CHAPTER I
INTRODUCTION

Introduction of Fungi

The Kingdom Fungi includes some of the most important organisms, both in terms of their ecological and economic roles. By breaking down dead organic material, they continue the cycle of nutrients through ecosystems. In addition, most vascular plants could not grow without the symbiotic fungi, or mycorrhizae, that inhabit their roots and supply essential nutrients. Other fungi provide numerous drugs (such as penicillin and other antibiotics), foods like mushrooms, truffles and morels, and the bubbles in bread, champagne, and beer.

Fungi also cause a number of plant and animal diseases: in humans, ringworm, athlete's foot, and several more serious diseases are caused by fungi. Because fungi are more chemically and genetically similar to animals than other organisms, this makes fungal diseases very difficult to treat. Plant diseases caused by fungi include rusts, smuts, and leaf, root, and stem rots, and may cause severe damage to crops. However, a number of fungi, in particular the yeasts, are important "model organisms" for studying problems in genetics and molecular biology.[1]

Fungi[2] are plant-like organisms that lack chlorophyll. They are one of the five kingdoms of life which comprise over 100,000 species. Many of them are useful such as *Penicillium* and *Stachybotrys* while some cause problems in plants and human. Since they do not have chlorophyll, fungi must absorb food from others. They can get food from almost everything. Without fungi, we would have piles of trash everywhere.

Drug Discovery from Fungi

At the beginning of the 21st century, Fungi were involved in the industrial processing of more than 10 of the 20 most profitable products used in medicine. Two anti-cholesterol statins, the antibiotic penicillin and the immunosuppressant cyclosporine cyclosporine A are among the 10. Fungi are extremely useful organisms in biotechnology. Fungi contruct unique complex molecules using established metabolic pathways. Different taxa produce seta of related molecules, each with

slightly different final products. Metabolites formed along the metabolic pathway may also be biologically active. In addition, the final compounds are often released into the environment. Manipulation of the genome, and environmental conditions during formation of compounds, enable the optimization of product formation. On the negative side, single isolates of fungi in manufacture may lose their capacity to form or release the target molecules. Indeed, the target compound may only be expressed under specific conditions, or at a specific point in the life cycle of fungus. It is amazing that so many biologically active compounds have been discovered and taken to point where they are medically important.[3]

The serendipitous discovery of penicillin from the filamentous fungus, *Penicillium notatum*, by Fleming in 1929, and the observation of the broad therapeutic use of this agent in the 1940s, promoted the intensive investigation of nature as a source of novel bioactive agents. Microorganisms have proved to be a prolific source of structurally diverse bioactive metabolites, which have yielded some of the most important products of the pharmaceutical industry.[4] Terrestrial microorganisms are a plentiful source of structurally diverse bioactive substances, and have provided 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.[5]

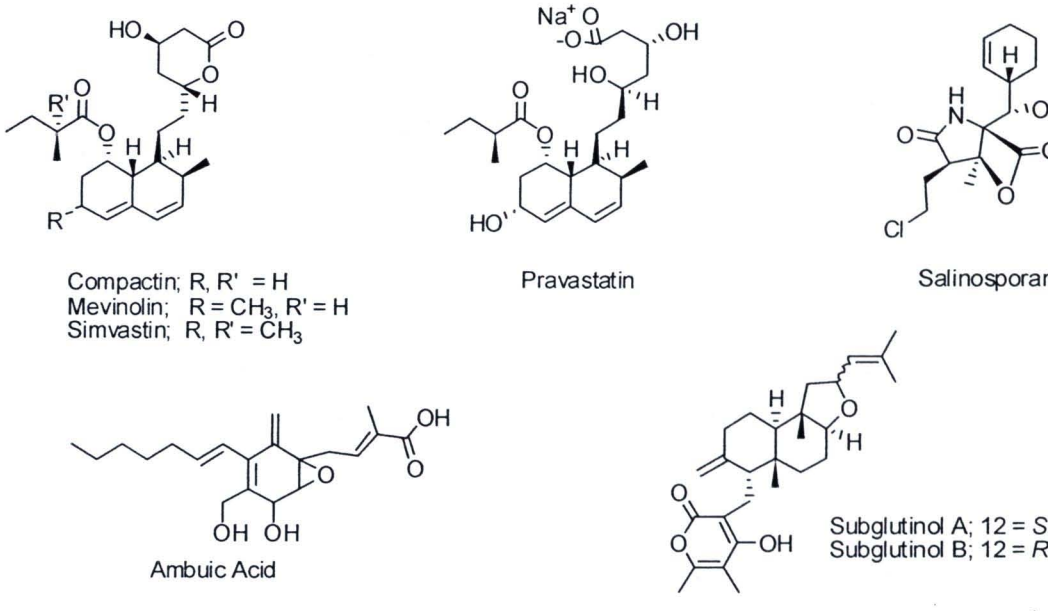


Figure 1.1 The structures of new drugs from terrestrial microorganisms.[4]

Many approved drugs were derived from microorganisms which are one of the natural sources for drug discovery. Thus, it is indicated that microorganisms still play a very important role for mankind. Our research focuses on the isolation of bioactive metabolites from fungi against human diseases, including malaria, tuberculosis, and cancer, these diseases still cause death of humans at increasing rate every year due to drug resistant behavior. Preliminary bioactive screening of all the crude extracts of *Chaetomium brasiliense, C. bostrychodes, and C. siamense* were tested for antimalarial (*Plasmodium falciparum*) and antiTB (*Mycobacterium tuberculosis*) found that hexane and EtOAc extracts of *C.brasiliense*, showed *in vitro* antimalarial activity against *P. falciparum* with IC_{50} values of 3.0 and 2.9 μg/mL, respectively. The EtOAc extract also showed antimycobacterial activity against *M. tuberculosis* of MIC 50 μg/mL).

Chaetomium (Figure 1.2) is a dematiaceous filamentous fungus found in soil, air, and plant debris.[6] The genus *Chaetomium* contains several species. Some species are thermophilic and neurotropic in nature. 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 phaeohyphomycosis. *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.

