RSC Advances



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REVIEW

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

Recent advances in the chemistry and biology of azaphilones

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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

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1. Introduction

Natural products have been evidenced as important sources of drug entities and 49% of small molecules functioning as antitumor 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, antioxidative, 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, deflectintypes, bulgarialactone-types, hydrogenated spiro-azaphilones, O-containing Monascus pigments, angular lactone-types, hydrogenated ones, chaetoviridins and chaephilones, pulvilloric acidtypes, sclerotiorins, cohaerins, and nitrogenated ones.³ They were majorly obtained from fungi examplified 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

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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 annulohypoxyloside (6),¹¹ and the novel pentaketide (7).¹⁸

The fungus *Penicillium* sp., collected in the sediment of the hyper saline lake Wadi El-Natrun in Egypt, produced two novel cytotoxic citrinin analogues, (3S,4R)-6-hydroxy-8-methoxy-3,5-dimethyl isochromanol (8) and (3S)-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 μ M, respectively.²⁰

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



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

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, monascuspilorin (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 glomerate* with antioxidative abilities, stereochemistry of which were deduced by $Rh_2(-OCOCF_3)_4$ -induced ECD experiments and calculations.⁶ Significantly, **22** (5 μ M) 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 *Penicilium 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 μ M).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 μ M, 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

Review

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

No.	Species	Activity
Annulohypoxylomans A–C (1–3)	Annulohypoxylon truncatum JS540 ¹¹	
Annulohypoxylomanols A–B (4–5)	Annulohypoxylon truncatum JS540 ¹¹	
Annulohypoxyloside (6)	Annulohypoxylon truncatum JS540 ¹¹	
7	Talaromyces stipitatus ATCC 10500 ¹⁸	
(3 <i>S</i> ,4 <i>R</i>)-6-Hydroxy-8-methoxy-3,5-dimethyl	Penicillium sp. ¹⁹	Cytotoxic (L5178Y: 26.20% at 10 μ g mL ⁻¹)
isochromanol (8)	ĩ	
(3 <i>S</i>)-6-Hydroxy-8-methoxy-3-methylisochroman	Penicillium sp. ¹⁹	Cytotoxic (L5178Y: 16.10% at 10 $\mu g \ m L^{-1})$
(S)-3.6-Dihydroxy-8-methoxy-3-	Aspergillus fumigatus ²⁰	Cytotoxic (MV4-11: 38.39 µM)
methylisochroman-4-one (10)	1.5p or general junit gundo	
(R)-3.6-Dihydroxy-8-methox-3-	Aspergillus fumigatus ²⁰	
methylisochroman-4-one (11)		
8-Methoxy-3-methylisochromane-3.6-diol (12)	Aspergillus fumigatus ²⁰	Cytotoxic (MV4-11: 30.00 µM)
3.8-Dimethoxy-3-methylisochroman-6-ol (13)	Aspergillus fumigatus ²⁰	
3.6.7.8-Tetramethoxy-3-methylisochromane (14)	Aspergillus fumigatus ²⁰	
Colletobredin A (15)	Colletotrichum aotearoa BCRC 09F0161 ²¹	Anti-inflammatory (inhibit NO production:
