New Biologically Active Metabolites from Chinese Higher Fungi

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Abstract: The chemical constituents produced by Chinese higher fungi, including thirty two basidiomycete and six ascomycete species, have been investigated in the past decades. A variety of new secondary metabolites associated with diverse structural types of terpenoids, steroids, sphingolipids, perylenequinones, *p*-terphenyls**,** pyranones, and heterocyclic compounds, which exhibited antitumor, anti-inflammatory, cytotoxic, enzyme inhibitory, antiviral, neuritogenic, antibiotic, and other activities, have been discovered. Recent progress in the structures and interesting biological properties of compounds isolated from these higher fungi is discussed in this review.

INTRODUCTION

Fungi, from time immemorial, have played an important role in the history of humans - for example, in the production of foodstuffs, such as cheese, bread dough, and soy sauce or in alcoholic fermentation processes. In some Asian and American cultures, fungi have been employed by cults as a source of hallucinogens. Also when it comes to delicacies, the fruiting bodies of fungi, namely mushrooms, have been valued since ancient times, none more so than the truffles highly appreciated by gourmets. However, the importance of fungi as medicines was traditionally rather low compared with that of plants. This situation remained basically unchanged until the groundbreaking discovery of penicillin by Alexander Fleming in 1928 and its development as the first highly active antibiotic obtained from a mould. Since then the importance of fungi as sources of antibiotics and other pharmacologically active natural products has become ever more evident. Natural product chemists have also increasingly devoted their efforts to the research into terrestrial micro-organisms, such as bacteria, fungi.

Fungi, which consist of the phycomycetes, archimycetes, ascomycetes, basidiomycetes, and deutermycetes, are geographically widely distributed in the world. Higher fungi, namely macrofungi or macromycetes, characterised by the production of macroscopic fruiting bodies to generate and to distribute their spores, comprise basidiomycetes known as mushrooms, including toadstools, and members of the Clavicipitaceae, the Hypocreaceae, and the Xylariaceae in ascomycetes. These fungi are known to produce several hundred secondary metabolites, many of which are reported to be phytotoxic and some of which have antibacterial or antifungal activities. Only recently were the compounds tested in screens targeted for specific enzyme inhibitors or receptor agonists/antagonists. This group of fungi is attractive for screening for novel natural products because of the diversity of species and physiology.

Over the past decades, higher fungi have proven to be a prodigious source of new biologically active secondary metabolites. The chemistry and biology of European higher fungi have been investigated systematically, and a large number of important or lead compounds have been found to possess a wide range of remarkably diverse bioactivity and to show structural variants. Some synthetic analogues of these have successfully been put into commercial use or clinical trials. It is worth noting that a variety of fascinating antibiotic compounds have been isolated from higher fungal species. Strobilurine A, for example, the first member of a novel class of β-methoxyacrylic acid derivatives was isolated from fermentations of a basidiomycete by Anke and Steglich in 1977 [1]. Most metabolites of this type are known to exhibit various antibiotic actions. The importance of β-methoxyacrylate as lead structure within the agrochemical industry is demonstrated by the fact that some companies are now conducting research in the area. Additionally, higher fungi are found to produce several important compounds, such as ibotenic acid which served as a template for developing agents selective at different subtypes of glutamic acid receptors; illudin S as lead for the synthesis of a highly potent antitumor drug, hydroxymethylacylfulvene, which has progressed to phase II clinical trials [2], as well as (+)-muscarine, a principal alkaloid of the poisonous mushroom of the genus *Amanita* and its synthetic analogues as useful probes for understanding the biochemical processes for Alzheimer's disease [3].

The chemistry of Chinese higher fungi has received less attention, notwithstanding the larger number of existing species used for taxonomical studies, and previous research is confined mainly to several traditionally used medicinal higher fungi, from which the number of secondary metabolites so far discovered is only about 160. China is one of the richest resources in the world of a huge number of

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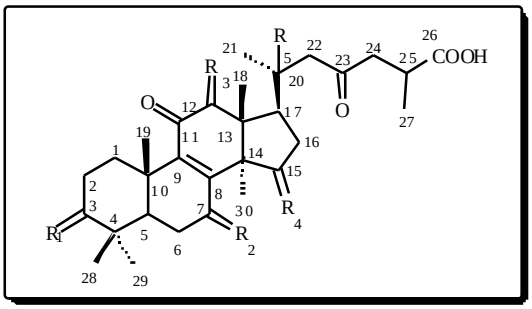


ganoderic acid A (**1**) R_1=O, R_2=β-OH, α-H, R_3= H, H, R_4=α-OH, β-H, R_5=H
ganoderic acid B (**2**) R_1=β-OH, α-H, R_2=β-OH, α-H, R_3= H, H, R_4=O, R_5=H
ganoderic acid G (**3**) R_1=β-OH, α-H, R_2=β-OH, α-H, R_3= β-OH, R_4=O, R_5=H
ganoderic acid H (**4**) R_1=β-OH, α-H, R_2=O, R_3= β-OAc, α-H, R_4=O, R_5=H
20-hydroxylganoderic acid G (**5**) R_1=β-OH, α-H, R_2=β-OH, α-H, R_3= β-OH, R_4=O, R_5= OH
12-deacetylganoderic acid H (**6**) R_1=β-OH, α-H, R_2=O, R_3= β-OH, α-H, R_4=O, R_5=H
ganoderic acid C1 (**7**) R_1=O, R_2=β-OH,α-H, R_3=H,H, R_4=O, R_5=H
ganolucidic acid A (**8**) R_1=O, R_2= R_3=H,H, R_4=α-OH, β-H, R_5=H

fungi. There are approximately 10,000 species of higher fungi known up to now in China. Edible and inedible mushrooms represent about 600 and 500 species, respectively, including some 100 strongly toxic lethal species [4]. Higher fungi are the more productive bio-resources with a large and diversified variety of secondary metabolites. Great attention has been paid to the different activities of these metabolites and attempts have been made to use them in medicinal and agricultural chemistry. In the past decades, biologically active chemical constituents from the fruiting bodies and mycelial cultures of Chinese higher fungi, 32 Basidiomycetes and 6 Ascomycetes species, have been isolated and characterized. This overview describes the chemistry and interesting biological properties of the different types of terpenoids, steroids, sphingolipids, phenolics and heterocyclic compounds.

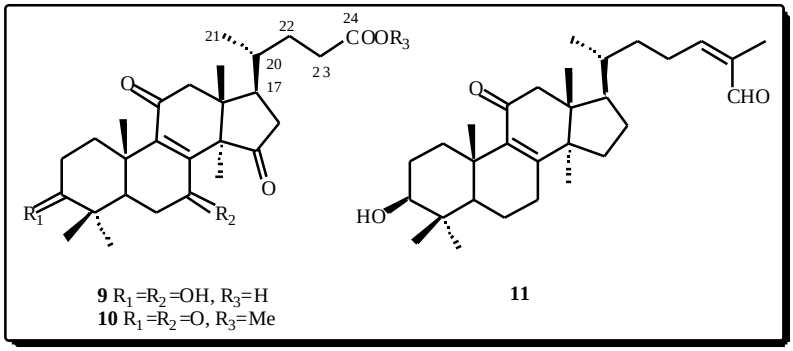
TRITERPENOIDS AND ERGOSTEROIDS

Various wood-rotting fungi are known to contain lanostane-type triterpenes, in particular the medicinal mushroom *Ganoderma lucidum* (Fr.) Karst (G. *lucidum* in short, Reishi or Ling Zhi) (Ganodermataceae), which grows in many different regions of the world, is widely used in Asian traditional medicine and regarded as a panacea for all types of diseases. The fruiting bodies, mycelia, and spores of *G. lucidum* have been well investigated and produce more than 130 highly oxygenated lanostane-triterpene derivatives. Some newly-discovered triterpenoids isolated from *G. lucidum* grown in various regions of China have been reported. Most of them are responsible for a variety of bioactive effects such as cytotoxicity [5], inhibitory activity against farnesyl protein transferase [6], β-glucosidase inhibitory and hepatoprotective effects [7]. The triterpene-enriched extracts from mycelia of *G. lucidum* inhibited growth of human hepatoma Huh-7 cells *via* suppression of protein kinase C, activating mitogen-activated protein kinases and G2-phase cell cycle arrest [8].

Ganoderic acids A (**1**), B (**2**), G (**3**) and H (**4**) were isolated as the antinociceptive components from the fruiting bodies of *G. lucidum* examined by the acetic acid-induced writhing method [9], along with other new compounds 20-hydroxylganoderic acid G (**5**) [10], 12-deacetylganoderic acid H (**6**) [10], ganoderic acid C1 (**7**) [11,12], ganolucidic acid A (**8**) [11].

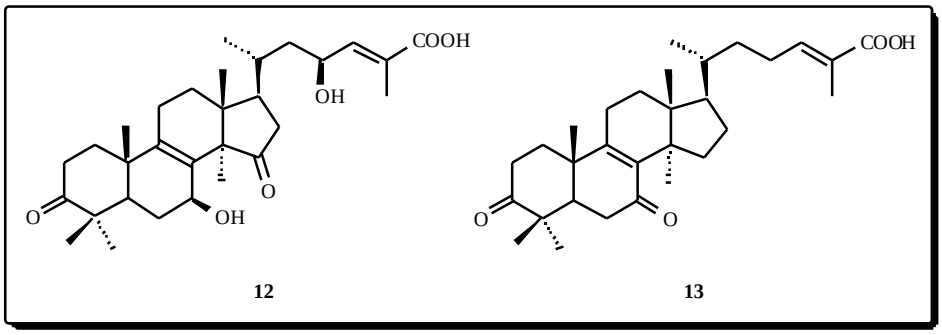
Further new triterpenes, lucidenic acid N (**9**), methyl lucidenate F (**10**) [13], ganoderic aldehyde A (**11**) [14], ganoderic acid LM2 (**12**) [15], ganoderic acid DM (**13**) [15], were obtained from the same species.

Among them, lucidenic acid N (**9**) showed cytotoxicity against the growth of human Caucasian hepatocyte carcinoma Hep G2, Hep G2,2,15, lymphocytic leukemia P-388, nasopharyngeal carcinoma KB, and cerebral cavernous malformation CCM2 cells with IC_{50} values of 2.06×10^{-4}, 1.66×10^{-3}, 1.20×10^{-2}, 26.69, and 35.49 μM [13], respectively. Ganoderic aldehyde A (**11**) exhibited potent inhibition of



9 R_1 =R_2 =OH, R_3=H
10 R_1 =R_2 =O, R_3=Me

11

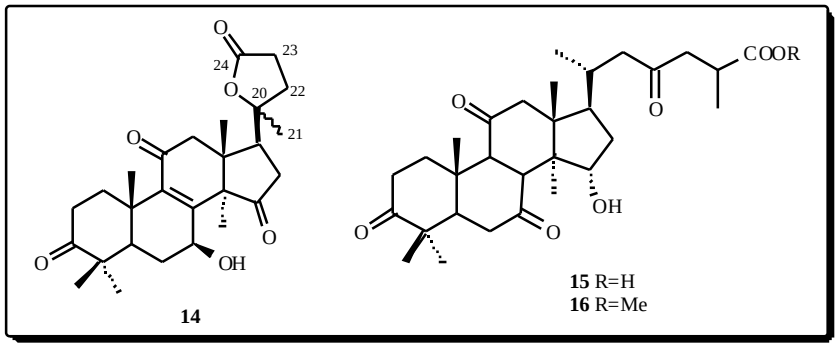


12 **13**

human hepatoma PLC/PRF/5 and KB cells in vitro [14]. Ganoderic acid LM2 (**12**) exhibited *in vitro* potent enhancement of concanavalin A (ConA)-induced mice splenocyte proliferation [16].

Other novel products, ganolactone (**14**) [18], 8β,9α-dihydroganoderic acid J (**15**) [10], methyl 8β,9α-dihydroganoderic acid J (**16**) [10], ganodermic acid S (**17**) [19], were isolated from the fruiting body of *G. lucidum*. Ganodermic acid S (**17**) inhibited platelet response to thromboxane A_2 on the receptor-Gq-phospholipase C β1 pathway, but not on the receptor-G1 pathway [19].

