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Chemistry and biological activities of hetisine-type diterpenoid alkaloids†

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Hetisine-type C_{20}-diterpenoid alkaloids (DAs) are one of the most important DA subtypes. During the past decades, a total of 157 hetisine-type DAs were obtained from plants from seven genera in three families, most of which were isolated from the genera *Aconitum* and *Delphinium* in the Ranunculaceae family. Structurally, hetisine-type DAs are characterized by a heptacyclic hetisane skeleton formed by the linkage of C(14)–C(20) and N–C(6) bonds in an atisine-type DA, and their structural diversity is created by the states of the *N* atom and various substituents. Pharmacological studies have revealed a wide range of pharmacological actions for hetisine-type DAs, including antiarrhythmic, antitumor, antimicrobial and insecticidal activities, as well as effects on peripheral vasculature, which are closely related to their chemical structures. In particular, the prominent antiarrhythmic effects and low toxicity of hetisine-type DAs highlight their potential in antiarrhythmic drug discovery. Hetisine-type DAs with diverse bioactivities are promising lead structures for further development as commercial agents in medicine.

1. Introduction

Diterpenoid alkaloids (DAs) are a large group of highly specialized metabolites that are distributed mainly in plants from the genera *Aconitum*, *Delphinium*, and *Consolida* in the Ranunculaceae family, as well as the genus *Spiraea* in the Rosaceae family.[1–3] For centuries, the complex structures and multiple prominent pharmacological activities of DAs have attracted extensive and lasting attention from scientists.[4–6] DAs are the active components of several widely used traditional Chinese medicines (TCMs) from Ranunculaceae, such as Fuzi (*Aconitum carmichaelii*), which has been used medicinally for thousands of years in China and other Asian countries[7–9]. Modern pharmacological studies have demonstrated a wide range of remarkable pharmacological activities for DAs, especially prominent anti-inflammatory, analgesic, and antiarrhythmic effects, emphasizing their great potential for drug discovery.[10,11] Currently, a series of DAs have been developed as new drugs and are used extensively in the clinic, for example the analgesic agents 3-acetylaconitine, lappaconitine, and crassicauline A.[12]

DAs are also well known for their complex chemical structures, which feature a polycyclic fused cage-like skeleton along with various kinds of substituents. Structurally, DAs are usually classified into four types according to the number of carbons on their skeleton: C_{18}–, C_{19}–, C_{20}– or bis-type, which can be further divided into several dozen subtypes. Among them, C_{20}-DAs are famed for their abundant structurally diverse skeletons: nearly thirty C_{20}-DA subtypes have already been reported, and large numbers of C_{20}-DAs with new skeletons continue to emerge.[13,14] Hetisine-type DAs are one of the most important C_{20}-DA subtypes. Since the time when hetisine-type was defined in 1960s,[15] numerous compounds have been isolated and identified, making this type the most abundant subtype of C_{20}-DAs in terms of quantity. In addition, preliminary studies have revealed that hetisine-type DAs have a wide range of pharmacological actions, including antiarrhythmic,[16,17] antitumor,[18,19] antimicrobial and insecticidal activities,[20,21] as well as effects on peripheral vasculature.[22] In particular, hetisine-type DAs possess more prominent antiarrhythmic effects than the other DAs along with low toxicity, which highlights their potential in antiarrhythmic drug discovery. Fortunately, a representative compound of hetisine-type DAs, Guan-fu base A (**49**), has been discovered and introduced as a new antiarrhythmic drug (acehytisine hydrochloride injection) by Chinese scientists.[12] These findings underscore the still largely untapped potential of hetisine-type DAs and encourage their further extensive investigation.

Several previously published review articles and monographs have involved the hetisine-type DAs.[1,14,23] However, these literatures mainly focus on the research advances of all types of DAs

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or C_{20}-DAs, and only a small portion of contents has been devoted to the hetisine-type DAs. Deserving more attention are the works by Wang and Liang,[13] in which there are plentiful descriptions on structures and bioactivities of hetisine-type DAs with literatures coverage to the end of 2000. Besides, Bessonova and Saidkhodzhaeva listed 107 hetisine-type C_{20}-DAs that had been isolated up to 1998.[104] During the past two decades, a number of new hetisine-type DAs have been discovered, and their bioactivities were also studied. Hence, this review was prepared to summarize the structural features and biological activities of natural hetisine-type DAs, intending to provide a complete overview of the existing knowledge of the chemical structures and biological properties of hetisine-type DAs, which will facilitate further research and exploitation of these types of compounds.

2. Structures and classifications

Although the first hetisine-type DA, paniculatine (**56**), has been isolated in the early 1920s,[24] and several representative compounds, such as hetisine (**13**) and kobusine (**9**), were found during the 1940s,[25,26] the structures of hetisine-type DAs were established much later due to their complex fused polycyclic skeleton. The chemical skeleton of hetisine-type DAs was first proposed in 1963 and finally established by single crystal X-ray diffraction studies of several representative compounds.[15] Hetisine-type DAs possess a heptacyclic hetisane-type C_{20}-diterpenoid framework (Fig. 1), whereas hetisane-type diterpenoid itself has never been found from plants. It is generally assumed that atisine-type DAs, which formed by amination of serine at atisane-type diterpenoid skeleton, are the biosynthetic precursors of hetisine-type DAs.[13] Atisine-type DAs might undergo Mannich reaction to generate hetidine-type DAs, and a subsequent linkage of *N*–C(6) bond led to the formation of hetisine-type DAs.[27] Besides, the cleavage of the *N*–C(19) bond of hetisine-type DAs could generate vakognavine-type DAs. Although vakognavine-type has been regarded as a subtype of hetisine-type DAs in some situations in the past mainly due to their small quantity, this review exclusively examined vakognavine-type DAs considering the discovery of numerus vakognavine-type DAs over the past decades.[9,14,28] Additionally, several hetisine-derived compounds with new skeletons are not included in this review, for example anthriscifolsine A from *Delphinium anthriscifolium* var. *majus* with a cleaved *N*–C(20) bond,[29] and grandiflodine A from *D. grandiflorum* bearing a *seco* C ring.[30]

