NEW HOPE ON DRUG LEADS DEVELOPMENT FROM DEEP OCEAN: HALOGENATED ALKALOIDS OF AGELAS SPONGES

Triana Hertiani

ABSTRACT

Agelas sponge is found in abundance from Indonesia's ocean. This sponge produces an important chemotaxonomic group of compounds, derived from pyrrole-imidazole alkaloids. This group of compounds is one of those exclusively found from marine environment. Marine sponges are reported to be promising drug lead producers having unique chemical structures of which many have no terrestrial counterparts. The objective of this report is to give an overview of the reported attempts from up to down stream to develop pyrrole-imidazole alkaloids as new drug lead. Literature up to 2013 reporting this group of compounds from Agelas sponges were studied. Discussion on the halogenated alkaloids covers the producers, description of high chemical diversity, identification, biosynthesis and ecological relevance as well as their role as a promising drug candidate. Alternatives to provide continuous supplies for drug development are also discussed considering that wild harvesting of the sponge producers can lead to ecological damage in the future. Broad range of interesting pharmacological importance as well as several success in developing synthetic route for production supports its development as drug candidate.

Key words: Agelas, halogenated alkaloids, drug lead, sponge

INTRODUCTION

A coverage of almost 75% of the Earth's surface has positioned the ocean as the major producer of natural products (Whitehead, 1999). Unlike its terrestrial counterpart, unique structures has been encountered and the utilization has lack of ethno-medical history. This issue together with technical difficulties in collecting marine organisms held back the development of marine-derived natural products as therapeutic agents. Nevertheless, synergism collaboration involving pharmaceutical companies, academic institutions, governmental and so non-governmental agencies, has made a significant progress in form of systemic investigations directed towards the collection and characterizations of marine natural products, as well as the evaluation of their biological activity (Christian et al., 1997; Amador et al., 2003). Large numbers of novel marine-derived compounds reported in the literatures in the last decades exhibit the positive development (Mayer and Gustafson, 2003; Amador et al., 2003). Some promising agents which are naturally derived or the synthetic derivates have entered preclinical and also clinical trials which can be expected that the number will increase in the near future (Amador et al., 2003).

According to Proksch and co-workers (2002), the majority of marine natural products currently in clinical trial or under clinical evaluation are produced by invertebrates. The soft bodied, sessile or slow-moving marine invertebrates having lack of morphological defense structure in form of spines or a protective shell make them more vulnerable for predation which justifies the ecological importance of utilizing chemical constituents for surveillance in the respective invertebrates (Proksch et al., 2002).

Database provided by MarinLit (2002) shows that the source of new marine natural products is dominated by sponges (37%) followed by coelenterates (21%). Blunt et al. in a review of marine natural products (2005) and Hu et al. (2011) supported the above mentioned statement. This data somehow define the role of marine invertebrates as a potential source of new drug candidates. Up to now more than 17,000 marine products have been described (MarinLit, 2006) of which sponges are...
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responsible for more than 5300 different products (Faulkner 2000, 2001, 2002). Moreover, the chemical diversity of sponge products is remarkable, in addition to the unusual nucleosides, bioactive terpenes, sterols, cyclic peptides, alkaloids, fatty acids, peroxides, and amino acid derivatives (which are frequently halogenated) (Sipkema et al., 2005).

Pharmaceutical interest in sponges itself was aroused in the early 1950s by the discovery of the unusual nucleosides spongithymidine and spongouridine in the marine sponge Cryptotethia crypta (Bergmann and Feeney, 1950, 1951). These nucleosides were the basis for the synthesis of Ara-C, the first marine-derived anticancer agent, and the antiviral drug Ara-A (Proksch et al., 2002).

As also found in terrestrial metabolites, many of marine natural products act as regulators of specific biological functions. Some of them have pharmacological activity due to their specific interactions with receptors and enzymes which are not found in their terrestrial counterpart. Marine metabolites face the problem that they become immediately diluted by large volumes of seawater which requires a highly potency on a molecular basis and retains a relatively low solubility (McConnel et al., 1994). It has been repeatedly shown that the accumulation of toxic or distasteful natural product is an effective strategy to repel potential predators (e.g. fishes) or in a competition for living space (Proksch et al., 2002; Proksch and Ebel, 1998; Proksch, 1999; McClintock and Baker, 2001). These secondary metabolites, which are produced as a result of evolutionary pressures to reserve or enhance an organisms ecological success (Proksch, 1999), have evolved into structurally diverse and usually stereo-chemically complex compounds with specific biological activity (Edrada et al., 2000) many of which belong to novel chemical groups solely found in marine environment (Carte, 1993).

The Agelas sponge classification falls into phylum Porifera; class Demospongiae; order Agelasida; family Agelasidae and genus Agelas. This sponge found in abundance in Indonesia suggesting evolutionary fitness. Agelas linnæi, A. nakamura (Hertiani et al., 2010; Murti, 2006; Eder et al., 1999), and A. nemocina (Pedradab, 2005) were examples of secondary metabolite producers from the Agelas collected from Indonesia sea, of which A. nakamura as the most reported sponge from this genus (Hertiani et al., 2010; Murti, 2001, 2006; Sapar et al., 2013; Eder et al., 1999; Trianto, 2005). Several other reports on this particular sponge are also derived from the neighbour sea, Papua New Guinea (Iwagawa et al., 1998). Many pharmacological-interesting compounds found in these particular sponges including the marine specific halogenated alkaloids.

