Advances in Fungal Phenaloenones—Natural Metabolites with Great Promise: Biosynthesis, Bioactivities, and an In Silico Evaluation of Their Potential as Human Glucose Transporter 1 Inhibitors

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Abstract: Phenaloenones are structurally unique aromatic polyketides that have been reported in both microbial and plant sources. They possess a hydroxy perinaphthenone three-fused-ring system and exhibit diverse bioactivities, such as cytotoxic, antimicrobial, antioxidant, and anti-HIV properties, and tyrosinase, α-glucosidase, lipase, AchE (acetylcholinesterase), indoleamine 2,3-dioxygenase 1, angiotensin-I-converting enzyme, and tyrosine phosphatase inhibition. Moreover, they have a rich nucleophilic nucleus that has inspired many chemists and biologists to synthesize more of these related derivatives. The current review provides an overview of the reported phenalenones with a fungal origin, including their structures, sources, biosynthesis, and bioactivities. Moreover, more than 135 metabolites have been listed, and 71 references have been cited. SuperPred, an artificial intelligence (AI) webserver, was used to predict the potential targets for selected phenalenones. Among these targets, we chose human glucose transporter 1 (hGLUT1) for an extensive in silico study, as it shows high probability and model accuracy. Among them, aspergillussanones C (60) and G (60) possessed the highest negative docking scores of −15.082 and −14.829 kcal/mol, respectively, compared to the native inhibitor of 5RE (score: −11.206 kcal/mol). The MD (molecular dynamics) simulation revealed their stability in complexes with GLUT1 at 100 ns. The virtual screening study results open up a new therapeutic approach by using some phenalenones as hGLUT1 inhibitors, which might be a potential target for cancer therapy.

Keywords: phenaloenones; fungi; bioactivities; biosynthesis; human glucose transporter 1 (hGLUT1) inhibitors; in silico screening; molecular docking; molecular dynamics

1. Introduction

In the last few decades, fungi have attracted tremendous scientific attention due to their capability to biosynthesize diverse classes of bio-metabolites, with varied bioactivities that
are utilized for pharmaceutical, medicinal, and agricultural applications [1–14]. Obviously, the number of reported biomolecules from a fungal origin is rapidly growing [15–19]. Fungi can produce a wide variety of structurally unique polyketide-derived metabolites; among them are phenalenones, in which various post-modifications, including prenylation, transamination, rearrangement, and oxidation diversify their structures [20–22]. Phenalenones belong to the aromatic ketones, consisting of a hydroxyl-perinaphthenone three-fused-ring system that has been reported as from both microbial and plant sources [21]. They are recognized as the higher plants’ phytalexins, which confer resistance toward pathogens [23,24]. Phenalenones are also known as pollutants, resulting from the combustion of fossil fuels [21]. The first report of the isolation of a phenalenone derivative from a fungal source was in 1955 [25,26]. Fungal phenalenones have immense structural diversity, such as hetero- and homo-dimerization, and high degrees of nitrogenation and oxygenation, as well as the capacity to be complexed with metals, incorporating additional carbon frameworks or an isoprene unit by the formation of either a linear ether or a trimethyl-hydrofuran moiety [20,21]. Moreover, many acetone adducts of phenalenones were also reported that have an extended carbon chain at ring A, such as the acyclic diterpenoid adducts. These fungal metabolites have been demonstrated to exhibit a wide range of bioactivities, such as cytotoxic, antimicrobial, antioxidant, and anti-HIV, and tyrosinase, α-glucosidase, lipase, AchE (acetylcholinesterase), indoleamine 2,3-dioxygenase 1, angiotensin-I-converting enzyme, and tyrosine phosphatase inhibition. They are of great interest as potential lead compounds for synthetic organic chemistry because of the stability of their anions, phenalenyl radicals, and cations, as well as their interesting photophysical properties [27–29]. In a previous review, Elsebai et al. reported that up to the end of 2013, 72 phenalenone derivatives of fungal origin have been separated [21]. Phenalenones represent a rapidly growing class of bio-metabolites; therefore, an updated review is needed. In the current review, the fungal phenalenone derivatives that have been published from 2014 to 2021 have been summarized. Herein, 139 phenalenones have been listed along with their sources, bioactivities, and biosynthetic pathways (Tables 1 and 2, Schemes 1–5, and Figures 1–15). A literature search of the published studies was conducted over different databases: PubMed, Web of Science, Google Scholar, SciFinder, and Scopus, as well as through various publishers: SpringerLink, Wiley, Bentham, Taylor & Francis, Thieme Medical, and ACS.

The reported data regarding phenalenone derivatives revealed its anticancer potential; therefore, we chose human glucose transporter 1 (hGLUT1) for an extensive in silico study and, by using SuperPred “AI tools for targets prediction” and other computational tools, such as QikProp “ADMET characteristics prediction”, molecular docking to “measure the binding affinity between the ligands and the targets”, as well as MD (molecular dynamics) to assess the stability of the target–ligand interaction under simulated physiological circumstances, has been implemented.

2. Biosynthesis of Phenalenones

The phenalene nucleus is the basic structure of phenalenones, which are oxidized for a series of phenalenone derivatives. It was reported that fungal phenalenones (Table 1) are of polyketide origin, i.e., derived merely from acetate and malonate units [20,21,25,30]. Zhang et al. postulated the biosynthetic pathway of flaviphenalenones A–C (45–47) [31]. The heptaketide chain is first cyclized to produce a tricyclic aromatic skeleton, followed by oxidation and acetone addition at C-6, to form intermediate I. The subsequent addition of OH at the C-1, CH$_3$ group and at C-14 and C-1, and of prenyl at C-10, yielded 45. The oxidative loss of C-6 of I formed another intermediate II that was oxidized to yield the cyclic anhydride C (III) [20,21]. Successive C-1-hydroxylation, C-14/C-1 methylation, and the C-10 prenylation of III produced 46. The cyclization of the heptaketide chain yielded another intermediate IV that underwent dehydroxylation at C-10 and C-11 methylation, to generate V. Lastly, the methylation, oxidation, and prenylation of V gave 47. The immediate oxidation or oxidative cleavage of II and the subsequent lactonization of VI produced VII,
which was methylated and prenylated to yield 47 [31] (Scheme 1). Moreover, Nazir et al. utilized [1–13C]-labeled acetate to postulate the biosynthetic pathways for 37, 44, 85, 90, 98, 111, 113, and 115, which is biosynthesized by the marine algae-derived Coniothyrium cereale. Nazir et al. hypothesized that these metabolites originated from a common joint heptaketide precursor that underwent successive oxidative cleavage reactions [20]. Some of them (e.g., 90, 98, 111, and 115) are hexaketides with methyl groups that are added through methyltransferases (Scheme 1). Moreover, it was suggested that the polyketide skeleton of 115 was formed through the degradation of heptaketide by the loss of two carbon atoms [20].

Duclauxin (120) is an oligophenalenone heptacyclic dimer, consisting of dihydroiso-coumarin and isocoumarin units that are joined together by a cyclopentane ring. The previously reported labeling experiment revealed that 120 originated from a heptaketide chain, which was cyclized to produce phenalenone (i) [21,61]. A triketone (ii) was formed by the oxidative loss of one of its carbons to yield a contracted ring, C. Its decarboxylation and regio-selective oxygen insertion, induced by enzymes or air, yielded dione (iii) and naphthalic anhydride (iv) [21]. Then, the selective reduction of (iv) generated a lactone (v). The dimerization of two lactone units through oxidative radical coupling between C-8 and C-9’a, which was catalyzed by oxidative enzymes, yielded a biaryl (vi) [62,63]. The latter underwent an intramolecular aldol condensation between the C-8’a and C-7 ketone group to furnish the aldol fragment (vii). The latter could experience a group of successive tailoring modifications in terms of reduction, methylation, acetylation, and dehydration, to produce 120 [56,64]. Compound 119 was assumed to be biosynthesized through ammonolysis, with the aid of one serine as a nitrogen donor and a further serine moiety’s decarboxylation, to provide 119 (Scheme 2) [56].

On the other hand, it was hypothesized that the compounds 49, 50, 52, and 54 were artifacts, resulting from the spontaneous addition of acetone or methyl ethyl ketone to the unstable triketone (Scheme 3) [48]. Meanwhile, the use of 3-pentanone as an initial extracting solvent ultimately led to the formation of 51 and 53 [48].

Li et al. proposed a biosynthetic pathway for compounds 21, 28, 31, and 76–81, which have a phenalenone nucleus fused to a trimethylfuran ring [39]. The trimethylfuran ring was biologically related to mevalonic acid [65]. The oxidative loss of C-6 of the heptaketide-derived phenalenone nucleus yielded P1, which could be prenylated in two various paths (A and B), leading to the formation of P2 and 28. The enzymatic epoxidation of the P2 double bond, followed by hydrolysis and then dehydration, yielded 76. The later oxidation produced 77 and 78. Similarly, the oxidation of 28 resulted in the formation of 21 and 31. Compound 28 was a precursor of 79–81 by the oxidative loss of C-7 (80) or C-5 (79 and 81) and then formed a lactone ring (80 and 81) [39]. The linkage of a prenyl side chain to 5-OH of the tricyclic intermediate II was catalyzed by prenyltransferase to yield the prenylated intermediate (III). Additionally, IV was generated from the Claisen rearrangement and cyclization of III [21] (Scheme 4).
Table 1. List of fungal phenalenones (fungal source, host, and place of origin).

| Compound Name                      | Mol. Wt. | Mol. Formula | Fungal Source | Host (Part, Family) | Place                        | Ref.                  |
|-----------------------------------|----------|--------------|---------------|---------------------|-----------------------------|-----------------------|
| Paecilomycone A (1)               | 288      | C_{15}H_{12}O_{6} | Paecilomyces gunnii | Culture             | China                       | [32]                  |
| Paecilomycone B (2)               | 286      | C_{15}H_{12}O_{6} | Paecilomyces gunnii | Culture             | China                       | [32]                  |
| Paecilomycone C (3)               | 287      | C_{15}H_{12}NO_{5} | Paecilomyces gunnii | Culture             | China                       | [32]                  |
| Myeloconone A (4)                 | 286      | C_{15}H_{12}O_{6} | Paecilomyces gunnii | Culture             | China                       | [32]                  |
| Aspergillussanone A (5)           | 540      | C_{31}H_{40}O_{8} | Aspergillus sp. PSU-RSPG185 | Soil             | Surat Thani, Thailand       | [33]                  |
| Aspergillussanone B (6)           | 540      | C_{31}H_{40}O_{8} | Aspergillus sp. PSU-RSPG185 | Soil             | Surat Thani, Thailand       | [33]                  |
| Peniciherqueinone (7)             | 388      | C_{20}H_{20}O_{8} | Penicillium herquei PSU-RSPG93 | Soil             | Gagudo, Korea               | [34]                  |
| Herqueinone (9)                   | 372      | C_{20}H_{20}O_{7} | Penicillium herquei PSU-RSPG93 | Soil             | Gagudo, Korea               | [34]                  |
| 12-Hydroxynorherqueinone (10)     | 388      | C_{20}H_{20}O_{7} | Penicillium sp. G1071 | Mushroom fruiting body | Freshwater stream, Hebron, Connecticut, USA | [36] |
| 12-Hydroxyisoherqueinone (11)     | 374      | C_{19}H_{16}O_{6} | Penicillium sp. G1071 | Mushroom fruiting body | Freshwater stream, Hebron, Connecticut, USA | [36] |
| Isoherqueinone (12)               | 372      | C_{20}H_{20}O_{7} | Penicillium sp.     | Marine sediment     | Gagudo, Korea               | [35]                  |
| ent-Isoherqueinone (13)           | 372      | C_{20}H_{20}O_{7} | Penicillium sp.     | Marine sediment     | Gagudo, Korea               | [35]                  |
| Deoxyherqueinone (14)             | 356      | C_{20}H_{20}O_{6} | Penicillium herquei PSU-RSPG93 | Soil             | Surat Thani, Thailand       | [34]                  |
| Oxopropylisoherqueinone A (15)    | 414      | C_{22}H_{22}O_{6} | Penicillium sp. PSU-RSPG93 | Soil             | Gagudo, Korea               | [35]                  |
| Oxopropylisoherqueinone B (16)    | 414      | C_{22}H_{22}O_{6} | Penicillium sp. PSU-RSPG93 | Soil             | Gagudo, Korea               | [35]                  |
| Diketoacetonylphenalenone = Acetone adduct of a triketone (17) | 398 | C_{20}H_{20}O_{7} | Penicillium herquei PSU-RSPG93 | Soil             | Gagudo, Korea               | [35]                  |
| Antatrovenetinone (18)            | 398      | C_{20}H_{20}O_{7} | Penicillium herquei PSU-RSPG93 | Soil             | Gagudo, Korea               | [35]                  |
| Sclerodin (20)                    | 328      | C_{18}H_{16}O_{6} | Penicillium herquei PSU-RSPG93 | Soil             | Surat Thani, Thailand       | [34]                  |
| (+)-Sclerodin (21)                | 328      | C_{18}H_{16}O_{6} | Penicillium sp. ZZ901 | Savoura broughtonii (Schrenck blood clam, Arcidae) | Sea shoal, East China, Zhourshan Archipelago, China | [39] |
| Chrysosporium lobatum TM-237-S5   |          |               | Penicillium herquei PSU-RSPG93 | Soil             | Gagudo, Korea               | [35]                  |
| Acanthella cavernosa (Sponge, Dictyonellidae) |          |               | Penicillium herquei PSU-RSPG93 | Soil             | Gagudo, Korea               | [35]                  |
Table 1. Cont.

