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Review

Aspergillus niger: A Hundred Years of Contribution to the Natural Products Chemistry

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Aspergillus niger is a phytopathogenic fungus responsible for the plant disease called "black mold", and it is considered the most versatile microorganism for producing acids, proteins, and enzymes of industrial value, besides a variety of compounds of pharmacological interest. This review presents a century of contribution of *A. niger* in the natural products chemistry under two different perspectives: (*i*) an overview of the structural diversity of secondary metabolites produced by *A. niger* from different habitats and their biological activities; (*ii*) a general discussion of the enzymatic potential of *A. niger* on the selective biotransformation of terpenes, highlighting the most uncommon microbial transformations.

Keywords: *Aspergillus niger*, secondary metabolites, biological activities, biotransformation, terpenes

1. Introduction

Aspergillus niger is a member of a group of species named *Aspergillus* section Nigri, formerly known as *A. niger* group.[1] This fungus causes the "black mold" disease and it is the most common contaminant of stored food, being responsible for postharvest decay of fresh fruits, grains, and crops worldwide.[2]

The productive metabolism of *A. niger* acquired a great economic importance when James Currie[3] (1917) published a study describing the ability of the fungus to biosynthesize high amounts of citric acid by culturing it in sugar solutions at low pH. This remarkable discovery showed the direct influence of the ambient and nutritional factors in the yield of the citric acid production and was the basis for the birth of the biotechnology industry in 1919 by Pfizer.[4]

The biotechnological revolution after Currie's discovery constituted the major focus of the investigation of *A. niger*, that rapidly grew in the next 40 years. The initial studies were predominantly related to the biochemical mechanism of accumulation of citric acid, the impact of micro and macronutrients in the cultivation media and the optimization of the growth parameters. These investigations generated an efficient high yielding bioprocess, and actually, citric acid is one of the most valuable commercial chemical products due to its widespread use in food, cosmetics, and pharmaceutical formulations.[4-8]

The modernization of the analytical techniques in the following decades also revealed this microorganism to be a prolific secretor of a diverse range of useful proteins. A large number of unique proteins involved in certain mechanisms do not occur in other filamentous fungi, proving that this species is quite versatile at the level of cellular production.[9] These discoveries significantly contributed to the fundamental understanding of enzyme function and to the production of numerous extracellular enzymes, such as α-amylase, oxidase, catalase, dehydrogenase, hydrolase, cellulase, pectinase, among others.[10-15]

The advent of molecular biology and the development of the transcriptomic and metabolomic techniques revealed scores of hitherto unknown information and allowed the elucidation of the full genome sequence of some *A. niger* strains.[9,10,16,17] These events opened a new perspective for both chemical studies and biotechnological applications and facilitated a great insight into the secondary metabolites genes for the understanding of the growth, differentiation, physiology, and mainly the biosynthesis of natural products.

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Therefore, all these scientific achievements over a century of the investigation resulted in a range of new processes and compounds and contributed to the great interest about the chemical versatility and the pharmacological potential of secondary metabolites from *A. niger*. Investigations focused on the screening of bioactive compounds using strains from different habitats, modifications on the fermentation routes,[8] genome editing,[18,19] epigenetic modulation,[20,21] and microbial biotransformation,[22-24] and revealed *A. niger* as a powerful tool for the production of diverse and structurally complex compounds endowed with an ingenious structure for the experimental drug research area.

In order to celebrate the centenary contribution of *A. niger* to the natural products chemistry, in this review we present an overview of the origin of the chemically investigated strains and the structural diversity of secondary metabolites produced so far by this fungus, besides the biological activities of the evaluated compounds in the literature. Additionally, the potential of *A. niger* on the selective biotransformation of terpenes is summarized, and examples of the most uncommon microbial transformations are highlighted.

2. Characteristics and Occurrence of *A. niger*

Species from *Aspergillus* genus section Nigri present a thin stalk with a round black conidial head made up of spores of a characteristic shape, which bud from the organism's body as part of asexual reproduction. Its name is derived from this appearance since it resembles the holy water sprinkler called aspergillum, used by priests during the Asperges ceremony.[25]

A. niger is considered a cosmopolitan asexual saprophyte, occurring in almost all aerobic environments. It is thermotolerant, being able to thrive in freezing conditions and very hot weather, and to multiply within a temperature range of between 6 and 47 °C. The optimal pH for this fungus growing is 6, although it tolerates wide pH range (from 1.5 to 9.8). In addition, the most favorable water activity and relative humidity to observe the growth of this species is 0.97 and 96-98%, respectively.[26] The black spores of *A. niger* apparently provide protection from sunlight and UV irradiation, leading to a competitive advantage over other microorganisms in their habitats. These abilities besides the profuse production of conidiospores spread through air, ensure its more frequent occurrence in warm and humid habitats.[27]

According to our literature survey, the chemical investigations of *A. niger* for secondary metabolites production were accomplished with strains from different sources/habitats and the percentage distribution is shown at Figure 1.

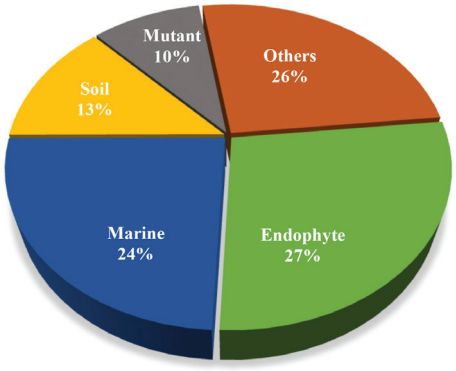


Figure 1. Percentage distribution of sources/habitats reported to *A. niger* strains investigated for secondary metabolites production.

Endophyte strains of *A. niger* were the most predominant sources used in chemical studies, which was closely followed by strains associated to marine habitats and others. This latter comprises those strains coming from either fungi collections or without information of their source/habitat. Additionally, it was possible to note a significant contribution of chemical investigations of strains derived from genetic mutation. It is important to mention that some compounds were produced by strains from different sources/habitats, suggesting that environmental conditions had no influence on this fungus metabolism.

3. Secondary Metabolites from *A. niger* Strains

The literature survey (from 1917 to 2018) revealed 213 secondary metabolites produced by *A. niger* strains from different sources and corroborated this fungus species as a proficuous source of natural products. Herein, these compounds were classified into 13 different groups based on their structural characteristics (sections 3.1 to 3.12), whose presentation order follows their natural abundance. Additionally, a miscellaneous group (section 3.13) was included which display those minor or structurally unique compounds. Although all chemical structures and their sources were present in all groups, only some representatives and/or bioactive compounds were discussed.

Structures of compounds were displayed in Figures 2-14 where their numbering system was based on that described in the literature. All compounds' names were listed in alphabetical order in Tables 1-13.

3.1. Naphto-γ-pyrones

Naphtho-γ-pyrones (NGPs) are an important group of

aromatic polyketides that have been isolated of *A. niger* from a wide variety of habitats (**1**-**40**, Figure 2, Table 1) and, among these compounds, bis-naphtho-γ-pyrones (BNPs) represent the major secondary metabolites produced by *Aspergillus* species.[28-45] Based on the diaryl bond connection, BNPs are commonly found in this genus as asperpyrone- and nigerone-types being, therefore, taxonomically significant.

The asperpyrone-type BNPs have large natural abundance in *A. niger* and display C-10-C-7', C-10-C-9', C-6-C-7' or C-6-C-9' linkages between the monomeric unities. According to these linkage patterns, they are named as aurasperones, isoaurasperones, asperpyrones, fonsecinones, and nigerasperones.[45] Aurasperonas A-H (**6**-**13**, Figure 2) are 10,7'-bisnaphtho-γ-pyrones that have been isolated from different strains and habitats,

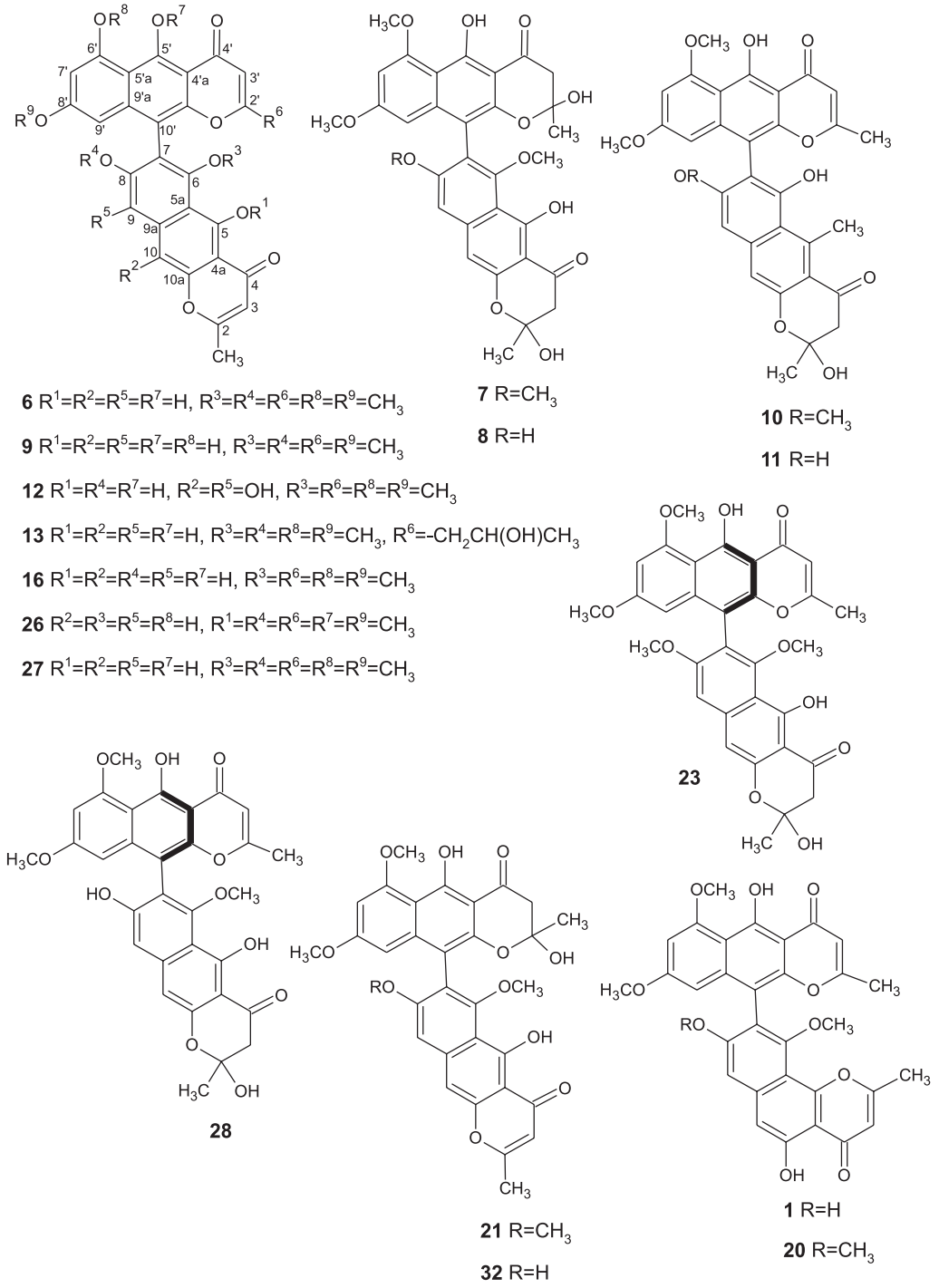


Figure 2. Chemical structures of naphyto-γ-pyrones (**1**-**40**) produced by *A. niger* strains.

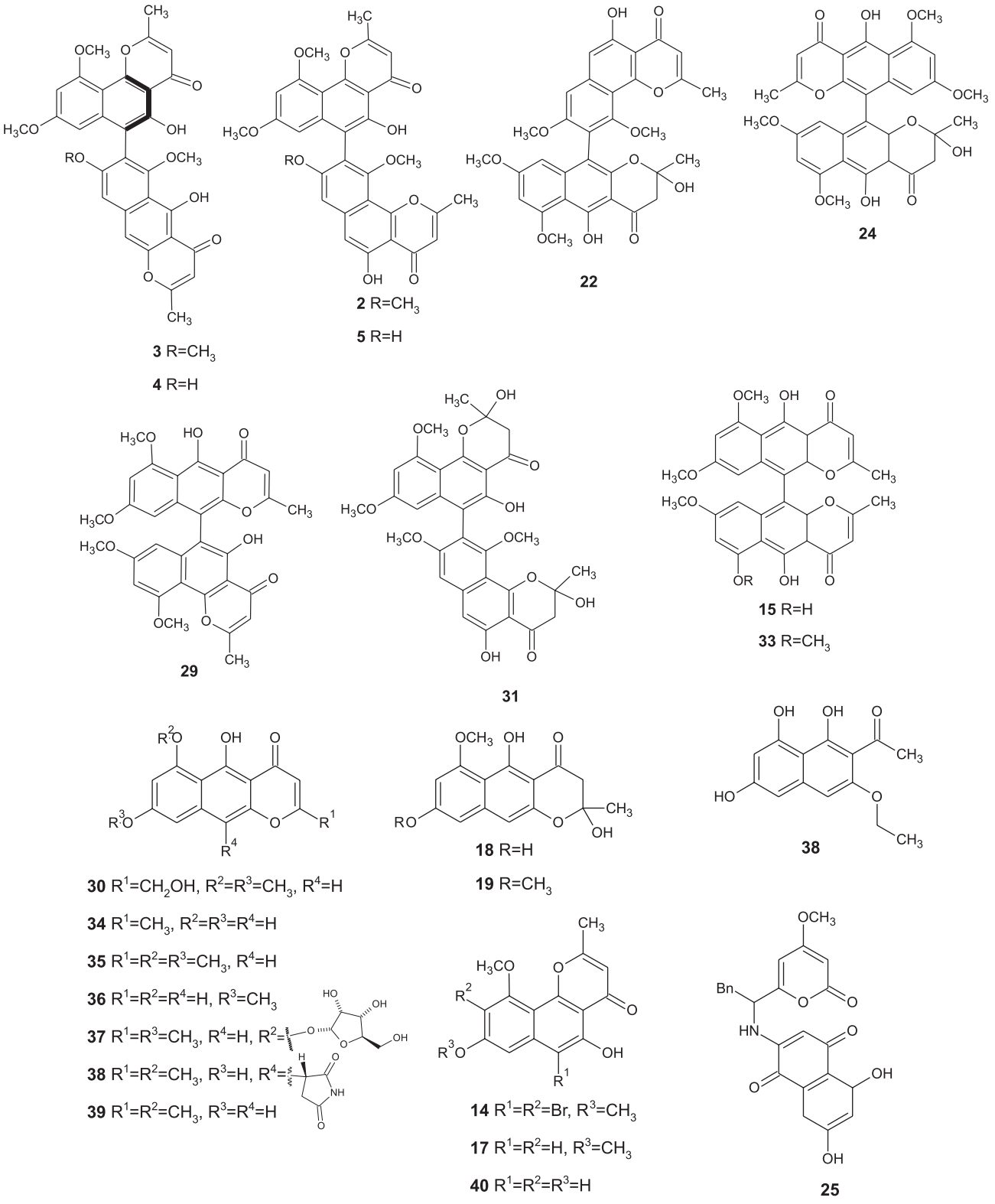


Figure 2. Chemical structures of naphyto-γ-pyrones (**1**-**40**) produced by *A. niger* strains (cont.).

