A Review: Halogenated Compounds from Marine Actinomycetes

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Abstract: Marine actinomycetes, Streptomyces species, produce a variety of halogenated compounds with diverse structures and a range of biological activities owing to their unique metabolic pathways. These halogenated compounds could be classified as polyketides, alkaloids (nitrogen-containing compounds) and terpenoids. Halogenated compounds from marine actinomycetes possess important biological properties such as antibacterial and anticancer activities. This review reports the sources, chemical structures and biological activities of 127 new halogenated compounds originated mainly from Streptomyces reported from 1992 to 2020.

Keywords: marine actinomycetes; natural products; chemical structures; halogenated compounds

1. Introduction

Marine actinomycetes are a rich source of biologically active compounds, which have been widely studied worldwide. They can efficiently produce different secondary metabolites including simple benzene derivatives, polyketides and complex cyclic peptides. These secondary metabolites exhibit a wide range of biological activities including antibacterial, antifungal, anticancer and enzyme inhibition. Most of marine actinomycetes were Streptomyces species, but rarer actinomycetes genera have been reported in the past twenty years. Consequently, more novel natural products including new halogenated compounds have been isolated in recent years. According to a review on marine microbial natural products from 2010 to 2013 [1], secondary metabolites from marine actinomycetes possess various structures, including terpenes, peptides, polyketides, alkaloids and halogenated molecules [2]. Due to the high concentration of chloride and bromine ions in seawater, marine actinomycetes usually produce more halogenated compounds than those of their terrestrial counterparts. The majority of the marine halogenated compounds showed certain kind of biological properties including antibacterial and anticancer activities [3]. This review focuses on the sources of marine actinomycetes, structures and biological activities of 127 new halogenated compounds derived from marine-derived actinomycetes from 1992 to 2020.

2. Halogenated Compounds from Streptomyces Species

2.1. Sponges-Associated Streptomyces sp.

Two indole-containing peptides JBIR-34 (1) (Figure 1) and JBIR-35 (2) were obtained from Streptomyces sp. Sp080513GE-23 strain collected from a marine sponge, Haliclona sp. [4]. The nonribosomal peptidase has an unusual 4-methyloxazoline moiety. Experiments showed that the methyl group comes from alanine rather than methionine [5]. Ageloline A (3), a new chlorinated quinolone separated from a fermentation of Streptomyces sp. SBT345, showed antioxidant effect and reduced oxidative stress and genomic damage
induced by an oxidative stress inducer 4-nitroquinoline-1-oxide [6]. Compound 3 also inhibited the growth of Chlamydia trachomatis with an IC_{50} value of 9.54 µM [7]. New 3-phenylpropanoic acids 3-(3,5-dichloro-4-hydroxyphenyl) propanoic acid (4), 3-(3,5-dichloro-4-hydroxyphenyl) propanoic acid methyl ester (5) and 3-(3-chloro-4-hydroxyphenyl) propanoic acid (6) were isolated from Streptomyces coelicolor LY001, which demonstrated a broad spectrum of antibacterial activities with MIC values ranging from 16 to 250 µg/mL [8].

2.2. Corals-Associated Streptomyces sp.

Streptochloritides A (7) and B (8) were separated from a culture of Streptomyces sp. OUCMDZ-1703 and were cytotoxic against MCF-7 with IC_{50} values of 9.9 and 20.2 µM, respectively [9].

2.3. Streptomyces sp. from Other Marine Animals

A new depsipeptide salinamide B (9) was isolated from Streptomyces hygroscopicus. Compound 9 exhibited inhibitory activity against Streptococcus pneumoniae and Staphylococcus pyogenes, with MIC values of 4 and 2 µg/mL, respectively. Compound 9 also exhibited 83% inhibition of edema with a testing dose of 50 pg/ear [10]. Polyketide–cyclic peptide hybrid metabolites totopotensamides A (10) and B (11) were separated from Streptomyces sp. 1053U.I.1a.1b [11]. New napyradiomycin, MDN-0170 (12) was purified from Streptomyces sp. strain CA-271078 [12]. Streptomyces sp. strain CA-271078 yielded napyradiomycin analogs napyradiomycin B7a, napyradiomycin B7b and napyradiomycin D1 (13–15), which were cytotoxic against HepG-2 tumor cell line with IC_{50} values of 41.7, 109.5 and 14.9 µM, respectively. Compounds 13 and 15 showed anti-bacterial activity against methicillin resistant Staphylococcus aureus (MRSA) and Mycobacterium tuberculosis with MIC values in the range of 12 to 48 µg/mL [13].