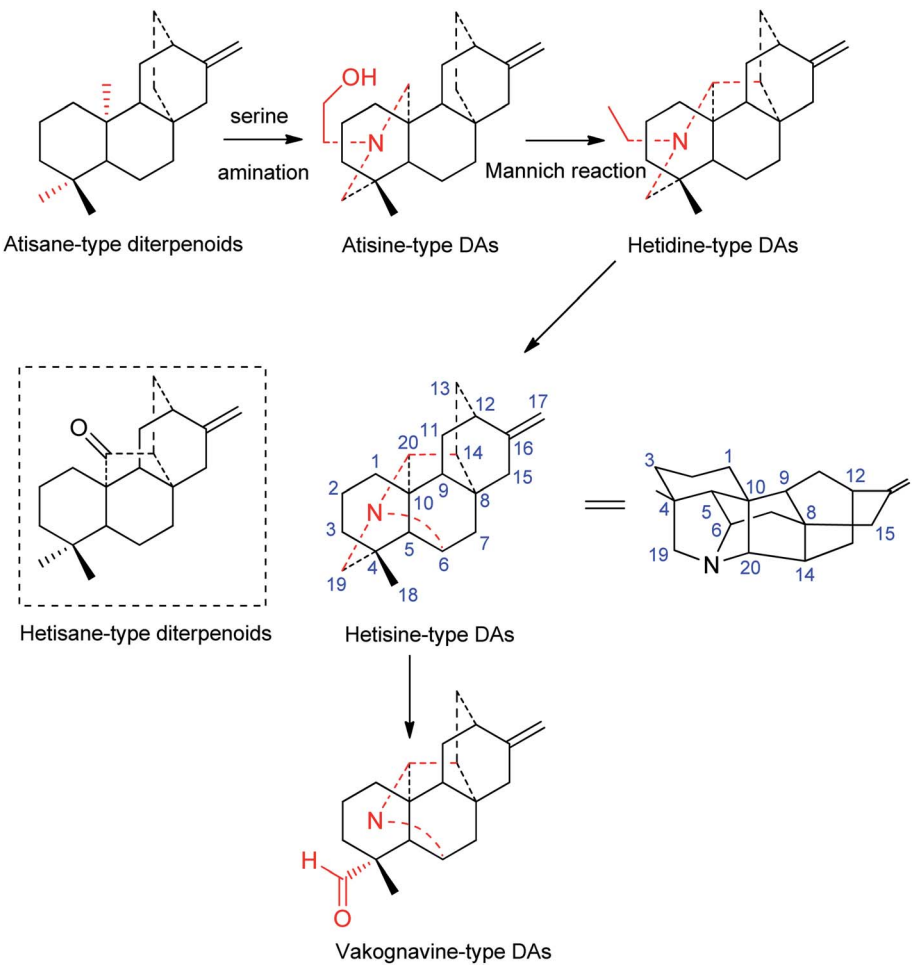


Fig. 1 The skeletons of hetisine-type and its closely related types of C_{20}-DAs.

According to single crystal X-ray diffraction analysis of corresponding hetisine-type DAs for example hetisine (**13**),[15] the six-membered cyclohexane rings A (C(1), C(2), C(3), C(4), C(5), C(10)) and B (C(5), C(6), C(7), C(8), C(9), C(10)) found in hetisine-type DAs have the chair conformation (projection formula in Fig. 1), while piperidine ring F (C(4), C(5), C(10), C(20), *N*, C(19)) exists in a boat conformation. Rings C (C(8), C(9), C(11), C(12), C(13), C(14)), D (C(8), C(9), C(11), C(12), C(16), C(15)) and E (C(8), C(14), C(13), C(12), C(16), C(15)) form the bicyclo-[2,2,2]-octane system, which is fixed in the boat form. The five-membered G ring (C(4), C(5), C(6), *N*, C(19)) adopts the twist form, while ring H (C(5), C(6), *N*, C(20), C(10)) is in the envelope form; and ring I (C(8), C(9), C(10), C(20), C(14)) is found in an equal mixture of the twist and envelope conformations. The fusion of rings A, B, and C is identical for all hetisine-type DAs: A/B, *trans*; B/C, *cis*.

Based on the state of the *N* atom, hetisine-type DAs can be divided into four subtypes, namely, the amine subtype (I), the *N*,*O*-mixed acetal subtype (II), the *N*-oxide derivatives (III), and the quaternary ammonium bases (IV). Table S1† listed the names, subtypes, plant sources, and the references of a total of 157 natural-occurring hetisine-type DAs reported in the past decades. Herein, the structural features of hetisine-type DAs are discussed by category.

2.1. The amine subtype compounds

The amine subtype with 94 members constitutes the majority (60%) of the hetisine-type C_{20}-DAs (Fig. 2). The chemical diversity of these amines (and other subtypes of hetisines) depends mainly on the variety, quantity, position, and orientation of the oxygenated substituents. The common oxygenated substituents found in hetisine-type DAs are hydroxyl (OH), ketone carbonyl (=O), and ester groups such as acetyl (Ac), isobutyl (*i*Bu), 2-methylbutyryl (MeBu), and benzoyl (Bz) groups. Rarely, palmasine (**20**) and palmadine (**21**) from *A. palmatum* feature an uncommon cinnamoyl (Cn) group at C-13,[31] and acoridine (**48**), Guan-fu bases R (**39**) and O (**50**) from *A. coreanum* possess a propionyl (Pr) group at C-2.[32–34] Most hetisine-type DAs have an exocyclic terminal olefinic bond at C-16 and C-17. However, four hetisines, including Guan-fu bases S (**91**), N (**92**),[35] and W (**93**)[36] from *A. coreanum* and zeraconine (**94**) from *A. zeravschanicum*,[37] possess a cyclic olefinic bond at C-15 and C-16. Guan-fu base S (**91**) has an extra double bond at C-2 and C-3,[33,38] while zeraconine (**94**) features a rare hordenine substituted at C-17.[37]

Only three monosubstituted amines have been reported, namely, spirasines XI (**1**), IV (**2**), and IX (**3**), from *Spiraea japonica* var. *fortunei*.[39] The other amine subtype compounds possess between two and six oxygenated substituents at different positions in the molecular skeleton. The most likely substituted positions are C-2, C-6 and C-7, with probabilities greater than 50%. The other positions, including C-1, C-3, C-5, C-6, and C-15, are also easy to substitute. The reported amine subtype hetisines mainly contain oxygenated substituents at the abovementioned positions, with the exception of davisinol (**89**) and 18-benzoyldavisinol (**90**), which have an oxygenated

