Secondary Metabolites from Marine Sponges of the Genus Oceanapia: Chemistry and Biological Activities

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Abstract: In this review, we summarized the distribution of the chemically investigated Oceanapia sponges, including the isolation and biological activities of their secondary metabolites, covering the literature from the first report in 1989 to July 2019. There have been 110 compounds reported during this period, including 59 alkaloids, 33 lipids, 14 sterols and 4 miscellaneous compounds. Besides their unique structures, they exhibited promising bioactivities ranging from insecticidal to antibacterial. Their complex structural characteristics and diverse biological properties have attracted a great deal of attention from chemists and pharmaceuticals seeking to perform their applications in the treatment of disease.

Keywords: Oceanapia; sponge; secondary metabolites; biological activities

1. Introduction

Marine sponges, living in harsh marine conditions from tropic to polar regions, offer an enormous source of natural products bearing unique structures and significant bioactivities, making them ideal candidates for drug discovery projects [1]. Of them, the animals belonging to the genus Oceanapia (phylum, Porifera; class, Demospongiae; subclass, Heteroscleromorpha; order, Haplosclerida; family, Phloeodictyidae) have proven to be a biochemical warehouse for secondary metabolites, such as alkaloids, lipids, sterols, etc. It is particularly interesting that these compounds exhibited a wide range of biological features ranging from antibacterial and cytotoxic to ichthyotoxic activities [2]. In order to better understand the natural products from this genus, there would be a demand for a review.

Notably, several other generic names (Phloeodictyon Carter, 1882; Rhizochalina Schmidt, 1870; Biminia Wiedenmayer, 1977; Foliolina Schmidt, 1870) are now considered as synonyms for Oceanapia [3]. However, there is no associated reference on secondary metabolites of two genera Biminia and Foliolina listed in SciFinder Scholar. Therefore, this review covers topics on three nominal genera, Oceanapia, Phloeodictyon and Rhizochalina, covering different types of compounds, with a literature survey from 1989 to July 2019. During this period, 110 compounds have been reported, including 59 alkaloids, 33 lipids, 14 sterols and 4 other miscellaneous compounds. More than eight species of Oceanapia sponges have been chemically investigated including Oceanapia sagittaria, Oceanapia fistulosa, Oceanapia bartschi, Phloeodictyon sp., Rhizochalina incrustata, Oceanapia ramsayi, Oceanapia phillipensis, Oceanapia cf. tenuis and Oceanapia sp. The global distribution of the chemically investigated marine Oceanapia sponges according to their species is shown in Figure 1.
2. Alkaloids

Alkaloids were encountered most frequently. They can be classified as pyridoacridine alkaloids, quinolizidine alkaloids, sesquiterpene alkaloids, phloeodictine alkaloidalkaloids, bromotyrosine alkaloids, indole alkaloids and nucleotide alkaloids, according to their skeletons.