2.4. Streptomyces sp. from Marine Sediments

Cultivation of Streptomyces sp. M045 afforded chinikomycins A-B (16–17). Compound 16 inhibited tumor cell lines MAXF 401NL, MEXF 462NL and RXF 944L with IC_{50} values of 2.41, 4.15 and 4.02 µg/mL, respectively. Compound 17 inhibited MAXF 401NL with an IC_{50} value of 3.04 µg/mL [14]. An unusual meroterpenoid phthalazinone azamerone (18) was isolated from Streptomyces sp. CNQ766 [15]. In the synthesis of azamerone, Lewis-acid-induced cyclization, enantioselective synthesis of an epoxysilane and the formation of the pyridazine ring were three key steps [16]. A bohemamine-type pyrrolizidine alkaloid 5-chlorobohemamine C (19) was obtained from a culture of Streptomyces sp. CNQ-583 [17]. A pentacyclic C-glycoside marmycin B (20) was obtained from Streptomyces sp. CNH990, which displayed inhibitory activity against HCT-116 with an IC_{50} value of 1.09 µM [18]. Streptomyces sp. 04DH110 produced a new 3-substituted indole streptochlorin (21), which displayed cytotoxicity against human leukemia cells with an IC_{50} value of 1.05 µg/mL [19]. Total synthesis of streptochlorin started from indole, the synthetic product exhibited potential antifungal activity [20]. Three new hexadepsipeptides piperazipimycins A–C (22–24) were isolated from Streptomyces sp. CNQ-593, which showed cytotoxicity against HCT-116 with an equal IC_{50} value of 76 ng/mL [21]. The formation of dipeptide moiety and a macrocyclization by an SN2 reaction were the two key steps in the synthesis of piperazipimycin A [22]. Three new chlorinated dihydroquinones (25–27) were separated from culture of Actinomycete strain CNQ-525, and compounds 25–27 were active against MRSA and vancomycin-resistant Enterococcus faecium with MIC values of 1.95 and 3.90, 15.6 and 15.6, and 1.95 and 1.95 µg/mL, respectively. Compounds 25 and 26 showed cytotoxicity against HCT-116 with the IC_{50} values of 2.40 and 0.97 µg/mL, respectively [23].
Figure 1. Structures of compounds 1–32.
Heterologous expression of the CNQ-525-based nap biosynthetic cluster in *Streptomyces albus* produced 2-deschloro-2-hydroxy-A80915C (28), a new napyradiomycin [24]. Four napyradiomycin derivatives napyradiomycin CNQ525.510B (29), napyradiomycin CNQ525.538 (30), napyradiomycin CNQ525.554 (31) and napyradiomycin CNQ525.600 (32), were purified from the same strain, of which compounds 29, 30 and 32 displayed inhibitory activity against HCT-116 with IC$_{50}$ values of 17, 6 and 49 µM, respectively [25]. New marinopyrroles dimeric marinopyrroles A (33) (Figure 2) and B (34) were obtained from *Streptomyces* sp. CNQ-418 and were cytotoxic toward HCT-116 with IC$_{50}$ values of 8.8 and 9.0 µM, respectively. Compounds 33 and 34 were also active against methicillin-resistant *S. aureus* (MRSA) with MIC values of 0.61 and 1.1 µM, respectively [26]. Marinopyrroles C–F (35–38) were obtained from the same strain, which displayed inhibitory activity against HCT-116 with IC$_{50}$ values ranging from 1 to 5 µg/mL. Compound 35 was active against MRSA with an MIC value less than 1 µg/mL [27]. Ammosamides A (39) and B (40) were separated from *Streptomyces* sp. CNR-698, which showed cytotoxicity against HCT-116 cells with an equal IC$_{50}$ value of 320 nM [28]. Ammosamides A and B were synthesized from 4-chloroisatin [29].

