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Antimicrobial alkaloids isolated from marine sponges-MINIREVIEW

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Abstract: Marine natural products have attracted the attention of scientists to isolate novel biologically active metabolites. Several promising metabolites were discovered from marine sponges with different biological activities including antimicrobial and anticancer. By far, more than 36% of the metabolites discovered from marine organisms were isolated from sponges. In this study, the alkaloids isolated from marine sponges with antimicrobial activity were described.

INTRODUCTION

Secondary metabolites are very wide-ranging groups of compounds produced by organisms under certain conditions such as nutrient limitation, defence mechanisms, and regulator molecules (Samuelsson, 2004; Castillo, 2008). In fact, organisms producing secondary metabolites have attracted scientists from different disciplines such as chemistry, pharmacology, and biology. The studies conducted by chemists, pharmacologist, and biologist on secondary metabolites have led to the discovery of thousands of secondary metabolites with promising biological activities (Mayer et al., 2011; Adam and Abdull Rasad, 2015; Majali et al., 2015).

Traditionally, terrestrial plants were the main sources of drugs. Presently, plants still provide many new potent drugs. Until 1950, the research on the chemistry of natural products was limited mainly to the investigation of terrestrial plants. After that, the search for bioactive compounds was extended to microorganisms. For more than 30 years, marine natural products have attracted the attention of scientists to isolate novel biologically active metabolites (Fusetani, 2010; Qaralleh et al., 2010; Shawa et al., 2015).

Marine organisms are not widely used in traditional medicine, but currently they represent an enormous resource for the development of potential therapeutic agents (Pomponi, 1999). Most of the marine organisms are soft-bodied and they are not able to use mechanical defence mechanisms like shelter or ability to escape, thus they need chemical defence mechanisms to survive (Debitus, 1998). Therefore, they have created an efficient defence mechanism that helps them to survive during evolution and to avoid extinction (Muller et al., 1999). This mechanism encompasses the ability to synthesise or accumulate toxic metabolites and the secretion of highly toxic metabolites as they are rapidly diluted in the ocean water (Haefner, 2003). The metabolites secreted by marine organisms are characterised by the presence of halogen unlike the terrestrial secondary metabolites (Rinehart, 1992; Faulkner, 2002). For these reasons, and because of the high biological diversity in the sea (Mayer and Lehmann, 2000; Proksch et al., 2002), marine organisms have attracted researchers to find useful drugs for mankind (Satheeshkumar et al., 2010).

Therefore, the aim of this paper is to review the antimicrobial alkaloids isolated from marine sponges, primarily focusing on their phytochemical characteristics.

Sponges

Sponges represent the major rich organisms with promising active pharmaceutical metabolites. The interest for drugs discovery in sponges has started since 1950s due to the discovery of the nucleosides spongothymidine and spongouridine from the marine sponge *Cryptotethya crypta* (Laport et al., 2009). Both metabolites were later developed to ara-C, the first marine-derived anticancer agent, and the antiviral drug ara-A (Proksch et al., 2002). Later, several promising metabolites were discovered from marine sponges with different biological activities including antimicrobial and anticancer (Kobayashi, 2000). By far, more than 36% of the metabolites discovered from marine organisms were isolated from sponges.

Sponge crude extracts showed variable antimicrobial activities against terrestrial pathogenic bacteria, and against marine bacteria. Reports have shown that terrestrial microbes are more sensitive than marine microbes (Becerro et al., 1994; Newbold et al., 1999). Due to the presence of antimicrobial substances, sponges are rarely infected by exogenous microbes (Newbold et al., 1999).

