Pigments of fungi (macromycetes)

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This review surveys the chemical, biological and mycological literature dealing with the isolation, structure elucidation, biological activities, and synthesis of pigments manufactured by those fungi that produce conspicuous fruiting bodies (macromycetes).

1 Introduction

This review, like its predecessors,[1–5] surveys the chemical, biological and mycological literature dealing with the isolation, structure elucidation, biological activities, and synthesis of pigments manufactured by those fungi that produce conspicuous fruiting bodies (macromycetes). Also included, as before, are some pigments from slime moulds (myxomycetes) and, in certain circumstances, pigments produced by fungi grown in mycelial culture and some colourless metabolites where they are significant. This review covers the literature from June 2003 to December 2009, and compounds are grouped according to their perceived biosynthesis.

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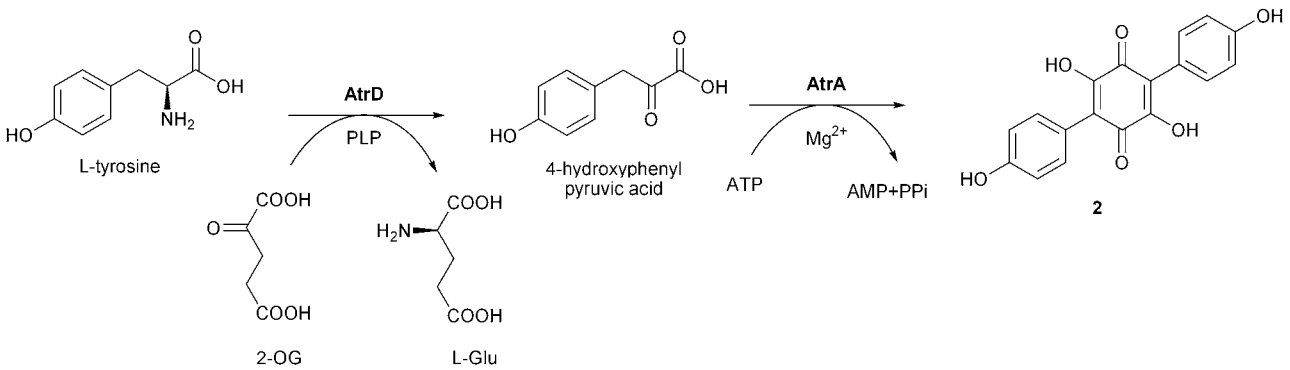
2 Compounds from the shikimate–chorismate pathway

2.1 Compounds derived from arylpyruvic acids

2.1.1 Terphenylquinones. Terphenyls are aromatic hydrocarbons consisting of a chain of three benzene rings. There are three isomers in which the terminal rings are *o*-, *m*-, or *p*-substituents of the central ring. Most of the natural terphenyls are *p*-terphenyl derivatives. Very few *m*-terphenyl derivatives occur naturally, and *o*-terphenyls have not been found in Nature. *p*-Terphenyl compounds, which have so far only been present in lichens and fungi, are a large class of fungal pigments. The isolation, structure elucidation, biological activities, transformation, and total synthesis of terphenyl derivatives from natural sources since 1877 has been extensively reviewed.[6]

The isolation of polyporic acid **1**,[7,8] atromentin **2**,[9] and thelephoric acid **3**[10] early in the 1870s marked the start of the chemical investigation of fungal pigments. Atromentin **2** is the central terphenylquinone intermediate for a prominent and widely occurring class of basidiomycete pigments. Biochemical characterization of a multi-domain biosynthetic enzyme for basidiomycete secondary metabolism – namely the tri-domain enzyme atromentin synthetase AtrA from *Tapinella panuoides*, which adenylates and dimerizes 4-hydroxyphenylpyruvic acid into atromentin **2** (Scheme 1) – has been reported. Also, the L-tyrosine:2-oxoglutarate aminotransferase AtrD, which provides the substrate for this dimerization step (Scheme 1), has been characterized. The genes atrA and atrD were cloned and found to be clustered within one genetic locus.[11]

Sarcodonins α **4**, β **5**, and γ **6**, episarcodonin **7**, and episarcodonins α **8** and β **9** have been isolated from the EtOAc extract of the fruiting bodies of *Sarcodon leucopus*.[12] From the EtOH extract of the fruiting bodies of the same fungus, a mixture of two violet pigments, sarcoviolin α **10** and episarcoviolin α **11**, were obtained.[12] Sarcodonins α **4** and γ **6**, episarcodonin **7**, a mixture of **10** and **11** (sarcoviolins), and sarcodonin **12** were found to be cytotoxic at a concentration of 5×10^{-5} M against NCI-H460 (lung), MCF7 (breast), and SF-268 (CNS) cells. In particular, **6**, **7** and **12** showed the highest cytotoxicity towards



Scheme 1 Atromentin biosynthesis. L-Tyrosine is deaminated to 4-hydroxyphenylpyruvic acid by the PLP-dependent transaminase AtrD, which transfers the amino group onto 2-oxoglutaric acid (2-OG). Condensation of two molecules of 4-hydroxyphenylpyruvic acid to atromentin is catalyzed by the quinone synthetase AtrA.

SF-268 cells, with 93, 95 and 96% of cells killed, respectively. Sarcoviolins significantly reduced the growth of all cell lines at 10^{-4} M (MCF7 totally blocked). A mixture of sarcodonins was tested for anti-HIV activity and showed EC_{50} 5 μg ml^{-1} (the concentration at which the viral antigen p24 or progeny virus in infected cell cultures is reduced by 50%).[12]

Episarcodonin **7**, episarcodonin α **8**, and episarcodonin β **9** were characterized as the *N*-oxide epimers of **4**, **5**, and **12**, respectively, by a molecular mechanics study, carried out using the molecular dynamics methodology and assuming the obtained energy minima as the preferred conformations in solution. Examination of stereomodels of **4** and **8** showed that an intramolecular hydrogen bond between the hydroxyl proton and the oxygen atom of the *N*-oxide function (OH···ON) played an important role in the *N*-epimerisation of **4** to **8**. A possible mechanism to explain the role of the bridge proton in the *N*-epimerisation of **4** to **8** resembles the Cope β-elimination of *N*-oxides, followed by a stereoselective retro-Cope of the unstable intermediate, to give the isomer **8** as the final stable product.[12]

Sarcodonin δ **13** and two known *p*-terphenyl metabolites **14** and **15** were isolated from the fruiting bodies of *Sarcodon scabrosus*.[13] Sarcodan **16** and three known terphenyls co-occur in the Chinese mushroom *S. laevigatum*.[14] Hydnellins A **17** and B **18**, and sarcodonin δ **13** have been found in methanol extracts of the fruiting bodies of the inedible mushroom *Hydnellum suaveolens*.[15] Sarcodonin δ **13** was also found in *H. geogerirum*.

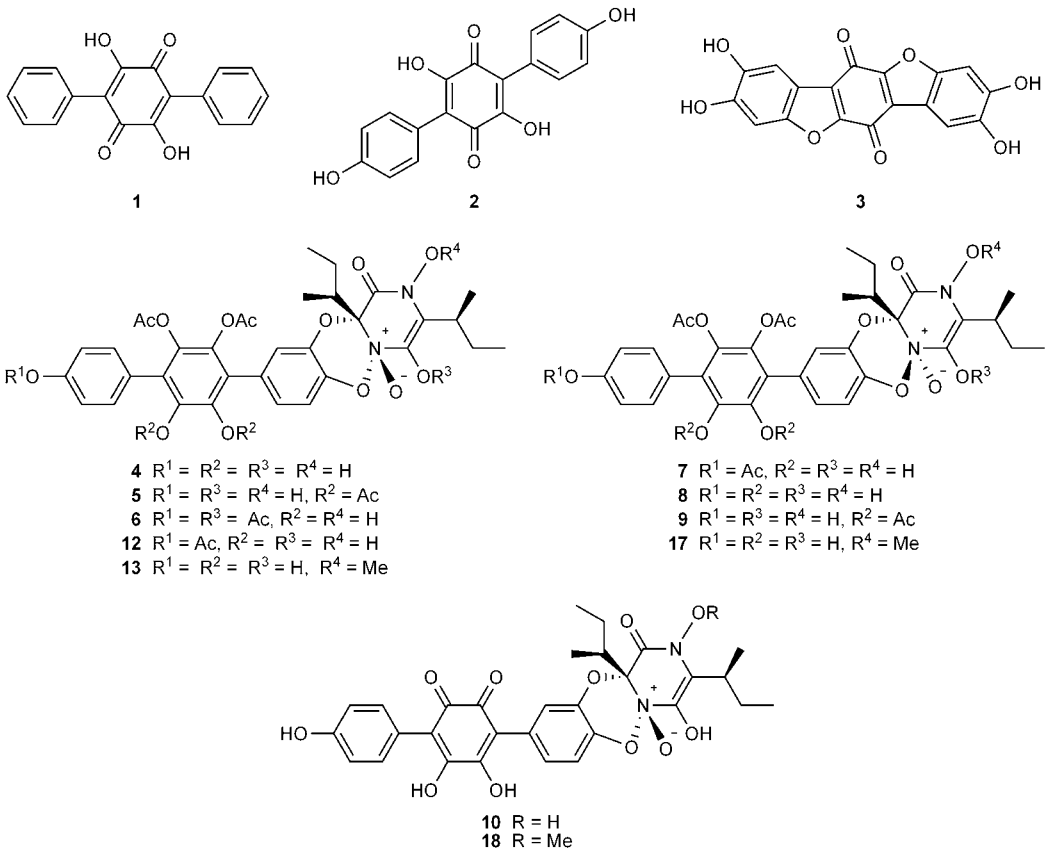
The *p*-terphenyl derivatives named curtisians A–V **19–40**, known to be free-radical scavengers, together with previously reported kynapcin-12 **41**, were found in the methanolic extract of fruiting bodies of *Paxillus curtisii*.[16–20] Curtisians A–D **19–22** were first described by Yoo from Korean *P. curtisii* early in 2000,[20] of which the structure of **21** was only partially determined, since the location of four substituents on the *p*-terphenyl was unclear. Nonetheless, Gill had not covered these curtisians in the previous review of this area.[1] To determine the absolute configuration of curtisians E–H **23–26**, a mixture of curtisians E–H was saponified with potassium hydroxide in methanol, followed by methylation and acetylation to afford 3-acetoxy-*n*-butyric acid methyl ester.[17] It was analyzed by GC–MS on a chiral column with authentic samples (each 3*R*- and 3*S*-acetoxy-*n*-butyric acid methyl ester) derived from 3*R*- and 3*S*-hydroxy-*n*-butyric acid to give the chromatograms.

Zhong-Yu Zhou

Zhong-Yu Zhou was born in Hunan province, P. R. China, in 1982, and has carried out postgraduate and doctoral research at Kunming Institute of Botany, Chinese Academy of Sciences, since 2005, under the supervision of Professor Ji-Kai Liu. She is currently studying the isolation, structure elucidation, bioactivities and chemical modification of natural products.

Ji-Kai Liu

Ji-Kai Liu has been a professor at Kunming Institute of Botany since 1997. He acquired his Ph.D. degree at Lanzhou University in 1988. From 1993 to 1994 he worked as a research fellow of Alexander von Humboldt at the University of the Saarland in Germany. Then he worked as a research scientist at the Pharma Research Center of Bayer AG in Germany. His field of interest concerns natural bioactive compounds from higher fungi. He has published over 180 peer-reviewed articles in international journals. He is the author of the book Mycochemistry and also one of the inventers for ten patents.

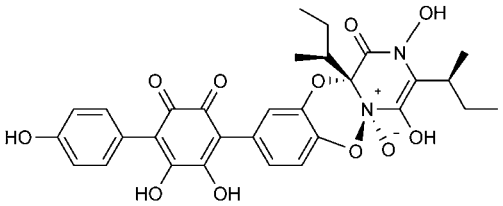


Consequently, the absolute configuration at C3a,3b of the side-chain of curtisians E–H was established to be *S*.[17]

The Thelephoraceae family has been shown to be a rich source of *p*-terphenyl compounds. Thelephantins D–H **42–46** from the inedible mushroom *Thelephora aurantiotincta*,[21] thelephantins I–N **47–52** from the inedible mushroom *Hydnellum caeruleum*,[22] terrestrins A–G **53–59** from the inedible mushroom *Thelephora terrestris*,[23] vialinins A **53** (same as terrestrin A)[24] and B **60** from an edible mushroom *T. vialis*,[25,26] and aurantiotinin A **61** from *T. aurantiotincta*,[27] along with related known compounds, have been reported. The structure of terrestrin A **53** was confirmed by X-ray crystallographic analysis. Vialinins A **53** and B **60** strongly inhibited tumour necrosis factor (TNF-α) production in rat basophilic leukemia (RBL-2H3) cells (IC_{50} values of 0.09 nM and 0.02 nM, respectively).[25,28] *p*-Terphenyls are attractive for their antioxidant activities. Therefore, 2,2-diphenyl-1-picryhydrazyl (DPPH) radical scavenging activities of ten natural *p*-terphenyl derivatives from three edible mushrooms (*Thelephora ganbajun*, *T. aurantiotincta* and *Boletopsis grisea*) indigenous to China were investigated and compared with BHA and α-tocopherol.[29] Vialinin A **53** showed strong DPPH free-radical-scavenging activity (EC_{50} 14.0 μM), almost equal to that of butylated hydroxytoluene (BHT, EC_{50} value of 10.0 μM). The proposed DPPH radical-scavenging mechanism of vialinin A was also reported from its conversion into product **62** during the DPPH radical-scavenging reaction.[26]

Thelephantin G, whose structure was revised from **45** to **63** by total synthesis (Schemes 2 and 3), strongly inhibited TNF-α production in RBL-2H3 cells (IC_{50} value of 3.5 μM), while a mixture of **45** and its regioisomer **64** showed no such activity.[30] The key steps of total synthesis of thelephantin G involved a double Suzuki–Miyaura coupling and an esterification reaction. By a similar strategy, the synthesis of ganbajunins D **65** and E **66** was also accomplished (Scheme 4).[30] The total synthesis of vialinin A **53** was achieved from sesamol in 11 steps with 28% overall yield.[31] The key reactions included a double Suzuki coupling of an electron-rich aryl triflate with phenylboronic acid and an oxidative deprotection of bis-MOM ether (Scheme 5).[31] In addition, the proposed structure of ganbajunin C **67** was also synthesized by a similar strategy (Scheme 6). However, the spectral data of synthetic **67** were not in accordance with those of reported ganbajunin C, which suggested the need to reinvestigate the structure of natural ganbajunin C.[31] The same research group also reported the total synthesis of vialinin B **60** in 11 steps with 18% overall yield from a known sesamol derivative (Scheme 7).[32]

Kehokorins A–C **75–77** are yellow pigments occurring in field-collected fruiting bodies of the myxomycete *Trichia favoginea* var. *persimilis*.[34] Kehokorins D **78** and E **79** have been isolated from field-collected fruiting bodies of *T. favoginea*.[35] Kehokorin A is a α-L-rhamnopyranoside of kehokorin B, and kehokorins A, D and E showed cytotoxic activity against HeLa cells with IC_{50} values of 1.5, 6.1 and 4.5 μg ml^{-1}, respectively.[34,35]



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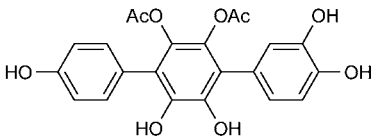

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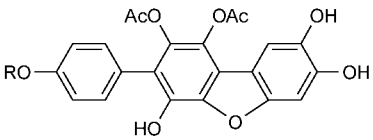
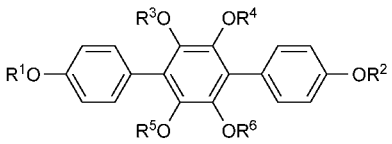
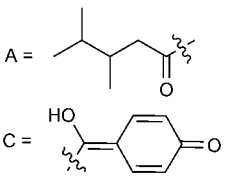
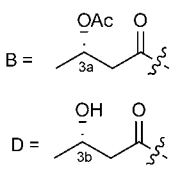
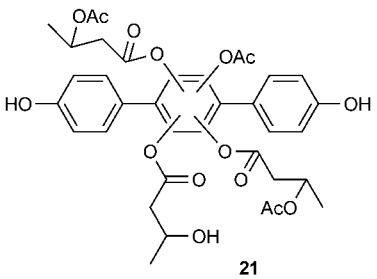


15 R = H
16 R = Ac



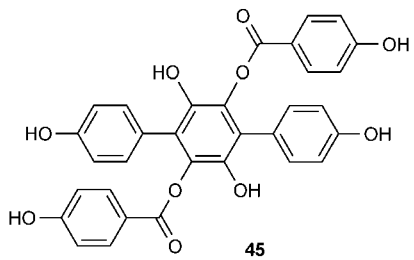






21

19 $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Ac$, $R^6 = PhCO$
20 $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Ac$, $R^6 = PhCH_2CH_2CO$
22 $R^1 = R^2 = H$, $R^3 = R^4 = Ac$, $R^5 = CH_3CH(OH)CH_2CO$, $R^6 = PhCH_2CH_2CO$
23 $R^1 = R^2 = H$, $R^3 = PhCH_2CH_2CO$, $R^4 = R^5 = D$, $R^6 = Ac$
24 $R^1 = R^2 = H$, $R^3 = R^6 = B$, $R^4 = R^5 = D$
25 $R^1 = R^2 = H$, $R^3 = PhCH_2CH_2CO$, $R^4 = R^5 = R^6 = D$
26 $R^1 = R^2 = H$, $R^3 = R^5 = D$, $R^4 = B$, $R^6 = PhCH_2CH_2CO$
27 $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = B$, $R^6 = D$
28 $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = B$, $R^6 = PhCH_2CH_2CO$
29 $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = D$, $R^6 = PhCH_2CH_2CO$
30 $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = D$, $R^6 = Ac$
31 $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = R^6 = B$
32 $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = B$, $R^6 = Ac$
33 $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CH_3CH_2CH_2CO$, $R^6 = Ac$
34 $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = PhCH_2CH_2CO$, $R^6 = Ac$
35 $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = PhCH_2CH_2CO$, $R^6 = PhCO$
36 $R^1 = R^2 = R^3 = R^6 = H$, $R^4 = R^5 = PhCH_2CH_2CO$
37 $R^1 = R^2 = R^3 = R^6 = H$, $R^4 = CH_3CH_2CH_2CO$, $R^5 = PhCH_2CH_2CO$
38 $R^1 = R^2 = R^3 = R^6 = H$, $R^4 = B$, $R^5 = PhCO$
39 $R^1 = R^2 = H$, $R^3 = R^6 = Ac$, $R^4 = R^5 = D$
40 $R^1 = R^2 = H$, $R^3 = Ac$, $R^4 = PhCH_2CH_2CO$, $R^5 = R^6 = D$
41 $R^1 = R^2 = R^3 = R^6 = H$, $R^4 = R^5 = Ac$
42 $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = PhCH_2CO$, $R^6 = CH_3CH_2CH_2CO$
43 $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = PhCO$, $R^6 = PhCH_2CO$
44 $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = PhCH_2CO$, $R^6 = A$
48 $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = R^6 = PhCO$
49 $R^1 = R^2 = R^4 = H$, $R^3 = R^5 = R^6 = PhCO$
50 $R^1 = R^2 = H$, $R^3 = R^5 = R^6 = PhCO$, $R^4 = Ac$
53 $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = R^6 = PhCH_2CO$
54 $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = R^6 = CH_3CH_2CH_2CO$
55 $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = PhCH_2CO$, $R^6 = CH_3CH_2CH_2CO$
56 $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = PhCH_2CO$, $R^6 = Ac$
61 $R^1 = C$, $R^2 = PhCH_2CO$, $R^3 = R^4 = R^5 = R^6 = H$



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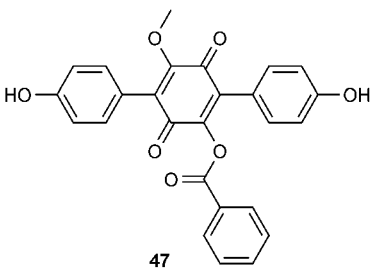

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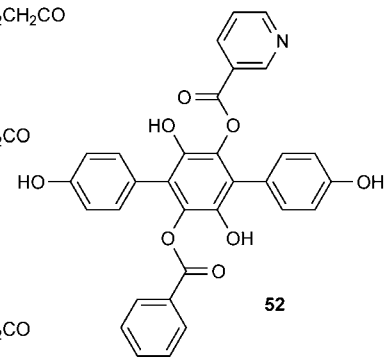

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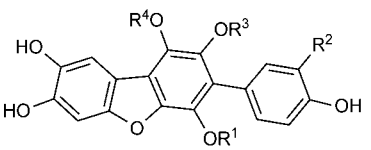
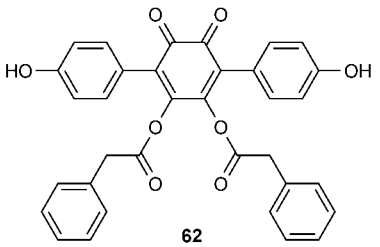


46 $R^1 = p\text{-}HOC_6H_4CO$, $R^2 = R^3 = H$, $R^4 = PhCH_2CO$
51 $R^1 = R^4 = PhCO$, $R^2 = R^3 = H$
57 $R^1 = R^3 = R^4 = PhCH_2CO$, $R^2 = OH$
58 $R^1 = R^4 = PhCH_2CO$, $R^2 = H$, $R^3 = Ac$
59 $R^1 = p\text{-}HOC_6H_4CO$, $R^2 = H$, $R^3 = R^4 = PhCH_2CO$
60 $R^1 = R^2 = H$, $R^3 = R^4 = PhCH_2CO$



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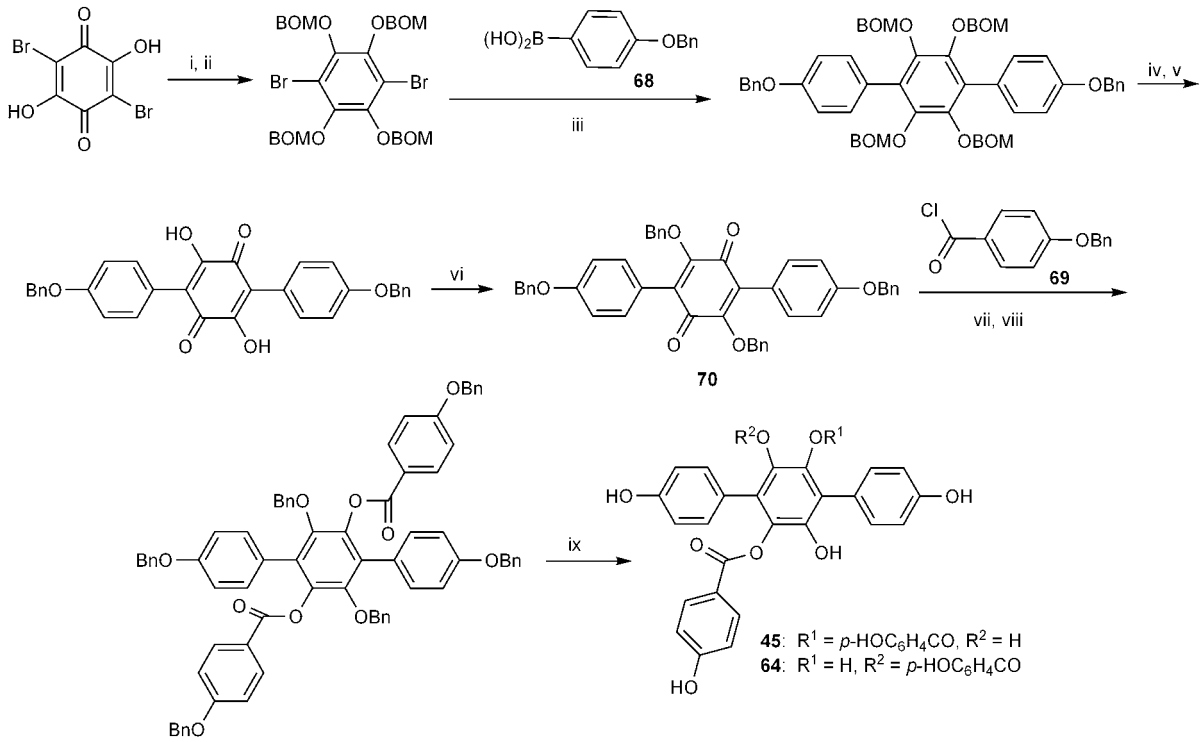
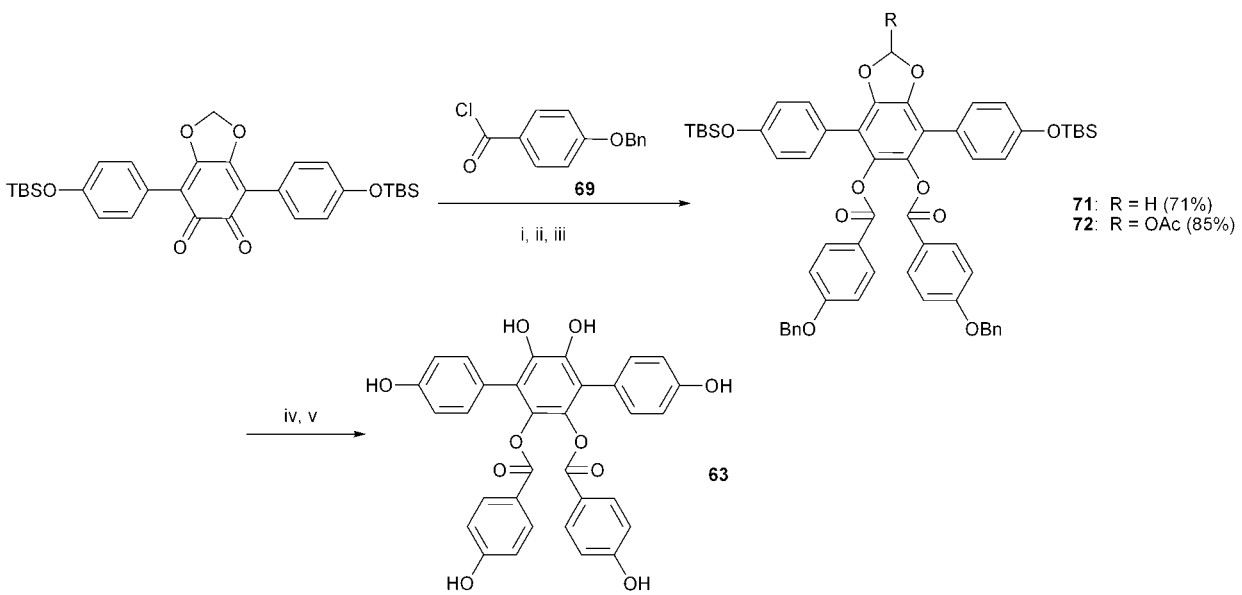
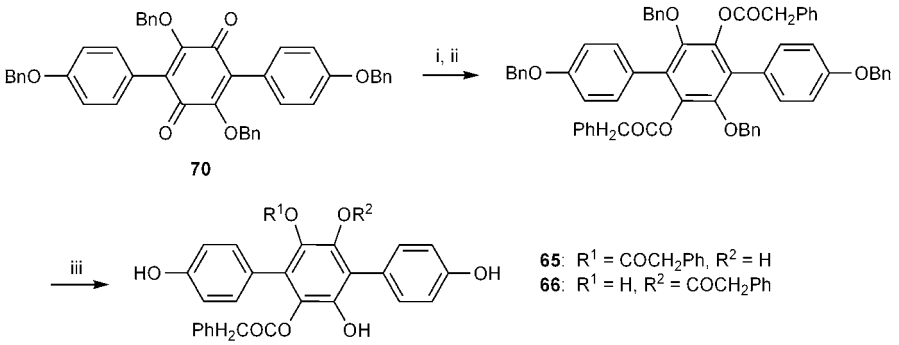


Scheme 2 *Reagents and conditions*: i, $Na_2S_2O_4$, aq. EtOAc, rt; ii, MOMCl, NaH, DMF, 0 °C (80%); iii, **68** (2.3 mol equiv), $Pd(OAc)_2$ (0.05 mol equiv), Ph_3P (0.15 mol equiv), Na_2CO_3, aq. 1-propanol, 100 °C, 4 h; iv, HCl, CH_2Cl_2–MeOH, rt; v, O_2, DMF, rt (90%); vi, BnBr, K_2CO_3, *n*-Bu_4NI, DMF, 80 °C (72%); vii, $Na_2S_2O_4$, EtOAc–aq. MeOH, rt; viii, *n*-BuLi, **69**, THF, from −78 to 0 °C; ix, H_2, $Pd(OH)_2$, THF–MeOH, rt (86%).

