Chapter 6

Diterpenes from Different Fungal Sources and Their ^{13}C-NMR Data

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Additional information is available at the end of the chapter

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Abstract

Diterpenes are one of the classes of natural products with about 7000 structures. The basic skeleton of diterpene contains 20 carbon atoms. Microbes contain a large number of diterpenoid with many oxidized carbons and nitrogen atoms. To date, a number of secondary metabolites have been isolated from fungal sources, and some of these examples showed diverse structural features and interesting biological activities. These classes of compounds have attracted the interest of natural product scientist due to their potential biological activities. This chapter includes recently (2013–2018) isolated compounds from various fungal sources especially cythane, clerodanes, halimanes, abietane, and indole-type diterpenes. Biosynthetic pathway of plants and fungi diterpenes showed homology at initial steps but showed differences at latter steps. The biological activity and ^{13}C-NMR data of these recently isolated compounds have been discussed. These diterpenes exhibited potential nitric oxide, anticancer, antioxidant, and antitumor properties. The diterpenes are clerodane, labdane, and kaurane derivatives. A brief discussion on the ^{13}C-NMR chemical shifts of these diterpenes has been discussed at the end of each type.

Keywords: fungal, biosynthesis, diterpenes, biological activities, ^{13}C-NMR

1. Introduction

Terpenoids comprise the largest, structurally most diverse family of natural products and play important roles in all living organisms [1, 2]. Fungi (*Ascomycota* and *Basidiomycota*) are prolific producers of structurally diverse terpenoid compounds. Classes of terpenoids identified in fungi include the sesqui-, di-, and triterpenoids.

As the largest group of documented natural products, terpenoids have attracted attention from a broad scientific community and have been heavily investigated due to their interesting structural characteristics and profound biological effects [3–6].

Fungi are important source of potential bioactive compounds which play an important role in pharmacology industry [7–11]. Among fungi, mushrooms are the most attractive sources of bioactive compounds both of chemical and biomedical interests. Approximately 2000 mushrooms are safe for human consumption, and about 650 of them have medicinal properties out of 15,000 documented species of mushrooms [12]. These are also important in industrial processes to enhance composition of bioactive compounds in fermented grain assays [13–15].

2. Diterpene biosynthesis

Diterpenoid biosynthesis has been studied in plants, bacteria, and fungi [16]; still lots of work are required to clone many important respective genes to characterize and engineer diterpenoid pathways in these representative organisms which remain a big challenge [17]. Fungal di-TPS enzymes show homology to plant enzymes in terms of its size and the combination of biochemical studies with molecular genetics. This also facilitated the comparison of plant and fungal biochemical pathways leading to the formation of gibberellins in plants and fungi [18].

The first committed step in diterpenoid biosynthesis is the cyclization of GGPP to produce the diterpene scaffold, which occurs via a carbocation cascade. Classically, activation of the carbocation cascade by terpene synthases corresponds to the removal of the pyrophosphate group from the linear substrate. This ionization-dependent reaction is catalyzed by class I terpene synthases [19]. Fusicoccanes are potent phytotoxins known to be synthesized by a few fungal species. *P. amygdali* was the first monofunctional diterpene synthase cloned and characterized in *E. coli* [20, 21]. Diterpenoids cyclized by the first, one-step route involves a monofunctional class I diterpene synthase that catalyzes ionization-dependent diphosphate cleavage and subsequent carbocation migration and quenching using a mechanism similar to sesquiterpene synthases, except the prenyl chain is now longer by one isoprene unit [22].

Biosynthesis of labdane-type diterpenoids requires a two-step cyclization pathway involving first a protonation dependent cyclization of GGPP to form the characteristic labdane bicycle and, in the second step, ionization-dependent cyclization at a separate active site to generate the final cyclic product (**Figure 1**). Cyclization of GGPP to ent-CDP and then to the tetracyclic ent-kaurene generates the precursor for gibberellin (gibberellic acids, GA) phytohormones that are major regulators of plant growth and development. It is believed that because of its essential role in plants, ent-kaurene represents the ancestral diterpenoid cyclization pathway from which alternative cyclization routes evolved to generate the large diversity of labdane-type compounds known today [22]. In fact, it has been shown that single amino acid changes are sufficient to alter the product profile of the class I ent-kaurene synthase to form new cyclic scaffolds [23, 24].

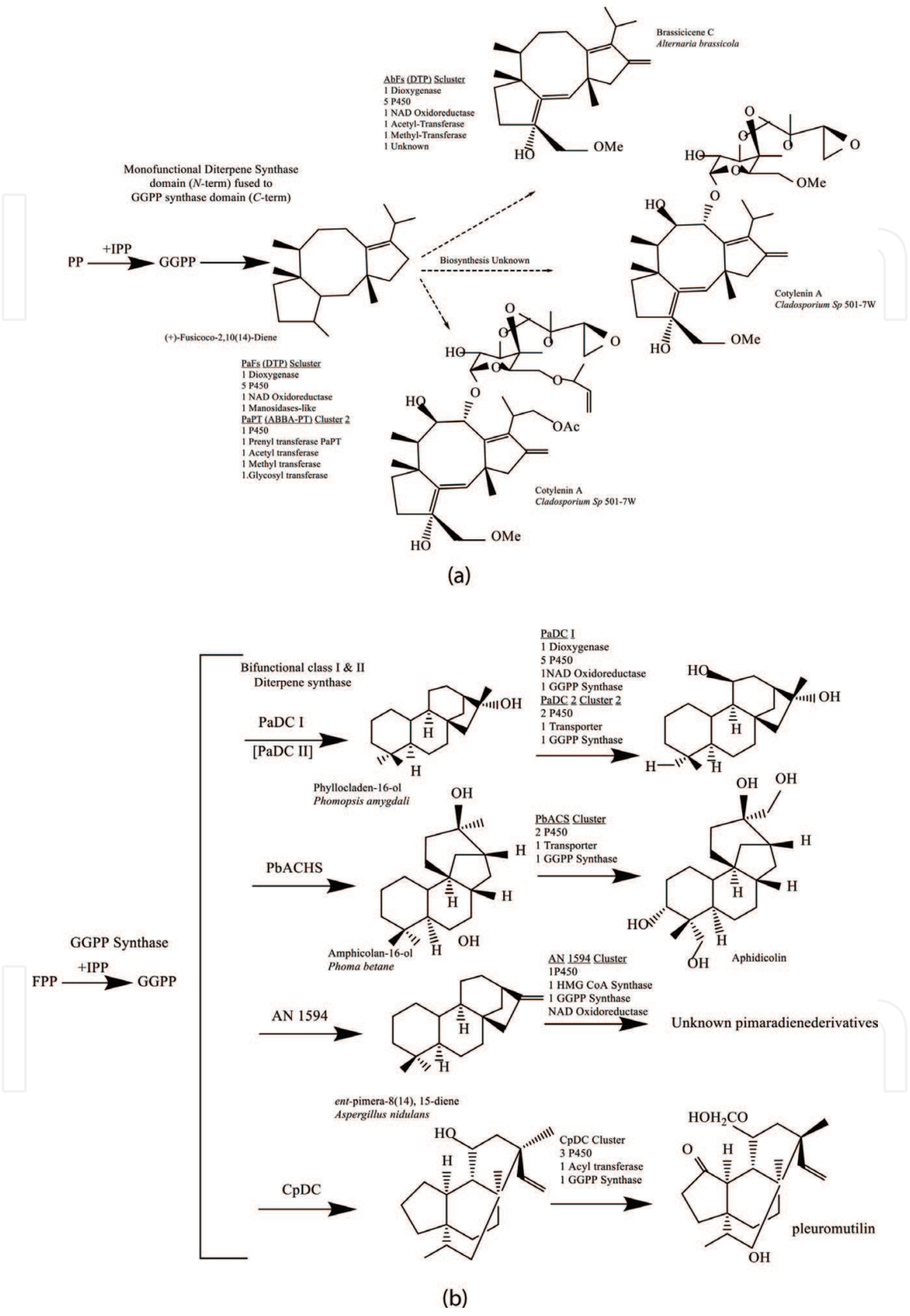


Figure 1. Overview of diterpenoid biosynthesis: (a) monofunctional-2,10(14)-diene is modified into different fusicoccane compounds and (b) bifunctional diterpene synthases make different labdane-related scaffolds that are modified into bioactive compounds.

3. Diterpenoid classification

3.1. Bicyclic diterpenoids

3.1.1. Clerodane diterpenes

Clerodane diterpenes are the natural group of secondary metabolites holding an utmost pharmacological significance. These are bicyclic structures consisting of a fused ring (decalin moiety from C-1 to C-10) with a six-carbon side chain (C-11 to C-16) attached at C-9. The rest of the carbons (C-17 to C-20) are bonded at C-8, C-4, C-5, and C-9, correspondingly [25]. Only 25% of the clerodane diterpenes showed 5:10 *cis* ring junction, while the rest possess 5:10 *trans* ring fusion as presented here in the form of columbin and clerodin, respectively. Columbin exhibited dose-dependent anti-inflammatory activity as well as chemopreventive activity against colorectal cancer [26–28]. During the last 25 years, over 1300 diterpenoids and nor-diterpenoids with the clerodane carbon skeleton have been isolated [29, 30]. The detailed classification of clerodane diterpenes is given in **Figure 2**.

3.1.1.1. Clerodane diterpenes by biotransformation from endophytic fungi

Three strains of endophytic fungi *L. gonubiensis*, *N. ribis*, and *P. stromaticum* produced one known and five unknown compounds (B1–B4) through a process of biotransformation, while compounds Q1–Q2 are derived as chemical derivatization of compound 2 [30]. These compounds were actually isolated for the first time from *Croton argyrophylloides* (Euphorbiaceae) and further biotransformed by *Cunninghamella echinulata* and *Rhizopus stolonifer* fungi and produced a new diterpene, as previously described by Monte et al. [31] and Mafezoli et al. [32] (**Figure 3**).

