Review

Fused Tricyclic Guanidine Alkaloids: Insights into Their Structure, Synthesis and Bioactivity

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Abstract: A marine natural product possesses a diverse and unique scaffold that contributes to a vast array of bioactivities. Tricyclic guanidine alkaloids are a type of scaffold found only in marine natural products. These rare skeletons exhibit a wide range of biological applications, but their synthetic approaches are still limited. Various stereochemical assignments of the compounds remain unresolved. Batzelladine and ptilocaulins are an area of high interest in research on tricyclic guanidine alkaloids. In addition, mirabilins and netamines are among the other tricyclic guanidine alkaloids that contain the ptilocaulin skeleton. Due to the different structural configurations of batzelladine and ptilocaulin, these two main skeletons are afforded attention in many reports. These two main skeletons exhibit different kinds of compounds by varying their ester chain and sidechain. The synthetic approaches to tricyclic guanidine alkaloids, especially the batzelladine and ptilocaulin skeletons, are discussed. Moreover, this review compiles the first and latest research on the synthesis of these compounds and their bioactivities, dating from the 1980s to 2022.

Keywords: marine sponges; tricyclic guanidine; guanidine alkaloids; batzelladines; ptilocaulins; netamines; mirabilins; bioactivities; synthesis

1. Introduction

The marine natural product has excellent potential as a drug source. Between 1969 and 2018, eight approved drugs of marine natural product origin were reported [1]. These eight drugs have anti-cancer, antiviral, and analgesic properties, and can be used for treating cardiovascular disease. Six of these drugs were approved in the 2000s, indicating the growing interest in marine natural products in the pharmaceutical area. The harsh environment of the deep sea, in terms of its pressure, light source, temperature, and salinity, causes the marine organism to adopt a different biochemical pathway that might result in a novel mode of action in regard to its bioactivity [2]. The only downfall is the difficulty of isolating the compounds from marine organisms, requiring advanced technology or extensive labor, which limits their further study. Spongistatin, for instance, is one of the most active compounds exhibiting antitumor activity (IC₅₀: 10⁻¹⁰ M for colon cancer, 10⁻¹² M for breast cancer cells). Upon the isolation of three tonnes of sponge, only 0.8 mg of Spongistatin was isolated, limiting the further study of its physiological activity [3]. In terms of structure, marine natural products have larger skeletons than terrestrial natural products, and usually, their skeletons are interlinked by an ester bond [4]. Additionally, marine natural products contain more nitrogen and halogen atoms, which suggests that they can be synthesized through more diverse biosynthetic pathways. One type of marine natural product that has garnered a great deal of attention is the marine guanidine alkaloids. Guanidine has high basicity that causes it to bind different functional groups, such as metals, carboxylates, and phosphates, increasing its biological properties [5]. The guanidine alkaloids can be classified into four main chemotypes: bicyclic or monocyclic...
guanidine, tricyclic guanidine, polycyclic guanidine, and alkaloids that contain more than one guanidine moiety [6]. Among these chemotypes, the synthesis of tricyclic guanidine is less widely reported and is studied, herein, in this review.

Batzelladines are a type of tricyclic guanidine that are mostly linked through an ester linkage to another guanidine moiety (Figure 1). These guanidine moieties can be 4-guanidino-butyl, bicyclic guanidine, and tricyclic guanidine. The simplest structure of batzelladine contains only one tricyclic guanidine core, such as batzelladine K (7) or merobatzelladine B (11). These tricyclic guanidine cores also have different degrees of unsaturation that may affect their bioactivities (Table 1). On the other hand, ptilocaulins, mirabilins, and netamines from marine sponges possess a rare heterocycles skeleton, having a tricyclic (5,6,8b)-triazaperhydroacenaphthylene structure without any ester linkage (Figure 2) [7]. In contrast to batzelladines that have an embedded guanidine structure between the tricyclic rings, the ptilocaulins, mirabilins, and netamines have a terminal guanidine skeleton that is positioned on one of the six-membered rings. These skeletons can also be grouped, depending on the degree of unsaturation and double bond positions, i.e., pyrimidines, saturated heterocycles, $\Delta^{9,10}$, $\Delta^{10,11}$, and $\Delta^{11,12}$ [7]. These alkaloids are reported to have various biological activities, such as antimicrobial [8,9], anti-malarial [10–12], antifungal [10], and antiprotozoal properties [10] (Tables 2 and 3). They are also cytotoxic for specific tumor and leukemia cells [9,13].
Figure 1. Structures of batzelladines.
In 1995, Patil et al. discovered the first set of compounds from batzelladine skeletons, which were batzelladines A–E (1, 4, 12–14) from Batzella sp. [14]. Among these compounds, batzelladine A (1) and B (12) showed significant anti-HIV activity by inhibiting gp120-CD4
binding [14]. These compounds were also the first low-molecular-weight natural products that could inhibit the gp120-CD4 interaction. The presence of three guanidine moieties in batzelladine A (1) and B (12) might be responsible for their bioactivity. Two years later, Patil et al. isolated new batzelladines from Jamaican Batzella sp. [15]. These batzelladines showed a unique structural feature with two tricyclic guanidines connected through an ester linkage. Batzelladine F (5) and G (6) and a combination of H (18) and I (19) exhibited moderate immunosuppression activity by inhibiting p56Lck-CD4 dissociation. This immunosuppression activity helps to treat autoimmune diseases such as adjuvant-induced arthritis, murine lupus, and allergic encephalomyelitis. Batzelladine J (15) was isolated in 2005 from Monanchora unguifera, with two repetitive units of tricyclic guanidine with an additional 4-guanidino-butyl ester moiety [16]. This compound exhibited anti-cancer activity against P-388, DU-145, A-549, MEL-28, and HT-29 cells, with IC_{50} values of more than 1 µg/mL. In 2007, batzelladines K–N (7–8, 16–17) were isolated from the sponge of M. unguifera in Jamaica [17]. Together with dehydrobatzelladine C (23), these compounds showed significant activity against protozoa, HIV-1, and AIDS opportunistic infectious pathogens (AIDS-OIs), including Mtb and cancer cell lines, with a wide range of bioactivities. It was observed that batzelladine L (8) showed potential as a leading drug among the compounds tested. Batzelladine L (8) also showed higher activity against Mycobacterium intracellulare (IC_{50}: 0.25 µg/mL) and comparable activity against leishmania (IC_{50}: 1.9 µg/mL) compared to the positive controls, which were ciprofloxacin, pentamidine, and amphotericin B. The compound showed the most potent activity as an inhibitor of Mycobacterium tuberculosis, with a MIC value of 1.68 µg/mL. In addition, batzelladine L (8) exhibits anti-cancer activity against A549, DU-145, SK-BR3, SK-MEL-28, PANCL, LOVO-DOX, LOVO, HeLa, HT-29, IGROV, and leukemia L-562. In 2020, it was reported that batzelladine D (4) and norbatzelladine L (9) inhibit the Pdr5p transporter of Saccharomyces cerevisiae in terms of its catalytic and functional activity [18]. This inhibition induces the reversal of fluconazole resistance once the compounds are consumed together with theazole drug, which helps to counter multidrug resistance in fungi. The newest bioactivity of batzelladine was reported in 2022 when 15 batzelladines were screened for their inhibitory activities against the SARS-CoV-2 main protease (M^{pro}P) through molecular docking studies [19]. Most of the batzelladines tested showed good binding energy, ranging from −7.12 ± 0.60 to −6.22 ± 0.37 kcal/mol, which is similar to that of the tested native ligands O6K (−7.36 ± 0.34 kcal/mol) and N3 (−6.36 ± 0.31 kcal/mol). Among the batzelladines, the most promising compounds in terms of their anti-SARS-CoV-2 activity were batzelladine H (18) and batzelladine I (19). Based on a structure-activity relationship study, the factors that affect the protein-ligand interaction were identified as the position of the N-OH functionality, the length of the spacer between the two active sides, and the compounds’ degree of unsaturation. The bioactivities of batzelladines are tabulated in Tables 1 and 3.
Table 1. Bioactivities of batzelladines.

| Sponge Source | Synthesized | Anti-Cancer | Anti-Malarial | Anti-Microbial | HIV Inhibitor | Reference |
|---------------|-------------|-------------|---------------|----------------|---------------|-----------|
| **Skeleton 1** |             |             |               |                |               |           |
| Batzelladine A (1) | Batzella sp., Monanchora arbuscula, Clathria calla | / | / | / | / | [1–4] |
| Norbatzelladine A (2) | M. arbuscula, C. calla | / | / | / | / | [2] |
| Dinorbatzelladine A (3) | M. arbuscula, C. calla | / | / | / | / | [2] |
| Batzelladine D (4) | Batzella sp., M. arbuscula | / | / | / | / | [1,3,5–9] |
| Batzelladine F (5) | Batzella sp., M. arbuscula | / | / | / | / | [5,10–14] |
| Batzelladine G (6) | Batzella sp. | / | / | / | / | [10] |
| Batzelladine K (7) | M. unguifera | / | / | / | / | [15,16] |
| Batzelladine L (8) | M. unguifera, M. arbuscula, C. calla | / | / | / | / | [2,5,16] |
| Norbatzelladine L (9) | M. arbuscula, C. calla | / | / | / | / | [2,5] |
| Merobatzelladine A (10) | Monanchora sp. | / | / | / | / | [17] |
| Merobatzelladine B (11) | Monanchora sp. | / | / | / | / | [17,20,21] |
| **Skeleton 2** |             |             |               |                |               |           |
| Batzelladine B (12) | Batzella sp. | / | / | / | / | [1,22,23] |
| Batzelladine E (13) | Batzella sp. | / | / | / | / | [1,24] |
| **Skeleton 3** |             |             |               |                |               |           |
| Batzelladine C (14) | Batzella sp., M. unguifera | / | / | / | / | [1,16,25] |
| Batzelladine J (15) | M. unguifera | / | / | / | / | [26] |
| Batzelladine M (16) | M. unguifera | / | / | / | / | [16] |
| Batzelladine N (17) | M. unguifera | / | / | / | / | [16] |
| **Skeleton 4** |             |             |               |                |               |           |
| Batzelladine H (18) | Batzella sp. | / | / | / | / | [10] |
| Batzelladine I (19) | Batzella sp. | / | / | / | / | [10] |
Table 1. Cont.

