Biologically functional molecules from mushroom-forming fungi

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ABSTRACT

Fungi including mushrooms have been proved to be an important biosource of numerous metabolites having a huge variety of chemical structures and diverse bioactivities. Metabolites of mushrooms are of remarkable importance as new lead compounds for medicine and agrochemicals. This review presents some of our studies on biologically functional molecules purified from mushroom-forming fungi; 1) endoplasmic reticulum stress suppressor, 2) osteoclast-forming suppressing compounds, 3) plant growth regulators.

Key words: ER stress suppressor; fungal metabolites; osteoclast-formation suppressor; plant growth regulator, natural products

At present, estimates of the total number of fungal species on earth are about 1.5 million species, whereas the number of fungi described worldwide is just about 7% of the number.[1, 2)] There is a well-known axiom that "plants act as producers, animals as consumers, and fungi as restorers and decomposers". In other words, the plants create organic compounds by means of photosynthesis and animals consume such plants. Then fungi, including mushrooms, play an important role in restoring the plants and animals back to the land. Fungi can be found in almost all types of habitats. To survive, fungi have developed a number of strategies for protection and communication using different types of secondary metabolites. There are some differences in the structures of metabolic products by mushroom-forming fungi compared to those by plants and animals. These differences sometimes indicate biological activities indigenous to mushroom-forming fungi. Fungi including mushrooms have been proved to be an important biosource of numerous metabolites having a huge variety of chemical structures and diverse bioactivities.[3, 4)]

Our group have been studying various bioactive compounds produced by some mushrooms. Bioactivity-guided fractionation of the extract of mushroom resulted in the isolation of active compounds and structure determination. This review presents some of our studies on biologically functional molecules isolated from mushroom-forming fungi.

Endoplasmic reticulum (ER) stress suppressors

Endoplasmic reticulum (ER) is an extensive membranous network that provides a unique environment for the synthesis, folding, and modification of secretory and cell surface proteins.[5)] Certain pathological stress conditions can disrupt homeostasis in the ER, causing loss of the ER intraluminal oxidative environment and depletion of intracellular calcium stores, and lead to accumulation of misfolded proteins in the ER.[5)] ER stress-dependent neurons death via amyloid-beta (Aβ) peptides has been reported to cause diseases, such as Alzheimer, Parkinson, and Huntington diseases.[6-9)] ER stress has

been reported to cause not only neurodegenerative diseases but also some other diseases, such as diabetes, atherosclerosis, heart and liver disease.[10] Therefore, the protective activity against ER stress is an important target for the cure or prevention of these diseases and the demand for new protective substances prompted us to screen the protective activity of the extracts from edible mushrooms. The extracts of mushrooms were subjected to the protective activity assay against ER stress-dependent cell death caused by tunicamycin (TM) or thapsigargin (TG). ER stress was induced by the addition of TM or TG into the culture medium of Neuro2a cells in the presence or absence of samples. TM is an inhibitor of *N*-linked glycosylation and the formation of *N*-glycosidic protein-carbohydrate linkages.[11] It specifically inhibits dolichol pyrophosphate-mediated glycosylation of asparaginyl residues of glycoproteins and induces the ER stress.[12] TG, an inhibitor of the sarcoplasmic/ER Ca^{2+}-ATPase, also induces ER stress by disrupting the homeostatic balance of the Ca^{2+} concentration in the ER.[13]

Hericium erinaceus is a well-known edible and medicinal mushroom in Japan as known Yamabushitake, and in Europe and the United States as Lion's Mane. It showed some important bioactivities in the reduction of ER stress induced by amyloid β–peptide[14-16] and anti-dementia such as the promotion of nerve growth factor (NGF) synthesis[17-24]. NGF, belongs to a family of neurotrophins that induce survival and proliferation of neurons, plays an important role in the repair, regeneration, and protection of neurons. A finding reported a woman with Alzheimer's dementia improved her symptoms, such as enhancing mental ability, after the administration of NGF directly into her brain using catheter.[23] It has been suggested by scientists that NGF may be used to treat Alzheimer's disease.[25] However, there is a high risk in such treatment since NGF is a protein which cannot pass through the blood-brain barrier and it needs to be injected directly into the brain to be effective. If a compound can be taken by oral administration that can pass through the barrier and stimulates the NGF synthesis inside the brain, it may be applied saferly. Based on the above concept,

Kawagishi et al. searched for natural stimulators of NGF synthesis and found hericenones C to H (**1**−**6**) from the fruiting bodies of *H. ericaceus* in 1991.[17, 18] These compounds were the first NGF stimulators isolated. Later, erinacines A to I (**7**−**15**) from the mycelia of the fungus were obtained (Figure 1a).[19-22, 24] Recently, the neuroprotective activity of erinacine A of the *Hericium erinaceus* mycelium *in vitro* and *in vivo* has been reported,[26] which thus may be promising candidates for the treatment of neurodegenerative diseases such as Parkinson's disease.