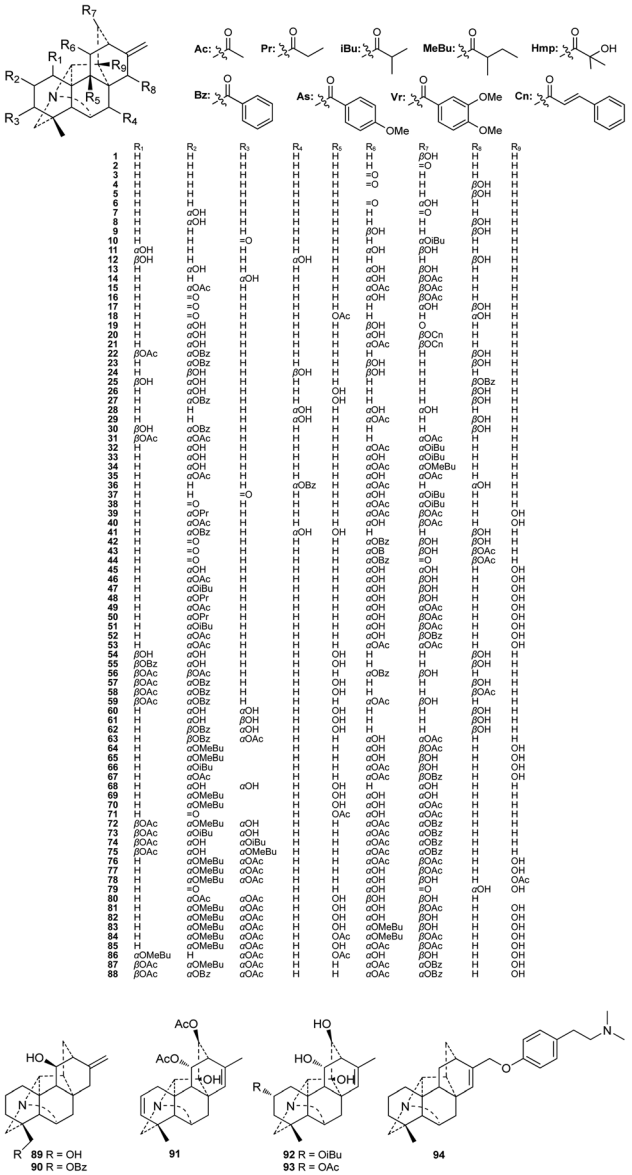
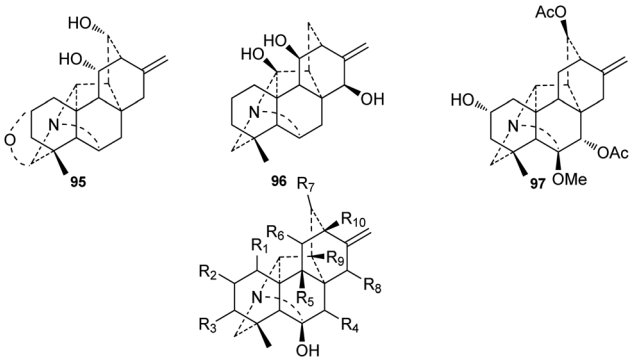


Fig. 2 The amine subtype alkaloids (**1–94**) of hetisine (the names of the alkaloids are given in ESI Table S1†).

substituent at C-18, a rare substituted position.[40] The orientation of these oxygenated substituents may vary when they are substituted on a methylene, for example on C-1, C-2, C-3, C-11, C-13, C-15, or C-19. However, these oxygenated substituents at rigid bridged-ring methines such as C-6, C-9, and C-14 fix the β-orientation for all of hetisine-type DAs.

2.2. The *N*,*O*-mixed acetal subtype compounds

A total of 55 alkaloids belonging to the *N*,*O*-mixed acetal subtype (II) have been reported (Fig. 3). Among them, delatisine (**95**) from *D. elatum* possesses an *N*–C(19)–O–C(2) mixed acetal unit,[41] and orgetine (**96**) from *A. recemulosum*[42] features an *N*–C(20)–OH mixed acetal group. Generally, methoxy groups are rarely found in C_{20}-DAs. However, racemulosine A (**97**)[43] and flexiosine (**146**)[44] have methoxy groups at C-6 and C-19, respectively, forming a special kind of *N*,*O*-mixed acetal unit.



	R_1	R_2	R_3	R_5	R_6	R_7	R_8	R_9	R_{10}
98	H	H	H	H	=O	H	H	H	H
99	H	H	H	H	OH	H	H	H	H
100	H	H	H	H	αOH	H	H	H	H
101	H	H	H	H	OAc	H	H	H	H
102	H	H	H	H	H	αOH	H	H	H
103	H	H	H	H	H	βOH	H	H	H
104	H	H	H	H	H	H	βOH	H	H
105	H	H	H	H	βOH	H	βOH	H	H
106	H	αOH	H	H	H	O	H	H	H
107	H	H	H	H	=O	αOH	H	H	H
108	H	H	H	H	=O	βOH	H	H	H
109	H	H	H	H	=O	O	H	H	H
110	H	=O	H	H		βOH	H	H	H
111	H	H	H	H	βOH	H	βOMeBu	H	H
112	H	H	H	H	βOH	H	βOBz	H	H
113	H	H	H	H	βOH	H	βOVr	H	H
114	H	αOH	H	H	H	βOH	H	H	H
115	H	H	H	H	H	βOH	βOH	H	H
116	H	H	=O	H	H	αOiBu	H	H	H
117	H	H	αOH	H	βOH	αOAc	H	H	H
118	H	=O	H	H	αOH	βOH	H	H	H
119	H	=O	H	H	αOH	βOAc	H	H	H
120	H	=O	H	H	αOMeBu	βOH	H	H	H
121	H	=O	H	OH	H	βOAc	H	H	H
122	H	H	H	H	βOH	H	αOiBu	H	OH
123	H	H	H	H	βOAc	H	αOiBu	H	OH
124	H	αOAc	H	H	H	αOAc	H	OH	H
125	H	αOH	αOH	H	H	=O	H	H	H
126	βOAc	αOH	H	H	H	=O	H	H	H
127	βOH	αOH	H	H	H	=O	H	H	H
128	H	αOH	βOH	H	H	=O	H	H	H
129	H	αOiBu	αOH	H	H	H	βOH	H	H
130	H	αOH	OAc	H	αOMeBu	βOH	H	H	H

