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REVIEW ARTICLE

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Abstract

Plants interact with fungi in their natural growing environments, and relationships between plants and diverse fungal species impact plants in complex symbiotic, parasitic, and pathogenic ways. Over the past 10 years, we have intensively investigated plant growth regulators produced by mushrooms, and we succeeded in finding various regulators from mushroom-forming fungi: (1) fairy chemicals as a candidate family of new plant hormones from *Lepista sordida*, (2) agrocybynes A to E from fungus *Agrocybe praecox* that stimulate strawberry growth, (3) armillariols A to C and sesquiterpene aryl esters from genus *Armillaria* that are allelopathic and cause Arimillaria root disease, and (4) other plant growth regulators from other mushrooms, such as *Stropharia rugosoannulata*, *Tricholoma flavovirens*, *Hericium erinaceus*, *Leccinum extremiorientale*, *Russula vinosa*, *Pholiota lubrica* and *Cortinarius caperatus*.

Introduction

The fruiting body of basidiomycetes and ascomycetes is known as a “mushroom”. It produces spores, and the spores germinate and create mycelium. The mycelium eventually produces a primordium, which grows into a new whole mushroom, and the life cycle continues. Together with their long history as a food source, mushrooms are also important for their healing capacities and properties in traditional medicine. Additionally, the 14,000 species of mushrooms in the world serve as important sources of bioactive compounds. In order to develop new functional compounds from mushrooms, we have been screening various mushrooms for plant growth regulatory activity.

Interactions between plants and fungi are diverse and multileveled. Fungi can stimulate plant growth in various ways, including by increasing tolerance to abiotic stress or by suppressing plant diseases [1]. Plant growth regulators also serve as research tools for clarifying the mechanisms of plant growth. Thus, we are interested in secondary metabolites from mushrooms that have activity as plant growth regulators, and we have reported the isolation of various compounds that regulate the growth of bentgrass, lettuce, and/or rice.

Fairy chemicals from *Lepista sordida*

The natural phenomenon of “fairy rings”, or zones of stimulated grass growth, is due to the interaction between a fungus and a plant [2–5]. In the first scientific article on fairy rings in 1675 and in subsequent studies reviewed in *Nature* in 1884, this phenomenon was attributed to an unknown “fairy” [6]. In 2010, we discovered two plant growth regulating compounds related to the formation of fairy rings, 2-azahypoxanthine (AHX, **1**) and imidazole-4-carboxamide (ICA, **2**) from the culture broth of *Lepista sordida* [7, 8]. We additionally isolated a metabolite of AHX, which is common in plants, 2-aza-8-oxohypoxanthine (AOH, **3**) [9] (Fig. 1). We name these three compounds “fairy chemicals” (FCs) based on an article by the same title in *Nature* [10]. FCs exhibited growth regulatory activity against all of the plants tested regardless of the families they belong to, and conferred tolerance to various and continuous stresses (low or high temperature, salt, drought stress, etc.) on the plants [7–9]. For example, when bentgrass (*Agrostis palustris* Huds.) and rice (*Oryza sativa* L.) were cultivated with AHX or AOH solution, shoot and root elongation of the seedlings was accelerated [7, 9]. AHX treatment of rice recovered its germination rate under low-temperature stress (15°C) and shoot growth under salt stress (0.1 M NaCl). Additionally, rice seedlings developed tolerance to high-temperature stress (35°C) after AHX treatment. Furthermore, yields of rice, wheat (*Triticum aestivum* L.), and other crops were increased by treatment with each of the FCs in greenhouse and/or field experiments. In greenhouse experiments, when rice and potato (*Solanum tuberosum* L.) were cultivated with 5 or 50 μM AHX, the yield per plant increased by 25% (rice), 19.3% (potato, total yield), or 40.6% (potato, esculent size) [7]. When rice was cultivated with 2 μM ICA, grain yield per plant also increased by 25% [8]. In field experiments, treatment with FCs drastically increased grain yields up to 20.4% and 9.6% (AHX), 10.6% and 10.2% (AOH), and 9.8% and 6.3% (ICA) for wheat and rice, respectively [11, 12]. These results suggest the possible application of FCs in agriculture. We have also reported the presence of endogenous FCs in plants and mushrooms, as well as the discovery of a new route in the purine metabolic pathway through which FCs are biosynthesized [9, 13]. In addition, we discovered three *N*-glucosides of AOH (**4**–**6**), an *N*-glucoside of AHX (**7**), and two ribosides (**8**, **9**) and a ribotide (**10**) of ICA, as FC metabolites in rice [14, 15]. Compounds **4**–**7** exhibited no significant activity against rice, indicating that rice regulates the activity of AHX (**1**) and AOH (**3**) by converting them into their constituent glucosides. On the other hand, compounds **8** and **9** showed inhibition activity against the shoots of rice only at high concentration (0.1 mM) and showed no significant effect on roots. Cytokinins are interconvertible to their constituent ribosides and ribotides, and those glycosides are the inactive forms of the corresponding free base forms [16–18]. The free base forms are usually more active than the corresponding ribosides and ribotides in various bioassays, which may be related to their rapid uptake and high intrinsic activity [19–21]. The inhibitory activity of **8** and **9** might be due to ICA (**2**), which was converted from **8** and **9** in rice. Many enzymes involved in cytokinin biosynthesis, interconversion, inactivation, and degradation have been identified and play very important roles in the regulation of endogenous cytokinin homeostasis. These findings suggest that the interconversion among ICA (**2**), **8** and **9** regulates homeostasis of ICA (**2**) in rice. All of these findings allow us to conclude that FCs are a new family of plant hormones [22–25], and our group is currently conducting research to put FCs into practical use in agriculture. We also isolated three diketopiperazines (**11** to **13**) from the culture broth of *L. sordida* (Fig. 1) and showed that these compounds inhibited the root growth of bentgrass at 0.1 and 1 μmol/paper [26]. In our previous report, we showed that ICA (**2**) strongly inhibited the growth of bentgrass shoot and root [8], which corroborates the finding that grass is occasionally killed or damaged in fairy rings [2]. In addition to ICA (**2**), these diketopiperazines (**11** to **13**) might contribute to growth inhibition by the fungus in the rings.