| Sponge Source | Synthesized | Anti-Cancer | Anti-Malarial | Anti-Microbial | HIV Inhibitor | Reference |
|---------------|-------------|-------------|---------------|----------------|---------------|-----------|
| Dinordehydrobatzelladine B (20) | *M. arbuscula, C. calla* | / | / | / | / | [2] |
| Dihomodehydrobatzelladine C (21) | *M. arbuscula, C. calla* | / | / | / | / | [2] |
| Clathriadic acid (22) | *M. arbuscula, C. calla* | / | / | / | / | [2] |
| Skeleton 5 | | | | | | |
| Dehydrobatzelladine C (23) | *M. unguifera* | / | / | / | / | [16] |

/ = exhibited bioactivities.
Before the first batzelladines were found, in 1981, Rinehart et al. isolated isoptilocaulin (43) and ptilocaulin (62) from the Caribbean sponge *Ptilocaulis spiculifer* [27]. The study also reported their antimicrobial and antitumor activities, with more potent activities exhibited by ptilocaulin (62) than isoptilocaulin (43). It is cytotoxic for L1210 leukemia cells, with an IC₅₀ value of 0.39 µg/mL. It showed a low µg/mL MIC activity against *Escherichia coli*, *Streptococcus pyogenes*, *Streptococcus faecalis*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*. Several years later, the isolation of ptilocaulin derivatives from the sponges *Monanchora arbuscula* and *Batzellia* sp. was reported [28–30]. In 1996, a similar skeleton derived from ptilocaulin was isolated and became known as mirabilin. Mirabilins A–F (40, 49, 50, 53, 64) were isolated in 1996, and mirabilin G (60) was isolated in 2001, from *Arenochalina mirabilis* and *Clathria* sp., respectively [31,32]. Mirabilin G (60) showed antifungal and antimicrobial activities against *Saccharomyces cerevisiae*, *E. coli*, and *Serratia marcescens* [32]. In terms of anti-cancer activity, mirabilin C (26) and mirabilins F–J (31, 41, 60, 64, 66) showed moderate activity against intestinal (Intestine-407), gastric (AGS), neuroblastoma (SH-SY5Y), and colorectal (HT29) cancer cell lines [33]. The isolation of new ptilocaulin derivatives, netamines A–S (24–27, 29–30, 32–35, 44–48, 57–59, 61), sparked the interest of natural product chemists [34–36]. Netamine K (57) and netamines O–Q (30, 32–33) exhibited significant anti-malarial activity against *Plasmodium falciparum* [35,36]. Netamines also showed anti-cancer activity towards lung (A549), colon (HT29), breast (MDS-MB-231), and KB cell lines [34–36]. Under tumor-promoting conditions, netamine M (59) and mirabilin G (60) exhibited antitumor activity via PDCD4 stabilization, with EC₅₀ values of 2.8 µg/mL and 1.8 µg/mL, respectively [37]. These compounds were the first marine natural products reported with this bioactivity. In combatting the SARS-CoV-2 virus, Ramadhan et al. reported that mirabilin G (60) (−7.38 kcal/mol) possesses a similar binding activity with the native ligand N3 (−7.30 kcal/mol) to the SARS-CoV-2 main protease (Mₚₚο) [38]. The stability of the compound and its good binding affinity to the enzyme prove that it could be a potential target for inhibiting the SARS-CoV-2 virus.
Table 2. Bioactivities of ptilocaulin, netamine, and mirabilin.

| Sponge Source                  | Synthesized | Anti-Cancer | Anti-Malarial | Antimicrobial | Hemolytic Activities | Reference |
|-------------------------------|-------------|-------------|---------------|---------------|----------------------|-----------|
| Saturated                     |             |             |               |               |                      |           |
| Netamine A (24)               | Bienna laboutei |             |               |               |                      | [34]      |
| Netamine B (25)               | Bienna laboutei |             |               |               |                      | [34]      |
| Netamine C (26)               | Bienna laboutei |             |               |               |                      | [34,39]   |
| Netamine D (27)               | Bienna laboutei |             |               |               |                      | [34]      |
| Mirabilin K (28)              | Acanthella cavernosa |         |               |               |                      | [37]      |
|                               |             |             |               |               |                      |           |
| ∆11,12                        |             |             |               |               |                      |           |
| Netamine E (29)               | Bienna laboutei |             |               |               |                      | [34,40]   |
| Netamine O (30)               | Bienna laboutei |             |               |               |                      | [36]      |
| Mirabilin H (31)              | Clathria sp. |             |               |               |                      | [33]      |
| Netamine P (32)               | Bienna laboutei |             |               |               |                      | [36]      |
| Netamine Q (33)               | Bienna laboutei |             |               |               |                      | [36]      |
| Netamine R (34)               | Bienna laboutei |             |               |               |                      | [36]      |
| Netamine S (35)               | Bienna laboutei |             |               |               |                      | [36]      |
| 7-Epineoptilocaulin (36)       | Batzella sp. |             |               |               |                      | [29,40]   |
| Mirabilin E (37)              | Arenochalina mirabilis |       |               |               |                      | [31]      |
| 8α-Hydroxy-7-epineoptilocaulin (38) | Batzella sp. |             |               |               |                      | [29]      |
| Mirabilin E diacetate (39)    | Arenochalina mirabilis |         |               |               |                      | [31]      |
| Mirabilin D (40)              | Arenochalina mirabilis |         |               |               |                      | [31]      |
| Mirabilin J (41)              | Clathria sp. |             |               |               |                      | [33]      |
| Mirabilin D diacetate (42)    | Arenochalina mirabilis |         |               |               |                      | [31]      |
|                               |             |             |               |               |                      |           |
| ∆9,10                         |             |             |               |               |                      |           |
| Isoptilocaulin (43)           | Ptilocaulis aff. Ptilocaulis spiculifer |       |               |               |                      | [27]      |
| Pyrimidines                   |             |             |               |               |                      |           |
| Netamine F (44)               | Bienna laboutei |             |               |               |                      | [34]      |
| Netamine G (45)               | Bienna laboutei |             |               |               |                      | [34,40]   |
| Netamine H (46)               | Bienna laboutei |             |               |               |                      | [35]      |
| Netamine I (47)               | Bienna laboutei |             |               |               |                      | [35]      |
| Netamine J (48)               | Bienna laboutei |             |               |               |                      | [35]      |
Table 2. Cont.

| Sponge Source | Synthesized | Anti-Cancer | Anti-Malarial | Antimicrobial | Hemolytic Activities | Reference |
|---------------|-------------|-------------|---------------|---------------|----------------------|-----------|
| **Mirabilin A (49)** | Arenochalina mirabilis, Biemna laboutei | / | / | / | [31,35] |
| **Mirabilin C (50)** | Arenochalina mirabilis, Biemna laboutei, Clathria sp. | / | / | / | [31,33,35] |
| **Mirabilin A acetate (51)** | Arenochalina mirabilis | / | X | / | [30,31,41] |
| **Mirabilin C acetate (52)** | Arenochalina mirabilis | / | X | / | [31] |
| **Mirabilin B (53)** | Arenochalina mirabilis, Monanchora unguifera | / | / | / | [30,31,41] |
| **Mirabilin B acetate (54)** | Arenochalina mirabilis | / | / | / | [31] |
| **8α-Hydroxymirabilin (55)** | Batzella sp., Monanchora unguifera | / | / | / | [29,30] |
| **8β-Hydroxymirabilin (56)** | Monanchora unguifera | / | / | / | [30] |

= exhibit bioactivity, X = did not exhibit any bioactivity.
Table 3. Specification of the bioactivities of batzelladines, ptilocaulin, netamines, and mirabilins.

