

Review Article

Biologically active guanidine alkaloids

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ABSTRACT

Guanidine alkaloids widely exist in terrestrial microorganisms, peptides, and marine invertebrates, and have a multitude of biological activities. Consequently, these molecules have attracted attention as potential drug leads among chemists and biologists. This review provides an overview of research progress in bioactive guanidine alkaloids since 2012, describing their most important biological properties, including antimicrobial, antiparasitic, antiviral, and anticancer activities. The contents include new compounds reported since 2012 and the biological activities of known compounds reported before 2012.

Keywords: guanidine alkaloids, biological activities, antimicrobial, antiparasitic, antiviral, anticancer

1. INTRODUCTION

For many decades, natural products have been a focus of medical, pharmaceutical, and biological research, because of their unique structures and properties. Natural products have been developed from sources including terrestrial and marine organisms [1, 2]. Terrestrial plants and microorganisms found throughout nature provided initial ways for humans to exploit and use natural resources [3]. Subsequently, with the development of modern science and technology, humanity has known the importance of using and developing resources from the vast ocean [4, 5]. Diverse and complex microbial secondary metabolites with unique structures and extensive biological activities exist under these complex environmental conditions [6]. Exploitation and utilization of natural products, and structural modification of natural products, are major strategies for solving increasingly serious drug resistance and safety problems [7].

Alkaloids are a class of natural compounds characterized by negative nitrogen atoms present in their molecular structure, which impart high pharmacological potency and activity [8, 9]. Alkaloids and their analogues are main active ingredients in many drugs, thus underscoring their potential in the development of new drugs [10–12]. These compounds can be classified

into quinolines, indoles, carbazoles, and other types, according to their functional groups. Among them, the guanidine motif has strong basicity ($pK_a = 13.6$) and is involved in enzyme/substrate complex interactions, and therefore is a particularly suitable group for structural modification and activity promotion [13]. The considerable biological activity of guanidine derivatives has received substantial interest in the scientific community. Several reviews in recent decades have described the isolation, structure determination, total synthesis, biosynthesis, and biological activities of guanidino compounds [3, 4, 13–18]. For instance, Gupta reviewed the biological activities of marine guanidine alkaloids in 2021 [19].

Guanidine alkaloids are classified as acyclic, monocyclic, bicyclic, tricyclic, tetracyclic, or pentacyclic, according to their structure. For acyclic guanidines, such as agelasidines G–I (3–5) (Figure 1) and nitensidines A–D (6–9) (Figure 2), the guanidine group exists in a non-cyclic linear structure. In bicyclic guanidine alkaloids, the guanidine motifs form a five-membered ring or a six-membered ring between amino groups, as in monanchoradins A–C (105–107) (Figure 24). Furthermore, tricyclic guanidine alkaloids, except for several new structures such as monanchorins (108, 109) (Figure 25) and massinidine (114) (Figure 27), usually have a

cyclopentapyrimidinamine skeleton. Tetracyclic guanidines, such as eudistidines A (**152**) and B (**153**), have a novel tetracyclic core and are not typically found in nature [20]. Pentacyclic guanidine families are conventionally divided into three structural blocks—a “vessel” part, an “anchor” part, and a polymethylene chain; examples of these compounds include crambescidins (**162–166**) (Figure 39) and monanchocidins (**170–174**) (Figure 40). The structures of guanidine alkaloids have complex diversity and are interconnected in intricate ways; these aspects contribute to their potent biological activities.

This article presents a comprehensive review of the structural features and bioactivity of guanidine alkaloids reported in the scientific literature since 2012, and discusses the relationships between structures and biological activities. Our aim is to facilitate clinical, agricultural, and food applications of guanidine alkaloids with high efficiency, and to provide an updated reference for researchers.

2. RECENTLY STUDIED BIOACTIVE GUANIDINE ALKALOIDS

2.1 Acyclic guanidine

The structural complexity of acyclic guanidine alkaloids, a chemically diverse and pharmacologically promising family of natural products, arises from broad biological sources (marine sponges, terrestrial plants, and microorganisms) and unique biosynthetic pathways. This class—originating from marine sponges (*Agelas* spp.), leguminous plants (*Pterogyne nitens*), microorganisms (*Streptomyces* spp.), bivalves, and other biological systems—exhibits remarkable structural heterogeneity.

2.1.1 Agelasidines. Agelasidines E and F (**1,2**) (Figure 1), first reported in 2012 from the Caribbean sponge *Agelas citrina*, are structurally unique hypotaurocyamine diterpene alkaloids featuring guanidine functional groups. These compounds were obtained through bioassay-guided fractionation of antifungal extracts

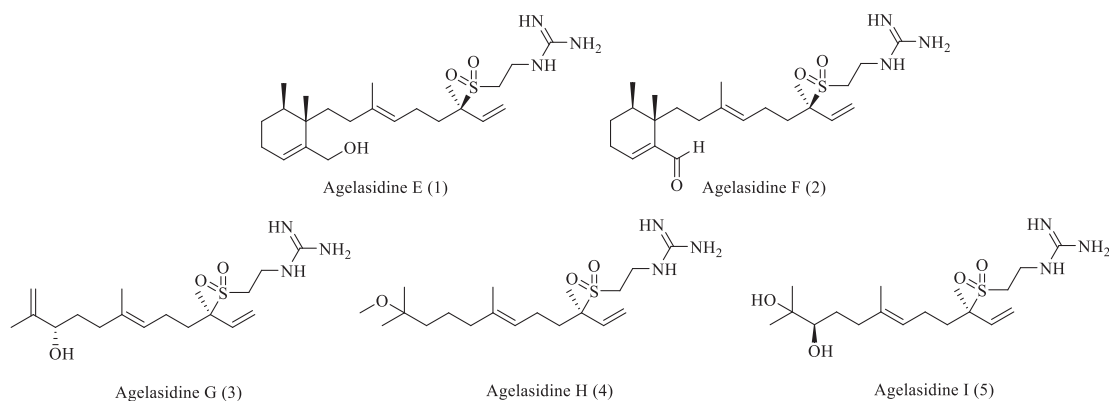


Figure 1 | Structures of agelasidines E–I (1–5).

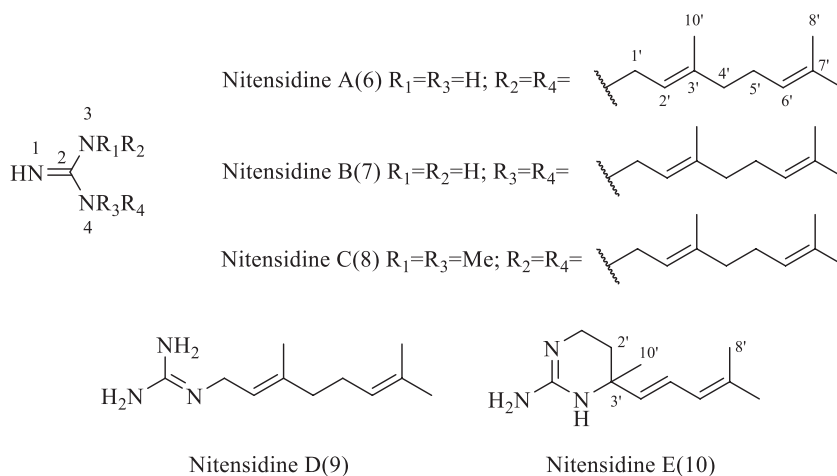


Figure 2 | Structures of nitensidines A–E (6–10).

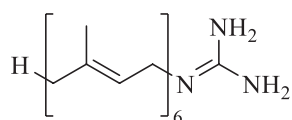
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showing potent inhibitory effects against clinically relevant *Candida* species, including the *Cryptococcus* variants *grubii* and *gattii* [21]. After a decade of research, three novel 2-guanidinoethanesulfonyl sesquiterpenes, denoted agelasidines G–I (3,4,5) (Figure 1), were successfully extracted from a marine sponge (*Agelas nakamura*) collected on Orchid Island by Lin et al. [22].

2.1.2 Nitensidines. Nitensidines, guanidine alkaloids with several prenyl units, isolated from the Fabaceae plant *Pterogyne nitens*, including nitensidines A–E (6–10) (Figure 2), exhibit properties including cytotoxic effects against human cancer cell lines, antimicrobial activity against opportunistic fungi species, and antiparasitic activity against *Trypanosoma cruzi* [23–26]. Notably, nitensidine E (10), unlike nitensidines A–D (6–9), is a monocyclic alkaloid. Moreover, in contrast to other compounds, nitensidine E (10) has a structure containing an acyclic monoterpene derivative on a guanidine moiety; this monocyclic guanidine alkaloid was the first natural product reported to have this characteristic [26]. The specific structure of the nitensidine family had been described in identification and total synthesis studies [23, 24, 27, 28].

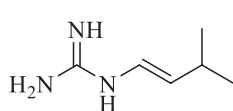
2.1.3 Zillamycin. The deuterium adduct bioactivity screening platform revolutionized microbial natural product discovery in 2023 and enabled the identification of zillamycin (11) (Figure 3), a novel isoprenylated guanidine alkaloid from *Streptomyces griseofuscus*. This structurally unique secondary metabolite demonstrates dual pharmacologic efficacy comprising cytotoxicity against cancer cell lines and growth inhibition of multi-drug-resistant pathogens [29].

2.1.4 Galegine. First characterized in 1923 through phytochemical investigations of *Galega officinalis* L. [30],

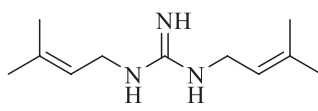


zillamycin (11)

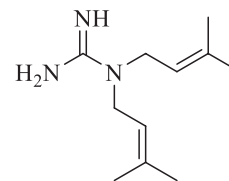
Figure 3 | Structure of zillamycin (11).



galegine(12)



pterogynine(13)



pterogynidine(14)

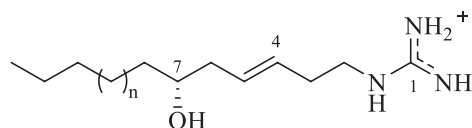
Figure 4 | Structures of galegine, pterogynine, and pterogynidine (12–14).

the guanidine-type alkaloid galegine (12) (Figure 4) has maintained enduring scientific interest in natural product research. Its structural simplicity and pleiotropic bioactivities have prompted extensive pharmacological exploration. Phytochemical profiling has revealed substantial quantitative variation in this secondary metabolite across vegetative tissues and developmental phases [31]. Galegine (12) has anti-diabetic [32, 33], antihypertensive [34], antimicrobial [35], cytotoxic [24, 36, 37], and insecticidal [38, 39] properties. In addition, studies before 2012 indicated galegine's contribution to weight loss in mice [40, 41]. This compound has also been used in the synthesis of biguanides, metformin, and phenformin [42–44].

2.1.5 Pterogynine and pterogynidine. Pterogynine (13) and its isomer pterogynidine (14) (Figure 4) are guanidine alkaloids extracted from the bark of *Pterogyne nitens* Tul. (Leguminosae) in 1969 and 1970, respectively [45, 46]. Both compounds are analogues of galegine (12) and nitensidines. Pterogynine (13) has selective cytotoxicity across multiple cancer cell lines, whereas pterogynidine (14) exhibits broader bioactivity, notably including antiparasitic activity against *Trypanosoma cruzi*, reported in 2009 [26]. The structure-activity relationships of nitensidine A (6), galegine (12), pterogynine (13), and pterogynidine (14) have been associated with their biological activities. The quantity of isoprenyl moieties in guanidine alkaloids, in conjunction with the number and binding characteristics of the constituent components, such as the site and degree of polymerization, and the imino nitrogen atom, collectively contributes to the observed activities of these substances [36, 37].

2.1.6 Pulchranins. The chemical exploration of *Monanchora pulchra* sponges has yielded three novel guanidine alkaloids denoted pulchranin A–C (15–17) (Figure 5) [47, 48]. Pulchranin A (15), a critical biosynthetic intermediate, might potentially be the metabolic precursor of both monanchomycalins A/B (175, 176) and pentacyclic guanidine alkaloids from the same source. Pulchranins B and C (16, 17), featuring hydroxylated monounsaturated hydrocarbon chains with 12 and 11 carbons, have inhibitory activity toward TRPV1, TRPV3, and TRPA1 receptors.

2.1.7 Unguiculins. To date, only three unguiculins with two terminal guanidine motifs have been described:

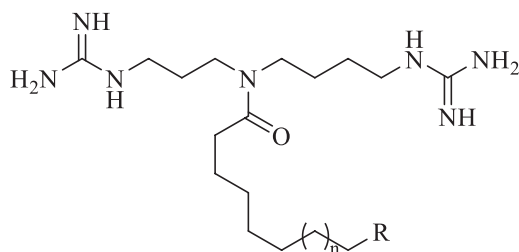


pulchranin A (15), $n=3$
 pulchranin B (16), $n=2$
 pulchranin C (17), $n=1$

Figure 5 | Structures of pulchranins A–C (15–17).

unguiculins A, B, and C (18–20) (Figure 6). These compounds were identified in 2017 from the French Polynesian *Monanchora* sp. marine sponge [49, 50]. All three compounds, with median inhibitory concentration (IC_{50}) values in the micromolar range, are cytotoxic to human cancer cells. Unguiculin A (18) additionally has antimalarial effects. Structurally, unguiculin C (20) is four carbons shorter than the other two compounds, whereas unguiculin B (19) has a hydroxyl substitution at the end of the side chain. Structural variations (chain length and hydroxylation) highlight potential structure-activity relationships for optimizing the anticancer and antiparasitic profiles of these compounds.

2.1.8 Dopargimine and mellpaladines. Uchimasu et al. have successfully characterized four unprecedented guanidine-type alkaloid derivatives, dopargimine (21) and mellpaladines A–C (24–26) (Figure 7), featuring a marine-derived tetrahydroisoquinoline scaffold; these compounds are putative products of dopamine and arginine-derived precursors formed via Pictet-Spengler condensation [51]. Sakai et al. have further explored the constituents of this tunicate extract and isolated the dopargimine derivative 1-carboxydopargimine (22). That investigation also led to the isolation of mellpaladines D–F (27–29) and serotodopargimine (23) [52]. This iterative discovery underscores the chemical richness of



unguiculin A (18), $R=CH_3$, $n=9$
 unguiculin B (19), $R=OH$, $n=9$
 unguiculin C (20), $R=CH_3$, $n=5$

Figure 6 | Structures of unguiculins A–C (18–20).

tunicate-derived metabolites and the utility of targeted isolation strategies.

2.1.9 Actinofide and dotofide. The novel diacylguanidine actinofide (30) (Figure 8) was isolated from the marine bivalve *Actinocyclus papillatus* by Carbone et al. in 2017 [53]. After its initial purification from *Dictyota pinnatifida* by Putz's team, dotofide (31) was evaluated by Carbone et al. for broad-spectrum anticancer activity [54]. The structures have significant growth inhibitory activity, as indicated by their ability to inhibit the proliferation of multiple cancer cell types [53].

2.1.10 Chlorocatechelins and heterobactins. In 2014, a novel siderophore, chlorocatechelin A (32) (Figure 9), was isolated from a *Streptomyces* sp. culture broth. Determination of its structure was achieved through spectroscopic analysis and a degradation study [55]. Bosello et al. have reported successful isolation of heterobactins (33–35) from *Rhodococcus erythropolis* PR4, and the subsequent structural characterization and elucidation of these compounds' biosynthetic origin [56]. Although heterobactin A (33) was first reported in 2001 [57], Bosello et al. revised the structure [56]. The acylguanidine structure has been found to be indispensable for Fe(III)-chelating activity. The conserved acylguanidine moiety in heterobactins highlights its evolutionary optimization for Fe(III) coordination, aligning with siderophore functional requirements.

2.1.11 Hordatines. Hordatines A–C (36–38) (Figure 10), isolated from a pilsner-type beer by Spreng et al. in 2018, have antioxidant activity [58].

2.1.12 Dragmacidins. Dragmacidin G (39) (Figure 11), initially characterized through independent investigations by Wright et al. and Hitora et al., was first isolated from the organic extract of a marine sponge of *Lipastrotethya* sp. This bis-indole alkaloid has since been demonstrated to exhibit a remarkably broad spectrum of biological activity and is therefore a chemically significant marine natural product [59, 60]. Dragmacidin H (40) (Figure 11) was simultaneously isolated by Hitora et al. [60]. The co-isolation of dragmacidins G and H highlights the metabolic richness of *Lipastrotethya* sponges. Because of its polypharmacological profile, dragmacidin G is a high-priority candidate for drug discovery pipelines.

2.2 Monocyclic guanidines

Monocyclic guanidine alkaloids have remarkable chemical diversity and target selectivity, on the basis of their characteristic cyclic guanidine scaffolds and multidimensional substitution patterns.

2.2.1 Celosiadines. Celosiadines A and B (41, 42) (Figure 12), two structurally unique di-isopentenyl-substituted guanidine alkaloids, were first isolated from the aerial parts of *Iresine diffusa* by Killian et al. Their

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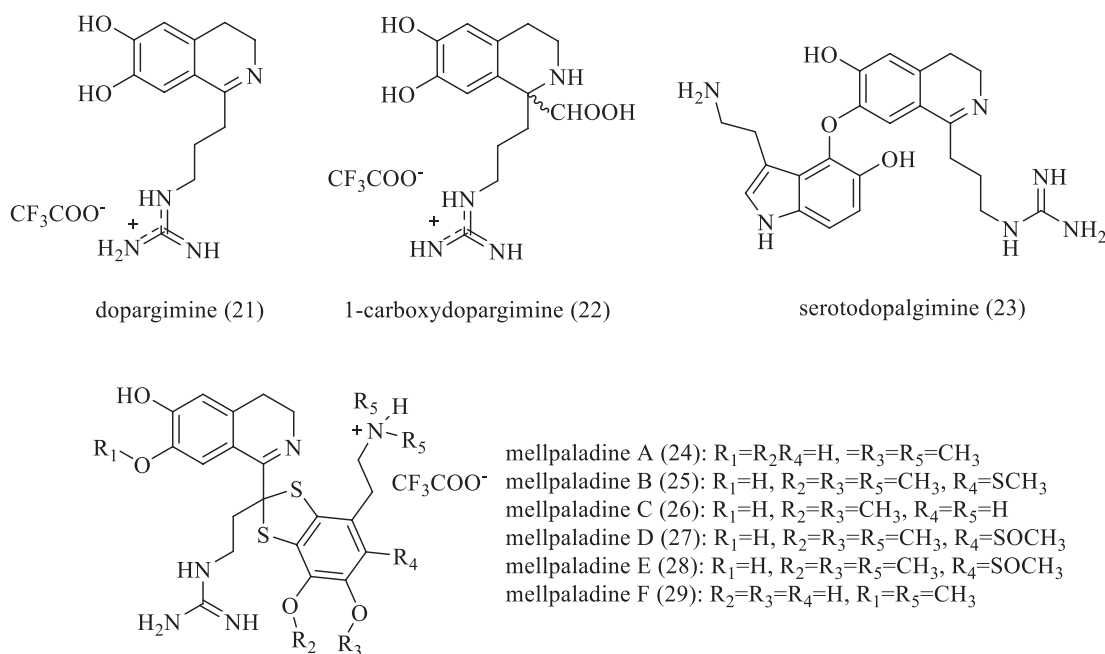


Figure 7 | Structures of dopargimine (21), 1-carboxydopargimine (22), serotodopargimine (23), and mellpaladines A–F (24–29).