2.1. Pyridoacridine Alkaloids

Faulkner’s group found the sponge Oceanapia sagittaria from Palau contained two pyridoacridine alkaloids dercitamide (1) and sagitol (2) (Figure 2). Of them, 2 was the first pyridoacridine alkaloid from a marine sponge in which the aromatic system had been disrupted. Interestingly, 2 could be obtained by autoxidation of 1. Faulkner et al. suggested that 2 was not an artifact that was supported by CD measurements. [4]. Two years later, Proksch et al. reported three pyridoacridine alkaloids kuanoniamine C (1), kuanoniamine D (3) and N-deacetylkuanoniamine C (4) were afforded by the Micronesian sponge Oceanapia sp. [5]. It may be worthy to point out that the structures of dercitamide and kuanoniamide C were established to be identical by Faulkner and his co-workers [6]. Herein, the same numbering was assigned for these two different nomenclative compounds. Proksch et al. performed many bioassays for these three alkaloids. When incorporated into an artificial diet, compounds 1 and 3 exhibited insecticidal activity toward neonate larvae of the polyphagous pest insect Spodoptera littoralis (LC50 of 156 and 59 ppm, respectively). Both compounds also showed toxicity in the brine shrimp lethality test with LC50 values of 37 and 19 µg/mL, respectively. Although the N-deacyl derivative 4 did not show any remarkable effect in either of the abovementioned bioassays, it appeared to be active in the cytotoxic biotests against two human cell lines. The IC50 of 4 was 1.2 µg/mL toward HeLa cells and 2.0 µg/mL toward MONO-MAC 6 cells. In receptor binding assays, compound 3 showed affinity to A1- and A2A-adenosine receptors with Ki values of 2.94 and 13.7 µM, respectively. Compound 1 was less active than its homologue 3, whereas the N-deacetyl derivative 4 showed no affinity toward adenosine receptors. In addition, compounds 1, 3 and 4 exhibited moderate affinity to benzodiazepine binding sites of GABA_A receptors [5]. Meanwhile, Proksch et al. explored the distribution of compounds 1 and 3 in the sponge Oceanapia sp., as well as its ecological implications. It was found that the secondary metabolites 1 and 3 showed a sharp increase from the basal root to the capitum. The feeding assays against the spongivorous angelfish Pomacanthus imperator showed that 1 and 3 significantly deterred fishing by natural assemblages of reef fishes at fistule concentrations, confirming their role as defensive agents [7].
Kijjoa and his co-workers reported another specimen, O. sagittaria from the Gulf of Thailand, afforded kuanoniamine C (1) and its relative compound kuanoniamine A (5). In this study, compounds 1 and 5 were evaluated for cytotoxic effects against five human tumor cell lines MCF-7 (ER+), MDA-MB-231 (ER-), SF-268, NCI-H460 and UACC-62, and one human non-tumor cell line, MRC-5, by the SRB method. Compound 5 was found to be a potent growth inhibitor of all tumor and the non-tumor cell lines while 1 was less potent but showed high selectivity toward the estrogen-dependent (ER+) breast cancer cell line MCF-7. Furthermore, 5 was shown to be a more potent inhibitor of DNA synthesis than 1. It was also found that 5 caused an extensive reduction in the MCF-7 cells in the G2/M phase as well as an increase in the apoptotic cells [8].

Bioassay-guided fractionation of the MeOH extract of an Australian sponge Oceanapia sp. performed by Carroll’s group, using the aspartyl semialdehyde dehydrogenase (ASD) to detect antibacterial activity, led to the discovery of a bright blue compound, petrosamine B (6). It was found 6 was a weak inhibitor of ASD with an IC₅₀ of 306 μM [9]. In Ibrahim’s investigation of the Indonesian sponge Oceanapia sp., sagitol C (7) together with the two abovementioned compounds 1 and 2 were disclosed. The cytotoxic effect of 7 was tested against mouse lymphoma (L5178Y), rat brain (PC12) and human cervix (Hela) cell lines. It exhibited 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 values of 0.7, 0.9 and 2.3 μM, respectively [10].

2.2. Quinolizidine Alkaloids

A bisquinolizidine alkaloid, petrosin (8), and a series of bis-1-oxaquinolizidine alkaloids, xestospongins C–J (9–16) (Figure 3), were all obtained by Singh and his partners from the ethyl acetate extract of the sponge Oceanapia sp., which was collected from the southern coast of India. The relative stereochemistry of 8 was established by single-crystal X-ray analysis as 1S*,2R*,4R*,9S*,15R*,17R*,22S*,23S*. Compounds 9 and 10 were found to be active against several pathogens such as Cryptococcus neoformans, Aspergillus funigatus, Candida albicans and Aspergillus niger [11].

2.3. Sesquiterpene Alkaloid

Faulkner’s group disclosed the major metabolite of the Philippine sponge Oceanapia sp. was the antimicrobial alkaloid oceanapamine (17) (Figure 4), isolated as trifluoroacetate (TFA) salt. The structure of 17 consisted of a monocyclic sesquiterpene attached to a histamine residue, representing the sole sesquiterpene–alkaloid hybrid from the genus Oceanapia. Compared with related model compounds, the absolute configuration of 17 was assigned as 6R. The TFA salt of 17 was screened rather broadly but only exhibited antimicrobial activity. In the standard disk (6-mm) assay, 17 inhibited Bacillus subtilis and Escherichia coli at 25 μg/disk, Staphylococcus aureus and C. albicans at 50 μg/disk and Pseudomonas aeruginosa at 100 μg/disk [12].
2.4. Phloeodictyne Alkaloids

