Spirobisnaphthalenes from Fungi and their Biological Activities

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Abstract: Spirobisnaphthalenes have a unique structural feature involving two or three oxygen atoms acting as bridges connecting two original naphthalene subunits. Most of these metabolites isolated from fungi exhibit significant antifungal, antibacterial and cytotoxic properties to show great potential applications in medicine and agriculture. This review focuses on their structural characters and biological activities, as well as their structure-activity relationship, mechanism of action, synthesis and biosynthesis.

Keywords: Spirobisnaphthalenes, spiroxin, preussomerin, deoxypreussomerin, fungi, biological activities.

INTRODUCTION

Spirobisnaphthalenes (also called bisnaphthospiroketals) belong to a relatively new and rare family of bioactive natural products based on a 1,8-dihydroxynaphthalene derived spiroketal unit linked to a second, oxidized naphthalene moiety [1-3]. Ogish *et al*. first isolated a spirobisnaphthalene named MK 3018 (**28**) from cultures of the fungus *Tetraploa aristata* in 1989 [4]. After that, more and more spirobisnaphthalenes have been isolated from fungi especially for which growing under extreme conditions (e.g. endophytic fungi, freshwater aquatic fungi, and marine fungi). Spirobisnaphthalenes have received a particular attention as their biosynthesis is considered to help these fungi survive from the diverse environmental conditions [5-8].

Spirobisnaphthalenes exhibit an elaborate range of hydroxylation, oxidation, and unsaturation patterns. They possess a wide range of biological properties, including antibacterial [9], antifungal [10], algicidal [2], herbicidal [9], antiplasmodial [11], nematicidal [12], antileishmanial [13], cytotoxic [11] and anti-tumor activities [14]. Some of these compounds have been identified as novel inhibitors of rasfarnesyltransferase [15], DNA gyrase [16], topoisomerase II [17] and thioredoxin-thioredoxin reductase [18], and thus are of interest in terms of their potential in cancer chemotherapy.

On the basis of the structural skeletons, spirobisnaphthalenes can be divided into three types namely spiroxin-, preussomerin- and deoxypreussomerin-type. This review mainly deals with the structural types of spirobisnaphthalenes as well as their biological activities. In addition, structure-activity relationship, mechanism of action, biosynthesis and synthesis, interaction between plants and fungi, as well as the potential applications of these compounds will also be discussed. This report concentrates on work that appeared in the literature from 1989 to December 2009.

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1. SPIROXIN-TYPE SPIROBISNAPHTHALENES AND BIOACTIVITIES

The structures of the spiroxins are described as two partially saturated naphthalene rings joined together by two oxygen bridges and one carbon-carbon bridge. The saturated portion of each naphthalene ring is fused with an epoxide resulting in an unusual octacyclic ring system [14]. There was only five spiroxin-type spirobisnaphthalenes, that were spiroxins A (**2**), B (**3**), C (**1**), D (**4**) and E (**5**), isolated from an unidentified marine-derived fungus LL-37H248 from a soft orange coral collected from the waters of Dixon Bay, Vancouver Island, Canada (Fig. (**1**), Table **1**). Of them, spiroxin A (**2**) showed anti-tumor activity in nude mice against ovarian carcinoma. In evaluating its probable mechanism of action, it was observed that in the presence of either dithiothreitol or 2-mercaptoethanol, spiroxin A (**2**) caused a concentration-dependent nicking of pBR322 DNA, indicating that the compound partly exerted its cytotoxic effect through a single-stranded DNA cleavage. Cytotoxicity of quinones has been attributed to DNA modification, alkylation of essential protein thiol groups, oxidation of essential protein thiol groups by superoxide radicals or a combination of these mechanisms. The oxidation state of the spiroketal carbon, a masked ketone, could allow the spiroxins to behave chemically as quinone epoxides, possibly causing DNA cleavage under reducing conditions *via* an oxidative stress mechanism involving the formation of thiol conjugates [14]. Among these five spiroxins, only spiroxin A (**2**) was evaluated for its bioactivities as it was the major component produced in culture, other spiroxins should also be screened in detail on their antimicrobial and anti-tumor activity by focusing on their structure-activity relationships.

2. PREUSSOMERIN-TYPE SPIROBISNAPHTHALENES AND BIOACTIVITIES

The preussomerins are a class of spirobisnaphthalenes which were first isolated as antifungal agents from the coprophilous fungus *Preussi isomera* [1,10]. These compounds are comprised of two unsaturated decalin units connected *via* three oxygen bridges through two spiroketal carbons located in each of the upper and lower decalin units. Twenty

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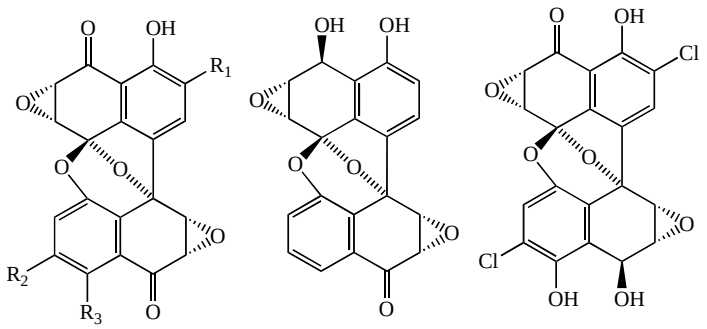


1 R_1=R_2=R_3=H
2 R_1=Cl, R_2=H, R_3=OH
3 R_1=R_2=Cl, R_3=OH

Spiroxin D (**4**)

Spiroxin E (**5**)

Fig. (1). Structures of spiroxin-type spirobisnaphthalenes (**1**-**5**).

Table 1. Spiroxin-Type Spirobisnaphthalenes and their Biological Activities

Compound	Fungus	Biological activity	Reference
Spiroxin C (**1**)	Unidentified marine-derived fungus LL-37H248	-	[14]
Spiroxin A (**2**)	Unidentified marine-derived fungus LL-37H248	Anti-tumor activity; antibacterial activity on Gram-positive bacteria	[14]
Spiroxin B (**3**)	Unidentified marine-derived fungus LL-37H248	-	[14]
Spiroxin D (**4**)	Unidentified marine-derived fungus LL-37H248	-	[14]
Spiroxin E (**5**)	Unidentified marine-derived fungus LL-37H248	-	[14]

preussomerins, which demonstrated multi-biological activities (Fig. (**2**), Table **2**), have been isolated from the fungi so far.

