

CHAPTER I

INTRODUCTION

Introduction of Fungi

Fungi¹ are plant-like organisms which lack chlorophyll. Fungi are one of the five kingdoms of life. Many fungi are useful such as *Penicillium* and *Stachybotrys* while some cause problems in plants and human. There are over 100,000 species of fungi in nature. Since they do not have chlorophyll, fungi must absorb food from others. They can get food from almost everything. Without them, we would have piles of trash everywhere.

Filamentous fungi,² in common with some other micro-organisms and plants, have two distinct areas of metabolism termed primary and secondary, linked by common intermediates and in some cases enzymes. Primary metabolism is mainly concerned with the processes for growth and development, such as carbon and nitrogen source utilization, enzyme and DNA production. Secondary metabolism in filamentous fungi mainly involves the synthesis of small molecular weight compounds such as alkaloids, terpenes and phenols. There is not an obvious role for secondary metabolism in terms of the overall bioenergetics of cells. Many of the metabolic pathways involved are different and unrelated. Secondary metabolites do not form a chemical category and do not necessarily have common molecular structures. Because of this, they are usually classified by the metabolic pathways by which they are produced (e.g. polyketide, mevalonate, isoprenoid).

Research and development in biological control agents against plant diseases have been undertaken by both government and private sectors, as natural fungicides.³ The implementation of practical integrated biological control technology for diseases control has been successful by using microorganisms such as fungi. The accomplished biological control mechanisms have been represented and discussed in many ways, which generally fall into two categories. The first one takes place within host plants and includes such specific activities as cross-protection, competition for sites, production of inhibitors such as phytoalexins or antibiotics, and hypovirulence.

The second is some degree of antagonism directed at pathogens from the outside of the plant. This includes antibiotic, competition for nutrients, predaceous exploitation, and parasitism. Fungi play an enormously important role in plant disease control. As naturally occurring resident antagonists, they can be managed or exploited to achieve the desired results. They are responsible for the crop production which is possibly still the single most important disease management tool used worldwide. Various fungi such as *Chaetomium* spp, *Trichoderma* spp. and *Cyathus* spp. have been reported as biocontrol agents both in the greenhouse and in the field.³ The soil-borne saprophytic fungus *Chaetomium globosum* is one of microorganism, which has been reported as an antagonist of several soil-borne and seed-borne plant pathogens and has the potential to control certain diseases.

Drug Discovery from Natural Sources⁴

For thousands of years, natural products have played an important role throughout the world in treating and preventing human diseases. Natural medicines have come from various source materials including terrestrial plants, terrestrial microorganisms, marine organisms, and terrestrial vertebrates and invertebrates. The importance of natural products in modern medicine has been discussed in recent reviews and reports. Terrestrial plants, especially higher plants, have a long history of use in the treatment of human diseases. Furthermore, morphine, codeine, noscapine (narcotine), and papaverine isolated from *Papaver somniferum* have been developed as single chemical drugs and are still clinically used. Until the development of penicillin in the early 1940s, most natural product-derived drugs were obtained from terrestrial plants. The success of penicillin in treating infection led to an expansion in the area of drug discovery from microorganisms. Terrestrial microorganisms are a plentiful source of structurally diverse bioactive substances, and provide important contributions to the discovery of antibacterial agents including penicillins, cephalosporins, aminoglycosides, tetracyclines, and polyketides. Recently approved new drugs derived from terrestrial microorganisms are summarized below and their structures are shown in Figures 1.1.

Amrubicin is a synthetic 9-aminoanthracycline and converts to its active form in the body. Amrubicin, a derivative of doxorubicin isolated from *Streptomyces*

peucetius var *caesius*, demonstrated activity comparable to that of doxorubicin on transplantable animal tumors, including P388 leukemia, sarcoma 180, and Lewis lung carcinoma, and more potent antitumor activity against human tumor xenografts of breast, lung, and gastric cancer.

Biapenem is a new analog of carbapenem based on thienamycin, isolated from *Streptomyces cattleya*, an antibacterial agent effective against both Gram-negative and Gram-positive bacteria including species producing β -lactamases. Biapenem is more stable to hydrolysis by human renal dehydropeptidase-I than imipenem, meropenem, and panipenem. The early carbapenems such as imipenem are not stable to hydrolysis by human renal dihydropeptidase-I (DHP-I) and consequently are coadministered with a DHP-I inhibitor (eg, cilastatin). Biapenem can be administered as a single agent without a DHP-I inhibitor.

Cefditoren pivoxil is an oral prodrug of cefditoren, a derivative of cephalosporin isolated from *Cephalosporium* spp., and is rapidly hydrolyzed by intestinal esterases to the microbiologically active form. Cefditoren has a broad spectrum of activity against both Gram-positive and Gram-negative bacteria, and is stable to hydrolysis in the presence of a variety of β -lactamases. This drug was approved in 2001 for acute bacterial exacerbation of chronic bronchitis (AECB), group A beta-hemolytic streptococcal pharyngotonsillitis, and uncomplicated skin/skin structure infections in adult and adolescent patients.

Ertapenem is a new 1 β -methylcarbapenem based on thienamycin, isolated from *Streptomyces cattleya*, with broad-spectrum antibacterial activity and improved stability to hydrolysis by renal dehydropeptidase enzymes located in the brush border of the kidneys. Ertapenem exhibits excellent antibacterial activity against clinically relevant Enterobacteriaceae including *Escherichia coli*, *Klebsiella* spp., *Citrobacter* spp., *Enterobacter* spp., *Morganella morganii*, *Proteus* spp., and *Serratia marcescens*.

Everolimus is an orally active 40-*O*-(2-hydroxyethyl) derivative of rapamycin, originally produced from *Streptomyces hygroscopicus*. Everolimus exhibits its immunosuppressive effect by blocking growth factor (interleukin (IL)-2 and IL-15) mediated proliferation of hematopoietic (T cells and B cells), and non-hematopoietic (vascular smooth muscle cells) cells through inhibiting p70 S6 kinase, leading to arrest of the cell cycle at the G₁/S phase.

Micafungin is an antifungal agent of the echinocandin type obtained from the culture broth of the fungus *Coleophoma empetri*, and inhibits β -(1,3)-D-glucan synthase of fungi. Micafungin exhibited good antifungal activity against a broad range of *Candida* species, including azole-resistant strains, and *Aspergillus* spp., during *in vitro* and animal studies.

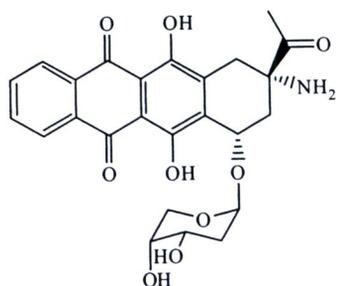
Rosuvastatin is an effective lipid-lowering agent approved internationally (in most of Europe, the United States, and Canada) for the management of dyslipidemias, isolated from *Penicillium citrinum* and *P. brevicompactum*. Rosuvastatin exhibited inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and a derivative of mevastatin.

Tigecycline is the 9-*tert*-butyl-glycylamido derivative of minocycline, which is a semi-synthetic product of chlortetracycline isolated from *Streptomyces aureofaciens*. Tigecycline exhibited antibacterial activity typical of other tetracyclines, but with more potent activity against tetracycline-resistant organisms. Tigecycline is only utilized in an injectable formulation for clinical use, unlike currently marketed tetracyclines that are available in oral dosage forms.

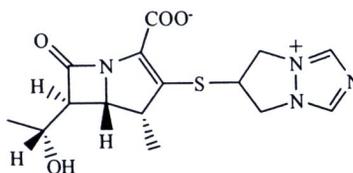
***Chaetomium* spp.⁵**

Chaetomium is a dematiaceous filamentous fungus found in soil, air, and plant debris. As well as being a contaminant, *Chaetomium* spp. are also encountered as causative agents of infections in humans. Some species are thermophilic and neurotropic in nature. The genus *Chaetomium* contains several species. The most common ones are *C. atrobrunneum*, *C. funicola*, *C. globosum*, and *C. strumarium*. *Chaetomium* spp. are among the fungi causing infections wholly referred to as phaeohyphomycosis. Fatal deep mycoses due to *C. atrobrunneum* have been reported in an immunocompromised host. Brain abscess, peritonitis, cutaneous lesions, and onychomycosis may also develop due to *Chaetomium* spp.. *Chaetomium* colonies are rapidly growing, cottony and white in color initially. Mature colonies become grey to olive in color. From the reverse, the color is tan to red or brown to black. Septate hyphae, perithecia, asci and ascospores are visualized. Perithecia are large, dark brown to black in color, fragile, globose to flask shaped and have filamentous, hair-like, brown to black appendages (setae) on their surface. Perithecia have ostioles

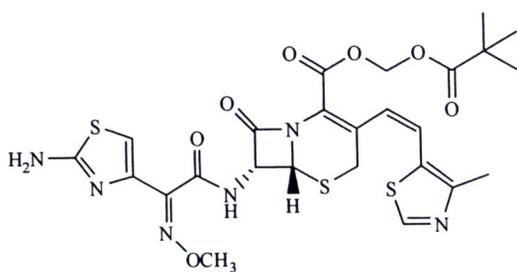
(small rounded openings) and contain asci and ascospores inside. Asci are clavate to cylindrical in shape and rapidly dissolve to release their ascospores (4 to 8 in number). Ascospores are one-celled, olive brown in color, and lemon shaped.