Soliciobrealit A (15)	Soution what ablanda BORO 0910101	182.2 μM)
Colletobredins B-D (16-18)	<i>Colletotrichum aotearoa</i> BCRC 09F0161 ²¹	
Monascuspilorin (19)	Monascus pilosus BCRC 38072 ²²	
Monascupurpurin (20)	Monascus purpureus BCRC 31499 ²³	
Peyronellone A (21)	Peyronellaea glomerate ⁶	Antioxidant (ABTS: 88.8 μM, DPPH: 126.3 μM)
Peyronellone B (22)	Peyronellaea glomerate ⁶	Antioxidant (ABTS: 95.2 µM, DPPH: 83.5 µM);
	<i>y b</i>	hypoxia-protective activity (improved the
		survival rate of H/R-treated human umbilical
		vein endothelial cells from 35% to 70% at 5 μ M)
Penicitol A (23)	Penicillium chrysogenum HND11-24 ²⁴	Cytotoxic (HeLa: 4.6 µM, BEL-7402: 10.5 µM,
		НЕК-293: 6.7 иМ. НСТ-116: 5.6 иМ. А549: 7.6
Citrifuran A (24)	Asperoillus sp. ⁷	Anti-inflammatory (inhibit NO production: 18.3
	noperginuo op.	uM)
Citrifuran B (25)	Asperoillus sp. ⁷	Anti-inflammatory (inhibit NO production: 22.6
Chinaran D (23)	nsporgenus sp.	uM)
Citrifuran C (26)	Aspergillus sp. ⁷	Anti-inflammatory (inhibit NO production: 25.3
	nspergittus sp.	uM)
Citrifuran D (27)	Aspergillus sp. ⁷	μινι)
Fusaraisochromenone (28)	Eusarium sp. $PDB51F5^{25}$	
Fusitable from (20)	Pequipria faling EN-125 ¹⁶	Prine shrimp toxic (61.4% at 100 µg mI $^{-1}$)
Yularinhilana (20)	Vularialas op. DSU ES162 ³⁰	Anti inflammatory (inhibit NO production, 17 5
xylaripinione (30)	Ayiariales sp. PSO-ES163,	Anti-initialization $(1111011 \text{ NO production}; 17.5)$
	Hypoxylon sp. BCRC 12F0687	μ M, Infibit IL-6 production: 5.3 μ M, Infibit
		(in hibit TND μ and μ at the production: 19.4 μ M); and tunior
	A	(infibit TNF- α production: 37.6 μ M)
Asperginusone C (31) $= (3)$	Aspergilius clavatus	Cytotoxic (MCF-7: 2.5 µM, A549: 41.9 µM)
/(S)-/-Hydroxy-3,/-dimethyl-isochromene-6,8-	Nigrospora sp. YE3033	
$\frac{dione(32)}{dione(32)}$	D I I I I I I I	
Chlamyphilone (33)	Pochonia chlamydosporia"	Insecticidal (Acyrthosiphon pisum: $LD_{50} = 1/5 \ \mu g$
Nomenceing A $C(24, 26)$	Nomenia en $BCC 20050^{27}$	mL , MIC = 150 μ g mL)
Nemanecins A-C (34-36)	Nemania sp. BCC 30850	
Perangustols A–B (37–38)	Claaosportum perangustum FS62	
Dotnideomynone C (40)	Dothlaeomycete sp. CRI7	Cytotoxic (A549: 46.5 μ g mL , HuCCA-1: 48.1 μ g
$\mathbf{D}_{\mathbf{x}}(1;1,\ldots,\mathbf{D},\mathbf{D},\mathbf{D},\mathbf{D},\mathbf{D},\mathbf{D},\mathbf{D},\mathbf{D}$	$\mathbf{D} = (1, 1, 1, \dots, 1, 1, \dots, 1, \dots, 1, \dots, \dots, 1, \dots, \dots, 1, \dots, \dots, 1, \dots, \dots, \dots, 1, \dots, \dots,$	mL , MOLI-3: 17.4 μ g mL)
Dotnideomynones B (39), D-F (41-43)	Dotniaeomycete sp. CRI/	Crtatania (DC2, 10,0,M), antilaichmenial
Mycoleptone A (44)	Mycolepiouiscus inalcus	Cytotoxic (PC3: 10.0 µM); antileisnmaniai
$\mathbf{P}(\mathbf{A}, \mathbf{P})$	16	(Leisnmania major: 28.5 μ M)
Mycoleptone B (45)	mycoleptoalscus inalcus-"	Cytotoxic (PO3: 7.1 μ M); antileisnmanial
	1 1 1 1 1 1 5	(Leishmania major: 21.7 µM)
Mycoleptone C (46)	Mycoleptodiscus indicus ²⁶	
Deflectin C1 (47)	Aspergillus deflectus NCC0415 ³⁰	Inhibit enzyme (SHP2: 29.3 µM, PTP1B: 40.4
	111 1 1 1 1 2 2 2 2 2 3 6	μ M)
Deflectin C2 (48)	Aspergillus deflectus NCC0415 ³⁰	Inhibit enzyme (SHP2: 21.1 µM, PTP1B: 19.8
	· · · · · · · · · · · · · · · · · · ·	μM)
Defiectin C3 (49)	Aspergillus deflectus NCC0415	Innibit enzyme (SHP2: 16.2 μ M, PTP1B: 16.5
		3.63

