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Bioactive Natural Compounds from the Plant Endophytic Fungi *Pestalotiopsis* spp.

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Abstract: The plant-endophytic strains of the fungus *Pestalotiopsis* (Amphisphaeriaceae) are distributed throughout the world. Previous chemical investigation of members of the genus resulted in the discovery of various bioactive secondary metabolites including chromones, cytosporones, polyketides, terpenoids and coumarins with diverse structural features. The present report reviews the papers, which have appeared in the literature till now, concerning the isolation, structural elucidation, and biological activities of the secondary metabolites from *Pestalotiopsis* species.

Keywords: *Pestalotiopsis*, metabolites, structure, biological activities.

1. INTRODUCTION

Endophytes are microorganisms which reside in the tissues beneath the epidermal cell layers and cause no apparent harm to the host [1]. Endophytic fungi have been shown to produce a large number of natural products belonging to various structural classes [2, 3]. The plant-endophytic strains of the fungus *Pestalotiopsis* (Amphisphaeriaceae) are distributed throughout the world, with most species associated with living plants, and some being saprobes in soil or plant debris [4-10]. Previous chemical investigation of members of the genus resulted in the discovery of various bioactive secondary metabolites including chromones, cytosporones, polyketides, terpenoids and coumarins with diverse structural features. The present report reviews the papers, which have appeared in the literature till now, concerning the isolation, structural elucidation, and biological activities of the secondary metabolites from *Pestalotiopsis* species.

2. AROMATIC COMPOUNDS

2.1. Chromones

Pestalotiopsones A-F (**1**-**6**), six new chromones having both an alkyl side chain substituted at C-2 and a free or substituted carboxyl group at C-5, and a known derivative 7-hydroxy-2-(2-hydroxypropyl)- 5-methylchromone (**7**) have been isolated [11] from the mangrove endophytic fungus *P.* spp, which was isolated from leaves of the Chinese Mangrove plant *Rhizophora mucronata*. **6** exhibited moderate cytotoxicity against the murine cancer cell line L5178Y with an EC_{50} value of 8.93 μg/mL. Studies on the plant endophyte *P. fici* have yielded [12-14] sixteen new chromone derivatives pestaloficiols A-P (**8**-**23**), including one heterodimer (**19**). **8**, **9**, **11**, **17**, and **21** displayed inhibitory effects on HIV-1 replication in C8166 cells, with EC_{50} values of 26.0, 98.1, 64.1, 8.0 and 56.5 μM, respectively, whereas **19**, **22** and **23** showed cytotoxic activity against the human tumor cell lines HeLa with IC_{50} values of 8.7, 56.2, and 74.9 μM, respectively. Compound **22** also showed antifungal activity against *Aspergillus fumigatus*, with IC_{50} values of 8.2 μM. Examination of plant endophytic fungus *P. theae* afforded [15] four new metabolites pestalotheols A-D (**24**-**27**). Pestalotheol C (**26**) displayed an inhibitory effect on HIV-1_{LAI} replication in C8166 cells. Three new chromones, pestalochromones A-C (**28**-**30**) were isolated from the mangrove-derived fungus *Pestalotiopsis* sp. PSU-MA69. Compounds **28**-**30** are the rare chlorinated fungal metabolites of chromones [16].

2.2. Benzofuranones

Isopestacin (**31**), an isobenzofuranone having a substituted benzene ring attached at the C-3 position of the furanone ring, has been obtained [17] from the culture broths of the endophytic fungus *P. microspora*. **31** show antifungal activity, with total inhibition of *Pythium ultimum* at 40 μg/mL at 48 h, and behave as an antioxidant scavenging both superoxide and hydroxy free radicals. Novel 1, 5, 7-trisubstituted isobenzofuranone pestacin (**32**) has been isolated [18] from *P. microspora*, an endophytic fungus native to the rainforest of Papua New Guinea. **32** exhibits moderate antifungal properties, with a minimum inhibitory concentration of approximately 10 μg/mL to *Pythium ultimum*, and antioxidant activity 11 times greater than the vitamin E derivative trolox. Photinides A-F (**33**-**38**), six new unique benzofuranone-derived γ-lactones, and a known compound 6-methoxy-9-methyl-4'-hydroxyaurone (**39**) have been isolated [19] from the crude extract of the plant endophytic fungus *P. photiniae*. **33**-**38** displayed modest cytotoxic effects against the human tumor cell line MDA-MB-231, with inhibitory rates of 24.4%, 24.2%, 23.1%, 24.4%, and 24.6%, respectively, when tested at 10 μg/mL. **37** and **38** could originate from **33** and **34** by an epoxidation

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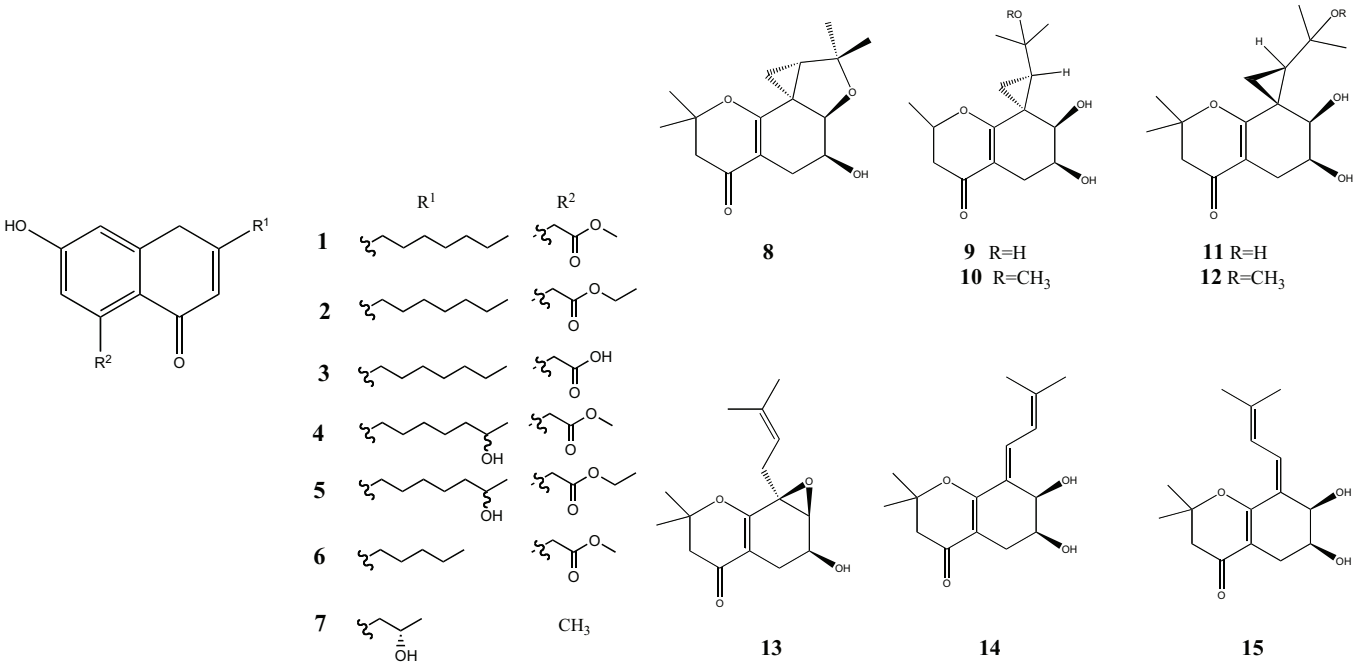
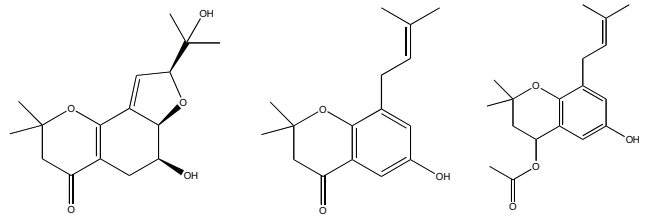
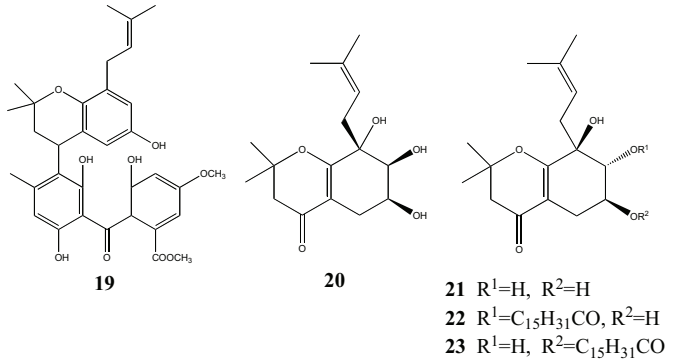
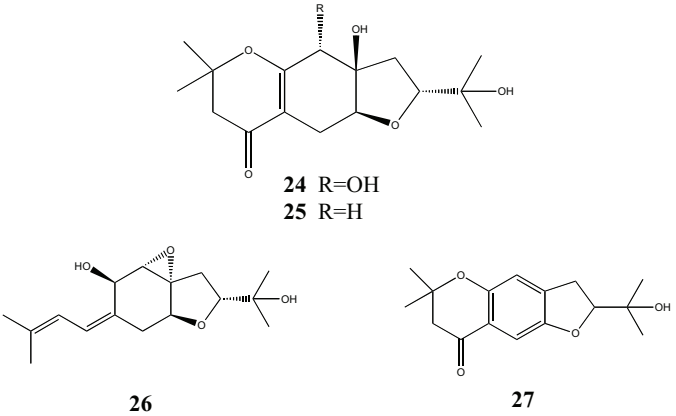
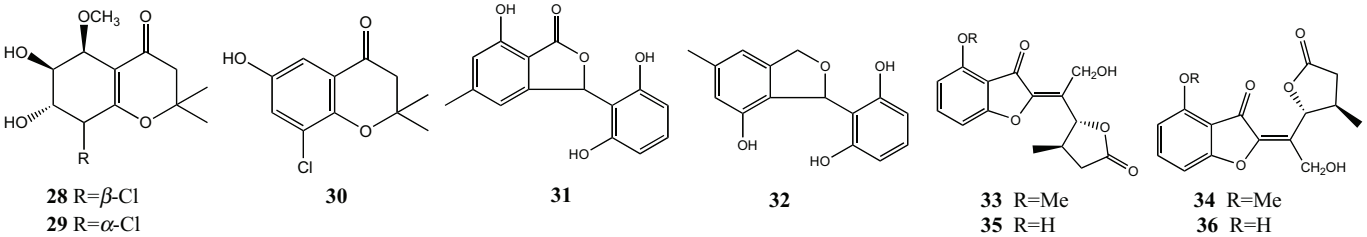