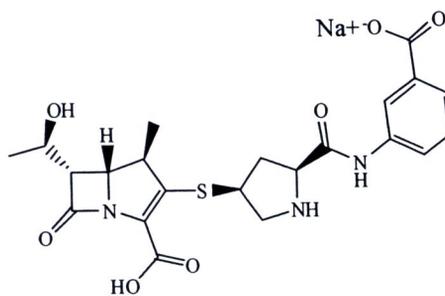
Amrubicin



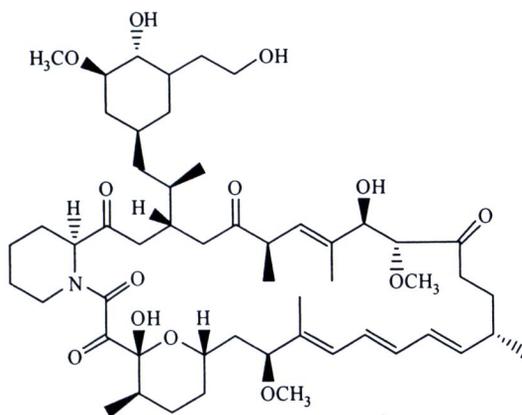
Biapenem



Cefditoren pivoxil



Ertapenem



Everolimus

Figure 1.1 Some structures of new drugs derived from microorganisms.⁴

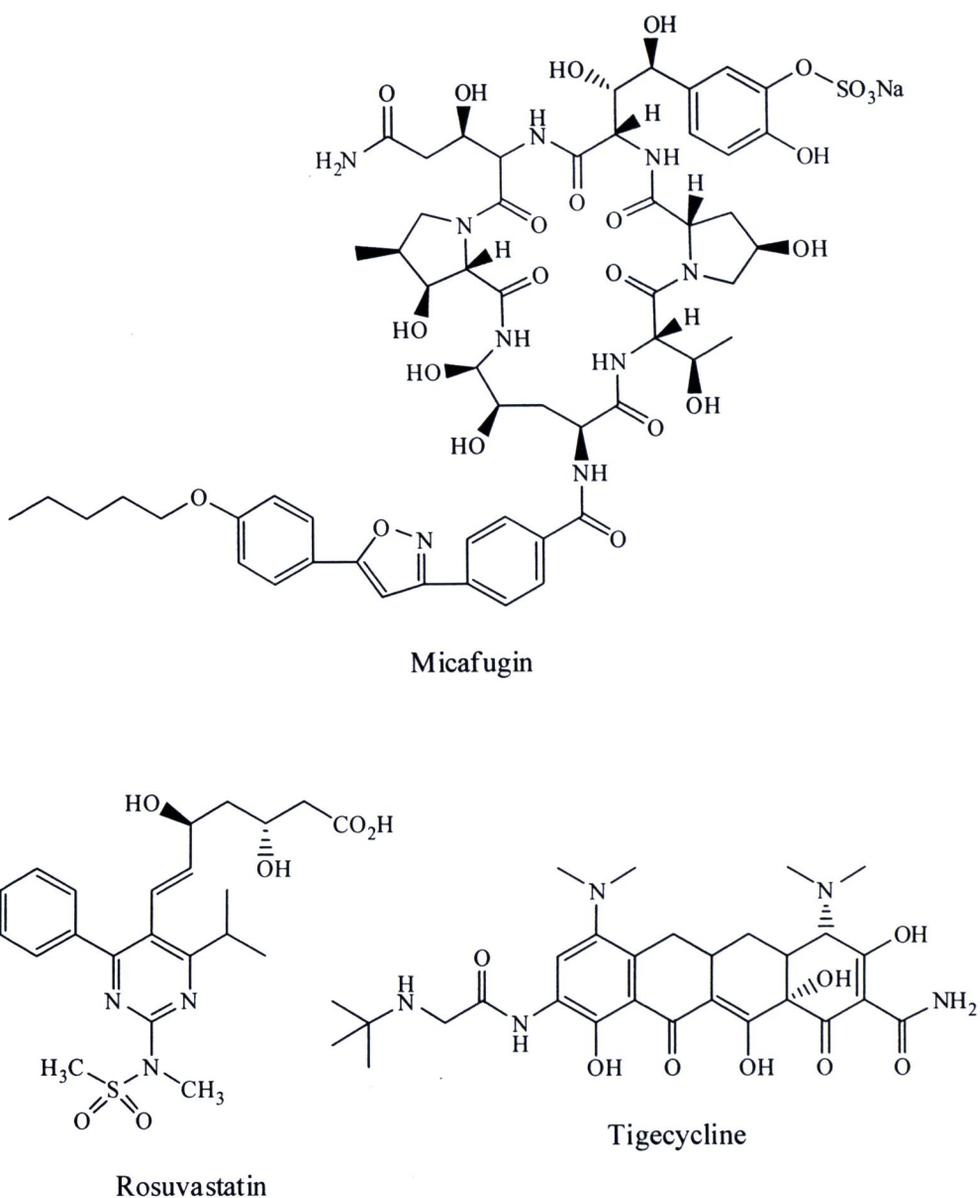


Figure 1.1 Some structures of new drugs derived from microorganisms (cont.).

On our search for bioactive compounds from fungi, the crude extracts of *C. elatum* and *C. lucknowense* were tested for antimalarial (*Plasmodium falciparum*), anti-TB (*Mycobacterium tuberculosis*) and cytotoxicity towards human epidermoid carcinoma in the mouth (KB), human breast cancer cell (BC1), and small cell lung cancer (NCI-H187). The results found that all of the crude extracts of *C. elatum* were active against anti-TB as shown in Table 1.1.

Table 1.1 Bioactivities of the crude extracts of *C. elatum* and *C. lucknowense*

<i>Chaetomium</i> spp.	crude extract	Antimalaria, IC ₅₀ (µg/mL)	Anti-TB (MIC, µg/mL)	Cytotoxic, (IC ₅₀ (µg/mL))		
				KB	BC1	NCI- H187
<i>C. elatum</i>	hexane	inactive	100	inactive	inactive	inactive
	EtOAc	inactive	25	inactive	inactive	inactive
	MeOH	inactive	200	inactive	inactive	inactive
<i>C. lucknowense</i>	hexane	inactive	nd	nd	nd	nd
	EtOAc	inactive	nd	nd	nd	nd
	MeOH	inactive	nd	nd	nd	nd

*nd = not determine

Although, the crude extracts of *C. lucknowense* showed no activity against these tests, this fungus still interest in term of chemical constituents and chemotaxonomy of *chaetomium* spp.. In addition, the chemical investigation of *C. elatum* and *C. lucknowense* have not been previously reported. Thus, this research focuses on these two fungi, *C. elatum* and *C. lucknowense* (Figure 1.2).

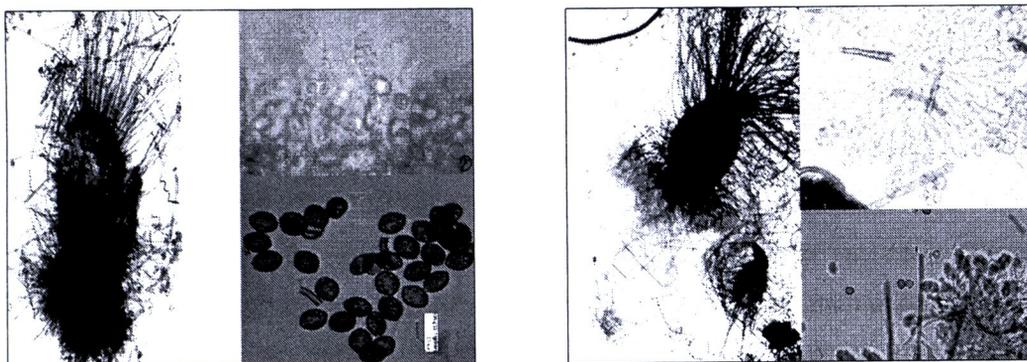


Figure 1.2 *C. elatum* (left) and *C. lucknowense* (right).

Literature Reviews

According to Scifinder Scholars 2007 data base, *Chaetomium* spp. were investigated by numerous groups. Some of their reports are summarized as follows and some isolated structures are shown in Figure 1.3.

C. amygdalisporum

In 1983, Sekita⁶ investigated the dichloromethane extract of the culture on rice of *C. amygdalisporum* UDAGAWA & MUROI strain NHL 2874 and reported the structural elucidation of a new bis-(3-indolyl)-dihydroxybenzoquinone, neocochliodinol (**1**) as well as a known compound mollicellin G (**2**).

C. atrobrunneum

In 1993, Okeke and coworkers⁷ investigated the ethyl acetate extract of *C. atrobrunneum* and found a mycotoxin, patulin (**3**) which inhibited the growth of *Pyricularia oryzae*, *Drechslera oryzae* and *Gerlachia oryzae*. In 2000, Hwang and coworkers⁸ found a novel metabolite, chaetoatrosin A (**4**) from the culture broth of *C. atrobrunneum* F449. This new compound inhibited chitin synthase and also showed antifungal activities against *Rhizoctonia solani*, *Pyricularia oryzae*, *Botrytis cinerea*, *Cryptococcus neoformans* and *Trichophyton mentagrophytes*.

C. brasilinense

In 1998, Oh and coworkers⁹ investigated the ethyl acetate extract of *C. brasilinense* Batista & Pontual (NRRL 22999), and a new bioactive fungal metabolite, chaetochalasin A (**5**) was isolated along with four known compounds chaetoglobosins D (**6**) and F_{ex} (**7**), and 19-*O*-acetyl-chaetoglobosin A (**8**) and D (**9**). Chaetochalasin A (**5**) displayed cytotoxic in the NCI's 60 cell lines of human tumor cell panel. It also exhibited antibacterial activity in standard disk assays against *Bacillus subtilis* (ATCC 6051) and *Staphylococcus aureus* (ATCC 25923).

C. chiversii

In 2006, Wijeratne and coworkers¹⁰ investigated the ethyl acetate extract of *C. chiversii* and found two new isocoumarins, chaetochiversins A (**10**) and B (**11**), and the three known chromones, eugenetin (**12**), 6-methoxy-methyleugenin (**13**), and 6-hydroxy-methyleugenin (**14**). The study also reported the isolation of cytotoxic and heat shock protein inhibitor.

C. coarctatum

In 1975, Burrows and coworker¹¹ investigated *C. coarctatum* and found two inactive metabolites 2-(buta-1,3-dienyl)-3-hydroxy-4-(penta-1,3-dienyl)-tetrahydrofuran (**15**) and coarctatin (**16**). In 1978, Seto and coworkers¹² reported that the biosynthesis of coarctatin (**16**) has been proved to be derived from four acetic acid

molecules. Later in 1983, they¹³ studied on the biosynthetic mechanism of **15** by an incorporation of ¹⁸O₂ gas. It was found that epoxide intermediate produced by air oxidation of polyketide intermediate was transformed in to **15** via an epoxide rearrangement accompanying the cleavage between C-4 and C-9.

C. cochliodes

In 1968, Brewer and coworkers¹⁴ isolated cochliodinol (**17**) from three isolate strains of *C. cochliodes* (HLX 374, HLX 577 and HLX 366). In 1972, they¹⁵ reported that chetomin (**18**) was a metabolite of *C. cochliodes* (HLX 440). It was produced by *C. cochliodes* on a defined medium and the yield was increased about 50-folds by the addition of corn steep liquor to the culture medium. It was also found to be bacteriostatic against several Gram-positive bacteria but has little or no activity against Gram-negative organisms. In addition, it inhibited the mycelial growth of some fungi and protein synthesis in culture of HeLa cells. In 1992, Abraham and Arfmann¹⁶ investigated the ethyl acetate extract of *C. cochliodes* Palliser DSM 63353, and two tetrahydrofurans with a branched alkene skeleton were isolated. The major compound was proved to be 2-(buta-1,3-dienyl)-3-hydroxy-4-(penta-1,3-dienyl)-tetrahydrofuran (**15**), and the minor compound was a new spiroketal named (1*RS*,9*RS*)-3-hydroxymethyl-8*Z*-(2'*E*-pentenylydene)-2,6-dioxa-spiro[4,4]nonanol-9 (**19**). In 1999, Kang and coworkers¹⁷ found that *C. cochliodes* produced chaetoglobosin A (**20**) which exhibited strong inhibitory activities against *Pythium ultimum*, *Phytophthora capsici*, *Rhizoctonia solani*, *Botrytis cinerea*, and *Fusarium oxysporum*. In 2006, Li and coworkers¹⁸ reported that three new epipolythiodioxopiperazines, chaetocochins A (**21**), B (**22**), and C (**23**), along with dethio-tetra (methylthio) chetomin (**24**) and chaetomin (**18**), were isolated from the ethyl acetate extract of the solid-state fermented rice culture of the fungus *C. cochliodes*. In addition, compounds **21**, **23**, and **24** exhibited significant cytotoxicity *in vitro* against some cancer cells.

C. cupreum

In 2006, Kanokmedhakul and coworkers¹⁹ isolated three new azaphilones named rotiorinols A (**25**), B (**26**), and C (**27**), two new stereoisomers, (-)-rotiorin (**28**) and *epi*-isochromophilone II (**29**), and a known compound, rubrorotiorin (**30**), from

C. cupreum CC3003. Among these, compounds **25**, **27**, **28**, and **30** exhibited antifungal activity against *Candida albicans*.

C. funicola

In 1988, Ito and coworkers²⁰ investigated *C. funicola* JS 525 and found a new ubiquinone, 2,3-dimethoxy-5-methyl-6-IX,X-tetrahydrofarnesylfarnesylgeranylgeranyl-1,4-benzoquinone (**31**).