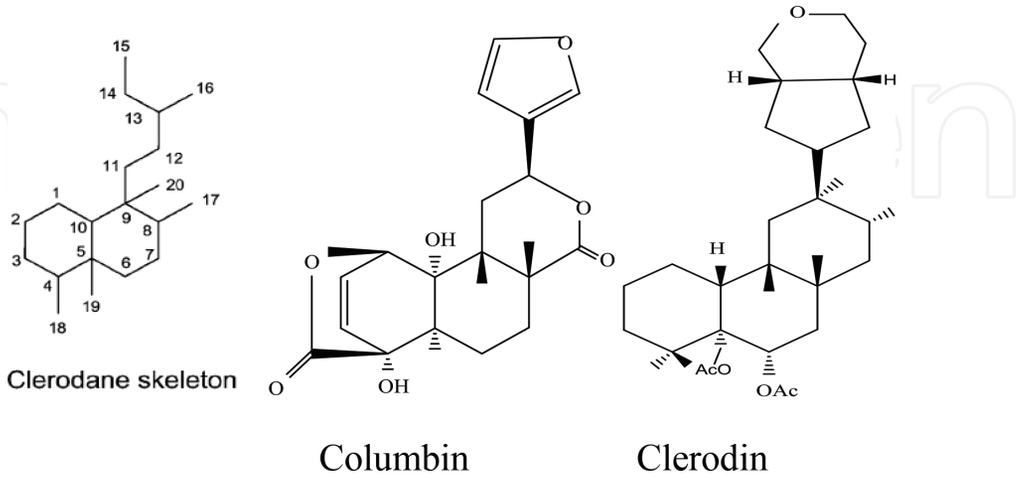
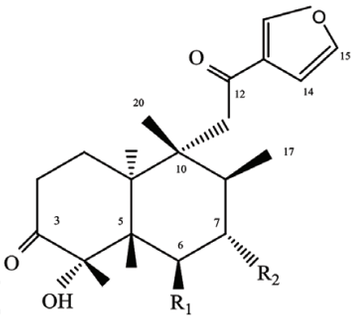


Figure 2. Clerodane skeleton, cis and trans structures of clerodane.



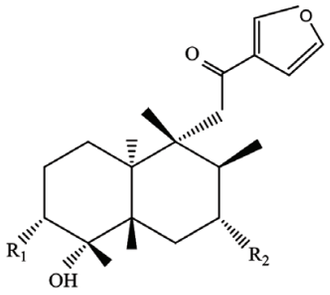
R_1=H, R_2=H (Substrate)

R_1=H R_2=OH (Compound B2)

R_1=H R_2=$OCOCH_2CH_3$ (compound Q1)

R_1=H R_2=OCH_2Ph (compound Q2)

R_1=OH R_2=H (compound B4)



1. R_1=OH, R_2=H (B1)

R_1=OH R_2=OH (compound B3)

[31]

Figure 3. Chemical structures of the metabolites by and chemical derivatives of the (3*R*,4*S*,5*S*,8*S*,9*R*,10*S*)-3,12-dioxo-15,16-epoxy-4-hydroxycleroda-13(16),14-diene (compound 1) [35].

3.1.1.2. ^{13}C-NMR date

^{13}C-NMR spectra of substrate 1 and B2 suggested the C-7 hydroxylation making the signal at δ 70.1 (CH) in B2. Compound B2 is identified as new metabolite (4S,5S,7R,8R,9S,10S)-4,7-dihydroxy-15,16-epoxy-3,12-dioxocleroda-13(16),14-diene, and its molecular formula $C_{20}H_{28}O_5$ is sorted by HRMS. Compound B3 was unique for cultures of *N. ribis*. The ^{13}C-NMR spectrum of B3 showed the presence of one at δ 72.2 in the spectrum confirmed that compound 1 was regioselectively bioreduced at C-3. The new compound B3 was named (3*R*,4*S*,5*S*,7*R*,8*S*,9*R*,10*S*)-3,4,7-trihydroxy-15,16-epoxy-12-oxocleroda-13(16),14-diene, which is in agreement with the molecular formula $C_{20}H_{30}O_5$. The biotransformation product B4 was obtained only in the *P. stromaticum* culture. The ^{13}C-NMR spectrum of B4 showed no reduction of carbonyl group at δ 213.5 (C-3) and the appearance of carbinol methane group at δ 71.8 (C-6). And it is named as (4S,5R,6R,8S,9R,10S)-4,6-dihydroxy-15,16-epoxy-3,12-dioxocleroda-13(16),14-diene, which is in agreement with the molecular formula $C_{20}H_{28}O_5$. The new compound Q1 was named (4S,5S,7R,8R,9S,10S)-7-propionyloxy-4-hydroxy-15,16-epoxy-3,12-dioxocleroda-13(16),14-diene. The new derivative Q2 was named (4*S*,5*S*,7*R*,8*R*,9*S*,10*S*)-7-benzyloxy-4-hydroxy-15,16-epoxy-3,12-dioxocleroda-13(16),14-diene [30].

3.1.1.3. Biological activity

Clerodane diterpenes possessed effective insect antifeeding and related insecticidal properties. There are approximately more than 400 natural and semisynthetic products that have been assayed in the laboratories showing potential antifeedant properties [33].

3.1.2. Labdanes

The labdane-related diterpenoids are a special group, consisting of over 7000 members, which are distinguished by their unique biosynthesis. Gibberellin phytohormones as well as antibiotics such as some of phytoalexins and phytoanticipins fall into this family [34]. Labdanolic acids have been identified as biomarkers for the botanical origin of French ambers [35], while copalic acid and its relatives have been associated with the biological activity of the resins from *Copaifera* species. The lanceolatins are a group of **labdanes** and **abietanes** which were obtained [40] from *Cephalotaxus lanceolata* (Cephalotaxaceae). Some of the abietanes were described in this chapter as well (**Figure 4**).

3.2. Tricyclic diterpenoids

See **Figure 5**

3.2.1. Abietanes

Abietane is a class of diterpenoids with excellent metabolic profile. Compounds of this class showed broad spectrum antiviral, antibacterial, and antifungal activity [36, 37]. Abietane diterpenoids are extracted from few fungal species [38]. The intervention of quinone methides in the antioxidant activity of the phenolic diterpenoids ferruginol and carnosic acid has been discussed. The antifungal activity of some abietic acid esters in the context of their use as wood preservatives and the antiviral activity of podocarpic acid derivatives have been examined. In case of human cells, antiproliferative effect on tumor cells has been reported [39].

About 200 compounds of this family have been identified commonly known as dehydroabietic derivatives (dehydroabietanes) [40] assuming 20-carbon saturated aromatic ring I, abietane as standard (**Figure 6**).

3.2.1.1. Tricyclic abietatrienes

This group of abietane terpenes includes a tricyclic ring, three double bonds on B or C rings. Carboxylic acids are representatives of this group, of which the earliest example is the biologically active dehydroabietic acid (**Figure 6**), which possess an acid group at C-18 [42].

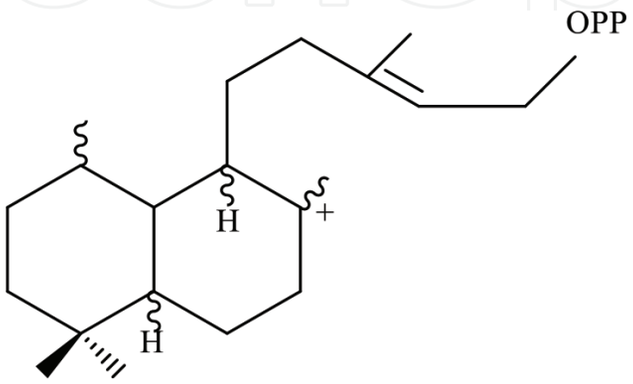


Figure 4. Skeleton of labdanes.

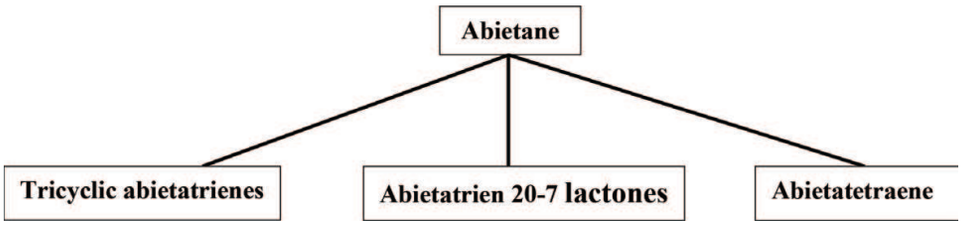


Figure 5. Classification of tricyclic abietane diterpenes.

3.2.1.1.1. Abietic acid

Abietic acid was extensively studied in various organisms for its biological activities. Current data also suggest that abietic acid is an important compound for synthesis of novel metabolites. They contribute to the body of knowledge related to compound 1 and deepen the understanding of the potential and properties of 1 and its derivatives (**Figure 7**).

3.2.1.1.2. Dehydroabietic acid

Dehydroabietic acid displays not only antiulcer and antimicrobial properties but also antitumor and anti-inflammatory effects (compound 2). Antimicrobial effects of DHA have been studied, specifically against methicillin-resistant strains of *Staphylococcus aureus* [43].

Biological activity: It also showed activity against other Gram-positive organisms such as *Salmonella* sp., *Bacillus subtilis*, and *E. coli* [44]. This latter study also described the inhibition of nitric oxide (NO) production by DHA, which was reported by other researchers as well [49]. Kawada et al. [45] have reported in relation with the inhibition of pro-inflammatory cytokines that DHA is useful for treating obesity-related diseases.