and some of them have been shown relevant biological activity. Aurasperone A (**6**), produced by an endophyte strain from *Cynodon dactylon*, showed strong inhibitory action on xanthine oxidase (XO), antimicrobial activity against *Candida albicans* and *Trichophyton rubrum*, similar to the positive reference ketoconazole.[32] This compound, biosynthesized by a strain recovered from Japanese soil, also acted on Taq DNA polymerase.[28]

Table 1. Naphtho-γ-pyrones (NPGs, **1**-**40**) produced by *A. niger* strains

Compound	Strain	Source	Reference
Asperpyrone A (**1**)	JV 33-48	soil	28
	SCSIO Jcsw6F30	marine	29
	nr	endophyte	30
	EN 13	marine	31
Asperpyrone B (**2**)	IFBE 003	endophyte	32
	JV 33-48	soil	28
	2HL M-8	marine	33
Asperpyrone C (**3**)	JV 33-48	soil	28
	2HL M-8	marine	33
	EN 13	marine	31
Asperpyrone D (**4**)	SCSIO Jcsw6F30	marine	29
	nr	endophyte	30
Asperpyrone E (**5**)	SCSIO Jcsw6F30	marine	29
Aurasperone A (**6**)	IFBE 003	endophyte	32
	JV 33-48	soil	28
	CMI-IMI 205879	endophyte	34
	SCSIO Jcsw6F30	marine	29
	EN 13	marine	31
Aurasperone B (**7**)	MSA 773	marine	35
	SCSIO Jcsw6F30	marine	29
	EN 13	marine	31
	C 433	endophyte	36
	BL-5-1	nr	37
Aurasperone C (**8**)	SCSIO Jcsw6F30	marine	29
	C 433	endophyte	36
	BL-5-1	nr	37
Aurasperone D (**9**)	CMI-IMI 205879	endophyte	34
	nr	endophyte	30
	C 433	endophyte	36
Aurasperone E (**10**)	CMI-IMI 205879	endophyte	34
	C 433	endophyte	36
Aurasperone F (**11**)	SCSIO Jcsw6F30	marine	29
	C 433	endophyte	36,38
Aurasperone G (**12**)	C 433	endophyte	38
Aurasperone H (**13**)	2HL M-8	marine	33
6,9-Dibromoflavasperone (**14**)	MSA 773	marine	35
6'-*O*-Demethylnigerone (**15**)	MRC 278	endophyte	39
Dianhydroaurasperone C (**16**)	nr	endophyte	30
	EN 13	marine	31
Flavasperone (**17**)	MSA 773	marine	35
	CMI-IMI 205879	endophyte	34
	TC 1629	soil	40
Fonsecin (**18**)	MSA 773	marine	35
	TC 1629	soil	40
	C 433	endophyte	36
	SCSIO Jcsw6F30	marine	41
	IBT 29019	endophyte	42
Fonsecin B (**19**)	TC 1629	soil	40
Fonsecinone A (**20**)	IFBE 003	endophyte	32
	JV 33-48	soil	28
	SCSIO Jcsw6F30	marine	29
	2HL M-8	marine	33
	EN 13	marine	31
Fonsecinone B (**21**)	SCSIO Jcsw6F30	marine	29
	2HL M-8	marine	33
	EN 13	marine	31
Fonsecinone C (**22**)	SCSIO Jcsw6F30	marine	29
	2HL M-8	marine	33
	EN 13	marine	31
	SCSIO Jcsw6F30	marine	41
Fonsecinone D (**23**)	SCSIO Jcsw6F30	marine	29
	2HL M-8	marine	33
	EN 13	marine	31
	SCSIO Jcsw6F30	marine	41
2-Hydroxydihydronigerone (**24**)	AKRN	endophyte	43
5,7-Dihydroxy-2-[1-(4-methoxy-6-oxo-6*H*-pyran-2-yl)-2-phenyl-ethylamino]-[1,4]naphthoquinone (**25**)	EN 13	marine	44
Isoaurasperone (**26**)	CMI-IMI 205879	endophyte	34
Isoaurasperone A (**27**)	2HL M-8	marine	33
	nr	endophyte	30
Isoaurasperone F (**28**)	nr	endophyte	30
Isonigerone (**29**)	MRC 278	endophyte	39
Nigerasperone A (**30**) Nigerasperone B (**31**) Nigerasperone C (**32**)	EN 13	marine	31
Nigerone (**33**)	AKRN	endophyte	43
	MRC 278	endophyte	39
Rubrofusarin (**34**)	CMI IMI 205879	endophyte	34
	SCSIO Jcsw6F30	marine	41
Rubrofusarin B (**35**)	IFBE 003	endophyte	32
	TC 1629	soil	40
	SCSIO Jcsw6F30	marine	41
nor-Rubrofusarin (**36**)	BL 5-1	nr	37
Rubrofusarin-6-*O*-α-D-ribofuranoside (**37**)	nr	endophyte	30
(*R*)-10-(3-Succinimidyl)-TMC-256A1 (**38**)	nr	endophyte	30
TMC-256A1 (**39**)	MSA 773	marine	35
	TC 1629	soil	40
TMC-256C1 (**40**)	TC 1629	soil	40

nr: not reported.

Potent radical scavenging activity of aurasperone B (**7**), isolated of a marine-mudflat-derived strain, was reported,[35] while its analogue aurasperone D (**9**), produced by a strain isolated from infected mango fruit, showed marked central nervous system depressant effects in albino mice and rats.[34] Aurasperones C and F (**8** and **11**, respectively), both metabolized by a marine strain isolated from the alga *Sargassum* sp., exhibited COX-2 inhibitory activities. Notwithstanding, only compound **11** presented the best inhibitory rates of cytotoxicity when tested against cervical cancer HeLa, breast cancer MCF-7, acute lymphoblastic leukemia Molt-4, hepatocellular carcinoma Huh-7, and lung cancer H1975 cell lines.[29] Aurasperone H (**13**), obtained from a marine-derived strain, exhibited moderated

inhibitory activity against the lung adenocarcinoma A549 and leukemia HL-60 human cell lines.[33]

The chemical study of *A. niger* strain recovered from soil samples collected in Sakai, Japan, yielded asperpyrone A (**1**) and fonsecinone A (**20**), which showed inhibitory activity on Taq DNA polymerase.[28] Additionally, compound **1**, obtained from a marine strain isolated from alga (*Sargassum* sp.), also exhibited COX-2–inhibitory activity.[29] Fonsecinone A (**20**), produced by an endophyte strain associated to *Cynodon dactylon*, exhibited growth inhibition against the bacteria *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas fluorescence*, besides the fungi *T. rubrum* and *C. albicans*.[32] 2-Hydroxydihydronigerone (**24**) was isolated from a strain endophyte associated to *Entandrophragma congoense* and showed weak antimicrobial activity against *Enterobacter aerogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae* and *E. coli*.[43]

The nigerone-type BNPs, which display C-10-C-10' linkage, have more restricted occurrence in *A. niger*. Nigerone (**33**) was produced by a strain isolated from the inner tissues of *Entandrophragma congoense* and showed weak antimicrobial activity on *Enterobacter aerogenes*, *E. cloacae*, *Klebsiella pneumoniae*, and *E. coli*.[43] It is noteworthy that derivatives 6'-*O*-demethylnigerone (**15**) and isonigerone (**29**) were so far biosynthesized only by *A. niger* MRC-278 isolated from infected Mozambican ground nuts.[39]

Monomeric naphtho-γ-pyrones, such as rubrofusarin B (**35**), fonsecin (**18**), fonsecin B (**19**) and flavasperone (**17**), were considered intermediates in the biosynthesis of bis-naphtho-γ-pyrones (BNPs).[45] These compounds, together with TMC-256 A1 (**39**) and C1 (**40**), produced by a soil strain collected in Japan, showed suppression of the production of IgE via inhibition of IL-4 signal transduction and were considered useful models to the treatment of allergic disease.[40] Rubrofusarin B (**35**), obtained from an endophytic fungus strain isolated from *Cynodon dactylon*, also displayed significant inhibitions on XO with IC_{50} (half maximal inhibitory concentration) values comparable to that of the positive control allopurinol. In addition, this compound showed significant cytotoxicity against colon cancer cell line SW1116 and growth inhibition against the pathogens *C. albicans* and *T. rubrum*.[32] Strong radical scavenging activities were reported for 6,9-dibromoflavasperone (**14**), flavasperone (**17**), fonsecin (**18**) and TMC-256 A1 (**39**), isolated from a strain of a marine-mudflat-derived, being more potent than the positive control, acid ascorbic.[35]

3.2. α-Pyrones

α-Pyrones is a class of six-membered unsaturated lactones naturally existing in *A. niger* as vital biosynthetic intermediates of coumarin ring system (**41**-**60**, Figure 3, Table 2).[46-52] An endophytic strain of the fungus associated to the marine mangrove plant *Avicennia marina* was source of eight α-pyrone derivatives named nigerapyrones A-H (**51**-**58**), along with the two analogues asnipyrones A (**41**) and B (**42**).[46] Asnipyrone A (**41**) showed activity against human lung carcinoma cell line A549, while nigerapyrone B (**52**) displayed selective cytotoxicity activity against human liver cancer HepG2 cell line. Nigerapyrone D (**54**) showed moderated or weak activity when tested against breast cancer MCF-7, human liver cancer HepG2 and human lung carcinoma A549 cell lines. Nigerapyrone E (**55**) showed strong cytotoxicity against human pancreatic adenocarcinoma cell line SW1990, breast cancer cell line MDA-MB-231 and human lung carcinoma cell lines A549 but weak or moderate activity against breast cancer MCF-7, human liver cancer HepG2, human prostate cancer Du145 and human lung cancer NCI-H460 cell lines.[46]

Table 2. α-Pyrones (**41**-**60**) produced by *A. niger* strains

Compound	Strain	Source	Reference
Asnipyrone A (**41**) Asnipyrone B (**42**)	MA 132	marine	46
Aspergillusol (**43**)	EN 13	marine	47
Campyrone A (**44**)	nr	endophyte	48
	CAFT 160	endophyte	49
Campyrone B (**45**)	CAFT 160	endophyte	49
	nr	endophyte	48
Campyrone C (**46**)	CAFT 160	endophyte	49
	nr	endophyte	48
4-(Hydroxymethyl)-5-hydroxy-2*H*-pyran-2-one (**47**)	AKRN	endophyte	43
4-(Hydroxymethyl)-5,6-dihydro-pyran-2-one (**48**)	nr	endophyte	48
Isopyrophen (**49**)	EN 13	marine	47
Nafuredin (**50**)	FT 0054	marine	50
Nigerapyrone A (**51**) Nigerapyrone B (**52**) Nigerapyrone C (**53**) Nigerapyrone D (**54**) Nigerapyrone E (**55**) Nigerapyrone F (**56**) Nigerapyrone G (**57**) Nigerapyrone H (**58**)	MA 132	marine	46
Pyrophen (**59**)	AKRN	endophyte	43
	UCSC 4-1212	marine	51
	ATCC 36533	nr	52
	EN 13	marine	47
Walterolactone (**60**)	nr	endophyte	48

nr: not reported.

Campyrones A-C (**44**-**46**) were isolated from an endophyte strain occurring in *Zanthoxylum lemairei* leaves and exhibited weak toxicity on brine shrimp larvae.[49] In addition, nafuredin (**50**), obtained from a marine strain

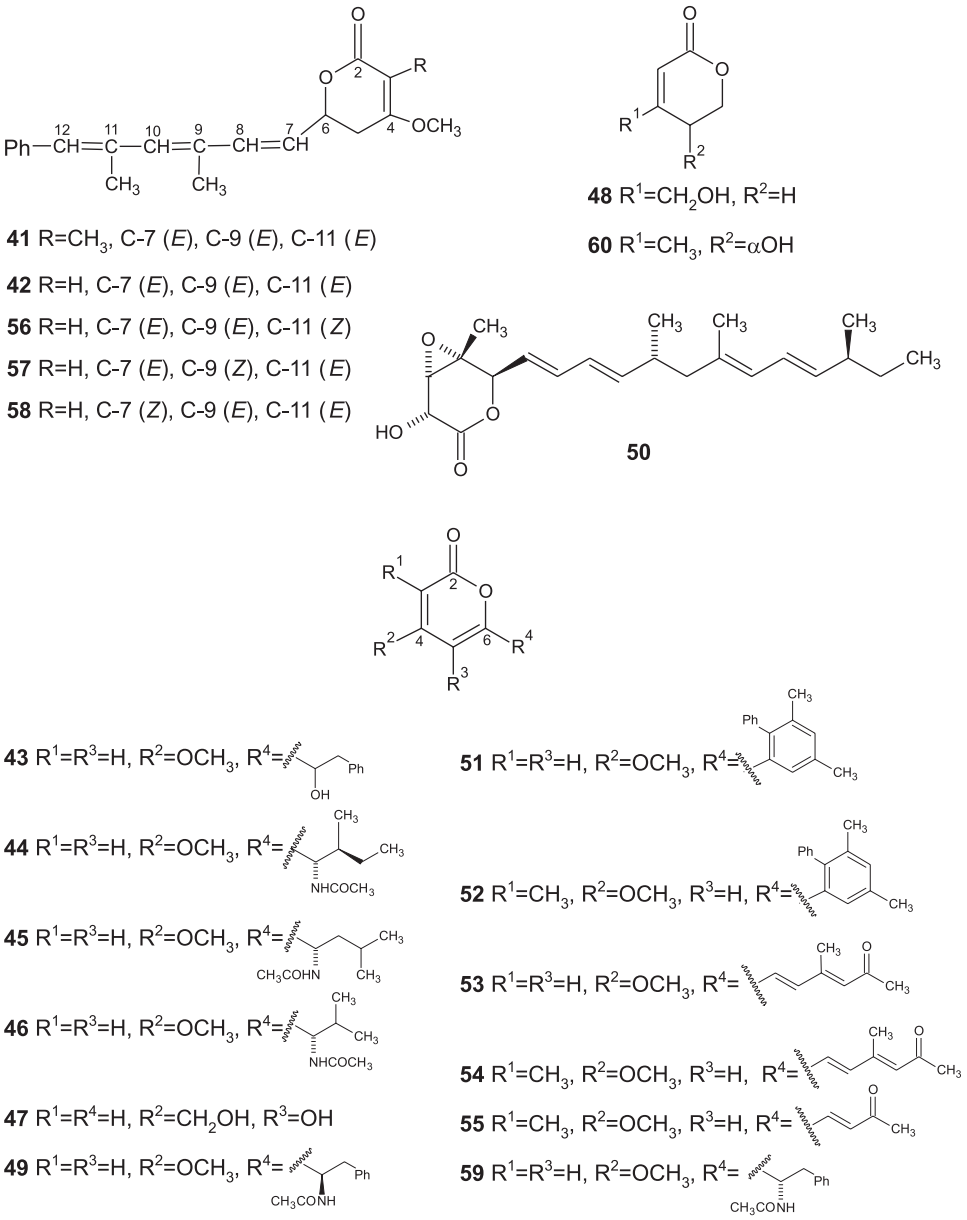


Figure 3. Chemical structures of α-pyrones (**41**-**60**) produced by *A. niger* strains.

of the fungus associated to a sponge collected in Palau Islands, exhibited inhibitory activity against *Ascaris suum* nicotinamide adenine dinucleotide plus hydrogen (NADH)-fumarate reductase, revealing this compound as a potentially selective antiparasitic agent.[50] It is worth mentioning that pyrophen (**59**) was the first α-pyrone amino acid derivative isolated from fungi.[52]