Table 1: Antimicrobial alkaloids isolated from marine sponges

Metabolites	**Inhibited Microorganisms**	**References**
Arenosclerins A, B, C (1-3) and haliclonacyclamine E (4)	*S. aureus*	Torres et al. (2002)
Nagelamide A (5)	*Micrococcus luteus*, *Bacillus subtilis*, and *E. coli*	Endo et al. (2004)
Cribrostatin 6 (6)	*S. pneumoniae*	Pettit et al. (2004)
Purpuramine L (7)	*S. aureus*, *B. subtilis*, and *Chromobacterium violaceum*	Goud et al. (2003)
Ptilocaulis guanidine (8)	*S. aureus*	Yang et al. (2003a)
Isoaaptamine (9)	*S. aureus*	Jang et al. (2007a)
Deoxytopsentin (10)	*S. aureus*	Oh et al. (2005)
Hamacanthin A (11)	*S. aureus*	Oh et al. (2005)
Batzellaside A (12)	*Staphylococcus epidermidis*	Segraves and Crews, (2005)
Dendridine A (13)	*B. subtilis* and *Micrococcus luteus*	Tsuda et al. (2005)
Batzelladine L and M (14, 15)	*S. aureus* and methicillin resistant *S. aureus*	Hua et al. (2007)
Massadine (16)	*C. albicans*	Nishimura et al. (2003)
Naamine G (17)	*Cladosporium herbarum*	Hassan et al. (2004)

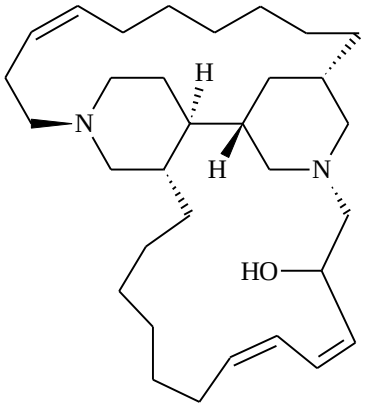
The studies on screenings of marine organisms for antimicrobial activity lead to the isolation and characterisation of a wide range of bioactive metabolites.

More than 800 antibiotic metabolites have been isolated from marine sponges (Torres et al., 2002), and new metabolites are being discovered every year. A total of 62 metabolites from marine sponges with potent antimicrobial activity were reported in the literature within the period of 2001 to 2008 (Mayer and Hamann, 2005; Mayer et al., 2007; 2009; 2011; Majali et al., 2015). As the secondary metabolite composition of sponges is dominated by alkaloid and terpenes metabolites, it is not surprising that antimicrobial sponge natural products are also dominated by polyketide and sterol-derived metabolites.

ALKALOIDS

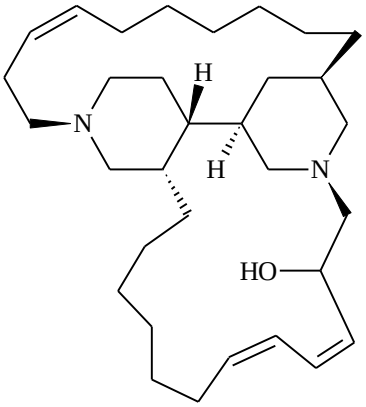
Heterocyclic nitrogen compounds are called alkaloids. Alkaloids are well-known for their antimicrobial activity. The occurrence of active antimicrobial alkaloids in sponges is widespread. As shown in Table 1, many potent antimicrobial alkaloids were isolated from marine sponges.

Torres et al. (2002) reported that the metabolites of arenosclerins A, B, C (1-3) and haliclonacyclamine E (4) were isolated from *Arenosclera brasiliensis*. These isolated alkaloids showed potent antibiotic activity against antibiotic-resistant *S. aureus* (MIC = 5 - 400 µg/mL).

