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Review

Diversity of natural products of the genera *Curvularia* and *Bipolaris*

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ABSTRACT

Covering from 1963 to 2017.
This review provides a summary of some secondary metabolites isolated from the genera *Curvularia* and *Bipolaris* from 1963 to 2017. The study has a broad objective. First to afford an overview of the structural diversity of these genera, classifying them depending on their chemical classes, highlighting individual examples of chemical structures. Also some information regarding their biological activities are presented. Several of the compounds reported here were isolated exclusively from endophytic and pathogenic strains in culture, while few from other sources such as sea Anemone and fish. Some secondary metabolites of the genus *Curvularia* and *Bipolaris* revealed a fascinating biological activities included: anti-malarial, anti-biofouling, anti-larval, anti-inflammatory, anti-oxidant, anti-bacterial, anti-fungal, anti-cancer, leishmanicidal and phytotoxicity. Herein, we presented a bibliography of the researches accomplished on the natural products of *Curvularia* and *Bipolaris*, which could help in the future prospecting of novel or new analogues of active metabolites from these two genera.

1. Introduction

The genus *Curvularia* Boedijn (1933) is a hyphomycete fungus, it is cosmopolitan and ubiquitous. This genus is known to be comprised species associated with plant and human as pathogens (Hyde *et al.*, 2014). However, most *Curvularia* species occur as tropical and subtropical facultative plant pathogens and as endophytes from some Sudanese plants (Khiralla *et al.*, 2016, 2015). Several species previously included in *Pseudocochliobolus* are now regarded as *Curvularia* spp. Therefore, the genus name *Pseudocochliobolus* is no longer regarded as a distinct genus as the type is synonymized under *Curvularia* (Marin-Felix *et al.*, 2017). About 133 species epithets of *Curvularia* are listed in Index Fungorum

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(2015) and molecular data are available for only 59 species. Lack of the sporulation in older cultures and lack of the fresh collections are a bottleneck to understanding the genus (Manamgoda *et al.*, 2015).

The genus *Bipolaris* includes a number of significant plant pathogens with worldwide distribution. These species are commonly associated with leaf spots, leaf blights, melting outs, root rots, foot rots and other disease symptoms mainly in high value field crops in the family Poaceae, including rice, maize, wheat and sorghum and on various other host plants (Manamgoda *et al.*, 2014). In Rossman et al., (2015) stated that the generic name *Bipolaris* should be conserved over *Cochliobolus* (teleomorph of *Bipolaris*). Thus, herein SMs of *Cochliobolus* were presented as *Bipolaris* metabolites. This review was set out to summarize the isolated secondary metabolites (SMs) of the two genera *Curvularia* and *Bipolaris*, their chemical class and biological activities.

2. Molecular phylogene of the genera *Curvularia* and *Bipolaris*

Curvularia and *Bipolaris* are sister genera sharing some morphological similarities. When the generic descriptions of *Bipolaris* and *Curvularia* are compared, the two genera are morphologically very similar and cannot easily be distinguished by any distinct taxonomic criteria (Sivanesan, 1987). However, morphological characters of different isolates of the same species can be variable. Also morphological characters of distinct phylogenetic species are commonly overlapping. Although the key feature of the genus *Curvularia* is curved conidia, some species do not always produce the characteristic conidia. Some *Curvularia* species such as *C. cymbopogonis*, *C. oryzae-sativae*, *C. protuberata* and *C. ryleyi* usually have straight conidia (Manamgoda *et al.*, 2015).

3. Importance of *Curvularia* and *Bipolaris*

Some species of *Curvularia* and *Bipolaris* are economically important pathogens worldwide, conversely several species are found in association with various hosts as epiphytes or pathogens. The most serious epidemic caused by a *Bipolaris* was the famine of Bengal, in India (1943–1944), caused by *C. miyabeanus*. According to the data, the disease reduced rice yield in India by 40%–90% (Scheffer, 1997). *Bipolaris sativus* was confirmed to be the most economically important wheat foliar pathogen in all warm regions (Duveiller and Gilchrist, 1994). *Bipolaris heterostrophus* causes a serious disease worldwide in warm humid conditions (Carson, 1998). Besides, other organisms such as sponges, an unidentified *Bipolaris* sp. has been recorded inhabiting marine sponges although the ecological role of the fungus is poorly understood (Paz *et al.*, 2010).

Curvularia spp. have a wide host range, including humans and animals such as *C. lunata*, *C. geniculate*, *C. brachyspora*, *C. clavata*, *C. inaequalis*. Plants include: *C. oryzae*, *C. affinis*, *C.*

Table 1 – Some biological activities of the crude extracts of *Curvularia* and *Bipolaris* spp.

Sources	Fungi	Biological activities	References
Cymbopogon caesius	*Curvularia lunata*	Antibacterial: *Staphylococcus aureus* Antifungal: *Candida albicans*	(Avinash *et al.*, 2015)
Catharanthus roseus	*Curvularia* sp.	Antioxidant	(Khiralla *et al.*, 2015)
Phyllostachys edulis Moso bamboo (seeds)	*Curvularia* sp.	Antibacterial: *Bacillus subtilis*, *Listeria monocytogenes*, *Salmonella bacteria*. Antifungal: *Candida albicans*.	(Shen *et al.*, 2014)
Garcinia spp.	*Curvularia* sp.	Antibacterial: *Mycobacterium tuberculosis*	(Phongpaichit *et al.*, 2007)
Litchi chinensis	*Curvularia lunata*	Phytotoxicity	(Wells *et al.*, 1981)
Marine algea	*Curvularia tuberculata*	Antibacerial: *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*. Antioxidant	(Geetha *et al.*, 2011)
Laguncularia racemosa	*Curvularia pallescens*	Antibacterial: *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus luteus*, *Escherichia coli*.	(Silva *et al.*, 2011)
Ipomoea carnea	*Curvularia* spp.	Antibacterial: *Bacillus subtilis*, *Escherichia coli*	(Tayung *et al.*, 2012)
Piptadenia adiantoides	*Bipolaris* sp	Leishmanicidal.	(Campos *et al.*, 2008)
Cynodon dactylon, *Dactyloctenium aegyptium*	*Bipolaris geniculatus*, *B. spicifer*, *B. lunatus*, *B. hawaiiensis*	Antibacterial: *Enterococcus faecalis*, *Salmonella enterica*, *Staphylococcus aureus*. Antifungal: *Candida albicans*. Antioxidant	(Rekha and Shivanna, 2014)
Plumeria obtusifolia	*Bipolaris* sp.	Antibacterial: *Pseudomonas aeruginosa*.	(Ramesha and Srinivas, 2014)
Costus spiralis	*Bipolaris* spp.	Antibacterial: *Pseudomonas aeruginosa*, *Salmonella enterica* subsp. *enterica* serovar Typhi, *Bacillus subtilis*, and *Enterococcus faecalis*. Antifungal: *Candida albicans*, *C. parapsilosis*. Antioxidant	(Ascêncio *et al.*, 2014)

Table 2 – Some secondary metabolites isolated from *Curvularia* and *Bipolaris*, their classes and biological activities.

Chemical classes	Natural products	Biological activities	Fungi	Sources	References
Alkaloids	curvulamine	antimicrobial anti-inflammatory	*Curvularia* sp. IFBZ10	*Argyrosomus argentatus*	(Han *et al.*, 2014)
	curindolizine	anti-inflammatory	*Curvularia* sp. IFBZ10	*Argyrosomus argentatus*	(Han *et al.*, 2016)
	cytochalasin B		*Curvularia lunata*	*Litchi chinensis* Sonn	(Wells *et al.*, 1981)
	curvupallide A		*Curvularia pallescens*		(Abraham *et al.*, 1995 a, b)
	curvupallide B				
	curvupallide C				
	spirostaphylotrichin A				
	spirostaphylotrichin C				
	spirostaphylotrichin D				
	spirostaphylotrichin Q				
	spirostaphylotrichin R				
	spirostaphylotrichin U				
	spirostaphylotrichin V				
	bipolaramide		*Bipolaris sorokiniana*		(Sugawara *et al.*, 1985)
Peptides	victorin C	phytotoxicity	*Bipolaris victoriae*	*Avena sativa*	(Kastin 2006)
	HC-toxin		*Bipolaris arbonum*	*Zea mays*	(Walton, 2006)
Polyketides	apralactone A	cytotoxicity	*Curvularia* sp.	*Acanthophora spicifera*	(Greve *et al.*, 2008b)
	(+)-(15R)-10,11-E-dehydrocurvularin	cytotoxicity			
	(+)-(15R)-12-hydroxy-10,11-E-dehydrocurvularin				
	(+)-(11R,15R)-11-hydroxycurvularin	cytotoxicity			
	(+)-(15R)-12-oxocurvularin				
	curvulide A		*Curvularia* sp.	*Acanthophora spicifera*	(Greve *et al.*, 2008a)
	curvulide B1				
	curvulide B2				
	modiolide A				
	1,14-dihydroxy-6-methyl-6,7,8,9,10,10α,14,14α-octahydro-1H-benzo[f][1]oxacyclododecin-4(13H)-one.	antioxidant anticancer	*Curvularia trifolii*	*Usnea* sp.	(Samanthi *et al.*, 2015)
	5-methoxy-4,8,15-tri methyl-3,7-dioxo-1,3,7,8,9,10,11,12,13,14,15, 15α dodecahydrocyclododeca [de] isochromene -15-carboxylic acid	anti-inflammatory antioxidant			
	curvulinic acid		*Curvularia siddiqui*		(Kamal *et al.*, 1963)
	curvulol				
	methyl2-acetyl-3,5 dihydroxyphenylacetate		*Curvularia siddiqui* *Curvularia lunata*		(Varma *et al.*, 2006a)
	methyl2-acetyl-5-hydroxy-3-methoxyphenylacetate		*Curvularia lunata*		
	curvulin				
	11-α-methoxycurvularin	antibacterial antifungal antilarval	*Curvularia oryzae*	*Oryza sativa*	(Busi *et al.*, 2009)
	(S)-5-ethyl-8, 8-dimethylnonanal				
	bipolarinone		*Bipolaris* sp. PSU-ES64	seagrass	(Arunpanichlert *et al.*, 2012)
	bipolarilide				
	paecilin B				

(continued on next page)

Table 2 (*continued*)