3-Hydroxyhericenone F (**16**) was isolated as an ER stress suppressor from the fruiting bodies of *H. erinaceus*.[16] Ueda et al. also found active compounds (**17**−**20**) in an extract from the scrap cultivation bed of the mushroom (Figure 1b).[15] The cultivation bed is usually discarded by the mushroom growers after harvesting the fruiting bodies. The scrap cultivation of the mushroom can be a useful resource of biological active compounds.

Leccinum extremiorientale, having a red brown areolate cap, belongs to the higher fungus of the genus *Leccinum* in the family Boletaceae and grows worldwide, especially in the northern temperate zone. *L. extremiorientale* is a very tasty mushroom. We succeeded in the isolation and structural determination of the active compound, leccinine A (**21**), and structure activity relationship by comparing the activity of **21** with those of its seven synthesized analogues (**21a** −**g**) (Figure 2a).[27] These results indicated that the formamide group in **21** is indispensable for the protective activity.

The edible mushroom *Mycoleptodonoides aitchisonii* belongs to the *Climacodontaceae* family, is mainly found in the Kashmir region of India and in East Asia. This mushroom is popular in Korea (called "Champanul") and in Japan (called "Bunaharitake"). We found the protective activity in the extract of the mushroom *M. aitchisonii*, whose enhancing effect on the synthesis of NGF and catecholamine metabolites in the rat brain had been reported.[28, 29] The structures of **22**−**37** were determined by the interpretation of spectroscopic data including NMR and X-ray analysis (Figure 2b).[30-32] Many γ-lactones and phenylpentanols were possessed of the

protective activity against TM- or TG-toxicity. This mushroom has potential utility in preventing of ER stress.

Termitomyces titanicus with a cap diameter of up to 1 m is the largest edible mushroom in the world according to Guinness Book of Records. The genus *Termitomyces* live in an obligate mutualistic symbiosis with termites of the subfamily *Macrotermitinae*.[33-35] Termites cultivate the mycelia in their nest and fruiting bodies can be seen rising on or near the mounds.[36] We reported the isolation of ER stress protective compounds, termitomycamides A to E (**38**−**42**), from the fruiting bodies of *T. titanicus* (Figure 3).[37, 38] To investigate further the structure-activity relationship, their analogues (**39a**−**c** and **42a**−**c**) that have different fatty acid parts (stearyl, oleyl and arachidonyl) were synthesized (Figure 3).[38] The linoleyl moiety in **39** and **42** was indispensable for the activity of the substances.

Osteoclast-formation suppressors

Osteoporosis is a serious health problem that predominantly affects postmenopausal women and aged people, and leads to a high risk of fracture. Bone homeostasis during remodeling is maintained by osteoclastic bone resorption and osteoblastic bone formation.[39] Exceeding calcium resorption in the bone gradually decreases bone mineral density. For this reason, osteoclast, the cell responsible for calcium resorption, is the major medicinal target to treat osteoporosis. Therefore, substances which can suppress the formation of osteoclasts are candidates for drugs or functional foods to prevent osteoporosis. The assay is based on the principle that osteoclast-like multinucleated cells can be formed *in vitro* from co-cultures of mouse bone marrow cells and osteoblastic cells by treatment with osteotropic factors, 1α,25-dihydroxyvitamin D_3 and prostaglandin E2.[40] By adding suppressive agents, the formation of osteoclast is inhibited during the differentiation. During our screening for the osteoclast-formation suppressive effects of extracts of mushrooms, Choi et al. found

very strong activity in the extract of verious mushrooms *Agrocybe chaxingu, Grifola gargal,* and *Leccinum extremiorientale.*

Agrocybe chaxingu is an edible fungus belonging to the family Strophariaceae, grows in dry and died boles of broadleaf, such as grease tea plant and poplar, and exists only in mountainous areas in South China. By using the assay, Choi et al. found three known compounds (**43**− **45**) and five new compounds named as chaxines A (**46**) to E (**50**) from this mushroom (Figure 4a) as biological active ingredients. The compounds suppressed the formation of osteoclast without cytotoxicity.[41-44)] In addition, chaxins A−C (**46**−**48**) as possible lead compounds, have been synthesized.[43, 45)]

Grifola gargal is an edible mushroom with a characteristic almond flavor, collected and eaten by native people of southern Argentina and Chile. The species has only been occured from the Nothofagus-dominated forests of the area. Nutraceutical properties and pharmacological potential of the mushroom have been studied; aqueous extracts of the mushroom showed the anti-oxidant and anti-inflammatory effects and the methanol extracts displayed a free radical scavenging activity.[46)] Wu and Choi et al. have reported the isolation of novel osteoclast-forming suppressing compounds, gargalols A to C (**51**−**53**) together with some known steroids (**54**−**57**) and sphingosine (**58**) from the mushroom (Figure 4b).[47, 48)]

