Cytotoxic compounds from marine actinomycetes: sources, structures and bioactivity

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ABSTRACT

Marine actinomycetes produce a substantial number of natural products with cytotoxic activity. Actinomycete strains have been isolated from sources including fishes, coral, sponges, seaweeds, mangroves and sediments. These cytotoxic compounds can be broadly categorized into four classes: polyketides; non-ribosomal peptides and hybrids; isoprenoids and hybrids; and others, among which the majority are polyketides (146 of 254). Twenty-two of the 254 compounds show potent cytotoxicity, with IC50 values at the ng/mL or nM level. This review highlights the sources, structures and antitumor activity of 254 natural products isolated from marine actinomycetes and first reported between 1989 and 2020.

Keywords: marine actinomycetes, marine natural products, chemical structures, antitumor bioactivity

1. INTRODUCTION

The oceans occupy more than two-thirds of the Earth’s surface and contain more than four-fifths of the world’s plant and animal species, in addition to a vast number of microorganisms [1]. Marine natural products usually refer to compounds isolated from marine microorganisms and phytoplankton, algae, sponges, cnidarians, bryozoans, mollusks, tunicates, echinoderms, mangroves, and other intertidal plants and microorganisms [2]. The discovery rate of new marine natural products has increased since the advent of this field and has continued at a substantial rate despite the ever-increasing number of reported natural products [3]. To date, 17 marine-derived drugs have been approved for clinical use: cytarabine (Cytosar-U®), vidarabine (Arasena A®), ziconotide (Prialt®), eicosapentaenoic acid ethyl ester (Vascepa®), omega-3-carboxylic acid (Epanova®), omega-3-acid ethyl esters (Lovaza®, whose status is currently debated), eribulin mesylate (ET389, Halaven®), trabectedin (ET-743, Yondelis®), panobinostat (Farydak®), plitidepsin (Aplidin®), lurbinectin (Zepzelca™), belantamab mafodotin-blmf (Blenrep™), brentuximab vedotin (SGN-35, Adcetris®), polatuzumab vedotin (DCDS-4501A, Polivy™), enfortumab vedotin-ejfv (PADCEV™), disitamab vedotin (Aidixi™) and tisotumab vedotin-tftv (Aidixi™) [4]. More marine natural products are highly likely to be developed for clinical use. Some of the lead compounds developed into the above-mentioned clinical drugs are likely to be produced by microorganisms including actinomycetes, given the growing recognition in recent decades that metabolic processes in microorganisms including actinomycetes are the most productive source of unique secondary metabolites [5]. Actinomycetes are a diverse family of filamentous bacteria that produce a plethora of natural products with relevance to agriculture, biotechnology and medicine, including most antibiotics approved by the U.S. Food and Drug Administration [6]. In the 1940s, actinomycetes were first discovered for their antibiotic functions [7]. Subsequently, secondary metabolites of actinomycetes were widely exploited as antitumor drugs in the
pharmaceutical industry. Several anticancer drugs have been developed from enediyne, such as gemtuzumab ozogamicin (Mylotarg®) and inotuzumab ozogamicin (Besponsa®) [8, 9]. However, the high toxicity, undesirable adverse effects and extensive drug resistance of current treatments have increased the demand for novel antimut drugs. Marine actinomycetes are a valuable source of biologically active secondary metabolites. According to a statistical analysis, marine-derived actinomycetes account for the production of 39% of all bioactive microbial metabolites [10]. This review describes the sources, chemical structures and cytotoxic activities of 254 compounds derived from marine actinomycetes, reported from 1989 to 2020.

2. STRUCTURAL CLASSES OF ANTITUMOR SECONDARY METABOLITES FROM MARINE ACTINOMYCETES

2.1 Polyketides

2.1.1 Macrolides (lactones), lactams and αβ-pyrones.

Two new kijanimicin derivatives, lobophorins C (1) and D (2), have been purified from Streptomyces carni- sus A2517 (Figure 1). Compounds 1 and 2 each have a unique β-keto-γ-spiro-γ-lactone moiety with a double bond at the α-position. Compound 1 showed cytotoxicity toward the 7402 human breast cancer cell line and MDA-MB 435 human breast cancer cells with IC_{50} values of 0.6 μg/mL and 61.8 μM, respectively, while compound 2 was toxic against the same two cancer cell lines with IC_{50} values of 723.1 μg/mL and 7.5 μM, respectively [11]. Octalactin A (3), a fully saturated eight-membered lactone, has been isolated from a marine bacterium, Streptomyces sp. PG-19. Compound 3 displays inhibitory activity toward the B-16-F10 and HCT-116 cell lines, with IC_{50} values of 7.2 and 500 ng/mL, respectively [12]. The macrolides PM100117 (4) and PM100118 (5) have been obtained from Streptomyces caniferus GUA-06-05-006A [13]. Compounds 4 and 5 each have a 36-membered macrolide ring system together with three six-membered hemiketal rings and a napthoquinone moiety on the bulky tail. Compound 4 displays cytotoxicity toward A549, MDA-MB-231 and HT29 cell lines, with GI_{50} values of 1.3, 2.7 and 3.8 μM, respectively, and compound 5 is active toward these three cell lines, with GI_{50} values of 0.83, 1.7 and 9.2 μM, respectively. A 16-membered diene macrolide, bafilomycin M (6), has been obtained from Streptomyces sp. GI10-1, which has been isolated from the Theonella marine sponge species [14]. Compound 6 exhibits potent anticancer activity toward HL-60, SUPT-1, K-562 and LNCAp cells, with IC_{50} values of 11, 47, 60 and 389 ng/mL, respectively. The cytotoxic bafilomycin analogs bafilomics N (7) and O (8) have been obtained from Streptomyces sp. GI10-1 [15]. Compound 7 is cytotoxic to LNCAp, SUP-T1, MOLT-4 and K562 cells, with IC_{50} values of 3.9, 6.0, 0.01 and 31.8 nM, respectively, and compound 8 is active toward the same cancer cell lines, with IC_{50} values of 118.6, 64.4, 389.6 and 54.2 nM, respectively. The new compound lobophorin K (9) has been separated from the culture of Streptomyces sp. M-207 isolated from the cold-water coral Lophelia pertusa [16]. Compound 9 exhibits cytotoxicity toward THLE-2, MCF-7 and MiaPaca-2, with IC_{50} values of 6.3 ± 8.2, 23.0 ± 8.9 and 34.0 ± 85.1 μM, respectively. A new spirotetronate lobophorin F (10) has been isolated from Streptomyces sp. SCIO 01127 and shown activity toward the SF-268, MCF-7 and NCI-H460 cell lines, with IC_{50} values of 6.82, 2.93 and 3.16 μM, respectively [17].

The new αβ-pyrene derivatives violapyrones H (11) and I (12) have been obtained from Streptomyces sp. isolated from the crown-of-thorns starfish, Acanthaster planci [18]. Compounds 11 and 12 are cytotoxic toward HCT-15, HCT-116, MDA-MB-231, NCI-H23, NCI-H460, NUGC-3, Hep-G2 and PC-3 cells, with IC_{50} values in the range of 1.10 to 25.05 μM. Nocardiosis sp. NHF48 has been found to produce a new αβ-pyrene compound (13) exhibiting cytotoxic activity toward the melanoma cell line B16, with a GI_{50} value of 61.7 μg/mL [19]. From Streptomyces sp. HKI0576, ansa-macrolides divergolides A–D (14–17) have been obtained [20]. Compound (17) displays cytotoxicity toward lung cancer (LXFA 629L), pancreatic cancer (PANC-1), renal cancer (RKF 486L) and sarcoma (Saos-2) cells, with IC_{50} values in the range of 1.0 to 2.0 μM. Aureoverticillactam (18), a 22-atom macrocyclic lactam incorporating both triene and tetrane conjugated olefins, has been obtained from Streptomyces aureoverticillatus NPS001583, and has shown cytotoxicity toward HT-29, B16-F10 and Jurkat cells, with EC_{50} values of 3.6, 2.2 and 2.3 μM, respectively [21]. Two new 16-membered macrolides, 21,22-en-bafilomycin D (19) and 21,22-en-9-hydroxybafilomycin D (20), have been purified from the seaweed-derived Streptomyces sp. HZP-2216E [22]. Compound 19 displays cytotoxicity toward U251 and C6 glioma cell lines, with IC_{50} values of 1.08 and 0.21 μM, respectively, and compound 20 is toxic toward the same cell lines, with IC_{50} values of 0.36 and 0.12 μM, respectively. A 42-membered macrolide, desertomycin G (21), has been obtained from cultures of the marine actinomycete Streptomyces altithiopticus MSM3 isolated from samples of Ulva sp. intertidal seaweed collected in the Cantabrian Sea (Northeast Atlantic Ocean) [23]. Bioevaluation results have indicated that, at day 3, DLD-1 and MCF-7 cancer cell lines show a decrease in viability to approximately 50% that of controls after treatment with 2.5 and 5.0 μM desertomycin G (21). From a mangrove actinomycete strain, Streptomyces sp. 219807, which produces a high yield (4,486 mg/L) of elaiophylins, has been isolated [24]. A new elaiophyllin derivative, halichoblelide D (22), has been obtained and identified from 219807 [24]. Compound 22 exhibits cytotoxic activity toward MCF-7 and HeLa cells, with IC_{50} values of 0.33 and 0.30 μM, respectively.