Chemical classes	Natural products	Biological activities	Fungi	Sources	References
	(5S, 10aR)-gonytolide C				
	T-toxin		*Bipolaris heterostrophus*		(Baker *et al.*, 2006)
	cochliomycin A	antibacterial	*Bipolaris lunatus*	*Dichotella gemmacea*	(Liu *et al.*, 2014; Shao *et al.*, 2011)
	cochliomycinB				
	cochliomycinC				
	cochliomycin D	antifouling			
	cochliomycin E				
	cochliomycin F	antifouling			
	zeaenol				
	LL-Z1640-1	cytotoxicity antifouling			
	LL-Z1640-2	fungicide			
	paecilomycin F				
	(7′E)-6′-oxozeaenol	antifouling			
	aigialomycin B				
	deoxy-aigialomycin C	antifouling			
	cochliobolic acid		*Bipolaris lunatus*		(Robinson *et al.*, 1997)
	ethyl 2-[(3,5-dihydroxy)phenyl] acetate		*Bipolaris* sp. PSU-ES64	seagrass	(Arunpanichlert *et al.*, 2012)
	(2-carboxy-3-hydroxy-5-methoxyphenyl) acetic acid				
	4-epiradicinol	antibacterial			
	radicinol	phytotoxicity	*Bipolaris lunata*		(Nukina and Marumo, 1977a)
	epi-radicinol	phytotoxicity			
	radicinin	phytotoxicity	*Bipolaris* sp.	Grapevine	(Aldrich *et al.*, 2015)
	lunatoic acid A	antifungal	*Bipolaris lunata*		(Nukina and Marumo, 1977b; Marumo *et al.*, 1982)
	lunatoic acid B				
	α-acetylorcinol				
Quinones	cynodontin		*Curvularia lunata*		(van Eijk and Roeymans, 1977)
	lunatin		*Curvularia lunata*	*Niphates olemda*	(Jadulco *et al.*, 2002)
	cytoskyrin A				
	mitorubrinic acid A		*Bipolaris lunatus*		(Steglich *et al.*, 2000)
	mitorubrinic acid B				
	chrysophanol		*Bipolaris* sp. PSU-ES64	seagrass	(Arunpanichlert *et al.*, 2012)
	emodin				
Terpenes	abscisic acid		*Curvularia lunata*	*Niphates olemda*	(Jadulco *et al.*, 2002)
	zaragozic acid A		*Curvularia lunata*		(Bills *et al.*, 1994)
	3α-hydroxy-5β-*chol*- 11-en-24-oic acid		*Curvularia* sp.		(Munro and Musgrave, 1974)
	cochlioquinone A	leishmanicidal	*Bipolaris* sp.	*Piptadenia adiantoides*	(Campos *et al.*, 2008)
	isocochlioquinone A	leishmanicidal			
	cochlioquinone B		*Bipolaris miyabeanus*	Rice	(Carruthers *et al.*, 1971)
	isocochlioquinone C		*Bipolaris oryzae*	Rice leaves	(Phuwapraisirisan *et al.*, 2007)
	anhydrocochlioquinone A				
	ophiobolin A	cytotoxicity antimalarial	*Bipolaris heterostrophus* race O		(Li *et al.*, 1995; Shen *et al.*, 1999)
	3-anhydroophiobolin A		*Bipolaris oryzae*	Rice	(Phuwapraisirisan *et al.*, 2007)

6-*epi*-ophiobolin A				
6-*epi*-3-anhydroophiobolin A				
ophiobolin B				
6-*epi*-3-anhydroophiobolin B				
ophiobolin I				
3-anhydro-6-hydroxy-ophiobolin A	antiproliferative	*Bipolaris oryzae*	Phytopathogenic fungus	(Wang et al., 2013b)
cis-sativenediol		*Bipolaris setariae*		(Nukina et al., 1975)
isosativendiol				
IFO 6635 aversion factor	antifungal	*Bipolaris setariae*		(Nukina and Marumo, 1976)

brachyspora. Nevertheless, some species were reported from the soil such as *C. lunata*, *C. ovoidea*, *C. pallescens* (Manamgoda et al., 2011, 2015). In fresh water: *C. robusta*, *C. senegalensis*, *C. clavata*, *C. intermedia*, *C. prasadii* (Verma *et al.*, 2013), and in air such as *C. lunata*, *Curvularia* spp (De Aldana *et al.*, 2013; Hossain and Pasha, 2012; Rangaswamy *et al.*, 2013). There are several new host records for the species indicating the necessity for redefining the host range and geographic distribution of species of *Curvularia*. Madrid et al., (2014) reported *C. hominis* and *C. muehlenbeckiae*, as human pathogenic isolates, they were first recorded from herbaceous hosts. This situation has been observed with other *Curvularia* species such as *C. hawaiiensis*, *C. lunata*, and *C. spicifera*, which are found to be in association with both human and plants (Manamgoda *et al.*, 2015).

4. Biological activities of *Curvularia* and *Bipolaris* spp. crude extracts

Several crude extracts of the genera *Curvularia* and *Bipolaris* were investigated and revealed potent biological activities including antibacterial, antifungal, antioxidant, leishmanicidal, cytotoxicity and phytotoxicity (Table 1).

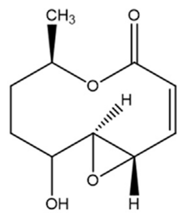
5. Secondary metabolites of the genera *Curvularia* and *Bipolaris*

Crude extracts of *Curvularia* and *Bipolaris* spp. are rich with diverse SMs showing interesting and promising activities, which could help to combat several chronic diseases. However, it could be exploited on the pharmaceutical and agricultural fields. These SMs belong to several chemical classes such as: alkaloids, anthraquinones, polyketides, quinones, terpenes and peptides. However, these SMs were obtained from *Curvularia* and *Bipolaris* spp. isolated from different sources such as seeds and plants (Table 2).

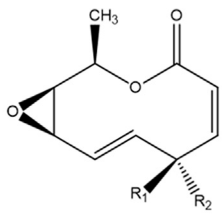
Polyketides

Polyketides are structurally a very diverse family of natural products with various biological activities and pharmacological properties (Katz, 1997). In this review we reported 46 and 35 polyketides isolated from the crude extracts of *Curvularia* and *Bipolaris* respectively. However, five compounds were produced by both *Curvularia* and *Bipolaris*. Some of them showed potent biological activities including: cytotoxcicity, phytotoxicity, antimicrobial, antioxidant and anti-larval activities.

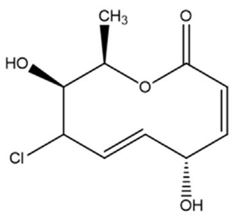
Investigation of the secondary metabolites of the marine-derived fungus *Curvularia* sp. (strain no. 768) which was isolated from the red alga *Acanthophora spicifera* collected at Fingers Reef, Apra Harbor, Guam., yielded four new 10-membered lactones Curvulides A, B1, B2 **1–3,** compound **4**, along with the known modiolide A **5**. The structures of **1–5** were characterized on the basis of spectroscopic and MS data and resemble known 10-membered lactones, but feature modified oxidation patterns around their macrocycles (Greve *et al.*, 2008a).



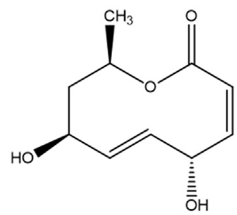
Curvulide A **1**



R^1 = OH, R^2 = H (4S, 7R, 8R, 9R), Curvulide B1 **2**
R^1 = H, R^2 =OH (4R, 7R, 8R, 9R), Curvulide B2 **3**

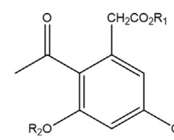


Compound **4**

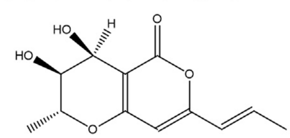


Modiolide A **5**

Phenylacetic acid derivatives **14**–**17**, methyl 2-acetyl-3,5-dihydroxyphenylacetate **14**, methyl 2-acetyl-5-hydroxy-3-methoxyphenylacetate **15**, curvulin or ethyl 2-acetyl-3,5-dihydroxyphenylacetate **16** and 4-epiradicinol **17** were produced by *Curvularia siddiqui*. Also 4-epiradicinol **17** have been isolated from the culture mycelia of *Curvularia lunata* grown on YMG, a medium consisting of yeast, malt extract and glucose. Compounds **14**–**16** lack antimicrobial and antioxidant activity, but 4-epiradicinol **17** inhibited the growth of *Escherichia coli*, *Staphylococcus aureus*, *Salmonella choleraesuis* and *Bacillus subtilis*. The structures of compounds **14**–**17** were determined by analyses of IR, MS, 1D and 2D NMR data, assisted by chemical shift comparison to related and model compounds (Varma *et al.*, 2006a). Also *Bipolaris* sp. PSU-ES64 associated with the seagrass produced two secondary metabolites, curvulin ethyl 2-[(3,5-dihydroxy)phenyl] acetate **16** and (2-carboxy-3-hydroxy-5-methoxyphenyl) acetic acid **18** (Arunpanichlert *et al.*, 2012).

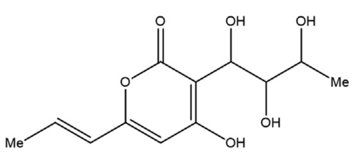


R_1= CH_3,R_2=R_3= H, Methyl 2-acetyl-3,5-dihydroxyphenylacetate **14**
R_1=R_2= CH_3, R_3= H, Methyl 2-acetyl-5-hydroxy-3-methoxyphenylacetate **15**
R_1=CH_2CH_3, R_2=R_3=H, Ethyl 2-acetyl-3,5-dihydroxyphenylacetate **16**

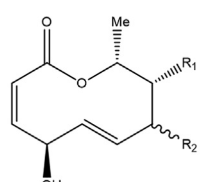


4-epiradicinol **17**

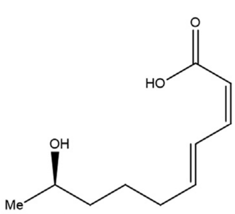
Investigation of secondary metabolites from the sea fan-derived fungus *Curvularia* sp. PSUF22 resulted in isolation of some metabolites, curvulapyrone **6**, curvulalide **7**, curvulalic acid **8**, modiolides A **5** and B **9**, pyrenolide A **10**, stagonolide E **11**, mycoepoxydiene **12**, and deacetylmycoepoxydiene **13**. Their antimicrobial activity against *Staphylococcus aureus* ATCC 25923, methicillin-resistant *S. aureus* and *Microsporum gypseum* SH-MU-4 were examined (Trisuwan *et al.*, 2011).



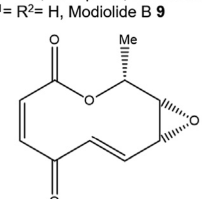
Curvulapyrone **6**



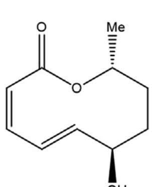
R^1= OH, R^2 = β OH, Curvulalide **7**
R^1= R^2= H, Modiolide B **9**



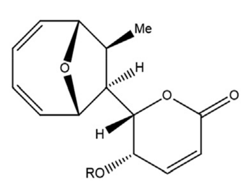
Curvulalic acid **8**



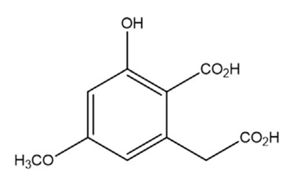
Pyrenolide A **10**



Stagonolide E **11**

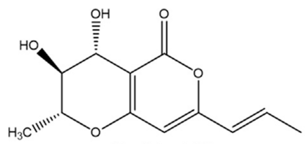


R= Ac, Mycoepoxydiene **12**
R= H, Deacetylmycoepoxydiene **13**

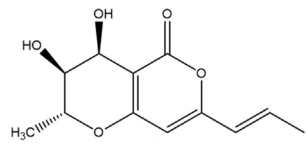


(2-carboxy-3-hydroxy-5-methoxy phennyl) acetic acid **18**

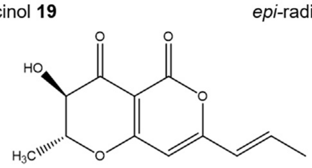
Radicinol or 3,4-dihydroxy-2-methyl-7-(1E)-1-propenyl-2H,5H-pyrano[4,3-b]-pyran-5-one **19** and *epi*-radicinol **20,** the diastereomer of radicinolarephytotoxins produced by *Bipolaris lunata* (Nukina and Marumo, 1977a). Besides, radicinin **21** produced by a strain of *Bipolaris* sp. isolated from grapevine by Aldrich *et al.* (2015) inhibits *Xylella fastidiosa in vitro*, suggesting a possible mechanism for tolerance of Pierce's Disease.