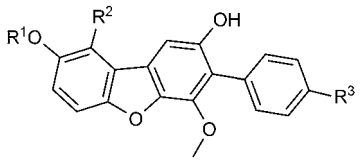


Scheme 3 *Reagents and conditions*: i, $Na_2S_2O_4$, EtOAc–aq. MeOH, rt; ii, *n*-BuLi, **69**, THF, from −78 to 0 °C; iii, lead tetraacetate, benzene, 80 °C; iv, 10% HCl–MeOH, CH_2Cl_2, rt; v, H_2, $Pd(OH)_2$, THF–MeOH, rt (81%).

Induction of cellular phase 2 detoxifying enzymes is associated with cancer preventive potential, while quinone reductase (QR) has been used as a prototype for anticarcinogenic phase 2 enzymes. Polyozellin **82** from *Polyozellus multiplex* was found to induce phase 2 enzymes in mouse hepatoma cells and differentiation in HL-60 human promyelocytic leukemia cells. In contrast, thelephoric acid **3**, which was isolated from the same mushroom and is similar to polyozellin in its chemical structure except for the absence of two acetyl groups, was not effective in QR induction, suggesting a crucial role of the acetyl groups attached to the benzofuran dimer in the activation of phase 2 enzyme expression.[36] It was also reported that polyozellin inhibited nitric oxide production by down-regulating lipopolysaccharide (LPS)-induced activity of NF-κB and stress-activated

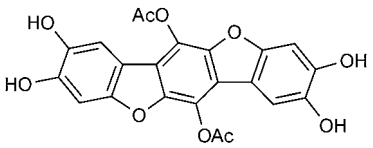


Scheme 4 *Reagents and conditions*: i, $Na_2S_2O_4$, aq. EtOAc, rt; ii, *n*-BuLi, $PhCH_2COCl$, THF, from −78 to 0 °C (73%); iii, H_2, $Pd(OH)_2$, EtOAc–CH_2Cl_2, rt (80%) (see Scheme 2 for earlier steps).



75 R^1 = α-L-Rha, R^2 = OMe, R^3 = OMe
76 R^1 = H, R^2 = OMe, R^3 = OMe
77 R^1 = R^2 = H, R^3 = OMe
78 R^1 = R^2 = R^3 = H
79 R^1 = Me, R^2 = R^3 = H

protein kinase (SAPK)/c-Jun N-terminal kinase (JNK) in RAW 264.7 cells.[37]



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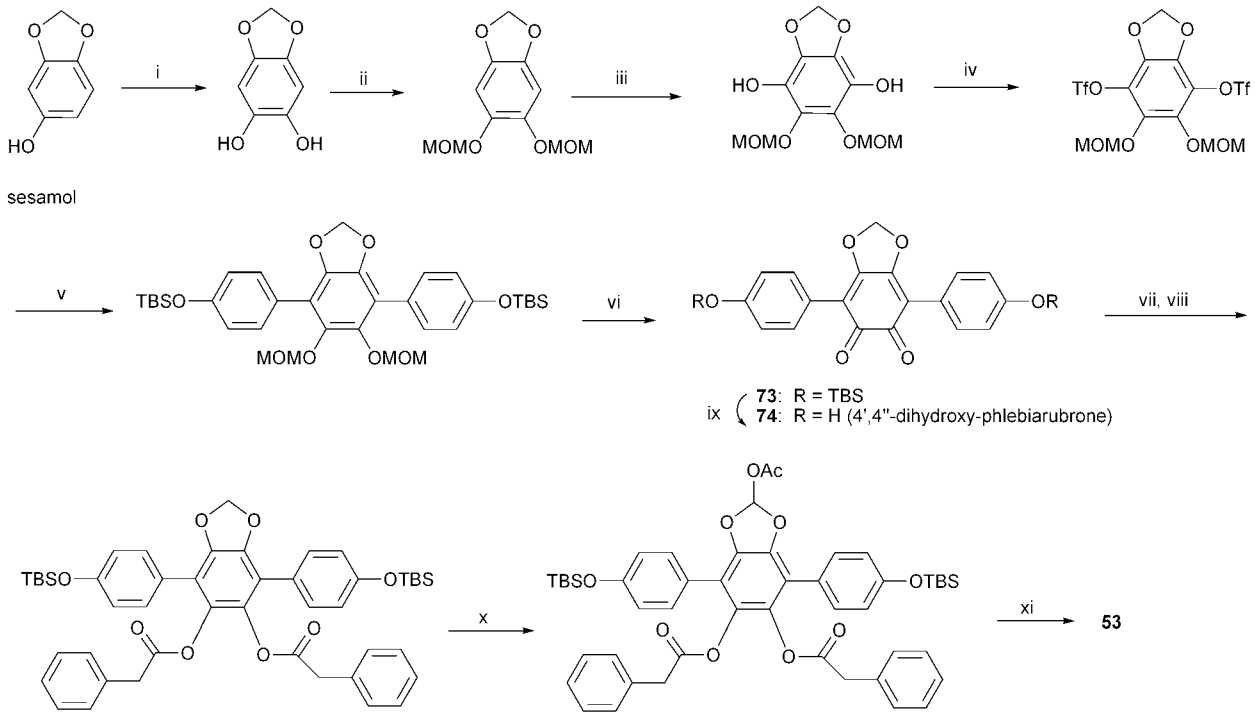
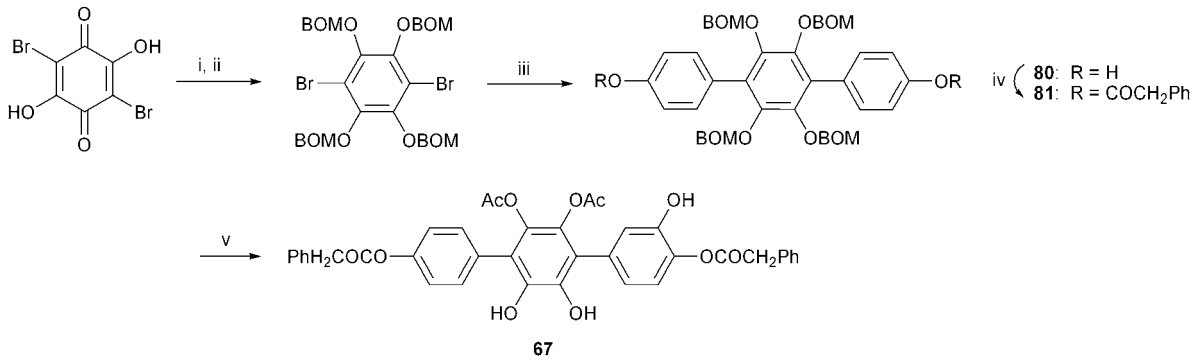
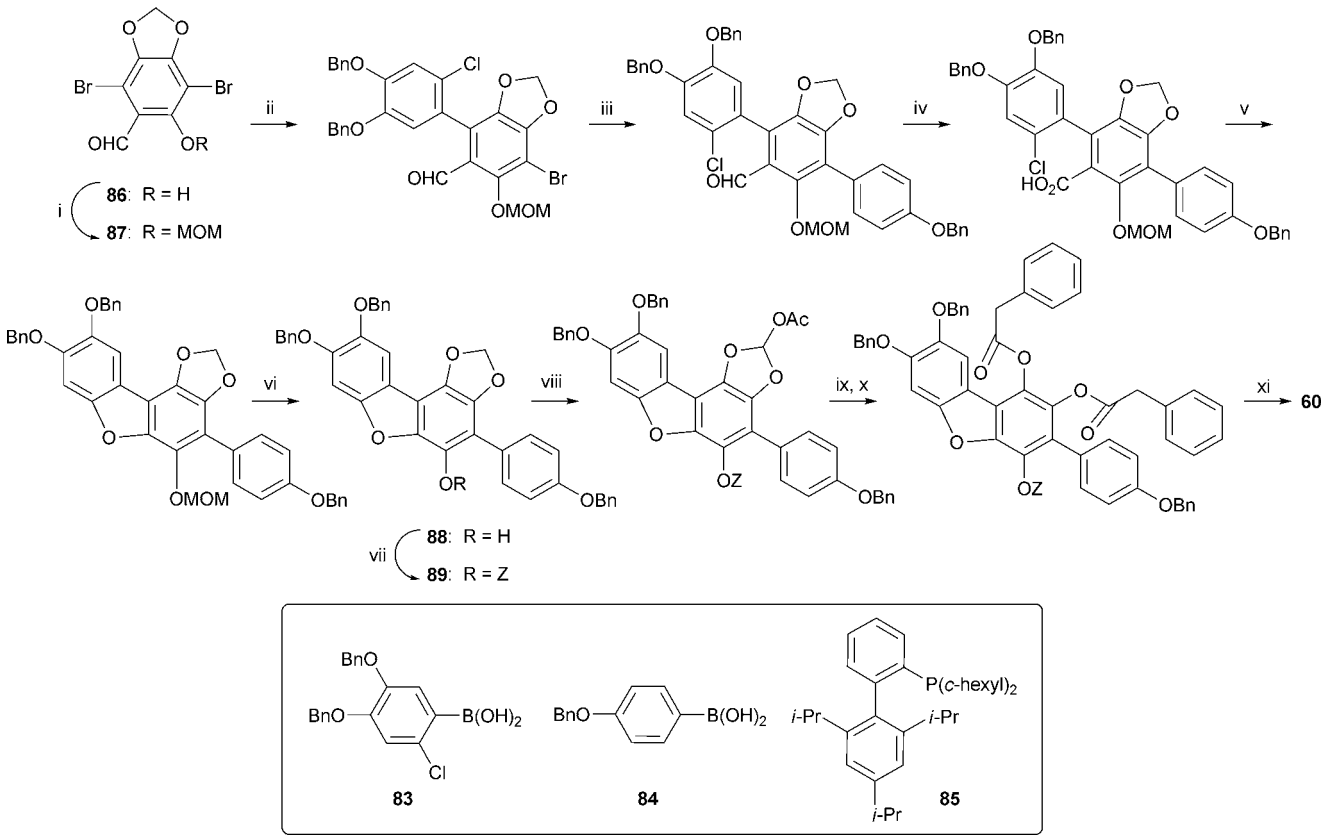
The neuroprotective mechanism of *p*-terphenyl leucomentins from the mushroom *Paxillus panuoides* was reported.[38] Leucomentins showed potent inhibition of lipid peroxidation and H_2O_2 neurotoxicity, but were free from any role as reactive oxygen



Scheme 5 *Reagents and conditions*: i, see ref. 33 (65%); ii, NaH, MOMBr, DMF, 0 °C (87%); iii, *n*-BuLi, THF, 0 °C, and then $(i\text{-PrO})_3B$, 0 °C followed by addition of H_2O_2, AcOH, 0 °C to rt (87%); iv, Tf_2O, pyridine, 0 °C (89%); v, 4-(*tert*-butyldimethylsilyloxy)phenylboronic acid, $(Ph_3P)_4Pd$, K_3PO_4, KBr, dioxane, 100 °C (96%); vi, DDQ, *p*-TsOH, benzene, 80 °C (95%); vii, 10% HCl–MeOH, CH_2Cl_2, rt (95%); viii, $Na_2S_2O_4$, EtOAc, aq. MeOH, rt; ix, $PhCH_2COCl$, *n*-BuLi, THF, from −78 to 0 °C (86%); ix, 10% HCl–MeOH, CH_2Cl_2, rt (95%); x, $Pb(OAc)_4$, benzene, 80 °C (90%); xi, 10% HCl–MeOH, CH_2Cl_2, rt (92%).

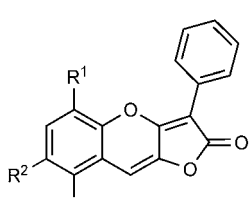


Scheme 6 *Reagents and conditions*: i, NaS_2O_4, aq. EtOAc, rt; ii, BOMBr, NaH, DMF, 0 °C (92%); iii, 4-(*tert*-butyldimethylsilyloxy)phenylboronic acid, $Pd(OAc)_2$, Ph_3P, Na_2CO_3, aq. Propanol, 100 °C (83%); iv, $PhCH_2COCl$, *n*-BuLi, THF, 0 °C (79%); v, $Pd(OH)_2$, H_2, EtOAc, methanol, rt (82%).

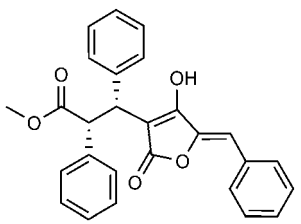


Scheme 7 *Reagents and conditions*: i, NaH, MOMBr, DMF, 0 °C (90%); ii, **83**, $Pd(OAc)_2$, K_3PO_4, Ph_3P, aq. THF, 65 °C (78%); iii, **84**, $Pd(OAc)_2$, K_3PO_4, **85**, aq. THF, 65 °C (91%); iv, *m*CPBA, KF, CH_2Cl_2, 0 °C (78%); v, Cu_2O, pyridine, 110 °C (88%); vi, HCl, CH_2Cl_2, MeOH, rt, quant; vii, Z-Cl, pyridine, CH_2Cl_2, 0 °C (89%); viii, $Pb(OAc)_4$, benzene, 80 °C (73%); ix, aq. AcOH, 60 °C; x, LHMDS, THF, −78 °C, then $PhCH_2COCl$, 0 °C (71%); xi, H_2, $Pd(OH)_2$, EtOAc, rt (89%).

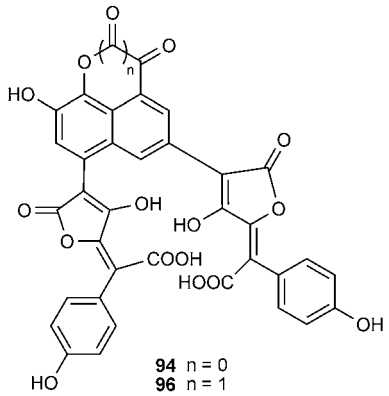
species (ROS) scavengers. Iron-mediated oxidative damage has been implicated in these processes, as a provider of ROS *via* iron. Leucomentins could chelate iron when DNA was present with iron and H_2O_2, and so inhibited DNA single-strand breakage. These results suggest that the neuroprotective action of leucomentins is dependent on their ability to chelate iron.[38] Also, *p*-terphenyl curtisians from the mushroom *Paxillus curtisii* protected cultured neuronal cells against glutamate neurotoxicity *via* iron chelation.[39]

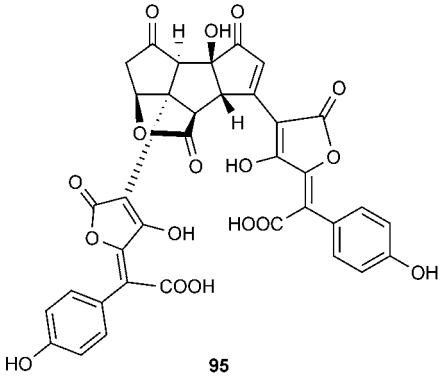


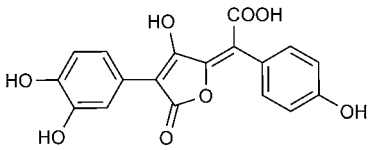
90 R^1 = OMe, R^2 = H
92 R^1 = H, R^2 = OMe

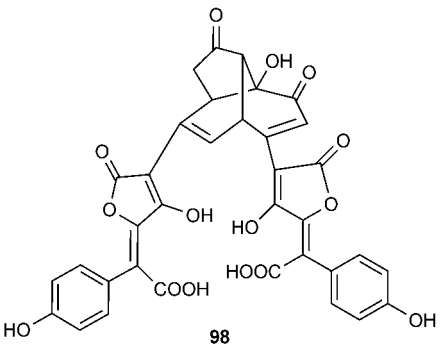


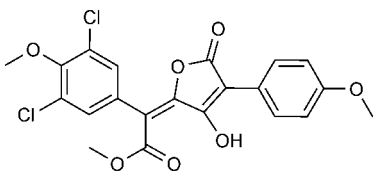
91

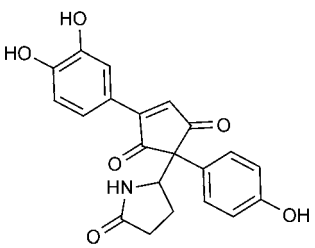


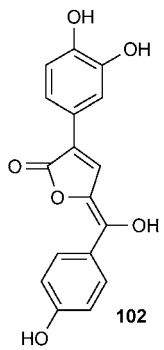


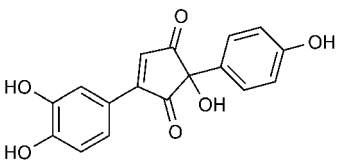


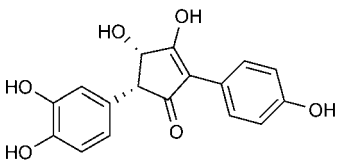






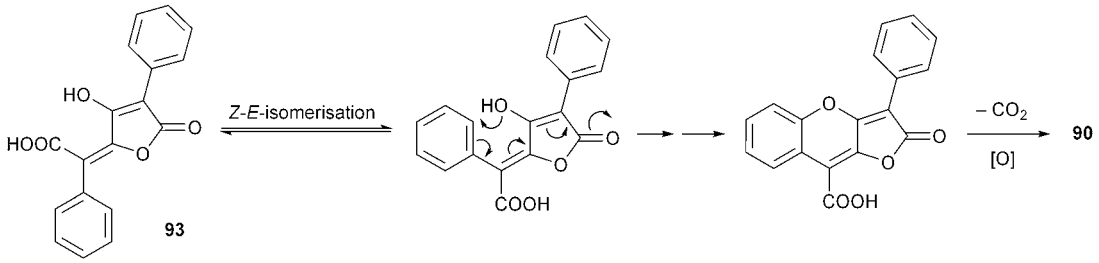






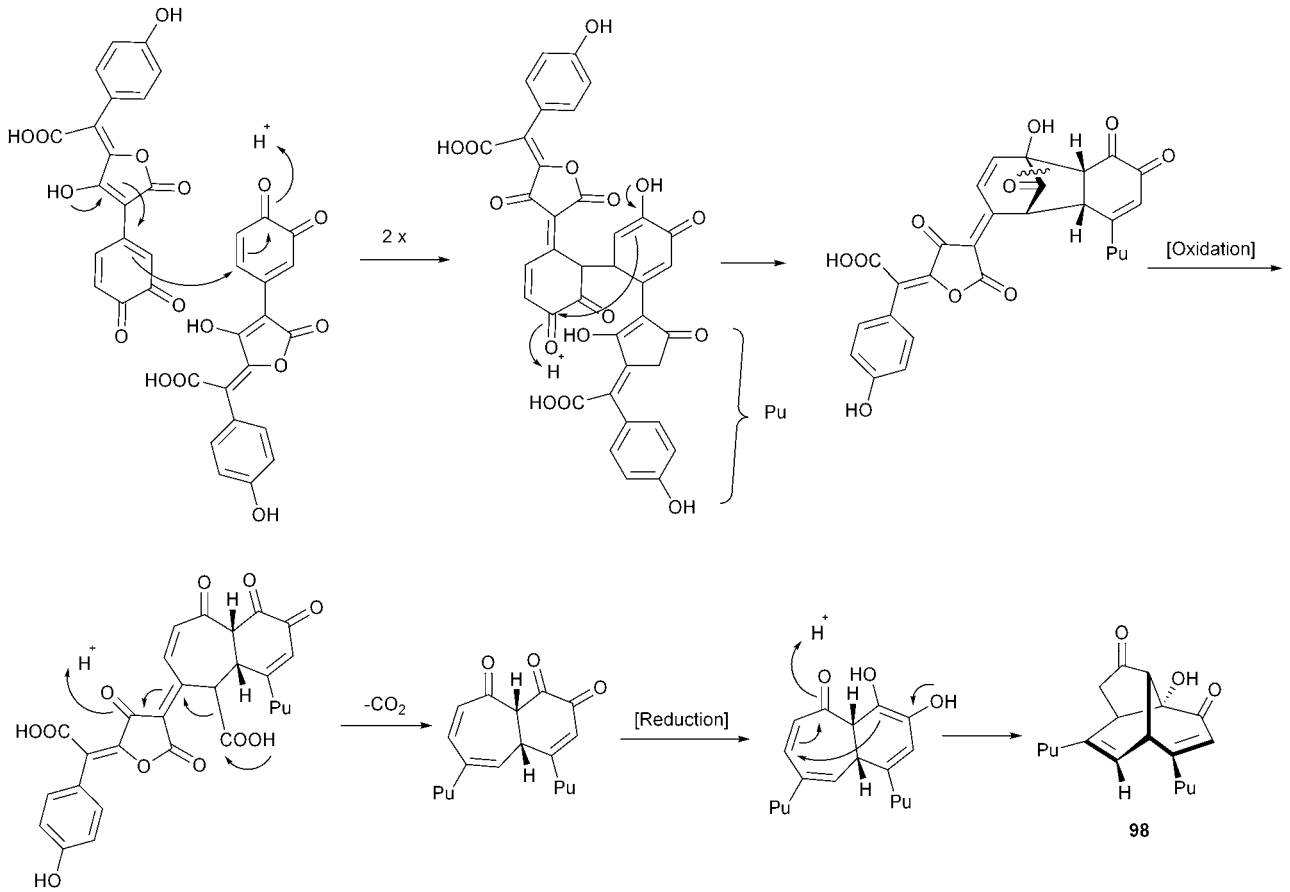
2.1.2 Pulvinic acids and related butenolides. Pulverolide **90** and pulveraven A **91** were found in the acetone extracts of the fresh fruiting bodies of *Pulveroboletus ravenelii*.[40] The structure of pulverolide has now been corrected to **92** by total synthesis.[41] A possible biosynthetic pathway of pulverolide from vulpinic acid **93** was proposed, as shown in Scheme 8.