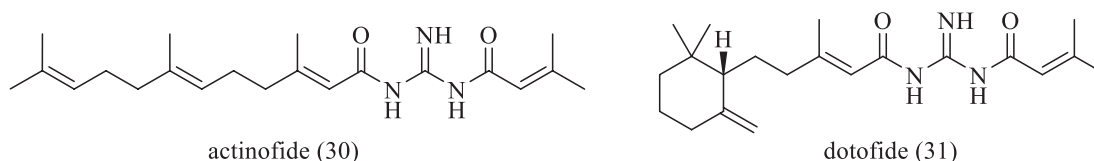


Figure 8 | Structures of actinofide (30) and dotofide (31).

molecular architectures were rigorously characterized through integrated spectroscopic interrogation, combining high-resolution mass spectrometry, multi-nuclear NMR, and electronic circular dichroism conformational analysis [61]. The ethnopharmacological importance of *Iresine diffusa* stems from its historical use in managing prostate disorders. Its standardized aerial part ethanol extract (30% v/v) is commercially used for multiple therapeutic indications, despite a prior lack of comprehensive phytochemical characterization. *Iresine diffusa* has been suggested to contain additional bioactive guanidine alkaloids that warrant further investigation.

2.2.2 Plumbagines and plumbagosides. In 2013, Cong et al. discovered two new guanidine alkaloid families, plumbagines and plumbagosides, isolated from the aerial parts of *Plumbago zeylanica* L. (Plumbaginaceae), including plumbagines A–G (43–49) and plumbagosides A–D (54–57) (Figure 13) [62]. Five new members, plumbagines H–K (50–53) and plumbagoside E (58) (Figure 13),

were isolated from the roots of *Plumbago zeylanica* by Zheng et al. in 2023. Plumbagines and plumbagosides include some bicyclic guanidine alkaloids (Figure 13), and their core skeleton consists of two five-membered rings. However, to date, only plumbagine D (46) has been reported to possess slightly antihyperglycemic activity [63]. Moreover, no LPS-induced anti-inflammatory activity has been detected for plumbagines H–K (50–53) and plumbagoside E (58) in RAW 264.7 cells. However, all compounds increase NO production, thus suggesting their potential novel immune potentiation activity [64].

2.2.3 Ecliptamines. A phytochemical investigation of *Eclipta prostrata* L. aerial parts in 2015 yielded four novel guanidine alkaloids, ecliptamines A–D (59–62), alongside the previously characterized analog plantagogaunadinic acid (63) (Figure 14) [65]. All these compounds contain a terminal monocyclic guanidine motif except ecliptamine D (62), which has an aliphatic chain structure. The ecliptamine family members share the same

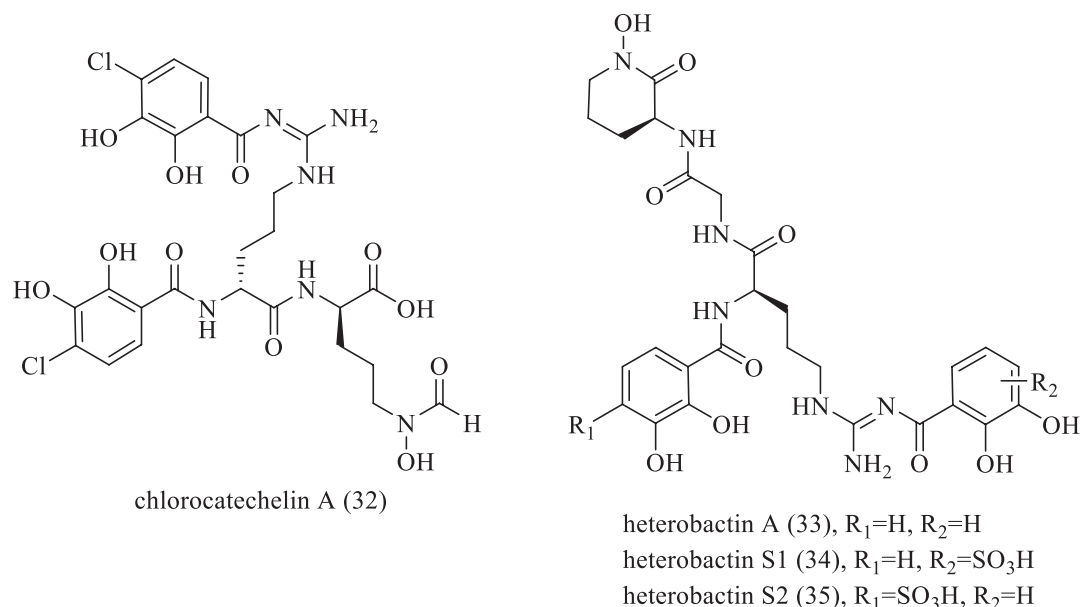


Figure 9 | Structures of chlorocatechelin A (32) and heterobactins (33–35).

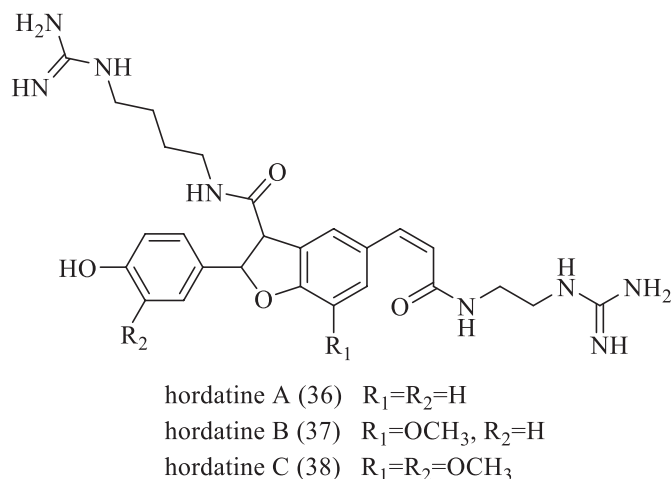


Figure 10 | Structures of hordatines A–C (36–38).

skeletal core with plantagoguanidinic acid (**63**), which was first discovered in 2008 from the seeds of *Plantago asiatica* [66]. This finding expands the structural diversity of plant-derived guanidine alkaloids.

2.2.4 Plantagoguanidinic acid. As a traditional Chinese medicine component, plantagoguanidinic acid (**63**) (Figure 14) has attracted substantial attention from natural chemists. Recent studies have focused on its pharmacokinetics and drug interactions [67, 68]. This compound might also have potential against human immunodeficiency virus (HIV), according to molecular

docking and molecular dynamics simulations [69]. In 2015, Zheng et al. isolated its analog, 1'-(4''-hydroxybutyl) plantagoguanidinic acid (**64**) (Figure 15), from the seeds of *Plantago depressa*. However, this compound has no antihyperglycemic properties [63].

2.2.5 Alchornedine. In a phytochemical investigation, Barrosa et al. have documented the isolation of alchornedine (**65**) (Figure 16), a guanidine-based alkaloid biosynthesized in the leaves of *Alchornea glandulosa*. Structural elucidation via multidimensional NMR analysis and X-ray crystallography revealed a unique tricyclic

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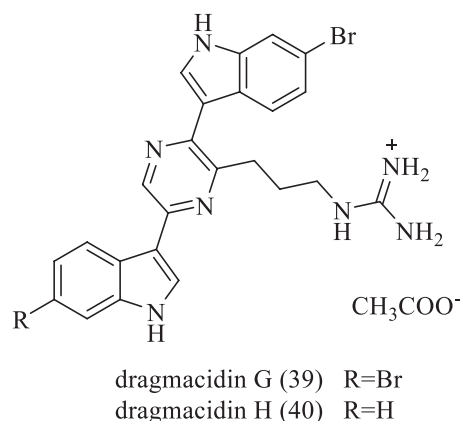


Figure 11 | Structures of drarmacidins (39–40).

scaffold. Subsequent pharmacological evaluation indicated antiprotozoal activity against *Trypanosoma cruzi* trypomastigotes and intracellular amastigotes [70].

This finding has expanded the structural diversity of plant-derived guanidine alkaloids and demonstrated the pharmacological relevance of tricyclic guanidine scaffolds in antiparasitic drug discovery.

2.2.6 Crambescin C1. Crambescins, guanidinic alkaloids that are either mono- or bi-cyclic in nature, were first isolated from the Mediterranean sponge *Crambe crambe*. Among them, crambescin C1 (**66**) (Figure 17), a monocyclic guanidine alkaloid with an oxidized 2-amino pyrimidine ring, differs from crambescin A, a bicyclic guanidine alkaloid. Crambescin C1 (**66**) was discovered before 2000, and its bioactivity has been extensively studied [71, 72].

2.2.7 Cernumidine and isocernumidin. Cernumidine (**67**) and isocernumidin (**68**) (Figure 18) were isolated from the ethanol extract of the leaves of *Solanum cernuum* Vell in 2011 by Lopes et al. [73]. These compounds have antitumor [73, 74], anti-inflammatory [75], antigenotoxic, and antioxidant [76] functions. These findings highlight *Solanum cernuum* as a rich source of

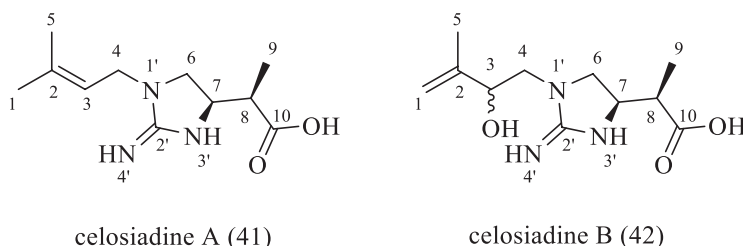


Figure 12 | Structures of celosiadines A (41) and B (42).

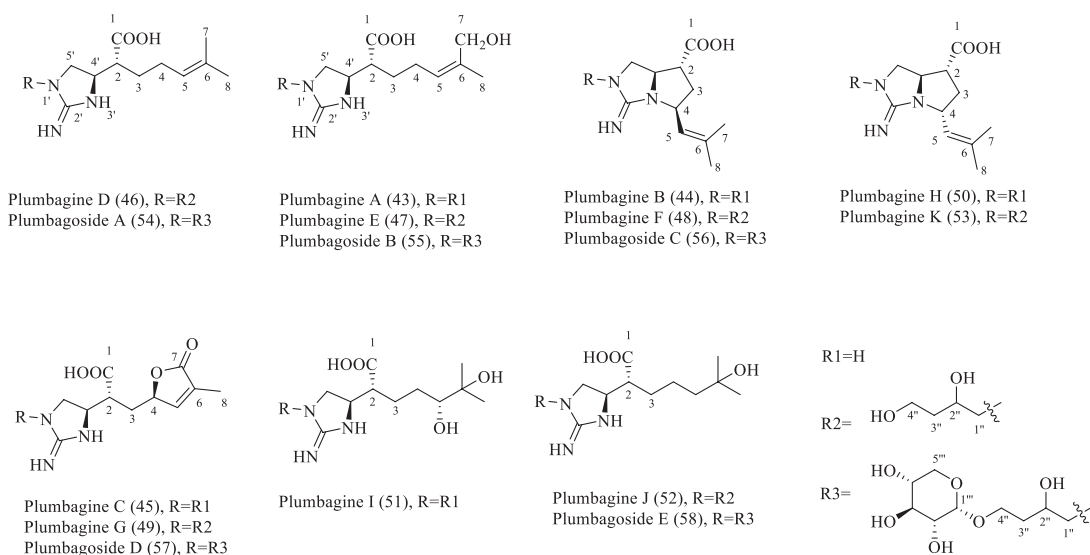


Figure 13 | Structures of the monocyclic and bicyclic guanidine alkaloids plumbagines A–K (43–53) and plumbagosides A–E (54–58).

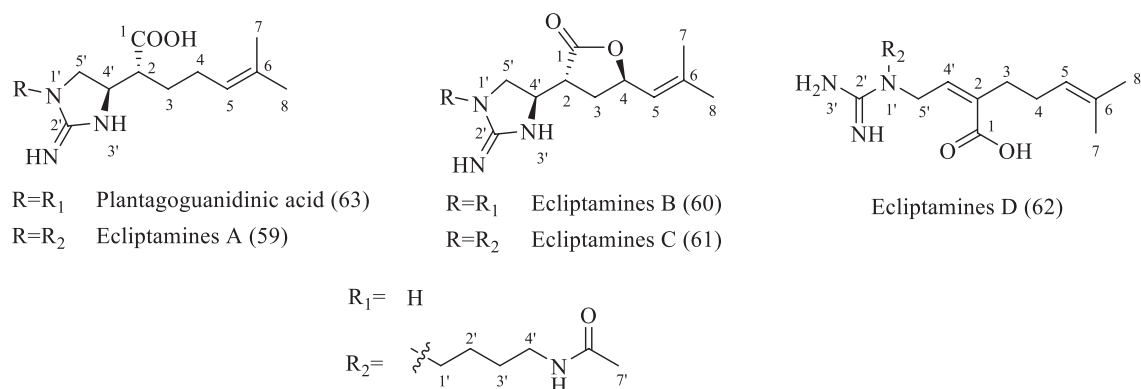
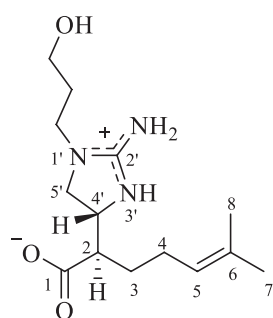


Figure 14 | Structures of ecliptamines A–D (59–62) and plantagoganidinic acid (63).



1'-(4''-hydroxybutyl) plantagoganidinic acid (64)

Figure 15 | Structure of 1'-(4''-hydroxybutyl) plantagoganidinic acid (64).

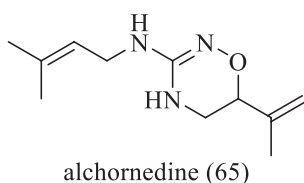


Figure 16 | Structure of alchornedine (65).

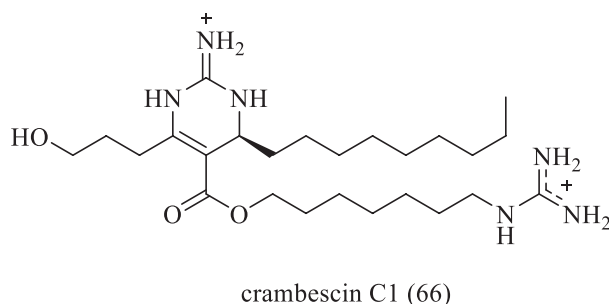


Figure 17 | Structure of crambescin C1 (66).

multifunctional alkaloids, and support further exploration of these compounds for cancer chemoprevention and inflammatory disease management.

2.2.8 Hymenialdisines and stevensines. Hamed et al. have documented the isolation of novel pyrrole-type alkaloids from the Red Sea demosponge *Stylissa carteri*, and performed subsequent pioneering pharmacological characterization of these secondary metabolites with a bioactivity screening platform targeting 21 therapeutically relevant protein kinases in vitro (Figure 19) [77].

2.2.9 Bromopyrrole guanidine alkaloids. Jiang et al. isolated N(1)-methylisoageliferin (73) and six known agelifेरins (74–79) from extract of the coralline demosponge *Astrosclera willeyana* in 2021 (Figure 20) [78]. Moreover, Freire and colleagues have isolated several natural guanidine alkaloids, including disparamides A–C (80–82), and nagelamides H2 and H3 (83, 84), as well as the known nagelamide H (85), citrinamine B (86), ageliferin (87), bromoageliferin (88), and dibromoageliferin (89) (Figure 20) [79]. Several structurally unique bromopyrrole alkaloids, agelamadin A–F (90–95), together with tauroacidin E (96), have been isolated from *Agelas* sp. marine sponges by Kusama et al. (Figure 20) [80–82]. In 2014, dispacamide E (97) (Figure 20), a new metabolite, was identified from the extracts of two Indonesian marine sponges, *Stylissa massa* and *Stylissa flabelliformis*, by Ebada et al. [83].

2.2.10 Enduracyclinones. Monciardini et al. built upon high-throughput screening assays, thus leading to the identification of enduracyclinones A (98) and B (99) (Figure 21). These compounds are characterized by aromatic polyketides bearing the unusual amino acid enduracididine. These polyketides are fused to a hexacyclic skeleton, a structural feature that distinguishes them from other compounds [84]. This work identified a novel structural class among polyketides, thus expanding their known biosynthetic diversity. The hexacyclic framework suggests potential for unique target

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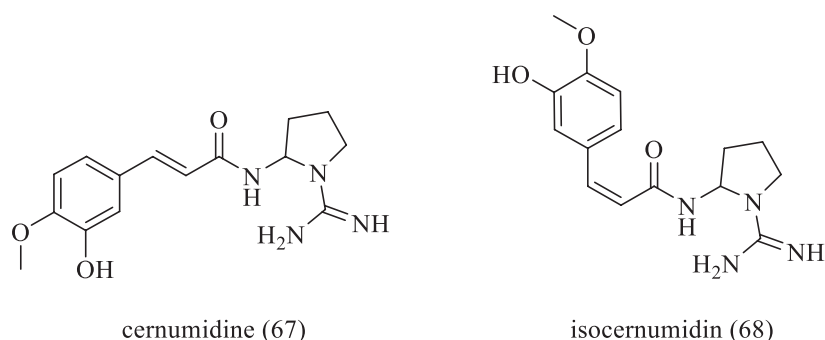


Figure 18 | Structures of cernumidine (67) and isocernumidin (68).

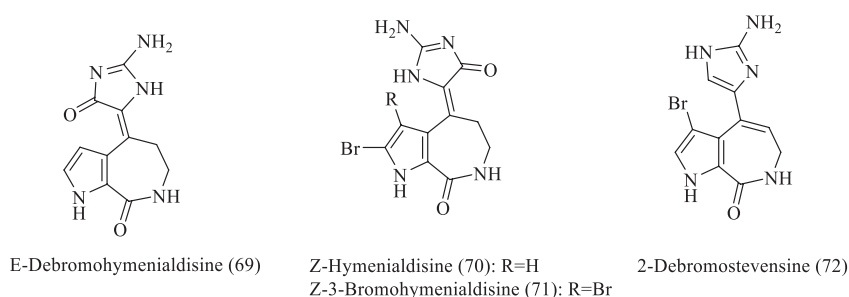


Figure 19 | Structures of hymenialdisines (69–71) and 2-debromostevensine (72).

interactions; therefore, further pharmacological exploration is warranted.

