


Cite this: *RSC Adv.*, 2020, 10, 10197

Recent advances in the chemistry and biology of azaphilones

Chunmei Chen,^{ac} Huaming Tao,^d Weihao Chen,^{ac} Bin Yang,^a Xuefeng Zhou,^{id a}
Xiaowei Luo^{id *b} and Yonghong Liu^{*abce}

Azaphilones have continuously aroused considerable attention owing to their structural diversity and significant biological activities recently. This review attempts to give a comprehensive summary of recent progress on the isolation, identification, and biological activity, along with synthetic and biosynthetic studies of azaphilones reported from October 2012 to December 2019. Herein, a total of 252 compounds predominantly originated from 32 genera of fungi, such as *Penicillium* (20%) and *Talaromyces* (11%), were included in this research with citations of 105 references. Among these azaphilones, approximately half of them were found with various biological activities, of which over 40% displayed cytotoxic/anti-tumor effects. This review would shed light on the future development and research of azaphilones.

Received 30th January 2020
Accepted 3rd March 2020

DOI: 10.1039/d0ra00894j

rsc.li/rsc-advances

1. Introduction

Natural products have been evidenced as important sources of drug entities and 49% of small molecules functioning as anti-tumor agents are directly or indirectly derived from natural products.¹ Polyketides represent one of the most structurally diverse classes of natural products arising from simple aromatics to highly modified complex ones, meanwhile fungi have been regarded as a major source of bioactive polyketides.²

Azaphilones or azaphilonoids, known as fungal pigments, are also fungal polyketides, featuring the isochroman scaffold containing a pyrone–quinone bicyclic core and a quaternary carbon center.^{3,4} Besides, they have been proved with various activities, such as enzyme inhibitions, antimicrobial, cytotoxic, anti-oxidative, and anti-inflammatory activities.^{3,4} Due to their structural diversity and promising bioactivity, in 2013, J. Gao *et al.* summarized the information on 373 azaphilones of 18 categories covered between the end of 1932 and September 2012.³

Recently, a series of azaphilones with novel structures and remarkable bioactivities were reported. Penicilones A–D (192–195)

with different configurations at the quaternary carbon center, were found with anti-MRSA activity.⁵ Peyronellones A and B (21–22) were identified as a pair of unusual tetracyclic caged adducts of azaphilones and pyruvic acid with hypoxia-protective activity.⁶ Four unusual dimers of azaphilones and furanone derivatives *via* Michael addition, citrifurans A–D (24–27), were found with inhibitory activities against LPS-induced NO production.⁷

Over last seven years, 252 newly reported naturally-derived azaphilones are classified into 13 types based on structural patterns (Fig. 1), including citrinin-types, austdiols, deflectin-types, bulgarialactone-types, hydrogenated spiro-azaphilones, O-containing *Monascus* pigments, angular lactone-types, hydrogenated ones, chaetoviridins and chaephilones, pulvilloric acid-types, sclerotiorins, cohaerins, and nitrogenated ones.³ They were majorly obtained from fungi exemplified by *Penicillium* sp. and *Talaromyces* sp. with a large range of biological activities, such as cytotoxicity,⁸ antitumor activity,⁹ antimicrobial activity,¹⁰ anti-inflammatory,¹¹ enzyme inhibitions,¹² antioxidant activity,⁶ antiviral activity,^{13,14} antileishmanial activity,¹⁵ brine shrimp toxicity,¹⁶ insecticidal activity,¹⁷ and hypoxia-protective activity.⁶ Given the continuing interests of azaphilones arising from chemists and pharmacologists, recent advances in the chemistry and biology of azaphilones covered from October 2012 to December 2019 were concluded in this review, focusing on fungal sources, isolation, structural identification, biological activities, chemical synthesis and biosynthesis.

2. Azaphilones

2.1 Citrinin-type azaphilones

Recently, twenty-seven citrinin-type azaphilones (1–27) were isolated from several fungal strains (Fig. 2 and Table 1). Most of

^aCAS Key Laboratory of Tropical Marine Bio-resources and Ecology, Guangdong Key Laboratory of Marine Materia Medica, South China Sea Institute of Oceanology, Chinese Academy of Sciences, Guangzhou 510301, P. R. China. E-mail: yonghongliu@scsio.ac.cn; Fax: +86-20-89023174; Tel: +86-20-89023174

^bInstitute of Marine Drugs, Guangxi University of Chinese Medicine, Nanning 530200, P. R. China. E-mail: luoxiaowei1991@126.com; Fax: +86-771-4733826; Tel: +86-771-4733826

^cUniversity of Chinese Academy of Sciences, Beijing 100049, P. R. China

^dSchool of Traditional Chinese Medicine, Southern Medical University, Guangzhou 510515, P. R. China

^eWuya College of Innovation, Shenyang Pharmaceutical University, Shenyang 110016, P. R. China



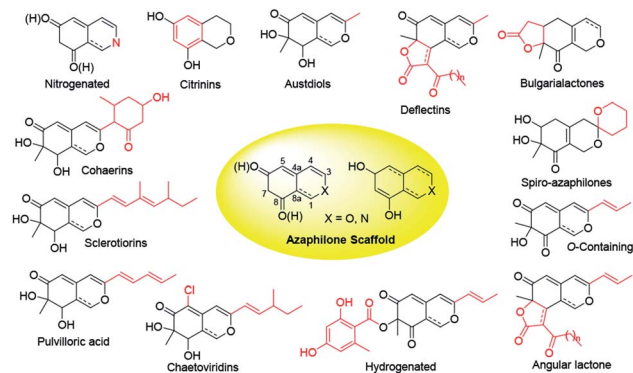


Fig. 1 Structural patterns of 13 types of azaphilones.

them were monomeric citrinin derivatives like annulohypoxylomans A–C (1–3),¹¹ annulohypoxylomanols A and B (4–5),¹¹ annulohypoxylolide (6),¹¹ and the novel pentaketide (7).¹⁸

The fungus *Penicillium* sp., collected in the sediment of the hyper saline lake Wadi El-Natron in Egypt, produced two novel cytotoxic citrinin analogues, (3*S*,4*R*)-6-hydroxy-8-methoxy-3,5-dimethyl isochromanol (8) and (3*S*)-6-hydroxy-8-methoxy-3-methylisochroman (9).¹⁹ An endophytic fungus from *Cordyceps sinensis*, *Aspergillus fumigatus*, gave five new isochromanes (10–14), among which 10 and 11 were determined as a pair of enantiomers purified by chiral HPLC methods.²⁰ Meanwhile, 10 and 12 exhibited moderate activities against MV4-11 cell line with IC₅₀ values of 38.4 and 30.0 μM, respectively.²⁰

As the first report on isochroman glycoside metabolites from the genus *Colletotrichum*, colletobredins A–D (15–18) were

extracted from *Colletotrichum aotearoa* BCRC 09F0161, an endophytic fungus found in the leaves of an endemic Formosan plant *Bredia oldhamii* Hook. f. (Melastomataceae).²¹ Colletobredin A (15) exhibited weak NO inhibitory activity in LPS activated murine macrophage RAW264.7 cells.²¹ Besides, *Monascus pilosus* BCRC 38072 and *Monascus purpureus* BCRC 31499 also produced the isochroman glycoside metabolites, monascuspilolin (19)²² and monascupurpurin (20),²³ respectively.

Among citrinin dimers, peyronellones A–B (21–22), a pair of rare tetracyclic caged adducts of azaphilone with pyruvic acid, were isolated from *Peyronellaea glomerata* with antioxidative abilities, stereochemistry of which were deduced by Rh₂(-OCOCF₃)₄-induced ECD experiments and calculations.⁶ Significantly, 22 (5 μM) could inhibit hypoxia/reoxygenation (H/R)-induced late-stage apoptosis of human umbilical vein endothelial cells and displayed the same hypoxia-protective activity as the positive control verapamil.⁶

Chemical investigation of a mangrove-derived fungus *Penicillium chrysogenum* HND11-24, led to the characterization of penicitol A (23), a citrinin dimer with a novel tetracyclic skeleton, which was found with cytotoxicity against HeLa, BEL-7402, HEK-293, HCT-116, and A549 cell lines (IC₅₀ = 4.6–10.5 μM).²⁴ Citrifurans A–D (24–27), four uncommon heterodimers of azaphilone and furanone derivatives, were discovered from *Aspergillus* sp., meanwhile structure of 24 was confirmed by single-crystal X-ray diffraction, among which 24–26 displayed moderate inhibitory on NO production in RAW 264.7 macrophages with IC₅₀ values of 18.3, 22.6, and 25.3 μM, respectively.⁷

2.2 Austdiol-type azaphilones

This subgroup of azaphilones is characterized by an austdiol core with nineteen members (28–46) (Fig. 3 and Table 1), including fusaraisochromenone (28),²⁵ 7(*S*)-7-hydroxy-3,7-dimethyl-isochromene-6,8-dione (32),²⁶ nemanecins A–C (34–36),²⁷ and perangustols A and B (37–38).²⁸

Felinone A (29) was obtained from a marine bryozoan derived fungus *Beauveria felina* EN-135 with weak activity against brine shrimp with the lethal rate of 61.4% (100 μg mL⁻¹),¹⁶ while absolute configuration of which was revised by chemical synthesis.²⁹ Moreover, xylariphilone (30), the diastereoisomer of 29, was metabolized by the seagrass-derived fungus *Xylariales* sp. PSU-ES163 and *Hypoxylon* sp. BCRC12F 0687,^{30,31} which exhibited significant inhibitory effects on the productions of NO (IC₅₀ = 17.5 μM)³¹ and also demonstrated inhibitory activities towards IL-6 (IC₅₀ = 5.3 μM), IL-12 p40 (IC₅₀ = 19.4 μM), and TNF-α (IC₅₀ = 37.6 μM).¹¹ Another diastereoisomer of 29, aspergillusone C (31) was produced by *Aspergillus clavatus* with cytotoxicity against MCF-7 and A549 cell lines with IC₅₀ values of 2.5 and 41.9 μM, respectively.³²

Recently, Cavallo's group described the isolation and determination of an insecticidal azaphilone, chlamyphilone (33), yielded by *Pochonia chlamydosporia*.¹⁷ Chemical analysis of the fungus *Dothideomycete* sp. CRI7 afforded five austdiol-like azaphilones, dothideomynones B–F (39–43), while compounds 41–43 were obtained from the fermentation broths under deionized water supplemented with potassium bromide.^{33,34} Of particular

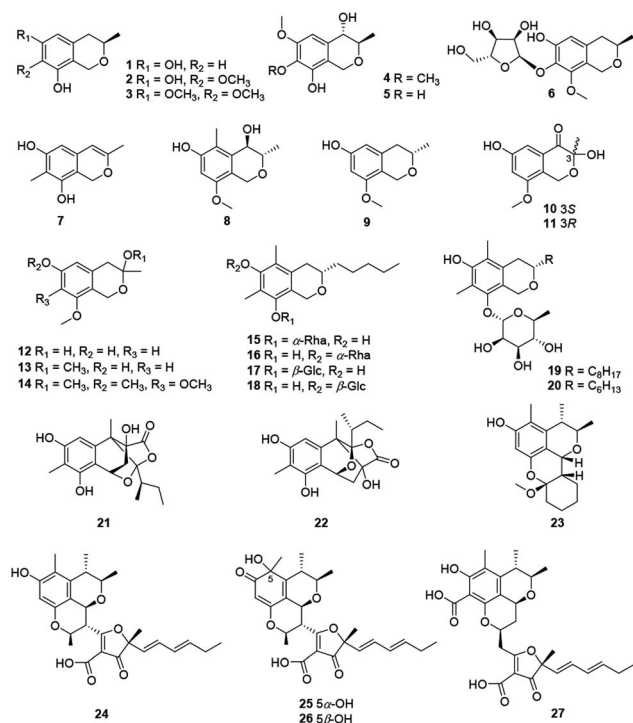


Fig. 2 Chemical structures of citrinin-type azaphilones (1–27).



Table 1 The sources and biological activities of recently reported azaphilones (1–252)

No.	Species	Activity
Annulohypoxyloman A–C (1–3)	<i>Annulohypoxylo truncatum</i> JS540 ¹¹	
Annulohypoxylomanols A–B (4–5)	<i>Annulohypoxylo truncatum</i> JS540 ¹¹	
Annulohypoxyloside (6)	<i>Annulohypoxylo truncatum</i> JS540 ¹¹	
7	<i>Talaromyces stipitatus</i> ATCC 10500 ¹⁸	
(3 <i>S</i> ,4 <i>R</i>)-6-Hydroxy-8-methoxy-3,5-dimethyl isochromanol (8)	<i>Penicillium</i> sp. ¹⁹	Cytotoxic (L5178Y: 26.20% at 10 µg mL ⁻¹)
(3 <i>S</i>)-6-Hydroxy-8-methoxy-3-methylisochroman (9)	<i>Penicillium</i> sp. ¹⁹	Cytotoxic (L5178Y: 16.10% at 10 µg mL ⁻¹)
(<i>S</i>)-3,6-Dihydroxy-8-methoxy-3-methylisochroman-4-one (10)	<i>Aspergillus fumigatus</i> ²⁰	Cytotoxic (MV4-11: 38.39 µM)
(<i>R</i>)-3,6-Dihydroxy-8-methoxy-3-methylisochroman-4-one (11)	<i>Aspergillus fumigatus</i> ²⁰	
8-Methoxy-3-methylisochromane-3,6-diol (12)	<i>Aspergillus fumigatus</i> ²⁰	Cytotoxic (MV4-11: 30.00 µM)
3,8-Dimethoxy-3-methylisochroman-6-ol (13)	<i>Aspergillus fumigatus</i> ²⁰	
3,6,7,8-Tetramethoxy-3-methylisochromane (14)	<i>Aspergillus fumigatus</i> ²⁰	
Colletobredin A (15)	<i>Colletotrichum aotearoa</i> BCRC 09F0161 ²¹	Anti-inflammatory (inhibit NO production: 182.2 µM)
Colletobredins B–D (16–18)	<i>Colletotrichum aotearoa</i> BCRC 09F0161 ²¹	
Monascuspilorin (19)	<i>Monascus pilosus</i> BCRC 38072 ²²	
Monascupurpurin (20)	<i>Monascus purpureus</i> BCRC 31499 ²³	
Peyronellone A (21)	<i>Peyronellaea glomerata</i> ⁶	Antioxidant (ABTS: 88.8 µM, DPPH: 126.3 µM)
Peyronellone B (22)	<i>Peyronellaea glomerata</i> ⁶	Antioxidant (ABTS: 95.2 µM, DPPH: 83.5 µM); hypoxia-protective activity (improved the survival rate of H/R-treated human umbilical vein endothelial cells from 35% to 70% at 5 µM)
Penicitol A (23)	<i>Penicillium chrysogenum</i> HND11-24 ²⁴	Cytotoxic (HeLa: 4.6 µM, BEL-7402: 10.5 µM, HEK-293: 6.7 µM, HCT-116: 5.6 µM, A549: 7.6 µM)
Citrifuran A (24)	<i>Aspergillus</i> sp. ⁷	Anti-inflammatory (inhibit NO production: 18.3 µM)
Citrifuran B (25)	<i>Aspergillus</i> sp. ⁷	Anti-inflammatory (inhibit NO production: 22.6 µM)
Citrifuran C (26)	<i>Aspergillus</i> sp. ⁷	Anti-inflammatory (inhibit NO production: 25.3 µM)
Citrifuran D (27)	<i>Aspergillus</i> sp. ⁷	
Fusaraisochromenone (28)	<i>Fusarium</i> sp. PDB51F5 ²⁵	
Felinone A (29)	<i>Beauveria felina</i> EN-135 ¹⁶	Brine shrimp toxic (61.4% at 100 µg mL ⁻¹)
Xylariphilone (30)	<i>Xylariales</i> sp. PSU-ES163, ³⁰ <i>Hypoxylo</i> sp. BCRC 12F0687 ³¹	Anti-inflammatory (inhibit NO production: 17.5 µM, ³¹ inhibit IL-6 production: 5.3 µM, inhibit IL-12 p40 production: 19.4 µM); anti-tumor (inhibit TNF-α production: 37.6 µM) ¹¹
Aspergillusone C (31)	<i>Aspergillus clavatus</i> ³²	Cytotoxic (MCF-7: 2.5 µM, A549: 41.9 µM)
7(<i>S</i>)-7-Hydroxy-3,7-dimethyl-isochromene-6,8-dione (32)	<i>Nigrospora</i> sp. YE3033 ²⁶	
Chlamyphilone (33)	<i>Pochonia chlamydosporia</i> ¹⁷	Insecticidal (<i>Acyrtosiphon pisum</i> : LD ₅₀ = 175 µg mL ⁻¹ , MIC = 150 µg mL ⁻¹)
Nemanecins A–C (34–36)	<i>Nemania</i> sp. BCC 30850 ²⁷	
Perangustols A–B (37–38)	<i>Cladosporium perangustum</i> FS62 ²⁸	
Dothideomynone C (40)	<i>Dothideomycete</i> sp. CRI7 ³³	Cytotoxic (A549: 46.5 µg mL ⁻¹ , HuCCA-1: 48.1 µg mL ⁻¹ , MOLT-3: 17.4 µg mL ⁻¹)
Dothideomynones B (39), D–F (41–43)	<i>Dothideomycete</i> sp. CRI7 ³⁴	
Mycoleptone A (44)	<i>Mycoleptodiscus indicus</i> ¹⁵	Cytotoxic (PC3: 10.0 µM); antileishmanial (<i>Leishmania major</i> : 28.5 µM)
Mycoleptone B (45)	<i>Mycoleptodiscus indicus</i> ¹⁵	Cytotoxic (PC3: 7.1 µM); antileishmanial (<i>Leishmania major</i> : 21.7 µM)
Mycoleptone C (46)	<i>Mycoleptodiscus indicus</i> ¹⁵	
Deflectin C1 (47)	<i>Aspergillus deflectus</i> NCC0415 ³⁶	Inhibit enzyme (SHP2: 29.3 µM, PTP1B: 40.4 µM)
Deflectin C2 (48)	<i>Aspergillus deflectus</i> NCC0415 ³⁶	Inhibit enzyme (SHP2: 21.1 µM, PTP1B: 19.8 µM)
Deflectin C3 (49)	<i>Aspergillus deflectus</i> NCC0415 ³⁶	Inhibit enzyme (SHP2: 16.2 µM, PTP1B: 16.5 µM)



Table 1 (Contd.)