Two major pigments, norbadione A **94** and sclerocitrin **95**, have been isolated from *Scleroderma citrinum* (Common Earthball), while small amounts of badione A **96** and xerocomic acid **97** could be detected by HLPC.[42] In the same paper, compounds **94**, **95**, **97** and chalcitrin **98** were also reported from *Chalciporus piperatus* (Peppery Bolete). The biosynthesis of chalcitrin **98**

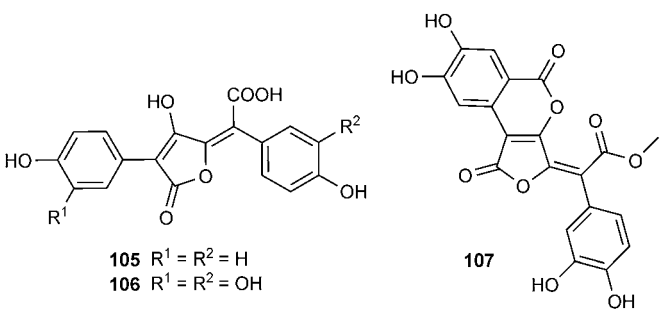


Scheme 8 Possible biosynthetic pathway of pulverolide **90** from vulpinic acid **93**.

from the oxidation of xerocomic acid **97** was shown in Scheme 9.[42] Norbadione A was shown to display important antioxidant properties,[43,44] and its total synthesis has been performed.[45] The key steps were a Diels–Alder cycloaddition employed in the preparation of an appropriately substituted naphtholactone intermediate and a double Suzuki–Miyaura coupling, allowing

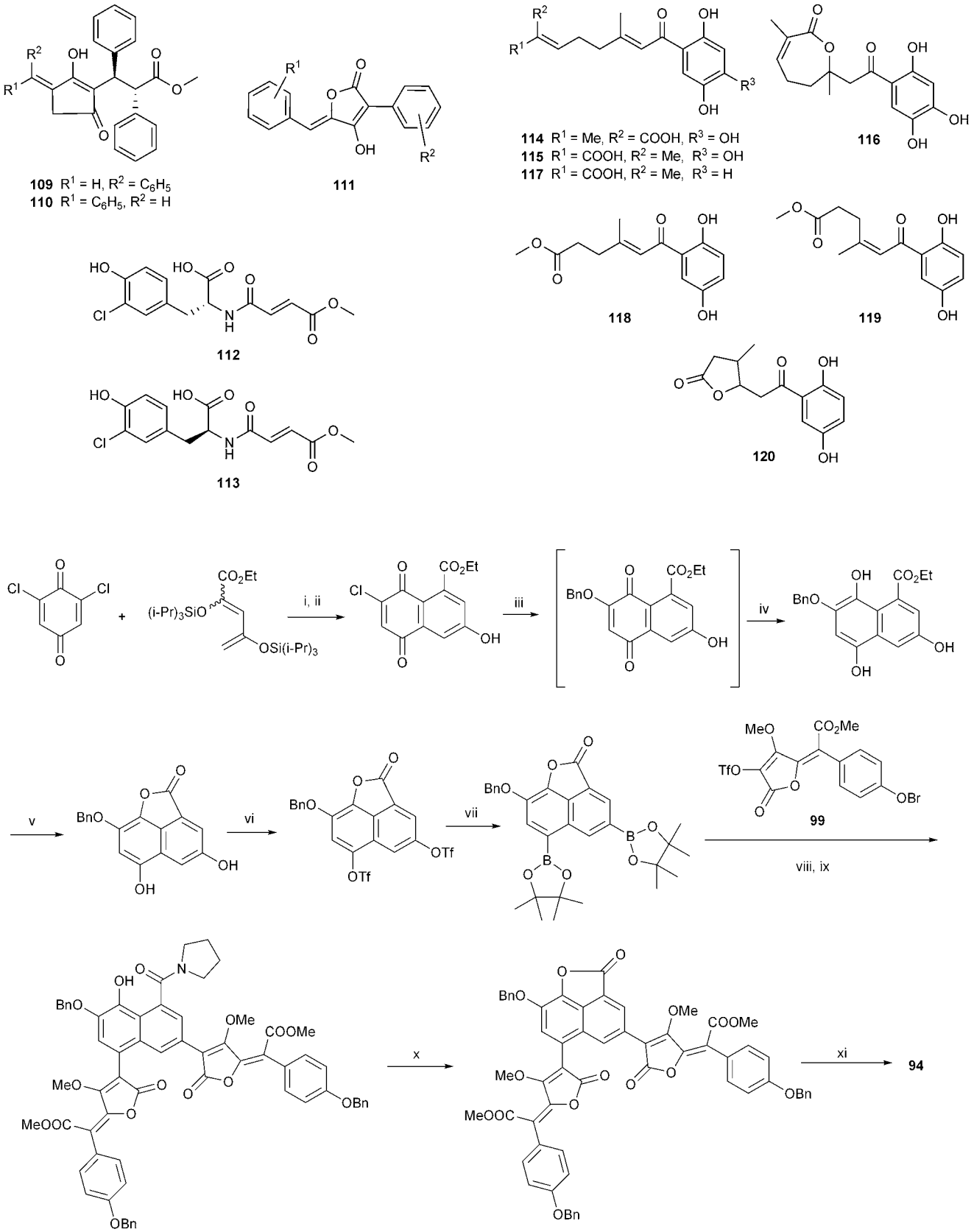


Scheme 9 Proposed biosynthesis of chalcitrin **98** from the oxidation of xerocomic acid **97**.

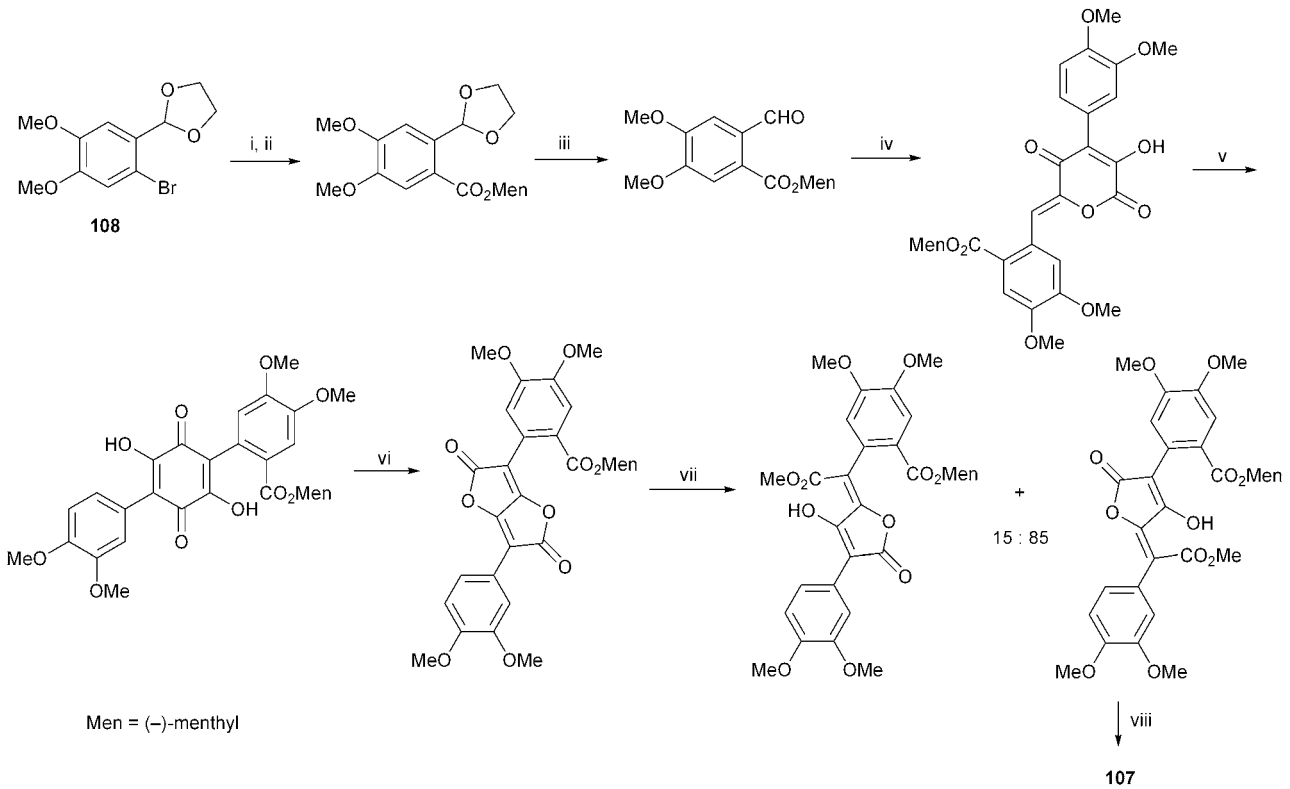


the completion of the carbon framework of norbadione A **94** (Scheme 10).[45]

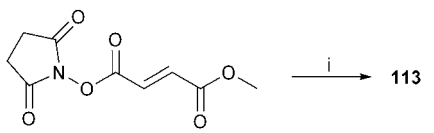
Methyl-3′,5′-dichloro-4,4′-di-*O*-methylatromentate **100** has been reported from the fruiting bodies of *Scleroderma* sp. The structure of **100** was elucidated by spectroscopic methods and X-ray analysis, and **100** displayed moderate antimicrobial activity against *Bacillus subtilis*.[46] Four phenolic pigments, (3,4-dihydroxyphenyl)-2-(4-hydroxyphenyl)-2-(2-pyrrolidon-5-yl)-4-cyclopentene-1,3-dione **101**, (4*Z*)-5-hydroxy-2-(3,4-dihydroxyphenyl)-5-(4-hydroxyphenyl)-2,4-pentadien-4-olide **102**,



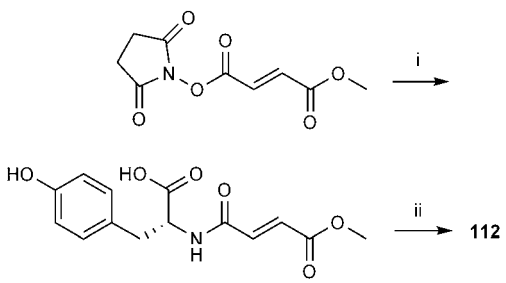
Scheme 10 *Reagents and conditions*: i, toluene, reflux, 15 h; ii, conc. HCl, EtOH, reflux, 5 h (67%); iii, BnOLi, THF, −40 °C to rt (77%); iv, $Na_2S_2O_4$, rt, 15 min; v, *p*-TsOH, toluene, acetone, reflux, 22 h (57%); vi, Tf_2O, pyridine, CH_2Cl_2, −40 °C to rt, 3 h, quant.; vii, bis(pinacolato)diboron, $Pd(OAc)_2$, 2-(dicyclohexylphosphino)biphenyl, *i*-Pr_2NEt, dioxane, 4 h, rt (59%); viii, pyrrolidine, THF, rt, 15 min; ix, **99**, $PdCl_2(PPh_3)_2$, THF, 2 M Na_2CO_3, reflux, 3.5 h (58%); x, AcOH, reflux, 2 h (74%); xi, Me_3SiI (15 equiv), $CDCl_3$, 55 °C, 11 days (28%).



Scheme 11 *Reagents and conditions*: i, BuLi, THF, −78 °C; ii, $ClCO_2Menthyl$ (70%); iii, acetone, cat. HCl (98%); iv, pyrandione, AcOH, NH_4OAc (69%); v, MeONa, MeOH (47%); vi, Ac_2O, DMSO (82%); vii, 2% KOH, MeOH, separation on a SiO_2 column (>99%); viii, BBr_3 (69%).



Scheme 12 *Reagents and conditions*: i, 3-chloro-L-tyrosine, BSA, DMF, 55 °C, 24 h.



Scheme 13 *Reagents and conditions*: i, D-tyrosine, BSA, DMF, 60 °C, 16 h (54%); ii, Oxone, KCl, $CH_3CN–H_2O$, rt, 72 h (78%).

involutone **103**, and involutin **104**, have been isolated from the fruiting bodies of *Paxillus involutus*.[47,48]

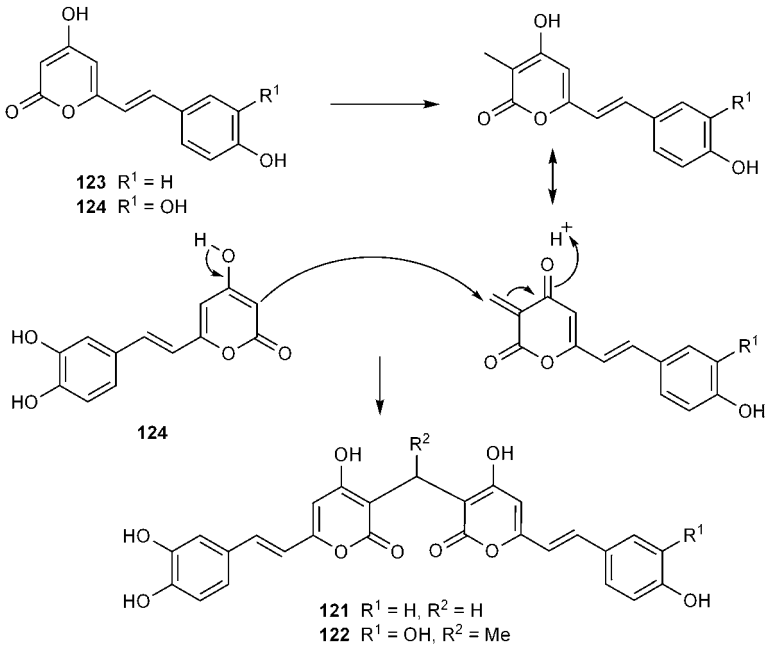
Xerocomic acid **97**, atromentic acid **105**, and variegatic acid **106** were isolated from the fruiting bodies of *Suillus bovinus*.[49] Compounds **97** and **106** have also been found in the fruiting bodies of *Boletus calopus*.[49] These compounds showed cytochrome P450 (CYP) inhibitory effects with ferrylheme-reducing properties.[49] Cultures and fruiting bodies of *S. bovinus* also produce methyl bovinate **107**, which contains an extra carbonyl group that bridges ring A of methyl variegatate with the hydroxy group at the central butenolide ring. This unprecedented structure was deduced from the spectroscopic data and confirmed by total synthesis from bromoacetal **108** in 7 steps with 11% overall yield (Scheme 11).[50]

Isoravenelone **109**, ravenelone **110**, and a large amount of vulpinic acid **93**, are butenolides isolated from a methanolic extract of the Japanese fungus *Pulveroboletus ravenelii* (Boletales).[51]

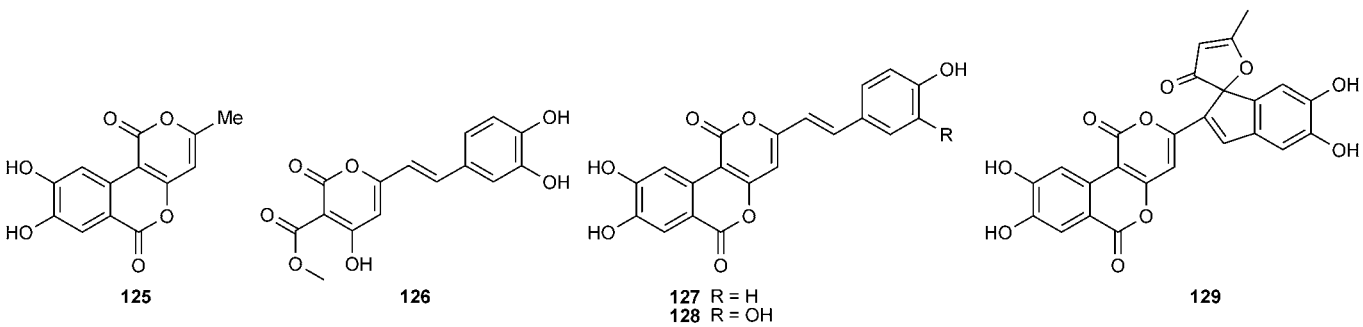
Pulvinic acid and related derivatives containing a γ-alkylidenebutenolide ring system are yellow pigments that are common in fungi and lichens, and have attracted a great deal of interest among synthetic organic chemists due to their diverse bioactivities and drug-like structure. Numerous robust and straightforward syntheses of pulvinic acid and its derivatives have been accomplished.[52–58] Various isomerically pure (*Z*)-pulvinones **111** have been synthesized in 75–91% yield by tandem Claisen condensation–transesterification between arylacetate enolates and arylmethylene-substituted 2,2-dimethyl-1,3-dioxolan-4-ones.[59] In addition, structure–activity relationships between monoaromatic derivatives of pulvinic acid and antioxidant properties were studied for the first time.[60]

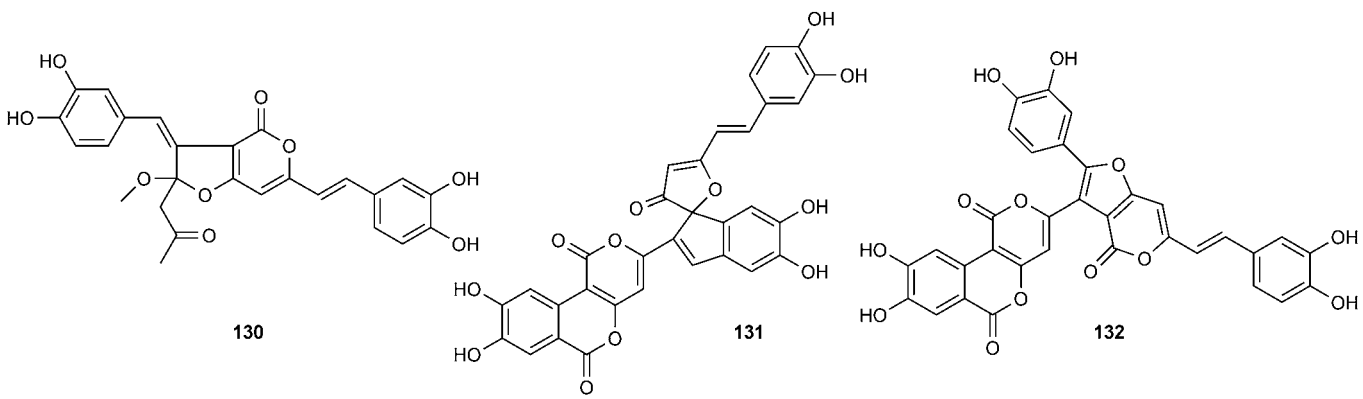
2.2 Compounds derived from phenylalanine and tyrosine

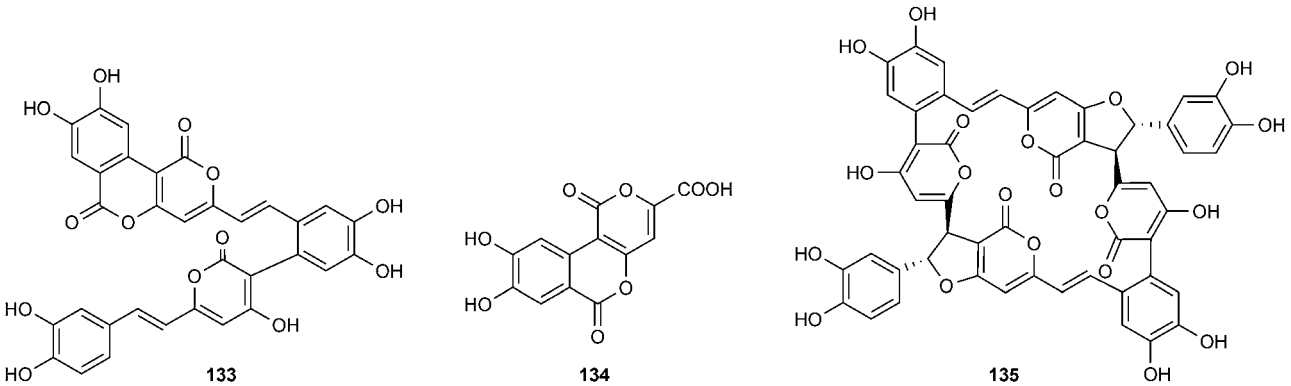
(−)-Xylariamide A **112**, isolated from a culture of *Xylaria* sp., had its absolute stereochemistry determined by the total synthesis of its enantiomer, (+)-xylariamide A **113** (Scheme 12).[61] Later, the synthesis of (−)-xylariamide A was also achieved by

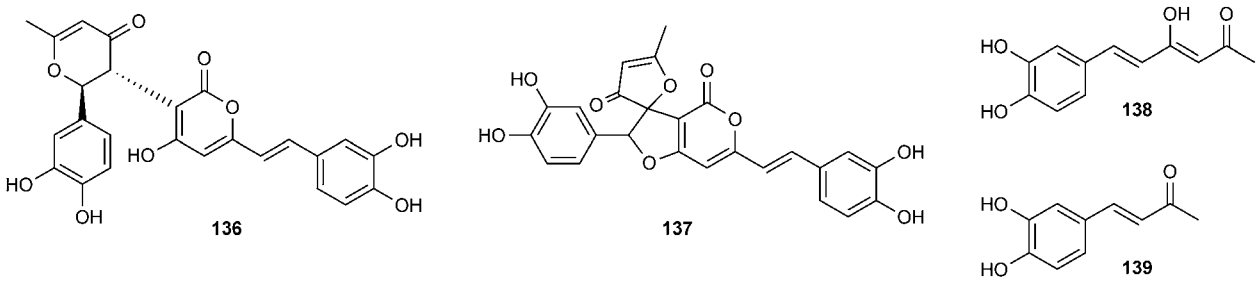


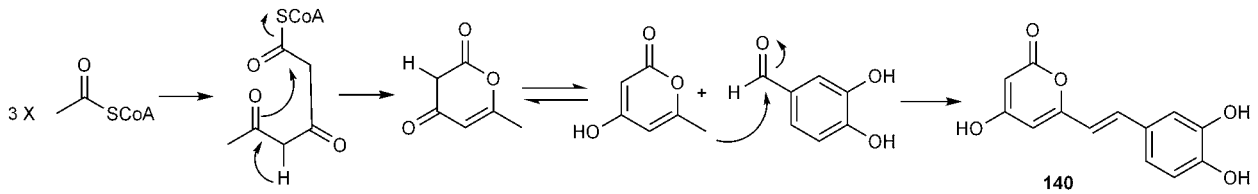
Scheme 14 Biosynthetic model for the formation of bis(styrylpyrones) **121** and **122**.



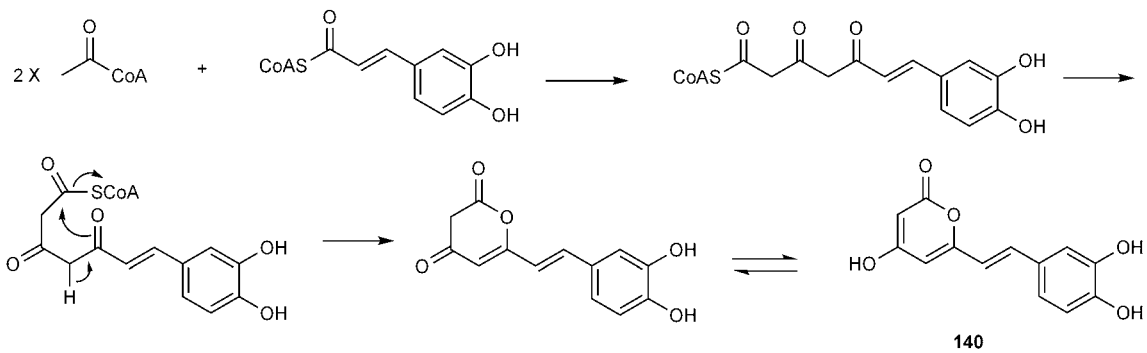




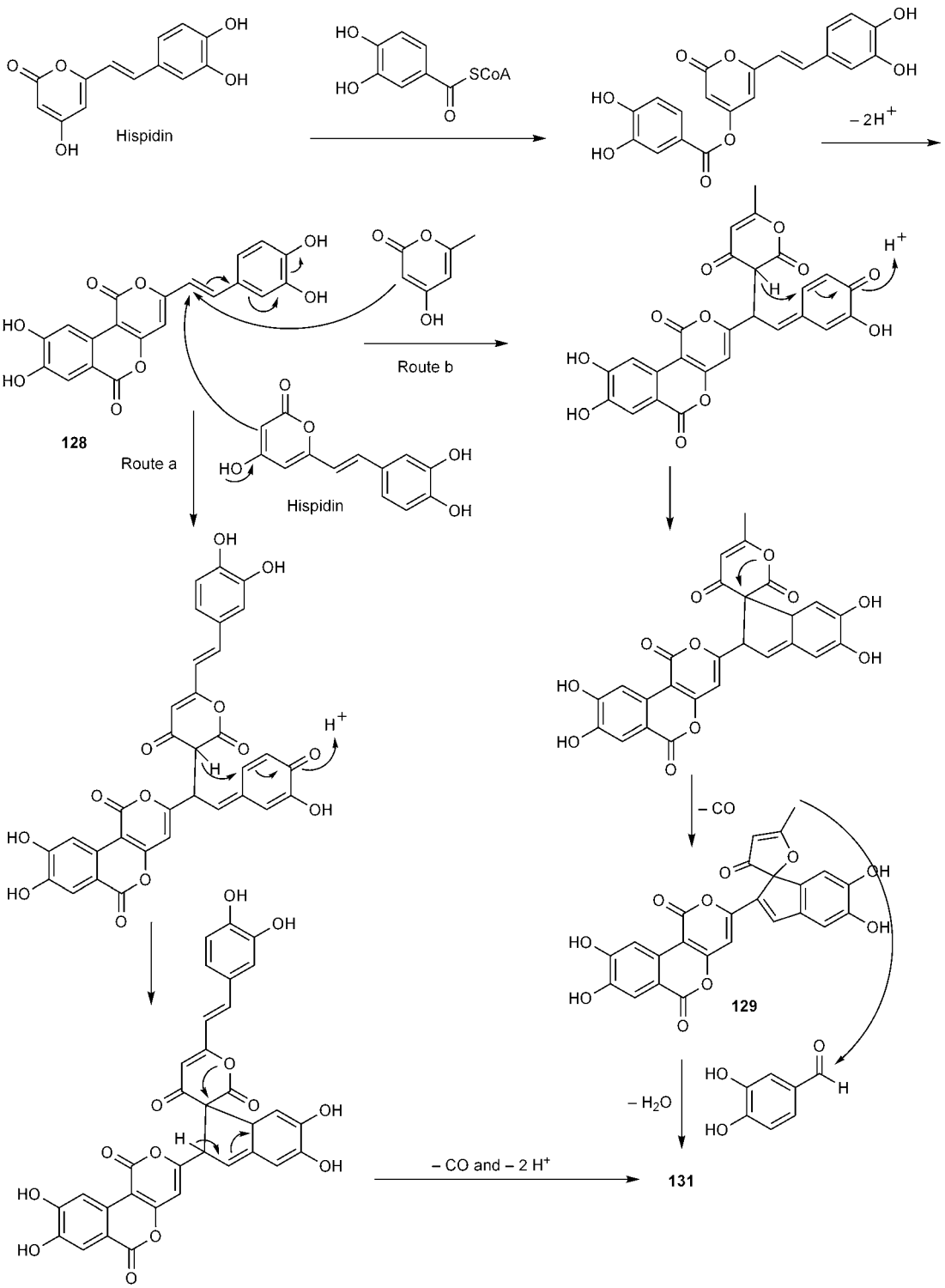




Scheme 15 One mechanism for the biosynthesis of hispidin **140**.



Scheme 16 An alternative mechanism for the biosynthesis of hispidin **140**.

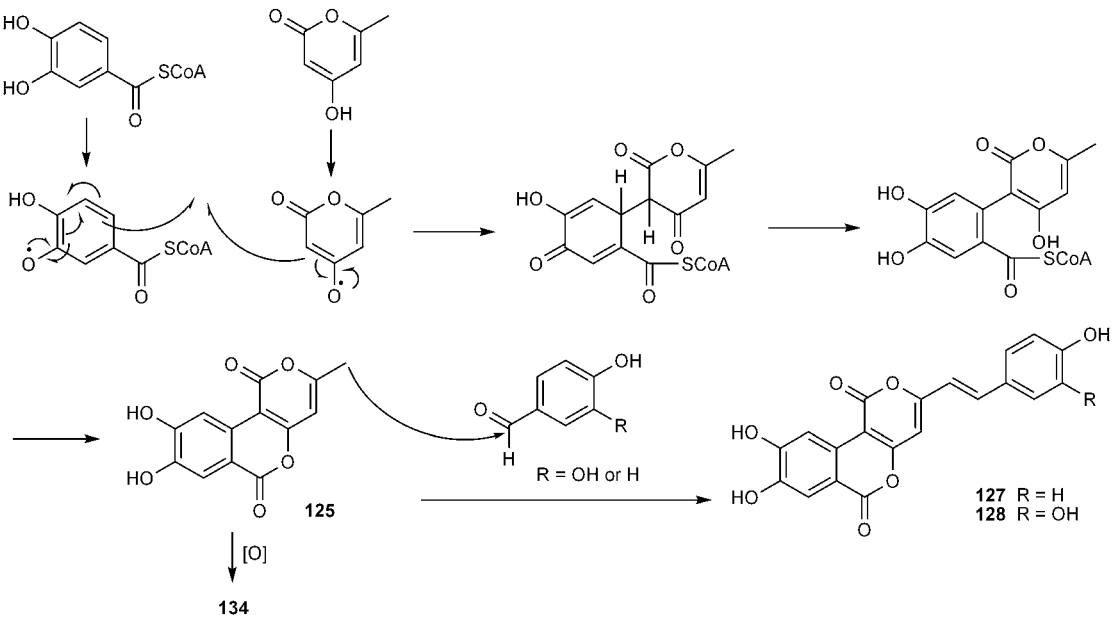


Scheme 17 Proposed biosynthesis of phelligridins D **128**, E **129** and G **131** (see Scheme 15 for earlier steps).