3.3. Yanuthones

Yanuthones (**61**-**79**, Figure 4, Table 3) are compounds containing core structure constituted of an epoxylated six-membered ring with a sesquiterpene chain at C-13 and varied side chains at C-15 and C-16. The core structure may be derived from different precursors, which lead to the formation of two classes of yanuthones (I and II). In *A. niger*, yanuthones from class I are derived from the polyketide 6-methylsalicylic acid (6-MSA), that delivers a C7 scaffold containing a six-membered methylated ring at C-16. Class II yanuthones contain a C6-core scaffold oxygenated at C-16 derived from an unknown precursor.[53-55]

22-Deacetylyanuthone A (**62**), 1-hydroxyyanuthone A (**63**), 1-hydroxyyanuthone C (**64**) and yanuthones A-E (**65**-**69**) were biosynthesized by a marine fungal strain associated to the ascidia *Aplidium* sp. All compounds were tested against *Staphylococcus aureus*, *E. coli*, *Enterococcus* and *C. albicans*, and the most active compounds (**68** and **69**)

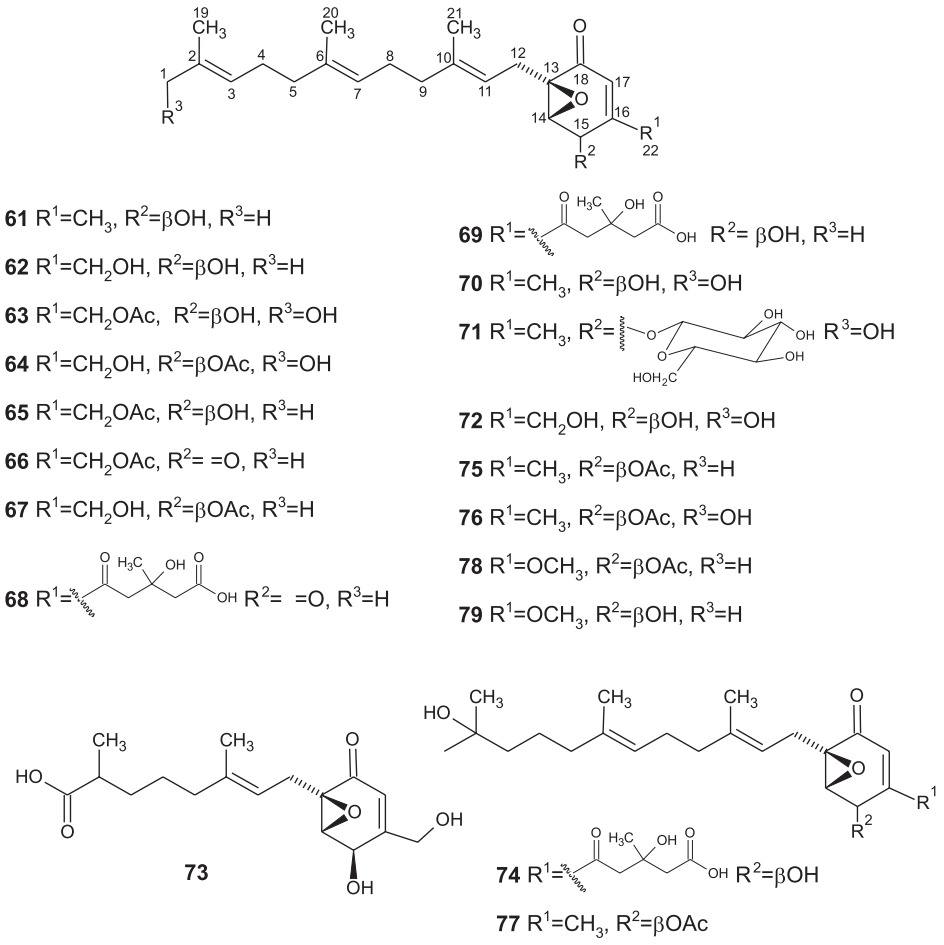


Figure 4. Chemical structures of yanuthones (**61-79**) produced by *A. niger* strains.

Table 3. Yanuthones (**61**-**79**) produced by *A. niger* strains

Compound	Strain	Source	Reference
7-Deacetoxyyanutone A (**61**)	BR 1001	mutant strain	53
22-Deacetylyanuthone A (**62**)			
1-Hydroxyyanuthone A (**63**)			
1-Hydroxyyanuthone C (**64**)			
Yanuthone A (**65**)	F 97S11	marine	54
Yanuthone B (**66**)			
Yanuthone C (**67**)			
Yanuthone D (**68**)			
Yanuthone E (**69**)			
Yanuthone F (**70**)			
Yanuthone G (**71**)			
Yanuthone H (**72**)	BR 1001	mutant strain	53
Yanuthone I (**73**)			
Yanuthone J (**74**)			
Yanuthone K (**75**)			
Yanuthone L (**76**)	KB 1001	mutant strain	55
Yanuthone M (**77**)			
Yanuthone X1 (**78**)	BR 1001	mutant strain	53
Yanuthone X2 (**79**)	KB 1001	mutant strain	55

were those containing a hydroxymethyl glutarate (HMG) at position 22.[54] The genetic and biosynthetic pathway of yanuthone D (**68**) from *A. niger* was deduced and revealed yanuthones F-J (**70**-**74**) besides the first component of class II, named yanuthone X1 (**78**).[53] Yanuthones K-M (**75**-**77**) and class II yanuthone X2 (**79**) were produced by *A. niger* KB 1001 (recipient mutant strain) and considered antimicrobials when tested toward *C. albicans*. In this case, the structure-activity relationship was investigated and revealed that functionalization at C-15 has significant impact in the antimicrobial activity. *O*-Glycosylation and *O*-acetylation at this carbon increased the antifungal activity when compared with analogues displaying OH groups.[55]

3.4. Cyclopeptides

The cyclopeptides (**80**-**92**) produced by *A. niger* strains are presented in Figure 5 and Table 4, where malformins are the major constituents.[30,56-68] They are a group of cyclic pentapeptides containing a disulfide bond from two cysteine thiols, that typically induces malformations in bean plants

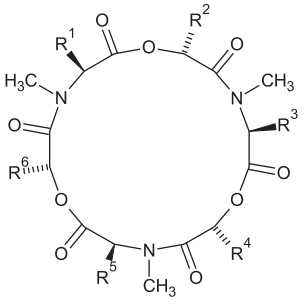
and in the curvature of corn roots.[56] These compounds were originally isolated from fluid culture of *A. niger* and classified into three sub-groups: malformins A (from *A. niger* strain 56-39), malformins B (from *A. niger* strain 56-30) and malformins C (from *A. niger* strain AN-1).[65]

Malformin A sub-group consists mainly of malformins MA1-MA4 (**82**-**85**), from which MA1 (**82**), containing five amino acids (L-isoleucine, L-valine, D-leucine, and two D-cysteines), is the most abundant and well-studied representative. Although originally reported from *A. niger* strain 56-39,[59] malformin **82** was also produced by various strains of the fungus from different sources and many biological activities were reported for this compound. MA1 (**82**) exhibited strong cytotoxic effects against various human cancer cell lines related to the inhibiting cell proliferation, inducing apoptosis, arresting the cell cycle and inhibiting cell migration and invasion.[67] This significant cytotoxic activity was detected for **82**, produced by an endophyte strain associated to the Chinese liverwort *Heteroscyphus tener*, against the human ovarian carcinoma cell line A2780, lung cancer cell line H1688, a human erythroleukemic cell line K562, human breast carcinoma

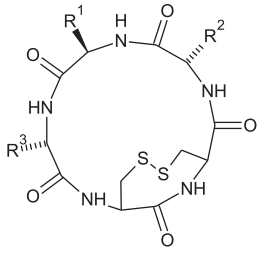
Table 4. Cyclopeptides (**80**-**92**) produced by *A. niger* strains

Compound	Strain	Source	Reference
Beauvericin (**80**)	DS 3.1	mutant strain	56
Enniantin B (**81**)			
Malformin A1 (**82**)	nr	endophyte	30
	BRF 074	marine	57
	nr	air	58
	56-39	soil	59
	F 7586	nr	60
Malformin A2 (**83**)	56-39	soil	61
Malformin A3 (**84**)			
Malformin A4 (**85**)			
Malformin B1a (**86**)	56-30	soil	62
Malformin B1b (**87**)			
Malformin B2 (**88**)			
Malformin B3 (**89**)			
Malformin B4 (**90**)			
Malformin B5 (**91**)			
Malformin C (**92**)	SCSIO Jcsw6F30	marine	41
	UCSC94-1212	marine	51
	FKI 2342	soil	63
	nr	endophyte	64
	AN-1	endophyte	65
	nr	endophyte	66

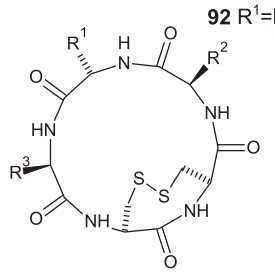
nr: not reported.



80 R^1=R^3=R^5=Bn, R^2=R^4=R^6=$CH(CH_3)_2$
81 R^1=R^2=R^3=R^4=R^5=R^6=$CH(CH_3)_2$



82 R^1=$CH_2CH(CH_3)_2$, R^2=$CH(CH_3)_2$,
R^3=$CH(CH_3)CH_2CH_3$, βS-S
83 R^1=$CH_2CH(CH_3)_2$, R^2=R^3=$CH(CH_3)_2$, βS-S
84 R^1=R^3=$CH_2CH(CH_3)_2$, R^2=$CH(CH_3)_2$, βS-S
85 R^1=$CH(CH_3)CH_2CH_3$, R^2=R^3=$CH(CH_3)_2$, βS-S
92 R^1=R^3=$CH_2CH(CH_3)_2$, R^2=$CH(CH_3)_2$, αS-S



86 R^1=$CH_2CH(CH_3)_2$, R^2=R^3=$CH(CH_3)_2$
87 R^1=R^3=$CH_2CH(CH_3)_2$, R^2=$CH(CH_3)_2$
88 R^1=R^2=$CH(CH_3)_2$, R^3=$CH_2CH(CH_3)_2$
89 R^1=$CH(CH_3)CH_2CH_3$, R^2=$CH(CH_3)_2$, R^3=$CH_2CH(CH_3)_2$
90 R^1=R^3=$CH(CH_3)CH_2CH_3$, R^2=$CH(CH_3)_2$
91 R^1=R^2=$CH(CH_3)_2$, R^3=$CH(CH_3)CH_2CH_3$

Figure 5. Chemical structures of cyclopeptides (**80**-**92**) produced by *A. niger* strains.

cell line M231 and prostate cancer PC3 cell line *in vitro*.[30] Additionally, the same compound biosynthesized by a marine strain recovered from sediments of the Northeast Brazilian coast was cytotoxic against human colon cancer cell line HCT-116.[57] The antibacterial effects of MA1 (**82**) isolated from soil strain on *E. coli*, *S. aureus* and *Proteus mirabilis*,[68] besides the mammalian toxicity of the same compound produced by a strain isolated from the air in Kochi-Indian were also reported.[58] In both studies, the authors concluded that the disulfide group plays an important role in auxin metabolism due to interactions with essential thiol compounds. In addition, malformin **82** also showed potent physiological effect by inducing root curvatures in corn and stimulating growth in mung bean hypocotyls through the modulation of the ethylene production.[59] More recently, MA1 from a soil strain collected in Okinawa, Japan, enhanced the fibrinolytic bioactivity, affecting the cell-mediated response to initiate and/or propagate the activity, and its effect appeared to be unique among the known active agents.[60]

Among malformins B isolated from *A. niger* strain 56-30, malformin B1a (**86**) showed optimum curvature activity in the corn root test, while analogues B1b (**87**) and B2 (**88**) presented lower activities.[62] Malformin C (**92**), produced by a marine strain associated to the alga *Sargassum* sp., exhibited potent HIV-1 inhibitory activity and was considered a promising anti-HIV lead drug.[41] The same compound biosynthesized by a strain recovered from soil collected at Nagasaki, Japan, was effective against bleomycin-induced G2 arrest in adenocarcinoma HCT-116 cell line.[63] Moreover, malformin **92**, produced by *A. niger* strain isolated from mold-damaged rice in Thailand, presented antibacterial activity against *B. subtilis*, *B. megaterium*, *S. aureus*, *Streptococcus faecalis*, *Proteus mirabilis* and *Sarcina lutea*,[64] and induced grown abnormalities similar to MA1 (**82**).[65]

3.5. Pyranonigrins

Pyranonigrins are compounds with a unique pyrano[3,2-*b*]pyrrole bicyclic skeleton (**93**-**105**, Figure 6, Table 5) that are restricted to *A. niger* strains.[69-72] Pyranonigrins A-D (**93**-**96**) were biosynthesized by the fungus associated to the Mediterranean sponge *Axinella damicornis*.[70] These compounds, besides pyranonigrin S (**105**), were also produced by *A. niger* LL-LV3020 grown on solid culture.[72] Gene knockout and transcriptional activation of the pyranonigrin biosynthetic gene cluster in *A. niger* ATCC 1015, besides *in vitro* and *in vivo* assays, allowed the isolation of pyranonigrin E1 (**97**) and F-K (**99**-**104**), and contributed to the understanding of pyranonigrin biosynthetic pathway.[71] Pyranonigrin A (**93**), E2 (**98**) and S (**105**), exhibited a high level of 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radical scavenging activity.[72]

3.6. Diketopiperazines

Diketopiperazines (DKPs) are the smallest constrained cyclic peptide consisting of heterocyclic molecules with the double lactam core structure formed by cyclization of two alpha-amino acids. The cyclization leads to the formation of three regioisomers, 2,3-DKP, 2,5-DKP, and 2,6-DKP, based on the relative position of the carbonyl groups. 2,5-DKPs are the best-known group in the field of chemistry and are the only DKP-type found in *A. niger* (**106**-**117**, Figure 7, Table 6).[47,48,51,57,73] Asperazine (**106**), the first diketopiperazine heterodimer, was isolated from a marine strain associated to a Caribbean *Hyrtios* sponge. This compound displayed an unusual profile of cytotoxicity by significant selective activity against human leukemia murine colon 38 and human colon H116 or CX1 cell lines.[73] In addition, **106**, asperazine A (**107**), cyclo(D-Phe-L-Trp) (**108**) and cyclo(L-Trp-L-Trp) (**114**) were produced by the endophytic fungus from *Heteroscyphus tener*. Among these compounds, asperazines **106** and **107** showed weak cytotoxicity against ovarian cancer cell line A2780.[48]

It is worth mentioning that, despite the reports on the occurrence of DKPs in *A. niger* strains, in a recent review article[74] the authors question the origin of compounds asperazine **106**, asperazine A (**107**), cyclo(D-Phe-L-Trp) (**108**), cyclo(L-Trp-L-Trp) (**114**) besides campyrones A-C (**44**-**46**) and walterolactone A (**60**) as being from *A. niger*. This is because some strains that biosynthesized these compounds were re-classified as *A. tubingensis* which is known to produce them.

