frontiers | Frontiers in Marine Science

REVIEW
published: 27 June 2022
doi: 10.3389/fmars.2022.929561

Deep-Sea-Derived Fungi as Valuable Producers of Cytotoxic Secondary Metabolites and Their Leads Potential

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Cancer is the leading lethal disease worldwide. Natural products have contributed significantly to the development of approved therapeutic agents. Therefore, research into new bioactive naturally sourced metabolites with lead potential is urgently needed. It is well-known that marine microorganisms are by far one of the most notable and prolific sources of bioactive natural products. Among them, deep-sea-derived fungi are extraordinarily adapted and metabolically active under extreme environmental conditions, which enable them to produce a large number of novel secondary metabolites. Chemical examination of deep-sea-derived fungi has yielded enormous amounts of cytotoxic natural products and potential drug leads. This review summarizes a total of 229 cytotoxic compounds isolated from deep-sea-derived fungi from 2010 to 2021. The emphasis is on the unique chemical diversity of these metabolic products, together with their relevant cytotoxic properties. Among the isolated metabolites, 82 compounds have been found to possess moderate to potent cytotoxic activities. Meanwhile, we also highlight some compounds with potent cytotoxicities (namely "star molecules") considering their high drug lead potential. This review reveals deep-sea-derived fungi as considerable resources for the development of new drugs and the potential of the newly discovered secondary metabolites as valuable antitumor lead compounds.

Keywords: deep-sea, fungi, secondary metabolites, cytotoxic activity, lead compounds

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Specialty section:
This article was submitted to Marine Biotechnology and Bioproducts, a section of the journal Frontiers in Marine Science

Received: *27 April 2022*
Accepted: *16 May 2022*
Published: *27 June 2022*

Citation:
Zhao G, Tang W, Zhang J, Shi P, Li Y, Wang J, Shen Q, Si H, Jiang L, Yu X, Zhu H, Chen G, Zhang X and Jia H (2022) Deep-Sea-Derived Fungi as Valuable Producers of Cytotoxic Secondary Metabolites and Their Leads Potential. Front. Mar. Sci. 9:929561. doi: 10.3389/fmars.2022.929561

1 INTRODUCTION

Covering approximately 72% of the Earth's surface, the oceans are considered to make significant contributions to the development of novel pharmaceutical resources. Of the total sea areas, 60% are deep seas that are covered by seawater at a depth of more than 2,000 m. The deep sea is quite a complicated and extreme ecosystem characterized by elevated hydrostatic pressure, low or high temperature (such as hydrothermal vents), absence of light, fickle salinity, oligotrophy, and low oxygen concentration (Zeng et al., 2010). It is the largest remaining unexplored aqueous habitat on Earth, and organisms in this realm are confronted by various fundamental challenges (Wu J. et al., 2013). To overcome these multiple extreme stresses, organisms that reside in deep sea ecosystems have evolved specific genetic capabilities to produce a large number of metabolic products, including small molecules such as secondary metabolites, proteins and enzymes, saccharides, and so on. These deep-sea-derived metabolic products have played important roles in adaptation to species communications and biotechnological and pharmaceutical applications.

Fungi are regarded as the richest and most varied eukaryotes on Earth, and their existence in every possible extreme environment makes them a valuable source for new drug discovery (Zain Ul Arifeen et al., 2019). Marine-derived fungi have proven to be untapped sources of novel marine natural products for exploitation in medicine. In addition to fungi living in terrestrial environments, marine-derived fungi suffer from the abovementioned extreme environmental stresses, and therefore, they have enjoyed specific metabolic pathways to synthesize structurally creative metabolites with remarkable biological activities (Zhang et al., 2020). However, although massive metabolites have been reported from marine-derived fungi thus far (Zhang et al., 2020; Carroll et al., 2021), it is a matter of fact that the search for new marine natural products is gradually approaching saturation. As a result, the discovery of new marine natural products from unexplored environments has become an alternative pathway. Extremophiles isolated from the deep sea, hydrothermal vents, cold water, and polar regions, have attracted much attention (Soldatou and Baker, 2017). They are extraordinarily adapted and metabolically active under extreme environmental conditions, which affords a large number of marine natural products.

Cancer is the leading lethal disease worldwide. Although localized surgery and radiation approaches play an important role in the treatment of cancer, it is impossible to prevent the dissemination of tumor cells. Chemotherapy has become the most preferred treatment of choice for patients, which has aroused an urgent necessity and priority to discover new molecules (Yuan et al., 2020). Natural products have benefited greatly from the growth of the pharmaceutical industry, especially pharmacologically attractive leads and potential clinical therapeutic drugs. It is estimated that among all 75 small-molecule approved antitumor drugs from 1946 to 1980, 53.3% are derived from unaltered natural products or their derivatives (Newman and Cragg, 2020). Among them, marine natural product-originated drugs have attracted more and more attention. As for antitumor drugs, **Figure 1** listed representative marine natural products originated antitumor drugs, which have been approved and in phase III, II, and I clinical trials. For example, cytarabine obtained from a marine sponge is mainly used to treat acute and chronic lymphocyte in clinic (Deshmukh et al., 2018) (**Figure 1**). Eribulin (E7389), which was isolated from a marine sponge, was approved by FDA for metastatic breast cancer. In addition, plinabulin, which was previously

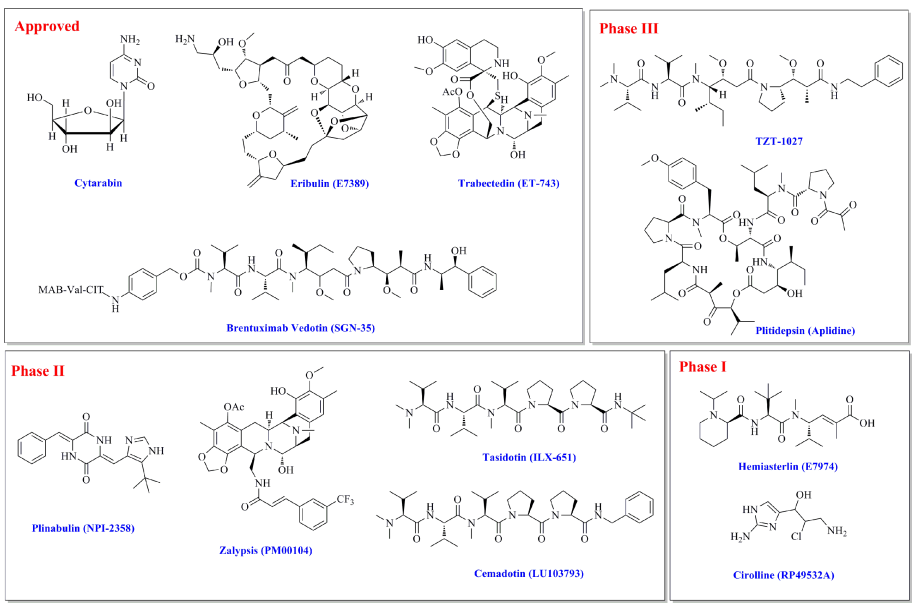

FIGURE 1 | Marine natural products originated antitumor drugs (approved and in phase III, II, and I clinical trial).

isolated from a marine-derived fungus, is in a phase II clinical trial for the treatment of non-small-cell lung cancer (Zhou et al., 2016).

As previously mentioned, deep-sea-derived fungi (depth > 1000 m) have been recognized as valuable treasure houses for structurally novel and biologically active secondary metabolites. Many interesting reviews of deep-sea-derived secondary metabolites have been published in recent years. For example, Sun et al. summarized 442 new molecules obtained from deep-sea-derived fungi, actinomycetes, bacteria, and archaea, with emphasis on structural characteristics, biological activities, and biogenetic origins (Sun et al., 2020). Wang et al. described 98 secondary metabolites with various bioactivities such as antitumor, antibacterial, antiviral, and anti-inflammatory isolated from deep-sea fungi and bacteria during 2018–2020 (Wang et al., 2020a). Wang et al. reported 180 metabolites with anticancer, antimicrobial, antifungal, antiprotozoal, and antiviral activities from deep-sea fungi (Wang et al., 2015). However, to the best of our knowledge, there are no reviews particularly focused on cytotoxic secondary metabolites isolated from deep-sea fungi. Considering their interesting chemical structures and potent lead potential, in this review, we summarize a total of 229 cytotoxic compounds isolated from deep-sea fungi from 2010 to 2021. The emphasis is on their unique chemical diversity, their relevant cytotoxic properties, and their potential as drug leads. This review will reveal deep-sea-derived fungi as considerable resources for the development of new drugs and the potential of newly discovered secondary metabolites as valuable antitumor lead compounds.

