marine drugs

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Review

Genus *Acanthella*—A Wealthy Treasure: Secondary Metabolites, Synthesis, Biosynthesis, and Bioactivities

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Abstract: Marine sponges are multicellular and primitive animals that potentially represent a wealthy source of novel drugs. The genus *Acanthella* (family Axinellidae) is renowned to produce various metabolites with various structural characteristics and bioactivities, including nitrogen-containing terpenoids, alkaloids, and sterols. The current work provides an up-to-date literature survey and comprehensive insight into the reported metabolites from the members of this genus, as well as their sources, biosynthesis, syntheses, and biological activities whenever available. In the current work, 226 metabolites have been discussed based on published data from the period from 1974 to the beginning of 2023 with 90 references.

Keywords: marine sponges; *Acanthella*; Axinellidae; nitrogen-containing terpenoids; life below water; health and wellbeing

Citation: Ibrahim, S.R.M.; Ghazawi, K.F.; Miski, S.F.; ALsiyud, D.F.; Mohamed, S.G.A.; Mohamed, G.A. Genus *Acanthella*—A Wealthy Treasure: Secondary Metabolites, Synthesis, Biosynthesis, and Bioactivities. *Mar. Drugs* **2023**, *21*, 257. https://doi.org/10.3390/md21040257

Academic Editors: Ali Al-Mourabit and Sylvain Petek

Received: 22 March 2023
Revised: 16 April 2023
Accepted: 18 April 2023
Published: 21 April 2023

1. Introduction

Natural metabolites from various sources, including microbes, animals, minerals, and plants, have been traditionally utilized for treating various human illnesses [1–6]. Recently, the developments in high-throughput screening and spectroscopic and analytical technologies have significantly boosted natural drug discovery, including marine-based drugs [7]. The marine environment is a rich source of a vast group of structurally unparalleled metabolites with diverse pharmacological activities that are reported from different marine organisms such as tunicates, sponges, mollusks, and bryozoans [8]. These metabolites are potential candidates for biotechnological applications and a number of them are in clinical trials; therefore, their impact on the pharmaceutical industry is continually growing [9–11]. They have been found to display an array of bioactivities, primarily antimicrobial, immunosuppressive, antifouling, anticancer, anthelmintic, antiprotozoal, neuroprotection, antiviral, and anti-inflammatory [7,8]. Among the marine organisms that have been investigated, sponges (Porifera), which are soft-bodied and sessile organisms, have become the focal point of natural product investigations due to the vast range of structurally unique biometabolites separated from these organisms [12,13].

The Axinellidae family (class Demospongiae, order Bubarida, family Dictyonellidae) [14] members, including *Axinella* and *Acanthella* genera, produce structurally varied terpenes

with various nitrogen-containing functionalities [15]. Marine sponges of the genus *Acanthella* (Schmidt, 1862) are present in large numbers in the world's oceans, especially in the South China Sea [16]. The accepted species of this genus and their status are listed in Table 1.

Table 1. List of the accepted species of the genus *Acanthella* and their status [14].

Species	Accepted as	Type Locality
Acanthella aculeata (Thiele, 1898)	-	Central Kuroshio Japan
Acanthella annulata (Sarà, 1958)	-	Western Mediterranean [#]
Acanthella acuta (Schmidt, 1862)	-	Adriatic Sea [#]
Acanthella aurantiaca (Keller, 1889) *	*Stylissa carteri* (Dendy, 1889)	Southern Red Sea
Acanthella branchia Sim (Kim and Byeon, 1990)		East China Sea South Korea
Acanthella cactiformis (Carter, 1885) **	*Rhaphoxya cactiformis* (Carter, 1885)	Bassian
Acanthella calyx (Dendy, 1922)		Cargados Carajos/Tromelin Island [#]
Acanthella carduus (Lamarck, 1814) **	*Phakellia carduus* (Lamarck, 1814)	-
Acanthella carteri (Dendy, 1889)	*Stylissa carteri* (Dendy, 1889)	South India Sri Lanka
Acanthella cavernosa (Dendy, 1922)	-	Seychelles [#]
Acanthella columnata (Burton, 1928)	*Phakellia columnata* (Burton, 1928)	-
Acanthella corrugata (George and Wilson, 1919)	*Axinella corrugata* (George and Wilson, 1919)	Virginian
Acanthella costata (Kieschnick, 1898)		Banda Sea Ambon
Acanthella cristagalli (Dendy, 1924) **	*Tedania (Tedaniopsis) cristagalli* Dendy, 1924)	-
Acanthella cubensis (Alcolado, 1984)	-	Greater Antilles
Acanthella danerii Costa (Bavestrello, Pansini, and Bertolino, 2020)	-	Chilean Exclusive Economic Zone [#] Chiloense
Acanthella dendyi (Bergquist, 1970)	-	Northeastern New Zealand
Acanthella ehrenbergi (Keller, 1889) **	*Biemna ehrenbergi* (Keller, 1889)	Southern Red Sea
Acanthella elongata (Dendy, 1905)	*Auletta elongata* (Dendy, 1905)	-
Acanthella erecta (Carter, 1876)	-	Celtic Seas
Acanthella euctimena (Hentschel, 1912) **	*Phakettia euctimena* (Hentschel, 1912)	Arafura Sea
Acanthella flabellata (Tanita, 1961)	-	Central Kuroshio Current
Acanthella flabelliformis (Keller, 1889) **	*Echinodictyum flabelliforme* (Keller, 1889)	Southern Red Sea
Acanthella flagelliformis (van Soest and Stentoft, 1988)		Eastern Caribbean [#]
Acanthella gorgonoides (Thomas, 1984)	-	Eastern India
Acanthella hirciniopsis (Carter, 1885) *	*Rhaphoxya cactiformis* (Carter, 1885)	Bassian
Acanthella hispida (Pulitzer-Finali, 1982)		Southern China [#]
Acanthella inflexa (Pulitzer-Finali, 1982) **	*Stylissa inflexa* (Pulitzer-Finali, 1982)	Central and Southern Great Barrier Reef [#]
Acanthella insignis (Thiele, 1898)	-	Central Kuroshio Current Japan
Acanthella klethra (Pulitzer-Finali, 1982)	-	Central and Southern Great Barrier Reef [#]
Acanthella ligulata (Burton, 1928)	-	Andaman Sea Coral Coast

Table 1. *Cont.*

Species	Accepted as	Type Locality
Acanthella lyrata (Esper, 1794) **	*Auletta lyrata* (Esper, 1794)	-
Acanthella mastophora (Schmidt, 1870)	-	Floridian #
Acanthella megaspicula (Thomas, 1984)	-	Eastern India
Acanthella minuta (Tanita, 1968)	-	Central Kuroshio Current
Acanthella multiformis (Vosmaer, 1885)	-	Northern Norway and Finnmark
Acanthella obtusa (Schmidt, 1862) **	*Dictyonella obtusa* (Schmidt, 1862)	Adriatic Sea
Acanthella oviforma (Tanita and Hoshino, 1989)	-	Central Kuroshio Current
Acanthella pulcherrima (Ridley and Dendy, 1886)	-	Central Kuroshio Current
Acanthella ramosa (Kumar, 1925)	-	Eastern India #
Acanthella ramus (Sim, Kim, and Byeon, 1990)	-	East China Sea #
Acanthella saladinorum (Sim-Smith, Hickman Jr, and Kelly, 2021)	-	Eastern Galapagos Islands #
Acanthella simplex (Thiele, 1898)	-	Central Kuroshio Current
Acanthella stanleei (Nascimento, Cavalcanti, and Pinheiro, 2019)	-	Northeastern Brazil #
Acanthella stipitata (Carter, 1881) **	*Phakellia stipitata* (Carter, 1881)	Bassian
Acanthella styloida (Tanita and Hoshino, 1989)	-	Central Kuroshio Current
Acanthella tenuispiculata (Dendy, 1897)	-	Great Australian Bight, Australia
Acanthella vaceleti (van Soest and Stentoft, 1988)	-	Eastern Caribbean # Barbados Exclusive Economic Zone
Acanthella vulgata (Thiele, 1898)	-	Central Kuroshio Current
Acanthella xutha (de Laubenfels, 1954)	-	East Caroline Islands

* Genus transfer and junior synonym; ** genus transfer; # halotype.

These sponges have been proven to be a prosperous source of sesquiterpenes and diterpenes featuring various nitrogen-containing groups, such as –NC (isonitrile), –NCS (isothiocyanate), –NCO (isocyanate), and –NHCHO (formamide) functionalities. Additionally, alkaloids and sterols are reportedly derived from these sponges. Some of these metabolites possess bioactivities such as antimalarial, cytotoxic, antimicrobial, anthelmintic, and antifouling [17–25]. Furthermore, some of them with promising bioactivities and unique structures have drawn the attention of chemists to investigate their synthesis in alignment with an in-depth biological evaluation for discovering new drug leads [26–29]. It is noteworthy that there are no available reported works that focus on the genus *Acanthella*. Therefore, this work aimed at highlighting the potential of this genus in terms of natural metabolite production. Herein, all reported studies on this genus are discussed, including secondary metabolites and their sources, as well as their biosynthesis, synthesis, and bioactivities whenever applicable.

2. Methodology

The reported studies on the genus *Acanthella* were collected by carrying out a literature search on different Publishers and databases, including Web of Science, PubMed, Scopus, Google-Scholar, Science Direct, Thieme, Bentham, Springer, Willey, and Taylor/Francis using the keywords: "*Acanthella* + compound" OR "*Acanthella* + NMR" OR "*Acanthella* + Biological

activity" OR "*Acanthella* + nanoparticles" OR "*Acanthella* + Terpenoids" OR "*Acanthella* + Semi-synthesis". This review involved investigations published in the English language in peer-reviewed journals in the period from 1974 to the beginning of 2023. A total of 85 published articles have been highlighted. The suggests irrelevant and non-reviewed journals' published articles, as well as all non-English written articles, were not included. For the non-English work, the data were extracted from the English abstracts whenever available.

3. Secondary Metabolites of Genus *Acanthella*

Different metabolites were separated and characterized from different species of this genus using various spectroscopic and chromatographic techniques. The isolated metabolites are categorized according to their chemical classes into sesquiterpenes, diterpenes, alkaloids, steroid compounds, and others. Additionally, their reported biosynthetic and synthetic studies are also highlighted whenever applicable.

3.1. Sesquiterpenes

The reported investigations revealed the purification of various classes of sesquiterpenes that are substituted by isonitrile or isothiocyanate functionalities, including mono-, bi-, and tri-cyclic skeletons with 3-, 5-, 6-, and/or 7-membered rings (Figure 1 and Table 2). Frequently, formamide derivatives were reported along with both isothiocyanate and/or isonitrile moieties. Isonitrile-containing metabolites have been reported from some species belonging to *Penicillium* and *Axinella* genera [30]. Several reports stated their characterization from *Acanthella*. It was reported that *A. cavernosa* (Dendy, 1922) can convert cyanide and thiocyanate for isocyanide and isothiocyanate biosynthesis, which could be attributed to the presence of rhodanese or the equivalent enzyme [31]. Therefore, thiocyanate was postulated to be the precursor for the isothiocyanate moiety in terpenes by direct utilization or oxidative desulphurization of cyanide, conversion to isocyanide terpenes, and reinsertion of sulfur [31].

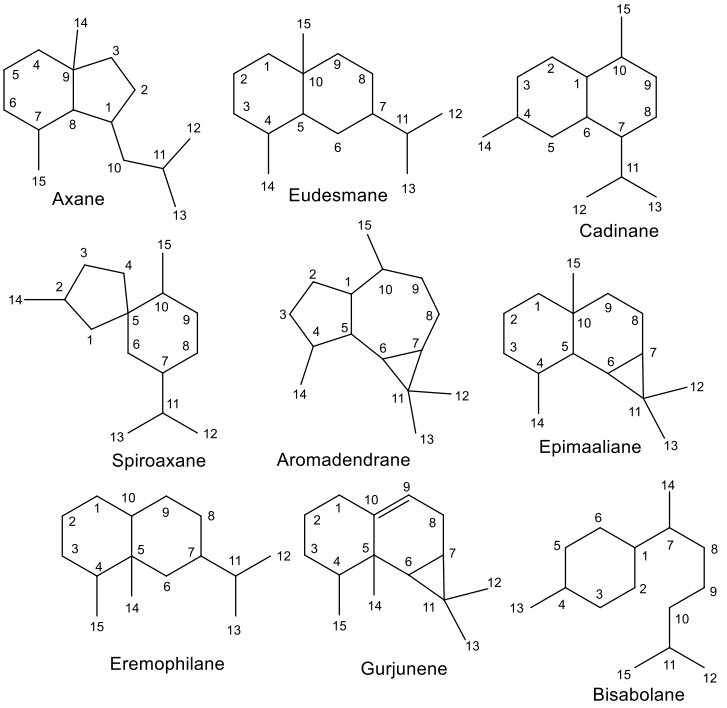


Figure 1. Classes of sesquiterpenes reported from the genus *Acanthella*.

Table 2. Sesquiterpenes from the genus *Acanthella* (molecular weight and formulae, chemical class, species, and sampling locations).

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
Aromadendrane-type sesquiterpenes					
Axisonitrile-2 (**1**)	231	$C_{16}H_{25}N$	*A. cavernosa*	Hachijo-Jima Island, Japan	[32]
(+)-Axamide 2 (**2**)	249	$C_{16}H_{27}NO$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
l-Isocyanoaromadendrane (**3**)	231	$C_{16}H_{25}N$	*A. acuta*	Near Banyuls, France	[34,35]
	-	-	*A. pulcherrima*	Weed Reef, Darwin, Australia	[35]
	-	-	*A. acuta*	Near Banyuls, France	[36]
	-	-	*A. cavernosa*	Tani's Reef, Mooloolaba, Australia	[37]
	-	-	*A. cavernosa*	Tani's Reef or Coral Gardens dive sites	[38]
Isonitrile 2 (**4**)	231	$C_{16}H_{25}N$	*A. acuta*	Bay of Naples, southern Italy	[39]
(+)-Axisothiocyanate 2 (**5**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Hachijo-jima Island, Japan	[40]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[41]
	-	-	*A. cavernosa*	Tani's Reef or Coral Gardens dive sites	[38]
l-Isothiocyanatearomadendrane (**6**)	263	$C_{16}H_{25}NS$	*A. acuta*	Near Banyuls, France	[36]
	-	-	*A. cavernosa*	Tani's Reef, Mooloolaba, Australia	[37]
1-Isocyanatearomadendrane (**7**)	247	$C_{16}H_{25}NO$	*A. acuta*	Near Banyuls, France	[36]
	-	-	*A. cavernosa*	Tani's Reef or Coral Gardens dive sites	[38]
1-Isothiocyanatoaromadendrane (**8**)	263	$C_{16}H_{25}NS$	*A. acuta*	Bay of Naples, southern Italy	[39]
	-	-	*A. cavernosa*	Tani's Reef or Coral Gardens dive sites	[38]
(+)-10*R*-Isothiocyanatoalloaromadendrane (**9**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Hachijo-jima Island, Japan	[40]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[41]
	-	-	*Acanthella* sp.	Yalong Bay, Hainan, China	[42]
	-	-	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
10α-Isothiocyanoalloaromadendrane (**10**)	263	$C_{16}H_{25}NS$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[35]
	-	-	*A. cavernosa*	Tani's Reef or Coral Gardens dive sites	[38]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[41]
	-	-	*A. cavernosa*	Tani's Reef, Mooloolaba, Australia	[37]
Ximaocavernosin O (**11**)	368	$C_{24}H_{36}N_2O$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
ent-4β,10α-Dihydroxyaromadendrane (**12**)	238	$C_{15}H_{26}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[43]
Palustrol (**13**)	222	$C_{15}H_{26}O$	*A. acuta*	Near Banyuls, France	[34]
	-	-	*A. acuta*	Near Banyuls, France	[36]
10*S*-Viridiflorol (**14**)	222	$C_{15}H_{26}O$	*A. cavernosa*	Hachijo-jima Island, Japan	[40]
10*R*-Viridiflorol (**15**)	222	$C_{15}H_{26}O$	*A. cavernosa*	Hachijo-jima Island, Japan	[40]
(+)-Ximaocavernosin P (**16**)	234	$C_{15}H_{22}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[43]
Spiroaxane-type sesquiterpenes					
Axisonitrile-3 (**17**)	231	$C_{16}H_{25}N$	*A. acuta*	Near Banyuls, France	[34]
	-	-	*A. cavernosa*	Thailand	[18]
	-	-	*A. klethra*	Pelorus Island, Queensland, Australia	[19]
	-	-	*A. klethra*	Vicinities of Phantom and Pelom Islands, Queensland, Australia	[44]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[31]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[45]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[41]
	-	-	*A. cavernosa*	Tani's Reef, Mooloolaba, Australia	[37]
Isonitrile 1 (**18**)	245	$C_{17}H_{27}N$	*A. acuta*	Bay of Naples, southern Italy	[39]
3-Oxoaxisonitrile-3 (**19**)	245	$C_{16}H_{23}NO$	*Acanthella* sp.	Ximao Sea, Hainan, China	[41]

Table 2. *Cont.*

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
Axisonitrile-4 (**20**)	231	$C_{16}H_{25}N$	*A. acuta*	Sidi Elghdamssi island, Monastir region, Tunisia	[25]
Axisocyanate-3 (**21**)	247	$C_{16}H_{25}NO$	*A. cavernosa*	Tani's Reef, Mooloolaba, Australia	[37]
(+)-Axisothiocyanate (**22**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
Axisothiocyanate 3 (**23**)	263	$C_{16}H_{25}NS$	*A. klethra*	Pelorus Island, Queensland, Australia	[19]
	-	-	*A. klethra*	Vicinities of Phantom and Pelom Islands, Queensland, Australia	[44]
	-	-	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[46]
	-	-	*A. cavernosa*	Hachijo-jima Island, Japan	[40]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[31]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[45]
Ximaocavernosin H (**24**)	277	$C_{16}H_{22}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
Ximaocavernosin I (**25**)	279	$C_{16}H_{25}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
Ximaocavernosin J (**26**)	279	$C_{16}H_{25}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
Ximaocavernosin K (**27**)	263	$C_{16}H_{25}NO_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
Ximaocavernosin L (**28**)	265	$C_{16}H_{27}NO_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
Ximaocavernosin M (**29**)	265	$C_{16}H_{27}NO_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
Ximaocavernosin N (**30**)	368	$C_{24}H_{36}N_2O$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
(–)-Axamide 3 (**31**)	249	$C_{16}H_{27}NO$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
Axamide 3 (**32**)	249	$C_{16}H_{27}NO$	*A. cavernosa*	Hachijo-jima Island, Japan	[40]
Isothiocyanate 1 (**33**)	277	$C_{17}H_{27}NS$	*A. acuta*	Bay of Naples, southern Italy	[39]
Eudesmane-type sesquiterpenes					
Acanthellin-1 (**34**)	231	$C_{16}H_{25}N$	*A. acuta*	Bay of Naples, southern Italy	[30]
	-	-	*A. acuta*	Near Banyuls, France	[34]
	-	-	*A. acuta*	Bay of Taranto near Porto Cesareo, Southern Italy	[47]
	-	-	*A. acuta*	Sidi Elghdamssi Island, Monastir region, Tunisia	[25]
Acanthene B (**35**)	263	$C_{16}H_{25}NS$	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[46]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[41]
	-	-	*A. cavernosa*	Tani's Reef or Coral Gardens dive sites	[38]
Acanthine B (**36**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
Acanthene C (**37**)	249	$C_{16}H_{27}NO$	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[46]
Axiriabiline A (**38**)	249	$C_{16}H_{27}NO$	*A. cavernosa*	Xidao Island, Hainan, China	[48]
6α-Isocyano-5αH,7αH,10α-eudesm-4(14)-ene) (**39**)	231	$C_{16}H_{25}N$	*A. acuta*	Bay of Taranto near Porto Cesareo, Southern Italy	[47]
	-	-	*A. acuta*	Bay of Naples, southern Italy	[39]
11-Isocyano-7βH-eudesm-5-ene (**40**)	231	$C_{16}H_{25}N$	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[46]
11-Formamido-7βH-eudesm-5-ene (**41**)	249	$C_{16}H_{27}NO$	*A. cavernosa*	Xidao Island, Hainan, China	[48]
11-Isothiocyano-7βH-eudesm-5-ene (**42**)	263	$C_{16}H_{25}NS$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[35]
	-	-	*A. klethra*	Pelorus Island, Queensland, Australia	[19]

Table 2. *Cont.*

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
	-	-	*A. klethra*	Vicinities of Phantom and Pelom Islands, Queensland, Australia	[44]
	-	-	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[46]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[31]
6α-Isothiocyano-5αH,7αH,10α-eudesm-4(14)-ene (**43**)	263	$C_{16}H_{25}NS$	*A. acuta*	Bay of Taranto near Porto Cesareo, Southern Italy	[47]
	-	-	*A. acuta*	Bay of Naples, southern Italy	[39]
	-	-	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[46]
(l*R*,5*R*,6*R*,8*R*)-Dec[4.4.0]ane-1,5-dimethyl-8-(1′-methylethenyl)-5-isothiocyanate (**44**)	263	$C_{16}H_{25}NS$	*A. klethra*	Pelorus Island, Queensland, Australia	[19]
	-	-	*A. klethra*	Vicinities of Phantom and Pelom Islands, Queensland, Australia	[44]
	-	-	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[46]
(l*R*,5*R*,6*R*,8*S*)-Dec[4.4.0]ane-1,5-dimethyl-8-(1′-methylethenyl)-5-isothiocyanate (**45**)	263	$C_{16}H_{25}NS$	*A. klethra*	Pelorus Island, Queensland, Australia	[19]
	-	-	*A. klethra*	Vicinities of Phantom and Pelom Islands, Queensland, Australia	[44]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[45]
Cadinene-type sesquiterpenes					
10-Isothiocyanato-4-cadinene (**46**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[45]
	-	-	*A. cavernosa*	Tani's Reef or Coral Gardens dive sites	[38]
10-Isothiocyanato-4-amorphene (**47**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[45]
	-	-	*A. cavernosa*	Several locations off the Japanese coast	[49]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[41]
	-	-	*A. cavernosa*	Tani's Reef or Coral Gardens dive sites	[38]
Isomer-10-isothiocyanato-4-amorphene (**48**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[45]
(+)-Ximaocavernosin A (**49**)	295	$C_{16}H_{25}NO_2S$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[43]
(±)-Ximaocavernosin A (**50**)	279	$C_{16}H_{25}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
(±)-Ximaocavernosin B (**51**)	279	$C_{16}H_{25}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
(±)-Ximaocavernosin C (**52**)	279	$C_{16}H_{25}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
(+)-Ximaocavernosin D (**53**)	293	$C_{17}H_{27}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
(±)-Ximaocavernosin E (**54**)	295	$C_{16}H_{25}NO_2S$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
(+)-Ximaocavernosin F (**55**)	309	$C_{17}H_{27}NO_2S$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
(±)-Ximaocavernosin G (**56**)	277	$C_{16}H_{23}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
(±)-Axinisothiocyanate J (**57**)	279	$C_{16}H_{25}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
(±)-Axinisothiocyanate D (**58**)	295	$C_{16}H_{25}NO_2S$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]

Table 2. *Cont.*

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
Axinisothiocyanate A (**59**)	295	$C_{16}H_{25}NO_2S$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[33]
ent-Epicubenol (**60**)	222	$C_{15}H_{26}O$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[35]
Isothiocyanate 4 (**61**)	263	$C_{16}H_{25}NS$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[35]
Epipolasin-A enantiomer-2 (**62**)	263	$C_{16}H_{25}NS$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[35]
10α-Isocyano-4-amorphene (**63**)	231	$C_{16}H_{25}N$	*A. cavernosa*	Hachijo-Jima Island, Japan	[32]
	-	-	*A. cavernosa*	Several locations off the Japanese coast	[49]
10-Isocyano-4-cadinene (**64**)	231	$C_{16}H_{25}N$	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[45]
	-	-	*A. cavernosa*	Several locations off the Japanese coast	[49]
	-	-	*A. cavernosa*	Tani's Reef or Coral Gardens dive sites	[38]
10-Formamido-4-cadinene (**65**)	249	$C_{16}H_{27}NO$	*A. cavernosa*	Several locations off the Japanese coast	[49]
	-	-	*A. cavernosa*	Xidao Island, Hainan, China	[48]
(+)-α-Muurolene (**66**)	204	$C_{15}H_{24}$	*A. cavernosa*	Hachijo-jima Island, Japan	[40]
T-cadinol (**67**)	222	$C_{15}H_{26}O$	*A. cavernosa*	Several locations off the Japanese coast	[49]
(+)-Maninsigin D (**68**)	234	$C_{15}H_{22}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[43]
	234	$C_{15}H_{22}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[43]
(-)-Maninsigin D (**69**)	234	$C_{15}H_{22}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[43]
(+)-Ximaocavernosin Q (**70**)	234	$C_{15}H_{22}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[43]
(-)-Ximaocavernosin Q (**71**)	234	$C_{15}H_{22}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[43]
Cadalene (**72**)	198	$C_{15}H_{18}$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[43]
trans-4,5-Dihydroxycorocalane (**73**)	234	$C_{15}H_{22}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[43]
Axane-type sesquiterpenes					
Cavernoisonitrile (**74**)	245	$C_{16}H_{23}NO$	*A. cavernosa*	Hachijo-Jima Island, Japan	[32]
(-)-Cavernothiocyanate (**75**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Hachijo-Jima Island, Japan	[32]
	-	-	*A. cavernosa*	Hachijo-jima Island, Japan	[40]
1β-H,7α-methyl,8α-H,9β-methyl-Cavernothiocyanate (**76**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Hachijo-jima Island, Japan	[40]
Bisabolene-type sesquiterpenes					
7-Isocyano-7,8-dihydro-α-bisabolene (**77**)	231	$C_{16}H_{25}N$	*A. cavernosa*	Hachijo-Jima Island, Japan	[32]
Epimaaliane-type sesquiterpenes					
(+)-Epipolasin-A (**78**)	263	$C_{16}H_{25}NS$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[35]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[31]
Epipolasin-A enantiomer-1 (**79**)	263	$C_{16}H_{25}NS$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[35]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[41]
5-Formamide-isonitrile (**80**)	249	$C_{16}H_{27}NO$	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[46]
Isonitrile 4 (**81**)	231	$C_{16}H_{25}N$	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[46]
Maaliol (**82**)	222	$C_{15}H_{26}O$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[35]
Acanthene A (**83**)	240	$C_{15}H_{25}Cl$	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[46]
Gurjunene					
(+)-Aristolone (**84**)	218	$C_{15}H_{22}O$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[43]
	-	-	*A. cavernosa*	South China Sea	[50]
(+)-9-Aristolene (**85**)	204	$C_{15}H_{24}$	*A. cavernosa*	Hachijo-jima Island, Japan	[40]

Table 2. *Cont.*

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
Isonitrile 3 (**86**)	231	$C_{16}H_{25}N$	*A. acuta*	Bay of Naples, southern Italy	[39]
Isothiocyanate 3 (**87**)	263	$C_{16}H_{25}NS$	*A. acuta*	Bay of Naples, southern Italy	[39]

3.1.1. Aromadendrane-Type Sesquiterpenes

In 1987, l-isocyanoaromadendrane (**3**) was reported as a novel isonitrile sesquiterpene from the fish toxic CH_2Cl_2 fraction of *A. acuta* using SiO_2CC (silica gel column chromatography), assigned by spectral and chemical methods [34].

