# 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.

Keywords: 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].

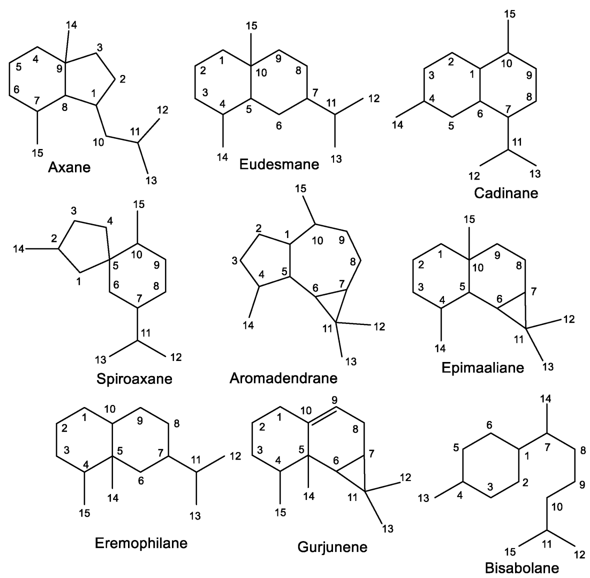



**Figure 1.** Classes of sesquiterpenes reported from the genus *Acanthella*.

**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** | | | | | |

| Compound Name | Mol. Wt. | Mol. Formula | Species | Sampling Locations | Ref. |
|---|---|---|---|---|---|
| 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, Australia | [8] |
| | - | - | *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] |
| 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] |

| Compound Name | Mol. Wt. | Mol. Formula | Species | Sampling Locations | Ref. |
|---|---|---|---|---|---|
| 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] |
| | - | - | *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] |
| | - | - | *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] |

| Compound Name | Mol. Wt. | Mol. Formula | Species | Sampling Locations | Ref. |
|---|---|---|---|---|---|
| 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. cavernosa* | Hachijo-jima Island, Japan | [11] |
| 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] |
| 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] |

| Compound Name | Mol. Wt. | Mol. Formula | Species | Sampling Locations | Ref. |
|---|---|---|---|---|---|
| | - | - | *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, Queensland, Australia | [17] |
| | - | - | *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, China | [14] |
| (±)-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] |

| Compound Name | Mol. Wt. | Mol. Formula | Species | Sampling Locations | Ref. |
|---|---|---|---|---|---|
| (±)-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] |
| 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, China | [14] |

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

## 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 $SiO_2$CC (silica gel column chromatography), assigned by spectral and chemical methods [5].

Furthermore, **5** and **9** were isolated from Japanese *A. cavernosa* by $SiO_2$ CC and RP-HPLC and identified by different spectroscopic methods [11]. 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 [4]. 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** [4]. 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**) [4].

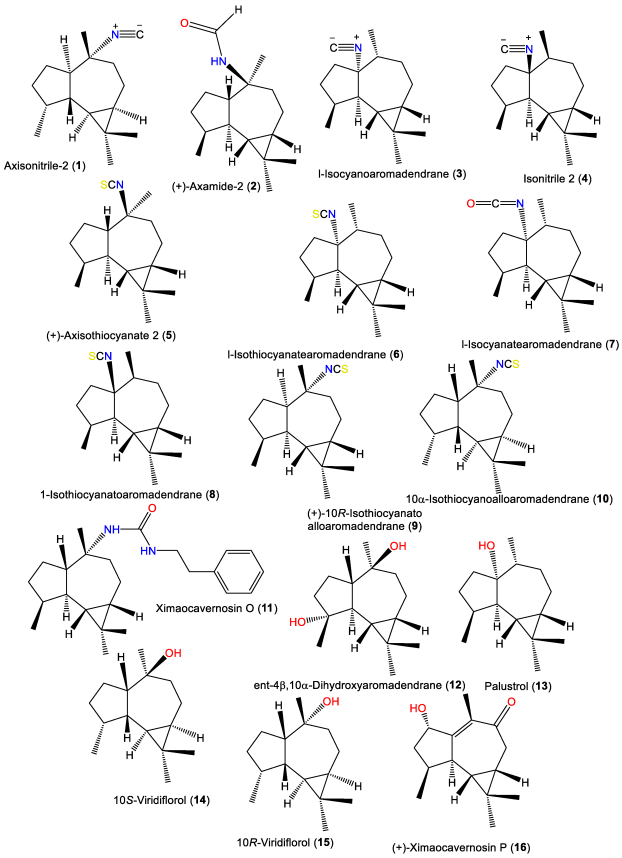



**Figure 2.** Aromadendrane-type sesquiterpenes (**1**–**16**) reported from the genus *Acanthella*.

## 1.2. Spiroaxane-Type Sesquiterpenes

Spiroaxane skeletons containing sesquiterpenes are of rare natural occurrence. Compound **19**, a new sesquiterpene isocyanide with a spiroaxane (spiro [25][26] decane) skeleton was obtained from Chinese *Acanthella* sp., which is a 3-oxo derivative of **17** [12]. 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** [8][16].

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 [4]. 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**) [4] (**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 [22].

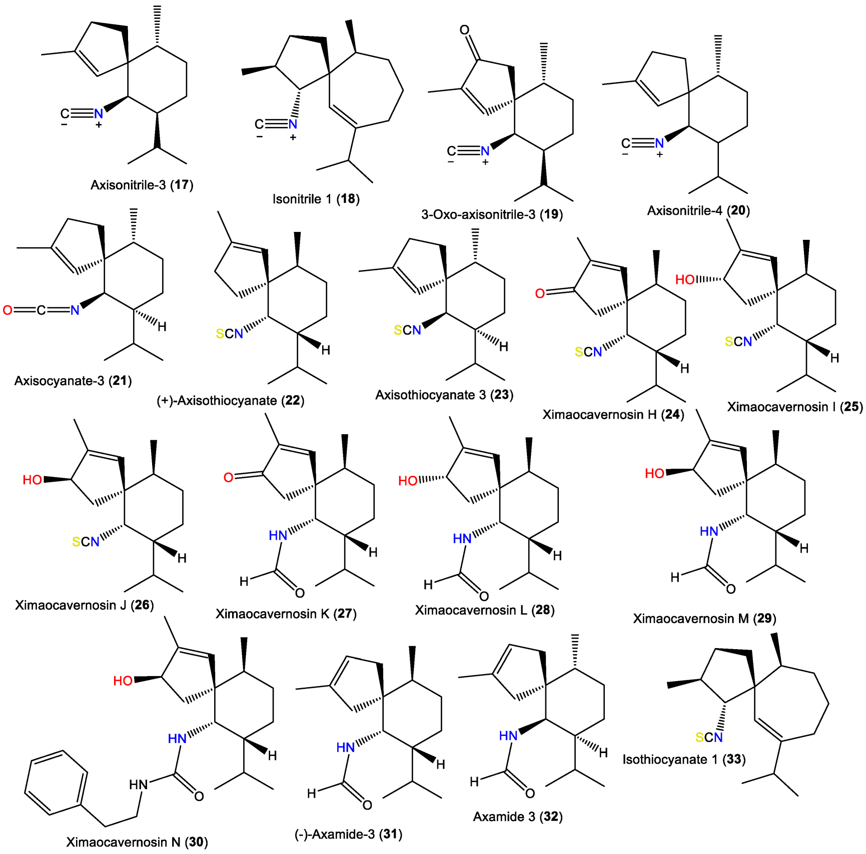



**Figure 3.** Spiroaxane-type sesquiterpenes (**17**–**33**) reported from the genus *Acanthella*.

### 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 $SiO_2$CC, 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].