**Halogen containing metabolites**

Marine sponges are a rich source of highly halogenated compounds. They may function to resist feeding by fish and fouling by barnacles, bacteria, and fungi (Gribble, 2004). One of the widest group of halogenated alkaloids are bromine-containing alkaloids (Dembitsky and Tolstikov, 2003). High halogen concentration in sea water has a consequence of its contribution in the biosynthesis of some marine metabolites. Catalyzed by haloperoxidases, halogenide anions from sea-water are oxidized (Hoffmann and Lindel, 2003) and then incorporated into organic compounds by specific halogenases (Van Pee, 2001). Enormous reactivity towards electrophilic halogenation reactions is probably the cause why heteroatom containing secondary metabolites such as pyrroles, indoles, phenols, and tyrosines are commonly found to be halogenated in sponges. Despite the relative concentrations of chloride, bromide and iodide ions exist in sea water (559mM, 0.86mM and 0.45µM respectively); marine organisms oxidize more bromide than chloride for incorporation into organic compounds (Faulkner, 1995). This may reflect the higher importance of bromoperoxidase (BPO) relative to chloroperoxidase (CPO) in marine life, and underline the fact that chlorine cannot be oxidized to active chlorine by BPO (Gribble, 1996b, 1998). Therefore bromide ions have greater ease to be oxidized and give bromonium species which react readily as electrophils with unsaturated species (Whitehead, 1999).
Brominated pyrroles have been isolated on several occasions as major constituents of marine sponges. Many of the simpler members of this class of compounds are structurally related as they comprise two heterocyclic rings linked by a linear chain (Whitehead, 1999). Over the last thirty years, numerous similar alkaloids with various structures and interesting biological activities have been isolated essentially (but not exclusively) from various species of Agelasidae, Hymeniactididae and Axinellidae (Williams and Faulkner, 1996).

**Characterization of halogenated alkaloids by LC/MS**

The presence of bromine and chlorine in a molecule can be easily distinguished from the molecular ion peak shown by their mass spectra. The molecular ions of chlorine and bromine-containing compounds will show multiple peaks due to the fact that each halogen exists as two isotopes. While $^{79}\text{Br}$ and $^{81}\text{Br}$ exist in relatively equal abundance, the natural chlorine isotopes consist of 75.77% of $^{35}\text{Cl}$ and of 24.23% $^{37}\text{Cl}$ (Smith, 2005). Thus the molecular ion of a chlorine-containing compound will have two peaks, separated by two mass units, in an intensity ratio of $\approx$3:1, while in a bromine-containing compounds these two peaks occur in approximately equal intensities. Therefore the presence of one bromine in a molecule e.g. in mukanadin C will be represented by two molecular ion peaks having a difference of two mass units in an equal height. In the meantime, the presence of two bromines as in midpacamide will appear as three molecular ion peaks having a difference of two mass units in an intensity ratio of 1:2:1. Furthermore in a compound bearing three bromines such as aplysamine-2, the molecular ion will appear as multiple peaks having two mass unit differences in a ratio of 1:2:2:1 (Hertiani et al., 2009; Hertiani et al., 2010).

The presence of fluorine and iodine, by contrast, is mono isotopic, having masses of 19 and 127 amu respectively (Smith, 2005). Thus neither fluorine nor iodine substitution will cause the above phenomenon as can be observed in agelanesin B and agelanesin D (Hertiani et al., 2010).

A distinct pseudomolecular ion pattern of brominated compounds in LC/MS is very important for preliminary characterization. This method can easily distinguish the presence of different brominated metabolites from sponge crude extracts. In LC/MS, after having the HPLC separation, the resulted peaks are detected by the UV detector and mass spectrometer. As more compounds can share the same UV pattern, the possibility of sharing the same molecular weight is less. In the case of brominated compounds, it is very rare to find different compounds having the same molecular weight with the same degree of bromination.

**Structural diversity of pyrrole-imidazole alkaloids in Agelas sponges**

Pyrrole-imidazole alkaloids are exclusively found in marine sponges, mainly of the families Agelasidae, Axinellidae, and Halichondridae. The underlying C11N5 building block consists of a pyrrolyl-2-carbonyl unit being connected via an amide linkage to a 2-amino-5-(3-amino) propylimidazole partial structure (Lindel et al., 2000a). The pyrrole-2-carbonyl unit can be non-, mono-, or dibrominated in the 4- and 5- positions. Bromination of the pyrrole 3-position or of the imidazole part has not been observed (Hoffmann and Lindel, 2003). In some metabolites, the linear chain is cyclized to form an AB core of a pyrrolopyrazinone bicyclic system such as in dibromophakellin, agelastatin A, pal’a‘umine, longamide A, and cyclooroidin (Figure 1) (Jacquot et al., 2004).

A comparison of bromopyrolyridine congeners reported from *Agelas nakamura* and *Agelas linnaei* reveals interesting finding (Figure 2). In the *A. nakamura* most reported congeners are monobrominated (Hertiani et al., 2010; Murti, 2006; Uemoto et al., 2009; Iwagawa et al., 1998) or dimers of monobrominated monomers (Eder et al., 1999), with an exception in Ageladine A (Most of *A. linnaei* metabolites, the pyrrole rings are dibrominated with exception of agelanesin A, agelanesin B and agelonine which are monobrominated. Another difference observed is that all metabolites of *A. nakamura* found in
Figure 1. Example of pyrrole-imidazole compounds having a pyrrolopyrazinone bicyclic system (Jacquot et al., 2004).

* Only relative stereochemistry is shown.