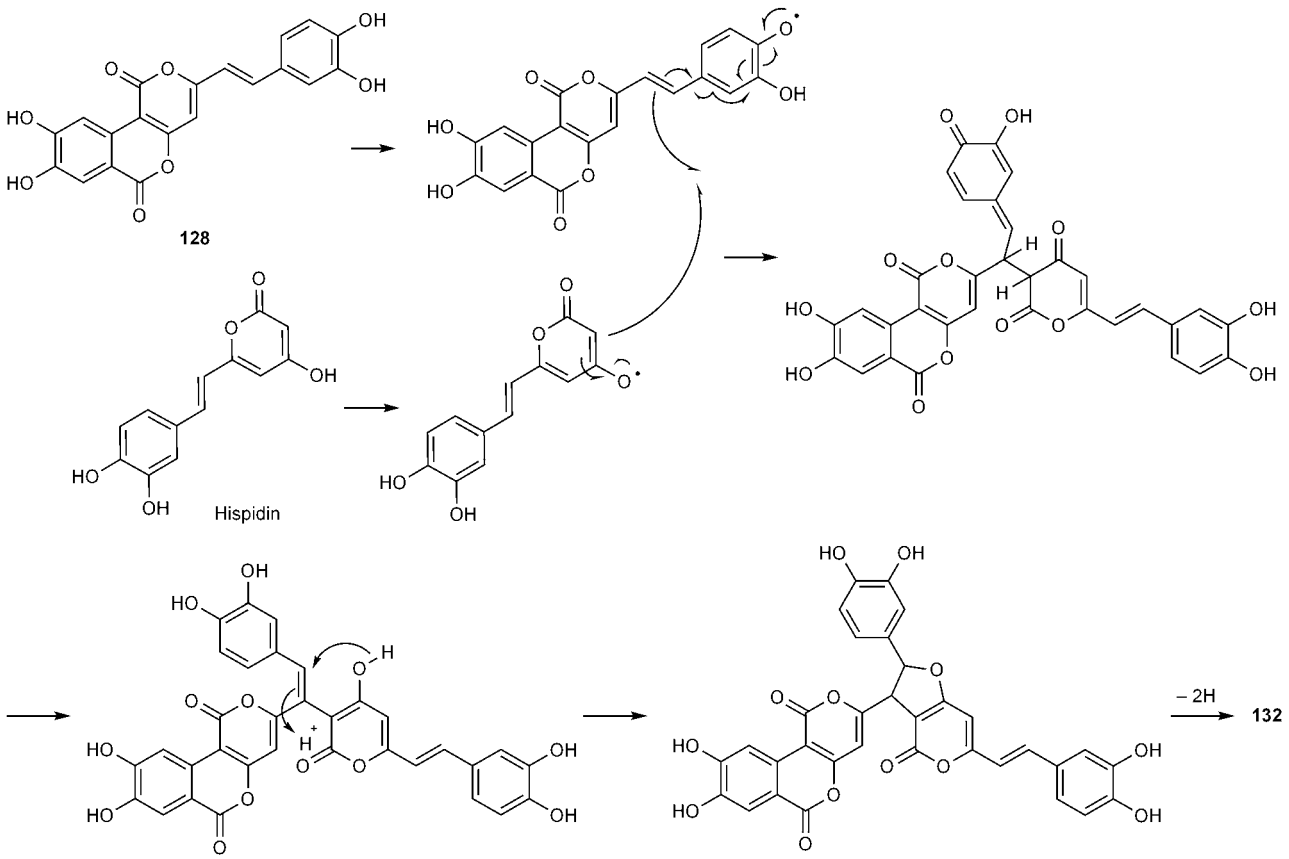
a similar methodology (Scheme 13).[62] (–)-Xylariamide A displayed some toxicity in a brine shrimp lethality assay.[61]

2.3 Compounds derived from cinnamic acids

Orirubenones A–G **114–120** have been isolated from the mushroom *Tricholoma orirubens*.[63,64] Compounds **114–116** exhibited hyaluronan-degradation inhibitory activity, with IC_{50} values of 15, 21 and 57 μM, respectively, while **117–120** showed no such activity. These results suggest that the catechol moiety in orirubenones is indispensable for hyaluronan-degradation inhibitory activity.[63,64] Bioassay-guided isolation of the fruiting bodies of the mushroom *Pholiota squarrosa* and the mycelium of *Phellinus pini* have led to two fungal phenylpropanoid-derived polyketides, squarrosidine



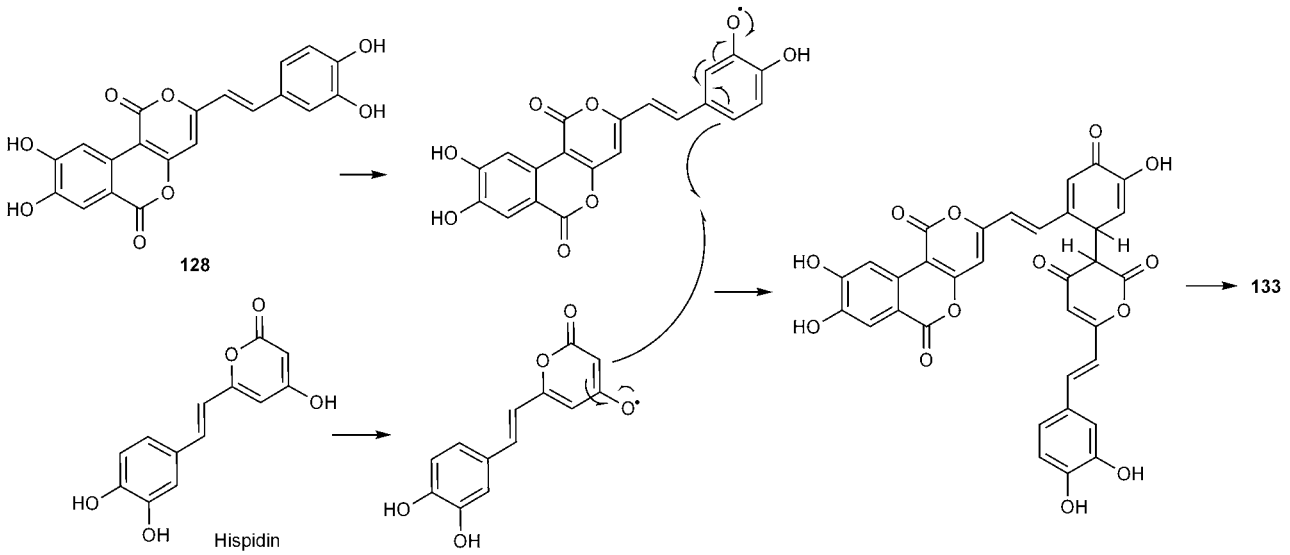
Scheme 18 Proposed biosynthesis of phelligridins A **125**, C **127**, D **128** and J **134**.



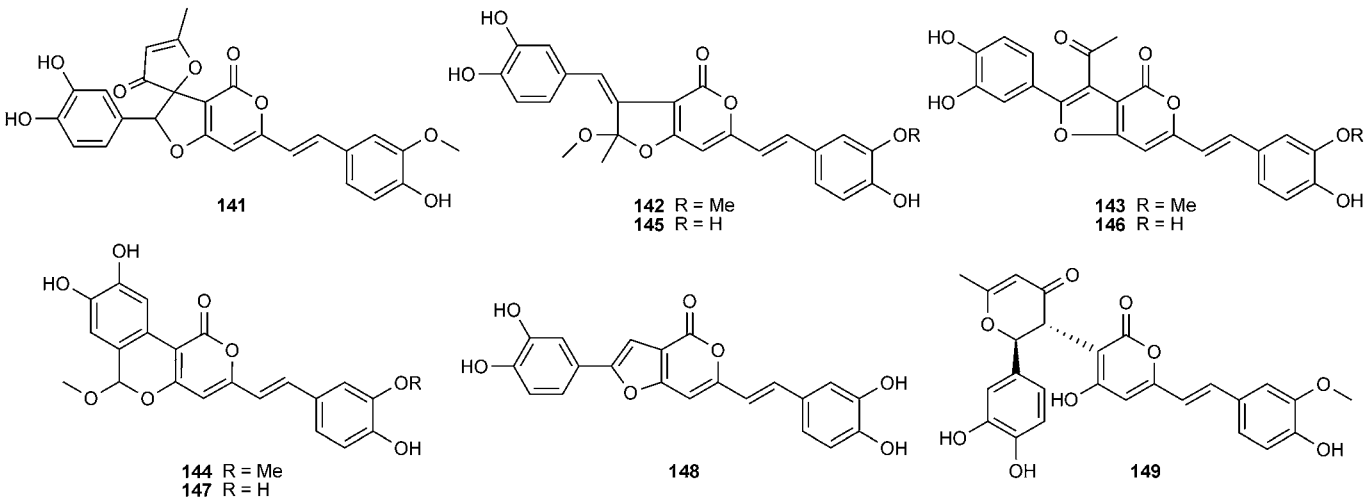
Scheme 19 Proposed biosynthesis of phelligridin H **132** (see Scheme 18 for earlier steps).

121 and pinillidine **122**, with an unprecedented 3,3′-fused bis-(styrylpyrones) structure and potent xanthine oxidase (XO) inhibitory activities.[65] The biosynthesis of **121** was rationalized by the nucleophilic vinylogous addition of **124** to an oxidation product of a methylated bisnoryangonin derivative. In the formation of **122**, the additional methyl group could be derived from subsequent methylation of the methylene bridge, whereas an ethyl substituent at the pyrone ring would be less likely (Scheme 14).[65]

Phelligridins A–J **125–134** and phelligridimer A **135** were new pigments reported by the same group from the Chinese medicinal



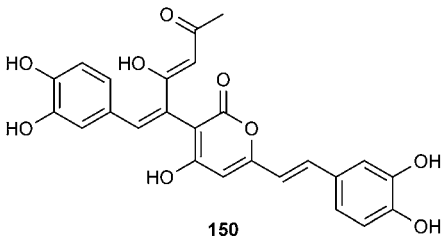
Scheme 20 Proposed biosynthesis of phelligridin I **133** (see Scheme 18 for earlier steps).



fungus *Phellinus igniarius*.[66–70] Other related compounds from this fungus included davallialactone **136**, inoscavin A **137**, hispolon **138**, and (*E*)-4-(3,4-dihydroxyphenyl)but-3-en-2-one **139**.[66–70] Phelligridins show diverse bioactivities – phelligridins D **128**, E **129**, G **131**, and J **134** exhibit *in vitro* cytotoxic activity against several human cancer cell lines,[66,68,69] while phelligridins G–I **131–133** and phelligridimer A **135** showed antioxidant activity, inhibiting rat liver microsomal lipid peroxidation with IC_{50} values of 3.9, 4.8, 3.7 and 10.2 μM, respectively.[68,69] Phelligridins H **132** and I **133** inhibited protein tyrosine phosphatase 1B (PTP1B) (IC_{50} values of 3.1 and 3.0 μM, respectively).[69]

Hispidin **140** in mushrooms is known to be biosynthesized by two different mechanisms: (i) the condensation of 4-hydroxy-6-methyl-2-pyrone which is formed by the reaction of three molecules of acetyl-SCoA and one molecule of 3,4-dihydroxybenzoyl-SCoA (or 3,4-dihydroxybenzaldehyde) (Scheme 15),[66,71] (ii) from phenylalanine *via* a cinnamyl derivative that is combined with either acetate or malonate through the polyketide pathway (Scheme 16).[71,72] The co-occurrence of hispolon **138**, hispidin **140**, 3,4-dihydroxybenzoic acid, 3,4-dihydroxybenzaldehyde, and 4-hydroxybenzaldehyde in *P. igniarius* led to the postulated biosynthetic formation of phelligridins A and C–J (Schemes 17–20 and 24)[66,68,69] and phelligridimer A (Scheme 21).[70]

Twelve new hispidin derivative pigments, methylinoscavins A–D **141–144**,[73–75] inoscavins B–E **145–148**,[73–76] methyldavallialactone **149**,[75] and interfungins A–C **150–152**,[71] together with known phelligridins D **128** and F **130**, davallialactone **136**, and inoscavin A **137**, have been isolated from the fruiting bodies of *Inonotus xeranticus*.[71,73–76] The mycelial culture of the same species provided hispidin **140**, 3,14-bihispidinyl **153**, hypholomine B **154**, and 1,1-distyrylpyrylethane **155**.[77] This class of compounds showed free-radical scavenging activity against the



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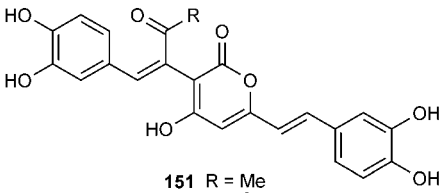
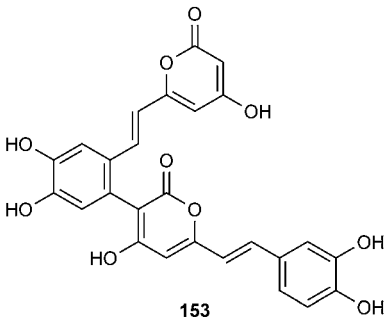


151 R = Me
152 R = OMe



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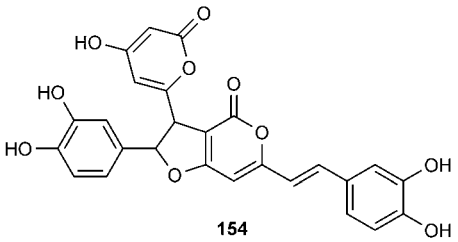

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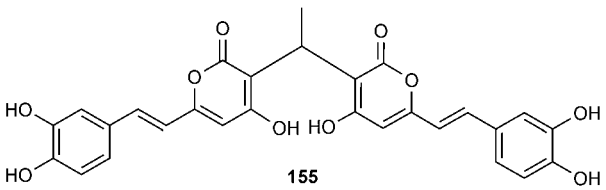

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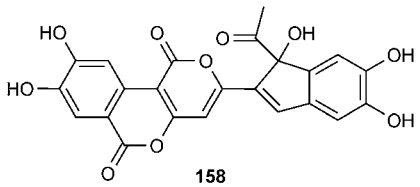

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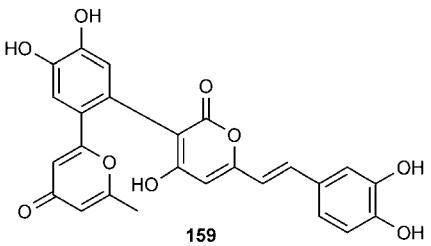

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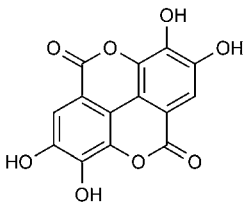

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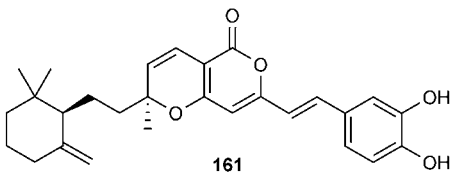

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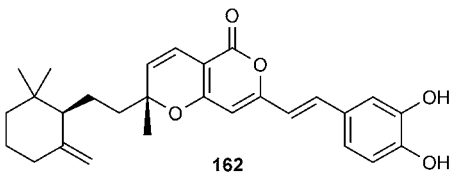

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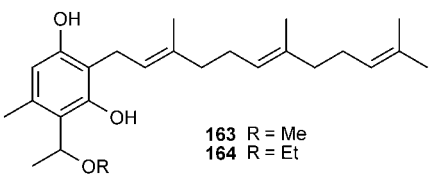
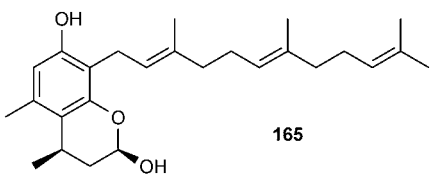
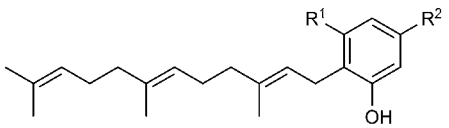


163 R = Me
164 R = Et

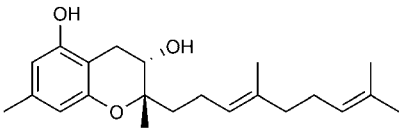


165

superoxide radical cation, the ABTS radical anion, and the DPPH radical. Compounds **128**, **144**, **147**, **150**, and **151** might be biosynthesized by the oxidative coupling of **140** and **156**, **140** and **157**, **140** and **156**, **138** and **140**, and **139** and **140**, respectively.[71,73] Phelligridin F **130**, davallialactone **136** and inoscavin A **137** may be derived from **150**, and inoscavins B **145** and C **146** may be biosynthesized from **151**.[71] All the condensation processes proposed are shown in Schemes 22–25.



166 R^1 = OH, R^2 = Me
167 R^1 = Me, R^2 = OH



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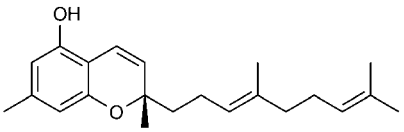

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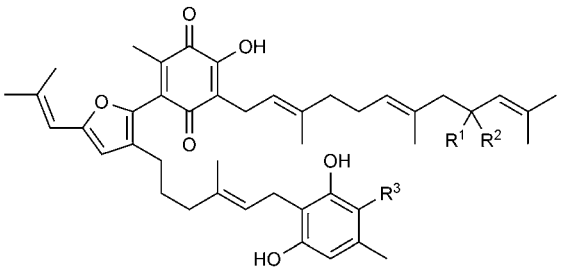
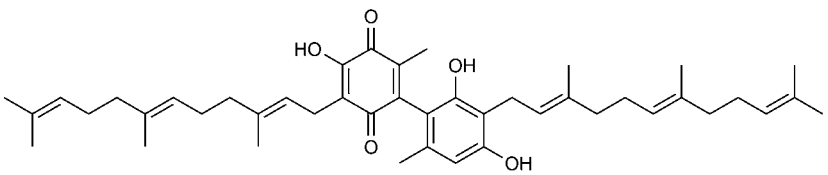


170 R^1 = R^2 = H, R^3 = H
171 R^1,R^2 = O, R^3 = H
172 R^1 = OH, R^2 = R^3 = H
175 R^1 = R^2 = H, R^3 = COOH



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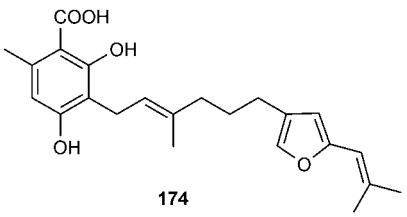

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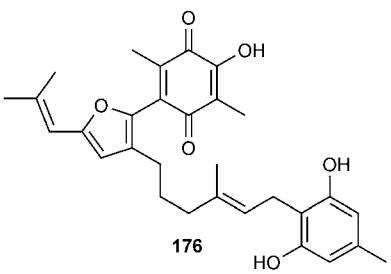

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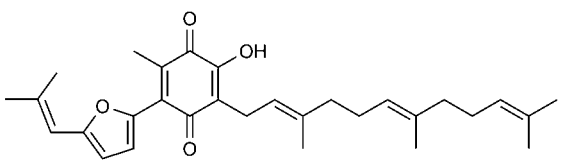

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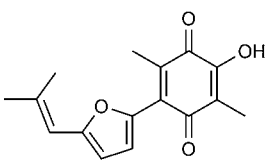

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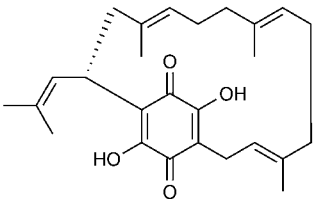
Chemical investigation of the medicinal mushroom *Inonotus obliquus* has led to the isolation of inonoblins A **133** (same as phelligridin I),[24] B **158** and C **159** and known phelligridins D **128**, E **129** and G **131**.[78] Compounds **128**, **129**, **131**, **133**, **158** and **159** exhibited scavenging activities against the ABTS radical cation and DPPH radical, and showed moderate superoxide radical anion scavenging activity.[78] Meshimakobnols A **128** (same as phelligridin D)[24] and B **127** (same as phelligridin C),[24,79] phelligridin G **131**, and phellifuropyranone A **148** (same as inoscavin E)[24,80] have been identified from fruiting bodies of Japanese wild *Phellinus linteus* ('*meshimakobu*' in Japanese). Meshimakobnols A **128** and B **127**, and phellifuropyranone A **148** exhibited an antiproliferative effect against mouse melanoma cells and human lung cancer cells *in vitro*.[79,80] Another research group in Korea have isolated phelligridimer A **135**, davallialactone **136**, inoscavin A **137**, hispidin **140**, methyldavallialactone **149**, interfungins A **150**, hypholomine B **154**, and ellagic acid **160** from the fruiting bodies of *P. linteus*. Among them, **136**, **154** and **160** exhibited potent rat lens aldose reductase and human recombinant aldose reductase inhibitory activity, with IC_{50} values of 0.33, 0.82 & 0.63 μM and 0.56, 1.28 & 1.37 μM, respectively.[81] Phellinins A_1 **161** and A_2 **162**, hispidin **140** and 1,1-distyrylpyrylethane **155** have



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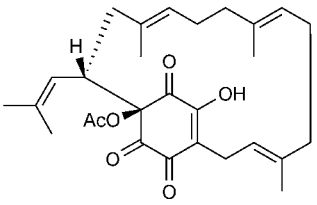

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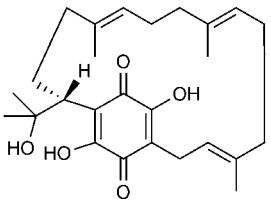

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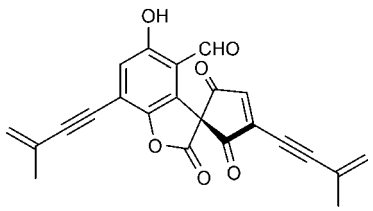

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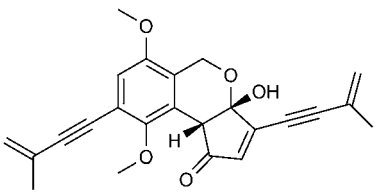

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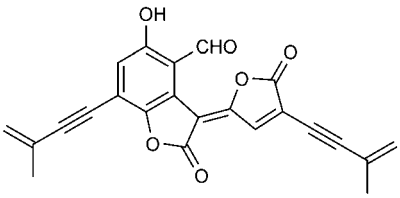


198

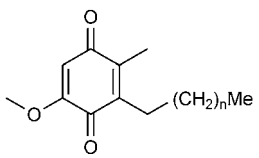
been found in the cultured broth of *Phellinus* sp. KACC93057P.[82] These compounds significantly scavenged free-radicals such as 1,1-diphenyl-2-picrylhydrazyl, 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) and superoxide.

2.4 Compounds derived from 4-hydroxybenzoic acid

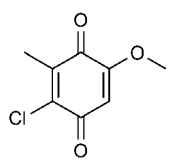
Three new grifolin derivatives **163–165**, and four known phenolic compounds **166–169** have been afforded from MeOH extract of the Korean wild mushroom *Boletus pseudocalopus.* The structures of **163–169** were elucidated as 4-(1-methoxyethyl)-5-methyl-2-[(2*E*,6*E*)-3,7,11-trimethyldodec-2,6,10-trienyl]benzene-1,3-diol, 4-(1-ethoxyethyl)-5-methyl-2-[(2*E*,6*E*)-3,7,11-trimethyldodec-2,6,10-trienyl]benzene-1,3-diol, 3,4-dihydro-4,5-diemethyl-8-[(2*E*,6*E*)-3,7,11-trimethyldodec-2,6,10-trienyl]-2*H*-[1]benzopyran-2,7-diol, grifolin, neogrifolin, 2-(4,8-dimethylnona-3,7-dienyl)-3,4-dihydro-2,7-dimethyl-2*H*-[1]benzopyran-3,5-diol, and 2-((2*E*,6*E*)-4,8-dimethylnona-3,7-dienyl)-2,7-dimethyl-2*H*-[1]benzopyran-5-ol, respectively.[83] In the original paper, all compounds **163–169** were described as coloured substances. However, their colour might not be inherent, but instead be due to impurities.