Plant growth regulators from the fungus *Agrocybe praecox* that stimulate strawberry growth

In 2007, abnormal enlargement of strawberries was observed along with a kind of mushroom growing near the stimulated fruit in a greenhouse in Niigata Prefecture, Japan. The mushroom was identified as *Agrocybe praecox* (English name, Spring Fieldcap; Japanese name, Fumizukitake), which is edible and widespread in the northern temperate zone throughout the world. An earlier report provided evidence of *Agrocybe* species causing stunt syndrome of strawberries [27]. These widely varying phenomena related to growth stimulation and suppression suggest that *Agrocybe* genus produces plant growth regulator(s). *A. praecox* is a litter degrading fungus that is able to grow in forest soil and produces non-specific extracellular enzymes, which depolymerize soil detritus, including cellulose, hemicellulose, and sulfur-containing compounds, to monomers and oligomers, which then become available to microbes and plants [28]. The fungus has been in focus for various application according to the hydrolytic and ligninolytic enzymatic activities for bioremediation, however it has not yet been reported as environmental adaptation by coexisting with plant [29–36]. Thus, we focused on plant growth regulators from the fungus *A. praecox.*

In our study to isolate the active compounds, the culture broth of *A. praecox* was partitioned between EtOAc and water, followed by *n*-BuOH and water. The EtOAc-soluble part was fractionated by repeated chromatography. We discovered five novel compounds (**14** to **16**, **18**, **19**) and two known ones (**17**, **20**) based on observation of the growth-regulating activity on lettuce [37] (Fig. 2). Compounds **14** to **18** were named agrocybynes A to E and have triple bonds. Compound **19** was a new compound and determined to be 2-formyl-3,5-dihydroxybenzyl acetate. The effects of the compounds on plant growth were tested for three kinds of plants belonging to different families: lettuce (*Asteraceae*), rice (*Poaceae*), and strawberry (*Rosaceae*). As a result, agrocybynes A–D (**14** to **17**) inhibited hypocotyl growth, and agrocybynes A, C, and D (**14**, **16**, and **17**) inhibited root growth of lettuce at 1 μmol. Agrocybynes A and C (**14** and **16**) inhibited root growth of rice at 0.1 and 1 μM, respectively. Agrocybynes A to E (**14** to **17**) produced strawberries that were dwarfed and had altered color at 1 nmol/soil-mL.

Plant/mycelial growth regulators from the genus *Armillaria* that cause Arimillaria root disease

Genus *Armillaria* (English name, Honey fungus; Japanese name, Naratake) belonging to family Physalacriaseae is a well-known group of edible mushrooms found throughout the world. The mushrooms belonging to *Armillaria* spp. display a wide array of biological activities, including anticancer [38, 39], anti-inflammatory [40–42], and antioxidant properties [43], and they have been used in traditional Chinese medicine to treat hypertension, insomnia, and dizziness [44, 45]. Additionally, members of this genus have been known to be serious plant pathogens that cause root rot in various plant species, which is called Arimillaria root disease [46–48]. Root rot is one of the most serious diseases of plants and occurs in many broadleaf trees and conifers and several herbaceous plants [49]. Furthermore, it is known that penetration of *Armillaria* mycelia to the fungi

Entoloma abortivum and *Wynnea americana* induces spherical deformity of the fruiting bodies of those mushrooms [50]. These observations indicate that *Armillaria* produces allelopathic substance(s). Protoilludane sesquiterpene aryl esters have been isolated from *Armillaria* mushrooms and *Clitocybe illudens* [51–58]. However, there is no evidence that the compounds are the principle toxic factors for Armillaria root disease, and the inducers of deformity in other fungi. Therefore, we sought to isolate compounds with plant and mycelial growth regulatory activity from the culture broth of strains of the genus.