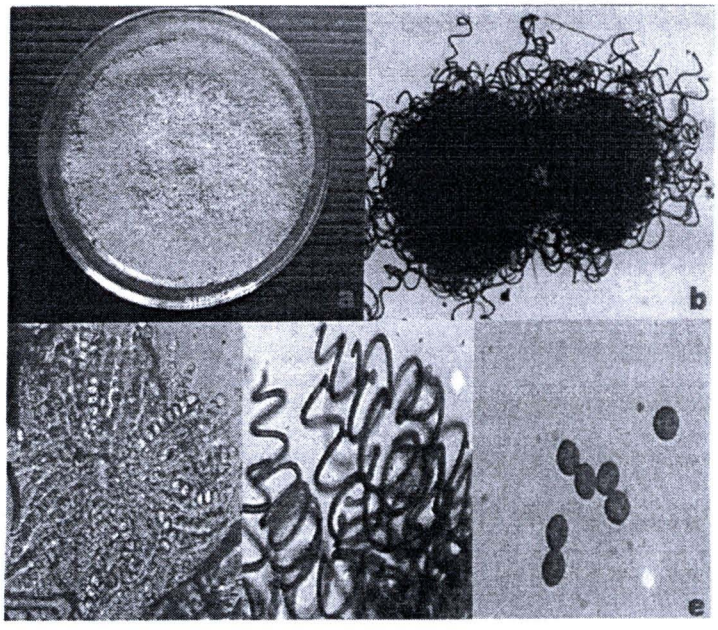


Figure 1.2 Perithecium and Ascospores of *Chaetomium brasiliense.*

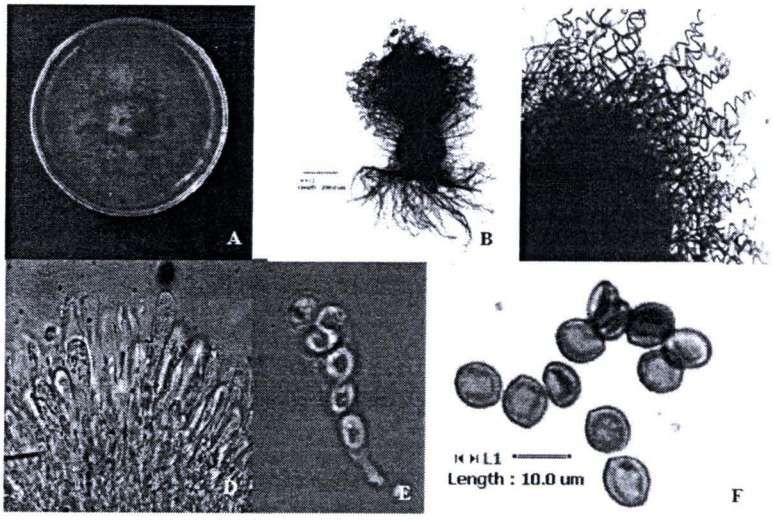


Figure 1.3 Perithecium and Ascospores of *Chaetomium bostrychodes.*

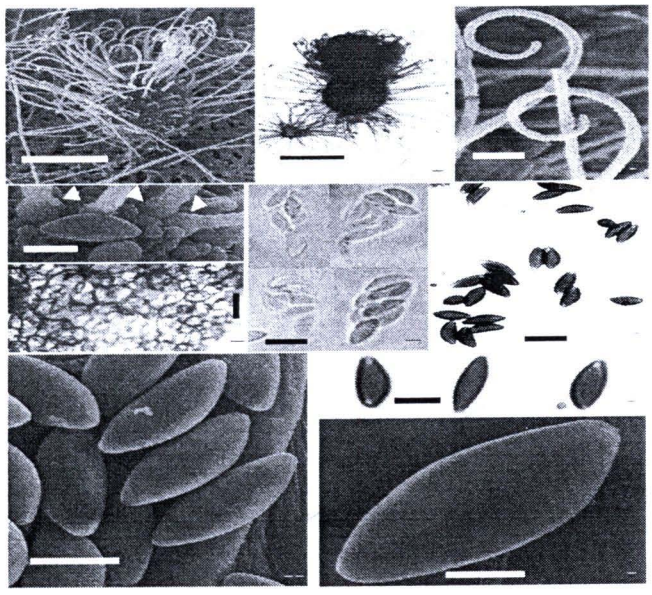


Figure 1.4 Perithecium and Ascospores of *Chaetomium siamese.*

According to Scifinder Scholars 2010 data base, previous investigation on secondary metabolites from the *Chaetomium* spp. resulted in the isolation of numerous types of compounds such as benzoquinone derivatives[7], tetra-*S*-methyl derivatives[8], azaphilones[9,10], indol-3-yl-[13]cytochalasans, and chaetoglobosin analogs. In addition, anthraquinone-chromanone[11] orsellinic acid, and globosumones[12] have also been reported. The isolated structures are shown in Figure 1.5 and some of their reports are summarized as follows :-

C. amygdalisporum

In 1983, Sekita[13] 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)-dihydroxybenzoquinones, neocochlio-dinol (**1**) as well as a known compound mollicellin G (**2**).

C. atrobrunneum

In 1993, Okeke and coworkers[14] investigated the ethyl acetate extract of *C. atrobrunneum* and found a mycotoxin, patulin (**3**) which inhibited the growth of three rice pathogens: *Pyricularia oryzae*, *Drechslera oryzae*, and *Gerlachia oryzae.*

In 2000, Hwang and his group[15] 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. brasiliense

In 1998, Oh and his group[16] investigated the ethyl acetate extract of *C. brasiliense* 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*-acetylchaetoglobosins A (**8**) and D (**9**). Chaetochalasin A (**5**) displayed cytotoxicity against the NCI's panel of 60 human tumor cell lines. Moreover, it also exhibited antibacterial activity in standard disk assays against *Bacillus subtilis* (ATCC 6051) and *Staphylococcus aureus* (ATCC 25923). In 2008, Li and coworkers[17] isolated two new depsidones, mollicellins I (**10**) and J (**11**), and a new chromone, 2-(hydroxymethyl)-6-methylmethyleugenin (**12**), together with six known compounds: mollicelins D (**13**) and H (**14**), eugenetin (**15**), *O*-methyl-sterigmatocystin (**16**), sterigmatocystin (**17**), and chaetocin (**18**) from the ethyl acetate extract of a solid-state fermented culture of *C. brasilinese*. Mollicellins I (**10**) and H (**14**) exhibited significant growth inhibitory activity against human breast cancer (Bre04), human lung (Lu04), and human neuroma (N04) cell lines. In 2009, Kanokmedhakul and coworkers[18] isolated four new depsidone, mollicellin K **(23),** mollicellin L **(24),** mollicellin M **(25)**, and mollicellin N **(26)**, and six know depsidones, mollicellins B **(19)**, C **(20)**, E **(21)**, F **(22)**, H **(14)**, and J **(23)**, along with two know sterols were isolated from the fungus *C. brasiliense*. Their structures were elucidated on the basis of 1D and 2D NMR spectroscopic data and chemical transformation. Among these isolates, **11, 19-21**, and **23-25** exhibited antimalarial activity against *P. falciparam*. Only **19** exhibited antimycobacterial activity against *M. tuberculosis* and antifungal against *C. albicans* using *in vitro* assays. In addition, all of them showed cytotoxicity against the KB, BC1, NCI-H187, and five cholangiocarcinoma cell lines.

C. chiversii

In 2006, Wijeratne and coworkers[19] investigated the ethyl acetate extract of *C.chiversii* and found two new isocoumarins, chaetochiversins A (**27**) and B (**28**), and the three known chromones, eugenetin (**15**), 6-methoxy-methyleugenin (**29**), and 6-hydroxy-methyleugenin (**30**), and radicicol (**31**). The study also reported the isolation of cytotoxic and heat shock protein inhibitor.

C. coarctatum

In 1975, Burrows and coworker[20] investigated *C. coarctatum* and found two inactive metabolites 2-(buta-1,3-dienyl)-3-hydroxy-4-(penta-1,3-dienyl)-tetrahydrofuran aureonitol (**32**) and coarctatin (**33**). In 1978, Seto and coworkers[21] reported that the biosynthesis of coarctatin (**33**) has been proved to be derived from four acetic acid molecules. Later in 1983, they[22] studied on the biosynthetic mechanism of **33** by an incorporation of $^{18}O_2$ gas. It was found that epoxide intermediate produced by air oxidation of polyketide intermediate was transformed into **33** *via* an epoxide rearrangement accompanying the cleavage between C-4 and C-9.

C. cochliodes

In 1968, Brewer and coworkers[7] isolated cochliodinol (**34**) from three isolate strains of *C.cochliodes* (HLX 374, HLX 577 and HLX 366). In 1972, they[23] reported that chetomin (**35**) was produced by *C. cochliodes* (HLX 440) 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. It also inhibited the mycelial growth of some fungi. In addition, it inhibited protein synthesis in culture of HeLa cells. In 1992, Abraham and Arfmann[24] 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 (**32**), and the minor compound was a new spiroketal named (1*RS*,9*RS*)-3-hydroxymethyl-8*Z*-(2′*E*-pentenylidene)-2,6-dioxa-spiro[4,4]nonanol-9 (**36**). In 1999, Kang and coworkers[25] found that *C. cochliodes* produced chaetoglobosin A (**37**) which exhibited strong inhibitory activities against *Pythium ultimum*, *Phytophthora capsici*, *Rhizoctonia*

solani, *Botrytis cinerea*, and *Fusarium oxysporum*. In 2006, Li and coworkers[26] reported that three new epipolythiodioxopiperazines, chaetocochins A (**38**), B (**39**), and C (**40**), along with dethio-tetra (methylthio) chetomin (**41**) and chetomin (**35**) were isolated from the ethyl acetate extract of the solid-state fermented rice culture of the fungus *C. cochliodes*. In addition, compounds **38**, **39**, and **40** exhibited significant cytotoxicity *in vitro* against some cancer cells. In 2008, Kanokmedhakul and coworkers[27] isolated four new dimeric spiro–azaplilones named cochliodones A (**42**), B (**43**), C (**44**) and D (**45**), two new azaphliones, chaetoviridines E (**46**) and F (**47**), a new *epi*–chaetoviridin A (**48**) and five known compounds, chaetoviridin A (**49**), ergosterol (**50**), chaetochalasin A (**5**) 24(R)-5α, 8α-epidioxyergosta-6-22-diene-3β-ol (**51**) and ergosterol-β-D-glucoside (**52**) from *C. cochliodes* VTh01 and *C. cochliodes* VTh05. Compounds **46**, **48**, **45**, and **41** exhibited antimalarial activity against *Plasmodium falciparum*, while **44**, **46**, **47**, **5**, and **51** showed antimycobacterial activity against *Mycobacterium tuberculosis*. In addition, **46** and **47** also showed cytotoxity against the KB, BC1, and NCI-H187 cell lines.

C. cupreum

In 2006, Kanokmedhakul and coworkers[10] isolated three new azaphilones named rotiorinols A (**53**), B (**54**), and C (**55**), two new sterioisomers, (-)-rotiorin (**56**) and *epi*-isochromophilone II (**57**), and a known compound, rubrorotiorin (**58**), from *C. cupreum* CC3003. Among these, compounds **53**, **55**, **56**, and **58** exhibited antifungal activity against *Candida albicans*.