Furthermore, **5** and **9** were isolated from Japanese *A. cavernosa* by SiO_2 CC and RP-HPLC and identified by different spectroscopic methods [40]. Ximaocavernosin O (**11**) was isolated from an *A. cavernosa* Et_2O fraction using silica gel/MCI/Sephadex LH-20/(RP)-HPLC/chiral-phase HPLC and was characterized by spectroscopy, X-ray diffraction, and QM-NMR analyses as well as Mosher's method and TDDFT-ECD calculations [33]. Compound **11** is similar to **2** and was formerly reported from nudibranch *Hexabranchus sanguineus* with a C-10 phenyl urea fragment instead of a C-10 formamide in **2** [33]. New aromadendrane-type sesquiterpenoids, **16** and **12**, were purified from the Hainan *A. cavernosa* using SiO_2/Sephadex LH-20 CC/chiral-phase HPLC by Shen et al.. Their configurations were elucidated based on spectral, TDDFT-ECD, and X-ray analyses and optical rotation measurements. Compound **16** with a 2S/4S/5R/6S/7S configuration ($[\alpha]_D$ +169.6]) is identical to 2β-hydroxyaromadendr-1(10)-en-9-one ($[\alpha]_D$ −186]) except for the optical rotation (Figure 2) [33].

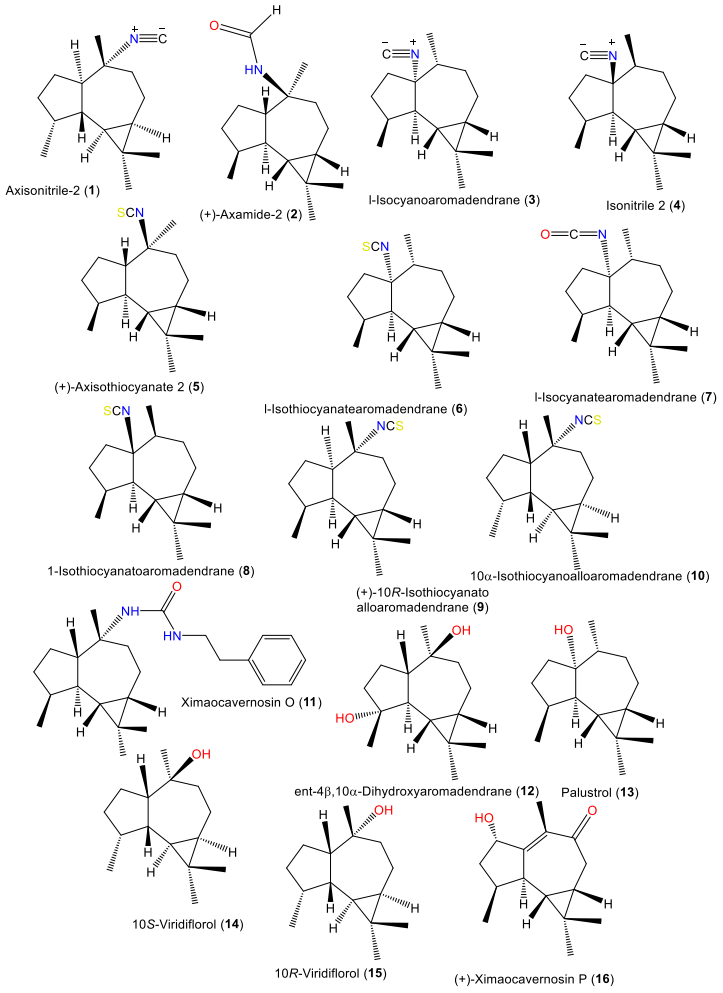


Figure 2. Aromadendrane-type sesquiterpenes (**1**–**16**) reported from the genus *Acanthella*.

3.1.2. Spiroaxane-Type Sesquiterpenes

Spiroaxane skeletons containing sesquiterpenes are of rare natural occurrence. Compound **19**, a new sesquiterpene isocyanide with a spiroaxane (spiro [5,6] decane) skeleton was obtained from Chinese *Acanthella* sp., which is a 3-oxo derivative of **17** [41]. Additionally, **23** is a spiroaxane sesquiterpene with a C-6 isocyanate and was purified and characterized by Jumaryatno et al. from *A. cavernosa* specimens collected from Coral gardens/Gneerings reef/Mooloolaba/Australia and from *A. klethra* collected from Pelorus Island, Queensland, in addition to **17** [19,37].

Additionally, **23**–**30** were isolated from *A. cavernosa* Et_2O fractions using silica gel/MCI /Sephadex LH-20/(RP)-HPLC/chiral-phase HPLC and characterized by spectral, X-ray diffraction, and QM-NMR analyses as well as Mosher's method and TDDFT-ECD calculations [33]. Compounds **23**–**30** are spiroaxane derivatives involving compounds with C-6 isothiocyanate (e.g., **23**–**25**) and formamide or a 1-phenethyl urea fragment (e.g., **26**–**30**) [33] (Figure 3). In 2019, Wu et al. reported the purification of axamide-3 (**32**) from the acetone fraction of *A. cavernosa* collected from Xidao Island (Hainan Province, China) which was characterized by NMR spectral data and optical rotation [48].

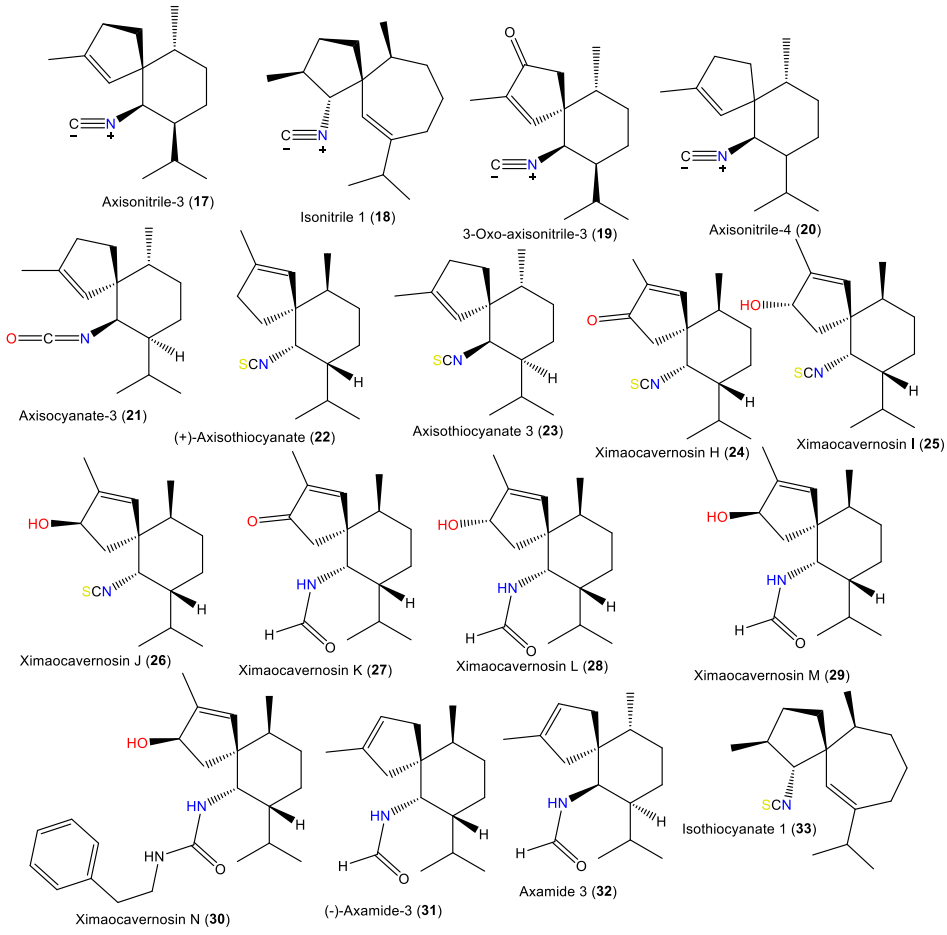


Figure 3. Spiroaxane-type sesquiterpenes (**17**–**33**) reported from the genus *Acanthella*.

3.1.3. Eudesmane-Type Sesquiterpenes

Acanthellin-1 (**34**) is a bicyclic sesquiterpene with isopropylidene and isonitrile moieties. It was separated as an optically active oil from the ether fraction of the acetone extract of *A. acuta* collected from the Bay of Naples using SiO_2CC, and was characterized by NMR and chemical methods, as well as optical rotation [30] (Figure 4). A chromatographic investigation of *A. klethra* collected from Pelorus Island, Queensland, yielded sesquiterpenoids with isothiocyanate and isonitrile groups, i.e., **42**, **44**, and **45**, that were assigned by spectral

and X-ray analyses. Compounds **42**, **44**, and **45** are of eudesmane-type and are related to **34**. Compounds **45** and **44** are different in stereo-configuration at C-7 [19,44]. Additionally, **39** and **43** are in the bicyclic cis-eudesmane class of sesquiterpenes, possessing isocyanate and isothiocyanate functionalities, respectively, and were purified and specified from *A. acuta* [47], whereas **35** is a stereoisomer of **5** [46].

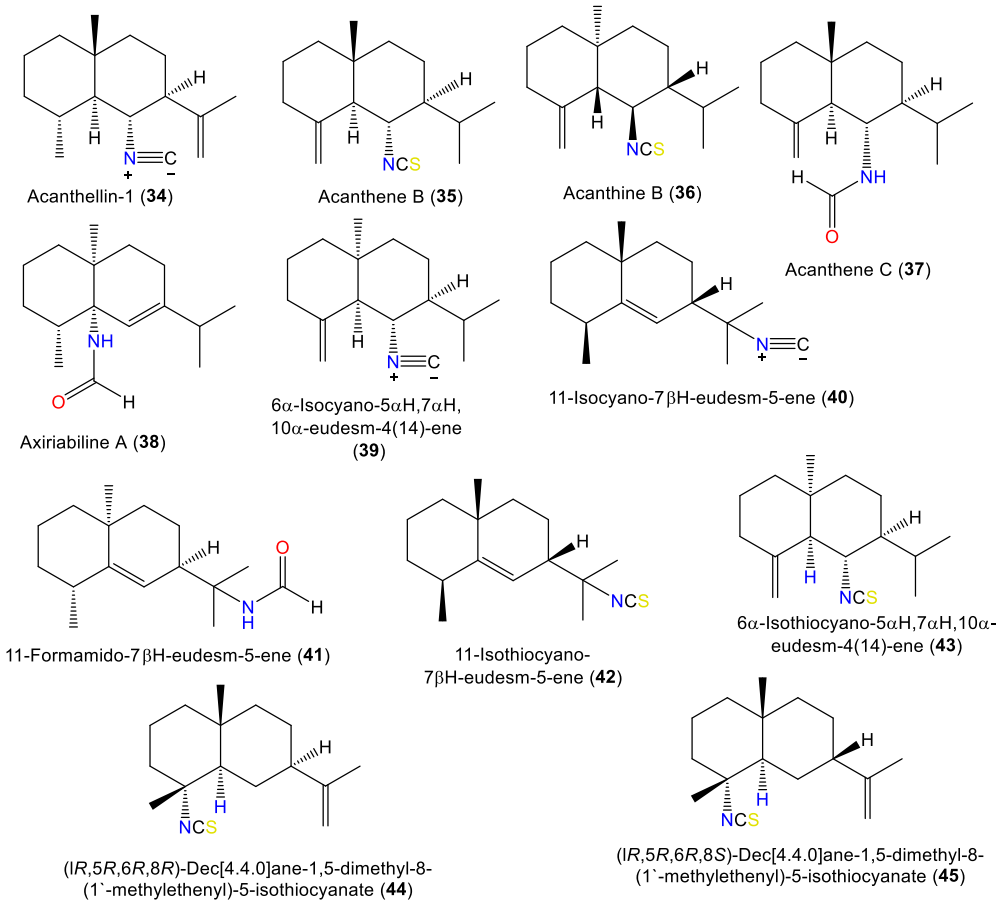


Figure 4. Eudesmane-type sesquiterpenes (**34**–**45**) reported from the genus *Acanthella*.

Axiriabiline A (**38**) was obtained from the acetone fraction of *A. cavernosa* collected from Xidao Island (Hainan Province, China) and characterized by NMR spectral data and optical rotation [48]. Burgoyne et al. (1993) purified two new sesquiterpenoid acanthenes B and C (**35** and **37**) along with **40** and **42**–**44** from the hexane fraction of unidentified *Acantbella* species using SiO_2 flash CC/HPLC. The compounds were characterized by spectral analyses [46].

3.1.4. Cadinene-Type Sesquiterpenes

In 2000, Clark et al. isolated a new sesquiterpene, **46**, that has a 1R/6R/7S/10R configuration and C-10 isothiocyanato functionality and $[\alpha]_D$ +3 [45]. In addition, Nogata et al. purified a new sesquiterpene, **65**, and the known **67** from *A. cavernosa* EtOH extracts utilizing SiO_2/Sephadex LH-20/ODS HPLC. These compounds were assigned based on spectral data and chemical transformations [49] (Figure 5). Compound **65** has a C-10 formamido functionality instead of the C-10-OH in **67** [49].

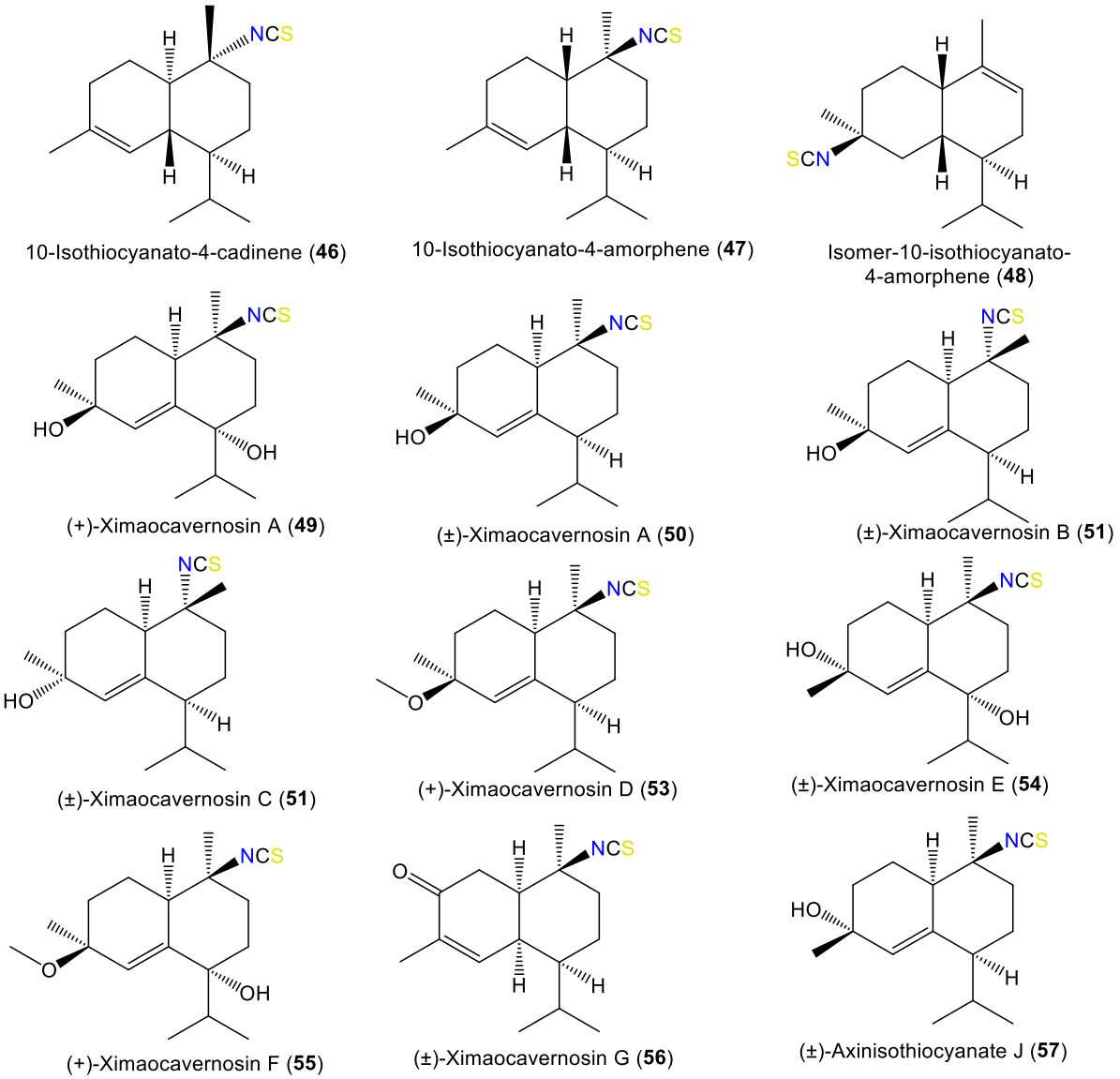


Figure 5. Cadinene-type sesquiterpenes (**46**–**57**) reported from the genus *Acanthella*.

New cadinane-type sesquiterpenoids, ximaocavernosins A–G (**49**–**56**), were isolated from *A. cavernosa* Et_2O fractions using SiO_2/MCI/Sephadex LH-20/(RP)-HPLC/chiral-phase HPLC and characterized by spectroscopy, X-ray diffraction, and QM-NMR analyses as well as Mosher's method and TDDFT-ECD calculations [33]. Compounds **49**–**56** have cadinane frameworks with a $\Delta^{5,6}$ double bond and a C-10 isothiocyanate but differ in stereochemistry and oxidation patterns [33]**.** In 2019, Wu et al. reported the purification of 10-formamido-4-cadinene (**65**) from the acetone fraction of *A. cavernosa* collected from Xidao Island (Hainan Province, China), which was characterized by NMR spectral data and optical rotation [48]. New cadinane-type sesquiterpenoids, **49** and **68**–**73**, were purified from Hainan *A. cavernosa* using SiO_2/Sephadex LH-20 CC/chiral-phase HPLC (Figure 6). Their configurations were elucidated based on spectral, TDDFT-ECD, and X-ray analyses and optical rotation measurements. Maninsigin D and ximaocavernosin Q were obtained as racemic forms, which were separated into their enantiomers [(+)-**68**/(−)-**69** and (+)-**70**/(−)-**71**] using chiral-phase HPLC [43].

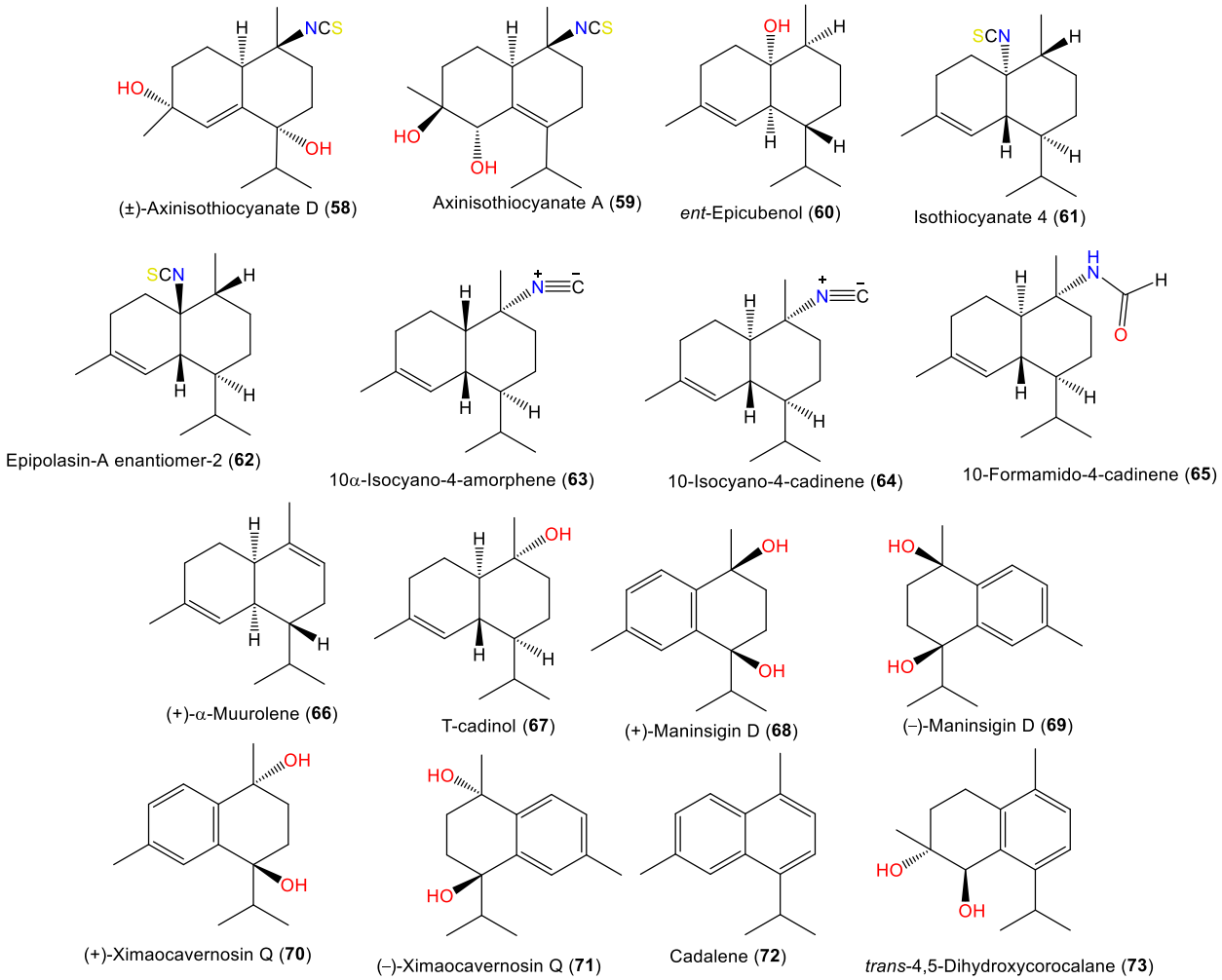


Figure 6. Cadinene-type sesquiterpenes (**58**–**73**) reported from the genus *Acanthella*.