Compound 23 is composed of four partial structures: cyclopenta[a]indene, 3′-chloro-5′-hydroxy-β-tyrosine, benzoxazine and amino sugar. Compound
Figure 1 | Structures of compounds 1–27.
23 shows cytotoxicity toward MDA-MB231, HCT-116, A549, SNU638, K562 and SK-HEP1, with IC50 values of 0.9, 2.7, 14.7, 9.8, 25.1 and 7.9 μM, respectively [25]. Compound 23 shows cytotoxicity toward MCF-7, with an IC50 of 27.0 μg/mL. Four new nonacyclic dilactones, antimycins E–H (24–27), have been obtained from Streptomyces sp. TH5-55 [26]. Compounds 24–27 each contain a N-[3-(acetylamino)-2-hydroxybenzoyl] moiety. Compounds 24–26 are cytotoxic to Sih, K562, HL-60 and 293T cancer cell lines, with IC50 values of 0.8–13.8 μM. Two new benzamido nonacyclic dilactones, neoantimycins A (28) and B (29), have been obtained from Streptomyces antibioticus H12-15 (Figure 2) [27]. The actinomycete strain S. antibioticus H12-15 has been isolated from a sea sediment in a mangrove district. Compounds 28 and 29 exhibit anticancer activity toward SF-268 cells, with IC50 values of 68.7 and 87.6 μM, respectively. Three new 4H-chromen-4-one polyketides, phaeochromycins F–H (30–32), have been separated from Streptomyces sp. D5S-18, a strain isolated from a deep-sea sediment collected from the western Pacific [28]. Compounds 30–32 are active toward HeLa cells, with inhibition rates of 9.4%, 1.0% and 46.0% at 10 μM, respectively.

Tartrolon D (33), a cytotoxic macrolide with two hemiketal rings, has been separated from Streptomyces sp. MDG-04-17-06 isolated by spreading a marine sediment collected near the east coast of Madagascar on 1728 modified agar medium plates supplemented with nalidixic acid (1%) [29]. Compound 33 has cytotoxic activity toward A549, HT29 and MDA-MB-231 cells, with GI50 values of 0.16, 0.31 and 0.79 μM, respectively. Two new macrocyclic lactones, azolomycin F4a 2-ethylpentyl ester (34) and azolomycin F5 2-ethylpentyl ester (35), have been separated from a culture of Streptomyces sp. 211726 isolated from a mangrove rhizosphere soil sample [30]. Compounds 34 and 35 are cytotoxic toward HCT-116 cells, with IC50 values of 5.64 μg/mL and 2.58 μg/mL, respectively. Seven new azolomyacin F analogs (36–42) have been obtained from Streptomyces sp. 211726 [31]. These macrolides (36–42) display inhibitory activity toward HCT-116 cells, with IC50 values ranging from 1.81 to 5.00 μg/mL.

Six new polycyclic tetramate macrolactams, pactamides A–F (43–48), have been purified from the marine-derived strain Streptomyces pactum SC51002999, and have shown cytotoxicity toward four cancer cell lines (MCF-7, SF-268, Hep-G2 and NCI-H460), with IC50 values ranging from 0.24 to 25.47 μM [32].

Two new macrolides, pulvovalycin B (49) and pulvovalycin D (50), have been discovered from an estuarine Streptomyces strain [33]. Compound 49 displays cytotoxic activity toward HT116, SNU638, SK-Hep-1 and MDA-MB-231 cells, with IC50 values in the range of 3.7–25 μM, whereas compound 50, which bears a 1,2-diketone functional group, strongly inhibits the same cancer cell lines, with IC50 values ranging from 0.21 to 0.40 μM. A new curvularin glycoside, curvularin-7-O-α-D-glucopyranoside (51), has been isolated from Pseudonocardia sp. H57 obtained from the cloacal aperture of the sea cucumber Holothuria moebii [34]. Compound 51 displays inhibitory activity against six cancer cell lines (HCT-15, C6, U251, SHG-44, U87-MG and SW620), with IC50 values in the range of 20.84 to 81.01 μM. Three new polyene macrolactams, kenalactams C–E (52–54), have been separated from Nocardiosis CG3 (DSM 106572) isolated from the siltpan of Kenada [35]. Compounds 52 and 53 show cytotoxicity toward L929, KB3.1, MCF-7, PC-3, A549 and SKOV-3 cells, with IC50 values ranging from 5.4 to 42.2 μM. Compound 54 is also active toward KB3.1, PC-3, SKOV-3 and A549 cells, with IC50 values ranging from 2.1 to 6.5 μM. Cultivation of Micromonospora sp. FIM05328 has yielded the macrolactam FW05328-1 (55) [36].

Compound 55 inhibits the KYSE30 and KYSE180 tumor cell lines, with IC50 values of 15.92 and 30.77 μM, respectively. Interestingly, compound 55 strongly inhibits the esophageal cancer EC109 cell line, with an IC50 value of 0.2 nM. The Micromonospora strain FIM07-0019 has yielded a new 20-membered macrolide, levantilide C (56) [37]. The strain FIM07-0019 has been recovered from shallow coastal water near the island of Chiloé, Chile. Compound 56 displays inhibitory activity toward HL-60, MDA-MB-231, SW620 and SMMC7721 cells, with IC50 values of 32.5, 26.8, 16.4 and 39.9 μM, respectively.

A polycyclic tetramate macrolactam, 16-hydroxymatophilin (57), isolated from Actinoalloteichus cyanogriseus WH1-2216-6, shows cytotoxicity toward BXPC-3, HCT-116, Jurkat, PAN-C1, A549, MCF-7 and L-02 cell lines, with IC50 values of 4.5, 5.7, 7.5, 7.9, 9.5, 9.7 and 235.9 μM, respectively [38].