Ras (p21) farnesyl-protein transferase (FPTase) is a hetero-dimeric enzyme that catalyses the transfer of the farnesyl group from farnesyl pyrophosphate (FPP) onto cysteine 186 at the C-terminus of the Ras peptide. This enzyme plays a critical role in the post-translational modification of a huge range of different proteins involved in intracellular signaling [19,20]. There is now evidence that FPTase inhibitors have been developed as potential anti-tumor therapeutic drugs, blocking the growth of human cancers. It is considered to be the first step toward the development of an effective agent for treatment of cancers, particularly those with mutated *ras* gene such as colon and pancreatic carcinomas [21]. Four preussomerins (**7**, **9**, **19**, **21**), isolated from an unidentified fungus MF5916, acted as novel inhibitors of FPTase with the median inhibitory concentration (IC_{50}) values range of 1.2-17 μM. Preussomerins G (**9**) and D (**7**), which contained a conjugated ketone in the lower half of the molecule, exhibited more active than preussomerins H (**19**) and I (**21**), which were reduced product and Michael adduct, respectively. This characteristic seems to be critical for the activity and may serve as a Michael acceptor for nucleophilic Ras-CVLS. It is of interest in terms of the potential of preussomerins in cancer chemotherapy though the accurate mechanism of inhibition is not clear [15].

Similarly, three preussomerins EG_1 (**10**), EG_2 (**24**) and EG_3 (**25**) from the endophytic fungus *Edenia gomezpompae* derived from the leaves of *Callicarpa acuminata* (Verbenaceae) collected from the ecological reserve El Eden, Quintana Roo, Mexico [22]. Of them, preussomerin EG_1 (**10**) displayed the strongest antifungal activity on almost all the tested fungi. The structure-activity relationship reveals that the presence of the C-2', C-3' double bond is possibly responsible for the higher bioactivity of preussomerin EG_1 (**10**). Preussomerin EG_1 (**10**) was also isolated from the Panamanian endophytic fungus *Edenia* sp. which caused significant inhibition of the growth of *Leishmania donovani* in the amastigote form with the IC_{50} value of 0.12 μM [13].

Tuberculosis and malaria are by far the most serious of the world's deadly diseases, and the search for new drug leads is an urgent need due to the emergence of drug-resistant strains of both mycobacteria and parasites. Preussomerins E (**8**), F (**13**), G (**9**), H (**19**) and I (**21**) along with 3'-demethylpreussomerin I (**20**) were isolated from a lichen fungus *Microsphaeropsis* sp. BCC 3050 to show the moderate antimycobacterial activity on *Mycobacterium tuberculosis* $H_{37}Ra$, antiplasmodial activity on *Plasmodium falciparum*, and significant cytotoxicity against KB, BC-1 and vero cell lines [11].

Six preussomerins (**7**, **12**, **14**-**17**) from the freshwater fungus YMF 1.01029 were screened to show moderate nematicidal activities with the IC_{50} values between 100 and

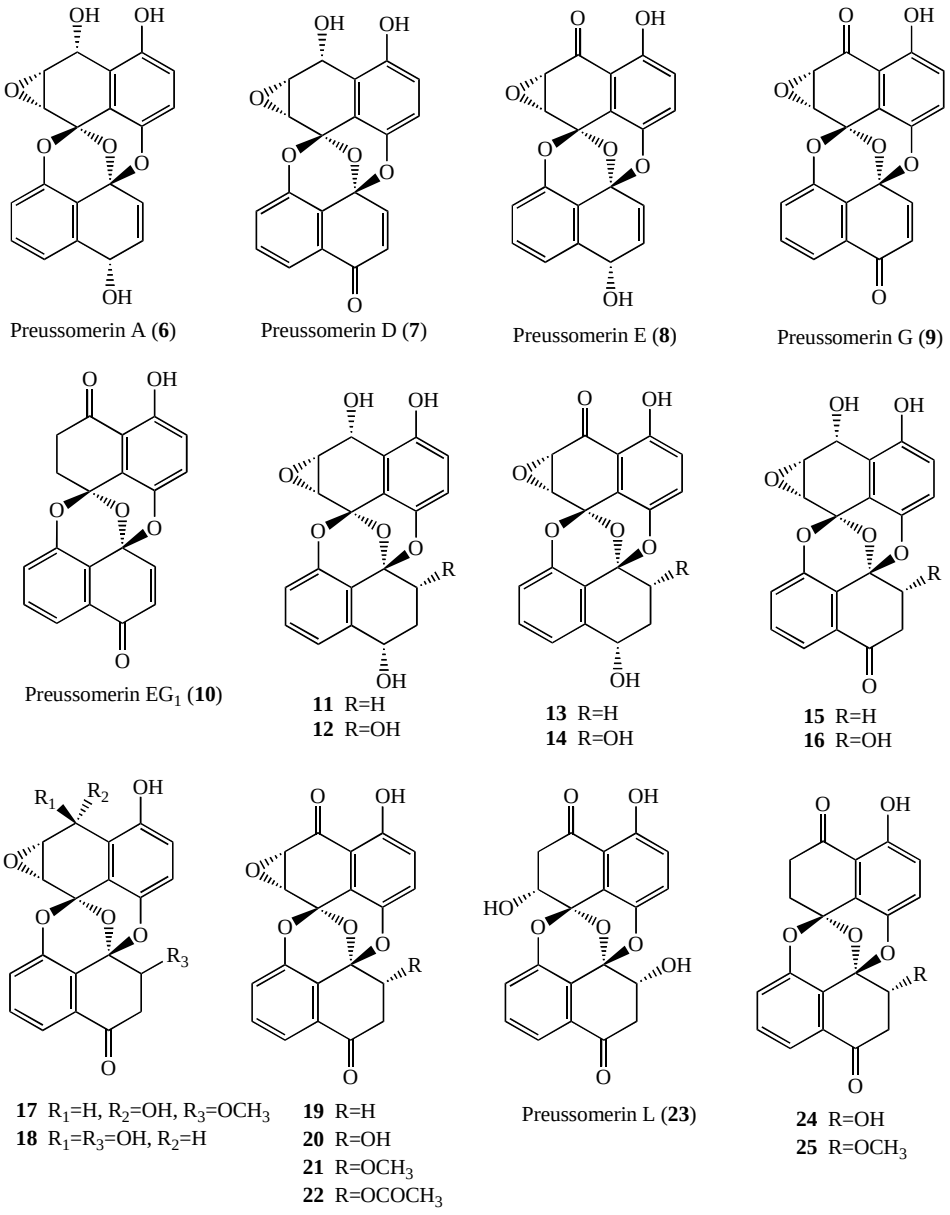


Fig. (2). Structures of preussomerin-type spirobisnaphthalenes (**6-25**).