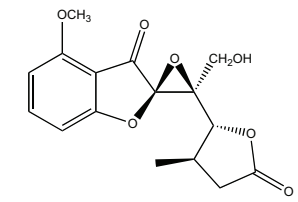








of the C-2/C-8 olefin. Chemical examination of the endophytic fungus *P. foedan*, yielded [20] two new isobenzofuranones pestaphthalides A (**40**) and B (**41**) with antifungal properties. **40** showed activity against *Candida albicans* (ATCC 10231), causing a zone of inhibition of 13 mm at 100 μg/disk, and **41** showed activity against *Geotrichum candidum* (AS 2.498) with a 11 mm zone of inhibition when tested at the same level.



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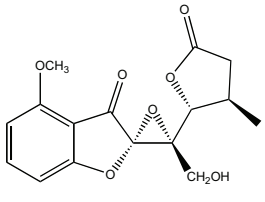

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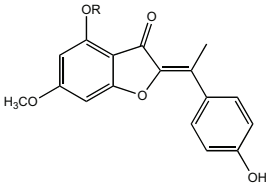

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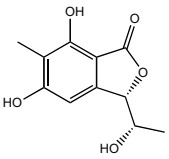

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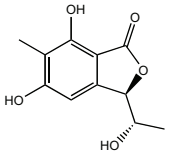

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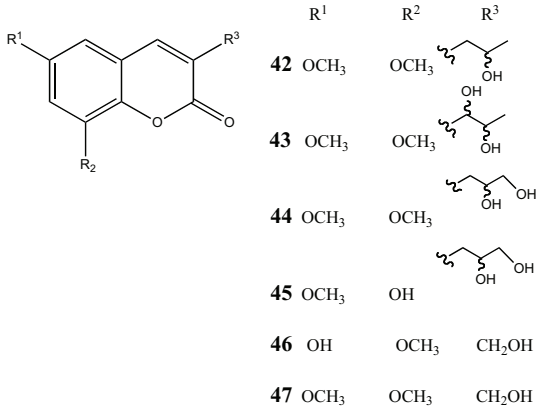
2.3. Coumarins

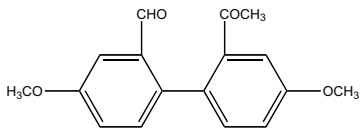
Study on the endophytic fungus *P.* spp., isolated from the leaves of the Chinese mangrove *Rhizophora mucronata*, yielded [21] five new coumarins pestalasins A–E (**42**–**46**), along with the known compound 3-hydroxymethyl-6, 8-dimethoxycoumarin (**47**). None of the compounds showed any significant activity when tested at an initial concentration of 10 μg/mL.

2.4. Other Aromatic Compounds

The investigation of the chemical constituents of the plant endophytic fungus *P. zonata*, isolated from *Cyrtotachys lakka* in Hainan, China, resulted in the isolation [22] of a new biphenyl compound named 2'-acetyl-4', 4-dimethoxybiphenyl-2-carbaldehyde (**48**). **48** show weak antibacterial activity against the bacteria *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, methicillin resistant *Staphylococcus aureus*, *Acinetobacter baumannii* and vancomycin-resistant *Enterococcus faecium* with the IC_{50} values of 0.75, 0.75, 0.82, 0.81, 0.84, 0.90, and 0.87 μg/mL, respectively. Three new *a*-pyrones, pestalotiopyrones A–C (**49**–**51**) were isolated [23] from the mangrove- derived fungi *P.* spp. (PSU-MA92 and PSU-MA119). Three new *a* -pyrones, scirpyrones A–C (**52**–**54**), and four new pyranes, scirpyranes A–D (**55**–**58**), were isolated from solid cultures of the plant pathogen *P. scirpina*. **52** is the first described 6-(5-oxotetrahydrofuran-2-yl)-2H-pyran-2-one. Compounds **55**–**57** showed significant cytotoxicity towards MCF-7 cells, with IC_{50} values of 5.84, 4.34, and 8.22 μM, respectively (the positive control cisplatin showed an IC_{50} value of 11.9 μM) [24]. Chloropupukeananin (**59**), the first pupukeanane chloride with highly functionalized tricyclo-[4.3.1.0 ^{3,7}]-decane skeleton, has been isolated [25] from the plant endophyte *P. fici*. Biogenetically, **59** could be derived from the Diels-Alder adduct of iso-A82775C and pestheic acid. **59** showed an inhibitory effect against HIV-1 replication in C8166 cells with an IC_{50} value of 14.6 μM, and displayed antimicrobial activity against *Staphylococcus aureus* (ATCC 6538), with IC_{50} and MIC values of 21.8 and 97.3 μM, respectively. Three unusual chlorinated benzophenone derivatives pestalachlorides A–C (**60**-**62**), have been isolated [26] from cultures of an isolate of the plant endophytic fungus *P. adusta*. **60** was obtained as a mixture of two inseparable atropisomers (**1a** and **1b**), whereas **62** was found to be a racemic mixture. anddisplayed significant antifungal activities against three plant pathogens. **60** displayed potent antifungal activity against *Fusarium culmorum*, with an IC_{50} value of 0.89 μM, while **61** exhibited remarkable activity against *Gibberella zeae*, with an IC_{50} value of 1.1 μM. Chemical examination of the endophytic fungus *P.* spp, isolated from the leaves of the Chinese mangrove *Rhizophora mucronata*, yielded [21] 5 new compounds cytosporones J–N (**63**-**65**, **57**, **68**), along with two known compounds cytosporone C (**66**), dothiorelone B (**69**). Four new diphenyl ethers, pestalotethers A-D (**70**-**73**), one new xanthone, pestaloxanthone (**74**), and one new butenolide, pestalolide (**75**) were isolated from the mangrove-derived fungus *Pestalotiopsis* sp. PSU-MA69 [16]. Compounds **70**-**72** are the rare chlorinated fungal metabolites of diphenyl ethers. Pestalolide (**75**) displayed weak antifungal activity against *Candida albicans* and *Cryptococcus neoformans* with the MIC values of 0.25 and 0.50 μg/mL, respectively.