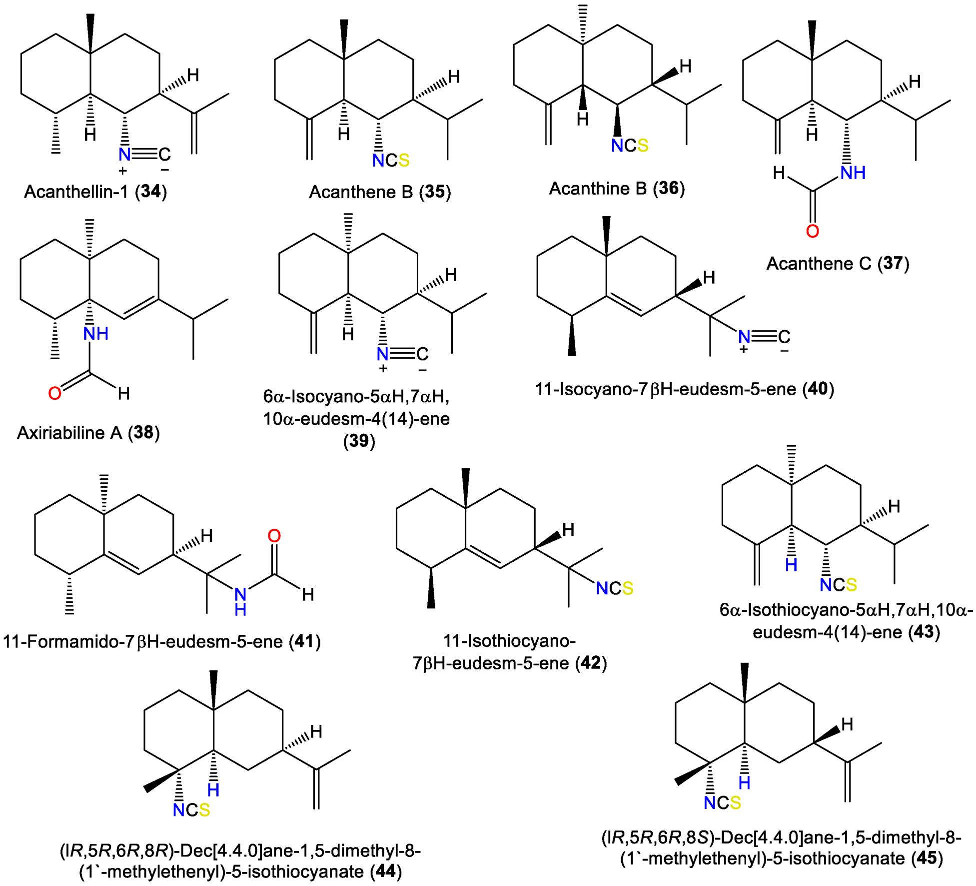



**Figure 4.** Eudesmane-type sesquiterpenes (**34**–**45**) reported from the genus *Acanthella*.

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].

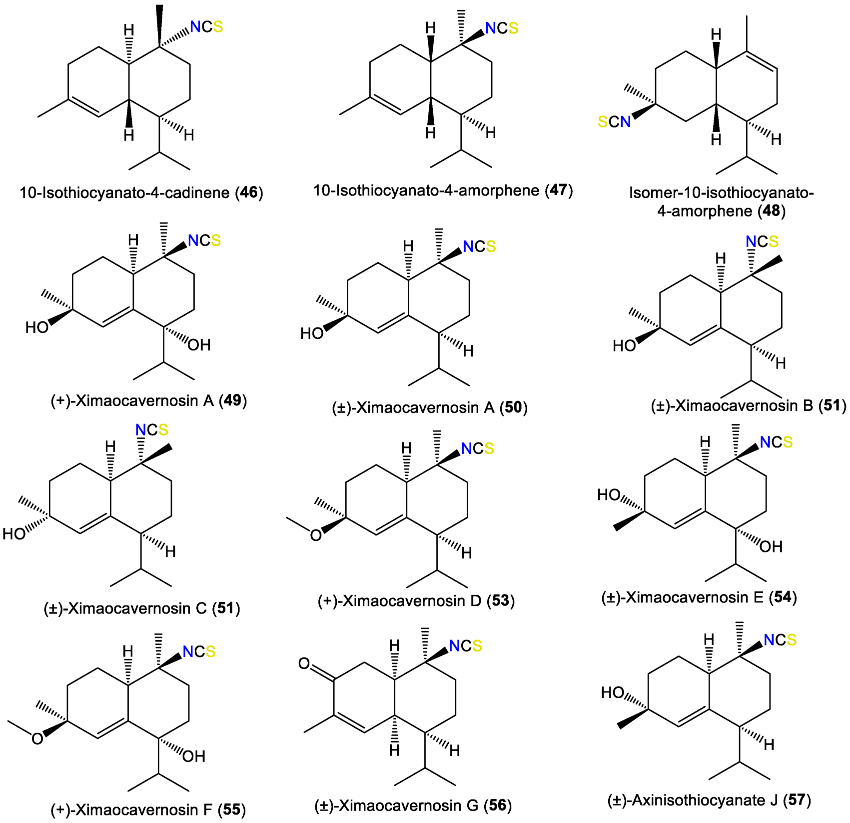



**Figure 5.** Cadinene-type sesquiterpenes (**46**–**57**) reported from the genus *Acanthella*.

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].

