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Endophytic fungi: A treasure trove of novel anticancer compounds

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ABSTRACT

Cancer is a multifactorial disease with a convoluted genesis and progression. The emergence of multidrug resistance to presently be offered drug and relapse is by far, the most critical concern to tackle this deteriorating disease. Henceforth, there is undeniably an inflated necessity for safe, promising, and less harmful new anticancer drugs. Natural compounds from various sources like plants, animals, and microorganisms have occupied a center stage in drug discovery due to their tremendous chemical diversity and potential as therapeutic agents. Endophytic microbes are symbiotically associated with plants and have been proven to produce novel or analogues of host bioactive metabolites exhibiting a variety of biological activities including anticancer activity. This review emphasizes on structurally diverse unprecedented anticancer natural compounds that have been reported exclusively from endophytic fungi from 2016 to 2020. It covers chemical nature of metabolites, its fungal source associated with terrestrial, as well as marine plants and anticancer activity based on their cytotoxicity profile against various cancer cell lines. Many of these fungal metabolites with promising anticancer activity can be used as lead molecules for *in silico* experiments and deserve special attention from scientists for further *in vitro* and clinical research.

1. Introduction

Cancer is a global health problem that affects all population, regardless of age, gender, ethnicity, wealth, or socioeconomic status and therefore, it is undeniably the biggest obstacle in the twenty-first century that is jeopardizing medical system and research community. Cancer is the second leading cause of death worldwide, accounting for about 10 million deaths per year and this number is still rising (GLOBOCAN, 2020). A variety of clinical methods, including surgery, chemotherapy, and/or radiation are the key treatment for cancer (Subramaniam et al., 2019). Currently present chemotherapeutic drugs in cancer treatment offer temporary relief to the patients and extend their longevity, but with this come other disadvantages which includes side effects, lack of selectivity and overpriced that not only impairs the quality of life but is also unaffordable by millions of patients living in developing nations (Reis-Mendes et al., 2018). Additionally, the emergence of multidrug resistance and relapse of malignancy is by far, the most critical concern in the treatment of this multifactorial condition with a convoluted genesis and progression (Cree and Charlton, 2017; Patel et al., 2018). To tackle this deteriorating disease, there is certainly an unmet need for new promising, safe, and less harmful medicines produced from natural compounds. Research findings suggest that phytochemicals possess antitumor ability, and many of them are currently being used to treat this high-profile disease (Patel et al., 2018; Bhadresha et al., 2021; Shah et al., 2015). Despite the fact that phytochemicals are recognized as the most significant source of potential drugs, their use in drug research has recently seen a decline in interest due to some remarkable challenges with the plant as a drug molecule source, such as its unusual habitat, slow growth rate, limited yield and non-reproducibility of the desired phytochemicals and an unwavering threat by the civilization (Kala et al., 2006; Garcia-Oliveira et al., 2021). On the other side, microorganisms have sparked a lot more interest as a source of therapeutic agents because of their abundance, high biodiversity, and unique scaffold of produced bioactive components. They are often rudimentary to culture in a fermenter under controlled environments, and consistently deliver the desired molecules. (Abdel-Razek et al., 2020).

The great discovery of the billion-dollar chemotherapeutic drug Paclitaxel originally known to be produced only by plant *Taxus longifolia* (discovered in 1971), was later identified to be produced by an endophytic fungus *Taxomyces andreanae* (discovered in 1993), from the same

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plant, *Taxus longifolia* has led scientists to appreciate plants as reservoirs for an infinite range of microorganisms, normally alluded as the endophytes (Stierle et al., 1995). Endophytes are microorganisms that live within plant tissues with mutualistic association for at least part of their life cycle without causing any apparent disease manifestation (Arora et al., 2016). Some endophytes have evolved the ability to synthesize bioactive compounds in a de novo manner that are identical or related to those produced by their host plants during mutualistic association (Jia et al., 2016). For instance, endophytic fungi isolated from *Taxus chinensis* var. *mairei, Podophyllum hexandrum, Camptotheca acuminata* and *Catharanthus roseus* can produce anticancer drug taxol, podophyllotoxin, camptothecin and vincristine, respectively (Palem et al., 2015; Nadeem, 2012; Qiao et al., 2017; Ran et al., 2017). Moreover, these endophytes also produce novel secondary metabolites with unprecedented scaffolds (Pang et al., 2018) and sometimes hybrid chemical skeletons (Chen et al., 2017). The most widely found endophyte fungal species belong to the genus of *Aspergillus*, *Chaetomium*, *Penicillium*, *Fusarium* and *Pestalotiopsis*. Research on endophytic fungi have evinced that, they are an auspicious resource of bioactive compounds and to access this valuable source, the diversity of endophytic fungi and their species richness in different parts of world has been explored.

Large number of secondary metabolites, especially from fungal endophytes are extracted, isolated, and characterized, of which, some of these have been discussed in earlier reviews in detail (Bedi et al., 2018a; Deshmukh et al., 2014; Kharwar et al., 2011; Guo et al., 2008). Most of these fungal metabolites are bioactive and classified under various chemical classes like, alkaloids, terpenoids, polyketides, flavonoids, steroids, lactones, lignans, depsipeptides, quinones, etc. In the past three decades, around 180 natural molecules with significant cytotoxicity towards selected tumor cell lines are reported from the endophytic fungi harbored in various plants (Bedi et al., 2018a; Kharwar et al., 2011). This review summarizes 205 novel compounds produced by terrestrial and marine plant-associated endophytic fungi from 2016 to 2020, including detailed chemical structures, structural type classifications, and cytotoxicity towards particular cancer cell lines.

2. Cytotoxic secondary metabolites from endophytic fungi

Endophytic fungi are valuable source of natural bioactive compounds in drug discovery and have a wide range of medical applications. Secondary metabolites from endophytic fungi have diverse biological activities, such as cytotoxic, antifungal, antibacterial, antiviral, antioxidant, anti-inflammatory, phytotoxic, antimalarial, antialgae, antimigratory, and pro-apoptotic activity. In past thirty years, researchers have been driven for the use of novel and promising cytotoxic compounds in pharmaceuticals. Herein, 205 new natural compounds synthesized by terrestrial as well as marine plant associated 95 endophytic fungi from 4 phyla and 41 genera, collected from 16 countries during the period of 2016–2020 are described (Fig. 1). In the subsequent sections, we discuss about the cytotoxic profile of compounds which are majorly classified as polyketides, terpenoids, sterols, macrolides, lactones, azaphilones, alkaloids, preussomerins, *p*-terphenyls, hybrid structures and miscellaneous

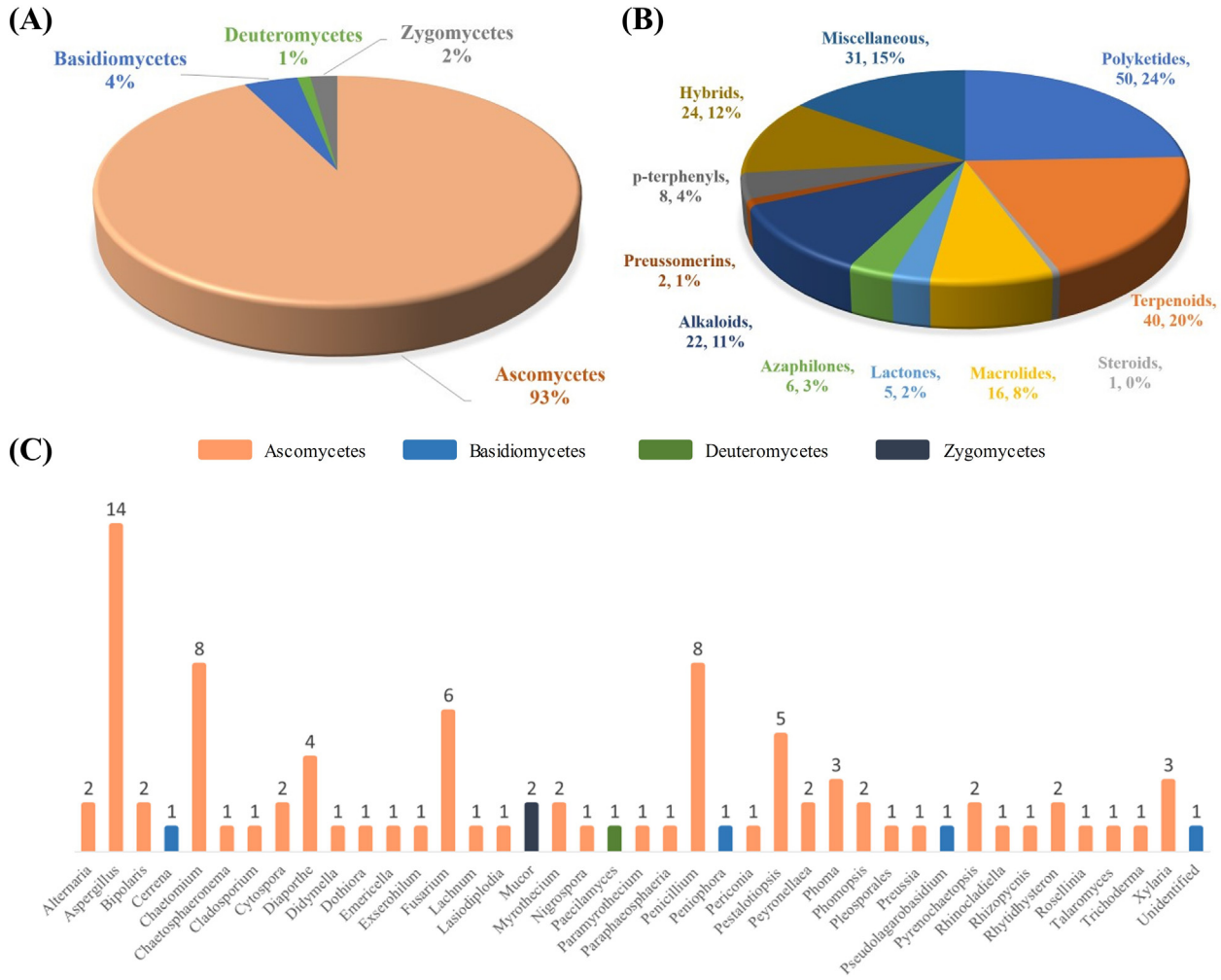

Fig. 1. (A) Proportions of endophytic fungi belonging to various phyla, (B) total number and percentage of structural varieties of novel cytotoxic compounds from endophytic fungi, and (C) the quantity of endophytic fungi researched in each genus.

compounds based on their chemical nature. List of secondary metabolites from endophytic fungi, with their plant host and cytotoxic activities towards specific tumor cell lines are provided in Table 1.

2.1. Polyketides

Polyketides are biologically active and chemically diverse family of secondary metabolites that come from mammals, plants, fungi, and bacteria. Doxorubicin is a well-known anticancer molecule obtained as a polyketide from fungi (Tacar et al., 2013). Herein, 50 polyketides are classified as chromones, pyrones, isocoumarins, lactones, xanthones, phenalenones, diphenyl ethers, and unclassified polyketides.

2.1.1. Chromones

Chromones are phenolic derivatives of chromone and isomers of coumarin that have been confirmed to have anti-tumor, anti-viral, anti-microbial, anti-inflammatory, and antioxidant properties (di Duan et al., 2019). A chromone derivative, **Botryochromone (1)** was isolated from unidentified strain (BCC 54265) of Botryosphaeriaceae family, which was obtained from a leaf of the Vietnamese coriander, *Polygonum odoratum* and exhibited weak cytotoxicity to epidermoid (KB) and human small cell lung cancer (NCI–H187) cell lines with IC_{50} values of 43 and 18 μg/mL, while remain inactive against MCF-7, a human breast cancer cell line (Isaka et al., 2018). **Rhytidchromones A–D (2-5)** are highly oxygenated chromones, which were separated from the culture broth of fungus *Rhytidhysteron rufulum*, an endophyte associated with marine Thai *Bruguiera gymnorrhiza*. All compounds were tested for cytotoxic activity against four tumor cell lines human breast (MCF-7), liver (HepG2), gastric (KATO-3) and cervical (CaSki), in which they remain inactive against HepG2 and CaSki cells with IC_{50}s of >25 μM. Compound Rhytidchromone A and Rhytidchromone D were active against MCF-7 and KATO-3 cells with IC_{50} value of 19.3 ± 2.5, 23.3 ± 1.1 μM and 17.7 ± 3.7, 16.0 ± 1.9 μM, respectively, while compound Rhytidchromone B and Rhytidchromone C were cytotoxic towards only KATO-3 cells with IC_{50}s of 21.4 ± 2.3 and 16.8 ± 3.6 μM, respectively (Chokpaiboon et al., 2016). A new **Secalonic acid derivative, F-7 (6)**, an ergochrome which is dimeric xanthene linked at second position, was discovered from the endophytic fungus *Aspergillus aculeatus* MBT 102, obtained from *Rosa damascene*. It showed strong cytotoxic activity against triple negative breast cancer cell line (MDA-MB-231) with 16.6 ± 0.28 μM IC_{50} value and found to induce apoptosis through phase contrast and scanning electron microscopy. It also exhibited moderate cytotoxicity against PC-3 (prostatic cancer), MCF-7, HT-29 (human colon carcinoma), SW620 (colon cancer), PANC-1 (pancreatic cancer) and FR-2 (normal human breast epithelial cells) with IC_{50} values in the range of 6.86–30.23 μM (Farooq et al., 2020). The structures of chromones **(1–6)** are shown in Fig. 2.

2.1.2. Pyrones

Dibenzo-pyrones are polyketides with a 6H-benzo [c]-chromen-6-one tricyclic skeleton that have been shown to be biologically active in nature. Two unprecedented isochromane molecules, **(R)-3,6-dihydroxy-8-methoxy-3-methylisochroman-4-one (7), and 8-methoxy-3-methylisochromane-3,6-diol (8)** were obtained from the fermentation broth of *Aspergillus fumigatus*, an endophytic fungus associated with *Cordyceps sinensis*. Compounds **(7)** and **(8)** exhibited moderate antiproliferative activity against a FLT3 positive acute myeloid leukemia cell line (MV4-11) with IC_{50}s of 38.39 and 30.00 μM respectively, while remain inactive against MCF-7, HCT116 (colon cancer) and A-549 (human lung adenocarcinoma) cell lines (Li et al., 2019a). A novel dibenzospiroketal, **Aspermicrone B (9)** was obtained from the culture of endophytic fungus *Aspergillus micronesiensis*, which was derived from edible red seaweed *Kappaphycus alvarezii*. It showed selective antiproliferative activity towards HepG2 cell line with IC_{50} value of 9.9 μM, while other compounds remain inactive (Luyen et al., 2019). A fermented culture of fungus *Pestalotiopsis palmarum*, an endophyte harbored in the leaves of medicinal plant *Sinomenium acutum* (Thunb.) Rehd et Wils was detected with the novel α-pyrone, **5,6-dihydro-4-methoxy-6-hydroxymethyl-2H-pyran-2-one (10)**. It showed cytotoxic activity against HeLa (human cervical carcinoma cells), HCT116, and A-549 cell lines with IC_{50}s of 15.60 ± 0.28 μM, 24.35 ± 0.56 μM, and 47.82 ± 2.19 μM, respectively, that is comparatively higher than known anticancer compound doxorubicin, which showed cytotoxicity in the range of 0.86–8.9 μM (Xiao et al., 2018). Two new α-pyrone derivatives, **Phomone D (11) and Phomone E (12)** were separated from the fermented culture of fungus *Phoma* sp. YN02–P-3, an endophyte associated with the plant *Sumbaviopsis* J. J. Smith. Phomone D and Phomone E showed cytotoxicity against three human cancer cell lines HL-60 (acute leukemia), PC-3 and HCT-116 with IC_{50}s of 0.65, 1.09, 2.31 μM and 1.04, 5.9, 9.84 μM, respectively (Sang et al., 2017). **Pleospyrone A (13), Pleospyrone D (14),** and **Pleospyrone E (15)** were extracted as new chlamydosporol derivatives with an α-pyrone motif from the EtOAc extract of endophytic fungus *Pleosporales* sp. Sigrf05, which was obtained from the healthy tuberous roots of the medicinal plant *Siraitia grosvenorii*. Pleospyrone A and Pleospyrone E were cytotoxic against HepG2, BGC-823 (gastric cancer), NCI–H1650 (non-small-cell lung carcinoma) and DAOY (medulloblastoma) cell lines in the range of 1.26–20.7 μM of IC_{50} values, while Pleospyrone D was active against only NCI–H1650 with IC_{50} of 29.6 μM. Pleospyrone E also possess cytotoxicity against HCT-116 cancer cell line with 1.17 μM of IC_{50} value, while other compounds remain inactive (Lai et al., 2020). An unprecedented dibenzo-α-pyrone, **Rhizopycnin C (16)** was separated from culture of endophytic fungus *Rhizopycnis vagum* Nitaf22 harbored in *Nicotiana tabacum*. It exhibited cytotoxicity against only A-549 and HCT116 cell lines with IC_{50}s of 25.5 and 37.3 μM, respectively, while remain inactive (IC_{50} > 50 μM) against human melanoma cell line (A375), MCF-7 and pancreatic adenocarcinoma (Capan2) cell lines, which suggests interaction towards specific protein expressed in tumor cells and need to be explored further to find mode of action (Lai et al., 2016). One novel furanodione, **Xylarione A (17)** was separated from ethyl acetate extract of fermented culture of endophytic fungus *Xylaria psidii*, harbored in the medicinal plant *Aegle marmelos*. It showed cytotoxic ability towards MCF-7, pancreatic cancer cells (MIA-Pa-Ca-2), non-small cell lung cancer cells (NCI–H226), HepG2 and prostate carcinoma cells (DU145) with IC_{50}s in the range of 16–25 μM. Detailed *in vitro* analysis of compound **(17)** on MIA-Pa-Ca-2 suggested that it showed cytotoxicity due to mitochondrial dependent apoptosis and could be served as compound of interest to studied further evaluation of definite mechanism for its activity (Arora et al., 2016). The structures of pyrones **(7–17)** are shown in Fig. 2.

2.1.3. Isocoumarins

Isocoumarins are a large group of natural substances that belong to the well-known polyketide family. They are the structural isomer of coumarin and have a wide range of chemical configurations and therapeutic effects (Saddiqa et al., 2017). Four new isocoumarin derivatives, **Oryzaeins A–D (18–21)** were extracted from solid cultures of fungus *Aspergillus oryzae*, an endophyte associated with *Paris polyphylla* var. *yunnanensis*. All compounds showed antiproliferative activity towards human tumor cell lines NB4 (human leukemia), A-549, SHSY5Y (human neuroblastoma), PC-3, and/or MCF-7 with IC_{50}s in the range between 2.8 and 8.8 μM (Zhou et al., 2016). **Aspergisocoumrin A (22) and Aspergisocoumrin B (23)** are new cytotoxic isocoumarin derivatives, which were isolated from the fungus *Aspergillus* sp. HN15-5D, an endophyte harbored in the leaves of the mangrove plant *Acanthus ilicifolius*. Compound **(22)** exhibited cytotoxic activity against human breast cancer cell line (MDA-MB-435), human hepatocellular carcinoma cell line (HepG2), lung carcinoma cell line (H460) and non-cancer breast epithelial cells (MCF10A) with IC_{50} value in the range of 5.08–43.70 μM, while compound **(23)** showed activity against only MDA-MB-435 and MCF10A cells with IC_{50}s of 4.98 ± 0.74 and 21.40 ± 1.71 μM, respectively and remain inactive against other tested cell lines (Wu et al., 2019). An unprecedented halogenated dihydroisocoumarin, **Palmaerone E (24)** was

Table 1
Novel cytotoxic compounds of the fungal endophytes reported during 2016–2020.