A variety of dimeric meroterpenoid pigments have been reported from *Albatrellus* species, which included (i) a purple pigment, named grifolinone B **170**, from the methanolic extract of the inedible mushroom *A. caeruleoporus*,[84] (ii) grifolinone B **170**, albatrellin **171** and 16-hydroxyalbatrellin **172** from fruiting bodies of *A. flettii*,[85] (iii) grifolinone B **170**, albatrellin **171**, and grifolinone C **173** from the fruiting bodies of the basidiomycete *A. confluens*.[86] Grifolinone B displayed inhibitory activity against lipopolysaccharide (LPS)-induced production of nitric oxide (NO) in RAW 264.7 cells with an IC_{50} value of 22.9 μM.[84] Albatrellin **171** exhibited cytotoxic activity against HepG2 human lung carcinoma cells with IC_{50} value of 1.55 μg ml^{-1} (the positive controls were DDP, which had an IC_{50} value of 0.28 μg ml^{-1}, and **173**, which had no activity under the same conditions).[86]

The structure of albatrellin **171** suggests its formation from two components, one derived from grifolin **166** and the other from cristatic acid **174**. Albatrellin **171** and its analogues **175–178** were synthesized by a biomimetic route *in vitro*. Coupling of **179** and **180** in dichloromethane gave **171**, which could be isolated in 30% yield (Scheme 26).[85] Compound **175** was very unstable and underwent easy decarboxylation to albatrellin, even when kept in the refrigerator. All biomimetically synthesized products, including the simplest derivative **178**, were blue and displayed UV spectra similar to those of the albatrellins. On the basis of this observation, Steglich suggested that the colour originated from electronic interactions between the benzoquinone and the conjugated furan chromophore rather than from a charge transfer interaction of the quinone with the remote resorcinol group.[87]



200 n = 19
201 n = 20
202 n = 21



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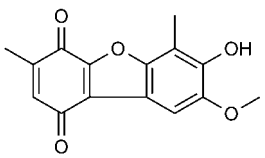

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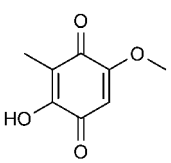

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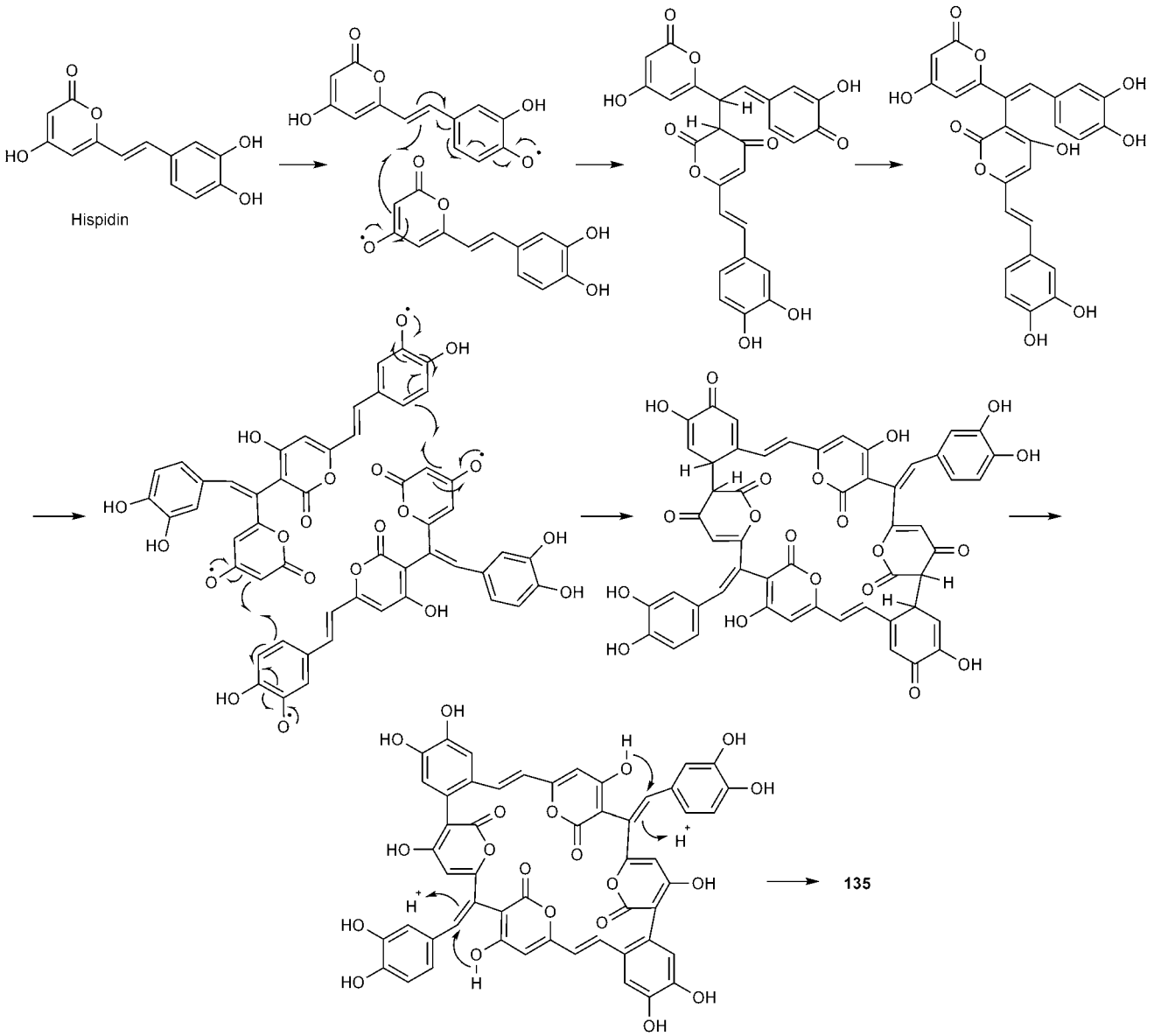
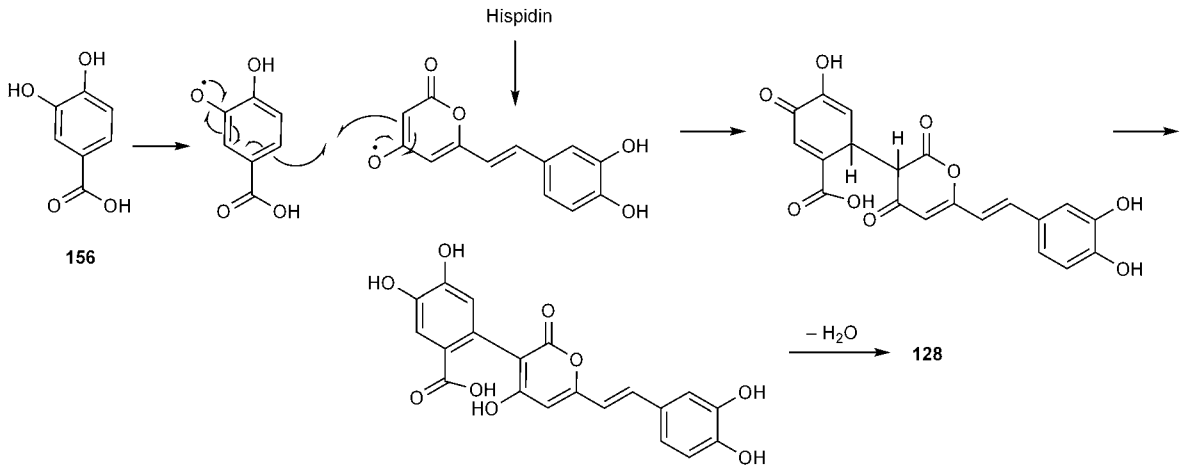
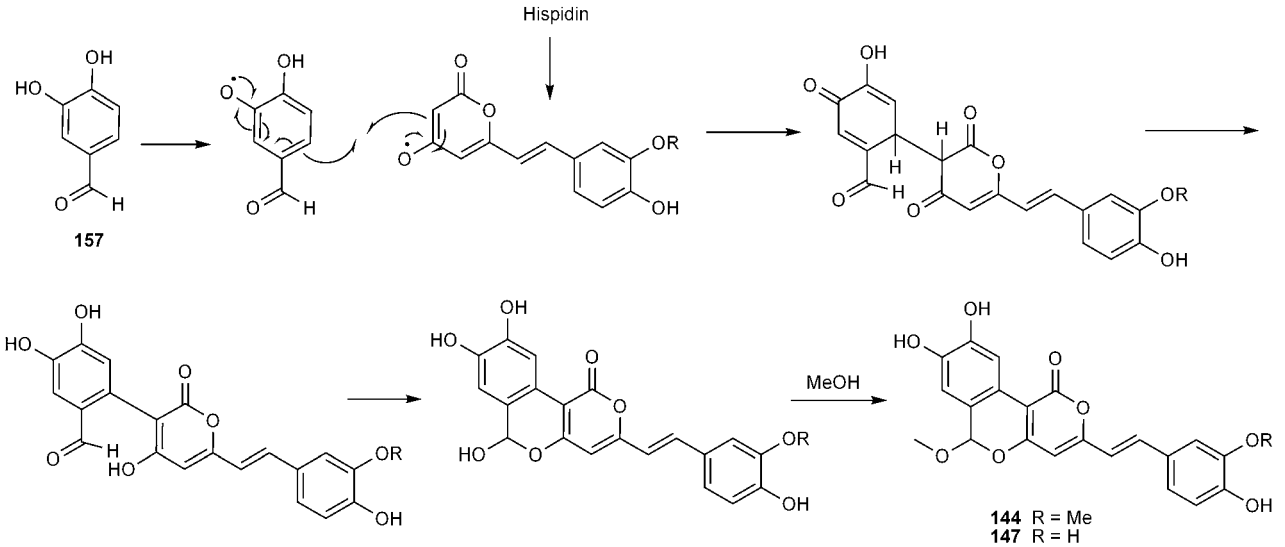


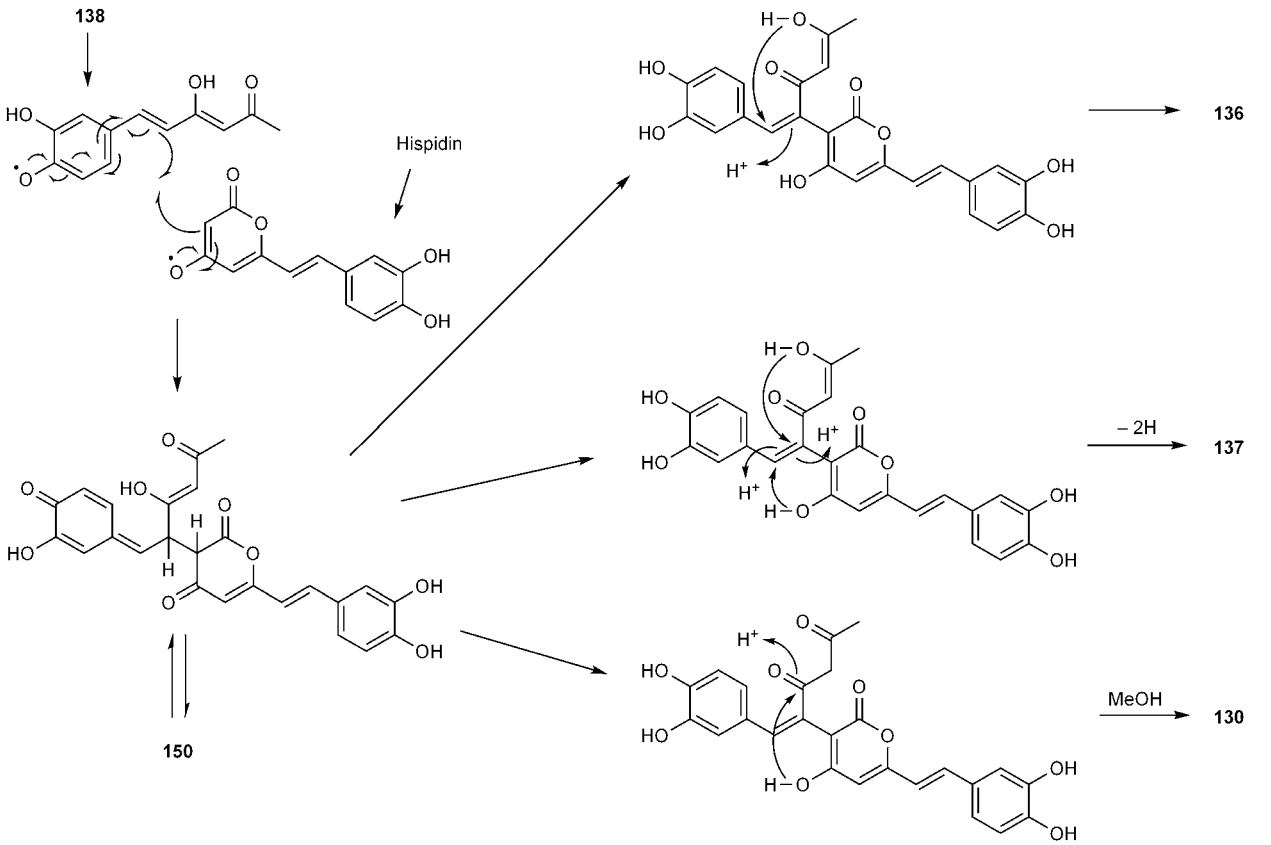
Scheme 21 Proposed biosynthesis of phelligridimer A **135** from hispidin.



Scheme 22 Proposed biosynthesis of phelligridin D **128**.

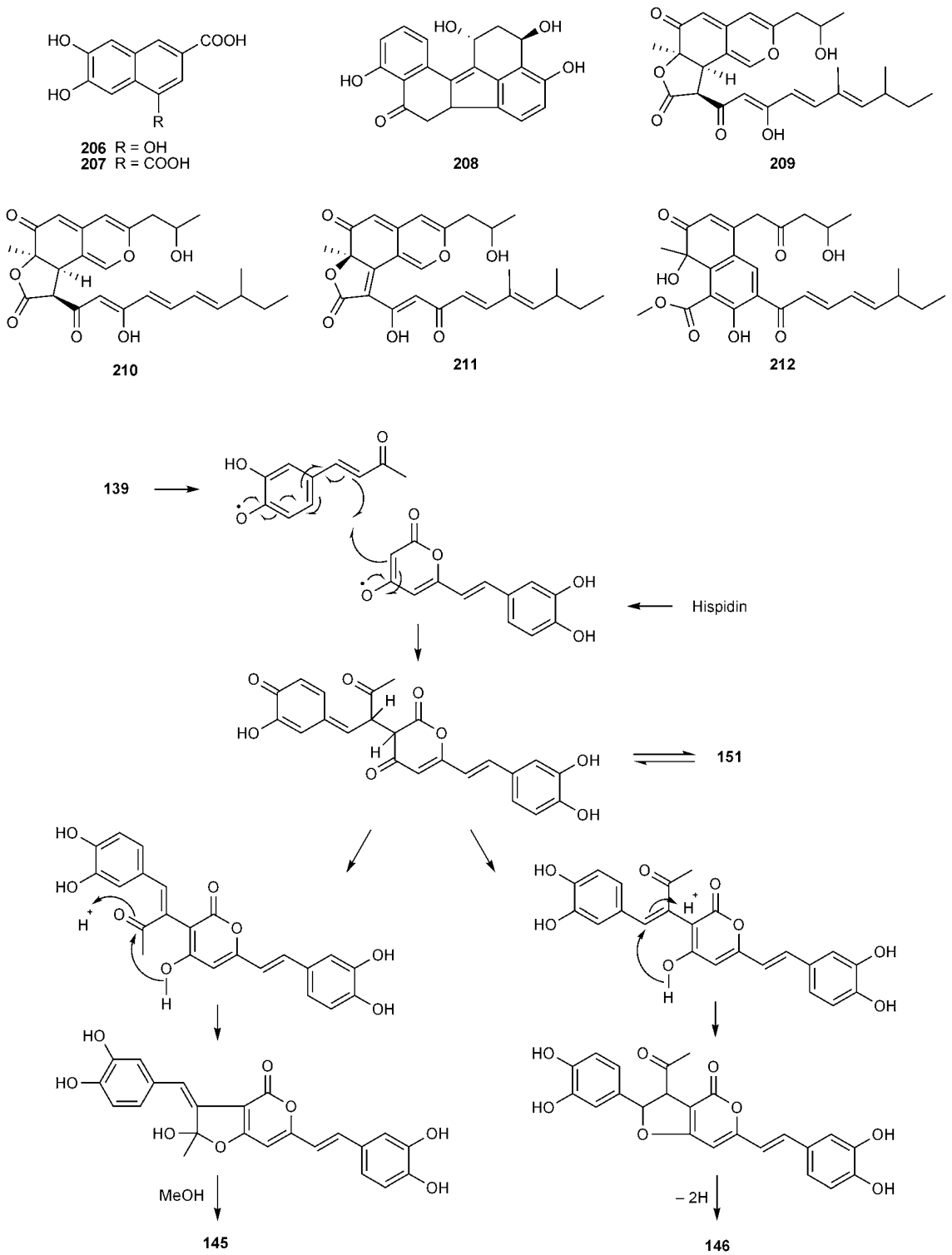


Scheme 23 Proposed biosynthesis of methylinoscavin D **144** and inoscavins D **147**.



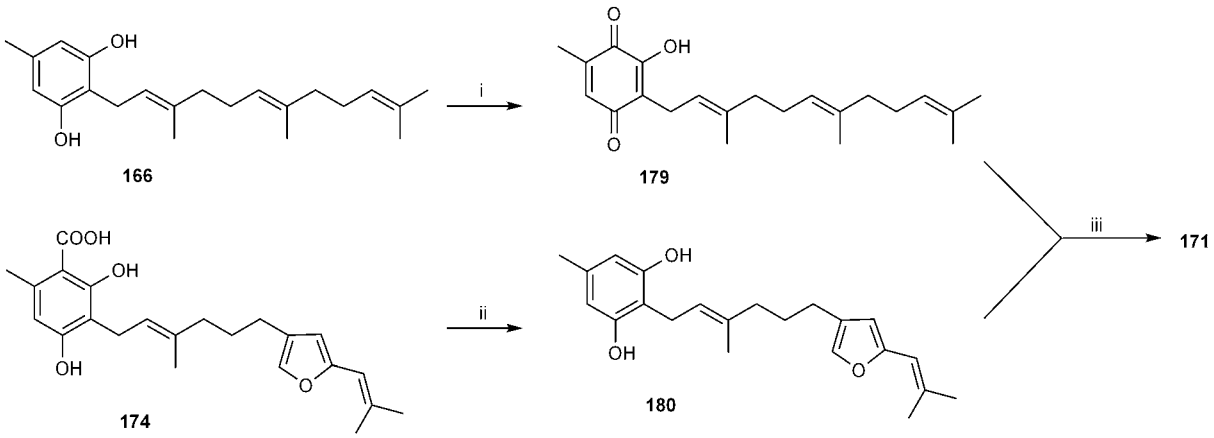
Scheme 24 Proposed biosynthesis of phelligridin F **130**, davallialactone **136**, inoscavin A **137** and interfungin A **150**.

Tridentoquinone **181**, the main pigment of *Suillus tridentinus*, was accompanied by its dimer tridentorubin **182** and deoxytridentoquinone **183**. The absolute configuration of **181** was established as 14′*R* by a single-crystal X-ray diffraction analysis of the corresponding (−)-camphanoate. The structure of **182** was elucidated by 2D NMR techniques including an INADEQUATE experiment.[88] The biosynthesis of **181** and **182** has been studied by feeding experiments of 4-hydroxy-[1-^{13}C]benzoic acid **184** or 3,4-dihydroxy-[1-^{13}C]benzoic acid **185** to the fruiting bodies of *Suillus tridentinus*.[88] Tridentoquinone **181** was monolabeled at C-1, suggesting the formation of the ansa ring by oxidative cyclisation of 2-geranylgeranyl-6-hydroxy-1,4-benzoquinone **186** (Scheme 27), which was confirmed by the isolation of the expected intermediate **183** from the same

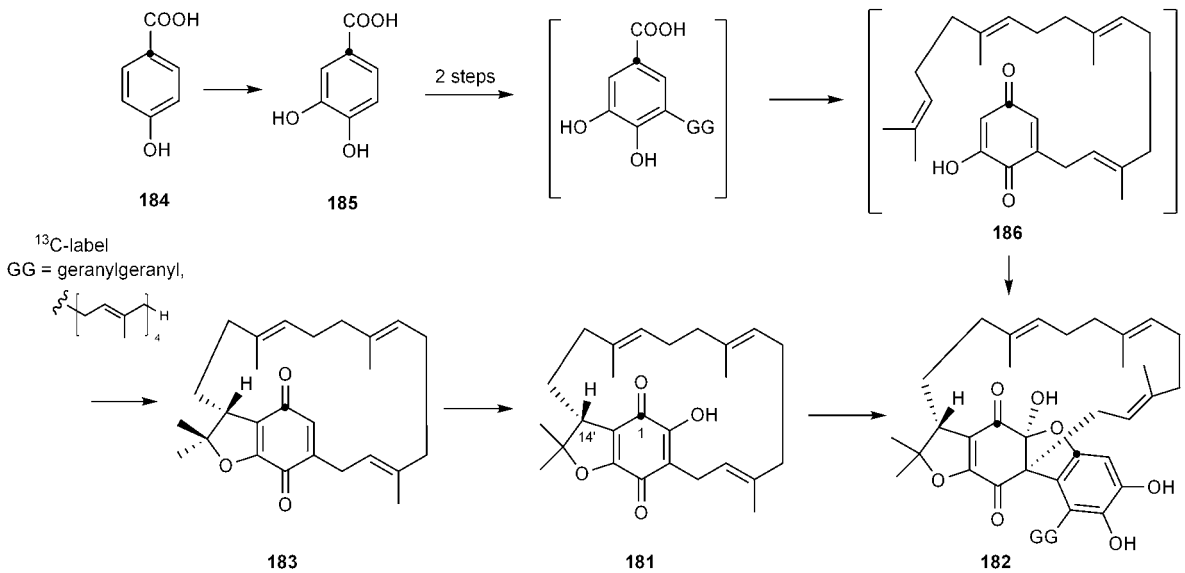


Scheme 25 Proposed biosynthesis of inoscavins B **145** and C **146**, and interfungin B **151**.

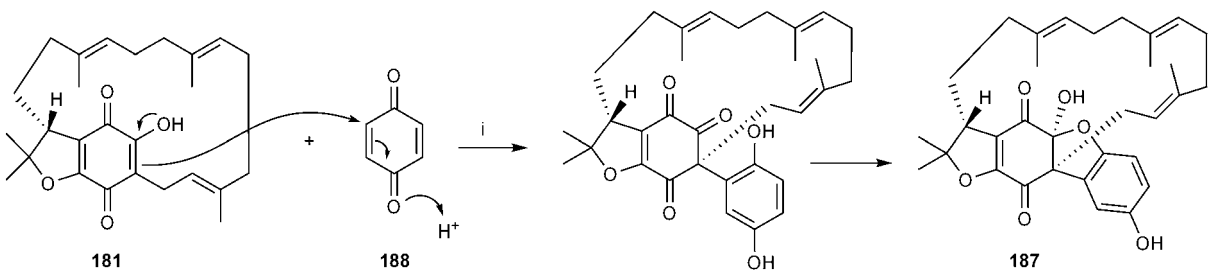
mushroom. Tridentorubin **182** may be biosynthesized by addition of precursor **186** to tridentoquinone **181** (Scheme 27). This hypothesis is supported by the *in vitro* synthesis of an analogous compound (**187**) from **181** and 1,4-benzoquinone **188** (Scheme 28).[88] The biosynthesis of suillin **189**, boviquinone-4 **190** and bovilactone-4,4 **191** was also studied by feeding experiments of **184** or **185** to the fruiting bodies of *S. suillus* and *S. tridentinus*. Unlike **181** and **182**, the biosynthesis of which starts with geranylgeranylation of 3,4-dihydroxybenzoic acid **185** at C-5, the initial step in the biosynthesis of



Scheme 26 *Reagents and conditions*: i, $NO(SO_3K)_2$; ii, $-CO_2$, 120 °C; iii, CH_2Cl_2, 20 °C, 2 weeks.



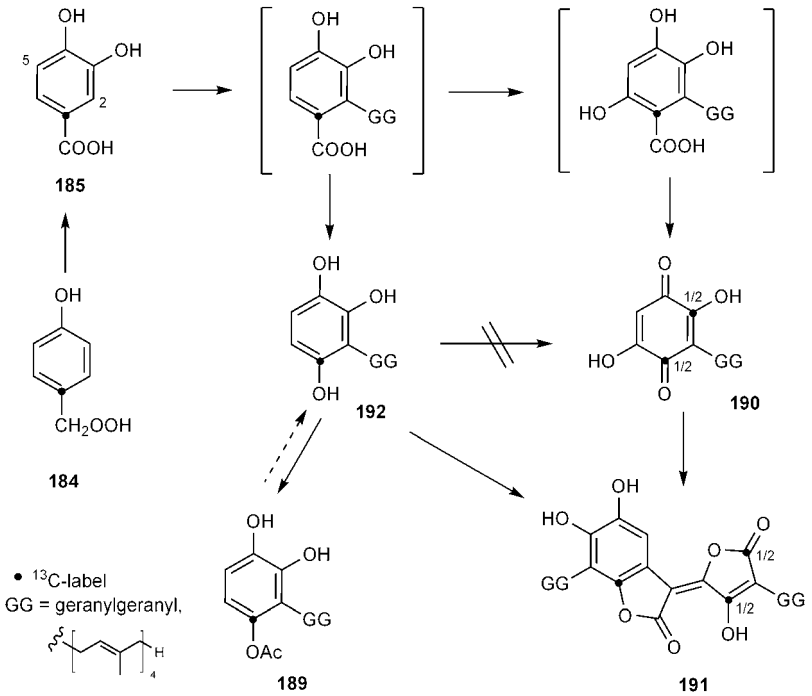
Scheme 27 Labeling patterns of the meroterpenoids **181** and **182** after feeding of 4-hydroxy-[1-^{13}C]benzoic acid (**184**) or 3,4-dihydroxy-[1-^{13}C]benzoic acid (**185**) to the fruiting bodies of *Suillus tridentinus*.



