Secondary Metabolites of Genus *Acanthella*

Subjects: Marine & Freshwater Biology
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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. 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.

Acanthella Axinellidae nitrogen-containing terpenoids Life below water

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 1**). 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 [1]. 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 [2]. 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 [2].

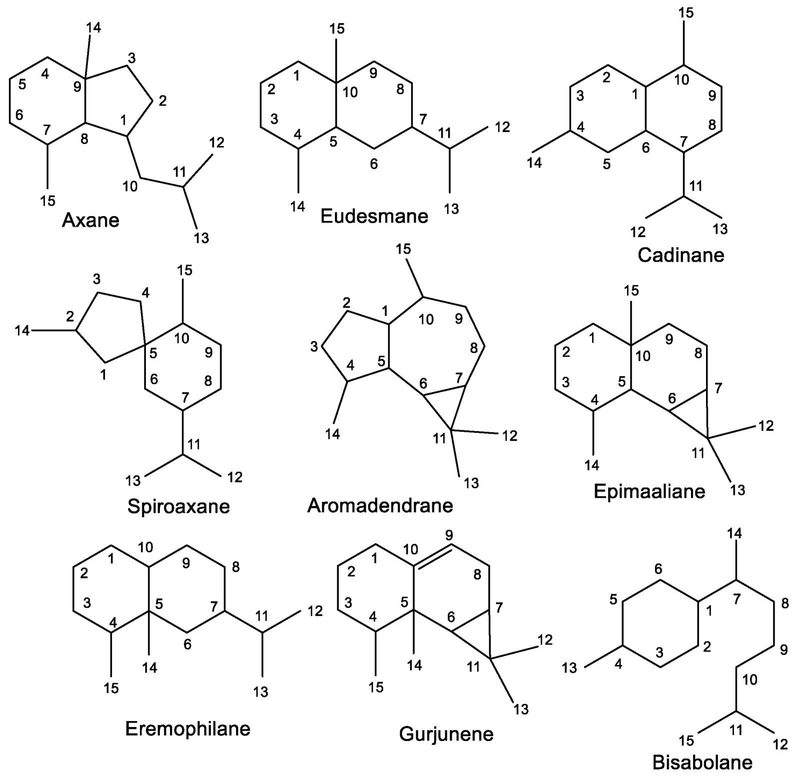


Figure 1. Classes of sesquiterpenes reported from the genus *Acanthella*.

Table 1. 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	[3]
(+)-Axamide 2 (**2**)	249	$C_{16}H_{27}NO$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
l-Isocyanoaromadendrane (**3**)	231	$C_{16}H_{25}N$	*A. acuta*	Near Banyuls, France	[5] [6]
	-	-	*A. pulcherrima*	Weed Reef, Darwin, Australia	[6]
	-	-	*A. acuta*	Near Banyuls, France	[7]
	-	-	*A. cavernosa*	Tani's Reef, Mooloolaba,	[8]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
				Australia	
	-	-	*A. cavernosa*	Tani's Reef or Coral Gardens dive sites	[9]
Isonitrile 2 (**4**)	231	$C_{16}H_{25}N$	*A. acuta*	Bay of Naples, southern Italy	[10]
(+)-Axisothiocyanate 2 (**5**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Hachijo-jima Island, Japan	[11]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[12]
	-	-	*A. cavernosa*	Tani's Reef or Coral Gardens dive sites	[9]
l-Isothiocyanatearomadendrane (**6**)	263	$C_{16}H_{25}NS$	*A. acuta*	Near Banyuls, France	[7]
	-	-	*A. cavernosa*	Tani's Reef, Mooloolaba, Australia	[8]
1-Isocyanatearomadendrane (**7**)	247	$C_{16}H_{25}NO$	*A. acuta*	Near Banyuls, France	[7]
	-	-	*A. cavernosa*	Tani's Reef or Coral Gardens dive sites	[9]
1-Isothiocyanatoaromadendrane (**8**)	263	$C_{16}H_{25}NS$	*A. acuta*	Bay of Naples, southern Italy	[10]
	-	-	*A. cavernosa*	Tani's Reef or Coral Gardens dive sites	[9]
(+)-10*R*-Isothiocyanatoalloaromadendrane (**9**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Hachijo-jima Island, Japan	[11]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[12]
	-	-	*Acanthella* sp.	Yalong Bay, Hainan, China	[13]
	-	-	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
10α-Isothiocyanoalloaromadendrane (**10**)	263	$C_{16}H_{25}NS$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[6]
	-	-	*A. cavernosa*	Tani's Reef or Coral Gardens dive sites	[9]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[12]
	-	-	*A. cavernosa*	Tani's Reef, Mooloolaba, Australia	[8]
Ximaocavernosin O (**11**)	368	$C_{24}H_{36}N_2O$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
ent-4β,10α-Dihydroxyaromadendrane (**12**)	238	$C_{15}H_{26}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[14]
Palustrol (**13**)	222	$C_{15}H_{26}O$	*A. acuta*	Near Banyuls, France	[5]
	-	-	*A. acuta*	Near Banyuls, France	[7]
10*S*-Viridiflorol (**14**)	222	$C_{15}H_{26}O$	*A. cavernosa*	Hachijo-jima Island, Japan	[11]
10*R*-Viridiflorol (**15**)	222	$C_{15}H_{26}O$	*A. cavernosa*	Hachijo-jima Island, Japan	[11]
(+)-Ximaocavernosin P (**16**)	234	$C_{15}H_{22}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[14]
Spiroaxane-type sesquiterpenes					
Axisonitrile-3 (**17**)	231	$C_{16}H_{25}N$	*A. acuta*	Near Banyuls, France	[5]
	-	-	*A. cavernosa*	Thailand	[15]
	-	-	*A. klethra*	Pelorus Island, Queensland, Australia	[16]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
	-	-	*A. klethra*	Vicinities of Phantom and Pelom Islands, Queensland, Australia	[17]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[2]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[18]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[12]
	-	-	*A. cavernosa*	Tani's Reef, Mooloolaba, Australia	[8]
Isonitrile 1 (**18**)	245	$C_{17}H_{27}N$	*A. acuta*	Bay of Naples, southern Italy	[10]
3-Oxoaxisonitrile-3 (**19**)	245	$C_{16}H_{23}NO$	*Acanthella* sp.	Ximao Sea, Hainan, China	[12]
Axisonitrile-4 (**20**)	231	$C_{16}H_{25}N$	*A. acuta*	Sidi Elghdamssi island, Monastir region, Tunisia	[19]
Axisocyanate-3 (**21**)	247	$C_{16}H_{25}NO$	*A. cavernosa*	Tani's Reef, Mooloolaba, Australia	[8]
(+)-Axisothiocyanate (**22**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
Axisothiocyanate 3 (**23**)	263	$C_{16}H_{25}NS$	*A. klethra*	Pelorus Island, Queensland, Australia	[16]
	-	-	*A. klethra*	Vicinities of Phantom and Pelom Islands, Queensland, Australia	[17]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
	-	-	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[20]
	-	-	*A. cavernosa*	Hachijo-jima Island, Japan	[11]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[2]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[18]
Ximaocavernosin H (**24**)	277	$C_{16}H_{22}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
Ximaocavernosin I (**25**)	279	$C_{16}H_{25}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
Ximaocavernosin J (**26**)	279	$C_{16}H_{25}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
Ximaocavernosin K (**27**)	263	$C_{16}H_{25}NO_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
Ximaocavernosin L (**28**)	265	$C_{16}H_{27}NO_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
Ximaocavernosin M (**29**)	265	$C_{16}H_{27}NO_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
Ximaocavernosin N (**30**)	368	$C_{24}H_{36}N_2O$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
(–)-Axamide 3 (**31**)	249	$C_{16}H_{27}NO$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
Axamide 3 (**32**)	249	$C_{16}H_{27}NO$	*A.*	Hachijo-jima Island,	[11]

Compound Name	**Mol. Wt.**	**Mol. Formula**	**Species**	**Sampling Locations**	**Ref.**
			cavernosa	Japan	
Isothiocyanate 1 (**33**)	277	$C_{17}H_{27}NS$	*A. acuta*	Bay of Naples, southern Italy	[10]
Eudesmane-type sesquiterpenes					
Acanthellin-1 (**34**)	231	$C_{16}H_{25}N$	*A. acuta*	Bay of Naples, southern Italy	[1]
	-	-	*A. acuta*	Near Banyuls, France	[5]
	-	-	*A. acuta*	Bay of Taranto near Porto Cesareo, Southern Italy	[21]
	-	-	*A. acuta*	Sidi Elghdamssi Island, Monastir region, Tunisia	[19]
Acanthene B (**35**)	263	$C_{16}H_{25}NS$	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[20]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[12]
	-	-	*A. cavernosa*	Tani's Reef or Coral Gardens dive sites	[9]
Acanthine B (**36**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
Acanthene C (**37**)	249	$C_{16}H_{27}NO$	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[20]
Axiriabiline A (**38**)	249	$C_{16}H_{27}NO$	*A. cavernosa*	Xidao Island, Hainan, China	[22]
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	[21]
	-	-	*A. acuta*	Bay of Naples, southern Italy	[10]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
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.	[20]
11-Formamido-7βH-eudesm-5-ene (**41**)	249	$C_{16}H_{27}NO$	*A. cavernosa*	Xidao Island, Hainan, China	[22]
11-Isothiocyano-7βH-eudesm-5-ene (**42**)	263	$C_{16}H_{25}NS$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[6]
	-	-	*A. klethra*	Pelorus Island, Queensland, Australia	[16]
	-	-	*A. klethra*	Vicinities of Phantom and Pelom Islands, Queensland, Australia	[17]
	-	-	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[20]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[2]
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	[21]
	-	-	*A. acuta*	Bay of Naples, southern Italy	[10]
	-	-	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[20]
(I*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	[16]
	-	-	*A. klethra*	Vicinities of Phantom and Pelom Islands,	[17]

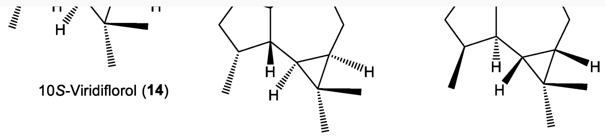
Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
				Queensland, Australia	
	-	-	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[20]
(I*R*,5*R*,6*R*,8*S*)-Dec[4.4.0]ane-1,5-dimethyl-8-(1′-methylethenyl)-5-isothiocyanate (**45**)	263	$C_{16}H_{25}NS$	*A. klethra*	Pelorus Island, Queensland, Australia	[16]
	-	-	*A. klethra*	Vicinities of Phantom and Pelom Islands, Queensland, Australia	[17]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[18]
Cadinene-type sesquiterpenes					
10-Isothiocyanato-4-cadinene (**46**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[18]
	-	-	*A. cavernosa*	Tani’s Reef or Coral Gardens dive sites	[9]
10-Isothiocyanato-4-amorphene (**47**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[18]
	-	-	*A. cavernosa*	Several locations off the Japanese coast	[23]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[12]
	-	-	*A. cavernosa*	Tani’s Reef or Coral Gardens dive sites	[9]
Isomer-10-isothiocyanato-4-amorphene (**48**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[18]
(+)-Ximaocavernosin A (**49**)	295	$C_{16}H_{25}NO_2S$	*A. cavernosa*	Coast of Ximao Island, Hainan,	[14]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
				China	
(±)-Ximaocavernosin A (**50**)	279	$C_{16}H_{25}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
(±)-Ximaocavernosin B (**51**)	279	$C_{16}H_{25}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
(±)-Ximaocavernosin C (**52**)	279	$C_{16}H_{25}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
(+)-Ximaocavernosin D (**53**)	293	$C_{17}H_{27}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
(±)-Ximaocavernosin E (**54**)	295	$C_{16}H_{25}NO_2S$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
(+)-Ximaocavernosin F (**55**)	309	$C_{17}H_{27}NO_2S$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
(±)-Ximaocavernosin G (**56**)	277	$C_{16}H_{23}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
(±)-Axinisothiocyanate J (**57**)	279	$C_{16}H_{25}NOS$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
(±)-Axinisothiocyanate D (**58**)	295	$C_{16}H_{25}NO_2S$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
Axinisothiocyanate A (**59**)	295	$C_{16}H_{25}NO_2S$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[4]
ent-Epicubenol (**60**)	222	$C_{15}H_{26}O$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[6]
Isothiocyanate 4 (**61**)	263	$C_{16}H_{25}NS$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[6]
Epipolasin-A enantiomer-2 (**62**)	263	$C_{16}H_{25}NS$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[6]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
10α-Isocyano-4-amorphene (**63**)	231	$C_{16}H_{25}N$	*A. cavernosa*	Hachijo-Jima Island, Japan	[3]
	-	-	*A. cavernosa*	Several locations off the Japanese coast	[23]
10-Isocyano-4-cadinene (**64**)	231	$C_{16}H_{25}N$	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[18]
	-	-	*A. cavernosa*	Several locations off the Japanese coast	[23]
	-	-	*A. cavernosa*	Tani’s Reef or Coral Gardens dive sites	[9]
10-Formamido-4-cadinene (**65**)	249	$C_{16}H_{27}NO$	*A. cavernosa*	Several locations off the Japanese coast	[23]
	-	-	*A. cavernosa*	Xidao Island, Hainan, China	[22]
(+)-α-Muurolene (**66**)	204	$C_{15}H_{24}$	*A. cavernosa*	Hachijo-jima Island, Japan	[11]
T-cadinol (**67**)	222	$C_{15}H_{26}O$	*A. cavernosa*	Several locations off the Japanese coast	[23]
(+)-Maninsigin D (**68**)	234	$C_{15}H_{22}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[14]
	234	$C_{15}H_{22}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[14]
(-)-Maninsigin D (**69**)	234	$C_{15}H_{22}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[14]
(+)-Ximaocavernosin Q (**70**)	234	$C_{15}H_{22}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[14]
(-)-Ximaocavernosin Q (**71**)	234	$C_{15}H_{22}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[14]
Cadalene (**72**)	198	$C_{15}H_{18}$	*A. cavernosa*	Coast of Ximao Island, Hainan,	[14]

1.1. Aromadendrane-Type Sesquiterpenes

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
				China	
trans-4,5-Dihydroxycorocalane (**73**)	234	$C_{15}H_{22}O_2$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[14]
Axane-type sesquiterpenes					
Cavernoisonitrile (**74**)	245	$C_{16}H_{23}NO$	*A. cavernosa*	Hachijo-Jima Island, Japan	[3]
(-)-Cavernothiocyanate (**75**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Hachijo-Jima Island, Japan	[3]
	-	-	*A. cavernosa*	Hachijo-jima Island, Japan	[11]
1β-H,7α-methyl,8α-H,9β-methyl-Cavernothiocyanate (**76**)	263	$C_{16}H_{25}NS$	*A. cavernosa*	Hachijo-jima Island, Japan	[11]
Bisabolene-type sesquiterpenes					
7-Isocyano-7,8-dihydro-α-bisabolene (**77**)	231	$C_{16}H_{25}N$	*A. cavernosa*	Hachijo-Jima Island, Japan	[3]
Epimaaliane-type sesquiterpenes					
(+)-Epipolasin-A (**78**)	263	$C_{16}H_{25}NS$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[6]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[2]
Epipolasin-A enantiomer-1 (**79**)	263	$C_{16}H_{25}NS$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[6]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[12]
5-Formamide-isonitrile (**80**)	249	$C_{16}H_{27}NO$	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[20]
Isonitrile 4 (**81**)	231	$C_{16}H_{25}N$	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[20]