No.	Species	Activity
Deflectin D1 (50)	<i>Aspergillus deflectus</i> NCC0415 ³⁶	Inhibit enzyme (SHP2: 19.2 μM , PTP1B: 19.2 μM)
Deflectin D2 (51)	<i>Aspergillus deflectus</i> NCC0415 ³⁶	Inhibit enzyme (SHP2: 7.0 μM , PTP1B: 6.1 μM)
Deflectin E (52)	<i>Aspergillus deflectus</i> NCC0415 ³⁶	Inhibit enzyme (SHP2: 16.0 μM , PTP1B: 24.0 μM)
8,11-Didehydrohermesinone B (53)	<i>Nigrospora</i> sp. YE3033 ²⁶	
Colletotrichone A (54)	<i>Colletotrichum</i> sp. BS4 ³⁷	Antimicrobial (<i>Bacillus subtilis</i> : 0.1 $\mu\text{g mL}^{-1}$, <i>Escherichia coli</i> : 1.0 $\mu\text{g mL}^{-1}$)
Colletotrichone B (55)	<i>Colletotrichum</i> sp. BS4 ³⁷	Antimicrobial (<i>Staphylococcus aureus</i> : 5.0 $\mu\text{g mL}^{-1}$)
Colletotrichone C (56)	<i>Colletotrichum</i> sp. BS4 ³⁷	Antimicrobial (<i>Escherichia coli</i> : 5.0 $\mu\text{g mL}^{-1}$)
Coniellin A (57)	<i>Coniella fragariae</i> ⁹	Anti-tumor (MDA-MB-231: 21.5 μM , inhibit NF- κB activation: 4.4 μM)
Coniellin B (58)	<i>Coniella fragariae</i> ⁹	Anti-tumor (MDA-MB-231: 19.6 μM)
Coniellin C (59)	<i>Coniella fragariae</i> ⁹	Anti-tumor (MDA-MB-231: 21.0 μM)
Coniellin D (60)	<i>Coniella fragariae</i> ⁹	Anti-tumor (MDA-MB-231: 18.6 μM , inhibit NF- κB activation: 37.8 μM)
Coniellin E (61)	<i>Coniella fragariae</i> ⁹	Anti-tumor (MDA-MB-231: 79.3 μM , inhibit NF- κB activation: 29.4 μM)
Coniellin F (62)	<i>Coniella fragariae</i> ⁹	Anti-tumor (inhibit NF- κB activation: 70.7 μM)
Coniellin G (63)	<i>Coniella fragariae</i> ⁹	Anti-tumor (MDA-MB-231: 21.6 μM , inhibit NF- κB activation: 11.3 μM)
Coniellins H-I (64–65)	<i>Coniella fragariae</i> ³⁵	
5',6'-Dihydroxyacetosellin (66)	<i>Epicoccum nigrum</i> strain 749 ³⁸	
Monakaocinol (67)	<i>Monascus kaoliang</i> ³⁹	
Monascuspirolide A (68)	<i>Monascus purpureus</i> BCRC 38110 ⁴²	Anti-inflammatory (inhibit NO production: 17.5 μM)
Monascuspirolide B (69)	<i>Monascus purpureus</i> BCRC 38110 ⁴²	Anti-inflammatory (inhibit NO production: 23.5 μM)
Thielavialides A–E (70–74)	<i>Thielavia</i> sp. PA0001 ⁴⁰	
5-O-Acetyl- <i>epi</i> -pestafulide A (75)	<i>Trichocladium</i> sp. ⁴¹	
5- <i>epi</i> -Pestafulide A (76)	<i>Trichocladium</i> sp. co-cultured with <i>Bacillus subtilis</i> ⁴¹	
Peniazaphilin A (77)	<i>Penicillium</i> sp. CPCC 400786 ¹³	Antiviral (HIV: 60.4 μM)
Monapilosusazaphilone (78)	<i>Monascus pilosus</i> ¹⁰³	
Monascusazaphilone A (79)	<i>Monascus purpureus</i> BCRC 38108 ⁴³	Anti-inflammatory (inhibit NO production: 4.6 $\mu\text{g mL}^{-1}$); cytotoxic (LPS-induced RAW264.7: cell viability 83%)
Monascusazaphilone B (80)	<i>Monascus purpureus</i> BCRC 38108 ⁴³	Anti-inflammatory (inhibit NO production: 8.88 $\mu\text{g mL}^{-1}$); cytotoxic (LPS-induced RAW264.7: cell viability 85%)
Berkchaetoazaphilone C (81)	<i>Pleurostomophora</i> sp. ⁴⁹	
Monascuskadione (82)	<i>Monascus kaoliang</i> ⁴⁴	
Monascuspurone (83)	<i>Monascus ruber</i> ⁴⁵	
Monasfluol B (84)	<i>Monascus</i> spp. ⁴⁶	
Monascusazaphilone C (85)	<i>Monascus purpureus</i> BCRC 38108 ⁴³	Anti-inflammatory (inhibit NO production: 6.77 $\mu\text{g mL}^{-1}$); cytotoxic (LPS-induced RAW264.7: cell viability 86%)
Acetyl-monasfluol B (86)	<i>Monascus ruber</i> ⁴⁷	
MC-2, MC-4 (87–88)	<i>Monascus purpureus</i> (<i>mppC</i> mutant) ⁴⁸	
Berkchaetoazaphilone A (89)	<i>Pleurostomophora</i> sp. ⁴⁹	Anti-tumor (inhibit TNF- α production: 95% at 100 μM , inhibit IL-1 β production: 95% at 100 μM); anti-inflammatory (inhibit IL-6 production: 100% at 100 μM , inhibit IL-33 production: 100% at 100 μM); inhibit enzyme (caspase 1: 150 μM , MMP-3: 130 μM)
Berkchaetoazaphilone B (90)	<i>Pleurostomophora</i> sp. ⁴⁹	Cytotoxic (Y79: 1.1 μM , MOLT-4: 10 μM , RPMI-8226: 10 μM , SR: 10 μM , LOX IMVI: 10 μM , CCRF-CEM: 10 μM); anti-tumor (inhibit TNF- α production: 95% at 100 μM , inhibit IL-1 β production: 95% at 100 μM); anti-inflammatory (inhibit IL-6 production: 100% at 100 μM , inhibit IL-33 production: 100% at 100 μM); inhibit enzyme (caspase 1: 25 μM , MMP-3: 15 μM)



Table 1 (Contd.)

No.	Species	Activity
Lenormandin A (91)	<i>Hypoxylon lenormandii</i> ⁵⁰	Antimicrobial (<i>Rhodotorula glutinis</i> : 33.3 $\mu\text{g mL}^{-1}$, <i>Bacillus subtilis</i> : 67.0 $\mu\text{g mL}^{-1}$, <i>Staphylococcus aureus</i> : 67.0 $\mu\text{g mL}^{-1}$)
Lenormandin B (92)	<i>Hypoxylon lenormandii</i> ⁵⁰	Cytotoxic (L929: 18.0 $\mu\text{g mL}^{-1}$); antimicrobial (<i>Mycobacterium</i> sp.: 67.0 $\mu\text{g mL}^{-1}$, <i>Rhodotorula glutinis</i> : 67.0 $\mu\text{g mL}^{-1}$)
Lenormandin C (93)	<i>Hypoxylon lenormandii</i> ⁵⁰	Cytotoxic (L929: 32.0 $\mu\text{g mL}^{-1}$); antimicrobial (<i>Rhodotorula glutinis</i> : 67.0 $\mu\text{g mL}^{-1}$)
Lenormandin D (94)	<i>Hypoxylon lenormandii</i> ⁵⁰	Antimicrobial (<i>Bacillus subtilis</i> : 67.0 $\mu\text{g mL}^{-1}$, <i>Staphylococcus aureus</i> : 67.0 $\mu\text{g mL}^{-1}$)
Lenormandin E (95)	<i>Hypoxylon lenormandii</i> ⁵⁰	Cytotoxic (L929: 22.0 $\mu\text{g mL}^{-1}$); antimicrobial (<i>Rhodotorula glutinis</i> : 67.0 $\mu\text{g mL}^{-1}$)
Peyronellone F (96)	<i>Peyronellaea glomerata</i> ⁶	
Lenormandin F (97)	<i>Hypoxylon lenormandii</i> ⁵⁰	Antimicrobial (<i>Rhodotorula glutinis</i> : 67.0 $\mu\text{g mL}^{-1}$)
Lenormandin G (98)	<i>Hypoxylon lenormandii</i> ⁵⁰	Antimicrobial (<i>Rhodotorula glutinis</i> : 67.0 $\mu\text{g mL}^{-1}$)
Phialomustin A (99)	<i>Phialophora mustea</i> ⁵²	Cytotoxic (MIAPaCa2: 35 μM , A549: 98 μM , HCT-116: 8 μM , T47D: 10 μM)
Phialomustin C (100)	<i>Phialophora mustea</i> ⁵²	Cytotoxic (MIAPaCa2: 38 μM , HCT-116: 100 μM , T47D: 7 μM); antimicrobial (<i>Candida albicans</i> : 14.3 μM , <i>Aspergillus fumigatus</i> : 60.6 μM , <i>Aspergillus parasiticus</i> : 35.2 μM , <i>Aspergillus flavus</i> : 88.4 μM)
Phialomustin D (101)	<i>Phialophora mustea</i> ⁵²	Cytotoxic (MIAPaCa2: 60 μM , HCT-116: 30 μM , T47D: 9.2 μM); antimicrobial (<i>Candida albicans</i> : 73.6 μM)
Fragirubins A–E (102–106)	<i>Hypoxylon fragiforme</i> ⁵¹	
(+)-6''-Hydroxymitorubrinol acetate (107)	<i>Hypoxylon rubiginosum</i> ⁵⁶	Cytotoxic (L929: 21 $\mu\text{g mL}^{-1}$)
(+)-6''-Hydroxymitorubrinol (108)	<i>Hypoxylon rubiginosum</i> ⁵⁶	
6''-Hydroxy-(R)-mitorubrinic acid (109)	<i>Aspergillus</i> sp. 16-5C ⁵³	
Purpurquinone D (110)	<i>Aspergillus</i> sp. 16-5C ⁵³	
Talarophilones A–B (111–112)	<i>Talaromyces</i> sp. CMB-W045 ⁵⁴	
Pinophilins D–F (113–115)	<i>Penicillium pinophilum</i> XS-20090E18 ⁵⁵	
Rutilins C–D (116–117)	<i>Hypoxylon fragiforme</i> ⁵¹	
Pinazaphilone A (118)	<i>Penicillium</i> sp. HN29-3B1 ¹²	
Montagnuphilone B (120)	<i>Montagnulaceae</i> sp. DM0194 ⁵⁷	Anti-inflammatory (inhibit NO production: 39.58 μM)
Montagnuphilones A (119), C–D (121–122), F–G (124–125)	<i>Montagnulaceae</i> sp. DM0194 ⁵⁷	
Montagnuphilone E (123)	<i>Montagnulaceae</i> sp. DM0194 ⁵⁷	Anti-inflammatory (inhibit NO production: 25.48 μM)
Glaziellin A (126)	The fruiting body of <i>Glaziella splendens</i> ¹⁴	Antiviral (H1N1: 230.6 μM , H3N2: 235.8 μM , H5N1: 165.4 μM)
Comazaphilone G (127)	<i>Penicillium variabile</i> ⁵⁸	Anti-inflammatory (inhibit NO production: 4.35 μM)
Comazaphilone H (128)	<i>Penicillium variabile</i> ⁵⁸	Anti-inflammatory (inhibit NO production: 40.52 μM)
Pinazaphilone B (129)	<i>Penicillium</i> sp. HN29-3B1 ¹²	Inhibit enzyme (α -glucosidase: 28.0 μM)
Pinophilin G (130)	<i>Penicillium pinophilum</i> ⁵⁹	Antimicrobial (<i>Vibrio parahemolyticus</i> : 25.0 μM)
Talaraculone A (131)	<i>Talaromyces aculeatus</i> ⁶⁰	Inhibit enzyme (α -glucosidase: 78.6 μM)
Talaraculone B (132)	<i>Talaromyces aculeatus</i> ⁶⁰	Antimicrobial (<i>Vibrio anguillarum</i> : 0.26 $\mu\text{g mL}^{-1}$); inhibit enzyme (α -glucosidase: 22.9 μM)
Talaraculones C–F (133–136)	<i>Talaromyces aculeatus</i> ⁶⁰	
Pleosporalone E (137)	<i>Pleosporales</i> sp. CF09-1 ⁶¹	Antimicrobial (<i>Vibrio alginolyticus</i> : 25 $\mu\text{g mL}^{-1}$)
Pleosporalone F (138)	<i>Pleosporales</i> sp. CF09-1 ⁶¹	Antimicrobial (<i>Vibrio alginolyticus</i> : 25 $\mu\text{g mL}^{-1}$)
Pleosporalone G (139)	<i>Pleosporales</i> sp. CF09-1 ⁶¹	Antimicrobial (<i>Vibrio anguillarum</i> : 13 $\mu\text{g mL}^{-1}$, <i>Vibrio parahemolyticus</i> : 6.3 $\mu\text{g mL}^{-1}$)
Pleosporalone H (140)	<i>Pleosporales</i> sp. CF09-1 ⁶¹	Antimicrobial (<i>Vibrio anguillarum</i> : 6.3 $\mu\text{g mL}^{-1}$, <i>Vibrio parahemolyticus</i> : 25 $\mu\text{g mL}^{-1}$)
epi-Pinophilin B (141)	<i>Aspergillus fumigatus</i> 14–27 ¹⁰⁴	



Table 1 (Contd.)

No.	Species	Activity
Chaetoviridin J (142)	<i>Chaetomium globosum</i> ⁶³	Anti-tumor (inhibit NF-κB activation: 32.6% at 50 μM); anti-inflammatory (inhibit NO production: 95.4%, at 50 μM)
Chaetoviridin K (143)	<i>Chaetomium globosum</i> ⁶³	Anti-tumor (inhibit NF-κB activation: 33.4% at 50 μM); anti-inflammatory (inhibit NO production: 39.4%, at 50 μM)
Chaephilones A–B (144–145)	<i>Chaetomium globosum</i> ⁶²	
Chaephilone C (146)	<i>Chaetomium</i> sp. NA-S01-R1 ⁶⁴	Cytotoxic (A549: 15.7 μM, HeLa: 7.7 μM, Hep G2: 20.2 μM); antimicrobial (<i>Vibrio vulnificus</i> : 32.2 μg mL ⁻¹ , <i>Vibrio campbellii</i> : 30.1 μg mL ⁻¹ , MRSA: 7.6 μg mL ⁻¹)
Nigbeauvin A (147)	<i>Nigrospora oryzae</i> co-cultured with <i>Beauveria bassiana</i> ⁶⁵	Antimicrobial (<i>Bacillus bassiana</i> : 128 μg mL ⁻¹ , <i>Nigrospora oryzae</i> : 512 μg mL ⁻¹ , <i>Bacillus subtilis</i> : 128 μg mL ⁻¹); anti-inflammatory (inhibit NO production: 37%, at 50 μM)
Nigbeauvin B (148)	<i>Nigrospora oryzae</i> co-cultured with <i>Beauveria bassiana</i> ⁶⁵	Anti-inflammatory (inhibit NO production: 39%, at 50 μM)
Nigbeauvins C–E (149–151)	<i>Nigrospora oryzae</i> co-cultured with <i>Beauveria bassiana</i> ⁶⁵	
Nigirpexins A–C (152–154)	<i>Nigrospora oryzae</i> co-cultured with <i>Irpex lacteus</i> ⁶⁶	
Nigirpexin D (155)	<i>Nigrospora oryzae</i> co-cultured with <i>Irpex lacteus</i> ⁶⁶	Antimicrobial (<i>Irpex lacteus</i> : 256 μg mL ⁻¹ , <i>Nigrospora oryzae</i> : 512 μg mL ⁻¹ , <i>Bacillus subtilis</i> : 512 μg mL ⁻¹)
Isonigirpexin C (156)	<i>Nigrospora oryzae</i> cocultured with <i>Irpex lacteus</i> ⁶⁷	
Dechloroisochromophilone II (157)	<i>Penicillium multicolor</i> CM01 ⁷⁰	
epi-Isochromophilone III (158)	<i>Penicillium multicolor</i> CM01 ⁷⁰	Cytotoxic (NCI-H187: 6.2 μg mL ⁻¹ , KB: 6.9 μg mL ⁻¹ , MCF-7: 10.6 μg mL ⁻¹)
159	<i>Penicillium</i> 303 ⁷¹	Cytotoxic (MDA-MB-435: 24.62 μg mL ⁻¹ , HepG2: 17.92 μg mL ⁻¹ , HCT-116: 11.09 μg mL ⁻¹ , A549: 16.63 μg mL ⁻¹)
Hypocrellone A (160)	<i>Hypocrella</i> sp. isolate WYTY-21 ⁷²	
Eupenicilazaphilone A (161)	<i>Eupenicillium</i> sp. 6A-9 ⁷³	Cytotoxic (MCF-7: 49.95 μM)
Eupenicilazaphilone B (162)	<i>Eupenicillium</i> sp. 6A-9 ⁷³	Cytotoxic (MCF-7: 40.71 μM, A549: 63.32 μM)
Eupenicilazaphilone C (163)	<i>Eupenicillium</i> sp. 6A-9 ⁷³	Cytotoxic (MCF-7: 36.88 μM, A549: 43.96 μM)
Geumsanols A–B (164–165), D–E (167–168)	<i>Penicillium</i> sp. KCB11A109 ⁷⁴	
Geumsanol C (166)	<i>Penicillium</i> sp. KCB11A109 ⁷⁴	Cytotoxic (HL-60: 88.9 μM)
Penidioxolanes A–B (169–170)	<i>Penicillium</i> sp. KCB12C078 ⁶⁸	
Penicilazaphilone C (171)	<i>Penicillium sclerotiorum</i> M-22 ⁷⁵	Cytotoxic (B-16: 0.065 mM, SGC7901: 0.720 mM); antimicrobial (<i>Staphylococcus aureus</i> : 31.25 μg mL ⁻¹ , <i>Pseudomonas aeruginosa</i> : 62.5 μg mL ⁻¹ , <i>Klebsiella pneumoniae</i> : 16.53 μg mL ⁻¹ , <i>Escherichia coli</i> : 16.53 μg mL ⁻¹)
Penicilazaphilones D–E (172–173)	<i>Penicillium sclerotiorum</i> ⁷⁶	
Sclerketide B (174)	<i>Penicillium sclerotiorum</i> CHNSCLM-0013 ⁷⁷	Anti-inflammatory (inhibit NO production: 3.4 μM)
Helicusin E (175)	<i>Bartalinia robillardoides</i> strain LF550 ⁷⁸	
Isochromophilone XI (176)	<i>Bartalinia robillardoides</i> strain LF550 ⁷⁸	Antimicrobial (<i>Bacillus subtilis</i> : 55.6 μM, <i>Staphylococcus lentus</i> : 78.4 μM, <i>Trichophyton rubrum</i> : 41.5 μM); inhibit enzyme (PDE4: 8.30 μM)
Bromophilone A (177)	<i>Penicillium canescens</i> ⁷⁹	Cytotoxic (L5178Y: 13.9 μM, A2780: 37 μM)
Bromophilone B (178)	<i>Penicillium canescens</i> ⁷⁹	Cytotoxic (L5178Y: 8.9 μM, A2780: 2.7 μM)
Isochromophilanol (179)	<i>Chaetomium cupreum</i> RY202 ¹⁰⁵	Cytotoxic (KB: 9.63 μg mL ⁻¹ , NCI-H187: 27.18 μg mL ⁻¹)
Ochrephilanol (180)	<i>Chaetomium cupreum</i> RY202 ¹⁰⁵	Cytotoxic (KB: 30.2 μg mL ⁻¹)
Isochromophilone A (181)	<i>Diaporthe</i> sp. SCSIO 41011 ⁸	Cytotoxic (ACHN: 27 μM, 786-O: 34 μM, OS-RC-2: 45 μM)
Isochromophilones B–C (182–183)	<i>Diaporthe</i> sp. SCSIO 41011 ⁸	
Isochromophilone D (184)	<i>Diaporthe</i> sp. SCSIO 41011 ⁸	Cytotoxic (786-O: 38 μM, OS-RC-2: 44 μM)
Isochromophilone E (185)	<i>Diaporthe</i> sp. SCSIO 41011 ⁸	Cytotoxic (ACHN: 14 μM, 786-O: 8.9 μM, OS-RC-2: 13 μM)



Table 1 (Contd.)