Isolation of the active compounds was guided by plant growth regulatory activity on lettuce. The active fractions, the hexane and EtOAc soluble parts were subjected to repeated chromatography respectively to afford armillariols A to C (**21** to **23**), and nine sesquiterpene aryl esters (**24** to **32**) from the culture broth of *Armilaria* sp. (Fig.3) [59, 60]. (+)- and (–)-Armillariol C (**23**) and their analogues were synthesized on a gram scale using Suzuki-Miyaura cross-coupling and Sharpless asymmetric dihydroxylation by Watkins's group [61]. Compounds **24** and **25** were new compounds, which were named 10-dehydroxymelleolide (**24**) and 13-hydroxymelleolide K (**25**). Compounds **26** to **32** were identified as 5'-*O*-methylmelledonal (**26**), melleolide D (**27**), 13-hydroxydihydromelleolide (**28**), melleolide (**29**), armillarinin (**30**), armillaridin (**31**), and armillarikin (**32**). These known compounds had been isolated from the same genus *Armillaria* as antimicrobial compounds [52–55, 62–64]. The plant growth regulatory activity of the isolated compounds was measured using lettuce, and all compounds (**21** to **32**) showed statistically significant inhibition of growth of lettuce at 1 μmol/paper, indicating that the protoilludane skeleton itself was important for growth inhibition activity against lettuce. In addition, compounds **24** to **32** were subjected to the mycelial growth assay against *Coprinopsis cinerea* (English name, Gray shag; Japanese name, Ushigusotake) and *Flammulina velutipes* (English name, Enoki; Japanese name, Enokitake). Melleolide (**29**) inhibited the mycelial growth of *C. cinerea* and *F. velutipes*, and armillarikin (**32**) inhibited the mycelial growth of *C. cinerea*, each producing a radially shaped clear zone. The activity of melleolide (**29**) was stronger than positive control amphotericin B. The formyl group at C-1 and the absence of a hydroxy at C-13 in the molecule were important for the antifungal activities.

Plant growth regulators in other mushrooms

The edible and cultivated mushroom *Stropharia rugosoannulata* (Saketsubatake in Japanese, and wine-cap stropharia in English) belongs to family Strophariaceae and is widespread in northern temperate zones throughout the world. We reported the isolation of three steroids (**33** to **35**) from the fruiting bodies of *S. rugosoannulata* (Fig. 4). Examination of the effects of compounds **33** to **35** on lettuce growth showed that compounds **34** and **35** showed statistically significant inhibition of hypocotyl growth of lettuce at 1, 10, 100, 1000 nmol/paper and promoted root growth at 1, 10, 100 nmol/paper with statistically significant differences. Compound **33** exhibited no activity. Comparison of the structures of compounds **33** to **35** indicated that the double bond between C-8 and C-9 or C-8 and C-14 in the sterol skeleton is the key structural component for regulating lettuce growth [65].

Since ancient times, *Tricholoma flavovirens* (English name, Yellow knight; Japanese name, Kishimeji) belonging to the family Tricholomataceae has been known throughout the world as an edible mushroom. Two novel indole derivatives (**36**, **38**) and three known compounds (**37**, **39**, **40**) were isolated from the fruiting bodies (Fig. 4). Compound **36** showed the promotion effect on the growth of root of lettuce at 10 nmol/paper with significant differences, and compound **37** showed a similar tendency to promote growth. Compounds **38** and **39** promoted root growth of lettuce and inhibited hypocotyl growth at 1 μmol/paper. Compound **40** inhibited hypocotyl and root growth in a dose-dependent manner. In a comparison of **38** and **39**, **39** showed stronger promotion activity than **38**, suggesting that the methoxy group at C-7 weakened the activity [66, 67].

Hericium erinaceus is an edible and medicinal mushroom belonging to family Hericiaceae. It is called Yamabushitake in Japanese, Houtougu (monkey head) in Chinese, and Lion's mane in English after its shape. In the past 30 years, we have isolated phenols (hericenones A and B), a series of benzyl alcohol derivatives (hericenones C to H, 3-hydroxyhericenone F), and other hericenone analogues (hericenones I and J) from fruiting bodies [68–72]. Chlorinated orcinol derivatives and a series of diterpenoid derivatives (erinacines A to K) have been isolated from mycelia of the fungus [73–79]. Hericenones C to H and erinacines A to I significantly induced the synthesis of nerve growth factor (NGF) *in vitro* and/or *in vivo*. Erinacine K showed anti-MRSA activity. 3-Hydroxyhericenone F showed protective activity against endoplasmic reticulum (ER) stress-dependent cell death [80, 81]. Several ER stress-suppressive compounds were also isolated from scrap cultivation beds of this mushroom [82]. Erinapyrones A and B have been isolated from the culture broth of the fungus [83], and they were shown to have cytotoxicity toward HeLa cells.

In our continuing search for bioactive compounds from culture broth, we identified nineteen compounds (**41**–**59**) that are plant growth regulators (Fig. 4). Novel compounds **41**–**45** were named erinaceolactone A (**41**), B (**42**), erinachromane A (**43**), B (**44**), and erinaphenol A (**45**). While compounds **48**, **49**, and **58** had been synthesized, this is the first report of them as natural products [84, 85]. In the bioassay examining plant growth regulatory activity, all of the compounds suppressed the growth of lettuce.