C. funicola

In 2002, Payne and his group[28] found a series of tricyclic natural products, SB236049 (**59**), SB236050 (**60**), and SB238569 (**61**) from *C. funicola*. These metabolites exhibited activity against broad-spectrum of metallo-β-lactamases.

C. globosum

In 1968, Brewer and coworker[8] investigated two strains of *C. globosum* (HLX 707 and HLX 819) and found a purple pigment, named cochliodinol (**34**). In 1972, they[29] further reported that chetomin (**35**) was produced by two isolated strains

of *C. globosum*. In general, chetomin (**35**) was produced by *C. cochliodes* in higher yield than *C. globosum*. In 1973, Sekita and coworkers[30] isolated three cytotoxic indol-3-yl-[13]cytochalasan metabolites, chaetoglobosin A (**37**), B (**62**), and C(**63**) from *C. globosum*. In 1976, they[31] further reported the structures of chaetoglobosins C (**63**), D (**6**), E (**64**) and F (**65**). One year later, they[32] reported the structures of chaetoglobosin G (**66**) and J (**67**). In 1980, Itoh and coworkers[33,34] found a new sesquiterpene antibiotic, heptelidic acid (**68**) from *C. globosum* (SANK 13379). The antimicrobial spectrum of the antibiotic **68** revealed its specific activity anaerobic bacteria, especially against *Bacteroides fragillis* and *Propionibacterium acnes*. In 1982, Kikuchi and coworkers[35] further reported the isolation and structural elucidation of a new metabolite, dethio-tetra(methylthio) chetomin (**41**), and a known chetomin (**35**) 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 group[36] reported that chaetoglobosins affected the structure and functions of mammalian cell; they caesed inhibition of cellular movements including cell division motility, secretion and also caused changes in cell shape. In 1983, they[37] studied the biosynthetic pathways of chaetoglobosins A (**37**), B (**62**), C (**63**), D (**6**), and J (**67**) and found that the molecules were formed from nine units of acetate/malonate, three C_1 units, and one unit of tryptophan. In 1990, Takahashi and coworkers[9] reported that *C. globosum* var. *flavo-viridae* (TRTC 66.631a) produced four new azaphilones of angular type, named chaetoviridins A (**49**) as the major metabolite, B (**69**), C (**70**), and D (**71**) as the minor congers. Chaetoviridin A (**49**) showed a weak inhibitory activity on monoamine oxidase, an induction of chlamydospose-like cell, and an inhibition of growth of *Pyricularia oryzae*. In 1992, Di Pietro and coworkers[38] reported that *C. globosum* produced 2-(buta-1,3-dienyl)-3-hydroxy-4-(penta-1,3-dienyl)-tetrahydrofuran (**32**) and chetomin (**35**). In 1996, Breinholt and coworkers[39] found a novel metabolite, named prenisatin (**72**), exhibited *in vitro* growth inhibitory activity against *Botrytis cinerea*.

In 2000, Yuji's group[40] investigated *C. globosum* PF1138 and found the novel *trans*-epoxysuccinyl peptides named PF1138 A (**73**) and B (**74**). These compounds demonstrated inhibitory effect on cysteine proteases, such as cathepsin B,

papain, and ficin, but have no effect on serine protease, such as trypsin. In 2002, Kanokmedhakul and coworkers[11] investigated on *C. globosum* KMITL-N0802 and found a novel anthraquinone-chromanone compound, name chaetomanone (**75**), along with seven known compounds, ergosterol (**50**), ergosteryl palmitate (**76**), chrysophanol (**77**), chaetoglobosin C (**63**), alternariolmonomethyl ether (**78**), echinulin (**79**), and isochaetoglobosin D (**80**). Chaetomanone (**75**) and echinulin (**79**) exhibited activity towards *Mycobacterium tuberculosis*. In 2004, Jiao and coworkers[41] reported that nine cytotoxic metabolites, including three novel compounds, chaetoglobosins Q (**81**), R (**82**), and T (**83**), and six known compounds, chaetoglobosins A (**37**), B (**62**), D (**6**), and J (**67**), prochaetoglobosins I (**84**), and II (**85**), have been isolated from cultures of the fungus *C. globosum*. One year later, Bashyal and coworkers[12] proposed that three new esters of orsellinic acid, globosumones A (**86**), B (**87**), and C (**88**), and three known compounds, orsellinic acid (**89**), orcinol (**90**), and trichodion (**91**), 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 (**86**) and B (**87**) were found to be moderately active.

In 2006, Ding and coworkers[42] 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 (**92**), along with four known analogues, chaetoglobosins C (**63**), E (**64**), and F (**65**) and penochalasin A (**93**). Chaetoglobosin U (**92**) exhibited cytotoxic activity against the human nasopharyngeal epidermoid tumor KB cell line. The known analogues **63**, **64**, and **7** were moderately active to the cell lines. In 2006 Wijeratne and colleagues[43] reported a new dihydroxyxanthenone, globosuxanthone A (**94**), a new tetrahydroxanthenone, globosuxanthone B (**95**), two new xanthones, globosuxanthones C (**96**) and D (**97**), 2-hydroxyvertixanthone (**98**), and two known anthraquinones, chrysazin (**99**) and 1,3,6,8-tetrahydoxyanthraquinone (**100**) from bioassay-guided fractionation of a cytotoxic EtOAc extract of *C. globosum*. Of the compounds encountered, **94** was found to exhibit strong cytotoxicity against a panel of seven human solid tumor cell lines, disrupt the cell cycle leading to the accumulation of cells in either G_2/M or S phase, and induce classic signs of apoptosis. In 2006 Wang's group[44] found a new benzaldehyde

secondary metabolite, chaetopyranin (**101**), from cultivation of the endophytic *C. globosum*, which was isolated from the inner tissure of the marine red alga *Polysiphonia urceolata*. Ten known compounds were also isolated, including two benzaldehyde congeners, 2-(2',3-epoxy-1',3'-heptadienyl)-6-hydroxy-5-(3-methyl-2-butenyl) benzaldehyde (**102**) and isotetrahydroauroglaucin (**103**), two anthraquinone derivatives, erythroglaucin (**104**) and parietin (**105**), five asperentin derivatives including asperetin (**106**), 5'-hydroxy-asperentin-8-methylether (**107**), asperentin-8-methylether (**108**), 4'-hydroxyasperentin (**109**), and 5'-hydroxyasperentin (**110**), and the prenylated diketopiperazine congener neoechinulin (**111**). Each isolate was tested for its DPPH (1,1-diphenyl-2-picrylhydrazy) radical-scavenging property. Compounds **101-104** were found to have moderate activity. Chaetopyranin (**101**) also exhibited moderate to weak cytotoxic activity toward three tumor cell lines including human microvascular endothelial cells (HMEC), hepatocellular carcinoma cells (SMMC-7721), and human lung epithelial cells (A549). In the same year, Yang and coworkers[45] found two novel chemokine receptor CCR-5 inhibitors, Sch 210971 (**112**) and Sch 210972 (**113**) from the fungal fermentation broth of *C. globosum*. The major component **112** demonstrated a potent inhibitory activity in the CCR-5 receptor *in vitro* binding assay.

More recently in 2007, Wang and his group[46] reported four known benzaldehyde derivatives from *C. globosum*, a marine-alga-derived endophytic fungus. They were determined as: 2-(1-heptenyl)-3,6-dihydroxy-5-(3-methyl-2-butenyl) benzaldehyde (**114**), 2-heptyl-3,6-dihydroxy-5-(3-methyl-2-butenyl) benzaldehyde (**115**), 2-(3,5-heptadienyl)-3,6-dihydroxy-5-(3-methyl-2-butenyl) benzaldehyde (**116**), and 2-(1,3,5-heptatrienyl)-3,6-dihydroxy-5-(3-methyl-2-butenyl) benzaldehyde (**117**). While Yang's group[47] found a novel fungal secondary metabolite, Sch 213766 (**118**) from the fungal fermentation broth of *C. globosum*. It exhibited activity in the CCR-5 receptor *in vitro* binding assay. Yamada and coworkers[48] isolated three new azaphilones, chaetomugilins A-C (**119-121**) from a strain of *C. globosum* OUPS-T106B-6 originally obtained from the marine fish *Mugil cephalus*. The metabolites exhibited significant cytotoxic activity against the murine P388 leukemia cell line and the human HL-60 leukemia cell line.