3.1.5. Other Sesquiterpenes

New axane sesquiterpenoids, **74** and **75**, in addition to **77**, were separated from the antifungal hexane fraction of *A. cavernosa* collected from the Hachijo-Jima Islands using flash CC/sephadex LH-20/HPLC. They were elucidated based on spectral data [23]. Compound **74** is a rare oxygenated tricyclic sesquiterpene cyanide belonging to axane-type sesquiterpenes [23]. Furthermore, **66**, **75, 76**, and **85** were isolated by SiO_2 CC and RP-HPLC and identified by alpha-D, spectral data, and chemical methods from Japanese *A. cavernosa* [40]. Additionally, the new epimaaliane sesquiterpene **79**, along with **78**, were specified from the antimicrobial acetone extracts of *A. pulcherrima* using spectral and optical rotation measurements. Compound **79** is an enantiomer of **78** with an opposite $[\alpha]_D$ value and differs at the ring junction [35]. Burgoyne et al. purified epimaaliane-type sesquiterpenes **80** and **81** from the hexane fraction of an unidentified *Acantbella* species using SiO_2 flash CC and HPLC. The compounds were characterized by spectral analyses [46] (Figure 7).

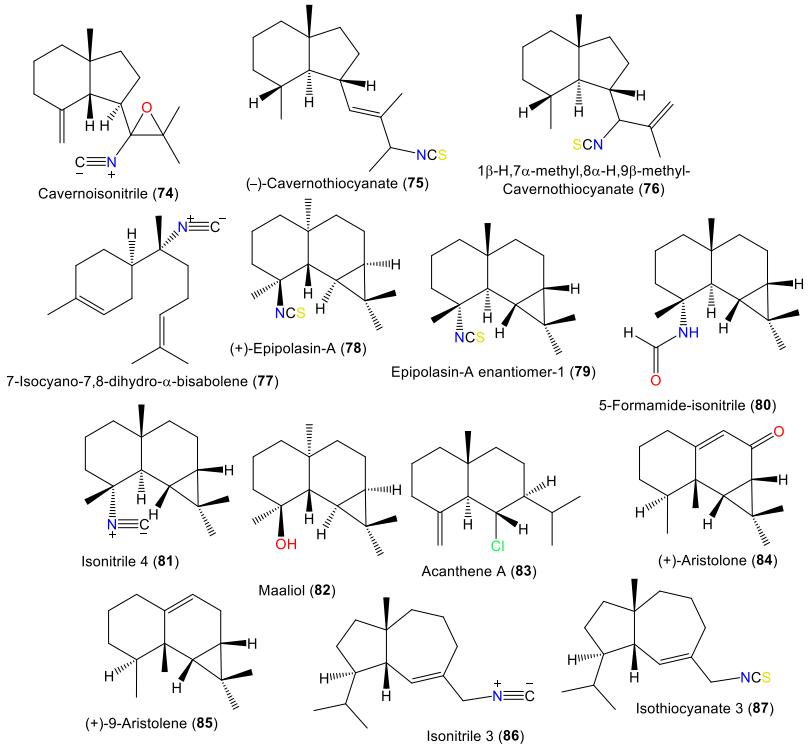
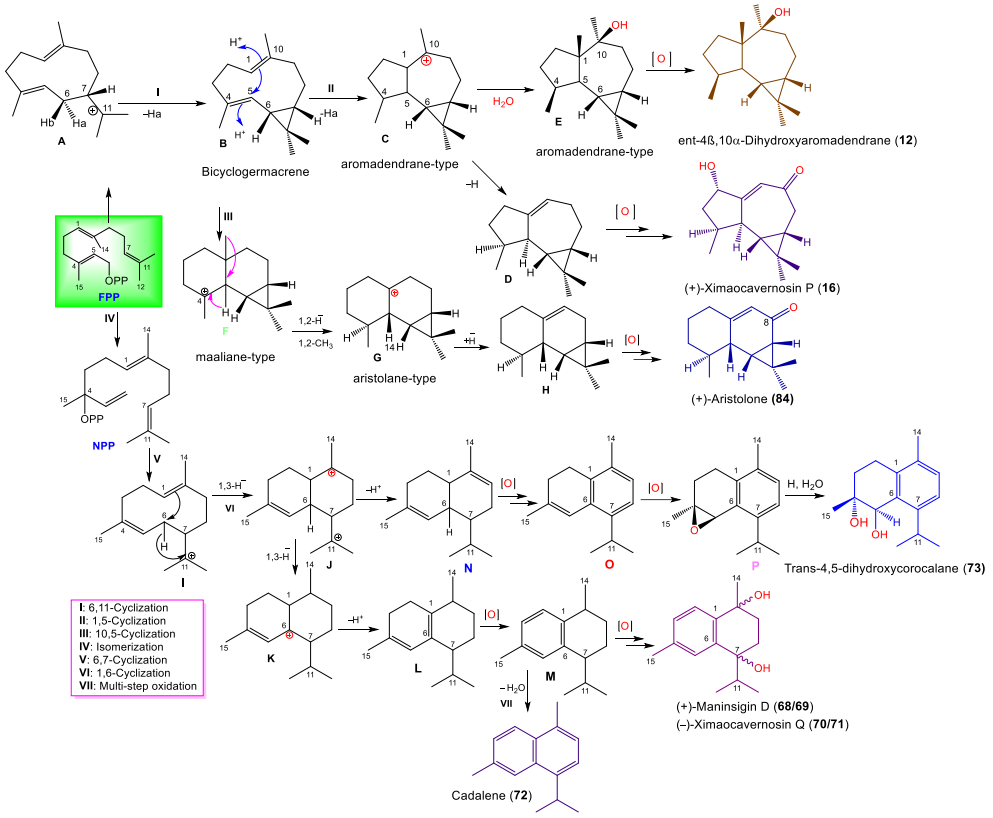


Figure 7. Other sesquiterpenes (**74**–**87**) reported from the genus *Acanthella*.

Notably, Shen et al. proposed that **12, 16**, **49**, **68–73**, and **84** originate from E,E-farnesyl diphosphate (E,E-FPP), as illustrated in Scheme 1 [43].



Scheme 1. Biosynthesis pathway of **12, 16**, **49**, **68–73**, and **84** [43].

3.2. Diterpenoids

Diterpenoids are among the common metabolites reported from various *Acanthella* species. These compounds are characterized by the existence of nitrogenous functionalities such as isothiocyanato, isocyano, and/or formamido groups. These diterpenes are classified into two major classes, kalihinanes and biflorane derivatives, according to the 8C side chain (Figure 8 and Table 3). Kalihinanes have a decalin frame structure with C-7-attached dihydropyran, tetrahydropyran, or tetrahydofuran moiety. Additionally, these rings may carry various substituents such as OH, Cl, isothiocyanato, isocyano, and formamido groups or chlorine. They include kalihinenes, kalihinols, and kalihipyranes. Kalihinols are spilt into two main categories, tetrahydrofuran (**I**) and tetrahydropyran (**II**) groups, according to the C-7 substitution. Commonly, they have *trans*-decalin framework with a C-4 or C-5 tertiary alcohol and an isocyanate moiety at C-10 and/or C-5. The first group has a tetrahydrofuran moiety featuring NCS, NC, or Cl at C-15, or the gem-dimethyl is substituted by an isopropenyl moiety, whereas the tetrahydropyran group possesses Cl atom at C-14. Kalihinenes have a Δ^4-trisubstituted double bond and possess similar structural features to kalihinols, while biflorane diterpenoids are a class of kalihinane diterpenes featuring a linear eight-carbon open chain substituent at C-7. Biosynthetically, these metabolites are proposed to result from the cyclization of the biflorane skeleton (trans or cis form) and geranylgeranyl pyrophosphate [51]. Their stereochemistry has been determined using spectroscopic, X-ray and/or CD analyses, as well as chemical and computational methods.

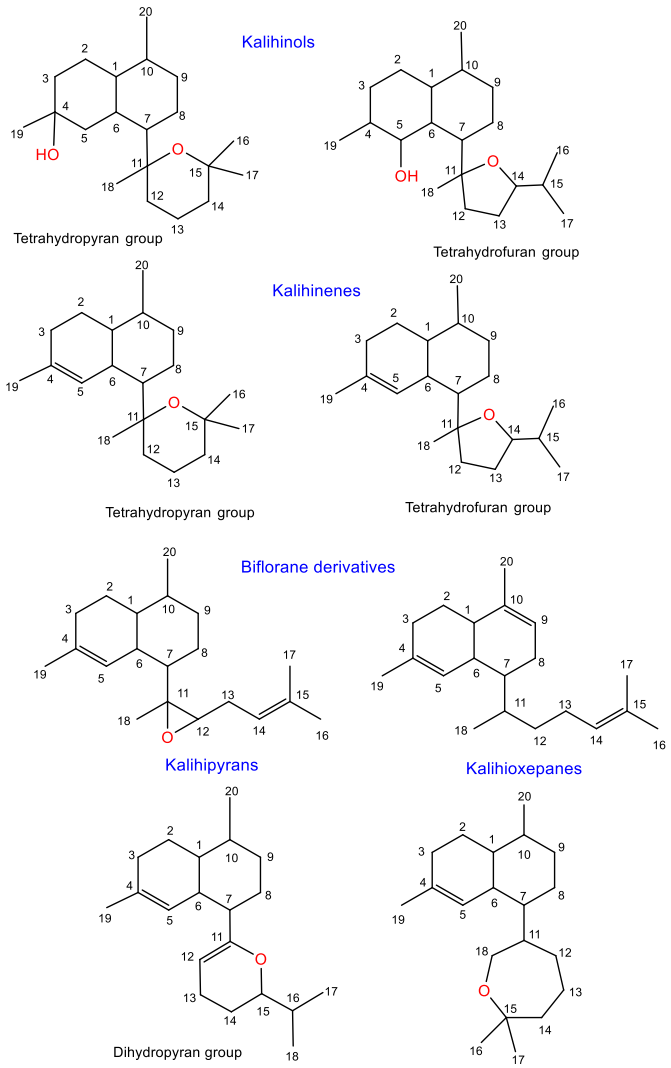


Figure 8. Classes of diterpenes reported from genus *Acanthella*.

Table 3. Diterpenes from the genus *Acanthella* (molecular weight and formulae, chemical class, species, and sampling locations).

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
Kalihinols					
Kalihinol A (**88**)	392	$C_{22}H_{33}ClN_2O_2$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[52]
	-	-	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[22]
	-	-	*A. caruenosa*	Fiji, South Pacific Ocean	[53]
	-	-	*A. klethra*	Kuchinoerabu Island of the Satsunan Archipelago, Japan	[23]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
	-	-	*A. cavernosa*	Fiji, South Pacific Ocean	[51]
	-	-	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[55,56]
	-	-	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japa	[57]
	-	-	*A. cavernosa*	Dibud, Philippines	[21]
	-	-	*A. cavernosa*	Shallow water reef in Sanya Bay, Hainan Island, China	[58]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[41]
	-	-	*Acanthella* sp.	Yalong Bay, Hainan, China	[42]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[16]
	-	-	*A. cavernosa*	South China Sea	[50]
trans 10β-Formamidokalihinol A (**89**)	410	$C_{22}H_{35}ClN_2O_3$	*A. cavernosa*	Hachijo-jima Island, Japan	[40]
	-	-	*A. cavernosa*	Shallow water reef in Sanya Bay, Hainan Island, China	[58]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[16]
cis 10β-Formamidokalihinol A (**90**)	410	$C_{22}H_{35}ClN_2O_3$	*A. cavernosa*	Shallow water reef in Sanya Bay, Hainan Island, China	[58]
10β-Formamido-5-isocyanatokalihinol A (**91**)	426	$C_{22}H_{35}ClN_2O_4$	*A. cavernosa*	Hachijo-jima Island, Japan	[40]
	-	-	*A. cavernosa*	Xidao Island, Hainan, China	[48]
10β-Formamido-5β-isothiocyanatokalihinol A (**92**)	442	$C_{22}H_{35}ClN_2O_3S$	*A. cavernosa*	Hachijo-jima Island, Japan	[40]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[16]
	-	-	*A. cavernosa*	Xidao Island, Hainan, China	[48]
Bisformamidokalihinol A (**93**)	428	$C_{22}H_{37}ClN_2O_4$	*A. cavernosa*	Xidao Island, Hainan, China	[48]
Kalihinol B (**94**)	392	$C_{22}H_{33}ClN_2O_2$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[22]
	-	-	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[46]
	-	-	*A. klethra*	Kuchinoerabu Island of the Satsunan Archipelago, Japan	[23]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
Isokalihinol B (**95**)	392	$C_{22}H_{33}ClN_2O_2$	*A. klethra*	Kuchinoerabu Island of the Satsunan Archipelago, Japan	[23]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
	-	-	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[59]
Kalihinol C (**96**)	328	$C_{20}H_{28}N_2O_2$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[22]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
Kalihinol D (**97**)	392	$C_{22}H_{33}ClN_2O_2$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[22]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
	-	-	*Acanthella* sp.	Yalong Bay, Hainan, China	[42]
Kalihinol E (**98**)	392	$C_{22}H_{35}ClN_2O_3$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[22]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
	-	-	*A. cavernosa*	Hachijo-jima Island, Japan	[40]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[16]
	-	-	*A. cavernosa*	South China Sea	[50]
10β-Formamidokalihinol E (**99**)	410	$C_{22}H_{33}ClN_2O_2$	*A. cavernosa*	Hachijo-jima Island, Japan	[40]
Kalihinol F (**100**)	383	$C_{23}H_{33}N_3O_2$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[22]
	-	-	*A. caruenosa*	Fiji, South Pacific Ocean	[53]
	-	-	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[60]
	-	-	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[46]
	-	-	*A. klethra*	Kuchinoerabu Island of the Satsunan Archipelago, Japan	[23]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
	-	-	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[59]
	-	-	*Acanthella* sp.	Coast of Cape Sada, Ehime Prefecture, Japan	[61]
	-	-	*A. cavernosa*	Dibud, Philippines	[21]

Table 3. *Cont.*

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
Isokalihinol F (**101**)	383	$C_{23}H_{33}N_3O_2$	*A. cavernosa*	Fiji, South Pacific Ocean	[53]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
	-	-	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[59]
	-	-	*A. cavernosa*	Fiji, South Pacific Ocean	[51]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[45]
8-Hydroxy-isokalihinol F (**102**)	399	$C_{23}H_{33}N_3O_3$	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[45]
10-*epi*-Isokalihinol F (**103**)	383	$C_{23}H_{33}N_3O_2$	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[59]
trans 10-Formamido-kalihinol F (**104**)	401	$C_{23}H_{35}N_3O_3$	*A. cavernosa*	Dibud, Philippines	[21]
cis 10-Formamido-kalihinol F (**105**)	401	$C_{23}H_{35}N_3O_3$	*A. cavernosa*	Dibud, Philippines	[21]
trans 15-Formamido-kalihinol F (**106**)	401	$C_{23}H_{35}N_3O_3$	*A. cavernosa*	Dibud, Philippines	[21]
cis 15-Formamido-kalihinol F (**107**)	401	$C_{23}H_{35}N_3O_3$	*A. cavernosa*	Dibud, Philippines	[21]
Kalihinol G (**108**)	415	$C_{23}H_{33}N_3O_2S$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[22]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
	-	-	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[57]
	-	-	*A. cavernosa*	Dibud, Philippines	[21]
10-Isothiocyanatokalihinol G (**109**)	447	$C_{23}H_{33}N_3O_2S_2$	*A. cavernosa*	Xisha Islets, South China Sea	[16]
5,10-*bis*-Isothiocyanatokalihinol G (**110**)	479	$C_{23}H_{33}N_3O_2S_3$	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[57]
Kalihinol H (**111**)	415	$C_{23}H_{33}N_3O_2S$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[22]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
	-	-	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[57]
Isokalihinol H (**112**)	415	$C_{23}H_{33}N_3O_2S$	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[59]
10-*epi*-Isokalihinol H (**113**)	415	$C_{23}H_{33}N_3O_2S$	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[59]
Kalihinol I (**114**)	456	$C_{22}H_{33}ClN_2O_2S_2$	*A. cavernosa*	Thailand	[18]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
	-	-	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[57]
10-*epi*-Kalihinol I (**115**)	456	$C_{22}H_{33}ClN_2O_2S_2$	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[57]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[16]
	-	-	*A. cavernosa*	South China Sea	[50]
Kalihinol J (**116**)	442	$C_{22}H_{35}ClN_2O_3S$	*A. cavernosa*	Thailand	[18]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
	-	-	*A. cavernosa*	Dibud, Philippines	[21]
Kalihinol M (**117**)	442	$C_{22}H_{35}ClN_2O_3S$	*A. cavernosa*	Xisha Islets, South China Sea	[16]
Kalihinol N (**118**)	442	$C_{22}H_{35}ClN_2O_3S$	*A. cavernosa*	Xisha Islets, South China Sea	[16]
Kalihinol O (**119**)	424	$C_{22}H_{33}ClN_2O_2S$	*A. cavernosa*	Xisha Islets, South China Sea	[16]
Kalihinol P (**120**)	424	$C_{22}H_{33}ClN_2O_2S$	*A. cavernosa*	Xisha Islets, South China Sea	[16]
Kalihinol Q (**121**)	424	$C_{22}H_{33}ClN_2O_2S$	*A. cavernosa*	Xisha Islets, South China Sea	[16]
Kalihinol R (**122**)	456	$C_{22}H_{33}ClN_2O_2S_2$	*A. cavernosa*	Xisha Islets, South China Sea	[16]
Kalihinol S (**123**)	410	$C_{22}H_{35}ClN_2O_3$	*A. cavernosa*	Xisha Islets, South China Sea	[16]
Kalihinol T (**124**)	424	$C_{22}H_{33}ClN_2O_2S$	*A. cavernosa*	Xisha Islets, South China Sea	[16]
Kalihinol X (**125**)	424	$C_{22}H_{33}ClN_2O_2S$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[22]
	-	-	*A. cavernosa*	Fiji, South Pacific Ocean	[53]
	-	-	*A. cavernosa*	Thailand	[18]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
	-	-	*A. cavernosa*	Dibud, Philippines	[21]
	-	-	*Acanthella* sp.	Yalong Bay, Hainan, China	[42]
10-*epi*-Kalihinol X (**126**)	424	$C_{22}H_{33}ClN_2O_2S$	*Acanthella* sp.	Yalong Bay, Hainan, China	[42]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[16]
	-	-	*A. cavernosa*	South China Sea	[50]
Kalihinol Y (**127**)	365	$C_{21}H_{32}ClNO_2$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[22]
	-	-	*Acanthella caruenosa*	Fiji, South Pacific Ocean	[53]
	-	-	*A. cavernosa*	Thailand	[18]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
	-	-	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[57]
	-	-	*A. cavernosa*	Dibud, Philippines	[21]
Kalihinone Ya (**128**)	367	$C_{20}H_{30}ClNO_3$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[22]
Δ^9-Kalihinol Y (**129**)	365	$C_{21}H_{32}ClNO_2$	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[57]
Kalihinol Z (**130**)	392	$C_{22}H_{33}ClN_2O_2$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[22]
	-	-	*A. cavernosa*	Fiji, South Pacific Ocean	[53]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
Kalihiacyloxyamide A (**131**)	468	$C_{25}H_{41}ClN_2O_4$	*A. cavernosa*	Xisha Island, South China Sea	[62]
Kalihiacyloxyamide B (**132**)	468	$C_{25}H_{41}ClN_2O_4$	*A. cavernosa*	Xisha Island, South China Sea	[62]
Kalihiacyloxyamide C (**133**)	552	$C_{30}H_{49}ClN_2O_5$	*A. cavernosa*	Xisha Island, South China Sea	[62]
Kalihiacyloxyamide D (**134**)	552	$C_{30}H_{49}ClN_2O_5$	*A. cavernosa*	Xisha Island, South China Sea	[62]
Kalihiacyloxyamide E (**135**)	586	$C_{33}H_{47}ClN_2O_5$	*A. cavernosa*	Xisha Island, South China Sea	[62]
Kalihiacyloxyamide F (**136**)	586	$C_{33}H_{47}ClN_2O_5$	*A. cavernosa*	Xisha Island, South China Sea	[62]