No.	Species	Activity
Isochromophilone F (186)	<i>Diaporthe</i> sp. SCSIO 41011 ⁸	Cytotoxic (ACHN: 13 μ M, 786-O: 10 μ M, OS-RC-2: 38 μ M)
Sclerotiorins A–C (187–189)	<i>Penicillium sclerotiorum</i> OUCMDZ-3839 ⁶⁹	
Cohaerin G (190)	<i>Annulohyphoxylon cohaerens</i> ⁸¹	Antimicrobial (<i>Nocardia</i> sp.: 33.3 μ g mL ⁻¹)
Cohaerin H (191)	<i>Annulohyphoxylon cohaerens</i> ⁸¹	Cytotoxic (L929: 4.9 μ g mL ⁻¹)
Cohaerin I (192)	<i>Annulohyphoxylon cohaerens</i> ⁸¹	Cytotoxic (L929: 0.4 μ g mL ⁻¹); antimicrobial (<i>Nocardia</i> sp.: 33.3 μ g mL ⁻¹)
Cohaerin K (193)	<i>Annulohyphoxylon cohaerens</i> ⁸¹	Antimicrobial (<i>Nocardia</i> sp.: 16.6 μ g mL ⁻¹ , <i>Staphylococcus aureus</i> : 16.6 μ g mL ⁻¹)
Minutellin A (194)	<i>Annulohyphoxylon minutellum</i> ⁸²	Cytotoxic (L929: 5.1 μ g mL ⁻¹ , KB3.1: 5.3 μ g mL ⁻¹); antimicrobial (<i>Micrococcus luteus</i> : 16.7 μ g mL ⁻¹ , <i>Bacillus subtilis</i> : 66.7 μ g mL ⁻¹)
Minutellin B (195)	<i>Annulohyphoxylon minutellum</i> ⁸²	Antimicrobial (<i>Bacillus subtilis</i> : 66.7 μ g mL ⁻¹)
Minutellin C (196)	<i>Annulohyphoxylon minutellum</i> ⁸²	Cytotoxic (L929: 10 μ g mL ⁻¹ , KB3.1: 25 μ g mL ⁻¹); antimicrobial (<i>Micrococcus luteus</i> : 66.7 μ g mL ⁻¹ , <i>Bacillus subtilis</i> : 66.7 μ g mL ⁻¹ , <i>Rhodoturulula glutinis</i> : 33.3 μ g mL ⁻¹ , <i>Mucor hiemalis</i> : 66.7 μ g mL ⁻¹)
Minutellin D (197)	<i>Annulohyphoxylon minutellum</i> ⁸²	Antimicrobial (<i>Micrococcus luteus</i> : 16.7 μ g mL ⁻¹ , <i>Bacillus subtilis</i> : 33.3 μ g mL ⁻¹ , <i>Staphylococcus aureus</i> : 33.3 μ g mL ⁻¹)
Penicilone A (198)	<i>Penicillium janthinellum</i> HK1-6 ⁵	
Penicilone B (199)	<i>Penicillium janthinellum</i> HK1-6 ⁵	Cytotoxic (SMMC-7721: 32 μ M); antimicrobial (<i>Staphylococcus aureus</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecium</i> : 3.13 μ g mL ⁻¹ , <i>Escherichia coli</i> : 3.13 μ g mL ⁻¹) ⁸³
Penicilone C (200)	<i>Penicillium janthinellum</i> HK1-6 ⁵	Cytotoxic (SMMC-7721: 21 μ M); antimicrobial (<i>Staphylococcus aureus</i> : 6.25–12.5 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 12.5 μ g mL ⁻¹ , <i>Enterococcus faecium</i> : 12.5 μ g mL ⁻¹) ⁸³
Penicilone D (201)	<i>Penicillium janthinellum</i> HK1-6 ⁵	Cytotoxic (SMMC-7721: 27 μ M); antimicrobial (<i>Staphylococcus aureus</i> : 3.13–12.5 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 6.25 μ g mL ⁻¹ , <i>Enterococcus faecium</i> : 12.5 μ g mL ⁻¹) ⁸³
Penicilone G (202)	<i>Penicillium janthinellum</i> HK1-6 ⁸³	Cytotoxic (SMMC-7721: 21 μ M); antimicrobial (<i>Staphylococcus aureus</i> : 12.5–50 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 25 μ g mL ⁻¹ , <i>Enterococcus faecium</i> : 25 μ g mL ⁻¹)
Penicilone H (203)	<i>Penicillium janthinellum</i> HK1-6 ⁸³	Cytotoxic (SMMC-7721: 24 μ M); antimicrobial (<i>Staphylococcus aureus</i> : 3.13–12.5 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecium</i> : 12.5 μ g mL ⁻¹)
Meliasendanin A (204)	The fruits of <i>Melia toosendan</i> ⁸⁴	Antioxidant (ABTS: 62.8 μ M)
Pleosporalone A (205)	<i>Pleosporales</i> sp. CF09-1 ⁸⁵	Antimicrobial (<i>Botrytis cinerea</i> : 0.39 μ M, <i>Rhizopus oryzae</i> : 0.78 μ M, <i>Phytophthora capsici</i> : 0.78 μ M)
Pleosporalone B (206)	<i>Pleosporales</i> sp. CF09-1 ⁶¹	Antimicrobial (<i>Alternaria brassicicola</i> : 1.6 μ g mL ⁻¹ , <i>Botryosphaeria dothidea</i> : 1.3 μ g mL ⁻¹ , <i>Fusarium oxysporum</i> : 1.6 μ g mL ⁻¹)
Pleosporalone C (207)	<i>Pleosporales</i> sp. CF09-1 ⁶¹	Antimicrobial (<i>Alternaria brassicicola</i> : 6.3 μ g mL ⁻¹ , <i>Botryosphaeria dothidea</i> : 3.1 μ g mL ⁻¹ , <i>Fusarium oxysporum</i> : 25 μ g mL ⁻¹)
Chaetomugilide A (208)	<i>Chaetomium globosum</i> DAOM 240359, ⁸⁹ <i>Chaetomium globosum</i> TY1 ⁸⁸	Cytotoxic (HePG2: 1.7 μ M), ⁸⁸ antimicrobial (<i>Pseudomonas putida</i> : < 20 μ M, <i>Bacillus subtilis</i> : < 20 μ M <i>Saccharomyces cerevisiae</i> : 20–200 μ M) ⁸⁹
Chaetomugilide B (209)	<i>Chaetomium globosum</i> TY1 ⁸⁸	Cytotoxic (HePG2: 19.8 μ M)
Chaetomugilide C (210)	<i>Chaetomium globosum</i> DAOM 240359, ⁸⁹ <i>Chaetomium globosum</i> TY1 ⁸⁸	Cytotoxic (HePG2: 53.4 μ M) ⁸⁸
Isochromophilone XIII (211)	<i>Chaetomium globosum</i> DAOM 240359 ⁸⁹	Antimicrobial (<i>Pseudomonas putida</i> : 20–200 μ M, <i>Bacillus subtilis</i> : 20–200 μ M)



Table 1 (Contd.)

No.	Species	Activity
Chaetoviridide A (212)	<i>Chaetomium</i> sp. NA-S01-R1 ⁶⁴	Cytotoxic (A549: 15.2 μM , HeLa: 12.3 μM , Hep G2: 3.9 μM); antimicrobial (<i>Vibrio vulnificus</i> : 30.5 $\mu\text{g mL}^{-1}$, <i>Vibrio rotiferianus</i> : 7.3 $\mu\text{g mL}^{-1}$, <i>Vibrio campbellii</i> : 32.7 $\mu\text{g mL}^{-1}$, MRSA: 15.5 $\mu\text{g mL}^{-1}$)
Chaetoviridide B (213)	<i>Chaetomium</i> sp. NA-S01-R1 ⁶⁴	Cytotoxic (A549: 16.3 μM , HeLa: 5.6 μM , Hep G2: 18.2 μM); antimicrobial (<i>Vibrio vulnificus</i> : 7.4 $\mu\text{g mL}^{-1}$, <i>Vibrio rotiferianus</i> : 31.3 $\mu\text{g mL}^{-1}$, <i>Vibrio campbellii</i> : 32.3 $\mu\text{g mL}^{-1}$, MRSA: 7.3 $\mu\text{g mL}^{-1}$)
Chaetoviridide C (214)	<i>Chaetomium</i> sp. NA-S01-R1 ⁶⁴	Cytotoxic (A549: 23.1 μM , HeLa: 17.7 μM , Hep G2: 22.2 μM); antimicrobial (<i>Vibrio vulnificus</i> : 15.7 $\mu\text{g mL}^{-1}$, <i>Vibrio rotiferianus</i> : 15.3 $\mu\text{g mL}^{-1}$, MRSA: 7.6 $\mu\text{g mL}^{-1}$)
N-Glutarylchaetoviridin A (215)	<i>Chaetomium globosum</i> HDN151398 ⁹⁰	Cytotoxic (HL-60: 10.3 μM , K562: 20.3 μM , BEL-7402: 23.9 μM)
N-Glutarylchaetoviridin B (216)	<i>Chaetomium globosum</i> HDN151398 ⁹⁰	Cytotoxic (HL-60: 11.1 μM , K562: 11.7 μM , BEL-7402: 10.9 μM , HCT-116: 11.3 μM , HeLa: 22.1 μM , L-02: 18.2 μM , MGC-803: 6.6 μM , HO8910: 9.7 μM , SH-SY5Y: 26.5 μM , NCL-H1975: 11.2 μM , U87: 18.3 μM , MDA-MB-231: 13.2 μM)
N-Glutarylchaetoviridin C (217)	<i>Chaetomium globosum</i> HDN151398 ⁹⁰	
Peniazaphilones A–D (218–221)	<i>Penicillium</i> sp. ZJ-27 ⁸⁶	Anti-inflammatory (inhibit NO production: 2.7 μM) ⁷⁷ Inhibit enzyme (PDE4: 11.7 μM) Anti-inflammatory (inhibit NO production: 15.29 μM)
Sclerotiorin D (222)	<i>Penicillium sclerotiorum</i> OUCMDZ-3839, ⁶⁹ <i>Penicillium sclerotiorum</i> CHNSCLM-0013 ⁷⁷	
Isochromophilone X (223)	<i>Bartalinia robillardoides</i> strain LF550 ⁷⁸	
Penazaphilone A (224)	<i>Penicillium sclerotiorum</i> cib-411 ⁹¹	
Penazaphilones B–D, (225–227), G (230), I (232)	<i>Penicillium sclerotiorum</i> cib-411 ⁹¹	Anti-inflammatory (inhibit NO production: 9.34 μM) Anti-inflammatory (inhibit NO production: 9.50 μM)
Penazaphilone E (228)	<i>Penicillium sclerotiorum</i> cib-411 ⁹¹	
Penazaphilone F (229)	<i>Penicillium sclerotiorum</i> cib-411 ⁹¹	Anti-inflammatory (inhibit NO production: 7.05 μM) Inhibit enzyme (caspase 1: 50 μM , MMP-3: 45 μM)
Penazaphilone H (231)	<i>Penicillium sclerotiorum</i> cib-411 ⁹¹	
Berkchaetorubramine (233)	<i>Pleurostomophora</i> sp. ⁴⁹	
(6-[(Z)-2-Carboxyvinyl]-N-GABA-PP-V) (234)	<i>Talaromyces albobiverticillius</i> 30548 ⁸⁷	
Atrorosins A, C–I, K–N, Q–R, T, V–W, Y (235–252)	<i>Talaromyces atroroseus</i> ⁹²	

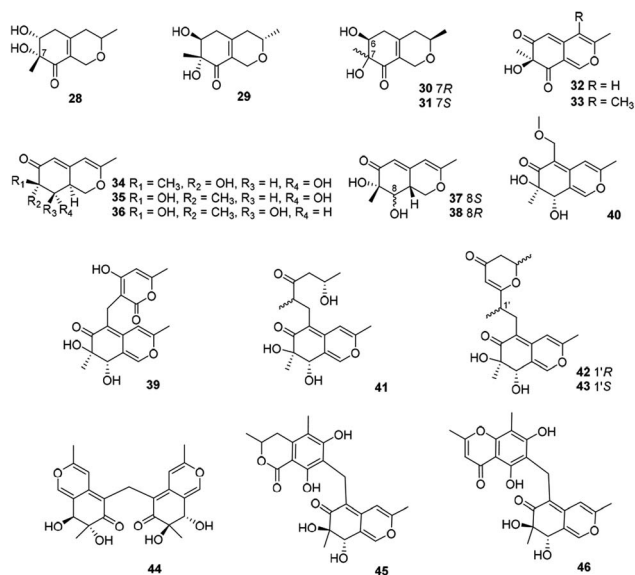


Fig. 3 Chemical structures of austdiol-type azaphilones (28–46).

note, **40** exhibited cytotoxicity against HuCCA-1, A549, and MOLT-3 with IC_{50} values of 48.1, 46.5, and 17.4 $\mu\text{g mL}^{-1}$, respectively.³³

Mycocleptodiscus indicus, an endophytic fungus of the official plant *Borreria verticillate* from the South American, was found to produce three azaphilones with an unusual methylene bridge, mycoleptones A–C (**44–46**).¹⁵ Amongst, **44** and **45** showed cytotoxicity against PC3 cell line with IC_{50} values of 10.0 and 7.1 μM , respectively.¹⁵

2.3 Deflectin-type azaphilones

This angular deflectin-type azaphilones included fourteen compounds (**47–65**) (Fig. 4 and Table 1) were characterized with a methyl at C-3 and an angular γ -lactone ring, along with a ketone aliphatic chain at C-2' like 8,11-didehydrochermesinone B (**53**),²⁶ or at C-8 such as conieillins H–I (**64–65**).³⁵

Chromatographic separation of crude extracts from *Aspergillus deflectus* NCC0415 gave six deflectins with inhibitory activity against protein tyrosine phosphatases, SHP2 and



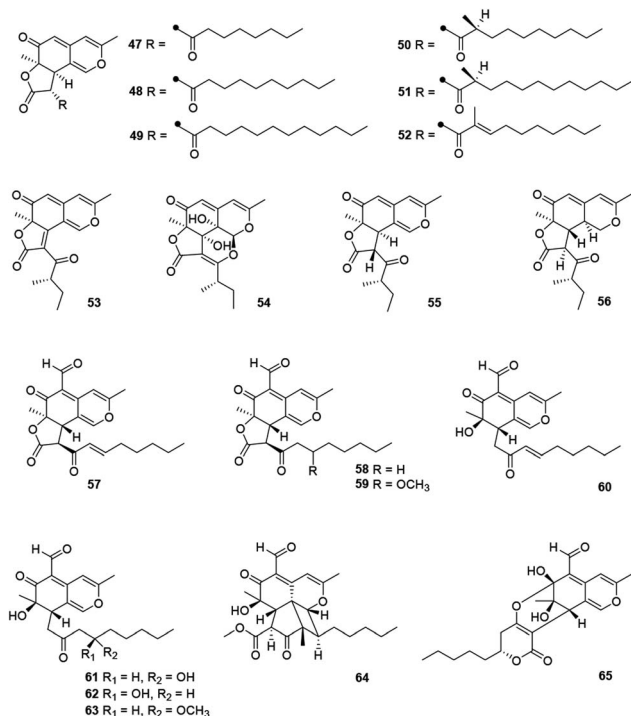


Fig. 4 Chemical structures of deflectin-type azaphilones (47–65).

PTP1B, deflectins C1–C3, D1–D2, and E (47–52), absolute configurations of which were assigned by ECD analyses and the GIAO ^{13}C NMR calculation.³⁶ And it was proposed that the ketone aliphatic side chain in 47–52 had an impact on the enzyme inhibition activities.³⁶

Chemical investigations of the endophytic fungus *Colletotrichum* sp. BS4 resulted in the achievements of colletotrichones A–C (54–56), while 54 exhibited notable antibacterial potencies against *Escherichia coli* and *Bacillus subtilis* with MIC values of 1.0 and 0.1 $\mu\text{g mL}^{-1}$, respectively.³⁷ Additionally, antibacterial activity of 55 was comparable to the standard antibiotics against *Staphylococcus aureus* and 56 displayed inhibitory activity against *Escherichia coli* with the MIC value of 5.0 $\mu\text{g mL}^{-1}$.³⁷

Furthermore, conieclins A–I (57–65) were obtained from the goose dung derived fungus *Coniella fragariae*.^{9,35} And conieclins H and I (64–65) shared a unique tetracyclic core and an aldehyde group at C-5.³⁵ Remarkably, 57 demonstrated inhibition of NF- κB activation in MDA-MB-231 with an IC_{50} value of 4.4 μM and reduced the migration of tumor cells with 60% inhibition at 5 μM and 98% inhibition at 10 μM after 24 h.⁹

2.4 Bulgarialactone-type azaphilones

5',6'-Dihydroxyacetosellin (66) and monakaocinol (67) were classified into this subgroup harboring an extensively conjugated and a linear γ -lactone ring, which were isolated from the marine-derived fungi *Epicoecum nigrum* (strain 749)³⁸ and *Monascus kaoliang*,³⁹ respectively.

2.5 Hydrogenated spiro-azaphilones

Ten compounds belonged to hydrogenated spiro-azaphilones with a five- or six-membered ring spiroketal system on the

azaphilone skeleton (Fig. 5 and Table 1), such as thielavialides A–E (70–74),⁴⁰ 5-O-acetyl-*epi*-pestafolide A (75),⁴¹ and 5-*epi*-pestafolide A (76).⁴¹

Herein, monascuspirolides A and B (68–69) bearing with an unique 5',6'-dihydrospiro[isochromane-1,2'-pyran]-4'(3'H)-one pattern, were isolated from *Monascus purpureus* BCRC 38110. Of note, compounds 68 and 69 indicated stronger NO inhibitory activity than that of the positive control quercetin with the IC_{50} values of 17.5 and 23.5 μM , respectively.⁴² Moreover, the fungus *Penicillium* sp. CPCC 400786 yielded peniazaphilin A (77) with anti-HIV activity (IC_{50} = 60.4 μM).¹³

2.6 O-Containing Monascus pigments

This category consisted of four azaphilones (78–81) were obtained from *Monascus* sp., characterized with a 1H-isochromene skeleton linked with a propenyl side chain and an acyl chain from the acetyl to the decanoyl unit (Fig. 5 and Table 1).

The cultures of the pink mutant of *Monascus purpureus* BCRC 38108 afforded monascusazaphilones A and B (79–80), which inhibited NO production by macrophages and the inhibition of 79 was stronger than that of the positive control quercetin.⁴³

2.7 Angular lactone-type azaphilones

This subgroup including thirteen compounds were characterized by an angular lactone on the azaphilone nucleus with a propenyl side chain and an acyl chain (Fig. 6 and Table 1), for example, monascuskaodione (82),⁴⁴ monascuspurone (83),⁴⁵ monasfluol B (84),⁴⁶ acetyl-monasfluol B (86),⁴⁷ MC-2 (87), and MC-4 (88).⁴⁸

Monascusazaphilone C (85), carrying with an acetoxy group attached at the side chain, was obtained from *Monascus*

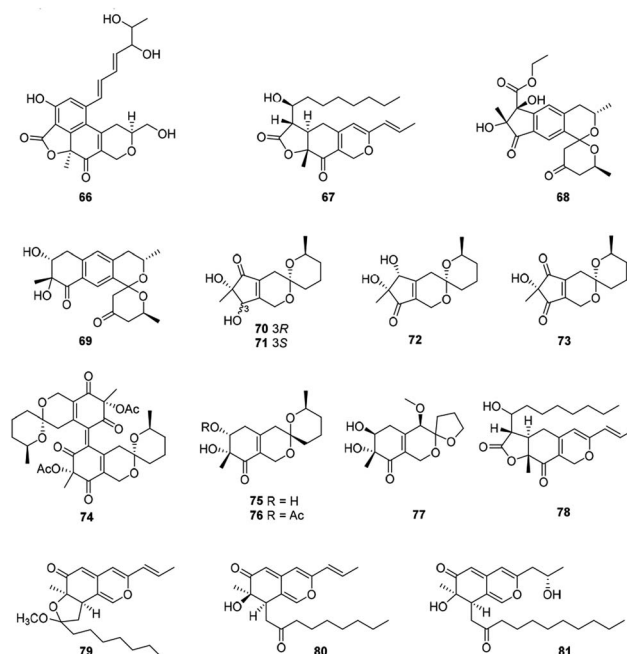


Fig. 5 Chemical structures of bulgarialactone-type, hydrogenated spiro-azaphilones, and O-containing Monascus pigments (66–81).



