Molecules **2014**, *19*, 7169-7188; doi:10.3390/molecules19067169

OPEN ACCESS

molecules

ISSN 1420-3049

www.mdpi.com/journal/molecules

Review

Bis-naphtho-γ-pyrones from Fungi and Their Bioactivities

Shiqiong Lu [1], Jin Tian [1], Weibo Sun [1], Jiajia Meng [1], Xiaohan Wang [1], Xiaoxiang Fu [1], Ali Wang [1], Daowan Lai [1], Yang Liu [2,*] and Ligang Zhou [1,*]

[1] MOA Key Laboratory of Plant Pathology, Department of Plant Pathology, College of Agronomy and Biotechnology, China Agricultural University, Beijing 100193, China; E-Mails: shiqionglu@126.com (S.L.); pstianjin@cau.edu.cn (J.T.); sunweibo.1001@163.com (W.S.); mengjiajiax@163.com (J.M.); wangxiaohan99@126.com (X.W.); xiaoxiaofu@cau.edu.cn (X.F.); wangali526@163.com (A.W.); dwlai@cau.edu.cn (D.L.)

[2] Institute of Agro-products Processing Science and Technology, Chinese Academy of Agricultural Sciences, Beijing 100193, China

* Authors to whom correspondence should be addressed; E-Mails: liuyang01@caas.cn (Y.L.); lgzhou@cau.edu.cn (L.Z.); Tel.: +86-10-6281-5874 (Y.L.); +86-10-6273-1199 (L.Z.).

Received: 6 May 2014; in revised form: 23 May 2014 / Accepted: 27 May 2014 / Published: 30 May 2014

Abstract: Bis-naphtho-γ-pyrones are an important group of aromatic polyketides derived from fungi. They have a variety of biological activities including cytotoxic, antitumor, antimicrobial, tyrosine kinase and HIV-1 integrase inhibition properties, demonstrating their potential applications in medicine and agriculture. At least 59 bis-naphtho-γ-pyrones from fungi have been reported in the past few decades. This mini-review aims to briefly summarize their occurrence, biosynthesis, and structure, as well as their biological activities. Some considerations regarding to synthesis, production, and medicinal and agricultural applications of bis-naphtho-γ-pyrones are also discussed.

Keywords: bis-naphtho-γ-pyrones; chaetochromin; asperpyrone; nigerone; fungi; biological activities

1. Introduction

Bis-naphtho-γ-pyrones (also known as dimeric naphtho-γ-pyrones, bis(naphtho-γ-pyrone)s, or bis-naphthopyran-4-ones) are an important group of fungal polyketides [1]. The interest of many

investigators in this class of compounds is due to their broad-range biological activities with potential applications in medicine and agriculture [2–4]. Until now, fungal bis-naphtho-γ-pyrones and their biological activities have not been reviewed. This comprehensive mini-review describes the occurrence, biosynthesis, and biological activities of fungal bis-naphtho-γ-pyrones. We also discuss their synthesis, production and applications.

2. Occurrence

Bis-naphtho-γ-pyrones have a diverse distribution in fungi (Tables 1–3). Their structures are shown in Figures 1–3. Based on the diaryl bond connection, bis-naphtho-γ-pyrones can be divided into three types (or groups), namely chaetochromin-, asperpyrone-, and nigerone-type. The absolute configurations of dimeric naphtho-γ-pyrones have been determined by circular dichroism (CD), 2D-NMR as well as X-ray diffraction analysis of some derivatives [5–7]. According to the literature, *R*-configured dimeric naphtho-γ-pyrones exhibit a first negative Cotton effect in the long-wavelength region, and a positive second one at shorter wavelength. On the contrary, *S*-configured dimeric naphtho-γ-pyrones exhibit a positive Cotton effect first in the long-wavelength region, and a negative one second at shorter wavelength [6,8].

To date, twenty-six chaetochromin-type bis-naphtho-γ-pyrones (Table 1 and Figure 1) with C-9-C-9' linkages have been isolated from the genera *Chaetomium*, *Hypocrea*, *Nectria*, *Penicillium*, *Verticillium*, and *Villosiclava* (*Ustilaginoidea*). The absolute configurations of ustilaginoidin A (**15**) and the congeners from *Ustilaginoidea virens* were proved to be *R*, and the congeners of chaetochromin A (**1**) from *Chaetomium* spp. were *S* [9]. Both isochaetochromins B_1 (**5**) and B_2 (**6**) from *Fusarium* sp., *Penicillium* sp. and *Metarhizium anisopliae* were considered as the diastereomers of chaetochromin B (**4**) [10].

Table 1. Occurrence of chaetochromin-type bis-naphtho-γ-pyrones **1**–**26** in fungi.

Bis-naphtho-γ-pyrone	Fungal Species	Reference
Chaetochromin A (**1**)	Endophytic fungus *Chaetomium chiversii*	[11]
	Chaetomium gracile	[10]
	Chaetomium microcephalum	[12]
	Chaetomium virenscens (*C. thielavioideum*)	[13]
Isochaetochromin A_1 (**2**)	*Penicillium* sp. FK I-4942	[14,15]
Isochaetochromin A_2 (**3**)	*Chaetomium microcephalum*	[12]
Chaetochromin B (**4**)	*Chaetomium gracile*	[6,10]
	Chaetomium microcephalum	[12]
Isochaetochromin B_1 (**5**)	Endophytic fungus *Fusarium* sp.	[3]
	Penicillium sp. FKI-4942	[14]
Isochaetochromin B_2 (**6**)	Endophytic fungus *Fusarium* sp.	[3]
	Sponge-derived fungus *Metarhizium anisopliae*	[16]
	Penicillium sp. FKI-4942	[14]
Oxychaetochromin B (**7**)	Endophytic fungus *Fusarium* sp.	[3]
Chaetochromin C (**8**)	*Chaetomium gracile*	[10]
Chaetochromin D (**9**)	*Chaetomium gracile*	[10]
Isochaetochromin D_1 (**10**)	Endophytic fungus *Fusarium* sp.	[3]

Table 1. *Cont.*

Bis-naphtho-γ-pyrone	Fungal Species	Reference
Cephalochromin = Sch 45752 (**11**)	*Cephalosporium* sp.	[17]
	Cosmospora vilior YMJ89051501	[18]
	Nectria flavoviridis	[19]
	Nectria viridescens	[19]
	Endophytic fungus *Pseudoanguillospora* sp.	[20]
	Verticillium sp. K-113	[21]
	Unidentified fungal isolate SCF-125	[22]
Hypochromin A (**12**)	Marine-derived fungus *Hypocrea vinosa*	[23]
Hypochromin B (**13**)	Marine-derived fungus *Hypocrea vinosa*	[23]
SC2051 (**14**)	Marine-derived fungus *Hypocrea vinosa*	[23]
Ustilaginoidin A (**15**)	*Villosiclava virens* (*Ustilaginoidea virens*)	[24]
Isoustilaginoidin A (**16**)	*Verticillium* sp. K-113	[21]
Dihydroisoustilaginoidin A (**17**)	*Verticillium* sp. K-113	[21]
	Unidentified fungal isolate SCF-125	[22]
Ustilaginoidin B (**18**)	*Villosiclava virens* (*Ustilaginoidea virens*)	[25]
Ustilaginoidin C (**19**)	*Villosiclava virens* (*Ustilaginoidea virens*)	[25]
Ustilaginoidin D (**20**)	Sponge-derived fungus *Metarhizium anisopliae*	[16]
	Villosiclava virens (*Ustilaginoidea virens*)	[26]
Ustilaginoidin E (**21**)	*Villosiclava virens* (*Ustilaginoidea virens*)	[26]
Ustilaginoidin F (**22**)	*Villosiclava virens* (*Ustilaginoidea virens*)	[26]
Ustilaginoidin G (**23**)	*Villosiclava virens* (*Ustilaginoidea virens*)	[26]
Ustilaginoidin H (**24**)	*Villosiclava virens* (*Ustilaginoidea virens*)	[26]
Ustilaginoidin I (**25**)	*Villosiclava virens* (*Ustilaginoidea virens*)	[26]
Ustilaginoidin J (**26**)	*Villosiclava virens* (*Ustilaginoidea virens*)	[26]

Figure 1. Structures of chaetochromin-type bis-naphtho-γ-pyrones (**1**–**26**) from fungi.

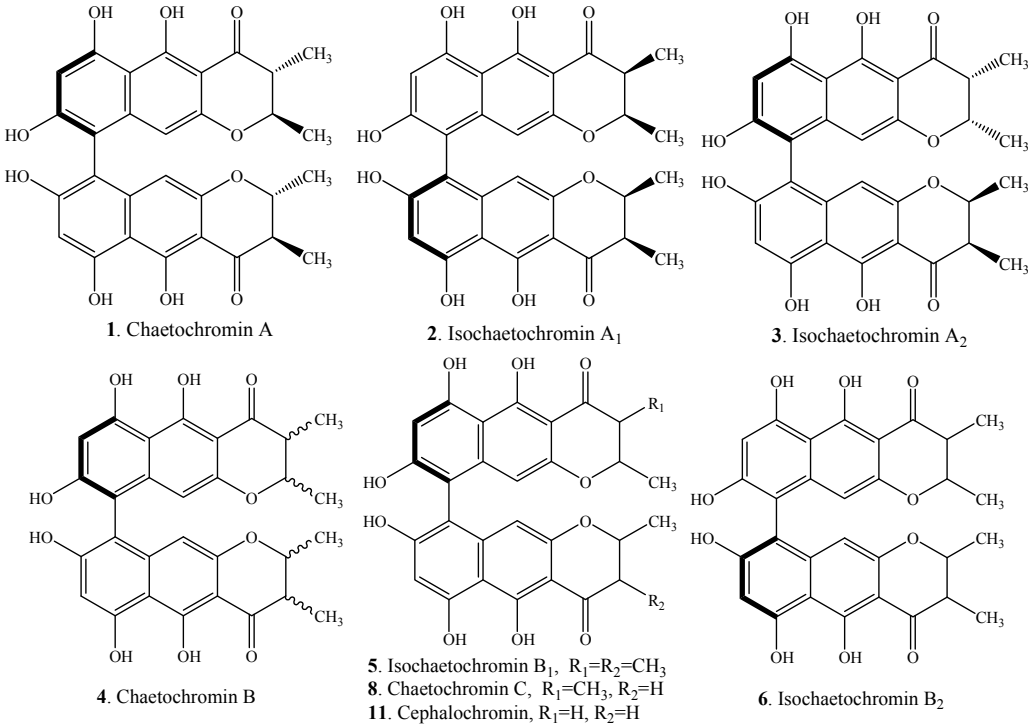
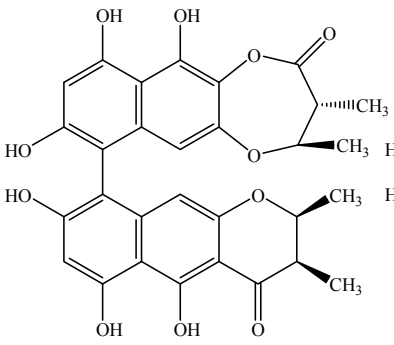
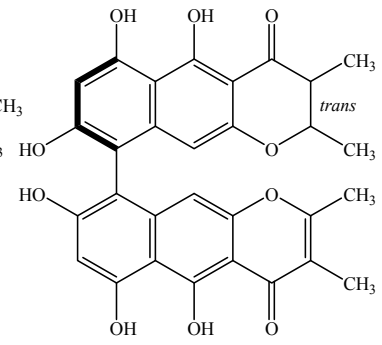