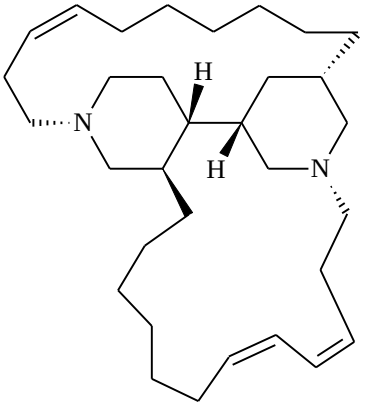


Arenosclerin A (1)

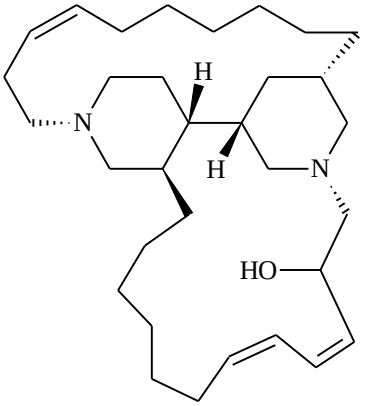
A dimeric bromopyrrole alkaloid, nagelamide G (5) was isolated from Agelas sp. (Endo et al., 2004). Nagelamide G exhibited antibacterial activity against *M. luteus*, *B. subtilis*, and *E. coli*. Gram-positive alkaloid inhibitor was reported for cribrostatin 6 (6), which was isolated from *Cribochalina* sp. sponge (Pettit et al., 2004). The maximum activity for Cribostatin 6 was reported against *Streptococcus pneumoniae* (MIC = 0.5 µg/mL).



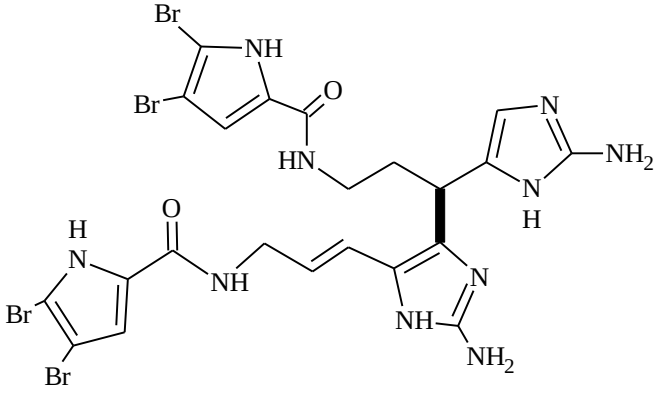
Arenosclerin B (2)



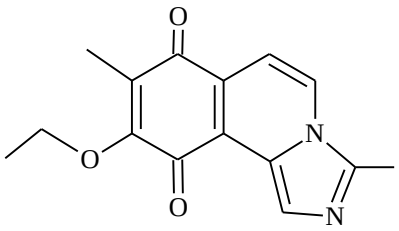
Arenosclerin C (3)



Haliclonacyclamine E (4)



Nagelamide (5)

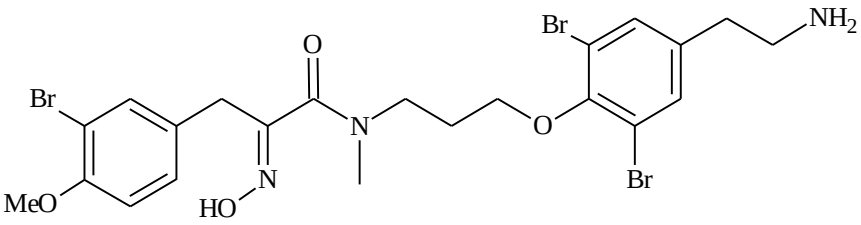


Cribrostatin 6 (6)

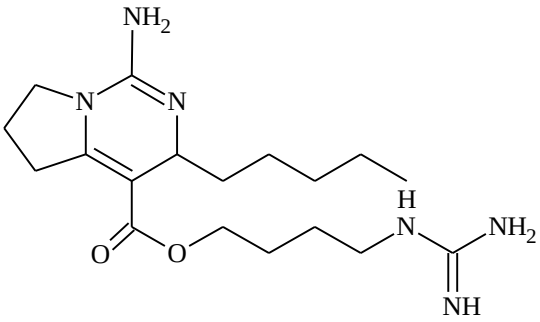
Goud et al. (2003) reported the isolation of purpuramine L (7) from *Psammaplysilla purpurea*. This alkaloid showed potent inhibition activity against *S. aureus*, *B. subtilis*, and *C. violaceum*.

