

Half a Century of Hawaiian Marine Natural Products*

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Key words

- Hawaii
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Abstract

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The following review covers the primary literature concerning marine natural products isolated for the first time from organisms collected around the islands of Hawaii published in the 51-year period 1964 to July 2015. The review is divided into seven main sections based on major taxonomic groupings; algae, sponges, mollusks, miscellaneous invertebrates, cyanobacteria, bacteria, and fungi. The aim of the review is to discuss the compounds and information concerning their original biological activity and other potentially interesting properties. The majority of the 320 structures of isolated compounds are not shown directly in

the review but are contained in the Supporting Information section in 22 figures, **Figs. 1 S–22 S**. The Supporting Information section also contains **Table 1 S** that has information relating to the taxonomic identification of the source organism of each compound, collection location of the source organism, a trivial or semi-systematic name for each compound, as well as its general structural class. The authors hope that this review will be the spawning ground for other reviews and the basis for a great deal more research into the marine life found in Hawaiian waters.

Supporting information available online at <http://www.thieme-connect.de/products>

Introduction

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The Pacific islands, commonly referred to as the State of Hawaii, are regarded as the most geologically isolated pieces of land on our planet. The State is composed of eight main islands that cover 6423.4 miles² (16636.5 km²): Niihau, Kauai, Oahu, Molokai, Lanai, Maui, Kahoolawe, and Hawaii, often referred to as the “Big Island”, and an upcoming island, the seamount named Loihi. All of the islands are volcanic in origin with the Big Island and Loihi still growing in area as a result of them being volcanically active. Due to their remote location and geological youth, their ocean-based biodiversity must be considered as depauperate, which is untypical of a tropical region. In general, moving down the island chain from Niihau to the Big Island reveals a marked decrease in ocean-based biodiversity especially for slow-moving and sessile life forms like nudibranchs,

sea hares, algae, corals, sponges, tunicates and the like, and to some extent this is reflected in this review. The review itself covers the primary literature concerning marine natural products isolated from organisms collected around the islands of Hawaii published between 1964 and July 2015. In order to portray the chemical diversity of Hawaiian natural products, the structures shown are mainly for compounds first described from Hawaiian waters, and not of those previously reported from other locations. The bulk of the natural products discovered from the State of Hawaii were isolated from organisms collected from the waters around Oahu (○ **Fig. 1**).

Where applicable, the review also describes the isolated compounds in terms of their structures and activities as well as other relevant facts the reader may find useful. The review is organized into seven sections. The first four sections cover marine macro-organisms (algae, sponges, mollusks, and miscellaneous invertebrates), while the latter sections cover marine microbes (cyanobacteria, bacteria, and fungi). ○ **Fig. 2** shows the number of compounds originally isolated from a Hawaiian source organism according to five-year

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periods after 1970 and the main taxonomic groupings (in the seven sections mentioned above) used in the review. At the end of the review, there is a Concluding Comments section that summarizes the highlights of the marine natural products research undertaken in the 51-year time period covered by the review as well as providing some suggestions and insights into the area in general.

Algae

Brown algae

One of the earliest reported studies into marine natural products elaborated by Hawaiian organisms concerned algae and was conducted by the Moore group in 1968 [1]. In this paper, the authors reported the structure of an unstable dialkenylcyclopropane C_{11} hydrocarbon, dictyopterene A (**1** [Fig. 3]), isolated from the brown algae *Dictyopteris plagiogramma* and *Dictyopteris australis* [1] from Waikiki, Oahu.

In 1970, a trialkenylcyclopropane named dictyopterene B (**2**) was isolated together with *trans,cis,cis*-1,3,5,8-undecatetraene (**3**) from the same algae by Pettus and Moore [2]. Further research into samples of these two algal species, *D. plagiogramma* and *D. australis*, by Pettus and Moore [3] yielded dictyopterenes C' and D' (**4**, **5**), the latter compound was shown to be identical with ectocarpene [4], *trans,trans,cis*-1,3,5,8-undecatetraene (**6**), *trans,cis*-undeca-1,3,5-triene (**7**), and *trans,trans*-undeca-1,3,5-triene (**8**). In 1971, Roller et al. worked with a sample of *D. plagiogramma*, presumably also from Waikiki, Oahu, and found it to contain four new sulphur-containing lipids; *S*-(3-oxoundecyl) thioacetate (**9**), *bis*-(3-oxoundecyl) disulphide (**10**), 3-hexyl-4,5-dithiacycloheptanone (**11**), and *S*-(*trans*-3-oxoundec-4-enyl) thioacetate (**12**) [5]. In 1971, Moore investigated two further samples of *D. plagiogramma* and *D. australis*, from unspecified locations, but presumably somewhere on Oahu, and isolated two *bis*-(3-oxoundecyl) polysulphides, *bis*-(3-oxoundecyl)trisulphide (**13**) and *bis*-(3-oxoundecyl)tetrasulphide (**14**), as low melting point crystalline solids [6]. When left to stand in methanol (CH_3OH) for a prolonged period, the tetrasulphide (**14**) decomposed to yield the trisulphide (**13**) and elemental sulphur. From another investigation of *D. plagiogramma* and *D. australis* samples, again from an unspecified location in Hawaii, Moore and his colleagues identified a number of hydrocarbons and sulphur-containing compounds, two of which were new natural products (**15**, **16**) [7]. In this report, it is suggested that both (-)-*bis*-(3-acetoxyundec-5-enyl) disulphide (**15**) and (-)-*bis*-(3-acetoxyundec-5-enyl)thioacetate (**16**) are possible precursors of the aforementioned undeca-1,3,5-trienes [3]. Other new natural products reported from algae belonging to the genus *Dictyopteris* were the two cyclic ketones (+)-(*R*)-4-butylcyclohepta-2,6-dienone (**17** [Fig. 3]) and (+)-(*R*)-6-butylcyclohepta-2,4-dienone (**18** [Fig. 3]) [8], both of which were noted for their strong odors. The absolute configurations of both molecules were determined by synthesis and CD spectral comparisons. Surprisingly, the optical rotation of **18** was reported as +1120, while that for **17** was given as +96. It seems likely that there might be a factor of 10 error in the value reported for **18**, with +112 being a more realistic value based on what is known about the molecular weights and absolute configurations of the two molecules. The final report concerning the natural products yielded by algae from the genus *Dictyopteris* found in Hawaii was published in 1974 and was a review summarizing the current knowledge about the

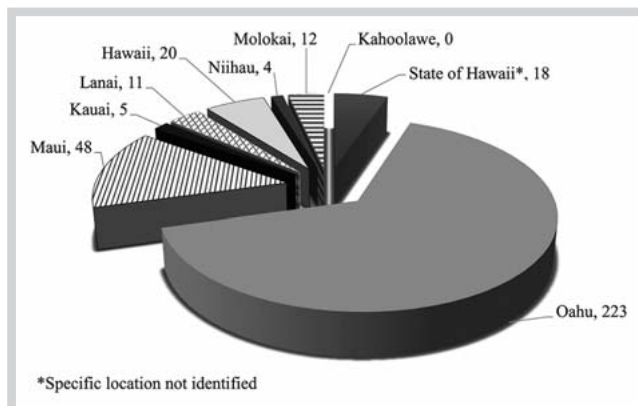


Fig. 1 Number of compounds discovered from each of the Hawaiian Islands.

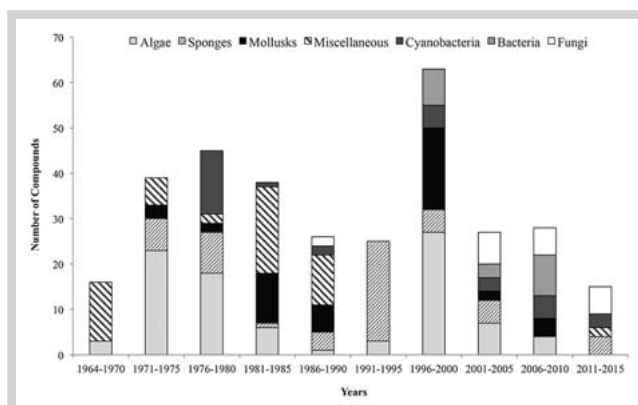


Fig. 2 Number of compounds originally isolated from the Hawaiian Islands according to five-year periods after 1970 and the main taxonomic groupings used throughout this review.

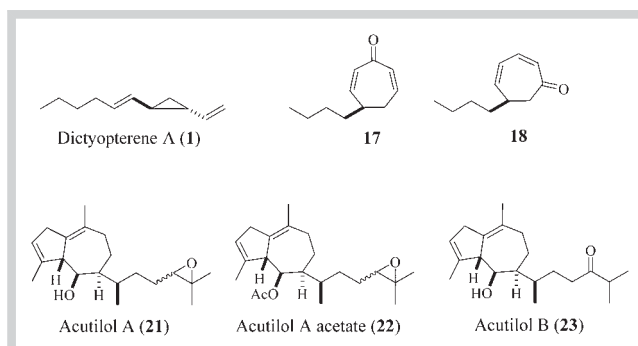


Fig. 3 Selected isolates from brown algae.

odoriferous C_{11} hydrocarbon research undertaken by the Moore group since 1968 [9]. In terms of bio- and ecological activity, only the previously reported compound, ectocarpene (dictyopterene D', **5**), is implicated by being the Cope rearrangement product of the sperm-attracting substance 1-((1*E*,3*Z*)-hexa-1,3-dien-1-yl)-2-vinylcyclopropane.

Species from the cosmopolitan algal genus *Dictyota* are relatively common to parts of Hawaii and have been the subject of several investigations. The first of these examined a sample of *Dictyota acutiloba* collected off Kahala and Ala Moana Reefs, Oahu [10]. Two diterpenes, new and unusual for their time, were isolated and characterized as dictyoxepin (**19**) and dictyolene (**20**). The absolute configuration of dictyoxepin was determined by single-crystal X-ray crystallographic analysis of its *p*-bromophenylurethane derivative. Nineteen years later, the second investigation of this species employed a sample collected from Tun-nels Beach, Kauai [11]. This study resulted in the isolation of three bicyclic diterpene metabolites, acutilol A (**21** [● Fig. 3]), acutilol A acetate (**22** [● Fig. 3]), and acutilol B (**23** [● Fig. 3]). All three compounds were shown to be potent herbivore deterrents against both temperate and tropical fishes and sea urchins.

