International Journal of Biomedical and Pharmaceutical Sciences ©2008 Global Science Books

Antitumor Extrolites Produced by *Penicillium* Species

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ABSTRACT

Biodiversity is increasingly exploited worldwide for the finding of new pharmaceuticals. In relation to a competitive aptitude developed in many and diverse environments, microorganisms are able to produce secondary metabolites with cytotoxic and antiproliferative properties that are valuable in the perspective of antitumor drug discovery. Particularly, fungal species in the genus *Penicillium* represent a prolific source of biologically active extrolites that in some cases have already disclosed possible relevance for an application in cancer chemotherapy. Antiproliferative, pro-apoptotic, anti-angiogenic, anti-metastatic, DNA synthesis and cell cycle inhibitory properties of these compounds are reviewed in the present paper.

Keywords: antiproliferative compounds, apoptosis, cancer chemotherapy, cell cycle inhibitors, *Eupenicillium*, fungal metabolites, *Talaromyces*

Abbreviations: AML, acute myelogenous leukemia; **bFGF**, basic fibroblast growth factor; **cdk**, cyclin-dependent kinase; **FTase**, farnesyltransferase; **GGTase**, geranylgeranyltransferase I; **GRP78**, glucose-regulated protein 78; **MMP**, matrix metalloproteinase; **PAI-1**, plasminogen activator inhibitor-1; **PI3K**, phosphatidylinositol-3-kinase; **pRB**, retinoblastoma protein; **TNF**, tumor necrosis factor; **VEGF**, vascular endothelial growth factor

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INTRODUCTION

Recently, there is an increasing awareness of the importance for humanity to exploit natural resources to find new pharmaceuticals. After decades when the development of the pharmaceutical industry was essentially founded on synthetic chemistry, such instances have stimulated the search of novel natural products from diverse environments and organisms. In this context, secondary metabolites of microbial origin deserve special consideration, provided that it is generally possible to produce them on a large scale as a result of fermentative processes carried out in controlled conditions. The relevance of low molecular mass compounds remains undisputed in many fields of application in human medicine, but the breakthroughs that occurred in genetic engineering, cell and molecular biology have determined paramount progresses particularly in the therapy of tumor diseases. Moreover, the ongoing elucidation of the human genome is expected to provide access to many new potential targets that may be valuable for drug discovery.

So far plenty of microbial products have been characterized at different levels for their antitumor properties; some of them have already entered pharmaceutical use, and novel ones are continuously discovered. This quite convulse accumulation of new findings is creating a fragmented knowledge that fosters an organization of the current experimental data on these compounds in order to accomplish a comprehensive overview. Several criteria of classification have been proposed and continuously revised as anticancer drug discovery progresses and novel mechanisms of action are pointed out. Most of them are not concurrent, as it is not easy to establish the primary organizing aspect that should be followed (Espinosa *et al.* 2003; Wu 2006). However, a classification of antitumor drugs based on their biological properties seems to be more fundamental as it allows an evaluation for classes of similar compounds. On the other hand, inferences on the mechanism of action can be made on account of their molecular structures that are helpful for a profitable definition of the appropriate biological assays (Cruciani *et al.* 2004).

Within the multitude of micro-organisms so far exploited in this field, fungal species in the genus *Penicillium* stand out in both quantitative and qualitative terms, along the lines of the fruitful and ongoing experience of antibiotic

Received: 4 January, 2008. Accepted: 23 March, 2008.

Review

Table 1 Antitumor extrolites treated in this review and their producing *Penicillium* species.

Extrolite[a]	Producing species	Reference
Acetophthalidin (38)	*Penicillium* sp.	Cui *et al.* 1996b
Andrastins (46)	*Penicillium* sp.	Omura *et al.* 1996
	P. albocoremium	Overy *et al.* 2005a
	P. allii	Overy *et al.* 2005b
	P. radicicola	idem
	P. tulipae	idem
	P. crustosum	Sonjak *et al.* 2005
	P. roqueforti	Nielsen *et al.* 2005
	P. paneum	O'Brien *et al.* 2006
Anicequol (52)	*P. aurantiogriseum*	Igarashi *et al.* 2002
Asterric acid (48) and derivatives	*P. glabrum*	Mahmoodian and Stickings 1964
	P. vulpinum	Svendsen and Frisvad 1994
	P. aragonense	Pairet *et al.* 1995
	P. estinogenum	database CBS[b]
Aurantiamine (19)	*P. aurantiogriseum*	Frisvad and Filtenborg 1989
	P. neoechinulatum	idem
	P. freii	Lund and Frisvad 1994
Aurantiomides B-C	*P. aurantiogriseum*	Xin *et al.* 2007a
Barceloneic acids	*P. concentricum*	Frisvad *et al.* 2004
	P. albocoremium	Overy *et al.* 2005a
	P. allii	Overy *et al.* 2005b
	P. radicicola	idem
Berkeleyones (50)	*Penicillium* sp.	Stierle *et al.* 2004
Berkelic acid	*Penicillium* sp.	Stierle *et al.* 2006
Bis(methylthio)silvatin (7)	*P. brevicompactum*	Ayer *et al.* 1990
	P. bilaiae	Capon *et al.* 2007
Bisvertinolones (11)	*P. chrysogenum*	Frisvad *et al.* 2004
	P. crustosum	Liu *et al.* 2005a
Botryodiplodin (29)	*T. stipitatus*	Fuska *et al.* 1988
	P. brevicompactum	Frisvad *et al.* 1989
	P. carneum	Frisvad and Filtenborg 1989
	P. paneum	Boysen *et al.* 1996
	P. coalescens	Cabedo *et al.* 2007
Bredinin (26)	*E. brefeldianum*	Mizuno *et al.* 1974
Brefeldin A (22)	*P. decumbens*	Singleton *et al.* 1958
	P. cyaneum	Betina *et al.* 1962
	E. brefeldianum	Härri *et al.* 1963
	P. simplicissimum	Betina *et al.* 1966
	E. ehrlichii	Frisvad *et al.* 1990c
	P. cremeogriseum	Frisvad and Filtenborg 1990
	P. onobense	idem
	P. piscarium	idem
Brocaenols (1)	*P. brocae*	Bugni *et al.* 2003
Chaetoglobosins (34)	*P. expansum*	Frisvad and Filtenborg 1989
	P. marinum	Numata *et al.* 1995
	P. discolor	Frisvad *et al.* 1997
Chrysophanol	*P. islandicum*	Howard and Raistrick 1949
	T. wortmannii	Turner 1971
Citreohybridones	*E. euglaucum*	Kosemura *et al.* 1991
Citromycins	*P. glabrum*	Evans and Staunton 1988
	P. bilaiae	Capon *et al.* 2007
	P. striatisporum	idem
Communesins (4)	*P. marinum*	Numata *et al.* 1993
	P. expansum	Larsen *et al.* 1998
	P. rivulum	Dalsgaard *et al.* 2005a
Compactin (32)	*P. cyclopium*	Doss *et al.* 1986
	P. hirsutum	Frisvad and Filtenborg 1989
	P. solitum	idem
	P. lanosum	Frisvad and Filtenborg 1990
	P. aurantiogriseum	Wagschal *et al.* 1996
	P. janczewskii	Chu *et al.* 1999
Cyclopiazonic acid (53)	*P. camemberti*	Still *et al.* 1978
	P. griseofulvum	Leistner and Eckardt 1979
	P. commune	Frisvad 1985
	P. palitans	idem
	P. dipodomycola	Frisvad *et al.* 1987
	P. clavigerum	Svendsen and Frisvad 1994
Dehydroaltenusin (25)	*T. flavus*	Fuska *et al.* 1991
	P. verruculosum	Nakanishi *et al.* 1995
	P. simplicissimum	Komai *et al.* 2006b
Dehydroisopenicillide	*Penicillium* sp.	Sassa *et al.* 1974
	T. derxii	Suzuki *et al.* 1991
	P. simplicissimum	Komai *et al.* 2006b

Table 1 (Cont.)

Extrolite[a]	Producing species	Reference
Deoxyverticillin	*Penicillium* sp.	Son *et al.* 1999
Duclauxin (30)	*P. duclauxii*	Shibata *et al.* 1965
	T. stipitatus	Kuhr *et al.* 1973
	P. herquei	Frisvad and Filtenborg 1990
	T. macrosporus	Frisvad *et al.* 1990a
Emodin (41), Islandicin	*P. islandicum*	Howard and Raistrick 1949
	P. brunneum	Shibata and Udagawa 1963
	P. janthinellum	Marinho *et al.* 2005
	T. stipitatus	Frisvad *et al.* 1990a
Epolactaene (44)	*Penicillium* sp.	Kakeya *et al.* 1995
Ergosterol derivatives	*P. oxalicum*	Yang Kuo *et al.* 2005
	Penicillium sp.	Sun *et al.* 2006
	P. chrysogenum	Xin *et al.* 2007b
Eupenifeldin (2)	*E. brefeldianum*	Mayerl *et al.* 1993
Farnesylquinones (10)	*Penicillium* sp.	Li *et al.* 2003
	P. chrysogenum	Maskey *et al.* 2005
Fellutamides (5)	*P. fellutanum*	Shigemori *et al.* 1991
Fellutanines (6)	*P. fellutanum*	Kozlovsky *et al.* 2000b
	P. piscarium	Kozlovsky *et al.* 2000a
Fumagillin (49)	*P. scabrosum*	Frisvad *et al.* 1990b
	P. janczewskii	Kwon *et al.* 2000
	P. jamesonlandense	Frisvad *et al.* 2006
	P. soppii	idem
Fumitremorgins (39)	*P. piscarium*	Gallagher and Latch 1977
	P. janthinellum	Lanigan *et al.* 1979
	P. raistrickii	Mantle and Wertheim 1982
	P. mononematosum	Svendsen and Frisvad 1994
	P. brasilianum	Tuthill *et al.* 2001
GKK1032 (8)	*Penicillium* sp.	Hasegawa *et al.* 2001
Gliotoxin (47)	*P. corylophilum*	Mull *et al.* 1945
	P. glabrum	Brian 1946
Griseofulvin (20)	*P. griseofulvum*	Oxford *et al.* 1939
	P. janczewskii	Brian et al. 1949
	P. raistrickii	Brian *et al.* 1955
	P. sclerotigenum	Clarke and McKenzie 1967
	P. canescens	El-Banna *et al.* 1987
	P. concentricum	idem
	P. dipodomycola	Frisvad *et al.* 1987
	P. aethiopicum	Frisvad and Filtenborg 1989
	P. coprophilum	idem
	P. jensenii	Frisvad and Filtenborg 1990
	P. lanosum	idem
	P. soppii	Christensen *et al.* 1999
	P. persicinum	Wang *et al.* 2004
	P. waksmanii	Petit *et al.* 2004
	P. murcianum	Larsen *et al.* 2005
	P. nodositanum	idem
	P. yarmokense	idem
	P. algidum	Dalsgaard *et al.* 2005b
	P. jamesonlandense	Frisvad *et al.* 2006
	P. berlinense	Rebacz *et al.* 2007
Hadacidin (27)	*P. camemberti*	Dulaney and Gray 1962
	P. crustosum	idem
	P. glabrum	idem
	P. implicatum	idem
	P. janthinellum	idem
	P. purpurascens	idem
	P. spinulosum	idem
	P. turbatum	idem
HY558 (36)	*P. minioluteum*	Lee *et al.* 2002a
Isochromophilones	*P. sclerotiorum*	Omura *et al.* 1993
Leptosphaerone C	*Penicillium* sp.	Lin *et al.* 2008b
Luteusin A and analogues	*T. luteus*	Fujimoto *et al.* 1990
	Penicillium sp.	Toki *et al.* 1999
Methylenolactocin (13)	*Penicillium* sp.	Park *et al.* 1987
3-*O*-Methylfunicone (23)	*P. pinophilum*	De Stefano *et al.* 1999
MT81 (42)	*P. janczewskii*	Gupta *et al.* 1997
Mycophenolic acid (28)	*P. bialowiezense*	Clutterbuck and Raistrick 1933
	P. brevicompactum	Clutterbuck and Raistrick 1933
	P. roqueforti	Lafont *et al.* 1979
	P. carneum	Frisvad and Filtenborg 1989
	P. raciborskii	Frisvad and Filtenborg 1990
	P. rugulosum	Vinokurova *et al.* 2005

Table 1 (Cont.)

