Abstract: Fungi represent a huge reservoir of structurally diverse bio-metabolites. Although there has been a marked increase in the number of isolated fungal metabolites over the past years, many hidden metabolites still need to be discovered. Depsides are a group of polyketides consisting of two or more ester-linked hydroxybenzoic acid moieties. They possess valuable bioactive properties, such as anticancer, antidiabetic, antibacterial, antiviral, anti-inflammatory, antifungal, antifouling, and antioxidant qualities, as well as various human enzyme-inhibitory activities. This review provides an overview of the reported data on fungal depsides, including their sources, biosynthesis, physical and spectral data, and bioactivities in the period from 1975 to 2020. Overall, 110 metabolites and more than 122 references are confirmed. This is the first review of these multi-faceted metabolites from fungi.

Keywords: fungi; depsides; biosynthesis; spectral data; biological activities

1. Introduction

Fungi are widespread cosmopolitan organisms that represent the second-largest class of organisms after insects [1]. For decades, they have been seen as harmful, causing health hazards and spoiling foods. Today, the view on fungi has altered to take into account their advantageous effects, which have become apparent in biotechnological and industrial fields, as well as the production of structurally unique and life-saving metabolites [2–5]. In the past decades, the number of bioactive metabolites isolated from fungi has been rapidly increased due to their wide diversity of ecological and environmental niches across the globe, including marine, terrestrial, and water environments where they function as pathogens, symbionts, and saprobes [6,7]. Fungi-derived metabolites have made remarkable contributions to the process of drug discovery [8–16]. They have been used as antibiotics, herbicides, pesticides, anti-infectives, immuno-suppressants, and anticancer agents [6,7,17]. Depsides are simple polyketides that are formed by the condensation of two or more hydroxybenzoic acid moieties via ester linkage; the COOH group of one molecule is esterified with a phenolic OH group of the second molecule. They could be β-orcinol (β-orsellinic acid) or orcinol (orsellinic acid) derivatives, relying on the existence of the C3 methyl group on both rings (Figure 1). The ring with an ester-carbonyl is referred to as ring A and the other as ring B. Their major structural variations are the attached alkyl chains' length, the degree of chain oxidation, and the degree of methylation of OH and COOH groups [18]. The OH groups usually exist at the aromatic carbons,
C-3′/C-4′/C-2 or C-4, and other oxygenated substituents are usually connected to the skeleton, such as carboxyl and methoxyl substituents [19].

![Figure 1. Basic structures of orcinol paradepsides, orcinol metadepsides, β-orcinol paradepsides, β-orcinol metadepsides, and mixed orcinol β-orcinol depsides.](image-url)

Depsides are common lichen metabolites [20–22]. However, they have also been reported in some higher plants and fungi [19,23–27]. Contrary to the lichen depsides, fungal depsides are not widely distributed and are isolated only from a restricted number of fungi (Table 1). It was reported that depsides possess remarkable bioactivities: anti-cancer, anti-diabetic, antibacterial, antiviral, anti-inflammatory, antifungal, antifouling, antioxidant, and various enzyme inhibitory activities. Therefore, these metabolites are of considerable importance as a prospective lead motif for medicinal chemistry. Our review of the literature indicated that there is currently no review on fungal depsides. Herein, 110 depsides reported in the literature from fungal sources have been listed, with a summary of their biosynthesis, physical constants, spectral data, sources, bioactivities, and references (Tables 1, 2 and S1, Figures 2–17). The data was displayed for each compound in the following manner: name, chemical structure, optical rotation, melting point, UV, molecular and weight formulae, NMR, and reference(s) (Table S1). The principal goal of this work is to provide the researchers with detailed references that can assist them in the rapid identification of isolated depsides by comparing their physical and spectral data. Nevertheless, highlighting the bioactivities of these metabolites may attract the attention of synthetic and medicinal chemists to synthesize new agents, using known depsides as start materials. Literature searches for published studies were performed through diverse databases: Web of Science, PubMed (MedLine), GoogleScholar, Scopus, SciFinder, Springer-Link, Wiley, and ACS (American Chemical Society) Publications using keywords (depsides, isolation, fungi, biosynthesis, NMR, and biological activities).

2. Biosynthesis of Depsides

Depsides are acetyl-poly-malonyl-derived polyketides that are biosynthesized by polyketide synthase (PKS) [28–34]. PKS is composed of a minimal set of KS (ketosynthase), AT (acyltransferase), and ACP (acyl carrier protein) domains [30]. The non-reduced framework of the depside rings reveals that its corresponding PKS belongs to non-reducing PKSs.
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(NR-PKSs). Depsides consist of two orsellinic acid molecules, connected by an ester linkage. Therefore, orsellinic acid can be considered the constructing unit of all depsides [28]. Biosynthetically, orsellinic acid is produced from a linear tetraketide chain. This chain is formed through an acetate-malonate pathway that is catalyzed by PKSs [29,30]. The tetraketide chain forming β-orsellinic acid (methyl-3-orsellinate) is produced by introducing a \( \text{CH}_3 \) group obtained from SAM (S-adenosylmethionine) by the methyl transferase (CMeT) domain of the corresponding PKS [31]. Then, the non-enzymatic 2,7-aldol condensation of these chains produces orsellinic and β-orsellinic acids. Furthermore, the molecular skeleton is probably designed by post-biosynthetic tailoring enzymes, such as cyclases and hydrolases [18]. 

\( \text{p} \)-Depsides are produced by the condensation of either orsellinic acid and orcinol derivatives or by two methyl-3-orsellinate or orsellinate moieties, through the formation of an ester [12]. The consequent condensation of an additional unit produces a tri-depside, and two moieties yield a tetra-depside [32]. Moreover, depsides containing alkyl side-chains can be produced by the reduction of the terminal ketone groups, resulting in the required saturated alkyl moieties. 

\( \text{m} \)-Depsides are formed through the hydroxylation of the para-depside B-ring, subsequently followed by rearrangement [33] (Figure 2).

3. Biological Activities

Despite the unique structures of depsides, they have not been well investigated in terms of their pharmacological activities. The literature survey revealed that depsides have various biological activities (Table 2). Thus, an overview of their reported pharmacological activities is summarized in Table 2 and is described in detail below.

3.1. Antitumor Activity

Cancer is considered the second cause of death after cardiovascular diseases [34]. In 2020, around 10 million deaths were estimated to have been due to cancer, 70% of which were in middle- and low-income countries [35]. Most of the anticancer agents cannot distinguish between abnormal and normal cells; thus, researchers have been directed to develop selective and safe anticancer drugs that target the abnormal cancerous cells and have minimal effects on normal cells. Fungi represent an important source of anticancer agents, with significant benefits against various tumors [36]. It is noteworthy to mention that most of the reported depsides showed activity on cancer cells with no or little effect on normal cells.

Lünne et al. [37] evaluated the antitumor effect of lecanoric acid (1) and ethyl lecanorate (2) purified from *Claviceps purpurea* on HepG2 (human liver cancer cells) and CCF-STTG1 (human astrocytoma cells) using the CTC (5-cyano-2,3-bis(4-methylphenyl)-2H-tetrazolium chloride) assay. Both metabolites produced a dose-dependent antitumor effect on the tested cell lines. They reduced the CCF-STTG1 cell viability down to ~60%, at a concentration of 40 \( \mu \text{M} \), and HepG2 cell viability by ~30% and 40%, respectively. Similar to HepG2 cells, 2 had the strongest antitumor effect on CCF cells (IC\( _{50} \) value of 54 \( \mu \text{M} \)) [37]. In the MTT (3-(4,5-dimethylthiazol-2-yl))-2,5-diphenyl-2H-tetrazolium bromide) assay, aspergisides A (3), B (4), and C (5) showed weak antitumor activity, with IC\( _{50} \) values in the range of 45–114 \( \mu \text{M} \) toward Vero, MCF-7, and KB cell lines, compared with doxorubicin [38]. MS-3 (22) was inactive against Ehrlich ascites for leukemia and carcinoma in vivo; however, it was active toward Yoshida sarcoma cells (ID\( _{50} \) value of 85 \( \mu \text{g/mL} \)) in vitro. Its activity was suggested to be due to a glyoxalase inhibition, as it possessed a glyoxalase inhibitory effect with an ID\( _{50} \) value of 12 \( \mu \text{g/mL} \) in the spectrophotometric assay [39]. In addition, 23 possessed significant antitumor activity toward A549 and HepG2, with IC\( _{50} \) values of 13.14 and 49.02 \( \mu \text{M} \), respectively, compared to cisplatin (IC\( _{50} \) 14.33 and 18.74, respectively) in the MTT assay [40]. Compounds 27–29 were assayed against NCI-H187, Vero, BC, and KB cell lines, employing an MTT assay. Compounds 27 and 28 exhibited a significant antitumor effect against BC, with IC\( _{50} \) values of 8.8 and 4.4 \( \mu \text{M} \), respectively, compared to ellipticine (IC\( _{50} \) 0.49 \( \mu \text{M} \)), while they showed weak to moderate effectiveness toward other cell lines, with IC\( _{50} \) values ranging from 13.0 to 34.3 \( \mu \text{M} \) [41]. Arenicolins A (30) and B (31), two new dep-
sides having C-glycosyl moiety and dual heptyl side-chains, were isolated from *Penicillium arenicola* and assessed for antitumor activity at a concentration of 30.0 µM toward IMR-32, HCT-116, and BT-474 cell lines using an ICC (immunocytochemistry) assay. Compound 30 reduced cell viability with IC₅₀ values of 6.0, 7.3, and 9.7 µM, respectively, compared to 5-FU (5-fluorouracil, IC₅₀ 6.5 µM for HCT-116 and 5.7 µM for IMR-32). However, 31 did not have a significant antitumor effect toward the tested cell lines at a concentration of >30 µM [42].

CRM646-A (36) and CRM646-B (37) were discovered from *Acremonium* sp. that showed a potent anti-metastatic capacity toward B16-F10 melanoma cells, with an IC₅₀ value of 15 µM for 36 and IC₅₀ 30 µM for 37 [43]. They also caused the dose-dependent inhibition of heparinase, with IC₅₀ values of 3 and 10 µM, respectively, in comparison to suramin (IC₅₀ value of 5 µM) [43,44]. Asami et al. established that CRM646-A (36) induced the inhibition of cells’ invasion, migration, and growth in tumor cells, due to its induction of nucleus condensation, plasma membrane disruption, and morphological changes in result to the increase in Ca²⁺ levels; thus, it could potentially be used as an effective anti-metastatic agent [45]. Compounds 45 and 46 in the MTT assay showed an antitumor effect against A549 and MAD-MB-435, with IC₅₀ values of 16.82 and 37.01 µM, and 20.75 and 37.73 µM, respectively, compared with epirubicin (IC₅₀ 0.26 and 5.60 µM, respectively); however, 11 did not exhibit obvious activity [46]. Togashi et al. reported that 36 and 49 prohibited telomerase activity at doses of 3.2 and 32 µM, respectively. In addition, they inhibited viral reverse transcriptase activity at almost the same dose levels; therefore, they may inhibit universal RNA-dependent DNA polymerases [47]. Compound 50, a tridepside, was obtained from MSX 55526 fungus and showed moderate activity against the MCF-7, H460, and SF268 cell lines in the SRB assay, with IC₅₀ values of 7.3, 6.6, and 8.1 µM, respectively, compared to camptothecin (IC₅₀ 0.07, < 0.01, and 0.04 µM, respectively) [48].
Table 1. List of fungal depsides (Fungal source, host, and place).

