Fusarium-Derived Secondary Metabolites with Antimicrobial Effects

Subjects: Pharmacology & Pharmacy

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Fungal microbes are important in the creation of new drugs, given their unique genetic and metabolic diversity. As one of the most commonly found fungi in nature, *Fusarium* spp. has been well regarded as a prolific source of secondary metabolites (SMs) with diverse chemical structures and a broad spectrum of biological properties. However, little information is available concerning their derived SMs with antimicrobial effects. By extensive literature search and data analysis, as many as 185 antimicrobial natural products as SMs had been discovered from *Fusarium* strains by the end of 2022.

Keywords: Fusarium ; secondary metabolite ; antimicrobial effect ; antibacterial

1. Introduction

Antimicrobial agents play a significant role in the treatment of infectious diseases caused by pathogenic microorganisms with various modes of action. Since the fortuitous discovery of penicillin in 1928, hundreds of antibiotics have been approved for clinical use. However, some of these drugs have become less efficacy or unavailability simultaneously owing to the development of antimicrobial resistance (AMR), in which a pathogenic microbe evolves a survival mechanism that protects the drug target by modification or replacement, or degradation or modification of the antibiotic to render it harmless, such as MRSA (methicillin-resistant *Staphylococcus aureus*), multidrug-resistant *S. aureus* (MDRS), VREF (vancomycin-resistant *Enterococcus faecium*), CRKP (cephalosporin-resistant *Klebsiella pneumoniae*) [1]. Antimicrobial resistance has become an increasing threat to human health and is widely considered to be the next global pandemic [2]. Therefore, it is an urgent need for the discovery of new antimicrobial drugs with novel structural scaffolds and new modes of action.

2. Antibacterial Secondary Metabolites

Bacterial infection is a common clinical disease that can affect a variety of organs and tissues. *Fusarium*-derived antibacterial SMs have a wide array of structural motifs, most of which are polyketides, followed by alkaloids, terpenoids, and cyclopeptides. According to antibacterial properties, these chemicals are divided into three groups, including anti-Gram-positive bacterial SMs (**1**–**50**, **Figure 1**), anti-Gram-negative bacterial SMs (**51**–**64**, **Figure 2**) and both anti-Gram-positive and anti-Gram-negative bacterial SMs (**65**–**81**, **Figure 3**).

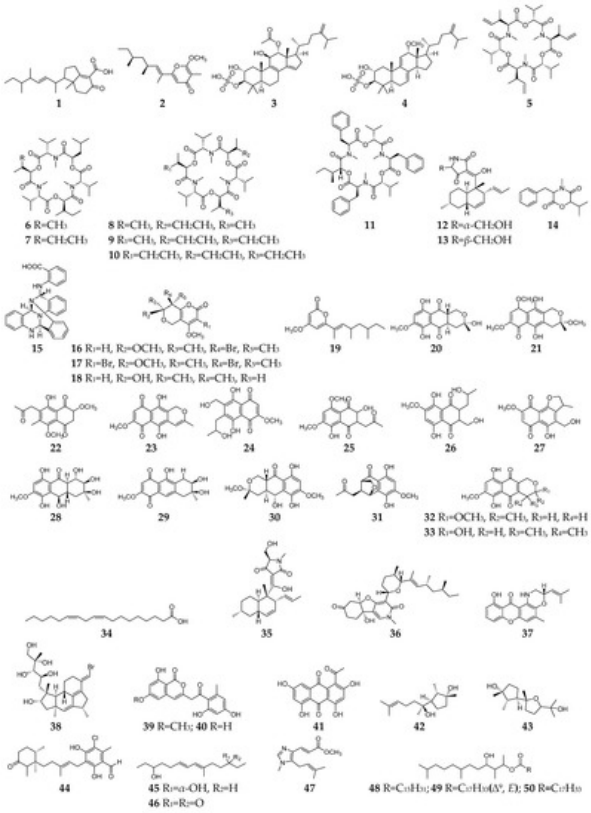

Figure 1. *Fusarium*-derived anti-Gram-positive bacterial SMs (**1**–**50**).