Chemical nature	Secondary metabolite	Cell lines	Activity (IC_{50})	Endophytic fungi	Host plant (T/M)[b]	Location	Reference
Chromones	Botryochromone **(1)**	KB	43 μg/mL	Botryosphaeriaceae family (unidentified strain BCC 54265)	*Polygonum odoratum* **(T)**	Thailand	Isaka et al. (2018)
		NCI–H187	18 μg/mL				
	Rhytidchromone A **(2)**	MCF-7	19.3 ± 2.5 μM	*Rhytidhysteron rufulum*	*Bruguiera gymnorrhiza* **(M)**	Thailand	Chokpaiboon et al. (2016)
		KATO-3	23.3 ± 1.1 μM				
	Rhytidchromone B **(3)**	KATO-3	21.4 ± 2.3 μM				
	Rhytidchromone C **(4)**	KATO-3	16.8 ± 3.6 μM				
	Rhytidchromone D **(5)**	MCF-7	17.7 ± 3.7 μM				
		KATO-3	16.0 ± 1.9 μM				
	Secalonic acid derivative F-7 **(6)**	PC-3	10.38 ± 0.14 μM	*Aspergillus aculeatus* MBT 102	*Rosa damascene* **(T)**	India	Farooq et al. (2020)
		MCF-7	12.97 ± 0.02 μM				
		HT-29	30.23 ± 0.54 μM				
		SW620	22.80 ± 0.14 μM				
		MDA-MB-231	16.60 ± 0.28 μM				
		PANC-1	06.86 ± 0.09 μM				
		FR-2	10.14 ± 0.43 μM				
Pyrones	(R)-3,6-dihydroxy-8-methoxy-3-methylisochroman-4-one **(07)**	MV4-11	38.39 μM	*Aspergillus fumigatus*	*Cordyceps sinensis* **(T)**	China	Li et al. (2019a)
	8-methoxy-3-methylisochromane-3,6-diol **(08)**	MV4-11	30.00 μM				
	Aspermicrone B **(09)**	HepG2	9.9 μM	*Aspergillus micronesiensis*	*Kappaphycus alvarezii* **(T)**	Vietnam	Luyen et al. (2019)
	5,6-dihydro-4-methoxy-6-hydroxymethyl-2H-pyran-2-one **(10)**	HeLa	15.60 ± 0.28 μM	*Pestalotiopsis palmarum*	*Sinomenium acutum* (Thunb.) **(T)**	China	Xiao et al. (2018)
		HCT116	24.35 ± 0.56 μM				
		A-549	47.82 ± 2.19 μM				
	Phomone D **(11)**	HL-60	0.65 μM	*Phoma* sp. YN02–P-3	*Sumbaviopsis* J. J. Smith **(T)**	China	Sang et al. (2017)
		PC-3	1.09 μM				
		HCT-116	2.31 μM				
	Phomone E **(12)**	HL-60	1.04 μM				
		PC-3	5.90 μM				
		HCT-116	9.84 μM				
	Pleospyrone A **(13)**	HepG2	5.07 μM	*Pleosporales* sp. Sigrf05	*Siraitia grosvenorii* **(T)**	China	Lai et al. (2020)
		BGC-823	1.26 μM				
		NCI–H1650	15.1 μM				
		Daoy	2.72 μM				
	Pleospyrone D **(14)**	NCI–H1650	29.6 μM				
	Pleospyrone E **(15)**	HCT-116	1.17 μM				
		HepG2	20.3 μM				
		BGC-823	20.7 μM				
		NCI–H1650	6.26 μM				
		Daoy	19.9 μM				
	Rhizopycnin C **(16)**	A-549	25.5 μM	*Rhizopycnis vagum* Nitaf22	*Nicotiana tabacum* **(T)**	China	Lai et al. (2016)
		HCT116	37.3 μM				
	Xylarione A **(17)**	MCF-7	18 ± 1.08 μM	*Xylaria psidii*	*Aegle marmelos* **(T)**	India	Arora et al. (2016)
		MIA-Pa-Ca-2	16 ± 1.09 μM				
		NCI–H226	25 ± 1.98 μM				
		HepG2	37 ± 1.99 μM				
		DU145	22 ± 1.12 μM				
Isocoumarins	Oryzaein A **(18)**	NB4	4.2 μM	*Aspergillus oryzae*	*Paris polyphylla* var. *yunnanensis* **(T)**	China	Zhou et al. (2016)
		A-549	6.5 μM				
		SHSY5Y	7.6 μM				
		MCF-7	8.2 μM				
	Oryzaein B **(19)**	NB4	2.8 μM				
		A-549	4.2 μM				

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Table 1 (*continued*)

Chemical nature	Secondary metabolite	Cell lines	Activity (IC_{50})	Endophytic fungi	Host plant (T/M)[b]	Location	Reference
		SHSY5Y	3.5 μM				
		PC-3	4.8 μM				
		MCF-7	3.0 μM				
	Oryzaein C **(20)**	NB4	7.9 μM				
		MCF-7	5.5 μM				
	Oryzaein D **(21)**	A-549	6.8 μM				
		SHSY5Y	8.8 μM				
		MCF-7	6.5 μM				
	Aspergisocoumrin A **(22)**	MDA-MB-435	05.08 ± 0.88 μM	*Aspergillus* sp. HN15-5D	*Acanthus ilicifolius* **(M)**	China	Wu et al. (2019)
		HepG2	43.70 ± 1.26 μM				
		H460	21.53 ± 1.37 μM				
		MCF10A	11.34 ± 0.58 μM				
	Aspergisocoumrin B **(23)**	MDA-MB-435	04.98 ± 0.74 μM				
		MCF10A	21.40 ± 1.71 μM				
	Palmaerone E **(24)**	HepG2	42.8 μM	*Lachnum palmae*	*Przewalskia tangutica* **(T)**	China	Zhao et al. (2018a)
Xanthones	Asperanthone **(25)**	HepG2	35.5 ± 0.06 μM	*Aspergillus* sp. TJ23	*Hypericum perforatum* L **(T)**	China	Qiao et al. (2018)
	Xanthoquinodin B9 **(26)**	KB	7.04 μM	*Chaetomium globosum* 7s-1	*Rhapis cochinchinensis* (Lour.) Mart. **(T)**	Thailand	Tantapakul et al. (2020)
		MCF-7	18.4 μM				
		NCI–H187	0.98 μM				
	Chryxanthone A **(27)**	A-549	41.7 ± 1.9 μM	*Penicillium chrysogenum* AD-1540	*Grateloupia turuturu* **(M)**	China	Zhao et al. (2018b)
		BT-549	20.4 ± 1.2 μM				
		HeLa	23.5 ± 0.2 μM				
		HepG2	33.6 ± 1.4 μM				
		MCF-7	46.4 ± 1.2 μM				
	Chryxanthone B **(28)**	A-549	20.4 ± 0.9 μM				
		THP-1	41.1 ± 0.5 μM				
	Incarxanthone B **(29)**	A375	8.6 ± 0.2 μM	*Peniophora incarnata*	*Bruguiera gymnorrhiza* **(M)**	China	Li et al. (2020a)
		MCF-7	6.5 ± 0.4 μM				
		HL-60	4.9 ± 0.2 μM				
	Chryxanthone C **(30)**	HeLa	23.6 ± 2.1 μM	*Paecilamyces* sp. TE-540	*Nicotiana tabacum* L. **(T)**	China	Li et al. (2020b)
Phenalenone	Hispidulone B **(31)**	A-549	02.71 ± 0.08 μM	*Chaetosphaeronema hispidulum*	Dessert plant **(T)**	China	Zhang et al. (2020)
		Huh7	22.93 ± 1.61 μM				
		HeLa	23.94 ± 0.33 μM				
Diphenyl ethers	Sinopestalotiollide A **(32)**	HeLa	18.92 ± 0.77 μM	*Pestalotiopsis palmarum*	*Sinomenium acutum* (Thunb.) **(T)**	China	Xiao et al. (2018)
		HCT116	15.69 ± 0.09 μM				
		A-549	31.29 ± 0.72 μM				
	Sinopestalotiollide B **(33)**	HeLa	12.80 ± 0.16 μM				
		HCT116	22.67 ± 0.59 μM				
		A-549	44.89 ± 1.26 μM				
	Sinopestalotiollide C **(34)**	HeLa	14.66 ± 0.64 μM				
		HCT116	18.49 ± 2.81 μM				
		A-549	36.13 ± 1.33 μM				
	Sinopestalotiollide D **(35)**	HeLa	1.19 ± 0.02 μM				
		HCT116	2.66 ± 0.08 μM				
		A-549	2.14 ± 0.05 μM				
Unclassified Polyketide	Lijiquinone **(36)**	RPMI-8226	129 μM	*Ascomycete* sp. F53	*Taxus yunnanensis* **(T)**	China	Cain et al. (2020)
	(3E,8E,6S)-undeca-3,8, 10-triene-1,6-diol **(37)**	H1975	10 μM	*Cladosporium* sp. OUCMDZ-302	*Excoecaria agallocha* **(M)**	China	Wang et al. (2018)
	Cytosporaphenone A **(38)**	MCF-7	70 μM	*Cytospora rhizophorae*	*Morinda officinalis* **(T)**	China	Liu et al. (2017)
		HepG2	60 μM				
	Fusarielin J **(39)**	A2780	12.5 μM	*Fusarium tricinctum*	*Aristolochia paucinervis* **(T)**	Morocco	Hemphill et al. (2017)
	Fusarielin K **(40)**	A2780	36.5 μM				
	Fusarielin L **(41)**	A2780	84.6 μM				
	Sporulosaldein F **(42)**	LM3	39.2 μM	*Paraphaeosphaeria* sp. F03	*Paepalanthus planifolius* **(T)**	Brazil	De Amorim et al. (2019)
		MCF-7	34.4 μM				
	Peyronetide A **(43)**	A2780S	24.1 ± 0.8 μM	*Peyronellaea* sp. FT431	*Verbena* sp. **(T)**	USA	Li et al. (2019b)

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Table 1 (*continued*)

Chemical nature	Secondary metabolite	Cell lines	Activity (IC_{50})	Endophytic fungi	Host plant (T/M)[b]	Location	Reference
		A2780CisR	28.3 ± 7.2 μM				
		TK-10	29.2 ± 2.9 μM				
	Peyronetide B **(44)**	A2780S	21.5 ± 0.3 μM				
		A2780CisR	27.2 ± 1.3 μM				
		TK-10	22.7 ± 1.3 μM				
	Preussilide A **(45)**	L929	6.5 μM	*Preussia similis*	*Globularia alypum* **(T)**	Algeria	Noumeur et al. (2017)
		KB3.1	6 μM				
		A431	20.3 μM				
		A-549	60.3 μM				
		SKOV-3	22.6 μM				
		PC-3	47.7 μM				
		MCF-7	24.3 μM				
		U2OS	7.03 μM				
	Preussilide B **(46)**	L929	17.3 μM				
		KB3.1	11.3 μM				
		A431	35.1 μM				
		A-549	70.3 μM				
		SKOV-3	32.4 μM				
		PC-3	60.2 μM				
		MCF-7	22.1 μM				
	Preussilide C **(47)**	L929	9.1 μM				
		KB3.1	2.5 μM				
		A431	10.1 μM				
		A-549	22.9 μM				
		SKOV-3	15.6 μM				
		PC-3	18.4 μM				
		MCF-7	7.3 μM				
		U2OS	6.8 μM				
	Preussilide D **(48)**	L929	24.7 μM				
		KB3.1	17.4 μM				
		A431	17.9 μM				
		A-549	47.9 μM				
		SKOV-3	20.19 μM				
		PC-3	45.4 μM				
		MCF-7	15.4 μM				
	Preussilide E **(49)**	L929	80 μM				
		KB3.1	23 μM				
		A431	55.8 μM				
		A-549	41.2 μM				
		SKOV-3	29.1 μM				
		PC-3	41.2 μM				
		MCF-7	55.8 μM				
	Preussilide F **(50)**	L929	53.6 μM				
		KB3.1	51.2 μM				
		U2OS	22.2 μM				
Meroterpenoids	Isocochlioquinone D **(51)**	SF-268	32.8 ± 0.5 μM	*Bipolaris sorokiniana* A606	*Pogostemon cablin* **(T)**	China	Wang et al. (2016)
		MCF-7	28.3 ± 1.1 μM				
		NCI–H460	42.6 ± 2.5 μM				
		HepG2	38.7 ± 1.1 μM				
	Isocochlioquinone E **(52)**	SF-268	17.2 ± 1.1 μM				
		MCF-7	28.1 ± 0.7 μM				
		NCI–H460	31.1 ± 1.1 μM				
		HepG2	13.6 ± 0.5 μM				
	Cochlioquinone G **(53)**	SF-268	35.9 ± 1.3 μM				
		MCF-7	21.1 ± 0.6 μM				
		NCI–H460	26.9 ± 2.8 μM				

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Table 1 (*continued*)

Chemical nature	Secondary metabolite	Cell lines	Activity (IC_{50})	Endophytic fungi	Host plant (T/M)[b]	Location	Reference
		HepG2	11.3 ± 1.9 μM				
	Cochlioquinone H **(54)**	SF-268	6.4 ± 0.2 μM				
		MCF-7	8.6 ± 0.2 μM				
		NCI–H460	15.5 ± 0.7 μM				
		HepG2	7.6 ± 0.1 μM				
	Bipolahydroquinone C **(55)**	NCI–H226	5.5 μM	*Bipolaris* sp. L1-2	*Lycium barbarum* **(T)**	China	Long et al. (2019)
		MDA-MB-231	6.7 μM				
	Cochlioquinone I **(56)**	MDA-MB-231	8.5 μM				
	Cochlioquinone K **(57)**	MDA-MB-231	9.5 μM				
	Cochlioquinone L **(58)**	MDA-MB-231	7.5 μM				
	Cochlioquinone M **(59)**	MDA-MB-231	5.6 μM				
	Emeridone B **(60)**	SMMC-7721	18.80 ± 0.23 μM	*Emericella* sp. TJ29	*Hypericum perforatum* **(T)**	China	Li et al. (2019c)
		SW-480	18.35 ± 0.53 μM				
	Emeridone D **(61)**	A-549	11.33 ± 0.82 μM				
		SMMC-7721	8.19 ± 0.39 μM				
		SW-480	14.67 ± 1.12 μM				
	Emeridone F **(62)**	SMMC-7721	17.49 ± 0.59 μM				
		SW-480	16.84 ± 1.08 μM				
	11-dehydroxy	MCF-7	2.0 μM	*Peyronellaea*	*Pritchardia lowreyana* **(T)**	USA	Li et al. (2016)
	epoxyphomalin A **(63)**	MDA468	1.3 μM	*coffeaearabicae* FT238			
		MDA-MB-231	2.2 μM				
		T24	1.8 μM				
		OVCAR5	1.8 μM				
		OVCAR4	1.4 μM				
		OVCAR3	0.5 μM				
		IGROV-1/Pt	1.6 μM				
		A2780 CisR	0.6 μM				
		A2780	0.8 μM				
	Rhizovarin A **(64)**	A-549	11.5 μM	*Mucor irregularis*	*Rhizophora stylosa* **(M)**	China	Gao et al. (2016)
		HL-60	09.6 μM				
	Rhizovarin B **(65)**	A-549	6.3 μM				
		HL-60	5.0 μM				
	Rhizovarin E **(66)**	A-549	9.2 μM				
	Isopenicin A **(67)**	SW480	07.91 ± 0.53 μM	*Penicillium* sp. sh18	*Isodon eriocalyx* var. *laxiflora* **(T)**	China	Tang et al. (2019)
		SW620	08.63 ± 0.15 μM				
		HCT116	09.03 ± 0.61 μM				
		CaCo2	12.56 ± 0.91 μM				
		SMMC-7721	27.66 ± 0.88 μM				
		A-549	37.06 ± 2.24 μM				
		MCF-7	27.89 ± 0.70 μM				
	Isopenicin B **(68)**	SW480	11.60 ± 0.18 μM				
		SW620	15.48 ± 1.39 μM				
		HCT116	14.95 ± 0.22 μM				
		CaCo2	20.34 ± 0.25 μM				
		SMMC-7721	33.49 ± 0.17 μM				
		MCF-7	33.05 ± 0.19 μM				
Sesquiterpenoids	Fumagillene A **(69)**	MV4-11	8.40 ± 2.9 μg/mL	*Aspergillus fumigatus*	*Ligusticum wallichii* **(T)**	China	Li et al. (2020c)
		MDA-MB-231	14.3 ± 5.8 μg/mL				
	Fumagillene B **(70)**	MV4-11	11.2 ± 3.6 μg/mL				
		MDA-MB-231	17.3 ± 6.4 μg/mL				
	Proversilin C **(71)**	HL-60	7.30 ± 1.2 μM	*Aspergillus versicolor* F210	*Lycoris radiata* **(T)**	China	Li et al. (2020d)
		SMMC-7721	12.6 ± 0.9 μM				
		A-549	15.0 ± 0.8 μM				
		MCF-7	11.8 ± 0.5 μM				
		SW-480	12.4 ± 0.4 μM				
	Proversilin E **(72)**	HL-60	9.90 ± 1.4 μM				

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Table 1 (*continued*)

Chemical nature	Secondary metabolite	Cell lines	Activity (IC_{50})	Endophytic fungi	Host plant (T/M)[b]	Location	Reference
		SMMC-7721	19.4 ± 0.7 μM				
		A-549	28.4 ± 1.2 μM				
		MCF-7	18.3 ± 1.2 μM				
		SW-480	16.4 ± 1.0 μM				
	Lithocarin B **(73)**	SF-268	41.68 ± 0.88 μM	*Diaporthe lithocarpus* A740	*Morinda officinalis* **(T)**	China	Liu et al. (2019a)
		MCF-7	37.68 ± 0.30 μM				
		HepG2	48.33 ± 0.10 μM				
		A-549	53.36 ± 0.91 μM				
	Lithocarin C **(74)**	SF-268	69.46 ± 7.08 μM				
		MCF-7	97.71 ± 0.72 μM				
		HepG2	79.43 ± 0.63 μM				
	(R,2E,4E)-6-((2S,5R)-5-ethyltetrahydrofuran-2-yl)-6-hydroxy-4-methylhexa-2,4-dienoic acid **(75)**	MV4-11	22.29 μM	*Fusarium tricinctum*	*Ligusticum chuanxiong* **(T)**	Morocco	Cao et al. (2020)
		HCT116	54.97 μM				
		MCF-7	93.47 μM				
		A-549	69.62 μM				
	(S,2E,4E)-6-((2S,5R)-5-ethyltetrahydrofuran-2-yl)-6-hydroxy-4-methylhexa-2,4-dienoic acid **(76)**	MV4-11	70.20 μM				
		MCF-7	81.21 μM				
	Periconianone E **(77)**	MCF-7	17.9 μM	*Periconia* sp. F-31	*Annona muricata* **(T)**	China	Liu et al. (2016a)
	Periconianone H **(78)**	HeLa	16.5 μM				
	Pestathenol A **(79)**	HeLa	78.2 μM	*Pestalotiopsis theae*	*Camellia sinensis* **(T)**	China	Guo et al. (2020)
	Pestathenol B **(80)**	HeLa	88.4 μM				
	Rhinomilisin A **(81)**	L5178Y	5.0 μM	*Rhinocladiella similis*	*Acrostichums aureum* **(M)**	Cameroon	Liu et al. (2019b)
	Rhinomilisin G **(82)**	L5178Y	8.7 μM				
	Merulinol C **(83)**	KATO-3	35.0 ± 1.20 μM	Basidiomycetous fungus XG8D	*Xylocarpus granatum* **(M)**	Thailand	Choodej et al. (2016)
	Merulinol D **(84)**	KATO-3	25.3 ± 0.82 μM				
	Cerrenin D **(85)**	SF-268	41.01 ± 0.34 μM	*Cerrena* sp. A593	*Pogostemon cablin* **(T)**	China	Liu et al. (2020a)
		MCF-7	14.34 ± 0.45 μM				
		NCI–H460	29.67 ± 0.81 μM				
		HepG2	44.32 ± 2.12 μM				
	7-epi-merulin B **(86)**	HuCCA-1	37.46 ± 3.77 μM	*Pseudolagarobasidium acaciicola*	*Bruguiera gymnorrhiza* **(M)**	Thailand	Wibowo et al. (2016)
		A-549	24.75 ± 1.09 μM				
		MOLT-3	2.39 ± 0.95 μM				
		HepG2	8.91 ± 3.13 μM				
		HL-60	0.28 ± 0.18 μM				
		MDA-MB231	12.22 ± 9.26 μM				
		T47D	22.25 ± 3.35 μM				
		MRC-5	17.92 ± 4.58 μM				
	3-epi-merulin A **(87)**	MOLT-3	17.28 ± 3.66 μM				
		HepG2	20.71 ± 3.50 μM				
		HL-60	12.09 ± 3.50 μM				
		MRC-5	17.83 ± 2.72 μM				
Diterpenoid	(10S)-12,16-epoxy-17 (15 → 16)-abeo-3,5,8,12,15-abietapentaen-2,7,11,14-tetraone **(88)**	HL-60	12.54 ± 1.18 μM	*Pestalotiopsis adusta*	*Clerodendrum canescens* **(T)**	China	Xu et al. (2016)
Triterpenoids	Integracide H **(89)**	BT-549	1.82 μM	*Fusarium* sp.	*Mentha longifolia* L. **(T)**	Saudi Arabia	Ibrahim et al. (2016a)
		SKOV-3	1.32 μM				
		KB	0.18 μM				
	Integracide J **(90)**	BT-549	2.46 μM				
		SKOV-3	3.01 μM				
		KB	2.54 μM				
Steroid	Demethylincisterol A5 **(91)**	A-549	11.05 μM	*Aspergillus tubingensis* YP-2	*Taxus yunnanensis* **(T)**	China	Yu et al. (2019)
		HepG2	19.15 μM				
Macrolides	Myrothecine D **(92)**	K562	8.20 μM	*Myrothecium roridum*	*Trachelospermum jasminoides* (Lindl.) Lem **(T)**	China	Shen et al. (2019)
		SW1116	0.57 μM				

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Table 1 (*continued*)