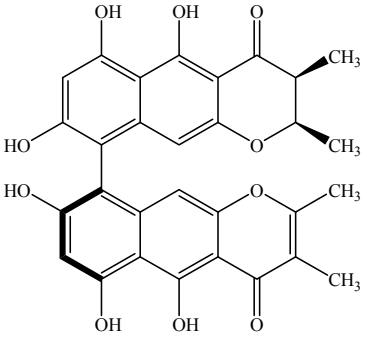
Figure 1. *Cont.*



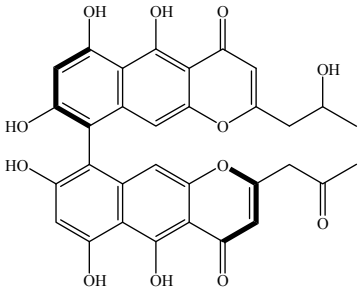
7. Oxychaetochromin B



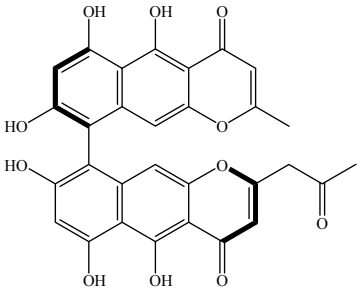
9. Chaetochromin D



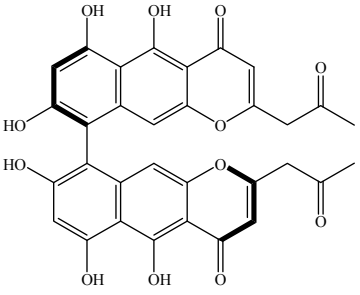
10. Isochaetochromin D_1



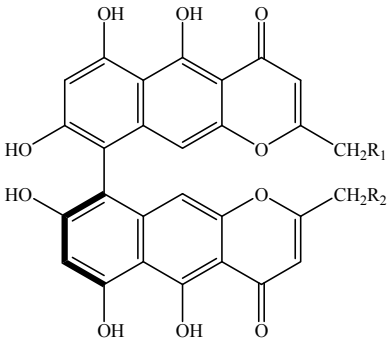
12. Hypochromin A



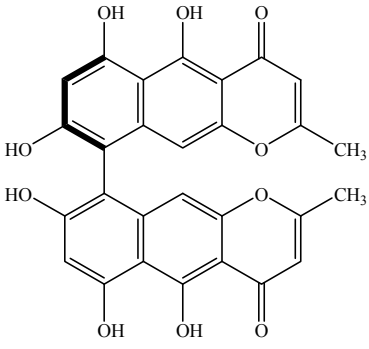
13. Hyprochromin B



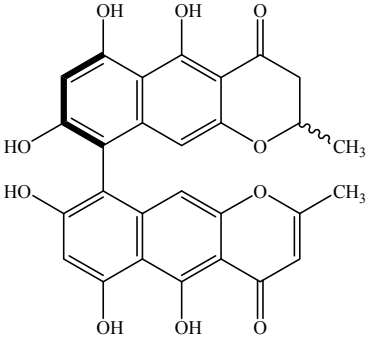
14. SC2051



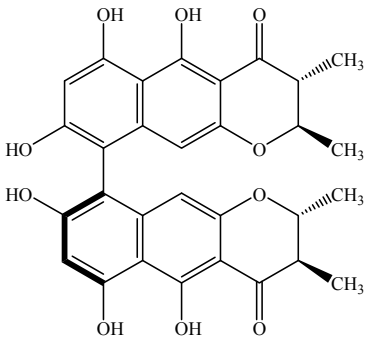
15. Ustilaginoidin A, R_1=R_2=H
18. Ustilaginoidin B, R_1=H, R_2=OH
19. Ustilaginoidin C, R_1=R_2=OH



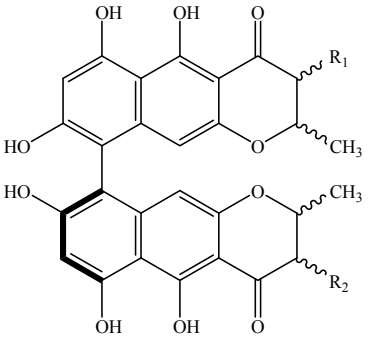
16. Isoustilaginoidin A



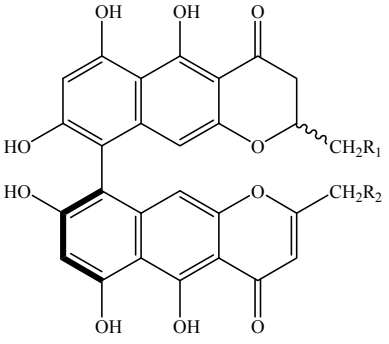
17. Dihydroisoustilaginoidin A



20. Ustilaginoidin D



21. Ustilaginoidin E, R_1=H, R_2=CH_3
22. Ustilaginoidin F, R_1=R_2=H



23. Ustilaginoidin G, R_1=R_2=H
24. Ustilaginoidin H, R_1=H, R_2=OH
25. Ustilaginoidin I, R_1=OH, R_2=H
26. Ustilaginoidin J, R_1=R_2=OH

Twenty-seven asperpyrone-type bis-naphtho-γ-pyrones (Table 2 and Figure 2) with C-10-C-7' or C-10-C-9' or C-6-C-7' or C-6-C-9' linkages have been isolated from the genera *Alternaria* and *Aspergillus*.

Aurasperone A (**32**) is a 10,7'-bisnaphtho-γ-pyrone from *Alternaria alternata* [27] and a few *Aspergillus* species [4,28–33]. This compound clearly has a positive Cotton effect first in the long wavelength region, and a negative one second at shorter wavelength, indicating positive chirality of the chromophores and the *S*-configuration of the compound [6]. The absolute configurations for some asperpyrone-type bis-naphtho-γ-pyrones remain to be determined.

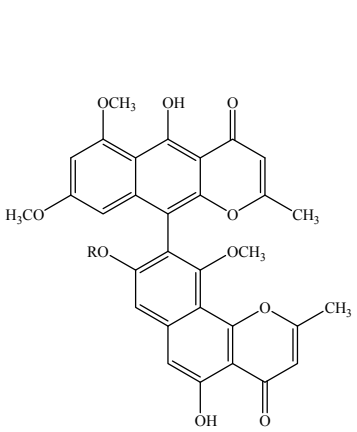
Table 2. Occurrence of asperpyrone-type bis-naphtho-γ-pyrones **27**–**53** in fungi.

Bis-naphtho-γ-pyrone	Fungal Species	Reference
Asperpyrone A (**27**)	Endophytic fungus *Aspergillus* sp.	[34]
	Endophytic fungus *Aspergillus* sp. DCS31	[35]
	Aspergillus niger	[30]
	Endophytic fungus *Aspergillus niger*	[8]
	Endophytic fungus *Aspergillus tubingensis*	[36]
Asperpyrone B (**28**)	*Aspergillus niger*	[30]
	Aspergillus niger IFB-E003	[31]
	Aspergillus niger ATCC 11414	[33]
Asperpyrone C (**29**)	*Aspergillus niger*	[30]
Asperpyrone D (**30**)	Endophytic fungus *Aspergillus* sp. DCS31	[35]
	Endophytic fungus *Aspergillus niger*	[8]
	Endophytic fungus *Aspergillus tubingensis*	[36]
Asperpyrone E (**31**)	Endophytic fungus *Aspergillus niger*	[8]
Aurasperone A (**32**)	*Alternaria alternata*	[27]
	Aspergillus sp. FKI-3451	[4]
	Aspergillus awamori	[28,37]
	Endophytic fungus *Aspergillus auleatus*	[32]
	Aspergillus fonsecaeus	[29]
	Aspergillus niger	[28,37]
	Aspergillus niger	[38]
	Aspergillus niger	[30]
	Aspergillus niger IFB-E003	[31]
	Aspergillus niger ATCC 11414	[33]
	Endophytic fungus *Aspergillus tubingensis*	[36]
Isoaurasperone A (**33**)	Endophytic fungus *Aspergillus* sp.	[34]
	Aspergillus niger	[38]
	Endophytic fungus *Aspergillus niger*	[8]
Aurasperone B (**34**)	*Alternaria alternata*	[27]
	Aspergillus sp. FKI-3451	[4]
	Aspergillus awamori	[28,39]
	Aspergillus fonsecaeus	[29]
	Aspergillus niger	[28,39]
	Aspergillus niger	[38]
	Aspergillus niger ATCC 11414	[33]
	Aspergillus niger C-433	[40]