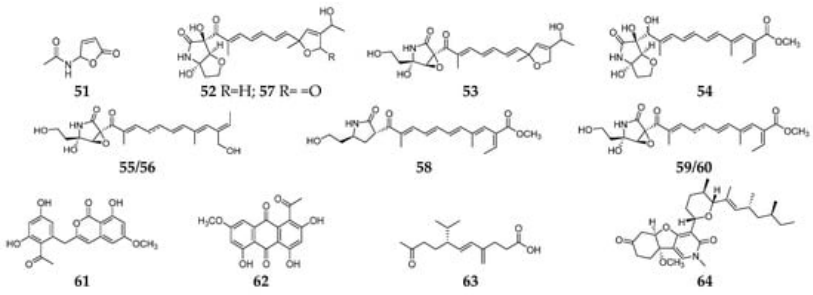

Figure 2. *Fusarium*-derived anti-Gram-negative bacterial SMs (**51**–**64**).

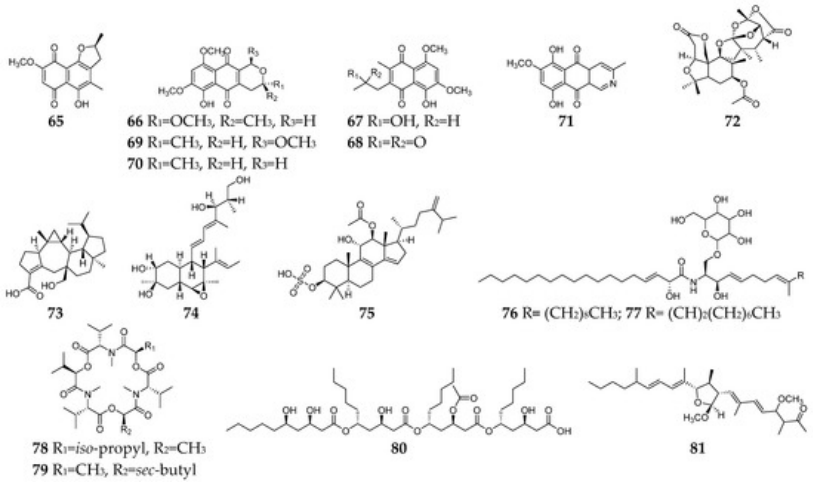

Figure 3. *Fusarium*-derived anti-Gram-positive and anti-Gram-negative bacterial SMs (**65**–**81**).

2.1. Anti-Gram-Positive Bacterial SMs

Fifty *Fusarium*-derived SMs (**1**–**50**, **Figure 1**) had been characterized and displayed various bactericidal effects on Gram-positive strains, such as *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, multidrug-resistant *S. aureus*, *Mycobacterium tuberculosis*, *Bacillus subtilis*, etc. Fusariumins C (**1**) and D (**2**) are two new polyketides produced by an endophytic strain *F. oxysporum* ZZP-R1 from coastal plant *Rumex midair* Makino displayed medium effect on *S. aureus* with MIC (minimum inhibitory concentration) values of 6.25 and 25.0 μM, respectively [3]. Two triterpene sulfates (**3** and **4**) isolated from *F. compactum* exhibited weak activity toward *S. aureus* and *Streptococcus* strains in the range of 6–

50 μg/mL [4]. Enniatins (**5**–**10**), a group of antibiotics commonly synthesized by various *Fusarium* strains, are six-membered cyclic depsipeptides formed by the union of three molecules of D-α-hydroxyisovaleric acid and three *N*-methyl-*L*-amino acids [5]. Three enniatins (**8**–**10**), beauvericin A (**11**) and trichosetin (**12**) were obtained from an endophytic fungus, *Fusarium* sp. TP-G1 and showed moderate anti-*S. aureus* and anti-methicillin-resistant *S. aureus* effects with MIC values in the range of 2–16 μg/mL [6]. Two enantiomers (**12** and **13**) were separated from the culture broth of *F. oxysporum* FKI-4553 and found to have an inhibitory effect on the undecaprenyl pyrophosphate synthase activity of *S. aureus* with IC_{50} values of 83 and 30 μM, respectively [7].