Chemical nature	Secondary metabolite	Cell lines	Activity (IC_{50})	Endophytic fungi	Host plant (T/M)[b]	Location	Reference
	Myrothecine E **(93)**	K562	15.98 μM				
		SW1116	11.61 μM				
	Myrothecine F **(94)**	K562	00.97 μM				
		SW1116	10.62 μM				
	Myrothecine G **(95)**	K562	01.53 μM				
		SW1116	04.25 μM				
	16-hydroxymytoxin B **(96)**	K562	2.87 μM				
		SW1116	0.18 μM				
	14′-dehydrovertisporin **(97)**	K562	0.056 μM				
		SW1116	0.200 μM				
	Epiroridin acid **(98)**	SF-268	0.751 ± 0.03 μM	*Myrothecium roridum* A553	*Pogostemon cablin* **(T)**	China	Liu et al. (2016b)
		MCF-7	0.170 ± 0.01 μM				
		NCI–H460	0.360 ± 0.05 μM				
		HepG2	0.380 ± 0.03 μM				
	Myrothecine H **(99)**	SF-268	6.75 ± 0.22 μM	*Paramyrothecium roridum*	*Morinda officinalis* **(T)**	China	Liu et al. (2020b)
		HepG2	6.72 ± 0.27 μM				
	Myrothecine I **(100)**	SF-268	0.20 ± 0.01 μM				
		HepG2	0.20 ± 0.03 μM				
	7-O-Methylnigrosporolide **(101)**	L5178Y	0.7 μM	*Pestalotiopsis microspora*	*Drepanocarpus lunatus* **(M)**	Cameroon	Liu et al. (2016c)
		A2780	28 μM				
	Pestalotioprolide C **(102)**	L5178Y	39 μM				
	Pestalotioprolide D **(103)**	L5178Y	5.6 μM				
	Pestalotioprolide E **(104)**	L5178Y	3.4 μM				
		A2780	1.2 μM				
	Pestalotioprolide F **(105)**	L5178Y	3.9 μM				
		A2780	12 μM				
	Pestalotioprolide G **(106)**	A2780	36 μM				
	Pestalotioprolide H **(107)**	L5178Y	11 μM				
Lactones	Asperlactone G **(108)**	A-549	65.3 ± 1.06 μM	*Aspergillus* sp.	*Pinellia ternate* **(T)**	China	Xin et al. (2019)
	Asperlactone H **(109)**	A-549	23.3 ± 2.01 μM				
	(−)-Asperteretone E **(110)**	AsPC-1	9.50 μM	*Aspergillus terreus*	*Hypericum perforatum* **(T)**	China	Deng et al. (2020)
		SW1990	11.7 μM				
		PANC-1	9.80 μM				
	(+)-Asperteretone E **(111)**	AsPC-1	9.90 μM				
		SW1990	10.3 μM				
		PANC-1	15.6 μM				
	Hispidulactone F **(112)**	HepG2	61.05 μM	*Chaetosphaeronema hispidulum* (TS-8-1)	Dessert plant **(T)**	China	Zheng et al. (2020)
Azaphilones	Chaephilone C **(113)**	HepG2	38.6 μM	*Chaetomium globosum* TY-2	*Polygonatum Sibiricum* **(T)**	China	Song et al. (2020)
	Isochromophilone A **(114)**	ACHN	27 μM	*Diaporthe* sp. SCSIO 41011	*Rhizophora stylosa* **(M)**	China	Luo et al. (2018)
		786-O	34 μM				
		OS-RC-2	45 μM				
	Isochromophilone D **(115)**	ACHN	14 μM				
		786-O	8.9 μM				
		OS-RC-2	13 μM				
	Isochromophilone F **(116)**	ACHN	13 μM				
		786-O	10 μM				
		OS-RC-2	38 μM				
	Isochromophilone C **(117)**	786-O	38 μM				
		OS-RC-2	44 μM				
	Phomopsone C **(118)**	A-549	08.9 μM[a]	*Phomopsis* sp. CGMCC No.5416	*Achyranthes bidentata* **(T)**	China	Yang et al. (2020a)
		MDA-MB-231	03.2 μM[a]				
		PANC-1	17.3 μM[a]				
Alkaloids	Asperchalasin A **(119)**	A-549	55.5 ± 1.87 μM	*Aspergillus* sp.	*Pinellia ternate* **(T)**	China	Xin et al. (2019)
	Asperchalasin B **(120)**	A-549	54.2 ± 1.22 μM				
	Asperchalasin C **(121)**	A-549	47.2 ± 0.92 μM				

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Table 1 (*continued*)

Chemical nature	Secondary metabolite	Cell lines	Activity (IC_{50})	Endophytic fungi	Host plant (T/M)[b]	Location	Reference
	Asperchalasin D **(122)**	A-549	40.6 ± 1.30 μM				
	Asperchalasin E **(123)**	A-549	55.2 ± 1.85 μM				
	Asperchalasin F **(124)**	A-549	70.2 ± 1.76 μM				
	Pchaeglobosal B **(125)**	MCF-7	8.59 ± 0.40 μM	*Chaetomium*	*Ptychomitrium* sp. **(T)**	China	Peng et al. (2020a)
		HepG2	7.09 ± 0.11 μM	*globosum* P2-2-2			
		CT26	1.04 ± 0.04 μM				
		HT29	9.90 ± 0.68 μM				
		A-549	6.92 ± 0.21 μM				
	Chaetomiamide A **(126)**	HL-60	35.2 μM	*Chaetomium* sp.	*Cymbidium Goeringii* **(T)**	China	Wang et al. (2017)
	Ascomylactam A **(127)**	MDAMB-435	4.9 μM	*Didymella* sp. CYSK-4	*Pluchea indica* **(M)**	China	Chen et al. (2019)
		MDAMB-231	5.9 μM				
		SNB19	6.8 μM				
		HCT116	5.5 μM				
		NCIH460	4.4 μM				
		PC-3	5.7 μM				
	Ascomylactam B **(128)**	MDAMB-435	12 μM				
		MDAMB-231	6.6 μM				
		SNB19	18 μM				
		HCT116	4.5 μM				
		NCIH460	13 μM				
		PC-3	20 μM				
	Ascomylactam C **(129)**	MDAMB-435	7.8 μM				
		MDAMB-231	5.1 μM				
		SNB19	7.8 μM				
		HCT116	4.2 μM				
		NCIH460	4.4 μM				
		PC-3	7.5 μM				
	Spirobrocazine C **(130)**	A2780	59 μM	*Penicillium brocae* MA-231	*Avicennia marina* **(M)**	China	Meng et al. (2016)
	Brocazine G **(131)**	A2780	0.664 μM				
		A2780 CisR	0.661 μM				
	Penochalasin I **(132)**	MDA-MB-435	07.55 ± 0.71 μM	*Penicillium chrysogenum* V11	*Myoporum bontioides* **(M)**	China	Huang et al. (2016)
		SGC-7901	07.32 ± 0.68 μM				
		A-549	16.13 ± 0.82 μM				
	Penochalasin J **(133)**	MDA-MB-435	36.68 ± 0.90 μM				
		SGC-7901	37.70 ± 1.30 μM				
		A-549	35.93 ± 0.66 μM				
	Penochalasin K **(134)**	MDA-MB-435	4.65 ± 0.45 μM	*Penicillium chrysogenum* V11	*Myoporum bontioides* **(M)**	China	Zhu et al. (2017a)
		SGC-7901	5.32 ± 0.58 μM				
		A-549	8.73 ± 0.62 μM				
	Penicisulfuranol A **(135)**	HeLa	0.5 μM	*Penicillium*	*Sonneratia caseolaris* **(M)**	China	Zhu et al. (2017b)
		HL-60	0.1 μM	*janthinellum* HDN13-309			
	Penicisulfuranol B **(136)**	HeLa	3.9 μM				
		HL-60	1.6 μM				
	Penicisulfuranol C **(137)**	HeLa	0.3 μM				
		HL-60	1.2 μM				
	Chromenopyridin A **(138)**	A-549	14.7 μM	*Penicillium nothofagi* P-6	*Abies beshanzuensis* **(T)**	China	Zhu et al. (2020)
		HeLa	11.3 μM				
	2′-aminodechloromaldoxin **(139)**	NCI–H460	18.63 ± 1.82 μM	*Pestalotiopsis flavidula*	*Cinnamomum camphora* **(T)**	China	Rao et al. (2019)
		SF-268	20.23 ± 2.15 μM				
		MCF-7	23.53 ± 2.33 μM				
		PC-3	20.48 ± 2.04 μM				
	2′-aminodechlorogeodoxin **(140)**	NCI–H460	16.47 ± 1.63 μM				
		SF-268	17.57 ± 2.12 μM				
		MCF-7	20.79 ± 2.39 μM				
		PC-3	19.43 ± 2.02 μM				
Preussomerins	Chloropreussomerin A **(141)**	A-549	8.5 ± 0.9 μM		*Acanthus ilicifolius* **(M)**	China	Chen et al. (2016)

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Table 1 (*continued*)

Chemical nature	Secondary metabolite	Cell lines	Activity (IC_{50})	Endophytic fungi	Host plant (T/M)[b]	Location	Reference
		HepG2	13 ± 1 μM	*Lasiodiplodia*			
		HeLa	19 ± 1 μM	*theobromae* ZJ-HQ1			
		MCF-7	5.9 ± 0.4 μM				
		HEK293T	4.8 ± 0.2 μM				
	Chloropreussomerin B **(142)**	A-549	8.9 ± 0.6 μM				
		HepG2	7.7 ± 0.1 μM				
		HeLa	27 ± 3 μM				
		MCF-7	6.2 ± 0.4 μM				
		HEK293T	11 ± 3.0 μM				
p-terphenyls	Prenylterphenyllin F **(143)**	L-02	19.9 μM	*Aspergillus candidus* LDJ-5	*Rhizophora apiculate* **(M)**	China	Zhou et al. (2020)
		MGC-803	11.0 μM				
		HCT-116	09.3 μM				
		BEL-7402	12.4 μM				
		A-549	10.2 μM				
		SH-SY5Y	10.4 μM				
		HeLa	08.3 μM				
		HL-60	07.1 μM				
	Prenylterphenyllin G **(144)**	L-02	29.7 μM				
		MGC-803	12.5 μM				
		HCT-116	16.9 μM				
		BEL-7402	12.6 μM				
		A-549	16.3 μM				
		SH-SY5Y	12.4 μM				
		HeLa	11.5 μM				
	Prenylterphenyllin H **(145)**	L-02	3.5 μM				
		MGC-803	0.7 μM				
		HCT-116	0.5 μM				
		A-549	0.4 μM				
		SH-SY5Y	0.6 μM				
		HeLa	2.0 μM				
		U87	13.8 μM				
	Prenylterphenyllin I **(146)**	L-02	24.4 μM				
		MGC-803	14.5 μM				
		HCT-116	14.7 μM				
		BEL-7402	11.1 μM				
		A-549	14.8 μM				
		SH-SY5Y	16.7 μM				
		HeLa	11.4 μM				
	Prenylterphenyllin J **(147)**	MGC-803	8.10 μM				
		HCT-116	6.20 μM				
		A-549	7.60 μM				
		SH-SY5Y	15.6 μM				
		HeLa	8.50 μM				
		K562	15.9 μM				
	Prenylcandidusin E **(148)**	L-02	16.7 μM				
		MGC-803	16.3 μM				
		HCT-116	19.8 μM				
		BEL-7402	14.9 μM				
		A-549	19.1 μM				
		SH-SY5Y	17.9 μM				
		HeLa	14.0 μM				
		U87	10.3 μM				
		K562	05.0 μM				
	Prenylcandidusin G **(149)**	L-02	17.9 μM				
		MGC-803	1.40 μM				
		HCT-116	0.90 μM				

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Table 1 (*continued*)

Chemical nature	Secondary metabolite	Cell lines	Activity (IC_{50})	Endophytic fungi	Host plant (T/M)[b]	Location	Reference
		BEL-7402	16.0 μM				
		A-549	2.80 μM				
		SH-SY5Y	2.20 μM				
		HeLa	10.1 μM				
		HL-60	3.40 μM				
	Gliocladinin C **(150)**	Hep-2	0.18 μM	*Chaetomium subaffine* L01	Potato **(T)**	China	Han et al. (2019)
		HepG2	0.12 μM				
Cytochalasans	Diaporthichalasin D **(151)**	A-549	13.7 ± 2.3 μM	*Diaporthe* sp. SC-J0138	*Cyclosorus parasiticus* **(T)**	China	Yang et al. (2020b)
		HeLa	15.3 ± 2.7 μM				
		HepG2	08.8 ± 1.7 μM				
	Diaporthichalasin E **(152)**	HepG2	30.6 ± 2.5 μM				
	Diaporthichalasin F **(153)**	HeLa	34.7 ± 5.6 μM				
		HepG2	16.5 ± 2.2 μM				
	Diaporthichalasin H **(154)**	A-549	13.9 ± 2.1 μM				
		HeLa	20.0 ± 1.5 μM				
		HepG2	09.9 ± 1.6 μM				
		MCF–7	32.1 ± 1.5 μM				
	Multirostratin B **(155)**	HepG2	31.95 ± 1.86 μM	*Phoma multirostrata*	*Parasenecio albus* **(T)**	China	Peng et al. (2020b)
		CT26	27.40 ± 0.68 μM				
	Multirostratin E **(156)**	MCF-7	34.08 ± 5.88 μM				
		HepG2	32.05 ± 1.54 μM				
		CT26	17.20 ± 0.23 μM				
		A-549	25.51 ± 0.83 μM				
	Multirostratin F **(157)**	MCF-7	22.29 ± 0.35 μM				
		HepG2	23.02 ± 0.24 μM				
		CT26	19.20 ± 1.63 μM				
		A-549	43.22 ± 4.49 μM				
	Multirostratin G **(158)**	MCF-7	10.22 ± 0.43 μM				
		HepG2	17.69 ± 0.27 μM				
		CT26	06.03 ± 0.85 μM				
		HT29	43.03 ± 1.79 μM				
		A-549	05.04 ± 0.18 μM				
	Multirostratin H **(159)**	MCF-7	31.52 ± 0.82 μM				
		HepG2	20.85 ± 0.48 μM				
		CT26	21.89 ± 0.35 μM				
		HT29	16.30 ± 0.60 μM				
		A-549	26.63 ± 0.49 μM				
	Multirostratin I **(160)**	CT26	19.31 ± 0.40 μM				
		HT29	24.09 ± 0.73 μM				
		A-549	36.58 ± 1.10 μM				
	Multirostratin J **(161)**	MCF-7	30.75 ± 1.48 μM				
		HepG2	25.29 ± 3.91 μM				
		CT26	14.53 ± 0.13 μM				
		HT29	21.33 ± 1.19 μM				
	Ergocytochalasin A **(162)**	HepG2	21.32 ± 0.30 μM	*Phoma multirostrata* XJ-2-1	*Parasenecio albus* **(T)**	China	Peng et al. (2020c)
		A-549	19.11 ± 0.99 μM				
		MCF-7	26.63 ± 0.13 μM				
		HCT116	22.28 ± 2.65 μM				
		HT-29	15.23 ± 0.67 μM				
		CT26	06.92 ± 0.71 μM				
	Jammosporin A **(163)**	MOLT-4	20 μM	*Rosellinia sanctaecruciana*	*Albizia lebbeck* **(T)**	India	Sharma et al. (2018a)
	Xylarichalasin A **(164)**	HL-60	17.3 ± 1.6 μM	*Xylaria* cf. *curta*	*Solanum tuberosum* **(T)**	China	Wang et al. (2019a)
		A-549	11.8 ± 0.2 μM				
		SMMC-7721	08.6 ± 0.2 μM				
		MCF-7	06.3 ± 0.1 μM				
		SW480	13.2 ± 0.3 μM				

(*continued on next page*)

Table 1 (*continued*)

Chemical nature	Secondary metabolite	Cell lines	Activity (IC_{50})	Endophytic fungi	Host plant (T/M)[b]	Location	Reference
	19-epi-cytochalasin P1 **(165)**	HL-60	13.31 ± 0.13 μM	*Xylaria* cf. *curta*	*Solanum tuberosum* **(T)**	China	Wang et al. (2019b)
	7-O-acetyl-6-epi-19, 20-epoxycytochalasin P **(166)**	HL-60	37.16 ± 1.90 μM				
		MCF-7	26.64 ± 1.37 μM				
	7-O-acetyl-19, 20-epoxycytochalasin D **(167)**	HL-60	25.83 ± 1.42 μM				
		MCF-7	34.03 ± 2.10 μM				
Other Hybrids	Gartryprostatin A **(168)**	MV4-11	7.20 μM	*Aspergillus* sp. GZWMJZ-258	*Garcinia multiflora* **(T)**	China	He et al. (2019)
	Gartryprostatin B **(169)**	MV4-11	10.0 μM				
	Aureochaeglobosin B **(170)**	MDA-MB-231	7.6 ± 0.5 μM	*Chaetomium globosum*	*Pinellia ternate* **(T)**	China	Yang et al. (2018)
	Aureochaeglobosin C **(171)**	MDA-MB-231	10.8 ± 0.64 μM				
	Cytorhizin B **(172)**	HepG2	29.4 ± 4.4 μM	*Cytospora rhizophorae* A761	*Morinda officinalis* **(T)**	China	Liu et al. (2019c)
		MCF-7	30.1 ± 3.3 μM				
		SF-268	34.8 ± 1.4 μM				
		NCI–H460	32.8 ± 4.1 μM				
	Cytorhizin C **(173)**	HepG2	68.6 ± 8.2 μM				
		MCF-7	58.6 ± 1.8 μM				
		SF-268	36.8 ± 5.1 μM				
		NCI–H460	54.7 ± 0.2 μM				
	Trichoderpyrone **(174)**	A-549	16.9 ± 1.3 μM	*Trichoderma gamsii*	*Panax notoginseng* (BurK.) F.H. Chen **(T)**	China	Chen et al. (2017)
		HepG2	30.8 ± 0.2 μM				
		HeLa	33.9 ± 0.7 μM				
Miscellaneous Compounds	Alternate C **(175)**	MDA-MB-231	20.1 μM	*Alternaria alternata*	*Paeonia lactiflora* **(T)**	China	Wang et al. (2019c)
		MCF-7	32.2 μM				
	Nigronapthaphenyl **(176)**	HCT 116	9.62 ± 0.5 μM	*Nigrospora sphaerica*	*Bruguiera gymnorrhyza* **(M)**	Sri Lanka	Ukwatta et al. (2019)
	Varioloid A **(177)**	A-549	3.5 μg/mL	*Paecilomyces variotii* EN-291	*Grateloupia turuturu* **(M)**	China	Zhang et al. (2016a)
		HCT116	6.4 μg/mL				
		HepG2	2.5 μg/mL				
	Altertoxin IV **(178)**	MG-63	14.81 μg/mL	*Alternaria* sp. G7	*Broussonetia papyrifera* **(T)**	China	Zhang et al. (2016b)
		SMMC-7721	22.87 μg/mL				
	Asperxin A **(179)**	A-549	11.72 μg/mL	*Aspergillus* sp. Y-2	*Abies beshanzuensis* **(T)**	China	Zhu et al. (2019)
		HeLa	16.78 μg/mL				
	6-formamidechetomin **(180)**	HeLa	21.6 nM	*Chaetomium* sp. M336	*Huperzia serrata* Trev. **(T)**	China	Yu et al. (2018)
		SGC-7901	23.0 nM				
		A-549	27.1 nM				
	Chaetominin A **(181)**	Hep-2	0.23 μM	*Chaetomium subaffine* L01	Potato **(T)**	China	Han et al. (2019)
		HepG2	0.38 μM				
	Xylarolide A **(182)**	MIA-PA-CA-2	20 ± 0.17 μM	*Diaporthe* sp.	*Datura inoxia* **(T)**	India	Sharma et al. (2018b)
		MCF-7	30 ± 1.02 μM				
		PC-3	14 ± 0.12 μM				
	Diportharine A **(183)**	MIA-PA-CA-2	34 ± 1.32 μM				
		PC-3	22 ± 0.83 μM				
	Hormonemate A **(184)**	HepG2	29.0 μM	*Dothiora* sp.	*Launaea arborescens* **(T)**	Spain	Pérez-Bonilla et al. (2017)
		MCF-7	15.6 μM				
	Hormonemate B **(185)**	HepG2	28.7 μM				
		MCF-7	11.1 μM				
	Hormonemate C **(186)**	MCF-7	27.8 μM				
	Hormonemate D **(187)**	HepG2	36.2 μM				
		MCF-7	18.3 μM				
	Hormonemate E **(188)**	HepG2	26.2 μM				
		MCF-7	19.0 μM				
		MiaPaca_2	36.4 μM				
	(13R,14S,15R)- 13-hydroxy-14 -deoxyoxacy-clododecindione **(189)**	A-549	9.2 μM	*Exserohilum rostratum*	*Gymnadenia conopsea* **(T)**	China	Lin et al. (2018)
	Fusarithioamide B **(190)**	SK-MEL	11.2 ± 0.95 μM	*Fusarium chlamydosporium*	*Anvillea garcinii* (Burm.f.) DC. **(T)**	Egypt	Ibrahim et al. (2018)

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Table 1 (*continued*)

Chemical nature	Secondary metabolite	Cell lines	Activity (IC_{50})	Endophytic fungi	Host plant (T/M)[b]	Location	Reference
		KB	6.9 ± 0.75 μM				
		BT-549	0.09 ± 0.05 μM				
		SKOV-3	1.23 ± 0.03 μM				
		MCF-7	0.21 ± 0.07 μM				
		HCT-116	0.59 ± 0.01 μM				
	Fusarithioamide A **(191)**	SK-MEL	9.3 ± 0.86 μM	*Fusarium chlamydosporium*	*Anvillea garcinia*	Egypt	Ibrahim et al. (2016b)
		KB	7.7 ± 0.95 μM		(Burm.f.) DC. **(T)**		
		BT-549	0.4 ± 0.07 μM				
		SKOV-3	0.8 ± 0.01 μM				
	9-desmethylherbarine **(192)**	WI38	10.3 μM	*Fusarium solani*	*Aponogeton undulatus* **(T)**	Bangladesh	Chowdhury et al. (2017)
		NCI HI975	30.72 μM				
		MIA PaCa2	20.46 μM				
		MDA MB 231	27.73 μM				
		HeLa	54.34 μM				
	7-desmethylscorpinone **(193)**	WI38	0.96 μM				
		NCI HI975	1.51 μM				
		MIA PaCa2	0.98 μM				
		MDA MB 231	0.61 μM				
		HeLa	5.84 μM				
	7-desmethyl-6-methylbostrycoidin **(194)**	WI38	0.71 μM				
		NCI HI975	0.73 μM				
		MIA PaCa2	0.64 μM				
		MDA MB 231	0.34 μM				
		HeLa	6.42 μM				
	Penctrimertone **(195)**	HL-60	16.77 μM	*Penicillium* sp. T2-11	*Gastrodsia elata* **(T)**	China	Li et al. (2020e)
		SMMC-7721	23.63 μM				
		A-549	28.62 μM				
		MCF-7	21.53 μM				
		SW480	39.32 μM				
	Cosmochlorin D **(196)**	HL60	6.1 μM	*Phomopsis* sp. N-125	*Ficus ampelasa* **(T)**	Japan	Shiono et al. (2017)
	Cosmochlorin E **(197)**	HL60	1.8 μM				
	Pyrenosetin A **(198)**	A-375	2.8 μM	*Pyrenochaetopsis* sp. FVE-001	*Fucus vesiculosus* **(M)**	Germany	Fan et al. (2020a)
		HaCaT	4.2 μM				
	Pyrenosetin B **(199)**	A-375	6.3 μM				
		HaCaT	35 μM				
	Pyrenosetin C **(200)**	A-375	140.3 μM				
		HaCaT	142.9 μM				
	Pyrenosetin D **(201)**	A-375	77.5 μM	*Pyrenochaetopsis* sp. FVE-087	*Fucus vesiculosus* **(M)**	Germany	Fan et al. (2020b)
		HaCaT	39.3 μM				
	Rhytidenone G **(202)**	Ramos	17.98 μM	*Rhytidhysteron rufulum* AS21B	*Azima sarmentosa* **(M)**	Thailand	Siridechakorn et al. (2017)
		H1975	07.30 μM				
	Rhytidenone H **(203)**	Ramos	0.018 μM				
		H1975	0.252 μM				
	3-demethyl-3-(2-hydroxypropyl)-skyrin **(204)**	MCF-7	20.76 ± 3.41 μg/mL	*Talaromyces* sp. YE3016	*Aconitum carmichaeli* **(T)**	China	Xie et al. (2016)
	Terezine E **(205)**	HUVEC	28.02 μg/mL[a]	*Mucor* sp.	*Centaurea stoebe* **(T)**	USA	Abdou et al. (2020)
		K-562	27.31 μg/mL[a]				
		HeLa	60.43 μg/mL[a]				

[a] CC_{50}

[b] T: terrestrial plant; M: marine plant.

separated from SAHA (histone deacetylase inhibitor) exposed fermented culture of fungus *Lachnum palmae*, an endophyte associated with *Przewalskia tangutica*. It exhibited weak cytotoxic activity towards only HepG2 cell line with the IC_{50} value of 42.8 μM, while remain inactive ($IC_{50} > 50$ μM) against HL-60 and SGC-7901 (human gastric carcinoma) cells (Zhao et al., 2018a). The structures of isocoumarins **(18–24)** are shown in Fig. 2.