| Compound Name       | Mol. Wt. | Mol. Formula | Fungal Source    | Host (Part, Family)               | Place                                      | Ref. |
|---------------------|----------|--------------|------------------|-----------------------------------|--------------------------------------------|------|
| (-)-Sclerodin (22)  | 328      | C₁₈H₂₀O₅     | Trypethelium eluteriae Sprengl | Anacardium occidentale (Bark, Anacardiaceae) | Vadanemmeli, Kanchipuram, Tamil Nadu, India | [41] |
| Penicillium sp.     |          |              |                  | Marine sediment                    | Gagado, Korea                              | [35] |
| Taeniolella sp. BCC31839 | 344    | C₁₈H₂₀O₅     | Lophiostoma bipolare BCC25910 | Mangrove wood                      | Beach in Haad Wanakorn National Park, Prachuap Khiri Khan, Thailand | [42] |
| Coniothyrium cereale |         |              |                  | Enteromorpha sp. (Algae, Ulvaceae) | Felmarn, Baltic Sea, Germany               | [20] |
| (+)-8-Hydroxyslerodin (23) | 344 | C₁₈H₂₀O₅ | Chrysosporium lobatum TM-237-5S | Acanthella cavernosa (Sponge, Dictyonellidae) | Mesophotic reef in Eilat, Dekel Beach, Gulf of Aqaba, Israel | [40] |
| (-)-Sclerodinzel (24) | 344 | C₁₈H₂₀O₅ | Pleosporales sp. HDN1811400 | Sediment sample                    | Fildes Peninsula                           | [44] |
| Coniothyrium cereale |         |              |                  | Enteromorpha sp. (Algae, Ulvaceae) | Felmarn, Baltic Sea, Germany               | [20] |
| (-)-Bipolaride D (25) | 342 | C₁₈H₂₀O₅ | Lophiostoma bipolare BCC25910 | Mangrove wood                      | Beach in Haad Wanakorn National Park, Prachuap Khiri Khan, Thailand | [42] |
| Bipolarol C (26)    | 344      | C₁₈H₂₀O₅     | Taeniolella sp. BCC31839 | Wood of mangrove forest (Poaceae)  | Bangkok, Thailand                           | [43] |
| 4-Hydroxysclerodin (27) | 346 | C₁₈H₂₀O₅ | Penicillium sp.       | Marine sediment                    | Gagado, Korea                              | [35] |
| (+)-Sclerodione (28) | 312 | C₁₈H₂₀O₅ | Penicillium sp. ZZ2001 | Scapharca brougainii (Schrenck blood clam, Arcidae) | Sea shoal, East China, Zoushan Archipelago, China | [39] |
| (-)-Sclerodione (29) | 312 | C₁₈H₂₀O₅ | Pseudolophiostoma sp. MFLUCC 17-2081 | Clematis fulvicomum (Ranunculaceae) | Chiang Rai, Thailand                        | [45] |
| Coniothyrium cereale |         |              | Taeniolella sp. BCC31839 | Wood of mangrove forest (Poaceae)  | Bangkok, Thailand                           | [43] |
| (-)-Bipolaride B (30) | 326 | C₁₈H₂₀O₅ | Lophiostoma bipolare BCC25910 | Mangrove wood                      | Beach in Haad Wanakorn National Park, Prachuap Khiri Khan, Thailand | [42] |
| Peniciphalenin H (31) | 328 | C₁₈H₂₀O₅ | Pleosporales sp. HDN1811400 | Sediment sample                    | Fildes Peninsula                           | [44] |
| Bipolarol A (32)    | 342      | C₁₈H₂₀O₅     | Lophiostoma bipolare BCC25910 | Mangrove wood                      | Beach in Haad Wanakorn National Park, Prachuap Khiri Khan, Thailand | [42] |
| (+)-Sclerdoselide (33) | 328 | C₁₈H₂₀O₅ | Penicillium sp. ZZ2001 | Scapharca brougainii (Schrenck blood clam, Arcidae) | Sea shoal, East China, Zoushan Archipelago, China | [39] |
| Chrysosporium lobatum TM-237-55 | 328 | C₁₈H₂₀O₅ | Acanthella cavernosa (Sponge, Dictyonellidae) | Mesophotic reef in Eilat, Dekel Beach, Gulf of Aqaba, Israel | Mesophotic reef in Eilat, Dekel Beach, Gulf of Aqaba, Israel | [40] |
| Penicillium herquei MA-370 |          |              | Pleosporales sp. HDN1811400 | Sediment sample                    | Fildes Peninsula                           | [44] |
| Bipolarol (34)      | 328      | C₁₈H₂₀O₅     | Lophiostoma bipolare BCC25910 | Mangrove wood                      | Beach in Haad Wanakorn National Park, Prachuap Khiri Khan, Thailand | [42] |
| Compound Name                      | Mol. Wt. | Mol. Formula | Fungal Source                    | Host (Part, Family)                                      | Place                          | Ref.   |
|------------------------------------|----------|--------------|----------------------------------|----------------------------------------------------------|--------------------------------|--------|
| (+)-8-Hydroxyscleroderolide        | 344      | C_{18}H_{20}O_{7} | Chrysosporium lobatum TM-237-55  | Acanthella cavernosa (Sponge, Dictyonellidae)            | Mesophotic reef in Elat, Dekel Beach, Gulf of Aqaba, Israel | [40]   |
| (−)-Bipolaride A (36)              | 342      | C_{18}H_{20}O_{5} | Lophostoma bipolar BCC25910      | Mangrove wood                                            | Beach in Haad Wanakorn National Park, Prachuap Khiri Khan, Thailand | [42]   |
| (−)-Cereolactone = (−)-7,8-Dihydro-3,6-dihydroxy-1,7,7,8-tetramethyl-5H-furo-[2′,3′:5,6]-naphtho[1,8-b:5,4-b′]furan-5-one | 300      | C_{12}H_{15}O_{5} | Penicillium herquei PSU-RSPG93   | Soil                                                      | Surat Thani, Thailand          | [34]   |
| Bipolarol B (40)                   | 314      | C_{16}H_{18}O_{5} | Lophostoma bipolar BCC25910      | Mangrove wood                                            | Beach in Haad Wanakorn National Park, Prachuap Khiri Khan, Thailand | [42]   |
| Bipolarol D (41)                   | 302      | C_{12}H_{18}O_{5} | Lophostoma bipolar BCC25910      | Mangrove wood                                            | Beach in Haad Wanakorn National Park, Prachuap Khiri Khan, Thailand | [42]   |
| Bipolaride C (42)                  | 328      | C_{12}H_{18}O_{5} | Lophostoma bipolar BCC25910      | Mangrove wood                                            | Beach in Haad Wanakorn National Park, Prachuap Khiri Khan, Thailand | [42]   |
| Rousselianone A = 4,9-Dihydroxy-6-methyl-7-(3′-methylbut-2-en-1-yloxy)-1H-phenalene-1,2,3-trione | 302      | C_{12}H_{18}O_{5} | Coniothyrium cereale             | Enteromorpha sp. (Algae, Ulvaceae) | Fehmamn, Baltic Sea, Germany | [20,37]|

**Table 1. Cont.**

| Compound Name                      | Mol. Wt. | Mol. Formula | Fungal Source                    | Host (Part, Family)                                      | Place                          | Ref.   |
|------------------------------------|----------|--------------|----------------------------------|----------------------------------------------------------|--------------------------------|--------|
| Penicillium sp.                    |          |              | Marine sediments                 | Gagudo, Korea                                            |                                | [35]   |
| Pseudolophiostoma sp. MFLUCC 17-2081 |          |              | Clematis fulicoma (Ranunculaceae) | Chiang Rai, Thailand                                     |                                | [45]   |
| Tannicella sp. BCC31839            |          |              | Wood of mangrove forest (Poaceae) | Bangkok, Thailand                                       |                                | [43]   |
| Penicillium herquei MA-370         |          |              | Rhizospheric soil of the mangrove plant Rhizophora mucronata (Rhizophoraceae) | Hainan Island, China |                                | [46]   |
| Coniothyrium cereale               |          |              | Enteromorpha sp. (Algae, Ulvaceae) | Fehmamn, Baltic Sea, Germany                              |                                | [20]   |

| Compound Name                      | Mol. Wt. | Mol. Formula | Fungal Source                    | Host (Part, Family)                                      | Place                          | Ref.   |
|------------------------------------|----------|--------------|----------------------------------|----------------------------------------------------------|--------------------------------|--------|
| Penicillium sp.                    |          |              | Marine sediments                 | Gagudo, Korea                                            |                                | [35]   |
| Pseudolophiostoma sp. MFLUCC 17-2081 |          |              | Clematis fulicoma (Ranunculaceae) | Chiang Rai, Thailand                                     |                                | [45]   |
| Tannicella sp. BCC31839            |          |              | Wood of mangrove forest (Poaceae) | Bangkok, Thailand                                       |                                | [43]   |
| Penicillium herquei MA-370         |          |              | Rhizospheric soil of the mangrove plant Rhizophora mucronata (Rhizophoraceae) | Hainan Island, China |                                | [46]   |
| Coniothyrium cereale               |          |              | Enteromorpha sp. (Algae, Ulvaceae) | Fehmamn, Baltic Sea, Germany                              |                                | [20]   |
| Compound Name | Mol. Wt | Mol. Formula | Fungal Source | Host (Part, Family) | Place | Ref. |
|---------------|---------|--------------|---------------|---------------------|-------|------|
| Flaviphenalenone A (45) | 442 | C_{24}H_{26}O_{8} | *Aspergillus flavipes* PJ03-11 | Wetland mud | Panjin Red Beach National Nature Reserve, Liaoning, China | [31] |
| Flaviphenalenone B (46) | 372 | C_{23}H_{26}O_{7} | *Aspergillus flavipes* PJ03-11 | Wetland mud | Panjin Red Beach National Nature Reserve, Liaoning, China | [31] |
| Flaviphenalenone C (47) | 372 | C_{23}H_{26}O_{7} | *Aspergillus flavipes* PJ03-11 | Wetland mud | Panjin Red Beach National Nature Reserve, Liaoning, China | [31] |
| Rousselianone A' = Acetone adduct of 4,9-dihydroxy-6-methyl-7-(3-methylbut-2-en-1-yl)oxy-1H-phenalene-1,2,3-trione (48) | 398 | C_{22}H_{22}O_{7} | *Coniothyrium cereale* Enteromorpha sp. (Algae, Ulvaceae) | Fehmarn, Baltic Sea, Germany | | [37] |
| Auxarthrone A (49) | 358 | C_{19}H_{18}O_{7} | *Auxarthron pseudauxarthron* TTI-0363 | *Sylvilagus audubonii* (Desert rabbit dung, Leporidae) | U.S. Route 385, Marathon, and the north entrance of Big Bend National Park, Brewster, Texas, USA | [48] |
| Auxarthrone B (50) | 358 | C_{19}H_{18}O_{7} | *Auxarthron pseudauxarthron* TTI-0363 | *Sylvilagus audubonii* (Desert rabbit dung, Leporidae) | U.S. Route 385, Marathon, and the north entrance of Big Bend National Park, Brewster, Texas, USA | [48] |
| Auxarthrone D (51) | 372 | C_{20}H_{20}O_{7} | *Auxarthron pseudauxarthron* TTI-0363 | *Sylvilagus audubonii* (Desert rabbit dung, Leporidae) | U.S. Route 385, Marathon, and the north entrance of Big Bend National Park, Brewster, Texas, USA | [48] |
| Auxarthrone C (52) | 340 | C_{19}H_{16}O_{6} | *Auxarthron pseudauxarthron* TTI-0363 | *Sylvilagus audubonii* (Desert rabbit dung, Leporidae) | U.S. Route 385, Marathon, and the north entrance of Big Bend National Park, Brewster, Texas. | [48] |
| Auxarthrone E (53) | 354 | C_{20}H_{20}O_{6} | *Auxarthron pseudauxarthron* TTI-0363 | *Sylvilagus audubonii* (Desert rabbit dung, Leporidae) | U.S. Route 385, Marathon, and the north entrance of Big Bend National Park, Brewster, Texas, USA | [48] |
| FR-901235 (54) | 344 | C_{19}H_{18}O_{7} | *Auxarthron pseudauxarthron* TTI-0363 | *Sylvilagus audubonii* (Desert rabbit dung, Leporidae) | U.S. Route 385, Marathon, and the north entrance of Big Bend National Park, Brewster, Texas, USA | [48] |
| 9-Demethyl FR-901235 (55) | 330 | C_{18}H_{16}O_{7} | *Talaromyces stipitatus* | Soil | Collaroy, New South Wales, Australia | [49] |
| (10S)-6-Amino-3,6,8-trihydroxy-1,9,9,10-tetramethyl-9,10-dihydro-6H-furo[2',3':5,6]furo[1,8-bc]oxepine-5,7(6H)-dione (56) | 373 | C_{19}H_{19}NO_{7} | *Coniothyrium cereale* | *Enteromorpha sp.* (Algae, Ulvaceae) | Fehmarn, Baltic Sea, Germany | [37] |
| (5S)-3,8-Dihydroxy-6-amino-1,9,9,10-tetramethyl-9,10-dihydro-6H-furo[2',3':5,6]furo[1,8-bc]oxepine-5,7(6H)-dione (57) | 355 | C_{19}H_{18}NO_{6} | *Coniothyrium cereale* | *Enteromorpha sp.* (Algae, Ulvaceae) | Fehmarn, Baltic Sea, Germany | [37] |
| 5-Dehydroazasirosterol (58) | 320 | C_{18}H_{18}O_{5} | *Coniothyrium cereale* | *Enteromorpha sp.* (Algae, Ulvaceae) | Fehmarn, Baltic Sea, Germany | [37] |
| Conio-azasterol (59) | 733 | C_{22}H_{25}O_{5} | *Coniothyrium cereale* | *Enteromorpha sp.* (Algae, Ulvaceae) | Fehmarn, Baltic Sea, Germany | [37] |
| Aspergillussanone C (60) | 624 | C_{20}H_{16}O_{10} | *Aspergillus* | Pinnellia ternate (Tuber, Araceae) | Suburb of Nanjing, Jiangsu, China | [50] |
### Table 1. Cont.

| Compound Name          | Mol. Wt. | Mol. Formula | Fungal Source | Host (Part, Family)                      | Place                                      | Ref. |
|------------------------|----------|--------------|---------------|------------------------------------------|--------------------------------------------|------|
| Aspergillus sanone D   | 592      | C_{35}H_{44}O_{8} | Aspergillus sp. | Pinellia ternate (Tuber, Araceae)        | Suburb of Nanjing, Jiangsu, China          | [50] |
| Aspergillus sanone E   | 592      | C_{35}H_{44}O_{8} | Aspergillus sp. | Pinellia ternate (Tuber, Araceae)        | Suburb of Nanjing, Jiangsu, China          | [50] |
| Aspergillus sanone F   | 594      | C_{35}H_{44}O_{8} | Aspergillus sp. | Pinellia ternate (Tuber, Araceae)        | Suburb of Nanjing, Jiangsu, China          | [50] |
| Aspergillus sanone G   | 610      | C_{35}H_{44}O_{8} | Aspergillus sp. | Pinellia ternate (Tuber, Araceae)        | Suburb of Nanjing, Jiangsu, China          | [50] |
| Aspergillus sanone H   | 606      | C_{35}H_{44}O_{8} | Aspergillus sp. | Pinellia ternate (Tuber, Araceae)        | Suburb of Nanjing, Jiangsu, China          | [50] |
| Aspergillus sanone I   | 634      | C_{35}H_{44}O_{8} | Aspergillus sp. | Pinellia ternate (Tuber, Araceae)        | Suburb of Nanjing, Jiangsu, China          | [50] |
| Aspergillus sanone J   | 666      | C_{35}H_{44}O_{8} | Aspergillus sp. | Pinellia ternate (Tuber, Araceae)        | Suburb of Nanjing, Jiangsu, China          | [50] |
| Aspergillus sanone K   | 652      | C_{35}H_{44}O_{8} | Aspergillus sp. | Pinellia ternate (Tuber, Araceae)        | Suburb of Nanjing, Jiangsu, China          | [50] |
| Aspergillus sanone L   | 594      | C_{35}H_{44}O_{8} | Aspergillus sp. | Pinellia ternate (Tuber, Araceae)        | Suburb of Nanjing, Jiangsu, China          | [50] |
| (S)-2-((S,2E,6E,10Z)-14,15-Dihydroxy-11-(hydroxymethyl)-3,7,15-trimethylhexadeca-2,6,10-trien-1-yl)-2,4,6,9-tetrahydroxy-5,7-dimethyl-1H-phenalene-1,3(2H)-dione | 610 | C_{35}H_{44}O_{8} | Aspergillus sp. | Pinellia ternate (Tuber, Araceae)        | Suburb of Nanjing, Jiangsu, China          | [50] |
| Asperphenalenone A     | 576      | C_{35}H_{44}O_{7} | Aspergillus sp. CPCC 400735 | Kadsura longipedunculata (Schisandraceae) | Leishan, in Guizhou province, China        | [51] |
| Asperphenalenone B     | 624      | C_{35}H_{44}O_{10} | Aspergillus sp. CPCC 400735 | Kadsura longipedunculata (Schisandraceae) | Leishan, in Guizhou province, China        | [51] |
| Asperphenalenone C     | 624      | C_{35}H_{44}O_{10} | Aspergillus sp. CPCC 400735 | Kadsura longipedunculata (Schisandraceae) | Leishan, in Guizhou province, China        | [51] |
| Asperphenalenone D     | 654      | C_{35}H_{44}O_{10} | Aspergillus sp. CPCC 400735 | Kadsura longipedunculata (Schisandraceae) | Leishan, in Guizhou province, China        | [51] |
| Asperphenalenone E     | 610      | C_{35}H_{44}O_{8} | Aspergillus sp. CPCC 400735 | Kadsura longipedunculata (Schisandraceae) | Leishan, in Guizhou province, China        | [51] |
| Peniciphenalenin A     | 328      | C_{16}H_{24}O_{6} | Penicillium sp. ZZ901 | Scapharca broughtonii (Schrenck blood clam, Arcidae) | Sea shoal, East China, Zhoushan Archipelago, China | [39] |
| Peniciphenalenin B     | 404      | C_{16}H_{24}O_{6} | Penicillium sp. ZZ901 | Scapharca broughtonii (Schrenck blood clam, Arcidae) | Sea shoal, East China, Zhoushan Archipelago, China | [39] |
| Peniciphenalenin C     | 418      | C_{16}H_{24}O_{6} | Penicillium sp. ZZ901 | Scapharca broughtonii (Schrenck blood clam, Arcidae) | Sea shoal, East China, Zhoushan Archipelago, China | [39] |
| Peniciphenalenin D     | 316      | C_{16}H_{24}O_{6} | Penicillium sp. ZZ901 | Scapharca broughtonii (Schrenck blood clam, Arcidae) | Sea shoal, East China, Zhoushan Archipelago, China | [39] |