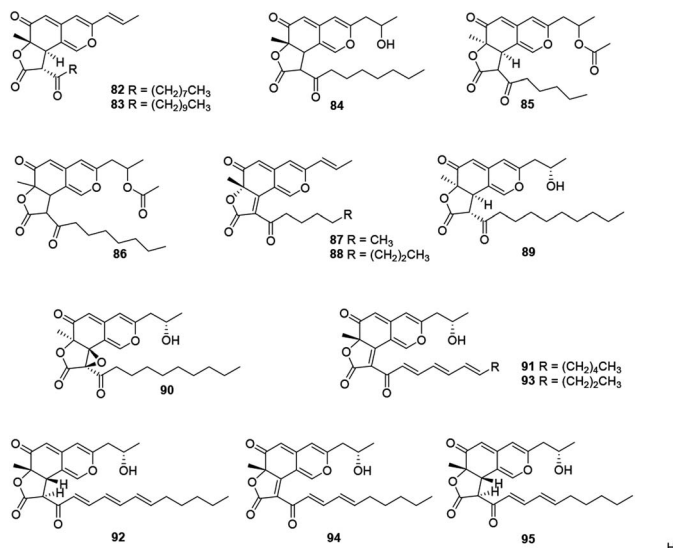


Fig. 6 Chemical structures of angular lactone-type azaphilones (82–95).

purpureus BCRC 38108, which showed moderate NO inhibitory activity ($IC_{50} = 6.8 \mu\text{g mL}^{-1}$).⁴³ The culture broth of an acid mine extremophile strain *Pleurostomophora* sp. yielded two novel compounds, berkchaetozaphilones A–B (89–90). Notably, 90 displayed significant anti-inflammatory activity by inhibiting IL-1 β , TNF α , and IL-6 production and also exhibited strong cytotoxicity against several human tumor cell lines.⁴⁹

A series of angular lactone-type azaphilones, named lenormandins A–E (91–95), were obtained from stromata of the *xylariaceous* fungus, *Hypoxylon lenormandii*. They were demonstrated weak antimicrobial activities and weak cytotoxicity against mouse fibroblast cell line L929.⁵⁰

2.8 Hydrogenated azaphilones

Recently, forty-six hydrogenated azaphilones (96–141) could be divided into three subgroups according to different connections of benzoyl moiety (Fig. 7, 8 and Table 1).³

2.8.1 Hydrogenated azaphilones missing the benzoyl moiety. Azaphilones (96–106) were characterized with an aliphatic chain at C-7 lacking the benzoyl moiety, *e.g.*, peyronellone F (96),⁶ lenormandins F–G (97–98),⁵⁰ as well as fragirubins A–E (102–106).⁵¹

Phialomustins A, C, and D (99–101), three azaphilones sharing with an unprecedented skeleton, were discovered from an endophytic fungus *Phialophora mustea*. Interestingly, they showed moderate activities toward several human cancer cells, meanwhile 94 and 95 also displayed antifungal activities with IC_{50} values of 14.3 and 73.6 μM against *Candida albicans*, respectively.⁵²

2.8.2 Mitorubrin derivatives with a 7-benzoyl. The azaphilones with a benzoyl group substituted at C-7 included 12 mitorubrin (107–118), such as 6''-hydroxy-(*R*)-mitorubrinic acid (109),⁵³ purpurquinone D (110),⁵³ talarophilones A–B (111–112),⁵⁴ pinophilins D–F (113–115),⁵⁵ rutilins C–D (116–117)⁵¹ and pinazaphilone A (118).¹²

Apart from these, (+)-6''-hydroxymitorubrinol acetate (107) and (+)-6''-hydroxymitorubrinol (108), were encountered in *Hypoxylon rubiginosum*, a novel species from northern Thailand. Remarkably, 107 exhibited activity against the mouse fibroblast cell line L929 ($IC_{50} = 21 \mu\text{g mL}^{-1}$), whereas 108 was inactive.⁵⁶

2.8.3 Mitorubrins with a 6- or 8-benzoyl unit. Structurally, this subgroup comprising 23 compounds (119–141) featured with a benzoyl group substituted at C-6 (119–128) or C-8 (129–141).

Montagnulaceae sp. DM0194, a fungal endophyte from roots of *Persicaria amphibia*, produced seven mitorubrins with a benzoyl moiety at C-6, montagnuphilones A–G (119–125). Among them, 123 and 120 showed inhibitions on NO production in LPS-activated RAW264.7 macrophage cells with IC_{50} values of 25.5 and 39.6 μM , respectively, without cytotoxicity in RAW264.7 cells.⁵⁷

Glaziellin A (126) was isolated from the fruiting body of *Glaziella splendens* with weak inhibitory activity against three types of neuraminidases, H1N1, H3N2, and H5N1, with the IC_{50} values of 230.6, 235.8, and 165.4 μM respectively.¹⁴ Chemical study of an endophytic fungus *Penicillium variabile*, resulted in two novel azaphilones, comazaphilones G and H (127–128), which displayed NO inhibitory activities with IC_{50} values of 4.35 and 40.52 μM , respectively.⁵⁸ Another endophytic fungus *Penicillium* sp. HN29-3B1, harboring in a fresh branch of the mangrove plant *Cerbera manghas* in the South China Sea, metabolized pinazaphilones A and B (128–129), while 129 exhibited stronger α -glucosidase inhibitory effect ($IC_{50} = 28.0 \mu\text{M}$) than that of acarbose ($IC_{50} = 446.7 \mu\text{M}$).¹²

Pinophilin G (130) was isolated from *Penicillium pinophilum* with antibacterial activity against *Vibrio parahemolyticus* (MIC = 25.0 μM).⁵⁹ Fermentation of the saline soil-derived fungus *Talaromyces aculeatus* was proved to produce talaraculones A–F (131–136), amongst 131 and 135 were the first reported azaphilones with a C4 aliphatic side chain and a methylal group at C-3, respectively. Curiously, 131 and 132 showed stronger inhibitory activity against α -glucosidase with IC_{50} values of 78.6 and 22.9 μM , respectively, compared to the positive control acarbose ($IC_{50} = 101.5 \mu\text{M}$).⁶⁰

Pleosporalones E–H (137–140) were encountered in an isolate of *Pleosporales* sp. CF09-1. And the absolute configurations of C-11 in both 137 and 138 were assigned *via* the GIAO ¹³C NMR calculations, while the configurations of C-11 in 139 and 140 remained unassigned due to the impracticable calculations.⁶¹ They displayed anti-*Vibrio anguillarum* activities with MIC values from 6.3 to 25 $\mu\text{g mL}^{-1}$.⁶¹

2.9 Chaetoviridins and chaephilones

There were five compounds (142–146) obtained from *Chaetomium* sp. with a chlorine atom at C-5 and a methyl group at C-7, as well as a branched pentenyl side chain at C-3 within this family (Fig. 9 and Table 1), like chaephilones A and B (144–145).⁶²

The endophytic fungus *Chaetomium globosum*, isolated from leaves of *Wikstroemia uva-ursi*, yielded chaetoviridins J and K (142–143), whilst 143 was obtained as a mixture of unresolvable



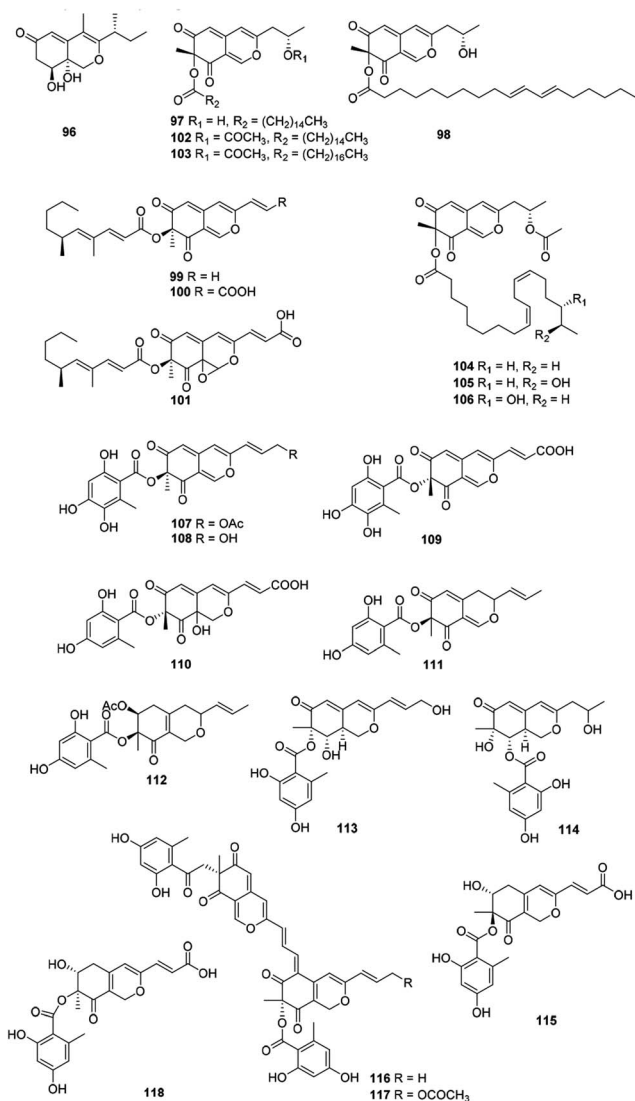


Fig. 7 Chemical structures of hydrogenated azaphilones (96–117).

diastereoisomer failing to be purified by chiral columns. Of note, compound **142** showed obvious activity against NO production while **143** exhibited a weak response.⁶³

In 2018, Wang described the isolation and determination of the chlorinated azaphilone pigment, chaephilone C (**146**), which was strongly cytotoxic against the HeLa cell line, and also showed anti-MRSA activity compared to the positive control chloramphenicol.⁶⁴

2.10 Pulvilloric acid azaphilones

This group consisted of nine novel azaphilones (**147–156**) were characteristic of an *n*-pentyl side chain at C-3 (Fig. 10 and Table 1).

The co-culture of *Nigrospora oryzae* and *Beauveria bassiana* afforded nigbeauvins A–E (**147–151**), while **148** possessed a novel skeleton with a bicyclic oxygen bridge. Bioactive assays revealed compounds **147** and **148** showed comparable activities on NO production ($IC_{50} = 50 \mu M$).⁶⁵ However, when *Nigrospora*

oryzae co-cultured with *Irpex lacteus*, nigirpexins A–D (**152–155**) and isonigirpexin C (**156**), the stereoisomer of **142**, were obtained.^{66,67} Among them, **155** showed weak activities in anti-bacterial and antifungal assays.⁶⁶

2.11 Sclerotiorin-like azaphilones

These recently reported sclerotiorin-like azaphilones including thirty-three ones were mainly isolated from *Penicillium* sp., *Emericella* sp., and *Diaporthe* sp. (Fig. 11 and Table 1), like penidioxolanes A–B (**169–170**)⁶⁸ as well as sclerotiorins A–C (**187–189**).⁶⁹ Dechloroisochromophilone II (**157**) and *epi*-isochromophilone III (**158**) were metabolized by *Penicillium multicolor* CM01. Significantly, **157** showed AChE inhibitory activity with a minimum inhibition requirement of 0.03 nM, while **158** exhibited notable antimalarial activity and cytotoxicity.⁷⁰

The mangrove endophytic fungus *Penicillium* sp. 303, produced a novel azaphilone **159**, which exhibited weak cytotoxicity toward a series of human cancer lines.⁷¹ Isolated from the entomopathogenic fungus *Hypocrella* sp., hypocrellone A (**160**) presented moderate cytotoxicity against hepatoma cells BEL-7404 with an IC_{50} value of 17.4 μM .⁷² The sponge-derived fungus *Eupenicillium* sp. 6A-9 metabolized eupenicilazaphilones A–C (**161–163**), and they were weakly cytotoxic against human cancer lines MCF-7 and A549.⁷³

Derived from a ginseng field, *Penicillium* sp. KCB11A109 yielded five highly oxygenated azaphilones, geumsanols A–E (**164–168**). Among them, **168** displayed cytotoxic activities and toxic effects on zebrafish embryos.⁷⁴ As a novel antineoplastic and antibacterial azaphilone, penicilazaphilone C (**171**) was found from the marine derived fungus *Penicillium sclerotiorum* M-22, which showed cytotoxicity against human tumor cells B-16 ($IC_{50} = 0.065$ mM) and SGC7901 ($IC_{50} = 0.720$ mM), and also indicated significant antibacterial activity against four bacteria.⁷⁵ Moreover, penicilazaphilones D and E (**172–173**) were obtained from the sponge-derived fungus *Penicillium sclerotiorum* and the structure of **172** was further confirmed by single-crystal X-ray diffraction.⁷⁶

Fermentation of the gorgonian-derived fungus *Penicillium sclerotiorum* CHNSCLM-0013 produced sclerketide B (**174**), which denoted significant inhibitory activities against the NO production in the LPS-induced macrophage cell RAW 264.7 and suppressed the expression of iNOS and COX-2 in mRNA level.⁷⁷ The fungus *Bartalinia robillardoides* strain LF550, obtained from the Mediterranean sponge *Tethya aurantium*, metabolized two novel chloroazaphilones, heliculin E (**175**) and isochromophilone XI (**176**).⁷⁸

Inducing the Mediterranean sponge *Agelas oroides* derived fungus *Penicillium canescens* by using 5% NaBr, resulted in two new brominated azaphilones, bromophilones A and B (**177–178**). Notably, **178** showed moderate cytotoxicity against the mouse lymphoma cell line L5178Y and the human ovarian cancer cell line A2780 with IC_{50} values of 8.9 and 2.7 μM , respectively, while **177** was less active.⁷⁹ Two new angular types of azaphilones, isochromophilonol (**179**) and ochrephilonol (**180**), were identified from *Chaetomium cupreum* RY202, and



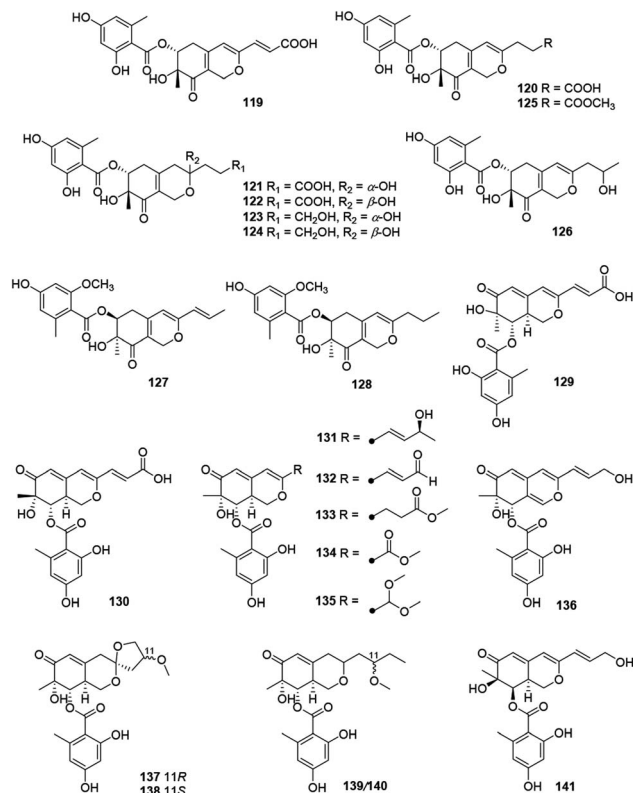


Fig. 8 Chemical structures of hydrogenated azaphilones (119–141).

179 exhibited moderated cytotoxicity against KB and NCI-H187 cell lines, while 180 showed weak cytotoxic activity against KB.⁸⁰ Six new highly oxygenated chloroazaphilone derivatives, namely isochromophilones A–F (181–186), were isolated from the mangrove-derived fungus *Diaporthe* sp. SCSIO 41011. Among them, 184 showed cytotoxicity against 786-O cells (IC_{50} = 8.9 μ M) and induced apoptosis in 786-O cells in a dose- and time-dependent manner.⁸

2.12 Cohaerins and related azaphilones

Eighteen novel compounds (190–207) constituted this unique group of azaphilones (Fig. 12 and Table 1). Cohaerins G–I and K (190–193) were produced by *Annulohypoxylon cohaerens*, along

with cohaerins C–F, whose absolute configurations were revised.⁸¹ 190–193 demonstrated cytotoxicity towards mouse fibroblast L-929 cancer cells, meanwhile, 190, 192, and 193 showed weak activity against the Gram-positive bacteria.⁸¹

Chemical and biological study of the stromata of *Annulohypoxylon minutellum* resulted in four novel azaphilones, minutellins A–D (194–197). Meanwhile, they displayed cytotoxicity towards mouse fibroblast L-929 cancer cells and also showed weak activity against the Gram-positive bacteria.⁸²

Four anti-MRSA azaphilones (MIC = 3.13–6.25 μ g mL^{−1}), named penicilones A–D (198–201), were obtained from the mangrove marine-derived fungus *Penicillium janthinellum* HK1-6.⁵ Interestingly, cultivation of this strain with NaBr led to the isolation of two new brominated azaphilones, penicilones G and H (202–203). Moreover, penicilone H (203) showed antibacterial activity against three bacteria with MIC values ranging from 3.13 to 12.5 μ g mL^{−1}.⁸³

With significant antioxidant activity (IC_{50} = 62.8 μ M), meliasendanin A (204) was obtained from the fruits of *Melia toosendan*.⁸⁴ The marine-derived fungus *Pleosporeles* sp. CF09-1 yielded three new azaphilone derivatives carrying with aromatic A-ring, pleosporalones A–C (205–207).^{61,85} Among them, 205 displayed strong antifungal activity against three plant pathogenic fungi with the MIC values ranging from 0.39 to 0.78 μ M.⁸⁵ Additionally, 206 exhibited stronger antifungal activities against *Alternaria brassicicola* and *Fusarium oxysporum* with the same MIC value of 1.6 μ g mL^{−1} than that of the positive control ketoconazole, whilst 206 displayed significant activity against *Botryosphaeria dothidea* (MIC = 3.1 μ g mL^{−1}).⁶¹

2.13 Nitrogenated azaphilones

This family included forty-five N-containing azaphilones (208–252), which were mainly obtained from *Penicillium* sp. and *Chaetomium* sp., (Fig. 13 and Table 1), such as peniazaphilones A–D (218–221),⁸⁶ berkchaetorubramine (233),⁴⁹ and (6-[(Z)-2-carboxyvinyl]-N-GABA-PP-V) (234).⁸⁷

The fermentation of an endophytic fungus *Chaetomium globosum* TY1, isolated from medicinal plant *Ginkgo biloba*, produced three metabolites, chaetomugilides A–C (208–210), which were cytotoxic against HePG2 with the IC_{50} values of 1.7, 19.8, and 53.4 μ M, respectively.⁸⁸ Meanwhile, 208 and 210 were also found in *Chaetomium globosum* (DAOM 240359) derived

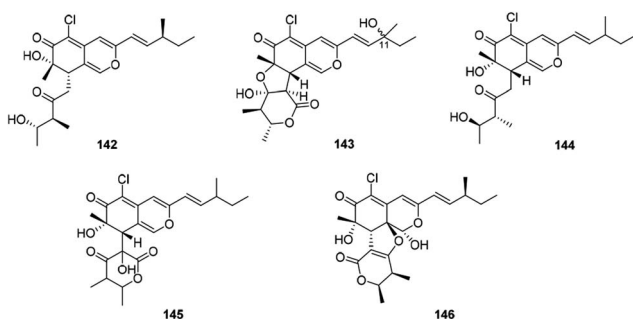


Fig. 9 Chemical structures of chaetoviridins and chaephilones (142–146).