| Compound Name                         | Fungus                                      | Host (Part)                             | Source, Place                                           | Ref. |
|----------------------------------------|---------------------------------------------|-----------------------------------------|--------------------------------------------------------|------|
| Lecanoric acid (1)                     | *Claviceps purpurea* (PKS7)                 | -                                       | Culture                                                | [37] |
| Ethyl lecanorate (2)                    | *Claviceps purpurea* (PKS7)                 | -                                       | Culture                                                | [37] |
| Aspergiside A (3)                      | *Aspergillus unguis* PSU-RSPG204 (BCC56860) | -                                       | Soil, Surat Thani Province, Thailand                   | [38] |
| Aspergiside B (4)                      | *Aspergillus unguis* PSU-RSPG204 (BCC56860) | -                                       | Soil, Surat Thani Province, Thailand                   | [38] |
| Aspergiside C (5)                      | *Aspergillus unguis* PSU-RSPG204 (BCC56860) | -                                       | Soil, Surat Thani Province, Thailand                   | [38] |
| Lecanorin D (6)                        | *Setophoma* sp. (KM288713)                 | Fruits of *Psidium guajava*             | Sio Carlos local trade, Sao Paulo state, Brazil        | [19] |
| Lecanorin E (7)                        | *Setophoma* sp. (KM288713)                 | Fruits of *Psidium guajava*             | Sio Carlos local trade, Sao Paulo state, Brazil        | [19] |
| Lecanorin F (8)                        | *Setophoma* sp. (KM288713)                 | Fruits of *Psidium guajava*             | Sio Carlos local trade, Sao Paulo state, Brazil        | [19] |
| 3-Hydroxy-2,5-dimethylphenyl 2,4-dihydroxy-3,6-dimethylbenzoate (9) | *Setophoma* sp. (KM288713) | Fruits of *Psidium guajava*             | Sio Carlos local trade, Sao Paulo state, Brazil        | [49] |
| 3-Hydroxy-2,4,5-trimethylphenyl 2,4-dihydroxy-3,6-dimethylbenzoate (10) | *Setophoma* sp. (KM288713) | Fruits of *Psidium guajava*             | Sio Carlos local trade, Sao Paulo state, Brazil        | [49] |
| Colletotric acid C (11)                | *Phoma* sp. (SYSU-SK-7)                     | Healthy branch of *Kandelia candel*     | Shankou Mangrove Nature Reserve, Guangxi Province, China | [46] |
| Agonodepside A (12)                    | Fungal strain (F7524)                      | Leaves of *Derris thyrsiflora*          | Singapore                                               | [50] |
| Agonodepside B (13)                    | Fungal strain (F7524)                      | Leaves of *Derris thyrsiflora*          | Singapore                                               | [50] |
| Guisinol (14)                          | *Emericella unguis* (isolate 1 (M87-2))     | *Stomolopus melagris*                   | Paria Bay, Venezuela                                     | [51] |
|                                       | *Emericella unguis* (M90B-10)               | Soft part of an unidentified mollusc    | Paria Bay, Venezuela                                     | [51] |
| Thielavin Z7 (15)                      | *Thielaviu* sp (UST030930-004)             | -                                       | 12-d Biofilms developed at the pier of the Hong Kong University of Science and Technology in Port Shelter, Hong Kong, China | [52] |
| Sterenin J (16)                        | *Stereum hirsutum* (EU851110)              | -                                       | Tibetan mountain                                         | [53] |
| Sterenin E (17)                        | *Stereum hirsutum* (EU851110)              | -                                       | Tibetan mountain                                         | [53] |
| Sterenin F (18)                        | *Stereum hirsutum* (EU851110)              | -                                       | Tibetan mountain                                         | [53] |
| Compound Name | Fungus | Host (Part) | Source, Place | Ref. |
|---------------|--------|-------------|---------------|-----|
| Sterenin G (19) | *Stereum hirsutum* (EU851110) | - | Tibetan mountain | [53] |
| Sterenin H (20) | *Stereum hirsutum* (EU851110) | - | Tibetan mountain | [53] |
| Sterenin I (21) | *Stereum hirsutum* (EU851110) | - | Tibetan mountain | [53] |
| MS-3 (22) | *Stereum hirsutum* (EU851110) | - | Tibetan mountain | [39,53–56] |
| Sterenin J (23) | *Stereum rameale* (strain 2511) | The bark of a dead tree | Native forest of *Nothofagus* species (Nothofagaceae), near Ñuble National Reserve, Ñuble Province, Chile | [57,58] |
| 4′-Hydroxy-5′-methoxy-6′-(3′'-methyl-2′'-butenyl)-phenyl-2,4-dihydroxy-6′-methylbenzoate | *Stereum hirsutum* (AB733150.1) | - | Tibetan Plateau, China | [40] |
| 4-Hydroxy-3-methoxy-2-(3-methylbut-2-en-1-yl)phenyl | *Stereum hirsutum* (EU851110) | - | Tibetan mountain | [53] |
| 4′-Hydroxy-6′-(3′'-methyl-2′'-butenyl)-phenyl-2,4-dihydroxy-6′-methylbenzoate | *Stereum hirsutum* (AB733150.1) | - | Tibetan Plateau, China | [40] |
| Nordivaricatic acid (25) | Fungal strain | - | Soil, Yunnan Province, China | [25] |
| 65-Divarinyl divarate (26) | Fungal strain | - | Soil, Yunnan Province, China | [25] |
| KS-501a (3-Heptyl-5-hydroxyphenyl 2-heptyl-4,6-dihydroxybenzoate) (27) | *Acremonium* sp. (BCC 14080) | Palm leaf | Khao Yai National Park, Nakhon Ratcasima Province, Thailand | [41,56] |
| KS-501a-2-O-β-D-galactopyranose (28) | *Acremonium* sp. (BCC 14080) | Palm leaf | Khao Yai National Park, Nakhon Ratcasima Province, Thailand | [41] |
| KS-501a-2-O-β-D-digalactopyranose (29) | *Acremonium* sp. (BCC 14080) | Palm leaf | Khao Yai National Park, Nakhon Ratcasima Province, Thailand | [41] |
| Arenicolin A (30) | *Penicillium arenicola* (NRRL 8095) | - | Soil, British Columbia, Canada | [42] |
Table 1. Cont.

