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The Alkaloids from Indonesian Marine Sponges

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Abstract

A large variety of alkaloids compounds have been isolated from marine sponges. Many of these compounds show interesting biological activities. In this review, we report the alkaloid isolated from Indonesian marine sponges complete with their structure, names, literatures and biological activities. The major part of the alkaloid isolated from the Indonesian marine sponges: Leucteta chagosensis, Agelas linnaei, Acanthostrongylophora sp with majority of alkaloid groups: imidazole alkaloid, brominated pyrrole, manzamine alkaloid and other type of alkaloids.

Keywords: Alkaloids; Marine sponges; Immunomodulation; Imidazoles

Introduction

The marine environment has proven to be a very rich source of extremely potent compounds that have demonstrated significant activities in antitumor, anti-inflammatory, analgesia, immunomodulation, allergy, and anti-viral assays [1]. Currently, more than 25,000 marine natural products have been isolated from 3,000 marine organisms and reported in about 8,000 publications. Bioactive natural products have been isolated from marine macro or microorganisms.

Marine sponges (*phylum Porifera*) are among the oldest multicellular invertebrate organisms [2] exhibiting a wide variety of colors and shapes. About 8,000 species of sponges, inhabiting different marine and freshwater ecosystems have been described to date [1]. Marine sponges continue to attract wide attention from marine natural product chemists and pharmacologists alike due to their remarkable diversity of bioactive compounds [3]. More than 5,300 different natural products are known from sponges, and more than 200 additional new metabolites from sponges are reported each year [4]. Most bioactive compounds from sponges can be classified as anti inflammatory, antitumor, immuno or neurosupressive, antiviral, anti malarial, anti tubercolussis, antibiotic or antifouling, cytotoxic or cardiovascular properties, enzyme inhibitors, cell division-inhibitors. Sponges are host organisms for various symbiotic microorganisms such as archaea, bacteria, cyanobacteria and microalgae. Symbiotic microorganisms in sponges can be sources of various natural products, because metabolites previously ascribed to sponges have recently been demonstrated to be biosynthesized by symbionts [5].

Indonesia as the world's largest archipelagic country with 17.508 islands and 81,000 km of coastline is worldwide recognized as being the richest in the world in term of diversity of marine organisms. Indonesian coral reefs in particular have the highest biodiversity in the world, forming the centre of high diversity of marine organisms [6]. A large variety of biologically active compounds with great biomedical interest such as anticancer, antibiotic, antioxidant, anti-AIDS, anti-TBC and anti-Alzheimer have recently been discovered from Indonesian marine invertebrates including microorganisms associated with them. [7].

The first alkaloid compound isolated from Indonesian marine sponge was discovered by Scheuer et al. in 1995 [8]. Recently, more than 70 alkaloids compounds have been isolated from Indonesian marine sponges. Most of the alkaloids were isolated from the genus of *Leuctetta, Agelas*, *Acanthostrongylophora*, with majority of type alkaloid groups: imidazole alkaloid, brominated pyrrole, manzamine alkaloid and other type of alkaloids.

The genus Agelas is placed in the family Agelasidae and this currently remains a monotypic family [9]. The taxonomic placement of the family has been in debate for many decades and recently, the family was placed together with the Astroscleridae in its own order Agelasida [10]. In addition, most of these species contain brominated pyrroles, which are known to have cytotoxic, antibacterial and anticancer properties [11,12]. The genus Leucetta known possesses a distinctive lemon yellow color and oval shape, and placed in the family Leucettidae. The chemistry of Leucetta as being dominated by 2-amino imidazoles, polyunsaturated fatty amino alcohols (PUFAA), and leucettamols. Acanthostrongylophora genus is family Petrosiidae and order Haplosclerida. This sponge contains complex molecules of the manzamine class. The manzamines, which show potent activity against human parasites, are thought to be produced by a bacterium found within the sponge [13].

Discussion

Imidazole alkaloids

Imidazoles are well known heterocyclic 5-membered ring structure with the formula C3H4N2. A group of imidazole alkaloids have been reported as biologically active metabolites from marine sponges of the genera *Leucetta* [14], *Clathrina* [15], *Leucosolenia* [16] and *Hyrtios* [17]. Some of these alkaloids show very important biological activities such as cytotoxic [18], antimicrobial [18-20], anticryptococcal [21], nitric oxide synthase inhibitory activity [21] and antitumor activity [22] Figure 1.

Seven new imidazole alkaloids named naamine F (1) naamine G (2), kealinine A (3), kealinine B (4), kealinine C (5), methyldorimidazole (6) and preclathridine B (7) were isolated in 2004 on the sponge *Leucetta chagosensis* colected from South Sulawesi, Indonesia by Hassan et

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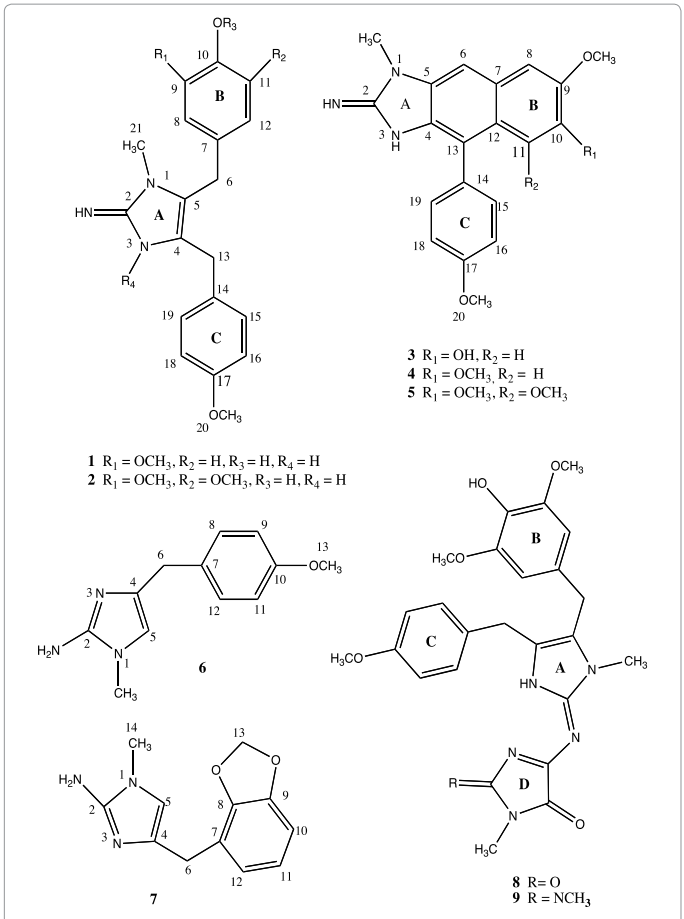

