Antifouling Compounds from Marine Invertebrates

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Abstract: In this review, a comprehensive overview about the antifouling compounds from marine invertebrates is described. In total, more than 198 antifouling compounds have been obtained from marine invertebrates, specifically, sponges, gorgonian and soft corals.

Keywords: marine invertebrate; sponge; coral; antifouling compound

1. Introduction

Biofouling includes microfouling (mainly by bacteria and diatoms) and macrofouling (by macro-algae and invertebrates) in the marine environment [1]. Biofouling is a thorny issue that brings tremendous losses in both marine technical and economic fields around the world. In past years, paints containing toxic materials like copper, lead, mercury, arsenic, and organotins such as tributyltin (TBT) were commonly used to control biofouling [2,3]. However, with the increasing global appeal for marine ecological protection, most of these toxic antifouling (AF) coatings were banned [4,5]. It is urgent to have environmentally benign, no or low-toxic AF agents. Marine natural small molecules were secondary metabolites of marine organisms, having the characteristics of high efficiency, low/non-toxicity, being easily degradable, and having less influence on the marine ecological environment, which are thought to be important channels for no or low-toxic AF agents.

Marine invertebrates have developed prominent chemical defense systems against biofouling in the course of evolution. Lots of AF compounds have been isolated from marine invertebrates. Several books [6,7] and reviews [2,8–14] on AF marine natural products, including compounds from marine invertebrates, have been published in the last 30 years. However, these reviews were partially about some representative AF compounds isolated from marine invertebrates over several years. The review contained in this paper covers almost all of the AF compounds from marine invertebrates from the last 30 years. Its aim is to give the readers a brief, yet comprehensive, overview of AF compounds from marine invertebrates and provide models for synthesis of more efficacious no or low-toxic antifoulants.

2. Results

Marine invertebrates, specifically, sponges, gorgonian and soft corals, are rich sources of novel and bioactive secondary metabolites. Studies of the natural chemistry of these interesting groups of marine invertebrates began in the late 1950s. They are recognized to mainly produce novel diterpenoids, sesquiterpenoids, prostanoids, alkaloids, and highly functionalized steroids that are largely unknown from terrestrial sources. Most of these compounds showed AF activity.
2.1. Terpenoids

2.1.1. Terpenoids from Sponges

Terpenoids, especially isocyanoterpenoids, were the typical AF metabolites of marine sponges.

AF isocyanoterpenoids and analogues (Figure 1): Kalihinenes X-Z (l–3) [15] and kalihipyrans A-B (4–5) [16] were isolated from the marine sponge *Acanthella cavernosa*, showing strong AF activity towards *Balanus amphitrite* (= *Amphibalanus amphitrite*) larvae with EC50 values of 0.45–1.3 μg/mL. Isocyanoterpenoids 15-formamidokalihinene (6) [16] and 10β-formamidokalihinol A (7) [17] also obtained from *A. cavernosa*, inhibited the *B. amphitrite* larval settlement with EC50 < 0.5 μg/mL and low toxicity (LD50s > 100 μg/mL). A similar AF activity was found for 10-isocyano-4-cadinene (8) and isocyanotheonellin (9) that were isolated from nudibranchs of the family Phyllidiidae [18]. Kalihinols M-Q (10–15) and six analogues (16–21) were isolated from the Chinese marine sponge *A. cavernosa*, showing significant AF activity against *B. amphitrite* larvae with EC50 values of 0.27–1.85 μM [19]. The diterpene isonitrile 22 isolated from *Cymbastela hooperi*, and the sesquiterpene axisonitrile-3 (23) isolated from *Acanthella kletra*, were effective in deterring the settlement of the diatom *Nitzschia closterium* [20]. Sesquiterpenes axinyssimides A–C (24–26) containing a rare dichloromethyleneamino functionality were isolated from a marine sponge *Axinyssa sp*. Among them, 24 inhibited the *B. amphitrite* larval settlement with EC50 value of 1.2 μg/mL, and 25 and 26 were more active (EC50s < 0.5 μg/mL) [21].