Radicinol **19**

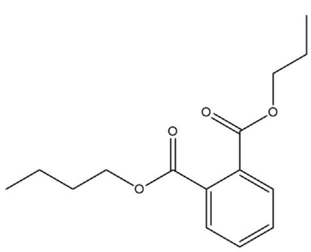


epi-radicinol **20**



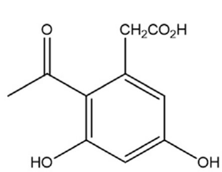
Radicinin **21**

Two main phytotoxic and antifungal phthalic acid butyl isobutyl ester **22** and radicinin **21** were isolated from the culture of *Curvularia* sp. FH01, a fungus residing in the *Atractomorpha sinensis* gut. The structures of isolated metabolites were established on the basis of spectral analysis. Metabolites **21** and **22** exhibited significant phytotoxic activity against the radical growth of *Echinochloa crusgalli* with their IC_{50} values of 61.9 and 5.9 μg/mL, respectively, which were comparable to that 2,4-dichlorophenoxyacetic acid (2.0 μg/mL) used as a positive control. The antifungal test results showed that compound **21** possessed strong antifungal activity against *Magnaporthe grisea* (IC_{50} = 16.3 μg/mL) and (IC_{50} = 18.2 μg/mL) (Zhang *et al.*, 2011).

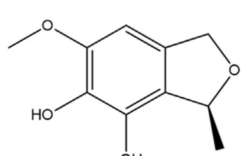


Phthalic acid butyl isobutyl ester **22**

Curvulinic acid or 2-acetyl-3,5-dihydroxyphenylacetic acid **23**, curvulol or 4- acetyl-5-b-hydroxyethyl resorcinol **24** and curvulin **16** were isolated from *Curvularia siddiqui* (Kamal *et al.*, 1963).

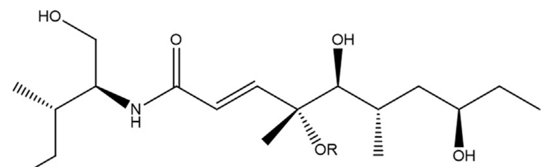


Curvulinic acid **23**

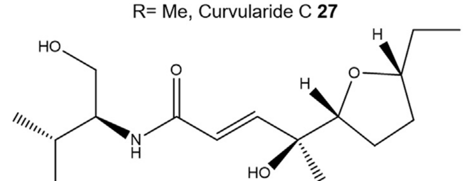


Curvulol **24**

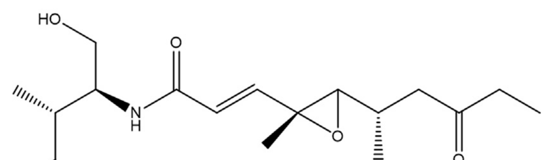
Five new hybrid peptide–polyketides, curvularides A–E (**25**–**29**), were isolated from the endophytic fungus *Curvularia geniculata*, which was obtained from the limbs of *Catunaregam tomentosa*. Structure elucidation for curvularides A–E (**25**–**29**) was accomplished by analysis of spectroscopic data, as well as by single-crystal X-ray crystallography. Curvularide B **26** exhibited antifungal activity against *Candida albicans*, and it also showed synergistic activity with a fluconazole drug (Chomcheon *et al.*, 2010).



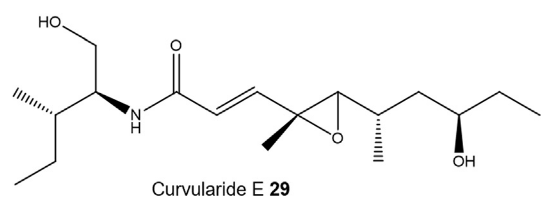
R= H, Curvularide A **25**
R= Me, Curvularide C **27**



Curvularide B **26**

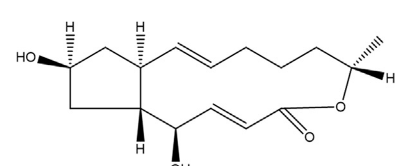


Curvularide D **28**

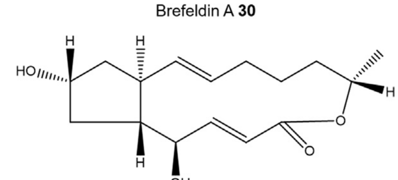


Curvularide E **29**

The macrolide antibiotic brefeldin A **30** and 7-*epi*-brefeldin A **31** have been isolated from cultures of *Curvularia lunata*. The structure of 7-*epi*-brefeldin A was determined by spectrometric and chemical means (Gorst-allman, 1982).

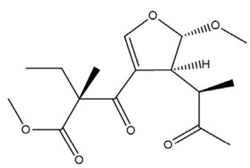


Brefeldin A **30**

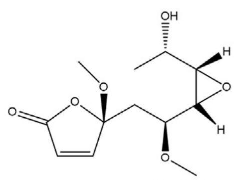


7-*epi*-brefeldin A **31**

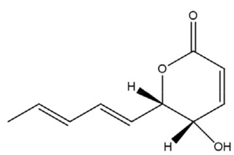
The endophytic fungus *Curvularia* sp., strain M12, was isolated from a leaf of the medicinal plant *Murraya koenigii* and cultured on rice medium followed by chemical screening of the culture extract. Chromatographic analysis led to the isolation of four new compounds, murranofuran A **32**, murranolide A **33**, murranopyrone **34**, and murranoic acid A **35**, along with six known metabolites, N-(2-hydroxy-6-methoxyphenyl)acetamide **36**, 8-hydroxy-6-methoxy-3-methylisocoumarin **37**, curvularin **38**, (S)-dehydrocurvularin **39**, pyrenolide A **10**, and modiolide A **5**. Compound **10** showed a strong motility impairing activity against *Phytophthora capsici* zoospores at a low concentration (100% at 0.5 μg/mL) in a short time (30 min). Compounds **22**, **34**, **38**, **39**, **5** and **40** exhibited zoospore motility impairment activity at higher concentrations (IC_{50}: 50–100 μg/mL) (Mondol et al., 2017).



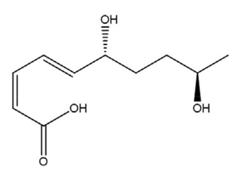
Murranofuran A **32**



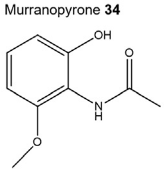
Murranolide A **33**



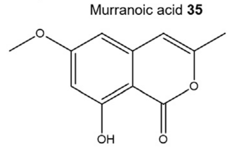
Murranopyrone **34**



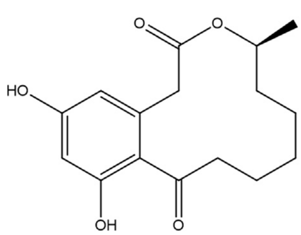
Murranoic acid **35**



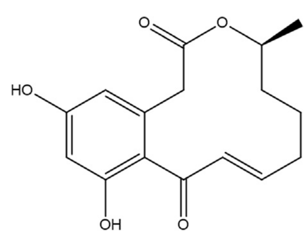
N-(2-hydroxy-6-methoxyphenyl)acetamide **36**



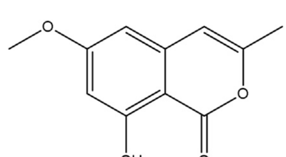
8-hydroxy-6-methoxy-3-methylisocoumarin **37**



Curvularin **38**

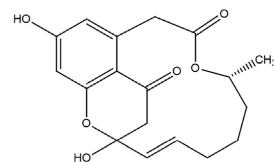


(S)-dehydrocurvularin **39**

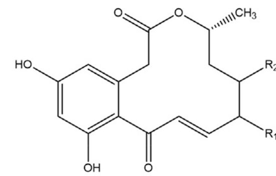


8-hydroxy-6-methoxy-3-methylisocoumarin **40**

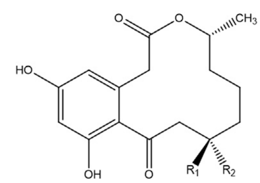
Chemical investigations of the cytotoxic extract of the marine-derived fungus *Curvularia* sp. (strain no. 768), isolated from the red alga *Acanthophora spicifera*, yielded the novel macrolide apralactone A **41**, as well as the antipodes of curvularin macrolides **42**–**47**. The structures of **41**–**47** were elucidated by interpretation of their spectroscopic data (1D and 2D NMR, CD, MS, UV and IR). Apralactone A **41** is a 14-membered phenyl acetic acid macrolactone, and the first such compound with a 4-chromanone substructure. Compounds **41**, **42**, **44**, **45** and **46** were found to be cytotoxic towards human tumor cell lines with mean IC_{50} values in the range of 1.25–30.06 μM (Greve et al., 2008b).



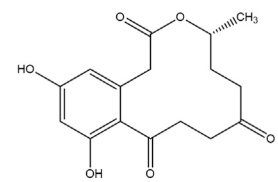
Apralactone A **41**



R_1=R_2=H, (+)-(15R)-10,11-*E*-dehydroocurvularin **42**
R_1=OH, R_2= H, (+)-(15R)-12-hydroxy-10,11-*E*-dehydrocurvularin **43**
R_1=H, R_2= OH, (+)-(15R)-13-hydoxy-10,11-*E*-dehydrocurvularin **44**

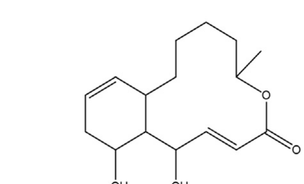


R_1=H, R_2=OH, (11S), (+)-(11S,15R)-11-hydroxycurvularin **45**
R1=OH, R2= H, (11R), (+)-(11R,15R)-11-hydroxycurvularin **46**

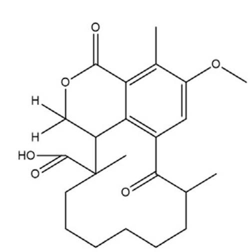


(+)-(15R)-12-oxocurvularin **47**

Two new polyketides 1,14-dihydroxy-6-methyl-6,7,8,9,10,10α,14,14α-octahydro-1H-benzo[f][1]oxacyclododecin-4(13H)-one **48** and 5-methoxy-4,8,15-tri methyl-3,7-dioxo-1,3,7,8,9,10,11,12,13,14,15,15α dodecahydrocyclododeca [de] isochromene -15-carboxylic acid **49** were isolated from the EtOAc extract of an endolichenic fungus, *Curvularia trifolii* obtained from *Usnea* sp. in Sri Lanka. Compounds **48** and **49** showed radical scavenging activity with IC_{50} values of 4.0 ± 2.6 and 1.3 ± 0.2 mg/mL, respectively. Moreover, compound **49** exhibited a significant anti-inflammatory activity comparable to the standard anti-inflammatory drug, aspirin. Compound **48** was evaluated for the inhibition of cell proliferation in a panel of five cancer cell lines NCI-H460, MCF-7, SF-268, PC-3M and MIA Pa Ca-2, and exhibited >90 % inhibitory activity at 5 μg/mL with all of the above cell lines (Samanthi et al., 2015).

