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# N-Containing Compounds of Macromycetes

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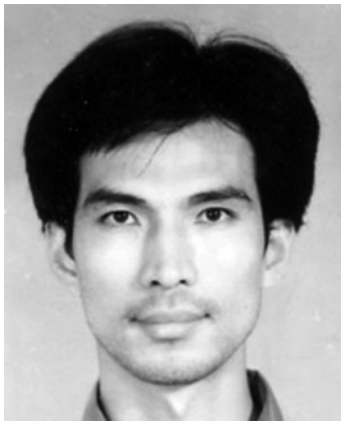
## Contents





Ji-Kai Liu was born in Anhui province of P. R. China in 1962, studied pharmacy from 1978 to 1982 at Anhui College of Traditional Chinese Medicine in Hefei and obtained his M.S. in 1985 at the China Pharmaceutical University in Nanjing. In 1988 he acquired his doctorate at Lanzhou University (organic chemistry). After that he worked at the Department of Chemistry, Zhongshan University in Guangzhou. During 1993-1994 he worked as a research fellow of Alexander von Humboldt at the Institute of Pharmacognosy and Analytical Phytochemistry, University of the Saarland in Germany. Between 1996-1997 he worked as a chemical researcher at the Pharma Research Center of Bayer AG in Wuppertal/Germany. Since 1998 he has been professor of natural products chemistry at the Kunming Institute of Botany, the Chinese Academy of Sciences. His field of work concerns natural bioactive compounds from higher fungi. He has published over 80 scientific papers in international journals. He is the author of the book *Mycochemistry* and also one of the inventors for 8 patents.

## 1. Introduction

Macromycetes are characterized by the production of macroscopic fruiting bodies which generate and distribute their spores. This review surveys the chemical, biological, and mycological literature dealing with the isolation, structure elucidation, biological activities, and synthesis of nitrogen-containing compounds from the fruiting bodies of macromycetes, concentrating on work that has appeared in the literature up to December 2003. In addition, this paper examines the research into some nitrogen-containing compounds produced by macromycetes grown in mycelial culture.

Macromycetes, among the many diverse organisms, are a major source of biologically active natural products. They have often been found to contain biologically active compounds, and they provide a rich variety of active secondary metabolites. There are potentially many compounds still to be discovered in macromycetes since until now only a relatively small number of macromycetes have been chemically investigated, and many of the remaining species are involved in interesting biological phenomena. These as yet unstudied species hold the promise of providing new natural products, many of which will no doubt be nitrogen-containing compounds. That these fungi are often involved in interesting biological processes indicates not only that the new metabolites involved will be chemically interesting but also that the new metabolites may be biologically interesting and significant.

Nitrogen-containing compounds of macromycetes represent unique secondary metabolites with respect to their chemodiversity. The large biodiversity of macromycetes provides a huge resource for extending

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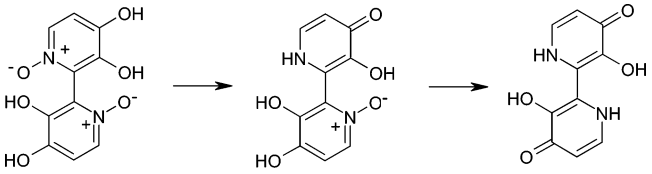
the chemodiversity of nitrogen-containing compounds and for finding new lead structures for medicinal chemistry.

The isolation, characterization, and chemistry of pigments from fungi belonging to the macromycetes have been reviewed comprehensively.[1−5] Turner and Aldridge's monograph presented a comprehensive fungus secondary metabolite list including N-containing compounds that was classified according to biosynthetic origin.[6] While these reviews deal primarily with the chemistry of coloring substances, or more generally, of all types of metabolites manufactured by macromycetes, they also touch upon the subject of nitrogen-containing compounds from macromycetes.

## 2. Nitrogen Heterocycles

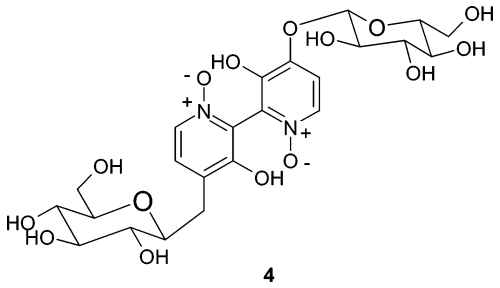
The genus *Cortinarius* represents a complex group of fungi found throughout the world. The abundance of species, together with the high potency of some of their toxins, has led to regular reports of serious intoxications. For example, the toxicity of *C. orellanus* and *C. speciosissimus* is well-known and well-documented.[7] The structure of the toxin was elucidated as 3,3′,4,4′-tetrahydroxy-2,2′-bipyridine-1,1′-dioxide (orellanine) **1** by Antkowiak and Gessner.[8,9] These authors were also the first to mention that this compound undergoes chemical reduction and decomposition by heat or light to the orellinine **2** and finally to a nontoxic compound, the orelline **3** (Scheme 1).[10]

**Scheme 1**



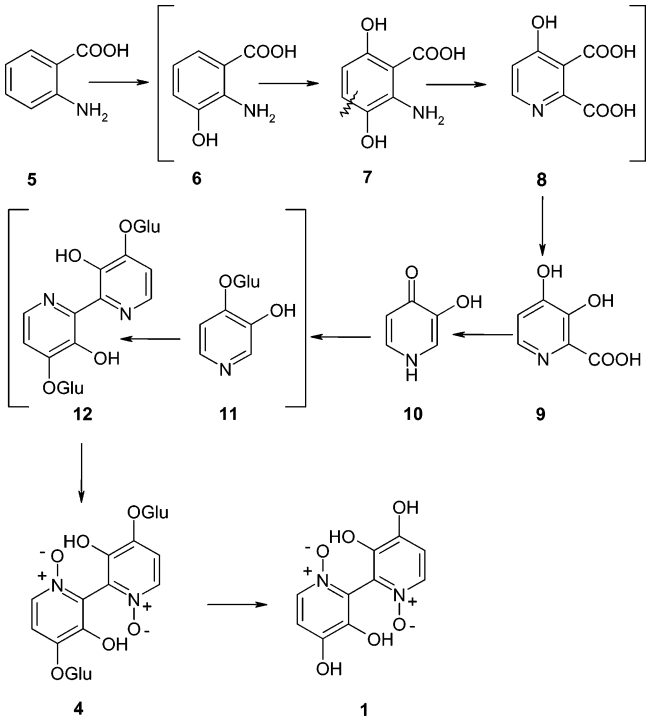
Orellanine is a nephrotoxic bipyridine *N*-oxide found in some *Cortinarius* species. Its mechanism of action is not fully understood, but it has been shown to inhibit protein synthesis and to generate free oxygen radicals. It was reported that generation of oxygen radicals from an iron complex of orellanine may play a major role in some of the known toxic effects of orellanine, and the mechanism of toxicity was correlated with a depletion of glutathione and ascorbate, which are implicated in the defense against oxidative damage.[11] Early symptoms of poisoning by this compound are often lacking or vague, and so initially the possibility of poisoning may be overlooked or the symptoms may be misinterpreted. Unfortunately, this means that affected patients usually appear at the clinic with established renal damage for which supportive care including kidney transplant is the only therapeutic option.[12] Recently, the use of antioxidant therapy in two patients with acute failure caused by *Cortinarius speciosissimus* intoxication was reported from Munich, Germany.[13] The authors presented the case reports of a 30-year-old man and his 29-year-old wife who ingested a mushroom meal containing *C. speciosissimus*.

**Scheme 2**



As mentioned above, the deadly poisonous toadstool *Cortinarius orellanus* causes an irreversible loss of kidney function within 1−2 weeks of ingestion. The responsible toxin, orellanine, was assigned the structure **1,** which has been confirmed by several syntheses and a crystal structure analysis. During the investigation on the biosynthesis of orellanine, it was discovered that the toxin occurs mainly as the water-soluble 4,4′-diglucopyranoside **4** (Scheme 2).[14] On the basis of the results obtained from biosynthetic experiments, a hypothetical pathway depicted in Scheme 3 was proposed even though the order of some steps

**Scheme 3. Hypothetical Biosynthesis of Orellanine 1 from Anthranilic Acid 5[a]**

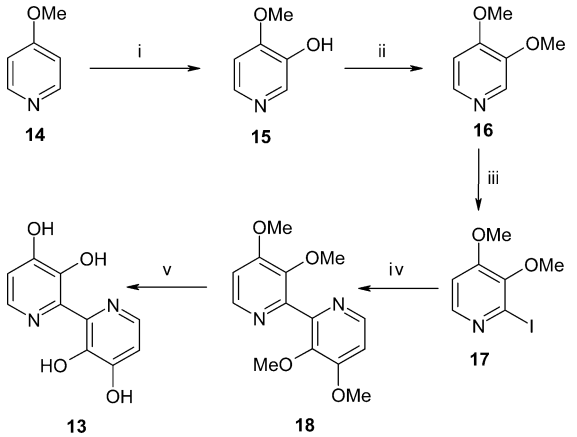


[a] Intermediates in brackets have not been identified in the toadstool.

remains arbitrary. The biosynthesis starts with anthranilic acid **5**, which is converted via **6** into **7.** After oxidative ring opening and a new ring closure, **8** could be generated and then converted by oxidative decarboxylation into **9**, the precursor of **10**. Finally, orellanine (**1**) itself is generated by hydrolysis of the diglucoside **4**.[14]

Orelline **13** is another substance commonly present in the poisonous mushroom *C. orellanus*.[8] It was synthesized by Dehmlow and Schulz[15,16] (eight steps, 1.4% yield), Tiecco et al.[17] (eight steps, 4.4%

**Scheme 4**[a]

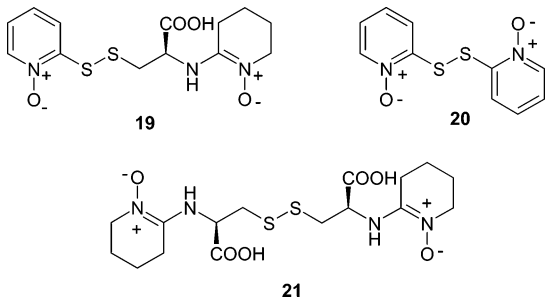


[a] Reagents and conditions: (i) 2.2 PhLi/THF/0 °C/1 h; $B(OMe)_3$/−70 °C; $CH_3CO_3H$ (ii) $CH_2N_2$; (iii) 2.2 *n*-BuLi/THF/−70 or 0 °C/1 h; $I_2$ (iv) $NiCl_2/PPh_3/Zn$; DMF/50 °C/1.5 h; (v) HBr/AcOH.

yield), Hasseberg and Gerlach[18] (five steps, 4.8% yield), and Trecourt et al.[19] (five steps, 16.6% yield, Scheme 4).

Three disulfide metabolites were isolated from the fruiting bodies of a basidiomycete *Cortinarius* sp., collected in the Catlins, New Zealand. The structures of these compounds were determined as the unsymmetric disulfide cortamidine oxide **19**, as 2,2′-dithiobis(pyridine *N*-oxide) **20**, and as the symmetric disulfide **21** (Scheme 5). Both **19** and **20** showed

**Scheme 5**



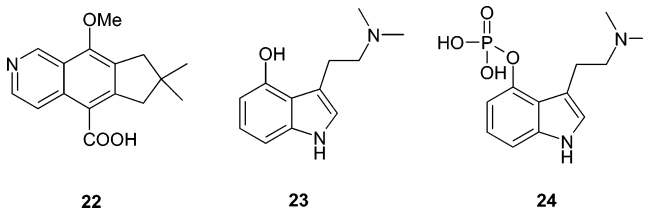
significant antimicrobial activity and cytotoxicity.[20]

The illudins are a group of sesquiterpene antibiotics from *Clitocybe illudens* that have been widely reported as antibacterial and antitumor agents. From the culture of the same species (*C. illudens*), illudinine **22**, a sesquiterpenoid alkaloid, was isolated.[21]

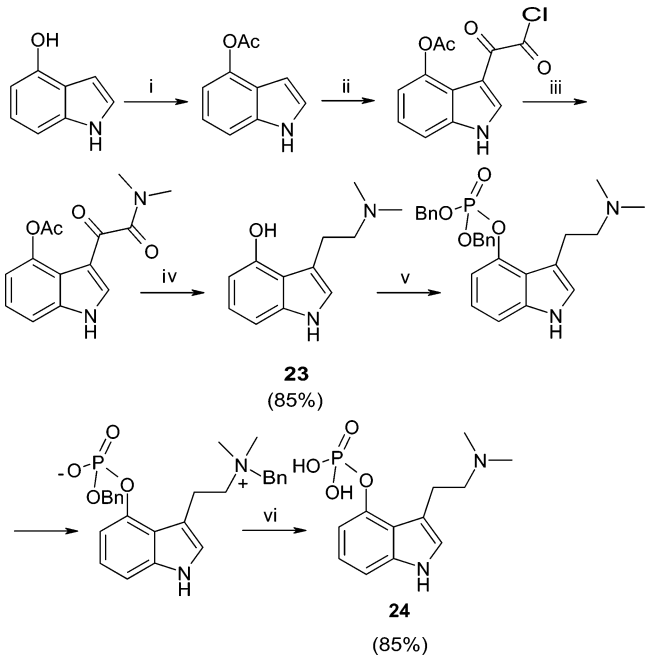
"Magic mushrooms" is the name most commonly given to hallucinogenic fungi containing the psychoactive constituents psilocin **23** and psilocybin **24**, the principal active constituents of *Psilocybe* mushrooms.[22,23] These compounds closely resemble the neurotransmitter serotonin, and the hallucinogenic effect of magic mushrooms is probably caused by their interference with the normal actions of brain serotonin.[24] The use of magic mushrooms has become popular among young people because it is relatively inexpensive and because there is lower awareness of guilt than with other drugs. The concise large-scale syntheses of **23** and **24** were achieved without chromatographic purification (Scheme 7).[25]

Muscimol **25**, a structural analogue of γ-aminobutyric acid (GABA), exhibits central nervous system

**Scheme 6**



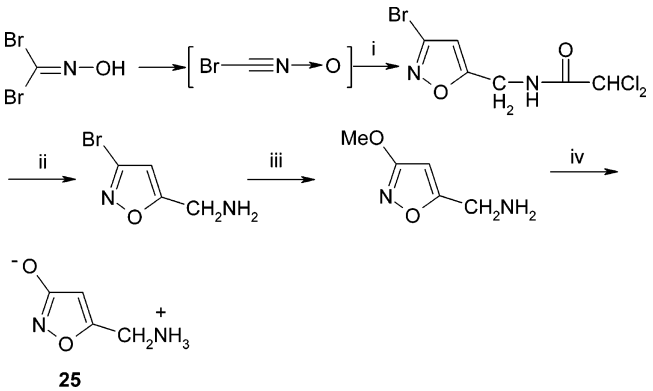
**Scheme 7**[a]



[a] Reagents and conditions: (i) $Ac_2O$, pyridine, $CH_2Cl_2$, 0 °C to room temperature; (ii) $(COCl)_2$, ether, 0 °C, *n*-hexane, then −20 °C; (iii) $(CH_3)_2NH$, THF; (iv) $LiAlH_4$, THF, Δ; (v) $[(BnO)_2PO]_2O$, *n*-BuLi, THF, −78 °C to 0 °C; (vi) $H_2$, Pd/C, MeOH, rt.

activity and is a constituent of the psychotropic mushroom *Amanita muscaria*.[26] It has been the subject of considerable pharmacological interest and synthetic effort (Scheme 8).[27−29]

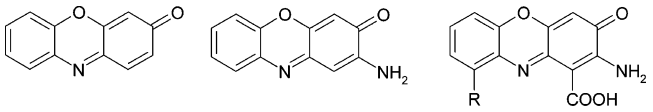
**Scheme 8**[a]



[a] Reagents and conditions: (i) *N*-dichloroacetylpropargylamine, $K_2CO_3$/AcOEt; (ii) 36% HBr ($H_2O$), 120 °C, 4 h; (iii) KOH, MeOH, reflux 48 h; (iv) 33% HBr ($CH_3COOH$), reflux 10 min.