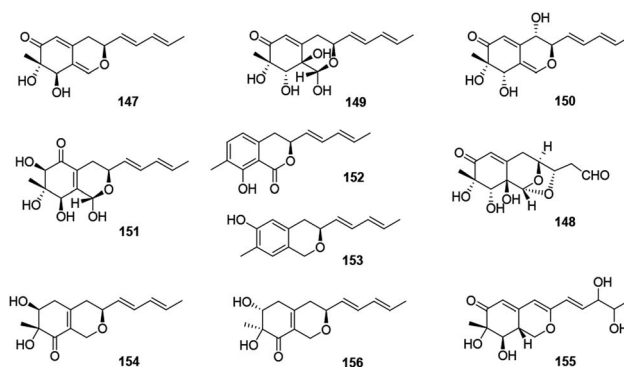


Fig. 10 Chemical structures of pulvilloric acid azaphilones (147–156).



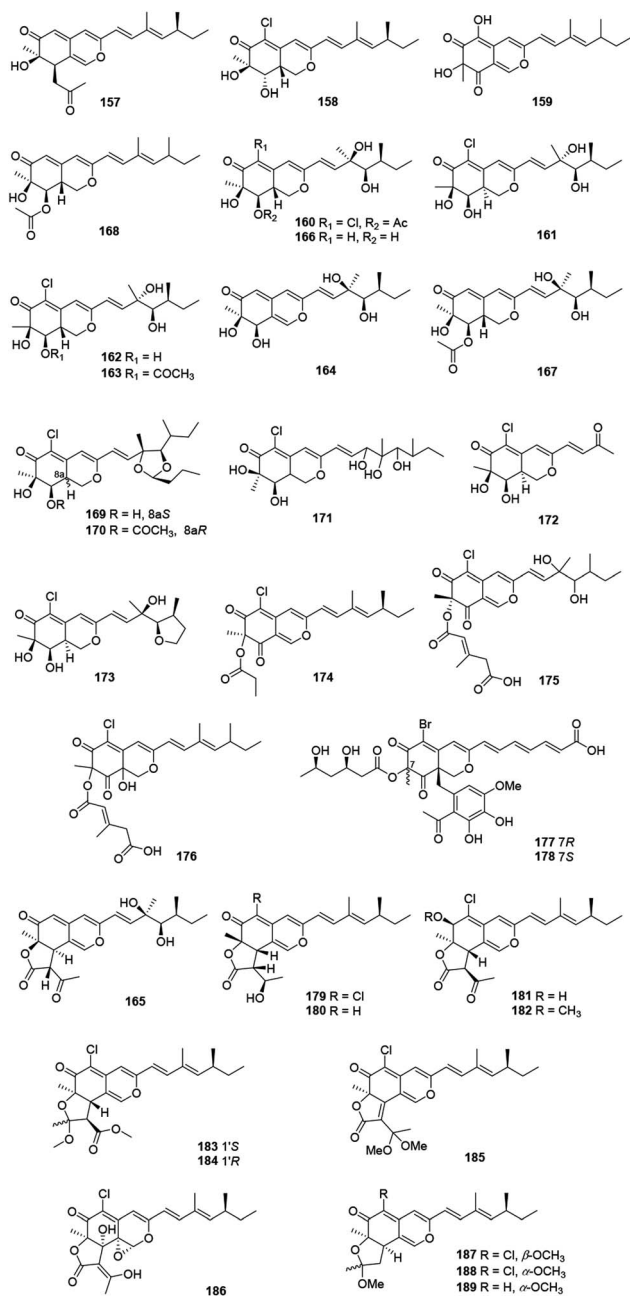


Fig. 11 Chemical structures of sclerotiorin-like azaphilones (157–189).

from an indoor air sample, together with isochromophilone XIII (211). Besides, **208** and **210** showed anti-microbial activities, while **208** (20 μM) reduced the growth of bacteria comparable to the effect of chloramphenicol at the same concentration.⁸⁹

The culture of *Chaetomium* sp. NA-S01-R1, derived from the deep sea, yielded chaetoviridides A–C (**212**–**214**). Notably, **212** and **213** showed activities against *Vibrio rotiferianus* and shared the MIC value of 7.3 $\mu\text{g mL}^{-1}$. Moreover, **213** and **214** exhibited equal anti-MRSA activities compared to positive control. Compounds **212** and **213** demonstrated significant cytotoxicity against the HepG.2 and HeLa cell lines, respectively.⁶⁴

N-Glutarylchaetoviridins A–C (**215**–**217**), embedded with glutamine residues, were obtained from *Chaetomium globosum* HDN151398, a deep-sea sediment derived fungus collected in the South China Sea. Remarkably, **217** exhibited strong cytotoxicity against human cancer cell lines MGC-803 and HO8910 with the IC_{50} values of 6.6 and 9.7 μM , respectively.⁹⁰ Sclerotiorin D and sclerketide C (**222**) sharing with the same structure and configuration, were simultaneously reported from the two strains of *Penicillium sclerotiorum*, CHNSCLM-0013 and OUCMDZ-3839, respectively.^{69,77} Compound **222** inhibited the NO production in the LPS-induced macrophage cell RAW 264.7 with the IC_{50} value of 2.7 μM and also suppressed the expression of iNOS and COX-2 in mRNA level.^{69,77} *Bartalinia robillardoides* LF550 metabolized a cytotoxic compound, isochromophilone X (**223**), which showed inhibitory activity against PDE4 (IC_{50} = 11.7 μM).⁷⁸

In 2019, Tang's group described the isolation and characterization of nine new azaphilone alkaloids, penazaphilones A–I (**224**–**232**), which were isolated from the rice solid fermented culture of *Penicillium sclerotiorum* cib-411. Meanwhile, structures of **228** and **231** were confirmed by X-ray diffraction analysis. Cell viability assay indicated that **224**, **228**, **229**, and **231** inhibited NO production with IC_{50} values ranging from 7.05 to 15.29 μM , without cytotoxicity towards RAW 264.7 cells (50.0 μM).⁹¹

Recently, a series of azaphilone pigments named atrorosins A, C–I, K–N, Q, R, T, V, W, and Y (**235**–**252**) have been isolated from the filamentous fungus *Talaromyces atroroseus*. Structurally, these atrorosins shared a carboxylic acid group at C-3 and an amino acid tethered to the isochromene core.⁹²

3. Chemical synthesis

Total synthesis could be the desirable alternatives to provide enough materials for further biological studies and determination of the absolute configurations. General synthetic protocol for azaphilones scaffolds had been concluded in 2013.³ Recently, several synthetic strategies of significance have been developed for these novel diversified azaphilones, which mainly focused on stereoselectivity,²⁹ complementary biocatalysts,⁹³ and the formation of angular lactone and chiral azaphilone dimers.⁹⁴ In general, cazisochromene and dioxinone have been employed as important intermediates and precursors, whilst AzaH and AfoD have been applied in synthesis as common biocatalysts.^{93,95} The recently reported chemical synthetic study of azaphilones were summarized herein.

3.1 The total synthesis of felinone A

Recently, Ito, *et al.* have reported the first total synthesis of felinone A (**29a**) and also revised the absolute configurations of natural felinone A (**29**).²⁹ The synthesis of dihydropyran ring was based on Shi asymmetric epoxidation of a bicyclic lactone, and intramolecular oxymercuration/demercuration.²⁹

The synthesis began with starting material propargyl alcohol (**253**), which underwent 2 steps to provide the precursor of enantioselective epoxidation, bicyclic lactone (**254**). Then **254**



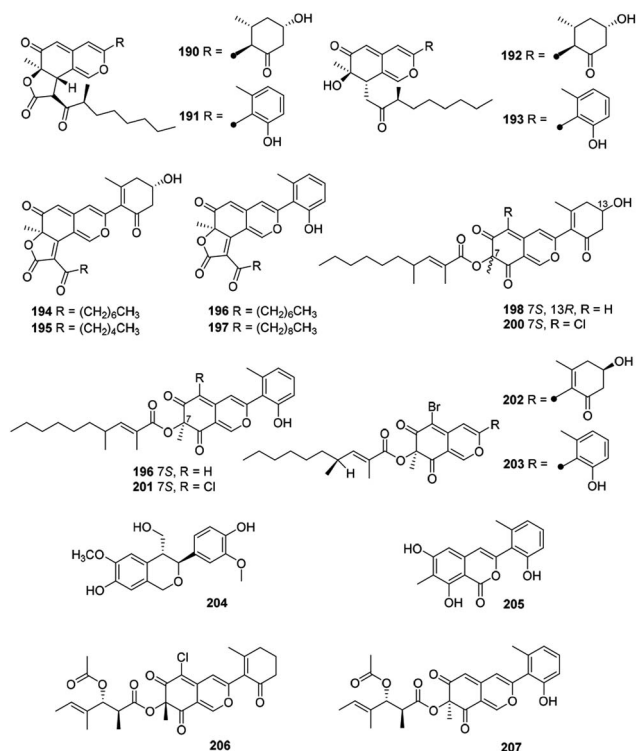


Fig. 12 Chemical structures of cohaerins and related azaphilones (190–207).

went through chemo- and enantio-selective epoxidation and gave the epoxide **255**, and then gave **256** in four steps with high diastereoselectivity. Simultaneously, **256** went through reduction to afford **257**, and then *via* Wittig reaction to afford alcohol **258** in high yield as an isomer. The cyclization of *E*-**258** afforded the hexahydroisochromene derivative (**259**). Selectively cleaved the acetonide group of **259** provided **260**, which went through Ley oxidation to form **261**. Treatment of the resulting ketone **261** with TBAF provided the target felinone A (**29a**) in middle yield (Scheme 1).

3.2 Total synthesis of trichoflectin, (*S*)-deflectin-1a, and lunatoic acid A

Total synthesis of trichoflectin (**262**), (*S*)-deflectin-1a (**263**), and lunatoic acid A (**264**) were accomplished using complementary biocatalysts.⁹³

The synthesis of trichoflectin (**262**) was initiated through a five-step route to enone **265**. Dearomatization of **265** afforded azaphilone scaffold (*R*)-**266** in high yield. Then, acylation of (*R*)-**266** provided (*S*)-**262**. The enantiomeric tricycle was synthesized from the AfoD generated product (*S*)-**266**. Finally, it is proposed that the structure of the natural product should be revised to the *R*-configuration (Scheme 2A).

Methyl ketone **267** was dearomatized with AzaH to afford bicycle **268**. Acylation and Knoevenagel condensation with the acylketene derived from precursor **269** furnished the desired butenolide to deliver (*S*)-deflectin-1a (**263**) in high yield (Scheme 2B).

Lunatoic acid A (**264**) was constructed from (*R*)-**266**, which went through Yamaguchi esterification with **270** to produce **271**. Lunatoic acid A (**264**) was provided by saponification of methyl ester **272** using LiOH (Scheme 2C).

3.3 The first total synthesis of chaetoglobin A

The first total synthesis of chiral azaphilone dimer, chaetoglobin A (**273**), was finished in 12 steps by Kang and his co-workers in 2017.⁹⁴ The vanadium-catalyzed atroposelective oxidative phenol coupling was a key step to form stereoaxis of chiral azaphilone dimer.⁹⁴

Optimization of Sonogashira coupling between iodide **274** and alkyne **275** afforded oxidative phenol coupling precursor **276** in 98% yield. Catalytic **276** with chiral vanadyl catalyst **277** led to the formation of dimer **278**, which underwent the Vilsmeier–Haack formylation to provide **279** in 86% yield. Cycloisomerization of **279** afforded bicyclic dimer **280**. And acetylation of **280** gave **281**, which then afforded **282** after hydroxylation. Treatment of **282** with excess NH_4OAc led to the nearly quantitative formation of chaetoglobin A (**273**) in 96% yield (Scheme 3).

3.4 Total synthesis of chaetoviridins

The first synthesis of chaetoviridin A (**283**) had been achieved in 10 steps in 2017.⁹⁵ Vanadium-catalyzed oxidative phenol coupling is a vital step in the formation of the axial chirality.⁹⁵

The synthesis of the key intermediate cazisochromene (**290**) started with chlorination of methyl atratate (**284**). Benzylic deprotonation of **285** yielded **286**, which was activated as pentafluorophenol ester (**287**). Following Cossy's procedure of **287** formed the β -ketoester **288**. Treating **288** *via* Horner–Wadsworth–Emmons reaction and lactonization led to the formation of **289**. Lactone **289** was then reduced and oxidatively dearomatized to yield **290**. Condensation of a chiral dioxin-4-one **291** to cazisochromene **290** formed angular lactone. (*S,R*)-dioxinone (**291**) and **290** were heated in toluene for 30 min before adding Et_3N and then afforded **292**, which was directly treated by HF/pyridine to give the (*7S,4'S,5'R*)-chaetoviridin A (**283a**) and (*7R,4'S,5'R*)-chaetoviridin A (**283b**) with 17% and 20% yield, respectively (Scheme 4).

Starting from (*S,S*)-**291**, (*7S,4'S,5'S*)-chaetoviridin A (**283c**) and (*7R,4'S,5'S*)-chaetoviridin A (**283d**) were obtained with 14% and 15% yield, respectively. Whereas the other set of (*7S,4'R,5'R*)-chaetoviridin A (**283e**) and (*7R,4'R,5'R*)-chaetoviridin A (**283f**) were prepared starting from (*R,R*)-**291** (Scheme 4).

3.5 Total synthesis of chlorofusin and its chromophore diastereomers

Yao and his group developed a newly stereo divergent total synthesis of chlorofusin (**293a**), along with seven chromophore diastereomers (**293b–h**) of **293a** in enantiopure forms.⁹⁶

Synthesis of them started from a racemic azaphilone precursor **296**, which was prepared from *O*-alkynylbenzaldehyde (**294**) *via* 3 steps. The site-selective chlorination from *rac*-**296** to *rac*-**297** was performed with SO_2Cl_2 in DCM. The reaction of *rac*-**297** with (*R*)-(+)-4-methoxy- α -methylbenzylamine led to the



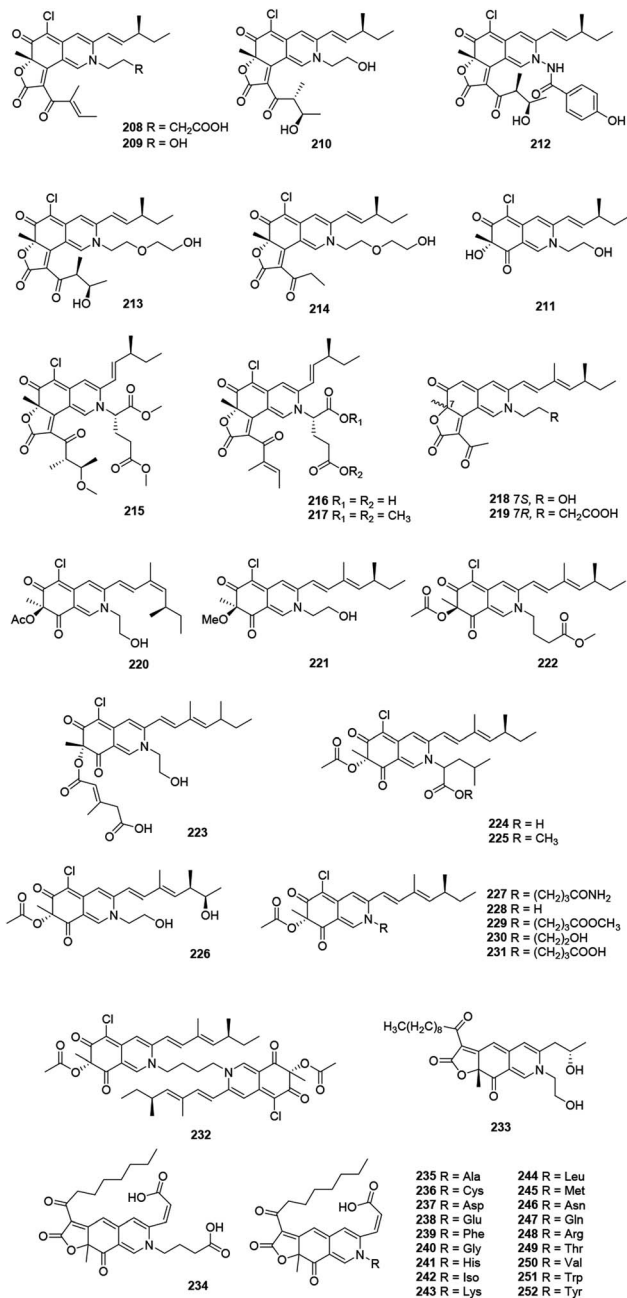


Fig. 13 Chemical structures of nitrogenated azaphilones (208–252).

formation of two diastereomeric vinylogous γ -pyridones (4*R*)-298 and (4*S*)-298. Parallely, removing the chiral auxiliary of (4*R*)-298 and (4*S*)-298 and then replacing them with allyl bromide led to the formation of (4*R*)-299 and (4*S*)-299 (Scheme 5).

In parallel, the reaction of acetate (4*R*)-299 and (4*S*)-299 with K₂CO₃ in MeOH at room temperature, followed by intramolecular iodoetherification and *in situ* hydrolysis carried out four inseparable diastereomers, (4*R*)-300 and (4*S*)-300, in high yields. Each mixture underwent Dess–Martin oxidation and yielded two separable single diastereomeric ketones (4*R*,9*S*)-301/(4*R*,9*R*)-301 and (4*S*,9*R*)-301/(4*S*,9*S*)-301, respectively. The

reduction of ketones furnished eight fully functionalized chromophores, (4*R*,8*R*,9*S*)-302/(4*R*,8*S*,9*S*)-302, (4*R*,8*S*,9*R*)-302/(4*R*,8*R*,9*R*)-302, (4*S*,8*R*,9*R*)-302/(4*S*,8*S*,9*R*)-302, (4*S*,8*R*,9*S*)-302/(4*S*,8*S*,9*S*)-302 (Scheme 5).

(4*R*,8*S*,9*R*)-302 underwent removal of *N*-allylation and condensed with iodoornithine derivative 303 to generate the chromophore-ornithine derivative 304 in 62% yield by two steps. The precursor 305 was provided in 83% yield from 304 *via* three steps. Removal of both *N*-Cbz and benzyl ester groups of 305 afforded natural (4*R*,8*S*,9*R*)-chlorofusin (293a), with 35% yield in two steps (Scheme 5).

Starting from the corresponding chromophore diastereomers, (4*R*,8*R*,9*S*)-302, (4*R*,8*S*,9*S*)-302, (4*R*,8*R*,9*R*)-302, (4*S*,8*R*,9*R*)-302, (4*S*,8*S*,9*R*)-302, (4*S*,8*R*,9*S*)-302, (4*S*,8*S*,9*S*)-302, the parallel total synthesis of other seven chlorofusin chromophore diastereomers were formed through this reproducible route.⁹⁶

4. Biosynthesis

In 2019, Chen and co-workers have presented an overview of a unified biosynthetic pathway with the diverse structures of the 111 *Monascus* azaphilones congeners.⁹⁷ Generally, biosynthesis of azaphilones contain the polyketide pathway and the fatty acid synthesis pathway, while some may involve polyketide–amino acid mixed biosynthesis.⁴ The azaphilone polyketide is synthesized by an NR-fPKS with a reductive release domain, and the pyran ring cyclization is based on hydroxylation-mediated dearomatization of a benzaldehyde intermediate.⁴⁸ The structural complexity of azaphilones may result from interaction of biosynthesis with metabolic and chemical fluke. Herein, the recently proposed biosynthetic pathways of novel azaphilones were summarized.

4.1 Biosynthesis of mycoleptone A

Andrioli proposed that mycoleptone A (44) was originated from the condensation of two austdiol units.¹⁵ It was assumed that two austdiol units underwent decarbonylation and reduction to afford two units, respectively, which then led to the formation of mycoleptone A by Friedel–Crafts alkylation (Scheme 6).

