


Review

Alcyonium Octocorals: Potential Source of Diverse Bioactive Terpenoids

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Abstract: *Alcyonium* corals are benthic animals, which live in different climatic areas, including temperate, Antarctic and sub-Antarctic waters. They were found to produce different chemical substances with molecular diversity and unique architectures. These metabolites embrace several terpenoidal classes with different functionalities. This wide array of structures supports the productivity of genus *Alcyonium*. Yet, majority of the reported compounds are still biologically unscreened and require substantial efforts to explore their importance. This review is an entryway to push forward the bio-investigation of this genus. It covers the era from the beginning of reporting metabolites from *Alcyonium* up to March 2019. Ninety-two metabolites are presented; forty-two sesquiterpenes, twenty-five diterpenes and twenty-five steroids have been reported from sixteen species.

Keywords: Alcyoniidae; mevalonates; steroids; anti-inflammatory; antimicrobial; antifeedant

1. Introduction

The marine environment is represented by two-thirds of the earth and epitomizes harsh parameters. It has a wide range of temperature; ranged from -1.5 °C to 350 °C, pressure ranged from 1 to over 1000 atmosphere, light ranged from complete darkness to extensive photic zones and nutritional-rich till nutrient-spar [1–3].

Thirty-four animal phyla were taxonomically identified, however, thirty-six were found in a marine habitat. The marine species counts around 240,000 known species, albeit less than five percent of the deep sea has been explored [4,5]. Production of the unique metabolites from marine organisms could be explained by the harsh and competitive conditions. Although the terrestrial sources are providing unique bioactive metabolites, the marine organisms produce a considerable number of unprecedented bioactive substances, which have a great possibility to be a lead drug [6]. Blunt and his co-workers reported that the identified marine metabolites estimated to be 31,000 (i.e., 1000 substances per year) [7]. The molecular structures associated, particularly, produced from marine organisms, are varying from low molecular weight to complex form [8–14]. These metabolites enhance marine

invertebrate's survival by providing chemical defense. They play a crucial role in the adaptation of the marine organisms to the physical and chemical extreme conditions. The marine metabolites interfere with receptors and enzymes of coexisting marine competitors and predators. This emphasized the hypothesis that several of those compounds could interfere with molecular targets [15–19].

Alcyonacea (Phylum, Cnidaria; class, Anthozoa; subclass, Octocorallia; order, Alcyonacea) constitutes an important group of marine invertebrates, widely distributed in the coral reefs. They are quite numerous throughout the tropical waters, mainly live in the intertidal zones on inner reefs below the stony corals [14]. They are less prone to damage or ailments from collecting and shipping than the stony corals. They protect themselves by the production of certain chemical mediators, due to the absence of skeletal defenses [3,14].

Soft corals have proven to be a biochemical warehouse for production of bioactive terpenoidal metabolites particularly, those belonging to the family, Alcyoniidae (37 genera) [3,20]. These types of metabolites show roles in protection and taxonomical identification (i.e., markers) [21]. Genus *Alcyonium* (Flame corals) are small soft corals. They live in colonies of polyps (round body) and forming erect fleshy masses. The absence of an internal skeleton was observed. Each polyp contains eight small, feathery tentacles called pinnates. These pinnates contain stinging cells that they utilized to catch their prey. They are micro carnivores that feed on planktonic animals. Their body is a pale yellow color, however, the stem of the polyp is orange and the polyps are bright red. Genus *Alcyonium* comprises 141 species, of which 71 were accepted to be transferred to other genera [4,5,8].

In the current review, the isoprenoidal derivatives which, isolated from genus *Alcyonium*, are presented. These compounds showed certain effects on some diseases and could have a coming role in drug discovery. It is interesting to discuss the future perspectives of the chemical structures and possible biological activity relationships. Sixteen *Alcyonium* species of different geographical locations have been chemically investigated, resulted in the identification of ninety-two metabolites which categorized under three classes; sesquiterpenes, diterpenes and steroids. Extensive literature surveys were performed employing different scientific databases (e.g., SciFinder, Scopus, PubMed, Scholar, ScienceDirect and Web of Science), indicated the scarce or almost absence of review interested in this theme.

2. Terpenoids from *Alcyonium*

Soft corals of the genus *Alcyonium* are widely spread all over the oceans. Some of them were chemically and biologically investigated (Table 1, Figure 1). Up to March 2019, ninety-two terpenoidal derivatives have been isolated and identified from sixteen species of genus *Alcyonium*, namely, *Alcyonium* sp., *A. antarcticum*, *A. coralloides*, *A. fauri*, *A. flaccidu*, *A. foliatum*, *A. gracillimum*, *A. grandis*, *A. molle*, *A. paessleri*, *A. palmatum*, *A. patagonicum*, *A. utinomii*, and *A. valdiviae* (Table 1 and Figure 2).

Eighty-six isoprenoids have been recorded from *Alcyonium* for the first time, and the remaining six were previously reported from other marine sources. Sesquiterpenoids are eminent metabolites from *Alcyonium*, which were categorized under eleven carbo-skeleton types; aphanmalane, aromadendrane, bulgarane, cadinane, bicyclogermacrane, eudesmane, furanosesquiterene, guaiazulene illudalane, paesslerane, and triprenylhydroquinone (Figures 2 and 3). Besides, diterpenoids from *Alcyonium* are classified into six classes, cembrane, cladiellin, eunicellin, prenylbicyclogermacrane, xenicin, and xenicane. Finally, twenty-five steroids have been identified. Interestingly, steroids cholestane (C-27), campestane (C-28), gorgostane (C-30) along with pregnane (C21) carbon skeleton were all identified. The diversity of the terpenoidal content of genus *Alcyonium* is a source of 92 metabolites which categorized under 21 classes. This addressed that, the metabolites were obtained from 20% of the identified species, thus, the chem-biological investigations of the rest (80%) are urgently required.

Table 1. Terpenoidal metabolites isolated from genus *Alcyonium*.

Cpd. No.	Cpd. Name	Species	Biological Effects	Class of Cpd	Ref. No.
1	Guaiazulene	<i>Alcyonium</i> sp.	-	Guaiazulene	[22]
2	(+)-Coralloidin-A	<i>A. coralloides</i>	-	Eudesmane sesquiterpene	[23,24]
3	(-)-Coralloidin- B		-	Bicyclogermacrane	
4–6	Coralloidin C, D and E		-	Eudesmane sesquiterpene	
7–8	Millecrone A and B	<i>A. foliatum</i> and <i>A. valdiviae</i>	Antifungal	Aphanmalane sesqui. Aromadendrane sesqui.	[25]
9–10	Millecrol A and B		Antimicrobial	Aphanmal sesqui. Cadinane sesqui.	[26]
11	Furanosesquiterpenoid	<i>A. palmatum</i>	Antifeedant	Furanosesquiterpene	[27]
12	Rietone	<i>A. fauri</i>	Anti-HIV	Triprenylhydroquinone	[28]
13	8'-Acetoxyrietoneand				
14	8'-Desoxyrietone				
15–29	Alcyopterosins A-O	<i>A. paessleri</i>	Cytotoxic	Illudalane Sesquiterpene	[29]
30–31	Paesslerins A and B	<i>A. paessleri</i>	-	Paesslerane sesquiterpene	[30]
32	4,12-Bis- <i>n</i> -butanoylalcyopterosin O,	<i>A. grandis</i>	Antifeedant	Illudalane Sesquiterpene	[31]
33	13-Acetoxy-12-acetylalcyopterosin D				
34	4,12-Bis(acetyl) alcyopterosin O				
35	12-Acetyl-13- <i>n</i> -butanoxyalcyopterosin D				
36	12-Acetyl-4- <i>n</i> -butanoylalcyopterosin O				
37	12-Acetylalcyopterosin D				
38	12- <i>n</i> -Butanoylalcyopterosin D				
39	13-Hydroxy alcyopterosin and				
40	Alcyopterosin P				
41	Alcyonicene				
42	Deacetoxyalcyonicene		-		

Table 1. Cont.

