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Review Article

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 IC_{50} 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 (E7389, Halaven®), trabectedin (ET-743, Yondelis®), panobinostat (Farydak®), plitidepsin (Aplidin®), lurbinectedin (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 enediynes, 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 antitumor 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 α/γ-pyrones. Two new kijanimicin derivatives, lobophorins C (**1**) and D (**2**), have been purified from *Streptomyces carnosus* AZS17 (**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 liver 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 naphthoquinone 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. GIC10-1, 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 bafilomycins N (**7**) and O (**8**) have been obtained from *Streptomyces* sp. GIC10-1 [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. SCSIO 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 α-pyrone 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. *Nocardiopsis* sp. NHF48 has been found to produce a new α-pyrone 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 (RXF 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 tetraene 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 althioticus* 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 elaiophylin 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

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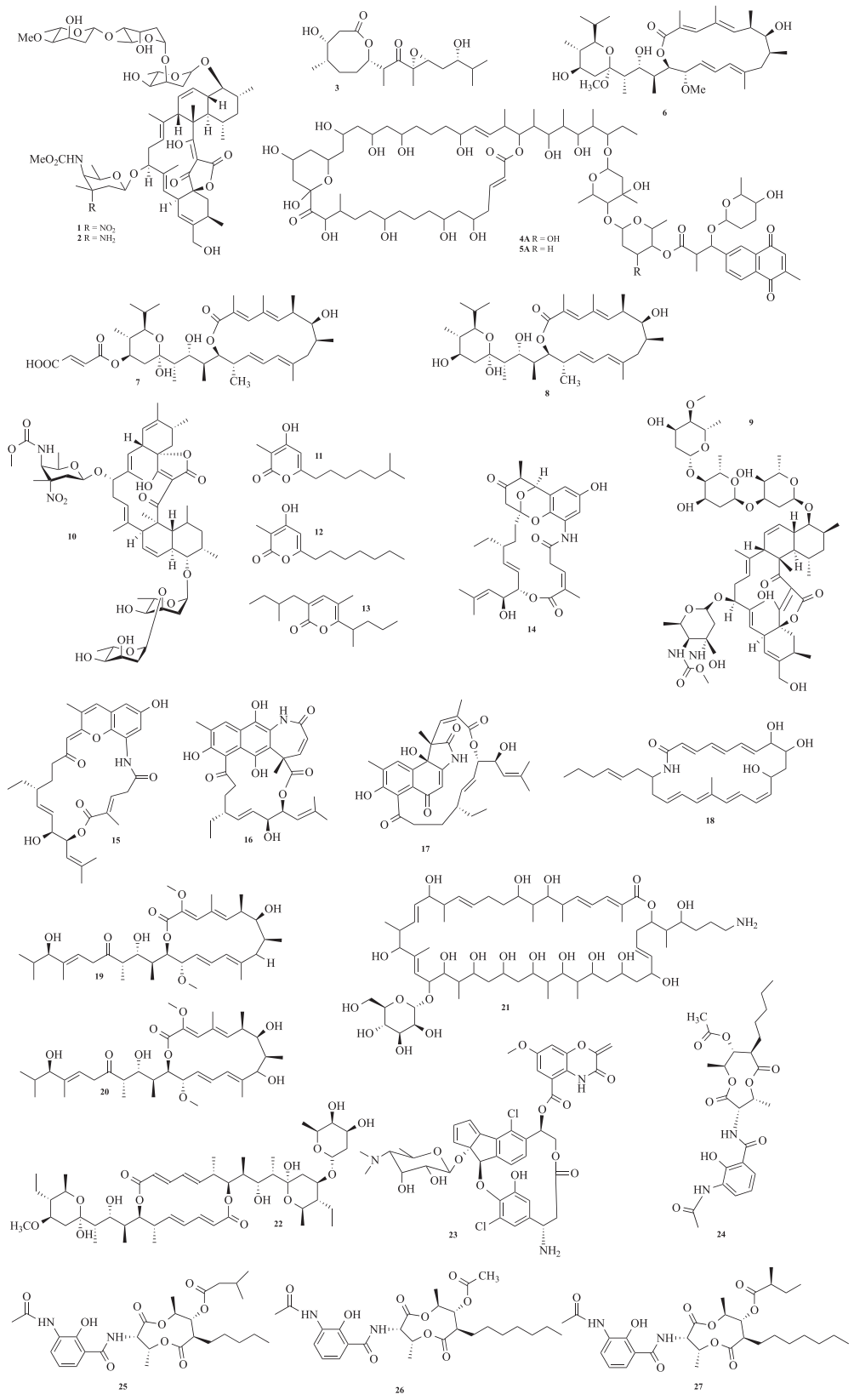

Figure 1 | Structures of compounds 1–27.

23 shows cytotoxicity toward MDA-MB231, HCT-116, A549, SNU638, K562 and SK-HEP1, with IC_{50} 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 IC_{50} of 27.0 μg/mL. Four new nonacyclic dilactones, antimycins E–H (**24–27**), have been obtained from *Streptomyces* sp. THS-55 [26]. Compounds **24–27** each contain a N-[3-(acetylamino)-2-hydroxybenzoyl] moiety. Compounds **24–26** are cytotoxic to Siha, K562, HL-60 and 293T cancer cell lines, with IC_{50} 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 IC_{50} 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. DSS-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 μg/mL, respectively.

Tartrolon D (**33**), a cytotoxic macrodiolide 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 172B modified agar medium plates supplemented with nalidixic acid (1%) [29]. Compound **33** has cytotoxic activity toward A549, HT29 and MDA-MB-231 cells, with GI_{50} values of 0.16, 0.31 and 0.79 μM, respectively. Two new macrocyclic lactones, azalomycin F_{4a} 2-ethylpentyl ester (**34**) and azalomycin F_{5a} 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 IC_{50} values of 5.64 μg/mL and 2.58 μg/mL, respectively. Seven new azalomycin F analogs (**36–42**) have been obtained from *Streptomyces* sp. 211726 [31]. These macrolides (**36–42**) display inhibitory activity toward HCT-116 cells, with IC_{50} 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* SCSIO02999, and have shown cytotoxicity toward four cancer cell lines (MCF-7, SF-268, Hep-G2 and NCI-H460), with IC_{50} values ranging from 0.24 to 25.47 μM [32].

Two new macrolides, pulvomycin B (**49**) and pulvomycin D (**50**), have been discovered from an estuarine *Streptomyces* strain [33]. Compound **49** displays cytotoxic activity toward HCT116, SNU638, SK-Hep-1 and MDA-MB-231 cells, with IC_{50} 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 IC_{50} 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. HS7 obtained from the cloacal aperture of the sea cucumber *Holothuria moebii* [34]. Compound **51** displays inhibitory activity against all six cancer cell lines (HCT-15, C6, U251, SHG-44, U87-MG and SW620), with IC_{50} values in the range of 20.84 to 81.01 μM. Three new polyene macrolactams, kenalactams C–E (**52–54**), have been separated from *Nocardiopsis* CG3 (DSM 106572) isolated from the saltpan of Kenadsa [35]. Compounds **52** and **53** show cytotoxicity toward L929, KB3.1, MCF-7, PC-3, A549 and SKOV-3 cells, with IC_{50} 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 IC_{50} 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 IC_{50} values of 15.92 and 30.77 μM, respectively. Interestingly, compound **55** strongly inhibits the esophageal cancer EC109 cell line, with an IC_{50} 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 Chiloe, Chile. Compound **56** displays inhibitory activity toward HL-60, MDA-MB-231, SW620 and SMMC7721 cells, with IC_{50} values of 32.5, 26.8, 16.4 and 39.9 μM, respectively.