Figure 2. Selected pyrrole-imidazole compounds isolated from *A. linnai* (Hertiani et al., 2010) and *A. nakamura* (Hertiani et al., 2010; Murti, 2005) and from *A. nemocinata* (Pedradab, 2005) showing the similarities and differences in the structure of related compound.
Brominated pyrroles: UV spectra characteristics

Databases of this group of compounds revealed their distinct UV spectra due to a shared chromophore, a pyrrole-2-carbonyl ring. According to Jaffe and Orehin (1962), a maximum absorption at around 270 nm is detected for this particular group.

Comparison of several pyrrole imidazole alkaloids showed different characteristics in their UV spectra (Figure 3a). Pyrrole imidazoles having an additional tyramine in the molecules experience reduced intensity of the absorption band at around 270 nm and have an increase of the absorption band at around 210 nm which represent the additional phenolic unit (Figure 3b). A cyclization of the linear chain to form the pyrrolopyrazinone bicyclic system as can be observed in mukanadin C, longamide C, as well as in the phakellins intensifies the absorption band at around 230 nm (Figure 3d). Agelain B, on the other hand, forms a cyclization between N-7 and the imidazole ring which causes a major modification. A pronounced bathoeromic shift of the major band to λ 340 nm is observed (Figure 3a) (Hertiani et al., 2010). This kind of bathoeromic shift can also be observed in hymenialdisins (Figure 3e) (Baker, 2004).

Stevensine which differs in the imidazole ring part, loses the second band and only shows a major peak at around 240 nm, while in 2-bromoaldisin the second band is encountered at around 315 nm (Pedradab, 2005).

Brominated pyrroles: biosynthesis aspect

Despite the importance on pharmacological activities and chemotaxonomic considerations (Brackman et al., 1992), knowledge on pyrrole-imidazole alkaloids biosynthesis remains in question (Travert and Al-Mourabit, 2004). Symbiotic microorganisms were suggested to play a role in the biosynthesis based on the fact that bromopyrrole alkaloids is reported from an assortment of sponge genera. Moreover, populations of heterotrophic bacteria were found in Carribean sponge Agelas conifera. Nevertheless, cellular localization studies by differential centrifugation and Ficoll density gradients demonstrated that oroidin and sceptrin were associated with sponge spherulous cells and not with the bacterial fraction (Richelle-Maurer et al., 2003).
Figure 3. UV absorption pattern of several pyrrole imidazole alkaloids. Note: a-d are from *Agelai linnaei* and *Agelas nakamurai* (Hertiani, 2007); e was modified from Baker, 2004; Pedradah, 2005)
Several studies showed that spherulous cells, when present, are producers of the bioactive metabolites (Marin et al., 1998; Müller et al., 1986; Salomon et al., 2001; Thompson et al., 1983; Turon et al., 2000; Uriz et al., 1996; Richelle-Maurer et al., 2003). The production of an oroidin dimer, stevensine, by adding amino acid precursors into a sponge cells culture performed by Andrade et al. (1999) supports that these alkaloids are produced by sponge cell and not by symbiont (Richelle-Maurer et al., 2003).

A shared biosynthetic pathway is proposed for pyrrole imidazole alkaloids based on a common key metabolite, oroidin (Al Mourabit and Potier, 2001; Hoffman and Lindel, 2003). Several alternatives have been discussed with regard to their biosynthesis. While the pyrrole part is generally expected to be derived from proline/ornithine, different proposals have been put forward for the 2-amino-5-(3-amino) propylimidazole part (Lindel et al., 2000a). Considering that the metabolism of proline in some plants and microorganisms is known to be stress dependent (Hare and Cress, 1997; Ballantyne and Storey, 1983), even though the ecological role of proline in sponges is not known, its role under stress conditions is assumed crucial for surveillance. Thus, if proline is involved in C11N5 formation under oxidative conditions, this would be in accordance with the ecological role of “oroidin-based” alkaloids used by sponges as a chemical arsenal for their defense (Travert and Al-Mourabit, 2004).

Braekman and collaborators (1992) proposed that proline, ornithine, and guanidine are probable precursors of both the bromopyrrole and 2-aminoimidazolinone moieties, based on the fact that proline and ornithine are two closely related amino acids of the glutamate group and the oxidation of proline into pyrrole-2-carboxylic acid is a general catabolic pathway (Michal, 1972). Saxitoxin which is an analogue of aminopropylimidazole has been reported to be aroze from ornithine (Shimizu et al., 1984). Other finding revealed the occurence of girtoline with its linear or cyclized pyrrole derivatives in “Pseudaxynissa” cantharella (Ahond et al., 1988), suggests the biosynthetic pathway of these alkaloids proceeds by formation of an amide bond between a pyrrole-2-carboxylic acid precursor and an amino propylimidazole moiety (Braekman et al., 1992).

Hoffmann and Lindel (2003) suggested a different pathway of which ornithine is incorporated into proline, and being oxidized to form the pyrrole-2-carboxylic acid moiety. A biosynthetic experiment performed by Andrade and collaborators (1999) in the sponge cell cultures revealed that [14C]-labeled proline, ornithine, and histidine were incorporated into stevensine. Natural compounds 3-amino-1-(2-aminoimidazolyl)-prop-1-ene and 4,5-dibromo-pyrrole carboxylic acid were proposed as intermediates (Andrade et al., 1999). Furthermore, Hoffman and Lindel (2003) proposed that if histidine is a biogenetic precursor, the natural product clathramide A could be a biogenetic intermediate in Agelas clathratae (Cafieri et al., 1998a; Cafieri et al., 1996). The missing carbon atom would be incorporated into the histidine-derived portion via methylation of the imidazole 5-portion, followed by conversion of clathramide A to a cyclopropane and subsequent ring opening (Figure 4) (Hoffman and Lindel, 2003).

