Natural Products and Bioprospecting

REVIEW

Open Access

Chemistry and biology of marine-derived *Trichoderma* metabolites

Yin-Ping Song[1] and Nai-Yun Ji[1*]

Abstract

Marine-derived fungi of the genus *Trichoderma* have been surveyed for pharmaceuticals and agrochemicals since 1993, with various new secondary metabolites being characterized from the strains of marine animal, plant, sediment, and water origin. Chemical structures and biological activities of these metabolites are comprehensively reviewed herein up to the end of 2022 (covering 30 years). More than 70 strains that belong to at least 18 known *Trichoderma* species have been chemically investigated during this period. As a result, 445 new metabolites, including terpenes, steroids, polyketides, peptides, alkaloids, and others, have been identified, with over a half possessing antimicroalgal, zooplankton-toxic, antibacterial, antifungal, cytotoxic, anti-inflammatory, and other activities. The research is highlighted by the molecular diversity and antimicroalgal potency of terpenes and steroids. In addition, metabolic relevance along with co-culture induction in the production of new compounds is also concluded. *Trichoderma* strains of marine origin can transform and degrade heterogeneous molecules, but these functions need further exploration.

Keywords *Trichoderma*, Metabolite, Terpene, Polyketide, Peptide, Bioactivity
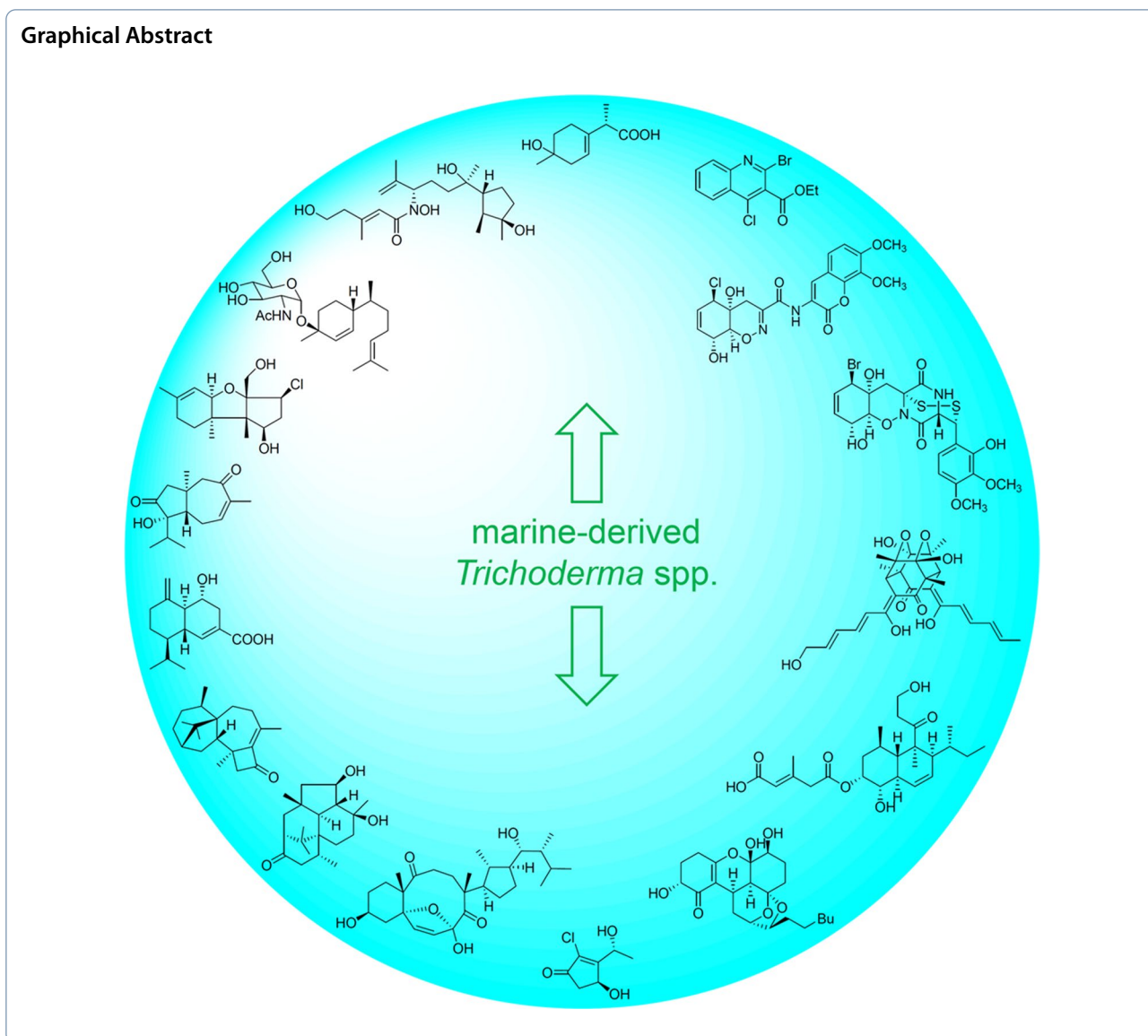
*Correspondence:
Nai-Yun Ji
nyji@yic.ac.cn
Full list of author information is available at the end of the article

Graphical Abstract

1 Introduction

Trichoderma was first described as a genus of filamentous fungi by Persoon in 1794 [1]. It belongs to the family Hypocreaceae of the order Hypocreales in the class Sordariomycetes of the phylum Ascomycota, rather than the previous deuteromycetous taxa, according to the Dictionary of the Fungi (10th edition) [2]. Fungal species of this genus feature numerous conidia in varying shades of green, rapid growth rate, and high adaptability to various terrestrial and aquatic ecosystems. They are free-living or occur as mycoparasites and opportunistic, avirulent plant symbionts [3]. Their identification is difficult due to the few morphological characteristics available and the slight variations among different species [4]. Most of them can be linked to the teleomorphic *Hypocrea* species

(Ascomycota), but this generic name has not been suggested to be further used by the proposal from Rossman et al. [5]. Several species were once assigned to other genera, such as *Aphysiostroma, Eidamia, Cordyceps, Gliocladium, Podostroma, Sarawakus, Sphaeria, Sporotrichum, Stilbella, Stilbum,* and *Thuemenella*, and 65 names inclusive of the basionyms of accepted species in *Trichoderma* and other genera are not currently adopted [6]. Totally, 254 species and two varieties with at least 1100 strains were characterized until 2015 [6, 7], and new species have been continually recognized thereafter [8–11].

Since the initial work by Weindling regarding the parasitism of *T. lignorum* on other fungi in the early 1930s [12, 13], *Trichoderma* species have achieved great successes to suppress plant diseases and promote plant growth in

agriculture [7], and more than 250 *Trichoderma*-based products have been commercialized so far [14]. Their interactions with pathogens and plants appear complicated, but the production of bioactive secondary metabolites is regarded as one of the key mechanisms [15–17]. Investigations toward the antagonism of *Trichoderma* species against phytopathogenic fungi have resulted in the isolation and identification of a number of antifungal antibiotics, including terpenes, polyketides, peptides, and alkaloids [18]. A series of metabolites have been reported as plant growth promoters or inhibitors [19], and a plethora of metabolites with other activities, such as antibacterial, cytotoxic, and enzyme-inhibitory properties, have also been discovered [19–23]. Over the past eight decades, some a thousand new polar and nonpolar metabolites have been isolated and identified from *Trichoderma* species of various origin including terrestrial and marine environments.

Since 1993, secondary metabolites from marine-derived *Trichoderma* have gradually been surveyed [24]. Until the end of 2022, 445 new compounds have been identified from 77 strains of *Trichoderma* fungi, 60 of which belong to 18 known species involving *T. asperelloides* (1 strain), *T. asperellum* (5), *T. atroviride* (9), *T. aureoviride* (1), *T. brevicompactum* (2), *T. citrinoviride* (4), *T. erinaceum* (1), *T. hamatum* (1), *T. harzianum* (12), *T. koningii* (3), *T. longibrachiatum* (8), *T. orientale* (1), *T. reesei* (4), *T. saturnisporum* (1), *T. virens* (4), *T. viride* (1), *H. lixii* (1), and *H. vinosa* (1) (Figs. 1, 2). These 77 *Trichoderma* strains have been isolated from animal (sponge (19 strains), mussel (4), fish (1), tunicate (2), sea star (2), sea fan (1), and soft coral (2)), plant (alga (18), mangrove (4), and halophyte (1)), sediment (20), and seawater (3) samples (Fig. 3). The new compounds (Tables 1, 2, 3) can be divided into terpenes, steroids, polyketides, peptides, alkaloids, and others (Fig. 4), of which 235 members possess antimicroalgal, zooplankton-toxic, antibacterial,
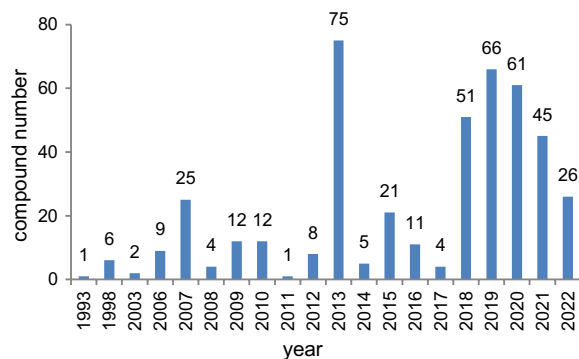
antifungal, cytotoxic, anti-inflammatory, antiviral, phytotoxic, insect-toxic, zebrafish-toxic, antifouling, antioxidant, enzyme-inhibitory, NF-κB-inhibitory, anti-pulmonary fibrosis, anti-Aβ fibrillization, and neuroprotective activities (Fig. 5) [24–130]. The present review attempts to give a comprehensive compilation of these molecules and highlights their chemical diversity and biological activity.

2 Structure and occurrence

2.1 Terpenes

A total of 165 new terpenes (**1**–**165**, Table 1) were isolated and identified from 10 marine-derived *Trichoderma* species, including *T. asperelloides* (18 compounds), *T. asperellum* (47), *T. atroviride* (2), *T. brevicompactum* (20), *T. citrinoviride* (4), *T. erinaceum* (5), *T. hamatum* (3), *T. harzianum* (27), *T. longibrachiatum* (4), and *T. virens* (19), and five unidentified strains (16) [25–65]. These terpenes can be classified to monoterpenes with a menthane skeleton, sesquiterpenes with cyclonerane, bisabolane, trichothecane, carotane, cadinane, acorane, cuparane, farnesane, synderane, pupukeanane, and harzianoic acid skeletons, and diterpenes with harziane, proharziane, wickerane, citrinovirin, fusicoccane, cleistanthane, and

Fig. 2 Numbers of new compounds from different marine-derived *Trichoderma* species

Fig. 1 Numbers of new compounds from marine-derived *Trichoderma* during 1993–2022

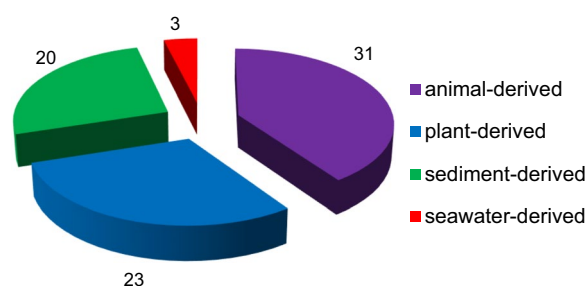**Fig. 3** Sources and numbers of marine-derived *Trichoderma* strains possessing new compounds

Table 1 Terpenes (**1**–**165**) and steroids (**166**–**168**) from the marine-derived *Trichoderma*

No	Name	Bioactivity	Producer	Source	Locality	References
1	(7*S*)-1-Hydroxy-3-*p*-menthen-9-oic acid		*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[25]
2	(7*R*)-1-Hydroxy-3-*p*-menthen-9-oic acid		*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[25]
3	9-Cycloneren-3,7,11-triol	Zooplankton-toxic	*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[26]
4	11-Cycloneren-3,7,10-triol	Zooplankton-toxic	*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[26]
5	7,10-Epoxycycloneran-3,11,12-triol	Antibacterial and zooplankton-toxic	*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[26]
6	Cyclonerpyranol	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[27]
7	3,7,11-Trihydroxycycloneran-10-one	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[28]
8	Cycloneran-3,7,10,11-tetraol	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[28]
9	Cycloneran-3,7,11-triol	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[28]
10	7,10*S*-Epoxycycloneran-3,15-diol	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[28]
11	7,10*R*-Epoxycycloneran-3,15-diol	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[28]
12	(10*Z*)-15-Acetoxy-10-cycloneren-3,7-diol	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[28]
13	(10*E*)-12-Acetoxy-10-cycloneren-3,7-diol		*T. harzianum* P1-4	Sediment	Bohai Sea, China	[29]
14	12-Acetoxycycloneran-3,7-diol		*T. harzianum* P1-4	Sediment	Bohai Sea, China	[29]
15	11-Methoxy-9-cycloneren-3,7-diol	Antimicroalgal and antibacterial	*T. harzianum* X-5	Alga *Laminaria japonica*	Chang Islands, China	[30]
16	10-Cycloneren-3,5,7-triol	Antimicroalgal and antibacterial	*T. harzianum* X-5	Alga *Laminaria japonica*	Chang Islands, China	[30]
17	Methyl 3,7-dihydroxy-15-cycloneranate	Antimicroalgal and antibacterial	*T. harzianum* X-5	Alga *Laminaria japonica*	Chang Islands, China	[30]
18	5-Hydroxyepicyclonerodiol oxide	Antimicroalgal and antibacterial	*T. hamatum* Z36-7	Alga *Grateloupia* sp.	Zhoushan Islands, China	[31]
19	4-Hydroxyepicyclonerodiol oxide	Antimicroalgal and antibacterial	*T. hamatum* Z36-7	Alga *Grateloupia* sp.	Zhoushan Islands, China	[31]
20	Cyclonerodiol A		*T. erinaceum* F1-1	Sea star *Acanthaster planci*	Hainan Sanya National Coral Reef Reserve, China	[32]
21	Cyclonerodiol B		*T. erinaceum* F1-1	Sea star *Acanthaster planci*	Hainan Sanya National Coral Reef Reserve, China	[32]
22	(10*E*)-Isocyclonerotriol	Antimicroalgal and antibacterial	*T. citrinoviride* A-WH-20-3	Alga *Laurencia okamurai*	Weihai, China	[33]
23	(10*Z*)-Isocyclonerotriol	Antimicroalgal and antibacterial	*T. citrinoviride* A-WH-20-3	Alga *Laurencia okamurai*	Weihai, China	[33]
24	Isoepicyclonerodiol oxide	Antimicroalgal and antibacterial	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela confervoides*	Dalian, China	[34]
25	Cycloner-3-en-7,11-diol	Antimicroalgal	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela confervoides*	Dalian, China	[34]
26	11,12,15-Trinorcycloneran-3,7,10-triol	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[28]
27	Norepicyclonerodiol oxide	Antimicroalgal and antibacterial	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela confervoides*	Dalian, China	[34]

Table 1 (continued)

No	Name	Bioactivity	Producer	Source	Locality	References
28	Cyclonerin A	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[27]
29	Cyclonerin B	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[27]
30	Deoxycyclonerin A	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[27]
31	Deoxycyclonerin B	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[27]
32	Deoxycyclonerin C	Antimicroalgal	*T. asperellum* A-YMD-9-2	alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[27]
33	Deoxycyclonerin D	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[27]
34	Cyclonerinal	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[27]
35	Cyclonerizole	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[27]
36	5′-Acetoxy-deoxycyclonerin B	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[35]
37	5′-Acetoxy-deoxycyclonerin D	Antimicroalgal	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[35]
38	Trichaspside A	Antibacterial and zooplankton-toxic	*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[26]
39	Bisabolan-1,10,11-triol	Antimicroalgal and antibacterial	*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[25, 34]
40	Trichobisabolin A	Antimicroalgal	*T. asperellum* Y6-2	Alga *Chondrus ocellatus*	Yangma Island, Yantai, China	[36]
41	Trichobisabolin B	Antimicroalgal	*T. asperellum* Y6-2	Alga *Chondrus ocellatus*	Yangma Island, Yantai, China	[36]
42	Trichobisabolin C	Antimicroalgal	*T. asperellum* Y6-2	Alga *Chondrus ocellatus*	Yangma Island, Yantai, China	[36]
43/44	Trichobisabolins O_1/O_2	Antimicroalgal	*T. brevicompactum* A-DL-9-2	Alga *Chondria tenuissima*	Dalian, China	[37]
45	Trichobisabolin P	Antimicroalgal	*T. brevicompactum* A-DL-9-2	Alga *Chondria tenuissima*	Dalian, China	[37]
46	Trichobisabolin T	Antimicroalgal and antibacterial	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela confervoides*	Dalian, China	[34]
47	Trichobisabolin U	Antimicroalgal and antibacterial	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela confervoides*	Dalian, China	[34]
48	Trichobisabolin V	Antimicroalgal and antibacterial	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela confervoides*	Dalian, China	[34]
49	Trichobisabolin W	Antimicroalgal and antibacterial	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela confervoides*	Dalian, China	[34]
50	Trichobisabolin X	Antimicroalgal	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela confervoides*	Dalian, China	[34]
51	Trichodermaerin A		*T. erinaceum* F1-1	Sea star *Acanthaster planci*	Hainan Sanya National Coral Reef Reserve, China	[32]
52	12-Nor-11-acetoxybisabolen-3,6,7-triol	Antimicroalgal and antibacterial	*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[25]
53	Trichaspside B	Antibacterial and zooplankton-toxic	*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[26]
54	Trichaspside C	Antimicroalgal and antibacterial	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[38]
55	Trichaspside D	Antimicroalgal and antibacterial	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[38]
56	Trichaspside E	Antimicroalgal and antibacterial	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[38]

Table 1 (continued)

No	Name	Bioactivity	Producer	Source	Locality	References
57	Trichobisabolin D	Antimicroalgal and zoo-plankton-toxic	*T. asperellum* Y6-2	Alga *Chondrus ocellatus*	Yangma Island, Yantai, China	[36]
58	Trichobisabolin E	Antimicroalgal	*T. asperellum* Y6-2	Alga *Chondrus ocellatus*	Yangma Island, Yantai, China	[36]
59	Trichobisabolin F	Antimicroalgal	*T. asperellum* Y6-2	Alga *Chondrus ocellatus*	Yangma Island, Yantai, China	[36]
60	Trichobisabolin G	Antimicroalgal	*T. asperellum* Y6-2	Alga *Chondrus ocellatus*	Yangma Island, Yantai, China	[36]
61	Trichobisabolin H	Antimicroalgal and zoo-plankton-toxic	*T. asperellum* Y6-2	Alga *Chondrus ocellatus*	Yangma Island, Yantai, China	[36]
62	Trichobisabolin I	Antimicroalgal and anti-bacterial	*T. asperellum* A-YMD-9-2	Alga *Gracilaria ver-rucosa*	Yangma Island, Yantai, China	[38]
63	Trichobisabolin J	Antimicroalgal and anti-bacterial	*T. asperellum* A-YMD-9-2	Alga *Gracilaria ver-rucosa*	Yangma Island, Yantai, China	[38]
64	Trichobisabolin K	Antimicroalgal and anti-bacterial	*T. asperellum* A-YMD-9-2	Alga *Gracilaria ver-rucosa*	Yangma Island, Yantai, China	[38]
65	Trichobisabolin L	Antimicroalgal and anti-bacterial	*T. asperellum* A-YMD-9-2	Alga *Gracilaria ver-rucosa*	Yangma Island, Yantai, China	[38]
66	Trichobisabolin M	Antimicroalgal and anti-bacterial	*T. atroviride* RR-dl-3-9	Alga *Rhodomela con-fervoides*	Dalian, China	[39]
67	Trichobisabolin N	Antimicroalgal and anti-bacterial	*T. atroviride* RR-dl-3-9	Alga *Rhodomela con-fervoides*	Dalian, China	[39]
68	Trichobisabolin Q	Antimicroalgal and anti-bacterial	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela con-fervoides*	Dalian, China	[34]
69	Trichobisabolin R	Antimicroalgal and anti-bacterial	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela con-fervoides*	Dalian, China	[34]
70	Trichobisabolin S	Antimicroalgal and anti-bacterial	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela con-fervoides*	Dalian, China	[34]
71	Trichobisabolin Y	Antimicroalgal and anti-bacterial	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela con-fervoides*	Dalian, China	[34]
72	Trichobisabolin Z	Antimicroalgal and anti-bacterial	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela con-fervoides*	Dalian, China	[34]
73		Anti-inflammatory	*T. brevicompactum* NTU439	Alga *Mastophora rosea*	Yilan coast, China	[40]
74		Anti-inflammatory	*T. brevicompactum* NTU439	Alga *Mastophora rosea*	Yilan coast, China	[40]
75		Anti-inflammatory	*T. brevicompactum* NTU439	Alga *Mastophora rosea*	Yilan coast, China	[40]
76		Anti-inflammatory	*T. brevicompactum* NTU439	Alga *Mastophora rosea*	Yilan coast, China	[40]
77	Trichobreol A	Antifungal	*Trichoderma* sp. TPU199 (cf. *T. brevicompactum*)	Unidentified alga	Palau	[41]
78	Trichobreol B	Antifungal	*Trichoderma* sp. TPU199 (cf. *T. brevicompactum*)	Unidentified alga	Palau	[41]
79	Trichobreol C	Antifungal	*Trichoderma* sp. TPU199 (cf. *T. brevicompactum*)	Unidentified alga	Palau	[41]
80	Trichobreol D	Antifungal	*Trichoderma* sp. TPU199 (cf. *T. brevicompactum*)	Unidentified alga	Palau	[42]
81	Trichobreol E	Antifungal	*Trichoderma* sp. TPU199 (cf. *T. brevicompactum*)	Unidentified alga	Palau	[42]
82	Trichodermol chloro-hydrin	Antimicroalgal and anti-bacterial	*T. hamatum* Z36-7	Alga *Grateloupia* sp.	Zhoushan Islands, China	[31]
83	Trichodermarin G	Antimicroalgal and anti-fungal	*T. brevicompactum* A-DL-9-2	Alga *Chondria tenuis-sima*	Dalian, China	[43]
84	Trichodermarin H	Antimicroalgal and anti-fungal	*T. brevicompactum* A-DL-9-2	Alga *Chondria tenuis-sima*	Dalian, China	[43]

Table 1 (continued)

No	Name	Bioactivity	Producer	Source	Locality	References
85	Trichodermarin I	Antimicroalgal and antifungal	*T. brevicompactum* A-DL-9-2	Alga *Chondria tenuissima*	Dalian, China	[43]
86	Trichodermarin J	Antimicroalgal	*T. brevicompactum* A-DL-9-2	Alga *Chondria tenuissima*	Dalian, China	[43]
87	Trichodermarin K	Antimicroalgal	*T. brevicompactum* A-DL-9-2	Alga *Chondria tenuissima*	Dalian, China	[43]
88	Trichodermarin L	Antimicroalgal and antifungal	*T. brevicompactum* A-DL-9-2	Alga *Chondria tenuissima*	Dalian, China	[43]
89	Trichodermarin M	Antimicroalgal and antifungal	*T. brevicompactum* A-DL-9-2	Alga *Chondria tenuissima*	Dalian, China	[43]
90	Trichodermarin N		*T. brevicompactum* A-DL-9-2	Alga *Chondria tenuissima*	Dalian, China	[43]
91	Trichocarotin A		*T. virens* Y13-3	Alga *Gracilaria vermiculophylla*	Yangma Island, Yantai, China	[44]
92	Trichocarotin B		*T. virens* Y13-3	Alga *Gracilaria vermiculophylla*	Yangma Island, Yantai, China	[44]
93	Trichocarotin C	Antimicroalgal and zooplankton-toxic	*T. virens* Y13-3	Alga *Gracilaria vermiculophylla*	Yangma Island, Yantai, China	[44]
94	Trichocarotin D	Antimicroalgal	*T. virens* Y13-3	Alga *Gracilaria vermiculophylla*	Yangma Island, Yantai, China	[44]
95	Trichocarotin E	Antimicroalgal	*T. virens* Y13-3	Alga *Gracilaria vermiculophylla*	Yangma Island, Yantai, China	[44]
96	Trichocarotin F		*T. virens* Y13-3	Alga *Gracilaria vermiculophylla*	Yangma Island, Yantai, China	[44]
97	Trichocarotin G		*T. virens* Y13-3	Alga *Gracilaria vermiculophylla*	Yangma Island, Yantai, China	[44]
98	Trichocarotin H	Antimicroalgal and zooplankton-toxic	*T. virens* Y13-3	Alga *Gracilaria vermiculophylla*	Yangma Island, Yantai, China	[44]
99	14-*O*-Methyltrichocarotin G	Antimicroalgal	*T. virens* RR-dl-6-8	Alga *Rhodomela confervoides*	Dalian, China	[45]
100	14-*O*-Methyl CAF-603	Antimicroalgal	*T. virens* RR-dl-6-8	Alga *Rhodomela confervoides*	Dalian, China	[45]
101	Trichocadinin A	Zooplankton-toxic	*T. virens* Y13-3	Alga *Gracilaria vermiculophylla*	Yangma Island, Yantai, China	[44]
102	4-Cadinen-11,12-diol	Antimicroalgal and antibacterial	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[46]
103	4-Cadinen-11,13-diol	Antimicroalgal and antibacterial	*T. asperellum* A-YMD-9-2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[46]
104	Cadin-4-en-11-ol	Antimicroalgal and antibacterial	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela confervoides*	Dalian, China	[34]
105	Trichocadinin K	Antimicroalgal	*T. virens* RR-dl-6-8	alga *Rhodomela confervoides*	Dalian, China	[45]
106	Trichocadinin L	Antimicroalgal	*T. virens* RR-dl-6-8	Alga *Rhodomela confervoides*	Dalian, China	[45]
107	Trichocadinin M	Antimicroalgal	*T. virens* RR-dl-6-8	Alga *Rhodomela confervoides*	Dalian, China	[45]
108	Trichocadinin N	Antimicroalgal	*T. virens* RR-dl-6-8	Alga *Rhodomela confervoides*	Dalian, China	[45]
109	Trichodermaloid A	Cytotoxic	*Trichoderma* sp. SM16	Sponge *Dysidea* sp.	Xisha Islands, China	[47]
110	Trichodermaloid B	Cytotoxic	*Trichoderma* sp. SM16	Sponge *Dysidea* sp.	Xisha Islands, China	[47]
111	Trichodermaloid C	Cytotoxic	*Trichoderma* sp. SM16	Sponge *Dysidea* sp.	Xisha Islands, China	[47]
112	Trichocadinin I	Antimicroalgal	*T. virens* RR-dl-6-8	Alga *Rhodomela confervoides*	Dalian, China	[45]
113	Trichocadinin J	Antimicroalgal	*T. virens* RR-dl-6-8	Alga *Rhodomela confervoides*	Dalian, China	[45]

Table 1 (continued)

No	Name	Bioactivity	Producer	Source	Locality	References
114	Trichocadinin H	Antimicroalgal	*T. virens* RR-dl-6-8	Alga *Rhodomela confervoides*	Dalian, China	[45]
115	Methylhydrohepteli-date	Antimicroalgal	*T. virens* RR-dl-6-8	Alga *Rhodomela confervoides*	Dalian, China	[45]
116	Ethyl hydroheptelidate	Antibacterial and anti-fungal	*T. harzianum* R1	Mangrove *Myoporum bontioides*	Leizhou Peninsula, China	[48]
117	8-Acoren-3,11-diol	Antimicroalgal and anti-bacterial	*T. harzianum* X-5	Alga *Laminaria japonica*	Chang Islands, China	[30]
118	Trichoacorin A	Antimicroalgal	*T. brevicompactum* A-DL-9-2	Alga *Chondria tenuis-sima*	Dalian, China	[37]
119	Trichoacorside A	Antibacterial and anti-fungal	*T. longibrachiatum* EN-586	Alga *Laurencia obtusa*	Qingdao, China	[49]
120	Trichocuparin A		*T. brevicompactum* A-DL-9-2	Alga *Chondria tenuis-sima*	Dalian, China	[43]
121	Trichocuparin B		*T. brevicompactum* A-DL-9-2	Alga *Chondria tenuis-sima*	Dalian, China	[43]
122/123	Trichonerolins A/B	Antimicroalgal	*T. brevicompactum* A-DL-9-2	Alga *Chondria tenuis-sima*	Dalian, China	[37]
124	Trichodermoside	Cytotoxic	*Trichoderma* sp. PT2	Alga *Blidingia minina*	Wuyu Island, China	[50]
125	Trichodermene A	Antifungal	*T. longibrachiatum*	Halophile plant *Suaeda glauca*	intertidal zone of Jiaozhou Bay, Qing-dao, China	[51]
126	Harzianoic acid A	Antiviral	*T. harzianum* LZDX-32-08	Sponge *Xestospongia testudinaria*	near Leizhoudao Island, China	[52]
127	Harzianoic acid B	Antiviral	*T. harzianum* LZDX-32-08	Sponge *Xestospongia testudinaria*	near Leizhoudao Island, China	[52]
128	Trichaspin	Zooplankton-toxic	*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[26]
129	Harzianone	Antimicroalgal, antibac-terial, and zooplankton-toxic	*T. longibrachiatum* cf-11	Alga *Codium fragile*	coast of Yantai, China	[53, 54]
130	3*S*-Hydroxyharzianone	Antimicroalgal and anti-bacterial	*T. asperellum* A-YMD-9-2	Alga *Gracilaria ver-rucosa*	Yangma Island, Yantai, China	[46]
131	Harziandione A		*T. erinaceum* F1-1	Sea star *Acanthaster planci*	Hainan Sanya National Coral Reef Reserve, China	[32]
132	Harzianol K	Anti-inflammatory	*Trichoderma* sp. SCSIOW21	Sediment	South China Sea (-2134 m), China	[55]
133	Harzianol L	Anti-inflammatory	*Trichoderma* sp. SCSIOW21	Sediment	South China Sea (-2134 m), China	[55]
134	Harzianol M		*Trichoderma* sp. SCSIOW21	Sediment	South China Sea (-2134 m), China	[55]
135	Harzianol N		*Trichoderma* sp. SCSIOW21	Sediment	South China Sea (-2134 m), China	[55]
136	Harzianol O		*Trichoderma* sp. SCSIOW21	Sediment	South China Sea (-2134 m), China	[55]
137	Harzianone E	Antibacterial	*T. harzianum* XS-20090075	Unidentified soft coral	Xisha Islands, China	[56]
138	Harzianone A	Phytotoxic	*T. harzianum* XS-20090075	Unidentified soft coral	Xisha Islands, China	[57]
139	Harzianone B	Phytotoxic	*T. harzianum* XS-20090075	Unidentified soft coral	Xisha Islands, China	[57]
140	Harzianone C	Phytotoxic	*T. harzianum* XS-20090075	Unidentified soft coral	Xisha Islands, China	[57]
141	Harzianone D		*T. harzianum* XS-20090075	Unidentified soft coral	Xisha Islands, China	[57]

Table 1 (continued)

No	Name	Bioactivity	Producer	Source	Locality	References
142	Harziane	Phytotoxic	*T. harzianum* XS-20090075	Unidentified soft coral	Xisha Islands, China	[57]
143	11-Hydroxy-9-harzien-3-one	Antibacterial and zoo-plankton-toxic	*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[26]
144	(9*R*,10*R*)-Dihydro-harzianone	Cytotoxic	*Trichoderma* sp. Xy24	Mangrove *Xylocarpus granatum*	Sanya district, Hainan province, China	[58]
145	3*R*-Hydroxy-9*R*,10*R*-dihydroharzianone	Antimicroalgal and anti-bacterial	*T. harzianum* X-5	Alga *Laminaria japonica*	Chang Islands, China	[30]
146	3*S*-Hydroxy-9*R*,10*R*-dihydroharzianone	Antimicroalgal	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela confervoides*	Dalian, China	[59]
147	Harzianelactone		*Trichoderma* sp. Xy24	Mangrove *Xylocarpus granatum*	Sanya district, Hainan province, China	[58]
148	Harzianelactone A	Phytotoxic	*T. harzianum* XS-20090075	Unidentified soft coral	Xisha Islands, China	[57]
149	Deoxytrichodermaerin	Antimicroalgal and zoo-plankton-toxic	*T. longibrachiatum* A-WH-20-2	Alga *Laurencia okamurai*	Weihai, China	[54]
150	Trichodermaerin		*T. erinaceum* 2011F1-1 (or F1-1)	Sea star *Acanthaster planci*	Hainan Sanya National Coral Reef Reserve, China	[60]
151	Harzianelactone B	Phytotoxic	*T. harzianum* XS-20090075	Unidentified soft coral	Xisha Islands, China	[57]
152	3*S*-Hydroxytrichodermaerin	Antimicroalgal	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela confervoides*	Dalian, China	[59]
153	Methyl 3*S*-hydroxy-10,11-*seco*-harzianate	Antimicroalgal	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela confervoides*	Dalian, China	[59]
154	11*R*-Methoxy-5,9,13-proharzitrien-3-ol	Antimicroalgal and anti-bacterial	*T. harzianum* X-5	Alga *Laminaria japonica*	Chang Islands, China	[30]
155	11*R*-Methoxy-5,9,13-proharzitrien-19-ol	Antimicroalgal	*T. asperelloides* RR-dl-6-11	Alga *Rhodomela confervoides*	Dalian, China	[59]
156	Trichodermanin C	Cytotoxic	*T. harzianum* OUPS-111D-4	Sponge *Halichondria okadai*	Osaka bay, Japan	[61]
157	Trichodermanin D	Cytotoxic	*T. harzianum* OUPS-111D-4	Sponge *Halichondria okadai*	Osaka bay, Japan	[61]
158	Trichodermanin E	Cytotoxic	*T. harzianum* OUPS-111D-4	Sponge *Halichondria okadai*	Osaka bay, Japan	[61, 62]
159	Trichodermanin F	Cytotoxic	*T. harzianum* OUPS-111D-4	Sponge *Halichondria okadai*	Osaka bay, Japan	[62]
160	Trichodermanin G		*T. harzianum* OUPS-111D-4	Sponge *Halichondria okadai*	Osaka bay, Japan	[62]
161	Trichodermanin H	Cytotoxic	*T. harzianum* OUPS-111D-4	Sponge *Halichondria okadai*	Osaka bay, Japan	[62]
162	Citrinovirin	Antibacterial, antimicroalgal, and zooplankton-toxic	*T. citrinoviride* cf-27	Alga *Dictyopteris prolifera*	Zhoushan Islands, China	[63]
163	Trichocitrin	Antimicroalgal and anti-bacterial	*T. citrinoviride* cf-27	Alga *Dictyopteris prolifera*	Zhoushan Islands, China	[64]
164	Harzianolic acid A		*T. harzianum* XS-20090075	Unidentified soft coral	Xisha Islands, China	[56]
165	Trichosordarin A	Antimicroalgal and zoo-plankton-toxic	*T. harzianum* R5	Sediment	Bohai Sea, China	[65]
166	Isoergokonin B	Antimicroalgal and anti-bacterial	*T. brevicompactum* A-DL-9-2	Alga *Chondria tenuissima*	Dalian, China	[37]
167	Tricholumin A	Antimicroalgal, antibacterial, and antifungal	*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[66]
168	4-(*p*-Hydroxyphenethoxy)demethylincisterol A$_3$	Antimicroalgal and anti-bacterial	*T. atroviride* RR-dl-3-9	Alga *Rhodomela confervoides*	Dalian, China	[39]