3.7. Itaconic acid derivatives

Itaconic acid (**122**) is an unsaturated C5 dicarboxylic acid used worldwide as monomer or co-monomer in the polymer industry. Although it was produced commercially by *A. terreus*, strains of *A. niger* have been selected as novel itaconic acid and derivatives producer using genetic modification and medium optimization (**118**-**128**, Figure 8, Table 7).[77,78,80] Hexylitaconic acid (**121**), produced by a marine strain isolated from sponge *Hyrtios proteus*,[51] and from *A. niger* K-88,[76] was reported as plant growth regulator. Asperitaconic acids A-C (**118**-**120**), also produced by a marine strain, associated to the sponge *Haliclona* sp. from Hainan, China, exhibited antibacterial effect against *S. aureus*.[75] Tensyuic acids A-F (**122-128**), metabolized by a fungus strain recovered from soil collected in Nagasaki, Japan, were the first compounds belonging to the itaconic

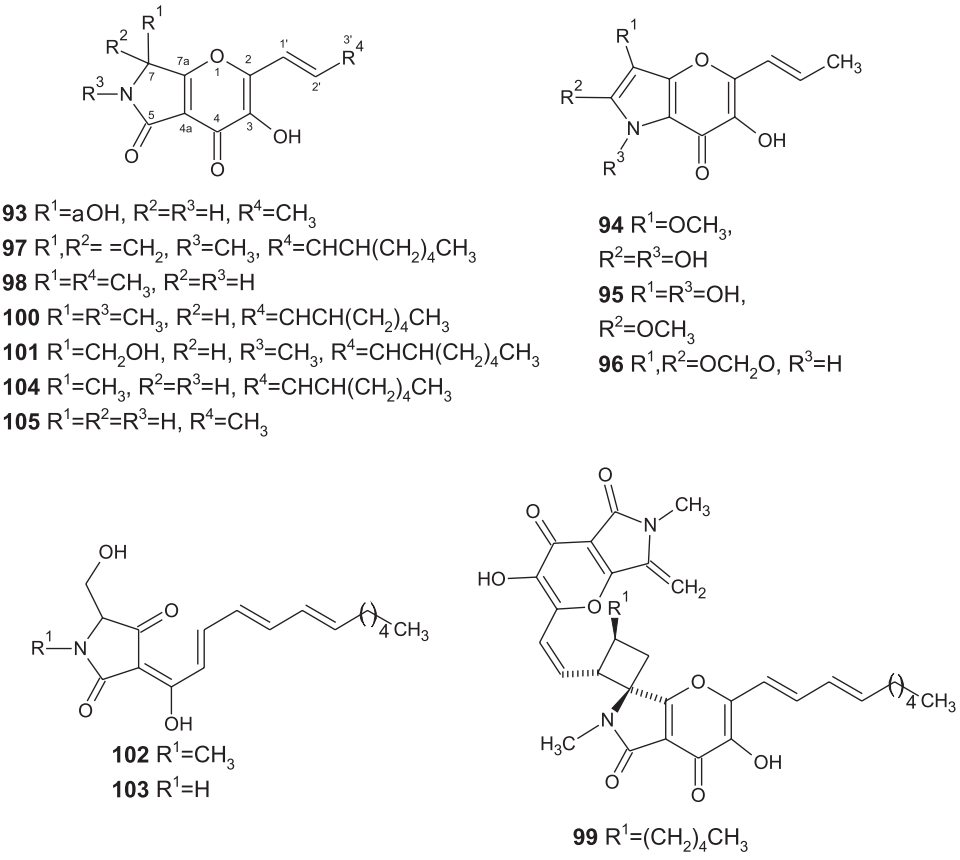


Figure 6. Chemical structures of pyranonigrins (**93**-**105**) produced by *A. niger* strains.

Table 5. Pyranonigrins (**93**-**105**) produced by *A. niger* strains

Compound	Strain	Source	Reference
Pyranonigrin A (**93**)	LL-LV 3020	marine	69
	CBX 146 2002	marine	70
Pyranonigrin B (**94**)			
Pyranonigrin C (**95**)	CBX 146 2002	marine	70
Pyranonigrin D (**96**)			
Pyranonigrin E1 (**97**)	A 1179	mutant strain	71
Pyranonigrin E2 (**98**)	NBRC 5374	nr	72
Pyranonigrin F (**99**)			
Pyranonigrin G (**100**)			
Pyranonigrin H (**101**)	A 1179	mutant strain	71
Pyranonigrin I (**102**)			
Pyranonigrin J (**103**)			
Pyranonigrin K (**104**)			
Pyranonigrin S (**105**)	LL-LV 3020	marine	69

nr: not reported

acid family containing ester carboxyl moieties at the end of the alkyl side chain. Among them, tensyuic acid C (**125**) showed moderate antimicrobial activity against *B. subtilis*.[79]

3.8. Terpenes

Terpenes have limited occurrence to volatile compounds in *A. niger* (**129**-**138**, Figure 9, Table 8). The only report[81] that revealed the production of terpenes by this fungus involved the comparative analysis of the volatile constituents from wild-type and mutant *A. niger* strains. Both strains produced a series of compounds, from which most of the identified ones were sesquiterpenes. Compound (6*S*,10*S*)-6,10-dimethylbicyclo[4.4.0]dec-1-en-3-one (**134**) was identified only in the mutant strain analysis.

3.9. Steroids

Steroids were found only in *A. niger* from marine sources (**139**-**145**, Figure 10, Table 9).[82,83] Ergosterimide (**143**) was isolated and characterized as the first Diels-Alder adduct skeleton of ergosteroid and maleimide. It was produced from a marine endophytic isolated from the inner tissue of the brown alga *Colpomenia sinuosa*, together with (22*E*,24*R*)-5α,8α-epidioxyergosta-6,22-dien-3β-ol (**139**), (22*E*,24*R*)-ergosta-4,6,8(14),22-tetraen-3-one (**140**), (22*E*,24*R*)-ergosta-5,7,22-trien-3β-ol (**141**) and (22*E*,24*R*)-ergosta-7,22-dien-3β,5α,6β-triol (**142**).[82]

Nigerasterols A (**144**) and B (**145**) are uncommon 5,9-epidioxy-sterols and the first representatives of this class to be produced by a marine-derived fungus, that was

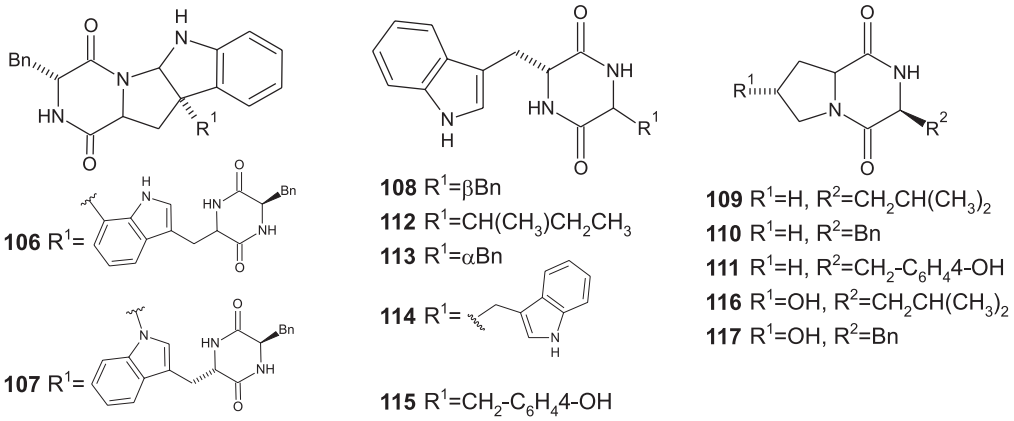


Figure 7. Chemical structures of diketopiperazines (**106**-**117**) produced by *A. niger* strains.

Table 6. Diketopiperazines (**106-117**) produced by *A. niger* strains

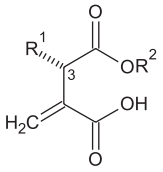
Compound	Strain	Source	Reference
Asperazine (**106**)	nr	endophyte	48
	UCSC 94-1212	marine	51
	nr	marine	73
Asperazine A (**107**)	nr	endophyte	48
Cyclo-(D-Phe-L-Trp) (**108**)			
Cyclo-(L-Pro-L-Leu) (**109**)	BRF 074	marine	57
Cyclo-(L-Pro-L-Phe) (**110**)			
Cyclo-(L-Pro-L-Tyr) (**111**)			
Cyclo-(L-Trp-L-Ile) (**112**)	EN 13	marine	47
Cyclo-(L-Trp-L-Phe) (**113**)			
Cyclo-(L-Trp-L-Trp) (**114**)	nr	endophyte	48
Cyclo-(L-Trp-L-Tyr) (**115**)	EN 13	marine	47
Cyclo-(*trans*-4-hydroxy-L-Pro-L-Leu) (**116**)	BRF 074	marine	57
Cyclo-(*trans*-4-hydroxy-L-Pro-L-Phe) (**117**)			

nr: not reported.

A. niger strain isolated from the mangrove plant *Avicennia marina*. Noteworthy is the fact of only five 5,9-epidioxysterols were reported from edible mushrooms before.[83] It was found that both nigerasterols (**144** and **145**) displayed potent activity against the human leukemia cell line HL60 and human lung adenocarcinoma cell line A549. Preliminary structure-activity relationship studies speculated that the α-OH at C15 in compound **144** could be responsible for its stronger activity than that from compound **145** which displays a β-OH group at the same carbon.[83]

3.10. Azaphilones

Azaphilones are pyrone-quinone structures containing a highly oxygenated bicyclic core and a chiral quaternary center. This class of compounds had its first occurrence in *A. niger* through the study of an activated azaphilone gene cluster in ATCC 1015 strain, which led to the obtention of six new azanigerones A-F (**146**-**151**, Figure 11). Additionally, this investigation allowed the authors[84] to identify the flavin adenine dinucleotide (FAD)-dependent hydroxylase as responsible for the formation of the bicyclic core characteristic of this class of compounds. Among the reported compounds, azanigerone D (**149**) is the only representative that contains a nitrogen-containing heterocycle at the main core.



118 $R^1=(CH_2)_6OH$, $R^2=CH_3$
119 $R^1=(CH_2)_6OAc$, $R^2=H$
120 $R^1=(CH_2)_4COCH_3$, $R^2=H$
121 $R^1=(CH_2)_5CH_3$, $R^2=H$
122 $R^1=R^2=H$
123 $R^1=(CH_2)_3CO_2CH_3$, $R^2=CH_3$
124 $R^1=(CH_2)_5CO_2CH_3$, $R^2=H$
125 $R^1=(CH_2)_5CO_2CH_2CH_3$, $R^2=H$
126 $R^1=(CH_2)_5CO_2CH_3$, $R^2=CH_3$
127 $R^1=(CH_2)_7CO_2CH_3$, $R^2=H$
128 $R^1=(CH_2)_3CO_2CH_2CH_3$, $R^2=CH_3$

Figure 8. Chemical structures of itaconic acids (**118**-**128**) produced by *A. niger* strains.

Table 7. Itaconic acids (**118**-**128**) produced by *A. niger* strains

Compound	Strain	Source	Reference
Asperitaconic acid A (**118**)			
Asperitaconic acid B (**119**)	LS 11	marine	75
Asperitaconic acid C (**120**)			
Hexylitaconic acid (**121**)	UCSCm 94-1212	marine	51
	K 88	soil	76
Itaconic acid (**122**)	AB1 13	mutant	77,78
Tensyuic acid A (**123**)			
Tensyuic acid B (**124**)			
Tensyuic acid C (**125**)	FKI 2342	soil	79
Tensyuic acid D (**126**)			
Tensyuic acid E (**127**)			
Tensyuic acid F (**128**)			

Table 8. Terpenes (**129**-**138**) produced by *A. niger* strains

Compound	Strain	Source	Reference
6,11-Epoxy-isodaucane (**129**)			
Geosmin (**130**)			
Germacra-[1(10)*E*,5*E*]-dien-11-ol (**131**)			
Germacrene D (**132**)			
(1*S*,6*S*,10*S*)-6,10-Dimethylbicyclo[4.4.0] dec-2-en-4-one (**133**)	AB1.13	mutant strain	81
(6*S*,10*S*)-6,10-Dimethylbicyclo[4.4.0]dec-1-en-3-one (**134**)			
2-Methylisoborneol (**135**)			
(8*S*,10*S*)-8,10-Dimethyl-1 (9)-octalin (**136**)			
β-Copaene (**137**)			
β-Ylangene (**138**)			

3.11. Bicoumarins

Bicoumarins produced by *A. niger* consist of a group of heterocycle dimers derived from cinnamic acid lactone that are further categorized by the type of connection between the coumarins moieties (**152**-**155**, Figure 12, Table 10).[70,85-87] A marine strain isolated from the Mediterranean sponge *Axinella damicornis* yielded the bicoumanigrin A (**152**) that showed moderate antiproliferative activity toward a panel of 10 different human leukemia and carcinoma cell lines.[70] Orlandin (**155**) (both C8-C8') was produced by a strain isolated from orange leaves in Florida, USA, and significantly inhibited wheat coleoptile growth.[87]

3.12. Pigments

Only four compounds (**156**-**159**, Figure 13, Table 11) considered by the authors[70,88-91] as pigments were reported for *A. niger*. Aspergillin (**157**) is the native black spore pigment of *A. niger* that was extensively studied and showed enzymatic proteolytic activity.[91] On the other hand, the polyene asperenone (**156**) is a yellow pigment which was isolated from *A. niger* mycelium and displayed inhibitory activities against soybean lipoxygenase (15-LOX) and platelet aggregation.[89] This pigment and another yellow pigment named asperrubrol (**158**) were biosynthesized by an *A. niger* strain cultured on synthetic medium containing toxic concentrations of Zn^{+2} and Cd^{+2} and high concentration of Mg^{+2}.[90] In addition, the deep green color pigment cycloleucomelone (**159**) was identified in the mycelium of a marine strain associated to the Mediterranean sponge *Axinella damicornis*.[70]

3.13. Sphingolipids

Sphingolipids containing unprecedent 9-methyl-C20-sphingosine moiety were found in *A. niger* (**160**-**163**, Figure 14).[92,93] Asperamides A (**160**) and B (**161**), a sphingolipid and its corresponding glycosphingolipid,

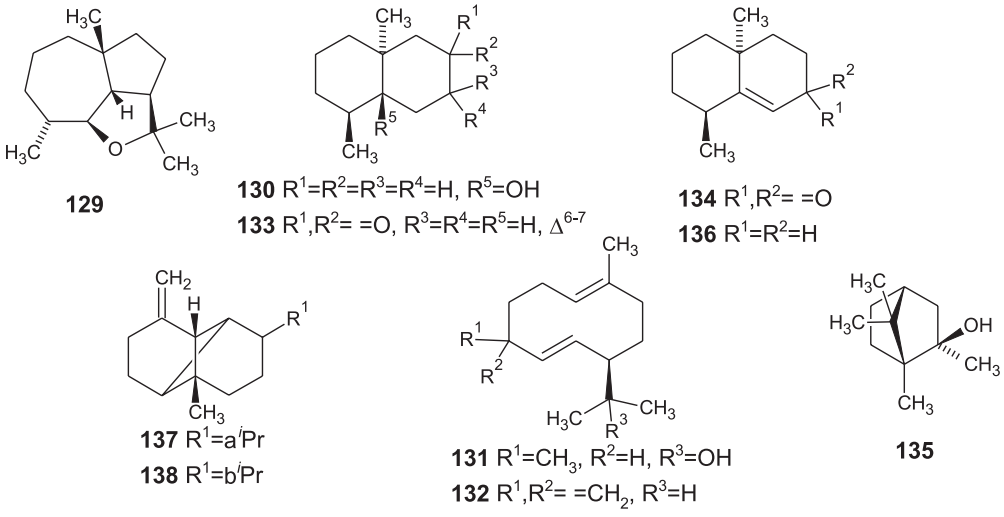


Figure 9. Chemical structures of terpenes (**129**-**138**) produced by *A. niger* strains.