| Common Names       | Mode of Action/Cells Inhibited                                                                 | References |
|--------------------|------------------------------------------------------------------------------------------------|------------|
| **HIV inhibitor**  |                                                                                                |            |
| Batzelladine A (1) | Inhibits gp120 binding to CD4, protein kinase C activity, binding of interleukin-8 (IL8) and calcitonin gene-related peptide (CGRP) to their receptors, inhibits Vero cells | [1]        |
| Batzelladine D (4) | Vero cells                                                                                     | [1]        |
| Batzelladine F (5) | Induces p56\(^{\text{ck}}\)-CD4 dissociation                                                   | [10]       |
| Batzelladine G (6) |                                                                                                |            |
| Batzelladine L (8) | Shows inhibitory activity against human HIV-1 virus                                            | [16]       |
| Batzelladine B (12)| Inhibits gp120 binding to CD4, protein kinase C activity, binding of interleukin-8 (IL8) and calcitonin gene-related peptide (CGRP) to their receptors, inhibits Vero cells | [1]        |
| Batzelladine C (14)| Vero cells, shows inhibitory activity against the human HIV-1 virus                            | [1,16]     |
| Batzelladine M (16)| Shows inhibitory activity against human HIV-1 virus                                            | [16]       |
| Batzelladine N (17)|                                                                                                |            |
| Batzelladine H (18)| Induces p56\(^{\text{ck}}\)-CD4 dissociation when combined with batzelladine I                | [10]       |
| Batzelladine I (19)| Induces p56\(^{\text{ck}}\)-CD4 dissociation when combined with batzelladine H               |            |
| Dehydrobatzelladine C (23)| Shows inhibitory activity against human HIV-1 virus                         | [16]       |
| **SARS-CoV-2 inhibitor** |                                                                                           |            |
| Batzelladine H (18)| Inhibits SARS-CoV-2 main protease (M\(^{\text{pro}}\))                                      |            |
| Batzelladine I (19)|                                                                                               |            |
| Mirabilin G (60)  | Inhibits SARS-CoV-2 main protease (M\(^{\text{pro}}\))                                      |            |
| **Anti-cancer**   |                                                                                                |            |
| Norbatzelladine A (2)| MDA-MB-231, A549, HT29                                                                         | [2]        |
| Dinorbatzelladine A (3)|                                                                                              |            |
| Batzelladine L (8) | DU-145, IGROV, SK-BR3, leukemia L-562, PANCL, HeLa, SK-MEL-28, A549, HT-29, LOVO, and LOVO-DOX | [16]       |
| Norbatzelladine L (9)| MDA-MB-231, A549, HT29                                                                         | [2]        |
| Batzelladine C (14)| DU-145, IGROV, SK-BR3, leukemia L-562, PANCL, HeLa, SK-MEL-28, A549, HT-29, LOVO, and LOVO-DOX | [16]       |
| Common Names          | Mode of Action/Cells Inhibited                                                                 | References |
|-----------------------|-----------------------------------------------------------------------------------------------|------------|
| Batzelladine J (15)   | P-388, A-549, HT-29, MEL-28, DU-145                                                          | [26]       |
| Batzelladine M (16)   | DU-145, IGROV, SK-BR3, leukemia L-562, PANCL, HeLa, SK-MEL-28, A549, HT-29, LOVO, and LOVO-DOX | [16]       |
| Batzelladine N (17)   |                                                                                              |            |
| Dinordehydrobatzelladine B (20) |                                                                                             |            |
| Dihomodehydrobatzelladine C (21) | Clathriadic acid (22)                                                                        | [2]        |
| Dehydrobatzelladine C (23) | DU-145, IGROV, SK-BR3, leukemia L-562, PANCL, HeLa, SK-MEL-28, A549, HT-29, LOVO, and LOVO-DOX | [16]       |
| Netamine C (26)       |                                                                                              | [34]       |
| Netamine D (27)       |                                                                                              | [34]       |
| Netamine O (30)       |                                                                                              | [36]       |
| Mirabilin H (31)      |                                                                                              | [33]       |
| Netamine Q (33)       |                                                                                              | [36]       |
| Mirabilin J (41)      |                                                                                              | [33]       |
| Isoptilocaulin (43)   |                                                                                              | [27]       |
| Mirabilin C (50)      |                                                                                              | [33]       |
| Netamine M (59)       |                                                                                              | [35,37]    |
| Mirabilin G (60)      |                                                                                              | [33,37]    |
| Ptilocaulin (62)      |                                                                                              | [27,41,42] |
| 8b-Hydroxyptilocaulin (63) |                                                                                             | [41]       |
| Mirabilin F (64)      |                                                                                              | [33]       |
| Mirabilin I (66)      |                                                                                              | [33]       |

Anti-malarial
Table 3. Cont.

| Common Names | Mode of Action/Cells Inhibited | References |
|--------------|--------------------------------|------------|
| Batzelladine A (1) | *P. falciparum* (FcB1) | [2] |
| Norbatzelladine A (2) | *P. falciparum* (FcB1) and its D6 clone and W2 clone | [2,16] |
| Dinorbatzelladine A (3) | *P. falciparum* (FcB1) | [2] |
| Batzelladine L (8) | *P. falciparum* (FcB1) | [2] |
| Norbatzelladine L (9) | *P. falciparum* (FcB1) and its D6 clone and W2 clone | [2,16] |
| Merobatzelladine A (10) | *P. falciparum* | [17] |
| Merobatzelladine B (11) | *P. falciparum* | [17] |
| Batzelladine C (14) | Against *P. falciparum* D6 clone and W2 clone | [16] |
| Batzelladine M (16) | Against *P. falciparum* D6 clone and W2 clone | [16] |
| Dinordehydrobatzelladine B (20) | *P. falciparum* (FcB1) | [2] |
| Dihomodehydrobatzelladine C (21) | *P. falciparum* (FcB1) | [2] |
| Clathriadic acid (22) | *P. falciparum* (FcB1) | [2] |
| Dehydrobatzelladine C (23) | Against *P. falciparum* D6 clone and W2 clone | [16] |
| Netamine O (30) | *P. falciparum* | [36] |
| Netamine P (32) | *P. falciparum* | [36] |
| Netamine Q (33) | *P. falciparum* | [36] |
| Mirabilin A (49) | *P. falciparum* | [35] |
| Netamine K (57) | *P. falciparum* | [35] |

**Antimicrobial**

| Common Names | Mode of Action/Cells Inhibited | References |
|--------------|--------------------------------|------------|
| Batzelladine D (4) | *Trypanosoma cruzi* trypomastigotes, *Leishmania infantum* promastigotes, *Saccharomyces cerevisiae* | [5,18] |
| Batzelladine F (5) | *Trypanosoma cruzi* trypomastigotes, *Leishmania infantum* promastigotes | [5] |
| Batzelladine L (8) | *T. cruzi* trypomastigotes, *L. infantum* promastigotes Strong activities against AIDS-OIs *Candida albicans*, *Cryptococcus neoformans*, *S. aureus*, methicillin-resistant *S. aureus* (MRS), *Pseudomonas aeruginosa*, and *M. intracellulare*, as well as *Aspergillus fumigatus*, *M. tuberculosis*, and *Leishmania donovani* | [5,16] |
| Norbatzelladine L (9) | *T. cruzi* trypomastigotes, *L. infantum* promastigotes, *S. cerevisiae* | [5] |
| Merobatzelladine A (10) | *Vibrio anguillarum*, *Trypanosoma brucei brucei* | [17] |
| Merobatzelladine B (11) | *Vibrio anguillarum*, *Trypanosoma brucei brucei* | [17] |
| Common Names                  | Mode of Action/Cells Inhibited                                                                 | References |
|------------------------------|------------------------------------------------------------------------------------------------|------------|
| Batzelladine C (14)          | Strong activities against AIDS-Ols *C. albicans*, *C. neoformans*, *S. aureus*, methicillin-resistant *S. aureus* (MRS), *P. aeruginosa*, *M. intracellulare*, and *A. fumigatus* | [16]       |
| Batzelladine M (16)          | *M. tuberculosis*                                                                                   | [16]       |
| Batzelladine N (17)          | Strong activities against AIDS-Ols *C. albicans*, *C. neoformans*, *S. aureus*, methicillin-resistant *S. aureus* (MRS), *P. aeruginosa*, *M. intracellulare*, and *A. fumigatus* | [16]       |
| Dehydrobatzelladine C (23)   | *S. pyogenes*, *S. pneumoniae*, *E. faecalis*, *S. aureus*, *E. coli*                              | [27]       |
| Isoptilocaulin (43)          | *C. neoformans*, *L. donovani*                                                                     | [30]       |
| Mirabilin B (53)             | *E. coli*, *Serratia marcescens*, and *S. cerevisiae*                                              | [32]       |
| Mirabilin G (60)             | *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *E. faecalis*, *S. aureus*, *E. coli*        | [27]       |
| Ptilocaulin (62)             | Hemolytic activities                                                                               |            |
| Ptilocaulin (62)             | *The plasma membrane of mouse erythrocytes*                                                        | [41]       |
| 8β-Hydroxyptilocaulin (63)   |                                                                                                   |            |
Despite having unusual skeletons and intriguing bioactivities, these alkaloids are only found in marine sponges, limiting their availability for further research. The scope of bioactivity studies is also constrained by the minute quantities of the compounds isolated (<0.1%) and the high consumption of solvents, time, and money during the isolation and purification processes. To further investigate their biological potential, it is critical to understand the synthesis of these tricyclic guanidine alkaloids. This review is designed to help readers to understand the strategies utilized for synthesizing the tricyclic guanidine alkaloids and, hence, to help researchers to develop more economical routes to improve our understanding of this type of skeleton.

2. Methodology

The literature was obtained from Google Scholar, ScienceDirect, SciFinder, and PubMed. The search terms used were “batzelladine”, “ptilocaulin”, “netamine” and “mirabilin”. In total, 155 related articles were obtained after removing duplicate articles. Only articles written in English were included in the study. All of the 155 articles were evaluated, and only 62 articles were included in this study due to their eligibility for the focus of the study.