Choi et al. also isolated two osteoclast-forming suppressing sterols from the mushroom *L. extremiorientale*.[49)] Ergosterol peroxide and cerevisterol exsist widespread in many mushrooms,[27, 50-52)] and exhibited no activity. However, slight (or deep) modification of common substances like **43**−**57** could give the active principles. In general, mushrooms contain various kinds of steroids at higher concentrations. Edible mushrooms are suitable for the sources of the suppressors, since they can be eaten daily without serious secondly effects. Therefore, mushrooms are suitable for daily intake, our group propose that the mushroom could be the promising functional food for postmenopausal women and aged people to improve and/or prevent osteoporosis.

Plant growth regulators

Microbes secrete diverse classes of molecules that directly or indirectly affect plant growth, development, productivity and overall health.[53] Microbial secondary metabolites represent a kind of chemical communication between microbes and other microbes or nonmicrobial systems including higher plants, lower animals or mammalian (humans) systems, which reflects antagonistic, synergistic, regulatory or modulatory and any other biochemical or either biophysical interactions.[54] Plants interact with fungal species in their natural growing environments. For example, it has been reported that strigolactones as a plant hormone induce hyphal branching in symbiotic arbuscular mycorrhizal fungi to roots of plants and promote plants growth by establishing mutualism with the fungi.[55] In addition, gibberellins (GAs) are a large family of isoprenoid plant hormones, some of which are bioactive growth regulators, controlling seed germination, stem elongation, and flowering.[56] The rice pathogen *Gibberella fujikuroi* is able to produce large amounts of GAs, especially the bioactive compounds gibberellic acid (GA_3). The commercial source of the bioactive GAs, particularly GA_3, is by fermentation of the fungus, *G. fujikuroi*, from which the GAs were originally discovered.[57]

Our group are interested in biological activity of components from mushroom towards plants and have reported isolation of some compounds that regulate lettuce growth.[58-63]

The genus *Armillaria* (Honey Fungus in English, Naratake in Japenese), belonging to the family Physalacriaceae, is an edible mushroom throughout the world. This mushroom is delicious, and people also have utilized it for its medicinal properties. On the other hand, the genus has been known as a serious plant pathogen that causes root rot in various plant species, [64] and the phenomenon is called Armillaria root disease.[65, 66] Root rot is one of the most serious diseases of plants and occurs in many broadleaf trees including oak, fruit, and nut trees as well as several herbaceous plants.[65-67] These facts indicate that *Armillaria* produces allelopathic substances. In addition, armillariols A−C (**58**−**60**) have been isolated from the culture broth of *Armillaria* sp. as plant growth regulators by our group[68]. The synthesis of (+)- and (−)-**60** and their analogues

using Suzuki−Miyaura cross-coupling and Sharpless asymmetric dihydroxylation on a gram-scale is described by Reddy et al[69]. In addition, two new compounds (**61**, **62**) and seven known analogues (**63**−**69**) from the culture broth of same genus (Figure 5a). Compounds **63**−**69** were identified as 5'-O-methylmelledonal[70], melleolide D[71], 13-hydroxydihydromelleolide[72], melleolide[73], armillarinin[74], armillaridin[75], and armillarikin[76], respectively, which have been isolated from the mushroom genus *Armillaria* as antimicrobial compounds. The protoilludane skeleton itself is important for growth inhibitory activity against lettuce. The formyl group at C-1 and the absence of a hydroxy at C-13 in the molecule were important for the antifungal activities.

"Fairy rings" is a disease symptom in woodlands and grasslands; rapidly growing, lush green rings (or arcs bands) of grass and/or circles of mushrooms are observed, owing to the interaction between a fungus and a plant[77, 78]. It has been found that more than 60 of basidiomycete fungi produce fairy rings in grasslands[79]. Since the first scientific article about "fairy rings" in 1675 and subsequent studies reviewed in Nature in 1884[80], this phenomenon had been attributed to unknown "fairies" before our chemical disclosure[77-81]. Choi et al. found that 2-azahypoxanthine (AHX, **70**) and imidazole-4-carboxamide (ICA, **71**) are plant growth regulators produced by a fairy ring forming fungus, *Lepista sordida* (Figure 5b)[82, 83]. Furthermore, Choi et al. isolated a common metabolite of **70** in plants, 2-aza-8-oxohypoxanthine (AOH, **72**)[84] and futher metabolites (*N*-glucosides; **73**−**76**) (Figure 5b)[85]. Kawagishi and Choi named the three compounds "fairy chemicals" (**70**−**73**; FCs) after the title of the article in Nature[86].