Figure 1: Imidazole alkaloids from marine sponges *Leucetta chanonensis* : naamine F (1) ; naamine G (2); kealinine A (3) ; kealinine B (4) ; kealinine C (5) ; methyldorimidazole (6) ; preclathridine B (7) ; Naamidine H (8) and naamidine I (9)

al. [23,24]. Later, it was also reported by Tsukamoto et al. [25], two imidazole alkaloids naamidine H (8) and naamidine I (9) from the same marine sponges Leucetta chagosensis from different geographic locations, North Sulawesi, Indonesia in 2007. The chemical structure of naamidine H (8) and naamidine I (9) is similar with naamine G (2) in the B rings, and the structures of 8 and 9 possess additional D rings compared to 2. This indicates that the two sponges from South Sulawesi and North Sulawesi commonly contain enzymes to produce 2, and moreover the sponge in North Sulawesi may contain additional enzymes to successively produce 8 and 9 [25].

Numerous marine imidazole alkaloids have recently been isolated, and many exhibit some form of antimicrobial and/or antitumor activity [22]. On the basis of the bioassays conducted by Hassan et al, naamine G (2) exhibited strong antifungal activity against the phytopathogenic fungus *Cladosporium herbarum* and also showed mild cytotoxicity against mouse lymphoma (L5178Y) and human cervix carcinoma (HeLa) cell lines [23]. In the brine shrimp assay conducted by Tsukamoto et al, from Leucetta *chagosensis* collected from North Sulawesi, kealiinine A (3) was more active than naamine G (2). Naamidine H (8) and naamidine I (9) were cytotoxic against HeLa cells at IC_{50} values of 5.6 and 15 μg/mL, respectively [25].

Spironaamidine (10) Figure 2 is a unique spiroquinone-containing alkaloid, that was isolated from the marine sponge, *Leucetta microraphis* collected in North Sulawesi, Indonesia. Spironaamidine (10) showed antimicrobial activity against Bacillus cereus with inhibitory zones of 12 by disk assay (10 mg/6 mm disk) [26].

Chemical investigation of indonesian marine sponge *Hyrtios reticulatus* resulted reticulatin A (11) and reticulatin B (12) Figure 2. Reticulatin A (11) and reticulatin B (12) were found to be novel 1,3-dimethyl-5-(methylthio) imidazolium alkaloids [10]. Reticulatins A (11) and B (12), were tested for E1 activity and found to be inactive even at 200 μM. The compounds were neither cytotoxic against HeLa cells at 5 μg/mL nor microbial against Bacillus subtilis, *Candida albicans*, and *Escherichia coli* at 10 μg/disk [17].

Bromopyrrole alkaloid

Bromopyrrole alkaloids constitute a class of marine compounds found exclusively in marine sponges [3]. Oroidin (13) Figure 3 was the first bromopyrrole alkaloids and isolated in 1971 from the marine sponge Agelas oroides [27]. Since the discovery of oroidin, more than 150 derivatives, with a wide variety of structures and interesting bioactivities, have been isolated from more than 20 different sponge taxa from different genera belonging mainly to the families Agelasidae, Axinellidae, and Halichondridae [28]. Bromopyrrole alkaloids are also of interest due to their pronounced pharmacological activities including cytotoxicity, antimicrobial, and immunosuppressive activities which have driven the research interest of natural product chemists toward their total syntheses primarily during the last decade [3].

Four brominated alkaloids, including 12-N-methyl stevensine (14),12-N-methyl-2-debromostevensine (15), 3-debromolatonduine B methyl ester (16), 3-debromolatonduine A (17) was isolated from marine sponge Stylissa species, which was collected at 2008 from Derawan Islands, Berau, North East Kalimantan, Indonesia [29]. 12-N-methyl stevensine (14) showed significant in vitro activity for cytotoxicity against mouse lymphoma cell line L5187Y with EC50 values of 3.5. μg/mL.

Two samples of the sponge *Stylissa carteri* (syn. *Axinella carteri*) collected in 1997 at Ambon and Sulawesi [30], resulted two bromopyrrole alkaloids; debromostevensine (18) and debromohymenin (19)

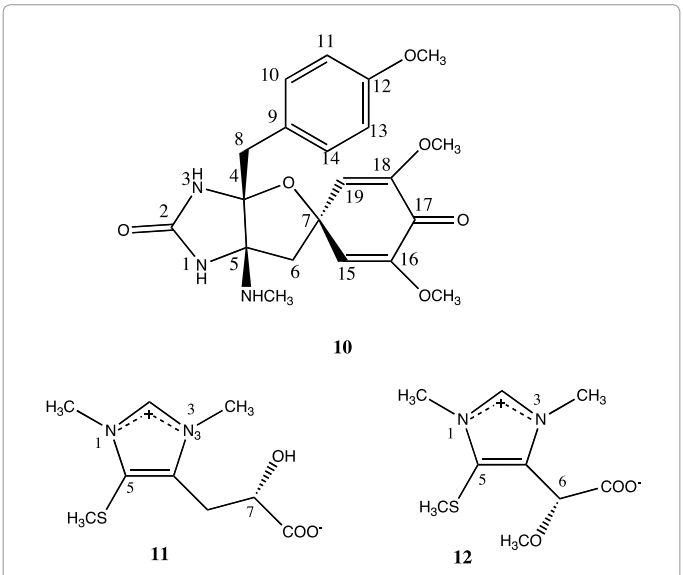

Figure 2: Structure of Spironaamidine (10) from Leucetta microraphis and *Reticulatin A* (11) and B (12) from *Hyrtios reticulatus*.