10*S*-Viridiflorol (**14**)

10*R*-Viridiflorol (**15**)

(+)-Ximaocavernosin P (**16**)

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
Maaliol (**82**)	222	$C_{15}H_{26}O$	*A. pulcherrima*	Weed Reef, Darwin, Australia	[6]
Acanthene A (**83**) [12]	240	$C_{15}H_{25}Cl$ [25][26]	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[20]
Gurjunene					
[8][16] (+)-Aristolone (**84**)	218	$C_{15}H_{22}O$	*A. cavernosa*	Coast of Ximao Island, Hainan, China	[14]
	-	2 - [4]	*A. cavernosa*	South China Sea	[24]
(+)-9-Aristolene (**85**)	204	$C_{15}H_{24}$	*A. cavernosa*	Hachijo-jima Island, Japan	[11]
Isonitrile 3 (**86**) [22]	231	$C_{16}H_{25}N$	*A. acuta*	Bay of Naples, southern Italy	[10]
Isothiocyanate 3 (**87**)	263	$C_{16}H_{25}NS$	*A. acuta*	Bay of Naples, southern Italy	[10]

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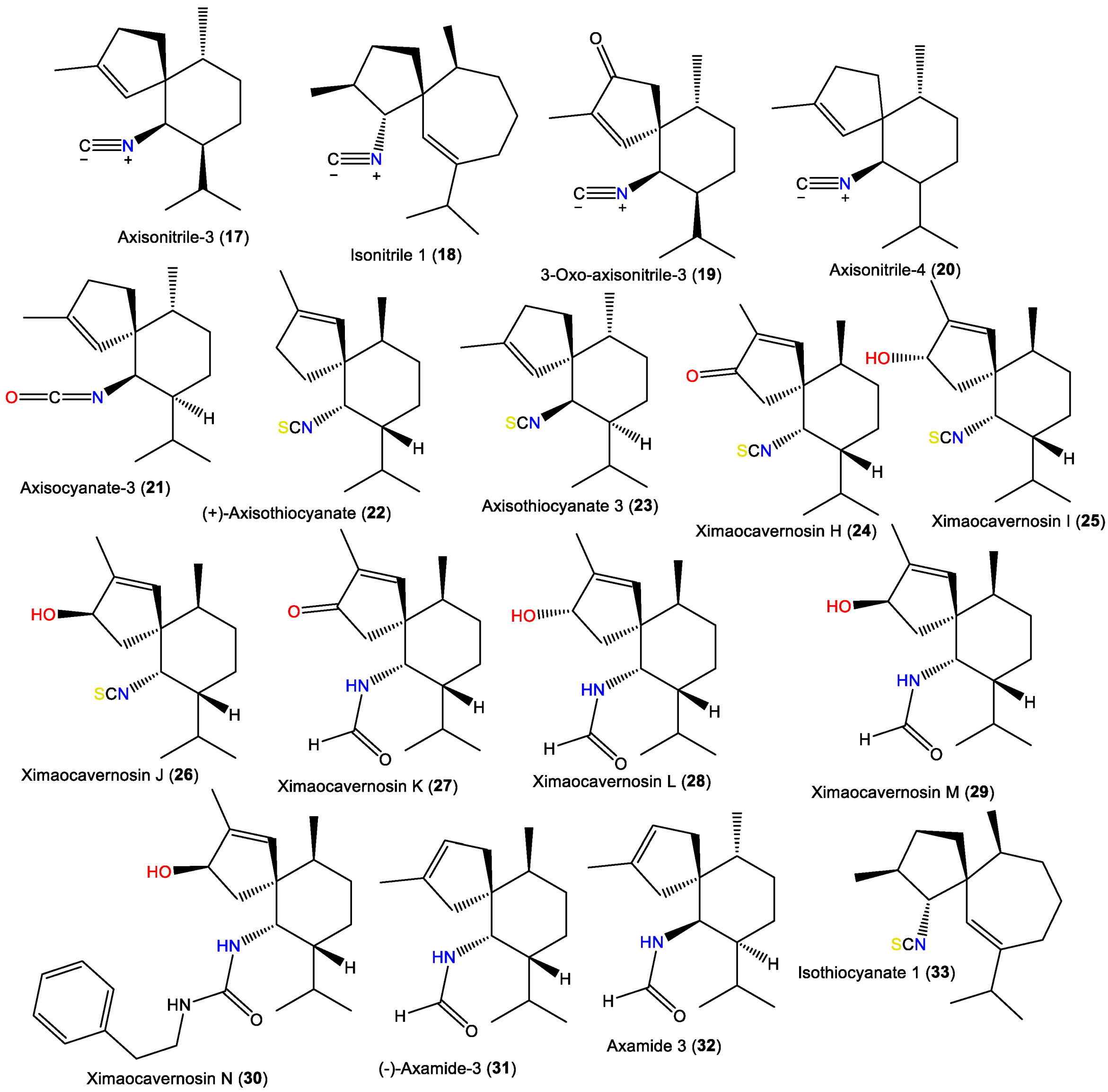


Figure 3. Spiroaxane-type sesquiterpenes (**17**–**33**) reported from the genus *Acanthella*.

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 [1] (**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 [16][17]. 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* [21], whereas **35** is a stereoisomer of **5** [20].

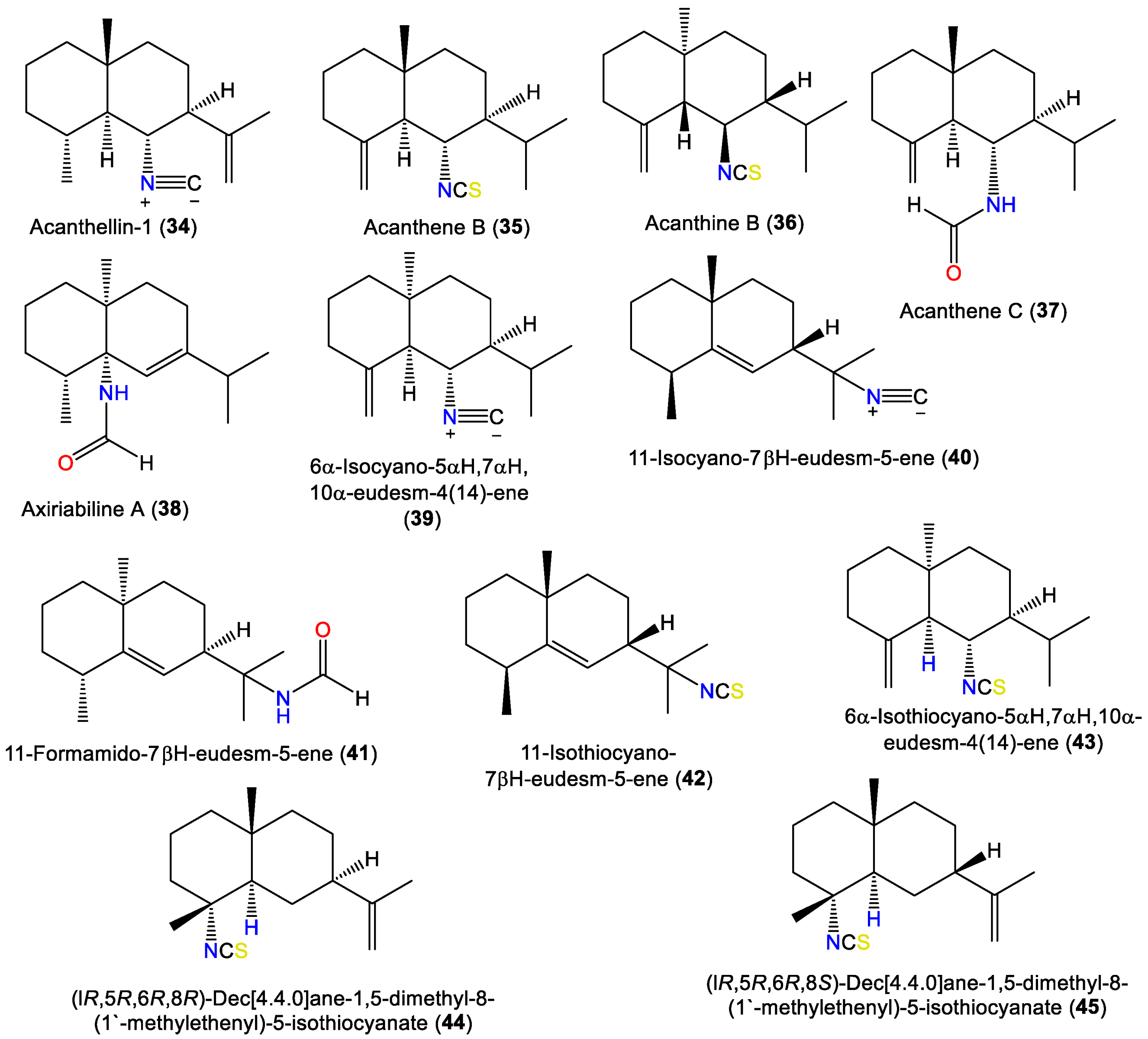


Figure 4. Eudesmane-type sesquiterpenes (**34**–**45**) reported from the genus *Acanthella*.

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 [22]. 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 [20].

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 [18]. 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 [23] (**Figure 5**). Compound **65** has a C-10 formamido functionality instead of the C-10-OH in **67** [23].

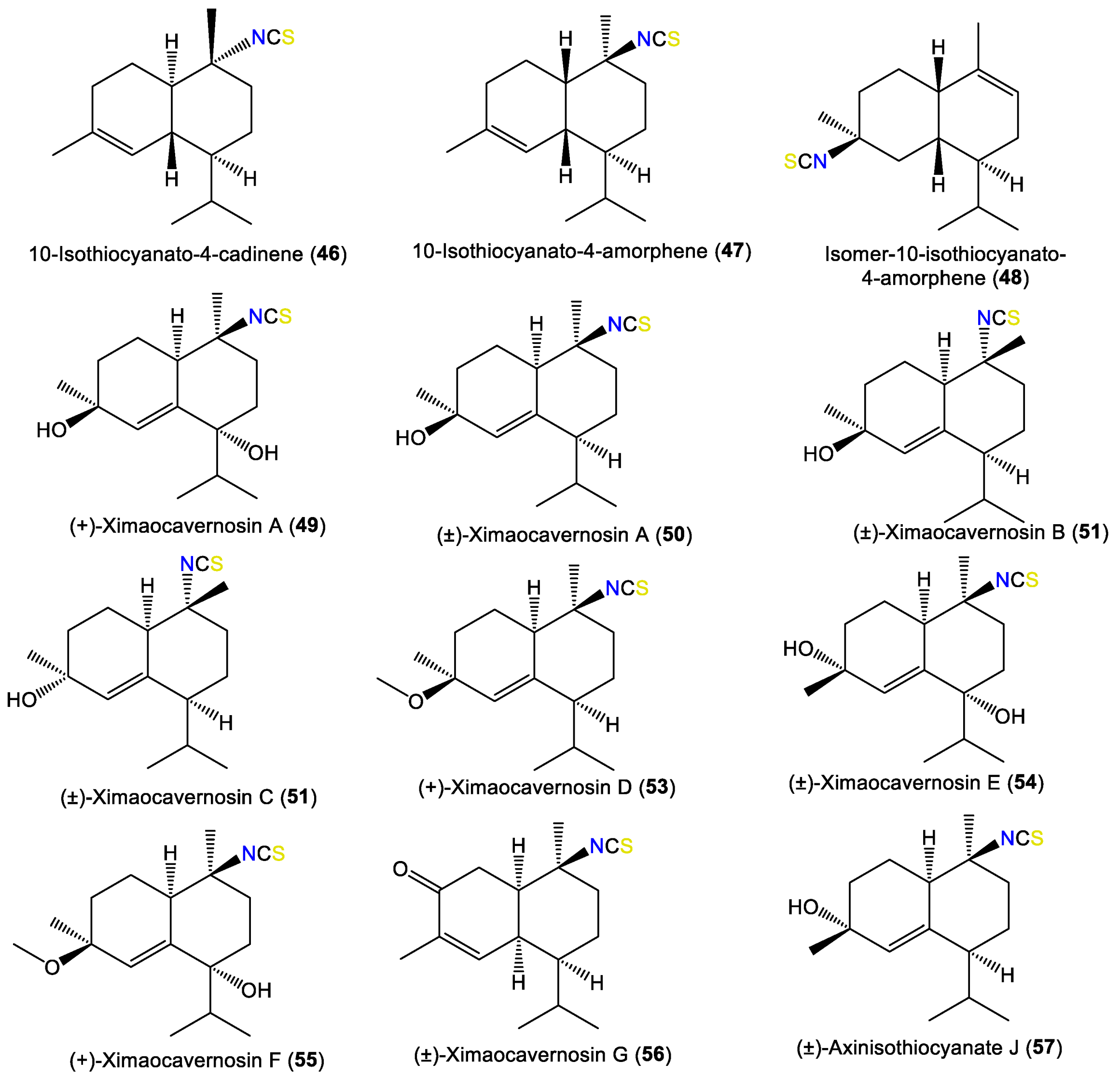


Figure 5. Cadinene-type sesquiterpenes (**46**–**57**) reported from the genus *Acanthella*.

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 [4]. 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 [4]**.** 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 [22]. 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 [14].