In 2008, Matthew's group[49] reported that *C. globosum* could grow on potato dextrose agar ranging in pH from 4.3 to 9.4. The optimal growth of this fungus, as well as chaetoglobosin C (**63**) production, occurred at a neutral pH. and the sporulation favored in anacidic environment. Hui Ming Ge and coworkers[50] isolated chaetoglobins A **(122)** and B **(123)**, two azaphilone alkaloid dimers with an unprecedented skeleton, were characterized from an endophytic fungus *C. globosum* with the former ascertained to be a significant cytotoxin valuable for anti–tumor drug discover. Muroga Yasuhide's group[51,52] isolated chaetomugilins A **(124),** chaetomugilins B **(125)**, chaetomugilins C **(126)**, chaetomugilins D **(127)**, chaetomugilins E **(128)**, chaetomugilins F **(129),** chaetomugilins G **(130)**, and chaetomugilins H **(131)** from a strain of *C. globosum* originally isolated from the marine fish *Mugil cephalus*, and their absolute stereostructures have been elucidated on the basis of spectroscopic analyses, including 1D and 2D NMR techniques, some chemical transformations and an X–ray analysis. There compounds exhibited significant growth inhibition against cultured P388 cells and HL – 60 cells. In addition, **124**, **126**, and **129** showed selective cytotoxic activities against 39 human cancer cell lines and **130** and **131** exhibited a growth inhibitory activity againt cultured P388, HL – 60, L1210, and KB cells. One year later, they[53] isolated chaetomugilins I **(132)** , chaetomugilins J **(133)**, chaetomugilins K **(134)**, chaetomugilins L **(135)**, chaetomugilins M **(136)**, chaetomugilins N **(137)**, and chaetomugilins O **(138)** from the marine fish *Mugil cephalus*. These compounds exhibited significant growth inhibition of cultured P388, HL – 60, L1210, and KB cell lines. In addition, **132** showed selective cytotoxic activity against 39 human cancer cell lines. In the same year, Hartmut Lattsch and cowerkers[54] isolated a novel polyhydroxylated C_{29}-sterol, 25ε-methyl-22-homo-5α-cholest-7,22-diene-3β,6β,9β-triol, designated globosterol (**139**), together with one known tetrahydroxylated ergosterol (22E, 24R)-ergosta-7,22-diene-3β,5α,6β,9α-tetraol (**140**). Takeshi Yamada and coworkers[55], isolated new azaphilones, seco–chaetomugilins A **(141)**, and seco – chaetomugilins D **(142)** by a marine fish derived *C. globosum* and **142** exhibited growth inhibitory activity against cultured P388, HL–60, L1210, and KB cells.

C. gracile

In 1987, Koyama and Natori[56] investigated the dichloromethane extract of *C. gracile* and three new related bis(naphtho-γ-pyrone) derivatives named chaetochromins B (**143**), C (**144**), and D (**145**) and a known chaetochromin A (**146**) were isolated. They also indicated that both of the vicinal methyl groups in **146** and one of the two in **143** were *trans*, while the other in **143** was *cis*. Two years later, they[57] studied the biosynthesis of chaetochromin A (**146**), a metabolite of *C. gracile*, by using [$^{13}CH_3$] methionine, sodium [1-^{13}C]acetate, sodium [1,2-$^{13}C_2$]acetate, sodium [1-^{13}C,2,2,2-$^{2}H_3$]acetate, and sodium [1-^{13}C,1,1-$^{18}O_2$]acetate as precursors. The result showed that the folding pattern of the polyketide chain in chaetochromin A (**146**) was determined to be the same as those of rubrofusarin by ^{13}C-NMR analysis.

C. indicum

In 2006, Li and coworkers[58] isolated three novel alkaloids, chaetoindicins A (**146**), B (**147**), and C (**148**) from the solid-state fermented culture of *C. indicum*.

C. mollicellum

In 1978, Stark and coworkers[59] found eight mollicellins (depsidones), mollicellins A (**150**), B (**19**), C (**20**), D (**13**), E (**21**), F (**22**), G (**2**), and H (**14**) from the fungus *C. mollicellum* MIT M-37. Mollicellins C (**20**) and E (**21**) which contained a 3-methylbutenoic acid moiety, were mutagenic and bactericidal against *Salmonella typhimurium* in the absence of microsome. While mollicellins D (**13**) and F (**26**), which each contained a chloride atom, were bactericidal but not mutagenic.

C. murorum

In 1983, Sekita[60] reported the structural elucidation of isocochliodinol (**150**), a metabolite of *C. murorum* NHL (78-SH-271-4) and NHL 2240.

C. nigricolor

In 1988, Saito and coworkers[61] investigated the ethyl acetate extract of the culture on rice of *C. nigricolor* AMES. A new dimeric epipolythiodioxopiperazine

with two tetrasulfide bridges named chetracin A (**151**) was isolated along with a known compound cochliodinol (**34**).

C. olivaceum

In 2001, Smetanina and coworkers[62] reported the isolation of a pentacyclic triterpenoid, 3β-methoxyolean-18-ene (miliacin) (**152**) from the marine fungus *C. olivaceum* for the first time.

C. quadrangulatum

In 2002, Fujimoto and coworkers[63] isolated five new chromones named chaetoquadrins A (**153**), B (**154**), C (**155**), D (**156**) and E (**157**) from the ethyl acetate extract of *C. quadrangulatum* 71-NG-22. Among these, compounds **153-157** were tetracyclics and compound **157** contains a sulfonyl group. One year later, they[64] further reported six constituents named chaetoquadrins F (**158**), G (**159**), H (**160**), I (**161**), J (**162**) and K (**163**). Chaetoquadrins G (**159**) and H (**160**) have shown appreciable monoamine oxidase inhibitory activity.

C. retardatum

In 1988, Saito and coworkers[61] found chetracin A (**151**) and 11α,11′α-dihydroxychaetocin (**164**) from *C. retardatum* TRTC 66.1778b.

C. seminudum

In 2004, Fujimoto and coworkers[65] investigated focusing on immunomodulatory activity of the ethyl acetate extract of *C. seminudum* 72-S-204-1 and yielded a known epipolythiodioxopiperazine, chetomin (**35**), together with three new chetomin-related metabolites named chetoseminudins A (**165**), B (**166**), and C (**167**).

C. subaffine

In 1993, Oikawa and coworkers[66] found that *C. subaffine* produced two new metabolites of chaetoglobosins named chaetoglobosin F_{ex} (**7**) and 20-dihydrochae-toglobosin A (**168**).

C. subspirale

In 2004, Jan's group[67] reported the isolation of oxaspirodion (**169**), a new inhibitor of inducible TNF-α expression, from *C. subspirale*.

C. thielavioideum

In 1980, Sekita and coworkers[68] investigated the metabolites of *C. thielavioideum* NHL 2829 and isolated a new phenolic chaetochromin A (**145**) as well as known five compounds chaetocin (**18**), sterigmatocystin (**17**), *O*-methyl-sterigmatocystin (**16**), ergosterol (**50**) and eugenitin (**15**). In 1988 Saito's groups[61] reported that chaetocins B (**170**) and C (**171**) were isolated from *C. thielavioidium* NHL 2827, and were proved to be homologus with one disulfide and one trisulfide bridge for **170** and with two trisulfide bridges for **171**, respectively. These metabolites also showed strong activities against *Staphylococcus aureus* FDA 209P.

C. trilaterale

In 1974, Cole and coworkers[69] 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) **(172)**, which had a median oral lethal dose of 6.12 mg/kg in day-old cockerels. The toxin **172** also exhibited plant growth inhibiting and phytotoxic effects.

***Chaetomium* spp.**

In 2007, Lösgen and coworkers[70] found three new fungal polyketide metabolites, chaetocyclinones A-C (**173-175**) together with two known compounds, SB238569 (**61**) and anhydrofulvic acid (**176**) from *Chaetomium* sp. (strain Gö 100/2) which was isolated from a marine algae. Chaetocyclinone A (**173**) exhibited inhibitory activity against selected phytopathogenic fungi. Marwah's group[71] found a new furano-polyene, (–)-musanahol (**177**), a known furano-polyene, 3-*epi*-aureonitol (**178**), and a fatty acid, linoleic acid (**179**) from the laboratory cultures of a *Chaetomium* spp. accessed from tomato fruits and grown on YMG medium (yeast extract, glucose, malt extract and water). (–)-Musanahol (**177**) and 3-*epi*-aureonitol (**178**) were presented in the culture filtrate of the fungus. While 3-*epi*-aureonitol

(**178**) completely inhibited the growth of *Streptococcus pyogenes*, *Escherichia coli*, *Staphylococcus aureus*, *Salmonella choleraesuis*, and *Corynebacterium diphtheriae*. However (–)-musanahol (**177**) lacked the antimicrobial potency of compound **178** in spite of the similarities in their structures. In addition, linoleic acid (**179**) inhibited the growth of *S. aureus* and *Bacillus subtillus*.

