationship studies revealed that the analgesic activities and structures of these compounds were closely related. In particular, methoxylation at the C-1 position significantly reduced the activity. In addition, the configuration of the arabinoside moiety also affects the activity of the compounds. The new  $C_{19}$ -DA grandifloline G (B91) and several known compounds isolated from *D. grandiflorum* were also tested for their analgesic activity *via* an

acetic acid-induced mouse model.<sup>83</sup> The results revealed that deoxylapaconitine, a known aconitine-type DA, exhibited significant analgesic activity, with an  $ED_{50}$  of 0.35  $\text{mg kg}^{-1}$  and a therapeutic index (TI) of 46.22, which were better than the corresponding values of the reference drug aconitine ( $ED_{50} = 3.5 \text{ mg kg}^{-1}$ , TI = 3.34), highlighting deoxylapaconitine as a candidate substance for the development of new analgesic drugs. However, the new compound, grandifloline G (B91), showed only a weak analgesic effect at a dose of 10  $\text{mg kg}^{-1}$ .

Hu *et al.* used an acetic acid-induced abdominal contraction assay in mice to evaluate the analgesic effects of a series of new  $C_{19}$ -DAs discovered in *Aconitum* plants in Southwest China and reported that new compounds, including episcopine A (G6), isolated from *A. episcopale* ( $ID_{50} = 66.1 \mu\text{M kg}^{-1}$ ),<sup>61</sup> pseudostapine A (A73) ( $ID_{50} = 83.2 \mu\text{M kg}^{-1}$ ) and pseudostapine B (A74) ( $ID_{50} = 71.0 \mu\text{M kg}^{-1}$ ), found in *A. pseudostapfianum*,<sup>13</sup> austroyunnanine B (A124), isolated from *A. austroyunnanense* ( $ID_{50} = 48.0 \mu\text{M kg}^{-1}$ ),<sup>17</sup> and nagarumine C (G9), isolated from *A. nagarum* (76.0  $\mu\text{M kg}^{-1}$ ),<sup>63</sup> presented greater analgesic activity than the positive controls aspirin ( $ID_{50} = 135.0 \mu\text{M kg}^{-1}$ ) and acetaminophen ( $ID_{50} = 127.7 \mu\text{M kg}^{-1}$ ).

In addition, franchetine, a known  $C_{19}$ -DA component isolated from *A. sinoaxillare*, exhibited a significant analgesic effect in a mouse writhing model, with an  $ED_{50}$  of 2.15  $\text{mg kg}^{-1}$ , and significantly increased the latency of foot licking in the hot plate experiment. These findings suggest that franchetine has central analgesic effects.<sup>79</sup> Whole-cell patch clamp experiments revealed that franchetine inhibited NaV1.7 and NaV1.8 channel currents in a state-dependent manner, with inhibition rates of 30.07% and 45.73% (resting state) and 59.15% and 65.49% (semiactive state), respectively. Molecular docking studies revealed that the carbonyl group of franchetine interacts with the amino acid residues Trp-1567, Ser-1568 and Arg-1620 through hydrogen bonds, which may be critical for the inhibition of NaV1.7 activity. Rearranged  $C_{19}$ -DA acosinomonine B (G3), found in *A. sinomontanum*, has a significant inhibitory effect on capsaicin-mediated activation of TRPV1 channels at 10  $\mu\text{M}$ , with an inhibition rate of 31.78%, and may become the lead structure of analgesic drugs.<sup>58</sup> In addition, the aconitine-type DAs pendulumines A–F (A55–A59, A171), isolated from *A. pendulum*, also exhibited analgesic activity in a thermal avoidance response experiment in the roundworm *Pristionchus pacificus*.<sup>84</sup>

#### 4.4. Biocontrol effects

Plants of the genera *Aconitum* and *Delphinium* have been applied as pesticides, indicating that their main components, DAs, may have biocontrol effects and could be used as a source of botanical pesticides. Feed repellents are a type of insecticide that controls the number of pests by interfering with the appetite center of the pests, making them develop a sense of disgust for food, reduce or stop feeding, and finally die of starvation. Zhou *et al.* discovered a series of novel  $C_{19}$ -DAs from *Aconitum* and *Delphinium* with significant antifeeding effects on *Spodoptera exigua* larvae.<sup>43</sup> With the exception of rockidine C (E5), which is a franchetine-type DA, these DAs were all