A polycyclic tetramate macrolactam, 16-hydroxymaltophilin (**57**), isolated from *Actinoalloteichus cyanogriseus* WH1-2216-6, shows cytotoxicity toward BXPC-3, HCT-116, Jurkat, PANC-1, A549, MCF-7 and L-02 cell lines, with IC_{50} 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 *Haliclona* sp. marine sponge [39]. Compound **58** is cytotoxic toward HeLa and HL-60 cells, with IC_{50} 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 demospongiae class of marine sponge [40]. Compound **59** displays inhibitory activity toward HeLa cells, with an IC_{50} 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, GXF251L, LXF529L, PAXF1657L and RXF486L cells, with IC_{50} 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 IC_{50} values ranging from 0.092 to

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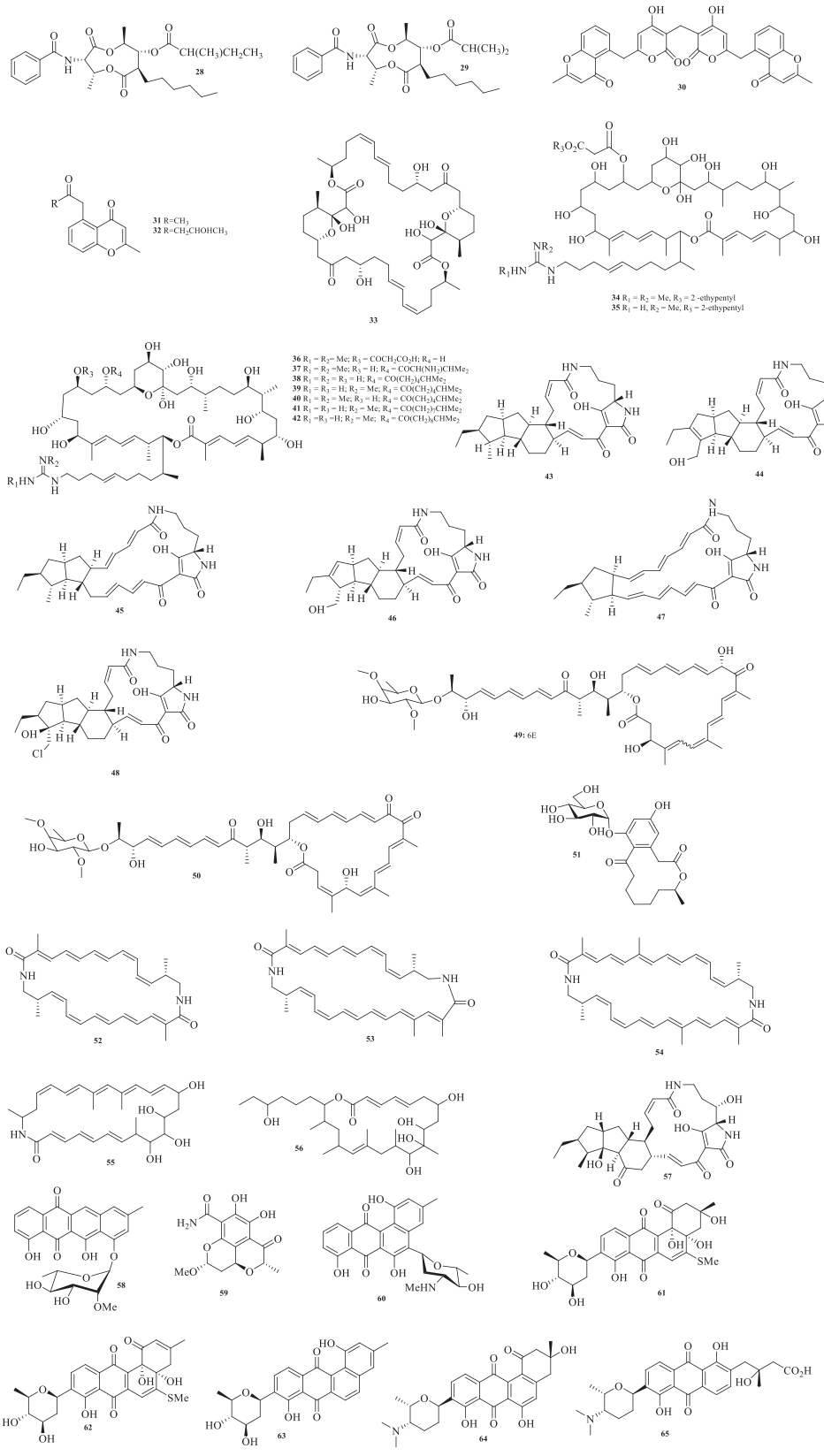

Figure 2 | Structures of compounds 28–65.

0.45 μg/mL, whereas compounds **63** is much less active toward these three cancer cell lines, with IC_{50} 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 IC_{50} values of 1.71, 3.05 and 10.07 μg/mL, respectively. Three angucyclinone derivatives, monacyclinone C (**64**), monacyclinone E (**65**) and monacyclinone F (**66**; **Figure 3**), have been purified from *Streptomyces* sp. M7_15 associated with the sponge *Scopalina ruetzleri*, which displays inhibitory activity toward SJCRH30 cells, with IC_{50} 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 angucyclinone moiety. The chlorinated strepchloritides 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 IC_{50} values of 9.9 and 20.2 μM, respectively [44]. Naquihexcin A (**69**), an *S*-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 IC_{50} value of 16.1 μM. A coral-derived strain, *Streptomyces* sp. RKBHB7, 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 IC_{50} values of 7.8, 10.0, 11.9, 10.1, 23.7 μM, respectively [46]. *Streptomyces* sp. ZZ406 has yielded l-hydroxymethyl-8-hydroxy-anthraquinone-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 IC_{50} 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 IC_{50} 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**)-pyrromycin (**73**), (*7R*9R*10R**)-pyrromycin (**74**), 1-hydroxyauramycin T (**75**), and 1-hydroxysulfurmycin T (**76**) [48]. Compounds **73–76** are cytotoxic toward the P388 tumor cell line, with ID_{50} values in the range of 0.4–0.06 μg/mL. A new anthraquinone, 1,8-dihydroxy-2-ethyl-3-methylanthraquinone (**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 IC_{50} 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 IC_{50} 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 IC_{50} values of 2.41, 4.15 and 4.02 μg/mL, respectively, and compound **80** is active toward MAXF 401NL cells, with an IC_{50} 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 IC_{50} 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 IC_{50} values ranging from 7 to 58 nM, but compound **82** shows cytotoxicity toward the above 12 human tumor cell lines, with IC_{50} 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 IC_{50} values of 106.6, 103.5 and 101.9 μM, respectively. A new anthracene derivative, 3-hydroxy-1-oxo-3-methyl-8-methoxy-1,2,3,4-tetrahydro-benz[α]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 leukemic 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 IC_{50} values in the range of 2.1 to 31 μM. *Streptomyces* sp. SNE-011 has yielded the arylamine derivatives carpatamides 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 IC_{50} values of 2.8, 4.1 and 8.4 μM, respectively, and compound **92** inhibits HCC366 and A549 cells, with IC_{50} values of 2.2 and 3.7

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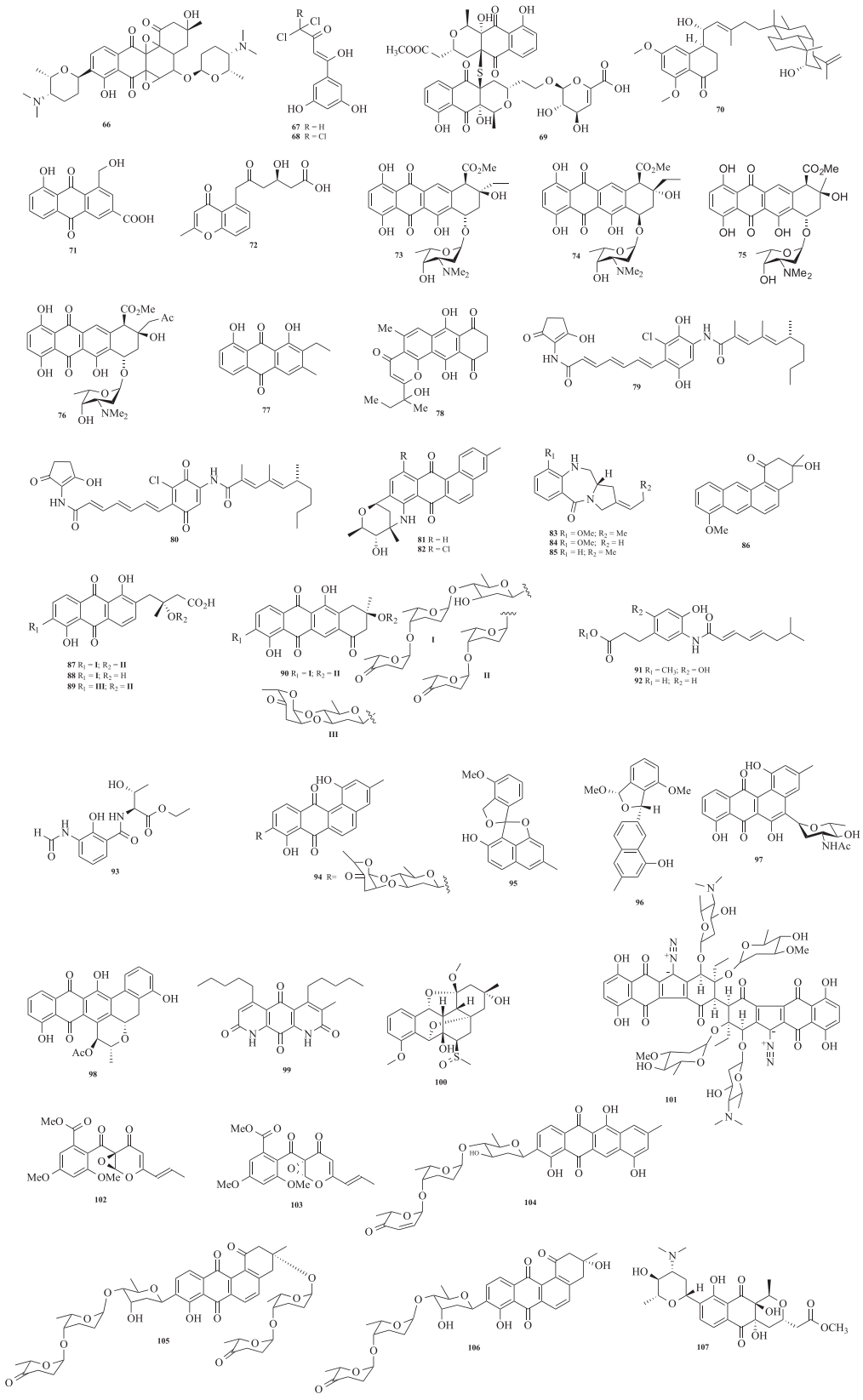

Figure 3 | Structures of compounds 66–107.