In 2008, Ahmed Abdel–Lateff[72] isolated a novel benzonaphthyridinedione derivative, chaetominedione **(180)**. In addition to the known fungal metabolites, 2 – furancarboxylic acid **(181)**, and 5-(hydroxymethyl)–2–furancarboxylic acid **(182)** from an isolated marine fungal, *Chaetomium* spp. The total extract and **180** had significant inhibitory activity toward $p56^{lck}$ tyrosine kinase.

List of these isolated compounds are summerized in Table 1.1 and their stuctures are shown in Figure 1.5.

Table 1.1 Chemical constituents from *Chaetomium* spp.

Chaetomium spp.	compound name	year	ref.
C. amygdalisporum	bis-(3-indolyl)-dihydroxybenzoquinones,neocochlio-dinol (**1**), and mollicellin G (**2**).	1983	13
C. atrobrunneum	patulin (**3**).	1993	14
	chaetoatrosin A (**4**).	2000	15
C. brasiliense	chaetochalasin A (**5**), chaetoglobosins D (**6**) and F_{ex} (**7**) and 19-*O*-acetylchaetoglobosins A (**8**) and D (**9**).	1998	16
	mollicellins I (**10**) and J (**11**), 2-(hydroxymethyl)-6-methylmethyleugenin (**12**), mollicellins D (**13**) and H (**14**), eugenetin (**15**), *O*-methyl-sterigmatocystin (**16**), sterigmatocystin (**17**), and chaetocin (**18**).	2008	17
	mollicellins H **(14),** Mollicellins B **(19),** mollicelline C **(20),** mollicellins E **(21),** mollicellins F **(22),** mollicellins K **(23),** mollicellin L **(24),** mollicellins M **(25),** and mollicellins N **(26).**	2009	18
C. chiversii	eugenetin (**15**), chaetochiversins A (**27**) and B (**28**), 6-methoxy-methyleugenin (**29**), and 6-hydroxy-methyleugenin (**30**), and radicicol (**31**).	2006	19
C. coarctatum	2-(buta-1,3-dienyl)-3-hydroxy-4-(penta-1,3-dienyl)-tetrahydrofuran- aureonitol (**32**) and coarctatin (**33**).	1975	20
C. cochliodes	cochliodinol (**34**).	1968	7
	chetomin (**35**).	1972	23
	2-(buta-1,3-dienyl)-3-hydroxy-4-(penta-1,3-dienyl)-tetrahydrofuran (**32**). and (1*RS*,9*RS*)-3-hydroxymethyl-8*Z*-(2′*E*-pentenylidene)-2,6-dioxa-spiro[4,4] nonanol-9 (**36**).	1992	24
	chaetoglobosin A (**37**).	1999	25
	chetomin (**35**), chaetocochins A (**38**), B (**39**), C (**40**), and adethio-tetra (methylthio) chetomin (**41**).	2006	26
	chaetochalasin A (**5**), cochliodones A (**42**), B (**43**), C (**44**), and D (**45**), chaetoviridines E (**46**) and F (**47**), *epi*–chaetoviridin A (**48**), chaetoviridin A (**49**), ergosterol (**50**), 24(R)-5α, 8α-epidioxyergosta-6-22-diene-3β-ol (**51**) and ergosterol-*β*-D-glucoside (**52**).	2008	27
C. cupreum	rotiorinols A (**53**), B (**54**), and C (**55**), (-)-rotiorin (**56**), *epi*-isochromophilone II (**57**), and rubrorotiorin (**58**)	2006	10
C. funicola	SB236049 (**59**), SB236050 (**60**), and SB238569 (**61**).	2002	28
C. globosum	cochliodinol (**34**).	1968	7
	chetomin (**35**).	1972	29
	chaetoglobosin A (**37**), B (**62**), and C(**63**).	1973	30
	chaetoglobosins C (**63**), D (**6**), E (**64**) and F (**67**).	1976	31
	chaetoglobosin G (**66**) and J (**67**).	1977	32
	heptelidic acid (**68**).	1980	33, 34
	chetomin (**35**) and dethio-tetra(methylthio) chetomin (**41**).	1982	35

Table 1.1 Chemical constituents from *Chaetomium* spp. (cont.)

Chaetomium spp.	compound name	year	ref.
C. globosum (cont.)	chaetoglobosins A (**37**), B (**62**), C (**63**), D (**6**), and J (**67**).	1983	37
	chaetoviridins A (**49**), metabolite, B (**69**), C (**70**), and D (**71**).	1990	9
	2-(buta-1,3-dienyl)-3-hydroxy-4-(penta-1,3-dienyl)-tetrahydrofuran (**32**) and chetomin (**35**).	1992	38
	prenisatin (**72**).	1996	39
	trans-epoxysuccinyl peptides PF1138 A (**73**) and B (**74**).	2000	40
	ergosterol (**50**), chaetoglobosin C (**63**), chaetomanone (**75**), ergosterylpalmitate (**76**), chrysophanol (**77**), alternariolmonomethyl- ether (**78**), echinulin (**79**), and isochaetoglobosin D (**80**).	2002	11
	chaetoglobosins A (**37**), B (**62**), D (**6**), J (**67**), Q (**81**), R (**82**), T (**83**), prochaetoglobosins I (**84**), and II (**85**).	2004	41
	globosumones A (**86**), B (**87**), and C (**88**), orsellinic acid (**89**), orcinol (**90**), and trichodion (**91**).	2005	12
	chaetoglobosin U (**92**), chaetoglobosins C (**63**), E (**64**), and F (**65**) and penochalasin A (**93**).	2006	42
	globosuxanthone A (**94**), globosuxanthone B (**95**), globosuxanthones C (**96**) and D (**97**), 2-hydroxyvertixanthone (**98**), anthraquinones, chrysazin (**99**) and 1,3,6,8-tetrahydoxyanthraquinone (**100**).	2006	43
	chaetopyranin (**101**), benzaldehyde congeners, 2-(2',3-epoxy-1',3'-heptadienyl)-6-hydroxy-5-(3-methyl-2-butenyl) benzaldehyde (**102**) and isotetrahydroauroglaucin (**103**), erythroglaucin (**104**), parietin (**105**), asperetin (**106**), 5'-hydroxy-asperentin-8-methylether (**107**), asperentin-8-methylether (**108**), 4'-hydroxyasperentin (**109**), 5'-hydroxyasperentin (**110**), and neoechinulin (**111**).	2006	44
	Sch 210971 (**112**) and Sch 210972 (**113**).	2006	45
	2-(1-heptenyl)-3,6-dihydroxy-5-(3-methyl-2-butenyl) benzaldehyde (**114**), 2-heptyl-3,6-dihydroxy-5-(3-methyl-2-butenyl) benzalde- hyde (**115**), 2-(3,5-heptadienyl)-3,6-dihydro-xy-5-(3-methyl-2-butenyl) benzaldehyde (**116**), and 2-(1,3,5-heptatrienyl)-3,6-dihy-droxy-5-(3-methyl-2-butenyl) benzaldehyde (**117**).	2007	46
	Sch 213766 (**118**).	2007	47
	chaetomugilins A-C (**119-121**).	2008	48
	chaetoglobosin C (**63**).	2008	49
	chaetoglobins A **(122),** chaetoglobins B **(123).**	2008	50
	chaetomugilins A-F **(124- 129).**	2008	51.
	chaetomugilins G-H **(130-131).**	2009	52
	chaetomugilins I-O **(132- 138).**	2009	53
	25ε-methyl-22-homo-5α-cholest-7,22-diene-3β,6β,9β-triol **(139),** (22E, 24R)-ergosta-7,22-diene-3β,5α,6β,9α-tetraol **(140).**	2009	54

Table 1.1 Chemical constituents from *Chaetomium* spp. (Cont.)