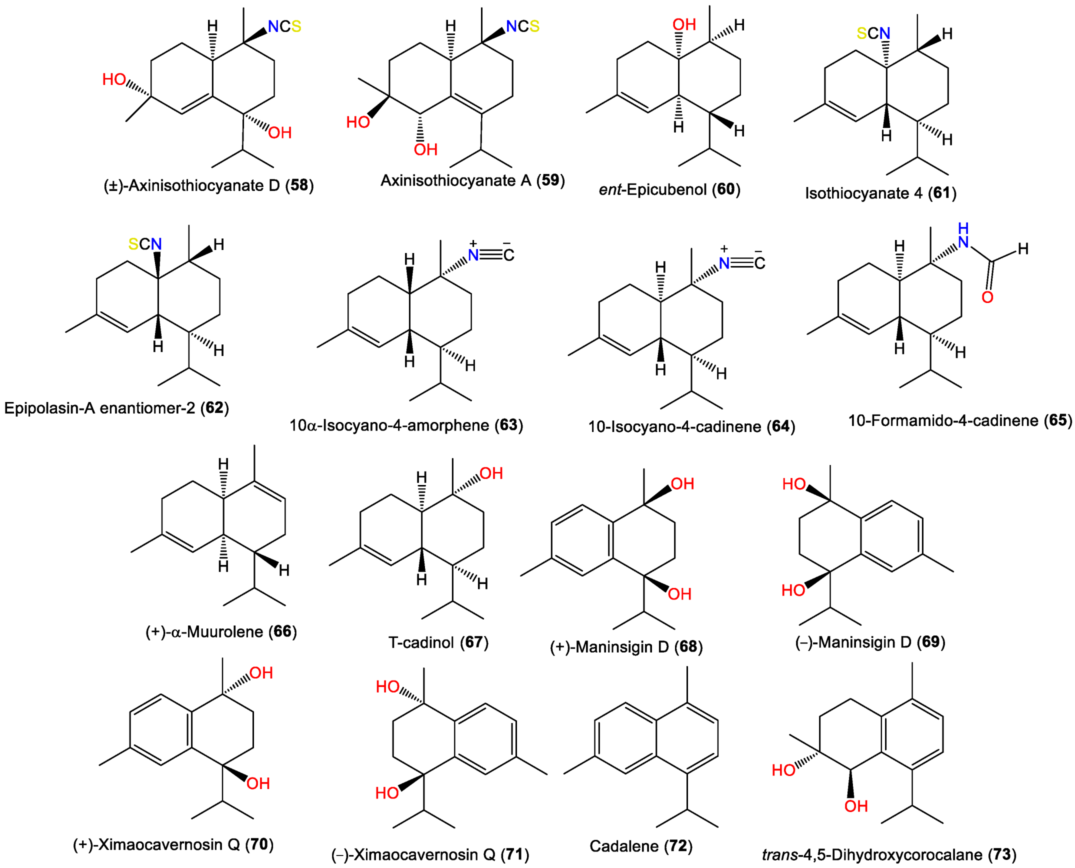


Figure 6. Cadinene-type sesquiterpenes (**58**–**73**) reported from the genus *Acanthella*.

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 [27]. Compound **74** is a rare oxygenated tricyclic sesquiterpene cyanide belonging to axane-type sesquiterpenes [27]. 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* [11]. 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 [6]. 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 [20] (**Figure 7**).

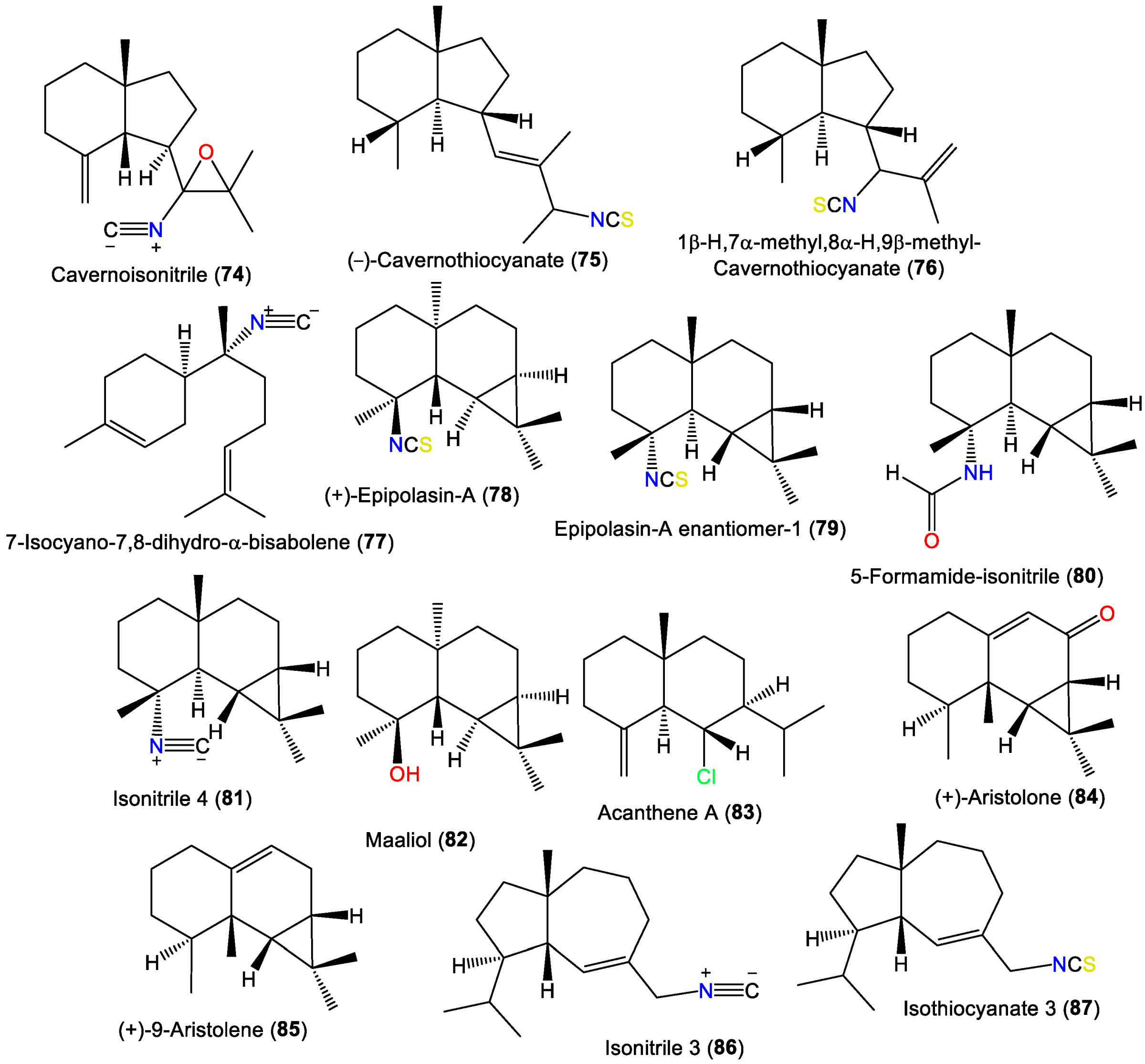
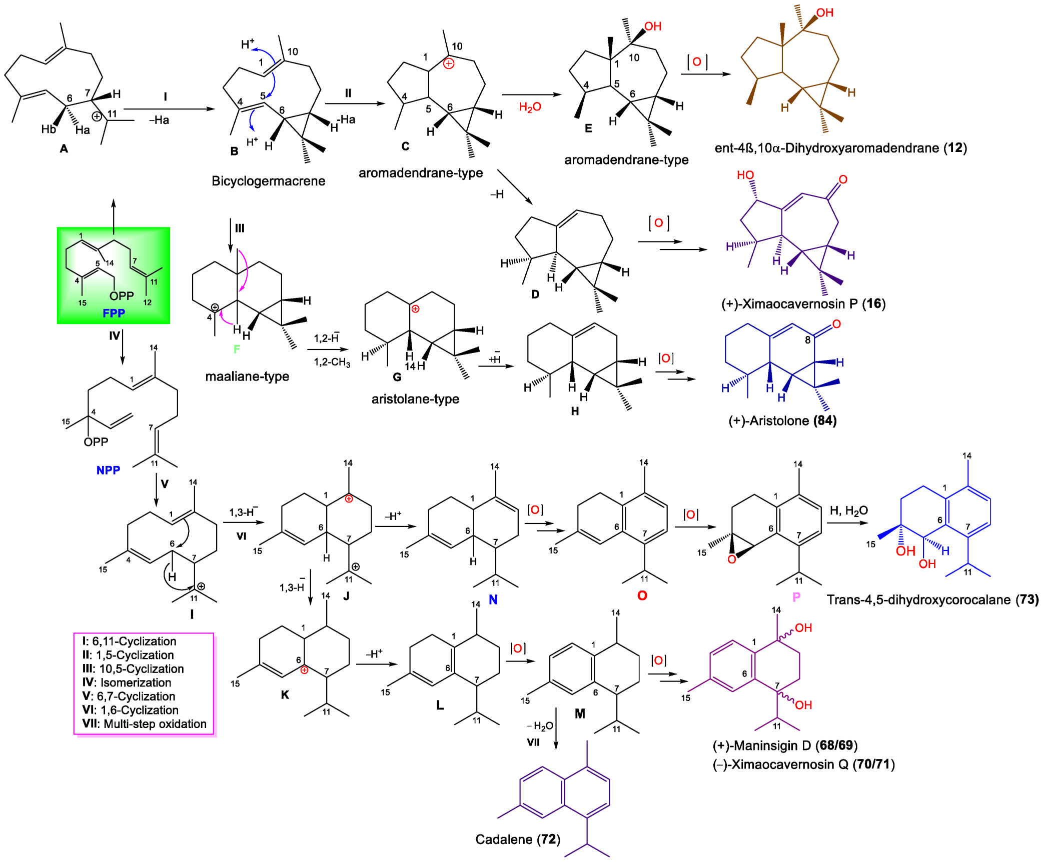


Figure 7. Other sesquiterpenes (**74**–**87**) reported from the genus *Acanthella*.

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 [14].



Scheme 1. Biosynthesis pathway of **12, 16**, **49**, **68–73**, and **84** [14].

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 2**). 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 [28]. Their stereochemistry has been determined using spectroscopic, X-ray and/or CD analyses, as well as chemical and computational methods.

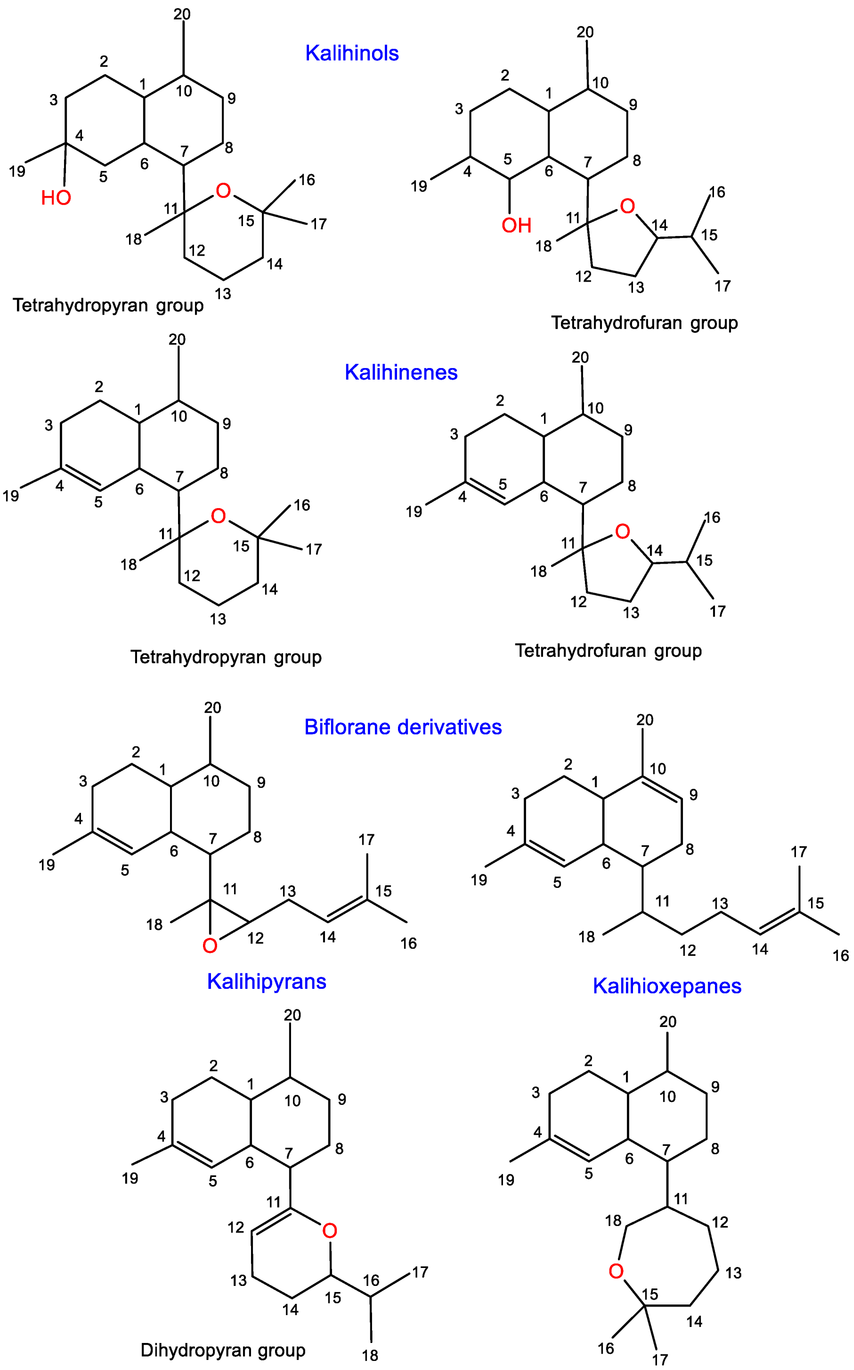


Figure 8. Classes of diterpenes reported from genus *Acanthella*.