Chrysosporium lobatum TM-237-5S Acanthella cavernosa (Sponge, Dictyonellidae) Mesophotic reef in Eilat, Dekel Beach, Gulf of Aqaba, Israel [40]
| Compound Name | Mol. Wt. | Mol. Formula | Fungal Source | Host (Part, Family) | Place | Ref. |
|---------------|----------|--------------|---------------|---------------------|-------|------|
| Peniciphenalenin E, Peniciphenalenin Ea (80) | 300 | C_{17}H_{16}O_{5} | *Penicillium* sp. ZZ901 | *Scapharca broughtonii* (Schrenck blood clam, Arcidae) | Sea shoal, East China, Zhoushan Archipelago, China | [39] |
| Peniciphenalenin F (81) | 300 | C_{17}H_{16}O_{5} | *Penicillium* sp. ZZ901 | *Scapharca broughtonii* (Schrenck blood clam, Arcidae) | Sea shoal, East China, Zhoushan Archipelago, China | [39] |
| (−)-Peniciphenalenin F (82) | 300 | C_{17}H_{16}O_{5} | *Chrysosporium lobatum* TM-237-55 | *Acanthella cavernosa* (Sponge, Dictyonellidae) | Mesophotic reef in Eilat, Dekel Beach, Gulf of Aqaba, Israel | [40] |
| Peniciphenalenin G (83) | 364 | C_{18}H_{20}ClO_{6} | Pleosporales sp. HDN1811400 | Sediment | Fildes Peninsula | [44] |
| Peniciphenalenin I (84) | 328 | C_{18}H_{16}O_{6} | Pleosporales sp. HDN1811400 | Sediment | Fildes Peninsula | [44] |
| Coniosclerodione (85) | 312 | C_{18}H_{16}O_{5} | *Pleosporales* sp. HDN1811400 | Sediment | Fildes Peninsula | [44] |
| Trypethelamide A (86) | 399 | C_{21}H_{20}NO_{5} | *Trypethelium eluteriae* Sprengl | - | Hainan, China | [52] |
| 5′-Hydroxytrypethelone (87) | 288 | C_{16}H_{16}O_{5} | *Trypethelium eluteriae* Sprengl | - | Hainan, China | [52] |
| (+)-8-Hydroxy-7′-methoxytrypethelone (88) | 302 | C_{17}H_{18}O_{5} | *Trypethelium eluteriae* Sprengl | - | Hainan, China | [52] |
| (+)-Trypethelone (89) | 272 | C_{16}H_{16}O_{4} | *Trypethelium eluteriae* Sprengl | *Anacardium occidentale* (Bark, Anacardiaceae) | Vadanemmeli, Kanchipuram, Tamil Nadu, India | [41] |
| (−)-Trypethelone (90) | 272 | C_{16}H_{16}O_{4} | *Trypethelium eluteriae* Sprengl | - | Hainan, China | [52] |
| *Pseudolophiostoma* sp. MFLUCC 17-2081 | 286 | C_{17}H_{16}O_{5} | *Anacardium occidentale* (Bark, Anacardiaceae) | Vadanemmeli, Kanchipuram, Tamil Nadu, India | [41] |
| Coniosclerodione (85) | 312 | C_{18}H_{16}O_{5} | *Pseudolophiostoma* sp. MFLUCC 17-2081 | *Clematis fulvicoma* (Ranunculaceae) | Chiang Rai, Thailand | [45] |
| Trypethelone methyl ether (91) | 286 | C_{17}H_{16}O_{5} | *Trypethelium eluteriae* Sprengl | *Anacardium occidentale* (Bark, Anacardiaceae) | Vadanemmeli, Kanchipuram, Tamil Nadu, India | [41] |
| 8-Hydroxytrypethelone methyl ether (92) | 302 | C_{17}H_{16}O_{5} | *Trypethelium eluteriae* Sprengl | *Anacardium occidentale* (Bark, Anacardiaceae) | Vadanemmeli, Kanchipuram, Tamil Nadu, India | [41] |
| 8-Methoxytrypethelone (93) | 302 | C_{17}H_{16}O_{5} | *Trypethelium eluteriae* Sprengl | *Anacardium occidentale* (Bark, Anacardiaceae) | Vadanemmeli, Kanchipuram, Tamil Nadu, India | [41] |
| 4′-Hydroxy-8′-methoxytrypethelone methyl ether (94) | 332 | C_{18}H_{20}O_{6} | *Trypethelium eluteriae* Sprengl | *Anacardium occidentale* (Bark, Anacardiaceae) | Vadanemmeli, Kanchipuram, Tamil Nadu, India | [41] |
| 5′-Hydroxy-8′-thoxytrypethelone (95) | 332 | C_{18}H_{20}O_{5} | *Trypethelium eluteriae* Sprengl | *Anacardium occidentale* (Bark, Anacardiaceae) | Vadanemmeli, Kanchipuram, Tamil Nadu, India | [41] |
| 8-Methoxytrypethelone methyl ether (96) | 316 | C_{18}H_{20}O_{5} | *Trypethelium eluteriae* Sprengl | *Anacardium occidentale* (Bark, Anacardiaceae) | Vadanemmeli, Kanchipuram, Tamil Nadu, India | [41] |
| Isoconiolactone (97) | 300 | C_{17}H_{16}O_{5} | *Chrysosporium lobatum* TM-237-55 | *Acanthella cavernosa* (Sponge, Dictyonellidae) | Mesophotic reef in Eilat, Dekel Beach, Gulf of Aqaba, Israel | [40] |
| Coniolactone (98) | 300 | C_{17}H_{16}O_{5} | *Chrysosporium lobatum* TM-237-55 | *Acanthella cavernosa* (Sponge, Dictyonellidae) | Mesophotic reef in Eilat, Dekel Beach, Gulf of Aqaba, Israel | [40] |
| Compound Name                        | Mol. Wt | Mol. Formula | Fungal Source | Host (Part, Family)                                      | Place                                      | Ref.              |
|--------------------------------------|---------|--------------|---------------|----------------------------------------------------------|--------------------------------------------|-------------------|
| Coniosclerodin (99)                  | 328     | C_{16}H_{24}O_{6} | Chrysoseporium lobatum TM-237-55 | *Acanthella cernonosa* (Sponge, Dictyonellidae) | Mesophotic reef in Eilat, Dekel Beach, Gulf of Aqaba, Israel [40] |
| O-Desmethylfulvenolone (100)         | 274     | C_{14}H_{20}O_{5} | *Coniothyrium cereale* | Soil | Collaroy, New South Wales, Australia [49] |
| Fulvenolone (101)                   | 288     | C_{14}H_{20}O_{5} | *Aspergillus sp. SF-5929* | Coral | Ross Sea, Antarctica [53] |
| Hispidulone A (102)                 | 276     | C_{14}H_{20}O_{5} | Chaetosphaeromona hispidulon TS-8-1 | Desert plant | Desert, arid, and grassland areas, China [54] |
| Hispidulone B (103)                 | 290     | C_{14}H_{20}O_{5} | Chaetosphaeromona hispidulon TS-8-1 | Desert plant | Desert, arid, and grassland areas, China [54] |
| Aceneoherqueinone A (104)           | 414     | C_{22}H_{20}O_{5} | Penicillium herquei MA-370 | Rhizospheric soil of the mangrove plant *Rhzophora mucronata* (Rhzophoraceae) | Hainan Island, China [46] |
| Aceneoherqueinone B (105)           | 414     | C_{22}H_{20}O_{5} | Penicillium herquei MA-370 | Rhizospheric soil of the mangrove plant *Rhzophora mucronata* (Rhzophoraceae) | Hainan Island, China [46] |
| (+)-Aceatrovenetinone A (106)       | 398     | C_{22}H_{20}O_{5} | Penicillium herquei MA-370 | Rhizospheric soil of the mangrove plant *Rhzophora mucronata* (Rhzophoraceae) | Hainan Island, China [46] |
| (+)–Aceatrovenetinone B (107)       | 398     | C_{22}H_{20}O_{5} | Penicillium herquei MA-370 | Rhizospheric soil of the mangrove plant *Rhzophora mucronata* (Rhzophoraceae) | Hainan Island, China [46] |
| (+)–Aceatrobenetinone A (108)       | 398     | C_{22}H_{20}O_{5} | Penicillium herquei MA-370 | Rhizospheric soil of the mangrove plant *Rhzophora mucronata* (Rhzophoraceae) | Hainan Island, China [46] |
| Lameliolic anhydride (110)          | 260     | C_{16}H_{20}O_{6} | *Coniothyrium cereale* | Enteromorphia sp. (Algae, Ulvaceae) | Fehmarn, Baltic Sea, Germany [20] |
| (+)-Cereolactone (111)              | 301     | C_{16}H_{20}O_{5} | *Coniothyrium cereale* | Enteromorphia sp. (Algae, Ulvaceae) | Fehmarn, Baltic Sea, Germany [20] |
| Z-Coniosclerodinol (112)             | 344     | C_{16}H_{20}O_{5} | *Coniothyrium cereale* | Enteromorphia sp. (Algae, Ulvaceae) | Fehmarn, Baltic Sea, Germany [20] |
| E-Coniosclerodinol (113)             | 344     | C_{16}H_{20}O_{5} | *Coniothyrium cereale* | Enteromorphia sp. (Algae, Ulvaceae) | Fehmarn, Baltic Sea, Germany [20] |
| Coniosclerodolide (114)              | 328     | C_{16}H_{20}O_{5} | *Coniothyrium cereale* | Enteromorphia sp. (Algae, Ulvaceae) | Fehmarn, Baltic Sea, Germany [20] |
| Cereolactam (115)                   | 299     | C_{16}H_{20}O_{5} | *Coniothyrium cereale* | Enteromorphia sp. (Algae, Ulvaceae) | Fehmarn, Baltic Sea, Germany [20] |
| Herqueilenone A (116)               | 581     | C_{20}H_{20}NO_{11} | Penicillium herquei FT729 | Volcanic soil sample | Big Island, Hawaii [55] |
| Erabulenol B (117)                  | 550     | C_{20}H_{20}O_{5} | Penicillium herquei FT729 | Volcanic soil sample | Big Island, Hawaii [55] |
| Erabulenol C (118)                  | 550     | C_{20}H_{20}O_{5} | Penicillium herquei FT729 | Volcanic soil | Big Island, Hawaii [55] |
| Ducauxamide A (119)                 | 557     | C_{20}H_{20}O_{5} | Penicillium mangium YIM PH30375 | Penax notoginseng (Root, Araliaceae) | Wenshan, Yunnan, China [56] |
| Ducauxin (120)                      | 546     | C_{20}H_{20}O_{5} | Penicillium mangium YIM PH30375 | Penax notoginseng (Root, Araliaceae) | Wenshan, Yunnan, China [56] |
| Talaromyces verruculosus            | 380     | C_{16}H_{20}O_{5} | Coniothyrium cereale | Enteromorphia sp. (Soft coral, Poritidae) | Sanya, Hainan Island, South China Sea, China [57] |
| Talaromyces stipitatus              | 380     | C_{16}H_{20}O_{5} | Coniothyrium cereale | Soil | Collaroy, New South Wales, Australia [49] |
| Talaromyces sp. IQ-313               | 380     | C_{16}H_{20}O_{5} | Coniothyrium cereale | Anthill soil | Hidalguense, Hidalgo State, Mexico [58] |
| Talaromycesone A (121)              | 548     | C_{20}H_{20}O_{5} | Talaromyces sp. LF458 | Axinellaverrucosa (Sponge, Axinellidae) | Punta di Fetovaia, Isle of Elba, Mediterranean Sea, Italy [59] |
Table 1. Cont.

| Compound Name                  | Mol. Wt. | Mol. Formula    | Fungal Source                  | Host (Part, Family)                     | Place                                    | Ref. |
|--------------------------------|----------|----------------|--------------------------------|----------------------------------------|------------------------------------------|------|
| Talaromycosone B (122)         | 502      | C₂₂H₁₆O₁₀       | Talaromyces sp. LF458          | Axinella verrucosa (Sponge, Axinellidae) | Punta di Fetovaia, Isle of Elba, Mediterranean Sea, Italy [59] |      |
| Bacilliosporin A (123)         | 516      | C₂₀H₁₆O₁₀       | Talaromyces stipitatus ATCC 10500 | Culture                                | France                                   | [58] |
| 9a-Epi-bacilliosporin F (124)  | 532      | C₂₀H₁₆O₁₄       | Talaromyces stipitatus ATCC 10500 | Culture                                | France                                   | [60] |
| Bacilliosporin F (125)         | 546      | C₂₀H₁₆O₁₄       | Talaromyces verruculosus       | Goniopora sp. (Soft coral, Poritidae)   | Sanya, Hainan Island, South China Sea, China [57] |      |
| 1-Epi-bacilliosporin F (126)   | 546      | C₂₀H₁₆O₁₄       | Talaromyces stipitatus ATCC 10500 | Culture                                | France                                   | [60] |
| Bacilliosporin G (127)         | 488      | C₁₇H₁₂O₈         | Talaromyces stipitatus ATCC 10500 | Culture                                | France                                   | [60] |
| Bacilliosporin H (128)         | 545      | C₂₀H₁₆NO₁₀      | Talaromyces verruculosus       | Goniopora sp. (Soft coral, Poritidae)   | Sanya, Hainan Island, South China Sea, China [57] |      |
| Verruculosin A (129)           | 604      | C₁₇H₁₆O₁₂       | Talaromyces verruculosus       | Goniopora sp. (Soft coral, Poritidae)   | Sanya, Hainan Island, South China Sea, China [57] |      |
| Verruculosin B (130)           | 620      | C₁₇H₁₆O₁₂       | Talaromyces verruculosus       | Goniopora sp. (Soft coral, Poritidae)   | Sanya, Hainan Island, South China Sea, China [57] |      |
| Xenoclauxin (131)              | 562      | C₂₀H₁₂O₁₂       | Talaromyces verruculosus       | Goniopora sp. (Soft coral, Poritidae)   | Sanya, Hainan Island, South China Sea, China [57] |      |
| Talauxin E (132)               | 675      | C₃₄H₂₆NO₁₄     | Talaromyces stipitatus         | Soil                                   | Collaroy, New South Wales, Australia [49] |      |
| Talauxin I (133)               | 659      | C₃₄H₂₆NO₁₂     | Talaromyces stipitatus         | Soil                                   | Collaroy, New South Wales, Australia [49] |      |
| Talauxin L (134)               | 659      | C₃₄H₂₆NO₁₂     | Talaromyces stipitatus         | Soil                                   | Collaroy, New South Wales, Australia [49] |      |
| Talauxin Q (135)               | 674      | C₃₄H₂₆NO₁₂     | Talaromyces stipitatus         | Soil                                   | Collaroy, New South Wales, Australia [49] |      |
| Talauxin V (136)               | 645      | C₃₄H₂₆NO₁₂     | Talaromyces stipitatus         | Soil                                   | Collaroy, New South Wales, Australia [49] |      |
| Epitalauxin I (137)            | 659      | C₃₄H₂₆NO₁₂     | Talaromyces stipitatus         | Soil                                   | Collaroy, New South Wales, Australia [49] |      |
| Epitalauxin L (138)            | 659      | C₃₄H₂₆NO₁₂     | Talaromyces stipitatus         | Soil                                   | Collaroy, New South Wales, Australia [49] |      |
| Desacetyldesmethyltalauxin V   | 571      | C₃₁H₂₃NO₁₀     | Talaromyces stipitatus         | Soil sample                            | Collaroy, New South Wales, Australia [49] |      |
| Pseudolophiostoma sp. MFLUCC 17-2081 |            |                |                                |                                        | Chiang Rai, Thailand [45] |      |
| Clematis fulvicoma (Ranunculaceae) |        |                |                                |                                        |                                          |      |
The enol inter-conversion of the C-4 and C-3 of IV generated an intermediate V that was converted by reduction to form VI, which was very active due to the C-8 two hydroxyl groups. Then, pyruvic acid was added to one of the hydroxyl groups to give VII. Finally, 104 and 105 were produced by the VII COOH group reduction, which was catalyzed by reductase [46]. Yu et al. proposed biosynthetic pathways for 116–118 (Scheme 5). The intermediate I was trans-aminated to yield II, which underwent oxidative cleavage to form a naphthoquinone (III) [55]. Then, a benzo[f]chromene-1,7,10-trione derivative (IV) was generated through the cyclization between 7-OH and the 3-carbonyl group. The prenylation of IV, followed by a Claisen rearrangement, yielded VI. The coupling of communal F with VI generated 116 [66]. Furthermore, 112 and 117 were produced from the coupling between communal F and VIII [55].
Scheme 3. Proposed pathways for the formation of compounds 49–54 [48].

Scheme 4. Biosynthetic pathway of compounds 21, 28, 31, and 76–81 [21,39,46].
Scheme 5. Biosynthetic pathway of compounds 116–118 [55,66].