Cpd. No.	Cpd. Name	Species	Biological Effects	Class of Cpd	Ref. No.
43	Flaccidoxide	<i>A. flaccidum</i>	-	Cembrane diterpene	[33]
44	Cembrene-C				
45	Sarcophytol B				
46	Alcyonol-A	<i>A. utinomii</i>	-		[34]
47	Alcyonol-B				
48	Alcyonol-C				
49–54	Coralloidolide (A–F)	<i>A. coralloides</i>		Cembrane diterpene	[35–37]
55	Alcyonolide	<i>Alcyonium</i> sp.		Xenicin diterpene	[38]
56	Alcyonolide-5				
57	(1 <i>S</i> ,2 <i>R</i> ,3 <i>S</i> ,4 <i>R</i> ,5 <i>R</i> ,6 <i>S</i> ,8 <i>E</i> ,11 <i>S</i> ,12 <i>R</i> ,13 <i>S</i> ,14 <i>S</i>)-3-Acetoxy-2,12-dibutanoyloxycladiell-8-ene-4,11-diol	<i>A. molle</i>		Cladiellin diterpene	[40]
58	Patagonicol	<i>A. patagonicum</i>		Eunicellin diterpene	[41]
59	Valdivone A	<i>A. valdiviae</i>	Anti-inflammatory	Eunicellin diterpene	[42]
60	Valdivone B				
61	4- <i>O</i> -Methyl valdivone A				
62	4- <i>O</i> -Methyl valdivone B				
63	Dihydrovaldivone A				
64	Palmatol	<i>A. palmatum</i>		Prenylbicyclogermacrane	[43]
65–66	Zahavin A, and zahavin B	<i>A. aureum</i>	Cytotoxic	Xenicane diterpene	[44]
67	Pukalide	<i>A. antarcticum</i>	Feeding-deterrence	Cembrane diterpene	[45]

Table 1. Cont.

Cpd. No.	Cpd. Name	Species	Biological Effects	Class of Cpd	Ref. No.
68	Gorgosterol	<i>A. molle</i>		Gorgosterol	[40]
69	24-Methylenecholest-5-ene-3 β ,16 β -diol-3- <i>O</i> - α -L-fucoside	<i>Alcyonium</i> sp.	-	Campestone	[46]
70	24-Methylenecholest-5-ene-3 β ,7 β ,16 β -triol-3- <i>O</i> - α -L-fucopyranoside				
71	24-Methylenecholest-5-ene-3 β ,7 α ,16 β -triol-3- <i>O</i> - α -L-fucopyranoside				
72	3 β ,7 β -Dihydroxy-24-methylenecholesterol				
73	3 α ,7 α ,12 α -Triacetoxo-5 β -cholanic acid			Cholestane	[47]
74	Pregnedioside-A	<i>Alcyonium</i> sp.		Pregnane	[48]
75	4'- <i>O</i> -Acetyl-pregnedioside-A				
76	3'- <i>O</i> -Acetyl-pregnedioside-A				
77	Pregnedioside-B				
78	4'- <i>O</i> -Acetyl-pregnedioside				
79	3-Methoxy-19-norpregna-1,3,5(10),20-tetraene	<i>A. gracillimum</i>	Antifoulants	Pregnane	[49]
80	3-(4- <i>O</i> -Acetyl-6-deoxy- β -galactopyranosyloxy)-19-nor-pregna-1,3,5(10),20-tetraene				
81	22,23-Dihydroxycholesta-1,24-dien-3-one				
82	methyl Methyl-3-oxochola-1,4,22-trien-24-oate				
83	24-Methylenecholest 4-ene-3 β ,6 β -diol	<i>A. patagonicum</i>	Cytotoxic	Campestone	[41]
84	Pregnenolone	<i>A. antarcticum</i>	-	Pregnane	[32]
85	Pregnenolone-3-acetate				
86	Furospirostan				
87–88	Cholestane derivative with hemiketal functionality	<i>A. gracillimum</i>	Cytotoxic	Cholestane	[50]
89	Steroid with unusual dihydropyran ring				
90	Ketosteroidal derivatives				
91	Pregnadienone				
92	Pregnenone				
			-	Pregnane	

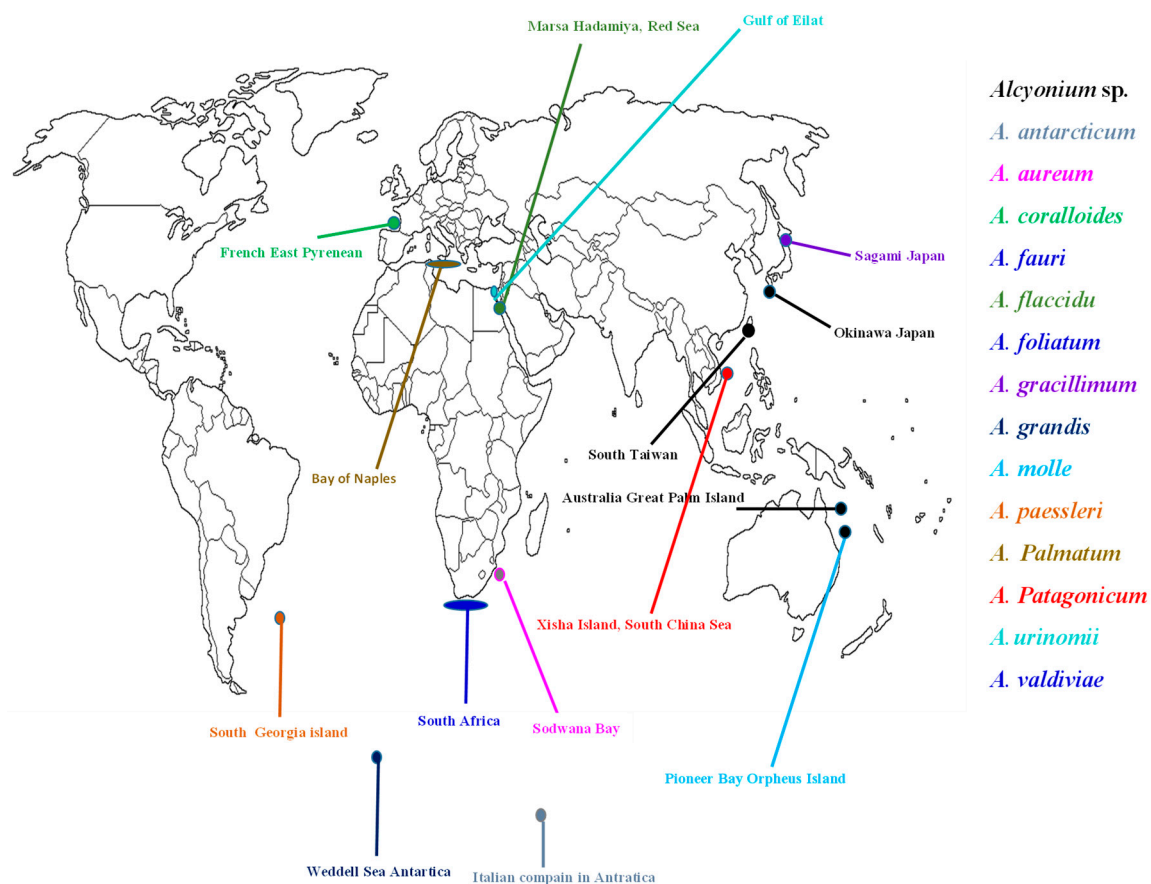


Figure 1. Locations of the investigated *Alcyonium* species.

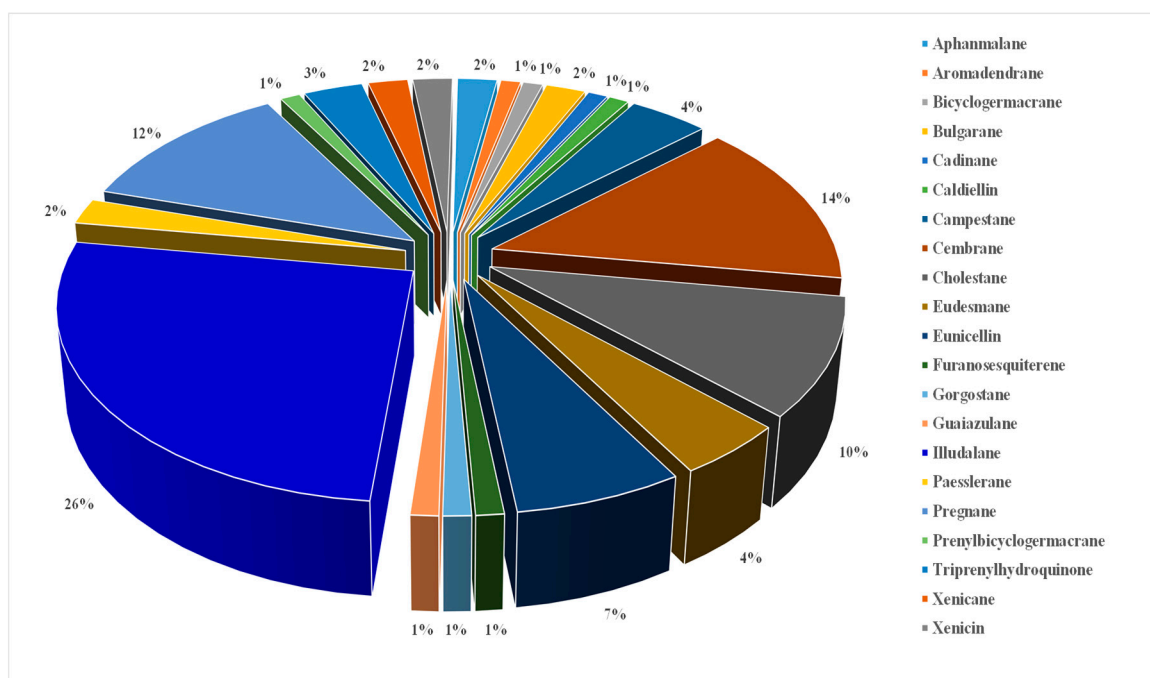


Figure 2. Percentage of chemical classes of *Alcyonium* terpenoids.