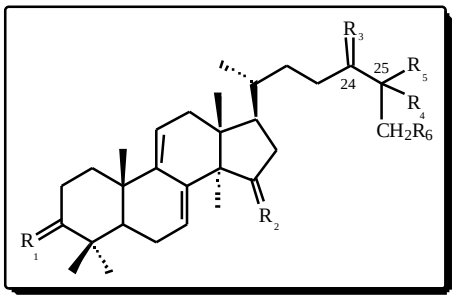
triterpene alcohols (**19-21**) showed a strong anticomplement activity against the classical pathway (CP) of the complement system (IC_{50} 4.8, 41.7, and 17.2 μmol/l, respectively). The potency of these products (**19-21**) in inhibiting CP activity was improved when the number of hydroxymethyl groups on the side chain moiety was increased [21]. Ganoderic alcohols lucidumols A (**22**) and B (**18**), and **19-21** showed cytotoxic effects on Meth-A (sarcoma, murine) and Lewis lung carcinoma (LLC) tumor cells (ED_{50} 4.7-16 μg/ml) [12]. And lucidumol A (**22**) exhibited the most potent cytotoxicity against LLC cells



14

15 R=H
16 R=Me

In addition, of these triterpenes isolated from the spores of *G. lucidum*, lucidumol B (**18**), ganodermanondiol (**19**), ganodermanontriol (**20**) and ganolucidic acid A (**8**) showed significant anti-human immunodeficiency virus (anti-HIV)-1 protease activity with IC_{50} values of 20-90 μmol/l [11]; ganodermanontriol (**20**) and ganoderiol F (**21**) were found to be active as anti-HIV-1 agents (IC_{50} 7.8 μg/ml) [20]; these

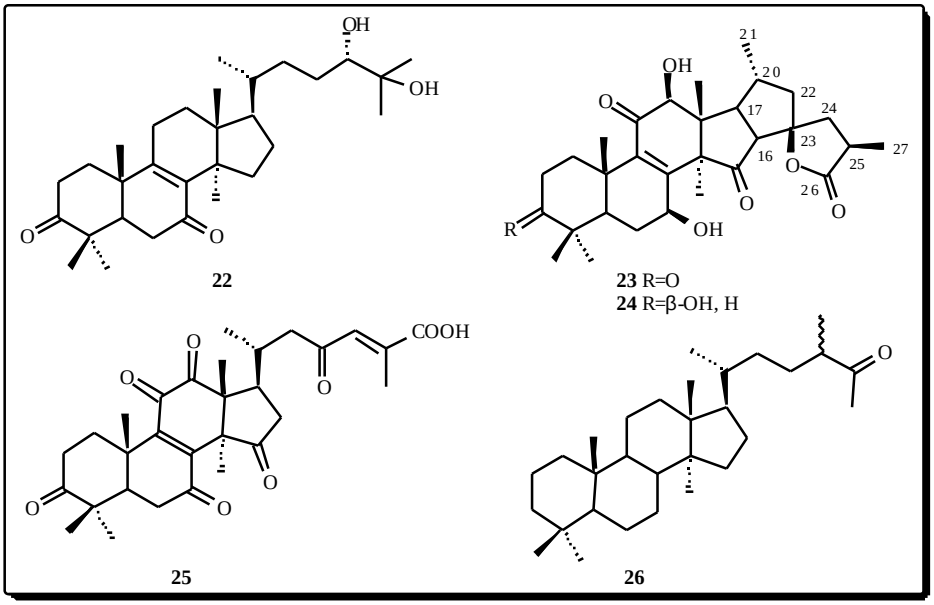


17 R_1=β-OAc,α-H, R_2=α-OAc,β-H, R_3= $\Delta^{24(25)}$, R_5= COOH, R_6=H
18 R_1=β-OH,α-H, R_2=H,H, R_3=α-OH,β-H, R_4=OH, R_5=Me, R_6=H
19 R_1=O, R_2=H,H, R_3=α-OH,β-H, R_4=OH, R_5=Me, R_6=H
20 R_1=O, R_2=H,H, R_3=α-OH,β-H, R_4=OH, R_5= CH_2OH, R_6=H
21 R_1=O, R_2=H, H, R_3=$\Delta^{24(25)}$, R_5= CH_2OH, R_6=O

(ED_{50} 2.3 μg/ml) and ganodermanondiol (**19**) against Meth-A cells (ED_{50} 3.4 μg/ml) [5].

From the spores of *G. lucidum*, the structures of two unusual triterpenes, ganosporelactones A (**23**) and B (**24**) have been elucidated by ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, ^{1}H-^{13}C COLOC and NOESY experiments, which may be biogenetically derived from a lanostane skeleton through the construction of C-16 and C-23 bonds [22], as well as ganosporeric acid A (**25**) [23]. The fruiting bodies of *Ganoderma applanatum* (Pers.) Pat. (Ganodermataceae) provided a new lanostanoid (**26**), characterized as 24ξ-methyl-5α-lanosta-25-one [24].

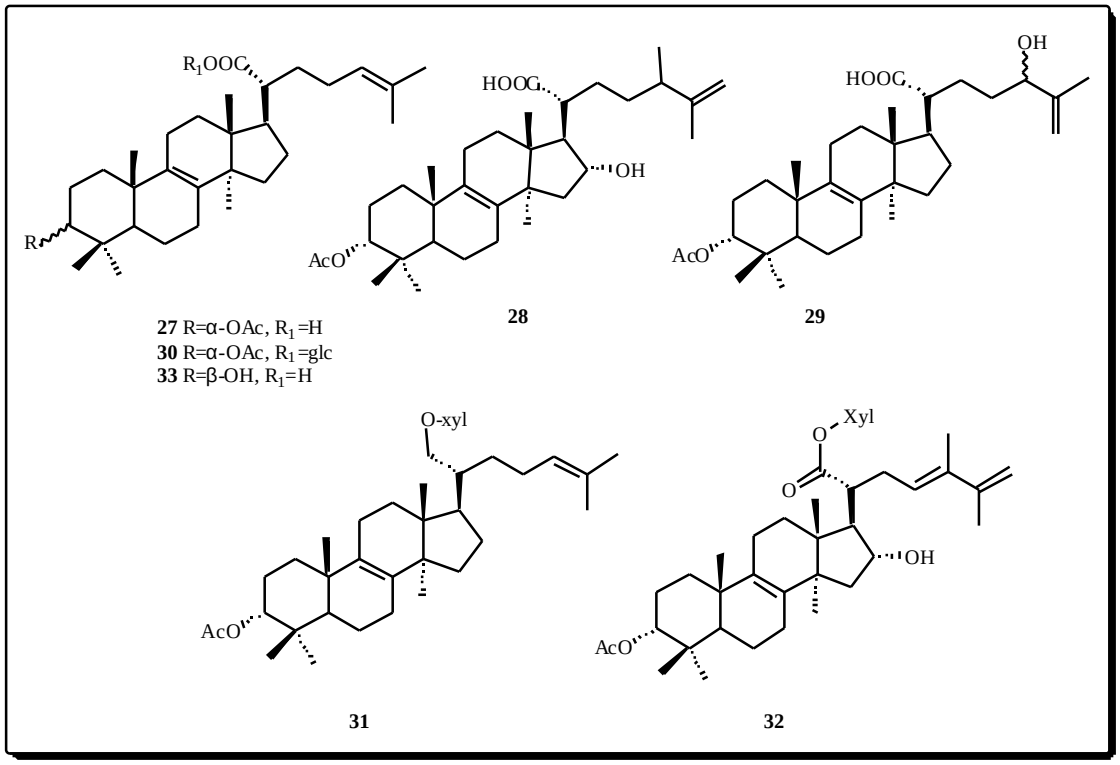
Crude extracts of Formosan *Ganoderma tsugae* Murr. (*G. tsugae* in short) (Ganodermataceae), a traditional Chinese medicine, have been demonstrated to enhance splenic natural killer cell activity and serum interferon production in mice. Recently, six new lanostanoids, tsugaric acid A (**27**), tsugaric acid B (**28**) [25], and tsugaric acid C (**29**) [26], as well as three lanostanoid ester glycosides, tsugarioside A (**30**) [27], tsugarioside B (**31**), and tsugarioside C (**32**) [26], along with 3β-hydroxy-5α-lanosta-8, 24-dien-21-oic acid (**33**), were isolated from the fruit bodies of *G. tsugae*. Compound **30** caused cell death by apoptosis [27] and exhibited cytotoxic

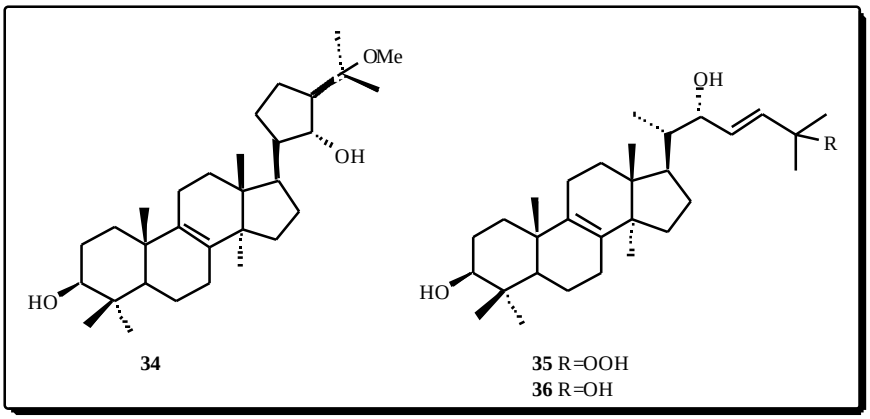


activity against human hepatoma T-24 cells, human cervical carcinoma (HT-3, SiHa) with ED_{50} values of 1.73, 6.8, and 8.4 μg/ml, respectively, while both compounds (**27**) and (**33**) showed significant activity against T-24 with ED_{50} values of 3.1-4.4 μg/ml. Compound (**33**) displayed cytotoxic activity against HT-3 and SiHa cells with 3.5 and 5.5 μg/ml [26], respectively. Tsugarioside C (**32**) showed cytotoxicity against PLC/PRF/5, T-24, HT-3, and SiHa tumour cells with ED_{50} values of 6.5, 8.6, 7.2, and 9.5 μg/ml [26], respectively.

Recently, three new lanostane triterpenoids, fuscoporianol A (**34**), B (**35**), and C (**36**) were isolated from the anti-tumor birch tree fungus *Fuscoporia obliqua* Fr Te. LáT (Polyporaceae) and their structures were determined on the basis of chemical, spectroscopic methods and X-ray crystallographic analysis [28].

Bioassay-guided fractionation of the fruiting bodies of *Antrodia camphorate* Chang & Chou, sp.nov. (Polyporaceae), a fungal parasite of the tree *Cinnamomum micranthum*, which has been utilized in Chinese medicine for the treatment of various disorders, yielded four new triterpene acids, zhankuic acids A-C (**37**-**39**) and antcin K (**40**). Zhankuic acids A (**37**)and C (**39**) exhibited cytotoxicity





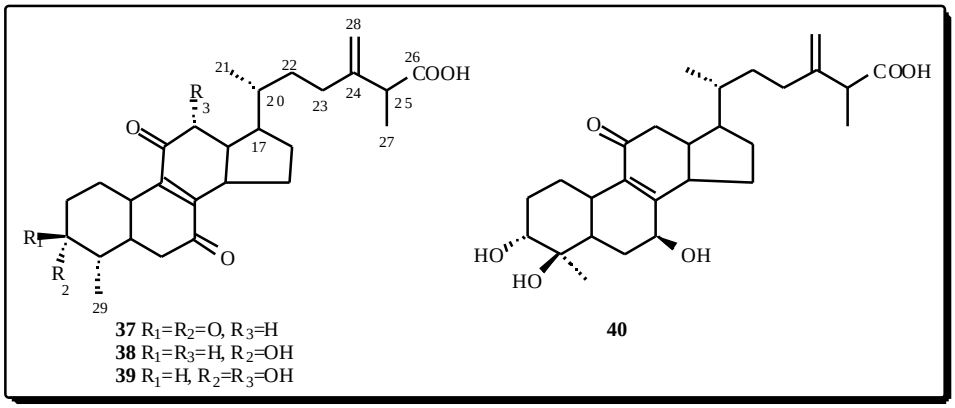
34

35 R=OOH
36 R=OH

against P-388 murine lymphocytic leukemia cells with IC_{50} values of 1.8 and 5.4 μg/ml [29], respectively. Zhankuic acid B (**38**) showed anticholinergic and antiserotonergic activities with an IC_{50} value of 10 μg/ml [29]. These three compounds **(37-39)** were determined as major immunomodulatory principles in human mononuclear cell proliferation and expression of hepatitis B surface antigen (HBsAg) [30] and recently reported to possess the anti-inflammatory effects using an acute cellular model in isolated peripheral human neutrophils [31]. Reactive oxygen species (ROS) production and firm adhesion by neutrophils are known to display two important responses during inflammation. Further studies suggest that zhankuic acids **(37-39)** and antcin K (**40**) exhibit leukocyte modulating activity by inhibiting both ROS production and firm adhesion by neutrophils without significant cytotoxic effects, implying that these drugs could be potential anti-inflammatory agents for clinical treatment [31].

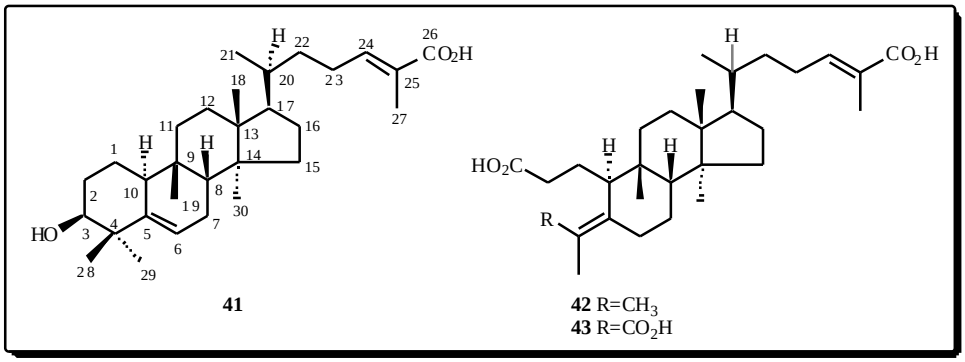
The Russulaceae family is one of the largest in the subdivision Basidiomycotina in Witthaker's Kingdom of Fungi and comprises hundreds of species [32]. While secondary metabolites occurring in the fruiting bodies of European *Lactarius* species have been well investigated, the *Russula* mushrooms have received less attention, notwithstanding the larger number of existing species [33].