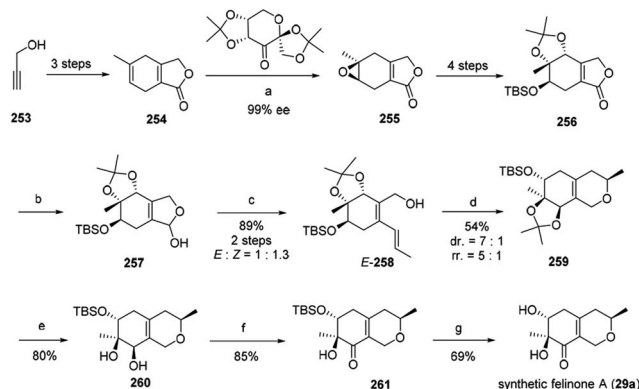
4.2 Biosynthesis of monasfluols A and B, MC-2 and MC-4

Balakrishnan and his co-workers thought that monasfluol A (306) and monasfluol B (84) were derived from the presumed intermediate 307 by nonenzymatic Knoevenagel condensation and reduction.⁴⁶ In 2017, it was assumed that MC-2 (87) and MC-4 (88) might share similar biosynthetic pathway, both of which were catalyzed by *Δmpc*⁹⁸ (Scheme 7).

4.3 Proposed biosynthetic route to azaphilone 7

It was assumed that azaphilone 7 could be converted from the pentaketide, 2,4-dihydroxy-3-methyl-6-(2-oxopropyl) benzaldehyde, which started from acetate, 4 malonates, and methionine in the *A. oryzae* transformant harbouring pTAtspsk2 (ref. 18) (Scheme 8).

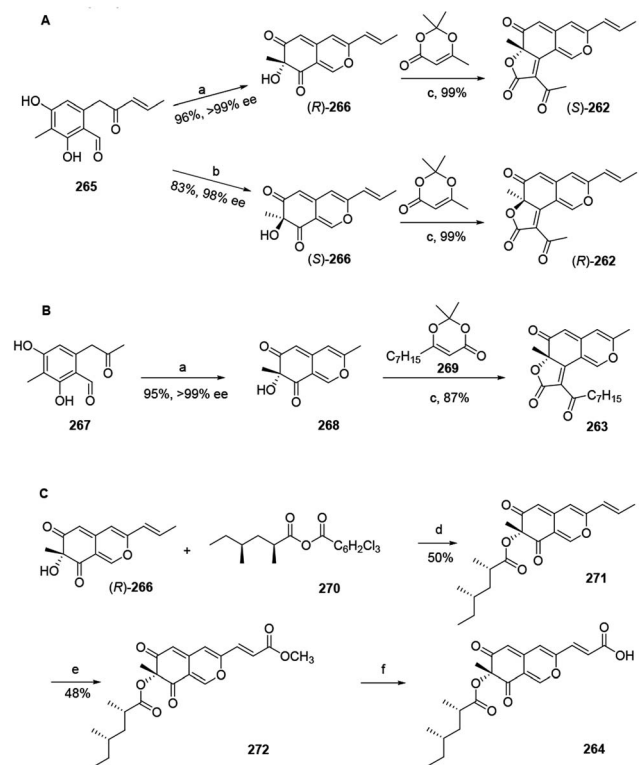




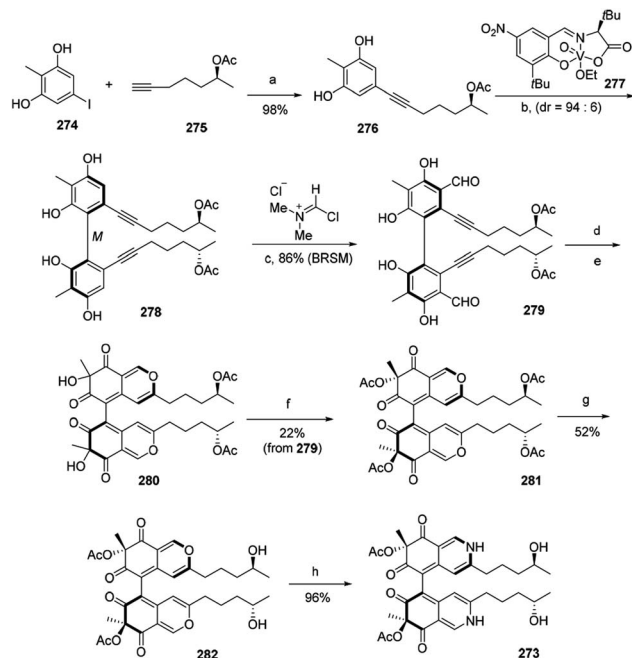
Scheme 1 Synthesis of felinone A²⁹ Reagents and conditions: (a) Oxone®, K₂CO₃, CH₃CN-DMM-buffer, 98%, 87% ee, then recrystallization; (b) DIBALH, toluene; (c) Ph₃PCH₂CH₃ Br, LHMDS THF; (d) Hg(OCOCF₃)₂, MeOH, then NaBH₄; (e) TFA, CH₂Cl₂-H₂O; (f) TPAP, NMO, CH₂Cl₂; (g) TBAF, THF.

4.4 Postulated biogenetic pathway for penicilazaphilone E

Wang, *et al.* thought WB could be the precursor of penicilazaphilone E (173).⁷⁶ Firstly, WB went through oxidation to provide intermediate 308. Then 308 underwent cyclization between 7'-methyl and 4'-OH to afford 173 in two different possible pathways (Scheme 9).



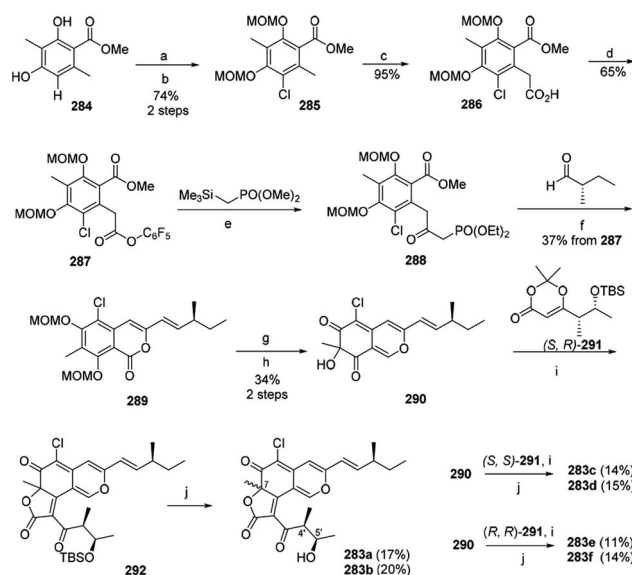
Scheme 2 Synthesis of trichoflectin, (S)-deflectin-1a, and lunatoic acid A by Pyser and his co-worker.⁹³ Reagents and conditions: (a) AzaH (0.2 mol%), NADPH recycling system, KPi buffer, pH 8.0; (b) AfoD (0.8 mol%), NADPH recycling system, KPi buffer, pH 8.0; (c) Et₃N, mol sieves, toluene, 110 °C; (d) DMAP, toluene, 110 °C; (e) Grubbs 2nd Gen, methyl acrylate, DCM, 45 °C; (f) LiOH, THF : MeOH : H₂O, r.t.



Scheme 3 Synthesis of chaetoglobins A.⁹⁴ Reagents and conditions: (a) PdCl₂(PPh₃)₂, CuI, Et₃NH, DMF, 65 °C, 18 h; (b) HOAc, O₂, ClPh, 0 °C, 48 h, 67% (BRSM); (c) CH₂Cl₂, -35 °C, 12 h; (d) AgOTf, DCE/TFA, r.t., 1.5 h; (e) IBX, Bu₄Ni, r.t., 18 h; (f) Ac₂O, DMAP, Et₃N, CH₂Cl₂, -78 °C, 0.5 h; (g) Ti(Oi-Pr)₄, THF, 50 °C, 24 h; (h) NH₄OAc, CH₂Cl₂, r.t., 20 h.

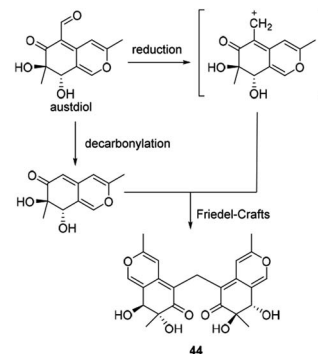
4.5 Proposed biosynthesis of chaephilone B

The biogenetic pathway of chaephilone B (145) was suggested from the precursor chaetomugilin S, which was extensively investigated in *C. globosum* by C. Chen and co-workers.⁶² The



Scheme 4 Synthesis of chaetoviridins.⁹⁵ Reagents and conditions: (a) NCS; (b) NaH/MOMCl; (c) LDA/CO₂; (d) C₆F₅OH, EDC/DMAP; (e) *n*-BuLi; (f) K₂CO₃, EtOH; (g) DIBAL-H; (h) IBX/TFA/H₂O; (i) Et₃N, toluene, reflux; (j) HF/pyridine.



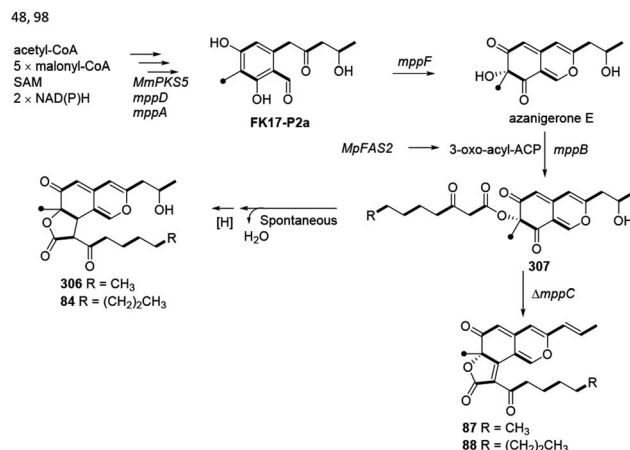


312. The reduction and subsequent cyclization of **310** formed the naphthopyran moiety of **309** (ref. 38) (Scheme 11).

The biogenetic pathway of chaephilone C (**146**) was postulated to start from chaetoviridin A (**313**).⁶⁴ Hydration of **313** formed intermediate **314**, which then followed hydrolytic opening of the γ -lactone and post dehydration to obtain **146** (Scheme 12A). The biogenetic pathway of chaetoviridides A (**212**) and B (**213**) was assumed to include a Schiff base formation and dehydration reaction (Scheme 12B).

Colletotrichones A–C (**54–56**) and chermesinonen B (**317**) might proceed from a pentaketide **316** by several steps. **316** could be formed by the condensation of a 4-methyl-3-oxohexanoic acid and an isochromene analogue **315**³⁷ (Scheme 13).

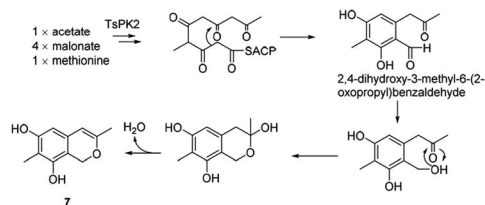
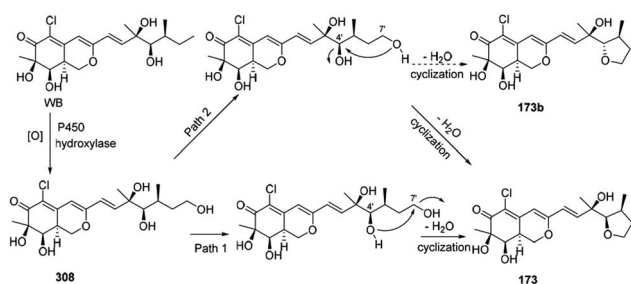
The azaphilone intermediate **318** was formed through esterification of a β -ketoacid to the polyketide chromophore and



Scheme 5 Synthesis of chlorofusin and its chromophore diastereomers.⁹⁶ Reagents and conditions: (a) AgNO₃, TFA, ClCH₂CH₂Cl; (b) IBX, *n*-Bu₄NI; (c) butyryl chloride pyridine, DMAP, DCM; (d) SO₂Cl₂, DCM; (e) aq. NaHCO₃ (sat.), CH₃CN, r.t.; (f) TFA : H₂O (v/v = 10 : 1), (i-Pr)₃SiH; (g) allyl bromide Pd(PPh₃)₄, KF·Al₂O₃, DMF; (h) K₂CO₃, MeOH; (i) I₂, NaHCO₃, *n*-Bu₄NI, CH₃CN/H₂O; (j) DMP, NaHCO₃, DCM; (k) NaBH₃-CN, CeCl₃·7H₂O, MeOH, r.t.; (l) Pd(Ph₃)₄, NDMA, DCM, MW; (m) KF·Al₂O₃, DMF; (n) Pd/C, H₂, THF/DMF; (o) Cbz-OSu, NaHCO₃, THF/H₂O; (p) TFA : H₂N-octapeptide-OBn **71**, EDCl, HOBT, DIEA, DCM/DMF; (q) Pd/C, H₂, THF/DMF; (r) EDCl, HOAt, NaHCO₃, DMF.

4.6 Biosynthesis of acetosellin

Acetosellin (**309**) was proposed from epicocconone (**310**) by the condensation of two polyketide-derived intermediates, **311** and

Scheme 8 Proposed biosynthetic route to azaphilone 7.¹⁸Scheme 9 Postulated biogenetic pathway for penicilazaphilone E.⁷⁶

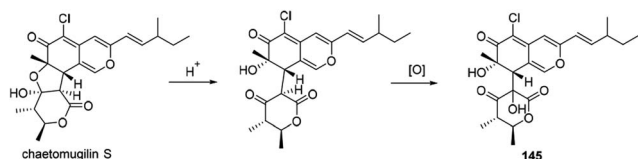
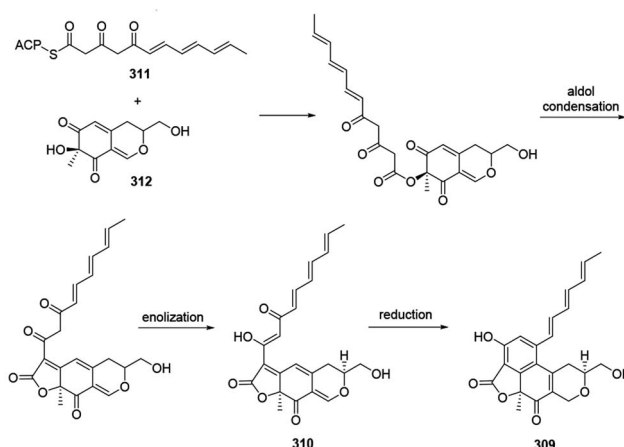
followed by a C-8/C-12 Knoevenagel cyclization and reduction. Elimination of intermediate **318** afforded coniellin A (**57**). Hydrolysis of intermediate **318** gave the product **319**. Coniellin H (**64**) was derived from the intermediate **319** by elimination, [2 + 2] cycloaddition, and methylation. The pathway from **319** to coniellin I (**65**) involved esterification and the formation of hemiketal group³⁵ (Scheme 14).

4.10 Proposed biogenesis of thielavialides A–E

Biosynthetically, it was proposed that the biosynthetic pathway of thielavialides A–E (**70–74**) was started from pestafolide A (**317**).⁴⁰ The probable biosynthetic pathway of thielavialides A–D (**70–73**) from **320** involved a favorskii-like rearrangement of its oxidation product, 5-dehydropestafolide A (**321**). Biosynthesis of thielavialide E (**74**) might involve a radical oxidative coupling of the intermediate **321** or its acetate (Scheme 15).

4.11 Proposed biosynthetic relationships among dothideomynones D–F

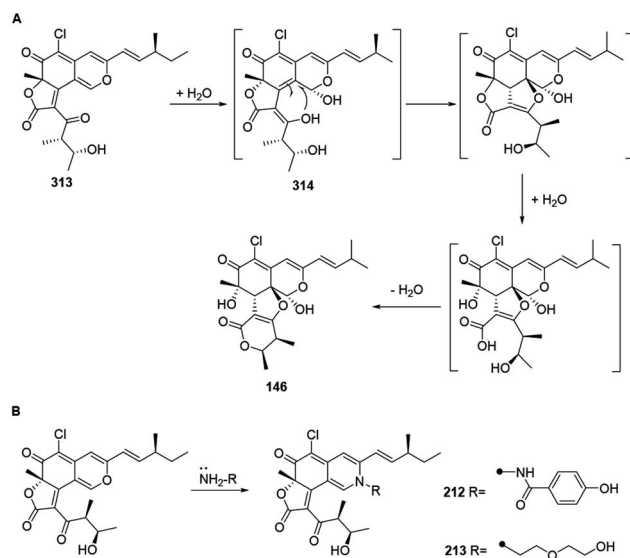
Dothideomynone D (**41**) was assumed as a potential biosynthetic precursor of dothideomynones E and F (**42–43**).³⁴ The condensation of acetyl-CoA and malonyl-CoA gave the linear intermediate, which followingly went through cyclization to form dothideomynone D (**41**). **41** underwent oxidation to afford the intermediate **322**, which in turn employed malonyl-CoA as an extender to give **323**. The reduction of the intermediate **323**

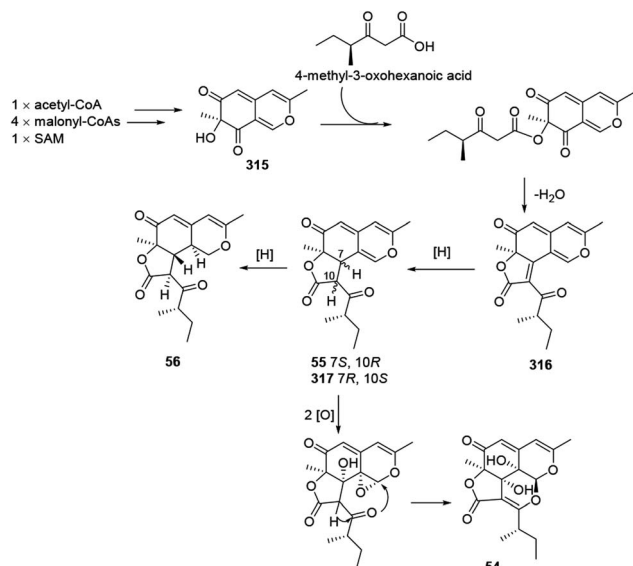
Scheme 10 Proposed biosynthesis of chaephilone B.⁶²Scheme 11 Biosynthesis of acetosellin.³⁸

could generate the intermediate **324**. Cyclization of the intermediate **324** led to the formations of **42** and **43** (Scheme 16).

4.12 Proposed biosynthesis of cochliodone A and chaetogloblin A

Biosynthetic pathways of cochliodone A (**325**) and chaetogloblin A (**326**) were proposed in 2013.⁹⁹ CHGG_10027 was confirmed its involvement in the biosynthesis of **325**, which accepted acetyl-CoA as a starting unit and added four malonyl-CoA units to provide 6-methylorsellinic acid. Acetylation of the alcohol group on the ring system could be achieved by an *O*-acetyltransferase, and dimerization was likely performed by a fungal laccase-like CHGG_10025. A nonenzymatic reaction with ammonia of **325** could generate **326** (Scheme 17).