Table 2. 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	[29]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
	-	-	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[30]
	-	-	*A. caruenosa*	Fiji, South Pacific Ocean	[31]
	-	-	*A. klethra*	Kuchinoerabu Island of the Satsunan Archipelago, Japan	[27]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]
	-	-	*A. cavernosa*	Fiji, South Pacific Ocean	[28]
	-	-	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[33] [34]
	-	-	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japa	[35]
	-	-	*A. cavernosa*	Dibud, Philippines	[36]
	-	-	*A. cavernosa*	Shallow water reef in Sanya Bay, Hainan Island, China	[37]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[12]
	-	-	*Acanthella* sp.	Yalong Bay, Hainan, China	[13]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[38]
	-	-	*A. cavernosa*	South China Sea	[24]
trans 10β-Formamidokalihinol A (**89**)	410	$C_{22}H_{35}ClN_2O_3$	*A. cavernosa*	Hachijo-jima Island, Japan	[11]
	-	-	*A. cavernosa*	Shallow water reef in Sanya Bay, Hainan Island, China	[37]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[38]
cis 10β-Formamidokalihinol A (**90**)	410	$C_{22}H_{35}ClN_2O_3$	*A. cavernosa*	Shallow water reef in Sanya Bay, Hainan	[37]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
				Island, China	
10β-Formamido-5-isocyanatokalihinol A (**91**)	426	$C_{22}H_{35}ClN_2O_4$	*A. cavernosa*	Hachijo-jima Island, Japan	[11]
	-	-	*A. cavernosa*	Xidao Island, Hainan, China	[22]
10β-Formamido-5β-isothiocyanatokalihinol A (**92**)	442	$C_{22}H_{35}ClN_2O_3S$	*A. cavernosa*	Hachijo-jima Island, Japan	[11]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[38]
	-	-	*A. cavernosa*	Xidao Island, Hainan, China	[22]
Bisformamidokalihinol A (**93**)	428	$C_{22}H_{37}ClN_2O_4$	*A. cavernosa*	Xidao Island, Hainan, China	[22]
Kalihinol B (**94**)	392	$C_{22}H_{33}ClN_2O_2$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[30]
	-	-	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[20]
	-	-	*A. klethra*	Kuchinoerabu Island of the Satsunan Archipelago, Japan	[27]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]
Isokalihinol B (**95**)	392	$C_{22}H_{33}ClN_2O_2$	*A. klethra*	Kuchinoerabu Island of the Satsunan Archipelago, Japan	[27]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]
	-	-	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[39]
Kalihinol C (**96**)	328	$C_{20}H_{28}N_2O_2$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[30]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
Kalihinol D (**97**)	392	$C_{22}H_{33}ClN_2O_2$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[30]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]
	-	-	*Acanthella* sp.	Yalong Bay, Hainan, China	[13]
Kalihinol E (**98**)	392	$C_{22}H_{35}ClN_2O_3$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[30]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]
	-	-	*A. cavernosa*	Hachijo-jima Island, Japan	[11]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[38]
	-	-	*A. cavernosa*	South China Sea	[24]
10β-Formamidokalihinol E (**99**)	410	$C_{22}H_{33}ClN_2O_2$	*A. cavernosa*	Hachijo-jima Island, Japan	[11]
Kalihinol F (**100**)	383	$C_{23}H_{33}N_3O_2$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[30]
	-	-	*A. caruenosa*	Fiji, South Pacific Ocean	[31]
	-	-	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[40]
	-	-	*Acanthella* sp.	Queen Charlotte Island chain off the coast of British Columbia.	[20]
	-	-	*A. klethra*	Kuchinoerabu Island of the Satsunan Archipelago, Japan	[27]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]
	-	-	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[39]
	-	-	*Acanthella*	Coast of Cape Sada,	[41]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
			sp.	Ehime Prefecture, Japan	
	-	-	*A. cavernosa*	Dibud, Philippines	[36]
Isokalihinol F (**101**)	383	$C_{23}H_{33}N_3O_2$	*A. cavernosa*	Fiji, South Pacific Ocean	[31]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]
	-	-	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[39]
	-	-	*A. cavernosa*	Fiji, South Pacific Ocean	[28]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[18]
8-Hydroxy-isokalihinol F (**102**)	399	$C_{23}H_{33}N_3O_3$	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[18]
10-*epi*-Isokalihinol F (**103**)	383	$C_{23}H_{33}N_3O_2$	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[39]
trans 10-Formamido-kalihinol F (**104**)	401	$C_{23}H_{35}N_3O_3$	*A. cavernosa*	Dibud, Philippines	[36]
cis 10-Formamido-kalihinol F (**105**)	401	$C_{23}H_{35}N_3O_3$	*A. cavernosa*	Dibud, Philippines	[36]
trans 15-Formamido-kalihinol F (**106**)	401	$C_{23}H_{35}N_3O_3$	*A. cavernosa*	Dibud, Philippines	[36]
cis 15-Formamido-kalihinol F (**107**)	401	$C_{23}H_{35}N_3O_3$	*A. cavernosa*	Dibud, Philippines	[36]
Kalihinol G (**108**)	415	$C_{23}H_{33}N_3O_2S$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[30]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]
	-	-	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[35]
	-	-	*A. cavernosa*	Dibud, Philippines	[36]
10-Isothiocyanatokalihinol G (**109**)	447	$C_{23}H_{33}N_3O_2S_2$	*A. cavernosa*	Xisha Islets, South China Sea	[38]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
5,10-*bis*-Isothiocyanatokalihinol G (**110**)	479	$C_{23}H_{33}N_3O_2S_3$	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[35]
Kalihinol H (**111**)	415	$C_{23}H_{33}N_3O_2S$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[30]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]
	-	-	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[35]
Isokalihinol H (**112**)	415	$C_{23}H_{33}N_3O_2S$	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[39]
10-*epi*-Isokalihinol H (**113**)	415	$C_{23}H_{33}N_3O_2S$	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[39]
Kalihinol I (**114**)	456	$C_{22}H_{33}ClN_2O_2S_2$	*A. cavernosa*	Thailand	[15]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]
	-	-	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[35]
10-*epi*-Kalihinol I (**115**)	456	$C_{22}H_{33}ClN_2O_2S_2$	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[35]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[38]
	-	-	*A. cavernosa*	South China Sea	[24]
Kalihinol J (**116**)	442	$C_{22}H_{35}ClN_2O_3S$	*A. cavernosa*	Thailand	[15]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]
	-	-	*A. cavernosa*	Dibud, Philippines	[36]
Kalihinol M (**117**)	442	$C_{22}H_{35}ClN_2O_3S$	*A. cavernosa*	Xisha Islets, South China Sea	[38]
Kalihinol N (**118**)	442	$C_{22}H_{35}ClN_2O_3S$	*A. cavernosa*	Xisha Islets, South China Sea	[38]
Kalihinol O (**119**)	424	$C_{22}H_{33}ClN_2O_2S$	*A. cavernosa*	Xisha Islets, South China Sea	[38]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
Kalihinol P (**120**)	424	$C_{22}H_{33}ClN_2O_2S$	*A. cavernosa*	Xisha Islets, South China Sea	[38]
Kalihinol Q (**121**)	424	$C_{22}H_{33}ClN_2O_2S$	*A. cavernosa*	Xisha Islets, South China Sea	[38]
Kalihinol R (**122**)	456	$C_{22}H_{33}ClN_2O_2S_2$	*A. cavernosa*	Xisha Islets, South China Sea	[38]
Kalihinol S (**123**)	410	$C_{22}H_{35}ClN_2O_3$	*A. cavernosa*	Xisha Islets, South China Sea	[38]
Kalihinol T (**124**)	424	$C_{22}H_{33}ClN_2O_2S$	*A. cavernosa*	Xisha Islets, South China Sea	[38]
Kalihinol X (**125**)	424	$C_{22}H_{33}ClN_2O_2S$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[30]
	-	-	*A. cavernosa*	Fiji, South Pacific Ocean	[31]
	-	-	*A. cavernosa*	Thailand	[15]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]
	-	-	*A. cavernosa*	Dibud, Philippines	[36]
	-	-	*Acanthella* sp.	Yalong Bay, Hainan, China	[13]
10-*epi*-Kalihinol X (**126**)	424	$C_{22}H_{33}ClN_2O_2S$	*Acanthella* sp.	Yalong Bay, Hainan, China	[13]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[38]
	-	-	*A. cavernosa*	South China Sea	[24]
Kalihinol Y (**127**)	365	$C_{21}H_{32}ClNO_2$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[30]
	-	-	*Acanthella caruenosa*	Fiji, South Pacific Ocean	[31]
	-	-	*A. cavernosa*	Thailand	[15]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
	-	-	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[35]
	-	-	*A. cavernosa*	Dibud, Philippines	[36]
Kalihinone Ya (**128**)	367	$C_{20}H_{30}ClNO_3$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[30]
Δ^9-Kalihinol Y (**129**)	365	$C_{21}H_{32}ClNO_2$	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[35]
Kalihinol Z (**130**)	392	$C_{22}H_{33}ClN_2O_2$	*Acanthella* sp.	Apra Harbor, Guam, western side of the USA	[30]
	-	-	*A. cavernosa*	Fiji, South Pacific Ocean	[31]
	-	-	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]
Kalihiacyloxyamide A (**131**)	468	$C_{25}H_{41}ClN_2O_4$	*A. cavernosa*	Xisha Island, South China Sea	[42]
Kalihiacyloxyamide B (**132**)	468	$C_{25}H_{41}ClN_2O_4$	*A. cavernosa*	Xisha Island, South China Sea	[42]
Kalihiacyloxyamide C (**133**)	552	$C_{30}H_{49}ClN_2O_5$	*A. cavernosa*	Xisha Island, South China Sea	[42]
Kalihiacyloxyamide D (**134**)	552	$C_{30}H_{49}ClN_2O_5$	*A. cavernosa*	Xisha Island, South China Sea	[42]
Kalihiacyloxyamide E (**135**)	586	$C_{33}H_{47}ClN_2O_5$	*A. cavernosa*	Xisha Island, South China Sea	[42]
Kalihiacyloxyamide F (**136**)	586	$C_{33}H_{47}ClN_2O_5$	*A. cavernosa*	Xisha Island, South China Sea	[42]
Kalihiacyloxyamide G (**137**)	518	$C_{30}H_{50}N_2O_5$	*A. cavernosa*	Xisha Island, South China Sea	[42]
Kalihiacyloxyamide H (**138**)	518	$C_{30}H_{50}N_2O_5$	*A. cavernosa*	Xisha Island, South China Sea	[42]
Kalihinene					
Kalihinene (**139**)	340	$C_{22}H_{32}N_2O$	*A. klethra*	Kuchinoerabu Island of the Satsunan Archipelago, Japan	[27]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
	-	-	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[39]
	-	-	*A. cavernosa*	Fiji, South Pacific Ocean	[28]
	-	-	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[35]
	-	-	*A. cavernosa*	Dibud, Philippines	[36]
	-	-	*Acanthella* sp.	Ximao Sea, Hainan, China	[12]
1-*epi*-Kalihinene (**140**)	340	$C_{22}H_{32}N_2O$	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[39]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[18]
15-Isothiocyanato-l-epi-kalihinene (**141**)	372	$C_{22}H_{32}N_2OS$	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[39]
1,10-di*epi*-Kalihinene (**142**)	340	$C_{22}H_{32}N_2O$	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[39]
Kalihinene A (**143**)	340	$C_{22}H_{32}N_2O$	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[43]
Kalihinene B (**144**)	340	$C_{22}H_{32}N_2O$	*A. cavernosa*	Seychelles and Desnceufs Islands	[32]
Kalihinene E (**145**)	367	$C_{21}H_{34}ClNO_2$	*A. cavernosa*	Xisha Islets, South China Sea	[43]
Kalihinene F (**146**)	331	$C_{21}H_{33}NO_2$	*A. cavernosa*	Xisha Islets, South China Sea	[43]
Kalihinene X (**147**)	367	$C_{21}H_{34}ClNO_2$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[33] [34]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[43]
Kalihinene Y (**148**)	367	$C_{21}H_{34}ClNO_2$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[33] [34]

Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[43]
Kalihinene Z (**149**)	367	$C_{21}H_{34}ClNO_2$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[33] [34]
10-Formamidokalihinene (**150**)	358	$C_{22}H_{34}N_2O_2$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[33] [34]
	-	-	*A. cavernosa*	Fiji, South Pacific Ocean	[28]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[43]
15-Formamidokalihinene (**151**)	358	$C_{22}H_{34}N_2O_2$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[33]
	-	-	*A. cavernosa*	Fiji, South Pacific Ocean	[28]
	-	-	*A. cavernosa*	Xisha Islets, South China Sea	[43]
10,l5-*bis*-Formamidokalihinene (**152**)	376	$C_{22}H_{36}N_2O_3$	*A. cavernosa*	Fiji, South Pacific Ocean	[28]
6-Hydroxy-kalihinene (**153**)	356	$C_{22}H_{32}N_2O_2$	*A. cavernosa*	Fiji, South Pacific Ocean	[28]
	-	-	*Acanthella* sp.	Coral reef of Ishigaki Island, Okinawa, Japan	[35]
6-Hydroxy-15-Formamidokalihinene (**154**)	374	$C_{22}H_{34}N_2O_3$	*A. cavernosa*	Fiji, South Pacific Ocean	[28]
6-Hydroxy-10-Formamidokalihinene (**155**)	374	$C_{22}H_{34}N_2O_3$	*A. cavernosa*	Fiji, South Pacific Ocean	[28]
6-Hydroxy-10-Formamido-15-thyocyano-kalihinene (**156**)	406	$C_{22}H_{34}N_2O_3S$	*A. cavernosa*	Fiji, South Pacific Ocean	[28]
Kalihioxepanes					
Kalihioxepane A (**157**)	365	$C_{21}H_{32}ClNO_2$	*A. cavernosa*	Xisha Island, South China Sea	[44]
Kalihioxepane B (**158**)	365	$C_{21}H_{32}ClNO_2$	*A. cavernosa*	Xisha Island, South China Sea	[44]
Kalihioxepane C (**159**)	383	$C_{21}H_{34}ClNO_3$	*A. cavernosa*	Xisha Island, South China Sea	[44]

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Compound Name	Mol. Wt.	Mol. Formula	Species	Sampling Locations	Ref.
Kalihioxepane D (**160**)	383	$C_{21}H_{34}ClNO_3$	*A. cavernosa*	Xisha Island, South China Sea	[44]
Kalihioxepane E (**161**)	383	$C_{21}H_{34}ClNO_3$	*A. cavernosa*	Xisha Island, South China Sea	[44]
Kalihioxepane F (**162**)	365	$C_{21}H_{32}ClNO_2$	*A. cavernosa*	Xisha Island, South China Sea	[44]
Kalihioxepane G (**163**)	365	$C_{21}H_{32}ClNO_2$	*A. cavernosa*	Xisha Island, South China Sea	[44]
Kalihipyran (**164**)	311	$C_{21}H_{29}NO$	*A. cavernosa*	Beau Vallon Beach, Mahé, Seychelles	[39]
	-	-	*A. cavernosa*	Heron Island, Great Barrier Reef, Australia	[18]
Kalihipyrans					
Kalihipyran A (**165**)	329	$C_{21}H_{31}NO_2$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[33]
Kalihipyran B (**166**)	365	$C_{21}H_{32}ClNO_2$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[33]
Kalihipyran C (**167**)	329	$C_{21}H_{31}NO_2$	*A. cavernosa*	Xisha Islets, South China Sea	[43]
Biflorane diterpenes					
Biflora-4,9,15-triene (**168**)	272	$C_{20}H_{32}$	*A. cavernosa*	Yakushima Island, southwest of Tokyo	[33]
	-	-	*A. cavernosa*	Hachijo-jima Island, Japan	[11]
Cavernene A (**169**)	315	$C_{21}H_{33}NO$	*A. cavernosa*	Xisha Islets, South China Sea	[43]
Cavernene B (**170**)	317	$C_{21}H_{35}NO$	*A. cavernosa*	Xisha Islets, South China Sea	[43]
Cavernene C (**171**)	317	$C_{21}H_{35}NO$	*A. cavernosa*	Xisha Islets, South China Sea	[43]
Cavernene D (**172**)	331	$C_{21}H_{33}NO_2$	*A. cavernosa*	Xisha Islets, South China Sea	[43]

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

Compound Name	Mol. Wt.	Mol. Formula [30]	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	[18]
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	[18]