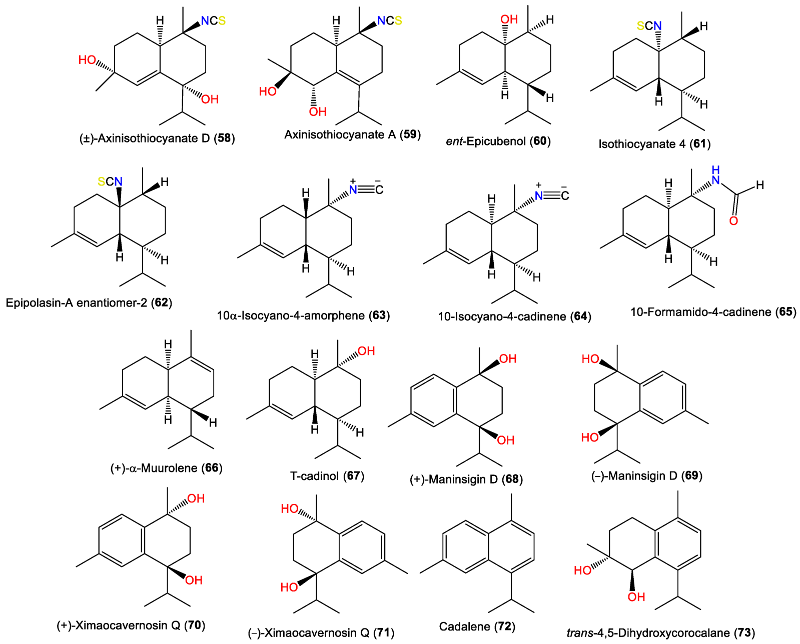



**Figure 6.** Cadinene-type sesquiterpenes (**58**–**73**) reported from the genus *Acanthella*.

## 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**).

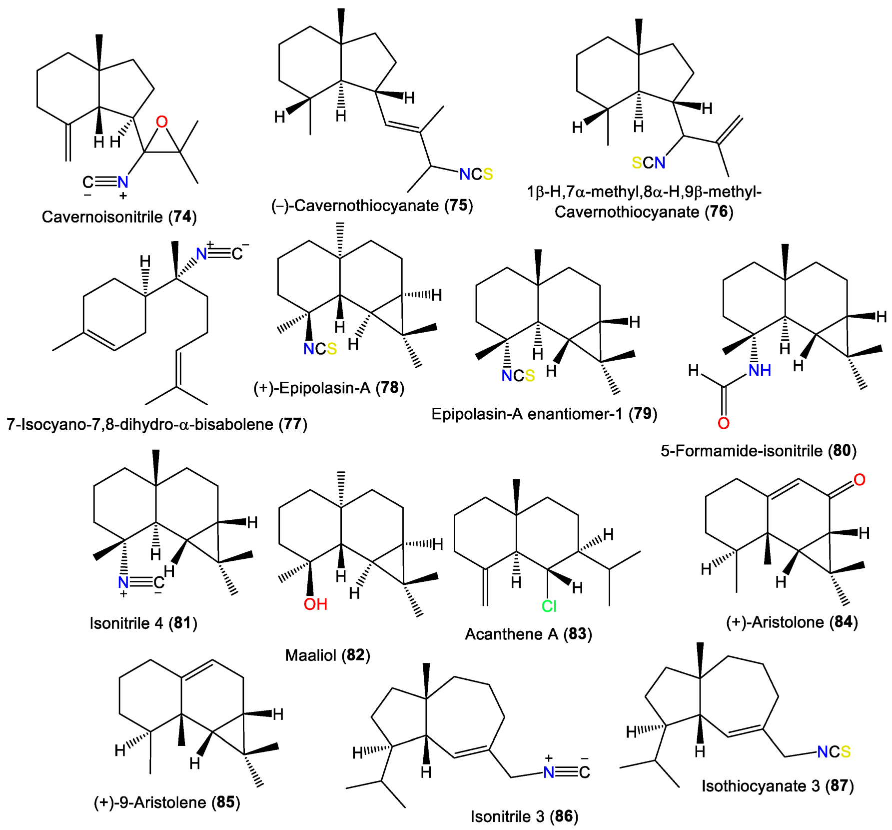
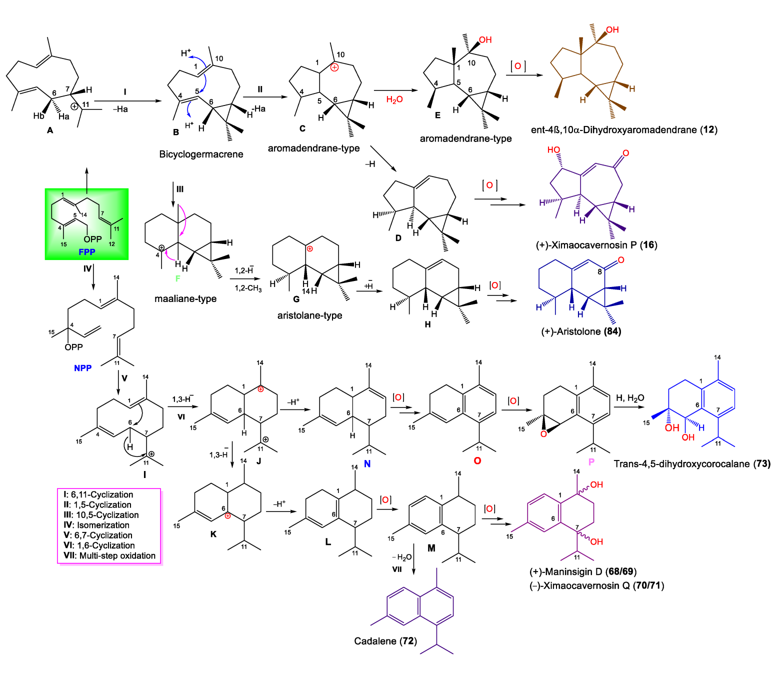



**Figure 7.** Other sesquiterpenes (**74**–**87**) reported from the genus *Acanthella*.

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 $\Delta^4$-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.

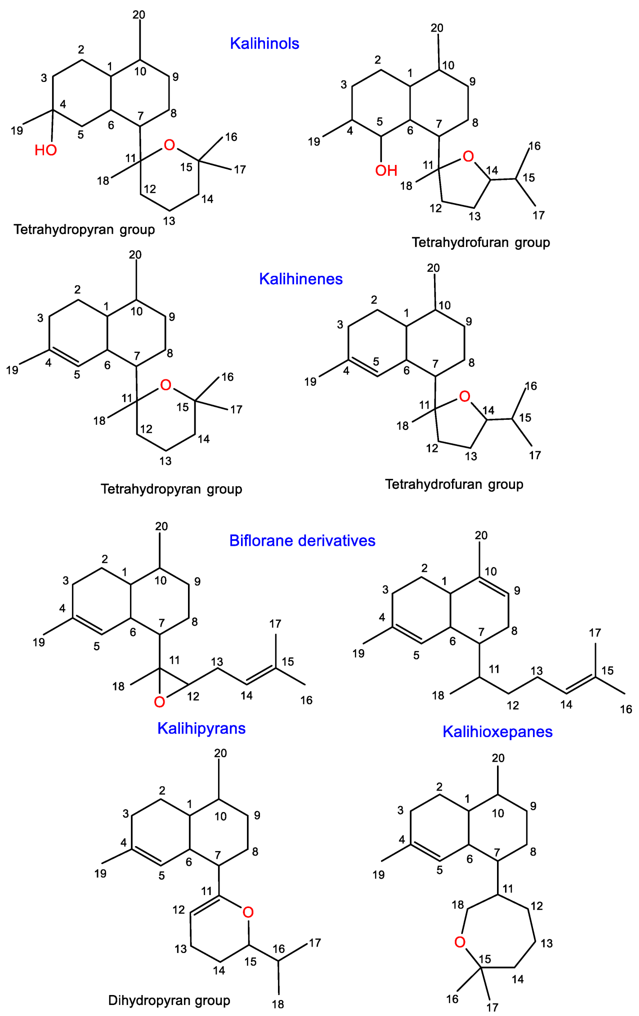



**Figure 8.** Classes of diterpenes reported from genus *Acanthella*.

**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** | | | | | |

| Compound Name | Mol. Wt. | Mol. Formula | Species | Sampling Locations | Ref. |
|---|---|---|---|---|---|
| Kalihinol A (88) | 392 | $C_{22}H_{33}ClN_2O_2$ | *Acanthella* sp. | Apra Harbor, Guam, western side of the USA | [29] |
| | - | - | *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 Island, China | [37] |
| 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] |

| Compound Name | Mol. Wt. | Mol. Formula | Species | Sampling Locations | Ref. |
|---|---|---|---|---|---|
| | - | - | *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] |
| 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* sp. | Coast of Cape Sada, Ehime Prefecture, Japan | [41] |
| | - | - | *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] |

| Compound Name | Mol. Wt. | Mol. Formula | Species | Sampling Locations | Ref. |
|---|---|---|---|---|---|
| *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] |
| 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] |
| 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] |

| Compound Name | Mol. Wt. | Mol. Formula | Species | Sampling Locations | Ref. |
|---|---|---|---|---|---|
| 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] |
| | - | - | *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] |
| $\Delta^9$-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] |
| | - | - | *A. cavernosa* | Beau Vallon Beach, Mahé, Seychelles | [39] |
| | - | - | *A. cavernosa* | Fiji, South Pacific Ocean | [28] |

| 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] |
| | - | - | *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-die*pi*-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] |
| | - | - | *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] |

| Compound Name | Mol. Wt. | Mol. Formula | Species | Sampling Locations | Ref. |
|---|---|---|---|---|---|
| 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] |
| 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] |
| 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] |

## 2.1. Kalihinols

Kalihinol A (**88**) was the first reported member of this diterpenoid class in 1984 [29] (**Table 2**). 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 [29] and its configuration was assigned as 1S/4R/5R/6S/7S/10S/11R/14S using the CD exciton chirality method [45] (**Figure 9**).