2 CYTOTOXIC SECONDARY METABOLITES FROM DEEP-SEA FUNGI

2.1 Alkaloids and N-Containing Compounds

2.1.1 Diketopiperazines

Thirty-one diverse diketopiperazines (**1**–**31**, **Figure 2**) with considerable cytotoxic activity were isolated from deep-sea fungi. Three diketopiperazines with a sulfur bridge, bisdethiobis(methylthio)-dehydrogliotoxin (**1**), bisdethiobis-(methylthio)gliotoxin (**2**), and gliotoxin (**3**), were isolated from *Aspergillus* sp. SCSIO Ind09F01, which was obtained from deep-sea sediment collected from the Indian Ocean (Lat: 82.04513333' N, Long: 0.497883333' E) at a depth of 4530 m (Luo et al., 2017). Compound **3** displayed significant cytotoxicity against the K562, A549, and Huh-7 cell lines, with IC_{50} values of 0.191, 0.015 and 95.4 μM, respectively. Two new bisindole diketopiperazines, luteoalbusins A–B (**4**–**5**), along with eight known compounds (**6**–**13**), were isolated from the fungus *Acrostalagmus luteoalbus* SCSIO F457 originating from deep-sea sediment (South China Sea, N 21°28.567', E 118°57.297'; 2801 m depth) (Wang et al., 2012). The bisindole diketopiperazines **4**–**8** showed more potent cytotoxicities against SF-268, MCF-7, NCI-H460, and HepG-2 cell lines than monoindole compounds (**9**–**13**), especially for the new compounds **4**–**5**, which were stronger than the positive control cisplatin (**Supplementary Table 1**). The polysulfide bridge of **4**–**8** can contribute more to their cytotoxicity. Three new diketopiperazines, dichotocejpins A–C (**14**–**16**), together

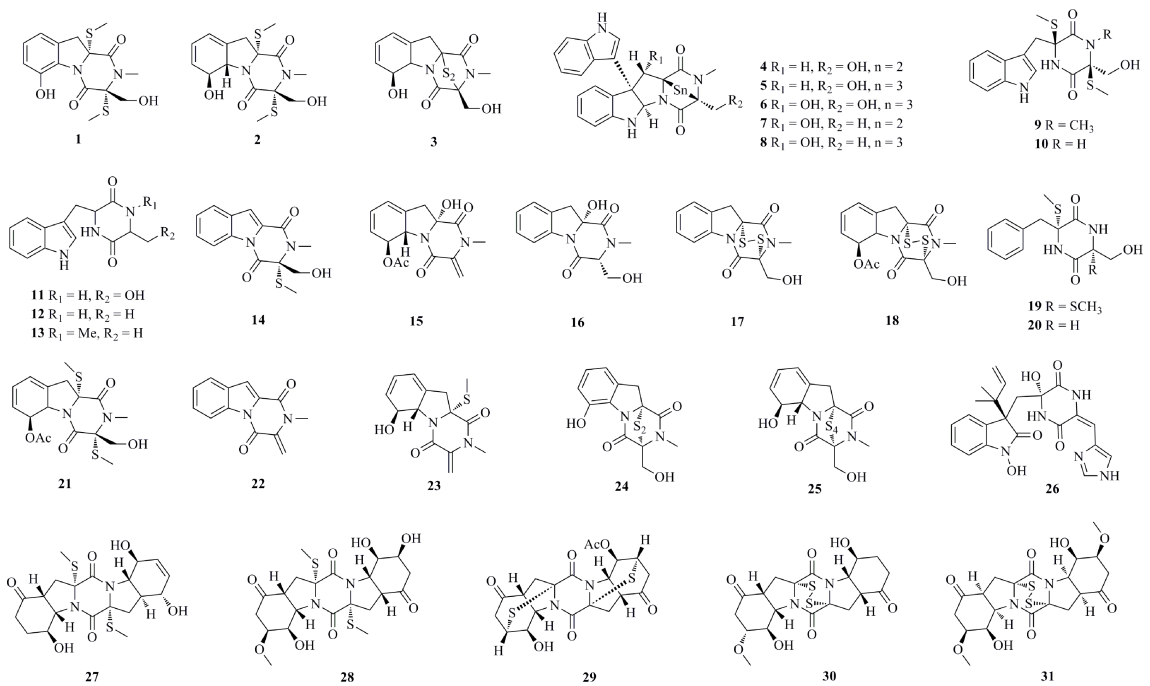

FIGURE 2 | Diketopiperazines isolated from deep-sea fungi (**1**–**31**).

with eight known analogs (**2**–**3**, **17**–**22**), were isolated from *Dichotomomyces cejpii* FS110 (isolated from a deep-sea sediment sample from the South China Sea, N 19°0.368', E 117°58.233'; 3941 m depth) (Fan et al., 2016). Compounds **17**, **3**, and **18**, which contain a disulfide bond, exhibit the most potent inhibitory activities against SF-268, MCF-7, NCI-H460, and HepG-2 cell lines, with IC_{50} values in the range of 0.08–1.52 μM. Chemical studies of *Penicillium* sp. JMF034, which was isolated from deep-sea sediments collected from Fujikawa, Suruga-Bay, Japan, at a depth of 1151 m, yielded seven gliotoxin-related metabolites, **1**–**3**, **17**, and **23**–**25** (Sun et al., 2012). All of them show significant activity against P388 murine leukemia cells. Compounds **3**, **17**, **24**, and **25** exhibit the most potent activity, with IC_{50} values of 0.024, 0.058, 0.056, and 0.020 μM, respectively. A new indolyl diketopiperazine derivative, penilline C (**26**), was isolated from *P. chrysogenum* SCSIO 07007, separated from a deep-sea hydrothermal vent environment sample (Western Atlantic, 126.8983°E, 27.7875° N, 1028 m depth) (Han et al., 2020). Four new thiodiketopiperazines, 5'-hydroxy-6'-ene-epicoccin G (**27**), 7-methoxy-7'-hydroxyepicoccin G (**28**), 8'-acetoxyepicoccin D (**29**), and 7'-demethoxyrostratin C (**30**), as well as a known analog **31** were isolated from *Epicoccum nigrum* SD-388, a fungus obtained from deep-sea sediments (West Pacific, 4500 m depth) (Chi et al., 2020). Compounds **30** and **31** display strong activity against Huh7.5 liver tumor cells with IC_{50} values of 9.52 and 4.88 μM, respectively, which were comparable to that of the positive control, sorafenib (IC_{50} = 8.2 μM).

2.1.2 N-Containing Compounds

Cytotoxic N-containing compounds (**32**–**52**) isolated from deep-sea fungi are shown in **Figure 3**. Three new prenylated indole alkaloids, penipalines A–C (**32**–**34**), as well as two known analogs **35**–**36**, were isolated from the deep-sea-sediment-derived fungus *P. paneum* SD-44 (Li et al., 2014). The new compounds **32** and **33** are β-carbolines, while **34** is an indole carbaldehyde derivative. Compounds **33** and **34** are active against the A-549 and HCT-116 cell lines, with IC_{50} values of 20.44 and 21.54 μM for A-549 cells and 14.88 and 18.54 μM for HCT-116 cells, respectively. A new acremolin-type alkaloid acremolin D (**37**) and a known compound **38**, both containing an unprecedented 1*H*-azirine unit, were isolated from *A. sydowii* MCCC 3A00324, which was obtained from the deep sea sediment (2246 m) of the South Atlantic Ocean (W13.6639°, S14.2592°) (Niu et al., 2021). Compound **37** shows certain effects against HeLa-S3 and K562 cells, with inhibition rates of 30.6% and 25.1%, respectively, at a concentration of 20 μM, whereas **38** is active against A549, HepG2, and K562 cells, with inhibition rates of 20.9–35.5%. Seven new pyridone alkaloids (**39**–**45**) were isolated from the deep-sea fungus *Phomopsis tersa* FS441 obtained from a sediment sample (Indian Ocean, 88°58'640" E, 0°00'307" S, 3000 m depth) (Chen et al., 2019). Structurally, **39**–**41** and **43** represent phenylfuropyridone racemates with a rare 6-6/5/5 ring system, and **42** was reported as a phenylpyridone racemate with a 6-6/6 core. In addition, **45** is the first 5-phenylpyridone derivative with an unprecedented furo [3,2-c]pyridin-4(5*H*)-one skeleton. Compound **43b** possesses mild cytotoxic activities against

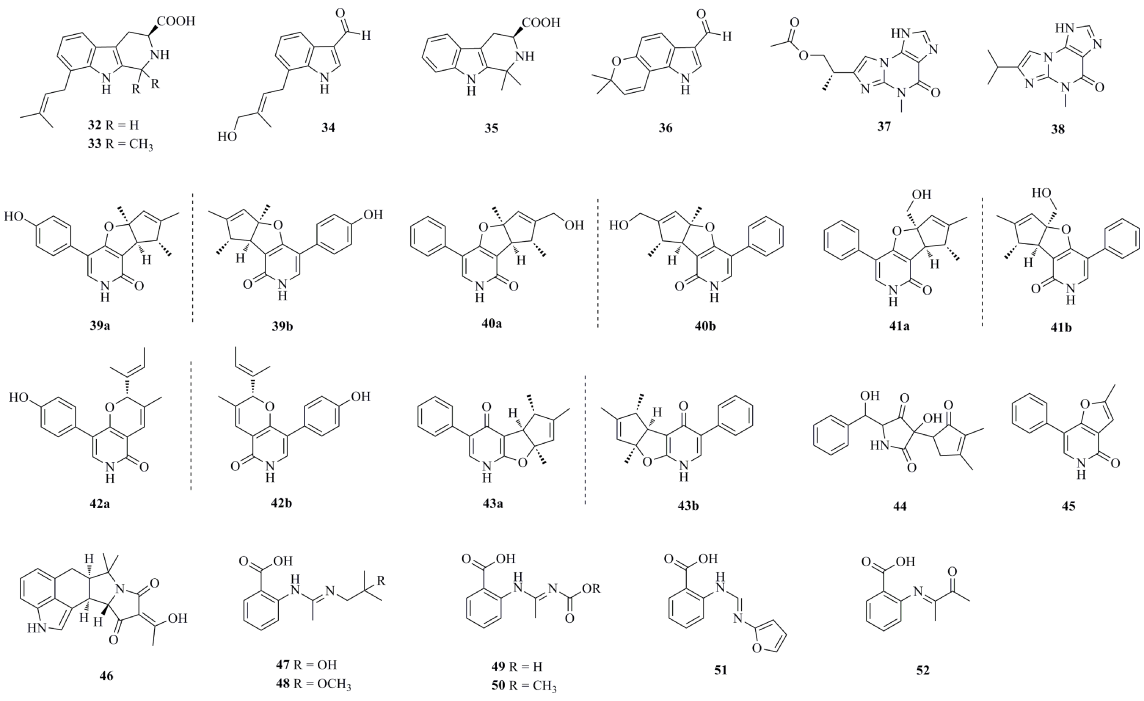

FIGURE 3 | N-containing compounds isolated from deep-sea fungi (**32**–**52**).