Table 2 Polyketides (**169**–**295**) from the marine-derived *Trichoderma*

No.	Name	Bioactivity	Producer	Source	Locality	References
169	Harzianumol A		*T. harzianum* HMS-15–3 (or HNS-15–3)	Sponge *Petrospongia nigra*	South China Sea, China	[67]
170	Harzianumol B		*T. harzianum* HMS-15–3 (or HNS-15–3)	Sponge *Petrospongia nigra*	South China Sea, China	[67]
171	Harzianumol C		*T. harzianum* HMS-15–3 (or HNS-15–3)	Sponge *Petrospongia nigra*	South China Sea, China	[67]
172	Harzianumol D		*T. harzianum* HMS-15–3 (or HNS-15–3)	Sponge *Petrospongia nigra*	South China Sea, China	[67]
173	Harzianumol E		*T. harzianum* HMS-15–3 (or HNS-15–3)	Sponge *Petrospongia nigra*	South China Sea, China	[67]
174	Harzianumol F		*T. harzianum* HMS-15–3 (or HNS-15–3)	Sponge *Petrospongia nigra*	South China Sea, China	[67]
175	Harzianumol G		*T. harzianum* HMS-15–3 (or HNS-15–3)	Sponge *Petrospongia nigra*	South China Sea, China	[67]
176	Harzianumol H		*T. harzianum* HMS-15–3 (or HNS-15–3)	Sponge *Petrospongia nigra*	South China Sea, China	[67]
177	Methyl 3,5-dihydroxydodecanoate	Antimicroalgal and antibacterial	*T. atroviride* RR-dl-3–9	Alga *Rhodomela confervoides*	Dalian, China	[39]
178	(2*S**,3*S**,5*R**,8*E*)-2-Methyl-8-decene-1,3,5-triol	Antimicroalgal and antibacterial	*T. citrinoviride* A-WH-20–3	Alga *Laurencia okamurai*	Weihai, China	[68]
179	Citrinoviric acid	Cytotoxic	*T. citrinoviride*	Sediment	Langqi Island, Fujian, China	[69]
180	Nafuredin C	Antifungal	*T. harzianum* D13	Mangrove *Excoecaria agallocha*	Hainan province, China	[70]
181	Harzialactone B	Cytotoxic	*T. harzianum* OUPS-N 115	Sponge *Halichondria okadai*	Tanabe Bay, Japan	[71]
182	Trichodenone A	Cytotoxic	*T. harzianum* OUPS-N 115	Sponge *Halichondria okadai*	Tanabe Bay, Japan	[71, 72]
183	Trichodenone B	Cytotoxic	*T. harzianum* OUPS-N 115	Sponge *Halichondria okadai*	Tanabe Bay, Japan	[71, 72]
184	Trichodenone C	Cytotoxic	*T. harzianum* OUPS-N 115	Sponge *Halichondria okadai*	Tanabe Bay, Japan	[71, 72]
185	Trichoderone	Cytotoxic	*Trichoderma* sp. GIBH-Mf082	Deep sea sediment	South China Sea, China	[73]
186	Dechlorotrichodenone C	Antimicroalgal and antibacterial	*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[25]
187	3-Hydroxytrichodenone C	Antimicroalgal and antibacterial	*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[25]
188	Hypocnone A		*H. koningii* (*T. koningii*)	Sponge *Haliclona* sp.	Sanya, Hainan Island, China	[74]
189	Methyl 3-(3-oxocyclopent-1-enyl)propionate		*T. atroviride* G20-12	Sediment on the root of mangrove *Ceriops tagal*	South China Sea, China	[75]
190	Trichodermacid A		*T. atroviride* H548	Sediment	Fujian province, China	[76]
191	Trichodermester A	Antifungal	*T. atroviride* H548	Sediment	Fujian province, China	[76]
192	Trichodermester B		*T. atroviride* H548	Sediment	Fujian province, China	[76]
193	Hypocrenone A		*H. koningii* (*T. koningii*) PF04	Sponge *Phakellia fusca*	Yongxing Island in the South China Sea, China	[77]
194	Hypocrenone B		*H. koningii* (*T. koningii*) PF04	Sponge *Phakellia fusca*	Yongxing Island in the South China Sea, China	[77]
195	Hypocrenone C		*H. koningii* (*T. koningii*) PF04	Sponge *Phakellia fusca*	Yongxing Island in the South China Sea, China	[77]

Table 2 (continued)

No.	Name	Bioactivity	Producer	Source	Locality	References
196	5-Hydroxycyclopeni cillone	Antioxidant, anti-Aβ fibrillization and neuro-protective	*Trichoderma* sp. HPQJ-34	Sponge *Hymeniacidon perleve*	Dongji Island, Zhejiang province, China	[78]
197	6-Demethyl-sorbicillin	Cytotoxic	*Trichoderma* sp. f-13	Sediment	Fujian province,China	[79]
198	(4'Z)-Sorbicillin		*Trichoderma* sp. AF007	Sea star *Acanthaster planci*	Hainan Sanya National Coral Reef Reserve, China	[80]
199	(2S)-2,3-Dihydro-7-hydroxy-6-methyl-2-[(E)-prop-1-enyl]-chroman-4-one	Cytotoxic	*Trichoderma* sp. AF007	Sea star *Acanthaster planci*	Hainan Sanya National Coral Reef Reserve, China	[80]
200	Trichosorbicillin B	Anti-inflammatory	*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
201	Trichosorbicillin C	Anti-inflammatory	*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
202	Trichosorbicillin D		*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
203	12-Hydroxysorbicillin	Anti-inflammatory	*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
204	8,9-Dihydro-12-hydrox-ysorbicillin	Anti-inflammatory	*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
205	Trichosorbicillin E	Anti-inflammatory	*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
206	Trichosorbicillin F	Anti-inflammatory	*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
207	Trichosorbicillin G		*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
208	Isotrichosorbicillin E	Anti-inflammatory	*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
209	Trichosorbicillin H		*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
210	3-Methyltrichosorbicillin H		*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
211	Trichosorbicillin I	Anti-inflammatory	*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
212	1-(2,4-Dihydroxy-3,5-dimethylphenyl)-3,4,5-trihydroxyhexan-1-one		*H. jecorina* (*T. reesei*) H8	Mangrove sediment	Fujian province, China	[82]
213	Sorbicilliside B	Antibacterial and anti-fungal	*T. longibrachiatum* EN-586	Alga *Laurencia obtusa*	Qingdao, China	[49]
214	Sorbicilliside A	Antibacterial and anti-fungal	*T. longibrachiatum* EN-586	Alga *Laurencia obtusa*	Qingdao, China	[49]
215	(−)-Trichodermatone	Cytotoxic	*Trichoderma* sp. FM652	Sediment	Hawaii, USA	[83]
216	Saturnispol E		*T. saturnisporum* DI-IA	Sponge *Dictyonella incisa*	Seferihisar bay, Turkey	[84]
217	Epoxysorbicillinol		*T. longibrachiatum*	Sponge *Haliclona* sp.		[85]
218	24-Hydroxy-trichodimerol	Cytotoxic	*T. reesei* HN-2016–018	Unidentified sponge	South China Sea, China	[86]
219	7,7′,9′-Hydroxy-trichodi-merol		*H. jecorina* (*T. reesei*) H8	Mangrove sediment	Fujian province, China	[82]
220	Isobisvertinol A	Antifungal and zebrafish-toxic	*H. jecorina* (*T. reesei*) H8	Mangrove sediment	Fujian province, China	[82]
221	15-Hydroxy-bisvertinol		*T. reesei* HN-2016–018	Unidentified sponge	South China Sea, China	[86]
222	Saturnispol A		*T. saturnisporum* DI-IA	Sponge *Dictyonella incisa*	Seferihisar bay, Turkey	[84]
223	Saturnispol B	Anti-inflammatory	*T. saturnisporum* DI-IA	Sponge *Dictyonella incisa*	Seferihisar bay, Turkey	[81, 84]

Table 2 (continued)

No.	Name	Bioactivity	Producer	Source	Locality	References
224	Trichobisvertinol A	Anti-inflammatory	*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
225	Trichobisvertinol B	Anti-inflammatory	*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
226	Trichobisvertinol C	Anti-inflammatory	*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
227	Trichobisvertinol D	Anti-inflammatory	*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
228	12-*Epi*-trichobisvertinol D	Anti-inflammatory	*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
229	10,11-Dihydrobisverti-nolone	Cytotoxic	*Trichoderma* sp. f-13	Sediment	Fujian province, China	[79]
230	2,3-Dihydro 2-hydroxy vertinolide	Cytotoxic and NF-κB-inhibitory	*Trichoderma* sp. FM652	Sediment	Hawaii, USA	[83]
231	Saturnispol F	Antibacterial	*T. saturnisporum* DI-IA	Sponge *Dictyonella incisa*	Seferihisar bay, Turkey	[84]
232	Saturnispol C		*T. saturnisporum* DI-IA	Sponge *Dictyonella incisa*	Seferihisar bay, Turkey	[84]
233	Saturnispol D		*T. saturnisporum* DI-IA	Sponge *Dictyonella incisa*	Seferihisar bay, Turkey	[84]
234	Trichodermanone A	Antioxidant	*Trichoderma* sp.	Sponge *Agelas dispar*	Island of Dominica	[87]
235	Trichodermanone B	Antioxidant	*Trichoderma* sp.	Sponge *Agelas dispar*	Island of Dominica	[87]
236	Trichodermanone C	Antioxidant, anti-inflammatory	*Trichoderma* sp.	Sponge *Agelas dispar*	Island of Dominica	[87, 88]
237	Trichodermanone D		*Trichoderma* sp.	Sponge *Agelas dispar*	Island of Dominica	[87]
238	Trichoreeseione A		*T. reesei* HN-2016-018	Unidentified sponge	South China Sea, China	[86]
239	Trichoreeseione B		*T. reesei* HN-2016-018	Unidentified sponge	South China Sea, China	[86]
240	Trichodermolide B		*T. reesei* HN-2016-018	Unidentified sponge	South China Sea, China	[86]
241	13-Hydroxy-trichoder-molide		*T. reesei* HN-2016-018	Unidentified sponge	South China Sea, China	[86]
242	Trichodermolide C		*H. jecorina* (*T. reesei*) H8	Mangrove sediment	Fujian province, China	[82]
243	Trichodermolide D		*H. jecorina* (*T. reesei*) H8	Mangrove sediment	Fujian province, China	[82]
244	Trichodermatide A	Cytotoxic	*T. reesei* YZ48-08	Mud in the tideland	Lianyungang, China	[89]
245	Trichodermatide B	Cytotoxic	*T. reesei* YZ48-08	Mud in the tideland	Lianyungang, China	[89]
246	Trichodermatide C	Cytotoxic	*T. reesei* YZ48-08	Mud in the tideland	Lianyungang, China	[89]
247	Trichodermatide D	Cytotoxic	*T. reesei* YZ48-08	Mud in the tideland	Lianyungang, China	[89]
248	4-(5,7-Dimethoxy-4-oxo-4*H*-chromen-2-yl)hepta-noic acid methyl ester		*H. lixii* SCSIO 41520	Unidentified soft coral	Daya Bay, Shenzhen, China	[90]
249	7-*O*-Methylkoninginin D		*T. koningii* MF349	Mud	South China Sea, China	[91]
250	Trichodermaketone A	Synergistic antifungal	*T. koningii* MF349	Mud	South China Sea, China	[91]
251	Trichodermaketone B		*T. koningii* MF349	Mud	South China Sea, China	[91]
252	Trichodermaketone C		*T. koningii* MF349	Mud	South China Sea, China	[91]
253	Trichodermaketone D		*T. koningii* MF349	Mud	South China Sea, China	[91]
254	Trichoketide A	Enzyme-inhibitory	*Trichoderma* sp. TPU1237	Seawater	Ashizaki-Bay in Mutsu city, Japan	[92]
255	Trichoketide B	Enzyme-inhibitory	*Trichoderma* sp. TPU1237	Seawater	Ashizaki-Bay in Mutsu city, Japan	[92]
256	Trichoharzianin		*T. harzianum* PSU-MF79	Unidentified tunicate	Phuket Province, Thailand	[93]
257	Tandyukisin G		*Trichoderma* sp. JWM29-10–1	Hydrothermal vent sediment	Kueishantao, China	[94]
258	Tandyukisin H		*Trichoderma* sp. JWM29-10–1	Hydrothermal vent sediment	Kueishantao, China	[94]

Table 2 (continued)

No.	Name	Bioactivity	Producer	Source	Locality	References
259	Tandyukisin I		*Trichoderma* sp. JWM29-10–1	Hydrothermal vent sediment	Kueishantao, China	[94]
260	Trichoharzin		*T. harzianum*	Sponge *Micale cecilia*	Amami Island, Japan	[24]
261	Tandyukisin (or tandyukisin A)	Cytotoxic	*T. harzianum* OUPS-111D-4	Sponge *Halichondria okadai*	Osaka bay, Japan	[95]
262	Tandyukisin B	Cytotoxic	*T. harzianum* OUPS-111D-4	Sponge *Halichondria okadai*	Osaka bay, Japan	[96]
263	Tandyukisin C	Cytotoxic	*T. harzianum* OUPS-111D-4	Sponge *Halichondria okadai*	Osaka bay, Japan	[96]
264	Tandyukisin D	Cytotoxic	*T. harzianum* OUPS-111D-4	Sponge *Halichondria okadai*	Osaka bay, Japan	[96]
265	Tandyukisin E	Cytotoxic	*T. harzianum* OUPS-111D-4	Sponge *Halichondria okadai*	Osaka bay, Japan	[97]
266	Tandyukisin F	Cytotoxic	*T. harzianum* OUPS-111D-4	Sponge *Halichondria okadai*	Osaka bay, Japan	[97]
267	Trichoharzin B		*T. harzianum* XS-20090075	Unidentified soft coral	Xisha Islands, China	[98]
268	Methyl-trichoharzin	Antifouling	*T. harzianum* XS-20090075	Unidentified soft coral	Xisha Islands, China	[98]
269	Trichodermaxanthone		*T. aureoviride* PSU-F95	Sea fan *Annella* sp.	Similan Islands, Thailand	[99]
270	Trichodermaquinone		*T. aureoviride* PSU-F95	Sea fan *Annella* sp.	Similan Islands, Thailand	[99]
271	Harzianumnone A		*T. harzianum* XS-20090075	Soft coral	Xisha Islands coral reef in the South China Sea, China	[100]
272	Harzianumnone B		*T. harzianum* XS-20090075	Soft coral	Xisha Islands coral reef in the South China Sea, China	[100]
273	7-Acetyl-1,3,6-trihydroxy-anthracene-9,10- dione		*Trichoderma* sp. SCSIO41004	Sponge *Callyspongia* sp.	near Xuwen County, Guangdong Province, China	[101]
274	5,7-Dihydroxy-3-methyl-2-(2-oxopropyl)naphthalene-1,4-dione		*Trichoderma* sp. SCSIO41004	Sponge *Callyspongia* sp.	near Xuwen County, Guangdong Province, China	[101]
275	Trichbenzoisochromen A		*Trichoderma* sp. SCSIO41004	Sponge *Callyspongia* sp.	near Xuwen County, Guangdong Province, China	[101]
276	Hypochromin A	Enzyme-inhibitory and cytotoxic	*H. vinosa*	Sediment (beach sand)	Okinawa Prefecture, Japan	[102]
277	Hypochromin B	Enzyme-inhibitory and cytotoxic	*H. vinosa*	Sediment (beach sand)	Okinawa Prefecture, Japan	[102]
278	Trichorenin A	Antimicroalgal	*T. virens* Y13-3	Alga *Gracilaria vermiculophylla*	Yangma Island, Yantai, China	[103]
279	Trichorenin B	Antimicroalgal	*T. virens* Y13-3	Alga *Gracilaria vermiculophylla*	Yangma Island, Yantai, China	[103]
280	Trichorenin C	Antimicroalgal	*T. virens* Y13-3	Alga *Gracilaria vermiculophylla*	Yangma Island, Yantai, China	[103]
281	Harzialactone A	Cytotoxic	*T. harzianum* OUPS-N 115	Sponge *Halichondria okadai*	Tanabe Bay, Japan	[71, 104]
282	3-Hydroxy-5-(4-hydroxy-benzyl)dihydrofuran-2(3*H*)-one		*T. atroviride* G20-12	Sediment on the root of mangrove *Ceriops tagal*	South China Sea, China	[105]
283	Trichoderolide C		*T. erinaceum* F1-1	Sea star *Acanthaster planci*	Hainan Sanya National Coral Reef Reserve, China	[32]
284	Trichoderolide D		*T. erinaceum* F1-1	Sea star *Acanthaster planci*	Hainan Sanya National Coral Reef Reserve, China	[32]

Table 2 (continued)

No.	Name	Bioactivity	Producer	Source	Locality	References
285	Trichoderolide E		*T. erinaceum* F1-1	Sea star *Acanthaster planci*	Hainan Sanya National Coral Reef Reserve, China	[32]
286	Trichoderolide F		*T. erinaceum* F1-1	Sea star *Acanthaster planci*	Hainan Sanya National Coral Reef Reserve, China	[32]
287	Trichoderolide A		*T. erinaceum* F1-1	Sea star *Acanthaster planci*	Hainan Sanya National Coral Reef Reserve, China	[32]
288	Trichoderolide B	Cytotoxic	*T. erinaceum* F1-1	Sea star *Acanthaster planci*	Hainan Sanya National Coral Reef Reserve, China	[32]
289	Trichophenol A	Antimicroalgal and anti-bacterial	*T. citrinoviride* A-WH-20–3	Alga *Laurencia okamurai*	Weihai, China	[33]
290	(2*E*)-1-[(5-Hydroxy-7-methoxy-2-methyl-4-oxo-4*H*-1-benzopyran-3-yl)methyl]3-methyl-2-pentenedioate	Antibacterial and anti-fungal	*Trichoderma* sp. JWM29-10–1	Hydrothermal vent sediment	Kueishantao, China	[94]
291	(2*S*,3*S*)-5-Hydroxy-3-hydroxymethyl-7-methoxy-2-methyl-4-chromanone	Antibacterial	*Trichoderma* sp. JWM29-10–1	Hydrothermal vent sediment	Kueishantao, China	[94]
292	Trichoharzianone		*T. harzianum* PSU-MF79	Unidentified tunicate	Phuket Province, Thailand	[93]
293	Trichopyrone		*T. viride*	Sponge *Agelas dispar*	Island of Dominica	[106]
294	Saturnispol G		*T. saturnisporum* DI-IA	Sponge *Dictyonella incisa*	Seferihisar bay, Turkey	[84]
295	Saturnispol H	Antibacterial	*T. saturnisporum* DI-IA	Sponge *Dictyonella incisa*	Seferihisar bay, Turkey	[84]

sordaricin skeletons. The above 19 basic scaffolds along with the degraded and substituted ones demonstrate the high structural diversity of terpenes from marine-derived *Trichoderma*.

Monoterpenes have seldom been discovered from *Trichoderma* species, including marine-derived ones. Monoterpenes **1** and **2** (Fig. 6) were obtained from the alga-endophytic *T. asperellum* and represent the only two menthane derivatives from this genus [25]. These two compounds with only two chiral centers were identified as mutual epimers by the similar but different NMR data, because those of enantiomers are the same as each other. Their absolute configurations at C-7 were assigned to be *S* and *R*, respectively, by quantum chemical calculations of electronic circular dichroism (ECD) spectra. Based on the epimeric relationship between **1** and **2**, these two metabolites were proposed to have the same absolute configuration at C-1, but it was not determined spectroscopically. As a chlorinated analog of them, 3-chloro-menthan-1,2,7-triol had also been isolated from a fungus, *Tryblidiopycnis* sp. of mangrove origin [131]. Based on previous reports, monoterpenes were rarely encountered not only in *Trichoderma* species but also in other marine and even terrestrial-derived fungi [132].

Sesquiterpenes with 126 new members (**3**–**128**, Table 1) make up the largest group of terpenes from marine-derived *Trichoderma*, and they comprise 11 basic carbon skeletons [26–52]. A common cyclonerane skeleton is present in 23 isolates (**3**–**25**, Fig. 7), obtained from *T. asperellum* [26–28], *T. harzianum* [29, 30], *T. hamatum* [31], *T. erinaceum* [32], *T. citrinoviride* [33], and *T. asperelloides* [34]. This scaffold is characterized by the dimethylated cyclopentane ring attached by a 1,6-dimethylhexanyl side chain. Oxidation, reduction, cyclization, and substitution construct their diverse structures. All of them feature an oxygen atom bonded to C-7. The hydroxy group at C-3 of **22**–**24** possesses an opposite orientation, and the double bond in the five-membered ring of **25** also renders this molecule unique [33, 34]. Two isolates (**26** and **27**, Fig. 7) from *T. asperellum* and *T. asperelloides*, respectively, have degraded cyclonerane frameworks, with the degradation happening at the side chain or the ring unit [28, 34]. In addition, 10 nitrogenous cyclonerane derivatives (**28**–**37**, Fig. 8) were obtained from *T. asperellum* [27, 35]. Each of them contains a nitrogen-bearing substitute, and the highlight is the presence of an isoxazole ring in **35** [27]. Cyclonerins A (**28**) and B (**29**) harbor a hydroxamic acid unit, that can chelate ferric

Table 3 Peptides (**296**–**426**), alkaloids (**427**–**440**), and others (**441**–**445**) from the marine-derived *Trichoderma*

No.	Name	Bioactivity	Producer	Source	Locality	Reference
296	DC1149R		*Trichoderma* sp. TPU199 (cf. *T. brevi-compactum*)	Unidentified alga	Palau	[107]
297	Iododithiobrevamide		*Trichoderma* sp. TPU199 (cf. *T. brevi-compactum*)	Unidentified alga	Palau	[107]
298	5-*epi*-Pretrichodermamide A		*Trichoderma* sp. TPU199 (cf. *T. brevi-compactum*)	Unidentified alga	Palau	[41]
299	5-*epi*-Trithiopretrichoderma-mide A		*Trichoderma* sp. TPU199 (cf. *T. brevi-compactum*)	Unidentified alga	Palau	[41]
300	Chlorotrithiobrevamide		*Trichoderma* sp. TPU199 (cf. *T. brevi-compactum*)	Unidentified alga	Palau	[108]
301	Dehydroxymethylbis(dethio)bis(methylthio)gliotoxin		*T. virens* Y13-3	Alga *Gracilaria vermiculophylla*	Yangma Island, Yantai, China	[109]
302	(3*S*,6*R*)-6-(Para-hydroxybenzyl)-1,4-dimethyl-3,6-bis(methylthio)piperazine-2,5-dione		*T. virens* Y13-3	Alga *Gracilaria vermiculophylla*	Yangma Island, Yantai, China	[109]
303	Methylcordysinin A		*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[25]
304	Cyclo(L-5-MeO-Pro-L-5-MeO-Pro)	Antimicroalgal	*T. asperellum* A-YMD-9–2	Alga *Gracilaria verrucosa*	Yangma Island, Yantai, China	[35]
305	Atroviridetide		*T. atroviride* G20-12	Sediment on the root of mangrove *Ceriops tagal*	South China Sea, China	[110]
306	Trichoderide A	Cytotoxic	*T. reesei* YZ48-08	Mud in the tideland	Lianyungang, China	[111]
307	Trichodermamide A		*T. virens* CNL910	Ascidian *Didemnum molle*	near Madang, Papua New Guinea	[112]
308	Trichodermamide B	Antibacterial, antifungal, cytotoxic	*T. virens* CNL910 & CNK266	Ascidian *Didemnum molle* & alga *Halimeda* sp.	near Madang, Papua New Guinea	[112]
309	Trichodermamide G		*T. harzianum* D13	Mangrove *Excoecaria agallocha*	Hainan province, China	[70]
310	Dithioaspergillazine A	Cytotoxic	*Trichoderma* sp. TPU199 (cf. *T. brevi-compactum*)	Unidentified alga	Palau	[113]
311	Trichoderin A	Antibacterial	*Trichoderma* sp. 05FI48	Unidentified sponge		[114, 115]
312	Trichoderin A1	Antibacterial	*Trichoderma* sp. 05FI48	Unidentified sponge		[114]
313	Trichoderin B	Antibacterial	*Trichoderma* sp. 05FI48	Unidentified sponge		[114]
314	Aspereline A		*T. asperellum* Y19-07 (or Y19-17)	Sediment	Antarctic Penguin Island	[116]
315	Aspereline B		*T. asperellum* Y19-07 (or Y19-17)	Sediment	Antarctic Penguin Island	[116]
316	Aspereline C		*T. asperellum* Y19-07 (or Y19-17)	Sediment	Antarctic Penguin Island	[116]
317	Aspereline D		*T. asperellum* Y19-07 (or Y19-17)	Sediment	Antarctic Penguin Island	[116]
318	Aspereline E		*T. asperellum* Y19-07 (or Y19-17)	Sediment	Antarctic Penguin Island	[116]
319	Aspereline F		*T. asperellum* Y19-07 (or Y19-17)	Sediment	Antarctic Penguin Island	[116]
320	Aspereline G		*T. asperellum*	Sediment	Langqi Island, Fujian, China	[117]
321	Aspereline H		*T. asperellum*	Sediment	Langqi Island, Fujian, China	[117]

Table 3 (continued)

No.	Name	Bioactivity	Producer	Source	Locality	Reference
322–353	Asperelines G-U, W-Z, and Z_1-Z_{13}		*T. asperellum* Y19-17 (or Y19-07)	Sediment	Antarctic Penguin Island	[118]
354	Trichobrachin A I		*T. longibrachiatum* MMS 151	Mussel *Mytilus edulis*	Tharon, France	[119]
355	Trichobrachin A II		*T. longibrachiatum* MMS 151	Mussel *Mytilus edulis*	Tharon, France	[119]
356	Trichobrachin A III		*T. longibrachiatum* MMS 151	Mussel *Mytilus edulis*	Tharon, France	[119]
357	Trichobrachin A IV		*T. longibrachiatum* MMS 151	Mussel *Mytilus edulis*	Tharon, France	[119]
358	Trichobrachin B I		*T. longibrachiatum* MMS 151	Mussel *Mytilus edulis*	Tharon, France	[119]
359	Trichobrachin B II		*T. longibrachiatum* MMS 151	Mussel *Mytilus edulis*	Tharon, France	[119]
360	Trichobrachin B III		*T. longibrachiatum* MMS 151	Mussel *Mytilus edulis*	Tharon, France	[119]
361	Trichobrachin B IV		*T. longibrachiatum* MMS 151	Mussel *Mytilus edulis*	Tharon, France	[119]
362–382	Trichobrachin A-IX		*T. longibrachiatum* DAOM 234100	Mussel *Mytilus edulis*	estuary of the Loire River (Tharon, France)	[120]
383	TA-19A-Ia		*T. atroviride* MMS927, MMS639, MMS925, MMS1295, MMS1513	Seawater, sediments, and blue mussels	La Couplasse, Le Croisic, and Bonne Anse	[121]
384	TA-19A-IIa		*T. atroviride* MMS927, MMS639, MMS925, MMS1295, MMS1513	Seawater, sediments, and blue mussels	La Couplasse, Le Croisic, and Bonne Anse	[121]
385	TA-19A-IIIa		*T. atroviride* MMS927, MMS639, MMS925, MMS1295, MMS1513	Seawater, sediments, and blue mussels	La Couplasse, Le Croisic, and Bonne Anse	[121]
386	Trichorzianine 1938	Antibacterial	*T. atroviride* NF16	Sponge *Axinella* sp.	Mediterranean sea, Akhziv, Israel	[122]
387	Trichorzianine 1909	Antibacterial	*T. atroviride* NF16	Sponge *Axinella* sp.	Mediterranean sea, Akhziv, Israel	[122]
388	Trichorzianine 1895	Antibacterial	*T. atroviride* NF16	Sponge *Axinella* sp.	Mediterranean sea, Akhziv, Israel	[122]
389	Trichorzianine 1896	Antibacterial	*T. atroviride* NF16	Sponge *Axinella* sp.	Mediterranean sea, Akhziv, Israel	[122]
390	Trichorzianine 1924	Antibacterial	*T. atroviride* NF16	Sponge *Axinella* sp.	Mediterranean sea, Akhziv, Israel	[122]
391	Trichorzianine 1910	Antibacterial	*T. atroviride* NF16	Sponge *Axinella* sp.	Mediterranean sea, Akhziv, Israel	[122]
392	Trichorzianine 1924a	Antibacterial	*T. atroviride* NF16	sponge *Axinella* sp.	Mediterranean sea, Akhziv, Israel	[122]
393	Trichorzianine 1909a	Antibacterial	*T. atroviride* NF16	Sponge *Axinella* sp.	Mediterranean sea, Akhziv, Israel	[122]
394	Longibrachin A-0		*T. longibrachiatum* MMS151	Mussel *Mytilus edulis*	Estuary of the river Loire, Tharon, France	[123]
395	Longibrachin A-II-a	Cytotoxic, antibacterial, antifungal, and insect-toxic	*T. longibrachiatum* MMS151	Mussel *Mytilus edulis*	Estuary of the river Loire, Tharon, France	[123]
396	Longibrachin A-IV-b		*T. longibrachiatum* MMS151	Mussel *Mytilus edulis*	Estuary of the river Loire, Tharon, France	[123]
397	Hyporientalin A	Antibacterial and antifungal	*T. orientale* LSBA1	Sponge *Cymbaxinella damicornis*	Mediterranean Sea, Mahdia, Tunisia	[124]
398–426	TA-17A-Ix to -IVx and TA-17S-Ix to -IIIx		*T. atroviride* MMS927, MMS639, MMS1295	Seawater, sediments, and blue mussels	La Couplasse, Le Croisic, and Bonne Anse	[121]

Table 3 (continued)

No.	Name	Bioactivity	Producer	Source	Locality	Reference
427	Trichocarboline A	Anti-pulmonary fibrosis	*Trichoderma* sp. MCCC 3A01244	Seawater (deep sea- 3300 m)	South China Sea	[125]
428	Trichocarboline C		*Trichoderma* sp. MCCC 3A01244	Seawater (deep sea- 3300 m)	South China Sea	[125]
429	(–)-Trichocarboline B	Anti-pulmonary fibrosis	*Trichoderma* sp. MCCC 3A01244	Seawater (deep sea- 3300 m)	South China Sea	[125]
430	(+)-Trichocarboline B	Anti-pulmonary fibrosis	*Trichoderma* sp. MCCC 3A01244	Seawater (deep sea- 3300 m)	South China Sea	[125]
431	Trichodin A	Antibacterial and anti- fungal	*Trichoderma* sp. MF106		Greenland Sea (Fram Strait)	[126]
432	Trichodin B		*Trichoderma* sp. MF106		Greenland Sea (Fram Strait)	[126]
433	Ethyl 2-bromo-4-chloroquin- oline-3-carboxylate		*T. harzianum* XS-20090075	Unidentified soft coral	Xisha Islands, China	[98]
434	2-Methylimidazo[1,5-*b*] isoquinoline-1,3,5(2*H*)-trione		*H. virens*	Mangrove *Rhizophora apiculata*	Guangxi Province, China	[127]
435	4-Oxazolepropanoic acid		*T. asperellum* cf44-2	Alga *Sargassum* sp.	Zhoushan Islands, China	[25]
436	(3′-Hydroxybutan-2′-yl)5- oxopyrrolidine-2-carboxylate		*T. atroviride* G20-12	Sediment on the root of mangrove *Ceriops tagal*	South China Sea, China	[110]
437	Trichosorbicillin A		*T. reesei* 4670	Sponge	Shantou, Guangdong Province, China	[81]
438	Penicillenol F	Cytotoxic	*T. citrinoviride*	Sediment	Fuzhou, China	[128]
439	Penicillenol D	Cytotoxic	*T. citrinoviride*	Sediment	Langqi Island, Fujian, China	[69]
440	2-Hydroxybutan-3-yl 5′-(2″-hydroxy-*N*-(2‴- oxobutan-3‴-yl)propana- mido)butanoate		*T. atroviride* G20-12	Sediment on the root of mangrove *Ceriops tagal*	South China Sea, China	[105]
441	4′-(4,5-Dimethyl-1,3-diox- olan-2-yl)methyl-phenol		*T. atroviride* G20-12	Sediment on the root of mangrove *Ceriops tagal*	South China Sea, China	[110]
442	Hypofuran A	Antibacterial and anti- oxidant	*H. koningii* (*T. koningii*) PF04	Sponge *Phakellia fusca*	Yongxing Island in the South China Sea, China	[77]
443	Hypofuran B		*H. koningii* (*T. koningii*) PF04	Sponge *Phakellia fusca*	Yongxing Island in the South China Sea, China	[77]
444	Hypocrol A	Antibacterial and anti- oxidant	*H. koningii* (*T. koningii*) PF04	Sponge *Phakellia fusca*	Yongxing Island in the South China Sea, China	[129]
445	Gliocladinin D		*T. reesei* HN-2016-018	Unidentified sponge	South China Sea, China	[130]

ion, and represent the first two fungal hydroxamic acids with a terpene-derived scaffold [27]. The identification of these compounds was performed through various spectroscopic methods. Quantum chemical calculations were used to aid the assignments of relative configurations for **22** and **26** and absolute configurations for **22**, **28**–**32**, and **34**, and X-ray diffraction was employed to determine the absolute configuration of **6** [27, 28, 33]. Although the relative configuration at C-7 of **7**–**9** and **12** was not given in literature [28], it should be the same as that **26** based on

biogenetic considerations. Cyclonerane sesquiterpenes, especially the known cyclonerodiol, can be produced by many species of *Trichoderma* and other fungal genera, such as *Trichothesium*, *Fusarium*, and *Epichloe* [33], but they have rarely been detected in plants and animals. It is worth mentioning that marine-derived *Trichoderma* strains have contributed more diverse cycloneranes than terrestrial-derived ones so far [20, 22].