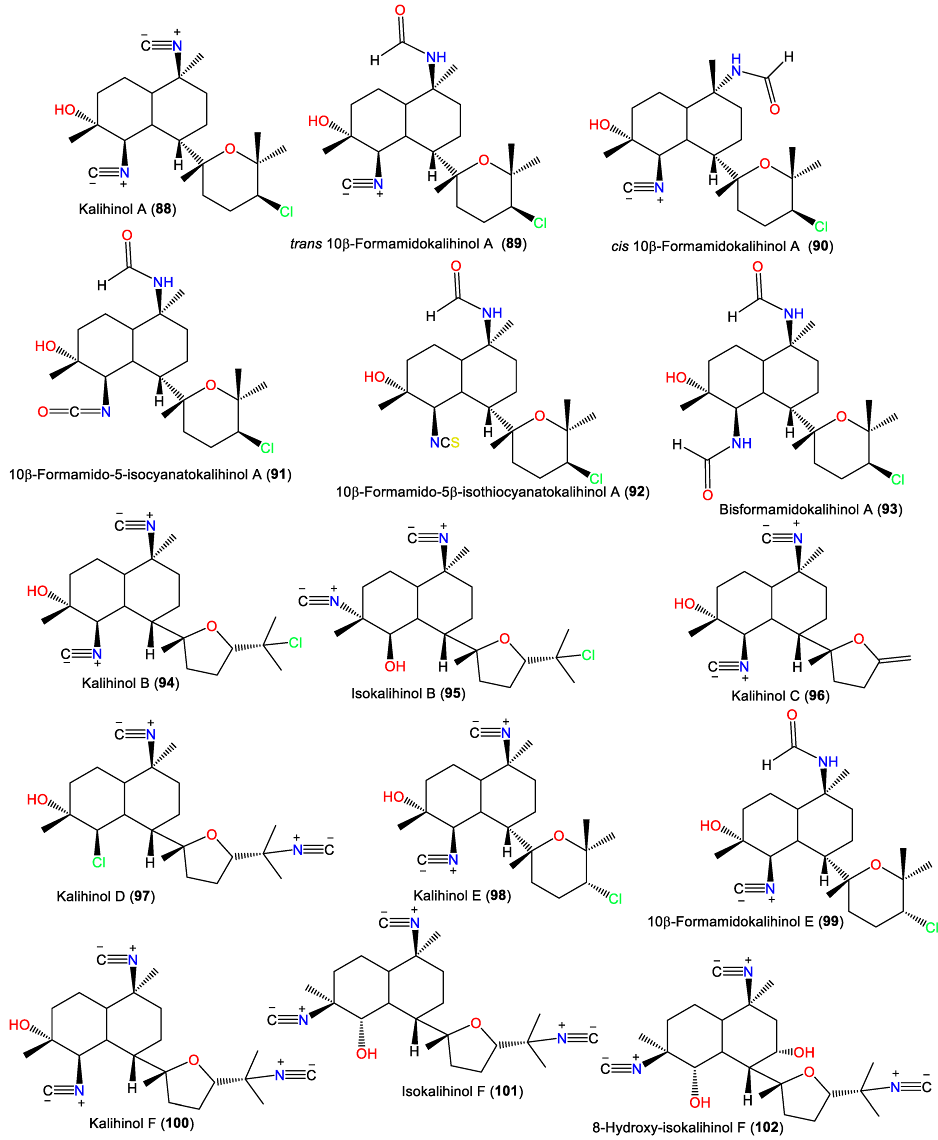



**Figure 9.** Kalihinol diterpenes (**88**–**102**) reported from the genus *Acanthella*.

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**) [30] (**Figure 10**).

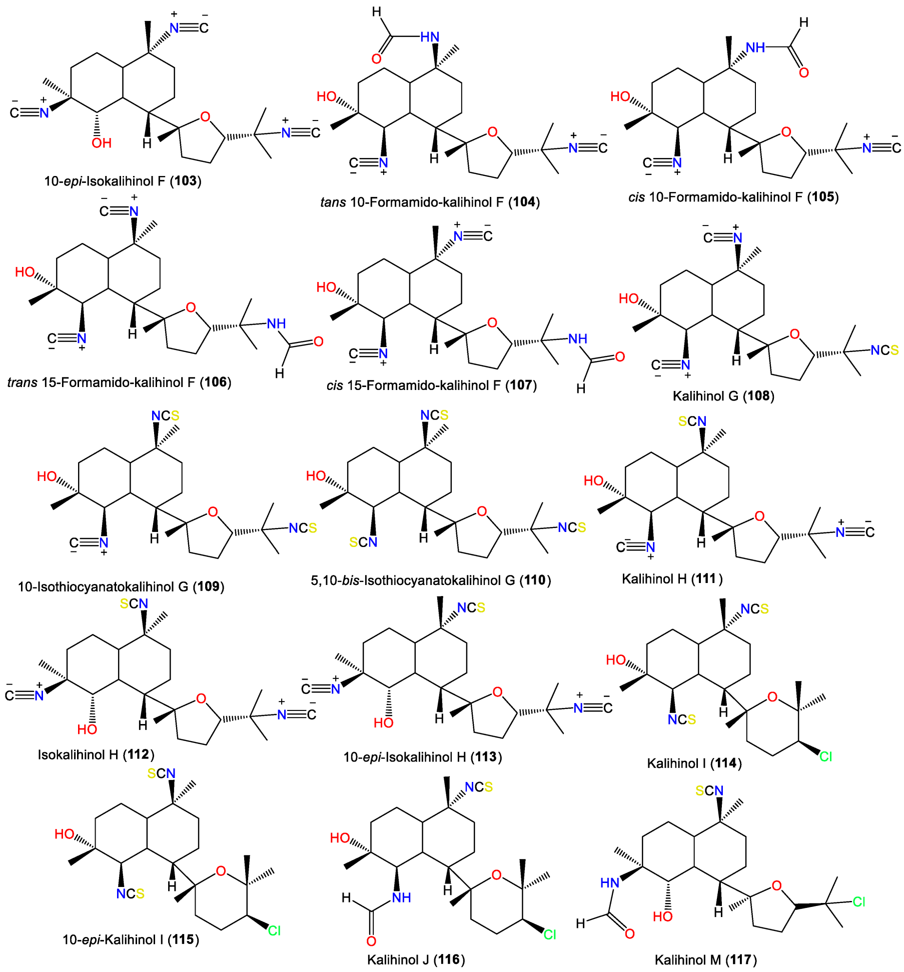



**Figure 10.** Kalihinol diterpenes (**103**–**117**) reported from the genus *Acanthella*.

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 $C_5$ [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**).

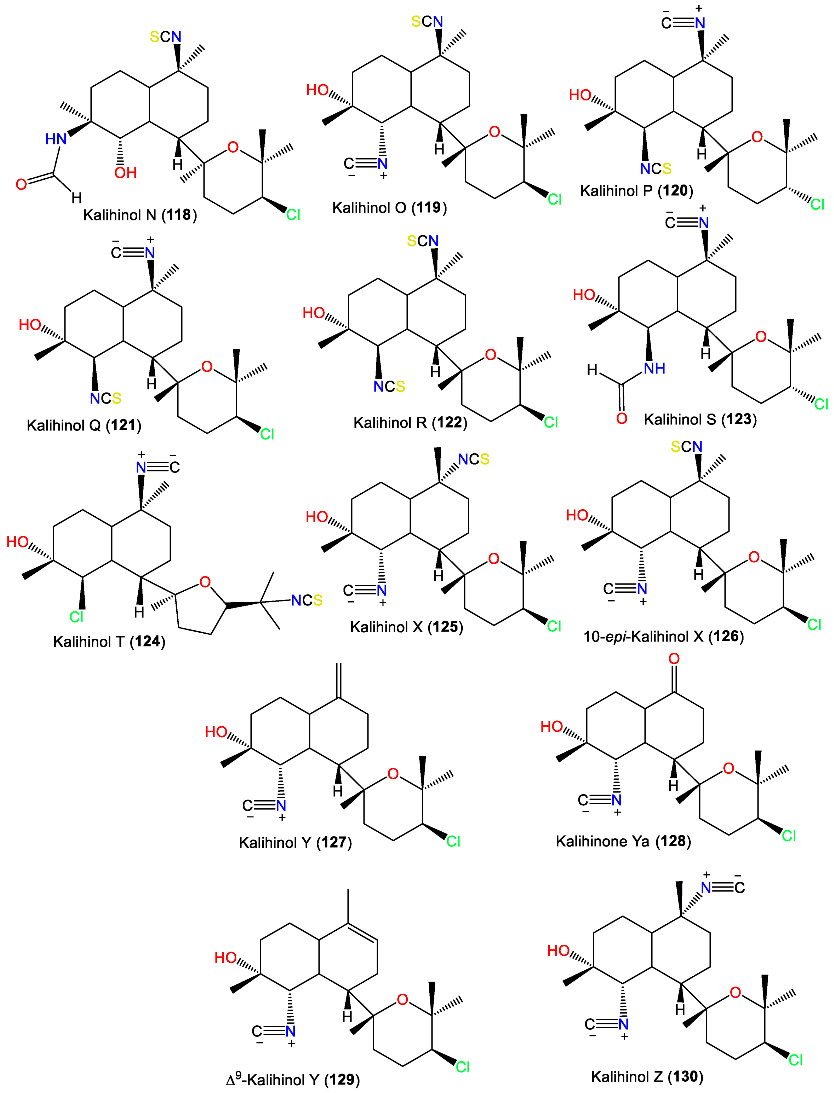



**Figure 11.** Kalihinol diterpenes (**118**–**130**) reported from the genus *Acanthella*.

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].