Russula lepida Fr. (Russulaceae) has been used as a food and medicinal agent in China. From the extract of the fruiting bodies of *Russula lepida* Fr. with anti-tumor activity, four new cucurbitane-type triterpenoids, namely (24*E*)-3β-hydroxycucurbita-5, 24-dien-26-oic acid (**41**), (24*E*)-3,4-*seco*-cucurbita- 4,24-diene-3,26-dioic acid (**42**), (24*E*)-3,4-*seco*-cucurbita-4,24-diene-3, 26, 29-trioic acid (**43**), and lepidolide (**44)** have been isolated and their structures were established by spectral methods [34, 35]. Compounds (**42-44**) are the first example of naturally occurring *seco*-ring-A cucurbitane triterpenoids. The bioassay indicated that **41**



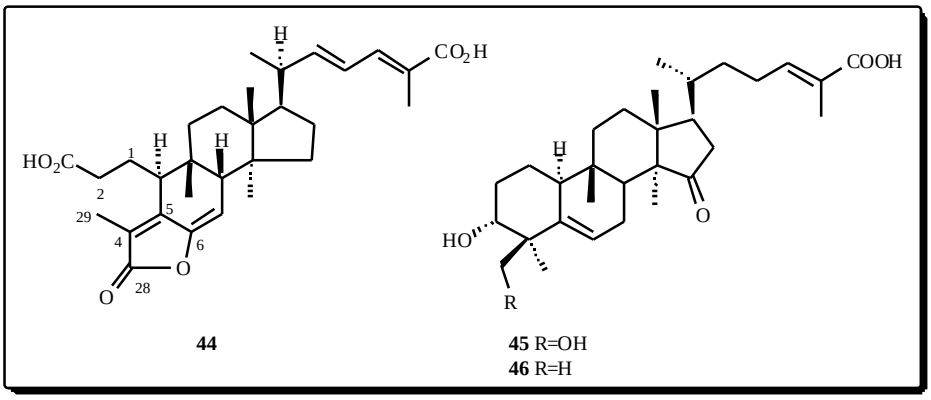
37 R_1=R_2=O, R_3=H
38 R_1=R_3=H, R_2=OH
39 R_1=H, R_2=R_3=OH

40



41

42 R=CH_3
43 R=CO_2H



44

45 R=OH
46 R=H

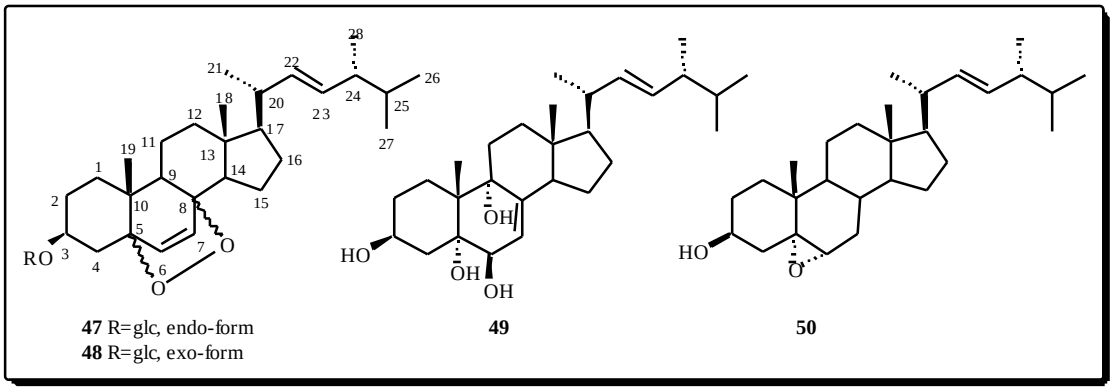
showed antifungal activity (IC_{50} 2.9 μg/ml for *Candida albicans*; IC_{50} 2.3 μg/ml for *Candida glabrata*) and compound (**42**) showed farnesyl transferase inhibitory activity (IC_{50} 24 μg/ml) [34, 35].

Two additional new triterpenes with the same skeleton, rosacea acids A (**45**) and B (**46**), were isolated from the fruiting bodies of *Russula rosacea* (Bull) Grray em. Fr. (Russulaceae) [36].

The edible milk mushroom *Lactarius volemus* Fr. (Russulaceae) yielded three new ergosteroids, 3-O-β-D-glucopyranosyl-22*E*,24*R*-5α,8α-epidioxyergosta-6,22-diene (**47**), 3-O-β-D-glucopyranosyl- 22*E*,24*R*-5β,8β-epidioxyergosta-6,22-diene (**48**) and 9-hydroxycerevisterol (**49**) [37]. Compound **49** showed *in vitro* marked cytotoxic activity against human hepatoma HeLa cells [38] and was antinociceptive using the acetic acid-induced writhing method [39].

Cordyceps sinensis (Berk.) Sacc. (Clavicipitaceae), a popular Chinese tonifying herb, is a parasitic fungus that has long been used as a Chinese medicine to treat numerous illnesses like nephritis, promote longevity, relieve exhaustion and increase athletic prowess. Activity-guided fractionations led to the isolation of two antitumor compounds (**47**) and 5α,6α-epoxy-24(*R*)-methylcholesta-7, 22-dien-3β-ol (**50**) from the mycelia of *C. sinensis* (Berk.) Sacc. The glycosylated form of ergosterol peroxide was found to be a better inhibitor of the proliferation of five tumor malignant cell lines K 562 (erythroleukemia), Jurkat (T-lymphoblastic), WM-1341(malignant melanoma), HL-60 (promyelocytic leukemia) and RPMI-8226 (multiple myeloma) at 10 μg/ml than its aglycone [40].

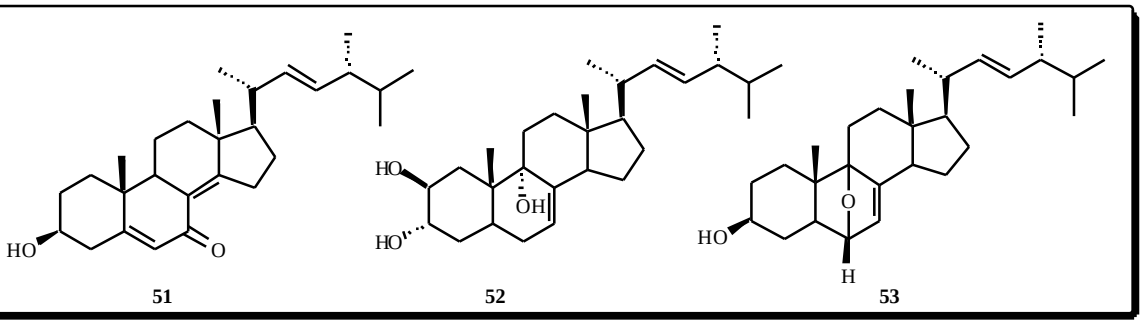
More recently, another product of the same fungus, H1-A (**51**), can suppress the activated human mesangial cells and alleviate immunoglobulin A nephropathy (Berger's disease) with clinical and histologic improvement [41]. The fruiting bodies of *Ganoderma tsugae*a Murr. produced 2β, 3α, 9α-trihydroxy-5α-ergosta-7,22-diene (**52**), which inhibited the cell cycle progression of hepatocellular carcinoma (Hep 3B) cells at the G2/M phase with an IC_{50} value of about 87.1 μg/ml, indicating **52** may possess the activity of cell cycle



47 R=glc, endo-form
48 R=glc, exo-form

49

50



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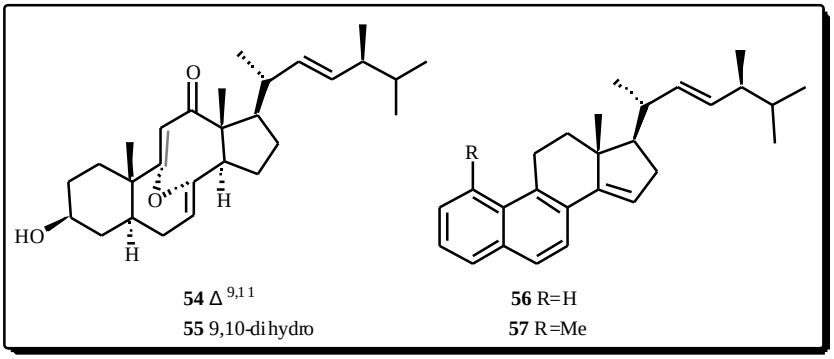
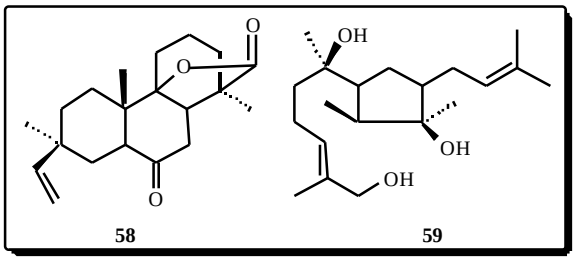


inhibition [27]. The mycelia of *Mycena dendrobii* Fan et Guo (Tricholomataceae) produced a new ergosterol oxide 6, 9-epoxyergosta-7,22-dien-3-ol (**53**) [42].

Two novel seco-ergosterols, tylopiol A (**54**) and tylopiol B (**55**), were isolated from the fruiting bodies of inedible and bitter fungus *Tylopilus plumbeoviolaceus* (Snell) Snell & Dick (Strobilomycotaceae**).** The structures of these two compounds are based on the ergostane skeleton, in which the bond between C-8 and C-9 is cleaved to form an enol ether oriented in the α position. Although this type of modified skeleton is very rare, a similar ergostane compound, jereisterol A, has been isolated from a marine sponge. The structures and stereochemistry of **54** and **55** were confirmed by X-ray crystallography [43]. Two new natural aromatic steroids as potential molecular fossils, (17β,20*R*,22*E*,24*R*)-19-norergosta-1,3,5,7,9,14,22-heptaene (**56**) and (17β, 20*R*, 22*E*, 24*R*)-1-methyl- 19-norergosta-1,3, 5,7,9,14,22-heptaene (**57**), were isolated from the fruiting bodies of the ascomycete *Daldinia concentrica* (Bolt.: Fr.) Ces. & De Not. (Xylariaceae), of which compound **57** bears an unusual methyl group at position 1 [44]. It is proposed that the origin of these compounds is derived from the transformation undergone by their precursor due to microbial action. Diaromatic and 1-methyl diaromatic steroid hydrocarbons have never been found in any living organism. Compounds **56** and **57** could be the long-sought, biological precursor steroids for organic matter in Earth's subsurface. Their existence provides a link between biomarker compounds or fossil molecules and biological origin. Moreover, these compounds potentially can be used as biological markers for the contribution of microorganism to sediments.

DITERPENES

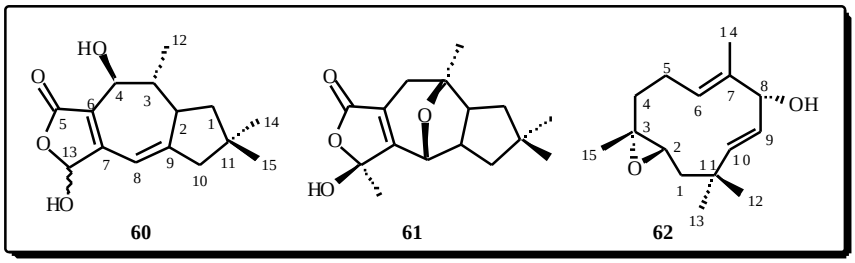
The inedible fungus *Engleromyces goetzii* P. Henn. (Hypocreaceae) growing on the bamboo of high mountains, has been used as a folk remedy against infection and cancer diseases in southwest China. The culture mycelia of this ascomycete yielded a new diterpenoid, resenonolactone (**58**) [45]. Another monocyclic diterpenoid metabolite, moreloriol (**59**), was obtained from the mycelia of *Morchella conica* Pers. (Mochellaceae) [46].

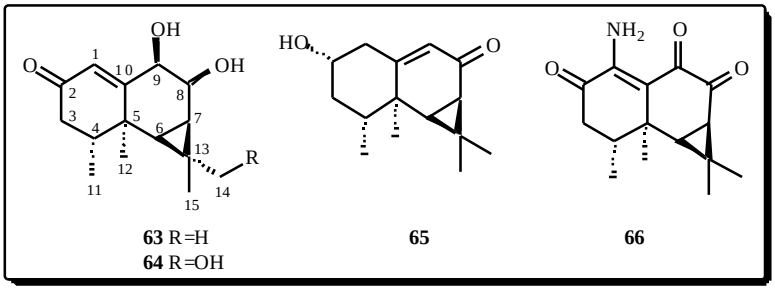


SESQUITERPENES

The fungal subdivision basidiomycotina produce toxic sesquiterpenes, many of them derived from the protoilludane skeleton. This skeleton is transformed and rearranged to a large number of compounds. Some of these sesquiterpenes show interesting biological properties concerning insecticidal, antifungal, antibacterial, cytotoxic and enzyme inhibition which may be attractive for medicinal and agricultural chemistry [47, 48]. The different types of bioactive fungal sesquiterpenes derived from humulene are known to date in basidiomycotina [49]. It is well known that most of both *Lactarius* and *Russula* fungi produce a series of sesquiterpenes, belonging mainly to the types of marasmane, lactarane, isolactarane, and secolactarane [48].

The fungus *Lactarius subvellereus* Peck. (Russulaceae) is used in Chinese folk medicine. Its EtOAc extract has cytotoxic and antitumour activities. Two sesquiterpenes, subvellerolactones A (**60**) and C (**61**), were isolated from this fungus and cytotoxic effects against some cancer cells were shown [50, 51]. The first newly discovered humulene-type sesquiterpene, 2β, α-epoxy-6*Z*, 9*Z*-humuladien-8α-ol (**62**) in higher fungi, was isolated from *Lactarius hirtipes* J. Z. Ying (Russulaceae) [52].



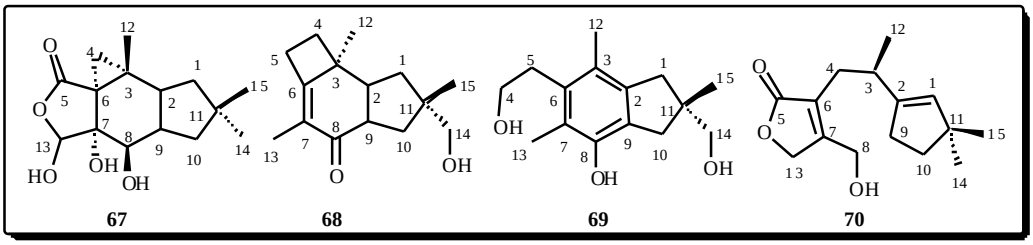


63 R=H
64 R=OH
65
66

Four new aristolane sesquiterpenoids, namely rulepidadiol (**63**), rulepidatriol (**64**), rulepidol (**65**), and lepidamine (**66**), have been isolated from the fruiting bodies of *Russula lepida* Fr. and established by spectroscopic methods [34, 53]. Compounds (**63-66**) belonging to the aristolane type sesquiterpenoid are of a type rather rare in the fungal species. Compound **63** is the first aristolane-type sesquiterpene alkaloid isolated from nature.

new triquinane metabolite with antimicrobial effects, isolated from the fermentation broth of *Gloeostereum incarnatum* S. Ito et Imai (Meruliaceae), was identified by X-ray diffraction and spectroscopic methods [56].