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[Diagram of plausible biosynthetic pathways leading to the key pyrrole-imidazole alkaloid (according to Hoffmann and Lindel, 2003).]
First specific step in the pyrrole 2-aminoimidazole biosynthesis involves proline-based peptide synthesis, followed by an oxidation of the proline to pyrrole section and then by an oxidation rearrangement of proline-guanidine moiety to the 2-aminoimidazolinon. Bio mimetic spontaneous conversion study of proline to 2-aminoimidazolinonone derivatives suggested dispacamide A as the forerunner of oroidin. As a consequence of this proposed pathway, 4,5-dibromopyrrole-2-carboxylic acid and 2-amino-5-(3-aminopropylimidazole are probably exist as hydrolysis products and not precursors (Travert and Al-Mourabit, 2004).

Actually, either oroidin or dispacamide A are good candidates as a key metabolite linking the amino acid precursors to the pyrrole 2-aminoimidazole family. Moreover, both compounds are frequently found in sponges together with their closely related polycyclic derivatives (Travert and Al-Mourabit, 2004).

Moreover, homoarginine derivatives eventually open the possibility of another alternative biosynthetic pathway of which indicates the existence of a biosynthetic pathway via an open chain intermediate (Assman et al., 1999). Hoffmann and Lindel (2003) proposed that hydroxylation of homoarginine at the δ-position, followed by oxidation and cyclization generates 2-aminohomohistidine which then undergoes oxidative decarboxylation and isomerization of the resulting double bond, eventually forms oroidin (Figure 4) (Lindel et al., 2000a).

Similar co occurrence of homoarginine and 2-amino-3-prop(eny)limidazoles in the case of the alysinsamines I and II in Aplysia sp. (Rodriguez and Piña, 1993) and the similar biogenesis pathway of enduracididine, an arginine-derived amino acid which has an imidazoline analogue of aminohistidine in its structure (Horii and Kameda, 1968; Hatano, et al., 1984; Garcia et al., 1996; Hemscheidt et al., 1995) support the above hypothesis (Hoffman and Lindel, 2003).

To explain the high structure diversity of this compound group members, Al Mourabit and Potier (2001) proposed different intra molecular cyclization mechanisms. Positions N-1 and C-3 of the pyrrole part participate in intramolecular cyclizations (Figure 6) (Al Mourabit and Potier, 2001), while position C-2, which is the most nucleophilic in a free pyrrole has only rarely been quaternized (Hoffmann and Lindel, 2003). Among the simple heterocycles, free or N-methylated pyrrole exhibits a relatively strong nucleophicity at C-2 which even rivals nucleophilic solvents (Richard et al., 1998; Maier et al., 2003; Hoffmann and Lindel, 2003).

The 2-amino-imidazole building block possesses tautomeric property which is important for the molecular diversity of pyrrole-imidazole alkaloids (Figure 7).
Each tautomer engaged in this process may act as an initiator of controlled chain reactions leading to various and complex compounds. The tautomerism which can exist simultaneously will give rise to polycyclic metabolites through various combinations with pyrrole building blocks and diverse modes of cyclization and/or dimerization (Al-Mourabit and Potier, 2001).

Based on the available theory about the pyrrole-imidazole alkaloids biosynthesis, it is more likely that hymenidin is the key building block in their biosynthesis in *A. nakamura* rather than oroidin. Intermolecular cyclization involving the N-pyrrole and C-9 of this building block leads to compounds like mukanadnin C and its new derivative longamide C.

In the case of Seribu Islands sample, *A. linnaei*, beside its possession of more diverse pyrrole-imidazole alkaloids, there are no oroidin or dispacamide as well as homoarginine alkaloids present, whereas some metabolite functionalities is unmatch with the available theory. Midpacamide as the major metabolite together with the co-existence of mauritamides which exhibit relatively similar functional groups in the imidazole ring with a dehydro dispacamide A recommends a putative biosynthetic pathway as described in figure 8. This pathway may explain the relation of almost all *A. linnaei* metabolites including, midpacamide, mauritamides, agelanin A as well as the phakellins.

Figure 8. Proposed chemical pathway leading to several *A. linnaei* metabolites
An involvement of other amino acids such as taurine and tyrosine may also be involved in the diversity of this group of compounds. Mauritamides and N-methyl-4,5-dibromopyrrolo taurorcarboxamide biosynthesis may require taurine as precursor. Meanwhile, tyrosine may involve in the agelanesins biosynthesis through a brominated tyramine related intermediate. Bioconversion pathway of several bromopyrrole alkaloids remains in question. On the other hand, a co-existence of the agelongine alcoholic portion, pyridinebetaine A (Figure 9) in Agelas longissima by Cafieri et al. (1998b) may somehow correlate to the agelongine unusual structure.

Figure 9. Agelongine and pyridinebetaine A (Cafieri et al., 1998b).

**Halogenated pyrroles: Ecology approach towards pharmacology prospects**

Biosynthesis of alkaloids consumes valuable amino acids while efficiency should become a basis consideration for compounds production. It should be an evolutionary advantage for a living organism to generate a maximum degree of molecular diversity and function, on the basis of a common building block. It would be even better, if the building block itself can be part of life saving efforts. Oroidin is a perfect example. This compound has been reported as the chemical weapon of Agelas sponges against predation by reef fishes and in the same time takes part as a key building block of the pyrrole imidazole alkaloids. (Hoffmann and Lindel, 2003). The conservation of brominated pyrrole-imidazole alkaloids as natural products in the tissue of sponges within the genus Agelas suggests that these compounds have been elaborated and retained as part of chemical defenses (Lindel et al., 2000b). From an ecological point of view, the anti-predatory role of oroidin-based alkaloids could be their most important biological function (Assmann et al., 2000; Assmann et al., 2001).