2.1.2 Benzoquinones, naphthoquinones, anthraquinones and other aromatic compounds. One anthracycline, tetracenoquinocin (58), has been separated from a culture of Streptomyces sp. Sp080513GE-26 associated with a Haliclonia sp. marine sponge [39]. Compound 58 is cytotoxic toward HeLa and HL-60 cells, with IC50 values of 120 and 210 μM, respectively. The new salicylamide derivative JBIR-58 (59) has been obtained from Streptomyces sp. Spd081030ME-02 isolated from a demosponge class of marine sponge [40]. Compound 59 displays inhibitory activity toward HeLa cells, with an IC50 value of 28 μM. Streptomyces sp. HB202 has been found to produce the new benz[a]anthracene derivative mayamycin (60), which displays cytotoxicity toward HepG2, MAXF401NL, MEXF462NL, HT-29, GIX251L, LFX529L, PAXF1657L and RXF486L cells, with IC50 values ranging from 0.13 to 0.33 μM [41]. Streptomyces sp. BCC45596 has yielded three new C-glycosylated benz[a]anthraquinone derivatives: urdamycinone E (61), urdamycinone G (62) and dehydroxyaquayamycin (63) [42]. Compounds 61 and 62 display inhibitory activity toward KB, MCF-7 and NCI-H187 cancer cell lines, with IC50 values ranging from 0.092 to
Figure 2 | Structures of compounds 28-65.
0.45 μg/mL, whereas compounds 63 is much less active toward these three cancer cell lines, with IC50 values of 6.96, 3.41 and 3.97 μg/mL, respectively. All three compounds (61–63) are less toxic toward non-cancerous (Vero) cells than cancer cells, with IC50 values of 1.71, 3.05 and 10.07 μg/mL, respectively. Three angucycline derivatives, monacycline C (64), monacycline E (65) and monacycline F (66; Figure 3), have been purified from *Streptomyces* sp. M7_15 associated with the sponge *Scopalaria ruetzleri*, which displays inhibitory activity toward SJCRH30 cells, with IC50 values of 160, 270 and 0.73 μM, respectively [43]. The potent anticancer activity of compound 66 might be due to the two unique epoxide rings attached to the angucycline moiety. The chlorinated streptorhodinates A (67) and B (68) have been separated from the oligotrophic culture of a soft coral-associated actinomycete strain, *Streptomyces* sp. OUCMDZ-1703, and have shown cytotoxicity toward MCF-7 cells, with IC50 values of 9.9 and 20.2 μM, respectively [44]. Naquihexcin A (69), an 5-bridged pyranonaphthoquinone dimer bearing an unsaturated hexuronic acid moiety, has been obtained from the sponge-derived *Streptomyces* sp. HDN-10-293 [45]. Compound 69 is cytotoxic toward MCF-7 ADM, with an IC50 value of 16.1 μM. A coral-derived strain, *Streptomyces* sp. RKBB87, produces a new meroterpenoid with a sesterterpene skeleton, guanahanolide A (70), with cytotoxicity toward MCF-7, NCI-60, HCT-116, HTB-26 and Vero cells, with IC50 values of 7.8, 10.0, 11.9, 10.1, 23.7 μM, respectively [46]. *Streptomyces* sp. ZZ406 has yielded l-hydroxymethyl-8-hydroxy-angucycline-3-carboxylic acid (71) and a 2-methylchromone derivative, phaeochromycin I (72) [47]. Compound 71 displays inhibitory activity toward the glioma cells U251, U87MG and SHG, with IC50 values of 5.7, 4.7 and 8.1 μM, respectively, whereas compound 72 is less active toward U251, U87MG and SHG glioma cells, with IC50 values of 21.6, 25.7 and 25.8 μM, respectively. *Streptomyces* sp. CANU Fox 21-2-6a, isolated from the outer layer of driftwood material collected at the mouth of the Fox River on the West Coast of New Zealand, has yielded four new anthracycline derivatives: (7S*9R*10R*)-pyrroymycin (73), (7R*9R*10R*)-pyrroymycin (74), 1-hydroxyauramycin T (75), and 1-hydroxysulfurmycin T (76) [48]. Compounds 73–76 are cytotoxic toward the P388 tumor cell line, with IC50 values in the range of 0.04–0.6 μg/mL. A new anthracine, 1,8-dihydroxy-2-ethyl-3-methylantrachainone (77), has been separated from a fermentation of *Streptomyces* sp. FX58-1 isolated from the marine plant *Salicornia herbacea* collected in Qingdao, Shandong province, China [49]. Compound 77 is cytotoxic toward HL-60, BCTC-823 and MDA-MB-435 cells, with IC50 values of 6.83, 82.2 and 56.59 μg/mL, respectively. A culture of *Streptomyces* sp. B8652 has been found to produce parimycin (78) [50]. The strain B8652 has been isolated from a sediment of the Laguna de Terminos at the Gulf of Mexico. Compound 78 is cytotoxic toward LXFA629L, LXFL529L, MCF-7, MAXF401NL, MEXF462NL and MEXF 514L cells, with IC50 values in the range of 0.9–6.7 μg/mL. Fermentation of *Streptomyces* sp. M045 derived from a sediment collected at Jiaozhou Bay in China has led to the identification of chinikomycins A (79) and B (80) [51]. Compound 79 is a hydroquinone derivative, whereas compound 80 is a 1,4-benzoquinone analog, which might be oxidized from 79. Compound 79 is cytotoxic toward MAXF 401NL, MEXF 462NL and RXF 944L cells, with IC50 values of 2.41, 4.15 and 4.02 μg/mL, respectively, and compound 80 is active toward MAXF 401NL cells, with an IC50 value of 3.04 μg/mL. Two anthraquinones of the angucycline class, marmycins A (81) and B (82), have been obtained from *Streptomyces* sp. CNH990 [52]. Compound 81 is a monochloro derivative of compound 82. Compounds 81 and 82 show cytotoxicity toward HCT-116 cells, with IC50 values of 60.5 nM and 1.09 μM, respectively. Compound 81 shows cytotoxicity toward 12 human tumor cell lines (lung, colon, breast, prostate or leukemia) after 72 h drug exposure, with IC50 values ranging from 7 to 58 nM, but compound 82 shows cytotoxicity toward the above 12 human tumor cell lines, with IC50 values ranging from 1.0 to 4.4 μM. The results contrast with general observations that chlorination usually markedly enhances the pharmacological activity of compounds [53]. Three new anthramycin-type analogues, usabamycins A–C (83–85), have been purified from *Streptomyces* sp. NPS853, a bacterial strain found in a marine sediment [53]. Compounds 83–85 are pyrrolo[1,4]benzodiazepine derivatives that display weak inhibitory activity toward HeLa cells, with IC50 values of 106.6, 103.5 and 101.9 μM, respectively. A new anthrancene derivative, 3-hydroxy-1-oxo-3-methyl-8-methoxy-1,2,3,4-tetrahydro-benz[a]anthracene (86), has been isolated from the fermentation broth of *Streptomyces* sp. W007 [54]. In cytotoxicity tests, compound 86 shows no cytotoxicity toward the human leukaemic cell line HL-60 and weaker cytotoxicity toward the human hepatoma cell line BEL-7402 than adriamycin, but potent inhibitory activity toward the human lung adenocarcinoma cell line A549, with a rate of inhibition at 1 μM of 61.8%. Four angucycline C-glycosides, grincamycins B–E (87–90), have been isolated from *Streptomyces lusitanus* SCSIO LR32, an actinomycete of deep-sea origin [55]. The disaccharide moiety in compound 89 forms a 1,4-dioxane ring through 3-2' and 4-1' linkages. Compounds 87–90 show cytotoxicity toward MCF-7, Hela, HepG2, B16, NCI-H460 and SW-1990 cells, with IC50 values in the range of 2.1 to 31 μM. *Streptomyces* sp. SNE-011 has yielded the alylamine derivatives carptamides A (91) and C (92) [56]. Strain SNE-011 has been isolated from a marine sediment sample collected from South Carolina. Compound 91 exhibits inhibitory activity toward HCC366, A549 and HCC44 cells, with IC50 values of 2.8, 4.1 and 8.4 μM, respectively, and compound 92 inhibits HCC366 and A549 cells, with IC50 values of 2.2 and 3.7
Figure 3 | Structures of compounds 66–107.
μM, respectively. The compound (2S,3R)-L-threonine, N-[3-(formylamino)-2-hydroxybenzoyl]-ethyl ester (streptomyceamide C, 93) has been isolated from EtOH extract of the fermented mycelium of the marine-derived streptomycete strain H74-21 isolated from a sea sediment in a mangrove site [57]. Compound 93 shows cytotoxicity toward MCF-7, with an IC50 of 27.0 μg/mL. Deep-sea sediment-derived Streptomyces sp. SCSSIO 11594 has yielded an angucycline C-glycoside, marangucycline B (94), which displays cytotoxic activity toward A549, CNE2, MCF-7, HepG2 and HL7702 cells, with IC50 values of 0.45, 0.56, 0.24, 0.43 and 3.67 μM, respectively [58]. Compound 94, with a keto-sugar moiety and a 1,4-dioxane ring between sugars, is approximately 10–20-fold more potent than cisplatin. Elmonin (95) and elmenol B (96) have been separated from Streptomyces sp. IFM11490 and shown cytotoxicity toward the human gastric adenocarcinoma (AGS) cell line, with almost equal IC50 values of approximately 50.0 μM [59]. Cultivation of Streptomyces sp. 1825MLY has afforded two polycyclic anthraquinones, N-acetyl-N-demethylmayamycin (97) and streptaanthraquinone A (98) [60]. Compounds 97 and 98 display inhibitory activity toward C6, U251, U87-MG and SHG-44c cells, with IC50 values of 0.57/3, 0.7/3.3, 1.4/4.6 and 3.9/6.5 μM, respectively. The cell viability of normal human astrocytes from each tested concentration of both compounds 97 and 98 is 100%, and both compounds have IC50 values of 25 and 100 μM, respectively. Diazaquinomycin E (99) has been obtained from Streptomyces sp. F001 and has been found to display cytotoxicity toward OVCAR5, with an IC50 value of 9.0 μM [61]. A study of the Streptomyces griseus strain M268 has led to the identification of a unique cage-like compound, griseumycin (100), which is cytotoxic toward HL-60, with an IC50 value of 31.54 μM [62]. A novel dimeric diazobenzofluorene glycolide, lomavimicin A (101), has been obtained from a halophilic strain, Micromonaspora lomavitensiss LL-371366 [63]. Compound 101 is a dimeric benzofluorene glycolide attached to two diazo functional groups at C-5 and -5’, which shows potent cytotoxic activity toward several cancer cell lines, with IC50 values in the range of 0.01 to 98 ng/mL. The compounds (9R,14S)-epoxy-11-deoxyxifunicone (102) and (9S,14R)-epoxy-11-deoxyxifunicone (103) have been obtained from co-cultivation of Streptomyces fradiae 007 and Penicillium sp. WC-29-5 [64]. A racemic mixture of enantiomers 102 and 103 has been separated with chiral chromatography. Compound 102 inhibits H1975 cells, with an IC50 value of 3.97 μM, and compound 103 inhibits HL-60 and H1975 cells, with IC50 values of 3.73 and 5.73 μM, respectively. Deep-sea-derived Streptomyces lusitanus SCSSIO LR32 has been found to produce a new angucycline glycoside, designated grincamycin H (104), which is cytotoxic toward Jurkat T cells, with an IC50 value of 3.0 μM [65]. Two new angucycline glycosides, grincamycin I (105) and grincamycin J (106), are produced by marine-derived Streptomyces lusitanus SCSSIO LR32 [66]. Compound 105 displays inhibitory activity toward MDA-MB-435, MDA-MB-231, NCI-H460, HCT-116, HepG2, and MCF10A cells, with IC50 values of 10.20, 25.87, 11.87, 8.79, 9.41 and 2.90 μM, respectively, and compound 106 is active toward the same cancer cell lines, with IC50 values of 2.63, 4.68, 5.40, 2.63, 4.80 and 2.43 μM, respectively. A culture of Streptomyces sp. XMA39 has afforded two medermycin-type naphthoquinones, strepoxepinmycin C (107) and D (108); Figure 4), which show cytotoxic activity toward HCT116 cells, with IC50 values of 4.4 ± 0.1 and 2.9 ± 0.1 μM, respectively [67]. Lagumycin B (109) has been discovered from Micromonaspora sp. G039 [68]. Strain G039 has been isolated from a sediment sample collected by PONAR at a depth of 22 m, approximately 3.3 miles off the coast southeast of Cát Bà Peninsula in Vietnam. Compound 109 is cytotoxic to non-cancerous murine ovarian surface epithelial and murine oviductal epithelial cell lines, with IC50 values of 9.80 μM and 10.8 μM, respectively. Investigation of a bacterial strain from the South China Sea, Micromonaspora echinospora SCSSIO 04089, has led to the discovery of homophanathroviridone (110), homophanathridonamide (111) and nenesophanol (112) [69]. Compound 110 shows cytotoxicity toward the SF-268, MCF-7 and HepG2 cell lines, with IC50 values of 5.4 ± 0.4, 6.8 ± 0.3 and 1.4 ± 0.1 μM, respectively. Compound 111 is also active toward SF-268, MCF-7 and HepG2 cell lines, with IC50 values of 7.6 ± 0.9, 10.4 ± 0.5 and 8.1 ± 0.4 μM, respectively. Saccharothrix sp. 10-10 has yielded a new tetacenomycin analogue, saccharothrixone D (113), which exhibits cytotoxicity toward HepG2 cells, with an IC50 value of 7.5 μM [70]. Akazamicin (114), a new aromatic polyketide, has been obtained from the liquid culture of Nonomuraea sp. AKA32 was isolated from deep-sea water collected from a depth of 800 m in Sagami Bay, Japan, and compound 114 shows cytotoxicity toward murine B16 melanoma, Hep G2 and Caco-2 cells, with IC50 values of 1.7, 75 and 185 μM, respectively [71].