A cytotoxic compound, mansouramycin B (41) was isolated from the fermentation broth of *Streptomyces* sp. Mei37 [30]. Compound 41 was synthesized by using a new method through a catalytic acid-mediated cyclization of α-benzyl TosMIC derivatives [31]. *Streptomyces malaysiensis* CNQ-509 afforded nitropyrorolins C (42) and E (43), and 42 displayed cytotoxic activity against HCT-116 with an IC$_{50}$ value of 31.0 µM [32]. *Streptomyces* sp. CNH-189 produced merochlorins A–D (44–47) [33]. Spiroindimicins A–D (48–51) [34], indimicins A–E (52–56), lymamicin F (57) and lymamicin G (58) were separated from *Streptomyces* sp. SCSIO 03032, among which 49–52 displayed cytotoxic activity against a panel of cancer cell lines with IC$_{50}$ values ranging from 4 to 15 µM. Compound 53 also showed cytotoxicity toward MCF-7, with an IC$_{50}$ value of 10.0 µM [35]. Merochlorins A and B were synthesized by heterologously produced enzymes and chemical synthesis [36]. (+)-Spiroindimicins B and C were synthesized, and central to the successful strategy was installing the spirocenter [37]. Chloroxiamycin (59), was isolated from *Streptomyces* sp. SCSIO 02999, which displayed antimicrobial activity against *E. coli* ATCC 25922, *S. aureus* ATCC29 213 and *B. subtilis* SCSIO BS01 with MIC values of 4, 8 and 64 µg/mL, respectively [38]. *Streptomyces varibilis* SNA-020 afforded an oxidatively ring opened ammosamide analog ammosamide D (60), which displayed cytotoxic activity against the MIA PaCa-2 with an IC$_{50}$ value of 3.2 µM [39]. Cultivation of *Streptomyces* sp. CNT-179 strain afforded cyanosporasides C–E (61–63) [40]. Chlorizidine A (64) was isolated from *Streptomyces* sp. CNH-287, which showed cytotoxic activity against the HCT-116 adenocarcinoma cell line with an IC$_{50}$ value of 3.2–4.9 µM [41]. (+)-Chlorizidine A was synthesized by decarboxylative coupling and late-stage oxidation, Reformatsky reaction and Mitsunobu reactions [42]. *Streptomyces* sp. CNQ-329 yielded five new halogenated napyradiomycins A and C–E (65–68) (Figure 3), of which compounds 65, 67 and 68 exhibited inhibitory activity towards HCT-116 with IC$_{50}$ values of 4.2, 16.1 and 4.8 µg/mL, respectively. Compound 65 displayed antibacterial activity against MRSA with an MIC value of 16 µg/mL [43]. Napyradiomycin F (69) from *Streptomyces* sp. CNH-070 showed inhibitory activity against HCT-116, with an IC$_{50}$ value of 9.42 µg/mL [43].

*Streptomyces* sp. SCSIO 10,428 afforded three new napyradiomycins 4α-dechloronapapyradiomycin A1 (70), 3-dechloro-3-brominapapyradiomycin A1 (71) and 3-chloro-6,8-dihydroxy-α-lapachone (72). Compound 70 demonstrated antibacterial activity against *Staphylococcus aureus* ATCC 29213, *Bacillus subtilis* SCSIO BS01 and *Bacillus thuringensis* SCSIO BT01 with MIC values of 4, 4 and 8 µg/mL; 71 exhibited antibacterial activity against *Staphylococcus aureus* ATCC 29213, *Bacillus subtilis* SCSIO BS01 and *Bacillus thuringensis* SCSIO BT01 with MIC values of 0.5, 1 and 1 µg/mL; and 72 showed antibacterial activity against *Bacillus subtilis* SCSIO BS01 and *Bacillus thuringensis* SCSIO BT01 with MIC values of 8 and 16 µg/mL, respectively. Compound 70 also displayed inhibitory activity against SF-268, MCF-7, NCI-H460 and HepG-2 with IC$_{50}$ values of 22.8 ± 0.3, 20.6 ± 0.1, 22.4 ± 0.1 and 21.8 ± 0.5 µM,
respectively; 71 showed inhibitory activity against SF-268, MCF-7, NCI-H460 and HepG-2 with IC\(_{50}\) values of 11.5 ± 1.2, 16.2 ± 0.7, 18.1 ± 0.3 and 17.1 ± 1.0 µM, respectively; and 72 exhibited inhibitory activity against SF-268, MCF-7, NCI-H460 and HepG-2 with IC\(_{50}\) values of 23.8 ± 2.2, 71.1 ± 0.4, 127.1 ± 0.9 and 59.4 ± 0.7 µM, respectively [44]. C-1027 chromophore-V (73) was obtained from a marine-derived Streptomyces sp. ART5, which showed inhibitory activity against Candida albicans isocitrate lyase with an IC\(_{50}\) value of 37.9 µM.