From a sample of *Dictyota crenulata* collected near Hauula Beach, Oahu, Finer et al. isolated and characterized dictyodial (**24**), employing both standard spectroscopic methods (NMR, IR, UV, MS), and by X-ray crystallographic analysis of the reduced form of this compound [12]. Dictyodial was found to have good antimicrobial properties but was not responsible for the observed antitumoral activity noted for the original algal extract. A winter collection of *D. crenulata* yielded β -crenulatol (**25**) [13], which was shown to be identical to sanadaol isolated from a Japanese sample of the brown alga *Pachydictyon coriaceum* [14]. Two further diterpenes, 4 β -hydroxydictyodial A and 18,0-dihydro-4 β -hydroxydictyodial A (**26**, **27**), were isolated and characterized from *D. crenulata* collected near Kualoa Beach Park, Oahu, reported by Kirkup and Moore in 1983, and brings to an end the direct investigations of *Dictyota* species in Hawaii [15].

Red algae

As would be expected, specimens belonging to the red algal genus *Laurencia*, due to the prevalence of this algal genus worldwide, are the most studied of any Hawaiian algal genus. The CH₃OH extract of *Laurencia nidifica* ("non-clumpy" variety) collected from Kahala Reef, Oahu, was found to have antimicrobial properties [16]. Fractionation of this material led to the isolation of a number of known metabolites and two new halogenated chamigrane derivatives, nidificene (**28** [● Fig. 4]) and nidifidiene (**29**) [16]. The observed antimicrobial activity of the extract was attributed to the presence of the known compound laurinterol (**30**).

A third new chamigrane derivative was isolated from a "clumpy" variety of *L. nidifica*, also from Kahala Reef, Oahu, nidifidiol (**31**) [17]. The third investigation of *L. nidifica*, this time from Black Point Reef, Oahu, led to the isolation and characterization of two sesquiterpene alcohols, 3-methyl-5-(2,3,6-trimethylcyclohexa-2,5-dien-1-yl)pent-1-en-3-ol (**32**) and 3-methyl-5-(2,3,6-trimethylphenyl)pent-1-en-3-ol (**33**) [18]. When allowed to stand for several days at 25 °C, **32** converts to the more stable **33**. From the "non-clumpy" variety of *L. nidifica*, another chamigrane derivative was isolated, this time one that contained a third ring in the form of an ether (nidifocene, **34**) [19]. Treatment of **34** with chromous sulphate cleanly removed the halogens to yield **35**. From a green variety of *L. nidifica*, collected from the southern shores of Oahu, three new C₁₅-halogenated non-terpenoid tricyclic ethers possessing a terminal ene-yne functionality, known as *cis*-maneonenes A and B (**36**, **37**) and *trans*-maneonene B (**38**), were isolated [20]. Continued investigation of the extract yielded a further three new metabolites, *iso*-maneonenes A and B (**39**, **40**), and *cis*-maneonene C (**41**) [21]. In this paper, the authors

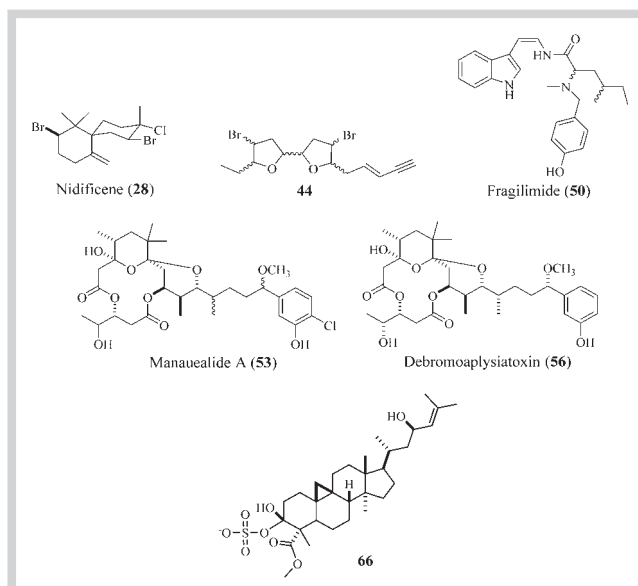


Fig. 4 Selected isolates from red algae.

note that the green variety of *L. nidifica* from which the latter compounds came, **39–41**, may itself consist of several different varieties – chemotypes. Also from the green variety of *L. nidifica*, from an undefined collection site on Oahu, the unstable selinane derivative (+)-selin-4,7(11)-diene (**42**) was isolated and characterized [22]. The most recent report on *L. nidifica* (green variety) from Oahu summarized all of the authors' own work concerning the C₁₅ non-terpenoid halogenated compounds discussed above [23], with the only new experimental data being the addition of X-ray data for *iso*-maneonene B (**40**). Only one sample of *L. nidifica* from another Hawaiian island has been investigated. This sample came from near Port Allen, Kauai, and on workup yielded (+)-2(*S*)-*N*-acetamido-3(*R*)-acetoxyoctadecan-1-ol (**43**), a diacetate of dihydrosphingosine [24].

The lauroxane (**44** [● Fig. 4]), at the time of its discovery from *Laurencia majuscula*, sampled from the north shore of Oahu, was the first example of a C₁₅ compound containing a 2,2'-bis-tetrahydrofuran moiety [25]. Another sample of *L. majuscula* was collected on the north shore of Oahu near Kahuku, and found to contain kahukuenes A and B (**45**, **46**), unprecedented diterpenes having a prenylated chamigrane structure as part of a decalin ring [26]. Clearly, these compounds are quite stable, as it seems the extract was not processed until many years after the alga was collected. The most recent report on algae from this genus comes from *Laurencia cartilaginea*, collected from Wai'anae, Oahu [27]. In this report, Juagdan and his colleagues describe the isolation and structure elucidation of two new halogenated sesquiterpenes, 8-bromo-9-hydroxychamigra-2(3),11(12)-dien-1-one (ma'ilione) (**47**) and 2-chloro-1,8-dibromo-11(12)-en-9-ol (*allo*-*iso*obtusol) (**48**), together with four known halogenated sesquiterpenes, elatol, [1(15)Z,2Z,4R,8S,9R]-8,15-dibromo-11(12)-en-9-ol, [1(15)E,2Z,4R,8S,9R]-8,15-dibromo-11(12)-en-9-ol, and *iso*-obtusadiene.

Asparagopsis taxiformis is an algal species traditionally consumed by Hawaiians known to contain a wealth of halogenated hydrocarbon-based metabolites [28–32]. The essential oil recovered from samples of *A. taxiformis* collected in Waikiki, Oahu, was ob-

served to have bromoform as a major component, along with 17 other compounds including haloforms, carbon tetrabromide, tetrahalopropenes, polyhalo-but-4-en-2-ones, monohaloacetones, and 3,3-dihaloacroleins [28]. A second investigation of this alga focused on the volatile halogenated compounds found in its essential oil, collected from Waikiki, Oahu, between 1974 and 1975 [29]. This study resulted in the identification of 24 additional halogenated methanes, ethanes, ethanols, formaldehydes, acetaldehydes, acetones, 2-propanols, 2-acetoxypropanes, propenes, epoxypropanes, acroleins, and butenones. A sample collected from an unknown location in Hawaii, presumably somewhere on Oahu, was shown to contain five halogenated acetamides, seven halogenated but-3-en-2-ols, and 20 halogenated isopropanols [30]. In the report, there is no clear distinction between the new and known compounds. The last report by the same authors on the same algal species also provides no information on the site of collection, but again we assume it was somewhere on Oahu [31]. In this report, the authors investigated the aqueous extract of the alga and identified nine halogenated acetic acids, like ClCH_2COOH and BrCH_2COOH , and nine halogenated acrylic acids, like $\text{ClCH}=\text{CHCOOH}$ and $\text{BrCH}=\text{CHCOOH}$. Unfortunately, the authors do not indicate which of their isolates are new and which are known.

Chemical investigation of *Amansia glomerata* from Black Point, Oahu, resulted in the isolation of a mixture of *N*-acylsphingosines (**49**) that were identified via a series of chemical transformations and separations [24]. These compounds had not previously been found in algae.

The first basic indole alkaloids, fragilamide (**50** [● Fig. 4]), and martensines A and B (**51**, **52**) to be isolated from a marine eukaryotic plant came from *Martensia fragilis* samples collected at both Black Point and Mokeleia, Oahu [33].

The known toxic alga, *Gracilaria coronopifolia* [34], collected from Waiehu, Maui, yielded the toxic compounds manaeualides A–C (**53–55** [● Fig. 4]) [35]. Manaeualides A and C (**53**, **55**) are new macrolides, whereas while manaeualide B (**54**) was previously known as a semisynthetic derivative of debromoaplysiatoxin (**56** [● Fig. 4]) [36]. A further investigation of another sample of *G. coronopifolia* from Maui enabled the absolute configuration of manaeualide C (**55**) to be determined and also led to the isolation of anhydrodebromoaplysiatoxin (**57**) [37]. In several bioassays, **57** was shown to be inactive, however, low-dose injections into mice caused them to have diarrhea, thus revealing the potentially toxic nature of this and other related compounds. The most recent report on *G. coronopifolia* described the isolation and characterization of malngamides M and N (**58**, **59**) and malngamide I acetate (**60**) from a sample also collected from Waiehu, Maui, one week after a food poisoning event [38]. The absolute configuration of **60** was deduced employing the reverse octant rule. As the type of compounds **58–60** represent are found almost exclusively from cyanobacteria, the authors' suggest that their collection may well have contained significant quantities of such a contaminant.