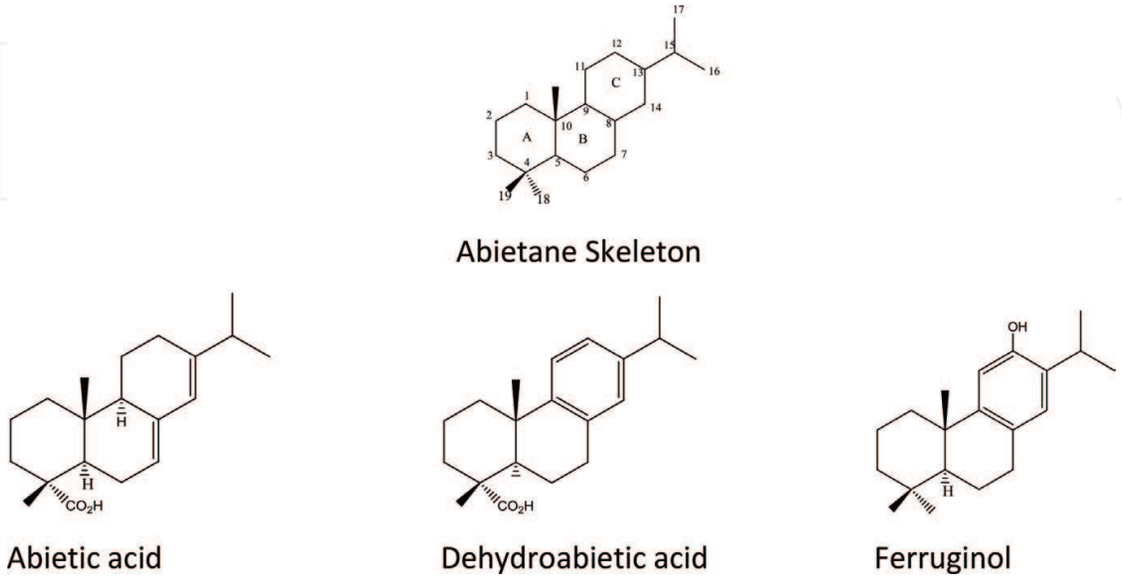


Figure 6. Abietane skeleton with some standard compounds [41].

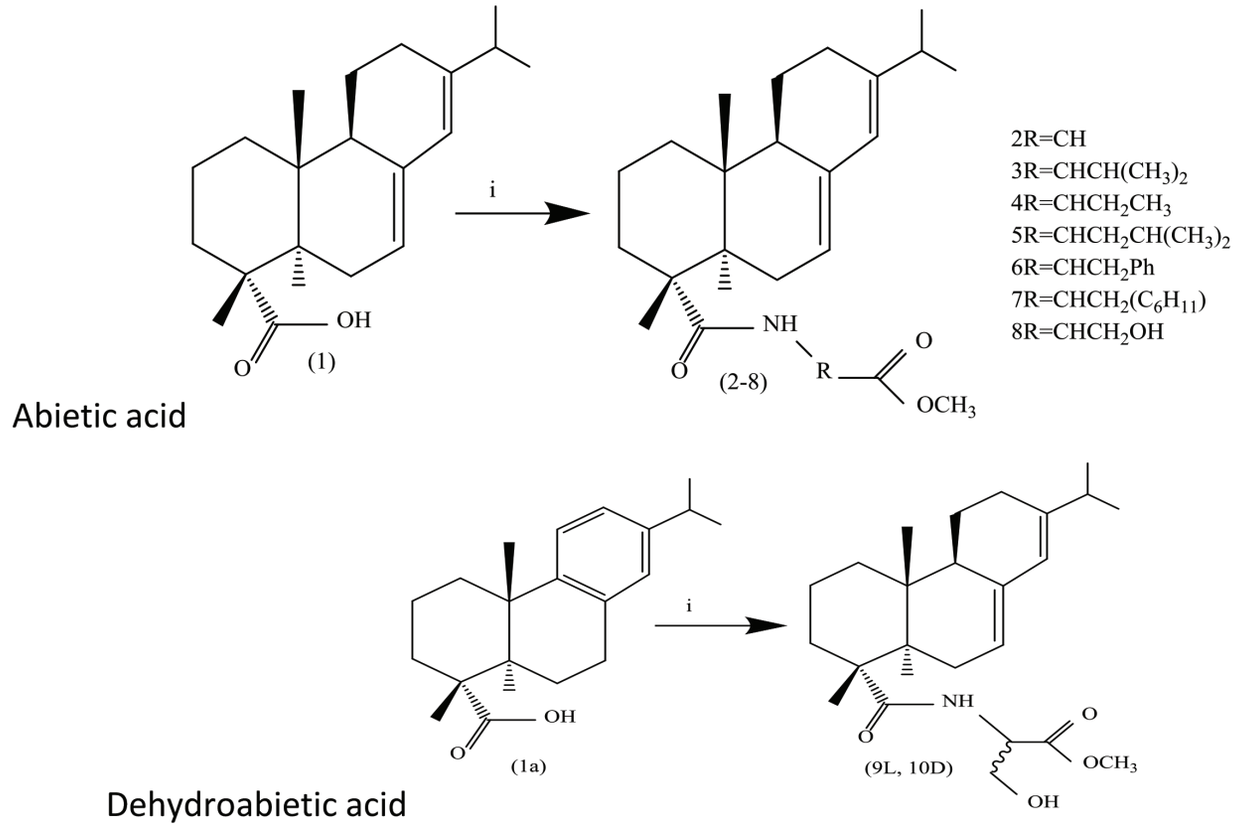


Figure 7. Synthesis of compounds 2–10 [42].

3.2.1.1.3. Ferruginol

Ferruginol (abieta-8, 11, 13-triene-12-ol) is the simplest phenolic abietane diterpenoid (3). This abietane occurs in plants belonging to the Podocarpaceae and Lamiaceae families [22].

Biological activity: This diterpene has attracted much attention since it has exhibited important bioactivities, such as antimicrobial [46], miticidal [47], cardioactive [48], and antioxidative [49]. Moreover, it accelerates the gastric ulcer healing process, and such effects have been related with the ability of ferruginol to increase the gastric prostaglandin content in vitro [50–52].

3.2.1.1.4. Callitrisic acid

Callitrisic acid is a diterpenoid acid contained in the resins of several *Callitris* species (Cupressaceae). It was simultaneously reported as a new natural product [53, 54]. This acid also occurs in plants of the genus *Juniperus* and *Calceolaria*, and it has also been found in the genus *Illicium*. Recently, a series of related acids to callitrisic acid having a C-19 carboxylic group have been isolated [55].

Biological activity: All these acids demonstrated important antiviral activity and significant anti-inflammatory activity [56].

3.2.2. Abietatriene 20-7 lactones

The abietatriene lactones are a group of compounds which possess an oxygen-containing ring which predominantly is in the form of lactones (i.e., abietatrien-20,7-olides). This group

of abietanes are exemplified by carnosol (11,12-dihydroxy-8,11,13-20,7-olide). Carnosol possesses an aromatic C ring, carbon C-20 is a keto group, and carbons C-11 and C-12 are hydroxy groups. This abietane has displayed several biological activities. It displayed antioxidant, antimicrobial, anti-inflammatory, antitumor, and anti-HIV (IC50 = 8.0 μM) properties [57, 58].

3.2.3. Abietatetraenes

The abietatetraenes are a group of compounds which possess a fourth double bond which can be located at different positions. Among the 5,6-dehydro derivatives are coleon C and coleon U and related compounds (**Figure 8**). These metabolites are common in plants of the genus *Coleus* (synonym *Plectranthus*) and have described to possess antitumor, antimicrobial, and antiproliferative activity [59, 60] (**Table 1**).

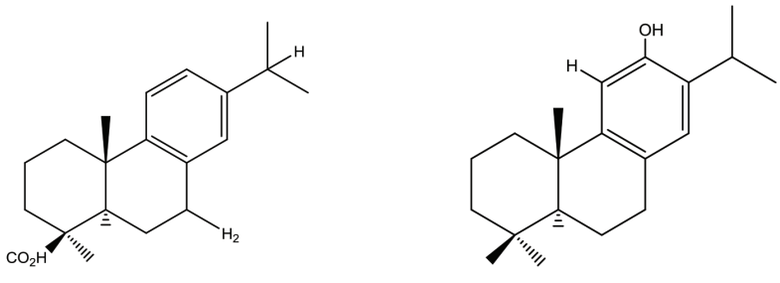
3.3. Tetracyclic diterpenoids

3.3.1. Cythane diterpenes

Cyathus is a genus of fungi in the Nidulariaceae, a family collectively known as the bird's nest fungi. Such compounds are named so, as they resemble tiny bird's nests filled with "eggs," structures large enough to have been mistaken in the past for seeds. The first cyathin A_3 and allocyathin B_3 were reported from fungus *C. helenae* in 1972, and since then a number of other diterpenes being isolated and documented from different species belong to genus *Cyathus* [61]. In particular, the species belonging to the genus *Cyathus* is recognized as prolific producer of bioactive cyathane diterpenoids with inimitable tricyclic ring skeleton [62]. Cyathane diterpenoids also represent a group of natural products with versatility both in structure and bioactivity [63, 64]. Cyathane diterpenes are important bioactive metabolites extracted from the genus *Cyathus*, *Hericium*, and *Sarcodon*. Genus *Cyathus* is beneficial in producing healthy food and possesses the potential of nitric oxide (NO) inhibition and antibacterial activities [64].

3.3.1.1. Diversity of cythane diterpenes

A number of other biologically significant cyathane diterpenoids have been isolated from the fruiting bodies of mushroom *Sarcodon scabrosus* [65–67], *Sarcodon glaucopus* [68, 69], and *Sarcodon cyrneus* [70, 71] and the culture of fungi *C. helenae* [72], *C. africanus* [73], *C. earlei*



Callistric acid (11) **Pisiferic acid (12)**

Figure 8. Representative member of tricyclic abietatrienes *Callitris* species.