Table 3. *Cont.*

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
Kalihiacyloxyamide G (**137**)	518	$C_{30}H_{50}N_2O_5$	*A. cavernosa*	Xisha Island, South China Sea	[62]
Kalihiacyloxyamide H (**138**)	518	$C_{30}H_{50}N_2O_5$	*A. cavernosa*	Xisha Island, South China Sea	[62]
Kalihinene					
Kalihinene (**139**)	340	$C_{22}H_{32}N_2O$	*A. klethra*	Kuchinoerabu Island of the Satsunan Archipelago, Japan	[23]
	-	-	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[59]
	-	-	*A. cavernosa*	Fiji, South Pacific Ocean	[51]
	-	-	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[57]
	-	-	*A. cavernosa*	Dibud, Philippines	[21]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[41]
1-*epi*-Kalihinene (**140**)	340	$C_{22}H_{32}N_2O$	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[59]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[45]
15-Isothiocyanato-l-epi-kalihinene (**141**)	372	$C_{22}H_{32}N_2OS$	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[59]
1,10-di*epi*-Kalihinene (**142**)	340	$C_{22}H_{32}N_2O$	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[59]
Kalihinene A (**143**)	340	$C_{22}H_{32}N_2O$	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[63]
Kalihinene B (**144**)	340	$C_{22}H_{32}N_2O$	*A. cavernosa*	Seychelles and Desnceufs Islands	[54]
Kalihinene E (**145**)	367	$C_{21}H_{34}ClNO_2$	*A. cavernosa*	Xisha Islets, South China Sea	[63]
Kalihinene F (**146**)	331	$C_{21}H_{33}NO_2$	*A. cavernosa*	Xisha Islets, South China Sea	[63]
Kalihinene X (**147**)	367	$C_{21}H_{34}ClNO_2$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[55,56]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[63]
Kalihinene Y (**148**)	367	$C_{21}H_{34}ClNO_2$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[55,56]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[63]
Kalihinene Z (**149**)	367	$C_{21}H_{34}ClNO_2$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[55,56]
10-Formamidokalihinene (**150**)	358	$C_{22}H_{34}N_2O_2$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[55,56]
	-	-	*A. cavernosa*	Fiji, South Pacific Ocean	[51]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[63]
15-Formamidokalihinene (**151**)	358	$C_{22}H_{34}N_2O_2$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[55]
	-	-	*A. cavernosa*	Fiji, South Pacific Ocean	[51]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[63]
10,l5-*bis*-Formamidokalihinene (**152**)	376	$C_{22}H_{36}N_2O_3$	*A. cavernosa*	Fiji, South Pacific Ocean	[51]
6-Hydroxy-kalihinene (**153**)	356	$C_{22}H_{32}N_2O_2$	*A. cavernosa*	Fiji, South Pacific Ocean	[51]
	-	-	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[57]
6-Hydroxy-15-Formamidokalihinene (**154**)	374	$C_{22}H_{34}N_2O_3$	*A. cavernosa*	Fiji, South Pacific Ocean	[51]
6-Hydroxy-10-Formamidokalihinene (**155**)	374	$C_{22}H_{34}N_2O_3$	*A. cavernosa*	Fiji, South Pacific Ocean	[51]
6-Hydroxy-10-Formamido-15-thyocyano-kalihinene (**156**)	406	$C_{22}H_{34}N_2O_3S$	*A. cavernosa*	Fiji, South Pacific Ocean	[51]
Kalihioxepanes					
Kalihioxepane A (**157**)	365	$C_{21}H_{32}ClNO_2$	*A. cavernosa*	Xisha Island, South China Sea	[64]
Kalihioxepane B (**158**)	365	$C_{21}H_{32}ClNO_2$	*A. cavernosa*	Xisha Island, South China Sea	[64]
Kalihioxepane C (**159**)	383	$C_{21}H_{34}ClNO_3$	*A. cavernosa*	Xisha Island, South China Sea	[64]
Kalihioxepane D (**160**)	383	$C_{21}H_{34}ClNO_3$	*A. cavernosa*	Xisha Island, South China Sea	[64]
Kalihioxepane E (**161**)	383	$C_{21}H_{34}ClNO_3$	*A. cavernosa*	Xisha Island, South China Sea	[64]
Kalihioxepane F (**162**)	365	$C_{21}H_{32}ClNO_2$	*A. cavernosa*	Xisha Island, South China Sea	[64]
Kalihioxepane G (**163**)	365	$C_{21}H_{32}ClNO_2$	*A. cavernosa*	Xisha Island, South China Sea	[64]
Kalihipyran (**164**)	311	$C_{21}H_{29}NO$	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[59]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[45]
Kalihipyrans					
Kalihipyran A (**165**)	329	$C_{21}H_{31}NO_2$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[55]
Kalihipyran B (**166**)	365	$C_{21}H_{32}ClNO_2$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[55]
Kalihipyran C (**167**)	329	$C_{21}H_{31}NO_2$	*A. cavernosa*	Xisha Islets, South China Sea	[63]
Biflorane diterpenes					
Biflora-4,9,15-triene (**168**)	272	$C_{20}H_{32}$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[55]
	-	-	*A. cavernosa*	Hachijo-jima Island, Japan	[40]
Cavernene A (**169**)	315	$C_{21}H_{33}NO$	*A. cavernosa*	Xisha Islets, South China Sea	[63]
Cavernene B (**170**)	317	$C_{21}H_{35}NO$	*A. cavernosa*	Xisha Islets, South China Sea	[63]
Cavernene C (**171**)	317	$C_{21}H_{35}NO$	*A. cavernosa*	Xisha Islets, South China Sea	[63]
Cavernene D (**172**)	331	$C_{21}H_{33}NO_2$	*A. cavernosa*	Xisha Islets, South China Sea	[63]

Table 3. *Cont.*

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
Isocyanobifloradiene epoxide A (**173**) 11,12-epoxy-10-isocyano-4, 14-bifloradiene (**173**)	313	$C_{21}H_{31}NO$	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[45]
Isocyanobifloradiene epoxide B (**174**) 11,18-epoxy-10-isocyano-4, 14-bifloradiene (**174**)	313	$C_{21}H_{31}NO$	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[45]

3.2.1. Kalihinols

Kalihinol A (**88**) was the first reported member of this diterpenoid class in 1984 [52] (Table 3). It is a tricyclic diterpenoid belonging to group **II**, containing isocyano, hydroxyl, and chlorine moieties. It was separated from the CCl_4 extract of *Acanthella* sp. and characterized by NMR and X-ray analyses [52] and its configuration was assigned as 1S/4R/5R/6S/7S/10S/11R/14S using the CD exciton chirality method [65] (Figure 9).

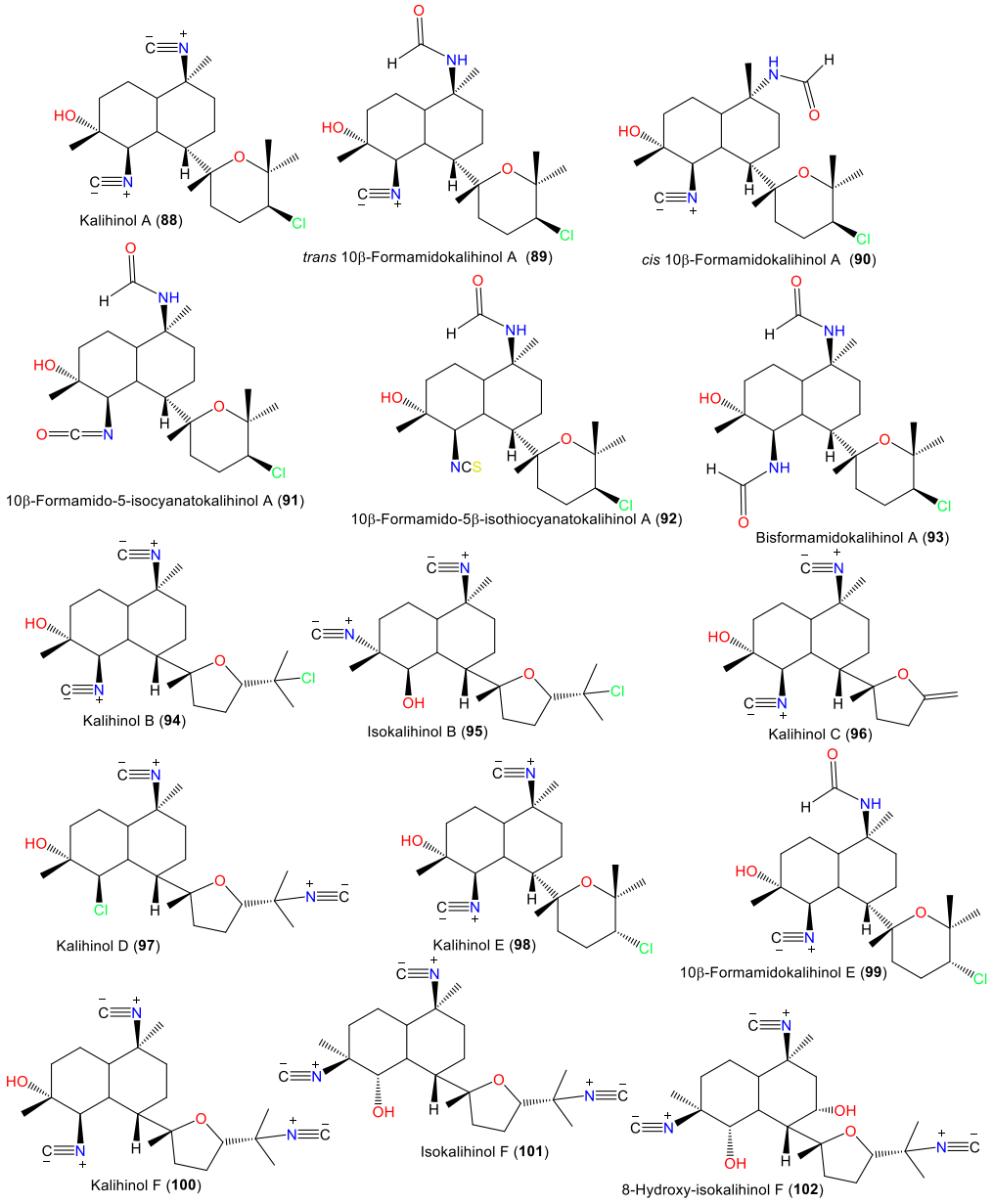


Figure 9. Kalihinol diterpenes (**88**–**102**) reported from the genus *Acanthella*.

In 1987, Chang et al. purified and characterized isocyano-diterpenoids kalihinols A–H (**88**, **94**, **96**–**98**, **100**, **108**, and **111**) and X–Z (**125**, **127**, and **130**) from *Acanthella* sp. obtained from Guam and Fiji using spectral and X-ray analyses. They differ in the C-7 attached moiety; the tetrahydropyran with C-14 chlorine (e.g., **25**, **88**, **98**, **130,** and **127**); or the tetrahydro-furanyl moiety, with 15-NC (e.g., **97** and **100**), 15-NCS (e.g., **108**), 15-C1 (e.g., **94**), or isopropenyl replacing gem-dimethyl (e.g., **96**) [22] (Figure 10).

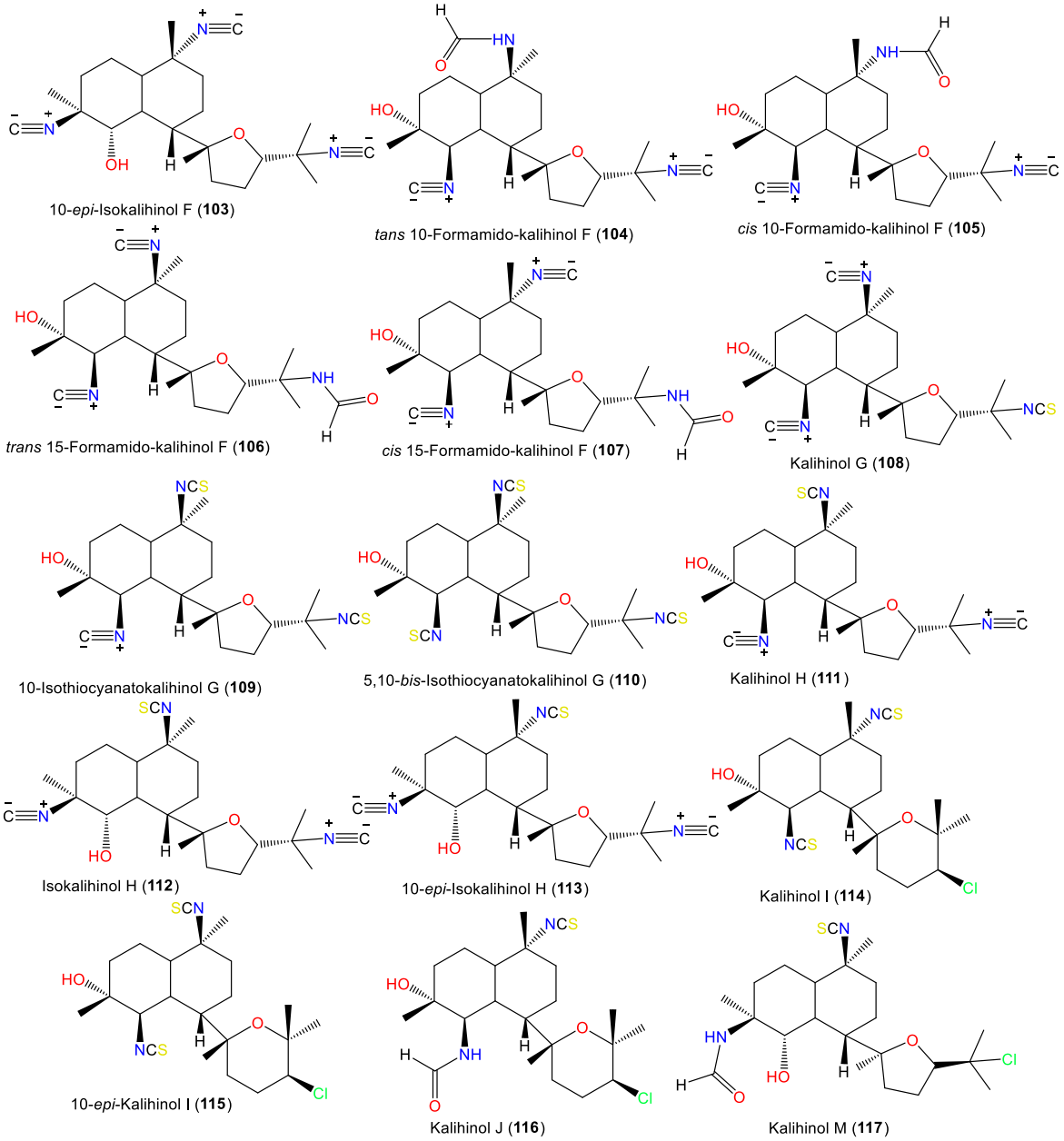


Figure 10. Kalihinol diterpenes (**103**–**117**) reported from the genus *Acanthella*.

Additionally, **101** was isolated as colorless needles from *A. carvenosa* by flash chromatography and HPLC. It resembles **100** with a difference in the substitution at C_4 and C_5 [53]. Additionally, new members of the kalihinols family, **114** and **116**, along with **125** and **127**, were purified from *A.cavernosa* collected from Thailand by SiO_2 CC and HPLC and identified by extensive NMR data. Compound **114** is similar to **125** with a C-5-N-formyl instead of the isothiocyanoate moiety in **125** [18]. Compounds **117** and **118** are two novel C-4 formamido analogs of isokalihinols reported from the South China Sea specimen of

A. cavernosa. They have a *trans*-decalin ring at C-7 of the tetrahydrofuran and tetrahydropyran rings, respectively. Compound **117** possesses a C-15 chlorine atom and a C-10 isothiocyanato group, whereas **118** is an example of tetrahydropyran-type isokalihinol. They have 1S/4S/5S/6S/7S/10S/11R/14S and 1S/4S/5S/6S/7S/10S/11R/14R configurations, respectively [16]. From Okinawan *Acanthella* sp., new members of kalihinane-type diterpenes, **110**, **115**, and **129**, were purified from the EtOAc fraction using SiO_2 CC and HPLC. Compound **129** is of tetrahydropyran type and is closely similar to **127**, with a trisubstituted olefinic bond in **129** instead of the exo-methylene group in **127**, while **110** and **115** have three and two isothiocyano groups, respectively [57] (Figure 11).

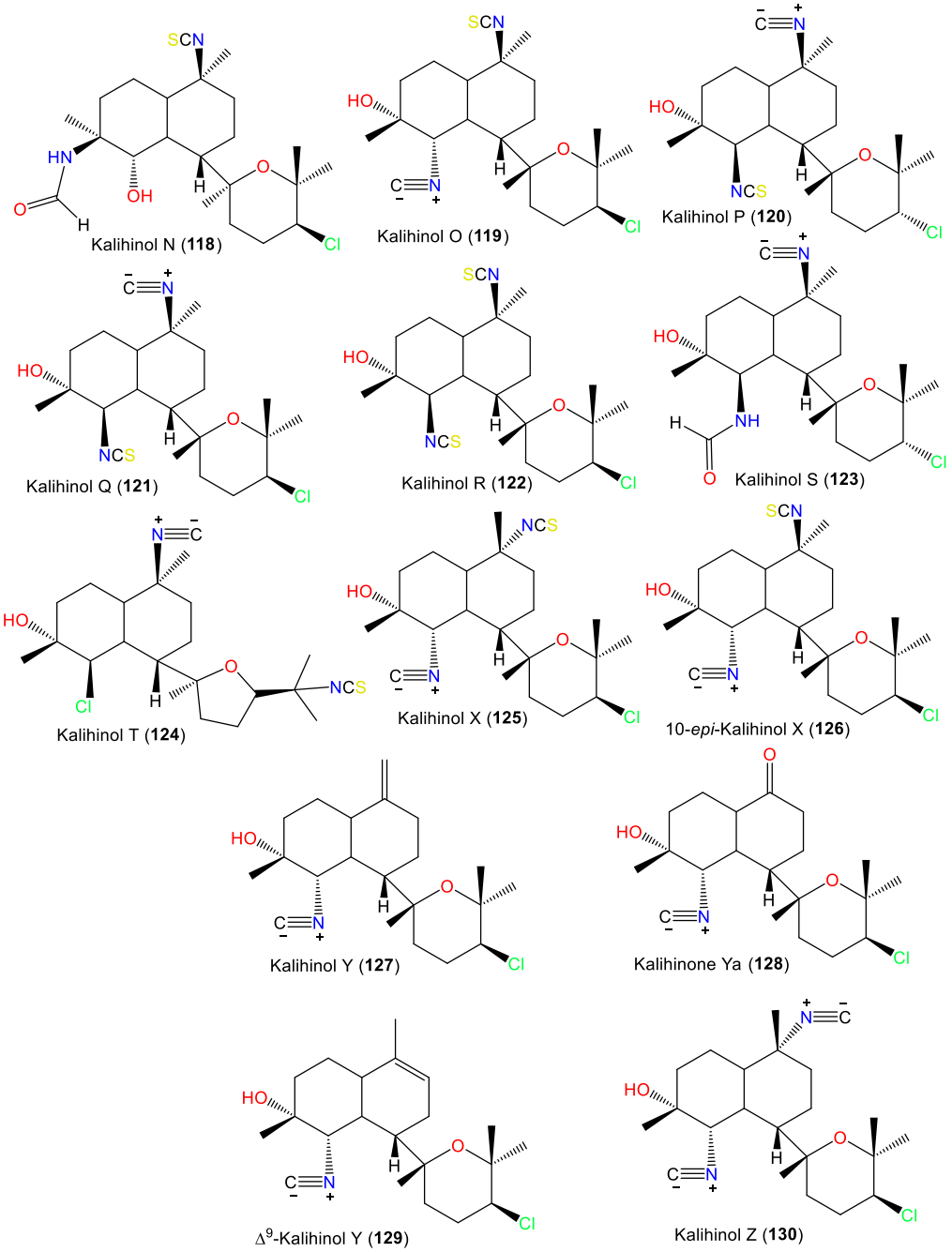


Figure 11. Kalihinol diterpenes (**118**–**130**) reported from the genus *Acanthella*.

In 1994, Trimurtulu et al. reported new diterpene isonitriles, **103** and **113**, from *A. carvenosa* collected from The Seychelles. Compound **103** differs from **101** in the *trans*-decalin

ring system configuration, whereas **113** has an isothiocyanate group instead of one of the C-10 isonitrile groups of **103** [59]. Besides, Xu et al. reported new diterpenoids, kalihinols O–T (**119**–**124**), together with **88**, **98**, **109**, **115**, and **126**, from *A. cavernosa* in the South China Sea using SiO_2 and Sephadex LH-20 CC [16]. Their structures and stereo-structures were determined by NMR/CD/X-ray analyses [16]. Compound **119** is structurally similar to **98**, with a C-10 isothiocyanate instead of a C-10 isonitrile in **98,** whereas **120** is an isocyanato analog of **88** and **123** is a C-5 formamide analog of **126**. Furthermore, **121** and **122** are the C-14 epimers of 120 and 115, respectively, and 124 is the C-15-isothiocyanato analog of **97** [16]. Clark et al. in 2000, purified a new kalihinol-type diterpenoid, 8-OH-isokalihinol F (**102**), from *A. cavernosa* obtained from Heron Island, Great Barrier Reef, Australia, which was structurally similar to **101** with an additional C-8 OH [45]. In addition, new formamide analogs, **104** and **106**, were purified by Bugni et al. in 2004 from two Philippine *A. cavernosa* specimens. They featured formamide moieties at C-10 and C-15, respectively, instead of the isonitrile in **100** [21]. Furthermore, a new kalihinol diterpene, **126**, was isolated from Hainan *Acanthella* sp. by SiO_2 and Sephadex LH-20 CC and was assigned as a C-10 epimer of **127** [42]. Additionally, new α-acyloxy-amide-substituted diterpenoids, kalihiacyloxyamides A–H (**131**–**138**), were separated from South China Sea *A. cavernosa* EtOAc fractions using SiO_2/Rp-18 CC/RP-HPLC that were elucidated based on spectral, X-ray, and CD analyses (Figure 12). These metabolites featured isobutyl amide (e.g., **131** and **132**), iso-amyl ester (e.g., **133**, **134**, **137**, and **138**), and phenethyl ester (e.g., **135** and **136**) groups [62].

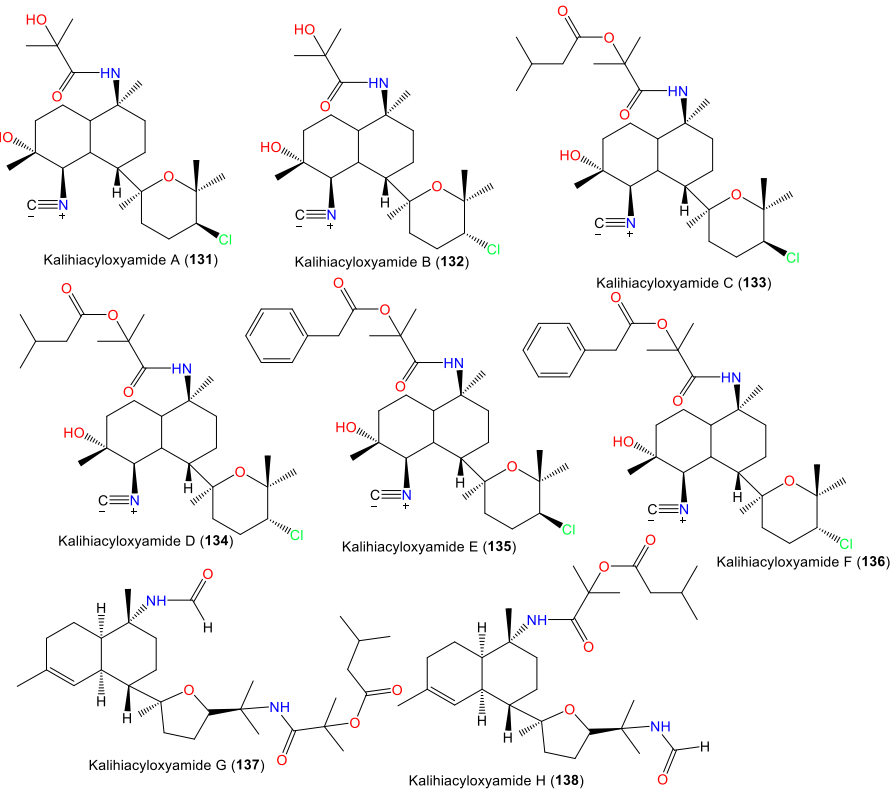


Figure 12. Kalihinol diterpenes (**131**–**138**) reported from the genus *Acanthella*.

3.2.2. Kalihinenes

The first member of this group is kalihinene (**139**), which was purified from an *A. klethra* EtOH extract using SiO_2 CC/Develosil ODS-5 CC/HPLC and assigned by NMR and X-ray analyses [23]. Furthermore, compounds **143** and **144** were reported as novel monounsaturated kalihinane class diterpenes derived from *A. Cavernosa* toxic CH_2Cl_2 extracts against *Artemia salina* and *Lebistes reticulatus* using VLC/Flash/Rp-18 CC. These two

compounds are diastereoisomers of **139** that feature a trans-decalin skeleton instead of the trans-decalin skeleton of kalihinene. On the other hand, **143** and **144** are epimers at C-10 [54]. Additionally, **145** and **146** are tertrahydropyran/trans-decalin and tetrahydrofuran/cis-decalin analogs bearing formamido groups at C-10 and C-15, respectively (Figure 13). Kalihinene E (**145**) is a C-14 epimer of **148** with 1*S*/6*S*/7*S*/10*S*/11*R*/14*R* configuration [63]. In 1994, Rodríguez et al. purified new diterpenoids belonging to kalihinene and 6-OH kalihinene groups (**148** and **150–156**), along with **139** from *A. cavernosa* collected from a Fijian location. These compounds were characterized based on spectral and X-ray analyses as well as biogenetic evidence [51]. Additionally, **140–142** are new metabolites reported from *A. carvenosa* collected from The Seychelles [59]. Compound **140** is a C-1 isomer of **139**, **141** has C-15 isothiocyanate instead of C-15 isonitrile in **140**, and **142** is an isomer of **140** and **139** [59].