Bisabolane sesquiterpenes have been known as metabolites of plants, animals, and microbes for a long time,
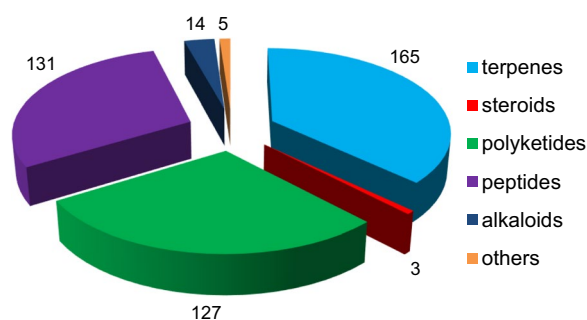
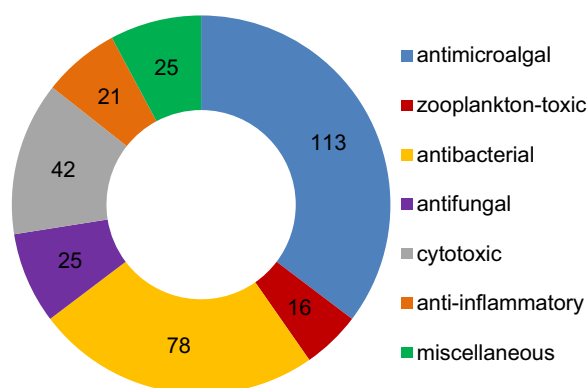**Fig. 4** Types and numbers of new compounds from marine-derived *Trichoderma*

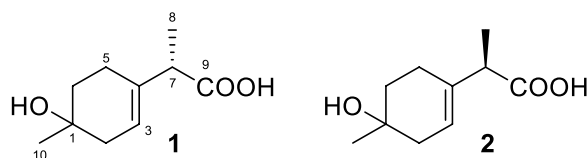**Fig. 5** Numbers of bioactive new compounds from marine-derived *Trichoderma*

Fig. 6 Monoterpenes from marine-derived *Trichoderma*

but the first discovery from *Trichoderma* just happened in 2011 [133, 134]. Bisabolane derivatives from marine-derived *Trichoderma* also exhibit high structural diversity. 14 members (**38**–**51**, Fig. 9) with an untouched bisabolane skeleton were isolated from four *Trichoderma* species, including *T. asperellum* [25, 26, 36], *T. brevicompactum* [37], *T. asperelloides* [34], and *T. erinaceum* [32]. Among them, trichaspside A (**38**) represents the first natural bisabolane aminoglycoside, and all the others possess oxygenated side chain termini. Meanwhile, 21 norbisabolane sesquiterpenes (**52**–**72**, Fig. 10), with four (**53**–**56**) containing an aminoglycoside moiety, were discovered from *T. asperellum* [25, 26, 36, 38], *T.*

atroviride [39], and *T. asperelloides* [34]. All the norbisabolanes are possibly produced by elimination of a terminal methyl group from the side chain moieties of their precursors, and the majority of them bear an oxygen atom at C-11. It is regretted that absolute configurations for most of the bisabolane and norbisabolane derivatives remain unsolved because of lacking ECD signals and perfect crystals. However, trichobisabolin Z (**72**) has a Cotton effect at 328 nm due to the presence of an α,β-unsaturated carbonyl group, which enabled the assignment of the absolute configuration at C-6 by quantum chemical calculations [34]. An acidic hydrolysis reaction was performed during the absolute configuration establishment of **38** [26]. Trichodermaerin A (**51**) with no optical activity was deduced to be a racemic mixture, but the separation failed via various chiral HPLC columns [32]. In general, the high populations of norbisabolane sesquiterpenes and aminoglycosides may be characteristic of marine-derived *Trichoderma*.

As secondary metabolites of some *Trichoderma* and *Fusarium* species, trichothecane sesquiterpenes have been regarded as a class of mycotoxins for animals and humans [20]. Besides the known trichodermin, 18 trichothecane derivatives (**73**–**90**, Fig. 11) were isolated from marine-derived *Trichoderma* species, including *T. brevicompactum* and *T. hamatum* as well as an unidentified strain [31, 40–43]. Similar to the known trichothecane sesquiterpenes [135], the majority of these new isolates possess a 2,11-epoxy unit. However, trichodermol chlorohydrin (**82**) and trichodermarin N (**90**) are exceptions, with the former being the first natural halogenated trichothecane derivative. Both 2,11-epoxy and 11,12-epoxy units are present in trichodermarin H (**84**), of which the absolute configuration along with that of trichodermarin G (**83**) was assigned by X-ray crystallography. The absolute configurations of **77**–**80** were ascertained by analysis of their ECD data aided by quantum chemical calculations, while that of **81** was determined by agreement of its specific optical rotation with the hydrolysate of **77**. It is interesting that glycosides are also not absent in this class of metabolites. Three members (**88**–**90**) were identified to possess sugar moieties, with **90** being the first glucosamine-coupled trichothecane. It is worth noting that the production of trichothecane toxins may decrease the application of their producers, though some strains display excellent antifungal effects [136].

Carotane, also designated daucane, sesquiterpenes with 10 new members (**91**–**100**, Fig. 12) were purified from two strains of the marine algicolous *T. virens* [44, 45]. Among *Trichoderma* species, *T. virens* is the main producer of carotane sesquiterpenes, but their origin is not confined to only this species. A soil-borne
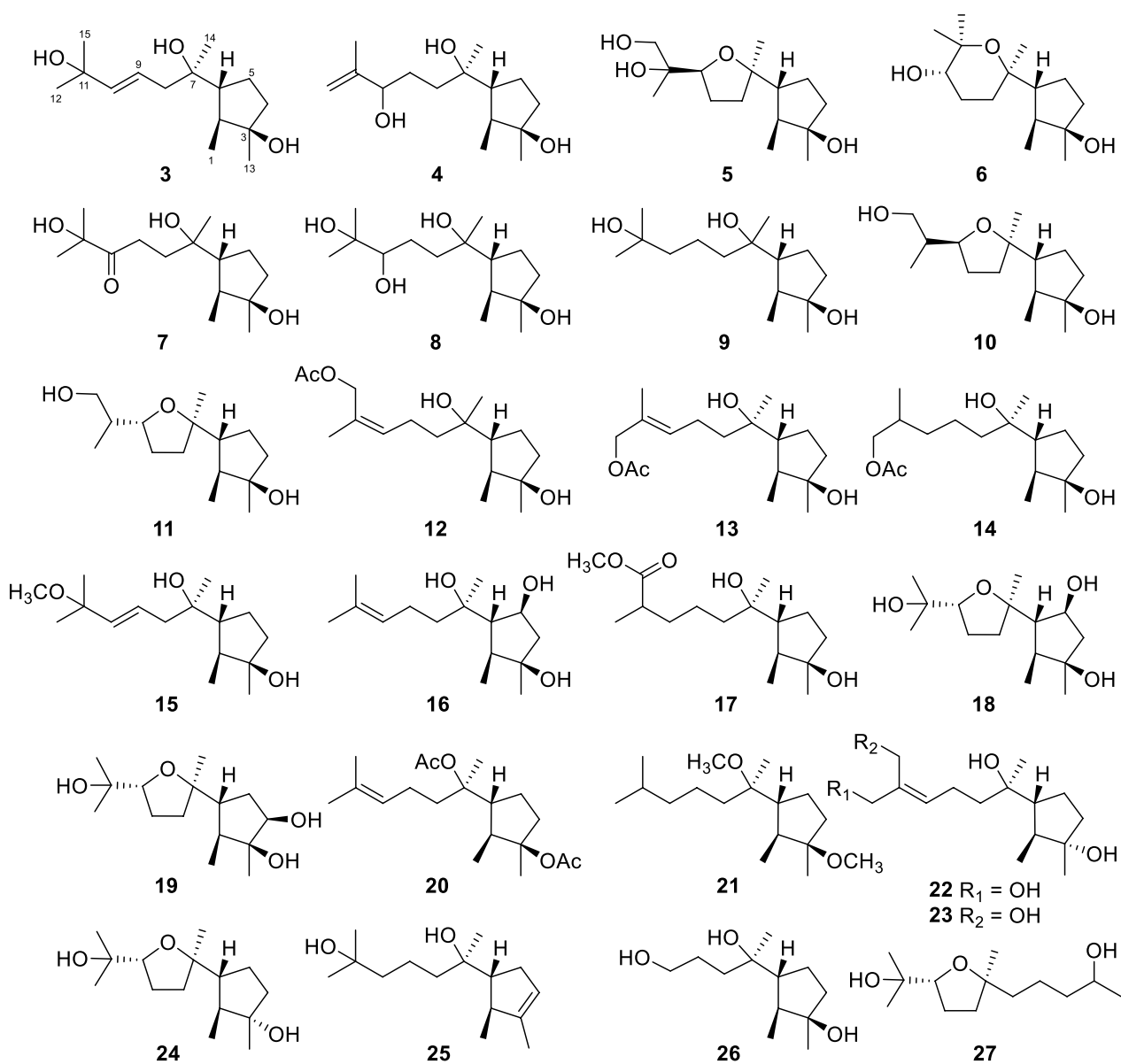
Fig. 7 Cyclonerane sesquiterpenes and catabolites from marine-derived *Trichoderma*

T. crassum strain was also reported to yield carotanes [137]. All these 10 isolates are oxygenated at C-3 and C-4, and the peculiarity is a carbonyl group, rather than a hydroxy group, at C-3 of trichocarotin C (**93**). The absolute configuration of trichocarotin A (**91**) was determined by analysis of X-ray crystallographic data, while those of trichocarotin B (**92**) and 14-*O*-methyl-trichocarotin G (**99**) were established by ECD spectra. Although other filamentous fungi, such as *Byssochlamys*, *Penicillium*, and *Aspergillus* species, also produce carotane sesquiterpenes, the oxidation at C-3 and C-4 are uncommon [138]. Thus, the oxygenated carotanes

at both C-3 and C-4 have chemotaxonomic significance for their *Trichoderma* producers.

Besides carotanes, cadinane sesquiterpenes also exist in *T. virens* [44, 45]. However, this class of sesquiterpenes (**101–116**, Fig. 13) are distributed in a broader spectrum of other *Trichoderma* species, such as *T. asperelloides* [34], *T. asperellum* [46], *T. harzianum* [48], and an unidentified strain [47]. The first untouched cadinane sesquiterpene trichocadinin A (**101**) from *Trichoderma* was reported in 2018, even if a 2,3-seco derivative, named heptelidic acid, was found from *T. viride* in 1980 [20]. The 2,3-seco cadinane sesquiterpenes (**114–116**) were also
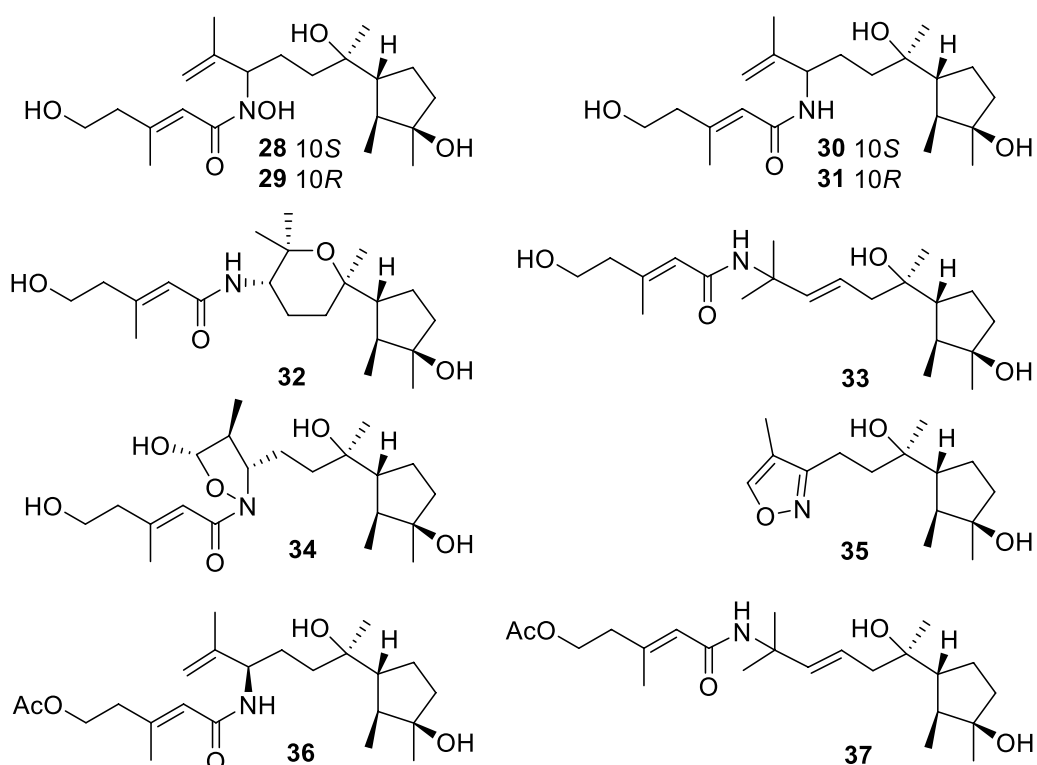
Fig. 8 Nitrogenous cyclonerane sesquiterpenes from marine-derived *Trichoderm*
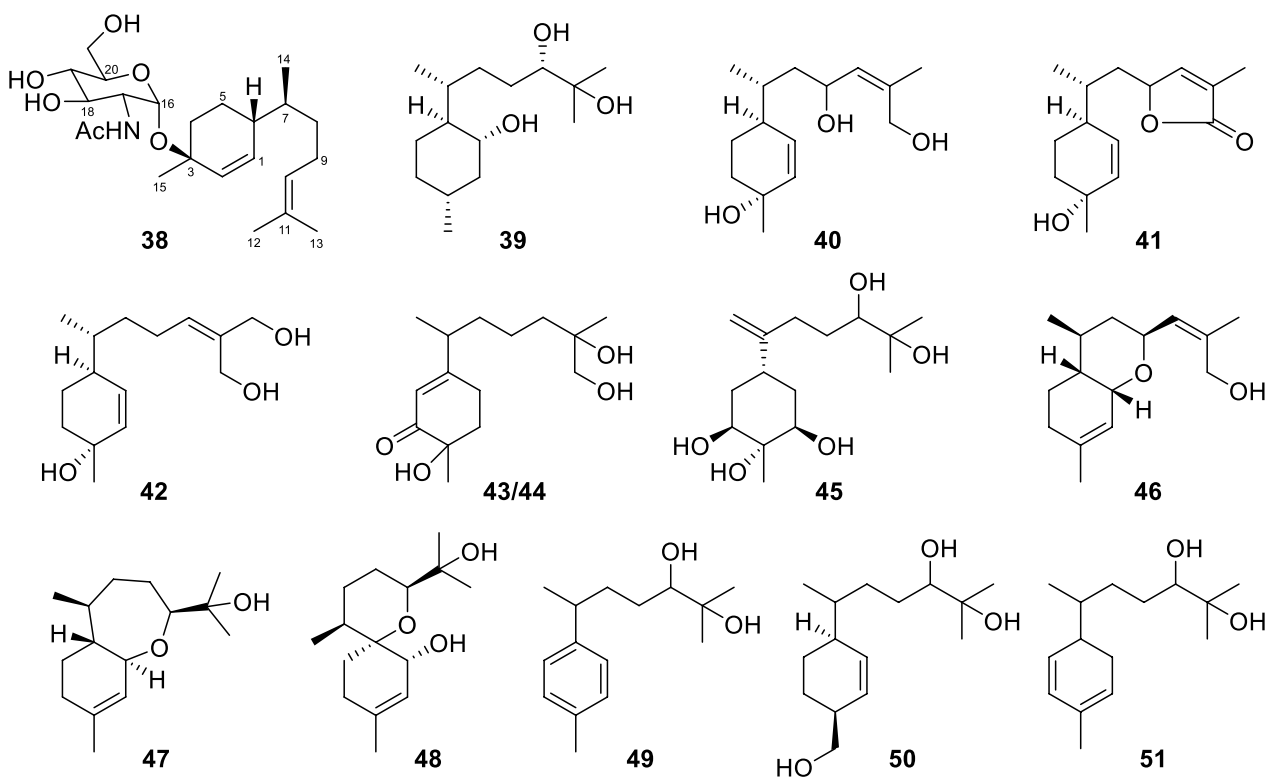
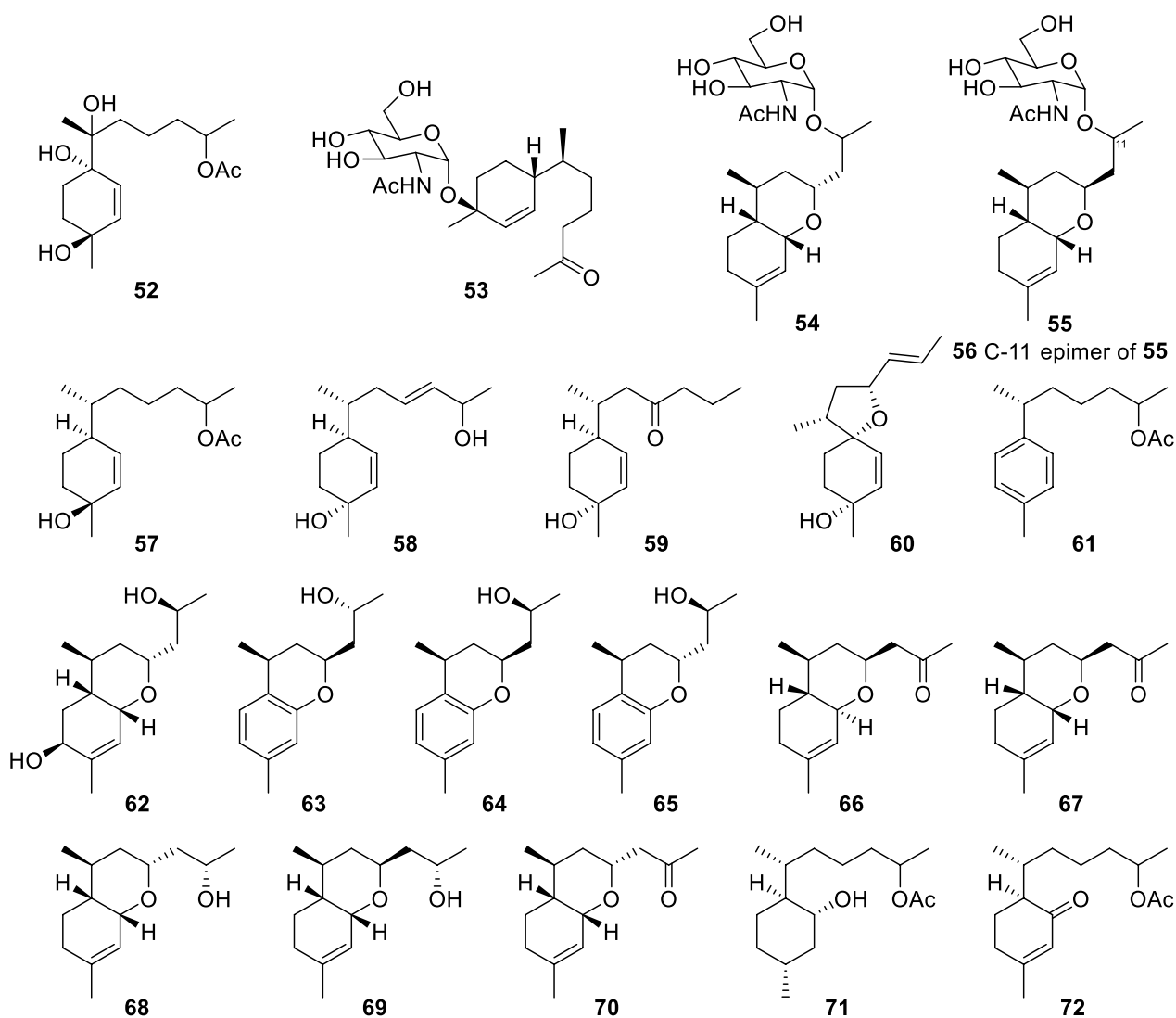**Fig. 9** Bisabolane sesquiterpenes from marine-derived *Trichoderma*

Fig. 10 Norbisabolane sesquiterpenes from marine-derived *Trichoderma*

obtained from two other *Trichoderma* species of marine origin, with halogenation being present in **114**. Moreover, trichocadinins I (**112**) and J (**113**) possess a 2-norcadinane framework. Except for **102–104**, these cadinane derivatives feature a carboxyl group at C-11. Relying on the presence of a conjugated carboxyl group, the absolute configurations of **101** and **105–115** were established by ECD spectra. Additionally, the absolute configuration of **104** was determined by X-ray diffraction. Although cadinane sesquiterpenes have occurred frequently in plants and fungi, the ring-opening derivatives are distributed narrowly in nature [139].

Other 12 sesquiterpenes (Fig. 14) with acorane (**117–119**) [30, 37, 49], cuparane (**120** and **121**) [43], farnesane (**122** and **123**) [37], synderane (**124**) [50],

norpupukeanane (**125**) [51], harzianoic acid (**126** and **127**) [52], and ethylated bisabolane (**128**) [26] frameworks were discovered from *T. harzianum*, *T. brevicompactum*, *T. asperellum*, *T. longibrachiatum*, and an unidentified strain. 8-Acoren-3,11-diol (**117**), trichoacorin A (**118**), and trichoacorside A (**119**) are the only three spiro-fused sesquiterpenes characterized from marine-derived *Trichoderma*, with **119** being the first acorane aminoglycoside. Trichocuparins A (**120**) and B (**121**) represent the first two *Trichoderma*-derived cuparane derivatives, and the absolute configuration of the former was determined by analysis of X-ray crystallographic data. This carbon skeleton harbors the same ring system as trichothecane, but one of the four methyl groups resides at a different position. Trichonerolins
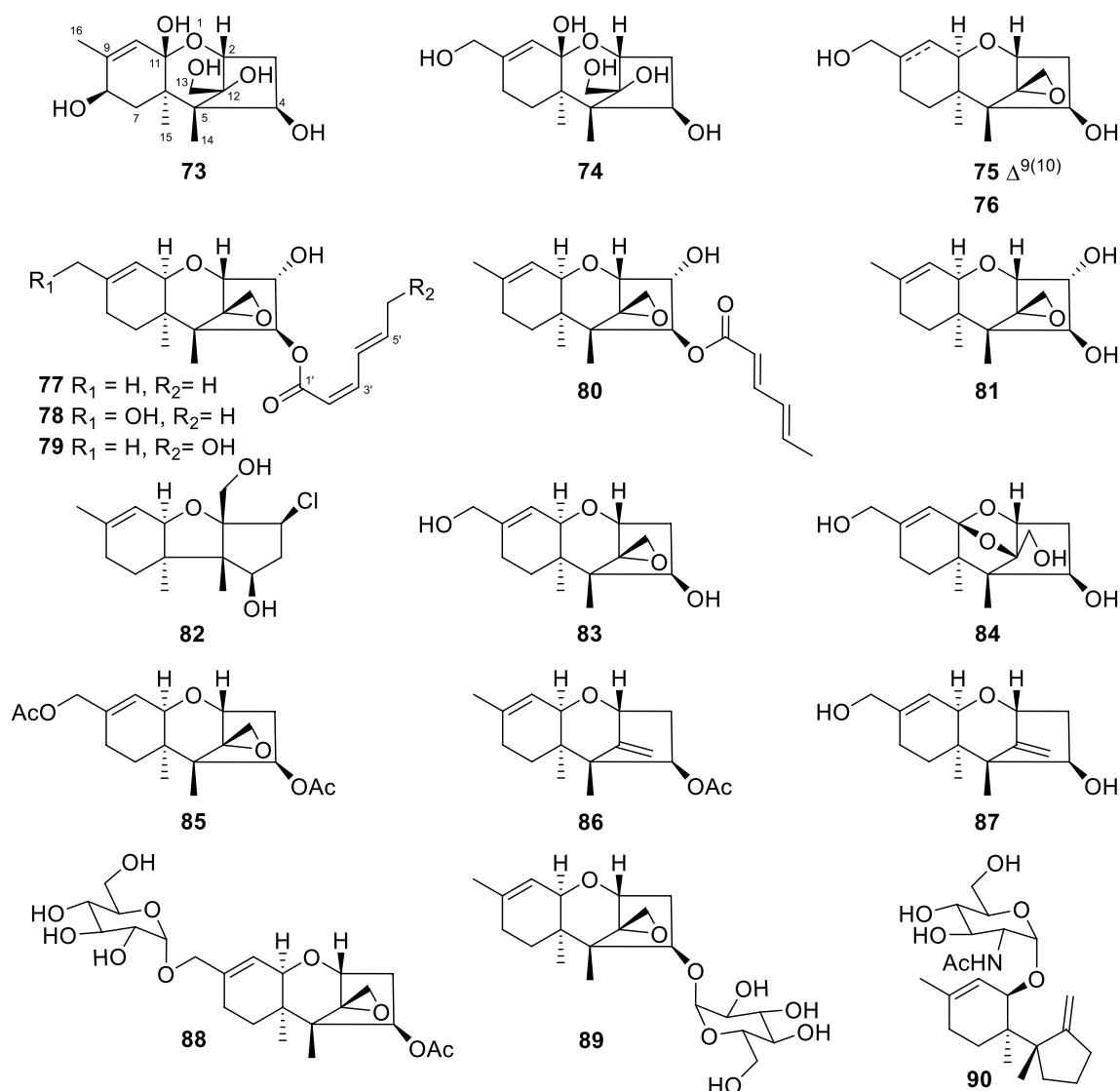
Fig. 11 Trichothecane sesquiterpenes from marine-derived *Trichoderma*

A/B (**122**/**123**), trichodermoside (**124**), and trichodermene A (**125**) are also firstly occurring structural types in *Trichoderma* metabolites, especially an aminosugar unit in **124** and a complicated ring system in **125**. There are two chiral centers in **122** and **123**, of which the chemical shift deviations undoubtedly arise from their epimeric relationship. Harzianoic acid B (**127**) features a new natural scaffold with a cyclobutane nucleus, and harzianoic acid A (**126**) is its 15-nor derivative. In addition, the ethylated bisabolane skeleton of trichaspin (**128**) is unprecedented, too. Most of these skeletons have been discovered in only one or two species, their universality in marine-derived *Trichoderma* needs to be further explored.

The number of new diterpenes with seven basic carbon skeletons from marine-derived *Trichoderma* amounts to 37 (**129**–**165**, Table 1) [26, 30, 32, 46, 53–65]. Of those, 25 members (**129**–**153**, Fig. 15) are harziane derivatives, that were isolated from *T. asperellum* [26, 46], *T. longibrachiatum* [53, 54], *T. harzianum* [30, 56, 57], *T. asperelloides* [59], *T. erinaceum* [32, 60], and two unidentified strains [55, 58]. The common harziane skeleton harbors a fused cyclobutane, cyclopentane, cyclohexane, and cycloheptane ring system, that is unique in nature. Harzianone (**129**) was reported as the second harziane diterpene in 2012, 20 years later than the discovery of harziandione with a second carbonyl group at C-3. The absolute configuration of **129** was ascertained by quantum chemical
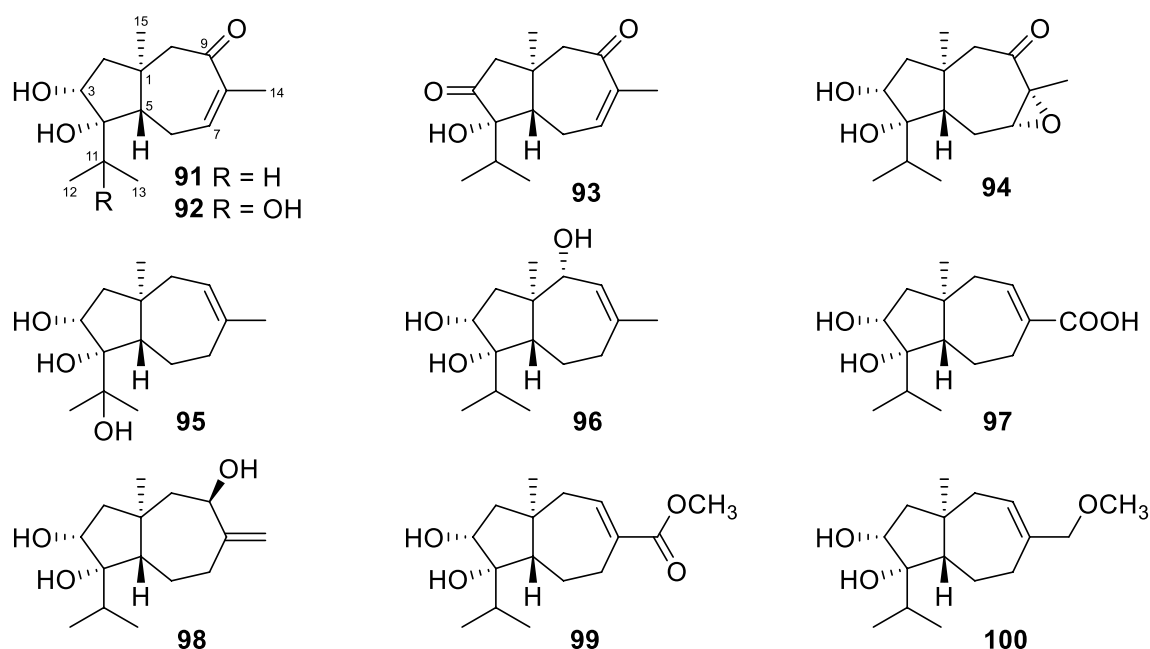
Fig. 12 Carotane sesquiterpenes from marine-derived *Trichoderma*

calculations of ECD data, and that of harziandione was confirmed by simulation of the specific optical rotation at the same time [53]. Other isolates with this rigid scaffold have different oxidation degrees and positions, and the double bond at C-9 is hydrogenated in **144–146** in particular. The first total synthesis of a harziane diterpene was reported in 2020, with highly diastereocontrolled construction of the cyclobutane ring via enyne cycloisomerization being a key step [140]. This work also resulted in configurational revision at C-9 of the target harzian-9-ol, isolated from the tree-associated *T. atroviridae*. Harzianelactone (**147**) and trichodermaerin (**150**) represent the first 11,12-lactone and 10,11-lactone, respectively, that are possibly produced by catalysis of the Baeyer–Villiger monooxygenase [58, 60]. X-ray diffraction with Mo Kα radiation secured the relative configuration of **150**, that was isolated from *T. asperellum* later [141]. Lactonation seemingly happens only in the four-membered ring, and a subsequent reaction may yield ring-opening products, such as **153** [59]. In addition, two proharziane diterpenes (**154** and **155**) with a 14-membered macroring being inlaid with a cyclohexane unit were identified from *T. asperelloides* and *T. harzianum* [30, 59], and they seem intermediates during the biosynthesis of corresponding harzianes [142]. The absolute configurations of all these 27 isolates were confirmed by chiral techniques. As the assignment of **129**, ECD analysis played an important role in determining the absolute configurations of most isolates. X-ray diffraction was also used to determine the absolute configurations of several

molecules, including **131**, **132**, **140**, and **142**. The distribution of harziane, secoharziane, and proharziane diterpenes is not confined to only the above *Trichoderma* species, and they rarely occur in other fungal genera. Thus, these diterpenes with tetracyclic and bicyclic scaffolds are promising to be regarded as biomarkers for *Trichoderma* fungi.

Wickerane diterpenes look like exclusive metabolites of *Trichoderma*, six members (**156–161**, Fig. 16) were discovered from sponge-derived *T. harzianum* [61, 62]. Their distribution is not as broad as that of harziane derivatives. *T. atroviride* of soil or plant origin contributed the first two wickerane diterpenes, wickerols A and B (also named trichodermanin A), and their biogenetic route was predicted with ¹³C-labeled acetate [143, 144]. In the pathway, the verticillyl cation is the same as the intermediate in the biosynthesis of harziane diterpenes [142, 143]. The complicated tetracyclic scaffold and its relative configuration were guaranteed by X-ray crystallographic analysis [144]. A stereocontrolled synthesis from commercial sitolactone led to the assignment of absolute configurations and the revision of the original specific optical rotation sign of wickerol A [145]. Compared to wickerols A and B, trichodermanins C–H (**156–161**) feature high degrees of oxidation. The lack of any olefinic and aromatic unit is also characteristic of these diterpenes. The absolute configurations of **156**, **157**, and **159** were determined by application of the modified Mosher's method, while that of **158** was established by the negative Cotton
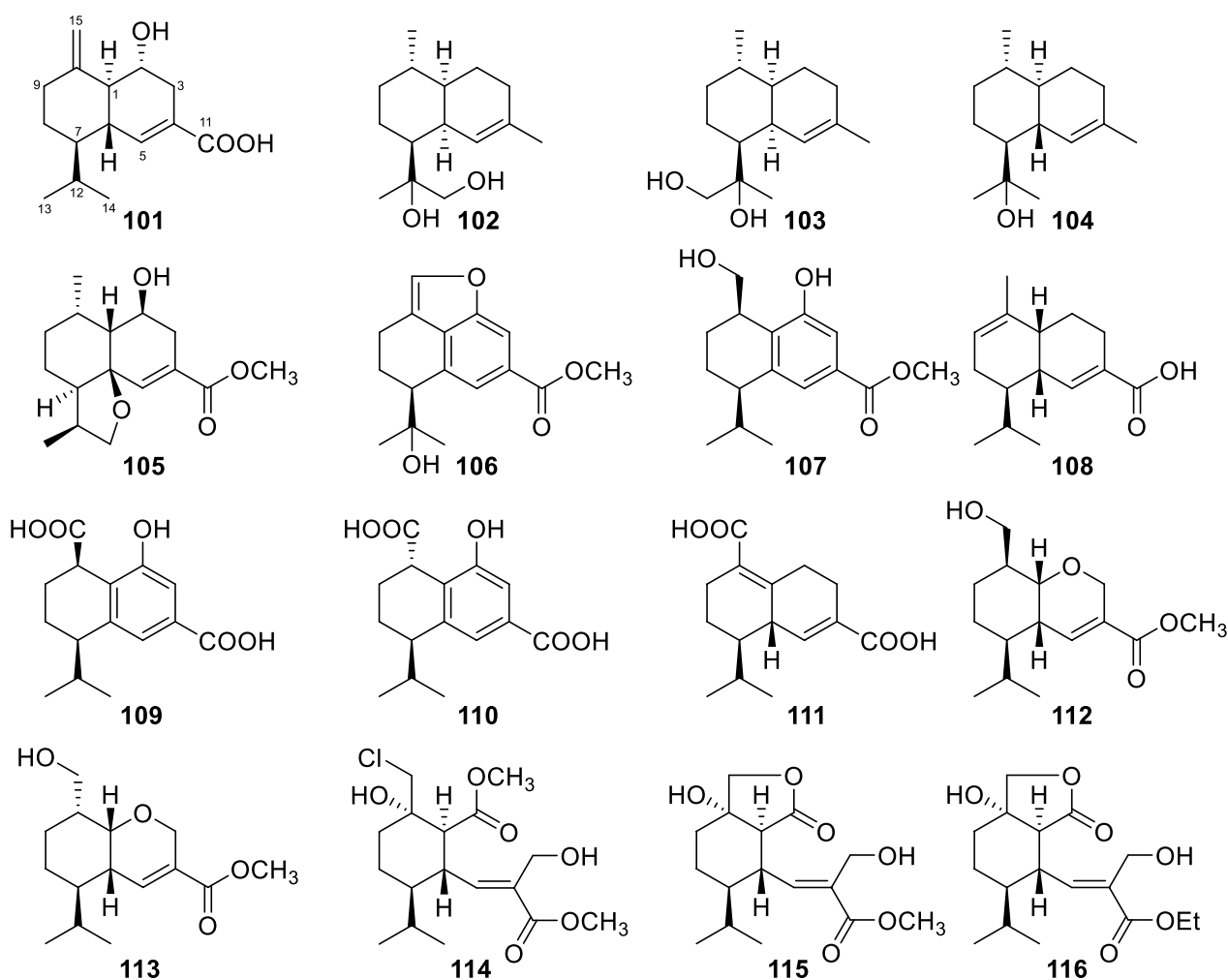
Fig. 13 Cadinane sesquiterpenes and catabolites from marine-derived *Trichoderma*

effect at 258 nm in the ECD spectrum of its dibenzoate. In view of the narrow distribution spectrum, this class of diterpenes may also be potential biomarkers for several *Trichoderma* species.

Besides the above harziane and wickerane, there are also four diterpene skeletons (Fig. 17) occurring in marine-derived *Trichoderma*. Citrinovirin (**162**) with a new norditerpene skeleton and trichocitrin (**163**) with a fusicoccane skeleton were isolated from *T. citrinoviride* [63, 64]. Harzianolic acid A (**164**) with a cleistanthane skeleton and trichosordarin A (**165**) with a 15-nor transformed sordaricin skeleton were obtained from *T. harzianum* [56, 65]. The latter three metabolites (**163**–**165**) are firstly occurring structural types in this genus, and the furan ring in **163**, the chlorine atom in **164**, and the deoxymonosaccharide in **165** greatly enhance their novelty.