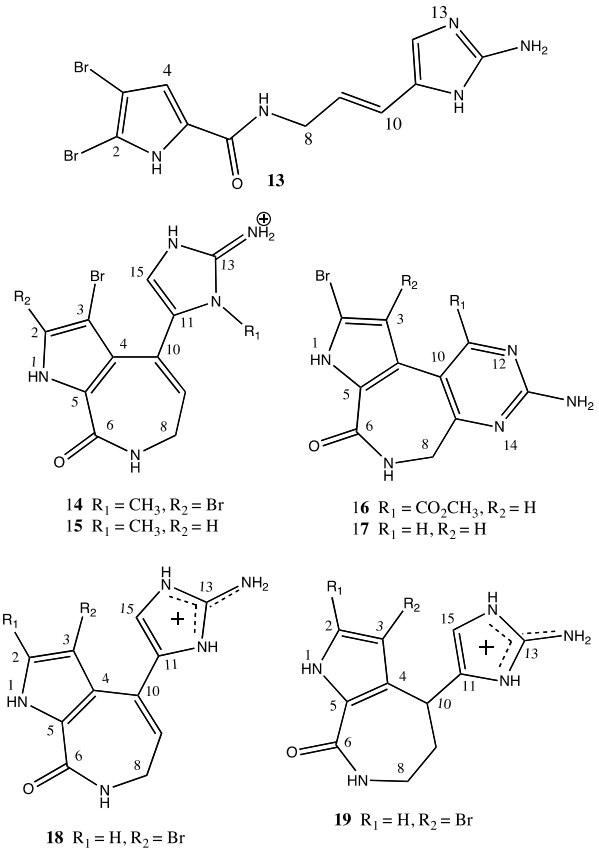

Figure 3: Bromopyrrole alkaloids from sponge *Stylissa* species: 12-N-methyl stevensine (14); 12-N-methyl-2-debromostevensine (15); 3-debromolatonduine B methyl ester (16); 3-debromolatonduine A (17); debromostevensine (18); debromohymenin (19)

The Indonesian marine sponge *Agelas linnaei* was collected from the Seribu Islands, resulted in the isolation of 11 new brominated pyrrole derivatives [31] Figure 4, named dibromohydroxyphakellin (20), 4-(4,5-dibromo-1-methylpyrrole-2-carboxamido)-butanoic acid (21), agelanin A (22), agelanin B (23), agelanesin A (24), agelanesin B (25), agelanesin C (26), agelanesin D (27), mauritamide B (28), mauritamide C (29) and mauritamide D (30) Table 1.

Agelanesins A–D (24–27) proved to be new tyramine containing haloderivatives, which so far have only been described from Agelas oroides. The presence of an iodide substituent on the tyramine moiety only found in 25 and 27 makes this group of compounds even more attractive. The agelanesins (24–27) showed prominent activity for cytotoxicity against the murine L1578Y mouse lymphoma cell line. IC_{50} values of the agelanesins were 9.55 (24), 9.25 (25), 16.76 (26), and 13.06μM (27), respectively. Compounds 24 and 25 exhibited the lowest IC_{50} values. This implied that cytotoxicity of the agelanesins is related to the degree of bromination of the pyrrole ring [31].

The bromopyrrole alkaloid longamide C (31) was isolated from a second Agelas species collected from Menjangan Island, Bali, Indonesia was taxonomically identified as *A. nakamurai* [31]. *Latonduines A* (32) and *Latonduines B* (33) were isolated from indonesian marine sponge *Stylissa carteri* collected on shallow reefs off of Latondu Island, Taka Bonerate [32]. Their skeleton cannot be derived from the C11N5 building block of the oroidins; it has been proposed that ornithine is the biogenetic precursor to the aminopyrimidine fragment of the lantoduines.

β-Carboline alkaloid

The marine sponges *Hyrtios erectus* collected in South West Sulawesi resulted a β-carboline alkaloid named hyrtiosulawesine (34) Figure 5 [33]. Two β-carboline alkaloids, variabine A (35) and variabine B (36), were isolated from marine sponge Luffariella variability [34]. Variabine A (35) is the first β-carboline derivative containing a sulfate group. Variabine B (36) inhibited chymotrypsin-like activity of the proteasome and Ubc13–Uev1A interaction with IC_{50} values of 4 and 5 μg/mL (16 and 20 dan μM), respectively, whereas 35, a sulfonated derivative of 36, had little effect at 5 μg/mL (16 μM), indicating that the inhibitory activities are lost by sulfonation.

The manzamines, first described in 1986 [35], are an intriguing group of marine alkaloids, which are characterized by a fused and bridged tetra- or pentacyclic ring system that is joined to a β-carboline. This class of alkaloids has been reported previously to show a number of significant biological activities including cytotoxic [35], insecticidal [36], antibacterial [37], anti-infective [38], and antiparasitic activities [39], with the greatest potential for possible clinical applications existing for the control of Plasmodium falciparum and *Mycobacterium tuberculosis* [40].

8-hydroxymanzamine A (37) Figure 6 is the first manzamine alkaloid, was isolated from an undescribed sponge Pachypellina sp, collected at Manado Bay, Sulawesi, Indonesia [8]. Compounds 37 exhibit moderate antitumor and anti-HSV-I1 activity. Kauluamine (38) is the manazamine alkaloid isolated from Indonesian sponges Prianos sp collected in Manado Bay [41].

Acanthostrongylophora sp., has been shown to be a highly rich source of bioactive manzamine related alkaloids [42-44]. *Manadomanzamines A* (39) and *Manadomanzamines B* (40) were isolated from a sopnge *Acanthostrongylophora sp.* (Haplosclerida: Petrosiidae), collected from Manado Bay [42]. *Manadomanzamines A* (39) and *B* (40) represent an unprecedented rearrangement of the manzamine skeleton and exhibit significant activities against Mycobacterium tuberculosis (Mtb) and human immunodeficiency virus (HIV-1) and moderate activity against several AIDS opportunistic infections (OI).

Seven manzamine alkaloids also isolated from Acanthostrongylophora sp. (Haplosclerida: Petrosiidae), collected from Manado Bay [43,44], named 12,34-oxamanzamine E (41), 8-hydroxymanzamine J (42), 6-hydroxymanzamine E (43), 12,28-oxamanzamine E (44) Figure 7, 12,34-oxa-6-hydroxymanzamine E (45), 8-hydroxymanzamine B (46), and 12,28-oxaircinal A (47) Figure 8. Their structures of the compounds have been established on the basis of 1D and 2D NMR spectroscopic analysis and comparison of the data to literature values of related compounds.