| Compound Name       | Fungus                  | Host (Part) | Source, Place                                          | Ref.   |
|---------------------|-------------------------|-------------|-------------------------------------------------------|--------|
| Arenicolin B (31)   | *Penicillium arenicola* (NRRL 8095) | -           | Soil, British Columbia, Canada                        | [42]   |
|                     | *Penicillium arenicola* (3392) | -           | Soil, pine forest sample, near Kiev, Ukraine          | [42]   |
|                     | *Penicillium arenicola* (31507) | -           | Mineral soil, under *Pinus resinosa*, Ontario, Canada | [42]   |
|                     | *Penicillium arenicola* (31509) | -           | Oil-soaked soil sample, Norman Wells, NW Territories, Canada | [42] |
| Aquastatin A (32)   | *Fusarium aquaeductuum* (SANK 11089) | -           | Slime fluxes, Karuizawa, Nagano Prefecture, Japan     | [59]   |
|                     | *Cosmospora* sp. SF-5060       | -           | Inter-tidal sediment, Gejae Island, Korea            | [60]   |
|                     | *Sporothrix* sp. (FN611)      | -           | Soil, Jeonju City, Jeollabuk-do, Korea               | [61]   |
| Depsitinuside (33)  | Endophytic fungus, internal strain (8984) | Leaves of *Viburnum tinus* | -                                                   | [62]   |
| KS-501 (34)         | *Sporothrix* sp. (KAC-1985)   | Fallen leaf | Yamakita-cho, Ashgarakami-gun, Kanagawa Prefecture, Japan | [56,63] |
| CRM646-A (36)       | *Acremonium* sp. (MT70646)    | -           | Soil, Geryong, Kongju, Korea                         | [43,44,47] |
| CRM646-B (37)       | *Acremonium* sp. (MT70646)    | -           | Soil, Geryong, Kongju, Korea                         | [43,44,47] |
| Sterenin A (38)     | *Stereum* sp. (SANK 21205)    | -           | Spore print of fresh basidiocarps, Gunma Prefecture, Japan | [64]   |
| Compound Name         | Fungus                     | Host (Part) | Source, Place                                                                 | Ref. |
|-----------------------|----------------------------|-------------|-------------------------------------------------------------------------------|------|
| Sterenin B (39)       | Stereum sp. (SANK 21205)   | -           | Spore print of fresh basidiocarps, Gunma Prefecture, Japan                    | [64] |
| Sterenin C (40)       | Stereum sp. (SANK 21205)   | -           | Spore print of fresh basidiocarps, Gunma Prefecture, Japan                    | [64] |
| Sterenin D (41)       | Stereum sp. (SANK 21205)   | -           | Spore print of fresh basidiocarps, Gunma Prefecture, Japan                    | [64] |
| Sterenin K (42)       | Stereum hirsutum (EU851110)| -           | Tibetan mountain                                                              | [53] |
| Sterenin L (43)       | Stereum hirsutum (EU851110)| -           | Tibetan mountain                                                              | [53] |
| Sterenin M (44)       | Stereum hirsutum (EU851110)| -           | Tibetan mountain                                                              | [53] |
| Colletotric acid A (45)| Phoma sp. (SYSU-SK-7)   | Healthy branch of Kandelia candel | Shankou Mangrove Nature Reserve, Guangxi Province, China | [46] |
| Colletotricum gloeosporioides | Stem of Artemisia mongolica | | Hillsides of the Zijin Mountain, suburb of Nanjing, China | [65] |
| Colletotric acid B (46)| Phoma sp. (SYSU-SK-7)   | Healthy branch of Kandelia candel | Shankou Mangrove Nature Reserve, Guangxi Province, China | [46] |
| PS-990 (47)           | Acremonium sp. (KY12702)  | -           | Soil, Tokyo, Japan                                                            | [66] |
| Thielavin A (48)      | Chaetomium cariniiacum (ATCC 46463) | - | American Type Culture Collection | [62] |
| Thielavia sp. (UST030930-004) | - | 12-d Biofilms developed at the pier of the Hong Kong University of Science and Technology in Port Shelter, Hong Kong, China | [52] |
| Endophytic fungus MEXU (27905) | Healthy leaves of Hintonia latiflora | México | | [67] |
| Thielavin B (49)      | Coniochaeta sp. (10F058a) | -           | Soil, Korea                                                                   | [68] |
| Chaetomium cariniiacum (ATCC 46463) | - | American Type Culture Collection | [62] |
| Coniochaeta sp. (10F058a) | - | Soil, Ochang, Korea. | [68] |
| Thielavin B methyl ester (50) | Mycosynethetic fungal strain 55526 | - | Leaf litter, North Carolina Smoky Mountains, United States. | [48] |
| Compound Name | Fungus | Host (Part) | Source, Place | Ref. |
|---------------|--------|-------------|---------------|-----|
| Thielavin C (51) | Chaetomium carinthiacum (ATCC 46463) | - | American Type Culture Collection | [62] |
| Thielavia terricola (SANK 10475) | - | | [69] |
| Thielavin D (52) | Chaetomium carinthiacum (ATCC 46463) | - | American Type Culture Collection | [62] |
| Thielavin E (53) | Chaetomium carinthiacum (ATCC 46463) | - | American Type Culture Collection | [62] |
| Thielavia terricola RF-143 | - | | [70] |
| Thielavin F (54) | Chaetomium carinthiacum (ATCC 46463) | - | American Type Culture Collection | [62] |
| Coniochaeta sp. (10F058a) | - | Soil, Ochang, Korea | [68] |
| Thielavin G (55) | Chaetomium carinthiacum (ATCC 46463) | - | American Type Culture Collection | [62] |
| Thielavin H (56) | Chaetomium carinthiacum (ATCC 46463) | - | American Type Culture Collection | [62] |
| Thielavia sp UST030930-004 | - | 12-d Biofilms developed at the pier of the Hong Kong University of Science and Technology in Port Shelter, Hong Kong, China | [52] |
| Thielavin I (57) | Chaetomium carinthiacum (ATCC 46463) | - | American Type Culture Collection | [62] |
| Thielavin J (58) | Chaetomium carinthiacum (ATCC 46463) | - | American Type Culture Collection | [62] |
| Thielavia sp UST030930-004 | - | 12-d Biofilms developed at the pier of the Hong Kong University of Science and Technology in Port Shelter, Hong Kong, China | [52] |
| Endophytic fungus MEXU 27905 | Healthy leaves of Hintonia latiflora | México | [67] |
| Thielavin K (59) | Chaetomium carinthiacum (ATCC 46463) | - | American Type Culture Collection | [62] |
| Thielavia sp UST030930-004 | - | 12-d Biofilms developed at the pier of the Hong Kong University of Science and Technology in Port Shelter, Hong Kong, China | [52] |
| Endophytic fungus MEXU 27905 | Healthy leaves of Hintonia latiflora | México | [67] |
| Thielavin L (60) | Chaetomium carinthiacum (ATCC 46463) | - | American Type Culture Collection | [62] |
| Thielavin M (61) | Chaetomium carinthiacum (ATCC 46463) | - | American Type Culture Collection | [62] |
| Thielavin N (62) | Chaetomium carinthiacum (ATCC 46463) | - | American Type Culture Collection | [62] |
| Thielavin O (63) | Chaetomium carinthiacum (ATCC 46463) | - | American Type Culture Collection | [62] |
| Compound Name | Fungus | Host (Part) | Source, Place | Ref. |
|---------------|--------|-------------|---------------|------|
| Thielavin P (64) | *Chaetomium carinthiacum* (ATCC 46463) | - | American Type Culture Collection | [62] |
| Thielavin Q (65) | Coniochaeta sp. (10F058a) | - | Soil, Ochang, Korea | [68] |
| Thielavin S (66) | The endophyte *Setophoma* sp. (KM288713) | Fruits of *Psidium guajava* | Sio Carlos local trade, Sao Paulo state, Brazil | [19] |
| Thielavin T (67) | The endophyte *Setophoma* sp. (KM288713) | Fruits of *Psidium guajava* | Sio Carlos local trade, Sao Paulo state, Brazil | [19] |
| Thielavin U (68) | The endophyte *Setophoma* sp. (KM288713) | Fruits of *Psidium guajava* | Sio Carlos local trade, Sao Paulo state, Brazil | [19] |
| Thielavin V (69) | The endophyte *Setophoma* sp. (KM288713) | Fruits of *Psidium guajava* | Sio Carlos local trade, Sao Paulo state, Brazil | [19] |
| Thielavin W (70) | *Thielavia* sp UST030930-004 | - | 12-d Biofilms developed at the pier of the Hong Kong University of Science and Technology in Port Shelter, Hong Kong, China | [52] |
| Thielavin X (71) | *Thielavia* sp UST030930-004 | - | 12-d Biofilms developed at the pier of the Hong Kong University of Science and Technology in Port Shelter, Hong Kong, China | [52] |
| Thielavin Y (72) | *Thielavia* sp (UST030930-004) | - | 12-d Biofilms developed at the pier of the Hong Kong University of Science and Technology in Port Shelter, Hong Kong, China | [52] |
| Thielavin Z (73) | *Thielavia* sp (UST030930-004) | - | 12-d Biofilms developed at the pier of the Hong Kong University of Science and Technology in Port Shelter, Hong Kong, China | [52] |
| Thielavin Z₁ (74) | *Thielavia* sp (UST030930-004) | - | 12-d Biofilms developed at the pier of the Hong Kong University of Science and Technology in Port Shelter, Hong Kong, China | [52] |
| Thielavin Z₂ (75) | *Thielavia* sp (UST030930-004) | - | 12-d Biofilms developed at the pier of the Hong Kong University of Science and Technology in Port Shelter, Hong Kong, China | [52] |
| Thielavin Z₃ (76) | *Thielavia* sp (UST030930-004) | - | 12-d Biofilms developed at the pier of the Hong Kong University of Science and Technology in Port Shelter, Hong Kong, China | [52] |
| Thielavin Z₄ (77) | *Thielavia* sp (UST030930-004) | - | 12-d Biofilms developed at the pier of the Hong Kong University of Science and Technology in Port Shelter, Hong Kong, China | [52] |
| Compound Name | Fungus | Host (Part) | Source, Place | Ref. |
|---------------|--------|-------------|---------------|------|
| Thielavin Z₅ (78) | *Thielavia* sp (UST030930-004) | - | 12-d Biofilms developed at the pier of the Hong Kong University of Science and Technology in Port Shelter, Hong Kong, China | [52] |
| Thielavin Z₆ (79) | *Thielavia* sp (UST030930-004) | - | 12-d Biofilms developed at the pier of the Hong Kong University of Science and Technology in Port Shelter, Hong Kong, China | [52] |
| Hydroxy-2,5-dimethylphenyl 4-[(2,4-dihydroxy-3,6-dimethylbenzoyl)oxy]-2-hydroxy-3,6-dimethylbenzoate (80) | *Cladosporium uredinicola* | Fruits of *Psidium guajava* | São Carlos local trade, São Paulo state, Brazil | [49] |
| Hydroxy-2,4,5-trimethylphenyl 4-[(2,4-dihydroxy-3,6-dimethylbenzoyl)oxy]-2-hydroxy-3,6-dimethylbenzoate (81) | *Cladosporium uredinicola* | Fruits of *Psidium guajava* | São Carlos local trade, São Paulo state, Brazil | [49] |
| Gyrophoric acid (82) | *Humicola* sp. FO-2942 | - | Soil, Nagasaki, Japan | [71,72] |
| Trivaric acid (83) | Fungal strain | - | Soil, Yunnan Province, China | [25] |
| Cytonic acid A (84) | *Cytonaema* sp. (F32027) | *Quercus* sp. | United Kingdom | [73] |
| Cytonic acid B (85) | *Cytonaema* sp. (F32027) | *Quercus* sp. | United Kingdom | [73] |
| Amidepsine D (86) | *Humicola* sp. (FO-2942) | - | Soil, Nagasaki, Japan | [74,75] |
| Amidepsine K (87) | *Humicola* sp. (FO-2942) | - | Soil, Nagasaki, Japan | [71] |
| Amidepsine A (88) | *Humicola* sp. (FO-2942) | - | Soil, Nagasaki, Japan | [74,75] |
| Amidepsine B (89) | *Humicola* sp. (FO-2942) | - | Soil, Nagasaki, Japan | [74,75] |
| Amidepsine C (90) | *Humicola* sp. (FO-2942) | - | Soil, Nagasaki, Japan | [74,75] |
| Amidepsine E (91) | *Humicola* sp. (FO-5969) | - | Soil, Asaka, Saitama, Japan | [76] |
| Amidepsine F (92) | *Humicola* sp. (FO-2942) | - | Soil, Nagasaki, Japan | [71] |
| Amidepsine G (93) | *Humicola* sp. (FO-2942) | - | Soil, Nagasaki, Japan | [71] |
| Amidepsine H (94) | *Humicola* sp. (FO-2942) | - | Soil, Nagasaki, Japan | [71] |
| Amidepsine I (95) | *Humicola* sp. (FO-2942) | - | Soil, Nagasaki, Japan | [71] |
| Amidepsine J (96) | *Humicola* sp. (FO-2942) | - | Soil, Nagasaki, Japan | [71] |
| Compound Name | Fungus                          | Host (Part) | Source, Place | Ref. |
|---------------|--------------------------------|-------------|---------------|------|
| 44-CJ-21,164 (97) | *Chloridium* sp. (CL48903). | -           | China         | [77] |
| Thielocin A1α (98) | *Thielavia terricola* (RF-143) | -           | Culture       | [78] |
| Thielocin A1β (99) | *Thielavia terricola* (RF-143) | -           | Culture       | [78] |
| Thielocin A2α (100) | *Thielavia terricola* (RF-143) | -           | Culture       | [70] |
| Thielocin A2β (101) | *Thielavia terricola* (RF-143) | -           | Culture       | [70] |
| Thielocin A4α (102) | *Thielavia terricola* (RF-143) | -           | Culture       | [79] |
| Thielocin A4β (103) | *Thielavia terricola* (RF-143) | -           | Culture       | [79] |
| Thielocin A3 (104) | *Thielavia terricola* (RF-143) | -           | Culture       | [70] |
| Thielocin B1 (105) | *Thielavia terricola* (RF-143) | -           | Culture       | [70] |
| Thielocin B2 (106) | *Thielavia terricola* (RF-143) | -           | Culture       | [70] |
| Thielocin B3 (107) | *Thielavia terricola* (RF-143) | -           | Culture       | [80] |
| Thielocin B3 monomethyl ester B (108) | *Thielavia terricola* (RF-143) | -           | Culture       | [80] |
| Thielocin B3 monomethyl ester C (109) | *Thielavia terricola* (RF-143) | -           | Culture       | [80] |
| Thielocin B3 monomethyl ester D (110) | *Thielavia terricola* (RF-143) | -           | Culture       | [80] |
Figure 3. Chemical structures of di-depsides 1–16.
Figure 4. Chemical structures of di-depsides 17–27.
| Compound Name       | Activity | Assay/Microorganism/Model/Enzyme | Results          | Positive Control                  | Ref.  |
|---------------------|----------|----------------------------------|------------------|-----------------------------------|-------|
| Lecanoric acid (1)  | Antitumor| Colorimetric CTC/HepG2           | 40.0 µM (IC₅₀)   | T-2 toxin 10.0 µM (IC₅₀)          | [37]  |
| Ethyl lecanorate (2)| Antitumor| Colorimetric CTC/HepG2           | 40.0 µM (IC₅₀)   | T-2 toxin 10.0 µM (IC₅₀)          | [37]  |
|                     |          |                                  |                  |                                   |       |
| Aspergiside A (3)   | Antibacterial | Agar diffusion assay / *S. aureus* ATCC25923 | 8 µg/mL (MIC) | Vancomycin 0.25 µg/mL (MIC) | [38]  |
|                     | Antibacterial | Agar diffusion assay / MRSA | 8 µg/mL (MIC) | Vancomycin 0.50 µg/mL (MIC) | [38]  |
|                     | Antifungal  | Agar diffusion assay / *C. albicans* NCPF3153 | 200 µg/mL (MIC) | Amphotericin B 0.25 µg/mL (MIC) | [38]  |
|                     | Antibacterial | Agar diffusion assay / *C. neoformans* ATCC 9013 | 64 µg/mL (MIC) | Amphotericin B 0.25 µg/mL (MIC) | [38]  |
|                     | Antifungal  | Agar diffusion assay / *M. gypseum* SH-MU-4 | 128 µg/mL (MIC) | Miconazole 1.0 µg/mL (MIC) | [38]  |
|                     | Antitumor   | MTT/KB                           | 53.69 µM (IC₅₀)  | Ellipticine 10.56 µM (IC₅₀) Doxorubicin 0.65 µM (IC₅₀) | [38]  |
|                     | Antitumor   | MTT/MCF-7                        | 54.42 µM (IC₅₀)  | Doxorubicin 16.83 µM (IC₅₀) Tamoxifen 20.78 µM (IC₅₀) | [38]  |
|                     | Antitumor   | MTT/Vero cells                   | 83.75 µM (IC₅₀)  | Ellipticine 4.55 µM (IC₅₀) | [38]  |
| Aspergiside B (4)   | Antibacterial | Agar diffusion assay / *S. aureus* ATCC25923 | 128 µg/mL (MIC) | Vancomycin 0.25 µg/mL (MIC) | [38]  |
|                     | Antibacterial | Agar diffusion assay / MRSA | 128 µg/mL (MIC) | Vancomycin 0.50 µg/mL (MIC) | [38]  |
|                     | Antibacterial | Agar diffusion assay / *C. neoformans* ATCC 9013 | 32 µg/mL (MIC) | Amphotericin B 0.25 µg/mL (MIC) | [38]  |
|                     | Antitumor   | MTT/Vero cells                   | 114.40 µM (IC₅₀) | Ellipticine 4.55 µM (IC₅₀) | [38]  |
| Aspergiside C (5)   | Antibacterial | Agar diffusion assay / *S. aureus* ATCC25923 | 200 µg/mL (MIC) | Vancomycin 0.25 µg/mL (MIC) | [38]  |
| Compound Name | Activity       | Assay/Microorganism/Model/Enzyme                 | Results                  | Positive Control                              | Ref. |
|---------------|----------------|-----------------------------------------------|--------------------------|-----------------------------------------------|------|
| MS-3 (22)     | Antibacterial  | Plate diffusion/B. cereus                     | 25 mm (IZD)              | Streptomycin 28 mm (IZD)                       | [57] |
| Sterenin G (19) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 6.03 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin H (20) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 22.70 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin I (21) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 72.50 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin J (16) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 65.70 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin E (17) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 7.62 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin F (18) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 3.06 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Thielavin Z7 (15) | Antifouling | Balanus Amphiutrite(cyprid larvae) | 3.20 µM (EC50) | Butenolide 4.62 µM (EC50) | [52] |
| Sterenin I (21) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 72.50 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin H (20) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 22.70 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin G (19) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 6.03 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin E (17) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 7.62 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin F (18) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 3.06 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin J (16) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 65.70 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Thielavin Z7 (15) | Antifouling | Balanus Amphiutrite(cyprid larvae) | 3.20 µM (EC50) | Butenolide 4.62 µM (EC50) | [52] |
| 3-Hydroxy-2,5-dimethylphenyl 2,4-dihydroxy-3,6-dimethylbenzoate (9) | Antibacterial | Microbroth dilution/S. aureus | 250 µg/mL (MIC) | Vancomycin and tetracycline | [49] |
| Colletotric acid C (11) | Antibacterial | Agar diffusion assay/B. subtilis | 9.70 µg/mL (MIC) | Ampicillin 0.07 µg/mL (MIC) | [46] |
| Agonodepside A (12) | Enoyl-ACP reductase inhibition | Fluorometric InhA assay/M. tuberculosis InhA | 74 µM (IC50) | Triclosan 3 µM (IC50) | [50] |
| Sterenin J (16) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 65.70 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin E (17) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 7.62 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin F (18) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 3.06 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin G (19) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 6.03 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin H (20) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 22.70 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin I (21) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 72.50 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin G (19) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 6.03 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin H (20) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 22.70 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin I (21) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 72.50 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin G (19) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 6.03 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin H (20) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 22.70 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Sterenin I (21) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 72.50 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| Compound Name | Activity | Assay/Microorganism/Model/Enzyme | Results | Positive Control | Ref. |
|---------------|----------|----------------------------------|---------|------------------|-----|
| Antibacterial | Plate diffusion/B. subtilis | 25 mm (IZD) | Streptomycin 32 mm (IZD) Penicillin G 28 mm (IZD) | [57] |
| Antibacterial | Plate diffusion/S. aureus | 28 mm (IZD) | Streptomycin 30 mm (IZD) Penicillin G 27 mm (IZD) | [57] |
| α-Glucosidase inhibitory | Colorimetric/α-Glucosidase inhibitor | 23.82 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| 4′-Hydroxy-5′-methoxy-6′-(3″-methyl-2″-butenyl)-phenyl-2,4-dihydroxy-6-methylbenzoate | Anti-inflammatory NO inhibitory potential | LPS-induced macrophages RAW 264.7 | 19.17 µM (IC50) | Hydrocortisone 48.15 µM (IC50) | [40] |
| Antibacterial | Agar plate diffusion/MRSA | 25 µg/mL (MIC) | Ancomycin 1.0 µg/mL (MIC) | [40] |
| Antibacterial | Agar plate diffusion/S. aureus | 25 µg/mL (MIC) | Ancomycin 1.0 µg/mL (MIC) | [40] |
| Antibacterial | Agar plate diffusion/B. subtilis | 25 µg/mL (MIC) | Ancomycin 0.5 µg/mL (MIC) | [40] |
| Antitumor | MTT/A549 | 13.14 µM (IC50) | Cisplatin 14.33 µM (IC50) | [40] |
| Antitumor | MTT/HepG2 | 49.02 µM (IC50) | Cisplatin 18.74 µM (IC50) | [40] |
| α-Glucosidase inhibitory | Colorimetric/α-Glucosidase inhibitor | 14.17 µM (IC50) | Acarbose 640.88 µM (IC50) | [53] |
| 4′-Hydroxy-6′-(3″-methyl-2″-butenyl)-phenyl-2,4-dihydroxy-6-methylbenzoate | Antibacterial | Agar plate diffusion/MRSA | 25 µg/mL (MIC) | Ancomycin 1.0 µg/mL (MIC) | [40] |
| Antibacterial | Agar plate diffusion/S. aureus | 25 µg/mL (MIC) | Ancomycin 1.0 µg/mL (MIC) | [40] |
| Antibacterial | Agar plate diffusion/B. subtilis | 50 µg/mL (MIC) | Ancomycin 0.5 µg/mL (MIC) | [40] |
| Antitumor | MTT/KB | 13.0 µM (IC50) | Ellipticine 1.99 µM (IC50) | [41] |
| Antitumor | MTT/BC | 8.8 µM (IC50) | Ellipticine 0.49 µM (IC50) | [41] |
| Antitumor | MTT/NC1-H187 | 13.6 µM (IC50) | Ellipticine 1.77 µM (IC50) | [41] |
| Antitumor | MTT/Vero cells | 34.3 µM (IC50) | Ellipticine 1.94 µM (IC50) | [41] |
| KS-501a (27) | Antimalarial activity | Microculture radioisotope technique/Plasmodium falciparum K1 | 9.9 µM (IC50) | Dihydroartemisinin 0.0039 µM (IC50) | [41] |
| Antitumor | MTT/KB | 13.0 µM (IC50) | Ellipticine 1.99 µM (IC50) | [41] |
| Antitumor | MTT/BC | 8.8 µM (IC50) | Ellipticine 0.49 µM (IC50) | [41] |
| Antitumor | MTT/NC1-H187 | 13.6 µM (IC50) | Ellipticine 1.77 µM (IC50) | [41] |
| KS-501a-2-O-β-D-galactopyranose (28) | Antitumor | MTT/KB | >25 µM (IC50) | Ellipticine 1.99 µM (IC50) | [41] |
| Antitumor | MTT/BC | 4.4 µM (IC50) | Ellipticine 0.49 µM (IC50) | [41] |
| Antitumor | MTT/NC1-H187 | 13.9 µM (IC50) | Ellipticine 1.77 µM (IC50) | [41] |
Table 2. Cont.