The phloeodictyne framework was characterized by a fused alkaloidal skeleton, 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidinium, bearing a variable-length alkyl (or alkenyl) side chain at C-6 and a four/five methylene chain ending in a guanidine group at N-1, while a thioethylguanidine chain may have been present at C-7 or not. Kourany-Lefoll et al. first reported this group of alkaloids in the haplosclerid sponge *Phloeodictyon* sp. living in deep New Caledonian waters. Included were the pure compounds phloeodictines A (18) and B (19) and the inseparable mixtures of phloeodictines A1 (20) and A2 (21), A3 (22), A4 (23) and A5 (24), A6 (25) and A7 (26) and C1 (27) and C2 (28) (Figure 5). Compounds 18 and 19 had been tested against several bacteria using the standard microdilution plate assay and revealed to have potent activity with the following respective MICs (µg/mL): *S. aureus* (1, 3), *E. coli* (1, 30), *P. aeruginosa* (10, >30) and *Streptococcus fecalis* (5, >15). On the other hand, the mixtures A (20+21), B (22+23+24), C (25+26) and D (27+28) were found to possess a wider spectrum of antibacterial activity (respective MICs, µg/mL): *S. aureus* (3, 30, 1, 3), *E. coli* (3, 30, 3, >30), *P. aeruginosa* (30, >30, 30, >30), *Clostridium perfringens* (30, >30, 1, >100), *Bacteroides frugilis* (10, ~30, 3, >100) and *Peptococcus assaccharyoticus* (10, >30, 3, >100). Furthermore, compounds 18, 19 and mixtures A–D also exhibited in vitro cytotoxicity toward KB human nasopharyngeal carcinoma cells with IC50 values of 1.5, 11.2, 2.2, 3.5, 0.6 and 1.8 µg/mL, respectively [13,14]. Ten years later, Snider and his co-worker completed the first synthesis of (±)-21 [15].

**Figure 3.** The chemical structures of quinolizidine alkaloids 8–16.

**Figure 4.** The chemical structure of sesquiterpene alkaloid 17.
Phloeodictines were also found to be components of the sponge *Oceanapia* [= *Phloeodictyon*] *fistulosa* in New Caledonian shallow waters by Mancini et al. They were clarified as a wide structural variety including the known 18–28 and new analogues 29–45 as corresponding mixtures. The complexity of the mixtures, and the very similar behavior of their components, prevented their isolation in pure form. However, crude mixtures and HPLC-enriched fractions were suitable for bioassays and proved to be active against chloroquine-resistant *Plasmodium falciparum*, with IC$_{50}$ values ranging from 0.6 to 6 µM, while cytotoxicity against the human A-549 cell line was low. These biological data might serve to illustrate preliminary structure–activity relationships: 1. The length of the C-6 chain had a greater influence on the bioactivity level than the nature of its terminal portion; 2. methylation of the guanidine moiety lowered the activity.

2.5. Bromotyrosine Alkaloids

Four bromotyrosine alkaloids 46–49 (Figure 6) were all isolated from an Australian non-verongid sponge *Oceanapia* sp. by Bewley’s group. Among them, 46 contained an unprecedented imidazolyl-quinololine substructure attached to a bromotyrosine-derived spiro-isoxazoline. In the bioassay, compounds 46–49 inhibited mycothiol S-conjugate amidase by 50% at 2, 100, 3 and 37 mM, respectively. These four alkaloids represented the first examples of natural products that inhibited an enzyme central to a mycothiol-dependent detoxification pathway found in mycobacteria [17].

|   |   |   |
|---|---|---|
| 20 | n = 7, R = -CH$_2$CH=CH$_2$ | 18 | n = 9, R = -CH$_2$CH=CH$_2$ |
| 22 | n = 5, R = -CH$_2$CH=CH$_2$ | 21 | n = 7, R = -CH$_2$CH=CH$_2$ |
| 24 | n = 4, R = -CH$_2$CH=CH$_2$ | 23 | n = 5, R = -CH$_2$CH=CH$_2$ |
| 25 | n = 8, R = -CH(CH$_3$)$_2$ | 26 | n = 8, R = -CH(CH$_3$)$_2$ |
| 29 | n = 4, R = -CH(CH$_3$)$_2$ | 38 | n = 5, R = -CH(CH$_3$)$_2$ |
| 30 | n = 5, R = -CH(CH$_3$)$_2$ | 39 | n = 6, R = -CH$_2$CH=CH$_2$ |
| 31 | n = 6, R = -CH(CH$_3$)$_2$ | 40 | n = 6, R = -CH(CH$_3$)$_2$ |
| 32 | n = 7, R = -CH(CH$_3$)$_2$ | 41 | n = 7, R = -CH(CH$_3$)$_2$ |
| 33 | n = 8, R = -CH$_2$CH=CH$_2$ | 42 | n = 8, R = -CH$_2$CH=CH$_2$ |
| 34 | n = 9, R = -CH$_2$CH=CH$_2$ | 43 | n = 10, R = -CH$_2$CH=CH$_2$ |
| 35 | n = 9, R = -CH(CH$_3$)$_2$ | 44 | n = 10, R = -CH(CH$_3$)$_2$ |
| 36 | n = 10, R = -CH$_2$CH=CH$_2$ | 45 | n = 11, R = -CH$_2$CH=CH$_2$ |
| 37 | n = 10, R = -CH(CH$_3$)$_2$ |   |   |