2.3 Bicyclic guanidines

Bicyclic guanidine alkaloids exhibit unique ion channel modulation and antimicrobial activity through their rigid scaffolds and diverse substitution patterns.

2.3.1 Crambescin A. The general skeleton of crambescin A is an oxidized 2-amino pyrimidine ring structure with a gamma-guanidine butyl ester moiety at C-7 and an aliphatic alkyl chain at C-13. As described above, crambescin A contains a bicyclic guanidine core, whereas crambescin C1 (66) is a monocyclic guanidine with two guanidine motifs. Different structures of bioactive homologues of crambescin A are continually being discovered (Figure 22). For crambescin-like guanidine alkaloids, many synthetic analogues of crambescin, such as racemic carboxylic acid of crambescins A–C, have been shown to inhibit voltage-gated sodium channels [85–87].

2.3.2 Monalidine A. Monalidine A (104) (Figure 23), isolated from the demosponge *Monanchora arbuscula* in 2015, is a structurally novel alkaloid scaffold phylogenetically associated with crambescins. Its molecular architecture features an oxidized 2-aminopyrimidine pharmacophore and is devoid of the γ -guanidine butyl

ester moiety [88]. This finding of a novel alkaloid subclass has expanded known marine natural product diversity. The 2-aminopyrimidine moiety may enable unique target interactions, thus suggesting potential for kinase or nucleic acid-targeted therapies.

2.3.3 Monanchoradins. The monanchoradin family of alkaloids, comprising compounds A–C (105–107) (Figure 24), was first isolated in 2016 through the work of El-Demerdash et al. from specimens of the marine sponge *Monanchora* n. sp. collected in French Polynesian waters. These pyrrole-imidazole derivatives are structurally distinguished from their congener monalidine A (105) by the presence of a carboxylic acid functional group at the C-12 position, a modification that significantly alters their physicochemical properties [89]. This finding expands structural diversity within sponge-derived pyrrole-imidazole alkaloids. The C-12 carboxylation suggests tailored biosynthetic adaptations, thus potentially enhancing ecological or pharmacological functionality.

2.3.4 Monanchorins. Phytochemical investigation of the cold-water demosponge *Halichondria panicea* in 2016 led to the isolation of 6-epi-monanchorin (108), a novel bicyclic guanidine alkaloid characterized as a configurational isomer of its biosynthetic congener monanchorin (109) (Figure 25) [90, 91]. Structural analysis has

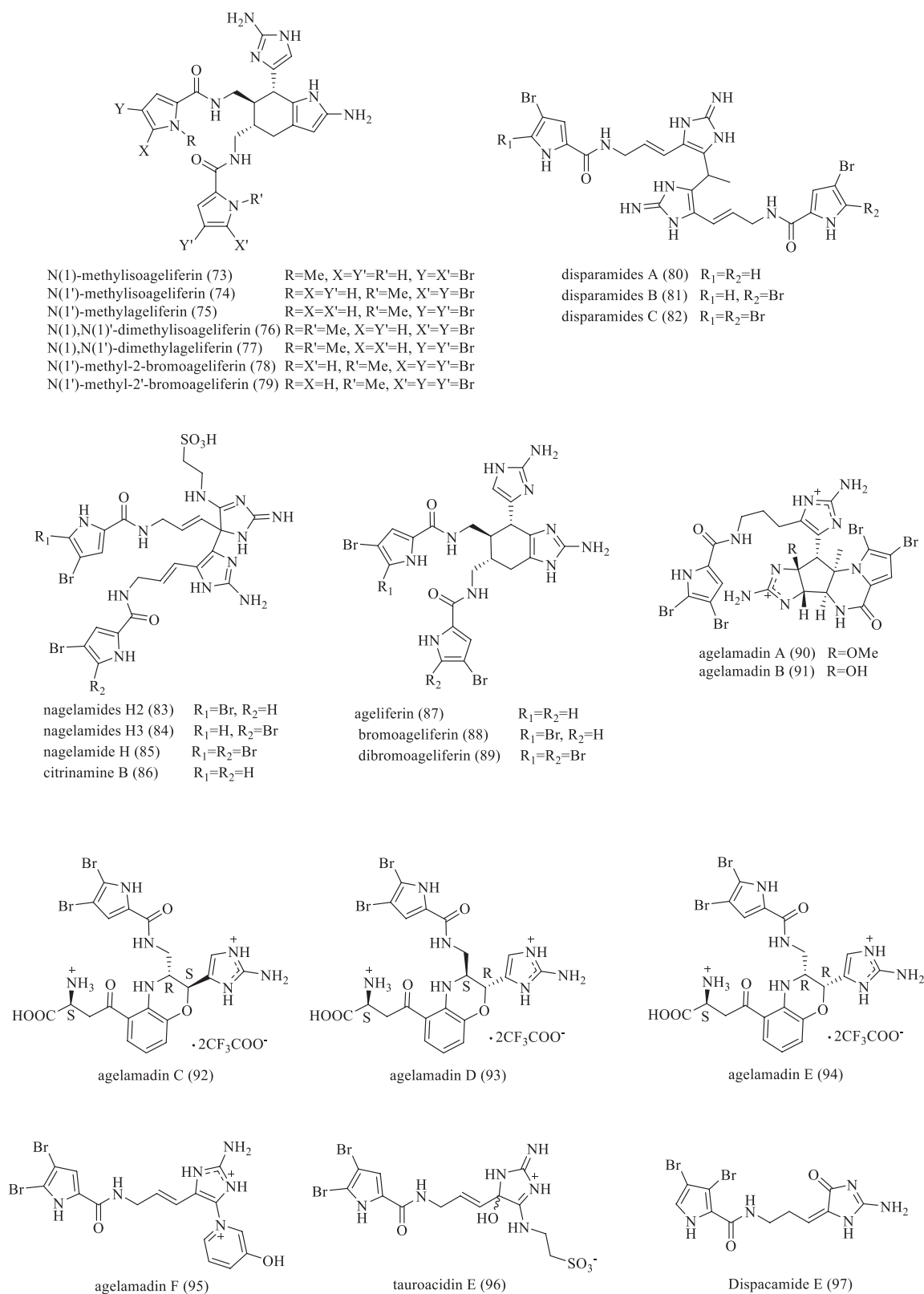


Figure 20 | Structures of bromopyrrole guanine alkaloids (73–97).

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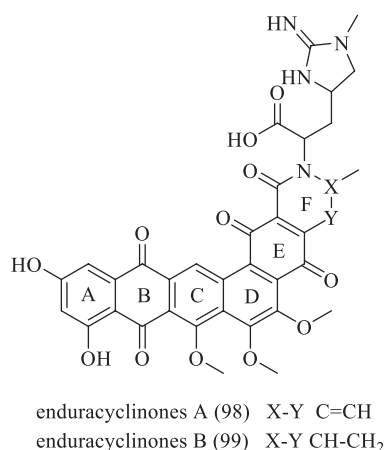
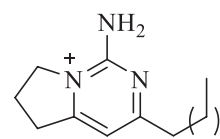


Figure 21 | Structures of enduracyclinones A (98) and B (99).

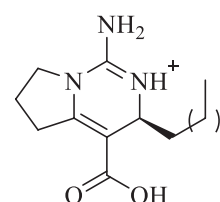
assigned the relative configurations at C-1, C-5, and C-6 in 6-epi-monancherin (**108**) as 1R, 5R, and 6R, whereas monancherin (**109**) has 1R, 5R, and 6S configurations [90]. These findings are consistent with the conclusion of another report that isolated the new compound from the marine polychaete *Chaetopterus variopedatus*. In addition, the distributions of 6-epi-monancherin (**108**) and monancherin (**109**) across body parts of *C. variopedatus* have been described [92].

2.3.5 Urupocidins. Urupocidins A, B, and C (**110–112**) (Figure 26) have been identified in the sponge *Monanchora pulchra*. These compounds feature a novel trisubstituted bicyclic skeletal structure integrating an N-alkyl-N-hydroxyguanidine moiety in one of the side chains [93, 94]. Structural analysis has indicated that urupocidins A (**110**) and C (**112**) contain the same aliphatic chain structures, whereas urupocidin B (**111**) has two fewer carbons. In addition, urupocidins A and B (**110, 111**) share the same bicyclic guanidine portion; however, urupocidin C (**112**) is a dehydro-analogue of these compounds. That is, urupocidin C (**112**) has bicyclic guanidine structures comparable to that in dehydrocrambine A (**113**) (Figure 26) [89, 95]. In 2003, the marine sponge *Monanchora* sp. was the first source



Monalidine A (104)

Figure 23 | Structure of monalidine A (104).

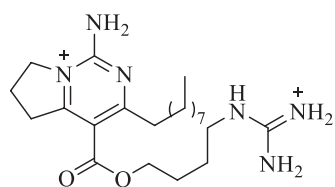


monanchoradin A (105), n=5
monanchoradin B (106), n=6
monanchoradin C (107), n=7

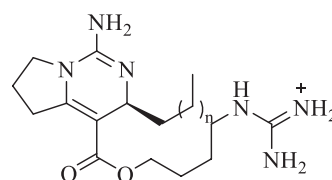
Figure 24 | Structures of monanchoradins A–C (105–107).

of isolation of dehydrocrambine A (**113**). In vitro, this substance exhibits weak inhibition of HIV-1 envelope-mediated fusion, with an IC₅₀ of approximately 35 mM [95].

2.3.6 Massinidine. Massinidine (**114**) (Figure 27), a bicyclic guanidine alkaloid with antiparasitic activity first isolated from the Gram-negative bacterium *Massilia* sp. in 2022, has a novel scaffold originating from L-phenylalanine, acetate, and L-arginine. The genes *mssA-D*, which facilitate the formation of massinidine (**114**), have been identified and validated through heterologous expression in *Myxococcus xanthus*. In addition, 8-amino-7-oxononanoate synthases and ornithine cyclodeaminases have been demonstrated to be involved in its biosynthesis [96]. This first report of a guanidine alkaloid biosynthetic pathway integrating polyketide and amino acid metabolisms highlights *Massilia*



dehydrocrambescine A2 418 (100)



(-)-crambescine A2 392 (101), n=5
(-)-crambescine A2 406 (102), n=6
(-)-crambescine A2 420 (103), n=7

Figure 22 | Structures of dehydrocrambescine A2 418 (100) and (-)-crambescins A2 392, 406, and 420 (101–103).

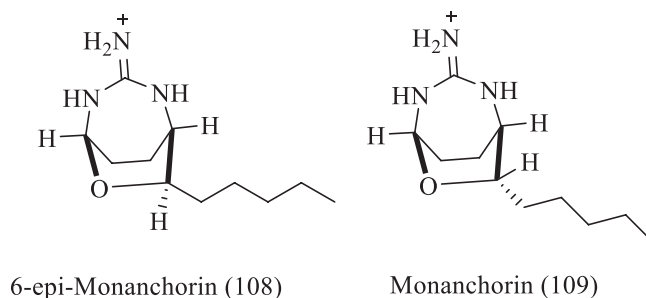


Figure 25 | Structures of 6-epi-monanchorin (108) and monanchorin (109).

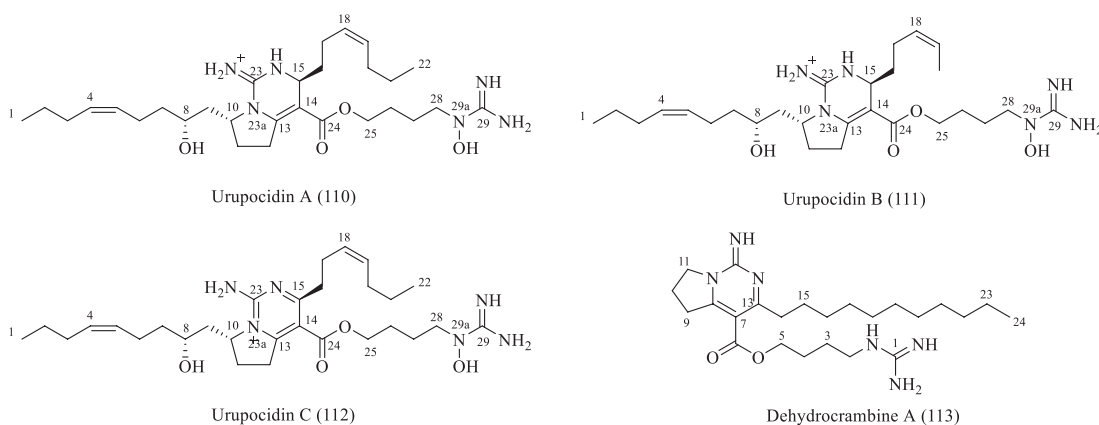


Figure 26 | Structures of urupocidins A–C (110–112) and dehydrocrabamine A (113).

sp. as an underexplored source of bioactive guanidine derivatives.

2.4 Tricyclic guanidines

Tricyclic guanidine alkaloids have shown unique advantages in antiviral and targeted cancer therapies through their rigid polycyclic frameworks and dynamic ester-linked architectures.

2.4.1 Batzelladines. Batzelladine alkaloids isolated from the red Caribbean sponge *Batzella* sp. have long attracted the attention of natural product scientists for their unique structure and broad bioactivity. The unique core skeleton of the batzelladine alkaloids contains at least one tricyclic

pyrrolidine guanidine in either cis- or trans-stereoconfiguration, and the guanidine motifs are connected through an ester linkage. Although two new structures of these alkaloids have been discovered since 2012 (batzelladines O and P (**129**, **130**)), researchers have focused on the synthesis of and bioactivity of these known compounds and their analogues [97, 98]. The chemotaxonomic hallmark of this alkaloid family is their structurally diverse guanidine-bearing side chains, as exemplified by the polycyclic architectures of batzelladine D and K (**118**, **125**), which exhibit distinct annulation patterns and stereochemical configurations that govern their molecular complexity. In 1995, the first compounds with a batzelladine skeleton were discovered from a *Batzella* sp. marine sponge by Patil and co-workers and named batzelladines A–E (**115–119**) (Figure 28). Batzelladines A and B (**115**, **116**) have potential AIDS inhibition ability and were the first natural products found to inhibit the binding of HIVgp-120 to CD4 [99]. These compounds' significant antiviral activity might be due to the three guanidine motifs in the structure. Two years later, four new members with the same skeleton, batzelladines F–I (**120–123**) (Figures 28, 29), from a Jamaican sponge of the genus *Batzella*, were reported by the same team [100]. In addition, batzelladine J (**124**) and batzelladines K–N (**125–128**) (Figures 29, 30)

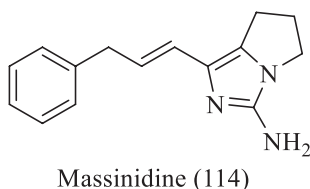


Figure 27 | Structure of massinidine (114).

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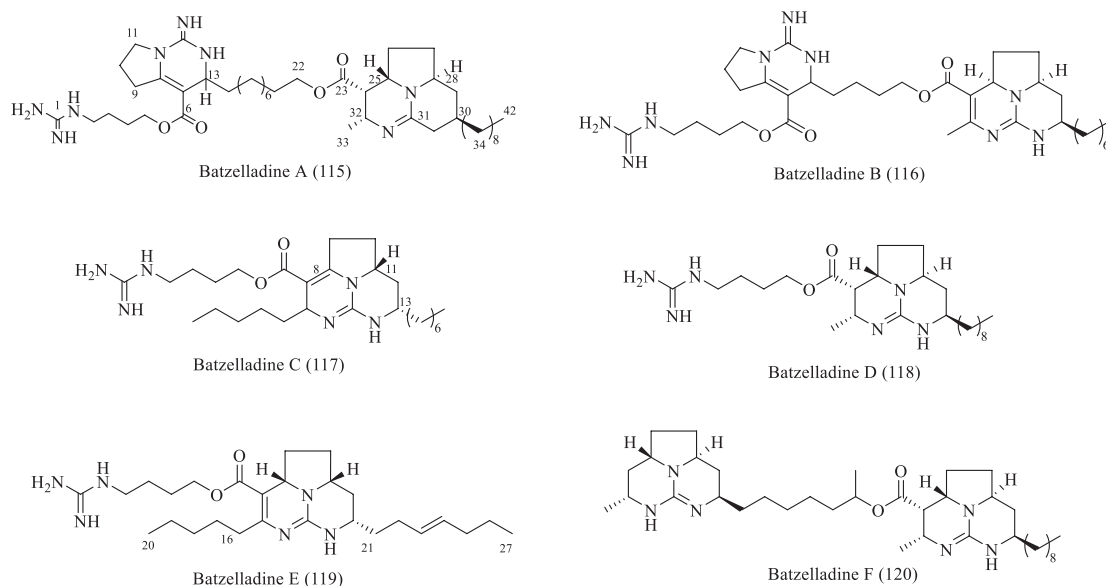


Figure 28 | Structures of batzelladines A–F (115–120).

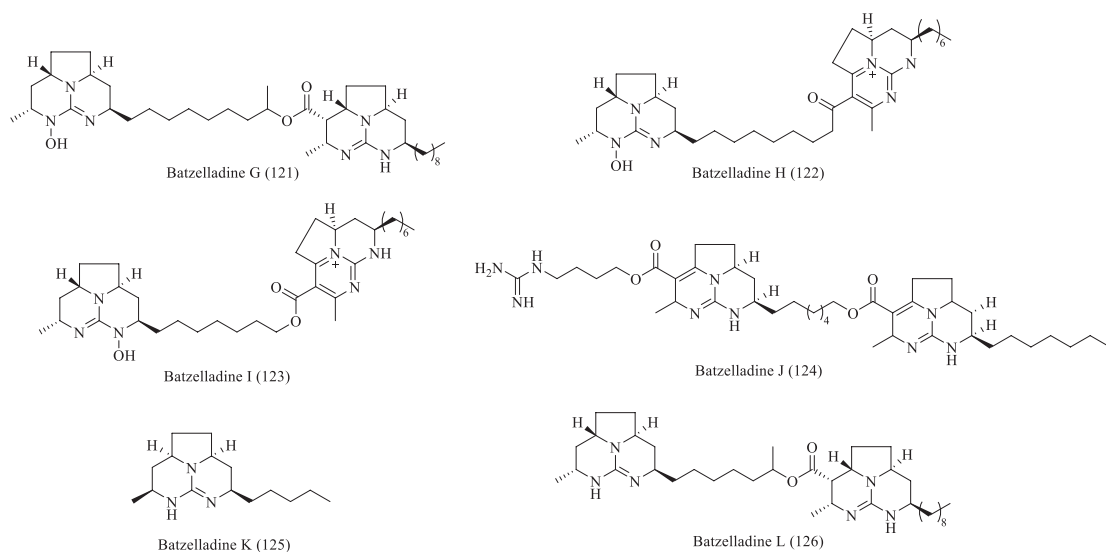


Figure 29 | Structures of batzelladines G–L (121–126).

were isolated from the Caribbean sponge *Monanchora unguifera* in 2005 and 2007, respectively [101, 102]. Most of these compounds have considerable activity against protozoa, HIV-1, *Mycobacterium tuberculosis*, and various cancer cell lines, in addition to numerous strains of pathogenic bacteria, thus exhibiting a significant bioactivity range. The unique core skeleton of the batzelladine alkaloids contains at least one tricyclic guanidine, and the guanidine motifs are connected through an ester linkage.