2.1.4. Xanthones

Xanthones are tricyclic secondary metabolites which are derived from dibenzo-pyrone, mainly possess anti-inflammatory, antimicrobial, antioxidant, and cytotoxic properties (Bedi et al., 2018b). **Asperanthone (25)** is a new prenylxanthone derivative, which was obtained from the endophytic fungus *Aspergillus* sp. TJ23 isolated from traditional chienese medicinal plant *Hypericum perforatum* L. It exhibited weak cytotoxicity

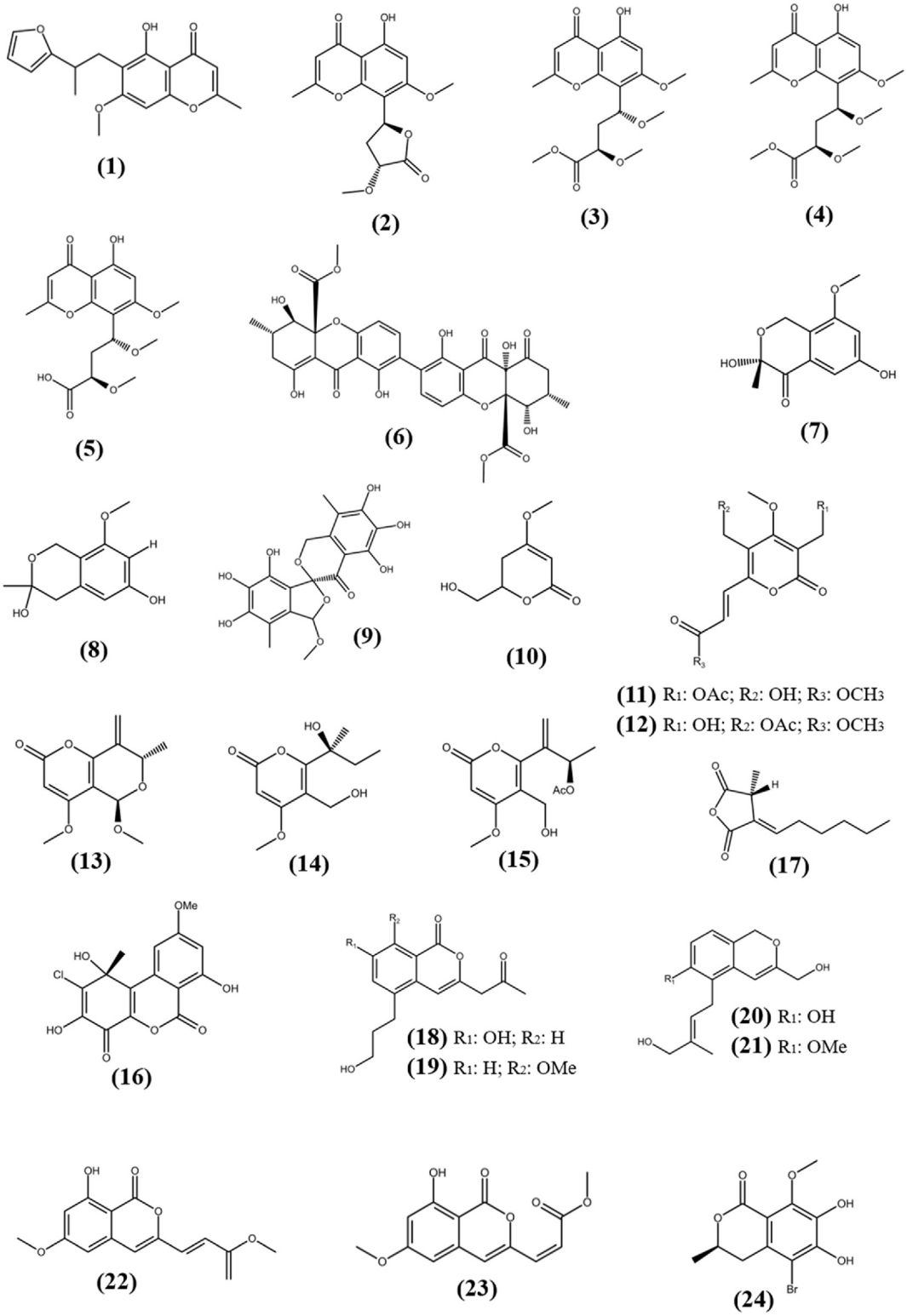

Fig. 2. Chemical structures of chromones **(1–6)**, pyrones **(7–17)** and isocoumarins **(18–24)**.

towards HepG2 cell line with IC_{50} of 35.5 ± 0.06 μM, while remain inactive against B16 (murine), MDA-MB-231, 4T1 (breast cancer) and LLC (Lewis lung carcinoma) cell lines with IC_{50} > 40 μM (Qiao et al., 2018). A new natural metabolite, **Xanthoquinodin B9 (26)** was separated from the fermented culture of endophytic fungus *Chaetomium globosum* 7s-1, harbored in *Rhapis cochinchinensis* (Lour.) Mart. It showed cytotoxic ability towards the three cancer cell lines (KB, MCF-7, NCI–H187) and normal cell line (Vero cell) with the IC_{50} values of 7.04, 18.4, 0.98 and 1.78 μM, respectively (Tantapakul et al., 2020). Because Xanthoquinodin B9 does have a lower IC_{50} value towards NCI–H187 cells than the Vero cells, it requires exploratory research into discovering its mechanism of action. **Chryxanthone A (27) and Chryxanthone B (28)** were separated from a culture of endophytic fungus *Penicillium chrysogenum* AD-1540, which was harbored in the marine red alga *Grateloupia turuturu*. Chryxanthone A possess cytotoxic ability towards A-549, BT-549 (Triple negative breast cancer), HeLa, HepG2 and MCF-7 cell lines with IC_{50}s of 41.7 ± 1.9, 20.4 ± 1.2, 23.5 ± 0.2, 33.6 ± 1.4 and 46.4 ± 1.2 μM, respectively, while Chryxanthone B possess activity against A-549 and THP-1 (acute monocytic leukemia) cell lines with IC_{50}s of 20.4 ± 0.9 and 41.1 ± 0.5 μM, respectively (Zhao et al., 2018b). The mangrove plant *Bruguiera gymnorrhiza* derived endophytic fungus *Peniophora incarnata* Z4 was detected with a new cytotoxic xanthone derivative named **Incarxanthone B (29)**. It exhibited cytotoxicity towards A375 (human melanoma), MCF-7, and HL-60 tumor cell lines with IC_{50}s in the range of 4.9–8.6 μM (Li et al., 2020a). An endophytic fungus *Paecilamyces* sp. TE-540 was isolated from the leaves of *Nicotiana tabacum* L., which was collected from China in August 2016. One novel compound with xanthone moiety, **Chryxanthone C (30)** was separated from the EtOAc crude extract of isolated fungus, which possess cytotoxic ability against only HeLa cell line with IC_{50} value of 23.6 ± 2.1 μM while remain inactive (IC_{50}s > 100 μM) against other tested A-549, BT-549, HepG2, and MCF-7 cell lines (Li et al., 2020b). The structures of xanthones **(25–30)** are shown in Fig. 3.

2.1.5. Phenalenone

Phenalenones are a special class of fungal metabolites with three-ring systems of hydroxyl-perinaphthenones that have a wide range of biological activities, including anti-HIV, antimicrobial, anti-malarial, and cytotoxic activity (Gombodorj et al., 2017). A new phenalenone analogue, **Hispidulone B (31)** with naphthalene backbone was isolated from dessert plant associated endophytic fungus *Chaetosphaeronema hispidulum*. It possess significant cytotoxic ability towards A-549, human hepatoma cell line (Huh7), and HeLa cell lines with IC_{50}s of 2.71 ± 0.08, 22.93 ± 1.61, and 23.94 ± 0.33 μM, respectively, compared to the positive control cis-platinum which had an IC_{50}s of 8.73 ± 1.77, 5.89 ± 0.15, and 14.68 ± 0.10 μM, respectively (Zhang et al., 2020). As the compound had a better cytotoxic ability against particular cancer cell lines than the positive control, it should be investigated further to determine its molecular mechanism to develop it as a new anti-cancer therapeutic agent after thorough pharmacological evaluation. The structure of phenalenone **(31)** is shown in Fig. 3.

2.1.6. Diphenyl ethers

Prenylated diphenyl ethers have been shown to have antimicrobial, cytotoxic, antioxidant, and antiviral effects on a number of cases (Zhang et al., 2018). **Sinopestalotiollides A-D (32–35)** are new diphenyl ether derivatives, which were isolated from fermented culture of fungus *Pestalotiopsis palmarum*, an endophyte harbored in the leaves of medicinal plant *Sinomenium acutum* (Thunb.) Rehd et Wils. Sinopestalotiollides A-C showed cytotoxic activity against HeLa and HCT116, an A-549 cell lines with IC_{50}s in the range of 12.80–47.82 μM. Sinopestalotiollide D exhibited potent cytotoxic ability towards all tested cell lines with IC_{50}s of 1.19 ± 0.02, 2.66 ± 0.08, and 2.14 ± 0.05 μM, respectively, compared to the known anticancer compound doxorubicin that showed cytotoxicity at 8.96 ± 0.19, 2.38 ± 0.24, and 0.86 ± 0.03 μM, respectively (Xiao et al., 2018). Since Sinopestalotiollide D does have a higher activity against HeLa cells than doxorubicin, it needs to be explored further in order to be

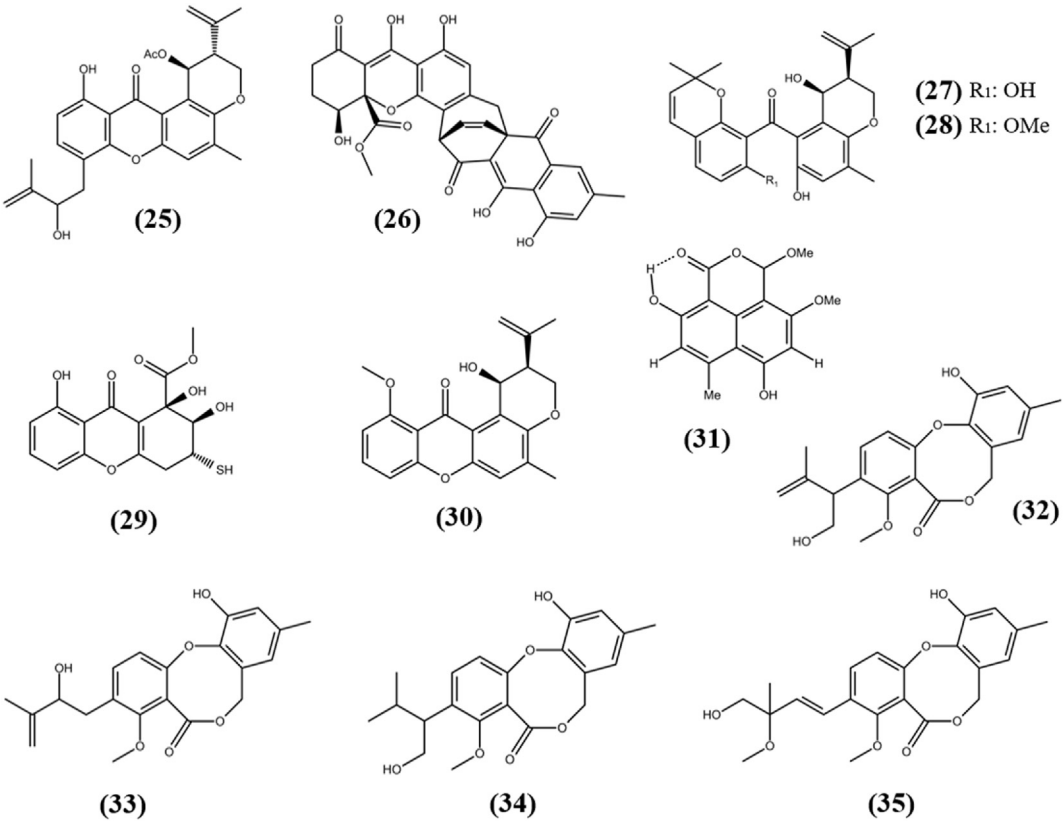

Fig. 3. Chemical structures of xanthones **(25–30)**, phenalenone **(31)** and diphenyl ethers **(32–35)**.

developed as an anticancer agent. The structures of diphenyl ethers **(32–35)** are shown in Fig. 3.

2.1.7. Unclassified polyketide

A novel polyketide, **Lijiquinone (36)**, was obtained from fungus *Ascomycete* sp. F53, an endophyte of the traditional Chinese medicinal plant *Taxus yunnanensis* (Chinese yew) and exhibited cytotoxicity against human myeloma cells (RPMI-8226) with IC_{50} value of 129 μM (Cain et al., 2020). **(3E,8E,6S)-undeca-3,8,10-triene-1,6-diol (37)**, a new polyketide was separated from the fermented culture of the fungus *Cladosporium* sp. OUCMDZ-302, an endophyte harbored in the mangrove plant *Excoecaria agallocha*. Compound **(37)** showed antiproliferation activity towards gefitinib resistance non-small cell lung cancer cell line (H1975) with an IC_{50} values of 10.0 μM, while remain inactive against

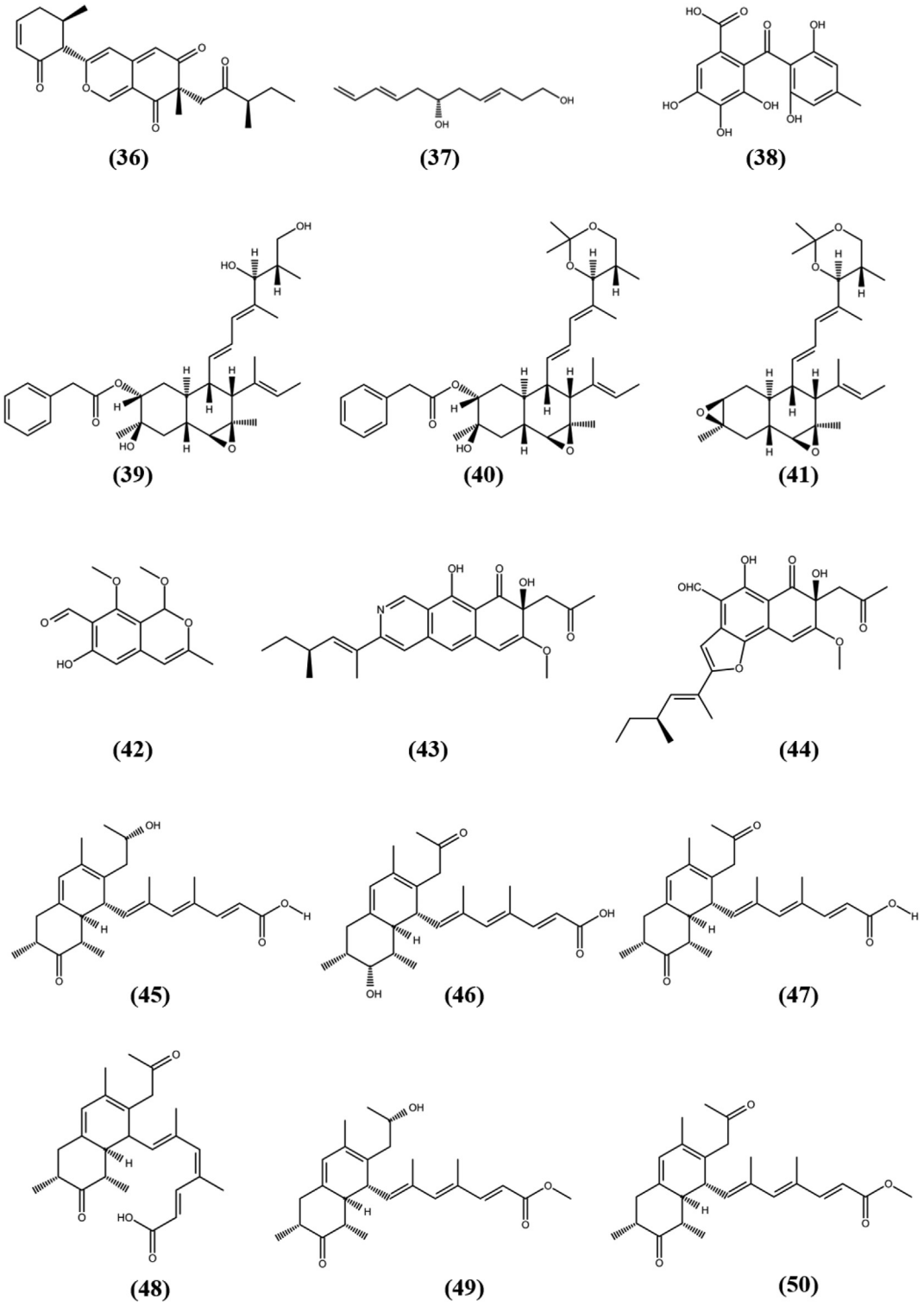

Fig. 4. Chemical structures of unclassified polyketides **(36–50)**.

HL-60, BEL-7402 (hepatoma carcinoma), K562 (chronic myeloid leukemia), A-549 and HeLa cell lines (Wang et al., 2018). **Cytosporaphenone A (38)**, with polyhydric benzophenone moiety was obtained from fungus *Cytospora rhizophorae*, an endophyte harbored in *Morinda officinalis* and showed cytotoxic activities against the two cancer cell lines MCF-7 and HepG2 with IC_{50}s of 70 and 60 μM, respectively, while remain inactive against non-small cell lung cancer (NCI–H460) and human central nervous system cancer (SF-268) cell lines (Liu et al., 2017). Three new natural products, **Fusarielin J (39)**, **Fusarielin K (40)** and **Fusarielin L (41)**, were obtained from the fungal endophyte *Fusarium tricinctum*, isolated from rhizomes of *Aristolochia paucinervis.* All isolated compounds displayed cytotoxic activity against the human ovarian cancer cell line (A2780) with IC_{50} values of 12.5, 36.5 and 84.6 μM, respectively (Hemphill et al., 2017). The endophytic fungus *Paraphaeosphaeria* sp. F03

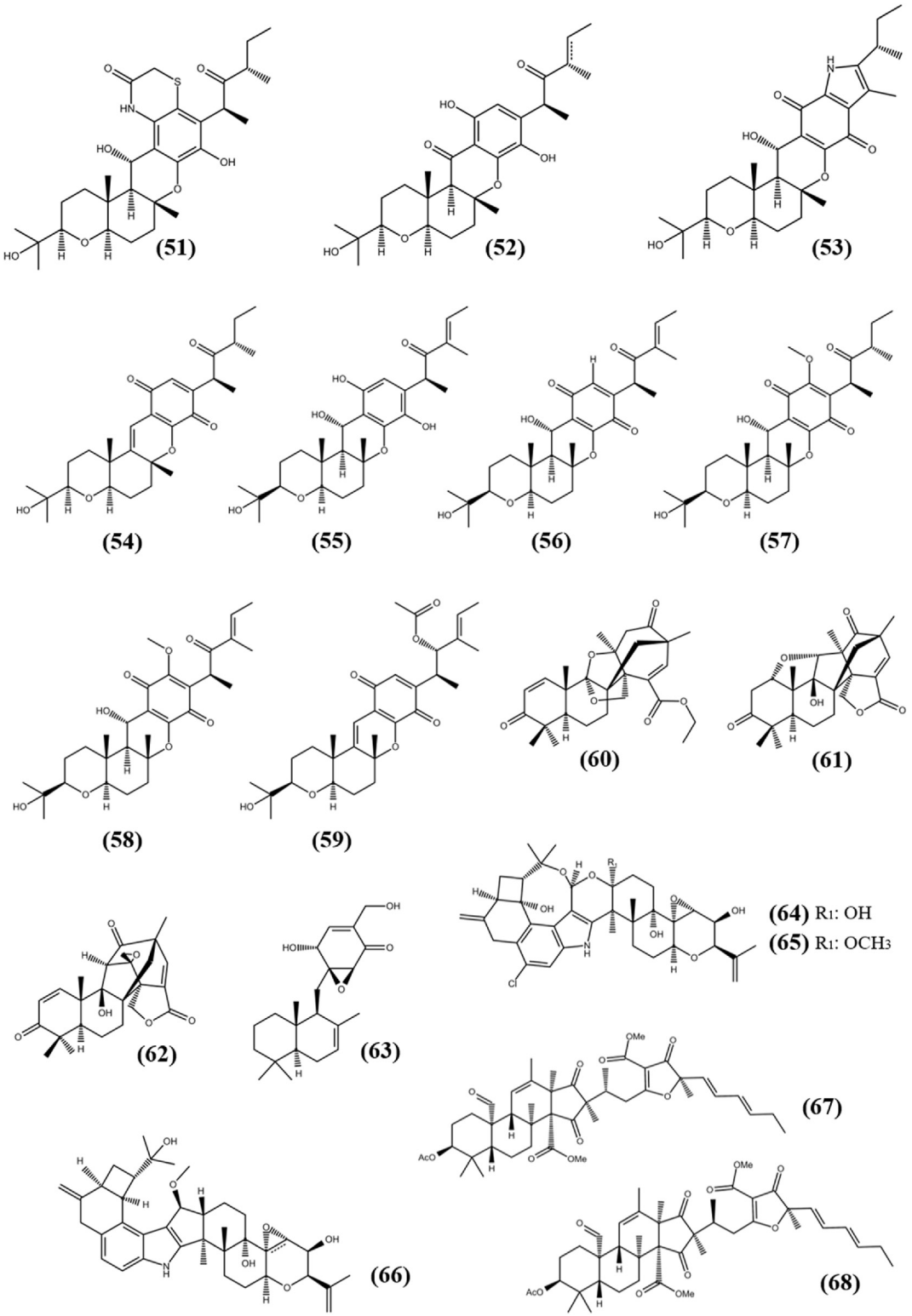

Fig. 5. Chemical structures of meroterpenoids **(36–50)**.