Lindel et al. (2000b) formulated the structure-activity relationship of several oroidin related compounds for feeding deterrent activity. They reported that even though the pyrrole ring is required for the activity, this alone is not sufficient. A dibrominated pyrrole exhibited higher activity in comparison to less brominated analogues. On the other hand, the imidazole moiety is not feeding deterrent on its own, but enhances the activity of the pyrrole ring. A methylation of the N-pyrrole, the oxidation state of the imidazole ring at the 4-position and the functionalization of the imidazole 2-position were found to give no influence on activity. Removal of the imidazole moiety with retention of the chain resulted in loss of activity, except for the acid. Among the similar, active compounds, increasing polarity appeared to enhance feeding deterrence. This anti feeding assay also revealed an additive effect of the active compounds but no synergy was observed (Lindel et al., 2000b).

Field assays performed by Richele-Maurer et al. (2003) showed that concentration of pyrrole imidazole alkaloids, oroidin and sceptrin in A. conifera were unaffected by prolonged protection from fish predators. It is suggested that these compounds were produced possibly at the limit of effectiveness. Wounding induced a three- to four-fold increase production of both compounds and higher amount of these bromopyrroles exuded into the surrounding seawater than normal. This action may prevent further predation as well as protection against invading microorganisms and from fouling (Richele-Maurer et al., 2003). This argument is in accordance with the activity of oroidin and several other bromopyrrole alkaloids against fouling and bacterial infection (Tsukamoto et al., 1998). The strategy to enhance production of bioactive compounds in response to environmental changes would optimize fitness. Defence are known to be costly, while energy is needed for other functions such as growth and reproduction (Schupp et al., 1999; Richele-Maurer et al., 2003).
An attempt to translate the result of the ecological function of the halogenated pyrroles reveals possible development of this compound group as drug lead. Based on the assumption that effect of calcium influx and calcium levels in neurons, secretory cells may be related to the feeding deterrence through smell and taste, Bickmeyer et al. (2004; 2005) performed an experiment to observe the effect of several bromopyrrole alkaloids on calcium levels in PC12 cells (rat phaeochromocytoma cell line). It was reported that unpalatable 4,5-dibromopyrrole-2-carboxylic acid against predatory reef fish is not (only) transduced by specific membrane receptors present on sensory nerve cells but (additionally) has a more general pharmacological effect on the cellular calcium homeostasis (Bickmeyer et al., 2004).

Basically, chemo-receptive cells are exposed to the environment, and cellular signalling may be modulated by substances interacting with the basic physiology of the cell, but not necessarily by binding to specific taste receptors (Bickmeyer et al., 2004, 2005). As the same mechanism may work in sensory cells of predatory fishes and other animals like snails the inhibition of Ca$^{2+}$ influx into receptor cells may be one reason for chemoreceptive detection (Bickmeyer et al., 2004, 2005). In harmony with the ecological point of view, blockade on calcium entry may be pharmacologically important since it can induce vasorelaxation as observed in many hypertension drugs (Bickmeyer et al., 2004).

Midpacamide is the major constituent of the A. linnaei (1.01% of sponge dried weight) (Hertiani et al., 2010). It is a dibrominated pyrrole having a N-methylated hydantoin ring connected through a propylamide chain. According to Lindel and collaborators (2000b), this compound is the most potent as feeding deterrent in comparison to the other six pyrrole imidazole alkaloids tested, 4,5-dibromopyrrole carboxamide, 4,5-dibromopyrrole-2-carboxylic acid, oroidin, keramadine dispacamide and racemic longamide A. Based on this finding accompanied with its predominance in the sponge, it is likely to assume that midpacamide functions as the main chemical weapon of A. linnaei against its predators.

Relatively high structure diversity and predominance of the pyrrole-imidazole alkaloids in A. linnaei may be due to their function as chemical defense for the host sponge in order to provide broader spectrum of protection. Midpacamide, as a main feeding deterrent (Lindel et al., 2000b) displays moderate cytotoxicity against mouse lymphoma cell L5178Y (46.7% inhibition in 10μg/mL sample concentration) and only low antibacterial activity against B. subtilis. The role of cytotoxic activity as well as antimicrobial and antifouling activity is presumably taken by other metabolites.

A different finding was observed in A. nakamurai which relies more on their diterpene alkaloids but not pyrrole-imidazole compounds for chemical defences. Considering that these diterpenoids play a major role in sponge defense may answer to the less diverse production of pyrrole-imidazole alkaloids in this sponge. Among the pyrrole-imidazole metabolites, 4-bromo-1H-pyrrole-2-carboxylic acid and hymenidin are discovered to be predominating. From their structure one can predict that these compounds contribute in the feeding deterrent mechanism of the sponge producer, together with the other congener, 4-bromo-1H-pyrrole-2-carboxamide.