Importantly, two new batzelladines discovered by Dyshlovoy et al. in 2022, batzelladines O (129) and P (130) (Figure 30), are the only two new structures discovered

in the past decade, and have been found to induce apoptosis and autophagy in prostate cancer cells. This investigation provided the first mechanistic delineation of batzelladine-induced cytotoxicity in human malignancies [103]. The side chain of batzelladine O (129) is identical to that of batzelladine E (119), whereas the location of the double bond in the tricyclic guanidine structure differs. Moreover, batzelladine P (130) possesses two more carbons than batzelladine O (129) in the side chain of C15. Although the exploration of new members of the batzelladine family is challenging, more novel alkaloids with various bioactivities and clinical value are awaited.

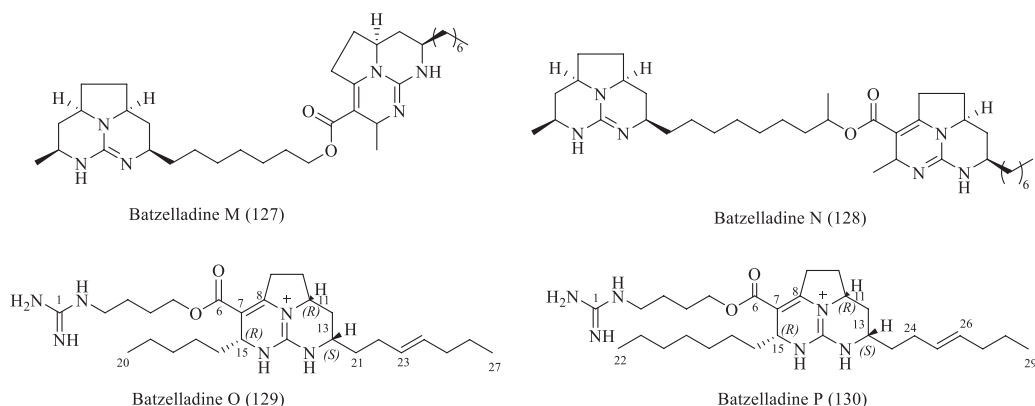


Figure 30 | Structures of batzelladines M–P (127–130).

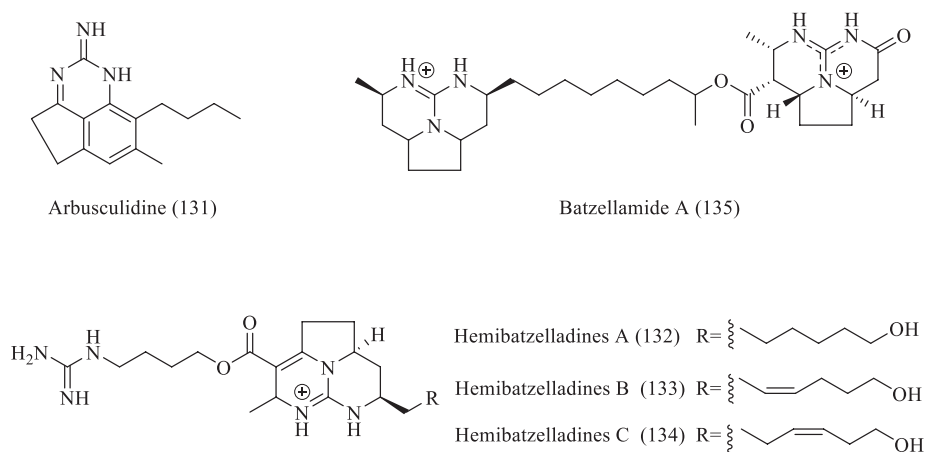


Figure 31 | Structures of arbusculidine (131), hemibatzelladines A–C (132–134), and batzellamide A (135).

Batzelladine J (124) has a unique structure containing two repetitive tricyclic guanidine units. Both batzelladines F and I are active in the dissociation of p56^{lck}-CD4 at

micromolar concentrations and thus exhibit moderate immunosuppressive activity for the treatment of several autoimmune diseases [100]. Batzelladine L (126), a structurally distinct guanidine alkaloid first documented in 2007 from the Caribbean demosponge *Monanchora unguifera*, exhibits broad-spectrum biological activity, including antimicrobial, antiviral, antiprotzoal, and anticancer properties. Notably, batzelladine A (115) signified a pioneering advancement in the field of batzelladine alkaloid research, because it was the first compound of its kind lacking an alkyl chain associated with C-27, thus offering a novel structural framework for further investigation.

In addition, several new tricyclic guanidine alkaloids with similar structures to batzelladines, including arbusculidine (131), hemibatzelladines A–C (132–134), and batzellamide A (135) (Figure 31), were isolated from the marine sponge *Monanchora arbuscul*, and found to have antiparasitic activity [88].

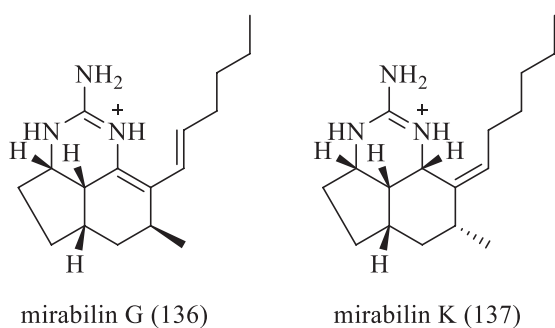


Figure 32 | Structures of mirabilin G and K (136, 137).

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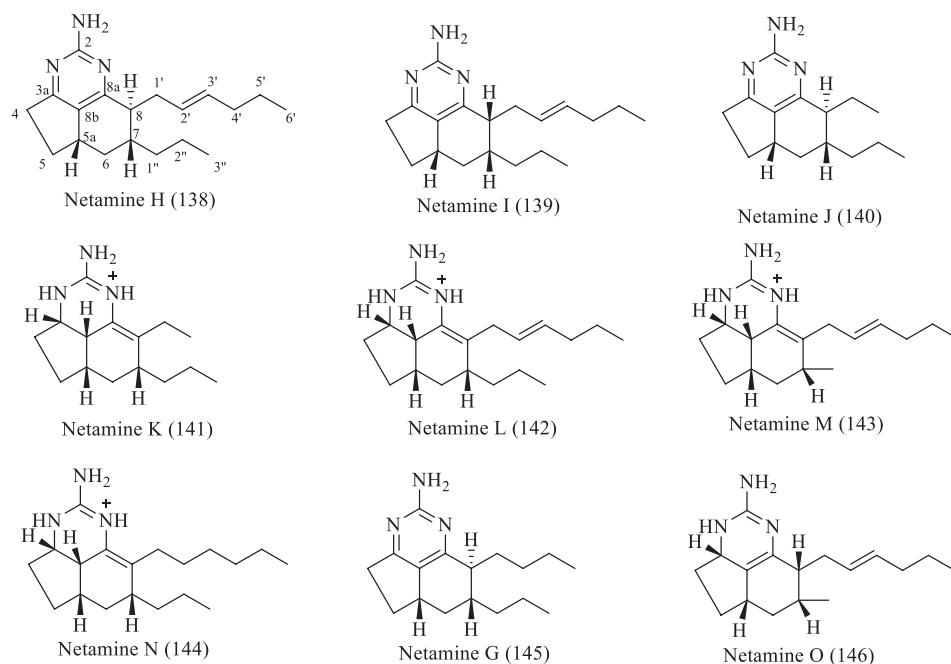


Figure 33 | Structures of netamines H–O (138–146).

2.4.2 Mirabilins. Tricyclic guanidine alkaloids with a skeleton similar to that of ptilocaulin (an early discovered guanidine alkaloid), named mirabilins, including mirabilins A–J, were isolated from southern Australian marine sponges *Arenochalina mirabilis* and *Clathria* species in 1996, 2001, and 2009 [104–106]. These molecules exhibit antifungal and antimicrobial properties, as well as cytotoxicity toward several human cancer cell lines [104–106]. In 2014, a new tricyclic guanidine alkaloid with identical characteristics, named mirabilin K (137) (Figure 32), was extracted from the marine sponge *Acanthella cavernosa* by Grkovic et al. [107]. This structure is the only new structure in the mirabilin family to emerge in the past 10 years. In addition, mirabilin G (136) (Figure 23) was found to have cytotoxic and antiviral properties in 2014 and 2022, respectively.

2.4.3 Netamines. The first compounds from the Madagascar sponge *Biemna laboutei* were discovered in 2006 by Sorek et al. and named netamines [108]. In the past decade, the netamine family has grown, and has been demonstrated to have moderate cytotoxic, anti-malarial, and antiviral properties [109–111]. Netamines H–S (138–150) (Figures 33, 34) isolated from the sponge *Biemna laboutei* after 2014 possess a (5,6,8b)-triazaperhydroacenaphthylene skeleton associated with the ptilocaulin and mirabilin family [109]. Among them, except for netamines K–N (141–144), which possess a C(8) = C(8a) bond, the other compounds (netamines H–J (138–140) and netamines O–S (146–150)) have a C(8a) = C(8b) bond similar to that of netamine E. In addition, netamines H–J (138–140) share a pyrimidine ring system with

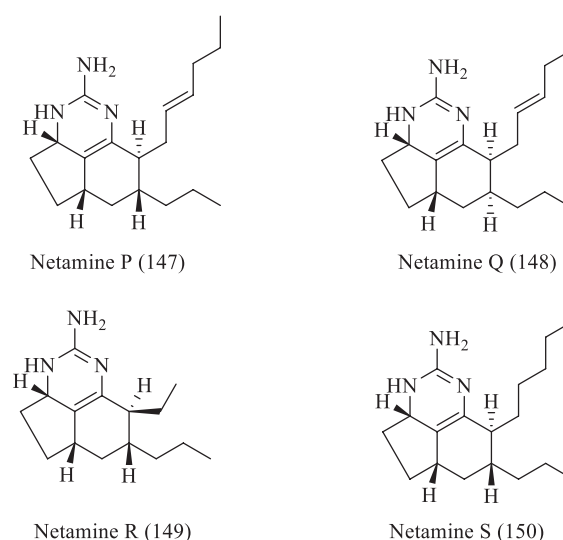
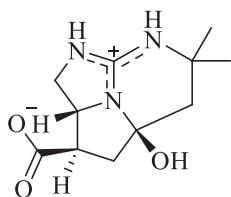


Figure 34 | Structures of netamines P–S (147–150).

netamines F and G. Nonetheless, only approximately one-third of netamines have been found to be biologically active, despite their structural diversity.

2.4.4 Plantadeprate. Plantadeprate A (151) (Figure 35), isolated from the seeds of *Plantago depressa* in 2015 by Zheng et al., possesses a tricyclic ring system [63]. Its putative biogenetic pathway has been proposed to involve generation from plantagoguanidinic acid (63), which has a component that coexists with plantadeprate A (151),



Plantadeprate A (151)

Figure 35 | Structure of plantadeprate A (151).

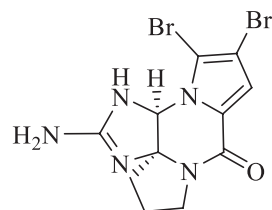
through oxidation and subsequent cyclization [63]. This finding provides mechanistic insights into the oxidative diversification of guanidine alkaloids in *Plantago* species and highlights enzymatic plasticity in plant secondary metabolism for generating structural complexity.

2.5 Tetracyclic guanidines

Tetracyclic guanidine alkaloids exhibit good performance in epigenetic regulation and kinase inhibition through a condensed polycyclic system and halogen substitution strategy.

2.5.1 Eudistidines. The 2015 phytochemical exploration of the Indo-Pacific ascidian *Eudistoma* sp. yielded eudistidines A (152) and B (153) (Figure 36), two architecturally unprecedented heterocyclic alkaloids featuring a fused imidazoloquinoline core. The inhibitory activity of these alkaloids has been demonstrated in relation to the protein-binding domains of p300 (CH1) and HIF-1 α (C-TAD). These compounds contain a novel tetracyclic core [20]. In the next year, eudistidine C (154) (Figure 36) was also isolated from the extract of *Eudistoma* sp. [112]. These findings have expanded the chemical diversity of ascidian-derived alkaloids with therapeutic potential in oncology.

2.5.2 (+)-Dibromohakelline. The brominated pyrrole alkaloid (+)-dibromohakelline (155) (Figure 37) was isolated from the Red Sea demosponge *Stylissa carteri*



(+)–Dibromohakelline (155)

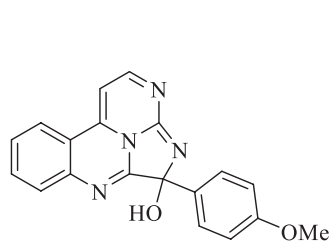
Figure 37 | Structure of (+)-dibromohakelline.

by Hamed et al. While pharmacological evaluations of (+)-dibromohakelline (155) with in vitro kinase inhibition assays have demonstrated no inhibitory effect of the protein kinases in vitro, it showed cytotoxic activities in the L5178Y cell line with inhibition of growth 57.0% at the concentration of 10 μ g/mL [77].

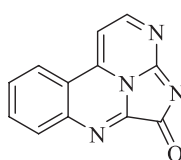
2.6 Pentacyclic guanidines

Pentacyclic guanidine alkaloids have exceptional structure-activity programmability in anticancer and anti-infective applications.

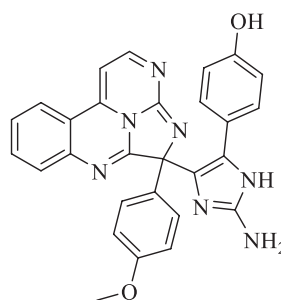
2.6.1 Ptilomycalins. The ptilomycalin alkaloid family is a chemotaxonomic group characterized by a pentacyclic guanidinium core usually linked by a linear ω -hydroxy fatty acid to a spermidine or hydroxyspermidine unit, as in other pentacyclic guanidine families such as cram-bescidins, monanchomycalins, monanchocidins, and normonanchocidins. The most extensively researched member, ptilomycalin A (160) (Figure 38), was first discovered in 1989 and has a broad spectrum of biological activities [113–115]. Remarkably, the new members ptilomycalins E–H (156–159) (Figure 38), isolated from the marine sponge *Monanchora unguiculata* by Campos in 2017, have shown promising cytotoxicity and antimalarial activity [49]. The discovery of ptilomycalins E–H expands the structural and functional diversity of the family and highlights marine sponges as reservoirs of polypharmacological guanidine alkaloids.



Eudistidine A (152)



Eudistidine B (153)



Eudistidine C (154)

Figure 36 | Structures of eudistidine A (152), B (153) and C (154).

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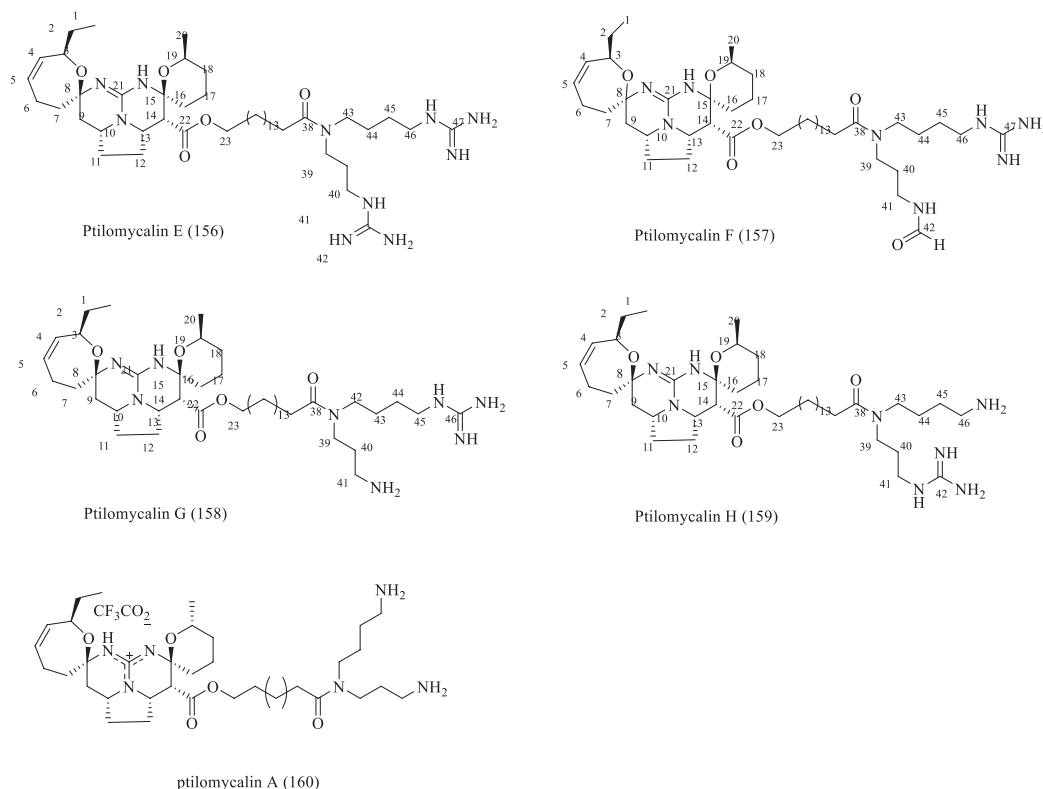


Figure 38 | Structures of ptilomycalins E–H (156–159) and ptilomycalin A (160).

2.6.2 Crambescidins. Crambescidins are a family of compounds bearing strong resemblance to the well-known marine alkaloid ptilomycalin A (**160**). These compounds comprise pentacyclic guanidines bound to a linear omega-hydroxy fatty acid via a connection to spermidine or hydroxyspermidine units [116]. In accordance with the established conventions in the structural characterization of pentacyclic guanidine families, the structural composition of these compounds is traditionally delineated into three discrete structural blocks: a “vessel” part, “anchor” part, and polymethylene chain. Crambescidins differ in their C-8 spiro ring, the presence of a hydroxyl group at C-13, and the nature of the side chain terminus at C-14. In addition, crambescidic acids contain the same pentacyclic core as crambescidins, including three compounds, crambescidic acid (**167**), norcrambescidic acid (**168**), and crambescidic acid-671 (**169**) (Figure 39). The structures of the above types of compounds are shown in Figure 39.