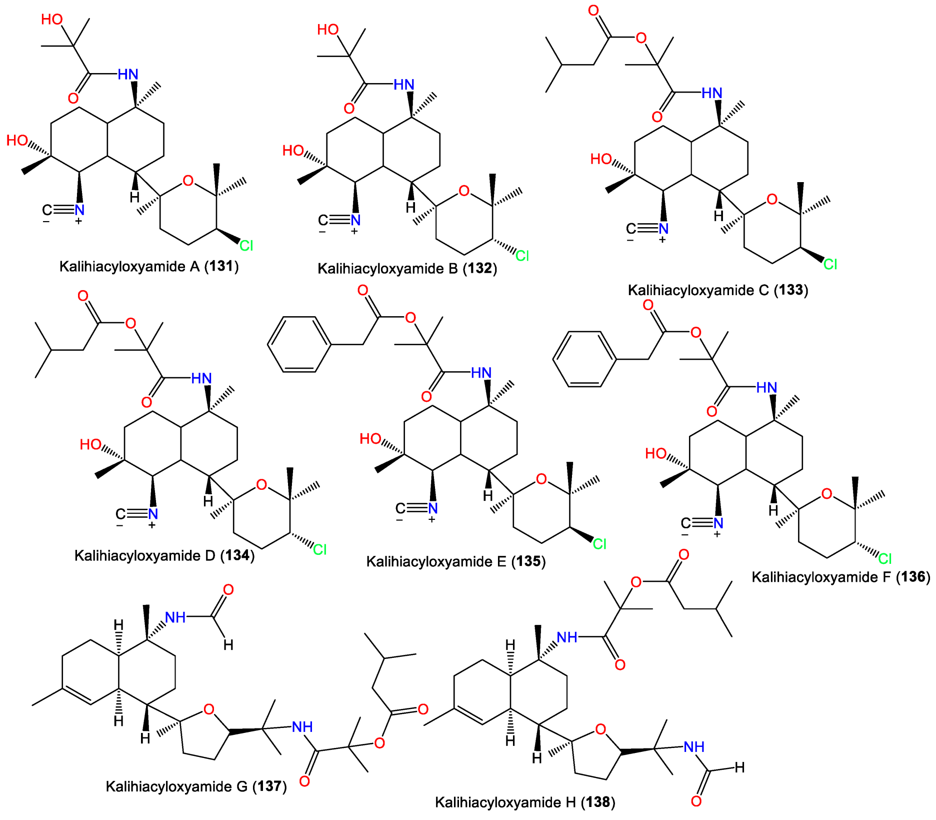


**Figure 12.** Kalihinol diterpenes (**131**–**138**) reported from the genus *Acanthella*.

## 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].

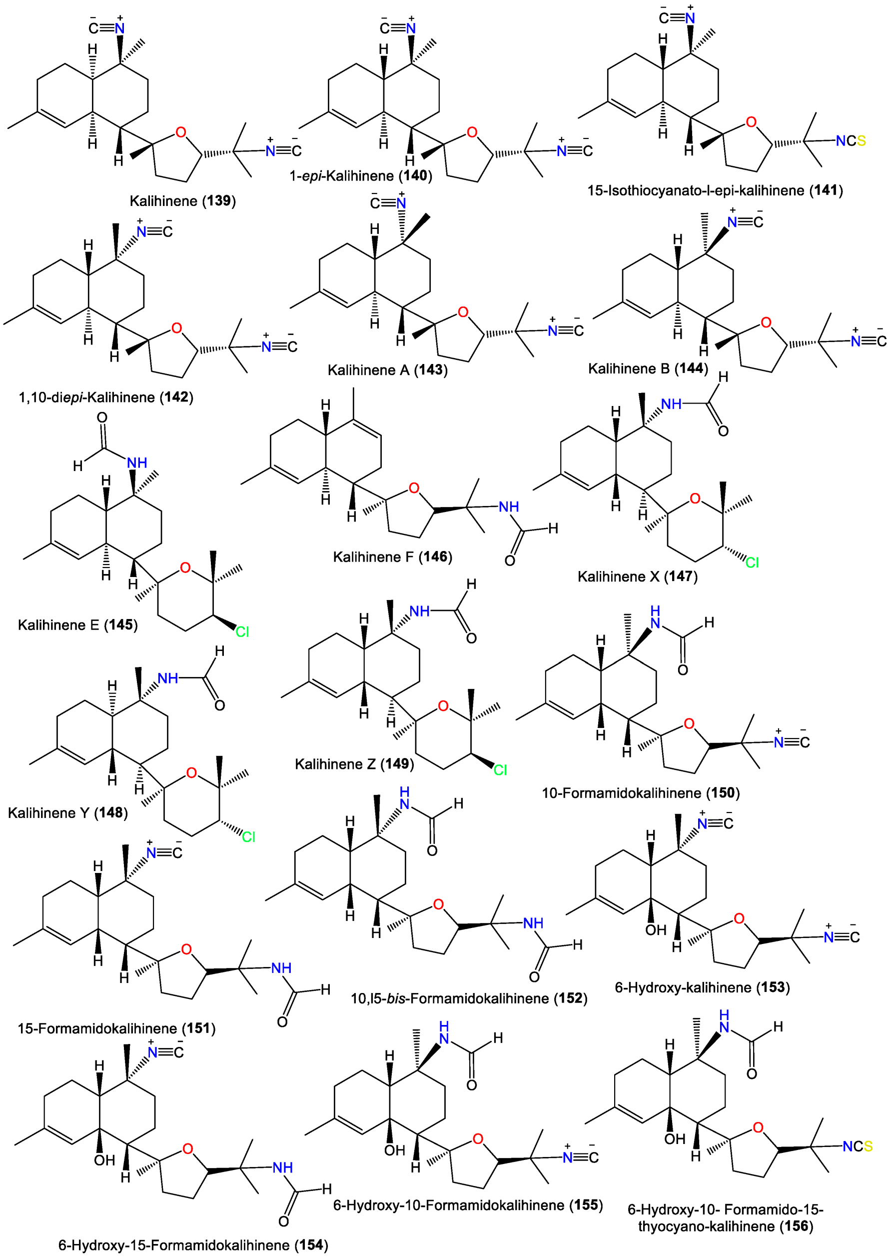



**Figure 13.** Kalihinene diterpenes (**139**–**156**) reported from the genus *Acanthella*.

## 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**).

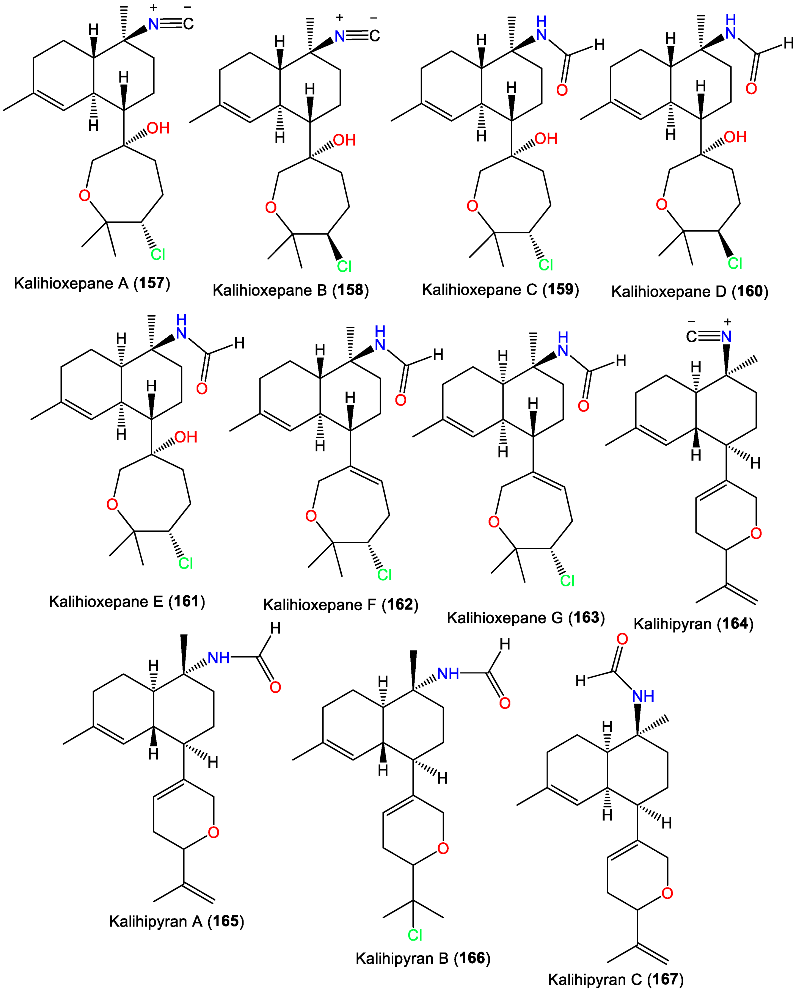