3. Bioactivities of Phenalenones

The bioactivities of some of the reported metabolites have been investigated. In this regard, 70 metabolites have been associated with some type of biological action, including cytotoxic, antimalarial, antimycobacterial, anti-inflammatory, anti-angiogenic, immunosuppressive, and antioxidant properties, as well as IDO1, α-glucosidase (AG), ACE, tyrosinase, and PTP inhibition. This information has been discussed and listed in Table 2.

Paecilomycones A–C (1–3) were purified from Paecilomyces gunnii culture extract with the aid of a preparatory HSCCC, guided by HPLC-HRESIMS, used as a tyrosinase inhibitor. Compound 1 was similar to myeloconone A2 (4), which was formerly separated from the lichen Myeloconis erumpens [67], except that 1 has an OH group at C-8 instead of an OCH₃ group. Compound 3 was deduced as 9-amino-6,7,8-trihydroxy-3-methoxy-4-methyl-1H-phenalen-1-one; the existence of NH₂ in 3 was confirmed by a positive purple reaction with a ninhydrin reagent in the TLC plate. They were characterized by means of spectroscopic analyses. These metabolites exhibited potent tyrosinase inhibitory potential (IC₅₀s 0.11, 0.17, and 0.14 mM, respectively) in the form of kojic acid (IC₅₀ 0.10 mM), being stronger than arbutin (IC₅₀ 0.20 mM). This influence was found to be positively related to the number of OH groups [32] (Figure 1).
Table 2. Biological activities of the most active fungal phenalenones.

| Compound Name | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|---------------|---------------------|-------------------------------|--------------------|------------------|------|
| Paecilomycone A (1) | Tyrosinase inhibition | Colorimetric-microtiter plates/Tyrosinase enzyme | 0.11 mM (IC_{50}) | Kojic acid 0.10 mM (IC_{50}) | [32] |
| | | | | Arbutin 0.20 mM (IC_{50}) | |
| Paecilomycone B (2) | Tyrosinase inhibition | Colorimetric-microtiter plates/Tyrosinase enzyme | 0.17 mM (IC_{50}) | Kojic acid 0.10 mM (IC_{50}) | [32] |
| | | | | Arbutin 0.20 mM (IC_{50}) | |
| Paecilomycone C (3) | Tyrosinase inhibition | Colorimetric-microtiter plates/Tyrosinase enzyme | 0.14 mM (IC_{50}) | Kojic acid 0.10 mM (IC_{50}) | [32] |
| | | | | Arbutin 0.20 mM (IC_{50}) | |
| Aspergillussanone A (5) | Cytotoxicity | Resazurin microplate/KB | 48.4 µM (IC_{50}) | Ellipticine 4.1 µM (IC_{50}) | [33] |
| | | | | Ellipticine 4.5 µM (IC_{50}) | |
| | | | | | |
| ent-Penicillicerqueinone (8) | Adipogenesis induction | Adiponectin production assay/hBM-MSC(B7) | 57.5 µM (IC_{50}) | Pioglitazone 0.69 µM (IC_{50}) | [35] |
| | | | | | |
| Herqueinone (9) | Antioxidant | DPPH/DPPH• | 0.48 mM (IC_{50}) | Butylated hydroxytoluene 0.11 mM (IC_{50}) | [34] |
| | | | | Tannic acid 0.26 mM (IC_{50}) | |
| | | | | | |
| Isoherqueinone (12) | Adipogenesis induction | | 39.7 µM (IC_{50}) | Pioglitazone 0.69 µM (IC_{50}) | [35] |
| | | | | | |
| Acetone adduct of a triketone (17) | Anti-inflammatory | Nitric oxide synthase/RAW 264.7 | 3.2 µM (IC_{50}) | AMT 0.2 µM (IC_{50}) | [35] |
| (+)-Sclerodin (21) | Cytotoxicity | SRB/U87MG | 55.99 µM (IC_{50}) | Doxorubicin 1.2 µM (IC_{50}) | [39] |
| | | | | Doxorubicin 0.47 µM (IC_{50}) | [39] |
| (−)-Sclerodinol (24) | Antimicrobial | Agar dilution/B. cereus | 25.0 µM (MIC) | Ciprofloxacin 0.39 µM (MIC) | [44] |
| | | | | Ciprofloxacin 0.78 µM (MIC) | [44] |
| | | | | Ciprofloxacin 0.39 µM (MIC) | [44] |
| | | | | Ciprofloxacin 0.39 µM (MIC) | [44] |
| | | | | | |
| Bipolarol C (26) | Antibacterial | REMA/B. cereus | 25.0 µg/mL (MIC) | Vancomycin 1.0 µg/mL (MIC) | [42] |
| 4-Hydroxysclerodin (27) | Anti-angiogenic | Tube formation assay/HUVECs | 20.9 µM (IC_{50}) | Sunsitinib 1.5 µM (IC_{50}) | [35] |
| (+)-Sclerodione (28) | Cytotoxicity | SRB/U87MG | 60.93 µM (IC_{50}) | Doxorubicin 1.2 µM (IC_{50}) | [39] |
| | | | | Doxorubicin 0.47 µM (IC_{50}) | [39] |
| | | | | | |
| (−)-Sclerodione (29) | α-Glucosidase inhibition | Colorimetric/α-Glucosidase | 120 µM (IC_{50}) | N-deoxynojirimycin 130.5 µM (IC_{50}) | [45] |
| | | | | | |
| | | | | Porcine-lipase inhibition | Colorimetric/Porcine lipase | 1.0 µM (IC_{50}) | Orlistat 9.4 µM (IC_{50}) | [45] |
| Compound Name             | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|---------------------------|---------------------|-------------------------------|--------------------|------------------|------|
| (-)-Bipolaride B (30)     | Antibacterial       | REMA/B. cereus                | 25.0 µg/mL (MIC)   | Vancomycin 1.0 µg/mL (MIC) | [42] |
|                           | Cytotoxicity        | REMA/MCF-7                    | 79.4 µM (IC₅₀)     | Doxorubicin 12.99 µM (IC₅₀) | [42] |
|                           |                     | REMA/KB                       | 96.8 µM (IC₅₀)     | Tamoxifen 19.39 µM (IC₅₀) | [42] |
|                           |                     | REMA/NCI-H187                 | 56.5 µM (IC₅₀)     | Ellipticine 8.32 µM (IC₅₀) | [42] |
|                           |                     |                               |                    | Doxorubicin 1.15 µM (IC₅₀) | [42] |
|                           |                     |                               |                    | Ellipticine 9.74 µM (IC₅₀) | [42] |
|                           |                     |                               |                    | Doxorubicin 0.19 µM (IC₅₀) | [42] |
| Penicilphanerolin H (31)  | Antimicrobial       | Agar dilution/Proteus species | 50.0 µM (MIC)      | Ciprofloxacin 0.78 µM (MIC) | [44] |
|                           |                     | Agar dilution/B. subtilis     | 25.0 µM (MIC)      | Ciprofloxacin 0.39 µM (MIC) | [44] |
|                           |                     | Agar dilution/V. parahaemolyticus | 25.0 µM (MIC)  | Ciprofloxacin 0.39 µM (MIC) | [44] |
|                           |                     | Agar dilution/MRCNS           | 25.0 µM (MIC)      | Ciprofloxacin 25.0 µM (MIC) | [44] |
|                           |                     | Agar dilution/REMAB. cereus   | 50.0 µM (MIC)      | Ciprofloxacin > 50 µM (MIC) | [44] |
| B. cereus                 | Antibacterial       | REMA/MCF-7                    | 110.4 µM (IC₅₀)   | Doxorubicin 12.99 µM (IC₅₀) | [42] |
|                           | Cytotoxicity        |                               |                    | Tamoxifen 19.39 µM (IC₅₀) | [42] |
| (+)-Scleroderolide (33)   | Antibacterial       | SIRB/US7MG                    | 37.26 µM (IC₅₀)   | Doxorubicin 1.2 µM (IC₅₀) | [39] |
|                           |                     | SRB/C6                        | 23.24 µM (IC₅₀)   | Doxorubicin 0.47 µM (IC₅₀) | [39] |
|                           |                     | Micro-broth dilution/REMAB. cereus | 7.0 µg/mL (MIC) | Gentamicin 0.5 µg/mL (MIC) | [39] |
|                           |                     | Micro-broth dilution/E. coli  | 9.0 µg/mL (MIC)   | Gentamicin 1.0 µg/mL (MIC) | [39] |
| (-)-Scleroderolide (34)   | α-Glucosidase inhibition | Colorimetric/α-Glucosidase   | 48.7 µM (IC₅₀)    | N-Doxynorleucine 130.5 µM (IC₅₀) | [45] |
|                           | porcine-lipase inhibition | Colorimetric/Porcine lipase | 3.4 µM (IC₅₀)     | Orlistat 9.4 µM (IC₅₀) | [45] |
| (-)-Bipolaride A (36)     | Antibacterial       | REMA/B. cereus                | 12.5 µg/mL (MIC)   | Vancomycin 1.0 µg/mL (MIC) | [42] |
|                           | Cytotoxicity        | REMA/NCI-H187                 | 60.2 µM (IC₅₀)    | Ellipticine 9.74 µM (IC₅₀) | [42] |
|                           |                      |                               |                    | Doxorubicin 0.19 µM (IC₅₀) | [42] |
| (-)-Bipolaride E (39)     | Antibacterial       | REMA/B. cereus                | 12.5 µg/mL (MIC)   | Vancomycin 1.0 µg/mL (MIC) | [42] |
|                           | Cytotoxicity        | REMA/MCF-7                    | 65.1 µM (IC₅₀)    | Doxorubicin 12.99 µM (IC₅₀) | [42] |
|                           |                      | REMA/KB                       | 94.4 µM (IC₅₀)    | Tamoxifen 19.39 µM (IC₅₀) | [42] |
|                           |                      | REMA/NCI-H187                 | 86.9 µM (IC₅₀)    | Ellipticine 8.32 µM (IC₅₀) | [42] |
|                           |                      |                               |                    | Doxorubicin 1.15 µM (IC₅₀) | [42] |
|                           |                      |                               |                    | Ellipticine 9.74 µM (IC₅₀) | [42] |
|                           |                      |                               |                    | Doxorubicin 0.19 µM (IC₅₀) | [42] |
| Bipolar B (40)            | Cytotoxicity        | REMA/MCF-7                    | 65.3 µM (IC₅₀)    | Doxorubicin 12.99 µM (IC₅₀) | [42] |
|                           |                      | REMA/KB                       | 52.5 µM (IC₅₀)    | Tamoxifen 19.39 µM (IC₅₀) | [42] |
|                           |                      | REMA/NCI-H187                 | 48.3 µM (IC₅₀)    | Ellipticine 8.32 µM (IC₅₀) | [42] |
|                           |                      |                               |                    | Doxorubicin 1.15 µM (IC₅₀) | [42] |
|                           |                      |                               |                    | Ellipticine 9.74 µM (IC₅₀) | [42] |
|                           |                      |                               |                    | Doxorubicin 0.19 µM (IC₅₀) | [42] |
| Bipolar D (41)            | REMA/MCF-7          | REMA/MCF-7                    | 108.7 µM (IC₅₀)   | Doxorubicin 12.99 µM (IC₅₀) | [42] |
|                           |                      |                               |                    | Tamoxifen 19.39 µM (IC₅₀) | [42] |
| (-)-Bipolaride C (42)     | Antibacterial       | REMA/B. cereus                | 12.5 µg/mL (MIC)   | Vancomycin 1.0 µg/mL (MIC) | [42] |
|                           | Cytotoxicity        | REMA/MCF-7                    | 48.9 µM (IC₅₀)    | Doxorubicin 12.99 µM (IC₅₀) | [42] |
|                           |                      | REMA/KB                       | 34.4 µM (IC₅₀)    | Tamoxifen 19.39 µM (IC₅₀) | [42] |
|                           |                      | REMA/NCI-H187                 | 59.8 µM (IC₅₀)    | Ellipticine 8.32 µM (IC₅₀) | [42] |
|                           |                      | REMA/Vero                     | 53.1 µM (IC₅₀)    | Doxorubicin 1.15 µM (IC₅₀) | [42] |
|                           |                      |                               |                    | Ellipticine 9.74 µM (IC₅₀) | [42] |
|                           |                      |                               |                    | Doxorubicin 0.19 µM (IC₅₀) | [42] |
|                           |                      |                               |                    | Ellipticine 2.13 µM (IC₅₀) | [42] |
| Compound Name | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|---------------|---------------------|-----------------|-----------------|-----------------|-----|
| Flaviphenalenone A (45) | Cytotoxicity | MTT/A549 | 6.6 µg/mL (IC50) | Doxorubicin HCl 0.2 µg/mL (IC50) | [31] |
| Flaviphenalenone A (45) | Cytotoxicity | MTT/MCF-7 | 10.0 µg/mL (IC50) | Doxorubicin HCl 0.4 µg/mL (IC50) | [31] |
| Flaviphenalenone B (46) | α-Glucosidase inhibition | Colorimetrically/α-Glucosidase | 94.95 µM (IC50) | Acarbose 685.36 µM (IC50) | [31] |
| Flaviphenalenone B (46) | α-Glucosidase inhibition | MTT/A549 | 78.96 µM (IC50) | Doxorubicin HCl 0.2 µg/mL (IC50) | [31] |
| Auxarthrone A (49) | Antifungal | Serial dilution/C. neoformans | 3.2 µg/mL (MIC) | Amphotericin B 0.8 µg/mL (MIC) | [48] |
| Auxarthrone B (50) | Antifungal | Serial dilution/C. neoformans | 12.8 µg/mL (MIC) | Amphotericin B 0.8 µg/mL (MIC) | [48] |
| Auxarthrone D (54) | Antifungal | Serial dilution/C. neoformans | 25.6 µg/mL (MIC) | Amphotericin B 0.8 µg/mL (MIC) | [48] |
| Aspergillussanone D (61) | Antibacterial | Broth microdilution/P. aeruginosa | 38.47 µg/mL (MIC50) | Streptomycin 0.34 µg/mL (MIC50) | [50] |
| Aspergillussanone E (62) | Antibacterial | Broth microdilution/E. coli | 7.83 µg/mL (MIC50) | Streptomycin 0.34 µg/mL (MIC50) | [50] |
| Aspergillussanone F (63) | Antibacterial | Broth microdilution/P. aeruginosa | 26.56 µg/mL (MIC50) | Streptomycin 0.34 µg/mL (MIC50) | [50] |
| Aspergillussanone G (64) | Antibacterial | Broth microdilution/P. aeruginosa | 24.46 µg/mL (MIC50) | Streptomycin 0.34 µg/mL (MIC50) | [50] |
| Aspergillussanone H (65) | Antibacterial | Broth microdilution/E. coli | 8.59 µg/mL (MIC50) | Streptomycin 0.34 µg/mL (MIC50) | [50] |
### Table 2. Cont.