C. globosum

C. globosum is the species which has been received the most attention from many research groups worldwide in term of chemical constituents and bioactivities. In 1968, Brewer and coworker¹⁴ investigated two strains of *C. globosum* (HLX 707 and HLX 819) and found a purple pigment, named cochliodinol (**17**). In 1972, they¹⁵ further reported that chetomin (**18**) was produced by two isolated strains of *C. globosum*. In general, chetomin (**18**) was produced by *C. cochliodes* in higher yield than *C. globosum*. In 1973, Sekita and coworkers²¹ isolated three cytotoxic indol-3-yl-[13]cytochalasan metabolites, chaetoglobosin A (**20**), B (**32**) and C (**33**) from *C. globosum*. In 1976, they²² further reported the structures of chaetoglobosins C (**33**), D (**6**), E (**34**) and F (**35**). One year later, they²³ reported the structures of chaetoglobosin G (**36**) and J (**37**). Biosynthetic pathways of chaetoglobosins A-G and J were proved by Sekita and coworkers²⁴ in 1983 and they found that the molecules were formed from nine units of acetate/malonate, three C₁ units, and one unit of tryptophan. In 1980, Itoh and coworkers^{25, 26} found a new sesquiterpene antibiotic, heptelidic acid (**38**) from *C. globosum* (SANK 13379). The antimicrobial spectrum of the antibiotic **38** revealed its specific activity anaerobic bacteria, especially against *Bacteroides fragillis* and *Propionibacterium acnes*. In 1981, Probst and Tamm²⁷ investigated the dichloromethane extract of *C. globosum* (strain Lederle H-124) and found five cytochalasans, chaetoglobosin A (**20**), 19-*O*-acetylchaetoglobosin A (**8**), chaetoglobosin C (**33**), 19-*O*-acetylchaetoglobosin B (**39**) and 19-*O*-acetylchaetoglobosin D (**9**), which **9** and **39** were reported as new compounds. In the same year, Kikuchi and coworkers²⁸ isolated geosmin (**40**), an earthy musty smelling compound from *C. globosum*. One year later, they²⁹ further reported the isolation and structural elucidation of a new metabolite, dethio-tetra(methylthio) chaetomin (**24**), and a known chaetomin (**18**) from the ethyl acetate extract of *C. globosum*. These

metabolites showed antimicrobial activity against *Escherichia coli* W3110, *Staphylococcus aureus* 209P, and etc. In the same year, Sekita group³⁰ reported that chaetoglobosins affected the structure and functions of mammalian cell; they ceased inhibition of cellular movements including cell division motility, secretion and also caused changes in cell shape. In 1990, Takahashi and coworkers³¹ reported that *C. globosum* var. *flavo-viridae* (TRTC 66.631a) produced four new azaphilones of angular type, named chaetoviridins A (41) as the major metabolite, B (42), C (43), and D (44) as the minor congeners. Chaetoviridin A (41) showed a weak inhibitory activity on monoamine oxidase, an induction of chlamydomonad-like cell, and an inhibition of growth of *Pyricularia oryzae*. In 1992, Di Pietro and coworkers³² reported that *C. globosum* produced 2-(buta-1,3-dienyl)-3-hydroxy-4-(penta-1,3-dienyl)-tetrahydrofuran (15) and chetomin (18) which showed activity against *Pythium ultimum*, a causal agent of damping-off of sugarbeet. In 1994, Yasukawa and coworkers³³ reported that chaetoviridin A (41) exhibited the inflammatory activity of 12-*O*-tetradecanoylphorbol-13-acetate in mice. In 1996, Breinholt and coworkers³⁴ found a novel metabolite, named prenisatin (45), exhibited *in vitro* growth inhibitory activity against *Botrytis cinerea*. In 2002, Kanokmedhakul and coworkers³⁵ investigated on *C. globosum* KMITL-N0802 and found a novel anthraquinone-chromanone compound, name chaetomanone (46), along with seven known compounds, ergosterol (47), ergosteryl palmitate (48), chrysophanol (49), chaetoglobosin C (32), alternariolmonomethyl ether (50), echinulin (51), and isochaetoglobosin D (52). Chaetomanone (46) and echinulin (51) exhibited activity towards *Mycobacterium tuberculosis*. In 2004, Jiao and coworkers³⁶ reported that nine cytotoxic metabolites, including three novel compounds, chaetoglobosins Q (53), R (54), and T (55), and six known compounds, chaetoglobosins A (20), B (32), D (6), and J (37), prochaetoglobosins I (56), and II (57), have been isolated from cultures of the fungus *C. globosum*. One year later, Bashyal and coworkers³⁷ proposed that three new esters of orsellinic acid, globosumones A (58), B (59), and C (60), and three known compounds, orsellinic acid (61), orcinol (62), and trichodion (63), were isolated from *C. globosum* endophytic on *Ephedra fasciculata* (Mormon tea). All compounds were evaluated for inhibition of cell proliferation in a panel of four cancer cell lines. Only globosumones A (58) and B (59) were found to be moderately active.

In 2006, Ding and coworkers³⁸ investigated the ethyl acetate extract of a solid culture of *C. globosum* IFB-E019 and yielded a new cytotoxic cytochalasan-based alkaloid named chaetoglobosin U (**64**), along with four known analogues, chaetoglobosins C (**32**), E (**34**), and F (**35**) and penochalasin A (**65**). Chaetoglobosin U (**64**) exhibited cytotoxic activity against the human nasopharyngeal epidermoid tumor KB cell line. The known analogues **32-35**, and **65** were moderately active to the cell lines tested. In the same year, Yang and coworkers³⁹ reported that two novel chemokine receptor CCR-5 inhibitors, Sch 210971 (**66**) and Sch 210972 (**67**), were isolated from the fungal fermentation broth of *C. globosum*, which the structure and relative configuration of **67** were determined unequivocally by X-ray crystallographic analysis. The major compound **67** demonstrated a potent inhibitory activity. Wang and coworkers⁴⁰ proposed that cultivation of the endophytic fungus *C. globosum*, which was isolated from the inner tissue of the marine red alga *Polysiphonia urceolata*, resulted in the isolation of chaetopyranin (**68**), a new benzaldehyde secondary metabolite. Ten known compounds were also isolated, including two benzaldehyde congeners, 2-(2',3'-epoxy-1',3'-heptadienyl)-6-hydroxy-5-(3methyl-2-butenyl)benzaldehyde (**69**) and isotetrahydroauroglaucin (**70**), two anthraquinone derivatives, erythroglaucin (**71**) and parietin (**72**), five asperentin derivatives including asperentin (**73**), 5'-hydroxy-asperentin-8-methylether (**74**), asperentin-8-methyl ether (**75**), 4'-hydroxyasperentin (**76**), and 5'-hydroxyasperentin (**77**), and the prenylated diketopiperazine congener neoechinulin A (**78**). Compounds **68-73** were found to have moderate activity. Chaetopyranin (**68**) also exhibited moderate to weak cytotoxic activity toward several tumor cell lines. In 2006, Wijeratne and coworkers⁴¹ investigated bioassay-guided fractionation of a cytotoxic ethyl acetate extract of *C. globosum*, and afforded a new dihydroxanthone, globosuxanthone A (**79**) a new tetrahydro-xanthone, globosuxanthone B (**80**), two new xanthenes, globosuxanthone C (**81**) and D (**82**), a known xanthone, 2-hydroxyvertixanthone (**83**), and two known anthraquinones, chrysazin (**84**) and 1,3,6,8-tetrahydroxyanthraquinone (**85**). Of the compounds encountered, **79** was found to exhibit strong cytotoxic against a panel of several human solid tumor cell lines. Recently in 2007, Marwah and coworkers⁴² isolated two antibacterial furano-polyenes, (-)-musanol (**86**), and 3-*epi*-aureonitol (**87**), and a fatty acid, linoleic acid (**88**) from the cultures of



a *C. globosum*. Linoleic acid (**88**) was isolated from the mycelia of the fungus and it inhibited the growth of *Staphylococcus aureus* and *Bacillus subtilis*.

C. gracile

In 1987, Koyama and Natori⁴³ investigated the dichloromethane extract of *C. gracile* and three new related bis(naphtho- γ -pyrone) derivatives named chaetochromins B (**89**), C (**90**), and D (**91**) and a known chaetochromin A (**92**) were isolated. They also indicated that both of the vicinal methyl groups in **92** and one of the two in **89** are *trans*, while the other in **89** is *cis*. Two years later, they⁴⁴ studied the biosynthesis of chaetochromin A (**92**), a metabolite of *C. gracile*, by using [¹³CH₃] methionine, sodium [1-¹³C]acetate, sodium [1,2-¹³C₂]acetate, sodium [1-¹³C,2,2,2-²H₃]acetate, and sodium [1-¹³C,1,1-¹⁸O₂]acetate as precursors. The result showed that the folding pattern of the polyketide chain in chaetochromin A (**92**) was determined to be the same as those of rubrofusarin by carbon-13 nuclear magnetic resonance (¹³C-NMR) analysis.

C. indicum

In 2006, Li and coworkers⁴⁵ isolated three novel alkaloids, chaetoindicins A (**93**), B (**94**), and C (**95**) from the solid-state fermented culture of *C. indicum*.

C. mollicellum

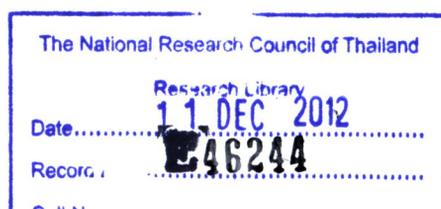
In 1978, Stark and coworkers⁴⁶ found eight mollicellines (depsidones), the major products of the fungus *C. mollicellum* MIT M-37, mollicellines A (**96**), B (**97**), C (**98**), D (**99**), E (**100**), F (**101**), G (**2**), and H (**102**). Mollicellines C (**98**) and E (**100**) which contained a 3-methylbutenoic acid moiety, were mutagenic and bactericidal for *Salmonella typhimurium* in the absence of microsome. While mollicellines D (**99**) and F (**101**), which each contained a chloride atom, were bactericidal but not mutagenic.

C. murorum

In 1983, Sekita⁶ reported the structural elucidation of isocochliodinol (**103**), a metabolite of *C. murorum* NHL (78-SH-271-4) and NHL 2240.

C. nigricolor

In 1988, Saito and coworkers⁴⁷ investigated the ethyl acetate extract of the culture on rice of *C. nigricolor* AMES. A new dimeric epipolythiodioxopiperazine



nemed chetracin A (**104**) with two tetrasulfide bridges was isolated along with a known compound cochliodinol (**17**).

C. olivaceum

In 2001, Smetanina and coworkers⁴⁸ reported that a pentacyclic triterpenoid, 3 β -methoxyolean-18-ene (miliacin) (**105**), was isolated for the first time from the marine fungus *C. olivaceum*.

C. quadrangulatum

In 2002, Fujimoto and coworkers⁴⁹ isolated five new chromones named chaetoquadrins A (**106**), B (**107**), C (**108**), D (**109**) and E (**110**) from the ethyl acetate extract of *C. quadrangulatum* 71-NG-22. Among these, compounds **106-108** were tetracyclics and compound **109** contains a sulfonyl group. One year later, they⁵⁰ further reported six constituents named chaetoquadrins F (**111**), G (**112**), H (**113**), I (**114**), J (**115**) and K (**116**). Chaetoquadrins G (**112**) and H (**113**) have shown appreciable monoamine oxidase inhibitory activity.

C. retardatum

In 1988, Saito and coworkers⁴⁷ found chetracin A (**104**) and 11 α ,11' α -dihydroxychaetocin (**117**) from *C. retardatum* TRTC 66.1778b.

C. seminudum

In 2004, Fujimoto and coworkers⁵¹ investigated focusing on immunomodulatory activity of the ethyl acetate extract of *C. seminudum* 72-S-204-1 and yielded a known epipolythiodioxopiperazine, chetomin (**18**), together with three new chetomin-related metabolites named chetoseminudins A (**118**), B (**119**), and C (**120**).

C. subaffine

In 1993, Oikawa and coworkers⁵² found that *C. subaffine* produced two new metabolites of chaetoglobosins named chaetoglobosin F_{ex} (**7**) and 20-dihydrochaetoglobosin A (**121**).

C. thielavioideum

In 1980, Sekita and coworkers⁵³ investigated the metabolites of *C. thielavioideum* NHL 2829 and isolated a new phenolic chaetochromin A (**92**) as well as known compounds chaetocin (**122**), sterigmatocystin (**123**), *O*-methylsterigmatocystin (**124**), ergosterol (**47**) and eugenitin (**125**). In 1988 Saito and work groups⁴⁷ reported that chaetocins B (**126**) and C (**127**) were isolated from

C. thielavioidium NHL 2827, and were proved to be homologous with one disulfide and one trisulfide bridge for **126** and with two trisulfide bridges for **127**, respectively. These metabolites also showed strong activities against *Staphylococcus aureus* FDA 209P.