Extrolite[a]	Producing species	Reference
Neoxaline	*P. tulipae*	Overy and Frisvad 2003
	P. atramentosum	Frisvad *et al.* 2004
	P. coprobium	idem
	P. coprophilum	idem
Nidulalins (45)	*Penicillium* sp.	Sato *et al.* 1997
Oxaline (18)	*P. oxalicum*	Nagel *et al.* 1974
	P. atramentosum	Frisvad and Filtenborg 1989
	P. coprophilum	idem
	P. glandicola	idem
	P. melanoconidium	idem
	P. vulpinum	idem
	P. allii	Frisvad *et al.* 2004
	P. concentricum	idem
Oxazine derivative (15)	*P. brevicompactum*	Moya *et al.* 1998
	P. sizovae	Ciavatta *et al.* 2006
Penicillenols	*Penicillium* sp.	Lin *et al.* 2008a
Penicillenone C	*Penicillium* sp.	Lin *et al.* 2008b
Penicillones (12)	*P. crustosum*	Liu *et al.* 2005c
Penochalasins	*P. marinum*	Numata *et al.* 1995
Penostatins	*P. marinum*	Takahashi *et al.* 1996
Psychrophilin D	*P. algidum*	Dalsgaard *et al.* 2005b
Pyrenocines (3)	*E. euglaucum*	Niwa *et al.* 1980
	P. waksmanii	Amagata *et al.* 1998
	P. paxilli	Rukachaisirikul *et al.* 2007
Quinolactacins (55)	*Penicillium* sp.	Kakinuma *et al.* 2000
	P. citrinum	Kim *et al.* 2001
	P. bialowiezense	Frisvad *et al.* 2004
	P. sizovae	database CBS[b]
Quinolinone derivatives (14)	*P.* cf. *simplicissimum*	Hayashi *et al.* 1997
	P. janczewskii	He *et al.* 2005
	Penicillium sp.	Uchida *et al.* 2006
Rubratoxin B (37)	*P. rubrum*	Townsend *et al.* 1966
	P. purpurogenum	Natori *et al.* 1970
Sch 642305 (16)	*P. verrucosum*	Chu *et al.* 2003
	P. canescens	Nicoletti *et al.* 2007
Sclerotiorines (35)	*P. sclerotiorum*	Curtin and Reilly 1940
	E. euglaucum	Udagawa, 1963
	T. luteus	Fujimoto *et al.* 1990
	P. glabrum	Chidananda *et al.* 2006
Secalonic acid D (21)	*P. oxalicum*	Steyn 1970
	P. dendriticum	Samson *et al.* 1989
	P. funiculosum	Van Reenen-Hoekstra *et al.* 1990
	P. minioluteum	idem
	P. chrysogenum	Frisvad *et al.* 2004
	P. confertum	idem
Sequoiatones	*P. funiculosum*	Katayama *et al.* 1989
	Penicillium sp.	Lin *et al.* 2008b
Shearinines (40)	*E. shearii*	Belofsky *et al.* 1995
	P. janthinellum	Smetanina *et al.* 2007
	Penicillium sp.	Xu *et al.* 2007
	E. catenatum	database CBS[b]
Sorbicillactone A (9)	*P. chrysogenum*	Bringmann *et al.* 2003
Taxol (17)	*P. raistrickii*	Stierle *et al.* 1995
Topopyrones (43)	*Penicillium* sp.	Kanai *et al.* 2000
Trachyspic acid (51)	*T. trachyspermus*	Shiozawa *et al.* 1995
Trichodimerols	*P. chrysogenum*	Warr *et al.* 1996
	P. crustosum	Liu *et al.* 2005b
Vermistatin (24)	*T. flavus*	Fuska *et al.* 1979
	P. verruculosum	Murtaza *et al.* 1997
	E. euglaucum	Rusman 2006
	P. simplicissimum	Komai *et al.* 2006a
	T. thailandiasis	Dethoup *et al.* 2007
Vermixocins (31)	*T. flavus*	Proksa *et al.* 1992
Verrucosidins (54)	*Penicillium* sp.	Burka *et al.* 1983
	P. aurantiogriseum	El-Banna *et al.* 1987
	P. polonicum	Frisvad and Filtenborg 1989
	P. melanoconidium	Lund and Frisvad 1994
Verruculogen	*P. verruculosum*	Cole *et al.* 1972
	P. brasilianum	Yoshizawa *et al.* 1976
	P. piscarium	Gallagher and Latch 1977
	P. janthinellum	Lanigan *et al.* 1979
	P. paxilli	Cockrum *et al.* 1979

Table 1 (Cont.)

Extrolite[a]	Producing species	Reference
Verruculogen	*P. estinogenum*	Day *et al.* 1980
	P. raistrickii	Mantle and Wertheim 1982
	E. crustaceum	Horie *et al.* 1985
	P. mononematosum	Svendsen and Frisvad 1994
Wortmannin (33)	*T. wortmanni*	Brian *et al.* 1957
	T. flavus	MacMillan *et al.* 1972
	P. funiculosum	Haefliger and Hauser 1973
	P. duclauxii	Dodge and Sato 1995

[a] Number in parentheses refers to the molecular structure represented in **Table 1**
[b] Database of the Centraalbureau voor Schimmelcultures, Utrecht, the Netherlands: http://www.cbs.knaw.nl/databases/index.htm

discovery. This paper provides a review of aspects concerning production, molecular structure and biological activity of their extrolites that have evidenced some extent of antitumor properties (**Table 1**). Taxonomically, *Penicillium* is the anamorphic stage of ascomycetous fungi belonging to the genera *Eupenicillium* and *Talaromyces* (*Eurotiales*, *Trichocomaceae*); the anamorph is of more general occurrence than the corresponding teleomorph, or perfect stage, and usually represents the form that can be isolated and cultured on artificial substrates. However, as the denomination of the teleomorph prevails in nomenclature, the species for which it has been described are cited in this review with such a reference, while species of *Eupenicillium* and *Talaromyces* presenting an anamorph other than *Penicillium* are not considered. After having been reported for the production of a certain extrolite, a number of *Penicillium* species have been separated by, or considered synonyms of other taxa deserving priority. Actually, the nomenclatural problem and its implications on a correct report of extrolite production have been adequately introduced and debated by leading specialists of chemotaxonomy (Frisvad *et al.* 2004; Larsen *et al.* 2005). Species are treated herewith under their latest accepted denomination, which therefore does not necessarily correspond to the one used in the pertinent references. However, the taxonomic revision that is continuously ongoing after the application of new biomolecular techniques may have already determined further changes in the species status of some taxa that we could not have considered in this manuscript.

PENICILLIUM EXTROLITES: FROM MYCOTOXINS TO PHARMACEUTICALS

In a broad sense, the term extrolite refers to any microbial secondary metabolite that is outwards directed with ecological implications (Larsen *et al.* 2005), that is either released or accumulated in the cell wall. As they are deputed to signalling to other organisms in the biocenosis, most of them are involved in competitive relationships, and present antifeedant and/or antibiotic activities. In fact, several *Penicillium* extrolites have been first described as mycotoxins and mostly considered for their toxicological properties that make their presence in foodstuffs and forage undesired. Generally, mycotoxins and antibiotics present cytotoxic effects that may have direct or indirect implications concerning cell division, thereby exhibiting the fundamental properties of typical antitumor products. However, some compounds cannot be included in this category, provided that their biological activity is not compatible with a pharmaceutical application under many aspects. In fact, the majority of data demonstrating their cytotoxic effect has been gathered in toxicological studies carried out on human or mammalian cells that have often pointed out notable genotoxic, teratogenic and/or carcinogenic properties (Ueno *et al.* 1995; Keblys *et al.* 2004); this is the case of compounds, such as citrinin, ochratoxin A, patulin, penicillic acid, alternariol and PR-toxin, that are not considered in this review. Nevertheless, other extrolites usually regarded as mycotoxins, such as cyclopiazonic acid, gliotoxin, secalonic acid D, the chatoglobosins and anthraquinone compounds, have disclosed interesting properties that may deserve a more careful consideration for their possible implications in cancer therapy.

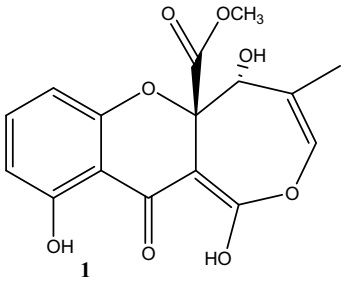
Despite the history of antibiotics dating back at least to the discovery of an antibacterial compound by Gosio (1896), later characterized as mycophenolic acid, the *Penicillia* are tightly linked by the name itself to the discovery of penicillin that, after its quite accidental finding by Alexander Fleming in 1928, turned out to produce dramatically beneficial effects. Afterwards, antibiotic properties have been repeatedly evidenced for many other *Penicillium* extrolites, but their quite diverse mechanisms of action have led to a diversification in the pharmaceutical employment. Particularly, the availability of human and mammalian cell lines has allowed carrying out direct assays of cytostatic activity, thereby stimulating their consideration as candidate antitumor products. The discovery of apoptosis, or programmed cell death, and of the genes controlling it by means of a number of biomolecular factors has further refined the possibility to accomplish an accurate evaluation of their biological properties for the development of new therapeutic agents of cancer.

Considering the complexity of cancer diseases, and of the biomolecular events involved into their onset, development and progression, there are many targets that can be evaluated in the search of new chemotherapeutic agents, and actually many compounds possess multiple mechanisms of action, ranging from a simple cytostatic effect to more complex interactions with gene expression and enzyme functions. Such variation is also reflected by quite diverse and sometimes peculiar molecular structures (**Fig. 1**), that represent a substantial basis for further studies aiming at exploring not only the foundations of their biological properties, but also the possibility to design new synthetic analogues.

ANTIPROLIFERATIVE EXTROLITES

Any secondary metabolite showing cytostatic or antiproliferative properties on mammalian cells should be regarded as a potential antitumor compound. Based on this assumption, we first consider a number of *Penicillium* extrolites that have been preliminarily evaluated for their growth inhibitory aptitude on various tumor cells lines, and are possibly waiting to be further investigated for their biomolecular mechanisms of action.

Brocaenols A-C (e.g. brocaenol A, **1**), polyketides with some structural similarity to secalonic acids produced by a strain of *P. brocae* isolated from a Fijan sponge (*Zyzzya* sp.), were found to be cytotoxic against the human colon carcinoma cell line HCT116 (Bugni *et al.* 2003). Cytotoxic properties against the same cell line and the related multidrug resistant HCT/VM46, as well as in the P388 murine leukemia model, have been shown by the pentacyclic bistropolone eupenifeldin (**2**), isolated from *E. brefeldianum* (anamorph *P. dodgei*) (Mayerl *et al.* 1993). Inhibitory capacities against P388 have also been shown by the cyclic nitropeptide psychrophilin D (Dalsgaard *et al.* 2005b), the asterric acid analogue barceloneic acid B (Overy *et al.* 2005a), the polyketide penicillenone (Lin *et al.* 2008b), and the pyrenocines (e.g. citreopyrone, **3**), so far detected in the three taxonomically unrelated species *E. euglaucum* (anamorph *P.*



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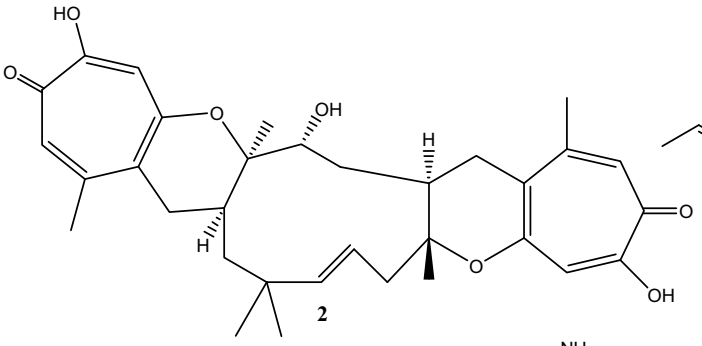

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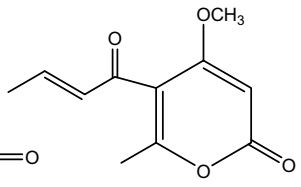

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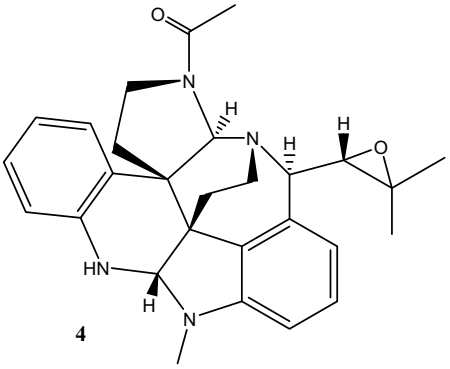

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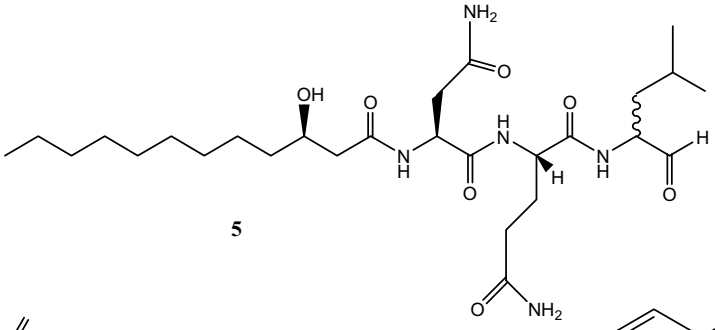

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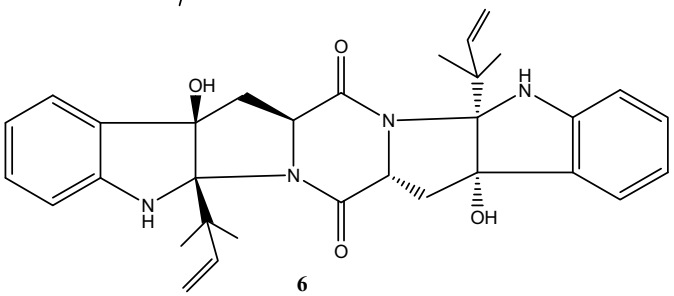