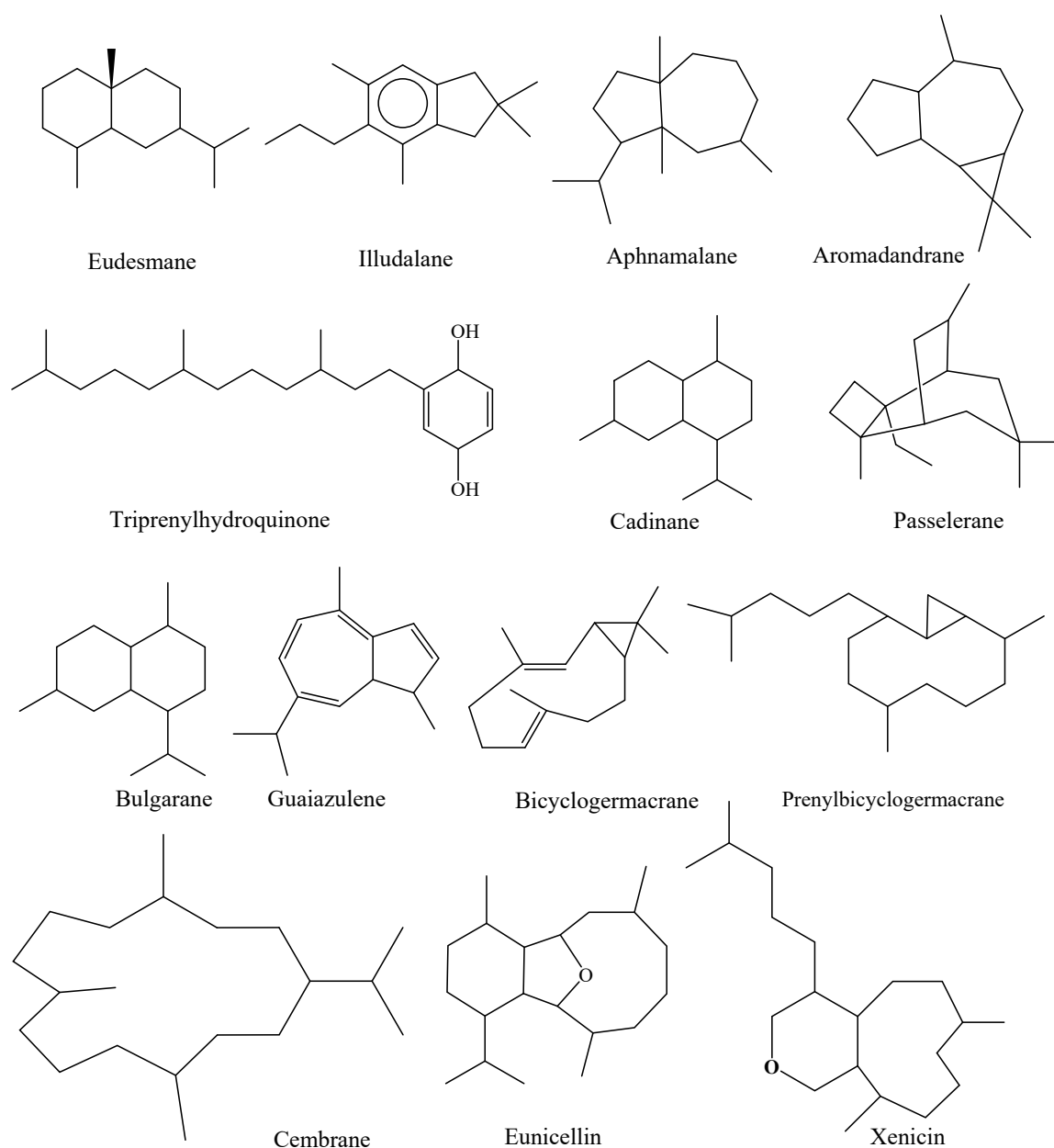


Figure 3. Selected chemical structures of *Alcyonium* terpenoidal classes.

2.1. Sesquiterpenes

The chemical diversity of the aforementioned sesquiterpenoidal classes emphasizes the importance of genus *Alcyonium* as a potential source of novel metabolites. A bicyclic sesquiterpenoidal, guaiazulene (1), a pigment obtained from *Alcyonium* sp., which was collected from the North East Bay, Great Palm Island of Australia. It was used as a taxonomical marker for the gorgonian soft coral [22]. Chemical investigation of the Mediterranean *A. coralloides*, collected from the French East Pyrenean, yielded two novel sesquiterpenes (+)-coralloidin-A (2), and (–)-coralloidin-B (3) (Figure 4 and Table 1) [23]. Novel eudesmane sesquiterpenes, coralloidin C, D and E (4–6) have been identified from the same species. The absolute stereochemistry of 4 was estimated by application of the exciton-coupling method and confirmed by interpretation of the negative and positive cotton effects after measuring the Circular Dichroism spectra [24].

