

Review

Fungal Bergamotane Sesquiterpenoids—Potential Metabolites: Sources, Bioactivities, and Biosynthesis

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Abstract: The marine environment represents the largest ecosystem on the Earth's surface. Marine-derived fungi are of remarkable importance as they are a promising pool of diverse classes of bioactive metabolites. Bergamotane sesquiterpenoids are an uncommon class of terpenoids. They possess diverse biological properties, such as plant growth regulation, phototoxic, antimicrobial, anti-HIV, cytotoxic, pancreatic lipase inhibition, antidiabetic, anti-inflammatory, and immunosuppressive traits. The current work compiles the reported bergamotane sesquiterpenoids from fungal sources in the period ranging from 1958 to June 2022. A total of 97 compounds from various fungal species were included. Among these metabolites, 38 compounds were derived from fungi isolated from different marine sources. Furthermore, the biological activities, structural characterization, and biosynthesis of the compounds are also discussed. The summary in this work provides a detailed overview of the reported knowledge of fungal bergamotane sesquiterpenoids. Moreover, this in-depth and complete review could provide new insights for developing and discovering new valuable pharmaceutical agents from these natural metabolites.

Keywords: bergamotanes; sesquiterpenoids; marine; fungi; biosynthesis; biological activities



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1. Introduction

Nature has substantially participated in the discovery of drugs for human remedial treatments since the beginning of mankind [1]. The marine environment, with more than 70% of the surface of the Earth, represents the largest ecosystem and is characterized by quite variable physicochemical parameters (e.g., limited light access, low temperature, high pressure, and high salinity) [2]. Among the various marine microbes, fungi are a superabundant and ecologically substantial component of marine microbiota [3]. Fungi are one of nature's treasures that inhabit various environments on the earth's surface, including the marine environment [4–7]. They play a growing relevant role in drug development and biomedicine research, either directly as drugs or indirectly as lead structures for bio-inspired drug synthesis [8–12]. In the last decades, natural product chemists and pharmacologists have turned their research interests to marine-derived fungi, which are renowned as a vast unexploited reservoir of metabolic diverseness and found to have the capability to produce structurally unique bio-metabolites [6,7,12–16]. Furthermore, research on fungi-derived metabolites has tremendously increased because of the need for compounds with potential economical values and pharmaceutical applications. Sesquiterpenes belonging to various classes, including hirsutane, alliacane, tremulane, bergamotane, drimane, etc.,

are reported from fungi [17–19]. The biosynthesis of their C15 skeleton from FPP (farnesyl pyrophosphate) was catalyzed by sesquiterpene synthases [19,20].

Among these metabolites, the bergamotane family represents an uncommon class of natural sesquiterpenes that includes bi-, tri-, or tetracyclic derivatives [19]. Bergamotane sesquiterpenoids having a bridged 6/4 bicyclic skeleton involved in an isopentyl unit are biosynthesized by fungi and plants [21,22]. Interestingly, polyoxygenated derivatives featuring a 6/4/5/5 tetracyclic framework represent a rare class of natural metabolites, and all polycyclic bergamotanes are mainly encountered in fungi [23–26]. Bergamotane sesquiterpenoids have been reported from various marine sources such as sponges, sea mud, deep-sea hydrothermal sulfide deposits, and sea sediments. These metabolites could gain the interest of chemists and biologists because of their unusual structural features and diversified activities, such as phytotoxicity, plant growth regulation, antimicrobial, anti-HIV, cytotoxic, pancreatic lipase inhibition, immunosuppressive, antidiabetic, and anti-inflammatory properties. It is noteworthy that no available work has addressed this class of sesquiterpenes in term of their sources, bioactivities, and biosynthesis. In the current work, the reported fungal bergamotane sesquiterpenoids ranging from 1958 to June 2022 have been listed. They have been classified according to their ring system, i.e., into bi-, tri-, or tetracyclic derivatives (Table 1). Additionally, their fungal sources, structural characterization, biosynthesis, and biological relevance have been provided. Moreover, some of their reported structural characteristics and methods of separation and characterization, as well as their structure–activity relation, are discussed.

Table 1. Naturally occurring fungal bergamotane sesquiterpenoids (name, source, extract/fraction, molecular weights and formulae, and location).