Manzamine alkaloids have been also isolated from Indonesia marine sponge Petrosiidae genus (Order *Haplosclerida*, Family *Petrosiidae*). ent-12,34-oxamanzamine E (48), 12,34-oxamanzamine A (49) Figure 9, 32,33-dihydro-31-hydroxymanzamine A (50), 32,33-dihydro-6-hydroxymanzamine A-35-one (51), des-N-methylxestomanzamine A (52), 32,33-dihydro-6,31-dihydroxymanzamine A (53), and 1,2,3,4-tetrahydronorharman-1-one (54) isolated from *Petrosiidae* sp [45,46], collected from vertical slopes between 33 and 40 m from Knife Cape, Manado Bay. All compounds have been assigned on the basis of NMR and X-ray data. ent-12,34-oxamanzamine F (55) also isolated from *Petrosiidae* genus [45], collected from reef slopes and vertical surfaces between 6 and 33 m from Black Reef Point, Manado Bay.

Alkaloid	Sponge	Bilogical activties	Reference
Naamine F (1)	*Leucetta chanonensis*		[23]
Naamine G (2)	*Leucetta chanonensis*	antifungal activity against the phytopathogenic fungus *Cladosporium herbarum*	[23]
Kealinine A (3)	*Leucetta chanonensis*		[23]
Kealinine B (4)	*Leucetta chanonensis*		[23]
Kealinine C (5)	*Leucetta chanonensis*		[23]
Methyldorimidazole (6)	*Leucetta chanonensis*		[24]
Preclathridine B (7)	*Leucetta chanonensis*		[24]
Naamidine H (8)	*Leucetta chanonensis*	cytotoxicity against HeLa cells	[25]
Naamidine I (9)	*Leucetta chanonensis*	cytotoxicity against HeLa cells	[25]
Spironaamidine (10)	*Leucetta chanonensis*	antimicrobial activity against *Bacillus cereus*	
Reticulatin A (11)	*Hyrtios reticulatus*		[17]
Reticulatin B (12)	*Hyrtios reticulatus*		[17]
12-N-methyl stevensine (14)	*Stylissa sp*	cytotoxicity against mouse lymphoma cell line L5187Y	[29]
12-N-methyl-2-debromostevensine (15)	*Stylissa sp*		[29]
3-debromolatonduine B methyl ester (16)	*Stylissa sp*		[29]
3-debromolatonduine A (17)	*Stylissa sp*		[29]
Debromostevensine (18)	*Stylissa carteri*		[30]
Debromohymenin (19)	*Stylissa carteri*		[30]
Dibromohydroxyphakellin(20)			[31]
4-(4,5-Dibromo-1-methylpyrrole-2-carboxamido)-butanoic acid (21)	*Agelas linnaei*		[31]
Agelanin A (22)	*Agelas linnaei*		[31]
Agelanin B (23)	*Agelas linnaei*		[31]
Agelanesin A (24)	*Agelas linnaei*	cytotoxicity against the murine L1578Y mouse lymphoma cell line	[31]
Agelanesin B (25)	*Agelas linnaei*	cytotoxicity against the murine L1578Y mouse lymphoma cell line	[31]
Agelanesin C (26)	*Agelas linnaei*	cytotoxicity against the murine L1578Y mouse lymphoma cell line	[31]
Agelanesin D (27)	*Agelas linnaei*	cytotoxicity against the murine L1578Y mouse lymphoma cell line	[31]
Mauritamide B (28)	*Agelas linnaei*		[31]
Mauritamide C (29)	*Agelas linnaei*		[31]
Mauritamide D (30)	*Agelas linnaei*		[31]
Longamide C (31)	*Agelas nakamurai*		[31]
Latonduine A (32)	*Stylissa carteri*		[32]
Latonduine B (33)	*Stylissa carteri*		[32]
Hyrtiosulawesine (34)	*Hyrtios erectus*		[33]
Variabines A (35)	*Luffariella variability*		[35]
Variabine B (36)	*Luffariella variability*	Inhibit chymotrypsin-like activity of the proteasome and Ubc13–Uev1A	[35]
8-hydroxymanzamine A (37)	*Prianos sp*	antitumor and anti-HSV-I1 activity	[8]
Kauluamine (38)	*Prianos sp*		[41]
Manadomanzamines A (39)	*Acanthostrongylophora sp*	Antitubercolusis and anti HIV	[42]
Manadomanzamines B (40)	*Acanthostrongylophora sp*	Antitubercolusis and anti HIV	[42]
12,34-oxamanzamine E (41)	*Acanthostrongylophora sp*		[43]
8-hydroxymanzamine J (42)	*Acanthostrongylophora sp*		[43]
6-hydroxymanzamine E (43)	*Acanthostrongylophora sp*		[43]
12,28-oxamanzamine E (44)	*Acanthostrongylophora sp*		[44]
12,34-oxa-6-hydroxymanzamine E (45)	*Acanthostrongylophora sp*		[44]
8-hydroxymanzamine B (46)	*Acanthostrongylophora sp*		[44]
12,28-oxaircinal A (47)	*Acanthostrongylophora sp*		[44]
ent-12,34-oxamanzamine E (48)	*Petrosiidae sp*		[45]
12,34-oxamanzamine A (49)	*Petrosiidae sp*		[45]
32,33-dihydro-31-hydroxymanzamine A (50)	*Petrosiidae sp*		[46]
32,33-dihydro-6-hydroxymanzamine A-35-one (51)	*Petrosiidae sp*		[46]
des-*N*-methylxestomanzamine A (52)	*Petrosiidae sp*		[46]
32,33-dihydro-6,31-dihydroxymanzamine A (53)	*Petrosiidae sp*		[46]
1,2,3,4-tetrahydronor-harman-1-one (54)	*Petrosiidae sp*		[46]