200 μg/mL at the 24 h time point against *Bursaphelenchus xylophilus*, a plant-parasitic and fungal-feeding nematode that caused great losses to pine forests, especially in several Asian countries. Among them, preussomerin D (**7**) was the most potent [12]. Furthermore, in the standard disk assay at 50 μg/disk, preussomerin D (7) was found to be active against some fungi (*Bipolaris maydis*, *Cochliobolus sativus*, *Fusarium verticillioides*) and bacteria (*Bacillus subtilis*, *Bacillus laterosporus*, *Staphylococcus aureus*) [23].

3. DEOXYPREUSSOMERIN-TYPE SPIROBISNAPHTHALENES AND BIOACTIVITIES

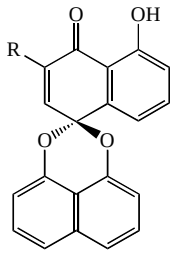
The deoxypreussomerins are comprised of two unsaturated decalin units connected *via* two oxygen bridges through one spiroketal carbon located in one of the decalin units. About 56 deoxypreussomerins have been isolated from the fungi so far with their multi-biological activities (Fig. (**3**), Table **3**).

Four antileishmanial deoxypreussomerins, palmarumycin CP_2 (**30**), palmarumycin CP_{17} (**31**), palmarumycin CP_{18} (**37**) and CJ-12,371 (**33**) were isolated from the Panamanian endodphytic fungus *Edenia* sp. which caused significant inhibition of the growth of *Leishmania donovani* in the amastigote form with the IC_{50} values range of 0.62-8.40 μM [13].

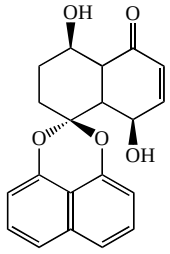
Two deoxypreussomerins CJ-12,371 (**33**) and CJ-12,372 (**34**) from the fermentation broth of an unidentified fungus N983-46 were screened to inhibit both DNA supercoiling and relaxation mediated by *Escherichia coli* DNA gyrase. Both compounds had antibacterial activity against several species of Gram-positive pathogenic bacteria, including ciprofloxacin-resistant and susceptible *Staphylcoccus aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*,

Table 2. Preussomerin-Type Spirobisnaphthalenes and their Biological Activities

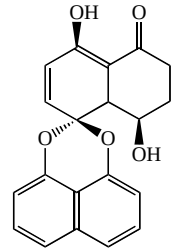
Compound (alternative name)	Fungus	Biological activity	Reference
Preussomerin A (**6**)	*Preussia isomera* Cain (CBS 415.82)	Antifungal activity	[1,2]
Preussomerin D (**7**)	*Preussia isomera* Cain (CBS 415.82)	Antifungal activity	[1]
	Unidentified fresh-water-derived fungus YMF 1.01029	Nematicidal activity	[12]
	Unidentified fungus MF5916	Inhibitory on Ras FPTase	[15]
	Hormonema dematioides	Antimicrobial activity	[24]
	Unidentified fresh-water-derived fungus YMF 1.01029	Antifungal and antimicrobial activity	[23]
Preussomerin E (**8**)	*Preussia isomera* Cain (CBS 415.82)	Antifungal activity	[1]
	Microsphaeropsis sp. BCC 3050	Antimycobacterial, antiplasmodial and cytotoxic activity	[11]
Preussomerin G (**9**)	*Microsphaeropsis* sp. BCC 3050	Antimycobacterial, antiplasmodial and cytotoxic activity	[11]
	Unidentified fungus MF5916	Inhibitory on Ras FPTase	[15]
Preussomerin EG_1 (**10**)	*Edenia* sp.	Antileishmanial activity	[13]
	Edenia gomezpompae	Antifungal activity	[22]
Preussomerin B (**11**)	*Preussia isomera* Cain (CBS 415.82)	Antifungal activity	[1]
Ymf 1029 A (**12**)	Unidentified fresh-water-derived fungus YMF 1.01029	Nematicidal activity	[12]
Preussomerin F (**13**)	*Preussia isomera* Cain (CBS 415.82)	Antifungal activity	[1]
	Microsphaeropsis sp. BCC 3050	Antimycobacterial, antiplasmodial and cytotoxic activity	[11]
Ymf 1029 B (**14**)	Unidentified fresh-water-derived fungus YMF 1.01029	Nematicidal activity	[12]
Ymf 1029 D (**15**)	Unidentified fresh-water-derived fungus YMF 1.01029	Nematicidal activity	[12]
Ymf 1029 C (**16**)	Unidentified fresh-water-derived fungus YMF 1.01029	Nematicidal activity	[12]
Preussomerin C (**17**)	*Preussia isomera* Cain (CBS 415.82)	Antifungal activity	[1]
3'-*O*-desmethyl-1-epipreussomerin C (**18**)	*Sporormiella vexans*	Antifungal and antibacterial activity	[25]
Preussomerin H (**19**)	*Microsphaeropsis* sp. BCC 3050	Antimycobacterial, antiplasmodial and cytotoxic activity	[11]
	Unidentified fungus MF5916	Inhibitory on Ras FPTase	[15]
Preussomerin K (**20**) (3'-*O*-demethylpreussomerin I)	*Microsphaeropsis* sp. BCC 3050	Antimycobacterial, antiplasmodial and cytotoxic activity	[11]
	Unidentified endophytic fungus	-	[26]
Preussomerin I (**21**)	*Microsphaeropsis* sp. BCC 3050	Antimycobacterial, antiplasmodial and cytotoxic activity	[11]
	Unidentified fungus MF5916	Inhibitory on Ras FPTase	[15]
Preussomerin J (**22**)	Unidentified endophytic fungus	-	[26]
Preussomerin L (**23**)	Unidentified endophytic fungus	-	[26]
Preussomerin EG_2 (**24**)	*Edenia gomezpompae*	Antifungal activity	[22]
Preussomerin EG_3 (**25**)	*Edenia gomezpompae*	Antifungal activity	[22]



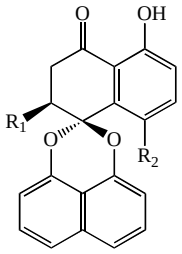
26 R=H
27 R=Cl



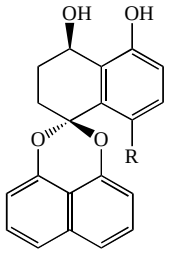
MK 3018 (**28**)