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No.	Species	Activity
Deflectin D1 (50)	Aspergillus deflectus NCC0415 ³⁶	Inhibit enzyme (SHP2: 19.2 μM, PTP1B: 19.2 μM)
Deflectin D2 (51)	Asperoillus deflectus NCC0415 ³⁶	Inhibit enzyme (SHP2: 7.0 µM PTP1B: 6.1 µM
Deflectin $E(52)$	Aspergillus deflectus NCC0415 ³⁶	Inhibit onzumo (SHD2: 16.0 µM, PTD1B: 24.0 µM
0.11 Didebudge ek erre sein en e. D. (52)	Aspergilius deficitus NCC0415	1111bit enzyme (5HP2: 16.0 μM, P1P1B: 24.0 μM
8,11-Didenydrochermesinone B (53)	Nigrospora sp. YE3033	
Colletotrichone A (54)	Colletotrichum sp. BS4 37	Antimicrobial (<i>Bacillus subtilis</i> : 0.1 μ g mL ⁻¹ , <i>Escherichia coli</i> : 1.0 μ g mL ⁻¹)
Colletotrichone B (55)	Colletotrichum sp. BS4 ³⁷	Antimicrobial (<i>Staphylococcus aureus</i> : 5.0 μ g mL ⁻¹)
Colletotrichone C (56)	Colletotrichum sp. BS4 ³⁷	Antimicrobial (<i>Escherichia coli</i> : 5.0 μ g mL ⁻¹)
Coniellin A (57)	Coniella fragariae9	Anti-tumor (MDA-MB-231: 21.5 μM, inhibit N κB activation: 4.4 μM)
Conjellin B (58)	Coniella fragariae ⁹	Anti-tumor (MDA-MB-231: 19.6 µM)
Conjellin C (59)	Coniella fragariae ⁹	Anti-tumor (MDA-MB-231: 21.0 μ M)
Conicllin D (60)	Coniclla fragarias ⁹	Anti tumor (MDA MD 231, 21.0 µM)
		KB activation: 37.8 µM)
Coniellin E (61)	Coniella fragariae ³	Anti-tumor (MDA-MB-231: 79.3 μM, inhibit NI κB activation: 29.4 μM)
Coniellin F (62)	Coniella fragariae ⁹	Anti-tumor (inhibit NF-κB activation: 70.7 μM
Coniellin G (63)	Coniella fragariae ⁹	Anti-tumor (MDA-MB-231: 21.6 μM, inhibit NI κB activation: 11.3 μM)
Conjellins H–I (64–65)	Coniella fragariae ³⁵	
E' (C' Dibudrowraatosollin (66))	Enicoccum nigrum strain 740 ³⁸	
5,6-Dillydroxyacetosenin (66)	Epicoccum nigrum Sciani 749	
Monakaocinol (67)	Monascus kaoliang	Anti inflammatory (inhibit NO production, 17
Monascuspironde A (68)	Monascus purpureus BCRC 38110	μM)
Monascuspirolide B (69)	Monascus purpureus BCRC 38110	Anti-inflammatory (inhibit NO production: 23 μM)
Thielavialides A–E (70–74)	<i>Thielavia</i> sp. PA0001 ⁴⁰	
5-O-Acetyl-epi-pestafolide A (75)	Trichocladium sp. ⁴¹	
5-epi-Pestafolide A (76)	<i>Trichocladium</i> sp. co-cultured with <i>Bacillus</i> subtilis ⁴¹	
Peniazaphilin A (77)	Penicillium sp. CPCC 400786 ¹³	Antiviral (HIV: 60.4 µM)
Monapilosusazaphilone (78)	Monascus nilosus ¹⁰³	
Monascusazaphilone A (79)	Monascus purpureus BCRC 38108 ⁴³	Anti-inflammatory (inhibit NO production: 4.6 μ g mL ⁻¹); cytotoxic (LPS-induced RAW264.7:
Monascusazaphilone B (80)	Monascus purpureus BCRC 38108 ⁴³	cell viability 85%) Anti-inflammatory (inhibit NO production: 8.8 μg mL ⁻¹); cytotoxic (LPS-induced RAW264.7:
\mathbf{D}	plannation and and an 49	cell vlability 83%)
Berkchaetoazaphilone C (81)	Pleurostomophora sp. 44	
Monascuskaodione (82)	Monascus kaoliang ⁴⁴	
Monascuspurone (83)	Monascus ruber ⁴⁵	
Monasfluol B (84)	<i>Monascus</i> spp. ⁴⁶	
Monascusazaphilone C (85)	Monascus purpureus BCRC 38108 ⁴³	Anti-inflammatory (inhibit NO production: 6.7 μ g mL ⁻¹); cytotoxic (LPS-induced RAW264.7:
	1 47	
Acetyi-monastiuoi B (86)	Monascus ruber	
MC-2, MC-4 (87–88)	Monascus purpureus (mppC mutant)**	
Berkchaetoazaphilone A (89)	Pleurostomophora sp. ⁴⁹	Anti-tumor (inhibit TNF- α production: 95% at 100 μ M, inhibit IL-1 β production: 95% at 100 μ M); anti-inflammatory (inhibit IL-6 production: 100% at 100 μ M, inhibit IL-33 production: 100% at 100 μ M); inhibit enzyme
Berkchaetoazaphilone B (90)	Pleurostomophora sp. ⁴⁹	(caspase 1: 150 μ M, MMP-3: 130 μ M) Cytotoxic (Y79: 1.1 μ M, MOLT-4: 10 μ M, RPMI-822 10 μ M, SR: 10 μ M, LOX IMVI: 10 μ M, CCRF-CEN 10 μ M); anti-tumor (inhibit TNF- α production: 95 at 100 μ M, inhibit IL-1 β production: 95% at 100 μ M); anti-inflammatory (inhibit IL-6 production: 100% at 100 μ M, inhibit IL-33 production: 100% 100 μ M); inhibit enzyme (caspase 1: 25 μ M, MMP 15 μ M)