aconitine-type DAs, and the  $EC_{50}$  values of many of the tested compounds were  $<1$  mg  $cm^{-2}$  (Table 5).<sup>43</sup> Zhou *et al.* reported that chasmanthinine, a known component of aconitine-type DA with a cinnamoyl group, exhibited the best antifeedant activity and could be used as a lead compound for further study.<sup>18</sup> In addition, the aconitine-type DA pubescensine (A41), isolated from *A. soongaricum* var. *pubescens*, had a significant antifeedant effect on *Pieris rapae* larvae, with an  $EC_{50}$  of 0.03 mg  $cm^{-2}$ .<sup>59</sup> Furthermore, the study revealed that aconitine-type  $C_{19}$ -DAs had strong antifeedant activity, whereas napelline-type  $C_{20}$ -DAs had only weak activity. The above studies show that  $C_{19}$ -DAs can be used as a potential resource to develop new antifeedant agents, providing a new strategy for the green control of agricultural pests. In addition, 13-hydroxypatentine (A88), isolated from *A. pendulum*, had a moderate contact effect on two-spotted spider mites, *Tetranychus urticae*, with an  $LC_{50}$  of 0.86 mg  $mL^{-1}$ .<sup>85</sup> Acoapetaldine A (A133), isolated from *A. apetalum*, showed moderate anti-TMV (tobacco mosaic virus) activity, with an inhibition rate of 61.27% at 50  $\mu$ g  $mL^{-1}$ , comparable to that of the positive control ningnamycin (55.12%).<sup>75</sup>

#### 4.5. Antipathogenic effects

Some  $C_{19}$ -DAs have been reported to have antipathogenic effects on microorganisms including bacteria, fungi and viruses. The aconitine-type DA sinchiangensine A (A104), discovered in *A. sinchiangense*, showed strong antibacterial activity against *S. aureus*, with an MIC of 0.147  $\mu$ M,<sup>29</sup> and had an inhibitory effect on *E. coli*, with an MIC of 2.55  $\mu$ M, which was greater than that of the positive control drug berberine hydrochloride (MIC values of were 0.67  $\mu$ M and 1.34  $\mu$ M against *S. aureus* and *E. coli*, respectively). The MIC values of the 15,16-seco-type DAs stylosines A (F9) and B (F10) against *S. aureus* were 2.0 mg  $mL^{-1}$  and 32.0  $\mu$ g  $mL^{-1}$ , respectively.<sup>55</sup> Acoapetaludines D (A129) and E (A130), isolated from *A. apetalum*, showed weak inhibitory activity against *Helicobacter pylori*, with MICs of 100  $\mu$ g  $mL^{-1}$  and 50  $\mu$ g  $mL^{-1}$ , respectively.<sup>86</sup> Ajacisines D–E (B24–B25), isolated from *D. ajacis*, showed moderate antirespiratory syncytial virus (RSV) activity, with  $IC_{50}$  values of 75.2  $\mu$ M and 35.1  $\mu$ M, respectively,<sup>30</sup> while the  $IC_{50}$  value of the positive control drug ribavirin was 3.1  $\mu$ M, indicating that  $C_{19}$ -DAs may be a natural resource against RSV. The  $IC_{50}$  value of grandiflodine B (H1) from *D. grandiflorum* for the growth and proliferation of RSV was 75.3  $\mu$ M.<sup>64</sup>

Table 4 Inhibitory effects of  $C_{19}$ -DAs against AChE and BChE ( $IC_{50}$ ,  $\mu$ M)

Name	AChE	BChE	Type of inhibition	Ref.
Uncinatine B (A145)	188.1	—	—	11
Uncinatine C (A75)	94.3	—	—	11
Uncinatine D (A76)	367.0	—	—	11
Hemsleyaline (A50)	471.0	—	—	87
1 $\beta$ -Hydroxy,14 $\beta$ -acetyl condelphine (A17)	19.8	31.5	Non competitive	28
Jadwarine A (A23)	9.2	19.6	Competitive	28
Jadwarine B (A126)	16.8	34.7	Non competitive	28
Swatinine C (B63)	3.7	12.2	Competitive	88
6 $\beta$ -Methoxy,9 $\beta$ -dihydroxylheteratisine (D1)	5.4	8.6	Non competitive	39



**Table 5** Antifeedant activities of the compounds against *Spodoptera exigua*

Name	EC <sub>50</sub> (mg cm <sup>-2</sup> )	Ref.
Rockidine A (A65)	4.03	43
Rockidine B (A66)	0.32	43
Leucostosine A (A64)	19.77	94
Leucostosine B (A139)	1.54	94
Apetaldine A (A137)	0.45	18
Apetaldine B (A136)	0.94	18
Apetaldine C (A138)	1.18	18
Apetaldine D (A135)	0.64	18
Apetaldine E (A148)	0.28	18
Apetaldine F (A127)	0.68	18
Apetaldine G (A191)	9.23	18
Rockidine C (E5)	0.79	43