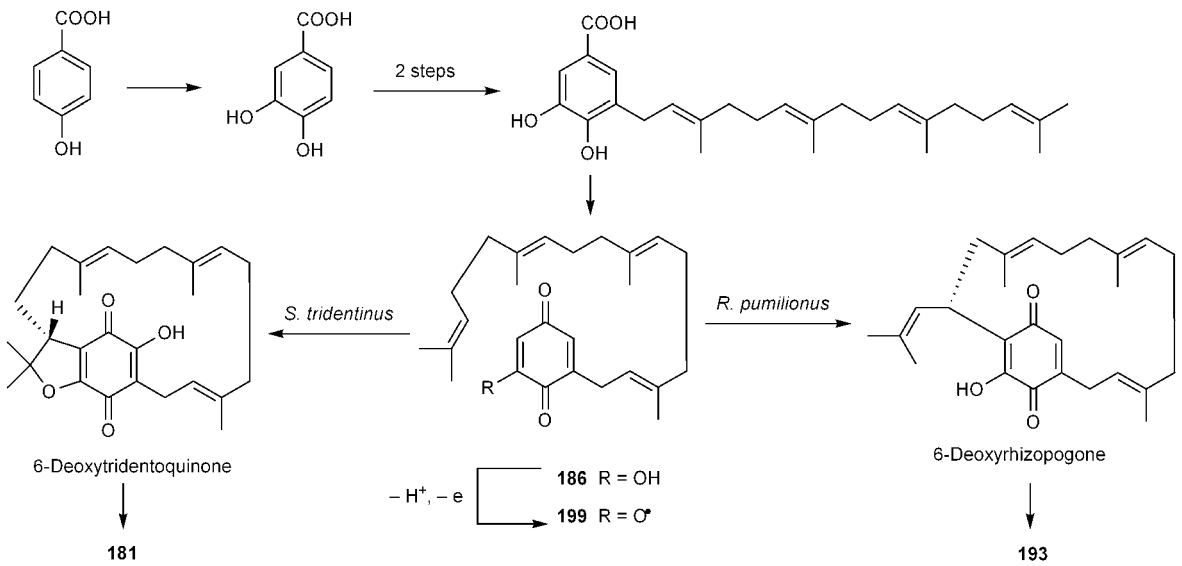
Scheme 28 *Reagents and conditions*: i, THF, rt (10–16%).

suillin **189**, boviquinone-4 **190** and bovilactone-4,4 **191** in *Suillus* species is the geranylgeranylation of 3,4-dihydroxybenzoic acid at the 2-position. Feeding experiments with advanced precursors have identified **190** and deacetylsuillin **192** as building blocks for the dilactone and catechol moieties of **191**, respectively. The results of the feeding experiments are depicted in Scheme 29.[89]

A major pigment, rhizopogone **193**, and a minor pigment, 2-acetoxyrhizopogone **194**, were identified from the fruiting bodies of the basidiomycete *Rhizopogon pumilionus*.[90] The absolute configuration of **193** was determined as 13′*S* by comparison of its CD spectrum with that of secotridentoquinone **195**. The structure of **193** suggests a similar biosynthetic pathway to that for



Scheme 29 Proposed sequences for the formation of **189–191** and labeling patterns after feeding of [1-^{13}C]-labeled **184** or **185** to *S. bovinus* and *S. variegates*.



Scheme 30 Proposed biosynthesis of rhizopogone **193** and tridentoquinone **181**.

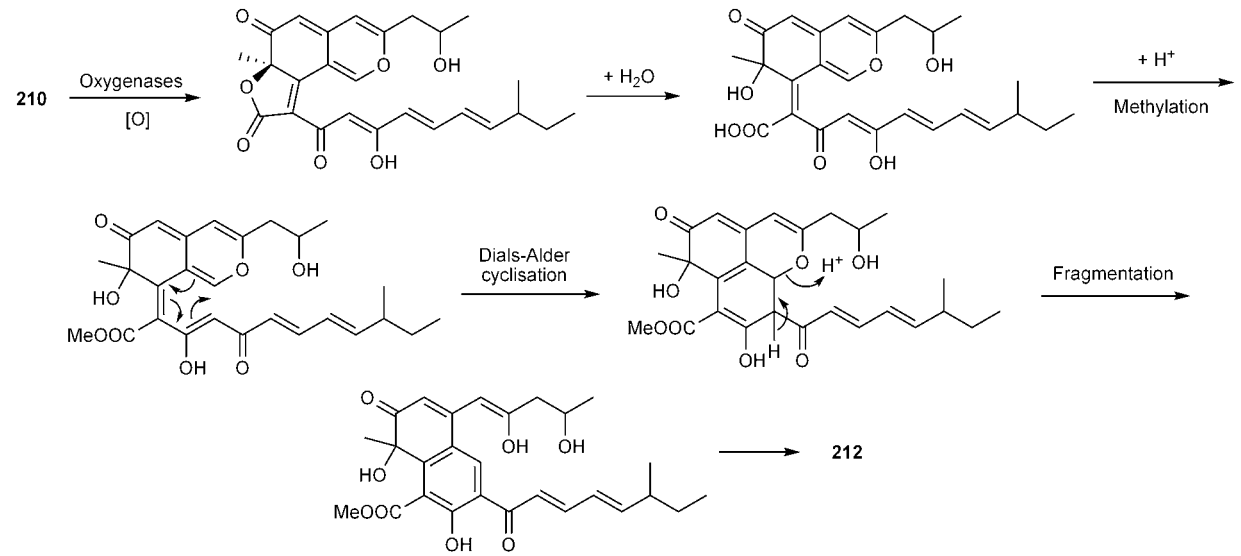
tridentoquinone **181**, originating from 2-geranylgeranyl-6-hydroxy-1,4-benzoquinone **186** (Scheme 30).[90]

Ochroleucin A_1 **196** and ochroleucin B **197** were isolated from the fruiting bodies of *Russula ochroleuca*.[91] Yellow ochroleucin A_1 **196** is very labile and rearranges rapidly into a stable red isomer, ochroleucin A_2 **198**, which is responsible for the red colour produced when the stalk base of *R. ochroleuca* is treated with aqueous KOH. The absolute configurations of **196** and **197** have been determined by quantum chemical calculation of their CD spectra.[91]

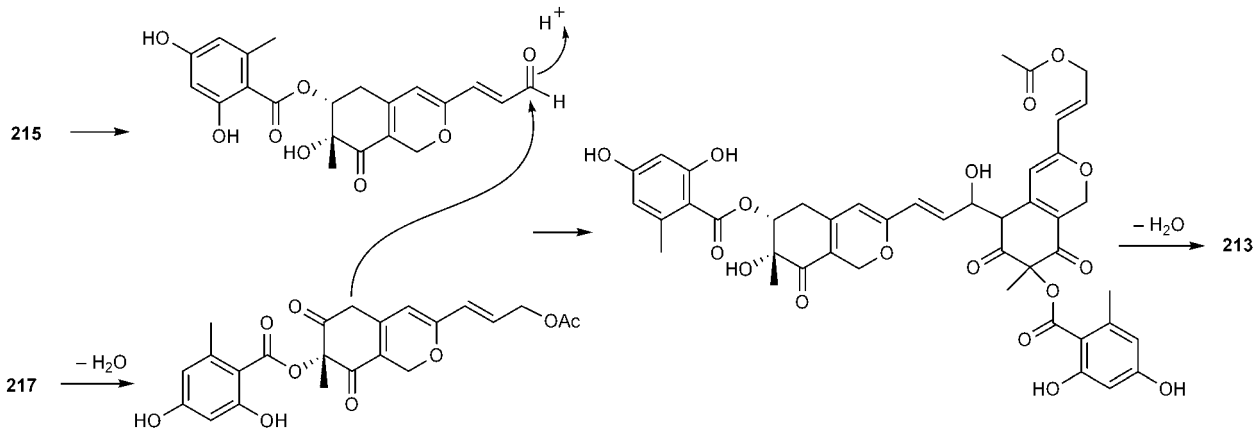
3 Pigments from the acetate–malonate pathway

3.1 Pentaketides

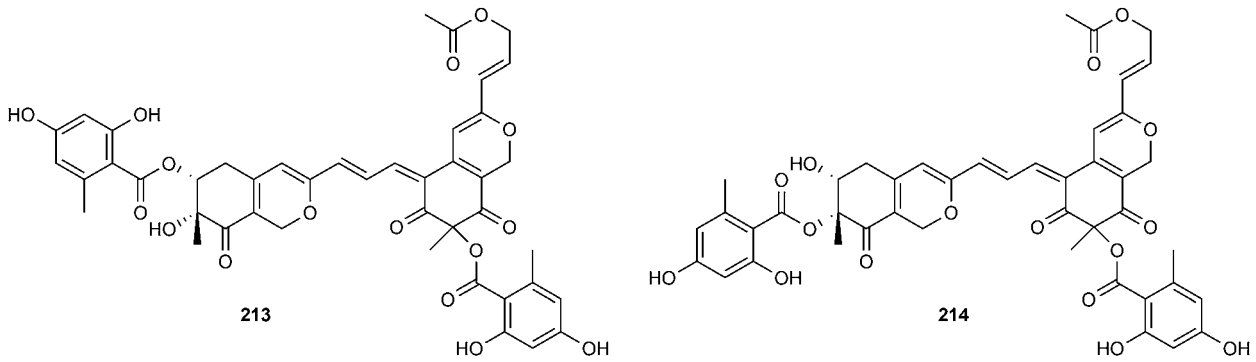
Three new homologous 3-alkyl-1,4-benzoquinones **200–202**, with chain lengths of C_{21} to C_{23}, respectively, were isolated from



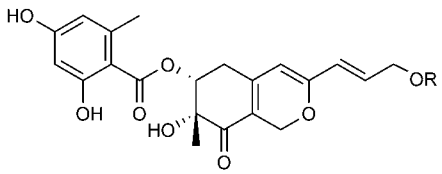
Scheme 31 Proposed biosynthetic pathway to sassafrin D **212**.



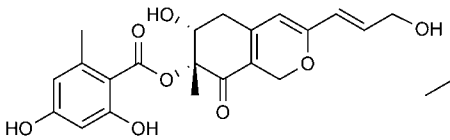
Scheme 32 Proposed biosynthetic pathway to rutilin A **213**.



the fruiting bodies of *Daldinia concentrica*.[92] 2-Chloro-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione **203**, xylariaquinone A **204** and 2-hydroxy-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione **205** have been isolated from the culture of an endophytic fungus, *Xylaria* sp.[93] The structures of **203** and **205** were confirmed by X-ray crystallographic analysis. Pigments **203** and **204** exhibited antimalarial activity against *Plasmodium falciparum* (IC_{50} values of 1.84 and 6.68 μM, respectively) and cytotoxicity against African green monkey kidney fibroblasts (Vero cells) with IC_{50} values of 1.35 and >184 μM, respectively.[93]



215 R = H
216 R = Ac



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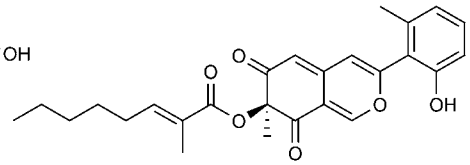

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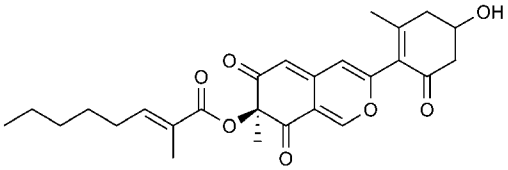

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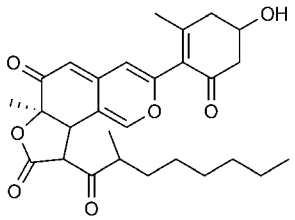

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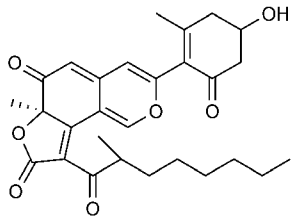

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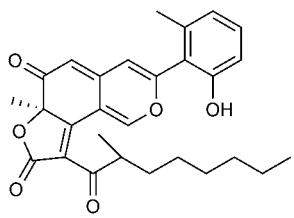

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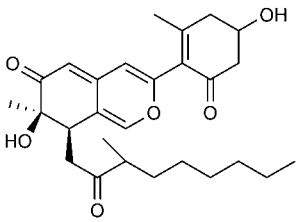

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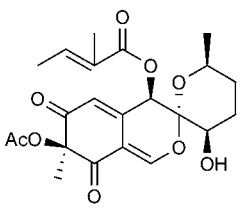

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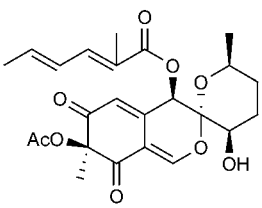

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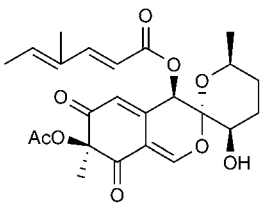

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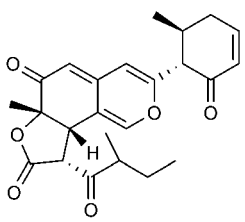

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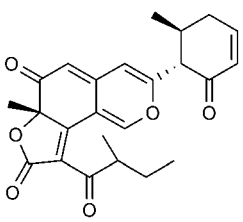

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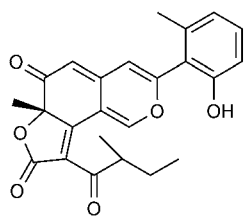

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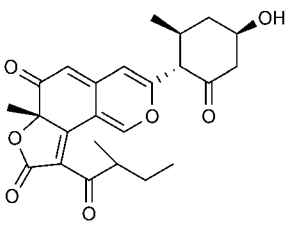

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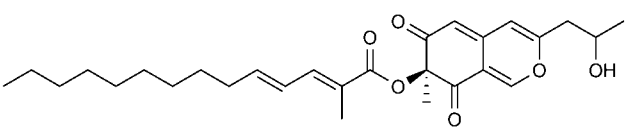
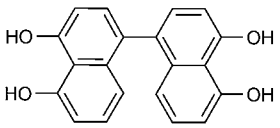


231

Austrogracilins A **206** and B **207** have been easily obtained pure by preparative reverse-phase HPLC of the methanol extract of air-dried fruiting bodies of *Austroboletus gracilis*.[94] Xylarenol **208** was found in the xylariaceous fungus PSU-A80, which was isolated from the leaves of *Garcinia atroviridis*.[95] Four azaphilones, named sassafrins A–D **209–212**, were isolated from the methanol extract of the stromata of the fungus *Creosphaeria sassafras*.[96] Sassafrin D **212** possessed an unprecedented skeleton, and its biosynthetic pathway from **210** is depicted in Scheme 31. All four compounds **209–212** showed broad-spectrum antimicrobial activity.[96]

Azaphilone pigments are produced in abundance in *Hypoxylon* and its relatives, and are known to be chemotaxonomically significant for *Hypoxylon* and allied genera.[97–99] These



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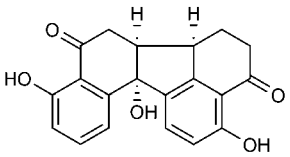

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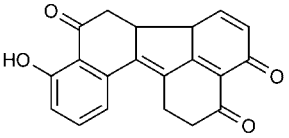

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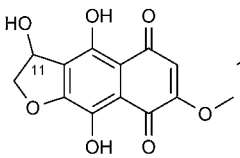
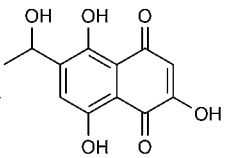


238



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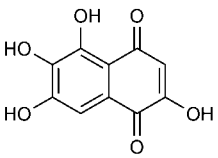

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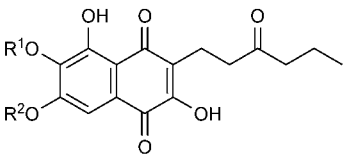
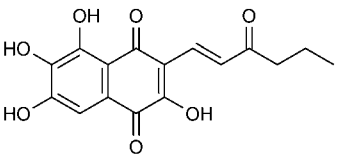


241 $R^1 = R^2 = Me$
242 $R^1 = R^2 = H$
243 $R^1 = Me$, $R^2 = H$



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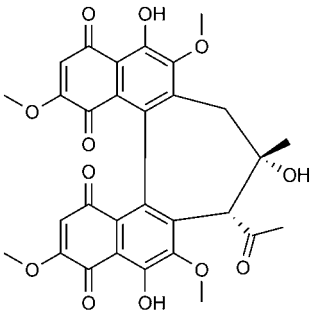

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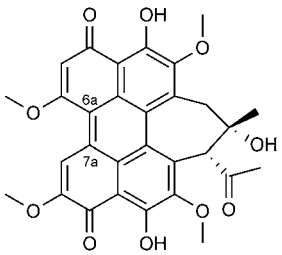
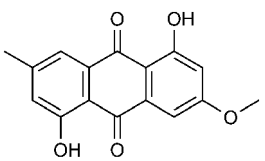


246

azaphilones include rutilins A **213** and B **214**, entonaemin A **215**, and rubiginosins A **216** and B **217** from *Hypoxylon rutilum*,[100] cohaerins A–F **218–223** from *H. cohaerens* (= *Annulohypoxylon cohaerens*),[97,98] daldinins C–F **224–226** from *H. fuscum*,[101] multiformins A–D **227–230** from *H. multiforme* (= *Annulohypoxylon multiforme*),[102] and entonaemin A **215**, rubiginosins A **216**, B **217** and C **231**, and daldinin C **224** from *H. rubiginosum*.[103] A biosynthetic aldol condensation of entonaemin A **215** with dihydromitorubrinol acetate to synthesize **213** is proposed in Scheme 32.[100] Cohaerins C–F displayed moderate inhibitory activity of nitric oxide production in RAW cells, and nonselective antimicrobial effects,[98] while multiformins A–D showed potent and apparently nonselective antimicrobial activity.[102]

Asakawa's group in Japan have used HPLC profiling as a routine procedure in chemotaxonomic studies of *Hypoxylon* and allied genera. According to their chemotaxonomic results, the metabolites that are frequently encountered in *Annulohypoxylon* are cohearins, multiformins, 4,5,4′,5′-tetrahydroxy-1,1′-binaphthyl (BNT) **232**, daldinone A **233**, and truncatone **234**, whereas the genus *Hypoxylon* is instead characterized by the



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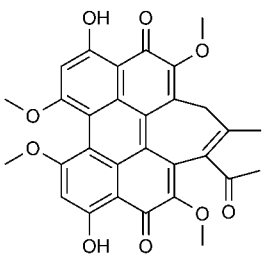

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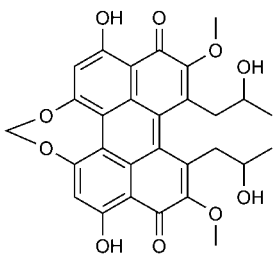

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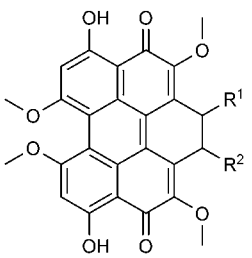
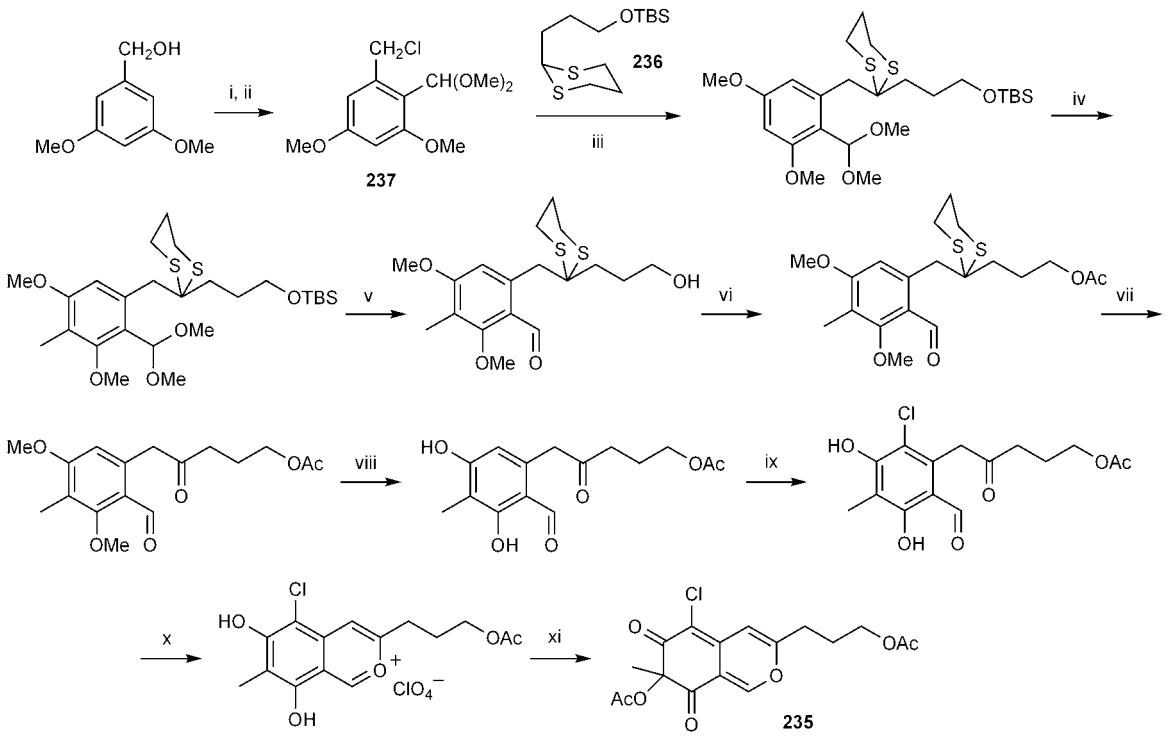
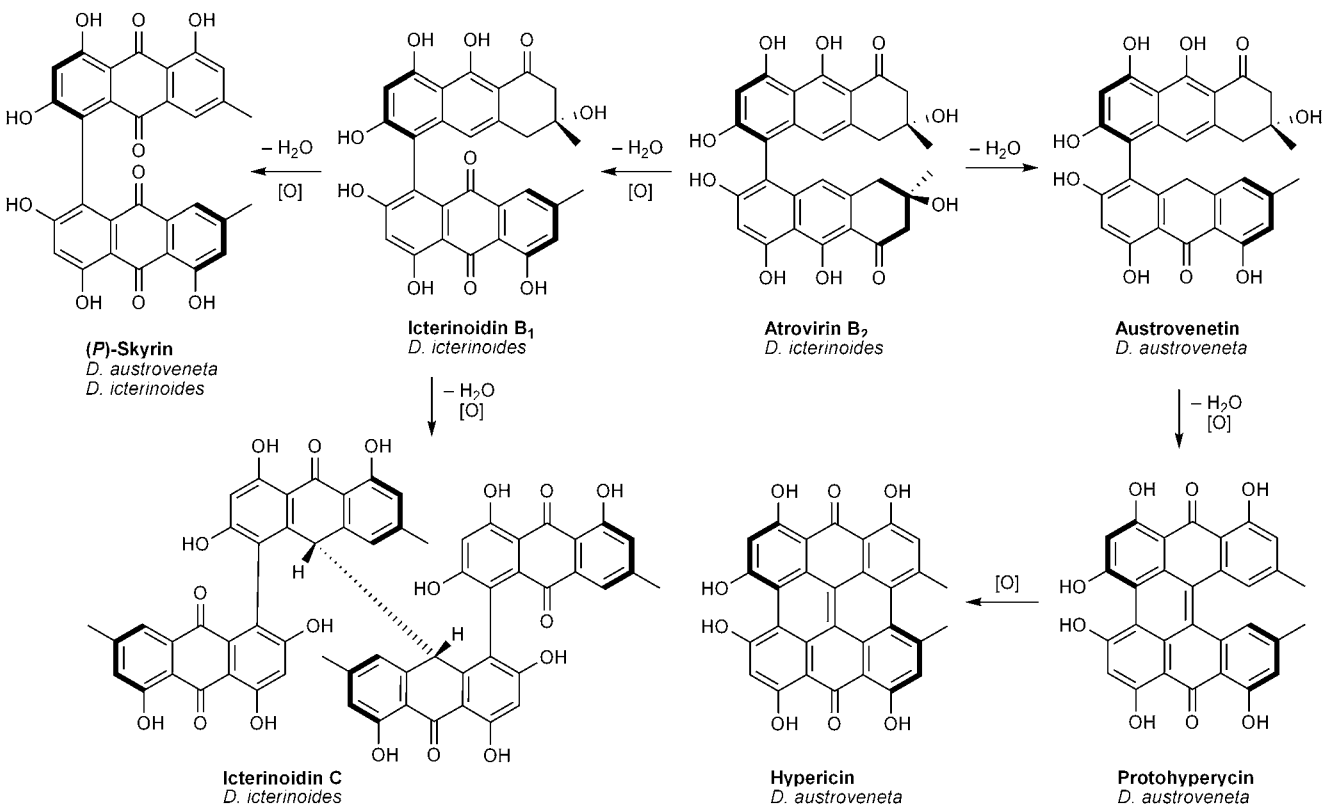


249 $R^1 = R^2 = Ac$
250 $R^1 = Ac$, $R^2 = CH(OH)Me$
251 $R^1 = R^2 = CH(OH)Me$



Scheme 33 *Reagents and conditions*: i, DMF, $POCl_3$, 60 °C (87%); ii, $CH(OMe)_3$, *p*-TsOH, MeOH, 4 Å MS, 50 °C (95%); iii, **236**, *n*-BuLi, THF, −78 °C to −20 °C, then **237** (42%); iv, *n*-BuLi, THF, MeI, −78 °C to −10 °C (75%); v, 1 N HCl, acetone (92%); vi, Ac_2O, Et_3N, CH_2Cl_2, DMAP (cat.) (96%); vii, $Hg(OAc)_2$, CH_3CN–H_2O (4 : 1 v/v) (95%); viii, $AlCl_3$, CH_2Cl_2, reflux (86%); ix, SO_2Cl_2, CH_2Cl_2 (72%); x, HOAc, $HClO_4$, rt, 1 h; xi, HOAc, $Pb(OAc)_4$, rt (51%) (over two steps).



Scheme 34 Possible biosynthetic relationships between members of the 'atrovirin B_2 cascade'.

occurrence of, *e.g.*, mitorubrins, entonaemins, rubiginosins and daldinin-type azaphilones, and by the lack of truncatone, cohaerins and multiformins.[98] This confirmed the acceptance of the new genus *Annulohypoxylon*,[104] which had previously been treated as *Hypoxylon* sect. *Annulata*.

Chloroazaphilone is a common structure found in a number of fungal pigments. A practical synthesis of a model chloroazaphilone **235** (Scheme 33), and reaction of **235** with various primary amines to afford the corresponding vinylogous γ-pyridones, has been fully investigated.[105]

3.2 Hexaketides

Cribrariones A–C **238–240** are naphthoquinone pigments isolated from myxomycetes *Cribraria purpurea*, *C. cancellata*, and *C. meylanii*, respectively.[106–108] Unfortunately, the absolute stereochemistry of C-11 in cribrarione A could not be determined by the Mosher method, since MTPA esterification easily led to dehydration of 11-hydroxyl group to give a furan.[107] Shintani has reported cribrarione C **240** as a natural product for the first time,[108] although it had previously been synthesized from gallic acid by Natori and Kumada.[109] Compound **238** showed antimicrobial activity against *Bacillus subtilis*, whereas compound **239** was inactive against *B. subtilis*.[106,107] Compound **240** exhibited mild TNF-related apoptosis inducing ligand (TRAIL)-resistance overcoming activity against TRAIL-resistant human gastric adenocarcinorma (AGS) cells, but it was inactive against *Staphylococcus aureus* at 50 μg ml^{-1}.[108] 6,7-Dimethoxydihydrolindbladione **241**, dihydrolindbladione **242** and 6-methoxydihydrolindbladione **243** were reported from a myxomycete *Lindbladia tubulina*, while lindbladione **244** has been found in a myxomycete, *Cribraria intricata*.[110]

3.3 Heptaketides

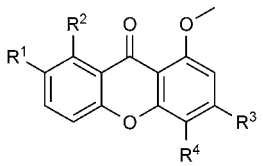
Hypocrellin D **245** and three related perylenequinone derivatives were isolated from the fruiting bodies of *Shiraia bambusicola* collected from China.[111] Structurally, **245** is a 6a,7a-seco product of hypocrellin A **246**, and it significantly inhibited the growth of tumour cell lines Bel-7721, A-549 and Anip-973 with IC_{50} values of 1.8, 8.8, 38.4 μg ml^{-1}, respectively.