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No.	Species	Activity
Lenormandin A (91)	Hypoxylon lenormandii ⁵⁰	Antimicrobial (<i>Rhodotorula glutinis</i> : 33.3 μ g mL ⁻¹ , <i>Bacillus subtilis</i> : 67.0 μ g mL ⁻¹ ,
Lenormandin B (92)	Hypoxylon lenormandii ⁵⁰	Staphylococcus aureus: 67.0 μ g mL ⁻¹) Cytotoxic (L929: 18.0 μ g mL ⁻¹); antimicrobial (<i>Mycobacterium</i> sp.: 67.0 μ g mL ⁻¹ , <i>Rhodotorula</i>
Lenormandin C (93)	Hypoxylon lenormandii ⁵⁰	<i>glutinis</i> 67.0 μ g mL ⁻¹) Cytotoxic (L929: 32.0 μ g mL ⁻¹); antimicrobial (<i>Phodotorula glutinic</i> : 67.0 μ g mL ⁻¹)
Lenormandin D (94)	Hypoxylon lenormandii ⁵⁰	Antimicrobial (<i>Bacillus subtilis</i> : 67.0 μ g mL ⁻¹ , <i>Staphylococcus aureus</i> : 67.0 μ g mL ⁻¹)
Lenormandin E (95)	Hypoxylon lenormandii ⁵⁰	Cytotoxic (L929: 22.0 μ g mL ⁻¹); antimicrobial (<i>Rhodotorula glutinis</i> : 67.0 μ g mL ⁻¹)
Peyronellone F (96)	Peyronellaea glomerate ⁶	
Lenormandin F (97)	Hypoxylon lenormandii ⁵⁰	Antimicrobial (<i>Rhodotorula glutinis</i> : 67.0 μg mL ⁻¹)
Lenormandin G (98)	Hypoxylon lenormandii ⁵⁰	Antimicrobial (<i>Rhodotorula glutinis</i> : 67.0 μ g mL ⁻¹)
Phialomustin A (99)	Phialophora mustea ⁵²	Cytotoxic (MIAPaCa2: 35 µM, A549: 98 µM, HCT 116: 8 µM, T47D: 10 µM)
Phialomustin C (100)	Phialophora mustea 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</i>
Phialomustin D (101)	Phialophora mustea ⁵²	flavus: 88.4 μM) Cytotoxic (MIAPaCa2: 60 μM, HCT-116: 30 μM, T47D: 9.2 μM); antimicrobial (<i>Candida albicans</i> :
Fragirubrins A-E (102-106)	Hypoxylon fragiforme ⁵¹	75.0 μω)
(+)-6"-Hydroxymitorubrinol acetate (107)	Hypoxylon rubiginosum ⁵⁶	Cytotoxic (L929: 21 μ g mL ⁻¹)
(+)-6"-Hydroxymitorubrinol (108)	Hypoxylon rubiginosum ⁵⁶	
6″-Hydroxy-(<i>R</i>)-mitorubrinic acid (109)	Aspergillus sp. 16-5C ⁵³	
Purpurquinone D (110)	Aspergillus sp. 16-5C ⁵³	
Гalarophilones А-В (111-112)	Talaromyces sp. CMB-W045 ⁵⁴	
Pinophilins D-F (113–115)	Penicillium pinophilum XS-20090E18 55	
Rutilins C–D (116–117)	Hypoxylon fragiforme ⁵¹	
Pinazaphilone A (118)	Penicillium sp. HN29-3B1 ¹²	
Montagnuphilone B (120)	Montagnulaceae sp. DM0194 ³⁷	Anti-inflammatory (inhibit NO production: 39.58 μM)
Montagnuphilones A (119), C–D (121–122), F–C (124–125)	G Montagnulaceae 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)	Penicillium variabile ⁵⁸	Anti-inflammatory (inhibit NO production: 4.35 μM)
Comazaphilone H (128)	Penicillium variabile ⁵⁸	Anti-inflammatory (inhibit NO production: 40.52 μM)
Pinazaphilone B (129)	Penicillium sp. HN29-3B1 ¹²	Inhibit enzyme (α-glucosidase: 28.0 μM)
Pinophilin G (130)	Penicillium pinophilum ⁵⁹	Antimicrobial (Vibrio parahemolyticus: 25.0 μM)
Talaraculone A (131)	Talaromyces aculeatus ⁶⁰	Inhibit enzyme (α-glucosidase: 78.6 μM)
Talaraculone B (132)	Talaromyces aculeatus ⁶⁰	Antimicrobial (<i>Vibrio anguillarum</i> : 0.26 μ g mL ⁻¹); inhibit enzyme (α -glucosidase: 22.9 μ M
Talaraculones C–F (133–136)	Talaromyces aculeatus ⁶⁰	
Pleosporalone E (137)	Pleosporales sp. CF09-1	Antimicrobial (<i>Vibrio alginolyticus</i> : $25 \ \mu g \ mL^{-1}$)
Pleosporalone F (138)	Pleosporales sp. CF09-1	Antimicrobial (<i>Vibrio alginolyticus</i> : 25 μ g mL ⁻¹)
Pleosporalone G (139)	Placeparales sp. CE09-1 ⁶¹	Antimicrobial (<i>Vibrio anguillarum</i> : 13 μ g mL ⁻¹ , <i>Vibrio parahemolyticus</i> : 6.3 μ g mL ⁻¹) Antimicrobial (<i>Vibrio anguillarum</i> : 6.2 μ g mL ⁻¹)
ricosporatone H (140)	Amountillus functions of the 27 104	Antimicrobial (<i>vibrio anguitarum</i> : 6.3 μ g mL ⁻¹ , <i>Vibrio parahemolyticus</i> : 25 μ g mL ⁻¹)
<i>epi</i> -Pinophilin B (141)	Aspergillus fumigatus 14–27 ¹⁰⁴	