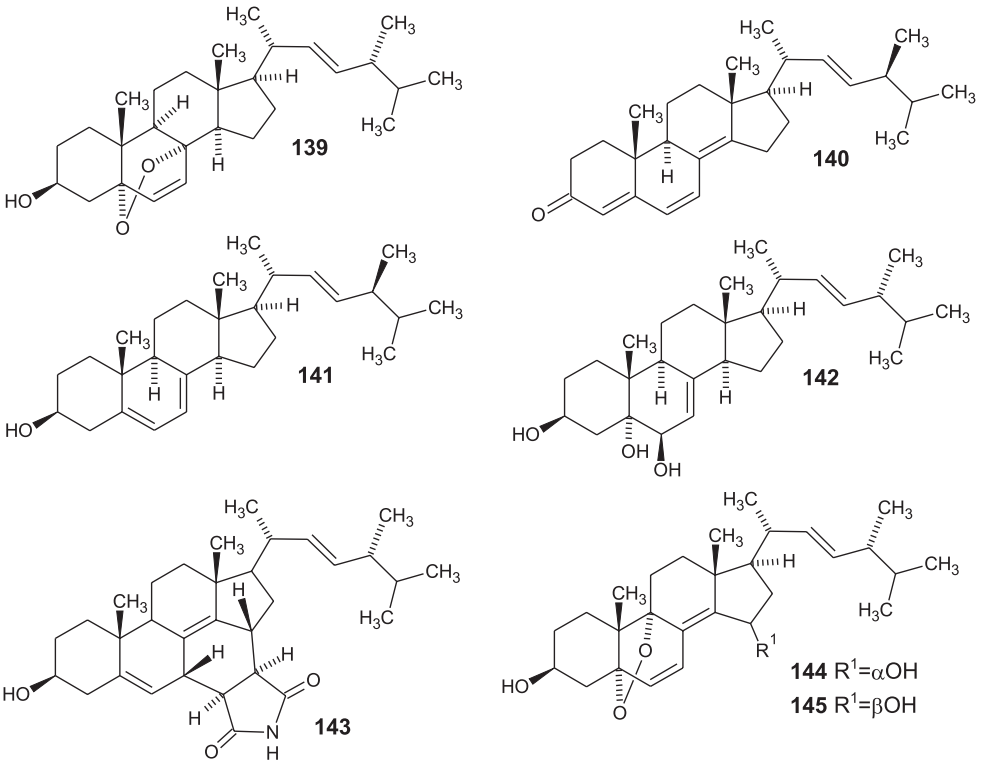


Figure 10. Chemical structures of steroids (**139**-**145**) produced by *A. niger* strains.

Table 9. Steroids (**139**-**145**) produced by *A. niger* strains

Compound	Strain	Source	Reference
(22*E*,24*R*)-5α,8α-Epidioxyergosta-6,22-dien-3β-ol (**139**)			
(22*E*,24*R*)-Ergosta-4,6,8(14),22-tetraen-3-one (**140**)			
(22*E*,24*R*)-Ergosta-5,7,22-trien-3β-ol (**141**)	EN 13	endophyte	82
(22*E*,24*R*)-Ergosta-7,22-dien-3β,5α,6β-triol (**142**)			
Ergosterimide (**143**)			
Nigerasterol A (**144**)	MA 132	endophyte	83
Nigerasterol B (**145**)			

respectively, possessing a hitherto unreported 9-methyl-C20-sphingosine moiety, were first characterized from an endophytic strain isolated from the marine brown alga *Colpomenia sinuosa* (EN 13). Among these isolated compounds, asperamide A (**160**) displayed moderate activity against *C. albicans*.[92] Asperiamides B (**162**) and C (**163**) were produced by *A. niger* isolated from seawater collected in Fujian Province in China (MF 16).[93] However, in a recent review,[74] the authors pointed out that the same strain was able to produce the aflatoxin precursors averufin and nidurufin and suggested that this strain was probably *A. flavus* instead of *A. niger*.

3.14. Miscellaneous

The miscellaneous group comprises those less representative or unique compounds (**164**-**213**, Figure 15, Table 12).[41-43,57,69,70,81,84,93-112] Antafumicins A (**166**) and B (**167**), isolated from a collection *A. niger* strain, inhibited the germination of the fungi *Colletotrichum lagenarium*, *Pyricularia oryzae*, *Fusarium oxysporum* and *Botrytis cinerea*, as well as the bacteria *B. subtilis*, *E. coli* and *Aeromonas liquefaciens*.[95] Aspernigrin B (**172**) was obtained from a marine strain isolated from the sponge *Axinella damicornis* and displayed a pronounced neuroprotective effect against glutamic acid.[70] Aspernigrin C (**173**), produced by a marine strain associated to an alga *Sargassum* sp. collected in south China sea, exhibited significant HIV-1 inhibitory activities by SF162 infection in TZM-bl cells.[41] Nigerloxin (**202**) showed dose-dependent aldose reductase activity (rat lens aldose reductase (RLAR)), inhibition against soy bean (lipoxygenase-1 (LOX-1)) and free radical scavenging activity.[109] Asperaldin (**168**) showed aldose reductase inhibition (RLAR),[96] while 2-(2'-methyl, 4'-hydroxyphenyl)2-(4''-hydroxyphenyl)-propane (**196**) showed inhibition (RLAR) of lipoxygenase-1 (LOX-1).[106] Funalenone (**183**), produced by a strain recovered from soil collected in Funabashi, Japan, inhibited type I collagenase activity dose-dependently,[100] and the furan

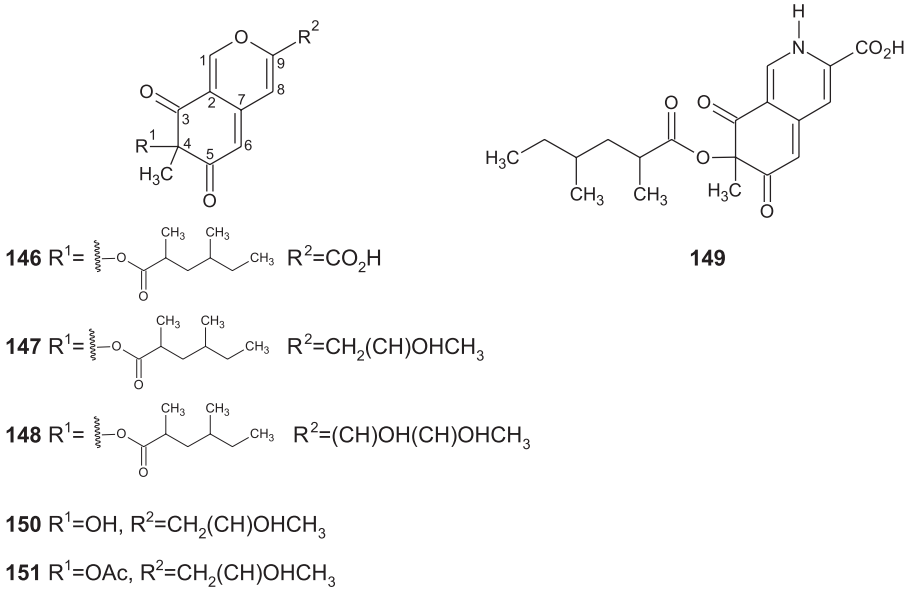


Figure 11. Chemical structures of azaphilones (**146**-**151**) produced by *A. niger* strains.

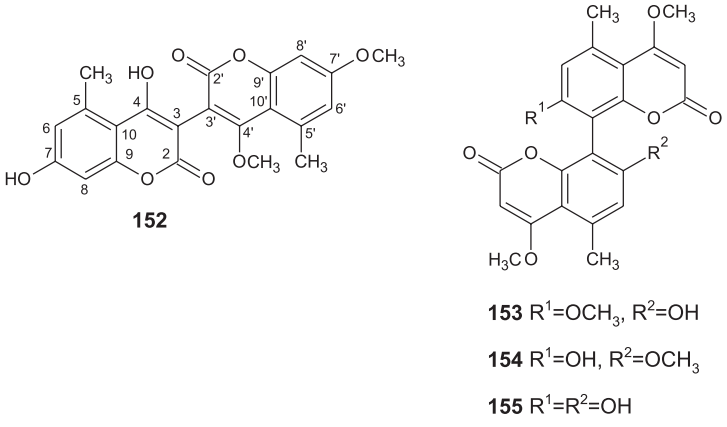


Figure 12. Chemical structures of bicoumarins (**152**-**155**) produced by *A. niger* strains.

Table 10. Bicoumarins (**152**-**155**) produced by *A. niger* strains

Compound	Strain	Source	Reference
Bicoumanigrin A (**152**)	CBX 146 2002	marine	70
Demethylkotanin (**153**)	nr	nr	85
Kotanin (**154**)	ATCC 36626	nr	86
Orlandin (**155**)	ATCC 36626	nr	86
	ATCC 36626	endophyte	87

ester compound **184**, isolated from a marine strain recovered from sediments collected in the Brazilian coast, was cytotoxic against HCT-116 cell line.[57] Compounds *p*-methoxyphenylacetic acid (**192**), phenoxyacetic acid (**207**), phenylacetic acid (**208**) and 2-pheynylethanol (**209**) were produced by a strain isolated from decaying platelets of *Kalanchoe daigremontiana* and inhibited the germination of cress and lettuce seeds.[104] In addition, the furopyrrols, tensidols A (**212**) and B (**213**) potentiated miconazole activity against *C. albicans* and moderated activity against *Pyricularia oryzae*,[112] and aspernigerin (**170**) showed cytotoxicity against tumor cell lines nasopharyngeal epidermoid KB, cervical carcinoma Hela, and colorectal carcinoma SW1116.[97]

In summary, the literature survey on the secondary metabolites produced by *A. niger* revealed that NGPs are the major compounds, of which dimeric BNGPs are the most abundant. Pyranonigrins are restricted to *A. niger* and, together with yanuthones and steroids, these compounds were isolated only from marine strains of this fungus. Most of compounds were produced from strains collected in two or more different habitats, leading to the understanding that the environmental conditions frequently did not alter the metabolism of this fungus. The large miscellaneous group reveals the great versatility of this microorganism to produce secondary metabolites.

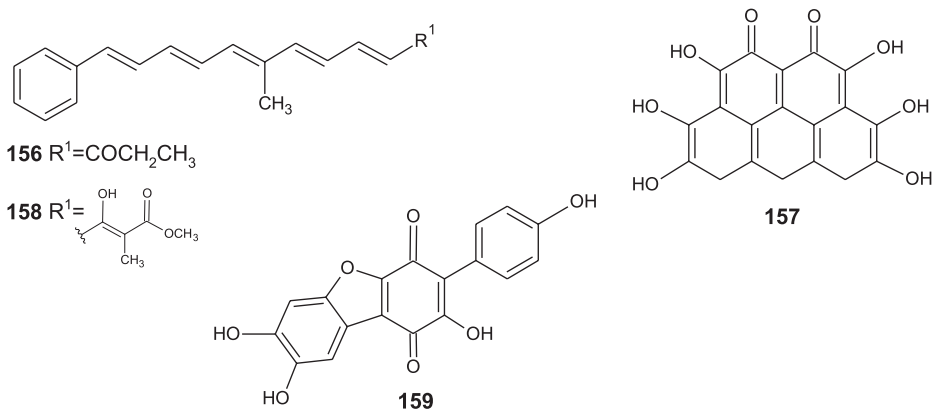
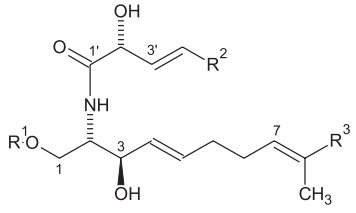


Figure 13. Chemical structures of pigments (**156**-**159**) produced by *A. niger* strains.

Table 11. Pigments (**156**-**159**) produced by *A. niger* strains

Compound	Strain	Source	Reference
Asperenone (**156**)	NRRL 3	nr	88
	CFTRI 1105	nr	89
	ATCC 9029	nr	90
Aspergillin (**157**)	nr	nr	91
Asperrubrol (**158**)	ATCC 9029	nr	90
Cycloleucomelone (**159**)	CBX 146 2002	marine	70

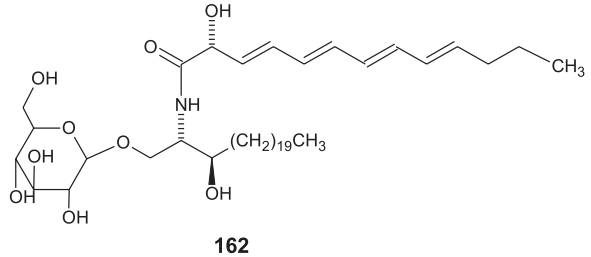
nr: not reported.



160 R^1=H, R^2=$(CH_2)_{11}CH_3$, R^3=$(CH_2)_{10}CH_3$

161 R^1=β-D-glucopyranoside, R^2=$(CH_2)_{11}CH_3$, R^3=$(CH_2)_{10}CH_3$

163 R^1=β-D-glucopyranoside, R^2=$(CH_2)_{11}CH_3$, R^3=$(CH_2)_{12}CH_3$



162

Figure 14. Chemical structures of sphingolipids (**160**-**163**) produced by *A. niger* strains.

4. Mycotoxins from *A. niger* Strains

Mycotoxins are a special group of secondary metabolites that are toxic and present health hazards or death in vertebrates if naturally taken (orally, by inhalation, or via the skin) even in low concentrations.[74] Although considered a ubiquitous innocuous contaminant, only a few cases of toxins formation in *A. niger* were reported[74,113] and medical cases of opportunistic diseases and hypersensitivity reactions involving this fungus were observed only in persons with severe illness or during immunosuppressive treatment.[113] Thus, *A. niger* is generally regarded as a non-pathogenic fungus to humans and it received the GRAS (generally regarded as safe) status by the Joint FAO/WHO Expert Committee of Food Additives.[27]

Fumonisins (**214**-**216**), gliotoxin (**217**) and ochratoxins (**218**-**220**) (Figure 16, Table 13), are the only mycotoxins reported for *A. niger* so far. The production of these toxic compounds was considered strain-specific and environmental-dependent and many culture parameters were investigated.[114,118,120-122]

For many years, fumonisins were known as carcinogenic mycotoxins reported only from *Fusarium* species.[123] However, studies of genome sequence identified a putative gene cluster for fumonisin biosynthesis in *A. niger* and, since then, fumonisin production has been produced by several *A. niger* isolates that came from culture collections of commercial foods.[74] Fumonisins B2 (**214**), B4 (**215**) and B6 (**216**)[66,74,115,116] were produced by strains from cereals, coffees and grapes,[74,114,124] and by strains of industrial use.[74] However, some industrial strains were developed, and they are currently in use, by classical mutagenesis through which the genes involved in the biosynthesis of fumonisins were deleted.[125]

Ochratoxin A (OTA) (**218**) was originally isolated from a strain of *A. ochraceus* in 1965, but during the subsequent years, a great variety of *A. niger* strains were considered as the main responsible for contamination of grapes by OTA worldwide.[66,126] OTA is the major clinically relevant

mycotoxin that causes immunosuppressive, teratogenic, neurotoxic, genotoxic, mutagenic and carcinogenic effects.[127] Ochratoxin α (OTα) (**219**) and ochratoxin β (OTβ) (**220**), which are OTA analogues, were also found in some *A. niger* strains.[118,119] Ochratoxin α (**219**) was reported as a degradation product of the fungus when OTA was treated with its crude enzymes. This compound did not exert cytotoxic effect on cell metabolism, probably due to