![Figure 1. Structures of antifouling (AF) isocyanoterpenoids and analogues from sponges.](image-url)
Non-isocyanoterpenoids with AF activity from sponges (Figures 2 and 3) included sesquiterpenes, diterpenoids, sesterterpenes, and triterpenes. For examples:

Sesquiterpenes hydroquinone avarol (27) and avarone (28) obtained from the sponge Dysidea avara, and their synthetic analogs 3′-(p-chlorophenyl)avarone (29) and 4′-propylthioavarone (30) showed strong inhibition against B. amphitrite larvae with EC$_{50}$ values of 0.45–3.41 µg/mL [22]. Sesquiterpenes, phenol derivatives (+)-curcuphenol (31) and (+)-curcudiol (32) from the sponge Myrmekioderma dendyi showed antilarval activity against B. amphitrite larvae at non-toxic concentrations with EC$_{50}$ values of 2.5 and 2.8 µg/mL, respectively [23].

Diterpenoid alkaloids (−)-agelasine D (33) and (−)-ageloxime D (34) from an Indonesian sponge Agelas sp. showed significant toxicity towards B. amphitrite larvae rather than just inhibiting settlement, and the toxicity of 34 was about 10 times than its congener 33, which indicated the importance of the oxime group for the activity of the diterpene alkaloids. Compound 33 also showed antibacterial activity against the planktonic form of Staphylococcus epidermidis (MIC < 0.0877 µM) but did not inhibit its biofilm formation [24].

![Figure 2. Structures of AF sesquiterpenes and diterpenoids from sponges.](image)

Sesterterpenes cavernosolide (35), lintenolide A (36) and 7E,12E,20Z-variabilin (37) isolated from the sponge Semitaspongia bactriana, showed strong toxicity against the diatom Nitzschia closterium and against Bugula neritina larvae with EC$_{50}$ values from 1.22 to 7.41 µM [25]. Two analogues of 37, dihydrofurospongin II (38) and hydroquinone-A acetate (39) obtained from multiple mediterranean sponge extracts showed significant AF activity against B. amphitrite larvae at nontoxic concentrations with EC$_{50}$ values of about 2.5 and 1.0 µg/mL, respectively [26].

Nortriterpenoids manoalide (40), seco-manoalide (41), manoalide 25-acetate (42) and (4E,6E)-dehydromanoalide (43) from a sponge Smenospongia sp., strongly inhibited the B. amphitrite larval settlement at nontoxic concentrations with EC$_{50}$ values of 0.24–2.7 µg/mL [24]. Compound 40 could also inhibit bacterial quorum sensing (QS) at low concentrations [27]. Formoside (44), a triterpene glycoside from the sponge Erylus formosus, could strongly deter the biofouling of invertebrates and algae [28].
2.1.2. Terpenoids from Corals

The principal terpenoids elaborated by gorgonian and soft corals are sesquiterpenes and diterpenes. The representative structures of diterpenoids by carbon skeleton class from corals included briarane type, cembrane type, eunicellan type, xenicane type, pseudopterosin type, dilophol type, etc. Many of these diterpenoids were reported to have AF activity against marine invertebrate larvae.