FCs regulated the growth of all of the plants tested regardless of their species, and various examinations indicated that plants developed tolerance to various and continuous stress (low or high temperature, salt, or drought stress, etc.) from the environment by treatment with FCs, resulting in the growth promotion. Furthermore, FCs increased the yields of rice, wheat, and other varied crops in greenhouse and/or field experiments[82-84, 86-88], suggesting that they might find practical application in agriculture. For practical use of **70**−**72**, field experiments are necessary and large

amounts of them are required for them. Compounds **70**−**72** are chemically synthesized readily[89, 90]. Choi et al. have also reported the endogenous presence of **70** and **72** in plants and the discovery of a new route in purine metabolic pathway in which **70** and **72** are biosynthesized[84, 91]. Based on the above results, our group hypothesize that FCs (**70**−**72**) are a new family of hormones in plants.

Conclusion

Today fungi are one of the major parts of pharmaceutical industries, but still there is a need to continue to find new bioactive molecules from fungi. Fungi are easy to cultivate and scale up as compared to plant cells. There are more than 140,000 species of mushroom-forming fungi on the earth. However, only about 7% of the fungi have been given names. The nameless fungi also must be producing compounds with new functions and structures. Mushrooms are unexplored biological resources. Our group are presently trying to isolate the active compounds from various mushrooms.

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Disclosure statement

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Figure legends

Figure 1. Simulators of nerve growth factor-synthesis (a) and ER stress protecting compounds (b) from *Hericium erinaceus.*

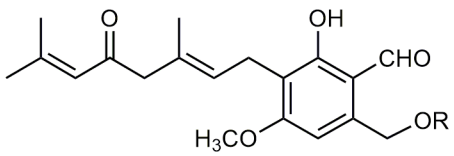
Figure 2. Bioactive compound isolated from the edible mushroom *Leccinum extremiorientale* and its synthetic analogues (a) and comounds from *Mycoleptodonoides aitchisonii* (b).

Figure 3. Bioactive compounds isolated from the edible mushroom *Termitomyces titanicus* and their synthetic analogues.

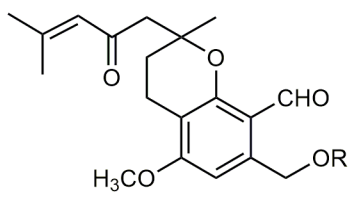
Figure 4. Bioactive compounds isolated from the edible mushrooms *Agrocybe chaxingu* (a) and *Grifola gargal* (b).

Figure 5. Bioactive compounds isolated from the culture broth of *Armillaria* sp. (a), and fairy chemicals and their metabolites in rice (b).

(a)



1 R = palmytoyl
2 stearoyl
3 linoleoyl



4 R = palmytoyl
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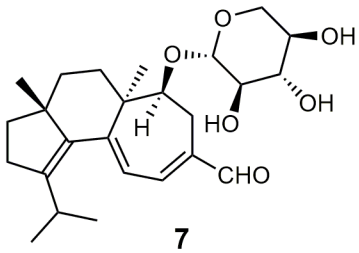
6 linoleoyl



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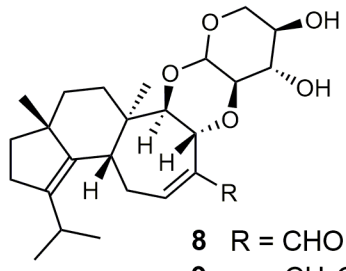

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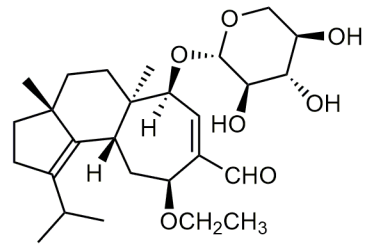
9 CH_2OH



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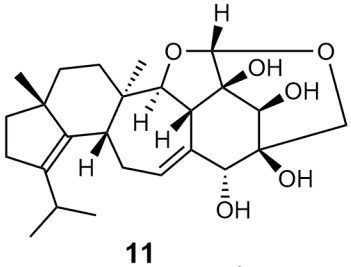

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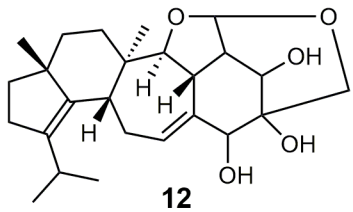

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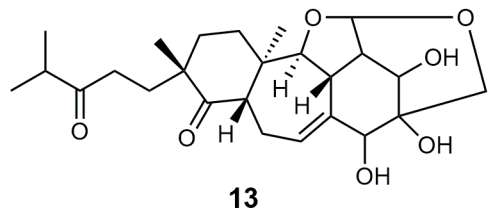