Figure 5. The chemical structures of phloeodictine alkaloids 18–45.

![Figure 5](image-url)
2.6. Indole Alkaloids

6-Bromo-5-hydroxy-3-indolecarboxyaldehyde (50) along with two other brominated indoles 6-bromo-3-indolecarboxyaldehyde (51) and 3-bromoindole (52) (Figure 7) were discovered in the Caribbean sponge Oceanapia bartschi by Fattorusso’s group [18]. Their structurally related non-brominated indole 3-formylindole (53) was disclosed in the Thai sponge O. sagittaria [8]. Crews’ group investigated the Indonesian sponge Oceanapia sp., leading to another two brominated indoles, 6-Br-conicamin (54) and 6-Br-8-keto-conicamin A (55). Meanwhile, they synthesized 55 in this study. In the bioassay, the low micromolar in vitro activity of 55 against the PANC-1 cell line (IC\textsubscript{50} 1.5 mM for the natural product vs. 4.1 mM for the synthetic material) was exciting, which was similar to that of the clinical therapeutics (SFU: IC\textsubscript{50} = 7.0 mM; gemcitabine: IC\textsubscript{50} = 0.02 mM). Furthermore, ten additional analogs were prepared for further study on the structure–activity relationship. The continued study indicated that the quaternary amine functionality and bromination of the indole ring of 55 were critical for activity against PANC-1 [19]. The Indian sponge Oceanapia sp. afforded coixol (56), an active compound in the brine shrimp assay (LC\textsubscript{50} = 52.93 ± 6.48 ppm). This was the first report of coixol from a marine source [20].

Figure 6. The chemical structures of bromotyrosine alkaloids 46–49.

Figure 7. The chemical structures of indole alkaloids 50–56.
2.7. Nucleotide Alkaloids

In the study of an Australian sponge *Oceanapia* sp., uranidine (57) (Figure 8) was discovered as one component of the major alkaloids [17]. Very recently, N⁶-isopentenyladenosine (i⁶A, 58), along with N⁶-isopentenyladenosine 5'-monophosphate (i⁶AP, 59), was isolated from a Japanese sponge *Oceanapia* sp. This was the first report of i⁶A (58) and i⁶AP (59) from a marine sponge. In the cytotoxic biotest, 58 exhibited cytotoxic activity against HeLa cells with an IC₅₀ value of 2.1 µM. On the other hand, 59 was inactive at a concentration of 50 µM. Further observations demonstrated that the cell cycle was arrested at the G1 phase by 58, which indicated targeting of the Akt/NF-κB pathway [21].

![Chemical structures of nucleotide alkaloids](image)

**Figure 8.** The chemical structures of nucleotide alkaloids 57–59.

3. Lipids

Lipids were the second-largest group of the *Oceanapia* secondary metabolites. They could be divided into sphingolipids, ceramides and cerebrosides, dithiocyanates and polyacetylenes, according to their structure features.