2.1.3 Decalin derivatives. Nahuic acid A (115) has been obtained from Streptomyces sp. RJA2928 and found to inhibit SETD8 activity, with an IC50 value of 6.5 μM [72]. Nahuic acids B–E (116–119) have been purified from the same strain, and 116–119 have been found to inhibit SETD8 activity with IC50 values of 27, 41, 76 and 13 μM, respectively [73]. The compound (1α,4α,5c,7β,8β)-5,8a-dimethyl-decahydro-pha-thalene-1,4a,7-triol (120) has been isolated from Streptomyces sp. 0616208 and has shown moderate inhibitory effects toward SMMC-7721 cells [74].

2.1.4 Polyenes. Piericidins C7 (121) and C8 (122) have been obtained from the culture of Streptomyces sp. YM14-060 isolated from unidentified greenish ascidians
Figure 4 | Structures of compounds 108–148.
collected at Iwayama Bay, Palau [75]. Compounds 121 and 122 show cytotoxicity toward RG-E1A-7 and Neuro-2a cells, with IC50 values of 1.5 and 0.83, and 0.21 and 0.45 nM, respectively. A new nitro-tetraene spiro-β-lactone-γ-γ-lactam, lajollamycin (123), has been isolated from Streptomyces nodosus (NPS007994) [76]. The strain NPS007994 has been isolated from a marine sediment sample collected at Scripps Canyons, La Jolla, California. Compound 123 exhibits cytotoxic activity toward the B16-F10 cell line, with an EC50 value of 9.6 μM. Piericidin F (124) has been isolated from the fermentation broth of Streptomyces sp. CHQ-64 and has shown cytotoxicity toward HeLa, NB4, H1975 and A549 cell lines, with IC50 values of 3, 37, 490 and 560 nM, respectively [77].

Four new pyrones, PM050514 (125), PM050463 (126), PM060054 (127) and PM060431 (128), have been isolated and identified from Streptomyces albus (Por-04-15-053. Compounds 125 and 128 show strong inhibition against MDA-MB-231, HT-29 and A549 cells, with IC50 values ranging from 0.24–0.69 μM [78]. Glucopiericidin C (129) has been isolated from an extract of a cultured Streptomyces sp. B8112 and found to display a concentration-dependent cytotoxicity toward a panel of 36 human tumor cell lines, with a mean IC50 of 2.0 μM (mean IC50 1.6 μM). [79]. Pterocidin (130) has been isolated and identified from Streptomyces sp. TP-A0879 isolated from a sediment sample collected at a depth of 44.5 m in Ottsu Bay, Iwate, Japan by using the Smith–McIntyre isolation method [80]. Compound 130 exhibits cytotoxic activity toward 26-L5 cells, with an IC50 value of 0.25 μM. Succinilenne A (131) has been identified from Streptomyces strain SAK1 collected in the southern area of Jeju Island, Republic of Korea [81]. Compound 131 shows cytotoxicity toward SNU638 cells, with an IC50 value of 12.1 μg/mL (27.6 μM). The compound (2E,4Z,6E,8Z)-5,9-dimethyl-10-oxodec-2,4,6,8-tetraenoic acid (132), a polyunsaturated acid, has been obtained from the liquid culture of Streptomyces violans HTTA-F0412 and has shown cytotoxicity toward A2780 cells, with an IC50 value of 4.36 μM [82]. Separacene A (133) has been isolated from Streptomyces sp. SNU210 and found to display weak inhibitory activity toward HCT116 and A549 cells, with IC50 values of 14.0 μg/mL and 37.6 μg/mL, respectively [83].

2.1.5 Other polyketides. Daryamides A (134), B (135) and C (136), and (2E,4E)-7-methylocta-2,4-dienoic acid amide (137) have been discovered from Streptomyces sp. CNQ-085; these compounds exhibit cytotoxicity toward HCT116 cells, with IC50 values of 3.15, 9.99, 10.03 and 21.69 μg/mL, respectively [84]. Streptomyces sp. NPS-643 has yielded the tricyclic polypropionate indoxamycin A (138) and indoxamycin F (139), which exhibit cytotoxicity toward human colon adenocarcinoma HT-29 cells, with IC50 values of 0.59 and 0.31 μM, respectively [85]. Cyclizidines C (140) and D (141), each with a cyclopropane ring, have been isolated from Streptomyces sp. HNA39. Compound 140 shows cytotoxicity toward PC3, HCT116 and ROCK2 cells, with IC50 values of 0.52 ± 0.03, 8.3 ± 0.1 and 7.0 ± 0.8 μM, respectively. Compound 141 is much less active toward PC3 and HCT116 cells, with IC50 values of 33± 1 and 40 ± 1 μM, respectively [86].

A new hydroxamate derivative, MBJ-0003 (142), has been isolated from Micromonospora sp. 29867 and has shown cytotoxic activity toward the SKOV-3 cell line, with an IC50 value of 11 μM [87]. Paulomycin G (143) has been discovered from Micromonospora matsumotoensense M-412 isolated from Cantabrian Sea sediments collected at 2,000 m depth; this compound exhibits cytotoxicity toward pancreatic adenocarcinoma (MiaPaca2), MCF-7 and HepG2 cells, with IC50 values of 2.70, 1.58 and 4.30 μM, respectively [88]. An extract of Verrucosipora sp. SCSIO 07399 has yielded three new kendomycin analogues, kendomycins B–D (144–146) [89]. Compounds 144–146 are macrocyclic polyketides, each containing a benzofuran-(6(2H)-one connected to a tetrahydropyran moiety at C-4 of benzofuran-(6(2H)-one). One compound 144–146 shows cytotoxicity toward MGC803, A549, HeLa, HepG2, MCF-7 and KRO cells, with IC50 values ranging from 2.2 to 44 μM.

Among these 146 polyketides (1–146), compounds 3 [12], 6–8 [14], 55 [38], 73–76 [49], 81 [53], 101 [63], 121 and 122 [75], and 124 [77] show substantial cytotoxicity, with IC50 values at the ng/mL (or nM) level. Compounds 1, 2, 9, 10, 93, 101, 123, 140, 141 and 144–146 are structurally interesting. Notably, compound 101 is not only structurally unique but also cytotoxically potent. The structure of compound 101 is complex, and this molecule shows promise in anticancer drug development.