The pathogenic *Armillaria mellea* (Vahl. Ex Fr) Quél (Tricholomataceae) is a fungus symbiotic with the Chinese medicinal herb, Tian Ma (*Castrodia elata* Blume). A range of biologically active sesquiterpenoid aromatic esters with



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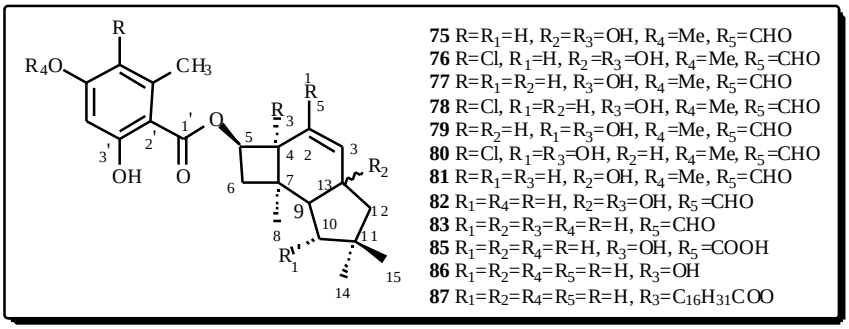
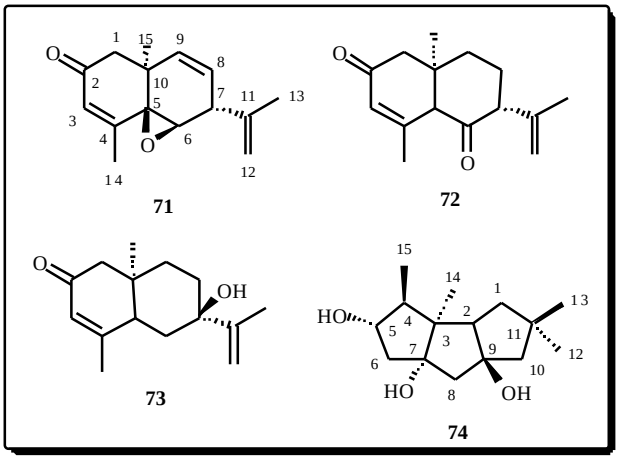


75 R=R$_1$=H, R$_2$=R$_3$=OH, R$_4$=Me, R$_5$=CHO
76 R=Cl, R$_1$=H, R$_2$=R$_3$=OH, R$_4$=Me, R$_5$=CHO
77 R=R$_1$=R$_2$=H, R$_3$=OH, R$_4$=Me, R$_5$=CHO
78 R=Cl, R$_1$=R$_2$=H, R$_3$=OH, R$_4$=Me, R$_5$=CHO
79 R=R$_2$=H, R$_1$=R$_3$=OH, R$_4$=Me, R$_5$=CHO
80 R=Cl, R$_1$=R$_3$=OH, R$_2$=H, R$_4$=Me, R$_5$=CHO
81 R=R$_1$=R$_3$=H, R$_2$=OH, R$_4$=Me, R$_5$=CHO
82 R$_1$=R$_4$=R=H, R$_2$=R$_3$=OH, R$_5$=CHO
83 R$_1$=R$_2$=R$_3$=R$_4$=R=H, R$_5$=CHO
85 R$_1$=R$_2$=R$_4$=R=H, R$_3$=OH, R$_5$=COOH
86 R$_1$=R$_2$=R$_4$=R$_5$=R=H, R$_3$=OH
87 R$_1$=R$_2$=R$_4$=R$_5$=R=H, R$_3$=C$_{16}$H$_{31}$COO

The inedible hot milk mushroom *Lactarius piperatus* (Fr.) S. F. Gray (Russulaceae) is distributed widely in China. Its ethanolic extract has been reported to inhibit the growth of several tumor cell lines and contained four novel sesquiterpenes, namely 7α, 8β, 13-trihydroxy-5, 13-marasmanolide (**67**), isoplorantinone (**68**), 4, 8,14-trihydroxyilludala-2, 6, 8-triene (**69**), and 8-hydroxy-8,9-secolactara- 1,6- dien-5,13-olide (**70**) [54]. The structures of these sesquiterpenes, representing diversified structural types, were determined mainly by 2D-NMR techniques. The structure of **69** was further confirmed by X-ray-diffraction analysis. The protoilludane and illudane types of sesquiterpenes have been found in the genus *Lactarius* for the first time [54].

The fungus *Dictyophora indusiata* (Vent.: Pers.) Fisch (Phallaceae), an edible mushroom used in Chinese food and medicine, furnished three sesquiterpenes with eudesmane skeleton, dictyophorines A and B (**71** and **72**), which promoted nerve growth factor (NGF)-synthesis by astroglial cells, along with teucrenone (**73**) [55]. Gloeosteretriol (**74**), a

the protoilludane skeleton have been isolated from the mycelium of different strains of this fungus. The crude drug is used for the treatment of geriatric patients with palsy, dizziness, headache, neurasthenia, insomnia, numbness in



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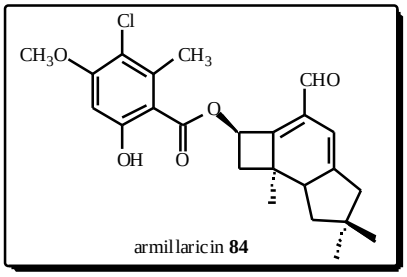
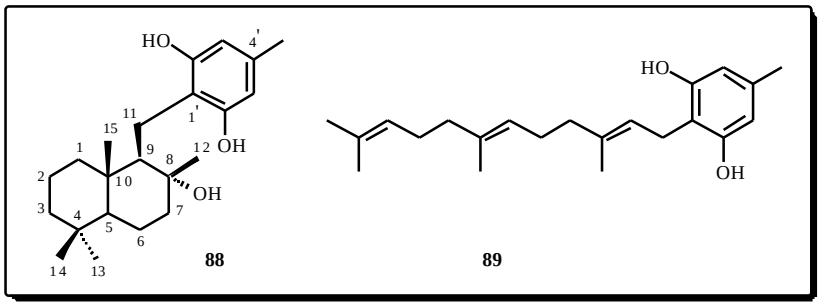


armillaricin **84**

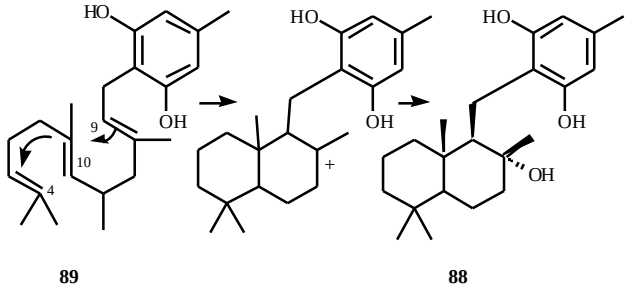
limbs, and infantile convulsion. This Chinese fungus produced the group of new metabolites, armillarilin (**75**), armillarinin (**76**) [57], armillarin (**77**), armillaridin (**78**) [58], armillarigin (**79**), armillarikin (**80**) [59], armillaripin (**81**) [60], armillaritin (**82**), armillarivin (**83**) [61], armillaricin (**84**) [62], armillaric acid (**85**) [63], and armillasin (**86**), armillatin (**87**) [64], and their structures were identified on the basis of spectral and X-ray analyses, respectively. These compounds show certain antimicrobial effects, while armillaric acid (**85**) exhibits marked inhibitory activity against gram-positive bacteria and yeast.

It was found that the inedible mushroom *Albatrellus confluens* (Alb. Et Schw.) Kotl. & Pouz. (Polyporaceae) contained a high content of a drimane-type sesquiterpene, albaconol (**88**) [65], which acted as a human vanilloid receptor 1 (VR1) antagonist with an IC_{50} value of 5 μM and induced contraction and desensitization of guinea pig trachea *in vitro* as a partial agonist for VR [66]. The new metabolite (**88**) most probably biosynthetically arises from rearrangements of the isoprene units of its co-occurring grifolin (**89**) also as a weak antagonist (Scheme **1**). We prepared **88** for the first time from starting material drimanal (Scheme **2**).

Albaconol (**88**) significantly inhibited the growth of four human tumor cell lines, K562 (human chronic myelogenous leukemia cell line), A549 (human lung cancer), BGC-823 (human gastric cancer), and Bcap-37 (human breast cancer) with IC_{50} values of 7.99, 3.17, 4.18 and 7.45 μM, respectively. It stabilized and increased the topoisomerase (topo) II-mediated DNA cleavable complex and inhibited the religation activity of topo II in a dose-dependent manner, but it failed to affect the activity of topo I. This compound (**88**) directly broke pBR322 DNA at high concentrations, but there was no effect on the macromolecule of K562 cells. These results strongly suggest that **88** targeted specifically to DNA topo II and that this is one of the mechanisms of its antitumor action; the direct action of **88** on DNA may partly contribute to its antitumor activity at high concentrations [67].



88 **89**

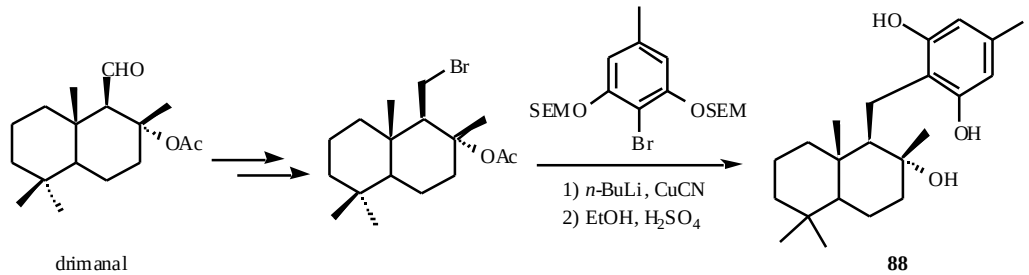


89 **88**

Scheme 1. Proposed biosynthetic route to albaconol (**88**) from the precursor grifolin (**89**).

SPHINGOLIPIDS AND OTHER LIPIDS

In recent years, sphingolipids have been the source of increasing research interest due to their diverse biological functions. Their function is to anchor lipid-bound carbohydrates to cell surfaces and to create an epidermal water permeability barrier, as well as to participate in antigen-antibody reactions and transmission of biological information [68, 69]. Some are also anti-ulcerogenic, ionophoretic, antihepatotoxic, antitumor, and immunostimulatory or stimulatory to axon growth [70].



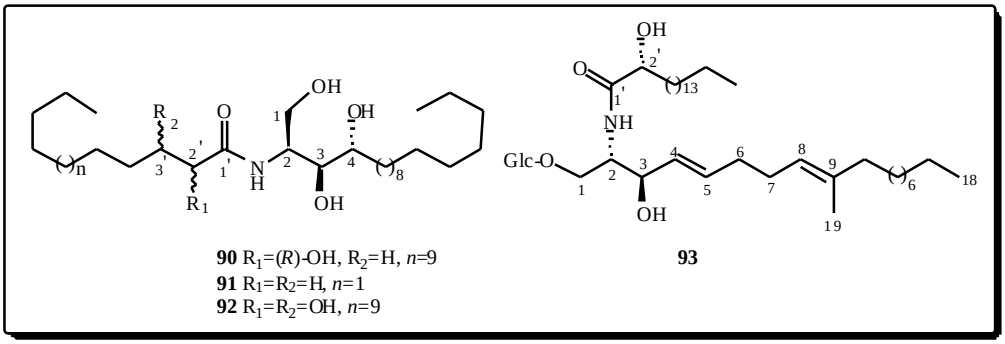
drimanal **88**

Scheme 2. First synthesis of albaconol (**88**).

We investigated sphingolipid constituents of several higher fungi, the basidiomycetes *Russula cyanoxantha* (Schaeff.) Fr. (Russulaceae), *Paxillus panuoides* Fr. (Paxillaceae), *Armillaria mellea* (Vahl. Ex Fr) Quél, *Polyporus ellisii* Berk. (Polyporaceae). Three new phytosphingosine-derived ceramides showing fruiting-inducing activity, russulamide (**90**) [71], armillaramide (**91**) with non-hydroxy fatty acid [72], paxillamide (**92**) with unusual 2, 3-dihydroxytetracosanoic acid [73], and one new glycosphingolipid (**93**) containing an unusual sphingoid base [74], have been isolated from the fruiting bodies of the above-mentioned fungi and structures established from spectroscopic and chemical analysis, respectively. Compound (**90**) was found to be antinociceptive using the acetic acid-induced writhing method [39] and showed weak phospholipase A_2 inhibitory activity [75].

to induce neuronal differentiation in clonal rat pheochromocytoma cells (PC12). The major cerebroside B obtained from the same mushroom was not hydroxylated around the middle of the long chain base (LCB) and was inactive against PC12 cells, suggesting the importance of the extra hydroxyl group on LCB [76,77]. The di- and tetra-hydroxylation of this inactive cerebroside resulted in the enhancement of its neuritogenic activity [76, 77]. Termitomycesphins A (**94**) and C (**96**) possessing a C-16 α-hydroxy fatty acid showed a higher neuritogenic activity than did termitomycesphins B (**95**) and D (**97**) having a C-18 α-hydroxy fatty acid [76].