., **94**), or

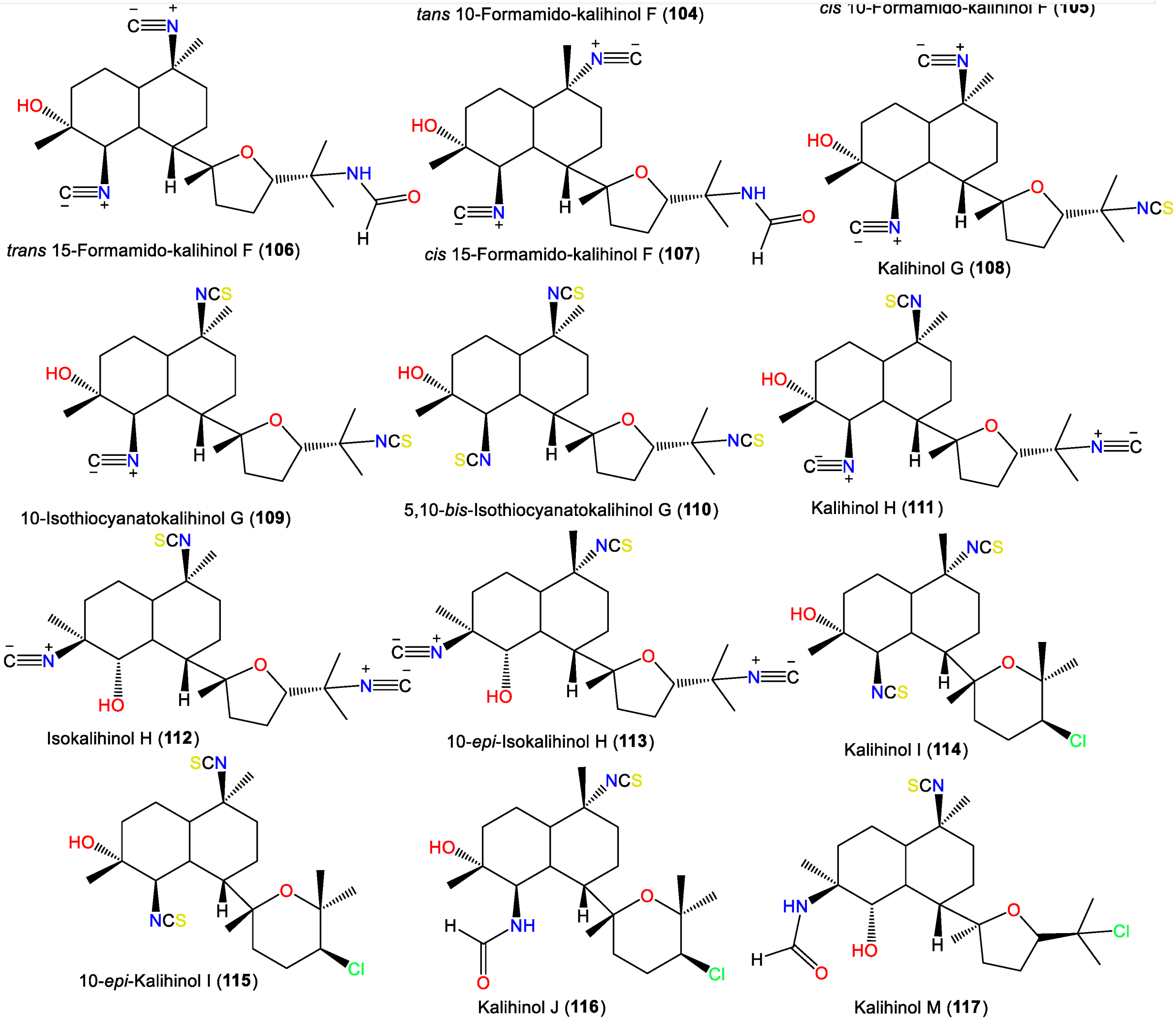


Figure 10. Kalihinol diterpenes (**103**–**117**) reported from the genus *Acanthella*.

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 [31]. 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** [15]. 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 [38]. 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 [35] (**Figure 11**).

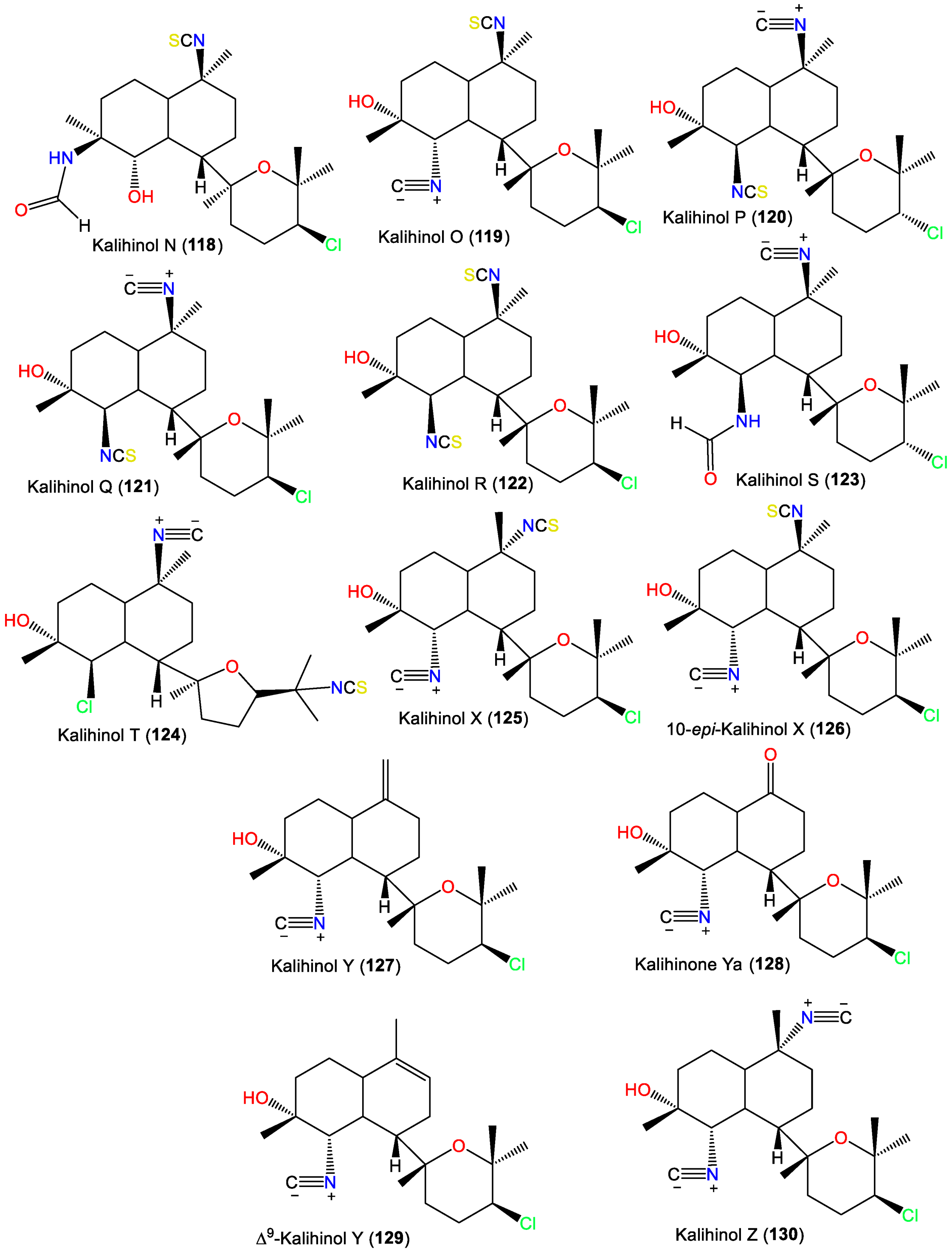


Figure 11. Kalihinol diterpenes (**118**–**130**) reported from the genus *Acanthella*.

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** [39]. 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 [38]. Their structures and stereo-structures were determined by NMR/CD/X-ray analyses [38]. 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** [38]. 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 [18]. 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** [36]. 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** [13]. 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 [42].

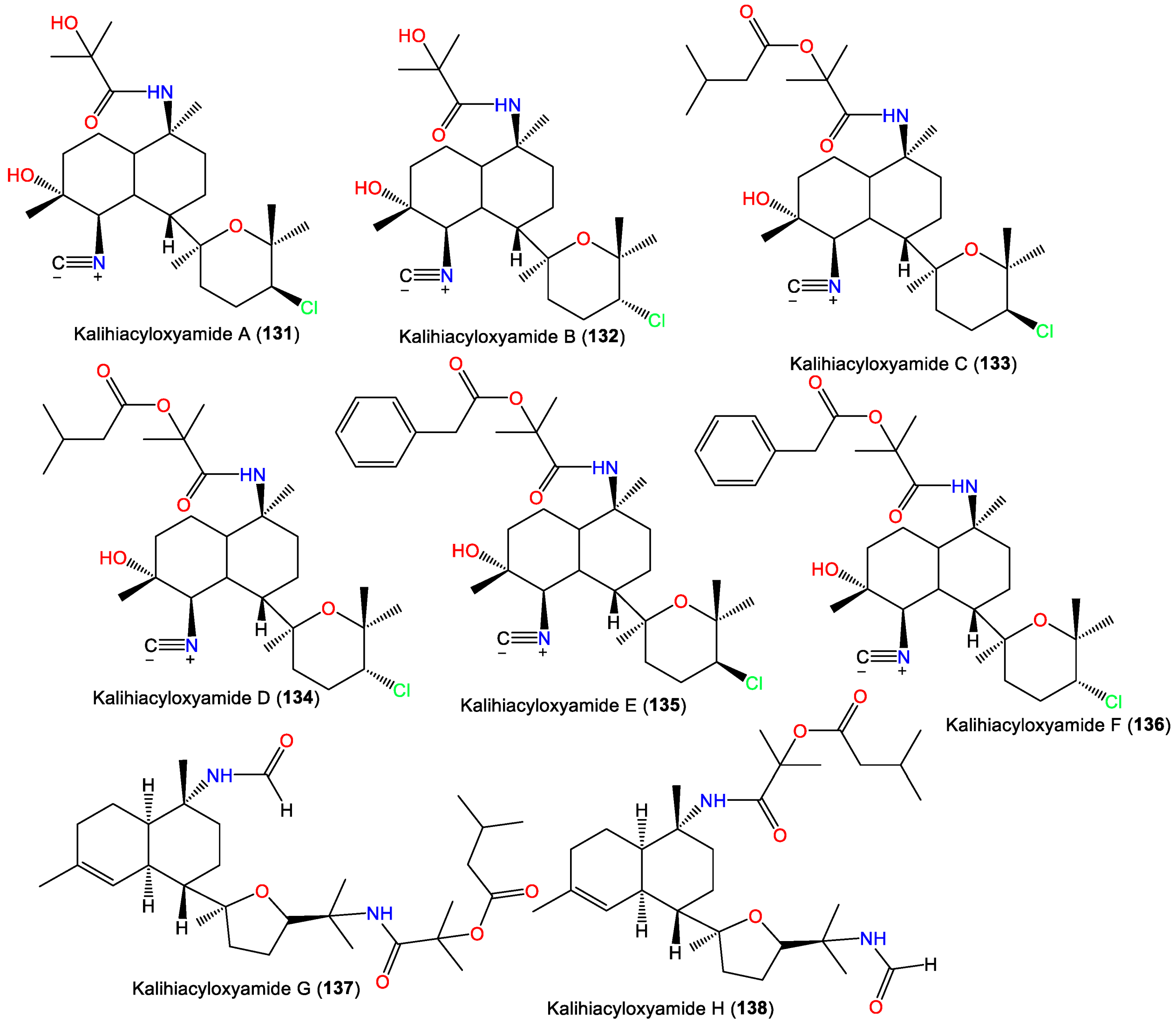


Figure 12. Kalihinol diterpenes (**131**–**138**) reported from the genus *Acanthella*.

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 [27]. 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 [32]. 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 [43]. 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 [28]. Additionally, **140**–**142** are new metabolites reported from *A.*

carvenosa collected from The Seychelles [39]. 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** [39].

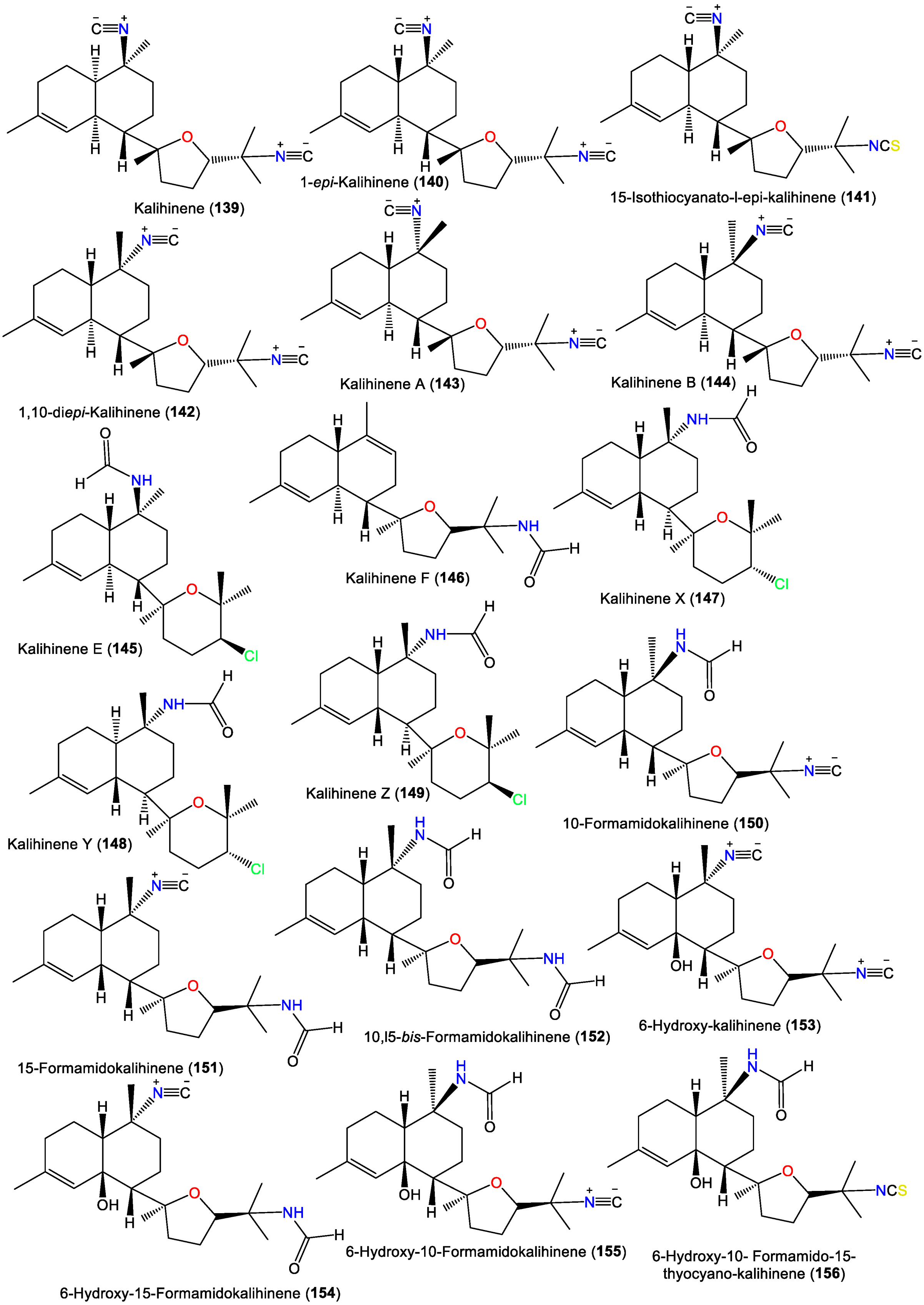


Figure 13. Kalihinene diterpenes (**139**–**156**) reported from the genus *Acanthella*.