3. Synthesis

3.1. Batzelladine Skeleton

There are five skeletons of batzelladines varying in terms of the degree of unsaturation within their tricyclic guanidine skeletons (Figure 1). Only three of these five skeletons have been synthesized, with most studies focusing on Skeleton I (Figure 3). In most cases, the batzelladine skeleton, comprising a tricyclic guanidine, is linked to another guanidine moiety through an ester linkage. The cyclization of the tricyclic guanidine is commonly conducted through tethered Biginelli condensation, Mitsunobu reaction, or ring-closing iodoamination reaction [3,6,11,12,14,20,22,25]. The coupling of the bicyclic guanidine with the ester linkage must be performed before the cyclization of the bicyclic guanidine into tricyclic guanidine, because the axially orientated ester complicates the coupling reaction [6,43]. The starting material for synthesizing different kinds of batzelladines is visualized in Figure 3.

Figure 3. Starting material for synthesizing batzelladine skeleton.
3.1.1. Batzelladine A

In 1995, Rama Rao et al. reported the first synthesis of the tricyclic guanidine fraction of batzelladine A (Figure 4) [4]. The azetidinone derivative 67 was alkylated through the Grignard reaction. Thiolactam 69 was obtained through the successive reduction of 68, acetylation, oxidation, and sulfide contraction. Afterwards, 13 steps were conducted to obtain 70. The tricyclic guanidine fragment of batzelladine A was obtained after the reaction of 70 with dimethyl sulfate, hydrogenation, and desilylation.

For a long time, the rare annulation of vinyl carbodiimides and imines was only possible using the achiral coupling partner PhCH = NPh [44]. In 2006, Arnold and his co-workers attempted a new strategy for the total synthesis of batzelladine A by performing the annulation using chiral N-alkyl imines as the coupling partner [3] (Figure 5). As the starting material, the vinyl carbodiimide was formed from the 1,4-but-2-ynoic acid benzyl ester 72. Then, 72 underwent 1,4 addition and Staudinger–aza-Wittig condensation to form the E and Z of the vinyl carbodiimides 73. Additionally, 75 was obtained through the reaction of the previously separated isomer of 73 with the chiral amine 2-(2-O-TBDPS-ethyl)-3,4-dihydro-2H-pyrrole 74. The subsequent Ir-catalyzed reduction of 75 followed by IBX oxidation yielded the tricyclic guanidine hemiaminal 76 in a 98% yield. The hydrogenolysis and cis-selective Wittig olefination of 76 afforded the right-hand side of batzelladine A 77 in a 72% yield.

To obtain the left-hand side of the compound, sequential O-benzylation and C-acylation followed by the 1,4-addition of azide and Staudinger–aza-Wittig condensation of 78 yielded the vinyl carbodiimide 79 in a 63% yield (Figure 6). Racemate 79 reacted with the chiral amine 74 to undergo enantioselective annulation to provide a single diastereomer of dihydropyrimidine of 80 with an 89% yield. Subsequent reactions resulted in a pyrrolidine ring-opening reaction of 80 to form 81. The ring closure of 81 was accomplished through an intramolecular aza-Mitsunobu reaction to generate the bicyclic guanidine skeleton. The acylation of the compound then afforded the bicyclic vinylogous carbamate 82 with an 85% yield. The vinylogous carbamate 82 was then esterified by 83 and converted into methanesulfonate ester derivative to yield the bicyclic guanidine of batzelladine A 84.

Figure 4. Rama Rao, synthetic approach to the tricyclic guanidine fraction of batzelladine A.
Figure 5. Arnold, synthetic approach to the right-hand side of batzelladine A.

Figure 6. Arnold, synthetic approach to the left-hand side of batzelladine A.
Both enantiomers, 77 (right-hand side) and 84 (left-hand side) underwent alkylation to couple both of the compounds by an ester linkage, affording 85 (Figure 7). The intramolecular iodoamination and reductive iodination of 85 produced the cyclization reaction to form the tricyclic guanidine, followed by TFA-mediated deprotection, providing the batzelladine A 1 in a 75% yield.

![Chemical structures](image)

Figure 7. Arnold, synthetic approach to batzelladine A.

### 3.1.2. Batzelladine D

In 1999, Cohen and his co-workers reported on the first enantioselective total synthesis of a batzelladine alkaloid through tethered Biginelli condensation, which provided the anti-stereochemistry required to synthesize batzelladine D [7] (Figure 8). The guanylation of 87 with 88 yielded the guanidine 89. The guanidine was subjected to tethered Biginelli condensation with 90 in the presence of morpholinium acetate and sodium sulfate, affording the guanidium acetate 91 in a 55% yield. The guanidium acetate 91 was mesylated and then cyclized in the presence of triethylamine to provide the tricyclic guanidine 92 in a 60% yield. The subsequent reduction of 92 with Rh/Al₂O₃ yielded a mixture of 93, 94, and 95. An optimal product of 93 was obtained when the hydrogenation was conducted at 50 psi. The batzelladine D bistrifluoroacetate 4 was then acquired in a 75% yield upon the guanylation of 88 with 93.
As previously reported regarding the synthesis of batzelladine A, intermediate 77 was also used to synthesize batzelladine D [3] (Figure 9). The subsequent O-alkylation of 77 with 96 afforded 97 in a 93% yield. The cyclization of bicyclic guanidine was conducted by intramolecular iodoamination and reductive deiodination, followed by deprotection, affording the batzelladine D 4 in an 82% yield.
In 2007, Evans and co-workers approached the synthesis of (−)-batzelladine D through allylic amination catalyzed by rhodium and free-radical cyclization [8] (Figure 10). The study highlighted the presence of azide in the selective homolytic cleavage of the methyl halide, removing the need for a nitrogen-protecting group. The reaction was initiated by the acid-catalyzed Biginelli condensation of 99 followed by regioselective sulfonylation to afford 100, which was the fragment required for the allylic amination catalyzed by rhodium. The reaction between the lithium anions of 100 and 101 in the presence of a rhodium catalyst was modified based on Wilkinson’s catalyst, yielding 102 as a mixture of diastereoisomers. The hydrosilylation of 102 followed by transesterification and Mitsunobu inversion afforded 103 in an 82% yield. The diazide 103 was then oxidized using Tamao–Fleming oxidation followed by an Appel reaction to afford alkyl iodide functionality. Subsequently, a radical cyclization with tributyltin hydride and triethylborane produced pyrrolo[1,2-\(f\)]pyrimidine 104 in an 80% yield. The removal of the camphorsulfonyl group methyl triflate yielded 105 in an 81% yield. The subsequent hydrogenation of 105 followed by cyclization in the presence of an acyclic guanidine moiety afforded (−)-batzelladine D 4 in a good yield.

In 2002, Ishiwata and co-workers synthesized the absolute stereochemistry of batzelladine D through three main strategies, which were 1,3-dipolar cycloaddition, esterification of the side chain, and tricyclic guanidine formation [6] (Figure 11). The initial strategy was to form the ester linkage between guanidinobutyl alcohol and guanidinecarboxylic acid, but the reaction failed. Similarly, this scenario was also observed by Snider and Chen [43]. It was proposed that the failure was caused by the axially orientated ester or carboxylic acid of the guanidinecarboxylic acid at the C7 position. Hence, the tricyclic guanidine formation was conducted after the coupling of the fragments. The synthesis was initiated by two sequential 1,3-dipolar cycloadditions, alternated with oxidation, yielding isoxazoline 110 in a 62% yield. The sequential reaction of isoxazoline 110 via LiAlH\(_4\)-mediated reduction, followed by hydroxyl protection and then a second reduction with H\(_2\) on Pd/c, afforded pyrrolidine 111 in a 70% yield. The incorporation of 111 and 112 followed by the Mitsunobu reaction, selective cleavage of silyl ether, and Jones oxidation resulted in bicyclic guanidine 113. The esterification of 113 with 114, followed by benzylamino group deprotection, yielded 115. The Mitsunobu reaction of 115 followed by deprotection afforded batzelladine D 4, whereas the oxidation of 115 followed by hydrogenation afforded the 13-epi-batzelladine D 118.
In 2002, Ishiwata and co-workers synthesized the absolute stereochemistry of batzelladine D through three main strategies, which were 1,3-dipolar cycloaddition, esterification of the side chain, and tricyclic guanidine formation [6] (Figure 11). The initial strategy was to form the ester linkage between guanidino butyl alcohol and guanidinecarboxylic acid, but the reaction failed. Similarly, this scenario was also observed by Snider and Chen [43]. It was proposed that the failure was caused by the axially orientated ester or carboxylic acid of the guanidinecarboxylic acid at the C7 position. Hence, the tricyclic guanidine formation was conducted after the coupling of the fragments. The synthesis was initiated by two sequential 1,3-dipolar cycloadditions, alternated with oxidation, yielding isoxazoline 110 in a 62% yield. The sequential reaction of isoxazoline 110 via LiAlH₄-mediated reduction, followed by hydroxyl protection and then a second reduction with H₂ on Pd/c, afforded pyrrolidine 111 in a 70% yield. The incorporation of 111 and 112 followed by the Mitsunobu reaction, selective cleavage of silyl ether, and Jones oxidation resulted in bicyclic guanidine 113. The esterification of 113 with 114, followed by benzyl-amino group deprotection, yielded 115. The Mitsunobu reaction of 115 followed by

Figure 10. Evans, synthetic approach to (−)-batzelladine D.