C. trilaterale

In 1974, Cole and coworkers⁵⁴ reported that a strain of *C. trilaterale* Chivers ATCC 24912 produced the major toxic metabolite as the dibenzoquinone, oosporein (3,3',6,6'-tetrahydroxy-5,5'-dimethyl-2,2'-bi-*p*-benzoquinone) (**128**), which had a median oral lethal dose of 6.12 mg/kg in day-old cockerels. The toxin **128** also exhibited plant growth inhibiting and phytotoxic effects.

Chaetomium spp.

In 2006, Jiao and coworkers⁵⁵ isolated chaetominine (**129**), an alkaloidal metabolite with a new framework, from the solid-substrate culture of *Chaetomium* spp. IFB-E015, an endophytic fungus on the apparently healthy *Adenophora axilliflora* leaves. Chaetominine (**129**) was more cytotoxic than 5-fluorouracil against the human leukemia K562 and colon cancer SW1116 cell lines.

The isolation compounds of *Chaetomium* spp. can be classified into many groups as follows: alkaloides, azaphilones, benzenoids, chromones, cytochalasans, epipolythiodioxopiperazines, quinones and others (acids, aldehydes, isocumarins, steroids, terpenes, terpenoids, xanthenones and xanthone). These compounds are presented in Table 1.2.

Table 1.2 Isolated compounds from *Chaetomium* spp.

Classified Groups	Isolated Compounds	Referents
alkaloides	45, 51, 78, 93, 94, 95, 129	34, 35, 40, 45, 55
azaphilones	25, 26, 27, 28, 29, 30, 41, 42, 43, 44	19, 31
benzenoids	2, 4, 50, 62, 89, 90, 91, 92, 98, 99, 100, 101, 102, 122, 123, 124, 125	6, 8, 35, 37, 43, 46, 53,
chromones	12, 13, 14, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116	10, 49, 50
cytochalasans	5, 6, 7, 8, 9, 20, 32, 33, 34, 35, 36, 37, 39, 52, 53, 54, 55, 57, 64, 65, 121	6, 17, 21, 22, 23, 27, 35, 36, 38, 52
epipolythiodioxopiperazines	18, 21, 22, 23, 24, 104, 117, 118, 119, 120, 122, 126, 127	15, 18, 47, 51, 53
quinones	1, 17, 31, 46, 49, 71, 72, 73, 84, 85, 103, 128	6, 14, 20, 35, 40, 41, 54
others	3, 10, 11, 15, 16, 19, 38, 47, 48, 58, 59, 60, 61, 66, 67, 68, 69, 70, 74, 75, 76, 77, 79, 80, 81, 82, 83, 86, 87, 88, 105	7, 10, 11, 12, 16, 25, 26, 35, 37, 39, 40, 41, 42, 48

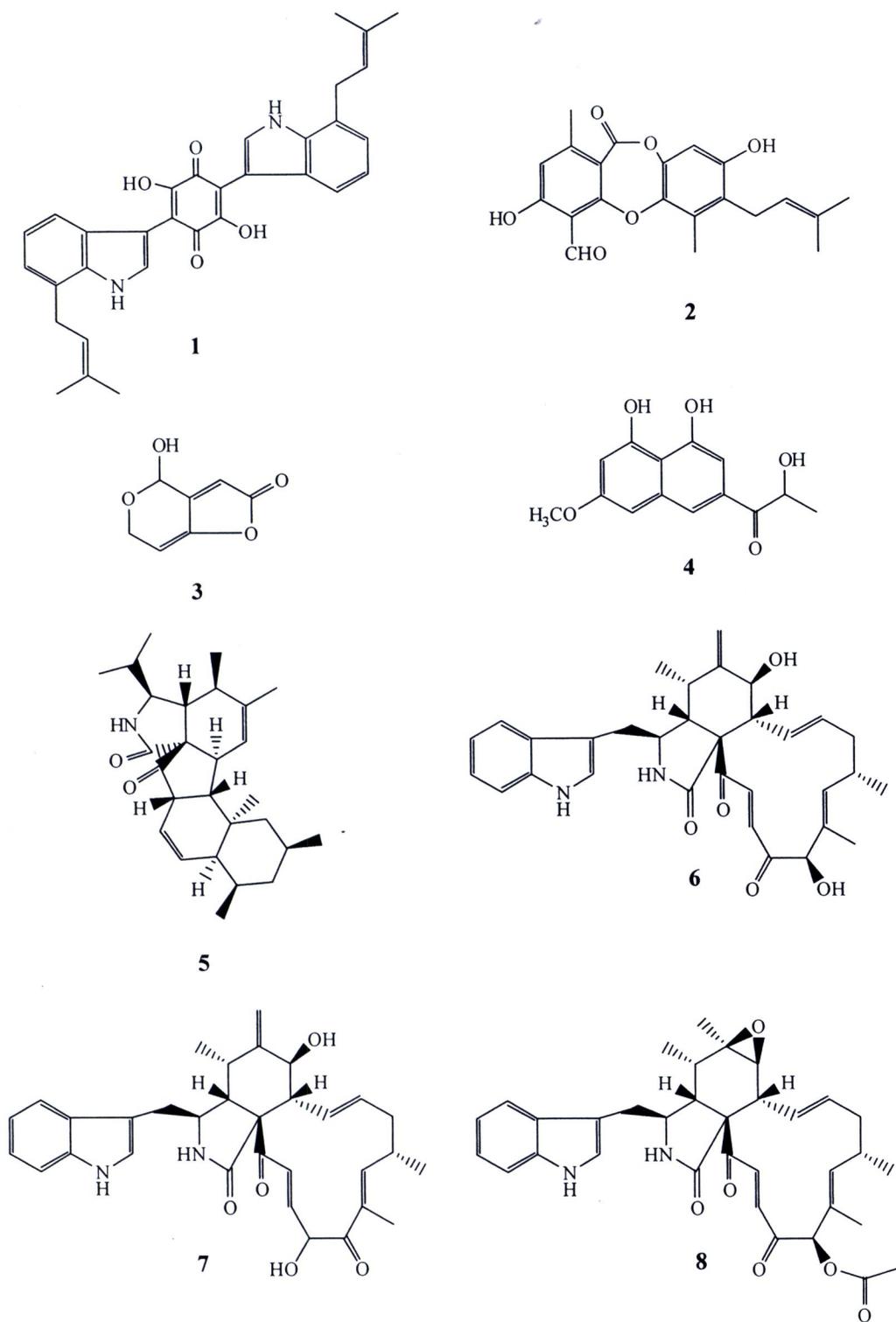


Figure 1.3 Some chemical constituents from *Chaetomium* spp..

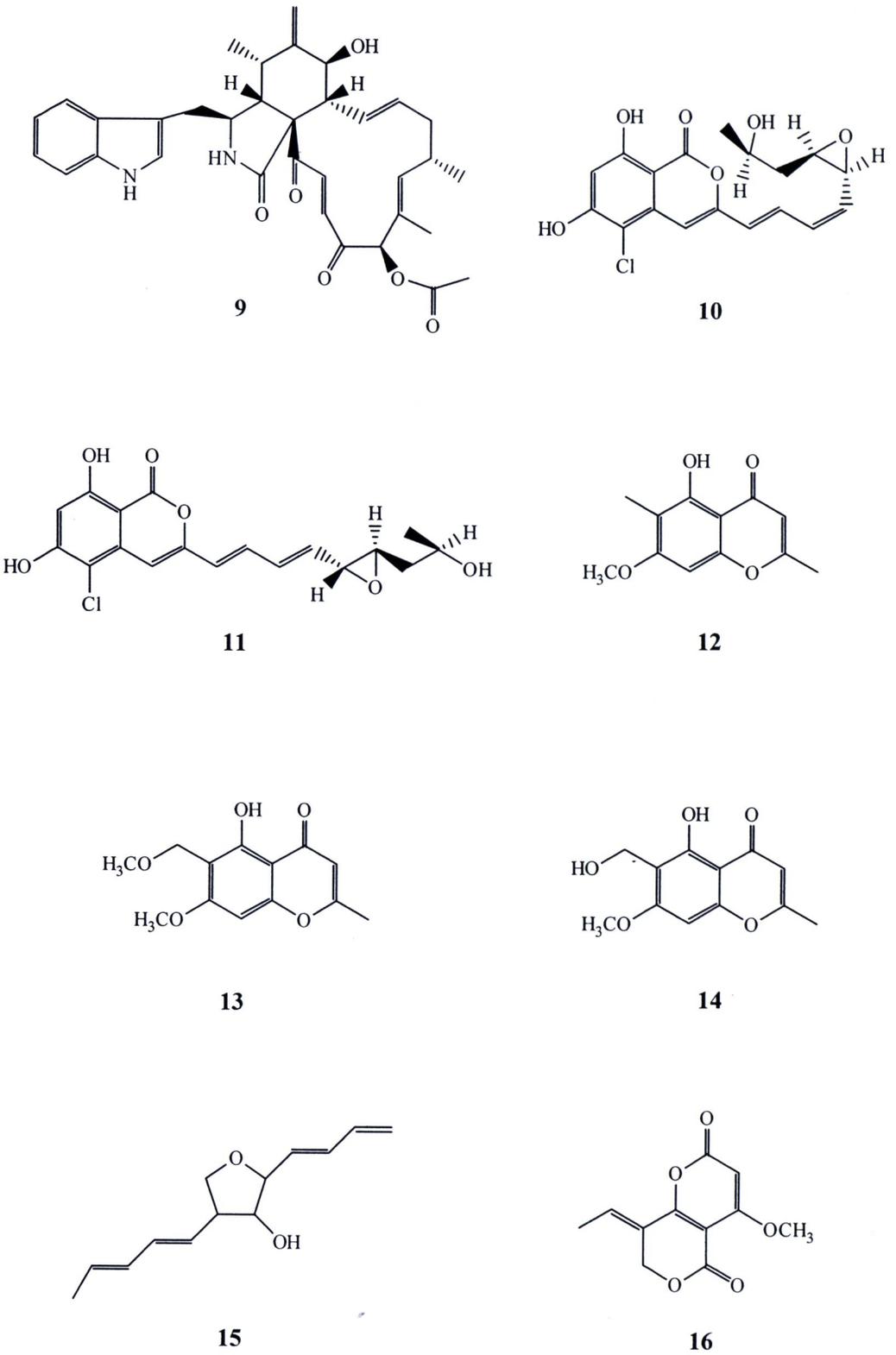
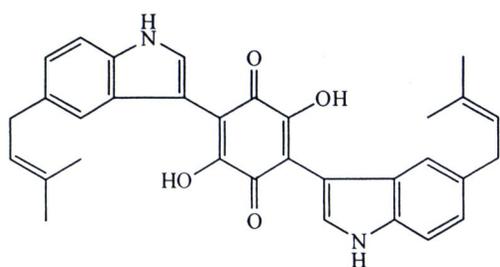
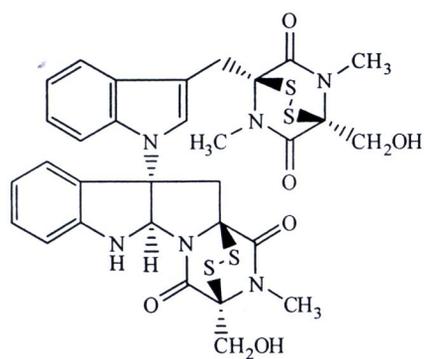


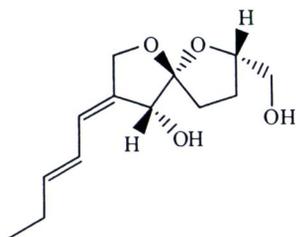
Figure 1.3 Some chemical constituents from *Chaetomium* spp. (cont.).