was isolated from leaves of *Paepalanthus planifolius*, collected from Minas Gerais, Brazil. It produced six novel polyketides, one of which, **Sporulosaldein F (42)** with benzopyran backbone exhibited *in vitro* cytotoxicity against the LM3 and MCF-7 cell lines with IC_{50} values of 39.2 and 34.4 μM, respectively and remains inactive against murine lung adenocarcinoma (LP07) cell line ($IC_{50} > 100$ μM). None of the other novel compounds showed cytotoxicity at the concentrations tested (De Amorim et al., 2019). **Peyronetide A (43)** is a novel polyketide with benzoisoquinoline-9-one backbone, extracted from endophytic fungus *Peyronellaea* sp. FT431 along with its derivative **Peyronetide B (44)**. Both the novel polyketide showed antiproliferative ability against three cancer lines A2780S (cisplatin sensitive human ovarian carcinoma), A2780CisR (cisplatin resistant human ovarian carcinoma), and TK-10 (human kidney adenocarcinoma) with IC_{50} values between 21.5 ± 0.3 and 29.2 ± 2.9 μM in CyQuant cell proliferation assay (Li et al., 2019b). Six new bicyclic polyketides, **Preussilides A—F (45–50)**, were obtained

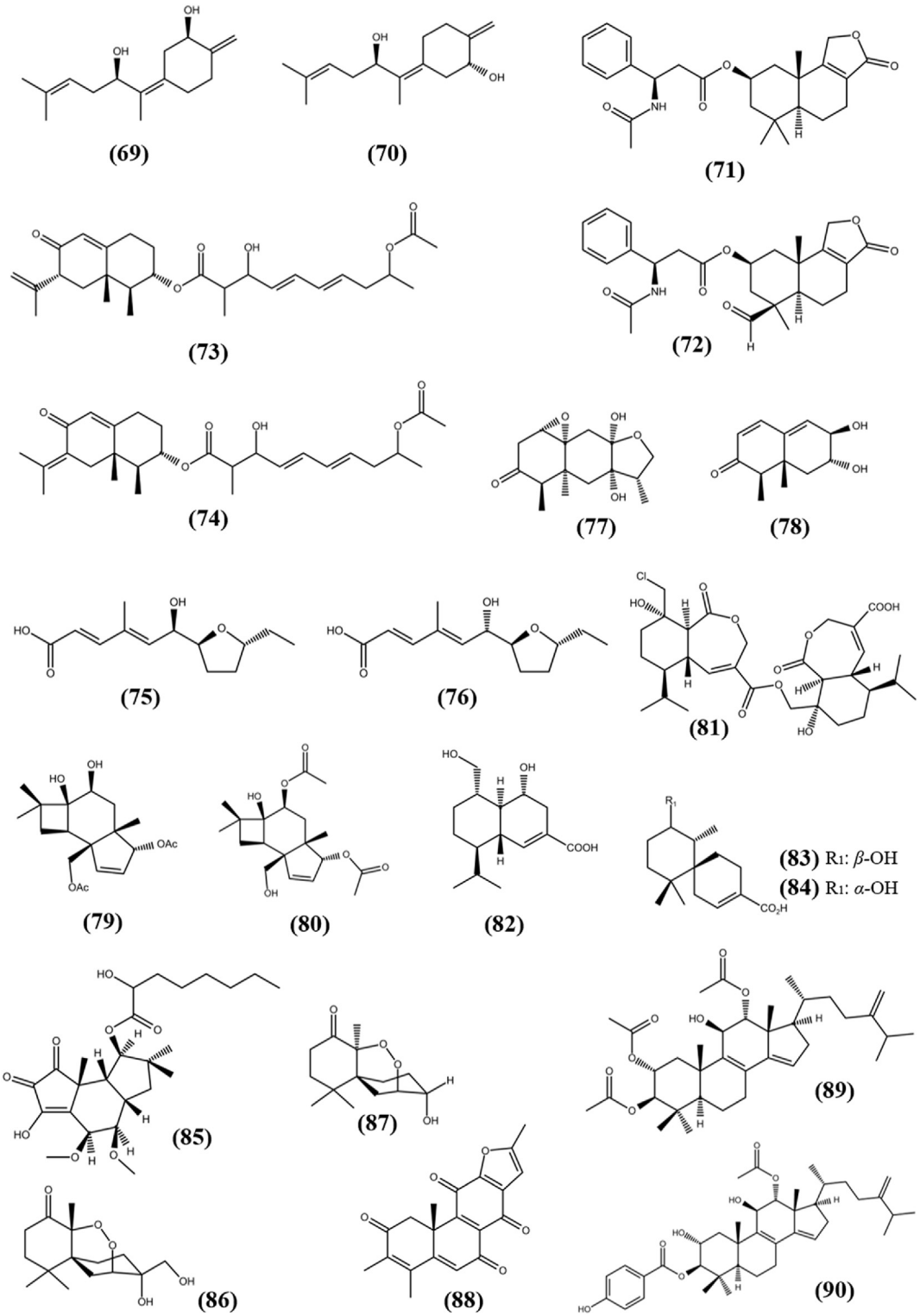

Fig. 6. Chemical structures of sesquiterpenoids **(69–87)**, diterpenoid **(88)**, and triterpenoids **(89–90)**.

from the fermented culture of endophytic fungi *Preussia similis* harbored in medicinal plant *Globularia alypum*, which was collected in Batna, Algeria. All isolated preussilides exhibited antiproliferative activity against either some or all tested cell lines L929, KB3.1, A431, A-549, SKOV-3 (ovarian cancer), PC-3, MCF-7 and U2OS with IC_{50} values in the range of 2.5–80 μM (Noumeur et al., 2017). Selective cytotoxicity of Preussilide A and Preussilide C and influence on the morphology of human osteosarcoma cells (U2OS) suggest that these two compounds might affects the cell division process and more research is needed to determine the molecular mechanism. The structures of unclassified polyketides **(36–50)** are shown in Fig. 4.

2.2. Terpenoids

Terpenoids are a class of natural bioactive substances which have isoprene as a scaffold and are found in a wide range of organisms. Many

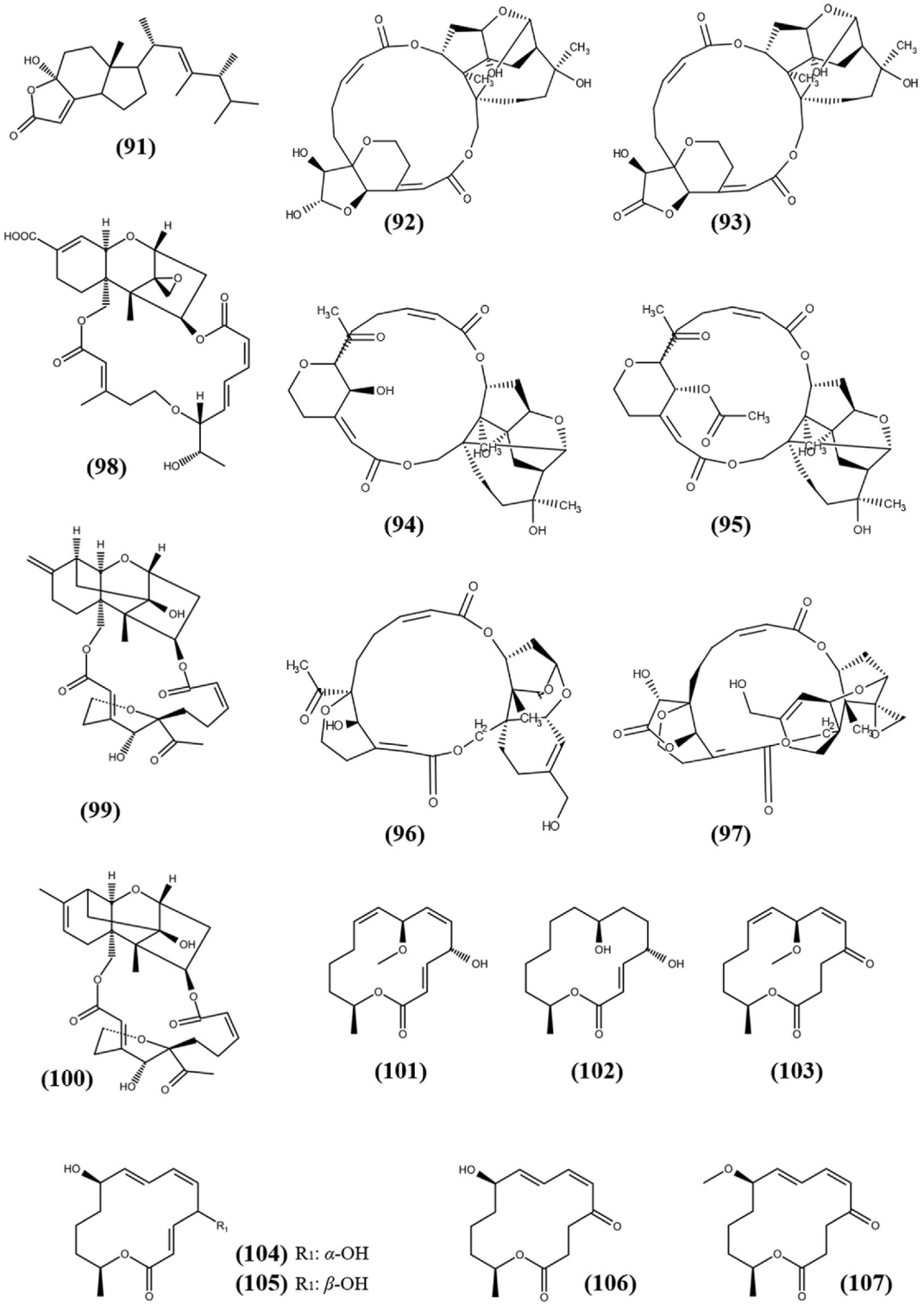

Fig. 7. Chemical structures of Steroid **(91)** and macrolides **(92–107)**.

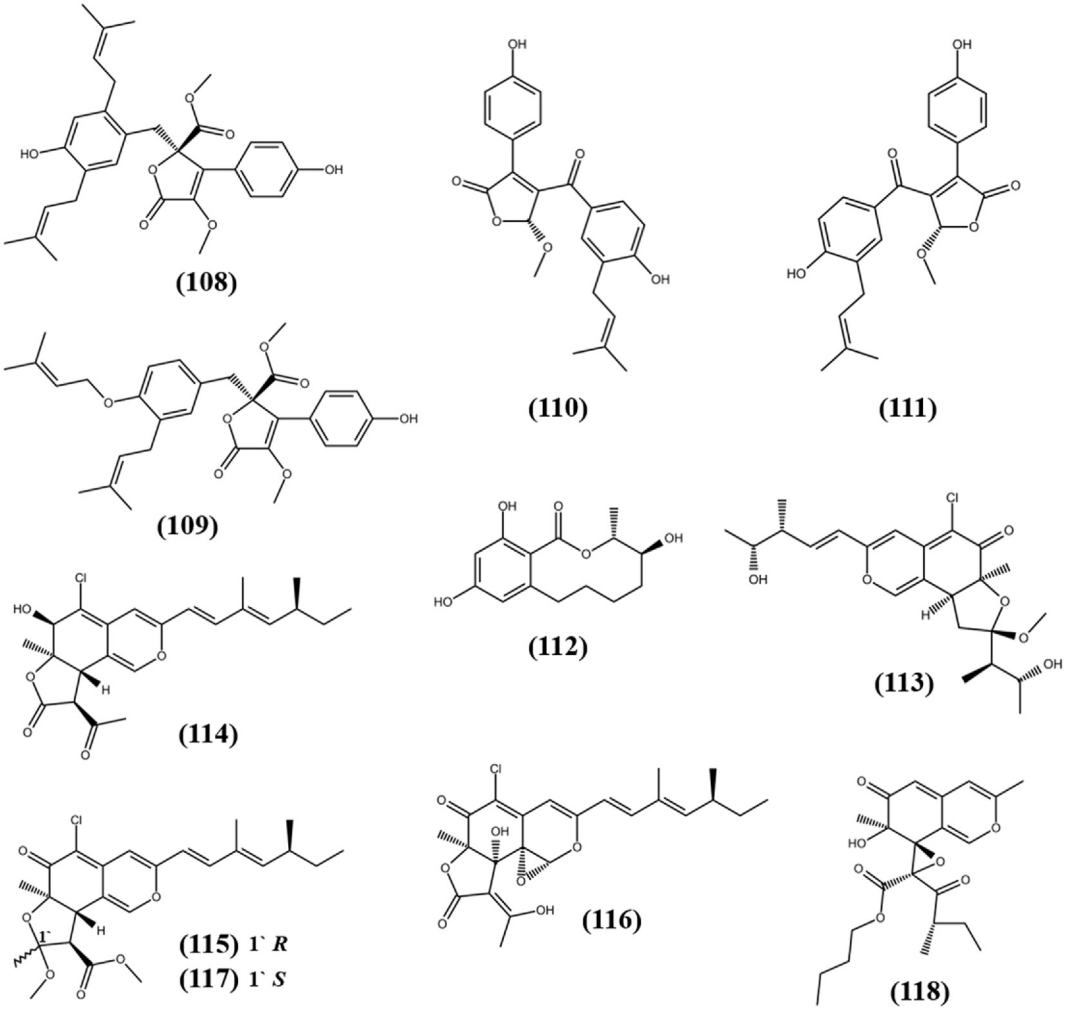

Fig. 8. Chemical structures of lactones **(108–112)** and azaphilones **(113–118)**.

terpenoids are studied for anticancer activity, antimicrobial activities, lethal toxicity, anti-inflammatory action, enzyme inhibitor activity, and other biological activities (Jiang et al., 2020). Herein, 40 terpenoids are divided into four categories: meroterpenoids, sesquiterpenoids, diterpenoid, and triterpenoids.

2.2.1. *Meroterpenoids*

A chemical compound with a partial terpenoid structure is known as a meroterpenoid. Four new meroterpenoids, **Isocochlioquinones D-E (51–52)** and **Cochlioquinones G-H (53–54)** were separated from EtOAc extract of fungus *Bipolaris sorokiniana* A606, an endophyte associated with the medicinal plant *Pogostemon cablin*. All compounds possess antiproliferative activity against SF-268, MCF-7, NCI–H460 and HepG2 tumor cell lines with the IC_{50}s between 6.4 ± 0.2 and 42.6 ± 2.5 μM (Wang et al., 2016). An endophytic fungus *Bipolaris* sp. L1-2 was isolated from leaves of the *Lycium barbarum*, which were collected from Ningxia Province, China. Ethyl acetate extract of fermented fungus, detected with eleven new meroterpenoids, including **Bipolahydroquinone C (55), Cochlioquinones I (56), K (57), L (58) and M (59)**, which have cytotoxic activity in the range of 5.6–9.5 μM of IC_{50}s against MDA-MB-231 cancer cell line (Long et al., 2019). Bipolahydroquinone C was also found to be cytotoxic against the NCI–H226 cancer cell line, with an IC_{50} of 5.5 μM, making it an appealing molecule for further scientific research as a chemotherapeutics for lung cancer treatment. A series of 3,5-demethylorsellinic acid-based meroterpenoids including **Emeridone B (60)**, **Emeridone D (61) and Emeridone F (62)** were separated from EtOAc extract of fungus *Emericella* sp. TJ29, an endophyte associated with the plant *Hypericum perforatum*. All three compounds possess cytotoxic activity against two cancer cell lines SMMC-7721 (human hepatocellular carcinoma) and SW-480 (colon cancer) with IC_{50}s in the range of 8.19–18.80 μM. **Emeridone D** also showed antiproliferative activity to A-549 with IC_{50} value of 11.33 ± 0.82 μM, while other compounds remain inactive against tested cell lines (Li et al., 2019c). The new meroterpenoid, **11-dehydroxy epoxyphomalin A (63)** with epoxyphomalin backbone was extracted from fermented culture of fungus *Peyronellaea coffeae-arabicae* FT238, an endophyte associated with the native Hawaiian plant *Pritchardia lowreyana*. It showed antiproliferative activity against panel of tumor cell lines MCF-7, MDA468, MDA-MB-231, T24 (human urinary bladder carcinoma), OVCAR5, OVCAR4, OVCAR3 (epithelial carcinoma), IGROV-1/Pt (drug-resistant ovarian carcinoma), A2780 CisR and A2780 with IC_{50}s of 2, 1.3, 2.2, 1.8, 1.8, 1.4, 0.5, 1.6, 0.6 and 0.8 μM, respectively (Li et al., 2016). **Rhizovarin A (64), Rhizovarin B (65) and Rhizovarin F (66)** with cytotoxic ability were extracted from *Mucor irregularis QEN-189*, an endophyte associated with marine mangrove plant *Rhizophora stylosa*. Compound **(64)** and **(65)** showed cytotoxic activity towards HL-60 and A-549 tumor cell lines with IC_{50}s of 11.5, 9.6 μM and 6.3, 5 μM, respectively, while compound **(66)** showed activity against only A-549 cells with IC_{50} value of 9.2 μM and remain inactive (IC_{50} > 10 μM) against HL-60 cells (Gao et al., 2016). Two novel meroterpenoids, **Isopenicin A (67) and Isopenicin B (68)** with unprecedented hybrid skeleton of polyketide-terpenoid moiety were obtained from fermented culture of endophytic fungus *Penicillium*

sp. sh18, which was harbored in fresh stems of *Isodon eriocalyx* var. *laxiflora*. Both the compounds possess cytotoxic ability against several cancer cell lines SW480, SW620, HCT116, CaCo2 (human colorectal adenocarcinoma), SMMC-7721 (human hepatocellular carcinoma), A-549 and MCF-7 with the IC_{50}s of 7.91 ± 0.53, 8.63 ± 0.15, 9.03 ± 0.61, 12.56 ± 0.91, 27.66 ± 0.88, 37.06 ± 2.24, 27.89 ± 0.70 μM and 11.60 ± 0.18, 15.48 ± 1.39, 14.95 ± 0.22, 20.34 ± 0.25, 33.49 ± 0.17, >40, 33.05 ± 0.19 μM, respectively (Tang et al., 2019). Detailed analysis of both compounds on human embryonic kidney cell line (HEK293), SW620, and HCT116 cells revealed that they selectively suppress the Wnt pathway in colon cancer cells. However, more research and in vivo experiments are essential before it could be termed an effective anticancer compound. The structures of meroterpenoid **(51–68)** are shown in Fig. 5.

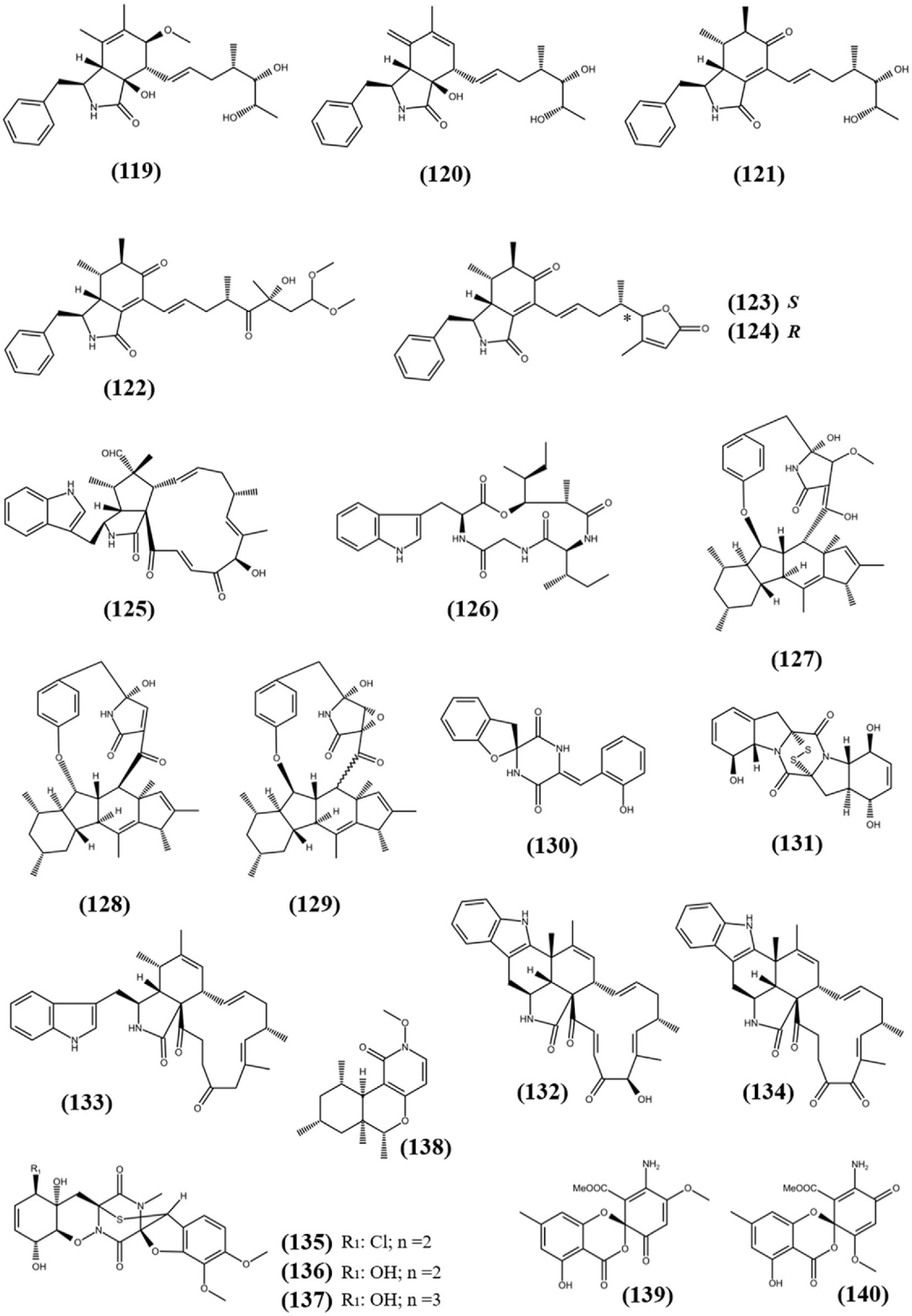

Fig. 9. Chemical structures of alkaloids **(119–140)**.