The edible mushroom *Leccinum extremiorientale* (Japanese name, Akayamadori) belongs to genus *Leccinum* in family Boletaceae, and it can be found from summer to autumn. The mushroom has a red brown areolate cap and has a distribution mainly in the northern temperate zone. In our previous research on bioactive compounds from the mushroom, two sterols showed the ability to suppress formation of osteoclasts, and leccinine A showed protective activity against ER stress-dependent cell death [86, 87]. In order to find plant growth regulatory compounds from the mushroom, we obtained two compounds (**60**, **61**) (Fig. 4). Compound **60** dose-dependently promoted root growth at levels as low as 100 nmol/paper and inhibited hypocotyl growth at 1 μmol/paper. Compound **61** inhibited root and hypocotyl growth of lettuce [88].

Russula vinosa is an edible wild mushroom with high medicinal value. Extracts of *R. vinosa* have an inhibitive effect on bacteria, yeasts and molds. Our group reported that five compounds (**62** to **66**) that were isolated from the fruiting bodies regulated the growth of plants (Fig. 4). Compound **65** weakly inhibited the root and hypocotyl growth of lettuce at 1 μmol/paper, while compound **64** showed an inhibition at as low as 100 nmol/paper. As for the root growth of lettuce, compound **63** showed promotion at 10 and 100 nmol/paper but showed inhibition at 1 nmol/paper and 1 μmol/paper. As for hypocotyl growth of lettuce, compound **62** showed inhibition at 10 and 100 nmol/paper and promotion at 1 nmol/paper, and compound **63** showed promotion at 100 nmol/paper, while compound **66** showed promotion at lower doses (1 and 10 nmol/paper) [89].

Pholiota lubrica (Japanese name, Chanametsumutake) belongs to genus *Pholiota* of family Strophatiaceae and has a widespread distribution, especially in temperate regions, and it frequently grows on wood or at the base of trees. This mushroom exhibited an allelopathic activity against lettuce. Recently, a new cinnamamide (**67**) and four compounds (**68** to **71**) were isolated from the fruiting bodies (Fig. 4). Compound **71** was first isolated from natural sources. All the compounds were subjected to plant regulatory assays against lettuce. Toward the hypocotyl, compounds **67**, **70**, and **71** showed significant inhibition of growth at 0.1 and 1 μmol/paper, while the other compounds had no activity. For the root, we observed growth inhibitory activity of **67** at 1 μmol/paper and **70** at 0.1 and 1 μmol/paper. Compounds **68** and **69** exhibited promotion activity at 0.1 and 1 μmol/paper, respectively, and (22*E*,24*S*)-5α,8α-epodioxy-24-methyl-cholesta-6,9,(11)22-trien-3β-ol] that was also isolated from this mushroom showed no activity. This finding indicates that the carbonyl group at C-7 of **68** and **69** plays an important role in plant growth promotion activity. Cinnamamide and its derivative, betaine cinnamamide, have been reported to promote and stimulate the length of the root and shoot of wheat [90]. In order to investigate the structure activity relationship of **67**, commercially available compounds, cinnamamide and cinnamic acid, were used in the lettuce growth regulatory assay. These results showed that compound **67** and cinnamic acid inhibited growth of the hypocotyl at 0.01, 0.1, and 1 μmol/paper. Meanwhile, cinnamamide inhibited growth at all concentrations. As for the root, compound **67** inhibited growth at 1 μmol/paper, while cinnamamide and cinnamic acid showed inhibition activity at 0.1 and 1 μmol/paper. These results suggest that the cinnamoyl moiety in tested compounds was essential for plant growth inhibition activity [91].

Cortinarius caperatus (English name, Gypsy mushroom; Japanese name, Shogenji) is an edible mushroom and grows widely in the temperate zone of the northern hemisphere. This species has been reported to produce an antiviral compound, RC-183, toward herpes simplex virus. We isolated four compounds (**72** to **75**) from the fruiting bodies (Fig. 4). For growth regulatory activities toward rice seedlings, compounds **72** and **75** promoted growth of the root at 1 mM. Compound **73** promoted root growth at 100 μM, but inhibited root and shoot growth at 1 mM. Compound **75** showed the strongest promoting activity against the root among compounds tested. For the shoot, compound **74** inhibited growth of the shoot at 1 mM. In the lettuce growth experiment, compounds **74** and **75** inhibited growth of the root at 1 μmol/paper. For the hypocotyl, compounds **73** and **74** showed inhibition at 1 and 1000 nmol/paper, respectively. Compounds **74** and **75** promoted the plant at 10 and 100 nmol/paper, respectively [92].

Conclusion

Mushrooms remain a largely unexplored biological resource. Plant growth regulators from mushrooms play important roles in the development of fungus-plant interactions, and/or the life cycle of mushrooms themselves. Our study findings provide useful information not only for understanding those roles but also regarding utilization of these compounds in agriculture and other fields.