Phenoxazone **26** and α-amino-phenoxazone **27** have been detected in cultured mycelium of *Calocybe gambosa*.[30] Culture fluids of the wood-rotting basidiomycete *Pycnoporus cinnabarinus* produce cinnabarinic acid **28** by the laccase-induced oxidation of

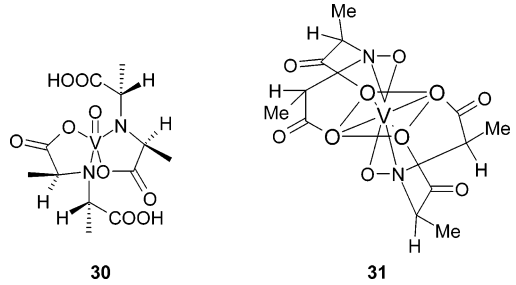
**Scheme 9**




3-hydroxyanthranilic acid.[31] Cinnabarinic acid **28** is active against several Gram-positive bacteria of the *Streptococcus* group. Cinnabarin **29** from *Pycnoporus cinnabarinus* and *Pycnoporus sanguineus* shows antibacterial, antifungal, and antiviral activities.[32] Cinnabarin has a basic ring similar to that of actinomycin D, which is an antibiotic used routinely to treat certain forms of cancer. However, actinomycin D is very toxic to humans. By contrast, cinnabarin at a concentration of 0.31 mg/mL had no effect on mouse neuroblastoma cells, and at doses of 1000 mg/kg it did not cause toxic effects in mice. In addition, at concentrations of 0.31 mg/mL, it produced a 4-fold reduction in the titers of the rabies virus.

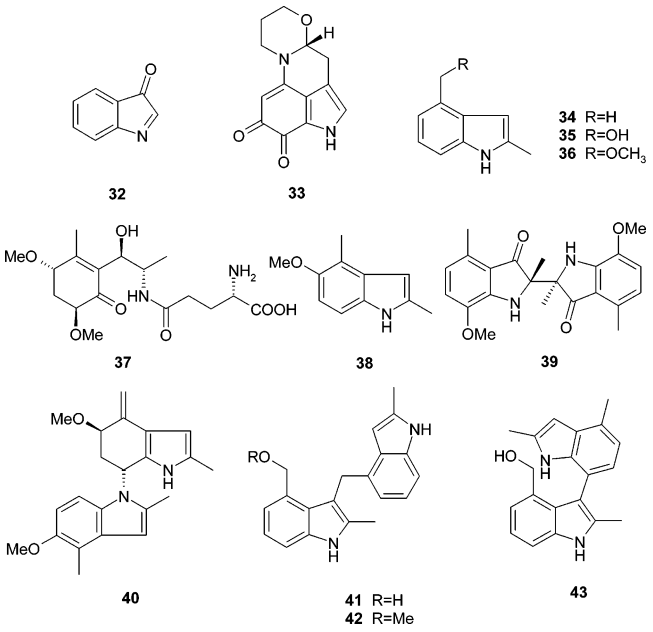
The unusual pale-blue complex amavadin, which contains a vanadium ion and two molecules of *N*-(1-carboxyethyl)-*N*-hydroxyalanine, was first isolated from aqueous extracts of *Amanita muscaria* and was originally assigned the structure **30**. Further investigation with the *N*-(1-hydroxyethyl)-*N*-hydroxyalanine ligand and various cations has revealed exceptionally high selectivity for, and strong binding of, vanadium(IV) and has led to the revised structure **31** for amavadin (Scheme 10).[33]

**Scheme 10**




The simple indolone **32** was isolated from the edible mushroom *Pleurotus salmoneostramineus* as a glycoprotein conjugate by aqueous extraction.[34] Indolone **32** plays a role in the photochemical generation of oxygen from water, suggesting the possible involvement of indolone in photosynthesis. Another indole-based pigment, haematopodin **33**, has been isolated from the red-violet methanolic extracts of the wood-rotting fungus *Mycena haematopus*[35] and was the first pyrroloquinone alkaloid found in a fungus (Scheme 11). Indoles **34**−**36** were isolated from the fruiting bodies of *Tricholoma sciodes* and *T. virgatum*.[36] The indole derivatives found in basidiomycetes are shikimate metabolites whose biosyntheses involve trytophan. A possible precursor of the indoles **34**−**36** is lascivol **37**, isolated as the bitter principle of the fruiting bodies of *T. lascivum*.[37] Upon treatment with a strong acid, lascivol **37** yields the 2,4-dimethyl-5-methoxyindole derivative **38**. The dimeric indoles **39**−**43** are obtained from the bitter-tasting

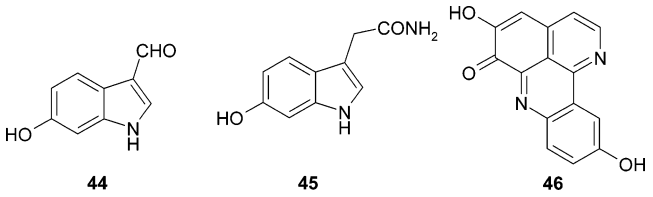
**Scheme 11**




fruiting bodies of *Tricholoma sciodes* and *T. virgatum* (Scheme 11).[38,39]

In the course of screening for free-radical scavenging substances from microorganisms, two simple indoles, **44** and **45**, have been found in the fruiting bodies of *Agrocybe cylindracea* (Scheme 12).[40] **44** and

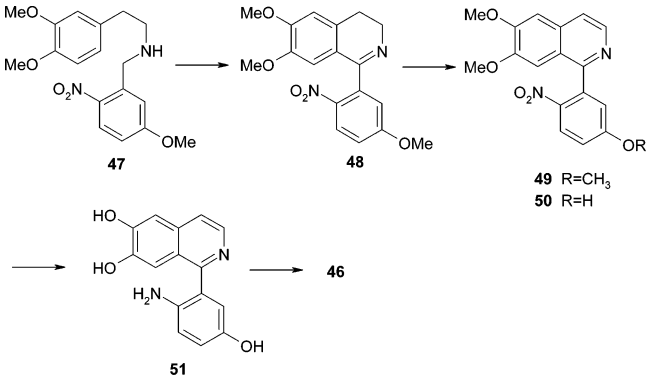
**Scheme 12**




**45** inhibit lipid peroxidation in rat liver microsomes, with $IC_{50}$ values of 4.1 and 3.9 $\mu$g/mL, respectively. Extracts of another toadstool, *Lactarius necator*, exhibit considerable mutagenic activity according to the Ames test.[41−43] Later, Suortti and co-workers isolated a highly mutagenic compound, necatorin, from this fungus and proposed a coumarocinnoline formula for it.[44] Independent work on the pigments of *L. necator* has led to the isolation of an alkaloid, necatorone, for which structure **46** was deduced from spectroscopic data (Scheme 12).[45] Necatorone has the same molecular formula as necatorin, and direct comparison of the two compounds has established their identity. Because of the scarcity of necatorone and its interesting biological activity, Steglich and co-workers[46] finished its synthesis.

Condensation of 2-(3,4-dimethoxyphenyl)ethylamine with 5-methoxy-2-nitrobenzoyl chloride yielded the amide **47**, which on Bischler-Napieralski cyclization ($POCl_3$, acetonitrile, reflux, 4.5 h) was converted into the dihydroisoquinoline derivative **48.** Dehydrogenation was achieved most satisfactorily with $MnO_2$ in benzene under azeotropic water removal; this produced a yield of 90−98% of the isoquinoline derivative **49.** Demethylation of **49** with 48% HBr (11-h reflux, argon atmosphere) and hydrogenation of the

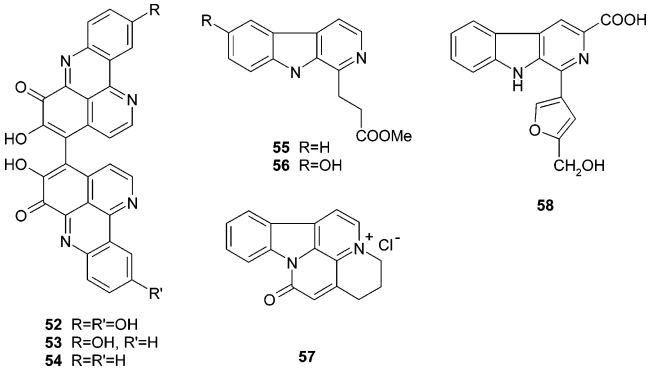
**Scheme 13**



resulting phenol **50** with $H_2$/Pd−C in methanol/water/acetic acid (2:2:1) gave amine **51**, which could be oxidatively cyclized to necatorone by stirring with 5% aqueous sodium hydroxide (Scheme 13).[46]

Necatorone **46**, 4,4′-binecatorone **52**, and the 10-deoxy-4,4′-bineca-torone **53** are the principal pigments of the green-brown cap skin of the toadstool *Lactarius necator* (Scheme 14).[47] In young specimens,

**Scheme 14**

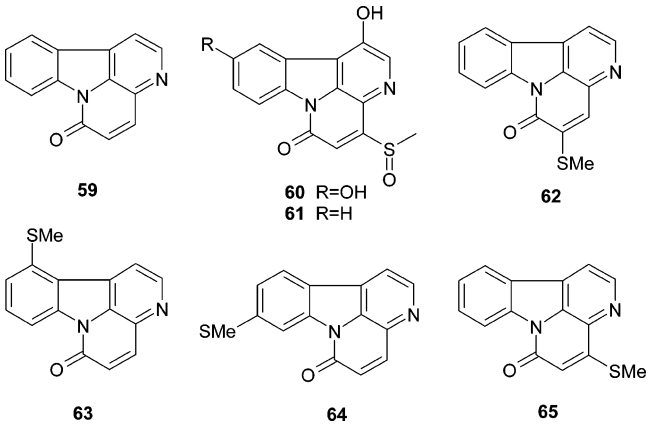


necatorone **46** and its dehydrodimer **52** are found in almost equal proportions whereas in aged fruiting bodies the dimer predominates. Necatorone is responsible for the characteristic purple color that develops when the cap of *L. necator* is exposed to alkali. The American species *L. atroviridis* contains 10,10′-dideoxy-4,4′-binecatorone **54** as the main alkaloid; this is responsible for the dark green appearance of this toadstool.[47]

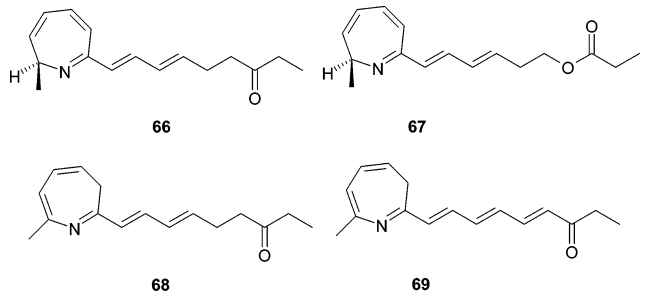
The highly fluorescent $\beta$-carboline derivatives infractin **55** and 6-hydroxyinfractin **56** and the pentacyclic infractopicrin **57** have been isolated from *Cortinarius infractus* (Scheme 14).[48] The latter alkaloid is responsible for the bitter taste of this toadstool. Recently, we also identified a highly fluorescent compound, flazin **58**, from the fruiting bodies of *Suillus granulatus.* This compound was previously isolated from Japanese soy sauce.[49] Another N-containing compound with the canthin-6-one skeleton **59** and several S-containing derivatives **60**−**65** are present in *Boletus curtisii* (Scheme 15).[50]

*Chalciporus piperatus* owes its peppery taste to the 2*H*-azepines chalciporone **66** and chalciporyl propionate **67**, which co-occur with the 3*H*-azepines isochalciporone **68** and dehydroisochalciporone **69**.[51] Because of the unique structure of chalciporone **66**, its

**Scheme 15**

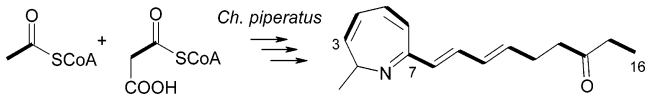


**Scheme 16**



biosynthesis was investigated. It appeared reasonable to speculate that **66** could be formed by cyclization of a linear polyketide chain. Young fruiting bodies of *Chalciporus piperatus*, while growing in their natural forest habitat, were fed with a mixture of [U-$^{13}$C]-labeled fats. This experiment revealed the degradation of the fatty acids to doubly labeled acetate and the incorporation of seven acetate units into chalciporone, leading to $^{13}$C-enrichment of carbons 3−16 (see Scheme 17). In contrast, the methyl

**Scheme 17. Incorporation of Seven Acetate Units into Chalciporone**

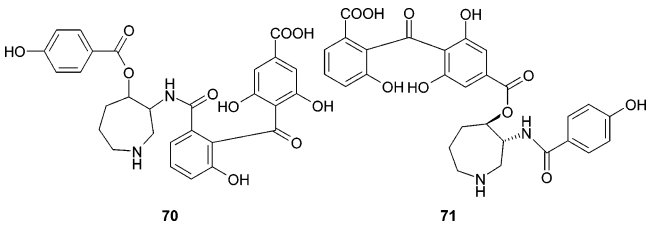


group and the neighboring ring carbon atom C-2 exhibited no detectable $^{13}$C-enrichment.[52] Labeled L-alanine is also incorporated into chalciporone. It provides the methyl group, C-2, and probably the nitrogen atom with concomitant loss of the carboxyl group.

König et al. reported the isolation of ophiocordin **70** from the fungus *Cordyceps ophioglossoides*.[53] A later study was designed to determine if ophiocordin **70** and balanol **71**, a potent protein kinase C inhibitor from *Verticillium balanoides*, are the same compound. The results indicated that the two fungi produced the same compound, the structure being that assigned to balanol **71** (Scheme 18).[54]

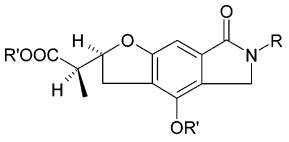
In a screening program, new aldose reductase inhibitors, designated as salfredins $A_3$ **72**, $A_4$ **73**, $A_7$ **74**, $C_1$ **75**, $C_2$ **76**, and $C_3$ **77**, were obtained from the fermentation broth of *Crucibulum* sp. RF-3817 (Scheme 19).[55]

**Scheme 18**



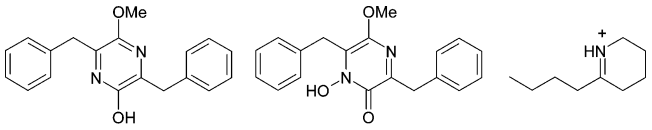
70 71

**Scheme 19**



**72** R=HOOCCH-$CH_2CH_2$COOH R'=H
**73** R=$CH_2$-COOH R'=$CH_3$
**74** R=$CH_3$CH-COOH R'=H
**75** R=H R'=H
**76** R=$CH_2$-COOH R'=H
**77** R=$CH_3$-CH-COOH R'=H

**Scheme 20**

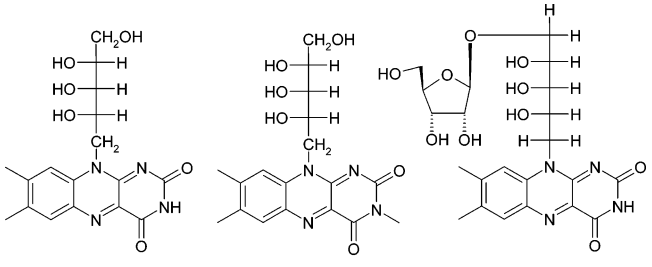


78 79 80

A pyrazine derivative, 3,6-dibenzyl-2-hydroxy-5-methoxypyradine **78**, and emeheterone **79** were isolated from the mushroom *Albatrellus confluens* (Scheme 19).[56] The compound **78** was reported to promote melanin synthesis by B16 melanoma cells.[57] Recently, guided by acute toxicity against mice, a toxic principle, 2-butyl-1-azacyclohexane iminium salt **80**, was obtained from a *Tylopilus* species (Boletaceae) (Scheme 19).[58] 2-Butyl-1-azacyclohexane iminium salt **80** exhibited moderate acute toxicity against ddY mice.