Naturally occurring perylenequinonoid pigments (PQPs), such as hypocrellins A **246** and B **247** from *Shiraia bambusicola* and *Hypocrella bambuase*,[112–114] cercosporin **248** from *Cercospora kikuchii*,[115–117] and elsinochromes A–C **249–251** from *Elsinoe* species,[118,119] have long been known as excellent nonporphyrin photosensitizers. Upon exposure to light, perylenequinones initiate the generation of reactive oxygen species, including the superoxide radical anion ($O_2^{\bullet-}$) and singlet oxygen ($^1O_2$), that kill cells. Thus, the perylenequinones are promising photodynamic therapy (PDT) agents for cancer and viral infections. The development of perylenequinonoid PDT agents with lower aggregation tendency, longer absorption wavelengths, higher quantum yields, greater stability, and greater selectivity against cancer cells is of current interest.[120–122]

3.4 Octaketides

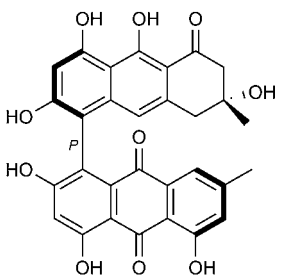
3.4.1 Anthraquinones and anthraquinone carboxylic acids. Shiraiarin **252** was reported for the first time from the submerged fermentation of *Shiraia bambusicola*.[123] The effects of fermentation conditions upon the production of shiraiarin by a submerged culture of *S. bambusicola* were also reported,[123] and lactose as the carbon source, $NaNO_3$ as the nitrogen source, and a pH >8 during the stationary phase were favorable for the production of shiraiarin.

2-Hydroxy-6-methyl-8-methoxy-9-oxo-9*H*-xanthene-1-carboxylic acid **253**, 2-hydroxy-6-hydroxymethyl-8-methoxy-9-oxo-9*H*-xanthene-1-carboxylic acid **254**, 7-hydroxy-3-(hydroxyl-methyl)-1-methoxy-9*H*-xanthen-9-one **255** and 2,5-dihydroxy-8-methoxy-6-methyl-9-oxo-9*H*-xanthene-1-carboxylic acid **256** were four new xanthones found in the microfungus *Xylaria* sp. isolated from the Australian rainforest tree *Glochidion ferdinandi*.[124,125] Methylation of **253** using diazomethane afforded the crystalline compound 2,8-dimethoxy-6-methyl-9-oxo-9*H*-xanthene-1-carboxylic acid methyl ester **257**, whose structure was determined by single-crystal X-ray analysis.[125]



253 R^1 = OH, R^2 = COOH, R^3 = Me, R^4 = H
254 R^1 = OH, R^2 = COOH, R^3 = CH_2OH, R^4 = H
255 R^1 = OH, R^2 = R^4 = H, R^3 = CH_2OH
256 R^1 = OH, R^2 = COOH, R^3 = Me, R^4 = OH
257 R^1 = OMe, R^2 = COOMe, R^3 = Me, R^4 = H

3.4.2 Coupled pre-anthraquinones. The axial stereochemistry of dimeric pre-anthraquinones has been deduced from CD spectroscopy using 'exciton coupling' between the two extended naphthalene chromophores.[126] A compound exhibiting a negative Cotton effect at longer wavelength and a positive one at shorter wavelength (an 'A-type' curve according to Steglich) is consonant with 'negative chirality' (an anticlockwise twist



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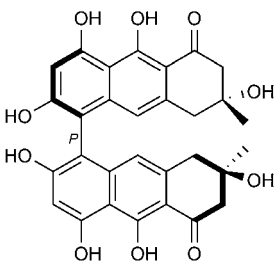

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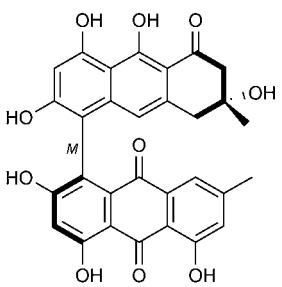

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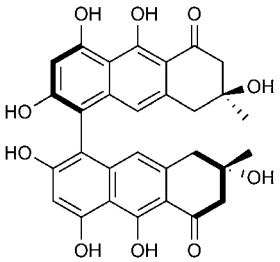
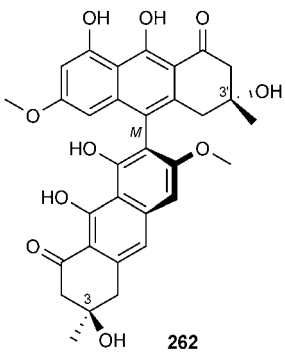


261

between the aromatic chromophores), while a compound showing the mirror-image Cotton effect (a 'B-type' curve) corresponds to 'positive chirality' (a clockwise aromatic helical twist). According to the Prelog–Helmchen rules, a *P*-axial stereochemistry for icterinoidin B_1 **258** and atrovirin B_2 **259**, and an *M*-axial chirality for icterinoidin A_1 **260** were determined. Furthermore, the *P*-axial stereochemistry of **258** was confirmed by Steglich's kinetic resolution method, while the absolute central stereochemistry of **258–261** was assigned by application of the '*syn–anti* rule', which exploits the empirical relationship between the respective CD and ^{1}H NMR spectra of individual pre-anthraquinones.[126] A possible biosynthetic relationship between members of the atrovirin B_2 cascade from *Dermocybe icterinoides* and *D. austroveneta* represents the absolute configuration as *P* (and 3*R*,3′*R*, where appropriate), and is shown in Scheme 34.[126]

The absolute stereostructures of phlegmacins A_1 **262** and B_1 **263** were determined as (*M*,3*R*,3′*R*) and (*P*,3*R*,3′*R*) configurations, respectively, by biosynthetic studies, quantum chemical CD calculations, and NOE experiments. Feeding synthetic (*R*)- and (*S*)-[*methoxy*-^{13}C]torosachrysone to *Cortinarius odorifer*, only the former **264** was incorporated into **262** and **263**. Each of the stereoisomers, **262** and **263**, exhibited a ^{13}C-enrichment of about 3.5% for each methoxy group. By contrast, the mixture of **262** and **263** obtained after feeding (*S*)-[*methoxy*-^{13}C]torosachrysone showed no enhancement of the methoxy signals in the ^{13}C NMR spectrum. This indicated that both **262** and **263** were *R*-configured at C-3 and C-3′ and differed only in their absolute configurations at the chiral axes.[127]



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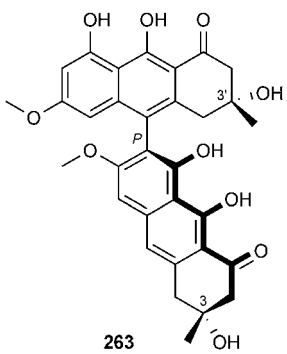

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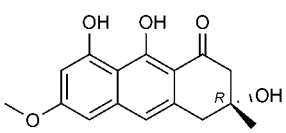
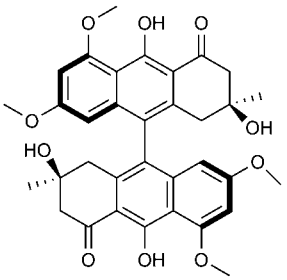


264

The 10,10′-coupled dimers of the dihydroanthracenones are referred to as the tricolorins. The atropisomeric austrocolorins A_1 **265** and B_1 **266** from Australian toadstool *Dermocybe* sp. WAT 26641, are new members of this tricolorin class.[128] Their absolute central and axial configurations were deduced from respective ^{1}H NMR and CD spectra, and confirmed by chemical degradation and chiral HPLC analysis. The ascomycete *Xylaria euglossa* produces phlegmacin A 8,8′-di-*O*-methyl ether **267** and two related pigments.[129] The absolute configuration of **267** was assigned as *P*,3′*S* by comparing the CD and ^{1}H NMR spectra of **267** with those of phlegmacins A_1 **262** and B_1 **263**. It is noteworthy that **267** is the first report of a phlegmacin-type pigment from an ascomycete.[129]



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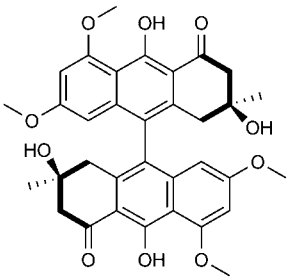

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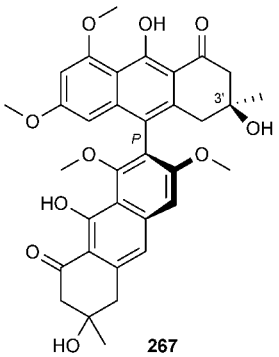
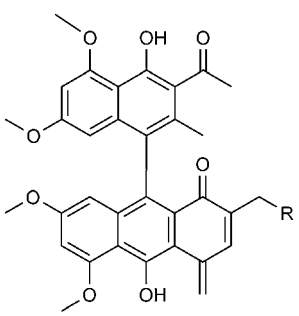


267

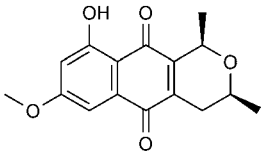
Rufo-olivacin B **268** and rufo-olivacin **269** are two red pigments produced by the fruiting bodies of the Chinese toadstool *Cortinarius rufo-olivaceus*.[130] Their structures were characterized by means of analysis of spectroscopic methods, including 2D-NMR experiments and HR-ESI-MS. Unfortunately, the axial configuration of **268** remains unknown.[130]

3.4.3 Pyranonaphthoquinones. The cardinalins are a series of pyranonaphthoquinone-type pigments isolated from a New Zealand toadstool, *Dermocybe cardinalis*,[131,132] while ventiloquinone L **270**, the monomer of cardinalin 3 **271**, was identified in the root bark of *Ventilago goughii*.[133] Several syntheses of **270** and **271** have been reported.[134–138]

An overview of the synthesis of the fungal metabolites (*S*)-dermolactone **272**, (*R*)-semixanthomegnin **273**, (*R*)-mellein **274**, (*S*)-mellein **275**, (*R*)-ochratoxin α **276**, (−)-(1*R*,3*S*)-thysanone **277**, and the enantiopure ventiloquinones L **270**, E **278** and G **279** from a common chiral intermediate, was presented by Gill.[139] Further methodology potentially leading towards extended



268 R = OH
269 R = H



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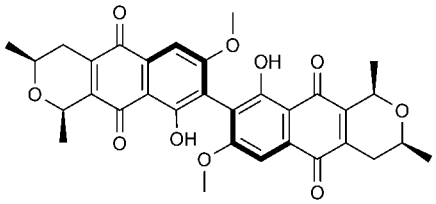


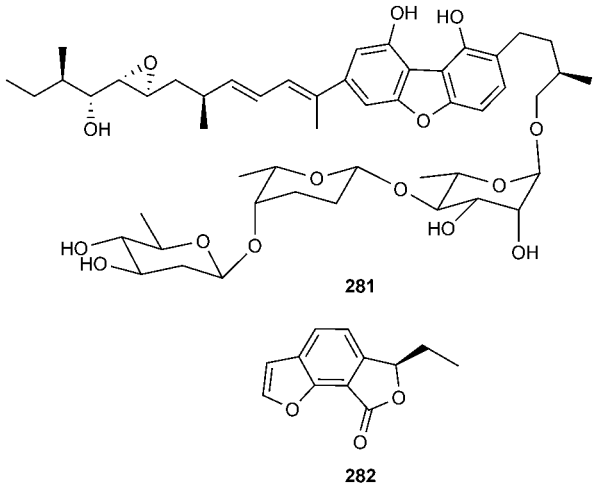
271

quinones such as (3*S*,3′*S*)-xylindein **280** was also outlined in the same paper.[139]

3.5 Other polyketides and compounds of fatty acid origin

The myxomycete *Fuligo cinerea* produces a glycosidic dibenzofuran metabolite, fulicineroside **281**, which was highly active against Gram-positive bacteria and crown gall tumours.[140] Concentricolide **282** has been found in the fruiting bodies of *Daldinia concentrica*, and its structure was confirmed by X-ray crystallographic analysis.[141] Concentricolide **282** inhibited HIV-1-induced cytopathic effects (EC_{50} 0.31 mg ml^{-1}), and it was also effective in the blockage (EC_{50} 0.83 mg ml^{-1}) of syncytium formation between HIV-1 infected cells and normal cells.[141] Synthesis of racemic concentricolide was accomplished recently (Scheme 35).[142]

Aurovertins B **283**, C **284** and E **285** were identified from the culture of *Albatrellus confluens*,[143,144] while aurovertins D **286**, F–H **287–289** have been isolated from the entomopathogenic fungus *Metarhizium anisopliae*.[145] Aurovertins are of polyketide origin and are characterized by a 2,6-dioxabicyclo[3.2.1]octane ring system with a conjugated α-pyrone moiety. **283** can bind to F1-ATPase and thus inhibits ATP synthesis and hydrolysis in mitochondorial enzyme systems.[146]



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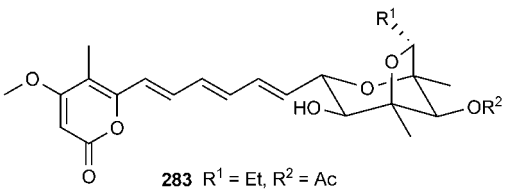
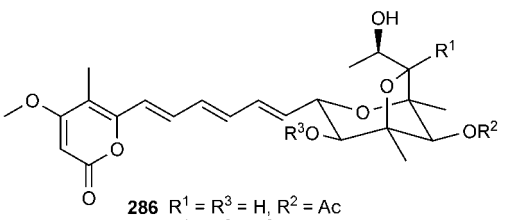
282

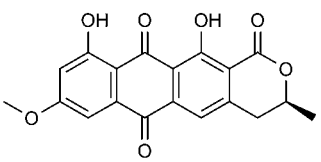
Cyathusals A–C **290–292**, cyathuscavins A–C **293–295**, and the known pulvinatal **296** have been isolated from the fermented mushroom *Cyathus stercoreus*.[147,148] These compounds showed



283 R^1 = Et, R^2 = Ac
284 R^1 = Me, R^2 = Ac
285 R^1 = Et, R^2 = H



286 $R^1 = R^3$ = H, R^2 = Ac
287 $R^1 = R^2 = R^3$ = H
288 R^1 = OH, R^2 = Ac, R^3 = H
289 R^1 = OH, R^2 = H, R^3 = Ac



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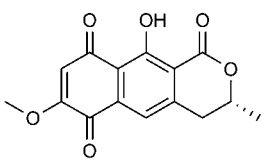

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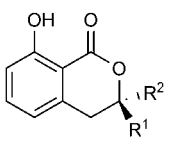
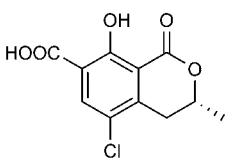


274 R^1 = H, R^2 = Me
275 R^1 = Me, R^2 = H



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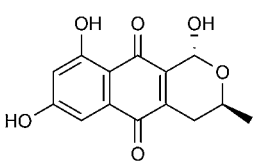

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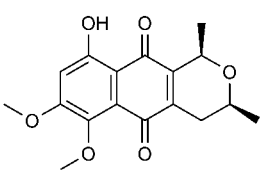

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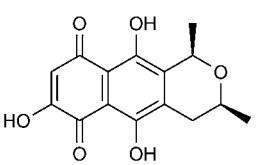

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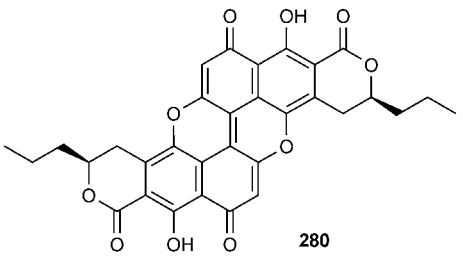

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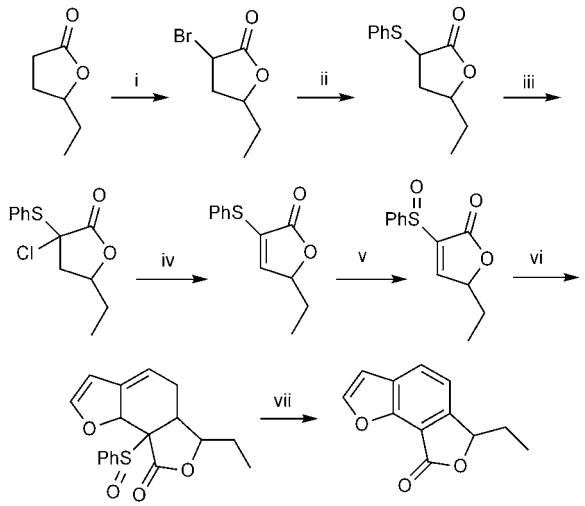
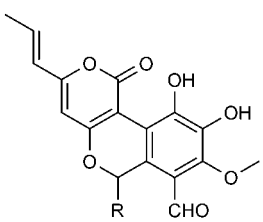


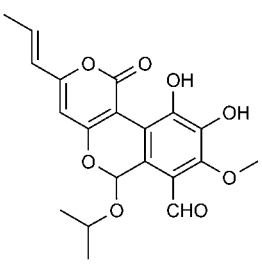
Scheme 35 *Reagents and conditions*: i, PBr_3/Br_2, 70–90 °C (57%); ii, PhSH, Et_3N, Et_2O (98%); iii, NCS, CCl_4, reflux (82%); iv, Li_2CO_3, LiBr, THF, reflux (35%); v, *m*-CPBA, DCM, 0 °C (82%); vi, 3-vinylfuran, hydroquinone (0.1 equiv), rt, toluene, 72 h; vii, $CaCO_3$, toluene, reflux, 19 h.

antioxidant activity, and **293–295** protected supercoiled plasmid DNA from $Fe^{2+}/H_2O_2^-$-induced breakage, which would be due to their abilities to scavenge free-radicals derived from the phenolic moiety and to chelate metal ions by means of the *o*-dihydroxy group of the structures. The metal ion chelating ability of the catechol moiety in **293–295** might combine the with free-radical scavenging ability to afford DNA protection from Fenton-mediated breakage.[147,148]

Fuligoic acid **297** is a yellow pigment with a chlorinated polyene–pyrone acid structure isolated from field-collected fruiting bodies of the myxomycete *Fuligo septica*. The structure of **297** was established by spectroscopic methods, and the absolute configuration of C-5 was assigned as *S* by comparing the CD data with that of a related compound, kawain.[149] Laetiporic acid **298**,[150] later re-named laetiporic acid A,[151] occurred as a mixture of *cis* and *trans* isomers at C-7 in a 6 : 4 ratio. This was the major



290 R = H
291 R = OH
296 R = OMe



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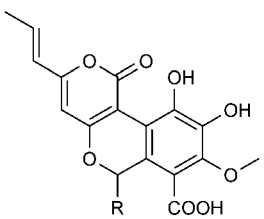
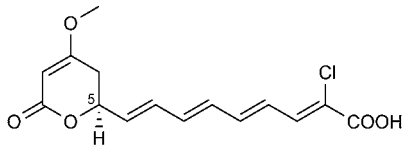
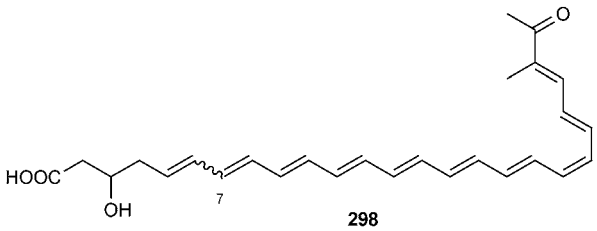


293 R = H
294 R = OMe
295 R = OH



297

orange pigment in the fruiting bodies and liquid cultures of *Laetiporus sulfureus*. A derivative, 2-dehydro-3-deoxylaetiporic acid A **299**, was also found in this fungus.[151] Since fruiting bodies of *L. sulfureus* are edible, laetiporic acids might have potential as food colourants.



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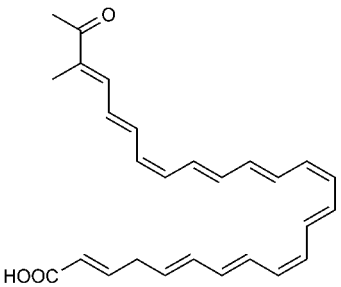
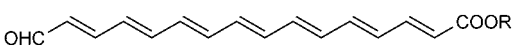


299

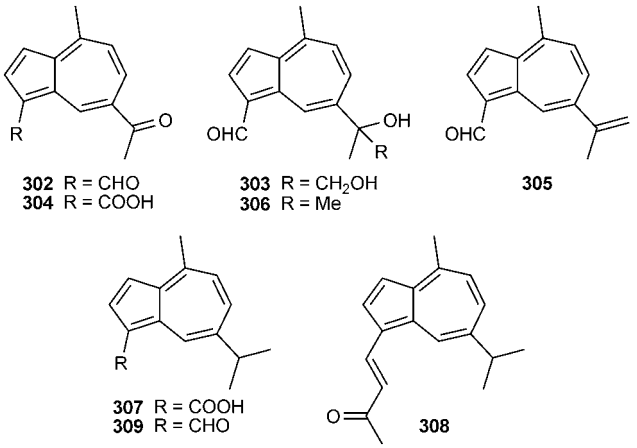
Calolstomal **300**, a polyene pigment, is responsible for the red-orange colour of the stalked puffball *Calostoma cinnabarinum*.[152] Its structure has been identified by ^1H and ^{13}C NMR spectra of the corresponding methyl ester **301** (due to the low solubility of **300**), **301** having been reported before as an intermediate in the total synthesis of a *Xanthomonas* pigment.[152] Fungi of the order Boletales, to which *C. cinnabarinum* belongs, are chemotaxonomically well characterized by the occurrence of hydroxylated pulvinic acids and biosynthetically related shikimate-derived pigments. Nevertheless, none of the typical Boletales pigments were detected in *C. cinnabarinum*.[152]



300 R = H
301 R = Me

4 Compounds from the mevalonate pathway

When the fruiting bodies of *Lactarius deliciosus* are injured, the latex is firstly carrot-coloured, but then slowly (within minutes) darkens, and eventually turns green, these colour changes having been reported to be due to guaiane sesquiterpenes.[153] Isolation of the fruiting bodies of *L. deliciosus* led to four azulene pigments,



302 R = CHO
304 R = COOH

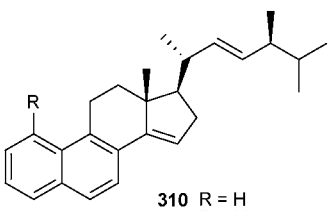
303 R = CH_2OH
306 R = Me

305

307 R = COOH
309 R = CHO

308

7-acetyl-4-methylazulene-1-carbaldehyde **302**, 7-(1,2-dihydroxy-1-methylethyl)-4-methylazulene-1-carbaldehyde **303**, 7-acetyl-4-methylazulene-1-carboxylic acid **304**, 4-methyl-7-(1-methylethenyl)azulene-1-carbaldehyde **305**.[154,155] 7-(1-Hydroxy-1-methylethyl)-4-methylazulene-1-carbaldehyde **306**, 4-methyl-7-(1-methylethyl)azulene-1-carboxylic acid **307**, 1-[(15*E*)-buten-17-one]-4-methyl-7-isopropylazulene **308**, and 4-methyl-7-(1-methylethyl)azulene-1-carbaldehyde **309** have been found in the fruiting bodies of *L. hatsudake*.[156,157] However, **307** had previously been obtained by organic synthesis,[158,159] while **308** might be a work-up product of **309** following aldolization with acetone.