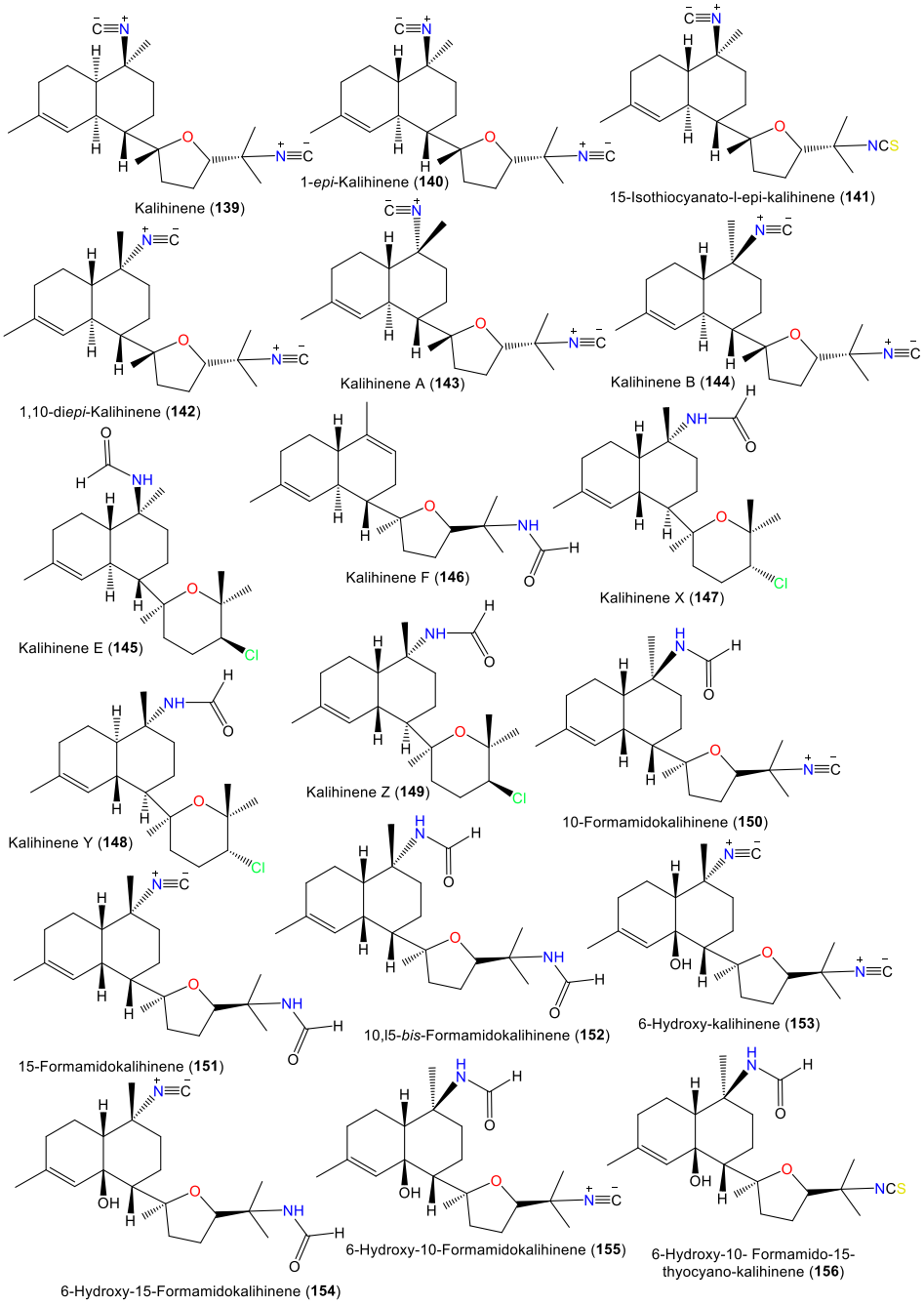


Figure 13. Kalihinene diterpenes (**139–156**) reported from the genus *Acanthella*.

3.2.3. Kalihipyrans and Kalihioxepanes

Kalihipyran (**164**) is a tricyclic kalihinene-type diterpene with a C-7 isopropenyl-containing dihydropyran moiety and a C-10 isonitrile [59]. Compound **167** is an isomer of **165** with cis-decalin [63], while **166** has a C-15 chlorine atom [55,56]. In 2022, Wang et al. purified new kalihinane diterpenoids, kalihioxepanes A–G (**157–163**), from South China Sea *A. cavernosa* by the means of SiO_2/Sephadex LH-20/HPLC. The structures were elucidated by spectral and X-ray analyses, in addition to quantum chemical calculation methods [64] (Figure 14).

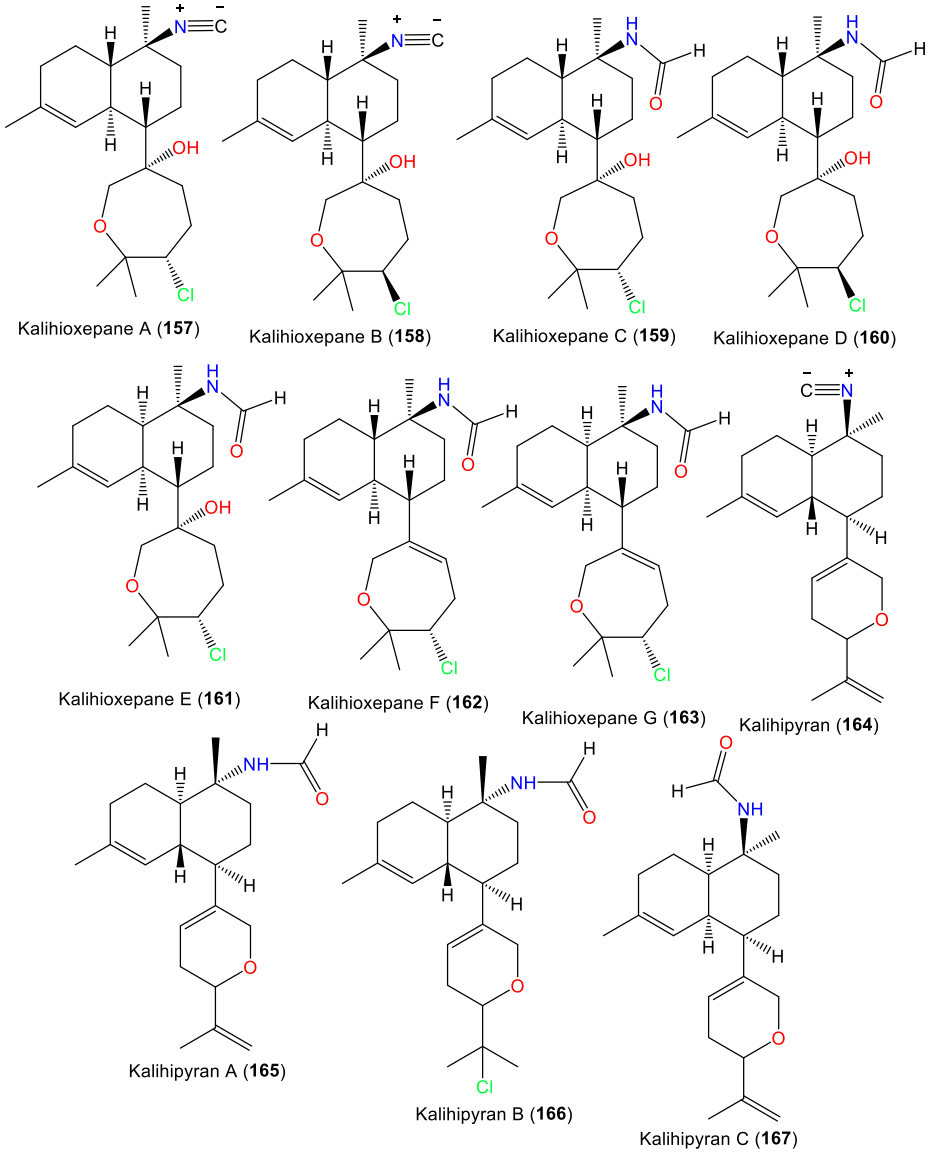
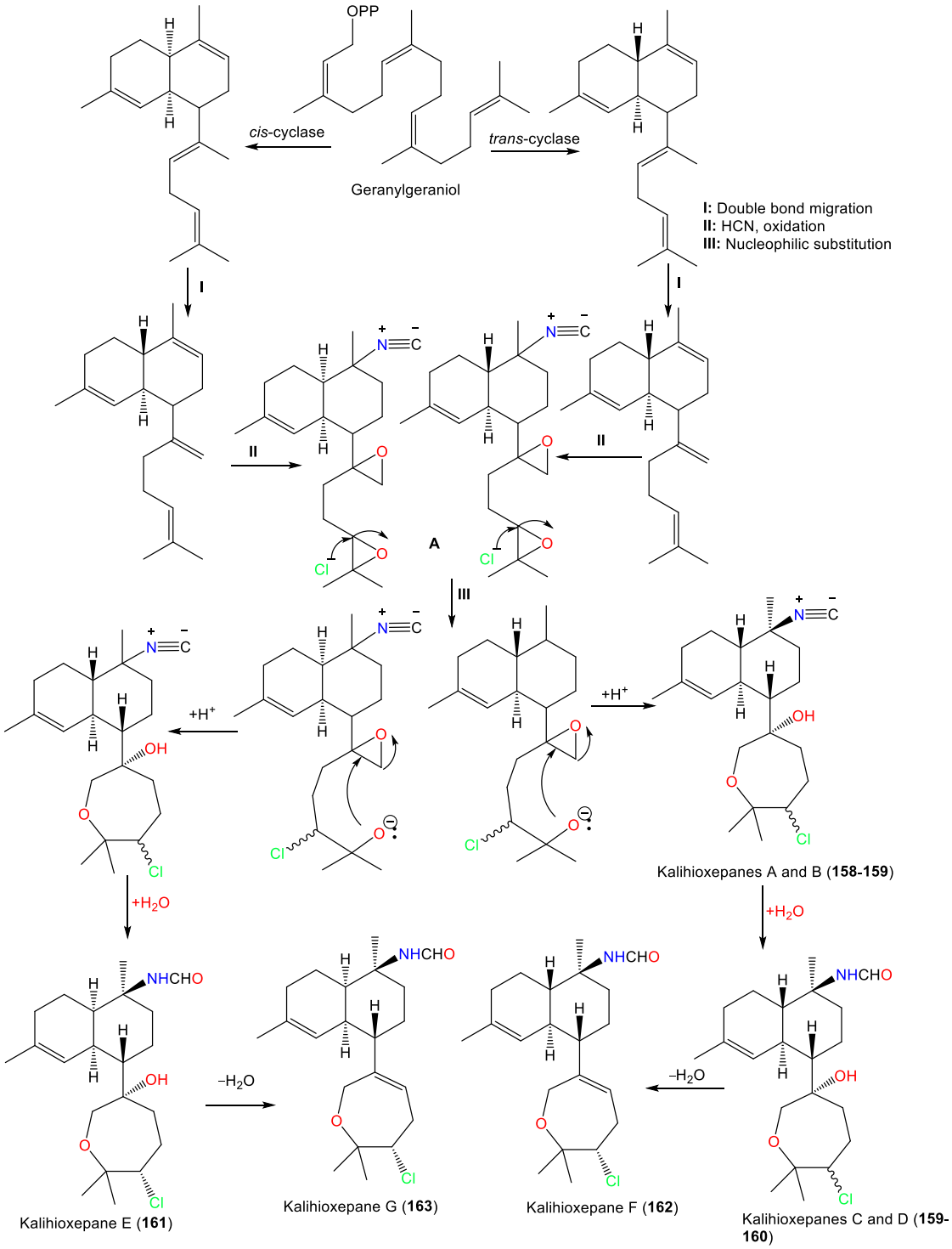


Figure 14. Kalihioxepanes (**157–163**) and kalihipyrans (**164–167**) diterpenes reported from the genus *Acanthella*.

These metabolites possess a rare C-7-attached oxepane ring with a C-14 Cl atom. Compounds **157–160** have a *trans* decalin skeleton; however, **161–163** have a cis-decalin skeleton with C-10 isonitrile (e.g., **157** and **158**) and formamide (e.g., **159–163**) groups [64]. Wang et al. proposed that **157–163** are biosynthesized using geranylgeraniol as a precursor (Scheme 2). The latter undergoes a series of reactions, including cyclization, double-bond migration, nucleophilic addition, and oxidation reactions, to give epoxide biflorane (**A**, the key inter-

mediate). Nucleophilic substitution of biflorane forms **157** and **158**. After that, hydration generates **159–161** which are then dehydrated to give **162** and **163**, respectively [64].



Scheme 2. Biosynthesis of kalihioxepanes A–G (**157–163**) [64].

3.2.4. Biflorane Diterpenes

From the Japanese *A. cavernosa*, biflora-4,9,15-triene (**168**) was separated, which is a rare biflorane diterpene related to **66**, by replacing the methyl hydrogen of the isopropyl group of **66** with a prenyl group [40]. In 2012, Xu et al. reported **169–172** from CH_2Cl_2 extracts of South China Sea *A. cavernosa*, bearing a C-10 formamide group that varied in

the decalin moiety (*cis* or *trans*) configuration and nature of C-7-linked side chain [63] (Figure 15). Their structures were assigned by spectral and X-ray analyses. Compounds **169**, **170**, and **172** are *trans*-decalin derivatives, with a C-7 isoprenoid unit, a mono-olefinic isoprenoid sidechain, and a trisubstituted epoxide in the side chain, respectively. In contrast, **171** had a *cis*-decalin moiety [63].

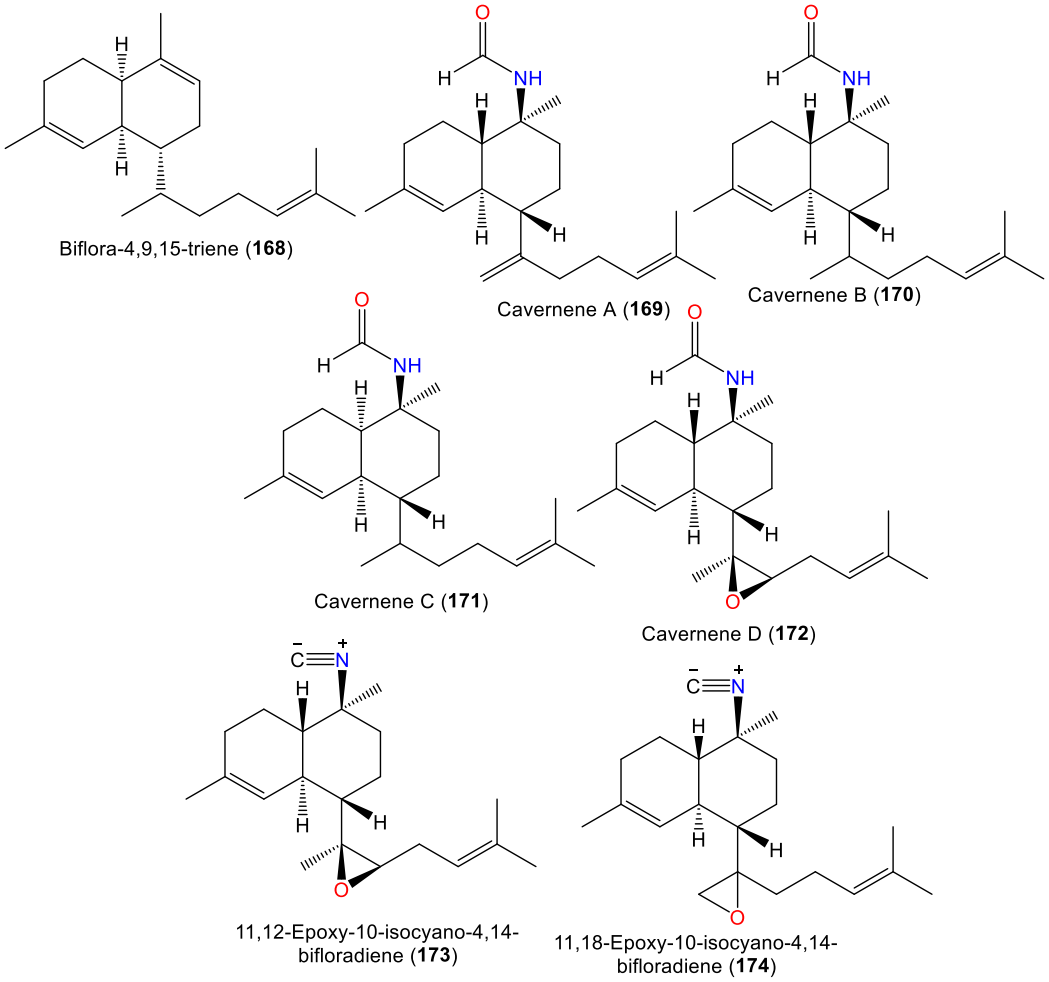
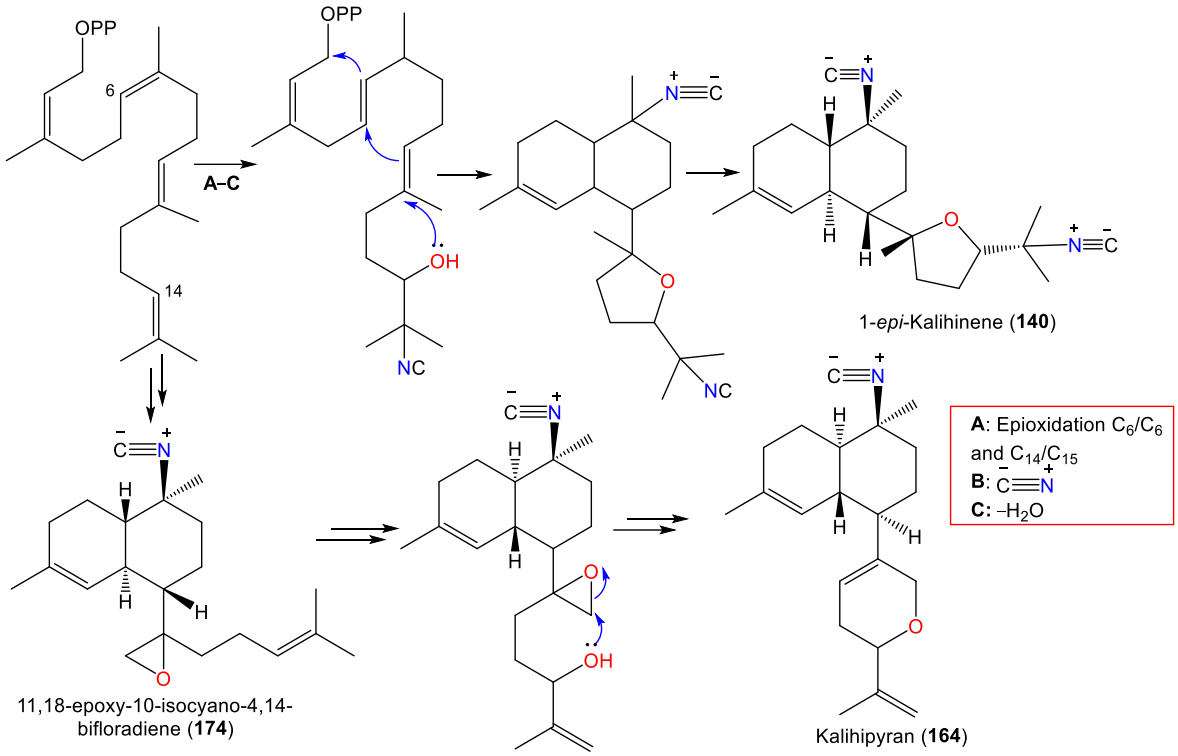


Figure 15. Biflorane (**168**–**174**) diterpenes reported from the genus *Acanthella*.

Investigation of *A. cavernosa* DCM/MeOH extracts led to the separation of two oxirane analogs with a trans-decalin framework, **173** and **174**, featuring a trisubstituted epoxide and a terminal epoxide group in the side chain, respectively. Compound **174** was suggested to be a precursor of the kalihipyran skeleton [45]. Clark et al. proposed that the biosynthesis of pyranyl and furanyl kalihinols involves epoxidation of the bifloradiene precursor's terminal double bond by a nucleophilic attack at either epoxide end by a cyanide ion to form a hydroxyisocyanide. The latter initiates cyclisation to afford a bicyclic system (Scheme 3). Compounds **173** and **174** are alternative epoxidation products. Compound **174** was suggested to be a precursor of the kalihipyran skeleton [45].



Scheme 3. Biosynthesis of **140**, **164**, and **174** [45].

3.3. Alkaloids

Several reports have stated the isolation of different classes of alkaloids from this genus. It is noteworthy that bromopyrrole alkaloids are the dominant type reported from the species of this genus (Table 4). Oroidin **177** is the first member of pyrrole 2-aminoimidazole alkaloids. These alkaloids were reported to have significant bioactivities, as well as chemical defense against predator fish.

Table 4. Alkaloids reported from the genus *Acanthella* (molecular weight and formulae, chemical class, species, and sampling locations).

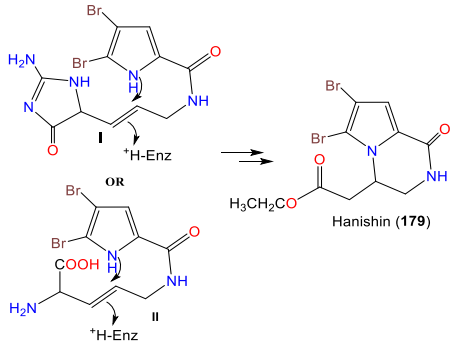
Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
4-Bromo-1H-pyrrole-2-carboxamide (**175**)	187	$C_5H_5BrN_2O$	*A. carteri*	Northern coast, Hanish Island Yemen, South Red Sea	[66]
4,5-Dibromo-1H-pyrrole-2-carboxamide (**176**)	265	$C_5H_4Br_2N_2O$	*A. carteri*	Northern coast, Hanish Island Yemen, South Red Sea	[66]
Oroidin (**177**)	386	$C_{11}H_{11}Br_2N_5O$	*A. carteri*	Northern coast, Hanish Island Yemen, South Red Sea	[66]
	-	-	*A. acuta*	Sidi Elghdamssi island, Monastir region, Tunisia	[25]
Axinellizine (**178**)	408	$C_{11}H_{10}Br_2N_5NaO$	*A. acuta*	Sidi Elghdamssi island, Monastir region, Tunisia	[25]
Hanishin (**179**)	377	$C_{11}H_{12}Br_2N_2O_2$	*A. carteri*	Northern coast, Hanish Island Yemen, South Red Sea	[66]
4-(2-Amino-4-oxo-2-imidazolin-5-ylidene)-2-bromo-4,5,6,7-tetrahydropyrrolo [2,3-c] azepin-8-one (**180**)	323	$C_{11}H_{10}BrN_5O_2$	*A. aurantiaca*	Bay of Naples, southern Italy	[67,68]