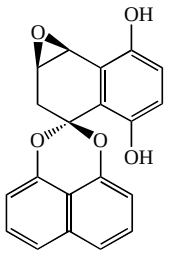
Palmarumycin CP_4 (**29**)



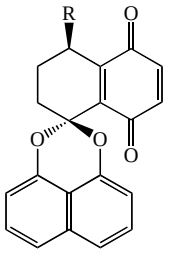
30 R_1= R_2=H
31 R_1=H, R_2=OH
32 R_1=R_2=OH



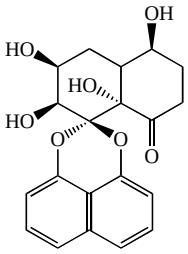
33 R=H
34 R=OH



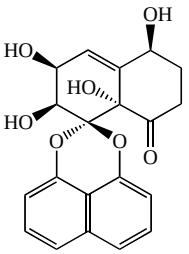
Cladospirone F (**35**)



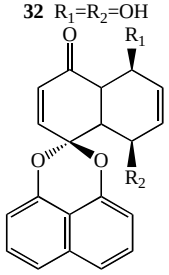
36 $R=OCH_3$
37 R=OH



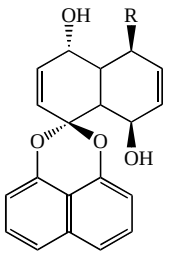
Cladospirone H (**38**)



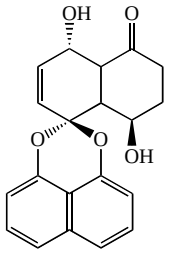
Cladospirone I (**39**)



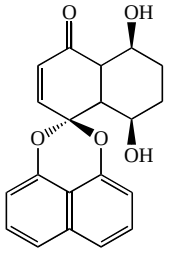
40 R_1= R_2=OH
41 R_1=OH, R_2=OAc
42 R_1=OAc, R_2=OH



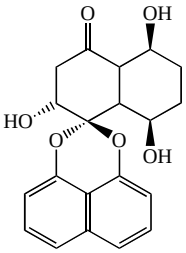
43 R=OH
44 R=OAc



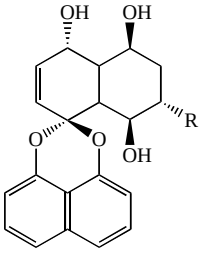
Decaspirone G (**45**)



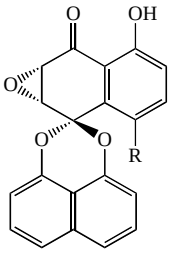
Decaspirone C (**46**)



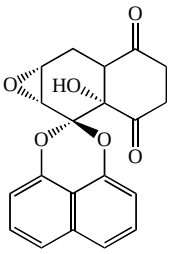
Palmarumycin M_2 (**47**)



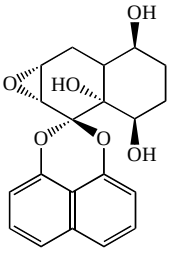
48 R=H
49 R=OH



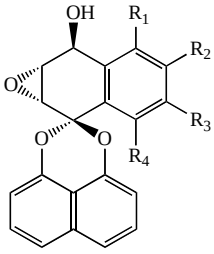
50 R=H
51 R=OH



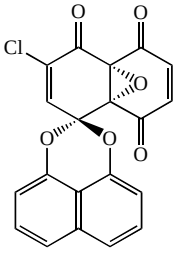
Cladospirone C (**52**)



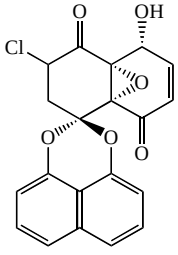
Cladospirone G (**53**)



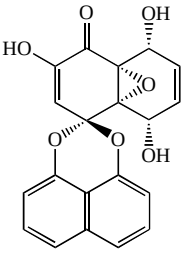
54 R_1=OH, R_2=R_3=R_4=H
55 R_1=R_2=H, R_3=OH, R_4=H
56 R_1=R_2=R_3=H, R_4=OH
57 R_1=OH, R_2=R_3=H, R_4=OH
58 R_1=OH, R_2=Cl, R_3=R_4=H



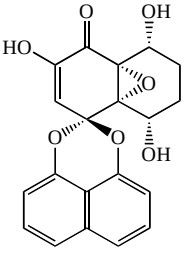
Palmarumycin C_4 (**59**)



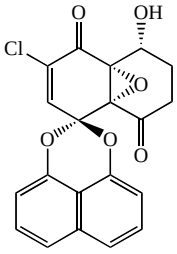
Palmarumycin C_7 (**60**)



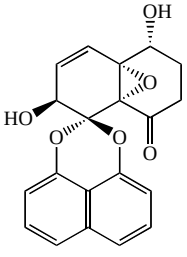
Sch 49211 (**61**)



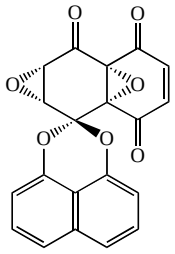
Sch 49212 (**62**)



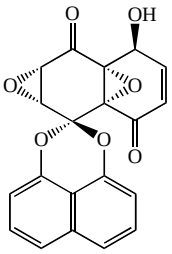
Palmarumycin C_8 (**63**)



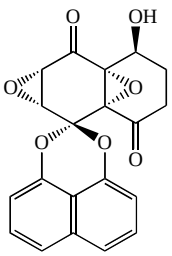
Cladospirone E (**64**)



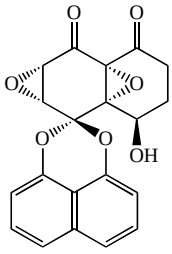
Palmarumycin C_9 (**65**)



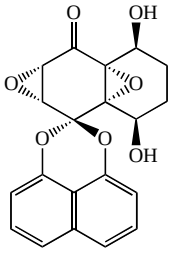
Diepoxine σ (**66**)



Diepoxine α (**67**)



Cladospirone D (**68**)



Sch 49210 (**69**)

(Fig. 3). Contd…..