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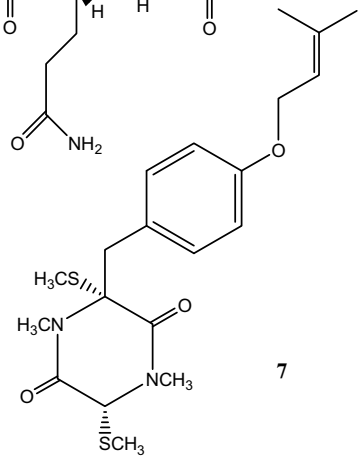

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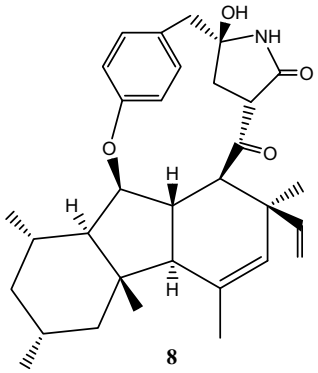

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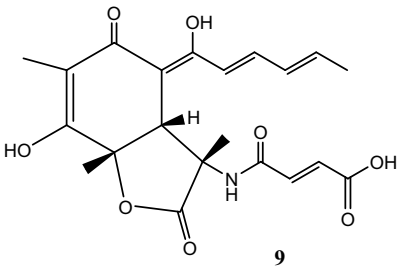

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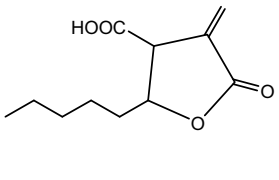

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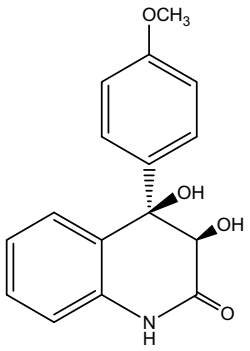

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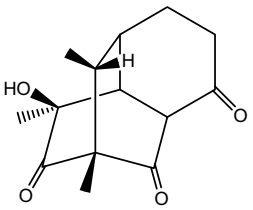

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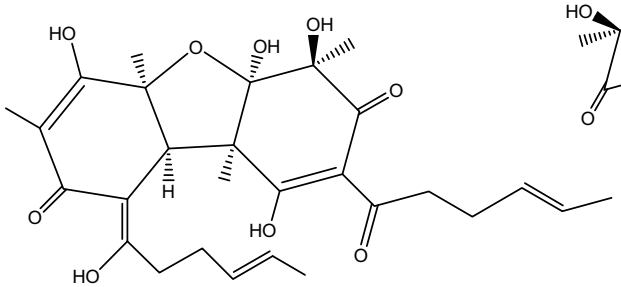

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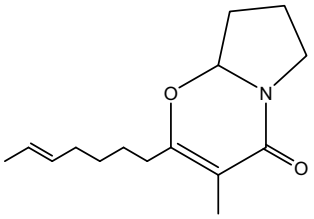

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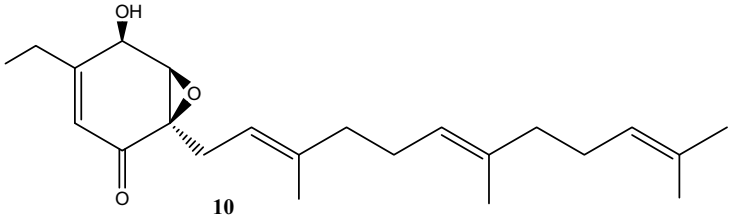

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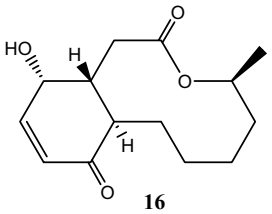

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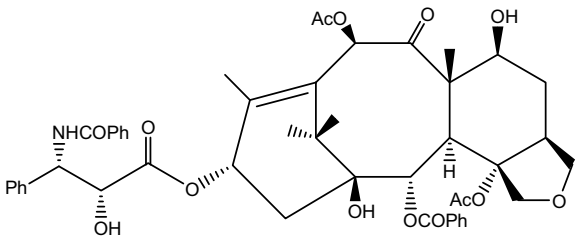

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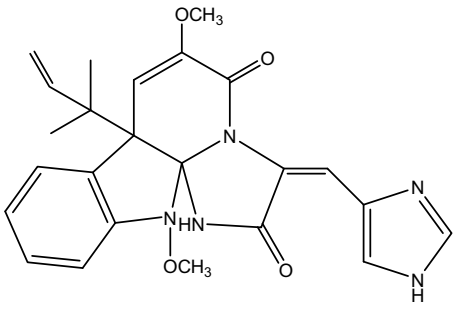

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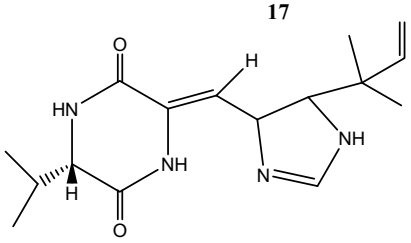

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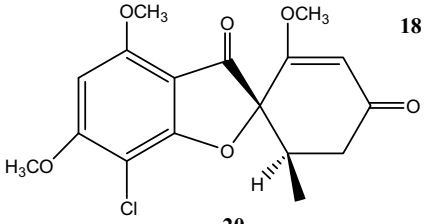

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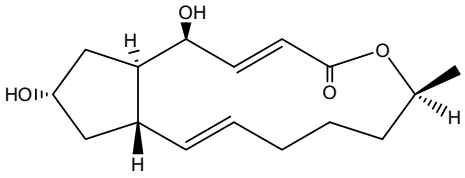

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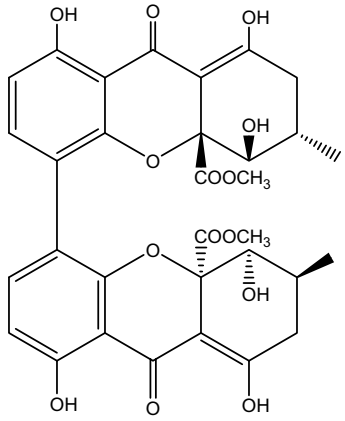

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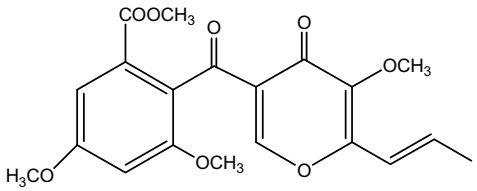

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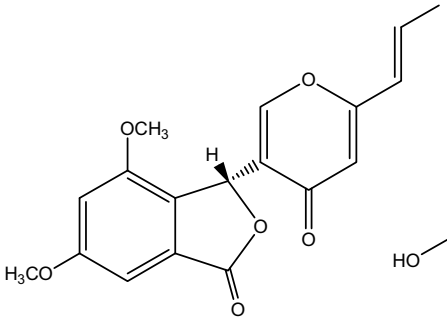

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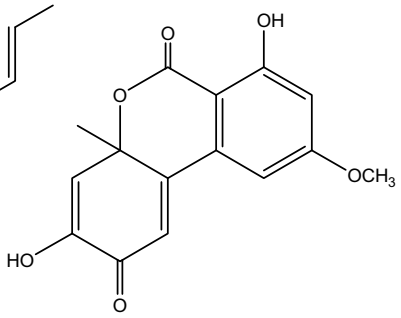

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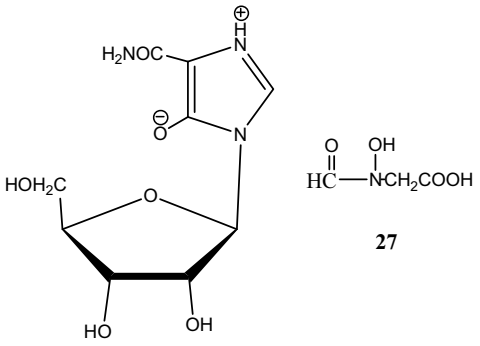

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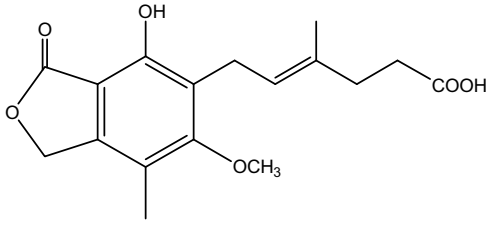

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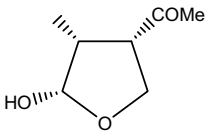

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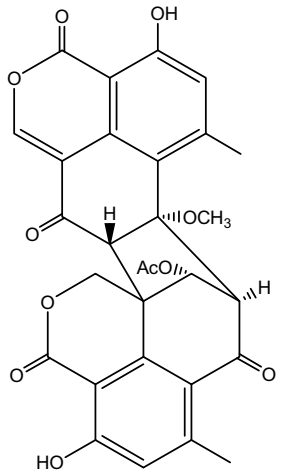

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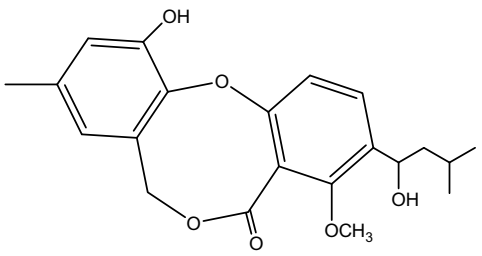

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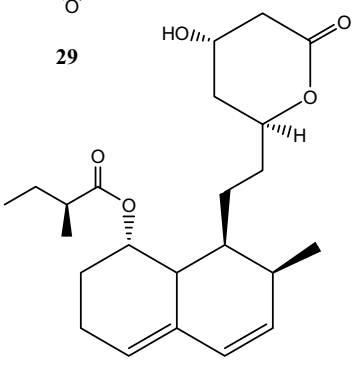

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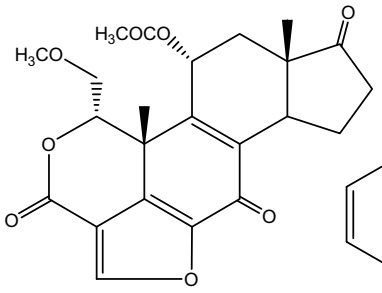

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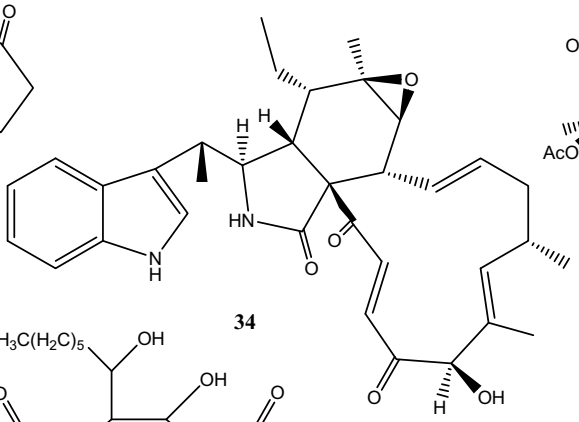

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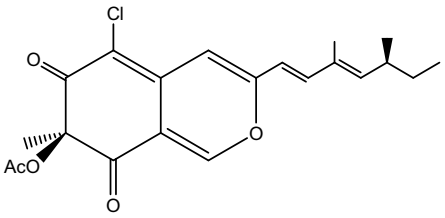

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$CH_3(CH_2)_{19}NHNHOH$

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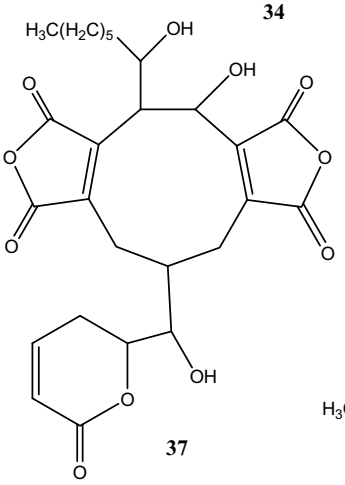

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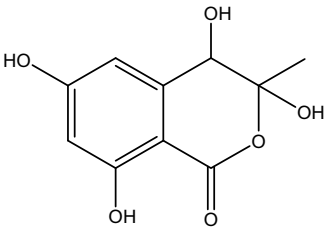

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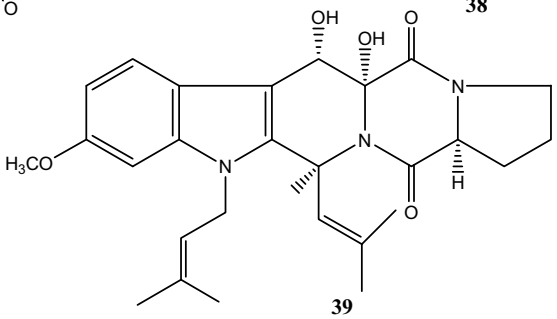

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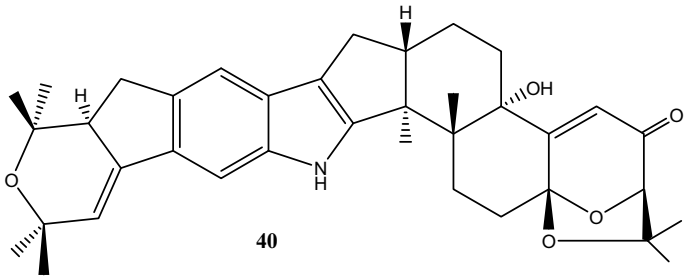