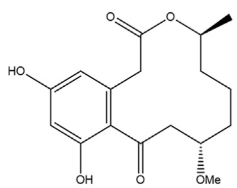


1,14-dihydroxy-6-methyl-6,7,8,9,10,10α,14,14α-octahydro-1H-benzo[f][1]oxacyclododecin-4(13H)-one **48**

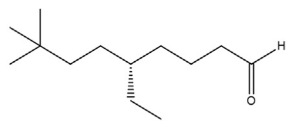


5-methoxy-4,8,15-tri methyl-3,7-dioxo-1,3,7,8,9,10,11,12,13,14,15,15α dodecahydrocyclododeca [de] isochromene -15-carboxylic acid **49**

Two pure compounds were purified from *Curvularia oryzae* MTCC 2605, 11-α-methoxycurvularin **50** and (S)-5-ethyl-8, 8-dimethylnonanal **51**. Compound **50** showed strong antibacterial activity against gram-positive bacteria *Staphylococcus aureus*, *Bacillus sphericus* and gram-negative bacteria *Pseudomonas aeruginosa*, *Pseudomonas oleovorans* with zone of inhibition between 12 and 16 mm. The MIC value of compound **51** was 100 μg/mL against *Staphylococcus aureus* and *Bacillus sphericus*. Moreover, compound **50** was tested for antifungal activity against eight fungi and showed moderate activity against *Aspergillus niger*, *Candida albicans* and *Saccharomyces cerevisiae*. Against *Spodoptera litura* larvae LD_{50} was determined to be 205.59 μg/mL while compound **51** didn't show any biological activity (Busi *et al*., 2009).

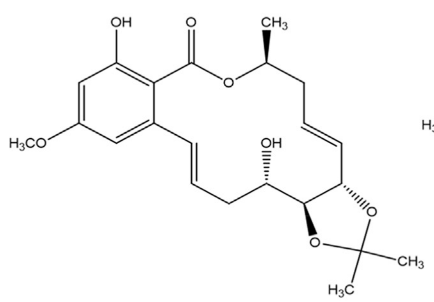


11-α-methoxycurvularin **50**

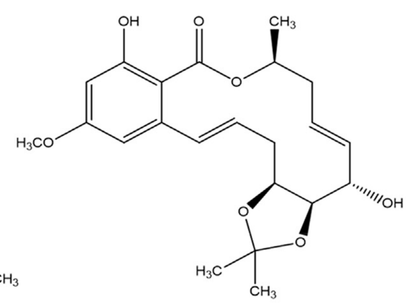


(*S*)-5-ethyl-8, 8-dimethylnonanal **51**

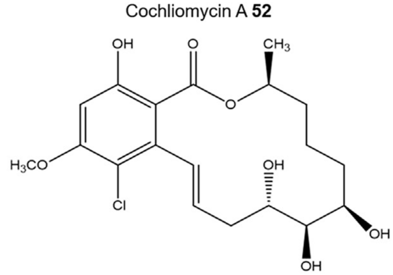
Three new 14-membered resorcylic acid lactones, two with a rare natural acetonide group and one with a 5-chloro-substituted lactone, named cochliomycins A-C **52**–**54**, together with four known analogues, zeaenol **55**, LL-Z1640-1 **56**, LL-Z1640-2 **57** and paecilomycin F **58** were isolated from the culture broth of *Bipolaris lunatus*, a fungus obtained from the gorgonian *Dichotella gemmacea* collected in the South China Sea. Compounds **52**, **55**, and **56** were evaluated against the larval settlement of barnacle *Balanus amphitrite*, and antifouling activity was detected. The antibacterial activities of compounds **52**, **55** and **58** were also determined against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Micrococcus tetragenus*. Only compound **52**, possessing the acetonide moiety, exhibited moderate antibacterial activity against *S. aureus*, with an inhibition zone of 11 mm in diameter at a concentration of 50 μg/mL. Moreover, compound **56** showed moderate cytotoxicity against A549 and HepG2 tumor cell lines with IC_{50} values of, 44.5 and 98.6 μM, respectively. However, the above antifouling compounds (**52**, **55** and **58**) were all found to be relatively non cytotoxic ($IC_{50} > 50$ μg/mL) against these two tumor cell lines (Shao *et al*., 2011).



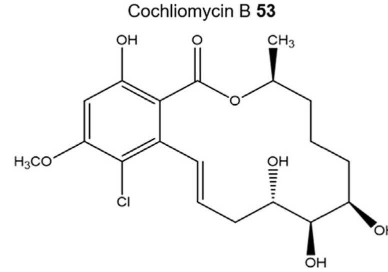
Cochliomycin A **52**



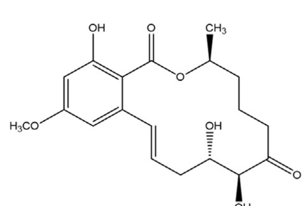
Cochliomycin B **53**



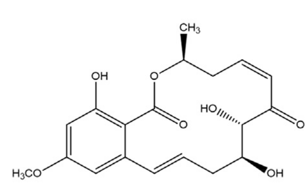
Cochliomycin C **54**



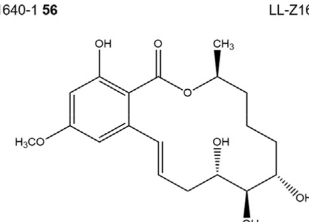
Zeaenol **55**



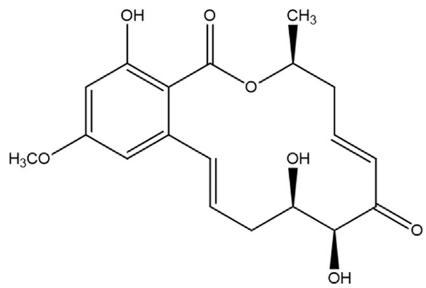
LL-Z1640-1 **56**



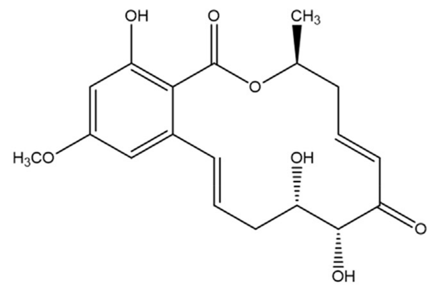
LL-Z1640-2 **57**



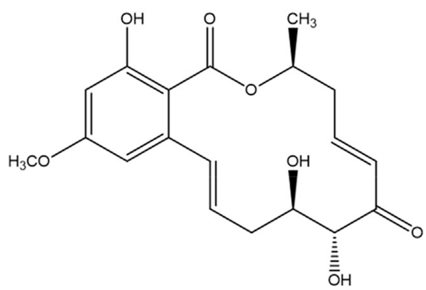
Paecilomycin F **58**



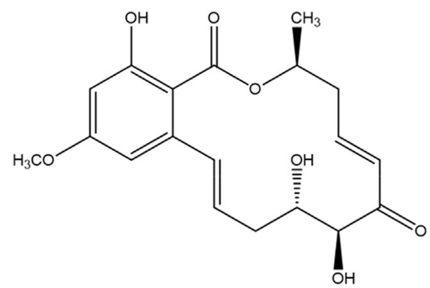
Cochliomycin D **59**



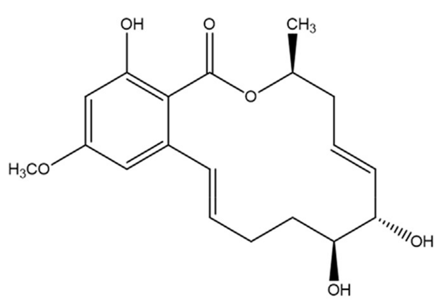
Cochliomycin E **60**



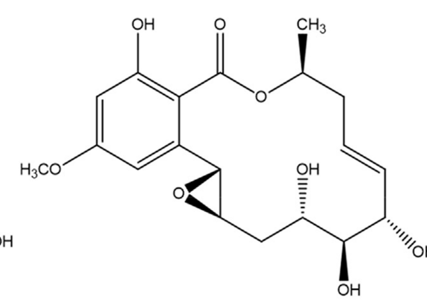
Cochliomycin F **61**



(7′E)-6′-Oxozeaenol **62**



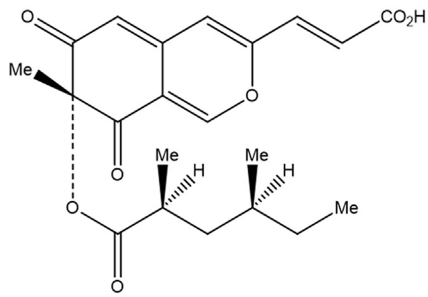
deoxy-aigialomycin C **63**



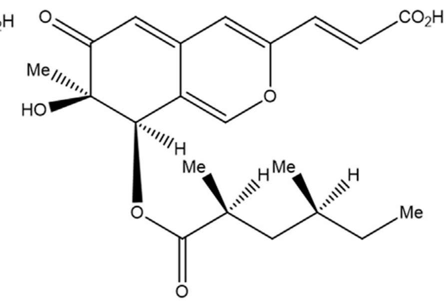
Aigialomycin B **64**

Three new 14-membered resorcylic acid lactones, cochliomycins D–F, **59**–**61**, and eight known analogues, (7′E)-6′-Oxozeaenol **62**, *deoxy*-aigialomycin C **63**, aigialomycin B **64,** cochliomycin A **52**, zeaenol **55**, LL-Z1640-1 **56**, LL-Z1640-2 **57** and paecilomycin F **58**, were isolated from the sea anemone-derived fungus *Bipoaris lunatus*. Compounds **59**–**62** are diastereomers differing from each other by the absolute configurations of the 4′,5′-diol chiral centers. In antifouling assays, **57**, **59**, **61**–**63**, exhibited potent antifouling activities against the larval settlement of the barnacle *Balanus amphitrite* at nontoxic concentrations, with EC_{50} values ranging from 1.82 to 22.5 μg/mL. Noticeably, fungicide whole-plant assays indicated that **57** showed excellent activity on the *Plasmopara viticola* preventative test at 6 ppm and concentration-dependent activity on the *Phytophthora infestans* preventative application at 200, 60, and 20 ppm (Liu *et al.*, 2014).