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 [39]. Compound **167** is an isomer of **165** with cis-decalin [43], while **166** has a C-15 chlorine atom [33][34]. 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 [44] (**Figure 14**).

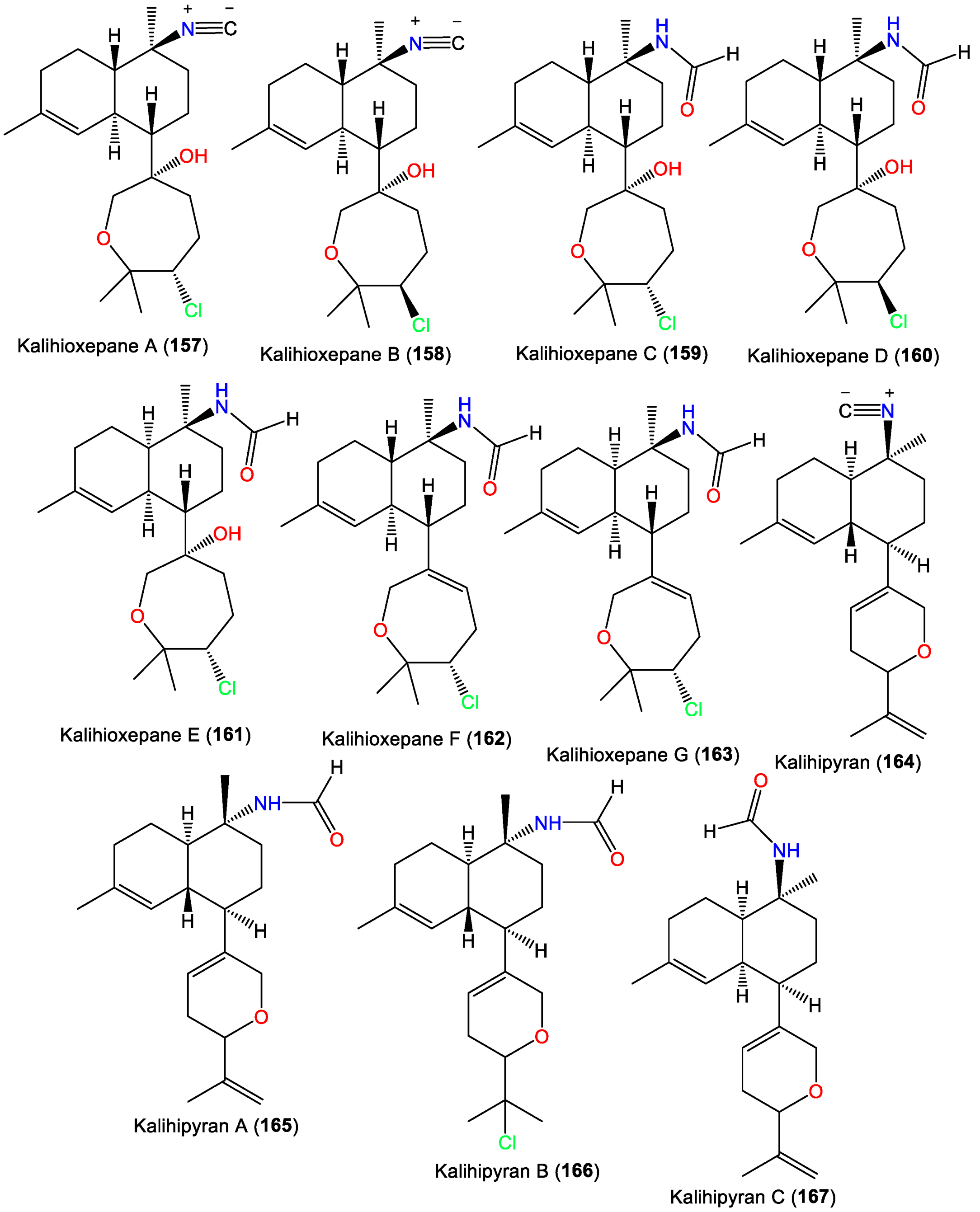
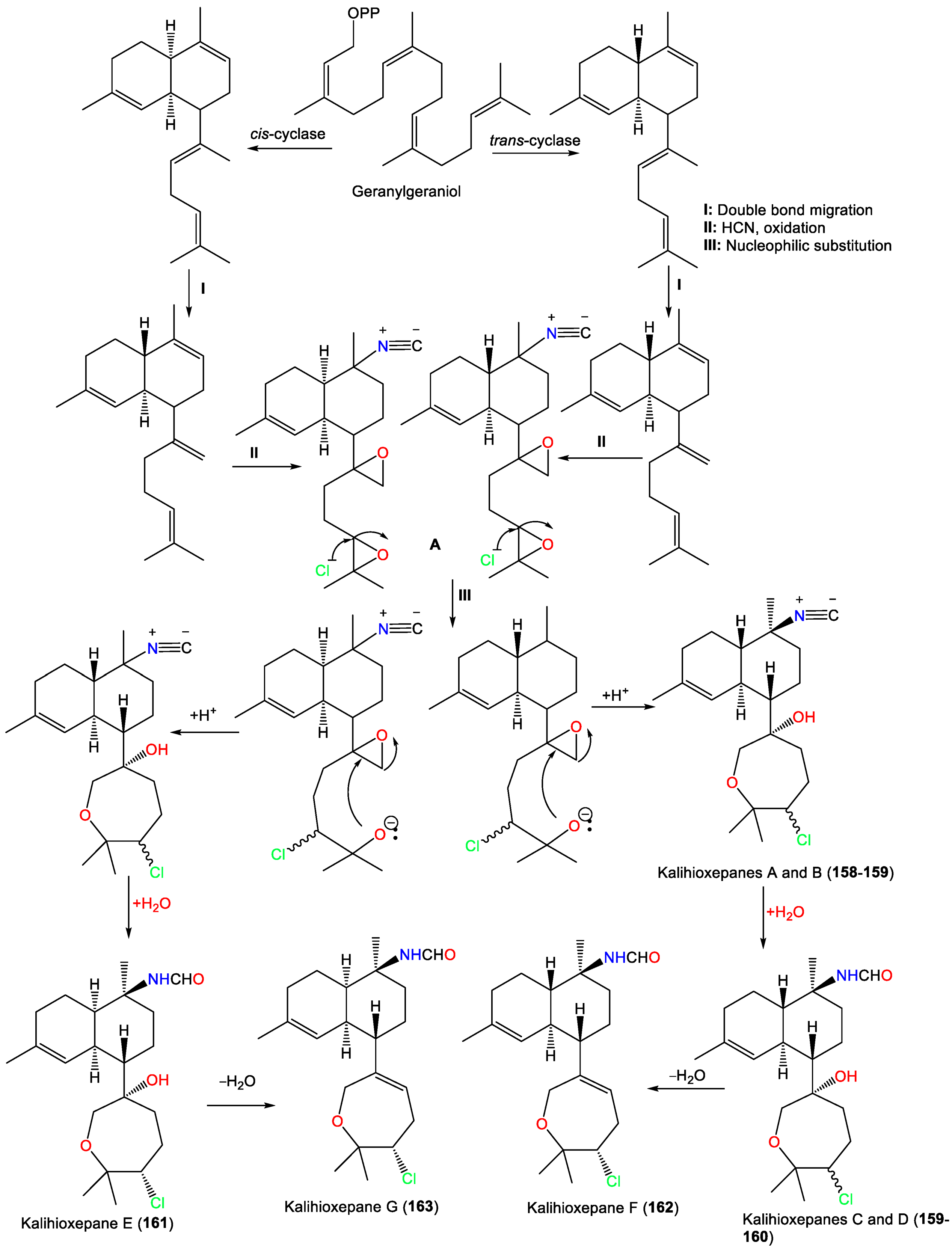


Figure 14. Kalihioxepanes (**157**–**163**) and kalihipyrans (**164**–**167**) diterpenes reported from the genus *Acanthella*.

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 [44]. 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 intermediate). Nucleophilic substitution of biflorane forms **157** and **158**. After that, hydration generates **159**–**161** which are then dehydrated to give **162** and **163**, respectively [44].



Scheme 2. Biosynthesis of kalihioxepanes A–G (**157**–**163**) [44].

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 [11]. 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 [43] (**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 [43].

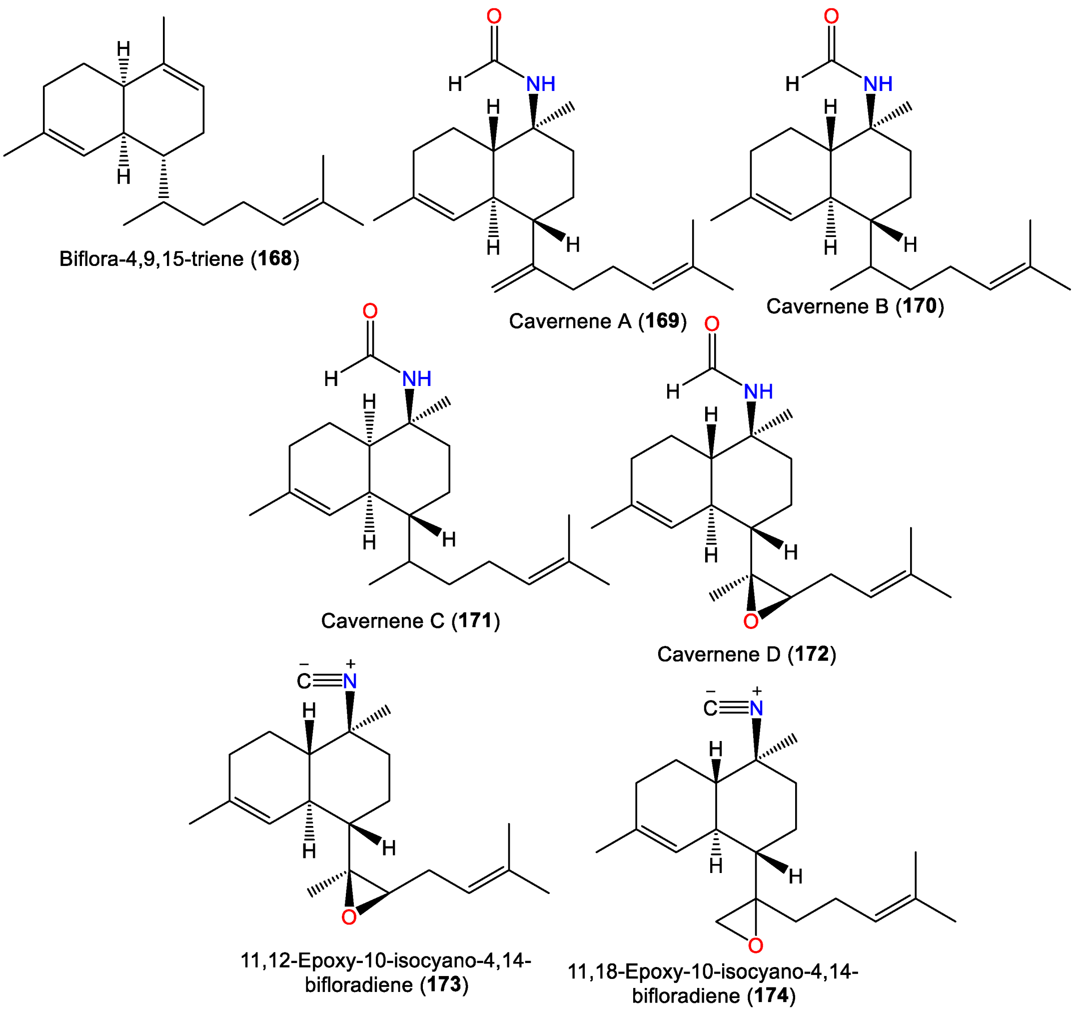
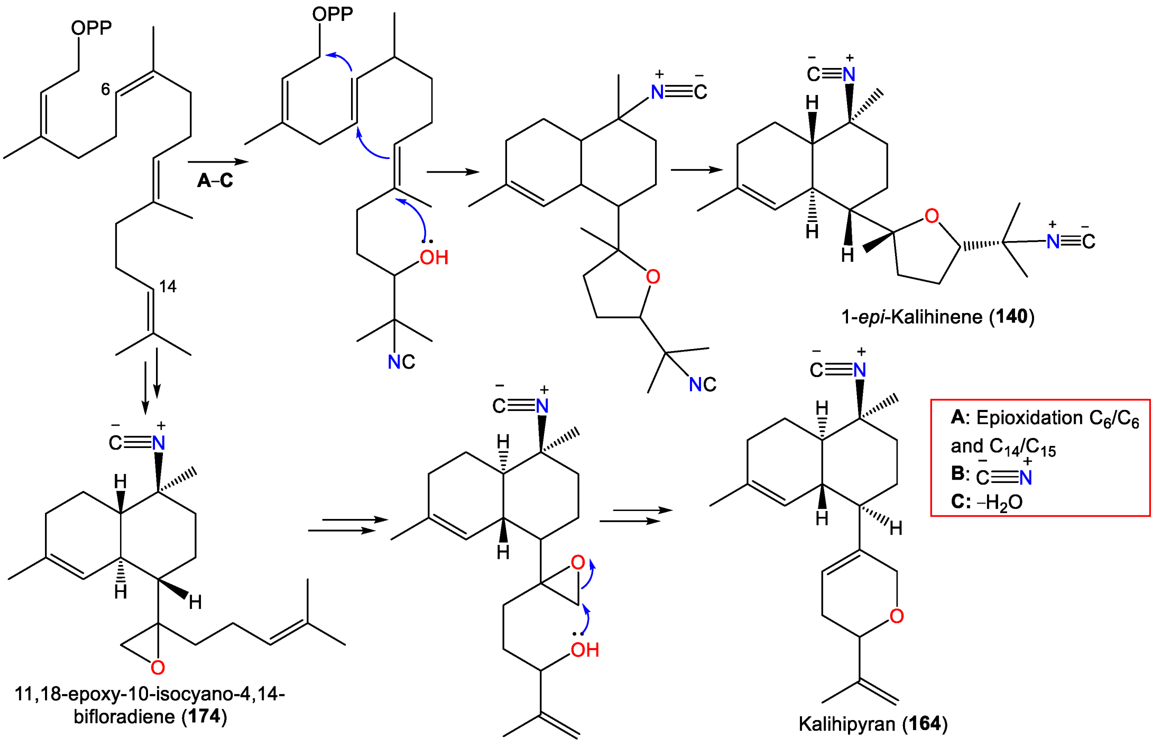


Figure 15. Biflorane (**168**–**174**) diterpenes reported from the genus *Acanthella*.