the known compounds 14-benzoylmesaconine and (−)-(Ab)-14 $\alpha$ -benzoyloxy-N-ethyl-1 $\alpha$ ,8 $\beta$ ,15 $\alpha$ -trihydroxy-6 $\alpha$ ,16 $\beta$ ,18-trimethoxyaconitane at 50  $\mu$ M decreased the survival rate of H9c2 cells to 46.73% and 48.80%, respectively. In zebrafish experiments, 14-benzoylmesaconine and (−)-(Ab)-14 $\alpha$ -benzoyloxy-N-ethyl-1 $\alpha$ ,8 $\beta$ ,15 $\alpha$ -trihydroxy-6 $\alpha$ ,16 $\beta$ ,18-trimethoxyaconitane significantly affected embryo morphology, leading to pericardial edema and yolk sac edema and significantly increasing embryonic malformation rate and heart rate. Liu *et al.* evaluated the H9c2 cytotoxicity of compounds isolated from *A. carmichaelii*,<sup>93</sup> including four novel aconitine-type DAs and seven known compounds. The results revealed that compound A12 (8 $\beta$ ,14 $\alpha$ -dibenzoyloxy-13 $\beta$ ,15 $\alpha$ -dihydroxy-1 $\alpha$ ,6 $\alpha$ ,16 $\beta$ ,18-tetramethoxy-N-methyaconitane)<sup>93</sup> and seven known compounds exhibited significant toxicity to H9c2 cells, with two known compounds with OBU-8 substituents being the most toxic. Further studies revealed that C<sub>19</sub>-DAs exhibited strong cardiotoxicity by increasing the intracellular Ca<sup>2+</sup> concentration, affecting the cell membrane potential and inducing mitochondria-mediated cell apoptosis. The above studies on the toxicity of C<sub>19</sub>-DAs not only help to develop DA drug lead compounds with high efficiency and low toxicity but also promote the safe use and quality control of related TCMs.

## 5. Conclusion

In the past ten years, 354 natural C<sub>19</sub>-DAs have been reported, including 192 aconitine-type C<sub>19</sub>-DAs (A), 108 lycocotonine-type C<sub>19</sub>-DAs (B), two pyro-type C<sub>19</sub>-DAs (C), four lactone-type C<sub>19</sub>-DAs (D), 23 franchetine-type C<sub>19</sub>-DAs (E), 14 seco-type C<sub>19</sub>-DAs (F), nine rearranged-type C<sub>19</sub>-DAs (G), and two grandifloline-type C<sub>19</sub>-DAs (H). C<sub>19</sub>-DAs are distributed only in *Aconitum* and *Delphinium* plants and show highly regular distribution patterns, which may be leveraged for the discovery and mining of corresponding bioactive natural products. Natural C<sub>19</sub>-DAs and their derivatives generated *via* structural modifications exhibit a wide range of biological activities, including antitumor, anti-inflammatory, analgesic, biocontrol, anti-pathogenic, neuroprotective, and cholinesterase inhibitory effects. Structural modifications of these natural compounds

can be carried out in the future to improve their efficacy. In summary, the rich diversity of the structures and biological activities of C<sub>19</sub>-DAs indicates the great potential of this type of compound for drug development, especially for antitumor, anti-inflammatory and analgesic drugs, which merits further investigation.

Although C<sub>19</sub>-DAs have attracted considerable interest, some deficiencies and research potential remain. First, most of the biological activities of C<sub>19</sub>-DAs have been investigated *via in vitro* chemical and cellular models, and little *in vivo* research has been performed. Few studies have focused on the toxicity, side effects, and clinical efficacy of C<sub>19</sub>-DAs, which hinders their application and promotion. Second, studies on the structure-activity relationships (SARs) and action mechanisms of these newly discovered components are still lacking, especially for those subtypes of C<sub>19</sub>-DAs with a smaller quantity, such as pyro-, lactone-, rearranged-, and grandifloline-types. Therefore, these areas should be addressed in the future.

## Author contributions

Min Yan: writing – original draft, resources, visualization. Xijing Wang: writing – review and editing. Haiwen Wang: supervision. Tianpeng Yin: resources, supervision, writing – review and editing, funding acquisition.

## Conflicts of interest

The authors declare no conflict of interest.

## Data availability

All relevant data are within the manuscript and its additional files.

Supplementary information (SI), which includes a table that lists the detailed information of natural C<sub>19</sub>-diterpenoid alkaloids reported in the past ten years, is available. See DOI: <https://doi.org/10.1039/d5ra02226f>.

## Acknowledgements

This work was financially supported by a grant from the National Natural Science Foundation of China (No. 32360106), a grant from Zunyi Medical University Zhuhai Campus Key Construction Discipline (No. ZHGY2024-1), a grant from the Science and Technology Innovation Team of Zhuhai Campus of Zunyi Medical University (ZHTD2024-2), and a grant from the University Characteristic Innovation Project of Guangdong Province (No. 2023KTSCX235).

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