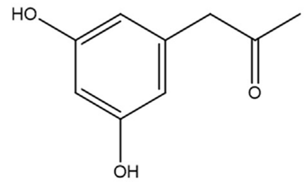
Aversion phenomenon is mutual inhibition of the mycelial growth by the growing colonies of different strains of the same fungal species, active principles causing this phenomenon, which called aversion factor by Nukina and Marumo, (1977a). They isolated an aversion factor produced by *Bipolaris lunata* lunatoic acid A **65** and also of its closely related new metabolite lunatoic acid B **66**. However, in 1977b Nukina and Marumo, they isolated new metabolite α-Acetylorcinol **67** from the fungus, *Bipolaris lunata*. Compound **65** was found to induce chlamydospore-like cells in two species of fungi, *C. lunatus* and *Curvularia trifolii* (Marumo *et al.*, 1982).



Lunatoic acid A **65**

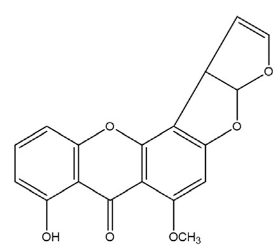


Lunatoic acid B **66**

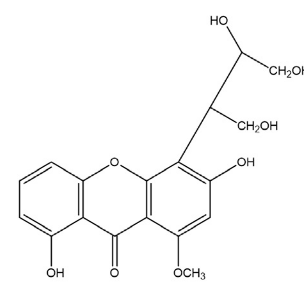


α-Acetylorcinol **67**

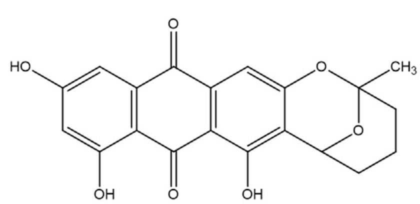
The metabolites averufin **68**, versiconol **69**, versiconal acetate **70**, versiconol acetate **71**, versicolorin C **72**, sterigmatocystin **73**, and 3,8-dihydroxy-4- (2,3-di hydroxy- 1 - hydroxymethylpropyl) -1 − methoxyxanthone **74** were isolated from cultures of *Bipolaris sorokiniana*. Evidence is presented for the reformulation of bipolarin as versiconol. The biosynthetic implications of the natural occurrence of versiconal acetate and of versiconol acetate are discussed. (Maes and Steyn, 1984).



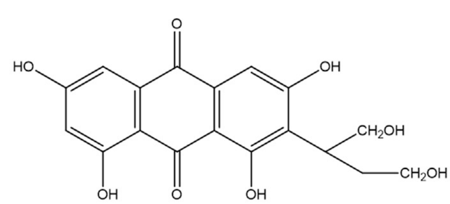
Sterigmatocystin **73**



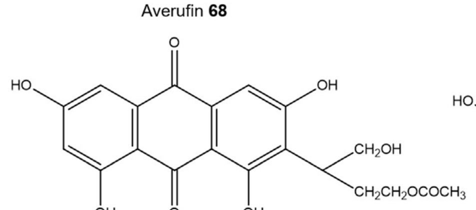
3,8-dihydroxy-4- (2,3-di hydroxy- 1 - hydroxymethylpropyl) -1 – methoxyxanthone **74**



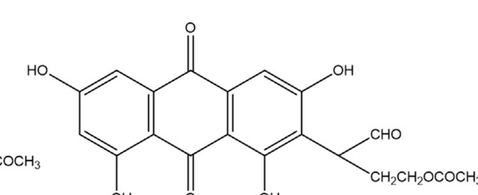
Averufin **68**



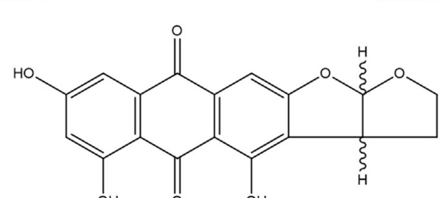
Versiconol **69**



Versiconal acetate **70**

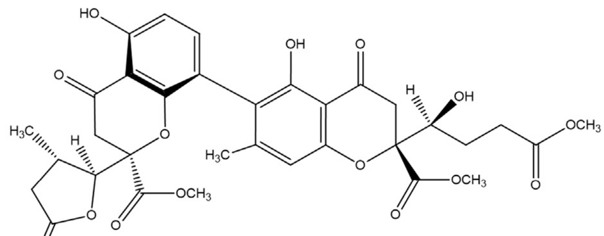


Versiconol acetate **71**

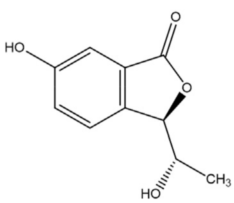


Versicolorin C **72**

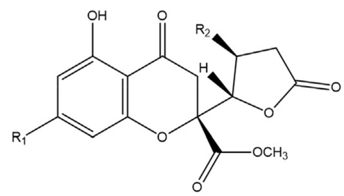
A dimeric chromanone, bipolarinone **75**, and a phthalide, bipolarilide **76**, paecilin B **77** and (5S, 10aR)-gonytolide C **78** have been isolated from the seagrass-derived fungus *Bipolaris* sp. PSU-ES64.



Bipolarinone **75**

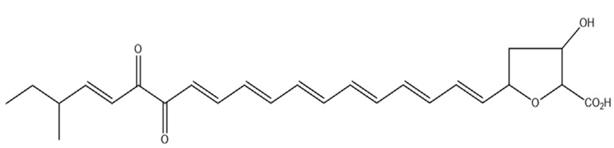


Bipolarilide **76**



R_1=H, R_2=CH_3, Paecilin B **77**
R_1=CH_3, R_2=H, (5S, 10aR)-gonytolide C **78**

Cochliobolic acid **79**, a biologically active natural product, is produced by submerged fermentation of *Bipolaria lunatus*. Compound **79** was determined to be a polyketide possessing a substituted tetrahydrofuran ring, a conjugated polyene chain and a 1,2-diketone moiety, by interpretation of NMR, MS, and UV/VIS spectroscopic data. Compound **79** inhibited the binding of TGF-R to the EGF receptor of the human epidermal cell line A431 in a SPA assay with an IC_{50} of 1.6 μM (Robinson *et al.*, 1997).



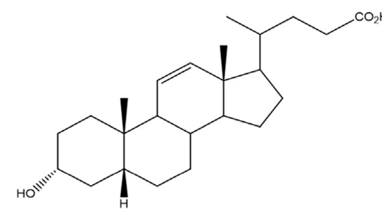
Cochliobolic acid **79**

Bipolaris heterostrophus, the filamentous ascomycete that causes southern corn leaf blight, exists in two forms: race T, which produces a family of linear, predominantly C41 (described variously as C35 to C47 or C35 to C49) polyketides called T-toxin **80** and **81**, and race O, which does not produce T-toxin. B. *heterostrophus* requires these toxin **80** and **81** for high virulence on T-cytoplasm maize (Baker *et al.*, 2006).

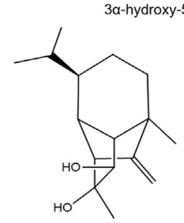
Terpenes

Terpenes are a large and diverse class of organic compounds, copious terpenoids from marine-derived fungi with unique structures showing astonishing biological activity (Elissawy *et al.*, 2015). Only five terpenes have been purified from *Curvularia*, whilst 33 terpenes were isolated from *Bipolaris* crude extracts. Some of them revealed antimalarial, cytotoxic and leishmanicidal activities.

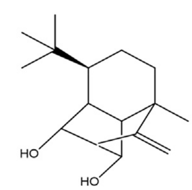
Munro and Musgrave (1974) isolated one triterpene compound from the culture filtrate of a *Curvularia* sp. 3α-hydroxy-5β-*chol*- 11-en-24-oic acid **82**. *cis*-sativenediol **83**, is a plant growth promotor, produced by the fungus *Bipolaris setariae*. However, isosativenediol **84** was originally assigned the structure of trans-sativenediol (Nukina *et al.*, 1975).



3α-hydroxy-5β-*chol*- 11-en-24-oic acid **82**



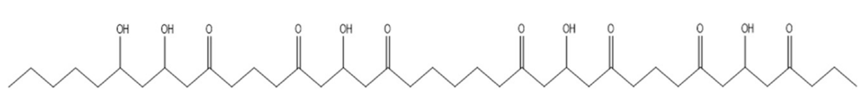
cis-sativenediol **83**



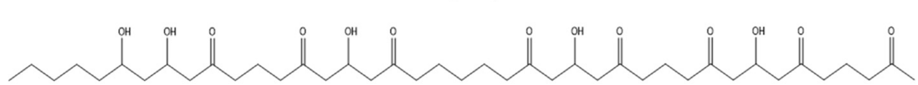
Isosativenediol **84**

Fungal cultures of *Curvularia lunata* were grown from a tissue sample of the marine sponge *Niphates olemda*, which was collected in Indonesia. The EtOAc extract from the culture broth and mycelia of the fungus afforded the known plant hormone (+)- abscisic acid **85** (Jadulco *et al.*, 2002). *C. lunata* was found to produce zaragozic acid A **86** (Bills *et al.*, 1994).

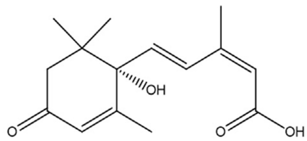
IFO 6635 aversion factor **87** produced by one strain of *Bipolaris setariae* and inhibiting the growth of other strains of the same organism (Nukina and Marumo, 1976).



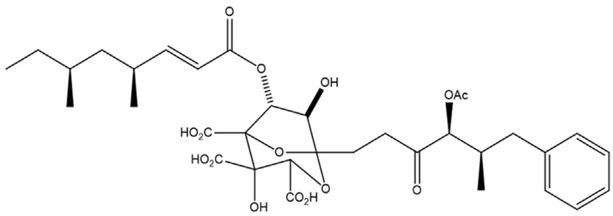
T-toxin (C39) **80**



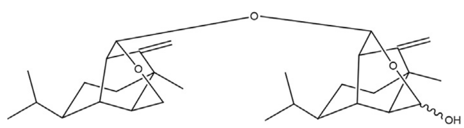
T-toxin (C41) **81**



(+)- abscisic acid **85**

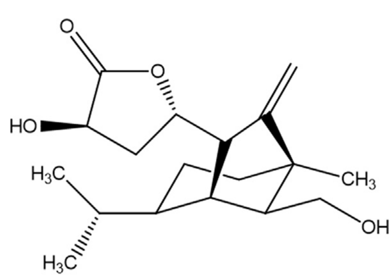


Zaragozic acid A **86**



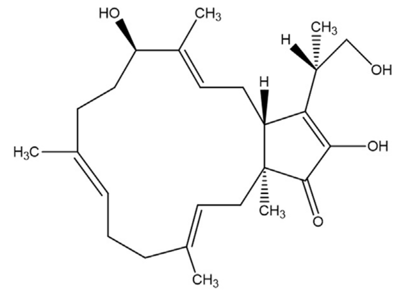
IFO 6635 aversion factor **87**

Structure of sorokinianin **88**, a phytotoxin from an isolate of *Bipolaris sorokiniana* was determined to be 3-hydroxy-5-(8′-hydroxymethyl-4′-isopropyl-1′- methy-7′-methylenebicyclo [3.2.1]oct6′-yl) tetrahydro-2-furanone predominantly on the basis of 2D NMR. One mM of sorokinianin inhibited germination of barley seeds (H. vtigme L.) completely and 300 μM of this compound reduced their germination ratio to 50%. ln the protoplast bioassay 300 μM of sorokinianin killed alI protoplasts obtained from the first leaves of barley and the-IC_{50} value of this compound in this bioassay was estimated to 150 μM (Nakajima *et al.*, 1994).