Two novel ceramide, lactariamides A and B (**100-101**) were isolated from *Lactarius volemus* Fr. [78], and lactariamide B (**101**) was identified to be antinociceptive [39]. Three new cerebrosides, cortenuamides A-C (**102-104**),

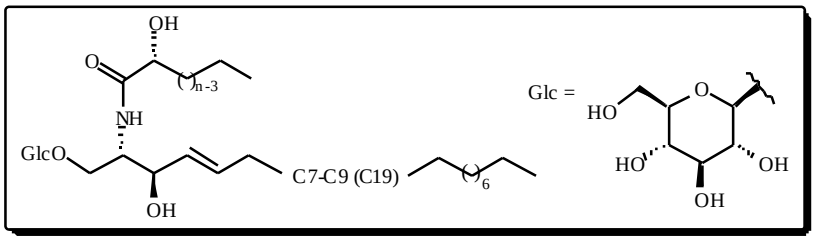


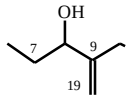
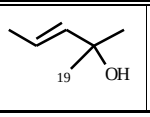
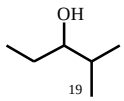
90 R_1=(*R*)-OH, R_2=H, *n*=9
91 R_1=R_2=H, *n*=1
92 R_1=R_2=OH, *n*=9

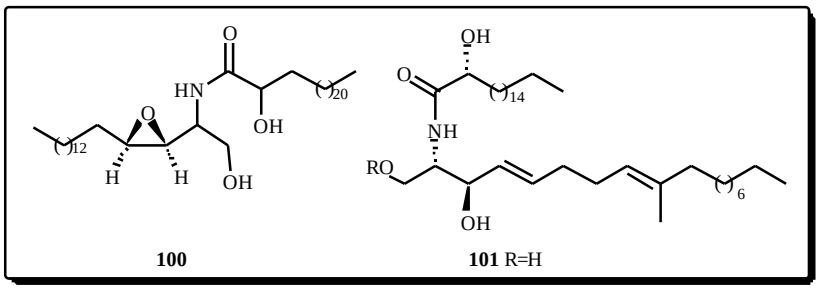
93

Termitomycesphins A-F (**94-99**), novel cerebrosides that have a unique C-19 hydroxylated sphingosine base with branching around the middle, have been isolated from the edible Chinese mushroom *Termitomyces albuminosus* Berk. Heim. ('Jizong' in Chinese) (Tricholomataceae), and shown

were isolated from the fruiting bodies of *Cortinarius tenuipes* Fr. (Cortinariaceae) [79]. Another three novel ceramide homologs (**105-107**) were isolated from *Cortinarius umidicola* Kauffm. (Cortinariaceae) [80]. Among these, **102** and **105** with the C_{24} fatty acid had no

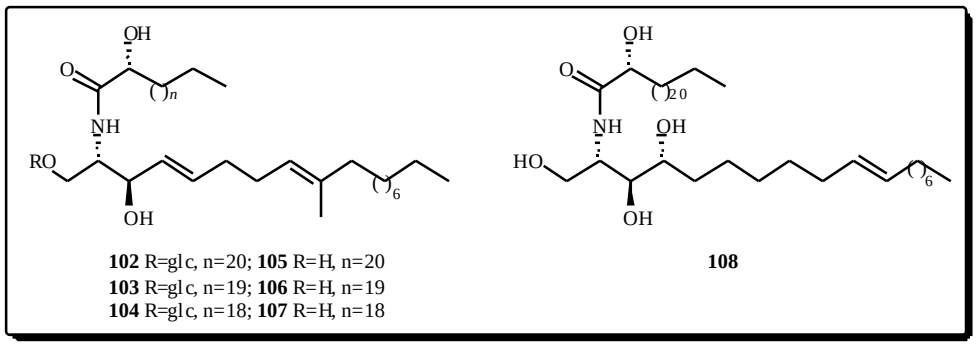


	C7-C9 (C19)	n		C7-C9 (C19)	n		C7-C9 (C19)	n
A(**94**) B(**95**)		15 17	C(**96**) D(**97**)		15 17	E(**98**) F(**99**)		15 17



100

101 R=H



102 R=glc, n=20; **105** R=H, n=20
103 R=glc, n=19; **106** R=H, n=19
104 R=glc, n=18; **107** R=H, n=18

108

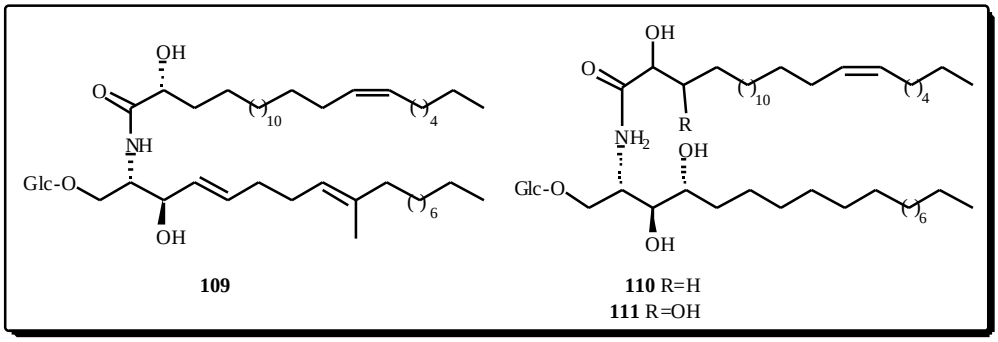
fruiting-inducing activity, and C_{22} and C_{23} must be the carbon chain lengths of the component fatty acid of the sphingolipids (**103-104** and **106-107**) critical for expression of biological activity. The fungus *Engleromyces goetzii* P. Henn. contained a new ceramide, (2*S*, 3*S*, 4*R*, 10*E*)-2-[(2′*R*)-2′-hydroxyltetra- cosanoylamino]-10-octadecene-1, 3, 4 (**108**) [81].

Three new glycolsphingolipids with a *cis*-Δ^{17}- fatty acyl moiety, catacerebrosides A-C (**109-111**), were isolated from the fungus *Catathelasma ventricosa* (PK.) Sing. (Tricholomataceae), and their structures were elucidated on the basis of spectroscopic analysis and chemical methods [82].

The fruiting bodies of the fungus *Engleromyces gotzii* P. Henn. produced an unusual novel nitrogenous lipid named neoengleromycin (**112**), which possesses the rare structure of a N-substituted hydroxamic acid and represent a new type of metabolite [83]. From the fruiting bodies of the ascomycete Chinese truffle *Tuber indicum* Cooke et Massee. (Tuberaceae), a hypogeous fungus, a trihydroxylated monounsaturated fatty acid (**113**) has been isolated [84]. The structure of this new linoleic acid-derived metabolite was established as 9,10,11-trihydroxy-(12Z)-12-octadecenoic acid by means of spectroscopic and chemical methods.

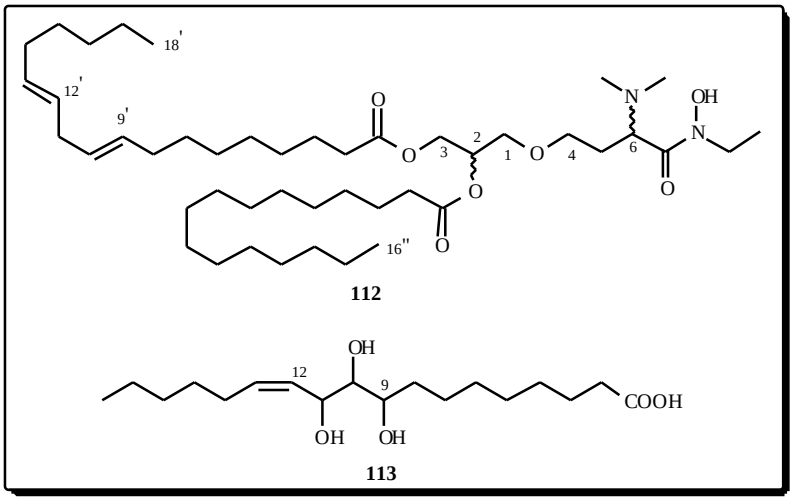
PERYLENEQUINONES

The mycelium of a number of phytopathogenic fungi shows deep red pigmentation due to the presence of secondary metabolites containing a perylenequinone nucleus. These fungal metabolites exert photodynamic activity towards bacteria and fungi, which is evidenced by their inhibition of the growth of other microorganisms upon



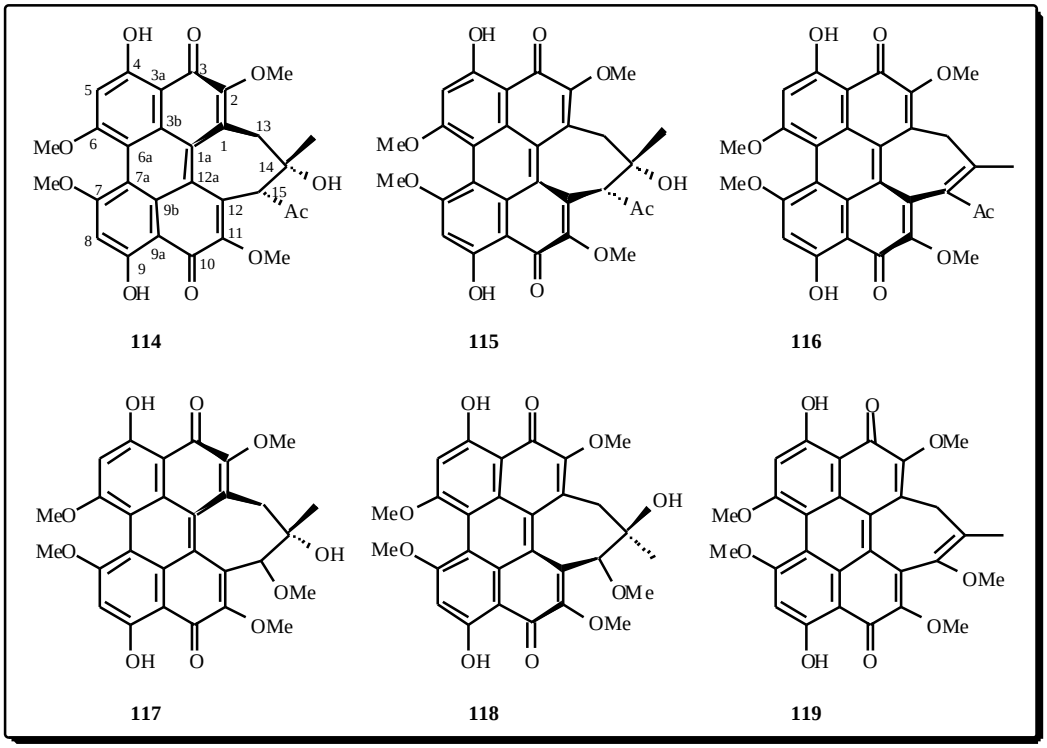
109

110 R=H
111 R=OH



112

113



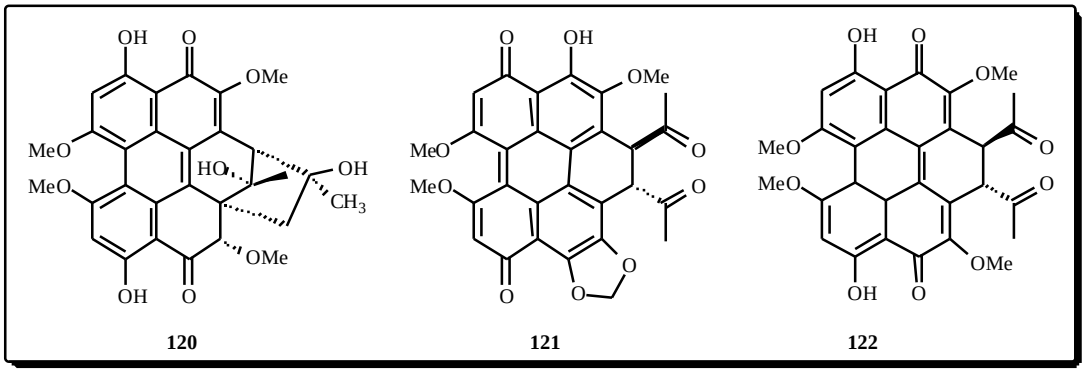
irradiation. This interesting biological activity arising from the chromophore is related to cellular lipid oxidation and has been used as a phototherapeutic agent for some dermatomycoses. Three new related metabolites, shiraiachromes A-C (**114-116**), were isolated from the Chinese bamboo fungus, *Shiraia bambusicola* P. Henn (Hypocreaceae) [85]. Investigation of the mechanism of action of shiraiachrome A (**114**) as a potent angiogenesis inhibitor demonstrated that this compound suppressed the autophosphorylation of four receptor tyrosine kinases (RTKs), with IC_{50} values ranging from 2.2 to 4.3 μM, suggesting that shiraiachrome A inhibits angiogenesis by blocking growth factor-stimulated autophosphorylation of RTKs [86]. Shiraiachrome A (**114**) may be an effective therapeutic agent in the treatment of diseases such as cancer and rheumatoid arthritis that require new blood vessel formation. Furthermore, the discovery of shiraiachrome A (**114**) provides new impetus for developing angiogenesis inhibitors.

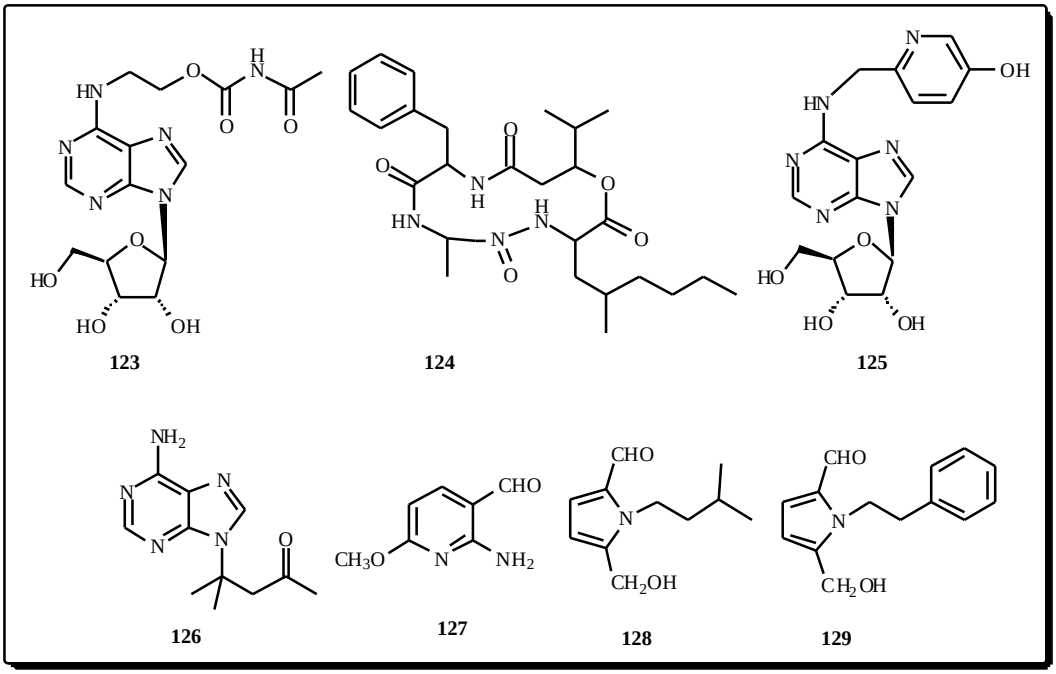
Three further analogues, hypocrellins A-C (**117-119**), are photodynamic agents isolated from another bamboo fungus *Hypocrella bambuase* (Berk. et Br.) Sacc. (Hypocreaceae) [87]. Hypocrellins A was used in the photodynamic therapy treatment of certain skin diseases.