2.2 Non-ribosomal peptides and hybrids of polyketides and peptides

Streptomyces sp. LS298, obtained from the marine sponge Geilliodes carnosa, has produced a new analogue of echinomycin, quinomycin G (147), an octapeptide (Val-Cys-Ala-Ser-Val-Cys-Ala-Ser) cyclized between cysteine moieties with two quinoxalines attached to serine moieties [90]. Compound 147 shows cytotoxicity toward ACHN, 786-O, U87 MG, Jurkat, SW1990, HepG2, MDA-MB-231 and A549 cells, with IC50 values of 5.52, 0.721, 0.827, 0.414, 2.56, 4.75, 5.17, 8.16 and 3.90 μM, respectively [91]. Streptomyces sp. SB7348 from the Mediterranean sponge Petrosia fici-formis has yielded a new cyclic dipeptide (hypogallate-Orn-Leu), petrocidin A (148), which exhibits cytotoxicity toward HT-29 and HL-60 cells, with IC50 values of 5.3 and 3.9 μg/mL, respectively [91]. Streptomyces sp. SNJ013 isolated from a deep-sea sediment collected off Jeju Island, Korea, has produced a new lasso peptide, sungsanpin [149, Figure 5] [92]. Compound 149 contains 15 amino acid units, composed of an eight-amino-acid macrocyclic ring (8-8-Gly-Phe-Gly-Ser-Lys-Pro-Ile-Aspβ9) and a seven-amino-acid chain (88-Ser-Phe-Gly-Leu-Ser-Trp-Leu15). Compound 149 displays inhibitory activity in cell invasion assays toward the human lung cancer cell line A549. The cyclic peptides omhyungasamycins A
(150) and B (151) have been found to be produced by Streptomyces sp. SNJ042 isolated from Shinyang Beach on Jeju Island [93]. Compounds 150 and 151 each contain 12 amino acid units with 10 amino acids in the ring (10-11Val-Phe-Val-Trp-Val-Leu-Val-Thr-Thr) and two on the side chain (11Val-Val). Compound 150 exhibits cytotoxic effects against HCT116, A549, SNU-638, MDAMB-231 and SKHEP-1 cells, with IC\textsubscript{50} values of...
G2 cell lines, with IC50 values of 1.73 ± 0.9, 6.44 ± 0.6 μM, respectively. A new cyclic lipopeptide, iturin A6 (M, respectively. A new cyclic hexapeptide, nocardiotide A (154), has been isolated from Streptomyces sp. SSA 13 isolated from the Arabian Sea [95]. Compound 154 is a cyclic lipopeptide containing a C16-β-amino fatty acid chain attached to a hydrophilic heptapeptide ((fatty acid)CO-Asn-Tyr-Asn-Gln-Pro-Asn-Ser-NH(amide) of seven α-amino acids. Compound 154 displays cytotoxicity toward HeLa, MCF-7 and Hep-G2 cell lines, with IC50 values of 1.73 ± 0.9, 6.44 ± 0.6 and 8.9 ± 1.09 μg/mL, respectively. Three new 2,5-diketopiperazines, 3-(3-hydroxy-4-methoxybenzyl)-6-isobutyl-2,5-diketopiperazine (155), 3-(1,3-benzodioxol-5-yl-methyl)-6-isobutyl-2,5-diketopiperazine (156) and 3-(1,3-benzodioxol-5-ylmethyl)-6-isopropyl-2,5-diketopiperazine (157), have been obtained from Streptomyces sp. MNU FJ-36 [96]. All three new compounds, 155–157, exhibit cytotoxic activity toward A-549 cells, with IC50 values of 89.4, 35.4 and 28.4 μg/mL, respectively. Compounds 156 and 157 inhibit the growth of HCT116 cells, with IC50 values of 75.4 and 45.4 μg/mL, respectively. The compounds (S)-6-(sec-butyl)-3-isopropylpyrazin-2(1H)-one (158) and (S)-6-(sec-butyl)-3-isobutylpyrazin-2(1H)-one (159) have been discovered from a tunicate-derived strain, Streptomyces sp. Did-27, and found to exhibit cytotoxicity toward HCT-166 cells with the same IC50 value of 30 μg/mL [97]. Compounds 158 and 159 show inhibitory effects toward MCF-7 cells, with IC50 values of 25 and 35 μg/mL, respectively. A new cyclic hexapeptide, nocardiotide A (160), has been isolated from the culture broth of Nocardiopsis sp. UR67 associated with the marine sponge Callyspongia sp. from the Red Sea [98]. However, the configuration of the amino acids in 160 has not been determined. Compound 160 inhibits the growth of human Hepa liver carcinoma, murine CT26 colon carcinoma and human MM.15 multiple myeloma cell lines, with IC50 values of 11, 12 and 8 μg/mL, respectively. Investigation of Nocardiopsis luenctensis CNR-712 has led to the discovery of two new 3-methyl-4-ethylideneproline-containing (Leu/Trp-Pro-HomoArg) tripeptides, lucentamycins A and B (161 and 162), which show cytotoxicity toward the HCT-116 cell line, with IC50 values of 0.20 and 11 μM, respectively [99]. Two tyrosine-derived diketopiperazines, nocazines F (163) and G (164), have also been obtained by culture of Nocardiopsis sp. YIM M13066 [100]. Compound 163 is cytotoxic to H1299, HeLa, HL7702, MCF-7, PC3 and U251 cells, with IC50 values of 3.87, 4.47, 7.10, 3.86, 8.17 and 22.5 μM, respectively, and compound 164 shows cytotoxicity toward H1299, HeLa, HL7702, MCF-7 and PC3 cells, with IC50 values of 2.60, 3.97, 8.73, 6.67 and 16.7 μM, respectively. Two new peptatibols, microbactin A (165) and B (166), have been obtained from Microbacterium sediminis sp. nov. YLB-01(T) [101]. Compound 165 is toxic toward HCT-8, Bel-7402, BGC-823, A549 and A2780 cells, with IC50 values of >10, 1.98, 2.11, 2.30 and >30 μM, respectively. Compound 166 displays cytotoxicity toward the same cell lines, with IC50 values of 5.93, 1.94, 1.03, 2.08 and 3.79 μM, respectively. Streptomyces sp. CNQ-593, isolated from a sediment sample collected at a depth of approximately 20 m near the island of Guam, has yielded three hexadepsipeptides (AMDA-γOHpip-HAA-αMeserγOHpip-γCipip), piperazimycins A–C (167–169) [102]. Compounds 167–169 exhibit cytotoxicity toward HCT-116 cells, with the same GI50 value of 76 ng/mL. Compound 167 also displays significant cytotoxicity toward 60 tumor cell lines. One 15-membered depsipeptide, rakicidin D (170), has been isolated from Streptomyces sp. MWV064 from a marine sediment sample collected in Samut Sakhon province, Thailand [103]. Compound 170 contains an N-Me glycine moiety, a β-hydroxyasparagine moiety, 2,4-dimethyl-3-hydroxydecanoic acid moiety and γ-amino-2,4-pentadienoic moiety. However, the stereochemistry of compound 170 has not been investigated. Compound 170 shows cytotoxicity toward murine carcinoma colon 26-L5 cells, with an IC50 value of 6.7 μM. Two newly modified linear tetrapeptides, padanamides A (171) and B (172), have been isolated from Streptomyces sp. RJA2928 [104]. Compound 171 is composed of a 2-methoxyacetic acid (Maa), 3-hydroxyleucine (Hleu), piperazic acid (Pip), 4-amino-3-hydroxy-2-methyl-5-phenylpentanoic acid (Ahpmp) and 3-amino-2-oxypyrrolidine-1-carboxamide (Aopc) residue. Compound 172 is almost the same as 171 except for an Aopc in 172 instead of an Aopc in 171. Compounds 171 and 172 show weak antioxidant activity toward Jurkat T lymphocyte cells (ATCC TIB-152), with IC50 values of 60 and 20 μg/mL, respectively. A new thiodepsipeptide, verrucosamide (173), has been isolated from Verrucosispora sp. CNX-026 [105]. Compound 173 is a cyclic octapeptide ((cyclo-(Gly-Cys-Ala-Cys-Gly-Cys-Ala-Cys-Gly)) connected to two 3-hydroxyquininal acid moieties. Compound 173 shows activity toward MDA-MB-468 breast carcinoma and COLO 205 colon adenocarcinoma cells, with LD50 values of 1.26 and 1.4 μM. Compound 173 displays moderate cytotoxicity toward NCI 60.

Among these 27 non-ribosomal peptides and hydribs of polyketides and peptides (147–173), compounds 167–169 show potent cytotoxicity, with IC50 values at ng/mL (nM) levels. In the past few decades, scientists have been overcoming the well-known limitations of bioactive...
peptides as therapeutics. More peptides or peptide derivatives have been approved for clinical use. Hence, these three cyclic peptides (167–169), each with three piperezic acid units, are worthy of further investigation.

2.3 Isoprenoids, terpenoids, sterols and hybrids of isoprenoids and peptides (or polyketides)

A new sesquiterpene, 15-hydroxy-T-muurolol (174), produced by Streptomyces sp. M491, has been found to exhibit weak cytotoxic effects toward 37 human tumor cell lines, with a mean IC50 value of 6.7 μg/mL [106]. A new ergosterol, ananstrep C (175), has been isolated from Streptomyces anandii H41-59 and found to display cytotoxic activity toward SF-268, MCF-7 and NCI-H460 cells, with IC50 values of 13.0, 18.1 and 23.5 μg/mL, respectively [107]. The culture of Actinomadura sp. SBSm009 has afforded a 3-keto sterol compound, bendigole D (176), which shows cytotoxic activity toward L929 cells, with an IC50 value of 30 μM [108].

Streptomyces sp. NBRCl05896 has been found to produce a new teleocidin analog, JBI-R31 (177) [109]. Compound 177 is composed of a monoterpenoid moiety, N-methyl valine moiety and tryptophan moiety. Compound 177 displays cytotoxicity toward HeLa and ACC-MESO-1 cells, with IC50 values of 49 and 88 μM, respectively. Streptomyces sp. CHQ-64 has been found to produce drimentine I (178) [110]. Compound 178 is a hybrid of a sesquiterpenoid and a diketopiperazine (ValTrp), possessing a rare heptacyclic skeleton. Compound 178 shows cytotoxicity toward HeLa cells, with an IC50 value of 16.73 μM.[110]

Streptomyces sp. CNQ-027 has afforded a new mero-

2.4 Heterocyclic, (hetero)aromatic and other compounds

Two new 3,6-disubstituted indoles (196 and 197) have been obtained from Streptomyces sp. BL49-58-005 [117]. Compound 196 shows cytotoxicity toward the KS62 cell line, with a GI50 value of 8.46 μM. Compound 197 exhibits activity with GI50 values within the micromolar range against LN-caP, HMEC1, K-562, PANC1, LOVO and LOVO-DOX, and slightly higher values against other tumor cell lines, without any particular specificity. A 10H-phenoxyazaine derivative, strepoxazine A (198), has been identified from the solid culture of Streptomyces sp. SBT345 and found to exhibit cytotoxicity toward HL-60, with an IC50 of 8 μM [118]. Two pentacyclic indoloseriqui-

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Figure 6 | Structures of compounds 183–242.
Compounds Streptomyces sp. CNQ-418, also produces marinopyrrole-fused indole alkaloids, spiroindimicins B–D (221–223) [130]. Strain SNA-020 has been isolated from a sediment sample collected at Sweetings Cay, Bahamas. Compound 226 displays cytotoxic activity toward Mia PaCa-2 cells, with an IC$_{50}$ value of 3.2 µM. Streptocarbazoles A and B (227 and 228) have been isolated from Streptomyces sp. FMA [134]. Compounds 227 and 228 are staurosporine analogs with differences at C-3–C-5 in the amino sugar moiety. Compound 227 shows cytotoxicity toward HL-60, A549, P388 and Hela cell lines, with IC$_{50}$ values of 1.4, 5.0, 18.9 and 34.5 µM, respectively. Compound 228 is active toward P388 and Hela cell lines, with IC$_{50}$ values of 12.8 and 22.5 µM. An aminophenoxazine alkaloid, maroxazinone (229), has been discovered from Streptomyces sp. Eg25, and shown activity against MCF-7, HEPG-2 and HCT-116 cells, with IC$_{50}$ values of 4.32, 2.90 and 8.51 µg/mL, respectively [135]. Streptomyces niveus SCSIO 3406 has produced two new geranylated phenazines, phenaziterpene A (230) and phenaziterpene B (231). [113] Compounds 230 and 231 are hybrids of a monoterpenoid and a phenazine moiety, probably derived from choricomic acid. Both 230 and 231 show cytotoxicity toward SF-268, MCF-7 and HEPG-2 cells, with IC$_{50}$ values ranging from 10.2 to 52.7 µM, and 230 is weakly active toward NCI-H460, with an IC$_{50}$ value of 68.9 µM. Streptomyces sp. CNS284 has afforded two phnazinones (232 and 233), which induce apoptosis in HL-60 cells [136]. Two new hexahydro-1H-pyrrolizine dimers, dibohemamines B and C (234 and 235), have been isolated from an extract of a cultured marine-derived Streptomyces spinoverrucosus SNB-032 [137]. Compounds 234 and 235 exhibit cytotoxic activity toward the A549 cell line, with IC$_{50}$ values of 0.140 and 0.145 µM, respectively. Compounds 234 and 235 also show inhibitory activity toward HCC1171 cells, with IC$_{50}$ values of 3.9 and 1.2 µM, respectively. In addition, compounds 234 and 235 inhibit HCC44 and HCC566 cells, respectively, with IC$_{50}$ values of 12.0 and 6.7 µM, respectively. An unique molecule composed of a pyrrolo[2,1-a]isoindole and a pyrrolizine moieties, chlorizidine A (236), has been isolated from Streptomyces sp. CNH-287.
and found to inhibit HCT-116 cells, with an IC50 value of 3.2–4.9 μg/mL [138]. Four new cyclic bipyridine glycosides, cyanogriseids E–H (237–240), have been isolated from Actinomalloteichus cyanogriseus WH1-2216-6 [139]. Compounds 237 and 240 show cytotoxicity toward K562 cells, with IC50 values of 6.0 and 0.8 μM, respectively. Compounds 238 and 239 inhibit A549, K562, HeLa, HCT116 and HL-60 cells, with IC50 values of 33.1/42.0, 13.6/23.6, 26.5/44.1, 0.8/3.6 and 3.1/2.0 μM, respectively. Saccharomonospora sp. UR66 co-culture [140]. Compound 241 is a brominated oxo-indole alkaloid connected to a 4-methoxy (hetero)aromatic and other (hetero)aromatic moieties.