AF sesquiterpenoids (Figure 4): Guaiazulene-based terpenoids anthogorgiene G (45) and analogues 46–48 were isolated from a gorgonian Anthogorgia sp., showing inhibition against the larval settlement of *B. amphitrite* larvae with EC_{50} < 7.0 µg/mL [29]. (+)-(7R,10S)-2-methoxy,5-acetoxy calamenene (49) obtained from the octocorals of Indian waters exhibited AF activity against *B. amphitrite* with EC_{50} value of 0.0335 µg/mL [30]. Subergorgic acid (50) obtained from the gorgonian *Subergorgia suberosa* showed inhibition against the larval settlement of both *B. amphitrite* and *B. neritina* larvae with EC_{50} values of 1.2 and 3.2 µg/mL, respectively [31]. Sinularones A–B (51–52) from a soft coral *Sinularia* sp. showed medium AF activity against *B. amphitrite* larvae [32].
AF briarane-type diterpenoids (Figure 5): Junceellolide (53) and praelolide (54) isolated from the gorgonian *Dichotella gemmacea*, showed medium AF activity against the settlement of *B. amphitrite* larvae [33]. Dichotellides H, I, K-P, U (55–63) and junceellolide C (64) were also isolated from *D. gemmacea*, showing potent AF activity at nontoxic concentrations with EC50 values of 0.2–7.6 μg/mL [34]. Juncins R-ZI (65–74), juncin ZII (75), gemmacolide B (76), gemmacolide A (77) and junceellolide D (78) were isolated from the gorgonian *Junceella juncea*, showing potent AF activity against *B. amphitrite* larvae at nontoxic concentrations with EC50 values from 0.004 to 21.06 μg/mL [35,36]. Briaranes (+)-junceellolide A (79), fragilisinins E (80), F (81) and J (82) from *J. fragilis* showed AF activity against *B. amphitrite* larvae with EC50 values of 5.6–14.0 μM and low toxicity [37]. Reticulolide (83) obtained from the gorgonian *S. mollis* showed strong inhibition against the larval settlement of *B. amphitrite* larvae with EC50 value of 0.35 μg/mL [38].
AF eunicellin-based diterpenoids (Figure 6): 14-Deacetoxycalicophirin B (84), astrogorgins B-D (85–87), and analogues 88–89 isolated from a gorgonian Astrogorgia sp., exhibited AF activity against B. amphitrite larvae with EC_{50} values of 0.59–17.8 μg/mL [39]. (-)-6α-Hydroxypolyanthelline A (90) from the soft coral Cladiella krempfi showed toxicity and AF activity against B. amphitrite larvae [40].
AF cembrane-type diterpenoids (Figure 7): Pukalide (91) from the gorgonian Leptogorgia virgulata showed strong inhibition against the larval settlement of B. amphitrite larvae with EC$_{50}$ value of 19 ng/mL [41]. Cembranoid epimers 92–95 isolated from the Colombian Caribbean gorgonian Pseudoplexaura flagellosa, could inhibit the biofilm maturation of Pseudomonas aeruginosa, Vibrio harveyi, and Staphylococcus aureus without interfering the bacterial growths [42]. Knightine (96), 11(R)-hydroxy-12(20)-en-knightal (97), and 11(R)-hydroxy-12(20)-en-knightol acetate (98) from the gorgonian Eunicella knighti, disrupted QS systems and showed anti-film activity against the bacterial biofilm of P. aeruginosa, V. harveyi, and S. aureus at lower concentrations than kojic acid [43]. Sinulariols J (99), P (100), Y (101) and its analogue 102 from the soft coral Sinularia rigida showed potent AF activity against the larval settlement of B. amphitrite and B. neritina larvae with EC$_{50}$ < 14.03 µg/mL [44,45]. Pavidolides C-D (103–104) from the soft coral S. pavida exhibited inhibition against the larval settlement of B. amphitrite larvae with ED$_{50}$ values of 4.32 and 2.12 µg/mL and low cytotoxicity (LD$_{50}$ > 50 µg/mL) [46]. Four cembrene diterpenoids 105–108 from the soft coral Sarcophyton infundibuliforme showed significant inhibition against the settlement of B. amphitrite larvae at nontoxic concentrations [47].

Figure 7. Structures of AF cembrane-type diterpenoids from corals.

2.1.3. Terpenoids from Other Marine Invertebrates

Briarane-type diterpenoids renillafoulins A (109) (Figure 8), B, and C from the sea pen Renilla reniformis showed strong inhibition against the barnacle settlement with EC$_{50}$ values ranging 0.02–0.2 µg/mL [48,49]. A labdane diterpene 110 from the pulmonate limpet Trimusculus reticulatus...
could inhibit the settlement of *Phragmatopoma californica* larvae at 10 µg/mL, and its lethal concentration to the larvae was 100 µg/mL [50].

2.2. Steroids and Saponins

2.2.1. Steroids from Sponges

Two steroids tri-2-aminoimidazolium halistanol sulfate (111) and halistanol sulfate (112) (Figure 9) from a marine sponge *Topsentia* sp, showed AF activity but no toxicity against *B. amphitrite* larvae with EC$_{50}$ values of 4.0 and 2.9 µg/mL, respectively [23]. Three new A-nor steroids, the ethyl esters of 2β-hydroxy-4,7-diketo-A-norcholest-5-en-2-oic acid (113), 24S-ethyl-2β-hydroxy-4,7-diketo-A-norcholest-5-en-2-oic acid (114), and 2β-hydroxy-4,7-diketo-24R-methyl-A-norcholest-5,22(E)-dien-2-oic acid (115) from the Chinese marine sponge *Acanthella cavernosa* showed medium AF activity against *B. albicostatus* larvae [51]. Cyclopropanated sterols aragusterol I (116) and 21-O-octadecanoyl-xestokerol A (117) isolated from the sponge *Xestospongia testudinaria*, inhibited the growth of *Pseudoalteromonas* and *Polaribacter* bacterial species at similar levels of activity to the positive control tributyltin oxide [52].
2.2.2. Steroids from Coals