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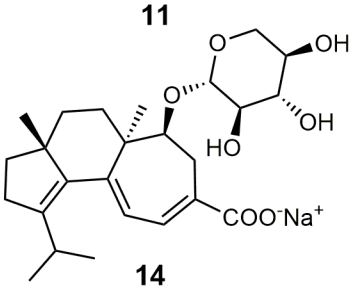

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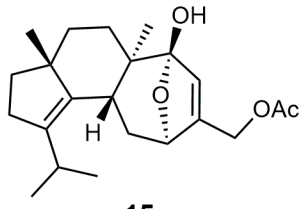

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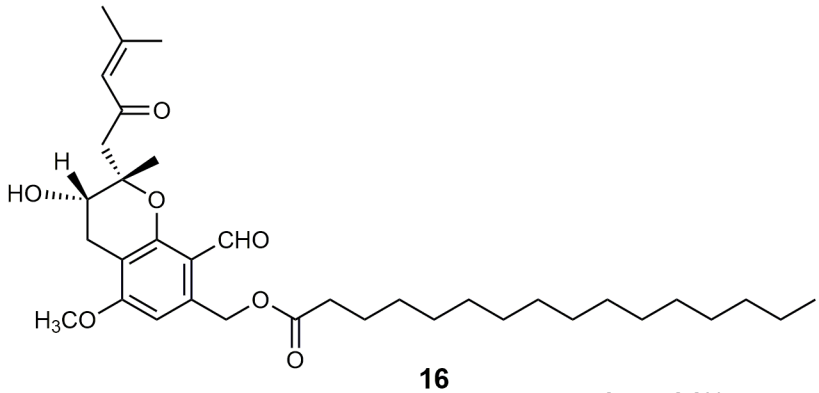

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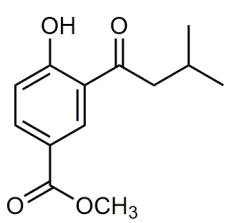

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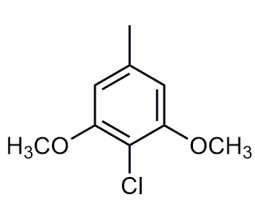

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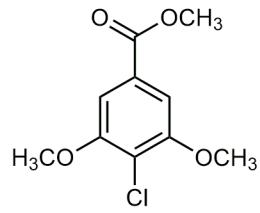

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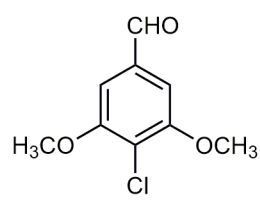