| Compound Name | Activity | Assay/Microorganism/Model/Enzyme | Results | Positive Control | Ref. |
|---------------|----------|---------------------------------|---------|------------------|------|
| KS-501a-2-O-β-D-digalactopyranose (29) | Antitumor | MTT/KB | >25 µM (IC₅₀) | Ellipticine 1.99 µM (IC₅₀) | [41] |
| | Antitumor | MTT/BC | 20.2 µM (IC₅₀) | Ellipticine 0.49 µM (IC₅₀) | [41] |
| | Antitumor | MTT/NC1-H187 | >25 µM (IC₅₀) | Ellipticine 1.77 µM (IC₅₀) | [41] |
| | Antitumor | MTT/Vero cells | 32.1 µM (IC₅₀) | Ellipticine 1.94 µM (IC₅₀) | [41] |
| Arenicolin A (30) | Antitumor | Immunocytochemistry ICC/HCT-116 | 7.3 µM (IC₅₀) | 5-FU 6.5 µM (IC₅₀) | [42] |
| | Antitumor | Immunocytochemistry ICC/IMR-32 | 6.0 µM (IC₅₀) | 5-FU 5.7 µM (IC₅₀) | [42] |
| | Antitumor | Immunocytochemistry ICC/BT-474 | 9.7 µM (IC₅₀) | - | [42] |
| Sterenin A (38) | 11β-HSD inhibitory | Luminescence immunoassay/HTRF cortisol | 240 nM (IC₅₀) | - | [64] |
| | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase inhibitor | 25.10 µM (IC₅₀) | Acarbose 640.88 µM (IC₅₀) | [53] |
| Sterenin B (39) | 11β-HSD inhibitory | Luminescence immunoassay/HTRF cortisol | 6600 nM (IC₅₀) | - | [64] |
| | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase inhibitor | 12.23 µM (IC₅₀) | Acarbose 640.88 µM (IC₅₀) | [53] |
| Sterenin C (40) | 11β-HSD inhibitory | Luminescence immunoassay/HTRF cortisol | 230 nM (IC₅₀) | - | [64] |
| | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase inhibitor | 3.31 µM (IC₅₀) | Acarbose 640.88 µM (IC₅₀) | [53] |
| Sterenin D (41) | 11β-HSD inhibitory | Luminescence immunoassay/HTRF cortisol | 2600 nM (IC₅₀) | - | [64] |
| | Antifungal | Plate diffusion/B. cinerea | 50 µg/mL (MFC) | Rovral 10 µg/mL (MFC) | [58] |
| | Antifungal | Plate diffusion/B. cinerea | 10 µg/mL (MIC) | Rovral 1 µg/mL (MFC) | [58] |
| Sterenin K (42) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 36.64 µM (IC₅₀) | Acarbose 640.88 µM (IC₅₀) | [53] |
| Sterenin L (43) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 13.09 µM (IC₅₀) | Acarbose 640.88 µM (IC₅₀) | [53] |
| Sterenin M (44) | α-Glucosidase inhibitory | Colorimetric/α-Glucosidase | 27.52 µM (IC₅₀) | Acarbose 640.88 µM (IC₅₀) | [53] |
Table 2. Cont.

| Compound Name       | Activity   | Assay/Microorganism/Model/Enzyme     | Results            | Positive Control         | Ref. |
|---------------------|------------|------------------------------------|--------------------|--------------------------|------|
| Colletotric acid A  | Antibacterial | Agar diffusion assay/B. subtilis | 25 µg/mL (MIC)     | Ampicillin 0.05 µg/mL (MIC) | [65] |
|                     | Antibacterial | Agar diffusion assay/B. subtilis | 6.55 µg/mL (MIC)   | Ampicillin 0.07 µg/mL (MIC) | [46] |
|                     | Antibacterial | Agar diffusion assay/S. aureus     | 50 µg/mL (MIC)     | Ampicillin 0.5 µg/mL (MIC) | [65] |
|                     | Antibacterial | Agar diffusion assay/S. lutea      | 50 µg/mL (MIC)     | Ampicillin 0.01 µg/mL (MIC) | [65] |
|                     | Antibacterial | Agar diffusion assay/H. lutea      | 50 µg/mL (MIC)     | Triadimefon 20 µg/mL (MIC) | [65] |
|                     | Antibacterial | Agar diffusion assay/P. aeruginosa | 3.27 µg/mL (MIC)   | Ampicillin 0.15 µg/mL (MIC) | [46] |
|                     | Antibacterial | Agar diffusion assay/MRSA          | 6.28 µg/mL (MIC)   | Ampicillin 0.15 µg/mL (MIC) | [46] |
|                     | Antibacterial | Agar diffusion assay/S. typhimurium | 26.20 µg/mL (MIC)   | Ampicillin 0.31 µg/mL (MIC) | [46] |
|                     | Antifungal   | Agar diffusion assay/C. albicans   | 3.27 µg/mL (MIC)   | Ketoconazole 0.10 µg/mL (MIC) | [46] |
|                     | Antitumor    | MTT/MDA-MB-435                    | 37.01 µM (IC₅₀)    | Epirubicin 0.26 µM (IC₅₀)   | [46] |
|                     | Antitumor    | MTT/A549                          | 37.73 µM (IC₅₀)    | Epirubicin 5.60 µM (IC₅₀)    | [46] |
| Colletotric acid B  | Antibacterial | Agar diffusion assay/P. aeruginosa | 1.67 µg/mL (MIC)   | Ampicillin 0.15 µg/mL (MIC) | [46] |
|                     | Antibacterial | Agar diffusion assay/MRSA          | 3.36 µg/mL (MIC)   | Ampicillin 0.15 µg/mL (MIC) | [46] |
|                     | Antitumor    | MTT/MDA-MB-435                    | 16.82 µM (IC₅₀)    | Epirubicin 0.26 µM (IC₅₀)    | [46] |
|                     | Antitumor    | MTT/A549                          | 20.75 µM (IC₅₀)    | Epirubicin 5.60 µM (IC₅₀)    | [46] |
|                     | Antibacterial | Agar diffusion assay/B. subtilis   | 26.90 µg/mL (MIC)  | Ampicillin 0.07 µg/mL (MIC) | [46] |
| Compound Name                                    | Activity                              | Assay/Microorganism/Model/Enzyme | Results                                                                 | Positive Control                                  | Ref. |
|-------------------------------------------------|---------------------------------------|----------------------------------|-------------------------------------------------------------------------|--------------------------------------------------|------|
| Phospholipase A (PLA) inhibition                 | Rat PLA2-II                           | 43 µM (IC₅₀)                    | Mepacrine 320 µM (IC₅₀)                                                | p-Bromophenacyl bromide 6.7 µM (IC₅₀)            | [70] |
|                                                 | Human PLA2-II                         | 29 µM (IC₅₀)                    | Mepacrine 76 µM (IC₅₀)                                                | p-Bromophenacyl bromide 34 µM (IC₅₀)             |      |
|                                                 |                                       |                                  | Manoalide 2.0 µM (IC₅₀)                                               | Manoalide 1.5 µM (IC₅₀)                          |      |
| Antifouling                                      | Balanus amphitrite (cyprid larvae)    | 54.99 µM (EC₅₀)                 | Butenolide 4.62 µM (EC₅₀)                                            |                                                  | [52] |
| Anti-diabetic                                    | Colorimetric/α-Glucosidase inhibitor (αGHY) | 23.8 µM (IC₅₀) | Acarbose 545 µM (IC₅₀)                                               |                                                  | [67] |
| Prostaglandin synthesis inhibition               | Conversion of AA into PGH₂            | 10 µM (IC₅₀)                    | Indomethacin 30 µM (IC₅₀)                                            |                                                  | [69,81] |
|                                                 | Conversion of PGH₂ into PGE₂          | 40 µM (IC₅₀)                    | Indomethacin 130 µM (IC₅₀)                                           |                                                  |      |
|                                                 | Conversion of PGE₂ into TXA₂          | 150 µM (IC₅₀)                   | Imidazole 200 µM (IC₅₀)                                              |                                                  |      |
| Phospholipase A (PLA) inhibition                 | Rat PLA2-II                           | 1.3 µM (IC₅₀)                   | Mepacrine 320 µM (IC₅₀)                                               | p-Bromophenacyl bromide 6.7 µM (IC₅₀)            | [70] |
|                                                 | Human PLA2-II                         | 2.4 µM (IC₅₀)                   | Mepacrine 76 µM (IC₅₀)                                               | p-Bromophenacyl bromide 34 µM (IC₅₀)             |      |
|                                                 |                                       |                                  | Manoalide 2.0 µM (IC₅₀)                                               | Manoalide 1.5 µM (IC₅₀)                          |      |
| Prostaglandin synthesis inhibition               | Conversion of AA into PGH₂            | 40 µM (IC₅₀)                    | Indomethacin 30 µM (IC₅₀)                                            |                                                  | [69,81] |
|                                                 | Conversion of PGH₂ into PGE₂          | 9 µM (IC₅₀)                     | Indomethacin 130 µM (IC₅₀)                                           |                                                  |      |
|                                                 | Conversion of PGE₂ into TXA₂          | 350 µM (IC₅₀)                   | Imidazole 200 µM (IC₅₀)                                              |                                                  |      |
| Thielavin methyl ester (50)                      | Antitumor                             | SRB/MCF-7                       | 7.3 µM (IC₅₀)                                                        | 0.07 µM (IC₅₀)                                   | [48] |
|                                                 | Antitumor                             | SRB/H460                        | 6.6 µM (IC₅₀)                                                        | <0.01 µM (IC₅₀)                                  | [48] |
|                                                 | Antitumor                             | SRB/SF268                       | 8.1 µM (IC₅₀)                                                        | 0.04 µM (IC₅₀)                                   | [48] |
Table 2. Cont.