42 R^1=OCH_3, R^2=OCH_3, R^3=
43 R^1=OCH_3, R^2=OCH_3, R^3=
44 R^1=OCH_3, R^2=OCH_3, R^3=
45 R^1=OCH_3, R^2=OH, R^3=
46 R^1=OH, R^2=OCH_3, R^3=CH_2OH
47 R^1=OCH_3, R^2=OCH_3, R^3=CH_2OH



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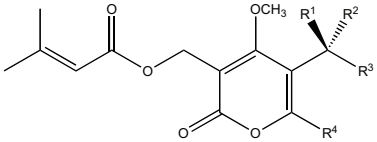
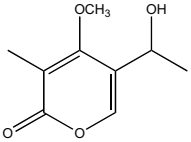


49 R^1=OH, R^2=R^4=H, R^3=CH_3
50 R^1= R^2=H, R^3=OH, R^4=CH_3



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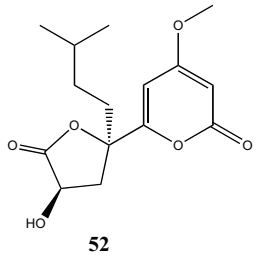

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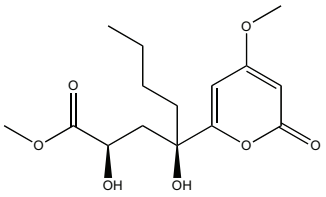

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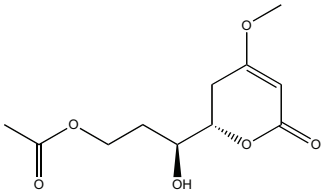

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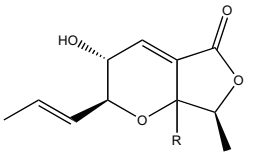

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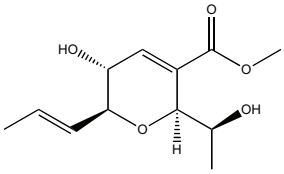
56 R=β-H



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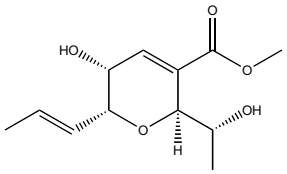

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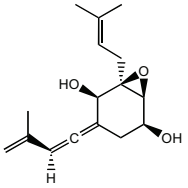

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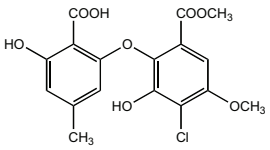
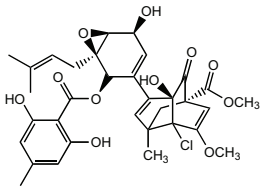


pestheic acid

Diels-Alder



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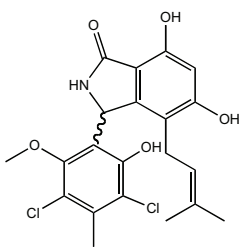
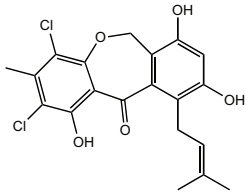


60 1a
60 1b



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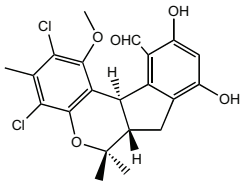

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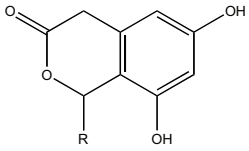

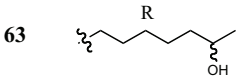

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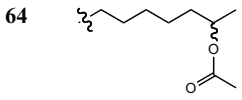

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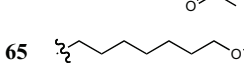

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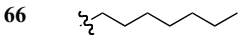

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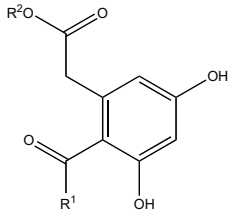

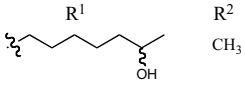

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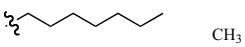

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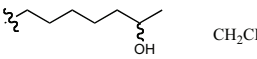

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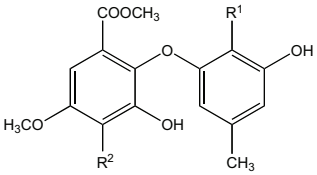
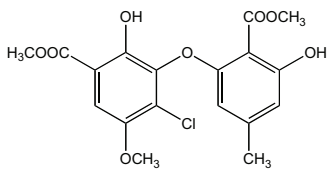


70 R^1= $COOCH_3$, R^2=Cl
71 R^1= H, R^2=Cl
73 R^1= $COOCH_3$, R^2=H



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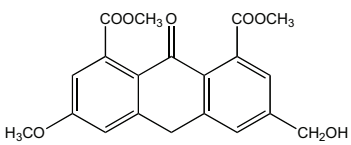
3. TERPENES AND ERGOSTEROLS

3.1. Sesquiterpenes

Examination of the cultures of the fungicolous fungus *P. disseminate* afforded [27] three new caryophyllene-type sesquiterpene alcohols, 6-hydroxypunctaporonin E (**76**), 6-hydroxypun- ctaporonin B (**77**), and 6-hydroxypunctaporonin A (**78**). The structure and absolute configuration of 6-hydroxy- punctaporonin E (**76**) was confirmed through X-ray crystallographic analysis of its monobromobenzoate derivative (**79**). **76** and **77** exhibited activity in standard agar disk diffusion assays at 100 μg/disk against Gram-positive bacteria *Bacillus subtilis* (ATCC 6051), each causing a 12-mm zone of inhibition. *Staphylococcus aureus* (ATCC 29213) was inhibited to a lesser extent by **76** and **77**, the zone being 8 mm in both cases.



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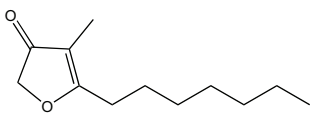
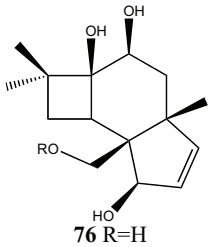


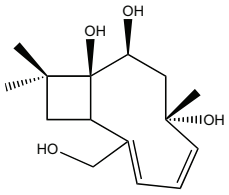
75

A new sesquiterpene 2α-hydroxydimeninol (**80**) was isolated [28] as the most polar metabolite produced by a cultured *P.* spp., a fungus associated with *Taxus* sp. Three new caryophyllene sesquiterpenes, pestalotiopsins A-C (**81** - **83**) and a known compound **84**, have been isolated [29, 30] from two strains of *P.* spp. (JCM 9685 and JCM 9686), endophytic fungi of *Taxus brevoblia*. **81** has a novel oxatricyclic ring system while **82** exists as two slowly equilibrating atropisomers (6: 5 ratio of $\alpha\alpha$: $\alpha\beta$) in chloroform solution at room temperature. **81** show immunosuppressive activity in the mixed lymphocyte reaction with IC_{50} of 3-4 μg/mL and cytotoxicity with IC_{50} at roughly the same level.



76 R=H

79 R=CO-p-C_6H_4Br



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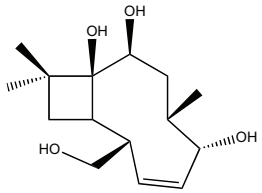

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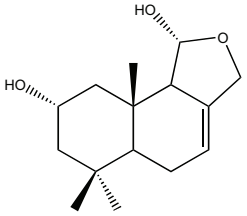

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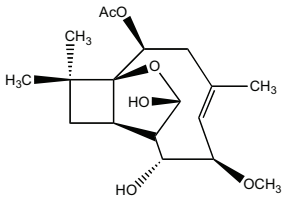

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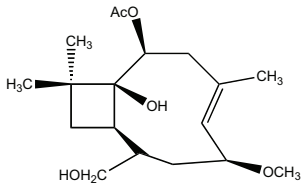

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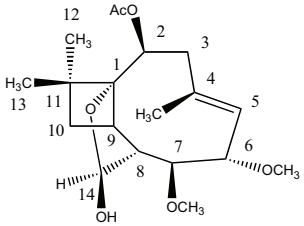

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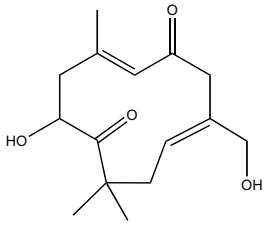
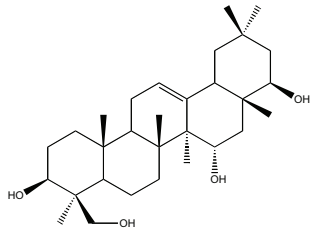


84

3.2. Triterpenes

Studyies on the cultures of the plant endophytic fungus *P. clavispora*, isolated from the Chinese Mangrove Plant *Bruguiera sexangula*, yielded [31, 32] three new triterpenoid derivatives, (15α)-15- hydroxysoyasapogenol B (**85**), (7β, 15α)-7, 15-dihydroxysoyasapogenol B (**86**), (7β)-7, 29-dihydroxyso- yasapogenol B (**87**), and two known compounds 3β, 22β, 24-trihydroxy-olean-12-ene (**88**) and ursolic acid (**89**).