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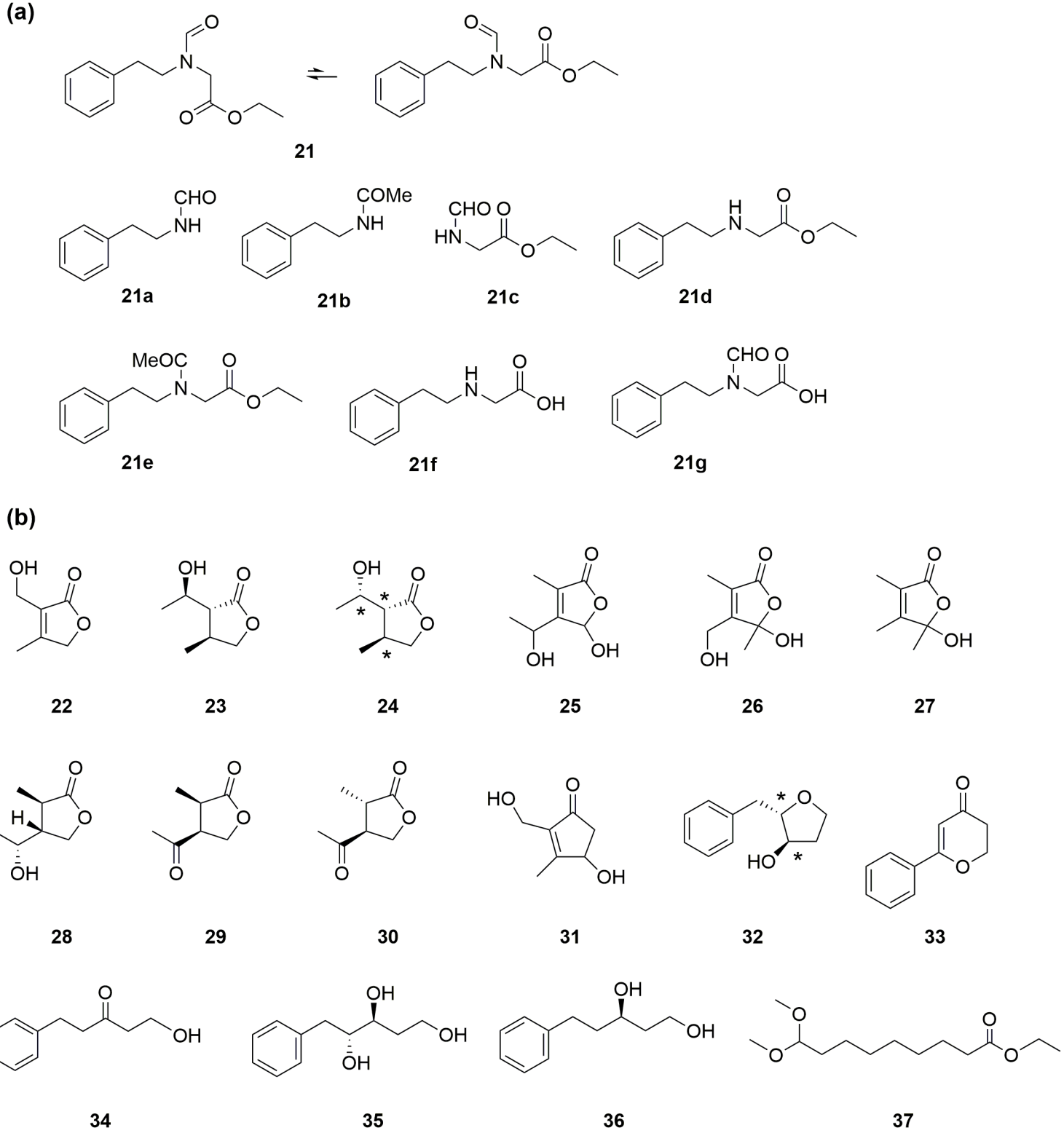
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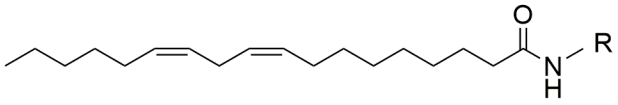
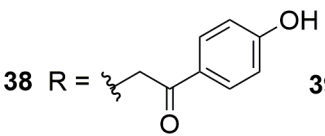
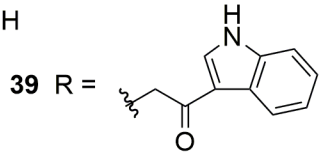
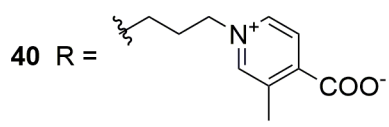
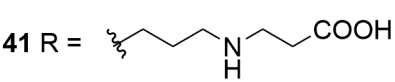
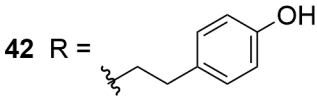


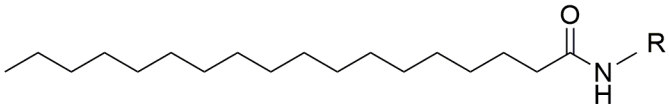




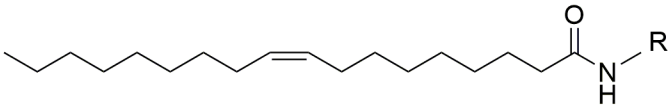








39a R = R_1
42a R = R_2



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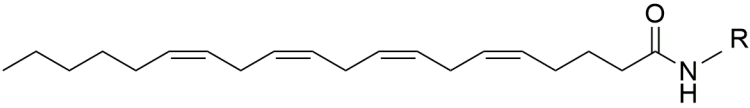

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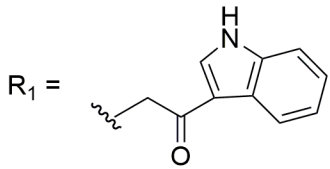

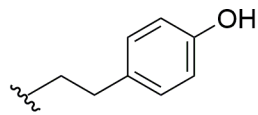

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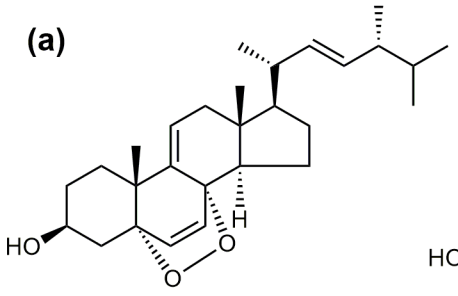

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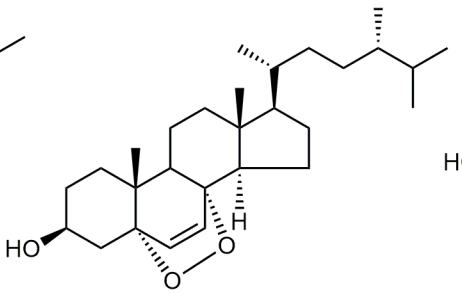