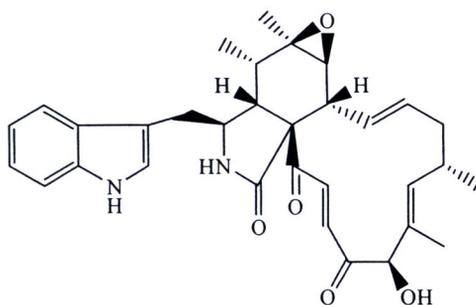
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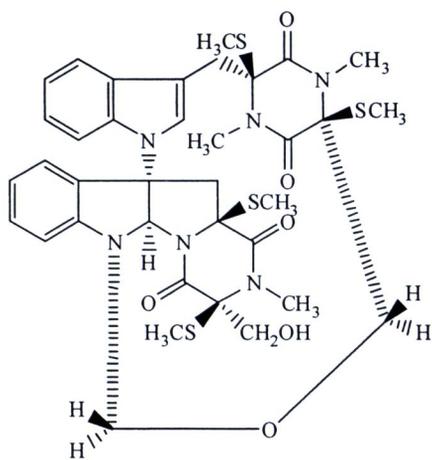
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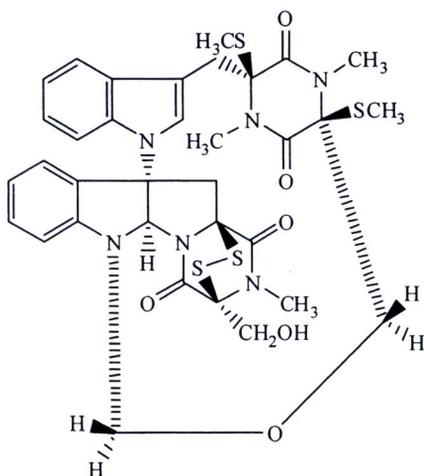
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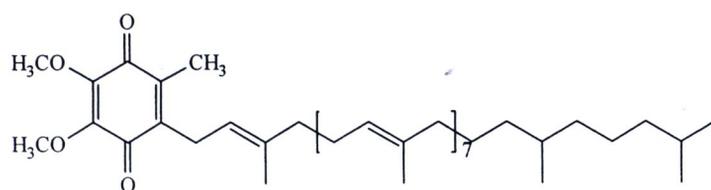


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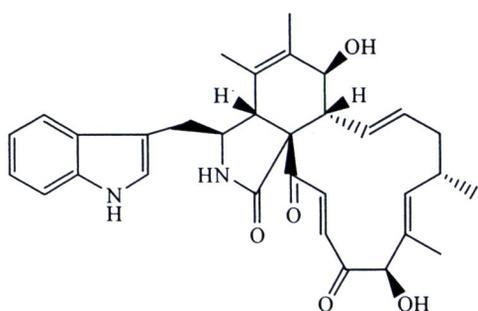


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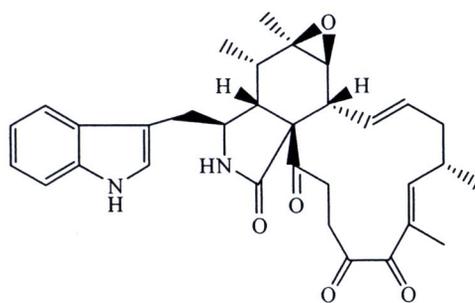
Figure 1.3 Some chemical constituents from *Chaetomium* spp. (cont.).



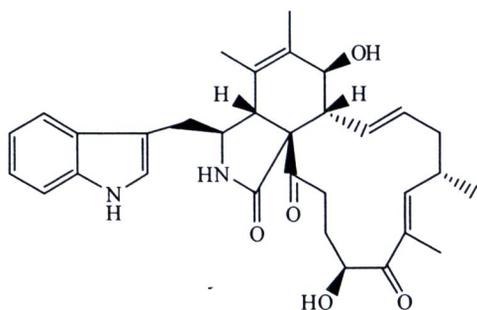
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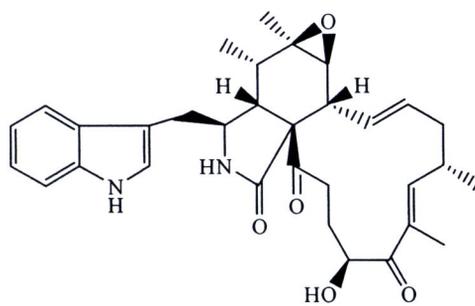
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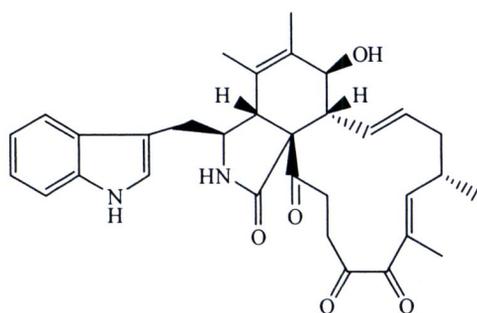
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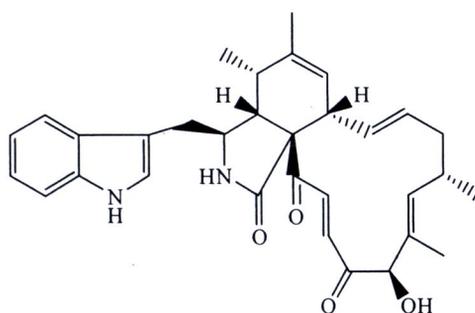
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Figure 1.3 Some chemical constituents from *Chaetomium* spp. (cont.).

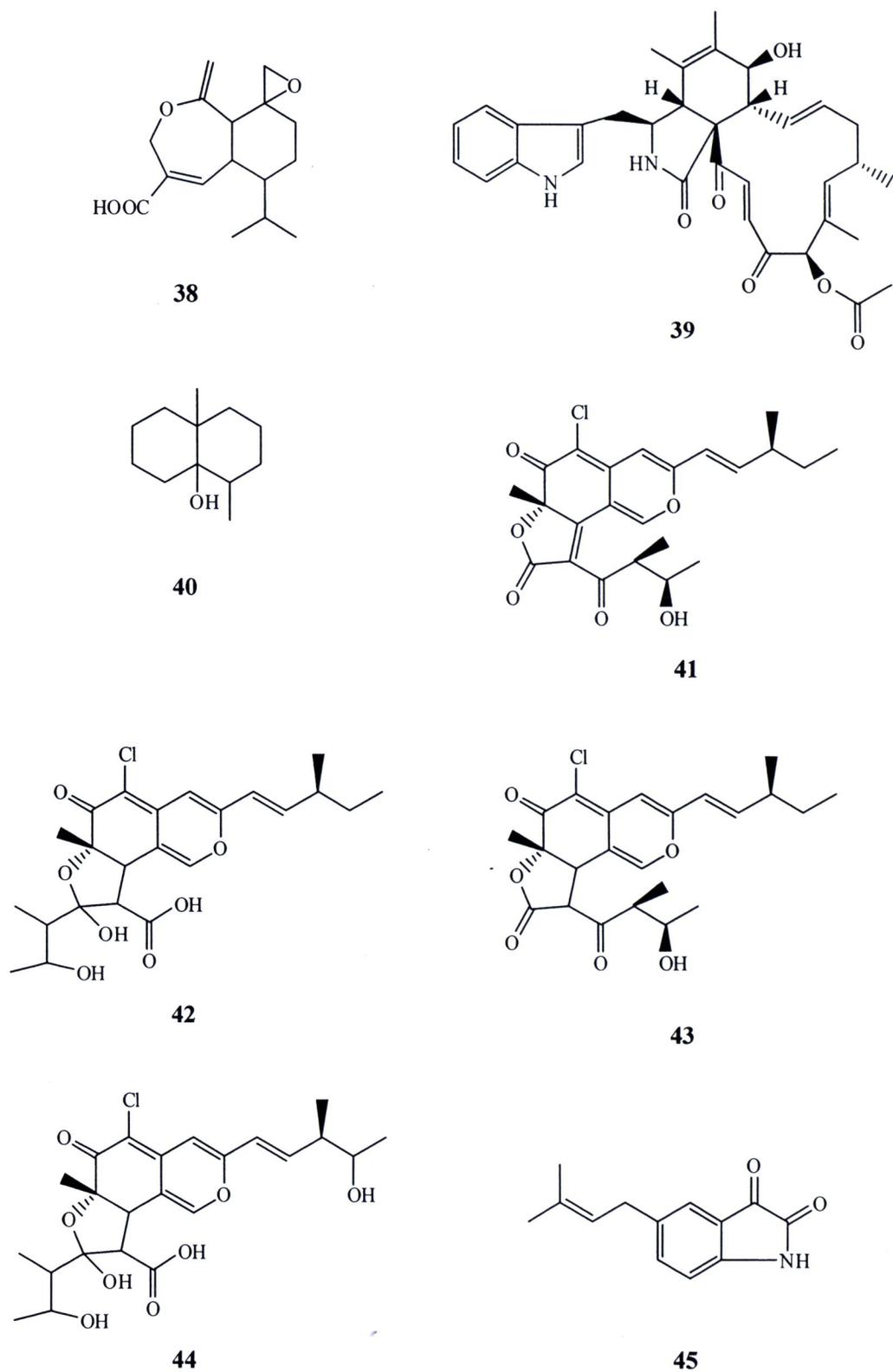


Figure 1.3 Some chemical constituents from *Chaetomium* spp. (cont.).

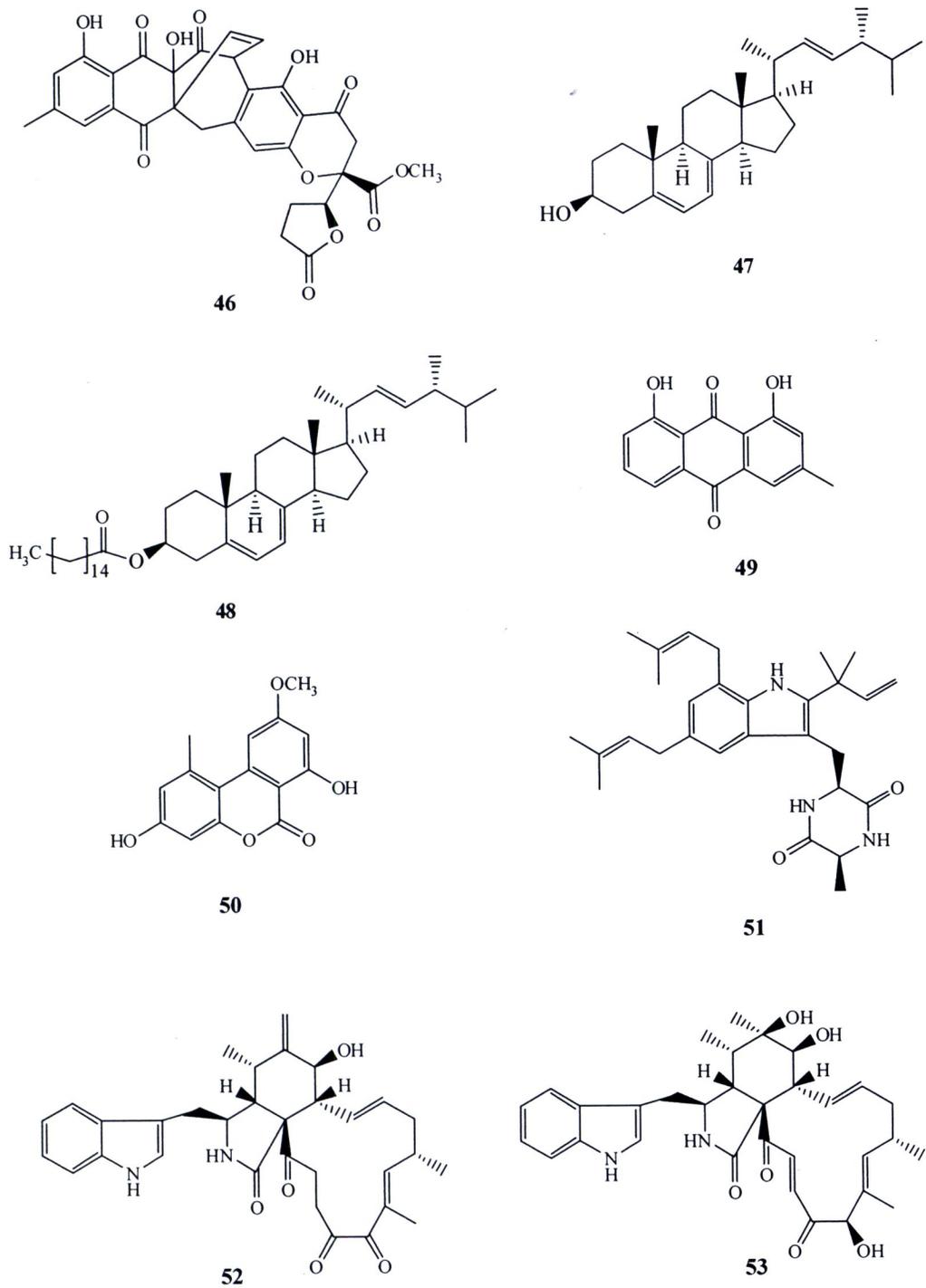


Figure 1.3 Some chemical constituents from *Chaetomium* spp. (cont.).