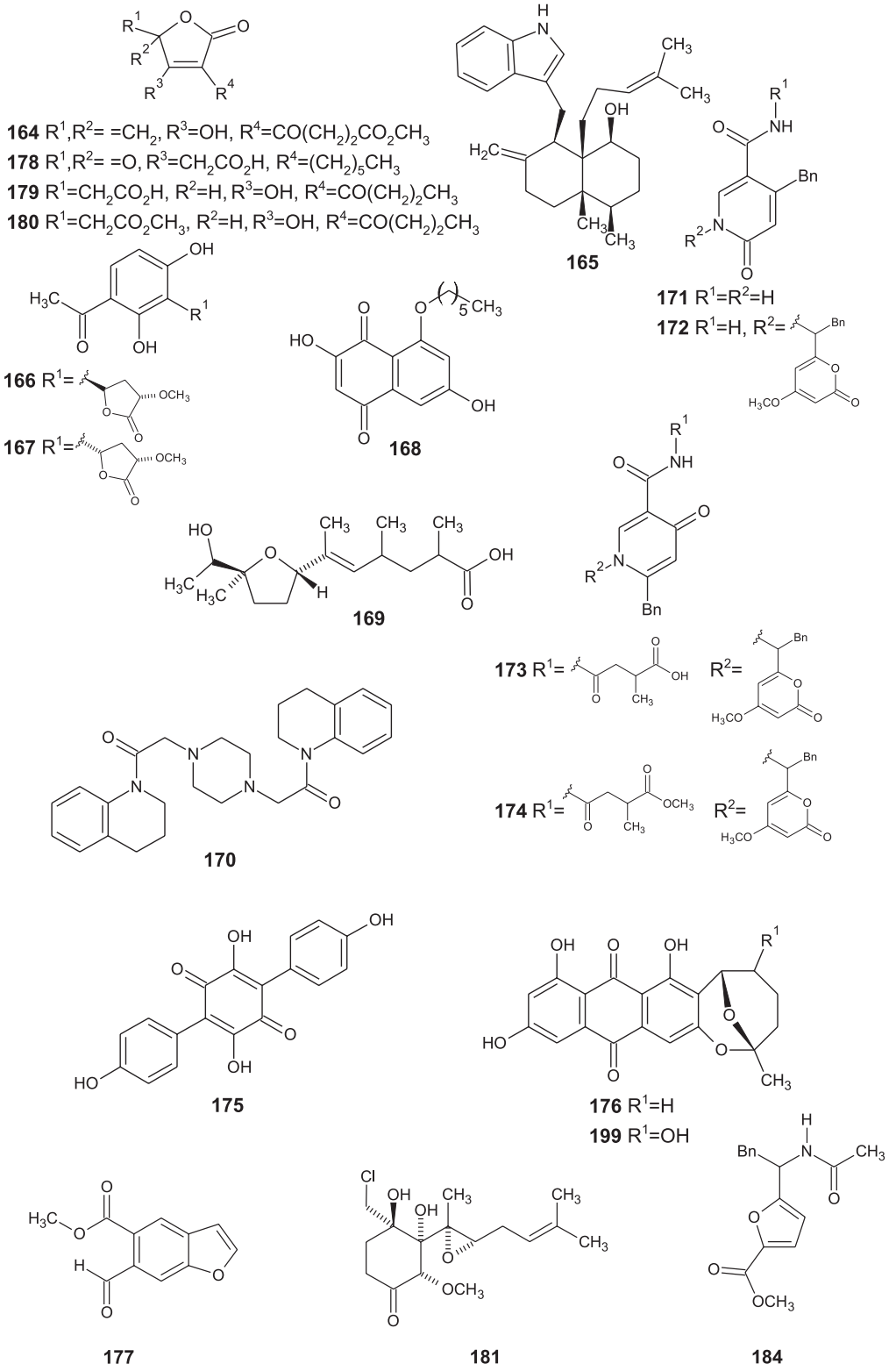


Figure 15. Chemical structures of miscellaneous compounds (**164**-**213**) produced by *A. niger* strains.

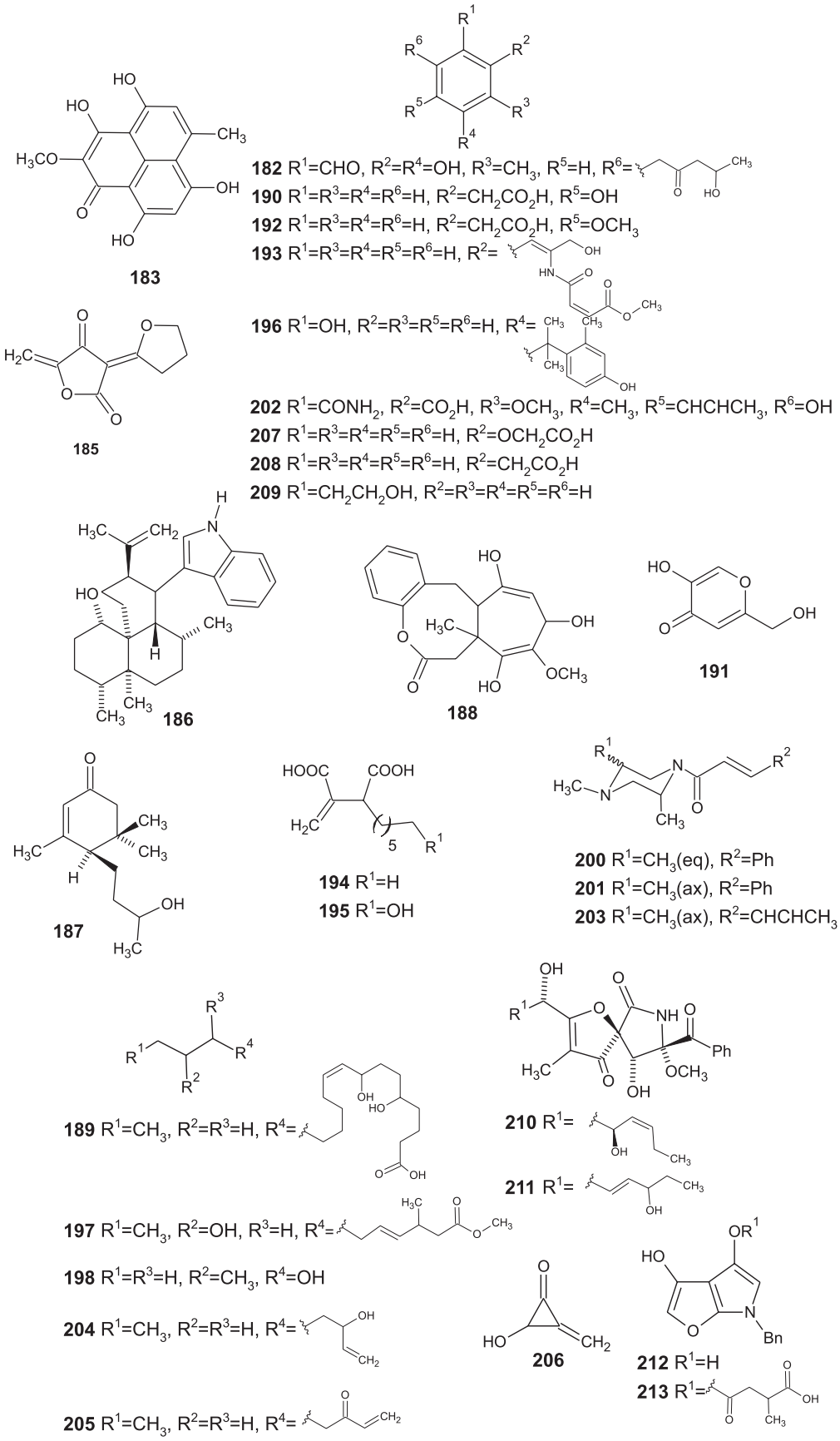


Figure 15. Chemical structures of miscellaneous compounds (**164**-**213**) produced by *A. niger* strains (cont.).

Table 12. Miscellaneous (**164-213**) produced by *A. niger* strains

Compound	Strain	Source	Reference
Agglomerin F (**164**)	ATCC 1015	nr	94
Anominine (**165**)	IBT 29019	endophyte	74
Antafumicin A (**166**)	NH-401	nr	95
Antafumicin B (**167**)	CFR-1046	nr	96
Asperaldin (**168**)			
Asperic acid (**169**)	UCSC 94-1212	marine	51
Aspernigerin (**170**)	IFB E003	endophyte	97
Aspernigrin A (**171**)	CBX 146 2002	marine	70
	SCSIO Jcsw6F30	marine	41
Aspernigrin B (**172**)	CBX 146 2002	marine	70
	SCSIO Jcsw6F30	marine	41
Aspernigrin C (**173**)	SCSIO Jcsw6F30	marine	41
Aspernigrin D (**174**)	SCSIO Jcsw6F30	marine	41
Atromentin (**175**)	LL-LV 3020	marine	69
Averufin (**176**)	MF 16	marine	93
5-Benzofuran carboxylic acid-6-formyl methyl ester (**177**)	nr	endophyte	98
2-Carboxymethyl-3-hexylmaleic acid anhydride (**178**)	*A. niger* 5 No. 22	nr	99
Carlosic acid (**179**)	ATCC 1015	nr	94
Carlosic acid methyl ether (**180**)			
Chlovalicin (**181**)	BRF 074	marine	57
FK17-P2a (**182**)	ATCC 1015	mutant strain	84
Funalenone (**183**)	FO 5904	soil	100
Furan ester derivative (**184**)	BRF 074	marine	57
Dihydrocarolic acid (**185**)	AM 410	soil	101
10,23-Dihydro-24,25-dehydroaflavinine (**186**)	IBT 29019	endophyte	42
4-(3'(*R*)-Hydroxybutyl)-3,5,5, trimethyl-cyclohex-2-en-1-one (**187**)	nr	endophyte	98
8,10,12-Trihydroxy-9-methoxy-7α-methyl-7,7α,12α,13-tetrahydrobenzocycloheptaoxocin-6-one (**188**)	nr	endophyte	102
5,8-Dihydroxy-9-octadecenoic acid (**189**)	KCCM 60318	nr	103
p-Hydroxyphenylacetic acid (**190**)	AKRN	endophyte	43
Kojic acid (**191**)			
p-Methoxyphenylacetic acid (**192**)	nr	endophyte	104
Methyl (*Z*)-4-{[(*Z*)-1-(hydroxymethyl)-2-phenyl-1-ethenyl] amino}-4-oxo-2-butenoate (**193**)	Ta 1	nr	105
2-Methylene-3-hexyl-butanedioic acid (**194**)	*A. niger* 5 No. 22	nr	99
2-Methylene-3-(6-hydroxyhexyl)-butanedioic acid (**195**)			
2-(2'-Methyl,4'-hydroxyphenyl)2-(4''-hydroxyphenyl)-propane (**196**)	CFTRI 1105	nr	106
Methyl 3-methyl-8-hydroxy-4-decenoate (**197**)	nr	endophyte	104
2-Methylpropan-1-ol (**198**)	nr	nr	107
Nidurufin (**199**)	MF 16	marine	93
Nigerazine A (**200**)	I 639	soil	108
Nigerazine B (**201**)			
Nigerloxin (**202**)	CFR-W 105	nr	109,110
Nigragillin (**203**)	IBT 29019	endophyte	42
1-Octen-3-ol (**204**)	nr	nr	107
1-Octen-3-one (**205**)	AB1.13	nr	81
Penitricin D (**206**)	AM 410	soil	101
Phenoxyacetic acid (**207**)	nr	endophyte	104
Phenylacetic acid (**208**)			
2-Phenylethanol (**209**)	nr	endophyte	104
	JUBT 3M	endophyte	111
Pseurotin A (**210**)	BRF 074	marine	57
Pseurotin D (**211**)			
Tensidol A (**212**)	FKI 2342	soil	112
Tensidol B (**213**)	IBT 29019	endophyte	42
	FKI 2342	soil	112

nr: not reported; FK17-P2a: 2,4-dihydroxy-6-(4-hydroxy-2-oxopentyl)-3-methylbenzaldehyde.

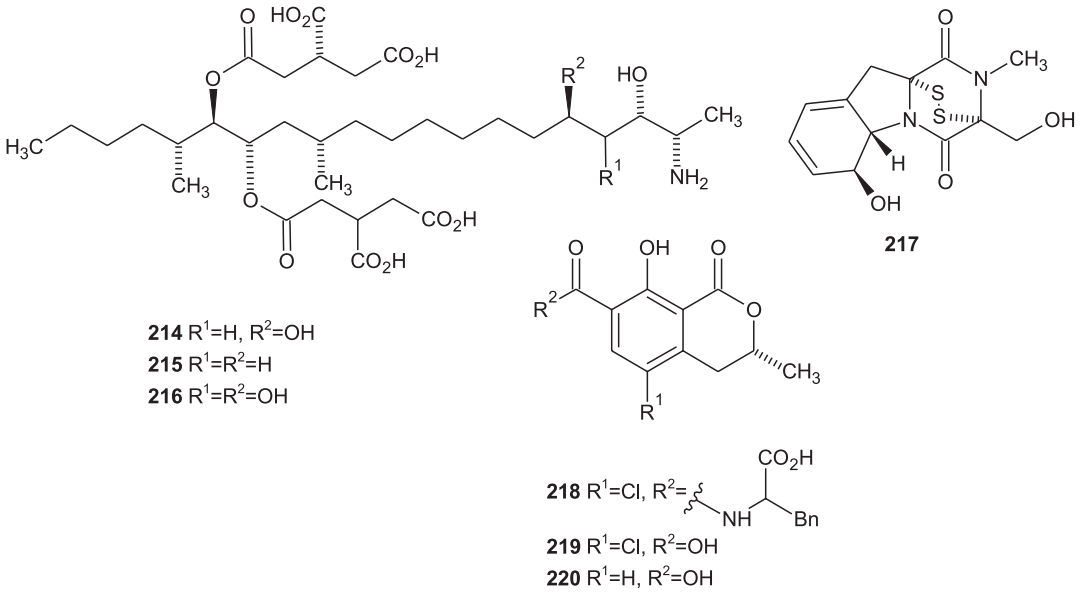


Figure 16. Chemical structures of mycotoxins (**214**-**220**) produced by *A. niger* strains.

Table 13. Mycotoxins (**214**-**220**) produced by *A. niger* strains

Compound	Strain	Source	Reference
Fumonisin B2 (**214**)	nr	endophyte	114
	NRRL 326	nr	115
	NRRL 3122	mutant strain	116
	nr	endophyte	66
Fumonisin B4 (**215**)	nr	endophyte	114
Fumonisin B6 (**216**)	NRRL 326	nr	115
Gliotoxin (**217**)	nr	nr	117
Ochratoxin A (**218**)	nr	endophyte	66
Ochratoxin α (**219**)	IBT 28144	nr	118
Ochratoxin β (**220**)	nr	nr	119

nr: not reported.

its more lipophilic nature when compared to OTA that has the hydrophilic L-β-phenylalanine group.[128] The capacity of *A. niger* 1062 to biosynthesize OTA, OTα and OTβ was removed through the disruption of its polyketide synthase gene An15g07920.[129] Gliotoxin (**217**) is a redox-active metabolite which inhibited the growth of other fungi and was found in *A. niger* strains from cancer patients.[117]

Despite BNPs have been reported as vertebral central nervous toxins, they cannot be regarded as mycotoxins because they were not shown to be toxic when administered by a natural route but rather after intraperitoneal injection.[37] Although malformin C (**92**, Figure 5) has been often referred as toxin, in this review it was allocated in the cyclopeptide class, since this compound is not considered mycotoxin by the Council of Agricultural Science and Technology (CAST).[130]

5. Biotransformation of Terpenes by *A. niger* Strains

Microbial-mediated transformations of organic compounds, including natural products, have been used as an important strategy for producing new bioactive compounds through chemo-, regio- and/or stereoselective reactions. In this field, many fungi species have been revealed as promising biocatalysts, being able to promote chemical modifications that are difficult to reproduce under conventional catalysis.[131,132] *A. niger* has been considered a cell factory of enzymes of industrial interest[133] and it is highlighted as an adaptable species for laboratory and industrial-scale microbial transformations.