In 2020, Lin and his co-workers not only managed to synthesize the (±)-batzelladine D, (±)-13-epi-batzelladine D and (±)-15-epi-batzelladine D, but they also managed to synthesize the single enantiomer of each compound [9] (Figure 12). In this review, only batzelladine D and 13-epi-batzelladine D are included. The synthesis of (+)-batzelladine was conducted using β-lactam 119, as it already has the necessary hydroxyethyl side chain as the starting material. The lactam was reacted with sodium benzenesulfinate and Grignard reagent 120 to afford 121 in an 87% yield. The subsequent cross-metathesis of 121 and 122 provided 123, which underwent aza-Michael addition and TBS deprotection to yield the precursor 124 in an 84% yield. Then, 124 underwent diastereoselective reduction and conversion to yield the (+)-batzelladine D 4 and (+)-13-epi-batzelladine D 118.
Figure 11. Ishiwata, synthetic approach to batzelladine D and 13-epi-batzelladine D.
3.1.3. Batzelladine F

Batzelladine F is composed of two tricyclic guanidines linked with an ester linkage. It was isolated in 1997, but its ambiguous stereochemical assignment remained a source of debate for several years. In 1998, through biomimetic studies synthesizing ptilomycalin A, Black and co-workers approached the synthesis of the batzelladine skeleton through sequential double Michael additions of guanidine and bis-α,β-unsaturated ketone [45,46]. This strategy was adapted one year later for the synthesis of the left-hand side of batzelladine F to reveal its absolute configuration [13] (Figure 13). With tetrahydropyran 125 as the starting material, it was converted into 126 in five steps, with a good overall yield of 91%. Sequential mesylation followed by a substitution reaction of 126 with NaI afforded 127 in a 67% yield. The subsequent reaction between 127 and phosphorane 128 generated the ylide 129, which was followed by the Wittig reaction with succinaldehyde, yielding 130 in a 54% yield. The bis-enone 131 was formed through another Wittig reaction between 130 and phosphorane 128. The sequential reaction of 131, involving the addition of guanidine, reduction, and a counter-ion exchange reaction, produced the tricyclic guanidine 132. The tricyclic guanidine 132 was deprotected and acetylated to form the desired product 133, the left-hand side of batzelladine F. The study also proposed that the hydrogens bonded to the chiral carbon of the pentacyclic moiety of the tricyclic guanidine 133 were in cis conformation, which readressed the earlier incorrect stereochemical assignment.

The stereochemical assignment of the left-hand side of tricyclic guanidine batzelladine F was further validated by Nagasawa and co-workers via a different synthetic route [11] (Figure 14). The isoxazolidine 134 was obtained from 106 using a similar approach to that for obtaining the isoxazolidine of batzelladine D through 1,3-dipolar cycloaddition, giving a 65% yield [6]. The isoxazolidine 134 was converted to 135 in three steps of the reaction, including mesylation, treatment with cesium acetate, and acetate hydrolysis. The subsequent oxidation of 135 with mCPBA yielded nitrone 136 that, upon reduction, afforded pyrrolidine 137 in a 49% yield. The pyrrolidine 137 was reacted with bis-Z-methylthiopseudourea in the presence of mercury (II) chloride and triethylamine to provide the guanylated pyrrolidine. This pyrrolidine was subjected to a Mitsunobu reaction to yield the bicyclic guanidine 138. The selective deprotection of 138 followed by another mesylation and hydrogenolysis afforded the syn form of tricyclic guanidine 139 in a 67% yield. This study confirmed that the natural batzelladine F possessed syn conformation on the left-hand side of its tricyclic guanidine.
Figure 13. Black, synthetic approach to the left-hand side of batzelladine F. The stereochemical assignment of the left-hand side of tricyclic guanidine batzelladine F was further validated by Nagasawa and co-workers via a different synthetic route [11] (Figure 14). The isoxazolidine 134 was obtained from 106 using a similar approach to that for obtaining the isoxazolidine of batzelladine D through 1,3-dipolar cycloaddition, giving a 65% yield [6]. The isoxazolidine 134 was converted to 135 in three steps of the reaction, including mesylation, treatment with cesium acetate, and acetate hydrolysis. The subsequent oxidation of 135 with mCPBA yielded nitrone 136 that, upon reduction, afforded pyrrolidine 137 in a 49% yield. The pyrrolidine 137 was reacted with bis-Z-methylthiopseudourea in the presence of mercury (II) chloride and triethylamine to provide the guanylated pyrrolidine. This pyrrolidine was subjected to a Mitsunobu reaction to yield the bicyclic guanidine 138. The selective deprotection of 138 followed by another mesylation and hydrogenolysis afforded the syn form of tricyclic guanidine 139 in a 67% yield. This study confirmed that the natural batzelladine F possessed syn conformation on the left-hand side of its tricyclic guanidine.

Figure 14. Nagasawa, synthetic approach to the left-hand side of batzelladine F. In 2006, Overman and Cohen also conducted an extensive study to reveal the absolute configuration of batzelladine F [12] (Figure 15). The synthesis was performed using two different strategies. The first strategy was to couple the alcohol on the left side with the acid on the right side of batzelladine F. This coupling causes epimerization at C19, which prolongs the mechanistic route for successful coupling. Hence, the second strategy was to use a tethered Biginelli reaction to condense the β-keto ester of the left-hand side of the batzelladine with the guanidine hemiaminal of its right-hand side. The ring-closing reaction of the right-hand side was conducted, which successfully synthesized the batzelladine F through a shorter route. Upon comparing the products obtained, it was observed that the HPLC of the compound of the natural batzelladine F was different. The mass spectrometry of the authentic batzelladine F suggested that the initial proposal of the compound structure was incorrect. The compound possessed an n-heptyl side chain on its right-hand tricyclic guanidine fragment, instead of the nonyl side chain initially proposed upon isolation.

The subsequent approach of this study was to synthesize the batzelladine F with the n-heptyl side chain. The synthesis began by converting the hydroxybutyrate 140 into a Weinreb amide, which was subjected to several steps involving a double Mitsunobu reaction, hydrogenation, and then Troc-protected guanidine synthesis, yielding the bicyclic guanidine hemiaminal 141 [12]. The tethered Biginelli reaction between 141 and β-keto ester 142 yielded the tricyclic guanidine 143 in an 82% yield. Upon a series of reactions, it afforded the tricyclic guanidine tetrafluoroborate 144 in a 60% yield. The acylation of 144 in the presence of DMAP successfully yielded the left-hand side of batzelladine F 145 in a 90% yield.
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Figure 15. Overman, synthetic approach to the left-hand side of batzelladine F.

The subsequent approach of this study was to synthesize the batzelladine F with the n-heptyl side chain. The synthesis began by converting the hydroxybutyrate 140 into a Weinreb amide, which was subjected to several steps involving a double Mitsunobu reaction, hydrogenation, and then Troc-protected guanidine synthesis, yielding the bicyclic guanidine hemiaminal 141 [12]. The tethered Biginelli reaction between 141 and β-keto ester 142 yielded the tricyclic guanidine 143 in an 82% yield. Upon a series of reactions, it afforded the tricyclic guanidine tetrafluoroborate 144 in a 60% yield. The acylation of 144 in the presence of DMAP successfully yielded the left-hand side of batzelladine F 145 in a 90% yield.

The right-hand side of batzelladine F was constructed in eight steps of the reaction of the (R)-β-hydroxy ketone 146 to obtain 147 in a 65% yield [14] (Figure 16). The coupling between the left side 145 with the right-hand side 147 was conducted using a tethered Biginelli condensation reaction, yielding the pentacyclic diguanidine 148 in a 59% yield. The ring-closing of 148 was achieved by exchanging the trifluoroacetate with tetrafluoroborate and converting the compound into a mesylate derivative. The product obtained was hexacycle diguanidine 149 in a 68% yield. The final step was the reduction of the carbon-carbon double bond to yield the batzelladine F 5 in a 21% yield. The stereochemical configuration of the synthesized compound is similar to the stereochemical structure of the authentic batzelladine F.
3.1.4. Merobatzelladine B

Merobatzelladine has a unique stereochemical structure compared with batzelladine B. In contrast to batzelladine B, exhibiting an anti-relationship of the C8 alkyl substituents with the C6 hydrogen atom, merobatzelladine has a syn-relationship. In 2012, Babij and Wolfe approached the total synthesis of merobatzelladine B by using a Pd-catalyzed alkene carboamination reaction [20] (Figure 17). The starting material 150 underwent six steps involving the asymmetric Mannich reaction to form compound 151. The carboamination of 151 with E-2-bromovinyltrimethylsilane using the Pd/P(2-furyl)3 catalyst afforded the cis-disubstituted pyrrolidine 152 in a 68% yield. The pyrrolidine 152 was obtained with high stereocontrol, with a more than 20:1 diastereomeric ratio. The pyrrolidine 152 was subjected to BOC group cleavage using TFA, followed by photodesilylation and p-methoxybenzylisocyanate coupling, yielding the pyrrolidinyl urea of 153 in a 72% yield. The second carboamination of 153 with (Z)-1-bromo-1-butene using the Pd/PCy3 catalyst generated the bicyclic guanidine 154 in a 91% yield. The functional group interconversion of 154 into guanidium salt 155 was conducted using POCl3 followed by an addition reaction with ammonia. The obtained product was washed with aqueous NaBF4 to trigger anion exchange to avoid complications during the next step. The subsequent hydrogenation, deprotection, and intramolecular Mitsunobu reaction afforded a ring-closure of 155 into 11 in a 41% yield. The merobatzelladine 11 was obtained in 15 steps, with an overall yield
of 6.7%. This study introduced the use of Pd-catalyzed carboamination for constructing 5,6-fused bicyclic urea.