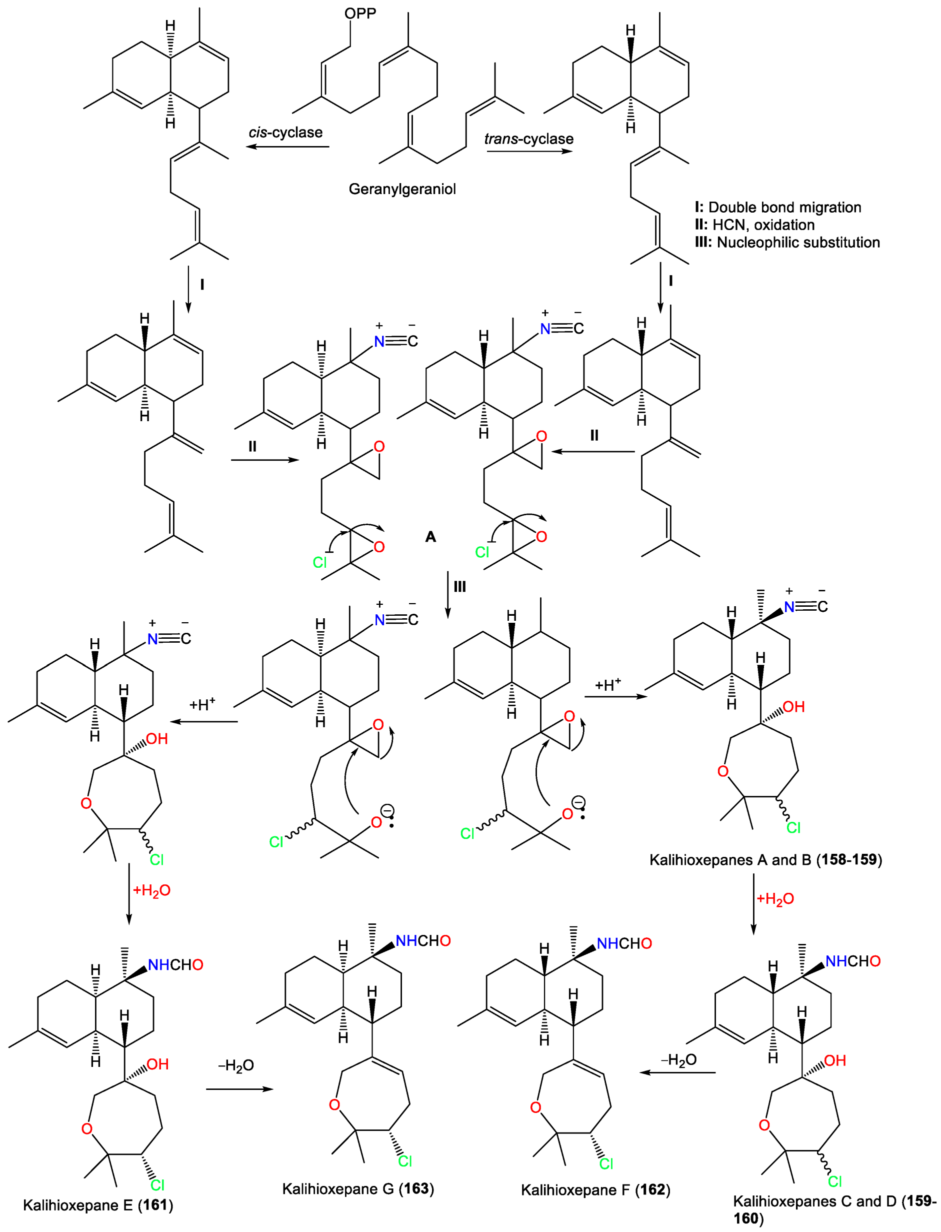



**Figure 14.** Kalihioxepanes (**157**–**163**) and kalihipyrans (**164**–**167**) diterpenes reported from the genus *Acanthella*.

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].

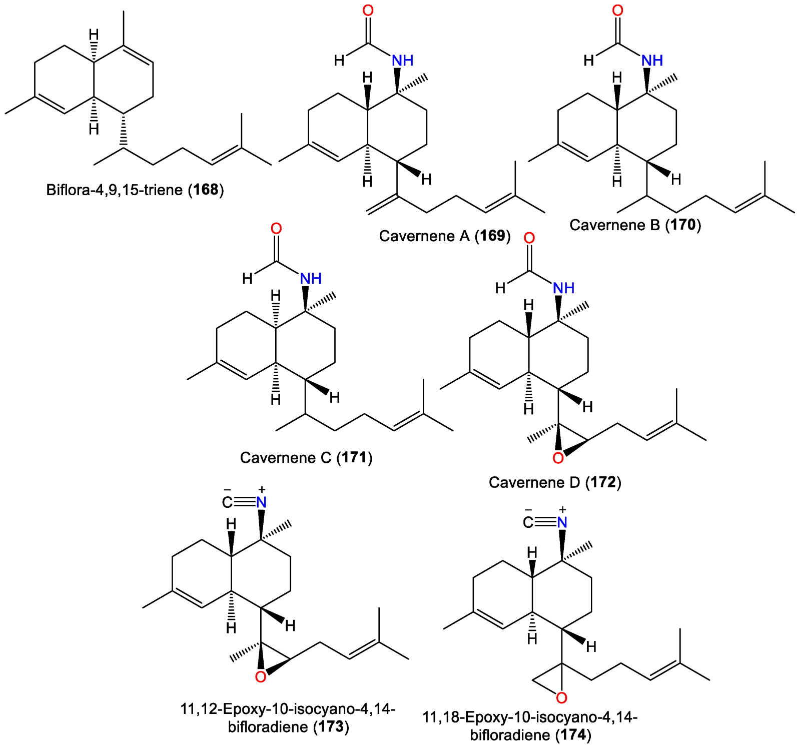
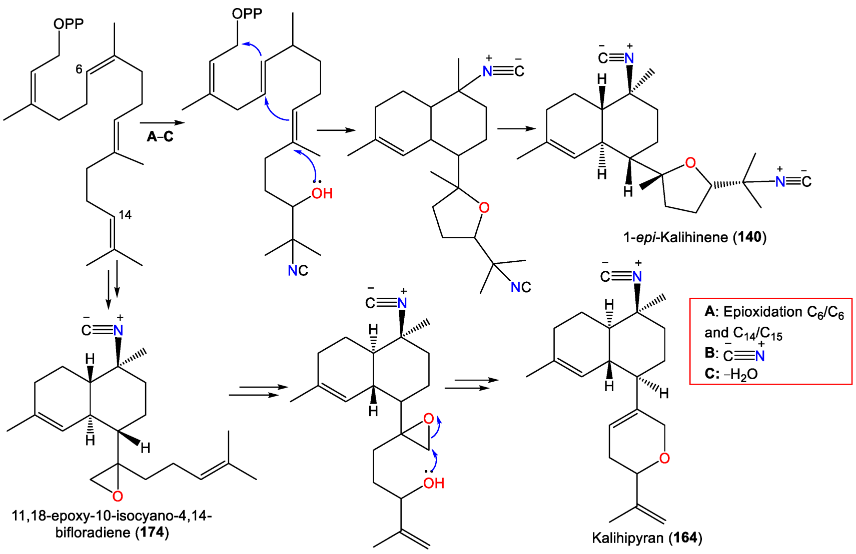



**Figure 15.** Biflorane (**168**–**174**) diterpenes reported from the genus *Acanthella*.

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].