More recently, in 2013, molecular techniques were applied to the analysis of microbes associated with native and invasive Hawaiian macro-algae, including samples of *G. coronopifolia* (native), *Gracilaria salicornia* (invasive), and *L. nidifica* (native). The authors found the clone library derived from *G. coronopifolia* contained 28% cyanobacterial sequences, and *G. salicornia* and *L. nidifica* had cyanobacterial sequence frequencies of 71% and 8%, respectively [39]. These findings may provide the basis for

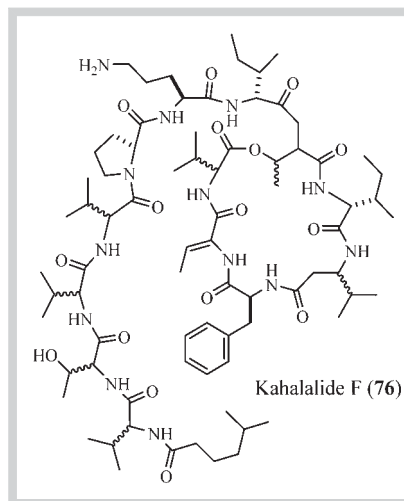


Fig. 5 Selected isolate from green algae.

the identification of the proposed cyanobacterial origins of *G. coronopifolia* toxins [34, 35, 37, 38].

Investigations of *Chondrococcus hornemanni*, now known as *Porteria hornemanni*, from Hawaii started in the mid-seventies [40, 41]. The first of these describes the isolation, from two different samples, of (3*S*)-*cis*-octa-1,5-dien-3-ol (**61**), which is proposed to be a possible precursor of the sperm-attracting compound fucoserratene, known from the brown alga *Fucus serratus* [40]. The samples came from Black Point and Halona Blowhole, both on Oahu. The second report describes a number of linear and bicyclic halogenated monoterpenes, including chondrocoles A and B (**62**, **63**) [41]. These compounds also came from samples collected from Black Point and Halona Blowhole, which demonstrate through their chemical variation that they might belong to different chemotypes. In the third paper related to plants of the genus *Porteria* (= *Chondrococcus*), the authors corrected the structure of **62** to **64** based on an X-ray study of a related compound, chondrocolactone (**65**) [42], isolated from a sample from Halona Blowhole, Oahu.

The final red alga to be discussed here, *Tricleocarpa fragilis*, was collected off of Nanakuli Beach Park, Oahu [43]. After workup, the extract was fractionated to yield 10 new sulphated terpenoids, including six cycloartenol sulphates (**66**, **67–71** [● Fig. 4]), two 29-*nor*-cycloartenol sulphates (**72**, **73**), and two 29-*nor*-lanosterol sulphates (**74**, **75**).

In the brine shrimp bioassay [43] some of the compounds demonstrated moderate to low activity (**66**, **68**). In cell-based cytotoxicity assays, compounds **72–75** demonstrated moderate to low activity, but nothing at a level that would have led to their being further developed.

Green algae

There are only six reports of research being undertaken on green algae from Hawaii, all concerning *Bryopsis* spp., collected around Oahu. The first of these appeared in 1993 and described the depsipeptide kahalalide F (**76**) isolated from both the sacoglossan mollusk *Elysia rufescens* and one of its dietary components, *Bryopsis* sp. [44]. Kahalalide F (**76** [● Fig. 5]), a depsipeptide, was shown to have a variety of biological activities, including selective antitumoral, antiviral, and antimicrobial, as well as being somewhat immunosuppressive, and was the only kahalalide to progress to any clinical trials, indeed the only one to have any significant activity in applied assays (see Concluding Comments).

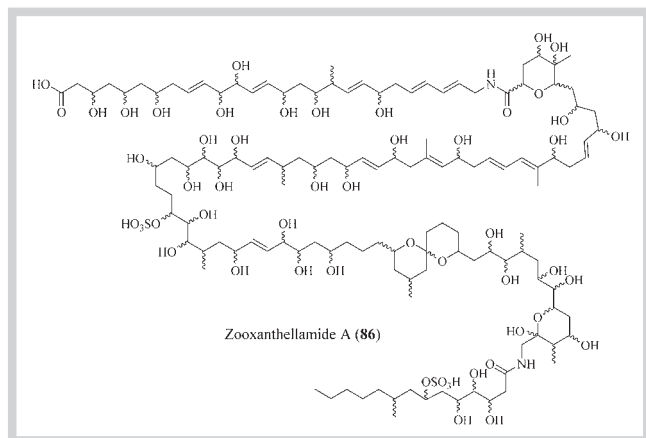


Fig. 6 Selected isolates from microalgae (protists).

The next report in 1996 also concerned *E. rufescens* and *Bryopsis* sp. samples [45]. This time a further six new depsipeptides were described of which three kahalalides, A, B, and G (**77–79**), were found to be in the alga. Of these, none were shown to have any biological activity. In 1999, a Japanese group reported the isolation of kahalalide K (**80**), a cyclic depsipeptide with a new array of three L- and three D-amino acids. This compound was devoid of bioactivity in the applied assays [46]. Towards the end of the discussion in this paper the authors suggest the origin of the kahalalides is still unclear as their algal samples clearly contained cyanobacterial epiphytes that could be the source of such molecules. Horgen and colleagues described kahalalide O (**81**) initially from samples of *Elysia ornata* (Mollusk) from Point Black, Oahu, and later from *Bryopsis* sp., collected from the west coast of Oahu [47]. This cyclic depsipeptide was also found to be devoid of activity in the applied cytotoxicity studies. Kahalalides P and Q (**82, 83**), both cyclic depsipeptides containing a 3-hydroxy-9-methyldecanoic acid residue, were isolated from a sample of *Bryopsis* sp., collected from Kewalo Basin, Oahu [48]. Like most of the other kahalalides discussed here, kahalalides P and Q (**82, 83**) were found to be inactive in the applied bioassays, including those related to cytotoxicity. The most recent report on *Bryopsis* spp. concerns samples of *Bryopsis pennata* collected from Kahala Bay, Oahu [49]. From 20 kg of material, the authors isolated two new cyclic-depsipeptides, 5-hydroxykahalalide F (**84**) and nor-kahalalide A (**85**). In terms of biological activity, the authors suggest their research results and insights gained from testing their molecules might lead to new research with natural products aimed at the search for ligands selective for the Y₁ receptor, a receptor implicated in a variety of psychiatric disorders.

Microalgae (protista)

Studies involving microalgae (protists) isolated from the ocean surrounding Hawaii focused on a culture of a free-swimming dinoflagellate, *Symbiodinium* sp. The source of the isolate was initially documented as sand collected from the beach of Coconut Island, Hawaii, in 1996 [50]. In two later reports by Onodera et al. the source was said to be a Hawaiian tide pool [51,52], and in a further report, from a Hawaiian sand beach [53]. From reading these papers it seems evident that Onodera and collaborators actually worked with a single strain of *Symbiodinium* sp., designated HA3–5, from which they isolated a series of polyhydroxylated diamides named zooxanthellamides A (**86**

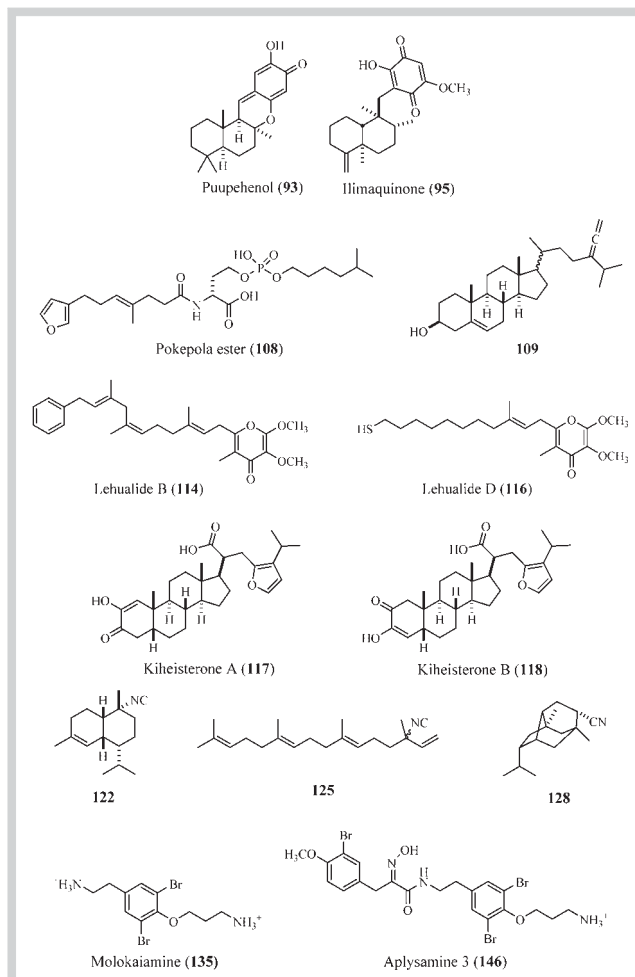


Fig. 7 Selected isolates from sponges.

[**Fig. 6**], B (**87**), C-1 (**88**), C-2 (**89**), C-3 (**90**), C-4 (**91**), and C-5 (**92**) [51–53]. The C-1 to C-5 (**88–92**) compounds are macrocyclic lactones. Testing of **88–92** determined they had vasoconstrictive activity, with the lactones being significantly more active than their non-lactonized counterparts [53]. In more recent times, 2010, 2012 and 2014, extracts obtained from Hawaiian algae have been screened for their antioxidant activity and fucoxanthin and polyphenolics have been suggested as likely major contributing constituents responsible for the observed activity in some of the algae [54–56].

Sponges

Order Chondrosiida

In 1979, sponge samples tentatively identified as *Chondrosia chucalla*, collected from Lanai, and the Blowhole, Oahu, were shown to contain puupehenone (**93** [**Fig. 7**]) [57]. The final structure of this compound was deduced by X-ray analysis of its ozonolysis product (**94**).

Order Dictyoceratida

Ilimaquinone (**95**) was first isolated from *Hippiospongia metachromia* (now *Dactylospongia metachromia*), a bristly yellow orange or brown sponge found in the waters around Lanai, and near

the Blowhole on the southeast coast and Shark's Cove on the north shore of Oahu [58]. The structure of **95** (Fig. 7), finally resolved by X-ray analysis, is quite an unusual one being composed of a rearranged drimane sesquiterpene part linked to a penta-substituted benzoquinone. Even though the original organic extract of this sample was shown to have antimicrobial activity, there appears to have been no further investigation of ilimaquinone's (**95**) potential as an antibiotic.