| Compound Name | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|---------------|---------------------|--------------------------------|---------------------|------------------|------|
| Aspergillussanone I (66) | Antibacterial | Broth microdilution/P. aeruginosa | 12.00 µg/mL (MIC<sub>50</sub>) | Streptomycin 0.34 µg/mL (MIC<sub>50</sub>) | [50] |
| Aspergillussanone J (67) | Antibacterial | Broth microdilution/P. aeruginosa | 28.50 µg/mL (MIC<sub>50</sub>) | Streptomycin 0.34 µg/mL (MIC<sub>50</sub>) | [50] |
| | | Broth microdilution/E. coli | 5.34 µg/mL (MIC<sub>50</sub>) | Streptomycin 0.25 µg/mL (MIC<sub>50</sub>) | [50] |
| | | Broth microdilution/S. aureus | 29.87 µg/mL (MIC<sub>50</sub>) | Penicillin 0.063 µg/mL (MIC<sub>50</sub>) | [50] |
| Aspergillussanone K (68) | Antibacterial | Broth microdilution/P. aeruginosa | 6.55 µg/mL (MIC<sub>50</sub>) | Streptomycin 0.34 µg/mL (MIC<sub>50</sub>) | [50] |
| | | Broth microdilution/S. aureus | 21.02 µg/mL (MIC<sub>50</sub>) | Penicillin 0.063 µg/mL (MIC<sub>50</sub>) | [50] |
| Aspergillussanone L (69) | Antibacterial | Broth microdilution/P. aeruginosa | 1.87 µg/mL (MIC<sub>50</sub>) | Streptomycin 0.34 µg/mL (MIC<sub>50</sub>) | [50] |
| | | Broth microdilution/S. aureus | 2.77 µg/mL (MIC<sub>50</sub>) | Penicillin 0.063 µg/mL (MIC<sub>50</sub>) | [50] |
| | | Broth microdilution/B. subtilis | 4.80 µg/mL (MIC<sub>50</sub>) | Penicillin 0.063 µg/mL (MIC<sub>50</sub>) | [50] |
| (5)-2-((5,2E,6E,10Z)-14,15-Dihydroxy-11-(hydroxymethyl)-3,7,15-trimethylhexadeca-2,6,10-trien-1-yl)-2,4,9-tetrahydroxy-5,7-dimethyl-1H-phenalene-1,3(2H)-dione (70) | Antibacterial | Broth microdilution/P. aeruginosa | 19.07 µg/mL (MIC<sub>50</sub>) | Streptomycin 0.34 µg/mL (MIC<sub>50</sub>) | [50] |
| | | Broth microdilution/E. coli | 1.88 µg/mL (MIC<sub>50</sub>) | Streptomycin 0.25 µg/mL (MIC<sub>50</sub>) | [50] |
| Asperphenalenone A (71) | Anti-HIV-1 | Luciferase assay/SupT1 cells | 4.2 µM (IC<sub>50</sub>) | Lamivudine 0.1 µM (IC<sub>50</sub>) | [51] |
| Asperphenalenone B (72) | Anti-HIV-1 | Luciferase assay/SupT1 cells | 32.6 µM (IC<sub>50</sub>) | Lamivudine 0.1 µM (IC<sub>50</sub>) | [51] |
| Asperphenalenone D (74) | Anti-HIV-1 | Luciferase assay/SupT1 cells | 2.4 µM (IC<sub>50</sub>) | Lamivudine 0.1 µM (IC<sub>50</sub>) | [51] |
| | Anti-HIV-1 | Luciferase assay/SupT1 cells | 22.1 µM (IC<sub>50</sub>) | Lamivudine 0.1 µM (IC<sub>50</sub>) | [51] |
| Periclophenalenin G (83) | Antimicrobial | Agar dilution/B. cereus | 25.0 µM (MIC) | Ciprofloxacin 0.39 µM (MIC) | [44] |
| | | Agar dilution/Proteus species | 50.0 µM (MIC) | Ciprofloxacin 0.39 µM (MIC) | [44] |
| | | Agar dilution/M. Pfiess | 50.0 µM (MIC) | Ciprofloxacin 0.39 µM (MIC) | [44] |
| | | Agar dilution/B. subtilis | 25.0 µM (MIC) | Ciprofloxacin 0.39 µM (MIC) | [44] |
| | | Agar dilution/V. Parahemolyticus | 50.0 µM (MIC) | Ciprofloxacin 0.39 µM (MIC) | [44] |
| | | Agar dilution/MRCNS | 25.0 µM (MIC) | Ciprofloxacin 0.39 µM (MIC) | [44] |
| | | Agar dilution/MRSA | 12.5 µM (MIC) | Ciprofloxacin 0.39 µM (MIC) | [44] |
| Coniosclerodione (85) | Antimicrobial | Agar dilution/B. cereus | 25.0 µM (MIC) | Ciprofloxacin 0.39 µM (MIC) | [44] |
| | | Agar dilution/Proteus sp. | 25.0 µM (MIC) | Ciprofloxacin 0.39 µM (MIC) | [44] |
| | | Agar dilution/M. Pfiess | 25.0 µM (MIC) | Ciprofloxacin 0.39 µM (MIC) | [44] |
| | | Agar dilution/B. subtilis | 12.5 µM (MIC) | Ciprofloxacin 0.39 µM (MIC) | [44] |
| | | Agar dilution/V. Parahemolyticus | 12.5 µM (MIC) | Ciprofloxacin 0.39 µM (MIC) | [44] |
| | | Agar dilution/MRCNS | 12.5 µM (MIC) | Ciprofloxacin 0.39 µM (MIC) | [44] |
| | | Agar dilution/MRSA | 6.25 µM (MIC) | Ciprofloxacin 0.39 µM (MIC) | [44] |
| Trypethalonamide A (86) | Cytotoxicity | CCK8/RKO | 63.6 µM (IC<sub>50</sub>) | Taxol 0.05 µM (IC<sub>50</sub>) | [52] |
| 5'-Hydroxytrypetholone (87) | Cytotoxicity | CCK8/RKO | 22.6 µM (IC<sub>50</sub>) | Taxol 0.05 µM (IC<sub>50</sub>) | [52] |
| (+)-6-Hydroxy-7-methoxytrypetholone (88) | Cytotoxicity | CCK8/RKO | 113.5 µM (IC<sub>50</sub>) | Taxol 0.05 µM (IC<sub>50</sub>) | [52] |
| | | CCK8/HeLa | 183.2 µM (IC<sub>50</sub>) | Taxol 1.0 µM (IC<sub>50</sub>) | [52] |
| Compound Name                     | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|-----------------------------------|---------------------|------------------------------|--------------------|------------------|------|
| (+)-Tryptophane (89)              | Cytotoxicity        | CCK8/RKO                     | 49.3 μM (IC₅₀)     | Taxol 0.05 μM (IC₅₀) | [52] |
| (−)-Tryptophane (90)              | Cytotoxicity        | CCK8/RKO                     | 30.3 μM (IC₅₀)     | Taxol 0.05 μM (IC₅₀) | [52] |
| O-Desmethylfulvenalene (100)      | Antibacterial       | W256-1                       | 265 μM (IC₅₀)      | Clotrimazole 0.4 μM (IC₅₀) | [49] |
|                                  | Cytotoxicity        | Resazurin microplate/NS-1    | 70 μM (IC₅₀)       | 5-Fluorouracil 4.6 μM (IC₅₀) | [49] |
| Furalenone (101)                  | hPBPB-40 inhibition | Photocolorimetric/hPBPB-40    | 6.1 μM (IC₅₀)      | Ursolic acid 4.3 μM (IC₅₀) | [53] |
| Hipsidulone B (103)               | Cytotoxicity        | MT4/6-549                    | 2.71 μM (IC₅₀)     | cis-Platinum 8.73 μM (IC₅₀) | [54] |
|                                  |                     | MT4/Huh-7/NS-1               | 22.93 μM (IC₅₀)    | cis-Platinum 5.89 μM (IC₅₀) | [54] |
|                                  |                     | MT4/HeLa                     | 23.94 μM (IC₅₀)    | cis-Platinum 14.68 μM (IC₅₀) | [54] |
| Aceneherqueinone A (104)          | Angiotensin-1-     | Spectrophotometric/Hippuryl-L-histidyl-L-leucine | 3.10 μM (IC₅₀) | Captopril 9.23 nM (IC₅₀) | [46] |
| conversion enzyme inhibition      |                     |                              |                    |                  |      |
| Aceneherqueinone B (105)          | Angiotensin-1-     | Spectrophotometric/Hippuryl-L-histidyl-L-leucine | 11.28 μM (IC₅₀) | Captopril 9.23 nM (IC₅₀) | [46] |
| conversion enzyme inhibition      |                     |                              |                    |                  |      |
| Erabulenol B (117)                | Indoleamine        | ELISA/Indoleamine 2,3-dioxygenase 1 | 13.69 μM (IC₅₀) | Epacadostat 0.015 μM (IC₅₀) | [55] |
| dioxynase 1 inhibition            |                     |                              |                    |                  |      |
| Erabulenol C (118)                | Indoleamine        | ELISA/Indoleamine 2,3-dioxygenase 1 | 14.38 μM (IC₅₀) | Epacadostat 0.015 μM (IC₅₀) | [55] |
| dioxynase 1 inhibition            |                     |                              |                    |                  |      |
| Duclauxin (120)                   | Antitumor          | ELISA/EGFR                   | 0.95 μM (IC₅₀)     | Afatinib 0.0005 μM (IC₅₀) | [57] |
|                                  | Cytotoxicity        | ELISA/CDC25B                 | 0.75 μM (IC₅₀)     | Na₂VO₃ 0.52 μM (IC₅₀) | [49] |
|                                  | hPBPB-40 inhibition | Photocolorimetric/hPBPB-40    | 140 μM (IC₅₀)      | 5-Fluorouracil 4.6 μM (IC₅₀) | [49] |
| Talaromycosome A (121)            | Antibacterial      | REMA/S. epidermidis          | 3.70 μM (IC₅₀)     | Chloramphenicol 1.81 μM (IC₅₀) | [59] |
|                                  | Antitumoral        | REMA/MRSA                    | 5.48 μM (IC₅₀)     | Chloramphenicol 2.46 μM (IC₅₀) | [59] |
|                                  | AchE inhibition     | Modified Ellman’s enzyme/Immunosorbent assay | 7.49 μM (IC₅₀) | Huperzine 11.60 μM (IC₅₀) | [59] |
| Talaromycosome B (122)            | Antibacterial      | REMA/S. epidermidis          | 17.36 μM (IC₅₀)    | Chloramphenicol 1.81 μM (IC₅₀) | [59] |
|                                  | hPBPB-40 inhibition | REMA/MRSA                    | 19.50 μM (IC₅₀)    | Chloramphenicol 2.46 μM (IC₅₀) | [59] |
|                                  |                     | Photocolorimetric/hPBPB-40    | 82.1 μM (IC₅₀)     | Ursolic acid 26.6 μM (IC₅₀) | [58] |
| Bacillispore A (123)              | Antibacterial      | Microtiter plate/S. aureus   | 5.2 μg/mL (MIC)    | Tetracycline 0.05 μg/mL (MIC) | [60] |
|                                  |                     | Microtiter plate/S. hemolyticus | 9.5 μg/mL (MIC)  | Tetracycline 29.2 μg/mL (MIC) | [60] |
|                                  |                     | Microtiter plate/E. faecalis | 2.4 μg/mL (MIC)    | Tetracycline 0.4 μg/mL (MIC) | [60] |
| 9a-Epi-bacillispore E (124)       | Antibacterial      | Microtiter plate/S. aureus   | 29.3 μg/mL (MIC)   | Tetracycline 0.05 μg/mL (MIC) | [60] |
| Bacillispore F (125)              | Antibacterial      | Microtiter plate/S. aureus   | 15.6 μg/mL (MIC)   | Tetracycline 0.05 μg/mL (MIC) | [60] |
|                                  | Antitumoral        | ELISA/EGFR                   | 4.41 μM (IC₅₀)     | Afatinib 0.0005 μM (IC₅₀) | [57] |
|                                  |                     | ELISA/CDC25B                 | 0.40 μM (IC₅₀)     | Na₂VO₃ 0.52 μM (IC₅₀) | [57] |
|                                  | Antitumoral        | ELISA/EGFR                   | 4.41 μM (IC₅₀)     | Afatinib 0.0005 μM (IC₅₀) | [57] |
|                                  |                     | ELISA/CDC25B                 | 0.40 μM (IC₅₀)     | Na₂VO₃ 0.52 μM (IC₅₀) | [57] |
Table 2. Cont.

| Compound Name         | Biological Activity         | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|-----------------------|-----------------------------|-------------------------------|--------------------|------------------|------|
| Bacillisporin G (127) | hPTP1B<sub>1-400</sub> inhibition | Photocolorimetric/hPTP1B<sub>1-400</sub> | 13.5 µM (IC<sub>50</sub>) | Ursolic acid 26.6 µM (IC<sub>50</sub>) | [58] |
| Bacillisporin H (128) | Cytotoxicity | MTT/HeLa | 49.5 µM (IC<sub>50</sub>) | Cisplatin 10.6 µM (IC<sub>50</sub>) | [60] |
|                       | Antibacterial | Microtiter plate/S. aureus | 5.0 µg/mL (MIC) | Tetracycline 0.05 µg/mL (MIC) | [60] |
|                       |                | Microtiter plate/S. hemolyticus | 20.4 µg/mL (MIC) | Tetracycline 29.2 µg/mL (MIC) | [60] |
| Verruculosin A (129)  | Antitumor | ELISA/EGFR | 0.92 µM (IC<sub>50</sub>) | Afatinib 0.0005 µM (IC<sub>50</sub>) | [57] |
|                       | Antitumor | ELISA/CDC25B | 0.38 µM (IC<sub>50</sub>) | Na<sub>3</sub>VO<sub>4</sub> 0.52 µM (IC<sub>50</sub>) | [57] |
| Verruculosin B (130)  | Antitumor | ELISA/EGFR | 1.22 µM (IC<sub>50</sub>) | Afatinib 0.0005 µM (IC<sub>50</sub>) | [57] |
| Xenoclauxin (131)     | Antitumor | ELISA/EGFR | 0.24 µM (IC<sub>50</sub>) | Afatinib 0.0005 µM (IC<sub>50</sub>) | [57] |
|                       | Antitumor | ELISA/CDC25B | 0.26 µM (IC<sub>50</sub>) | Na<sub>3</sub>VO<sub>4</sub> 0.52 µM (IC<sub>50</sub>) | [57] |
|                       | hPTP1B<sub>1-400</sub> inhibition | Photocolorimetric/hPTP1B<sub>1-400</sub> | 21.8 µM (IC<sub>50</sub>) | Ursolic acid 26.6 µM (IC<sub>50</sub>) | [58] |
Aspergilussanones A (5) and B (6) were separated from *Aspergillus* sp. PSU-RSPG185 broth extract. They differed from each other in the substitutions at C-8 and C-4, as well as in the C-4 configuration. The configuration of their double bonds was determined to be E, based on signal enhancement in the NOEDIFF experiment, and the 4S and 10′R in 5 and 4R and 10′R in 6 was assigned by the CD spectrum. Only compound 5 exhibited weak cytotoxic activity toward Vero cells and KB (IC\(_{50}\)s 34.2 and 48.4 μM, respectively) in the resazurin microplate assay, compared to ellipticine (IC\(_{50}\)s 4.5 and 4.1 μM, respectively), whereas 6 was inactive against the tested cell lines. Additionally, they showed no antimalarial or antimycobacterial potential toward *Plasmodium falciparum* and *Mycobacterium tuberculosis* when using GFP (green fluorescent protein) and the micro-culture radioisotope technique, respectively [33] (Figure 1).

Eleven metabolites of the herqueinone subclass, including six new derivatives, ent-penicicherqueinone (8), 12-hydroxynorherqueinone (11), ent-isoherqueinone (13), oxopropylisoverqueinones A (15) and B (16), and 4-hydroxysclerodon (27) and the known analogs, 9, 12, 17, 22, and 34 were extracted from a marine-derived *Penicillium* sp. (Figure 2). The new metabolites' configuration was assigned, based on specific rotations and chemical modifications. Compound 17 exhibited moderate anti-inflammatory activity (IC\(_{50}\) 3.2 μM) towards mouse macrophage RAW 264.7 cells, compared to AMT (IC\(_{50}\) 0.2 μM) in the nitric oxide synthase assay. In addition, 27 exhibited moderate anti-angiogenic potential (IC\(_{50}\) 20.9 μM) toward HUVECs (human umbilical vascular endothelial cells), compared to sunitinib (IC\(_{50}\) 1.5 μM), in the tube formation assay. Furthermore, 8 and 12 moderately induced adipogenesis (IC\(_{50}\) 57.5 and 39.7 μM, respectively) in the hBM-MSCs (human bone marrow-mesenchymal stem cells), compared to pioglitazone (IC\(_{50}\) 0.69 μM), in the adiponectin production assay [35].
Lee et al. purified 18 from a culture of *Penicillium herquei* FT729, derived from Hawaiian volcanic soil by LC-MS-guided chemical analysis. It was identified by spectroscopic analysis, optical rotation, and LC-MS analysis. The pretreatment of T cells with 18 remarkably reduced IL-2 production and the expression of surface molecules, including CD-25 and -69, and activated T cell proliferation after TCR-mediated stimulation, as well as abrogating the NF-κB and MAPK pathways. Therefore, it effectively down-regulated T cell activity via the MAPK pathway, which indicated its immunosuppressive potential [38]. Furthermore, *P. herquei* PSURSPG93, obtained from soil, produced a new derivative, peniciherqueinone (7), along with the formerly separated derivatives: herqueinone (9), deoxyherqueinone (14), the acetone adduct of atrovenetinone (18) (as a mixture of epimers), sclerodin (20), and (−)-7,8-dihydro-3,6-dihydroxy-1,7,7,8-tetramethyl-5H-furo[2′,3′;5,6]naphtho[1,8-bc]furan-5-one (37). Compound 7 was structurally similar to 9, except for the disappearance of one olefinic proton signal. Its R-configuration at C-4 was determined by an anisotropic effect and CD spectroscopy, which was opposite to 9. Compounds 9, 14, and 20 had no cytotoxic effect toward MCF-7, KB, and noncancerous Vero cell lines. In addition, only 9 exhibited mild antioxidant potential, where it inhibited OH•, DPPH•, and O2•− (IC50 0.48, 6.34, and 4.11 mM, respectively) in the hydroxyl radical, DPPH, and superoxide radical scavenging assays, respectively, in comparison with tannic acid (OH•, IC50 0.26), butylated hydroxytoluene (DPPH•, IC50 0.11), and trolox (O2•−, IC50 0.96 mM) [34].