2.2 Steroids

Compared to the high number of terpenes, only three new steroidal metabolites (**166**–**168**, Fig. 18) with ergostane and its transformed and degraded skeletons were discovered from marine-derived *Trichoderma* species, including *T. brevicompactum* [37], *T. asperellum* [66], and *T. atroviride* [39]. It is worth mentioning that all these isolates feature high degrees of oxidation, that even results in the broken ergostane scaffolds in **167** and **168**. Considering the structural complexity, the assignments of absolute configurations of **167** and **168** were completed by both ECD and X-ray crystallographic analyses. Unfortunately, no steroidal metabolites of the viridin series have been found in marine-derived *Trichoderma* [20].
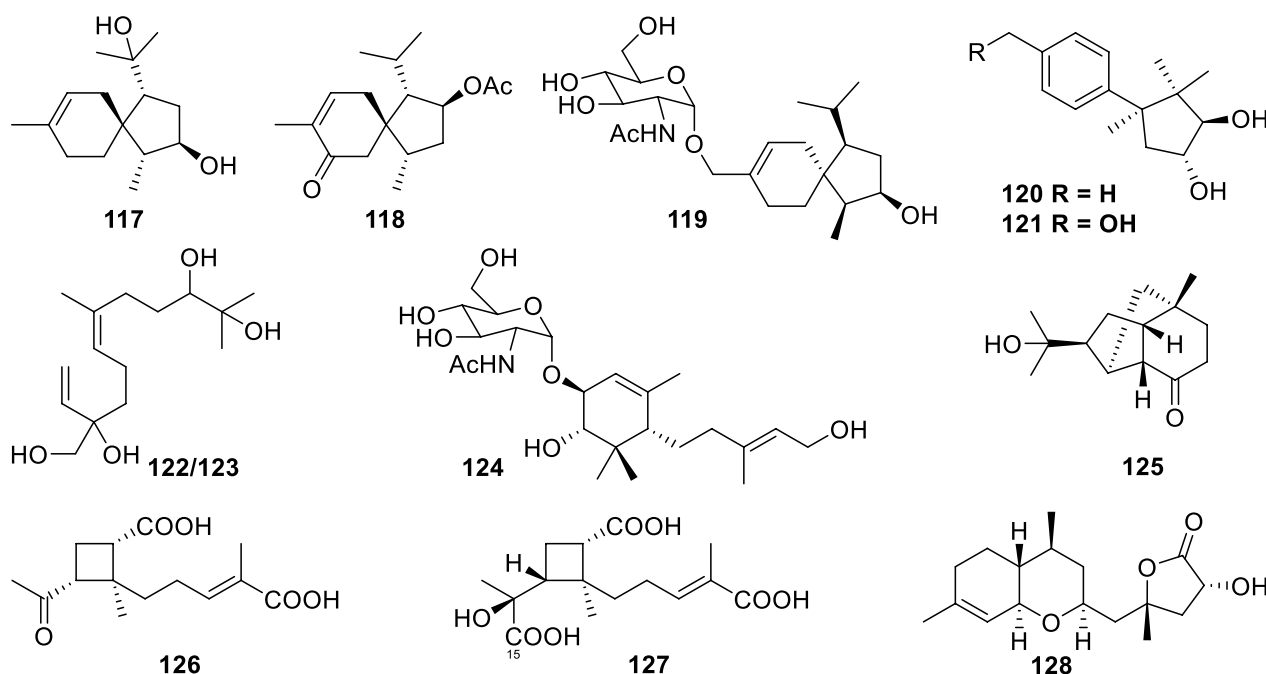
Fig. 14 Other sesquiterpenes from marine-derived *Trichoderma*

2.3 Polyketides

Despite the lower number of new polyketides (**169**–**295**) than that of terpenes, they have more prolific sources. Totally, 14 marine-derived *Trichoderma* species, including *T. asperellum* (2 compounds), *T. atroviride* (6), *T. aureoviride* (2), *T. citrinoviride* (3), *T. erinaceum* (6), *T. harzianum* (27), *T. koningii* (9), *T. longibrachiatum* (3), *T. reesei* (32), *T. saturnisporum* (8), *T. virens* (3), *T. viride* (1), *H. lixii* (1), and *H. vinosa* (2), and nine unidentified strains (22) have the ability to produce polyketides [24, 25, 32, 33, 39, 49, 67–106]. These metabolites can be classified into cyclopentenone, sorbicillinoid, koninginin, decalin, xanthone, anthraquinone, naphthopyrone, and other acyclic and cyclic categories, with several novel skeletons being present.

As shown in Fig. 19, four pairs of C_{13} lipids named harzianumols A-H (**169**–**176**) were isolated from the sponge-associated *T. harzianum* [67]. Each pair of them occurred as an inseparable enantiomeric mixture, and their absolute configurations were identified through the modified Mosher's method. As a possible derivative of lauric acid, oxylipin **177** was discovered from the alga-derived *T. atroviride* [39]. Additionally, two methyl-branched lipids (**178** and **179**) with the same backbone were identified from *T. citrinoviride*, and the latter contains a unique 1,3-dioxolane nucleus [68, 69]. Nafuredin C (**180**) with a δ-lactone unit was obtained from the mangrove-endophytic *T. harzianum*, occurring as the third member of this structural family [70]. An algicolous

T. citrinoviride strain can also yield a member of this type [64], but the producers of nafuredins are not only *Trichoderma* but also *Aspergillus*, *Penicillium*, and *Talaromyces* [146, 147]. *T. harzianum* of sponge origin gave harzia-lactone B (**181**), of which the δ-lactone moiety seems formed through the Baeyer–Villiger oxidation of a cyclopentenone precursor [71].

Cyclopentenone derivatives with 15 members (**182**–**196**, Fig. 20) were discovered from *T. harzianum* [71, 72], *T. asperellum* [25], *T. koningii* [74, 77], *T. atroviride* [75, 76], and two unidentified strains [73, 78]. This class of metabolites are structurally simple, and all of them contain an α,β-unsaturated carbonyl group in the five-membered ring. Seven (**182**–**188**) of the isolates possess only seven carbon atoms, with one olefinic carbon adjacent to the carbonyl group tending to be chlorinated. One more carbon atom is present the nucleic moieties of **189**–**195**, which exist as esters or acids without a chlorine atom at α position of the carbonyl group. The structure of **196** differs from those of the others by the presence of a long side chain and two methyl groups on the cyclopentenone nucleus. The configurational assignments of **182**–**184** were achieved by total syntheses, with the former one being speculated as scalemic enantiomers by consideration of its smaller specific rotation than that of the synthesized one [72]. On the other hand, the conjugated carbonyl group facilitates the stereochemical determination of some chiral members, such as **186**, **187**, and **196**, by ECD data [25, 78]. In spite of the similarity
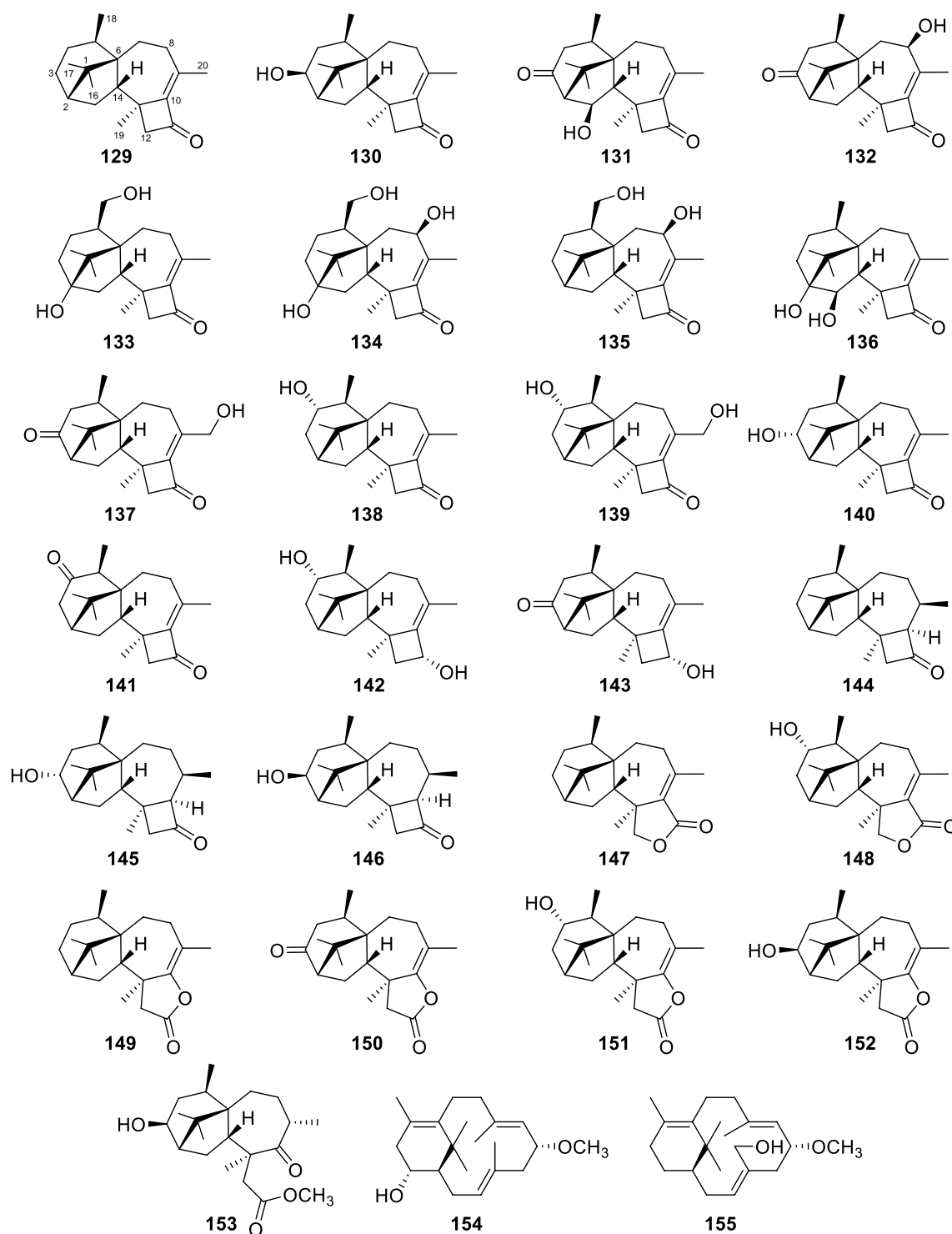
Fig. 15 Harziane, secoharziane, and proharziane diterpenes from marine-derived *Trichoderma*

between cyclopentenones and isonitriles of *Trichoderma* origin, the former should be synthesized through polyketide synthases, but the latter were deduced to be derived from tyrosine [148].

As the largest group of polyketides from marine-derived *Trichoderma*, sorbicillinoids and their derivatives consist of 47 new members. Monomeric sorbicillinoids (**197**–**217**, Fig. 21) from *T. reesei* [81,
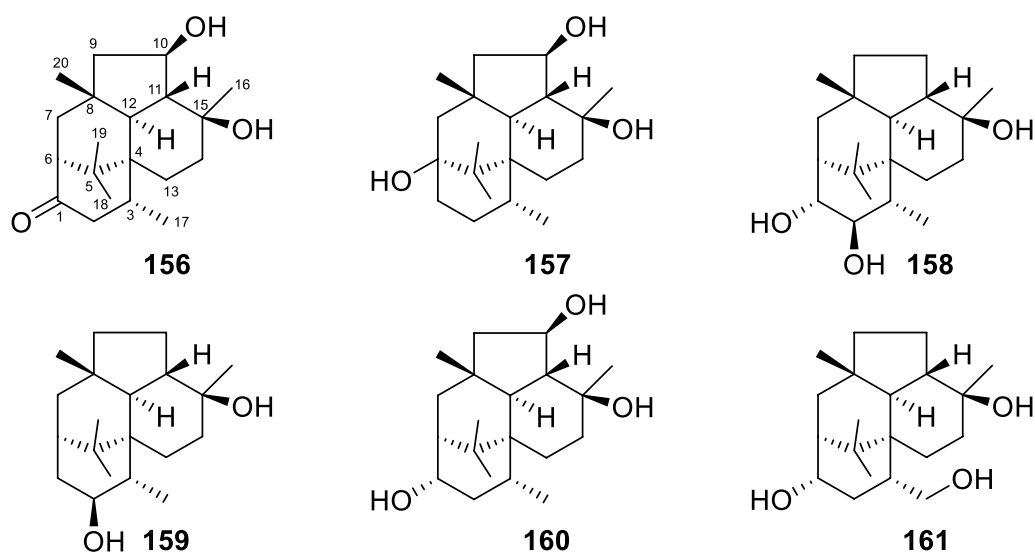
Fig. 16 Wickerane diterpenes from marine-derived *Trichoderma*
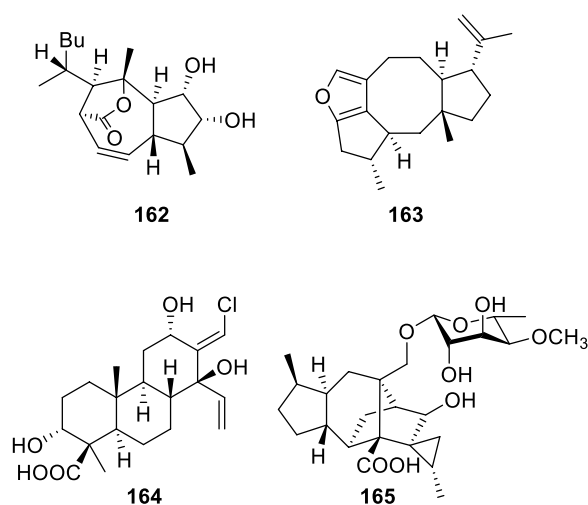
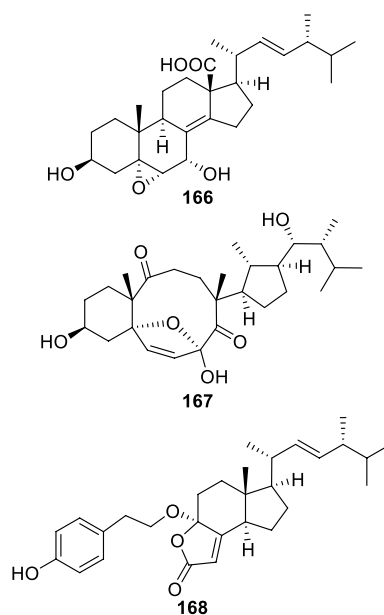**Fig. 17** Other diterpenes from marine-derived *Trichoderma*

Fig. 18 Ergosterol derivatives from marine-derived *Trichoderma*

82], *T. saturnisporum* [84], *T. longibrachiatum* [49, 85], and three unidentified strains [79, 80, 83] are the most primitive representatives, and the majority of them are constructed with a phenyl core substituted by a sorbyl-derived acyclic or epoxy side chain and one or two methyl groups. Methylation happens at C-3 and/or C-5 before cyclization of the hexaketide chain by the Claisen reaction [149], and hydroxylation commonly occurs at C-2 and/or C-4. However, the C-5 position of **206** is also bonded to a hydroxy group, rather than a methyl group. **202**, **209**, **210**, and **214** harbor nonstandard sorbyl chains, possibly arising from the length change in original polyketide chains or oxidation scission of C_6 units.

Based on biogenetic considerations, saturnispol E (**216**) and epoxysorbicillinol (**217**) with a cyclohexene core are possible deoxy and epoxy derivatives of the tautomeric intermediates of sorbicillin, while (-)-trichodermatone (**215**) is a regioisomer of sorbicillinol [149]. In addition, 12 dimeric sorbicillinoids (**218**–**229**, Fig. 22), also called bisorbicillinoids, were obtained from *T. reesei* [81, 82, 86], *T. saturnisporum* [84], and one unidentified strain [79]. All the isolates are heterogeneous dimers, and their skeletal dimerization happens between C-3 of one
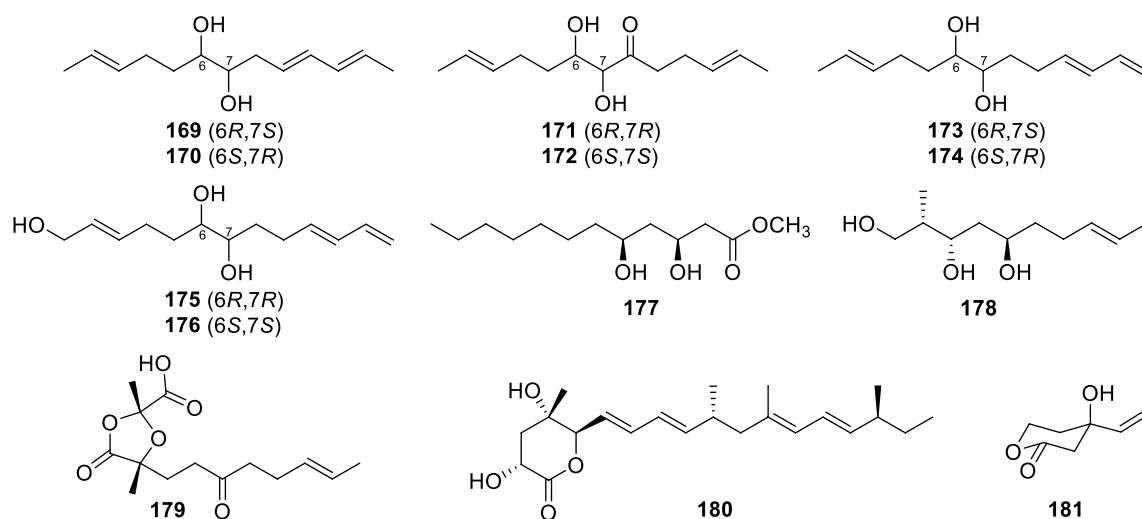
Fig. 19 Acyclic polyketides and lactones from marine-derived *Trichoderma*
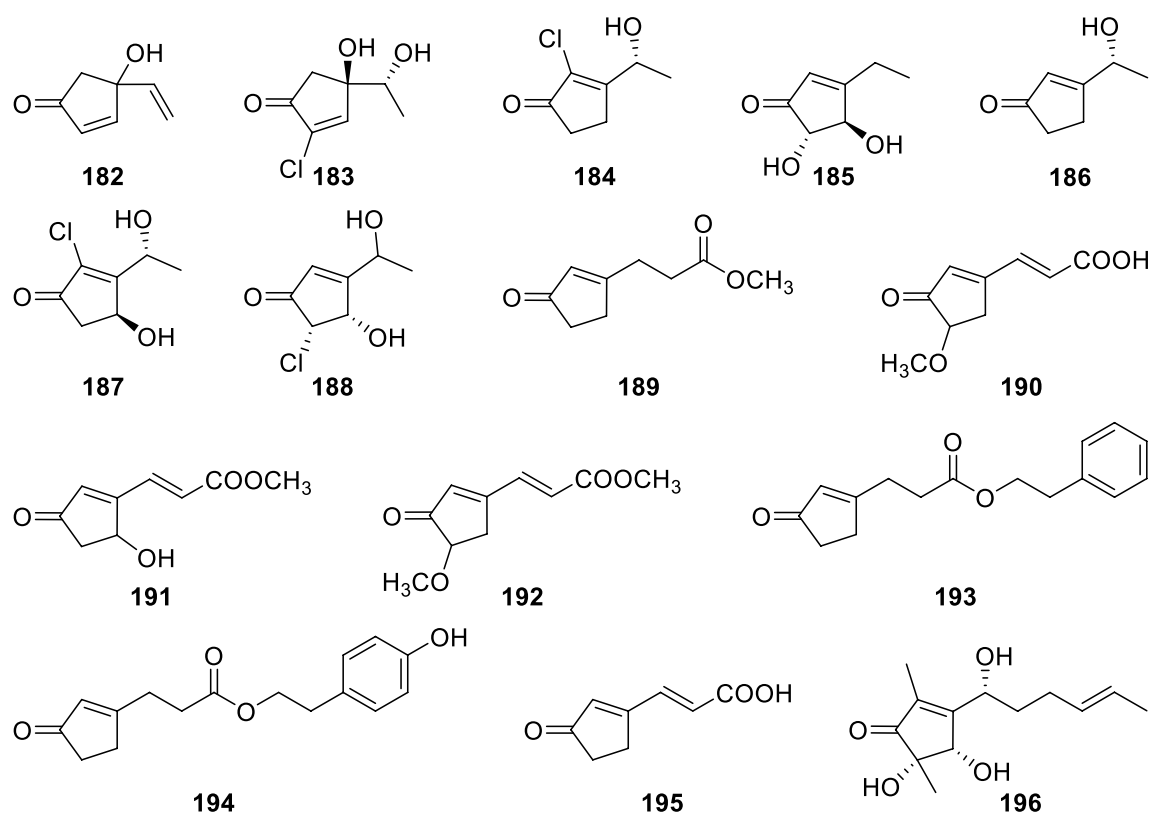

Fig. 20 Cyclopentenone derivatives from marine-derived *Trichoderma*

monomer and C-6 of the other. Their structures appear more complicated, especially the unique cage-like core in **218** and **219**. These dimers were proposed to be constructed through intermolecular single or double Michael reaction/ketalization, with sorbicillinol or its analogs serving as key intermediates [150]. Apart from the above monomers and dimers, there are also 14 other sorbicillinoid derivatives (**230–243**, Fig. 23) from marine-derived *T. saturnisporum* [84], *T. reesei* [82, 86], and two unidentified strains [83, 87]. 2,3-Dihydro 2-hydroxy vertinolide
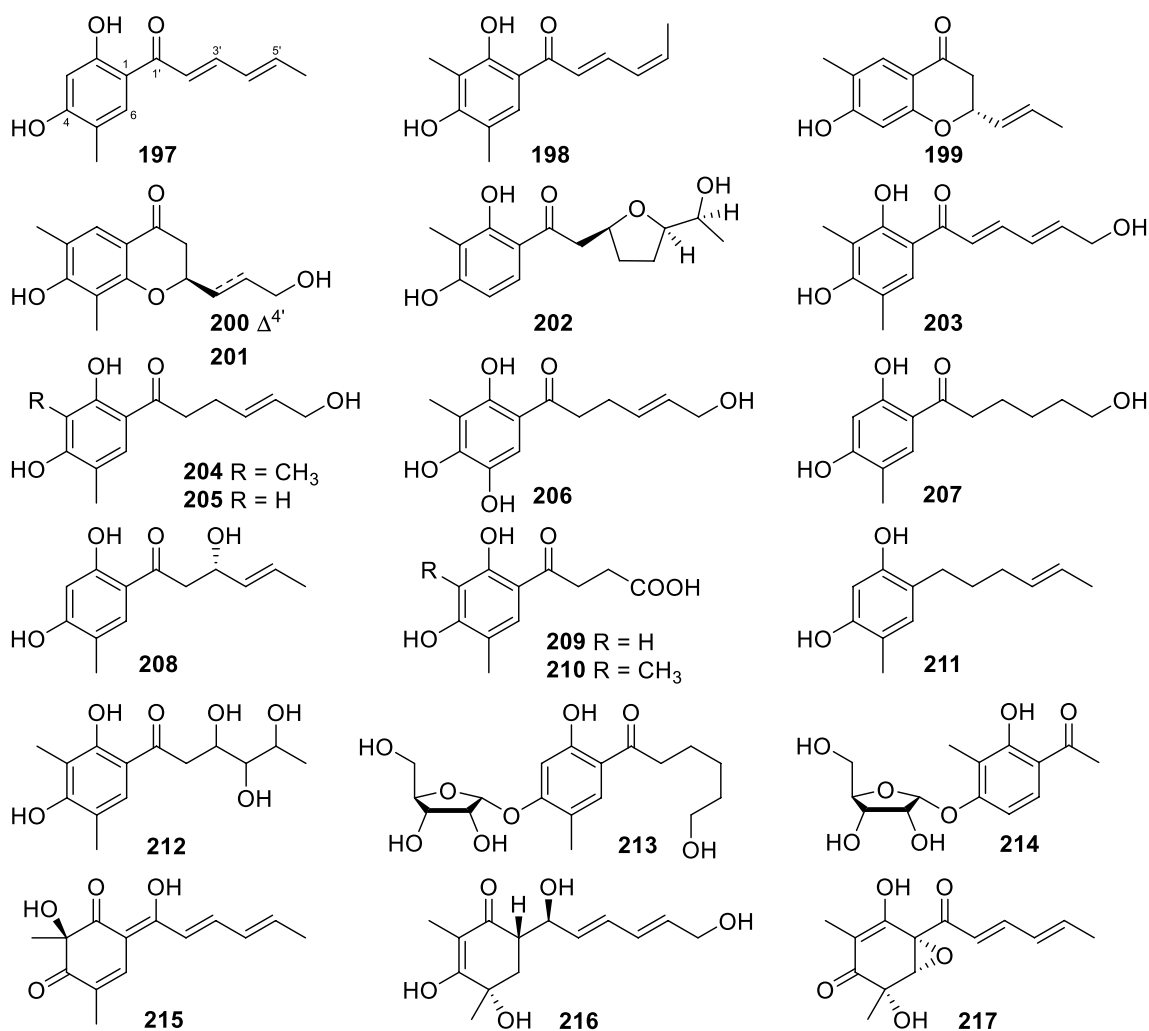
Fig. 21 Monomeric sorbicillinoids from marine-derived *Trichoderma*

(**230**) and saturnispol F (**231**) belong to the vertinolide subfamily, with the lactone unit being probably formed via intramolecular esterification and ring cleavage sequences. Saturnispols C (**232**) and D (**233**) feature a bicyclo[2.2.2]octanedione motif that arises from a Diels–Alder [4+2] cycloaddition between the corresponding sorbicillinoid monomer and phenylethylene. Based on the same mechanism, the formation of each trichodermanones A-D (**234**–**237**) appears rationalized by reaction between sorbicillinol and a dienophile. The last six members (**238**–**243**) differ greatly from the others, due to the presence of a methylene group between the sorbyl chains and the six-membered ring. Moreover, a naphthalene ring is present in **238** and **239**, and a bicycle [3.2.1] lactone unit appears in **240**–**243**. During the identification of chiral isolates, ECD spectra were widely used to confirm their absolute configurations, and X-ray diffraction was also used for several members, such as **200, 202,**

206, and **214**. A total synthesis of (±)-epoxysorbicillinol was fulfilled from commercial diethyl methylmalonate in 13 steps, simultaneously permitting epoxidation and avoiding aromatization [151]. A conversion from sorbicillin to (±)-epoxysorbicillinol was also achieved via the formation of a *p*-quinol intermediate by an oxidative dearomatization [152]. To date, the number of sorbicillinoid members exceeds 130, and they have been discovered from no less than 10 genera of ascomycetes [86, 153]. It is interesting that all the known marine-derived *Trichoderma* species that produce sorbicillinoids belong to the Longibrachiatum clade [154].

As a family of octaketides, koninginins with a narrow distribution are also the representative metabolites from *Trichoderma*. To date, 12 new members (**244**–**255**, Fig. 24) have been isolated from marine-derived *T. reesei* [89], *T. koningii* [91], *H. lixii* [90], and one unidentified strain [92]. The first koninginin, named
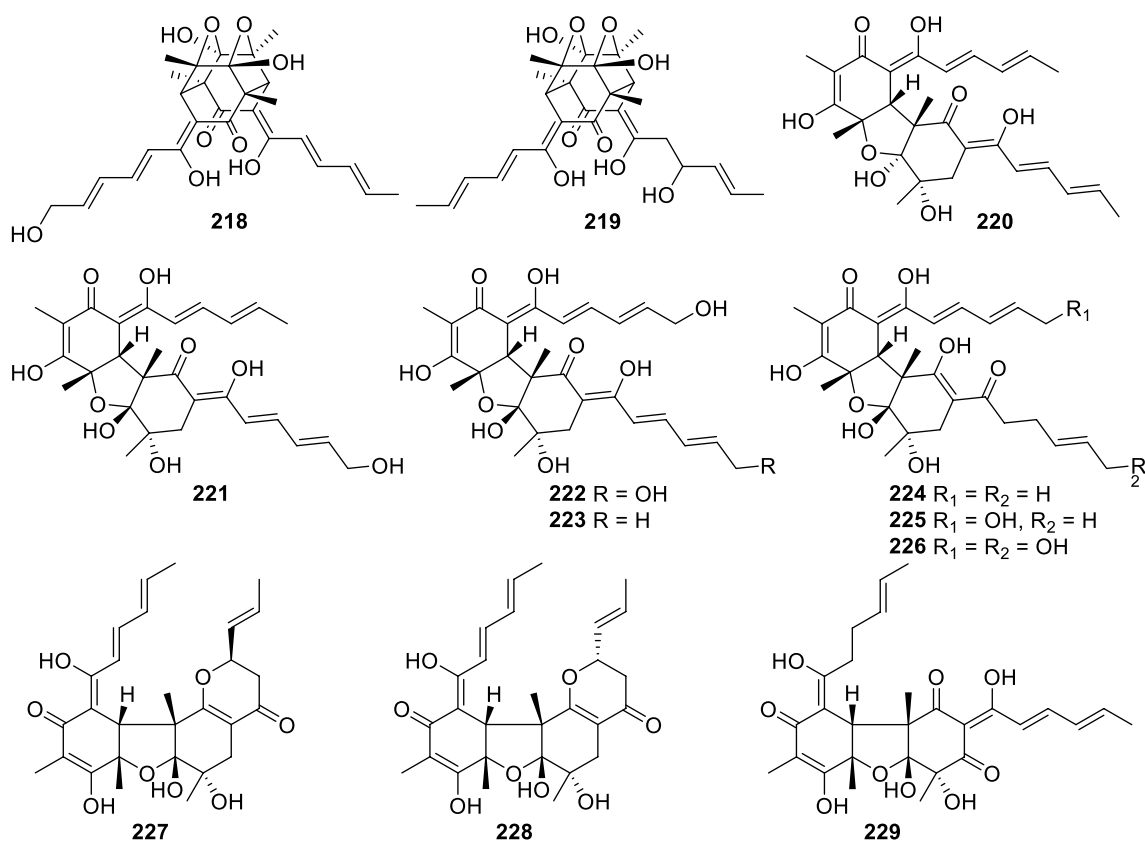
Fig. 22 Dimeric sorbicillinoids from marine-derived *Trichoderma*

koninginin A, was obtained from *T. koningii* in 1989 [20], and it defined the typical koninginin skeleton that contains a benzopyran nucleus and a heptyl side chain. This skeleton is present in **245**–**249**, especially a highly unsaturated chromone motif in **248**. In **244**, a second cyclohexene ring is incorporated into this basic structure, forming an unprecedented pentacyclic framework with a ketalic and a hemiketalic carbon. Starting from L-tartaric acid, a synthetic route for this complicated molecule, that harbors eight chiral carbons, was developed in a stereocontrolled manner [155]. Instead of the pyran ring, one or two furan rings exist in **250**–**255**. The former two are unprecedented due to the presence of a ditetrahydrofuran-bearing tricyclic skeleton. Although ECD spectra were applied to confirming the absolute configurations for most of the isolates [89, 91, 92], the relative configurations between the chiral carbon in cyclohexene ring and that in pyran or furan ring failed to be given in some structures due to the lack of any NOE correlation. Chemical syntheses suggested that epimeric pairs possess very similar spectroscopic data, which also make it difficult to distinguish their relative configurations by comparison of spectroscopic data [156].

Decalin derivatives, such as trichosetin and compactin, were previously detected in several *Trichoderma* species [20]. Marine-derived *T. harzianum* along with an unidentified strain gave another type of decalin derivatives (**256**–**268**, Fig. 25), with a C_3 and a C_4 side chain as well as two methyl groups [24, 93–98]. The bicyclic nucleus is a *trans*-fused ring system, with a double bond at C-6. Acylation of hydroxy groups on the decalin core and the C_3 side chain contributes to the structural diversity of this octaketide type, especially the formation of the dimer **266**. Except for trichoharzianin (**256**), the acyl groups are confined to (*Z*)- and (*E*)-3-methylpent-2-enedioic acid (3-methylglutaconic acid) and their monoesters, which are presumed to arise from mevalonic acid [24]. A tyrosol residue that can be converted from tyrosine exists in **265** [157], similar to **168** and **194**. The absolute configurations of most members were assigned by chemical conversion, including alkali-hydrolysis to yield triols or further acylation to furnish tribenzoates. Dimolybdenum tetraacetate $[Mo_2(OAc)_4]$ was used to form complexes with the *cis* vic-diol group in hydrolysates of **257**–**259**, and analyses of their ECD spectra resulted in determination of the absolute configurations. Analogs with the same or similar alkylated decalin skeletons were also
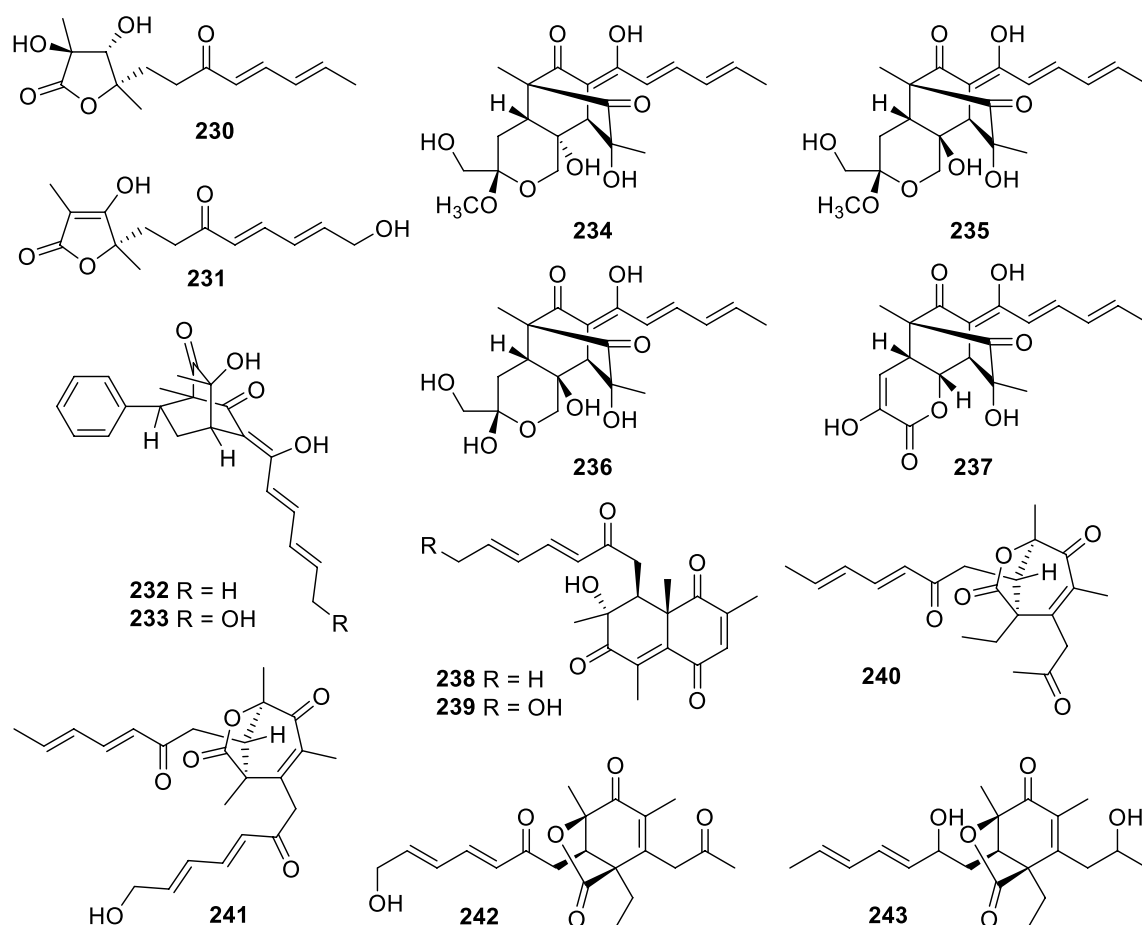
Fig. 23 Other sorbicillinoid derivatives from marine-derived *Trichoderma*

identified from other fungal species of the genera *Eupenicillium*, *Fusarium*, *Geomyces*, *Phoma*, *Spopormiella*, and *Stemphylium* [95, 96], but the 3-methylglutaconate units were rarely encountered therein.