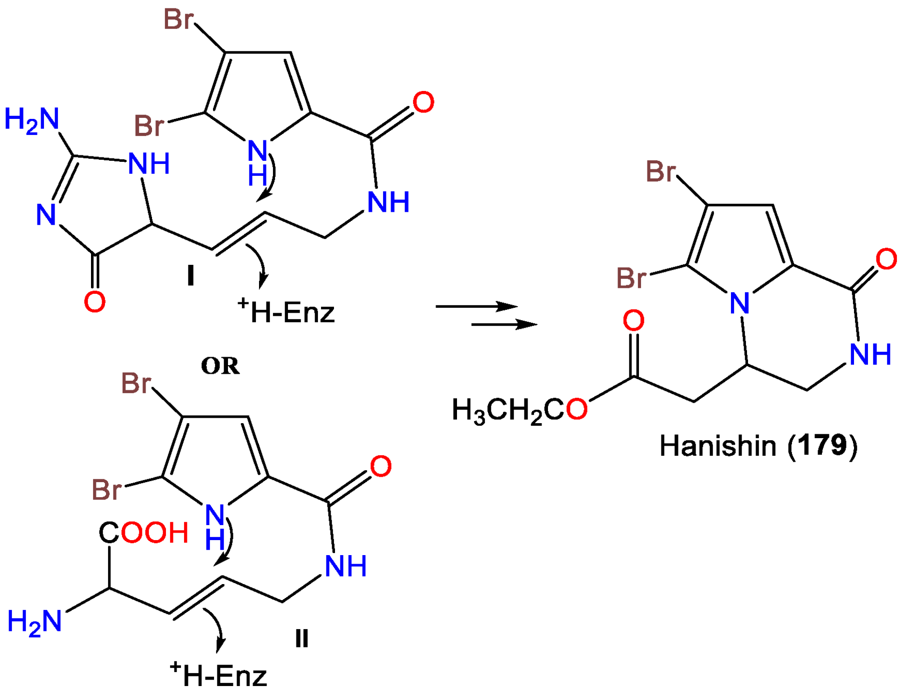



**Scheme 3.** Biosynthesis of **140**, **164**, and **174** [18].

## 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].

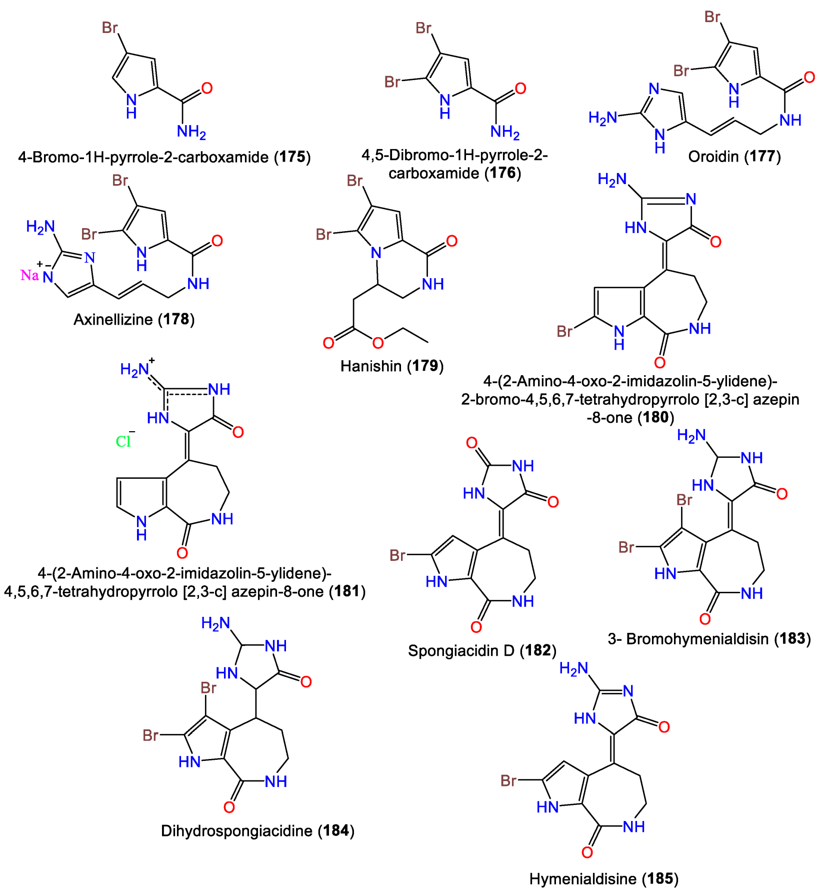
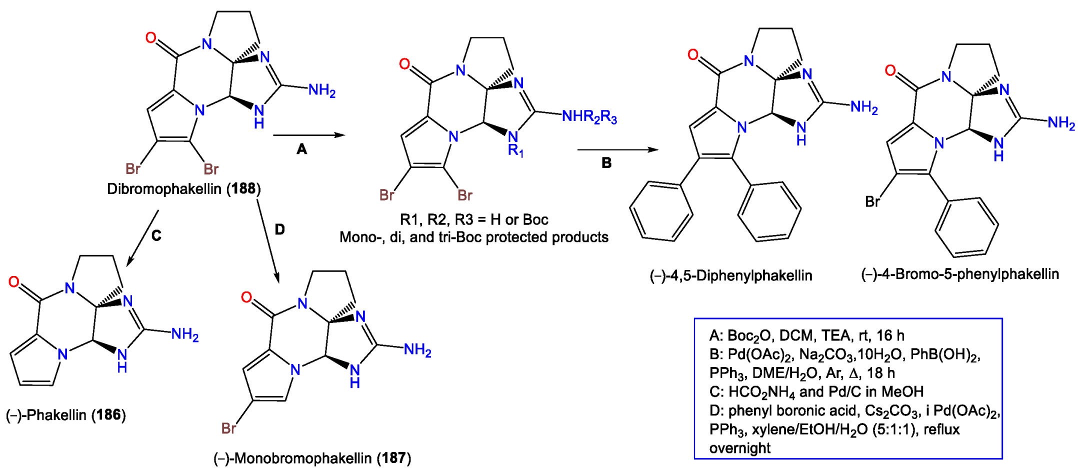


**Figure 16.** Alkaloids (**175**–**185**) reported from genus *Acanthella*.

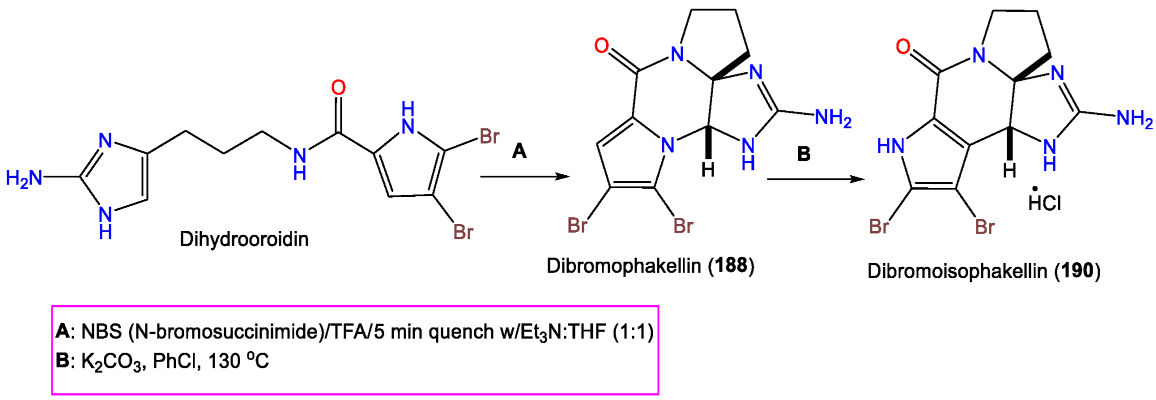
A series of synthetic reactions including Suzuki–Miyaura coupling and debromination resulted in natural analogs **186** and **187**, in addition to new synthetic derivatives (−)-4-bromo-5-phenylphakellin and (−)-4,5-diphenylphakellin. It was found that the C-5 Br substitution with phenyl or H led to 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].

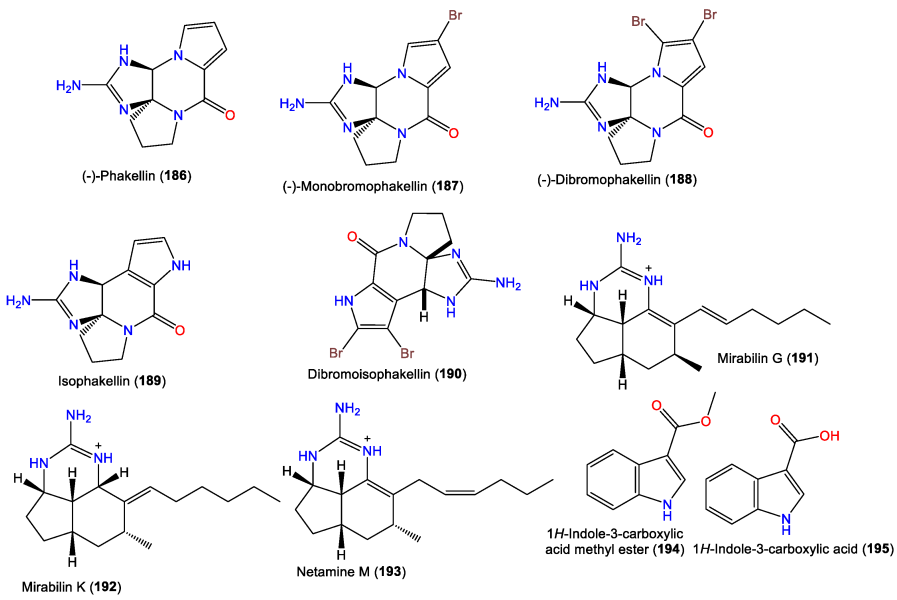



**Figure 17.** Alkaloids (**186**–**195**) reported from the genus *Acanthella*.

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].