3.1. Sphingolipids

An antimicrobial galactopyranosyl pseudodimeric α,ω-bipolar sphingolipid, rhizochalin (60) (Figure 9), was isolated by Makarieva et al. from the sponge *Rhizochalina incrustata* near the north-west shore of Madagascar Island [22]. This was the first report of sphingolipids in the sponge of the genus *Oceanapia*. The effects of 60 on cell membranes were studied in *Ehrlich ascites* cells, spleen lymphocytes and erythrocytes, and phospholipid liposomes, respectively. At 10–100 mg/mL, this compound altered membrane permeability. These effects might be related to the cytostatic activity of 60 [23]. Ten years later, Molinski and his co-workers determined the absolute stereochemistry of (-)-rhizochalin (60) as 2R,3R,26R,27R by application of a general CD method based on the superposition of additive excitation couplings in tetrabenzoyl derivatives of bis-amino alkanols [24]. In Gaydou et al.’s study of a specimen of *Oceanapia ramsayi* collected at Itampolo on the west coast of Madagascar, rhizochalin (60) was found together with its corresponding aglycone rhizochalinin (61), which were both identified by their corresponding peracetates 60a and 61a [25]. A series of cytotoxic bioassays for 60 and 61 against different cell lines including the mechanisms had been carried out. Fedorov et al. reported 60 and 61 were cytotoxic against JB6 P+ CH1, HeLa and THP-1 cell lines with IC₅₀ values ranging from 2.8 to 22.1 µM. A more in-depth study revealed 60 inhibited the EGF-induced transformation of JB6 P+ CH1 cells in a dose-dependent manner [26]. Stonik and Kwak observed 60 and 61 induced apoptosis of HL-60 cells, of which the latter showed a stronger ability. Further detailed study showed the usual mitochondrial membrane permeability changes and the decrease in protein levels of procaspases-8, -9 and -3 correlated with their apoptotic activity [27]. Choi et al. disclosed 61 induced apoptosis via activation of AMP-activated protein kinase in HT-29 colon cancer cells [28].
Figure 9. The chemical structures of sphingolipids 60–72.

Oceanapiside (62), a new bis-α,ω-amino alcohol glycoside from the marine sponge Oceanapia phillipensis collected in southern Australia, was reported by Molinski’s group [29]. Soon after, the absolute stereochemistry of 62 was assigned 2S,3R,26R,27R by analysis of CD spectra of its perbenzoate [30]. Compound 62 exhibited significant antifungal activity against the fluconazole-resistant yeast Candida glabrata with an MIC of 10 µg/mL in broth dilution experiments [29]. In addition, in vitro antifungal activity of a series of α,ω-bifunctionalized amino alcohols derived from 62 against C. glabrata was measured. The dimeric bifunctionalized lipids exhibited activity about 10-fold higher than D-sphingosine, which was a larger factor than expected from the simple additive effects of vicinal amino alcohol groups [31]. It may be worth pointing out that the application of a combined method including micromolar-scale Baeyer–Villiger oxidation and LC–MS interpretation by Makarieva et al. led to a revision of the structure of 62, in which the placement of the keto group should be at C-18 rather than C-11 [32]. Oceanalin A (63), a unique hybrid α,ω-bifunctionalized sphingoid tetrahydroisoquinoline β-glycoside, was discovered in the sponge Oceanapia sp. collected off the northwest coast of Australia. Its absolute structure 2R,3R was elucidated by chemical correlation with the known rhizochalin 60. Compound 63 exhibited in vitro antifungal activity against C. glabrata with an MIC of 30 µg/mL [33].

Rhizochalin A (64), the fourth representative of two-headed glycosphingolipids, was isolated as its peracetate (64a) from the sponge R. incrustata collected in the Seychelles.
was reported for these ceramides, the crude ethanolic extract exhibited antimicrobial activi-
ties against S. aureus, B. subtilis, E. coli and C. albicans as well as cytotoxic properties against
the Erlich murine carcinoma [40]. In another study on the Australian sponge Oceanapia sp.,
two cerebrosides 80 and 81 containing N-acetylglucosamine were obtained [41].
were confirmed by chemical synthesis and comparisons with synthetic model compounds. However, the stereochemical character of C-8 in 82 was reported for these ceramides, the crude ethanolic extract exhibited antimicrobial activities against both Gram positive and negative bacteria [44]. A bioassay-directed fractionation yielded the bioactive principle component thiocyanatin A (82) (LD$_{99}$ = 1.3 µg/mL), together with the inseparable pairs of inactive analogues thiocyanatins B (83) and C (84), β-methyl branched bisthiocyanates thiocyanatins D1 (85) and D2 (86) (LD$_{99}$ = 3.1 µg/mL) and thiocarbamate thiocyanates thiocyanatins E1 (87) and E2 (88) (Figure 11). Their structure assignments were confirmed by chemical synthesis and comparisons with synthetic model compounds. However, the stereochemical character of C-8 in 82 and 85–88 remained unknown. In addition to featuring an unprecedented dithiocyanate functionality, thiocyanatins 82–88 possessed an unusual 1,16-difunctionalized n-hexadecane carbon skeleton and were revealed as a hitherto unknown class of nematocidal agent. Preliminary structure–activity relationship investigations highlighted the importance of both the secondary -OH and -SCN functionalities and the influence of chain length on nematocidal activity [42,43].