SF-268, MCF-7, HepG-2 and A549 cell lines with IC_{50} values of 32.0, 29.5, 39.5 and 33.2 μM, respectively. **46** was isolated from the fungus *A. flavus* SCSIO F025 derived from deep-sea sediments in the South China Sea (117.062°E, 20.077°N, at a depth of 1781 m) (Xiang et al., 2021). Compound **46** shows broad-spectrum cytotoxicity against SF-268, HepG-2, MCF-7, and A549 cell lines with IC_{50} values ranging from 24.38 to 48.28 μM. Six anthranilic acid derivatives **47**–**52** were isolated from the marine sediment-derived fungus *P. paneum* SD-44 (Li et al., 2013). Compounds **47** and **51** exhibit higher inhibitory activity against the RKO cell line with IC_{50} values of 8.4 and 9.7 μM, respectively, while **52** exhibits higher inhibitory activity against the HeLa cell line with an IC_{50} value of 6.6 μM than against the positive control fluorouracil (with IC_{50} values of 25.0 and 14.5 μM).

2.1.3 Peptides

Figure 4 lists nine cytotoxic peptides isolated from deep-sea fungi. A bioassay-guided chemical investigation of *Aspergillus* sp. SCSIOW2 [separated from a deep marine sediment sample in the South China Sea (112°30.203E, 18°1.654N) at a depth of 2439 m] yielded a novel cyclic dipeptide, 14-hydroxy-cyclopeptine (**53**) (Zhou et al., 2016). This cyclodipeptide possesses NO production inhibitory activity and no cytotoxicity at the tested dose range (30–100 μg/mL). The fungus *Simplicillium obclavatum* EIODSF 020 was isolated from deep sea sediment collected from the East Indian Ocean (10°00' N, 84°33' E; 4571 m depth) (Liang et al., 2016). Eight new peptides, simplicilliumtides A–H (**54**–**61**), were isolated from this fungal strain. **54** and **55** are linear tetrapeptides bearing a 2-aminobenzoic acid residue, while **56**–**61** are acetylated linear tri- or dipeptides. Only weak cytotoxicity was observed for **54** and **60** toward the human leukemia HL-60 cell line and for **58** and **61** toward the K562 cell line.

2.2 Terpenoids and Steroids

As shown in **Figure 5**, four new chlorinated eremophilane-type sesquiterpenes **62**–**65** were isolated from an Antarctic deep-sea fungus, *Penicillium* sp. PR19N-1, which was obtained from marine sludge in Prydz Bay (1000 m depth), Antarctica (Wu G. et al., 2013). **62** demonstrated moderate activity against HL-60 and A549 cell lines, with IC_{50} values of 11.8 and 12.2 μM, respectively. The fungal strain *Penicillium* sp. F00120 isolated from a deep sea sediment sample collected at a depth of 1300 m produced a new sesquiterpene quinone, named penicilliumin A (**66**) (Lin et al., 2012). Compound **66** is active against the A375, B16 and HeLa cell lines with GI_{50} values of 22.88, 27.37, and 44.05 μg/mL, respectively. Two new tetranorlabdane diterpenoids, asperolides D (**67**) and E (**68**), were isolated from *A. wentii* SD-310, a fungus obtained from a deep sea sediment sample in the South China Sea at a depth of 2038 m (Li et al., 2016a). Compound **68** shows certain activities against HeLa, MCF-7, and NCI-H446 cell lines, with IC_{50} values of 10.0, 11.0, and 16.0 μM, respectively. A systematic isolation of *Botryotinia fuckeliana* MCCC 3A00494, a fungus isolated from the western Pacific Ocean (5572 m depth), provided 71 new and eight known aphidicolin derivatives (structures in **Figure S1** and **Figure S2 in Supplementary Material**) (Niu et al., 2019a). Among them, aphidicolin A8 (**69**) is found to observably induce apoptosis in T24 (IC_{50}, 2.5 μM) and HL-60 (IC_{50}, 6.1 μM) cells by causing DNA damage, suggesting that it is a promising lead compound. Asperethers A–E (**70**–**74**), five new 20-nor-isopimarane diterpenoids, were isolated from the abovementioned *A. wentii* SD-310 (Li et al., 2016b). **70**–**74** possess a cycloether unit with a unique 6/6/6/5 tetracyclic skeleton, which has not been reported up to date. Compounds **70**–**74** exhibit cytotoxic activities against the A549, HEK293, MCF-7, SMMC-7721, and T-47D cell lines, with IC_{50} values of 10–48 μM. A new pimarane-type diterpenoid, botryopimarene A (**75**), was discovered from the deep-sea fungus *B. fuckeliana* MCCC 3A00494 (Niu et al., 2019b). Photeroids A (**76**) and B (**77**), two unique phenol-sesquiterpene meroterpenoids, were isolated from *Phomopsis tersa* FS441, a fungus separated from a sediment sample that was collected at a depth of 3000 m in the Indian Ocean (88°58.640′ E, 0°00.307′ S) (Chen et al., 2020a). **76** and **77** represent the first examples of phenolic sesquiterpene meroterpenoids featuring a highly fused 6/6/6/6 tetracyclic ring skeleton. Compounds **76** and **77** exert mild cytotoxicities against SF-268, MCF-7, HepG-2, and A549 cell lines, with IC_{50} values ranging from 20.0 to 26.2 μM. Three novel meroterpenoids **78**–**80** were isolated from the same *P. tersa* FS441 fungus (Chen et al., 2020b). **78** represents the first tropolonic sesquiterpene having a highly fused 6/6/11/6/5/5 ring system, while **79** is the first meroterpenoid featuring a rare

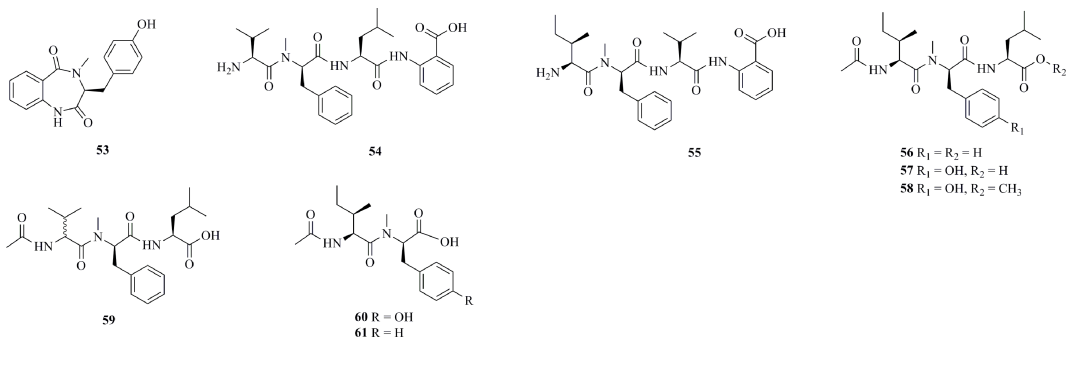

FIGURE 4 | Peptides isolated from deep-sea fungi (**53**–**61**).

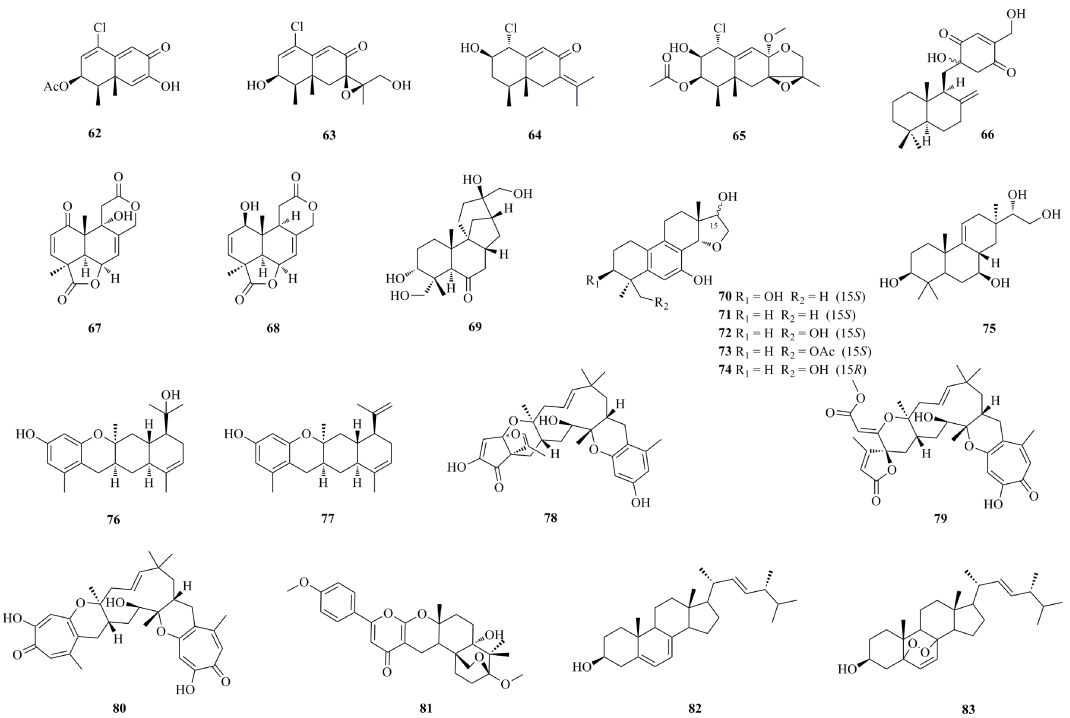

FIGURE 5 | Terpenoids and steroids isolated from deep-sea fungi (**62**–**83**).

7/6/11/6-5 spiral core skeleton. **79** and **80** exhibit potent antiproliferative effects against SF-268, MCF-7, HepG-2, and A549 cell lines, with IC_{50} values of 0.01–1.30 μM, which were even higher than the positive control adriamycin. A new merosesquiterpenoid, yaminterritrem C (**81**), was isolated from the deep-sea-derived strain *P. chrysogenum* SCSIO 41001, which was obtained from the deep sea sediment of the Indian Ocean (Lat: 10.00371667°N, Long: 88.72803333°E) at a depth of 3386 m (Chen et al., 2017). **81** possesses a rare naphtho[2,1-*b*]pyrano-[3,2-*e*]pyran moiety. *P. chrysogenum* strain S003, a fungus isolated from Red Sea deep sediment, yielded two cytotoxic steroids **82** and **83** (Alshehri et al., 2020). **82** and **83** show cytotoxic effects against A-549, DU-145, MCF-7, and HepG2 cell lines, with IC_{50} values ranging from 1.5 to 21.26 μM.