Carbon number	Compound B2[a]	Compound B3[b]	B4[b]	Q1[b]	Q2[b]	2[b]	3[b]	4[b]	5[b]	6[a]	7[b]	8[b]	9[b]	10[b]
1	24.6	21.4	23.5	23.5	23.5	14.3	14.2	9.8	14.3	14.3	14.3	14.3	16.3	16.3
2	37.6	30.2	35.8	36.1	36.1	17.1	17.1	14.3	17.1	17	17.1	17.1	18.6	18.6
3	215.7	72.2	213.5	214.4	214.3	18.4	18.1	17.1	18.4	18.4	18.4	18.4	21.1	21.0
4	83.0	79.0	83.0	81.4	81.3	21.0	18.4	18.4	21.0	21.0	21.0	21.0	23.9	23.9
5	46.7	43.1	48.9	45.6	45.6	21.6	19.1	21.0	21.6	21.6	21.6	21.6	25.2	23.9
6	41.7	41.4	71.9	37.3	37.1	22.7	20.9	21.6	22.2	22.6	22.6	22.6	30.0	25.2
7	70.1	70.0	34.4	72.2	77.4	25.4	21.5	22.6	22.6	25.3	25.4	25.5	33.4	30.0
8	45.9	44.9	35.3	41.8	41.8	27.6	22.6	25.4	23.0	27.6	26.3	27.6	37.1	33.4
9	44.0	42.8	42.0	42.7	42.7	34.8	25.5	25.6	25.2	34.8	26.4	34.8	37.2	37.1
10	42.7	42.0	41.2	41.0	40.9	35.0	27.5	27.6	25.4	35.0	26.5	35.1	37.9	37.2
11	48.3	47.4	46.8	47.1	47.0	37.7	31.3	34.8	27.6	37.7	27.6	37.5	45.6	37.9
12	197.4	194.8	196.8	194.5	194.3	38.5	34.7	35.0	34.8	38.1	32.7	38.4	47.4	45.6
13	131.0	129.6	129.6	129.5	129.5	41.7	35.0	37.7	35.0	38.4	33.7	45.9	52.6	47.4
14	109.4	108.8	108.8	108.8	108.8	45.9	37.8	38.4	37.8	45.7	34.6	46.6	54.8	52.6
15	146.1	144.5	144.7	144..6	144.7	46.5	38.4	45.8	38.5	46.5	34.8	51.1	63.6	54.8
16	149.9	147.0	147.1	147.0	147.1	51.1	45.6	46.5	41.8	51.1	35.0	53.0	123.9	63.5
17	12.2	11.8	16.3	11.6	11.6	52.4	46.6	51.1	45.8	52.4	37.7	55.3	124.0	123.9
18	22.2	16.0	22.0	22.0	21.9	120.7	51.0	52.14	46.5	53.4	38.5	63.9	126.8	124.0
19	16.7	16.1	9.4	15.9	19.0	122.6	52.1	53.6	51.1	120.7	40.1	120..5	134.5	126.8
20	19.2	18.8	17.8	19.0	15.8	135.7	57.3	120.6	52.3	122.6	45.8	122.5	145.7	134.5
21						145.3	120.5	122.6	120.7	127.3	46.5	135.7	146.7	145.7
22						170.3	122.6	135.7	122.6	128.8	50.4	145.5	171.1	146.8
23						178.8	135.6	145.3	135.7	129.4	51.1	171.3		171.2

Carbon number	Compound B2[a]	Compound B3[b]	B4[b]	Q1[b]	Q2[b]	2[b]	3[b]	4[b]	5[b]	6[a]	7[b]	8[b]	9[b]	10[b]
24							145.2	173.4	145.3	135.6	52.4	179.4		179.1
25							172.9	178.2	174.0	136.3	120.6			
26							178.2		178.3	145.2	122.6			
27										172.6	135.7			
28										178.1	145.3			
29											174.1			
30											178.2			
Ref	**[30]**	**[30]**	**[30]**	**[30]**	**[30]**	**[42]**	**[42]**	**[42]**	**[42]**	**[42]**	**[42]**	**[42]**	**[42]**	**[42]**

[a]^{13}C-NMR at 125 MHz.

[b]^{13}C-NMR at 75 MHz in $CDCl_3$.

Table 1. ^{13}C-NMR data of New Clerodane Diterpenes from Fungal Biotransformation of the3,12-Dioxo-15,16-Epoxy-4-Hydroxycleroda-13(16),14-Diene and abietane diterpenoids.

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[74], *C. striatius* [75], *Strobilurus tenacellus* [76], and *Hericium erinaceus* [77–84]. Some cyathane diterpenoids represented interesting and significant biological activities.

3.3.1.1.1. Cythane diterpenes from Cyathus gansuensis

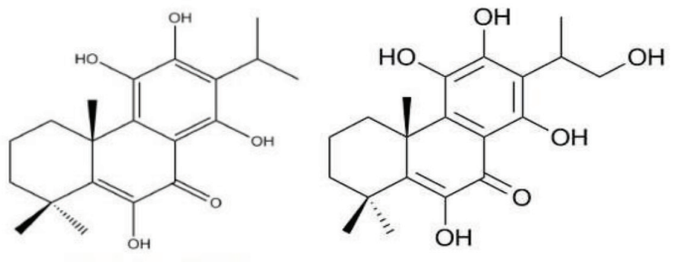
Cyathus gansuensis was reported in 2002 and produced valuable bioactive metabolites from fermented grains of barley and rice [13] by transformation. Recently, seven new [85] metabolites (8–14) named have been isolated from fruiting body of *C. gansuensis* as presented in **Figure 9**. The L69 fungal strain was used to isolate these compounds (8–14).

Biological activity: NO inhibition activity was tested on mouse monocyte, macrophages. Seven newly discovered cyathane diterpene derivatives showed inhibitory activity against the NO production in LPS-activated macrophages. The fungus can be a good choice for a transformation on a large scale to acquire enough pure metabolites for the future [85].

^{13}C-NMR structural elucidation: The detail of ^{13}C-NMR is presented in **Table 2**. ^{13}C-NMR data for compounds 8–14 revealed 20 carbons ascribable for 4 methyls, 4 methylenes (one oxygenated), 4 methines (two oxygenated), two quaternary carbons, and six sp^2 carbons. According to NMR and HRTOFMS at m/z 341.2079, [M + Na] + presented molecular formula of 8 and 9 (cyathin J and K) as $C_{20}H_{30}O_3$ (six degrees of unsaturation), 10 (cyathin L) $C_{22}H_{32}O_5$ (seven degrees of unsaturation degrees), 11 (cyathin M) $C_{20}H_{30}O_5$ (six degrees of unsaturation), 12 (cyathin N) $C_{20}H_{28}O_5$ (seven degrees of unsaturation), 13 (cyathin O) $C_{20}H_{30}O_5$ (six degrees of unsaturation), and 14 (cyathin P) $C_{20}H_{28}O_5$ (seven degrees of unsaturation) [85].

3.3.1.1.2. Cythane diterpenes from Cyathus africanus

Cyathus africanus is a medicinal basidiomycete fungus. Diterpenes have been reported to possess multiple bioactivities consisting of antimicrobial and anti-inflammatory properties [86]. The presently reported metabolites in this text are collected by the study of various scientists. Moreover, they have been characterized on the basis of their structural elucidation by spectroscopic methods and discussed in detail in this chapter (**Table 2**). Some of the new metabolites documented by various scientists are isolated from *C. africanus*. Cyathin Q (15) an important metabolite (**Figure 10**) showed autophagy-dependent apoptosis [87]. The gene sequence of this



Coleon U (13) **Coleon C (14)**

Figure 9. Representative members of abietatetraenes.

Carbon number	Compound 8[a]	9[a]	10[a]	11[a]	12[a]	13[a]	14[a]	15[c]	16[c]	17[c]	18[c]	19[c]	20[c]	21[c]	22[c]	23[c]
1	145.9	145.9	39.8	83.7	84.3	53.4	84.5	38.6	39.9	38.8	34.9	33.8	33.7	83.8	82.1	53.0
2	129.0	129.2	29.4	209.7	209.0	211.1	209.6	29.3	29.7	29.7	23.7	23.2	22.8	209.8	75.3	210.6
3	142.3	142.9	140.4	141.8	140.7	145.0	142.6	140.8	144.9	141.8	79.2	77.4	77.5	141.9	140.7	144.4
4	146.2	147.3	139.2	176.2	177.0	177.1	172.5	140.6	144.0	139.9	78.5	77.0	76.6	176.4	146.7	179.6
5	44.1	41.6	41.7	46.8	142.6	41.0	41.4	38.5	152.7	36.5	36.0	37.6	31.8	47.0	45.8	45.6
6	45.7	44.8	45.1	45.0	49.4	46.5	45.3	47.2	48.6	45.1	46.2	43.6	42.8	45.2	43.4	58.2
7	29.2	34.1	31.0	28.9	29.7	29.5	29.8	35.8	33.8	35.1	33.7	28.0	32.3	29.1	28.9	35.5
8	33.6	34.1	38.4	37.2	35.3	37.3	35.2	36.2	38.0	17.5	31.2	31.7	30.8	37.4	38.1	39.0
9	55.8	55.8	50.6	47.7	47.6	43.0	47.1	51.2	50.3	50.9	43.6	42.6	42.2	47.9	50.9	43.6
10	29.1	38.5	30.5	28.2	124.4	27.6	32.2	30.3	121.3	32.1	24.8	26.2	25.7	28.4	29.2	27.0
11	130.0	72.6	72.0	128.6	118.2	74.6	76.6	160.2	135.8	72.2	159.9	160.5	69.9	128.8	129.8	39.2
12	143.1	147.8	129.7	143.7	149.6	55.9	49.3	144.7	130.1	146.8	145.2	142.4	146.0	143.8	143.3	156.5
13	69.2	125.9	150.5	69.1	71.4	71.8	70.2	78.5	33.5	159.1	78.2	79.5	157.6	69.3	69.1	127.3
14	81.5	76.7	76.2	80.6	81.9	106.4	107.4	75.5	76.5	77.4	74.8	80.2	76.0	80.8	91.3	209.2
15	66.6	64.8	169.4	66.3	63.1	60.6	62.2	196.2	172.1	194.7	196.1	194.2	192.9	66.5	66.6	26.9
16	17.8	17.3	17.2	17.8	24.9	13.6	13.4	17.7	27.0	16.7	18.9	19.7	17.7	18.0	18.0	16.4
17	19.2	19.3	25.1	20.3	21.0	26.3	22.3	24.8	24.2	24.7	19.9	20.0	19.5	20.4	20.6	23.9
18	27.4	27.4	28.4	27.0	26.8	26.3	26.3	28.5	28.2	28.5	29.1	28.1	28.3	27.2	28.4	27.2
19	22.6	23.2	21.9	19.8	20.5	20.7	20.2	21.8	21.9	22.2	19.7	19.4	19.3	20.0	22.5	19.8
20	23.4	23.4	22.4	20.3	21.3	20.8	21.4	22.6	22.0	22.6	19.9	19.6	19.8	21.6	23.2	21.2
21			172.3					28.0		57.3	57.9	59.3	57.1			
22			21.1													
Ref.	**[85]**	**[85]**	**[85]**	**[85]**	**[85]**	**[85]**	**[85]**	**[87]**	**[88]**	**[88]**	**[88]**	**[88]**	**[88]**	**[89]**	**[89]**	**[89]**