Chaetomium spp.	compound name	year	ref.
C. globosum (cont.)	seco-chaetomugilins A (**141**), seco-chaetomugilins D (**142**).	2009	55
C. gracile	chaetochromins B (**143**), C (**144**), and D (**145**) and chaetochromin A (**146**).	1987	56
C. indicum	chaetoindicins A (**147**), B (**148**), and C (**149**).	2006	58
C. mollicellum	mollicellins A (**150**), B (**19**), C (**20**), D (**13**), E (**21**), F (**22**), G (**2**), and H (**14**).	1978	59
C. murorum	isocochliodinol (**151**).	1983	60
C. nigricolor	cochliodinol (**34**) and chetracin A (**152**).	1988	61
C. olivaceum	3β-methoxyolean-18-ene (miliacin) (**153**).	2001	62
C. quadrangulatum	chaetoquadrins A (**154**), B (**155**), C (**156**), D (**157**) and E (**158**).	2002	63
	chaetoquadrins F (**159**), G (**160**), H (**161**), I (**162**), J (**163**) and K (**164**).	2003	64
C. retardatum	chetracin A (**152**) and 11α,11′α-dihydroxychaetocin (**165**).	1988	61
C. seminudum	epipolythiodioxopiperazine, chetomin (**35**), chetoseminudins A (**166**), B (**167**), and C (**168**).	2004	65
C. subaffine	chaetoglobosin F_{ex} (**7**) and 20-dihydrochae-toglobosin A (**169**).	1993	66
C. subspirale	oxaspirodion (**170**).	2004	67
C. thielavioideum	eugenitin (**15**), sterigmatocystin (**16**), sterigmatocystin (**17**), chaetocin (**18**), *O*-methyl ergosterol (**50**) and chaetochromin A (**146**).	1980	68
	chaetocins B (**171**) and C (**172**).	1988	62
C. trilaterale	(3,3′,6,6′-tetrahydroxy-5,5′-dimethyl-2,2′-bi-*p*-benzoquinone) (**173**).	1974	69
Chaetomium spp.	SB238569 (**53**), chaetocyclinones A-C (**174-176**) and anhydrofulvic acid (**177**).	2007	70
	(–)-musanahol (**178**), 3-*epi*-aureonitol (**179**), and linoleic acid (**180**).	2007	71
	Chaetominedione (**181**), furancarboxylic acid (**181**), 5- (hydroxymethyl)–2–furancarboxylic acid (**182**).	2008	72

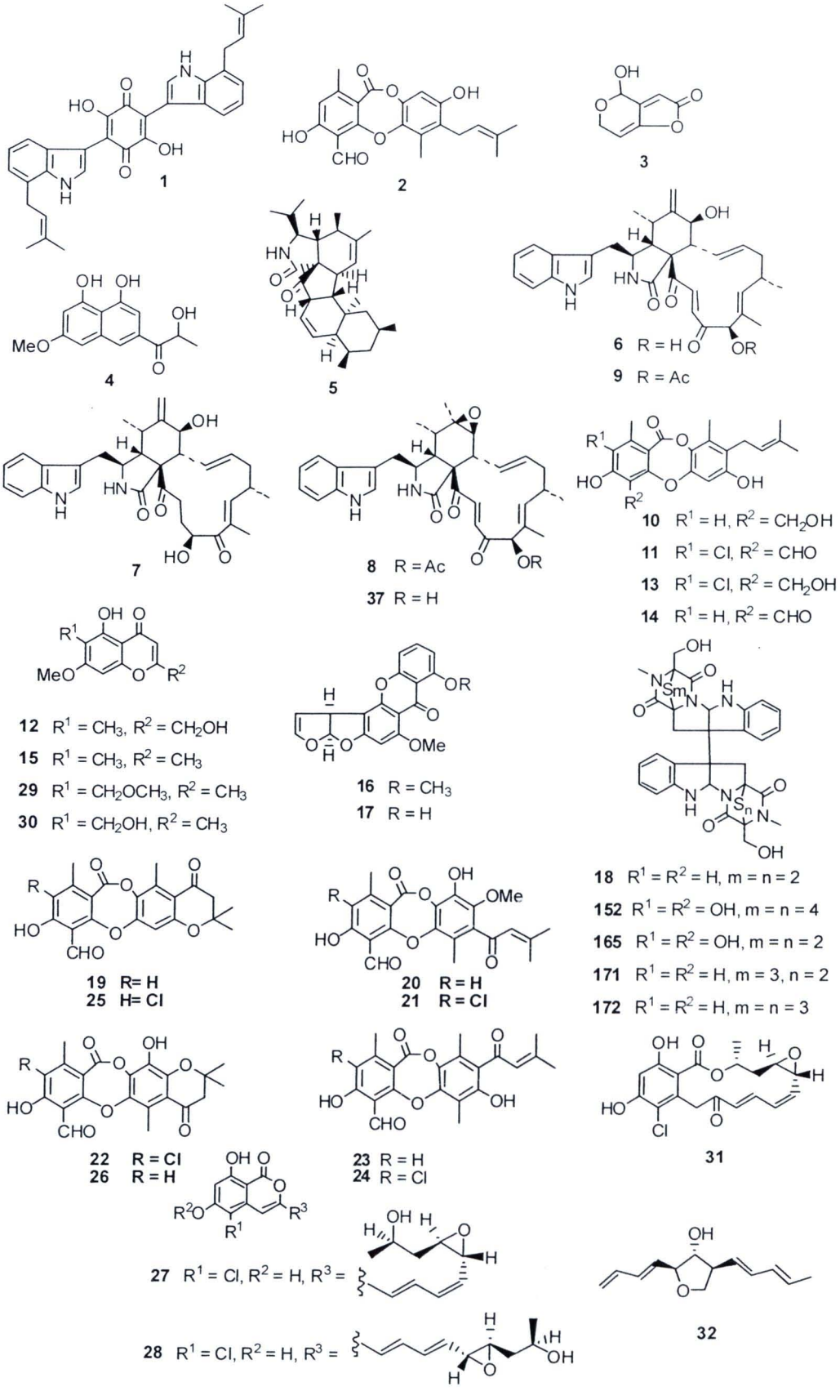


Figure 1.5 Some isolated compounds from *Chaetomium* spp..

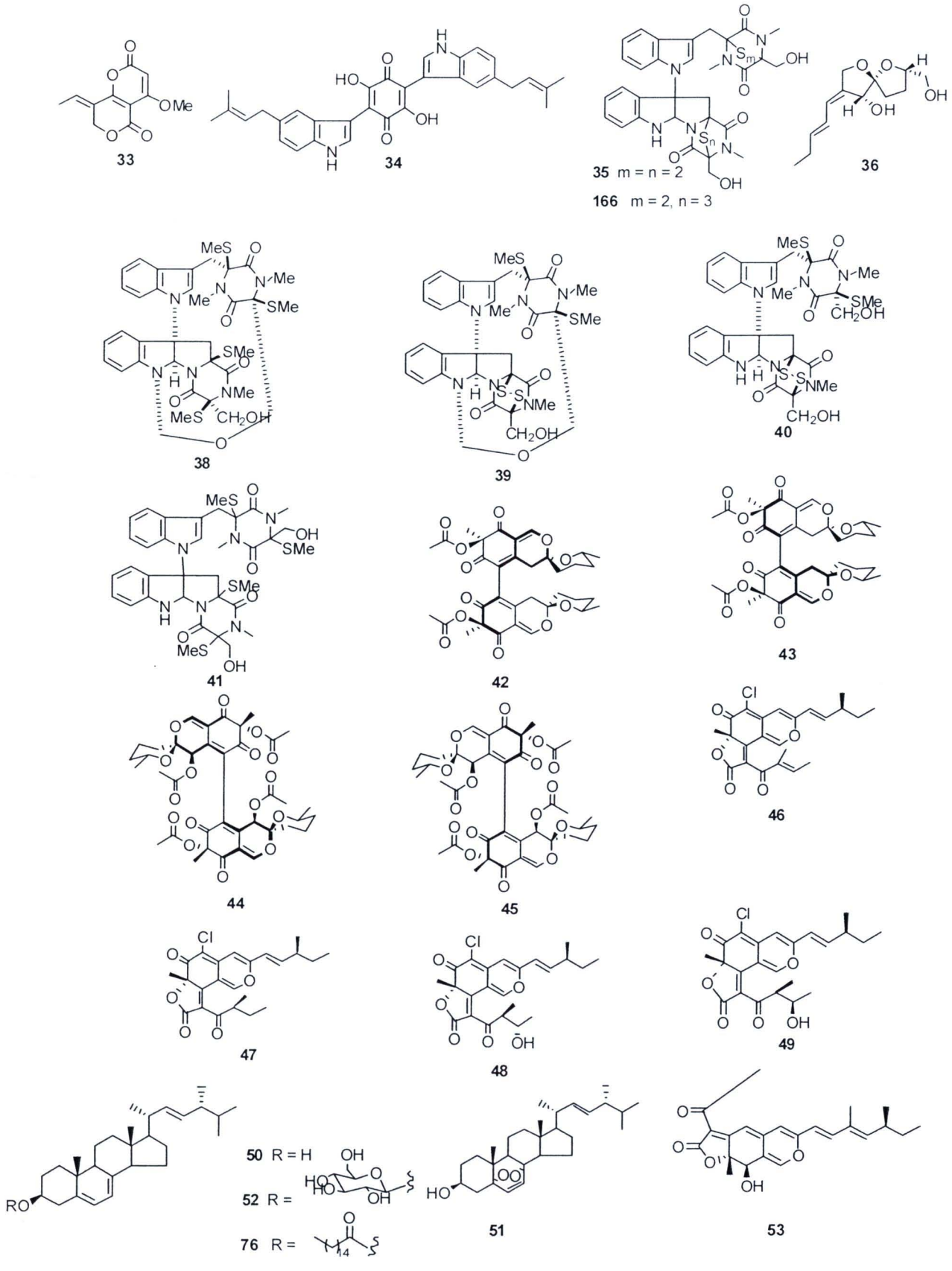


Figure 1.3 Some isolated compounds from *Chaetomium* spp. (cont.).