	R	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
131	βOH	H	αOAc	H	H	OH	H	H	H
132	βOH	H	H	αOH	H	OH	H	H	H
133	αOH	H	H	H	H	H	βOH	H	βOH
134	βOH	H	αOH	H	H	H	αOH	αOH	H
135	βOH	H	αOH	H	H	H	αOH	αOAc	H
136	βOH	βOH	αOAc	βOH	H	H	H	H	H
137	αOH	βOH	βOH	H	H	OH	H	H	H
138	αOH	βOH	αOAc	βOH	H	H	H	H	H
139	αOH	αOH	αOBz	H	H	H	αOH	H	H
140	OH	H	H	H	αOiBu	H	αOH	H	βOH
141	βOH	H	αOBz	H	H	H	OSO_3H	αOH	H
142	αOH	H	αOiBu	H	H	H	αOAc	αOAc	H
143	αOH	H	αOiBu	H	H	H	αOH	αOAc	H
144	αOH	H	αOiBu	H	H	H	αOH	αOH	H
145	βOH	βOAc	βOHmp	H	H	H	αOBz	αOCHO	H
146	βOMe	H	αOiBu	H	OAc	H	OAc	OBz	H
147	βOH	H	H	H	αOiBu	H	αOAc	αOAc	H
148	βOH	H	H	H	αOiBu	H	αOAc	αOH	H
149	βOH	H	αOiBu	αOAc	H	H	βOH	=O	H

Fig. 3 The *N*,*O*-mixed acetal subtype alkaloids (**95–149**) of hetisine.

The other *N*,*O*-mixed acetal subtype compounds can be classified into two groups, namely, alkaloids with *N*–C(6)–OH units (**98–130**), and the remaining alkaloids (**131–149**) that contain an *N*–C(19)–OH mixed acetal group. Among them, several possess uncommon substituent groups, for example, 15-veratroylpseudokobusine (**113**) from *A. yesoense* var. *macroyesoense* has a veratroyl group at C-15,[45] and tanguticuline D (**141**) *A. tanguticum* from features a sulfonate moiety (SO_3H) at C-11.[46] Besides, anthriscifolmine J (**145**) from *D. anthriscifolium* var. *savatieri* has an uncommon 2-hydroxy-2-methylpropionyl (Hmp) group at C-3.[47]

2.3. The *N*-oxide derivatives

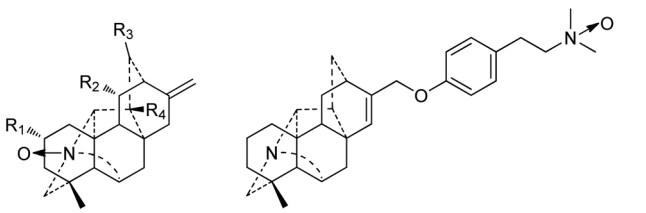
Currently, only four *N*-oxygenated hetisine-type DAs, namely, 14-hydroxyhetisinone *N*-oxide (**150**) from *D. gracile*,[48] Guan-fu bases Z and F *N*-oxide (**151** and **152**),[49–51] and Guan-fu base X (**153**) from *A. coreanum*,[35,36] have been reported (Fig. 4). In addition, compound **154** is a derivative of zeraconine (**94**),[37] an *N*-oxide at the nitrogen atom of the dimethylamino group.

2.4. The quaternary ammonium bases

A series of alkaloids were reported as quaternary ammonia bases or salt forms of hetisine-type DAs in the past decades. It has been well documented that hetidine-type DAs with a ketone at C-6 and vakognavine-type alkaloids (bearing an aldehyde group at C-19) can transform into their salt form bearing an *N*,*O*-acetal in the presence of acids and can return to their free alkaloid form after treatment with bases.[52] Since DAs in plants are mainly extracted by using acids, primarily dilute hydrochloric acid, these quaternary ammonia bases or hetisine salts might be artifact products of the corresponding hetidine-type or vakognavine-type DAs.[53] For example, chemical transformation experiments have suggested that orochrine and 2-*O*-acetylorochrine are artifacts of the corresponding hetidine-type DAs heterophylloidine and deacetylheterophylloidine, respectively,[54,55] and carmichaelines B–D are indeed the trifluoroacetates of corresponding vakognavine-type C_{20}-DAs.[56–58] Particularly, three hetisine-type DAs with 7,8-diol unit (Fig. 5), namely, vilmorrianines F and G (**155** and **156**) from *A. vilmorrianum*[54] and 2-*O*-acetyl-7*R*-hydroxyorochrine (**157**) from *A. orochryseum*,[55] cannot be transformed into their free alkaloid form possibly due to the intramolecular hydrogen bond between OH-7 and OH-8, indicating that they might be naturally-occurring quaternary ammonia bases.

3. Distribution

Currently, hetisine-type DAs have been found in plants from seven genera in three families. As shown in Table 1, the richest



150 R_1 = O, R_2 = R_4 = OH, R_3 = αOH,
151 R_1 = OiBu, R_2 = R_4 = OH, R_3 = βOH
152 R_1 = OiBu, R_2 = R_4 = OH, R_3 = βOAc
153 R_1 = OAc, R_2 = R_4 = OH, R_3 = βOH

154

Fig. 4 The *N*-oxide derivatives (**150–154**) of hetisine.

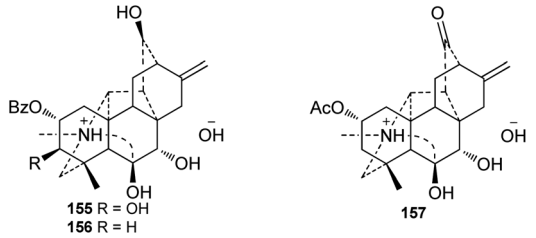


Fig. 5 The quaternary ammonium bases (155–157) of hetisine.

sources are plants from the genera *Aconitum* and *Delphinium* in the family Ranunculaceae, as approximately 55% and 39% of the reported hetisine-type DAs have been found in plants of the genera *Aconitum* and *Delphinium*, respectively. In addition, fifteen hetisine-type DAs (9%) have been proven to exist in the genus *Consolida* (Ranunculaceae),[59–62] a genus closely related to *Delphinium*. Only one hetisine-type DA was identified in the genus *Thalictrum* (Ranunculaceae), namely, spiradine A (**98**) from *Thalictrum sessile*.[63] In general, the family Ranunculaceae can be regarded as the main source of hetisine-type DAs.