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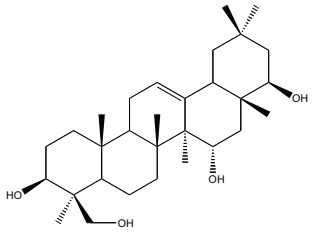

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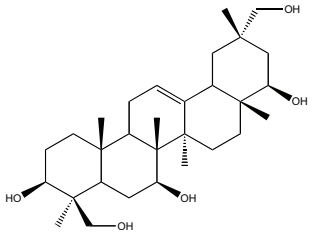

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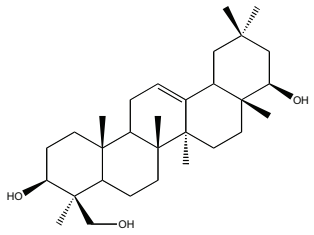
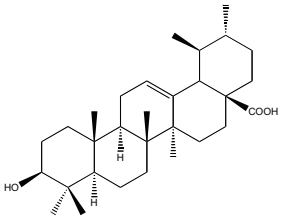


88

3.3. Ergosterols

Two ergosterols (22*E*, 24*R*)-ergosta-5, 7, 22-trien-3β-ol (**90**) and 5α, 8α-epidioxy-(22*E*, 24*R*)-ergosta- 6, 22-dien-3β-ol (**91**) were isolated [22] from the fermentation broth of the plant endophytic fungus *P. zonata* isolated from *Cyrtotachys lakka* in Hainan, China. Examination of the cultures of the plant endophytic fungus *P. clavispora*, isolated from the Chinese Mangrove Plant *Bruguiera sexangula*, afforded two ergosterols **91** and ergosta-4, 6, 8(14), 22-tetraen-3-one (**92**) [32].



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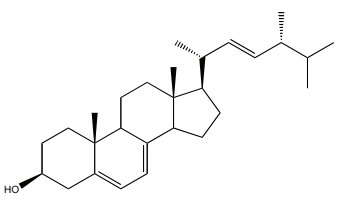

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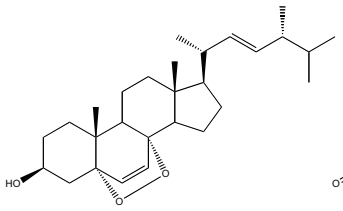

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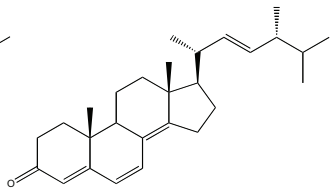
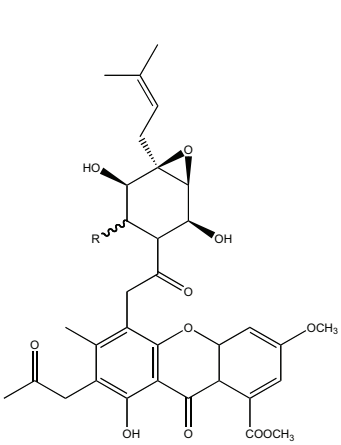


92

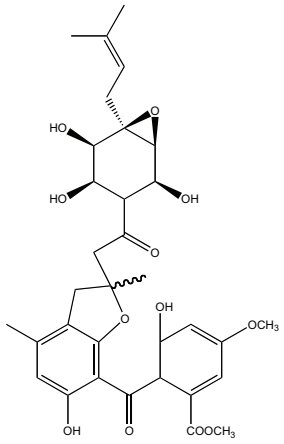
4. CYCLOHEXANONE DERIVATIVES

Novel cyclohexanone derivatives pestalofones A-H (**93**–**100**) and pestalodiols A–D (**101**–**104**) and four known compounds, pestalofone E (**105**), pestalofone D (**106**), precursors iso-A82775C (**107**) and isosulochrin

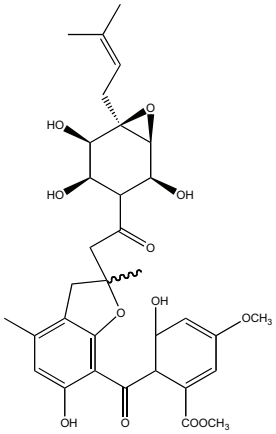
(**108**), have been isolated [33, 34] from cultures of the plant endophytic fungus *P. fici*. **93**, **94**, and **97** displayed inhibitory effects on HIV-1 replication in C8166 cells, with EC_{50} values of 90.4, 64.0, and 93.7 μM, respectively,whereas **95** and **97** showed significant antifungal activity against *Aspergillus fumigatus*, with IC_{50}/MIC values of 1.10/35.3, 0.90/31.2 μM, respectively. **98** and **103** showed cytotoxicity against HeLa and MCF-7 cells, with IC_{50} values of 14.4 and 16.7 μM, 11.9 and 57.5 μM, respectively. Ambuic acid (**109**), a highly functionalized cyclohexenone, was isolated [35] from *P.* spp. and *Monochaetia sp*. **109** was active against *Pythium ultimum* with a minimum inhibitory concentration of 7.5 μg/mL. Examination of the extract of endophytic fungus *P.* spp. inhabiting the lichen *Clavaroids* spp afforded [36] six new ambuic acid derivatives (**110**-**115**). **109** and **110** displayed antimicrobial activity against the Gram-positive bacterium *Staphylococcus aureus* (ATCC 6538), with IC_{50} values of 43.9 and 27.8 μM, respectively. Two novel highly functionalized cyclohexenone epoxides jesterone (**116**) and hydroxy-jesterone (**117**) have been isolated [37] from a newly described endophytic fungal species *P. jesteri.* **116** displayed selective antimycotic activity against the oomycetous fungi *Pythium ultimum*, *Aphanomyces* sp., *Phytophthora citrophthora, P. citrophthora*, *Rhizoctonia solani* and *P.* cinnamomi with MIC values of 25, 6.5, 25, 6.5, 25, 25 μg/mL.



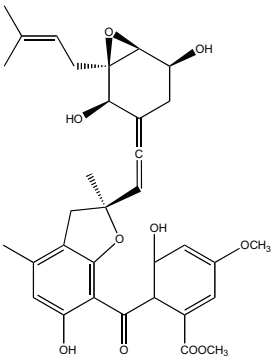
98 R=α-OH
105 R=*β*-OH



99 R=*β*-OH
100 R=*α*-OH



99 R=*β*-OH
100 R=*α*-OH



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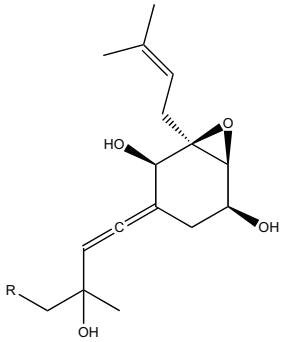
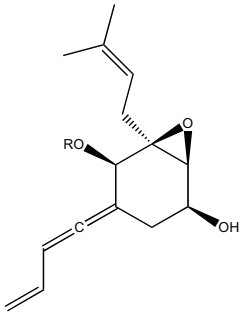
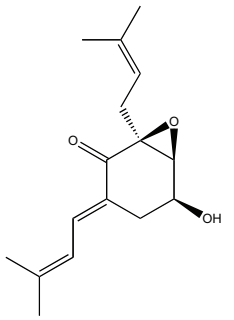


101 R=H
102 R=OH



103 R=Ac
107 R=H



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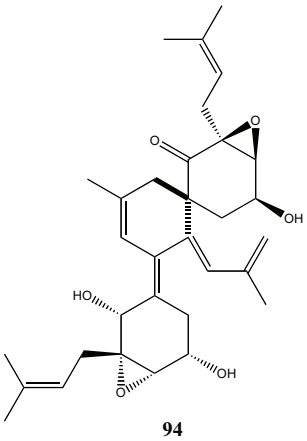

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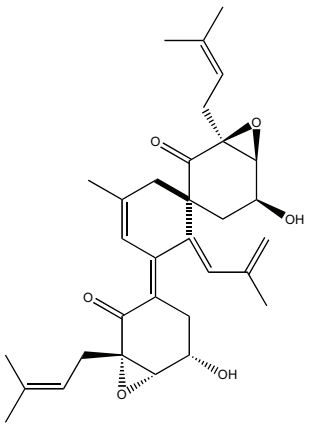