Puupehenol (**96**), a potent antioxidant antimicrobial meroterpenoid, was isolated from a *Dactylospongia* sp., collected from a depth of 130 m by a remotely operated vehicle (ROV) working in the Au'au channel between Maui and Hawaii [59]. From this same CH₃OH extract, a methoxypuupehenol dimer was also isolated and characterized (**97**). In this paper, the authors also report finding puupehenone (**93**) and propose it as an artifact of isolation.

A *Dysidea fragilis* sponge, collected from Kaneohe Bay, Oahu, yielded upial (**98**), an unusual tricyclic non-isoprenoid sesquiterpene aldehyde [60]. The structure of upial was confirmed from the results of a lanthanide shift reagent study performed with upiol (**99**), the reduced form of **98**. A second investigation of *D. fragilis* from Kaneohe Bay, Oahu, as well as of two of its known predators, the nudibranchs *Hypselodoris godeffroyana* and *Chromodoris maridadilus*, yielded two tricyclic furanosesquiterpenes, nakafuran-8 (**100**) and nakafuran-9 (**101**), with fish antifeedant properties [61].

Two sponge samples, *Hyrtios* spp., [62] one collected from the sandy bottom between Maui and Molokini carter (~30 m) and the other from submerged lava tubes on the north and west shores of Oahu (~10 m), were found to contain three new meroterpenoids (**102–104**) related to puupehenone (**93**). Compounds **102** (21-chloropuupehenol) and **103** (15-oxopuupehenol) were in both sponge samples while **104** (molokinenone – also chlorinated) was only noted in the sample from Maui. In bioassays, **102** was shown to have significant and selective antitumor and antimalarial activities. Poipuol (**105**), isolated from a *Hyrtios* sp., collected near Brenneke's Ledge, Kauai, in 2003, is an unusual small polyketide unique to the genus [63]. The structure of **105** suggests that it is more likely of microbial or cyanobacterial origin than being produced by the sponge itself. Cytotoxicity testing of **105** towards several cancer cell lines showed it to be inactive. The most recent investigation of a *Hyrtios* sp., collected in 2011 from a depth of 85 m in the Au'au channel between Maui and Lanai, led to the isolation of au'auamine (**106**) plus a peroxy dimer (**107**) [64], probably derived from **93**. The sponge was selected for investigation based on its CH₃OH extract having antioxidant and antimicrobial properties. Bioassays performed with **106** showed it to have significant antioxidant activity and to be antibacterial. From the south shore of Maui at a depth of about 13 m, a sample of *Spongia oceania* was collected. The ethanol (EtOH) extract of the dry sample yielded pokepola ester (**108** [Fig. 7]), a diester of phosphoric acid of mixed biosynthetic origin, after repeated solvent partitioning, countercurrent chromatography, gel permeation chromatography (LH-20), and finally reversed-phase HPLC (RP-HPLC) [65]. The molecule, like many others from sponges, may be of microbial origin. In bioassays, **108** was shown to have mild HIV inhibitory activity.

Order Haplosclerida

Callyspongia diffusa, collected from Kaneohe Bay, Oahu [66], yielded 24-ethyl- $\Delta^{5,24(28),28}$ -cholestatrien-3 β -ol (**109** [Fig. 7]) [67]. This was the first report of a naturally occurring steroidal alkalene.

Three new pregnanes (**110–112**) were isolated from a *Petrosia* sp., formerly *Strongylophora* sp., collected at Puako, west Hawaii [68]; all structural deductions were confirmed by X-ray. In cytotoxicity studies, **111** was found to be the most active compound with an MIC of 1 μ g/mL towards KB cells and 5 μ g/mL towards LoVo cells.

Order Homosclerophorida

Bioassay-guided fractionation (brine shrimp bioassay) of the extract obtained with 80% aqueous CH₃OH of a *Plakortis* sp., a sponge collected between Lehua Rock and Niihau Island, led to the isolation of four new polyketide derived metabolites, lehualides A to D (**113–116**) [69]. Cytotoxicity screening of the isolates showed lehualide B (**114** [Fig. 7]) and lehualide D (**116** [Fig. 7]) to have activity towards ovarian and leukemia cancer cell lines.

Order Poecilosclerida

From a sponge only assigned to order the Poecilosclerida, collected near Maalaea Bay, Maui, two mildly cytotoxic steroids oxidized at C-21, kiheisterones A (**117** [Fig. 7]) and B (**118** [Fig. 7]), were isolated [70].

The first halo-steroids, in this instance chloro-steroids, kiheisterones C–E (**119–121**) were discovered from an undescribed species of *Strongylacidon*, collected from Maalaea Bay, Maui [71]. The authors report no biological activity testing of these unusual halo-steroids.

Order Suberitida

From a *Halichondria* sp., a sample collected by trawling at a depth of 200 m north of Oahu, two of the first marine isocyanides were isolated, a bicyclic sesquiterpene (**122** [Fig. 7]) and a acyclic diterpene (**125** [Fig. 7]), together with their corresponding formamides (**123**, **126**) and isothiocyanates (**124**, **127**) [72–74].

Chemical investigation of a nudibranch, *Phyllidia varicosa*, led the authors to research samples of the off-white sponge *Hymeniacion* sp., known to be part of the animal's diet, collected from the Pupukeya Coast, Oahu. From the EtOH extract of the sponge, the authors isolated 9-isocyanopupukeanane (**128** [Fig. 7]) and confirmed its structure by X-ray analysis of its phenylthiourea derivative [75].

The sterol composition of the sponge *Terpios zeteki* (now *Suberites aurantiacus*) collected from Kaneohe bay, Oahu, was described by Delseth and collaborators in 1979 [76], and included the structure of a new C₂₆ sterol, 5 α -24-norcholestan-3 β -ol (**129**).

There are two reports on sponges from the genus *Ciocalypta* present in Hawaiian waters. The first of these described a specimen collected from Pupukeya, Oahu, and reported the isolation of three nitrogen containing bisabolene sesquiterpenes, 7-isocyanato-7,8-dihydro- α -bisabolene (**130**), 7-[(*p*-bromobenzyl)ureido]-7,8-dihydro- α -bisabolene (**131**), and 7-amino-7,8-dihydro- α -bisabolene chloride (**132**) [77]. The structure of **132** was confirmed by X-ray analysis of its *p*-bromobenzyl urea derivative. The second report, this time concerning a sponge from Ala Moana Reef on the west shore of Oahu, discussed a tricyclic sesquiterpene, isocyanoneopupukeanane (**133**) [78]. The structure solution of this rigid cage-like compound took advantage of several diagnostic 2D-NMR C–H long-range correlations (COLOC).

Order Verongida

Other common genera researched from Hawaiian waters are those belonging to the order Verongida. The first isolate from a sponge belonging to this order, with a tentative taxonomic assignment, was 15-cyanopuuphenol (**134**) [79]. The sample was collected from waters off the south shore of Molokai. Interestingly, the authors make no speculation that this molecule might have been a possible precursor of puuphenone (**93**). Other specimens of this order collected from Maui and several beaches on Oahu, identified as belonging to either the genus *Psammaphysilla* or *Pseudoceratina*, have yielded a variety of different compounds. Moloka'iamine (**135** [● Fig. 7]), a bromotyramine derivative, and five puuphenone-related compounds (**136–140**) were isolated from a sample belonging to an undescribed genus closely comparable to *Psammaphysilla purpurea*.

The samples were collected from a pier in Kaunakakai Harbour, Molokai, several locations along the south shore of Oahu, and waters south of Maui, and their extracts demonstrated activity towards KB cancer cells [80]. The authors report that all isolates exhibit a variety of biological activities, including cytotoxicity, antiviral, antifungal, and immunomodulatory activities. Re-examination of the sample previously discussed collected on the Wai'anae coast, Oahu, yielded moloka'iamine (**135**), and the new compounds *N*-methylceratinamine (**141**), two moloka'iamine derivatives, wai'anaeamines A (**142**) and B (**143**), together with psammaphysin A (**144**) [81]. Examination of the ethyl acetate (EtOAc) fraction obtained from the original extract after flash chromatography of the same sponge samples yielded bromotyramine derivatives named mololipids (**145**) for which there is no complete physical or spectroscopic information [82]. In the paper, the authors provide very general GC-MS data and spectroscopic data of lipid mixtures. Bioassays performed with the lipid mixtures showed them to have some selective activity towards the HIV-1 virus (EC_{50} of 52.2 μ M). The EC_{50} reported is clearly anomalous, as tests were undertaken with mixtures of lipids of varying molecular weights.

A sample positively identified as *P. purpurea* collected from a depth of 40 m off south Kihei, Maui, furnished three bromotyrosine derivatives, aplysamines 3–5 (**146–148** [● Fig. 7]) [83]. All compounds demonstrated moderate to weak nonselective cytotoxicity towards four cancer cell lines (KB, P388, A549, and HT-29), were mildly antibacterial towards various gram-positive bacteria, and were inactive towards the HIV-1 virus.

Mollusks



Sea hares

The early 1970s saw the first reports on sea hares. *Stylocheilus longicauda*, collected in Kaneohe Bay, Oahu, yielded two toxins, aplysiatoxin (**149**) and debromoaplysiatoxin (**56**), as well as their nontoxic monoacetates (**150**, **151**) [36,84], together with stylocheilamide (**152**) [85]. From the same source organism, the new compounds makalika ester (**153**), makalikone ester (**154** [● Fig. 8]), malyngamide O (**155**), and malyngamide P (**156**) were isolated from animals collected from Black Point, Oahu [86,87]. The paper concerning two proline esters (**153**, **154**) was also the first report of a naturally occurring lyngbyatoxin A acetate (**158**) [86].