Compound Name	Fungal Source/Host	Extract/Fraction	Mol. Wt.	Mol. Formula	Location	Ref.
Bicyclic Bergamotane Sesquiterpenoids						
α -trans Bergamotene (1)	<i>Nectria</i> sp. HLS206 (Nectriaceae)/ <i>Gelliodas carnosus</i> (marine sponge Geodiidae)	EtOAc extract	204	C ₁₅ H ₂₄	China	[27]
β -trans Bergamotene (2)	<i>Aspergillus fumigatus</i> (Trichocomaceae)/Cultured	Acetone extract	204	C ₁₅ H ₂₄	Japan	[28]
β -trans-2 β ,5,15-Trihydroxybergamot-10-ene (3)	<i>Aspergillus fumigatus</i> YK-7 (Trichocomaceae)/Sea mud	EtOAc extract	254	C ₁₅ H ₂₆ O ₃	Intertidal zone sea mud, Yingkou, China	[29]
<i>E</i> - β -trans-5,8,11-Trihydroxybergamot-9-ene (4)	<i>Aspergillus fumigatus</i> YK-7 (Trichocomaceae)/Sea mud	EtOAc extract	252	C ₁₅ H ₂₄ O ₃	Intertidal zone sea mud, Yingkou, China	[29]
Massarinolin C (5)	<i>Massarina tunicata</i> (Lophios-tomataceae)/Submerged twig	EtOAc extract	266	C ₁₅ H ₂₂ O ₄	Lemonweir River in Adams County, Wisconsin, USA	[23]
	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	-	-	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
	<i>Paraconiothyrium sporulosum</i> YK-03 Verkley (Leptosphaeriaceae)/Sea mud	EtOAc extract	-	-	Intertidal zone of Bohai Bay river in Liaoning, China	[31]
Donacinoic acid B (6)	<i>Montagnula donacina</i> (Montagnulaceae)/ <i>Craterellus odoratus</i> (fruiting bodies, Cantharellaceae)	EtOAc extract	266	C ₁₅ H ₂₂ O ₄	Southern part of the Gaoligong Mountains in Yunnan, China	[32]

Table 1. Cont.

Compound Name	Fungal Source/Host	Extract/Fraction	Mol. Wt.	Mol. Formula	Location	Ref.
Craterodoratin M (7)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	252	C ₁₅ H ₂₄ O ₃	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Craterodoratin N (8)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	268	C ₁₅ H ₂₄ O ₄	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Craterodoratin O (9)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	250	C ₁₅ H ₂₂ O ₃	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Craterodoratin P (10)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	250	C ₁₅ H ₂₂ O ₃	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Craterodoratin Q (11)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	308	C ₁₇ H ₂₄ O ₅	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Necbergamotenoic acid A (12)	<i>Nectria</i> sp. HLS206 (Nectriaceae)/ <i>Gellioidas carnosus</i> (marine sponge, Geodiidae)	EtOAc extract	264	C ₁₅ H ₂₀ O ₄	China	[27]
Necbergamotenoic acid B (13)	<i>Nectria</i> sp. HLS206 (Nectriaceae)/ <i>Gellioidas carnosus</i> (marine sponge, Geodiidae)	EtOAc extract	266	C ₁₅ H ₂₂ O ₄	China	[27]
Sporulamide C (14)	<i>Paraconiothyrium sporulosum</i> YK-03 Verkley (Leptosphaeriaceae)/Sea mud	EtOAc extract	265	C ₁₅ H ₂₃ NO ₃	Intertidal zone of Bohai Bay river in Liaoning, China	[31]
Sporulamide D (15)	<i>Paraconiothyrium sporulosum</i> YK-03 Verkley (Leptosphaeriaceae)/Sea mud	EtOAc extract	249	C ₁₅ H ₂₃ NO ₂	Intertidal zone of Bohai Bay river in Liaoning, China	[31]
Xylariterpenoid A (16)	<i>Xylariaceae</i> fungus (No. 63-19-7-3)/ <i>Everniastrum cirrhatum</i> (Fr.) Haleex Sipman (lichen, Parmeliaceae)	EtOAc extract	252	C ₁₅ H ₂₄ O ₃	Zixi Mountain, Yunnan, China	[33]
	<i>Graphostroma</i> sp. MCCC 3A00421/Deep-sea hydrothermal sulfide deposit	EtOAc extract	-	-	Atlantic Ocean, China	[34]
	<i>Eutypella</i> sp. MCCC 3A00281 (Diatrypaceae)/Deep-sea sediment	EtOAc extract	-	-	South Atlantic Ocean, China	[35]
Xylariterpenoid B (17)	<i>Xylariaceae</i> fungus (No. 63-19-7-3)/ <i>Everniastrum cirrhatum</i> (Fr.) Haleex Sipman (lichen, Parmeliaceae)	EtOAc extract	252	C ₁₅ H ₂₄ O ₃	Zixi Mountain, Yunnan, China	[33]
	<i>Graphostroma</i> sp. MCCC 3A00421/Deep-sea hydrothermal sulfide deposit	EtOAc extract	-	-	Atlantic Ocean, China	[34]
	<i>Eutypella</i> sp. MCCC 3A00281 (Diatrypaceae)/Deep-sea sediment	EtOAc extract	-	-	South Atlantic Ocean, China	[35]