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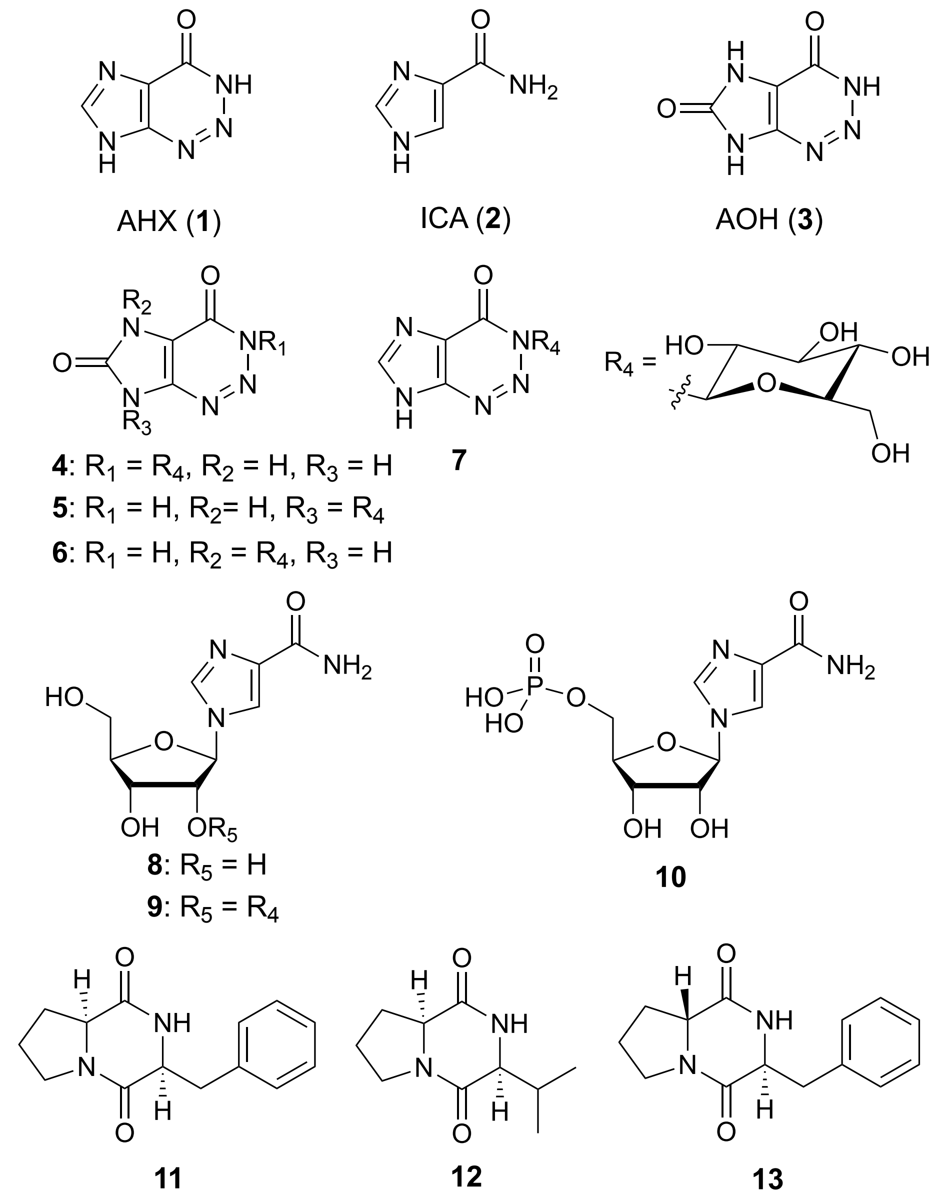
Titles and legends to figures

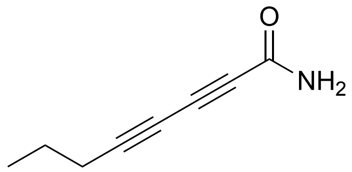
Fig. 1 Fairy chemicals (**1** to **10**) and diketopiperazines (**11** to **13**) isolated from *Lepista sordida*.

Fig. 2 Agrocybynes A to E (**14** to **18**) and two compounds (**19**, **20**) isolated from *Agrocybe praecox*.

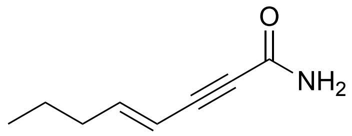
Fig. 3 Plant growth regulators isolated from *Armilaria* sp.

Fig. 4 Plant growth regulators from various mushrooms.


AHX (1)
ICA (2)
AOH (3)
4: R1 = R4, R2 = H, R3 = H
5: R1 = H, R2= H, R3 = R4
6: R1 = H, R2 = R4, R3 = H
7
8: R5 = H
9: R5 = R4
10
11
12
13



agrocybyne A (**14**)



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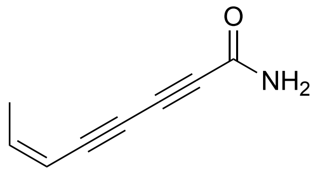
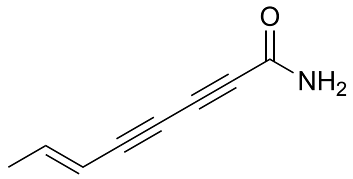


agrocybyne C (**16**)



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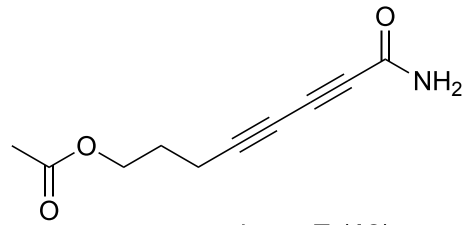
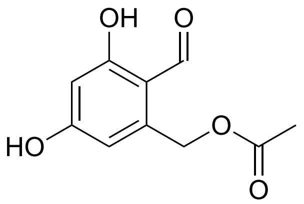


agrocybyne E (**18**)