2.6.3 Monanchocidin. Monanchocidin A (**170**) (Figure 40), a structurally unique guanidine alkaloid featuring a previously undescribed pentacyclic framework, was isolated in 2010 from the Northwest Pacific demosponge *Monanchora pulchra*. Its molecular architecture incorporates two novel contiguous spirocyclic systems: a 1-oxa-6-azaspiro[4.5]decane fused to a 1-oxa-7-azaspiro[5.5]undecane motif; this natural product was the first

reported to demonstrate this hybrid spiroannulation pattern [117]. In addition, the same team discovered four new compounds, monanchocidins B–E (**171–174**) (Figure 40), with the same skeleton as monanchocidin A and also isolated from *Monanchora pulchra* [118]. These compounds contain five- or seven-membered rings on the left half of the “vessel” portion of the pentacyclic nucleus, and morpholinone derivatives on the “anchor” portion. In contrast, some compounds bear a polymerized methyl group chain formed from a ω -hydroxy fatty acid, whereas in other compounds, the polymerized methyl group chain is formed from a 3- ω -hydroxy fatty acid. Monanchocidins have been widely studied for their strong antitumor activity.

2.6.4 Monanchomycalins. Three new pentacyclic guanidine alkaloids named monanchomycalins A, B, and C (**175–177**) (Figure 41), isolated from the sponge *Monanchora pulchra*, exhibit cytotoxicity [115, 119], and receptor and enzyme activity. Monanchomycalin C (**177**) is a new homologue of ptilomycalin A (**160**), in which a n-propyl group is attached at position C-19. The C-19 alkylation in monanchomycalin C (**177**) suggests a role of side-chain modifications in tuning bioactivity.

2.6.5 Normonanchocidins. The isolation of new pentacyclic guanidine alkaloids named normonanchocidins

from the Far Eastern marine sponge *Monanchora pulchra* has recently been reported. These compounds, including normonanchocidins A, B, D, G, and H (**178–182**) (Figure 42), bear a new derivative of 1,3-diaminopropane “anchor” part, instead of morpholinone or spermidine types [120]. Notably, unlike the previously identified monanchocidins A and E (**170, 174**) and normonanchocidin A (**178**), the “vessel” and “anchor” portions of normonanchocidin G (**181**) are interconnected by a 2- ω -hydroxy fatty acid rather than a 3- ω -hydroxy fatty acid [121]. These findings introduce a new branch

of pentacyclic guanidine alkaloids with modified anchor domains, thus expanding the biosynthetic diversity and highlighting *M. pulchra* as a prolific source of structurally nuanced guanidine derivatives for pharmacological exploration.

2.6.6 Monanchoxymycalins. Monanchoxymycals are an unconventional class of hybrid structures exhibiting a “vessel” component analogous to that in the monanchomycalins derived from the Far Eastern sponge *M. pulchra*. The “anchor” element, in contrast,

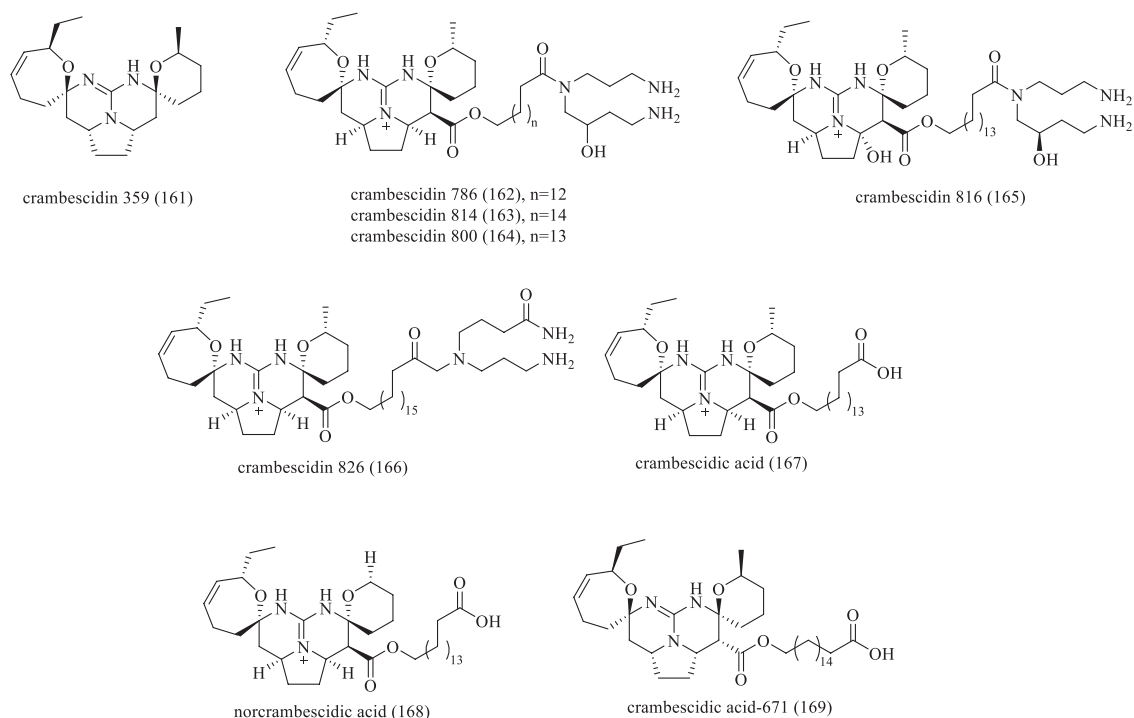


Figure 39 | Structures of crambescidin 359, 786, 814, 800, 816, 826, crambescidic acid, norcrambescidic acid, and crambescidic acid-671 (161–169).

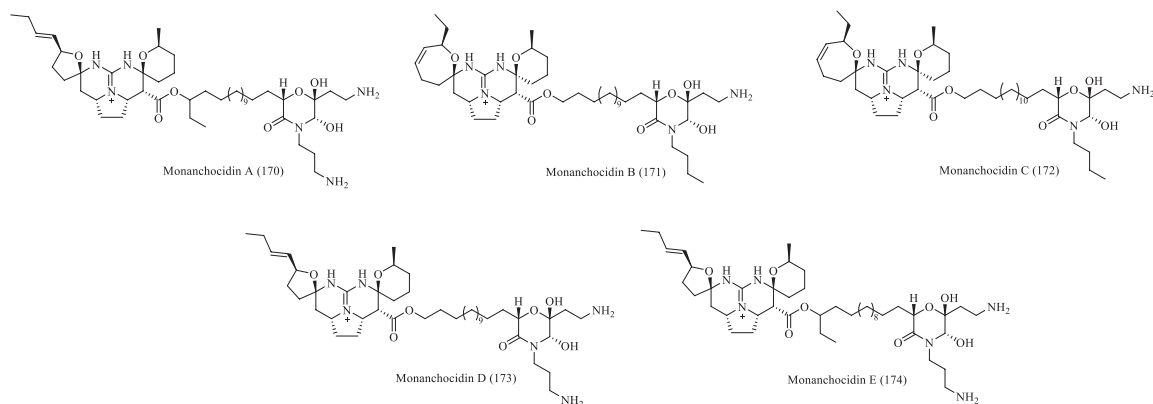


Figure 40 | Structures of monanchocidins A–E (170–174).

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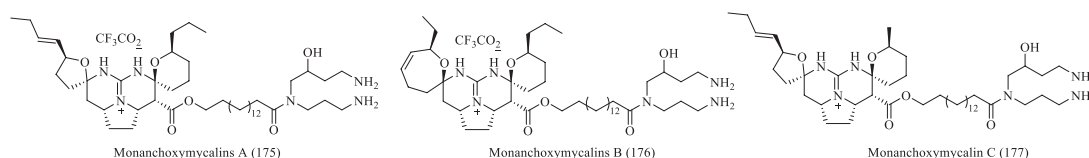


Figure 41 | Structures of monanchoxymycalins A, B, and C (175–177).

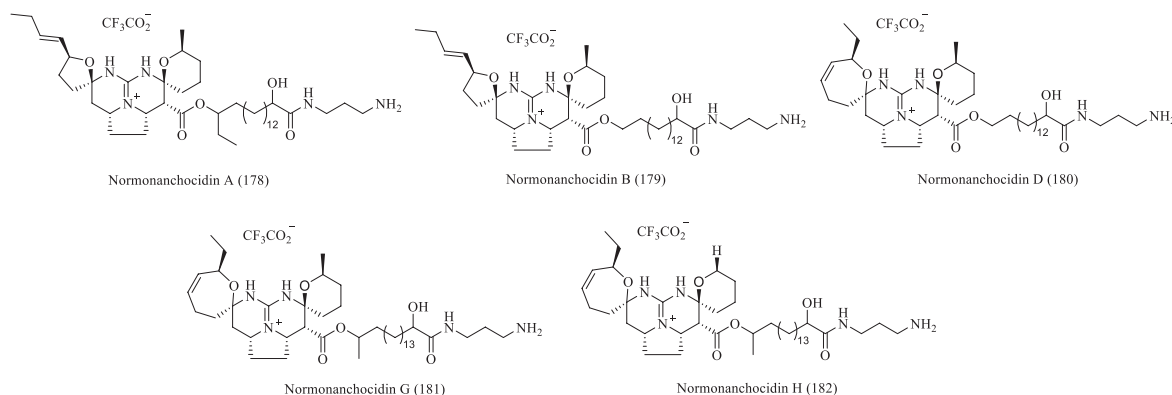


Figure 42 | Structures of normonanchocidin A, B, D, G, and H (178–182).

is analogous to the crambescidins found in tropical sponges [122].

The recent isolation of the new pentacyclic guanidine alkaloids monanchoxymycalin A (**183**) and monanchoxymycalin B (**184**) (Figure 43) from the Far Eastern marine sponge *Monanchora pulchra* importantly advanced knowledge in this field [122]. A new alkaloid found in 2017, monanchoxymycalin C (**185**) (Figure 43), is a structural analogue of monanchoxymycalin B (**184**) with an additional hydroxyl group attached to the C-43, “vessel” part and the hydroxyspermidine “anchor” [123]. Furthermore, this compound can be designated as an isomer of crambescidin 800 (**164**), which is characterized by the presence of a five-membered spiro-ring instead of a seven-membered spiro-ring.

2.6.7 Fromiamycalin. Fromiamycalin (**186**) (Figure 44), a typical pentacyclic guanidine alkaloid isolated from the New Caledonian starfish *Fromia monilis*, has structural similarities to the crambescidins [124]. Previous studies have demonstrated its cytotoxic [124] and anti-HIV [95]

functions. This rare example of a starfish-derived guanidine alkaloid challenges the paradigm that such compounds are exclusive to sponges. Fromiamycalin’s dual bioactivity underscores its potential as a lead for antiviral and anticancer drug discovery.

3. ANTIMICROBIAL ACTIVITY

Recent studies have demonstrated that guanidine alkaloids, isolated from marine sponges, exhibit antibacterial activity against a range of bacterial strains. These alkaloids therefore might serve as novel antibacterial leads, and are currently under investigation and awaiting further application. In this section, these antimicrobial guanidine alkaloids are divided into acyclic, tricyclic, and pentacyclic guanidine. This classification is also used in subsequent sections.

3.1 Acyclic guanidine alkaloids

The marine bromopyrrole alkaloids agelasidines E (**93**) and F (**94**) exhibit targeted antifungal efficacy against

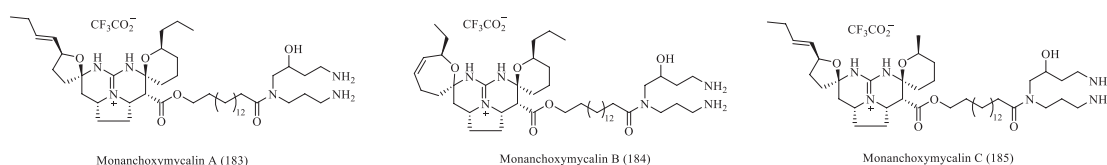


Figure 43 | Structures of monanchoxymycalin A, B, and C (183–185).

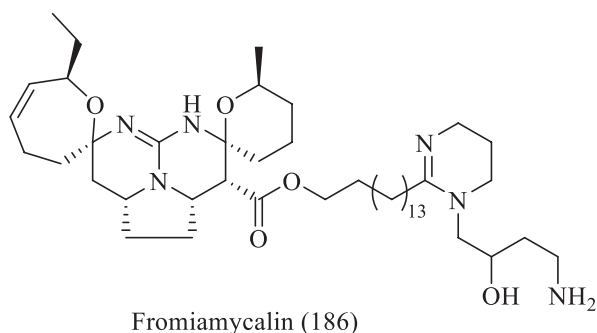


Figure 44 | Structure of fromiamycalin (186).

Candida albicans, but agelasidine F shows superior activity (minimum inhibitory concentration (MIC) = 4.0 µg/mL) [21]. Agelasidine G (95) has demonstrated broad-spectrum bacteriostatic effects at 25 µg/disk, showing uniform 3.0 mm inhibition zones against both Gram-positive (*Bacillus subtilis* ATCC 6633 and *Staphylococcus aureus* ATCC 25923) and Gram-negative (*Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 13883, and *Salmonella typhimurium* ATCC 14028) pathogens in Mueller-Hinton agar assays [22].

Evaluation of the antibacterial activity of galegine (12) and pterogynidine (14) has indicated excellent activity against various strains of *Staphylococcus aureus*, with MIC values of 4 µg/mL. According to experimental findings, the length of the side chain, in conjunction with the substitution pattern within the guanidine core, appears to be critical in determining the degree of antibacterial activity. With increasing side chain length, the electron transport ability of nitrogen decreases. In addition, the presence of substituent groups at nitrogen atoms within the guanidine core has been suggested to influence the reactivity and binding properties of these molecules. Moreover, the side chains modulate both lipid affinity and cellular bioavailability. Therefore, increasing the size or number of side chains has been shown to enhance membrane permeability but might concomitantly diminish aqueous solubility, thereby decreasing activity [35].

The antimicrobial activity of zillamycin (11) against a selection of Gram-positive bacteria has been reported, with an MIC value of 12.5 µM. In contrast, no activity has been observed against the yeast *Candida albicans* and the Gram-negative bacterium *Pseudomonas aeruginosa* at concentrations below 50 µM. The intracellular accumulation and distribution of compounds are regulated by their potency and specific protein targets, as well as the lipophilic properties of the substances [29].

Kishimoto et al. have successfully isolated chlorocatechelin A (32), a high-affinity siderophore with remarkable antimicrobial properties. Experimental data have revealed MICs of 128 µg/mL against *Staphylococcus aureus* FDA 209P, and 32 µg/mL against both *Pasteurella*

piscicida clinical isolates and *Mannheimia hemolytica* N811 BBP 0101; comparable activity has also been observed against *Escherichia coli* K-12. Mechanistic studies have indicated that this siderophore exerts antimicrobial effects through iron sequestration, mirroring the iron-limiting strategy of deferroxamine B. The observed concentration-dependent antimicrobial efficacy suggests potential therapeutic applications in combating multidrug-resistant pathogens, particularly through disruption of microbial iron homeostasis [125].

Drarmacidin G (39) exhibits antimicrobial activity against *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, and *Mycobacterium tuberculosis* CDC1551, with MICs of 1, 1, and 21.0 µM, respectively [59].

3.2 Monocyclic guanidine alkaloids

The marine-derived pyrrole-imidazole alkaloids ageliferin (87), bromogeliferin (88), and dibromoageliferin (89) have broad-spectrum antibacterial efficacy against multidrug-resistant Gram-positive and Gram-negative pathogens. Notably, dibromoageliferin (89) exhibits superior antimicrobial potency, with MIC values of 12.5 µM against *Escherichia coli*, 6.2 µM against *Enterococcus faecalis*, and 6.2 µM against *Staphylococcus aureus*, thereby suggesting structure-activity relationships influenced by bromination patterns. Notably, dibromoageliferin's enhanced activity against vancomycin-resistant enterococci and methicillin-resistant *S. aureus* strains highlights its therapeutic potential for treating infections recalcitrant to conventional β-lactam antibiotics [79].

The antimicrobial activity of agelamadins A (90) and B (91) has been evaluated against a range of bacterial and fungal strains. The MIC values for agelamadin A (90) and B (91) against *Bacillus subtilis* (16 µg/mL each) and *Micrococcus luteus* (4.0 µg/mL and 8.0 µg/mL, respectively) have been determined. Additionally, agelamadins A (90) and B (91) have substantial activity against *Cryptococcus neoformans*, with IC₅₀ values of 8.0 µg/mL and 4.0 µg/mL, respectively [80]. Agelamadins C (92) and E (94) have modest inhibitory effects against *Cryptococcus neoformans*, with an IC₅₀ of 32 µg/mL [82].

Enduracyclinone A (98) has potent narrow-spectrum antibacterial activity against Gram-positive pathogens, exhibiting MIC values of 0.0005–0.03 µg/mL against *Staphylococcus* spp., 0.25–0.5 µg/mL against *Streptococcus* sp., 2–4 µg/mL against enterococci, 2 µg/mL against *Clostridium difficile*, and 0.25 µg/mL against *Propionibacterium acnes*. This activity profile suggests selective membrane interaction mechanisms in Gram-positive organisms. However, it has no activity against *Mycobacterium smegmatis*, Gram-negative bacteria, or *Candida albicans* [84]. This marked selectivity might originate from structural features preventing penetration through mycobacterial cell walls or Gram-negative outer membranes. These compounds' noteworthy biological activity might be attributable to the presence of an aromatic polyketide containing the uncommon

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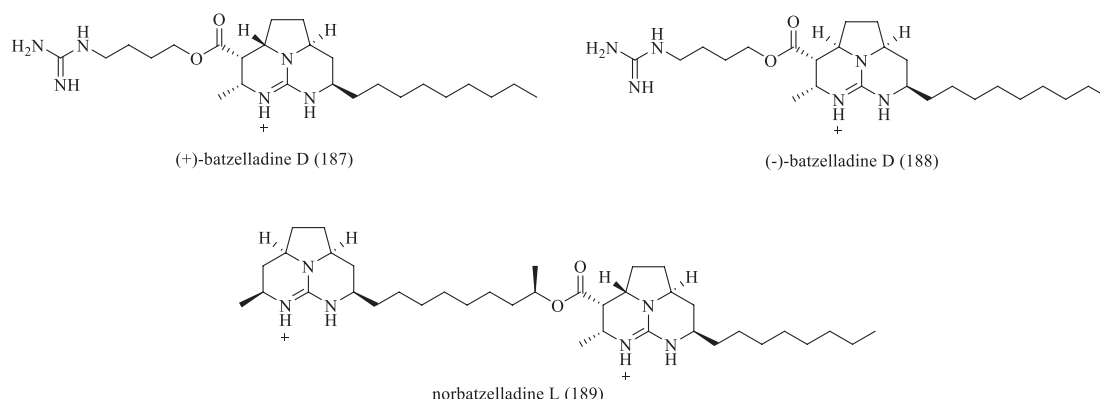


Figure 45 | Structures of (+)-batzelladine D (187), (-)-batzelladine D (188), and norbatzelladine L (189).

amino acid enduracididine, integrated within a hexacyclic framework.