2.3 Polyketides

2.3.1 Azaphilones

A total of 23 azaphilones with an oxabicyclic core were isolated from deep-sea fungi (**Figure 6**). Eight new nitrogenated azaphilones (**84**–**91**) and two known compounds (**92** and **93**) were isolated from *Chaetomium globosum* MP4-S01-7, a fungus obtained from a water sample collected at a depth of 4300 m (19° 57′32.9205″ N, 161°51′47.3181″ E) in the West Pacific Ocean (Wang et al., 2020b). **84**, **85**, and **88** exhibit potent cytotoxicities against MGC803 and AGS cell lines, with IC_{50} values less than 1 μM. Moreover, **85** arrests the cell cycle in the G1 phase. **84** and **85** induce apoptosis in a concentration-dependent manner. Eight chlorinated azaphilone derivatives (**94**–**101**), including five new derivatives (**94**–**98**), were isolated from the deep-sea fungus *Phomopsis tersa* FS441 (Chen et al., 2021). Structurally, **95** features a unique 6/6-6 carbon skeleton, rather than a tetrahydrofuranyl ring such as that in **96**. **97** and **98**, a pair of diastereomers with a characteristic and rare epoxide ring, exhibit potent cytotoxicity against MCF-7, SF-268, and A549 cell lines with IC_{50} values ranging from 5.4 to 8.3 μM. Another five chlorinated azaphilone pigments (**102**–**106**) were produced by a *Chaetomium* sp. strain NA-S01-R1, which was isolated from seawater at a depth of 4050 m (20°25′11.0321″ N, 155°51′ 22.1549″ E) in the West Pacific Ocean (Wang et al., 2018). **103** shows the strongest activity toward HepG2 cells, with an IC_{50} value of 3.9 μM, while **102** and **104** were found to be active against HeLa cells, with IC_{50} values of 5–8 μM.

2.3.2 Tetramic Acid and Sorbicillinoid Derivatives

Tetramic acid derivatives (**107**–**120**, **Figure 7**) are characterized as simple heterocycles with pyrrolidine-2,4-dione. Six new tetramic acid derivatives with a decalin ring (**107**–**112**) were characterized from the fungus *Trichobotrys effuse* DFFSCS021 derived from the deep sea sediment of the South China Sea (Sun et al., 2015). **107**, **108**, and **112** potently inhibit the KG-1a cell line with IC_{50} values of 5.44, 8.97, and 6.16 μM. *Cladosporium* sp. SCSIO z0025 derived from deep-sea sediment (at a depth of 1330 m from the Okinawa Trough, 27°48.12′N and 126°58.89′E) produced eight new tetramic acid derivatives, cladosporiumins A–H (**113**–**120**) (Huang et al., 2018). **113**–**115** were characterized as 3-acyltetramic acids incorporating a hexyl enic alcohol side chain and a six-membered lactone ring. Three new sorbicillinoids **121**–**123** were isolated from a deep-sea sediment-

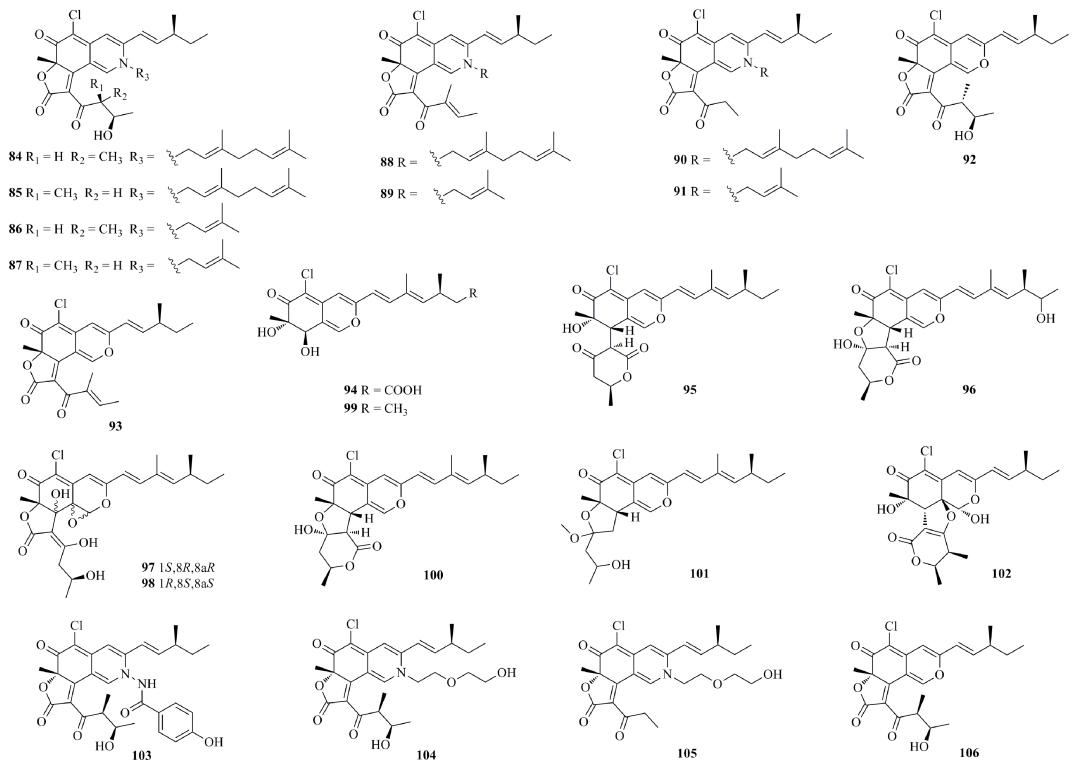

FIGURE 6 | Azaphilones isolated from deep-sea fungi (**84**–**106**).

derived fungus, *Phialocephala* sp. FL30r (obtained from an underwater sample from the east Pacific site W2003-03, W154° 04′57′′, N8°30′20′′, 5059 m depth) (Li et al., 2011). **121** possesses the rare bicyclo[3.2.1] lactone skeleton and displays moderate cytotoxic activity against P388 (IC_{50}, 11.5 μM) and K562 (IC_{50}, 22.9 μM) cell lines. **122** and **123** were found to display submicromolar activities against P388, with IC_{50} values of 0.1 and 0.2 μM, respectively. Two new bisorbicillinoids, **124** and **125**, were isolated from *Phialocephala* sp. FL30r derived from deep-sea sediment from ES304 (W145°23′03′′, N8°19′50′′, depth 5059 m) (Li et al., 2007). Both **124** and **125** only show weak cytotoxic activities against the P388, HL60, BEL7402, and K562 cell lines.

2.3.3 Chromones

Cytotoxic chromone polyketides (**126**–**154**) isolated from deep-sea fungi are listed in **Figure 8**. Two new xanthones **126**–**127** and a known compound **128** were isolated from an *A. sydowii* C1-S01-A7, separated from a seawater sample obtained at a depth of 4950 m (20°07′02.7264′′ N, 158°46′52.3352′′ E) from the West Pacific Ocean (Wang et al., 2019a). Compound **128** displays selective cytotoxicity against the A549 cell line with an IC_{50} value of 8.1 μM. The fungal strain *Engyodontium album* DFFSCS021 isolated from a marine sediment sample in the South China Sea (19°00′368″N, 117°58′223″E, 3739 m depth) was found to produce eight new chromones, **129**–**136** (Yan et al., 2014). Compound **136** shows strong cytotoxicity against the U937 cell line with an IC_{50} value of 4.9 μM. Five new chromone polyketides **137**–**141** were isolated from the deep-sea sediment-derived fungus *Diaporthe phaseolorum* FS431 collected from the Indian Ocean (depth 3605 m, 7°57.75944′ N, 89°19.43851′ E) (Guo et al., 2019). **138** was first reported as an unprecedented chromone with a recombined five-member lactone ring. Four new tetralone derivatives **142**–**145** and three known polyketides **146**–**148** were isolated from the deep-sea derived fungus *Cladosporium cladosporioides* HDN14-342 (collected from the Indian Ocean, depth 3471 m) (Zhang et al., 2016a). The 1-tetralone dimers linked by a C–C bond are widespread fungal polyketides. **142** and **143** are new dimeric forms of indanone and 1-tetralone adducts, and compound **145** is the first halogenated cladosporols. **145** shows relatively higher cytotoxic activity against HeLa cells with an IC_{50} value of 3.9 μM. The deep-sea sediment-derived fungus *Penicillium* sp. SCSIO Ind16F01 afforded a cytotoxic chromone dimer **149** against K562, MCF-7, and SGC7901 cells, with IC_{50} values of 16.6, 16.3, and 15.8 μM, respectively (Liu et al., 2017). Two new chromones **150** and **151**, one new anthraquinone **152**, and one known chromone dimer **153** were isolated from the fungus *D. phaseolorum* FS431 (Niu et al., 2019c). **153** shows strong activity against MCF-7, HepG-2, and A549 cells, with IC_{50} values of 2.60, 2.55, and 4.64 μM, respectively. Secalonic acid F (**154**) was isolated from the fungus *Penicillium* sp. F11 derived from deep-sea sediment samples at a depth of 1744 m in the Southwest Pacific (Li et al., 2012). **154** shows significant