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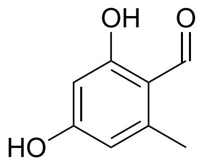

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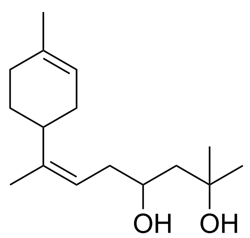
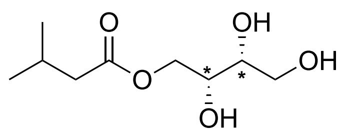


armillariol A (**21**)



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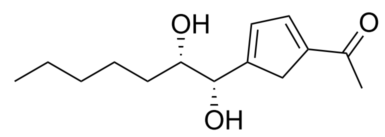

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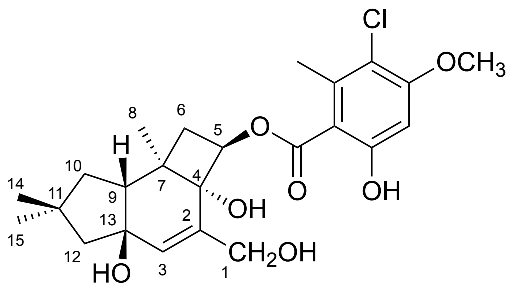
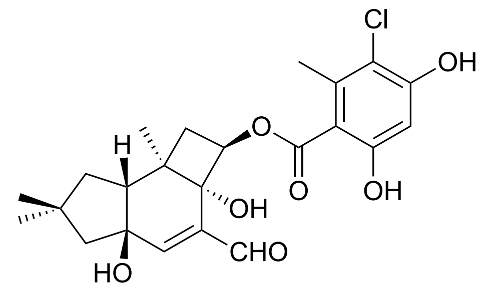
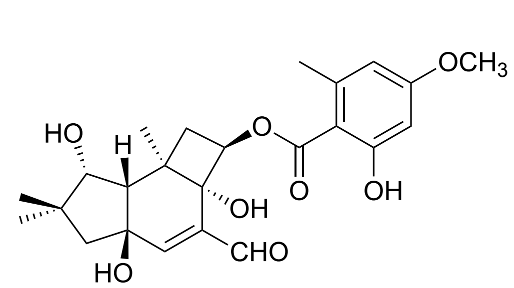


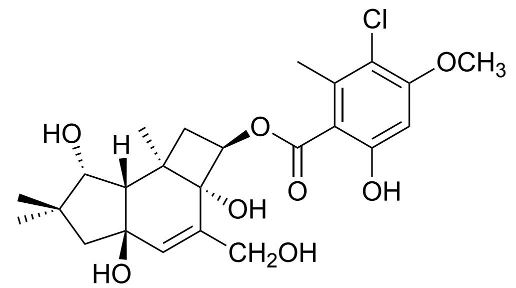
10-dehydroxymelleolide (**24**)



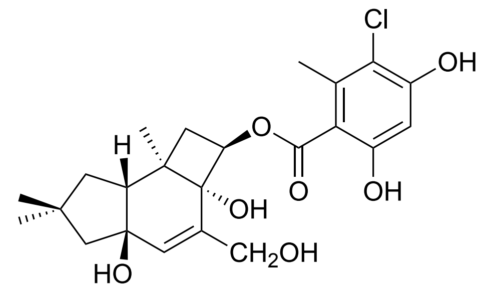
13-hydroxymelleolide K (**25**)



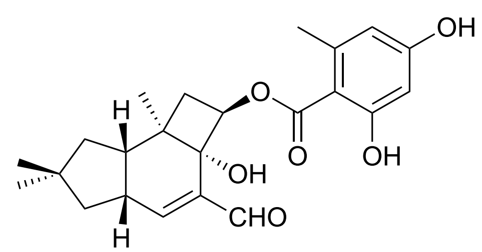
5'-*O*-methylmelledonal (**26**)



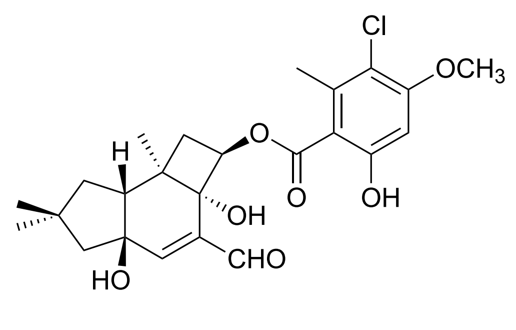
melleolide D (**27**)



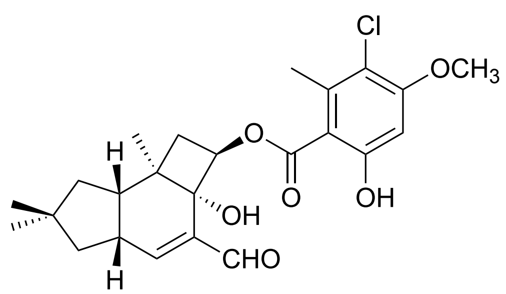
13-hydroxydihydromelleolide (**28**)