A green fluorescent substance extracted with cold water from the luminous mushroom *Lampteromyces japonicus* was identified as riboflavin **81**.[59] Riboflavin is widely distributed in macromycetes.[1] 3-*N*-Methylriboflavin **82** and riboflavin are responsible for the color of *Panellus serotinus*.[60] Lampteroflavin **83**, which was the first riboflavinyl α-ribofuranoside acting as a light emitter in the bioluminescence of moon night mushroom *Lampteromyces japonicus*, was reported (Scheme 21).[61] Lampteroflavin was

**Scheme 21**

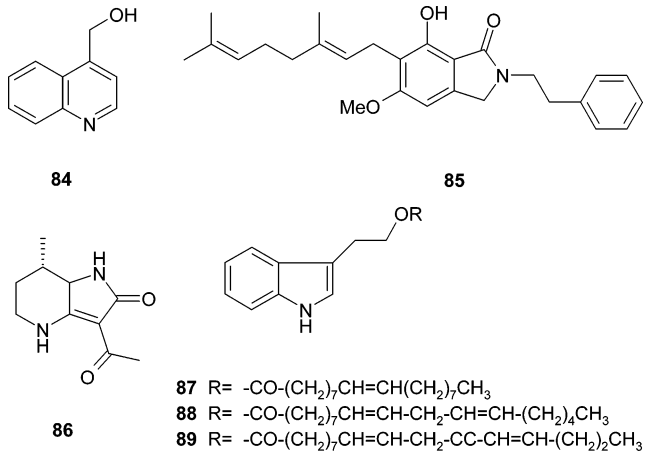


81 82 83

synthesized through coupling between 5-trityl-2,3-(*p*-methoxy)benzylidene-1-β-D-ribofuranosyl trichloroacetimidate and the 2′,4′-(*p*-methoxy)benzylidene derivative of riboflavin to produce the crucial alpha riboside.[62,63]

4-Hydroxymethyl-quinoline **84** was isolated from the wood-rotting fungi *Trametes versicolor* and

**Scheme 22**



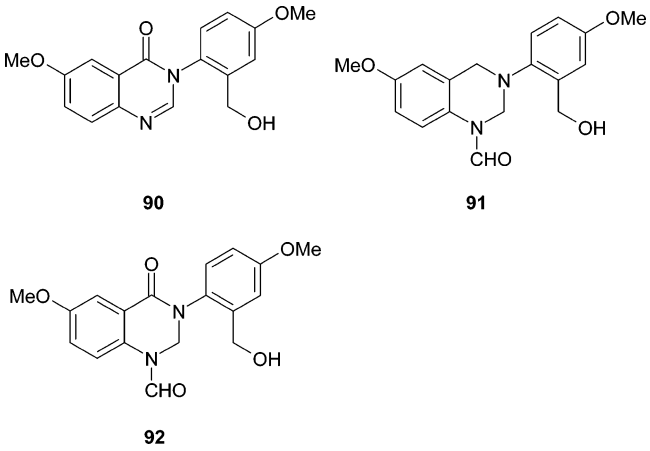
84 85 86

**87** R= -CO-$(CH_2)_7$CH=CH$(CH_2)_7CH_3$
**88** R= -CO-$(CH_2)_7$CH=CH-$CH_2$-CH=CH-$(CH_2)_4CH_3$
**89** R= -CO-$(CH_2)_7$CH=CH-$CH_2$-CC-CH=CH-$(CH_2)_2CH_3$

*Pycnoporus sanguineus*. This was the first detection in fungi of an unoxidized quinoline nucleus, and it is active against malaria.[64] Hericerin **85** from *Hericium erinaceum* inhibits pollen growth.[65] The fruiting bodies of *Laccaria vinaceoavellanea* contain laccarin **86** which shows phosphodiesterase inhibitory activity.[66] The first reports of compounds related to plant hormones concerned the tryptophol esters **87**−**89** which were formed in large amounts by *Craterellus cornucopioides*.[67] The tryptophol esters detected would be suitable for transport through lipid membranes and storage in lipophilic cell compartments.

In an effort to identify neuroprotective compounds effective against the excitatory neurotoxins in edible and medicinal mushrooms, dictyoquinazols A **90**, B **91**, and C **92** have been isolated from the methanolic extract of the mushroom *Dictyophora indusiata* (Scheme 23). Dictyoquinazols protected primary cul-

**Scheme 23**

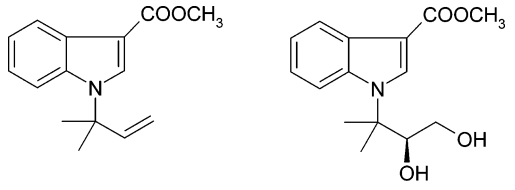


90 91 92

tured mouse cortical neurons from glutamate- and NMDA-induced excitotoxicities in a dose-dependent manner.[68]

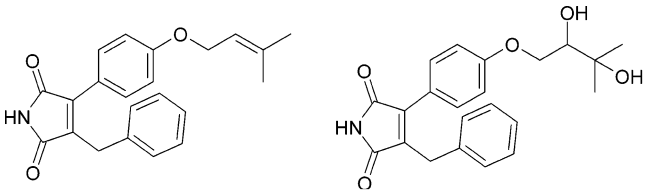
During screening for antifungal and antibacterial fungal metabolites, the fungus *Aporpium caryae* was investigated. The isolation and structural elucidation of two indole alkaloids **93** and **94**, which possess antifungal activity against the phytopathogenic fungus *Cladosporium cucumerinum*, are reported from a culture of *Aporpium caryae* (Scheme 24).[69] A culture of *Serpula himantioides* (Coniophoraceae) also pro-

**Scheme 24**

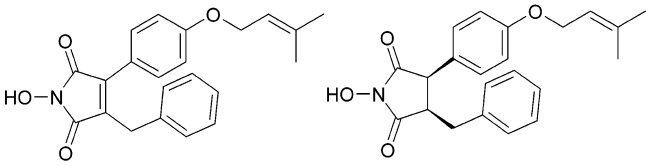



93 94

**Scheme 25**




95 96

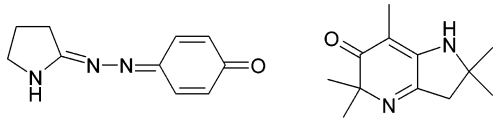



97 98

duced antibiotic metabolites, himanimides A–D **95**–**98** (Scheme 25).[70] Each of these four compounds is either a succinimide or a maleimide derivative, and two of them are N-hydroxylated. The himanimide C **97** exhibited fungicidal effects, especially against *Alternaria porri*, *Aspergillus ochraceus*, and *Pythium irregulare*. It also showed moderate antibacterial activity against Gram-positive bacteria and yeast. Furthermore, **97** also showed cytotoxic activity on HL 60 ($IC_{50}$ 10 $\mu$g/mL) and L1210 ($IC_{50}$ 25 $\mu$g/mL).

*Agaricus xanthoderma* (Agaricales) is a poisonous mushroom that has relatively large caps with prominent rings on the stalks. This mushroom can be easily distinguished because it stains bright yellow when bruised or cut. Careful treatment and chromatographic separation of extracts of *A. xanthoderma* at 0–3 °C isolates agaricone **99**.[71] It was found that *Agrocybe cylindracea* produces a new type of alkaloid, agrocybenine **100** (Scheme 26).[72] Two unusual ni-

**Scheme 26**







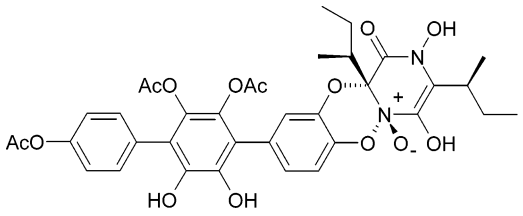
99 100

trogenous metabolites **101** and **102** with a *p*-terphenyl core were isolated from the fruiting bodies of the basidiomycetes *Sarcodon leucopus* and *S. scabrosus*, respectively.[73,74]

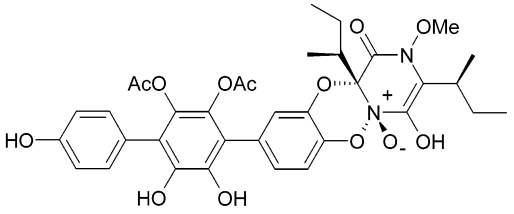
## 3. Nucleosides

Scheme 28 depicts three *N*(9)-alkylated adenines isolated from *Lentinula edodes*.[75,76] Eritadenine **103** in particular demonstrates a significant hypocholesteremic effect by improving the cholesterol transport

**Scheme 27**

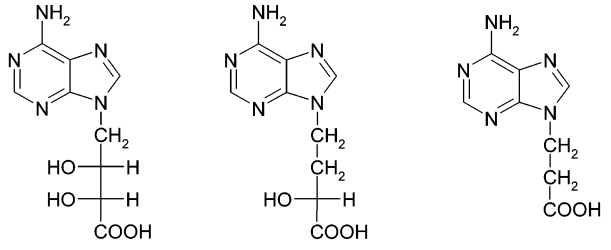



101

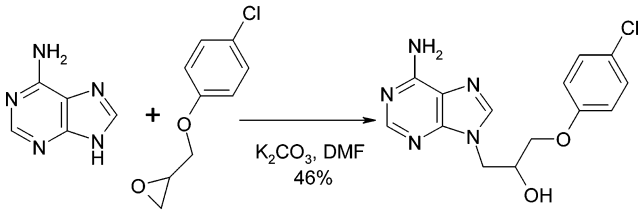



102

**Scheme 28**



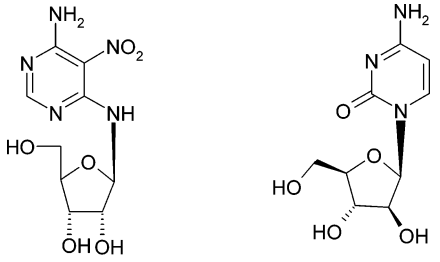

103 104 105




106

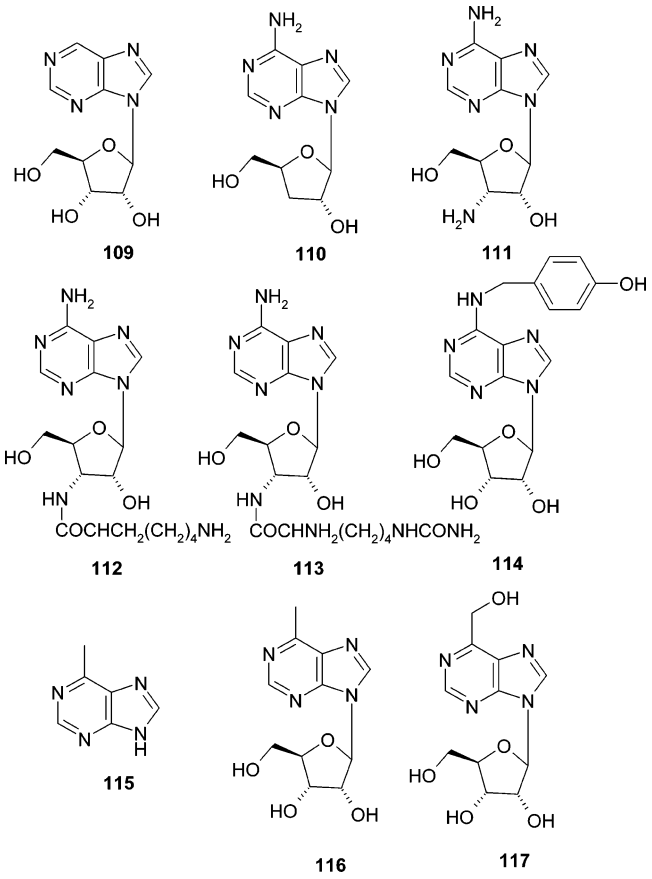
along the blood vessels.[77,78] Therefore, in Asia this mushroom is looked upon as a life elixir. Many eritadenine derivatives (e.g., **104** and **105**) have been synthesized in the past. Synthetic derivative **106** demonstrates the highest hypocholesteremic effect (Scheme 28).[79] Chemical investigation of insect pest control agents produced by mushrooms has led to the isolation of clitocine **107**. This compound showed strong insecticidal activity against the pink bollworm *Pectinophora gossypiella* (Scheme 29).[80] 1-$\beta$-D-Arabinofuranosyl-cytosine (ara-C) **108**, a synthetic anticancer drug, has been reported for the first time as

**Scheme 29**




107 108

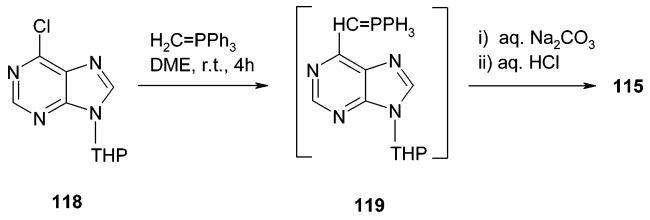
**Scheme 30**




occurring naturally in the mushroom *Xerocomus nigromaculatus* (Scheme 29).[81]

Unsubstituted purine does not exist in nature: the simplest form is the β-D-ribonucleoside nebularine **109**, a nucleoside antibiotic isolated from the mushroom *Lepista nebularis* (Scheme 30). Nebularine **109** is a highly toxic nucleoside. It exerts its toxicity by being a very potent inhibitor of adenosine deaminase.[82,83] Cordycepin **110** and 3′-amino-3′-deoxyadenosine **111**, isolated from the mushroom *Cordyceps militaris*, act as feedback inhibitors of purine nucleotide biosynthesis by inhibiting the phosphoribosylpyrophosphate amidotransferase.[84,85] Cordycepin **110** is also a chain terminator for the 3′-end of the growing RNA chain.[86,87] Antibiotics **112** and **113** from the same fungus inhibit aminoacyl-*t*RNA synthetases.[88,89] Successive purification of a crude extract of cultured Mi Huan Jun (*Armillariella mellea*) mycelia, followed by an assay of the effect on complete ischemia in mice, led to the isolation of AMG-1 **114**, an $N^6$-substituted adenosine with cerebral protecting activity.[90] The first C-alkylated purine, 6-methylpurine **115**, and its riboside **116** and also **117** were isolated from cultures of the mushroom *Collybia maculata* (Scheme 30). Since then, it has been found that these compounds exhibit significant antiviral activity, however, they demonstrate no antibacterial properties.[91] 6-Methylpurine **115** had already been synthesized by Taylor and Martin before its isolation from mushrooms.[92] The reaction involves alkylation of tetrahydropyranyl-protected 6-chloropurine **118** by the Wittig reagent and subsequent hydrolysis of intermediate **119** (Scheme 31).

