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.).

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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-pyrone and their biological activities have not been reviewed. This comprehensive mini-review describes the occurrence, biosynthesis, and biological activities of fungal bis-naphtho-γ-pyrone. We also discuss their synthesis, production and applications.

2. Occurrence

Bis-naphtho-γ-pyrone 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-pyrone can be divided into three types (or groups), namely chaetochromin-, asperpyrone-, and nigerone-type. The absolute configurations of dimeric naphtho-γ-pyrone 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-pyrone 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-pyrone 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-pyrone (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 B1 (5) and B2 (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-pyrone 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 virensens (C. thielavioideum) | [13] |
| Isochaetochromin A1 (2) | Penicillium sp. FK I-4942 | [14,15] |
| Isochaetochromin A2 (3) | Chaetomium microcephalum | [12] |
| Chaetochromin B (4)  | Chaetomium gracile | [6,10] |
|                      | Chaetomium microcephalum | [12] |
| Isochaetochromin B1 (5) | Endophytic fungus Fusarium sp. | [3] |
| Isochaetochromin B2 (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 D1 (10) | Endophytic fungus Fusarium sp. | [3] |
Table 1. Cont.

| Bis-naphtho-γ-pyrone | Fungal Species | Reference |
|----------------------|---------------|-----------|
| Cephalochromin = Sch 45752 (11) | Cephalosporium sp. | [17] |
| Cosmopsora vilior YMJ89051501 | | |
| 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) | | [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.
Twenty-seven asperpyrone-type bis-naphtho-\(\gamma\)-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-pyrene 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 |
|----------------------|----------------|-----------|
| Aperpyrone 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] |
| Aperpyrone B (28)    | *Aspergillus niger* | [30] |
|                      | *Aspergillus niger* IFB-E003 | [31] |
|                      | *Aspergillus niger* ATCC 11414 | [33] |
| Aperpyrone C (29)    | *Aspergillus niger* | [30] |
| Aperpyrone D (30)    | Endophytic fungus *Aspergillus* sp. DCS31 | [35] |
|                      | Endophytic fungus *Aspergillus niger* | [8] |
|                      | Endophytic fungus *Aspergillus tubingensis* | [36] |
| Aperpyrone 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 audeatus* | [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] |
| Bis-naphtho-γ-pyrone       | Fungal Species                                | Reference   |
|---------------------------|-----------------------------------------------|-------------|
| Aurasperone B (34)        | Aspergillus niger ATCC 11414                  | [33]        |
|                           | Aspergillus niger ATCC 11414                  | [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   | Endophytic fungus Aspergillus sp.             | [34]        |
| (36)                      | 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]        |
| Nigeraserpon 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.
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-pyrene | Fungal Species | Reference |
|----------------------|----------------|-----------|
| 10,10'-Bifonsecin B (54) | Marine-derived fungus *Aspergillus carbonarius* | [7] |
| Nigerone (55) | Marine-derived fungus *Aspergillus carbonarius* | [7] |
| Aspergillus niger | |
| 6'-O-Demethylnigerone (56) | Marine-derived fungus *Aspergillus carbonarius* | [7] |
| Aspergillus niger | |
| 8'-O-Demethylnigerone (57) | Marine-derived fungus *Aspergillus carbonarius* | [7] |
| Aspergillus niger | |
| 8'-O-Demethylisonigerone (58) | Marine-derived fungus *Aspergillus carbonarius* | [7] |
| Aspergillus niger | |
| Isonigerone (59) | Marine-derived fungus *Aspergillus carbonarius* | [7] |
| | Aspergillus niger | [5] |
Figure 3. Structures of nigerone-type bis-naphtho-γ-pyrone (54–59) from fungi.