Steroids 118 and 119 (Figure 10) from the gorgonian *S. suberosa* inhibited the settlement of *B. neritina* larvae with EC\(_{50}\) values of 6.25 and 7.8 \(\mu\)g/mL, respectively, and LD\(_{50}\) > 250 \(\mu\)g/mL [53]. Compound 120 was a 5a-hydroxylated analog of 115, having similar AF activity against *B. neritina* larvae and *B. amphitrite* larvae [51]. 1α,3β,7α,11α,12β)-Gorgost-5-ene-1,3,7,11,12-pentol 12-acetate (121) from the gorgonian *Isis minorgrachyblasta* inhibited the settlement of *B. neritina* larvae with EC\(_{50}\) value of 4.8 \(\mu\)g/mL and LC\(_{50}\) > 100 \(\mu\)g/mL [54]. Four 24-ketal steroids (122–125) from the gorgonian *S. mollis* showed AF activity against *B. amphitrite* larvae at nontoxic concentrations with EC\(_{50}\) values of 0.81–7.91 \(\mu\)g/mL [39]. Pregn-4-ene-3,20-dione (126) showed medium AF activity against the larval settlement of both *B. amphitrite* and *B. neritina* larvae [31]. A pentacyclic hemiacetal sterol nephthoacetal (127) from a soft coral *Nephtea* sp. showed significant AF activity against *B. amphitrite* larvae with EC\(_{50}\) value of 2.5 \(\mu\)g/mL and LC\(_{50}\) > 25.0 \(\mu\)g/mL [55]. Two cholestane derivatives, pentacyclic steroid 16,22-epoxy-20β,23S-dihydroxycholest-1-ene-3-one (128) and 20β, 23S-dihydroxycholest-1-ene-3,22-dione (129) from the gorgonian *S. suberosa* showed potent inhibition activity towards the settlement of *B. amphitrite* larvae [56]. Unprecedented D-secosteroids, isogosterones A (130) and C (131) isolated from a soft coral *Dendronephthya* sp. exhibited AF activity against *B. amphitrite* larvae with EC\(_{50}\) value of 2.2 \(\mu\)g/mL. 9,10-Secosteroids (132–133) from the gorgonian *Muricella sibogae* showed medium inhibition against the settlement of *B. amphitrite* larvae [57].

![Figure 10. Structures of AF steroids from corals.](image-url)
2.3. Alkaloids

Many types of AF alkaloids, especially brominated alkaloids, have been isolated from marine sponges.

AF bromotyrosine-derived compounds (Figure 11): Bromotyrosine-derived compounds were specially found in marine sponges of the families Aplysinidae and Pseudoceratinidae, particularly *Pseudoceratina* (=*Psammaplysilla*) *purpurea*. Ceratinamine (134) [58], moloka’iamine (135) [59], ceratinamides A-B (136–137) [58], and psammaplysins A (138) and E (139) [58] were isolated from the sponge *P. purpurea*, showing AF activity against *B. amphitrite* cyprids with EC_{50} values ranging from 0.10 to 8.0 µg/mL [58]. The AF activities of aplysamine-2 (140) from *P. purpurea*, a synthetized analog hemibastadin-1 (141), psammaplins A (142) from *Aplysinella rhaxand*, and three bastadins-9, -16, -3 (143–145) derivatives from *Ianthella basta* were also evaluated. Among them, 140 and 143–145 could significantly inhibit the settlement of *B. amphitrite* larvae at concentrations of 1 or 10 µM without increasing larval mortality, while 141, 142 and 144 showed inhibition against larval settlement at 10 µM with significant mortality of the cyprids [60].