ent-12,34-0xamanzamine F (55)	*Petrosiidae sp*		[45]
Bisdemethylaaptamine (57)	*Aaptos. sp*		[49]
bisdemethylaaptamine-9-O-sulfate (58)	*Aaptos. sp*		[49]
11-Methoxy-3H-[1,6]naphthyridino[6,5,4-def] quinoxalin-3-one (59)	*Aaptos suberitoides*		[51]
2,11-Dimethoxy-3H-[1,6]naphthyridino[6,5,4-def]-quinoxalin-3-one (60)	*Aaptos suberitoides*		[51]
5-benzoyldemethyaaptamine (61)	*Aaptos suberitoides*	cytotoxicity against the murine L1578Y mouse lymphoma cell line	[51]
3-amino demethyl(oxy)-aaptamine (62)	*Aaptos suberitoides*		[51]
2-methoxy-3-oxoaaptamine (63)	*Aaptos. sp*	anti-mycobacterial against *Mycobacterium smegmatis*	[52]
Tetradehydrohaliclonacyclamine A (64)	*Halichondria sp*		[53]
Tetradehydrohaliclonacyclamine A mono-N-oxide (65)	*Halichondria sp*		[53]
2-epi-Tetradehydrohaliclonacyclamine (66)	*Halichondria sp*		[53]
Labuanine A (67)	*Biemma fortis*		[54]
Sagitol C (68)	*Oceania sp*	cytotoxic activity against L5178Y, PC12, and Hela cell lines	[55]
(-)-agelasine D (69)	*Agelas nakamurai*	cytotoxicity against L5178Y mouse lymphoma cells and anti fouling	
(-)-ageloxime D (70)	*Agelas nakamurai*	cytotoxicity against L5178Y mouse lymphoma cells and anti fouling	
cortistatins J (71)	*Corticium simplex*	cytostatic anti-proliferative activity against HUVECs	
cortistatin K (72)	*Corticium simplex*		
cortistatin L (73)	*Corticium simplex*		
clathryimine A (74)	*Clathria basilana*		[57]
Hyrtioreticulin F (75)	*Hyrtios reticulatus*		[17]
Upenamide (76)	*Echinochalina sp*		[58]

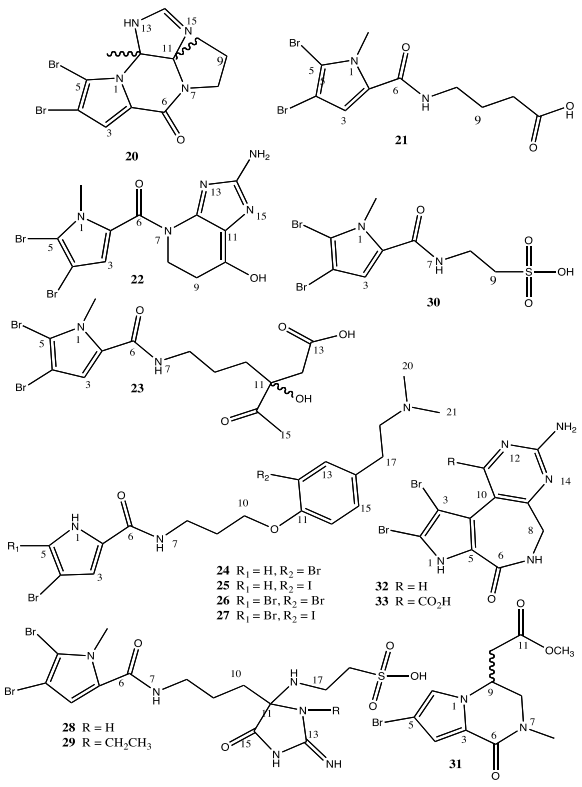

Figure 4: Bromopyrrole alkaloids from sponge *Agelas* species : dibromohydroxyphakellin (22); 4-(4,5-Dibromo-1-methylpyrrole-2-carboxamido)-butanoic acid (23); agelanine A (24); agelanin B (25); agelanesin A (26); agelanesin B (27); agelanesin C (28); agelanesin D (29); mauritamide B (30); mauritamide C (31); mauritamide D (32) and longamide C (33). Stylissa carteri: *Latonduines A* (32) and *B* (33)

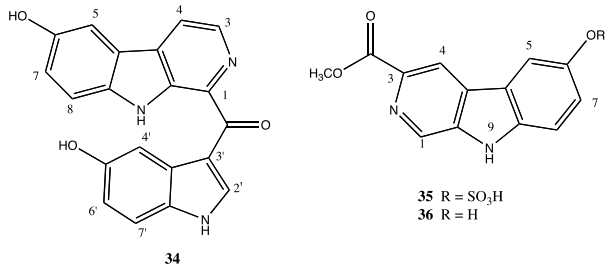

Figure 5: β-carboline alkaloid hyrtiosulawesine (34) from sponge *Hyrtios erectus* and variabine A (35) and variabine B (36) from *Luffariella* variability

Aaptamine alkaloid

Marine sponges of the genus, Aaptos have been found to be a rich source of a group of 1H-benzo [d,e]-[1,6] naphthyridine alkaloids known collectively as a aptamine (56) Figure 10 [47]. Aaptamine-like compounds have also been found in sponges of other genera such as *Xestospongia*, *Suberites*, *Hymeniacidon*, and *Luffarriella* [48]. In particular, the genus Aaptos continues to be an abundant source of novel aaptamine alkaloids which still spurs interest in finding new bioactive metabolites. This class of alkaloids has been reported previously to show a number of significant biological activities including cytotoxic, antiviral, antimicrobial, antifungal, antiparasitic, α-adrenergic antagonistic, radical scavenging, and antifouling activity [48].

Two aaptamines, bisdemethylaaptamine (57) and bisdemethylaaptamine-9-O-sulfate (58) isolated from Aaptos sp. marine sponge, collected from Bunaken Island, North Sulawesi [49]. Bisdemethylaaptamine (57) is the first instance of bisdemethylaaptamine being isolated as a natural product. In a previous paper by Nussbaum et al. [50], it was proposed that compound 57 was a possible biosynthetic precursor for aaptamine alkaloids and a concise synthesis of 52 based