Moreover, the mycelia of an ascomycete filamentous fungus, *Hypomyces* (Fr.) Tul. sp. (Hypocreaceae), afforded two new compounds, hypomycins A (**120**) [88] and B (**121**) [89], together with hypocrellin A (**117**) and elsinochrome A (**122**) [90]. Both compounds (**117**) and (**122**) exhibited potent photosensitive nematicidal activity toward the tested pine wood nematode, *Bursaphelenchus xylophilus* [90].

NITROGENOUS AND OXYGENOUS HETEROCYCLES

Fractionation of the culture sorophore of *Cordyceps militaris* (L. er. Fr.) Link (Clavicipitaceae) resulted in a series of adenosine-derived compounds, including a new analogue N^6-[β- (acetylcarbamoyloxy)ethyl]adenosine (**123**),





as well as a cyclic peptide, cordycepeptide A (**124**) [91]. N^6-(5-hydroxy-2-pyridyl)-methyl-adenosine, AMG-1 (**125**), which is 1000 times stronger than adenosine in cerebral protecting activity, was obtained from the mycelia of *Armillaria mellea* (Vahl. Ex Fr) Quél [92]. It has been shown that **125** acts on the presynapse (may be the A1 receptor) to attenuate the release of neurotransmitters. Compound **125** abolished the neurogenic twitch responses induced by electrical field-stimulation, while the responsiveness of rat vas deferens to exogenous acetylcholine was decreased showing both pre-synapse and post-synapse depression [93]. A novel purine alkaloid ganoderpurine (**126**), N^9-(α,α-dimethyl-γ-oxobutyl) adenine, has been isolated from the mycelia of *Ganoderma capense* (Lloyd) Teng (Ganodermataceae) [94]. A new natural pyridine derivative, 3-aldehyde-2-amino-6-methoxypyridine (**127**), was isolated from the fruiting bodies of *Cortinarius umidicola* Kauffm. [95].

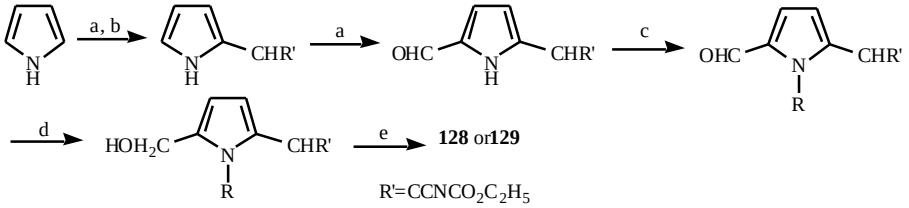
Two new pyrrole alkaloids, ganoine (**128**) and ganodine (**129**), were discovered in the hypha of deep fermented *Ganoderma capense* (Lloyd) Teng and showed anti-inflammatory activity in animal experiments [94]. Their synthesis was completed (Scheme **3**) [96].

More recently, five new succinic and maleic acid derivatives (**130-134**) were isolated from the mycelium of *Antrodia camphorate* Chang & Chou, sp. nov. (Polyporaceae). Their structures were determined by spectroscopic means and by X-ray analysis. Maleimide derivatives (**130**) and (**131**) showed appreciable cytotoxic activity against LLC cells with ED_{50} values of 3.6 and 7.5 μg/ml, respectively [97].

In addition, the fruiting bodies of *Lactarius subvellereus* Peck. (Russulaceae) contained a new 14-membered-ring lactone, lactariolide (**135**) [98]. Another novel highly symmetrical dilactone named tremellin (**136**) was isolated from the fruiting bodies of a basidiomycete *Tremella aurantialba* Bandoni et Zang (Tremellaceae) as anti-hepatitis agent and immunostimulant, and its relative configuration was determined by X-ray crystallography [99].

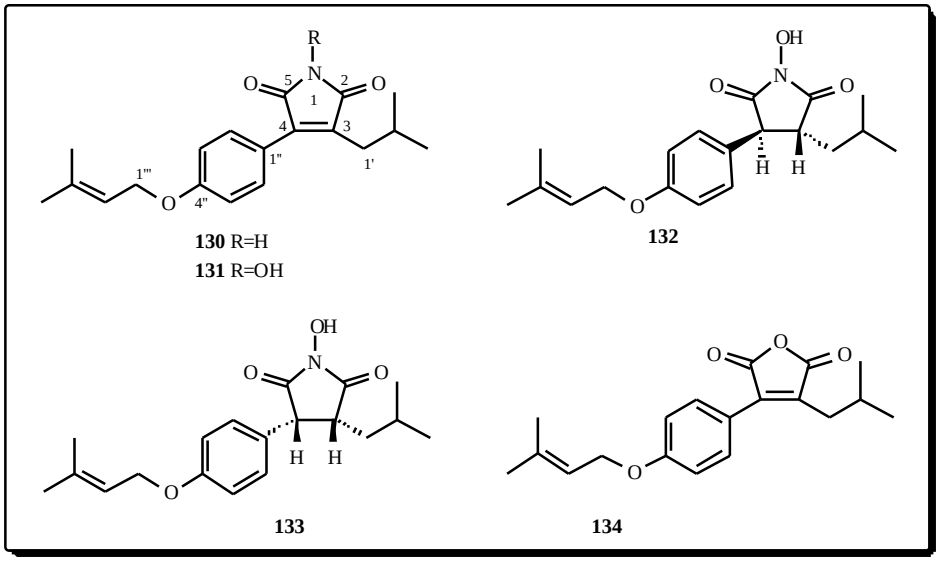
P-TERPHENYLS

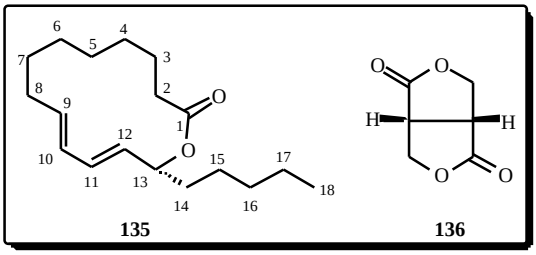
Natural *p*-terphenyl (=1,1′: 4,4″-terphenyl) compounds have been found so far only in lichens and fungi. In recent years, it has been reported that several *p*-terphenyl derivatives exhibit considerable bioactivities, such as inhibition of HeLa cells [100], potent immunoglobulin E



a. $POCl_3$, DMF; b. $CH_2CNCO_2C_2H_5$; c. $ICH_2CH_2CH(CH_3)_2$ or $BrCH_2CH_2C_6H_5$, K_2CO_3, DMF; d. $NaBH_3CN$; e. K_2CO_3

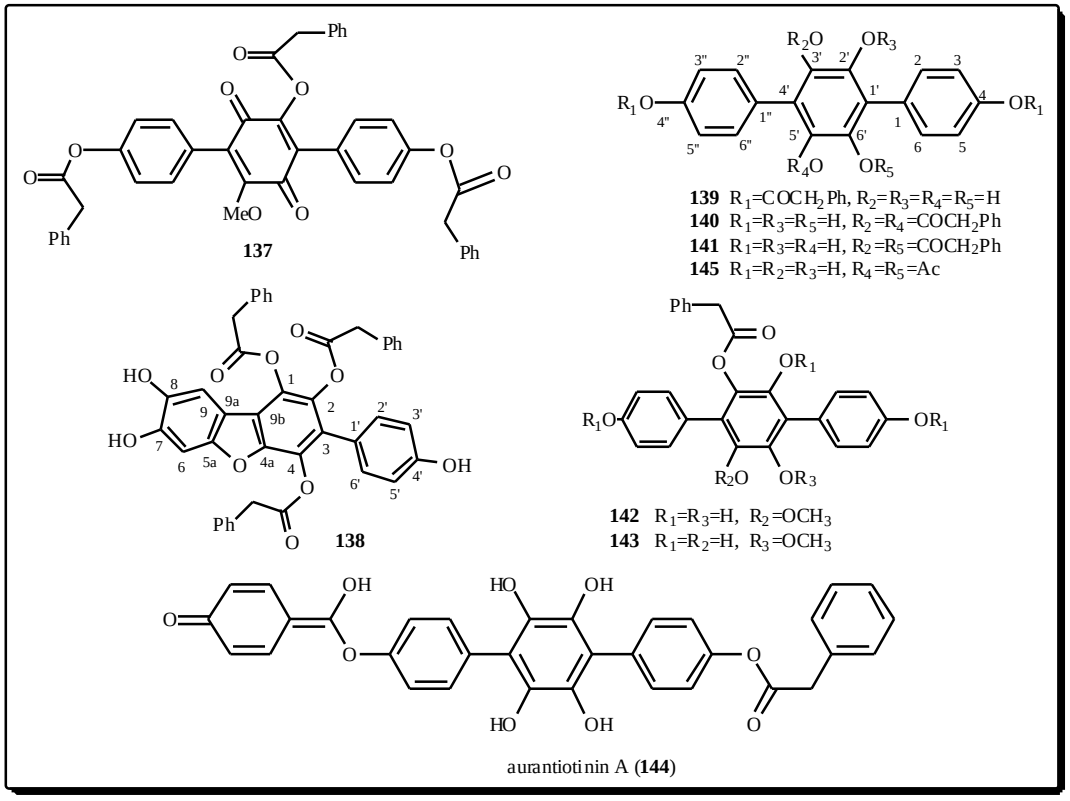
Scheme 3. Synthesis of compounds **128** and **129**.





antibody suppressant [101], anti-insect and antibacterial [102], specific 5-lipoxygenase inhibitory effects [103]. Because of their promising biological activities, they have created much research interest.

Eight unusual novel polyphenylacetoxylated *p*-terphenyl derivatives called ganbajunin A-G (**137**-**143**) and aurantiotinin A (**144**), as well as 2,3-diacetoxy-4′,4″,5,6-tetrahydroxy-*p*-terphenyl (**145**), respectively, were obtained from the fruiting bodies of three edible mushrooms, *Thelephora ganbajun* Mu Zang and *Thelephora aurantiotincta* Corner (Thelephoraceae), and *Boletopsis grisea* (Peck) Bond. & Singer (Polyporaceae), indigenous to China [104,105,106,107].