Figure 2. Structures of compounds 33–65.
Figure 3. Structures of compounds 66–87.
Compound 73 also inhibited MDA-MB231 and HCT-116 with IC$_{50}$ values of 0.9 and 2.7 µM, respectively [45]. Chlorinated alkaloids inducamides A (74) and C (75) were separated from Streptomyces sp. SNC-109-M3, of which compound 75 showed cytotoxicity against NSCLC cell line HCC44 with an IC$_{50}$ value of 10 µM [46]. Inducamide A (74) was synthesized from 6-hydroxy-3-chloro-2-methylbenzoic acid and L-6-chlorotryptophan [47]. Inducamide C (75) is unstable and easy to rearrange [48].

Hormaomycins B (76) and C (77) were obtained from a marine-derived Streptomyces sp. SNM55. Compounds 76 and 77 were active against S. aureus ATCC 25923, B. subtilis ATCC 6633, K. rhizophila NBRC 12708, S. pyogenes ATCC 19615, S. enterica ATCC 14,028 and P. hauseri NBRC 3851 with MIC values of 7/7, 14/56, 0.4/0.23, 14/8, 29/114 and 29/14 µM, respectively [49]. Two new phanazines marinocyanins A and B (78 and 79) were isolated from Streptomyces sp. CNS284, which inhibited the TNF-α-induced NF-κB activity with IC$_{50}$ values of 4.1 and 24.2 µM and suppressed the PGE2 production with IC$_{50}$ values of 7.15 and 0.89 µM, respectively [50]. Compound 78 inhibited LPS-induced nitric oxide production with an IC$_{50}$ value of 15.1 µM [50]. Compounds 78 and 79 showed cytotoxicity against HCT-116 cell with IC$_{50}$ values of 0.049 and 0.029 µM and inhibited S. aureus and C. albicans with MIC values of 2.37/33.92 and 0.95/5.79 µg/mL, respectively [51]. Marinocyanins A and B were synthesized through the establishment of the N-substituted phenazin-1-one skeleton [52]. Four phanazinone named marinocyanins C–F (80–83) were purified from the marine actinomycete Streptomyctaceae CNS-284, which were active against S. aureus and C. albicans with MIC values ranging from 3.90 to 36.62 µg/mL. They also showed cytotoxicity against HCT-116 cell with IC$_{50}$ values ranging from 0.078 to 17.14 µM [51]. A new tetrahydroantracene alokicenone D (84) was isolated from the cultures of Streptomyces sp. HN-A101 [53]. New cyclizidine-type alkaloids cyclizidines D (85), H (86) and I (87) were purified from Streptomyces sp. HNA39. Compounds 86 and 87 exhibited inhibition against the ROCK2 protein kinase with IC$_{50}$ values of 42 ± 3 and 39 ± 1 µM; 86 and 87 also showed cytotoxicity against PC-3 with IC$_{50}$ values of 33 ± 1 and 17 ± 1 µM, respectively. Compound 87 demonstrated cytotoxicity against HCT-116 with an IC$_{50}$ value of 40 ± 1 µM [54].

2,4-Dichlorophenyl 2,4-dichloro benzoate (88) (Figure 4) was obtained from Streptomyces sp. G212. Compound 88 was active against C. albicans with an MIC value of 64 µg/mL [55]. Streptomyces sp. CNH-189 afforded two new meroterpenoids merchlorins E (89) and F (90), which showed antibacterial activities against S. aureus, B. subtilis and K. rhizophila with MIC values ranging from 1 to 2 µg/mL [56]. Two new chlorinated bisindole alkaloids, dionemycin (91) and 6-OMe-7′,7′′-dichorochromopyrrolic acid (92) were isolated from Streptomyces sp. SCSIO 11,791 [57]. Compound 91 displayed cytotoxic activity against MD1-MB-435, MDA-MB-231, NCI-H460, HCT-116, HepG2, and MCF10A with MIC values in the range of 3.1–11.2 µM. Compound 92 showed cytotoxic activity against human cancer cell lines MD1-MB-435, HCT-116, HepG2, and MCF10A with MIC values ranging from 2.9 to 19.4 µM.