![Figure 10. The chemical structures of ceramides and cerebrosides 73–81.](image)

3.3. Dithiocyanates

The aqueous ethanol extract of an Oceanapia sp. collected off the northern Rottnest Shelf, Australia, displayed potent nematocidal activity against the commercial livestock parasite Haemonchus contortus (LD$_{99}$ = 135 µg/mL). Bioassay-directed fractionation yielded the bioactive principle component thiocyanatin A (82) (LD$_{99}$ = 1.3 µg/mL), together with the inseparable pairs of inactive analogues thiocyanatins B (83) and C (84), β-methyl branched bisthiocyanates thiocyanatins D1 (85) and D2 (86) (LD$_{99}$ = 3.1 µg/mL) and thiocarbamate thiocyanates thiocyanatins E1 (87) and E2 (88) (Figure 11). Their structure assignments were confirmed by chemical synthesis and comparisons with synthetic model compounds. However, the stereochemical character of C-8 in 82 and 85–88 remained unknown. In addition to featuring an unprecedented dithiocyanate functionality, thiocyanatins 82–88 possessed an unusual 1,16-difunctionalized n-hexadecane carbon skeleton and were revealed as a hitherto unknown class of nematocidal agent. Preliminary structure–activity relationship investigations highlighted the importance of both the secondary -OH and -SCN functionalities and the influence of chain length on nematocidal activity [42,43].

![Figure 11. The chemical structures of dithiocyanates 82–88.](image)

3.4. Polyacetylenes

The study on the Indonesian sponge Oceanapia sp. led to three bromo-substituted polyunsaturated C$_{16}$ fatty acids (7E,13E,15Z)-14,16-dibromohexadeca-7,13,15-trien-5-ynoic
acid (89), (5Z,7E,9E,13E,15Z)-6,14,16-tribromohexadeca-5,7,9,13,15-pentaenoic acid (90) and (7E,9E,13E,15Z)-14,16-dibromohexadeca-7,9,13,15-tetraen-5-ynoic acid (91) (Figure 12). Their common structural feature was a (13E,15Z)-14,16-dibromo-diene terminus. They differed in their C-5 to C-10 segments in unsaturation and halogenation. The cytotoxicity bioassay was tested on the mixture, since compounds 89–91 were unstable when pure, which showed only weak cytotoxicity (2+ at 10 μg/mL) against KB cells. Compound 91 showed mild antimicrobial activity against Gram-positive bacteria [44]. A C₁₄ acetylenic acid 7E,11E-tetradecadiene-5,9-dynoic acid (92) was isolated as an antimicrobial principle from the sponge of Oceanapia sp. collected in Kamagi Bay on the Sada Peninsula. This compound was the first example of a midchain acetylenic acid without a bromine atom, as well as the first reported member of a marine acetylene containing a CH=CH–C≡C–CH=CH–C≡C unit. In the bioassay, 92 exhibited some selectivity in antimicrobial activity. It was moderately active against four mutants of Saccharomyces cerevisiae and C. albicans but was inactive against Penicillium chrysogenum and Mortierella ramanniana. It also exhibited inhibitory effects against both Gram-positive and Gram-negative bacteria [45].

Figure 12. The chemical structures of polycetylenes 89–92.

4. Sterols

The sterol profile of a north-western Australian marine sponge Oceanapia sp. was reported for the first time by Stonik et al. It contained stanols (93–102) and Δ₅-sterols (103–105) with 24R-24,25-methylene-5α-cholestan-3β-ol (99) (Figure 13) as the main constituent [46]. Notably, the structure of the major cyclopane-containing stanol 99 was firstly obtained from Rhizochalina (= Oceanapia) incrustata off the coast of the Seychelles Islands [47]. In the investigation on the marine sponge O. sagittaria from the Gulf of Thailand, 24α-methylcholestanol (106) was isolated [8].