| Compound Name | Activity       | Assay/Microorganism/Model/Enzyme | Results                                      | Positive Control                                      | Ref. |
|---------------|----------------|----------------------------------|----------------------------------------------|-------------------------------------------------------|------|
| Thielavin C (51) | PLA inhibition | Rat PLA2-II                      | 0.46 µM (IC₅₀)                               | Mepacrine 320 µM (IC₅₀) p-Bromophenacyl bromide 6.7 µM (IC₅₀) Manoalide 2.0 µM (IC₅₀) | [70] |
|               |                | Human PLA2-II                    | 2.1 µM (IC₅₀)                               | Mepacrine 76 µM (IC₅₀) p-Bromophenacyl bromide 34 µM (IC₅₀) Manoalide 1.5 µM (IC₅₀) |      |
| Thielavin D (52) | PLA inhibition | Rat PLA2-II                      | 1.1 µM (IC₅₀)                               | Mepacrine 320 µM (IC₅₀) p-Bromophenacyl bromide 6.7 µM (IC₅₀) Manoalide 2.0 µM (IC₅₀) | [70] |
|               |                | Human PLA2-II                    | 6.2 µM (IC₅₀)                               | Mepacrine 76 µM (IC₅₀) p-Bromophenacyl bromide 34 µM (IC₅₀) Manoalide 1.5 µM (IC₅₀) |      |
| Thielavin E (53) | PLA inhibition | Rat PLA2-II                      | 4.5 µM (IC₅₀)                               | Mepacrine 320 µM (IC₅₀) p-Bromophenacyl bromide 6.7 µM (IC₅₀) Manoalide 2.0 µM (IC₅₀) | [70] |
|               |                | Human PLA2-II                    | 9.3 µM (IC₅₀)                               | Mepacrine 76 µM (IC₅₀) p-Bromophenacyl bromide 34 µM (IC₅₀) Manoalide 1.5 µM (IC₅₀) |      |
| Thielavin H (56) | Antifouling    | *Balanus amphitrite*             | 12.64 µM (EC₅₀)                             | Butenolide 4.62 µM (EC₅₀)                              | [52] |
| Thielavin J (58) | Anti-diabetic  | Colorimetric/α-Glucosidase inhibitor (αGHY) | 15.8 µM (IC₅₀) | Acarbose 545 µM (IC₅₀) | [67] |
| Thielavin K (59) | Anti-diabetic  | Colorimetric/α-Glucosidase inhibitor (αGHY) | 22.1 µM (IC₅₀) | Acarbose 545 µM (IC₅₀) | [67] |
| Thielavin S (66) | Antibacterial  | Microbroth dilution/*S. aureus* ATCC 25923 | 100 µg/mL (MIC) | Tetracycline 3.12 µg/mL (MIC) | [19] |
| Compound Name     | Activity   | Assay/Microorganism/Model/Enzyme                     | Results          | Positive Control            | Ref. |
|-------------------|------------|-----------------------------------------------------|------------------|-----------------------------|------|
| Thielavin T (67)  | Antimicrobial | Microbroth dilution assay / *S. aureus* ATCC 25923 | 6.25 µg/mL (MIC) | Tetracycline 3.12 µg/mL (MIC) | [19] |
| Thielavin U (68)  | Antibacterial | Microbroth dilution assay / *S. aureus* ATCC 25923 | 50 µg/mL (MIC)  | Tetracycline 3.12 µg/mL (MIC) | [19] |
| Thielavin V (69)  | Antibacterial | Microbroth dilution assay / *S. aureus* ATCC 25923 | 25 µg/mL (MIC)  | Tetracycline 3.12 µg/mL (MIC) | [19] |
| Thielavin W (70)  | Antifouling  | *Balanus Amphitrite* (cyprid larvae) | 2.95 µM (EC_{50}) | Butenolide 4.62 µM (EC_{50}) | [52] |
| Thielavin X (71)  | Antifouling  | *Balanus Amphitrite* (cyprid larvae) | 3.13 µM (EC_{50}) | Butenolide 4.62 µM (EC_{50}) | [52] |
| Thielavin Y (72)  | Antifouling  | *Balanus Amphitrite* (cyprid larvae) | 5.78 µM (EC_{50}) | Butenolide 4.62 µM (EC_{50}) | [52] |
| Thielavin Z₂ (75) | Antifouling  | *Balanus Amphitrite* (cyprid larvae) | 69.19 µM (EC_{50}) | Butenolide 4.62 µM (EC_{50}) | [52] |
| Thielavin Z₃ (76) | Antifouling  | *Balanus Amphitrite* (cyprid larvae) | 4.23 µM (EC_{50}) | Butenolide 4.62 µM (EC_{50}) | [52] |
| Thielavin Z₄ (77) | Antifouling  | *Balanus Amphitrite* (cyprid larvae) | 50.50 µM (EC_{50}) | Butenolide 4.62 µM (EC_{50}) | [52] |
| Thielavin Z₅ (78) | Antifouling  | *Balanus Amphitrite* (cyprid larvae) | 25.86 µM (EC_{50}) | Butenolide 4.62 µM (EC_{50}) | [52] |
| Thielavin Z₆ (79) | Antifouling  | *Balanus Amphitrite* (cyprid larvae) | 17.86 µM (EC_{50}) | Butenolide 4.62 µM (EC_{50}) | [52] |
| 3-Hydroxy-2,5-dimethylphenyl 4-[(2,4-dihydroxy-3,6-dimethylbenzoyl)oxy]-2-hydroxy-3,6-dimethylbenzoate (80) | Antibacterial | Microbroth dilution / *S. aureus* | 250 µg/mL (MIC) | Vancomycin and tetracycline | [49] |
|                   |             | Microbroth dilution / *B. subtilis* | 250 µg/mL (MIC) | Vancomycin and tetracycline | [49] |
|                   |             | Microbroth dilution / *P. aeruginosa* | 250 µg/mL (MIC) | Vancomycin and tetracycline | [49] |
|                   |             | Microbroth dilution / *E. coli* | 250 µg/mL (MIC) | Vancomycin and tetracycline | [49] |
| Compound Name | Activity | Assay/Microorganism/Model/Enzyme | Results | Positive Control | Ref. |
|---------------|----------|---------------------------------|---------|------------------|-----|
| 3-Hydroxy-2,4,5-trimethylphenyl 4-{[2,4-dihydroxy-3,6-dimethylbenzoyl]oxy}-2-hydroxy-3,6-dimethylbenzoate (81) | Antibacterial | Microbroth dilution/S. aureus | 250 µg/mL (MIC) | Vancomycin and tetracycline | [49] |
| | Antibacterial | Microbroth dilution/B. subtilis | 25 µg/mL (MIC) | Vancomycin and tetracycline | [49] |
| | Antibacterial | Microbroth dilution/P. aeruginosa | 25 µg/mL (MIC) | Vancomycin and tetracycline | [49] |
| | Antibacterial | Microbroth dilution/E. coli | 250 µg/mL (MIC) | Vancomycin and tetracycline | [49] |
| Amidepsine D (86) | DGAT1 inhibition | Rat liver microsomes | 17.5 µM (IC_{50}) | - | [74] |
| | DGAT2 inhibition | Rat liver microsomes | 30 µM (IC_{50}) | - | [71,82] |
| | Triacylglycerol inhibition | Raji cells | 2.82 µM (IC_{50}) | - | [74] |
| | Antibacterial | Disk diffusion/B. subtilis ATCC6633 | 8.0 mm (IZD) | - | [74] |
| Amidepsine A (88) | DGAT1 inhibition | Rat liver microsomes | 10.2 µM (IC_{50}) | - | [74] |
| | DGAT2 inhibition | Rat liver microsomes | 70 µM (IC_{50}) | - | [71,82] |
| | Triacylglycerol inhibition | Raji cells | 15.5 µM (IC_{50}) | - | [74] |
| | Antibacterial | Disk diffusion/B. subtilis ATCC6633 | 11.0 mm (IZD) | - | [74] |
| Amidepsine B (89) | DGAT1 inhibition | Rat liver microsomes | 19.2 µM (IC_{50}) | - | [74] |
| | DGAT2 inhibition | Rat liver microsomes | 60 µM (IC_{50}) | - | [71,82] |
| | Triacylglycerol inhibition | Raji cells | 3.35 µM (IC_{50}) | - | [74] |
| | Antibacterial | Disk diffusion/B. subtilis ATCC6633 | 7.0 mm (IZD) | - | [74] |
| Amidepsine C (90) | DGAT1 inhibition | Rat liver microsomes | 51.6 µM (IC_{50}) | - | [74] |
| | DGAT2 inhibition | Rat liver microsomes | 100 µM (IC_{50}) | - | [71,82] |
| | Triacylglycerol inhibition | Raji cells | 17.2 µM (IC_{50}) | - | [74] |
| | Antibacterial | Disk diffusion/B. subtilis ATCC6633 | 9.0 mm (IZD) | - | [74] |
| Amidepsine E (91) | Triacylglycerol inhibition | Raji cells | 91 µM (IC_{50}) | - | [76] |
| | DGAT1 inhibition | Rat liver microsomes | 124 µM (IC_{50}) | - | [76] |
| Compound Name | Activity           | Assay/Microorganism/Model/Enzyme                  | Results               | Positive Control         | Ref.                        |
|----------------|--------------------|--------------------------------------------------|-----------------------|--------------------------|----------------------------|
| Amidepsine J (96) | DGAT1 inhibition   | Rat liver microsomes                             | 40 µM (IC\textsubscript{50}) | -                        | [71]                       |
|                | DGAT2 inhibition   | Rat liver microsomes                             | 40 µM (IC\textsubscript{50}) | [71]                     |                            |
| CJ-21,164 (97)   | G6Pase inhibition  | Colorimetric assay                               | 102% (% inhibition)   | -                        | [77]                       |
|                | Glucose output inhibition | Colorimetric assay                           | 81% (% inhibition)    | -                        |                            |
| Thielocin A1i (99) | PLA inhibition     | Human PLA\textsubscript{2}-II                    | 6.2 µM (IC\textsubscript{50}) | -                        | [78,80,83,84]              |
|                |                    | Human PLA\textsubscript{2}-I                     | 140 µM (IC\textsubscript{50}) | -                        |                            |
|                | Ki value human PLA\textsubscript{2}-II | 12 µM                          | -                     |                          |                            |
|                | Rat PLA\textsubscript{2}-II | 0.0033 µM (IC\textsubscript{50})                 | Mepacrine 240 µM (IC\textsubscript{50}) | [78,80,83,84] |                            |
|                | Vipera russelli venom PLA\textsubscript{2}-II | 17 µM (IC\textsubscript{50})                     | -                     |                          |                            |
|                | Crotalus adamanteus venom PLA\textsubscript{2}-II | 17 µM (IC\textsubscript{50})                     | -                     |                          |                            |
|                | Porcine pancreas PLA\textsubscript{2}-I | 63 µM (IC\textsubscript{50})                     | -                     |                          |                            |
|                | Rat PLA\textsubscript{2}-I | 21 µM (IC\textsubscript{50})                     | Mepacrine 135 µM (IC\textsubscript{50}) | -                        |                            |
|                | Bee venom PLA\textsubscript{2}-I | 2 µM (IC\textsubscript{50})                     | -                     |                          |                            |
|                | Naja naja venom PLA\textsubscript{2}-I | 7.1 µM (IC\textsubscript{50})                    | -                     |                          |                            |
|                | N. mocambique venom PLA\textsubscript{2}-I | 9.3 µM (IC\textsubscript{50})                    | -                     |                          |                            |
|                | Bee venom PLA\textsubscript{2} | 1.4 µM (IC\textsubscript{50})                    | p-Bromophenacyl bromide 80 µM (IC\textsubscript{50}) | [83,84]                  |                            |
|                | Bee venom PLA\textsubscript{2}-induced paw edema | 42.4 (mg)                               | -                     |                          |                            |
|                | Ki value Bee venom PLA\textsubscript{2} | 0.57 µM                                   | -                     |                          |                            |
| Thielocin A2α (100) | PLA inhibition     | Rat PLA\textsubscript{2}-II                     | 0.051 µM (IC\textsubscript{50}) | p-Bromophenacyl bromide 6.7 µM (IC\textsubscript{50}) | [70]                       |
|                |                    | Human PLA\textsubscript{2}-II                    | 0.31 µM (IC\textsubscript{50}) | p-Bromophenacyl bromide 34 µM (IC\textsubscript{50}) | Manoalide 1.5 µM (IC\textsubscript{50}) |
| Compound Name   | Activity      | Assay/Microorganism/Model/Enzyme | Results                      | Positive Control                  | Ref. |
|-----------------|---------------|----------------------------------|------------------------------|-----------------------------------|------|
| Thielocin A2β (101) | PLA inhibition | Rat PLA2-II                      | 0.038 µM (IC<sub>50</sub>)   | Mepacrine 320 µM (IC<sub>50</sub>) | [70] |
|                 |               |                                  |                              | p-Bromophenacyl bromide 6.7 µM (IC<sub>50</sub>) |      |
|                 |               |                                  |                              | Manoalide 2.0 µM (IC<sub>50</sub>) |      |
|                 |               |                                  |                              | Mepacrine 76 µM (IC<sub>50</sub>) | [70] |
|                 |               |                                  |                              | p-Bromophenacyl bromide 34 µM (IC<sub>50</sub>) |      |
|                 |               |                                  |                              | Manoalide 1.5 µM (IC<sub>50</sub>) |      |
| Human PLA2-II   |               |                                  | 0.24 µM (IC<sub>50</sub>)    | Mepacrine 320 µM (IC<sub>50</sub>) | [70] |
|                 |               |                                  |                              | p-Bromophenacyl bromide 6.7 µM (IC<sub>50</sub>) |      |
|                 |               |                                  |                              | Manoalide 2.0 µM (IC<sub>50</sub>) |      |
| Rat PLA2-II     |               |                                  | 0.032 µM (IC<sub>50</sub>)   | Mepacrine 76 µM (IC<sub>50</sub>) | [70] |
|                 |               |                                  |                              | p-Bromophenacyl bromide 34 µM (IC<sub>50</sub>) |      |
|                 |               |                                  |                              | Manoalide 1.5 µM (IC<sub>50</sub>) |      |
| Human PLA2-II   |               |                                  | 0.39 µM (IC<sub>50</sub>)    | Mepacrine 320 µM (IC<sub>50</sub>) |      |
|                 |               |                                  |                              | p-Bromophenacyl bromide 6.7 µM (IC<sub>50</sub>) |      |
|                 |               |                                  |                              | Manoalide 2.0 µM (IC<sub>50</sub>) | [70] |
| Thielocin B1 (105) | PLA inhibition | Rat PLA2-II                      | 0.0078 µM (IC<sub>50</sub>)  | Mepacrine 320 µM (IC<sub>50</sub>) | [70] |
|                 |               |                                  |                              | p-Bromophenacyl bromide 6.7 µM (IC<sub>50</sub>) |      |
|                 |               |                                  |                              | Manoalide 2.0 µM (IC<sub>50</sub>) |      |
| Human PLA2-II   |               |                                  | 0.17 µM (IC<sub>50</sub>)    | Mepacrine 320 µM (IC<sub>50</sub>) | [70] |
|                 |               |                                  |                              | p-Bromophenacyl bromide 6.7 µM (IC<sub>50</sub>) |      |
|                 |               |                                  |                              | Manoalide 1.5 µM (IC<sub>50</sub>) |      |
| Thielocin B2 (106) | PLA inhibition | Rat PLA2-II                      | 0.070 µM (IC<sub>50</sub>)  | Mepacrine 320 µM (IC<sub>50</sub>) | [70] |
|                 |               |                                  |                              | p-Bromophenacyl bromide 6.7 µM (IC<sub>50</sub>) |      |
|                 |               |                                  |                              | Manoalide 2.0 µM (IC<sub>50</sub>) |      |
| Human PLA2-II   |               |                                  | 2.7 µM (IC<sub>50</sub>)     | Mepacrine 320 µM (IC<sub>50</sub>) | [70] |
|                 |               |                                  |                              | p-Bromophenacyl bromide 34 µM (IC<sub>50</sub>) |      |
|                 |               |                                  |                              | Manoalide 1.5 µM (IC<sub>50</sub>) |      |
Table 2. Cont.