Malikone ester (**154**) and lyngbyatoxin A acetate (**157** [● Fig. 8]) were determined to have moderate (IC_{50} s of 2.5–5 μ g/mL) and potent (IC_{50} of 0.05 μ g/mL) activities, respectively, against mouse

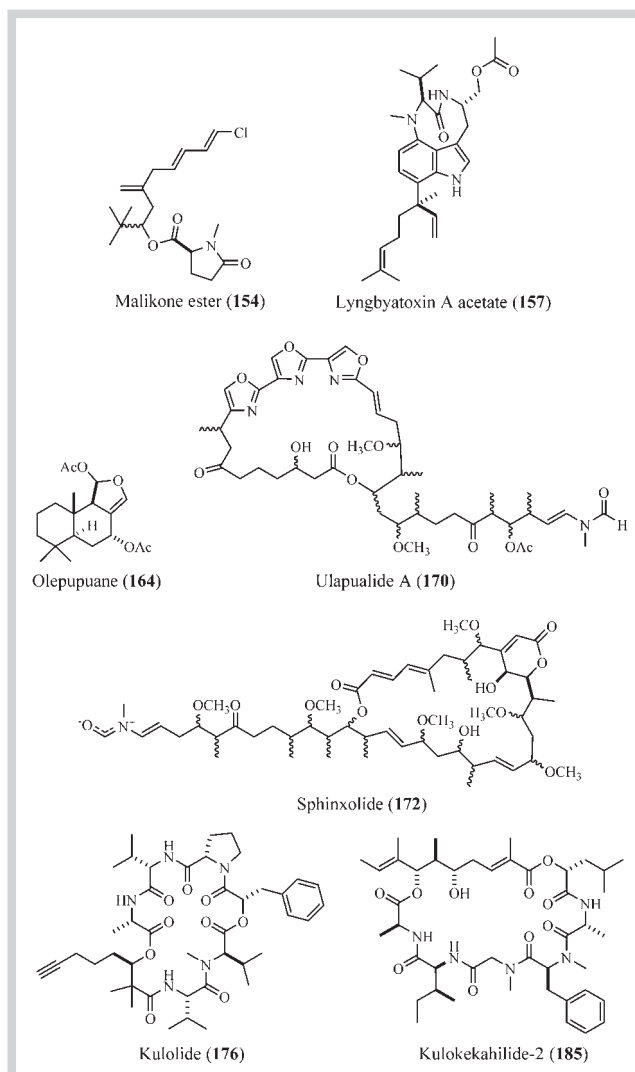


Fig. 8 Selected isolates from mollusks.

lymphoma (P-388) cells, human lung carcinoma (A-549) cells, and human colon carcinoma (HTB 38) cells. Malyngamide O (**155**) showed moderate anticancer activity against mouse lymphoma (P388) cells, human lung carcinoma (A-549) cells, and human colon carcinoma (HT-29) cells.

The lipid extract of a collection of sea hares, *Aplysia oculifera*, from the Pupukea Coast, Oahu, where they were observed feeding on an unidentified species of the red alga *Laurencia* sp., was found to contain two bicyclic di-bromo di-ether C₁₅ enynes, *E*-ocellenyne (**158**) and *Z*-ocellenyne (**159**) [88]. It is likely that both of the compounds play a role in the defense of the collected animals, but clearly not against humans!

Nudibranchs

From the nudibranch *Phyllidia varicosa*, collected from the Pupukea Coast, Oahu, 9-isocyanopupukeanane (**128**) was isolated [75]. The same compound was also isolated from the EtOH extract of a sponge identified as *Hymeniacidon* sp., which was collected and extracted specifically to provide a sufficient quantity of compound to enable its complete characterization [75]. Four years later, the 2-isomer, 2-isocyanopupukeanane (**160**), was isolated

and identified [89]. The final structure solution, including absolute configuration, was achieved through X-ray analysis.

The previously discussed compounds, nakafuran-8 (**98**) and nakafuran-9 (**99**), were isolated from two different mollusks, *Chromodoris maridadilus* and *Hypselodoris godeffroyana*, collected in Kaneohe Bay, Oahu. Both organisms had been observed feeding on the marine sponge *Dysidea fragilis*, suggesting a dietary source [60]. A separate study of the Pupukea Coast, Oahu, inhabitant *Chromodoris youngbleuthi* yielded three deacetylscalaradiols, only one of which was found in its prey (**161**), the sponge *Spongia oecania* [90], and two of which were new natural products (**162**, **163**).

Assessment of the sesquiterpene contents of eight porostome nudibranchs, two species from Hawaii collected at Ala Moana Reef, Fort Kamehameha, and the Pupukea Coast, belonging to the genus *Dendrodoris*, *Dendrodoris nigra* and *Dendrodoris tuberculosa*, found them to contain two new compounds, olepupuanes (**164** [● Fig. 8]) and its methoxy acetal (**165**) [91]. Olepupuanes (**164**) was shown to have antifeedant properties toward the Pacific damsel fish (*Dascyllus aruanus*), with an ED₅₀ of 15–20 µg/mg of food pellet.

The ilikonapyrone esters (**167–169**), all based on the bispyrone alcohol ilikonapyrone (**166**), were isolated from the nudibranch *Onchidium verruculatum*, collected from Portlock, Oahu [92]. These compounds have purported roles as defense allomones for this mollusk.

An analysis of the carbon tetrachloride (CCl₄) partition of the CH₃OH extract of eggs of the mollusk *Hexabranhus sanguineus* collected at Pupukea, Oahu, yielded two antitumor macrolides, both 28-membered lactones with three contiguous oxazole rings, ulapualides A (**170** [● Fig. 8]) and B (**171**) [93]. Both compounds inhibited leukemia (L1210) cell proliferation (IC₅₀s of 0.01–0.03 µg/mL) and the growth of *Candida albicans* [93], and are reported to be present in the adults, but in low concentrations.

Sphinxolide (**172** [● Fig. 8]) is a 26-membered macrolide isolated from an unidentified nudibranch found trapped in fishing nets off Oahu [94]. The compound was found to have potent activity against KB cells (IC₅₀ of 35 µg/mL).

With seven publications and twelve compounds, *Philineopsis speciosa* is one of the most investigated and productive mollusks so far researched in the Hawaiian Islands. Specimens of *P. speciosa* collected from sandy tide pools at Pupukea, Oahu, led to two reports. The first of these described pulo'upone (**173**), a C₁₆-alkadienone-substituted 2-pyridine [95]. The second publication describes two new polypropionates named niuhinone A and B (**174**, **175**) [96]. A larger re-collection of this organism at Shark's Cove, Pupukea, Oahu, in 1994 yielded the depsipeptide kulolide (**176** [● Fig. 8]), which exhibited significant biological activity against leukemia cells (L-1210) and murine leukemia cells (P388) with IC₅₀ values of 0.7 and 2.1 µg/mL, respectively [97]. Lethality of **176** to brine shrimp was not observed at 1.0 ppm. Furthermore, **176** caused a change in rat 3Y1 fibroblast cell morphology at 50 µM. From the same collection, the isolation and characterization of a linear tetrapeptide, pupukeamide (**177**), was also described [98]. The compound showed no cytotoxicity against murine leukemia (P388) cells. The authors use the presence of pupukeamide (**177**) to propose an ecological link via bioaccumulation through three trophic levels, *Lyngbya* spp. to *Stylocheilus longicaudus* to *Philineopsis speciosa*. The next report concerning the collection from Shark's Cove in 1994 yielded five new depsipeptides, kulolide-2 (**178**), kulolide-3 (**179**), kulokainalide-1 (**180**), kulomo'opunalide-1 (**181**), kulomo'opunalide-2

(**182**), and the unprecedented macrolide, tolytoxin-23-acetate (**183**) [99]. Kulokekahlilide-1 and -2 (**184**, **185**) represent the most recent depsipeptides isolated from *P. speciosa* samples [100, 101]. Kulokekahlilide-2 (**185** [● Fig. 8]) exhibited potent cytotoxicity towards P388, SK-OV-3, MDA-MB-435, and A-10 cells, with **184** being found to be significantly less active.

One of the more successful natural product stories from Hawaii concerns the genus *Elysia*. Investigations of this genus and its food source, *Bryopsis* sp., revealed the group of depsipeptides called the kahalalides. The first report involved both *E. rufescens* and *Bryopsis* sp., and yielded the aforementioned kahalalide F (**76**) [44]. Kahalalides A–E (**77**, **78**, **186**, **187**, **188**) were also reported from a collection of this mollusk [45]. Both collections of the organism occurred at Black Point during 1991. The acyclic octa- and nona-peptides kahalalide H (**189**) and kahalalide J (**190**) were also isolated from *E. rufescens* and, in common with other acyclic peptides, they are reported to lack significant cytotoxicity [102]. The most recent report of kahalalides from Hawaiian *E. rufescens* specimens details the isolation of four further kahalalides, kahalalides V–Y (**191–194**) from two collections made in Kahala Bay, Oahu, during the time period 2003–2004 [103]. Surprisingly, none of these new metabolites demonstrates any activity approaching that documented for **76**.

Although there are eight reported species of *Elysia* in Hawaii, only one other species has been studied for its secondary metabolite production/sequestration, *E. ornata*. This sample was collected from Black Point, Oahu, in 1997, and afforded the biologically inactive kahalalide O (**81**) [47].

Miscellaneous Invertebrates

▼ Cnidarians

One of the more infamous compounds to be discovered in Hawaii is the marine toxin known as palytoxin (PLTX) (**195** [● Fig. 9]).

Native Hawaiians previously collected a “seaweed” from a tide pool in Muolea, Hana, Maui, and used it to tip their spear points with a preparation that contained palytoxin to make “strikes” more likely to be fatal. It was later discovered that this “seaweed” was actually a species of zoanthid called *Palythoa toxica*. Chemical investigations of *P. toxica*, collected specifically from Muolea, resulted in Moore and Scheuer's first report in 1971 on the isolation of PLTX (**195**) [104]. It took another 10 years before the planar structure of PLTX was reported [105], and an additional year before the structure with its absolute configuration became available [106]. Palytoxin (**195**) has a molecular weight of approximately 3300 amu and is toxic to mice at 0.15 µg/kg [104], it also possesses potent anticancer activity [107]. Reinvestigations of *Palythoa tuberculosa* and *P. toxica* collected from the same location on Maui yielded two 42-hydroxypalytoxin stereoisomers (**196**, **197**) [108]. These compounds exhibited different activities. *P. tuberculosa* afforded the 42*S*-hydroxy-50*S*-palytoxin (**196**) that is cytotoxic to HaCaT keratinocytes (EC₅₀ of 9.3 × 10⁻¹⁰ M). The 42*S*-hydroxy-50*R*-palytoxin (**197**), isolated from *P. toxica*, had an EC₅₀ of 1.0 × 10⁻¹⁰ M in the same assay. Comparatively, these stereoisomers are at least one order of magnitude less cytotoxic than PLTX (EC₅₀ of 2.7 × 10⁻¹¹ M) [108].