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 [18]. 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 [18].

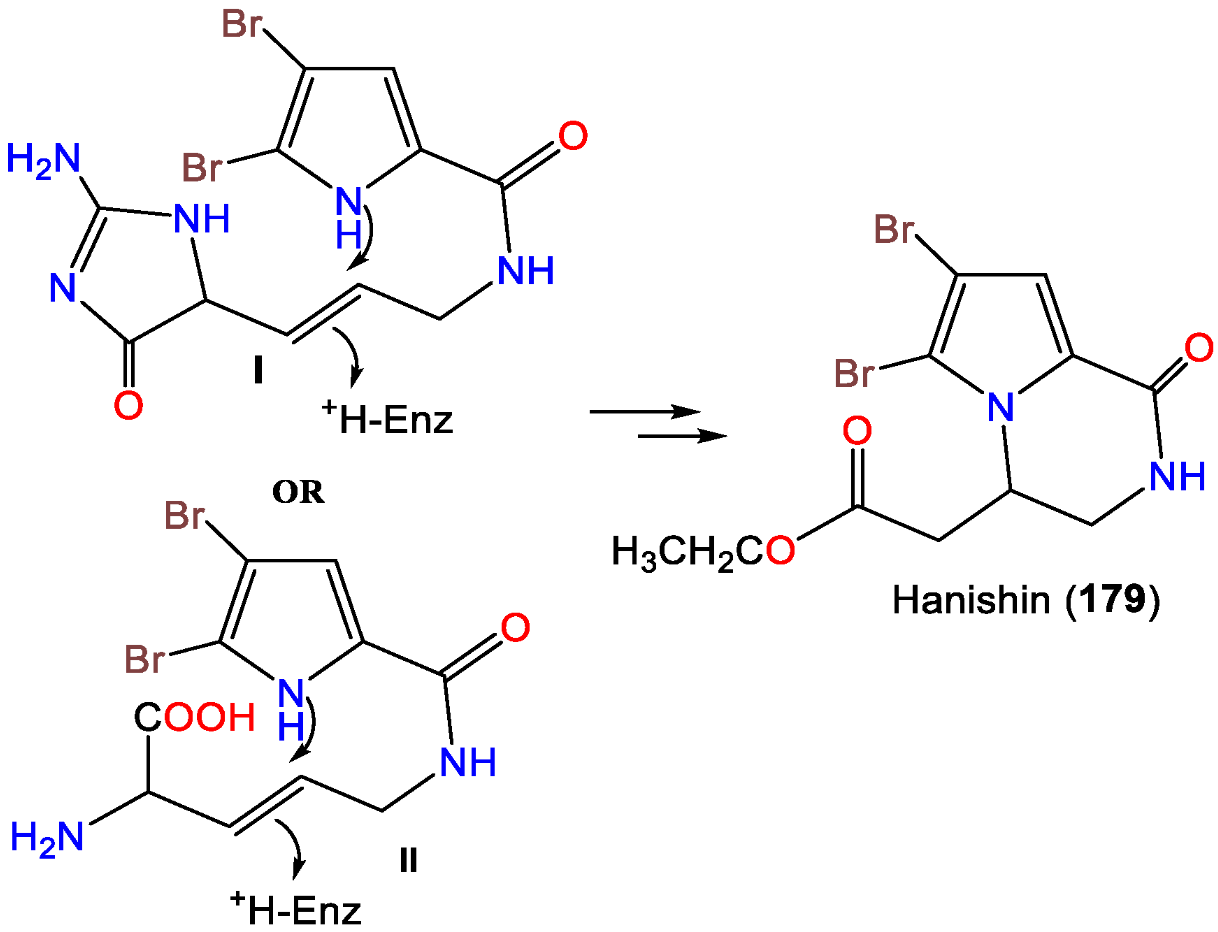


Scheme 3. Biosynthesis of **140**, **164**, and **174** [18].

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. 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.

In 2010, Hammami et al. purified a novel bromopyrolimidazole analog, **178**, along with **177** from Tunisian *A. acuta* diethyl ether extracts [19]. 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 [46] (Scheme 4).



Scheme 4. Proposed biosynthesis of **179** [46].

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**) [47]. 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 [48]. In 2014, Macabeo and Guce reported the bromopyrrole-imidazole alkaloids **182**–**184** from CH_2Cl_2-MeOH extracts of *A. carteri* from The Philippines [49], while **185** is a pyrrole alkaloid isolated from the n-BuOH fraction of *Acanthella* sp. using Sephadex LH-20/Rp-18 CC [50].

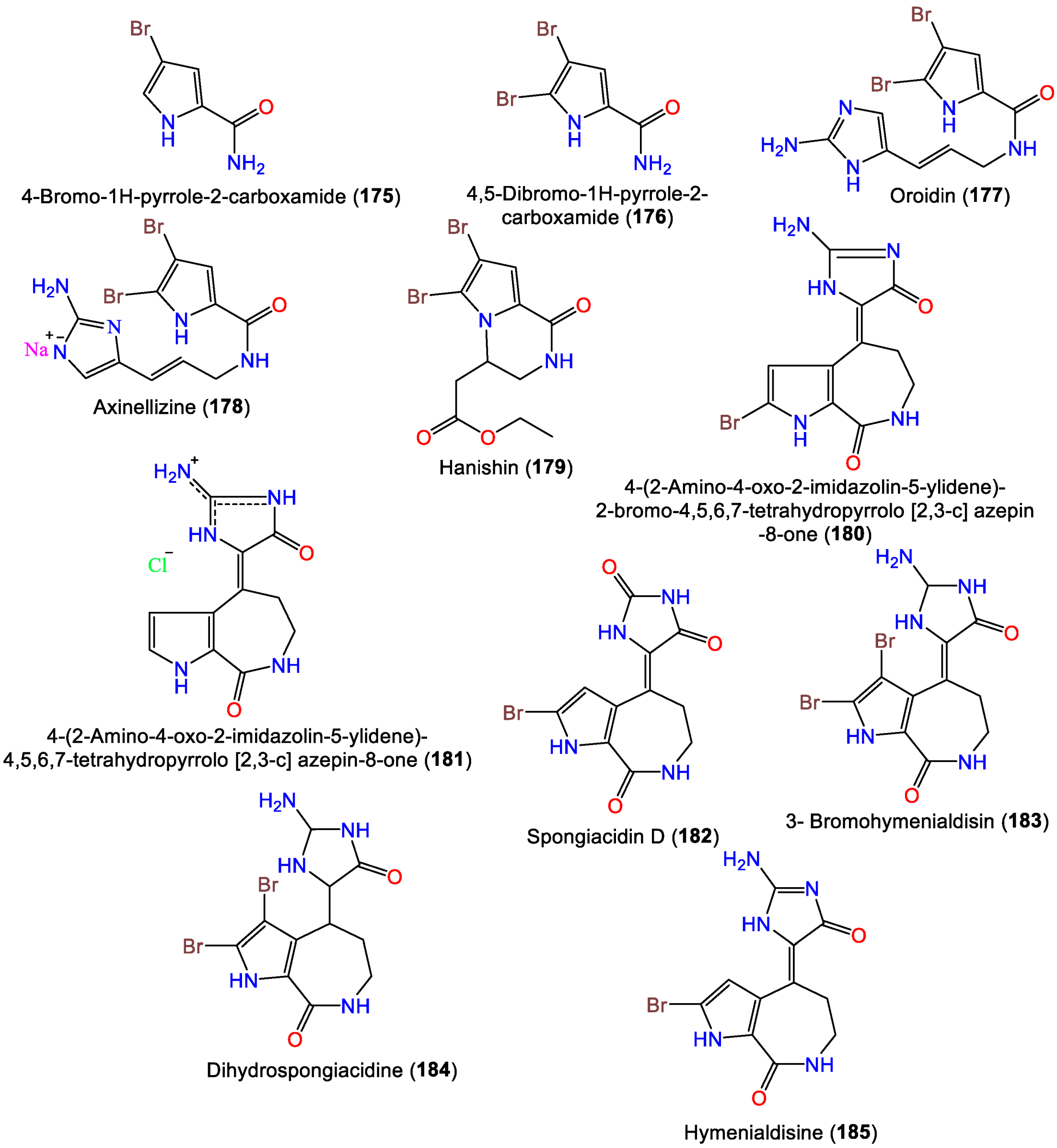
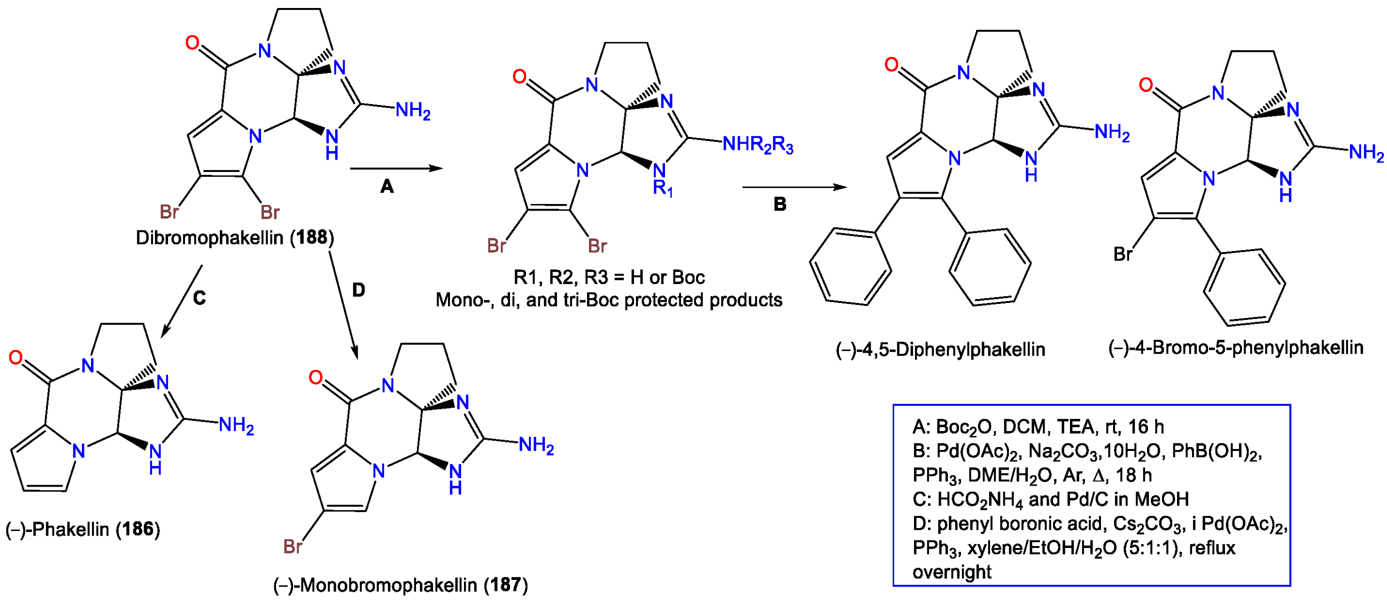


Figure 16. Alkaloids (**175**–**185**) reported from genus *Acanthella*.

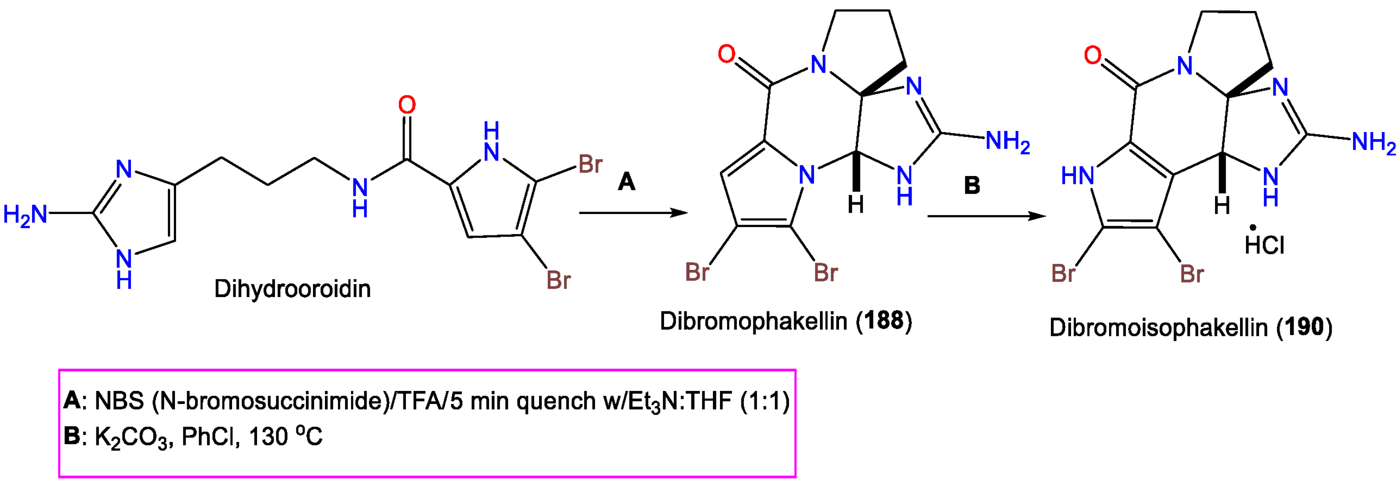
A series of synthetic reactions including Suzuki–Miyaura coupling and debromination resulted in natural analogs **186** and **187**, in addition to new synthetic derivatives (−)-4-bromo-5-phenylphakellin and (−)-4,5-diphenylphakellin. It was found that the C-5 Br substitution with phenyl or H led to a loss in activity, revealing that the C-5 Br is important for α2B adrenoceptor agonistic activity (Scheme 5) [51].



Scheme 5. Semisynthesis of (−)-dibromophakellin (**188**) derivatives [51].

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 [52].

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** [53].



Scheme 6. Synthesis of **190** using dihydrooroidin [53].

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**) [54]. Furthermore, **194** and **195** were obtained by Fan et al. from the acetone extracts of *A. cavernosa* collected from the South China Sea [24].