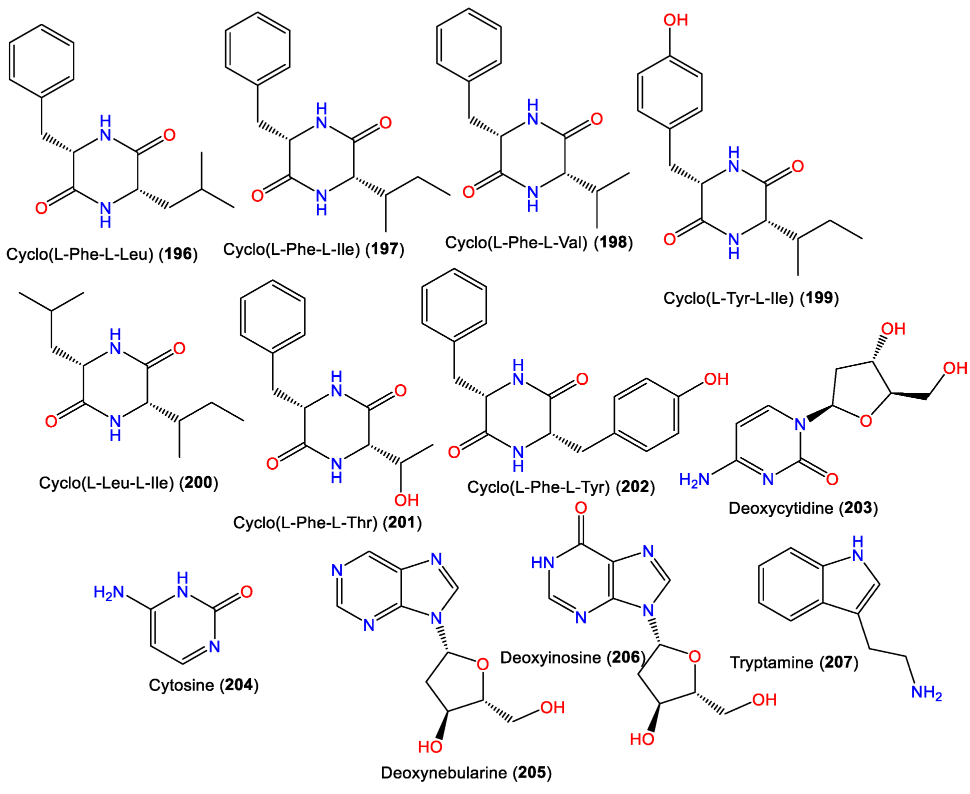



**Figure 18.** Alkaloids (**196**–**207**) reported from the genus *Acanthella*.

## 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].

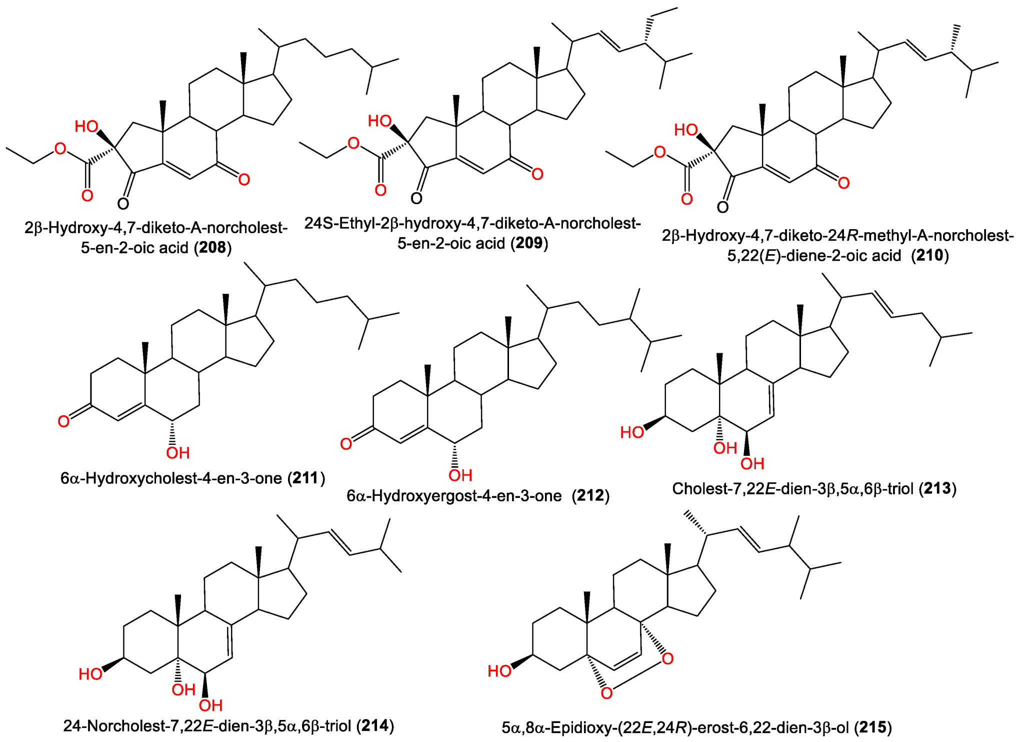



**Figure 19.** Steroid compounds (**208**–**215**) reported from the genus *Acanthella*.

## 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].

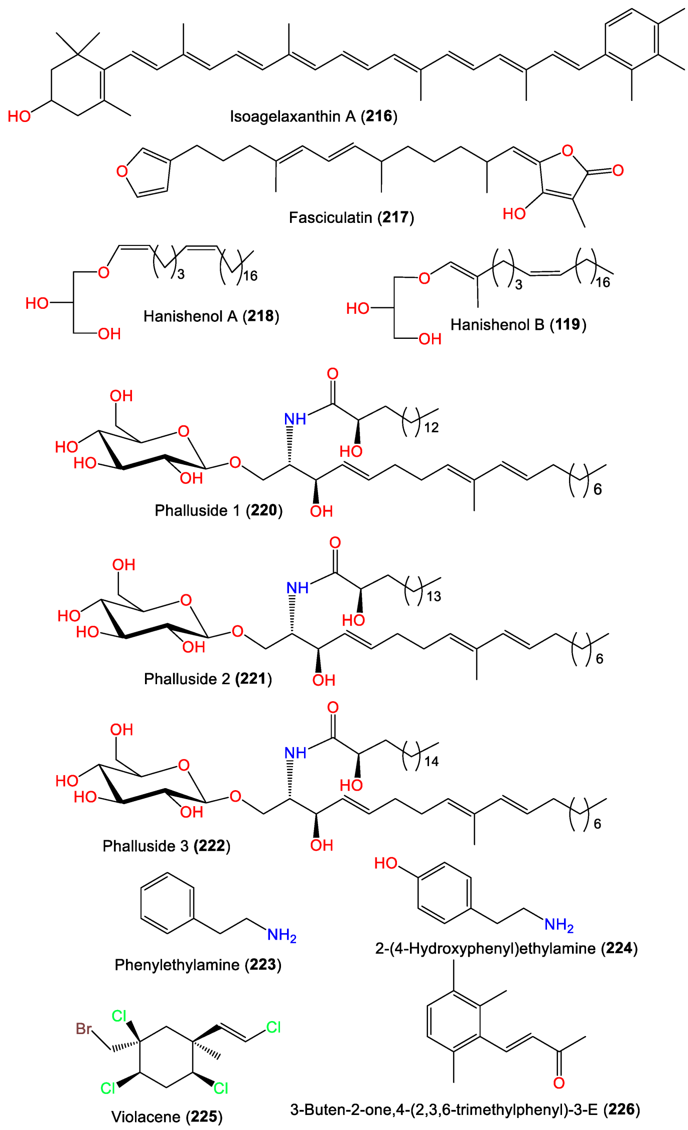



**Figure 20.** Other metabolites (**216**–**226**) reported from the genus *Acanthella*.

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