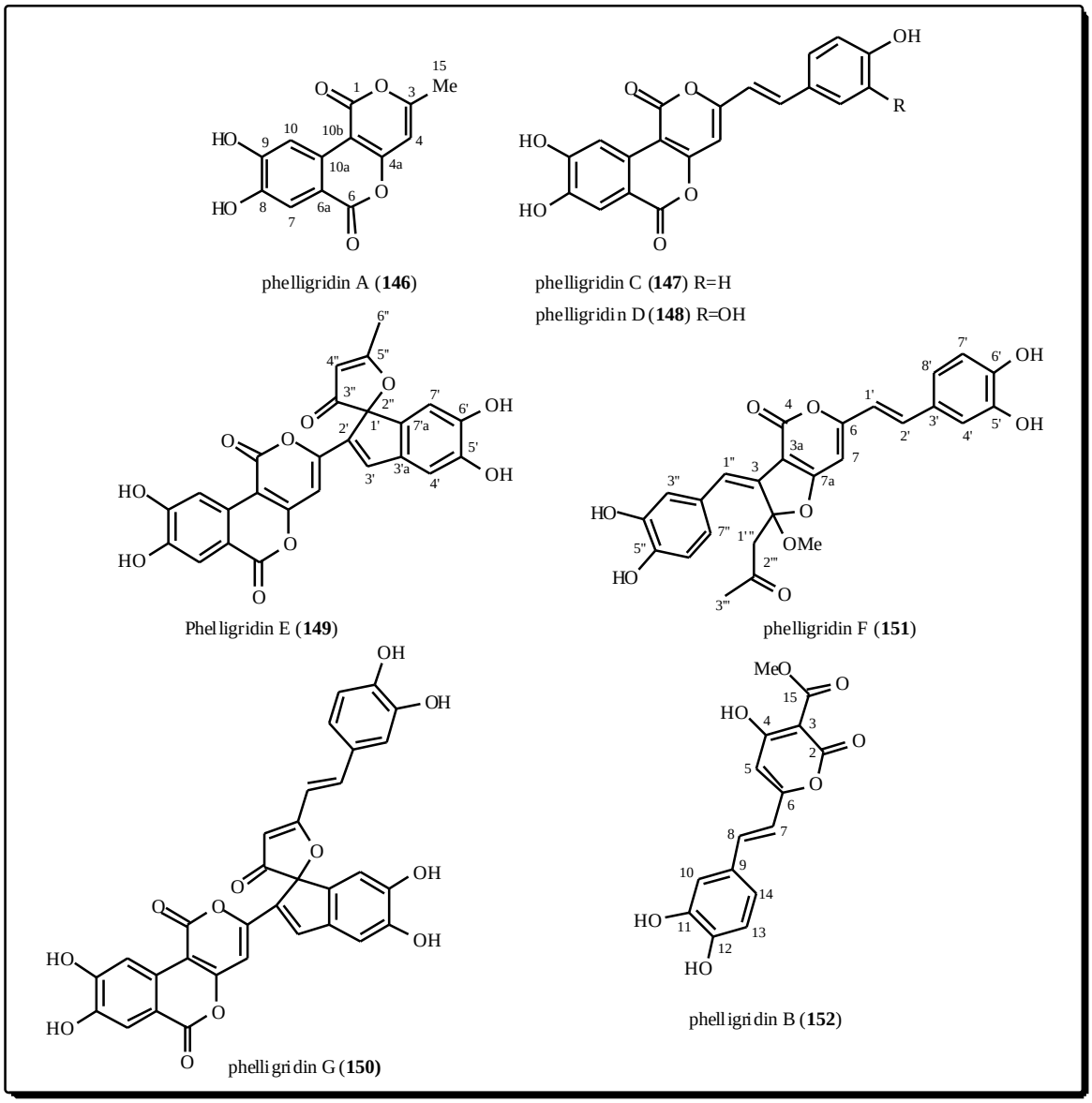


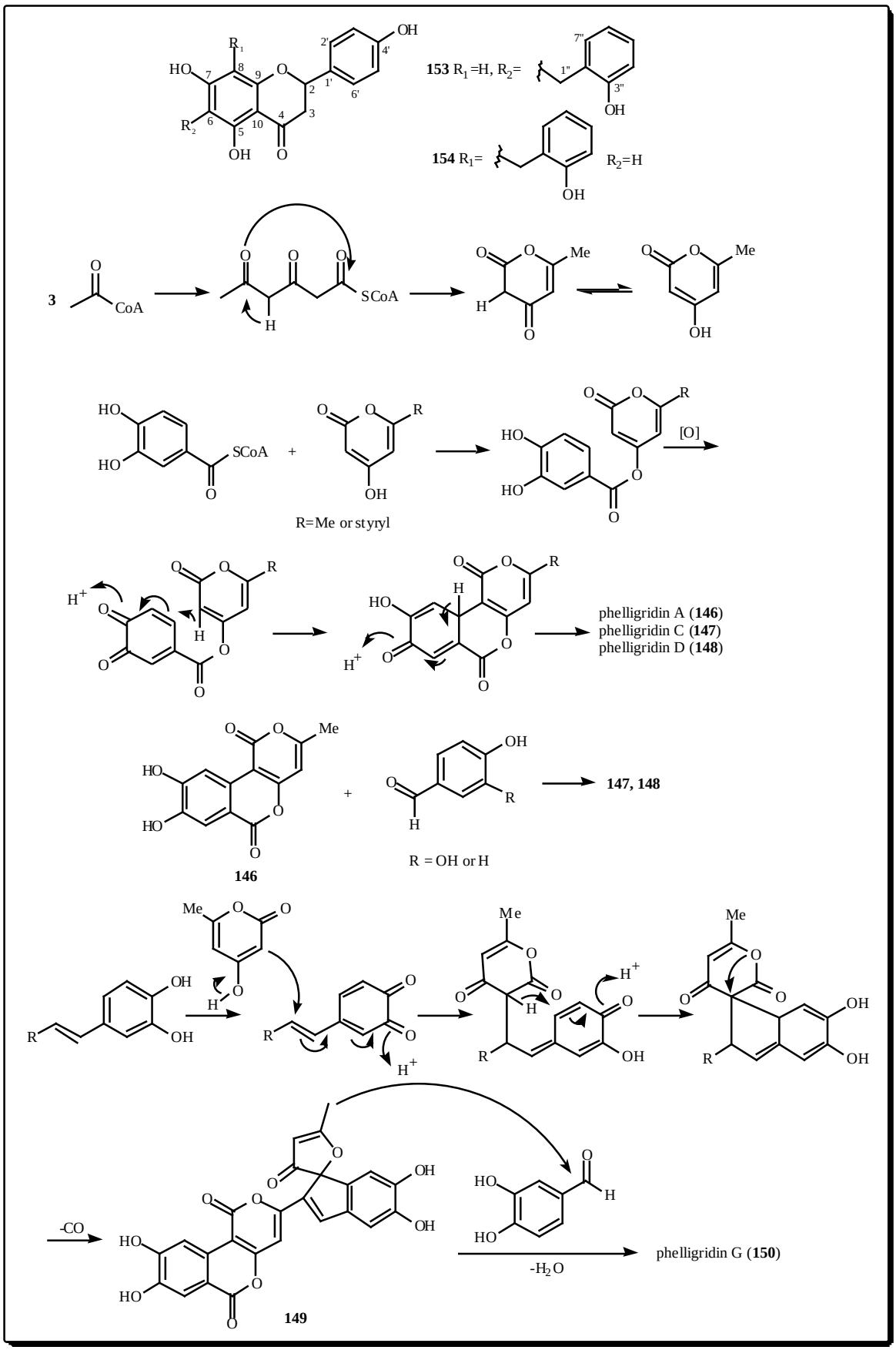
Phenylacetoxylated *p*-terphenyls have not been reported yet in the literature. These *p*-terphenyl derivatives all exhibited certain antioxidant activity in comparison with α-tocopherol used as a positive control in the DPPH (1,1-diphenyl-2-picrylhydrazyl) radical-scavenging test. Only ganbajunin B (**138**) showed more significant radical-scavenging activity than α-tocopherol with EC_{50} values of 0.13 and 0.25 mM, respectively [108,109]. Further studies showed that the presence of OH groups in *para*-positions and the formation of the furan ring might facilitate radical-scavenging activity for *p*-terphenyls.

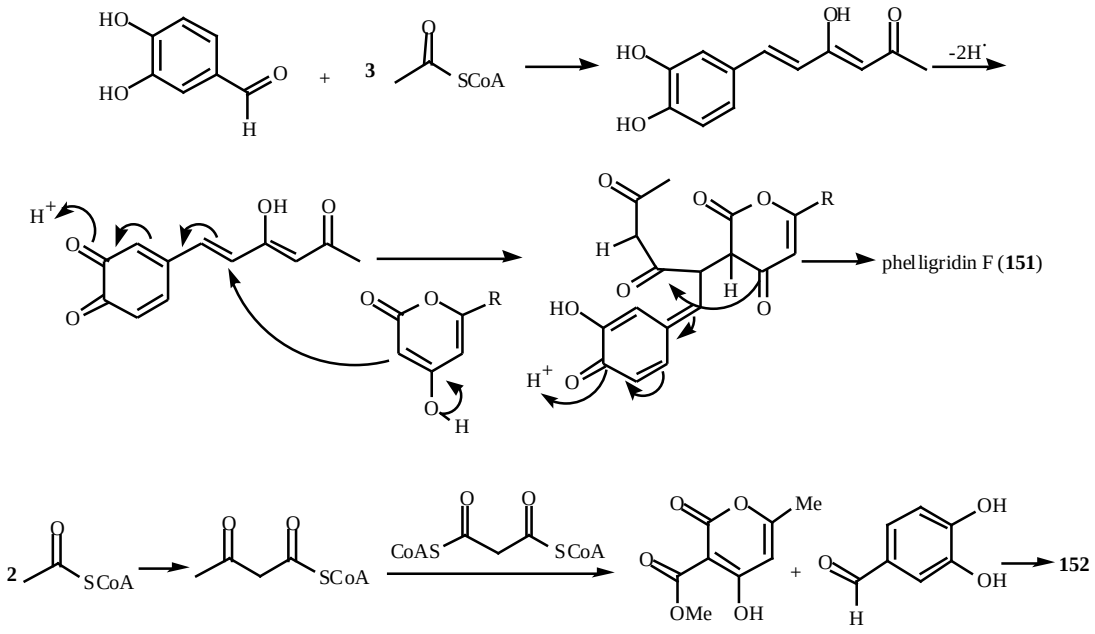
PYRANONES

Very recently, the fruiting body of *Phellinus igniarius* (DC. Ex Fr.) Quél (Polyporaceae), a fungus which is used to treat abdomnalgia and bloody gonorrhea in traditional Chinese medicine, provided five structurally unique pyrano[4,3-*c*][2]benzopyran-1,6-dione derivatives with an unprecedented carbon skeleton, phelligridins A (**146**) [110], C-E (**147-149**) [111] and phelligridin G (**150**) [112], an unusual furo[3,2-*c*]pyran-4-one derivatives phelligridin F (**151**) and a hispidin derivative phelligridin B (**152**) [110]. Both phelligridins C (**147**) and D (**148**) showed *in vitro* selective cytotoxicity against A549 and human liver cancer cell lines (Bel7402) with IC_{50} values of 0.012, 0.016, 0.010, and 0.008 μmol/L, respectively [111]. Phelligridin G (**150**) showed antioxidant activity, inhibiting rat liver microsomal lipid peroxidation with an IC_{50} of 3.86 μmol/L and moderate selective cytotoxic activities against human ovary cancer cell line (A 2780) and human colon cancer cell line (HCT-8) with IC_{50} values of 20.4 and 30.2 μmol/L [112], respectively. Possible biogenetic sequences to the formation of **146-152** are depicted in scheme **4**.

Another two benzylated dihydroflavones named phelligrins A (**153**) and B (**154**) were obtained and characterized from the same mushroom [113].




153 R1=H, R2=
154 R1=
R2=H
3
CoA
SCoA
Me
OH
HO
H
O
[O]
R=Me or styryl
H+
phelligridin A (146)
phelligridin C (147)
phelligridin D (148)
147, 148
146
R = OH or H
-CO
-H2O
phelligridin G (150)
149



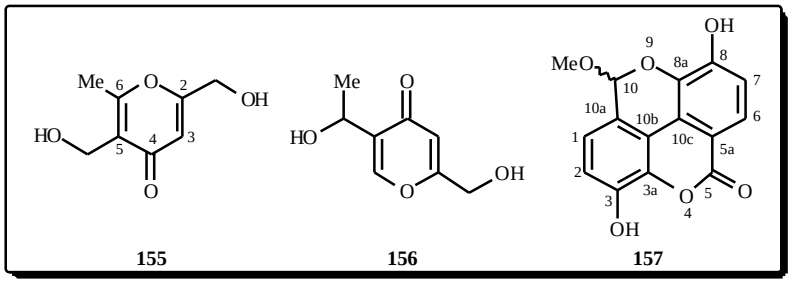
Scheme 4. Possible biogenetic pathway of compounds **146**-**152**.

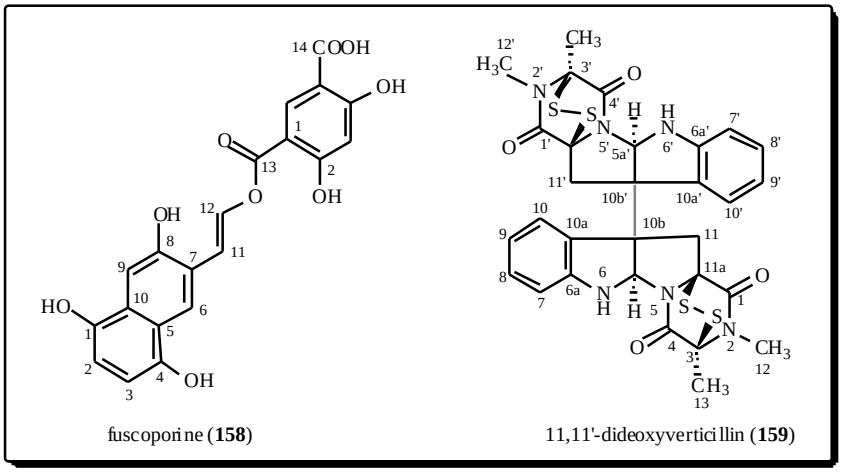
The solid cultures of the medicinal mushroom *Hericium erinaceus* Bull. pers (Hericiaceae) afforded two new γ-pyranone metabolites, herierin III (**155**) and herierin IV (**156**) [114].

Nigricanin (**157**), the first ellagic acid derived derivative from higher fungi, has been isolated from the fruiting bodies of the inedible mushroom *Russula nigricans* (Bull.) Fr. (Russulaceae) [115]. A pigment fuscoporine (**158**) was derived from *Fuscoporia oblique* Fr Te. LáT [116].

DIKETOPIPERAZINE

The fungus *Shiraia bambusicola* P.Henn mentioned above yields a bis-diketopiperazine metabolite, 11,11'-dideoxyverticillin (**159**), which is an analog of verticillin





originally extracted from a marine fungus [117]. It have been demonstrated for the first time that this compound (**159**) has been shown to possess potent anticancer activity both *in vitro* and *in vivo*, and also acts as a structurally novel potent angiogenesis inhibitor. This product inhibits angiogenesis *via* various steps and through interfering with vascular endothelial growth factor signal transduction [118].

CONCLUSIONS

Chinese higher fungi are well known to produce natural metabolites with a remarkable variety of structures. They are accepted as potentially useful sources of novel compounds with biomedical importance. Obviously, most of the compounds discussed here have been tested in biological assays. For some metabolites there are already interesting data on their different biological activities and some have even been determined as inhibitors of enzymes crucial in certain diseases. These findings have displayed a good future for the development and utilization of these fungal resources. All types of secondary metabolites isolated from Chinese macromycetes in relation to genus and family are listed in Table **1**. The known bioactivities of these fungal metabolites are summarised in Table **2**.

Table 1. Secondary metabolites produced by Chinese macromycetes

Compound	Family	Genus
Ganoderic acids A (**1**) and B (**2**)	Ganodermataceae	*Ganoderma*
Ganoderic acids G (**3**) and H (**4**)	Ganodermataceae	*Ganoderma*
20-Hydroxylganoderic acid G (**5**)	Ganodermataceae	*Ganoderma*
12-Deacetylganoderic acid H (**6**)	Ganodermataceae	*Ganoderma*
Ganoderic acid C1 (**7**)	Ganodermataceae	*Ganoderma*
Ganolucidic acid A (**8**)	Ganodermataceae	*Ganoderma*
Lucidenic acid N (**9**)	Ganodermataceae	*Ganoderma*
Methyl lucidenate F (**10**)	Ganodermataceae	*Ganoderma*
Ganoderic aldehyde A (**11**)	Ganodermataceae	*Ganoderma*
Ganoderic acid LM2 (**12**)	Ganodermataceae	*Ganoderma*
Ganoderic acid DM (**13**)	Ganodermataceae	*Ganoderma*
Ganolactone (**14**)	Ganodermataceae	*Ganoderma*
8β,9α-Dihydroganoderic acid J (**15**)	Ganodermataceae	*Ganoderma*
Methyl 8β,9α-dihydroganoderic acid J (**16**)	Ganodermataceae	*Ganoderma*
Ganodermic acid S (**17**)	Ganodermataceae	*Ganoderma*
Lucidumol B (**18**)	Ganodermataceae	*Ganoderma*
Ganodermanondiol (**19**)	Ganodermataceae	*Ganoderma*
Ganodermanontriol (**20**)	Ganodermataceae	*Ganoderma*
Ganoderiol F (**21**)	Ganodermataceae	*Ganoderma*
Lucidumols A (**22**)	Ganodermataceae	*Ganoderma*
Ganosporelactones A-B (**23-24**)	Ganodermataceae	*Ganoderma*
Ganosporeric acid A (**25**)	Ganodermataceae	*Ganoderma*
24ξ-Methyl-5α-lanosta-25-one (**26**)	Ganodermataceae	*Ganoderma*
Tsugaric acids A-C (**27-29**)	Ganodermataceae	*Ganoderma*
Tsugariosides A-C (**30-32**)	Ganodermataceae	*Ganoderma*
3β-Hydroxy-5α-lano-sta-8,24-dien-21-oic acid (**33**)	Ganodermataceae	*Ganoderma*
Fuscoporianols A-C (**34-36**)	Polyporaceae	*Fuscoporia*
Zhankuic acids A-C (**37-39**)	Polyporaceae	*Antrodia*
Antcin K (**40**)	Polyporaceae	*Antrodia*
(24*E*)-3β-Hydroxycucurbita-5,24-dien-26-oic acid (**41**)	Russulaceae	*Russula*
(24*E*)-3,4-S*eco*-cucurbita-4,24-diene- 3,26-dioic acid (**42**)	Russulaceae	*Russula*
(24*E*)-3,4-S*eco*-cucurbita-4,24-diene-3,26,29-trioic acid (**43**)	Russulaceae	*Russula*
Lepidolide (**44**)	Russulaceae	*Russula*
Rosacea acids A-B (**45-46**)	Russulaceae	*Russula*
3-O-β-D-Glucopyranosyl-22*E*,24*R*-5α,8α-epidioxyergosta-6,22-diene (**47**)	Russulaceae Clavicipitaceae	*Lactarius* *Cordyceps*
3-O-β-D-Glucopyranosyl-22*E*,24*R*-5β,8β-epidioxyergosta- 6,22-diene (**48**)	Russulaceae	*Lactarius*
9-Hydroxycerevisterol (**49**)	Russulaceae	*Lactarius*
5α,6α-Epoxy-24(*R*)-methylcholesta-7,22-dien-3β-ol (**50**)	Clavicipitaceae	*Cordyceps*
H1-A (**51**)	Clavicipitaceae	*Cordyceps*
2β, 3α, 9α-Trihydroxy-5α-ergosta-7,22-di- ene (**52**)	Ganodermataceae	*Ganoderma*
6, 9-Epoxyergosta-7,22-dien-3-ol (**53**)	Tricholomataceae	*Mycena*

(Table 1) contd….