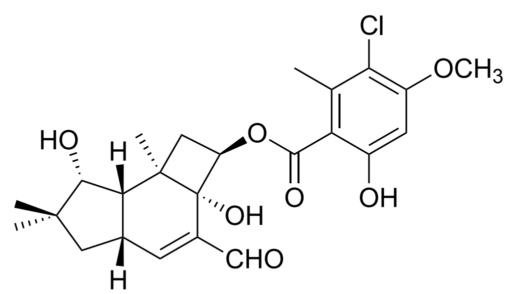
melleolide (**29**)



armillarinin (**30**)

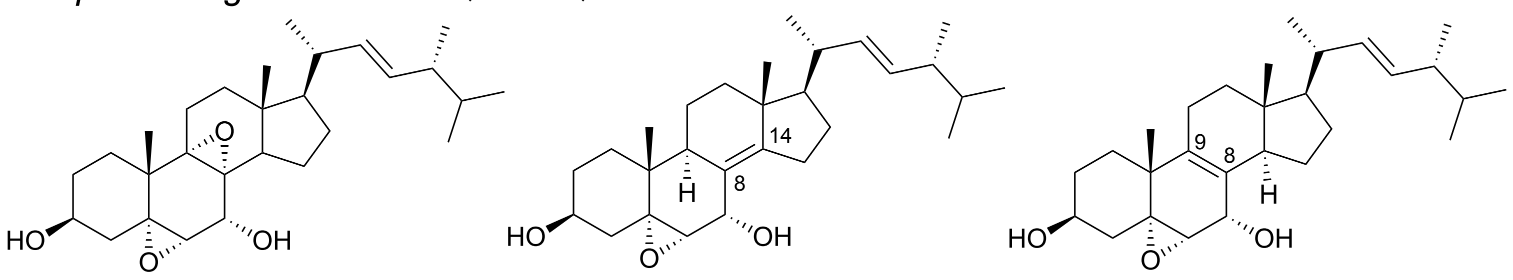


armillaridin (**31**)



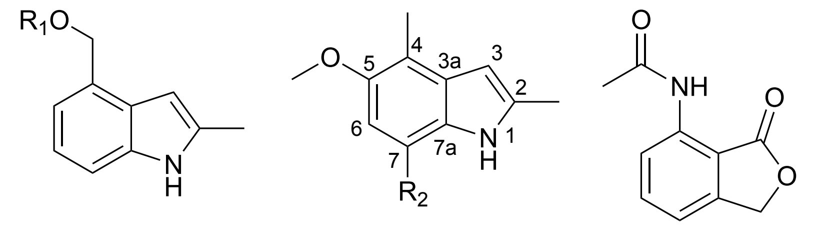
armillarikin (**32**)

Stropharia rugosoannulata (**33**–**35**)



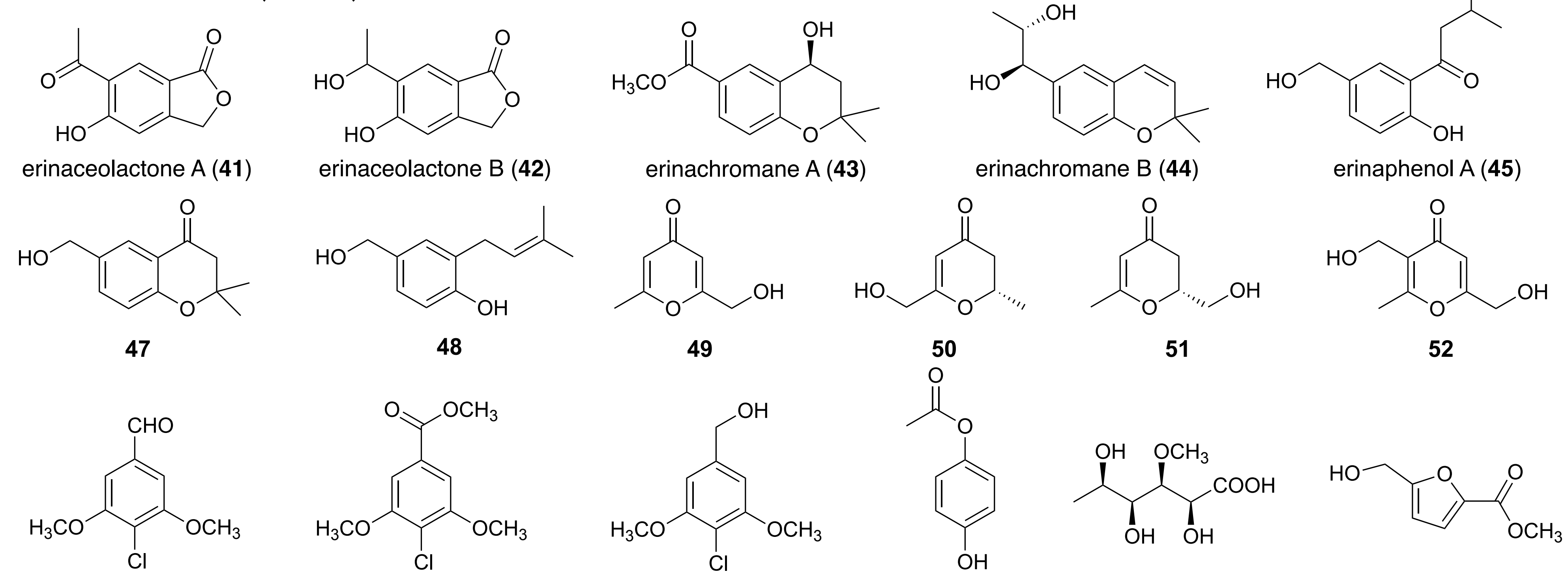
33 **34** **35**

Tricholoma flavovirens (**36**–**40**)