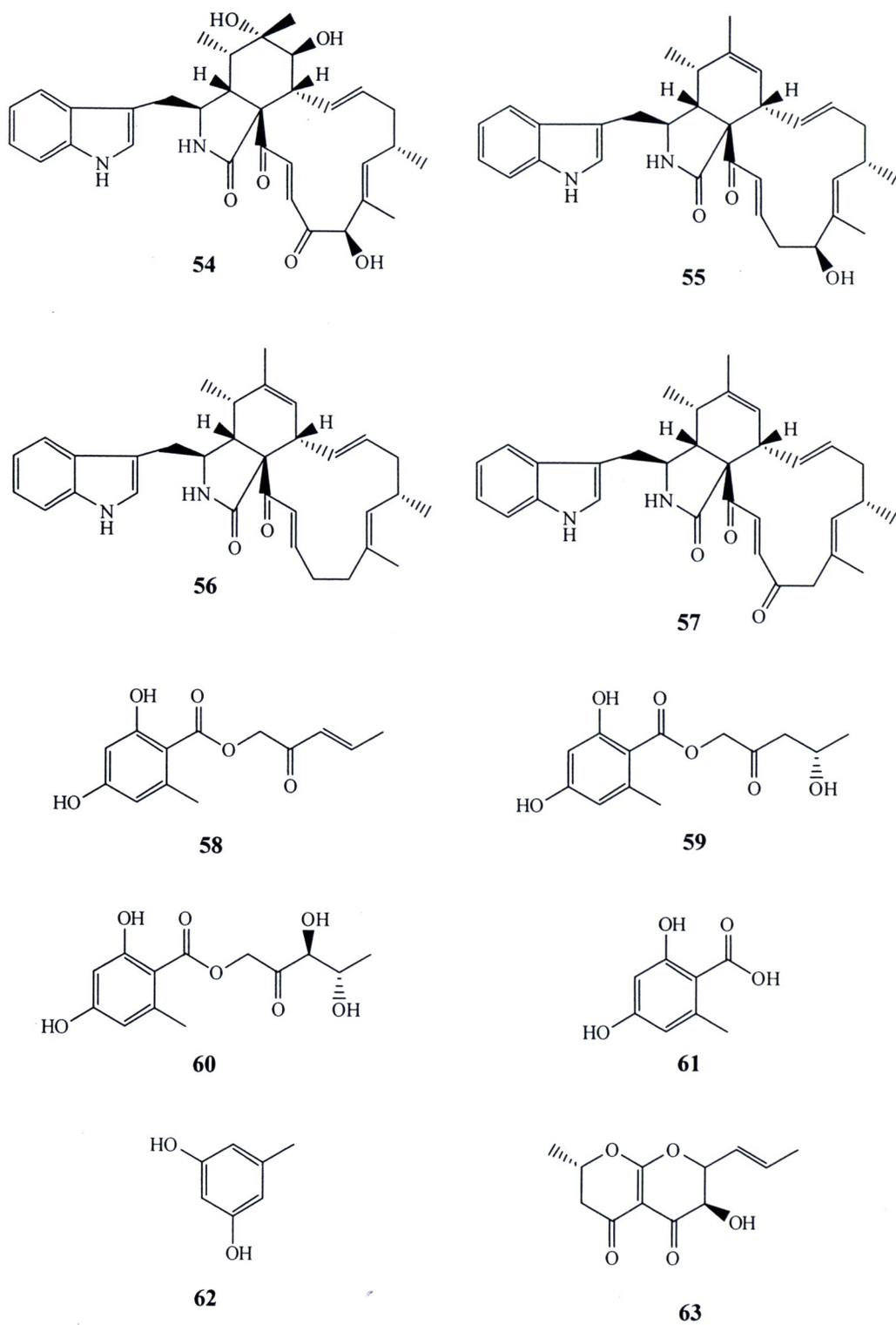


Figure 1.3 Some chemical constituents from *Chaetomium* spp. (cont.).

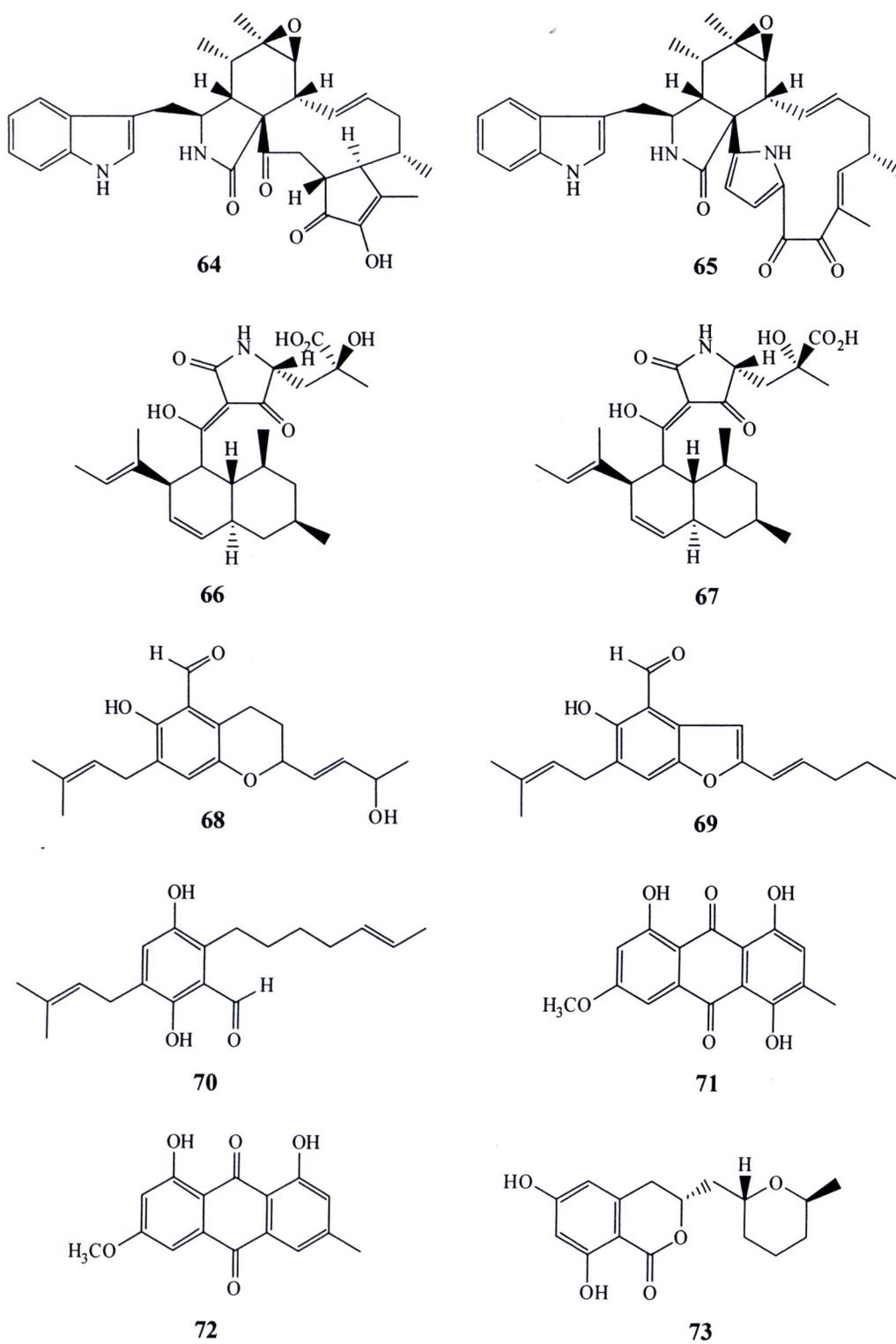


Figure 1.3 Some chemical constituents from *Chaetomium* spp. (cont.).

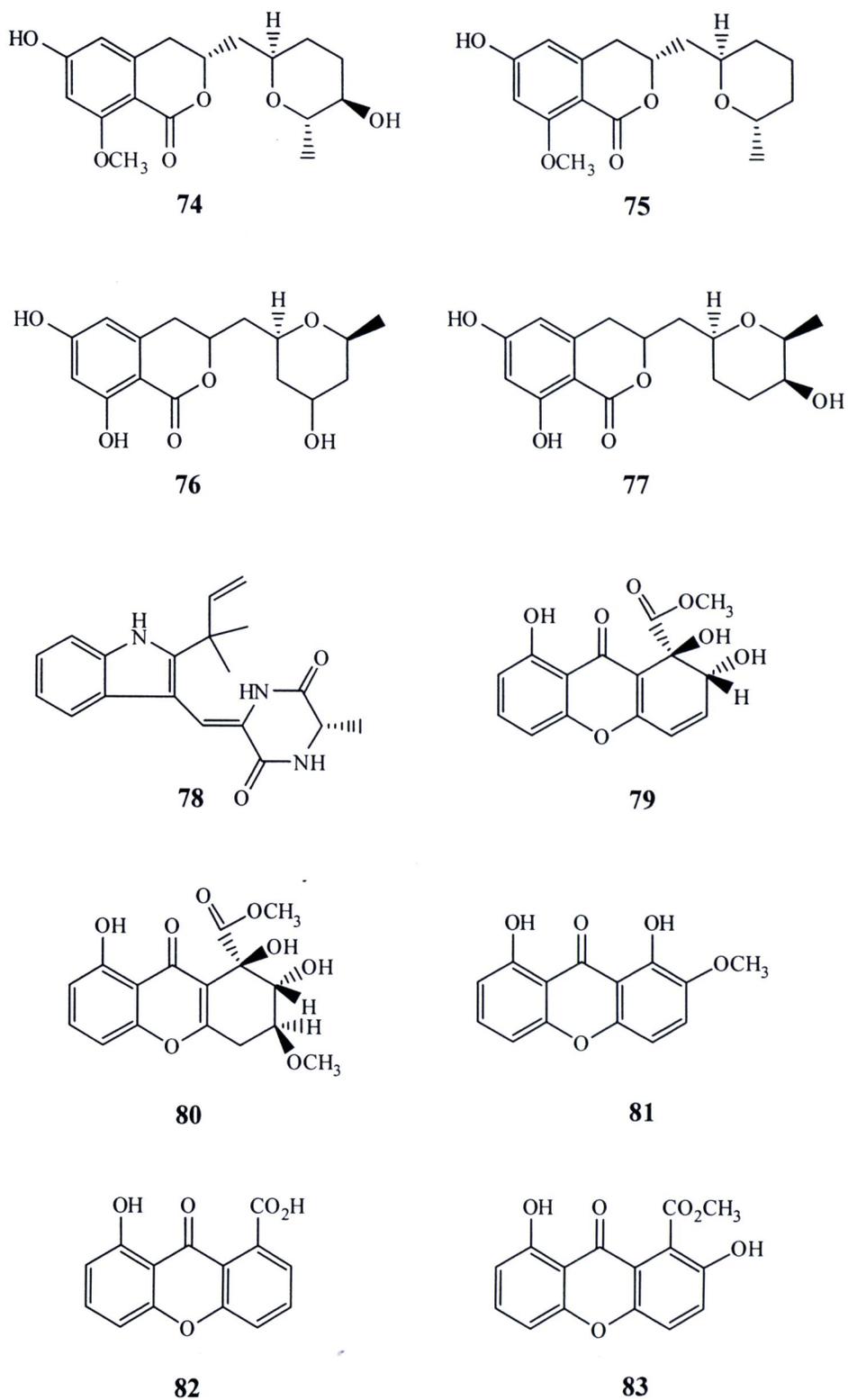


Figure 1.3 Some chemical constituents from *Chaetomium* spp. (cont.).