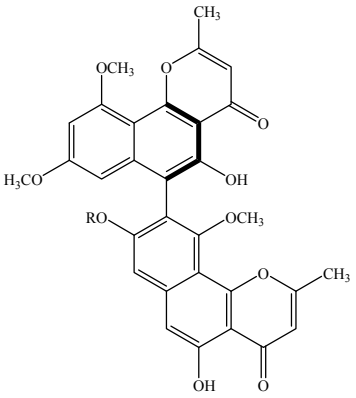
Table 2. *Cont.*

Bis-naphtho-γ-pyrone	Fungal Species	Reference
Aurasperone B (**34**)	*Aspergillus niger* ATCC 11414	[33]
	Aspergillus vadensis	[41]
Aurasperone C (**35**)	*Alternaria alternata*	[27]
	Aspergillus awamori	[28,39]
	Aspergillus niger	[28,39]
	Aspergillus niger	[38]
	Aspergillus niger C-433	[40]
	Aspergillus niger ATCC 11414	[33]
Dianhydro-aurasperone C (**36**)	Endophytic fungus *Aspergillus* sp.	[34]
	Aspergillus niger	[38]
	Endophytic fungus *Aspergillus niger*	[8]
	Endophytic fungus *Aspergillus tubingensis*	[36]
Aurasperone D (**37**)	*Aspergillus niger*	[42]
	Aspergillus niger	[38]
	Endophytic fungus *Aspergillus niger*	[8]
	Aspergillus niger C-433	[40]
Aurasperone E (**38**)	*Aspergillus niger*	[38]
	Aspergillus niger C-433	[40]
	Endophytic fungus *Aspergillus tubingensis*	[36]
Aurasperone F (**39**)	*Alternaria alternata*	[27]
	Aspergillus niger C-433	[40,43]
Isoaurasperone F (**40**)	Endophytic fungus *Aspergillus niger*	[8]
Aurasperone G (**41**)	*Aspergillus niger* C-433	[43]
Fonsecinone A (**42**)	Endophytic fungus *Aspergillus* sp.	[34]
	Endophytic fungus *Aspergillus auleatus*	[32]
	Aspergillus fonsecaeus	[29]
	Aspergillus niger	[30]
	Aspergillus niger IFB-E003	[31]
	Aspergillus niger ATCC 11414	[33]
	Endophytic fungus *Aspergillus tubingensis*	[36]
	Endophytic fungus *Cladosporium herbarum* IFB-E002	[44]
Fonsecinone B (**43**)	*Aspergillus fonsecaeus*	[29]
	Aspergillus niger ATCC 11414	[33]
Fonsecinone C (**44**)	*Aspergillus fonsecaeus*	[29]
	Aspergillus niger ATCC 11414	[33]
Fonsecinone D (**45**)	*Aspergillus fonsecaeus*	[29]
Nigerasperone B (**46**)	*Aspergillus niger* EN-13	[45]
Nigerasperone C (**47**)	*Aspergillus niger* EN-13	[45]
Rubasperone A (**48**)	Endophytic fungus *Aspergillus tubingensis*	[46]
Rubasperone B (**49**)	Endophytic fungus *Aspergillus tubingensis*	[46]
Rubasperone C (**50**)	Endophytic fungus *Aspergillus tubingensis*	[46]
Rubasperone D (**51**)	Endophytic fungus *Aspergillus tubingensis* (GX1-5E)	[47]
Rubasperone E (**52**)	Endophytic fungus *Aspergillus tubingensis* (GX1-5E)	[47]
Rubasperone F (**53**)	Endophytic fungus *Aspergillus tubingensis* (GX1-5E)	[47]

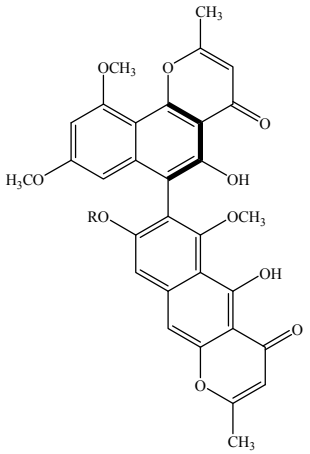
Figure 2. Structures of asperpyrone-type bis-naphtho-γ-pyrones (**27**–**53**) from fungi.



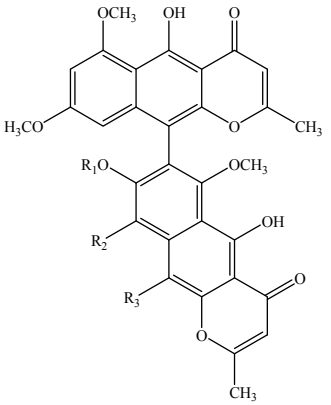
27. Asperpyrone A, R = H
42. Fonsecinone A, R = CH_3



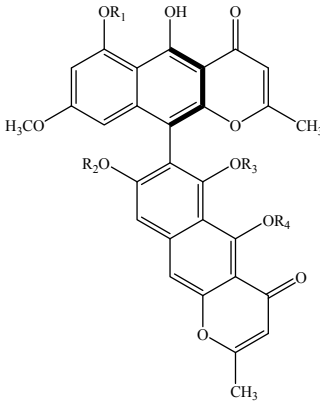
28. Asperpyrone B, R = CH_3
31. Asperpyrone E, R = H



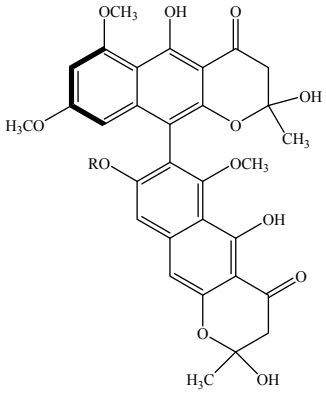
29. Asperpyrone C, R = CH_3
30. Asperpyrone D, R = H



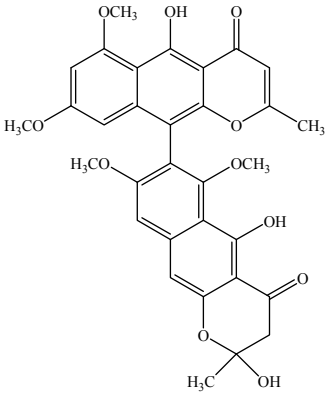
32. Aurasperone A, R_1=CH_3, R_2=H, R_3=H
41. Aurasperone G, R_1=H, R_2=OH, R_3=OH



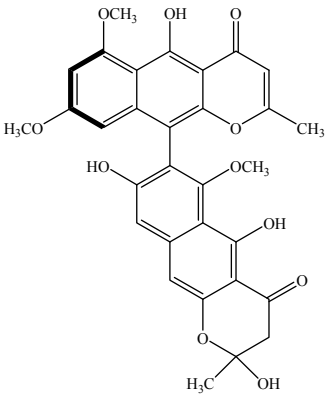
33. Isoaurasperone A, R_1=CH_3, R_2=CH_3, R_3=H, R_4=CH_3
36. Dianhydroaurasperone C, R_1=CH_3, R_2=H, R_3=CH_3, R_4=H
37. Aurasperone D, R_1=H, R_2=CH_3, R_3=CH_3, R_4=H



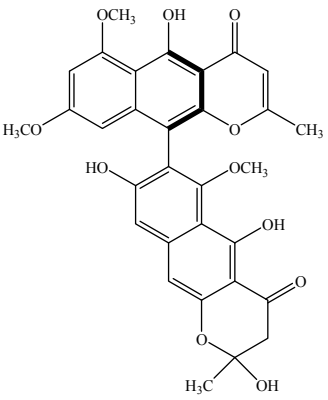
34. Aurasperone B, R = CH_3
35. Aurasperone C, R = H