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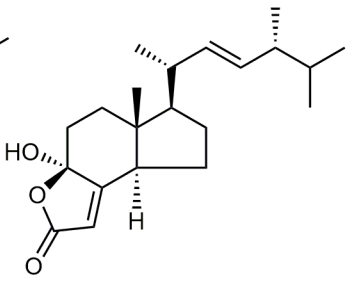

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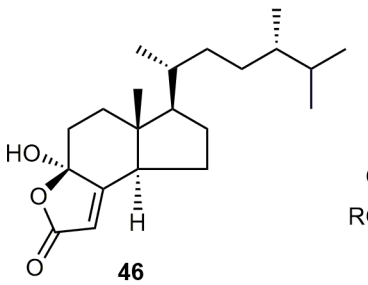

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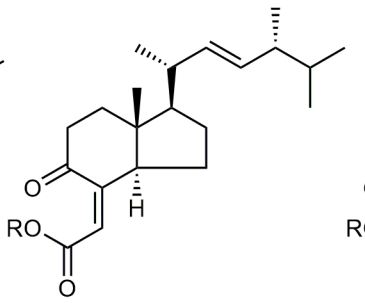

47: R = a
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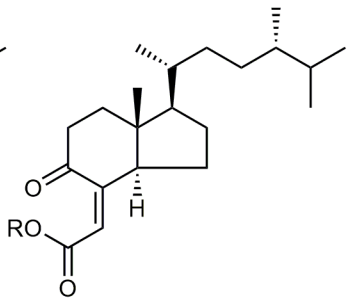

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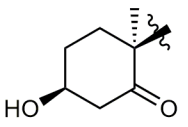

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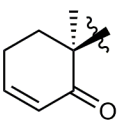

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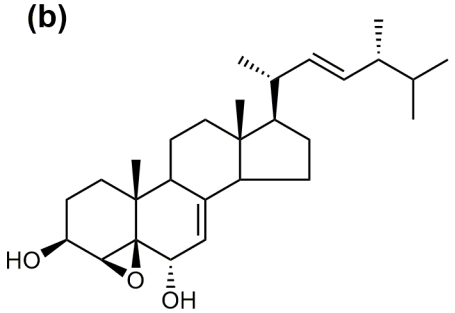

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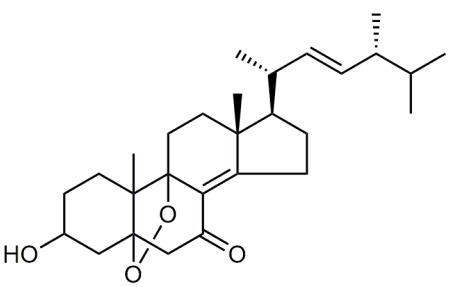

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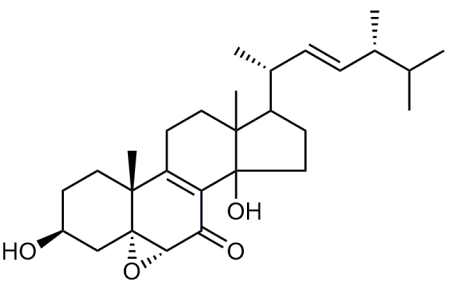

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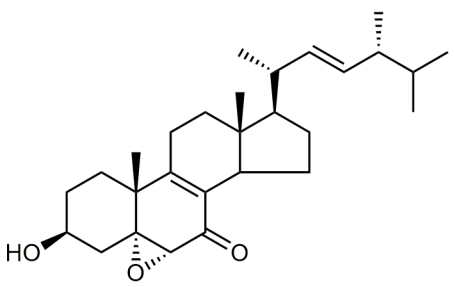

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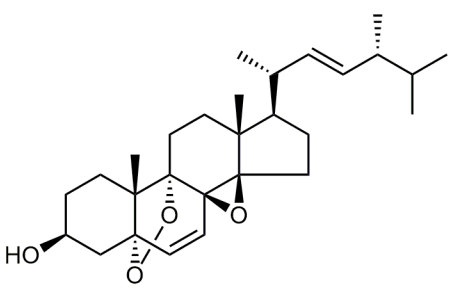

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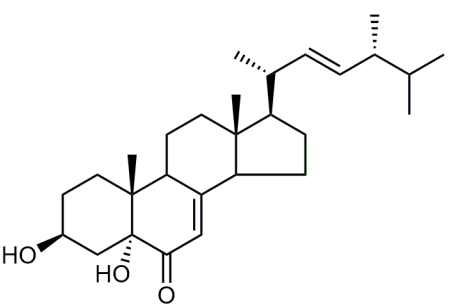