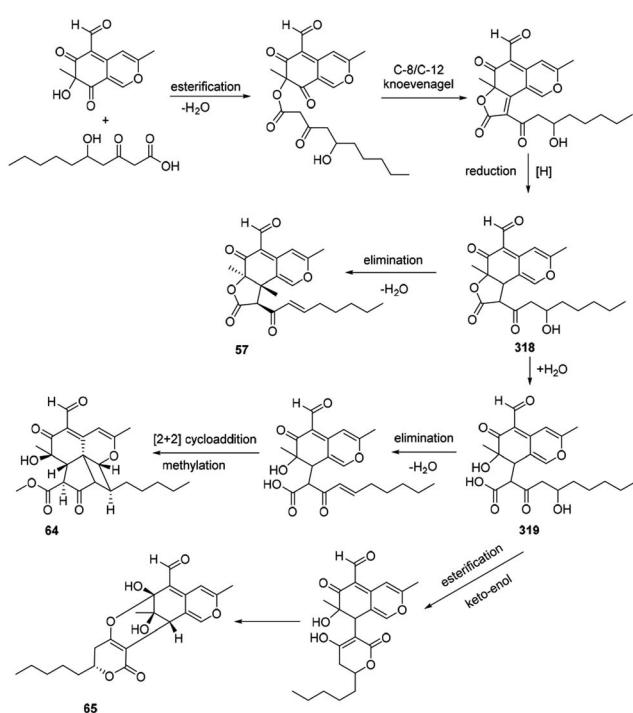
Scheme 12 Biosynthesis of chaephilone C, chaetoviridides A and B.⁶⁴



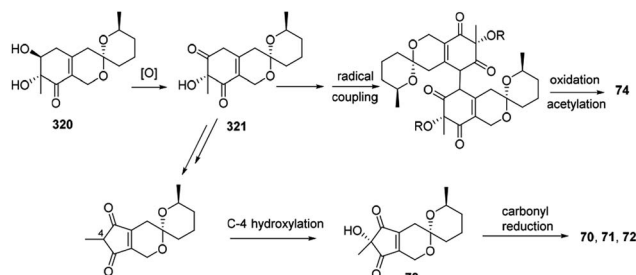
Scheme 13 Proposed biosynthesis of colletotrichones A–C, and chermesinonen B.³⁷

4.13 Biosynthesis of 6''-hydroxy-(R)-mitorubrinic acid, purpurquinone D (–)-mitorubrinic acid, (–)-mitorubrin, and purpurquinone A

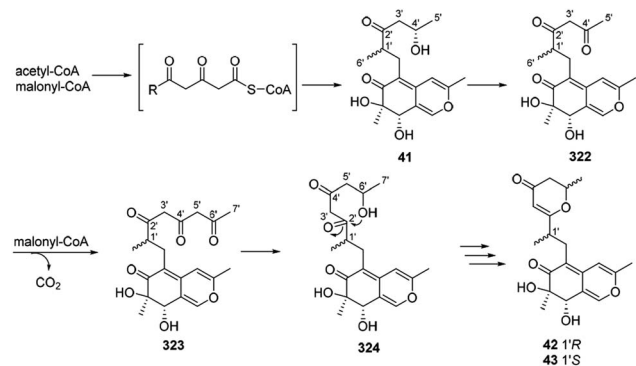
Xiao, *et al.*, hypothesized the biosynthesis of 6''-hydroxy-(R)-mitorubrinic acid (**109**), purpurquinone D (**110**), (–)-mitorubrinic acid (**327**), (–)-mitorubrin (**328**), and purpurquinone A (**329**) were started from six acetate units through 2, 7-



Scheme 14 Postulated biosynthesis of conellins A, H, and I.³⁵



Scheme 15 Proposed biogenesis of thielvalialides A–E.⁴⁰

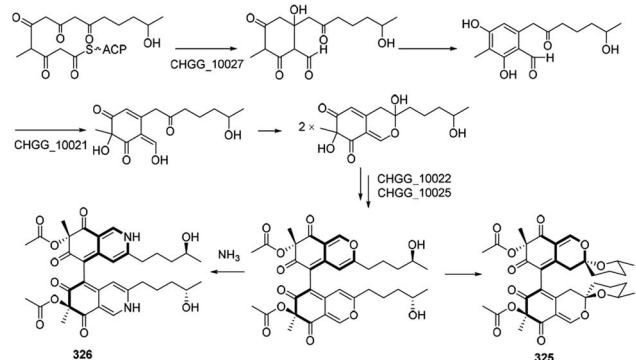


Scheme 16 Proposed biosynthetic relationships among dothideomynones D–F.³⁴

condensation.⁵³ Besides, orselilinic acid was proposed to be involved in the pathway (Scheme 18).

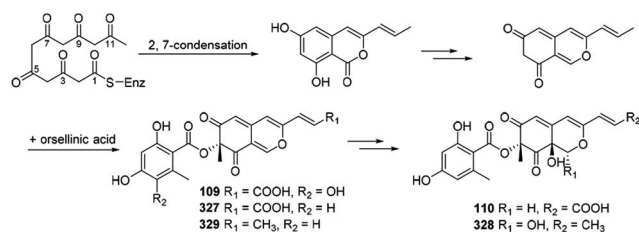
4.14 Possible biosynthesis of cazisochromene, chaetoviridin A, and chaetomugilin A

The biosynthesis of cazisochromene (**290**) was proposed to be derived from calaldehyde A, which was the product of the interaction between HR-PKS and NR-PKS.¹⁰⁰ **290** was transferred to chaetoviridin A (**330**) by 8-CazF and chaetomugilin A (**331**) would be generated in turn^{100,101} (Scheme 19).



Scheme 17 Proposed biosynthesis of cochliodone A and chaetoglobulin A.⁹⁹

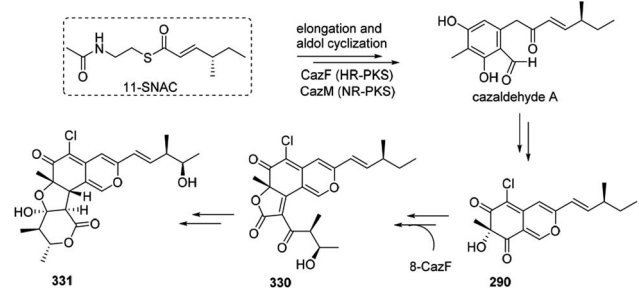




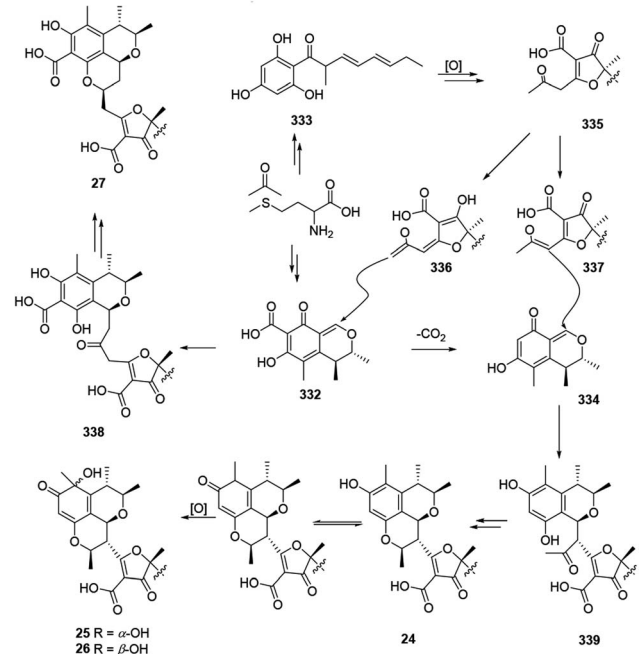
Scheme 18 Biosynthesis of 6''-hydroxy-(R)-mitorubric acid, purpurquinone D (–)-mitorubric acid, (–)-mitorubrin, and purpurquinone A.⁵³

4.15 Plausible biosynthesis of citrifurans A–D

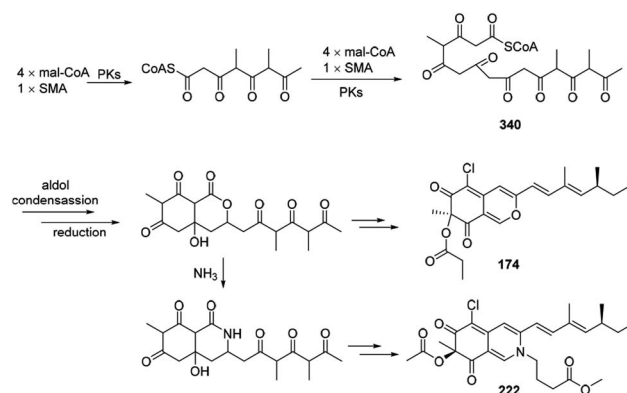
The plausible biosynthetic pathway for citrifurans A–D (24–27) was assumed by Yin, *et al.* in 2017.⁷ The presumed precursors 332 and 333 were originated from acetate and *S*-adenosyl methionine. Then decarbonylation of 332 and oxidation of 333 afforded intermediates 334 and 335, respectively. Afterward,



Scheme 19 Possible biosynthesis of cazisochromene, chaetoviridin A, and chaetomugilin A.¹⁰⁰

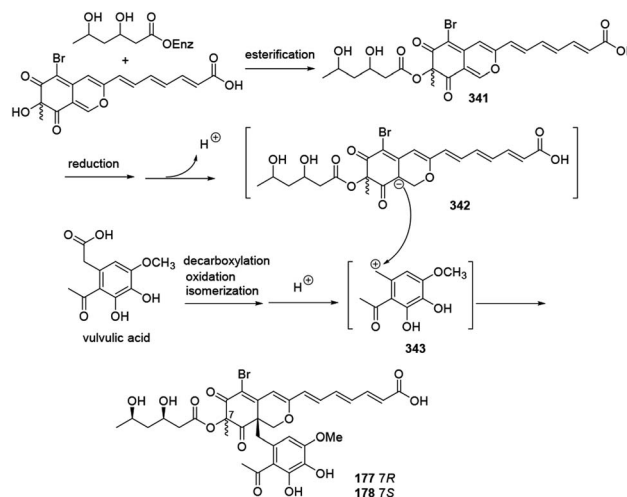


Scheme 20 Plausible biosynthesis of citrifurans A–D.⁷



Scheme 21 Postulated biosynthesis of sclerketides B and C.⁷⁷

deprotonation of 335 afforded two kinds of enolate anions, 336 and 337, which subsequently heterodimerized with 332 and 334 through a Michael addition reaction to form adducts 338 and 339, respectively. A subsequent intramolecular nucleophilic addition and reduction of 339 constructed a dihydropyran ring in citrifuran A (24), which further went *via* oxidation to form the epimers, citrifuran B (25) and citrifuran C (26). Similarly, the



Scheme 22 Plausible biosynthesis of bromophilones A and B.⁷⁹

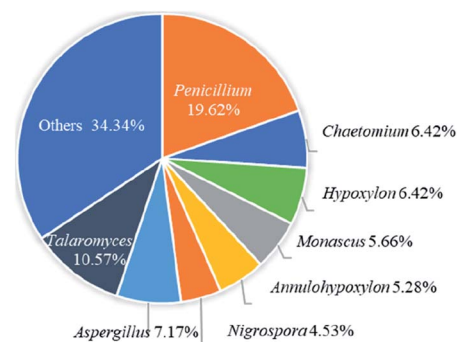


Fig. 14 Species distribution of azaphilones from fungal sources.



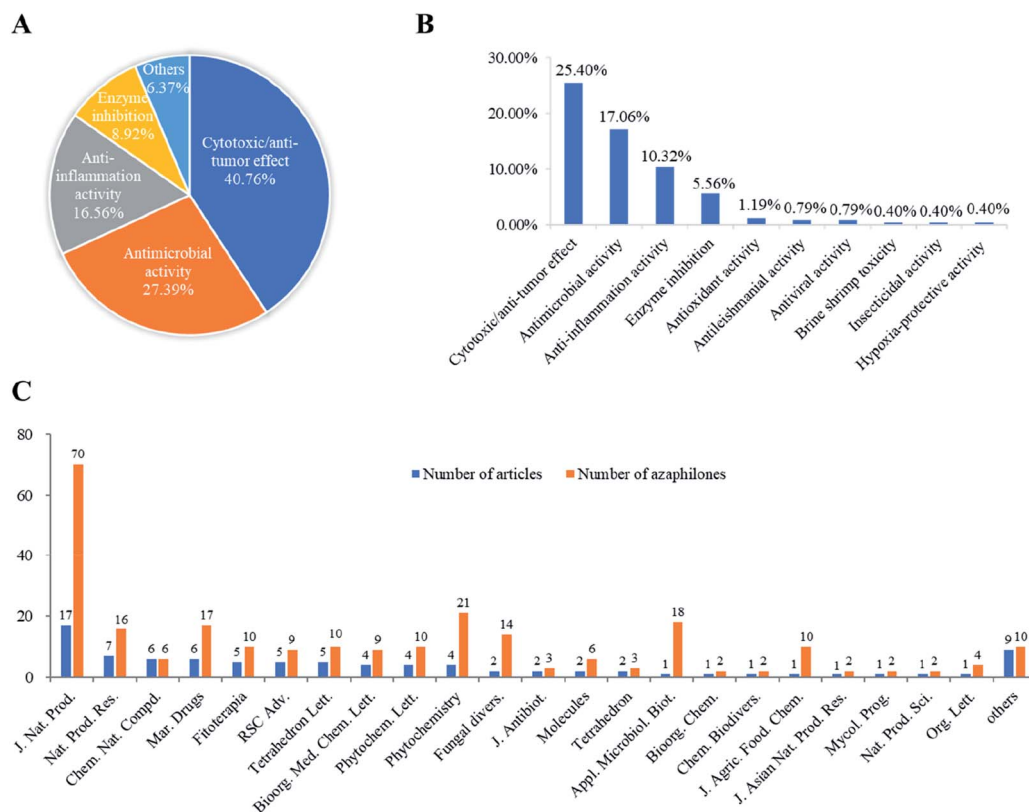


Fig. 15 The percent of types of bioactivity out of all bioactive azaphilones (A)/all azaphilones (B); numbers of recently reported new azaphilones and related articles published in different journals (2013–2019) (C).

intramolecular dehydration of **339** could produce citrifuran **D** (**27**) (Scheme 20).

4.16 Postulated biosynthesis of sclerketides B–C

Plausible biosynthetic pathway of sclerketides B–C (**174** and **222**) was proposed in 2019.⁷⁷ It was assumed that **340** could be generated by 4 mal-CoAs and SMA, following by the reduction, esterification, and condensation to yield **174** and **222** (Scheme 21).

4.17 Plausible biosynthesis of bromophilones A–B

A plausible biosynthetic pathway for bromophilones A–B (**177**–**178**) was proposed by Frank, *et al.* in 2019.⁷⁹

The intermediate **341** went through reduction, enolization, and deprotonation, followed by isomerization to form the carbanion intermediate **342**. Decarboxylation of vulvulic acid and followed by oxidation and isomerization resulted in formation of the *para* quinone methide intermediate **343**. **177** and **178** were formed by a nucleophilic attack of the carbanion **342** to the carbocation **343** (Scheme 22).

5. Conclusion

Recently, the fungal polyketides, azaphilones, have attracted continuous broad interests owing to their intriguing structural, biosynthetic, and pharmacological features. According to the

literature survey from 2012 October to December of 2019, 252 newly reported azaphilones covered from 35 species, including 32 genera of fungi, 2 plants, and 1 bacterium, were summarized in this research. In terms of the taxonomy of the fungal sources, the genera of *Penicillium* (20%), *Talaromyces* (11%), and *Aspergillus* (7%) were the predominant producers of azaphilones (Fig. 14).

Among these recently reported azaphilones, nearly 48% of them were discovered with a broad spectrum of bioactivities (122 of 252 compounds), including cytotoxic/anti-tumor effect (25%), antimicrobial activity (17%), anti-inflammatory activity (10%), enzyme inhibitions (5%), antioxidant activity (1%), antileishmanial activity (0.79%), antiviral activity (0.79%), brine shrimp toxicity (0.40%), insecticidal activity (0.40%), and hypoxia-protective activity (0.40%) (Fig. 15B). Moreover, cytotoxic/anti-tumor effect (40%), antimicrobial activity (27%), and anti-inflammatory activity (16%) were dominant in the above-mentioned bioactivities (Fig. 15A). In addition, a total of 88 articles involving 252 newly reported azaphilones have been published in 31 international journals during the past seven years. Amongst, 70 novel azaphilones (28%) in 17 articles (19%) were published in *Journal of Natural Products*, which was the most populous journal for recent reported azaphilones (Fig. 15C).

Based on the foregoing discussion, there are still some challenges in the chemical synthesis of azaphilones, such as stability of intermediates, stereoselectivity, reaction utilization,

and overall yield. Thus, comprehensive and in-depth research would yet be needed in the synthesis and biosynthesis of these azaphilones with novel and complex structures. Notably, the semi-synthesis of naturally occurring azaphilones through metabolic engineering would accelerate the discovery of advanced intermediates and lead compounds.¹⁰² Considering the significant and broad biological activities of this class of metabolites, the azaphilone family would probably continue to draw attention in the chemical synthetic and biosynthetic processes. Collectively, this review would shed light on the further development in chemical and pharmacological investigations of azaphilones with clinically therapeutic applications.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

This work was financially supported in part by the National Natural Science Foundation of China (No. 21772210, 81973235, 21977102), the Special Fund for Bagui Scholars of Guangxi (Yonghong Liu), the Scientific Research Foundation of Institute of Marine Drugs, Guangxi University of Chinese Medicine (2018ZD005-A01, 2018ZD005-A17), the Initial Scientific Research Foundation of Introduced Doctors in 2019 of Guangxi University of Chinese Medicine (2019BS021), and Guangdong Basic and Applied Basic Research Foundation (2019B151502042, 2018A0303130219).