μM, respectively. The compound (2*S*,3*R*)-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 IC_{50} of 27.0 μg/mL. Deep-sea sediment-derived *Streptomyces* sp. SCSIO 11594 has yielded an angucycline C-glycoside, marangucycline B (**94**), which displays cytotoxic activity toward A549, CNE2, MCF-7, HepG2 and HL7702 cells, with IC_{50} 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 IC_{50} values of approximately 50.0 μM [59]. Cultivation of *Streptomyces* sp. 182SMLY has afforded two polycyclic anthraquinones, *N*-acetyl-*N*-demethylmayamycin (**97**) and streptoanthraquinone A (**98**) [60]. Compounds **97** and **98** display inhibitory activity toward C6, U251, U87-MG and SHG-44c cells, with IC_{50} values of 0.5/7.3, 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 IC_{50} 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 IC_{50} 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, grisemycin (**100**), which is cytotoxic toward HL-60, with an IC_{50} value of 31.54 μM [62]. A novel dimeric diazobenzofluorene glycoside, lomaiviticin A (**101**), has been obtained from a halophilic strain, *Micromonospora lomaiwitiensis* LL-37I366 [63]. Compound **101** is a dimeric benzofluorene glycoside attached to two diazo functional groups at C-5 and -5′, which shows potent cytotoxic activity toward several cancer cell lines, with IC_{50} values in the range of 0.01 to 98 ng/mL. The compounds (9*R*,14*S*)-epoxy-11-deoxyfunicone **(102)** and (9*S*,14*R*)-epoxy-11-deoxyfunicone **(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 IC_{50} value of 3.97 μM, and compound **103** inhibits HL-60 and H1975 cells, with IC_{50} values of 3.73 and 5.73 μM, respectively. Deep-sea-derived *Streptomyces lusitanus* SCSIO LR32 has been found to produce a new angucycline glycoside, designated grincamycin H (**104**), which is cytotoxic toward Jurkat T cells, with an IC_{50} value of 3.0 μM [65]. Two new angucycline glycosides, grincamycin I (**105**) and grincamycin J (**106**), are produced by marine-derived *Streptomyces lusitanus* SCSIO LR32 [66]. Compound **105** displays inhibitory activity toward MDA-MB-435, MDA-MB-231, NCI-H460, HCT-116, HepG2, and MCF10A cells, with IC_{50} 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 IC_{50} 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, strepoxepinmycins C (**107**) and D (**108**; **Figure 4**), which show cytotoxic activity toward HCT116 cells, with IC_{50} values of 4.4 ± 0.1 and 2.9 ± 0.1 μM, respectively [67]. Lagumycin B (**109**) has been discovered from *Micromonospora* 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 LC_{50} values of 9.80 μM and 10.8 μM, respectively. Investigation of a bacterial strain from the South China Sea, *Micromonospora echinospora* SCSIO 04089, has led to the discovery of homophenanthroviridone (**110**), homophenanthridonamide (**111**) and nenesophanol (**112**) [69]. Compound **110** shows cytotoxicity toward the SF-268, MCF-7 and HepG2 cell lines, with IC_{50} values of 5.4 ± 0.4, 6.8 ± 0.3 and 1.4 ± 0.1 μM, respectively. Compound **111** is active toward these three cell lines, with IC_{50} values of 18 ± 1, 52 ± 2 and 4.0 ± 0.3 μM, respectively. Compound **112** is also active toward SF-268, MCF-7 and HepG2 cell lines, with IC_{50} 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 tetracenomycin analogue, saccharothrixone D (**113**), which exhibits cytotoxicity toward HepG2 cells, with an IC_{50} 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 IC_{50} values of 1.7, 75 and 185 μM, respectively [71].

2.1.3 Decalin derivatives. Nahuoic acid A (**115**) has been obtained from *Streptomyces* sp. RJA2928 and found to inhibit SETD8 activity, with an IC_{50} value of 6.5 μM [72]. Nahuoic acids B–E (**116–119**) have been purified from the same strain, and **116–119** have been found to inhibit SETD8 activity with IC_{50} values of 27, 41, 76 and 13 μM, respectively [73]. The compound (1α,4aα,5α,7β,8aβ)-5,8a-dimethyl-decahydrona-phthalene-1,4a,7-triol (**120**) has been obtained from *Streptomyces* sp. 0616208 and has shown moderate inhibitory effects toward SMMC-7721 cells [74].

2.1.4 Polyenes. Piericidins C_7 (**121**) and C_8 (**122**) have been obtained from the culture of *Streptomyces* sp. YM14-060 isolated from unidentified greenish ascidians

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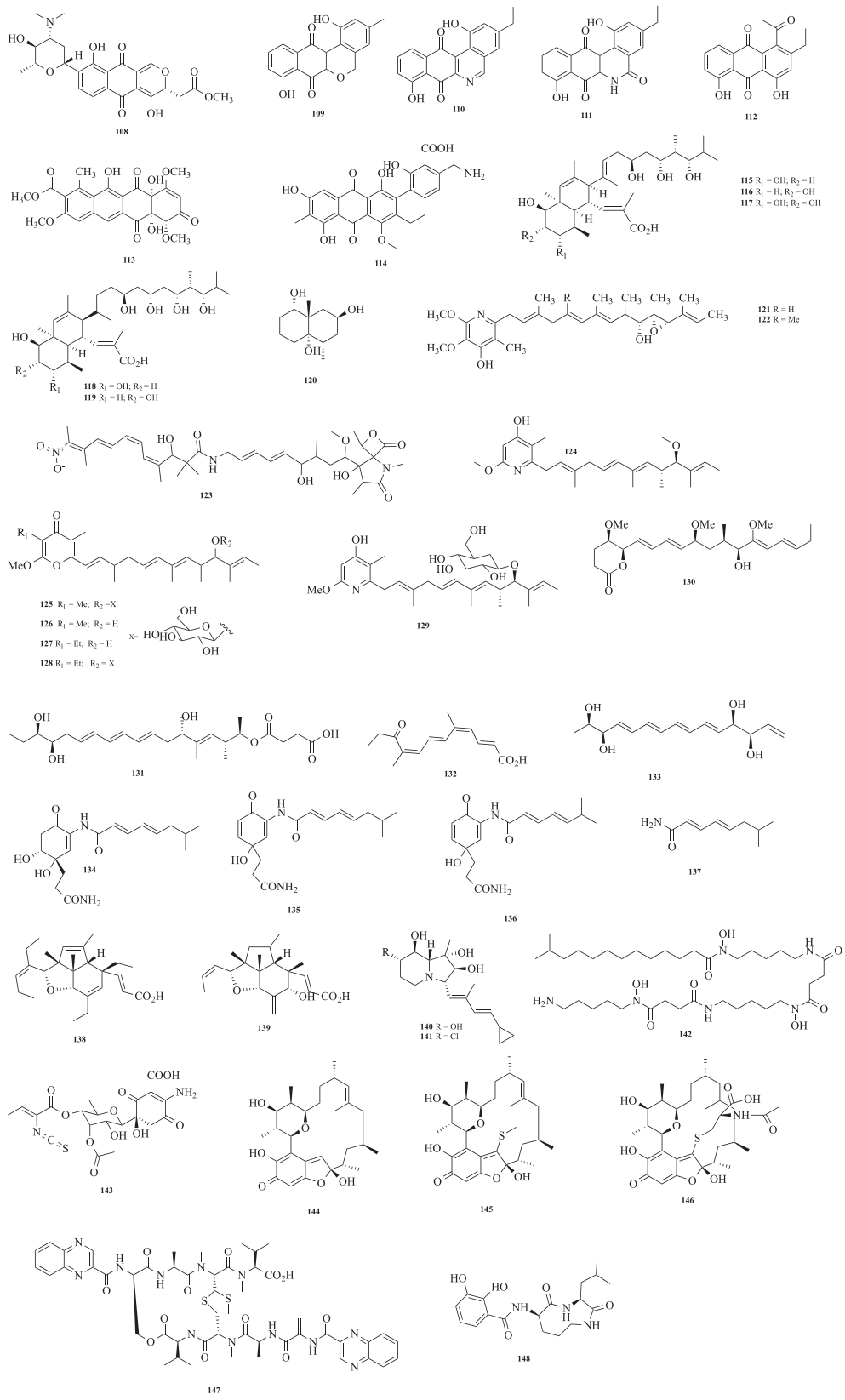