2.5. Streptomyces sp. from Other Marine Sources

New dibenzoazepinones mycemycins C–E (93–95) were separated from Streptomyces olivaceus FXJ8.012A1741 [58]. A sulfonate-containing analog totopotensamide C (96) was isolated from Streptomyces pactum SCSIO 02,999 [59]. One new polycyclitramate macrolactam pactamide F (97) was also purified from Streptomyces pactum SCSIO 02,999 [60]. Cultivation of Streptomyces sp. ZZ502 afforded a new cyclohexene 3-amino-2-carboxame-6(R)-chloro-4(R)-5(S)-dihydroxy-cyclohex-2-en-1-one (98) [61].
3. Halogenated Compounds from Other Marine Actinomycetes

3.1. Other Marine Sediments-Associated Actinomycetes

Actinomycete CNB-632 (sediment, the Tot-my Pines Estuary) yielded a sesquiterpenoid naphthoquinone marinone (99) that was active against *Bacillus subtilis* with an MIC value of 1 µg/mL [62]. An actinomycete strain (# CNH-099) produced isomarinone (100). Compound 100 displayed cytotoxicity against a colon carcinoma cell line HCT-116 with an MIC value of 8 µg/mL [63]. Salinosporamide A (101) with a γ-lactam-β-lactone bicyclic ring was isolated from *Salinospora* strain CNB-392 (later assigned as *Salinispora tropica*), which showed cytotoxicity against a panel of cancer cell lines with IC₅₀ values less than 10 nM and exhibited prominent inhibition of the 20S proteasome [64]. Compound 101 entered phase I human clinical trials for the treatment of multiple myeloma three years after its discovery in 2003 [64]. Salinosporamide A was synthesized from (R)-pyroglutamic acid [65]. *Salinispora tropica* CNB-392 produced sporolides A (102) and B (103) [66]. Compound 103 exhibited inhibitory activity against HIV-1 reverse transcriptase [67].
was synthesized by ruthenium-catalyzed [2+2+2] cycloaddition and Diels–Alder-type reaction [68]. *Salinispora tropica* CNB-392 yielded salinosporamide F (104), salinosporamide I (105), salinosporamide J (106) and bromosalinosporamide (107). Compound 106 displayed RPMI 8226 and chymotrypsin-like activity with IC$_{50}$ values of 52 and 250 nM, respectively [69]. Fermentation of *Salinispora pacifica* (designated CNS103) derived from sediments led to the identification of cyclopenta[al]indene glycosides cyanosporasides A and B (108 and 109). Compound 108 was cytotoxic against HCT-116 with an IC$_{50}$ value of 30 µg/mL [70]. Lynamincs A–E (110–114) were afforded by *Marinispora* sp. NPS12745, which showed antibacterial activity against MRSA and vancomycin-resistant *E. faecium* with IC$_{50}$ values in the range of 1.8–57.0 µg/mL [71].

Lodopyridone (115) (Figure 5) from *Saccharomonospora* sp. (marine sediment, the La Jolla Submarine Canyon) showed cytotoxicity against HCT-116 cell line with an IC$_{50}$ value of 3.6 µM [72]. *Saccharomonospora* sp. CNQ-490 afforded taromycin A (116), which exhibited antibacterial activity against MRSA and *Enterococcus faecalis* 613D with MIC values ranging from 6 to 100 µM [73]. Fijiolides A and B (117 and 118) were isolated from the cultures of bacterium of the genus *Nocardiopsis* CNS-653 (sediment sample, Fiji). Compound 117 showed QR1 activity and was active against TNF-R-induced NF-κB with an IC$_{50}$ value of 0.57 µM. Compound 118 showed activity against TNF-R-induced NFκB [74].

Figure 5. Structures of compounds 115–127.
Phocoenamicins B (119) and C (120) were isolated from *Micromonospora* sp. CA-214671, and both compounds showed a broad spectrum of antibacterial activities with MIC values ranging from 2 to 64 µg/mL [75].

3.2. Other Ascidian-Associated Actinomycetes

Halomadurones A–D (121–124) were obtained from *Actinomadura* sp. WMMB499 (ascidian *Ecteinascidia turbinata*), among which 123 and 124 showed activity against Nrf2-ARE [76]. A new halimane-type diterpenoid micromonohalimane B (125) was isolated from a culture of *Micromonospora* sp. WMMC-218, which inhibited MRSA with an MIC value of 40 µg/mL [77].