Xanthone, anthraquinone, and naphthopyrone derivatives have been discovered from multifarious plants and/or fungi [158, 159], but their distribution in *Trichoderma* is not much attractive. Only nine new members (**269**–**277**, Fig. 26) were obtained from marine-derived *Trichoderma*, including *T. aureoviride* [99], *T. harzianum* [100], *H. vinosa* [102], and one unidentified strain [101]. Trichodermaxanthone (**269**) contains a typical xanthone skeleton, which rarely occurs in the metabolites of this genus. Octaketides **270**–**273** possess a basic anthraquinone scaffold, but one of the two carbonyl functionalities is reduced to a hydroxy group in epimers **271** and **272**. Considering the similarity between **274** and **275**, they possibly arise from the same heptaketide intermediate. Hypochromins A (**276**) and B (**277**) have a dimeric naphtho-γ-pyrone framework, which are present in a broad spectrum of ascomycetous producers [160]. There

is one or more chiral centers in **271**, **272**, and **275**, of which the configurations were determined by interpretation of ECD spectra. A crystallographic analysis further confirmed the absolute configuration of **271**. In addition, **276** and **277** with atropisomerism are axially chiral molecules, and the single bond between the two monomers was assigned as *S*-configuration by the exciton chirality method. These highly unsaturated isolates exhibit yellow or red colors, which may be taken as pigments by their producers.

In addition to the above sorbicillinoid, xanthone, anthraquinone, and naphthopyrone derivatives, a few other aromatic polyketides (**278**–**295**, Fig. 27) with one or two benzene, furan, and/or pyran rings have been isolated from marine-derived *Trochoderma*. Trichorenins A-C (**278**–**280**) from *T. virens* harbor a 5/5/6/5-fused ring system, probably arising from the cyclization of an octaketide intermediate [103]. This tetracyclic scaffold had been reported previously, but it is contained in a diterpene with five methyl groups formed through a mevalonate pathway [161]. These two skeletons with
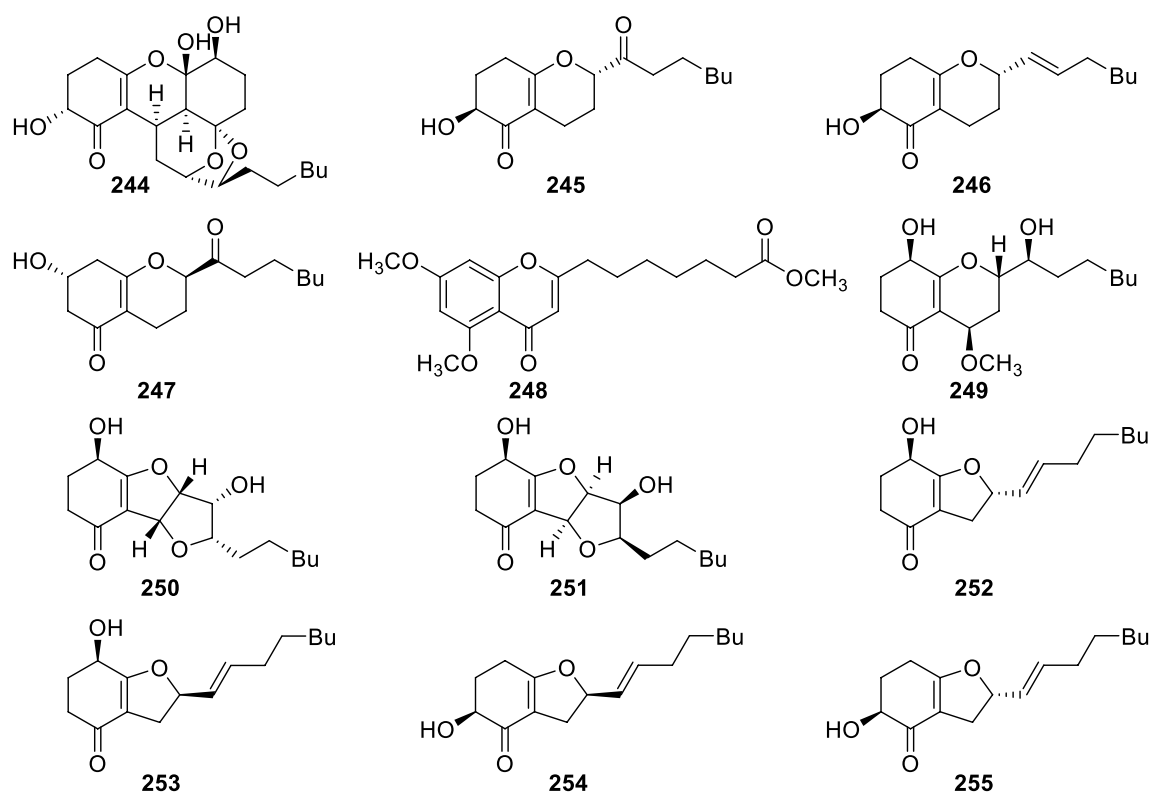
Fig. 24 Koninginins and their derivatives from marine-derived *Trichoderma*

the same ring system were guaranteed by single-crystal X-ray diffraction analysis, respectively [103, 161]. The structure of harzialactone A (**281**) with a benzylfuran motif from *T. harzianum* is shared in **282**–**286** from *T. atroviride* and *T. erinaceum* [32, 71, 104, 105]. Except for **282**, these analogous metabolites adopt the same 2*R* and 4*R* configurations. As established by the modified Mosher's method, the original 2*S* and 4*S* configurations of **281** were corrected by synthesis from monoacetone-D-glucose via a regioselective oxidation [104]. Later on, this compound and its stereo isomers were further synthesized from simple benzene derivatives through several other stereoselectively chemical and enzymatic routes [162–164]. The absolute configurations of **283**–**286** were assigned by comparison of experimental and calculated specific optical rotation data [32]. It is worth mentioning that polyketides of this series have been found not only in *Trichoderma* but also in *Aspergillus* [71]. Two diphenyl ethers, including a symmetrical (**287**) and an asymmetrical derivative (**288**), were identified from *T. erinaceum* [32]. This class of metabolites have been detected in various fungal genera, especially in *Aspergillus* and *Penicillium* [165, 166], and they were proposed to be formed through polyketide pathways by analysis of the biosynthetic gene cluster [167]. As a metabolite of

T. citrinoviride, trichophenol A (**289**) is the only 3-phenylisocoumarin member from this genus [33]. Its structure appears similar to flavonoids, and the isocoumarin nucleus is also present in azaphilones of *Trichoderma* origin [20]. A chromone unit exists in **290** and **291**, which were isolated from an unidentified *Trichoderma* strain of hydrothermal vent sediment origin [94]. They are structurally similar to **248**, but their substitution patterns and side chain lengths appear different. Four simple α-pyrone derivatives, named trichoharzianone (**292**), trichopyrone (**293**), and saturnispols G (**294**) and H (**295**), were obtained from *T. harzianum*, *T. viride*, and *T. saturnisporum* [84, 93, 106]. The latter two were postulated to be yielded by elimination of a C_3 fragment from the precursor sorbicillinol, followed by a lactonization reaction [84].

2.4 Peptides

Comprising 131 new members (**296**–**426**), peptides are the second largest family of metabolites from marine-derived *Trichoderma*. They were identified from seven *Trichoderma* species, including *T. asperellum* (42 compounds), *T. atroviride* (41), *T. harzianum* (1), *T. longibrachiatum* (32), *T. orientale* (1), *T. reesei* (1), *T. virens* (4), and two unidentified strains (9) [25, 35, 41, 70, 107–124]. Their structural types involve cyclic and linear peptides,
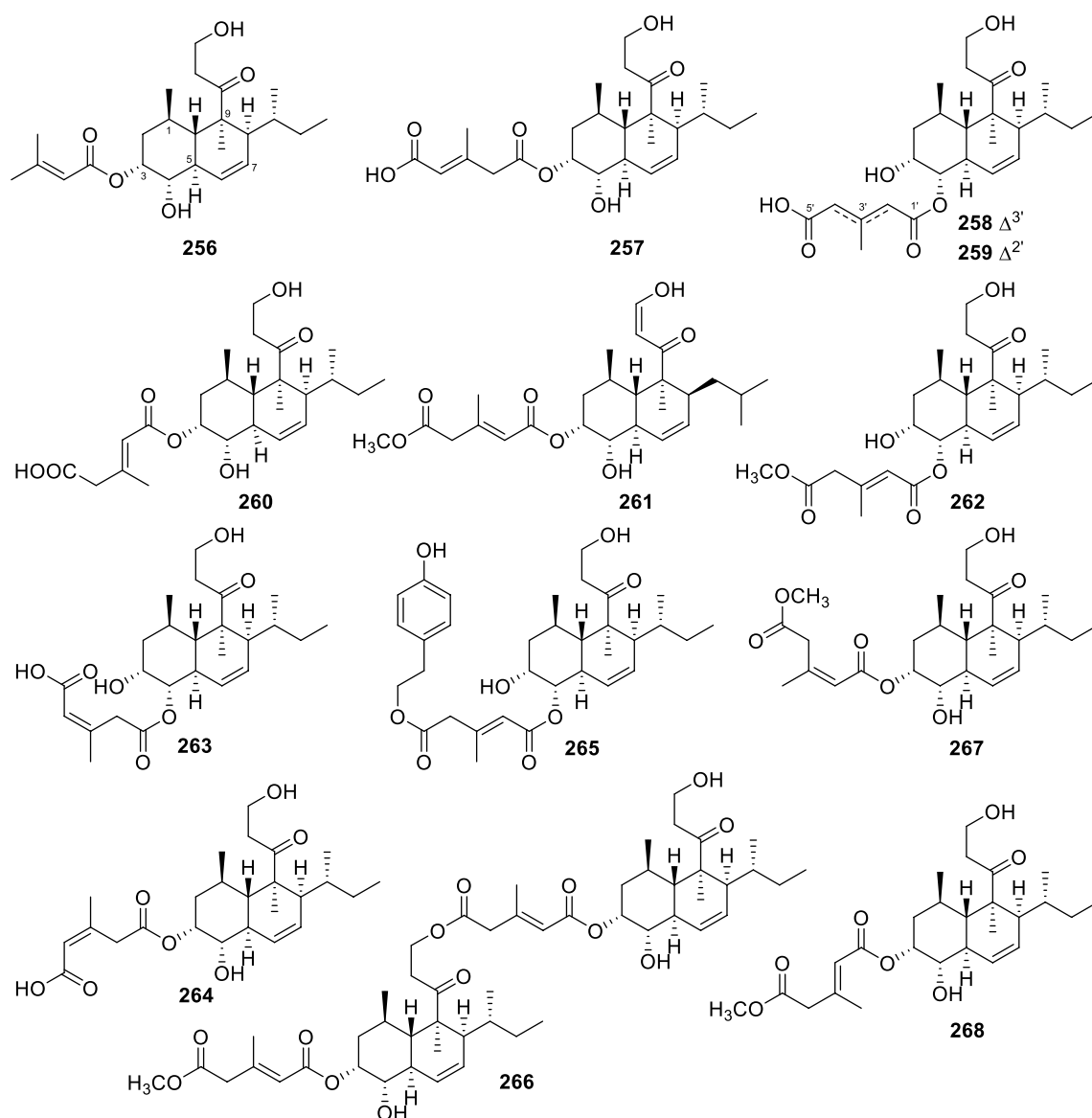
Fig. 25 Decalin derivatives from marine-derived *Trichoderma*

with the latter being composed of dipeptides, aminolipopeptides, peptaibols, and other peptaibiotics.

Cyclopeptides contain 10 diketopiperazines and one cyclotetrapeptide (**296–306**, Fig. 28), discovered from *T. asperellum* [25, 35], *T. virens* [109], *T. atroviride* [110], *T. reesei* [111], and one unidentified strain [41, 107, 108]. Among them, seven diketopiperazines (**296–302**) contain sulfur atoms, especially a disulfide bridge in **296–298** and a trisulfide bridge in **299** and **300**. One of the two modified amino acid residues is substituted by a bromine, an iodine, and a chlorine atom in **296, 297**, and **300**, respectively, and these halogenated moieties also feature a rarely occurring 1,2-oxazine ring. During the structure

elucidation of **301** and **302**, the ^{1}H and ^{13}C NMR signals of thiomethyl groups were found to resonate at δ_H 1.67–2.45 and δ_C 12.7–18.0, differing greatly from those of oxygen- and nitrogen-bearing methyl groups. ECD spectra played an important role in determining absolute configurations for these sulfides. Three other diketopiperazines (**303–305**) possess at least one modified amino acid residue, and the symmetrical member (**304**) was assigned the absolute configuration by X-ray diffraction. Trichoderide A (**306**) represents the only cyclotetrapeptide from marine-derived *Trichoderma*, and all the amino acid residues were determined to feature *R*-configuration on the basis of acid hydrolysis followed by chiral HPLC
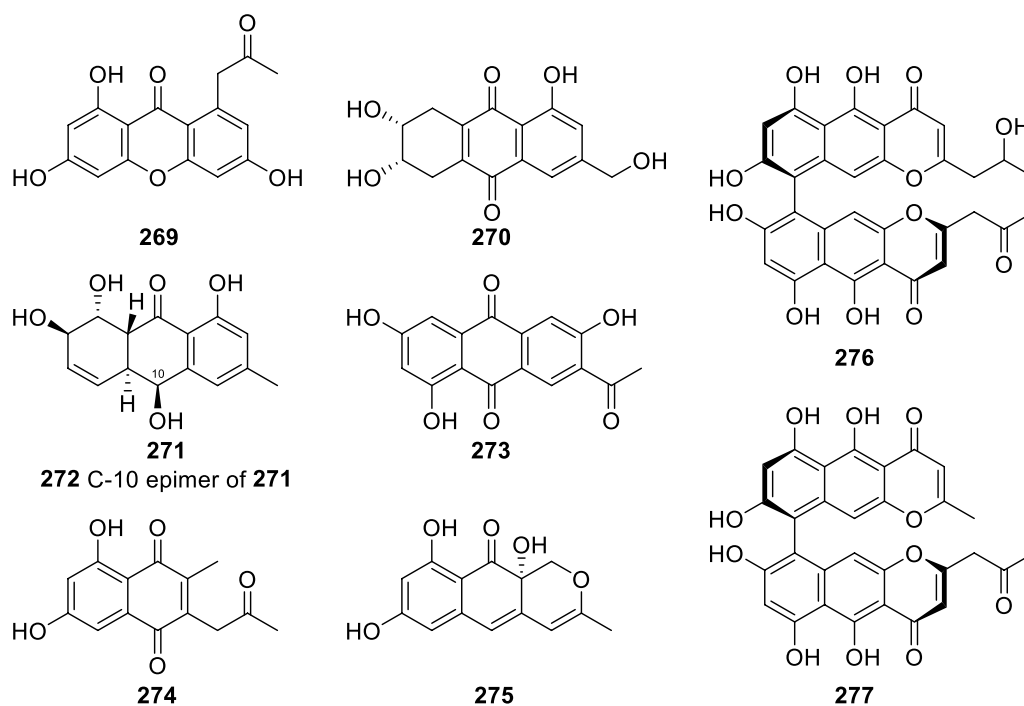
Fig. 26 Xanthone, anthraquinone, and naphthopyrone derivatives from marine-derived *Trichoderma*

analysis. In spite of the difference in ring sizes, both **305** and **306** have ornithine and succinic acid residues.

Four linear dipeptides (**307**–**310**, Fig. 29) were obtained from *T. virens* and *T. harzianum* as well as an unidentified strain [70, 112, 113]. Despite the different sources, these isolates exhibit high structural similarities. Besides the 1,2-oxazine ring that exists in diketopiperazines **296**–**300**, a coumarin motif substituted by two methoxy groups is also present in these four metabolites. The connectivity of oxazine and α-pyrone functionalities in **307** was confirmed by X-ray diffraction analysis. The difference between **307** and **308** is the replacement of a hydroxy group in the former by a chlorine atom in the latter. The chemical total syntheses of **307** and **308** as well as their analogs were achieved by at least three groups, and their focus was the construction of the oxazadecalin core [168–172]. Trichodermamide G (**309**) and dithioaspergillazine A (**310**) also feature a sulfide bridge with one or two sulfur atoms, respectively, located in only one amino acid residue. These two sulfides were assigned absolute configurations by analysis of their ECD spectra aided by quantum chemical calculations. A series of dipeptides with the same or similar structures have also been discovered from other fungal genera, such as *Aspergillus*, *Penicillium*, and *Spicaria* [173–175].

Marine-derived *Trichoderma* species have contributed a large number of linear polypeptides (**311**–**426**, Figs. 30, 31, 32, 33, 34) with 9 to 20 amino acid

residues, accounting for ca. 10% of all the *Trichoderma*-derived peptaibiotics (over 1000) [176, 177]. In view of the definitions given in literature [178], all of them can be sorted into aminolipopeptides, peptaibols, and other peptaibiotics, characterized by high contents of α-aminoisobutyric acid (Aib) and acylated N-termini. In the aminolipopeptide subfamily, there are only three members (**311**–**313**), arising from an unidentified *Trichoderma* strain [114]. Besides four Aibs, the non-proteinogenic 2-methyl decanoic acid, 2-amino-6-hydroxy-4-methyl-8-oxodecanoic acid (AHMOD), and 2-[(2′-aminopropyl) methylamino] ethanol residues are present in all the three isolates. These chiral units in **311** were assigned the absolute configurations by total synthesis [115]. Besides an α-methyl-branched fatty acid, the linkage between proline and a lipoamino acid residue at N-terminus conforms to the standard of this type. In the peptaibol subfamily, a total of 83 members (**314**–**350** and **352**–**397**) with 9, 10, 11, 19, and 20 residues were identified from four marine-derived *Trichoderma* species, including *T. asperellum* [116–118], *T. longibrachiatum* [119, 120, 123], *T. atroviride* [121, 122], and *T. orientale* [124]. Each member contains a β-amino alcohol or its acetate at C-terminus, derived from the reduction of the corresponding amino acid precursor [121]. The identification of **314**–**321** and **386**–**393** was performed by analysis of the NMR and mass spectroscopic data of pure compounds, and
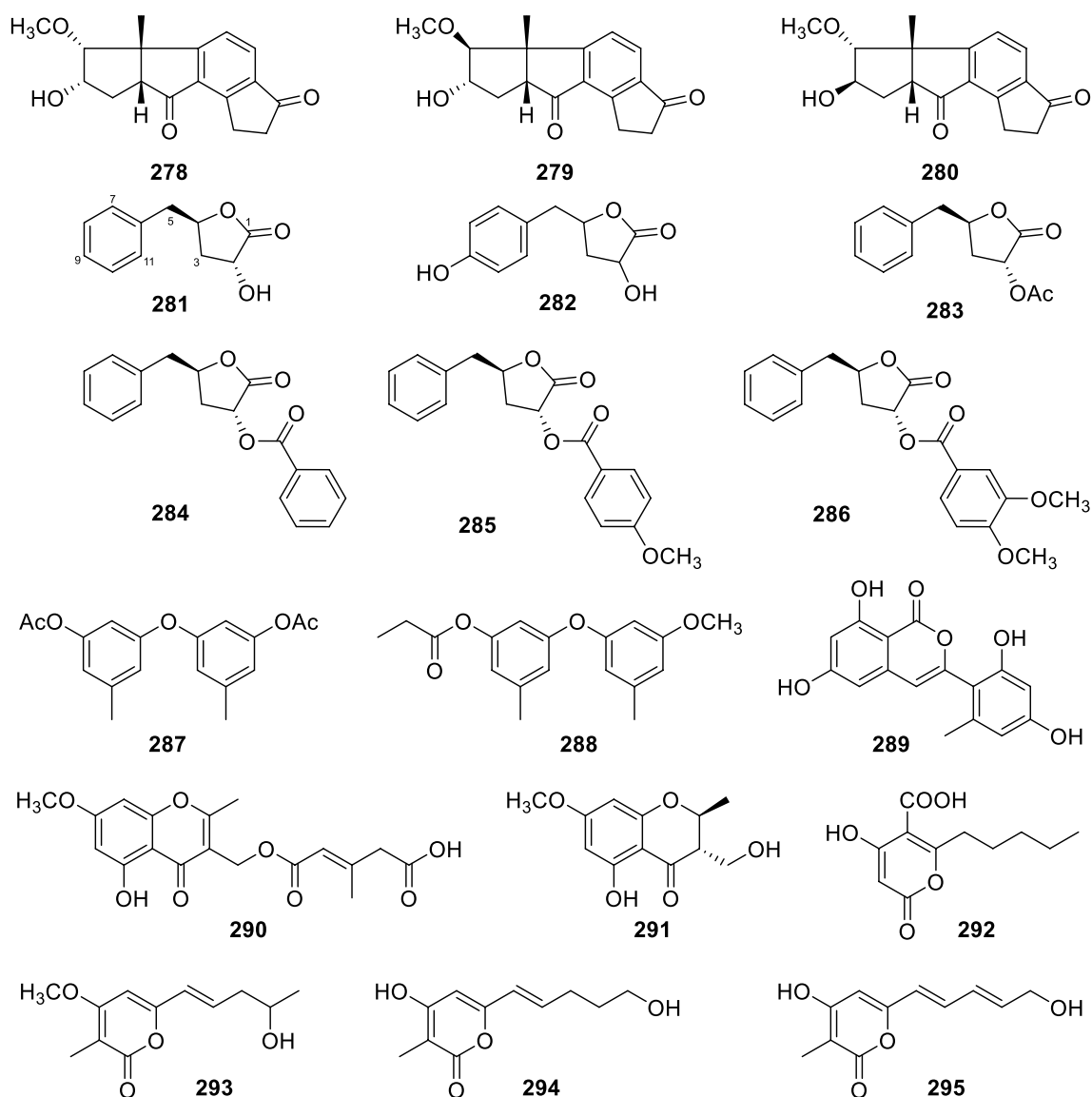
Fig. 27 Other aromatic polyketides from marine-derived *Trichoderma*

X-ray diffraction was used to determine the structure and relative configuration of **317**. Their absolute configurations were confirmed by acid hydrolysis followed by derivation with Ru(D₄-Por*)CO or Marfey's reagent [116, 117, 122]. Other peptaibol isolates were mainly identified by interpretation of mass spectra given by various techniques, such as ultrahigh pressure liquid chromatography/electrospray ionization tandem mass spectrometry (UHPLC/ESI–MS/MS) [118], electrospray ionization ion-trap mass spectrometry (ESI-IT-MS) [119–121, 123, 124], collision-induced dissociation mass spectrometry (CID-MS) [120], and gas chromatography/electron impact mass spectrometry (GC/

EI-MS) [119, 120, 123]. Although **351** from *T. asperellum* was claimed as a peptaibol in literature, it should belong to the peptaibiotic subfamily due to the lack of an amino alcohol at C-terminus [118]. Additionally, 29 unprecedented peptaibiotics (**398–426**) with 17 amino acid residues were identified from *T. atroviride* [121]. In addition to nine constant amino acid residues, a peculiar residue with a mass of 129 Da appears at C-terminus of these peptaibiotics. Unfortunately, the differentiation between some amino acid residues and their isomers, such as leucine/isoleucine, valine/isovaline, leucinol/isoleucinol, and valinol/isovalinol, remains not completed in many peptaibols and other

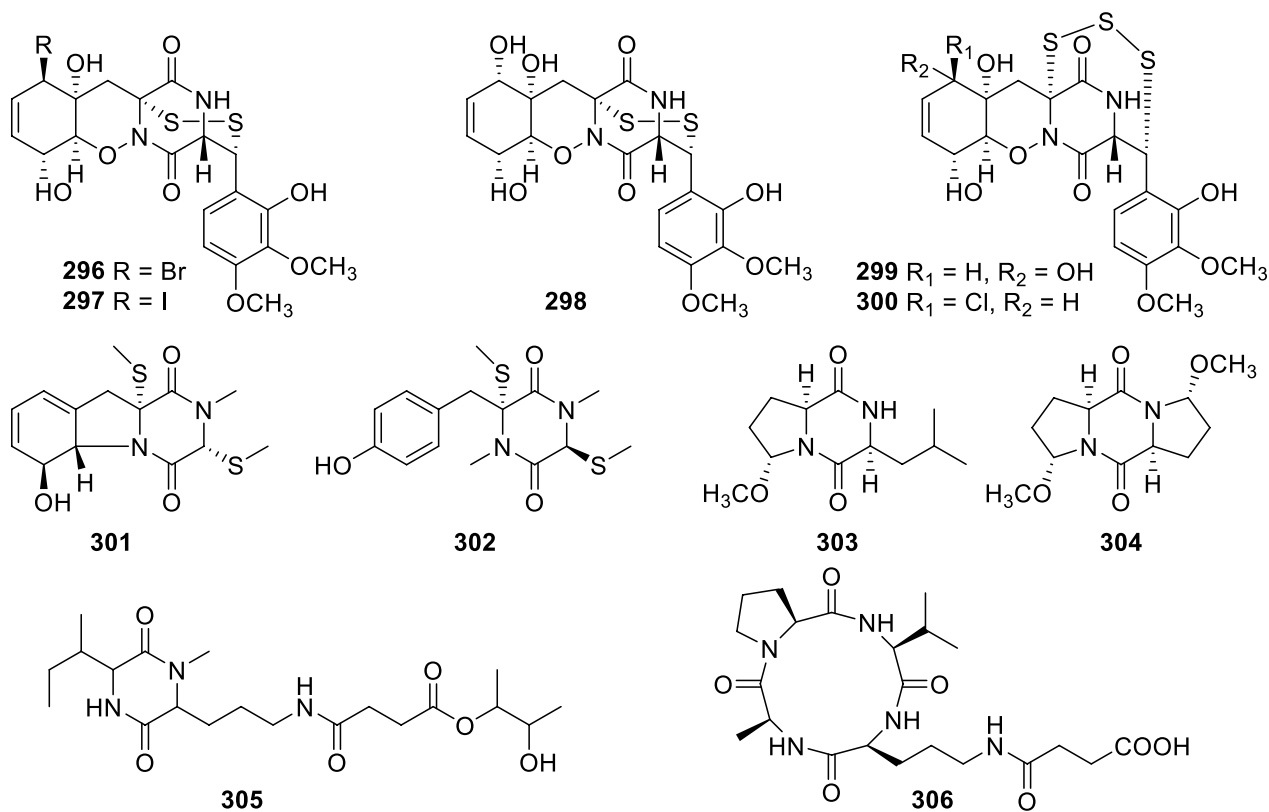**Fig. 28** Cyclopeptides including diketopiperazines from marine-derived *Trichoderma*
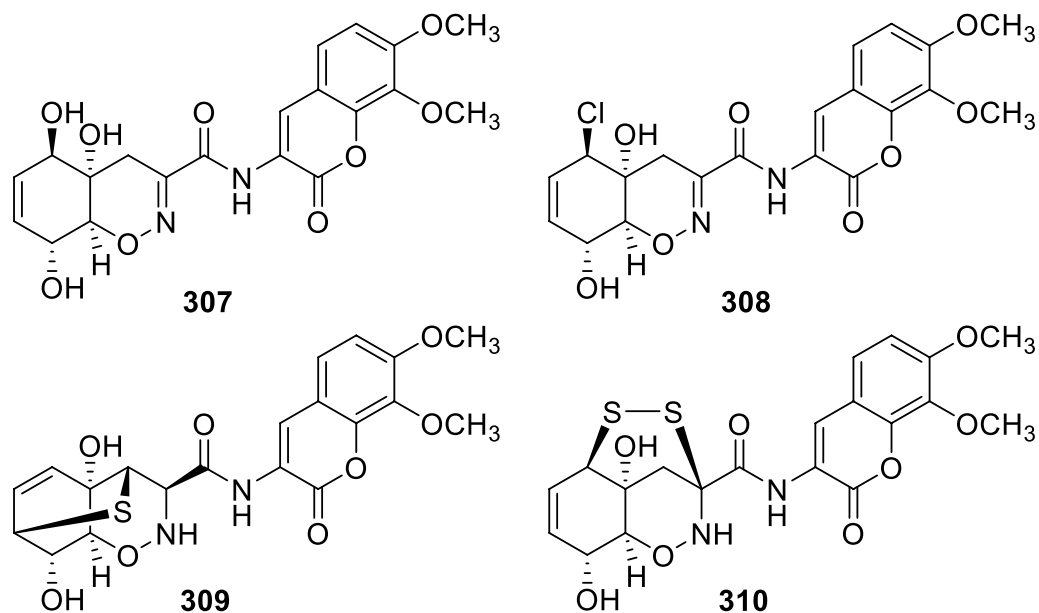

Fig. 29 Dipeptides from marine-derived *Trichoderma*

peptaibiotics. Natural peptaibiotics have been found in some 30 known genera of fungi [121], especially in mycoparasitic ones of the Hypocreales [177].

2.5 Alkaloids

Except for 17 nitrogen-bearing terpenes and 131 peptides, there are also 14 other nitrogenous metabolites
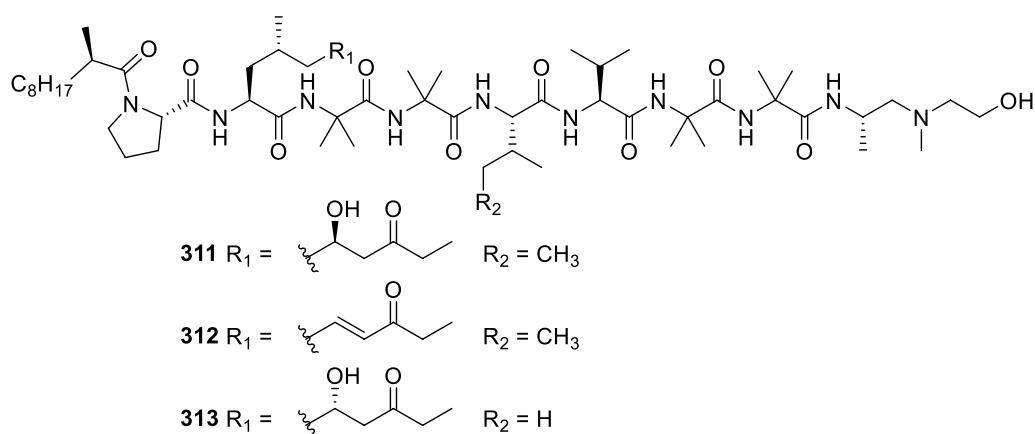
Fig. 30 Aminolipopeptides from marine-derived *Trichoderma*

(**427–440**, Fig. 35) from *T. asperellum* (1 compound) [25], *T. atroviride* (2) [105, 110], *T. citrinoviride* (2) [128], *T. harzianum* (1) [98], *T. reesei* (1) [81], *T. virens* (1) [127], and five unidentified strains (6) [125, 126]. An unidentified *Trichoderma* strain of deep sea origin (-3300 m) afforded β-carboline alkaloids **427–430**, with the latter two being synthesized previously. The absolute configurations of **427**, **429**, and **430** were determined by comparison of experimental and calculated specific optical rotation data. Trichodins A (**431**) and B (**432**) harbor an α-pyridone ring fused with a monoterpene unit. Regardless of the stereochemistry, these two alkaloids seem formed by reaction of deoxy-PF1140 with phenol and ribosylated phenol, respectively [179]. A quinoline motif substituted by both chlorine and bromine atoms exists in the new natural product **433**, and an imidazo[1,5-*b*]isoquinolone tricyclic system is present in **434**. As a naturally occurring compound, 4-oxazolepropanoic acid (**435**) features an oxazole ring, that has also been found in other metabolites of *Trichoderma* origin [20]. Seven members, including **436–442**, contain one or more pyrrole rings. The pyrrolidin-2-one unit in **437** is possibly incorporated into a sorbicillinoid precursor by a Diels–Alder reaction, and this class of molecules are not rich in nature [81]. Tetramic acids that possess a 2,4-pyrrolidinedione ring are widespread in terrestrial and marine organisms [180], but only two members (**438** and **439**) with the similar scaffold have been discovered from a marine-derived *Trichoderma* species. One C_3 and three C_4 units construct the acyclic **440**, which partially resembles diketopiperazine **305** of the same origin. In general, most of the heterocyclic units have been reported in other *Trichoderma* metabolites, but the halogenation in **433** and the ring system in **434** are peculiar to some extent.

2.6 Others

Five other metabolites (**441–445**, Fig. 36), possibly arising from amino acids or sugars, were obtained from *T. atroviride* (1 compound) [110], *T. koningii* (3) [77, 129], and *T. reesei* (1) [130]. Among them, both **441** and **442** possess an acetal linkage due to the reaction of 2,3-butandiol with 4-hydroxyphenylacetaldehyde (4-HPAA) or 5-hydroxymethylfurfural (5-HMF), while **443** seems formed through aldol condensation between 4-HPAA and 5-HMF. 4-HPAA is an intermediate during the conversion of tyrosine to tyrosol via tyramine or 4-hydroxyphenylpyruvate [157], and 5-HMF arises from hexoses, such as glucose and fructose, via dehydration [181]. A tyrosol residue exists in **444**, of which the 3-hydroxy-3-(*p*-hydroxyphenyl)propanoate moiety also looks like a tyrosine derivative. Gliocladinin D (**445**) is a terphenyl glycoside, and its core is initially condensed between two molecules of 4-hydroxyphenylpyruvate under the catalysis of a tridomain nonribosomal peptide synthetase [182]. Terphenyls have been detected in fungi for a long time [183], but their occurrence in *Trichoderma* is really poor.