310 R = H
311 R = Me

Two rare aromatic steroids, (17β,20*R*,22*E*,24*R*)-19-norergosta-1,3,5,7,9,14,22-heptaene **310** and (17β,20*R*,22*E*,24*R*)-1-methyl-19-norergosta-1,3,5,7,9,14,22-heptaene **311**, have been isolated from the fruiting bodies of *Daldinia concentrica*, of which **311** bears an unusual methyl group at position C-1.[160] The identification of aromatic steroid hydrocarbons bearing a methyl group at positions 1, 2, 3, 4 or 6 in sediments and petroleum has been puzzling, since possible steroidal precursors have not yet been reported from living organisms. Thus, compounds **310** and **311** could be the long-sought biological precursor steroids for organic matter in Earth's subsurface. Their existence provides a link between biological marker compounds (or 'fossil molecules') and their origin.[160]

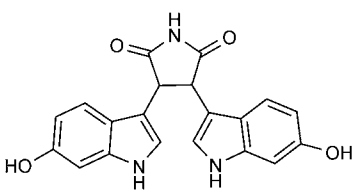
5 Pigments containing nitrogen

Nitrogen-containing compounds of macromycetes, including nitrogenous pigments, have been comprehensively reviewed by our group.[161]

5.1 Nitrogen heterocycles

5.1.1 Indoles. Two unusual 1-hydroxyindole pigments, named birnbaumins A **312** and B **313**, have been isolated from the Yellow Parasol or Flower Pot Parasol (*Leucocoprinus birnbaumii*).[162] Their structures were established by ESI MS/MS, NMR including ^{1}H and ^{15}N HMBC spectra, and chemical methods including permethylation with diazomethane and reduction with zinc in glacial acetic acid. A postulated pathway for the biosynthesis of the birnbaumins which starts from L-tryptophan, citrulline, glycine, and nitrite is depicted in Scheme 36.[162]

Various bisindole alkaoids have been isolated from myxomycetes. These include dihydroarcyriarubin C **314**, arcyriarubin C **315** and arcyriaflavin C **316** from *Arcyria ferruginea*,[163] arcyriaflavins B **317** and C **316** from *Tubifera casparyi*,[163] cinereapyrroles A **318** and B **319** from *Arcyria cinerea*,[164] three new bisindole alkaloids **320–322**, 6-hydroxystaurosporinone **323** and 5,6-dihydroxyarcyriaflavin A **324** from *Lycogala epidendrum*,[164,165] arcyriarubin B 6-*O*-sulfate **325** and arcyroxocin B **326** from *Arcyria denudata*,[166] dihydroarcyriacyanin A **327** from *Arcyria obvelata*,[166] and several related known bisindole alkaoids from these fungi. Both *cis*- and *trans*-dihydroarcyriarubin C were synthesized to determine the stereochemistry of



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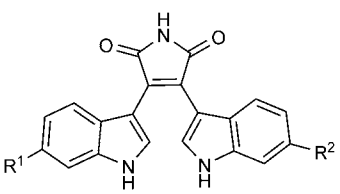
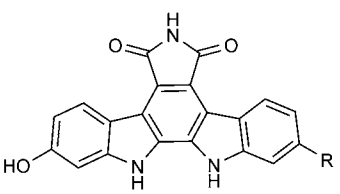
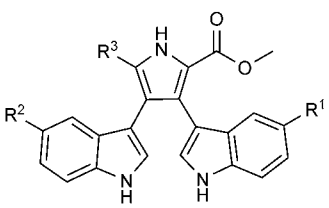


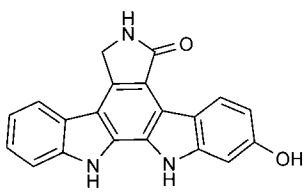
315 $R^1 = R^2 = OH$
325 $R^1 = OSO_3H$, $R^2 = H$



316 R = OH
317 R = H



318 $R^1 = R^2 = OH$, $R^3 = H$
319 $R^1 = OH$, $R^2 = R^3 = H$
320 $R^1 = R^2 = H$, $R^3 = COOH$
321 $R^1 = OH$, $R^2 = H$, $R^3 = COOH$
322 $R^1 = H$, $R^2 = OH$, $R^3 = COOH$



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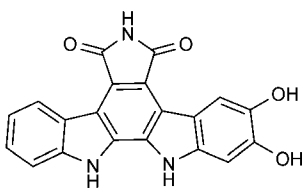

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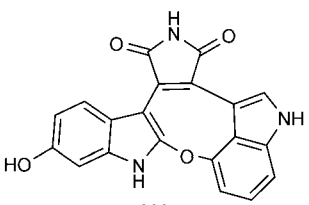

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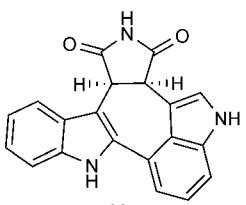

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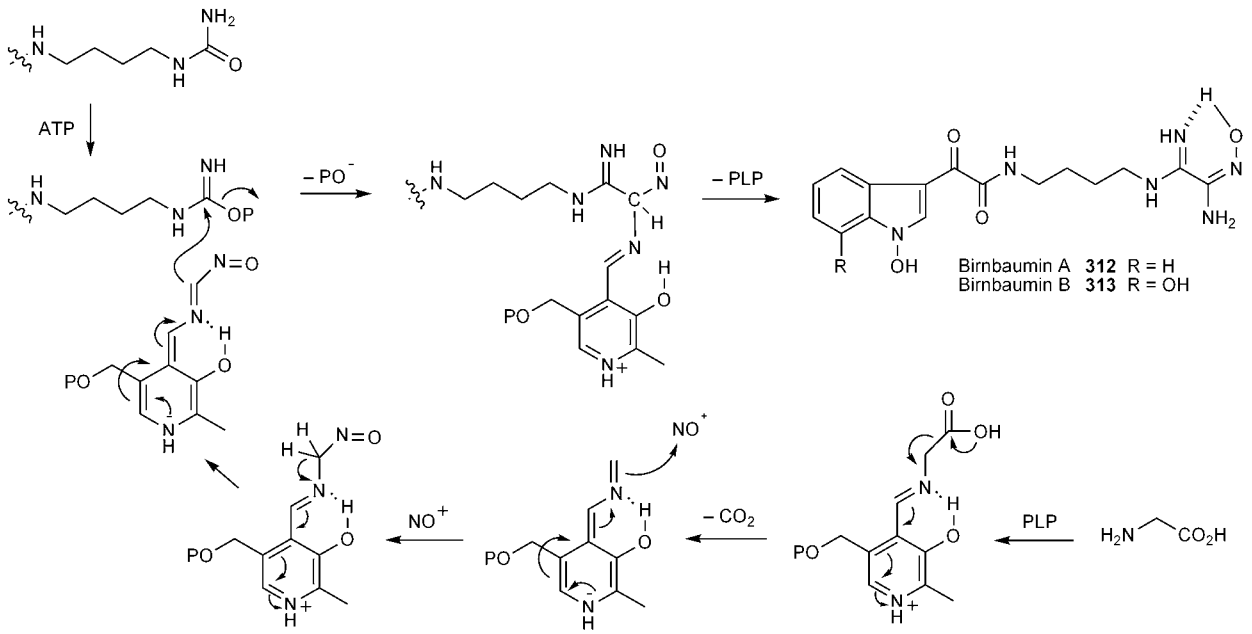
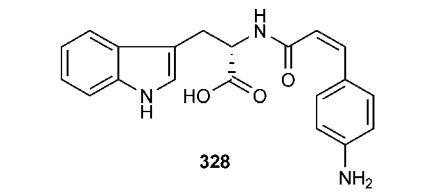


Scheme 36 Proposal for the formation of the *N*-hydroxyoxamidine terminus in the biosynthesis of birnbaumins A **312** and B **313** (the sequence of the C–N and C–C bond formation may be reversed).

dihydroarcyriarubin C **314**. Comparison of their NMR characteristics allowed the *trans* stereochemistry of the natural product to be confirmed.[167] Arcyriaflavin C **316** displayed cell cycle inhibition activity of the G1 and G2/M stages at 10 and 100 ng ml^{-1}, respectively,[163] while arcyriaflavin B **317** showed cytotoxicity (IC_{50} 2.28 μg ml^{-1}) against vincristine (VCR)-resistant KB cells.[164] 6-Hydroxystaurosporinone **323** exhibited protein tyrosine kinase inhibition activities.[165]

Two compounds, *cis*- and *trans*-tryptophan 4-aminocinnamamides (**328** and **329**), were isolated from field-collected fruiting bodies of myxomycete *Fuligo aurea*.[168] Tryptophan 4-aminobenzmide **330** was detected in fruiting bodies of myxomycete *F. candida*.[169] 1-(1-β-Glucopyranosyl)-3-(methoxymethyl)-1*H*-indole **331**, 1-(1-β-glucopyranosyl)-1*H*-indole-3-carbaldehyde **332**, *N*-1-β-glucopyranosyl-3-(carboxymethyl)-1*H*-indole **333** and *N*-1-β-glucopyranosyl-3-(2-methoxy-2-oxoethyl)-1*H*-indole **334** have been found in fruiting bodies of *Cortinarius brunneus*. Compound **333** is the *N*-glucoside of the plant-growth regulator 1*H*-indole-3-acetic acid (IAA), but, in contrast, it did not exhibit auxin-like activity in an *Arabidopsis thaliana* tap root elongation assay.[170]

5.1.2 Quinolines. A group of pyrroloquinoline alkaloid pigments were isolated from *Mycena* species by German chemists.[171–173] These pyrroloquinoline alkaloid pigments included mycenarubins A **335** and B **336** from fruiting bodies of *M. rosea*,[172] sanguinones A **337** and B **338**, sanguinolentaquinone **339**, and decarboxydehydrosanguinone A **340** from *M. sanguinolenta*,[173] mycenarubins A **335**, and D–F **343–345**, sanguinolentaquinone **339**, haematopodin **341**, and haematopodin B **342** from *M. haematopus*.[171] Surprisingly, the name of mycenarubin C was skipped and not used. The absolute configurations of mycenarubins A and B were determined as shown in the formulae **335** and **336** by comparison of their CD spectra with that of a synthetic model compound **346**, which (lacking only the side chain of **335**) was prepared from the known 6,7-bis(benzyloxy)indole **347** (Scheme 37).[172] The absolute configurations were determined as 4*S*,12*S* for **337** and **338**, 4*R* for **342**, and 4*S* for **343–345** by comparison of their CD spectra with that of mycenarubin A **335** or haematopodin **341**.[171,173] Mycenarubin B **336** is



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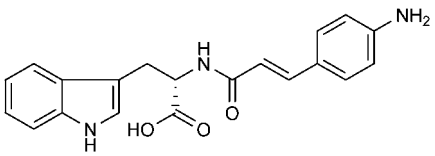

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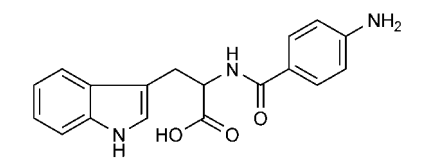

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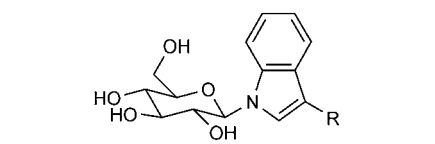
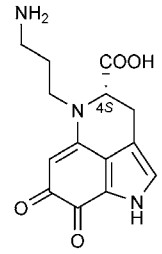


331 R = CH_2OCH_3
332 R = CHO
333 R = CH_2COOH
334 R = CH_2COOCH_3



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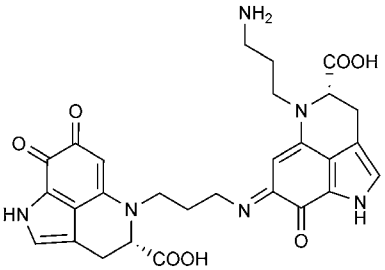

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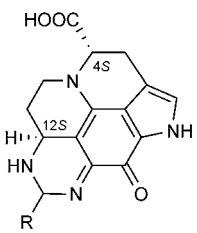
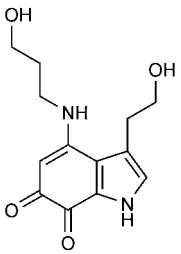


337 R = H
338 R = Me



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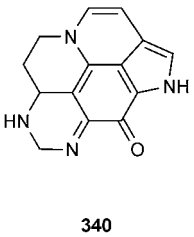

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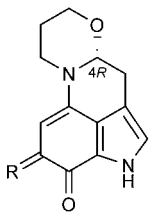
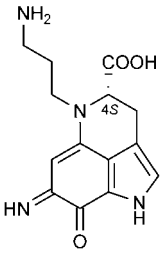


341 R = O
342 R = NH



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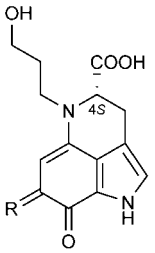
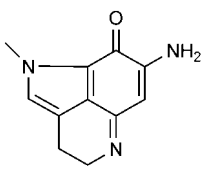


344 R = NH
345 R = O

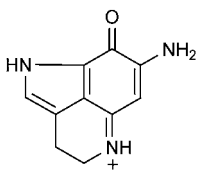


348

the first example of a dimeric pyrroloquinoline alkaloid occurring in Nature.[172] Decarboxydehydrosanguinone A **340** was identified as an oxidative decarboxylation artifact of sanguinone A **337**.[173] Metabolic profiling of the red pigments of intact and injured fruiting bodies of *M. haematopus* by HPLC indicated that the degradation product haematopodin **341** originated from haematopodin B **342**, which is the native main pigment of *M. haematopus*.[171] A hypothetical biosynthesis leading from **344** to **342** and **339** is shown in Scheme 38.[171]

Unlike the previously known pyrroloquinoline alkaloids, mycenarubins A **335**, B **336** and D–F **343–345** have carboxylic groups at C-4, which indicates that mycenarubins might be biosynthetically derived from L-tryptophan and *S*-adenosylmethionine. Previously, pyrroloquinoline alkaloids were isolated from marine sponges.[174] However, makaluvamin A **348** from a culture of the myxomycete *Didymium bahiense*,[175] and the presence of a series of such alkaloids from *Mycena* species,[171–173,176,177] confirmed that pyrroloquinoline alkaloids were not restricted to marine sources but appeared also to be common in some fungi.

A green pigment, makaluvamine I **351**, and a red pigment, damirone C **352**, were isolated from myxomycete *Didymium iridis*,[178] both compounds having previously been reported from a marine sponge, *Zyzzya fuliginosa*.[179] Two quinoline pigments **353** and **354**, and one isocarbostyryl alkaloid **355**, have been isolated from the fruiting bodies of the agaricoid fungus *Cortinarius subtortus*. Compound **353** showed inhibitory activity against the growth of phytopathogenic fungus *Colletotrichum coccodes*. Compounds **353–355** exhibited moderate antioxidant activity of DPPH free-radical scavenging.[180]



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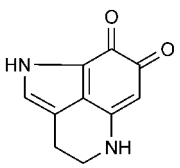

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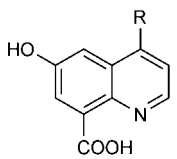
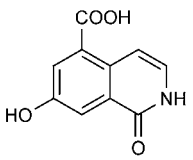


353 R = H
354 R = NH_2



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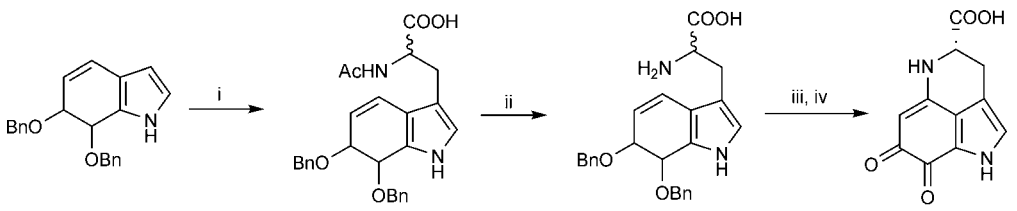
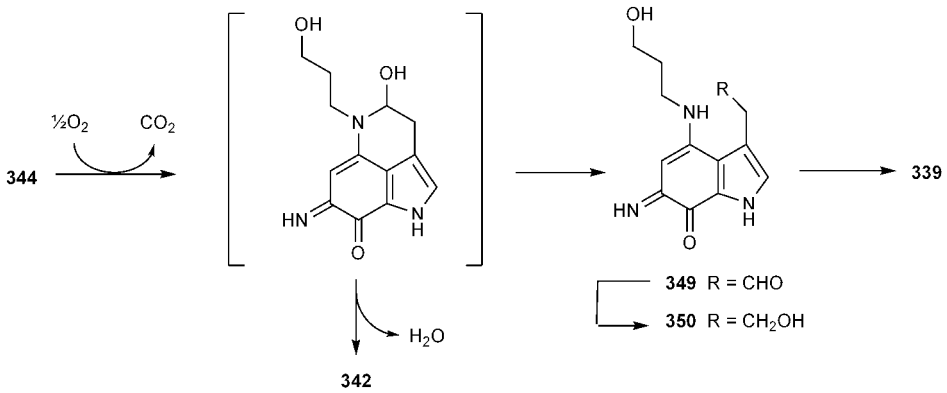
5.2 Compounds derived from anthranilic acid

Fruiting bodies of a myxomycete *Fuligo candida* contained a yellow pigment **356**, which was considered to be derived from

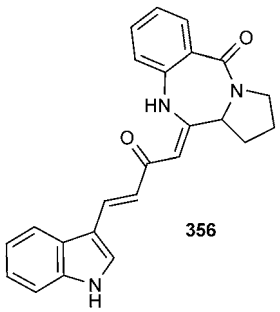


347 346

Scheme 37 *Reagents and conditions*: i, serine, AcOH, Ac_2O, 75 °C, 2 h (73%); ii, acylase I, cat. $CoCl_2$, pH 7.0, 37 °C, 3 h (59%); iii, Pd/C, H_2, 1 h; ix, cat. NEt_3, O_2, 10 min (23%).



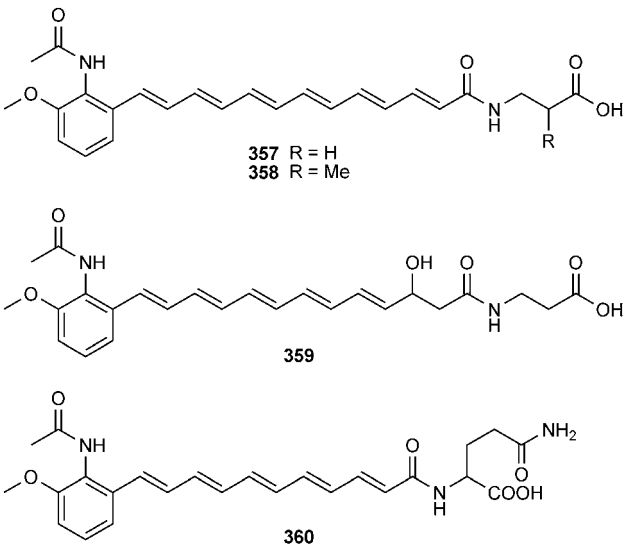
Scheme 38 Hypothetical biosynthesis of **339** and **342** from **344**.



condensation of a cycloanthranilic acid, an acetone, and an indole-3-carbaldehyde.[169]

5.3 Polyenes with tetramic acid or amino acid end groups

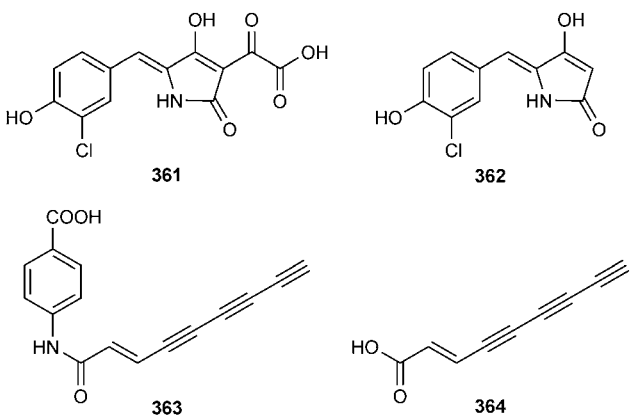
Three new yellow pigments, physarigins A–C **357–359**, have been reported from a cultured plasmodium of the myxomycete *Physarum rigidum*.[181] These yellow pigments are relatively unstable and not easily dissolved in organic solvents, and the HPLC analysis of physarigins A **357** and C **359** revealed that physarigin A was produced from physarigin C. Physarigins A–C are structurally similar to physarochrome A **360**, which is produced by *P. polycephalum* and considered to act as a photoreceptor in the physiology of this organism.[182]



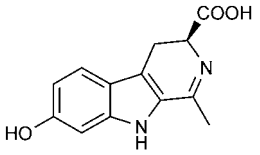
Pachydermin **361**, whose structure was deduced from its degradation product, 5-(3-chloro-4-hydroxybenzylidene)tetramic acid **362**, has been isolated from the fruiting bodies of New Zealand fungus *Chamonixia pachydermis*.[183] A ene-triyne antibiotic **363** from the culture of *Baeospora myosura* is an amide of the C9 ene-triyne carboxylic acid **364** with *p*-aminobenzoic acid.[184] **363** showed potent antibiotic activity against Gram-positive bacteria, while it was less active against Gram-negative bacteria and a yeast. MICs of **363** against several strains of *Staphylococcus aureus* were as low as 0.001 μg ml^{-1}. The potent antibacterial activity of **363** was attributed to its highly reactive property of the conjugated ene-triyne, since analogues of **363** that did not contain the ene-triyne moiety were inactive against all microorganisms.[184]

5.4 Other pigments containing nitrogen

Brunneins A–C **365–367** and 3-(7-hydroxy-9*H*-β-carboline-1-yl)propanoic acid **368** from *Cortinarius brunneus*,[185] harmane **369** and norharmane **370** from fruiting bodies of *Hygrophorus eburneus*,[186] brunnein A **365** from fruiting bodies of *H. hyacinthinus*,[186] and flazin **371** from *Suillus granulatus*,[187] are β-carboline alkaloid pigments. Brunnein A **365** showed very low cholinesterase inhibitory effects and no cytotoxicity,[185] while flazin **371** exhibited anti-HIV activity (EC_{50} = 2.36 μM, therapeutic index = 12.1). A series of flazin analogues were synthesized for



a structure–activity relationship study, and among them, flazinamide **372** showed the most potent anti-HIV activity (EC_{50} = 0.38 μM, therapeutic index = 312.0).[188,189]



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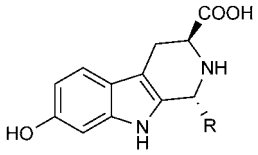
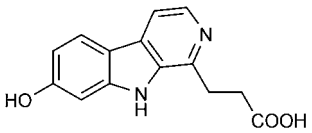


366 R = Me
367 R = H



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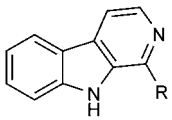
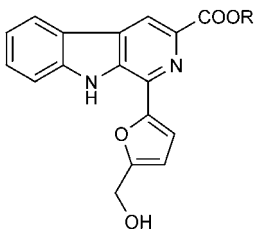
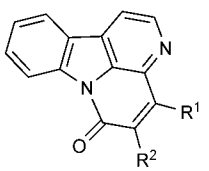


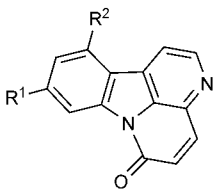
369 R = Me
370 R = H



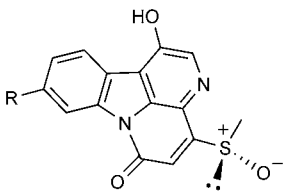
371 R = H
372 R = NH_2



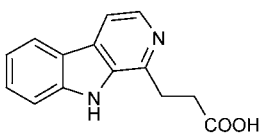
373 R^1 = SMe, R^2 = H
374 R^1 = H, R^2 = SMe
379 R^1 = R^2 = H



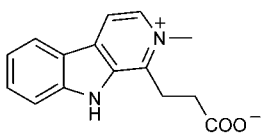
375 R^1 = SMe, R^2 = H
376 R^1 = H, R^2 = SMe



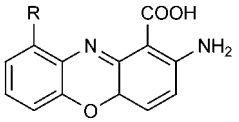
377 R = OH
378 R = H



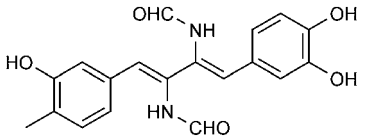
380



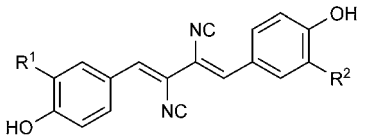
381



382 R = CH(OMe)OH
383 R = CH_2OH
384 R = CHO
385 R = COOH



386

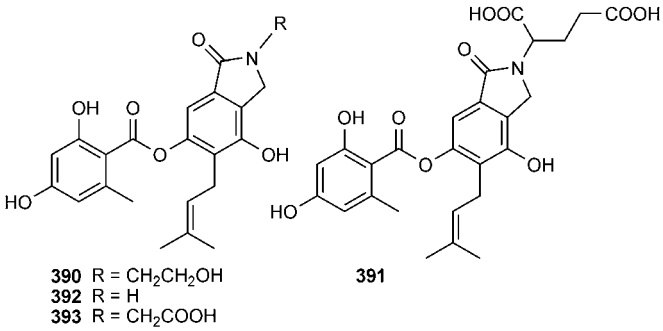


387 R^1 = R^2 = H
388 R^1 = OH, R^2 = H
389 R^1 = R^2 = OH

A unique set of thiomethylated canthin-6-one derivatives, **373–378**, were detected in *Boletus curtisii*, which were accompanied by canthin-6-one **379** and two carbolines **380** and **381**. Pigments **377** and **378**, named curtisin and 9-deoxycurtisin, respectively, are responsible for the bright yellow colour of this mushroom, while compounds **373** and **379** are colourless. The absolute configuration of the sulfoxides in curtisin was assigned as *S* by quantum chemical calculations.[190] These results were partially covered in a previous review.[3]

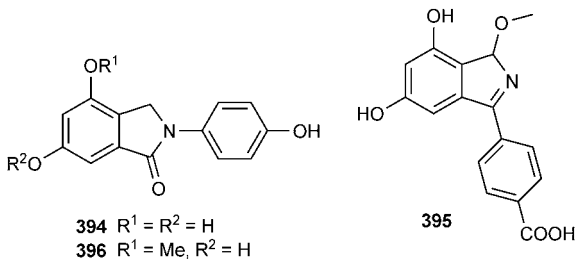
Pycnoporin **382**, cinnabarin **383**, tramesanguin **384** and cinnabarinic acid **385** are phenoxazone alkaloids isolated from the Australian fungus *Pycnoporus cinnabarinus*.[191] Compound **383** showed antitumour activity against murine leukaemia cell line (P388) with IC_{50} of 13 μM at 1 mg ml^{-1}.[191] Cordyformamide **386**, structurally close to xanthocillins X **387**, Y_1 **388** and Y_2 **389**, which are known to occur in *Penicillium notatum*, was isolated from a culture broth of the insect pathogenic fungus *Cordyceps brunnearubra* BCC 1395.[192] Cordyformamide **386** is a plausible biosynthetic precursor of **389**, and it showed activity against the malarial parasite *Plasmodium falciparum* K1 with an IC_{50} of 18 μM.[192]

Sterenins A–D **390–393**, from a solid-state culture of *Stereum* sp. SANK 21205, are potent 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors with IC_{50} values of 0.24, 6.6, 0.23 and 2.6 μM, respectively.[193] The first total synthesis of **390**, **392** and **393** has also been reported.[194] Clitocybins A **394**[195] and D **395**[196] were isolated from the culture broth of *Clitocybe aurantiaca*, while clitocybins B **396** and C **397** were synthesized from modification of **394** for studies of their effect on H_2O_2-induced apoptotic cell death and cellular senescence.[197] Xylopyridine A **398** and pyrocoll **399** have been found in the mangrove endophytic fungus *Xylaria* sp. (#2508) collected from the South China Sea coast.[198] Xylopyridine A **398** showed DNA-binding affinity, presumably *via* an intercalation mechanism in fluorescence quenching and spectrophotometric titration experiments.



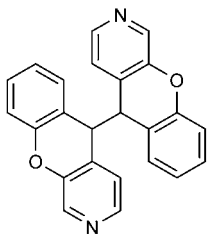
390 R = CH_2CH_2OH
392 R = H
393 R = CH_2COOH

391

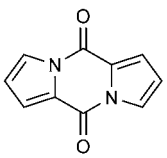


394 $R^1 = R^2 = H$
396 R^1 = Me, R^2 = H
397 $R^1 = R^2$ = Me

395



398



399

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