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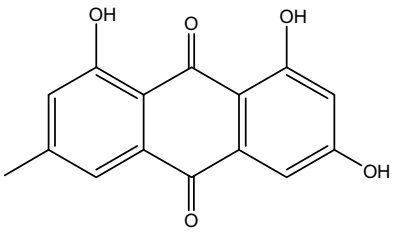

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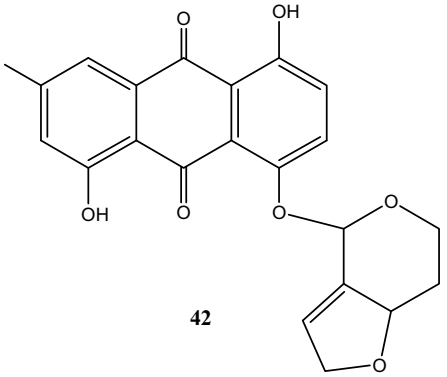

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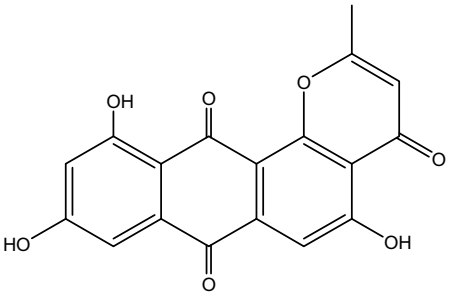

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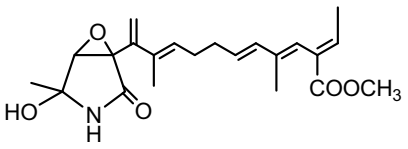

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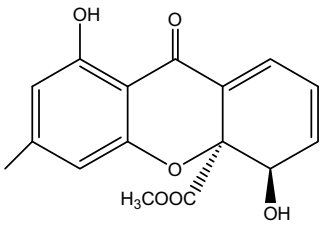

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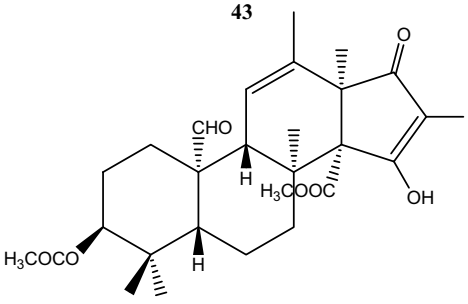

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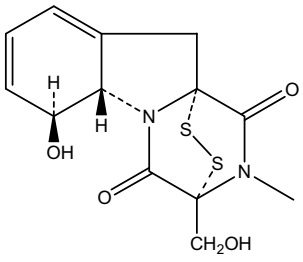

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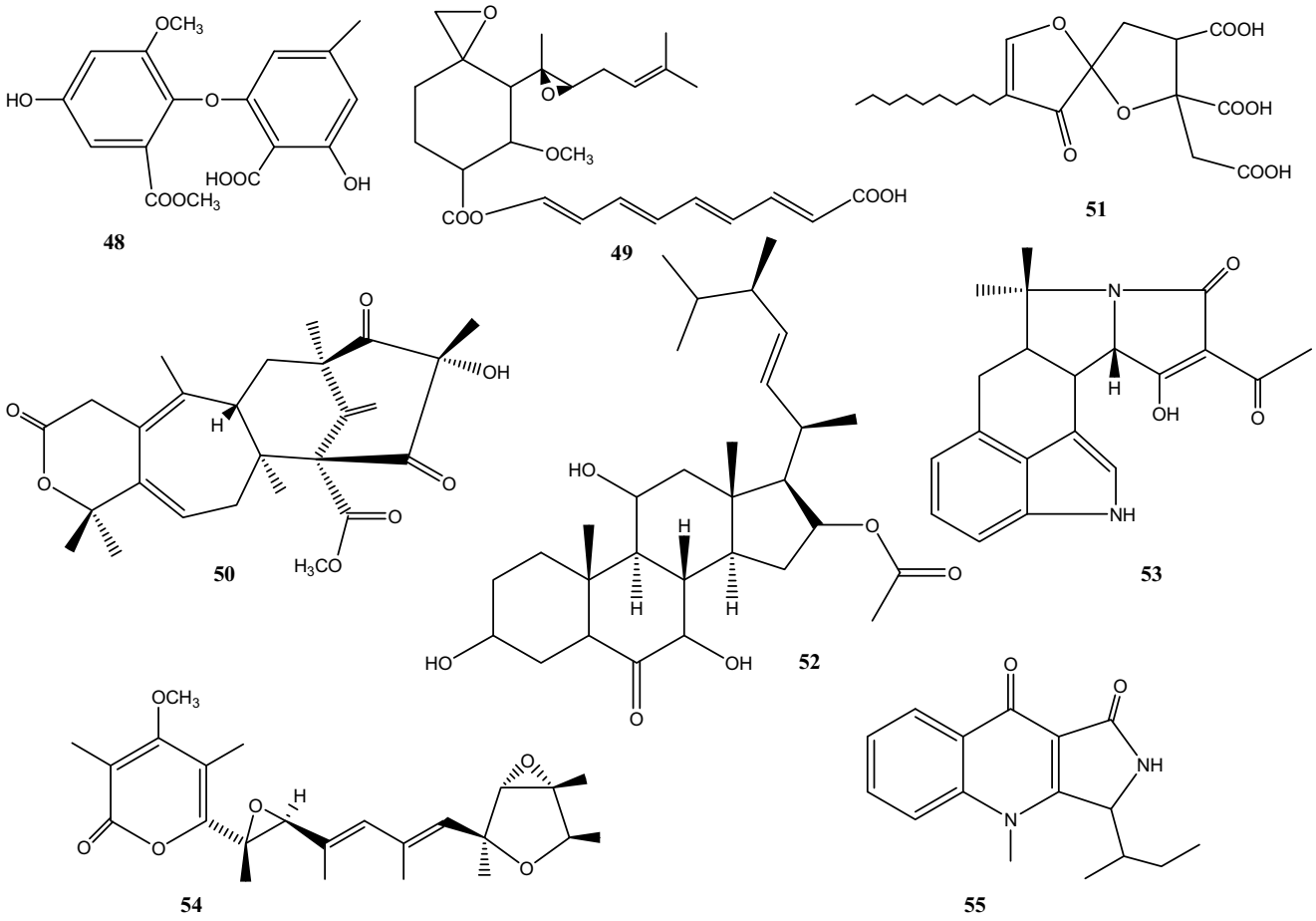

Fig. 1 Chemical structures of antitumor extrolites numbered according to their citation in the main text.

citreonigrum, syn. *P. citreoviride*) (Niwa *et al.* 1980), *P. waksmanii* (Amagata *et al.* 1998) and *P. paxilli* (Rukachaisirikul *et al.* 2007). Moderate cytotoxicity against P388 has been evidenced by the new quinazoline alkaloids aurantiomides B and C; moreover the compounds respectively induced cytotoxic effects against HL-60 (human promielocytic leukemia) and BEL-7402 (human hepatoma) (Xin *et al.* 2007a). Cytotoxicity against HL-60 has been shown by the pyrrolidinedione derivatives penicillenols A_1 and B_1 that have been characterized from an unidentified endophytic strain (Lin *et al.* 2008a). Communesins (A-H) (e.g. communesin A, **4**), also known as nomofungins, are alkaloids with a peculiar and quite complex carbon skeleton extracted from marine strains (Numata *et al.* 1993; Jadulco *et al.* 2004), later identified as *P. marinum* (Frisvad *et al.* 2004); these extrolites have also been reported from the common species *P. expansum* (Larsen *et al.* 1998), and the recently characterized psychrotolerant species *P. rivulum* (Dalsgaard *et al.* 2005a). Communesins showed antiproliferative effects against both P388 (Numata *et al.* 1993) and the human acute lymphoblastic leukemia cell lines SUP-B15 and MOLT-3 (Jadulco *et al.* 2004). The lipo-tripeptides fellutamides A (**5**) and B, isolated from the mycelium of an isolate of *P. fellutanum* (synonym *P. dierckxii*) from the marine fish *Apogon endekataenia*, were found to be cytotoxic against murine leukemic P388 and L1210 (Shigemori *et al.* 1991) and other cell lines, such as KB (human epithelial carcinoma), PC12 (rat pheochromocytoma) and L-M (mouse fibroblasts), on which their possible mechanism of action is thought to be protease or proteasome inhibition (Schneekloth *et al.* 2006). Together with *P. piscarium* (Kozlovsky *et al.* 2000a), which is considered here separately by its possible synonym *P. simplicissimum*, *P. fellutanum* also produces the diketopiperazine alkaloids fellutanines A-D; fellutanine D (**6**) has been reported for its cytotoxic properties against murine fibroblasts L929, and the human cell lines HeLa (cervix-uteri carcinoma) and K562 (myeloid leukemia) (Kozlovsky *et al.* 2000b). Another diketopiperazine, *cis*-bis(methylthio)silvatin (**7**), already known from *P. brevicompactum* (Ayer *et al.* 1990), has been recently extracted by a marine isolate of *P. bilaiae* together with the polyketides citromycin and dihydrocitromycin that were also found in an isolate of *P. striatisporum*; all the three extrolites displayed weak cytotoxicity against murine NS-1 cells (Capon *et al.* 2007). Inhibitory properties against HeLa cells have been also exhibited by compounds GKK1032 A_1, A_2 (**8**) and B, extracted by an unidentified *Penicillium* strain (Hasegawa *et al.* 2001). Antiproliferative activity by sorbicillactone A (**9**), characterized from a strain of *P. chrysogenum* recovered from the marine sponge *Ircinia fasciculata*, has been reported against mouse lymphoma cells (L5178Y) (Bringmann *et al.* 2003), together with the analogue compounds sorbivinetone and sorbivinetol, inducing cytotoxic effects on HeLa and PC12 cells at much higher concentrations (Bringmann *et al.* 2005). An unidentified marine strain has been found to produce other structurally related extrolites, deacetoxyyanuthone A (**10**) and farnesylhydroquinone, whose cytotoxic properties have been pointed out on a panel of human tumor cell lines, including A549 (non-small cell lung carcinoma), SK-OV-3 (ovary adenocarcinoma), SK-MEL-2 (melanoma), HCT15 (colon cancer) and XF498 (central nervous system cancer) (Li *et al.* 2003). Deacetoxyyanuthone A has been also isolated by *P. chrysogenum* (syn. *P. notatum*: Maskey *et al.* 2005), a well-known producer of other bisorbicillinoid compounds, such as the bisvertinolones (Frisvad *et al.* 2004). More recently four novel compounds of this series have been reported from an isolate of marine origin ascribed to *P. terrestre* (Liu *et al.* 2005a, 2005b), a species considered as a synonym of *P. crustosum* in the current taxonomy (Frisvad and Samson 2004): dihydro- and tetrahydrobisvertinolone (**11**) were found to be the most active products against P388 and A549 (Liu *et al.* 2005a).

Liu *et al.* (2005b) also reported cytotoxic activity on the same cell lines by dihydro- and tetrahydrotrichodimerol, which are derivatives of trichodimerol, an extrolite able to inhibit production of the tumor necrosis factor (TNF-α) in murine macrophages and human peripheral blood monocytes, which had been formerly reported as BMS-182123 by *P. chrysogenum* (Warr *et al.* 1996). The above-reported marine isolate of *P. crustosum* was also found to produce two polyketides with a tricyclo-undecane skeleton named penicillone A (**12**) and B, that again proved to be cytotoxic against P388 and A549 (Liu *et al.* 2005c). It must be remarked here that the compound more recently found in an endophytic isolate of *P. paxilli*, also named penicillone (Rukachaisirikul *et al.* 2007), has a different molecular structure and should not be confused. Cytotoxicity against A549 cells was exhibited by the polyketide compound leptosphaerone C (Lin *et al.* 2008b). In the same paper, inactivity towards A549 and P388 is reported for sequoiatones A and B, which previously displayed moderate inhibitory properties against several breast cancer cell lines (Stierle *et al.* 1999). Ehrlich ascites cells inoculated intraperitoneally in mice were used to evidence the antitumor properties of methylenolactocin, α-methylene-γ-lactone (**13**) characterized from an unidentified *Penicillium* species (Park *et al.* 1987). Weak to moderate cytotoxicity against several human tumor cells, such as MDA-MB231 (breast adenocarcinoma), DU-145 (prostate carcinoma), HT-29 (colon carcinoma), CAKI-1 (kidney carcinoma), SK-OV-3, SK-MEL 2, A549 and K562, was exhibited by the quinolinone compounds yaequinolinone A2 (3*R**,4*R**-dihydroxy-3,4-dihydro-4-(4'-methoxyphenyl)-2(1*H*)-quinolinone, **14**) and peniprequinolone, produced by some species belonging to the subgenus *Furcatum* (He *et al.* 2005; Uchida *et al.* 2006). Finally, the brevioxime analogue 2-(hept-5-enyl)-3-methyl-4-oxo-6,7,8,8a-tetrahydro-4*H*-pyrrolo[2,1-*b*]-1,3-oxazine (**15**, onwards mentioned as oxazine derivative), first detected in *P. brevicompactum* (Moya *et al.* 1998) and recently extracted from two isolates of *P. sizovae* (Ciavatta *et al.* 2006), and compound Sch 642305 (**16**), characterized from *P. verrucosum* (Chu *et al.* 2003), and later found as a fungitoxic extrolite of *P. canescens* (Nicoletti *et al.* 2007), have demonstrated antiproliferative and pro-apoptotic properties on MCF-7 (breast cancer) and A549 cells (Nicoletti *et al.* 2008), that are currently the subject of further investigations.