Lateritin (**14**) derived from *Fusarium* sp. 2TnP1–2 showed anti-*S. aureus* activity at 2 μg per disc with 7 mm of inhibition zone [8]. A new polycyclic quinazoline alkaloid (**15**) displayed moderate antibacterial activity against methicillin-resistant *S. aureus* and multidrug-resistant *S. aureus*, with the same MIC value of 6.25 μg/mL [9]. Three pyranopyranones (**16**–**18**) showed weak inhibitory activities against *S. aureus*, methicillin-resistant *S. aureus*, and multidrug-resistant *S. aureus* [10]. Compound **19** was a new pyran-2-one with weak activity against methicillin-resistant *S. aureus* and was shown to be the inhibitor of the quorum-sensing mechanism of *S. aureus* and *Pseudomonas aeruginosa* [11]. Trans-dihydrofusarubin (**20**) and seven analogs (**21**–**27**) had significant antibiotic activity against *S. aureus* (MIC values < 4 μg/mL), and compounds **26** and **27** exhibited potent activity against *S. pyogenes* [12]. Five naphthoquinones **28**–**32** showed anti-*Mycobacterium tuberculosis* activity with MICs ranging from 25 to 50 μg/mL [13]. Compounds **32** and **33** displayed moderate antibacterial activity against *S. aureus* and potent activities against *B. cereus* and *S. pyogenes* with MIC values of <1 μg/mL as compared to ciprofloxacin, whose MIC value was 0.15 and 10 μg/mL, respectively [14].

Linoleic acid (**34**) and *epi*-equisetin (**35**) had certain inhibitory activity against *S. aureus* and multidrug-resistant *S. aureus* [15]. (−)-4,6′-anhydrooxysporidinone (**36**) was obtained from *F. oxysporum* and showed weak anti-multidrug-resistant *S. aureus* and moderate anti-*B. subtilis* effects [16]. Fusaroxazin (**37**), a novel antimicrobial xanthone derivative from *F. oxysporum*, possessed significant antibacterial activity towards *S. aureus* and *B. cereus*, with MIC values of 5.3 and 3.7 μg/mL, respectively [17]. Neomangicol B (**38**) isolated from the mycelial extract of a marine *Fusarium* strain was found to inhibit *B. subtilis* growth with a potency similar to that of the antibiotic gentamycin [18]. Three aromatic polyketides (**39**–**41**) were produced by strain *F. proliferatum* ZS07 and possessed potent antibacterial activity against *B. subtilis* with the same MIC values of 6.25 μg/mL [19]. Two sesterterpenes (**42** and **43**) produced by *F. avenaceum* SF-1502 displayed stronger antibacterial activity against *B. megaterium* than positive controls (ampicillin, erythromycin, and streptomycin) [20]. 4,5-Dihydroascochlorin (**44**) had strong antibacterial activity towards *Bacillus megaterium* [21]. Fusariumnols A (**45**) and B (**46**) were two novel anti-*S. epidermidis* aliphatic unsaturated alcohols isolated from *F. proliferatum* 13,294 [22]. Fungerin (**47**) displayed weak antibacterial activity against *S. aureus* and *S. pneumoniae* [23]. Compounds **48**–**50** were purified from *F. oxysporum* YP9B and showed a potent inhibitory effect on *S. aureus*, *E.faecalis*, *S. mutans*, *B. cereus*, and *M. smegmatis* with MICs of less than 4.5 μg/mL [24].

2.2. Anti-Gram-Negative Bacterial SMs

Butenolide (**51**) was a fusarium mycotoxin from unknown origin strain *Fusaium* sp. and showed selective inhibitory activity against *E. coli* [25]. Extensive chemical investigation of the endophytic fungus *F. solani* JK10 afforded nine 2-pyrrolidone derivatives (**52**–**60**), which displayed antibacterial activity against *E. coli* with MIC values of 5–10 μg/mL. Particularly, three lucilactaene analogs (**52**–**54**) had strong inhibitory effects on *Acinetobacter* sp., comparable to the positive control streptomycin [26]. One new aromatic polyketide, karimunones B (**61**), together with compounds **62** and **63,** was obtained from sponge-associated *Fusarium* sp. KJMT.FP.4.3 and exhibited anti-multidrug resistant *Salmonella enterica* ser. Typhi activity with a MIC of 125 μg/mL [27]. Fusapyridon A (**64**) is produced by an endophytic strain, *Fusarium* sp. YG-45 demonstrated moderate antibacterial activity against *Pseudomonas aeruginosa* with a MIC value of 6.25 μg/mL [28].