3 Biological activity

3.1 Antimicroalgal

Eight marine microalgae (phytoplankton), including *Amphidinium carterae*, *Chattonella marina*, *Heterocapsa circularisquama*, *Heterosigma akashiwo*, *Karlodinium veneficum*, *Prorocentrum donghaiense*, *Phaeocystis globosa*, and *Scrippsiella trochoidea*, that can give rise to harmful algal blooms, have been employed to evaluate the antimicroalgal (algicidal) activity of metabolites from marine-derived *Trichoderma*. As a result, 113 isolates, including 89 sesquiterpenes, 12 diterpenes, three steroids, eight polyketides, and one peptide, exhibit more or
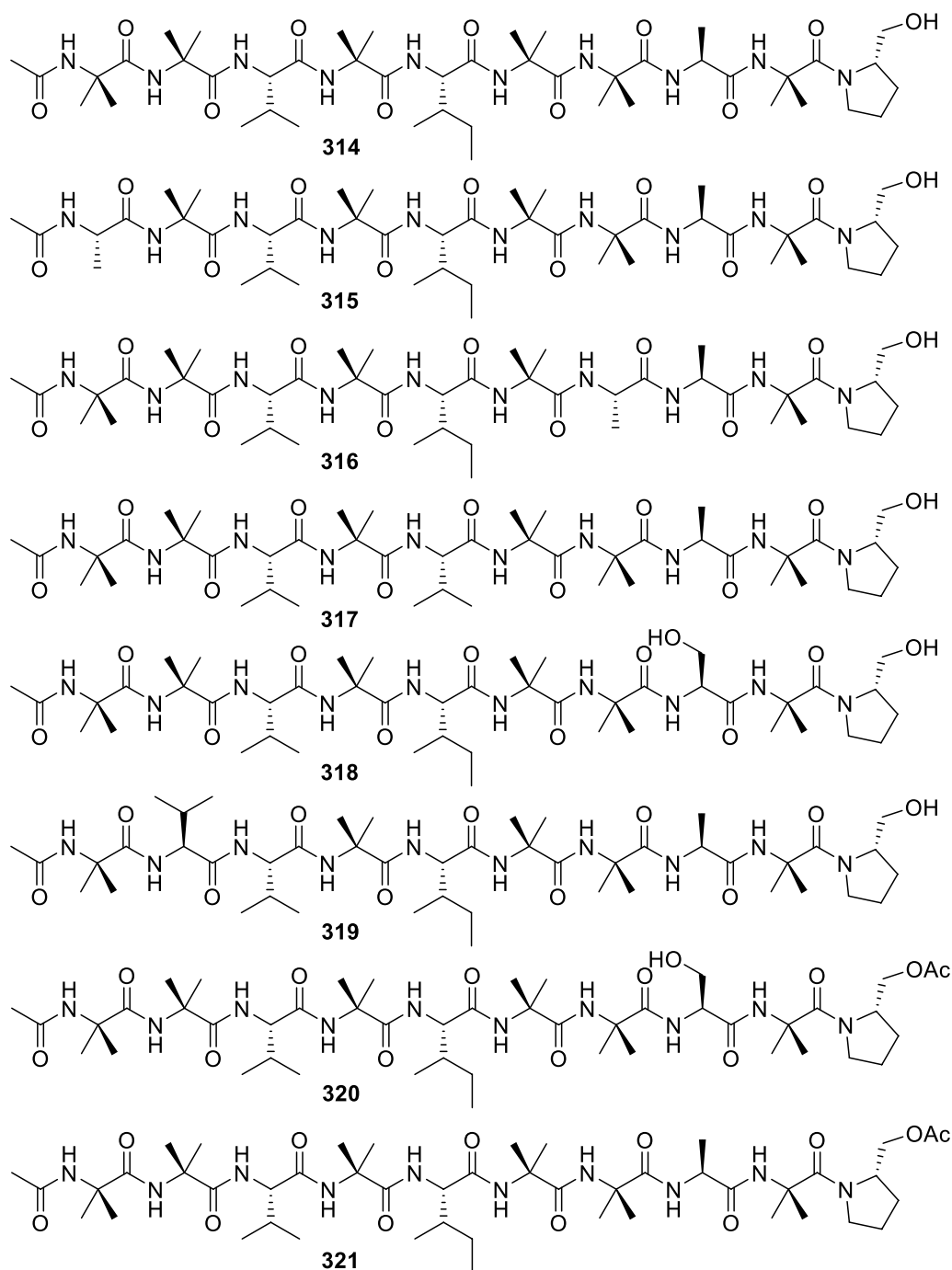
Fig. 31 10-Residue peptaibols from marine-derived *Trichoderma*

less inhibition of the phytoplankton tested (Tables 1, 2, 3). The half maximal inhibitory concentrations (IC$_{50}$) of 109 metabolites and two ferric complexes are shown in Table 4, and the remaining four ones (**162**, **163**, **165**, and **178**) display no more than 85% inhibitory rates against *A. carterae, C. marina, H. akashiwo, P. donghaiense, P.*

globosa, and/or *S. trochoidea* at a concentration of 80 or 100 μg/mL [63–65, 68]. It is worth mentioning that 19 molecules, including **15**, **32**, **65**, **68**, **69**, **93**–**95**, **104**, **106**, **107**, **114**, **115**, **129**, **149**, **167**, and **278**–**280**, that account for 16.8% of all the active ones, possess excellent inhibition effects on one or more microalga species, with IC$_{50}$

322 Ac-Aib-Aib-Val-Ile-Aib-Aib-Ala-Aib-prolinol

323 Ac-Aib-Val-Aib-Ile-Aib-Aib-Ala-Aib-Prolinol

324 Ac-Ala-Ala-Val-Aib-Lxx-Aib-Aib-Ala-Aib-Prolinol

325 Ac-Ala-Aib-Val-Aib-Lxx-Aib-Ala-Ala-Aib-Prolinol

326 Ac-Aib-Ala-Val-Aib-Lxx-Aib-Ala-Ala-Aib-Prolinol

327 Ac-Aib-Aib-Ala-Aib-Lxx-Aib-Aib-Ala-Aib-Prolinol

328 Ac-Ala-Aib-Val-Aib-Val-Aib-Aib-Ala-Aib-Prolinol

329 Ac-Aib-Ala-Val-Aib-Val-Aib-Aib-Ala-Aib-Prolinol

330 Ac-Aib-Aib-Val-Aib-Val-Aib-Ala-Ala-Aib-Prolinol

331 Ac-Aib-Aib-Val-Ala-Val-Aib-Aib-Ala-Aib-Prolinol

332 Ac-Aib-Aib-Val-Aib-Lxx-Ala-Aib-Ala-Aib-Prolinol

333 Ac-Ala-Val-Val-Aib-Lxx-Ala-Aib-Ala-Aib-Prolinol

334 Ac-Aib-Aib-Val-Aib-Lxx-Aib-Aib-Ala-Ala-Prolinol

335 Ac-Aib-Aib-Val-Aib-Lxx-Aib-Aib-Ala-Ala-Prolinol

336 Ac-Aib-Ala-Val-Aib-Lxx-Aib-Aib-Ala-Aib-Prolinol

337 Ac-Aib-Ala-Val-Aib-Lxx-Aib-Aib-Ala-Aib-Prolinol

338 Ac-Aib-Aib-Val-Ala-Lxx-Aib-Aib-Ala-Aib-Prolinol

339 Ac-Aib-Ala-Val-Aib-Lxx-Aib-Ala-Ser-Aib-Prolinol

340 Ac-Aib-Aib-Val-Aib-Val-Ala-Aib-Ser-Aib-Prolinol

341 Ac-Aib-Aib-Val-Aib-Val-Aib-Ala-Ser-Aib-Prolinol

342 Ac-Aib-Val-Val-Aib-Lxx-Aib-Aib-Ala-Ala-Prolinol

343 Ac-Ala-Val-Val-Aib-Lxx-Aib-Aib-Ala-Aib-Prolinol

344 Ac-Aib-Aib-Val-Aib-Leu-Aib-Aib-Ala-Aib-Prolinol

345 Ac-Aib-Aib-Val-Aib-Lxx-Aib-Ser-Ala-Aib-Prolinol

346 Ac-Aib-Aib-Val-Aib-Lxx-Ala-Aib-Ser-Aib-Prolinol

347 Ac-Aib-Aib-Val-Aib-Lxx-Aib-Ala-Ser-Aib-Prolinol

348 Ac-Aib-Ala-Val-Aib-Lxx-Aib-Aib-Ser-Aib-Prolinol

349 Ac-Aib-Aib-Val-Aib-Val-Aib-Aib-Ser-Aib-Prolinol

350 Ac-Aib-Aib-Val-Aib-Lxx-Ser-Aib-Ala-Aib-Prolinol

351 Ac-Aib-Aib-Val-Aib-Lxx-Aib-Aib-Ala-Aib-Proline

352 Ac-Aib-Aib-Val-Aib-Lxx-Aib-Aib-Ala-Aib-Hypol

353 Ac-Aib-Val-Val-Aib-Lxx-Aib-Aib-Ser-Aib-Prolinol

Fig. 32 9/10-Residue peptaibols and a 10-residue peptaibiotic from marine-derived *Trichoderma* (Lxx: Leu/Ile)

354 Ac-Aib-Asn-Leu-Leu-Aib-Pro-Leu-Aib-Aib-Pro-Leuol

355 Ac-Aib-Asn-Leu-Leu-Aib-Pro-Val-Leu-Aib-Pro-Valol

356 Ac-Aib-Asn-Val-Leu-Aib-Pro-Leu-Leu-Aib-Pro-Valol

357 Ac-Aib-Asn-Leu-Val-Aib-Pro-Leu-Leu-Aib-Pro-Valol

358 Ac-Aib-Asn-Leu-Leu-Aib-Pro-Val-Aib-Val-Pro-Leuol

359 Ac-Aib-Asn-Val-Leu-Aib-Pro-Leu-Aib-Val-Pro-Leuol

360 Ac-Aib-Asn-Leu-Val-Aib-Pro-Leu-Aib-Val-Pro-Leuol

361 Ac-Aib-Asn-Leu-Leu-Aib-Pro-Leu-Aib-Val-Pro-Valol

362-382 Ac-Aib-Asn/Gln-xxx-xxx-Aib-Pro-xxx-xxx-Aib-Pro-xxol

Fig. 33 11-Residue peptaibols from marine-derived *Trichoderma* (xxx: Val/Iva/Leu/Ile, xxol: Valol/Ivaol/Leuol/Ileol)

values being ≤ 1.0 μg/mL. The former 15 members are involved in five types of terpenes, inclusive of cyclonerane, bisabolane, carotane, cadinane, and harziane derivatives.

Structure–activity relationship analyses of cyclonerane sesquiterpenes reveal that the side chain and cyclopentane ring of **15** (IC$_{50}$ 0.66 μg/mL) play important roles in antagonism against *C. marina*. Although the activity of **33** (IC$_{50}$ 1.1 μg/mL) against *C. marina* also guarantees this deduction, the nitrogenous unit at the side chain terminus slightly reduces the inhibition effect. In contrast with **6** (IC$_{50}$ 13 μg/mL), the high inhibition ability of **32** (IC$_{50}$ 0.63 μg/mL) against *H. akashiwo* undoubtedly arises from the nitrogenous side chain at C-10. The enhanced inhibition against *H. akashiwo* due to the nitrogenous unit is also reflected by comparison of activities between **15** (IC$_{50}$ 23 μg/mL) and **33** (IC$_{50}$ 10 μg/mL). On the other hand, hydroxamic acids **28** and **29** do not feature attractive antimicroalgal activity, but their ferric complexes, Fe(**28**)$_3$ and Fe(**29**)$_3$, possess really more inhibition than themselves [27]. It is interesting that these two ferric complexes have no lethality to the marine zooplankton *Artemia salina* that has often been employed for screeing toxins. In view of the high and broad-spectrum activity and low toxicity of Fe(**28**)$_3$, it is promising to be applied as a potent inhibitor to control harmful algal blooms in mariculture.

Among bisabolanes and norbisabolanes, only **65**, **68**, and **69** exhibit IC$_{50}$ values being ≤ 1.0 μg/mL in the

383 Ac-Aib-Ala-Ala-Aib-Aib-Gln-Aib-Aib-Aib-Ala-Lxx-Aib-Pro-Vxx-Aib-Lxx-Gln-Gln-Pheol

384 Ac-Aib-Ala-Ala-Aib-Vxx-Gln-Aib-Aib-Aib-Ala-Lxx-Aib-Pro-Vxx-Aib-Lxx-Gln-Gln-Pheol

385 Ac-Aib-Ala-Ala-Aib-Vxx-Gln-Aib-Aib-Aib-Ala-Lxx-Aib-Pro-Lxx-Aib-Lxx-Gln-Gln-Pheol

386 Ac-Aib-Ala-Ala-Aib-Iva-Gln-Aib-Aib-Aib-Ser-Leu-Aib-Pro-Leu-Aib-Ile-Glu-Gln-Pheol

387 Ac-Aib-Ala-Ala-Aib-Aib-Gln-Aib-Aib-Ala-Ser-Leu-Aib-Pro-Leu-Aib-Ile-Gln-Gln-Pheol

388 Ac-Aib-Ala-Ala-Aib-Aib-Gln-Aib-Aib-Ala-Ser-Leu-Aib-Pro-Val-Aib-Ile-Gln-Gln-Pheol

389 Ac-Aib-Ala-Ala-Aib-Aib-Gln-Aib-Aib-Ala-Ser-Leu-Aib-Pro-Val-Aib-Ile-GluOMe-Gln-Pheol

390 Ac-Aib-Ala-Ala-Aib-Iva-Gln-Aib-Aib-Aib-Ser-Leu-Aib-Pro-Val-Aib-Ile-GluOMe-Gln-Pheol

391 Ac-Aib-Ala-Ala-Aib-Iva-Gln-Aib-Aib-Ala-Ser-Leu-Aib-Pro-Val-Aib-Ile-GluOMe-Gln-Pheol

392 Ac-Aib-Ala-Ala-Aib-Aib-Gln-Aib-Aib-Aib-Ser-Leu-Aib-Pro-Leu-Aib-Ile-GluOMe-Gln-Pheol

393 Ac-Aib-Ala-Ala-Aib-Iva-Gln-Aib-Aib-Ala-Ser-Leu-Aib-Pro-Val-Aib-Ile-Gln-Gln-Pheol

394 Ac-Aib-Ala-Aib-Ala-Aib-Ala-Gln-Aib-Val-Aib-Gly-Val-Aib-Pro-Val-Aib-Aib-Gln-Gln-Pheol

395 Ac-Aib-Ala-Aib-Ala-Aib-Ala-Gln-Aib-Val-Aib-Gly-Leu-Aib-Pro-Val-Aib-Val-Gln-Gln-Pheol

396 Ac-Aib-Ala-Aib-Ala-Aib-Aib-Gln-Aib-Val-Aib-Gly-Val-Aib-Pro-Val-Aib-Val-Gln-Gln-Pheol

397 Ac-Aib-Ala-Aib-Ala-Aib-Ala-Gln-Aib-Vxx-Aib-Gly-Lxx-Aib-Pro-Vxx-Aib-Vxx-Gln-Gln-Pheol

398-426 Ac-Aib/Ala-Ala-Ala-Aib/Ala-yyy-Gln-Aib-Aib-Aib-Ala/Ser-Lxx-Aib-Pro-xxx-Aib-Lxx-[C^129]

Fig. 34 19/20-Residue peptaibols and 17-residue peptaibiotics from marine-derived *Trichoderma* (Lxx: Leu/Ile, Vxx: Val/Iva, xxx: Val/Iva/Leu/Ile, yyy: Aib/Ala/Val/Iva)

antagonistic assay against microalgae. Their high effects may correlate with the presence of a pyran unit, but it is not the only reason by consideration of the activities of its analogs, such as **54–56** and **62–70**. Stereochemistry of the pyran unit and substitution of the side chain and cyclohexane ring also influence the antagonism. Compounds **65** and **68** have the same relative configurations at C-9 and C-11, which may contribute to their high activities against *C. marina*. As in **69**, the variation of relative configurations at C-9 and C-11 decreases the effect on *C. marina*, but increases the ability to inhibit *H. akashiwo*. Unfortunately, the aminoglycoside unit in **54–56** fails to effectively improve the antimicroalgal activity.

Carotane sesquiterpenes **93–95** have growth inhibition against *C. marina*, with IC$_{50}$ values ranging from 0.24 to 0.33 μg/mL. The carbonyl group at C-3, hydroxy group at C-11, and epoxy group at the seven-membered ring have been indicated to be the key functional groups [44]. Of the 16 cadinanes, five members (**104**, **106**, **107**, **114**, and **115**) possess inhibition against *C. marina*, *H. akashiwo*, and/or *P. donghaiense*, with IC$_{50}$ values of 0.22–0.96 μg/mL. Similar to **95**, both **104** and **106** feature an isopropanol unit that likely contributes to the high activities of these two molecules. On the other hand, the methyl ester group attached to a double bond or an aromatic ring may enhance the ability to inhibit *H. akashiwo* and *P. donghaiense* by consideration of the high activities of **106**, **107**, **114**, and **115**. As for the diterpenes, harzianes **129** and **149** are more inhibitory against *K. veneficum* and *H. akashiwo*, respectively, than the others tested. The double
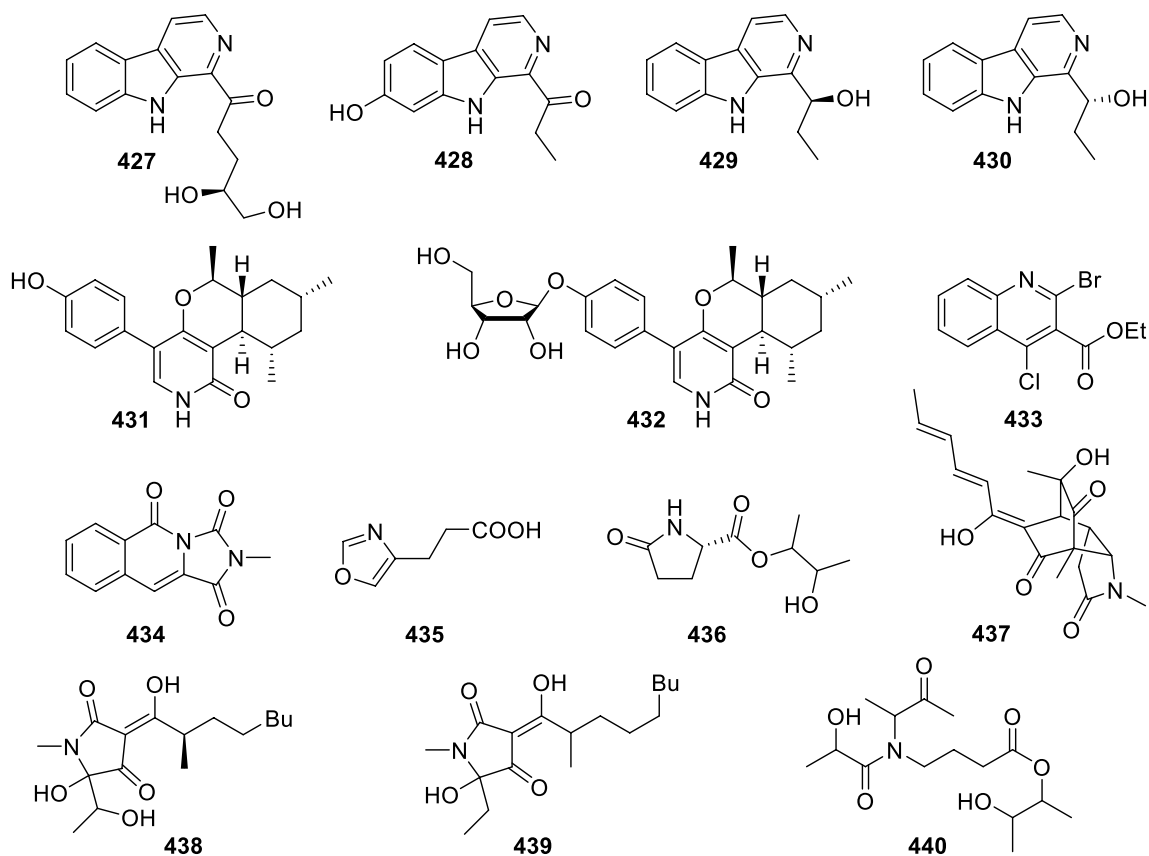
Fig. 35 Alkaloids from marine-derived *Trichoderma*
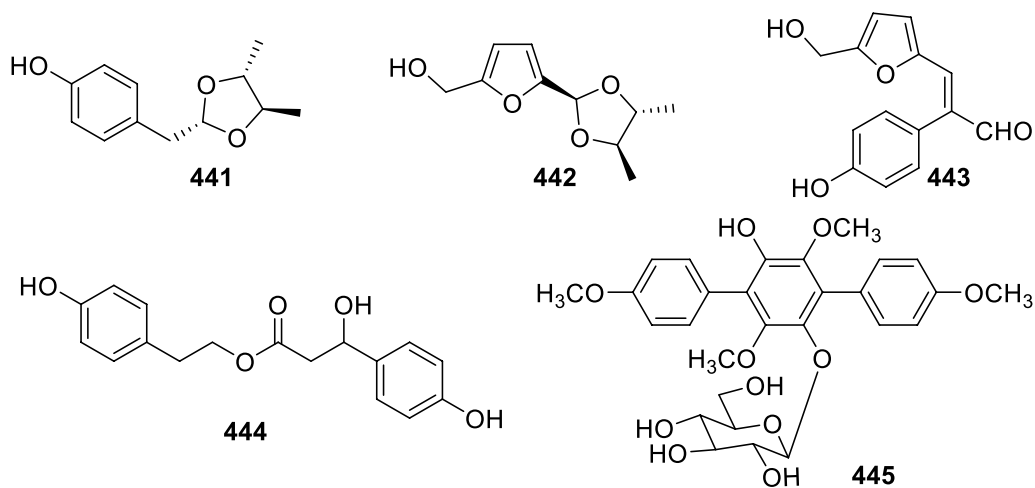
Fig. 36 Other metabolites from marine-derived *Trichoderma*

bond at C-9 seems helpful for their inhibition, but the hydroxy group at C-3 has obvious negative effect.

Among three ergosterol derivatives, the highly transformed steroid **167** features high inhibition against

C. marina, H. akashiwo, K. veneficum, and *P. donghaiense*, with IC_{50} values ranging from 0.27–0.59 μg/mL [66]. Despite the significant activities of this molecule against all the microalgae tested, its structure–activity

Table 4 Antimicroalgal activity of 109 metabolites from the marine-derived *Trichoderma*

Compound	IC$_{50}$ (µg/mL)						References
	Amphidinium carterae	*Chattonella marina*	*Heterocapsa circularisquama*	*Heterosigma akashiwo*	*Karlodinium veneficum*	*Prorocentrum donghaiense*	
6		12		13	3.8	20	[27]
7		5.2		8.0	10	9.9	[28]
8		8.8		21	76	6.5	[28]
9		61		73	71	40	[28]
10		2.4		26	3.9	20	[28]
11		5.8		37	5.5	15	[28]
12		59		14	35	7.3	[28]
15		0.66		23	2.2	37	[30]
16		9.9		75	14	66	[30]
17		12		68	41	55	[30]
18	na[a]	55				35	[31]
19	na[a]	24				na[a]	[31]
22				17	8.1	51	[33]
23				70	22	54	[33]
24	4.2	2.5		3.3		5.1	[34]
25	4.5	5.3		3.1		5.2	[34]
26		13		73	6.3	34	[28]
27	3.1	3.1		5.4		5.6	[34]
28		2.1		46	15	54	[27]
Fe(28)$_3$		0.12		2.7	0.21	0.99	[27]
29		5.1		55	19	40	[27]
Fe(29)$_3$		0.68		10	2.1	2.1	[27]
30		2.6		39	51	9.6	[27]
31		10		6.9	31	7.0	[27]
32		2.1		0.63	49	34	[27]
33		1.1		10	23	49	[27]
34		30		3.5	87	74	[27]
35		7.5		11	8.1	11	[27]
36		24		5.2	70	7.3	[35]
37		11		19	19	6.6	[35]
39		wa[b]		30	27	wa[b]	[25]
40		62		78	56	na[a]	[36]
41		6.9		2.2	5.2	48	[36]
42		50		85	53	na[a]	[36]
43/44	na[a]	8.5				19	[37]
45	1.8	12				37	[37]
46	1.6	7.0		4.2		3.4	[34]
47	5.2	1.6		13		1.7	[34]
48	6.6	8.4		11		5.7	[34]
49	2.0	4.8		2.5		6.8	[34]
50	4.6	6.4		7.1		4.7	[34]
52		15		8.4	10	14	[25]
54		6.7		2.9	6.6	10	[38]
55		5.4		5.8	8.4	14	[38]
56		3.7		6.9	9.4	12	[38]
57		3.3		6.5	4.6	20	[36]
58		5.7		14	4.0	2.6	[36]

Table 4 (continued)

Compound	IC$_{50}$ (µg/mL)						References
	Amphidinium carterae	*Chattonella marina*	*Heterocapsa circularisquama*	*Heterosigma akashiwo*	*Karlodinium veneficum*	*Prorocentrum donghaiense*	
59		18		34	26	42	[36]
60		16		41	12	33	[36]
61		2.1		3.8	1.9	2.5	[36]
62		11		4.6	12	23	[38]
63		1.2		4.3	1.3	5.7	[38]
64		3.3		9.2	1.5	6.8	[38]
65		0.93		7.8	2.7	4.9	[38]
66	23	15		25		24	[39]
67	71	11		83		33	[39]
68	1.4	0.54		6.2		5.7	[34]
69	12	3.4		1.0		4.5	[34]
70	4.6	5.4		7.2		8.3	[34]
71	4.6	2.2		5.0		3.9	[34]
72	3.5	3.3		6.3		8.4	[34]
82	97	26				35	[31]
83	21		13	16		19	[43]
84	53		66	63		wa[b]	[43]
85	14		31	25		wa[b]	[43]
86	wa[b]		28	30		23	[43]
87	68		wa[b]	64		55	[43]
88	20		18	24		wa[b]	[43]
89	25		22	34		wa[b]	[43]
93		0.24		3.1	5.2	3.8	[44]
94		0.33		4.4	7.6	3.2	[44]
95		0.27		4.2	5.0	3.6	[44]
98		1.2		6.2	12	6.5	[44]
99	24		19	22		10	[45]
100	4.7		9.8	9.2		8.3	[45]
102		1.8		1.1	2.1	8.9	[46]
103		4.3		2.7	3.2	5.8	[46]
104	1.4	0.54		5.4		4.3	[34]
105	6.7		2.7	1.5		2.4	[45]
106	2.4		1.8	0.88		0.68	[45]
107	1.8		5.2	2.1		0.54	[45]
108	8.6		11	1.1		3.2	[45]
112	6.2		3.6	3.2		1.7	[45]
113	1.7		1.3	2.3		1.4	[45]
114	1.5		2.6	0.87		0.83	[45]
115	2.1		1.6	0.96		0.22	[45]
117		2.8		56	54	54	[30]
118	na[a]	13				26	[37]
122/123	55	1.2				na[a]	[37]
129		2.6		2.2	0.58	1.2	[54]
130		6.9		3.1	4.5	7.7	[46]
145		7.0		42	24	70	[30]
146	34	31		35		18	[59]
149		1.9		1.0	2.5	1.4	[54]

Table 4 (continued)

Compound	IC$_{50}$ (μg/mL)						References
	Amphidinium carterae	*Chattonella marina*	*Heterocapsa circularisquama*	*Heterosigma akashiwo*	*Karlodinium veneficum*	*Prorocentrum donghaiense*	
152	32	25		22		18	[59]
153	47	22		31		20	[59]
154		1.2		1.3	3.2	4.3	[30]
155	33	26		35		29	[59]
166	na[a]	4.2				8.7	[37]
167		0.56		0.37	0.59	0.27	[66]
168	44	14		71		19	[39]
177	71	29		35		7.4	[39]
186		4.2		7.2	8.5	6.9	[25]
187		30		35	39	37	[25]
278		0.41		na[a]	1.0	na[a]	[103]
279		0.56		na[a]	0.87	na[a]	[103]
280		0.41		na[a]	0.69	na[a]	[103]
289		4.4		9.1	20	5.9	[33]
304		12/47		70/276	83/327	89/351	[35]

[a] na = no activity at 100 or 128 μg/mL

[b] wa = weak activity at 100 or 128 μg/mL

relationship fails to be speculated due to the lack of any analog. The broad-spectrum inhibition ability of this steroid derivative suggests its application potential in suppressing algal blooms, which will depend on more research on mechanism exploration and toxicity evaluation. Relative to this broad-spectrum algicide, polyketides **278–280** have inhibition effects on only two, *C. marina* and *K. veneficum*, of the four microalgae tested [103]. Their slight differences in activity suggest the configurations of two chiral carbons that link a hydroxy group and a methoxy group, respectively, to be weak to influence the algicidal ability.

Antimicroalgal mechanisms of **68** and **104** against *C. marina* have been preliminarily demonstrated by detecting superoxide dismutase (SOD) and malondialdehyde (MDA) as well as soluble protein (SP) under the influence of these two metabolites, respectively [34]. Both **68** and **104** can effectively decrease the SOD activity and increase MDA and SP levels of *C. marina*, intimating the damage to antioxidant and membrane systems.

3.2 Zooplankton-toxic
Besides phytoplankton, zooplankton are also widespread in the marine ecosystem and play indispensable roles in the global fishery. A low number of metabolites, **3–5**, **38**, **53**, **57**, **61**, **93**, **98**, **101**, **128**, **129**, **143**, **149**, **162**, and **165**, have been reported to be toxic to the zooplankton *Artemia salina*, a brine shrimp species. All these compounds belong to the terpene family, and their toxicities seem

not very strong. As metabolites of *T. asperellum*, **3–5**, **38**, **53**, **128**, and **143** have inhibitory rates of 52.2–78.7% at 100 μg/mL, while **57** and **61** possess half maximal lethal concentration (LC$_{50}$) values of 48 and 62 μg/mL, respectively [26, 36]. As metabolites of *T. virens*, sesquiterpenes **93**, **98**, and **101** are toxic to this zooplankton with LC$_{50}$ values of 66, 56, and 21 μg/mL, repectively [44]. As metabolites of *T. longibrachiatum*, diterpenes **129** and **149** have LC$_{50}$ values of 23.1 and 19 μg/mL, respectively [53, 54]. In addition, **162** from *T. citrinoviride* and **165** from *T. harzianum* also possess lethal effects on *A. salina*, with LC$_{50}$ values of 65.6 and 112 μg/mL, respectively [63, 65]. Apart from these hypotoxic molecules, there are also many nontoxic metabolites in the above or other *Trichoderma* species of marine origin [27, 44, 103]. In a whole, toxicities to zooplankton are not comparable to antimicroalgal activities for the metabolites from marine-derived *Trichoderma*.

3.3 Antibacterial
Regardless of unidentified strains, more than 20 Gram-positive and Gram-negative bacterial species, such as *Acinetobacter baumannii*, *Aeromonas hydrophilia*, *Bacillus subtilis*, *Enterococcus faecalis*, *E. faecium*, *Escherichia coli*, *Helicobacter pylori*, *Klebsiella pneumonia*, *Mycobacterium smegmatis*, *M. bovis*, *M. tuberculosis*, *Photobacterium angustum*, *Pseudoalteromonas citrea*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *S. epidermidis*, *Vibrio anguillarum*, *V. harveyi*, *V. parahaemolyticus*,

V. splendidus, methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *E. faecalis* (VRE), and vancomycin-resistant *E. faecium*, were used for antibacterial evaluation. Most of them are pathogens for human beings and aquacultural organisms. A total of 78 metabolites, comprising 47 terpenes, three steroids, 11 polyketides, 14 peptides, one alkaloid, and two others, feature bacteriostatic activities (Tables 1, 2, 3). However, most of these compounds have only moderate to weak inhibition of one or more bacterial species.

If a 10 μg/mL minimum inhibitory concentration (MIC) is taken as the threshold [184], only nine metabolites are regarded as active agents. Sesquiterpene **119** suppresses the aquatic pathogen *V. harveyi* with an MIC value of 4 μg/mL, while sorbicillinoids **213** and **214** inhibit *A. hydrophilia* at the same level [49]. Sorbicillinoid derivative **231** has been detected to inhibit *S. aureus*, VRE, *P. aeruginosa*, and *K. pneumonia*, with MIC values of 3.32, 1.63, 6.65, and 6.65 μg/mL, respectively [84]. During the same detection, **295** possesses an MIC value of 12.9 μg/mL to suppress *B. subtilis* and VRE, suggesting the γ-lactone moiety of **231** to be the key pharmacophore. Chromones **290** and **291** inhibit four *H. pylori* strains with MIC values of 2–8 μg/mL, and the former also suppresses four *S. aureus* strains, including MRSA, and one *E. faecalis* strain as well as one *E. faecium* strain within the same MIC range [94]. However, these two chromone derivatives have no activity against the Gram-negative *E. coli* and *P. aeruginosa* at 64 μg/mL. Aminolipopeptides **311**–**313** have MIC values of 0.02–2.0 μg/mL against *M. smegmatis*, *M. bovis*, and *M. tuberculosis* under both aerobic and hypoxic conditions, and the AHMOD moiety in **311** and **313** has been deduced to play a key role in anti-mycobacterial activity [114].

Peptaibols **386**–**393** have stronger inhibition of environmental bacteria than of laboratory ones, though the effects are not much attractive [122]. As a gram-negative bacterium, *E. coli* seems more resistant to these peptaibols than the gram-positive ones [122]. Compounds **162** and **442** also comply with this regular pattern in antagonism to *E. coli* and *S. aureus*, but **163** inhibits *E. coli* rather than *S. aureus* [63, 64, 77]. During the disk diffusion assays, 43 compounds, including **5**, **15**–**19**, **22**–**24**, **27**, **38**, **39**, **49**, **52**–**56**, **62**–**70**, **72**, **82**, **102**, **103**, **117**, **129**, **143**, **145**, **154**, **167**, **168**, **177**, **178**, **186**, **187**, and **289**, can inhibit the gram-negative *Vibrio* species with inhibitory zone diameters of 6–11 mm at a concentration of 20, 40, 50, or 100 μg/disk. As an outstanding representative, **177** has also been assayed for antagonistic activity using the double dilution method, but it features only MIC values of 13–50 μg/mL against the four *Vibrio* species tested [39]. Less than the number of *Vibrio* antagonists, 23 metabolites, inclusive of **24**, **27**, **46**–**49**, **63**–**66**, **68**–**71**,

102–**104**, **129**, **166**–**168**, **177**, and **289**, can suppress the gram-negative *P. citrea*. Of these, **289** is the most effective one as seen from the disk diffusion test, but it feature only an MIC value of 16 μg/mL in the microdilution detection [33].

3.4 Antifungal

The production of fungicidal antibiotics is one of the key mechanisms for *Trichoderma* to control phytopathogenic fungi [18]. However, only 25 new metabolites, **77**–**81**, **83**–**85**, **88**, **89**, **116**, **119**, **125**, **167**, **180**, **191**, **213**, **214**, **220**, **250**, **290**, **308**, **395**, **397**, and **431**, from marine-derived *Trichoderma* have antifungal activity against plant or human pathogens (Tables 1, 2, 3). Trichothecane sesquiterpenes, with active members accounting for over a half, are protruded in antagonism to yeast-like and filamentous fungi. Of them, **77**–**81** possess MIC values ranging from 1.6 to 50 μg/mL against *Candida albicans* and *Cryptococcus neoformans*, with **77** being the most potent (MIC values 3.1 and 1.6 μg/mL, respectively) [41, 42]. Structure–activity relationship analyses reveal that substituents at C-4 and C-16 greatly influence the fungistatic potency. Additionally, **83**–**85**, **88**, and **89** have MIC values of 32 or 64 μg/mL to inhibit *Botrytis cinerea*, *Cochliobolus miyabeanus*, *Fusarium oxysporum* f. sp. *cucumerium*, *F. oxysporum* f. sp. *niveum*, or *Phomopsis asparagi* [43]. The low MIC values (4.0–16 μg/mL) of trichodermin suggest that deacetylation and glycosylation at C-4 and hydroxylation and acetoxylation at C-16 are detrimental to the antifungal ability.