Figure 4 | Structures of compounds 108–148.

collected at Iwayama Bay, Palau [75]. Compounds **121** and **122** show cytotoxicity toward RG-E1A-7 and Neuro-2a cells, with IC_{50} values of 1.5 and 0.83, and 0.21 and 0.45 nM, respectively. A new nitro-tetraene spiro-β-lactone-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 EC_{50} 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 IC_{50} values of 3, 37, 490 and 560 nM, respectively [77]. Four new pyranones, PM050511 (**125**), PM050463 (**126**), PM060054 (**127**) and PM060431 (**128**), have been isolated from the culture of *Streptomyces albus* POR-04-15-053. Compounds **125** and **128** show strong inhibition against MDA-MB-231, HT-29 and A549 cells, with IC_{50} 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 IC_{50} of 2.0 μM (mean IC_{70} 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 Otsuchi Bay, Iwate, Japan by using the Smith–McIntyre grab method [80]. Compound **130** exhibits cytotoxic activity toward 26-L5 cells, with an IC_{50} value of 0.25 μM. Succinilene 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 IC_{50} value of 12.1 μg/mL (27.6 μM). The compound (2*E*,4*Z*,6*E*,8*Z*)-5,9-dimethyl-10-oxododeca-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 IC_{50} value of 4.36 μM [82]. Separacene A (**133**) has been isolated from *Streptomyces* sp. SNJ210 and found to display weak inhibitory activity toward HCT116 and A549 cells, with IC_{50} 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 (2*E*,4*E*)-7-methylocta-2,4-dienoic acid amide (**137**) have been discovered from *Streptomyces* sp. CNQ-085; these compounds exhibit cytotoxicity toward HCT116 cells, with IC_{50} values of 3.15, 9.99, 10.03 and 21.69 μg/mL, respectively [84]. *Streptomyces* sp. NPS-643 has yielded the tricyclic polypropionates indoxamycin A (**138**) and indoxamycin F (**139**), which exhibit cytotoxicity toward human colon adenocarcinoma HT-29 cells, with IC_{50} 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 IC_{50} 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 IC_{50} 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 IC_{50} value of 11 μM [87]. Paulomycin G (**143)** has been discovered from *Micromonospora matsumotoense* M-412 isolated from Cantabrian Sea sediments collected at 2,000 m depth; this compound exhibits cytotoxicity toward pancreatic adenocarcinoma (MiaPaca_2), MCF-7 and HepG2 cells, with IC_{50} values of 2.70, 1.58 and 4.30 μM, respectively [88]. An extract of *Verrucosispora* 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. Compounds **144–146** show cytotoxicity toward MGC803, A549, HeLa, HepG2, MCF-7 and RKO cells, with IC_{50} 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 IC_{50} 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 *Gelliodes 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, Mia-PaCa-2, SK-N-SH, HCT-116 and NCI-H1650 cells, with IC_{50} values of 0.552, 0.721, 0.627, 0.414, 2.56, 4.75, 5.17, 8.16 and 3.90 μM, respectively. *Streptomyces* sp. SBT348 from the Mediterranean sponge *Petrosia ficiformis* has yielded a new cyclic dipeptide (hypogallate-Orn-Leu), petrocidin A (**148**), which exhibits cytotoxicity toward HT-29 and HL-60 cells, with IC_{50} 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 ($^{8\text{-}1}$Gly-Phe-Gly-Ser-Lys-Pro-Ile-Asp$^{8\text{-}9}$) and a seven-amino-acid chain ($^{8\text{-}9}$Ser-Phe-Gly-Leu-Ser-Trp-Leu^{15}). Compound **149** displays inhibitory activity in cell invasion assays toward the human lung cancer cell line A549. The cyclic peptides ohmyungsamycins A

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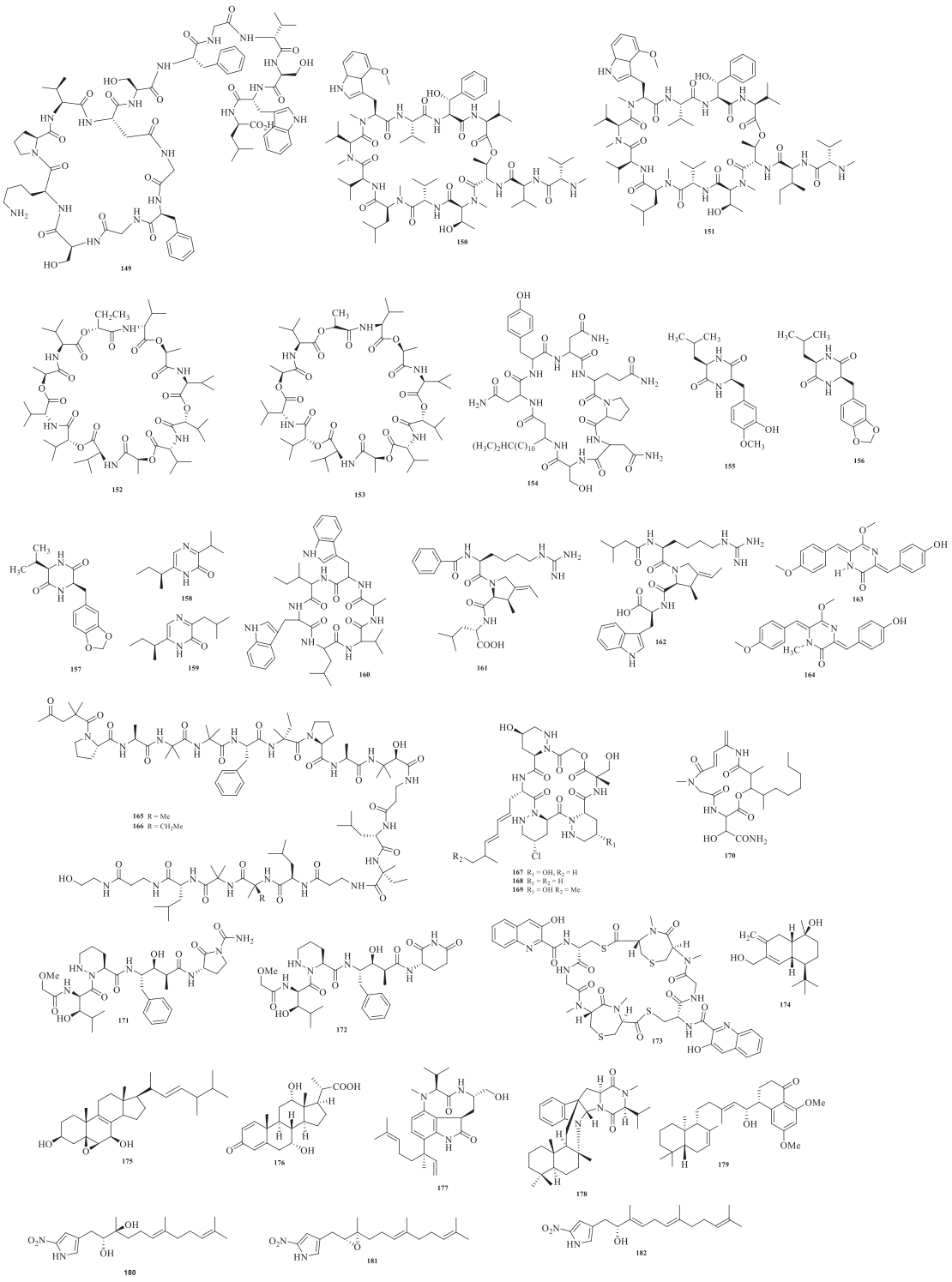

Figure 5 | Structures of compounds 149–182.