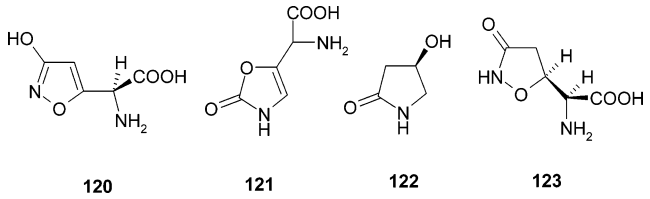
**Scheme 31**




## 4. Nonprotein Amino Acids

It is known that the genus *Amanita* contains various nonprotein amino acids of specific structure, and this area was concisely reviewed by Hatanaka.[93] The fly agaric, *Amanita muscaria*, and *A. pantherina* are the species mainly involved in the pantherina−muscaria poisoning syndrome which is characterized by central nervous system dysfunction. Ibotenic acid **120** and muscimol **25** are the most likely to be the biologically active components, but other active principles are suspected. Ibotenic acid **120** is an isoxazole derivative (Scheme 32).[94] Muscazone **121** would

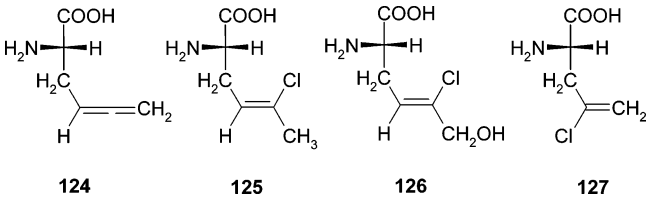
**Scheme 32**




result from photorearrangement of muscimol **25** and is produced during isolation.[95] This amino acid has always been isolated as a racemate. (−)-(*R*)-4-hydroxy-pyrrolidone-(2) **122**, whose structure is closely related to ibotenic acid and muscimol, was found in *Amanita muscaria* (Scheme 32).[96] Tricholomic acid **123**, a dihydro derivative of ibotenic acid, has been identified in *Tricholoma muscarium*.[97]

A naturally occurring allenic amino acid **124**, *trans*-2-amino-5-chloro-4-hexenoic acid **125**, and *trans*-2-amino-5-chloro-6-hydroxy-4-hexenoic acid **126** have been found in *Amanita solitaria* (Scheme 33).[98,99]

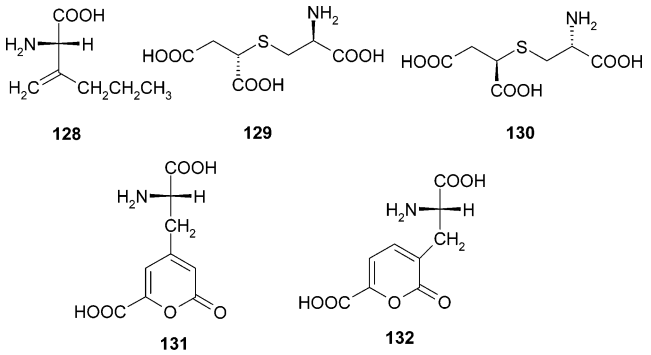
**Scheme 33**



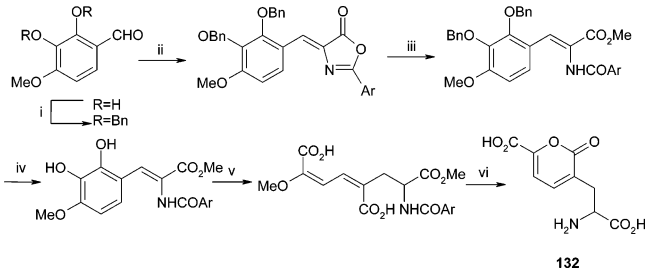

2-Amino-4-chloro-4-pentenoic acid **127**, a closely related derivative, has been reported from *A. pseudoporphyria*.[100]

(2*S*)-Amino-3-methylenehexanoic acid **128** has been found in *Amanita vaginata*.[101] Two compounds reported in *A. pantherina* are (1′*R*,2*R*)-[(2-amino-2-carboxyethyl)thio]butanedioic acid **129** and (1′*S*,2*R*)-[(2-amino-2-carboxyethyl)thio]butanedioic acid **130** (Scheme 34).[102] Stizolobic **131** and stizolobinic acids **132**, which are known to occur in *Stizolobium hasjoo*, have also been found in *A. pantherina* and in low levels in *A. gemmata*, but these compounds have not

**Scheme 34**



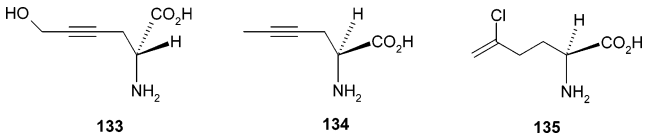
**Scheme 35**[a]



[a] Reagents and conditions: (i) BnBr/$K_2CO_3$/DMF/rt (89%); (ii) $Ac_2O$/3-$(CF_3)C_6H_4C(O)NHCH_2COOH$/NaOAC/100 °C (72%); (iii) MeOH/$Na_2CO_3$/Δ (95%); (iv) 10% Pd(C)/MeOH/$H_2$/rt (100%); (v) AcOH/AcOOH/$Fe(Oac)_2$OH/rt (45%); (vi) c.HCl/100 °C (65%).

been detected in *A. muscaria*.[103] **131** and **132** exhibit an excitatory action in isolated rat spinal cord.[104] A biomimetic synthesis of stizolobinic acid (±)**132** was achieved from an analogue of L-DOPA via an oxidative cleavage reaction (Scheme 35).[105]

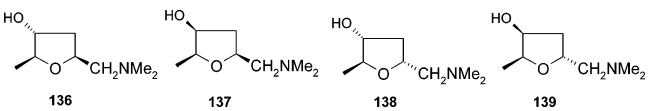
**Scheme 36**



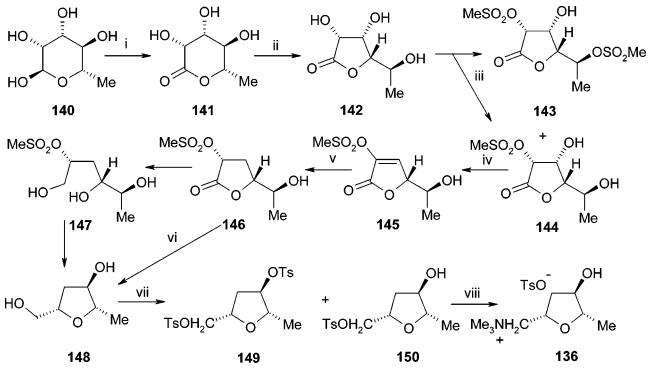
Scheme 36 depicts (2*R*)-2-amino-6-hydroxy-4-hexynoic acid **133**, (2*S*)-2-amino-4-hexynoic acid **134**, and 2-amino-5-chloro-5-hexenoic acid **135**, which were all isolated from the fruiting bodies of *Amanita miculifera*.[106] **134** had been found first in the fruiting bodies of *Tricholomopsis rutilans*.[107] **133** exists in pure D-form and its possible direct precursor, **134**, occurs predominantly in the L-form.

Muscarine was long considered to be the active principle in *A. muscaria*, because of a presumed action on the central nervous system. This has since been discredited. Muscarine **136**, *epi*-muscarine **137**, and *allo*-muscarine **138** have been detected in the mycelium of *A. muscaria* (Scheme 37).[108] The occurrence of *epiallo*-muscarine **139** was not demonstrated unambiguously.[109] Synthesis of muscarine has been accomplished several times from different precursors.[110−113] Moreover, a chemoenzymatic synthesis of eight stereoisomers of muscarine has been reported.[114] The renewed interest in this molecule is due, in part, to the suggestion that various subtypes of muscarinic receptors may be implicated in Alzheimer's Disease. Synthesis of (+)-muscarine from L-rhamnose was finished later. This synthesis does not require the use of any protecting group (Scheme 38).[115]

**Scheme 37**



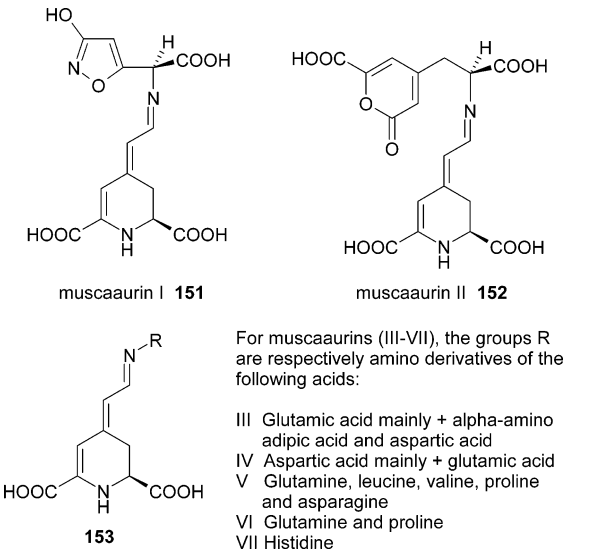
**Scheme 38**[a]



[a] Reagents: (i) $Br_2$, $BaCO_3$, $H_2O$; (ii) $CF_3CO_2H$, $H_2O$; (iii) $MeSO_2Cl$, DMAP, pyridine; (iv) $(CF_3CO)_2O$, $Et_3N$, THF; then AcOH, MeOH; (v) 10% Pd−C, EtOAc; (vi) $LiBH_4$, THF; then NaOAc, MeCN; (vii) TsCl, THF, pyridine; (viii) $Me_3N$, MeOH.

Several compounds, the muscaaurins I−VII **151**, **152**, **153**, have been proved to be the pigments responsible for the characteristic red-orange color of the caps of several *Amanita* species (Scheme 39).[116] Mus-

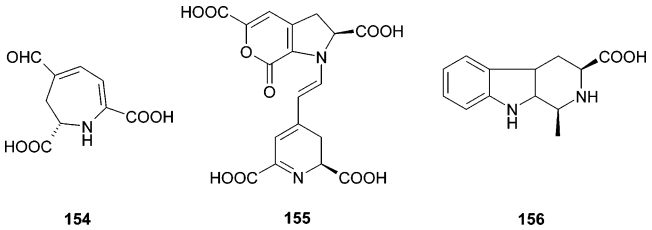
**Scheme 39**



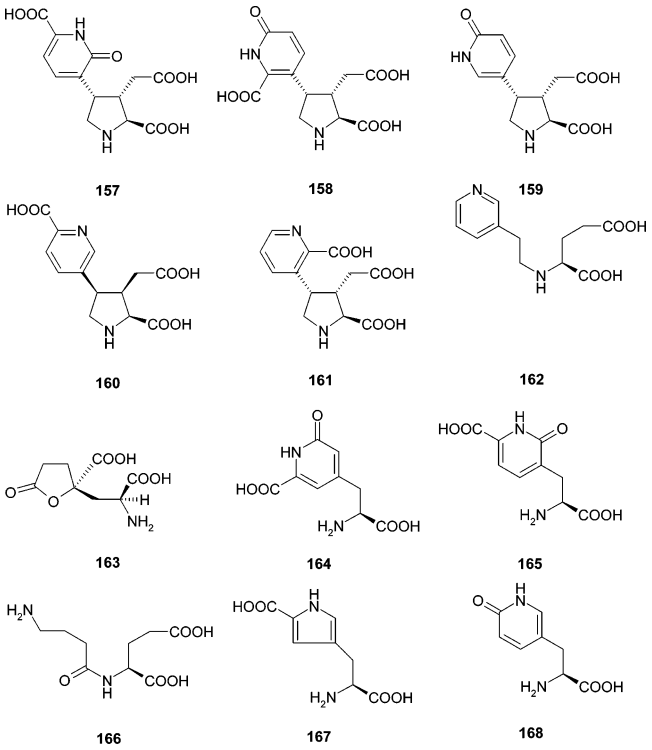

caflavin **154**, a yellow pigment, muscapurpurin **155**, a red-violet pigment, and 1,2,3,4-tetrahydro-1-methyl-β-carboline-3-carboxylic acid **156** have also been found in *A. muscaria* (Scheme 40).[116,117] The structure of **154** has been confirmed by synthesis.[118,119] It has also been detected together with L-Dopa in the blackening fruiting bodies of *Hygrocybe conica*.[120]

The isolation and concise syntheses of acromelic acid A **157** and acromelic acid B **158**, neuroexcitatory compounds from the mushroom *Clitocybe acromelalga*, have been variously reported.[121−124] The synthesis of **157** involves an oxidative cleavage−recyclization strategy to construct the C-4 pyridone from an

**Scheme 40**



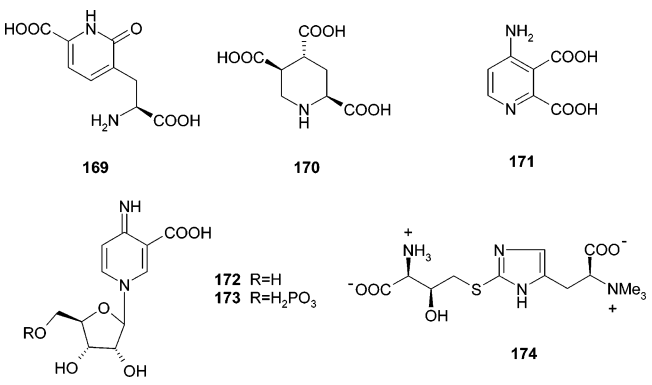
**Scheme 41**



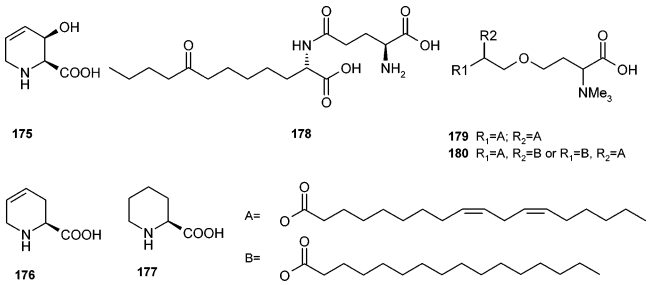
intermediate catechol. Acromelic acids C **159**, D **160**, and E **161** have also been found in *C. acromelalga*.[125,126] **162** from the same fungus is a possible intermediate in the biogenesis of acromelic acids. The structure of **162** is confirmed by synthesis.[127] The first synthesis of lycoperdic acid **163**, which occurs in the mushroom *Lycoperdon perlatum*, was reported.[128] Other nonprotein amino acids isolated from *C. acromelalga* include **164**−**168** (Scheme 41) and **169**−**174** (Scheme 42).[129−136]

The toxic mushroom *Russula subnigricans* is very similar to an edible mushroom, *R. nigricans*, and

**Scheme 42**



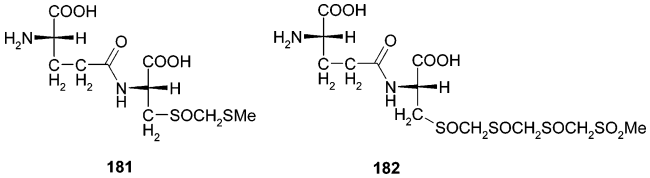
**Scheme 43**



therefore poses a considerable risk to humans. The amino acid (2*S*,3*R*)−(−)-3-hydroxy-baikiain **175**, together with baikiain **176** and pipecolic acid **177**, was isolated from *R. subnigricans*.[137] *N*-$\gamma$-Glutamyl boletine **178**, together with a toxin (as discussed earlier), has been found in the mushroom *Tylopilus* sp.[58] The absolute stereostructure of **178** was clarified on the basis of spectroscopic analysis, acidic hydrolysis, and total synthesis. It exhibited moderate antibacterial activity. Two homoserine lipids **179** and **180** from *Xerocomus langbianensis* have been reported (Scheme 43).[138]