MICROTUBULE, CELL CYCLE AND DNA SYNTHESIS INHIBITORS

Cytostatic and antiproliferative properties are based on inhibition of mitosis that occurs as a consequence of perturbations in the cell cycle, or in the DNA synthesis, or in the microtubule organization, effects that are often interrelated. Particularly, many successful antitumor drugs interfere with microtubule dynamics by mechanisms based either on the inhibition of tubulin polymerization, or on the stabilization of microtubule bundles (Desbène and Giorgi-Renault 2002; Jordan and Wilson 2004).

The best known compound representing the latter class is taxol (**17**), also known as paclitaxel, which determines cell cycle arrest at the G_2/M phase and subsequent apoptosis in consequence of interference in the microtubule dynamics. This highly functionalized diterpene was first extracted by the yew tree (*Taxus brevifolia*) (Wani *et al.* 1971), but afterwards found to be produced by several endophytic fungi, including a *Penicillium* species (*P. raistrickii*) (Stierle *et al.* 1995). The compound is undoubtedly the most important antitumor agent produced by *Penicillium*, as it has entered routine pharmaceutical use since almost a decade after having been approved for breast and ovarian cancer treatment (Demain 1999). A thorough review on the antitumor properties of paclitaxel and its analogue docetaxel considering its microtubule-targeted and other biomolecular effects has been recently published (Zhao *et al.* 2005). However, it must be also remarked that the drug may exert useful anti-angiogenic side effects, as it has been reported to inhibit neovascularization induced by the basic fibroblast growth factor (bFGF) and the vascular endothelial growth factor (VEGF) (Klauber *et al.* 1997).

Several other natural products act more substantially by inhibiting the formation of the mitotic spindle. They have been grouped into two subclasses according to whether or not they bind tubulin to the same site as colchicine (Desbène and Giorgi-Renault 2002). Compounds belonging to the first subclass, such as the podophyllotoxins, steganacin, combretastatin and the colchicine itself, present a molecular structure sharing a trimethoxyphenyl moiety which is highly reactive with sulphydryl groups of aminoacids and represents an important binding site. This kind of active site can be also observed in the case of a *Penicillium* extrolite, 3-*O*-methylfunicone, that is treated in detail below.

Oxaline (**18**) and neoxaline are alkaloids produced by several *Penicillium* species by transformation of roquefortine, a quite common diketopiperazine extrolite (Steyn and Vleggaar 1983). These compounds are able to inhibit cell proliferation and to induce cell cycle arrest at the M phase in T lymphoma Jurkat cells. Moreover, oxaline induces the disruption of microtubule assembly in mouse 3T3 fibroblasts, as a consequence of its ability to inhibit the polymerization of microtubule proteins; *in vitro*, purified tubulin is bound at the colchicine binding site (Koizumi *et al.* 2004). Aurantiamine (**19**), produced by *P. aurantiogriseum* and some closely related species, is another diketopiperazine reported to exert its biological activity on microtubule assembly (Hayashi *et al.* 2000).

Mechanisms of tubulin binding have not been clearly elucidated in the case of griseofulvin (**20**), an extrolite produced by many *Penicillium* species and commonly used in the past as an antimicotic pharmaceutical against dermatophytes. Its anti-mitotic properties have been considered for their implications in cancer therapy since long time (Grisham *et al.* 1973). Yet, the compound is responsible for a mild suppression of microtubule dynamics that impairs the organization and function of the mitotic spindle, an effect that in HeLa cells halts cell cycle progression at the G_2/M phase with ensuing apoptosis induction (Panda *et al.* 2005). Moreover, it has been found to induce multipolar spindles by inhibition of centrosome coalescence, mitotic arrest, and subsequent cell death in the human tumor cell lines SCC114 (oral cancer), HeLa, MCF-7, U2OS (osteosarcoma). This effect is selective, as it has not been observed in diploid fibroblasts and keratinocytes with normal centrosome content. The inhibition of centrosome clustering by griseofulvin is not restricted to mitotic cells but occurs during interphase as well. Most neoplastic cells contain multiple centrosomes, associated with the formation of multipolar mitotic spindles and chromosome segregation defects. Since it has been observed that tumor cells regain mitotic stability by the coalescence of multiple centrosomes into two functional spindle poles, a therapeutic strategy may be based on the inhibition of centrosomal clustering, which would trigger apoptosis by forcing multipolar mitoses in cells with supernumerary centrosomes (Rebacz *et al.* 2007). The reported mechanism of action of griseofulvin and its low toxicity introduce interesting perspectives for its use in combination with other antitumor agents. Ho *et al.* (2002) observed a synergism with nocodazole in determining inhibitory effects on tumor growth in mice bearing COLO 205 xenografts. They also found some clues of a direct effect on the cell cycle based on an increase in cyclin B1/cdc2 kinase activity and in a down-regulation of myt-1 protein expression; in addition, caspase 3 activation, Bcl-2 hyperphosphorylation and inhibition of the normal function of Bcl-2 associated with Bax were demonstrated to be the mechanisms responsible for apoptosis induction.

The octaketide mycotoxin secalonic acid D (**21**) is known to be produced by *P. oxalicum* and several taxonomically unrelated species. Antitumor properties were first evidenced in its 5-di-(2'-tetrahydropyranyl) derivative assayed on murine cell lines and mice implanted tumors (Iwaguchi *et al.* 1980; Shimizu *et al.* 1983). Afterwards, the

compound itself showed cytostatic activity against L1210 cells (Kurobane *et al.* 1987), and later found to affect proliferation of murine embryonic palatal mesenchymal cells (Hanumegowda *et al.* 2002). On these cells the compound inhibits G_1/S-phase specific cyclin-dependent kinase 2 (cdk 2) activity, reduces the level of cyclin E and increases the level of the cdk inhibitor p21; the same effects are induced on the corresponding human cell type, together with a reduction in the level of cdk 4/6 and cyclins A, D1, D2, D3, E, while the level of the cdk inhibitor p57 is increased (Dhulipala *et al.* 2005).

Brefeldin A (**22**), also known as ascotoxin, cyanein, decumbin, and synergisidin after its independent discovery in different fungal species (Singleton *et al.* 1958; Betina *et al.* 1962; Härri *et al.* 1963), is a macrocyclic lactone produced by a number of *Eupenicillium* and *Penicillium* species in the subgenus *Furcatum*. Its major biological activity was at first identified in the inhibition of intracellular protein transport from the endoplasmic reticulum to the Golgi apparatus, and the induction of a reversible disassembly of the latter (Fujiwara *et al.* 1988). Although this mechanism is important for tumor proliferation, it has been observed that the Golgi apparatus structure is unaffected in resistant cancer cell sublines (Erokhina *et al.* 1999). Actually, more consistent antitumor properties were evidenced on account of an antiproliferative activity detected in human melanoma athymic mouse xenografts and in PC3 prostate carcinoma cells (Sausville *et al.* 1996), while a pro-apoptotic effect resulted on HT-29 and a couple of human leukemic cell lines (HL-60, K562), evidencing DNA fragmentation with the typical internucleosomal pattern. Cell death is independent of a cyclin B1/cdc2 kinase upregulation, as their activity decreased after brefeldin A treatment in HL-60 cells, and clearly occurs following a p53-independent pathway, as HL-60 and K562 cells are p53 null and HT-29 are p53 mutant cells (Shao *et al.* 1996). These effects, resulting in an arrest in the G_1 to S phase transition of the cell cycle, have been confirmed on another prostatic cancer cell line (DU-145) (Chapman *et al.* 1999). Since p53 mediated pathways is frequently abrogated in prostatic cancer cells, agents inducing p53 independent cell death may be promising chemotherapeutic candidates (Wallen *et al.* 2000). Properties as a direct cell cycle modulator in PC3 cells depend on the effect on a growth pathway mediated by the retinoblastoma protein (pRB); in fact, the compound induces dephosphorylation of pRB, and a down-regulation of cyclin-dependent kinases (cdk 2/4) and cyclin D1 expression (Mordente *et al.* 1998). pRB hypophosphorylation has been again observed on primary prostate cancer cells (Wallen *et al.* 2000). Treatment with brefeldin A triggers apoptosis after arresting cell cycle in early G_0/G_1 phase on other cell lines, such as HCT116 and glioblastoma (SA4, SA146 and U87MG), with no alteration of p53, Bcl-2, Bax and Mcl-1 expression (Pommepuy *et al.* 2003); differentiation of the latter cell line is induced as a result of a modulatory effect by brefeldin-A on GM3 ganglioside biosynthesis, that introduces a new therapeutic target for cancer diseases (Nojiri *et al.* 1999). In fact, as GM3 ganglioside is able to down-regulate tetraspanin CD9 that is associated with control of tumor cell motility, its enhanced synthesis induced by brefeldin A treatment may reduce the invasiveness of bladder cancer cells and, consequently, their metastatic properties (Satoh *et al.* 2001). Observations carried out on cytotoxicity and induction of apoptosis in HCT116 cells have shown that the structural determinants for biological activity of the compound include the moiety of the Michael acceptor, the conformational rigidity of the 13-membered ring, and the configuration of the hydroxyl group at C-4 (Zhu *et al.* 2000). Very recently the inhibitory properties against the functions of the endoplasmic reticulum-Golgi transport apparatus have been reappraised as the compound, based on ensuing mitochondrial breach and subsequent caspase cascade activation, was successful in inducing apoptosis on several follicular lymphoma cell lines that are resistant to conventional anticancer agents (Wlodkowic *et al.* 2007).

3-*O*-Methylfunicone (**23**), characterized from *P. pinophilum* (De Stefano *et al.* 1999), is one of a series of structurally related compounds mostly characterized by species belonging to the subgenus *Biverticillium* and their *Talaromyces* teleomorphs (Nicoletti and Carella 2004), whose skeleton consists in a γ-pyrone ring linked through a ketide function to an α-resorcylic acid nucleus presenting a methylated carboxylic group. This extrolite is fungitoxic and responsible of the antagonistic properties toward plant pathogenic fungi (De Stefano *et al.* 1999; Nicoletti *et al.* 2004); moreover, it has displayed cytostatic and pro-apoptotic properties on several human tumor cell lines, such as HEp-2 (larynx carcinoma) (Stammati *et al.* 2002), A549 and MCF-7 (Nicoletti *et al.* 2008). Investigations carried out on HeLa cells have demonstrated its ability to cause growth arrest, modification in the organization of tubulin fibers and apoptosis, which is triggered following a p53 independent pathway (Buommino *et al.* 2004). An increase in p21 mRNA expression and a reduced expression of cyclin D1 and cdk 4 mRNA resulted at the same time. Besides the pro-apoptotic properties, the compound has been found to inhibit the gene expression of typical markers of tumor progression, such as survivin and human telomerase reverse transcriptase, and to strongly affect cell proliferation and motility of breast cancer MCF-7 cells by down-regulating αvβ5 integrin and inhibiting matrix metalloproteinase (MMP-9) secretion. This effect is selective, as it was not observed on a non-tumoral breast cell line (MCF-10) (Buommino *et al.* 2007). Inhibition of cell motility is also associated to modifications in cell shape and in the distribution of tubulin fibers of MCF-7 cells. As introduced above, this latter property may depend on the trimethoxylated aryl moiety; assays on its effect on tubulin polymerization are currently in progress in our laboratories to check this hypothesis.

Another funicone-like extrolite, vermistatin (**24**), has been characterized by *T. flavus* (anamorph *P. dangeardii*, synonym *P. vermiculatum*) (Fuska *et al.* 1979, 1986), and later found to be produced by *P. verruculosum* (Murtaza *et al.* 1997) and *P. simplicissimum* (Komai *et al.* 2006a). Cytotoxicity of the compound was first observed on leukemic cells (Fuska *et al.* 1979), but further evidences of its antitumor properties have been gathered more recently. In fact a weak activity of vermistatin was detected against L5178Y cells; moreover the compound proved to be slightly inhibitory toward several kinases, such as aurora A and B, cdk 4/cyclin D1, the insulin-like growth factor I receptor, ErbB2, BRAF-VE, Akt1 and VEGF receptor-2 involved in the cell cycle progression and apoptosis induction, or implicated in the pathologic angiogenesis associated with tumor growth (Rusman 2006). Very recently some funicone and vermistatin analogues, described as penicidones and differing by a γ-pyridone nucleus substituting the γ-pyrone ring, have been reported from an unidentified endophytic strain, and exhibited moderate cytotoxicity against several cell lines, such as KB, K562, HeLa and SW1116 (human colon cancer) (Ge *et al.* 2008).