![Figure 11. Structures of AF bromotyrosine-derived compounds from sponges.](image-url)
AF pyrrole-derived compounds (Figure 12): Bromopyrrole-derived compounds 4,5-dibromopyrrole-2-carbamide (146), oroidin (147) and mauritiamine (148) were isolated from the sponge Agelas mauritiana. Compounds 147 and 148 showed medium inhibition against the larval metamorphosis of B. amphitrite larvae, while 146 could promote the larval metamorphosis of the ascidian Ciona savignyi at 2.5 µg/mL [61]. A spermidine derivative pseudoceratidine (149) from P. purpurea showed AF activity against B. amphitrite larvae [62]. Hymenialdisine (150) and debromohymenialdisine (151) isolated from a sponge Axinella sp. were found to exhibit significant AF activity against the green mussel Perna viridis, the bryozoan Barretia barretti, and the green alga Ulva prolifera [63]. A pyrroloimidazole alkaloid 152 isolated from sponge, showed significant inhibition against the bacterial attachment of Pseudomonas with IC₅₀ value of 0.73 µM [64].

![Figure 12. Structures of AF pyrrole-derived compounds from sponges.](image)

AF pyridine-derived compounds (Figure 13): Two synthetic compounds haminol-A (153) and haminol-B (154), and three natural compounds haminol-2 (155), haminol-4 (156) and saraine-1 (157) from Haliclona fusari were evaluated for their AF activity, which showed that 153–157 significantly inhibited the larval settlement of B. amphitrite larvae with EC₅₀ values ranging from 0.28 to 3.6 µg/mL [65].

![Figure 13. Structures of AF pyridine-derived compounds from sponges.](image)

AF indole alkaloids (Figure 14): Alkaloids 2-bromo-N-methyltryptamine 158–159 from the gorgonian Paramuricea clavata showed significant anti-adhesion activity against one marine bacterial strain with nontoxicity [66]. Barettin (160) and 8,9-dihydrobarettin (161) from the sponge Geodia barretti showed inhibition against the settlement of B. improvises larvae with EC₅₀ values of 0.9 and 7.9 µM, respectively [67]. In 2006, 14 analogs of 161 were synthesized. Among them, benzo[g]dipodazine (162) and other four dipodazine analogs (163–166) with a dipodazine group significantly inhibited the settlement of B. improvisus larvae with EC₅₀ values of 0.034, 5.8, 1.5, 2.4 and 6.7 µM [68],...
respectively. Bromobenzisoxazolone barettin (167) from the sponge *G. barrette* inhibited the settlement of *B. improvisus* larvae with EC_{50} value of 15 nM [69].

![Chemical structures](image1.png)

**Figure 14.** Structures of AF indole alkaloids from sponges.

Other AF alkaloids (Figure 15): Aaptamine (168), isoaaptamine (169), and demethylated aaptamine (170) isolated from the sponge *Aaptos aaptos* showed AF activity against zebra mussel attachment [70]. A fraction of the acetone extract of the sponge *Haliclona exigua* was rich in bis-1-oxaquinolizidine alkaloid (171), exhibiting significant AF activity against the growths of seven fouling bacterial strains and against the settlement of *B. amphitrite* larvae [71].

![Chemical structures](image2.png)

**Figure 15.** Structures of other kinds of AF alkaloids from sponges.

2.4. Other Kinds of Compounds

Besides the above characteristic terpenoids, alkaloids and steroids, there were many other kinds of AF compounds isolated from marine invertebrates, such as polyacetylenes, butenolides, phenol derivatives, and peptides.

AF polyacetylene derivatives (Figure 16): Callytetryne (172), callypentayne (173), callytriols A-E (174–178) and callyspongins A-B (179–180) from the sponge *Callyspongia truncate* showed potent metamorphosis-inducing activity towards the ascidian *Halocynthia roretzi* larvae with ED_{100} values of 0.13–1.3 μg/mL, and 174–180 also showed AF activity against *B. amphitrite* larvae with ED_{50} values of 0.24–4.5 μg/mL [72].
AF butenolides (Figure 17): Sinularones G-I (181–183) from a soft coral *Sinularia* sp. showed moderate AF activity against the barnacle *B. amphitrite* [32]. Butenolide (5R)-5-(1-ethoxypropyl)-5-hydroxy-3,4-dimethylfuran-2(5H)-one (184) as a pair of inseparable epimers, along with (S)-5-hydroxy-3,4-dimethyl-5-propylfuran-2(5H)-one (185) and (S)-5-hydroxy-3,4-dimethyl-5-pentylfuran-2(5H)-one (186) were obtained from the gorgonian *S. suberosa*. Compounds 184–186 exhibited moderate AF activity against the settlement of *B. amphitrite* larvae [73]. The structure–activity relationship indicated that α,β-unsaturated 2,3-dimethyl-γ-lactone was a functional unit for the antilarval activity.