(**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 ($^{10\text{-}1}$Val-Phe-Val-Trp-Val-Val-Leu-Val-Thr-Thr$^{10\text{-}11}$) and two on the side chain (^{11}Val-Val^{12}). Compound **150** exhibits cytotoxic effects against HCT116, A549, SNU-638, MDAMB-231 and SKHEP-1 cells, with IC_{50} values of

0.359, 0.551, 0.532, 0.688 and 0.816 μM, respectively. Compound **151** exhibits much less of a cytotoxic effect against the above-mentioned cells, with IC_{50} values ranging from12.4 to 16.8 μM. Both compounds **150** and **151** show virtually no cytotoxicity toward normal MRC-5 lung cells (IC_{50} > 40 μM), thus indicating that these compounds exhibit more selective antiproliferative activity toward cancer cells than normal cells. *Streptomyces* sp. P11-23B has afforded two cyclodepsipeptides, streptodepsipeptides P11A (**152**, cyclo-(D-Val-L-Lac-L-Val-D-Hiv-D-Val-L-Lac-L-Val-D-Hiv-D-Val-L- Lac-L-Val-D-Hba)) and P11B (**153**, cyclo-(D-Val-L-Lac-L-Val-D-Hiv-D-Val-L-Lac-L-Val-D-Hiv-D-Val-L-Lac-L-Val-L-Lac)) [94]. Compounds **152** and **153** are cytotoxic toward SHG-44, U87-MG, U251 and C6 cells, with IC_{50} values in the ranges of 0.3–0.4 and 0.1–1.4 μM, respectively. A new cyclic lipopeptide, iturin A_6 (**154**), has been separated from *Streptomyces* sp. SSA 13 isolated from the Arabian Sea [95]. Compound **154** is a cyclic lipopeptide containing a C_{16} β-amino fatty acid chain attached to a hydrophilic heptapeptide ((fatty acid)CO-Asn-Tyr-Asn-Gln-Pro-Asn-Ser-NH(fatty acid)) of seven α-amino acids. Compound **154** displays cytotoxicity toward HeLa, MCF-7 and Hep-G2 cell lines, with IC_{50} 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-ylmethyl)-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 IC_{50} values of 89.4, 35.4 and 28.4 μg/mL, respectively. Compounds **156** and **157** inhibit the growth of HCT116 cells, with IC_{50} 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 IC_{50} value of 30 μg/mL [97]. Compounds **158** and **159** show inhibitory effects toward MCF-7 cells, with IC_{50} 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 HeLa cervix carcinoma, murine CT26 colon carcinoma and human MM.1S multiple myeloma cell lines, with IC_{50} values of 11, 12 and 8 μg/mL, respectively. Investigation of *Nocardiopsis lucentensis* 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 IC_{50} 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 IC_{50} 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 IC_{50} values of 2.60, 3.97, 8.73, 6.67 and 16.7 μM, respectively. Two new peptaibols, microbacterins 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 IC_{50} values of >10, 1.98, 2.11, 2.30 and >30 μM, respectively. Compound **166** displays cytotoxicity toward the same cell lines, with IC_{50} 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-αMeSer-γOHPip-γClPip), piperazimycins A–C (**167–169**) [102]. Compounds **167–169** exhibit cytotoxicity toward HCT-116 cells, with the same GI_{50} 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. MWW064 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-hydroxydecanoate moiety and γ-amino-2,4-pentadienoate moiety. However, the stereochemistry of compound **170** has not been investigated. Compound **170** shows cytotoxicity toward murine carcinoma colon 26-L5 cells, with an IC_{50} value of 6.7 μM. Two new highly 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 (Ahmpp) and 3-amino-2-oxopyrrolidine-1-carboxamide (Aopc) residue. Compound **172** is almost the same as **171** except for an Apd in **172** instead of an Aopc in **171**. Compounds **171** and **172** show weak antitumor activity toward Jurkat T lymphocyte cells (ATCC TIB-152), with IC_{50} values of 60 and 20 μg/mL, respectively. A new thiodepsipeptide, verrucosamide **(173)**, has been isolated from V*errucosispora* sp. CNX-026 [105]. Compound **173** is a cyclic octapeptide (cyclo-(Gly-Cys-Ala-Cys-Gly-Cys-Ala-Cys)) connected to two 3-hydroxy-quinaldic acid moieties. Compound **173** shows activity toward MDA-MB-468 breast carcinoma and COLO 205 colon adenocarcinoma cells, with LD_{50} values of 1.26 and 1.4 μM. Compound **173** displays moderate cytotoxicity toward NCI 60.

Among these 27 non-ribosomal peptides and hybrids of polyketides and peptides (**147–173**), compounds **167–169** show potent cytotoxicity, with IC_{50} values at ng/mL (nM) levels. In the past few decades, scientists have been overcoming the well-known limitations of bioactive

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peptides as therapeutics. More peptides or peptide derivatives have been approved for clinical use. Hence, these three cyclic peptides (**167–169**), each with three piperazic 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 IC_{50} 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 IC_{50} values of 13.0, 18.1 and 23.5 μg/mL, respectively [107]. The culture of *Actinomadura* sp. SBMs009 has afforded a 3-keto sterol compound, bendigole D (**176**), which shows cytotoxic activity toward L929 cells, with an IC_{50} value of 30 μM [108].

Streptomyces sp. NBRC105896 has been found to produce a new teleocidin analog, JBIR-31 (**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 IC_{50} 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 (Val-Trp), possessing a rare heptacyclic skeleton. Compound **178** shows cytotoxicity toward HeLa cells, with an IC_{50} value of 16.73 μM.

Streptomyces sp. CNQ-027 has afforded a new meroterpenoid, actinoranone (**179**), which is a hybrid of a diterpenoid and a polyketide. Compound **179** displays cytotoxicity toward the HCT-116 cell line, with an LD_{50} value of 2.0 μg/mL [111]. Three farnesyl-nitropyrroles—nitropyrrolin A (**180**), nitropyrrolin B (**181**) and nitropyrrolin D (**182**)—have been obtained from marine actinomycete strain CNQ-509 [112]. The structures of the nitropyrrolins (**180–182**) are composed of α-nitropyrroles with functionalized farnesyl groups at the C-4 position. Biogenetically, the pyrroles might be derived from succinyl-CoA and glycine. Compounds **180–182** exhibit cytotoxic activity toward HCT-116 cells, with IC_{50} values of 31.1, 31.0 and 5.7 μM, respectively. *Streptomyces niveus* SCSIO 3406 has been found to produce the new geranylated phenazines marfuraquinocins A–D (**183–186**; **Figure 6**) [113]. Compounds **183–186** each contain a sesquiterpenoid and a naphthoquinone moiety. Compounds **183–186** show cytotoxicity toward SF-268, MCF-7, NCI-H460 and HepG2 cells, with IC_{50} values in the range of 3.7 to 27.9 μM. Napyradiomycins A and D–F (**187–190**) have been obtained from liquid culture of *Streptomyces* sp. CNQ-329 [114]. Compounds **187–190** are each composed of a C_5 isoprenoid moiety, monoterpenoid moiety and naphthoquinone moiety, and each shows cytotoxicity toward HCT-116 cells, with IC_{50} values of 4.19, 16.1, 4.81 and 9.42 μg/mL, respectively. Four napyradiomycin derivatives, napyradiomycin CNQ525.510B, napyradiomycin CNQ525.538, napyradiomycin CNQ525.554 and napyradiomycin CNQ525.600 (**191–194**), have been obtained from a culture of actinomycete strain CNQ525 [115]. Compounds **191**, **192** and **194** have been found to be active toward HCT-116, with IC_{50} values of 17, 6 and 49 μM, respectively. A new pyrrolosesquiterpene, glaciapyrrole A (**195**), is produced by *Streptomyces* sp. NPS008187 [116]. Compound **195** displays inhibitory activity toward HT-29 and B16-F10 cells, with an IC_{50} value of 180 μM for both.

None of these 22 isoprenoids, terpenoids, sterols, and hybrids of isoprenoids and peptides (or polyketides) (**174–195**) demonstrate potent cytotoxicity. In addition, all the 22 structures were new at the time of their discovery. However, the linearly tricyclic/tetracyclic compounds **187** and **188** each uniquely have a C_8/C_6 linker bridging the first and second/third rings (C-2–C5a/C-2–C-6a).

2.4 Heterocyclic, (hetero)aromatic and other compounds

Two new 3,6-disubstituted indoles **(196** and **197)** have been obtained from *Streptomyces* sp. BL-49-58-005 [117]. Compound **196** shows cytotoxicity toward the K562 cell line, with a GI_{50} value of 8.46 μM. Compound **197** exhibits activity with GI_{50} 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 10*H*-phenoxazine 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 IC_{50} of 8 μM [118]. Two pentacyclic indolosesquiterpenes, xiamycin **(199)** and its methyl ester **(200)**, have been discovered from *Streptomyces* sp. GT2002/1503, an endophyte from the mangrove plant *Bruguiera gymnorrhiza* [119]. Compound **199** shows moderate cytotoxicity toward 12 tumor cell lines, whereas **200** is cytotoxic to 12 different tumor cell lines, with a geometric mean IC_{50} value of 10.4 μM.