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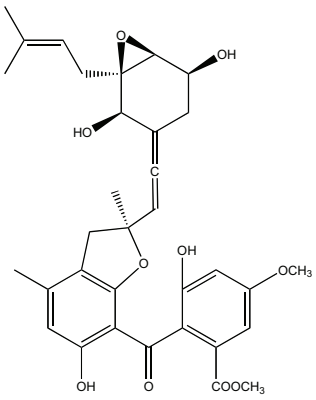

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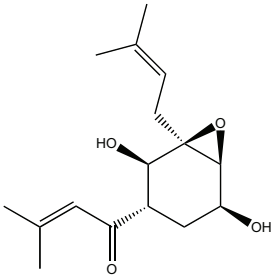

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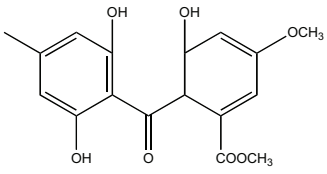

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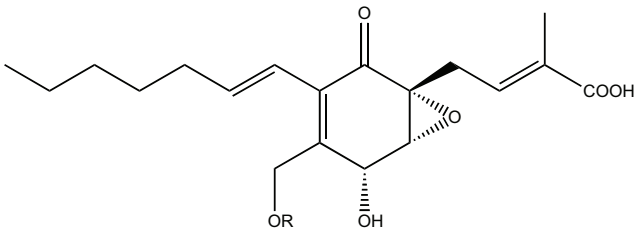
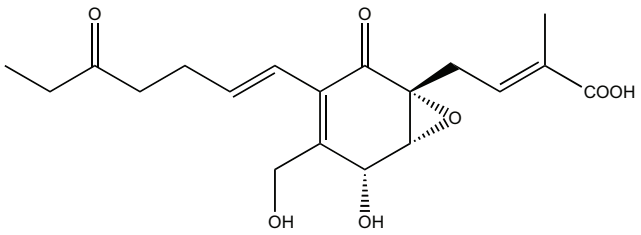


109 R=H
110 R=Ac



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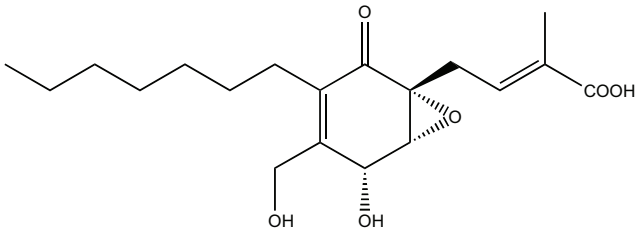

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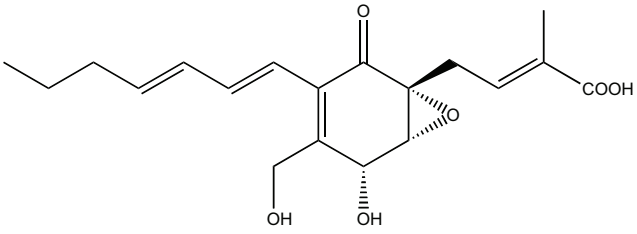

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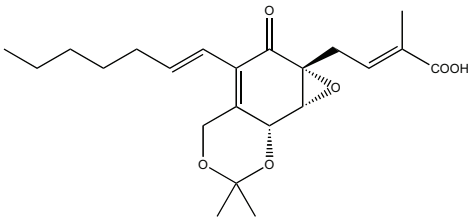

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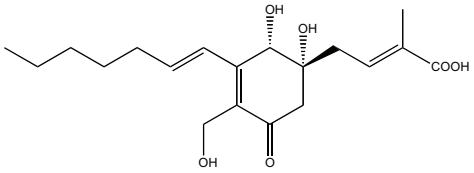

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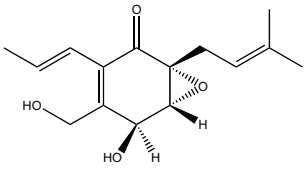

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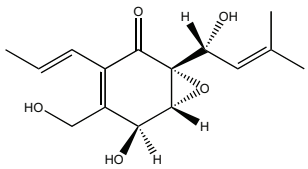

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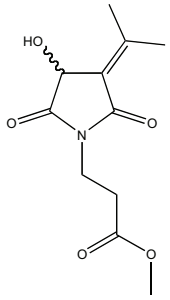

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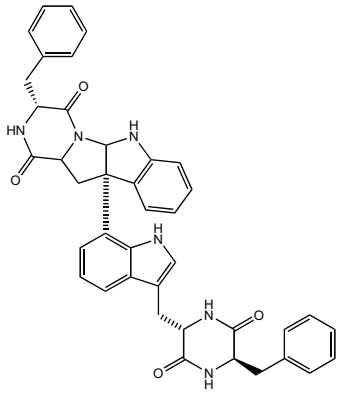
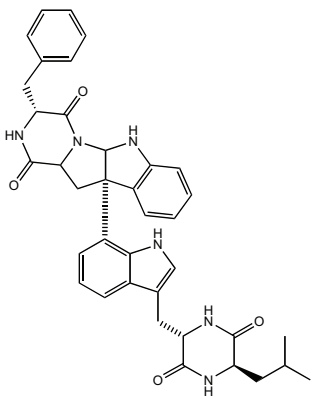


124

5. ALKALOIDS

Study on the endophytic fungus *P.* spp., isolated from the leaves of the Chinese mangrove *Rhizophora mucronata*, yielded [21] a new alkaloid named pestalotiopsoid A (**118**). Analysis of the cultures of the plant pathogenic fungus *P. theae*, yielded [38] two new diketopiperazine heterodimers pestalazines A (**119**) and B (**120**), and three new amides pestalamides A-C (**121**-**122**) along with the known compounds asperazine (**124**), aspernigrin A (**125**), and carbonarone A (**126**). **119**, **121**, and **124** displayed inhibitory effects on HIV-1 replication in C8166 cells, with EC_{50} values of 47.6, 64.2, and 98.9 μM, respectively. **121** also showed potent antifungal activity against *Aspergillus fumigatus*, with IC_{50}/MIC values of 1.50/57.8 μM.



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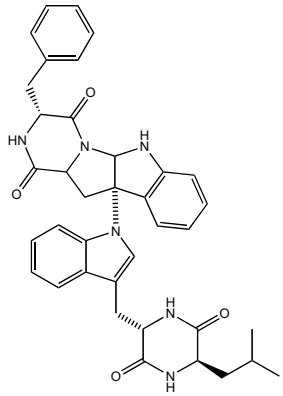

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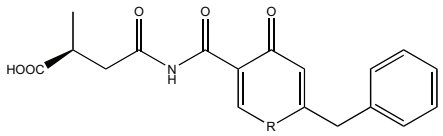
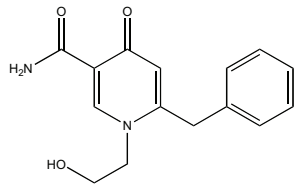


121 R=O
122 R=NH



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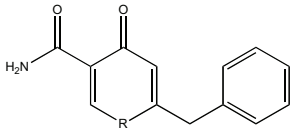
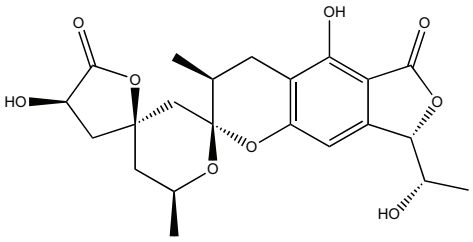


125 R=NH
126 R=O

6. SPIROKETAL COMPOUNDS

Virgatolides A-C (**127**-**129**), unique metabolites with a 3′, 4′, 5′, 6′-tetrahydrospiro [chroman-2, 2′-pyran]core, were isolated [39] from cultures of the plant endophytic fungus *P. virgatula*. **127**-**129** possess two previously undescribed skeletons originating from a benzannulated 6, 6-spiroketal and one (**128** and **129**) and two (**127**) γ-lactone units, respectively, and showed modest cytotoxicity against HeLa cells, with IC50 values of 19.0, 22.5, and 20.6 μM, respectively. Two dispiro derivatives pestalospiranes A and B (**130** and **131**), having a novel 1, 9, 11, 18-tetraoxadispiro [6.2.6.2] octadecane skeleton were isolated [40] from endophytic fungus *P. virgatula*, derived from the plant *Terminalia chebula*. Examination of the solid cultures of *P. foedan*, yielded [20] a new reduced spiro azaphilone derivative pestafolide A (**132**). **132** showed modest antifungal activity against *Aspergillus fumigatus* (ATCC 10894), affording a zone of inhibition of 10 mm at 100 μg/disk.