2.3. Both Anti-Gram-Positive and Anti-Gram-Negative Bacterial SMs

Seventeen *Fusarium*-derived SMs (**65**–**81**, **Figure 3**) were shown to have both anti-Gram-positive and anti-Gram-negative activity. Seven naphthoquinones (**65**–**71**) demonstrated moderate activities against an array of Gram-positive and Gram-negative bacteria, such as *B. megaterium*, *B. subtilis*, *C. perfringens*, *E. coli*, methicillin-resistant *S. aureus*, *P. aeruginosa*, *S. aureus*, and *S. pyogenes* [12][20][29][30]. The mechanism of action (MoA) study indicated that compounds **66** and **71** could stimulate the oxygen consumption of bacterial cells and induce cyanide-insensitive oxygen consumption, which results in the generation of superoxide anion and hydrogen peroxide [31]. Compounds **72**–**75** were polycyclic terpenoids, respectively, produced by three *Fusarium* strains [32][33][34]. Compound **72** had significant activity against *S. aureus* and *P. aeruginosa* with a MIC value of 6.3 μg/mL, and **73** showed moderate activities against *Salmonella enteritidis* and *Micrococcus luteus* with MIC values of 6.3 and 25.2 μg/mL, respectively, while **74** showed a broad spectrum of antibacterial activity and **75** exhibited moderate antibacterial activities against *S. aureus* and *E. coli* with the same MIC

value of 16 μg/mL. Two xanthine oxidase inhibitory cerebrosides (**76** and **77**) were identified and purified from the culture broth of *Fusarium* sp. IFB-121 and showed strong antibacterial activities against *B. subtilis*, *E. coli*, and *P. fluorescens* with MICs of less than 7.8 μg/mL [35]. Enniatins J_1 (**78**) and J_3 (**79**) were two hexadepsipeptides with an array of antibacterial activity toward *C. perfringens*, *E. faecium*, *E. coli*, *S. dysenteriae*, *S. aureus*, *Y. enterocolitica*, and lactic acid bacteria except for *B. adolescentis* [36]. Halymecin A (**80**) was produced by a marine-derived *Fusarium* sp. FE-71-1 and exhibited a moderate inhibitory effect on *E. faecium*, *K. pneumoniae*, and *P. vulgaris* with the MIC value of 10 μg/mL [37]. Fusaequisin A (**81**) was isolated from rice cultures of *F. equiseti* SF-3-17 and found to have moderate antimicrobial activity against *S. aureus* NBRC 13,276 and *P. aeruginosa* ATCC 15,442 [38].

3. Antifungal Secondary Metabolites

Invasive fungal infections are very common in immunocompromised patients (such as acquired immune deficiency syndrome and organ transplantation) and have become a global problem resulting in 1.7 million deaths every year [39][40][41]. Furthermore, the overuse of antifungal agents increases opportunistic pathogen resistance, which had been listed as one of the dominant threats by the World Health Organization in 2019. Therefore, the urgent need for new antimycotics with novel targets is undeniable. Till the end of 2022, twenty-seven antifungal SMs (**82**–**108**, **Figure 4**) had been discovered from *Fusarium* strains. Compounds **82**–**84** are three anti-*C. albicans* glycosides belong to the papulacandin class [42][43]. The MoA study suggested that compound **82** is an inhibitor of glutamine synthetase (GS) enzyme for (l,3)-*β*-glucan biosynthesis [42]. CR377 (**85**) was a new α-furanone derivative from an endophytic *Fusarium* sp. CR377 and showed a similar antifungal effect on *C. albicans* with nystatin [44]. Compounds **86** and **87** were two zearalenone analogs and exhibited weak activity against *Cryptococcus neoformans* [45]. Neofusapyrone (**88**) produced by a marine-derived *Fusarium* sp. FH-146 displayed moderate activity against *A. clavatus* F318a with a MIC value of 6.25 μg/mL [46]. Six cyclic depsipeptides **89**–**94** had been isolated from several *Fusarium* strains and found to have significant inhibitory activities against pathogenic fungi, such as *C. albicans* [47], *C. glabrata*, *C. krusei*, *V. ceratosperma*, and *A. fumigates* [48]. Cyclosporin A (**91**) has long been recognized as an immunosuppressant agent and could inhibit the growth of sensitive fungi after their germination [49][50]. Parnafungins A-D (**95**–**98**) were isoxazolidinone-containing natural products and demonstrated broad-spectrum antifungal activity with no observed activity against bacteria. The targeted pathway of these alkaloids was determined to be the mRNA 3`-cleavage and polyadenylation process [51][52]. One *N*-hydroxypyridine derivative (**99**) showed antifungal activity against *C. albicans* and *Penicillium chrysogenum* with MICs of 16 and 8 μg/mL, respectively [53]. Indole acetic acid (**100**) exhibited activity against the fluconazole-resistant *C. albicans* (MIC = 125 μg/mL) [54].