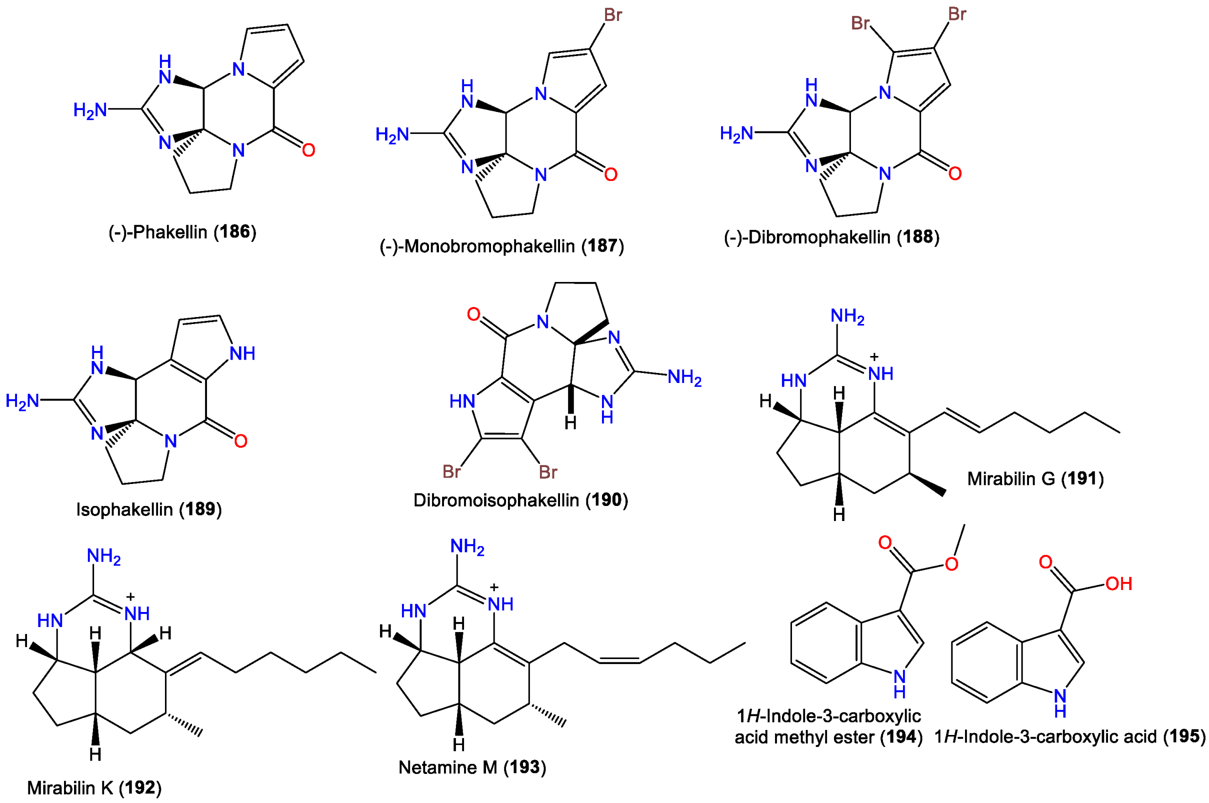


Figure 17. Alkaloids (**186**–**195**) reported from the genus *Acanthella*.

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 [55].

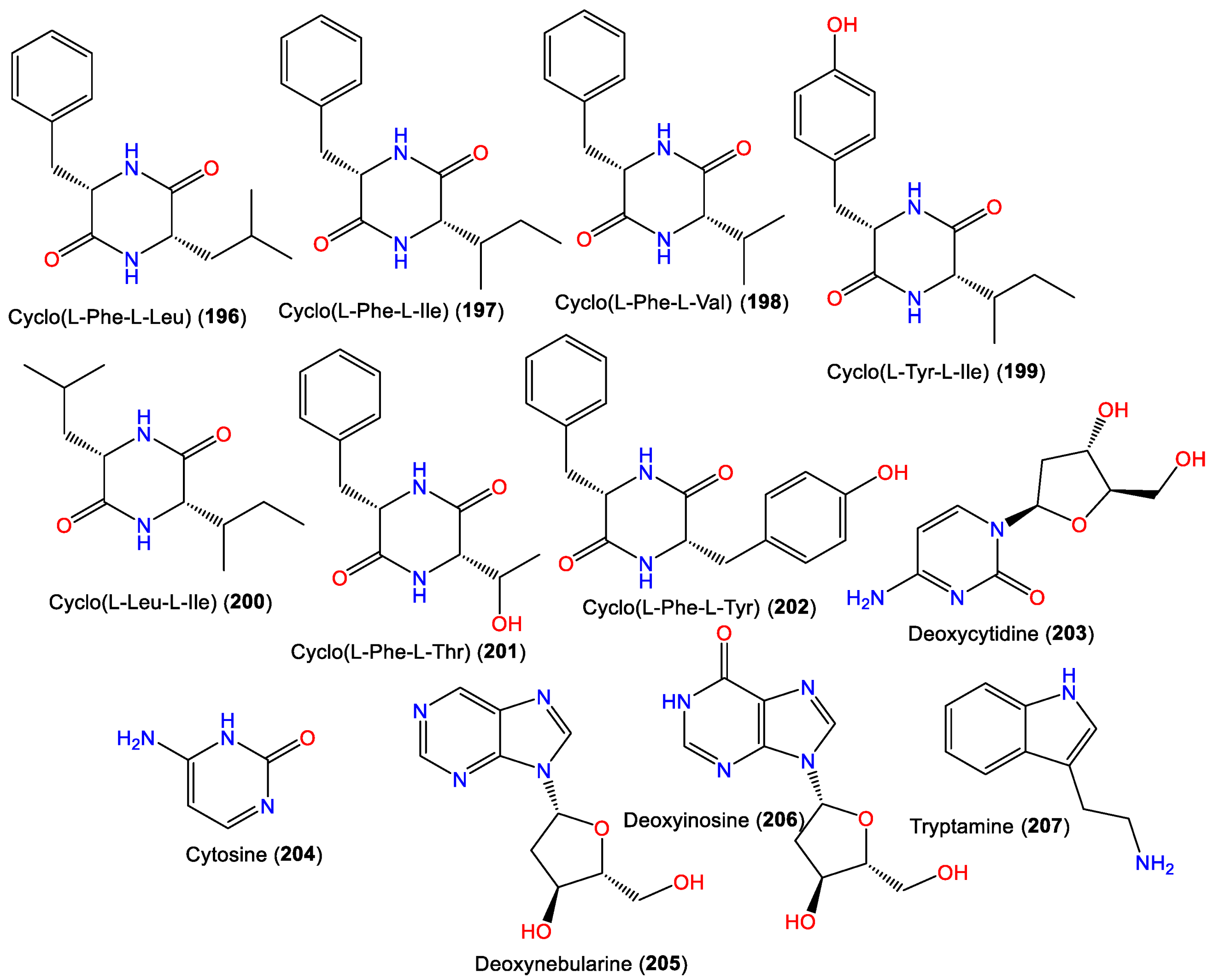


Figure 18. Alkaloids (**196**–**207**) reported from the genus *Acanthella*.

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 [56] (**Figure 19**). In addition, **215** was obtained from the acetone extract of the same sponge collected from the South China Sea [24].

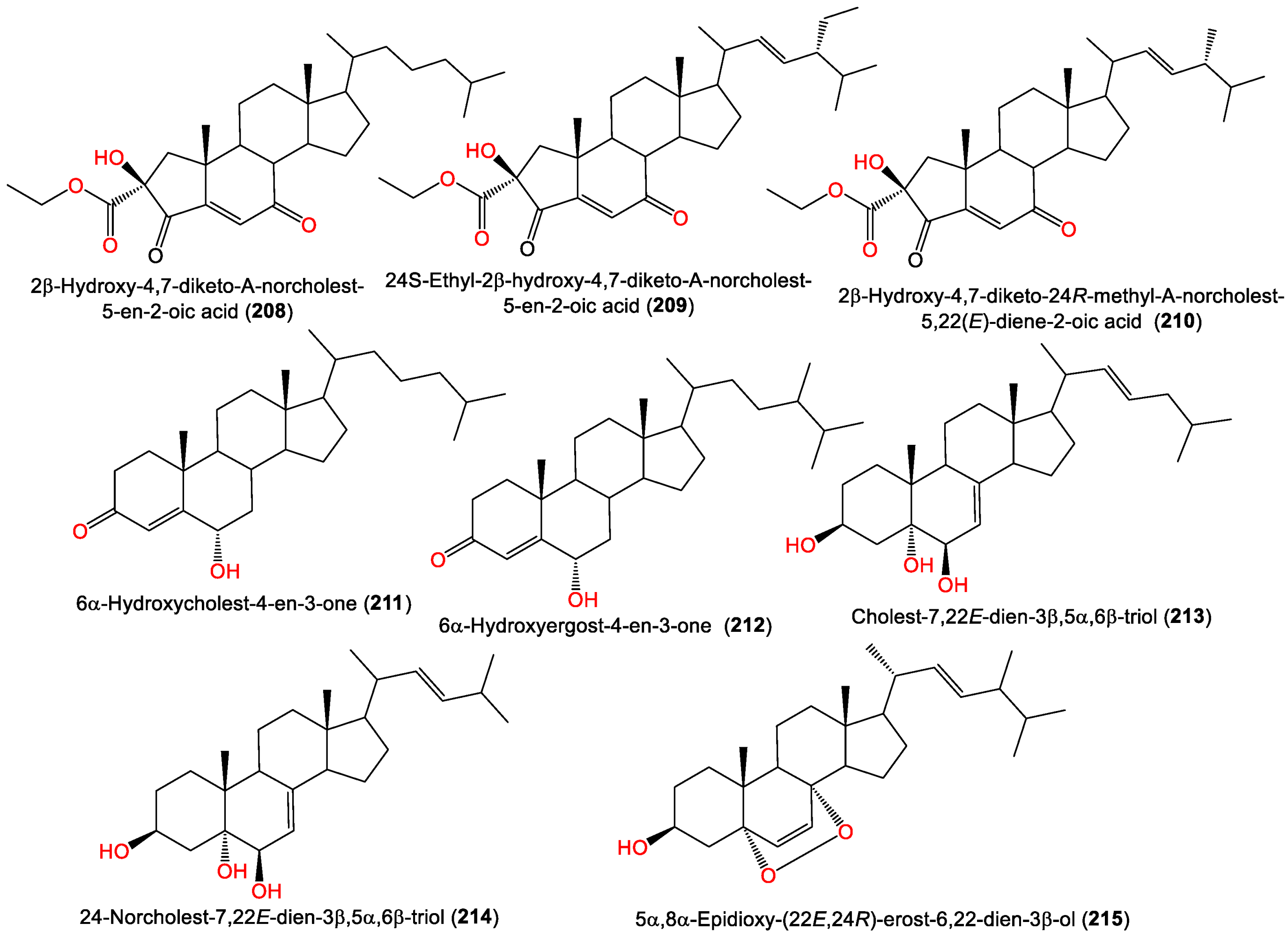


Figure 19. Steroid compounds (**208**–**215**) reported from the genus *Acanthella*.

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 [57] (**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 [58]. Compound **219** has an additional methyl group at C-2 of the sidechain compared to **218**, and both have a 2`S configuration [58]. In 2010, Hammami et al. separated the sesterterpene **217** and cerebrosides **220**–**222** from Tunisian *A. acuta* diethyl ether extracts [19], whereas **226** was purified from the Chinese *A. cavernosa* by Fan et al. [24].

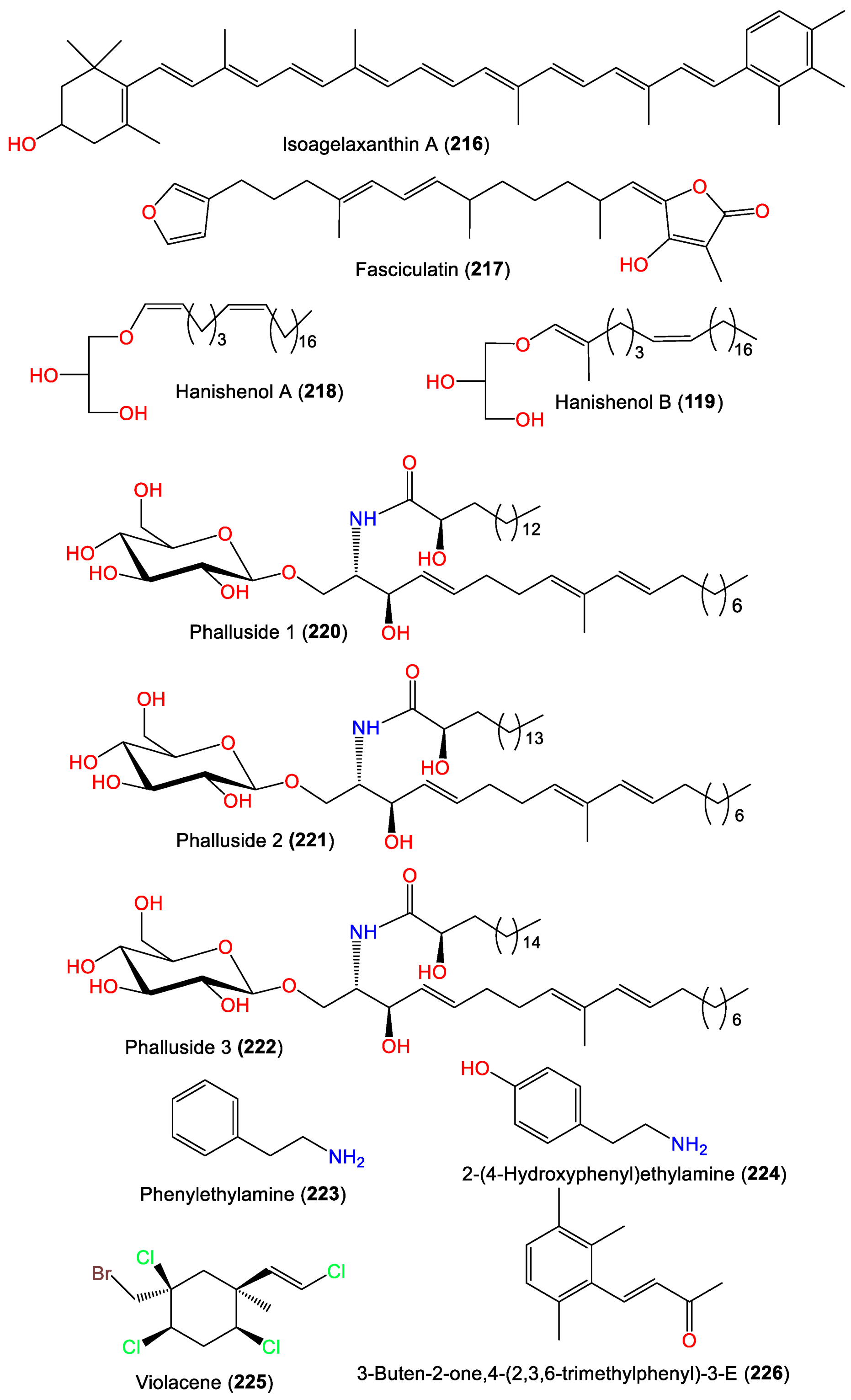


Figure 20. Other metabolites (**216**–**226**) reported from the genus *Acanthella*.

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