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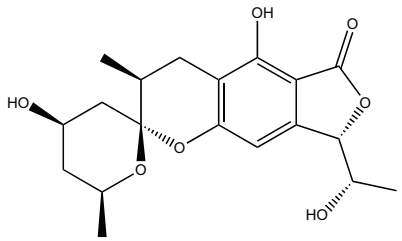

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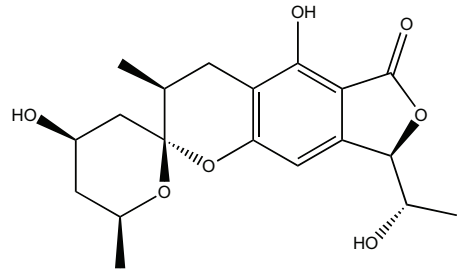

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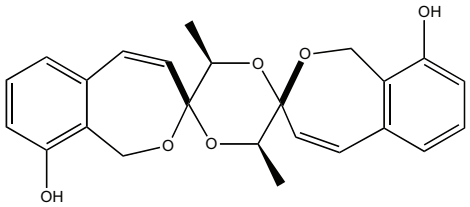

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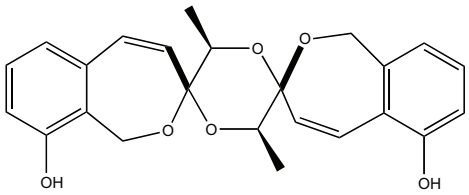

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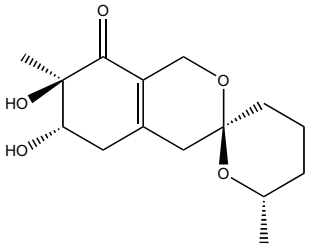


132

Chloropestolide A (**133**), a highly functionalized spiroketal with an unprecedented skeleton derived from a chlorinated bicyclo-[2. 2. 2]-oct-2-en-5-one ring and a 2, 6-dihydroxy-4-methylbenzoic acid unit, has been isolated [41] from the fermentation extract of endophytic fungus *P. fici*. **133** shows significant inhibitory effects on growth of two human cancer cell lines, HeLa and HT 29, with GI_{50} values of 0.7 and 4.2 μM, respectively. Examinaton of the fermentation extract of the plant endophytic fungus *P. fici*, afforded [42, 43] five highly functionalized secondary metabolites featuring a novel spiroketal skeleton derived from the chlorinated tricyclo-[4.3.1.0 ^{3,7}]-decane (pupukeanane) and the 2, 6-dihydroxy-4-methyl- benzoic acid moieties, chloropupukeanolides A–E (**134**–**138**). **134** showed a significant anti-HIV-1 effect with EC_{50} values of 6.9 μM, **134** showed cytotoxicity against the HeLa, MCF-7 and MDA-MB-231 human tumor cell lines with IC_{50} values of

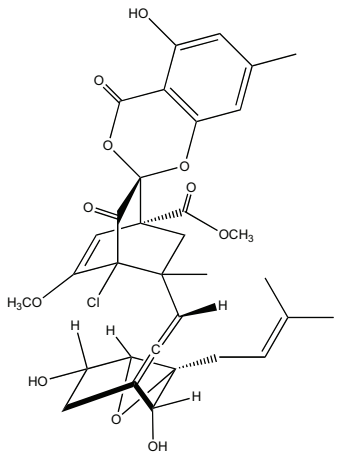
16.9, 15.5, and 15.9 μM, respectively. **136** and **137** showed significant cytotoxicity against human tumor cell lines including HeLa and HT29, with IC_{50} values ranging from 1.2 to 7.9 μM, with a higher activity than the positive control 5-fluorouracil, which gave IC_{50} values of 10.0 and 15.0 μM. In addition, **136 - 138** were tested against the pathogens of the tropical diseases malaria, Chagas disease, leishmaniasis, and African sleeping sickness. All compounds showed weak activities against these pathogens (Table **1**), but also exhibited cytotoxicities against rat skeletal myoblast (L6) cells at similar IC_{50} values. **137** revealed a general toxicity as demonstrated by the very similar IC_{50} values for all parasites. The most interesting value was the activity of **138** against *Trypanosoma brucei* rhodesiense, which is modest but selective for that parasite.

Torreyanic acid (**139**), isolated [44] from *P. microspora*, is an unusual dimeric quinone with selective cytotoxicity against human cancer cell lines. **139** is five-ten times more potent in cell lines that are sensitive to protein kinase C (PKC) agonists and causes cell death by apoptosis. IC_{50} values range from 3.5 (NEC) to 45 (A549) μg/mL with a mean value of 9.4 μg/mL for 25 different cell lines. **139** also show G1 arrest of G0 synchronized cells at the 1-5 μg/mL level depending on the cell line. A new torreyanic acid analogue **140** has been isolated [36] from the extract of endophytic fungus *P.* spp.

Table 1. Bioactivities of Compounds 136–138 against *Plasmodium falciparum* (strain K1), *Trypanosoma cruzi*, *T. brucei rhodesiense*, *T. brucei brucei*, and *Leishmania donovani*, and cytotoxicities against Rat Skeletal Myoblast (L6) Cells

Compound	IC50 μM					
	P. falciparum	*T. cruzi*	*T. brucei rhodesiense*	*T. brucei bruce*	*Leishmania donovan*	L6 Cells (Cytotoxicity)
136	5.73	60.93	19.27	- [a]	12.27	61.50
137	2.71	2.83	5.47	2.28	4.11	9.50
138	7.05	35.48	1.26	- [a]	37.52	112.35
Standard	0.17 [b]	1.75 [c]	0.006 [d]	0.003 [e]	0.48 [f]	0.012 [g]

[a] Not measured. [b] Chloroquine. [c] Benznidazole. [d] Melarsoprol. [e] Pentamidin. [f] Miltefosin. [g] Podophyllotoxin.



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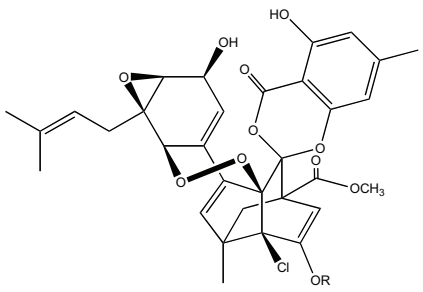
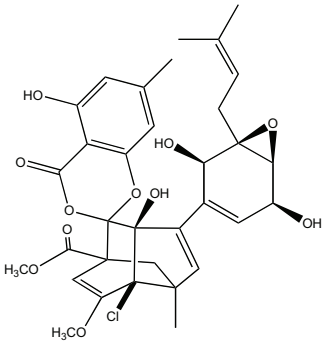


134 R=H
135 R=CH_3



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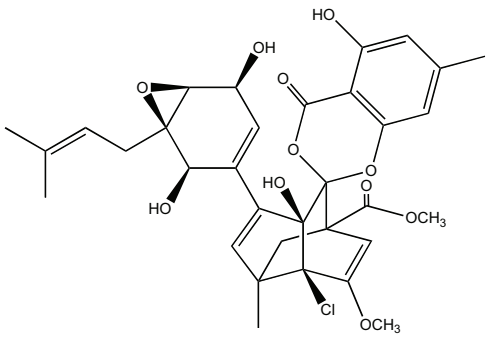

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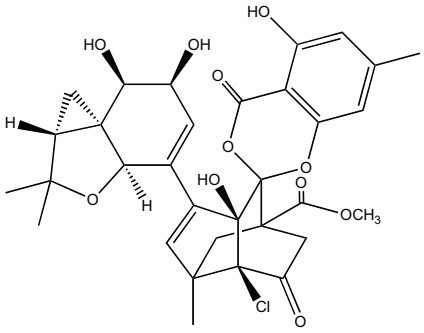

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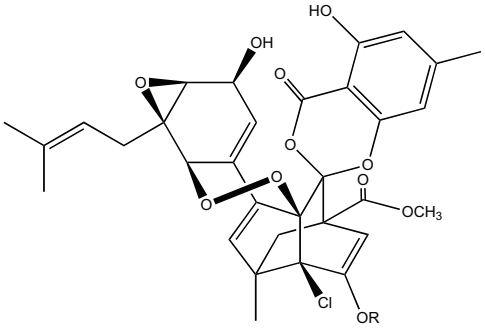
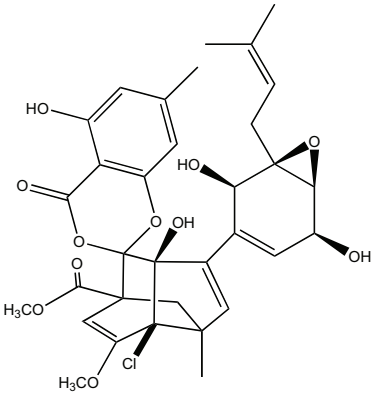