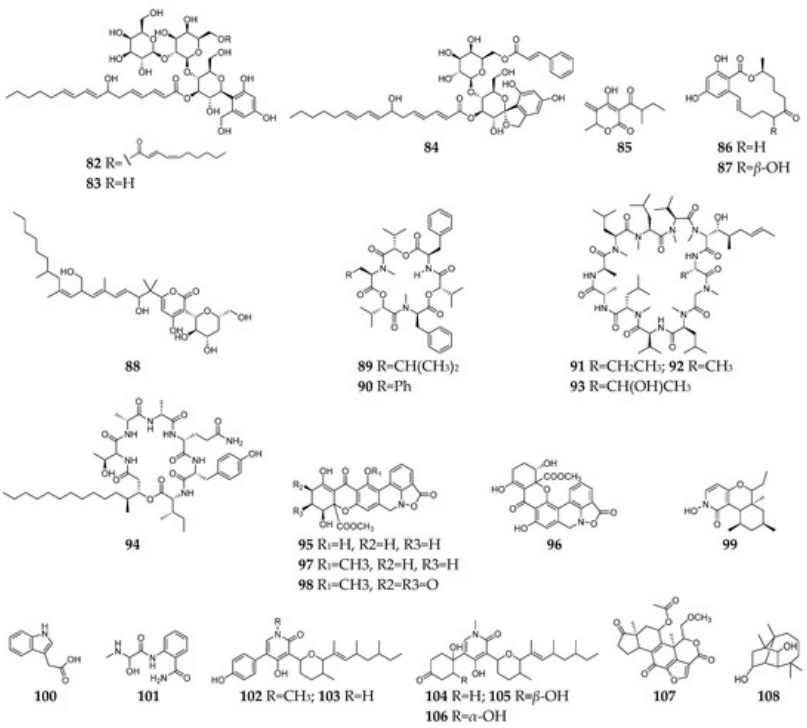

Figure 4. *Fusarium*-derived antifungal SMs (**82**–**108**).

Fusaribenzamide A (**101**) possessed a significant anti-*C. albicans* activity with MIC of 11.9 μg/disc compared to nystatin (MIC = 4.9 μg/disc) [55]. Three pyridone derivatives (**102**–**104**) displayed significant activities against multidrug-sensitive *S. cerevisiae* 12geneΔ0HSR-iERG6, and the MoA study indicated that these substances have a potent inhibitory effect on NADH-cytochrome C oxidoreductase [56]. Compounds **105**–**107** were derived from strain *F. oxysporum* N17B, and the

former (**105** and **106**) showed selective fungistatic activity against *Aspergillus fumigatus*, and the latter (**107**) had selective potent activity against *C. albicans* through inhibition of phosphatidylinositol 3-kinase [57]. Culmorin (**108**) displayed remarkable antifungal activity against both marine (*S. marina*, *M. pelagica*) and medically relevant fungi (*A. fumigatus*, *A. niger*, *C. albicans*, *T. mentagrophytes*) [58][59].