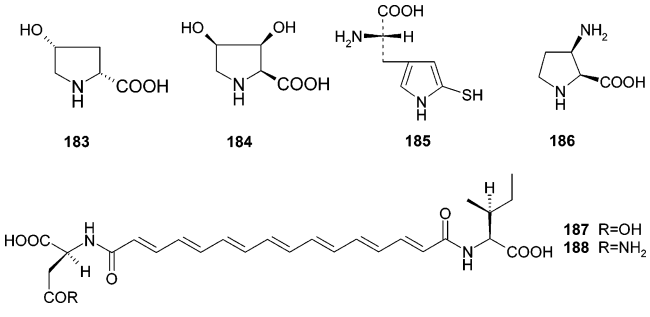
Particularly interesting examples of flavor generation by "allium-like" pathways in very different species are illustrated by the mushrooms *Marasmius alliaceus* and *Lentinula edodes* (shiitake mushroom). The flavor precursor in the former mushroom, which, as suggested by its Latin name, develops "a strong, garlic like odor − especially when wet or when crushed with water", is $\gamma$-glutamyl-marasmin **181.**[139,140] It is suggested that **181** is sequentially cleaved by a $\gamma$-glutamyl transpeptidase and by a *C*-*S* lyase giving a highly reactive sulfenic acid intermediate.[141,142] Of particular interest is the occurrence in *Lentinula edodes* of lentinic acid **182**, a "tetrathio" flavor precursor with a structure curiously reminiscent of that of the polyketides (Scheme 44).[143]

**Scheme 44**



(2*S*,4*S*)-4-Hydroxy-2-pyrrolidinecarboxylic acid **183** and (2*S*,3*R*,4*R*)-3,4- dihydroxy-2-pyrrolidinecarboxylic acid **184** were isolated from *Amanita phalloides* and *A. verna*, respectively (Scheme 45).[144,145] Scle-

**Scheme 45**

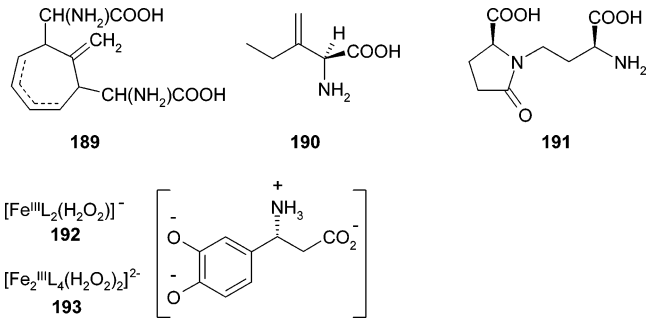


rothionine (STH) **185** is a sulfur-containing imidazole compound that has been isolated from sclerotia of *Sclerotinia libertiana* cultured on bran.[146]

Morel mushroom, a common edible fungi, especially *Morchella esculenta*, contains *cis*-3-amino-L-proline **186**,[147] which is also present in a free state in the fruiting bodies of *M. esculenta, M. conica,* and *M. crassipes*, as well as in their cultured mycelia. Two polyene pigments, boletocrocin A **187** and B **188**, were isolated (Scheme 45)[148] from the fruiting bodies of the Japanese mushroom *Boletus laetissimus.* These compounds are diamides of hexadecaheptaenedioic acid with isoleucine and either aspartic acid or asparagine.

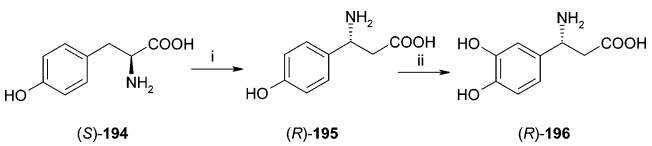
Extracts of the mushroom *Lactarius helvus* have been reported to contain several unusual amino acids.[149] For one of these, the structure **189** has been tentatively proposed, although the position of one double bond has not been determined.[150] The structure *β*-methylene- L-(+)-norvaline **190** was proposed[151] for an unusual amino acid also isolated from the fruiting bodies of this mushroom. Confirmation of this structure has been provided by a Strecker synthesis of the desired racemate from α-ethylacrolein. Another species of the same genus, *Lactarius piperatus*, was found to contain (2*S*,3′*S*)-1-(3-amino-3-carboxypropyl)-5-oxo-2pyrrolidinecarboxylic acid **191** (Scheme 46).[152]

**Scheme 46**




*Cortinarius violaceus* is a spectacular mushroom well-known for its dark blue-violet color and its cedar woodlike smell. The experimental evidence indicated that the pigment from *C. violaceus* is an ion−ligand 1:2 complex; however, it cannot be determined if it is mono- or binuclear (**192** or **193**).[153] The ligand is (*R*)-*β*-dopa. Steglich and co-workers confirmed by a successful feeding experiment with *rac*-3-fluoro-*β*-tyrosine that the biosynthesis of (*R*)-*β*-dopa proceeds through *β*-tyrosine, which is then hydroxylated (Scheme 47).[154]

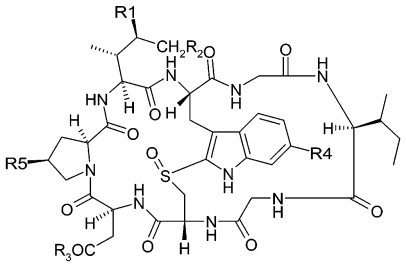
**Scheme 47. Biosynthesis of (*R*)-*β*-Dopa in *C. Violaceus*: (i) Tyrosine-2,3-aminomutase; (ii) Monooxygenase**




## 5. Cyclic Peptides and Peptide Antibiotics

Most of the reported cases of fatal mushroom poisoning in the world occur after the ingestion of

**Scheme 48**

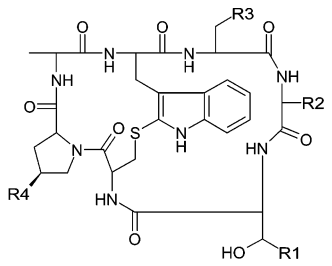



| | Compounds | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|---|---|---|
| **197** | α-Amanitin | $CH_2OH$ | OH | $NH_2$ | OH | OH |
| **198** | β-Amanitin | $CH_2OH$ | OH | OH | OH | OH |
| **199** | γ-Amanitin | $CH_3$ | OH | $NH_2$ | OH | OH |
| **200** | ε-Amanitin | $CH_3$ | OH | OH | OH | OH |
| **201** | Amanin | $CH_2OH$ | OH | OH | H | OH |
| **202** | Amanin amide | $CH_2OH$ | OH | $NH_2$ | H | OH |
| **203** | Amanullin | $CH_3$ | H | $NH_2$ | OH | OH |
| **204** | Amanullinic acid | $CH_3$ | H | OH | OH | OH |
| **205** | Proamanullin | $CH_3$ | H | $NH_2$ | OH | H |

*Amanita* species, primarily of *Amanita phalloides*. They contain toxins that are lethal to humans even in extremely small doses. The toxin molecules are cyclopeptides. They come in three varieties, known as amatoxins, which contain eight amino acid molecules, phallotoxins, which contain seven amino acid molecules, and virotoxins, which are monocyclic heptapeptides and contain D-serine instead of L -cysteine. Amatoxins and phallotoxins are bicyclic, cross-linked by the 2′-bound sulfur or sulfoxide group. When injected into mice, the phallotoxins are 10 times more lethal than cyanide: their $LD_{50}$ is 2 mg/kg. However, when taken by mouth, they have no effect. In contrast, the much more deadly amatoxins are actively toxic when eaten ($LD_{50}$ = 0.1 mg/kg). The structures of all groups of toxic peptides are shown: the amatoxines **197**−**205** in Scheme 48, the phallotoxins **206**−**213** in Scheme 49, and the vivotoxins **214**−**219** in Scheme 50.[155,156] Another group of cyclopeptides, antamanide **220** and cycloamanides A−D **221**−**224**, are also produced by *Amanita phalloides* (Scheme 51).[157] The chemistry, biochemistry, and molecular biological aspects of the toxic cyclic peptides in *Amanita* were concisely reviewed by Wieland.[158] The chemical structures of these toxins, including their stereochemistry and conformational analysis of their hydroxyamino acids, were reported mainly during the 1960s and 1970s from Wieland's laboratory.

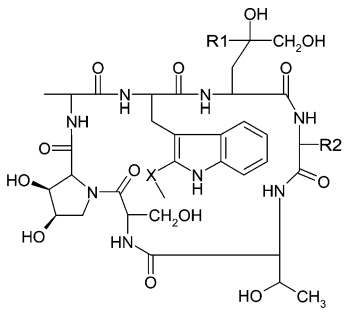
Hypelcins A I−IX **225**−**233** isolated from *Hypocrea peltata* are peptide antibiotics containing unusual amino acids, α-aminoisobutyric acid (Aib) and isovaline (Iva), and having the N- and C-terminal residues protected by an acetyl group (Ac) and an amino alcohol (Lol), respectively (Scheme 52).[159] These hypelcins belong to the class of membrane-modifying peptides named peptaibols. Hypelcin B is a mixture of five antibiotic peptides (hypelcins B-I, B-II, B-III, B-IV, and B-V, **234**−**238**) produced by *Hypocrea peltata* (Scheme 52).[160]

**Scheme 49**



| | Compounds | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|---|
| **206** | Phallacidin | COOH | $CH(CH_3)_2$ | $CH_3C(OH)CH_2OH$ | OH |
| **207** | Phallacin | COOH | $CH(CH_3)_2$ | $CH_3CHCH_2OH$ | OH |
| **208** | Phallisacin | COOH | $CH(CH_3)_2$ | $CH_2OHC(OH)CH_2OH$ | OH |
| **209** | Phallisin | $CH_3$ | $CH_3$ | $CH_2OHC(OH)CH_2OH$ | OH |
| **210** | Phalloidin | $CH_3$ | $CH_3$ | $CH_3C(OH)CH_2OH$ | OH |
| **211** | Phallin B | $CH_3$ | $CH_2Ph$ | $C(OH)(CH_3)_2$ | H |
| **212** | Phalloin | $CH_3$ | $CH_3$ | $C(OH)(CH_3)_2$ | OH |
| **213** | Prophallin | $CH_3$ | $CH_3$ | $C(OH)(CH_3)_2$ | H |

**Scheme 50**



| | Compounds | X | $R_1$ | $R_2$ |
|---|---|---|---|---|
| **214** | Viroidin | $SO_2$ | $CH_3$ | $CH(CH_3)_2$ |
| **215** | Deoxiviroidin | SO | $CH_3$ | $CH(CH_3)_2$ |
| **216** | /$Ala^1$/viroidin | $SO_2$ | $CH_3$ | $CH_3$ |
| **217** | /$Ala^1$/deoxiviroidin | SO | $CH_3$ | $CH_3$ |
| **218** | Viroisin | $SO_2$ | $CH_2OH$ | $CH(CH_3)_2$ |
| **219** | Deoxiviroisin | SO | $CH_2OH$ | $CH(CH_3)_2$ |

From a submerse culture of the ascomycetous fungus *Hypocrea muroiana,* two major groups of peptides belonging to the peptaibol family, designated hypomurocin (HM) A 1−5a **239**−**244** and B 1−6 **245**−**250**, were characterized by amino acid analysis and sequence determination using fast atom bombardment and electrospray tandem MS (Scheme 53).[161] Both groups showed antibiotic activity (*Bacillus subtilis*) and caused hemolysis of rat erythrocytes, with HM A being less active than HM B.

The natural product omphalotin A **251** belongs to a family of cyclic dodecapeptides from the basidiomycete *Omphalotus olearius*[162−164] and shows a selective activity against phytopathogenic nematodes such as *Meloidogyne incognita* (Scheme 54).[164] Under in vitro conditions, omphalotin A outperforms known nematicides such as ivermectin in terms of potency and selectivity.[165] The high specificity and the structure of **251**, both of which are unusual for a nematicide, lead to the assumption that a hitherto unknown biological target is responsible for the activity of **251**. To elucidate this target, larger amounts of the cyclopeptide are required than can be produced by fermentation alone.[165]

Jung et al. reported on the synthesis of **251** using Fmoc amino acids on a polystyrene support with a trityl linker (TCP resin). Starting from TCP resin preloaded with Fmoc-sarcosine, and using a combination of BTC (triphosgene), DIC/HOAt (diisopropylcarbodiimide/hydroxyaza-benzotriazole), and HATU-couplings, the linear dodecapeptide with C-terminal Sar [omphalotin A (7−6)] was obtained. Diastereomerically pure omphalotin A was obtained in a cyclization yield of 37% and in an overall yield of 31% with respect to the first loading of the resin with Fmoc-sarcosine.[166]

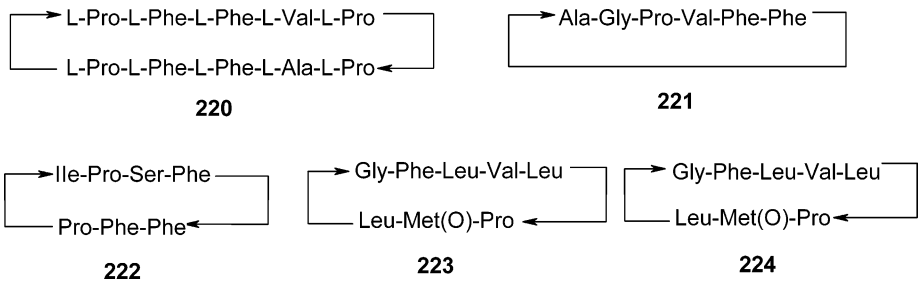
Beauvericin **252** is produced by the bright yellow polypore *Laetiporus sulfureus*, commonly known as "Chicken-of-the-Woods" (Scheme 55).[167] Beauvericin is a mycotoxin produced by hypocrealean ascomycetes in grain.[168]

## 6. Sphingolipids

Sphingolipids, for example, glycosphingolipid (GSL), sphingomyelin, and sphingosine derivatives or analogues are important building blocks of the plasma membranes of eukaryotic cells. In recent years, however, a great deal of attention has been devoted to studies of the biological processes regulated by sphingolipids, and evidence of newly discovered roles of these compounds in cell functions is continually being demonstrated. Their functions include anchoring lipid-bound carbohydrates to cell surfaces to create an epidermal water permeability barrier and participating in both antigen−antibody reactions and biological information transmission.[169,170]

We investigated the chemical constituents of the mushrooms *Russula cyanoxantha* and *Albatrellus ellisii*. The new ceramide **253** from *R. cyanoxantha* and the new glycosphingolipid **254** from *A. ellisii* contain unusual sphingoid bases (Scheme 56).[171,172]