134 R=H
135 R=CH_3



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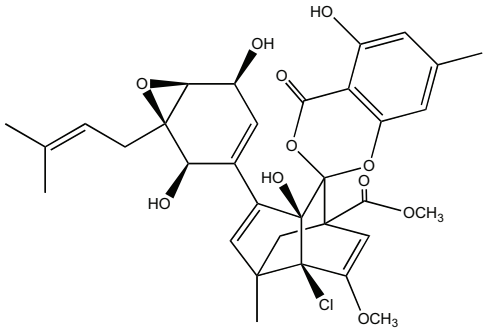

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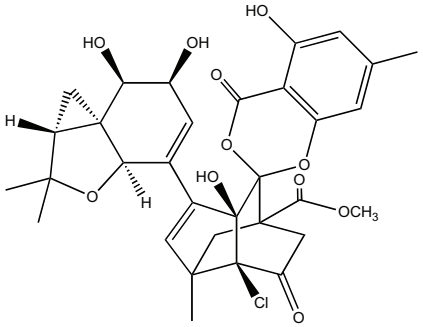

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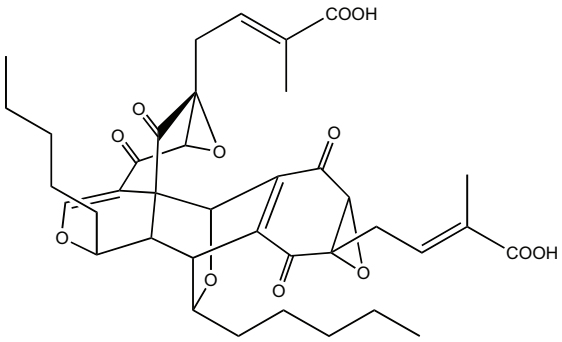

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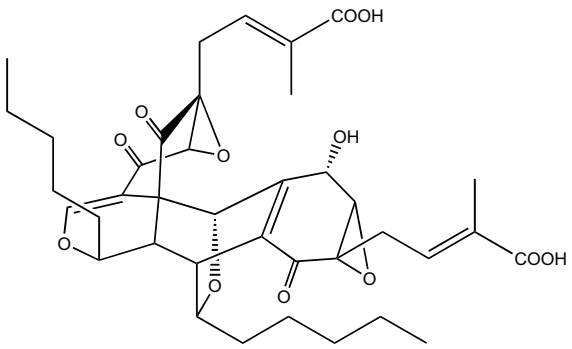
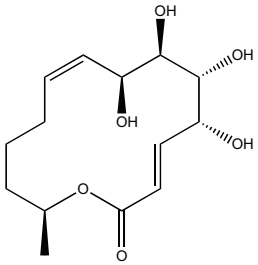


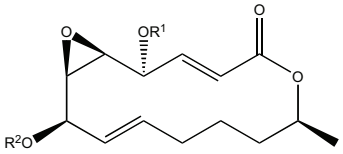
140

7. OTHER COMPOUNDS

Study on the mangrove-derived fungi *P.* spp. PSU-MA92 and PSU-MA119 resulted in the isolation [23] of two new seiricuprolides, pestalotioprolides A (**141**) and B (**142**). **142** was isolated as its diacetate derivative (**143**). The endophytic fungus *P. microspora* has been shown to produce heteropolysaccharides and the composition of polysaccharides depends strongly on the monosaccharides used for carbon source [45].



141



142 R^1= R^2= H

143 R^1= R^2= COCH3

8. CONCLUSION

The study on endophytic fungi from medicinal plants has received much attention in recent years as they are believed to be an excellent source of biologically active compounds. *Pestalotiopsis* species are of considerable interest to researchers and pharmacists due to their capabilities of synthesizing a wide range of economically important bioactive molecules.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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REFERENCES

[1] Stone J. K.; Bscon C. W.; White Jr. J. F. An overview of endophytic microbes: endophytism defined. In: Becon C. W.; White Jr J. F.; editors. *Microbial Endophytes*. New York: Marcel Dekker; **2000**. p. 3-29.

[2] Strobel G.; Daisy B.; Castillo U.; Harper J. Natural Products from Endophytic Microorganisms. *J. Nat. Prod*., **2004**, *67*, 257-268.

[3] Rodriguez R. J.; White J. F. Jr.; Arnold A. E.; Redman R. S. Fungal endophytes: diversity and functional roles. *New Phytol*., **2009**; 182: 314-330.

[4] Gunatilaka A. A. L. Natural Products from Plant-Associated Microorganisms: Distribution, Structural Diversity, Bioactivity, and Implications of Their Occurrence. *J. Nat. Prod*., **2006**, *69*, 509-526.

[5] Schulz B.; Boyle C.; Draeger S.; Rommert A. K.; Krohn K. Endophytic fungi: a source of novel biologically active secondary metabolites. *Mycol. Res*., **2002**, *106*, 996-1004.

[6] Tejesvi M.V.; Mahesh B.; Nalini M.S.; Prakash H.S.; Kini K.R.; Subbiah V.; *et al.* Fungal endophyte assemblages from ethnopharmaceutically important medicinal trees. *Can. J. Microbiol*., **2006**, *52*, 427-435.

[7] Tejesvi M. V.; Kini K. R.; Prakash H. S.; Subbiah V.; Shetty H. S. Genetic diversity and antifungal activity of species of *Pestalotiopsis* isolated as endophytes from medicinal plants. *Fungal Divers*., **2007**, *24*, 37-54.

[8] Tejesvi M. V.; Kini K. R.; Prakash H. S.; Subbiah V.; Shetty H. S. Antioxidant, antihypertensive, and antibacterial properties of endophytic *Pestalotiopsis* species from medicinal plants. *Can. J. Microbiol*., **2008**, *54*, 769-80.

[9] Wei J. G.; Xu T. Biodiversity of endophytic fungi *Pestalotiopsis*. *Biodivers. Sci*., **2003**, *11*(2), 162-168.

[10] Zhang H. W.; Song Y. C.; Tan R. X. Biology and chemistry of endophytes. *Nat. Prod. Rep*., **2006**, *23*, 753-771.

[11] Xu J.; Kjer J.; Sendker J.; Wray V.; Guan H.; Edrada R.; Lin W.; Wu J.; Proksch P. Chromones from the Endophytic Fungus *Pestalotiopsis* sp. Isolated from the Chinese Mangrove Plant *Rhizophora mucronata*. *J. Nat. Prod*., **2009**, *72*, 662-665.

[12] Liu L.; Tian R.; Liu S.; Chen X.; Guo L.; CheY. Pestaloficiols A-E, bioactive cyclopropane derivatives from the plant endophytic fungus *Pestalotiopsis fici*. *Bioorg. Med. Chem*., **2008**, *16*, 6021-6026.

[13] Liu L.; Liu S.; Niu S.; Guo L.; Chen X.; Che Y. Isoprenylated Chromone Derivatives from the Plant Endophytic Fungus *Pestalotiopsis fici*. *J. Nat. Prod*., **2009**, *72*, 1482-1486.

[14] Liu S.; Liu L. Isoprenylated chromones from the plant endophytic fungus *Pestalotiopsis fici*. *Mycosystema*, **2010**, *29*(4), 582-587.

[15] Li E.; Tian R.; Liu S.; Chen X.; Guo L.; Che Y. Pestalotheols A-D, Bioactive Metabolites from the Plant Endophytic Fungus *Pestalotiopsis theae*. *J. Nat. Prod*., **2008**, *71*, 664-668.

[16] Klaiklay S.; Rukachaisirikul V.; Tadpetch K.; Sukpondma Y.; Phongpaichit S.; Buatong J.; Sakayaroj J. Chlorinated chromone and diphenyl ether derivatives from the mangrove-derived fungus *Pestalotiopsis* sp. PSU-MA69. *Tetrahedron*, **2012**, *68*, 2299-2305.

[17] Strobel G.; Ford E.; Worapong J.; Harper J. K.; Atta M.A.; Grant D. M.; Fung P. C.W.; Chau R. M. W. Isopestacin, an isobenzofuranone from *Pestalotiopsis microspora*, possessing antifungal and antioxidant activities. *Phytochemistry*, **2002**, *60*, 179-183.