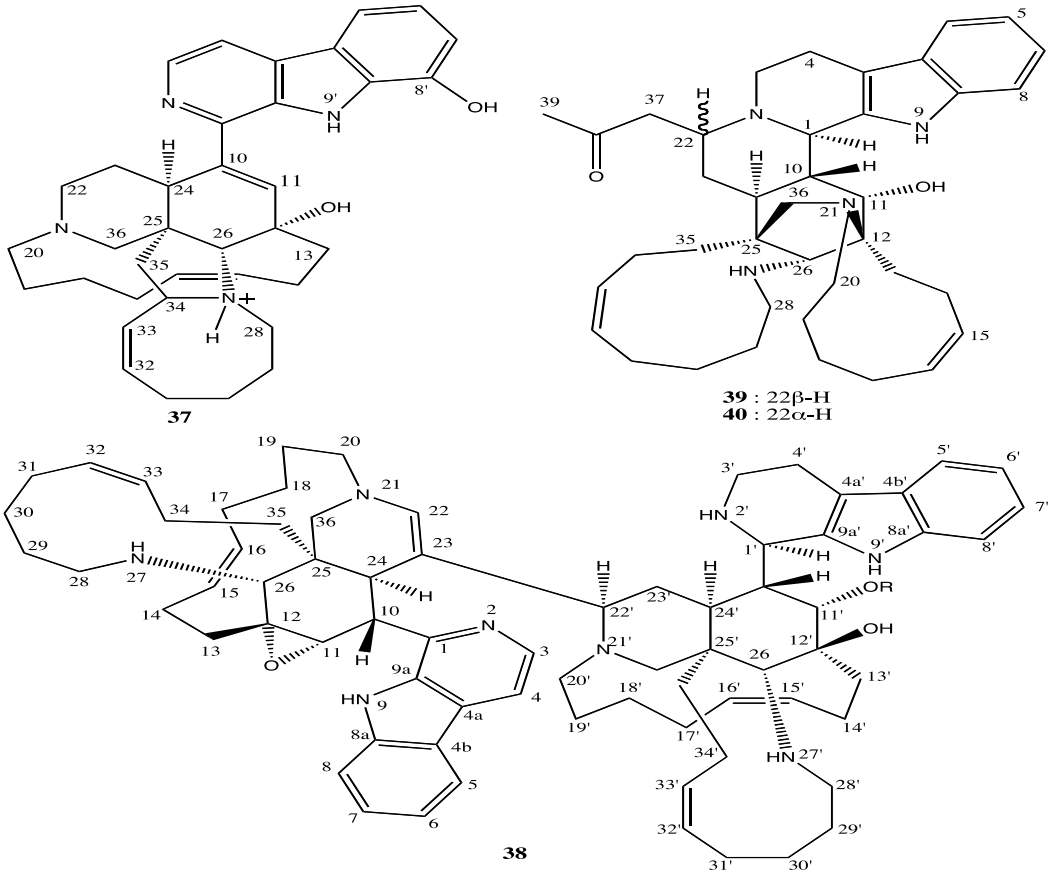

Figure 6: Manzamamine alkaloids 8-hydroxymanzamine A (37); Kauluamine (38); *Manadomanzamines A* (39) and *Manadomanzamines B* (40)

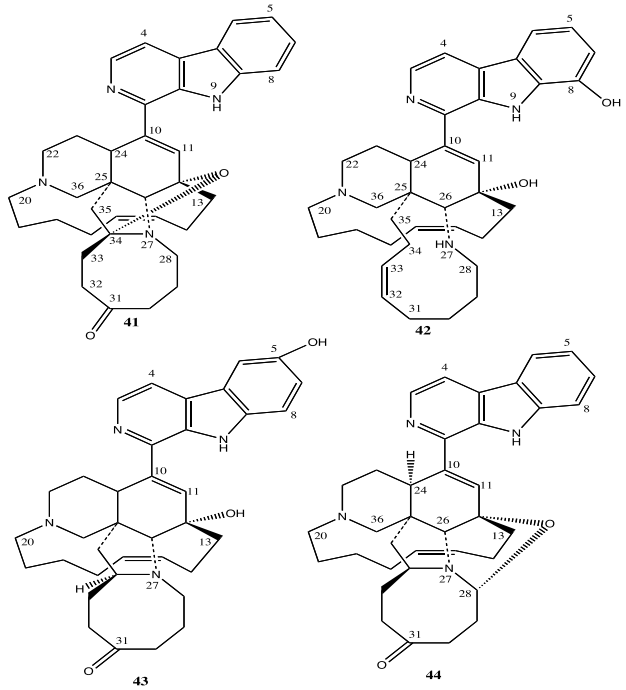

Figure 7: Manzamamine alkaloids from sponges *Acanthostrongylophora sp*

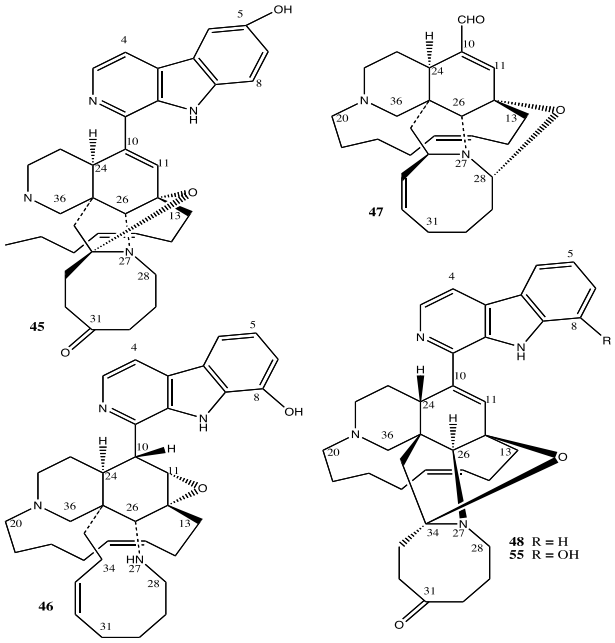

Figure 8: Manzamamine alkaloids from genus *Acanthostrongylophora* and *Petrosiedae*