The soft coral *Sinularia abrupta* collected near the Blowhole on the southeast coast of Oahu, yielded pukalide [● Fig. 9 (**198**)], a highly functionalized furanocembranolide [109], now known to have a significant ecological function in the life cycle of soft corals [110].

Collection of the endemic blue octocoral *Anthelia edmondsoni* (now *Sarcothelia edmondsoni*) collected from the north shore of Oahu, near Waimea Bay, lead to the isolation of the highly oxygenated xenicin diterpenoids waixenicin A and B (**199**, **200**) [111].

Punaglandins (**201–204**), a series of eicosanoids containing an unprecedented C-10 chloro-function, were isolated from the octocoral *Telesto riisei* collected at various sites along the coast of Oahu [112]. The octocoral is quite unusual in the respect that it lacks symbiotic algae. The report mentions no biological activity for this interesting class of molecule.

Investigations of a deep-sea coelenterate used in the jewelry making industry, *Gerardia* sp., or gold coral, stemmed from a collection made employing a minisubmarine working at a depth of 350 m. Initially referred to as *Parazoanthus* sp., the animal was later correctly identified as *Gerardia* sp., [113]. Interest in this organism was sparked by complaints of skin and mucous membrane reactions from the handling of freshly harvested coral. Unfortunately, no suitable laboratory bioassay was found to facilitate the hunt for the causative agent, but the brilliant fluorescence of the extract prompted the group to identify the responsible metabolites [113]. An EtOH extract made from the animals was found to be highly fluorescent [114]. Fractionation of this extract yielded 2-amino-3,9-dimethyl-5-dimethylamino-3H-1,3,4,6-tetrazacyclo[*e*]azulene monohydrate (**205**), a zoanthaxanthin whose structure was solved employing X-ray crystallography [114]. Later in 1978, Schwartz et al. reported the isolation of two new fluorescent nitrogenous pigments. From the acidified aqueous fraction of the EtOH extract of the animal [● Fig. 9], **205** and 2-amino-3,9-dimethyl-5-methylamino-3H-1,3,4,6-tetrazacyclo[*e*]azulene (**206** [● Fig. 9]) were isolated [113]. In response to the longstanding debate of the biosynthetic origin of organic molecules in marine coelenterates (soft corals) between the animals themselves or the symbiotic zooxanthellae they harbor, the authors concluded that the pigments recovered from these animals must be synthesized by the animals because of their depth of habitation (~350 m), where photosynthesis is most unlikely to occur.

Another commercially valuable coral, *Corallium* sp., or Hawaiian pink coral, was harvested from depths of 300–350 m from the Moloka'i Channel off Makapu'u, Oahu. After harvesting, polyps were scraped off of the animals' endoskeleton and soaked in CH₃OH. Fractionation of the resultant extract led to the isolation of five diterpenes structurally related to xenicins, coraxenolide A, B, C, and D (**207–210**), and corabohcin (**211**) [115]. The structures of all isolates were resolved from the X-ray crystal structure determined for coraxenolide A (**207**).

Investigations of a collection of six other deep-sea (~360 m) gorgonians from waters off Makapu'u, Oahu, lead to the isolation of papakusterol (**212**) from all samples and 7-dehydropapakusterol (**213**) from only one sample, *Acanthagorgia* sp. Identifications of the organisms was pending at the time of publication, with only *Acanthagorgia* sp. being identified in the report [116].

A gorgonian from the family Paramuriceidae collected off Oahu at depths around 350 m yielded the new natural products 3-chloro-7-isopropyl-1,4-dimethylazulene (**214**), 3-bromo-7-isopropyl-1,4-dimethylazulene (**215**), and ehuzulene (**216**) [117]. The chloro- and bromo-isolates were previously known from synthesis [118]. A nitrogenous viscous blue oily azulene derivative, *N,N*-dimethylamino-3-guaiazulenylmethane (**217**), was isolated from a different sample of the same species of organism, from the

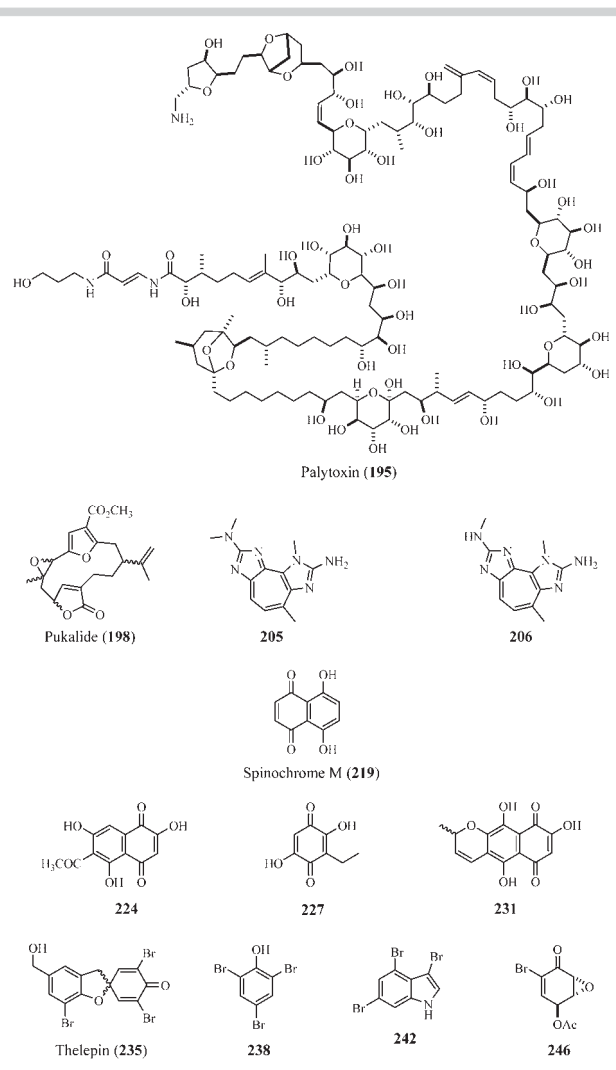


Fig. 9 Selected isolates from miscellaneous invertebrates.

same location, and from the same depth as the one just discussed [119].

Hexane extraction of a deep-sea example of the gorgonian *Placogorgia* sp., collected from a depth of 350 m, yielded a tricyclic yellow crystalline guaianolide pigment that was fully conjugated and contained both keto and lactone functionalities (**218**) [120]. From the box jellyfish (*Carybdea alata* reclassified as *Alatina alata*), the 43–45 kDa protein toxins CaTX-A and B were isolated, and the cDNA and amino acid sequences for CaTX-A were also reported [121]. Hemolytic activity tests performed with sheep red blood cells showed 50% hemolysis at concentrations of 70 and 80 ng/mL for the two compounds, respectively. A crayfish toxicity assay performed with *Procambarus clarkii*, using CaTX-A, showed it to have an LD₅₀ of 5–25 mg/kg.

Echinoderms

The earliest report concerning a marine natural product from Hawaiian waters concerned spinochrome M (**219** [● Fig. 9]), a polyhydroxylated naphthoquinone pigment, isolated from the spines of six species of Hawaiian sea urchins, *Echinometra oblonga*, *Colobocentrotus atratus*, *Tripneustes gratilla*, *Echinithrix diadema*, *E. calamaris*, and *Diadema paucispinum* [122]. This study

was undertaken to establish whether the chemical diversity of naturally occurring spinochromes actually matched that reported in the literature. Interestingly, the authors' findings supported their suspicion that the literature contained a larger variety of spinochromes than actually occur in nature!

From the spines of two species of *Echinithrix* sea urchins, *E. diadema* and *E. calamaris*, collected from Kaneohe Bay, Oahu, 16 compounds, predominantly polyhydroxylated naphthoquinones, were isolated, with the following 11 being new natural products: 2-hydroxy-3-acetyl-naphthazarin (**220**), 2-hydroxy-6-ethyljuglone (**221**), 2-hydroxy-6-ethylnaphthazarin (**222**), naphthopurpurin (**223**), 2,7-dihydroxy-6-acetyljuglone (**224** [Fig. 9]), 2,7-dihydroxy-3-ethylnaphthazarin (**225**), 2,7-dihydroxynaphthazarin (**226**), 2,5-dihydroxy-3-ethylbenzoquinone (**227** [Fig. 9]), 2-hydroxy-6-acetylnaphthazarin (**228**), 2,3,7-trihydroxy-6-acetyljuglone (**229**), and 2,3,7-trihydroxy-6-ethyljuglone (**230**) [123]. In 1968, the structure of the first pigment containing a four carbon unit attached to a naphthoquinone system was described; 2-methyl-8-hydroxy-2*H*-pyrano[3,2-*q*]naphthazarin (**231** [Fig. 9]) [124].

Annelid

The chloroform (CHCl₃) extract of the annelid *Thelepus setosus* collected in Kaneohe Bay, Oahu, was separated by preparative TLC and found to contain five new bromophenol-related metabolites (**232–236**; **235** [Fig. 9]) whose biological activities have yet to be reported [125].

Acorn worms

Investigations of a new species of acorn worm belonging to the genus *Ptychodera*, collected at a depth of 30 m from a cave at Kinau Point off the island of Maui, led to the isolation of 11 new brominated compounds (**237**, **238** [Fig. 9], **239–241**, **242** [Fig. 9], **243–245**, **246** [Fig. 9], **247**) [126].