3. CONCLUSION

From 1989 until the end of 2020, 254 new cytotoxic compounds have been obtained from marine actinomycetes. This review summarized the structures, strain sources, and cytotoxicity of these secondary metabolites (Table 1). Most of the compounds (206) were reported from 2010 to 2020 (Figure 8). The numbers of newly reported compounds have increased since 1989, peaked in the mid-2010s (2013–2017) and decreased in the following years. However, we expect the numbers to increase after the COVID-19 pandemic ends. Of these 254 compounds, most are moderately active, but approximately 20 compounds show potent cytotoxicity with IC50 values at the ng/mL/nM level (see the Prospects section). The articles reporting these compounds have been published in 30 different journals, and the “Journal of Natural Products” (72) published more articles than any other single journal, followed by “Marine Drugs” (36), “Organic Letters” (27), the Journal of Antibiotics” (21), and the “Journal of Organic Chemistry” (18; Figure 9). Interestingly, beyond these prominent natural-product journals, “Phytochemistry” published seven articles, although it is a peer-reviewed scientific journal covering pure and applied plant chemistry, plant biochemistry and molecular biology. This review classified the compounds into four classes: polyketides; non-ribosomal peptides, and hybrids of polyketides and peptides; isoprenoids, terpenoids, steroids, and hybrids of isoprenoids and peptides (or polyketides); and heterocyclic, (hetero) aromatic and other compounds. These cytotoxic compounds have diverse chemical structures, and most are polyketides (146) making up 58% of the 254 new antitumor compounds (Figure 10). Among these 146 polyketides, most are categorized as either macrolides (lactones), lactams and α/γ-pyrones (57), or benzoquinones, naphthoquinones, anthraquinones and other aromatic compounds (57), which together accounted for 45% of the total 254 compounds.