Figure 17. Babij, synthetic approach to (+)-merobatzelladine B.

The most recent study on tricyclic guanidine was conducted in 2020 by El-Demerdash and his co-workers, using a shorter synthetic route [21] (Figure 18). The study approached the synthesis of a pyrrolidine ring by a multicomponent reaction in one pot, which was initially proposed by Robinson in 1917 for synthesizing tropinone [47]. The multicomponent reaction of this synthesis consists of compounds 156–159, which were dissolved in an aqueous medium for one day to obtain the pyrrolidine 160 in a 47% yield. Under an acidic environment, the heminal 161 was obtained as the result of a nucleophilic attack of the 2-aminopyrimidine on the ketone. The deprotection of the surrogate guanidine was conducted using methyl hydrazine, affording methyl hydrazone 162. The purification using LH-20 eventually yielded 163 in a 14% yield. The product was then reduced to form 164 and 165.

3.1.5. 9-Epi-batzelladine K

A previous study by Babij and Wolfe reported the use of a Pd-catalyzed carboamination reaction for constructing bicyclic urea derivatives [48] (Figure 19). The reaction produced a good yield but involved many steps. Hence, they worked on another route via a Pd-catalyzed desymmetrization reaction, which provides the benefit of introducing a different substituent to form highly substituted urea derivatives. They observed that different N-aryl substituents affected the asymmetric induction, and the p-chlorophenyl substituent afforded the best yield and stereoselectivity. The Pd-catalyzed asymmetric desymmetrization of 167 with 1-bromo-but-1-ene produced 168, with an exceptional 20:1 diastereomeric ratio. The subsequent cleavage of the N-p-chlorophenyl group of 168 was performed via Pd-
catalyzed N-arylation with acetamide followed by Wacker oxidation to avoid base-mediated epimerization, acting against 168. The Wacker oxidation of 168 produced 169 in a 65% yield. The subsequent hydrogenation and deprotection afforded urea 170 in a 51% yield. The O-methylation reaction of 170 and treatment with ammonia afforded the guanidine aminal 171, which was subjected to reduction and purification, yielding the 9-epi-batzelladine K 172 in a 48% yield.

![Figure 18. El-Demerdash, synthetic approach to tricyclic guanidine for merobatzelladine B.](image)

3.1.6. Batzelladine K

In 2010, Ahmed and his co-workers synthesized batzelladine K in only four steps [15] (Figure 20). The initial idea, contributed by Yu et al., proposed that the addition of guanidine to α,β-unsaturated ketone produces a tricyclic guanidium core [40]. The phosphorane 173 was alkylated with 1-iodobutane using butyllithium as the base, affording phosphorane 174. The reaction was followed by a Wittig reaction between 174 and excess succinaldehyde, yielding the E-isomer of 175 in a 68% yield. The ketone 175 was then reacted with phosphorane 173 to form the α,β-unsaturated ketone 176, which upon condensation with guanidine afforded the desired batzelladine K 7 in 25% yield following Michael addition and reduction. The overall product was yielded at 12%.
In 2010, Ahmed and his co-workers synthesized batzelladine K in only four steps [15] (Figure 20). The initial idea, contributed by Yu et al., proposed that the addition of guanidine to α,β-unsaturated ketone produces a tricyclic guanidium core [40]. The phosphorane 173 was alkylated with 1-iodobutane using butyllithium as the base, affording phosphorane 174. The reaction was followed by a Wittig reaction between 174 and excess succinaldehyde, yielding the E-isomer of 175 in a 68% yield. The ketone 175 was then reacted with phosphorane 173 to form the α,β-unsaturated ketone 176, which upon condensation with guanidine afforded the desired batzelladine K 7 in 25% yield following Michael addition and reduction. The overall product was yielded at 12%.

The first synthesis of the E and Z isomers of batzelladine E was reported by Snider and Chen in 1998 [24] (Figure 21). Initially, the synthetic approach targeted the E isomer, and it was reported that the E isomer configuration could be adopted from the naturally isolated
batzelladine E. However, upon spectrum comparison, the authors found that the actual configuration of batzelladine E was in the $Z$ form. Batzelladine E was synthesized using a similar mechanism as that used for synthesizing a pentacyclic portion of ptilomycalin A [49]. The authors’ earlier studies revealed that the introduction of the ester group could not be achieved after the construction of a polycyclic skeleton [43]. For this reason, the guanidino butyl ester was introduced in the earlier steps of the synthetic route. The deprotonation and alkylation of phosphorane $173$ yielded $178$ in a 64% yield. Afterwards, $178$ underwent two different types of condensation. The first condensation of $178$ and succinaldehyde afforded $179$ in a 65% yield. Subsequently, the Knoevenagel condensation of $179$ and $180$ was carried out. Initially, piperidinium acetate was used as the catalyst in the next synthetic strategy, but it was revealed that the $E$ isomer was formed. Hence, the catalyst system was changed to 0.33 equivalent of piperidine in the presence of 0.30 equivalent of acetic acid to promote the $Z$ isomer formation of the adduct $181$. The subsequent treatment of $181$ with $o$-methylisourea followed by ammonolysis and reduction yielded $182$ in an 88% yield. The addition of guanidine in the presence of 2-chloro-$N$-methylpyridinium iodide $183$ and $N,N'$-di-(t-butoxycarbonyl)thiourea $184$ generated the batzelladine E $13$ in a 90% yield.

**Figure 21.** Snider, synthetic approach to batzelladine E.

### 3.1.8. Batzelladine B

In 1999, Franklin and his co-workers applied the tethered Biginelli reaction to construct the tricyclic guanidine skeleton of batzelladine B [22] (Figure 22). The starting material $185$ underwent various reactions, including the conversion into Weinreb amide, the addition of guanidine through Mitsunobu displacement, and the reduction of the diazide, producing a diamine. The condensation of the diamine followed by deprotection afforded $186$ from...
in a 32% yield. This intermediate 186 was used for the tethered Biginelli reaction with methyl acetoacetate in the presence of morpholinium acetate and sodium sulfate. The product obtained was the tricyclic guanidine of batzelladine B 187 in a 10:1 isomer ratio, producing an 82% yield upon purification. Although this was the first report on the enantioselective synthesis of the batzelladine B fragment, the tethered Biginelli reaction resulted in low stereoselectivity, and there is still room for improvement.

![Synthetic Approach to Batzelladine B](image)

Figure 22. Franklin, synthetic approach to the tricyclic portion of batzelladine B.

In 2015, Parr and his co-workers hypothesized that batzelladine B could be synthesized from pyrrole as a starting material for both sides of the compound [23] (Figure 23). The pyrrole 188 underwent formal cycloaddition with (S)-pantolactonyl-α-diazo ester 189 in the presence of dirhodium (II) tetrakis[N-phthaloyl-(S)-tert-leucinate (Rh₂[(S)-pttl]₄) as the catalyst. The product, 190, underwent several more reaction steps, including the introduction of TMS-EBX, lithium benzyl octanoate addition, and saponification to yield the left-hand side of (+)-batzelladine B 191. For the right-hand side of the compound, pyrrole 192 was treated with sulfinimine 193, followed by the cleavage of the tert-butanesulfanyl substituent and cyclization with bis(chlorodibutyltin)oxide, to afford the urea 194 in a 78% yield. Further O-ethylation with 2,4-(dimethoxy)benzylamine hydrogen chloride and the cleavage of the ester afforded a carboxylic acid adduct. This carboxylic acid was then reacted with alcohol followed by anti-Markovnikov reductive hydration and the addition of p-toluene sulfonic acid, yielding the right-hand side of (+)-batzelladine B 195. The addition of p-toluene sulfonic acid is crucial for protonating the guanidine. In the next step, EDC-HCl was used to couple both fragments of 191 and 195. The coupled product was subjected to carbamate cleavage cum cyclodehydration and alkene isomerization upon adding Pd/C. The final step involved regio- and stereoselective reduction, semihydrogenation-isomerization, and DMB cleavage by H₂. The product, batzelladine B (12), was obtained in a 40% isolated yield and a 45% yield based on the NMR spectrum.