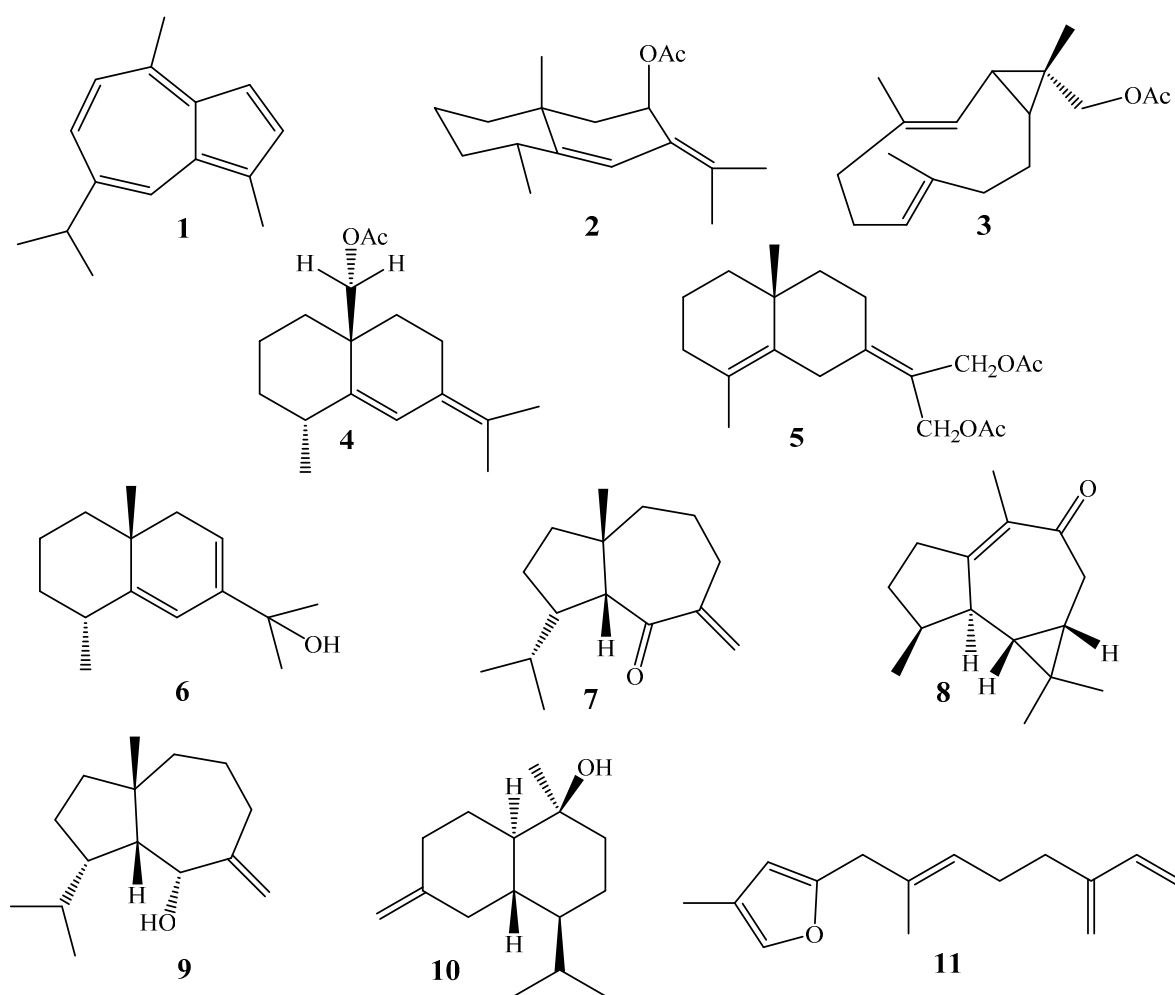


Figure 4. Chemical structures of compounds 1–11.

A south African nudibranch, *Leminda millecra*, was investigated chemically and led to the isolation of four novel aromadendrane and aphnamalane, namely, millecra A and B (7 and 8), and millecrol A and B (9 and 10). It was surprising that the same metabolites were obtained from the organic extract of spicules in the dissected digestive glands of the soft corals *A. foliatum* and *A. valdiviae* [25,26]. Although millecra B (8) was inactive against the growth of *Candida albicans* millecra A showed inhibition at 50 g/disk; while millecrol A and B (9 and 10) showed antimicrobial activity against *Staphylococcus aureus* and *Bacillus subtilis* [25,26].

As known, furanosesquiterpenoid (11) has been identified from the bay of Naples octocoral *A. palmatum*. This compound and its congeners (e.g., 2,4-disubstituted furanosesquiterpene) play a role in the taxonomy of the Alcyonacea order [27].

A. fauri is an endemic southern Africa soft coral, has been investigated and yielded three sesquiterpene hydroquinones, rietone (12), 8'-acetoxyrietone (13) and 8'-desoxyrietone (14) [28]. The NCI's CEM-SS cell line assay was designed to evaluate the metabolites which have effect at any stage of HIV virus reproductive cycle and fortunately, rietone (12) showed moderate effect. It was remarkable that *A. fauri* collected during this study was found growing on living *Hadromerida* sponges (*Tethya* species) and certain study has been done indicated that there is no chemical affinities or similarity between *A. fauri* and sponge or other soft coral, regarding the production of metabolites [28].

Fifteen rare illudalane sesquiterpenes (Figure 5); alcyopterosins A–O (15–29) had been isolated from sub-Antarctic soft coral *A. paessleri*, collected from the South Georgia Islands, eight out of fifteen compounds have a nitrate ester group (16, 17, 19–22, 24 and 27), while four compounds are chlorinated

(15, 18, 26 and 26) [29]. These metabolites were the first illudalane sesquiterpenoidal derivatives, which were reported from marine organisms. The stereochemistry of the alcyopterosins showed a different configuration of the hydroxylated position (C-10). Compound 22 was levorotatory while 23 and 27 were dextrorotatory. The absolute stereochemistry was established by the implementation of the modified Mosher method led to the establishment of the chemical structures of 23, 26, and 27 had 10*S* configuration, while 22 was 10*R*. Compound 19 showed mild cytotoxicity against Hep-2 (human larynx carcinoma) cell line (IC₅₀ 13.5 μM), while compounds 15, 17, and 22 were cytotoxic against HT-29 (human colon carcinoma) at 10 μg/mL. Further investigation of the same USA group and marine organisms led to the identification of two novel tricyclic sesquiterpenoids, paesslerins A and B (30–31) [30].

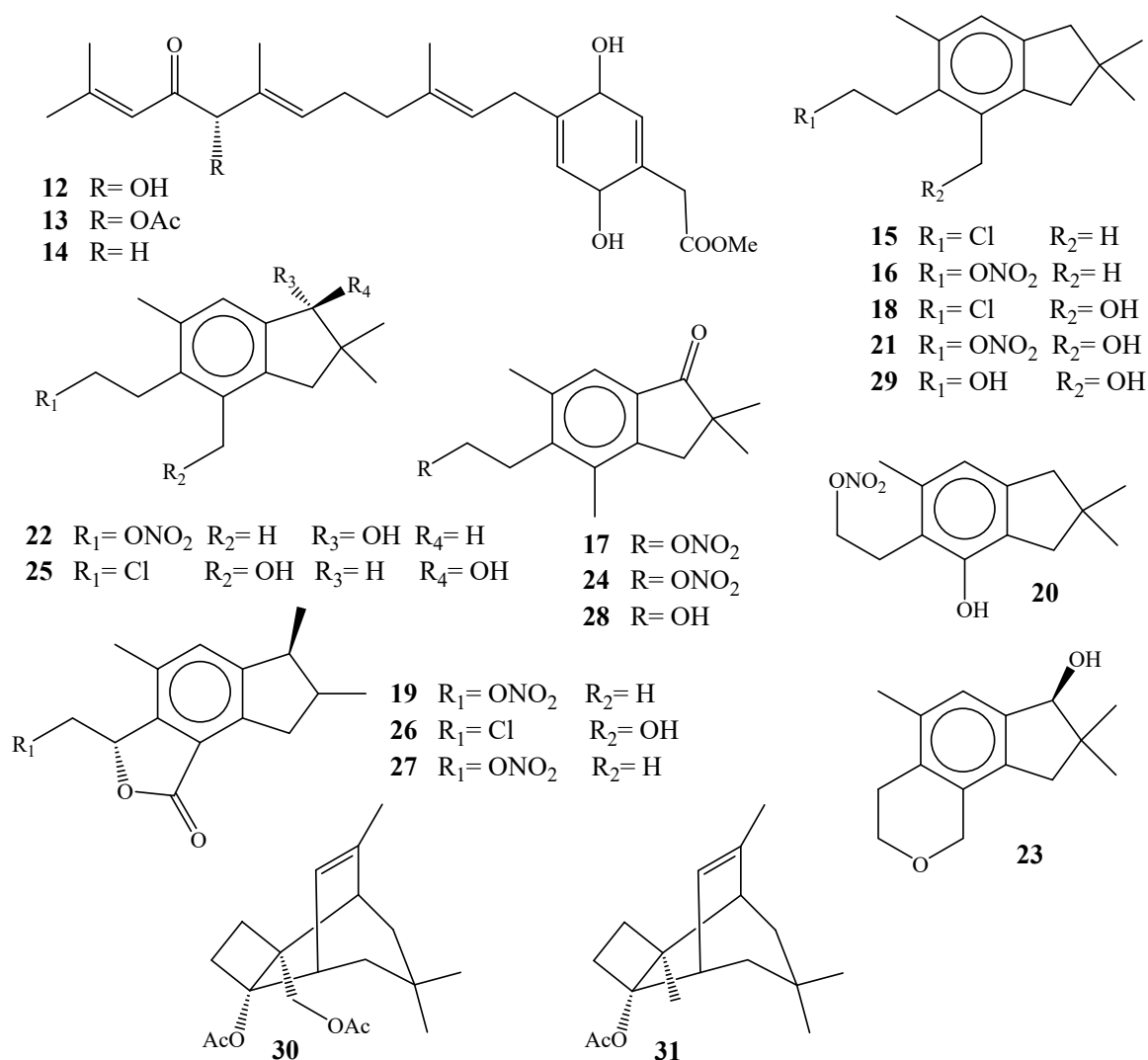


Figure 5. Chemical structures of compounds 12–31.

Lipophilic extract of the Antarctic *A. grandis*, collected from Weddell Sea, Antarctica yielded nine unreported sesquiterpenoids, 4,12-*bis-n*-butanoylalcyopterosin O (32), 13-acetoxy-12-acetyl alcyopterosin D (33) (Figure 6), 4,12-*bis*(acetyl) alcyopterosin O (34), 12-acetyl-13-*n*-butanoylalcyopterosin D (35), 12-acetyl-4-*n*-butanoylalcyopterosin O (36), 12-acetylalcyopterosin D (37), 12-*n*-butanoylalcyopterosin D (38), 13-hydroxy alcyopterosin (39) and alcyopterosin P (40). The lipophilic extract exhibited a feeding-deterrent effect towards the Antarctic predator *Odontaster validus* and proved to have a potent repellent effect [31].