2.2.2. Sesquiterpenoids

Sesquiterpenoids are a class of compounds that contain 15 carbon atoms and are made up of three isoprene units. Two novel sesquiterpenes named, **Fumagillene A (69)** and **Fumagillene B (70)** were separated from EtOAc extract of endophytic fungi *Aspergillus fumigatus* isolated from the root of *Ligusticum wallichii*. Compound **(69)** exhibited cytotoxicity against MDA-ME-231 and MV4-11 cancer cell lines with IC_{50}s of 8.4 ± 2.9 and 4.3 ± 5.8 μg/ml, while compound **(70)** showed activity at 11.2 ± 3.6 and 17.3 ± 6.4 μg/ml respectively (Li et al., 2020c). **Proversilin C (71)** and **Proversilin E (72)** are unprecedented drimane-type sesquiterpenoids which were obtained from fungi *Aspergillus versicolor* F210, an endophyte associated with *Lycoris radiata*. Both the compounds showed antiproliferation activity against HL-60, SMMC-7721, A-549, MCF-7 and SW-480 cells with IC_{50}s of 7.3 ± 1.2, 12.6 ± 0.9, 15.0 ± 0.8, 11.8 ± 0.5, 12.4 ± 0.4 μM and 9.9 ± 1.4, 19.4 ± 0.7, 28.4 ± 1.2, 18.3 ± 1.2, 16.4 ± 1.0 μM respectively, while remain inactive against normal colonic epithelial cells (NCM460) with IC_{50} of >40 μM (Li et al., 2020d). Two new eremophilane sesquiterpenes, **Lithocarin B (73)** and **Lithocarin C (74)** have been extracted along with two more new metabolites from EtOAc extract of fungus *Diaporthe lithocarpus* A740, an endophyte associated with medicinal plant *Morinda officinalis*. Lithocarin B and Lithocarin C showed weak antiproliferative activity against three cancer cell lines, SF-268, MCF-7, HepG2 in the range of 37 and 97.71 μM of IC_{50} values compared to known anticancer molecule, cisplatin which exhibited activity at 3.39 ± 0.29, 3.19 ± 0.12 and 2.42 ± 0.14 μM, respectively. Other compounds remain inactive against all tested cell lines at IC_{50}s of >100 μM (Liu et al., 2019a). **(R,2E,4E)-6-((2S, 5R)-5-ethyltetrahydrofuran-2-yl)-6-hydroxy-4-methylhexa-2, 4-dienoic acid (75)** and **(S,2E,4E)-6-((2S,5R)-5-ethyltetrahydrofuran-2-yl)-6-hydroxy-4- methylhexa-2,4-dienoic acid (76)** are two novel nor-sesquiterpenoids obtained from endophytic fungus *Fusarium tricinctum*, associated with the root of *Ligusticum chuanxiong*. Among these, compound **(75)** displayed cytotoxicity against MV4-11, HCT116, MCF-7 and A-549 cancer cell lines with an IC_{50} values between 22.29 and 93.47 μM, while compound **(76)** exhibited cytotoxicity against only MV4-11 and MCF-7 cells with an IC_{50} value of 70.2 and 81.21 μM, respectively (Cao et al., 2020). Two new polyoxygenated eremophilane sesquiterpenes, **Periconianone E (77) and Periconianone H (78)** were obtained from EtOAc extract of endophytic fungus *Periconia* sp. F-31, which was isolated from *Annona muricata*. Compound **(77)** showed cytotoxicity against MCF-7 cells with IC_{50} value of 17.9 μM, while compound **(78)** exhibited cytotoxic activity against HeLa cell line with IC_{50} of 16.5 μM (Liu et al., 2016a). The crude extract of the fungus *Pestalotiopsis theae*, an endophyte isolated from *Camellia sinensis* in Hangzhou, China, contains three new compounds including two caryophyllene-type sesquiterpenoids, **Pestathenol A (79)** and **Pestathenol B (80)**. Both the compounds exhibited weak cytotoxicity against HeLa cell line, with IC_{50} values of 78.2 and 88.4 μM, respectively,

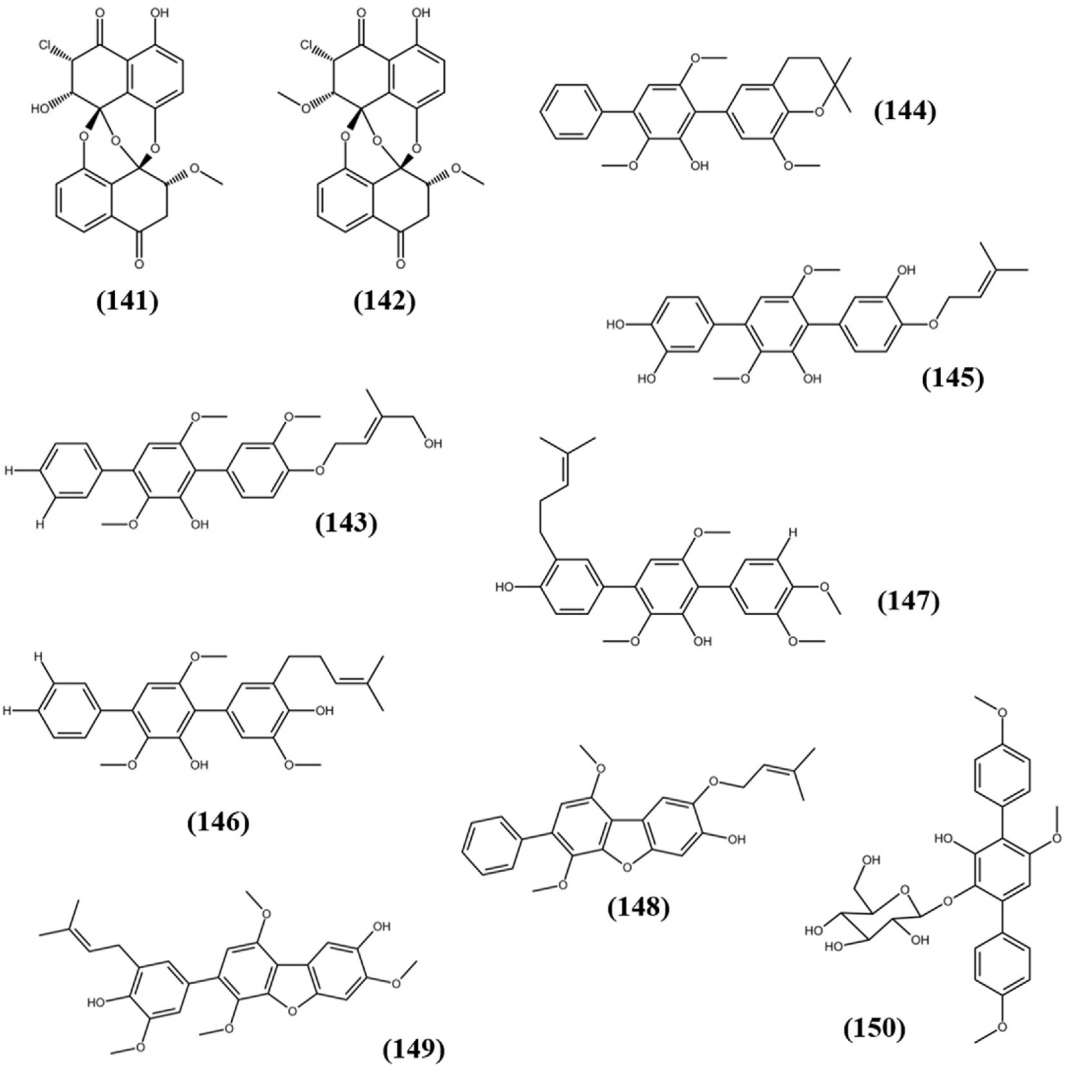

Fig. 10. Chemical structures of preussomerins **(141–142)** and *p*-terphenyls **(143–150)**.

compared to positive control cisplatin which possess IC_{50} value of 21.1 μM (Guo et al., 2020). Two new cytotoxic sesquiterpenoid derivatives, **Rhinomilisin A (81) and Rhinomilisin G (82)** were extracted from the culture of fungus *Rhinocladiella similis*, which was isolated from the leaves of mangrove fern *Acrostichums aureum*. Both the compounds showed cytotoxic ability towards mouse lymphoma cell line (L5178Y) with IC_{50} value of 5 and 8.7 μM, respectively (Liu et al., 2019b). **Merulinol C (83) and Merulinol D (84)** are two new chamigrane sesquiterpenes, which were separated from the EtOAc extract of the fungus XG8D of basidiomycetes phyla, harbored in the healthy leaves of Thai mangrove *Xylocarpus granatum*. Both the compound showed cytotoxicity against KATO-3 cells with IC_{50}s of 35.0 ± 1.20 and 25.3 ± 0.82 μM, respectively, while remain inactive against MCF-7 and HepG2 cell lines with IC_{50}s of >50 μM (Choodej et al., 2016). **Cerrenin D (85)**, a triquinane-type sesquiterpene had been isolated from endophytic fungus *Cerrena* sp. A593, which was harbored in *Pogostemon cablin* and

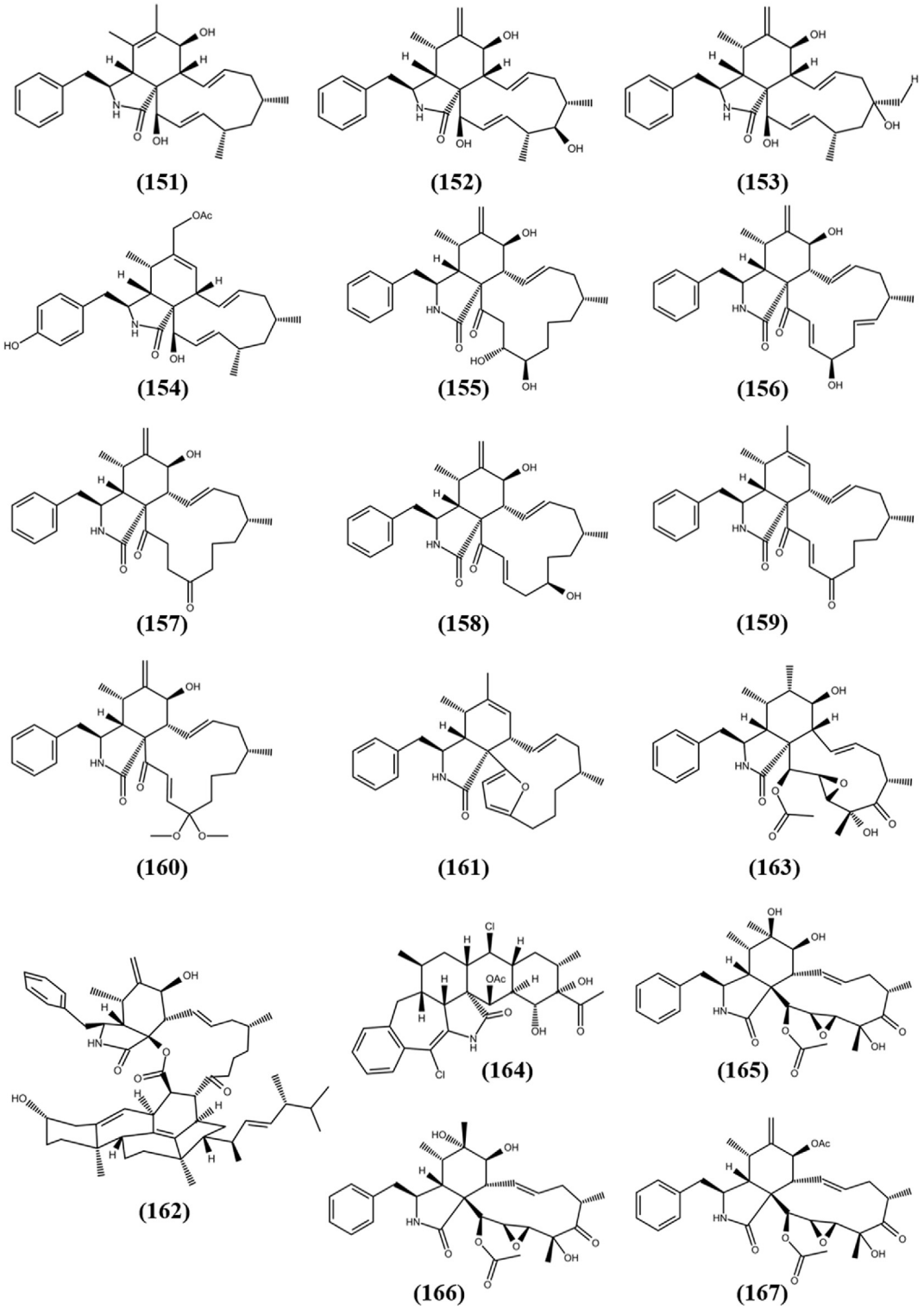

Fig. 11. Chemical structures of cytochalasans **(151–167)**.

possess weak antiproliferative activity against four cancer cell lines SF-268, MCF-7, NCI–H460 and HepG2 with IC_{50}s of 41.01 ± 0.34, 14.34 ± 0.45, 29.67 ± 0.81, and 44.32 ± 2.12 μM, respectively (Liu et al., 2020a). Two unprecedented fungal sesquiterpenoids, **7-epi-merulin B (86) and 3-epi-merulin A (87)** were separated from the culture of *Pseudolagarobasidium acaciicola*, an endophyte associated with mangrove plant *Bruguiera gymnorrhiza*. Compound **(86)** exhibited cytotoxicity against HuCCA-1 (human lung cholangiocarcinoma), A-549, MOLT-3 (T-lymphoblast), HepG2, HL-60, MDA-MB231, T47D (human mammary adenocarcinoma) and MRC-5 (normal human embryonic lung) cell lines with IC_{50} values of 37.46 ± 3.77, 24.75 ± 1.09, 2.39 ± 0.95, 8.91 ± 3.13, 0.28 ± 0.18, 12.22 ± 9.26, 22.25 ± 3.35 and 17.92 ± 4.58 μM, respectively, while compound **(87)** was active towards only MOLT-3, HepG2, HL-60 and MRC-5 cell lines with IC_{50}s of 17.28 ± 3.66, 20.71 ± 3.50, 12.09 ± 3.50 and 17.83 ± 2.72 μM, respectively (Wibowo et al., 2016). The structures of meroterpenoid **(69–87)** are shown in Fig. 6.

2.2.3. Diterpenoid

Diterpenoids are a substantial class of terpenoids that has a wide range of structures and bioactivities. A novel compound **(10S)-12,16-epoxy-17(15 → 16)-abeo-3,5,8,12,15-abietapentaen-2,7,11,14-tetraone (88)** with diterpenoid backbone was separated from the culture of endophytic fungus *Pestalotiopsis adusta*, obtained from the medicinal plant *Clerodendrum canescens*. It showed antiproliferative activity against HL-60 cancer cell line with IC_{50} of 12.54 ± 1.18 μM (Xu et al., 2016). The structure of diterpenoid **(88)** is shown in Fig. 6.

2.2.4. Triterpenoids

Triterpenoids are a group of chemical compounds composed of three terpene units that have a versatile chemistry and pharmacology and contain several pentacyclic motifs. Three new tetracyclic triterpenoids, including **Integracide H (89) and Integracide J (90)** were separated from the fermented culture of endophytic fungus *Fusarium* sp. associated with *Mentha longifolia* L. Both the compounds showed strong cytotoxicity towards BT-549, SKOV-3 and KB cell lines with IC_{50}s of 1.82, 1.32, 0.18 μM and 2.46, 3.01, 2.54 μM, respectively, compared to positive control doxorubicin (2.78, 0.16 and 0.41 μM). However, both the compounds remain inactive against SKOV-3 cell line, while other compound remain inactive against all tested cell lines (Ibrahim et al., 2016a). The structures of triterpenoids **(89–90)** are shown in Fig. 6.

2.3. Steroid

Steroids are a class of fungal metabolites with a wide range of chemical structures and biological functions. Many researchers are currently looking for steroidal metabolites to use as potential lead compounds in drug development (Ur Rahman et al., 2017). A new compound, **Demethylincisterol A5 (91)** with sterol moiety was separated from the rice fermented culture of endophytic fungus *Aspergillus tubingensis* YP-2, which was isolated from traditional Chinese medicinal plant *Taxus yunnanensis*. It showed weak cytotoxicity towards A-549 and HepG2 cells with the IC_{50}s of 11.05 and 19.15 μM, respectively, compared to positive control Doxorubicin, which had an IC_{50}s of 0.94 and 1.16 μM, respectively (Yu et al., 2019). The structure of steroid **(91)** is shown in Fig. 7.

2.4. Macrolides

The macrolides are a group of natural products that are made up of a large macrocyclic lactone ring with one or more deoxy sugars attached and have a wide range of biological activities, including antiparasitic, antifungal, and antimalarial properties (Karpiński, 2019). **Myrothecines D-G (92–95), 16-hydroxymytoxin B (96), and 14′-dehydrovertisporin (97)** are six unprecedented macrolides, which were obtained from endophytic fungus *Myrothecium roridum*, associated with *Trachelospermum jasminoides* (Lindl.) Lem. All compounds possess cytotoxic ability against two tumor cell lines K562 (chronic myeloid leukemia) and SW1116 (colorectal carcinoma) between 0.056 and 15.98 μM of

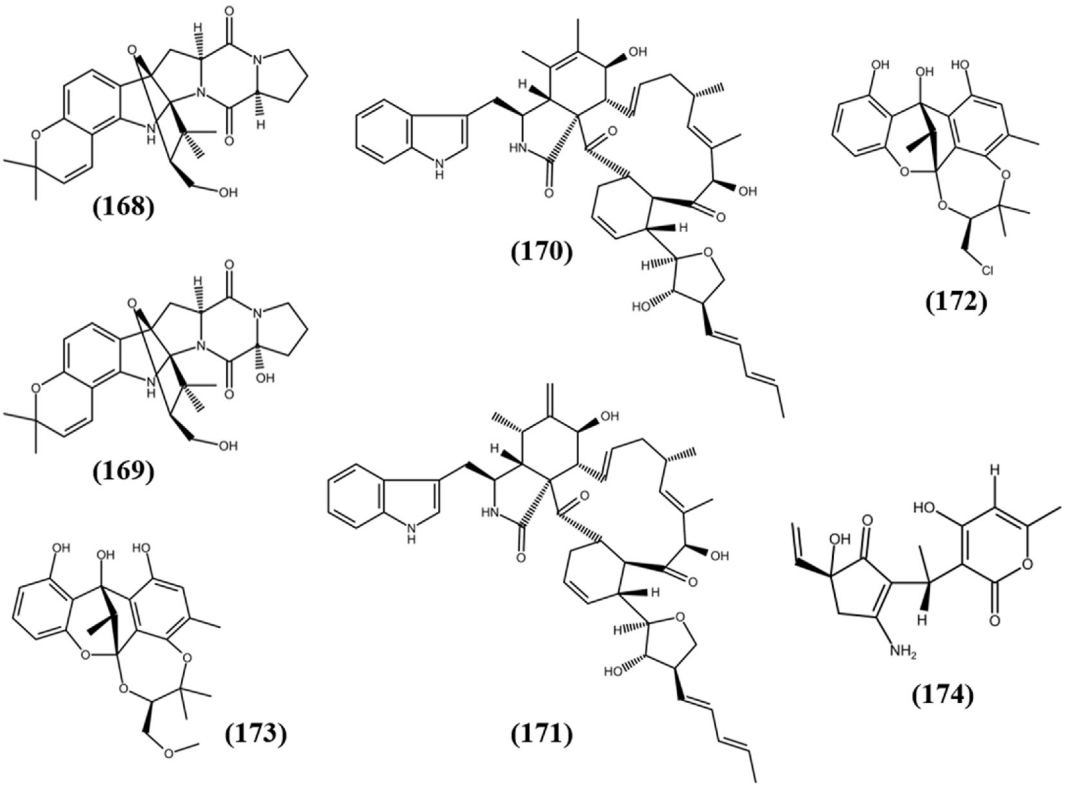

Fig. 12. Chemical structures of other hybrids **(168–174)**.