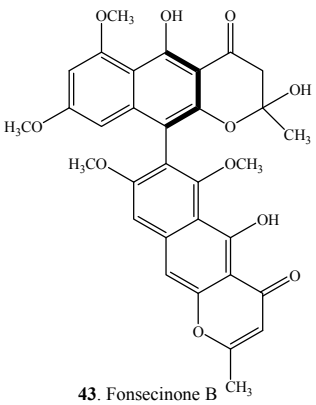
38. Aurasperone E



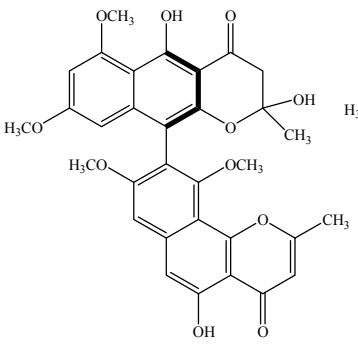
39. Aurasperone F



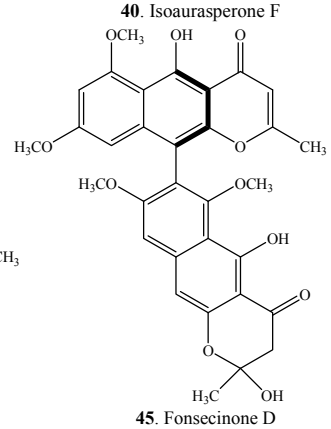
40. Isoaurasperone F



43. Fonsecinone B

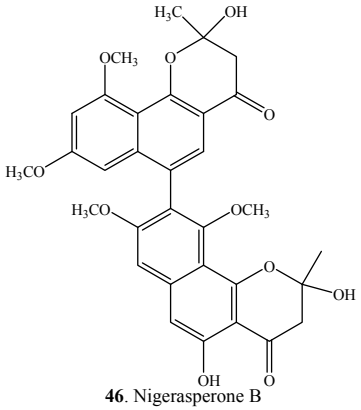


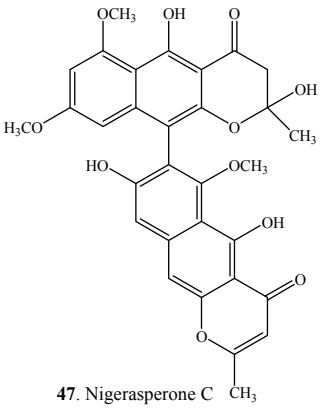
44. Fonsecinone C

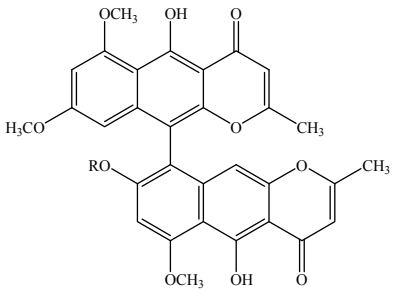


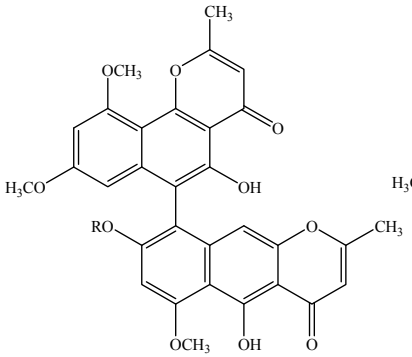
45. Fonsecinone D

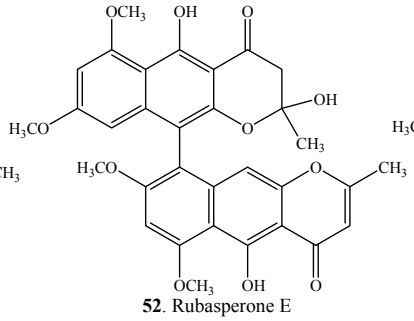
Figure 2. *Cont.*

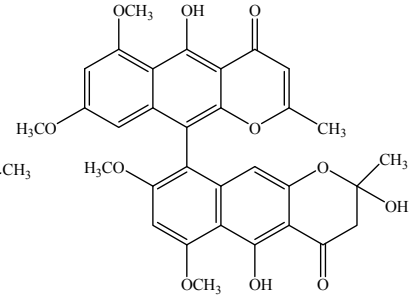

46. Nigerasperone B


47. Nigerasperone C


48. Rubasperone A, R = H
49. Rubasperone B, R = CH_3


50. Rubasperone C, R = CH_3
51. Rubasperone D, R = H


52. Rubasperone E


53. Rubasperones F

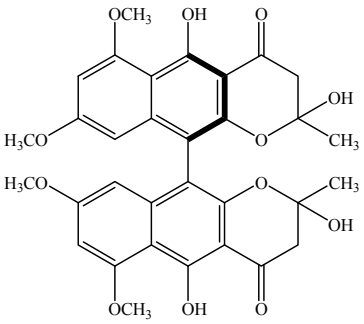
Six nigerone-type bis-naphtho-γ-pyrones (**54**–**59**) with C-10-C-10' or C-10-C-6' linkages have been isolated from the genus *Aspergillus* [5,7]. All these bis-naphtho-γ-pyrones have *R*-configurations of the 10-10' or 10-6' bonds.

It is worth mentioning that both asperpyrone and nigerone types of bis-naphtho-γ-pyrones are produced primarily by *Aspergillus* species where chaetochromin-type bis-naphtho-γ-pyrones do not distribute. This indicates that bis-naphtho-γ-pyrones should have taxonomic significance which needs to be further investigated [41]. Each fungal species also needs to be clearly identified [48–50].

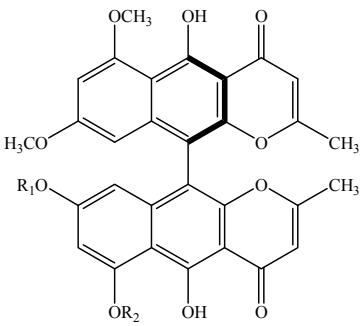
Table 3. Occurrence of nigerone-type bis-naphtho-γ-pyrones **54**–**59** in fungi.

Bis-naphtho-γ-pyrone	Fungal Species	Reference
10,10'-Bifonsecin B (**54**)	Marine-derived fungus *Aspergillus carbonarius*	[7]
Nigerone (**55**)	Marine-derived fungus *Aspergillus carbonarius*	[7]
	Aspergillus niger	[5]
6'-*O*-Demethylnigerone (**56**)	Marine-derived fungus *Aspergillus carbonarius*	[7]
	Aspergillus niger	[5]
8'-*O*-Demethylnigerone (**57**)	Marine-derived fungus *Aspergillus carbonarius*	[7]
8'-*O*-Demethylisonigerone (**58**)	Marine-derived fungus *Aspergillus carbonarius*	[7]
Isonigerone (**59**)	Marine-derived fungus *Aspergillus carbonarius*	[7]
	Aspergillus niger	[5]

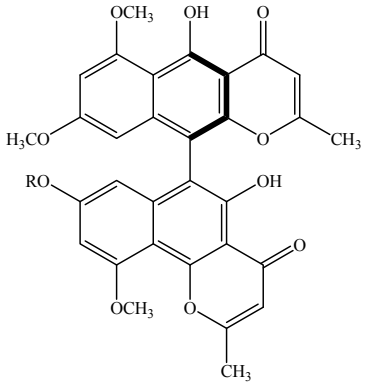
Figure 3. Structures of nigerone-type bis-naphtho-γ-pyrones (**54**–**59**) from fungi.



54. 10,10'-Bifonsecin B



55. Nigerone, R_1=CH_3, R_2=CH_3
56. 6'-*O*-Demethylnigerone, R_1=CH_3, R_2=H
57. 8'-*O*-Demethylnigerone, R_1=H, R_2=CH_3



58. 8'-*O*-Demethylisonigerone, R=H
59. Isonigerone, R=CH_3

3. Biosynthesis

Chaetochromin A (**1**) was the first bis-naphtho-γ-pyrone whose biosynthesis was studied by employing the fungus *Chaetomium gracile*. Both acetate and malonate were confirmed as the precursors in the biosynthesis of chaetochromin A (**1**) by employing *Chaetomium gracile* and addition of the carbon-13 labelled precussors [51]. The proposed biosynthetic pathway (Scheme 1) of asperpyrone-type bis-naphtho-γ-pyrones in the fungus *Aspergillus niger* was outlined by Chiang *et al.* [33]. The aromatic structure of naphtho-γ-pyrones suggests that a non-reducing polyketide synthase (NR-PKS) gene with the following domain organization is likely responsible for their biosynthesis: starter unit ACP transacylase (SAT), β-ketoacyl synthase (KS), acyl transferase (AT), product template (PT), acyl carrier protein (ACP), and thiolesterase/Claisen-cyclase (TE/CLC) [33]. Linear naphtho-γ-pyrone YWA1 (**61**) was known in equilibrium with the side-chain open form (**60**). After recyclization, angular naphtho-γ-pyrone **62** could be formed in the presence of C-14 phenol group (Scheme 1). The irreversible dehydration of hemiketal from aurasperone B (**34**) produced stable dimeric naphtho-γ-pyrones fonsecinone B (**43**) and aurasperone A (**32**). Table 4 shows some monomeric naphtho-γ-pyrones such as rubrofusarin B (**65**), fonsecin (**67**), fonsecin B (**68**) and flavasperone (**72**) which were considered as the intermediates in the biosynthesis of bis-naphtho-γ-pyrones in fungi [38]. Accordingly, the structures of these proposed intermediates are shown in Figure 4.

Table 4. Some monomeric naphtho-γ-pyrones **63**–**76** from fungi.

Monomeric Naphtho-γ-pyrone	Fungal Species	Reference
Nigerasperone A (**63**)	*Aspergillus niger* EN-13	[45]
Rubrofusarin (**64**)	*Aspergillus niger*	[38]
Rubrofusarin B = Heminigerone (**65**)	Endophytic fungus *Aspergillus tubingensis* GX1-5E	[46]
	Alternaria alternata	[27]
	Endophytic fungus *Aspergillus* sp.	[34]
	Endophytic fungus *Aspergillus niger* IFB-E003	[31]
	Marine-derived fungus *Aspergillus carbonarius*	[7]

Table 4. *Cont.*

Monomeric Naphtho-γ-pyrone	Fungal Species	Reference
	Aspergillus niger var. *niger* TC 1629	[52]
	Endophytic fungus *Aspergillus tubingensis* GX1-5E	[46]
	Endophytic fungus *Aspergillus tubingensis* NRRC 4700	[36]
	Endophytic fungus *Cladosporium herbarum* IFB-E002	[44]
Rubrofusarin-6-*O*-α-D-ribofuranoside (**66**)	Endophytic fungus *Aspergillus niger*	[8]
Fonsecin (**67**)	*Alternaria alternata*	[27]
	Marine-derived fungus *Aspergillus carbonarius*	[7]
	Aspergillus niger	[38]
	Aspergillus niger C-433	[40]
	Aspergillus niger var. *niger* TC 1629	[52]
	Endophytic fungus *Aspergillus tubingensis* GX1-5E	[47]
	Endophytic fungus *Aspergillus tubingensis* NRRC 4700	[36]
Fonsecin B = Fonsecin monomethyl ether (**68**)	*Alternaria alternata*	[27]
	Aspergillus niger	[38]
	Aspergillus niger var. *niger* TC 1629	[52]
	Endophytic fungus *Aspergillus tubingensis* NRRC 4700	[36]
TMC-256A1 (**69**)	Marine-derived fungus *Aspergillus carbonarius*	[7]
	Aspergillus niger var. *niger* TC 1629	[52]
	Endophytic fungus *Aspergillus tubingensis* GX1-5E	[46]
	Endophytic fungus *Aspergillus tubingensis* NRRC 4700	[36]
(*R*)-10-(3-succinimidyl)-TMC-256A1 (**70**)	Endophytic fungus *Aspergillus niger*	[8]
TMC-256C1 (**71**)	*Aspergillus niger* var. *niger* TC 1629	[52]
Flavasperone = Asperxanthon = TMC-256C2 (**72**)	Endophytic fungus *Aspergillus* sp. DCS31	[35]
	Aspergillus sp. FKI-3451	[4]
	Marine-derived fungus *Aspergillus carbonarius*	[7]
	Aspergillus niger	[38]
	Aspergillus niger var. *niger* TC 1629	[52]
	Endophytic fungus *Aspergillus tubingensis*	[47]
Indigotide B (**73**)	Entomopathogenic fungus *Cordyceps indigotica*	[53]
	Sponge-derived fungus *Metarhizium anisopliae* mxh-99	[16]
8-*O*-Methylindigotide B (**74**)	Entomopathogenic fungus *Cordyceps indigotica*	[53]
Indigotide G (**75**)	Sponge-derived fungus *Metarhizium anisopliae* mxh-99	[16]
Indigotide H (**76**)	Sponge-derived fungus *Metarhizium anisopliae* mxh-99	[16]

Scheme 1. Proposed biosynthetic pathway of asperpyrone-type bis-naphtho-γ-pyrones in *Aspergillus niger* [33].