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No.	Species	Activity
Chaetoviridin J (142)	Chaetomium globosum ⁶³	Anti-tumor (inhibit NF- κ B activation: 32.6% at 50 μ M); anti-inflammatory (inhibit NO production: 95.4% at 50 μ M)
Chaetoviridin K (143)	Chaetomium globosum ⁶³	Anti-tumor (inhibit NF- κ B activation: 33.4% at 50 μ M); anti-inflammatory (inhibit NO production: 39.4%, at 50 μ M)
Chaephilones A-B (144-145)	Chaetomium globosum ⁶²	
Chaephilone C (146)	Chaetomium sp. NA-S01-R1 ⁶⁴	Cytotoxic (A549: 15.7 μ M, HeLa: 7.7 μ M, Hep G2: 20.2 μ M); antimicrobial (<i>Vibrio vulnificus</i> : 32.2 μ g mL ⁻¹ , <i>Vibrio campbellii</i> : 30.1 μ g mL ⁻¹ , MRSA: 7.6 μ g mL ⁻¹)
Nigbeauvin A (147)	<i>Nigrospora oryzae</i> co-cultured with <i>Beauveria</i> bassiana ⁶⁵	Antimicrobial (<i>Bacillus bassiana</i> : 128 μ g mL ⁻¹ , <i>Nigrospora oryzae</i> : 512 μ g mL ⁻¹ , <i>Bacillus subtilis</i> : 128 μ g mL); anti-inflammatory (inhibit NO production: 37%, at 50 μ M)
Nigbeauvin B (148)	Nigrospora oryzae co-cultured with Beauveria bassiana ⁶⁵	Anti-inflammatory (inhibit NO production: 39%, at 50 μM)
Nigbeauvins C–E (149–151)	<i>Nigrospora oryzae</i> co-cultured with <i>Beauveria</i> bassiana 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 μ g mL ⁻¹ , <i>Nigrospora oryzae</i> : 512 μ g mL ⁻¹ , <i>Bacillus subtilis</i> : 512 μ g mL ⁻¹)
Isonigirpexin C (156)	<i>Nigrospora oryzae</i> cocultured with <i>Irpex lacteus</i> ⁶	7
Dechloroisochromophilone II (157)	Penicillium multicolor CM01 ⁷⁰	
epi-Isochromophilone III (158)	Penicillium multicolor CM01 ⁷⁰	Cytotoxic (NCI-H187: 6.2 μ g mL ⁻¹ , KB: 6.9 μ g mL ⁻¹ , MCF-7: 10.6 μ g mL ⁻¹)
159	Penicillium 303 ⁷¹	Cytotoxic (MDA-MB-435: 24.62 μ g mL ⁻¹ , HepG2: 17.92 μ g mL ⁻¹ , HCT-116: 11.09 μ g mL ⁻¹ , A549: 16.63 μ g mL ⁻¹)
Hypocrellone A (160)	<i>Hypocrella</i> sp. isolate WYTY-21 ⁷²	
Eupenicilazaphilone A (161)	Eupenicillium sp. $6A-9^{-73}$	Cytotoxic (MCF-7: 49.95 μ M)
Eupenicilazaphilone C (163)	Eupenicillium sp. $6A-9$	Cytotoxic (MCF-7: 36.88 µM, A549: 63.32 µM)
Geumsanols A–B (164–165), D–E (167–168)	Penicillium sp. KCB11A109 ⁷⁴	Cytotoxic (MCF 7: 50:00 µM, A545: 45:50 µM)
Geumsanol C (166)	Penicillium sp. KCB11A109 ⁷⁴	Cytotoxic (HL-60: 88.9 µM)
Penidioxolanes A-B (169-170)	Penicillium sp. KCB12C078 ⁶⁸	
Penicilazaphilone C (171)	Penicillium sclerotiorum 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 pneumonia</i> : 16.53 μg mL ⁻¹ , <i>Escherichia coli</i> : 16.53 μg mL ⁻¹)
Penicilazaphilones D-E (172–173)	Penicillium sclerotiorum ⁷⁶	
Sclerketide B (174)	Penicillium sclerotiorum CHNSCLM-0013 77	Anti-inflammatory (inhibit NO production: 3.4 μ M)
Helicusin E (175) Isochromophilone XI (176)	Bartalinia robillardoides strain LF550 ⁷⁸ Bartalinia robillardoides strain LF550 ⁷⁸	Antimicrobial (<i>Bacillus subtilis</i> : 55.6 μM, <i>Staphylococcus lentus</i> : 78.4 μM, <i>Trichophyton</i> <i>rubrum</i> : 41.5 μM); inhibit enzyme (PDE4: 8.30
	79	
Bromophilone R (177) Promophilone R (178)	Penicillium canescens ⁷⁹	UVIOTOXIC (L51/8Y: 13.9 μ M, A2780: 37 μ M)
Isochromophilonol (179)	Chaetomium cupreum RY202 ¹⁰⁵	Cytotoxic (LS1701: 0.5 μ M, A2780: 2.7 μ M) Cytotoxic (KB: 9.63 μ g mL ⁻¹ , NCI-H187: 27.18 μ g mL ⁻¹)
Ochrephilonol (180)	Chaetomium cupreum RY202 ¹⁰⁵	Cytotoxic (KB: 30.2 μ g mL ⁻¹)
Isochromophilone A (181)	Diaporthe sp. SCSIO 41011 ⁸	Cytotoxic (ACHN: 27 μM, 786-O: 34 μM, OS-RC-2: 45 μM)
Isochromophilones B–C (182–183)	Diaporthe sp. SCSIO 41011 ⁸	
Isochromophilone D (184)	Diaporthe sp. SCSIO 41011 ⁸	Cytotoxic (786-O: 38 µM, OS-RC-2: 44 µM)
Isochromophilone E (185)	Diaporthe sp. SCSIO 41011 °	Cytotoxic (ACHN: 14 μM, 786-O: 8.9 μM, OS-RC- 2: 13 μM)