**Scheme 51**



**Scheme 52. Primary Structures of Hypelcin A's and B's**

| | Hypelcin | |
|---|---|---|
| **225** | A-I | Ac-Aib-Pro-Aib-Ala-Aib-Aib-Gln-Aib-Leu-Aib-Gly-Aib-Aib-Pro-Val-Aib-Aib-Gln-Gln-Lol |
| **226** | A-II | Ac-Aib-Pro-Aib-Ala-Ala-Aib-Gln-Aib-Leu-Aib-Gly-Aib-Aib-Pro-Val-Aib-Iva-Gln-Gln-Lol |
| **227** | A-III | Ac-Aib-Pro-Aib-Ala-Aib-Aib-Gln-Aib-Leu-Aib-Gly-Aib-Aib-Pro-Val-Aib-Iva-Gln-Gln-Lol |
| **228** | A-IV | Ac-Aib-Pro-Aib-Ala-Aib-Aib-Gln-Aib-Ile-Aib-Gly-Aib-Aib-Pro-Val-Aib-Iva-Gln-Gln-Lol |
| **229** | A-V | Ac-Aib-Pro-Aib-Ala-Aib-Aib-Gln-Aib-Leu-Aib-Gly-Aib-Aib-Pro-Val-Aib-Iva-Gln-Gln-Iol |
| **230** | A-VI | Ac-Aib-Pro-Aib-Ala-Aib-Ala-Gln-Aib-Leu-Aib-Gly-Aib-Aib-Pro-Val-Aib-Iva-Gln-Gln-Iol |
| **231** | A-VII | Ac-Aib-Pro-Aib-Ala-Aib-Ala-Gln-Aib-Leu-Aib-Gly-Aib-Aib-Pro-Val-Aib-Iva-Gln-Gln-Lol |
| **232** | A-VIII | Ac-Aib-Pro-Aib-Ala-Aib-Ala-Gln-Aib-Ile-Aib-Gly-Aib-Aib-Pro-Val-Aib-Iva-Gln-Gln-Lol |
| **233** | A-IX | Ac-Aib-Pro-Aib-Ala-Aib-Aib-Gln-Aib-Ile-Aib-Gly-Aib-Aib-Pro-Val-Aib-Iva-Gln-Gln-Lol |
| **234** | B-I | Ac-Aib-Pro-Aib-Ala-Aib-Aib-Gln-Aib-Leu-Aib-Gly-Aib-Aib-Pro-Val-Aib-Aib-Glu-Gln-Lol |
| **235** | B-II | Ac-Aib-Pro-Aib-Ala-Aib-Ala-Gln-Aib-Leu-Aib-Gly-Aib-Aib-Pro-Val-Aib-Aib-Glu-Gln-Lol |
| **236** | B-III | Ac-Aib-Pro-Aib-Ala-Aib-Aib-Gln-Aib-Leu-Aib-Gly-Aib-Aib-Pro-Val-Aib-Iva-Glu-Gln-Lol |
| **237** | B-IV | Ac-Aib-Pro-Aib-Ala-Aib-Aib-Gln-Aib-Ile-Aib-Gly-Aib-Aib-Pro-Val-Aib-Aib-Glu-Gln-Lol |
| **238** | B-V | Ac-Aib-Pro-Aib-Ala-Aib-Aib-Gln-Aib-Leu-Aib-Gly-Aib-Aib-Pro-Val-Aib-Aib-Glu-Gln-Lol |

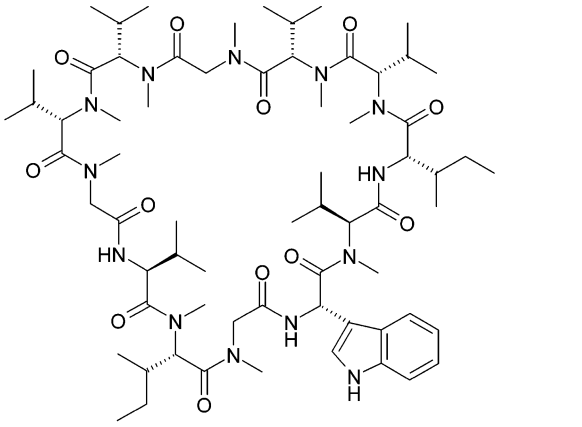
**Scheme 53. Primary Structures of Hypomurocin A's and B's**

| | HM | |
|---|---|---|
| **239** | A-1 | Ac-Aib-Gln-Val-Val-Aib-Pro-Leu-Leu-Aib-Pro-Lol |
| **240** | A-2 | Ac-Iva-Gln-Val-Val-Aib-Pro-Leu-Leu-Aib-Pro-Lol |
| **241** | A-3 | Ac-Aib-Gln-Val-Leu-Aib-Pro-Leu-Ile-Aib-Pro-Lol |
| **242** | A-4 | Ac-Aib-Gln-Ile-Val-Aib-Pro-Leu-Leu-Aib-Pro-Lol |
| **243** | A-5 | Ac-Aib-Gln-Ile-Ile-Aib-Pro-Leu-Leu-Aib-Pro-Lol |
| **244** | A-5a | Ac-Aib-Gln-Ile-Leu-Aib-Pro-Leu-Ile-Aib-Pro-Lol |
| **245** | B-1 | Ac-Aib-Ser-Ala-Leu-Aib-Gln-Aib-Val-Aib-Gly-Aib-Aib-Pro-Leu-Aib-Aib-Gln-Vol |
| **246** | B-2 | Ac-Aib-Ser-Ala-Leu-Aib-Gln-Aib-Val-Aib-Gly-Aib-Aib-Pro-Leu-Aib-Aib-Gln-Lol |
| **247** | B-3 | Ac-Aib-Ala-Ala-Leu-Aib-Gln-Aib-Val-Aib-Gly-Aib-Aib-Pro-Leu-Aib-Aib-Gln-Vol |
| **248** | B-4 | Ac-Aib-Ser-Ala-Leu-Aib-Gln-Iva-Val-Aib-Gly-Aib-Aib-Pro-Leu-Aib-Aib-Gln-Vol |
| **249** | B-5 | Ac-Aib-Ser-Ala-Leu-Aib-Gln-Aib-Val-Aib-Gly-Iva-Aib-Pro-Leu-Aib-Aib-Gln-Vol |
| **250** | B-6 | Ac-Aib-Ser-Ala-Leu-Aib-Gln-Aib-Val-Aib-Gly-Iva-Aib-Pro-Leu-Aib-Aib-Gln-Lol |

Truffles, also known as "black diamonds", are underground mushrooms which grow in symbiosis with certain trees. They are thought to be a "miracle of nature" and have long been regarded as the ultimate in gastronomic experience. There are more than a hundred different kinds of truffles, but some are not edible and only a few are of interest to world cuisine. The Chinese truffle *Tuber indicum*, a generally hypogeous fungus belonging to the family Tuberaceae, is found in the provinces of Yunnan and Sichuan in southwest China. This truffle closely resembles the European black winter truffle *Tuber melanosporum*. *T. indicum*'s skin is reddish before becoming brown/black, and the flesh is white veins and has a rubbery consistency.

The glycoshingolipid and ceramide composition of the fresh fruiting bodies of the mushroom *Cortinarius umidicola* were investigated resulting in the isolation

**Scheme 54**

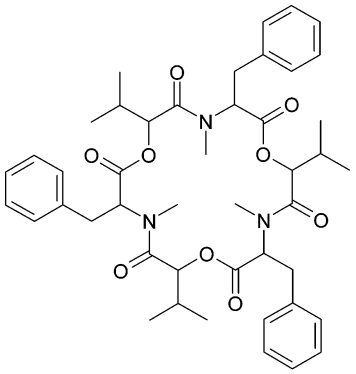


1 2 3 4 5 6 7 8 9 10 11 12

Cyclo(Trp-MeVal-Ile-MeVal-MeVal-Sar-MeVal-MeIle-Sar-Val-MeIle-Sar)

**251**

**Scheme 55**



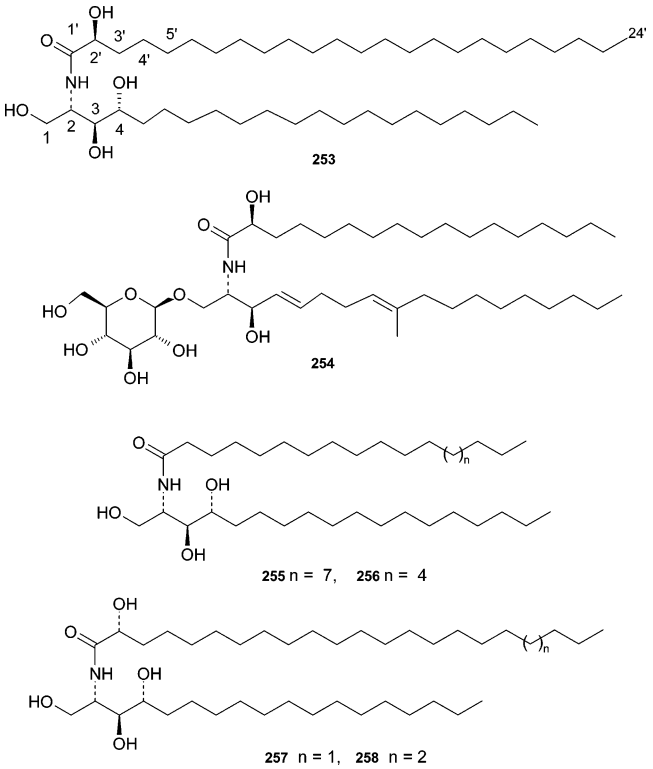
**252**

of a new glycoshingolipid **259** containing rare $C_{17}$-phytosphingosine and cerebroside B and D. In addition, three ceramides **260**−**262** derived from a 4-hydroxy-6-methyl-sphingosine were isolated (Scheme 57).[174]

In Scheme 58, the structures of cortenuamide A **263**, cortenuamide B **264**, and cortenuamide C **265** from the fruiting bodies of the basidiomycetes *Cortinarius tenuipes* together with (4*E*,8*E*)-*N*-D-2-hydroxyoctasanoyl-1-*O*-*β*-D-glycopyranosyl-9-methyl-4,8-sphinga-dienine **266** and (4*E*,8*E*)-*N*-D-2-hydroxypalmitoyl-1-*O*-*β*-D-glycopyranosyl-9-methyl-4,8-sphingadienine **267** are shown. The structures of these compounds were elucidated by spectroscopic and chemical methods.[175] Hygrophamide **268** was also obtained from the fruiting bodies of the basidiomycete *Hygrophorus eburneus*.[176] The white-rot fungus, *Phellinus pini,* contained two ceramides **269** and **270**.[177]

Fractionation of the extract of an edible Chinese mushroom, *Termitomyces albuminosus,* afforded six novel neuritogenic cerebrosides, termitomycesphins A−F **271**−**276**, which induced neuronal differentiation in rat PC12 cells (Scheme 59). The absolute stereostructures of the six metabolites were elucidated by spectroscopic analysis and chemical transformation.[178,179] Moreover, termitomycesphin E **275** was also obtained from *Russula ochroleuca*.[180] Cerebrosides A **277**, B **278**, and C **279**, along with glucoceramide **280**, were isolated from *Schizophyllum commune* (Scheme 60).[182] The study shows that

**Scheme 56**



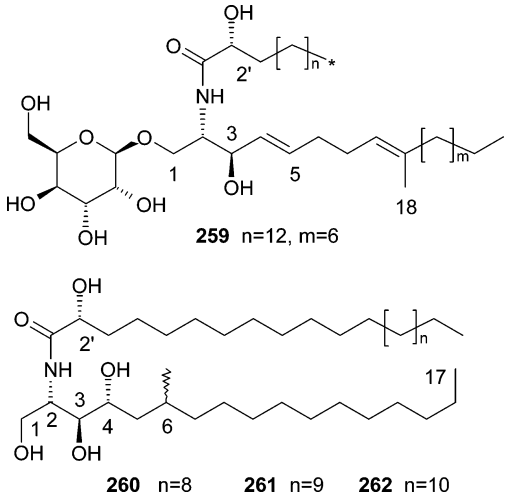
**253**

**254**

**255** n = 7, **256** n = 4

**257** n = 1, **258** n = 2

**Scheme 57**



**259** n=12, m=6

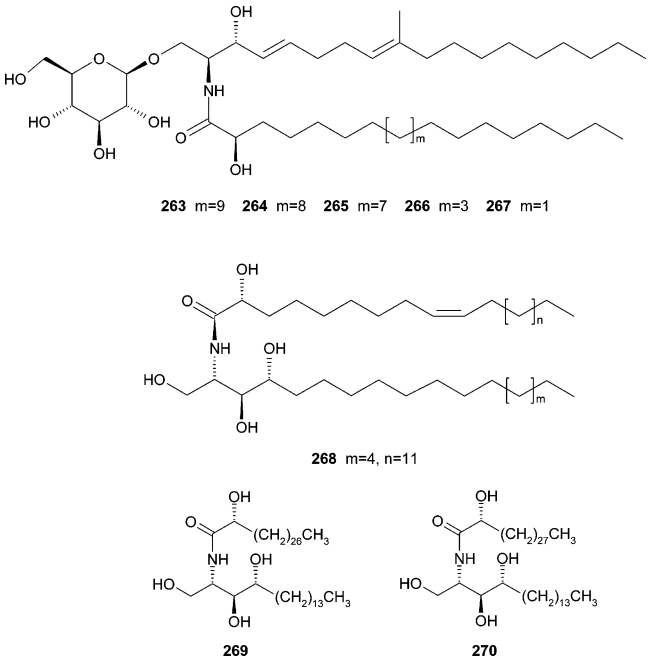
**260** n=8 **261** n=9 **262** n=10

sphingolipids have elicitor activity in plants. Treatment of rice leaves with cerebroside A induced the accumulation of antimicrobial compounds (phytoalexin), cell death, and increased resistance to subsequent infection by compatible pathogens.[181]

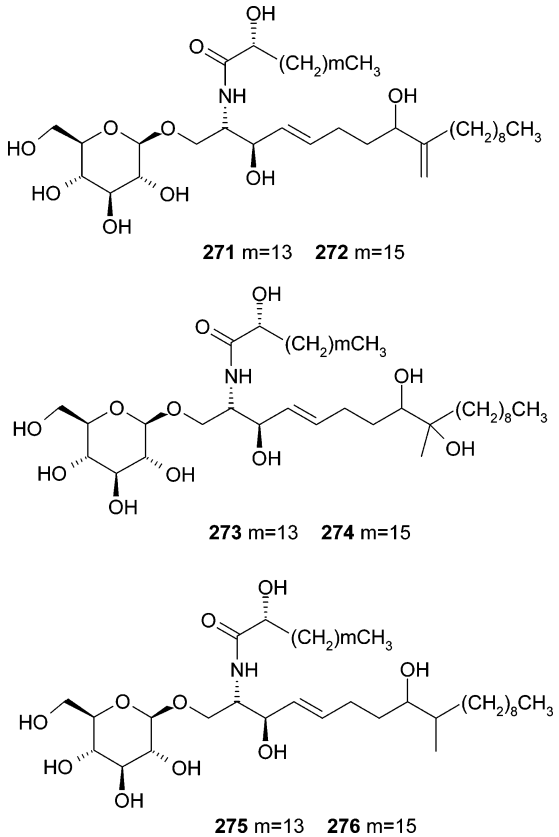
Novel glycoinositolphosphingolipids (GIPSL), such as the basidiolipids **281**−**284**, have been obtained from the edible mushrooms *Agaricus bisporus* and *A. campestris* (Schemes 61 and 62).[183]

Five mushrooms, *Panellus serotinus*, *Lyophyllum connatum*, *Amanita pantherina*, *Sarcodon asperatus*, and *Lepista nuda*, have been investigated chemically. Two new ceramides, **285** and **286**, have been isolated from *Panellus serotinus*. Compound **286** was also found in *Lyophyllum connatum*. Two more new ceramides, **288** and **289,** have been isolated from *Amanita pantherina* along with **287**, a known syn-