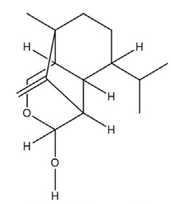
Sorokinianin **88**

Phytotoxic Sesterterpene, 11-epiterpestacin **89** produces by *Bipolaris sorokiniana* NSDR-011. The structure of 11-Epiterpestacin, was analyzed after chemical conversion by NMR spectroscopy (Nihashi *et al.*, 2002).



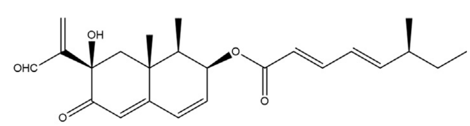
11-epiterpestacin **89**

Prehelminthosporol **90** is the most active and abundant phytotoxin formed by the plant parasitic fungus *Bipolaris sorokiniana*. The toxin is a hydrophobic sesquiterpene with restricted thermal stability and low water solubility (0.15 μg μl^{-1}). Prehelminthosporol was detected in conidia, hyphae and surrounding using "flash"-chromatography on silica gel and preparative HPLC.



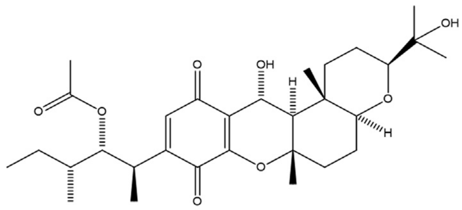
Prehelminthosporol **90**

Bipolal **91**, a new compound with marine antifouling potential, was isolated from the culture broth of *Bipolaris* sp. The structure was determined to be an eremophilane derivative on the basis of 2D NMR spectroscopy and chemical transformations (Watanabe *et al.*, 1995).

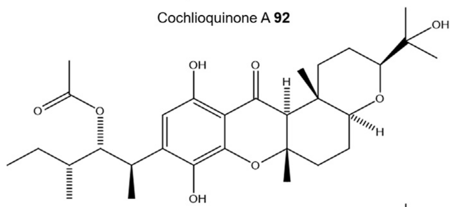


Bipolal **91**

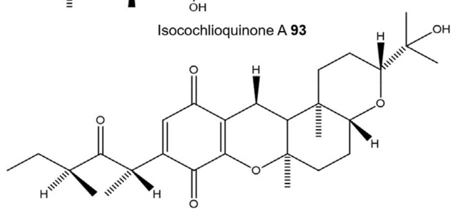
Two compounds cochlioquinone A **92** and isocochlioquinone A **93** were isolated from the crude extract *Biopolaris* sp. (UFMGCB-555), an endophytic fungus of *Piptadenia adiantoides*. Both compounds were active in the assay with *Leishmania amazonensis*, disclosing EC_{50} values (effective concentrations required to kill 50% of the parasite) of 1.7 μM (95% confidence interval = 1.6–1.9 μM) and 4.1 μM (95 confidence interval = 3.6–4.7 μM), respectively (Campos *et al.*, 2008). However, cochlioquinone A **92** has been isolated in 1971 by Carruthers *et al.* besides the pure compound cochlioquinone B **94** from n-hexane crude extract of mycelium and medium of *Bipolaris miyabeanus*, a parasitic mould of Rice.



Cochlioquinone A **92**

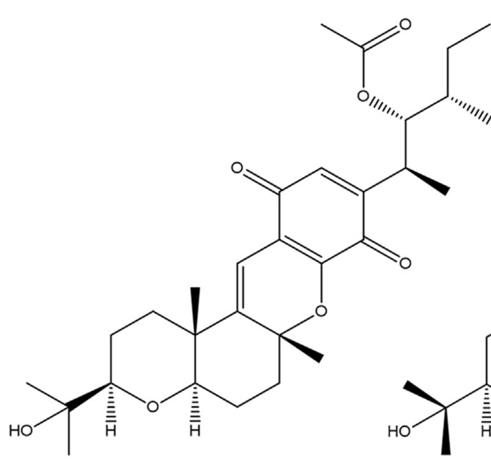


Isocochlioquinone A **93**

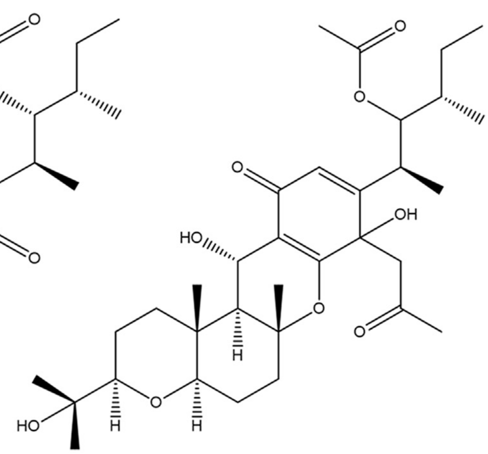


Cochlioquinone B **94**

In the search for antitumor compounds from *Bipolaris oryzae*, the coexistence of ophiobolins and cochlioquinones is reported for the first time. Of the compounds isolated, anhydrocochlioquinone A **95** was identified as a new antitumor agent. The structure of **95** was fully characterized by spectroscopic data, including COSY, HSQC, HMBC, and NOESY. The cytotoxicity of isolated compounds against HeLa and KB cells is also described (Phuwapraisirisan *et al.*, 2007). Cochlioquinone A1 **96** was isolated from the culture extract of *Bipolaris zeicola* as a potent anti-angiogenic agent. Compound **96** inhibited *in vitro* angiogenesis of bovine aortic endothelial cells (BAECs) such as bFGF-induced tube formation and invasion at the concentration (1 mg/mL) without cytotoxicity (Jung *et al.*, 2003).

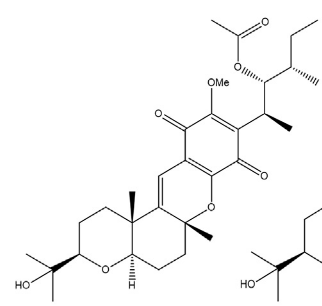


Anhydrocochlioquinone A **95**

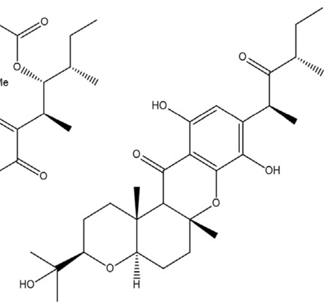


Cochlioquinone A1 **96**

Some cochlioquinones derivative, cochlioquinone F **97**, isocochlioquinone C **98**, isocochlioquinone A **92** and anhydrocochlioquinone A **95**, were isolated from the PDB (potato dextrose broth) culture of the phytopathogenic fungus *Bipolaris luttrellii*. The structure of **97** was elucidated on the basis of NMR techniques. Compound **95** exhibited the strongest activity in inducing apoptosis on HCT116 cells within the range of 10–30 mm. In addition, the caspase activation, the release of cytochrome c from mitochondria, and the downregulation of Bcl-2 protein in HCT116 cells treated with compound **90** were detected (Qi *et al.*, 2014).

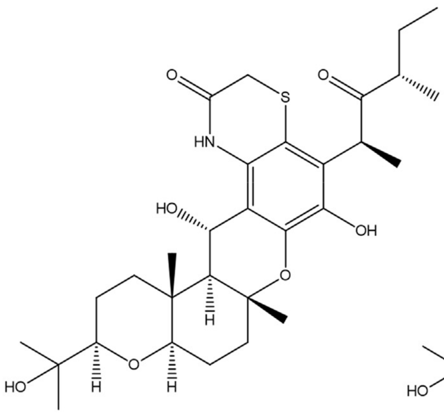


Cochlioquinone F **92**

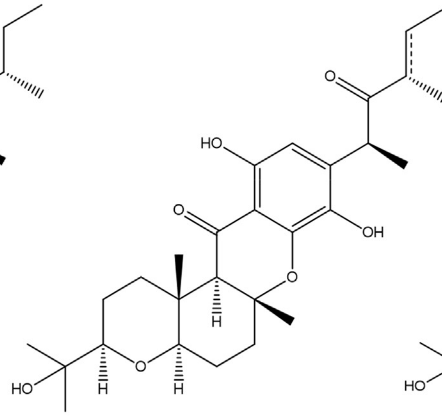


Isocochlioquinone C **93**

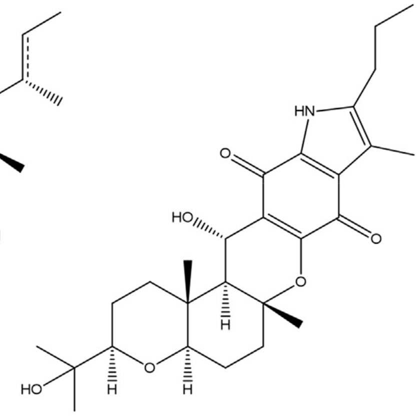
Chemical investigation of the liquid culture of the endophytic fungus *Bipolaris sorokiniana* A606, which was isolated from the medicinal plant *Pogostemon cablin* resulted in the isolation of four new cytotoxic compounds, named isocochlioquinones D–E (**99**–**100**) and cochlioquinones G–H (**101**–**102**), along with five cochlioquinone analogues cochlioquinone C **103**, cochlioquinone D **104**, cochlioquinone E **105**, cochlioquinone B **94** and isocochlioquinone C **98**. Their structures were determined on the basis of extensive spectroscopic analysis. Isocochlioquinone D **97** possessed a rare benzothiazin-3-one moiety and cochlioquinone G **99** was the first example of cochlioquinones bearing an indole-4,7-dione fragment. All of the isolates (**94**, **97**–**104**) were evaluated for their cytotoxic activities against MCF-7, NCI-H460, SF-268 and HepG-2 tumor cell lines by the sulforhodamine B (SRB) assay. Compounds **94**, **100** and **102**–**104**, featuring a cochlioquinone core, exhibited potent cytotoxicities *in vitro* against the four tumor cell lines, and a preliminary structure–activity relationship of these compounds was also discussed (Wang *et al.*, 2016).