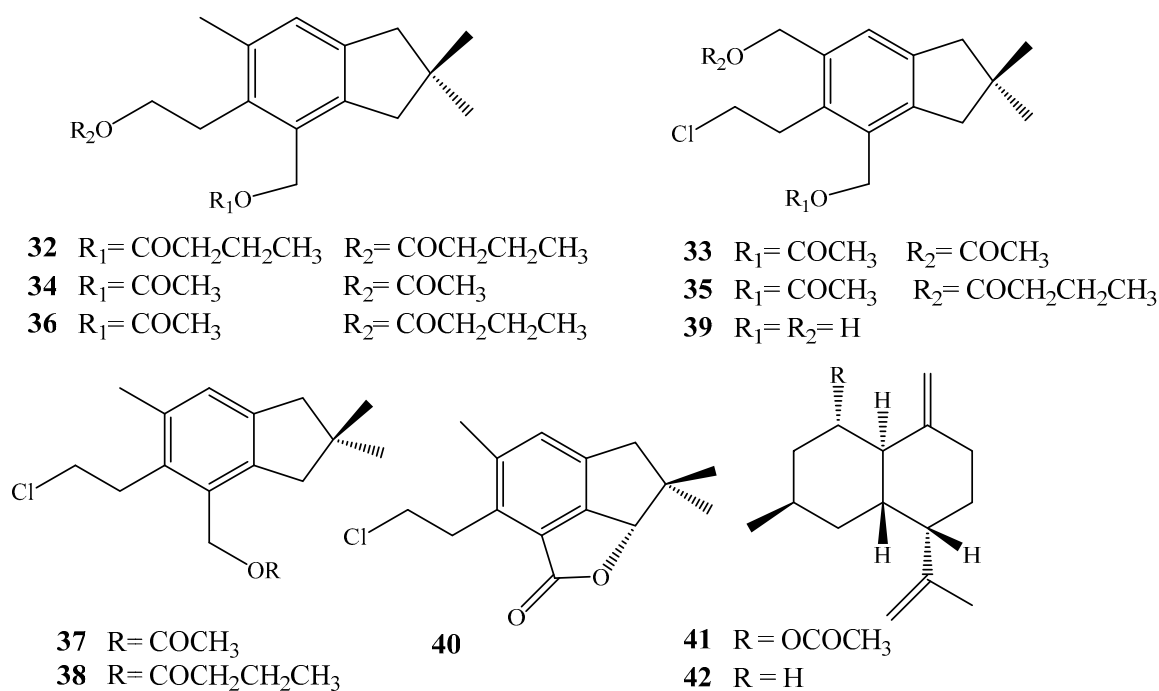


Figure 6. Chemical structures of compounds 31–42.

A. antarcticum, collected during the XVII Italian campaign in Antarctica off Terra Nova Bay [31], yielded a rare bulgarane sesquiterpene; alcyonicene (41), deacetoxyalcyonicene (42), and 4-methyl-2-[(*E*)-2-methyl-6-methyleneocta-2,7-dienyl]-furan (11) [32]. Feeding-deterrence and ichthyotoxic effects of alcyonicene (41), as well as 4-methyl-2-[(*E*)-2-methyl-6-methyleneocta-2,7-dienyl]-furan were preliminarily evaluated by conducting assays with *Carassius auratus* and *Gambusia affinis* [32].

2.2. Diterpenes

A cembranoid-type diterpene, 11,12-epoxy-13-hydroxy-14-acetoxycembrene-C (Flaccidoxide, 43) (Figure 7), was reported for the first time from *A. flaccidum*, along with known cembranoids, cembrene-C (44) and sarcophytol-B (45). This species was collected from Marsa-Hadamiya (Gulf of Suez, Red Sea) [33].

Examination of *A. utinomii*, was collected from the Gulf of Suze, led to the isolation of three cembranoidal derivatives with the same molecular weight, alcyonol-A (46), alcyonol-B (47), and alcyonol-C (48). The difference between the chemical structure of compounds 46 and 47 is mainly in the location of the hydroxyl group [34].

D' Ambrosio et al. reported two new cembranoidal metabolites, coralloidolide A (49) & B (50) with peculiar structure from the French East Pyrenean of the Mediterranean Sea *A. coralloides* (Figure 8). The two structures are peculiar with a rare (7*Z*)-configuration. This feature is rare in cembranoids [35]. A study from the same group reported three novel metabolites; 3,7-cyclized cembranoid (Coralloidolide C, 51), O-bridged diketonic cembranolide (Coralloidolide D, 52) and diketonic epoxycebranolide (coralloidolide E, 53) [36]. Further investigation of the same species and same group led to reporting of the first example of 2, 6-cyclized cembranolide (Coralloidolide F, 54) [37].

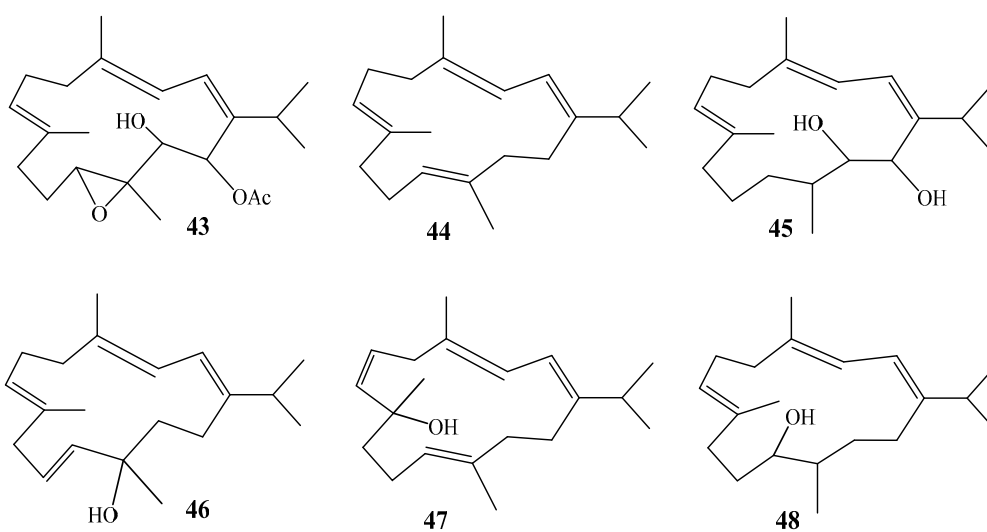


Figure 7. Chemical structures of compounds 43–48.