Apart from plants of the Ranunculaceae family, the genus *Spiraea* in the family Rosaceae is another important source of hetisines. Eleven hetisine-type DAs (7%) have been obtained from the genus *Spiraea*, and they are distributed exclusively in the species *S. japonica*[64–68] and its variety *S. japonica* var. *fortunei*.[39,69–73] It is also noteworthy that hetisine-type DAs from *Spiraea* plants possess relatively few and simple oxygenated substituents: they usually possess only one or two hydroxyl or ketone carbonyl substituents at C-6, C-11, and C-13, which is of chemotaxonomic significance.[3] In addition, hetisine-type DAs have been found in plants of the genera *Rumex* and *Polygonum* in the family Polygonaceae, including orientinine (**79**), panicudine (**106**), and acorientine (**115**) from *Rumex pictus*[74] and panicudine (**106**) from *Polygonum aviculare*.[20] Hetisine-type DA is the only type of DA that has been found in the polygonaceae family, which widens the distribution of DAs.

In terms of the distribution of certain compounds, hetisine (**13**) is the most widely distributed compound, which has been reported to be isolated from 26 species of plants and 3 varieties in three genera (Table 1S†), followed by hetisinone (**16**) distributed in 19 species and 2 varieties in three genera. The wide distribution of hetisine (**13**) and hetisinone (**16**) could support the hypothesis that hetisine (**13**) is the biosynthetic precursor of other hetisine-type compounds.

Table 1 The distributions of hetisine-type DAs[a]

Family	Genus	Number of hetisine-type DAs
Ranunculaceae	*Aconitum*	86
	Delphinium	62
	Consolida	15
	Thalictrum	1
Rosaceae	*Spiraea*	11
Polygonaceae	*Rumex*	3
	Polygonum	1

[a] The numbers of hetisine-type DAs were counted independently in different genera in the case that a particular alkaloid exists in plants in different genera.

4. Bioactivities

4.1. Antiarrhythmic activity

Since 1981, when Liu *et al.* first discovered the hetisine-type DA Guan-fu base A (**49**) from *A. coreanum* bearing considerable antiarrhythmic activity, the antiarrhythmic activity of guan-fu base A and its analogs has attracted much interest from pharmaceutical scientists.[75] Through a 20 year persistent effort by Chinese researchers, mainly Liu and coworkers, Guan-fu base A has been developed into a new antiarrhythmic drug (acehytisine hydrochloride injection) after passing through phase II and III clinical studies to treat paroxysmal supraventricular tachycardia, and this compound was approved by the China Food and Drug Administration (CFDA) in 2005.[12,75]

It was observed in experiments that Guan-fu base A can effectively antagonize aconitine-induced arrhythmia in rats, significantly reduce the $CaCl_2$-induced incidence of ventricular fibrillation in rats,[75] markedly raise the ventricular fibrillation threshold to electrical stimulation in rabbits and cats,[75] and increase the ouabain dose necessary to cause ventricular premature beats, ventricular fibrillation, and cardiac arrest in anesthetized guinea pigs.[75] The antiarrhythmic effects of Guan-fu base A might be due to its electrophysiological properties, which has been verified as a multi-ion channel blocker (sodium channel,[76,77] calcium channel,[77] potassium channel,[78,79] and hyperpolarization-activated cyclic nucleotide-gated (HCN) channel[80]). In clinical studies, Guan-fu base A (**49**) showed unambiguous therapeutic efficacy on paroxysmal supraventricular tachycardia (PSVT), paroxysmal atrioventricular reentrant tachycardia, and ventricular tachycardia,[81] along with reliable safety in humans.[81,82] In addition, it was found that Guan-fu base A did not affect the function of the atrionector when it exerted other electrophysiological effects, which is beneficial to its application.[83]

Guan-fu bases G (**53**) and I (Guan-fu base Y or acorine, **46**) in the same plant also exhibited antiarrhythmic activity in animal models with the decreasing order of **53** > **49** > **46**,[16] which are consistent with their acylation degrees. Besides, four hetisine-type DAs (**4**, **13**, **52** and **59**) from *A. zeravschanicum* exhibited antiarrhythmic activity in aconitine-introduced arrhythmia rat model greater than heteratisine, a C_{19}-DA with pronounced antiarrhythmic activity (ED_{50}, 12.5 mg kg^{-1}).[17] It is worth noting that the diester alkaloids tadzhaconine (**59**, $ED_{50} = 0.3$ mg kg^{-1}) and zeravshanisine (**52**, $ED_{50} = 0.5$ mg kg^{-1}) showed much better effects than the alcohol amines hetisine (**13**, $ED_{50} = 1$ mg kg^{-1}) and nominine (**4**, $ED_{50} = 5$ mg kg^{-1}). Moreover, it was found that the all acetylated derivatives of Guan-fu alcohol-amine (tangutisine, **45**) by different ester groups such as Ac, Pro and Bz could effectively enhance its antiarrhythmic activity.[84] The above findings indicated that the antiarrhythmic activity of Guan-fu base A analogues is closely related to the number and variety of acyl groups on certain positions, and enhanced

antiarrhythmic activity can be achieved by further chemical modifications. Another structure–activity relationship (SAR) study revealed that the propylene glycol amine group might be the key pharmacophore responsible for the antiarrhythmic activity of guan-fu base A analogues (Fig. 6).[85]

Since the sodium current plays a crucial role in the early depolarization and duration of the cardiac action potential and is involved in the propagation of electrical impulses from one cell to another, sodium current blockers could be a useful candidate target for new potential therapeutic agents against arrhythmia. The sodium current inhibitory effects of 21 compounds isolated from *A. coreanum* were tested using a whole-cell patch voltage-clamp technique, and five hetisine-type DAs exerted significant blocking activities.[35] Among them, Guan-fu base S (**91**, IC_{50} = 3.48 μM) showed a strong inhibitory effect on sodium current, which could suppress the sodium current of guinea pig ventricular myocytes in a dose-dependent manner by binding to open channels and exhibited potential for further development as an antiarrhythmic agent. Guan-fu base Q (**126**, IC_{50} = 82.65 μM), hetisine (**13**, IC_{50} = 75.72 μM), Guan-fu bases A (**49**, IC_{50} = 41.17 μM) and G (**53**, IC_{50} = 23.81 μM) showed moderate antiarrhythmic activities and were more effective than the positive control acehytisine hydrochloride (crude drug of Guan-fu base A injection, IC_{50} = 78.26 μM). Besides, it was reported that hetisinone (**16**) showed moderate inhibitory activity on the Nav 1.2 channel (inhibition rate 28% at 10 μM) in another study.[86]