3.1.9. Batzelladine C Methyl Ester

Batzelladine C was isolated in 1995, without the further assignment of its stereochemistry [1]. In 2009, Butters and his co-workers synthesized the methyl ester of batzelladine C by adapting the three-component coupling reaction and iodocyclization that had been developed previously [25,50,51] (Figure 24). These strategies were also used for developing the bicyclic portion of batzelladine A and the tricyclic guanidine of batzelladine D [51,52]. The synthesis route constituted a three-component coupling (aldehyde, alkylidenepyrrolidine, and isothiocyanate), followed by an iodocyclization reaction. The reduction and alkylation of 196 yielded 197, with a good diastereoisomers ratio of 4:4:1. The subsequent cleavage of the terminal double bond followed by a cis-selective Wittig reaction afforded 198 in a 58% yield. The alkylidenepyrrolidine 199 was obtained in several reaction steps, including deprotection, thionation, and Eschenmoser sulfide contraction. The three-component coupling of 199 with hexanal and isothiocyanate afforded a separable mixture of 200 and 201. The further reaction of 200 and 201 yielded the bicyclic guanidines 202 and 203 in a 96% yield, respectively. The final stage of the reaction was iodocyclization using iodine and potassium carbonate. It was observed that the reaction was successfully applied to 203, forming the tricyclic guanidine 205, but this was not the case for the bicyclic guanidine 202. The tricyclic guanidine 204 was obtained after changing the reagent to iodine monochloride in dichloromethane rather than iodine in acetonitrile. The underlying reason for this dif-
ference is unknown, but the modeling studies demonstrated a significant conformational difference between 202 and 203 that might be responsible for this difference. The overall yields of methyl ester batzelladine C 204 and 205 were 1.6% and 4.3%, respectively. Upon the comparison of the spectroscopic data with the authentic batzelladine C, the batzelladine C was observed to have similar stereochemistry to compound 204.

Figure 23. Parr, synthetic approach to (+)-batzelladine B.
successfully applied to 203, forming the tricyclic guanidine 205, but this was not the case for the bicyclic guanidine 202. The tricyclic guanidine was obtained after changing the reagent to iodine monochloride in dichloromethane rather than iodine in acetonitrile. The underlying reason for this difference is unknown, but the modeling studies demonstrated a significant conformational difference between 202 and 203 that might be responsible for this difference. The overall yields of methyl ester batzelladine C 204 and 205 were 1.6% and 4.3%, respectively. Upon the comparison of the spectroscopic data with the authentic batzelladine C, the batzelladine C was observed to have similar stereochemistry to compound 204.

Figure 24. Butters, synthetic approach to batzelladine C methyl ester.

3.2. Ptilocaulin and Its Derivatives Skeleton

Ptilocaulin, netamines, and mirabilins can be classified into five groups based on the degree of unsaturation of their tricyclic skeletons (Figure 2). Until now, only four groups have been successfully synthesized and reported. The skeleton of isoptilocaulin, bearing an unsaturation bond between C9 and C10, has yet to be explored. Most of the synthetic studies have been conducted using skeletons with unsaturation between C10 and C11, specifically targeting only the ptilocaulin structure. Over the years, the tricyclic guanidine of ptilocaulin was synthesized using Snider ketone 209 as its intermediate. Various starting materials and synthetic strategies have been used to form Snider ketone (Figure 25). Most previous studies performed aldol condensation followed by conjugate addition and cyclization to obtain the Snider ketone [40,53–56]. Before the synthesis of Snider ketones, some studies
focused on intramolecular nitrone cyclization to obtain an isoxazolidine, and some studies employed intramolecular nitrogen oxide olefin cyclization to obtain an isoxazoline [57,58]. Various catalysts, such as rhodium and ruthenium complexes, have been used to aid in the reaction [39,59,60]. Subsequently, ptilocaulin was obtained via the addition of guanidine to Snider ketone. Different types of alkyl chains and degrees of saturation of the tricyclic guanidine yielded the netamine and mirabilin derivatives. The alteration of the reaction temperature with subsequent oxidation resulted in different types of tricyclic guanidines. Recently, a study was conducted on the synthesis of a netamine C-bearing saturated tricyclic guanidine skeleton without the performance of Snider ketone synthesis [39]. This study utilized copper-hydride-catalyzed allenylboronate in the reaction. Details of this reaction are discussed in the following section.

Figure 25. Starting materials for synthesizing ptilocaulin, netamines, and mirabilins skeleton.

3.2.1. Ptilocaulin

The first synthesis of (±)-ptilocaulin 62 was initiated by the Snider group in 1983, two years after the tricyclic guanidine ptilocaulin 62 was isolated by Rinehart et al. [53] (Figure 26). The group synthesized (±)-ptilocaulin 62 in a 35% yield by adding guanidine to a polyketonide chain. The acidic hydrogen of 206 was deprotonated using sodium and displaced by a butyl group. This compound was then subjected to conjugate addition with crotonaldehyde and, upon cyclization and decarboxylation, afforded compound 207. The subsequent 1,4 addition with 3-buténylmagnesium bromide added another 3-butényl group to the cyclohexanone and yielded 208 in a 45% yield with a 1.7:1 trans:cis stereoisomer ratio. The functional group transformation of the alkene into a carbonyl was conducted via ozonolysis, followed by intramolecular cyclization to form enone 209 in a chromatographically separable mixture of 1:1. The cis conformation of 209 was refluxed with guanidine in benzene for 24 h in an azeotropic environment to afford the pure
ptilocaulin nitrate 62 after elution in silica. The next year, Snider and his co-worker used the same strategy to synthesize the (−)-ptilocaulin [54]. The LDA initiated the alkylation of 210 via enolate chemistry with crotyl bromide and HMPA, followed by the 1,4-addition of 210 using a Grignard reagent, yielding 211 in a 61% yield. The hydrogenation and acid hydrolysis of 211 formed the bicyclic enone 212 in a 33% yield and was converted into ptilocaulin 62. In 1990, Asaoka and his co-workers synthesized (+)-ptilocaulin [55]. The reaction began with the conjugate addition of 213 using a Grignard reagent of 3-bromo-propanal ethylene acetal. The subsequent trimethylsilyl group elimination yielded compound 214 in a 68% yield. Another 1,4-addition was conducted using dimethylcuprate with crotyl bromide, affording 215 in an 80% yield. The bicyclic enone 212 was formed from the hydrogenation of 215, followed by acidic hydrolysis to initiate intramolecular cyclization. The bicyclic enone 212 was then subjected, in the usual manner, to reflux with guanidine followed by treatment with diluted HNO₃ to afford (+)-ptilocaulin 62 and its C-3a epimer in a 1:1 ratio.

In 1986, Uyehara’s group synthesized (±)-ptilocaulin using another strategy incorporating Diels–Alder and photochemical 1,3-acyl migration reactions [61] (Figure 27). In the synthesis of the 5,6-fused-ring of the Snider ketones 221 and 222, the tropolone 216 underwent a Diels–Alder reaction with ethylene followed by hydrosilylation, forming the bridgehead methoxy ketone 217. The alkylolation and 1,2-addition of the ketone at a low temperature afforded 218 which, upon the treatment with p-sulfonic acid under reflux conditions, afforded a pinacol-type rearrangement, yielding 219 in a 77–90% yield. The irradiation of compound 219 using a 100 W high-pressure mercury lamp triggered the 1,3-acyl migration of the compound. Subsequently, the compound underwent L-selectride reduction and silylation to afford compound 220. The ptilocaulin intermediates of 221 and 222 were successfully obtained after several reactions in a 1:1 ratio, with a 48% yield. This intermediate was then converted into ptilocaulin 62 by the addition of guanidine. The intramolecular nitrile oxide olefin cycloaddition (INOC) reaction was also utilized for the formation of ptilocaulin [57] (Figure 28). The aldol condensation between hexanal oxime dianion 223 and ketone 224 yielded a β-hydroxy aldoxime 225 in a 90% yield. The isoxazoline 226 was obtained as a combination of four diastereomers that, upon dehydration, afforded unsaturated isoxazoline. Raney-Ni reduction further reduced this isoxazoline to form a single isomer of unsaturated ketol 227 in a 60% yield. Reducing 227 by Li-EtNH₂ afforded a 7β-methyl ketol, and further dehydration yielded ketone 209. The subsequent reaction step was the addition of guanidine under reflux conditions to afford ptilocaulin 62. Interestingly, upon increasing the temperature from 130 °C to 140 °C, a disproportionate product was obtained, with saturated 228 and aromatized cyclic guanidine skeleton 229. These findings were significant for understanding the formation of ptilocaulin derivatives, such as netamines and mirabilins.

In 2010, Shen and Livinghouse managed to synthesize the (±)-ptilocaulin using an intramolecular [4+2] cycloaddition reaction that was catalyzed by Rh(I) complex [59] (Figure 29). Cross-aldol condensation initiated the reaction between a hexanal 230 and an acetaldehyde 231. The (E)-2-ethylidenehexanal 232 was obtained in a 38% yield. A further reaction with sequential debrumalkylidenation and stereoselective reduction using palladium catalyst yielded (Z,E)-bromodiene 233 in a 73% yield. The addition of 234 to 233 afforded the alcohol 235. The protection of alcohol 235 using TIPOn, followed by intramolecular cycloaddition using the Rh(I) catalyst, yielded the hexahydrodine 236. The sequential hydroboration-oxidation of 236, followed by another oxidation using PCC and dehydration, afforded the ketone 209. Finally, ptilocaulin 62 was obtained after the addition of guanidine to 209.
Figure 26. Synthetic approach to ptilocaulin.
Using a new approach, Schellhaas and his co-workers used a chiral arene-Cr(CO)\textsubscript{3} complex as a starting material, due to its reactivity and stereochemistry [56] (Figure 30). Additionally, this complex is favorable because of its stereodirecting and activating functionality. The anisole complex 237 underwent enantioselective O-silylation using the chiral base 238. The product, 239, was obtained with a good yield of 87%. The O-methylation of 239 yielded compound 240 with an unsaturated side chain at the ortho position to the methoxide. Nucleophilic addition triggers a tele-substitution of 240. Hence, the acid-free TMSCl and HMPA were added to inhibit the tele-substitution. After light-induced decomplexation and acid hydrolysis, the desired enone 241 was obtained in a yield ranging...
from 45 to 53%. The enone 241 was then subjected to conjugate addition using a Grignard reagent of 2-bromoethyl-1,3-dioxolane, followed by aldol cyclization, affording the hydroindenone 221 and 222 in a 1:1 ratio. The hydroindenone mixture was subjected to reflux in the presence of guanidine, followed by protonation with diluted nitric acid, to afford ptilocaulin 62 and its C-3a-diastereomer 242.