**Scheme 58**



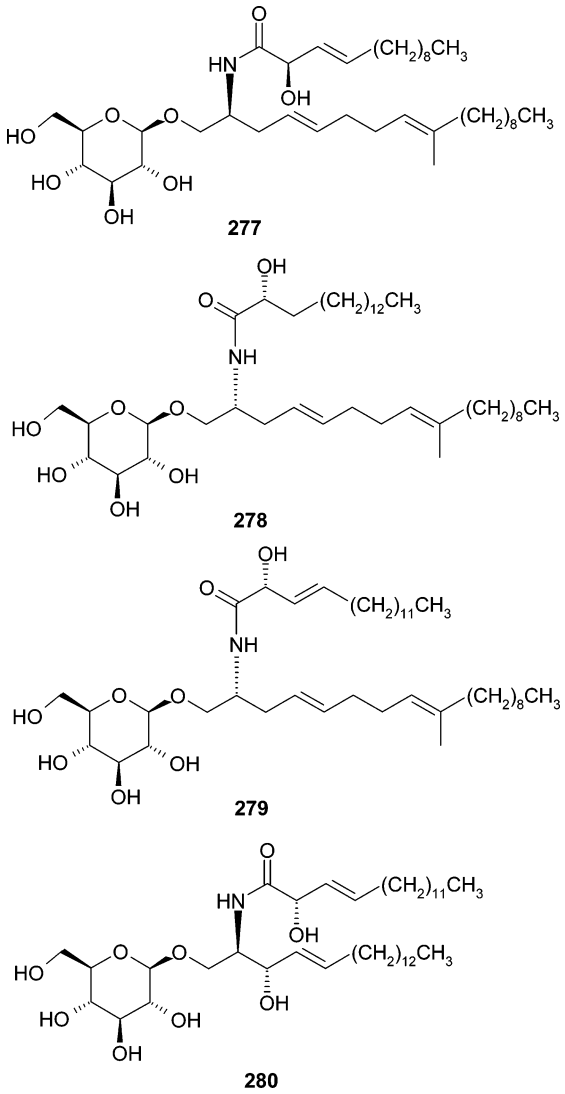

**Scheme 59**




thetic compound. Additionally, compounds **287** and **288** have been identified from *Sarcodon asperatus* and *Lepista nuda,* respectively.[184] The fruiting bodies of *Grifola frondosa* (Polyporaceae) contain the new ceramides **290**−**293** (Scheme 63).[185]

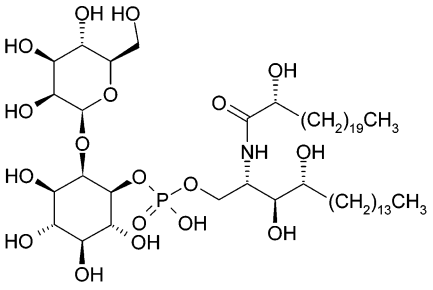
Three glycosphingolipids with a cis-$\Delta^{17}$-fatty acyl moiety, namely, catacerebrosides A−C **294**−**296**, were obtained from the fungus *Catathelasma ventricosum* (Scheme 64).[186] Lactariamides A **297** and B **298** were obtained from *Lactarius volemus*, and compound **299** was obtained from *Engleromyces goetzei.* (Scheme 65).[187,188]

**Scheme 60**

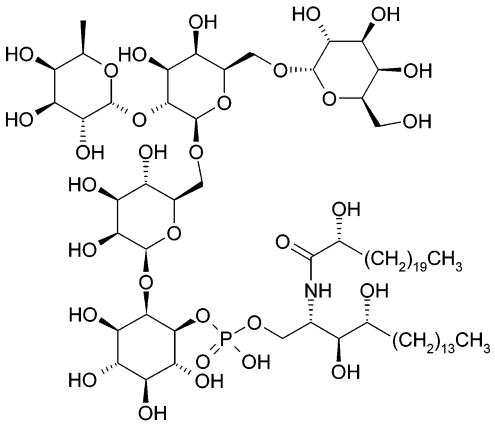



A recent publication described glycoinositolphosphophingolipids (basidiolipids) from the six basidiomycetes *Amanita virosa*, *Calvatia excipuliformis*, *Cantharellus cibarius*, *Leccinum scabrum*, *Lentinula edodes*, and *Pleurotus ostreatus*.[189] The immune properties of the basidiolipids have been also investigated.[190] It was determined that sera of normal adult human subjects contained IgG2 and IgM heterophile antibodies (hetAbs) that immunoreacted with these lipids. However, this immune recognition was not shared by the glycolipids of all mushroom species. The basidiolipids of *Amanita virosa* and *Cantharellus cibarius* did not bind antibodies of normal human sera. Only certain basidiolipids of *Agaricus bisporus*, *Leccinum scabrum*, *Lentinula edodes*, and *Pleurotus ostreatus* immunoreacted with human hetAbs. The basidiolipids that were recognized by the human hetAbs had either terminal Galalpha1-6Gal or Galbeta1-6Man epitopes. Enzymatic destruction of the respective carbohydrate epitopes negated the previous immune reactivity. It is assumed that contact with nonhuman antigens causes generation of the antibasidiolipid antibodies.

**Scheme 61**



**281**



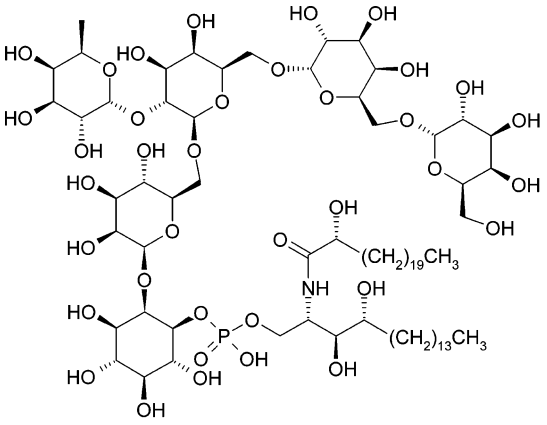
**282**

## 7. Cytochalasins

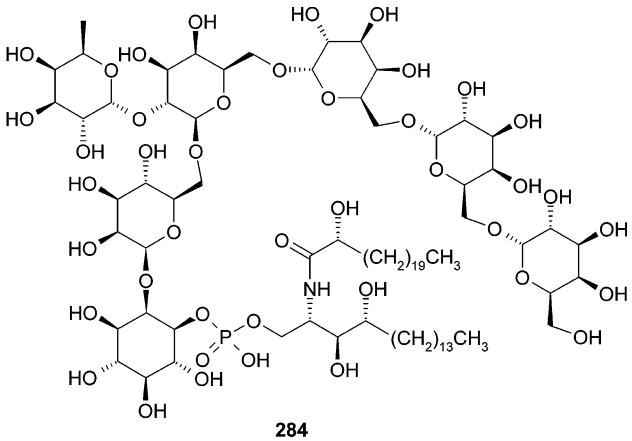
The cytochalasins are a group of toxic fungal metabolites that show marked cytostatic effects on mammalian cells in tissue culture and have a wide range of biological activities. They were first isolated and characterized by Aldridge and Turner[191] and independently by Tamm.[192] Since their initial isolation, these compounds have been identified as metabolites of many fungi. Cytochalasin E **300** is a metabolite of *Rosellinia necatrix*,[193,194] and engleromycin **301** is produced by *Engleromyces goetzei*.[195,196] In Scheme 66, the structures of cytochalasins **302**−**307** from the culture medium and mycelium of fungus *Hypoxylon terricola* are shown.[197]

L-696,474 **308**, an inhibitor of the HIV-1 protease, was discovered in extracts of fungal culture of *Hypoxylon fragiforme* (Scheme 67). L-696,474 inhibited HIV-1 protease activity with an $IC_{50}$ of 3 $\mu$M, and the mode of inhibition was competitive with respect to substrate. Furthermore, it was not a low-binding inhibitor. The inhibition due to L-696,474 was also independent of the HIV-1 protease concentration.[198] Cytochalasins **309** and **310** from *Xylaria obovata* were lethal to brine shrimp ($LC_{50}$ 2.5 $\mu$g/mL) and cytotoxic to HL-60 cells at 1 $\mu$g/ mL (Scheme 67). These cytochalasins also inhibited mammalian cell growth with high potency as demonstrated in the Vero monkey cell growth inhibition assay for cytotoxicity ($IC_{50}$ for **309**, 0.46 $\mu$g/mL; for **310**, 1.9 $\mu$g/mL).[199] Additionally, 17 new cytochalasins **311**−**327** have been isolated from an unidentified *Daldinia* sp. of fungus.[200−202] Their structures are shown in Schemes 67 and 68.

**Scheme 62**

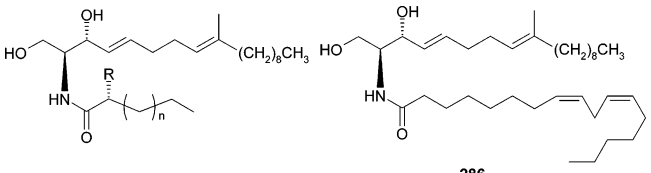


**283**



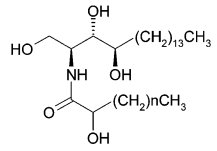
**284**

**Scheme 63**



**285** R=H, n=12
**287** R=OH, n=12
**288** R=OH, n=11
**289** R=OH, n=10

**286**



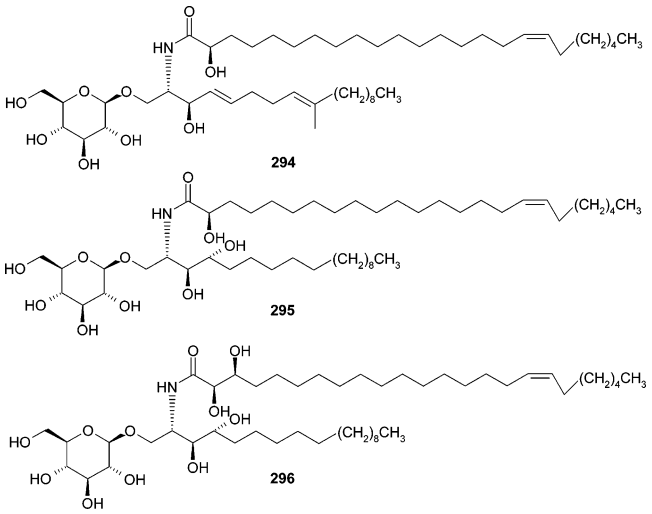
**290** n=19
**291** n=20
**292** n=22
**293** n=23

## 8. Miscellaneous

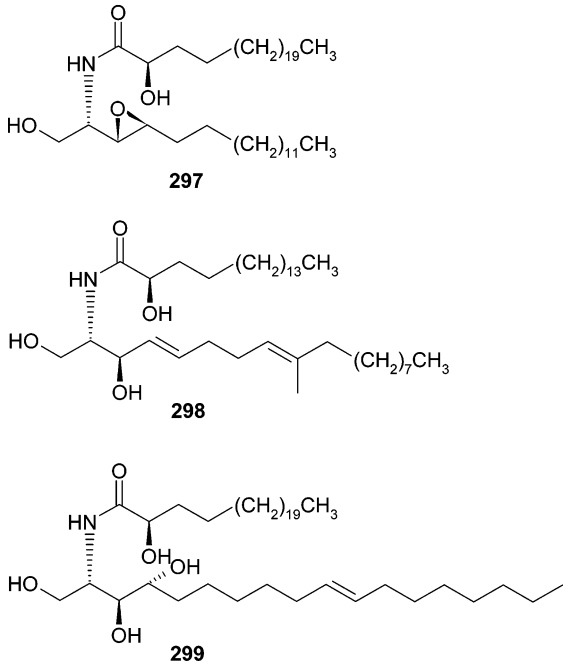
Neoengleromycin **328**, which contains the rare N-substituted hydroxamic acid structural moiety, was isolated from the fruiting bodies of the ascomycete *Engleromyces goetzii*.[203] Another compound, vibratilicin **329**, was isolated from the fruiting bodies of the basidiomycete *Cortinarius vibratilis*.[204] Vibratilicin, which contains a glycerol and a hydroxamic acid moiety, has a very similar structure to neoengleromycin with the only difference being that the N-substituted ethyl group of neoengleromycin is replaced by a proton in vibratilicin.

Piptamine **330**, an antibiotic produced by *Piptoporus betulinus*, showed antimicrobial activity against

**Scheme 64**




**Scheme 65**

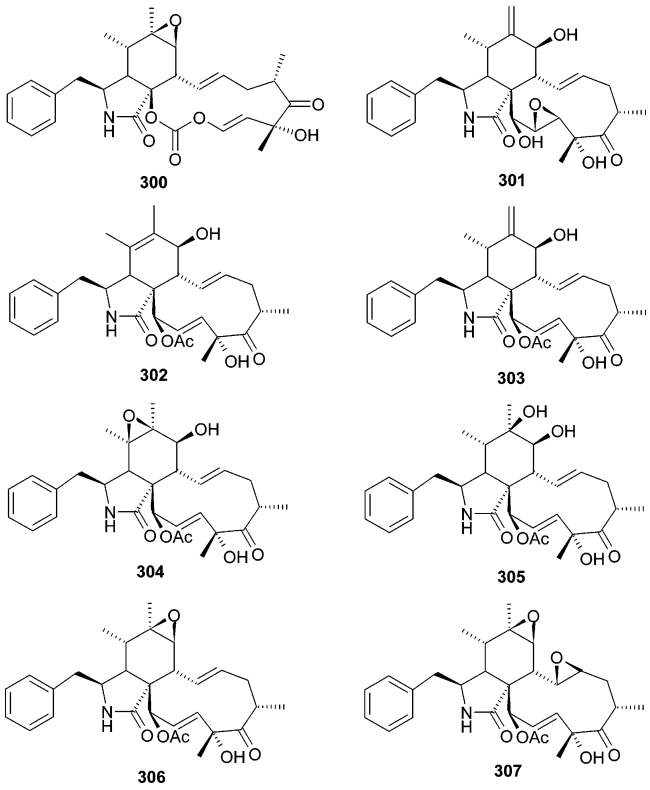



a series of Gram-positive bacteria, yeasts, and fungi, with particularly notable MIC values for *Staphylococcus aureus* SG 511 (0.78 $\mu$g/mL) and *Enterococcus faecalis* 1528, (1.56 $\mu$g/mL).[205] Piptamine exhibited hemolytic activity at 10−50 $\mu$g/mL using heparinized blood from beagle dogs.

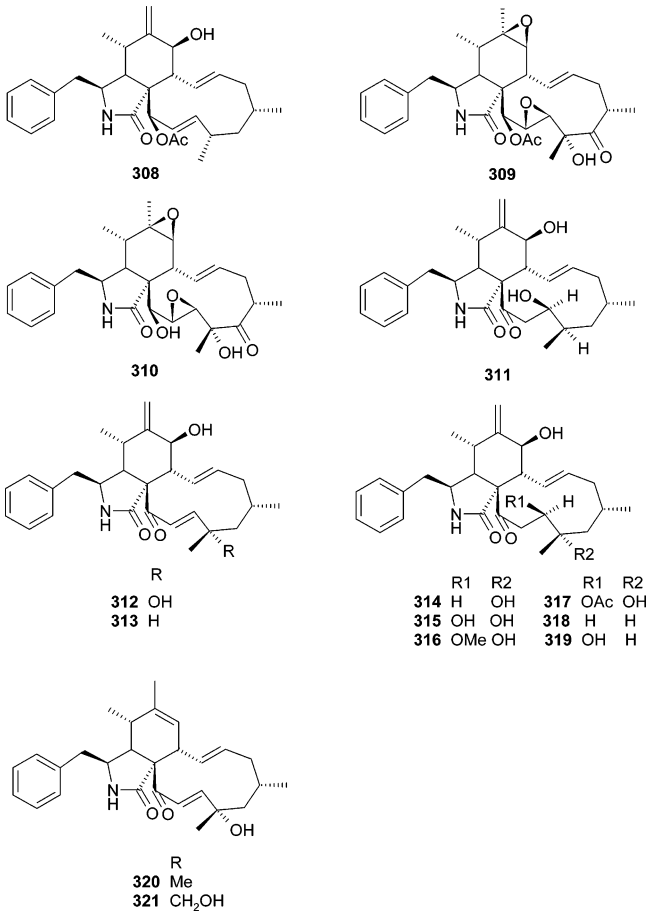
The characteristic violet color reaction with aqueous ferric chloride exhibited by fruiting bodies of *Lyophyllum connatum* is due to the hydroxamic acid derivatives connatin **331** and *N*-hydroxy-*N*′,*N*′-dimethylurea **332**.[206]

A third metabolite of *L. connatum* is the unusual hydroxycarboxamide lyophyllin **333**.[206,207] The biosynthesis of lyophyllin depicted in Scheme 70 was confirmed by experiments in which the formation of the azoxy compound lyophyllin **333** by oxidative condensation of *N*-hydroxy-*N*′,*N*′-dimethylurea **334** with *N*-methylhydroxylamine **335** was observed in fruiting bodies of the toadstool *Lyophyllum connatum*.[206] The condensing enzyme is remarkably unspecific and transforms a variety of hydroxyureas and *N*-alkyl-hydroxylamines into the corresponding lyophyllin analogues.