3.3 Tricyclic guanidine alkaloids

Batzelladine D (**118**) has the potential to reverse the fluconazole resistance phenotype mediated by the Pdr5p protein, a resistance transporter characterized in *Saccharomyces cerevisiae* [97]. Otherwise, this compound has been found to chemosensitize a Pdr5p overexpressing strain by interacting with fluconazole, with MIC values of 25 μ M alone and 8.5 μ M synergistically [97]. The intricate structural composition of these scaffolds, in conjunction with their bioactivity, has prompted substantial interest among the synthetic community. Lin et al. prepared (+)- and (-)-batzelladine D (**187**, **188**) (Figure 45) and established a platform for the synthesis of stereochemical isomers of the batzelladine alkaloid core in 2020 [98]. Stereocontrolled synthesis has been used to assess the enhanced antimicrobial properties of batzelladine D (**118**) in the treatment of *Staphylococcus aureus*, *Erwinella faecum*, *Pseudomonas aeruginosa*, and *Aphanizomenon baumannii* infections. This analysis underscores the therapeutic promise of natural stereoisomers [98]. Furthermore, batzelladine L (**126**), a bis-guanidine alkaloid from marine sponges, has demonstrated concentration-dependent fungicidal action against aflatoxin-producing *Aspergillus flavus* strains, with MIC values of 1.9–7.8 μ g/mL and corresponding MFC ranges of 3.9–15.6 μ g/mL [126]. Another alkaloid bearing the same core named norbatzelladine L (**189**) (Figure 45) also exerts substantial effects on the fluconazole resistance of *S. cerevisiae*, through interaction with fluconazole, with MIC values of 6.25 μ M alone and 2.25 μ M synergistically [97].

3.4 Pentacyclic guanidine alkaloids

A novel guanidine alkaloid, crambescidic acid-671 (**169**), has been identified in conjunction with the known alkaloids crambescidin 826 (**166**), crambescidin 800 (**164**), formiamycalin (**6**), and crambescidin 359 (**161**).

These compounds, isolated from the marine sponges *Monanchora clathrata* and *Monanchora unguiculata* by Raslan et al. in 2022, display moderate antibacterial activity and antifungal activity [127]. In fact, crambescidic acid-671 (**169**) and crambescidin 826 (**166**) have the following essential pharmacophoric features of CBSIs (tubulin inhibitors that act as colchicine binding site inhibitors): three hydrogen bond acceptors, two hydrophobic centers, and one planar group. Therefore, they are believed to be tubulin inhibitors that exhibit antimicrobial activity. Crambescidic acid-671 (**169**) has shown antifungal activity against three strains of *Cryptococcus*: *Cr. neoformans* 90113, with an MIC of 0.16 μ g/mL; *Cr. neoformans* H99, with an MIC of 0.16 μ g/mL; and *Cr. gattii*, with an MIC of 0.16 μ g/mL comparable to the positive control amphotericin B. In addition, different degrees of antibacterial activity have been observed against MASA, *E. coli*, *P. aeruginosa*, and *K. pneumoniae*, with MIC values of 5–20 μ g/mL [127]. To date, no other biological activities of crambescidic acid-671 (**169**) have been reported.

Crambescidin 826 (**166**), initially isolated from the marine sponge *Monanchora sp.* in 2003 [95], has antiviral activity [95, 128]. Crambescidin 800 (**164**), first isolated in 1995 [116], has a wide range of biological activities, including antimalarial, cytotoxic, and anti-cancer functions. This compound has notable activity against a range of bacterial pathogens, with MICs of 2 μ g/mL against *Acinetobacter baumannii*, 1 μ g/mL against *Klebsiella pneumoniae*, and 1 μ g/mL against *Pseudomonas aeruginosa* [129]. In addition, formiamycalin (**6**) and crambescidin 359 (**161**) were reported in 1995 [124] and 2000 [130], respectively. These pentacyclic guanidine alkaloids are a class of molecules with great development value among marine alkaloids. According to Raslan et al., compounds 4–6 show excellent antifungal activity against *Cr. neoformans* 90113, with MIC values of 0.25, 0.50, and 1.00 μ g/mL, respectively; *Cr. neoformans* H99, with MIC values of 0.25, 0.25, and 1.00 μ g/mL, respectively; and *Cr. gattii*, with

MIC values of 0.25, 0.25, and 1.00 $\mu\text{g/mL}$, respectively. However, ptilomycalin A (**160**) has relatively poor antibacterial activity [127]. Their other biological activities are indicated in subsequent sections.

Recent studies have revealed that marine-derived guanidine alkaloids exhibit various antimicrobial properties, according to diverse structural characteristics. Acyclic guanidine alkaloids exhibited a limited range of activity; increasing side chain length enhances membrane penetration, but excessive lengthening decreases water solubility and leads to loss of activity. Many guanidine alkaloids have considerable antimicrobial activity, but among them, pentacyclic guanidines, particularly crambescidins, have notable activity, possibly arising from their unique structure comprising a "vessel" part, "anchor" part, and polymethylene chain. In addition, no bicyclic or tetracyclic guanidine alkaloids exhibit antimicrobial activity. The presence or absence of a ring in guanidine alkaloids might also influence their antimicrobial activity. Bicyclic and tetracyclic analogs show no activity, whereas pentacyclic derivatives are the most promising structural type, because of enhanced target binding specificity arising from their polycyclic rigidity.

4. ANTIPARASITIC ACTIVITY

4.1 Monocyclic guanidine

The natural guanidine-based alkaloid alchorhedine (**65**) has antiprotozoal activity against *Trypanosoma cruzi*, with an IC_{50} of 93 $\mu\text{g/mL}$ (443 μM) against trypomastigotes and 27 $\mu\text{g/mL}$ (129 μM) against intracellular amastigotes (the most common form of the parasite) [70]. This compound shows activity similar to or even more effective than that of benznidazole, a standard drug for treating *T. cruzi* [70]. In vitro, this compound has been found to selectively eliminate parasites inside macrophages without influencing the morphology of the host cells [70]. In addition, its unique 3-amino-1,2,4-oxadiazine scaffold has favorable physicochemical properties (pK_a and $\log D$) and hepatic stability, thus showing promise for drug development [131]. The total synthesis of alchorhedine (**65**) was reported by Tang et al. in 2020, by using readily available N-Boc-amino acids as starting materials [131]. Nonetheless, the spectral differences observed between the synthetic alchorhedine (**65**) and the naturally occurring alchorhedine (**65**) isolated from the leaves of *A. glandulosa* have indicated a discrepancy in their proposed structures. Specifically, spectral evidence has suggested that the scaffold of alchorhedine (**65**) is not consistent with the previously reported scaffold but instead aligns with the imidazolidine-1-ol scaffold [131]. The total synthesis of the latter structure is underway to confirm this hypothesis [131]. In addition, galegine (**12**), pterogynine (**13**), and particularly pterogynidine (**14**) have shown excellent nematostatic activity by binding acetylcholinesterase, and therefore have promise in controlling the plant-parasitic nematode *Meloidogyne incognita* [132].

4.2 Bicyclic guanidine

The bicyclic guanidine alkaloid monalidine A (**104**) is active against *T. cruzi* trypomastigotes, with an IC_{50} of 8 μM , and *L. infantum* promastigotes, with an IC_{50} of 2 μM . However, no activity against *L. infantum* intracellular amastigotes has been observed [88]. These results might potentially be ascribed to one or more of the following possibilities: first, the lack of specific receptors on the part of the macrophages; second, the metabolism of the macrophages of the parasites; or third, the disparate metabolic processes of the *L. infantum* amastigotes [133]. In addition, the bicyclic guanidine massinidine (**114**) has moderate growth inhibitory activity ($\text{IC}_{50} = 10.1 \mu\text{M}$) against the main causal agent of malaria, *Plasmodium falciparum* (NF54 strain) [96].

4.3 Tricyclic guanidine

Tricyclic guanidine alkaloids have been demonstrated to have antiparasitic activity. For example, batzelladine L (**126**) and norbatzelladine L (**189**) isolated from the genus *Monanchora* have antiparasitic activity against *Leishmania infantum* and *T. cruzi* parasites through oxidative stress, with IC_{50} ranging from 1 to 7 $\mu\text{g/mL}$ [134]. The compounds are active against *T. cruzi* trypomastigotes, with IC_{50} values of 2 and 7 μM , respectively, and *L. infantum* promastigotes, with IC_{50} values of 2 and 2 μM , respectively [88]. Furthermore, the identified alkaloid batzelladine F (**120**) exhibits significant activity against *Trypanosoma cruzi* trypomastigotes, with an IC_{50} of 5 μM , and *Leishmania infantum* promastigotes, with an IC_{50} of 4 μM . In contrast, batzelladine D (**118**) has shown minimal activity against *T. cruzi* trypomastigotes at a concentration of 64 μM and the most pronounced activity against *L. infantum* promastigotes at a concentration of 2 μM [88]. Moreover, the other four guanidine alkaloids, batzelladine A (**115**), batzelladine J (**124**), arbusculidine (**131**), hemibatzelladine A–C (**132–134**), and batzellamide A (**135**), isolated by the same team have no antiparasitic activity [88]. Furthermore, guanidine compounds have potent antileishmanial activity, both in isolation as natural products and in the form of synthetic derivatives. The synthetic analogues of batzelladine K (**125**) significantly influence the bioenergetic metabolism of *Leishmania*, thereby leading to the selective elimination of parasites through a host-independent mechanism [135, 136]. In addition, batzelladine K (**125**) is expected to develop a new model of anti-malarial compounds, on the basis of its inhibition of the *Plasmodium falciparum* lactate dehydrogenase enzyme [137].

In addition, netamines K (**141**), O, P, and Q (**96–98**), with IC_{50} values of 2.4, 16.99, 32.62, and 8.37 μM , respectively, have shown significant antimalarial activity against *Plasmodium falciparum* [109, 110]. Unfortunately, the antimalarial activity of other netamine family members has been less than satisfactory; consequently, specific structural features might critically

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influence their bioactivity. Further exploration is needed to clarify the underlying mechanisms of action.

4.4 Tetracyclic guanidines

The inhibitory activity of eudistidines A (**152**) and C (**154**) against chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of the *Plasmodium falciparum* parasite has been evaluated. Eudistidine A (**152**) exhibits significant inhibitory activity, with IC_{50} values of 1.4 and 1.1 μ M [112].

4.5 Pentacyclic guanidine

Ptilomycalins E and F (**156**, **157**), as well as the combination of ptilomycalins G and H (**158**, **159**), display significant antimalarial activity, with IC_{50} values of 0.35, 0.23, and 0.46 μ M, respectively [49]. These encouraging findings indicate that these compounds might be effective against the *Plasmodium falciparum* parasite, which causes malaria. Fromiamycalin (**186**) has shown excellent antimalarial activity, with an IC_{50} of 0.24 μ M [49]. Moreover, this compound is a moderately potent anthelmintic against *Haemonchus contortus* [138]. Fromiamycalin (**186**) inhibits fourth-stage larval development (IC_{50} = 26.6 μ M) and motility (IC_{50} = 39.4 μ M), but has relatively low efficacy in inhibiting the motility of exsheathed third-stage larvae (IC_{50} $\geq$ 100 μ M) [138].

Guanidine alkaloids exhibit structure-dependent antiparasitic activity through mechanisms such as target enzyme inhibition and metabolic interference. Tricyclic and larger guanidine alkaloids have shown more broad-spectrum and efficient inhibitory effects on parasites than smaller guanidine alkaloids are significantly more active against *Plasmodium* than lower cyclic guanidine alkaloids.

5. ANTITUMOR AND CYTOTOXIC ACTIVITY

5.1 Acyclic guanidine

The acyclic guanidine alkaloid nitensidine A (**6**) from *Pterogyne nitens*, along with galegine (**12**), pterogynine (**13**), and pterogynidine (**14**), have been found to have significant cytotoxicity in the past 10 years. For example, nitensidine A (**6**) decreases the number of multinucleated osteoclasts in a concentration-dependent manner, with an IC_{50} of 0.93 μ M; this compound has been found to be the most effective among the four guanidine alkaloids from the same plant and to be approximately threefold more effective than pterogynine (**13**) (IC_{50} = 2.7 μ M) [37]. In contrast, galegine (**12**), with a single isoprenyl moiety amino nitrogen, and pterogynidine (**14**), with two isoprenyl moieties, exert no cytotoxic effects on osteoclasts [37]. In addition, nitensidine A (**6**) exhibits approximately 10- to 40-fold higher cytotoxicity against osteoblasts and four cell lines (Caco-2 cells, HepG2 cells, KB3-1 cells, and MCF-7 cells) than against osteoclasts [37]. Meanwhile, compared with multi-drug resistant CCRF-CEM cells, the CEM/ADR5000 human T-cell lymphoblast-like leukemia cell line is resistant to

all four guanidine alkaloids [36]. Except nitensidine A (**6**), galegine (**12**), pterogynine (**13**) and pterogynidine (**14**) were discovered to stimulate the ATPase activity of the human ATP-binding cassette transporter (ABCB1), and nitensidine A (**6**) has been found to be as effective as the control drug verapamil [36]. Moreover, all four guanidine alkaloids are cytotoxic to Flp-In-293/ABCB1 (human cells expressing ABCB1) and Flp-In-293/Mock cells [139]. Flp-In-293/ABCB1 cells exhibit higher resistance to the four guanidine alkaloids than Flp-In-293/Mock cells [139]. Consequently, ABCB1 can be considered a potential mediator of resistance to the cytotoxic guanidine alkaloids through substrate transformation. Among compounds, nitensidine A (**6**) showed the greatest effect [139]. Significantly, replacement of the amino nitrogen atom of nitensidine A (**6**) with sulfur or oxygen substantially decreased anti-osteoclastic activity [37] and stimulation of ABCB1-dependent ATPase activity by nitensidine A (**6**) [36]. The activity of guanidine alkaloids is attributable to the cooperative contributions of three factors—the number, binding site, and degree of polymerization of the isoprenyl moiety of the aforementioned compounds—as well as the imino nitrogen atom, which contributes to the observed activities both alone and synergistically [36, 37, 139].

Another member of nitensidin family, nitensidine B (**7**), exhibits concentration-dependent cytotoxicity against HPV16 immortalized cervical carcinoma lines via apoptosis via activation of caspases 3/7, with a 50% MIC of 40.98 μ M [140]. Differential proteomic analysis has identified several enzymes involved in the glycolysis pathway, including aldolase A, alpha-enolase, pyruvate kinase, and glyceraldehyde-3-phosphate dehydrogenase, as potential therapeutic targets for this compound in cervical cancer [140]. However, more thorough studies are required to more extensively explore the mechanism of action of antitumor activity.

In recent decades, pterogynine (**13**) and pterogynidine (**14**) have been evaluated for cytotoxic activity against cell lines including HL-60 (human myeloblastic leukemia), SF-245 (human glioblastoma) cells, and malignant breast cell lines, but not osteoclast cells [24, 141]. Both compounds have shown varying degrees of cytotoxicity, and have anti-proliferation and pro-apoptosis modes of action. Notably, pterogynidine (**14**) exhibits strong anti-angiogenic action in tumor development through the inhibition of nuclear factor κ B, a transcription factor implicated in angiogenesis. Inhibition of endothelial cell proliferation, as well as invasion and the formation of capillary-like structures, in conjunction with apoptosis induction, have been observed after treatment with this natural product [142]. Thus, these two alkaloids, particularly pterogynidine (**14**), have potential as novel agents for tumor treatment or prevention.

Zillamycin (**11**), a naturally occurring guanidine-based alkaloid derived from the extract of *Streptomyces griseofuscus*, exhibits significant anticancer properties, with an IC_{50} value of 8.81 μ M against HeLa cells. This

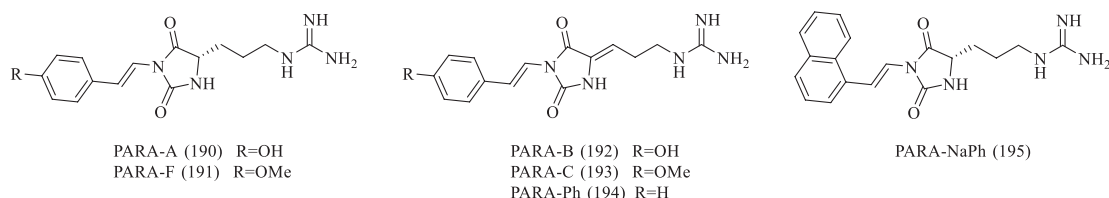


Figure 46 | Structures of parazoanthines (190–195).

finding corroborates the established cytotoxic potential of isoprenyl guanidine compounds [29].

Unguiculins A–C (**18–20**) have demonstrated significant cytotoxic activity against KB cell lines, with IC_{50} values of 0.2, 0.08, and 0.03 μ M, respectively. In addition, unguiculin B (**19**) is cytotoxic to the HCT-116, HL-60, and MRC-5 cell lines, with IC_{50} values of 3.6, 10, and 11.4 μ M, respectively. The two terminal guanidine ends on those compounds contribute to their biological activity. Moreover, the most active homologue, unguiculin C (**20**), has shorter chains, thus indicating that chain type and length play essential roles in the cell targets of action [50].

Beyond its isolation from marine sponge sources, pulchranin A (**15**) has been isolated from an endophytic fungus (*Aspergillus* TRL1) and has shown promising in vitro cytotoxic effects against breast (MCF-7), liver (Hep-G2), and colorectal (HCT) cell lines, with IC_{50} values of 63, 80, and 91 mg/mL, respectively [143]. Additionally, this compound inhibits three cyclin-dependent kinases, CDK1, CDK2, and CDK4, in MCF-7 cells, with IC_{50} values of 9.82 μ g/mL, 15.6 μ g/mL, and 2.7 μ g/mL, respectively [143]. Likewise, pulchranin A (**15**) induces activation of JNK1/2 (but not ERK1/2), and inhibits the EGF-induced neoplastic transformation of JB6 P^{+} Cl41 cells [114].

Actinofide (**30**) and dotofide (**31**), structurally distinct diacylguanidine derivatives, have shown selective cytotoxic effects in standardized MTT viability assays across multiple cancer models. Actinofide (**30**) exhibits potent anti-glioma activity, with GI_{50} values of 8.3 ± 1.8 μ M and 7.5 ± 3.1 μ M against Hs683 glioblastoma cells in replicate experiments, thereby suggesting consistent dose-dependent growth inhibition. Comparatively, dotofide (**31**) has moderate anti-melanoma efficacy, with a GI_{50} of 18.9 μ M against B16F10 murine melanoma cells, thus potentially indicating tissue-type specificity in its mechanism of action [53]. The differential activity profiles between these structural analogs highlight the importance of acyl group modifications in optimizing anticancer pharmacophores.