More literatures on the oroidin derivatives bioactivity were reports on biofilm inhibition effects (Richards et al., 2008a, 2008b, 2008c, 2008d, 2008e; Ballard et al., 200; Huigens et al., 2007) This effect has been proposed to be in correlation with the sponge’s antifouling defense mechanism (Hertiani, 2008). Sponges as filter-feeder organisms need to be free of fouling in order to pump water and nutrition. Therefore, a chemical defense in form of antifouling compounds can be one powerful strategy. Nevertheless a research done on several oroidin related from A. linnaei showed no inhibition on biofilm formation of S. epidermidis by in vitro method (Hertiani, 2008). This activity was reported from other type of compounds isolated from A. nakamurai, the (-)-Ageloxime (Hertiani et al., 2010; Hertiani, 2008). Considering that biofilm associated microbes have great significance for public health, since they may cause a dramatical decrease in susceptibility towards antimicrobial agents (Donlan, 2001). Finding a potential biofilm inhibitor is therefore of interest in combating infection especially in immunesuppressed condition.
Agelastatins (Figure 10) is probably the most important pyrrole-imidazole alkaloids isolated from Agelas sponges. These compounds have a unique fused tetracyclic skeleton which may formally be derived from an open chain pyrroloaminopropylimidazole precursor similar in structure to oroidin (Whitehead, 1999). In 1998, Hong et al. reported the isolation of the known Agelastatin A together with two new alkaloids, Agelastatins C and D from a West Australian sponge Cymbastela sp. (Axinellidae). Agelastatin A was highly toxic to brine shrimp with LC$_{50}$ of 1.7 ppm (5.0μM) whereas Agelastatin C was much less toxic with LC$_{50}$ of ~220ppm. Insecticidal activity of Agelastatin A was reported to be comparable to a commercial preparation of the biopesticide Bacillus thuringiensis (Hong et al., 1998; Whitehead, 1999).

Agelastatin A was reported to exhibit significant cytotoxicity towards many types of cancer cell lines (D’Ambrosio et al., 1993; 1996; Meijer et al., 2000; Pettit et al., 2005). This compound inhibited tumor cell growth from 1.5 to 16 times more potently than cisplatin, particularly, against human bladder, skin, colon, and breast carcinomas (Hale et al., 2005). Moreover, Agelastatin A was demonstrated to be very effective in down-regulating the expression of β-catenin and in up-regulating Tef-4, an inhibitor of osteopontin (OPN) at the cellular level. These two effects result in repression of OPN and inhibition of OPN-mediated malignant cell invasion, adhesion, and colony formation in vitro (Mason et al., 2008). Longley also highlighted the ability of this compound in inhibiting β-catenin, which controls transcription of multidrug resistance (Longley and Johnston, 2005). Therefore, it could be helpful in reducing drug resistance issues, possibly both as single agent as well as in combination therapy (Forte et al., 2009). Hale and collaborators reported that agelastatin A was also exhibited inhibition activity towards glycogen synthase kinase-3 β (GSK-3β), an enzyme responsible for the neurofibrillary tangles typically found in Alzheimer’s disease, and as a mimetic of insulin (Hale et al., 2003).

The Palau’amines (Figure 10) is another series of complex, halogen containing alkaloids belonging to oroidin family. These compounds exhibit six contiguous rings and an unbroken chain having eight chiral centers (Whitehead, 1999). Palau’amine and its 4-bromo and 4,5-dibromo derivatives were isolated in 1998 Kinnel et al. together with three previously reported ring A regioisomers (styloguanidines), from the sponge Stylostephanos aurantium. Palau’amine itself was reported to display a remarkable range of biological activities having an IC$_{50}$ value of less than 18 ng/ml in the mixed lymphocyte reaction, and values of IC$_{50}$ of 0.1 and 0.2μg/ml against P-3888 and A-549 cell lines, respectively (Whitehead, 1999).
The preclinical studies of this compound are currently in progress for anti-fungal, anti-tumor and immunosuppressive agent (Kinnel et al., 1998; Whitehead, 1999).

Tauroacidins A and B (Figure 10), two novel taurine-residue-containing bromopyrrole alkaloids which were isolated from an Okinawan sponge Hymeniacidon sp. (Figure 12) (Kobayashi et al., 1997). Both alkaloids were reported to show inhibitory activity against EGF receptor kinase and c-erb B-2 kinase (IC\textsubscript{50}, 20μg/mL. each) (Kobayashi et al., 1997). Three other novel taurine derived bromopyrrole alkaloids isolated from A. linnaei, Mauritamide B, C and 2-(4,5-dibromo-1-methyl-1H-pyrrole-2-carboxamido)ethanesulfonic acid (Figure 9), exhibited no inhibition on the protein kinases (Hertiani, 2007).

Other report from Scala et al. (2010) exhibit the potency of bromopyrrole alkaloids as a potential drug lead for anti protozoa. Dispacamide B and spongacidin B were reported as a potential antimalarial and can be developed as drug lead based on the result that these compounds showing significant activity with low or no toxicity towards mammalian cells (L6). Moreover, Scala et al. (2010) also described dibromopalau'amine and longamide B potency as trypanocidal and antileishmanial agents, with narrow therapeutic windows. Number of bromine substitution on the pyrrole carbon was reported to be important for the antiplasmodial activity (Tasdemir et al., 2007), which was also observed in the activity towards T. brucei rhodiense and Leishmania (Scala et al., 2010). The imidazol type ring was suggested to be of important for antimalarial activity (Scala et al., 2010).

**Tyrosine derived brominated compounds from A. linnaei**

Other important halogen containing secondary metabolites from sponges are the brominated compounds biogenetically related to tyrosine (Figure 11). Although this group of compounds is more likely to be found in Verongid sponges (Hamman et al., 1993; Tabudravu and Jaspars, 2002), nevertheless, König and Wright (1993) have reported the isolation of bromotyrosine-derived alkaloids (Agelorins A and B, and 11-Epifistularin-3) from Agelas omides.