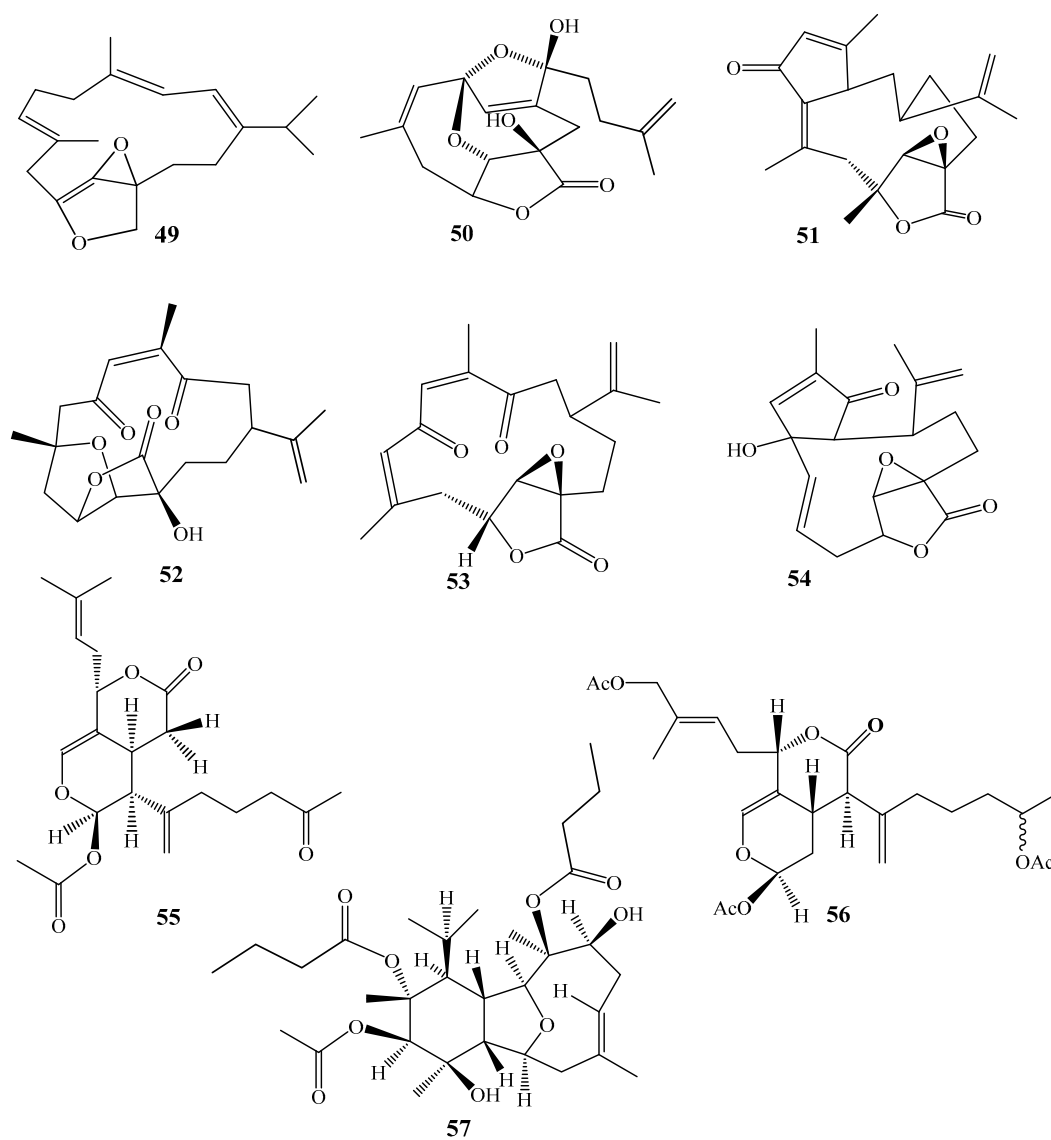


Figure 8. Chemical structures of compounds 49–57.

Alcyonolide (**55**) is an unusual diterpenoidal acetate, was isolated from an Okinawan soft coral *Alcyonium* sp. [38]. Alcyonolide-5 (**56**) is a triacetate derivative, obtained from *Alcyonium* sp. collected from Lamont Reef in the Capricorn Bunker group [39]. These metabolites were believed to be derived from a xenicin-type precursor.

A cladiellin-based diterpene (1*S*,2*R*,3*S*,4*R*,5*R*,6*S*,8*E*,11*S*,12*R*,13*S*,14*S*)-3-acetoxy-2,12-dibutanoyl oxycladiell-8-ene-4,11-diol (**57**) has been reported from *A. molle*, collected at Pioneer Bay, Orpheus Island. Its absolute configuration was based on the kinetic resolution method of Horeau [40].

Patagonicol (**58**) (Figure 9), a new diterpene of eunicellin skeleton has been reported from the Soft coral *A. patagonicum* collected from the Xisha islands off the south China Sea. Its structure was confirmed by X-ray diffraction [41].

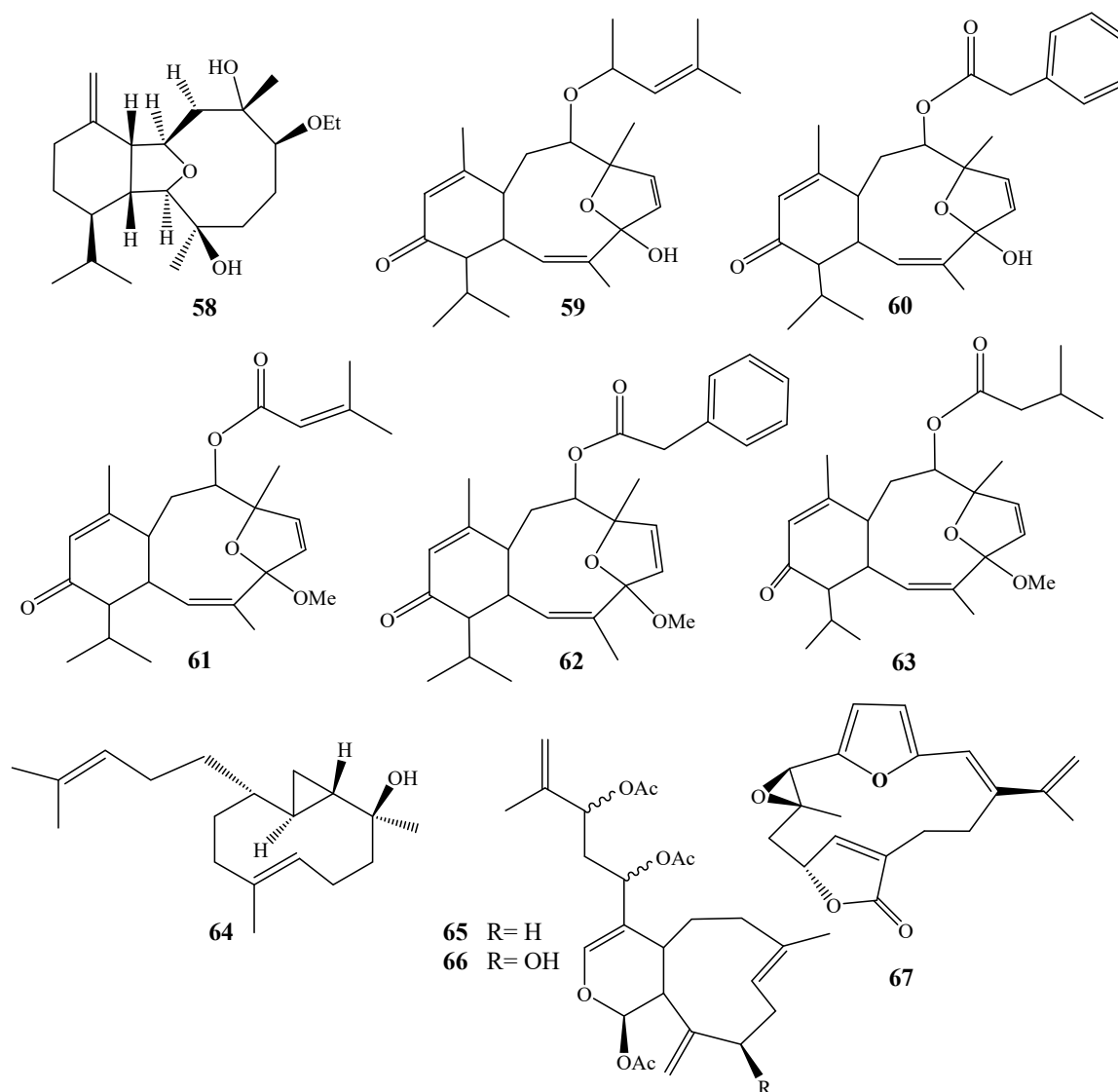


Figure 9. Chemical structures of compounds 58–67.

The soft coral *A. valdivae*, collected from Coffee Bay, Transkei, South Africa, yielded five diterpene esters, valdivone A (**59**), valdivone B (**60**), 4-*O*-methyl valdivone A (**61**), 4-*O*-methyl valdivone B (**62**) and dihydrovaldivone A (**63**). Carbon skeleton of valdivones is eunicellin-type which closely related to sarcodictyins. The difference between them is the location of the ether ring however they produced by different soft corals (i.e., *A. valdivae* (order Alcyonacea) and *Sarcodictyon roseum* (order Stolonifera)). Valdivones A (**59**) and B (**60**) show strong inhibition of chemically-induced inflammation in the mouse

ear assay, however, no inhibition on the bee venom phospholipase A. Finally, the valdivones showed no effect against a standard panel of bacteria and fungi [42].

A diterpene of the prenylbicyclogermacrane skeleton wasn't widely occurred among marine organisms. Fortunately, *A. palmatum* was collected from Mazara del Vallo (West Sicily), led to the isolation of palmamol (64). Palmamol showed toxicity against *Gambusia affinis* as well as cytotoxic against brine shrimp (*Artemia salina*) [43].

Xenicane-type diterpenoid was reported from *Alcyonium*, for instance, zahavin A (65), and zahavin B (66), were isolated from a specimen of *A. aureum*, which collected at depth more than 28 m at Sodwane Bay, South Africa. The two compounds showed a cytotoxic effect against P-388 mouse leukemia, A-549 human lung carcinoma, MEL-28 human melanoma, and HT-29 human colon carcinoma [44].