The inhibitory activity of dragmacidin G (**39**) and dragmacidin H (**40**) has been examined against a range of human pancreatic cancer cell lines, including PANC-1, MIA PaCa-2, BxPC-3, ASPC-1, and HeLa. The IC_{50} values were measured after 72 hours. Dragmacidin G exhibits inhibitory effects against PANC-1, MIA PaCa-2, and BxPC-3, with IC_{50} values of 18, 26, and 14 μ M,

respectively. Additionally, dragmacidin G shows significant activity against HeLa cells, with an IC_{50} of 4.6 μ M. Similarly, dragmacidin H demonstrates anti-proliferative properties toward HeLa cells, with an IC_{50} value of 4.6 μ M [59, 60].

Parazoanthines (**190–195**) (Figure 46) (also known as PARA), have been isolated from the Mediterranean sea anemone *Parazoanthus axinellae* and classified as hydantoin alkaloids. Parazoanthines (**190–195**) do not affect the viability of GH4C1 cells at a concentration of 1 μ M but inhibit CXCL12-induced GH4C1 cell migration as CXCR4 antagonists [144]. Despite their intriguing biological properties, their functional mechanisms and practical implications warrant comprehensive investigation.

Phidianidines A (**196**) and B (**197**), two indole alkaloids, contain an uncommon 1,2,4-oxadiazole ring in conjunction with the indole system. These compounds were identified as constituents within the specimen of the marine opisthobranch mollusk *Phidiana militaris* (Figure 47) [145]. Phidianidine A (**196**) also shows negligible cell cytotoxicity toward GH4C1 cells, and inhibits cell proliferation caused by CXCL12 serving as CXCR4 antagonists [146]. This dual functionality suggests selective targeting of chemokine receptor signaling pathways without general cellular toxicity. The unique indole-imidazoline scaffold of phidianidine A provides structural insights for developing non-peptidic CXCR4 modulators, thus potentially overcoming limitations of current therapeutic antibodies in crossing the blood-brain barrier.

5.2 Monocyclic guanidine

Celosiadines A and B (**41, 42**) exhibit excellent androgen receptor binding affinity in vitro and are cytotoxic to androgen receptor-dependent but not androgen

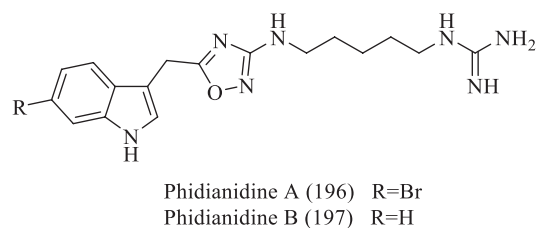


Figure 47 | Structures of phidianidines A (196) and B (197).

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receptor-independent human prostate cancer cells [61]. However, further molecular biology research is required to clarify whether the cytotoxic effects of celosiadines are associated with their modulation of the androgen receptor, although these compounds appear to have enhanced sensitivity to androgen receptor-sensitive cells.

A systematic evaluation of plumbagines A–G (43–49) and plumbagosides A–D (54–57) has been conducted, including PANC-1 human pancreatic adenocarcinoma and MDA-MB-231 triple-negative breast cancer cell lines. Despite the structural diversity across these naphthoquinone derivatives and triterpene glycosides, all tested compounds demonstrated limited cytotoxic potential, with IC_{50} values exceeding 10 μ M in both cellular systems, in sharp contrast to the nanomolar efficacy of paclitaxel ($IC_{50} < 1 \mu$ M) under identical experimental conditions. This pharmacological profile suggests potential limitations in cellular uptake or target engagement, possibly because of unfavorable physicochemical properties or metabolic instability. Nevertheless, these negative results provide critical structure-performance benchmarks for guiding future natural product derivatization strategies aimed at enhancing membrane permeability or introducing pro-apoptotic pharmacophores [62].

Crambescin C1 (66), even at low doses, protects against oxidative injury through the induction of metallothionein. However, at higher concentrations, the compound arrests the cell cycle in G0/G1 phase, thereby impeding tumor cell proliferation [71].

Cernumidine (67) has shown dual modulatory effects through distinct mechanisms of action in oncology models. In HT-29 colorectal carcinoma cells, this indole alkaloid suppresses interleukin-8 (IL-8) secretion in a concentration-dependent manner, achieving 50% inhibition at 50 μ M, thus suggesting potential anti-angiogenic properties through attenuation of this pro-inflammatory chemokine [73]. Parallel investigations by Miranda et al. have revealed enhanced therapeutic synergy of a combination of cernumidine and cisplatin derivatives, which achieved 62% less T24 bladder cancer cell migration (in Boyden chamber assays) than monotherapies. Although these findings position cernumidine as a promising adjunctive agent for combination chemotherapy regimens, comprehensive pharmacokinetic studies are warranted to evaluate its bioavailability and organ-specific distribution patterns [74].

The guanidine-containing pyrrole alkaloid N (1)-methylisoageliferin (73) and its structural analogues (74–79) have emerged as novel Cbl-b E3 ubiquitin ligase inhibitors, exhibiting dose-dependent suppression of ubiquitination activity ($IC_{50} = 18$ –35 μ M) in fluorescence polarization assays using a recombinant human Cbl-b/TKB domain [78].

Compared with actinoplanone, simaomicin, xantholipin, and echinosporamicin-associated compounds, enduracyclinone A (98) exhibits negligible cytotoxicity to cell lines such as the cancerous cell line PANC-1 and

the noncancerous cell line HEK-293 [84]. Its mild interaction profile suggests potential safety advantages under experimental conditions, although further investigations are required to fully characterize its biological behavior and possible research applications.

5.3 Bicyclic guanidines

Monalidine A (104) has antiproliferative and cytotoxic activity against KB, HCT116, HL60, MDA435, and MRC-5 cancer cells, with IC_{50} values of 0.2–1.3 μ M [89]. The antitumor activity of other dicyclic guanidine alkaloids has also been investigated. For example, monanchoradin A (105) and dehydrocrambescin A2 418 (100) show cytotoxic activity, with IC_{50} values of 7.7 and 0.1 μ M, respectively, against the KB cell line; 9.9 and 3.4 μ M, respectively, against HCT-116 cells; and 3.8 and 3.6 μ M, respectively, against HL-60 cells [89]. Unfortunately, the longer side chains of monanchoradin B and C (106, 107) did not result in greater cytotoxicity than that of monanchoradin A (105).

The novel bicyclic guanidine alkaloids with seven-membered rings 6-epi-monanchorin (108) and monanchorin (109) have been evaluated in cytotoxicity assays in Huh-7 hepatoma cells, and NCCIT and NCCIT-R human germ cell tumor cell lines [90, 92]. Both compounds were noncytotoxic to the tested cell lines but significantly interfered with the migration of cisplatin-resistant cancer NCCIT-R cells by arresting the cell cycle in G1 phase [92]. Furthermore, 6-epi-monanchorin (108) exhibits weak inhibition of colony formation of NCCIT-R cancer cells, whereas monanchorin (109) shows a strong inhibition [92]. Overall, additional antitumor activity research is required on 6-epi-monanchorin (108) and monanchorin (109).

Urupocidins have been documented to have cytotoxic activity against a range of human cancer cell lines. For instance, urupocidin A (110) impedes EGF-induced neoplastic transformation of epithelial cells and promotes G2/M-phase cell cycle arrest, thus resulting in apoptosis of human cervical carcinoma HeLa cells [114]. However, AP-1-dependent transcriptional activity is suppressed concomitantly with a decrease in cell viability after treatment with urupocidin A (110); therefore, this compound does not affect AP-1 transcriptional activity in living cells. Furthermore, this compound induces murine epithelial JB6 Cl41 apoptosis without variation in the transcriptional activity of the tumor suppressor protein p53. Moreover, its cellular response is not involved in caspase-associated apoptotic pathways, because minimal activation of caspase 3/7 has been detected in treated cells [114]. Both urupocidin A and C (110, 112) exhibit potent selectivity toward human prostate cancer cells, with low micromolar range IC_{50} values. Compared with that of cisplatin, both alkaloids show significant cytotoxicity toward human hormone-sensitive prostate cancer LNCaP cells. In contrast, the IC_{50} values were significantly lower (by 3–5 times) toward drug-treated hormone-dependent LNCaP cells and MRC-9 non-malignant human

lung fibroblasts. Therefore, urupocidin A and C (**110**, **112**) induce G1 and S cell cycle arrest and caspase-dependent cell apoptosis. Remarkably, mitochondrial targeting is a critical mechanism underlying the anticancer activity of these compounds. Simultaneously, in combination treatment with the PARP inhibitor olaparib, synergistic interaction of urupocidin A/C (**110/112**) has been observed [94]. In general, urupocidins warrant further research as new promising therapeutic drugs.

5.4 Tricyclic guanidine

Batzelladines O and P (**129**, **130**) have shown potent cytotoxic activity toward human prostate cancer cells, including drug-resistant types, by inducing apoptosis and cytoprotective autophagy. Batzelladine O (**129**) is more effective against cancer cells and has smaller IC_{50} values than batzelladine P; both compounds' IC_{50} values range from 2 to 3 μ M. Moreover, in combination with the autophagy inhibitor 3-methyladenine, the two compounds exhibit synergistic effects, whereas docetaxel demonstrates an additive effect. Although both compounds exhibit equivalent activity in docetaxel-sensitive and -resistant prostate cancer cells, slight p-glycoprotein substrate-like activity has been observed, thus constituting the primary basis for resistance to docetaxel. This conclusion requires further investigation [103]. Batzelladine L (**126**), a natural product derived from *M. arbuscula*, has demonstrated significant potential anticancer activity against various human cancer cell lines, including leukemia, colorectal, breast, melanoma, and glioblastoma cancers. The IC_{50} of this compound is less than 1 μ g/mL, thereby indicating its remarkable efficacy at low concentrations [147]. Therefore, this compound induces apoptosis in HCT-8 colorectal cancer cells through the activation of caspases and the arrest of cells in G1 stage of the cell cycle. Moreover, the alkaloids batzelladine L (**126**) and norbatzelladine L (**189**) have exhibited greater selectivity indices (7 and 12, respectively) than positive controls in assessment against a monolayer of monkey kidney cells (LLC-MK2) [88].

Despite its novel structure, mirabilin K (**137**) is ineffective against PDCD4, even at a maximal test concentration of 20 μ g/mL [107]. Mirabilin G (**136**) and netamine M (**143**), in contrast, display strong inhibitory activity toward PDCD4 (programmed cell death 4) degradation, with EC_{50} values of 1.8 and 2.8 μ g/mL, respectively; these compounds are the first marine natural products reported to stabilize PDCD4 under conditions that promote tumor development [107]. PDCD4 is a tumor suppressor that functions through the interaction of its domain with eukaryotic translation initiation factors, thereby suppressing protein translation [148]. Unfortunately, no other biological activity of mirabilin K (**137**) has been reported to date.

Netamines C and D have been identified to have notably high cytotoxic activity against lung (A549), colorectal (HT29) and breast (MDA-MB-231) carcinoma cell lines, with GI_{50} values in low concentration ranges

[108]. All new members of the netamine family (netamines H–S (**139–140**)) have been tested for cytotoxicity activity. Netamines M, O, and Q (**143**, **146**, **147**) are cytotoxic toward the KB tumor cell line, with an IC_{50} value in the micromolar range, whereas the others are inactive at the same concentration. The antitumor activity of the crude extract of *Biemna laboutei* sponge (96.9% inhibition at 10 mm concentration) might be due to these active compounds [109, 110].

5.5 Tetracyclic guanidines

Eudistidine A (**152**) has shown high efficacy in blocking the binding of soluble CH1 (p300) to immobilized C-TAD (HIF-1 α), with an IC_{50} of approximately 75 μ M, whereas eudistidine B (**153**) has no inhibitory effect at a relatively high dose of 250 μ M. Eudistidine C (**154**) exhibits moderate inhibition of the interaction between HIF-1 α and the p300 protein binding domain. Eudistidine A (**152**) is a readily synthesizable compound with potential for anticancer therapeutic use as a pharmaceutical agent. In addition, it can serve as a small molecule probe, thereby facilitating further elucidation of the roles of p300 and HIF-1 α in the adaptation of tumors to hypoxic environments [20, 112].

5.6 Pentacyclic guanidine

The presence of the chemical substance crambescidin 816 (**165**) alters transcription in HepG2 human liver carcinoma cells. Furthermore, these alterations inhibit tumor cell proliferation and disrupt both tumor cell adhesion and cytoskeletal integrity [149, 150]. Concomitantly, a significant antitumor effect of the compound has been observed in vivo, in a zebrafish xenotransplantation model with colorectal carcinoma implantation [149]. Crambescidin 800 (**164**) induces erythroid differentiation of K562 chronic myelogenous leukemia cells, according to a study by Aoki et al. in 2004 [151]. In 2018, this compound was found to have cytotoxic potency in breast cancer cells through the inhibition of the phosphorylation of Akt, NF- κ B, and MAPK pathways [152]. Among homologues of crambescidin 800 (**164**), tumor selectivity potency has been found to increase with increasing chain length [153]. Importantly, however, the cytotoxicity of two newly discovered natural crambescidin 800 (**164**) analogues has been found to increase and subsequently decrease with increasing chain length. The highest activity has been observed for crambescidin 800 (**164**) ($n = 13$, $IC_{50} = 0.005$, 0.007, and 0.004 μ M against KB, HCT-116, and HL-60, respectively), whereas the shorter analogue, crambescidin 786 (**162**) ($n = 12$, $IC_{50} = 0.3$, 3.1, and 5.0 μ M against KB, HCT-116, and HL-60, respectively), and the longer analogue, crambescidin 814 (**163**) ($n = 14$, $IC_{50} = 0.005$, 0.02, and 0.01 μ M against KB, HCT-116, and HL-60, respectively), have less activity. In addition, with an IC_{50} value of 0.5 μ M, norcrambescidic acid (**168**) also shows moderate cytotoxicity toward the KB cell line [89].

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Monanchoxymycalins A and B (**183**, **184**) inhibit cervical epithelioid carcinoma HeLa cells, with IC_{50} values of 2.80 μ M and 2.82 μ M, respectively, and breast adenocarcinoma MDA-MB231 with IC_{50} values of 5.60 μ M and 11.65 μ M, respectively [122]. Moreover, monanchoxymycalin C (**185**) at low micromolar concentrations induces apoptosis in HeLa human cervical cancer cells and impedes the proliferation of cancerous cells, thus suggesting its efficacy against cancerous cell growth [123]. This compound also inhibits EGF-induced neoplastic transformation [114]. In contrast, this compound is remarkably efficacious in eliminating human prostate cancer cells, through the induction of an atypical caspase-independent and non-apoptotic cell death process. Recent studies have revealed that activation of c-Jun N-terminal protein kinase (JNK1/2), a member of the mitogen-activated protein kinase (MAPK) family, is the primary mechanism through which monanchoxymycalin C (**185**) exerts its anti-prostate cancer activity [154]. This finding highlights that the mechanisms of cytotoxic effects can be cell specific and therefore may vary among models.

Monanchocidins exhibit equivalent levels of in vitro cytotoxic potential against the cisplatin-sensitive human embryonal carcinoma cell line NTERA2 and its resistant variant, NTERA2-R [155]. Dyshlovoy et al. have observed the induction of cytotoxic autophagy and lysosomal membrane permeabilization in human germ cell tumor cells treated with monanchocidin A (**170**), but not classical apoptosis induced by standard agents used to treat these tumors. Concurrently, this compound has potential to augment the activity of cisplatin in tumor cells [156]. Moreover, the compound at low concentrations demonstrates anti-migratory properties that are non-cytotoxic and non-antiproliferative [157]. It also exhibits potent selective activity toward the National Cancer Institute's cancer cell screening panel [158]. Consequently, this compound might potentially eliminate human cancer cells, while preventing both cancer cell formation and dissemination [114]. Therefore, monanchocidins might represent a novel class of pharmacological agents with potential to circumvent resistance phenomena associated with contemporary therapeutic interventions.

Monanchomycalins and normonanchocidins have potent cytotoxic and antitumor activity. For example, monanchomycalins A and B (**175**, **176**), and normonanchocidins G and H (**181**, **182**), exhibit cytotoxic activity against human leukemia HL-60 cells, with IC_{50} values of 0.12, 0.14, 3.6, and 13.5 μ M, respectively [119, 121]. Monanchomicin C (**177**) has cytotoxic activity against human breast cancer cells (MDA-MB-231), with an IC_{50} value of 8.2 μ M, and concomitantly inhibits EGF-induced neoplastic transformation [114, 115]. Furthermore, normonanchocidins A, G, and H (**178**, **181**, **182**) exhibit IC_{50} values of 2.1, 3.7, and 19.8 μ M, respectively, against THP-1 human leukemia cells, and 3.8, 3.3, and 21 μ M, respectively, against HeLa cervical epithelial carcinoma cells [120, 121]. Interestingly, normonanchocidins G and

H (**181**, **182**) considerably suppress HeLa cell migration ability at low concentrations [121].

In addition, ptilomycalin A (**160**) shows cytotoxic activity toward MDA-MB-231 cells, a human breast cancer cell line, with an IC_{50} of 4.3 μ M [115]. Likewise, this compound induces cell cycle arrest and programmed death of cancer cells. This compound also inhibits the EGF-induced neoplastic transformation of JB6 P⁺ Cl41 cells [114]. The new members of the ptilomycalins, including ptilomycalin E (**156**), ptilomycalin F (**157**), and the mixture of ptilomycalins G and H (**158**, **159**), exhibit IC_{50} values of 0.35, 0.23, and 0.46 μ M, respectively, against the KB cell line [49]. Notably, ptilomycalin F (**157**) exhibits the most elevated selectivity index (SI) value of 7.0 among the evaluated compounds, closely approaching the target value stipulated by the Medicine for Malaria Venture (SI >10). SI was used as the parameter of clinical significance for the test samples, through comparison of the calculated values of the inhibitory effect on *P. falciparum* and the toxicity on the KB cell line, as outlined in the report as IC_{50} (KB)/ IC_{50} (*P. falciparum*) [49]. Moreover, fromiamycalin (**186**) has been found to exhibit cytotoxicity, with an IC_{50} of 1.17 μ M against the KB cell line.