4. Both Antibacterial and Antifungal Secondary Metabolites

Till the end of 2022, forty-one SMs (**109**–**149**, **Figure 5**) with both antibacterial and antifungal effects had been discovered from *Fusarium* spp. Among these *Fusarium*-derived 1,4-naphthoquinone analogs (**109**–**115**), compound **109** showed potent anti-Gram-positive bacteria activity against *B. cereus* and *S. pyogenes* with MIC of <1 μg/mL and anti-*C. albicans* activity with IC_{50} (the half maximal inhibitory concentration) of 6.16 μg/mL [13], and **110**–**115** demonstrated moderate inhibitory effects on *S. aureus*, *C. albicans*, and *B. subtilis* [60]. Bikaverin (**116**) was found to have anti-*E. coli* and antifungal (*P. notatum*, *Alternaria humicola*, and *A. flavus*) activity [47][61][62]. Lateropyrone (**117**) was the same SM as *F. acuminatum*, *F. lateritium*, and *F. tricinctum* and displayed good antibacterial activity against *B. subtilis*, *S. aureus*, *S. pneumoniae*, methicillin-resistant *S. aureus*, *Mycobacterium tuberculosis*, and vancomycin-resistant of *E. faecalis* and significant inhibitory activity towards the growth of *C. albicans* [63][64][65][66]. BE-29,602 (**118**) was a novel antibiotic of the papulacandin family, showing good activity against *C. albicans*, *S. cerevisiae*, *S. pombe* with MIC values < 1 μg/mL and moderate activity against *B. subtilis* and *P. chrysogenum* with the MIC values < 8 μg/mL [43][67]. Fusarielin A (**119**) was a meroterpenoid with moderate antifungal activities against *A. fumigatus* and *F. nivale* and weak antibacterial effect on *S. aureus*, methicillin-resistant *S. aureus*, and multidrug-resistant *S. aureus* [10][68]. Three helvolic acid derivatives (**120**–**122**) displayed potent antifungal and antibacterial activities against *B. subtilis*, *S. aureus*, *E. coli*, *B. cinerea*, *F. Graminearum*, and *P. capsica* [69]. Fusartricin (**123**) had moderate antimicrobial activity against *E. aerogenes*, *M. tetragenu*, and *C. albicans* with the same MIC value of 19 μM [33].

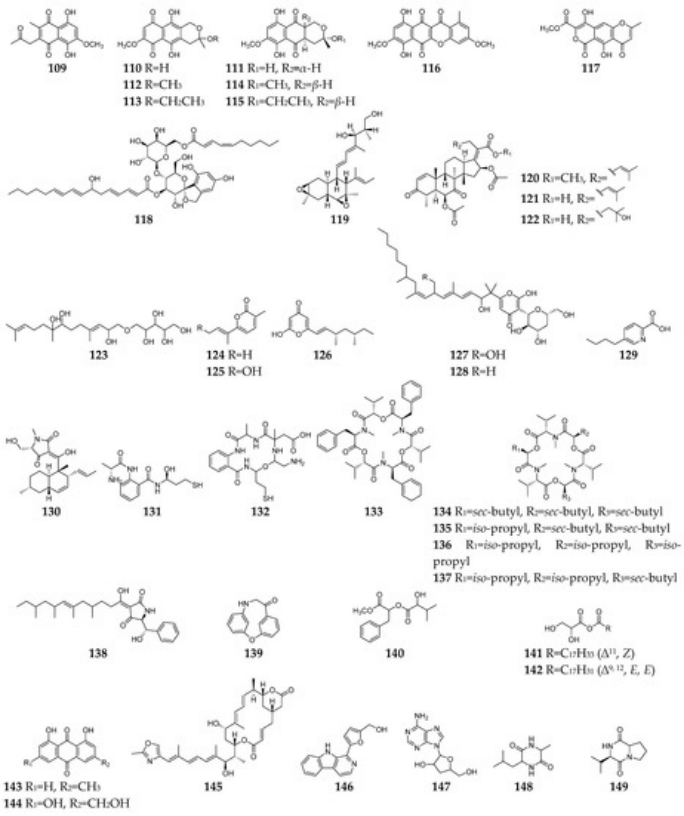

Figure 5. *Fusarium*-derived antibacterial and antifungal SMs (**109**–**149**).

Compounds **124**–**128** are pyrone family members and showed antimicrobial activity against bacteria (such as *B. subtilis*, *S. aureus*, *Vibrio parahaemolyticus*, *C. kefyr*, and *P. aeruginosa*) and fungi (such as *A. clavatus*, *Geotrichum candidum*, *C. albicans*, *M. albican*, and *S. cerevisiae*) [46][70][71][72][73]. Fusaric acid (**129**), one of the most significant mycotoxins from *Fusarium* strains, displayed a broad spectrum of moderate antimicrobial activity against *Bacillus* species, *Acinetobacter baumannii, Phytophthora infestans*, etc. [74][75][76]. Equisetin (**130**) was shown to be active against several strains of Gram-positive bacteria (*B. subtilis*, *Mycobacterium phlei*, *S. aureus*, *methicillin-resistant S. aureus*, and *S. erythraea*) and the Gram-negative bacteria *Neisseria perflava* at concentrations of 0.5–4.0 μg/mL, as well as antifungal activity toward *P. syringae* and *R. cerealis* [77][78]. Fusarithioamides A (**131**) and B (**132**) demonstrated antibacterial potential towards *B. cereus*, *S. aureus*, and *E. coli* compared to ciprofloxacin and selective antifungal activity towards *C. albicans* compared to