4.2. Antitumor activities

A certain number of naturally occurring hetisine-type DAs have been screened for their cytotoxic activities against various human cancer cell lines.[87] However, only a few have exhibited significant antiproliferative activity.[88] Trichodelphinines A–E (**32–35**, **38**) from *D. trichophorum* were evaluated for their *in vitro* cytotoxicity against the A549 cell line using the MTT method.[18] All of the above-mentioned compounds showed cytotoxicity against A549 cells with IC_{50} values ranging from 12.0 to 52.8 μM. The most active compounds, **33** and **38**, had low IC_{50} values of 18.64 and 12.03 μM, respectively, while the positive control doxorubicin showed an IC_{50} value of 0.60 μM. In addition, nagaconitine D (**124**) from *A. nagarum* var. *heterotrichum* showed cytotoxicity against the human ovarian cancer cell line SK-OV-3 with an inhibition rate of 24% (IC_{50} = 32.1 μM) compared to the reference drug cisplatin (89%) with an IC_{50} value of 11.6 μM.[89]

While natural hetisine-type DAs themselves are rarely active against certain human cancer cell lines, increasing cytotoxic activity has been observed after the corresponding hetisine-type DAs undergo acetylation.[88,90] Wada *et al.* synthesized a series of acylated derivatives of the natural hetisine-type DAs kobusine (**9**) and pseudokobusine (**105**), the main constituents of *A. japonicum*, and evaluated their cytotoxic activities against three human cancer cell lines: lung (A549), prostate (DU145), and nasopharyngeal (KB).[91–93] Some of these hetisine derivatives displayed impressive cytotoxicity against all of the tested cancer cells, with IC_{50} values ranging from 3.1 to 20.1 μM (Table 2). More significantly, all of active compounds displayed potency against vincristine-resistant nasopharyngeal (KB-VIN) cell line with ratios of KB to KB-VIN greater than 0.7, in contrast with the positive control paclitaxel (KB/KB-VIN ratio, 0.0067). Structurally, the most active kobusine derivatives were those with both C-11 and C-15 acylated, and the pseudokobusine derivatives containing a free hydroxy group at C-6 were more active than their acylated products. The results indicated that an acyl group replacement at both C-11 and C-15 resulted in the enhancement of activity of the parent alkaloids compared to hydroxy groups at these positions, and the presence of a hydroxy group at the C-6 position was required for cytotoxic effects (Fig. 6).

Some of these active pseudokobusine derivatives have been further studied for their pharmacological mechanism.[19,94] It was found that 11-*m*-trifluoromethylbenzoyl (Mb)-pseudokobusine clearly inhibited the phosphorylation of extracellular signal-regulated kinase, induced enhanced phosphoinositide 3 kinase phosphorylation and led to the subsequent accumulation of cells in the G1 and/or sub G1 phase in Raji cells.[19] In addition, no significant suppressive effects on the growth of human $CD34^+$ hematopoietic stem/progenitor cells (HSPCs)

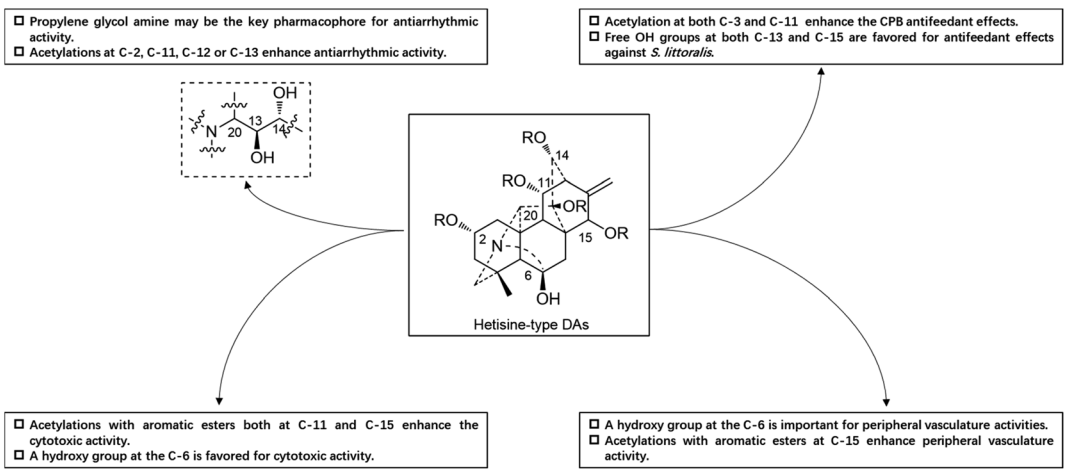
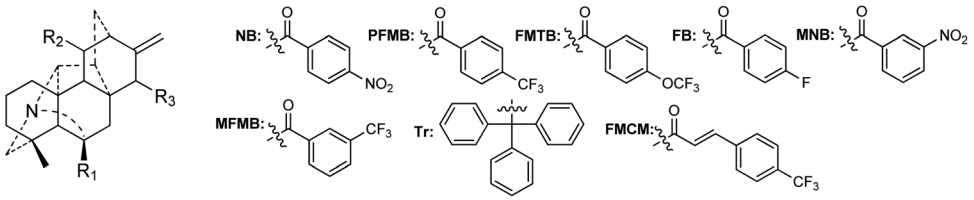


Fig. 6 The SAR of hetisine-type DAs.