![Figure 29. Shen, synthetic approach to (±)-ptilocaulin.](image)

![Figure 30. Schellhaas, synthetic approach to (+)-ptilocaulin.](image)

Through the former study by Cossy and Furet, it was demonstrated that 3-methylcycloalkanones can be synthesized via the photoreduction of alkyl-substituted bicyclo [4.1.0] heptanones [62] (Figure 31). Cossy and Bouzbouz utilized the same strategy to synthesize (+)-ptilocaulin [60]. Cyclohexenone 243 first underwent epoxidation followed by the addition of a butyl group at the α-position and acid workup to yield compound 244 in an 80% yield. To form the bicyclo [4.1.0] heptanone structure, 244 was reacted with (R,R)-1,2-diphenylethane-1,2-diol in the presence of PPTS to form an acetal. The acetal was subjected to Simmons–Smith cyclopropanation and hydrolysis to afford a 55% yield of the enone 241. The irradiation of 245 in the presence of triethylamine and LiCO₃ afforded a ketone, which underwent a sequential bromination and debromination to afford a 55% yield of the enone 246. The hydroboration of the alkene using Rh(PPh)₃Cl, followed by oxidation using H₂O₂, yielded an aldehyde.
which, upon subsequent oxidation using PCC and acid hydrolysis, generated bicyclic enones 221 and 222 in a 65% yield. The addition of guanidine formed the final target compound of (+)-ptilocaulin 62.

![Chemical structures](image)

**Figure 31.** Cossy, synthetic approach to (+)-ptilocaulin.

An approach utilizing intramolecular nitrone cyclization for synthesizing (−)-ptilocaulin was implemented by Roush and Walts [58] (Figure 32). The starting material, (R)-(+)·3-methylcyclohexanone 247, underwent sulfonylation, oxidation, and selective hydroboration to obtain 248 in a 68% yield. The subsequent treatment with excess lithium in ethylamine yielded alcohol, which was then oxidized with PCC to afford an aldehyde. This aldehyde was then converted to isoxazolidine 249 through a nitrene intermediate. The isoxazolidine’s nitrogen-oxygen bond was cleaved by zinc in acetic acid to yield compound 250 in a 95% yield. A further reaction with Jones reagent oxidized 250, followed by deprotection and condensation with guanidine to afford the (−)-ptilocaulin 62.

### 3.2.2. 7-Epineoptilocaulin and Mirabilin B

In 2009, the first attempt to synthesize other tricyclic guanidine compounds was conducted by Yu et al., upon the discovery of the disproportionation reaction of ptilocaulin by Murthy and Hassner [40,57] (Figure 33). The Robinson annulation of 251 to 252 afforded cyclohexenone 253 in a 77% yield. The presence of excess MeLi and CeCl3 afforded the conversion of cyclohexenone 253 into alcohol, followed by PCC-mediated oxidation to yield cyclohexenone 254 in a 79% yield. The successive Birch reduction of 254 afforded a 10:1 mixture of stereoisomers. The subsequent ozonolysis followed by triphenylphosphine reduction generated compound 255 in a 93% yield. To obtain the enone 256, an intramolecular aldol condensation reaction was conducted using microwave irradiation. The enone was then refluxed with guanidine to afford 7-epineoptilocaulin 36 and 257. It was also observed that heating the enone with guanidine in methanol for 24 h, followed by nitric acid workup, gave a better yield of around 50% 7-epineoptilocaulin 36 and 10% 3a,7-bisepiptilocaulin 257. Two routes were used to synthesize mirabilin B 53. In the first method, the oxidation of 7-epineoptilocaulin 36 with activated MnO2 afforded mirabilin B 53 in an 80% yield. The second method involved heating the bicyclic enone 256 at a higher temperature (130 °C to 140 °C) for 4 h, followed by a nitric acid workup. The latter approach afforded mirabilin B 53 with a significantly lesser yield of 39%. 

![Chemical structures](image)
Figure 32. Roush, synthetic approach to (−)-ptilocaulin.

3.2.2. 7-Epineoptilocaulin and Mirabilin B

In 2009, the first attempt to synthesize other tricyclic guanidine compounds was conducted by Yu et al., upon the discovery of the disproportionation reaction of ptilocaulin by Murthy and Hassner [40,57] (Figure 33). The Robison annulation of 251 to 252 afforded cyclohexenone 253 in a 77% yield. The presence of excess MeLi and CeCl₃ afforded the conversion of cyclohexenone 253 into alcohol, followed by PCC-mediated oxidation to yield cyclohexenone 254 in a 79% yield. The successive Birch reduction of 254 afforded a 10:1 mixture of stereoisomers. The subsequent ozonolysis followed by triphenylphosphine reduction generated compound 255 in a 93% yield. To obtain the enone 256, an intramolecular aldol condensation reaction was conducted using microwave irradiation. The enone was then refluxed with guanidine to afford 7-epineoptilocaulin 36 and 257. It was also observed that heating the enone with guanidine in methanol for 24 h, followed by nitric acid workup, gave a better yield of around 50% 7-epineoptilocaulin 36 and 10% 3a,7-bisepiptilocaulin 257. Two routes were used to synthesize mirabilin B 53. In the first method, the oxidation of 7-epineoptilocaulin 36 with activated MnO₂ afforded mirabilin B 53 in an 80% yield. The second method involved heating the bicyclic enone 256 at a higher temperature (130 °C to 140 °C) for 4 h, followed by a nitric acid workup. The latter approach afforded mirabilin B 53 with a significantly lesser yield of 39%.

Figure 33. Yu, synthetic approach to 7-epineoptilocaulin and mirabilin B.

3.2.3. Netamine E and Netamine G

Yu et al. synthesized netamine E 29 and netamine G 45 using the same materials, 251 and 252, that were employed for preparing 7-epineoptilocaulin 36 and mirabilin B 53 [40] (Figure 34). Both the starting materials, 251 and 252, in the presence of a 10 mol % catalyst and p-toluenesulfonic acid, generated the enone 253, which, after subsequent steps, yielded netamine E 29 with a propyl side chain instead of methyl, as observed in 7-
epineoptilocaulin 36 and mirabilin B 53. The oxidation of netamine E 29 afforded netamine G 45 from the bicyclic enone, with a 25% yield.

![Chemical Reaction Diagram]

Figure 34. Yu, synthetic approach to netamine E and netamine G.

3.2.4. Netamine C

Netamine C 26 is the latest compound to be synthesized from this tricyclic guanidine skeleton. Sun et al. employed copper-hydride-catalyzed allenylboronate synthesis to prepare netamine C 26 [39] (Figure 35). The cross-metathesis of 261 and 262 in the presence of Ru-2 as a catalyst yielded 263 in a 69% yield. The product was then subjected to catalytic SN2 reaction and allylic substitutions in the presence of alkyl zinc halide reagent and (S)-imid(S)-1b to yield 264. This was the first study on the reactivity of alkyl zinc halide. The next approach was to change the side chain of alkenyl-B (pin). The side chain of 264 was transformed into allylic alcohol 265 and then into phosphate 266. The gamma-alkyl substituted aldehyde 267 was obtained through another allylic substitution with 1b in the presence of (S)-imid(S)-1b. Further ring-closing metathesis of 267 afforded the cyclohexenyl intermediate 268 in a 93% yield. The subsequent [3+2] cycloaddition with N-benzyl hydrazone provided 269, which was converted into netamine C 26 in an 88% yield.
4. Conclusions

The compounds comprising fused tricyclic guanidine moieties have been reported to exhibit a wide range of bioactivities, such as anti-cancer, antiviral, antimicrobial, and antimalarial properties. Two main skeletons of tricyclic guanidine are exhibited by batzelladine and ptilocaulin. Netamines and mirabilins represent other derivations of ptilocaulins that exhibit significant bioactivities by inhibiting cancer cell lines. Various synthetic strategies have been employed to approach these skeletons over the years. In particular, the asymmetric version of the total synthesis of batzelladine C and F somewhat resolved the stereochemical ambiguities. Several synthetic approaches to the synthesis of ptilocaulins have been reported, with most of the strategies targeting the same precursor, the Snider ketone, which can ultimately be converted into ptilocaulin. On the contrary, only two studies have reported the synthesis of mirabilin and netamine, despite their potent bioactivities. Thus, there is still room for research aiming to achieve the total synthesis of these bioactive fused tricyclic guanidines for the further investigation of their biological potential. In addition, there is a need to create new approaches to the synthesis of these skeletons more economically and efficiently, especially in regard to the synthesis of less widely reported mirabilins and netamines, in order to pave the way for the further exploration of their biological potential and their plausible development as therapeutic drugs.
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