clotrimazole [79][80]. Beauvericin (**133**) and enniatins A, A1, B and B1 (**134**–**137**) are cyclic hexadepsipeptides with a wide array of highly antimicrobial activities against bacteria (such as *B. subtilis*, *S. aureus*, *methicillin-resistant S. aureus*, etc.) and fungi (such as *C. albicans*, *B. bassiana*, *T. harzianum*, etc.) [81][82][83][84][85]. Unlike most antibiotics, cell organelles or enzyme systems are the targets of the antibiotic **133** [86]. As a drug efflux pump modulator, furthermore, compound **133** had the capability to reverse the multi-drug resistant phenotype of *C. albicans* by blocking the ATP-binding cassette transporters and to repress the expression of many filament-specific genes, including the transcription factor BRG1, global regulator TORC1 kinase [87]. Fusaramin (**138**) displayed anti-Gram-positive and anti-Gram-negative bacterial activity and could inhibit the growth of *S. cerevisiae* 12geneΔ0HSR-iERG6 [56]. Compounds **139**–**142** were isolated from *F. oxysporum* YP9B and exhibited a significant antimicrobial effect against bacterial and fungi at concentrations of 0.8–6.3 μg/mL [24]. Seven SMs (**143**–**149**) were separated from an endophytic fungus *F. equiseti*, and showed antibacterial (such as *B. subtilis*, *S. aureus*, *B. megaterium*) and anti-*C. albicans* activities [88].

5. Antiviral Secondary Metabolites

The infections by viruses in humans resulted in millions of deaths globally and are accountable for viral diseases, including HIV/AIDS, hepatitis, influenza, herpes simplex, common cold, etc. [89]. The emergence of new viruses like Ebola and coronaviruses (SARS-CoV, SARS-CoV-2) emphasizes the need for more innovative strategies to develop better antiviral drugs. Twenty-three *Fusarium*-derived SMs (**64**, **99**, **105**, **135**–**137**, **140**–**142**, **144**–**147**, **149**–**158**, **Figure 6**) had been shown to have antiviral effects. The isolation of fusaricide (**99**) was guided by the Rev (regulation of virion expression) binding assay [53]. Fusapyridon A (**64**) and oxysporidinone (**105**) displayed antiviral activity against the coronavirus (HCoV-OC43) with IC_{50} values of 13.33 and 6.65 μM, respectively [90]. Their enniatins (**135**–**137**) were found to protect human lymphoblastoid cells from HIV-1 infection with an in vitro “therapeutic index” of approximately 200 (IC_{50} = 1.9, EC_{50} = 0.01 μg/ mL, respectively) [91]. The antiviral activity against HSV type-1 was determined to be 0.312 μM for compound **140** and 1.25 μM for **141** and **142** [24]. Three indole alkaloids (**150**–**152**) were obtained from a marine-derived *Fusarium* sp. L1 and exhibited inhibitory activity against the Zika virus (ZIKV) with EC_{50} values of 7.5, 4.2, and 5.0 μM, respectively [92]. A chemical study of an endophytic fungus *F. equiseti* led to the isolation of compounds **144**–**147** and **153**–**157**, of which **149** and **157** showed good potency against hepatitis C virus NS3/4A protease, while **144** and **155** were the most potent hepatitis C virus NS3/4A protease inhibitors [88]. Coculnol (**158**) was a penicillic acid from a coculture of *F. solani* FKI-6853 and *Talaromyces* sp. FKA-65 displayed an inhibitory effect on A/PR/8/34 (H1N1) with an IC_{50} value of 283 μg/mL [93].

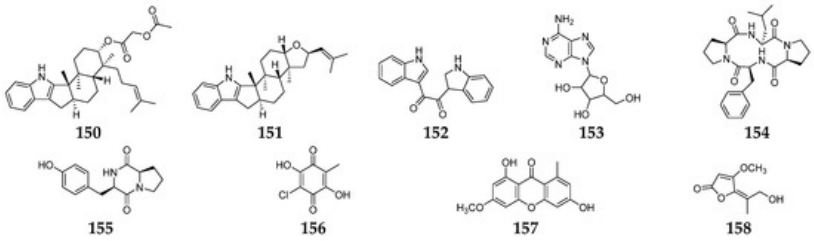

Figure 6. *Fusarium*-derived antiviral SMs (**150**–**158**).