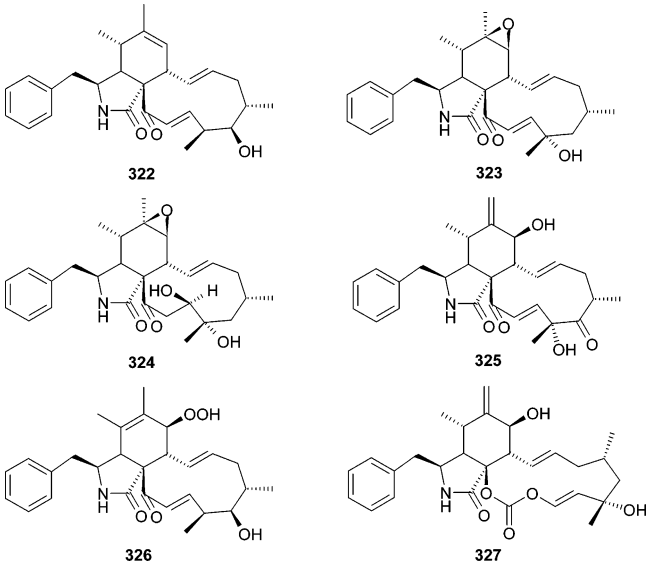
**Scheme 66**



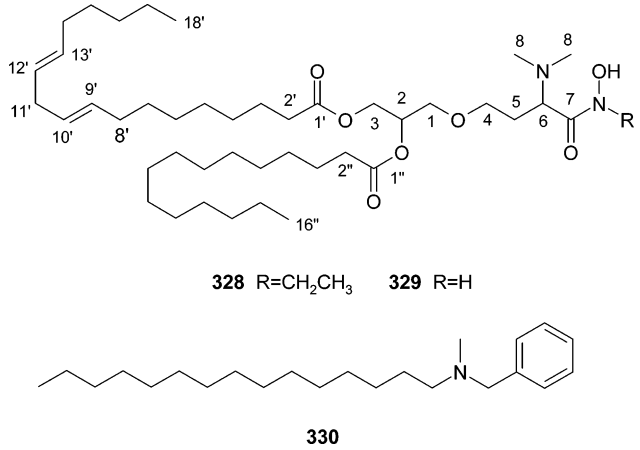

**Scheme 67**



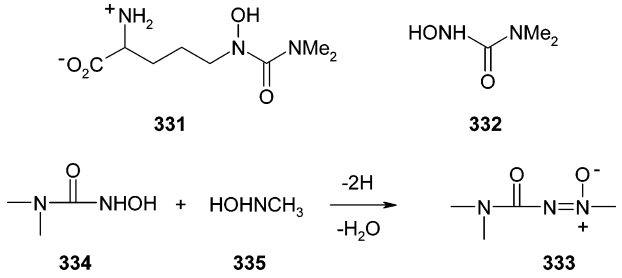
**Scheme 68**




**Scheme 69**



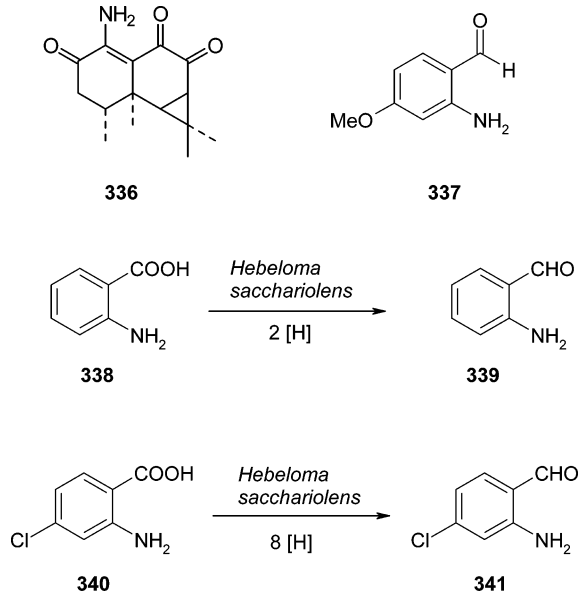

**Scheme 70**



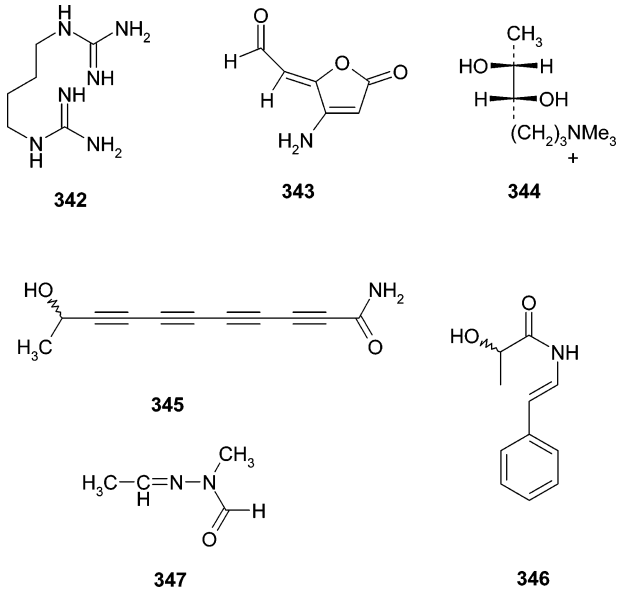

A nitrogen-containing aristolane sesquiterpenoid compound, lepidamine **336**, was isolated from the fruiting bodies of the basidiomycete *Russula lepida* (Scheme 71). It is the first aristolane-type sesquiterpene alkaloid isolated from nature.[208] **337**, an aromatic aminoaldehyde, was isolated from the fruiting bodies of *Cortinarius umidicola*.[209] Fruiting bodies of the mushroom *Hebeloma sacchariolens* reduce anthranilic acid and some of its analogues to the corresponding aromatic aminoaldehydes with high efficiency (Scheme 71).[210]

Arcaine **342** was identified from *Panus tigrinus*.[211] Basidalin **343** occurs in some basidiomycetes such as *Leucoagarious carneifolia*.[212] Muscaridine **344** (2R, 3R-form) is another compound present in *Amanita*

**Scheme 71**

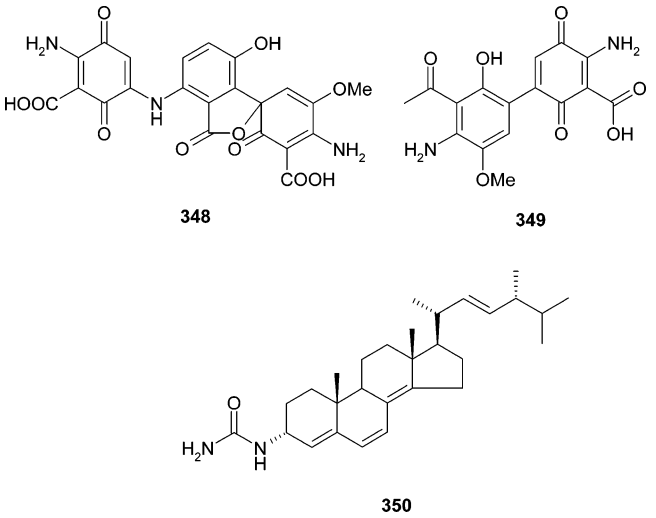



**Scheme 72**




*muscaria*.[213] The stereochemistry of this natural product could not be confirmed. It was claimed to have the erythro-configuration, but its properties do not coincide with those of the well-characterized synthetic stereoisomers later obtained. 10-Hydroxyundeca-2,4,6,8-tetraynamide **345**, produced by *Mycena viridimarginata*, is highly antibiotic and cytotoxic.[214] Xylaramide **346**, possessing potent antifungal activity toward *Nematospora coryli* and *Saccharomyces cerevisiae*, was isolated from the culture fluids of the wood-inhabiting ascomycete *Xylaria longipes*.[215] Gyromitrin **347**, acetaldehyde *N*-methyl-*N*-formylhydrazone, is a toxin present in the edible wild mushroom *Gyromitra esculenta* (Scheme 72).[216] Under pH and temperature conditions mimicking the milieu of the human stomach, gyromitrin is converted through the intermediate *N*-methyl-*N*-formylhydrazine to methylhydrazine, a known tumor inducer in mice and hamsters. In addition, methylhydrazine is formed in the mouse stomach after oral administration of gyromitrin.[217] These findings imply that

**Scheme 73**




consumption of *G. esculenta* could be a carcinogenic, as well as an acutely toxic, health hazard.

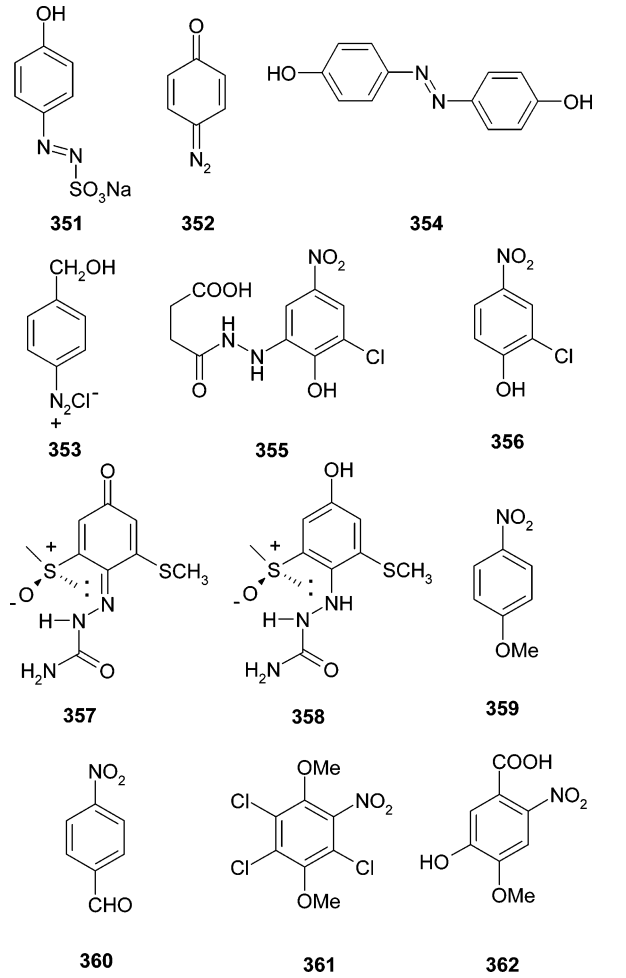
Lilacinone **348**, a red aminobenzoquinone pigment from *Lactarius lilacinus*, and blennione **349**, a green aminobenzoquinone derivative from *Lactarius blennius*, were extracted and purified (Scheme 73). They represent a novel type of fungal pigment and may be formed biosynthetically from anthranilic acid units.[218,219] A steroidal derivative **350** with the urea junction at the *C*-3 position was isolated from the fruiting bodies of *Chlorophyllum molybdites* (Agaricaceae) and was found to exhibit cytotoxicity against Kato III cells.[220]

In the initial separation of *Agaricus xanthoderma* on Sephadex, the last fractions contain yellow solid sodium 4-hydroxybenzenediazosulfonate **351**.[71] **351** is an artifact that is formed from the 4-diazo-2,5-cyclo-hexadien-1-one **352** present in the fruiting bodies of the aforementioned fungus. **352** can be detected in the methanolic extract of the fungus by azo coupling with resorcinol or $\beta$-naphthol. 4-(Hydroxymethyl)benzene-diazonium chloride **353** was reported from other *Agaricus* species.[221] Interestingly, neither phenol nor 4,4′-dihydroxyazobenzene **354** are detectable during the workup of the fungi with methanol containing $SO_2$, so these compounds isolated by Gill et al. are probably formed from the precursors during the workup.[222]

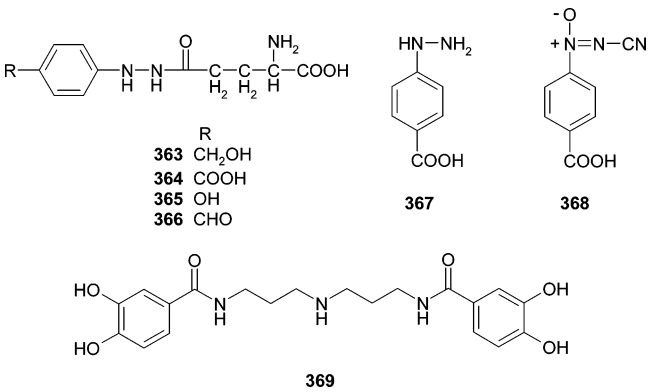
The carrot truffle, *Stephanospora caroticolor*, is a rare Gasteromycete. The fruiting bodies are tubers of 1−3 cm in diameter that mature underground. They may be recognized by their bright orange appearance in places where the soil is partially removed. The interior of the mushroom (gleba) is also of an intense orange color. Extraction of the fruiting bodies of *S. caroticolor* with methanol gives a yellow solution in which two pigments, **355** and **356** (Scheme 74), can be detected by HPLC.[223] Structure **355** was confirmed by synthesis.

The orange pigment rubroflavin **357** from the dried fruiting bodies of *Calvatia rubro-flava* (Lycoperdaceae) owes its high optical rotation ($[\alpha]^{22}_D$-2180, MeOH) to a methanesulfinyl group directly attached to a 1,4-benzoquinone semicarbazone chromophore

**Scheme 74**




**Scheme 75**




(Scheme 74). Rubroflavin is present in fresh fungi in its leuco form **358**, which is easily oxidized to **357**.[224]

Only a few nitroaromatic metabolites have so far been reported from basidiomycetes; *para*-nitroanisole **359** and *para*-nitrobenzaldehyde **360** occur in low concentrations in cultures of *Lepista diemii*,[225] while 3,5,6-trichloro-1,4-dimethoxy-2-nitrobenzene **361** and 6-nitro-*iso*-vaniliic acid **362** have been isolated from the fruiting bodies of *Fomes robiniae* and *Cortinarius anomalus*, respectively.[226,227]

Agaricales species synthesize compounds in which the glutamic acid is linked to phenylhydrazine (agaritine **363** and related compounds **364**−**366**, Scheme 75).[228−232] *p*-Hydrazinobenzoic acid **367** as a biosyn-

thetic intermediate has been characterized in *Agaricus bisporus*.[233] Another interesting biologically active metabolite, calvatic acid **368**, was reported from fermentation of a mushroom, *Calvatia craniformis*. Total synthesis of **368** was completed in four steps starting from *p*-hydrazinobenzoic acid hydrochloride.[234] In Scheme 75, the structure of pistillarine **369** from *Clavariadelphus pistillari* is shown.[235] Pistillarine is responsible for the dark green color reaction with $FeCl_3$ that is of significance in the chemotaxonomy of coral fungi, for example, the genus *Ramaria*.

## 9. Acknowledgment

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