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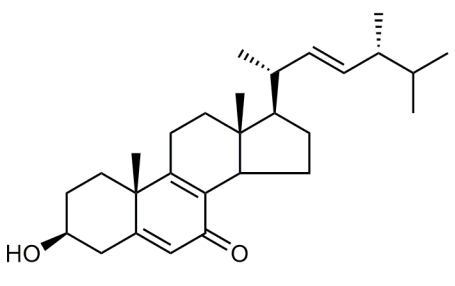

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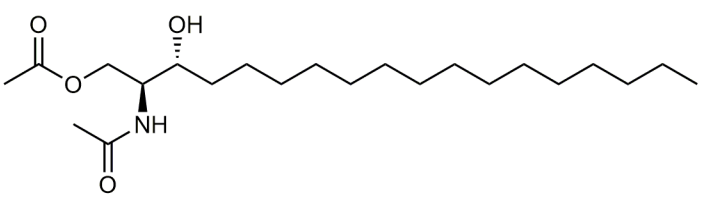

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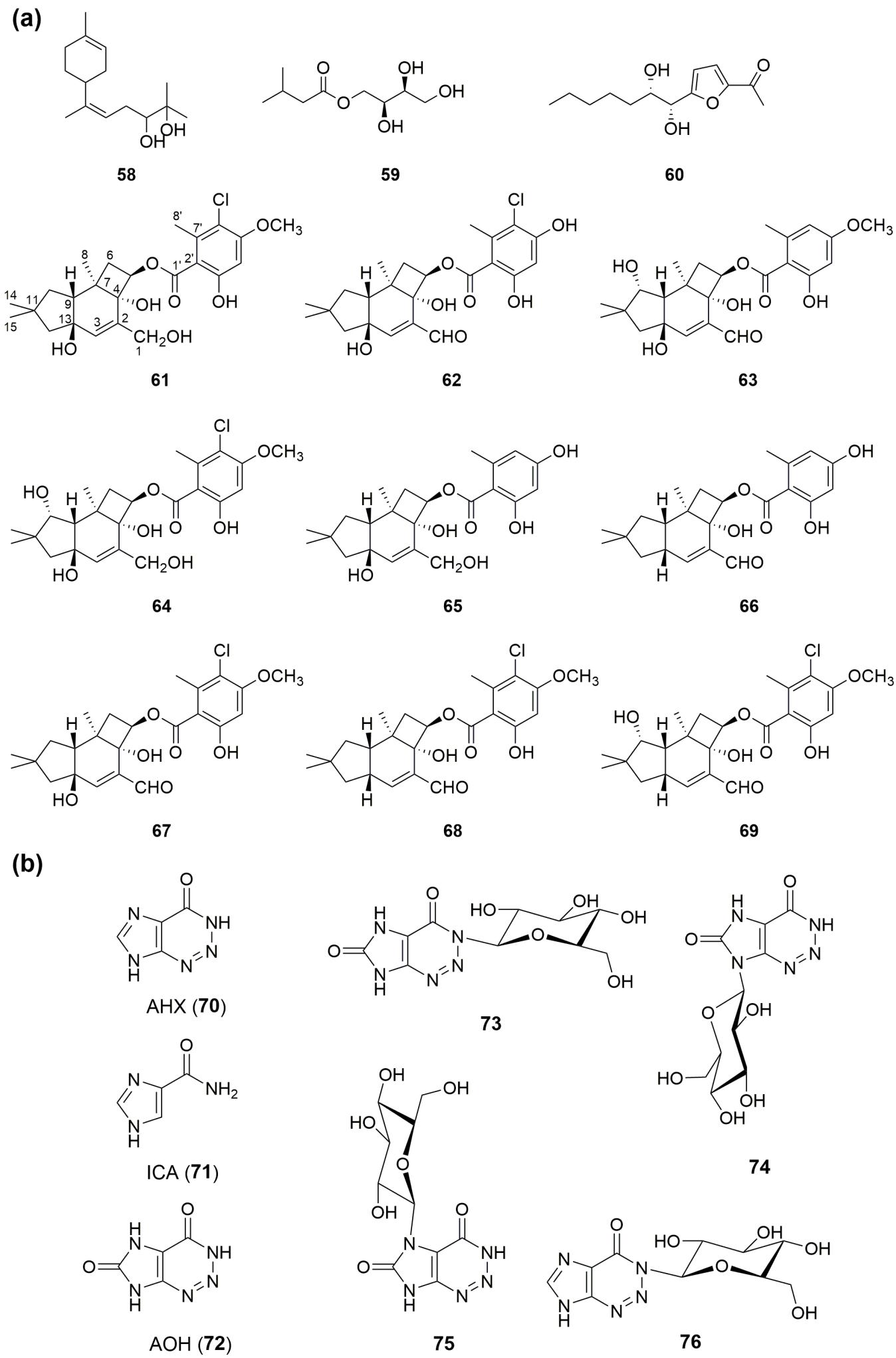
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