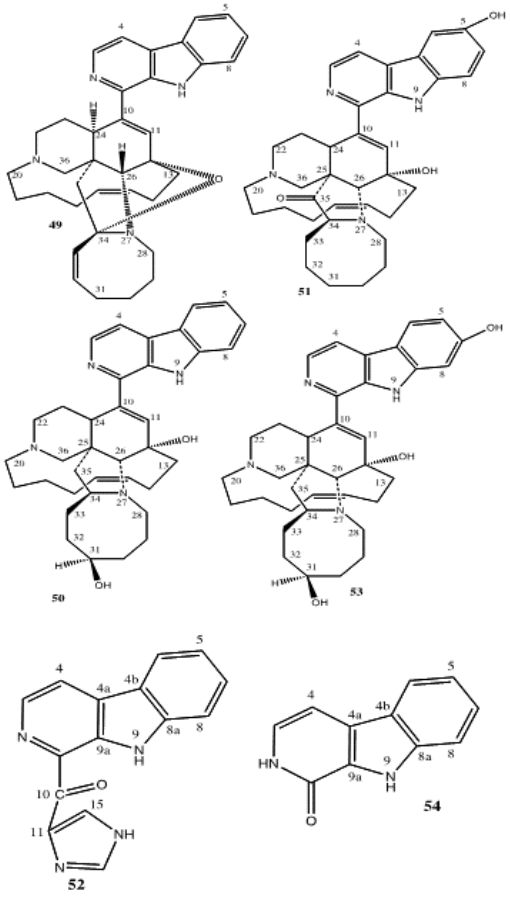

Figure 9: Manzamamine alkaloids from genus *Petrosiedae*

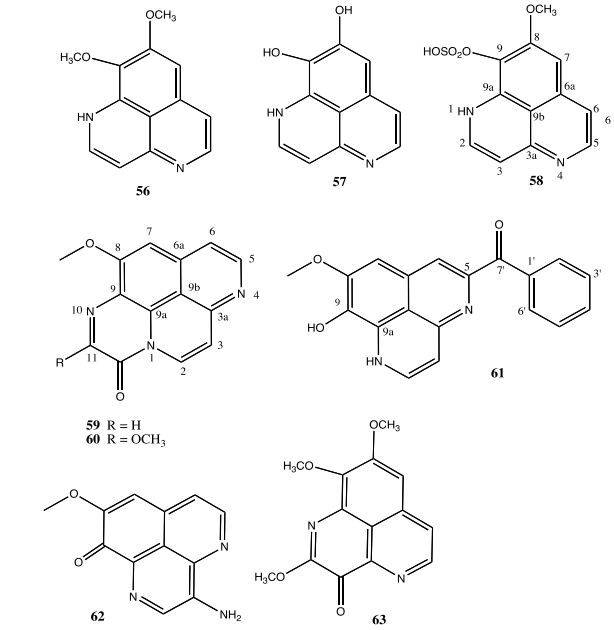

Figure 10: Aaptamine Alkaloids

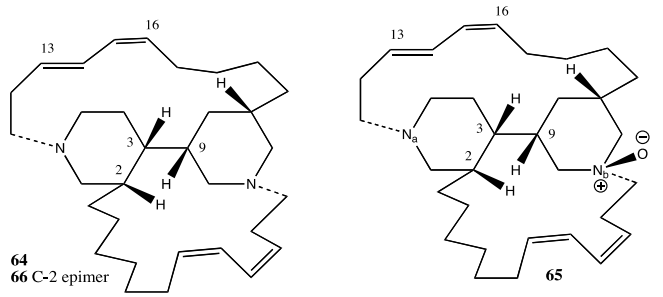

Figure 11: Alkylpiperidine alkaloids

on a biomimetic approach was reported. Bisdemethylaaptamine-9-O-sulfate (58) is the first compound of a naturally occuring a sulfated aaptamine [49].

From *Aaptos suberitoides* collected in Ambon resulted four aaptamines derivatives, 11-methoxy-3H-[1,6] naphthyridino [6,5,4-def] quinoxalin-3-one (59), 2,11-dimethoxy-3H-[1,6] naphthyridino[6,5,4-def]-quinoxalin-3-one (60), 5-benzoyldemethyaaptamine (61), 3-amino demethyl (oxy)-aaptamine (62). Compound 61 inhibited the growth of L5178Y cells, with IC_{50} value of 5,5 µM [51]. Another class alkaloid designated 2-methoxy-3-oxoaaptamine (63) was isolated from Aaptos sp. collected in 2009 at Kupang. Compound 63 was anti-mycobacterial against Mycobacterium smegmatis in both growing and dormancy-inducing hypoxic conditions with Minimum Inhibitory Concentration (MIC) of 6.25 5 µg/ml [52].

Alkylpiperidine alkaloids

TetradehydrohaliclonacyclamineA (64), Tetradehydrohaliclonacyclamine A mono-N-oxide (65), and 2-epi-Tetradehydrohaliclonacyclamine (66) Figure 11 were isolated from the Indonesian sponge

Halichondria sp., collected from Tulamben bay, Bali. The relatif configurations was deduced by coupling constant analysis combined with 1D-TOCSY data, and confirmed by an X-ray crystallographic analysis of 64. The absolute structure of compound 64 has been established by X-ray crystallographic from anomalous dispersion effects using Cu radiation, which determined that the absolute configuration is 2S, 3S, 7S, 9S while an HPLC study revealed that the alkaloid is enantiomerically pure [53].

Pyridoacridine alkaloids

Indoneian marine sponges *Biemma fortis* collected in August, 2001 at Labuanbajo, West Flores, Nusa Tenggara Timur, resulted a pyridoacridine alkaloid named Labuanine A (67) Figure 12 and the chemical structure was determined by spectroscopic study and chemical conversion. Labuanine A (67) induced multipolar neuritogenesis in more than 50% of cells at 0.03 – 3 μM concentration [54].

Sagitol C (68) Figure 12 is a pyridoacridine alkaloid isolate from Oceania sp [55]. The structure was established on the basis of physical and spectroscopic methods 1D and 2D NMR, in addition to mass spectrometry and comparison with literature data. The cytotoxic effect of 68 was tested against L5178Y, PC12, and Hela cell lines. It gave 93%, 88% and 76% growth suppression against the tested cell lines at a concentration of 24.6 μM and 81%, 74% and 37% at a concentration of 12.3 μM with ED50(s) of 0.7, 0.9, and 2.3 μM, respectively.

Terpenoid and steroidal alkaloids

Agelas nakamurai afforded diterpene alkaloids named (-)-agelasine D (69) and (-)-ageloxime D (70) Figure 13 [31]. Compound 69 and 70 exhibited cytotoxicity against L5178Y mouse lymphoma cells (IC_{50} 4.03 and 12.5 μM, respectively). Furthermore, (-)-agelasine D (69) and (-)-ageloxime D (70) inhibited settling of larvae of *Balanus improvisus* in an anti-fouling bioassay and proved to be toxic to the larvae. (-)-Agelasine D (69) inhibited the growth of planktonic forms of biofilm forming bacteria S. epidermidis (MIC < 0.0877 μM) but did not inhibit biofilm formation whereas (-)-ageloxime D (70) derivative showed the opposite activity profile and inhibited only biofilm formation but not bacterial growth.

An indonesian marine sponge Corticium simplex yielded four steroidal alkaloids, cortistatin J (71), cortistatin K (72), cortistatin L (73) Figure 14. The chemical structure were determined by 2D-NMR analysis to be unique abeo-9 (10-19)-androstane-type steroidal alkaloid having isoquinoline unit instead of the side chain part, respectively [56]. Cortistatin J (71) showed cytostatic anti-proliferative activity against HUVECs (IC_{50} = 8 nM), in which the selective index was 300–1100-fold higher in comparison with those of normal human dermal fibroblast (NHDF) and several tumor cell lines [KB epidermoid carcinoma cells (KB3-1), human chronic myelogenous leukemia cells (K562), and murine neuroblastoma cells (Neuro2A)].