Streptomyces sioyaensis SA-1758 produces a 2,4a,5,6,7,7a-hexahydro-1H-cyclopenta[c]pyridine derivative, altemicidin (**201**), which inhibits L1210 and IMC carcinoma cells, with IC_{50} values of 0.84 and 0.82 μg/mL, respectively [120]. A unique phenyl benzoate derivative with an N-acetyl-(*S*)-cysteine moiety, bagremycin C (**202**), has been isolated from *Streptomyces* sp. Q22 and found to display cytotoxicity toward U87MG, U251, SHG44 and C6 cells, with IC_{50} values of 2.2, 4.3, 2.4 and 6.4 μM, respectively [121]. *Streptomyces* sp. KORDI-3238 has yielded streptokordin (**203**), 4-acetyl-6-methylpyridin-2(1*H*)-one [122]. Compound **203** exhibits cytotoxicity toward MDA-MB-231, HCT15, PC-3, NCI-H23, ACHN, LOX-IMVI and K-562 cells, with IC_{50} values of 7.5, 7.8, 3.2, 3.5, 4.7, 7.4 and 8.6 μg/mL, respectively. Two phenyl(1*H*-pyrrol-2-yl)methanone dimers, marinopyrroles A (**204**) and B (**205**), have been obtained from *Streptomyces*

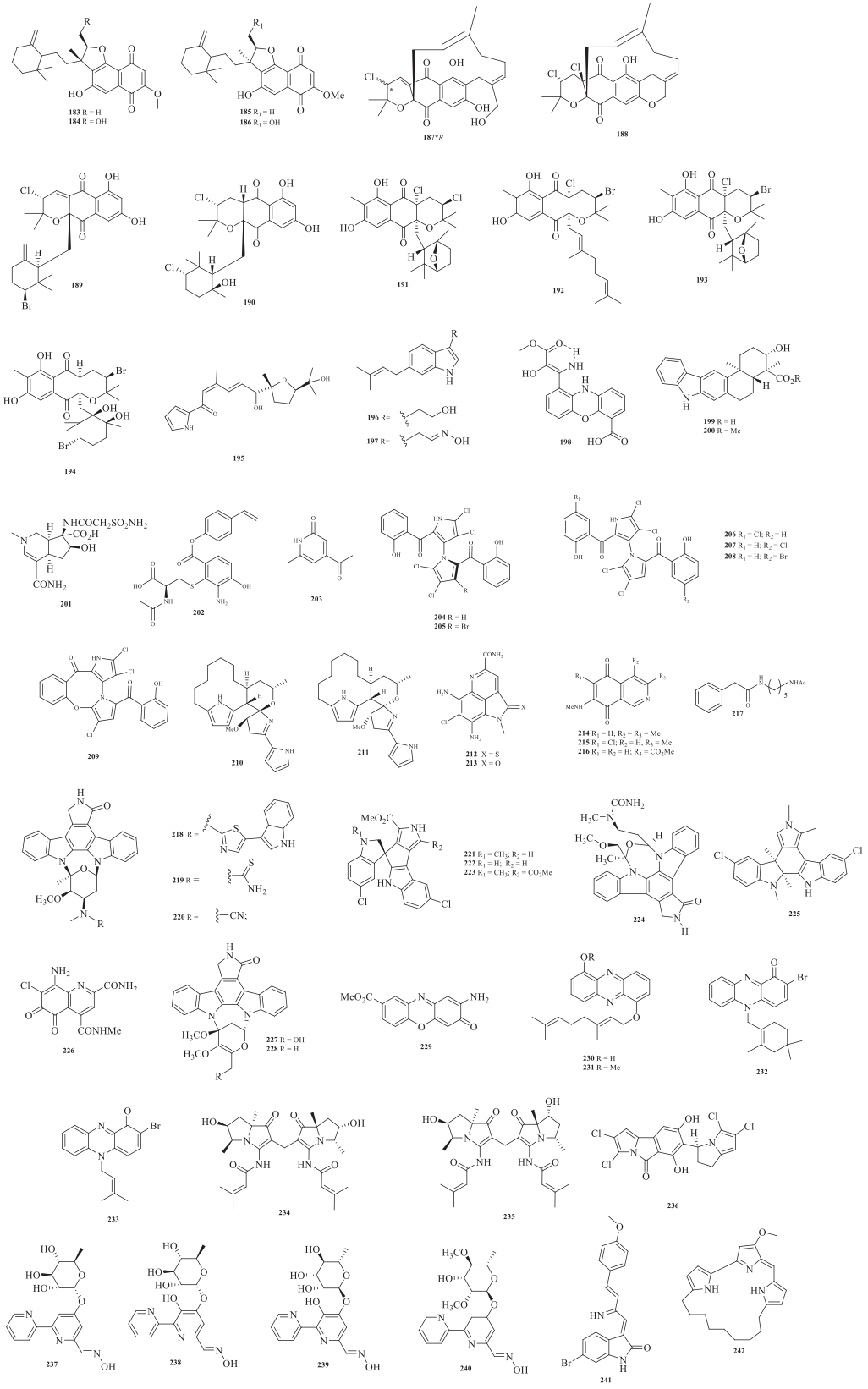

Figure 6 | Structures of compounds 183–242.

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sp. CNQ-418, and **204** and **205** exhibit cytotoxic activity toward HCT-116, with IC_{50} values of 8.8 and 9.0 μM, respectively [123]. Although configurationally stable at room temperature, *M*-(–)-**204** can be racemized at elevated temperatures, thus yielding the non-natural *P*-(+)-atropo-enantiomer, which inhibits HCT-116 with an IC_{50} value of 9.4 μM. The same strain, *Streptomyces* sp. CNQ-418, also produces marinopyrroles C–F (**206–209**) [124]. Compound **206** shows cytotoxic activity toward HCT-116, with an IC_{50} value of 0.21 μg/mL. Compounds **207–209** might be also active, but their cytotoxic activity has not been reported. Two novel spiroaminals, marineosins A and B (**210** and **211**), containing two pyrrole functionalities, have been isolated from cultures of the marine sediment-derived actinomycete *Streptomyces* sp. CNQ-617 [125]. Compounds **210** and **211** are active toward HCT-116 cell lines, with IC_{50} values of 0.5 and 46 μM, respectively. The difference in configuration at the spiroaminal center and in the tetrahydropyran conformation appears to significantly affect the bioactivity of compounds **210** and **211**. An investigation of *Streptomyces* sp. CNR-698 has afforded ammosamides A (**212**) and B (**213**) [126]. The strain CNR-698 has been isolated from bottom sediments collected at a depth of 1,618 meters in the Bahamas. Compound **213** is a pyrrolo[4,3,2-*de*]quinolin-2(1*H*)-one derivative, whereas **212** is a thiol amide (-NH-CS-) instead of an amide (-NH-CO-), and has potential to exist in an equilibrium with its bis-iminoquinone tautomer. Compounds **212** and **213** are cytotoxic toward the HCT-116 cell line, with IC_{50} values of 320 nM for both. The isoquinolinequinone derivatives mansouramycins A–C (**214–216**) have been obtained from *Streptomyces* sp. isolate Mei37 [127]. Compound **216** has been demonstrated to be the most active compound, with an overall potency of 89 nM (mean IC_{50} value toward 36 tumor cell lines tested), followed by **215** (mean IC_{50} value 2.7 μM). Compound **214** shows moderate concentration-dependent cytotoxicity, with a mean IC_{50} value of 13.44 μM. N_1-acetyl-N_7-phenylacetyl cadaverine (**217**) has been discovered from *Streptomyces* sp. WuXin, and the bisamide shows activity toward HL-60 cells, with an IC_{50} value of 58.43 μM [128]. *Streptomyces fradiae* 007 M135 has afforded three new indolocarbazoles, fradcarbazoles A–C (**218–220**) [129]. Structurally, compounds **218–220** are very similar to staurosporine, with the N-Me replaced by various functional groups. Compounds **218–220** are strongly cytotoxic toward the HL-60/K562/A-549/BEL-7402 cell lines, with IC_{50} values of 1.30/4.58/1.41/3.26, 1.60/1.47/0.001/1.74 and 0.13/0.43/0.02/0.68 μM, respectively. *Streptomyces* sp. SCSIO 03032 has afforded three bisindole alkaloids, spiroindimicins B–D (**221–223**) [130]. Compounds **221–223** are unique molecules, each containing six rings. The cyclic pentane ring in the tetrahydrocyclopenta[*c*]pyrrole moiety is fused to one indole moiety and forms a spiro functionality with another indole moiety. Compound **221** displays cytotoxic activity against CCRF-CEM, B16 and H460 cells, with IC_{50} values of 4, 5 and 12 μg/mL, respectively. Compound **222** inhibits HepG2 and H460 cells, with IC_{50} values of 6 and 15 μg/mL, respectively. Compound **223** displays moderate cytotoxic activity toward HepG2, H460 and B16 cells. A new staurosporinone, *N*-carboxamido-staurosporine (**224**), has been isolated from the culture broth of the marine-derived *Streptomyces* sp. QD518 [131]. Biogenetically, **224** can be derived from two molecules of tryptophan and an amino sugar. Compound **224** exhibits cytotoxic activity toward 37 human tumor cell lines, with a mean IC_{50} value of 16 ng/mL. *Streptomyces* sp. SCSIO 03032 has produced a new bisindole alkaloid, indimicin B (**225**), a compound similar to staurosporine without the amino sugar moiety [132]. Compound **225** exhibits cytotoxic activity toward MCF-7 cells, with an IC_{50} value of 10.0 μM. Investigation of *Streptomyces variabilis* SNA-020 *has* led to the isolation of a quinoline-5,6-dione derivative, ammosamide D (**226**) [133]. 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, respectively. An aminophenoxazinone 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 chorismic acid. Both **230** and **231** show cytotoxicity toward SF-268, MCF-7 and HepG2 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 phenazines (**232** and **233**), which induce apoptosis in HL-60 cells [136]. Two new hexahydro-1*H*-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 HCC366 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 IC_{50} value of 3.2–4.9 μg/mL [138]. Four new cyclic bipyridine glycosides, cyanogrisides E–H (**237–240**), have been isolated from *Actinoalloteichus cyanogriseus* WH1-2216-6 [139]. Compounds **237** and **240** show cytotoxicity toward K562 cells, with IC_{50} values of 6.0 and 0.8 μM, respectively. Compounds **238** and **239** inhibit A549, K562, HeLa, HCT116 and HL-60 cells, with IC_{50} 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. Saccharomonosporine A (**241**) has been isolated from the extract of *Saccharomonospora* sp. UR22 and *Dietzia* sp. UR66 co-culture [140]. Compound **241** is a brominated oxo-indole alkaloid connected to a 4-methoxy benzene ring through an imine containing linker (=CH-C(=NH)-CH=CH-). Compound **241** shows cytotoxicity toward the cancer cell lines HT-29 and HL-60, with IC_{50} values of 3.6 and 2.8 μM, respectively. Two prodiginine derivatives, cyclononylprodigiosin (**242**) and nonylprodigiosin (**243**; **Figure 7**), have been obtained from the actinomycete strain BRA 177 [141]. Compounds **242** and **243** are cytotoxic toward SK-Mel-147, HCT-116 and MRC-5 cells, with IC_{50} values of 2.40/2.70, 3.94/4.25 and 0.58/0.26 μM, respectively.