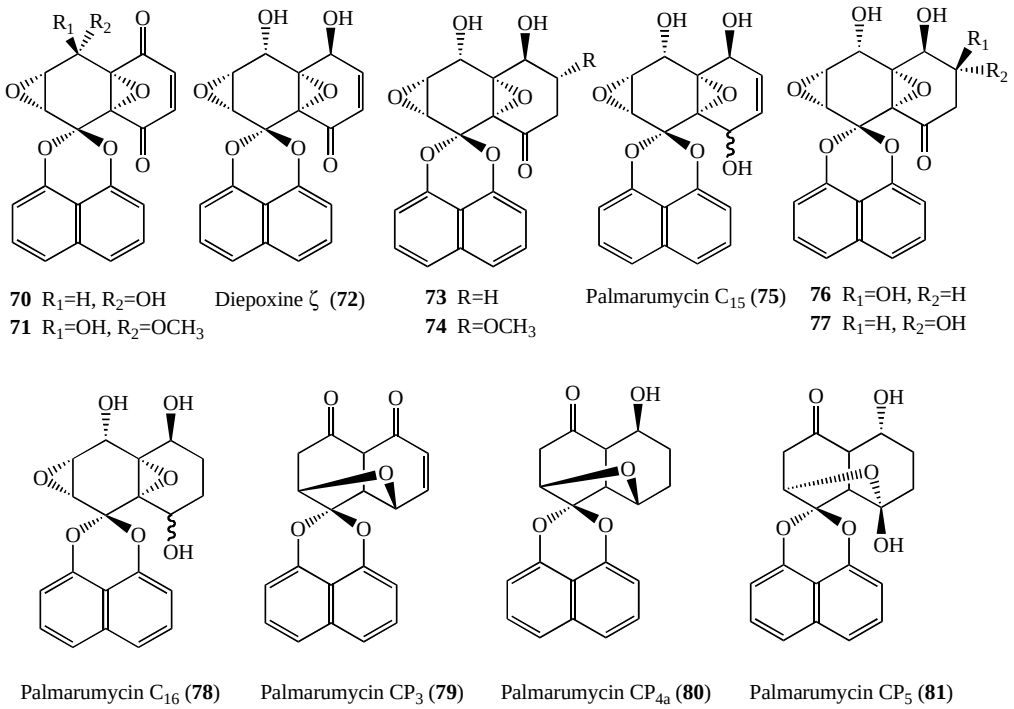


Fig. (3). Structures of deoxypreussomerin-type spirobisnaphthalenes (**26**-**81**).

agalactiae, and *Enterococcus faecalis* with minimum inhibitory concentrations (MICs) ranging from 25 to 100 μg/mL [16].

Deoxypreussomerins A (**50**) and B (**30**) were isolated from an unidentified fungus MF5916, with modest inhibitory activity on farnesyl-protein transferase (FPTase) with the IC_{50} values of 10 and 12 μM, respectively [15].

Eighteen deoxypreussomerins from the endophytic fungus *Coniothyrium palmarum* derived from *Lamium purpureum* (Labiatae) were tested for antibacterial, antifungal and algicidal activity. Palmarumycins C_2 (**50**), C_{12} (**57**) and CP_3 (**79**) were considerably more active than others. An oxygen function at C-8 seems to increase the general biological activity [9,27].

The cytosolic thioredoxin redox system composed of thioredoxin-1 and the NADPH-dependent thioredoxin reductase-1 reductase is an important regulator of cell growth and survival. As thioredoxin-1 is usually overexpressed in many human tumors where it is associated with increased cell proliferation, decreased apoptosis, and decreased patient survival, thioredoxin reductase-1 should provide a target to inhibit the activity of the overexpressed thioredoxin-1 for the development of novel anti-tumor agents. It was found that palmarumycin CP_1 (**26**) was a potent inhibitor of thioredoxin reductase-1 [31]. A water-soluble prodrug PX-916 of a palmarumycin CP_1 analogue was developed to rapidly release the parent compound either at physiologic pH or in plasma, but was stable in acid pH, allowing its i.v. administration [31]. Diepoxine σ (also named Sch 49209, **66**) was isolated from three fungal strains which were *Nattrassia mangiferae*, *Coniothyrium palmarum* and an unidentified fungus LL-07F275. It showed multi-biological activities such as inhibitory activity on thioredoxin-thioredoxin reductase system, antifungal and anti-tumor activities [17,28-30].

Diepoxine ζ (also named Sch 53514, palmarumycin C_{13} and cladospirone bisepoxide, **72**) was also isolated from some fungi which were *Cladosporium chlorocephalum*, *Nattrassia mangiferae*, and two unidentified fungal strains LL-07F275 and F-24'707. It showed antifungal, antibacterial and herbicidal activities as well as inhibitory activity on phospholipase D (PLD) [9,28,32-35].

A series of deoxypreussomerins were isolated from the fermentation broth of the fungi *Nattrassia mangiferae* and an unidentified fungus [17,29,32,36,37]. Of them, Sch 49209 (**66**), Sch 49210 (**69**), Sch 50673 (**71**), Sch 50676 (**56**), Sch 53514 (**72**) and Sch 53516 (**73**) revealed potent inhibitory activity against the invasion of HT1080 human fibrosarcoma cells through a matrigel membrane in the anti-tumor invasion chamber assay. Sch 49210 (**69**), Sch 49211 (**61**), Sch 49212 (**62**), Sch 53514 (**72**), Sch 53516 (**73**), Sch 53823 (**54**) and Sch 53825 (**58**) also exhibited potent inhibitory activity in phospholipase D (PLD) assay [17,29,32,36,37].

4. BIOSYNTHESIS

The biosynthesis investigation of spirobisnaphthalenes has been partially clarified. Biosynthesis of cladospirone bisepoxide (**72**) was studied by feeding ^{13}C-labeled acetate to growing cultures of the fungus *Sphaeropsidales* sp. (strain F-24'707) [47]. The results indicated that both naphthalene moieties derived from the same pentaketide precursor *via* a fungal polyketide synthase (PKS). Further modifications and incorporation of oxygen from air *via* postulated monooxygenase led to cladospirone bisepoxide (**72**). Otherwise, the

Table 3. Deoxypreussomerin-Type Spirobisnaphthalenes and Their Biological Activities