Dehydroaltenusin (**25**) has been found in the same species that produce vermistatin, that is *T. flavus* (Fuska *et al.* 1991), *P. verruculosum* (Nakanishi *et al.* 1995) and *P. simplicissimum* (Komai *et al.* 2006b): Rather than being occasional, these findings may be considered indicative of a common biosynthetic pathway shared by these extrolites. The compound showed cytostatic properties in preliminary tests carried out on P388 cells (Proksa *et al.* 1992), and was later found to inhibit the proliferation of human tumor cell lines, such as A549, BALL-1 (acute lymphoblastoid leukemia), NUGC3 (stomach carcinoma) and HeLa (Murakami-Nakai *et al.* 2004). Solid tumor development was suppressed as well in nude mice bearing HeLa cells, where histopathological examination revealed an increased tumor necrosis and a reduction of the mitotic index (Maeda *et al.* 2007). Biological activity of the compound relies on inhibition of DNA synthesis, which depends both on a direct inhibition of mammalian DNA polymerase α and on an indirect effect following intercalation and conformational changes of the

DNA molecule (Mizushina *et al.* 2000a). DNA does not seem to be damaged, as there is no influence on p53, bax and bcl-2 expression levels, and fragmentation only occurs when HeLa cells are treated at higher concentrations. These effects halt the cell cycle at the S phase, which is confirmed by the increased levels of cyclins A and E, while a significant reduction occurs in levels of cyclin B, which is regulated at the G_2/M phase (Murakami-Nakai *et al.* 2004).

Bredinin (**26**), characterized from *E. brefeldianum* (Mizuno *et al.* 1974), is an imidazole nucleoside antibiotic with potent cytotoxicity. Its aglycone is able to induce very similar effects, as it is active after conversion to bredinin catalysed by the enzyme adenine-phosphoribosyltransferase (Sakaguchi *et al.* 1975a). The compound inhibits proliferation of several mammalian cell lines; on L5178Y cells it causes marked chromosomal aberrations, such as breakages, translocations, and fragmentation, and inhibits nucleic acid synthesis without being intercalated (Sakaguchi *et al.* 1975b). Bredinin-resistant mutants have been found in cultured mouse mammary carcinoma FM3A cells as a consequence of a defective adenosine-kinase, an enzyme that in sensitive cells phosphorylates bredinin to a toxic nucleotide, bredinin 5'-monophosphate (Koyama and Tsuji 1983). Cell growth inhibitory effects by this derivative were confirmed again on L5178Y (Kusumi *et al.* 1989). Later, bredinin 5'-monophosphate also showed potent inhibitory effects on mammalian DNA polymerase α and β (Horie *et al.* 1998).

Hadacidin (N-formyl hydroxyaminoacetic acid, **27**), probably the structurally simplest antitumor extrolite in *Penicillium*, was characterized from isolates belonging to several species (Dulaney and Grey 1962), and soon found effective in the inhibition of growth of a human adenocarcinoma transplanted in embryonated eggs (Kaczka *et al.* 1962). The compound was also reported to be able to affect purine biosynthesis (Shigeura and Gordon 1962). Later this biological property was found to be dependent on a competitive inhibition of adenylosuccinate-synthetase, an enzyme involved in adenine nucleotide biosynthesis, resulting in an antiproliferative activity on canine kidney MDCK cells, whose cell cycle was arrested in the S phase (Ladino *et al.* 1989).

Mycophenolic acid (**28**) is undoubtedly one of the first microbial metabolites to have been characterized (Gosio 1896), although an appropriate species determination of the producing strains occurred much later (Clutterbuck and Raistrick 1933). Probably it was also one of the first extrolites to have been studied for its possible use as an antitumor pharmaceutical, after substantial evidence to this regard resulted by laboratory assays carried out on several murine implanted tumors (Williams *et al.* 1968; Suzuki *et al.* 1969; Sweeney *et al.* 1972). Mycophenolic acid depletes guanine nucleotides and blocks DNA synthesis by inhibiting inosine monophosphate-dehydrogenase (Franklin and Cook 1969), an enzyme representing a valuable chemotherapeutic target, as it is particularly active in cancer cells (Franchetti and Grifantini 1999). In nanomolar concentrations the compound blocks proliferative responses of cultured human, mouse and rat T and B lymphocytes (Eugui *et al.* 1991). The more potent cytostatic effect observed on lymphocytes explains why mycophenolic acid is better considered as an immunosuppressive compound. In fact, its mofetil ester is a widespread pharmaceutical used in organ transplantation (Lipsky 1996). For the same reason, therapeutic application may be indicated in lymphocytic or monocytic leukemiae and lymphomas.

DNA synthesis inhibition is a reported mechanism of action of botryodiplodin (or botryodiploidin) (**29**) and of the isocoumarin dimer duclauxin (**30**). Both extrolites are produced by *P. stipitatum* (synonym *P. emmonsi*, teleomorph *T. stipitatus*) (Fuska *et al.* 1988); moreover, the former has been reported by *P. brevicompactum* (Frisvad *et al.* 1989), *P. coalescens* (Cabedo *et al*. 2007) and *P. paneum* (Boysen *et al.* 1996), a species separated by the better known *P. roqueforti* from which the compound had been originally reported (Moreau *et al.* 1982), while the latter was first characterized by *P. duclauxii* (Shibata *et al.* 1965), and afterwards found to be also produced by *T. stipitatus* (Kuhr *et al.* 1973; Fuska *et al.* 1974), *T. macrosporus* (anamorph *P. macrosporum*) (Frisvad *et al.* 1990a) and *P. herquei* (Frisvad and Filtenborg 1990). Both extrolites showed antiproliferative activity against HeLa cells and murine-derived cell lines (Ehrlich ascites, L-5178, sarcoma 37), and caused the inhibition of incorporation of ^{14}C-labelled precursors of proteins and nucleic acids (Fuska *et al.* 1974). Inhibitory effects on DNA and RNA synthesis were again reported by Moulé *et al.* (1981), and referred to the induction of DNA-protein cross-links depending on the hemiacetal structure of the molecule (Douce *et al.* 1982; Moulé *et al.* 1982). Cross-links disappeared as soon as cells were transferred into fresh medium (Moulé *et al.* 1984). Duclauxin also exhibited inhibitory properties against L1210 cells, with a potent uncoupling effect accompanying a marked depression of state 3 respiration of mitochondria (Kawai *et al.* 1985).

Vermixocins (e.g. vermixocin A, **31**), detected as fermentation by-products of *T. flavus*, are able to inhibit the incorporation of labeled uridine into P388 cells, indicating that they may interfere with RNA synthesis (Proksa *et al.* 1992). Their structural analogue dehydroisopenicillide, isolated from unidentified *Penicillium* strains (Sassa *et al.* 1974; Kawamura *et al.* 2000) and from *T. derxii* (anamorph *P. derxii*) (Suzuki *et al.* 1991), has shown antiproliferative properties against several human cell lines, such as K562, MKN28 (gastric cancer), PC6 (lung cancer), MCF-7, HT1080 (fibrosarcoma) and HT29 (Kawamura *et al.* 2000).

Compactin (**32**), also known as mevastatin, is a nonaketide characterized independently and almost contemporarily by *P. brevicompactum* (Brown *et al.* 1976) and *P. citrinum* (Endo *et al.* 1976). Both producing isolates were later found to have been mistakenly identified, and ascribed to *P. solitum* and *P. hirsutum* (Frisvad and Filtenborg 1989). Further reports are known from *P. cyclopium* (Doss *et al.* 1986), *P. lanosum* (Frisvad and Filtenborg 1990) and *P. aurantiogriseum* (Wagschal *et al.* 1996), and some biologically active structural analogues, such as dihydrocompactin (Lam *et al.* 1981), solistatin (Sørensen *et al.* 1999) and solistatinol (Larsen *et al.* 2007), are also produced by these species. Compactin is the founder of a family of compounds of both natural and synthetic origin known as the statins, which are widely employed for cardiovascular diseases. However, several large-scale trials of these drugs evidenced a beneficial side effect on patients suffering for cancer (Wong *et al.* 2002; Jakobisiak and Golab 2003), that introduced a new field for their pharmaceutical employment (Chan *et al.* 2003). Particularly, the fundamental mechanism of action has been identified in the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A-reductase, which turns into a blockage in the mevalonate biosynthetic pathway and in ras protein farnesylation. However, antitumor properties of statins, that have been recently reviewed (Graaf *et al.* 2004), are quite more complex, and rely on pro-apoptotic, anti-metastatic and anti-angiogenetic effects. Apoptosis induction has been observed on several tumor cell lines, such as acute myelogenous leukemia (AML), juvenile myelomonocytic leukemia, squamous carcinoma of the cervix-uteri, rhabdomyosarcoma, medulloblastoma, mesothelioma, astrocytoma, pancreatic tumor, neuroblastoma and colorectal carcinoma. The growth arrest appears to be p53-independent and is mediated by down-regulation of cdk 2 activity, while the cdk inhibitors p21 and/or p27 are up-regulated (Dulak and Jozkowicz 2005). As combined with butyrate, the compound synergistically suppresses growth of colon carcinoma cells (Caco-2), that are arrested in the G_1 phase of the cell cycle after 24 h with a switch to the G_2/M phase after 72 h; these effects are accompanied by a down-regulation of cdk 4 and cdk 6, as well as cyclin D1, while cdk 2 and cyclin E levels are stable (Wächtershäuser *et al.* 2001). Statins may also produce anti-metastatic effects based on a reduced expression of MMP-9 and on a reduced invasiveness that has been experimentally observed on several tumor cell types (Graaf

et al. 2004). Although mevastatin have proved to be able to completely block the expression of VEGF in cultured rat primary endothelial cells, and VEGF down-regulation have been observed in several tumor cell types (Jones *et al.* 1999), the effects of statins on angiogenesis are quite controversial (Graaf *et al.* 2004).

Wortmannin (**33**), originally isolated from *T. wortmanni* (anamorph *P. kloeckeri* or *P. wortmanni*) (Brian *et al.* 1957), is a specific and potent inhibitor of the phosphatidylinositol-3-kinase (PI3K), that is bound at the ATP-binding site of its catalytic domain (Arcaro and Wymann 1993; Powis *et al*. 1994; Ui *et al.* 1995; Hazeki *et al.* 1996; Walker *et al.* 2000). The PI3K/Akt signalling pathway is involved in a large number of fundamental cellular processes, including apoptosis, proliferation, cell motility and adhesion, and its constitutive activation has been implicated in both the pathogenesis and the progression of a wide variety of neoplasiae, and in the malignant transformation of cells. Increased levels of PI3K products have been observed in colorectal tumors and in breast cancers, while their dephosphorylation suppresses tumor formation. Hence, this pathway is an attractive target for the development of novel chemotherapeutic strategies. For example, PI3K/Akt signaling is frequently activated in AML blasts and strongly contributes to proliferation, survival and drug resistance of these cells. Upregulation of the PI3K/Akt network may be due to several reasons, including *FLT3*, *ras* or *c-kit* mutations. Small molecules designed to selectively target key components of this signal transduction cascade induce apoptosis and/or markedly increase sensitivity of AML blasts to conventional drugs. Thus, inhibitory molecules are currently being developed for clinical use either as single agents or in combination with other antitumor pharmaceuticals (Martelli *et al.* 2006). Further evidence of the antitumor effects of wortmannin results by its ability to inhibit proliferation of KNS-62 and Colo-699 lung cancer cells, by a delayed growth of subcutaneously induced tumors as a consequence of PI3K inhibition occurring prior to xenotransplantation, and by increased survival of human non-small cell lung cancer after intrapulmonary xenotransplantation. However, the systemic toxicity of wortmannin appears to condition its pharmacological applications (Boehle *et al.* 2002).

Cytochalasans are cytostatically active metabolites produced by many and diverse fungal species presenting an isoindolone unit fused to an 11- to 14-membered carbocyclic or heterocyclic lactone or carbonic diester. A marine strain later identified as *P. marinum* has been reported to produce two series of compounds belonging to such class, penochalasins (Numata *et al.* 1995; Iwamoto *et al.* 2001) and penostatins (A-I) (Takahashi *et al.* 1996; Iwamoto *et al.* 1998), showing cytotoxic properties against P388 lymphocytes. *P. marinum* is also a source of other structurally related extrolites, the chaetoglobosins (indolylcytochalasins) (Numata *et al.* 1995), that are known in *P. expansum* (Frisvad and Filtenborg 1989) and *P. discolor* (Frisvad *et al.* 1997), too. Particularly, chaetoglobosin K (**34**) has been reported for its antitumor activity in rat glial cells and growth inhibitory effects in *ras*-transformed NIH 3T3 fibroblasts through a PI3K-mediated pathway (Numata *et al.* 1995). This effect is quite complex in that the compound suppresses cell growth by inducing overexpression of a gene encoding a large plus-end of a F-actin capping protein called tensin, and has a F-actin capping potential itself; moreover it induces apoptosis by inhibiting the kinase PKB/Akt (Tikoo *et al.* 1999). Growth inhibition was also observed in *ras*-transformed liver epithelial cells (WB-*ras*1), where treatment with chaetoglobosin K reduced the level of phosphorylation of Akt kinase and cytokinesis (Matesic *et al.* 2006).

Sclerotiorines (or sclerotiorins) and isochromophilones are azaphilone compounds isolated from *P. sclerotiorum* (synonym *P. multicolor*) (Curtin and Reilly 1940; Omura *et al.* 1993; Arai *et al.* 1995; Matsuzaki *et al.* 1995; Pairet *et al.* 1995; Yang *et al.* 1996). The former have been also found in *Eupenicillium* spp. (Udagawa 1963), in *T. luteus* (anamorph *P. luteum*) (Fujimoto *et al.* 1990) and in *P. glabrum* (reported under the synonym *P. frequentans*: Chidananda *et al.* 2006). Grb2 is an important adaptor protein in the mitogenic ras signaling pathway of receptor tyrosine kinases, containing one SH2 domain that binds to specific phosphotyrosine residues on receptors or adaptor proteins. SH2 domain antagonists may be developed as new antitumor agents that act by blocking the oncogenic ras signals. Sclerotiorin (**35**) and isochromophilone IV represent the first non-peptidic inhibitor of the SH2 domain from a natural source that significantly inhibits the binding Grb2-SH2 (Nam *et al.* 2000b). The analogue 8-*O*-methylsclerotiorinamine showed the same biological activity (Nam *et al.* 2000a), while antiproliferative properties on B-16 mouse melanoma cells were evidenced for isochromophilones III, V and VI (Arai *et al.* 1995).