The use of strains of this fungus on the biotransformation of organic compounds,[23] steroids and flavonoids[22] besides terpenoids[24] was reviewed in the literature. In the latter revision[24] (literature covered from 1960 to 2013), the authors present various examples of the use of *A. niger* strains that promoted stereoselective biotransformation in terpenoids to yield compounds of industrial interest to flavors, fragrances or pharmaceutical industries.

The first biotransformation of a terpene by *A. niger* was reported by Bhattacharyya *et al.*[134] (1960) on the study of microbiological hydroxylation of the monoterpene (+)-α-pinene. Since then, about 121 terpenoids (36 mono-, 52 sesqui-, 31 di- and 2 triterpenes) were biotransformed by various strains of *A. niger*, revealing the ability of this fungus to mediate different enzymatic reactions on the presence of the natural product and/or its derivative.

The microbial transformations reported to this class of compounds, although not unique to this species, are

extremally diverse. In general, the Csp^3 oxidation[24,135-147] is the most widespread reaction that occurs in various structural types of terpenoids, including monoterpenes, diterpenes and sesquiterpenes. Some examples of Csp^2 oxidation,[24,142,147-150] C=C dihydroxylation,[24] C=C reduction,[24,150] C=C migration,[24,145,150] C=O reduction,[24,150] hydrolyses,[24] epoxide opening,[24,135,150] ring opening,[24,139,149] elimination,[24,135,148,150] OH oxidation,[24,135,150] acetylation,[24] heterocyclization,[24] dehydrogenation,[24] esterification,[24,142,145] oxidative ring opening,[24] Baeyer-Villiger,[146,148] demethylation,[136] Michael addition,[24] peroxide deoxygenation,[24] *O*-alkylation,[24] aromatization,[24,139] Beckmann rearrangement,[146] Csp^3 halogenation,[145] CO_2H reduction (conversion of lactam to CN),[24,145] deoxygenation,[149] lactone isomerization,[144] lactonization,[146] oxidative cleavage at side chain,[24] phenyl oxidation[24] and spirolactonization[24] were also reported. However, few examples were found involving biotransformation of triterpenes by *A. niger*, which were restricted to saponins, and resulted in products from either partial or total hydrolysis of glycoside chains.[24]

Unlike the review from Parshikov and Sutherland,[24] which presents all examples of biotransformation of the terpenoids divided by their classes (mono-, sesqui-, di- and triterpenes), this topic will highlight some examples that involved the most uncommon microbial transformations.

Not so frequently mediated by *A. niger* on biotransformations of terpenes but with great importance to generate new uncommon terpenoids are the Baeyer-Villiger (BV), Michael addition, Beckmann rearrangement, spirolactonization and peroxide deoxygenation reactions. Therefore, the examples of these reactions on biotransformations of terpenes by *A. niger* will be discussed below. Whenever appropriate, some proposed pathways involved on the formation of products will be presented.

The microbial transformation of thymoquinone (**221**) by suspended cell-cultures of ATCC 16404 strain yielded compound 5-isopropyl-2-methyloxepin-1-one (**222**) besides 3-hydroxy-5-isopropyl-2-methylcyclohexa-2,5-diene-1,4-dione, and 5-isopropyl-2-methylbenzene-1,4-diol (Figure 17).[148] The proposed pathway for the synthesis of compound (**222**) suggested that it underwent BV type oxidation of regioselective C=C reduced benzoquinone, followed by reduction of C=O bond and elimination of water.

Baeyer-Villiger reaction was also observed on the microbial transformation of isosteviol oxime derivative (**223**) using BCRC 32720 strain, that yield isosteviol lactone (4*R*-carboxy-13*R*-hydroxy-13,16-*seco*-*ent*-19-norbeyeran-16-oic acid 13,16-lactone, **224**), besides products coming from abnormal Beckmann rearrangement (**225** and **226**), and the isosteviol lactam (4*R*-carboxy-13*R*-amino-13,16-*seco*-*ent*-19-norbeyeran-16-oic acid 13,16-lactam, **227**) from Beckmann rearrangement (Figure 18).[146] It is worth note that this was the first report of these products formation by microbial catalysis.

The production of these compounds can be justified by the sequence of reactions displayed at Figure 19.[151] The first step involves the formation of carbocations (**228** and **229**) as intermediates for the next steps. The regioisomeric compounds (**225** and **226**) are formed by α-proton elimination in the nitrile carbocation (**228**, path a), which were considered an abnormal Beckmann rearrangement.[146] Addition of water to this carbocation yields the unstable imidate (**230**), which easily hydrolyses to lactone (**224**, path b). Lactam (**227**) is formed through Beckmann rearrangement after water addition to carbocation (**229**, path c).

Chang and co-workers[144] also obtained isosteviol lactone (**224**) by derivatization of isosteviol (*ent*-16-oxobeyeran-19-oic acid, **231**) with *m*-chloroperbenzoic acid and submitted this compound to biotransformation by *A. niger* BCRC 32720 strain. Some products from regio- and stereoselective hydroxylation were formed besides a new lactone (4*R*-carboxy-15*R*-hydroxy-15,16-*seco*-*ent*-

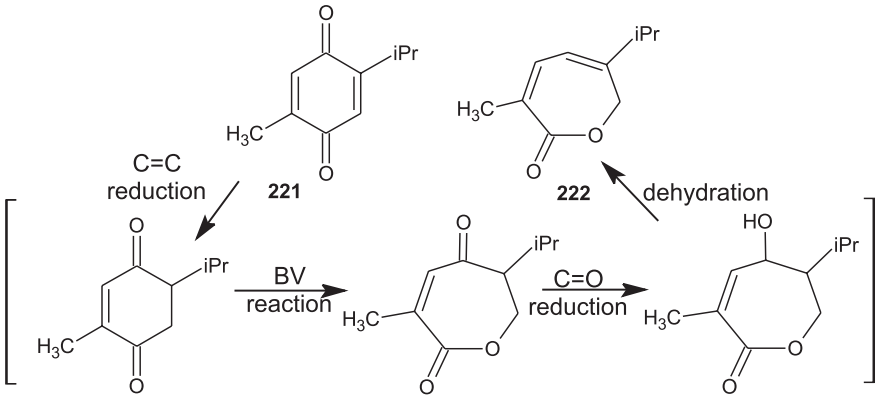


Figure 17. Proposed pathway for production of compound **222** through biotransformation of thymoquinone (**221**) by *A. niger* ATCC 16404.

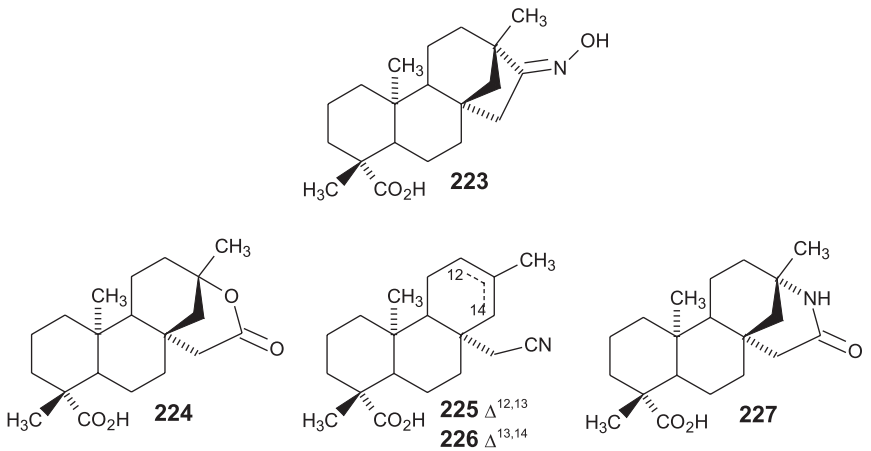


Figure 18. Chemical structures of isosteviol oxime (**223**) and its biotransformation products **224**-**227** by *A. niger* BCRC 32720.

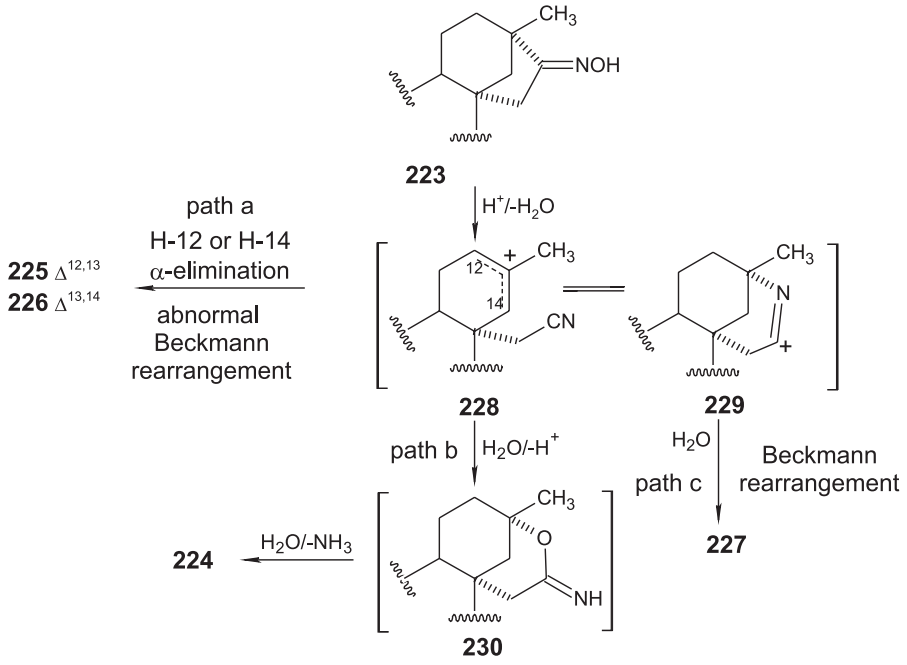


Figure 19. Proposed pathway for production of compounds **224**-**227** through biotransformation of isosteviol oxime (**223**) by *A. niger* BCRC 32720.

19-norbeyeran-16-oic acid 15,16-lactone, **232**) coming from the unexpected isomerization of the lactone ring, and its 1α,7β-hydroxylated derivatives (Figure 20).

Transformation of steviol lactam (**227**) by the same strain involved diverse reactions. Chlorination reactions occurred at C-15 from lactam (**227**) and at C-12 from compound (**234**) (Figure 21).[145] The mechanism to produce both chlorinated compounds (**233** and **234**) is not clear, but the authors[145] suggested that it may involve the action of chloroperoxidases, and that the chlorine atom was probably derived from the addition of NaCl to the fermentation medium.

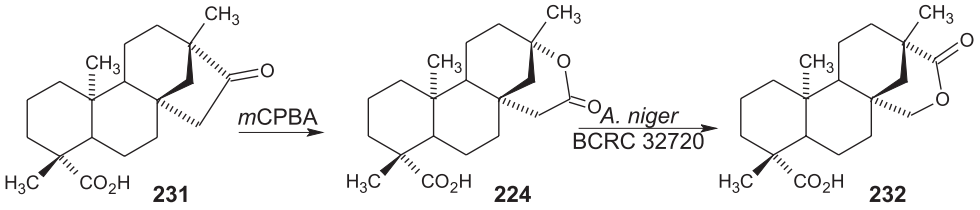


Figure 20. Chemical preparation of isosteviol lactone (**224**) from isosteviol (**231**) and biotransformation of **224** by *A. niger* BCRC 32720 to produce compound **232**.

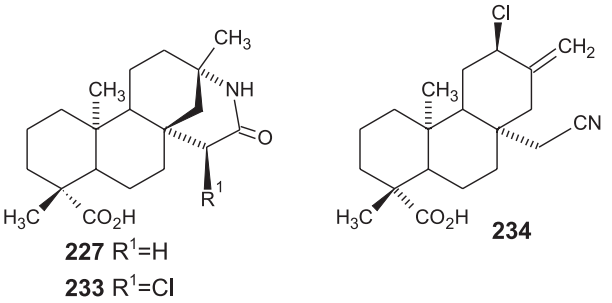


Figure 21. Chemical structures of steviol lactam (**227**) and its biotransformation products **233** and **234** by *A. niger* BCRC 32720.

The microbial transformation of the sesquiterpene endoperoxide artemisitene (**235**) by NRRL 599 strain revealed, among double bond hydrogenation products, the unusual 9β-hydroxydeoxy-11-*epi*-artemisinin (**236**) compound, obtained by the reduction of the peroxide linkage (Figure 22).[152] However, a similar transformation happened when the analogue artemisinin was investigated as substrate to be biotransformed by *A. niger* AS 3.1858.[153] In this case, the authors[153] also found the deoxy product in the substrate control, without any microorganisms, indicating that it may be an artifact produced by chemical reaction catalyzed by Fe^{+2} in potato medium.

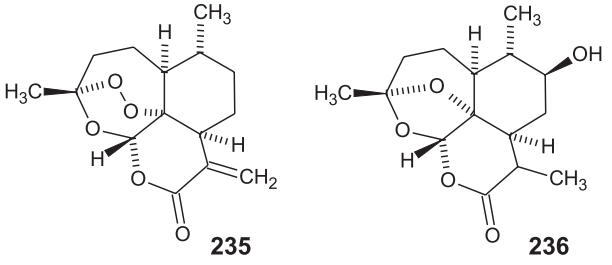


Figure 22. Chemical structures of artemisitene (**235**) and its biotransformation product **236** by *A. niger* NRRL 599.

Artemisinin (**237**) was also biotransformed by VKM F-1119 strain to produce the new products 3β-hydroxy-4,12-epoxy-1-deoxyartemisinin (**238**), 3,13-epoxyartemisinin (**239**) and 4α-hydroxy-1-deoxyartemisinin (**240**), which display epoxy structures, besides the ring rearranged product artemisinin G (**241**) (Figure 23).[149] Despite the existence of some studies of microbial transformation of artemisinin and derivatives, it was the first report of epoxidation and rearrangement of artemisinin using microbial strains.

α, β and γ-cyclocostunolide sesquiterpenes (**242**-**244**), obtained easily by treatment of costunolide with thionyl chloride in $CHCl_3$, were biotransformed by *A. niger* to give new derivatives.[154] Among them, it is highlighted the formation of the sulfide compounds (**245** and **246**, from α- and β-cyclocostunolides, respectively) through either Michael addition at **242** and **243** or nucleophilic substitution at C13 of compounds **247** and **248** (Figure 24). In both cases, compound ethyl 2-hydroxy-3-mercaptopropanate is the nucleophile which might be originated from Czapek-peptone medium. It is noteworthy that no sulfide product was detected on biotransformation of the γ-isomer. As far as we know, this is the first example of 3-mercaptopropanate products from terpene biotransformations by *A. niger*.

The same Michael addition reaction occurred when 7α-hydroxyfrullanolide (**249**) was incubated with *A. niger* ATCC 1004 strain, which yielded the acetylated compound (**250**) (Figure 25), besides oxidized derivatives.[155] This result was considered a novel "umpolung-type" microbial reaction.