Compound (alternative name)	Fungus	Biological activity	Reference
Palmarumycin CP_1 (**26**)	*Coniothyrium palmarum*	Inhibitory activity on the thioredoxin-thioredoxin reductase system	[18]
Palmarumycin C_1 (**27**)	*Coniothyrium* sp.	Antifungal, antibacterial and herbicidal activity	[9]
MK 3018 (**28**)	*Tetraploa aristata*	Antibacterial activity	[4]
Preussomerin CP_4 (**29**)	*Coniothyrium palmarum*	Antifungal and antibacterial activity	[27]
Palmarumycin CP_2 (**30**) (deoxypreussomerin B)	*Edenia* sp.	Antileishmanial activity	[13]
	Unidentified fungus MF5916	Inhibitory on Ras FPTase	[15]
	Coniothyrium palmarum	Antifungal and antibacterial activity	[27]
	Edenia gomezpompae	Antifungal activity	[22]
Palmarumycin CP_{17} (**31**)	*Edenia* sp.	Antileishmanial activity	[13]
	Unidentified fungus Dzf12	-	[39]
Cladospirone B (**32**)	*Sphaeropsidales* sp. F-24'707	-	[38]
CJ-12,371 (**33**)	*Edenia* sp.	Antileishmanial activity	[13]
	Unidentified fungus N983-46	Inhibitory activity on DNA gyrase	[16]
CJ-12,372 (**34**)	Unidentified fungus N983-46	Inhibitory activity on DNA gyrase	[16]
Cladospirone F (**35**)	*Sphaeropsidales* sp. F-24'707	-	[38]
Palmarumycin C_5(**36**)	*Coniothyrium* sp.	Antifungal, antibacterial and herbicidal activity	[9]
Palmarumycin CP_{18} (**37**)	*Edenia* sp.	Antileishmanial activity	[13]
Cladospirone H (**38**)	*Sphaeropsidales* sp. F-24'707	-	[38]
Cladospirone I (**39**)	*Sphaeropsidales* sp. F-24'707	-	[38]
Decaspirone A (**40**)	*Decaisnella thyridioides*	-	[40]
Decaspirone D (**41**)	*Decaisnella thyridioides*	-	[40]
Decaspirone E (**42**)	*Decaisnella thyridioides*	-	[40]
Decaspirone F (**43**)	*Helicoma viridis*	Antibacterial activity	[41]
Decaspirone B (**44**)	*Decaisnella thyridioides*	-	[40]
Decaspirone G (**45**)	*Helicoma viridis*	Antibacterial activity	[41]
Decaspirone C (**46**)	*Decaisnella thyridioides*	-	[40]
Palmarumycin M_2 (**47**)	*Microsphaeropsis* sp.	-	[42]
Palmarumycin M_1 (**48**)	*Microsphaeropsis* sp.	-	[42]
Decaspirone H (**49**)	*Helicoma viridis*	Antibacterial activity	[41]
Palmarumycin C_2 (**50**) (deoxypreussomerin A)	*Coniothyrium* sp.	Antifungal, antibacterial and herbicidal activity	[9]
	Microsphaeropsis sp. BCC 3050	Antimycobacterial, antiplasmodial and cytotoxic activity	[11]
	Unidentified fungus MF5916	Inhibitory on Ras FPTase	[15]
Palmarumycin C_3 (**51**)	*Coniothyrium* sp.	Antifungal, antibacterial and herbicidal activity	[9]
Cladospirone C (**52**)	*Sphaeropsidales* sp. F-24'707	Antibacterial and algicidal activity	[38]
Cladospirone G (**53**)	*Sphaeropsidales* sp. F-24'707	-	[38]
Bipendensin (**54**) (Sch 53823; palmarumycin C_{11}; palmarumycin JC1)	*Coniothyrium* sp.	Antifungal, antibacterial and herbicidal activity	[9]
	Microsphaeropsis sp. BCC 3050	Antimycobacterial, antiplasmodial and cytotoxic activity	[11]
	Unidentified fungus	Inhibitory activity on PLD	[29]

(Table 3). Contd…..

Compound (alternative name)	Fungus	Biological activity	Reference
Spiropreussione A (**55**)	*Preussia* sp.	-	[43]
Sch 50676 (**56**)	*Nattrassia mangiferae*	Anti-tumor activity	[17]
Palmarumycin C_{12} (**57**)	*Coniothyrium* sp.	Antifungal, antibacterial and herbicidal activity	[9]
Sch 53825 (**58**)	Unidentified fungus	Inhibitory activity on PL D	[29]
Palmarumycin C_4(**59**)	*Coniothyrium* sp.	Antifungal, antibacterial and herbicidal activity	[9]
Palmarumycin C_7 (**60**)	*Coniothyrium* sp.	Antifungal, antibacterial and herbicidal activity	[9]
Sch 49211 (**61**)	*Nattrassia mangiferae*	Inhibitory activity on PLD	[37]
Sch 49212 (**62**)	*Nattrassia mangiferae*	Inhibitory activity on PLD	[37]
Palmarumycin C_8 (**63**)	*Coniothyrium* sp.	Antifungal, antibacterial and herbicidal activity	[9]
Cladospirone E (**64**)	*Sphaeropsidales* sp. F-24'707	-	[38]
Palmarumycin C_9(**65**)	*Coniothyrium* sp.	Antifungal, antibacterial and herbicidal activity	[9]
Diepoxine σ (**66**) (Sch 49209)	Unidentified fungus LL-07F275	Antifungal activity	[28]
	Coniothyrium palmarum	Inhibitory activity on thioredoxin-thioredoxin reductase system	[18]
	Nattrassia mangiferae	Anti-tumor activity	[30]
	Nattrassia mangiferae	Anti-tumor activity	[36]
Diepoxine α (**67**)	Unidentified fungus LL-07F275	Antifungal activity	[28]
Cladospirone D (**68**)	*Sphaeropsidales* sp. F-24'707	Antibacterial, algicidal activity	[37]
Sch 49210 (**69**)	*Nattrassia mangiferae*	Inhibitory activity on PLD; anti-tumor activity	[32,44]
Palmarumycin C_{10}(**70**) (diepoxin φ)	*Coniothyrium* sp.	Antifungal, antibacterial and herbicidal activity	[9]
Sch 50673 (**71**)	*Nattrassia mangiferae*	Anti-tumor activity	[17]
	Unidentified fungus LL-07F275	-	[45]
Diepoxine ζ (**72**) (Sch 53514; palmarumycin C_{13}; cladospirone bisepoxide)	Unidentified fungus LL-07F275; *Coniothyrium* sp.	Antifungal, antibacterial and herbicidal activity	[9,28]
	Nattrassia mangiferae	Inhibitory activity on PLD; anti-tumor activity	[32]
	Cladosporium chlorocephalum	-	[33,34]
	Unidentified saprophytic fungus strain F-24'707	Antifungal and antibacterial activity	[35]
	Unidentified fungus Dzf12	Antibacterial and antifungal activity	[39]
Diepoxine η (**73**) (Sch 53516; palmarumycin C_{14})	Unidentified fungus LL-07F275; *Coniothyrium* sp.	Antifungal, antibacterial and herbicidal activity	[9,28]
	Nattrassia mangiferae	Inhibitory activity on PLD; anti-tumor activity	[32]
	Unidentified fungus Dzf12	Antibacterial and antifungal activity	[39]
Diepoxine κ (**74**)	Unidentified fungus Dzf12	Antibacterial and antifungal activity	[39]
Palmarumycin C_{15} (**75**)	*Coniothyrium* sp.	Antifungal, antibacterial and herbicidal activity	[9]
Diepoxin γ (**76**)	Unidentified fungus Dzf12	-	[39]
	Unidentified fungus LL-07F275	-	[45]
Diepoxin δ (**77**)	Unidentified fungus LL-07F275	-	[45]
Palmarumycin C_{16} (**78**)	*Coniothyrium* sp.	Antifungal, antibacterial and herbicidal activity	[9]
Preussomerin CP_3 (**79**)	*Coniothyrium palmarum*	Antifungal and antibacterial activity	[27]
Palmarumycin CP_{4a} (**80**)	*Coniothyrium palmarum*	-	[46]
Palmarumycin CP_5 (**81**)	*Coniothyrium palmarum*	-	[46]