Pukalide (67) has been reported from soft coral *A. antarcticum*, which was collected during the XVII Italian campaign in Antarctica off Terra Nova Bay [32]. It is a known diterpene, which was previously reported from *Sinularia abrupta*. Pukalide showed feeding-deterrence against *Carassius auratus* at a concentration of 50 µg/mL [32,45].

2.3. Steroids

Gorgosterol (68) has been reported from *A. molle*, collected at Pioneer Bay, Orpheus Island. Its structure was elucidated based on ¹H-NMR spectral data and other physical properties [40].

Investigation of *Alcyonium* sp., which, was collected from the Andaman and Nicobar coasts, led to identification of three new polyhydroxysterol glycosides, 24-methylenecholest-5-ene-3β, 16β-diol-3-O-α-L-fucoside (69) (Figure 10), 24-methylenecholest-5-ene-3β, 7β,16β-diol-3-O-α-L-fucopyranoside (70), and 24-methylenecholest-5-ene-3β,7α,16β-triol-3-O-α-L-fucopyranoside (71), along with the already reported polyhydroxy sterol 3β,7β-dihydroxy-24-methylenecholesterol (72). These compounds play an important role in the chemotaxonomical approach since they are rare in such soft coral [46].

A soft coral, *Alcyonium* sp., which was collected from the coast of southern Taiwan and found to produce 3α,7α,12α-triacetoxy-5β-cholanic acid (73). Its structure was assigned on the basis of spectroscopical data and its configuration was further supported by molecular mechanics calculations [47].

The acetone extract of *Alcyonium* sp., which was collected from Taketomijima, Okinawa, yielded rare five steroidal glycosides of pregnene-type (Pregnedioside-A, 74), 4'-O-acetyl-pregnedioside-A (75), 3'-O-acetyl-pregnedioside-A (76), pregnedioside-B (77) and 4'-O-acetyl-pregnedioside (78). This was the first report of these steroidal compounds reported as glyco-conjugates from marine organisms [48].

Four new steroid derivatives 3-methoxy-19-norpregna-1,3,5(10),20-tetraene (79), 3-(4-O-acetyl-6-deoxy-β-galactopyranosyloxy)-19-norpregna-1,3,5(10),20-tetraene (80), 22,23-dihydroxy cholesta-1,24-dien-3-one (81), and methyl 3-oxochola-1,4,22-trien-24-oate (82) were isolated from *A. gracillimum*, which was collected from the Gulf of Sagami, Japan. The new steroids (79–82) were lethal to cyprids of barnacle (*Balanus amphitrite*) larvae, at 100 µg/mL, albeit showed no inhibition of larval settlement of *B. amphitrite* at 50 µg/mL [49].

A dihydroxy sterol, 24-methylenecholest 4-ene-3β,6β-diol (83) (Figure 11), has been isolated from *A. patagonicum*, which was collected from the south China Sea. It had cytotoxic against the P-388 cell line [32].

Two well-known steroids, pregnenolone (84) and pregnenolone-3-acetate (85), have been isolated from the soft coral, *A. antarcticum*, which was collected during the XVII Italian campaign in Antarctica off Terra Nova Bay [31]. Seven steroids, five of which, were new steroids; furospirostan class with spiroketal functionality (86), two steroids with hemiketal functionality (87–88), steroid with unusual dihydropyran ring (89) and a steroidal ketoic derivatives (90) have been reported for the first time from *A. gracillimum* and already two known steroids of pregnane class pregnadienone and pregnenone (91–92). Interestingly, the crude extract of *A. gracillimum* exhibited moderate cytotoxicity (IC₅₀ 22.4 µg/mL) and antiviral activity (IC₅₀ 7.8 µg/mL) against P388 and HSV-I, respectively. Compounds

(87–88) exhibited moderate inhibition against human cytomegalovirus (IC_{50} 3.7 and 7.2 $\mu\text{g}/\text{mL}$, respectively) [50].

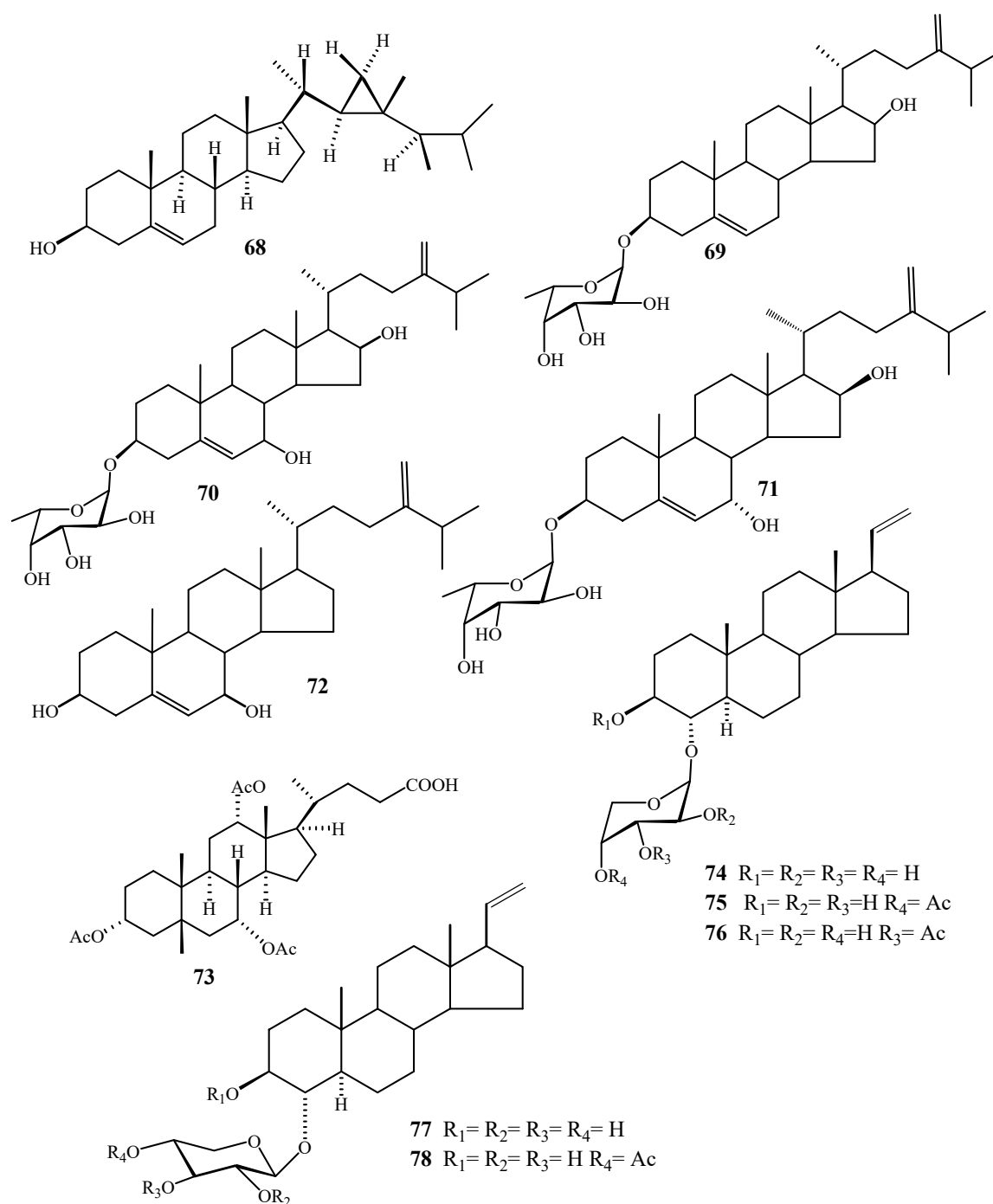


Figure 10. Chemical structures of compounds 68–78.