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No.	Species	Activity
Isochromophilone F (186)	Diaporthe sp. SCSIO 41011 ⁸	Cytotoxic (ACHN: 13 µM, 786-O: 10 µM, OS-RC-2: 38 µM)
Sclerotiorins A–C (187–189)	Penicillium sclerotiorum OUCMDZ-3839 ⁶⁹	
Cohaerin G (190)	Annulohypoxylon cohaerens ⁸¹	Antimicrobial (<i>Nocardia</i> sp.: 33.3 μ g mL ⁻¹)
Cohaerin H (191)	Annulohypoxylon cohaerens ⁸¹	Cytotoxic (L929: 4.9 $\mu g m L^{-1}$)
Cohaerin I (192)	Annulohypoxylon cohaerens ⁸¹	Cytotoxic (L929: 0.4 μ g mL ⁻¹); antimicrobial (<i>Nocardia</i> sp.: 33.3 μ g mL ⁻¹)
Cohaerin K (193)	Annulohypoxylon cohaerens ⁸¹	Antimicrobial (<i>Nocardia</i> sp.: 16.6 μ g mL ⁻¹ , Stanhylococcus aureus: 16.6 μ g mL ⁻¹)
Minutellin A (194)	Annulohypoxylon minutellum 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)	Annulohynoxylon minutellum ⁸²	Antimicrobial (<i>Bacillus subtilis</i> : 66.7 μ g mL ⁻¹)
Minutellin C (196)	Annulohypoxylon minutellum ⁸²	Cytotoxic (L929: 10 μg mL ⁻¹ , KB3.1: 25 μg mL ⁻¹); antimicrobial (<i>Micrococcus luteus</i> : 66.7 μg mL ⁻¹ , <i>Bacillus subtilis</i> : 66.7 μg mL ⁻¹ , <i>Rhodoturula glutinis</i> : 33.3 μg mL ⁻¹ , <i>Mucor hiemalis</i> : 66.7 μg mL ⁻¹)
Minutellin D (197)	Annulohypoxylon minutellum ⁸²	Antimicrobial (<i>Micrococcus luteus</i> : 16.7 μg mL ⁻¹ , <i>Bacillus subtilis</i> : 33.3 μg mL ⁻¹ , <i>Staphylococcus</i> <i>aureus</i> : 33.3 μg mL ⁻¹)
Penicilone A (198)	Penicillium ianthinellum HK1-6 ⁵	······································
Penicilone B (199)	Penicillium janthinellum 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 faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μ g mL ⁻¹ , <i>Enteroccus faecalis</i>
Penicilone C (200)	Penicillium janthinellum HK1-6 5	$mL^{-1})^{83}$ Cytotoxic (SMMC-7721: 21 μ M); antimicrobial (<i>Staphylococcus aureus</i> : 6.25–12.5 μ g mL ⁻¹ ,
Penicilone D (201)	Penicillium janthinellum HK1-6 5	Enterococcus faecalis: 12.5 μ g mL ⁻¹ , Enterococcus faecium: 12.5 μ g mL ⁻¹) ⁸³ Cytotoxic (SMMC-7721: 27 μ M); antimicrobial
Denicilone G (202)	Danicillium ignthinglum HK1-6 83	(Staphyticolcus unreas: 5:15-12.5 μ g mL ⁻¹ , Enterococcus faecalis: 6:25 μ g mL ⁻¹ , Enterococcus faecium: 12.5 μ g mL ⁻¹) ⁸³ Cytotoxia (SMMC-7221: 21 μ M): antimicrobial
remembre (202)	renaturan janunnettam TIKI-0	(Staphylococcus aureus: 12.5–50 μ g mL ⁻¹ , Enterococcus faecalis: 25 μ g mL ⁻¹ , Enterococcus faecium: 25 μ g mL ⁻¹)
Penicilone H (203)	Penicillium janthinellum HK1-6 ⁸³	Cytotoxic (SMMC-7721: 24 μM); antimicrobial (<i>Staphylococcus aureus</i> : 3.13–12.5 μg mL ⁻¹ , <i>Enterococcus faecalis</i> : 3.13 μg mL ⁻¹ , <i>Enterococcus</i> <i>faecium</i> : 12.5 μg mL ⁻¹)
Meliasendanin A (204)	The fruits of <i>Melia toosendan</i> ⁸⁴	Antioxidant (ABTS: 62.8 μ M)
Pleosporalone A (205)	Pleosporales sp. CF09-1 ⁸⁵	Antimicrobial (<i>Botrytis cinereal</i> : 0.39 μM, <i>Rhizopus oryzae</i> : 0.78 μM, <i>Phytophthora capsici</i> : 0.78 μM)
Pleosporalone B (206)	Pleosporales 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)	Pleosporales sp. CF09-1 ⁶¹	Antimicrobial (<i>Alternaria brassicicola</i> : 6.3 μg mL ⁻¹ , <i>Botryosphaeria dothidea</i> : 3.1 μg mL ⁻¹ , <i>Fusarium oxysporum</i> : 25 μg mL ⁻¹)
Chaetomugilide A (208)	Chaetomium globosum DAOM 240359, ⁸⁹ Chaetomium globosum TY1 ⁸⁸	Cytotoxic (HePG2: 1.7 μM); ⁸⁸ antimicrobial (<i>Pseudomonas putida</i> : < 20 μM, <i>Bacillus subtilis</i> : <20 μM Saccharomyces cerevisiae: 20–200 μM) ⁸⁹
Chaetomugilide B (209) Chaetomugilide C (210)	Chaetomium globosum TY1 ⁸⁸ Chaetomium globosum DAOM 240359, ⁸⁹ Chaetomium globosum TY1 ⁸⁸	Cytotoxic (HePG2: 19.8 µM) Cytotoxic (HePG2: 53.4 µM) ⁸⁸
Isochromophilone XIII (211)	Chaetomium globosum DAOM 240359 ⁸⁹	Antimicrobial (<i>Pseudomonas putida</i> : 20–200 μM, <i>Bacillus subtilis</i> : 20–200 μM)