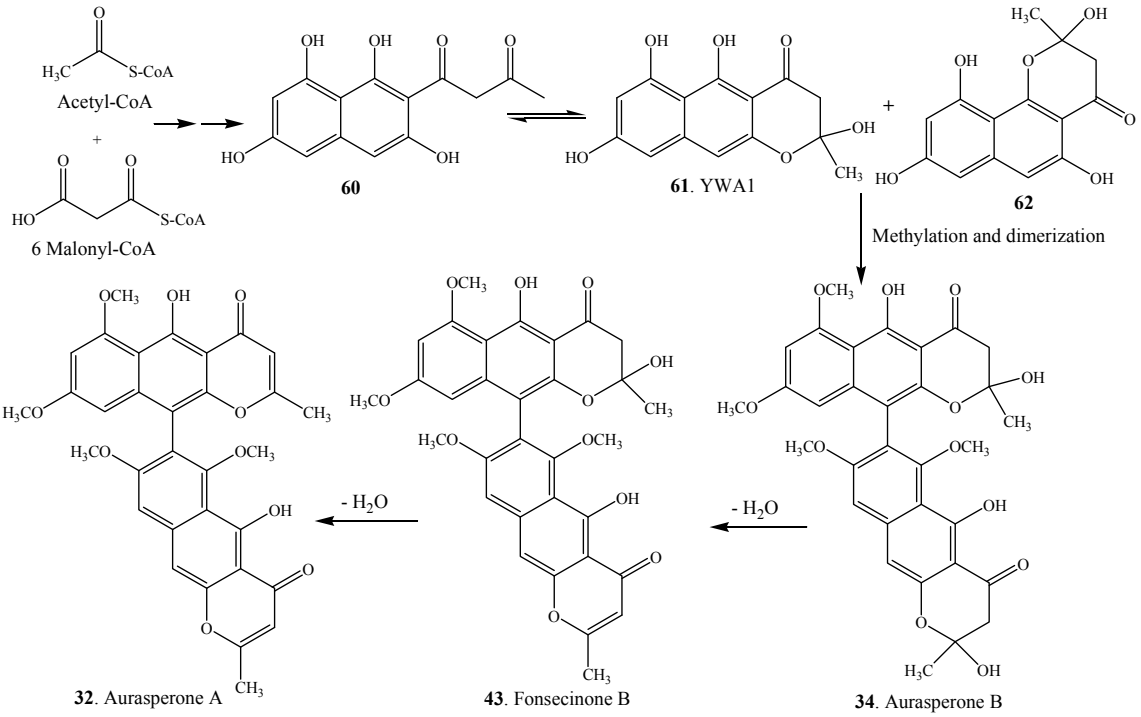
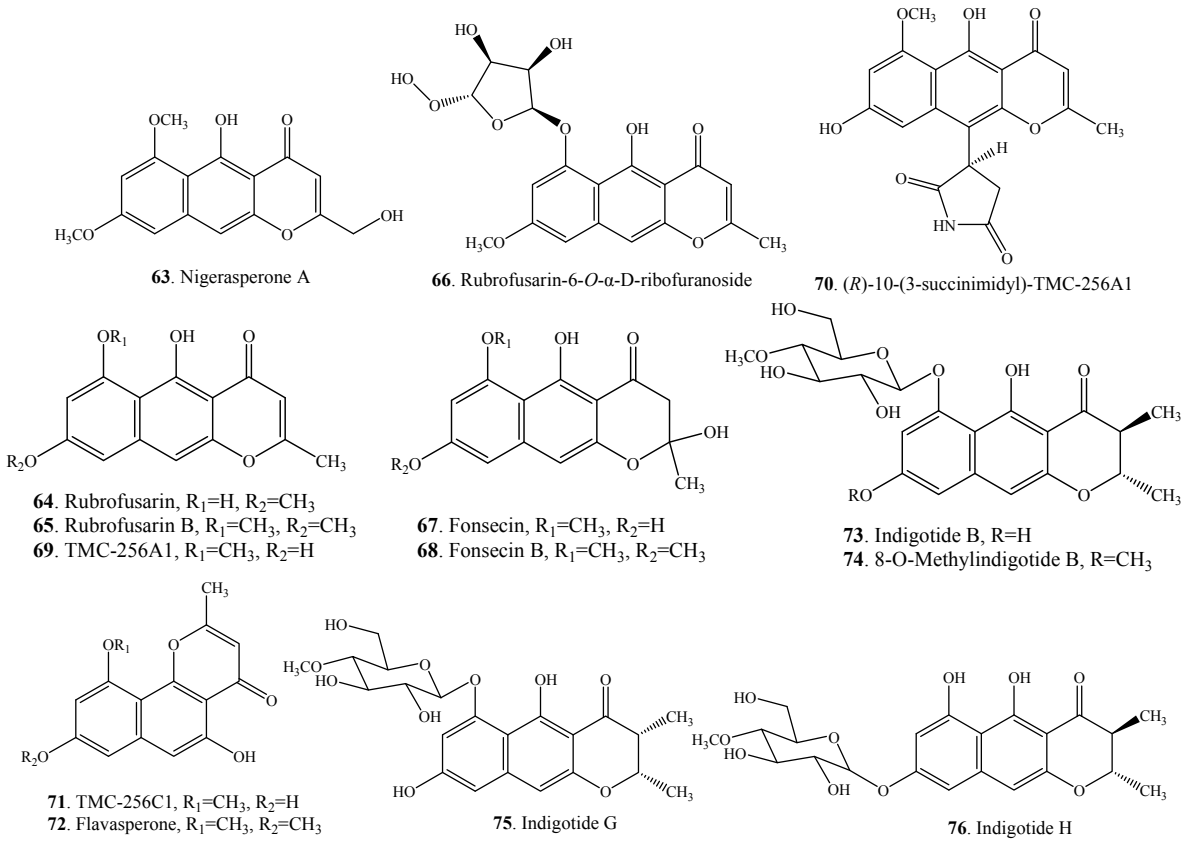


Figure 4. Structures of some monomeric naphtho-γ-pyrones **63**–**76** from fungi.



4. Biological Activities

Bis-naphtho-γ-pyrones have a broad-range of biological activities such as cytotoxic, antitumor and antimicrobial properties, which are outlined in Table 5.

4.1. Cytotoxic and Antitumor Activity

Chaetochromins A (**1**) and D (**9**) from *Chaetomium* sp. showed strong cytotoxicity with IC_{50} values ranging from 0.13 to 0.24 μg/mL in cell cultures of mouse embryo limb bud (LB) and midbrain (MB). Ustilaginoidin A (**15**) from *Ustilaginoidea virens* showed relatively weak cytotoxic activity [54]. Chaetochromins A (**1**), B (**4**), C (**8**) and D (**9**) exhibited strong cytotoxicity on KB cells by inhibiting deoxyribonucleic acid, ribonucleic acid and protein biosynthesis [2]. Further mechanism of action investigations for chaetochromin A (**1**) revealed that the ATP synthesis in mitochondria was inhibited by uncoupling oxidative phosphorylation and depressing state-3 respiration of mitochondria, which may explain their cytotoxicity and *in vivo* toxicity to animals [55].

Both ustilaginoidins D (**20**) and E (**21**) exhibited strong cytotoxicity on KB cells by inhibiting biosynthesis of nucleic acid and protein [2]. Ustilaginoidin A (**15**) also inhibited ATP synthesis in mitochondria by uncoupling oxidative phosphorylation and depressing state-3 respiration of mitochondria [55].

Cephalochromin (**11**) exhibited growth-inhibitory and apoptotic activity against human lung cancer A549 cells in a dose-dependent manner with an IC_{50} value of 2.8 μM at 48 h. Cephalochromin induced cell cycle arrest at the G0/G1 phase through down-regulation of cyclin D1, cyclin E, Cdk 2, and Cdk 4 expressions. It markedly increased the hypodiploid sub-G1 phase (apoptosis) of the cell cycle at 48 h as measured by flow cytometric analysis. Reactive oxygen species generation and loss of the mitochondrial membrane potential (MMP) were also markedly induced by cephalochromin [18]. Cephalochromin (**11**) also inhibited ATP synthesis in mitochondria by uncoupling oxidative phosphorylation and depressing state-3 respiration of mitochondria [55].

4.2. Antimicrobial Activity

Isochaetochromin B_2 (**6**) and ustilaginoidin D (**20**) isolated from the sponge-derived fungus *Metarhizium anisopliae* mxh-99 exhibited anti-tubercular activity with MIC values of 50.0 μg/mL [16]. 8'-*O*-Demethylnigerone (**57**) and 8'-*O*-demethylisonigerone (**58**) from the marine-derived *Aspergillus carbonarius* also showed weak anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv with MIC values of 43.0 and 21.5 μM, respectively [7].