If a threshold as in antibacterial evaluation is used, most of the other plant-pathogenic antagonists seem not much attractive. Eleven pathogens of the genera *Alternaria*, *Ceratobasidium*, *Colletotrichum*, *Curvularia*, *Fusarium*, *Penicillium*, and *Physalospora* have been employed to detect the effects of **119**, **213**, and **214**, but only *Curvularia spicifera* appears sensitive to the former two metabolites with MIC values of 8 μg/mL [49]. **116** suppresses the pathogenic fungi *Colletotrichum gloeosporioides* and *F. oxysporum* with MIC values of 50 and 100 μg/mL, respectively, the same as those of triadimefon [48]. **125** inhibits *Colletotrichum lagrnarium* and *C. fragariae* with MIC values of 8 and 16 μg/mL, respectively, but it is relatively weak to antagonize *B. cinerea* from grape (64 μg/mL) and strawberry (32 μg/mL), *F. oxysporum* f. sp. *cucumerinum* (128 μg/mL), and *F. oxysporum* f. sp. *lycopersici* (256 μg/mL) [51]. **167** possesses inhibition of *Glomerella cingulata* with an MIC value of 12 μg/mL [66]. **180** has been assayed for inhibitory activity against *B. cinerea*, *Pestallozzia theae*, *Phytophthora parasitica*, *Magnaporthe oryzae*, and *Valsa mali*, with the latter two species being the most sensitive to this metabolite (MICs 8.63 and 34.5 μM) [70]. **191** and **220** have an MIC value

of 125 µg/disk and a median effective dose (ED_{50}) of 9.13 µg/mL, respectively, to inhibit *Pestalotiopsis theae* through the paper disk dilution method, rather than the conventional broth dilution test [76, 82].

Besides trichothecanes, several other metabolites are also antagonistic to human pathogens. Chromone **290** has an MIC value of 16 µg/mL against two *C. albicans* strains and an MIC value of 64 µg/mL against one *Aspergillus fumigatus* strain [94]. Dipeptide **308** inhibits amphoterocin-resistant *C. albicans* with an MIC value of ca. 15 µg/mL, with the chlorine atom being a pharmacophore [112]. Among polypeptides, peptaibol **395** possesses only 63% inhibitory rate against *A. fumigatus*, a human-pathogenic fungus, at 100 µg/mL [123], while **397** inhibits *C. albicans* ATCC 10231 from bronchomycosis, 247 FN from finger nails, 311 FN from finger nails, and 098 VC from vaginal cavity with MIC values of 2.49, 4.92, 19.66, and 2.49 µM [124]. Alkaloid **431** suppresses human-pathogenic *C. albicans* with an IC_{50} value of 25.38 µM, and ribosylation of the phenolic hydroxy group dramatically reduces the effect as indicated by the low activity of **432**. Although **250** possesses no antagonistic effect on *C. albicans*, it features synergistic antifungal activity with ketoconazole [91]. It must be said that these tests are valuable tries to use *Trichoderma* metabolites to antagonize human-pathogenic fungi.

3.5 Cytotoxic

A series of human and murine cancer cell lines, such as A-375, A375-S2, A549, A2780, Bel-7402, CNE1, CNE2, DU-145, HCT-8, HCT-15, HCT-116, Hela, HepG2, HL-60, Huh-7, Jurkat, KB, Lovo, MCF-7, MDA-MB-435 s, NCIH-460, NCI-H929, SUNE1, SW620, P388, and L1210 cells, have been used for in vitro cytostatic evaluations, and most of them have been performed through the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) method. 42 metabolites, including 10 terpenes, 26 polyketides, four peptides, and two alkaloids, have been determined to possess more or less cytotoxicities (Tables 1, 2, 3). If an IC_{50} value of 10 µM is taken as the potency threshold [184], only 12 metabolites have potent activities.

Among these potent molecules, cadinane sesquiterpene **109** possesses cytotoxicities against NCI-H929 myeloma and SW620 colorectal cancer cells with IC_{50} values of ca. 6.8 and 9.3 µM, respectively, while **110** inhibits NCIH-460 lung and SW620 colorectal cancer cell lines with IC_{50} values of ca. 7.8 and 8.6 µM, respectively. The presence of two carboxylic acid groups in **109** and **110** has been deduced to be helpful to their activities [47]. Wickerane diterpenes **156**–**161** have been assayed for cytotoxicities against HL-60, P388, and L1210 leukemia cells, but only the carbonyl-bearing **156** with IC_{50}

values of 6.8–7.9 µM is potent [61, 62]. Cyclopentenones **182**–**184** significantly inhibit P388 leukemia cells with IC_{50} values of 1.69, 6.85, and 9.03 µM, respectively [71]. Bisorbicillinoid **218** features inhibition of human A549 lung and MCF-7 breast cancer cells with IC_{50} values of 5.1 and 9.5 µM, respectively [86]. Decalin derivatives **265** and **266** suppress HL-60, P388, and L1210 leukemia cells with IC_{50} values ranging from 3.8–6.7 µM [97], four orders of magnitude lower than that of **261** [95]. Dipeptides **308** and **310** are potential inhibitors for HCT-116 and Jurkat cells, with IC_{50} values of 0.71 and 1.3 µM, respectively. The chlorine atom in **308** and the disulfide bridge in **310** play key roles in their cytotoxicities [112, 113]. Dipeptide **308** can also inhibit the proliferation of Hela cells, with an IC_{50} value of 3.1 µM. Besides differences in potency, **308** also has distinct action mechanism, accumulating cells in the S phase, from several synthetic analogs. Its mechanistic specificity is probably attributed to the chlorohydrin moiety, which may contribute to developing DNA-damaging agents. However, numerous in vivo antitumor experiments are required before evaluating the therapeutic potential of this molecule [172]. In addition, peptaibol **395** has an IC_{50} value of 2.5 µM in inhibition of KB cells [123]. These positive results further strengthen the clinical potential of *Trichoderma* metabolites.

3.6 Anti-inflammatory

The anti-inflammatory property of some metabolites has been assayed for inhibiting the production of nitric oxide (NO) in different cell lines induced by lipopolysaccharide [40, 55, 81, 88]. The number of active metabolites amounts to 21, and all of them belong to terpene and polyketide families. Trichothecane sesquiterpenes **73**–**76** reduce the lipopolysaccharide-induced NO production in microglial BV-2 cells at 10 µM, with **75** being the most potent [40]. Harziane diterpenes **132** and **133** weakly suppress the production of NO in RAW264.7 macrophages at 100 µM [55]. Sorbicillinoids **200**, **201**, **203**–**206**, **208**, **211**, and **223**–**228** feature higher anti-inflammatory effects than indomethacin, a positive control with an IC_{50} value of 41 µM. In particular, the IC_{50} values of **200**, **203**–**206**, **223**, and **224** are lower than 10 µM. Monomeric sorbicillinoid **205** with an IC_{50} value of 0.94 µM is the most potent one, and substitution modes at the phenyl core and the side chain contribute to its high activity [81]. This molecule is promising to be developed as a therapeutic agent after a series of in vitro and in vivo determination in the future. It can be concluded that substitution and oxidation of the benzene ring and side chain have important impacts on anti-inflammatory activities of this type of molecules. In a dose-dependent manner across 3–60 µM, **236** can reduce

the nitrite production stimulated by lipopolysaccharide in J774A.1 macrophages [88].

3.7 Miscellaneous

There are 25 metabolites that possess other activities, such as antiviral, phytotoxic, insect-toxic, zebrafish-toxic, antifouling, antioxidant, enzyme-inhibitory, NF-κB-inhibitory, anti-pulmonary fibrosis, anti-Aβ fibrillization, and neuroprotective properties. Sesquiterpenes **126** and **127** have moderate activities against the hepatitis C virus, with half maximal effective concentration (EC$_{50}$) values being ca. 24.5 and 20.4 μM, respectively [52]. Harziane diterpenes **138**–**140**, **142**, **148**, and **151** exert growth inhibition of amaranth and lettuce seedlings at 200 ppm. Although they also have an inhibitory effect on amaranth roots, all of them are avirulent to the elongation of lettuce roots [57]. Besides antimicrobial and cytotoxic activities, the acute toxicity to the larvae of *Calliphora vomitoria* has also been detected for **395**, with the minimal effective dose (MED) being 250 μg/mg [123]. Despite the potent inhibition of *P. theae* by **220**, its high effects on mortality and malformation of zebrafish at a low concentration (0.625 μM) exclude the antifungal application [82]. Decalin derivative **268** prevents the settlement of *Bugula neritina*, a widespread fouling organism in marine environments, larvae with an EC$_{50}$ value of 29.8 μg/mL [98]. Six metabolites, **196**, **234**–**236**, **442**, and **444**, have been evaluated to be moderate antioxidants through the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging method [77, 78, 87, 129]. Of them, **196** is also an effective inhibitor of the Aβ fibril formation and a moderate protectant against the hydrogen peroxide-induced neuronal death [78]. Koninginins **254** and **255** have moderate inhibition of protein tyrosine phosphatase 1B (PTP1B), with IC$_{50}$ values of 53.1 and 65.1 μM, respectively [92]. In addition, naphthopyrones **276** and **277** possess IC$_{50}$ values of 58.7 and 18.0 μM, respectively, against tyrosine kinase, with the bisnaphtho-γ-pyrone nucleus being responsible for the inhibition [102]. Vertinolide **230** has an IC$_{50}$ value of 13.83 μM to inhibit TNF-α-induced NF-κB, and no cytotoxicity against the human embryonic kidney cell line 293 has been detected at 50 μM [83]. Alkaloids **427**, **429**, and **430** have been screened for inhibition of collagen accumulation, and only **427** with a ca. 85.21% inhibitory rate at 10 μM features high potency to reduce the pulmonary fibrosis [125].

4 Metabolic relevance

Trichoderma species have their own metabolic characteristics, reflected by the diverse cycloneranes, bisabolanes, harzianes, sorbicillinoids, and peptaibols. These metabolites may exist in a broad spectrum of species, as shown in Tables 1, 2, 3. On the other hand, it is easy to be understood that different *Trichoderma* species of marine origin also produce varied metabolites. For examples, carotanes, trichothecanes, wickeranes, and decalins have been encountered in one or a small number of species, demonstrating the interspecific differences of metabolites. Moreover, *Trichoderma* strains of the same species tend to feature discrepancies in metabolic profiles, evidenced by the discovery of new compounds from each isolate. This phenomenon can be attributed to the variation of strain sources, though technical divergence and personal tendency during isolation and identification processes also make differences to some extent.

The findings of more than 400 new compounds from marine-derived *Trichoderma* commendably explain the shaping effect of marine environments on biosynthetic routes. The impacts may be caused by genic or transcriptional variations, especially for the known species that have also been reported as terrestrial-derived ones. To date, several new or known skeletons, such as cuparane, synderane, pupukeanane, harzianoic acid, citrinovirin, fusicoccane, cleistanthane, and trichorenin, have been discovered from only marine-derived strains, but their uniqueness still requires more supports from both natural product chemistry and molecular biology. As for substitution, the aminosugar unit has exclusively been found in the metabolites, such as **38**, **53**–**56**, **90**, **119**, and **124**, of marine-derived *Trichoderma* so far. Moreover, marine-derived *Trichoderma* strains have contributed a series of halogenated metabolites, including **82**, **114**, **164**, **183**, **184**, **187**, **188**, **296**, **297**, **300**, **308**, and **433**, which exhibit higher structural diversity than those from terrestrial-derived strains [20]. Halogenation is characteristic of marine natural products, and the chlorine, bromine, and iodine atoms in these metabolites come from the seawater constituents or the added sodium halides [107, 112].

Culture substrates and conditions play important roles in the secondary metabolite production of marine-derived *Trichoderma* [185]. Algicolous *Trichoderma* sp. TPU199 was chemically investigated on the basis of several different cultivations, leading to the discovery of **77**–**81**, **296**–**300**, and **310** as well as several known terpenes, peptides, and polyketides [41, 42, 107, 108, 113]. Fermented in the freshwater medium under agitation for 7 days, this strain produced trichothecane sesquiterpenes **77**, **80**, and **81** [42]. Supplemented with 3.0% NaI, the culture broth further afforded trichothecane sesquiterpenes **78** and **79** and diketopiperazines **297**–**299**, besides **77** [41]. If only NaI was replaced by NaBr, a brominated diketopiperazine (**296**) was then yielded [107]. In the same freshwater medium, a long-term (5 weeks) static fermentation induced the production of dipeptide **310** [113]. Agitated for 7 days in the seawater medium, the

culture broth gave dipeptide **308** and diketopiperazine DC1149B, a chlorinated analog of **296** and **297** [107]. When 1% dimethyl sulfoxide (DMSO) was added into the seawater, rather than freshwater, medium, the production of diketopiperazine **300** was further induced under agitation for 7 days [108].

"One strain many compounds" (OSMAC) and chemical epigenetic manipulation strategies were also used to the coral-derived *T. harzianum* XS-20090075 [186], which resulted in the discovery of 12 new molecules [56, 57, 98, 100]. A culture for four weeks in the rice medium led to the production of harziane diterpenes **138**–**142**, **148**, and **151** [57]. When the culture period was elongated to 45 days, decalin derivatives **267** and **268** were produced in the same medium [98]. Treated with a histone deacetylase inhibitor (sodium butyrate), two new diterpenes (**137** and **164**) including a chlorinated one (**164**) were obtained from the culture in the rice medium [56]. Changed to the Czapek's medium, the culture afforded a alkaloid (**433**) that contains both bromine and chlorine atoms [98]. In the PDA (possibly an error of PDB) medium, a static culture for 45 days yielded hydroxyanthraquinones **271** and **272** [100].

Besides the whole substrate variation, a single nutritional factor may also alter the metabolic profile of a *Trichoderma* strain. Addition of a single amino acid, ʟ-phenylalanine, into the culture medium of *T. erinaceum* F1-1 elicited the production of 18 aromatic metabolites, with **283**–**288** being new ones. Simultaneously, an excess (2 g/L) of ʟ-phenylalanine also resulted in the morphological alteration of this fungal strain. However, it was strange that only one of the divergent molecules harbors a nitrogen atom, differing from the privileged production of alkaloids in other marine fungi. The result indicated the incapability of some *Trichoderma* strains to incorporate a single amino acid into metabolic pathways [32].

5 Co-culture induction

Trichoderma species are always present in extremely complex microbial communities. Apart from abiotic conditions, other microbes also interfere their growth and metabolism in nature. Undoubtedly, co-culture experiments are effective approaches to simulate the actual ecological situation and awake some sleeping genes. Mixed fermentation of marine-derived *Trichoderma* strains with other fungal and bacterial strains led to the production of nine new metabolites, **446**–**454** (Fig. 37) [187–190]. Chaunopyran A (**446**) was produced at an extremely low level by monoculture of *Chaunopycnis* sp. CMB-MF028, but its productivity was greatly improved by co-cultivation with *T. hamatum* CMB-MF030. Both the fungal isolates were obtained from the inner tissue of the mollusc *Siphonaria* sp [187]. (*Z*)-2-Ethylhex-2-enedioic acid (**447**) and (*E*)-4-oxo-2-propylideneoct-7-enoic acid (**448**) were yielded by co-culture of *Trichoderma* sp. Gc(M2) and *Penicillium* sp. Ma(M3)V, isolated from different marine sponge species [188]. Two new sesquiterpenes (**449** and **450**) and four new polyketides (**451**–**454**) were identified from co-culture extracts of fungus *Trichoderma* sp. 307 and bacterium *Acinetobacter johnsonii* B2, obtained from a mangrove plant and
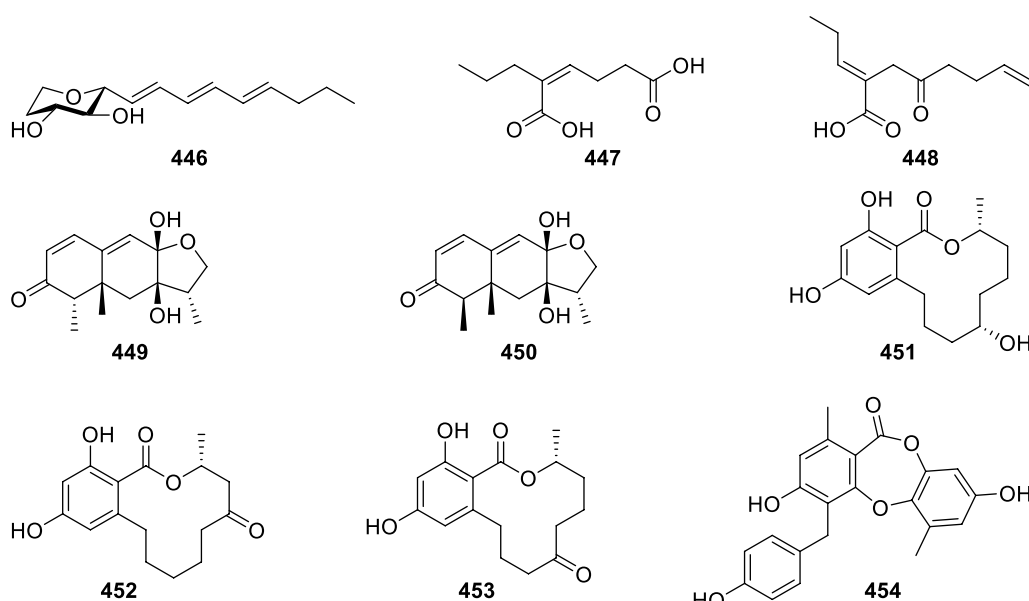

Fig. 37 Metabolites from co-cultures of marine-derived *Trichoderma* and other microbial strains

an aquaculture pond, respectively [189, 190]. It can be concluded that *Trichoderma* species or other microbes might produce extra products due to the activation of silent metabolic routes during co-culture processes [191]. At least 75 *Trichoderma* species have the mycoparasitic ability [7], and their fermentation mixed with other fungi means more intensive competition or antagonism that may involve the large-scale production of antibiotics.

6 Biotransformation and biodegradation

Trichoderma species exhibit biotransformation functions towards heterogeneous organic matters due to the production of enriched enzymes [192, 193], but marine-derived strains have less been examined. As the metabolites of *Chaunopycnis* sp., pyridoxatin atropisomers were transformed to a pair of methylated derivatives by the co-cultivated *T. hamatum* [187]. As a biogenetic precursor of many monoterpenes, geraniol was transformed to 1,7-dihydroxy-3,7-dimethyl-(*E*)-oct-2-ene by a marine-derived *Hypocrea* strain. During the process, a double bond was oxygenated to an alcohol [194]. On the other hand, three marine-derived *Trichoderma* strains effectively degraded malachite green, pentachlorophenol, and chlorpyrifos, respectively, which are industrial and agricultural agents causing environmental pollution [195–197]. These strains were obtained from mangrove, ascidian, and sponge organisms, respectively, and their degradation ability may rely on the production of exoenzymes, such as laccase and peroxidase [195, 198]. Considering the diverse substitution patterns in metabolites from marine-derived *Trichoderma*, their biotransformation and biodegradation potentials will not disappoint the relevant researchers in future.

7 Conclusions

Over a duration of 30 years, marine-sourced 77 *Trichoderma* strains have contributed 445 new metabolites, including many new structural types from this genus and new carbon skeletons in nature. Their metabolic characteristics are also reflected by the high populations of irregular carbon numbers and cyclization and cleavage patterns in some scaffolds. These phenomena might arise from the oxidation by reactive oxygen species produced under saline and alkaline stresses. Halogen and sulfur atoms as well as sugar units are incorporated into 12, nine, and 15 members, respectively, especially eight aminosugar-bearing ones. The production of halides probably profits from enriched halogen anions and related enzymes. The discovery greatly adds to the molecular diversity of *Trichoderma* metabolites, especially those with cyclonerane, bisabolane, harziane, sorbicillinoid, and peptaibol frameworks. Among the metabolites, 235 members feature antimicroalgal, zooplankton-toxic,

antibacterial, antifungal, cytotoxic, anti-inflammatory, and other activities, demonstrating the application potentials of marine-derived *Trichoderma* in aquaculture, agriculture, and healthcare. Marine environments probably shape the metabolic profiles of the involved *Trichoderma* strains, and culture methods seem also responsible for the metabolic diversity. Considering the mycoparasitic instinct of many *Trichoderma* species, co-culture with other fungi seems a prospective strategy to mine their valuable metabolites. On the other hand, marine-derived *Trichoderma* strains may methylate and oxidize heterogeneous molecules, and their biodegradation ability is also attractive. In view of the high structural diversity and various bioactivities, the molecules produced or transformed by marine-derived *Trichoderma* are promising candidates to develop potent drugs for human diseases and antagonistic agents in agriculture and aquaculture.

Declarations

Ethics approval and consent to participate
Ethical declaration is not applicable for this review.

Competing interests
The authors declare that there are no competing interests associated with this work.

Author details
[1]Yantai Institute of Coastal Zone Research, Chinese Academy of Sciences, Yantai 264003, People's Republic of China.

References
1. Persoon CH. Disposita methodica fungorum. Römer's Neues Mag Bot. 1794;1:81–128.
2. Kirk PM, Cannon PF, Minter DW, Stalpers JA. Anisworth & Bisby's Dictionary of the Fungi (10th edition). Wallingford: CAB International Publishing; 2008. p. 1–771.
3. Harman GE, Howell CR, Viterbo A, Chet I, Lorito M. *Trichoderma* species—opportunistic, avirulent plant symbionts. Nat Rev Microbiol. 2004;2:43–56.

4. Samuels GJ. *Trichoderma*: systematics, the sexual state, and ecology. Phytopathology. 2006;96:195–206.

5. Rossman AY, Seifert KA, Samuels GJ, Minnis AM, Schroers H-J, Lombard L, Crous PW, Põldmaa K, Cannon PF, Summerbell RC, Geiser DM, Zhuang W-Y, Hirooka Y, Herrera C, Salgado-Salazar C, Chaverri P. Genera in Bionectriaceae, Hypocreaceae, and Nectriaceae (Hypocreales) proposed for acceptance or rejection. IMA Fungus. 2013;4:41–51.

6. Bissett J, Gams W, Jaklitsch W, Samuels GJ. Accepted *Trichoderma* names in the year 2015. IMA Fungus. 2015;6:263–95.

7. Contreras-Cornejo HA, Macías-Rodríguez L, del-Val E, Larsen J. Ecological functions of *Trichoderma* spp. and their secondary metabolites in the rhizosphere: interactions with plants. FEMS Microbiol Ecol. 2016;92:036.

8. Chen K, Zhuang W-Y. *Trichoderma shennongjianum* and *Trichoderma tibetense*, two new soil-inhabiting species in the Strictipile clade. Mycoscience. 2016;57:311–9.

9. Qin W-T, Zhuang W-Y. Seven wood-inhabiting new species of the genus *Trichoderma* (Fungi, Ascomycota) in Viride clade. Sci Rep. 2016;6:27074.

10. Chen K, Zhuang W-Y. Discovery from a large-scaled survey of *Trichoderma* in soil of China. Sci Rep. 2017;7:9090.

11. Zhu Z-X, Xu H-X, Zhuang W-Y, Li Y. Two new green-spored species of *Trichoderma* (Sordariomycetes, Ascomycota) and their phylogenetic positions. MycoKeys. 2017;26:61–75.

12. Weindling R. *Trichoderma lignorum* as a parasite of other soil fungi. Phytopathology. 1932;22:837–45.

13. Weindling R. Studies on a lethal principle effective in the parasitic action of *Trichoderma lignorum* on *Rhizoctonia solani* and other soil fungi. Phytopathology. 1934;24:1153–79.

14. Woo SL, Ruocco M, Vinale F, Nigro M, Marra R, Lombardi N, Pascale A, Lanzuise S, Manganiello G, Lorito M. *Trichoderma*-based products and their widespread use in agriculture. Open Mycol J. 2014;8:71–126.

15. Singh A, Shukla N, Kabadwal BC, Tewari AK, Kumar J. Review on plant-*Trichoderma*-pathogen interaction. Int J Curr Microbiol App Sci. 2018;7:2382–97.

16. Vinale F, Sivasithamparam K, Ghisalberti EL, Marra R, Woo SL, Lorito M. *Trichoderma*–plant–pathogen interactions. Soil Biol Biochem. 2008;40:1–10.

17. Howell CR. Mechanisms employed by *Trichoderma* species in the biological control of plant diseases: the history and evolution of current concepts. Plant Dis. 2003;87:4–10.

18. Ghisalberti EL, Sivasithamparam K. Antifungal antibiotics produced by *Trichoderma* spp. Soil Biol Biochem. 1991;23:1011–20.

19. Keswani C, Mishra S, Sarma BK, Singh SP, Singh HB. Unraveling the efficient applications of secondary metabolites of various *Trichoderma* spp. Appl Microbiol Biotechnol. 2014;98:533–44.

20. Reino JL, Guerrero RF, Hernández-Galán R, Collado IG. Secondary metabolites from species of the biocontrol agent *Trichoderma*. Phytochem Rev. 2008;7:89–123.

21. Li M-F, Li G-H, Zhang K-Q. Non-volatile metabolites from Trichoderma spp. Metabolites. 2019;9:58.

22. Bai B, Liu C, Zhang C, He X, Wang H, Peng W, Zheng C. *Trichoderma* species from plant and soil: an excellent resource for biosynthesis of terpenoids with versatile bioactivities. J Adv Res. 2023;49:81–102.

23. Su D, Ding L, He S. Marine-derived *Trichoderma* species as a promising source of bioactive secondary metabolites. Mini-Rev Med Chem. 2018;18:1702–13.

24. Kobayashi M, Uehara H, Matsunami K, Aoki S, Kitagawa I. Trichoharzin, a new polyketide produced by the imperfect fungus *Trichoderma harzianum* separated from the marine sponge *Micale cecilia*. Tetrahedron Lett. 1993;34:7925–8.

25. Song Y-P, Miao F-P, Fang S-T, Yin X-L, Ji N-Y. Halogenated and nonhalogenated metabolites from the marine-alga-endophytic fungus *Trichoderma asperellum* cf44-2. Mar Drugs. 2018;16:266.

26. Song Y-P, Liu X-H, Shi Z-Z, Miao F-P, Fang S-T, Ji N-Y. Bisabolane, cyclonerane, and harziane derivatives from the marine-alga-endophytic fungus *Trichoderma asperellum* cf44-2. Phytochemistry. 2018;152:45–52.

27. Song Y-P, Miao F-P, Yin X-L, Ji N-Y. Nitrogenous cyclonerane sesquiterpenes from an algicolous strain of *Trichoderma asperellum*. Org Chem Front. 2019;6:3698–704.

28. Song Y-P, Miao F-P, Liu X-H, Yin X-L, Ji N-Y. Cyclonerane derivatives from the algicolous endophytic fungus *Trichoderma asperellum* A-YMD-9-2. Mar Drugs. 2019;17:252.

29. Fang S-T, Wang Y-J, Ma X-Y, Yin X-L, Ji N-Y. Two new sesquiterpenoids from the marine-sediment-derived fungus *Trichoderma harzianum* P1–4. Nat Prod Res. 2019;33:3127–33.

30. Song Y-P, Fang S-T, Miao F-P, Yin X-L, Ji N-Y. Diterpenes and sesquiterpenes from the marine algicolous fungus *Trichoderma harzianum* X-5. J Nat Prod. 2018;81:2553–9.

31. Ma X-Y, Song Y-P, Shi Z-Z, Ji N-Y. Three sesquiterpenes from the marine-alga-epiphytic fungus *Trichoderma hamatum* Z36–7. Phytochem Lett. 2021;43:98–102.

32. Guo Y-W, Gong B-Q, Yuan J, Li H-J, Mahmud T, Huang Y, Li J-F, Yang D-P, Lan W-J. L-Phenylalanine alters the privileged secondary metabolite production in the marine-derived fungus *Trichoderma erinaceum* F1–1. J Nat Prod. 2020;83:79–87.

33. Liu X-H, Hou X-L, Song Y-P, Wang B-G, Ji N-Y. Cyclonerane sesquiterpenes and an isocoumarin derivative from the marine-alga-endophytic fungus *Trichoderma citrinoviride* A-WH-20-3. Fitoterapia. 2020;141: 104469.

34. Zou J-X, Song Y-P, Liu X-H, Li X-N, Ji N-Y. Bisabolane, cadinane, and cyclonerane sesquiterpenes from an algicolous strain of *Trichoderma asperelloides*. Bioorg Chem. 2021;115: 105223.

35. Song Y, Miao F, Yin X, Ji N. Three nitrogen-containing metabolites from an algicolous isolate of *Trichoderma asperellum*. Mar Life Sci Technol. 2020;2:155–60.

36. Shi Z-Z, Miao F-P, Fang S-T, Yin X-L, Ji N-Y. Trichobisabolins A-H, eight new bisabolane derivatives from the marine-alga-epiphytic fungus *Trichoderma asperellum* Y6–2. Fitoterapia. 2019;134:372–7.

37. Shi Z-Z, Liu X-H, Song Y-P, Yin X-L, Ji N-Y. Sesquiterpenoids and a steroid from the algicolous *Trichoderma brevicompactum*. Fitoterapia. 2021;153: 104983.

38. Song Y-P, Miao F-P, Liu X-H, Yin X-L, Ji N-Y. Seven chromanoid norbisabolane derivatives from the marine-alga-endophytic fungus *Trichoderma asperellum* A-YMD-9-2. Fitoterapia. 2019;135:107–13.

39. Liu X-H, Song Y-P, Wang B-G, Ji N-Y. Sesquiterpenes and lipids from the algicolous fungus *Trichoderma atroviride* RR-dl-3-9. Phytochem Lett. 2021;45:6–12.

40. Safwan S, Wang S-W, Hsiao G, Hsiao S-W, Hsu S-J, Lee T-H, Lee C-K. New trichothecenes isolated from the marine algicolous fungus *Trichoderma brevicompactum*. Mar Drugs. 2022;20:80.

41. Yamazaki H, Takahashi O, Kirikoshi R, Yagi A, Ogasawara T, Bunya Y, Rotinsulu H, Uchida R, Namikoshi M. Epipolythiodiketopiperazine and trichothecene derivatives from the Nal-containing fermentation of marine-derived *Trichoderma* cf. *brevicompactum*. J Antibiot. 2020;73:559–67.

42. Yamazaki H, Yagi A, Takahashi O, Yamaguchi Y, Saito A, Namikoshi M, Uchida R. Antifungal trichothecene sesquiterpenes obtained from the culture broth of marine-derived *Trichoderma* cf. *brevicompactum* and their structure–activity relationship. Bioorg Med Chem Lett. 2020;30:127375.

43. Shi Z-Z, Liu X-H, Li X-N, Ji N-Y. Antifungal and antimicroalgal trichothecene sesquiterpenes from the marine algicolous fungus *Trichoderma brevicompactum* A-DL-9-2. J Agric Food Chem. 2020;68:15440–8.

44. Shi Z-Z, Fang S-T, Miao F-P, Yin X-L, Ji N-Y. Trichocarotins A-H and trichocadinin A, nine sesquiterpenes from the marine-alga-epiphytic fungus *Trichoderma virens*. Bioorg Chem. 2018;81:319–25.

45. Song Y-P, Shi X-S, Wang B-G, Ji N-Y. Cadinane and carotane derivatives from the marine algicolous fungus *Trichoderma* virens RR-dl-6-8. Fitoterapia. 2020;146: 104715.

46. Song Y-P, Miao F-P, Liang X-R, Yin X-L, Ji N-Y. Harziane and cadinane terpenoids from the alga-endophytic fungus *Trichoderma asperellum* A-YMD-9-2. Phytochem Lett. 2019;32:38–41.

47. Cui J, Shang R-Y, Sun M, Li Y-X, Liu H-Y, Lin H-W, Jiao W-H. Trichodermaloids A-C, cadinane sesquiterpenes from a marine sponge symbiotic *Trichoderma* sp. SM16 fungus. Chem Biodivers. 2020;17:e2000036.

48. Qin C, Hu Z, Xiong Y, Chen M, Li C, Ding W. A new sesquiterpene derivative from the mangrove endophytic fungus *Trichoderma harzianum* (strain No. R1). Chem Nat Compd. 2021;57:312–4.

49. Wang Y, Li X-M, Yang S-Q, Zhang F-Z, Wang B-G, Li H-L, Meng L-H. Sesquiterpene and sorbicillinoid glycosides from the endophytic

fungus *Trichoderma longibrachiatum* EN-586 derived from the marine red alga *Laurencia obtusa*. Mar Drugs. 2022;20:177.

50. Du X-P, Li Y-Y, Lu C-H, Zheng Z-H, Shen Y-M. A novel sesquiterpene glucoside from *Trichoderma* sp. PT2. Nat Prod Res Dev. 2010;22:544–7.

51. Du F-Y, Ju G-L, Xiao L, Zhou Y-M, Wu X. Sesquiterpenes and cyclodepsipeptides from marine-derived fungus *Trichoderma longibrachiatum* and their antagonistic activities against soil-borne pathogens. Mar Drugs. 2020;18:165.

52. Li B, Li L, Peng Z, Liu D, Si L, Wang J, Yuan B, Huang J, Proksch P, Lin W. Harzianoic acids A and B, new natural scaffolds with inhibitory effects against hepatitis C virus. Bioorg Med Chem. 2019;27:560–7.

53. Miao F-P, Liang X-R, Yin X-L, Wang G, Ji N-Y. Absolute configurations of unique harziane diterpenes from *Trichoderma* species. Org Lett. 2012;14:3815–7.

54. Zou J-X, Song Y-P, Ji N-Y. Deoxytrichodermaerin, a harziane lactone from the marine algicolous fungus *Trichoderma longibrachiatum* A-WH-20-2. Nat Prod Res. 2021;35:216–21.

55. Li H, Liu X, Li X, Hu Z, Wang L. Novel harziane diterpenes from deep-sea sediment fungus *Trichoderma* sp. SCSIOW21 and their potential anti-inflammatory effects. Mar Drugs. 2021;19:689.

56. Shi T, Shao C-L, Liu Y, Zhao D-L, Cao F, Fu X-M, Yu J-Y, Wu J-S, Zhang Z-K, Wang C-Y. Terpenoids from the coral-derived fungus *Trichoderma harzianum* (XS-20090075) induced by chemical epigenetic manipulation. Front Microbiol. 2020;11:572.

57. Zhao D-L, Yang L-J, Shi T, Wang C-Y, Shao C-L, Wang C-Y. Potent phytotoxic harziane diterpenes from a soft coral-derived strain of the fungus *Trichoderma harzianum* XS-20090075. Sci Rep. 2019;9:13345.

58. Zhang M, Liu J-M, Zhao J-L, Li N, Chen R-D, Xie K-B, Zhang W-J, Feng K-P, Yan Z, Wang N, Dai J-G. Two new diterpenoids from the endophytic fungus *Trichoderma* sp. Xy24 isolated from mangrove plant *Xylocarpus granatum*. Chin Chem Lett. 2016;27:957–60.

59. Zou J-X, Song Y-P, Zeng Z-Q, Ji N-Y. Proharziane and harziane derivatives from the marine algicolous fungus *Trichoderma asperelloides* RR-dl-6-11. J Nat Prod. 2021;84:1414–9.

60. Xie Z-L, Li H-J, Wang L-Y, Liang W-L, Liu W, Lan W-J. Trichodermaerin, a new diterpenoid lactone from the marine fungus *Trichoderma erinaceum* associated with the sea star *Acanthaster planci*. Nat Prod Commun. 2013;8:67–8.

61. Yamada T, Suzue M, Arai T, Kikuchi T, Tanaka R. Trichodermanins C-E, new diterpenes with a fused 6-5-6-6 ring system produced by a marine sponge-derived fungus. Mar Drugs. 2017;15:169.