Amycolactam (**244**), an indole alkaloid with an isoprenyl group at C-4 and 5-methyl-pyrrolidin-2-one moiety at C-3, has been discovered from the sponge-associated rare actinomycete *Amycolatopsis* sp., and found to cytotoxic to SNU638 and HCT116 cells, with IC_{50} values of 0.8 and 2.0 μM, respectively. Compound **244** is also cytotoxic to A546, K562 and SK-HEP1 cells, with IC_{50} values of 13.7, 9.6 and 8.3 μM, respectively [142]. Ten 2,9-dihydro-1*H*-pyrido[3,4-*b*]indol-1-one alkaloids—marinacarbolines E–G (**245–247**), I (**248**), K–M (**249–251**), O (**252**), Q (**253**) and caerulomycin N (**254**)—have been obtained from the actinomycete strain *Actinoalloteichus* sp. ZZ1866 [143]. Compounds **245–254** exhibit cytotoxic activity toward U87MG and U251 cells, with IC_{50} values in the range of 2.0–43 μM.

Among these 59 compounds classified as heterocyclic, (hetero)aromatic and other (**196–254**), compounds **212**, **213**, **216** and **224** show potent cytotoxicity, with IC_{50} values at the ng/mL (nM) level. Structurally, most of these 59 compounds markedly differ from the 195 compounds in Sections 2.1, 2.2 and 2.3, because of their heterocyclic or (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 IC_{50} 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, sterols, 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.

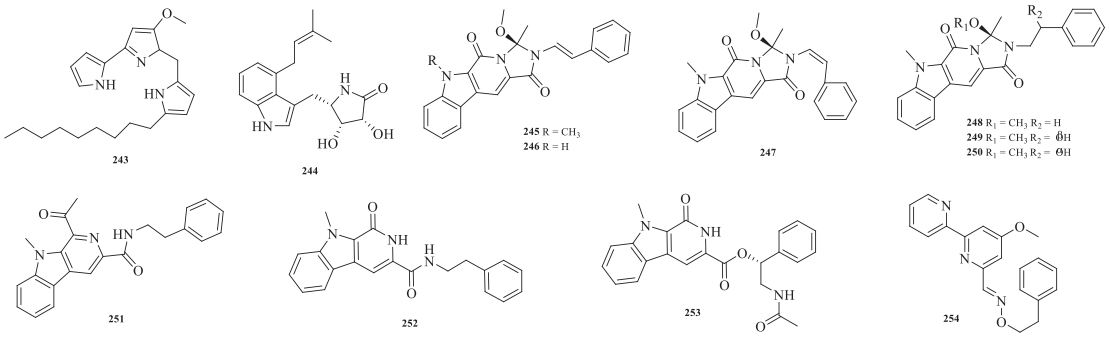

Figure 7 | Structures of compounds 243–254.

Table 1 | Cytotoxic compounds isolated from marine actinomycetes.

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		Polyketides	[20]
18	*Streptomyces aureoverticillatus* NPS001583	Marine sediment	Polyketides	[21]
19–20	*Streptomyces* sp. HZP-2216E	Traditional Chinese medicine sea lettuce *Ulva pertusa* (family Ulvaceae)	Polyketides	[22]
21	*Streptomyces althioticus* MSM3	Intertidal seaweed *Ulva* sp., Cantabrian Sea (Northeast Atlantic Ocean)	Polyketides	[23]
22	*Streptomyces* sp. 219807	Mangrove soil from Sanya	Polyketides	[24]
23	*Streptomyces* sp. ART5	Surface sediment from the East Siberian continental margin	Polyketides	[25]
24–27	*Streptomyces* sp. THS-55	Conserved mangrove in Hainan province, China	Polyketides	[26]
28–29	*Streptomyces antibioticus* H12-15	Sea sediment from a mangrove in the South China Sea	Polyketides	[27]
30–32	*Streptomyces* sp. DSS-18	Deep-sea sediment from the West Pacific	Polyketides	[28]
33	*Streptomyces* sp. MDG-04-17-069	Marine sediment from the east coast of Madagascar, 30 m depth	Polyketides	[29]
34–35	*Streptomyces* sp. 211726	Mangrove rhizosphere soil	Polyketides	[30]
36–42	*Streptomyces* sp. 211726	Mangrove broth	Polyketides	[31]
43–48	*Streptomyces pactum* SCSIO02999		Polyketides	[32]
49–50	*Streptomyces* sp.	Estuary between the Yellow Sea and the Han River, Republic of Korea	Polyketides	[33]
51	*Pseudonocardia* sp. HS7	Cloacal aperture of the sea cucumber *Holothuria moebii*	Polyketides	[34]
52–54	*Nocardiopsis* CG3 (DSM 106572)	Saltpan of Kenadsa	Polyketides	[35]
55	*Micromonospora* sp. FIM05328	Soil sample from the East China Sea	Polyketides	[36]
56	*Micromonospora* strain FIM07-0019	Shallow coastal waters near the island of Chiloe, Chile	Polyketides	[37]
57	*Actinoalloteichus cyanogriseus* WH1-2216-6	Submarine sediment	Polyketides	[38]

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Table 1 | Continued

Compound	Producing strain	Strain source	Architectural feature	References
58	*Streptomyces* sp. Sp080513GE- 26	*Haliclona* sp. marine sponge	Polyketides	[39]
59	*Streptomyces* sp. SpD081030ME-02	Demospongiae 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		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. IFM11490	Soil and seawater samples from different areas of Japan.	Polyketides	[59]
97–98	*Streptomyces* sp. 182SMLY	Marine sediments	Polyketides	[60]
99	*Streptomyces* sp. F001		Polyketides	[61]
100	*Streptomyces griseus* M268	Sediment from Kiaochow Bay, China	Polyketides	[62]
101	*Micromonospora lomaivitiensis* LL-37I366		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]

Table 1 | Continued

Compound	Producing strain	Strain source	Architectural feature	References
107–108	*Streptomyces* sp. XMA39		Polyketides	[67]
109	*Micromonospora* sp. G039	Sediment from the Cát Bà peninsula, East Sea of Vietnam	Polyketides	[68]
110–112	*Micromonospora echinospora* SCSIO 04089	Sediment from the northern South China Sea, 3,025 m depth	Polyketides	[69]
113	*Saccharothrix* sp. 10-10		Polyketides	[70]
114	*Nonomuraea* 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	*Saliconia* 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		Polyketides	[84]
138–139	*Streptomyces* sp. NPS-643	Marine sediment sample near Kochi Harbor, Japan, 30 m depth	Polyketides	[85]
140–141	*Streptomyces* sp. HNA39		Polyketides	[86]
142	*Micromonospora* sp. 29867	Suruga Bay, Shizuoka Prefecture, Japan	Polyketides	[87]
143	*Micromonospora 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	*Gelliodes carnosa m*arine sponge from the South China Sea	Non-ribosomal peptides, and hybrids of polyketides and peptides	[90]
148	*Streptomyces* sp. SBT348	*Petrosia ficiformis* Mediterranean sponge from Milos, Greece	Non-ribosomal peptides, and hybrids of polyketides and peptides	[91]

Table 1 | Continued

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	*Nocardiopsis* sp. UR67	Red Sea	Non-ribosomal peptides, and hybrids of polyketides and peptides	[98]
161–162	*Nocardiopsis 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	*Nocardiopsis* sp. YIM M13066	Deep-sea sediment	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]

Table 1 | Continued

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]

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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		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		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		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		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		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		Heterocyclic, (hetero)aromatic and other compounds	[136]
234–235	*Streptomyces spinoverrucosus* strain SNB-032		Heterocyclic, (hetero)aromatic and other compounds	[137]

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Table 1 | Continued

Compound	Producing strain	Strain source	Architectural feature	References
236	*Streptomyces* sp. strain CNH-287		Heterocyclic, (hetero)aromatic and other compounds	[138]
237–240	*Actinoalloteichus cyanogriseus* WH1-2216-6		Heterocyclic, (hetero)aromatic and other compounds	[139]
241	*Saccharomonospora* sp. UR22 and *Dietzia* sp. UR66	Red Sea sponge *Callyspongia siphonella*	Heterocyclic, (hetero)aromatic and other compounds	[140]
242–243	Actinomycete strain BRA 177	Saint Peter and Saint Paul Archipelago, Brazil	Heterocyclic, (hetero)aromatic and other compounds	[141]
244	*Amycolatopsis* sp.	Sponge	Heterocyclic, (hetero)aromatic and other compounds	[142]
245–254	*Actinoalloteichus* sp. ZZ1866	Sea mud from the coastal area of Putuo, Zhoushan, China	Heterocyclic, (hetero)aromatic and other compounds	[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 IC_{50} 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.