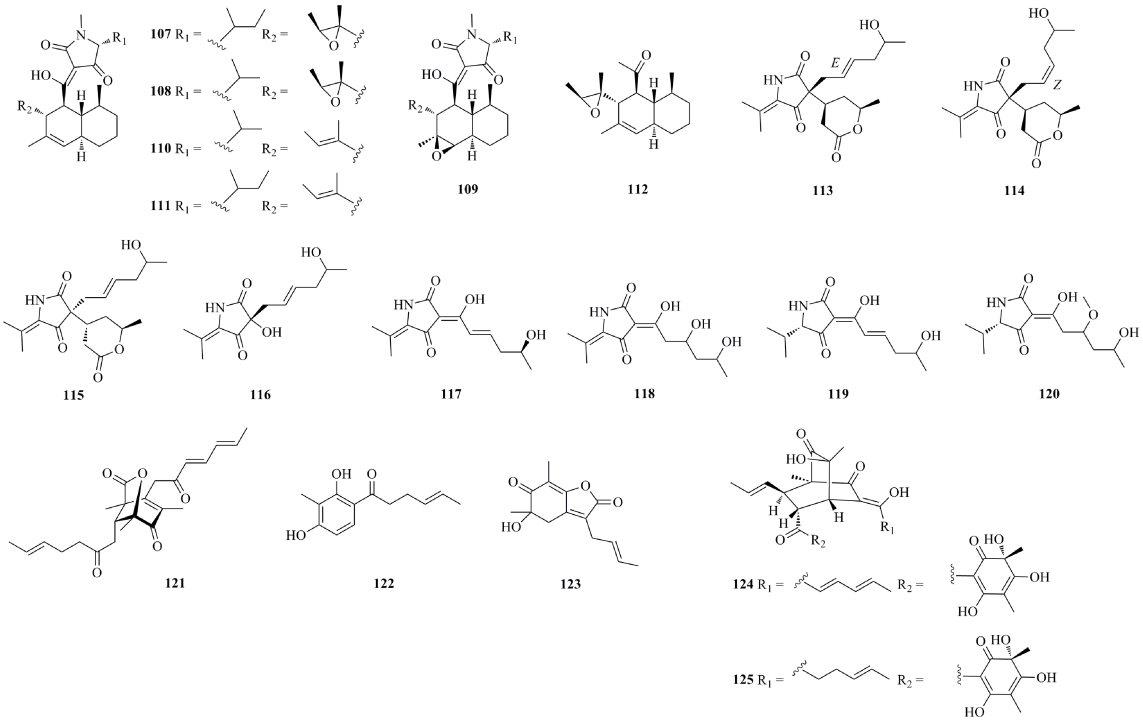

FIGURE 7 | Tetramic acid and sorbicillinoid derivatives isolated from deep-sea fungi (**107**–**125**).

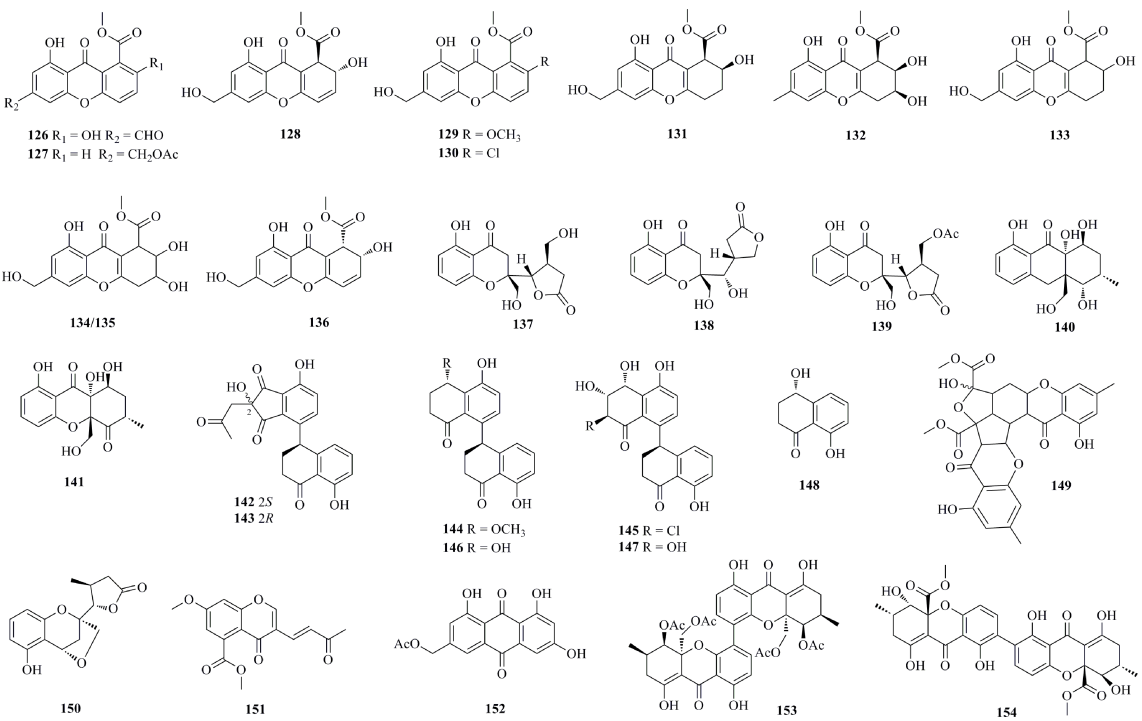

FIGURE 8 | Chromones isolated from deep-sea fungi (**126**–**154**).

cytotoxicity and induced apoptosis in HL60 cells with an IC_{50} value of 4.1 μg/mL.

2.3.4 Benzophenones

Figure 9 shows benzophenones (**155**–**163**) from deep-sea fungi. Four new benzophenones named tenellones J–M (**155**–**158**) were produced by culturing of *Phomopsis lithocarpus* FS508 (isolated from a deep-sea sediment sample collected from the Indian Ocean, 111°53.335′ E, 16°50.508′ N, depth 3606 m) (Liu et al., 2021a). **156** moderately inhibits the SF-268 cell line with an IC_{50} value of 11.36 μM. Five new highly substituted benzophenone derivatives, tenellones D–H (**159**–**163**), were isolated from the deep-sea sediment-derived fungus *Phomopsis lithocarpus* FS508, which was collected at a depth of 3606 m from the Indian Ocean (111°53.335′ E, 16°50.508′ N) (Xu et al., 2018). Compounds **159**–**163** possess naturally occurring aldehyde functionalities, which are rare in natural products. **163**, in particular, displays modest cytotoxic activity against HepG-2 and A549 cell lines, with IC_{50} values of 16.0 and 17.6 μM, respectively.

2.3.5 Other Polyketides

Other types of polyketides (**164**–**212**) isolated from the deep-sea are shown in **Figures 10** and **11**. Five new 2,3-dihydro-1*H*-indene derivatives (**164**–**168**) were isolated from the previously mentioned deep-sea sediment-derived fungus *Phomopsis lithocarpus* FS508 (Liu et al., 2021a). They possess a weak ability against SF-268, MCF-7, HepG-2, and A-549 cells (IC_{50} > 50 μM). Furthermore, chemical investigations of this fungal strain also led to the isolation of lithocarols A–F (**169**–**175**) possessing a novel highly oxygenated isobenzofuran (Xu et al., 2019). **169**–**173** were characterized as the first examples of polyketal derivatives in the tenellone family, while **174** is a rarely observed tenellone lactone. These compounds exerted moderate cytotoxicities against HepG-2, MCF-7, SF-268, and A549 cell lines (IC_{50}, 10.5 −38.7 μM). A new isopentylated dibenzodioxocinone **176** and a new isopentylated pyran-3,5-dione derivative **177** were isolated from *P. canescens* SCSIO z053, a fungus collected from deep-sea sediment from the Okinawa Trough (27°33.07′ N, 126°58.36′ E, 1387 m depth) (Dasanayaka et al., 2020). An *Alternaria* sp. fungus MCCC 3A00467 was isolated from a sediment of the Pacific Ocean at a depth of 5295 m. This fungus was found to produce three new phomalone derivatives **178**–**180** and seven known analogs **181**–**187** (Zhong et al., 2022). **179** shows cytotoxic activity against the U266 cell line with an IC_{50} value of 24.99 μg/mL, while **187**, the most active compound, possesses cytotoxicity against U266, HepG2, and A549 cells with IC_{50} values of 13.26, 14.69 and 24.39 μg/mL, respectively. A new dihydrobenzofuran-phenyl acrylate hybrid **188** was isolated from the culture of *A. terreus* CC-S06-18 obtained from a seawater sample at a depth of 5250 m from the North Pacific Ocean (Wang et al., 2020c). **188** shows selective cytotoxicity against HGC27, MGC803, BGC823, and AGS cells, with IC_{50} values of 3.4, 7.0, 6.2, and 8.2 μM, respectively. Further pharmacological studies indicate that **188** inhibits cell cycle progression and induced apoptosis. Two new citrinin dimers, **189** and **190** were isolated from the fungus *P. citrinum* NLG-S01-P1 obtained from a seawater sample at a depth of 4650 m (Wang et al., 2019b). **189** is active against the HeLa cell line with an IC_{50} value of 4.1 μM. A dimeric isocoumarin, bipenicilisorin (**191**), a citrinin dimer, penicitrinone F (**192**), and a *δ*-valerolacton **193** were isolated from the deep-sea fungus *P. chrysogenum* SCSIO 41001 (Chen et al., 2017). Cytotoxic evaluation indicated that **193** significantly inhibits K562, A549, and Huh-7 cell lines with IC_{50} values of 6.78, 6.94, and 2.59 μM, respectively, whereas **192** specifically shows inhibitory activity against EV71 with an IC_{50} value of 14.50 μM.