AF brominated phenol derivatives (Figure 18): Brominated diphenyl ethers are the characteristic secondary metabolites of the genus *Dyside*. It was believed that this type of compound was biosynthesised by the symbiotic cyanobacteria of the sponge. Five polybrominated diphenyl ethers including 187 from a sponge *Callyspongia* sp., 188 from *Dysidea granulosa*, and 189–191 from *D. herbacea*...
were investigated against several taxa of prominent fouling organisms including marine bacteria, the diatom *A. coffeaeformis*, the barnacle *B. amphitrite* and the mussel *Mytilus edulis*. All of these compounds exhibited significant antibacterial and AF activity. Compound 187 was the strongest in all the bioassays with non-toxicity. It inhibited the growth of all of the tested bacterial strains with MIC $\leq 0.02–1.52 \mu$M, and inhibited the larval settlement of *A. coffeaeformis*, *B. amphitrite* and *M. edulis* larvae with EC$_{50}$ values of 0.24, 0.66 and 1.26 $\mu$M, respectively [74].

![Figure 18. Structures of AF brominated phenol derivatives from sponges.](image1)

Other AF compounds (Figure 19): Four avermectin derivatives, avermectins B$_{1c}$ and B$_{1e}$ (192 and 193), avermectin B$_{2a}$ (194) and ivermectin A$_{1a}$ (195) from the gorgonian *Anthogorgia caerulea* exhibited potent antilarval activity towards *B. amphitrite* larvae with low-toxicity [75]. 1-O-palmityl-sn-glycero-3-phosphocholine (196) from the sponge *Crella incrustans* showed strong inhibition against the settlement of *B. amphitrite* larvae [76]. Two novel disulfide-containing peptides, barrettides A (197) and B (198) from the sponge *Geodia barrette* showed significant antilarval activity against the settlement of *B. improvises* larvae at concentrations of 0.6 and 6 $\mu$M, respectively [77].

![Figure 19. Structures of other kinds of AF compounds from sponges and corals.](image2)
3. Conclusions

Totally, over 198 AF compounds have been obtained from marine invertebrates, especially, sponges, gorgonian and soft corals. These compounds covered isocyanoterpenoids, sesquiterpenes, diterpenes, sesterterpenes, triterpenoids, alkaloids (including bromotyrosine-derived, pyrrole-derived, pyridine-derived and indole-derived compounds), steroids, polyacetylenes, butenolides, peptides, and phenol derivatives, which played important chemical defense roles in the marine invertebrates. In here, the AF activities of 198 compounds towards microfouling and macrofouling were summarized in Table 1. It is thought that AF compounds have medium to high bioactivity with a threshold of EC$_{50}$ < 15 µg/mL, and AF compounds having high LC$_{50}$/EC$_{50}$ ratios (>15) are potentially good candidate antifoulants [14]. From Table 1, we can see that some of these compounds are potent antifoulants with low/non-toxicity, such as some of the isocyanoterpenoids, briarane-type diterpenoids, and indole-type diterpenoids, and indole alkaloids. However, little was known about their mode of actions and AF activities in fields, because of the serious problems of the supplies from these marine invertebrates, which restricted the development of these potent AF compounds in antifouling paints. Although some studies about the total synthesis of several isocyanoterpenoids, briarane-type diterpenoids, and cembrane-type diterpenoids have been done, too many steps of these synthetic routes with low yields limited their applications. To overcome the problems, more studies about the organic syntheses of these potent AF compounds as models are needed. In addition, scientists have paid more attention to AF compounds from marine microorganisms, especially sponge-derived and gorgonian-derived microorganisms in recent years.