[18] Harper J. K.; Arif A. M.; Ford E. J.; Strobel G. A.; Porco J. A.; Tomer D.P.; Oneill K. L.; Heider E. M.; Grant. M. Pestacin: a 1, 3-dihydro isobenzofuran from *Pestalotiopsis microspora* possessing antioxidant and antimycotic activities. *Tetrahedron*, **2003**, *59*, 2471-2476.

[19] Ding G.; Zheng Z.; Liu S.; Zhang H.; Guo L.; Che Y. Photinides A-F, Cytotoxic Benzofuranone-Derived γ-Lactones from the Plant Endophytic Fungus *Pestalotiopsis photiniae*. *J. Nat. Prod*., **2009**, *72*, 942-945.

[20] Ding G.; Liu S.; Guo L.; Zhou Y.; Che Y. Antifungal Metabolites from the Plant Endophytic Fungus *Pestalotiopsis foedan*. *J. Nat. Prod*., **2008**, *71*, 615-618.

[21] Xu J.; Kjer J.; Sendker J.; Wray V.; Guan H.; Edrada R.; Müller W. E. G.; Bayer M.; Lin W.; Wu J.; Proksch P. Cytosporones, coumarins, and an alkaloid from the endophytic fungus *Pestalotiopsis* sp. isolated from the Chinese mangrove plant *Rhizophora mucronata*. *Bioorg. Med. Chem*., **2009**, *17*, 7362-7367.

[22] Yang X. L.; Zhang S.; Song S. J.; Zhang Y.; Luo D. Q.; Zhang M. A New Biphenyl from the Fermentation Broth of Plant Endophytic Fungus *Pestalotiopsis zonata* isolated from *Cyrtotachys lakka*. *Chin. J. Nat. Med*., **2011**, *9*(2), 0101-0104.

[23] Rukachaisirikul V.; Rodglin A.; Phongpaichit S.; Buatong J.; Sakayaroj J. α-Pyrone and seiricuprolide derivatives from the mangrove-derived fungi *Pestalotiopsis* spp. PSU-MA92 and PSU-MA119. *Phytochemistry Lett*., **2012**, *5*(1), 13-17.

[24] Li J.; Wu X.; Ding G.; Feng Y.; Jiang X.; Guo L.; Che Y. α-Pyrones and Pyranes from the Plant Pathogenic Fungus *Pestalotiopsis scirpina*. *Eur. J. Org. Chem*., **2012**, 2445-2452.

[25] Liu L.; Liu S.; Jiang L.; Chen X.; Guo L.; Che Y. Chloropupukeananin, the First Chlorinated Pupukeanane Derivative, and Its Precursors from *Pestalotiopsis fici*. *Org. Lett*., **2008**, *10*(7), 1397-1400.

[26] Li E.; Jiang L.; Guo L.; Zhang H.; Che Y. Pestalachlorides A-C, antifungal metabolites from the plant endophytic fungus *Pestalotiopsis adusta*. *Bioorg. Med. Chem*., **2008**, *16*, 7894-7899.

[27] Deyrup S. T.; Swenson D. C.; Gloer J. B.; Wicklow D. T. Caryophyllene Sesquiterpenoids from a Fungicolous Isolate of *Pestalotiopsis disseminate*. *J. Nat. Prod*., **2006**, *69*, 608-611.

[28] Pulici M.; Sugawara F.; Koshino H.; Uzawa J.; Yoshida S. A New Isodrimeninol from *Pestalotiopsis* sp. *J. Nat. Prod*., **1996**, *59*, 47-48.

[29] Pulici M.; Sugawara F.; Koshino H.; Uzawa J.; Yoshida S. Pestalotiopsins A and B: New Caryophyllenes from an Endophytic Fungus of *Taxus brevifolia*. *J. Org. Chem*., **1996**, *61*, 2122-2124.

[30] Pulici M.; Sugawara F.; Koshino H.; Okada G.; Esumi Y.; Uzawa J.; Yoshida S. Metabolites of *Pestalotiopsis* spp., Endophytic Fungi of *Taxus brevifolia*. *Phytochemistry*, **1997**, *46*(2), 313-319.

[31] Luo D. Q.; Deng H. Y.; Yang X. L.; Shi B. Z.; Zhang J. Z. Oleanane-Type Triterpenoids from the Endophytic Fungus *Pestalotiopsis clavispora* Isolated from the Chinese Mangrove Plant *Bruguiera sexangula*. *Helv. Chim. Acta*, **2011**, *94*, 1041-1047.

[32] Deng H. Y.; Xing J. G.; Luo D. Q. Metabolites of endophytic fungus *Pestalotiopsis clavispora* isolated from the stem of *Bruguiera sexangula*. *Mycosystema*, **2011**, *30*(2), 263-267.

[33] Liu L.; Liu S.; Chen X.; Guo L.; Che Y. Pestalofones A-E, bioactive cyclohexanone derivatives from the plant endophytic fungus *Pestalotiopsis fici*. *Bioorg. Med. Chem*., **2009**, *17*, 606-613.

[34] Liu S. C.; Ye X.; Guo L. D.; Liu L. Cytotoxic Isoprenylated Epoxycyclohexanediols from the Plant Endophyte *Pestalotiopsis fici*. *Chin. J. Nat. Med*., **2011**, *9*(5), 0374-0379.

[35] Li J. Y.; Harpper J. K.; Grand D. M.; Tombec B. O.; Bashyal B.; Hess W. M.; Strobel G. A. Ambuic acid, a highly functionalized cyclohexenone with antifungal activity from *Pestalotiopsis* spp. and *Monochaetia* sp. *Phytochemistry*, **2001**, *56*, 463-468.

[36] Ding G.; Li Y.; Fu S. B.; Liu S.; Wei J.; Che Y. Ambuic Acid and Torreyanic Acid Derivatives from the Endolichenic Fungus *Pestalotiopsis* sp. *J. Nat. Prod*., **2009**, *72*, 182-186.

[37] Li J. Y.; Strobel G. A. Jesterone and hydroxy-jesterone antioomycete cyclohexenone epoxides from the endophytic fungus *Pestalotiopsis jesteri*. *Phytochemistry*, **2001**, *57*, 261-265.

[38] Ding G.; Jiang L. H.; Guo L. D.; Chen X.; Zhang H.; Che Y. Pestalazines and Pestalamides, Bioactive Metabolites from the Plant Pathogenic Fungus *Pestalotiopsis theae*. *J. Nat. Prod*., **2008**, *71*, 1861-1865.

[39] Li J.; Li L.; Si Y.; Guo L.; Che Y. Virgatolides A-C, Benzannulated Spiroketals from the Plant Endophytic Fungus *Pestalotiopsis virgatula*. *Org. Lett*., **2011**, *13*(10), 2670-2673.

[40] Kesting J. R.; Olsen L.; Staerk D.; Tejesvi M. V.; Kini K. R.; Prakash H. S.; Jaroszewski J. W. Production of Unusual Dispiro Metabolites in *Pestalotiopsis virgatula* Endophyte Cultures: HPLC-SPE-NMR, Electronic Circular Dichroism, and Time-Dependent Density-Functional Computation Study. *J. Nat. Prod*., **2011**, *74*, 2206-2215.

[41] Liu L.; Li Y.; Liu S.; Zheng Z.; Chen X.; Zhang H.; Guo L.; Che Y. Chloropestolide A, an Antitumor Metabolite with an Unprecedented Spiroketal Skeleton from *Pestalotiopsis fici*. *Org. Lett*., **2009**, *11*(13), 2836-2839.

[42] Liu L.; Niu S.; Lu X.; Chen X.; Zhang H.; Guo L.; Che Y. Unique metabolites of *Pestalotionpsis fici* suggest a biosynthetic hypothesis involving a Diels-Alder reaction and then mechanistic deversifiction. *Chem. Commun*., **2010**, *46*, 460-462.

[43] Liu L.; Bruhn T.; Guo L.; Gotz D. C. G.; Brun R.; Stich A.; Che Y.; Bringmann G. Chloropupukeanolides C-E: Cytotoxic Pupukeanane Chlorides with a Spiroketal Skeleton from *Pestalotiopsis fici*. *Chem. Eur. J*., **2011**, *17*, 2604 - 2613.

[44] Lee J. C.; Strobel G. A.; Lobkovsky E.; *et al.* Torreyanic Acid: A Selectively Cytotoxic Quinone Dimer from the Endophytic Fungus *Pestalotiopsis microspora*. *J. Org. Chem*., **1996**, *61*, 3232-3233.

[45] Akira K.; Masayuki K.; Kenichi H.; Clardy J. Biosynthesis of hetero-polysaccharides by *Pestalotiopsis microspora* from various monosaccharides as carbon source. *Carbohyd. Polym*., **2003**, *54*, 381-383.

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