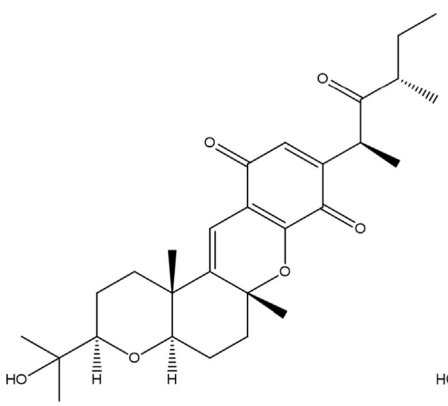
Isocochlioquinone D **94**



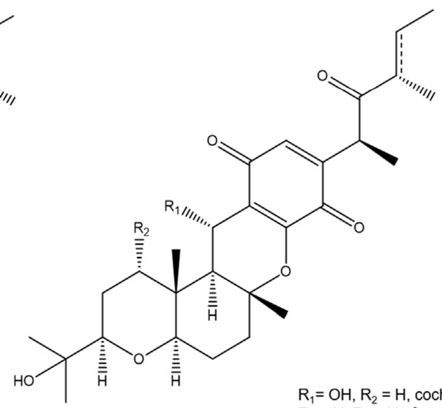
Isocochlioquinone E Δ^2 **95**



Cochlioquinone G **96**

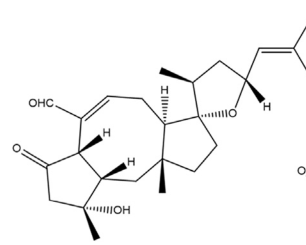


Cochlioquinone H **97**

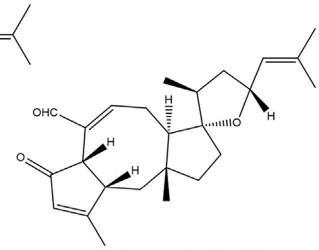


R_1= OH, R_2 = H, cochlioquinone C **98**
R_1 = H, R_2 = H Δ^2, cochlioquinone D **99**
R_1= H, R_2 = OH, cochlioquinone E **100**

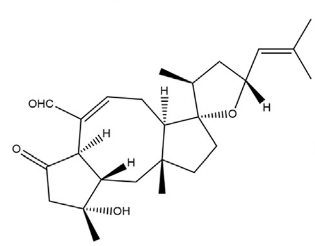
Ophiobolins are secondary metabolites of certain fungi belonging to the genera *Bipolaris*, *Drechslera*, *Acremonium* and *Aspergillus* (Au *et al.*, 2000; Li *et al.*, 1995; Shen *et al.*, 1999). These sesterterpene-type compounds (C25) are characterized by a unique tricyclic or tetracyclic sesterterpenoid structure (Hanson, 1986; Krizsán *et al.*, 2010). Several ophiobolins have revealed biological activities, such as antimicrobial (Nakamura and Ishibashi, 1958), phytotoxic (Sugawara *et al.*, 1987), antiviral (Jayasuriya *et al.*, 2004; Singh *et al.*, 2003), cytotoxic (Shen *et al.*, 1999; Wei *et al.*, 2004), and nematocidal activities (Tsipouras *et al.*, 1996). *Bipolaris heterostrophus* race O. was found to produce seven ophiobolins (**106**–**112**) ophiobolin A **106,** 3-anhydroophiobolin A **107,** 6-*epi*-ophiobolin A **108,** 6-*epi*-3-anhydroophiobolin A **109,** ophiobolin B **110,** 6-*epi*-3-anhydroophiobolin B **111** and ophiobolin I **112**. Only ophiobolin A **113** showed potent activity in cytotoxicity assays and marginal activity in antimalarial assays (Li *et al.*, 1995; Shen *et al.*, 1999). However, Rossi and Tuttobello, (1978), Ross and Tuttobello, purified ophiobolin A lactone **113** from the culture filtrates of EtOAc extract of the phytotoxic fungus *Bipolaris miyabeanus*. Ophiobolins **106**, **107**, **108**, **112** were reported also from *Bipolaris oryzae* (Phuwapraisirisan *et al.*, 2007).



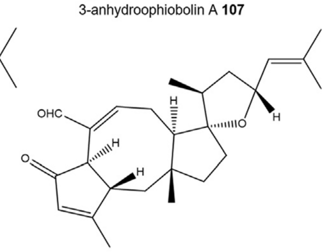
Ophiobolin A **106**



3-anhydroophiobolin A **107**

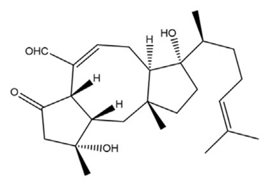


6-*epi*-ophiobolin A **108**

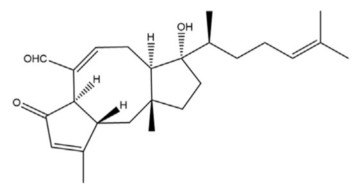


6-*epi*-3-anhydroophiobolin A **109**

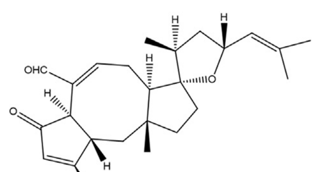
3-anhydro-6-hydroxy-ophiobolin A **114** and two ophiobolin derivatives, 3-anhydro-ophiobolin A **107** and 6-*epi*-3-anhydro-ophiobolin A **109** were isolated from the PDB culture of a phytopathogenic fungus *Bipolaris oryzae*. The structure of compound **114** was elucidated through 2D NMR and other spectroscopic techniques. Compound **114** exhibited strong antimicrobial activity against *Bacille Calmette–Guerin*, *Bacillus subtilis*, *Staphylococcus aureus*, and methicillin-resistant *Staphylococcus aureus* with MIC value of 12.5 μg/mL, and potent antiproliferative activity against cell lines HepG2 and K562 with IC_{50} of 6.49 μM and 4.06 μM, respectively (Wang *et al.*, 2013b).



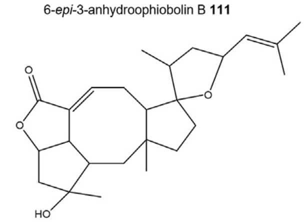
Ophiobolin B **110**



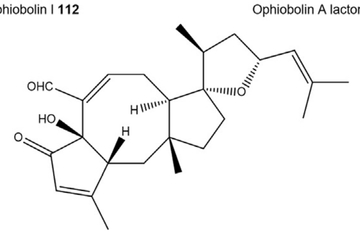
6-*epi*-3-anhydroophiobolin B **111**



Ophiobolin I **112**

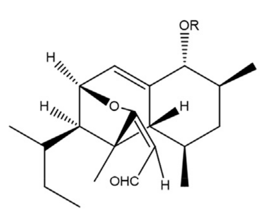


Ophiobolin A lactone **113**

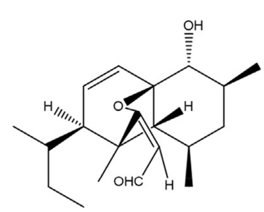


3-anhydro-6-hydroxy-ophiobolin A **114**

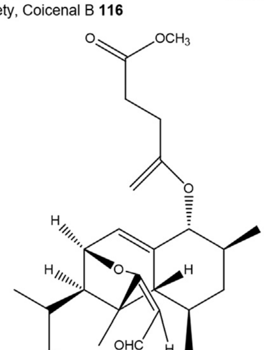
Coicenals A-C (**115**–**117**) possessing a previously undescribed 10-(sec-butyl)-6-hydroxy-1,7,9 trimethyl-1,6,7,8,9,9a-hexahydro-1,4-methanobenzo-[d]oxepin-2(4H) ylidene) acetaldehyde skeleton and coicenal D **118** with a new 2-(sec-butyl)-5-hydroxy-1,6,8-trimethyl-2,5,6,7,8,8a-hexahydro-1H-4a,1-(epoxymethano) naphthalen-10 ylidene) acetaldehyde skeleton were isolated from the solid culture of the plant pathogenic fungus *Bipolaris coicis*. The absolute configurations in 1 and 4 were assigned by electronic circular dichroism (ECD) calculations. Compounds **115**–**118** showed moderate inhibitory activity against NO release with IC_{50} values of 16.34 ± 1.12, 23.55 ± 1.37, 10.82 ± 0.83, and 54.20 ± 2.82 μM, respectively (Wang *et al.*, 2013a).



R= H, Coicenal A **115**
R= Succinyl moiety, Coicenal B **116**

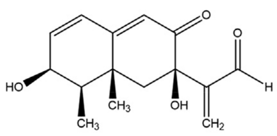


Coicenal D **118**

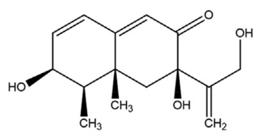


Coicenal C **117**

Two sesquiterpenes have been isolated from the fungal pathogen of *Bermuda grass Bipolaris cynodontis*. Chemical, spectral, and x-ray diffraction studies have led to the characterization of these as bipolaroxin **119** and dihydrobipolaroxin **120**, highly oxygenated members of the eremophilane family. Bipolaroxin is phytotoxic to some but not all of the plants tested. To our knowledge, a phytotoxin with host selectivity isolated from a weed pathogen has not been reported previously (Sugawara *et al.*, 1985).



Bipolaroxin **119**



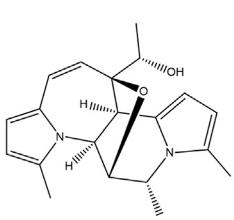
Dihydrobipolaroxin **120**

Alkaloids

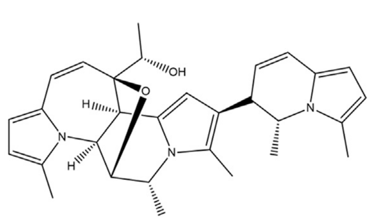
Alkaloids are a class of chemical compounds containing a nitrogen ring. 13 alkaloids have been isolated from the extracts of *Curvularia*, whereas only two alkaloids were purified from *Bipolaris*. The two genera shared one secondary metabolites (Spirostaphylotrichin R). These alkaloids exhibit a wide range of biological activities such as phytotoxicity and anti-inflammatory.

In 2014 Han and his co-workers discovered a skeletally undescribed antimicrobial alkaloid, curvulamine **121** from the broth of *Curvularia* sp. IFB-Z10, a white croaker-associated fungus, after cultured in shake flask in the Czapek's medium. The white croaker *Argyrosomus argentatus* derived *Curvularia* sp. IFB-Z10 produces curvulamine as a skeletally unprecedented alkaloid incorporating two undescribed extender units. Recently, curvulamine revealed an anti-inflammatory activity (Han *et al.*, 2016).

Curvularia sp. IFB-Z10, a white croaker associated fungus, generates skeletally unprecedented indolizine alkaloid named curindolizine **122**, which displays an anti-inflammatory action in lipopolysaccharides (LPS)-induced RAW 264.7 macrophages with an IC_{50} value of 5.31 ± 0.21 μM (Han *et al.*, 2016).

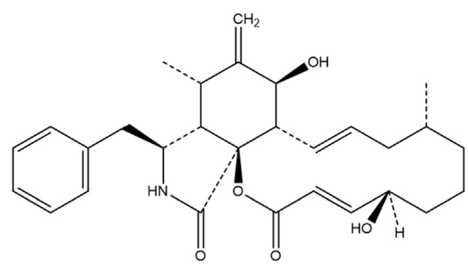


Curvulamine **121**



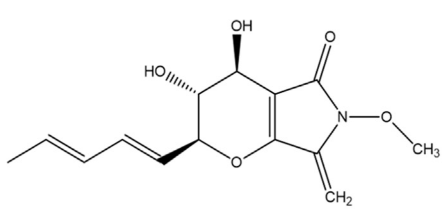
Curindolizine **122**

Cytochalasin B **123** was first described in 1967, when it had been isolated from moulds (Smith *et al.*, 1967). Compound **123** biologically active metabolite was found in crude extracts of *Curvularia lunata* (Wakker) Boedijn (ATCC 34690), isolated from decayed tissues of litchi fruit (*Litchi chinensis* Sonn). Chloroform extracts were toxic to day-old cockerels and caused abnormal distortion of wheat coleoptile segments. The major toxin had a 50% lethal dose of 700 mg/kg (oral dose) and was a colorless crystalline material. The crystalline preparation was identified as 97% cytochalasin B **123** and 3% cytochalasin A (Wells *et al.*, 1981).