http://dx.doi.org/10.5772/intechopen.79186

Carbon number	Compound 8[a]	9[a]	10[a]	11[a]	12[a]	13[a]	14[a]	15[c]	16[c]	17[c]	18[c]	19[c]	20[c]	21[c]	22[c]	23[c]
Carbon number	**Compound 24e**	**25[d]**			**26[d]**	**27[d]**	**28[d]**	**29[d]**	**30[d]**		**31[d]**	**32[d]**	**33[d]**	**34[f]**	**33[a]**	
1	213.7	53.1			88.5	47.0	82.8	84.5	90.5		215.4	216.0	53.3	38.5	38.3	
2	127.0	211.1			83.5	72.8	37.2	209.5	83.3		125.8	126.4	210.9	28.4	29.1	
3	188.5	144.2			140.2	77.8	137.2	141.6	139.6		192.3	193.2	144.9	139.9	140.7	
4	84.0	181.7			141.4	78.2	137.8	174.0	140.1		53.3	53.5	177.0	136.6	139.8	
5	43.7	43.2			39.0	37.1	41.6	43.3	41.3		38.9	37.5	40.5	40.4	36.1	
6	52.9	45.8			56.6	54.6	42.6	44.9	42.8		42.7	41.9	46.0	40.6	44.5	
7	33.1	32.0			34.8	34.7	31.0	30.5	30.9		29.7	29.9	29.7	30.4	34.3	
8	34.5	39.3			30.2	33.7	36.2	35.3	36.1		30.3	30.8	37.1	37.0	37.1	
9	54.0	43.5			48.7	42.6	49.9	47.3	47.2		50.2	50.4	42.9	49.2	50.4	
10	34.8	36.6			37.0	32.3	28.3	27.6	28.2		29.9	33.3	31.5	30.1	35.0	
11	73.0	71.6			72.4	72.3	80.0	79.9	79.9		74.6	76.9	76.3	72.4	62.1	
12	157.5	145.9			157.0	157.3	149.0	149.2	149.2		64.0	49.7	49.8	138.6	148.2	
13	122.6	127.3			123.2	123.2	126.6	126.9	126.6		57.0	70.6	70.2	158.2	154.6	
14	209.7	76.2			210.6	210.1	111.2	110.8	111.1		104.8	108.2	107.4	85.4	85.3	
15	64.4	65.0			64.5	64.4	58.9	58.9	58.9		59.1	62.1	62.0	192.9	194.2	
16	17.4	17.1			15.6	17.9	12.0	12.2	12.2		14.6	16.1	13.2	16.4	16.4	
17	14.5	24.3			23.6	20.7	17.3	22.4	19.6		20.5	22.4	26.0	24.5	24.7	
18	31.2	26.7			28.2	29.8	27.5	26.3	27.2		33.0	33.0	26.2	27.0	27.7	
19	22.2	21.0			24.3	20.5	21.2	20.2	19.3		23.4	21.0	20.5	21.5	22.0	
20	25.3	20.1			19.6	20.4	22.6	21.2	24.6		21.0	23.3	20.6	21.8	22.3	
21														56.6	***	
1′														105.3	106.3	

Carbon number	Compound 8[a]	9[a]	10[a]	11[a]	12[a]	13[a]	14[a]	15[c]	16[c]	17[c]	18[c]	19[c]	20[c]	21[c]	22[c]	23[c]
2′														73.5	74.6	
3′														69.6	70.3	
4′														75.5	73.3	
5′														65.1	65.0	
Ref.	**[90]**	**[90]**			**[90]**	**[90]**	**[90]**	**[90]**	**[90]**		**[90]**	**[90]**	**[90]**	**[96]**	**[96]**	

[a]^{13}C NMR at 125 MHz.

[b]^{13}C NMR at 75 MHz in CDCl3.

[c]^{13}C NMR at 150 MHz CD3OD.

[d]^{13}C-NMR spectroscopic data for compounds 24–33 in MeOH at 200 MHz.

[e]^{13}C-NMR at 125 MHz.

[f]^{13}C-NMR 175 MHz in acetone-d6.

Table 2. ^{13}C-NMR data of cyathane diterpenoids.

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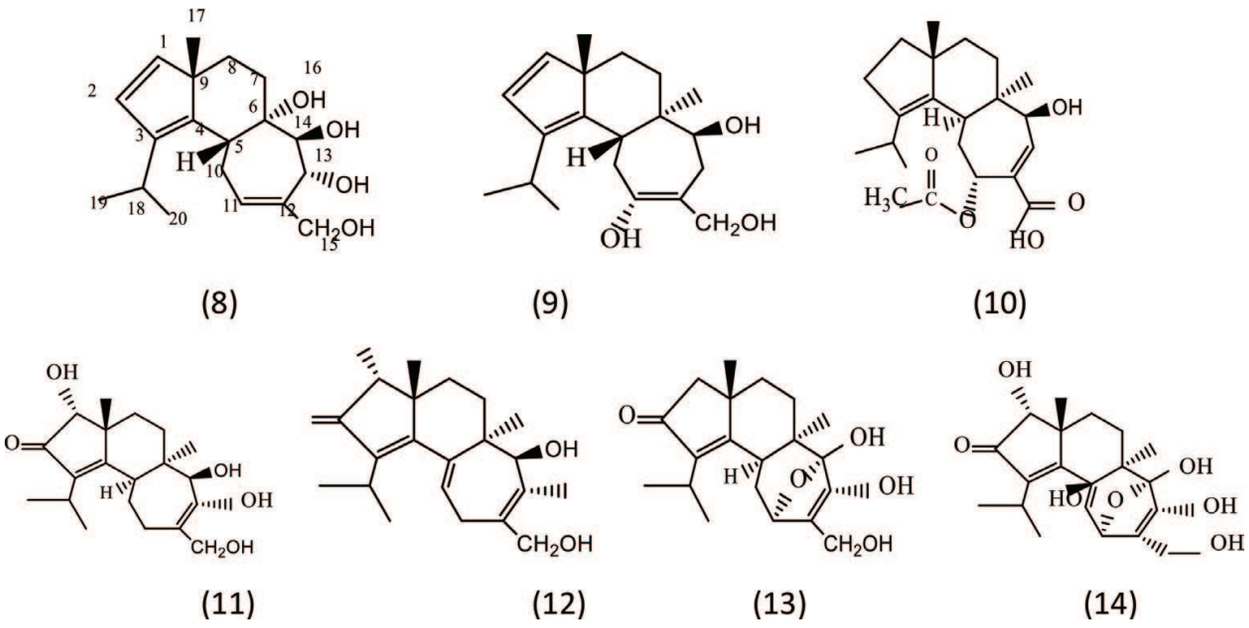


Figure 10. Newly (8–14) isolated metabolites from *C. gansuensis* [85].

strain has also been reported and submitted to GenBank with an accession numbers JX103204. Sequences of analysis exhibited 100% homology with that of fungus *C. africanus*. Compounds 16–20 (D–H) structurally represented new group of metabolites, while neosarcodonin O (21), cyathatriol (22), and 11-O-acetylcyathatriol (23) are also known cyathane diterpenes. Five novel compounds are isolated from *C. africanus* and show potential NO inhibition and cytotoxicity against HeLa cell line in vitro [88]. The structural elucidation is also described in **Figure 11**.

Ten new polyoxygenated cyathane diterpenoids, named as neocyathins (24–33), together with four known diterpenes are isolated from fungus *Cyathus africanus* (**Figure 12**). These compounds were isolated and identified by ^{13}C-NMR technique [90] (**Figure 13**).