Compound	Family	Genus
Tylopiol A (**54**) and Tylopiol B (**55**)	Strobilomycotaceae	*Tylopilus*
(17β,20*R*,22*E*,24*R*)-19-Norergosta-1,3,5,7,9,14,22-heptaene (**56**)	Xylariaceae	*Daldinia*
(17β, 20*R*, 22*E*, 24*R*)-1-Methyl-19-norergosta-1,3, 5,7,9,14,22-heptaene (**57**)	Xylariaceae	*Daldinia*
Resenonolactone (**58**)	Hypocreaceae	*Engleromyces*
Moreloriol (**59**)	Mochellaceae	*Morchella*
Subvellerolactones A (**60**)	Russulaceae	*Lactarius*
Subvellerolactones C (**61**)	Russulaceae	*Lactarius*
2β, α-Epoxy-6*Z*, 9*Z*-humuladien-8α-ol (**62**)	Russulaceae	*Lactarius*
Rulepidadiol (**63**)	Russulaceae	*Russula*
Rulepidatriol (**64**)	Russulaceae	*Russula*
Rulepidol (**65**)	Russulaceae	*Russula*
Lepidamine (**66**)	Russulaceae	*Russula*
7α, 8β, 13-Trihydroxy-5, 13- marasmanolide (**67**)	Russulaceae	*Lactarius*
Isoplorantinone (**68**)	Russulaceae	*Lactarius*
4, 8,14-Trihydroxyilludala-2, 6, 8-triene (**69**)	Russulaceae	*Lactarius*
8-Hydroxy-8,9-secolactara- 1,6- dien-5,13-olide (**70**)	Russulaceae	*Lactarius*
Dictyophorines A (**71**)	Phallaceae	*Dictyophora*
Dictyophorines B (**72**)	Phallaceae	*Dictyophora*
Teucrenone (**73**)	Phallaceae	*Dictyophora*
Gloeosteretriol (**74**)	Meruliaceae	*Gloeostereum*
Armillarilin (**75**)	Tricholomataceae	*Armillaria*
Armillarinin (**76**)	Tricholomataceae	*Armillaria*
Armillarin (**77**)	Tricholomataceae	*Armillaria*
Armillaridin (**78**)	Tricholomataceae	*Armillaria*
Armillarigin (**79**)	Tricholomataceae	*Armillaria*
Armillarikin (**80**)	Tricholomataceae	*Armillaria*
Armillaripin (**81**)	Tricholomataceae	*Armillaria*
Armillaritin (**82**)	Tricholomataceae	*Armillaria*
Armillarivin (**83**)	Tricholomataceae	*Armillaria*
Armillaricin (**84**)	Tricholomataceae	*Armillaria*
Armillaric acid (**85**)	Tricholomataceae	*Armillaria*
Armillasin (**86**)	Tricholomataceae	*Armillaria*
Armillatin (**87**)	Tricholomataceae	*Armillaria*
Albaconol (**88**)	Polyporaceae	*Albatrellus*
Grifolin (**89**)	Polyporaceae	*Albatrellus*
Russulamide (**90**)	Russulaceae	*Russula*
Armillaramide (**91**)	Tricholomataceae	*Armillaria*
Paxillamide (**92**)	Paxillaceae	*Paxillus*
Glycosphingolipid (**93**)	Polyporaceae	*Polyporus*
Termitomycesphins A-F (**94-99**)	Tricholomataceae	*Termitomyces*
Lactariamides A (**100**)	Russulaceae	*Lactarius*
Lactariamides B (**101**)	Russulaceae	*Lactarius*
Cortenuamides A-C (**102-104**)	Cortinariaceae	*Cortinarius*
Ceramide homologs (**105-107**)	Cortinariaceae	*Cortinarius*
(2*S*,3*S*,4*R*,10*E*)-2-[(2*R*)-2-Hydroxyl-tetracosanoylamino]- 10-octadecene-1, 3, 4 (**108**)	Hypocreaceae	*Engleromyces*
Catacerebrosides A-C (**109-111**)	Tricholomataceae	*Catathelasma*
Neoengleromycin (**112**)	Hypocreaceae	*Engleromyces*
9,10,11-Trihydroxy-(12Z)-12-octadecenoic acid (**113**)	Tuberaceae	*Tuber*
Shiraiachromes A-C (**114-116**)	Hypocreaceae	*Shiraia*
Hypocrellins A-C (**117-119**)	Hypocreaceae	*Hypocrella*
Hypomycin A-B (**120-121**)	Hypocreaceae	*Hypomyces*
Elsinochrome A (**122**)	Hypocreaceae	*Hypomyces*
N^6-[β- (Acetylcarbamoyloxy) ethyl] adenosine (**123**)	Clavicipitaceae	*Cordyceps*

(Table 1) contd….

Compound	Family	Genus
Cordycepeptide A (**124**)	Clavicipitaceae	*Cordyceps*
AMG-1 (**125**)	Tricholomataceae	*Armillaria*
Ganoderpurine (**126**)	Ganodermataceae	*Ganoderma*
3-Aldehyde-2-amino-6-methoxypyridine (**127**)	Cortinariaceae	*Cortinarius*
Ganoines (**128-129**)	Ganodermataceae	*Ganoderma*
Succinic and maleic acid derivatives (**130-134**)	Polyporaceae	*Antrodia*
Lactariolide (**135**)	Russulaceae	*Lactarius*
Tremellin (**136**)	Tremellaceae	*Tremella*
Ganbajunin A-G (**137-143**)	Thelephoraceae	*Thelephora*
Aurantiotinin A (**144**)	Thelephoraceae	*Thelephora*
2,3-Diacetoxy-4′,4″,5,6-tetrahydroxy-*p*-terphenyl (**145**)	Polyporaceae	*Boletopsis*
Phelligridin A (**146**)	Polyporaceae	*Phellinus*
Phelligridins C-E (**147-149**)	Polyporaceae	*Phellinus*
Phelligridins G (**150**) and F (**151**)	Polyporaceae	*Phellinus*
Phelligridin B (**152**)	Polyporaceae	*Phellinus*
Phelligrins A-B (**153-154**)	Polyporaceae	*Phellinus*
Herierins III-IV (**155-156**)	Hericiaceae	*Hericium*
Nigricanin (**157**)	Russulaceae	*Russula*
Fuscoporine (**158**)	Polyporaceae	*Fuscoporia*
11,11'-Dideoxyverticillin (**159**)	Hypocreaceae	*Shiraia*

Table 2. Bioactivities of secondary metabolites produced by Chinese macromycetes

Compound	Bioactivity	Ref
Ganoderic acid A (**1**)	antinociceptive	[9]
Ganoderic acid B (**2**)	antinociceptive	[9]
Ganoderic acid G (**3**)	antinociceptive	[9]
Ganoderic acid H (**4**)	antinociceptive	[9]
Ganolucidic acid A (**8**)	anti-HIV-1 protease	[11]
Lucidenic acid N (**9**)	cytotoxicity	[13]
Ganoderic aldehyde A (**11**)	cytotoxicity	[16]
Ganoderic acid LM2 (**12**)	mice splenocytes proliferation	[15]
Ganodermic acid S (**17**)	inhibition of platelet response to thromboxane A_2	
Lucidumol B (**18**)	anti-HIV-1 protease cytotoxicity	[11] [12]
Ganodermanondiol (**19**)	anti-HIV-1 protease anti-complement cytotoxicity	[11] [21] [12] [5]
Ganodermanontriol (**20**)	anti-HIV-1 protease anti-HIV-1 anti-complement cytotoxicity	[11] [20] [21] [12]
Ganoderiol F (**21**)	anti-HIV-1 anti-complement cytotoxicity	[20] [21] [12]
Lucidumols A (**22**)	cytotoxicity	[12] [5]
Tsugaric acid A (**27**)	cytotoxicity	[27]
Tsugarioside A (**30**)	cell death by apoptosis cytotoxicity	[27]
Tsugarioside B (**31**) Tsugarioside C (**32**)	cytotoxicity	[26]
3β-Hydroxy-5α-lanosta-8,24-dien-21-oic acid (**33**)	cytotoxicity	[27][26]
Zhankuic acids A (**37**)	cytotoxicity Immunomodulatory anti-inflammatory	[29] [30] [31]
Zhankuic acids B (**38**)	anticholinergic, antiserotonergic immunomodulatory anti-inflammatory	[29] [30] [31]

(Table 2) contd….

Compound	Bioactivity	Ref
Zhankuic acids C (**39**)	cytotoxicity Immunomodulatory anti-inflammatory	[29] [30] [31]
Antcin K (**40**)	anti-inflammatory	[31]
(24*E*)-3β-Hydroxycucurbita-5,24- dien-26-oic acid (**41**)	antifungal	[34]
(24*E*)-3,4-*Seco*-cucurbita-4,24-diene- 3,26-dioic acid (**42**)	farnesyl transferase inhibitory	[35]
3-O-β-D-Glucopyranosyl-22*E*,24*R*-5α,8α-epidioxyergosta-6,22-diene (**47**)	antitumor	[40]
9-Hydroxycerevisterol (**49**)	Cytotoxicity antinociceptive	[38] [39]
5α,6α-Epoxy-24(*R*)-methylcholesta-7,22- dien-3β-ol (**50**)	antitumor	[40]
H1-A (**51**)	anti-Berger's disease	[41]
2β, 3α, 9α-Trihydroxy-5α-ergosta-7,22-di-ene (**52**)	cell cycle inhibition	[27]
Subvellerolactones A (**60**)	cytotoxicity	[51]
Subvellerolactones C (**61**)	cytotoxicity	[51]
Dictyophorines A (**71**)	promoted nerve growth factor synthesis	[55]
Dictyophorines B (**72**)	promoted nerve growth factor synthesis	[55]
Gloeosteretriol (**74**)	antibiotic	[56]
Armillaric acid (**85**)	antibiotic	[63]
Albaconol (**88**)	human vanilloid receptor 1 antagonist antitumor	[66] [67]
Grifolin (**89**)	human vanilloid receptor 1 antagonist	
Russulamide (**90**)	antinociceptive phospholipase A_2 inhibitory	[39]
Termitomycesphins A (**94**)	neuritogenic	[76]
Termitomycesphins B (**95**)	neuritogenic	[76]
Termitomycesphins C (**96**)	neuritogenic	[76]
Termitomycesphins D (**97**)	neuritogenic	[76]
Termitomycesphins E (**98**)	neuritogenic	[77]
Termitomycesphins F (**99**)	neuritogenic	[77]
Lactariamides B (**101**)	antinociceptive	[39]
Shiraiachromes A (**114**)	antiangiogenesis	[86]
Hypocrellins A (**117**)	photodynamic photosensitive nematicidal	[87] [90]
Hypocrellins B (**118**)	photodynamic	[87]
Hypocrellins C (**119**)	photodynamic	[87]
Elsinochrome A (**122**)	photosensitive nematicidal	[90]
AMG-1 (**125**)	cerebral protecting	[92]
Maleimide derivatives (**130**) and (**131**)	cytotoxicity	[97]
Ganbajunin B (**138**)	antioxidant	[109]
Phelligridins C (**147**)	selective cytotoxicity	[111]
Phelligridins B (**148**)	selective cytotoxicity	[111]
Phelligridins G (**150**)	selective cytotoxicity antioxidant	[112]
11,11'-Dideoxyverticillin (**159**)	Anticancer antiangiogenesis	[118]

The formation of the different types of secondary metabolites, such as sesquiterpenes, lanostanes, and their different oxidation products is used in the chemotaxonomic classification of some taxa of the Basidiomycotina [119] [120] and the sections of the genera *Lactarius and Ganoderma*. Additionally, perylenequinones and *p*-terphenyls might be of use as chemotaxonomic markers for the genera *Hypocrella* and *Thelephora*, respectively.

Although some traditionally used mushrooms have been chemically and biologically investigated to some extent, the constituents of many others, however, are nearly unknown. It is a challenging task therefore to expand the chemical and pharmaceutical exploration on medically used, but chemically unexplored fungi. The large and well-preserved natural resources of China, with a rich diversity of the higher fungi, provides a good base for more extensive research on the isolation and biological evaluation of natural products from higher mushrooms.

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