Psammaplin A, a symmetrical bromotyrosine disulfide possessing oxime moieties isolated from Verongid sponges, was found to have potent cytotoxicity to P 388 cells (IC\textsubscript{50} of 0.3μg/mL\textsuperscript{-1}). Its dimeric metabolite, bisaprasin was also occured in the sponge producer.
(Arabshahi and Schmitz, 1987; Quiñoà and Crews, 1987; Rodríguez et al., 1987). The fact that the psammaplins have been isolated from a diversity of sponge “sources” and that brominated aromatic amino acid derivatives are common in marine bacteria suggest that these metabolites may actually be produced as a collaborative work between the sponge host and the associated microorganisms (Simmons et al., 2005).

Both psammaplin A and bisaprasin were reported as DNA methyl transferase and histone deacetylase inhibitors (Pina et al., 2003). This is an interesting finding considering the potential relationship between DNA methyl transferase and histone deacetylase as epigenetic modifiers of tumor suppressor gene activity (Pina et al., 2003). Furthermore, psammaplin A has also been reported to inhibit topoisomerase II (Kim et al., 1999) and aminopeptidase N with in vitro angiogenesis suppression (Shim et al., 2004).

Four new brominated pyrrole derivatives connected to a halogenated tyramine unit were obtained from A. linnaei (Hertiani et al., 2010). Halogenated tyrosine-derived metabolites are actually more likely to be found in Verongid sponges, although they were also reported from several others (Constantino et al., 1994; König and Wright, 1993). Agelorin A and B as well as 11-epi-fistularin-3 are other known tyrosine-related representatives from the marine sponge genus Agelas (König and Wright, 1993).

The presence of a halogenated tyramine moiety linked to a brominated pyrrole unit has never been reported before from natural products. Replacement of the brominated tyramine moiety in agelanesin A and agelanesin C with iodinated tyramine in agelanesin B and agelanesin D attract attention to this group of compounds.

It is very challenging to find out why this Agelas sponge incorporated iodine into the agelanesins to substitute the bromine. Iodoalkaloids are known to be very rare natural products which are until now only isolated from marine organisms, (Gribble, 1996a, 1996b, 1998, 2000; Faulkner, 1995) more specifically from very few algae and sponges (Niedleman and Geigert, 1986; Constantino et al., 1994). Iodide availability in sea water is far below other halogens such as bromide and chloride.

Despite its low concentration, unlike chloride, all known haloperoxidases are effective in oxidizing iodide (Niedleman and Geigert, 1986). According to Constantino et al. (1994), biosynthesis of iodinated metabolites seems to be related to the capability of organisms to concentrate iodine from sea

Figure 12. Chemical structures of tyrosine-derived brominated compounds from Agelas oroides (König and Wright, 1993) and from A. linnaei (agelanesin A-D) (Hertiani et al., 2010)
water, rather than to the presence of a specific peroxidase. This argument was based on the fact that most iodo-metabolites have been isolated from red algae, which are known to contain iodine concentrations as high as 0.5% of weight wt (Constantino et al., 1994). An iodotyrosine alkaloids sponge producer, *Iotrochota biretulata* was reported to contain significant amounts of iodine (0.12-1.21%), together with comparable quantities of bromine (0.16-2.66%) (Kaestner, 1967). Hence this supports the relationship between the presence of iodo-metabolites and high concentration of iodine in the sponge tissue (Constantino et al., 1994).

Another question arising from the agelanesins unique structure is their biosynthesis. As described earlier, pyrrole imidazole family of compounds such as oroidin and sceptrin are predicted to be produced by sponge cells and not by the associated bacteria (Richele-Maurer, 2003). Meanwhile Simmons and collaborators (2005) proposed that the brominated tyrosine metabolites may actually be derived from the biosynthetic pathway of microorganisms living in association with sponges. It is therefore more likely that in case of the agelanesins, the brominated pyrrole 2-carboxylic acids are produced by the sponge cell at first, and further converted by associated bacteria to afford agelanesins.

In addition to its unique chemical structure, this group of compounds also showed interesting bioactivity. Agelanesin A-D showed cytotoxicity against the mouse lymphoma cell line (L1578Y) with IC<sub>50</sub> value 4.5μg/mL; 4.8μg/mL; 9.2μg/mL; and 7.8μg/mL respectively. In comparison to other brominated pyrroles isolated from *A. linnaei*, only this group of compounds shows pronounced cytotoxicity (Hertiani et al., 2010).

At the same time, aplysamine-2 and aeropylsin-1, obtained from *Pseudoverratina purpurea* exhibits the same activity as well. Some other brominated tyrosine compounds have also been previously reported to be cytotoxic such as psammaplin A and bisaprasin (Arabshahi and Schmitz, 1987; Quiñoà and Crews, 1987; Rodriguez et al., 1987). Hence it is suggestive that the halotyramine moiety of agelanesin A-D is important for the activity (Hertiani et al., 2010).

Based on the IC<sub>50</sub> values of the agelanesines against mouse lymphoma cell line (L1578Y), a possible structure activity relationship is suggested. Since the highest activity was shown by agelanesin A followed by agelanesin B, D and C, respectively, less bromination on the pyrrole ring seems to be important for the activity (Hertiani et al., 2010). This is somehow in contrast to the result of feeding deterrent activity reported by Lindel et al., 2000b, since higher degree of the bromination in the pyrrole ring will increase the activity (Lindel et al., 2000b). Meanwhile, different halogen atom attached to the tyramine unit (C-12) causes only slight difference on the cytotoxicity (Hertiani et al., 2010).