Table 4. *Cont.*

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
4-(2-Amino-4-oxo-2-imidazolin-5-ylidene)-4,5,6,7-tetrahydropyrrolo [2,3-c] azepin-8-one (**181**)	281	$C_{11}H_{12}ClN_5O_2$	*A. aurantiaca*	Bay of Naples, southern Italy	[67]
Spongiacidin D (**182**)	323	$C_{11}H_9BrN_4O_3$	*A. carteri*	Dalahican Sea, near Ilaya, Lucena, Quezon, Philippines	[17]
3-Bromohymenialdisin (**183**)	402	$C_{11}H_{11}Br_2N_5O_2$	*A. carteri*	Dalahican Sea, near Ilaya, Lucena, Quezon, Philippines	[17]
Dihydrospongiacidine (**184**)	404	$C_{11}H_{13}Br_2N_5O_2$	*A. carteri*	Dalahican Sea, near Ilaya, Lucena, Quezon, Philippines	[17]
Hymenialdisine (**185**)	323	$C_{11}H_{10}BrN_5O_2$	*Acanthella* sp.	Yongxing Island, South China Sea	[69]
(-)-Phakellin (**186**)	231	$C_{11}H_{13}N_5O$	*A. costata*	Sykes Reef, Capricorn-Bunker Group Great Barrier Reef, Queensland, Australia	[70]
(-)-Monobromophakellin (**187**)	309	$C_{11}H_{12}BrN_5O$	*A. costata*	Sykes Reef, Capricorn-Bunker Group Great Barrier Reef, Queensland, Australia	[70]
(-)-Dibromophakellin (**188**)	386	$C_{11}H_{11}Br_2N_5O$	*A. costata*	Sykes Reef, Capricorn-Bunker Group Great Barrier Reef, Queensland, Australia	[70]
Isophakellin (**189**)	231	$C_{11}H_{13}N_5O$	*A. carteri*	Madagascan coast	[71]
Dibromoisophakellin (**190**)	386	$C_{11}H_{11}Br_2N_5O$	*A. carteri*	Madagascan coast	[71]
Mirabilin G (**191**)	274	$C_{17}H_{28}N_3$	*A. cavernosa*	Southwestern Australia	[24]
Mirabilin K (**192**)	276	$C_{17}H_{30}N_3$	*A. cavernosa*	Southwestern Australia	[24]
Netamine M (**193**)	274	$C_{17}H_{28}N_3$	*A. cavernosa*	Southwestern Australia	[24]
1*H*-Indole-3-carboxylic acid methyl ester (**194**)	175	$C_{10}H_9NO_2$	*A. cavernosa*	South China Sea	[50]
1*H*-Indole-3-carboxylic acid (**195**)	161	$C_9H_7NO_2$	*A. cavernosa*	South China Sea	[50]
Cyclo(L-Phe-L-Leu) (**196**)	260	$C_{15}H_{20}N_2O_2$	*A. cavernosa*	Coast of Vanua Levu (Fiji island), South Pacific Ocean	[72]
Cyclo(L-Phe-L-Ile) (**197**)	260	$C_{15}H_{20}N_2O_2$	*A. cavernosa*	Coast of Vanua Levu (Fiji island), South Pacific Ocean	[72]
Cyclo(L-Phe-L-Val) (**198**)	246	$C_{14}H_{18}N_2O_2$	*A. cavernosa*	Coast of Vanua Levu (Fiji island), South Pacific Ocean	[72]
Cyclo(L-Tyr-L-Ile) (**199**)	276	$C_{15}H_{20}N_2O_3$	*A. cavernosa*	Coast of Vanua Levu (Fiji island), South Pacific Ocean	[72]
Cyclo(L-Leu-L-Ile) (**200**)	226	$C_{12}H_{22}N_2O_2$	*A. cavernosa*	Coast of Vanua Levu (Fiji island), South Pacific Ocean	[72]
Cyclo(L-Phe-L-Thr) (**201**)	248	$C_{13}H_{16}N_2O_3$	*A. cavernosa*	Coast of Vanua Levu (Fiji island), South Pacific Ocean	[72]
Cyclo(L-Phe-L-Tyr) (202)	310	$C_{18}H_{18}N_2O_3$	*A. cavernosa*	Coast of Vanua Levu (Fiji island), South Pacific Ocean	[72]
Deoxycytidine (**203**)	227	$C_9H_{13}N_3O_4$	*A. cavernosa*	Coast of Vanua Levu (Fiji island), South Pacific Ocean	[72]
Cytosine (**204**)	111	$C_4H_5N_3O$	*A. cavernosa*	Coast of Vanua Levu (Fiji island), South Pacific Ocean	[72]
Deoxynebularine (**205**)	236	$C_{10}H_{12}N_4O_3$	*A. cavernosa*	Coast of Vanua Levu (Fiji island), South Pacific Ocean	[72]
Deoxyinosine (**206**)	252	$C_{10}H_{12}N_4O_4$	*A. cavernosa*	Coast of Vanua Levu (Fiji island), South Pacific Ocean	[72]
Tryptamine (**207**)	160	$C_{10}H_{12}N_2$	*A. cavernosa*	Coast of Vanua Levu (Fiji island), South Pacific Ocean	[72]

In 2010, Hammami et al. purified a novel bromopyrolimidazole analog, **178**, along with **177** from Tunisian *A. acuta* diethyl ether extracts [25]. Four bromo-pyrrole alkaloids, including novel alkaloid hanishin (**179**) in addition to **175**–**177**, were isolated from *A. carteri* collected from the northern coast of Hanish Island, Yemen, South Red Sea, by Mancini

et al. Compounds **177** and **179** are members of the oroidin family of alkaloids that are considered condensation products of prolines. Compound **179** was proposed to be derived from aminoimidazolinone (**I**) or amino acid (**II**) intermediates through 1N-C9 cyclization with subsequent side-chain oxidative breakdown [66] (Scheme 4).



Scheme 4. Proposed biosynthesis of **179** [66].

Mattia et al. purified **180** as a brominated alkaloid from Red Sea *A. Aurantiaca* BuOH extracts. The compound features an aminooxodihydroimidazole ring linked to a pyrroloazepine group via a double bond (Figure 16) [68]. Compounds **180** and **181** were obtained from *A. aurantiaca* BuOH extracts using Sephadex LH-20 and crystallization and were characterized by spectral and X-ray analyses [67]. In 2014, Macabeo and Guce reported the bromopyrrole-imidazole alkaloids **182–184** from CH_2Cl_2-MeOH extracts of *A. carteri* from The Philippines [17], while **185** is a pyrrole alkaloid isolated from the n-BuOH fraction of *Acanthella* sp. using Sephadex LH-20/Rp-18 CC [69].

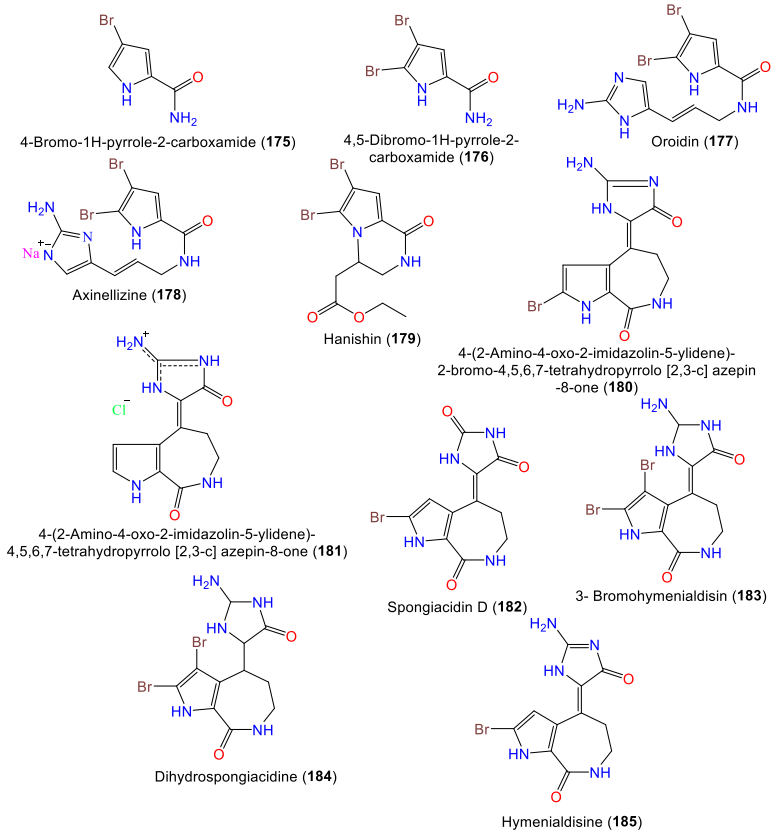
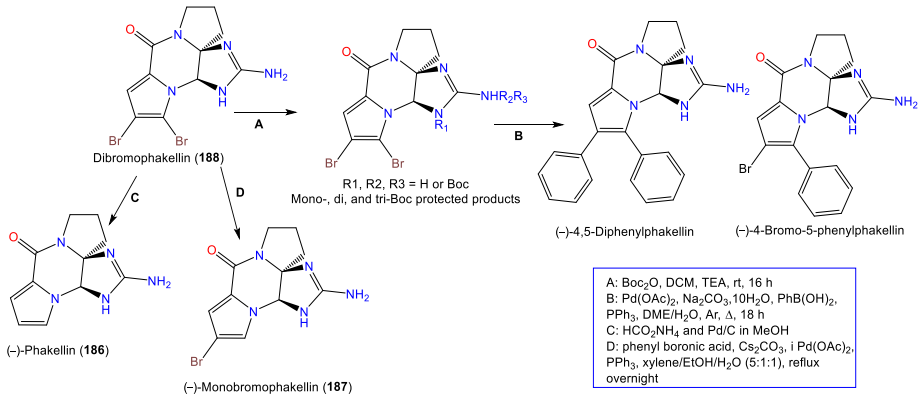


Figure 16. Alkaloids (**175–185**) reported from genus *Acanthella*.

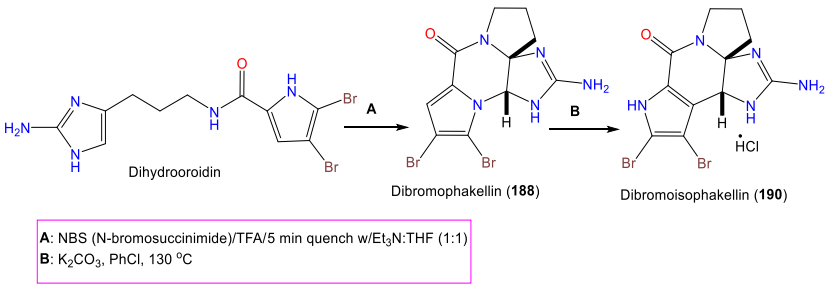
A series of synthetic reactions including Suzuki–Miyaura coupling and debromination resulted in natural analogs **186** and **187**, in addition to new synthetic derivatives (−)-4-bromo-5-phenylphakellin and (−)-4,5-diphenylphakellin. It was found that the C-5 Br substitution with phenyl or H led to a loss in activity, revealing that the C-5 Br is important for α2B adrenoceptor agonistic activity (Scheme 5) [70].



Scheme 5. Semisynthesis of (−)-dibromophakellin (**188**) derivatives [70].

Furthermore, **190** was purified from *A. carteri* using Sephadex LH-20/SiO_2 CC, giving a bright-orange color with a diazotized benzidine. The compound was characterized by NMR and X-ray analyses, as well as chemical methods. Compound **190** is a 6R/10S brominated alkaloid with a fused C-C pyrrole linkage to the cyclic guanidine core belonging to the **189** series [71].

In 2002, Wiese and his group reported the synthesis of **190** using dihydrooroidin that is converted to **188** (Scheme 6). Then, thermal rearrangement of **188** in the presence of K_2CO_3 produces **190** [73].



Scheme 6. Synthesis of **190** using dihydrooroidin [73].

Additionally, Grkovic et al. were able to separate tricyclic-guanidine-containing alkaloids, including a new analog mirabilin K (**192**), along with **191** and **193**, from *A. cavernosa* collected in Southwestern Australia using diol flash chromatography/Rp-18/HPLC. The compounds were characterized by spectroscopic analyses and optical rotation measurements. Compound **192** has a 4*S**/7*S**/9*R**/11*S**/12*R** configuration, which differs from **191** in the C9-CH_3 group and with the presence of a N-substituted methine group (Figure 17) [24]. Furthermore, **194** and **195** were obtained by Fan et al. from the acetone extracts of *A. cavernosa* collected from the South China Sea [50].

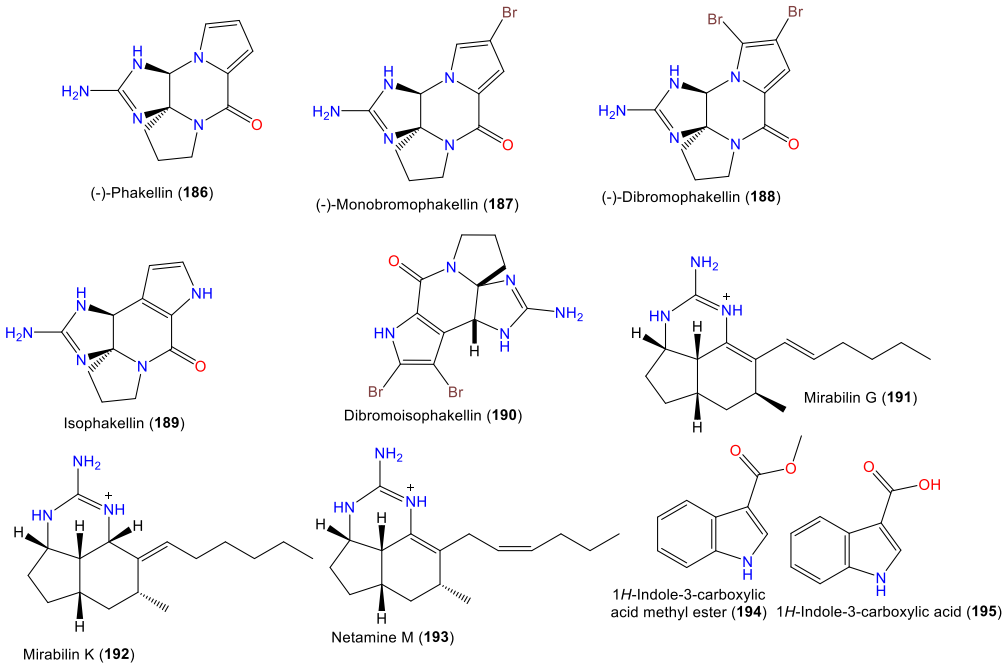


Figure 17. Alkaloids (**186**–**195**) reported from the genus *Acanthella*.

Diketopiperazines, including the rare cyclo(L-Phe-L-Thr) and cyclo(L-Tyr-L-Ile) (**196**–**202**), along with decarboxylated amino acid **207** and deoxyribonucleotides **203**–**206**, were reported and characterized from Fijian *A. cavernosa* (Figure 18). Their L-L absolute configuration was assigned based on an NMR and CD comparison with synthetic L-L analogs, as well as optical rotation measurements [72].

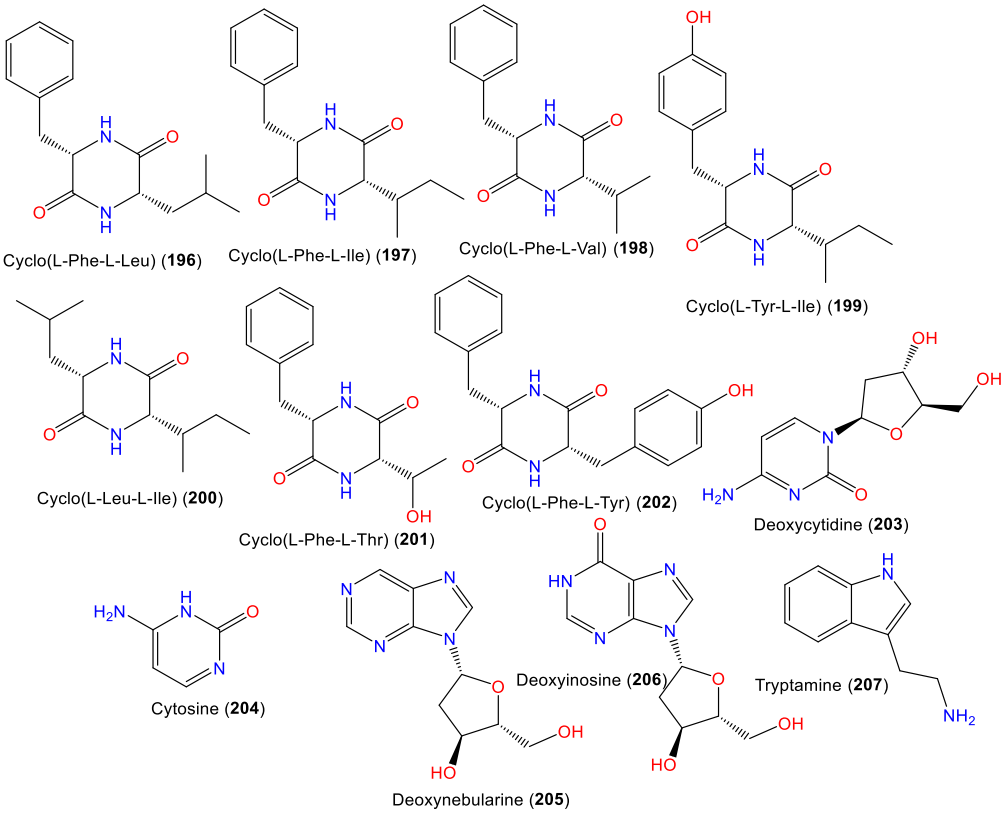


Figure 18. Alkaloids (**196**–**207**) reported from the genus *Acanthella*.

3.4. Steroid Compounds

In 2008, Qui et al. reported the purification of three new nor-steroids, **208**–**210**, along with the known steroids **211**–**214** from the petroleum ether fraction of *A. cavernosa* obtained from Hainan Island, China, using SiO_2 CC/HPLC. The new steroids are related to A-ring-contracted steroid analogs featuring carbonyl and ketone groups located at C-3 and C-4; they differ in their C-17 side chains [74] (Table 5 and Figure 19). In addition, **215** was obtained from the acetone extract of the same sponge collected from the South China Sea [50].

Table 5. Sterols and other metabolites reported from the genus *Acanthella* (molecular weight and formulae, chemical class, species, and sampling locations).

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
Steroids					
2β-Hydroxy-4,7-diketo-A-norcholest-5-en-2-oic acid (**208**)	472	$C_{29}H_{44}O_5$	*A. cavernosa*	Inner coral reef, Hainan Island, China	[74]
24*S*-Ethyl-2β-hydroxy-4,7-diketo-A-norcholest-5-en-2-oic acid (**209**)	500	$C_{31}H_{48}O_5$	*A. cavernosa*	Inner coral reef, Hainan Island, China	[74]
2β-Hydroxy-4,7-diketo-24*R*-methyl-A-norcholest-5,22(*E*)-diene-2-oic acid (**210**)	484	$C_{30}H_{44}O_5$	*A. cavernosa*	Inner coral reef, Hainan Island, China	[74]
6α-Hydroxycholest-4-en-3-one (**211**)	400	$C_{27}H_{44}O_2$	*A. cavernosa*	Inner coral reef, Hainan Island, China	[74]
6α-Hydroxyergost-4-en-3-one (**212**)	414	$C_{28}H_{46}O_2$	*A. cavernosa*	Inner coral reef, Hainan Island, China	[74]
Cholest-7,22*E*-dien-3β,5α,6β-triol (**213**)	416	$C_{27}H_{44}O_3$	*A. cavernosa*	Inner coral reef, Hainan Island, China	[74]
24-Norcholest-7,22*E*-dien-3β,5α,6β-triol (**214**)	402	$C_{26}H_{42}O_3$	*A. cavernosa*	Inner coral reef, Hainan Island, China	[74]
5α,8α-Epidioxy-(22*E*,24*R*)-erost-6,22-dien-3β-ol (**215**)	428	$C_{28}H_{44}O_3$	*A. cavernosa*	South China Sea	[50]
Other metabolites					
Isoagelaxanthin A (**216**)	548	$C_{40}H_{52}O$	*A. vulgata*	Makura-zaki, Kagoshima, Japan	[75]
Fasciculatin (**217**)	398	$C_{25}H_{34}O_4$	*A. acuta*	Sidi Elghdamssi island, Monastir region, Tunisia	[25]
Hanishenol A (**218**)	424	$C_{27}H_{52}O_3$	*A. carteri*	Northern coast, Hanish Island Yemen, South Red Sea	[76]
Hanishenol B (**219**)	438	$C_{28}H_{54}O_3$	*A. carteri*	Northern coast, Hanish Island Yemen, South Red Sea	[76]
Phalluside 1 (**220**)	739	$C_{42}H_{77}NO_9$	*A. acuta*	Sidi Elghdamssi Island, Monastir region, Tunisia	[25]
Phalluside 2 (**221**)	753	$C_{43}H_{79}NO_9$	*A. acuta*	Sidi Elghdamssi Island, Monastir region, Tunisia	[25]
Phalluside 3 (**222**)	767	$C_{44}H_{81}NO_9$	*A. acuta*	Sidi Elghdamssi Island, Monastir region, Tunisia	[25]
Phenylethylamine (**223**)	121	$C_8H_{11}N$	*A. cavernosa*	Coast of Vanua Levu (Fiji island), South Pacific Ocean	[72]
2-(4-Hydroxyphenyl)ethylamine (**224**)	137	$C_8H_{11}NO$	*A. cavernosa*	Coast of Vanua Levu (Fiji island), South Pacific Ocean	[72]
Violacene (**225**)	351	$C_{10}H_{13}BrCl_4$	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia	[46]
3-Buten-2-one,4-(2,3,6-trimethylphenyl)-3-E (**226**)	188	$C_{13}H_{16}O$	*A. cavernosa*	South China Sea	[50]

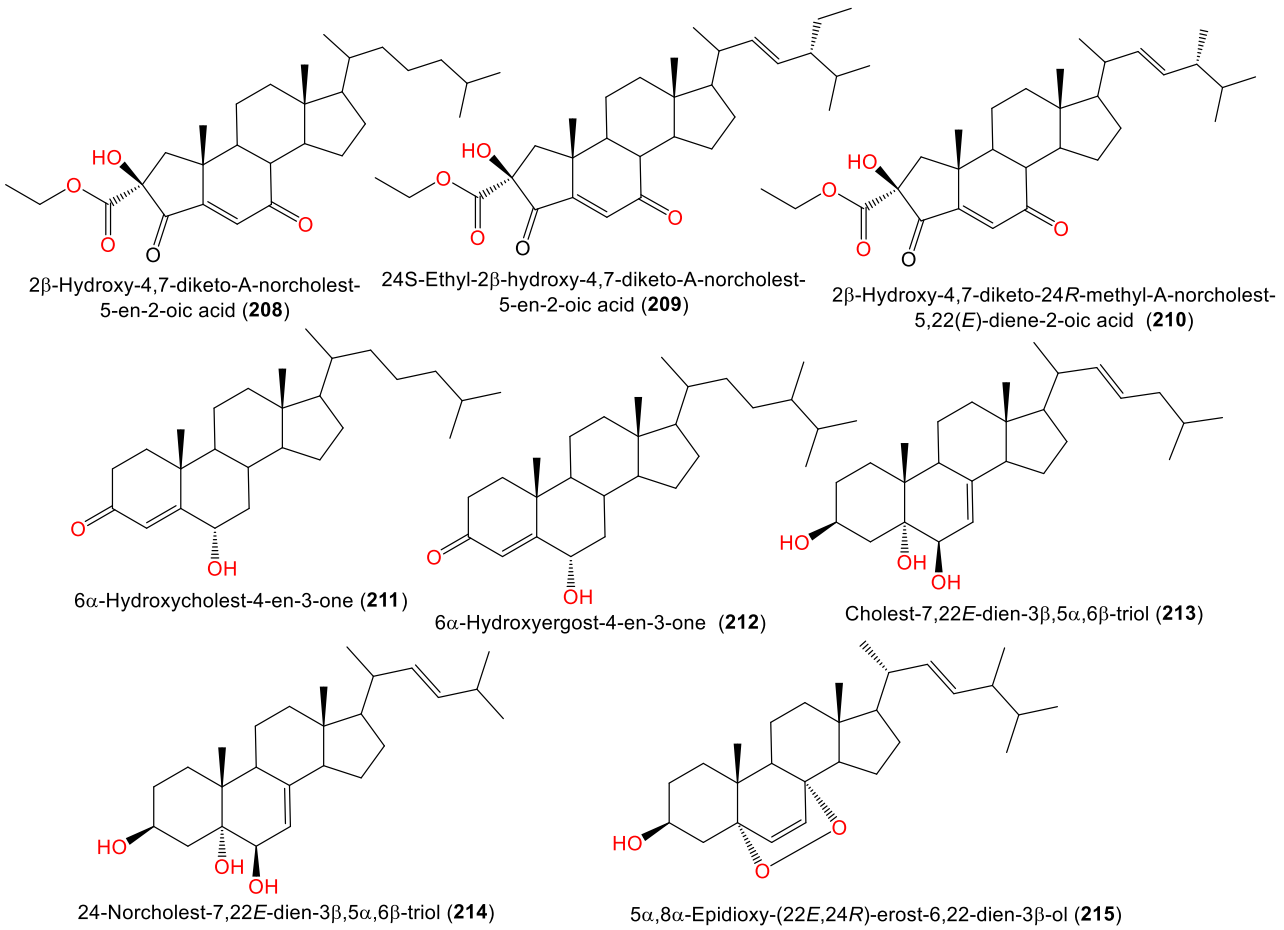


Figure 19. Steroid compounds (**208**–**215**) reported from the genus *Acanthella*.