| Compounds | AF Activity |
|-----------|-------------|
| 1–5       | against B. amphitrite larvae, EC$_{50}$ = 0.49, 0.45, 1.1, 1.3, 0.85 µg/mL. |
| 6–9       | against B. amphitrite larvae, EC$_{50}$ < 0.5 µg/mL. |
| 10–21     | against B. amphitrite larvae, EC$_{50}$ = 1.43, 0.72, 1.48, 1.16, 0.53, 0.74, 1.85, 0.92, 0.69, 0.27, 1.37, 0.41 µM |
| 22–23     | effective in deterring the settlement of the diatom N. closterium |
| 24–26     | against B. amphitrite larvae, EC$_{50}$ = 1.2, <0.5, <0.5 µg/mL |
| 27–30     | against B. amphitrite larvae, EC$_{50}$ = 0.65, 3.41, 0.65, 0.45 µg/mL |
| 31–32     | against B. amphitrite larvae, EC$_{50}$ = 2.5, 2.8 µg/mL |
| 33–34     | significant antilarval activity and toxicity towards B. amphitrite larvae |
| 35–37     | toxicity against the diatom N. closterium with EC$_{50}$ = 5.24, 6.72, 3.52 µM, and against B. neritina larvae with EC$_{50}$ = 1.59, 7.41, 1.22 µM |
| 38–39     | against B. amphitrite larvae, EC$_{50}$ = 2.5, 1.0 µg/mL |
| 40–43     | against B. amphitrite larvae, EC$_{50}$ = 0.24, 0.80, 0.53, 2.7 µg/mL |
| 44        | strongly deter fouling by invertebrates and algae |
| 45–48     | against B. amphitrite larvae, EC$_{50}$ < 7.0 µg/mL |
| 49        | against B. amphitrite larvae, EC$_{50}$ = 0.0335 µg/mL |
| 50        | against B. amphitrite larvae, EC$_{50}$ = 1.2 µg/mL; against B. neritina larvae, EC$_{50}$ = 3.2 µg/mL |
| 51–52     | against B. amphitrite larvae, EC$_{50}$ = 13.86, 23.50 µg/mL |
| 53–54     | against B. amphitrite larvae, EC$_{50}$ = 14.5, 16.7 µM |
| 55–64     | against B. amphitrite larvae, EC$_{50}$ = 4.1, 1.82, 6.3, 7.6, 4.6, 1.2, 5.6, 0.79, 2.0, 0.2 µg/mL |
| 65–78     | against B. amphitrite larvae, EC$_{50}$ = 0.004, 0.34, 2.65, 1.61, 3.77, 21.06, 0.004, 0.14, 1.47, 0.51, 0.004, 0.005, 2.82, 0.447 µg/mL |
| 79–82     | against B. amphitrite larvae, EC$_{50}$ = 5.6, 14.0, 12.6, 11.9 µM, LC$_{50}$/EC$_{50}$ > 33.3, > 13, > 14.5, > 11.5, respectively |
| 83        | against B. amphitrite larvae, EC$_{50}$ = 0.35 µg/mL |
| 84–89     | against B. amphitrite larvae, EC$_{50}$ = 0.59, 5.77, 5.14, 8.23, 10.7, 17.8 µg/mL |
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Table 1. Cont.