The fungus *P. chrysogenum* MCCC 3A00292 derived from the South Atlantic Ocean at a depth of 2076 m yielded five versiol-type derivatives **194**–**198** and two novel *γ*-lactones **199**–**200** (Niu et al., 2019d). **194**–**198** represent a rare class of fungal polyketides with an alkylated decalin nucleus, while **199**–**200** are the first report of *γ*-lactones bearing a 1,3-dihydroxy-5-methylbenzene unit. **194** shows potent inhibitory activity against the BIU-87 cell line with an IC_{50} value of 10.21 μM. **197** and **198** are active against the ECA109 cell line with IC_{50} values of 12.41 and 15.60 μM, respectively. Two new cytotoxic heteroatom-containing compounds **201** and **202** were isolated from the deep-sea sediment-derived fungus *P. citreonigrum* XT20-134 (Tang et al., 2019). Their IC_{50} values toward the Bel7402 cell line were 7.63 and 13.14 μM and toward the HT1080 cell line were

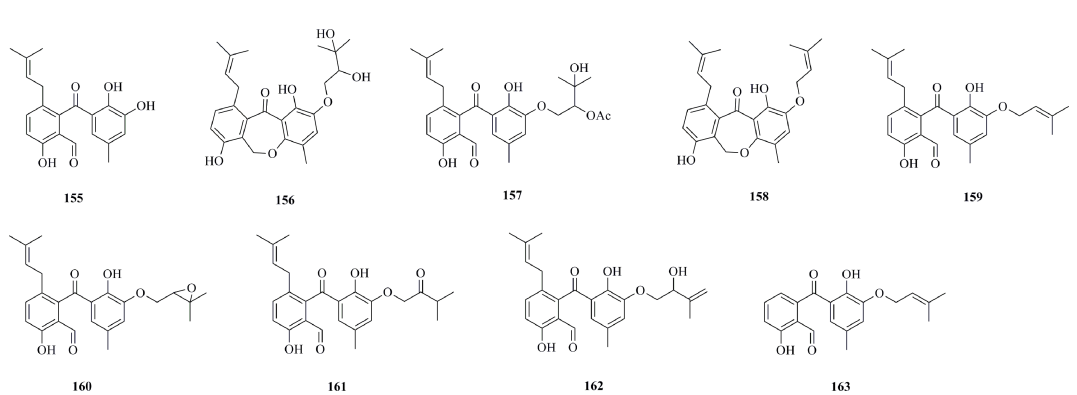

FIGURE 9 | Benzophenones isolated from deep-sea fungi (**155**–**163**).

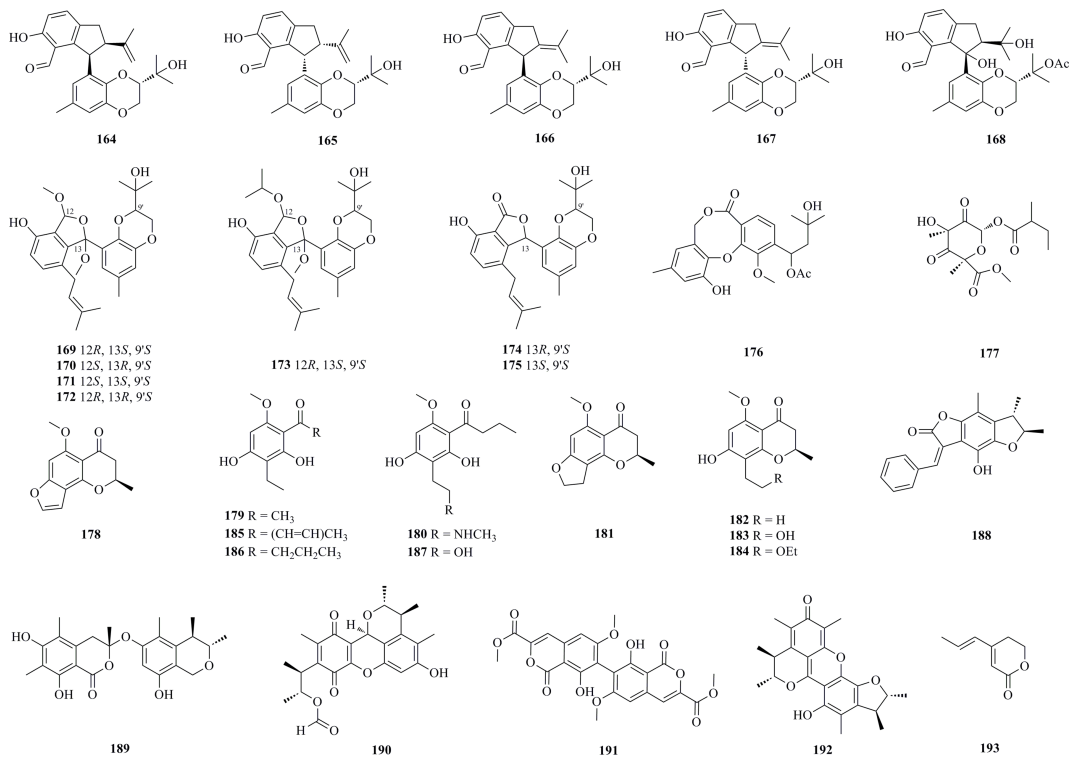

FIGURE 10 | Other polyketides isolated from deep-sea fungi (**164**–**193**).

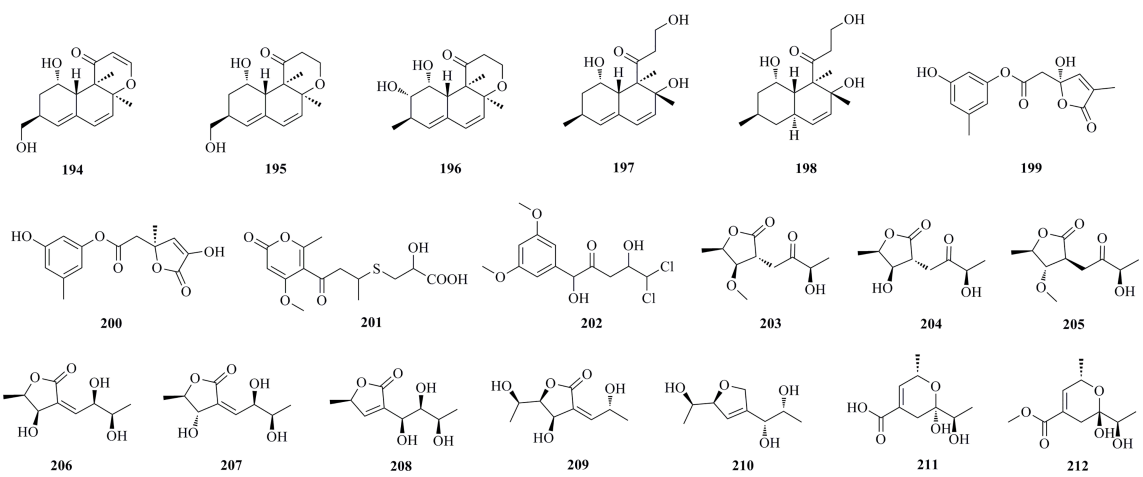

FIGURE 11 | Other polyketides isolated from deep-sea fungi (continued) (**194**–**212**).

10.22 and 16.53 μM, respectively. Ten new C_9 polyketides belonging to the aspyrone derivatives **203**–**212** were isolated from deep-sea-derived *A. ochraceus* (Zou et al., 2020). Compounds **207**–**210** exert cytotoxic effects on the BV-2 cell line with inhibition rates ranging from 72.81% to 50.29%.

2.4 Phenolic Derivatives

As shown in **Figure 12**, seventeen phenolic derivatives (**213**–**229**) have been isolated. *Engyodontium album*, isolated from marine sediments collected at a depth of 2530 m in the Pacific Ocean (176.45° W, 21.449° S), produced two new benzoate derivatives **213**

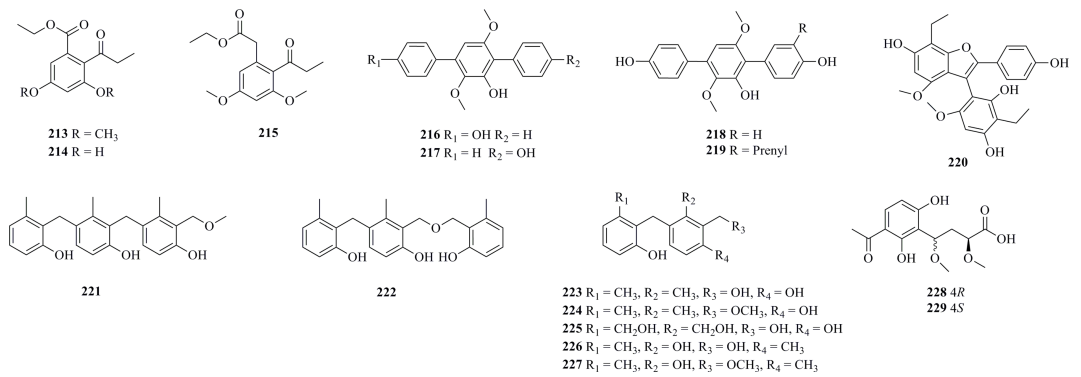

FIGURE 12 | Phenolic derivatives isolated from deep-sea fungi (**213**–**229**).

and **214** and a new phenylacetate derivative **215** (Wang et al., 2017). However, all of them only show weak cytotoxicity against HeLa cells (IC_{50} > 50 μM). One new (**216**) and three known (**217**–**219**) *p*-terphenyl derivates were isolated from the fungus *A. candidus* collected from the Atlantic Ocean at a depth of 3542 m (Lin et al., 2021). **213** and **214** display strong antiproliferative effects against HeLa, Eca-109, Bel-7402, and PANC-1 cells, with IC_{50} values ranging from 5.5 μM to 9.4 μM. A highly substituted phenol derivative **220** was isolated from the deep-sea-derived fungus *Trichobotrys effuse* FS524 (Liu et al., 2020). **220** with an interesting 6-5/6/6 tetracyclic ring system exhibits moderate activities against SF-268, MCF-7, HepG-2, and A549 cell lines with IC_{50} values ranging from 30.1 to 43.3 μM (compared with the positive control cisplatin, 2.5–3.2 μM). *P. fellutanum* HDN14-323, isolated from a sediment sample collected at a depth of 5725 m from the Indian Ocean, produced seven new 6-methylsaligenin derivatives, including two trimeric derivatives, **221** and **222**, and five dimeric derivatives, **223**–**227** (Zhang et al., 2016b). **224** was found to possess the best activity against the HeLa cell line with an IC_{50} value of 9.3 μM. Two new globoscin derivatives, **228** and **229**, were isolated from the deep-sea-derived fungus *A. fischeri* FS452 (Liu et al., 2021b). **229** demonstrates potential activities against SF-268, MCF-7, HepG-2, and A549 cell lines with IC_{50} values of 7.56–9.98 μM.