Yang et al. (2003a) reported bicyclic guanidine alkaloid (8) from *Ptilocaulis spiculifer*. Interestingly, the inhibition activity of 50 µg guanidine alkaloid was as potent as 10 µg gentamicin.

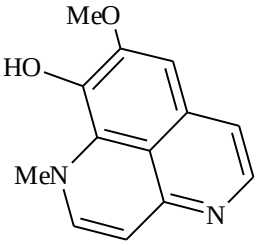
Jang et al. (2007a) reported the isolation of the alkaloid isoaaptamine (9) from the marine sponge *Aaaptos aaptos*. Isoaaptamine showed potent antimicrobial activity against *S. aureus*.



Purpuramine L (7)

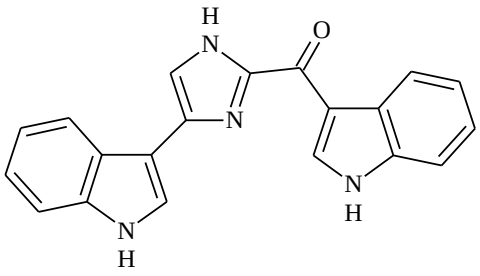


Guanidine alkaloid (8)

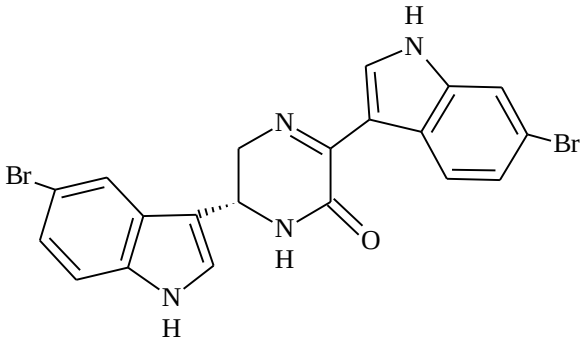


Isoaaptamine (9)

The bis(indole) alkaloids deoxytopsentin (10) and hamacanthin A (11) showed potent antibacterial activity against *S. aureus* (MIC = 3.12 - 6.35 µg/mL). These alkaloids were isolated from the marine sponge *Spongosorites* sp (Oh et al., 2005).



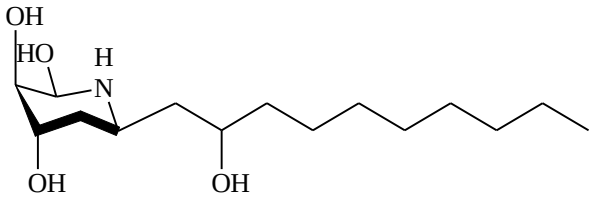
deoxytopsentin (10)



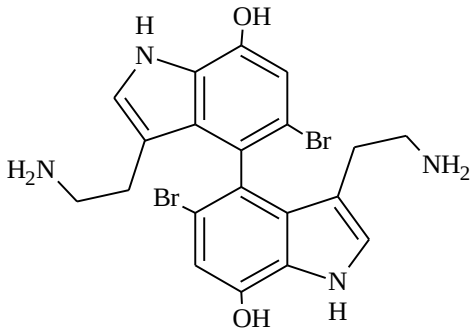
Hamacanthin A (11)

Potent marine antibacterial alkaloid was reported from the sponge *Batzella* sp. The isolated batzellaside A (12) showed promising antimicrobial activity against several antibiotic-resistant bacterial strains with MICs less than 10 µg/mL (Segraves and Crews, 2005).