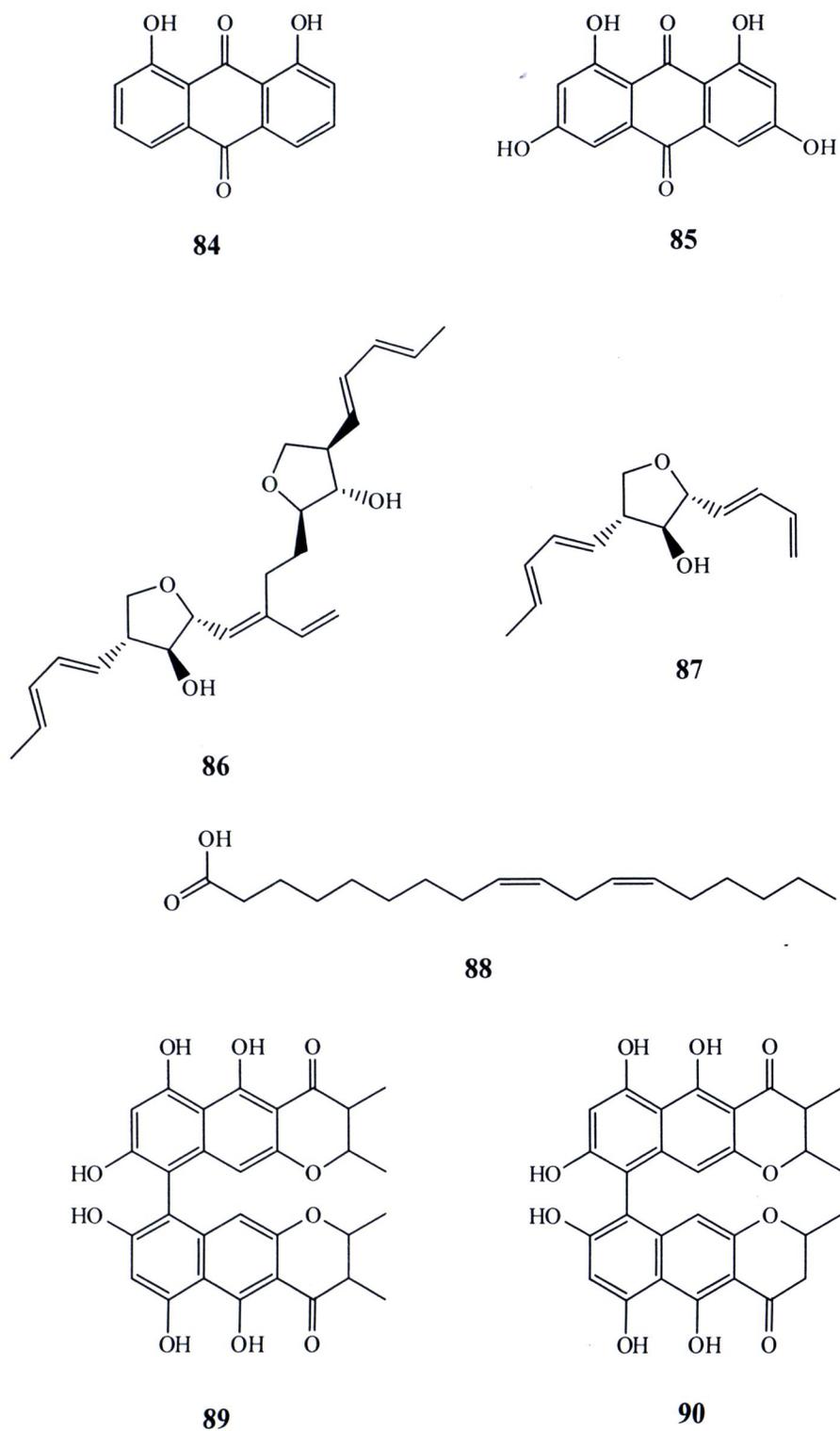


Figure 1.3 Some chemical constituents from *Chaetomium* spp. (cont.).

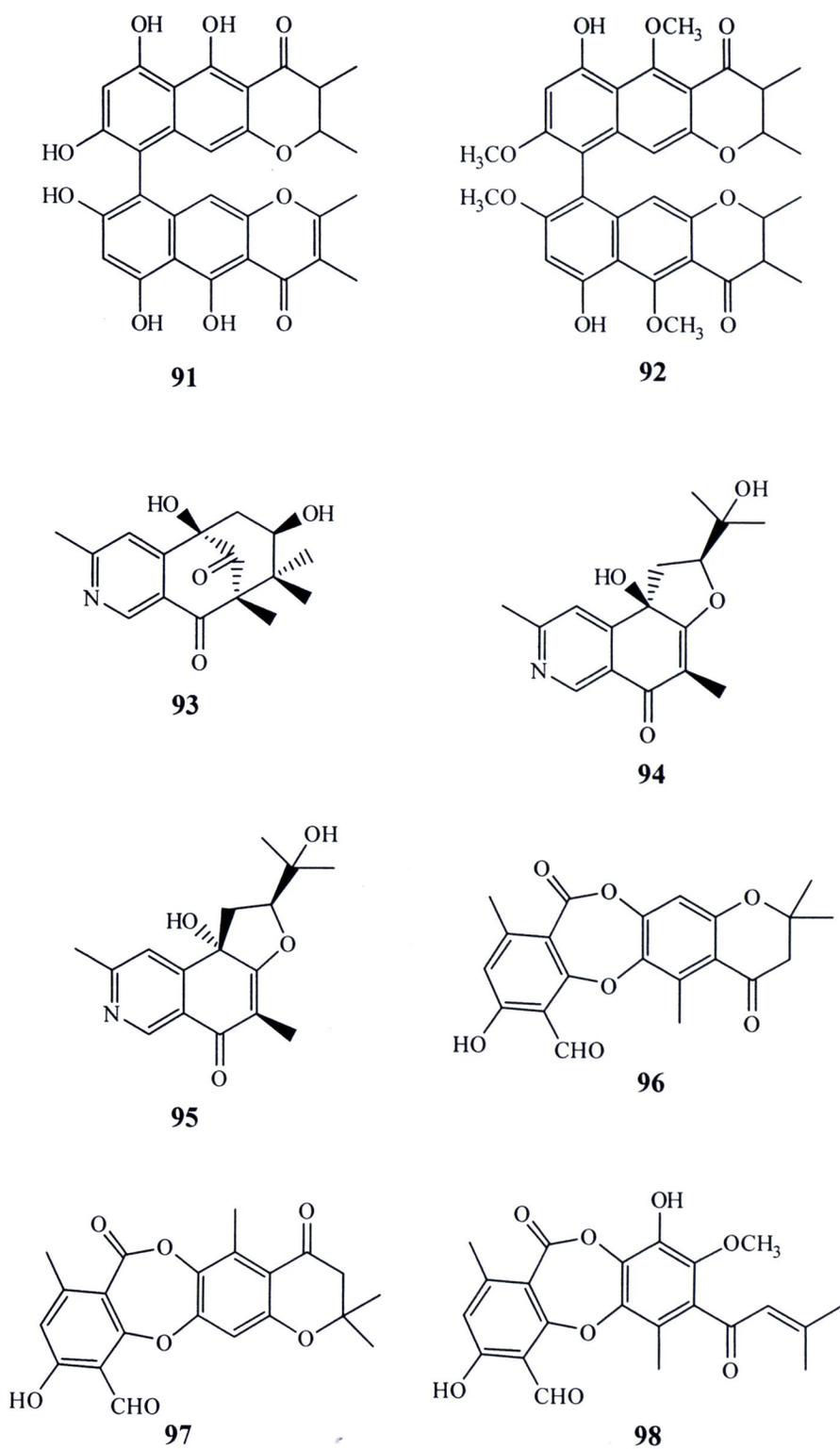


Figure 1.3 Some chemical constituents from *Chaetomium* spp. (cont.).

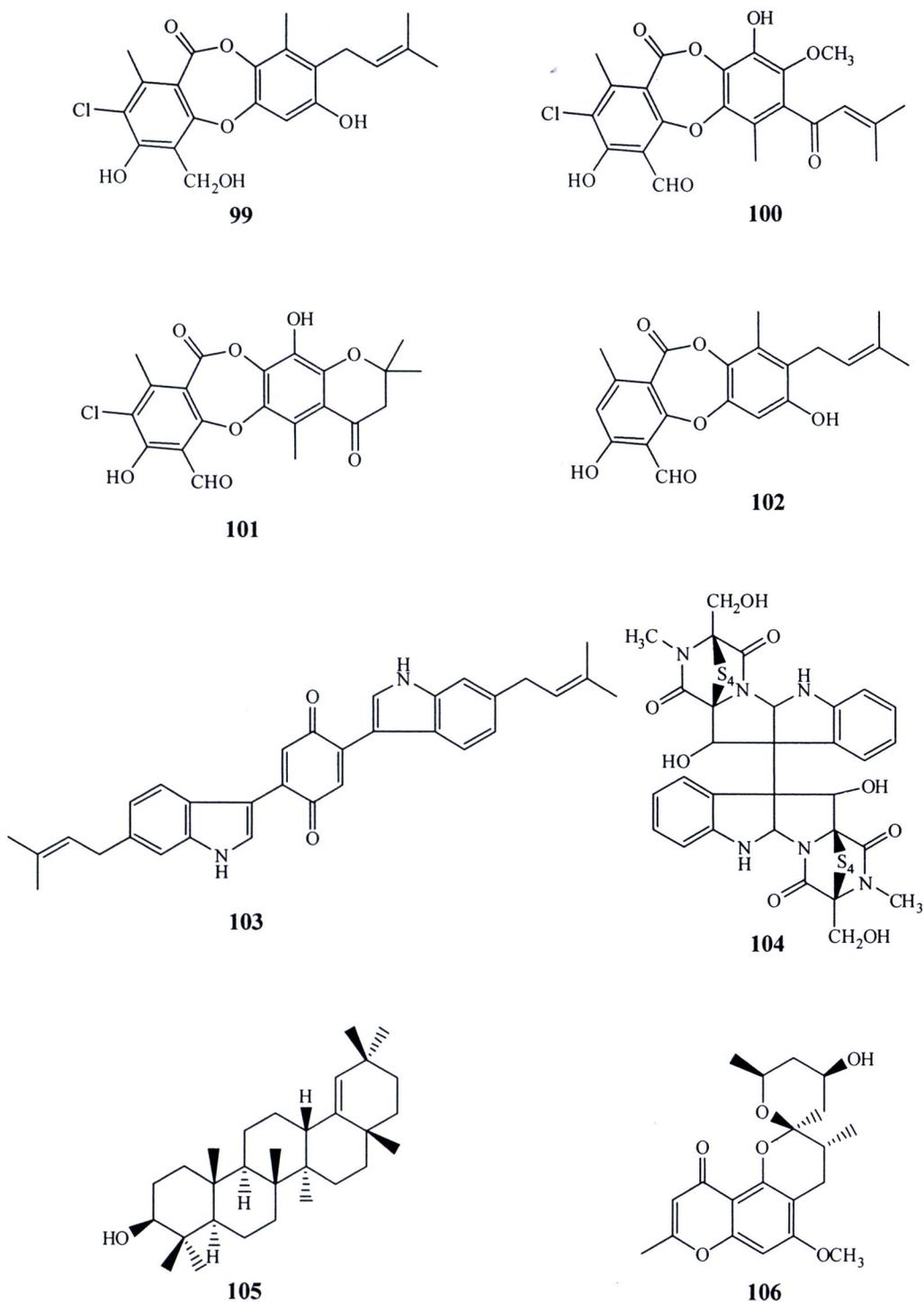


Figure 1.3 Some chemical constituents from *Chaetomium* spp. (cont.).