| Compound Name                        | Activity          | Assay/Microorganism/Model/Enzyme               | Results                        | Positive Control                      | Ref.     |
|--------------------------------------|-------------------|-----------------------------------------------|-------------------------------|---------------------------------------|----------|
| Thielocin B3 (107)                   | PLA inhibition    | Human PLA2-I                                  | 18 µM (IC\(_{50}\))           | Mepacrine 320 µM (IC\(_{50}\))       | [70,80] |
|                                      |                   | Rat PLA2-II                                  | 0.012 µM (IC\(_{50}\))        | p-Bromophenacyl bromide 6.7 µM (IC\(_{50}\)) Manoalide 2.0 µM (IC\(_{50}\)) |         |
|                                      |                   | Human PLA2-II                                 | 0.076 µM (IC\(_{50}\))        | p-Bromophenacyl bromide 34 µM (IC\(_{50}\)) Manoalide 1.5 µM (IC\(_{50}\)) |         |
|                                      |                   | Rat PLA2-I                                   | 2.8 µM (IC\(_{50}\))         | Mepacrine 76 µM (IC\(_{50}\))       |         |
|                                      |                   | Mean Ki                                       | 0.98 µM                       | p-Bromophenacyl bromide 34 µM (IC\(_{50}\)) Manoalide 1.5 µM (IC\(_{50}\)) |         |
|                                      |                   | Snake venom PLA2                              | 0.0045 µM (IC\(_{50}\))      | Indomethacin 1.08 mL (conc. 1 mg/kg) Dexamethasone 0.60 mL (conc. 0.1 mg/kg) |         |
|                                      |                   |                                               | 1.6 µM (ED\(_{50}\))         |                                       |         |
|                                      |                   | Exudate volume after carrageenan              | 1.60 mL (conc. 1 mg/kg)       | Indomethacin 7.36 pmol/minute/mL (conc. 1 mg/kg) Dexamethasone 7.94 pmol/minute/mL (conc. 0.1 mg/kg) |         |
|                                      |                   |                                               | 1.15 mL (conc. 3 mg/kg)       |                                       |         |
|                                      |                   | PLA\(_{2}\) activity in pleural exudate after carrageenan | 2.22 pmol/minute/mL (conc. 1 mg/kg) |                                      |         |
|                                      |                   |                                               | 0.76 pmol/minute/mL (conc. 3 mg/kg) |                                      |         |
| Thielocin B3 monomethyl ester B (108)| PLA inhibition   | Human PLA2-II                                 | 0.20 µM (IC\(_{50}\))        |                                       | [80]    |
|                                      |                   | Snake venom PLA2                              | 0.032 µM (IC\(_{50}\))       |                                       |         |
|                                      |                   |                                               | 5.2 µM (ED\(_{50}\))         |                                       |         |
| Compound Name                        | Activity    | Assay/Microorganism/Model/Enzyme | Results       | Positive Control | Ref. |
|------------------------------------|-------------|----------------------------------|---------------|-----------------|------|
| Thielocin B3 monomethyl ester C (109) | PLA inhibition | Human PLA$_2$-II | 0.28 µM (IC$_{50}$) | -               | [80] |
|                                    |             | Snake venom PLA$_2$             | 0.31 µM (IC$_{50}$) | 5.2 µM (ED$_{50}$) | -    |
| Thielocin B3 monomethyl ester D (110) | PLA inhibition | Human PLA$_2$-II | 51 µM (IC$_{50}$) | -               | [80] |
|                                    |             | Snake venom PLA$_2$             | >100 µM (IC$_{50}$) | 7.6 µM (ED$_{50}$) | -    |
Figure 5. Chemical structures of sugar-containing di-depsides 28–33.

Figure 6. Chemical structures of sugar-containing di-depsides 34–37.
3.2. Antimicrobial Activity

The wide use of antibiotics leads to the development of resistant microbes [85]. Moreover, the number of efficient drugs against life-threatening fungal and bacterial infections has decreased dramatically because of emerging pathogens that are multidrug-resistant (MDR), which is the biggest obstacle to success during the treatment of infectious diseases [86]. Therefore, there is a growing demand for new antimicrobial compounds. Fungi are considered an important source of novel antimicrobials because of their rich secondary metabolites and abundant species diversity. Bacterial enoyl-ACP (acyl carrier protein) reductase accelerates the last and rate-limiting step in type II FAS (bacterial fatty acid synthesis) [87,88]. Enoyl-ACP reductase includes three isoforms, FabK, FabI, and FabL. It is found in most bacteria: S. aureus (FabI), Streptococcus pneumonia (FabK), P. aeruginosa and Enterococcus faecalis (FabK and FabI), B. subtilis (FabI and FabL), and Mycobacterium tuberculosis (InhA, a FabI homolog) [61,89]. This enzyme has been established as a novel target for treatment against infections produced by MDR pathogens.

![Chemical structures of nitrogen-containing di-depsides](image)

Figure 7. Chemical structures of nitrogen-containing di-depsides 38–44.

Phainuphong et al. purified three new depsides, aspergisides A–C (3–5) from Aspergillus unguis, and assessed their antimicrobial potential against MRSA (methicillin-resistant S. aureus), S. aureus, C. albicans, flucytosine-resistant C. neoformans, and M. gypseum [38]. Compound 3 had a weak antibacterial activity toward S. aureus and MRSA, with an MIC (minimal inhibitory concentrations) value of 8 µg/mL, while 4 and 5 were inactive, with MIC values of 32–200 µg/mL in the agar diffusion method [38]. Setophoma sp. associ-
ated with guava fruits produced compounds 6–8 and 66–69 [19]. They did not have growth inhibition activity toward E. coli. However, 66–69 demonstrated inhibition of S. aureus with MIC values of 100, 6.25, 50, and 25 µg/mL, respectively, in comparison to tetracycline (MIC 3.12 µg/mL) [19]. Compounds 6 and 7 were inactive. Moreover, all compounds did not exhibit quorum-sensing inhibitory activity. Studying the structural activity relationship revealed that the activity increased with the full methylation of the B-ring; however, the additional CH₂ group at ring A, especially at C-2, resulted in a decrease in activity [19]. The agonodepsides A (12) and B (13) were isolated from the filamentous fungus, F7524 [50]. In the fluorometric InhA assay, 12 inhibited M. tuberculosis InhA with an IC₅₀ value of 75 µM, while 13 was inactive at 100 µM, compared with triclosan (IC₅₀ 3.0 µM) [50].

Emericella unguis yielded 14, which had antibacterial activity against S. aureus, and was inactive against Vibrio parahaemolyticus in the agar diffusion assay [51]. Stereum rameale afforded 22, which was found to show powerful antibacterial activity toward B. subtilis, B. cereus, and S. aureus, with IZDs (inhibition zone diameters) of 25, 25 and 28 mm, respectively, while it showed no antibacterial activity against E. coli, Salmonella sp., and P. aeruginosa. Its MBCs (minimal bactericidal concentrations) were 10, 50, and 100 µg/mL for B. subtilis, B. cereus, and S. aureus, respectively [57]. Compounds 23 and 24 showed inhibitory activity against both S. aureus and MRSA with MIC values of 25.0 µg/mL, and antibacterial potential toward B. subtilis (MICs 25.0 and 50.0 µg/mL, respectively), in comparison to vancomycin (MICs 1.0, 1.0, and 0.5 µg/mL, respectively) in the agar plate diffusion assay. They had a weak antibacterial potential against P. aeruginosa [40]. The new depsides, arenicolins A (30) and B (31) that were purified from Penicillium Arenicola, did not show any growth inhibition toward S. aureus, C. albicans, and C. neoformans at a concentration of 100 µg/mL, utilizing the agar diffusion assay [42]. Kwon et al. reported that the depside galactopyranoside derivative 32, isolated from Sporothrix sp., strongly inhibited S. pneumoniae FabK and S. aureus FabI, with IC₅₀ values of 9.2 and 3.2 µM, respectively [61]. It also exhibited antibacterial activity against MRSA CCARM 3506 and CCARM 3167, as well as S. aureus RN4220, with MIC values of 16–32 µg/mL and strong activity against B. subtilis (KCTC 1021) and E. faecalis (KCTC 5191), with MIC values of 8–16 µg/mL [61]. Another study by Kwon et al. revealed that 32 prohibited M. tuberculosis InhA with IC₅₀ value of 9.6 µM [89]. Moreover, 32 (conc. of 128) had a weak anti-bacterial capacity against M. tuberculosis, with a growth inhibition of 17.9% in the microbroth dilution [89]. Sporothrix sp. yielded 34 and 35. Compound 34 exhibited weak antimicrobial activity against S. aureus, E. faecium, and B. subtilis (MIC values of 12.5, 100, and 12.5 µg/mL, respectively) and showed no activity against C. albicans, P. aeruginosa, E. coli, P. vulgaris, S. sonnei, S. typhi, and K. pneumoniae at a concentration of 100 µg/mL. However, 35 had weak activity against S. aureus and B. subtilis and no activity against the others [63]. In 2017, Aquveque et al. isolated 41 from Stereum hirsutum, which showed an antifungal capacity against Botrytis cinerea, one of the most harmful phytopathogenic fungi, causing the crop disease known as grey mold [58]. It showed a significant inhibition of B. cinerea mycelial growth at concentrations of 1000 and 2000 µg/mL, reaching 67% and 76%, respectively. At a concentration of 500 µg/mL, it produced 96% inhibition of sporulation. It showed an MIC of 10 µg/mL and MFC (minimal fungicidal concentration) of 50 µg/mL, compared with rovral (MFC of 10 µg/mL and MIC of 1 µg/mL) in the microdilution plate assay [58].
Figure 8. Chemical structures of tri-depsides 45–54.

Compound 45, a new tridepside produced by Colletotrichum gloeosporioides and associated with Artemisia mongolica, was tested in the disk diffusion assay for B. subtilis, S. aureus, S. lutea, Pseudomonas sp., C. albicans, A. niger, C. elegans, H. sativum, and T. rubrum. It exhibited antibacterial potential toward B. subtilis (MIC 25 µg/mL), S. aureus (MIC 50 µg/mL), and S. lutea (MIC 50 µg/mL) in comparison to ampicillin (MIC values of 0.05, 0.5, and 0.01 µg/mL, respectively) and an antifungal effect toward H. sativum, with an MIC value of 50 µg/mL, relative to triadimefon (MIC value of 20 µg/mL) [65].
Figure 9. Chemical structures of tri-depsides 55–64.

Phoma sp. associated with Kandelia candel yielded the compounds 11, 45, and 46. Compound 45 showed marked antimicrobial activity against B. subtilis, P. aeruginosa, MRSA, and C. albicans, with MIC values ranging from 3.27 to 6.55 µg/mL, compared with ampicillin (MIC values of 0.07, 0.15, and 0.15, respectively) and ketoconazole (MIC 0.10 µg/mL) in the disk diffusion assay. Moreover, it had weak activity toward Salmonella typhimurium with an MIC value of 26.20 µg/mL. Compound 46 was active against MRSA and P. aeruginosa, with MIC values of 3.36 and 1.67 µg/mL, respectively, and was weakly active toward B. subtilis (26.9 µg/mL), while 11 had antibacterial activity toward B. subtilis with an MIC value of 9.70 µg/mL [46]. The novel depside, PS-990 (47), produced by Acremonium sp., had antibacterial potential against B. subtilis, with an MIC value of 0.65 µg/mL and weak activity against E. faecium and S. aureus (MICs 21.0 and 10.0 µg/mL, respectively) [66]. Compound 49 prohibited the formation of peptidoglycan in the in vitro assay, with an IC₅₀ value of 5 µg/mL in E. faecalis (strain A256) compared with a panel of antibiotics, suggesting that it interfered with cell wall trans-glycosylation [90].
Figure 10. Chemical structures of tri-depsides 65–76.

The endophytic fungus *Cladosporium uredinicola*, isolated from *Psidium guajava* fruits, produced 9, 10, 80, and 81. The metabolites 9, 80, and 81 were assessed against *S. aureus*, *E. coli*, *P. aeruginosa*, and *B. subtilis*. Compound 9 inhibited the growth of *P. aeruginosa* and *B. subtilis*, with MIC values of 25 µg/mL, and *E. coli* and *S. aureus*, with MIC values of 250 µg/mL. On the other hand, 80 displayed a bacteriostatic effect (dose of 250 µg/mL) toward all tested bacteria, while 81 had a bacteriostatic effect for *S. aureus* and *E. coli* at a dose of 250 µg/mL and at a dose of 25 µg/mL for *P. aeruginosa* and *B. subtilis* [49]. Moreover, 86 and 88–90 had antibacterial activity against *B. subtilis*, with IZDs ranging from 7 to 11 mm; however, they were inactive against *Saccharomyces sake*, *P. aeruginosa*, *E. coli*, *Mycobacterium smegmatis*, *Micrococcus luteus*, *Pyricularia oryzae*, *S. aureus*, *C. albicans*, *Mucor racemosus*, and *A. niger* with the paper-disk method [74]. In the disk diffusion method, compound 91, biosynthesized by *Humicola* sp., possessed no antimicrobial capacity against
B. subtilis, M. smegmatis, S. sake, M. luteus, P. aeruginosa, E. coli, M. racemosus, S. aureus, A. niger, P. oryzae, and C. albicans [76].

3.3. Antifouling Activity

The anti-larval settlement activities of 15, 48, 56, 59, and 70–79 were assessed towards cyprid larvae of B. amphitrite [52]. Compounds 15, 48, 56, 71–73, and 76–78 deterred larval settlement, with EC₅₀ ranging from 2.95 to 69.19 µM in comparison to butenolide (EC₅₀ 4.62 µM). At a concentration of 10 µM, 15, 71–73, and 77 exhibited narcotic potential toward B. amphitrite cyprids. They caused the loss of the phototactic response of cyprids, in addition to decreasing the appendage activity and cyprids becoming completely immobilized. The recovery rates of cyprids treated with 15, 71–73, and 77 (concentration of
10 µM) revealed that larvae possessed the highest recovery rate after treatment with 71, while no larvae recovered after treatment with 15 for 24 h. From all tested compounds, 71 had an excellent antifouling potential and cyprids treated with it had the highest recovery rate. Thus, 71, 72, and 77 were reversible inhibitors. Conversely, 58–59, 74, and 75 had no effect [52].