3.3. Other Marine Source-Associated Actinomycetes

Saccharochlorines A (126) and B (127) were isolated from *Saccharomonospora* sp. KCTC-19160, and both compounds showed BACE1 inhibition of 41.4 ± 3.6% and 32.0 ± 9.7%, respectively, at the same concentration of 50 µM (a positive control, isoliquiritigenin, 56.7% inhibition at 50 µM) [78].

4. Summary

According to the summary of halogenated compounds from marine-derived actinomycetes (Figure 6 and Table 1), the study of halogenated compounds from marine-derived actinomycetes could be traced back to 1992 when marinone (99) was purified from an actinomycete strain CNB-632 isolated from a sediment sample (Table 2) [62]. Since 2005, more new halogenated compounds from marine-derived actinomycetes have been isolated annually than ever before except for 2016. From 2010 to 2014 and in 2020, 10 or more new halogenated compounds were reported annually. By the end of 2020, 127 new halogenated compounds from marine-derived actinomycetes have been reported.

Figure 6. Numbers of new halogenated compounds from actinomycetes reported annually from 1992 to 2020.
Table 1. The initial research on halogenated compounds from marine-derived actinomycetes.

| First Producing Strain | Environment Source | Compound. | Time |
|------------------------|--------------------|-----------|------|
| *Streptomyces* sp. 1053U.1a.1b | *Lienardia totopotens*, Mahtan Island, Cebu, Philippines | totopotensamides A (10) and B (11) | 1994 |
| Actinomycete CNB-632 (other marine actinomycetes) | Sediment sample, Tot-my Pines Estuary, La Jolla, CA | marinone (99) | 1992 |

Table 2. Halogenated compounds isolated from marine-derived actinomycetes.

| Compound | Producing Strain | Environment Source | Bioactivity | Ref. |
|----------|------------------|--------------------|-------------|------|
| 1–2      | *Streptomyces* sp. Sp080513GE-23 | *Haliclona* sp. Sponge, Chiba, Japan | / | [4,5] |
| 3        | *Streptomyces* sp. SBT345 | *Agelas oroides* sponge, Mediterranean Sea | Antioxidant and antichlamydial effects | [6,7] |
| 4–6      | *Streptomyces* coelicolor LY001 | Sponges *Callyspongia siphonella*, the Saudi Red Sea | Antibacterial activity | [8] |
| 7–8      | *Streptomyces* sp. OUCMDZ-1703 | Unidentified soft coral, Weizhou Island, Guangxi, China | Cytotoxicity | [9] |
| 9        | *Streptomyces* hygroscopicus | Jellyfish *Cassiopeia xamachana*, Florida Keys | Antibacterial, Anti-inflammatory activity | [10] |
| 10–11    | *Streptomyces* sp. 1053U.1a.1b | *Lienardia totopotens*, Mahtan Island, Cebu, Philippines | / | [11] |
| 12–15    | *Streptomyces* sp. Strain CA-271078 | Ascidian, the sea shore in Baía Ana Chaves, Sao Tome | 13–15: Cytotoxicity | [12,13] |
| 16–17    | *Streptomyces* sp. Mo45 | Sediment, Jiaozhou Bay, China | Cytotoxicity | [14] |
| 18       | *Streptomyces* sp. CNQ766 | Sediment, Island of Guam | / | [15,16] |
| 19       | *Streptomyces* sp. CNQ-583 | Sediment, Island of Guam | / | [17] |
| 20       | *Streptomyces* sp. CNH990 | Sediment, Cabo San Lucas, Mexico. | Cytotoxicity | [18] |
| 21       | *Streptomyces* sp. 04DH110 | Sediments, Ayajin Bay, East Sea of Korea | Cytotoxicity | [19,20] |
| 22–24    | *Streptomyces* sp. CNQ-593 | Sediment, Island of Guam | Cytotoxicity | [21,22] |
| 25–32    | *Streptomyces* sp. CNQ525 | Sediment, La Jolla, CA | 26–27, 29–30, 32: Cytotoxicity 25–27: Antibacterial activity | [23–25] |
| 33–38    | *Streptomyces* sp. CNQ-418 | Sediment, La Jolla, CA | Cytotoxicity | [26,27] |
| 39–40    | *Streptomyces* sp. CNR-698 | Sediment, Bahamas Islands | Cytotoxicity | [28,29] |
| 41       | *Streptomyces* sp. Mei37 | Sediment, Jade Bay, German | Cytotoxicity | [30,31] |
| 42–43    | *S. malaysiensis* CNQ-509 | Sediment, California | 42: Cytotoxicity | [32] |
| 44–47    | *Streptomyces* sp. CNH-189 | Sediment, Oceanside, California | / | [33] |
| 48–58    | *Streptomyces* sp. SCSIO 01032 | Sediment, Bay of Bengal | 49–51, 53: Cytotoxicity 49–51: Antibacterial activity | [34–37] |
| 59       | *Streptomyces* sp. SCSIO 02999 | Sediment, South China Sea | Antibacterial activity | [38] |
| 60       | *Streptomyces* variabilis SNA-020 | Sediment, Bahamas | Cytotoxicity | [39] |
| 61–63    | *Streptomyces* sp. CNT-179 | Sediment, Bahamas | / | [40] |
| 64       | *Streptomyces* sp. CNH-287 | Sediment, San Diego, CA. | Cytotoxicity | [41,42] |
| 65–68    | *Streptomyces* sp. CNQ-329 | Sediment, San Diego, CA. | 65, 67–68: Cytotoxicity 65: Antibacterial activity | [43] |
| 69       | *Streptomyces* sp. CNH-070 | Sediment, Encinitas, California | Cytotoxicity | [43] |
| 70–72    | *Streptomyces* sp. SCSIO 10428 | Sediment, Beihai, Guangxi, China | Antibacterial activity | [44] |
| 73       | *Streptomyces* sp. ART5 | Sediment, East Siberian, Arctic Ocean | Cytotoxicity | [45] |
| 74–75    | *Streptomyces* sp. SNC-109-M3 | Sediment, Vava’u, Tonga | 74: Cytotoxicity | [46–48] |
| 76–77    | *Streptomyces* sp. SNM55 | Sediment, Buan, Korea | Antibacterial activity | [49] |
| 78–83    | *Streptomycetaceae* CNS-284 | Marine sediments, the Solomon Islands and in Palau | 78–79: TNF-α-induced NFkB activity and antibacterial activity; 80–83: Antibacterial activity and cytotoxicity | [50–52] |
Sediments were the richest source of marine-derived actinomycetes, which produced about 78% of new halogenated compounds (Figure 7). It was reported that sediments are rich in nutrients, which can harbor an enormous quantity of microorganisms, including actinomycetes. It is worth mentioning that, the deeper and older the sediment is, the less abundant the microbes. Nevertheless, marine actinobacteria in sediments will keep providing opportunities for natural product research and natural product drug discovery.