36: R_1 = ethyl
37: R_1 = methyl
38: R_2 = OCH_3
39: R_2 = H
40

Hericium erinaceus (**41**–**59**)

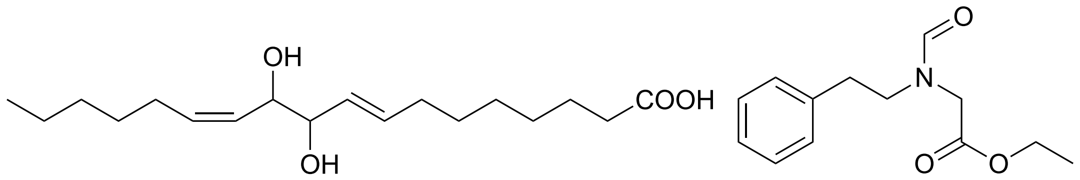


erinaceolactone A (**41**) erinaceolactone B (**42**) erinachromane A (**43**) erinachromane B (**44**) erinaphenol A (**45**) **46**

47 **48** **49** **50** **51** **52** **53**

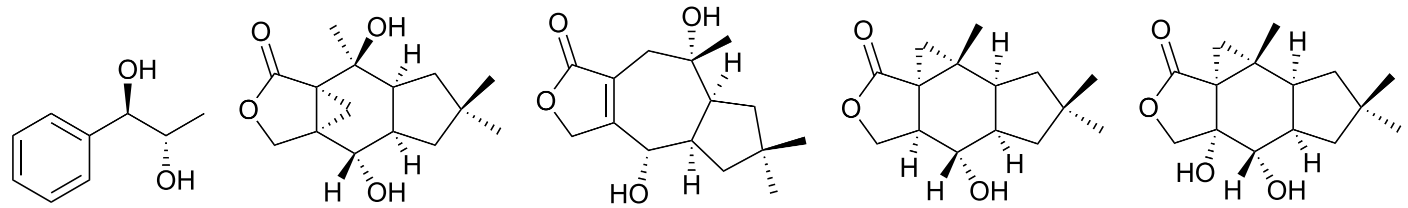
54 **55** **56** **57** **58** **59**

Leccinum extremiorientale (**60**, **61**)



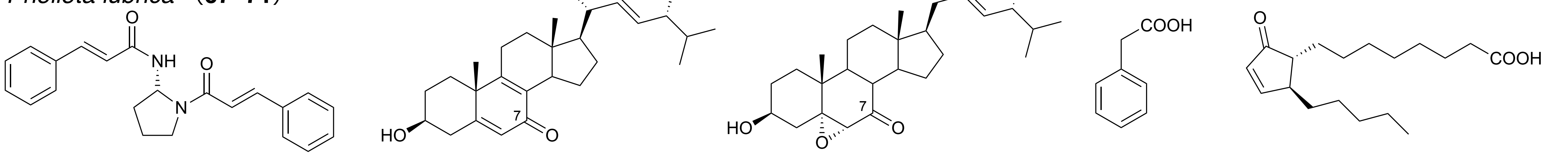
60 **61**

Russula vinosa (**62**–**66**)



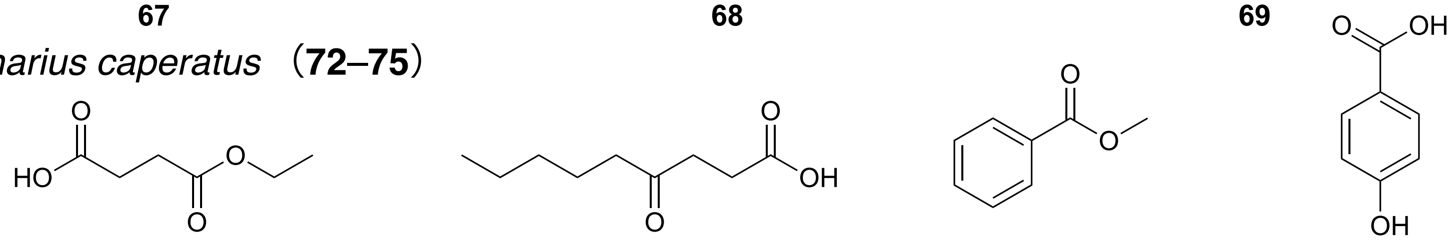
62 **63** **64** **65** **66**

Pholiota lubrica (**67**–**71**)



67 **68** **69** **70** **71**

Cortinarius caperatus (**72**–**75**)



72 **73** **74** **75**