Cephalochromin (**11**), isoustilaginoidin A (**16**), and dihydroisoustilaginoidin A (**17**) isolated from *Verticillium* sp. K-113 were active against Gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*, and *Streptococcus pyogenes*) with MIC values ranging from 3 to 10 μg/mL, but not against Gram-negative bacteria and fungi [21]. Chaetochromin A (**1**), isochaetochromin A_2 (**3**), and chaetochromin B (**4**) possessed significant antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis* [12]. Asperpyrone B (**28**), aurasperone A (**32**) and fonscinone A (**42**) isolated from the endophytic fungus *Aspergillus niger* IFB-E003 exhibited growth inhibition against bacteria

(*Bacilllus subtilis*, *Escherichia coli* and *Pseudomonas fluorescence*) and fungi (*Trichophyton rubrum* and *Candida albicans*) with MIC values ranging from 1.9 to 31.2 μg/mL [31].

Asperpyrone A (**27**), isoaurasperone A (**33**), dianhydroaurasperone C (**36**), and fonsecinone A (**42**) from an endophytic *Aspergillus* species showed antimicrobial activities. Among them, fonsecinone A (**42**) exhibited the strongest antifungal and antibacterial activity, with MIC values of 12.5 and 25 μM, respectively [34].

Bacterial enoyl-acyl carrier protein reductase (FabI) in bacterial fatty acid synthesis has been demonstrated to be an antibacterial target [56]. Cephalochromin (**11**) inhibited FabI of *Staphylococcus aureus* and *Escherichia coli* with IC_{50} values of 1.9 and 1.8 μM, respectively [57].

4.3. Other Biological Activities

In addition to the cytotoxic, antitumor and antimicrobial activities of bis-nathphtho-γ-pyrones mentioned above, other biological activities include tyrosine kinase inhibition [23], HIV-1 integrase inhibition [3], calmodulin-sensitive cycle nucleotide phosphodiestease inhibition [22], triacylglycerol synthesis inhibition [14], xanthine oxidase inhibition [31], acyl-CoA:cholesterol acyltransferase inhibition [4], central nerveous system depressant effects [42], immunological activity [12], botulinum neutotoxin serotype A inhibition [57], drug resistance-reversing activity [58], and *Taq* DNA polymerase inhibition [30], which are outlined in Table 5.

Table 5. Biological activities of bis-naphtho-γ-pyrones from fungi.

Bis-naphtho-γ-pyrone	Biological Activity	Reference
Chaetochromin A (**1**)	Cytotoxic and antitumor activity	[2,54,55]
	Teratogenicity to mice embryo	[59]
	Inhibitory effects on nitric oxide (NO) production by activated macrophages	[60]
	Antibacterial activity	[12]
	Immunological activity	[12]
	Inhibitory activity on botulinum neurotoxin serotype A	[58]
Isochaetochromin A_1 (**2**)	Inhibitory activity on triacylglycerol synthesis	[14]
Isochaetochromin A_2 (**3**)	Antibacterial activity	[12]
	Immunological activity	[12]
Chaetochromin B (**4**)	Cytotoxic and antitumor activity	[2,54]
	Antibacterial activity	[12]
	Immunological activity	[12]
Isochaetochromin B_1 (**5**)	HIV-1 integrase inhibitory activity	[3]
	Inhibitory activity on triacylglycerol synthesis	[14]
Isochaetochromin B_2 (**6**)	Anti-tubercular activity	[16]
	HIV-1 integrase inhibitory activity	[3]
	Inhibitory activity on triacylglycerol synthesis	[14]
Oxychaetochromin B (**7**)	HIV-1 integrase inhibitory activity	[3]
Chaetochromin C (**8**)	Cytotoxic and antitumor activity	[2,54]

Table 5. *Cont.*

Bis-naphtho-γ-pyrone	Biological Activity	Reference
Chaetochromin D (**9**)	Cytotoxic and antitumor activity	[2,54]
	Impairing effects on mitochondrial respiration and structure	[61]
Chaetochromin D_1 (**10**)	HIV-1 integrase inhibitory activity	[3]
Cephalochromin (**11**)	Cytotoxic and antitumor activity	[18,55]
	Inhibitory effects on nitric oxide (NO) production by activated macrophages	[57]
	Antimicrobial activity	[21,57]
	Inhibitory activity on calmodulin-sensitive cyclic nucleotide phosphodiestease	[22]
	Inhibitory activity on botulinum neurotoxin serotype A	[58]
Hypochromin A (**12**)	Tyrosine kinase inhibitory activity	[23]
Hypochromin B (**13**)	Tyrosine kinase inhibitory activity	[23]
SC2051 (**14**)	Tyrosine kinase inhibitory activity	[23]
Ustilaginoidin A (**15**)	Cytotoxic and antitumor activity	[54,55]
Isoustilaginoidin A (**16**)	Antimicrobial activity	[21]
Dihydroisoustilaginoidin A (**17**)	Antimicrobial activity	[21]
	Inhibitory effects on nitric oxide (NO) production by activated macrophages	[62]
Ustilaginoidin D (**20**)	Cytotoxic and antitumor activity	[2]
	Anti-tubercular activity	[16]
Ustilaginoidin E (**21**)	Cytotoxic and antitumor activity	[2]
Asperpyrone A (**27**)	Antimicrobial activity	[34]
	Inhibitory activity on *Taq* DNA polymerase	[30]
Asperpyrone B (**28**)	Antimicrobial activity	[31]
Aurasperone A (**32**)	Antimicrobial activity	[31]
	Inhibitory activity on xanthine oxidase	[31]
	Inhibitory activity on acyl-CoA:cholesterol acyltransferase	[4]
	Inhibitory activity on *Taq* DNA polymerase	[30]
Isoaurasperone A (**33**)	Antimicrobial activity	[34]
Dianhydro-aurasperone C (**36**)	Antibacterial activity	[34]
	Drug resistance-reversing activity	[59]
Aurasperone D (**37**)	Central nervous system depressant effects	[42]
	Inhibitory activity on acyl-CoA:cholesterol acyltransferase	[4]
Fonscinone A (**42**)	Antimicrobial activity	[31,34]
	Inhibitory activity on *Taq* DNA polymerase	[30]
8'-*O*-Demethylnigerone (**57**)	Anti-tubercular activity	[7]
8'-*O*-Demethylisonigerone (**58**)	Anti-tubercular activity	[7]

5. Conclusions and Future Perspectives

About 59 fungal bis-naphtho-γ-pyrones have been investigated in the past few decades. Some of them display diverse bioactivities, especially cytotoxic, antitumor and antimicrobial activities. The remaining bis-naphtho-γ-pyrones produced by fungi and their bioactivities need to be further studied. In recent years, an increasing number of bis-naphtho-γ-pyrones have been isolated from endophytic

fungi [3,10,20] and marine-derived fungi [7,16,23]. These fungi could be the rich sources of biologically active metabolites that are indispensable for medicinal and agricultural applications [1,63–66]. In most cases, biological activities, structure-activity relationships, and mode of action of bis-naphtho-γ-pyrones have been only primarily investigated and need to be studied in detail. The potential applications of bis-naphtho-γ-pyrones as antitumor agents, antimicrobials, and antivirus agents as well as their promising bioactivities have led to considerable interest within the pharmaceutical community. Chemical syntheses have been achieved for a few bioactive bis-naphtho-γ-pyrones such as ustilaginoidin A (**15**) [67] and nigerone (**55**) [68,69]. After comprehensive understanding of biosynthetic pathways of some bis-naphtho-γ-pyrones in the next few years, we can effectively not only increase yields of the bioactive bis-naphtho-γ-pyrones (*i.e.*, cephalochromin, isochaetochromins B_1 and B_2), but also prevent biosynthesis of some toxic bis-naphtho-γ-pyrones (*i.e*., ustilaginoidins A–J) [70]. In addition, the physiological and ecological roles of the bis-naphtho-γ-pyrones in fungi need to be clarified in detail [71,72].

Acknowledgments

This work was co-financed by the grants from the National Basic Research Program of China (2013GB127800), the Hi-Tech R&D Program of China (2011AA10A202), the Special Fund for Agro-Scientific Research in the Public Interest of China (200903039-6), and the National Natural Science Foundation of China (31271996).

Author Contributions

Shiqiong Lu performed bibliographic researches, drafted and corrected manuscript. Jin Tian, Weibo Sun, Jiajia Meng, Xiaohan Wang, Xiaoxiang Fu and Ali Wang participated in the discussions and supported manuscript corrections. Daowan Lai reviewed manuscript and helped to revised it. Yang Liu and Ligang Zhou conceived the idea, designed review structure, supervised manuscript drafting, and revised manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Nielsen, K.F.; Mogensen, J.M.; Johansen, M.; Larsen, T.O.; Frisvad, J.C. Review of secondary metabolites and mycotoxins from the *Aspergillus niger* group. *Anal. Bioanal. Chem*. **2009**, *395*, 1225–1242.
2. Koyama, K.; Ominato, K.; Natori, S.; Tashiro, T.; Tsuruo, T. Cytotoxicity and antitumor activities of fungal bis(naphtho-γ-pyrone) derivatives. *J. Pharmacobiodyn*. **1988**, *11*, 630–635.
3. Singh, S.B.; Zink, D.L.; Bills, G.F.; Teran, A.; Silverman, K.C.; Lingham, R.B.; Felock, P.; Hazuda, D. Four novel bis-(naphtho-γ-pyrones) isolated from *Fusarium* species as inhibitors of HIV-1 integrase. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 713–717.