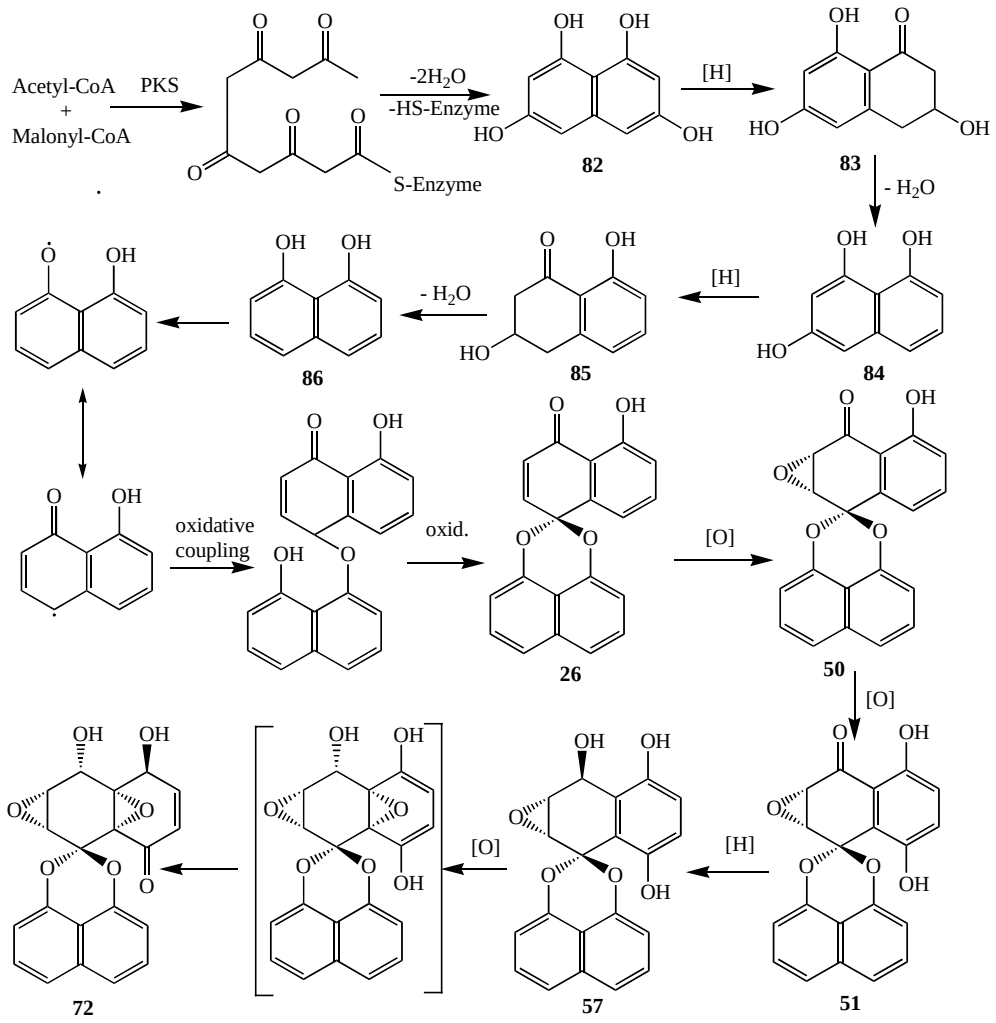


Fig. (4). Proposed biosynthesis pathway of cladospirone bisepoxide (**72**) in the fungus *Sphaeropsidales* sp. (strain F-24'707) [47]. PKS: polyketide synthase; – H_2O: dehydratase reactioin; [H]: reduction reaction; [O]: oxygenation reaction; **82**: 1,3,6,8-tetrahydroxynaphthalene; **83**: scytalone; **84**: 1,3,6-trihydroxynaphthalene; **85**: vermelone; **86**: 1,8-dihydroxynaphthalene (DHN).

inhibition of the biosynthesis after addition of tricyclazole confirmed that possible precursors could derive from the 1,8-dihydroxynaphthalene (DHN, **86**) biosynthesis as proposed by Krohn *et al.* [9]. The proposed intermediates of the cladospirone bisepoxide biosynthesis are outlined in Fig. (**4**).

Van der Sar *et al*. studied the biosynthesis of *spiro*-mamakone A (**87**), a potently cytotoxic and antimicrobial compound from an unidentified endophytic fungus isolated from the New Zealand native tree *Knightia excelsa* (Proteaceae), that confirmed the polyketide originating from palmarumycin CP_1 (**26**) belonging to the spirobisnaphthalene class [48]. The proposed biosynthesis pathway is shown in Fig. (**5**). The biosynthesis route before palmarumycin CP_1 (**26**) was the same as that in Fig. (**4**). Palmarumycin CP_1 (**26**) was oxidized by rearrangement of the coupled moiety to a dihydroxynaphthyl epoxide intermediate (**88**). After oxidative cleavage, decarboxylation and deprotonation steps, a symmetric enedione carbanion (**89**) was formed. In a Knoevenagel-type reaction this stabilized carbanion intermediate could attack the aldehyde to generate *spiro*-mamakone A (**87**). Furthermore, Bode and Zeeck used UV mutagenesis and enzyme inhibitors as tools to elucidate the late biosynthesis of the spirobisnaphthalenes in detail [49].