62. Yamada T, Fujii A, Kikuchi T. New diterpenes with a fused 6-5-6-6 ring system isolated from the marine sponge-derived fungus *Trichoderma harzianum*. Mar Drugs. 2019;17:480.

63. Liang X-R, Miao F-P, Song Y-P, Liu X-H, Ji N-Y. Citrinovirin with a new norditerpene skeleton from the marine algicolous fungus *Trichoderma citrinoviride*. Bioorg Med Chem Lett. 2016;26:5029–31.

64. Liang X-R, Miao F-P, Song Y-P, Guo Z-Y, Ji N-Y. Trichocitrin, a new fusicoccane diterpene from the marine brown alga-endophytic fungus *Trichoderma citrinoviride* cf-27. Nat Prod Res. 2016;30:1605–10.

65. Liang X-R, Ma X-Y, Ji N-Y. Trichosordarin A, a norditerpene glycoside from the marine-derived fungus *Trichoderma harzianum* R5. Nat Prod Res. 2020;34:2037–42.

66. Song Y-P, Shi Z-Z, Miao F-P, Fang S-T, Yin X-L, Ji N-Y. Tricholumin A, a highly transformed ergosterol derivative from the alga-endophytic fungus *Trichoderma asperellum*. Org Lett. 2018;20:6306–9.

67. Li B, Huang Q-X, Gao D, Liu D, Ji Y-B, Liu H-G, Lin W-H. New C_{13} lipids from the marine-derived fungus *Trichoderma harzianum*. J Asian Nat Prod Res. 2015;17:468–74.

68. Liu X-H, Ji N-Y. Isolation, identification, and bioactivity of a new triol from algicolous fungus *Trichoderma citrinoviride*. Chem Bioeng. 2022;39:15–8.

69. Hu X, Gong M-W, Zhang W-W, Zheng Q-H, Liu Q-Y, Chen L, Zhang Q-Q. Novel cytotoxic metabolites from the marine-derived fungus *Trichoderma citrinoviride*. Heterocycles. 2014;89:189–96.

70. Zhao D-L, Zhang X-F, Huang R-H, Wang D, Wang X-Q, Li Y-Q, Zheng C-J, Zhang P, Zhang C-S. Antifungal nafuredin and epithiodiketopiperazine derivatives from the mangrove-derived fungus *Trichoderma harzianum* D13. Front Microbiol. 2020;11:1495.

71. Amagata T, Usami Y, Minoura K, Ito T, Numata A. Cytotoxic substances produced by a fungal strain from a sponge: physico-chemical properties and structures. J Antibiot. 1998;51:33–40.

72. Usami Y, Ikura T, Amagata T, Numata A. First total syntheses and configurational assignments of cytotoxic trichodenones A-C. Tetrahedron: Asymm. 2000;11:3711–25.

73. You J, Dai H, Chen Z, Liu G, He Z, Song F, Yang X, Fu H, Zhang L, Chen X. Trichoderone, a novel cytotoxic cyclopentenone and cholesta-7, 22-diene-3β, 5α, 6β-triol, with new activities from the marine-derived fungus *Trichoderma* sp. J Ind Microbiol Biotechnol. 2010;37:245–52.

74. Qiu P, Ding L, Sun D, He S. A new cyclopentenone derivative from the sponge-associated fungus *Hypocrea koningii*. Chem Nat Compd. 2018;54:631–3.

75. Sun S, Tian L, Wang Y, Wu H, Lu X, Pei Y. A novel natural product from the fermentation liquid of marine fungus *Trichoderma atroviride* G20–12. Asian J Trad Med. 2009;4:123–7.

76. Tang X-X, Liu S-Z, Sun Y-Y, He F-M, Xu G-X, Fang M-J, Zhen W, Qiu Y-K. New cyclopentenoneacrylic acid derivatives from a marine-derived fungus *Trichoderma atroviride* H548. Nat Prod Res. 2021;35:3772–9.

77. Ding L-J, Gu B-B, Jiao W-H, Yuan W, Li Y-X, Tang W-Z, Yu H-B, Liao X-J, Han B-N, Li Z-Y, Xu S-H, Lin H-W. New furan and cyclopentenone derivatives from the sponge-associated fungus *Hypocrea Koningii* PF04. Mar Drugs. 2015;13:5579–92.

78. Fang F, Zhao J, Ding L, Huang C, Naman B, He S, Wu B, Zhu P, Luo Q, Gerwick WH, Yan X, Wang Q, Zhang Z, Cui W. 5-Hydroxycyclopenicillone, a new β-amyloid fibrillization inhibitor from a sponge-derived fungus *Trichoderma* sp. HPQJ-34. Mar Drugs. 2017;15:260.

79. Du L, Zhu T, Li L, Cai S, Zhao B, Gu Q. Cytotoxic sorbicillinoids and bisorbicillinoids from a marine-derived fungus *Trichoderma* sp. Chem Pharm Bull. 2009;57:220–3.

80. Lan W-J, Zhao Y, Xie Z-L, Liang L-Z, Shao W-Y, Zhu L-P, Yang D-P, Zhu X-F, Li H-J. Novel sorbicillin analogues from the marine fungus *Trichoderma* sp. associated with the seastar *Acanthaster planci*. Nat Prod Commun. 2012;7:1337–40.

81. Zhang P, Deng Y, Lin X, Chen B, Li J, Liu H, Chen S, Liu L. Anti-inflammatory mono- and dimeric sorbicillinoids from the marine-derived fungus *Trichoderma reesei* 4670. J Nat Prod. 2019;82:947–57.

82. Liu S-Z, Xu G-X, He F-M, Zhang W-B, Wu Z, Li M-Y, Tang X-X, Qiu Y-K. New sorbicillinoids with tea pathogenic fungus inhibitory effect from marine-derived fungus *Hypocrea jecorina* H8. Mar Drugs. 2022;20:213.

83. Zaman KAU, Wu X, Sarotti AM, Cao S. New and bioactive polyketides from Hawaiian marine-derived fungus *Trichoderma* sp. FM652. Nat Prod Res. 2022;36:5984–90.

84. Meng J, Cheng W, Heydari H, Wang B, Zhu K, Konuklugil B, Lin W. Sorbicillinoid-based metabolites from a sponge-derived fungus *Trichoderma saturnisporum*. Mar Drugs. 2018;16:226.

85. Sperry S, Samuels GJ, Crews P. Vertinoid polyketides from the saltwater culture of the fungus *Trichoderma longibrachiatum* separated from a *Haliclona* marine sponge. J Org Chem. 1998;63:10011–4.

86. Rehman SU, Yang L-J, Zhang Y-H, Wu J-S, Shi T, Haider W, Shao C-L, Wang C-Y. Sorbicillinoid derivatives from sponge-derived fungus *Trichoderma reesei* (HN-2016-018). Front Microbiol. 2020;11:1334.

87. Neumann K, Abdel-Lateff A, Wright AD, Kehraus S, Krick A, König GM. Novel sorbicillin derivatives with an unprecedented carbon skeleton from the sponge-derived fungus *Trichoderma* species. Eur J Org Chem. 2007;2007:2268–75.

88. Marra R, Nicoletti R, Pagano E, DellaGreca M, Salvatore MM, Borrelli F, Lombardi N, Vinale F, Woo SL, Andolfi A. Inhibitory effect of trichodermanone C, a sorbicillinoid produced by *Trichoderma citrinoviride* associated to the green alga *Cladophora* sp., on nitrite production in LPS-stimulated macrophages. Nat Prod Res. 2019;33:3389–97.

89. Sun Y, Tian L, Huang J, Ma H-Y, Zheng Z, Lv A-L, Yasukawa K, Pei Y-H. Trichodermatides A–D, novel polyketides from the marine-derived fungus *Trichoderma reesei*. Org Lett. 2008;10:393–6.

90. Wang X-H, Xu X-Y, Li Y, Yao F-H, Chen X, Qi S-H, Tao S-H. Secondary metabolites and antimicrobial activities of *Hypocrea lixii* SCSIO 41520. Nat Prod Res Dev. 2020;32:1522–8.

91. Song F, Dai H, Tong Y, Ren B, Chen C, Sun N, Liu X, Bian J, Liu M, Gao H, Liu H, Chen X, Zhang L. Trichodermaketones A–D and 7-*O*-methyl-koninginin D from the marine fungus *Trichoderma koningii*. J Nat Prod. 2010;73:806–10.

92. Yamazaki H, Saito R, Takahashi O, Kirikoshi R, Toraiwa K, Iwasaki K, Izumikawa Y, Nakayama W, Namikoshi M. Trichoketides A and B, two new protein tyrosine phosphatase 1B inhibitors from the marine-derived fungus *Trichoderma* sp. J Antibiot. 2015;68:628–32.

93. Nuansri S, Rukachaisirikul V, Rungwirain N, Kaewin S, Yimnual C, Phongpaichit S, Preedanon S, Sakayaroj J, Muanprasat C. α-Pyrone and decalin derivatives from the marine-derived fungus *Trichoderma harzianum* PSU-MF79. Nat Prod Res. 2022;36:5462–9.

94. Lai C, Chen J, Liu J, Tian D, Lan D, Liu T, Wu B, Bi H, Tang J. New polyketides from a hydrothermal vent sediment fungus *Trichoderma* sp. JWM29-10-1 and their antimicrobial effects. Mar Drugs. 2022;20:720.

95. Yamada T, Mizutani Y, Umebayashi Y, Inno N, Kawashima M, Kikuchi T, Tanaka R. Tandyukisin, a novel ketoaldehyde decalin derivative, produced by a marine sponge-derived *Trichoderma harzianum*. Tetrahedron Lett. 2014;55:662–4.

96. Yamada T, Umebayashi Y, Kawashima M, Sugiura Y, Kikuchi T, Tanaka R. Determination of the chemical structures of tandyukisins B–D, isolated from a marine sponge-derived fungus. Mar Drugs. 2015;13:3231–40.

97. Suzue M, Kikuchi T, Tanaka R, Yamada T. Tandyukisins E and F, novel cytotoxic decalin derivatives isolated from a marine sponge-derived fungus. Tetrahedron Lett. 2016;57:5070–3.

98. Yu J-Y, Shi T, Zhou Y, Xu Y, Zhao D-L, Wang C-Y. Naphthalene derivatives and halogenate quinoline from the coral-derived fungus *Trichoderma harzianum* (XS-20090075) through OSMAC approach. J Asian Nat Prod Res. 2021;23:250–7.

99. Khamthong N, Rukachaisirikul V, Tadpetch K, Kaewpet M, Phongpaichit S, Preedanon S, Sakayaroj J. Tetrahydroanthraquinone and xanthone derivatives from the marine-derived fungus *Trichoderma aureoviride* PSU-F95. Arch Pharm Res. 2012;35:461–8.

100. Shi T, Hou X-M, Li Z-Y, Cao F, Zhang Y-H, Yu J-Y, Zhao D-L, Shao C-L, Wang C-Y. Harzianumnones A and B: two hydroxyanthraquinones from the coral-derived fungus *Trichoderma harzianum*. RSC Adv. 2018;8:27596.

101. Pang X, Lin X, Tian Y, Liang R, Wang J, Yang B, Zhou X, Kaliyaperumal K, Luo X, Tu Z, Liu Y. Three new polyketides from the marine sponge-derived fungus *Trichoderma* sp. SCSIO41004. Nat Prod Res. 2018;32:105–11.

102. Ohkawa Y, Miki K, Suzuki T, Nishio K, Sugita T, Kinoshita K, Takahashi K, Koyama K. Antiangiogenic metabolites from a marine-derived fungus, Hypocrea vinosa. J Nat Prod. 2010;73:579–82.

103. Shi Z-Z, Miao F-P, Fang S-T, Yin X-L, Ji N-Y. Trichorenins A–C, algicidal tetracyclic metabolites from the marine-alga-epiphytic fungus *Trichoderma virens* Y13–3. J Nat Prod. 2018;81:1121–4.

104. Mereyala HB, Gadikota RR. A concise synthesis of harzialactone A from D-glucose and revision of absolute stereochemistry. Tetrahedron Asym. 1999;10:2305–6.

105. Sun S, Tian L, Wu Z-H, Chen G, Wu H-H, Wang Y-N, Pei Y-H. Two new compounds from fermentation liquid of the marine fungus *Trichoderma atroviride* G20–12. J Asian Nat Prod Res. 2009;11:898–903.

106. Abdel-Lateff A, Fisch K, Wright AD. Trichopyrone and other constituents from the marine sponge-derived fungus *Trichoderma* sp. Z Naturforsch. 2009;64c:186–92.

107. Yamazaki H, Rotinsulu H, Narita R, Takahashi R, Namikoshi M. Induced production of halogenated epidithiodiketopiperazines by a marine-derived *Trichoderma* cf. *brevicompactum* with sodium halides. J Nat Prod. 2015;78:2319–21.

108. Yamazaki H, Takahashi O, Murakami K, Namikoshi M. Induced production of a new unprecedented epitrithiodiketopiperazine, chlorotrithiobrevamide, by a culture of the marine-derived *Trichoderma* cf. *brevicompactum* with dimethyl sulfoxide. Tetrahedron Lett. 2015;56:6262–5.

109. Shi Z-Z, Miao F-P, Fang S-T, Yin X-L, Ji N-Y. Sulfurated diketopiperazines from an algicolous isolate of *Trichoderma virens*. Phytochem Lett. 2018;27:101–4.

110. Lu X, Tian L, Chen G, Xu Y, Wang H-F, Li Z-Q, Pei Y-H. Three new compounds from the marine-derived fungus *Trichoderma atroviride* G20–12. J Asian Nat Prod Res. 2012;14:647–51.

111. Sun Y, Tian L, Huang Y-F, Sha Y, Pei Y-H. A new cyclotetrapeptide from marine fungus *Trichoderma reesei*. Pharmazie. 2006;61:809–10.

112. Garo E, Starks CM, Jensen PR, Fenical W, Lobkovsky E, Clardy J. Trichodermamides A and B, cytotoxic modified dipeptides from the marine-derived fungus *Trichoderma virens*. J Nat Prod. 2003;66:423–6.

113. Yamazaki H, Rotinsulu H, Takahashi O, Kirikoshi R, Namikoshi M. Induced production of a new dipeptide with a disulfide bridge by long-term fermentation of marine-derived *Trichoderma* cf. *brevicompactum*. Tetrahedron Lett. 2016;57:5764–7.

114. Pruksakorn P, Arai M, Kotoku N, Vilchèze C, Baughn AD, Moodley P, Jacobs WR Jr, Kobayashi M. Trichoderins, novel aminolipopeptides from a marine sponge-derived *Trichoderma* sp., are active against dormant mycobacteria. Bioorg Med Chem Lett. 2010;20:3658–63.

115. Kavianinia I, Kunalingam L, Harris PWR, Cook GM, Brimble MA. Total synthesis and stereochemical revision of the anti-tuberculosis peptaibol trichoderin A. Org Lett. 2016;18:3878–81.

116. Ren J, Xue C, Tian L, Xu M, Chen J, Deng Z, Proksch P, Lin W. Asperelines A–F, peptaibols from the marine-derived fungus *Trichoderma asperellum*. J Nat Prod. 2009;72:1036–44.

117. Chen L, Zhong P, Pan J-R, Zhou K-J, Huang K, Fang Z-X, Zhang Q-Q. Asperelines G and H, two new peptaibols from the marine-derived fungus *Trichoderma asperellum*. Heterocycles. 2013;87:645–55.

118. Ren J, Yang Y, Liu D, Chen W, Proksch P, Shao B, Lin W. Sequential determination of new peptaibols asperelines G-Z₁₂ produced by marine-derived fungus *Trichoderma asperellum* using ultrahigh pressure liquid chromatography combined with electrospray-ionization tandem mass spectrometry. J Chromatogr A. 2013;1309:90–5.

119. Mohamed-Benkada M, Montagu M, Biard J-F, Mondeguer F, Verite P, Dalgalarrondo M, Bissett J, Pouchus YF. New short peptaibols from a marine *Trichoderma* strain. Rapid Commun Mass Spectrom. 2006;20:1176–80.

120. Ruiz N, Wielgosz-Collin G, Poirier L, Grovel O, Petit KE, Mohamed-Benkada M, du Pont TR, Bissett J, Vérité P, Barnathan G, Pouchus YF. New trichobrachins, 11-residue peptaibols from a marine strain of *Trichoderma longibrachiatum*. Peptides. 2007;28:1351–8.

121. Carroux A, Van Bohemen A-I, Roullier C, du Pont TR, Vansteelandt M, Bondon A, Zalouk-Vergnoux A, Pouchus YF, Ruiz N. Unprecedented 17-residue peptaibiotics produced by marine-derived *Trichoderma atroviride*. Chem Biodivers. 2013;10:772–86.

122. Panizel I, Yarden O, Ilan M, Carmeli S. Eight new peptaibols from sponge-associated *Trichoderma atroviride*. Mar Drugs. 2013;11:4937–60.

123. Mohamed-Benkada M, Pouchus YF, Vérité P, Pagniez F, Caroff N, Ruiz N. Identification and biological activities of long-chain peptaibols produced by a marine-derived strain of *Trichoderma longibrachiatum*. Chem Biodivers. 2016;13:521–30.

124. Touati I, Ruiz N, Thomas O, Druzhinina IS, Atanasova L, Tabbene O, Elkahoui S, Benzekri R, Bouslama L, Pouchus YF, Limam F. Hyporientalin A, an anti-*Candida* peptaibol from a marine *Trichoderma orientale*. World J Microbiol Biotechnol. 2018;34:98.

125. Hao M-J, Chen P-N, Li H-J, Wu F, Zhang G-Y, Shao Z-Z, Liu X-P, Ma W-Z, Xu J, Mahmud T, Lan W-J. β-Carboline alkaloids from the deep-sea fungus *Trichoderma* sp. MCCC 3A01244 as a new type of anti-pulmonary fibrosis agent that inhibits TGF-b/Smad signaling pathway. Front Microbiol. 2022;13:947226.

126. Wu B, Oesker V, Wiese J, Schmaljohann R, Imhoff JF. Two new antibiotic pyridones produced by a marine fungus, *Trichoderma* sp. strain MF106. Mar Drugs. 2014;12:1208–19.

127. Liu T, Li Z-L, Wang Y, Tian L, Pei Y-H, Hua H-M. A new alkaloid from the marine-derived fungus *Hypocrea virens*. Nat Prod Res. 2011;25:1596–9.

128. Ni M, Lin Y-N, Deng C-L. A novel alkaloid from the marine-derived fungus *Trichoderma citrinoviride*. Chin J Mar Drugs. 2020;39:71–6.

129. Ding L-J, Yuan W, Li Y-X, Liao X-J, Sun H, Peng Q, Han B-N, Lin H-W, Li Z-Y, Yang F, Xu S-H. Hypocrol A, a new tyrosol derivative from a sponge-derived strain of the fungus *Hypocrea koningii*. Nat Prod Res. 2016;30:1633–8.

130. Rehman SU, Wu J-S, Yang L-J, Ting S, Shao C-L, Wang C-Y. One new terphenyl glycoside from a sponge-derived fungus *Trichoderma reesei* (HN-2016-018). Nat Prod Commun. 2020;15:1–5.

131. Huang H-R, Xia X-K, She Z-G, Lin Y-C, Vrijmoed LLP, Jones EBG. A new chloro-monoterpene from the mangrove endophytic fungus *Tryblidiopycnis* sp. (4275). J Asian Nat Prod Res. 2006;8:609–12.

132. Ebel R. Terpenes from marine-derived fungi. Mar Drugs. 2010;8:2340–68.

133. Li C-S, Liu L-T, Yang L, Li J, Dong X. Chemistry and bioactivity of marine-derived bisabolane sesquiterpenoids: a review. Front Chem. 2022;10:881767.

134. Shu H-Z, Peng C, Bu L, Guo L, Liu F, Xiong L. Bisabolane-type sesquit-erpenoids: Structural diversity and biological activity. Phytochemistry. 2021;192: 112927.

135. Grove JF. Non-macrocyclic trichothecenes. Nat Prod Rep. 1988;5:187–209.

136. Degenkolb T, Dieckmann R, Nielsen KF, Gräfenhan T, Theis C, Zafari D, Chaverri P, Ismaiel A, Brückner H, von Döhren H, Thrane U, Petrini O, Samuels GJ. The *Trichoderma brevicompactum* clade: a separate lineage with new species, new peptaibiotics, and mycotoxins. Mycol Progress. 2008;7:177–219.

137. Yasumura R, Ashtekar KD, Tonouchi A, Nehira T, Borhan B, Hashimoto M. 7-β- and 10-β-Hydroxylated congeners of CAF-603; elucidation of absolute configuration of CAF-603 family, and their SAF studies in the anti-fungal activity. Tetrahedron. 2013;69:9469–74.

138. Liu X-H, Song Y-P, Yin X-L, Ji N-Y. Antimicrobial terpenoids and polyke-tides from the algicolous fungus *Byssochlamys spectabilis* RR-dl-2-13. J Agric Food Chem. 2022;70:4658–66.

139. Jiang L, Wen Y, Peng Y, Chen T, Chen J, Yang J, Gong T, Zhu P. Advances in biosynthesis of cadinane sesquiterpenes. Chin J Biotech. 2021;37:1952–67.

140. Hönig M, Carreira EM. Total synthesis and structural revision of a harzi-ane diterpenoid. Angew Chem Int Ed. 2020;59:1192–6.

141. Chantrapromma S, Jeerapong C, Phupong W, Quah CK, Fun H-K. Tricho-dermaerin: a diterpene lactone from *Trichoderma asperellum*. Acta Cryst. 2014;E70:o408–9.

142. Barra L, Dickschat JS. Harzianone biosynthesis by the biocontrol fungus *Trichoderma*. ChemBioChem. 2017;18:2358–65.

143. Yamamoto T, Izumi N, Ui H, Sueki A, Masuma R, Nonaka K, Hirose T, Sunazuka T, Nagai T, Yamada H, Ōmura S, Shiomi K. Wickerols A and B: novel anti-influenza virus diterpenes produced by *Trichoderma atro-viride* FKI-3849. Tetrahedron. 2012;68:9267–71.

144. Sun P-X, Zheng C-J, Li W-C, Jin G-L, Huang F, Qin L-P. Trichodermanin A, a novel diterpenoid from endophytic fungus culture. J Nat Med. 2011;65:381–4.

145. Deng J, Ning Y, Tian H, Gui J. Divergent synthesis of antiviral diterpenes wickerols A and B. J Am Chem Soc. 2020;142:4690–5.

146. Ui H, Shiomi K, Yamaguchi Y, Masuma R, Nagamitsu T, Takano D, Suna-zuka T, Namikoshi M, Ōmura S. Nafuredin, a novel inhibitor of NADH-fumarate reductase, produced by *Aspergillus niger* FT-0554. J Antibiot. 2001;54:234–8.

147. Zhang Z, He X, Zhang G, Che Q, Zhu T, Gu Q, Li D. Inducing secondary metabolite production by combined culture of *Talaromyces aculeatus* and *Penicillium variabile*. J Nat Prod. 2017;80:3167–71.

148. Baldwin JE, Derome AE, Field LD, Gallagher PT, Taha AA, Thaller V, Brewer D, Taylor A. Biosynthesis of a cyclopentyl dienyl isonitrile acid in cultures of the fungus *Trichoderma hamatum* (Bon) Bain. aggr. J Chem Soc Chem Commun. 1981;1981:1227–9.

149. Sugaya K, Koshino H, Hongo Y, Yasunaga K, Onose J-I, Yoshikawa K, Abe N. The biosynthesis of sorbicillinoids in *Trichoderma* sp. USF-2690: prospect for the existence of a common precursor to sorbicillinol and 5-epihydroxyvertinolide, a new sorbicillinoid member. Tetrahedron Lett. 2008;49:654–7.

150. Harned AM, Volp KA. The sorbicillinoid family of natural prod-ucts: isolation, biosynthesis, and synthetic studies. Nat Prod Rep. 2011;28:1790–810.

151. Wood JL, Thompson BD, Yusuff N, Pflum DA, Matthäus MSP. Total syn-thesis of (±)-epoxysorbicillinol. J Am Chem Soc. 2001;123:2097–8.

152. Pettus LH, Water RW, Pettus TRR. Synthesis of (±)-epoxysorbicillinol using a novel cyclohexa-2,5-dienone with synthetic applications to other sorbicillin derivatives. Org Lett. 2001;3:905–8.

153. Meng J, Wang X, Xu D, Fu X, Zhang X, Lai D, Zhou L, Zhang G. Sorbicil-linoids from fungi and their bioactivities. Molecules. 2016;21:715.

154. Samuels GJ, Ismaiel A, Mulaw TB, Szakacs G, Druzhinina IS, Kubicek CP, Jaklitsch WM. The Longibrachiatum clade of *Trichoderma*: a revision with new species. Fungal Divers. 2012;55:77–108.

155. Shigehisa H, Suwa Y, Furiya N, Nakaya Y, Fukushima M, Ichihashi Y, Hiroya K. Stereocontrolled synthesis of trichodermatide A. Angew Chem Int Ed. 2013;52:3646–9.

156. Liu G, Wang Z. Total synthesis of koninginin D, B and E. Synthesis. 2001;2001:119–27.

157. Satoh Y, Tajima K, Munekata M, Keasling JD, Lee TS. Engineering of a tyrosol-producing pathway, utilizing simple sugar and the central metabolic tyrosine, in *Escherichia coli*. J Agric Food Chem. 2012;60:979–84.

158. Fan D-M, Liu Y, Tang L. Review on pharmacological activities of natu-ral xanthone. Nat Prod Res Dev. 2017;29:503–10.

159. Siddamurthi S, Gutti G, Jana S, Kumar A, Singh SK. Anthraquinone: a promising scaffold for the discovery and development of therapeutic agents in cancer therapy. Future Med Chem. 2020;12:1037–69.

160. Xu Y, Vinas M, Alsarrag A, Su L, Pfohl K, Rohlfs M, Schäfer W, Chen W, Karlovsky P. Bis-naphthopyrone pigments protect filamentous asco-mycetes from a wide range of predators. Nat Commun. 2019;10:3579.

161. Bian G, Han Y, Hou A, Yuan Y, Liu X, Deng Z, Liu T. Releasing the potential power of terpene synthases by a robust precursor supply platform. Metab Eng. 2017;42:1–8.

162. Kumar DN, Reddy CR, Das B. Stereoselective synthesis of cytotoxic marine metabolite harzialactone A by three different routes. Synthe-sis. 2011;2011:3190–4.

163. Ballaschk F, Özkaya Y, Kirsch SF. Stereocontrolled synthesis of harzialactone A and its three stereoisomers by use of standardized polyketide building blocks. Eur J Org Chem. 2020;2020:6078–80.

164. Chen B, Yin H-F, Wang Z-S, Xu J-H. New synthesis of harzialactone A via kinetic resolution using recombinant *Fusarium proliferatum* lactonase. Tetrahedron Asymm. 2010;21:237–40.

165. Wang Y-N, Mou Y-H, Dong Y, Wu Y, Liu B-Y, Bai J, Yan D-J, Zhang L, Feng D-Q, Pei Y-H, Hu Y-C. Diphenyl ethers from a marine-derived *Aspergillus sydowii*. Mar Drugs. 2018;16:451.

166. Zhang Y, Li X-M, Shang Z, Li C-S, Ji N-Y, Wang B-G. Meroterpenoid and diphenyl ether derivatives from *Penicillium* sp. MA-37, a fungus isolated from marine mangrove rhizospheric soil. J Nat Prod. 2012;75:1888–95.

167. Xu X, Liu L, Zhang F, Wang W, Li J, Guo L, Che Y, Liu G. Identification of the first diphenyl ether gene cluster for pestheic acid biosynthesis in plant endophyte *Pestalotiopsis fici*. ChemBioChem. 2014;15:284–92.

168. Wan X, Doridot G, Joullié MM. Progress towards the total synthesis of trichodermamides A and B: construction of the oxazine ring moiety. Org Lett. 2007;9:977–80.

169. Wan X, Joullié MM. Enantioselective total syntheses of trichoderma-mides A and B. J Am Chem Soc. 2008;130:17236–7.

170. Lu C-D, Zakarian A. Total synthesis of (±)-trichodermamide B and of a putative biosynthetic precursor to aspergillazine A using an oxaza-cope rearrangement. Angew Chem Int Ed. 2008;47:6829–31.

171. Mfuh AD, Zhang Y, Stephens DE, Vo AXT, Arman HD, Larionov OV. Concise total synthesis of trichodermamides A, B, and C enabled by an efficient construction of the 1,2-oxazadecaline core. J Am Chem Soc. 2015;137:8050–3.

172. Jans PE, Mfuh AM, Arman HD, Shaffer CV, Larionov OV, Mooberry SL. Cytotoxicity and mechanism of action of the marine-derived fungal metabolite trichodermamide B and synthetic analogues. J Nat Prod. 2017;80:676–83.

173. Capon RJ, Ratnayake R, Stewart M, Lacey E, Tennant S, Gill JH. Aspergilla-zines A–E: novel heterocyclic dipeptides from an Australian strain of *Aspergillus unilateralis*. Org Biomol Chem. 2005;3:123–9.

174. Lin Y, Shao Z, Jiang G, Zhou S, Cai J, Vrijmoed LLP, Jones EBG. Penicilla-zine, a unique quinolone derivative with 4H–5,6-dihydro-1,2-oxazine ring system from the marine fungus *Penicillium* sp. (strain #386) from the South China Sea. Tetrahedron. 2000;56:9607–9.

175. Liu R, Gu Q-Q, Zhu W-M, Cui C-B, Fan G-T. Trichodermamide A and aspergillazine A, two cytotoxic modified dipeptides from a marine-derived fungus *Spicaria elegans*. Arch Pharm Res. 2005;28:1042–6.

176. Röhrich CR, Jaklitsch WM, Voglmayr H, Iversen A, Vilcinskas A, Nielsen KF, Thrane U, von Döhren H, Brückner H, Degenkolb T. Front line defenders of the ecological niche! Screening the structural diversity of peptaibiot-ics from saprotrophic and fungicolous *Trichoderma/Hypocrea* species. Fungal Divers. 2014;69:117–46.

177. Bills G, Li Y, Chen L, Yue Q, Niu X-M, An Z. New insights into the echino-candins and other fungal non-ribosomal peptides and peptaibiotics. Nat Prod Rep. 2014;31:1348–75.

178. Degenkolb T, Brückner H. Peptaibiomics: towards a myriad of bioac-tive peptides containing C^{α}-dialkylamino acids? Chem Biodivers. 2008;5:1817–43.

179. de Silva ED, Geiermann AS, Mitova MI, Kuegler P, Blunt JW, Cole ALJ, Munro MHG. Isolation of 2-pyridone alkaloids from a New Zealand marine-derived *Penicillium* species. J Nat Prod. 2009;72:477–9.
180. Ghisalberti EL. Bioactive tetramic acid metabolites. Stud Nat Prod Chem. 2003;28:109–63.
181. Pedersen AT, Ringborg R, Grotkjær T, Pedersen S, Woodley JM. Synthesis of 5-hydroxymethylfurfural (HMF) by acid catalyzed dehydration of glucose-fructose mixtures. Chem Eng J. 2015;273:455–64.
182. Clinger JA, Zhang Y, Liu Y, Miller MD, Hall RE, Van Lanen SG, Phillips GN Jr, Thorson JS, Elshahawi SI. Structure and function of a dual reductase-dehydratase enzyme system involved in *p*-terphenyl biosynthesis. ACS Chem Biol. 2021;16:2816–24.
183. Liu J-K. Natural terphenyls: developments since 1877. Chem Rev. 2006;106:2209–23.
184. Ji N-Y, Wang B-G. Mycochemistry of marine algicolous fungi. Fungal Divers. 2016;80:301–42.
185. Song Y, Miao F, Liu X, Ji N. Responses of marine-derived *Trichoderma* fungi to seawater and their potential antagonistic behavior. J Oceanol Limnol. 2019;37:525–34.
186. Pinedo-Rivilla C, Aleu J, Durán-Patrón R. Cryptic metabolites from marine-derived microorganisms using OSMAC and epigenetic approaches. Mar Drugs. 2022;20:84.
187. Shang Z, Salim AA, Capon RJ. Chaunopyran A: co-cultivation of marine mollusk-derived fungi activates a rare class of 2-alkenyl-tetrahydro-pyran. J Nat Prod. 2017;80:1167–72.
188. Kossuga MH, Ferreira AG, Sette LD, Berlinck RGS. Two polyketides from a co-culture of two marine-derived fungal strains. Nat Prod Commun. 2013;8:721–4.
189. Zhang L, Niaz SI, Khan D, Wang Z, Zhu Y, Zhou H, Lin Y, Li J, Liu L. Induction of diverse bioactive secondary metabolites from the mangrove endophytic fungus *Trichoderma* sp. (strain 307) by co-cultivation with *Acinetobacter johnsonii* (strain B2). Mar Drugs. 2017;15:35.
190. Zhang L, Niaz SI, Wang Z, Zhu Y, Lin Y, Li J, Liu L. α-Glucosidase inhibitory and cytotoxic botryorhodines from mangrove endophytic fungus *Trichoderma* sp. 307. Nat Prod Res. 2018;32:2887–92.
191. Marmann A, Aly AH, Lin W, Wang B, Proksch P. Co-cultivation-a powerful emerging tool for enhancing the chemical diversity of microorganisms. Mar Drugs. 2014;12:1043–65.
192. Noguchi A, Inohara-Ochiai M, Ishibashi N, Fukami H, Nakayama T, Nakao M. A novel glucosylation enzyme: molecular cloning, expression, and characterization of *Trichoderma viride* JCM22452 α-amylase and enzymatic synthesis of some flavonoid monoglucosides and oligoglucosides. J Agric Food Chem. 2008;56:12016–24.
193. Yang Y, Ding Y, Zhang T. Biotransformation of geniposide into genipin by immobilized *Trichoderma reesei* and conformational study of genipin. Biomed Res Int. 2018;2018:2079195.
194. Leutou AS, Yang G, Nenkep VN, Siwe XN, Feng Z, Khong TT, Choi HD, Kang JS, Son BW. Microbial transfromation of a monoterpene, geraniol, by the marine-derived fungus *Hypocrea* sp. J Microbiol Biotechnol. 2009;19:1150–2.
195. Saravanakumar K, Kathiresan K. Bioremoval of the synthetic dye malachite green by marine *Trichoderma* sp. Springerplus. 2014;3:631.
196. Vacondio B, Birolli WG, Ferreira IM, Seleghim MHR, Gonçalves S, Vasconcellos SP, Porto ALM. Biodegradation of pentachlorophenol by marine-derived fungus *Trichoderma harzianum* CBMAI 1677 isolated from ascidian *Didemnun ligulum*. Biocatal Agric Biotechnol. 2015;4:266–75.
197. Alvarenga N, Birolli WG, Nitschke M, de de O Rezende MO, Seleghim MHR, Porto ALM. Biodegradation of chlorpyrifos by whole cells of marine-derived fungi *Aspergillus sydowii* and *Trichoderma* sp. J Microb Biochem Technol. 2015;7:133–9.
198. Dini I, Alborino V, Lanzuise S, Lombardi N, Marra R, Balestrieri A, Ritieni A, Woo SL, Vinale F. *Trichoderma* enzymes for degradation of aflatoxin B1 and ochratoxin A. Molecules. 2022;27:3959.

Publisher's Note