54. 10,10′-Bifonsecin B

55. Nigerone, R1=CH₃, R₂=CH₃
56. 6′-O-Demethylnigerone, R₁=CH₃, R₂=H
57. 8′-O-Demethylnigerone, R₁=H, R₂=CH₃
58. 8′-O-Demethylisonigerone, R=H
59. Isonigerone, R=CH₃

3. Biosynthesis

Chaetochromin A (1) was the first bis-naphtho-γ-pyrene 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 precursors [51]. The proposed biosynthetic pathway (Scheme 1) of asperpyrone-type bis-naphtho-γ-pyrone in the fungus *Aspergillus niger* was outlined by Chiang et al. [33]. The aromatic structure of naphtho-γ-pyrone 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 thiolester/Claisen-cyclase (TE/CLC) [33]. Linear naphtho-γ-pyrene YWA1 (61) was known in equilibrium with the side-chain open form (60). After recyclization, angular naphtho-γ-pyrene 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-pyrone fonsecinone B (43) and aurasperone A (32). Table 4 shows some monomeric naphtho-γ-pyrone 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-pyrone in fungi [38]. Accordingly, the structures of these proposed intermediates are shown in Figure 4.

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

| Monomeric Naphtho-γ-pyrene | Fungal Species | Reference |
|---------------------------|---------------|-----------|
| Nigerasperone A (63)      | *Aspergillus niger* EN-13 | [45]      |
| Rubrofusarin (64)          | *Aspergillus* | [38]      |
|                           | Endophytic fungus *Aspergillus tubingensis* GX1-5E | [46]      |
| Rubrofusarin B = Heminigerone (65) | *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-    | Endophytic fungus *Aspergillus niger*               | [8]         |
| ribofuranoside (66)       |                                                     |             |
| 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     | *Alternaria alternata*                               | [27]        |
| monomethyl ether (68)     |                                                     |             |
|                            | *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*                                  | [38]        |
|                            | *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), isochnetochromin 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
(Bacillus 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 (Fab I) in bacterial fatty acid synthesis has been demonstrated to be an antibacterial target [56]. Cephalochromin (11) inhibited Fab I of Staphylococcus aureus and Escherichia coli with IC50 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-naphtho-γ-pyrone mentioned above, other biological activities include tyrosine kinase inhibition [23], HIV-1 integrase inhibition [3], calmodulin-sensitive cycle nucleotide phosphodiesterase inhibition [22], triacylglycerol synthesis inhibition [14], xanthine oxidase inhibition [31], acyl-CoA:cholesterol acyltransferase inhibition [4], central nervous system depressant effects [42], immunological activity [12], botulinum neurotoxin 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-pyrone from fungi.

| Bis-naphtho-γ-pyrones | 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 A1 (2)| Inhibitory activity on triacylglycerol synthesis | [14] |
| Isochaetochromin A2 (3)| Antibacterial activity | [12] |
|                       | Immunological activity | [12] |
| Chaetochromin B (4)   | Cytotoxic and antitumor activity | [2,54] |
|                       | Antibacterial activity | [12] |
|                       | Immunological activity | [12] |
| Isochaetochromin B1 (5)| HIV-1 integrase inhibitory activity | [3] |
|                       | Inhibitory activity on triacylglycerol synthesis | [14] |
| Isochaetochromin B2 (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-pyrene                  | Biological Activity                                                                 | Reference |
|---------------------------------------|--------------------------------------------------------------------------------------|-----------|
| Chaetochromin D (9)                   | Cytotoxic and antitumor activity                                                    | [2,54]    |
|                                       | Impairing effects on mitochondrial respiration and structure                         | [61]      |
| Chaetochromin D1 (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 phosphodiesterase     | [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]      |
| Auroraasperone 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]      |
| Auroraasperone 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-pyrone 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-pyrone produced by fungi and their bioactivities need to be further studied. In recent years, an increasing number of bis-naphtho-γ-pyrone 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, isochoetochromins B1 and B2), but also prevent biosynthesis of some toxic bis-naphtho-γ-pyrones (i.e., ustilaginoids 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].

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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.

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