Intaraudom et al. purified the new derivatives, 25, 26, 30, 32, 36, and 39–42, together with 22 and 34, from the broth EtOAc extract of the marine-derived *Lophiostoma bipolare*
BCC25910 (Figure 3). Their structures were assigned via spectroscopic analysis, whereas the C-2′, S-configuration was determined based on X-ray analysis, a chemical reaction, and a specific optical rotation negative sign. They showed no antimalarial activity toward the *P. falciparum* K-1 strain and no antifungal activity toward *C. albicans*. On the other hand, 25, 26, 36, 39, and 40 showed moderate antibacterial potential toward *B. cereus* (MICs 12.5 µg/mL). However, other compounds were inactive against *B. cereus* (concentration 25 µg/mL). Additionally, they exhibited weak cytotoxicity toward KB, MCF-7, NCI-H187, and Vero cells [42].

**Figure 3.** The structures of compounds 23–37.

Macabeo et al. purified 29, 34, and 90 from a culture of *Pseudolophiostoma* sp. MFLUCC-17-2081 obtained from a dried branch of *Clematis fulvicoma*. Compounds 29 and 34 conferred more potent α-glucosidase inhibition (IC$_{50}$ 48.7 and 120 µM, respectively) than N-deoxynojirimycin (IC$_{50}$ 130.5 µM). They also potently inhibited the hydrolysis of p-nitrophenylbutyrate, using porcine lipase. Interestingly, 29 and 34 showed stronger inhibitory potential (IC$_{50}$s 1.0 and 3.4 µM, respectively) than orlistat (IC$_{50}$ 9.4 µM). The in silico techniques employed revealed that 29 and 34 exhibited strong binding affinities to porcine pancreatic lipase and α-glucosidase through π–π and H-bonding interactions, while 90 was weakly active (IC$_{50}$ > 100 µM) toward both enzymes [45].
Zhang et al. purified new derivatives, flaviphenalenones A–C (45–47), from solid cultures of *Aspergillus flavipes* PJ03-11 (Figure 4). The 6S absolute configuration of 45 was determined by the computational ECD method. Compound 47 was a positional isomer of 46. They represented the first report of phenalenones with a directly connected C-10 isoprene unit, whereas 47 had a keto-lactone group at C-8. Compounds 46 and 47 possessed potent α-glucosidase inhibitory potential (IC₅₀ 94.95 and 78.96 μM, respectively) than acarbose (IC₅₀ 685.36 μM). On the other hand, 45 displayed significant cytotoxic capacities toward MCF-7 and A549 (IC₅₀ 10.0 and 6.6 μg/mL, respectively) compared to doxorubicin (IC₅₀ 0.4 and 0.2 μg/mL, respectively), while 47 showed moderate cytotoxicity toward A549 (IC₅₀ 28.5 μg/mL) [31].

![Figure 4. The structures of compounds 38–47.](image)

Auxarthones A–E (49–53) and FR-901235 (54) were obtained from the culture of the coprophilous fungus *Auxarthron pseudauxarthron* TTI-0363 (Figure 5). Compounds 52 and 53 possessed an unusual 7a,8-dihydrocyclopenta[α]phenalen-7,9-dione ring system. Compound 49 was separated into a mixture of racemic diastereomers; their structures were confirmed by X-ray crystallography. Compounds 49 and 51 showed moderate antifungal potential toward *C. albicans* and *C. neoformans* (MICs 6.4 and 3.2 μg/mL, respectively), compared to amphotericin B (MIC 0.8 μg/mL). The other phenalenones were weakly active (MIC ranging from 6.4 to 51.2 μg/mL). On the other hand, they showed no significant cytotoxic effects against MDA-MB-451 and MDA-MB-231 [48].
were weakly active (MIC ranging from 6.4 to 51.2 µg/mL). On the other hand, they showed no significant cytotoxic effects against MDA-MB-451 and MDA-MB-231 [48].

Figure 5. The structures of compounds 48–57.

Compound 56 obtained from the marine-derived endophytic fungus, Coniothyrium cereale, harboring the Baltic Sea algae Enteromorpha sp., which had unprecedented imine functionality between two carbonyls to produce an oxepane-imine-dione ring. It exhibited a moderate cytotoxic potential toward the SKM1, U266, and K562 cancer cell lines (IC50s 75.0, 45.0, and 8.5 µM, respectively) in the MTT assay [37]. The new phenalenone derivatives, aspergillussanones C–L (60–69), along with the known analog 70, were isolated from the solid culture of Aspergillus sp. that was associated with Pinellia ternate (Figures 6 and 7).

Compounds 60–69 are unusual acyclic diterpenoid adducts that are partly epoxidized to produce diverse heterocyclic analogs. Their structures and absolute configurations were established by spectroscopic, ECD, and Mo2(OCOCH3)4-induced ECD analyses. Their antibacterial effectiveness toward Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, and Bacillus subtilis was evaluated using the broth micro-dilution method. Compound 69 exhibited the most potent antibacterial potential against B. subtilis, S. aureus, and P. aeruginosa (MIC 4.80, 2.77, and 1.87 µg/mL, respectively), compared to streptomycin (MIC 0.34 µg/mL for P. aeruginosa) and penicillin (MIC 0.063 and 0.13 µg/mL for S. aureus and B. subtilis, respectively). Compounds 65–67 had potential...
versus *P. aeruginosa* (MICs 6.55–12.00 µg/mL). Meanwhile, 62, 63, 65, and 67 showed significant activity toward *E. coli* (MIC 3.93–7.83 µg/mL) [50].

![Structures of compounds 58-65](image)

**Figure 6.** The structures of compounds 58–65.

![Structures of compounds 66-71](image)

**Figure 7.** The structures of compounds 66–71.
Aspergillus sp. CPCC 400735, which is associated with Kadsura longipedunculata, was found to biosynthesize the structurally unusual phenalenones, asperphenalenones A–E (71–75), these having a linear diterpene moiety that is connected to the phenalenone skeleton through a C-C bond (Figure 8). Their structures were established from extensive NMR spectroscopic analyses, while the absolute configuration was determined based on the CD spectra. Compounds 71 and 74 exhibited anti-HIV activity (IC₅₀ 4.5 and 2.4 μM, respectively), in comparison to lamivudine (IC₅₀ 0.1 μM) and efavirenz (IC₅₀ 0.0004 μM), using SupT1 cells in the luciferase assay system, while 72 and 75 exhibited weak activity (IC₅₀ 32.6 and 22.1 μM, respectively) [51].

![Figure 8. The structures of compounds 72–78.](image)

The new derivatives, peniciphenalenins A–F (76–81), along with the formerly reported 21, 28, and 33, were obtained from Penicillium sp. ZZ901 culture, using ODS and HPLC (Figure 9). Their structures were determined by extensive spectroscopic analysis, ECD calculation, optical rotation, and single X-ray diffraction. The analyses identified a phenalenone skeleton, fused to a trimethyl-furan ring. Compounds 28 and 33 showed antimicrobial activity toward MRSA and E. coli (MICs 23–35 μg/mL for 28 and 7.0–9.0 μg/mL for 33). On the other hand, 21, 28, and 33 showed weak antiproliferative activity against the glioma cells (IC₅₀ 23.24–6.93 μM), compared to doxorubicin (IC₅₀ 1.2 and 0.47 μM, respectively) [39].
Figure 9. The structures of compounds 73–86.

Han et al. separated three new red-colored phenalenone derivatives, peniciphenalenins G–I (83, 31, and 84), along with coniosclerodione (85) and (−) sclerodinol (24) from the marine sediment-derived fungus, Pleosporales sp. HDN1811400, using UV-HPLC guided investigation. Their absolute configurations were determined by detailed spectroscopic and ECD analyses, in addition to the chemical method. Compound 83 was the first example of a chlorinated phenalenone derivative. Compounds 24, 31, 83, and 85 showed antimicrobial potential versus B. cereus, Proteus sp., M. phlei, B. subtilis, V. parahemolyticus, E. tarda, MRCNS, and MRSA (MICs 6.25–50.0 µM). Compound 85 (MIC 6.25 µM) was more active than compound 84, indicating that 19-OH reduced the activity. Notably, compounds 24, 31, 83, and 85 showed better inhibitory potential toward MRCNS and MRSA than that of ciprofloxacin, indicating their potential regarding drug-resistant strains [44].

Basnet et al. reported the isolation of a new yellow compound, trypethelonamide A (86), and a new dark violet-red compound, 5′-hydroxytrypethelone (87), along with a dark violet-red metabolites (+)-8-hydroxy-7-methoxytrypethelone (88), (+)-trypethelone (89), and (−)-trypethelone (90) from the cultured lichenized fungus Trypethelium eluteriae by using Sephadex LH-20, ODS, SiO₂, and HPLC. They were fully characterized via spectroscopic and ECD spectral analyses (Figure 10). They showed moderate to weak cytotoxicity versus the RKO cell line (IC₅₀ ranged from 22.6 to 113.5 µM), compared to taxol (IC₅₀ 0.05 µM) in the CCK8 assay, while they had no antioxidant potential in the DPPH assay (concentration 200 µM) [52].
Figure 10. The structures of compounds 87–102.

Two new metabolites, 8-methoxytrypethelone (93) and 5′-hydroxy-8-ethoxytrypethelone (95), along with compounds 20, 89, 91, 92, and 94 were separated from mycobiont culture of *Trypethelium eluteriae* by preparative TLC and column chromatography. They were fully characterized by using spectroscopic, ECD, and X-ray analyses. Compound 89 (MIC 12.5 µg/mL) showed potent antimycobacterial potential toward *M. tuberculosis*, followed by 89 and 94 (MIC 50.0 µg/mL). Moreover, 89 had moderate potential (MIC 25.0 µg/mL) toward *M. chitae*, *M. szulgai*, *M. phlei*, *M. flavescens*, *M. parafortuitum*, and *M. kansasii*. In addition, compounds 89 and 94 were active versus *S. aureus* (MIC 25 µg/mL) [41]. Funaenone (101) was also purified as a PTP inhibitor from a marine-derived fungal strain of *Aspergillus* sp. SF-5929 and was tested for its inhibitory potential on *hPTP1B1*-1401 in a photocolorimetric assay using the *hPTP1B1* enzyme. It exhibited powerful PTP1B inhibitory potential (*IC_{50} 6.1 \mu M*), compared to ursolic acid (*IC_{50} 4.3 \mu M*). It was found that 101 was a noncompetitive PTP1B inhibitor that targeted the active or allosteric site of the enzyme [53]. *Chaetosphaerena hispidulum* yielded two new phenalenones, hispidulones A (102) and B (103), which were assigned by spectroscopic and ECD analyses (Figure 11).
Compound 102 had a cyclohexa-2,5-dien-1-one moiety, whereas 103 possessed a hemiacetal OCH$_3$ group that was uncommon in phenalenone analogs. Compound 103 showed cytotoxic potential toward A-549, Hub7, and HeLa cells (IC$_{50}$ 2.71, 22.93, and 23.94 µM, respectively), compared with cis-platinum (IC$_{50}$ 8.73, 5.89, and 14.68 µM, respectively), whereas 102 did not show any effect in the MTT assay [54].

Aceneoherqueinones A (104) and B (105), (+)-aceatrovenetinone A (106), and (+)-aceatrovenetinone B (109), along with the known congeners, (+)-scleroderolide (33), (−)-scleroderolide (34), (−)-aceatrovenetinone B (107), and (−)-aceatrovenetinone A (108), were reported from the marine mangrove-derived fungus, *Penicillium herquei* MA-370. Among these, compounds 104 and 105 were rare phenalenones, having a cyclic ether unit between C-2′ and C-5 (Figure 11). Compounds 106–109 were unstable stereoisomers, possessing configurationally labile chiral centers that were characterized by HPLC-ECD analyses,
assisted by TDDFT-ECD calculations. The absolute configuration of \textit{104} was confirmed by X-ray, while those of \textit{105–109} were established by ECD spectra TDDFT-ECD calculations. Compounds \textit{104} and \textit{105} displayed ACE (angiotensin-I-converting enzyme) inhibitory activity (IC$_{50}$ 3.10 and 11.28 $\mu$M, respectively), compared to captopril (IC$_{50}$ 9.23 nM). The molecular docking study revealed that compound \textit{104} bound well with ACE via hydrogen interactions with the residues Gln618, Ala261, Asn624, and Trp621, while \textit{105} interacted with the Tyr360 and Asp358 residues. This difference in interactions was likely caused by the C-8 epimerization of both compounds [46].

\textit{Penicillium herquei} FT729, which is associated with Hawaiian volcanic soil, yielded herqueilenone A (\textit{116}) and erabulenols B (\textit{117}) and C (\textit{118}) (Figure 12). Their structures were determined by spectroscopic analysis, ECD calculations, and GIAO (gauge-including atomic orbital) NMR chemical shifts. Compounds \textit{117} and \textit{118} exhibited significant IDO1 (indoleamine 2,3-dioxygenase 1) inhibitory activities (with IC$_{50}$ values of 13.69 and 14.38 $\mu$M, respectively), compared to epacadostat (IC$_{50}$ 0.015 $\mu$M). Therefore, they can be developed into cancer immunotherapeutics. Compounds \textit{117} and \textit{118} also exhibited a protective effect toward acetaldehyde-induced damage in PC-12 cells and significantly increased cell viability [55].

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structures.png}
\caption{Structures of compounds 116–123.}
\end{figure}

Duclauxamide A1 (\textit{119}), a new polyketide heptacyclic-oligophenalenone dimer with an N-2-hydroxymethyl moiety, was isolated from \textit{Penicillium manginii} YIM PH30375, which is associated with \textit{Panax notoginseng}. It belongs to the 9'S-duclauxin epimers, based on spectroscopic data analysis, single-crystal X-ray diffraction, and the computational $^{13}$C NMR-DFT method. It is structurally related to duclauxin (\textit{120}), showing the replacement of the O-atom with the N-containing chain, without modification, on the original carbon skeleton. It showed moderate cytotoxicity toward MCF-7, SMML-7721, A-549, HL-60, and SW480 (IC$_{50}$ ranged from 11 to 32 $\mu$M), compared to cisplatin and paclitaxel [56]. Two new oxaphenalenone dimers, talaromycoses A (\textit{121}) and B (\textit{122}), were isolated from the marine fungus \textit{Talaromyces} sp. LF458 culture broth and mycelia. Their relative configu-
ration was determined by NOESY spectral data. Compound 116 was the first metabolite with a 1-nor oxaphenalenone dimer framework. They exhibited significant antibacterial potential toward S. epidermidis and S. aureus (IC50 3.70 and 5.48 µM, respectively, for 121, and 17.36 and 19.50, respectively, for 122), compared to chloramphenicol (IC50 1.81 and 2.46 µM, respectively) in the resazurin microplate assay. They revealed no antifungal effectiveness toward Trichophyton rubrum and C. albicans. Moreover, 121 exhibited AchE (acetylcholinesterase) inhibition (IC50 7.49 µM) that was more powerful than huperzine (IC50, 11.60 µM) in the modified Ellman’s enzyme/immunosorbent assay [59].

In the case of 9a-epi-bacillisporin E (124) and bacillisporins F–H (125, 127, and 128), new oligophenalenone dimers, along with bacillisporin A (123), were separated from a culture of Talaromyces stipitatus (Figure 13). Their absolute configurations and structures were determined based on spectroscopic analyses, ECD, and GIAO NMR shift calculation, followed by DP4 probability analysis. Only 128 was moderately active (IC50 49.5 µM) toward the HeLa cell, compared to cisplatin (IC50 10.6 µM). No effect was observed on the growth of E. coli (IC50 > 100 µg/mL) for all isolated compounds, while 123 displayed noticeable antibacterial potential versus Staphylococcus hemolyticus, S. aureus (ATCC 6538), and Enterococcus faecalis (MICs 9.5, 5.2, and 2.4 µg/mL, respectively), compared to tetracycline (MICs 29.2, 0.05, and 0.4 µg/mL, respectively). However, 128 had an observable effect on S. aureus (MIC 5.0 µg/mL) when using a microtiter plate assay [60].