3.5. Other Metabolites

Compound **216** was separated from *A. vulgata* acetone extracts using an MgO column and crystallization from petroleum ether. The compound belongs to carotenoids, as it has a polyene chain with terminal aromatic moieties on both ends [75] (Figure 20). Mancini et al. were able to purify and characterize **219**, a novel methyl-branched glycerol enol ether, and the related linear analog **218** from *A. carteri* obtained from Southern Red Sea Hanish Islands by utilizing flash CC/HPLC and spectral and chemical methods [76]. Compound **219** has an additional methyl group at C-2 of the sidechain compared to **218**, and both have a 2′S configuration [76]. In 2010, Hammami et al. separated the sesterterpene **217** and cerebrosides **220**–**222** from Tunisian *A. acuta* diethyl ether extracts [25], whereas **226** was purified from the Chinese *A. cavernosa* by Fan et al. [50].

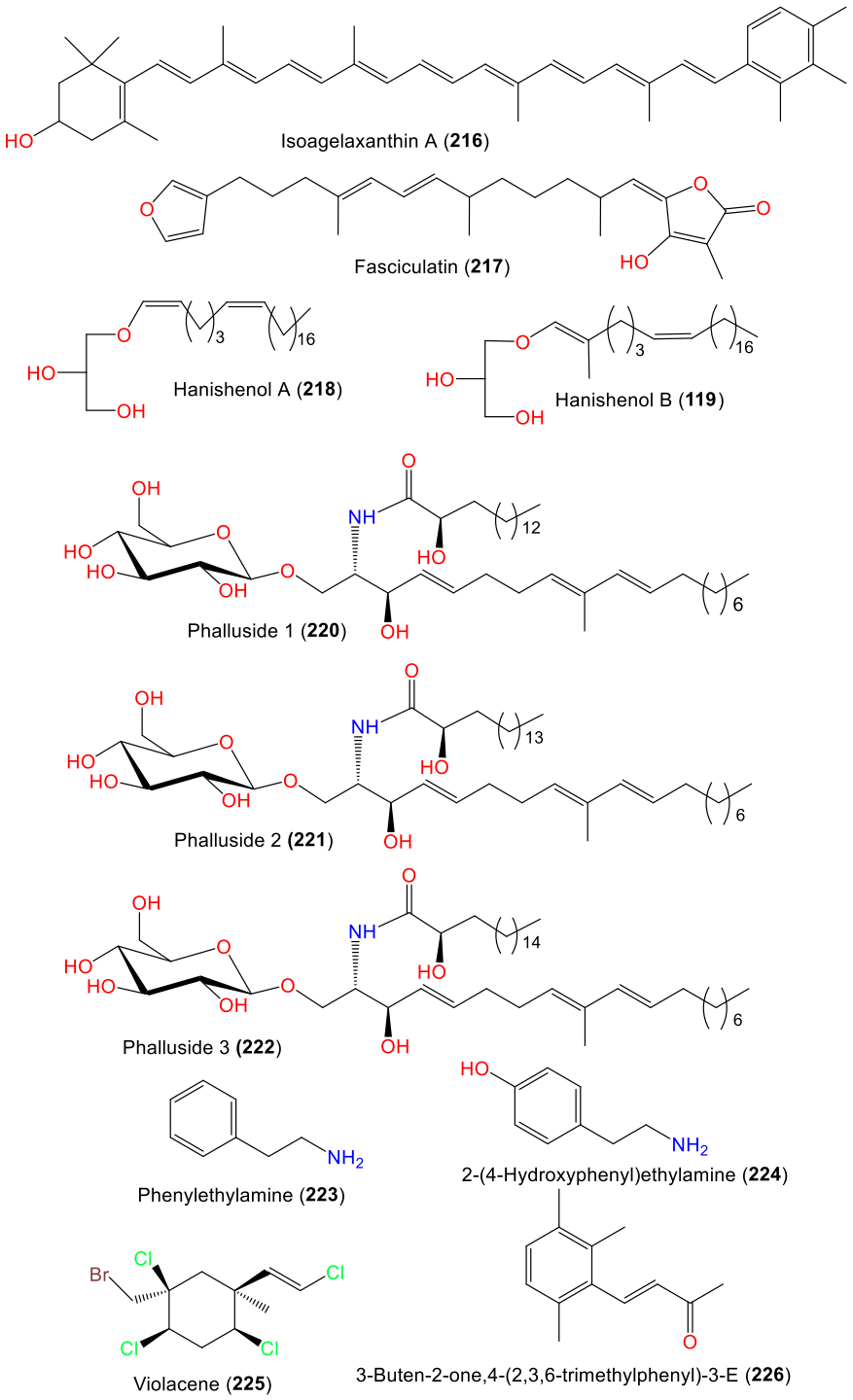


Figure 20. Other metabolites (**216**–**226**) reported from the genus *Acanthella*.

4. Biological Activities of *Acanthella* Species and Their Metabolites

Various *Acanthella* species and their metabolites have been found to display various bioactivities. The reported investigations are highlighted below, and some results are listed in Table 6.

4.1. Antimicrobial and Antifouling Activities

McCaffrey and Endean reported that *A. kleutha's* toluene/methanol (1:3 v/v) and CH_2Cl_2 extracts displayed antimicrobial potential comparable with penicillin G and streptomycin versus *B. subtilis*, *K. pneumoniae*, and *S. aureus* [77]. The *A. carteri* MeOH extract

that was collected from Ras Nusrani in the Gulf of Aqaba was significantly effective versus *B. subtilis*, *S. aureus*, *P. vulgaris*, *E. coli*, *C. tropicalis*, and *C. albicans* (inhibition zone 9.0–23.3 mm) [78]. On the other hand, the n-BuOH fractions of *A. acuta* showed more promising antimicrobial potential versus *A. niger*, *C. albicans*, and *S. aureus* than CH_3Cl fractions [79]. The MeOH extract of *Acanthella elongata* caused 100% and 87.5% inhibition of marine fish pathogens *Aeromonas hydrophila*, *Pseudomonas aeruginosa*, *Vibrio alginolyticus*, *V. anguillarum*, *V. fischeri*, *V. fluvialis*, *V. pelagius*, and *V. vulnificus* at 30°C and 20°C [20]. Additionally, *A. cavernosa* and *A. ramosa* from the Bay of Bengal exhibited activity versus the virulent fish pathogens *Edwardsiella tarda*, *A. hydrophila*, *P. aeruginosa*, *V. alginolyticus*, and *P. fluorescens* [80]. Rajendran et al. reported that the *A. elongata* CH_2Cl_2 fraction had antimicrobial properties versus *V. alginolyticus* (fish pathogen) and *R. solani*, while the EtOH extract prohibited *Vibrio fisherii* and *Micrococcus* sp. [81]. Nogata et al. reported that among the tested 86 Japanese sponge species, the EtOH extract of *A. cavernosa* obtained from Atami, Shizuoka prefecture, Tokyo, displayed 100% inhibition of *B. amphitrite* larval settlements with no toxicity [49]. Additionally, Okino et al. reported that the EtOH extract of *A. cavernosa* obtained from Yakushima Island had antifouling potential as it prohibited metamorphosis and larval settlement of the *Balanus amphitrite* barnacle [56].

Table 6. Biological activity of reported metabolites from the genus *Acanthella*.

Compound Name	Biological Activity	Assay, Organism or Cell Line	Biological Results		Ref.
			Compound	Positive Control	
(+)-10(*R*)-Isothiocyanatoalloaromadendrane (**9**)	Cytotoxicity	MTT/A549	1.98 μg/mL (IC_{50})	-	[42]
Axisonitrile-3 (**17**)	Antimalarial	*Plasmodium falciparum*-D6/Microculture radioisotope	142.0 ng/mL (IC_{50})	Chloroquine 1.95 ng/mL (IC_{50})	[19]
		Plasmodium falciparum-W2/Microculture radioisotope	16.5 ng/mL (IC_{50})	Chloroquine 22.8 ng/mL (IC_{50})	[19]
	Cytotoxicity	MTT/A549	2.44 μg/mL (IC_{50})	-	[42]
11-Isothiocyano-7βH-eudesm-5-ene (**42**)	Antimalarial	*Plasmodium falciparum*-D6/Microculture radioisotope	2240.0 ng/mL (IC_{50})	Chloroquine 1.95 ng/mL (IC_{50})	[19]
		Plasmodium falciparum-W2/Microculture radioisotope	610.0 ng/mL (IC_{50})	Chloroquine 22.8 ng/mL (IC_{50})	[19]
(1*R*,5*R*,6*R*,8*S*)-Dec[4.4.0]ane-1,5-dimethyl-8-(1′-methylethenyl)-5-isothiocyanate (**45**)	Antimalarial	*Plasmodium falciparum*-D6/Microculture radioisotope	4000.0 ng/mL (IC_{50})	Chloroquine 1.95 ng/mL (IC_{50})	[19]
		Plasmodium falciparum-W2/Microculture radioisotope	550.0 ng/mL (IC_{50})	Chloroquine 22.8 ng/mL (IC_{50})	[19]
Kalihinol A (**88**)	Antibacterial	Microbroth dilution/*B. subtilis* PY79	50.0 μg/mL (MIC)	-Trimethoprim 1.0 μg/mL (MIC) -Ciprofloxacin 1.0 μg/mL (MIC) -Rifampin 1.0 μg/mL (MIC) -Sulfamethoxazole 4.0 μg/mL (MIC) -Chloramphenicol 16.0 μg/mL (MIC) -Polymyxin B 16.0 μg/mL (MIC)	[21]
		Disc-diffusion/*Ruegeria CtaxMed-2*	0.67 mm (IZD) at 10 μg/Disc	Streptomycin 0.83 mm (IZD) at 10 μg/Disc	[58]
		Disc-diffusion/*Vibrio sp. (NAP-4)*	1.0 mm (IZD) at 10 μg/Disc	Streptomycin 1.83 mm (IZD) at 10 μg/Disc	[58]
		Disc-diffusion/*Vibrio furnissii*	6.33 mm (IZD) at 10 μg/Disc	Streptomycin 2.50 mm (IZD) at 10 μg/Disc	[58]
	Antifouling	Settlement inhibition/*Balanus amphitrite*	0.087 μg/mL (IC_{50})	$CuSO_4$ 0.15 μg/mL (IC_{50})	[55,56]
		Settlement inhibition/*Balanus amphitrite*	0.92 μM (EC_{50})	Seawater + DMSO	[16]

Table 6. *Cont.*

Compound Name	Biological Activity	Assay, Organism or Cell Line	Biological Results		Ref.
			Compound	Positive Control	
trans and *cis* 10β-Formamidokalihinol A (**89/90**)	Cytotoxicity	MTT/HCT-116	17.40 μM (IC_{50})	-	[16]
	Antibacterial	Disc-diffusion/*Vibrio sp.* (NAP-4)	1.0 mm (IZD) at 10 μg/Disc	Streptomycin 1.83 mm (IZD) at 10 μg/Disc	[58]
		Disc-diffusion/*Vibrio furnissii*	5.67 mm (IZD) at 10 μg/Disc	Streptomycin 2.50 mm (IZD) at 10 μg/Disc	[58]
	Antifouling	Settlement inhibition/*Balanus amphitrite*	1.37 μM (EC_{50})	Seawater + DMSO	[16]
	Cytotoxicity	MTT/CT-26	28.82 μM (IC_{50})	-	[16]
10β-Formamido-5β-isothiocyanatokalihinol A (**92**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	0.41 μM (EC_{50})	Seawater + DMSO	[16]
Isokalihinol B (**95**)	Cytotoxicity	MTT/P388	0.8 μg/mL	-	[23]
Kalihinol D (**97**)	Cytotoxicity	MTT/A549	3.17 μg/mL (IC_{50})	-	[42]
Kalihinol E (**98**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	1.85 μM (EC_{50})	Seawater + DMSO	[16]
	Cytotoxicity	MTT/HCT-116	18.31 μM (IC_{50})	-	[16]
Kalihinol F (**100**)	Antibacterial	Microbroth dilution/*B. subtilis* PY79	12.5 μg/mL (MIC)	-Trimethoprim 1.0 μg/mL (MIC) -Ciprofloxacin 1.0 μg/mL (MIC) -Rifampin 1.0 μg/mL (MIC) -Sulfamethoxazole 4.0 μg/mL (MIC) -Chloramphenicol 16.0 μg/mL (MIC) -Polymyxin B 16.0 μg/mL (MIC)	[21]
Trans 10-Formamido-kalihinol F (**104/105**)	Antibacterial	Microbroth dilution/*B. subtilis* PY79	50.0 μg/mL (MIC)	-Trimethoprim 1.0 μg/mL (MIC) -Ciprofloxacin 1.0 μg/mL (MIC) -Rifampin 1.0 μg/mL (MIC) -Sulfamethoxazole 4.0 μg/mL (MIC) -Chloramphenicol 16.0 μg/mL (MIC) -Polymyxin B 16.0 μg/mL (MIC)	[21]
15-Formamido-kalihinol F (**106/107**)	Antibacterial	Microbroth dilution/*B. subtilis* PY79	50.0 μg/mL (MIC)	-Trimethoprim 1.0 μg/mL (MIC) -Ciprofloxacin 1.0 μg/mL (MIC) -Rifampin 1.0 μg/mL (MIC) -Sulfamethoxazole 4.0 μg/mL (MIC) -Chloramphenicol 16.0 μg/mL (MIC) -Polymyxin B 16.0 μg/mL (MIC)	[21]
Kalihinol G (**108**)	Antibacterial	Microbroth dilution/*B. subtilis* PY79	3.12 μg/mL (MIC)	-Trimethoprim 1.0 μg/mL (MIC) -Ciprofloxacin 1.0 μg/mL (MIC) -Rifampin 1.0 μg/mL (MIC) -Sulfamethoxazole 4.0 μg/mL (MIC) -Chloramphenicol 16.0 μg/mL (MIC) -Polymyxin B 16.0 μg/mL (MIC)	[21]
10-*epi*-Kalihinol I (**115**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	0.27 μM (EC_{50})	Seawater + DMSO	[16]
	Cytotoxicity	MTT/HCT-116	28.67 μM (IC_{50})	-	[16]
Kalihinol J (**116**)	Antibacterial	Microbroth dilution/*B. subtilis* PY79	50.0 μg/mL (MIC)	-Trimethoprim 1.0 μg/mL (MIC) -Ciprofloxacin 1.0 μg/mL (MIC) -Rifampin 1.0 μg/mL (MIC) -Sulfamethoxazole 4.0 μg/mL (MIC) -Chloramphenicol 16.0 μg/mL (MIC) -Polymyxin B 16.0 μg/mL (MIC)	[21]
Kalihinol O (**119**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	1.43 μM (EC_{50})	Seawater + DMSO	[16]
	Cytotoxicity	MTT/HCT-116	5.97 μM (IC_{50})	-	[16]
Kalihinol P (**120**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	0.72 μM (EC_{50})	Seawater + DMSO	[16]
	Cytotoxicity	MTT/HCT-116	10.68 μM (IC_{50})	-	[16]
		MTT/H1299	26.21 μM (IC_{50})	-	[16]
Kalihinol Q (**121**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	1.48 μM (EC_{50})	Seawater + DMSO	[16]
	Cytotoxicity	MTT/HCT-116	20.55 μM (IC_{50})	-	[16]
Kalihinol R (**122**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	1.16 μM (EC_{50})	Seawater + DMSO	[16]
	Cytotoxicity	MTT/HCT-116	13.44 μM (IC_{50})	-	[16]
Kalihinol S (**123**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	0.53 μM (EC_{50})	Seawater + DMSO	[16]

Table 6. *Cont.*

Compound Name	Biological Activity	Assay, Organism or Cell Line	Biological Results		Ref.
			Compound	Positive Control	
Kalihinol T (**124**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	0.74 μM (EC_{50})	Seawater + DMSO	[16]
10-*epi*-Kalihinol X (**126**)	Cytotoxicity	MTT/A549	9.30 μg/mL (IC_{50})	-	[42]
	Antifouling	Settlement inhibition/*Balanus amphitrite*	0.69 μM (EC_{50})	Seawater + DMSO	[16]
	Cytotoxicity	MTT/HCT-116	8.21 μM (IC_{50})	-	[16]
Kalihiacyloxyamide C (**133**)	Cytotoxicity	SRB/L-02	14.6 μM (IC_{50})	Doxorubicin not detected	[62]
		MTT/K562	6.4 μM (IC_{50})	Doxorubicin < 1.04 μM (IC_{50})	[62]
		SRB/ASPC-1	19.0 μM (IC_{50})	Doxorubicin < 1.04 μM (IC_{50})	[62]
		SRB/H69AR	12.0 μM (IC_{50})	Doxorubicin 15.1 μM (IC_{50})	[62]
		SRB/MDA-MB-231	12.5 μM (IC_{50})	Doxorubicin < 1.04 μM (IC_{50})	[62]
Kalihiacyloxyamide D (**134**)	Cytotoxicity	SRB/L-02	8.0 μM (IC_{50})	Doxorubicin not detected	[62]
		MTT/K562	6.3 μM (IC_{50})	Doxorubicin < 1.04 μM (IC_{50})	[62]
		SRB/MDA-MB-231	7.3 μM (IC_{50})	Doxorubicin < 1.04 μM (IC_{50})	[62]
Kalihiacyloxyamide G (**137**)	Cytotoxicity	SRB/L-02	19.2 μM (IC_{50})	Doxorubicin not detected	[62]
		MTT/K562	15.0 μM (IC_{50})	Doxorubicin < 1.04 μM (IC_{50})	[62]
		SRB/MDA-MB-231	13.4 μM (IC_{50})	Doxorubicin < 1.04 μM (IC_{50})	[62]
Kalihiacyloxyamide H (**138**)	Cytotoxicity	SRB/H69AR	16.8 μM (IC_{50})	Doxorubicin 15.1 μM (IC_{50})	[62]
		SRB/MDA-MB-231	12.5 μM (IC_{50})	Doxorubicin < 1.04 μM (IC_{50})	[62]
Kalihinene (**139**)	Cytotoxicity	MTT/P388	1.2 μg/mL	-	[23]
	Antibacterial	Microbroth dilution/*B. subtilis* PY79	6.25 μg/mL (MIC)	-Trimethoprim 1.0 μg/mL (MIC) -Ciprofloxacin 1.0 μg/mL (MIC) -Rifampin 1.0 μg/mL (MIC) -Sulfamethoxazole 4.0 μg/mL (MIC) -Chloramphenicol 16.0 μg/mL (MIC) -Polymyxin B 16.0 μg/mL (MIC)	[21]
Kalihinene E (**145**)	Cytotoxicity	MTT/HCT-116	14.36 μM (IC_{50})	Camptothecin 9.25 μM (IC_{50})	[63]
		MTT/HeLa	13.36 μM (IC_{50})	Camptothecin 6.98 μM (IC_{50})	[63]
		MTT/QGY-7701	17.78 μM (IC_{50})	Camptothecin 4.05 μM (IC_{50})	[63]
		MTT/MDA-MB-231	12.84 μM (IC_{50})	Camptothecin 0.50 μM (IC_{50})	[63]
Kalihinene X (**147**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	0.49 μg/mL (IC_{50})	$CuSO_4$ 0.15 μg/mL (IC_{50})	[55,56]
	Antibacterial	Microbroth dilution/*B. subtilis* PY79	1.56 μg/mL (MIC)	-Trimethoprim 1.0 μg/mL (MIC) -Ciprofloxacin 1.0 μg/mL (MIC) -Rifampin 1.0 μg/mL (MIC) -Sulfamethoxazole 4.0 μg/mL (MIC) -Chloramphenicol 16.0 μg/mL (MIC) -Polymyxin B 16.0 μg/mL (MIC)	[21]
	Cytotoxicity	MTT/HCT-116	12.25 μM (IC_{50})	Camptothecin 9.25 μM (IC_{50})	[63]
		MTT/A549	8.55 μM (IC_{50})	Camptothecin 2.32 μM (IC_{50})	[63]
		MTT/HeLa	10.59 μM (IC_{50})	Camptothecin 6.98 μM (IC_{50})	[63]
		MTT/QGY-7701	13.02 μM (IC_{50})	Camptothecin 4.05 μM (IC_{50})	[63]
		MTT/MDA-MB-231	7.46 μM (IC_{50})	Camptothecin 0.50 μM (IC_{50})	[63]
Kalihinene Y (**148**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	0.45 μg/mL (IC_{50})	$CuSO_4$ 0.15 μg/mL (IC_{50})	[55,56]
	Antibacterial	Microbroth dilution/*B. subtilis* PY79	1.56 μg/mL (MIC)	-Trimethoprim 1.0 μg/mL (MIC) -Ciprofloxacin 1.0 μg/mL (MIC) -Rifampin 1.0 μg/mL (MIC) -Sulfamethoxazole 4.0 μg/mL (MIC) -Chloramphenicol 16.0 μg/mL (MIC) -Polymyxin B 16.0 μg/mL (MIC)	[21]
	Cytotoxicity	MTT/A549	16.12 μM (IC_{50})	Camptothecin 2.32 μM (IC_{50})	[63]
		MTT/HeLa	10.05 μM (IC_{50})	Camptothecin 6.98 μM (IC_{50})	[63]
		MTT/QGY-7701	14.41 μM (IC_{50})	Camptothecin 4.05 μM (IC_{50})	[63]
		MTT/MDA-MB-231	15.23 μM (IC_{50})	Camptothecin 0.50 μM (IC_{50})	[63]
Kalihinene Z (**149**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	1.1 μg/mL (IC_{50})	$CuSO_4$ 0.15 μg/mL (IC_{50})	[55,56]
10-Formamidokalihinene (**150**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	0.095 μg/mL (IC_{50})	$CuSO_4$ 0.15 μg/mL (IC_{50})	[55,56]
	Cytotoxicity	MTT/A549	6.98 μM (IC_{50})	Camptothecin 2.32 μM (IC_{50})	[63]
		MTT/HeLa	13.30 μM (IC_{50})	Camptothecin 6.98 μM (IC_{50})	[63]
		MTT/QGY-7701	14.53 μM (IC_{50})	Camptothecin 4.05 μM (IC_{50})	[63]
		MTT/MDA-MB-231	6.84 μM (IC_{50})	Camptothecin 0.50 μM (IC_{50})	[63]
15-Formamidokalihinene (**151**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	0.14 μg/mL (IC_{50})	$CuSO_4$ 0.15 μg/mL (IC_{50})	[55]
		MTT/A549	17.53 μM (IC_{50})	Camptothecin 2.32 μM (IC_{50})	[63]
		MTT/HeLa	14.74 μM (IC_{50})	Camptothecin 6.98 μM (IC_{50})	[63]
		MTT/QGY-7701	16.39 μM (IC_{50})	Camptothecin 4.05 μM (IC_{50})	[63]

Table 6. *Cont.*

Compound Name	Biological Activity	Assay, Organism or Cell Line	Biological Results		Ref.
			Compound	Positive Control	
Kalihipyran A (**165**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	1.3 μg/mL (IC_{50})	$CuSO_4$ 0.15 μg/mL (IC_{50})	[55]
	Cytotoxicity	MTT/A549	13.09 μM (IC_{50})	Camptothecin 2.32 μM (IC_{50})	[63]
		MTT/HeLa	11.19 μM (IC_{50})	Camptothecin 6.98 μM (IC_{50})	[63]
		MTT/QGY-7701	13.53 μM (IC_{50})	Camptothecin 4.05 μM (IC_{50})	[63]
Kalihipyran B (**166**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	0.85 μg/mL (IC_{50})	$CuSO_4$ 0.15 μg/mL (IC_{50})	[55]
Cavernene A (**169**)	Cytotoxicity	MTT/HCT-116	6.31 μM (IC_{50})	Camptothecin 9.25 μM (IC_{50})	[63]
	Cytotoxicity	MTT/HCT-116	8.99 μM (IC_{50})	Camptothecin 9.25 μM (IC_{50})	[63]
Biflora-4,9,15-triene (**168**)	Antifouling	Settlement inhibition/*Balanus amphitrite*	9.7 μg/mL (IC_{50})	$CuSO_4$ 0.15 μg/mL (IC_{50})	[55]
Hymenialdisine (**185**)	Cytotoxicity	AlamarBlue/A2780S	146.8 μM (IC_{50})	Cisplatin 31.4 μM (IC_{50})	[82]
2β-Hydroxy-4,7-diketo-A-norcholest-5-en-2-oic acid (**208**)	Antifouling	Settlement inhibition/*Balanus albicostatus*	8.2 μg/mL EC_{50})	Capsaicin 1.32 μg/mL (EC_{50})	[74]
24*S*-Ethyl-2β-hydroxy-4,7-diketo-A-norcholest-5-en-2-oic acid (**209**)	Antifouling	Settlement inhibition/*Balanus albicostatus*	23.5 μg/mL (EC_{50})	Capsaicin 1.32 μg/mL (EC_{50})	[74]
2β-Hydroxy-4,7-diketo-24*R*-methyl-A-norcholest-5,22(*E*)-diene-2-oic acid (**210**)	Antifouling	Settlement inhibition/*Balanus albicostatus*	31.6 μg/mL (EC_{50})	Capsaicin 1.32 μg/mL (EC_{50})	[74]

Additionally, **100** displayed antimicrobial effectiveness versus *S. aureus*, *B. subtilis*, and *C. albicans* [83]. Compound **125** was found to have notable antimicrobial potential against *S. aureus*, *C. albicans*, and *T. mentagrophytes* [18]. Bugni et al. assessed the antibacterial activity of **88**, **100**, **104**–**108**, **116**, **125**, **127**, and **139** through in vitro inhibition of *B. subtilis* PY79 growth, as well as inhibition of bacterial folate biosynthesis using agar diffusion/microbroth dilution and luminescence rescue assays, respectively [21]. The results showed that the pyranyl-type **127** and **125** (MICs of 1.56 μg/mL) revealed a potent antibacterial potential; however, they only weakly inhibited the folate biosynthesis, suggesting an additional mechanism of action for these pyranyl derivatives. On the other hand, the furanyl-type **100**, **108**, and **139** displayed a more selective folate biosynthesis inhibition than pyranyl-type kalihinols. The existence of a formamido moiety at any position markedly decreased the activity, which could be due to a reduced cellular uptake. Additionally, the C-10 substitution pattern greatly affected the potency, which was evident by loss of activity in **88**, which differs in the C-10 isonitrile group orientation from the potent **127** and **125** (which have an *exo*-methylene and isothiocyanate groups, respectively) [21]. Xu et al. reported that **151** showed antifungal activity against *T. rubrum* and *M. gypseum* (MICs of 8.0 and 32.0 μg/mL, respectively), while **150** had activity against *C. albicans*, *C. neoformans*, *T. rubrum*, and *M. gypseum* (MICs of 4.0–8.0 μg/mL). It was noted that the isonitrile functionalities had a substantial role in antifungal activity [63]. The antifungal effects of **20**, **177**, **178**, **217**, and **220**–**222** against phytopathogenic fungi *Fusarium oxysporum* f. sp. *niveum*, *F. solani* f. sp. *cucurbitae*, *Pythium ultimum*, and *Alternaria solani* were assessed. Compounds **177**, **178**, and **220**–**222** had antifungal activities against *A. solani*, whereas **20** was the most active against *F. oxysporom*, *F. solani*, and *A. solani* (IZDs of 11.5 to 25.0 mm) [25]. None of them exhibited activity towards *P. ultimum* [25].