Figure 7 | Structures of compounds 243–254.
| Compound | Producing strain | Strain source | Architectural feature | References |
|----------|-----------------|---------------|----------------------|------------|
| 1-2      | *Streptomyces carnosus* AZS17 | Coastal waters of the East China Sea | Polyketides | [11] |
| 3        | *Streptomyces* sp. PG-19 | Surface of the Sea of Cortez gorgonian octocoral *Pacifigorgia* sp. | Polyketides | [12] |
| 4-5      | *Streptomyces caniferus* GUA-06-05-006A | Marine-derived culture broth | Polyketides | [13] |
| 6        | *Streptomyces* sp. GIC10-1 | Marine sponge collected off the coast of Kenting, Taiwan | Polyketides | [14] |
| 7-8      | *Streptomyces* sp. GIC10-1 | Bacterial communities associated with the marine sponge *Theonella* sp. | Polyketides | [15] |
| 9        | *Streptomyces* sp. M-207 | Cold-water coral *Lophelia pertusa* | Polyketides | [16] |
| 10       | *Streptomyces* sp. SCSIO 01127 | South China Sea sediment | Polyketides | [17] |
| 11-12    | *Streptomyces* sp. | Crown-of-thorns starfish, *Acanthaster planci* | Polyketides | [18] |
| 13       | *Nocardiopsis* sp. NHF48 | South China Sea sediments | Polyketides | [19] |
| 14-17    | *Streptomyces* sp. HKI0576 | Marine sediment | Polyketides | [20] |
| 18       | *Streptomyces aureoverticillatus* NPS001583 | Traditional Chinese medicine sea lettuce *Ulva pertusa* (family Ulvaceae) | Polyketides | [21] |
| 19-20    | *Streptomyces* sp. HZP-2216E | Intertidal seaweed *Ulva* sp., Cantabrian Sea (Northeast Atlantic Ocean) | Polyketides | [22] |
| 21       | *Streptomyces althioticus* MSM3 | Mangrove soil from Sanya | Polyketides | [23] |
| 22       | *Streptomyces* sp. 219807 | Surface sediment from the East Siberian continental margin | Polyketides | [24] |
| 23       | *Streptomyces* sp. ART5 | Conserved mangrove in Hainan province, China | Polyketides | [25] |
| 24-27    | *Streptomyces* sp. THS-55 | Sea sediment from a mangrove in the South China Sea | Polyketides | [26] |
| 28-29    | *Streptomyces antibioticus* H12-15 | Deep-sea sediment from the West Pacific | Polyketides | [27] |
| 30-32    | *Streptomyces* sp. DSS-18 | Marine sediment from the east coast of Madagascar, 30 m depth | Polyketides | [28] |
| 33       | *Streptomyces* sp. MDG-04-17-069 | Mangrove rhizosphere soil | Polyketides | [29] |
| 34-35    | *Streptomyces* sp. 211726 | Mangrove broth | Polyketides | [30] |
| 36-42    | *Streptomyces* sp. 211726 | Estuary between the Yellow Sea and the Han River, Republic of Korea | Polyketides | [31] |
| 43-48    | *Streptomyces pactum* SCSIO02999 | Cloacal aperture of the sea cucumber *Holothuria moebii* | Polyketides | [32] |
| 49-50    | *Pseudomonascia* sp. HS7 | Saltpan of Kenada | Polyketides | [33] |
| 51       | *Nocardiopsis* CG3 (DSM 106572) | Soil sample from the East China Sea | Polyketides | [34] |
| 52-54    | *Micromonospora* strain FIM05328 | Shallow coastal waters near the island of Chiloe, Chile | Polyketides | [35] |
| 55       | *Actinoalloteichus cyanogriseus* WH1-2216-6 | Submarine sediment | Polyketides | [36] |
| Compound | Producing strain | Strain source | Architectural feature | References |
|----------|------------------|---------------|----------------------|------------|
| 58       | *Streptomyces* sp. Sp080513GE-26 | *Haliclona* sp. marine sponge | Polyketides | [39] |
| 59       | *Streptomyces* sp. SpD081030ME-02 | Demospongiaceae class of marine sponge, offshore of Ishigaki City, Okinawa Prefecture, Japan | Polyketides | [40] |
| 60       | *Streptomyces* sp. HB202 | *Halichondria panicea* sponge | Polyketides | [41] |
| 61–63    | *Streptomyces* sp. BCC45596 | Thailand | Polyketides | [42] |
| 64–66    | *Streptomyces* sp. M7_15 | Caribbean sponges | Polyketides | [43] |
| 67–68    | *Streptomyces* sp. OUCMDZ-1703 | Soft coral | Polyketides | [44] |
| 69       | *Streptomyces* sp. HDN-10-293 | Sponge | Polyketides | [45] |
| 70       | *Streptomyces* sp. RKBHB7 | *Eunicea* sp. unidentified octocoral | Polyketides | [46] |
| 71–72    | *Streptomyces* sp. ZZ406 | *Haliplanella lineata* sea anemone | Polyketides | [47] |
| 73–76    | *Streptomyces* sp. (CANU Fox 21-2-6) | New Zealand micro-organisms | Polyketides | [48] |
| 77       | *Streptomyces* sp. FX-58 | *Salicornia herbacea* | Polyketides | [49] |
| 78       | *Streptomyces* sp. B8652 | Polyketides | [50] |
| 79–80    | *Streptomyces* sp. M045 | Marine sediments | Polyketides | [51] |
| 81–82    | *Streptomyces* sp. CNH990 | Marine sediments | Polyketides | [52] |
| 83–85    | *Streptomyces* sp. NPS853 | Marine sediments | Polyketides | [53] |
| 86       | *Streptomyces* sp. W007 | Polyketides | [54] |
| 87–90    | *Streptomyces* lusitanus SCSIO LR32 | Marine sediments from South China Sea | Polyketides | [55] |
| 91–92    | *Streptomyces* sp. (strain SNE-011) | Sediment sample from Kiawah Island, South Carolina, | Polyketides | [56] |
| 93       | *Streptomyces* H74-21 | Sea sediment in a mangrove site | Polyketides | [57] |
| 94       | *Streptomyces* sp. SCSIO 11594 | South China Sea sediment, 2,403 m depth | Polyketides | [58] |
| 95–96    | *Streptomyces* sp. IFM11940 | Soil and seawater samples from different areas of Japan. | Polyketides | [59] |
| 97–98    | *Streptomyces* sp. 182MMLY | Marine sediments | Polyketides | [60] |
| 99       | *Streptomyces* sp. F001 | Polyketides | [61] |
| 100      | *Streptomyces griseus* MZ68 | Sediment from Kiaochow Bay, China | Polyketides | [62] |
| 101      | *Micromonospora lomaivitenensis* LL-371366 | Polyketides | [63] |
| 102–103  | *Streptomyces fradiae* 007 | Polyketides | [64] |
| 104      | *Streptomyces lusitanus* SCSIO LR32 | Deep sea | Polyketides | [65] |
| 105–106  | *Streptomyces lusitanus* SCSIO LR32 | Deep sea | Polyketides | [66] |
| Compound | Producing strain | Strain source | Architectural feature | References |
|----------|------------------|---------------|----------------------|------------|
| 107–108  | *Streptomyces* sp. XMA39 | | Polyketides | [67] |
| 109      | *Micromonaspora* sp. G039 | Sediment from the Cát Bà peninsula, East Sea of Vietnam | Polyketides | [68] |
| 110–112  | *Micromonaspora* echinospora SCSIO 04089 | Sediment from the northern South China Sea, 3,025 m depth | Polyketides | [69] |
| 113      | *Sacchararthrix* sp. 10-10 | | Polyketides | [70] |
| 114      | *Nanomurea* sp. AKA32 | Deep-sea water from Sagami Bay, Japan, 800 m depth | Polyketides | [71] |
| 115      | *Streptomyces* sp. RJA2928 | | Polyketides | [72] |
| 116–119  | *Streptomyces* sp. RJA2928 | | Polyketides | [73] |
| 120      | *Streptomyces* sp. 0616208 | | Polyketides | [74] |
| 121–122  | *Streptomyces* sp. YM14-060 | | Polyketides | [75] |
| 123      | *Streptomyces* nodosus NPS007994 | Marine sediment from Scripps Canyon, La Jolla, California | Polyketides | [76] |
| 124      | *Streptomyces* sp. CHQ-64 | | Polyketides | [77] |
| 125–128  | *Streptomyces* albus POR-04-15-053 | Extracts of the air-breathing gastropod *Siphonaria diemensis*, a marine mollusk | Polyketides | [78] |
| 129      | *Streptomyces* sp. B8112 | | Polyketides | [79] |
| 130      | *Streptomyces* sp. TP-A0879 | Stem of the bracken *Pteridium aquilinum* | Polyketides | [80] |
| 131      | *Streptomyces* sp. SAK1 | Southern area of Jeju Island, Republic of Korea | Polyketides | [81] |
| 132      | *Streptomyces violans* HTTA-F04129 | *Salicornia* sp. from the intertidal zone of Rushan County, Shandong Peninsula | Polyketides | [82] |
| 133      | *Streptomyces* sp. SNJ210 | Deep-sea areas from Jeju Island, Korea | Polyketides | [83] |
| 134–137  | *Streptomyces* sp. CNQ-085 | Marine sediment sample near Kochi Harbor, Japan, 30 m depth | Polyketides | [84] |
| 138–139  | *Streptomyces* sp. NPS-643 | | Polyketides | [85] |
| 140–141  | *Streptomyces* sp. HNA39 | | Polyketides | [86] |
| 142      | *Micromonaspora* sp. 29867 | Suruga Bay, Shizuoka Prefecture, Japan | Polyketides | [87] |
| 143      | *Micromonaspora matsumotoense* M-412 | Cantabrian Sea sediments, 2,000 m depth | Polyketides | [88] |
| 144–146  | *Verrucosispora* sp. SCSIO 07399 | Deep-sea marine sediment | Polyketides | [89] |
| 147      | *Streptomyces* sp. LS298 | *Gelidiodes carnosa* marine sponge from the South China Sea | Non-ribosomal peptides, and hybrids of polyketides and peptides | [90] |
| 148      | *Streptomyces* sp. SBT348 | *Petrasia ficiformis* Mediterranean sponge from Milos, Greece | Non-ribosomal peptides, and hybrids of polyketides and peptides | [91] |
| Compound | Producing strain       | Strain source                                           | Architectural feature                                             | References |
|----------|------------------------|--------------------------------------------------------|------------------------------------------------------------------|------------|
| 149      | Streptomyces sp. SNJ013| Deep-sea sediment from Jeju Island, Korea              | Non-ribosomal peptides, and hybrids of polyketides and peptides  | [92]       |
| 150–151  | Streptomyces sp. SNJ042| Sand beach at Jeju, a volcanic island in the Republic of Korea | Non-ribosomal peptides, and hybrids of polyketides and peptides  | [93]       |
| 152–153  | Streptomyces sp. P11-23B|                                                       | Non-ribosomal peptides, and hybrids of polyketides and peptides  | [94]       |
| 154      | Streptomyces sp. SSA 13| Arabian Sea sediments from the eastern edge of the seashore | Non-ribosomal peptides, and hybrids of polyketides and peptides  | [95]       |
| 155–157  | Streptomyces sp. MNU FJ-36| Intestinal fabric of *Katsuwonus* sp.                 | Non-ribosomal peptides, and hybrids of polyketides and peptides  | [96]       |
| 158–159  | Streptomyces sp. Did-27| Marine microbial bioactive leads                      | Non-ribosomal peptides, and hybrids of polyketides and peptides  | [97]       |
| 160      | Nocardopsis sp. UR67   | Red Sea                                               | Non-ribosomal peptides, and hybrids of polyketides and peptides  | [98]       |
| 161–162  | *Nocardopsis* lucentensis (strain CNR-712) | Sediment from a shallow saline pond on the island of Little San Salvador, Bahamas. | Non-ribosomal peptides, and hybrids of polyketides and peptides  | [99]       |
| 163–164  | *Nocardopsis* sp. YIM M13066 | Deep sea                                             | Non-ribosomal peptides, and hybrids of polyketides and peptides  | [100]      |
| 165–166  | *Microbacterium sediminis* sp. nov. YLB-01(T) | Deep sea                                             | Non-ribosomal peptides, and hybrids of polyketides and peptides  | [101]      |
| 167–169  | Streptomyces sp. CNQ-593| Marine sediments near the island of Guam              | Non-ribosomal peptides, and hybrids of polyketides and peptides  | [102]      |
| 170      | Streptomyces sp. MWW064| Marine sediment from Samut Sakhon province, Thailand  | Non-ribosomal peptides, and hybrids of polyketides and peptides  | [103]      |
| 171–172  | Streptomyces sp. RJA2928| Crude organic extracts from marine sediment collected near the passage Padana Nahua, Papua New Guinea | Non-ribosomal peptides, and hybrids of polyketides and peptides  | [104]      |
| 173      | *Verrucosispora* sp. CNX-026 |                                                         | Non-ribosomal peptides, and hybrids of polyketides and peptides  | [105]      |
| 174      | *Streptomyces* sp. M491| Sand sample from Qingdao (China)                      | Isoprenoids, terpenoids, sterols, and hybrids of isoprenoids and peptides (or polyketides) | [106]      |
| 175      | *Streptomyces* anandii H41-59| Sea sediment from a mangrove district                | Isoprenoids, terpenoids, sterols, and hybrids of isoprenoids and peptides (or polyketides) | [107]      |
| Compound | Producing strain | Strain source | Architectural feature | References |
|----------|------------------|---------------|----------------------|------------|
| 176      | Actinomadura sp. SBMs009 | New marine sponge | Isoprenoids, terpenoids, sterols, and hybrids of isoprenoids and peptides (or polyketides) | [108]       |
| 177      | Streptomyces sp. NBRC105896 | Haliclona sp. | Isoprenoids, terpenoids, sterols, and hybrids of isoprenoids and peptides (or polyketides) | [109]       |
| 178      | Streptomyces sp. CHQ-64 | | Isoprenoids, terpenoids, sterols, and hybrids of isoprenoids and peptides (or polyketides) | [110]       |
| 179      | Streptomyces sp. CNQ-027 | | Isoprenoids, terpenoids, sterols, and hybrids of isoprenoids and peptides (or polyketides) | [111]       |
| 180–182  | Actinomycete family Streptomycetaceae CNQ-509 | Marine sediment from La Jolla, California | Isoprenoids, terpenoids, sterols, and hybrids of isoprenoids and peptides (or polyketides) | [112]       |
| 183–186  | Streptomyces niveus SCSIO 3406 | South China Sea sediment, 3,536 m depth | Isoprenoids, terpenoids, sterols, and hybrids of isoprenoids and peptides (or polyketides) | [113]       |
| 187–190  | Streptomyces sp. CNQ-329 | | Isoprenoids, terpenoids, sterols, and hybrids of isoprenoids and peptides (or polyketides) | [114]       |
| 191–194  | Actinomycete strain CNQ525 | | Isoprenoids, terpenoids, sterols, and hybrids of isoprenoids and peptides (or polyketides) | [115]       |
| 195      | Streptomyces sp. NPS008187 | Marine sediment from Alaska | Isoprenoids, terpenoids, sterols, and hybrids of isoprenoids and peptides (or polyketides) | [116]       |
| 196–197  | Streptomyces sp. BL-49-58-005 | Unidentified marine invertebrate from Mexico | Heterocyclic, (hetero)aromatic and other compounds | [117]       |
| 198      | Streptomyces sp. SBT345 | Agelas oroides Mediterranean sponge | Heterocyclic, (hetero)aromatic and other compounds | [118]       |
| 199–200  | Streptomyces sp. GT2002/1503 | Stem of Bruguiera gymnorrhiza | Heterocyclic, (hetero)aromatic and other compounds | [119]       |
| 201      | Streptomyces sioyaensis SA-1758 | Sea mud from Gamo, Miyagi Prefecture, Japan | Heterocyclic, (hetero)aromatic and other compounds | [120]       |
| 202      | Streptomyces sp. Q22 | Mangrove soil | Heterocyclic, (hetero)aromatic and other compounds | [121]       |
### Table 1 | Continued