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Table 1 (Contd.)

No.	Species	Activity
Chaetoviridide A (212)	Chaetomium sp. NA-S01-R1 ⁶⁴	Cytotoxic (A549: 15.2 μ M, HeLa: 12.3 μ M, Hep G2: 3.9 μ M); antimicrobial (<i>Vibrio vulnificus</i> : 30.5 μ g mL ⁻¹ , <i>Vibrio rotiferianus</i> : 7.3 μ g mL ⁻¹ , <i>Vibrio</i>
Chaetoviridide B (213)	Chaetomium sp. NA-S01-R1 ⁶⁴	<i>campbellii</i> : 32.7 μ g mL ⁻¹ , MRSA: 15.5 μ g mL ⁻¹) Cytotoxic (A549: 16.3 μ M, HeLa: 5.6 μ M, Hep G2: 18.2 μ M); antimicrobial (<i>Vibrio vulnificus</i> : 7.4 μ g mL ⁻¹ , <i>Vibrio rotiferianus</i> : 31.3 μ g mL ⁻¹ , <i>Vibrio campbellii</i> : 32.3 μ g mL ⁻¹ MRSA: 7.3 μ g mL ⁻¹)
Chaetoviridide C (214)	Chaetomium sp. NA-S01-R1 ⁶⁴	Cytotoxic (A549: 23.1 μ M, HeLa: 17.7 μ M, Hep G2: 22.2 μ M); antimicrobial (<i>Vibrio vulnificus</i> : 15.7 μ g mL ⁻¹ , <i>Vibrio rotiferianus</i> : 15.3 μ g mL ⁻¹ , MRSA: 7.6 μ g mL ⁻¹)
<i>N</i> -Glutarylchaetoviridin A (215)	Chaetomium globosum HDN151398 ⁹⁰	Cytotoxic (HL-60: 10.3 μM, K562: 20.3 μM, BEL- 7402: 23.9 μM)
<i>N</i> -Glutarylchaetoviridin B (216)	Chaetomium globosum HDN151398 90	. ,
<i>N</i> -Glutarylchaetoviridin C (217)	Chaetomium globosum 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)
Peniazaphilones A-D (218-221)	<i>Penicillium</i> sp. ZJ-27 ⁸⁶	
Sclerotiorin D (222)	Penicillium sclerotiorum OUCMDZ-3839, ⁶⁹ Penicillium sclerotiorum CHNSCLM-0013 ⁷⁷	Anti-inflammatory (inhibit NO production: 2.7 μM) ⁷⁷
Isochromophilone X (223)	Bartalinia robillardoides strain LF550 ⁷⁸	Inhibit enzyme (PDE4: 11.7 μM)
Penazaphilone A (224)	Penicillium sclerotiorum cib-411 91	Anti-inflammatory (inhibit NO production: 15.29 μM)
Penazaphilones B-D, (225-227), G (230), I (232)	Penicillium sclerotiorum cib-411 91	. ,
Penazaphilone E (228)	Penicillium sclerotiorum cib-411 91	Anti-inflammatory (inhibit NO production: 9.34 μM)
Penazaphilone F (229)	Penicillium sclerotiorum cib-411 91	Anti-inflammatory (inhibit NO production: 9.50 μM)
Penazaphilone H (231)	Penicillium sclerotiorum cib-411 91	Anti-inflammatory (inhibit NO production: 7.05 μM)
Berkchaetorubramine (233)	Pleurostomophora sp. ⁴⁹	Inhibit enzyme (caspase 1: 50 μM, MMP-3: 45 μM)
(6-[(Z)-2-Carboxyvinyl]-N-GABA-PP-V) (234)	Talaromyces albobiverticillius 30548 87	F 7
Atrorosins A, C–I, K–N, O–R, T, V–W, Y (235–252)	Talaromyces atroroseus ²²	



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

note, **40** exhibited cytotoxicity against HuCCA-1, A549, and MOLT-3 with IC₅₀ values of 48.1, 46.5, and 17.4 $\mu g~mL^{-1}$, respectively.³³

Mycoleptodiscus indicus, an endophytic fungus of the officinal 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 IC₅₀ values of 10.0 and 7.1 μ M, 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 coniellins H–I (64–65).³⁵

Chromatographic separation of crude extracts from *Asper-gillus 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 μ 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 μ g mL⁻¹.³⁷

Furthermore, coniellins A–I (57–65) were obtained from the goose dung derived fungus *Coniella fragariae*.^{9,35} And coniellins 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 IC₅₀ value of 4.4 μ M and reduced the migration of tumor cells with 60% inhibition at 5 μ M and 98% inhibition at 10 μ M 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 *Epicoccum 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 IC₅₀ values of 17.5 and 23.5 μ M, respectively.⁴² Moreover, the fungus *Penicillium* sp. CPCC 400786 yielded peniazaphilin A (77) with anti-HIV activity (IC₅₀ = 60.4 μ M).¹³

2.6 O-Containing Monascus pigments

This category consisted of four azaphilones (78-81) were obtained from *Monascus* sp., characterized with a 1*H*-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 ($IC_{50} = 6.8 \ \mu g \ mL^{-1}$).⁴³ The culture broth of an acid mine extremophile strain *Pleurostomophora* sp. yielded two novel compounds, berkchaetoazaphilones 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 fragirubrins 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 IC₅₀ values of 14.3 and 73.6 μ M 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 ($IC_{50} = 21 \ \mu g \ mL^{-1}$), 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 μ M, 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 IC₅₀ values of 230.6, 235.8, and 165.4 μ M 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 IC₅₀ values of 4.35 and 40.52 μ M, 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 (IC₅₀ = 28.0 μ M) than that of acarbose (IC₅₀ = 446.7 μ 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 IC₅₀ values of 78.6 and 22.9 μM, respectively, compared to the positive control acarbose (IC₅₀ = 101.5 μM).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 μ 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