Fouling is the deposition and accumulation of living organisms (biofouling) and certain non-living materials on hard surfaces, most frequently in the aquatic environment, which results in serious economic problems [74]. Organotin compounds are the widely used chemicals for controlling these sessile organisms. These compounds are under criticism due to environmental and ecosystem concerns that necessitate the need for the development of nontoxic alternatives. Some soft corals and marine sponges produce environmentally friendly antifoulant secondary metabolites that provide chemical defenses against biofouling.

Compounds **5**, **9**, **23**, **32**, **66**, **75**, **76**, **85**, **89**, **91**, **92**, **98**, **99**, and **168** were examined for their antifouling potential through the prohibition of the settlement of the barnacle *Balanus amphitrite* larvae. Compounds **32**, **89**, **91**, **92**, **98**, and **99** inhibited metamorphosis and larval settlement by 100%. Additionally, **89**, **91**, **92**, **98**, and **99** showed 100% inhibition of the larval settlement and metamorphosis (at concentrations of 0.05 to 5.0 µg/mL). Isocyanate and isothiocyanate analogs **91** and **92** (EC_{50} ca. 0.05 µg/mL) had high antifouling capacities [40]. Compounds **65** and **67** (EC_{50}s 0.50 and 0.53 µg/mL, respectively) prohibited *B. amphitrite* larval settlement with much less toxicity to larvae than $CuSO_4$, while **65** had a much higher toxicity than **67** [49]. In addition, the related metabolites with isocyano and isothiocyanato moieties (**47**, **63**, and **64**) had marked antifouling capacities, with ED50 values of 7.2, 0.70, and 0.14 µg/mL, respectively [49]. In 2006, compounds **88**–**90** were evaluated against bacterial strains which induce *Hydroides elegans* larval settlement (*Micrococcus luteus*, *Loktanella hongkongensis*, *Pseudoalteromonas* sp., *Ruegeria CtaxMed-2*, *Rhodovulum* sp. MB-253, *Staphylococcus haemolyticus*, *Vibrio halioticoli*, *Vibrio* sp. NAP4, and *Vibrio fluvialis*) and marine pathogenic bacteria (*Shewanella algae*, *Moraxella phenylpyruvica*, *S. aureus*, *Vibrio vulnificus*, and *Vibrio furnissii*) using a disc diffusion assay [58]. These compounds strongly prohibited the growth of larval settlement-promoting strains *S. haemolyticus*, *L. hongkongensis*, and *M. luteus* (IZDs of 8.17–10.67 mm) compared to streptomycin. Additionally, they possessed powerful antibacterial efficacies versus pathogenic strains *V. furnissii* and *S. aureus* (IZDs of 5–7 mm) compared to streptomycin (IZD of 0.83–2.50 mm). Compound **88** was found to effectively suppress larval settlement (EC_{50} 0.5 µg/mL), and was further incorporated in Phytagel®. This compound slightly reduced thet bacterial abundance, but it modified the bacterial species composition in the biofilm, suggesting its capacity to change the bacterial community composition, which in turn modulates the larval settlement of fouling organisms [58]. Compounds **88**, **89**, **92, 98**, **115**, **119**–**124**, and **126** displayed significant antifouling activities against *B. amphitrite* larvae (EC_{50}s of 0.41 to 1.43 µM) [16]. It was found that the compounds with an equatorial-Cl and isothiocyanate group had more activity. Compound **92** had a significant antifouling activity without cytotoxicity, which could indicate its potential as an antifouling agent [16]. Compounds **88**, **147**–**151**,**165**, **166**, and **168** were assessed for their antifouling activity against cyprid larvae of the barnacle *Balanus amphitrite*. The novel compounds **165** and **166** suppressed larval settlement and metamorphosis of the barnacle *Balanus amphitrite* (IC_{50}s 1.3 and 0.85 µg/mL, respectively), which was comparable to **147**–**149** (IC_{50}s of 0.49, 0.45, and 1.1 µg/mL, respectively) with low toxicity, whereas the isocyano derivatives **88**, **150**, and **151** (IC_{50}s of 0.087, 0.095, and 0.14 µg/mL, respectively) were more efficient. Interestingly, **168** was moderately active (IC_{50} 4.6 µg/mL) and **88** and **150** were more active than $CuSO_4$ (IC_{50} 0.15 µg/mL) [55,56]. Besides, **185** was found to have a significant antifouling capacity against *P. viridis* (EC_{50} 31.77 µg/mL in a mussel bioassay), *B. neritina* (EC_{50} 3.43 µg/mL in a bryozoan bioassay), and *U. prolifera* (EC_{50} 8.31 µg/mL in an algal bioassay). These results suggest that **185** may play a role in chemical defense against fouling in *Acanthella* sp. [69]. In addition to the potent anti-fouling diterpenes reported from *A. cavernosa*, Qui et al. stated that the nor-steroids **208**–**210** biosynthesized by *A. cavernosa* also demonstrated marked antifouling potentials (EC_{50}s of 8.2, 23.5, and 31.6 µg/mL, respectively) towards the *Balanus albicostatus* larval settlement compared to capsaicin (EC_{50} of 1.32 µg/mL) in a settlement inhibition assay [74].

4.2. Cytotoxic Activity

The MeOH extracts of *A. elongata* from fishing nets of Kanyakumari revealed a toxicity (LC_{50} of 0.51 µg/mL) on *Artemia salina* in a brine shrimp bioassay [84]. In the MTT assay, *A. carteri* hydro-EtOH extracts had promising activities against HT-29, T47D, and Casky cell lines (IC_{50}s of 37.56, 482.84, and 37.64 µg/mL, respectively) [85], while *A. acuta* MeOH extracts displayed notable cytotoxic activities versus LS174 and HeLa cell lines (IC_{50}s of 9.92 and 29.51 µg/mL, respectively) [86].

Compounds **95** and **139** exhibited a cytotoxic efficacy on P388 murine leukemia cells (IC_{50}s of 0.8 and 1.2 µg/mL, respectively) [61]. Compound **100** is a tetrahydrofuran-containing kalihinol with three isonitrile functionalities at C-5, C-10, and C-15 and was obtained from *Acanthella* sp. from the Cape Sada coast (Ehime Prefecture, Japan). This compound was found to have topoisomerase-I inhibition capacity by prohibiting the chromosome separation in *Asterina pectinifera* (fertilized starfish) eggs, while it did not affect topoisomerase II and DNA polymerases (α, β, and γ) [61]. In an MTT assay, **9, 17**, **97**, and **126** exhibited moderate in vitro cytotoxic capacities versus A549 (IC_{50}s of 1.98–9.30 µg/mL) [42], whilst **88, 98**, **115, 119–121,** and **126** demonstrated cytotoxic potential against HCT-116 (IC_{50}s of 5.97 to 28.67 µM) [16]. Compounds **169** and **170** showed potent cytotoxic potential against HCT-116 (IC_{50}s of 6.31 and 8.99 µM, respectively) compared to camptothecin (IC_{50} of 9.25 µM), whereas **145** had activity against HCT-116, HeLa, QGY-7701, and MDA-MB-231 (IC_{50} of 12.84 to 17.78 µM) [63]. Furthermore, **157** was found to demonstrate a potent cytotoxic potential (IC_{50}s of 6.57 and 3.60 µM, respectively) towards K562 and H69 cells, whereas **158** revealed moderate (IC_{50} of 8.73 µM) capacity against K562 cells compared to doxorubicin (IC_{50}s of 0.252 and 0.980 µM, respectively) [64]. Compounds **133** and **135** exhibited cytotoxicity against K562 cell lines (IC_{50}s of 6.4 and 6.3 µM, respectively), while **135** and **138** were active against MDA-MB-231 cell lines (IC_{50}s of 7.3 and 7.9 µM, respectively) compared to doxorubicin (IC_{50} of <1 µM) [62]. Compounds **175–177** and **179** showed in vitro cytotoxic capacity against NSCLC-N6 (IC_{50}s ranging from 4.8 to 11.2 µg/mL) [66]. In 2021, Abdullah et al. reported that **185** was less toxic versus A2780S cells (IC_{50} of 146.8 µM) and had no activity versus A2780CP compared to cisplatin (IC_{50} of 31.4 µM for A2780S and 76.9 µM for A2780CP) in an alamarBlue® assay [82]. The guanidine-containing alkaloids **191–193** were evaluated for the cellular stability of PDCD4 (Programmed cell death 4) using HEK-293 cells [24]. Compounds **191** and **193** were found to suppress TPA (tetradecanoylphorbol-13-acetate)-induced degradation of PDCD4 (EC_{50}s of 1.8 and 2.8 µg/mL, respectively) compared to rapamycin (EC_{50} of 0.02 µg/mL), while **192** had no activity. It is noteworthy that **191** and **193** are the first marine natural metabolites that stabilized PDCD4 under tumor-promoting conditions [24].

4.3. Larvicidal and Antimalarial Activities

The larvicidal potential of *A. elongata* (doses of 0.01% to 10.0% for 24h) collected from Kanyakumari was assessed against s mosquito vector of filariasis, *Culex* sp. 3rd instar larvae. Its MeOH extract exhibited potent larvicidal capacity (LC_{50} of 0.066 mg/mL), suggesting the potential of *A. elongata* extracts for the development of novel larvicidal agents [87]. Whilst the *n*-BuOH, *n*-hexane, aqueous, and EtOAc fractions (IC50s of 9.5, 4.6, 15.0, and 3.3 µg/mL, respectively) of *A. cavernosa* extracts had the ability to prohibit heme polymerization, revealing their anti-malarial potential [88].

Compounds **17**, **23**, **42**, and **45** demonstrated in vitro, dose-dependent antimalarial activity against *P. falciparum* (IC_{50}s of 142 to 12340 ng/mL for D6 and 16.5 to 3110 ng/mL for W2) compared to chloroquine (IC_{50} of 1.95 ng/mL for D6 and 22.8 ng/mL for W2), where **17** was the most active. It was found that the isonitrile group was crucial and isothiocyanate derivative **23** was 500-fold less active than **17**. The eudesmane isothiocyanates **42** and **45** have lower potential than **17** [19]. Compounds **88**, **108**, **110**, **111**, **114**, **115**, **127**, **129**, **139**, and **153** were assessed for their antimalarial activity [57]. Among the tested compounds, **88** was found to display potent in vitro (EC_{50} of 1.2×10^{-9} M) and selective (SI of 317) antimalarial effectiveness, whereas **115**, **110**, **139**, and **153** had EC_{50}s from 8.0×10^{-8} M to $>1.8 \times 10^{-6}$ M against *P. falciparum* compared to mefloquine (EC_{50} of 3.2×10^{-8} M) [57].

4.4. Cyclooxygenase Inhibitory and α2B Adrenoceptor Agonistic Activities

Compound **84** displayed promising dose-dependent anti-inflammatory activity through inhibition of TNF-α and CCL2 (% inhibition ratios of 74.1% and 64.1%, respectively) at a concentration of 1 µM in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages [43]. Yan et al. reported that **88** revealed significant COX-2 (IC_{50} of 1.07 µM) inhibitory activity [41]. In 2009, Davis et al. stated that **188** showed α2B adrenoceptor agonist activity (EC_{50}

of 4.2 μM) compared to noradrenaline in a α2B adrenoceptor FLIPR (fluorescence imaging plate reader) assay in HEK 293 cells [70].

4.5. Insecticidal and Anthelmintic Activities

Hammami et al. evaluated the insecticidal effect of **34** against *Tribolium confusum* Duv (major pest of stored products) using the direct contact application method; it was found to prohibit *Tribolium confusum* Duv larvae growth (45% mortality at a concentration of 10 mg/mL) [25]. An in vitro anthelmintic assay of *A. carvenosa*-derived kalihinols against *Nippostrongylus brasilliensis* (gastrointestinal roundworm) (at 50 μg/mL) demonstrated that **127** had extreme activity; however, **114**, **88**, **125**, and **130** were potent and **101** was inactive [18,53].

4.6. Antioxidant Activity

A. carteri hydro-EtOH extracts revealed a DPPH scavenging ability (IC_{50} of 56.94 μg/mL) compared to ascorbic acid (IC_{50} of 0.67 μg/mL) [85]. Putra et al. stated that *n*-BuOH fractions of *A. cavernosa* had the largest phenolic content, followed by EtOAc, aqueous, and *n*-hexane fractions. These fractions demonstrated antioxidant potential with the % inhibition of DPPH radicals ranging from 16.40 to 40.57%, whereas the *n*-hexane fraction displayed the most powerful DPPH radical suppression (at a concentration of 171.86 μg/mL) [88].

5. Nanoparticles

Synthesis of nanoparticles (NPs) with green technology is beneficial over chemical procedures because of their lower environmental impacts [89,90]. The use of biological extracts of living organisms, such as actinomycetes, bacteria, yeast, plants, marine sponges, and fungi, in green synthetic processes indicates their considerable potential for NP synthesis [89]. Some researchers have reported the biosynthesis of NPs using species of the genus *Acanthella* that are cost-effective and compatible with pharmaceutical and biomedical applications and could be utilized commercially for large-scale production. In 2010, Inbakandan et al. synthesized highly stable AuNPs (gold nanoparticles) using an *A. elongata* extract by reducing aqueous $AuCl_4^-$, suggesting that this sponge is a perfect candidate for AuNP synthesis [91]. In another study in 2012, AgNPs were synthesized using the H_2O-soluble extract of *A. elongata*. These NPs were characterized by UV, XRD (X-ray diffraction), TEM (transmission electron microscopy), and FTIR (Fourier transform infrared spectroscopy). It was found that amines of the sponge extract were accountable for the bio-reduction of the silver salt to the AgNps [90].

6. Conclusions

The current work presents extensive documentation of the reported studies on the genus *Acanthella* with a special focus on their diverse chemical classes of metabolites and their bioactivities. The sponges of this genus were obtained from various marine environments. A total of 226 metabolites from various species of this genus were reported in the period from 1974 to the beginning of 2023. These metabolites illustrated in this work belong mainly to terpene (sesqui- and di-terpenes), alkaloid, and steroid chemical classes (Figure 21).

Metabolites have been reported from *A. cavernosa*, *A. pulcherrima*, *A. klethra*, *A. acuta*, *A. carteri*, *A. costata*, *A. vulgate*, and unidentified *Acanthella* species. *A. cavernosa* (177 compounds), *Acanthella* sp. (36 compounds), and *A. acuta* (17 compounds) are frequently studied members of this genus in terms of the number of isolated compounds and have proven to be rich in terpenes and alkaloids (Figure 22). Interestingly, kalihinane-type diterpenoids are commonly purified from *A. carvenosa*, which could be a chemotaxonomic marker for this sponge.

In addition, bioactivity investigations of some species extracts are detailed in the literature. Sesquiterpene- and diterpene-containing nitrogen and alkaloids were the dominant metabolites reported from the species of genus *Acanthella*. These metabolites were mainly assessed for antifouling, antimicrobial, and cytotoxic activities. Limited studies have reported the larvicidal, antimalarial, cyclooxygenase inhibitory, α2B adrenoceptor

agonistic, insecticidal, and anthelmintic capacities of these compounds. It is noteworthy that some kalihinol and kalihinene diterpenes have marked antifouling potentials. Additionally, **88** demonstrated notable antifouling, cytotoxic, antimalarial, COX-2 inhibition, and anthelmintic activities. The diverse structural features and bioactivities demonstrated by some of these metabolites make them attractive biological targets that are worthy of further investigation.

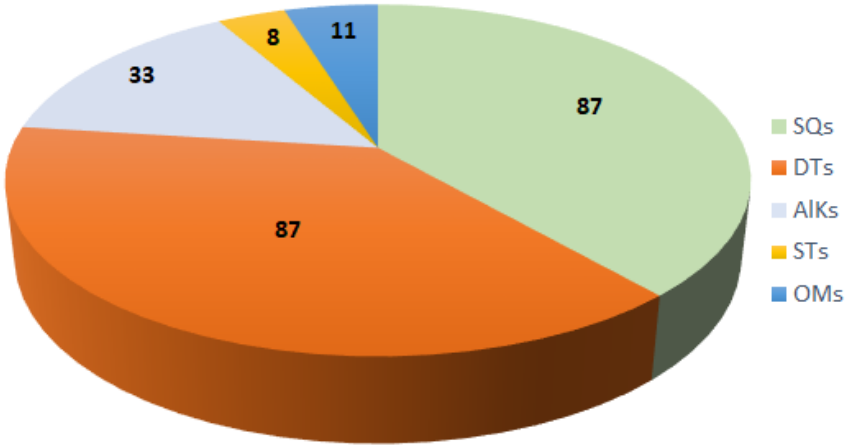


Figure 21. Different classes of metabolites reported from the genus *Acanthella*. SQs: sesquiterpenes; DTs: diterpenes; AlKs: alkaloids; STs: steroid compounds; OMs: other metabolites.

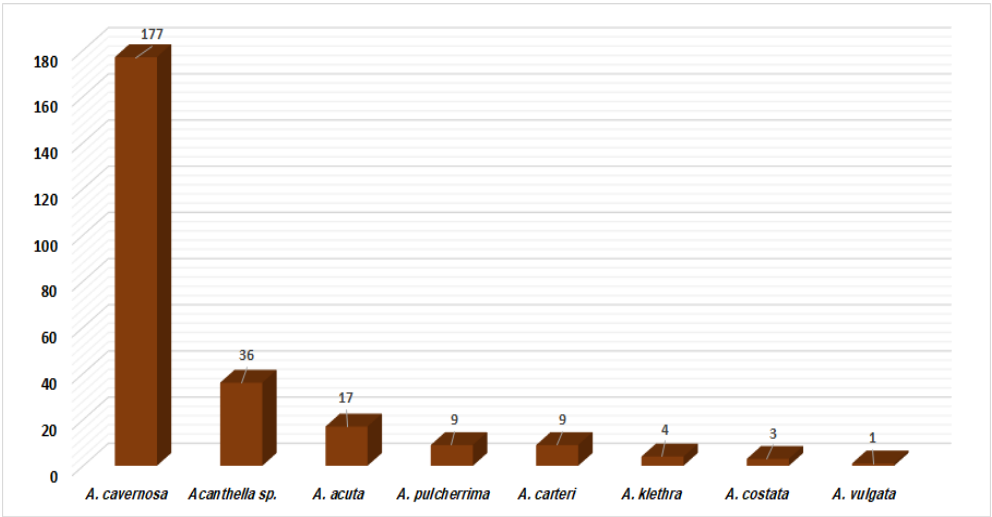


Figure 22. Number of compounds reported from each studied *Acanthella* species.

Author Contributions: Conceptualization, S.R.M.I. and G.A.M.; methodology, S.R.M.I., G.A.M., S.G.A.M., K.F.G., S.F.M. and D.F.A.; software, K.F.G., S.F.M. and D.F.A.; writing—original draft preparation, S.R.M.I., S.G.A.M. and G.A.M.; writing—review and editing, S.G.A.M., K.F.G., S.F.M. and D.F.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

A549	Human lung adenocarcinoma epithelial cell line
A2780s	Human ovarian cancer cell line
A2780CP	Human ovarian cancer cell line
ASPC-1	Human pancreatic cancer cell line
CCL2	C–C motif chemokine ligand 2
CD	Circular dichroism
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
COX-2	Cyclooxygenase-2
CT-26	Murine colorectal carcinoma cell line
DKPs	Diketopiperazines
DPPH	1,1-diphenyl-2-picrylhydrazyl
EC_{50}	Half maximal effective concentration
EtOAc	Ethyl acetate
H69	Chemo-sensitive human small cell lung cancer cell line
H69AR	Chemo-resistant human small cell lung cancer cell line
H1299	Human non-small cell lung carcinoma cell line
HCT-116	Human colon cancer cell line
HeLa	Human cervical epithelioid carcinoma cell line
HPLC	High-performance liquid chromatography
HRESIMS	High-resolution electrospray ionization mass spectroscopy
HT-29	Human colon cancer cell line
IZD	Inhibition zone diameter
K562	Human erythroleukemic cell line
KB	Human oral epidermoid carcinoma cell line
L02	Human liver cell line
LC_{50}	Lethal concentration that kills 50%
LD_{50}	Half maximal lethal concentration
LD100	Maximal lethal concentration
IR	Infrared
LPS	Lipopolysaccharide
Ls174T	Human colorectal cancer cell line
MDA-MB-231	Human breast cancer cell line
MeOH	Methanol
MRC-5	Human lung fibroblasts
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
n-BuOH	n-butanol
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NMR	Nuclear magnetic resonance
P 388	Human leukemia cell line
PC-3	Human prostatic testosterone-independent cell line
PDCD4	Programmed cell death **4**
QGY-7701	Human hepatocellular carcinoma cell line
QM-NMR	Quantum mechanical nuclear magnetic resonance
RP-18	Reversed phase-18
SiO_2 CC	Silica gel column chromatography
T47D	Human hormone-dependent breast cancer cell line
TDDFT-ECD	Time-dependent density functional theory/electronic circular dichroism
TNF-α	Tumor necrosis factor alpha
TPA	Tetradecanoylphorbol-13-acetate

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