4. Sakai, K.; Ohte, S.; Ohshiro, T.; Matsuda, D.; Masuma, R.; Rudel, L.L.; Tomoda, H. Selective inhibition of Acyl-CoA:Cholesterol acyltransferase 2 isozyme by flavasperone and sterigmatocystin from *Aspergillus* species. *J. Antibiot*. **2008**, *61*, 568–572.
5. Gorst-Allman, C.P.; Steyn, P.S.; Rabie, C.J. Structural elucidation of the nigerones, four new naphthopyrones from cultures of *Aspergillus niger*. *J. Chem. Soc. Perkin Trans. 1* **1980**, *1980*, 2474–2479.
6. Koyama, K.; Natori, S.; Iitaka, Y. Absolute configurations of chaetochromin A and related bis(naphtho-γ-pyrone) mold metabolites. *Chem. Pharm. Bull*. **1987**, *35*, 4049–4055.
7. Zhang, Y.; Ling, S.; Fang, Y.; Zhu, T.; Gu, Q.; Zhu, W.-M. Isolation, structure elucidation, and antimycobacterial properties of dimeric naphtho-γ-pyrones from the marine-derived fungus *Aspergillus carbonarius*. *Chem. Biodivers*. **2008**, *5*, 93–100.
8. Li, X.-B.; Xie, F.; Liu, S.-S.; Li, Y.; Zhou, J.-C.; Liu, Y.-Q.; Yuan, H.-Q.; Lou, H.-X. Naphtho-γ-pyrones from endophyte *Aspergillus niger* occurring in the liverwort *Heteroscyphus tener* (Steph.) Schiffn. *Chem. Biodivers*. **2013**, *10*, 1193–1201.
9. Koyama, K.; Aida, S.; Natori, S. Supplemental observations on atropisomerism of fungal bis(naphtho-γ-pyrone)s. *Chem. Pharm. Bull*. **1990**, *38*, 2259–2261.
10. Koyama, K.; Natori, S. Chaetochromins B, C and D, bis(naphtho-γ-pyrone) derivatives from *Chaetomium gracile*. *Chem. Pharm. Bull*. **1987**, *35*, 578–584.
11. Paranagama, P.A.; Wijeratne, E.M.K.; Gunatilaka, A.A.L. Uncovering biosynthetic potential of plant-associated fungi: Effect of culture conditions on metabolite production by *Paraphaeosphaeria quadriseptata* and *Chaetomium chiversii*. *J. Nat. Prod*. **2007**, *70*, 1939–1945.
12. Xu, G.-B.; Yang, T.; Bao, J.-K.; Fang, D.-M.; Li, G.-Y. Isochaetochromin A_2, a new bis(naphthodihydropyran-4-one) with antimicrobial and immunological activities from fungus *Chaetomium microcephalum*. *Arch. Pharm. Res*. **2014**, *37*, 575–579.
13. Sekita, S.; Yoshihira, K.; Natori, S. Chaetochromin, a bis(naphthodihydropyran-4-one) mycotoxin from *Chaetomium thielavioideum*: Application of ^{13}C-^{1}H long-range coupling to the structure elucidation. *Chem. Pharm. Bull*. **1980**, *28*, 2428–2435.
14. Ugaki, N.; Matsuda, D.; Yamazaki, H.; Nonaka, K.; Masuma, R.; Omura, S.; Tomoda, H. New isochaetochromin, an inhibitor of triacylalycerol synthesis in mammalian cells, produced by *Penicillium* sp. FKI-4942: I. Taxonomy, fermentation, isolation and biological properties. *J. Antibiot*. **2012**, *65*, 15–19.
15. Ugaki, N.; Yamazaki, H.; Uchida, R.; Tomoda, H. New isochaetochromin, an inhibitor of triacylglycerol synthesis in mammalian cells, produced by *Penicillium* sp. FKI-4942: II. Structure elucidation. *J. Antibiot*. **2012**, *65*, 21–24.
16. Kong, X.; Ma, X.; Xie, Y.; Cai, S.; Zhu, T.; Gu, Q.; Li, D. Aromatic polyketides from a sponge-derived fungus *Metarhizium anisopliae* mxh-99 and their antitubercular activities. *Arch. Pharm. Res*. **2013**, *36*, 739–744.
17. Haskins, R.H.; Knapp, C. *Cephalosporium* species (PRL 2070) and the production of cephalochromin. *Can. J. Microbiol*. **1969**, *15*, 435–437.
18. Hsiao, C.-J.; Hsiao, G.; Chen, W.-L.; Wang, S.-W.; Chiang, C.-P.; Liu, L.-Y.; Guh, J.-H.; Lee, T.-H.; Chung, C.-L. Cephalochromin induces G0/G1 cell cycle arrest and apoptosis in A549 human

non-small-cell lung cancer cells by inflicting mitochondrial disruption. *J. Nat. Prod*. **2014**, *77*, 758–765.

19. Carey, S.T.; Nair, M.S.R. Metabolites of Pyrenomycetes. V. identification of an antibiotic from two species of *Nectria*, as cephalochromin. *Lloydia* **1975**, *38*, 448–449.
20. Kock, I.; Draeger, S.; Schulz, B.; Elsasser, B.; Kurtan, T.; Kenez, A.; Antus, S.; Pescitelli, G.; Salvadori, P.; Speakman, J.-B.; *et al*. Pseudoanguillosporin A and B: Two new isochromans isolated from the endophytic fungus *Pseudoanguillospora* sp. *Eur. J. Org. Chem*. **2009**, *2009*, 1427–1434.
21. Matsumoto, M.; Minato, H.; Kondo, E.; Mitsugi, T.; Katagiri, K. Cephalochromin, dihydroisoustilaginoidin A, and isoustilaginoidin A from *Verticillium* sp. K-113. *J. Antibiot*. **1975**, *28*, 602–604.
22. Hegde, V.R.; Miller, J.R.; Patel, M.G.; King, A.H.; Puar, M.S.; Horan, A.; Hart, R.; Yarborough, R.; Gullo, V. Sch 45752—An inhibitor of calmodulin-sensitive cyclic nucleotide phosphodiesterase activities. *J. Antibiot*. **1993**, *46*, 207–213.
23. Ohkawa, Y.; Miki, K.; Suzuki, T.; Nishio, K.; Sugita, T.; Kinoshita, K.; Takhashi, K.; Koyama, K. Antiangiogenic metabolites from a marine-derived fungus, *Hypocrea vinosa*. *J. Nat. Prod*. **2010**, *73*, 579–582.
24. Shibata, S.; Ogihara, Y.; Ohta, A. Metabolic products of fungi. XXII. On ustilaginoidins. 2. The structure of ustilaginoidin A. *Chem. Pharm. Bull*. **1963**, *11*, 1179–1182.
25. Shibata, S.; Ogihara, Y. Metabolic products of fungi. XXIII. Ustilaginoidins. 3. The structure of ustilaginoidins B and C. *Chem. Pharm. Bull*. **1963**, *11*, 1576–1578.
26. Koyama, K.; Natori, S. Further characterization of seven bis(naphtho-γ-pyrone) congeners of ustilaginoidins, coloring matters of *Claviceps virens* (*Ustilaginoidea virens*). *Chem. Pharm. Bull*. **1988**, *36*, 146–152.
27. Shaaban, M.; Shaaban, K.A.; Abdel-Aziz, M.S. Seven naphtho-γ-pyrones from the marine derived fungus *Alternaria alternata*: Structure elucidation and biological properties. *Org. Med. Chem. Lett*. **2012**, *2*, 6.
28. Tanaka, H.; Wang, P.-L.; Yamada, O.; Tamura, L.T. Yellow pigments of *Aspergillus niger* and *Aspergillus awamori.* Part I. Isolation of aurasperone A and related pigments. *Agric. Biol. Chem*. **1966**, *30*, 107–113.
29. Priestap, H.A. New naphthopyrones from *Aspergillus fonsecaeus*. *Tetrahedron* **1984**, *40*, 3617–3624.
30. Akiyama, K.; Teraguchi, S.; Hamasaki, Y.; Mori, M.; Tatsumi, K.; Ohnishi, K.; Hayashi, H. New dimeric naphthopyrones from *Aspergillus niger*. *J. Nat. Prod*. **2003**, *66*, 136–139.
31. Song, Y.C.; Li, H.; Ye, Y.H.; Shan, C.Y.; Yang, Y.M.; Tan, R.X. Endophytic naphthopyrone metabolites are co-inhibitors of xanthine oxidase, SW1116 cell and some microbial growths. *FEMS Microbiol. Lett*. **2004**, *241*, 67–72.
32. Campos, F.R.; Barison, A.; Daolio, C.; Ferreira, A.G.; Rodrigues-Fo, E. Complete ^{1}H- and ^{13}C-NMR assignments of aurasperone A and fonsecinone A, two bis-naphthopyrones produced by *Aspergillus aculeatus*. *Magn. Reson. Chem*. **2005**, *43*, 962–965.
33. Chiang, Y.-M.; Meyer, K.M.; Praseuth, M.; Baker, S.E.; Bruno, K.S.; Wang, C.C.C. Characterization of a polyketide synthase in *Aspergillus niger* whose product is a precursor for

both dihydroxynaphthalene (DHN) melanin and naphtho-γ-pyrone. *Fungal Genet. Biol*. **2011**, *48*, 430–437.