Krohn and coworkers proposed a biosynthesis of palmarumycin CP_1 (**26**) based on a 1,8-dihydroxynaphthalene or suitable phenolic derivative precursor [9]. According to their hypothesis, coupling could occur *via* a phenol oxidation as often encountered in polyketide biosynthesis, and the chlorinated palmarumycins could be derived from addition of chloride ions to epoxides. In order to prove this mechanism, palmarumycin C_9 (**65**) was treated with methanolic hydrochloric acid (Fig. (**6**)). As expected, formation of chlorinated palmarumycin C_4 (**34**) from palmarumycin C_9 (**65**) could be successfully detected by TLC.

5. SYNTHESIS AND ABSOLUTE STEREOCHEMISTRY

The unique skeleton and various biological activities of spirobisnaphthalenes have been attracting the interests of synthetic chemists, and synthesis of this class of compounds has recently been appeared in the literature [18,50-72]. The synthesis of preussomerin G (**9**), preussomerin F (**13**), preus-

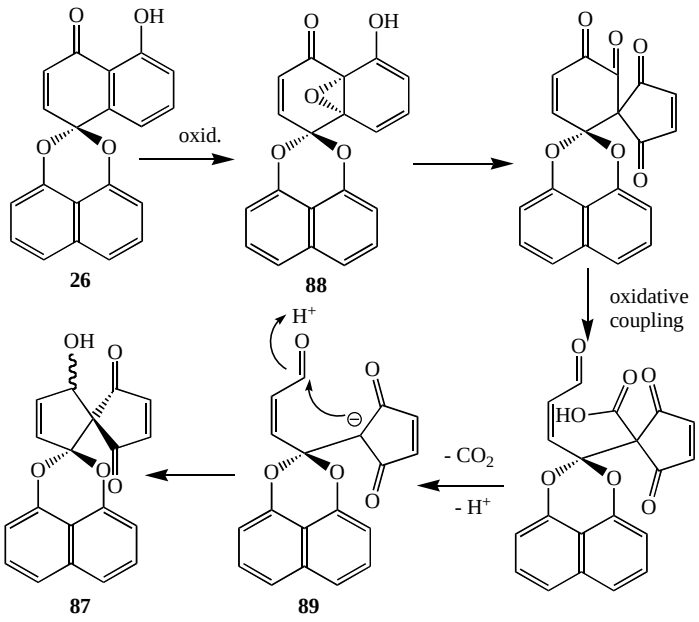


Fig. (5). Proposed biosynthesis pathway of *spiro*-mamakone A (**87**) [48].

somerin K (**20**), preussomerin L (**22**), preussomerin I (**24**), palmarumycin CP_1 (**25**), palmarumycin CP_2 (**29**), CJ-12,371 (**32**), deoxypeussomerin A (**49**), palmarumycin C_{11} (**53**), diepoxin σ (**65**) and their analogues have been reported since 1997 [18,50-72]. The absolute configurations of the palmarumycins CP_3 (**79**), C_2 (**50**), C_9 (**65**), C_{10} (**70**) and C_{12} (**57**) along with spiroxin A (**2**) were assigned with the circular dichroism (CD) spectra in detail [73-75].

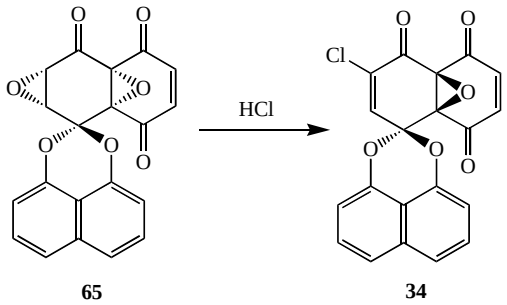


Fig. (6). Transformation of chlorinated palmarumycin C_4 (**34**) from palmarumycin C_9 (**65**).

6. SPIROBISNAPHTHALENES FROM PLANTS

Three deoxypreussomerin-type spirobisnaphthalenes, palmarumycins CP_1 (**26**), JC1 (**54**) and JC2 (**90**) were isolated from stems of *Jatropha curcas* (Euphorbiaceae) [76]. Both palmarumycins JC1 and JC2 showed their antibacterial activity on *Staphylococcus aureus* [76], and palmarumycin JC2 was further screened to exhibit antimycobacterial, antimalarial, antifungal, and cytotoxic activities [78]. Bipendensin (or called palmarumycin CP_1, **26**) was obtained from the sapwood of the African tree *Afzelia bipendensis* (Caesalpiniaceae) in 1993 [77]. Palmarumycins JC1 and JC2 were also isolated from fruits of *Diospyros ehretioides* (Ebenaceae) [78]. It is worth noticing that palmarumycin JC2 (**90**) has not been isolated from the fungal samples (Fig. (**7**)).

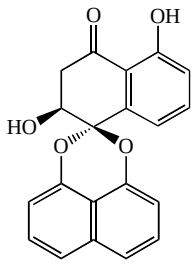


Fig. (7). Structure of palmarumycin JC2 (**90**).

Up to now, spirobisnaphthalenes have been isolated from the three different plant families i.e. Caesalpiniaceae (*Afzelia bipendensis*), Ebenaceae (*Diospyros ehretioides*) and Euphorbiaceae (*Jatropha curcas*). This is rather unusual from the chemotaxonomic point of view, while certain secondary metabolites could be employed as chemotaxonomic markers in particular plant genera [79-82]. It was proposed that the isolated spirobisnaphthalenes were not as the plant constituents, but they might be from the endophytic fungi present in the host plants. These findings suggested a new approach for searching new fungal metabolites on plant materials that may be deliberately infected by fungi, or on those with the associated endophytic fungi.

7. SPIROBISNAPHTHALENE PRODUCTION IN MYCELIAL SUSPENTION

Some spirobisnaphthalenes such as spiroxins A (**2**), B (**3**), C (**1**), D (**4**) and E (**5**) are easily excreted into liquid medium from the fungal cells in suspension culture by treatment of macroporous resin. Cultivation of the fungus LL-37H248 in potato dextrose broth containing suspended macroporous resin HP20 yielded high titers of spiroxins.

Production rates were approximately 35-fold greater in the presence of HP20 than in fermentations without the resin [14].

8. CLOSING REMARKS

In the past decades, about 81 spirobisnaphthalenes have been reported from at least 15 known fungal species and 9 un-identified fungal strains. This growing family of spirobisnaphthalenes exhibited a variety of biological activities especially for the cytotoxicity, inhibition of farnesyl-protein transferase and thioredoxin reductase-1 [83-85]. Research to date indicates that further studies on the biosynthetic pathway, metabolic regulation, structure-activity relationship, mechanism of action, physiological and ecological roles of the spirobisnaphthalenes in fungi as well as their practical applications in medicine and agriculture may be confidently expected.

ACKNOWLEDGEMENTS

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