Table 2 Cytotoxicity of kobusine (**9**) and pseudokobusine (**105**) and their acylated derivatives (IC_{50}, μM)



R_1–R_3	A549	DU145	KB	KB-VIN	KB/KB-VIN ratio
$R_2 = R_3 =$ OH (**9**)	>40	>40	>40	>40	—
$R_2 = R_3 =$ OBz (**9a**)	8.4	9.3	6.0	7.5	0.80
$R_2 = R_3 =$ OAs (**9b**)	6.7	7.1	5.3	5.2	1.02
$R_2 =$ ONB, $R_3 =$ OH (**9c**)	19.5	15.3	13.9	17.9	0.78
$R_2 = R_3 =$ ONB (**9d**)	6.9	7.0	5.3	5.5	0.96
$R_2 =$ OPFMB, $R_3 =$ OH (**9e**)	17.2	13.2	12.7	14.1	0.90
$R_2 =$ OFMTB, $R_3 =$ OH (**9f**)	14.1	9.6	11.7	10.9	1.07
$R_2 = R_3 =$ OFB (**9g**)	8.1	6.8	5.2	7.1	0.73
$R_2 = R_3 =$ OFMCM (**9h**)	5.5	6.2	4.1	3.1	1.32
$R_1 = R_2 = R_3 =$ OH (**105**)	>40	>40	>40	>40	—
$R_1 = R_2 =$ OBz, $R_3 =$ OH (**105a**)	19.3	15.3	12.8	10.2	1.25
$R_1 =$ OH, $R_2 = R_3 =$ OBz (**105b**)	8.8	7.6	5.2	6.3	0.83
$R_1 = R_3 =$ OH, $R_2 =$ OAs (**105c**)	15.4	13.2	11.1	15.7	0.70
$R_1 = R_3 =$ OH, $R_2 =$ OVr (**105d**)	8.0	15.3	14.9	20.1	0.74
$R_1 = R_2 =$ OVr, $R_3 =$ OH (**105e**)	16.0	16.9	19.7	14.7	1.34
$R_1 = R_3 =$ OVr, $R_2 =$ OH (**105f**)	15.2	16.6	18.1	12.2	1.48
$R_1 = R_2 =$ OH, $R_3 =$ ONB (**105g**)	5.8	7.2	6.4	6.4	1.00
$R_1 =$ OH, $R_2 = R_3 =$ OMNB (**105h**)	5.0	5.2	5.6	5.6	1.00
$R_1 = R_3 =$ OH, $R_2 =$ OMFMB (**105i**)	6.8	7.7	8.9	6.2	1.44
$R_1 = R_3 =$ OH, $R_2 =$ OFMTB (**105j**)	17.9	14.5	15.7	13.9	1.13
$R_1 = R_3 =$ OH, $R_2 =$ OCn (**105k**)	8.4	6.5	7.0	6.4	1.09
$R_1 = R_3 =$ OH, $R_2 =$ OTr (**105l**)	6.4	6.0	6.6	5.2	1.27
Paclitaxel (nM)	4.8	5.9	5.8	2405.4	0.0067

were observed with this compound, whereas its analogue 11-As-pseudokobusine showed a significant suppressive effect on the growth of HSPCs. These findings underscore the potential of hetisine-type DAs to be developed into new, specific antitumor compounds with an optimal balance between antitumor effects and myelosuppression and encourage further extensive investigations of the antitumor effects of hetisine-type alkaloids.

4.3. Effect on peripheral vasculature

A series of hetisine-type DAs, namely, kobusine (**9**) and pseudokobusine (**105**), from *A. yesoense* var. *macroyesoense* and their derivatives have been reported to exhibit peripheral vasculature activities by laser-flowmetrically measuring the cutaneous blood flow in the hind feet of mice after intravenous administration. An earlier study in 1997 by Wada *et al.* reported that both kobusine (**9**) and pseudokobusine (**105**) exhibited a rapid increase in blood flow, reaching a peak with a magnitude almost equal to that produced by hydralazine when administered intravenously at the same dose of 20 mg kg^{-1}, while other tested compounds showed only mild to moderate effects.[22] This effect on blood flow is probably due to the direct action on the cutaneous microvasculature that occurs in a similar fashion to that shown by hydralazine. A subsequent study showed that only the C-11 and C-15 esterified derivatives of kobusine and pseudokobusine showed significant effect on vasculature peripheral vasculature,[95] which inspired the authors to synthesize a series of esterified derivatives to search for more effective analogs.[96] Conclusively, these studies have led to the discovery of a certain number of hetisines with prominent effects on cutaneous blood flow in mice.[97] SAR analysis revealed that hydroxyl groups of these alkaloids, especially a free OH group at C-6, are important for action on the peripheral vasculature leading to dilatation, and that the alkaloids with a 15-aromatic ester groups, *e.g.*, As, Vr, or NB (nitrobenzoyl), may have enhanced activity compared with the parent alkaloids.

4.4. Insecticidal activity

Traditionally, plants from the genera *Aconitum*, *Delphinium* and *Consolida* have been widely used as natural insecticides against various kinds of agricultural pests, which implies that their major constituents, namely, DAs, possess insecticidal activity.[98,99] Hence, DA components from these plants, including a certain number of hetisine-type DAs, have been screened for their insecticidal activity.

Table 3 Antifeedant effects of hetisine-type DAs on *L. decemlineata* and *S. littoralis* (EC_{50}, μg cm^{-2}) and cytotoxicity on Sf9 and CHO cells (LD_{50}, mg mL^{-1})

Alkaloids	*L. decemlineata*	*S. littoralis*	Sf9 cells	CHO
16	13.1	>50	>100	>100
42	22.5	5.5	—	—
43	12.9	>100	—	—
42a	—	>100	5.3	12.5
42b	27.2	>100	>100	>100
42c	100	23.7	>100	>100
87	2.2	4.4	>100	>100
84	4.0	>50	>100	>100
88	>50	>50	—	—
151	>50	>50	—	—

Ulubelen *et al.* tested the insect repellent activities of 29 natural DA components, including six hetisines (**13**, **16**, **17**, **31**, **90** and **100**) isolated from Turkish *Delphinium* and *Consolida* species, against a common household pest, the red flour beetle (*Tribolium castaneum* Herbst.).[21] It was found that hetisine (**13**), with a repellency of 59.12% at 3 mg mL^{-1}, possessed the highest activity among all tested alkaloids. Alkaloids **17**, **31**, and **90** also showed a repellency class III effect (40.1–60%) with repellency values of 56.25%, 40.62%, and 45.87% at 3 mg mL^{-1}, respectively, while **16** and hetisinone (**16**) showed only a low-class II repellent effect, with a repellency value of 31.25% and 37.50% at 3 mg mL^{-1}, respectively.