IC_{50} values. A three-dimensional quantitative structure activity relationship (3D QSAR) analysis suggested that the cytotoxicity of these trichothecene macrolides at nanomolar to micromolar level is dependent on steric, electrostatic, hydrophobic, and H-bond accepting pharmacophore group present in them (Shen et al., 2019). Moreover, additional research could be useful in developing these fungal metabolites as anticancer agents with specific molecular mechanism. A macrolide molecule consists of sesquiterpenoid with a diacyl residue anchored at the 4β and 15 positions, named **Epiroridin acid (98)** was separated from fermented culture of fungus *Myrothecium roridum* A553, an endophyte harbored in the medicinal plant *Pogostemon cablin*. It exhibited strong cytotoxic capability against SF-268, MCF-7, NCI–H460, and HepG2 cell lines with IC_{50}s of 0.751 ± 0.03, 0.170 ± 0.01, 0.360 ± 0.05 and 0.380 ± 0.03 μM, respectively, compared to positive control cisplatin, which showed activity with IC_{50}s of 4.060 ± 0.16, 2.850 ± 0.45, 2.850 ± 0.15 and 2.470 ± 0.17 μM, respectively (Liu et al., 2016b). The fact that Epiroridin acid has lower IC_{50} values than the positive control signals that more *in vitro* investigations such as apoptosis, cell cycle-based studies, and so on, is needed to determine its mechanism of action. Two new trichothecene macrolides, named **Myrothecine H (99) and Myrothecine I (100)** were extracted from the culture of endophytic fungus *Paramyrothecium roridum,* associated with the medicinal plant *Morinda officinalis*. Both the compounds showed strong cytotoxicity towards SF-268 and HepG2 cell lines with IC_{50}s of 6.75 ± 0.22, 6.72 ± 0.27 μM and 0.20 ± 0.01, 0.20 ± 0.03 μM, respectively (Liu et al., 2020b). **7-O-Methylnigrosporolide (101) and Pestalotioprolide C–H (102–107)** are 14-membered macrolides, which were separated from the culture of *Pestalotiopsis microspora*, an endophytic fungus associated with mangrove *Drepanocarpus lunatus*. All compounds possess cytotoxic ability against murine lymphoma cell line L5178Y and/or A2780 with IC_{50}s between 1.2 and 39 μM (Liu et al., 2016c). The structures of macrolides **(92–107)** are shown in Fig. 7.

2.5. Lactones

Lactones are cyclic esters, which consist of a ring of two or more carbon atoms and a single oxygen atom with a ketone group next to one of the carbons. Lactones are used in the flavors and fragrances industry, and they also possess antioxidant, antimicrobial, and anticancer properties (Robinson et al., 2019). Two new compounds, **Asperlactone G (108) and Asperlactone H (109)** were separated from ethyl acetate extract of an endophytic fungus *Aspergillus* sp., associated with *Pinellia ternate*. Both the compounds showed weak cytotoxicity towards A-549 cells with IC_{50}s of 65.3 ± 1.06 and 23.3 ± 2.01 μM, respectively, while remain inactive against MCF-7/DOX cell line at IC_{50} of >100 μM (Xin et al., 2019). Four new compounds including a pair of butanolide derivatives, **(−)-asperteretone F (110)** and **(+)-asperteretone F (111),** were obtained from the endophytic fungus *Aspergillus terreus*, associated with *Hypericum perforatum*. Compounds **(110)** and **(111)** exhibited cytotoxic activity against human pancreatic cancer cells AsPC-1, SW1990 and PANC-1 cell line with IC_{50} values of 9.5, 11.7, 9.8 μM and 9.9, 10.3, 15.6 μM, respectively. Both the compounds remain inactive against HeLa and SW480 cancer cell lines, while other compounds were inactive against all tested cell lines (Deng et al., 2020). **Hispidulactone F (112),** a novel metabolite was separated from the EtOAc extract of dessert plant associated endophytic fungus *Chaetosphaeronema hispidulum* (TS-8-1) and showed antiproliferative activity against HepG2 cells with IC_{50} of 61.05 μM by the cell counting kit-8 (CCK-8) assay (Zheng et al., 2020). The structures of lactones **(108–112)** are shown in Fig. 8.

2.6. Azaphilones

A pyranoquinone oxabicyclic skeleton with an oxygenated non protonated carbon at C-7 distinguishes azaphilones, which can be classified into various groups. Azaphilones have a wide variety of biological activities, including antimicrobial, cytotoxic, anticancer, antiviral, and anti-inflammatory effects (Luo et al., 2018). **Chaephilone C (113)** is an unprecedented azaphilone, which was obtained from EtOAc extract of endophytic fungi *Chaetomium globosum* TY-2 isolated from the plant *Polygonatum sibiricum*. It showed moderate antiproliferative activity towards HepG2 tumor cell line with IC_{50} value of 38.6 μM (Song et al., 2020). **Isochromophilone A (114), Isochromophilone D (115), Isochromophilone F (116) and Isochromophilone C (117)** are cytotoxic chloroazaphilone derivatives, which were separated from the fermented culture of *Diaporthe* sp. SCSIO 41011, an endophyte associated with mangrove plant *Rhizophora stylosa*. Compounds **(114–116)** showed cytotoxic activity against ACHN, 786-O and OS-RC-2 cell lines of renal carcinoma with IC_{50}s between 8.9 and 38 μM, while compound **(117)** was active against only 786-O and OS-RC-2 cells with IC_{50}s of 38 and 44 μM, respectively. Additionally, effect of Isochromophilone D on apoptosis and cell cycle study showed that it induces apoptosis in time and dose dependent manner, while do not have any effect on cell proliferation (Luo et al., 2018). Fungus *Phomopsis* sp. CGMCC No.5416, an endophyte was isolated from the stems of *Achyranthes bidentata*, which was collected from Nan Ling County, Anhui Province of China. The fermented culture of isolated endophyte leads to separation of three novel azaphilones, including **Phomopsone C (118)**, which possess cytotoxic activity against three cancer cell lines A-549, MDA-MB-231 and PANC-1 with CC_{50}s of 8.9, 3.2 and 17.3 μM, respectively, while other compounds remain inactive at CC_{50} of >100 μM (Yang et al., 2020a). The structures of azaphilones **(113–118)** are shown in Fig. 8.

2.7. Alkaloids

Alkaloids are a class of basic organic substances that originate from plants, bacteria and fungi and contain at least one nitrogen atom in a ring structure. Vinblastine and vincristine are two well-recognized indole alkaloids which possess anticancer activity (Uzma et al., 2018). Six new alkaloids, **Asperchalasins A-F (119–124)** were separated from ethyl acetate extract of an endophytic fungus *Aspergillus* sp., associated with *Pinellia ternate*. All compounds showed weak cytotoxicity towards A-549 cells with IC_{50}s of 55.5 ± 1.87, 54.2 ± 1.22, 47.2 ± 0.92, 40.6 ± 1.30, 55.2 ± 1.85, and 70.2 ± 1.76, respectively, while remain inactive against MCF-7/DOX cell line at IC_{50} of >100 μM (Xin et al., 2019). **Pchaeglobosal B (125),** a novel rearranged cytochalasan with 13-aza-21-oxa-tetracyclo-[$10.6.1.2^{17,19}.0^{15,19}$]henicosane core was separated from the culture of endophytic fungus *Chaetomium globosum* P2-2-2, which was isolated from *Ptychomitrium* plant. It showed anticancer activity against MCF-7, HepG2, CT26, HT29, and A-549 with IC_{50}s of 8.59 ± 0.40, 7.09 ± 0.11, 1.04 ± 0.04, 9.90 ± 0.68 and 6.92 ± 0.21 μM, respectively (Peng et al., 2020a). Detailed research revealed that it halted the cell cycle progression of CT26 cells in the S phase and HT29 cells in the G0/G1 phase, as well as inducing apoptosis in both cell lines, which makes this compound substantial for additional pharmacokinetic study to foster it as strong chemotherapeutic drug. A rare natural metabolite, **Chaetomiamide A (126)** with the 13-membered ring skeleton was discovered from endophytic fungus *Chaetomium* sp., which was harbored in the roots of *Cymbidium goeringii*. Chaetomiamide A showed cytotoxicity against only HL-60 cell line with IC_{50} value of 35.20 μM, while remain inactive against other tested cell lines A-549, SMMC 7721, MCF-7 and SW480 (Wang et al., 2017). Three new compounds, **Ascomylactam A (127), Ascomylactam B (128) and Ascomylactam C (129)** are 12- or 13-membered-ring macrocyclic alkaloids, which were obtained from the endophytic fungus *Didymella* sp. CYSK-4 isolated from the marine semi mangrove *Pluchea indica*. All three compounds exhibited moderate to weak cytotoxic activity against MDAMB-435, MDAMB-231, SNB19, HCT116, NCIH460 and PC-3 cell lines in the range of 4.2–20 μM of IC_{50} values, compared to epirubicin as positive control, which had an IC_{50} values of 0.26, 5.6, 2.3, 0.37, 0.12 and 5.7 μM respectively (Chen et al., 2019). Two new cytotoxic compounds, **Spirobrocazine C (130) and Brocazine G (131)** were separated from the endophytic fungi *Penicillium brocae* MA-231, which was isolated from the marine plant *Avicennia marina*. Spirobrocazine C possess weak cytotoxic

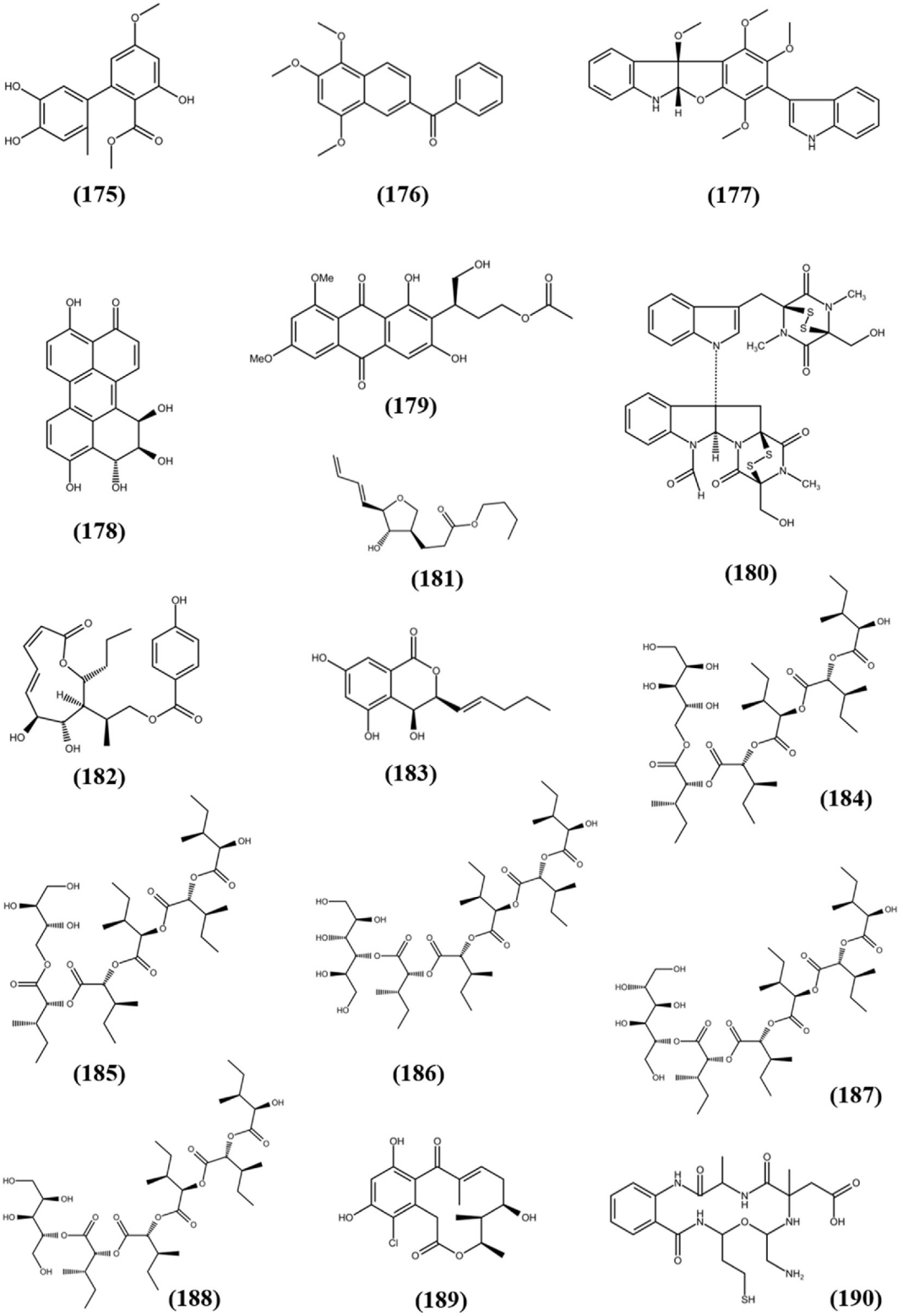

Fig. 13. Chemical structures of miscellaneous compounds **(175–190)**.

activity towards only A2780 cell line with IC_{50} value of 59 μM, while Brocazine G showed strong cytotoxicity against A2780 and A2780 CisR cell lines with IC_{50}s of 0.664 and 0.661 μM, respectively, compared to positive control cisplatin which had an IC_{50}s of 1.67 and 12.63 μM, respectively (Meng et al., 2016). The greater cytotoxicity of these molecules prompts us to explore their mechanism of action. Two new cytotoxic chaetoglobosin, **Penochalasin I (132)** and **Penochalasin J (133)** were separated from the fermented culture of *Penicillium chrysogenum* V11, an endophyte associated with mangrove *Myoporum bontioides*. Both the compounds showed cytotoxic activity against MDA-MB-435, SGC-7901 and A-549 human cancer cell lines with IC_{50}s in the range of 7.32–37.70 μM (Huang et al., 2016). **Penochalasin K (134)**, a new chaetoglobosin was extracted from the culture of fungus *Penicillium chrysogenum* V11, an endophyte harbored in *Myoporum bontioides* and

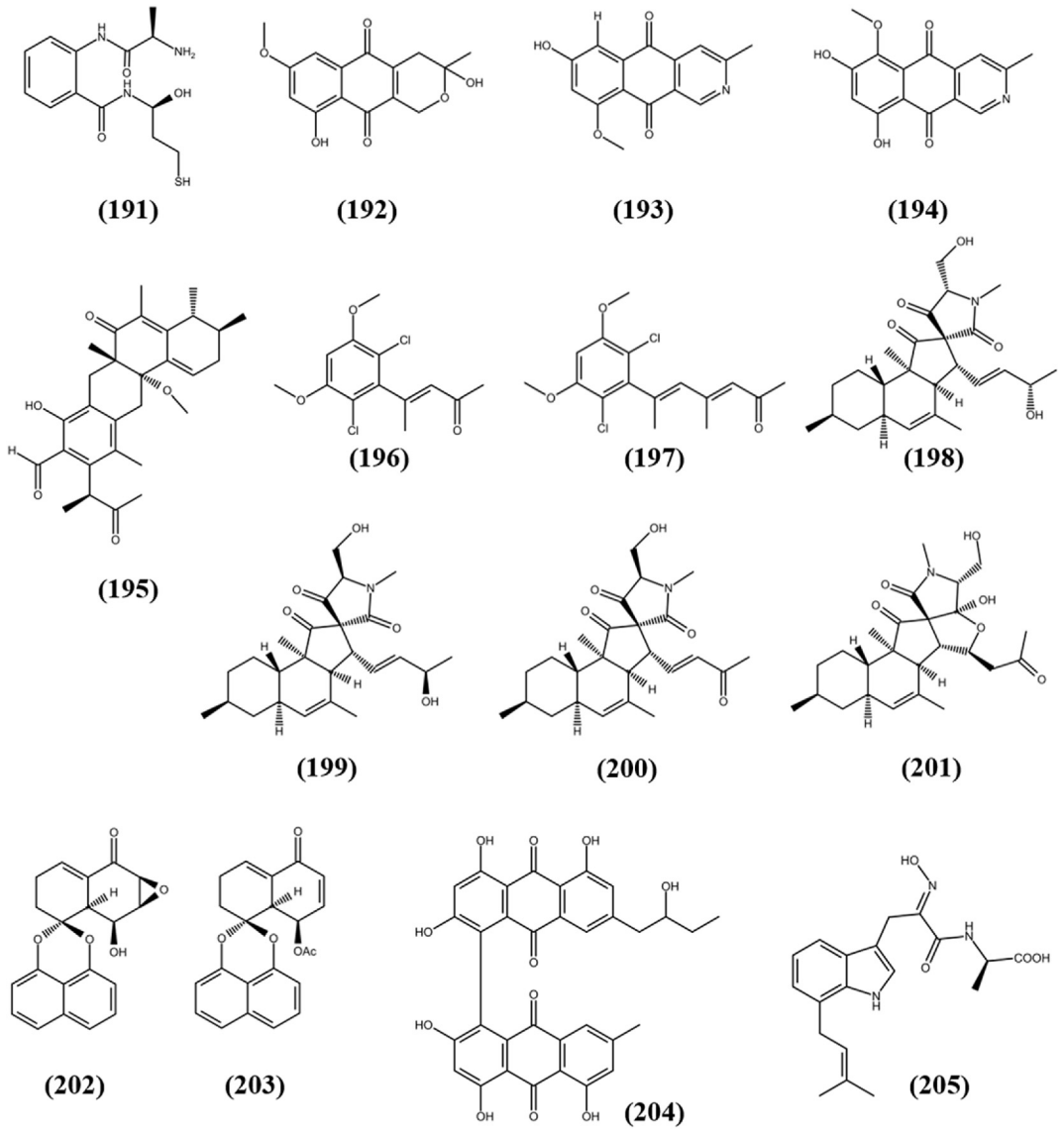

Fig. 14. Chemical structures of miscellaneous compounds **(191–205)**.

showed strong cytotoxic activity towards MDA-MB-435, SGC-7901 and A-549 tumor cell lines with IC_{50}s of 4.65 ± 0.45, 5.32 ± 0.58 and 8.73 ± 0.62 μM, respectively (Zhu et al., 2017a). An unprecedented epipolythiodioxopiperazine (ETP) alkaloids, **Penicisulfuranols A-C (135–137)** were separated from the fermented culture of *Penicillium janthinellum* HDN13-309, an endophyte associated with mangrove *Sonneratia caseolaris*. All compounds showed cytotoxic ability towards HeLa and HL-60 cell lines with IC_{50}s of 0.5, 0.1 μM and 3.9, 1.6 μM and 0.3, 1.2 μM, respectively (Zhu et al., 2017b). A new compound, **Chromenopyridin A (138)** with N-methoxy-1-pyridone alkaloid moiety was separated from the culture of fungus *Penicillium nothofagi* P-6, an endophyte harbored in the bark of the critically endangered conifer *Abies beshanzuensis*. It possesses cytotoxic activity towards A-549 and HeLa tumor cell lines with IC_{50}s of 14.7 and 11.3 μM, respectively (Zhu et al., 2020). **2′-aminodechloromaldoxin (139) and 2′-aminodechlorogeodoxin (140)** are two novel spiroketal derivatives with an amino group moiety, which were obtained from the *Cinnamomum camphora* endophytic fungus *Pestalotiopsis flavidula*. Both the new compounds exhibited cytotoxicity against four cancer cell lines NCI–H460, SF-268, MCF-7 and PC-3 with IC_{50}s in the range of 16.47–23.53 μM (Rao et al., 2019). The structures of alkaloids **(119–140)** are shown in Fig. 9.

2.8. Preussomerins

The compound consists of two unsaturated decalin units connected by three oxygen bridges through two spiroketal carbons, one at the upper decalin unit and the other at the lower decalin unit, defines preussomerins. **Chloropreussomerin A (141) and Chloropreussomerin B (142)** are chlorinated preussomerins, which were isolated from the culture of fungus *Lasiodiplodia theobromae* ZJ-HQ1, an endophyte associated with marine mangrove *Acanthus ilicifolius*. Both the compound possesses cytotoxic activity towards A-549, HepG2, HeLa, MCF-7 and HEK293T cancer cell lines with IC_{50}s of 8.5 ± 0.9, 13 ± 1, 19 ± 1, 5.9 ± 0.4, 4.8 ± 0.2 μM and 8.9 ± 0.6, 7.7 ± 0.1, 27 ± 3, 6.2 ± 0.4, 11 ± 3 μM, respectively (Chen et al., 2016). The structures of preussomerins **(141–142)** are shown in Fig. 10.