Cyanobacteria

Lyngbya majuscula Gomont, now *Moorea producens* [127], is the most studied marine cyanobacterial species, probably due to its notoriety as the causative agent for outbreaks of contact dermatitis, more commonly referred to as "swimmers' itch," in Hawaii. The new genus name *Moorea* is an acknowledgement of the many years of work that Richard E. Moore and his group undertook with this marine cyanobacterium that is phylogenetically distinct from the freshwater *Lyngbya*, whose name is retained based on precedent. The main toxic component of *L. majuscula* (now *M. producens*), lyngbyatoxin A (**248** [Fig. 10]), was first isolated in 1971 from a Laie Bay collection on Oahu [128], but its structure was not resolved until eight years later [129]. Other investigations concerning subsequent collections of the Kahala Beach strain of *L. majuscula* (now *M. producens*) yielded 18 additional metabolites. Two major constituents of the lipophilic extract, the epimeric lipodipeptides majusculamide A and B (**249**, **250**) [130], were the next two compounds to be described, followed by (+)- α (*S*)-butyramido- γ -butyrolactone (**251**) [131], and then (–)-trans-7(*S*)-methoxytetradec-4-enoic acid (**252**) together with malyngamides A (**253**) and B, the latter two compounds only being partially characterized [132]. The structure of malyngamide A (**253**) was eventually published in 1979 [133]. The next examination of the Kahala beach strain yielded malyngolide (**254**), which was found to have antibiotic activity against *Mycobacterium smegmatis*, *Streptococcus pyrogenes*, *Staphylococcus aureus* and *Bacillus subtilis* [134].

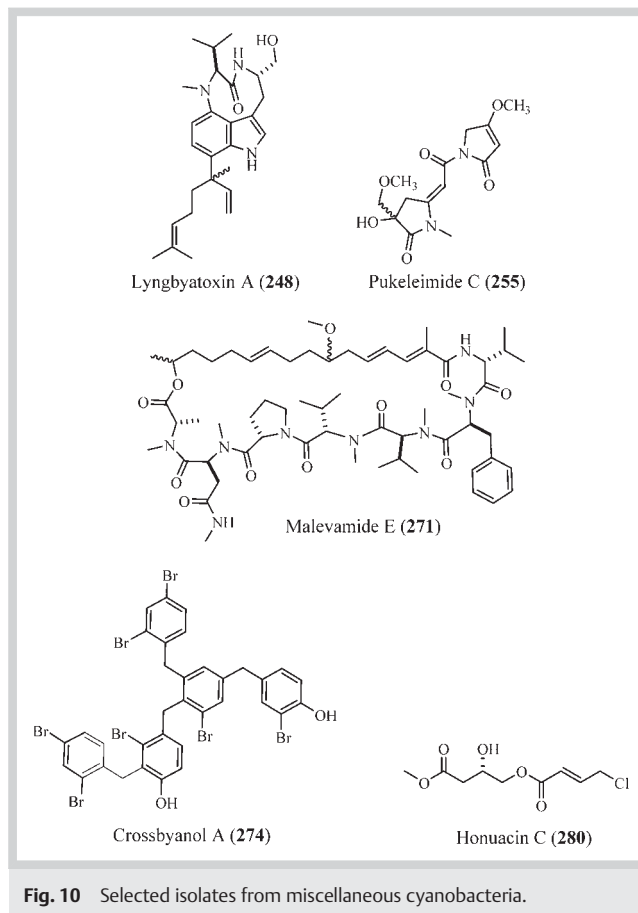


Fig. 10 Selected isolates from miscellaneous cyanobacteria.

Following this report came the next class of compounds to come from *L. majuscula*, the pukeleimides, 1*H*-pyrrol-2(5*H*)-one derivatives, pukeleimide C (**255** [Fig. 10]) being the first one to appear in the literature [135]. The structure of this compound was deduced by X-ray crystallographic examination. The authors also determined that their isolate exists as a racemic mixture having an optical rotation of 0 and no apparent CD activity. From the same sample of *L. majuscula* that yielded pukeleimide C (**255**), pukeleimides A, B, and D–G (**256–261**) were also isolated and their structures proposed on the basis of spectroscopic data interpretation [136]. Lyngbyatoxins B and C (**262**, **263**), also from the Kahala beach strain of *L. majuscula*, were identified as irritants via a mouse ear irritant test [137]. The final report on *L. majuscula* compounds described isomalyngamides A and B (**264**, **265**), which were shown to have lethal toxicity towards the crayfish *Procambarus clarkii* (250 and 500 $\mu\text{g}/\text{kg}$, respectively) [138]. From the dichloromethane (CH₂Cl₂)-soluble part of a 70% EtOH extract made from a sample of *L. aestuarii* Liebmann ex Gomont collected at Kamalo Jetty on Molokai, 2,5-dimethyldodecanoic acid (**266**) was reported and found to have pH-dependent herbicidal activity at concentrations above 200 ng/mL (*Lemna minor* growth inhibition with an ED₅₀ of 0.5 $\mu\text{g}/\text{mL}$) [139]. Three samples of the genus *Symploca*, all from Oahu, yielded five new peptides, malevamides A–E (**267–271**) [140–142] and symplostatins 3 (**272**) [143]. In an attempt to investigate Hawaiian samples of *Symploca hynoides*, cyanobacterial samples were collected from waters next to Ala Moana Beach Park. Later, it was

discovered that the sample was primarily *Symploca laete-viridis*, which is morphologically similar to *S. hynoides*, and was contaminated with the species of interest. Re-collection, specifically of *S. laete-viridis*, yielded malevamides A–C (**267–269**) [140]. The second investigation of *S. laete-viridis*, from the same location, led to the isolation of malevamide E (**271**) [141], which was shown to have a dose-dependent inhibitory effect on the store-operated calcium ion entry in thapsigargin-treated human embryonic kidney (HEK) cells at concentrations ranging from 2–45 μM . This was the first report of this type of depsipeptide as a modulator of calcium ion channels. In the paper, the authors also discuss a potential biosynthetic relationship between malevamide E (**271** [Fig. 10]) and dolastatin 14 (**273**) amongst *S. laete-viridis* and its grazer, *Dolabella auricularia*. Malevamide D (**270**) was isolated from a sample of *S. hynoides* collected off the south shore of Oahu [142].

Symplostatin 3 (**272**), a dolastatin 10 analogue, was isolated from a tumor selective extract of *Symploca* sp., VP452, collected from depths of 3–4 m inside Kaneohe Bay, Oahu [143]. In bioassays aimed at assessing the *in vitro* cytotoxicity of **272**, it was shown to have IC_{50} s ranging from 3.9–10.3 nM. Its mode of action, like that of dolastatin 10, was microtubule disruption.

Two articles by a San Diego-based group report on two new classes of natural products from a sample of *Leptolyngbya crossbyana* collected at a depth of 20 m from Honaunau, Big Island [144, 145]. The first of these reports describes the crossbyanols A–D (**274** [Fig. 10], **275–277**), toxic penta-cyclic brominated polyphenyl ethers [144]. In a variety of bioassays, antimicrobial, cytotoxicity, voltage-gated sodium channel, and brine shrimp lethality, all compounds, except for crossbyanols C and D, demonstrated activity in at least one assay. The second report on the extract describes the honaucins A–C (**278, 279, 280** [Fig. 10]), potent inhibitors of inflammation and bacterial quorum sensing [145].

Bacteria

A shallow-water sediment sample collected in 1996 from Wailupe Beach Park on the southeast shore of Oahu yielded the first Hawaiian bacterial strain, a *Streptomyces* sp., [Strain BD-26 T(20)] shown to contain interesting secondary metabolites, four new α -pyrones, wailupemycins A–C (**281–283**), and 3-epi-5-deoxyenterocin (**284** [Fig. 11]). Two of the isolates, wailupemycin A (**281**) and **284**, exhibited selective antibacterial activity towards *E. coli* and *S. aureus*, respectively [146]. *Streptomyces* sp., strain BD-18 T(41), isolated from sediments collected at the mouth of Halawa Stream on the north shore of Oahu, whose CCl_4 and CHCl_3 solubles were shown to be antimicrobial, yielded a group of quinone-containing metabolites called halawanones A–D (**285–288**), together with the known nanomycin D [147]. The absolute configurations of the new compounds were determined employing both NMR and CD analyses. Strain BD21-2, *Streptomyces* sp., originated from a shallow-water sediment sample from Kailua Beach, Oahu. The EtOAc extract of the whole broth culture yielded the ester bonactin (**289** [Fig. 11]), which showed weak to moderate broad spectrum antimicrobial activity towards a variety of microbes at the 100 μg per disc (6 mm dia.) level; *Bacillus megaterium* (zone of inhibition [Zoi]=8 mm), *Micrococcus luteus* (Zoi=8 mm), *Klebsiella pneumoniae* (Zoi=8.5 mm), *S. aureus* (Zoi=7 mm), *Alicagenes faecalis* (Zoi=10 mm), *E. coli*

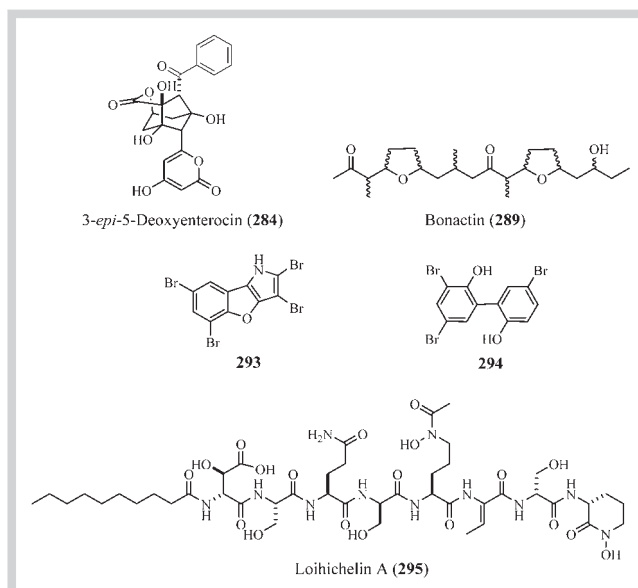


Fig. 11 Selected isolates from bacteria.

(Zoi=9 mm), and *Saccharomyces cerevisiae* (Zoi=7.5 mm); the first acyclic ester related to the nonactins to do so [148].

Nocardiopsis dassonvillei, actinomycete strain BH-609, purified from sediments collected along the high-tide line at Kahaka Beach Park, Kauai, was found to produce rare *N*-glycosyl indoles, kahakamides A and B (**290, 291**) related to neosidomycin [149]. This class of microbial compound contained only two other members prior to this report. Kahakamide A exhibited weak antimicrobial activity against *B. subtilis*.