Guanidine alkaloids exhibit multidimensional antitumor mechanisms with marked structure-activity correlations. Overall, the numbers of isoprene groups and binding sites, and the degree of polymerization, significantly affect cell toxicity. The imino nitrogen atom is crucial for activity, and replacing it with a sulfur or oxygen decreases antitumor activity. In addition, the length and characteristics of the chain are key factors determining target cell type and activity. Bicyclic and tricyclic guanidine alkaloids typically exhibit greater cytotoxicity than monocyclic compounds. The presence of multiple rings may strengthen the interaction with cellular targets. Different guanidine alkaloids target different cellular pathways (e.g., apoptosis, autophagy, and protein-protein interactions) and may display specific mechanisms that vary by cell type. Overall, the cytotoxicity and antitumor activity of the guanidine alkaloids are highly dependent on their structural properties. Further studies on the optimization of these structures for therapeutic applications and elucidation of their mechanisms of action in different cancer models are required.

6. HYPOTENSIVE AND HYPOGLYCEMIC EFFECTS

The low-molecular-weight acyclic guanidine alkaloid galegine (**12**), a well-known agent used in the management of elevated glucose levels in blood serum, was identified as a source of metformin after careful examination of the hypoglycemic properties of this substance [42-44]. This compound exerts its anti-diabetic effects through inhibiting complex IV activity. Subsequent analysis revealed that galegine (**12**) curtails the activity of glycerol-3-phosphate dehydrogenase, augments the redox status in the cytosol, and impedes glycerol-derived hepatic gluconeogenesis [33]. In addition, this

compound has hypotensive effects in rats. A series of acute toxicity experiments indicated that the safe dose of galegine (**12**) was one-tenth the LD₅₀ value [34]. The hypotensive mechanism of this compound has been suggested to be associated with the H₂-receptor agonist [159]. Nevertheless, further studies are necessary to substantiate the long-term safety and the mechanism of galegine (**12**) in regulating blood pressure.

Monocyclic guanidine plumbagine D (**46**), plantagoguanidinic acid (**63**), and tricyclic guanidine plantadeprate A (**151**), with inhibitory rates of 18.5%, 12.5%, and 8.2% at 40 μ M, respectively, have been found to have potential antihyperglycemic characteristics associated with inhibition of hepatic gluconeogenesis with metformin, whereas the positive control showed an inhibition rate of 25% at 2 mM [63]. However, its analog 1'-(4"-hydroxybutyl) plantagoguanidinic acid (**64**) has no inhibitory effects on α -glucosidase, angiotensin-converting enzyme, and gluconeogenesis [63]. In addition, whereas other tested compounds were ineffective, plantadeprate A (**151**) showed only slight inhibitory activity of 20% at 6.25 mM and 26% at 10 mM toward α -glucosidase and angiotensin-converting enzyme. According to Rubiolo et al., another monocyclic guanidine alkaloid, crambescine C1 (**66**) induces in vivo hypotensive effects and increases NO production by acting as a substrate of iNOS and eNOS [72].

Guanidine alkaloids have multi-target metabolic regulatory properties. The guanidine group plays a key role in all compounds with hypoglycemic, hypotensive, or antihyperglycemic activity, and may be the key pharmacophore involved in interaction with the target. The structures of different ring numbers, such as monocyclic, bicyclic, and tricyclic, significantly influence the activity. Overall, increasing the number of rings may enhance some activities but also result in changes in other activities. The effects of specific ring structural features on activity must be clarified through further studies.

7. RECEPTOR INHIBITORY EFFECTS

Acyclic guanidine alkaloids, namely pulchranins A–C (**15**–**17**), inhibit the activity of TRPV1, TRPV3, and TRPA1 channels [47, 48]. TRPV1, TRPV3, and TRPA1 receptor proteins are activated by noxious heat as well as the pungent compound capsaicin. These receptors are involved in the transmission and modulation of pain, and the regulation of body temperature. Among tested compounds, pulchranin A (**15**) exhibited the best activity

against TRPV1 (EC₅₀ = 27.5 μ M), TRPV1 (EC₅₀ = 27.5 μ M), and TRPA1 (EC₅₀ = 174.2 μ M). Pulchranins B and C (**16**, **17**) demonstrated moderate inhibitory activity against TRPV1 (EC₅₀ of 95.4 and 182.7 μ M, respectively) but exhibited diminished potency against TRPV3 and TRPA1 receptors. According to structure-activity relationships, the C14 compound pulchranin A (**15**) is much more active than the C13-compound pulchranin B (**16**), whereas the latter is more active than the C12-open chain derivative pulchranin C (**17**). In addition, the hydroxylated alkenyl moiety may play a major role in the inhibitory activity of pulchranins toward these ionic channels. The inhibitory potential of pulchranins might be subject to modulation by their direct effects on channel pores or on the diverse cell mechanisms involved in channel activation. Further studies on the mechanisms of action of pulchranins toward TRPV1, TRPV3, and TRPA1 channels are underway. Likewise, the derivative of pulchranin A (**15**) named dihydropulchranin A (**198**) (Figure 48), prepared from pulchranin A (**15**), shows potent TRPV channel-regulating activity, whereas another derivative, hexadecylguanidine (**199**) (Figure 48), is not active against related receptors [160].

Bicyclic guanidine urupocidin A (**110**) interacts with rTRPV1, mTRPV2, and hTRPV3 receptors, with EC₅₀ values of 21.47, 28.06, and 23.55 μ M for TRPV1, TRPV2, and TRPV3, respectively [161]. TRPV1, TRPV2, and TRPV3 are transient receptor potential receptors associated with multiple pathologies, such as inflammatory, neuropathic, and visceral pain. In addition, urupocidin A (**110**), when administered at micromolar concentrations, augments NO levels in murine macrophages. This observation is the first report of a marine alkaloid identified as a stimulant of NO production [93].

The pentacyclic guanidine alkaloid monanchomycalin B (**176**) also inhibits TRPV receptors, with an EC₅₀ of 6.02, 2.84, and 3.25 μ M for TRPV1, TRPV2, and TRPV3, respectively [161]. Furthermore, monanchocidin A (**170**) has exhibited inhibitory properties in electrophysiological experiments on mouse muscle and rat α 7 nicotinic acetylcholine receptors (nAChRs) [162]. Furthermore, this compound and crambescidin 359 (**161**) have relatively high affinities (K_i of 17 and 8 μ M, respectively) toward *Torpedo californica* nAChR. nAChRs have been demonstrated to play critical roles in a variety of cognitive processes and the regulation of inflammatory responses [162].

The guanidine moiety, a key pharmacophore exerting activity in all active compounds, might modulate

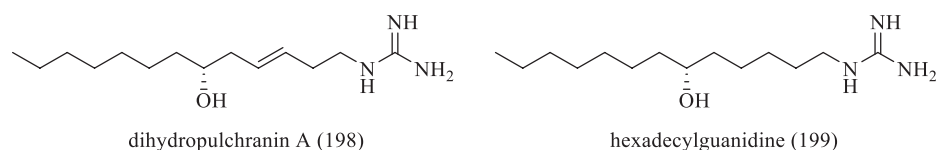


Figure 48 | Structures of pulchranin A (**15**) derivatives dihydropulchranin A and hexadecylguanidine (**198**, **199**).

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receptor function by forming hydrogen bonds and electrostatic interactions with key sites in the receptor or channel, thereby affecting channel opening or closing. Different numbers of rings in the structure significantly affect activity. Non-cyclic structures have relatively weak activity, whereas bicyclic and pentacyclic structures have greater activity. The ring structure may increase activity by increasing the rigidity and specific three-dimensional structure of the molecule, thus facilitating interactions with the binding site of the receptor. However, the differences in the activity of different ring structures also indicate that the activity depends not only on the presence of the ring but also on specific structural features of the ring (e.g., ring size and substituents).

8. ANTIVIRAL ACTIVITY

Whereas mellpaladine C shows weak anti-DENV-2 activity (18% inhibition in HuH-7 cells), dopargimine (**21**), 1-carboxydopargimine (**22**), mellpaladines A and B (**24–26**), mellpaladines D–F (**27–29**), and serotodopalgimine (**23**) do not exhibit any antiviral activity [51, 52]. This observation highlights the variability in biological activity among natural products, thus suggesting the need for deeper exploration of their structure-activity relationships and functional contexts.

Molecular compounds of the traditional Chinese medicine plantagoganidinic acid (**63**) have been found to inhibit viral infectivity factor, thus protecting against HIV, according to molecular docking and molecular dynamics simulations, with a dock score of 91.191. Viral infectivity factor, an HIV protein, prevents the human immune system from attacking the virus [69].

From a biological standpoint, the batzelladines have attracted interest for their ability to inhibit HIV gp120-human CD4 binding. Other batzelladine alkaloids have also shown potent antiviral effects. For example, norbatzelladine L (**189**), a constituent of the genus *Monanchora*, has antiviral properties, thereby inhibiting the replication of herpes simplex virus type 1 [163]. In 2022, Elgohary et al. conducted extensive virtual screening of 15 batzelladine marine alkaloids for inhibitory activity against the SARS-CoV-2 main protease (M^{pro}), through an integrated set of modern computational tools, including molecular docking [164]. Most examined compounds exhibited favorable binding energy. Among the congeners, batzelladines F–I (**120–123**) were the four most promising compounds, according to their prominent ligand-protein energy scores and relevant binding affinity toward (M^{pro}) pocket residues. The position of the N-OH functionality, the length of the spacer between sites of action, and the degree of unsaturation of the molecules were found to be the main factors affecting the protein-ligand interaction. According to Ahmed, batzelladine K (**125**) has no antiviral effect against HIV-1 [136].

Mirabilin G (**136**) has been identified as a potential inhibitor of the main protease protein of SARS-CoV-2, on the basis of docking with a binding energy of 7.38

kcal/mol, a value comparable to that of the native ligand inhibitor N3 (docking binding energy of 7.30 kcal/mol) [111]. Likewise, the pentacyclic alkaloids, particularly crambescidin 786 (**162**) and crambescidin 826 (**166**), have shown superior anti-COVID-19 activity [165]. These compounds exhibited the most promising binding affinities toward M^{pro} ($\Delta G = -8.05$ and -7.99 kcal/mol, respectively) and nucleocapsid phosphoprotein ($\Delta G = -6.49$ and -8.01 kcal/mol, respectively) among the tested compounds. Promising binding energies have been observed for other candidates, including the bicyclic guanidine alkaloid dehydrocrambescin A2 418 (**100**); (–)-crambescins A2 392, 406, and 420 (**101–103**); monalidine A (**104**); monanchoradins A–C (**105–107**); and the pentacyclic guanidine alkaloids crambescidin 359 (**161**), 814 (**163**), and 800 (**164**), crambescidic acid (**167**), and norcrambescidic acid (**168**). In addition, all these compounds have shown expected low toxicity against the tested models. These results indicate the great potential of natural guanidine alkaloids for their antiviral activity.

The guanidine moiety is a key pharmacophore exerting antiviral activity, and its positively charged properties might interfere with viral infection and replication process by interacting with negatively charged regions or polar residues on viral proteins. The ring structure (monocyclic, tricyclic, pentacyclic, etc.) significantly affects activity. The presence of a ring increases the rigidity of the molecule and the specific three-dimensional conformation, thus facilitating interactions with the binding site of the viral protein and consequently increasing the activity. The effects of different numbers of rings on activity may vary depending on the viral target, and must be analyzed according to the structure and function of the specific viral protein.

9. ANTI-INFLAMMATORY ACTIVITY

The isolation of four structural variants of the guanidine alkaloids ecliptamines, A–D (**59–62**) has been achieved from the aerial parts of *Eclipta prostrata* L. [65]. Since the utilization of this herb in the treatment of ocular inflammation in Japan, research has examined the inhibitory activity of ecliptamines A–D (**59–62**) and the analog plantagoganidinic acid (**63**) against cyclooxygenases 1 and 2 (COX-1 and COX-2, respectively). In an investigation by Tabata in 2015, plantagoganidinic acid (**63**) was found to have IC_{50} values of 3.0×10^{-3} M (against COX-1) and 8.3×10^{-4} M (against COX-2), whereas ecliptamines A and B (**59, 60**) had slightly lower inhibitory activity ($IC_{50} > 10^{-3}$ M) against both enzymes. The positive control, aspirin, had IC_{50} values of 4.2×10^{-4} M (against COX-1) and 7.1×10^{-4} M (against COX-2) [65].

Guanidine alkaloids have shown selective cyclooxygenase inhibition in anti-inflammatory applications. Plantagoganidinic acid (**63**) exhibits a preference for COX-2 over COX-1, with a selectivity index surpassing that of aspirin, thus suggesting synergistic effects between guanidine and carboxyl groups. Ecliptamines

A/B (59–60) show a weaker dual inhibition highlighting the critical roles of aromatic substitution patterns in target engagement. These findings validate the traditional use of *Eclipta prostrata* L. in ocular inflammation.

10. INSECTICIDAL ACTIVITY

Although no data support the insecticidal biological activity of galegine (12), this natural product has been used as a lead compound in the synthesis of a series of galegine analogues demonstrating a range of insecticidal activities, from moderate to significant, against *Hyalopterus pruni* Geoffroy and *Aphis gossypii* Glover [38, 39]. Structure-activity studies have shown that adding the long straight-chain alkyl, pyridine ring, and fluorine atom to target compounds increases insecticidal activity [38]. In addition, the molecules with a difluoro-substituted benzene ring have exhibited greater potency than those with a single fluoro-substituted ring [39]. These compounds are likely to target insect neuronal ion channels; therefore, galegine-based scaffolds may provide promising templates for next-generation insecticides.

11. NEUROACTIVE ALKALOIDS

According to Uchimasu, terminal guanidine alkaloids, including dopargimine (20) and mellepaladines A–C (21–23), bind synaptic receptors in the central nervous system, thereby manifesting concentration-dependent neuronal activity [51]. Moreover, the pentacyclic guanidine crambescidin 816 (165) has been shown to block the voltage-gated calcium channel Cav1 or L-type calcium channels, and to decrease neurotransmitter release and synaptic transmission in the central nervous system [166]. Moreover, crambescidin 816 (165) levels have been demonstrated to elevate the concentrations of calcium ions in the cytoplasm of cortical neurons, and subsequently decrease neuronal viability and curtail a dose-dependent increase in calcium ions in the cytoplasm—a process considered the principal mechanism underlying neuronal cell death. Glutamate receptor antagonists have been found to completely prevent the alkaloid cytotoxicity after 10 min exposure, thus suggesting that the glutamate receptor is the main factor associated with this effect [167]. This dual calcium homeostasis disruption-excitotoxicity profile positions this compound as a unique probe for studying neurodegenerative pathways and developing neuroprotective agents.

12. OTHER BIOLOGICAL ACTIVITIES

Hordatines A–C (36–38), a series of dihydroflavonol derivatives, exhibit remarkable multifunctional antioxidant activity across standardized evaluation systems. As quantified with oxygen radical absorbance ability assays, these polyphenols demonstrate potent peroxyl radical neutralization with values of 10–17.5 μmol

TE/ μmol , surpassing that of reference antioxidants such as α -tocopherol. Hydroxyl radical scavenging ability assays revealed dose-dependent protection against Fenton reaction-induced oxidative damage (2.0–4.1 μmol TE/ μmol), whereas lipid peroxidation inhibition (LA assay) in linoleic acid emulsions showed 1.1–6.1 μmol TE/ μmol efficacy, thereby suggesting superior membrane-protective properties. According to structure-activity correlations, ortho-dihydroxy configurations in hordatine B (37) contribute to its peak LA performance through enhanced metal chelation and chain-breaking mechanisms. This broad-spectrum antioxidant profile makes these barley-derived compounds promising candidates for nutraceutical development targeting oxidative stress-associated pathologies [58].

Cernumidine (67) scavenges free radicals, according to DPPH assays. Consequently, the protective effects of cernumidine (67) against H_2O_2 are attributable to its antioxidant activity [76]. Whereas initial observations have indicated free radical interaction ability, further experimental validation is required to enable comprehensive understanding of its protective mechanisms and biological relevance.

Dispacamide E (97) has considerable protein kinase inhibitory activity against nine protein kinases (DYRK1A, CDK5, GSK-3, CLK-1, CK-1, CDK1, CDK2/A, CDK9/cyclin T, and PfGSK-3), with IC_{50} values in the range of 2.1–18.8 μM [83].

Hamed et al. first studied the inhibitory effects of the pyrrole alkaloids by using 21 important protein kinases in vitro, and identified that the compound Z-3-bromohymenialdisine (71) is highly promising [77].

Phidianidine A (196) has notable potency against the barnacle *A. improvisus*, with an IC_{50} of 4.0 $\mu\text{g/ml}$, and serves as a potent marine antifoulant [168]. Although experimental observations have indicated bioactivity under tested conditions, further evaluation of environmental compatibility and long-term efficacy is necessary to ensure practical applicability.

P-coumaroylagmatine (pCAA) (200) and feruloylagmatine (FAA) (201) are bioactive phenolamides in barley, and feruloylagmatine (201) was the first guanidine alkaloid found in the Papaveraceae and dicotyledons (Figure 49). These compounds rapidly eliminate MGO

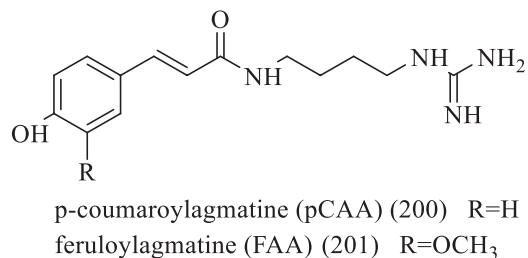


Figure 49 | Structures of p-coumaroylagmatine (200) and feruloylagmatine (201).

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through a mechanism involving formation of mono-MGO and bis-MGO adducts; consequently, they might potentially serve as diabetes therapeutics [169, 170].

The pentacyclic guanidine alkaloids monanchocidin A (170), normonanchocidin A (178), and monanchomycalin B (176) have inhibitory activity against α -galactosidase from the marine γ -proteobacterium *Pseudoalteromonas* sp., β -1,3-D-glucanase from the filamentous marine fungus *Chaetomium indicum*, and the marine bivalve mollusk *Spisula sachalinensis* [171, 172]. The conserved guanidinium group is critical for binding catalytic pockets.

13. CONCLUSION AND PERSPECTIVES

Guanidine-containing alkaloids are natural products with a variety of structures and biological activities, which are common in terrestrial microorganisms, plants, and marine invertebrates. The guanidine group is central to the biological activities of guanidine alkaloids. Notably, this class of compounds has distinct guanidine systems, including acyclic, monocyclic, bicyclic, tricyclic, tetracyclic, and pentacyclic guanidine systems, as classified and discussed in this review. The potential biological properties of this natural product have been investigated, because of its substantial structural diversity, including mainly antifungal, antibacterial, antiparasitic, and anti-tumor activity. For decades, researchers have studied not only the separation and extraction of bioactive guanidine alkaloids, but also their biosynthesis and structural derivation. Furthermore, many efficient and simple synthesis methods have been established. However, ongoing research is being conducted to develop and test the biological activities of these natural products.

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

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