**Synthesis approach: an alternative for continuous supply**

One of the most important requirement of a natural product being developed as medicine or drug lead, it should be obtained by a continuous supply. Despite being a promising lead for many medicinal purposes, halogenated alkaloids in Agelas sponges have been postulated to be originated from sponge cell itself and not from its symbiont (Richele-Maurer et al., 2003). This fact has closed the possibility of obtaining these alkaloids through cultivation of the endophytes/symbionts as one possible alternative in obtaining marine metabolites with more eco-friendly approach.

Mariculture is one approach in effort to provide continuous supply by cultivating sponge in its environment. This approach has advantages as cultivation can be managed in its natural condition and may be expected to produce compound of interest. Nevertheless *A. nakamura* collected from Menjangan Island in different collection time, resulted different chemical constituents as reported by Hertiani and collaborators (2010) and Murti (2006). Another report by Eder and collaborators (1999) reported dimers, i.e., Sceptrin, Debromosceptrin, Ageliferin, Nakamuric acid and its methyl ester derivates. *A. nakamura* from Okinawa has been reported to produce other constituents as well as the sponge.
collected from Papua New Guinea (Iwagawa et al., 1998). Even though the above finding can be due to different isolation procedures applied for each research groups, further evaluation should be done in order to define the best cultivation as well as isolation procedure of the target compounds.

Several of promising halogenated alkaloids from Agelas have been successfully synthesized in laboratory. One interesting example is the Agelastatins. These natural products share a complicated tetracyclic core having four stereocenters, which is a synthetically challenging structure. The impressive biological activity, following its scarce availability have triggered the total synthesis attempts for these intriguing substance. Fifteen total syntheses have been achieved for this compound, each presenting different strategies (Kitagawa et al., 1983; Stien et al., 1999; Feldman et al., 2002; Feldman et al., 2002; Domostoj et al., 2004; Davis and Deng, 2005; Nicolau et al., 2000).

Ageladine A which is 4-(4,5-dibromo-1H-pyrol-2-yl)-1H-imidazol[4,5-c]pyridin-2-amine has been reported to be successfully synthesized through a 12-step total synthesis by using a 6π-azaelectrocyclization and a Suzuki–Miyaura coupling of N-Boe-pyrole-2-boronic acid of which a chloropyridine roles as key step (Meketa and Weinreb, 2006). Ageladin A has been reported as a potential antiangiogenic matrixmetalloproteinase inhibitor isolated from A. nakamurai (Fujita et al., 2003).

Even though (Z)-hymenialdisine [(Z)-HMD] s not derived form Agelas sponge, its worth to be discussed here considering its properties as the only pyrrole imidazole alkaloids being potential kinase inhibitor. As it showed nanomolar kinase inhibitory activity against pan-kinases (Meijer et al., 2000), it is potentially useful not only for the treatment of cancer, but also for neurodegenerative disorders as Alzheimer’s, inflammatory pathologies, type-2 diabetes and cancer.

Synthetic approaches (Annoura et al., 1995; Xu et al., 1997, Sosa et al., 2000, Portevin et al., 2003; Papeo et al., 2005) towards (Z)-HMD have been reported to produce multigrams of yield. 1-Benzoyl-2-methyl-sulfanyl-1,5-dihydroimidazol-4-one employed in Papeo’s approach was also useful in the first total synthesis of (Z)-axinohydrantoin. Different series of analogues were synthesized (He et al., 2007; Chacun-Lefevre et al., 2000; Wan et al., 2004). Those derivatives left the main features of (Z)-HMD binding site in the kinase ATP unchanged. Efforts have been made to improve its selectivity and permeability (Kaiser et al., 2007; Mangu et al., 2008; Parmentier et al., 2009).

Psammaplin A, is a promising anti cancer candidate isolated from Verongid sponges. This compound has close structure relationship with the halogenated tyrosine derived alkaloids from Agelas sponges. This compounds has been developed as a drug lead of which its analogue substance, NP-LAQ824 (Remiszewski, 2003), has recently entered phase I clinical trials in patients with solid tumors or leukemia (Simmons et al., 2005).

The success of producing oroidin derivatives by several approach (Fresneda et al., 2001; Lindel and Hoffmann, 1997; Olofson et al., 1998; Sun and Chen, 2007; Ando et al., 2006) have offer more possibility of producing antiprotozoal compounds which are closely related to this compounds as described by Scala et al. (2010) by a synthetic route. The synthesis of the oroidin itself has been reported in many literatures (as reviewed in Forte et al., 2009). The method by Richards et al. (2008c) offers a possibility of producing the synthetic derivates related to this groups of compound for antibiofilm activity against P. aeruginosa.

A synthetic approach opens many doors for these compounds to be developed as drug lead. Their presence as a highly diverse group of compounds has offered new possibilities for utilization as medicinal purposes. As we know that marine sponge metabolites face difficulties to be developed as drug as it needs tremendous amount and a continuous supply, a possibility of having these compounds synthesized in the laboratory is relieving.

CONCLUSION

Halogenated alkaloids are marine sponge specific which offers a tremendous and unique structure diversity. These metabolites play significant role for their sponge producers and at the same time take part in the ecological aspects. Many halogenated alkaloids including
those found in Agelas sponges exhibit promising activity to be developed for medicinal purposes. Despite being sponge-originated metabolites, which put big question mark on their continuous supply has not stop its development. Many efforts have resulted successful production of selective metabolites through chemical synthesis, and many more analogues were created for better activity or bioavailability to fulfill the needs for new drug from the deep.

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