Figure 13. The chemical structures of sterols 93–106.
5. Other Miscellaneous

The organic extract from the Caribbean *O. bartschi* was shown to contain the antibiotic diterpene ambiol A (107) (Figure 14) [18]. Three aromatic compounds, *p*-hydroxybenzaldehyde (108), *p*-hydroxybenzoic acid (109) and phenylacetic acid (110), were found in the sponge *O. sagittaria* collected from the Gulf of Thailand [8].

![Figure 14](image-url). The chemical structures of miscellaneous 107–110.

6. Chemical Synthesis of Four Secondary Metabolites

6.1. Synthesis of (±)-Phloeodictine A1 ((±)-21)

The (±)-phloeodictine A1 ((±)-21) was synthesized by a convergent route by Snider et al. as shown in Scheme 1 [15]. Furan-maleic anhydride Diels–Alder adduct 111 was used as the starting material for the 6-hydroxy-1,2,3,4-tetrahydro-1H-pyrimidinium skeleton. Imide 112 was obtained from 111 via a reaction with 3-aminopropanol, which was quantitatively converted to mesylate 113. The reaction of 113 with NaN₃ provided azide 114. The Eguchi aza-Wittig reaction of 114 afforded 114b, which was followed by a thermal retro Diels–Alder reaction to liberate 115. The addition of Grignard reagents to 115 produced 116a. Washing a CH₂Cl₂ solution of 116a with 1 M NaOH solution afforded 116b. In addition, Snider et al. selected a convergent route for iodide 20 containing a protected guanidine on the other end of the chain. The approach was that the reaction of 117 with the appropriate ω-amino-1-alkanol in THF gave 118, then mesylation and successive displacement with iodide afforded 120. Finally, alkylation of 116b with 120 afforded 121, and subsequent deprotection of 121 completed the synthesis of 21.

![Scheme 1](image-url). Synthetic route of phloeodictine A1 (21). Reagents: (a) 3-aminopropanol, MeOH, 56 °C, 3 d; (b) Et₃N, MsCl, CH₂Cl₂, 0 °C; (c) NaN₃, DMF, 25 °C, 14 h; (d) Ph₃P, toluene, reflux, 4 h; (e) 11-dodecenyl magnesium bromide, CeCl₃, THF, 0 °C; (f) 1M NaOH; (g) ω-amino-1-pentanol, THF, 50 °C, 2 h; (h) MsCl, Et₃N, CH₂Cl₂, 0 °C (i) NaI, NaHCO₃, acetone, reflux, 4 h; (j) DMSO-d₆, 25 °C, 24 h; (k) TFA/CH₂Cl₂ (1:1), 2 h.
6.2. Synthesis of 6-Br-8-keto-conicamin A (55)

In Crews et al.’s work, indole-3-carboxaldehyde 122 was used as the starting material as outlined in Scheme 2 [19]. First, 122 was esterified to yield its cyanohydrin silyl ether 123, then the oxidation of 123 via DDQ followed by hydrogenation led to keto-tryptamine synthon 125. Bromination of 125 proceeded in a straightforward fashion, producing the bromo-keto-tryptamine 126. The final step involved the methylation of 126 to afford 6-Br-8-keto-conicamin A (55).

![Scheme 2](image)

Scheme 2. Synthetic route of 6-Br-8-keto-conicamin A (55). Reagents: (a) TMSCN, DME, reflux 1.5 h, cool; (b) DDQ (dropwise), Dioxane, rt; (c) H2, Pd/C, AcOH; (d) Br2, rt 24 h, HCOOH:CH3COOH (1:1); (e) Mel, rt 16 h, MeOH, KHCO3.

6.3. Synthesis of Rhizochalinin C (70)

Molinski et al. disclosed an optimized procedure for rapid diastereoselective access to L-threo-sphinogoid base synthons, using a remarkable one-pot conversion of unprotected D-glucosamine into useful D-serine synthons based on In^3+ mediated allylation. This method was successfully applied to rhizochalinin C (70), which was elaborated as shown in Scheme 3 [37].