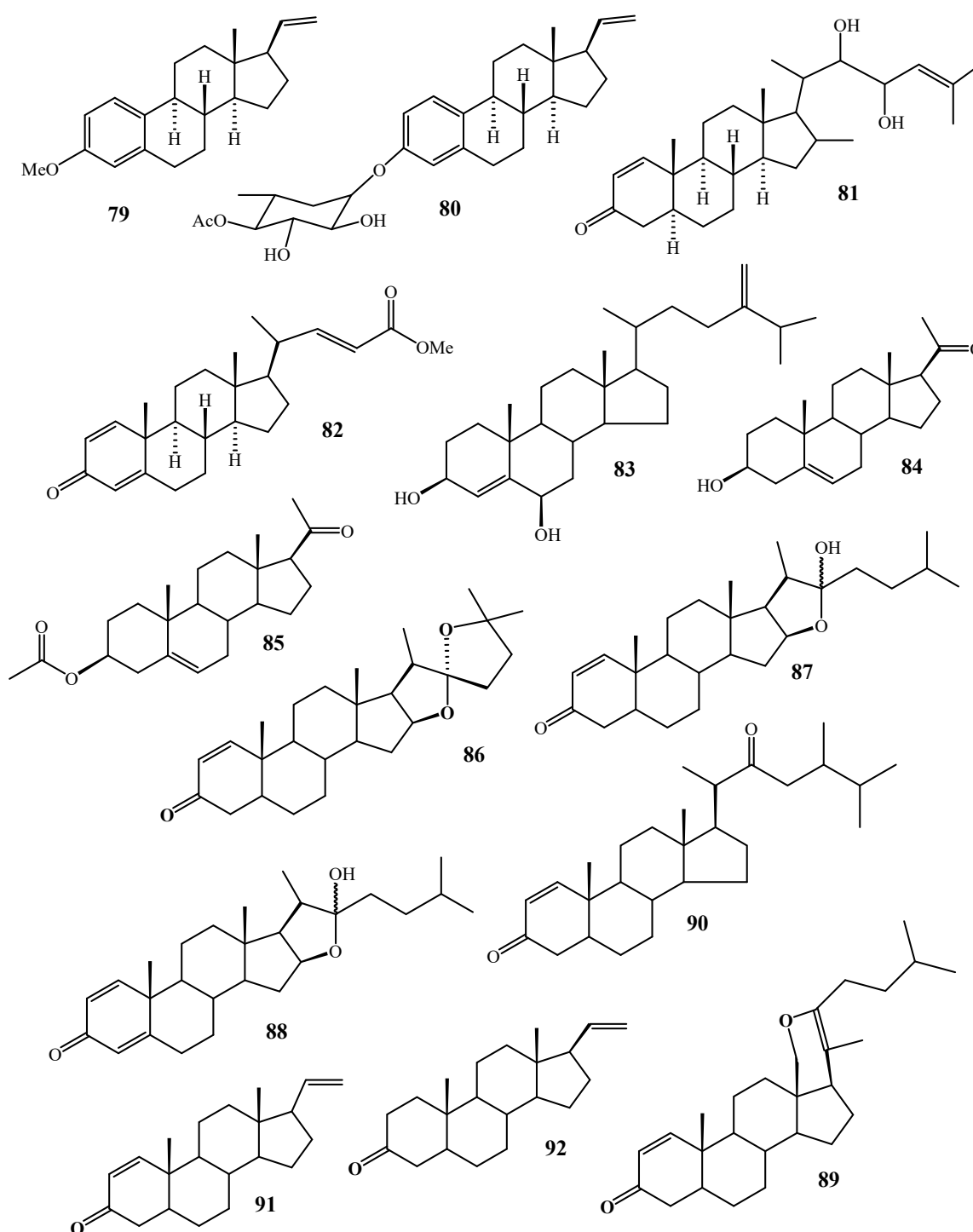


Figure 11. Chemical structures of compounds 79–92.

3. Alcyonium Terpenoids; Current State and Future Aspect

Terpenes are secondary metabolites, mainly derived from the five-carbon skeleton isoprene unit [51]. Derivatization or modifications of these units resulted in a diversity of molecular structures with unlimited chemical and biological characters. Up-to-date huge marine terpenoidal derivatives were reported from invertebrates, particularly, soft corals with interesting structures. Since discovering of marine terpenoids in the 1970s, several reviews devoted to describing the diversity of their chemical structures; monoterpenoids, diterpenoids, sesterterpenes, triterpenoid oligoglycosides and

sterols [52–71]. These publications described the importance and features of chemically mediated interactions among marine organism and their role as a defense mechanism [61–71].

As aforementioned there are diversity of terpenoidal classes are presented; sesquiterpenoids (aphanmalane, aromadendrane, bulgarane, cadinane, bicyclogermacrane, eudesmane, furanosesquiterene, guaiazulene illudalane, paesslerane, and triprenylhydroquinone); diterpenoids (cembrane, cladiellin, eunicellin, prenylbicyclogermacrane, xenicin, and xenicane); and steroids (cholestane (C-27), campestane (C-28), gorgostane (C-30) along with pregnane (C21)). Unfortunately, the reported alcyonacean metabolites are still biologically unscreened. For instance, thirteen macrocyclic ‘cembranoid’ diterpenes (43–54, 67) urgently require substantial examination. Other cembranoidal derivatives with similar features showed an important finger-print in terms of pharmacological applications, which embrace antimicrobial, anti-proliferative, and anti-inflammatory properties [72–81]

It is wealthy to highlight the fact, which is presented in Table 1, that eight out of 42 sesquiterpenes, 20 out of 25 diterpenes and 18 out of 25 steroids were biologically unscreened. This indicated that 50% of the isolated compounds from genus *Alcyonium* still require further examination.

Alcyonium is considered as a potential source for nitrogenous and non-nitrogenous terpenoidal derivatives. By the way, *A. paessleri* produces rare nitrogen containing illudalane sesquiterpene (alcyopterosins B, C, E, F, G, H, J and M) [29]. Thus, this review focused on elaborating the future plan for the natural products researchers to investigate the disremembered genus *Alcyonium*.

4. Conclusions

Alcyonium could be considered as a potential source of bioactive terpenoidal metabolites. The engagement of different approaches played a significant role in the facilitation of the forthcoming drug discovery process. Remarkable, many marine metabolites displaying fascinating molecular structures with diverse pharmacological effects have been reported from genus *Alcyonium* during the last four decades (1981–2019). Of the 92 distinctive structures accounted for in this review, 67 (72.8%) are terpenoidal metabolites.

Figure 12 illustrates terpenoidal metabolites produced by 16 species. The majority (41.8%) of the presented compounds were produced by three species; *A. paessleri* (17 compounds, 18.5%), *A. coralloides* (12 compounds, 12.0%) and *A. gracillimum* (11 compounds, 12.0%), respectively.

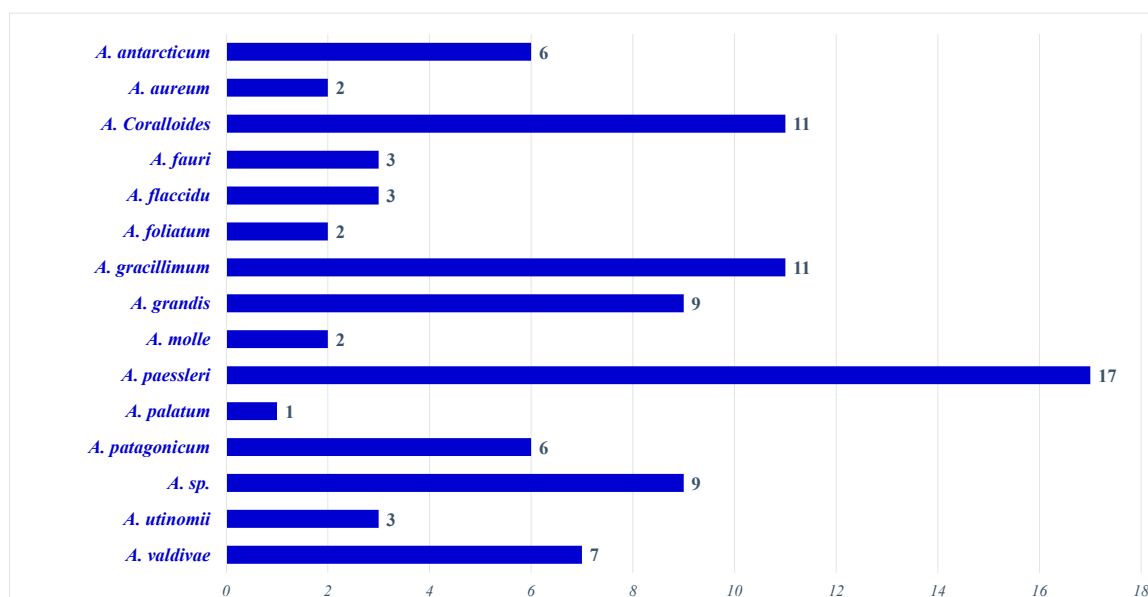


Figure 12. Number of compounds reported from *Alcyonium* species.

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