From the surface of a nudibranch and the sponge *Mycale armata* recovered from waters off Oahu, pure cultures of *Pseudoalteromonas rubra* were established. The acetone diethyl ether (2:3) extract of the culture was shown to have significant cytotoxicity towards human ovarian adenocarcinoma cells (SKOV-3). A work-up of this extract yielded the 2-substituted prodiginine, 2-(*p*-hydroxybenzyl)prodigiosin (**292**), that was active towards SKOV-3 cells (IC_{50} of 1.3 μM) [150]. A second strain of *Pseudoalteromonas* (CMMED 290), also isolated from the surface of a nudibranch, this time collected in Kaneohe Bay, Oahu, produced two highly brominated compounds identified as 2,3,5,7-tetra-bromobenzofuro[3,2-*b*]pyrrole (**293**) and 4,4',6-tribromo-2,2'-biphenol (**294**). Both compounds exhibited antimicrobial activity against methicillin-resistant *S. aureus* (IC_{50} of 1.93 μM for **293** [Fig. 11] and 2.19 μM for **294** [Fig. 11]) [151].

From a depth of 1714 m off of Loihi Seamount, 30 km south east of the Big Island, the basalt-weathering bacterium *Halimonas* sp. strain LOB-5 was isolated. Cultivation of the bacterium followed by purification employing solid-phase extraction (XAD-2 resin) and RP-HPLC yielded six new aphiphillic photoreactive siderophores, loihichelins A–F (**295** [Fig. 11], **296–300**) [152].

Fungi

Interestingly, all of the reports concerning fungal isolates derived from Hawaiian waters are from research groups based on the mainland USA. The first of these appeared in 1989 and concerned *Helicascus kanaloanus* ordered from the American Type Culture

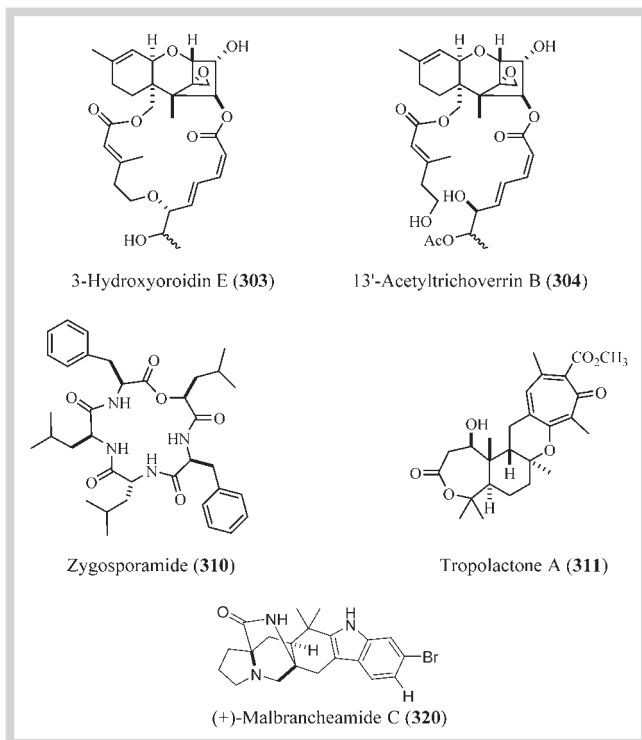


Fig. 12 Selected isolates from fungi.

Collection (ATCC 18591), initially derived from a Hawaiian Mangrove. After cultivation in liquid media and extraction with EtOAc, the fungus was found to have produced two isomeric δ -lactones, helicisolides A and B (301, 302) [153].

The next report concerning a marine fungus did not appear until 2003 and related to the extract made from *Myrothecium verrucaria* isolated from the sponge *Spongia* sp., collected from waters off of Maui. This investigation reported three new trichothecenes (303–305) and their cytotoxic properties. Activity against murine and human tumor cell lines was noted for 3-hydroxyxoroidin E (303 [Fig. 12]) and 13'-acetyltrichoverrin B (304 [Fig. 12]), with miophytoen C (305) being found inactive in the same assays [154].

A strain of *Exserohilum rostratum*, originally associated with a cyanobacterial mat found off the coast of Lanai, yielded rostratins A–D (306–309). All rostratins, for which their absolute configurations are given, showed cytotoxicity against human colon carcinoma (HCT-116) cells with IC_{50} values of 8.5, 1.9, 0.76, and 16.5 $\mu\text{g}/\text{mL}$, respectively [155], suggesting a link between lipophilicity and activity.

The fermentation broth of fungal strain CNK458, identified as *Zygosporium masonii* isolated from an unidentified marine cyanobacterium collected off the coast of Maui, yielded zygosporamide (310 [Fig. 12]). The molecule is a cyclic depsipeptide containing a D-amino acid residue that has significant activity in the National Cancer Institute's (NCI) 60 cell line panel with a median $GI_{50} = 9.1 \mu\text{M}$ [156].

Aspergillus is the most documented genus of marine fungi studied from Hawaii. Organisms from this genus have produced tropolactones A–D (311 [Fig. 12], 312–314), azonazine (315), presclerotiotide F (316), and sclerotiotide F (317). The first report focused on strain CNK-371 isolated from an unidentified sponge collected at Manele Bay, Lanai, and described tropolactones A–D

(311–314), which showed cytotoxicity against human colon carcinoma (HCT-116) cells with IC_{50} s of 13.2, 10.9, and 13.9 $\mu\text{g}/\text{mL}$ for tropolactone A, B, and C (311–313), respectively [157]. The strain of *A. insulicola* that produced azonazine (315), a unique hexacyclic dipeptide, was isolated from a marine sediment sample from Hawaii, with no further details given on the organism's origin [158]. Azonazine (315) proved to be inactive in applied assays [158]. A second study of *A. insulicola*, once again from a sediment collected in Hawaii, exact location not indicated, described the isolation of two new tripeptides, 316 and 317, both of which were devoid of activity in the applied test systems [159].

The final paper included in this review concerns a strain of *Malbranchea graminicola* isolated from an unidentified invertebrate collected by hand using self-contained underwater breathing apparatus (SCUBA) from Kona, Hawaii [160]. Investigation of the bioactive extract produced by the fungal culture led to the isolation of (–)-spiromalbramide (318) and (+)-isomalbrancheamide B (319), both apparently devoid of any bioactivity but of some chemical interest. The inspired part of this research was enrichment of the growth media of the fungus with bromine salts that caused the fungus to also produce the brominated compounds (+)-malbrancheamide C (320 [Fig. 12]) and (+)-isomalbrancheamide C (321) [160], hence revealing something more concerning the biosynthetic power of this microbe.

Concluding Comments

Prior to starting this review we had only an inkling of an idea of the amount of research into Hawaiian marine organisms the groups led by Richard E. Moore and Paul J. Scheuer had undertaken. In many ways this is almost a review of their groups' pioneering research in the area of marine natural products from Hawaiian waters, hence the dedication at the start of the review. This research led to the discovery of many unique molecules being reported for the first time, palytoxin (195) [104] being a prime example. Another highlight would have to be the investigations undertaken with cyanobacteria that spawned a whole new area of research and led to the discovery of many new classes of molecules, including the lyngbyatoxins, pukeleimides, and the mallevamides. In reality, much of the research undertaken in Hawaii formed the foundation of what we now know as modern marine natural products research.

Aside from the wonderful achievements highlighted above, our reading of the 160 publications that compose this review, plus many others read during the preparation of this review but not included, have left some other indelible impressions. The first of these is how little we actually still know about the hundreds of chemical entities discussed. Yes, we know a good deal about their chemical structures, their absolute configurations and the like, but for the vast majority, we know little or nothing about their roles in nature and, in a relative sense, our knowledge of their potential value to us as a species is restricted to a hand full of bioassays that mainly involve anticancer and antimicrobial studies. It is also astounding, given the amount of research funds, probably many millions of dollars, provided to the researchers cited in this review over the past 20–25 years by organizations like the US National Institutes of Health (NIH), that other organizations in Hawaii on islands other than Oahu, particularly in recent times, have not received similar funding or been encouraged to establish centers where the environment has been the subject of little or no scientific research investigation. We had also hoped to

be citing at least one success story in terms of a compound that made it to the market place, instead we have hundreds of chemical entities that are apparently of no real use! The one exception to this seemingly harsh critique would have to be the antitumoral compound kahalalide F (76) [44], which successfully reached phase II clinical trials for the treatment of patients with severe psoriasis. Unfortunately, the organization behind the development process, the Spanish-based pharmaceutical company PharmaMar, has apparently deprioritized further development of kahalalide F, probably due to a lack of significant efficacy and/or funds.

Our last two major impressions relate to the general lack of careful documentation of species being investigated and the environments from which they were collected, as well as the continued totally random approach as to how samples are selected for study. In the early years, the 1960s and 1970s, research was being undertaken by groups of chemists who were breaking new ground and probably had limited exposure to biology and to the importance of accurate taxonomic identifications and all this encompasses. Nowadays, most reports have this information in some form, but still we see articles where this is not the case [158, 159], and some that do not even provide identification to the level of order [160]. Molecular taxonomic techniques can now be carried out routinely, and the importance of good taxonomy should be paramount in ensuring that natural products research continues to be relevant and reproducible. Finally, with the advent of the “omics”-age (e.g., genomics, proteomics), it is probably time for researchers to coordinate what they do to ensure approaches become systematized, clearly documented, and that all isolates are assessed in as many and varied bioassay systems as is possible. Also, it would make far more sense to make careful surveys of the biodiversity in specific areas around the Hawaiian Islands and collect samples representative of these so as to enable a meaningful picture of their ecology and bioactivity to be developed. This probably means an organization should become responsible for the creation of a Hawaiian natural products repository. This repository would be responsible for coordination, storage, and documentation of any natural products and natural product-related activities undertaken within the State of Hawaii; Hawaii is an absolutely unique and special place in our world and its natural resources need to be carefully and sustainably managed and used, or not used, for the benefit of everyone now and into the future.

Supporting information

Figs. 1 S–22 S and **Table 1 S** contain the structural formulae of compounds discussed in the review together with the taxonomy and collection location of the compounds' source organism, where known, as well as the main structural class to which the compounds belong, and either their trivial or semi-systemic name.

Conflict of Interest



The authors declare no conflicts of interests.

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