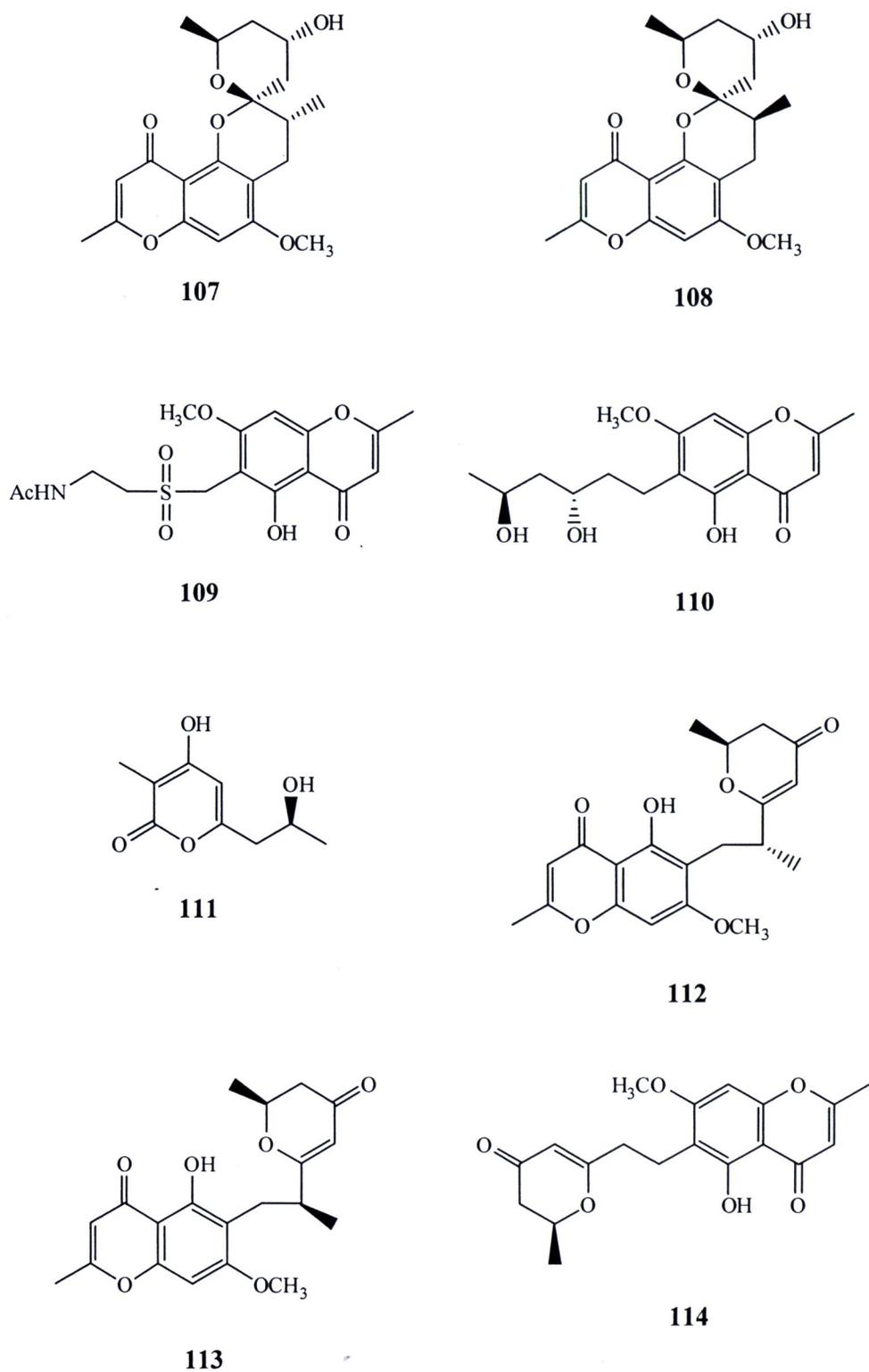


Figure 1.3 Some chemical constituents from *Chaetomium* spp. (cont.).

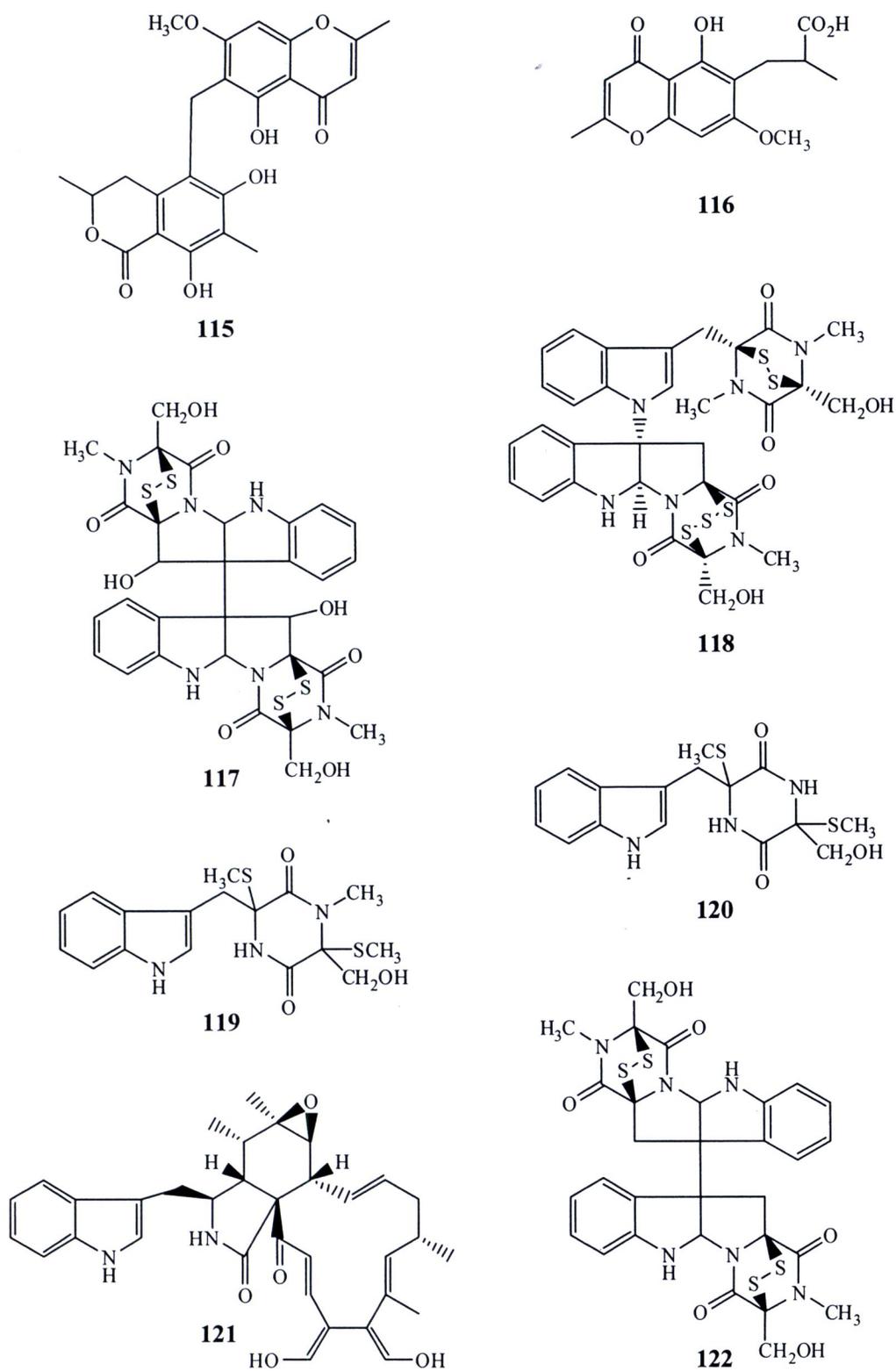


Figure 1.3 Some chemical constituents from *Chaetomium* spp. (cont.).

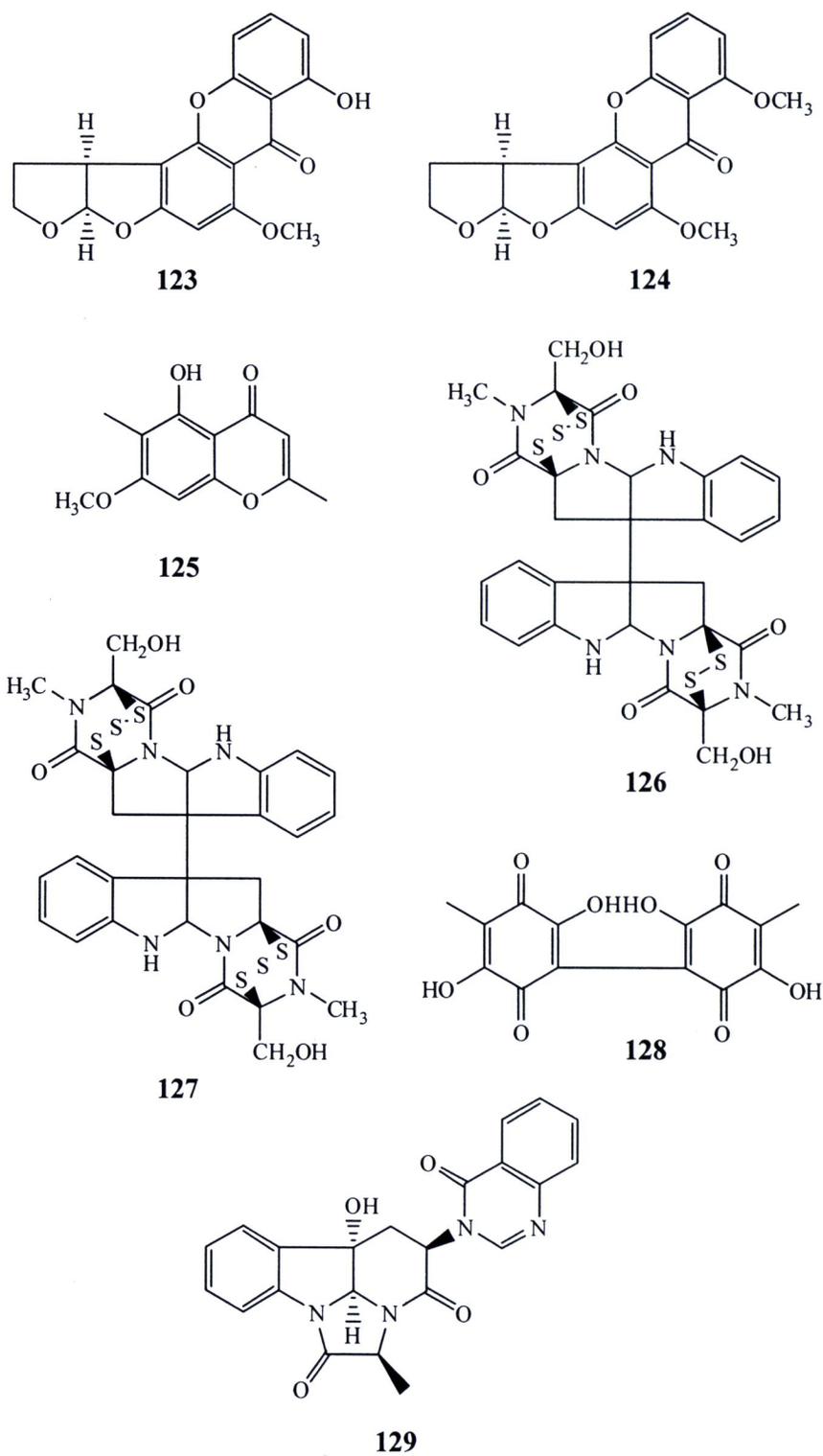


Figure 1.3 Some chemical constituents from *Chaetomium* spp. (cont.).