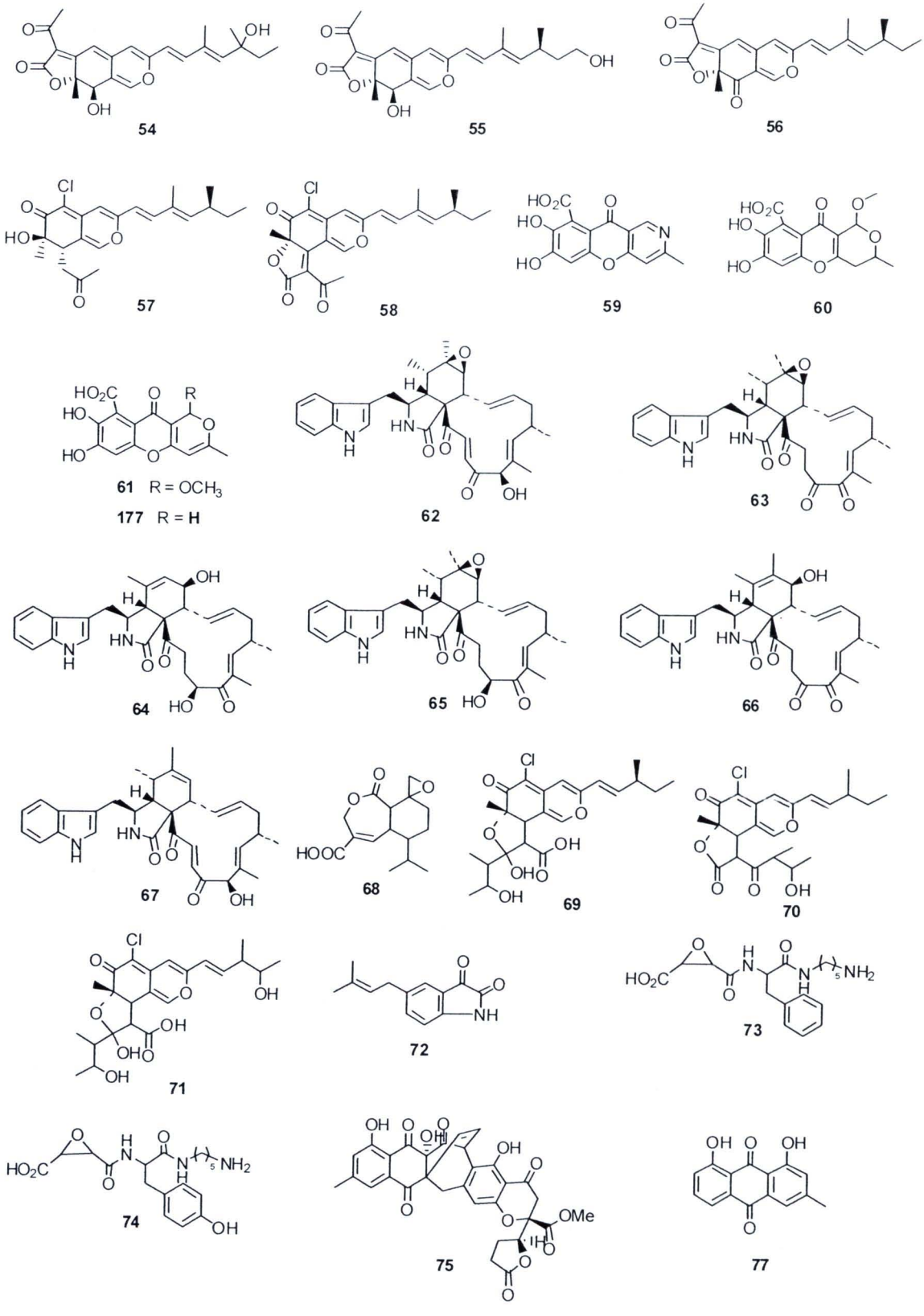


Figure 1.5 Some isolated compounds from *Chaetomium* spp. (cont.).

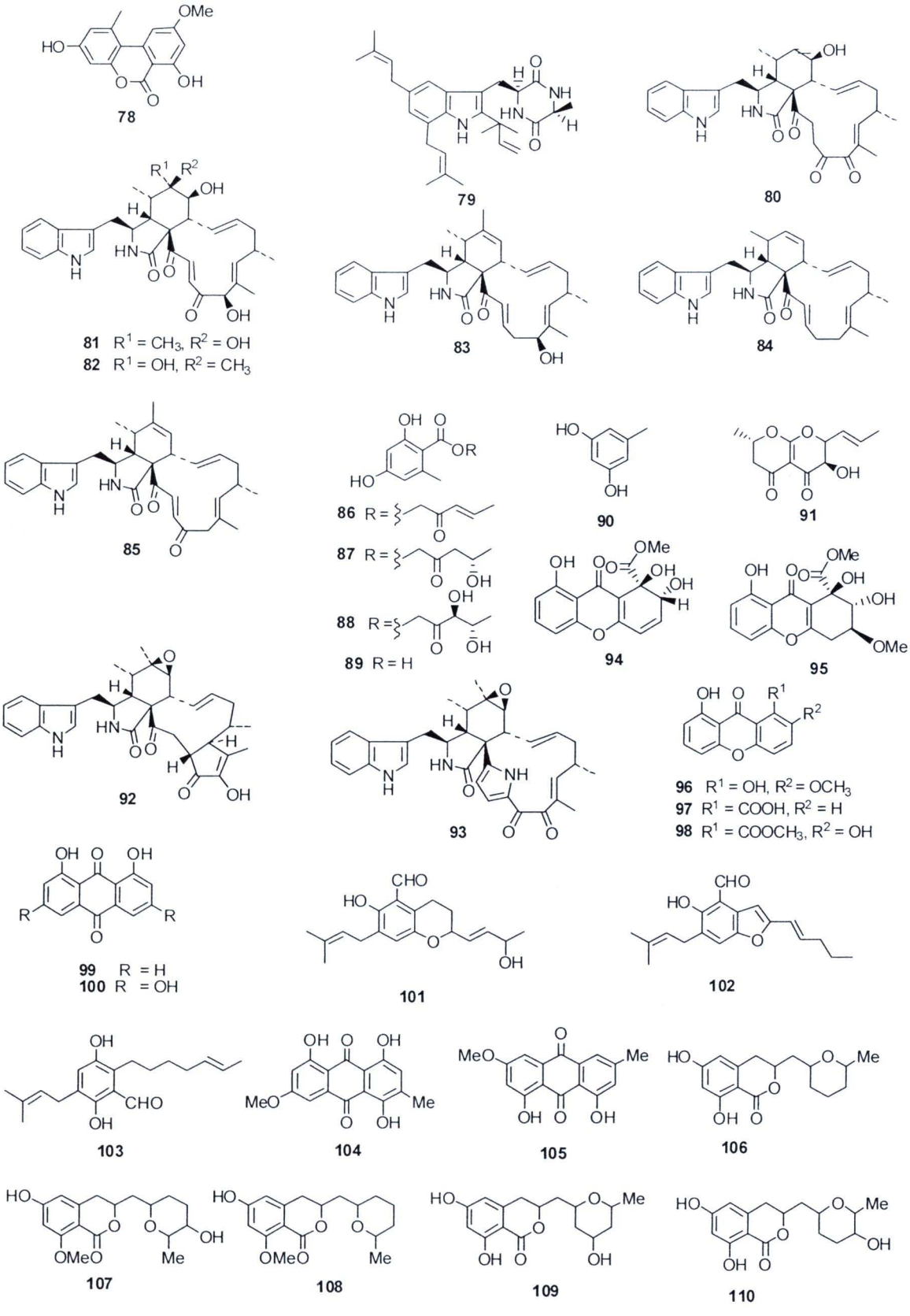


Figure 1.5 Some isolated compounds from *Chaetomium* spp. (cont.).