Marine Streptomyces spp. had the highest occurrence of halogenated compounds (98/127 = 77%) (Figure 8), which might be due to their unique and diverse biosynthetic machinery, high halogenase activity or simply Streptomyces being the largest genus of Actinobacteria. Overall, 70.1% of halogenated compounds from marine actinomycetes is biologically active, and 37.3% and 24.6% of the halogenated compounds showed anticancer and antimicrobial activity, respectively (Figure 9).
Figure 7. Percentages of new halogenated compounds from different sources of marine origins (1992–2020).

Figure 8. Numbers of new halogenated compounds from different marine actinomycetes (1994–2019).
The structure types of the new halogenated compounds were diverse, which could be classified as nitrogen-containing compounds, polyketides and terpenoids. Nitrogen-containing compounds and polyketides were two main classes of compounds produced by marine actinomycetes (Figure 10). The number of chlorinated compounds generated by marine actinomycetes is 10 times more than that of brominated compounds (Figure 11), which may be related to the concentrations of chloride and bromide ions in the ocean. Fluorinated natural products were reported before, but no new fluorinated compounds were discovered from marine actinomycetes recently.
In short, marine actinomycetes have unique and diverse biogenetic machinery, which can produce different halogenated compounds with novel structure skeletons and various biological activities, and *Streptomyces* spp. from sediments are the main producers. Some halogen-containing drugs such as chloramphenicol, vancomycin, chlorotetracycline, calicheamicin, rebeccamycin and complestatin have been developed from secondary metabolites isolated from terrestrial actinomycetes [3]. Marine natural products have higher success rate (1 in 3500) in drug discovery, compared with the industry average of 1 in 5000–10,000 compounds [79]. Therefore, halogenated compounds from marine actinomycetes are expected to be a promising source of lead compounds for natural product drug discovery.

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