| Compounds            | AF Activity                                                                 |
|----------------------|-----------------------------------------------------------------------------|
| 90                   | against B. amphitrite larvae, EC50 = 9.02 µg/mL, LC50 = 36 µg/mL.            |
| 91                   | against B. amphitrite larvae, EC20 = 19 ng/mL.                               |
| 92–95                | exhibited inhibition of biofilm maturation of P. aeruginosa, V. harveyi, and S. aureus |
| 96–98                | showed bacterial biofilm inhibition at lower concentrations                  |
| 99–100               | against B. amphitrite larvae, EC50 = 5.65, 14.03 µg/mL.                      |
| 101–102              | against B. amphitrite larvae, EC50 = 4.86, 4.57 µg/mL; against B. neritina larvae, EC50 = 12.34, 13.48 µg/mL. |
| 103–104              | against B. amphitrite larvae, ED50 = 4.32, 2.12 µg/mL, LD50 > 50 µg/mL.       |
| 105–108              | against B. amphitrite larvae, EC50 = 2.25, 1.75, 8.13, 7.50 µg/mL.            |
| 109                  | against B. amphitrite larvae, EC50 values ranging 0.02–0.2 µg/mL for 109 and renillafoulins B–C |
| 110                  | inhibited the settlement of the tube worm P. californica at 10 µg/mL.        |
| 111–112              | against B. amphitrite larvae, EC50 = 4.0, 2.9 µg/mL.                          |
| 113–115              | against B. albicostatus larvae, EC50 = 8.2, 23.5, 31.6 µg/mL.                |
| 116–117              | inhibited the growth of Pseudalleromonas and Polaribacter bacterial species  |
| 118–120              | against B. neritina with EC50 = 6.25, 7.8 µg/mL, LD50 > 250 µg/mL.           |
| 121                  | against B. neritina larvae, EC50 = 4.8 µg/mL, LC50 > 100 µg/mL.              |
| 122–125              | against B. amphitrite larvae, EC50 = 2.5, 7.91, 7.31, 0.81 µg/mL.            |
| 126                  | against B. amphitrite larvae, EC50 = 16.7 µg/mL; against B. neritina larvae, EC50 = 13.0 µg/mL. |
| 127                  | against B. amphitrite larvae, EC50 = 2.5 µg/mL, LC50 > 25.0 µg/mL.           |
| 128–129              | against B. amphitrite larvae, EC50 = 5.3, 14.5 µg/mL.                         |
| 130–131              | against B. amphitrite larvae, EC50 = 2.2 µg/mL.                              |
| 132–133              | against B. amphitrite larvae, EC50 = from 10.0 to 50.0 µg/mL.                |
| 134–135              | against B. amphitrite larvae, EC50 = 5.0, 4.3 µg/mL.                          |
| 136–139              | against B. amphitrite larvae, ED50 = from 0.10 to 8.0 µg/mL.                  |
| 140–145              | inhibited B. amphitrite larval settlement at 1 or 10 µM.                      |
| 146                  | promoted larval metamorphosis of the ascidian C. savignyi at a concentration of 2.5 µg/mL. |
| 147–148              | inhibited the larval metamorphosis of B. amphitrite larvae, ED50 = 19, 15 µg/mL. |
| 149                  | against B. amphitrite larvae, EC50 = 8.0 µg/mL.                              |
| 150–151              | against the green mussel F. viridis (EC50 = 31.77, 138.18 µg/mL), the bryozoan B. neritina (EC50 = 3.43, 8.17 µg/mL) and the green alga U. prolifera (EC50 = 8.31, 0.67 µg/mL). |
| 152                  | inhibited bacterial attachment towards Pseudomonas with an IC50 = 0.73 µM.    |
| 153–157              | against B. amphitrite larvae, EC50 = 2.22, 3.6, 0.28, 2.81, 0.53, µg/mL.      |
| 158–159              | anti-adhesion activity against one marine bacterial strain                   |
| 160–161              | against B. improvises cyprids, EC50 = 0.9, 7.9 µM.                            |
| 162–166              | against B. improvises cyprids, EC50 = 0.034, 5.8, 1.5, 2.4, 6.7 µM.           |
| 167                  | against B. improvises cyprids, EC50 = 15 nM.                                 |
| 168–170              | against zebra mussel attachment with EC50 = 24.2, 11.6, 18.6 µM.              |
| 171                  | against cyprids of B. amphitrite (EC50 = 6.6 µg/mL, LC50 = 18 µg/mL) and seven strains of fouling bacteria |
| 172–180              | against B. amphitrite larvae with ED50 = 0.24–4.5 µg/mL for 174–180; and metamorphosis-inducing activity in the ascidian H. roretzi larvae with ED10 = 0.13–1.3 µg/mL for 172–180. |
| 181–183              | EC50 = 18.65, 21.39, 12.58 µg/mL.                                            |
| 184–186              | against B. amphitrite larvae, EC50 = 13.5, 16.3, 12.8 µg/mL.                  |
| 187–191              | significant antibacterial and antifouling activity towards marine bacteria, A. coffeaeformis, B. amphitrite and M. edulis |
| 192–195              | against B. amphitrite larvae, ED50 = 15.81, 6.25, 4.81, 7.78 µg/mL, LD50 > 200 µg/mL. |
| 196                  | strong inhibition against the settlement of B. amphitrite larvae              |
| 197–198              | 197 inhibited the settlement of B. improvises larvae at both 0.6 and 6 µM, whereas 198 only at 6 µM |
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