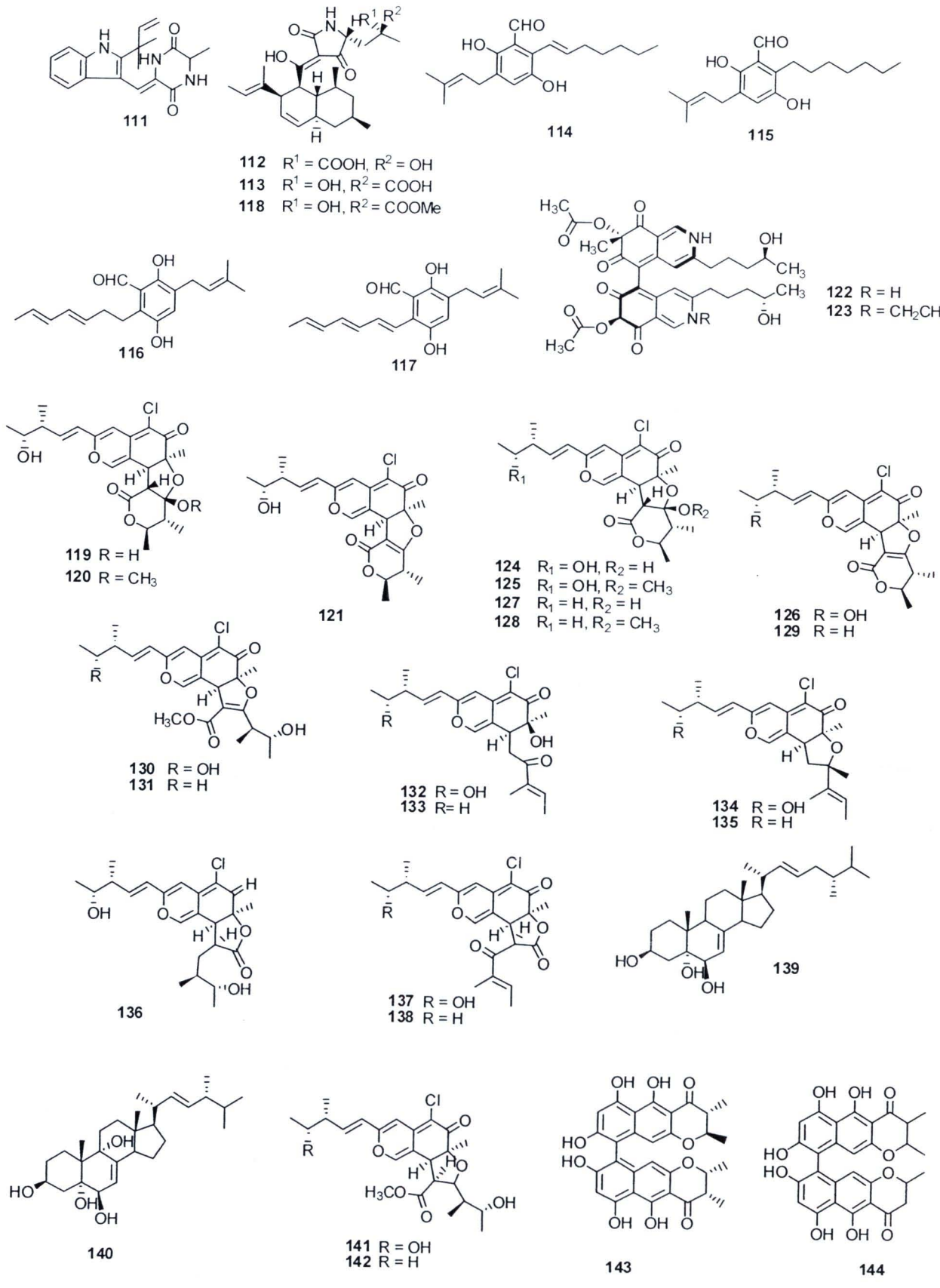


Figure 1.5 Some isolated compounds from *Chaetomium* spp. (cont.).

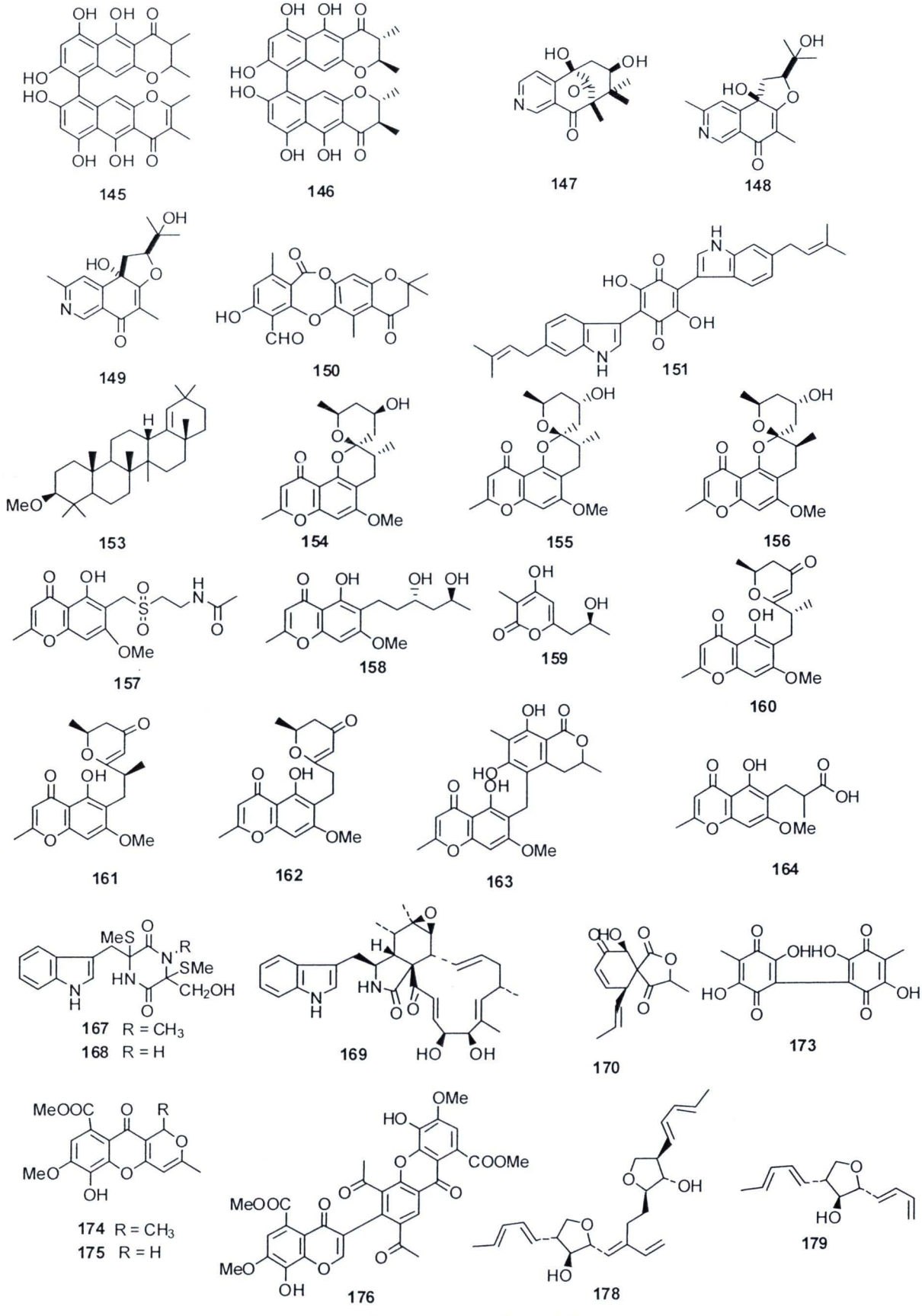
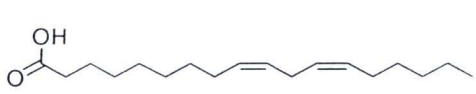
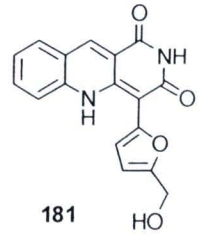


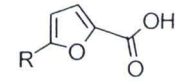
Figure 1.5 Some isolated compounds from *Chaetomium* spp. (cont.).



180



181



182 R = H
183 R = CH_2OH

Figure 1.5 Some isolated compounds from *Chaetomium* spp. (cont.).