![Chemical structures of nitrogen- and sugar-containing tri-depsides 88–96 and tetra-depside 97.](image)

**Figure 12.** Chemical structures of nitrogen- and sugar-containing tri-depsides 88–96 and tetra-depside 97.

### 3.4. Anti-Diabetic Activity

Diabetes is among the most prevalent chronic diseases and is characterized by hyperglycemia, which leads to damage of the blood vessels. This may produce macro- and micro-vascular disorders, as well as other complications, such as sexual dysfunction, dementia, lower-limb amputations, and depression [91]. Diabetes prevalence is expected to be at approximately 366 million cases by the year 2030 [92]. The side effects of the available hypoglycemic agents necessitate the discovery of efficient, low-side-effect, and affordable agents for treating diabetes.

Rivera-Chávez et al. reported that the tridepside, 59 (dose 3.1–31.6 mg/kg), reduced glucose blood levels after 30 min of oral administration of the sucrose load in mice (3.0 g/kg); however, only the highest dose (31.6 mg/kg) caused a marked reduction in
blood glucose levels in NA-STZ (nicotinamide-streptozotocin) diabetic mice, indicating that 59 (doses of 3.1 and 10 mg/kg) reduced the blood glucose levels in both diabetic and normal mice [67].

Figure 13. Chemical structures of terta- and penta-depside derivatives 98–105.

3.5. D-Glucose-6-Phosphate Phosphohydrolase Inhibitory Activity

G6Pase (D-glucose-6-phosphate phosphohydrolase) is a hepatic metabolism-regulating enzyme, that catalyzes the last steps of glycogenolysis and gluconeogenesis pathways [93]. Its inhibition decreases the output of hepatic glucose from both pathways, leading to lowering the blood glucose levels in diabetes. The tetra-depside, 97 isolated from Chloridium sp. CL48903 prohibited G6Pase in rat liver microsomes (IC₅₀ 1.6 µM) at a concentration of 133 µM, using a colorimetric assay and hepatocyte glucose output (81% inhibition), indicating the role of 97 as a G6Pase inhibitor [77].
3.6. α-Glucosidase Inhibitory (αGI) Activity

The α-glucosidase enzyme is an important therapeutic target for treating carbohydrate-mediated diseases. It catalyzes the breakdown of oligo- and disaccharides into monosaccharides in the final stage of carbohydrate digestion, leading to a rise in glucose levels [94–97]. Several studies revealed that α-glucosidase inhibitors (αGIs) slow down the digestion and absorption of carbohydrates, and thus reduce the postprandial blood glucose level [94–97]. The serious side effects of the current αGIs, such as liver injuries and gastrointestinal damage, have directed research efforts toward discovering and developing new and safer anti-diabetic agents.

*Stereum hirsutum* produced isoprenylated depsides; 17–23, 38–40, and 42–44, which possessed an αGI capacity with IC₅₀ values ranging from 3.06 to 36.64 µM, in comparison to acarbose (IC₅₀ 640.88 µM). Compounds 21 and 42 had no αGI activity (IC₅₀ > 50 µM). Compounds 17–19 displayed stronger αGI activities than 20–23, revealing that ring-B substitution with carbonyl functionality can increase activity. Furthermore, 17 showed much stronger activity than 16, confirming that the isoprenyl group strongly influences the activity. However, furan ring formation at C-2 and C-3 in 16, and C-8 connectivity of a propane-1,2,3-triol moiety in 21, greatly reduced activity levels [53]. Compounds 11, 45, and 46 exhibited significant αGI activity, with IC₅₀ values of 60.20, 36.2, and 35.80 µM, respectively, compared to 1-deoxynojirimycin (62.8 µM), in the colorimetric α-glucosidase assay [46]. The tridepsides, 48, 58, and 59, exhibited higher *Saccharomyces cerevisiae* α-glucosidase (αGHY) inhibitory activity, with IC₅₀ values of 23.8, 15.8, and 22.1 µM, respectively, than acarbose (IC₅₀ 545 µM). They are considered non-competitive inhibitors with Ki values of 27.8–66.2 µM. On the other hand, 58 prohibited the activity of αGHBs (α-glucosidase from *Bacillus stearothermophilus*), with an IC₅₀ of 30.5 µM, which was less active than acarbose (IC₅₀ 0.015 µM) [67].

3.7. Protein Tyrosine Phosphatase Inhibitory (PTP1BI) Activity

PTP1B (protein-tyrosine phosphatase 1B) is a negative regulator of the insulin signaling pathway. The inhibition of PTP1B activity has great promise for alleviating insulin and leptin resistance; hence, PTP-1BIs (PTP1B inhibitors) show potential for treating T2DM and other metabolic disorders [98].

*Cosmospora* sp. produced aquastatin A (32) (IC₅₀ 0.19 µM) that showed modest but selective PTP1BI activity over other PTPs (protein tyrosine phosphatases) such as TCPTP.
(T-cell protein tyrosine phosphatase) (IC\textsubscript{50} 0.51 µM), SHP-2 (IC\textsubscript{50} > 44 µM), CD45 (IC\textsubscript{50} > 44 µM), and LAR (IC\textsubscript{50} > 44 µM), compared with ursolic acid (IC\textsubscript{50} 2.5 µM). It was suggested that the 2,4-dihydroxy-6-pentadecylbenzoic acid moiety is critical for PTP1BI activity [60].

3.8. Diacylglycerol Acyltransferase Inhibitory (DGATI) Activity

Postprandial hypertriglyceridemia is considered the main risk factor for cardiovascular functions. Thus, triglyceride synthesis inhibition has remarkable therapeutic potential in metabolic disorder treatment. The enzymes known as diacylglycerol acyltransferases (DGATs) catalyze the final and only committed step in the biosynthesis of triglycerides [99]. Therefore, these enzymes could be a potential therapeutic target to combat cardio-metabolic disorders [71,82,99]. Compound 9 also inhibited TG synthesis (IC\textsubscript{50} 91 µM), as well as PC and PE syntheses, indicating that it had a non-specific DGATI effect [76]. The compounds 86 and 88–90 were purified from Humicola sp. by Tomoda et al. [74]. Compound 88 was the most potent DGATI, with an IC\textsubscript{50} of 10.2 µM, followed by 86 (IC\textsubscript{50} 17.5 µM), 89 (IC\textsubscript{50} 19.2 µM), and 90 (IC\textsubscript{50} 51.6 µM). They also inhibited the formation of triacylglycerol using Raji cells on the intact cell assay, with IC\textsubscript{50} values ranging from 2.82 to 17.2 µM. At high concentrations, 86 moderately inhibited the formation of phosphatidylethanolamine (PE) and phosphatidylcholine (PC), whereas 89 possessed a weak effect, indicating that 89 specifically suppressed the formation of triacylglycerol (TG) [74]. Moreover, 91, when isolated from Humicola sp. FO-5969, showed a dose-dependent inhibition of DGAT using rat liver microsomes in the enzyme assay. At an IC\textsubscript{50} 124 µM, it was weaker than 88 (IC\textsubscript{50} 10.2 µM), revealing the fact that the 11-OH group was important for potent DGAT-I. Inokoshi et al. purified from Humicola sp. six new tridepsides, 87 and 92–96, as well as the known metabolites, 86 and 88–90 [71]. In the enzyme assay, utilizing microsomal fractions prepared from S. cerevisiae expressing human DGAT-2 and DGAT-1, the non-glycoside compound 96 inhibited DGAT-1 and DGAT-2 with an IC\textsubscript{50} value of 40 µM, whereas the glycosylated metabolites 92–95 had no and/or very weak DGATI potential, suggesting that the sugar moiety at C-11 reduced the DGATI. However, the compounds 86 and 88–90 were dual DGATIs, with IC\textsubscript{50} values ranging from 20 to 170 µM for DGAT-1 and 30–170 µM for DGAT-2 [71,82].

3.9. Activity of 11β-Hydroxysteroid Dehydrogenase Inhibitory (11β-HSDI) Enzyme

High levels of glucocorticoid produce insulin resistance and glucose intolerance, leading to metabolic syndrome (MS) [100]. The enzyme 11β-HSD (11β-hydroxysteroid dehydrogenase) is accountable for the production of glucocorticoids in tissues, thus it plays a remarkable role in T2DM and MS. The 11β-HSD1 inhibitors (11β-HSD1Is) could be considered promising therapeutics in treating MS. Compounds 38–41 exhibited powerful and selective inhibitory activities against 11β-HSD1 in the HTRF immunoassay. They inhibited human 11β-HSD1 activity in a dose-dependent manner with IC\textsubscript{50} values ranging from 240 to 6600 nM. Compounds 38 and 40 were the most active with IC\textsubscript{50}s 240 and 230 nM, respectively, while they did not prohibit 11β-HSD2 (IC\textsubscript{50} > 10,000 nM) [64].

3.10. Anti-Inflammatory Activities

Inflammation is a beneficial and complicated immune system response to tissue damage or external challenges [101]. Prolonged uncontrolled inflammation leads to various diseases, such as cancer, diabetes, and neurodegenerative and cardiovascular disorders, due to the expression of various inflammatory mediators [102]. The anti-inflammatory potential was estimated by assessing the suppression of pro-inflammatory cytokine expression (e.g., IL-6, TNF-α, and IL-1β), pro-inflammatory enzymes (e.g., iNOS, COX-2), derived production (PGE\textsubscript{2} and NO), and various inflammatory signal pathways in immune monocytes and macrophages (e.g., RAW264.7 cells, BV2 cells), whether in vitro, stimulated by LPS (lipopolysaccharide) [103], or by the inhibited swelling rate in a mouse ear edema model in vivo [104].
Compound 23, biosynthesized by Stereum hirsutum, exhibited noticeable NO inhibitory potential (IC\textsubscript{50} 19.17 \(\mu\text{M}\)) in the LPS-induced macrophages, compared with hydrocortisone (IC\textsubscript{50} 48.15 \(\mu\text{M}\)) [40]. Moreover, 48 (IC\textsubscript{50} 12 \(\mu\text{M}\)) and 49 (IC\textsubscript{50} 9 \(\mu\text{M}\)) possessed considerable anti-inflammatory potential for the conversion of \(^{14}\text{C}\)-arachidonic acid into PGF\textsubscript{2}\(\alpha\) plus PGE\textsubscript{2} by the microsomes of ram seminal vesicles [69,81]. IC\textsubscript{50}s of the conversion of arachidonic acid (AA) into PGH\textsubscript{2} (prostaglandin H\textsubscript{2}), PGH\textsubscript{2} into (prostaglandin E\textsubscript{2}), and thromboxane A\textsubscript{2} (TXA\textsubscript{2}) synthetase are 10, 40, 150 \(\mu\text{M}\), respectively, for 48 in comparison to indomethacin (ID\textsubscript{50} 30 for PGH\textsubscript{2} and 130 \(\mu\text{M}\) for PGE\textsubscript{2}) and imidazole (ID\textsubscript{50} 200 \(\mu\text{M}\) for TXA\textsubscript{2} synthetase); meanwhile, 49 had ID\textsubscript{50} values of 40, 9, and 350 \(\mu\text{M}\), respectively. Compound 48 had a strong inhibitory effect on the conversion of AA into PGH\textsubscript{2}, while 49 specifically inhibited the step involving PGE\textsubscript{2} synthesis from PGH\textsubscript{2}. Moreover, they inhibited TXA\textsubscript{2} synthesis in bovine platelet microsomes (ID\textsubscript{50} values of 150 and 350 \(\mu\text{M}\), respectively), which was comparable to imidazole (200 \(\mu\text{M}\)) [69,81]. Both compounds (dose 50 \text{mg/kg, orally}) showed no significant anti-inflammatory effects on carrageenan-induced edema in rats. However, 49 caused a 70% inhibition of this edema system at an intravenous (IV) dose of 5 \text{mg/kg}, while 48 displayed no activity, even with IV administration [81]. Matsumoto et al. also stated that 8, 49, and 51–53 had powerful rat PLA\textsubscript{2}–II inhibitory potential (IC\textsubscript{50} values ranged from 0.45 to 43 \(\mu\text{M}\)) in comparison to manonoide (IC\textsubscript{50} 2.0 \(\mu\text{M}\)) [70], while they had marked capacities toward human PLA\textsubscript{2} (phospholipase A\textsubscript{2})–II (IC\textsubscript{50} 29, 2.4, 2.1, 6.2, and 9.3 \(\mu\text{M}\), respectively) relative to manonoide (IC\textsubscript{50} 1.5 \(\mu\text{M}\)) [70].

3.11. Antimalarial Activity

Malaria is among many prevalent health concerns and is caused by the Plasmodium parasite in several of the world’s tropical regions [105]. The emergence of malaria strains that are drug-resistant to the available therapeutics makes the discovery of new antimalarial agents a great scientific challenge [14,106].

The two new depside galactopyranosides, 28 and 29, and their aglycone 27, isolated from Acremonium sp., were tested against Plasmodium falciparum K1 using a microculture radioisotope technique. Only compound 27 was active towards P. falciparum K1, with an IC\textsubscript{50} value of 9.9 \(\mu\text{M}\) compared with dihydroartemisinin (IC\textsubscript{50} 0.0039 \(\mu\text{M}\)). However, 28 and 29 had weak effects (IC\textsubscript{50} > 10 \(\mu\text{M}\)) [41].

3.12. Antioxidant Activity

The depsides, 23 and 24 showed weak radicals scavenging capacity with EC\textsubscript{50} > 200 \(\mu\text{M}\) [40]. In the DPPH (2-diphenyl-1-picyrlhydrazyl) assay, 11, 45, and 46 also had weak antioxidant activity, compared with ascorbic acid [46].