6. Antiparasitic Secondary Metabolites

Parasitic diseases caused by protozoa, helminths and ectoparasites affect millions of people each year and result in substantial morbidity and mortality, particularly in tropical regions [94]. Therefore, new antiparasitic agents are urgently needed to treat and control these diseases. A total of 39 antiparasitic SMs (**23**, **28**, **29**, **59**, **108**, **93**, **116**, **133**–**137**, **159**–**185**, **Figure 7**) had been isolated and characterized from *Fusarium* strains. Five naphthoquinones (**23**, **29**, **30**, **109,** and **159**) and one anthraquinone (**160**) showed weak inhibitory activity toward the most deadly malaria parasite *Plasmodium falciparum* K1 with IC_{50} values in the range 9.8–26.1 μM [95]. However, compound **93** displayed significant antiplasmodial activity toward *P. falciparum* (D6 clone) with an IC_{50} value of 0.34 μM [48]. Bikaverin (**116**) was specifically effective against *Leishmania brasiliensis*, which is one of the main causes of cutaneous leishmaniasis in the Americas [96]. Beauvericin (**133**) was reported to inhibit *Trypanosoma cruzi* with an IC_{50} value of 2.43 μM and *L. braziliensis* with an EC_{50} value of 1.86 μM [97][98]. In addition to antibacterial and antifungal effects, enniatins (**134**–**137**) exhibited mild anti-leishmanial activity by inhibition of the activity of thioredoxin reductase enzyme of *P. falciparum* [5]. Integracides F, G, H, and J (**161**–**164**) were also shown to have stronger anti-leishmanial activity towards *L. donovani* than the positive control pentamidine (IC_{50} = 6.35 μM) [99]. Among twelve lucilactaene derivatives (**165**–**176**), compounds **166**–**168** showed very potent antimalarial activity toward *P. falciparum* (IC_{50} = 0.0015, 0.15, and 0.68 μM, respectively) [100][101][102]. Structure−activity relationship study suggested that epoxide is extremely detrimental, and demethylation of the lucilactaene methyl ester and

formation of the free carboxylic acid group resulted in a 300-fold decrease in activity. Nine cyclic tetrapeptides (**177**–**185**) are apicomplexan histone deacetylase (HDA) inhibitors [103][104][105]. Particularly, compound **177** was an excellent inhibitory agent (IC_{50} < 2 nM) and showed in vivo high efficacy against *P. berghei* malaria in mice at less than 10 mg/kg.

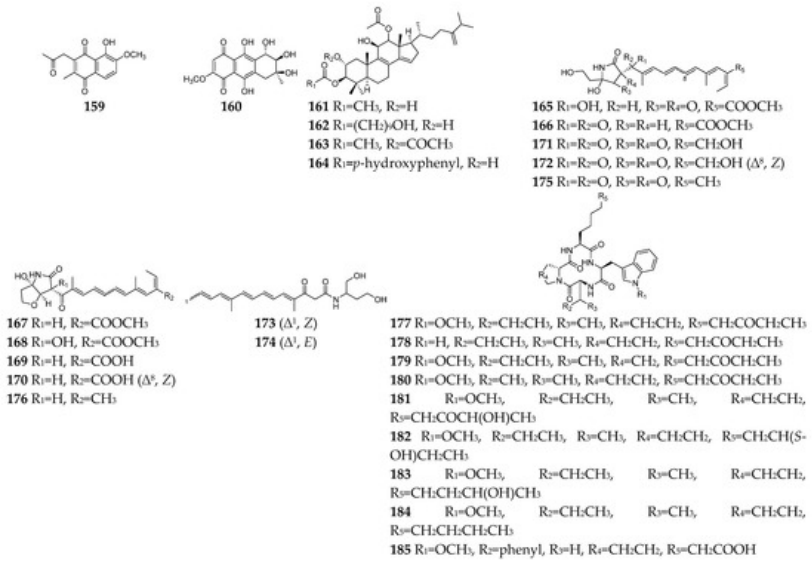

Figure 7. *Fusarium*-derived antiparasitic SMs (**159**–**185**).

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