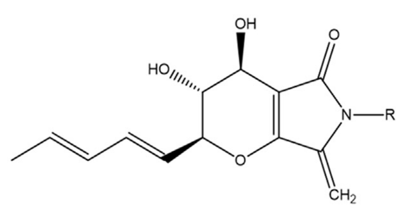


Cytochalasin B **123**

In 1995, three alkaloids with a novel skeleton, named curvupallides A-C (**124–126)** are described from the phytopathogenic fungus *Curvularia pallescens*. They possess an unusual α,β-unsaturated ene-amide γ-lactam. Curvupallides are produced together with phytotoxic spirostaphylotrichines showing structural similarities with them only under limitation of nitrogen in submerse culture. Their structures were determined using various NMR techniques and MSMS. They displayed no phytotoxic activity so their ecological function could not be determined (Abraham *et al.*, 1995b).

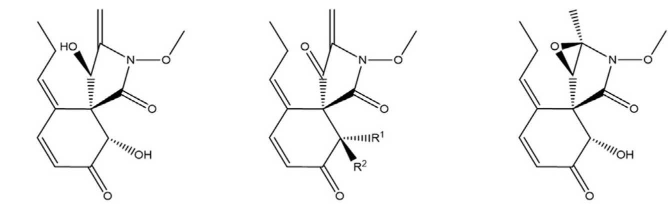


Curvupallide A **124**

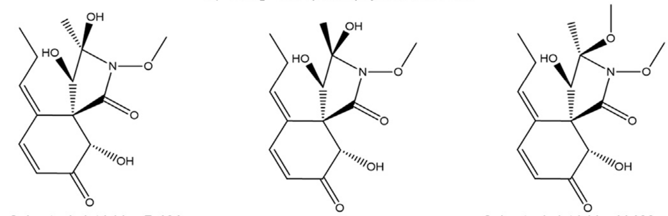


R= OCH_3, Curvupallide B **125**
R= H, Curvupallide C **126**

The fungus *Curvularia pallescens* DSM 62482 produces spirostaphylotrichins A, C, D, R, Q, U and V **127–133** spirostaphylotrichins in submerged culture under limited supply of nitrogen. The configuration of spirostaphylotrichin R could be determined as the 3,4-*cis*-diol. For spirostaphylotrichins U and V, no phytotoxic activity was detected (Abraham *et al.*, 1995a). Spirostaphylotrichin R **131** was isolated from the seagrass-derived fungus *Bipolaris* sp. PSU-ES64 (Arunpanichlert *et al.*, 2012).

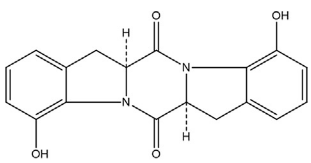


Spirostaphylotrichins A **127** R_1= OH, R_2= H Spirostaphylotrichins C **128** R_1= H, R_2= OH Spirostaphylotrichins D **129** Spirostaphylotrichins Q **130**



Spirostaphylotrichins R **131** Spirostaphylotrichins U **132** Spirostaphylotrichins V **133**

In 1985 Maes *et al.* elucidated the structure of bipolaramide **134**, a dioxopiperazine isolated from cultures of *Bipolaris sorokiniana*, is based on ^{1}H and ^{13}C NMR. data and X-ray crystallography (Sugawara *et al.*, 1985).



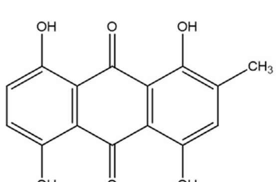
Bipolaramide **134**

Quinones

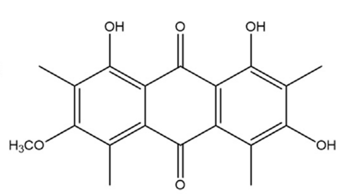
Quinones are widely distributed in nature and exhibit diverse biological or pharmacological activities (Feng *et al.*, 2015). Only three quinones were isolated from *Curvularia* meanwhile four quinones were reported from *Bipolaris* crude extracts.

In 1977, van Eijk and Roeymans have identified the isolated red tetrahydroxyanthraquinone as cynodontin (1,4, 5,8-*tetrahydr*oxy-2-methylanthraquinone) **135** from the mycelium of *Curvularia lunata* NRRL 2380.

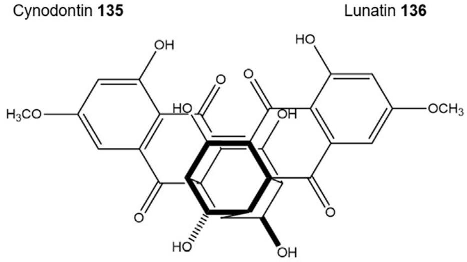
Fungal cultures of *Curvularia lunata* were grown from a tissue sample of the marine sponge *Niphates olemda*, which was collected in Indonesia. The EtOAc extract from the culture broth and mycelia of the fungus afforded the new anthraquinone lunatin **136** and bisanthraquinone cytoskyrin A **137** (Jadulco *et al.*, 2002).



Cynodontin **135**

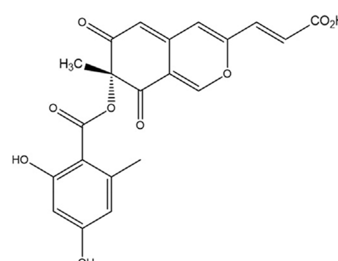


Lunatin **136**

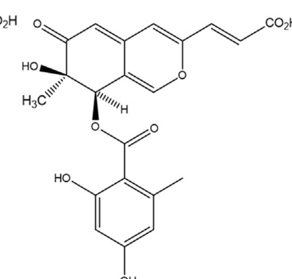


Cytoskyrin A **137**

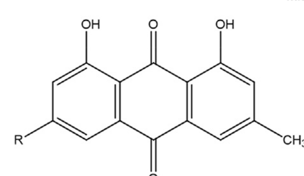
Mitorubrinic acids A and B (**138–139)** and lunatic acids formed by *Bipolaris lunatus*, belong to the morphogens substances that induce the formation of the thick wall mycelia. All compounds exhibited weak antibacterial activities (Steglich *et al.*, 2000). Also mitorubrinic acids produces by other fungi such as *Penicillium vermiculatum*, *Talaromyces austrocalifornicus* and *T. convolutus* (Proksa *et al.*, 1994; Suzuki *et al.*, 1999). Two anthraquinones chrysophanol **140** and emodin **141** were isolated the seagrass-derived fungus *Bipolaris* sp. PSU-ES64 (Engström *et al.*, 1993).



Mitorubrinic acid **138**



Mitorubrinic acid **139**

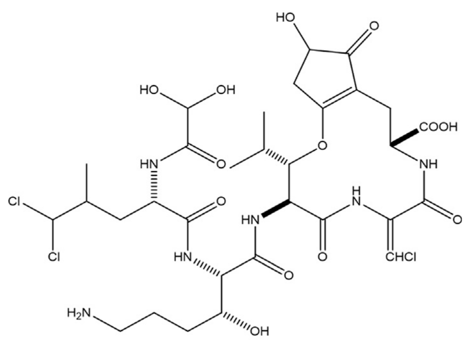


R= H, Chrysophanol **140**
R= OH, Emodin **141**

Peptides

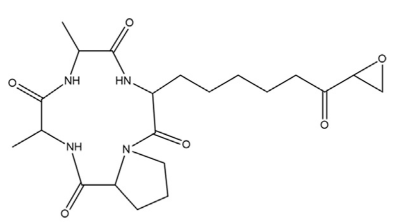
Antifungal peptides have great economic implications because they protect crops from the devastating damage brought about by fungal infections (Ng and Ngai, 2004). Only two peptides were purified from two pathogenic species of *Bipolaris*.

Pathogenic species of the fungal genus *Bipolaris* are known to cause toxin-mediated plant diseases. Some pathogenic *Bipolaris* sp. produce peptidic and despipeptidic host specific toxins that act as host recognition and virulence factors. Victorin C **142** is an NRP produced by *Bipolaris victoriae*, the causative agent of Victoria blight in oats. Victorin C is constituted by glyoxylic acid, 5, 5-dichloroleucine, erythro-β-hydroxyleucine, victalanine, threo-β-hydroxlysine and α-amino-β-chloroacrylic acid. The biological activity of victorin C is quite remarkable for instance, growth of susceptible oat (*Avena sativa*) roots was inhibited at a concentration of 0.1 ng/mL. Additionally, victorin C affects selectively susceptible oats (*Avena sativa* L.) reproducing disease symptoms caused by the pathogenic fungus (Kastin 2006).



Victorin C **142**

HC-toxin **143** is a cyclic tetrapeptide of structure cyclo (D-Pro-L-Ala-D-Ala-L-Aeo), where Aeo stands for 2-amino-9,10-epoxi-8-oxodecanoic acid. It is a determinant of specificity and virulence in the interaction between the producing fungus, *Bipolaris carbonum*, and its host, maize (Walton, 2006).



HC-toxin **143**

6. Conclusions

Fungal secondary metabolites are stressed as a promising source of novel compounds with potent biological activities. This review provides a summary of extinctive researches on SMs of the genera *Curvularia* and *Bipolaris* spp. About 143 SMs were purified from their crude extracts, they belong to several chemical classes such as: alkaloids, anthraquinones, polyketides, quinones, terpenes and peptides. Several isolated compounds revealed diverse biological activities including: antimalarial, antifouling, antilarval, antiinflammatory, antioxidant, anti-bacterial, anti-fungal, anti-cancer, leishmanicidal properties and phytotoxicity. The majority of the isolated compounds reported in this review from *Curvularia* or *Bipolaris* spp. were isolated from plants sources (either endophytic or pathogenic strains), besides few compounds were purified from fungal strains associated with lichens and marine. Most of the SMs reported here, were investigated using the classical discovery approach; combining chemical techniques and biological screening for a bioassay guided. However, recently metabolomics approaches have been adopted in fungal natural products detection, which will certainly accelerate and revolutionize fungal SMs discovery.

Chemotaxonomy or secondary metabolite profiling has also been assessed as one of the markers for differentiation among filamentous fungi. Frisvad *et al.* (2008) stated that, chemotaxonomy as a complementary method, may utilize secondary metabolites to distinguish fungi at the species or even strain level. Considering the data collected in this review we noticed that, despite the morphological similarities between *Curvularia* and *Bipolaris*, but at metabolomes level they do not produced the same SMs. Among 143 SMs reported in this review, only six SMs were produced by both of them. Thus, it could be valuable to differentiate the two genera using their metabolite profilings.

Conflict of interest statement

We declare that we have no conflict of interest.

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