3.13. Ca\textsuperscript{2+}/CaM Dependent Phosphodiesterase Inhibitory (CaM-PDEI) Activity

Calmodulin (CaM) is a prevalent Ca\textsuperscript{2+}-binding protein that regulates several Ca\textsuperscript{2+}-dependent cellular functions in physiological and pathophysiological processes [107]. It is implicated in the cytoskeleton function and architecture, cell motility, apoptosis, cell proliferation, autophagy, the dephosphorylation/phosphorylation of proteins, reproductive processes, ion channel function, the relaxation/contraction of smooth muscle, and gene expression [108]. CaM can regulate these processes via modulating various proteins, including enzymes: phosphodiesterase, kinases, NOS (nitric oxide synthases), phosphatases, and ion channels. CaM-PDE is a key enzyme that is embroiled in the complex interactions between the cyclic nucleotide and Ca\textsuperscript{2+}-second messenger systems [108]. Moreover, CaM is linked with several pathological states, including smooth muscle malfunctions and unregulated cell growth. CaM-PDEs may play an important role in treating various disorders, such as neurodegenerative diseases and cancer [109].

Nakanishi et al. reported that 34 and 35, purified from Sporothrix sp., inhibited heart and bovine brain PDEs (IC\textsubscript{50} 4.3 and 1.8 \(\mu\text{M}\) and 5.9 and 15.0 \(\mu\text{M}\), respectively) [63]. Moreover, they prohibited the CaM-dependent activities of CaM-PDEs but had a low effect against their CaM-independent effects, suggesting that these compounds interacted with
CaM to inhibit Ca\(^{2+}\)/CaM-dependent enzymes. On the other hand, they had no inhibitory activities on protein kinase C [63]. Moreover, PS-990 (47), isolated from Acronemum sp., inhibited brain CaM-PDE with an IC\(_{50}\) value of 3 \(\mu\)g/mL and did not elevate the intracellular cyclic AMP level. It markedly induced the neurite extension of Neuro2A (mouse neuroblastoma) at concentrations ranging from 10 to 30 \(\mu\)g/mL, suggesting its neuritogenic effect. It inhibited both cell growth and thymidine incorporation into the cells at the same concentration range. Interestingly, 47 reversibly induced neurite formation, with cell growth arrest through a mechanism other than increasing the intracellular cyclic AMP concentration [66,110].

3.14. Antiviral Activity

HCMV (human cytomegalovirus) is the most familiar viral cause of congenital infections, which can lead to severe birth defects. Its current treatments include viral DNA polymerase inhibitors, which block the late stages of HCMV replication; however, they do not prohibit the viral induction of multiple cell activation events [111]. Thus, it may be beneficial to discover new treatments for HCMV infections.

Compounds 27–29 were assessed against HSV-1 (Herpes simplex virus type 1), using the SBR technique. Only 28 showed potent activity, with an IC\(_{50}\) value of 7.2 \(\mu\)M, compared with acyclovir (IC\(_{50}\) 10.2 \(\mu\)M), while 27 and 29 displayed weak activity, with IC\(_{50}\) values of > 1000 and > 50 \(\mu\)M, respectively [41]. Cytonaema sp. yielded novel \(p\)-tridepsides; 84 and 85 showed in vitro inhibitory activities to hCMV protease, with IC\(_{50}\) values of 43 and 11 \(\mu\)M, respectively, in the scintillation proximity assay [73].

3.15. Human Leukocyte Elastase (HLE) Inhibitory Activity

HLE is one of the most destructive enzymes that can degrade tissue matrix proteins, such as collagen, elastin, fibronectin, proteoglycan, and laminin, by activating progelatinase, procollagenase, and prostromelysin [25]. It is released from PMNLs (polymorphonuclear leukocytes) as a result of inflammatory mediators and stimuli. HLE is considered an important therapeutic target for treating many inflammation-linked disorders [112].

The depsides, 25 (IC\(_{50}\) 45.1 \(\mu\)M) and 26 (IC\(_{50}\) 92.6 \(\mu\)M), weakly inhibited HLE in the spectro-photometric immunoassay, while the tridepside, 83 (IC\(_{50}\) 1.8 \(\mu\)M), exhibited high HLE inhibitory activity compared to ulinastatin (IC\(_{50}\) 1.1 \(\mu\)g/mL), which was 25–50-fold greater than that of depsides [25].

3.16. Indoleamine 2,3-Dioxygenase Inhibitory (IDOI) Activity

IDO (indoleamine 2,3-dioxygenase) catalyzes the tryptophan catabolism initial step via the KP (kynurenine pathway) [68]. Dysregulation of the KP is accompanied by the IDO activity elevation and production of quinolinic acid (an excitotoxin), which has been engaged in the pathogenesis of neurodegenerative disorders, neuroinflammatory, HIV encephalitis, age-related cataract, and depression [68]. Therefore, IDO is a promising target of new therapeutics for treating neurological disorders and cancer, as well as other disorders characterized by a defect in tryptophan metabolism.

Compounds 49, 54, and 65 isolated from Coniochaeta sp., inhibited the activity of IDO with IC\(_{50}\) values of 21.2, 14.5, and, 26 \(\mu\)M, respectively in comparison to menadione (IC\(_{50}\) 3.7 \(\mu\)M) [68].

3.17. Adenosine Triphosphatase Inhibitory Activity

Na\(^+\)/K\(^+\)-ATPase (sodium/potassium adenosine triphosphatase) is an integral membrane protein that is accountable for maintaining Na\(^+\) and K\(^+\) gradients across the plasma membrane, an important process for mammalian cell survival. Currently, it is extensively studied as a potential target for cancer treatment, especially in glioblastoma and lung cancer [113]. The proton pump, H\(^+\)/K\(^+\) ATPase, plays an important role in the stomach acidification process. Its inhibition in gastric parietal cells decreases gastric acid overpro-
duction [114]. H⁺/K⁺ ATPase inhibitors can be utilized as a target for developing drugs against gastric acid production disturbances.

Aquastatin A (32) was biosynthesized by *Fusarium aqueductuum*. It inhibited Na⁺/K⁺-ATPase (adenosine triphosphatase) (IC₅₀ 7.1 µM) and H⁺/K⁺-ATPase (IC₅₀ 6.2 µM) [59].

### 3.18. Proteasome Inhibitory Activity

Proteasome comprises one or two 19S RPs (regulatory particles) and 20S CPs (core particles). In humans, the 20S CP formation is assisted by proteasome-specific chaperones: PAC1–PAC4 and POMP (proteasome maturation protein) [115,116]. Proteasome accounts for misfolded, unneeded, or damaged cellular protein degradation. Therefore, it is a crucial target for the future treatment of various diseases, such as neurodegenerative and autoimmune diseases, cystic fibrosis, cancer, diabetes, and atherosclerosis [115]. The compound 105 (IC₅₀ 0.020 µM) had a potent PAC3 (proteasome-assembling chaperone 3 homodimer) inhibitory effect, while 103 and 107 (IC₅₀ > 250 µM) did not inhibit the PAC3 homodimer [116].

### 3.19. Phospholipase Inhibitory Activities

Phospholipase A₂ (PLA₂) catalyzes the hydrolysis of membrane phospholipids into arachidonic acid; therefore, its inhibitors have the potential for treating various inflammatory disorders [117]. Compound 107 showed a strong reversible and noncompetitive inhibition of human PLA₂-II (Ki value of 0.098 µM, IC₅₀ value of 0.076 µM); however, it showed weak inhibition of human PLA₂-I (IC₅₀ of 18 µM). Its inhibitory effect toward PLA₂-II human and PLA₂ *Naja mocambique* was noticeably reduced by methylation of the two COOH groups. Furthermore, 107, upon co-injection with carrageenan, remarkably reduced PLA₂ activity and exudate volume in the carrageenan-induced pleurisy rat model [80]. Rat PLA₂-II was the most sensitive to 99, with an IC₅₀ of 0.0033 µM and Ki of 0.0068 µM. Furthermore, it showed 50% quenching of the PLA₂ of *Naja naja* venom [78,83]. The metabolites, 48–53, 98–101, and 104–107, purified from *T. terricola* RF-143, were tested for PLA₂ inhibition [70,78]. Compound 99 (IC₅₀ 0.0033 µM) was the most potent inhibitor against rat PLA₂-II, and the other compounds had inhibitory effects, with an IC₅₀ of 0.0078–0.070 µM. Compounds 48–53 showed strong inhibition toward human PLA₂ (phospholipase A₂)-II and rat PLA₂-II, with IC₅₀s of 2.1–29 µM and 0.45–43 µM, respectively, compared to manoalide (IC₅₀s 1.5 µM and 2.0 µM, respectively) [70]. Moreover, 99 inhibited the histamine release from PLA₂-stimulated mast cells. In addition, 99 (IC₅₀ 1.4 µM) inhibited bee venom PLA₂. The co-injection of 99 (1 µg/paw) with bee venom PLA₂ reduced edema formation by 44.7%, via the inhibition of PLA₂ activity [84]. It was reported that 99 repressed various secretagogues for stimulated degranulation in rat and mouse mast cells, without affecting PGD₂ (prostaglandin D₂) synthesis. Thus, the secretory PLA₂ inhibition by 99 attenuated the severity of inflammation via repression of the degranulation process [118,119].

### 4. Conclusions

Recently, more focus has been given to fungi as they are excellent platforms for the biosynthesis of a huge number of structurally diverse metabolites. The knowledge of these metabolites offers a virtually untappped source of new bioactive metabolites with potential agrochemical and pharmaceutical uses. Fungi use these metabolites for defense, and many of these metabolites demonstrate a broad range of bioactivities. Among these metabolites are depsides that possess remarkable bioactivities. According to the listed results, there are 110 depsides that have been isolated from fungi. Most of them are reported from *Thielavia* (26.6%), *Stereum* (17.4%), *Chaetomium* (15%), and *Humicola* (12%) species (Figure 15).
Figure 15. Numbers of depsides isolated from different fungal genera.

Thielavia, Chaetomium, and Humicola belong to the Chaetomiaceae family; therefore, this family could be considered as one of the major producers of depsides. It is obvious that the largest number of depsides was isolated in 2002 (18 depsides), 2014 (17 depsides), 2017 (16 depsides), and 1995 (14 depsides) (Figure 16).

Figure 16. Annual numbers of isolated depsides, from 1975 to 2020.

Most of the reported depsides have been evaluated for their α-GI (α-glucosidase inhibitory), antimicrobial, antitumor, antifouling, PLA2 (phospholipase A2), and DGATI (diacylglycerol acyltransferase inhibitory) abilities (Figure 17). Thus, these studies revealed that fungal depsides are a rich source for the discovery of effective and novel pharmaceutical leads and should be further exploited.
They also demonstrate inhibitory activities against various enzymes that can be utilized as targets for the treatment of various diseases. These metabolites could have potential as lead compounds for treating metabolic syndrome, obesity, and diabetes via the inhibition of various enzymes, such as HSD, PTP1BI, α-GI, G6Pase, and DGAT. However, extensive explorations of their mechanism of action, as well as structure modification, chemical synthesis, and structure/activity relationship analysis are needed. Despite the extensive structural diversity of depsides, none of them has been approved by the FDA, and none of them has as yet progressed to clinical trials. Therefore, the impact of fungal depsides on human health concerns has to be considered in several ways.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/metabo11100683/s1, Table S1: Physical and spectral data of fungal depsides.

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Abbreviations

ACP: acyl carrier protein; AT: acyl transferase; 11β-HSD1; 11β-hydroxysteroid dehydrogenase type 1; 11β-HSD2:11β-hydroxysteroid dehydrogenase type 2; 5-FU: 5-fluorouracil; APPIHRMS: atmospheric pressure photoionization high-resolution; B16-F10: murine melanoma cell line; BC: human breast cancer; BT-474: ductal carcinoma; CaM: Calmodulin; CaM-PDE: calmodulin-dependent cyclic-nucleotide phosphodiesterase; CaM-PDEI: Ca2+/CaM dependent phosphodiesterase inhibitory; CCF-STTG1: human astrocytoma cells; CCF-STTG1: human astrocytoma; CD45: leucocyte common antigen;
CTC: 5-cyano-2,3-bis(4-methylphenyl)-2H-tetrazolium chloride; DGAT: diacylglycerol acyltransferase; DGATI: diacylglycerol acyltransferase inhibitory; DPPH: 2-diphenyl-1-picrylhydrazyl; EC50: Inhibition of settlement of 50% of the larval population; FSW: filtered sea water; GePase: D-glucose-6-phosphate phosphohydrolase; H+/K+ ATPase: hydrogen/potassium adenosine triphosphatase; H46: human non-small cell lung carcinoma; hCMV: human cytomegalovirus; HCT-116: colorectal carcinoma; HepG2: human liver cancer cells; HLE: human leukocyte elastase; HSV-1: Herpes simplex virus type 1; HTRF: homogeneous time resolved fluorescence; IC50: concentration required to inhibit cell growth by 50%; IC: immunocytotoxicity and binding; ID50: dose producing a 50% inhibition; IDo: indoleamine 2,3-dioxgenase; IDO1: indoleamine 2,3-dioxgenase producing; IMR-32: neuroblastoma; ISCID: collision-induced dissociation; IZDs: inhibition zone diameters; KB: human epidermoid carcinoma cell; KS: ketosynthase; LAR: leukocyte common antigen-related; MBGs: minimal bactericidal concentrations; MeT: methyl transferase; MCF-7: human breast adenocarcinoma; MFC: minimal fungicidal concentration; MRSA: methicillin-resistant S. aureus; MS: metabolic syndrome; MTT: (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide; NA-STZ: nicotinamide-streptozotocin; Na+/K+ ATPase: sodium/potassium adenosine triphosphatase; NCI-H187: small-cell lung cancer; PC: phosphatidylcholine; PE: phosphatidylethanolamine; PKSs: polyketide synthases; 

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