Other alkaloids

An Indonesian collection of the massive orange marine sponge *Clathria basilana* yielded a clathryimine A (74) Figure 15 [57], the structure of clathryimine A (74) provides the first example of a quinolizinium metabolite from a marine sponge. The best analogies to 74 among sponge derived alkaloids are not very similar because they have quite different bicyclic nitrogen containing rings.

Hyrtioreticulin F (75) was isolated from the water-soluble fraction of an extract of the Indonesian marine sponge, *Hyrtios reticulatus*.

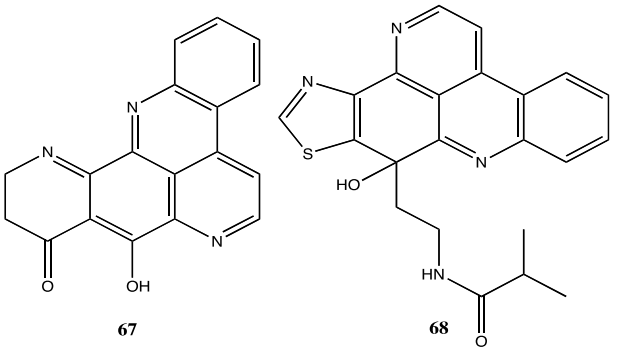

Figure 12: Pyridoacridine alkaloids

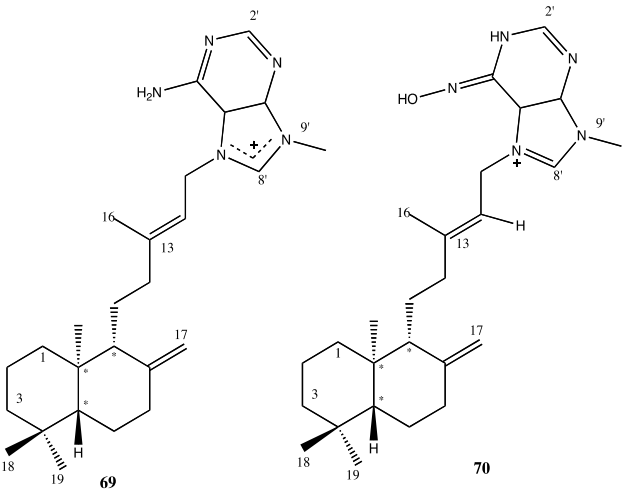

Figure 13: Diterpene Alkaloids

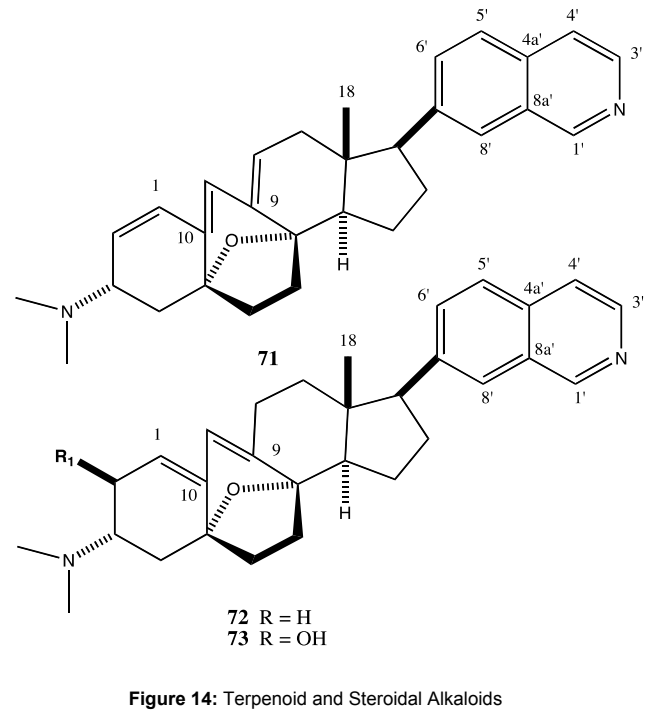

Figure 14: Terpenoid and Steroidal Alkaloids

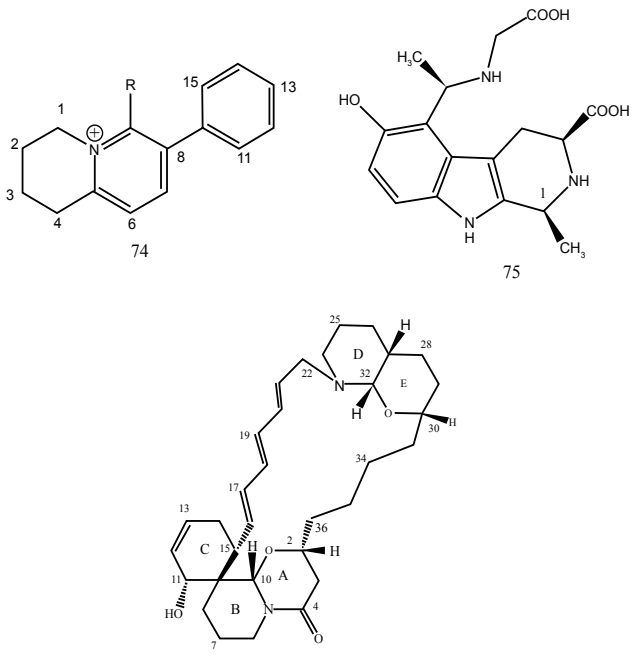

Figure 15: Other Alkaloids

Compound 75 is likely biosynthesized from L-tryptophan, two units of L-alanine, and glycine by the Pictete-Spengler reaction [17].

'Upenamide (76) represents a new class of macrocyclic marine alkaloid possessing both spirooxaquinolizidinone and hemiaminal ring systems. It was isolated from the Indonesian sponge Echinochalina sp [58].

Conclusions

Natural products have historically been a rich source of "lead compounds" for drug discovery. Although started only fifty years ago, the investigation of marine organisms aimed at searching new biologically active compounds has now gained a recognized role in this kind of studies. Alkaloids from indonesia marine sponges have been reviewed in this paper. The major part of the alkaloids was isolated from the Indonesian marine sponges: *Leucteta chagosensis*, *Agelas linnaei*, *Acanthostrongylophora* sp with majority of alkaloid groups: imidazole alkaloid, brominated pyrrole, manzamine alkaloid and other type of alkaloids. All the structure of alkaloids was clarified by spectroscopic analysis and synthetic methods. Biological activities of these alkaloids were not wholly investigated.

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