2.9. p-terphenyls

The para-terphenyls (*p*-terphenyls) is the major group of terphenyls which are aromatic compounds made up of three benzene chains. **Prenylterphenyllins F−J (143–147), Prenylcandidusin E (148) and Prenylcandidusin G (149)** are unprecedented fungal metabolites, which were separated from the culture of *Aspergillus candidus* LDJ-5, an

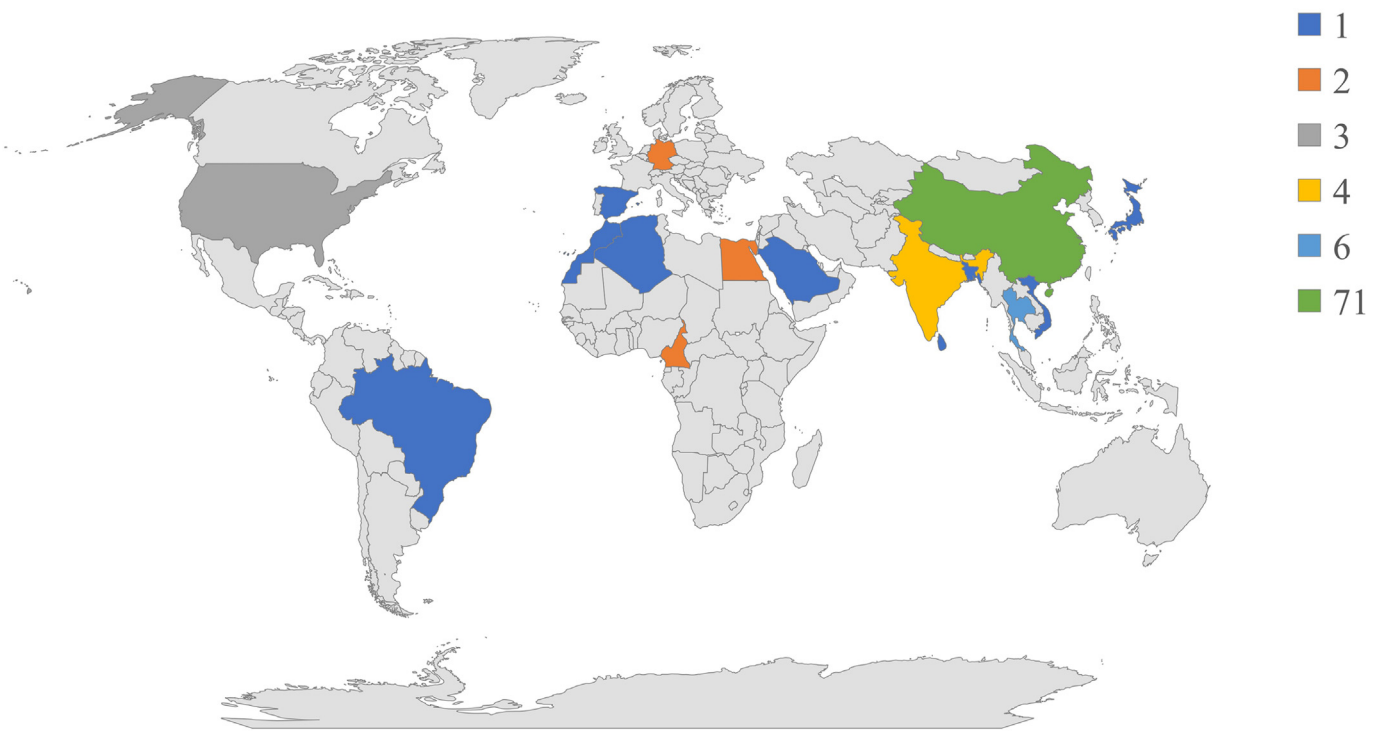

Fig. 15. Percentages of the endophytic fungi that have been isolated from highlighted sixteen countries and reported during 2016–2020.

endophyte associated with mangrove *Rhizophora apiculata* Blume. All compounds showed cytotoxicity against HL-60, K562, L-02, MGC-803, HCT-116, BEL-7402, A-549, SH-SY5Y, HeLa, and/or U87 with IC_{50}s between 0.4 and 29.7 μM (Zhou et al., 2020). **Gliocladinins C (150)**, a natural *p*-terphenyl glycoside was obtained from fungus *Chaetomium subaffine* L01, an endophyte obtained from healthy potato tissue, which was collected from Lincang county of Yunnan province, China. It possess cytotoxicity against two human tumor cell lines Hep-2 and HepG2 with the IC_{50} values of 0.18 and 0.12 μM, respectively (Han et al., 2019). Lower IC_{50} values against cancer cell lines suggest further research for this compound to be developed as a therapeutic molecule. The structures of *p*-terphenyls **(143–150)** are shown in Fig. 10.

2.10. Hybrid compounds

Secondary metabolite biosynthesis occurs in microorganisms through a variety of metabolic pathways. As a result, several hybrid secondary metabolites are generated by the simultaneous action of enzymes, building blocks, and cofactors from various pathways (Goyal et al., 2017).

2.10.1. Cytochalasans

Cytochalasans are fungal polyketide–amino acid hybrid metabolites, which are described by the hydrogenated isoindolone scaffold fused to a macrocyclic ring (Yang et al., 2020b). A terrestrial plant *Cyclosorus parasiticus* associated endophytic fungus *Diaporthe* sp. SC-J0138 was detected with unprecedented cytochalasans, **Diaporthichalasins D–F (151–153)** and **Diaporthichalasin H (154)**. All compounds tested for cytotoxic ability against four human cancer cell lines A-549, HeLa, HepG2 and MCF-7 and showed cytotoxic activity with IC_{50} value of wide range (Yang et al., 2020b). New '(Jia et al., 2016)cytochalasins', **Multirostratins B (155), E-J (156–161)** were separated from fermented culture of endophytic fungus *Phoma multirostrata* XJ-2-1, which was isolated from the fibrous root of *Parasenecio albus*. All compounds showed antiproliferative activity towards several cancer cell lines with IC_{50}s in the range of 5.04–43.22 μM (Peng et al., 2020b). Multirostratin G promotes G2-phase cell cycle arrest but not apoptosis in the CT26 and A-549 cancer cell lines, implying that this metabolite needs to be researched further to be established as a potent anticancer molecule. **Ergocytochalasin A (162)** is a novel merocytochalasan, which was isolated from the fungus *Phoma multirostrata* XJ-2-1, an endophyte of medicinal plant *Parasenecio albus*. It possess antiproliferative activity gainst HepG2, A-549, MCF-7, HCT116, HT-29 and CT26 with IC_{50}s of 21.32 ± 0.30, 19.11 ± 0.99, 26.63 ± 0.13, 22.28 ± 2.65, 15.23 ± 0.67 and 6.92 ± 0.71 μM, respectively (Peng et al., 2020c). **Jammosporin A (163)**, an unprecedented cytochalasin was separated from the fermented culture of the endophytic fungus *Rosellinia sanctaecruciana*, isolated from leaves of *Albizia lebbeck*. It showed cytotoxicity towards acute lymphoblastic leukemia cell line MOLT-4 with IC_{50} value of 20 μM, while remain inactive against three cancer cell lines A-549, MIA PaCa-2 and MDAMB-231 with IC_{50}s of >100 μM (Sharma et al., 2018a). A fermented culture of endophytic fungus *Xylaria* cf. *curta* associated with *Solanum tuberosum* was detected for halogenated hexacyclic cytochalasan, named **Xylarichalasin A (164)**. It possesses cytotoxic ability towards five tumor cell lines HL-60, A-549, SMMC-7721, MCF-7 and SW480 with IC_{50}s in range of 8.6–17.3 μM (Wang et al., 2019a). Three new 19,20-epoxycytochalasans, namely **19-epi-cytochalasin P1 (165), 7-O-acetyl-6-epi-19, 20-epoxycytochalasin P (166) and 7-O-acetyl-19,20-epoxycytochalasin D (167)** were separated from fungus *Xylaria* cf. *curta,* an endophyte associated with *Solanum tuberosum.* Mentioned three compounds showed cytotoxicity against HL-60 and MCF-7 with the IC_{50}s in the range of 13.31–37.16 μM, while remain inactive against A-549, SMMC-7721, and SW480 cell lines (Wang et al., 2019b). The structures of cytochalasans **(151–167)** are shown in Fig. 11.

2.10.2. Other hybrids

Two novel indolyl diketopiperazines, **Gartryprostatin A (168) and Gartryprostatin B (169)** were separated from the EtOAc extracts of a solid culture of endophytic fungus *Aspergillus* sp. GZWMJZ-258, which was isolated from the medicinal and edible plant *Garcinia multiflora*. Both the compounds possess selective antiproliferative activity towards MV4-11 cell line with IC_{50} values of 7.2 and 10.0 μM, respectively (He et al., 2019). **Aureochaeglobosin B (170) and Aureochaeglobosin C (171)** are hybrid products produced by the shared action of nonribosomal

peptide synthetases and polyketide synthases, which were produced by the fungus *Chaetomium globosum*, an endophyte associated with plant *Pinellia ternate*. Both the compounds showed moderate cytotoxicity towards MDA-MB-231 breast cancer cells with IC_{50}s of 7.6 ± 0.5 and 10.8 ± 0.64 μM, respectively, compared to the positive control doxorubicin which showed activity at IC_{50} value of 1.0 ± 0.10 μM (Yang et al., 2018). An endophytic fungus *Cytospora rhizophorae* A761 associated with *Morinda officinalis* was detected for novel polyketide heterodimers, **Cytorhizin B (172)** and **Cytorhizin C (173)** with benzophenone moiety. Both the compounds possess antiproliferative activity against cancer cell lines, HepG2, MCF-7, SF-268 and NCI–H460 with IC_{50} values between 29.4 and 68.6 μM (Liu et al., 2019c). A cyclopentenone−pyrone hybrid skeleton containing unique polyketide, **Trichoderpyrone (174)** was obtained from the endophytic fungus *Trichoderma gamsii*, associated with the *Panax notoginseng* (BurK.) F.H. Chen. It exhibited cytotoxicity against three cancer cell lines, A-549, HepG2, and HeLa with IC_{50} values of 16.9 ± 1.3, 30.8 ± 0.2, and 33.9 ± 0.7 μM, respectively, compared to standard anticancer compound etoposide, which had IC_{50} values of 16.6 ± 1.2, 16.1 ± 0.1, and 15.0 ± 0.2 μM, respectively (Chen et al., 2017). The structures of other hybrids **(168–174)** are shown in Fig. 12.

2.11. Miscellaneous compounds

A new natural compound, **Alternate C (175)** was separated from endophytic fungus *Alternaria alternata* associated with root of *Paeonia lactiflora*. Alternate C exhibited cytotoxic activity towards two cancer cell lines MDA-MB-231 and MCF-7 with 20.1 μM and 32.2 μM of IC_{50} values, respectively (Wang et al., 2019c). **Nigronapthaphenyl (176)**, a new cytotoxic metabolite was separated from the fermented culture of endophytic fungus *Nigrospora sphaerica*, associated with a mangrove plant *Bruguiera gymnorrhyza*. It possess cytotoxic ability towards colon cancer cell line HCT 116 with IC_{50} value of 9.62 ± 0.5 μM (Ukwatta et al., 2019). **Varioloid A (177),** a new cytotoxic fungal metabolite was extracted from fungus *Paecilomyces variotii* EN-291, an endophyte associated with the marine red alga *Grateloupia turuturu* and showed cytotoxic activity towards A-549, HCT116, and HepG2 cell lines, with IC_{50} values of 3.5, 6.4, and 2.5 μg/mL, respectively (Zhang et al., 2016a). A new compound **Altertoxin IV (178)** was separated from the ethyl acetate extract of culture of fungus *Alternaria* sp. G7, an endophyte harbored in the leaves of *Broussonetia papyrifera* (L.) Vent. It showed cytotoxic activity against MG-63 and SMMC-7721 tumor cell lines with IC_{50}s of 14.81 and 22.87 μg/mL, while remain inactive against A-549 cell lines with IC_{50} of >50 μg/mL (Zhang et al., 2016b). A new aflatoxin, **Asperxin A (179)** was isolated from the fungus *Aspergillus* sp. Y-2, an endophyte harbored in the needles of conifer *Abies beshanzuensis*. It showed significant cytotoxic activity towards A-549 and HeLa cells, with IC_{50}s of 11.72 and 16.78 μg/mL, respectively, compared to the positive control doxorubicin which showed activity at 1.7 ± 0.5 and 0.6 ± 0.3 μg/mL, respectively (Zhu et al., 2019). A novel metabolite, **6-formamide-chetomin (180)** was separated from fermented culture of fungus *Chaetomium* sp. M336, which was isolated from the traditional Chinese medicinal plant *Huperzia serrata* Trev. Compound **(180)** exhibited strong cytotoxic activity towards HeLa, SGC-7901 and A-549 cells with IC_{50}s of 21.6, 23.0 and 27.1 nM, respectively (Yu et al., 2018). 6-Formamide-chetomin exhibits cytotoxic effects in the nanomolar range, however its mechanism of action has yet to be discovered. After thorough pre-experimental and clinical studies, such fungal metabolites with low IC_{50} values could be valuable for therapeutic treatment. **Chaetominin A (181)** was obtained from fungus *Chaetomium subaffine* L01, an endophyte obtained from healthy potato tissue, which was collected from Lincang county of Yunnan province, China. It possess cytotoxicity against two human tumor cell lines Hep-2 and HepG2 with the IC_{50} values of 0.23 and 0.38 μM, respectively (Han et al., 2019). An endophytic fungus *Diaporthe* sp. was isolated from *Datura inoxia,* a traditional Indian medicinal plant. Addition of the valproic acid in the fermentation culture of fungus, induce synthesis of novel compounds, including **Xylarolide A (182) and Diportharine A (183)**, which showed weak antiproliferative activity against cancer cell lines MIA-PA-CA-2, MCF-7 and PC-3 with IC_{50}s of 20 ± 0.17, 30 ± 1.02, 14 ± 0.12 μM and 34 ± 1.32, >50, 22 ± 0.83 μM, respectively, compared to known anticancer drug paclitaxel which is active at nanomolar level for tested cell lines (Sharma et al., 2018b). Five new hormonemate derivatives, **Hormonemates A-E (184–188)** were separated from fermented culture of fungus *Dothiora* sp., an endophyte associated with the endemic plant *Launaea arborescens*. All compounds showed moderate cytotoxic ability towards HepG2, MCF-7 and/or MiaPaca-2 tumor cell lines with IC_{50}s between 11.1 and 36.4 μM, compared to positive control doxorubicin, which had an IC_{50} values of 0.2, 1.4 and 1.9 μM, respectively (Pérez-Bonilla et al., 2017). A new macrolactone, **(13R,14S,15R)- 13-hydroxy-14-deoxyoxacyclododecindione (189)** was obtained from endophytic fungus *Exserohilum rostratum*, associated with *Gymnadenia conopsea* and exhibited weak antiproliferative activity against A-549 lung cell line with an IC_{50} value of 9.2 μM compared to paclitaxel, which gave IC_{50} value of 0.11 μM (Lin et al., 2018). A new aminobenzamide derivative named **Fusarithioamide B (190)**, was extracted from EtOAc extract of an endophytic fungi *Fusarium chlamydosporium*, which was isolated from *Anvillea garcinii* (Burm.f.) DC. leaves. It showed potent and selective *in vitro* cytotoxic effect against SK-MEL (malignant melanoma), KB, BT-549, SKOV-3, MCF-7, and HCT-116 cell lines with IC_{50}s between 0.21 and 11.2 μM, compared to the standard compound doxorubicin with values of 0.159 ± 0.11, 0.024 ± 0.22, 0.045 ± 0.11, 0.321 ± 0.21, 0.05 ± 0.01, and 0.24 ± 0.04 μM, respectively (Ibrahim et al., 2018). A new benzamide derivative, named **Fusarithioamide A (191)** was isolated from fungus *Fusarium chlamydosporium*, an endophyte harbored in the leaves of *Anvillea garcinia* (Burm.f.) DC. It showed strong and selective cytotoxicity against BT-549 and SKOV-3 cell lines with IC_{50}s of 0.4 and 0.8 μM, respectively compared to doxorubicin which had IC_{50}s of 0.046 and 0.313 μM, respectively. It remains inactive against KB and SK-MEL tumor cell lines (Ibrahim et al., 2016b). Two azaanthraquinone derivatives, **7-desmethylscorpinone (192)** and **7-desmethyl-6-methylbostrycoidin (193)** and one new naphthoquinone, **9-desmethylherbarine (194),** were isolated from fungus *Fusarium solani*, an endophyte associated with *Aponogeton undulatus*. These compounds exhibited cytotoxicity with IC_{50} values between 0.34 and 54.34 μM against five cell lines, MDA-MB 231, MIA PaCa2, HeLa, and NCI H1975, compared to doxorubicin as the positive control, which shows IC_{50} values of 0.35, 0.07, 0.04, 0.05 and 0.03 μM, respectively (Chowdhury et al., 2017). An endophytic fungus *Penicillium* sp. T2-11 was isolated from the rhizomes of the *Gastrodia elata*. A new citrinin dimer, **Penctrimertone (195)** was separated from the EtOAc crude extract of isolated fungus, which showed cytotoxicity against five cancer cell lines HL-60, SMMC-7721, A-549, MCF-7 and SW480 with IC_{50}s of 16.77, 23.63, 28.62, 21.53 and 39.32 μM, respectively compared to positive control cisplatin, which showed activity at 3.50, 23.03, 23.90, 23.64 and 9.26 μM, respectively (Li et al., 2020e). Two new natural metabolites, **Cosmochlorin D (196) and Cosmochlorin E (197),** were isolated from *Phomopsis* sp. N-125, an endophytic fungus harbored in *Ficus ampelasa*. Both the compound showed selective cytotoxic ability towards HL60 cells with IC_{50} values of 6.1 and 1.8 μM, respectively, while remain inactive (IC_{50} > 100 μM) against HeLa cell line (Shiono et al., 2017). Two endophytic fungi, *Pyrenochaetopsis* sp. FVE-001 and *Pyrenochaetopsis* sp. FVE-087 were isolated from the marine brown alga *Fucus vesiculosus*. Three new metabolites, **Pyrenosetin A (198), Pyrenosetin B (199)** and **Pyrenosetin C (200)** possessing cytotoxic activity against A-375 and non-cancerous keratinocyte cell line (HaCaT) with IC_{50}s between 2.8 and 142.9 μM were separated from the culture of *Pyrenochaetopsis* sp. FVE-001 (Fan et al., 2020a). **Pyrenosetin D (201)** was separated from the culture of *Pyrenochaetopsis* sp. FVE-087 and exhibited cytotoxic activity against A-375 and HaCaT cell lines with IC_{50}s of 77.5 and 39.3 μM, respectively (Fan et al., 2020b). Two new spirobisnaphthalenes, **Rhytidenone G (202) and Rhytidenone H (203)** were separated from the broth culture of *Rhytidhysteron rufulum* AS21B,

an endophytic fungus harbored in leaves of mangrove plant *Azima sarmentosa*. Both the compound showed anticancer activity against human lymphoma Ramos cells and NSCLC H1975 cells with IC_{50}s in the range of 0.018–17.98 μM (Siridechakorn et al., 2017). A new compound, **3-demethyl-3- (2-hydroxypropyl)-skyrin (204)** with unsymmetrical dimeric anthraquinone moiety was separated from fermented culture of fungal strain *Talaromyces* sp. YE 3016, an endophyte harbored in the roots of *Aconitum carmichaeli* and showed cytotoxic activity against MCF-7 cell line with IC_{50} of 20.76 ± 3.41 μg/mL (Xie et al., 2016). **Terezine E (205)** is a prenylated tryptophan analogue isolated from the fungus *Mucor* sp., an endophyte of the medicinal plant *Centaurea stoebe*. It showed potent antiproliferative activity against human umbilical vein endothelial cells (HUVEC), multipotential leukemia cell line (K-562) and HeLa cancer cell lines with CC_{50} values of 28.02, 27.31, and 60.43 mg/mL respectively (Abdou et al., 2020). The structures of miscellaneous compounds are shown in Fig. 13 **(175–190)** and Fig. 14 **(191–205)**.

3. Conclusion and future aspects

The discoveries included in this review presents the cytotoxicity profile of 205 small compounds with novel skeletons, that have been isolated from 95 fungal species harbored in both terrestrial and marine plants, collected across 16 countries. From these 95 strains, a total of five endophyte genera, namely *Aspergillus*, *Chaetomium*, *Penicillium*, *Fusarium* and *Pestalotiopsis* were most frequently explored in the targeted time frame of our current study. In terms of chemical diversity, polyketides make up the majority of the chemical population, accounting for a total of 24%, followed by terpenoids, which account for 20% of the total. These findings reveal that metabolites of endophytic fungi are extremely valuable, and more novel skeletons with a variety of biological activities should indeed be hunted out. Remarkably, in the last few years, there are more findings on endophytic fungi metabolites than ever before, indicating that endophytic fungi are becoming progressively more valuable sources for discovering novel natural drug like molecules. However, as seen in Fig. 15, China dominates the study on endophytic fungi. There are many biodiversity hotspots on the Earth that are still untapped and therefore need to be investigated for new endophytes to inspect their metabolites.

Advances in the domain of structural biology has allowed us to identify new promising drug targets for tumors, as well as acquire better understanding of the molecular basis of tumor resistance for existing available chemotherapeutic agents, this scenario has led investigators to reevaluate their strategy for exploring new molecules to combat various types of cancer. The cytotoxic effect of the fungal metabolites under consideration is widespread, with inhibitory concentrations varying from low to high micromolar towards particular tumor cell lines. Some of these metabolites had a strong cytotoxic effect for particular cell lines, that was at par or even better than some of the frequently used chemotherapeutic agents. Irrefutably, such endophytic metabolites which are screened as leads have not rigorously been investigated to determine the molecular mechanism that induces cytotoxic effects. Evolving computational tools are the hallmark for modern pharmaceutical research and is perceived as a useful aspect in drug development (Parmar et al., 2020; Prajapati et al., 2021). This might aid in determining anticancer effects by interacting with different protein targets responsible for specific cancer, and it could also speed up the drug development process by limiting *in vitro* assays. A complete exploration of this area has potentials for causing quantum leap in the traditional drug development process. On the other hand, many concurrent efforts are indispensable to develop and sustain endophyte metabolite as a drug molecule. The creation of a computational database or library of bioactive chemically diverse compounds, as well as the establishment of regional and global amenities as an endophytic microbe culture reservoir, are two such requirements. Endophytic culture reservoir will aid not only in preserving these valuable cultures, which are, either collected from endangered plant species, or plants located in remote and challenging areas where human access is difficult, but also allowing their extended reach to diverse community of researchers. Additionally, a dedicated computational database featuring details on both biological activity and chemical structure of endophytic metabolites would allow us to assist in determining the credible qualities of such metabolites, along with the efforts to comprehend their mechanism of action. Researchers now must stay one step ahead of cancer and be equipped with the several therapeutic agents in the form of bullets to strike the tumor specific target in the bullseye.

Endophytic fungi are a gold mine of novel bioactive molecules with enormous potential in the healthcare industries. Getting to the bottom of interactions of these endophytic fungal metabolites with precise cellular targets that are responsible for their biological activity will succeed in unlocking their ultimate value. Advanced pharmacological tools, as well as evolving bioinformatic methods, combined with sophisticated metagenomic approaches, will strive to improve effective exploitation of secondary metabolite production by valuable fungal endophytic species, and even its development as a potential anticancer drug molecule.

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Additional information

Library for the 3D structures of reviewed fungal metabolites will be available upon request. Request for the library should be addressed to J.P.

CRediT authorship contribution statement

Jignesh Prajapati: Conceptualization, Writing – original draft, Drew the chemical structures of the compounds and prepared the library of 3D compounds. **Dweipayan Goswami:** Conceptualization, Writing – original draft. **Rakesh M. Rawal:** Reviewed the manuscript, Supervision, All authors discussed the manuscript critically for important intellectual content and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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