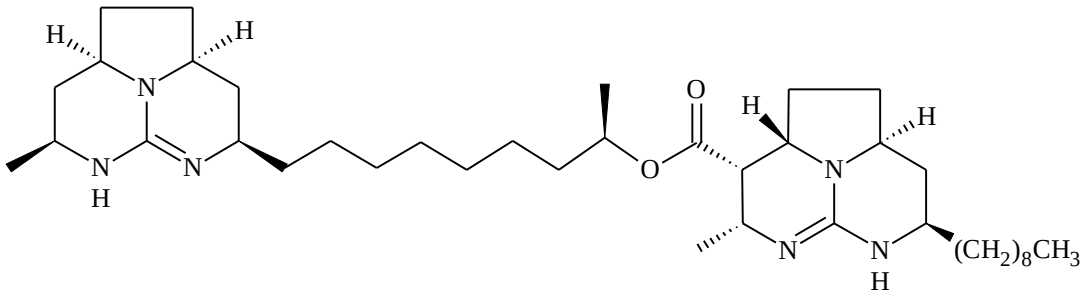
Three other alkaloids were reported with MIC less than 10 µg/mL including dendridine A (13) that were isolated from the sponge *Dictyodendrilla* sp. (Tsuda et al., 2005) and the alkaloids batzelladines L and M (14, 15) isolated from the Caribbean sponge *Monanchora unguifera*.



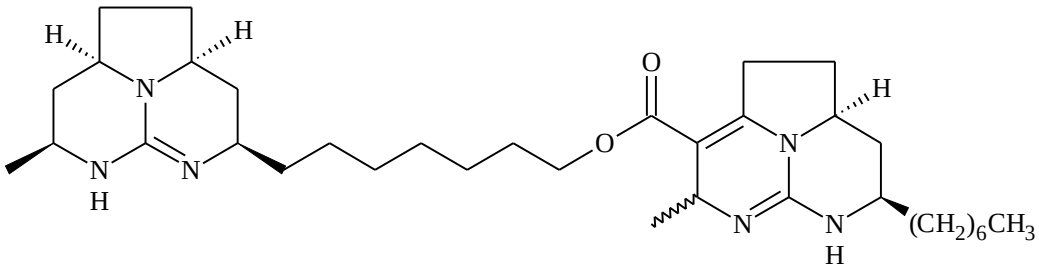
Batzellaside A (12)



Dendridine A (13)



Batzelladines L (14)

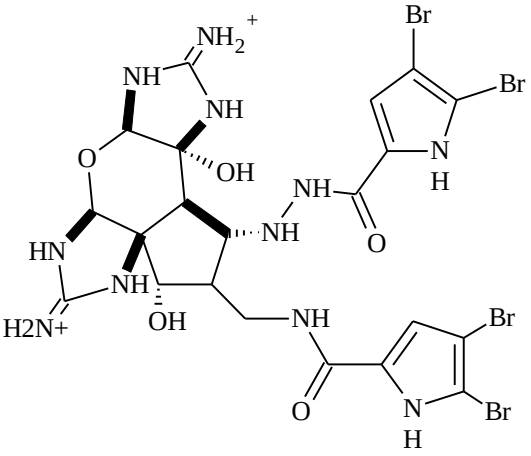


Batzelladines M (15)

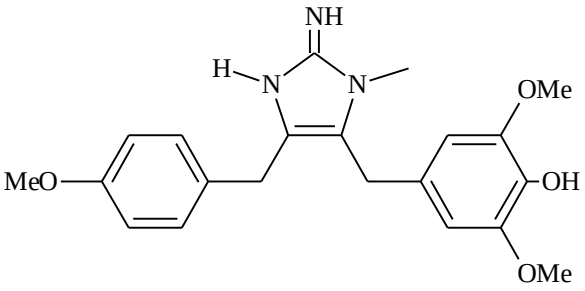
Only two alkaloids that showed antifungal activities were isolated from marine sponge in the period between 2001 and 2008.

The alkaloid massadine (16), which was isolated from the marine sponge *Stylissa aff. massa*, showed promising inhibition activity against *C. albicans*.

Imidazole alkaloid named naamine G (17) was isolated from the sponge *Leucetta chagosensis*. Naamine G exhibited strong antifungal activity against *Cladosporium herbarum* (Hassan et al., 2004).



Massadine (16)



Naamine G (17)

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