Figure 13. The structures of compounds 124–132.

Talaromyces verruculosus yielded two new oligophenalenone dimers, verruculosins A (129) and B (130), and the related known analogs, duclauxin (120), bacillisporin F (125), and xenoclauxin (131) (Figure 13). Compound 129 was a novel oligophenalenone dimer with a unique octacyclic skeleton. Compounds 129 and 130 were fully characterized by spectroscopic, X-ray crystallography, and ECD analyses as well as, optical rotation and NMR calculations. Compounds 120, 125, 129, and 131 exhibited potent CDC25B inhibitory activities (IC50 values of 0.75, 0.40, 0.38, and 0.26 µM, respectively), compared to Na3VO4 (IC50 0.52 µM). In addition, 120 and 129–131 displayed moderate EGFR/ERK inhibitory activities (IC50 values from 0.24 to 1.22 µM) in comparison to afatinib (IC50 0.0005 µM). The results revealed that oligophenalenone dimers could be used as CDC25B inhibitor candidates [57].
Duclauxin (120), talaromycesone B (122), bacillispior G (127), and xenoclauxin (131) were isolated from anthill soil fungus Talaromyces sp. IQ-313. They were evaluated for PTP (protein tyrosine phosphatases) inhibitory potential. They inhibited hPTP1B1,400 (IC50 values ranging from 12.7 to 82.1 µM), in comparison to ursolic acid (IC50 26.6 µM). Compounds 120 and 127 displayed the strongest inhibitory activity (IC50 12.7 and 13.5 µM, respectively) [58]. Five new polar pigments, talauxins E (132), I (133), L (134), Q (135), and V (136), along with the previously reported 9-demethyl FR-901235 (55), O-desmethylfunalenone (100), and duclauxin (120), were purified from Talaromyces stipitatus (Figure 14). Talauxins are unusual heterodimers that are produced from the coupling of 120 with amino acids and are closely related to duclauxamidine A (119), which was separated from Penicillium manginii [56]. They were fully characterized via spectroscopic and X-ray analysis. Compounds 120 and 132 exhibited weak cytotoxic effectiveness (IC50 140 and 70 µM, respectively) versus NS-1 cells, compared to 5-fluorouracil (IC50 4.6 µM) in the resazurin microplate assay, while 132 also had weak antibacterial potential versus B. subtilis (IC50 265 µM), compared to clotrimazole (IC50 0.4 µM) [49].

Figure 14. The structures of compounds 133–139.

4. Human Glucose Transporter 1 (hGLUT1) Inhibitory Activity

4.1. Artificial Intelligence (AI)-Based Target Prediction for Phenalenone Derivatives

The human glucose transporter 1 (hGLUT1) is one of 14 members of the GLUT family of integral proteins that are responsible for the facilitative transport of monosaccharides and polyols across the membrane bilayer of eukaryotic cells [68,69]. Structurally, GLUT1 consists of 12 α-helices that are folded into the C-terminal domain and the N-terminal domain, both of which consist of six transmembrane helices [70,71]. Due to its essential role in transporting glucose from the ECM (extracellular matrix) into the cells [72,73] and maintaining the viability of the cells [74], GLUT1 is ubiquitously expressed [74,75]. In many cancer types, the demand for glucose as a source of energy is increased, leading to the increased expression of glucose transporters, including GLUT1 [75,76]. Additionally, the upregulation of GLUT1 expression was found to be mediated by the stimulation of oncopgenes [71], while inhibiting GLUT1 activity reduced cell proliferation and apoptosis [71,77,78]. These
findings suggest that GLUT1 might be a potential target for cancer therapy [75]. Natural metabolites belonging to diverse classes have been found to possess hGLUT1 inhibition potential, such as resveratrol, phloretin, naringenin, WZB117, cytochalasin B, STF-31, pyrazolopyrimidines, (1H-pyrazol-4-yl)quinoline, and phenylalanine amides [71].

Ligand-based in silico target prediction was performed to choose a suitable target by which to investigate the potential inhibitory activity of the phenalenone derivatives [79,80]. Performing an anatomical-therapeutic chemical (ATC) code and predicting the potential targets for the investigated compounds were carried out using the SuperPred prediction web server [81,82]. From the prediction results, GLUT1 (PDB: 5EQG) was chosen as a target for the study as it had a high percentage of model accuracy and a very good probability (Table 3). After selecting the target, the docking method was validated by redocking the co-crystalized inhibitor back into the protein crystal structure, then the docking of the listed phenalenones followed. In silico ADMET properties prediction for the listed compounds, along with molecular dynamic (MD) simulation for the two top-scoring derivatives after docking, were performed as well.

Table 3. The prediction of target probability and model accuracy for phenalenone derivatives against GLUT1, using the SuperPred target prediction web server.

| Compound # | Probability * | Model Accuracy ** |
|------------|---------------|-------------------|
| 7          | 63.54%        | 98.75%            |
| 118        | 78.92%        | 98.75%            |
| 71         | 64.66%        | 98.75%            |
| 69         | 68%           | 99%               |
| 70         | 66%           | 99%               |
| 72         | 67.3%         | 99%               |
| 75         | 66%           | 99%               |
| 73         | 67.3%         | 99%               |
| 68         | 78%           | 99%               |
| 5          | 68%           | 99%               |
| 67         | 71.95%        | 98.75%            |
| 6          | 75%           | 99%               |
| 66         | NA            | NA                |
| 62         | 53%           | 99%               |
| 61         | 53%           | 99%               |
| 63         | 72%           | 99%               |
| 64         | 76%           | 99%               |
| 60         | 52.61%        | 98.75%            |
| 74         | 66%           | 99%               |
| 65         | 74%           | 99%               |

* The probability of the test compound binding to a specific target, as determined by the respective target machine learning model. ** The 10-fold cross-validation score of the respective logistic regression model is presented, as the model performance varies between different targets.

4.2. In Silico ADMET Properties of Selected Ligands

All 20 phenalenones were prepared for the study by utilizing Schrodinger’s Lig-Prep tool [83]. The 3D (three dimensional) structures of the compounds were generated using the OPLS3 force field setting, with an ionization state at pH 7.0 ± 0.2. After that, ADMET prediction was performed using the QikProp module on Schrodinger’s suite [84]. Table 4 presented the ADMET properties that estimated the phenalenones’ usefulness in terms of
their biological functions, drug-likeness, physiochemical properties, and expected toxicity. The ADMET descriptors that are predicted for the derivatives are molecular weight, drug-likeness, dipole moment, total solvent accessible surface area, number of hydrogen bond donors and acceptors, predicted octanol-water partitioning, predicted aqueous solubility, estimated binding to human serum albumin, number of possible metabolites, predicted blood-brain partitioning, percentage of human oral absorption, predicted IC_{50} for inhibiting HERG-K^+ channels, central nervous system activity, and the reactive functional group number. Most of the predicted values of ADMET descriptors fell within the recommended range.

4.3. Ligands and Protein Preparation

The compounds were prepared by converting their structures from 2D to 3D using LigPrep, and their ionization states and tautomeric forms were generated. After energy-minimizing, the 3D structures of the compounds were ready for docking into the crystal structure of GLUT1 (PDB ID: 5EQG). The protein was prepared for docking using the protein preparation wizard, where its crystal structure was minimized and its H-bond network was optimized. In addition, the proper force field was specified, and the protein’s formal charge was calculated after generating the amino acids’ correct ionization states and the missing hydrogen addition.

4.4. Grid Box Generation and Molecular Docking

Molecular docking was performed to evaluate the binding modes of the selected compounds inside a protein binding pocket. To do that, a grid box was generated around the protein binding pocket to determine the exact site for the docking in the minimized protein crystal structure, using Maestro’s Receptor-Grid-Generation tool [85]. The docking method was evaluated by re-docking the native inhibitors (PDB ID: 5RE) back into the crystal structure in which it was co-crystallized. The binding interactions of the re-docked inhibitor are shown in Figure 15. H-bonding was observed between the CO and the NH of the 4-fluorophenylalanine moiety, an adjacent water molecule, and with Glu380, respectively. The second carbonyl group seemed to have H-bonded with Gln161, as well as three nearby water molecules; the phenolic OH acted as both HBD and HBA with water molecules as well.
Table 4. Predicted in silico ADME properties of the phenalenone derivatives.

| Title | Mol_MW | # Stars | Dipole | SASA | HBD | HBA | QPlogPo/w | QPlogS | QPlogKhsa | # Metab | QPlogBB | %Human Oral Absorption | QPlogHERG | CNS | # RtvFG |
|-------|--------|---------|--------|------|-----|-----|-----------|-------|-----------|--------|--------|------------------------|-----------|-----|--------|
|       | (130–725) | (0.0–5.0) | (1–12.50) | (300–1000) | (0–6) | (2.0–20.0) | (−2–6.5) | (−6.5–0.5) | (−1.5–1.5) | (1–8) | (−3–1.2) | (<25% poor; >80% high) | concern below −5 | (−2 inactive) | (+2 active) | (0–2) |
| 7     | 388.373 | 0       | 3.013  | 566.818 | 2   | 6.5 | 1.851     | −3.559 | 0.097     | 6      | −1.437 | 74.987 | −3.478 | −2 | 0 |
| 118   | 550.561 | 1       | 7.485  | 794.384 | 2   | 8.25 | 3.782     | −6.151 | 0.715     | 9      | −2.297 | 69.345 | −5.022 | −2 | 0 |
| 71    | 576.278 | 3       | 8.802  | 910.147 | 3   | 6.7 | 6.314     | −7.258 | 1.316     | 18     | −2.368 | 79.595 | −5.491 | −2 | 0 |
| 69    | 594.744 | 2       | 9.484  | 789.214 | 4   | 7.45 | 5.322     | −4.622 | 0.981     | 17     | −2.174 | 57.778 | −3.532 | −2 | 0 |
| 70    | 610.743 | 7       | 9.975  | 1043.134 | 5 | 9.15 | 5.066     | −7.89  | 0.907     | 17     | −4.262 | 41.015 | −6.435 | −2 | 0 |
| 72    | 624.727 | 8       | 8.459  | 1026.611 | 5 | 9.45 | 5.31     | −7.68  | 0.735     | 16     | −4.35  | 28.338 | −4.482 | −2 | 1 |
| 75    | 610.743 | 7       | 9.879  | 1030.596 | 5 | 9.15 | 4.911     | −7.677 | 0.918     | 17     | −4.46  | 49.169 | −6.255 | −2 | 0 |
| 73    | 624.727 | 8       | 8.459  | 1026.616 | 5 | 9.45 | 5.31     | −7.61  | 0.735     | 16     | −4.35  | 28.338 | −4.482 | −2 | 1 |
| 68    | 652.78 | 8       | 12.335 | 1096.494 | 4 | 9.45 | 6.114     | −8.908 | 1.288     | 17     | −4.061 | 50.421 | −6.561 | −2 | 1 |
| 5     | 540.652 | 3       | 14.173 | 889.502 | 3 | 7.45 | 5.255     | −6.976 | 0.997     | 13     | −2.485 | 70.591 | −5.556 | −2 | 0 |
| 67    | 666.807 | 8       | 12.335 | 1027.334 | 3 | 9.45 | 6.512     | −7.869 | 1.359     | 16     | −3.158 | 73.463 | −5.735 | −2 | 1 |
| 6     | 540.652 | 2       | 7.928  | 919.785 | 3 | 7.45 | 5.282     | −7.502 | 1.084     | 13     | −2.834 | 67.029 | −5.832 | −2 | 0 |
| 66    | 634.808 | 6       | 10.74  | 970.033 | 2 | 6.5 | 7.963     | −8.898 | 1.935     | 15     | −1.591 | 100   | −5.533 | −2 | 1 |
| 62    | 592.728 | 6       | 12.392 | 1005.377 | 3 | 7.45 | 6.358     | −9.167 | 1.54      | 17     | −2.88  | 73.816 | −6.238 | −2 | 0 |
| 61    | 592.728 | 6       | 11.434 | 1011.989 | 3 | 7.45 | 6.379     | −9.284 | 1.561     | 17     | −2.954 | 73.171 | −6.288 | −2 | 0 |
| 63    | 592.771 | 5       | 11.447 | 968.98  | 3 | 5.75 | 7.264     | −8.949 | 1.821     | 13     | −2.355 | 85.225 | −5.777 | −2 | 0 |
| 64    | 608.77 | 5       | 12.352 | 986.08  | 4 | 7.45 | 5.988     | −8.302 | 1.398     | 14     | −3.232 | 53.649 | −5.838 | −2 | 0 |
| 60    | 624.727 | 4       | 11.95  | 974.752 | 4 | 11.15 | 4.249     | −7.089 | 0.71      | 14     | −3.346 | 52.716 | −5.828 | −2 | 3 |
| 74    | 654.796 | 7       | 10.567 | 1030.237 | 3 | 10.85 | 5.564     | −7.91  | 1.034     | 14     | −3.042 | 68.666 | −6.017 | −2 | 1 |
| 65    | 606.711 | 5       | 9.825  | 992.894 | 3 | 8.75 | 5.513     | −8.33  | 1.235     | 15     | −3.349 | 62.369 | −6.083 | −2 | 1 |
The in silico docking results of phenalenone derivatives with GLUT1 (PDB: 5EQG).

After validating the docking method, the 3D structures of the minimized phenalenone derivatives were docked into GLUT1. The docking results are presented in Table 5, which shows that, except for derivative 118, all phenalenones scored higher than the native inhibitor (−11.206 kcal/mol). Derivatives 60 and 64 were on the top of the list, scoring −15.777 and −15.239 kcal/mol, respectively.

Table 5. The in silico docking results of phenalenone derivatives with GLUT1 (PDB: 5EQG).

| Title | Docking Score | XP GScore | Glide Emodel | XP GScore |
|-------|---------------|------------|--------------|------------|
| 60    | −15.082       | −15.777    | −112.586     | −14.777    |
| 64    | −14.829       | −15.239    | −101.024     | −14.239    |
| 66    | −13.511       | −15.227    | −88.992      | −14.227    |
| 71    | −13.348       | −15.063    | −96.987      | −14.063    |
| 68    | −14.276       | −14.973    | −130.242     | −13.973    |
| 61    | −14.073       | −14.77     | −93.445      | −13.77     |
| 70    | −14.248       | −14.658    | −98.707      | −13.658    |
| 65    | −12.689       | −14.404    | −96.631      | −13.404    |
| 69    | −12.733       | −14.277    | −85.473      | −13.277    |
| 75    | −13.343       | −14.04     | −108.477     | −13.04     |
| 74    | −12.284       | −14.002    | −99.09       | −13.002    |
Table 5. Cont.

| Title | Docking Score | XP GScore | Glide Emodel | XP GScore |
|-------|---------------|-----------|--------------|-----------|
| 63    | −13.061       | −13.757   | −104.496     | −12.757   |
| 72    | −11.996       | −13.711   | −78.259      | −12.711   |
| 67    | −12.07        | −13.571   | −105.73      | −12.571   |
| 5     | −12.01        | −13.511   | −94.603      | −12.511   |
| 6     | −13.162       | −13.466   | −88.095      | −12.466   |
| 73    | −11.712       | −13.361   | −96.264      | −12.361   |
| 62    | −12.586       | −13.283   | −98.251      | −12.283   |
| 7     | −11.849       | −12.42    | −78.277      | −11.42    |
| 5RE   | −11.206       | −11.207   | −88.062      | −10.207   |
| 118   | −9.901        | −11.187   | −84.952      | −10.187   |

Figure 16 shows the binding interactions of compound 60 after docking. While the Phe26 side chain forms pi-pi stacking with the fused ring system of 60, several H-bonds are formed between the OH and carbonyl groups of the ring system and the amino acids Gln161, Asn411, Asn415, and Tyr292, as well as forming water bridges with the adjacent water molecules. Additional water bridges are formed with the oxygen and OH groups of the substituted tetrahydropyran at the end of the aliphatic chain.

As for compound 64, the carbonyl oxygens and the OH groups of the 3-membered ring system formed several water bridges and H-bonds with the water molecules and His160 and Gln161 side chains. The aliphatic chain and the cyclopentyl moiety interacted with Asn415 and the adjacent water molecules through the OH groups (Figure 17).