34. Xiao, J.; Zhang, Q.; Gao, Y.-Q.; Shi, X.-W.; Gao, J.-M. Antifungal and antibacterial metabolites from an endophytic *Aspergillus* sp. associated with *Melia azedarach*. *Nat. Prod. Res*. **2014**, *28*, doi:10.1080/14786419.2014.904308.
35. Meng, X.; Ge, F.; Zeng, Y.; Zhao, P. Chemical constituents from the endophytic fungus *Aspergillus* sp. DCS31 of *Daphniphyllum longeracemosum*. *Nat. Prod. Res. Dev*. **2013**, *25*, 190–192.
36. Zhan, J.; Gunaherath, G.M.K.B.; Wijeratne, E.M.K.; Gunatilaka, A.A.L. Asperpyrone D and other metabolites of the plant-associated fungal strain *Aspergillus tubingensis*. *Phytochemistry* **2007**, *68*, 368–372.
37. Wang, P.-L.; Tanaka, H. Yellow pigments of *Aspergillus niger* and *Aperigillus awamori.* Part II. Chemical structure of aurasperone A. *Agric. Biol. Chem*. **1966**, *30*, 683–687.
38. Ehrlich, K.C.; DeLucca, A.J; Ciegler, A. Naphtho-γ-pyrone production by *Aspergillus niger* isolated from stored cottonseed. *Appl. Environ. Microbiol*. **1984**, *48*, 1–4.
39. Tanaka, H.; Wang, P.-L.; Namiki, M. Structure of aurasperone C. *Agric. Biol. Chem*. **1972**, *36*, 2511–2517.
40. Bouras, N.; Mathieu, F.; Coppel, Y.; Lebrihi, A. Aurasperone F—A new member of the naphtho-gamma-pyrone class isolated from a cultured microfungus, *Aspergillus niger* C-433. *Nat. Prod. Res*. **2005**, *19*, 653–659.
41. De Vries, R.P.; Frisvad, J.C.; van de Vondervoort, P.J.I.; Burgers, K.; Kuijpers, A.F.A.; Samson, R.A.; Visser, J. *Aspergillus vadensis*, a new species of the group of black Aspergilli. *Antonie Van Leeuwenkoek* **2005**, *87*, 195–203.
42. Ghosal, S.; Biswas, K.; Chakrabarti, D.K. Toxic naphtho-γ-pyrones from *Aspergillus niger*. *J. Agric. Food. Chem*. **1979**, *27*, 1347–1351.
43. Bouras, N.; Mathieu, F.; Coppel, Y.; Strelkov, S.E.; Lebrihi, A. Occurrence of naphtho-gamma-pyrones- and ochratoxin A—Producing fungi in French grapes and characterization of new naphtho-gamma-pyrone polyketide (aurasperone G) isolated from *Aspergillus niger* C-433. *J. Agric. Food Chem*. **2007**, *55*, 8920–8927.
44. Ye, Y.H.; Zhu, H.L.; Song, Y.C.; Liu, S.J.; Tan, R.X. Structural revision of aspernigrin A, reisolated from Cladosporium herbarum IFB-E002. *J. Nat. Prod*. **2005**, *68*, 1106–1108.
45. Zhang, Y.; Li, X.-M.; Wang, B.-G. Nigerasperones A-C, new monomeric and dimeric naphtho-γ-pyrones from marine alga-derived endophytic fungus *Aspergillus niger* EN-13. *J. Antibiot*. **2007**, *60*, 204–210.
46. Huang, H.-B.; Feng, X.-J.; Liu, L.; Chen, B.; Lu, Y.-J.; Ma, L.; She, Z.-G.; Lin, Y.-C. Three dimeric naphtho-γ-pyrones from the mangrove endophytic fungus *Aspergillus tubingensis* isolated from *Pongamia pinnata*. *Planta Med*. **2010**, *76*, 1888–1891.
47. Huang, H.-B.; Xiao, Z.-E.; Feng, X.-J.; Huang, C.-H.; Zhu, X.; Ju, J.-H.; Li, M.-F.; Lin Y.-C.; Liu, L.; She, Z.-G. Cytotoxic naphtho-γ-pyrones from the mangrove endophytic fungus *Aspergillus tubingensis* (GX1–5E). *Helv. Chim. Acta* **2011**, *94*, 1732–1740.
48. Geiser, D.M.; Klich, M.A.; Frisvad, J.C.; Peterson, S.W.; Varga, J.; Samson, R.A. The current status of species recognition and identification in *Aspergillus*. *Stud. Mycol*. **2007**, *59*, 1–10.

49. Perrone, G.; Susca, A.; Cozzi, G.; Ehrlich, K.; Varga, J.; Frisvad, J.C.; Meijer, M.; Noonim, P.; Mahakarnchanakul, W.; Samson, R.A. Biodiversity of *Aspergillus* species in some important agricultural products. *Stud. Mycol*. **2007**, *59*, 53–66.
50. Samson, R.A.; Varga, J. What is a species in *Aspergillus*? *Med. Mycol*. **2009**, *47*, S13–S20.
51. Koyama, K.; Natori, S. Biosynthesis of chaetochromin A, a bis(naphtho-γ-pyrone), in *Chaetomium* spp. *Chem. Pharm. Bull*. **1989**, *37*, 2022–2025.
52. Sakurai, M.; Kohno, J.; Yamamoto, K.; Okuda, T.; Nishio, M.; Kawano, K.; Ohnuki, T. TMC-256A1 and C1, new inhibitors of IL-4 signal transduction produced by *Aspergillus niger* var. *niger* TC 1629. *J. Antibiot*. **2002**, *55*, 685–692.
53. Asai, T.; Yamamoto, T.; Oshima, Y. Aromatic polyketide production in *Cordyceps indigotica*, an entomopathogenic fungus, induced by exposure to a histone deacetylase inhibitor. *Org. Lett*. **2012**, *14*, 2006–2009.
54. Tsuchiya, T.; Sekita, S.; Koyama, K.; Natori, S.; Takahashi, A. Effect of chaetochromin A, chaetochromin D and ustilaginoidin A, bisnaphtho-γ-pyrone derivatives, on the mouse embryo limb bud and midbrain cells in culture. *Cong. Anom*. **1987**, *27*, 245–250.
55. Kawai, K.; Hisada, K.; Mori, S.; Nozawa, Y.; Koyama, K.; Natori, S. The impairing effect of chaetochromin A and related mycotoxins on mitochondrial respiration. *Proc. Jpn. Assoc. Mycotoxicol*. **1991**, *33*, 31–35.
56. Campbell, J.W.; Cronan, J.E. Bacterial fatty acid biosynthesis: Targets for antibacterial drug discovery. *Annu. Rev. Microbiol*. **2001**, *55*, 305–332.
57. Zheng, C.J.; Sohn, M.-J.; Lee, S.; Hong, Y.-S.; Kwak, J.-H.; Kim, W.-G. Cephalochromin, a FabI-directed antibacterial of microbial origin. *Biochem. Biophys. Res. Commun*. **2007**, *362*, 1107–1112.
58. Cardellina, J.H.; Roxas-Duncan, V.I.; Montgomery, V.; Eccard, V.; Campbell, Y.; Hu, X.; Khavrutskii, I.; Tawa, G.J.; Wallqvist, A.; Gloer, J.B.; *et al*. Fungal bis-naphthopyrones as inhibitors of botulinum neurotoxin serotype A. *ACS Med. Chem. Lett*. **2012**, *3*, 387–391.
59. Ikeda, S.-I.; Sugita, M.; Yoshimura, A.; Sumizawa, T.; Douzono, H.; Nagata, Y.; Akiyama, S.-I. *Aspergillus* species strain M39 produces two naphtho-γ-pyrones that reverse drug resistance in human KB cells. *Int. J. Cancer* **1990**, *45*, 508–513.
60. Ito, Y.; Ohtsubo, K. Teratogenicity of oral chaetochromin, a polyphenolic mycotoxin produced by *Chaetomium* spp., to mice embryo. *Bull. Environ. Contam. Toxicol*. **1987**, *39*, 299–303.
61. Mori, S.; Kawai, K.; Nozawa, Y.; Koyama, K.; Natori, S. The impairing effects of chaetochromin D on mitochondrial respiration and structure. *Mycotoxin Res*. **1993**, *9*, 85–93.
62. Ishii, R.; Horie, M.; Koyama, K.; Ishikawa, Y.; Kitanaka, S. Inhibitory effects of fungal bis(naphtho-γ-pyrone) derivatives on nitric oxide production by a murine macrophage-like cell line, RAW 264.7, activated by lipopolysaccharide and interferon-γ. *Biol. Pharm. Bull*. **2005**, *28*, 786–790.
63. Zhao, J.; Shan, T.; Mou, Y.; Zhou, L. Plant-derived bioactive compounds produced by endophytic fungi. *Mini Rev. Med. Chem*. **2011**, *11*, 159–168.
64. Gutierrez, R.M.P.; Gonzalez, A.M.N.; Ramirez, A.M. Compounds derived from endophytes: A review of phytochemistry and pharmacology. *Curr. Med. Chem*. **2012**, *19*, 2992–3030.

65. Debbab, A.; Aly, A.H.; Proksch, P. Mangrove derived fungal endophytes—A chemical and biological perception. *Fungal Divers*. **2013**, *61*, 1–27.
66. Lee, Y.M.; Kim, M.J.; Li, H.; Zhang, P.; Bao, B; Lee, K.J.; Jung, J.H. Marine-derived *Aspergillus* species as a source of bioactive secondary metabolites. *Mar. Biotechnol*. **2013**, *15*, 499–519.
67. Morishita, E.; Shibatam, S. Metabolic products of fungi. XXVII. Synthesis of racemic unstilaginoidin A and its related compounds. *Chem. Pharm. Bull*. **1967**, *15*, 1772–1775.
68. DiVirgilio, E.S.; Dugan, E.C.; Mulrooney, C.A.; Kozlowski, M.C. Asymmetric total synthesis of nigerone. *Org. Lett*. **2007**, *9*, 385–388.
69. Kozlowski, M.C.; Dugan, E.C.; DiVirgilio, E.S.; Maksimenka, K.; Bringmann, G. Asymmetric total synthesis of nigerone and ent-nigerone: Enantioselective oxidative biaryl coupling highly hindered naphthols. *Adv. Synth. Catal*. **2007**, *349*, 583–594.
70. Marin, P.; de Ory, A.; Cruz, A.; Magan, N.; Gonzalez-Jaen, M.T. Potential effects of environmental conditions on the efficiency of the antifungal tebuconazole controlling *Fusarium verticillioides* and *Fusarium proliferatum* growth rate and fumonisin biosynthesis. *Int. J. Food Microbiol*. **2013**, *165*, 251–258.
71. Jorgensen, T.R.; Park, J.; Arentshorst, M.; van Welzen, A.M.; Lamers, G.; van Kuyk, P.A.; Damveld, R.A.; van den Hondel, C.A.M.; Nielsen, K.F.; Frisvad, J.C.; *et al*. The molecular and genetic basis of conidial pigmentation in *Aspergillus niger*. *Fungal Genet. Biol*. **2011**, *48*, 544–553.
72. Zhou, L.; Lu, S.; Shan, T.; Wang, P.; Sun, W.; Chen, Z.; Wang, S. Chemistry and biology of mycotoxins from rice false smut pathogen. In *Mycotoxins: Properties, Applications and Hazards*; Melborn, B.J., Greene, J.C., Eds.; Nova Science Publishers: New York, NY, USA, 2012; pp. 109–130.