Seven natural hetisine-type DAs (**16**, **42**, **43**, **84**, **87–88**, and **150**), along with three hydrolysis products, 13-oxo-cardiopetamine (**42a**), 13-acetyl-15-oxo-cardiopetamine (**42b**), 15β-hydroxy-hetisinone (**42c**), were screened for their insect antifeedant activity against the Colorado potato beetle (CPB, *Leptinotarsa decemlineata*) and *Spodoptera littoralis*, as well as their toxicity to insect-derived Sf9 cells (derived from *Spodoptera frugiperda* pupal ovarian tissue) and mammalian Chinese hamster ovary (CHO) cells (Table 3).[100,101] Among the tested compounds, cardiodine (**87**), with an EC_{50} value of 2.2 μg cm^{-2}, was found to be the most active CPB antifeedant, followed by glandulosine (**84**), with an EC_{50} value of 4.0 μg cm^{-2}, which implied that acetylation at both C-3 and C-11 might enhance their CPB antifeedant effects. Hetisinone (**16**) and cardiopetamine (**42**) also showed certain activity against *L. decemlineata*, with EC_{50} values of 13.1 and 22.5 μg cm^{-2}, respectively. The most active antifeedants against *S. littoralis* were cardiodine (**87**, EC_{50}, 4.4 μg cm^{-2}) and cardiopetamine (**42**, EC_{50}, 5.5 μg cm^{-2}). In addition, 15β-hydroxy-hetisinone (**42c**) showed an EC_{50} value of 23.7 μg cm^{-2}, indicating that OH groups at both C-13 and C-15 are favored for antifeedant effects against *S. littoralis*. In addition, only **42a** with a ketone group at C-13 showed cytotoxicity to Sf9 and CHO cells with LD_{50} values of 5.3 and 12.5 mg mL^{-1}, respectively, indicating that its insecticidal effects could be the result of neurotoxicity and/or cytotoxicity. It was observed that the of hetisine-type DAs. In general, although hetisine-type C_{20}-DAs show relatively lower antifeedant activities than C_{19}-DAs,[102] they still have a certain advantage in serving as lead compounds in insecticide development because of their low toxicity to humans.

4.5. Antimicrobial and antiviral activities

Plants with abundant DA components have been used for the treatment of itch and other skin eruptions in folk medicine, which indicates that these plants may possess constituents with antifungal activity.[98] The bioactivity-guided separation of the chloroform fraction with antimicrobial activities from *P. aviculare* led to the isolation of the hetisine-type DA panicudine (**106**), which was evaluated for its antimicrobial activity against both Gram-negative bacteria (*Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Salmonella paratyphi* and *Shigella flexneri*), Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*, and *Streptococcus pyogenes*) and fungi by determining the diameter of the inhibition zone using the paper disk diffusion method.[20] Consequently, panicudine (**106**) displayed considerable activity against all tested Gram-negative and Gram-positive organisms (diameter of zone of inhibition ranging from 5–23 mm at 0.4–400 mg mL^{-1}), with the exception of *Candida albicans*. Hetisine-type DAs have also shown certain antiviral activity. Tanguticulines A (**68**) and E (**125**) from *A. tanguticum* exhibited obvious inhibitory effects on the cytopathic changes induced by the influenza A virus (H1N1), with IC_{50} values of 2.9 μg mL^{-1}.[46]

4.6. Toxicity

To date, only a few hetisine-type DAs have been assessed for their acute toxicity in mice. The LD_{50} values (ip) for alkaloids **49**, **59**, **52**, **13**, and **4** were 185.5 mg kg^{-1}, 12.8 mg kg^{-1}, 34.1 mg kg^{-1}, 26.2 mg kg^{-1}, and 68.0 mg kg^{-1}, respectively.[17,103] From the data available, the toxicity of hetisine-type DAs is much lower than that of diester-type C_{19}-DAs, such as aconitine (ip, LD_{50} = 0.30–0.38 mg kg^{-1}), hapaconitine, or yunaconitine, which is beneficial for the applications of hetisine-type DAs in the pharmaceutical industry.

5. Conclusions

To date, a total of 157 hetisine-type DAs have been discovered, which are the most abundant subtype of C_{20}-DAs. The reported hetisine-type DAs have been found in plants from seven genera in three families. The genera *Aconitum* and *Delphinium* of Ranunculaceae could be regarded as the richest resources of hetisine-type DAs. In terms of subtypes, the amine subtype with 94 members is the most common hetisine-type compounds, as they account for the largest proportion of reported compounds (60%), followed by the *N*,*O*-mixed acetal subtype with 56 members (35%). The other subtypes account for only a small portion of compounds (5%). The variety, quantity, position, and orientation of the oxygenated substituents make the large chemical diversity of hetisine-type DAs, which could serve as a vast resource for drug discovery.

Natural hetisine-type DAs have been reported to have various biological activities, including antiarrhythmic, antitumor, insecticidal, antifungal, and antiviral activities, as well as effect

on peripheral vasculature. Besides, SAR studies revealed that more potent biological activities could be acquired after chemical modifications at certain positions. These findings are not only conducive to illuminating the pharmacodynamic material basis of plants with abundant hetisine-type DA components but also indicate their potential in drug discovery. In particular, the antiarrhythmic effects of hetisine-type DAs are more prominent than that of other DAs, and their lower toxicity highlights the potential of hetisine-type DAs in antiarrhythmic drug discovery.

Although chemical and biological studies on hetisine-type DAs have attracted considerable interest, some deficiencies and research potential remain. First, some of the studies ignored the probable structural transformations of several types of C_{20}-DAs during the extraction processes. Thus, some of the reported hetisine-type quaternary ammonium hydroxides or salts are indeed artifacts of hetidine-type or vakognavine-type DAs. More detailed chemical studies on the structural identification of these alkaloids are required. Second, most of the biological activities of hetisine-type DAs have been investigated by using *in vitro* chemical and cellular models, and little clinical or *in vivo* research is currently available. These pharmacological studies are insufficient to validate the effects of hetisine-type DAs and their derived compounds, which hinders their application and promotion. It is necessary to evaluate the biological activities of the constituents using both *in vitro* and *in vivo* pharmacological models to facilitate further research and exploitation of these types of compounds.

Author contributions

Tianpeng Yin – resources, supervision, visualization, writing – original draft, writing – review and editing. Huixia Zhang –writing – review and editing. Wei Zhang – supervision, writing – review and editing, funding acquisition. Zhihong Zhang – supervision, writing – review and editing, funding acquisition.

Conflicts of interest

The authors declare no conflict of interest.

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