Biological activity: Diterpenes with diverse bioactivities have been identified from plants and fungi [91]. Cyathin Q has the capacity to induce the apoptosis in HCT116 cells in a time- and dose-dependent manner. It was observed, when HCT116 cells exposed to 10 mM cyathin Q for 24 h exhibited apoptotic cells 82.07% [87]. This compound induced hallmarks of apoptotic events in HCT116 cells, including caspase activation, cytochrome c release, poly (ADP-ribose) polymerase (PARP) cleavage, and depolarization of the mitochondrial inner transmembrane potential. Nitric oxide has the capacity to react with aqueous oxygen,

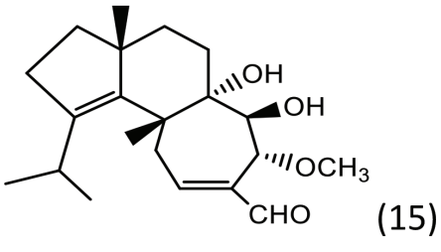


Figure 11. Structures of cyathane Q (15) isolated from *C. africanus* [87].

http://dx.doi.org/10.5772/intechopen.79186

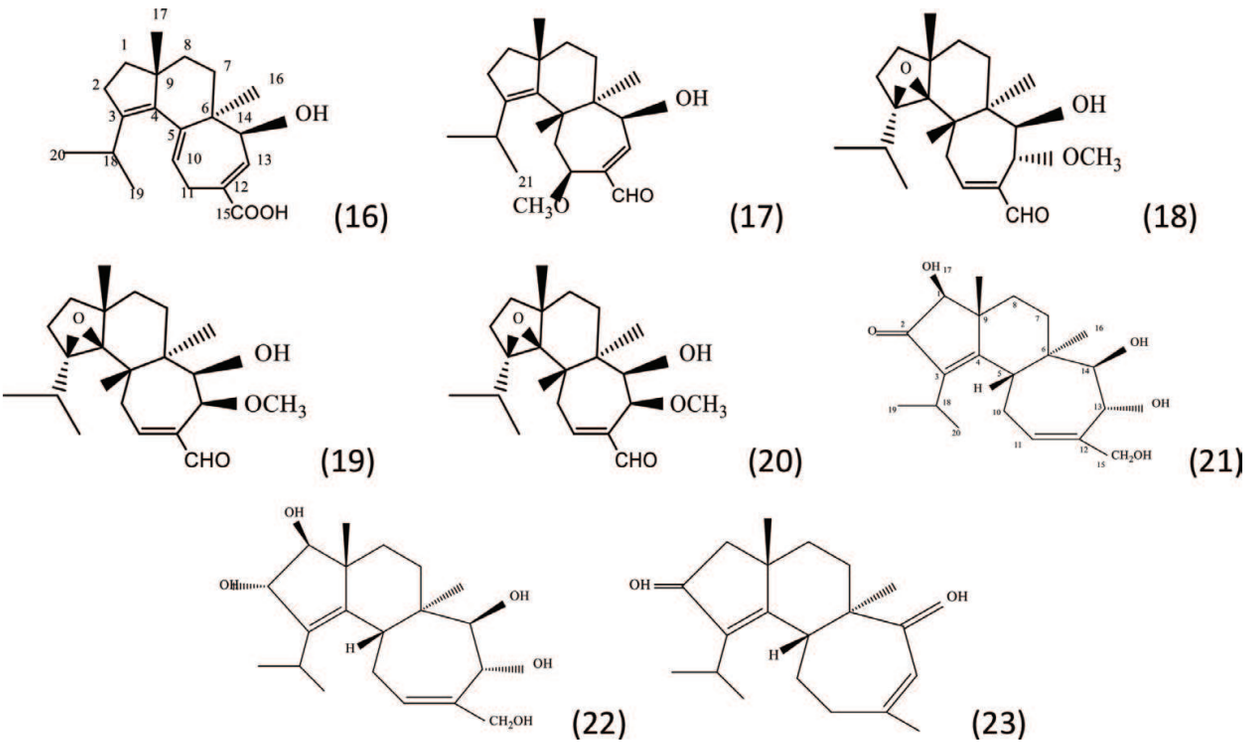


Figure 12. Structures of metabolites isolated from *C. africanus* [88, 89].

superoxide, and transition metals like iron or zinc-sulfur clusters, and overproduction of NO is involved in many pathogenic diseases, including inflammation and cancer. The inhibition of NO overproduction in cells may prevent the occurrence of inflammatory diseases and cancer. The inhibition capacity (IC50) was more pronounced for 16, 17, and 19 by exhibiting NO inhibition 79.44, 89.2 and 84.33% reduction, respectively [91]. Moreover, inhibition of NO is concentration dependent as compounds 16–23 showed no NO inhibition at concentration 100 μM [88, 89]. COX-2 and iNOS are two major inflammatory mediators in brain neurodegeneration [92, 93]. Compounds isolated from *C. africanus* [90] showed strong COX-2 and iNOS capacities. Western blot analysis demonstrated that compounds 24 and 28 significantly suppressed LPS-induced COX-2 expression, whereas compounds 27, 28, 30, 31, and 33 markedly inhibited LPS-induced iNOS expression. Among these compounds, 28 showed strong inhibitory effects on both COX-2 and iNOS. Interestingly, 30 abolished LPS-induced iNOS expression but did not affect LPS-induced COX-2 expression. In addition, we also assayed the activities of iNOS enzyme [90].

^{13}C-NMR structural elucidation: The ^{13}C-NMR spectrum of some of the compounds isolated from *C. africanus* presented in **Table 2**.

3.3.1.1.3. Cythane diterpene from Hericium erinaceus and H. flagellum

Hericium genus is among the most blessed medicinal and eatable mushrooms and known to produce secondary metabolites with the potential to treat neurodegenerative diseases. It enables improvement of many brain-related disorders [94]. In this regard, neurotrophins are nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) involved

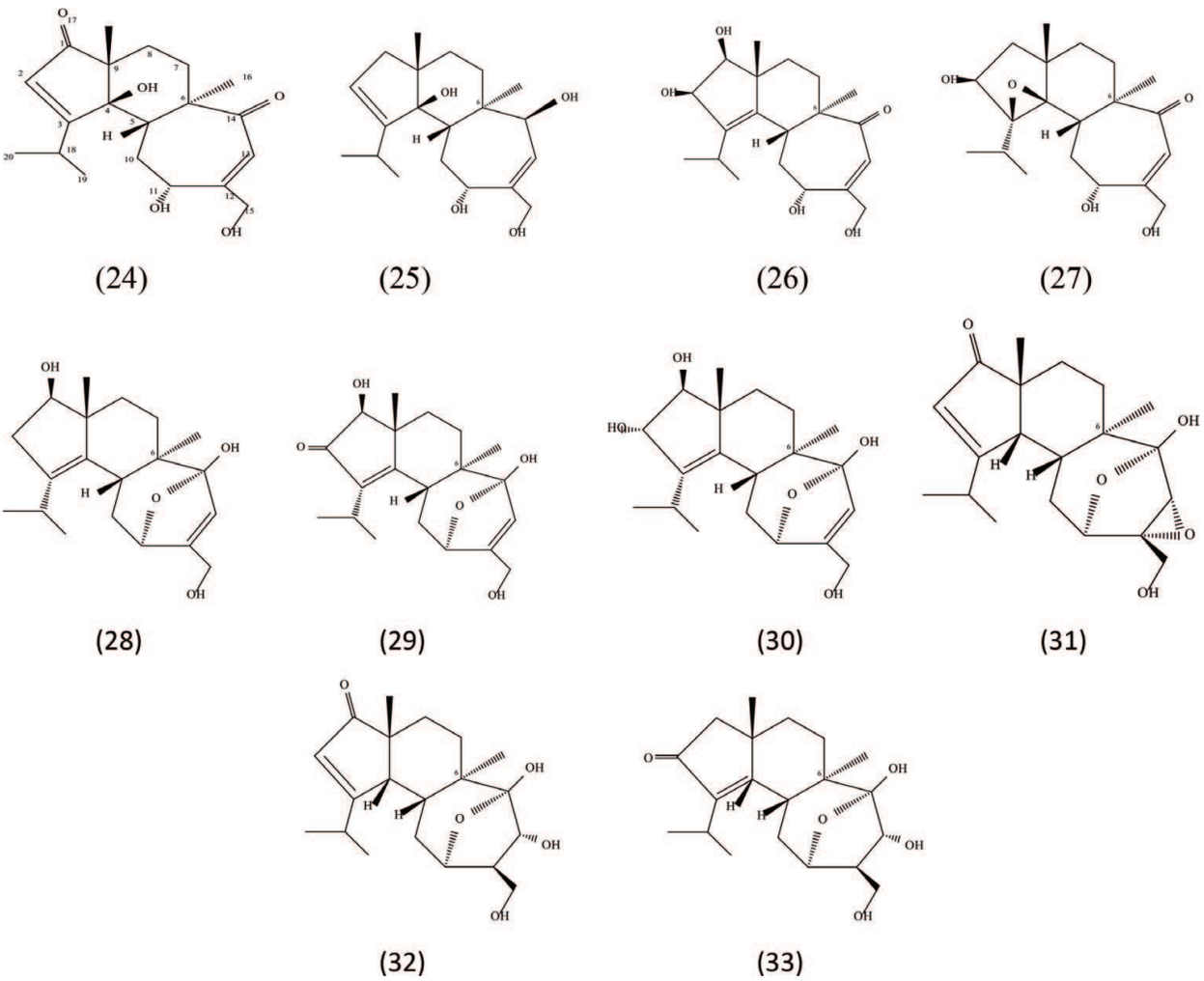


Figure 13. Structures of metabolites isolated from *C. africanus* [90].

in survival, maintenance, and regeneration of specific neuronal populations in the adult brain [95]. Therefore, the metabolites extracted from *Hericium* are important source of metabolites and source as remedy in the fight against neurodegenerative diseases such as Parkinson's, Alzheimer's, and Huntington's diseases, which are accompanied by decreased neurotrophic factor expression [102]. Two new potential metabolites have been isolated from *H. erinaceus* (strain STMA 06157B) and *H. flagellum* (strain CBS 103681) [96] (**Figure 14**).