Nine azaphilones designated RP-1551-1, -2, -3, -4, -5, -6, -7, -M1, and -M2 have been extracted from the culture broth of an unidentified *Penicillium* strain; RP-1551-7 corresponds to luteusin A, previously characterized from *T. luteus* (Fujimoto *et al.* 1990). The antitumor effect of these compounds depends on the irreversible inhibition of the binding to its α-receptor of the platelet-derived growth factor, which is a potent mitogen molecule for various cell types (Toki *et al.* 1999).

Compound HY558-1 (**36**) is a hydroxyhydrazinoeicosane isolated from liquid cultures of a strain of *P. minioluteum* showing cdk 1 inhibitory properties and antiproliferative effects on several human tumor cell lines, such as HepG2 (hepatoma), HeLa, HT-29, HL-60, and AGS (gastric epithelial cells), while low levels of inhibition were observed on A549 (Lee *et al.* 2002a). In HepG2 and HeLa, cell cycle is arrested at the G_1 and G_2/M phases, and treated cells show DNA fragmentation as an effect of apoptosis induction (Lee *et al.* 2002a; Lim *et al.* 2004). The compound inhibits the phosphorylation of pRb and reduces the expression of cdk 2, cdc2, and cyclin A, while the level of p21 increases. Accordingly, the compound inhibits HeLa cell proliferation through the induction of cell cycle arrest at the G_1 phase by inhibiting pRb phosphorylation in consequence of an upregulation of p21, and at the G_2/M phase by directly inhibiting cdc2 and cyclin A. Apoptotic induction is associated with the cleavage of Bid and release of cytochrome c from mitochondria into the cytosol. The mitochondrial pathway is primarily involved in the apoptotic process as suggested by the activation of caspase-3 and cleavage of poly(ADP-ribose) polymerase (Lim *et al.* 2004).

Rubratoxin B (**37**) was originally described as a metabolite of *P. rubrum* (Townsend *et al.* 1966), and later detected from a culture filtrate of *P. purpurogenum* by Natori *et al.* (1970), who also reported its cytotoxic effect on HeLa cells. Both identifications were later referred to *P. crateriforme* (Frisvad 1989), a species that is now considered as a synonym of *P. rubrum*. However, production of this extrolite by *P. purpurogenum* has been reported again very recently (Wang *et al.* 2007). Preliminary treatment with rubratoxin B of young rats in which Yoshida ascites sarcoma cells had been injected intraperitoneally produced an increase in the survival of the animals developing neoplasia (Fimiani and Richetti 1993). More recent evidence of antitumor properties of the compound has resulted on account of cytotoxicity and inhibitory activities against MMP-2 and -9 documented on HT1080 cells; in addition, it is able to inhibit at the G_2/M phase the cell cycle progression of tsFT210 cells, that is a cdc2 mutant cell line deriving from FM3A particularly sensitive for detecting cdc2 kinase inhibitors (Wang *et al.* 2007).

A similar effect on inhibition of cell cycle progression in tsFT210 cells has been also documented for acetophthalidin (**38**), isolated from an unidentified strain obtained from a marine sediment sample (Cui *et al.* 1996b), as well as for verruculogen and fumitremorgin B (**39**) (Cui *et al.* 1996a), prenylated indole alkaloids with a diketopiperazine structure produced by several *Penicillium* species. The structural analogue fumitremorgin C has been characterized

as a potent and specific chemosensitizing agent able to overcome multidrug resistance in breast cancer (Rabindran *et al.* 2000).

Some structural relationship with tremorgenic extrolites is showed by the shearinines, indole triterpenes isolated for the first time from *E. shearii* (e.g. shearinine A, **40**) (Belofsky *et al.* 1995). Very recently more analogues have been characterized from a marine-derived strain of *P. janthinellum* (Smetanina *et al.* 2007), and from an unidentified endophytic strain related to the latter species (Xu *et al.* 2007). Shearinines A, D, and E are able to induce apoptosis in HL-60 cells; in addition, shearinine E presents cancer preventive properties deriving from the capacity to inhibit malignant transformation of mouse epidermal JB6 P^+ Cl 41 cells (Smetanina *et al.* 2007).

Islandicin and its isomer emodin (**41**) are anthraquinone compounds produced by *P. islandicum* and a number of unrelated species. Emodin is known as a specific inhibitor of protein tyrosine kinase $p56^{lck}$ and protein kinase C (Jayasuriya *et al.* 1992; Fredenhagen *et al.* 1995), whose deregulation is associated with malignant transformation of tumors. These properties introduce a potential therapeutic use of this compound as an anticancer agent that also relies on its inhibitory effect on cell cycle modulation in specific oncogene overexpressed cells. Antiproliferative effects of emodin on hepatoma cell lines (HepG2/C3A, PLC/PRF/5, SK-HEP-1) were consequential to an arrest of the cell cycle at the G_2/M phase followed by apoptosis occurring with significant increase in the levels of p53, p21, Fas and caspase-3 (Shieh *et al.* 2004). On HeLa and other cervix-uteri cell lines (Ca Ski, ME-180 and Bu 25TK) the compound induces inhibition of DNA synthesis, followed by increased nuclear condensation and apoptosis; again the apoptotic pathway is caspase-dependent, as shown by the activation of caspases-3 and -9 and the cleavage of poly(ADP-ribose) polymerase (Srinivas *et al.* 2003). By its quinone structure emodin may also interfere with the electron transport process and alter the cellular redox status, with ensuing cytotoxic properties. Its possible use in combination with standard drugs to reduce toxicity and to enhance efficacy of chemotherapy has been recently proposed (Srinivas *et al.* 2007), also considering its inhibitory effects on metastasis and angiogenesis that have been demonstrated both *in vitro* and *in vivo* (Kwak *et al.* 2006). The antitumor activity of biosynthetic derivatives of emodin and of its structural analogue chrysophanol has also been investigated against L1210 and HL-60 cells (Kawai *et al.* 1984; Darzynkiewicz *et al.* 1989; Koyama *et al.* 1989), also with reference to DNA cleavage mediated by topoisomerase II (Kong *et al.* 1992). Some species producing anthraquinones are also able to synthesize a number of dimers (bis-anthraquinones), such as skyrin, rubroskyrin, luteoskyrin and rugulosin, releasing chrysophanol and/or emodin upon decomposition (Breen *et al.* 1955; Takeda *et al.* 1973; Kawai *et al.* 1984), and also directly exhibiting strong inhibitory effects on the growth of the above-mentioned leukemic cell lines (Kawai *et al.* 1984; Ueno *et al.* 1995). Very recently, some more anthraquinone derivatives, mostly known as intermediate in aflatoxin and sterigmatocystin biosynthesis, have been reported from a marine strain of *P. flavidorsum* (synonym of *P. glabrum*); these compounds, namely nidurufin, averantin, averufin, versicolorin A and B, versiconol, 8-*O*-methylaverufin and 6,8-*O*-dimethylaverufin possess antiproliferative properties against K562 cells, particularly consistent for the first two compounds (Ren *et al.* 2007).

Another anthraquinone compound, MT81 (**42**), has been reported from a strain of *P. nigricans*, a species that is now considered a synonym of *P. janczewskii*. This extrolite determined a remarkable decrease in volume of transplantable murine tumors and viable tumor cell count, more pronounced in sarcoma 180 than in Ehrlich ascites; at the cell level these effects corresponded to a reduction in mitotic activity and apoptotic symptoms, such as the appearance of membrane blebbing and intracytoplasmic vacuoles (Gupta *et al.* 1997).

Topopyrones are anthraquinone compounds (e.g. topopyrone C, **43**) isolated from the culture broth of an unidentified *Penicillium* strain that proved to be cytotoxic to HeLa cells and several murine tumor cell lines, such as B16 (melanoma), Colon 26 (colon adenocarcinoma), 3LL (lung carcinoma), P388 and L1210. Their activity and selectivity as topoisomerase-inhibitors were comparable to those of camptothecin, a well-known antitumor product. Particularly, they inhibit the relaxation of supercoiled pBR322 DNA by human DNA topoisomerase I, while DNA topoisomerase II is not affected (Kanai *et al.* 2000).

The same mechanism of action has been detected for ergosterol peroxide, extracted by a strain of *P. oxalicum*, that also showed selective cytotoxicity against human colon carcinoma cells (COLO 205) (Yang Kuo *et al.* 2005). Other ergosterol derivatives have very recently showed cytotoxic activity: ergosta-8(14),22-diene-3,5,6,7-tetraol from an unidentified strain of marine origin inhibiting HepG (Sun *et al.* 2006), and 5α,8α-epidioxy-23-methyl-(22*E*, 24*R*)-ergosta-6,22-dien-3β-ol from a halophilic strain of *P. chrysogenum* (reported under the synonym *P. notatum*) that was effective against P388 (Xin *et al.* 2007b).

Other extrolites acting as cell cycle and DNA synthesis inhibitors display a specific action on DNA topoisomerase. Actually, a combination of these properties is considered particularly effective to enhance the final therapeutic outcome of antitumor pharmaceuticals (Rudolf and Cervinka 2003). Epolactaene (**44**) is a lactam detected in the culture supernatant of an unidentified *Penicillium* strain (Kakeya *et al.* 1995). The compound is structurally unstable under light, and more thorough studies have been carried out using synthetic derivatives with a modified alkyl side chain. Actually this part of the molecule interacting with cell membranes is quite important for its biological activity, possibly related to a pro-apoptotic effect that has been experimentally observed in BALL-1, Jurkat and U937 myelomonocytic cells (Nakai *et al.* 2002). Moreover, arrest of the cell cycle at the G_0/G_1 phase and promotion of neurite outgrowth were found to be induced in the neuroblastoma cell line SH-SY5Y (Kakeya *et al.* 1997). It has been observed that epolactaene does not intercalate into DNA, but can alter DNA synthesis by inducing selective inhibition of mammalian α and β DNA polymerase and human DNA topoisomerase II, despite the dissimilarity in both structure and properties of these two enzymes; again the inhibitory action is possibly related to the neuritogenic effect (Mizushina *et al.* 2000b). Apart the side chain containing a α-conjugated (*E,E,E*)-triene, the molecular structure of epolactaene is characterized by a highly oxidized γ-lactam possessing electrophilic characteristics in its αβ-unsaturated ketone, epoxide, and hemiaminal carbon, which are potentially reactive with biological nucleophiles, such as the sulphydryl function of cysteine residues (Nagumo *et al.* 2004). In fact, the compound is effective in binding to Hsp60, which is inactivated by alkylation at the Cys^{442} residue and inhibited in its chaperone activity (Nagumo *et al.* 2005).

Nidulalins, a group of dihydroxanthone derivatives comprising nidulalin A (**45**), and compounds F390B and F390C, are produced by two different strains of unidentified *Penicillium* species. They exhibit cytotoxic activity against human (HCT-116, K562) and murine (P388, FM3A/ADR) cell lines (Sato *et al.* 1997). Nidulalin A and F390B inhibited DNA topoisomerase II, while F390C was more effective in inhibiting DNA topoisomerase I (Sato *et al.* 2000).

Another class of extrolites able to interfere in cell cycle progression is represented by inhibitors of prenylation of ras proteins. Mutant *ras* oncogenes are associated with carcinogenesis, and modulation of *ras* function represents a means by which tumor cells with oncogenic mutations can be sensitized to chemotherapy (Waddick and Uckun 1998). Prenylation of ras proteins plays a major role in cell proliferation of both normal and cancerous cells. Normal and oncogenic ras proteins are post-translationally modified by a farnesyl group that promotes membrane binding. Inhibition of farnesyltransferase (FTase), the main enzyme that

catalyzes the prenylation of ras proteins, turns into an arrest of growth of tumor cells. In addition, FTase inhibitors may indirectly help in cancer therapy by suppression of angiogenesis and induction of apoptosis (Ayral-Kaloustian and Salaski 2004).

Some *Penicillium* extrolites, such as andrastins and barceloneic acid A, may act as FTase inhibitors (Overy *et al.* 2005a). Andrastins (A-D) were originally described in an unidentified biverticillate *Penicillium* strain (Omura *et al.* 1996; Uchida *et al.* 1996), and later reported from several terverticillate species, such as *P. roqueforti* (Nielsen *et al.* 2005), *P. paneum* (O'Brien *et al.* 2006) and *P. albocoremium*, also producing barceloneic acid A (Overy *et al.* 2005a). Moreover, andrastin A (**46**) may directly interact with the *trans*-membrane glycoprotein (P170), an ABC-transporter involved in multidrug resistance of neoplastic cells, thus enhancing the chemotherapeutic effects of some antitumor agents (Rho *et al.* 1998). Citreohybridones produced by *E. euglaucum* (reported under the synonym *P. citreoviride*: Kosemura *et al.* 1991; Kosemura 2003) are structurally similar to andrastins and, especially citreohybridone B, also showed FTase inhibitory properties (Omura *et al.* 1996).