3 DISCUSSION

3.1 Structural Diversity of the Described Compounds Isolated From Deep-Sea Fungi

It is estimated that over 500 secondary metabolites have been isolated from deep-sea-derived fungi (> 1000 m). However, these microorganisms remain a relatively untapped source of bioactive molecules both structurally and biologically compared to the 24000 reported marine natural products (Carroll et al., 2021). This review first summarizes a total of 229 cytotoxic compounds isolated from deep-sea fungi from 2010 to 2021. They are further classified into diketopiperazines (**1**–**31**), alkaloids (**32**–**52**), peptides (**53**–**61**), terpenoids and steroids (**62**–**83**), azaphilones (**84**–**106**), tetramic acid and sorbicillinoid derivatives (**107**–**125**), chromones (**126**–**154**), benzophenones (**155**–**163**), other polyketides (**164**–**212**), and phenolic derivatives (**213**–**229**), according to their putative biogenetic sources. As shown in **Figure 13A**, among the 229 active compounds, approximately 56.33% are polyketides, which include 10.04% azaphilones, 8.30% tetramic acid and sorbicillinoid derivatives, 12.66% chromones, 3.93% benzophenones, and 21.40% other polyketides. These findings indicated that molecules grouped as polyketides are one of the most promising compounds as novel antitumor drug leads. Alkaloids are also the main structure type for these compounds. Taking into account diketopiperazines (13.54%) and peptides (3.93%), alkaloids account for 26.64% of the isolated compounds. In addition, compounds isolated from deep-sea fungi often contain heteroatoms, such as sulfur and chlorine. For example, compounds **1**–**9**, **17**–**20**, and **27**–**31** are rare sulfur-containing diketopiperazines, which were isolated exclusively from extreme marine environments. As mentioned earlier, the extreme marine environment can produce more natural products with novel structures, which is a potential resource for new antitumor drugs.

3.2 Diverse Fungal Species as Producers of Isolated Compounds

As shown in **Figure 13B**, a total of 15 fungal species in this review, including Acrostalagmus, Alternaria, Aspergillus, Botryotinia, Chaetomium, Cladosporium, Diaporthe, Dichotomomyces, Engyodontium, Epicoccum, Penicillium, Phialocephala, Phomopsis, Trichobotrys, and Simplicillium, have been reported as producing strains for these cytotoxic compounds. Among them, Penicillium, Phomopsis and Aspergillus are the most prolific fungal strains, with 55 (accounting for 23.40%), 38 (accounting for 16.17%), and 34 (accounting for 14.47%) compounds produced, respectively. The genera Aspergillus and Penicillium are regarded as the most widely studied fungal groups in nature. Interestingly, the deep-sea environment contains rare fungal species, such as Diaporthe, Dichotomomyces, and Engyodontium, which are rarely observed

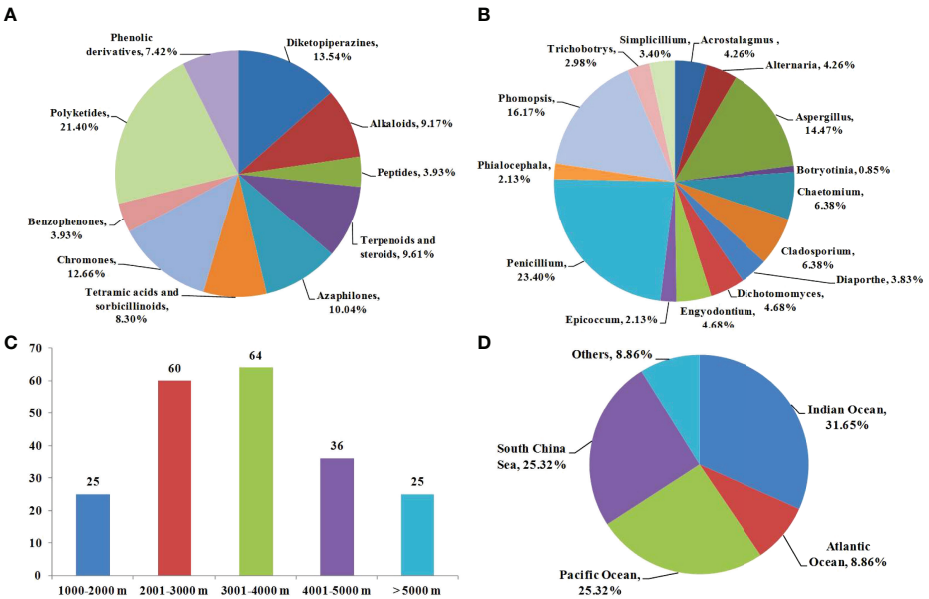

FIGURE 13 | **(A)** Chemical structures categories of the described compounds isolated from deep-sea fungi; **(B)** Producing strains categories of the isolated compounds; **(C)** Distribution categories of the producing strains; **(D)** Geographic origins of the isolated compounds.

in terrestrial environments. Moreover, the distributions of the producing strains are shown in **Figure 13C**. The deep-sea is defined as that more than 1000 m below the water surface. Among these compounds, a total of 25, 60, 64, 36, and 25 compounds were isolated from deep-sea samples at depths of 1000–2000 m, 2001–3000 m, 3001–4000 m, 4001–5000 m, and > 5000 m, respectively. It is clear that more compounds can be obtained at depths of 2000–4000 m. Organisms living in this area are considered to be more adapted to the environment. Therefore, fungi have evolved diverse metabolic pathways to produce more novel bioactive metabolites. Conversely, deeper depths mean much more demanding environments, which is disadvantageous for marine-derived fungi, although they still can produce metabolites when subjected to extreme environmental stresses. Regarding the geographic origins of deep-sea natural products in **Figure 13D**, 31.65% of them were isolated from the Indian Ocean, followed by the South China Sea (25.32%) and Pacific Ocean (25.32%).

3.3 Some "Star Molecules" With High Drug Lead Potential

Among the 229 isolated metabolites, a total of 82 compounds were found to possess moderate to potent cytotoxic activities. Among them, as shown in **Figure 14** and **Supplementary Table 1**, we highlight some compounds with potent cytotoxicities and name them "star molecules" considering their high drug lead potential. These molecules include diketopiperazines with sulfur bridges (such as compounds **3**, **4**, **17**, and **18**), anthranilic acid derivatives (such as compounds **47**, **51**, and **52**), nitrogenated azaphilones (such as compounds **84**, **85**, and **88**), aphidicolin (compound **69**), and meroterpenoids (compounds **79** and **80**). Their structures are classified into polyketides, alkaloids, and terpenoids according to their putative biogenetic sources. A variety of chemical structures helps synthetists design better antitumor molecules. All of these compounds not only possess diverse chemical structures but also show significant activities, even higher than those of the positive controls (usually clinical drugs such as adriamycin, cisplatin, taxol, and doxorubicin). For example, compound **3** shows remarkable cytotoxicity at the nanomolar or low micromolar level (IC_{50} values of 0.191, 0.015, and 0.008 μM against K562, A549, and MCF-7 cells), which are 10–100 times higher than that of the positive control. Compound **80**, in particular, shows potent activities against SF-268, MCF-7, HepG-2, and A549 cell lines, with IC_{50} values of 0.01–0.04 μM, approximately 100 times stronger than the positive control adriamycin. **Table 1** lists the common target cell types and cytotoxic activity of the isolated compounds. The A549, HepG2, and MCF-7 cell lines are the main tested cell lines. Meanwhile, the structure-activity relationship and mechanism of action has been studied for some of the isolated compounds. For the diketopiperazines, the polysulfide bridge contributes significantly to their cytotoxicities (Wang et al., 2012). Aphidicolin A8 (**69**) is found to observably induce apoptosis in T24 and HL-60 cells by causing DNA damage (Niu et al., 2019a). Nitrogenated azaphilone **85** arrests the cell cycle in the G1 phase, while **84** and **85** induced apoptosis in a concentration-dependent manner (Wang et al., 2020b). These "star molecules", with potent activities and clear mechanisms of action, are considered to be potential alternatives to antitumor drugs.

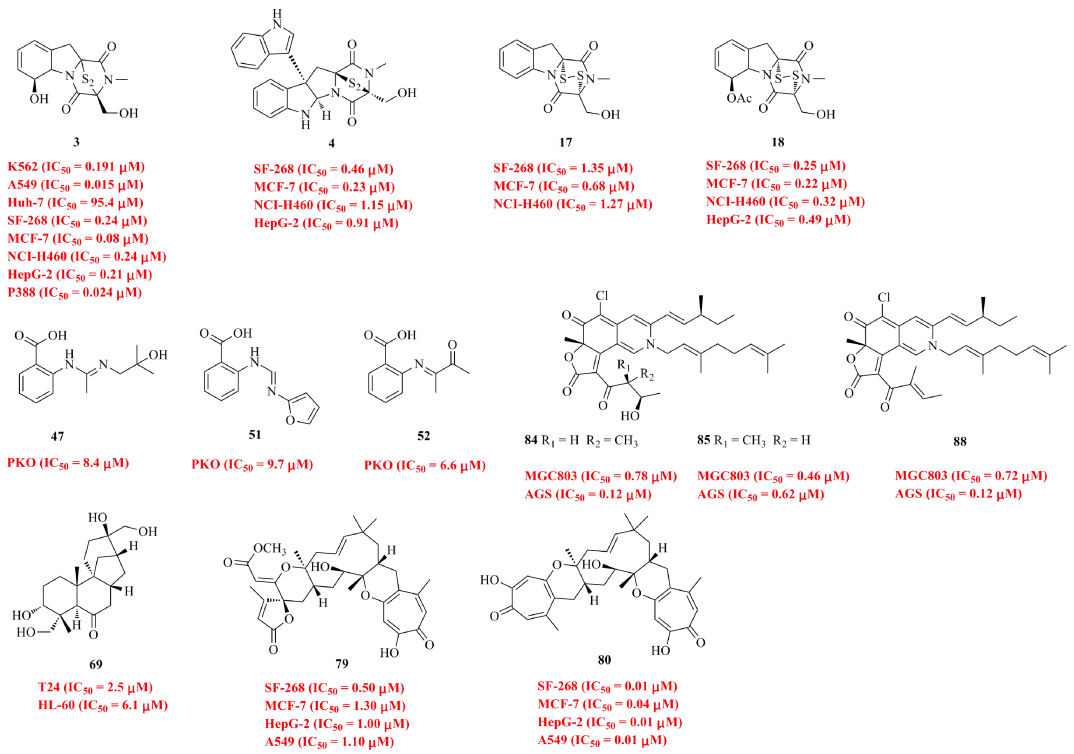

FIGURE 14 | Some "star molecules" with high drug leads potential.