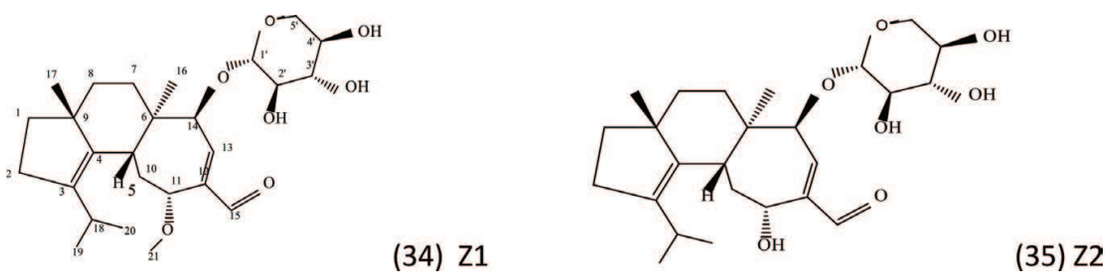


Figure 14. Structural elucidation of metabolites isolated from *H. erinaceus* and *H. flagellum* [96].

Biological activity and ^{13}C-NMR analysis: All of the metabolites isolated from *H. erinaceus* and *H. flagellum* exhibited strong neutrotrophin capacity [95, 96]. Metabolites were also studied through ^{13}C-NMR; compound 34 exhibited the presence of five non-proton-bearing carbons, including three olefinic (δC 139.9, 136.6, 138.6) and two aliphatic carbons (δC 40.6, 49.2). Furthermore, five methylene groups with corresponding carbons between δC 28.4 and 38.5 ppm, a further oxygenated methylene group at δC 65.1, vicinal to two aliphatic methines at δC 40.4, and six methines at δC 69.6–105.3 ppm were observed. ^{13}C shifts and correlations of the HSQC-DEPT spectrum showed high similarity to **35** which was a derivative of the cyathane diterpenoid **34**. The major difference between the two compound spectra was the missing methoxy group at C-11 in **35** (**Figure 13**). The detail of ^{13}C-NMR data is described in **Table 2**.

3.3.2. Indole diterpenes

Indole diterpenes are the broad class of secondary metabolites with enormous structural and functional diversity. They mostly occur in filamentous fungal members having most abundance in *Penicillium*, *Aspergillus*, *Neotyphodium*, and *Claviceps* [97, 98]. This class of diterpenes is generally divided into two main groups, paxilline type and non-paxilline type [98], though it mainly consists of cyclic diterpenoid backbone in addition to an indole moiety.

3.3.2.1. Diversity of indole diterpenes

3.3.2.1.1. Indole diterpenes from Aspergillus nidulans

The marine fungi *A. nidulans* was reported to be the source of 19-hydroxypenitrem A (1) and 19-hydroxypenitrem E (2). The ^{13}C-NMR spectrum of 19-hydroxypenitrem A ($C_{37}H_{44}ClNO_7$) provided 37 resonance states from 5 methyl, 8 methylene (with 2 sp_2 terminal), 1 sp_2 and 7 sp_3 methines (with 5 oxygenated), and 16 quaternary (with 5 oxygenated sp_3 and 9 sp_2) carbon atoms. In comparison, 19-hydroxypenitrem E ($C_{37}H_{45}NO_7$) lack chlorine atom but have one additional hydrogen atom [98] (**Figure 15**).

3.3.2.1.2. Drechmeria sp.: a rich source of indole diterpenes

An endophytic fungi *Drechmeria* sp. was found to be the reservoir of diverse indole diterpenes including drechmerin A (38), drechmerin B (39), drechmerin C (40), drechmerin D (41),

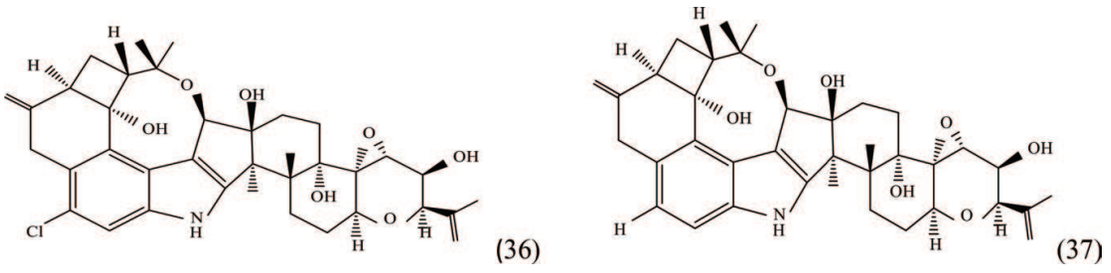


Figure 15. Indole diterpenes from *A. nidulans* [98].

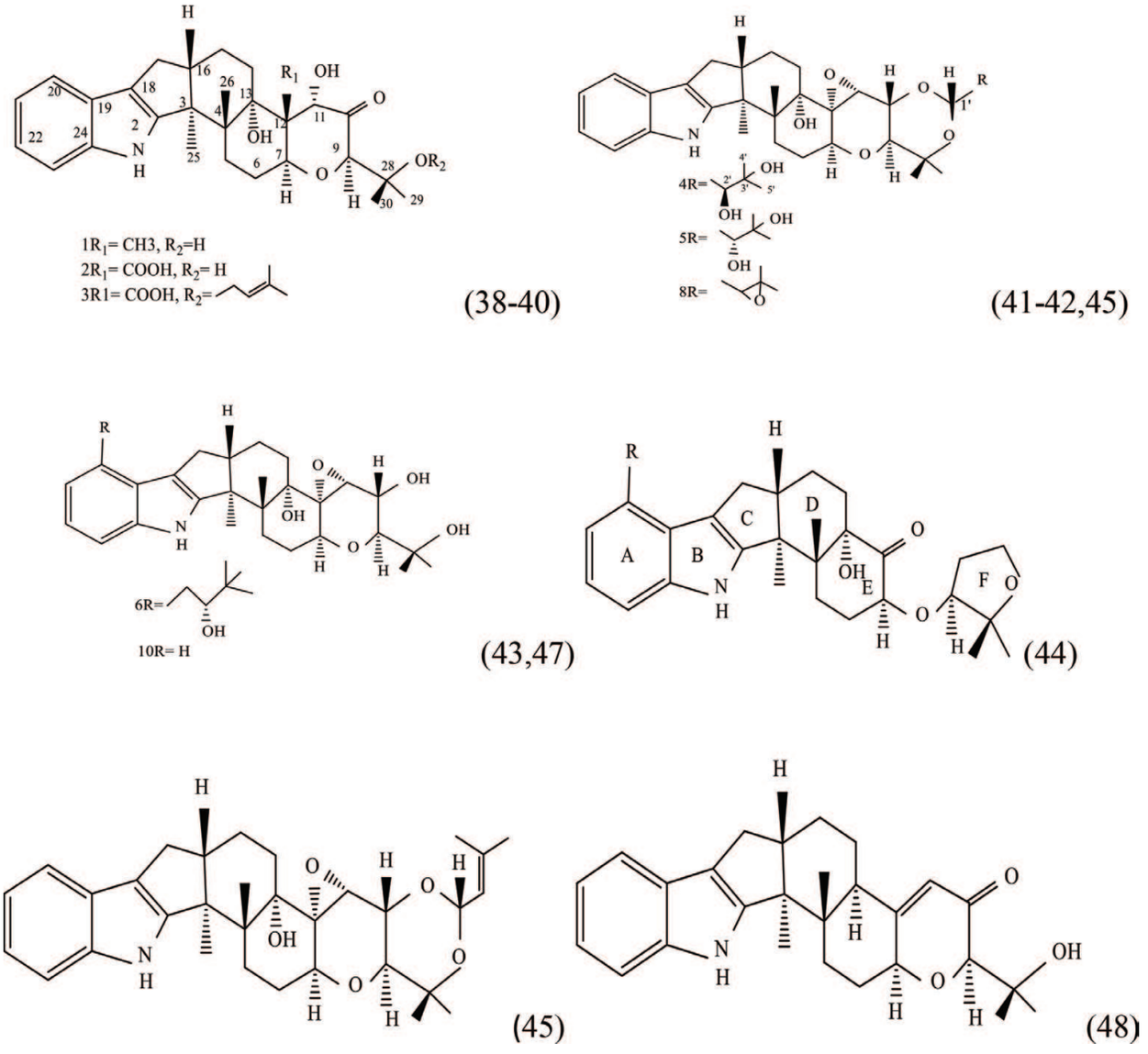


Figure 16. Indole diterpenes from (1–11) *Drechmeria* sp. [99].

drechmerin E (42), drechmerin F (43), drechmerin G (44), terpendole A (45), terpendole C (46), terpendole I (47), and dehydroxypaxilline (48) [99] (**Figure 16**).

The ^{13}C-NMR spectrum of drechmerin exhibited 28 carbon resonances, comprising 8 aromatic carbons, 4 oxygenated carbons, 6 methylene carbons, 2 methine carbons, 3 quaternary carbons, and 5 methyl carbons [100]. The detail of ^{13}C-NMR data is given in **Table 3**.