Curdione (**251**) was biotransformed by AS 3739 strain to yield new compounds. Among them, it is worth highlighting those bearing a spirolactone skeleton (**252**-**255**), Figure 26.[156] The spirolactonization of curdione

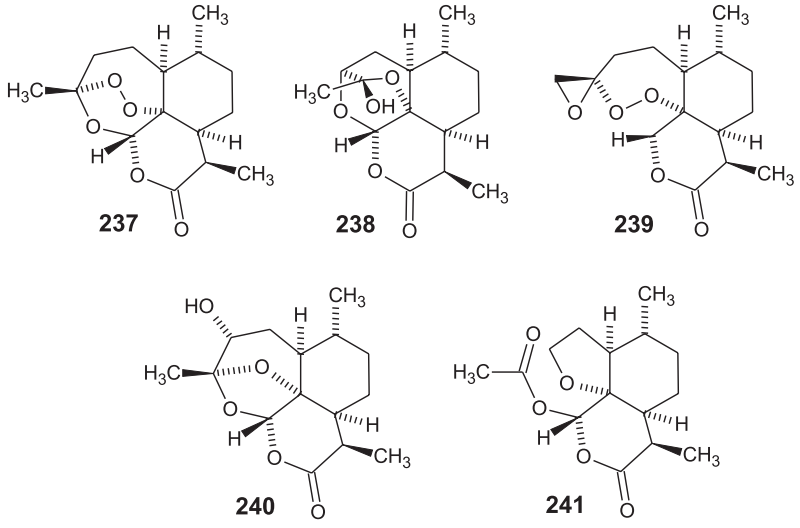


Figure 23. Chemical structures of artemisinin (**237**) and its biotransformation products **238**-**241** by *A. niger* VKM F-1119.

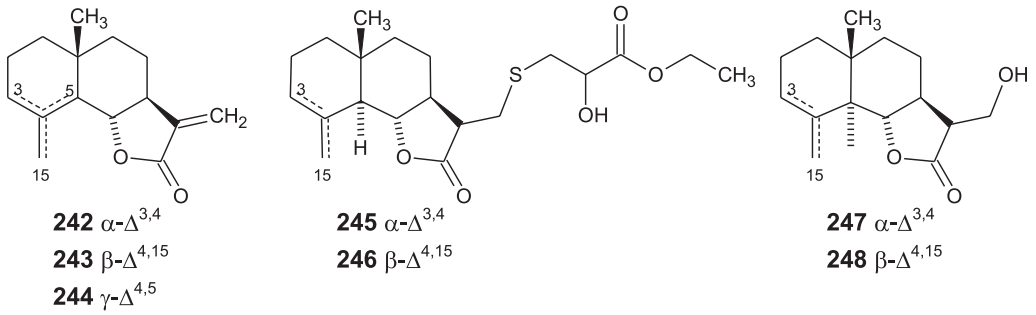


Figure 24. Chemical structures of α, β and γ-cyclocostunolides (**242**-**244**) and their biotransformation products **245**-**248** by *A. niger*.

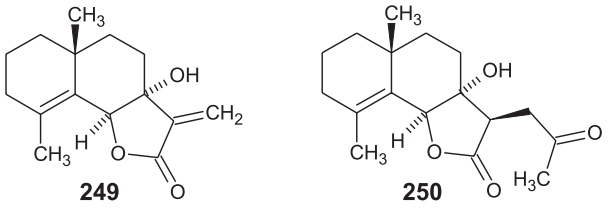


Figure 25. Chemical structures of 7α-hydroxyfrullanolide (**249**) and its biotransformation product **250** by *A. niger* ATCC 1004.

was previously reported from chemical transformation of this compound with catalytic amounts of HCl in chloroform.[157] The reaction happened via intramolecular ene-reaction which was considered a rearrangement catalyzed by acid. This result contributed to the proposition of the biogenetic pathway depicted in Figure 26, which agrees with the fact that *A. niger* cultured in nutrient medium excretes large amounts of acid.[156]

The microbial transformation of (−)-α-santonin (**256**) was carried out by *A. niger* M1L 5024 strain in the presence of α,α'-dipyridyl to yield the new B-ring opened aromatic compounds, 3,6,9-trihydroxy-9,10-*seco*-selina-l,3,5(10)-trien-12-oic acid 12,6-1actone (**257**) and 3,6-dihydroxy-9,10-*seco*-selina-l,3,5(10)-trien-9,12-dioic acid 12,6-1actone (**258**) (Figure 27), besides a hydroxylated product at C-11.[139] The authors suggested that the formation of these products might involve the microbial formation of a postulated 9-hydroxylated intermediate (**259**), that spontaneously undergoes reverse aldol reaction as represented in Figure 27. It is noteworthy that the breakdown of the B-ring accompanied by aromatization of the A-ring was previously reported from microbial transformation of steroids.[158]

Biotransformation of stypotriol acetate (**260**) by ATCC 16404 yielded 6',14-diacetoxy-stypol-4,5-dione (**261**), which bears a 1,2-benzoquinone moiety instead of the initial aromatic ring (Figure 28).[159] The authors suggested the initial formation of intermediates **262** and **263** through deacetylation reaction catalyzed by esterases followed by oxidation of the aromatic ring. Finally, the product **261** was formed through rapid air oxidation of intermediate **263** during the course of its isolation, as previously observed by Gerwick and Fenical[160] (1981) in the isolation of stypoldione.

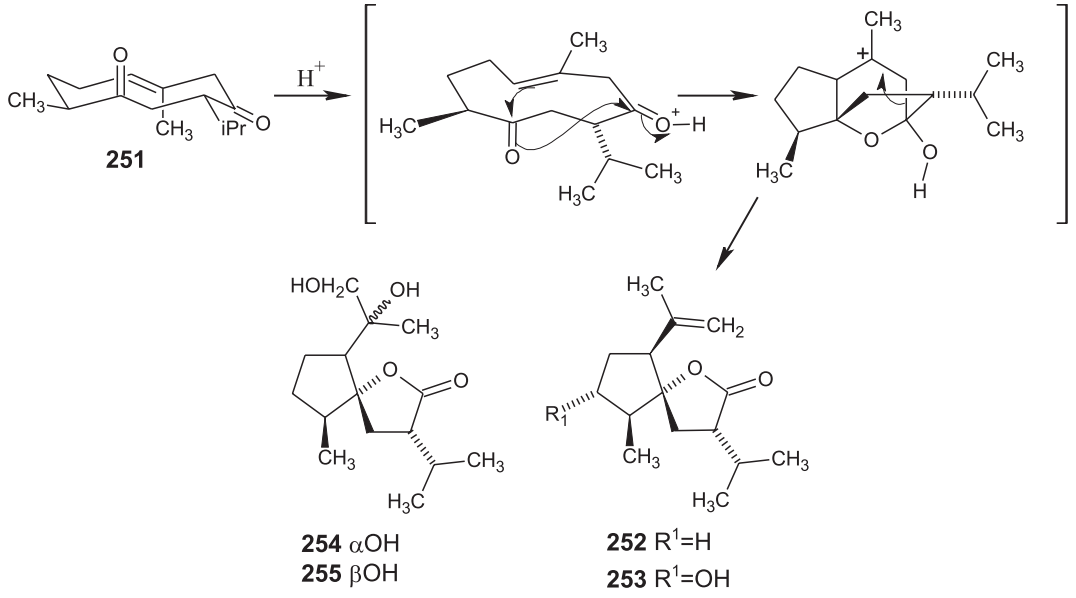


Figure 26. Proposed pathway for production of compounds **252**-**255** through biotransformation of curdione (**251**) by *A. niger* AS 3739.

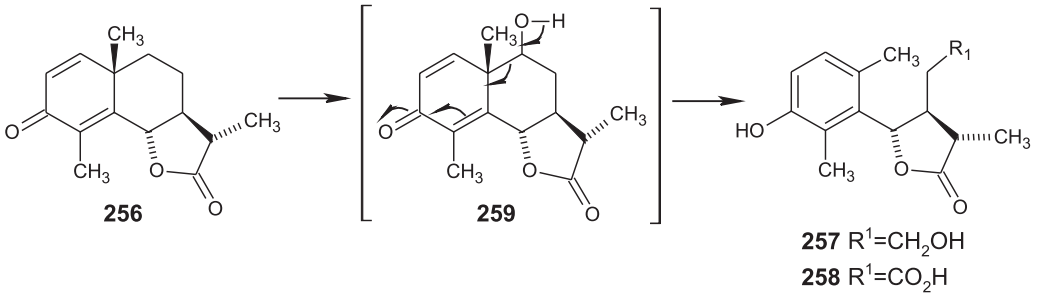


Figure 27. Proposed pathway for production of compounds **257** and **258** through biotransformation of (−)-α-santonin (**256**) by *A. niger* M1L 5024 in the presence of α,α'-dipyridyl.

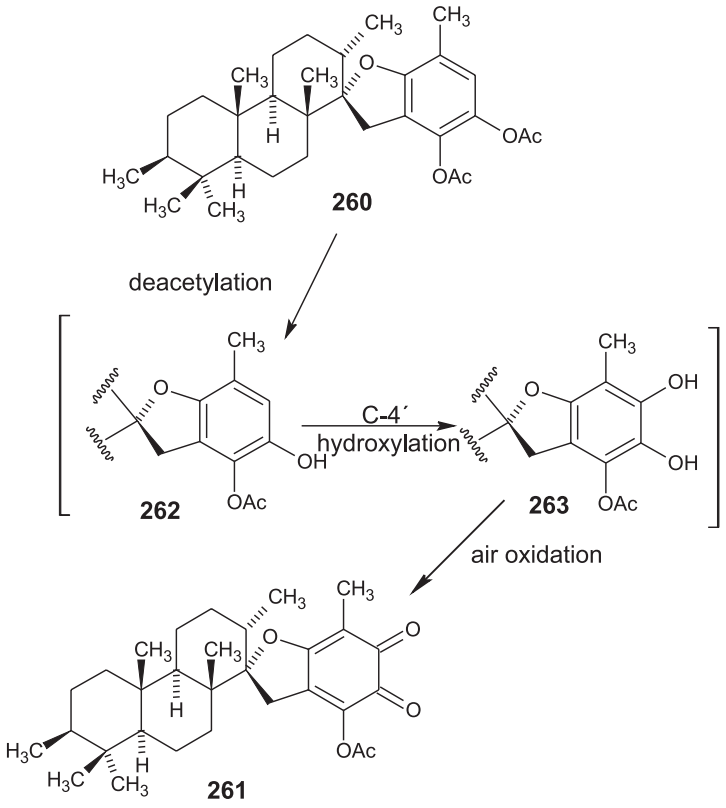


Figure 28. Proposed pathway for production of compound **261** through biotransformation of stypotriol acetate (**260**) by *A. niger* ATCC 16404.

Platycodin D (**264**) is a saponin bearing a 3-*O*-glucose and a 28-*O*-apiose-xylose-rhamnose-arabinose. The microbial transformation of this natural product by *A. niger* KCTC 6906 strain yielded the novel partially degraded platycodin glycoside (**265**) (Figure 29).[161] The cleavage of the sugar at C28 most likely occurred between xylose and rhamnose, resulting in the shorter disaccharide (**265**), lacking the apiose-xylose portion. It is worth mentioning that this was the first example of selective inner-glycosidic bond cleavage by crude microbial enzymes.

6. Conclusion and Future Perspectives

The fundamental and applied scientific investigations of *A. niger* over the last 100 years in the natural product area are extremely diverse. As herein presented, this microorganism was shown as a powerful platform to the biosynthesis of diverse structural classes of compounds, many of them displaying biological properties. In addition, a variety of enzymes from the fungus exhibited regio- and stereoselectivity catalytic activities on biotransformation of natural compounds, yielding unusual derivatives and being considered an alternative to chemical methods. Therefore, the biotechnological potential of *A. niger* highlights this fungus as one of the most important microorganisms for the production of molecules and enzymes of scientific and industrial interest.

The investigation of this fungus and its congeners along those years also brought significant progress to important areas, including taxonomy, genomics, genetics

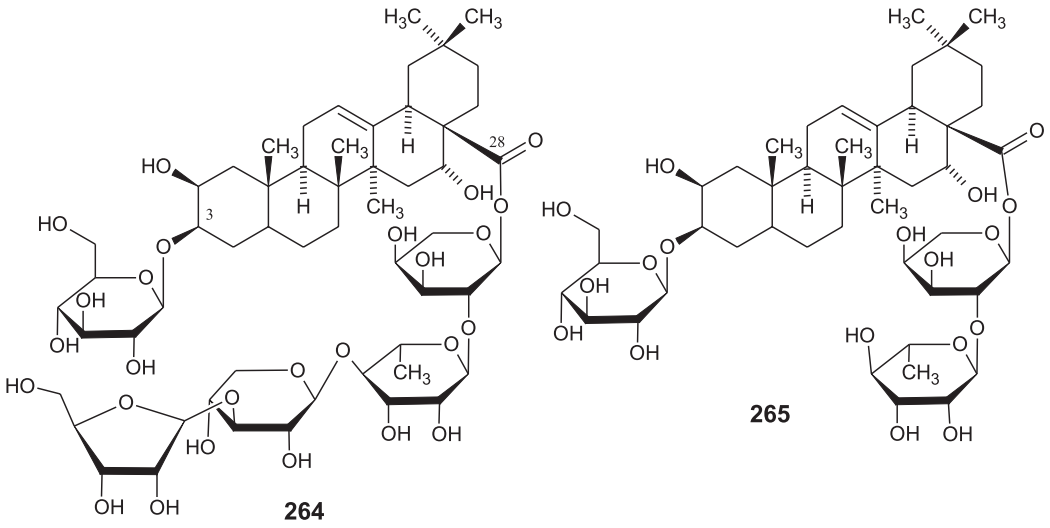


Figure 29. Chemical structures of platycodin D (**264**) and its partially degraded product **265** by *A. niger* KCTC 6906.

and molecular biology. In this latter area, considerable developments occurred in the last decades, allowing gene editing to produce new secondary metabolites.[162] Additionally, this fungus was used as heterologous host microorganism for expressing important enzymes of industrial interest.[162-164]

As previously reported by Sanchez *et al.*,[162] investigation on *Aspergillus* genomes revealed that this genus has potential to produce many more secondary metabolites than those reported so far. In the "omics" era, metabolomics has been considered a powerful strategy for the discovery of natural products, and much progress has been achieved on the investigation of secondary metabolites from fungi.[165] Nevertheless, few examples of the use of metabolomics to assess the metabolite profile of *Aspergillus* strains were found in the literature[166,167] and none of them involved *A. niger*. It is also worth mentioning that despite considerable progress in strategies for waking silenced genes from microorganisms, such as the use of small molecules (epigenetic chemicals) to manipulate the fungal epigenome, few are the examples with *A. niger* and congeners.[168] Additionally, the strategic use of *A. niger* in co-culture approach for producing new compounds lacks more investigative works.[169] Vadlapudi *et al.*[170] reported the development of the *Aspergillus* Secondary Metabolites Database (A2MDB), which contains information on *Aspergillus* and its secondary metabolome. Among the compounds included in this database, 90 of them were exclusively from *A. niger*. Thus, A2MDB will be of great importance in the future investigations on *A. niger* metabolites.

Despite the relevant results found along the years on researches with *A. niger*, that directly contributed to the natural products area, much more progress is expected to be done in the next years with the rapid technological advance on this research field. Therefore, it is presumed that the discovery of still unexpressed genes by *A. niger* continues to be a challenge on the production of new compounds and enzymes.

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