| Compound | Producing strain | Strain source | Architectural feature | References |
|----------|------------------|---------------|----------------------|------------|
| 203      | *Streptomyces* sp. KORDI-3238 | Deep-sea sediment | Heterocyclic, (hetero)aromatic and other compounds | [122] |
| 204-205  | *Streptomyces* sp. CNQ-418 | Marine sediment from La Jolla, California, 51 m depth | Heterocyclic, (hetero)aromatic and other compounds | [123] |
| 206-209  | *Streptomyces* sp. CNQ-418 | Marine sediment from La Jolla, California, 51 m depth | Heterocyclic, (hetero)aromatic and other compounds | [124] |
| 210-211  | *Streptomyces* sp. CNQ-617 | Marine sediment from La Jolla, California, 51 m depth | Heterocyclic, (hetero)aromatic and other compounds | [125] |
| 212-213  | *Streptomyces* sp. CNR-698 | Bahamas | Heterocyclic, (hetero)aromatic and other compounds | [126] |
| 214-216  | *Streptomyces* sp. Mei37 | Muddy sediment from Jade Bay, southern German North Sea coast | Heterocyclic, (hetero)aromatic and other compounds | [127] |
| 217      | *Streptomyces* sp. WuXin | Deep-sea sediment | Heterocyclic, (hetero)aromatic and other compounds | [128] |
| 218-220  | *Streptomyces* fradiae 007M135 | Sediment from Jiaozhou Bay, Shandong Province, China | Heterocyclic, (hetero)aromatic and other compounds | [129] |
| 221-223  | *Streptomyces* sp. SCSIO 03032 | Deep-sea sediment | Heterocyclic, (hetero)aromatic and other compounds | [130] |
| 224      | *Streptomyces* sp. QD518 | Deep-sea sediment | Heterocyclic, (hetero)aromatic and other compounds | [131] |
| 225      | *Streptomyces* sp. SCSIO 03032 | Deep-sea sediment | Heterocyclic, (hetero)aromatic and other compounds | [132] |
| 226      | *Streptomyces* variabilis SNA-020 | Deep-sea sediment | Heterocyclic, (hetero)aromatic and other compounds | [133] |
| 227-228  | *Streptomyces* sp. FMA | Mangrove soil from Sanya, Hainan province, China | Heterocyclic, (hetero)aromatic and other compounds | [134] |
| 229      | *Streptomyces* sp. Eg25 | Deep-sea sediment | Heterocyclic, (hetero)aromatic and other compounds | [135] |
| 230-231  | *Streptomyces* niveus SCSIO 3406 | South China Sea sediment, 3,536 m depth | Heterocyclic, (hetero)aromatic and other compounds | [113] |
| 232-233  | *Streptomyces* sp. CNS284 | Deep-sea sediment | Heterocyclic, (hetero)aromatic and other compounds | [136] |
| 234-235  | *Streptomyces* spinoverrucosus strain SNB-032 | Deep-sea sediment | Heterocyclic, (hetero)aromatic and other compounds | [137] |
| Compound | Producing strain | Strain source | Architectural feature | References |
|----------|------------------|---------------|----------------------|------------|
| Streptomyces sp. strain CNH-287 | Heterocyclic, (hetero)aromatic and other compounds | Red Sea sponge *Callyspongia siphonella* | [138] |
| Actinoboleichos cyanogriseus WH-2216-6 | Heterocyclic, (hetero)aromatic and other compounds | Saint Peter and Saint Paul Archipelago, Brazil | [139] |
| Saccharomonospora sp. UR22 and Dietzia sp. UR66 | Heterocyclic, (hetero)aromatic and other compounds | Sea mud from the coastal area of Putuo, Zhoushan, China | [140] |
| Amycolatopsis sp. | Heterocyclic, (hetero)aromatic and other compounds | Sponge | [142] |
| Actinoalloteichus sp. ZZ1866 | Heterocyclic, (hetero)aromatic and other compounds | Sea mud from the coastal area of Putuo, Zhoushan, China | [143] |

Marine actinomycetes produce different biologically active secondary metabolites. In 2012, Subramani and Aalbersberg published an article in "Microbiological Research" indicating that marine actinomycetes are an ongoing source of novel bioactive metabolites [144]. In 2009, a review article reported antitumor compounds from marine actinomycetes [145]. In 2020 and 2021, we reported the sources of marine actinomycetes, chemical structures and biological activities of 127 halogenated compounds and 313 antimicrobial compounds from multiple marine actinomycetes [146, 147]. Marine actinomycetes are a promising source of lead compounds for drug discovery.

Despite the discovery of many cytotoxic compounds from marine actinomycetes, several drawbacks of natural product anticancer drug discovery exist. Some cytotoxic compounds have been obtained through assay-guided separation, but in many cases, no assay-guided separation was performed, and cytotoxic compounds were identified simply through purification followed by cytotoxic evaluation. Most of the cytotoxic compounds have not been tested for their selectivity toward different cancer cell lines and normal human cell lines, mainly because of insufficient financial support to researchers. Bioassay-guided separation is sometimes very tedious, and dereplication does not always work well, as researchers expect. Because naturally occurring compounds in their original forms may not always be patentable in the USA, although simple derivatives can be patent protected, natural product chemists' enthusiasm for anticancer drug discovery from natural sources has been diminished.

Selection of strains, culturing strategies and analytical techniques for natural-product-library establishment and natural-product dereplication will be of great help in anticancer drug discovery from marine actinomycetes. A future direction may involve advancing genome mining and gene manipulation, as discussed below.

### 4. PROSPECTS

Some of the reviewed compounds have demonstrated potent cytotoxic activity, with IC₅₀ values at ng/mL or nM levels, for example, compounds 3 [12], 6–8 [14], 55 [38], 73–76 [49], 81 [53], 101 [63], 121 and 122 [75], 124 [77], 167–169 [102], 212 and 213 [126], 216 [127] and 224 [131]. However, the selectivity of some potent cytotoxic compounds has not been investigated. Selectivity study is important, because identifying cytotoxic drugs with a high selectivity toward cancer cells is critical to increase the low survival rates of patients with cancer. One approach to avoiding adverse effects of cytotoxic agents is targeted drug delivery. For instance, a cytotoxic drug can be hung on an antibody scaffold to form an antibody–drug conjugate. Subsequently, the complex targeted agent can overcome the unspecific toxic effects of conventional drug delivery, thereby decreasing the amount of drug required for therapeutic efficacy.
Figure 8 | Numbers of antitumor compounds isolated from marine actinomycetes each year (1989 to 2020).

Figure 9 | Journals publishing, and numbers of articles describing, antitumor compounds from marine actinomycetes.
Most of the secondary metabolites reviewed herein have been evaluated for their antimicrobial and cytotoxic activities. Other biological properties could be identified through testing of actinomycete secondary metabolites in other biological settings. For example, the fungal metabolites sinuxylamides A and B have shown no antibacterial activity or cytotoxicity at 40 μM, but when tested for their antithrombotic activity, have demonstrated strong inhibition of the binding of fibrinogen to purified integrin IIb/IIIa in a dose-dependent manner, with IC50 values of 0.89 and 0.61 μM, respectively [148].

Novel molecules with unprecedented structural and/or functional attributes usually have unique bioactivities. Some of the reviewed compounds in this article have unique structures, for example, compounds 1, 2, 9, 10, 23, 101, 123, 140, 141, 144–146 and most of the compounds classified as heterocyclic, (hetero)aromatic and other compounds (196–254). Compounds 101, 212, 213 and 224 are not only structurally interesting (particularly 101) but also exhibit potent cytotoxicity. The cytotoxicity of 101 arises from the induction of double-strand breaks in DNA [149]. Compound 101 has a molecular formula of C38H26N4O14. Its molecular weight is 762 Daltons, and the numbers of hydrogen-bond donors and acceptors in the molecule clearly violate Lipinski’s role of five; these findings, together with the compound’s structural complexity, suggest low druggability of 101. However, structural modification and/or formulation have made many undruggable compounds druggable. For example, halichondrin B (molecular formula: C60H86O19; molecular weight: 1111 Daltons) is a complex polyether macrolide originally isolated from the marine sponge Halichondria okadai [150], which was believed to be undruggable by many researchers. However, Eisai Co. has structurally simplified halichondrin B, and eribulin (brand name Halaven) was approved by the U.S. Food and Drug Administration on November 15, 2010, with an indication to treat metastatic breast cancer [151].

Most of these 254 compounds are analogs of previously reported molecules. In general, structurally unique compounds represent a decreasing percentage of the total number of compounds isolated from natural sources in the past few decades. However, exploring unexplored and unusual source organisms, or those from unique environments, could provide opportunities for finding novel natural products.

Currently, the genomes of actinomycete strains are routinely sequenced, and a host of bioinformatics tools are increasingly available for identifying potential biosynthetic gene clusters of actinomycete natural products. Developing universal expression systems for small-molecule biosynthesis with high yield, constructing genetic tools to access the biosynthetic potential of cultured marine actinomycetes and awakening “silent” biosynthetic pathways will be important approaches for discovery of small molecules from marine actinomycetes. Investigations aimed at understanding how the biosynthetic pathways operate at the genetic and biochemical levels in marine actinomycetes will open new doors to designing molecules with improved anticancer properties.

![Figure 10 | Structural classes of antitumor compounds from marine actinomycetes.](image-url)
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