3.3.2.1.3. Indole diterpenes from marine A. flavus

The marine *Aspergillus flavus* had provided 4b-deoxy-β-aflatrem (1),9-isopentenyl paxilline (2), 6,8-di-*O*-methylcitreoisocoumarin (3), β-aflatrem (4), and paspaline (5). 4b-Deoxy-β-aflatrem

Carbon Number	Compound 36[g]	37[g]	38[c]	39[c]	40[c]	41[c]	42[c]	43[c]	44[c]
2	152.2	151.3	152.6	152.2	152.3	153.8	153.8	153.5	150.7
3	116.7	116.4	54.7	53.8	53.9	52.1	52.1	51.8	51.9
4	132.7	131.0	41.1	40.9	40.9	43.9	43.9	43.7	46.6
5	123.4	125.9	34.0	34.1	34.1	27.5	27.5	27.4	33.2
6	122.6	118.9	26.5	26.4	26.5	29.8	29.8	29.5	32.3
7	110.4	110.3	79.3	77.7	77.9	73.1	73.1	73.0	84.5
8	120.3	121.1	***	***	***	***	***	***	***
9	138.5	138.9	80.6	79.9	78.4	72.7	42.7	77.7	88.6
10	33.7	37.1	31.0	32.5	32.7	72.9	72.7	68.7	74.1
11	148.7	150.0	71.1	68.3	68.5	61.4	61.4	65.0	175.8
12	45.4	45.7	42.0	53.6	53.6	68.9	69.0	70.7	212.8
13	23.9	24.0	39.2	41.6	41.6	78.8	78.9	78.6	52.2
14	52.9	53.0	22.9	24.9	24.8	30.6	30.6	30.8	23.8
15	80.3	80.4	25.7	26.3	26.3	22.0	22.0	22.0	24.7
16	74.6	74.6	50.4	50.5	50.5	51.6	51.6	51.7	50.5
17			28.6	28.4	28.4	28.2	28.3	30.7	28.2
18	79.5	79.8	118.0	118.1	118.1	117.2	117.3	116.7	118.3
19	86.9	87.0	126.4	126.4	126.4	126.5	126.5	126.4	126.3
20	27.7	27.7	118.8	118.9	118.9	118.9	118.9	131.7	119.0
21	23.4	23.4	119.8	119.8	119.8	119.8	119.8	121.0	120.
22	75.9	76.0	120.8	120.9	120.9	120.8	120.8	121.0	121.2
23	64.8	64.8	112.8	112.8	112.8	112.7	112.7	110.8	112.8
24	60.0	60.0	142.2	142.2	142.2	141.9	141.9	142.0	142.2
25	64.7	64.7	15.0	15.0	15.0	16.6	16.6	16.5	15.0
26	73.0	73.0	20.4	17.0	17.1	19.1	19.1	19.0	16.4
27	***	***	14.1	178.2	178.2	***	***	***	***
28	69.7	69.8	73.0	72.8	77.7	76.2	76.1	73.7	16.4
29	29.0	29.0	25.5	26.4	23.7	28.7	28.8	27.5	84.0
30	27.9	28.0	25.9	25.5	22.1	17.2	17.1	25.2	27.8
1′	42.8	42.8			60.1	95.5	96.0	36.4	22.9
2′	53.8	53.9			123.7	77.5	77.6	78.4	
3′	106.8	105.3			136.3	77.9	77.8	79.0	
4′	19.3	19.3			18.2	22.6	22.4	22.0	

Carbon Number	Compound 36[g]	37[g]	38[c]	39[c]	40[c]	41[c]	42[c]	43[c]	44[c]
5′	29.0	29.0			26.1	21.3	21.7	20.6	
36	19.8	19.8							
37	142.5	142.5							
38	110.7	110.7							
39	19.9	19.8							
40	16.9	17.1							
Ref.	[98]	[98]	[99]	[99]	[99]	[99]	[99]	[99]	[99]

[a]^{13}C-NMR at a 125 MHz.

[b]^{13}C-NMR at 75 MHz in $CDCl_3$.

[c]^{13}C-NMR at 150 MHz CD_3OD.

[g]^{13}C-NMR at 125 MHz for ^{13}C, measured in DMSO-d6.

Table 3. ^{13}C-NMR data of indole diterpenoids.

($C_{32}H_{39}NO_3$) exhibits 14 degrees of unsaturation and consists of an indole chromophore and a carbonyl group. As per ^{13}C-NMR spectrum, the respective structure owns resemblance to β-aflatrem, except that a methine replaced an oxygenated quaternary carbon, thereby resulting in an isopentenylated indole diterpenoid. Moreover, 9-isopentenyl paxilline ($C_{32}H_{39}NO_4$) comprised hexacyclic indole diterpenoid skeleton [100] (**Figure 17**).

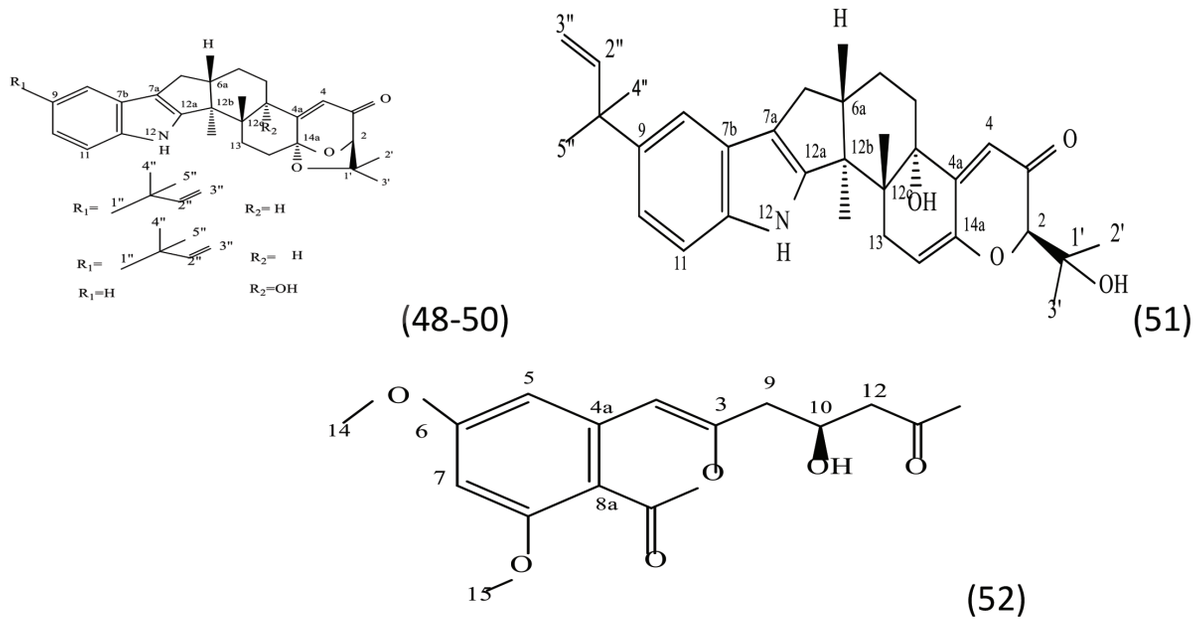


Figure 17. Skeleton by NMR indole diterpenes from *A. flavus* [100].

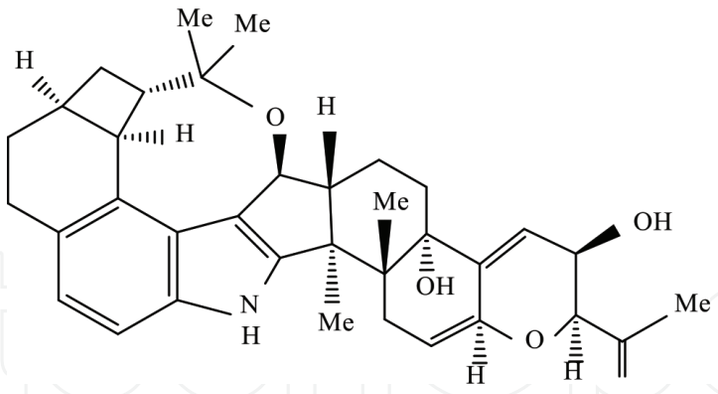


Figure 18. Structure and compound isolated from *P. crustosum* [102].

3.3.2.1.4. Penitrem D from Penicillium crustosum

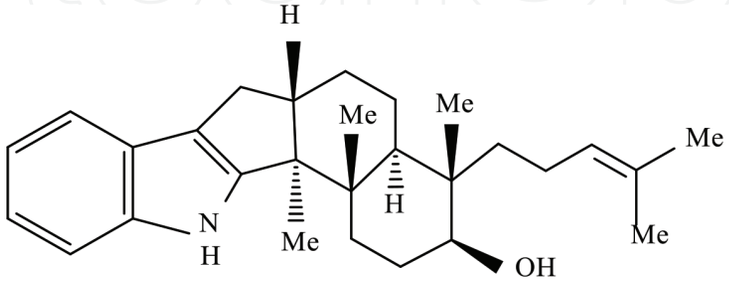
Penitrem D ($C_{37}H_{45}NO_4$) was first isolated from *P. crustosum* in 1983. It is a complex structure with 9 rings, an indole core, and 11 stereocenters [101] (**Figure 18**).

3.3.2.1.5. Emindole SB from Emericella striata

The mycelium of *E. striata* was reported to naturally produce emindole SB ($C_{28}H_{39}NO$). In its structure an indole unit fused to a tricyclic carbon scaffold, and it presented six stereocenters, including vicinal quaternary centers on the western cyclohexyl ring [103] (**Figure 19**).

3.3.2.1.6. Paspaline obtained from Claviceps paspali

The ergot fungus *Claviceps paspali* was found to be the source of paspaline ($C_{28}H_{39}NO_2$) in 1966. The structure owes similarity with emindole SB but contains one more ring comparatively [104] (**Figure 20**).



(54)

Figure 19. Structure and compound isolated from E. striata [103].

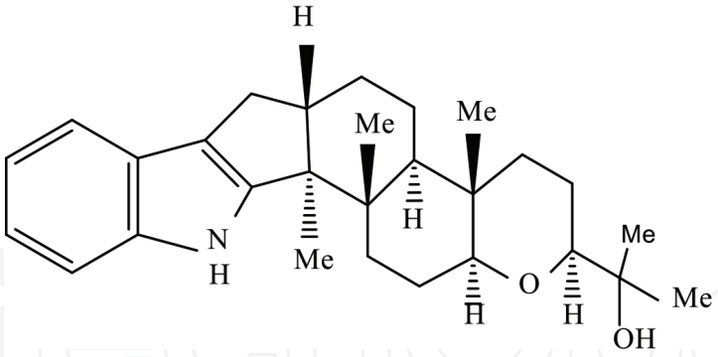


Figure 20. Structure and compound isolate from *Claviceps paspali* [104].

3.3.2.2. Biological activity

The indole diterpenes, famously called tremorgenic mycotoxins, put forward promising insecticidal potential via regulation of their glutamategated chloride ion channels [105], antibiotic activity [107, 108], antiproliferative against human breast cancer cells [109], and antifungal efficacy [110].

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