![Scheme 3](image)

Scheme 3. Synthetic route of rhizochalinin C (70). Reagents: (a) In^3+, allyl bromide, 1,4-dioxane:H2O (3:1), 100 °C; (b) CBz-Cl, NaHCO3 (aq); (c) In^3+, allyl bromide, 1,4-dioxane:H2O (3:1), 100 °C; (d) (Boc)2O, NaHCO3 (aq); (e) NaIO4, H2O2; (f) NaBH4, MeOH; (g) CSA, (MeO)2C(CH3)2; (h) NaIO4, H2O; (i) NaBH4, MeOH; (j) CSA, (MeO)2C(CH3)2; (k) tetradec-13-enyl acetate, Grubbs II catalyst, CH2Cl2, reflux; (l) NaOMe, MeOH; (m) DMP, CH2Cl2; (n) (EtO)2P(O)CH3, n-BuLi, THF, -78 °C; (o) DMP, CH2Cl2; (p) AlH3, Et2O, 0 °C; (q) PhSSPh, n-Bu3P, THF; (r) 4-penten-1-yllactate, Grubbs II cat., CH2Cl2, reflux; (s) NaOMe, MeOH; (t) Ra-Ni; (u) DMP, CH2Cl2; (v) Ba(OH)2, wet THF; (w) 10 M HCl, MeOH, H2, 2 atm, Pd — C.
The allyl-substituted compounds 127a and 128a that were procured from the Barbier allylation of D-glucosamine were followed by differential protections of NH2 and OH groups. 127a was subjected to olefin cross-metathesis with tetradec-13-ynyl acetate, after methanolation, to provide the primary alcohol 129. Then, Dess–Martin oxidation of 129 led to the corresponding aldehyde 130, which was followed by the addition of the anion derived from diethyl methylphosphonate, and oxidation delivered the β-ketophosphonate 131. The alcohol 132, the reduction product of 128a, was transformed into the phenyllithio ether to give 133. Olefin cross-metathesis of 133 with 4-penten-1-yl acetate followed by methanolation yielded the primary alcohol 134. Reduction of 134 delivered protected threo-2-amino-3-alkanol 135, and the subsequent oxidation of 135 led to the aldehyde 136. The Horner–Emmons–Wadsworth reaction of aldehyde 131 and 136 under Paterson conditions gave the α,β-unsaturated ketone 137, which was deprotected to yield 70.

6.4. Synthesis of Thiocyanatin A (82)

Capon et al. reported the seven-step total synthesis of thiocyanatin A (82) starting from 8-bromoocctanoic acid (138) [43]. The esterification of 8-bromoocctanoic acid (138) yielded its methyl ester 139, which was converted to the Wittig salt 140. The following one-pot oxidation–Wittig coupling afforded the olefin-diester 141. The triol 142 was obtained by the epoxidation of 141 with m-CPBA and the successive reduction of the corresponding epoxide with LiAlH4. Treatment of 142 with TsCl gave the ditosylate 143. Finally, the displacement of the tosylate groups by thiocyanate afforded racemic thiocyanatin A (82) as outlined in Scheme 4.

![Scheme 4](https://example.com/scheme4.png)

Scheme 4. Synthetic route of thiocyanatin A (82). Reagents: (a) H2SO4, MeOH, reflux 16 h; (b) PPh3, MeCN, reflux 16 h; (c) NaHMDS, THF/DMPU, O2, 60 °C, 16 h; (d) m-CPBA, CH2Cl2, rt, 16 h; (e) LiAlH4, reflux 20 h; (f) p-TsCl, CH2Cl2, DMAP/NEt3, rt, 32 h; (g) KSCN, THF, reflux 16 h.

7. Conclusions and Perspectives

A huge library of secondary metabolites was reported from the sponges of the genus Oceanapia, with up to 110 compounds with unique structures, from 1989 to July 2019. More than eight species of Oceanapia sponges have been chemically investigated, including Oceanapia sagittaria, Oceanapia fistulosa, Oceanapia bartschi, Phloeopecten sp., Rhizochalina incrustata, Oceanapia ramsayi, Oceanapia phillipensis, Oceanapia cf. tenvis and Oceanapia sp. The chemical structures were classified as alkaloids, lipids, sterols and other miscellaneous. Among them, alkaloids were encountered most frequently. These compounds exhibited diverse biological properties ranging from insecticidal, cytotoxic and antifeedant to antibacterial. Their unique structures and promising bioactivities have attracted a great deal of attention from synthetic chemists for their total synthesis.

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