TABLE 1 | Target cell types and cytotoxic activity of the isolated compounds.

Target cell types	Cytotoxic activity
K562	**3** (IC_{50} = 0.191 μM), **37** (25.1%, 20 μM), **58** (IC_{50} = 39.4 μM), **61** (IC_{50} = 73.5 μM), **121** (IC_{50} = 22.9 μM), **122** (IC_{50} = 4.8 μM), **123** (IC_{50} = 22.4 μM), **145** (IC_{50} = 8.8 μM), **149** (IC_{50} = 16.6 μM), **191** (IC_{50} = 6.78 μM)
A549	**3** (IC_{50} = 0.015 μM), **33** (IC_{50} = 20.44 μM), **34** (IC_{50} = 14.88 μM), **43b** (IC_{50} = 33.2 μM), **46** (IC_{50} = 48.28 μM), **62** (IC_{50} = 12.2 μM), **70** (IC_{50} = 20 μM), **71** (IC_{50} = 16 μM), **72** (IC_{50} = 19 μM), **73** (IC_{50} = 17 μM), **74** (IC_{50} = 20 μM), **76** (IC_{50} = 21.4 μM), **77** (IC_{50} = 22.1 μM), **78** (IC_{50} = 17.6 μM), **79** (IC_{50} = 1.10 μM), **80** (IC_{50} = 0.01 μM), **82** (IC_{50} = 21.26 μM), **83** (IC_{50} = 19.30 μM), **97** (IC_{50} = 8.3 μM), **98** (IC_{50} = 6.7 μM), **99** (IC_{50} = 4.9 μM), **101** (IC_{50} = 4.5 μM), **102** (IC_{50} = 15.7 μM), **103** (IC_{50} = 15.2 μM), **104** (IC_{50} = 16.3 μM), **128** (IC_{50} = 8.1 μM), **153** (IC_{50} = 4.64 μM), **163** (IC_{50} = 17.6 μM), **187** (IC_{50} = 24.39 μg/mL), **191** (IC_{50} = 6.94 μM), **229** (IC_{50} = 9.98 μM)
HepG2	**3** (IC_{50} = 0.21 μM), **4** (IC_{50} = 0.91 μM), **5** (IC_{50} = 1.29 μM), **6** (IC_{50} = 3.52 μM), **7** (IC_{50} = 0.53 μM), **8** (IC_{50} = 2.03 μM), **17** (IC_{50} = 1.52 μM), **18** (IC_{50} = 0.49 μM), **43b** (IC_{50} = 39.5 μM), **46** (IC_{50} = 27.19 μM), **76** (IC_{50} = 25.3 μM), **77** (IC_{50} = 24.0 μM), **78** (IC_{50} = 11.7 μM), **79** (IC_{50} = 1.00 μM), **80** (IC_{50} = 0.01 μM), **82** (IC_{50} = 16.95 μM), **83** (IC_{50} = 13.6 μM), **97** (IC_{50} = 14.0 μM), **98** (IC_{50} = 9.8 μM), **99** (IC_{50} = 3.7 μM), **101** (IC_{50} = 4.2 μM), **102** (IC_{50} = 20.2 μM), **103** (IC_{50} = 3.9 μM), **104** (IC_{50} = 18.2 μM), **153** (IC_{50} = 2.55 μM), **163** (IC_{50} = 16.0 μM), **187** (IC_{50} = 14.69 μg/mL), **229** (IC_{50} = 9.03 μM)
HeLa	**37** (30.6%, 20 μM), **52** (IC_{50} = 6.6 μM), **66** (GI_{50} = 44.05 μg/mL), **68** (IC_{50} = 10.0 μM), **102** (IC_{50} = 7.7 μM), **103** (IC_{50} = 12.3 μM), **104** (IC_{50} = 5.6 μM), **145** (IC_{50} = 3.9 μM), **189** (IC_{50} = 4.1 μM), **218** (IC_{50} = 9.2 μM), **219** (IC_{50} = 5.6 μM), **224** (IC_{50} = 9.3 μM)
MCF-7	**3** (IC_{50} = 0.08 μM), **4** (IC_{50} = 0.23 μM), **5** (IC_{50} = 0.25 μM), **6** (IC_{50} = 0.91 μM), **7** (IC_{50} = 0.23 μM), **8** (IC_{50} = 0.65 μM), **17** (IC_{50} = 0.68 μM), **18** (IC_{50} = 0.22 μM), **43b** (IC_{50} = 29.5 μM), **46** (IC_{50} = 63.44 μM), **68** (IC_{50} = 11.0 μM), **70** (IC_{50} = 18 μM), **71** (IC_{50} = 14 μM), **72** (IC_{50} = 27 μM), **73** (IC_{50} = 23 μM), **74** (IC_{50} = 28 μM), **76** (IC_{50} = 20.0 μM), **77** (IC_{50} = 26.2 μM), **78** (IC_{50} = 12.0 μM), **79** (IC_{50} = 1.30 μM), **80** (IC_{50} = 0.04 μM), **82** (IC_{50} = 2.89 μM), **83** (IC_{50} = 3.07 μM), **97** (IC_{50} = 7.8 μM), **98** (IC_{50} = 5.4 μM), **99** (IC_{50} = 2.8 μM), **101** (IC_{50} = 3.1 μM), **149** (IC_{50} = 16.3 μM), **153** (IC_{50} = 2.60 μM), **229** (IC_{50} = 8.45 μM)
SF-268	**3** (IC_{50} = 0.24 μM), **4** (IC_{50} = 0.46 μM), **5** (IC_{50} = 0.59 μM), **6** (IC_{50} = 1.04 μM), **7** (IC_{50} = 0.73 μM), **8** (IC_{50} = 2.49 μM), **17** (IC_{50} = 1.35 μM), **18** (IC_{50} = 0.25 μM), **43b** (IC_{50} = 32.0 μM), **46** (IC_{50} = 24.38 μM), **76** (IC_{50} = 21.4 μM), **77** (IC_{50} = 24.4 μM), **78** (IC_{50} = 14.2 μM), **79** (IC_{50} = 0.50 μM), **80** (IC_{50} = 0.01 μM), **97** (IC_{50} = 7.5 μM), **98** (IC_{50} = 5.6 μM), **99** (IC_{50} = 4.1 μM), **101** (IC_{50} = 5.2 μM), **156** (IC_{50} = 11.36 μg/mL), **229** (IC_{50} = 7.56 μM)

(Continued)

TABLE 1 | Continued

Target cell types	Cytotoxic activity
NCI-H460	**3** (IC_{50} = 0.24 μM), **4** (IC_{50} = 1.15 μM), **5** (IC_{50} = 1.31 μM), **6** (IC_{50} = 5.60 μM), **7** (IC_{50} = 6.57 μM), **8** (IC_{50} = 17.78 μM), **17** (IC_{50} = 1.27 μM), **18** (IC_{50} = 0.32 μM), **68** (IC_{50} = 16.0 μM),
P388	**3** (IC_{50} = 0.024 μM), **17** (IC_{50} = 0.058 μM), **24** (IC_{50} = 0.056 μM), **25** (IC_{50} = 0.020 μM), **121** (IC_{50} = 11.5 μM), **122** (IC_{50} = 0.1 μM), **123** (IC_{50} = 0.2 μM)
Huh-7	**3** (IC_{50} = 95.4 μM), **30** (IC_{50} = 9.52 μM), **31** (IC_{50} = 4.88 μM), **191** (IC_{50} = 2.59 μM)
HCT-116	**33** (IC_{50} = 21.54 μM), **34** (IC_{50} = 18.54 μM), **145** (IC_{50} = 19.4 μM)
HL-60	**54** (IC_{50} = 64.7 μM), **60** (IC_{50} = 100 μM), **62** (IC_{50} = 11.8 μM), **69** (IC_{50} = 6.1 μM), **154** (IC_{50} = 4.1 μg/mL)

4 CONCLUSIONS

In summary, deep-sea fungi are an untapped source of valuable marine natural products. Although a large number of metabolites have been isolated from deep-sea fungi, the further excavation of novel metabolites is expected. This review first summarizes 229 cytotoxic compounds isolated from deep-sea fungi. Among them, 82 members have been found to possess moderate to potent cytotoxic activities. Most importantly, some of these compounds, namely, "star molecules" herein, show potent cytotoxic activities (higher than that of the positive controls). It is believed that in the near future, studies of cytotoxic compounds isolated from deep-sea fungi will become more prolific, which will certainly be beneficial for the discovery of new antitumor drugs.

AUTHOR CONTRIBUTIONS

GZ, WT, and JZ wrote this manuscript; PS, YL, JW, QS, HS, LJ, XY, HZ, and GC collected and reorganized the literature data; JZ, XZ, and HJ supervised the research work and revised the manuscript; all authors reviewed the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Natural Science Foundation of Shandong Province (ZR2021QC167, ZR2020KC028, ZR2020QC227), Major Science and Technology Innovation Project of Shandong Province (2017GGH5129), Innovation Team Project for Modern Agricultural Industrious Technology System of Shandong Province (SDAIT-11-10), Cooperation Project of University and Local Enterprise in Yantai of Shandong Province (2020XDRHXMPT34, 2021XDRHXMXK23), Key Research and Development Plan of Yantai (2020XDRH101, 2021XDHZ076, 2021YT06000060), and Yantai Research Institute for Replacing Old Growth Drivers with New Ones (2020XJDN003).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmars.2022.929561/full#supplementary-material

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Conflict of Interest: Authors QS and HS are employed by Shandong New Times Pharmaceutical Co., LTD.

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