Some ras isoforms are also substrates for geranylgeranyltransferase I (GGTase), a related prenyltransferase that can carry on promoting cell proliferation after treatment with selective FTase inhibitors. Therefore a combination of FTase and GGTase inhibitors is required for therapeutic purposes, unless it be possible to use a product with combined properties. This is the case of gliotoxin (**47**), a widespread mycotoxin belonging to the class of the epipolythiodiketopiperazines, structurally characterized by a bridged disulphide ring which determines its antimicrobial and immunotoxic properties (Waring and Beaver 1996). This extrolite is also produced by some *Penicillium* species, such as *P. corylophilum* (Mull *et al.* 1945: original report as *P. obscurum*) and *P. glabrum* (Brian 1946: producing strain originally misidentified as *P. terlikowskii*). Antitumor properties of gliotoxin are known since over fifty years after its antiproliferative activity was observed on mouse lymphosarcoma and mammary carcinoma cells (Mason and Kidd 1951). After having been ascribed to effects on DNA fragmentation (Braithwaite *et al.* 1987), its cytostatic activity was more directly referred to FTase inhibition (van der Pyl *et al.* 1992). More recently antiproliferative effects have been pointed out on six breast cancer cell lines (MCF-7, T47D, BT-474, ZR75-1, MDA MB231 and MDA MB435), with conclusive evidence in favor of prenyltransferase inhibition (Vigushin *et al.* 2004). However, the compound also exhibits potent direct pro-apoptotic properties that have been reviewed by Waring and Beaver (1996). Furthermore, it has been shown that on HL-60 cells gliotoxin increases the phosphotransferase activities of c-Jun N-terminal kinase1 and p38, and inhibits the transcriptional activating protein AP-1 and NFκB (Chung *et al.* 1998). Apoptosis triggered by gliotoxin is associated with the induction of caspase-3-like proteases (Zhou *et al.* 2000), following the activation of the pro-apoptotic Bcl-2 family member Bak that is elicited by the generation of reactive oxygen species and the mitochondrial release of apoptogenic factors (Pardo *et al.* 2006).

ANGIOGENESIS INHIBITORS AND ANTI-METASTATIC COMPOUNDS

Angiogenesis is indispensable for solid tumor development and their metastatic progression (Zetter 1998). Antivascular effect is a recognized property of several known antitumor agents, especially the above-considered microtubule-targeted compounds that have been observed to readily induce a reduction of blood flow within solid tumors based on a mechanism of action yet to be understood (Jordan and Wilson 2004). The antiangiogenic effect of other natural products has been better elucidated. In fact, the formation of new blood vessels is mediated by proteins acting as specific mitogens for endothelial cells, such as bFGF and VEGF. However, interaction of VEGF with tumorigenesis also involves complex molecular mechanisms, such as the activation of oncogenes and the inactivation of tumor suppressor genes (Xie *et al.* 2004). Therefore, inhibition of VEGF production and/or its effects on endothelial cells is considered as a main target in cancer therapy. This mechanism of biological activity characterizes the antitumor properties of asterric acid (**48**) and some derivatives, namely sulochrin, methyl asterric acid, 3-chloroasterric acid and 3,5-dichloroasterric acid, that proved to be able to inhibit VEGF-induced tube formation of human umbilical vein endothelial cells (Lee *et al.* 2002b).

Fumagillin (**49**) is a sesquiterpene produced by some *Penicillium* species belonging to the section *Divaricatum* in the subgenus *Furcatum*. Its antitumor properties have been reported in correlation to the inhibition of endothelial cell proliferation *in vitro* and of tumor-induced angiogenesis *in vivo* (Ingber *et al.* 1990). These effects are consequential to cell cycle arrest and apoptosis resulting after the inhibition of methionine aminopeptidase type 2, an enzyme that removes the N-terminal methionine from most protein involved in cell cycle regulation (Kwon *et al.* 2000). The key reactive sites of the molecule are its spiroepoxide structure and side chain epoxide group (Griffith *et al.* 1998).

In a recent review, diketopiperazines are cited as the most potent inhibitors of plasminogen activator inhibitor-1 (PAI-1), whose increased levels are correlated to angiogenesis and metastatic evolution of cancer, as demonstrated by the resistance to invasion and angiogenesis by implanted malignant cells in PAI-1 knockout mice (Martins and Carvalho 2007). Besides possibly characterizing other above-mentioned compounds belonging to this class, anti-angiogenic activity has been reported by two diketopiperazine dimers biosynthetically related to gliotoxin, 11,11′-dideoxyverticillin A and 11′-deoxyverticillin A. These extrolites have been characterized by an unidentified *Penicillium* strain obtained from the Caribbean green alga *Avrainvillea longicaulis*, and showed potent cytostatic properties against HCT-116 cells (Son *et al.* 1999). Particularly, the first compound possesses an antiproliferative effect on human umbilical vein endothelial cells, based on the blockage of their tube formation and the inhibition of the anti-apoptotic and migration inducing effects of VEGF. Moreover, the compound completely blocks VEGF-induced microvessel sprouting from Matrigel-embedded rat aortic rings and vessel growth in Matrigel plugs in mice, and decreases VEGF secretion by MDA MB-468 cells (Chen *et al.* 2005).

Cancer cells must be able to degrade the extracellular matrix in order to become invasive and induce metastatic spread. Metalloproteinase are a family of zinc-dependent peptidases capable of degrading all kinds of extracellular matrix proteins, and playing a major role in cell proliferation, migration (adhesion/dispersion), differentiation and angiogenesis. MMP-inhibitors may therefore have multiple beneficial effects in cancer chemotherapy.

Berkeleydione (**50**) and berkeleytrione are hybrid polyketide-terpenoid compounds characterized as extrolites of an unidentified *Penicillium* species recovered from the unique environment of the Berkeley Pit Lake in Montana (USA) resulting from a copper mining activity. Both compounds inhibited MMP-3, while berkeleydione also showed a selective activity toward nonsmall cell lung cancer NCI-H460 (Stierle *et al.* 2004). Inhibitory effects on MMP-3 also characterize the spiroketal compound berkelic acid, which has been later recovered from the same strain and showed selective activity toward the ovarian cancer cell line OVCAR-3 (Stierle *et al.* 2006).

An endo-β-D-glucuronidase, heparanase, is capable of specifically degrading heparan sulphate, one of the components of the extracellular matrix, and this activity is associated with the metastatic potential of tumor cells. Heparanase mRNA is overexpressed in many human tumors, such as hepatomas and esophageal carcinomas (Simizu *et al.* 2004). Trachyspic acid (**51**), a polyketide compound iso-

lated from the culture broth of *T. trachyspermus* (anamorph *P. lehmanii*), has been found to be able to inhibit heparanase in B16BL6 murine melanoma (Shiozawa *et al.* 1995).

Another feature that is significantly correlated with metastatic properties of tumor cells is their ability to grow without a firm substrate attachment. To this regard anicequol (**52**), an ergosterol derivative produced by *P. aurantiogriseum*, is able to inhibit the anchorage-independent growth of human colon cancer DLD-1 cells (Igarashi *et al.* 2002).

EXTROLITES WITH OTHER MECHANISMS OF ANTITUMOR ACTIVITY

Cyclopiazonic acid (**53**) is a terpene mycotoxin produced by several terverticillate species. The compound was found to induce a non-univocal and strictly dose-dependent effect on the mouse EL-4 thymoma cells, as their proliferation was slightly increased at 100-1000 ng/mL but markedly depressed at 5-10 µg/mL (Marin *et al.* 1996). Visible signs of cell death by apoptosis induced by this compound have been found in the spleen of experimentally treated broilers, consisting in margination of chromatin against the nuclear membrane and shrinkage of lymphoid cells without any inflammatory reaction of the surrounding tissues (Kamala Venkatesh *et al.* 2005). However, its antitumor properties are more clearly introduced by quite a peculiar biochemical mechanism of action. It is known that cell transformation in tumorigenesis requires the influx of external Ca^{2+}, and in most cases the transformation itself has been found to increase intracytosolic Ca^{2+}; therefore, any interference in this mechanism might reduce tumor progression and represent a consistent target of cancer therapy. Ca^{2+} homeostasis is also related to apoptosis induction in tumor cells; in fact a reduced Ca^{2+} level in the endoplasmic reticulum is observed in early preneoplastic cells that undergo apoptosis compared to a higher level in late preneoplastic cells, which are less susceptible to apoptosis. Cyclopiazonic acid is able to bind to the sarcoendoplasmic reticulum Ca^{2+} ATPase that is actively implied in calcium influx and can therefore interfere in the neoplastic transformation (Rosado *et al.* 2004).

Glucose deprivation occurring in poorly vascularized solid tumors activates the unfolded protein response, that is a stress-signalling pathway in tumor cells associated with the glucose-regulated protein 78 (GRP78), an endoplasmic reticulum chaperone whose induction has been shown to protect against programmed cell death (Reddy *et al.* 2003). Thus, elevated GRP78 levels are correlated with malignancy, and screening for chaperone modulators may represent a novel strategy in anticancer drug development. Verrucosidin (**54**), a pyrone-type nonaketide originally characterized from a strain classified as *Penicillium verrucosum* var. *cyclopium* (Burka *et al.* 1983) that later was considered to have been misidentified (Frisvad *et al.* 2004), is a down-regulator of the *grp78* gene, inhibiting the expression of the GRP78 promoter under glucose-deprived conditions. As assayed on HT-29 cells, the inhibitory action of verrucosidin and induction of selective cell death were found to be strictly dependent on hypoglycemic conditions, as no cytotoxic effect was observed when a sufficient glucose supply was administered in the growth medium (Park *et al.* 2007). The same mechanism of action was also previously reported for the analogue compound deoxyverrucosidin (Choo *et al*. 2005).

Quinolactacins are quinolone antibiotics that were first isolated and characterized from an unidentified entomopathogenic biverticillate *Penicillium* strain (Kakinuma *et al.* 2000), and later reported from *P. citrinum* (Kim *et al.* 2001), *P. bialowiezense* (Frisvad *et al.* 2004), and from an isolate of *P. sizovae* (Samson, pers. comm.), already mentioned above as a producer of a cytostatic oxazine derivative. Evidence of antitumor properties by these compounds derives from the inhibitory activity of quinolactacin A (**55**) against the production of the tumor necrosis factor by murine peritoneal macrophages and the macrophage-like J774.1 cell line (Kakinuma *et al*. 2000).

FUTURE PERSPECTIVES

As many as 76 extrolites, or extrolite families comprising several analogue compounds, produced by species in the genus *Penicillium* have been considered in this review on account of their consistent biological properties that may present useful implications as antineoplastic pharmaceuticals. This number is expected to increase quickly, provided that, besides the likely discovery of novel drugs in the near future, some more known compounds may result to possess effective antitumor properties. In fact, after the recent preliminary evidence provided by the aurantiomides (Xin *et al*. 2007a), this is probably the case of anacin, auranthine, the verrucines, cyclopeptin and other members of the viridicatol family, produced by several terverticillate species (Larsen *et al*. 2000), that belong to the benzodiazepines, a class of natural products comprising known anticancer pharmaceuticals (Beurdeley-Thomas *et al.* 2000). Extrolites representing the janthitrem class, such as paxillin, paspalinine, penitrems, thomitrems and the janthitrems themselves, might also possess some extent of the biological activity exhibited by the related compounds verruculogen and the fumitremorgins. Penisimplicissin, a vermistatin analogue produced by *P. simplicissimum* (Komai *et al.* 2006a), and other funicone-like compounds might show some extent of cytostatic properties. Diketopiperazines also represent a widespread class among *Penicillium* extrolites; besides evidences of cytotoxicity reported for piscarinines A and B from *P. piscarium* (Kozlovsky *et al.* 2000c), several known compounds, such as rugulosuvine and other puberulines, or roquefortine and its analogues, are possible candidates for a more thorough evaluation of their biological activity in this particular field. Citreoisocoumarins produced by species such as *P. nalgiovense*, *P. roqueforti* (Frisvad *et al.* 2004) and *P. corylophilum* (Malmstrøm *et al.* 2000) might also disclose some antitumor effects as reported in duclauxin and other isocoumarin metabolites. So far the curvularins, polyketide macrolides produced by several taxonomically unrelated species such as *P. restrictum* (producing strain originally identified as *P. gilmanii*: Raistrick and Rice 1971), *E. euglaucum* (reported under the synonym *P. citreoviride*: Lai *et al.* 1989) and *P. sumatrense* (Malmstrøm *et al.* 2000), have displayed quite a weak cytotoxicity on human tumor cell lines (Zhan *et al.* 2004) but, as they were previously found to affect mitotic spindle formation in sea urchin embryos (Kobayashi *et al.* 1988), further investigations concerning their microtubule-targeted effects on human cell lines seem to be advisable.

The existence of quite diverse mechanisms of biological activity may also address the search of particular compounds within species-complexes that are known to produce extrolites with the desired properties. Actually a number of studies have been recently published reporting on the oriented search of microbial products, such as heparanase (Ishida *et al*. 2004) or FTase inhibitors (Iwasaki and Omura 2007). To this regard, the availability of standardized screening methods (Smedsgaard 1997; Larsen *et al*. 2005) coupled with assays for a quick detection of a given biological activity are expected to provide for a prolific and ongoing finding of extrolites to be submitted to clinical trials for the development of novel antineoplastic pharmaceuticals.

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