![Figure 16. GLUT1-60 complex after docking. (A) 2D view of the binding interactions between 60 complexed with GLUT1 (PDB: 5EQG). (B) 3D view of the binding interactions between 60 complexed with GLUT1 (PDB: 5EQG). (C) The 3D view of GLUT1-60 complex with the mesh surface view.](image-url)
Molecules 2022, 27, 6797

Figure 17. GLUT1-64 complex after docking. (A) 2D view of the binding interactions between compound 64 when complexed with GLUT1 (PDB: 5EQG). (B) 3D view of the binding interactions between compound 64 with the amino acids residues of GLUT1 within 3Å radius around the ligand (PDB: 5EQG). (C) The 3D view of the GLUT1-64 complex with the mesh surface indicating the electrostatic potential around the ligand.

4.5. Molecular Dynamic Simulation (MD)

The MD simulation is a tool that is applied to mimic the physiological environment, to monitor any changes in the protein’s 3D conformation and the binding affinity that might take place during the simulation, and then compare them to the original conformation and affinity of the crystal structure [86]. For that reason, Desmond software [87,88] was used to perform the MD study and evaluate the stability and the binding affinity of the protein-compound complexes at pH 7.0 ± 0.2, over a 100-ns period. The MD was performed only for the two phenalenone derivatives that scored the highest in the docking study, namely, compounds 60 and 64, as well as the co-crystallized inhibitor, 5RE. The root mean square deviation (RMSD) of the complexes of compounds and GLUT1 measures the mean change of atoms (of protein and of ligand) at the end of the simulation and compares it to the atoms in their original conformation at 0 ns. The RMSD graph for the GLUT1-5RE complex showed that their plots could be laid over each other, indicating high stability of the complex throughout the simulation, and their RMSD values were within the accepted 1–3 Å range (Figure 18A). For the compound 60-GLUT1 complex, the protein was relatively stable throughout the duration of the experiment, with an RMSD value within the accepted 1–3 Å range. Compound 60 RMSD, however, was stable for about 58% of the time (~1.4–1.5 Å), then the confirmation of the ligand atoms changed drastically afterward, where it re-stabilized again between 5.9 and 7.1 Å by the end of the run. This indicated a change in the 3D conformation of the compound inside the pocket during the run, as the compound adjusted its pose to one with lower free energy. This was most likely due to the presence of many rotatable bonds in the aliphatic side chain (Figure 19A). The RMSD for the GLUT1-64 complex fell within the acceptable range as well (Figure 20A).

The secondary structure of the protein was scrutinized throughout the MD analysis to ensure that the percentage secondary structure element (%SSE) is intact over the simulation time. Figure 18B demonstrated the integrity of the SSE of the protein when complexed with
5RE. The top plot showed the distribution of the SSE (α-helices and β-sheets) throughout the protein, represented by the residue index. The middle plot checked the overall %SSE, while the bottom plot assessed each SSE over the course of the simulation. Both plots indicated that the overall %SSE of the protein was maintained, and each SSE was stable over the course of the simulation. A similar result was observed for the GLUT1-60 and GLUT1-64 complexes (Figures 19B and 20B, respectively).

The interaction between the test compounds and GLUT1 was also examined by the MD study. Figure 21A illustrates the stacked-bar graph displaying the types of interactions between the pocket residues and the bound ligand. The binding interactions are color-coded in the legend of the figure. The three most prominent observed interactions were as follows. Glu380 achieved H-bonding with the amide nitrogen, with a value of 0.75, while Phe291 formed pi-pi stacking with the 4-fluorophenyl moiety, with a value of 0.8. The carbonyl oxygen of the compound interacted by a water bridge and through H-bonding with Gln161 (normalized value of ~0.83). Additional interactions included that of Gln283, which interacted with the second carbonyl indirectly through a water bridge. Figure 21B shows the 2D view of the binding interactions, depicting interactions that were maintained for at least 30% of the simulation time. Figure 21C is the timeline representation of the stacked-bar graph that presented the interaction pattern of each of the pocket residues of GLUT1 with the 5RE during the 100 ns of simulation time. The orange color means that there was an interaction, while the darker colors indicate that the residue formed more than one interaction with the ligand.

The interactions between GLUT1 and 60 included H-bonding and a water bridge with Asn411, yielding a ~1.4 value. In addition, H-bonding and the water bridge contact points were formed with the residues Thr137, Gln161, and Tyr292, along with a hydrophobic interaction with Trp388 (Figure 22A). The 2D view of 60 complexed with GLUT1 showed relatively stable interactions between the compound and the residues Asn411, Trp388, Tyr292, Gln161, and Thr137 throughout the MD run (Figure 22B). From the timeline representation of the stacked bar plot presented in Figure 22C, the same interactions that are illustrated in the stacked bar plot were maintained over 100 ns. However, the interaction of Thr137 with the ligand began strongly and then started disappearing at ~70 ns until the end of the run. This might explain the change in the RMSD plot for 60 after ~58 ns (Figure 19A).

The amino acid residues involved in binding to derivative 64 included Trp388, Gln238, His160, Gln161, Pro141, and Thr137, with values of between 0.5 and 1.4. A water bridge was observed with Pro401 and Gly138 (Figure 23A). The interactions in the 2D view (Figure 23B) and timeline plot (Figure 23C) agreed with those in the stacked bar graph (Figure 23A).

4.6. Material and Methods
4.6.1. ADMET Properties Prediction
The Maestro QikProp Schrodinger module [84] was utilized for the prediction of ADMET properties and drug-likeness for the selected compounds. The properties included absorption, distribution, metabolism, excretion, toxicity, and others.

4.6.2. Preparation of Protein and Ligands PDB Structures
The crystal structure of the GLUT1 with the PDB ID: 5EQG was selected for the experiment because the co-crystallized ligand has a similar structure to the compounds that are to be tested. From the protein databank (PDB), the protein crystal structure 5EQG was downloaded as a PDB file [89] and was then optimized and prepared by the Protein-Preparation wizard of Schrodinger [83,90,91]. Protein preparation and optimization included identifying the bond order for the known HET groups and untemplated residues, adding hydrogen, breaking bonds to metals, adding zero-order bonds between metals and adjacent atoms, and correcting the formal charges to metals and the nearby atoms. Water molecules further than 5 Å from HET groups were removed from the structure of HET groups, and the disulfide bonds were re-generated. Ligands were prepared using the Lig-Prep tool [83], which involved the generation of metal HET states and cofactors at pH 7 ± 2.0. Additionally,
the optimization of hydrogen bonds at pH 7.0 using PROPKA [92], the removal of water molecules of >3 Å from HET groups, and applying restrained minimization using the OPLS4 force field were performed.

Figure 18. (A) RMSD graph for the native inhibitor 5RE, complexed with the GLUT1 protein (PDB ID: 5EQG). The simulation time (100 ns) confirmed the stability of the complex, with no significant changes in the protein structure. (B) Stability of the secondary structure GLUT1 protein (PDB ID: 5EQG) throughout the MD simulation when complexed with 5RE. Protein secondary structure elements (SSE) were monitored during the simulation. The upper plot presented the SSE distribution by residue index across the protein structure. The middle plot summarized the SSE composition for each trajectory frame throughout the simulation, and the plot at the bottom monitored each residue and its SSE assignment over the simulation time.
Figure 19. (A) RMSD graph for compound 60 when complexed with the GLUT1 protein (PDB ID: 5EQG). The simulation time (100 ns) confirmed the stability of the complex, with no significant changes in the protein structure. (B) Stability of the secondary structure GLUT1 protein (PDB ID: 5EQG) throughout the MD simulation when complexed with 60. The protein secondary structure elements (SSE) were monitored during the simulation. The upper plot presents the SSE distribution according to residue index across the protein structure. The middle plot summarizes the SSE composition for each trajectory frame throughout the simulation, and the plot at the bottom monitors each residue and its SSE assignment over the simulation time.
Figure 20. (A) RMSD graph for compound 64 when complexed with the GLUT1 protein (PDB ID: 5EQG). The simulation time (100 ns) confirmed the stability of the complex, with no significant changes in the protein structure. (B) Stability of the secondary structure of the GLUT1 protein (PDB ID: 5EQG) throughout the MD simulation when complexed with 64. The protein secondary structure elements (SSE) were monitored during the simulation. The upper plot presents SSE distribution by residue index across the protein structure. The middle plot summarizes the SSE composition for each trajectory frame throughout the simulation, and the plot at the bottom monitors each residue and its SSE assignment over the simulation time.
Figure 21. (A) The interaction of GLUT1 (PDB: 5EQG) with the native inhibitor 5RE throughout the simulation. The interactions between the ligand and protein were classified into hydrophobic, hydrogen bond, ionic, and water bridge interactions. The stacked bar charts were normalized over the course of the trajectory: for example, a value of 0.65 suggested that the interaction with the specific amino acid residue was maintained during 65% of the simulation time. Values over 1.0 imply that some protein residue made multiple interactions of the same subtype with the ligand. (B) A schematic diagram showed the detailed 2D atomic interactions of 5RE with GLUT1, occurring for > 30% of the simulation time in the selected trajectory (0 through 100 ns). Interactions with > 100% occurrence meant that those residues may have multiple interactions of a single type with the same ligand atom. (C) A timeline representation of the GLUT1-5RE interactions shown in (A). The panel at the top illustrates the total number of specific interactions that the protein has made with the compound over the course of the trajectory. The panel below illustrates which residues interacted with the ligand in each trajectory frame. The dark or orange color indicated that more than one specific interaction was seen between certain residues and the ligand. # Number of contacts.

4.6.3. Grid Generation and Docking

Glide’s Receptor-Grid-Generation tool [85] was used to generate a grid box around the co-crystalized inhibitor 5RE in the binding site of the protein PDB: 5EQG. The docking of the phenalenones was performed inside this box. The non-polar atoms were set for a van der Waals (VdW) radii scaling factor of 1.0 and the cut-off of partial charge was 0.25. Schrodinger’s Ligand Docking tool was used to perform the docking procedure [85,93]. The docking protocol was set as standard precision (SP), while the ligand sampling method was flexible. The default settings were used for other parameters.
Figure 22. (A) The interaction of GLUT1 (PDB: 5EQG) with the native inhibitor 60 throughout the simulation. The interactions between the ligand and protein were classified into hydrophobic, hydrogen bond, ionic, and water bridge interactions. The stacked bar charts were normalized over the course of the trajectory: for example, a value of 0.65 suggested that the interaction with the specific amino acid residue was maintained during 65% of the simulation time. Values over 1.0 implied that some protein residues made multiple interactions of the same subtype with the ligand. (B) A schematic diagram showing the detailed 2D atomic interactions of 60 with GLUT1, occurring for >30% of the simulation time in the selected trajectory (0 through 100 ns). Interactions with >100% occurrence meant that residues may have multiple interactions of a single type with the same ligand atom. (C) A timeline representation of the GLUT1-60 interactions shown in (A). The panel on top illustrates the total number of specific interactions that the protein has made with the compound over the course of the trajectory. The panel below illustrates which residues interacted with the ligand in each trajectory frame. The dark or orange color indicates that more than one specific interaction was made between some residues and the ligand.

4.6.4. MD Simulation

MD simulation experiments were performed using the Schrodinger suite [87,88]. The selected protein-compound complexes were obtained from the docking results and were tuned through the “System-Builder” tool. TIP3P was selected as the solvent mode, and the chosen box shape was the orthorhombic shape. Na ions were added to neutralize the system, and the box dimensions were 10 Å. The duration of the MD simulations was 100 ns per trajectory, and the number of atoms, temperature, and pressure were kept constant (NPT ensemble). Conversely, the temperature was set at 300.0 K, the pressure was set at 1.01325 bar, and the force field was OPLS4.
Figure 23. (A) The interaction of GLUT1 (PDB: 5EQG) with the native inhibitor 64 throughout the simulation. The interactions between the ligand and protein were classified into hydrophobic, hydrogen bond, ionic, and water bridge interactions. The stacked bar charts were normalized over the course of the trajectory: for example, a value of 0.65 suggested that the interaction with the specific amino acid residue was maintained during 65% of the simulation time. Values over 1.0 implied that some protein residues made multiple interactions of the same subtype with the ligand. (B) Schematic diagram showing the detailed 2D atomic interactions of 64 with GLUT1, occurring > 30% of the simulation time in the selected trajectory (0 through 100 ns). Interactions with >100% occurrence meant that residues may have multiple interactions of a single type with the same ligand atom. (C) A timeline representation of the GLUT1-64 interactions shown in (A). The panel on top illustrated the total number of specific interactions the protein made with the compound over the course of the trajectory. The panel below illustrates which residues interacted with the ligand in each trajectory frame. The dark or orange color indicates that more than one specific interaction was made between some residues and the ligand.

5. Conclusions

Fungi-derived metabolites possess substantial medicinal values and a large structural diversity that can provide an untapped potential for drug candidates and medications. This review summarized 139 fungal phenalenone derivatives and their biosynthesis and biological activities, reported from 2014 until August 2021. Most of them are mainly identified from *Penicillium* (37 compounds), *Coniothyrium* (23 compounds), *Aspergillus* (22 compounds), and *Talaromyces* (22 compounds) (Figure 24).

Fungal phenalenones were derived from polyketide precursors that underwent different cyclization and tailoring reactions, leading to extreme structural diversity and high complexity. Hence, searching for diverse biosynthetic pathways for the various phenalenone derivatives will be a future challenge and offer an interesting research field for natural product researchers. These metabolites have been isolated and purified using various chromatographic tools, such as SiO₂, Sephadex LH-20, preparative TLC, ODS, and HPLC, as well as preparative HSCCC-guided HPLC-HRESIMS, LC-MS-guided, and UV-HPLC guided analyses. Most of the separated phenalenones possess unique and unprecedented functionality or ring systems. Their configuration was assigned using various tools and experiments, such as X-rays, CD, ECD calculation, specific rotations, and chemical modifications, as well as the NOESY, NOEDIFF, and GIAO NMR shift calculations. They were evaluated for various activities, such as cytotoxic, antimalarial, antimycobacterial, anti-inflammatory, anti-angiogenic, immunosuppressive, and antioxidant properties, as
Therefore, it is likely to be a potential target for treating cancer. Based on the in silico studies, such as molecular docking, ADMET characteristics predication, and MD, some phenalenones were found to possess remarkable capacity as GLUT1 inhibitors; therefore, they could be potential leads for cancer treatment. It is noteworthy that the described studies, such as molecular docking, ADMET characteristics predication, and MD, some phenalenones were found to possess weak or no bioactivity, which represents a common problem for the study of the natural product. This could be due to the insufficient numbers of the newly separated phenalenones possessed weak or no bioactivity, which represents a common problem for the study of the natural product. This could be due to the insufficient amounts of the new compounds and the lack of effective bioactivity screening methods. Cancer is one of the most significant worldwide health concerns and there is a continuous need for developing new targets for treating this disease. GLUT1 substantially increases the uptake of glucose into the cytoplasm and is over-expressed in various tumor cells. Therefore, it is likely to be a potential target for treating cancer. Based on the in silico studies, such as molecular docking, ADMET characteristics predication, and MD, some phenalenones were found to possess remarkable capacity as GLUT1 inhibitors; therefore, they could be potential leads for cancer treatment. It is noteworthy that the described results in this work are reported for the first time for this class of fungal metabolites and undoubtedly represent a substantial contribution in terms of further investigation, as well as in vitro and in vivo evaluations.

![Figure 24. The numbers of phenalenones isolated from the different fungal genera.](image)

Discovering bioactive phenalenones for drug use can be accelerated by applying and developing new technology, such as the methods of biosynthetic gene cluster (BGCs) activation for mining hidden new compounds [94], the use of metabolomic and genomic approaches [95], and modern machine deep learning techniques to discover the structurally distinct bioactive molecules [96,97]. Finally, we believe that the therapeutic potential and chemical diversity of the fungal phenalenones after more in-depth research will provide medicinal chemists and biologists with a more promising sustainable treasure trove for drug discovery.
Abbreviations

A-549 Human lung carcinoma
ACE Angiotensin-I-converting enzyme
AchE Acetylcholinesterase
AMT 2-Amino-5,6-dihydro-6-methyl-4H-1,3-thiazine hydrochloride
ASPC-1 Human pancreas adenocarcinoma ascites metastasis
C6 Rat glioma
CCK8 Cell counting kit-8
CD25 Interleukin-2 receptor alpha chain
CD69 Cluster of Differentiation 69
CDC25B Cell division cycle 25b
CFSE Carboxyfluorescein succinimidyl ester
CYP2E1 Cytochrome P450 2E1
DFT Density functional theory
DPPH 1,1-Diphenyl-2-picrylhydrazyl
DPPH* 1,1-diphenyl-2-picrylhydrazyl radical

Figure 25. Biological activities of isolated phenalenones and the number of articles.

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