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 antibacterial 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 IC₅₀ value of 17.4 μ M.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 (IC₅₀ = 0.065 mM) and SGC7901 (IC₅₀ = 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, helicusin E (**175**) and iso-chromophilone XI (**176**).⁷⁸

Inducing the Mediterranian 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 IC₅₀ values of 8.9 and 2.7 μ M, 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 (IC₅₀ = 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



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

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 = $3.13-6.25 \ \mu g \ mL^{-1}$), 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 $\ \mu g \ mL^{-1.83}$

With significant antioxidant activity (IC₅₀ = 62.8 μ M), meliasendanin A (**204**) was obtained from the fruits of *Melia* toosendan.⁸⁴ The marine-derived fungus *Pleosporales* 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 IC₅₀ 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. 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 μ M) 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 μ 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 IC50 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 IC₅₀ value of 2.7 μ M 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 IC₅₀ values ranging from 7.05 to 15.29 μ M, without cytotoxicity towards RAW 264.7 cells (50.0 μ M).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*. Structually, 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 dihydropyrane 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 afford 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 NH₄OAc 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 Et₃N and then afforded **292**, which was directly treated by HF/ pyridine to give the (7*S*,4'*S*,5'*R*)-chaetoviridin A (**283a**) and (7*R*,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 SO₂Cl₂ in DCM. The reaction of *rac*-**297** with (*R*)-(+)-4-methoxyl- α -methylbenzylamine led to the



formation of two diastereomeric vinylogous γ -pyridones (4*R*)-**298** and (4*S*)-**298**. Parallelly, 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 (4R)-299 and (4S)-299 with K_2CO_3 in MeOH at room temperature, followed by intramolecular iodoetherification and *in situ* hydrolysis carried out four inseparable diastereomers, (4R)-300 and (4S)-300, in high yields. Each mixture underwent Dess-Martin oxidation and yielded two separable single diastereomeric ketones (4R,9S)-301/(4R,9R)-301 and (4S,9R)-301/(4S,9S)-301, respectively. The reduction of ketones furnished eight fully functionalized chromophores, (4R,8R,9S)-**302**/(4R,8S,9S)-**302**, (4R,8S,9R)-**302**/(4R,8R,9R)-**302**, (4S,8R,9R)-**302**/(4S,8S,9R)-**302**, (4S,8R,9S)-**302**/(4S,8S,9S)-**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*S*,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 azapholones 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 austial units.¹⁵ It was assumed that two austial 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 pTA-tspks2 (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 oxidization 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 3 Synthesis of chaetoglobin A.⁹⁴ Reagents and conditions: (a) $PdCl_2(PPh_3)_2$, Cul, Et_2NH , DMF, 65 °C, 18 h; (b) HOAc, O₂, ClPh, 0 °C, 48 h, 67% (BRSM); (c) CH_2Cl_2 , -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.



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.

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/MOMCI; (c) LDA/CO₂; (d) C_6F_5OH , EDC/DMAP; (e) *n*-BuLi; (f) K₂CO₃, EtOH; (g) DIBAL-H; (h) IBX/TFA/H₂O; (i) Et₃N, toluene, reflux; (j) HF/pyridine.



Scheme 5 Synthesis of chlorofusin and its chromophore diastereomers.⁹⁶ Reagents and conditions: (a) AgNO₃, TFA, ClCH₂CH₂Cl; (b) IBX, *n*-Bu₄NI; (c) butytryl 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, NDMBA, 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.

pathway included two main steps of ring opening and oxidation (Scheme 10).

4.6 Biosynthesis of acetosellin

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



Scheme 6 Biosynthesis of mycoleptone A.¹⁵

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

4.7 Biosynthesis of chaephilone C, chaetoviridides A and B

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).

4.8 Proposed biosynthesis of colletotrichones A–C, and chermesinonen B

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).

4.9 Postulated biosynthesis of coniellins A, H, and I

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



Scheme 7 Biosynthesis of monasfluols A and B, MC-2 and MC- $4.^{46,48,98}$





Scheme II Biosynthesis of acctose

Scheme 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.62

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 chaetoglobin A

Biosynthetic pathways of cochliodone A (**325**) and chaetoglobin 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*-acetyl-transferase, 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





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 coniellins A, H, and I.³⁵

 $HO_{HO} \xrightarrow{0} (O) \xrightarrow{1} (O) \xrightarrow{1} HO' \xrightarrow{1} O \xrightarrow{1} (O) \xrightarrow{1}$

Scheme 15 Proposed biogenesis of thielavialides A-E.40



Scheme 16 Proposed biosynthetic relationships among dothideomynones $\mathsf{D}\mathsf{-}\mathsf{F}^{\mathbf{34}}$

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 cazaldehyde 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 chaetoglobin A. 99



Scheme 18 Biosynthesis of 6"-hydroxy-(R)-mitorubrinic acid, purpurquinone D (–)-mitorubrinic 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,



 $\mbox{Scheme 19}$ Possible biosynthesis of cazisochromene, chaetoviridin A, and chaetomugilin $A.^{100}$



Scheme 20 Plausible biosynthesis of citrifurans A–D.⁷





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* oxidization 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).

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