Notes and references

- D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2016, **79**, 629–661.
- H. Hussain, A. M. Al-Sadi, B. Schulz, M. Steinert, A. Khan, I. R. Green and I. Ahmed, *Future Med. Chem.*, 2017, **9**, 1631–1648.
- J. M. Gao, S. X. Yang and J. C. Qin, *Chem. Rev.*, 2013, **113**, 4755–4811.
- N. Osmanova, W. Schultze and N. Ayoub, *Phytochem. Rev.*, 2010, **9**, 315–342.
- M. Chen, N. X. Shen, Z. Q. Chen, F. M. Zhang and Y. Chen, *J. Nat. Prod.*, 2017, **80**, 1081–1086.
- T. X. Li, R. H. Liu, X. B. Wang, J. Luo, J. G. Luo, L. Y. Kong and M. H. Yang, *J. Nat. Prod.*, 2018, **81**, 1148–1153.
- G. P. Yin, Y. R. Wu, M. H. Yang, T. X. Li, X. B. Wang, M. M. Zhou, J. L. Lei and L. Y. Kong, *Org. Lett.*, 2017, **19**, 4058–4061.
- X. Luo, X. Lin, H. Tao, J. Wang, J. Li, B. Yang, X. Zhou and Y. Liu, *J. Nat. Prod.*, 2018, **81**, 934–941.
- H. Yu, J. Sperlich, A. Mandi, T. Kurtan, H. Dai, N. Teusch, Z. Y. Guo, K. Zou, Z. Liu and P. Proksch, *J. Nat. Prod.*, 2018, **81**, 2493–2500.
- D. Chen, S. Ma, L. He, P. Yuan, Z. She and Y. Lu, *Tuberculosis*, 2017, **103**, 37–43.
- W. Li, C. Lee, S. H. Bang, J. Y. Ma, S. Kim, Y. S. Koh and S. H. Shim, *J. Nat. Prod.*, 2017, **80**, 205–209.
- Y. Liu, Q. Yang, G. Xia, H. Huang, H. Li, L. Ma, Y. Lu, L. He, X. Xia and Z. She, *J. Nat. Prod.*, 2015, **78**, 1816–1822.
- D. Zhang, J. Zhao, X. Wang, L. Zhao, H. Liu, Y. Wei, X. You, S. Cen and L. Yu, *J. Antibiot.*, 2018, **71**, 905–907.
- J. Y. Kim, E. E. Woo, L. S. Ha, D. W. Ki, I. K. Lee and B. S. Yun, *Mycobiology*, 2019, **47**, 256–260.
- W. J. Andrioli, R. Conti, M. J. Araujo, R. Zanasi, B. C. Cavalcanti, V. Manfrim, J. S. Toledo, D. Tedesco, M. O. de Moraes, C. Pessoa, A. K. Cruz, C. Bertucci, J. Sabino, D. N. P. Nanayakkara, M. T. Pupo and J. K. Bastos, *J. Nat. Prod.*, 2014, **77**, 70–78.
- F. Y. Du, X. M. Li, P. Zhang, C. S. Li and B. G. Wang, *Mar. Drugs*, 2014, **12**, 2816–2826.
- F. Lacatena, R. Marra, A. Piccolo, C. Digilio Maria, M. Lorito, F. Vinale, P. Mazzei, P. Mazzei, A. Piccolo, M. Giorgini, L. Woo Sheridan, M. Lorito, F. Vinale, L. Woo Sheridan, P. Cavallo and P. Cavallo, *Molecules*, 2019, **24**, 750.
- M. Hashimoto, D. Wakana, M. Ueda, D. Kobayashi, Y. Goda and I. Fujii, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 1381–1384.
- R. S. Orfali, A. H. Aly, W. Ebrahim, Rudiysyah and P. Proksch, *Phytochem. Lett.*, 2015, **13**, 234–238.
- X. H. Li, X. H. Han, L. L. Qin, J. L. He, Z. X. Cao, D. L. Guo, Y. Deng and Y. C. Gu, *Nat. Prod. Res.*, 2019, **33**, 1870–1875.
- Y. Hsiao, M. J. Cheng, H. S. Chang, M. D. Wu, S. Y. Hsieh, T. W. Liu, C. H. Lin, G. F. Yuan and I. S. Chen, *Nat. Prod. Res.*, 2016, **30**, 251–258.
- M. J. Cheng, M. D. Wu, H. Y. Chan, Y. C. Cheng, J. J. Chen, I. S. Chen, Y. S. Su and G. F. Yuan, *Chem. Nat. Compd.*, 2017, **53**, 44–47.
- M. J. Cheng, M. D. Wu, Y. C. Cheng, J. J. Chen, H. Y. Chan, Y. L. Chen, I. S. Chen, P. H. Wu and G. F. Yuan, *Chem. Nat. Compd.*, 2016, **52**, 634–636.
- W. Guo, D. Li, J. Peng, T. Zhu, Q. Gu and D. Li, *J. Nat. Prod.*, 2015, **78**, 306–310.
- S. Boonyaketgason, K. Trisuwan, B. Bussaban, V. Rukachaisirikul and S. Phongpaichit, *Tetrahedron Lett.*, 2015, **56**, 5076–5078.
- S. P. Zhang, R. Huang, F. F. Li, H. X. Wei, X. W. Fang, X. S. Xie, D. G. Lin, S. H. Wu and J. He, *Fitoterapia*, 2016, **112**, 85–89.
- J. Kornsakulkarn, S. Saepua, R. Suvannakad, S. Supothina, N. Boonyuen, M. Isaka, S. Prabpai, P. Kongsaree and C. Thongpanchang, *Tetrahedron*, 2017, **73**, 3505–3512.
- Z. Fan, Z. H. Sun, H. X. Liu, Y. C. Chen, H. H. Li and W. M. Zhang, *J. Asian Nat. Prod. Res.*, 2016, **18**, 1024–1029.
- H. Abe, H. Tango, T. Kobayashi and H. Ito, *Tetrahedron Lett.*, 2017, **58**, 4296–4298.
- J. Arunpanichlert, V. Rukachaisirikul, S. Phongpaichit, O. Supaphon and J. Sakayaroj, *Nat. Prod. Res.*, 2016, **30**, 46–51.
- Y. S. Chen, M. J. Cheng, Y. Hsiao, H. Y. Chan, S. Y. Hsieh, C. W. Chang, T. W. Liu, H. S. Chang and I.-S. Chen, *Helv. Chim. Acta*, 2015, **98**, 1167–1176.
- J. Wang, G. Bai, Y. Liu, H. Wang, Y. Li, W. Yin, Y. Wang and F. Lu, *Chem. Lett.*, 2015, **44**, 1148–1149.



- 33 R. T. Hewage, T. Aree, C. Mahidol, S. Ruchirawat and P. Kittakoop, *Phytochemistry*, 2014, **108**, 87–94.
- 34 K. Wijesekera, C. Mahidol, S. Ruchirawat and P. Kittakoop, *Bioorg. Med. Chem.*, 2017, **25**, 2868–2877.
- 35 H. Yu, J. Sperlich, S. P. Hofert, C. Janiak, N. Teusch, F. Stuhldreier, S. Wesselborg, C. Wang, M. U. Kassack, H. Dai, Z. Liu and P. Proksch, *Fitoterapia*, 2019, **137**, 104249.
- 36 C. Huo, X. Lu, Z. Zheng, Y. Li, Y. Xu, H. Zheng and Y. Niu, *Phytochemistry*, 2019, **170**, 112224.
- 37 W. X. Wang, S. Kusari, H. Laatsch, C. Golz, P. Kusari, C. Strohmman, O. Kayser and M. Spiteller, *J. Nat. Prod.*, 2016, **79**, 704–710.
- 38 P. Hufendiek, S. S. M. Stoelben, S. Kehraus, N. Merten, H. Harms, M. Cruesemann, I. Arslan, M. Guetschow, T. Schneider and G. M. Koenig, *Planta Med.*, 2017, **83**, 1044–1052.
- 39 M. J. Cheng, M. D. Wu, H. Y. Chan, H. S. Chang, H. C. Wu, J. J. Chen, G. F. Yuan, J. R. Weng, C. T. Chang and H. C. Lin, *Chem. Nat. Compd.*, 2019, **55**, 79–81.
- 40 E. M. K. Wijeratne, P. Espinosa-Artiles, R. Gruener and A. A. L. Gunatilaka, *J. Nat. Prod.*, 2014, **77**, 1467–1472.
- 41 N. M. Tran-Cong, A. Mandi, T. Kurtan, W. E. G. Muller, R. Kalscheuer, W. Lin, Z. Liu and P. Proksch, *RSC Adv.*, 2019, **9**, 27279–27288.
- 42 H. C. Wu, M. J. Cheng, M. D. Wu, J. J. Chen, Y. L. Chen and H. S. Chang, *Phytochem. Lett.*, 2019, **31**, 242–248.
- 43 M. D. Wu, M. J. Cheng, Y. J. Yech, Y. L. Chen, K. P. Chen, P. H. Yang, I. S. Chen and G. F. Yuan, *Nat. Prod. Res.*, 2013, **27**, 1145–1152.
- 44 M. J. Cheng, M. D. Wu, H. Y. Chan, Y. C. Cheng, J. J. Chen, Y. L. Chen, I. S. Chen and G. F. Yuan, *Chem. Nat. Compd.*, 2015, **51**, 1091–1093.
- 45 M. J. Cheng, M. D. Wu, H. Y. Chan, J. J. Chen, Y. C. Cheng, Y. L. Chen, I. S. Chen and G. F. Yuan, *Chem. Nat. Compd.*, 2016, **52**, 231–233.
- 46 B. Balakrishnan, C. C. Chen, T. M. Pan and H. J. Kwon, *Tetrahedron Lett.*, 2014, **55**, 1640–1643.
- 47 Y. Hu, Y. Zhou, Z. Mao, H. Li, F. Chen and Y. Shao, *AMB Express*, 2017, **7**, 166.
- 48 B. Bijinu, J. W. Suh, S. H. Park and H. J. Kwon, *RSC Adv.*, 2014, **4**, 59405–59408.
- 49 A. A. Stierle, D. B. Stierle, T. Girtsman, T. C. Mou, C. Antczak and H. Djaballah, *J. Nat. Prod.*, 2015, **78**, 2917–2923.
- 50 E. Kuhnert, F. Surup, E. B. Sir, C. Lambert, K. D. Hyde, A. I. Hladki, A. I. Romero and M. Stadler, *Fungal Diversity*, 2015, **71**, 165–184.
- 51 F. Surup, A. Narmani, L. Wendt, S. Pfuete, R. Kretz, K. Becker, C. Menbrives, A. Giosa, M. Elliott, C. Petit, M. Rohde and M. Stadler, *Fungal Diversity*, 2018, **92**, 345–356.
- 52 Y. Nalli, D. N. Mirza, Z. A. Wani, B. Wadhwa, F. A. Mallik, C. Raina, A. Chaubey, S. Riyaz-Ul-Hassan and A. Ali, *RSC Adv.*, 2015, **5**, 95307–95312.
- 53 Z. E. Xiao, S. E. Lin, C. Tan, X. Huang, Z. She, Y. Lu and L. He, *Mar. Drugs*, 2015, **13**, 366–378.
- 54 P. Kalansuriya, Z. G. Khalil, A. A. Salim and R. J. Capon, *Tetrahedron Lett.*, 2019, **60**, 151157.
- 55 D. L. Zhao, C. L. Shao, Q. Zhang, K. L. Wang, F. F. Guan, T. Shi and C. Y. Wang, *J. Nat. Prod.*, 2015, **78**, 2310–2314.
- 56 E. B. Sir, E. Kuhnert, F. Surup, K. D. Hyde and M. Stadler, *Mycol. Prog.*, 2015, **14**, 28.
- 57 J. G. Luo, Y. M. Xu, D. C. Sandberg, A. E. Arnold and A. A. L. Gunatilaka, *J. Nat. Prod.*, 2017, **80**, 76–81.
- 58 Y. Shao, H. Yan, T. Yin, Z. Sun, H. Xie, L. Song, K. Sun and W. Li, *J. Antibiot.*, 2020, **73**, 77–81.
- 59 Y. Ma, H. Cai, M. Du, F. Cao and H. Zhu, *Gaodeng Xuexiao Huaxue Xuebao*, 2017, **38**, 1963–1967.
- 60 J. Ren, S. S. Ding, A. Zhu, F. Cao and H. J. Zhu, *Chem. J. Chin. Univ.*, 2017, **80**, 2199–2203.
- 61 F. Cao, Z. H. Meng, X. Mu, Y. F. Yue and H. J. Zhu, *J. Nat. Prod.*, 2019, **82**, 386–392.
- 62 C. Chen, J. Wang, H. Zhu, J. Wang, Y. Xue, G. Wei, Y. Guo, D. Tan, J. Zhang, C. Yin and Y. Zhang, *Chem. Biodiversity*, 2016, **13**, 422–426.
- 63 U. J. Youn, T. Sripisut, E. J. Park, T. P. Kondratyuk, N. Fatima, C. J. Simmons, M. M. Wall, D. Sun, J. M. Pezzuto and L. C. Chang, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 4719–4723.
- 64 W. Wang, Y. Liao, R. Chen, Y. Hou, W. Ke, B. Zhang, M. Gao, Z. Shao, J. Chen and F. Li, *Mar. Drugs*, 2018, **16**, 61.
- 65 Z. X. Zhang, X. Q. Yang, Q. Y. Zhou, B. Y. Wang, M. Hu, Y. B. Yang, H. Zhou and Z. T. Ding, *Molecules*, 2018, **23**, 1816.
- 66 Q. Y. Zhou, X. Q. Yang, Z. X. Zhang, B. Y. Wang, M. Hu, Y. B. Yang, H. Zhou and Z. T. Ding, *Fitoterapia*, 2018, **130**, 26–30.
- 67 Y. M. Wu, Q. Y. Zhou, X. Q. Yang, Y. J. Luo, J. J. Ojan, S. X. Liu, Y. B. Yang and Z. T. Ding, *J. Agric. Food Chem.*, 2019, **67**, 11877–11882.
- 68 S. M. Kim, S. Son, J. W. Kim, E. S. Jeon, S. K. Ko, I. J. Ryoo, K. S. Shin, H. Hirota, S. Takahashi, H. Osada, J. H. Jang and J. S. Ahn, *Nat. Prod. Sci.*, 2015, **21**, 231–236.
- 69 Q. Jia, Y. Du, C. Wang, Y. Wang, T. Zhu and W. Zhu, *Mar. Drugs*, 2019, **17**, 260.
- 70 C. Hemtasin, S. Kanokmedhakul, P. Moosophon, K. Soyong and K. Kanokmedhakul, *Phytochem. Lett.*, 2016, **16**, 56–60.
- 71 J. Li, X. Yang, Y. Lin, J. Yuan, Y. Lu, X. Zhu, J. Li, M. Li, Y. Lin, J. He and L. Liu, *Fitoterapia*, 2014, **97**, 241–246.
- 72 Q. Guo, L. Dong, X. Zang, Z. Gu, X. He, L. Yao, L. Cao, J. Qiu and X. Guan, *Nat. Prod. Res.*, 2015, **29**, 2000–2006.
- 73 B. B. Gu, Y. Wu, J. Tang, W. H. Jiao, L. Li, F. Sun, S. P. Wang, F. Yang and H. W. Lin, *Tetrahedron Lett.*, 2018, **59**, 3345–3348.
- 74 S. Son, S. K. Ko, J. W. Kim, J. K. Lee, M. Jang, I. J. Ryoo, G. J. Hwang, M. C. Kwon, K. S. Shin, Y. Futamura, Y. S. Hong, H. Oh, B. Y. Kim, M. Ueki, S. Takahashi, H. Osada, J. H. Jang and J. S. Ahn, *Phytochemistry*, 2016, **122**, 154–164.
- 75 S. L. Zhou, M. Wang, H. G. Zhao, Y. H. Huang, Y. Y. Lin, G. H. Tan and S. L. Chen, *Arch. Pharmacol. Res.*, 2016, **39**, 1621–1627.



- 76 C. Y. Wang, J. D. Hao, X. Y. Ning, J. S. Wu, D. L. Zhao, C. J. Kong, C. L. Shao and C. Y. Wang, *RSC Adv.*, 2018, **8**, 4348–4353.
- 77 Z. Liu, P. Qiu, H. Liu, J. Li, C. Shao, T. Yan, W. Cao and Z. She, *Bioorg. Chem.*, 2019, **88**, 102973.
- 78 N. Jansen, B. Ohlendorf, A. Erhard, T. Bruhn, G. Bringmann and J. F. Imhoff, *Mar. Drugs*, 2013, **11**, 800–816.
- 79 M. Frank, R. Hartmann, M. Plenker, A. Mandi, T. Kurtan, F. C. Ozkaya, W. E. G. Mueller, M. U. Kassack, A. Hamacher, W. Lin, Z. Liu and P. Proksch, *J. Nat. Prod.*, 2019, **82**, 2159–2166.
- 80 N. Panthama, S. Kanokmedhakul, K. Kanokmedhakul and K. Soyong, *Arch. Pharmacol. Res.*, 2015, **38**, 585–590.
- 81 F. Surup, K. I. Mohr, R. Jansen and M. Stadler, *Phytochemistry*, 2013, **95**, 252–258.
- 82 E. Kuhnert, F. Surup, S. Halecker and M. Stadler, *Phytochemistry*, 2017, **137**, 66–71.
- 83 M. Chen, Y. Y. Zheng, Z. Q. Chen, N. X. Shen, L. Shen, F. M. Zhang, X. J. Zhou and C. Y. Wang, *J. Nat. Prod.*, 2019, **82**, 368–374.
- 84 L. Wang, F. Li, C. Y. Yang, A. A. Khan, X. Liu and M. K. Wang, *Fitoterapia*, 2014, **99**, 92–98.
- 85 F. Cao, J. K. Yang, Y. F. Liu, H. J. Zhu and C. Y. Wang, *Nat. Prod. Res.*, 2016, **30**, 2448–2452.
- 86 L. H. Zhang, Y. Long, X. L. Lei, J. Y. Xu, Z. J. Huang, Z. G. She, Y. C. Lin, J. Li and L. Liu, *Phytochem. Lett.*, 2016, **18**, 180–186.
- 87 M. Venkatachalam, M. Zelena, F. Cacciola, L. Ceslova, E. Girard-Valenciennes, P. Clerc, P. Dugo, L. Mondello, M. Fouillaud, A. Rotondo, D. Giuffrida and L. Dufosse, *J. Food Compos. Anal.*, 2018, **67**, 38–45.
- 88 X. Li, Y. Tian, S. X. Yang, Y. M. Zhang and J. C. Qin, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 2945–2947.
- 89 D. R. McMullin, M. W. Sumarah, B. A. Blackwell and J. D. Miller, *Tetrahedron Lett.*, 2013, **54**, 568–572.
- 90 C. Sun, X. Ge, S. Mudassir, L. Zhou, G. Yu, Q. Che, G. Zhang, J. Peng, Q. Gu, T. Zhu and D. Li, *Mar. Drugs*, 2019, **17**, 253.
- 91 J. L. Tang, Z. Y. Zhou, T. Yang, C. Yao, L. W. Wu and G. Y. Li, *J. Agric. Food Chem.*, 2019, **67**, 2175–2182.
- 92 T. Isbrandt, G. Tolborg, A. Odum, M. Workman and T. O. Larsen, *Appl. Microbiol. Biotechnol.*, 2020, **104**, 615–622.
- 93 J. B. Pyser, S. A. Baker Dockrey, A. R. Benitez, L. A. Joyce, R. A. Wiscons, J. L. Smith and A. R. H. Narayan, *J. Am. Chem. Soc.*, 2019, **141**, 18551–18559.
- 94 H. Kang, C. Torruellas, Y. E. Lee and M. Kozlowski, *Org. Lett.*, 2018, **20**, 5554–5558.
- 95 M. Makrrougras, R. Coffinier, S. Oger, A. Chevalier, C. Sabot and X. Franck, *Org. Lett.*, 2017, **19**, 4146–4149.
- 96 H. B. Qiu, W. J. Qian, S. M. Yu and Z. J. Yao, *Tetrahedron*, 2015, **71**, 370–380.
- 97 W. Chen, F. Chen, Y. Feng and I. Molnar, *Nat. Prod. Rep.*, 2019, **36**, 561–572.
- 98 B. Balakrishnan, S. H. Park and H. J. Kwon, *Appl. Biol. Chem.*, 2017, **60**, 437–446.
- 99 T. Nakazawa, K. I. Ishiuchi, M. Sato, Y. Tsunematsu, S. Sugimoto, Y. Gotanda, H. Noguchi, K. Hotta and K. Watanabe, *J. Am. Chem. Soc.*, 2013, **135**, 13446–13455.
- 100 J. M. Winter, D. Cascio, D. Dietrich, M. Sato, K. Watanabe, M. R. Sawaya, J. C. Vederas and Y. Tang, *J. Am. Chem. Soc.*, 2015, **137**, 9885–9893.
- 101 J. M. Winter, M. Sato, S. Sugimoto, G. Chiou, N. K. Garg, Y. Tang and K. Watanabe, *J. Am. Chem. Soc.*, 2012, **134**, 17900–17903.
- 102 T. Asai, K. Tsukada, S. Ise, N. Shirata, M. Hashimoto, I. Fujii, K. Gomi, K. Nakagawara, E. N. Kodama and Y. Oshima, *Nat. Chem.*, 2015, **7**, 737–743.
- 103 M. J. Cheng, M. D. Wu, Y. L. Chen, I. S. Chen, Y. S. Su and G. F. Yuan, *Chem. Nat. Compd.*, 2013, **49**, 249–252.
- 104 Y. H. Zhang, X. Y. Peng, L. X. Feng, H. J. Zhu, F. Cao and C. Y. Wang, *Nat. Prod. Res.*, 2019, DOI: 10.1080/14786419.2019.1669028.
- 105 R. Paranjape Smita, P. Riley Andrew, D. Somoza Amber, C. E. Oakley, C. C. Wang Clay, E. Prisinzano Thomas, R. Oakley Berl, T. C. Gamblin, R. Paranjape Smita, P. Riley Andrew, D. Somoza Amber, C. E. Oakley, C. C. Wang Clay, E. Prisinzano Thomas, R. Oakley Berl and T. C. Gamblin, *ACS Chem. Neurosci.*, 2015, **6**, 751–760.