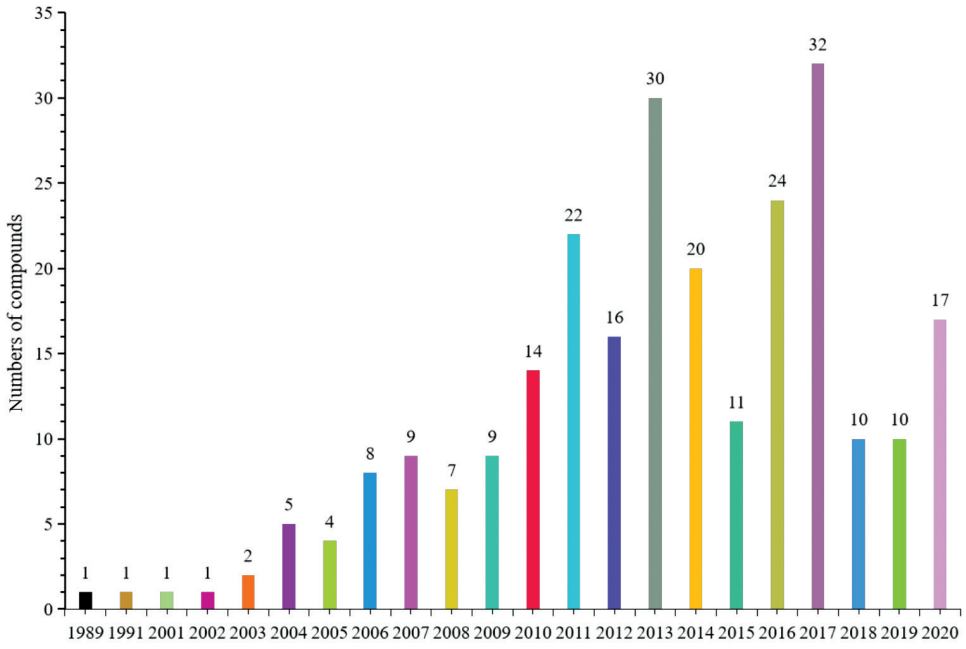

Figure 8 | Numbers of antitumor compounds isolated from marine actinomycetes each year (1989 to 2020).

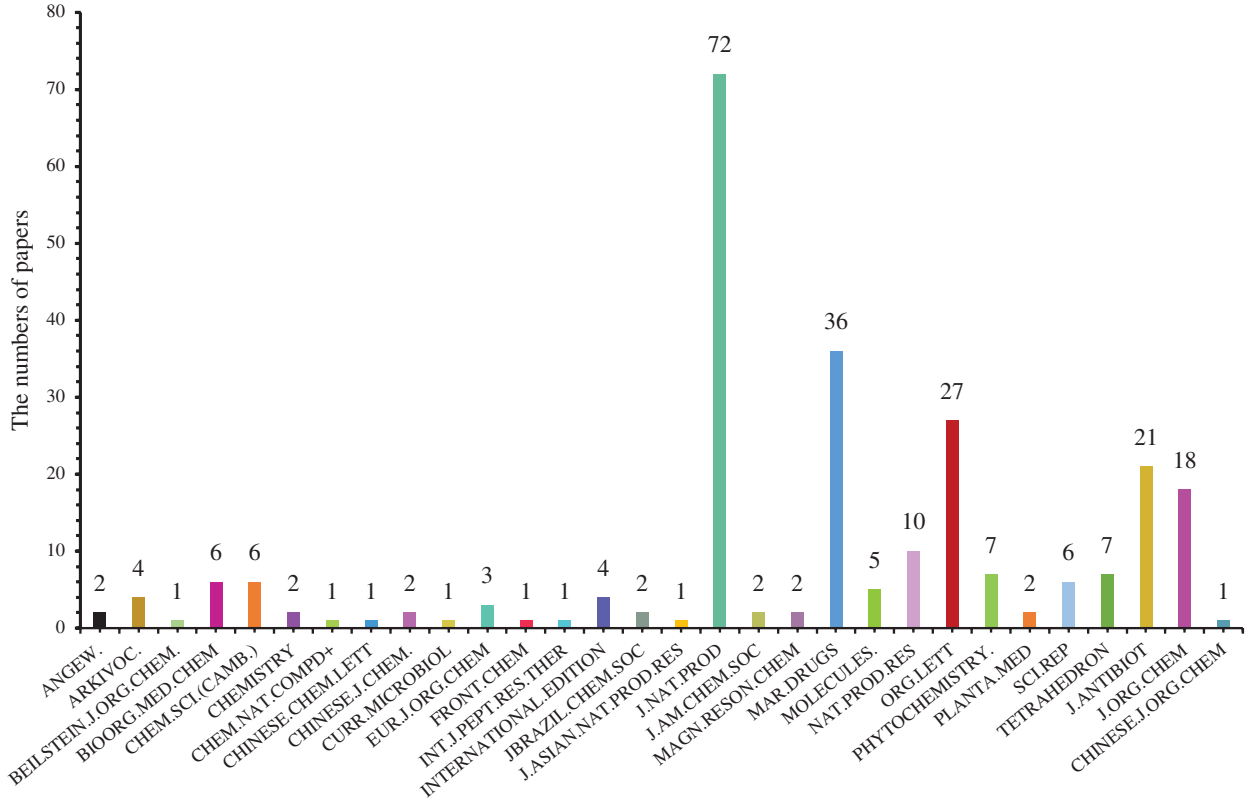

Figure 9 | Journals publishing, and numbers of articles describing, antitumor compounds from marine actinomycetes.

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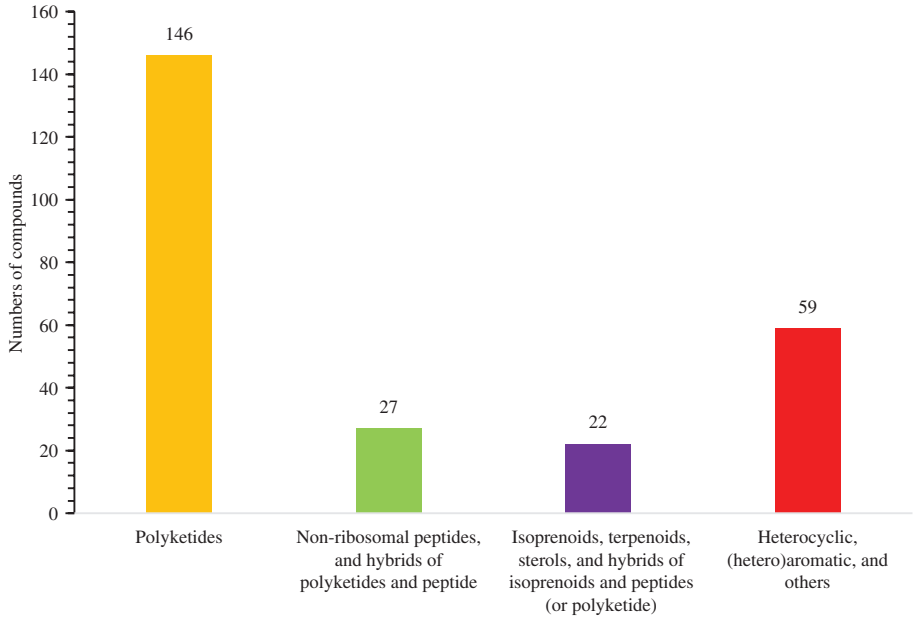

Figure 10 | Structural classes of antitumor compounds from marine actinomycetes.

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 IIIb/IIa in a dose-dependent manner, with IC_{50} 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 $C_{38}H_{26}N_4O_{14}$. 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: $C_{60}H_{86}O_{19}$; 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.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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