Table 1. Cont.

Compound Name	Fungal Source/Host	Extract/Fraction	Mol. Wt.	Mol. Formula	Location	Ref.
Eutypeterpene B (18)	<i>Eutypella</i> sp. MCCC 3A00281 (Diatrypaceae)/Deep-sea sediment	EtOAc extract	268	C ₁₅ H ₂₄ O ₄	South Atlantic Ocean, China	[35]
Eutypeterpene C (19)	<i>Eutypella</i> sp. MCCC 3A00281 (Diatrypaceae)/Deep-sea sediment	EtOAc extract	266	C ₁₅ H ₂₂ O ₄	South Atlantic Ocean, China	[35]
Eutypeterpene D (20)	<i>Eutypella</i> sp. MCCC 3A00281 (Diatrypaceae)/Deep-sea sediment	EtOAc extract	250	C ₁₅ H ₂₂ O ₃	South Atlantic Ocean, China	[35]
Eutypeterpene E (21)	<i>Eutypella</i> sp. MCCC 3A00281 (Diatrypaceae)/Deep-sea sediment	EtOAc extract	250	C ₁₅ H ₂₂ O ₃	South Atlantic Ocean, China	[35]
Eutypeterpene F (22)	<i>Eutypella</i> sp. MCCC 3A00281 (Diatrypaceae)/Deep-sea sediment	EtOAc extract	252	C ₁₅ H ₂₄ O ₃	South Atlantic Ocean, China	[35]
(10S)-Xylariterpenoid A (23)	<i>Graphostroma</i> sp. MCCC 3A00421/Deep-sea hydrothermal sulfide deposit	EtOAc extract	252	C ₁₅ H ₂₄ O ₃	Atlantic Ocean. China	[34]
(10R)-Xylariterpenoid B (24)	<i>Graphostroma</i> sp. MCCC 3A00421/Deep-sea hydrothermal sulfide deposit	EtOAc extract	252	C ₁₅ H ₂₄ O ₃	Atlantic Ocean. China	[34]
Xylariterpenoid E (25)	<i>Graphostroma</i> sp. MCCC 3A00421/Deep-sea hydrothermal sulfide deposit	EtOAc extract	208	C ₁₂ H ₁₆ O ₃	Atlantic Ocean. China	[34]
Xylariterpenoid F (26)	<i>Graphostroma</i> sp. MCCC 3A00421/Deep-sea hydrothermal sulfide deposit	EtOAc extract	270	C ₁₅ H ₂₆ O ₄	Atlantic Ocean. China	[34]
Xylariterpenoid G (27)	<i>Graphostroma</i> sp. MCCC 3A00421/Deep-sea hydrothermal sulfide deposit	EtOAc extract	270	C ₁₅ H ₂₆ O ₄	Atlantic Ocean. China	[34]
Eutypeterpene A (28)	<i>Eutypella</i> sp. MCCC 3A00281 (Diatrypaceae)/Deep-sea sediment	EtOAc extract	294	C ₁₆ H ₂₂ O ₅	South Atlantic Ocean, China	[35]
Craterodoratin A (29)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	252	C ₁₅ H ₂₄ O ₃	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Craterodoratin C (30)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	268	C ₁₅ H ₂₄ O ₄	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Craterodoratin D (31)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	268	C ₁₅ H ₂₄ O ₄	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Craterodoratin E (32)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	284	C ₁₅ H ₂₄ O ₅	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]

Table 1. Cont.

Compound Name	Fungal Source/Host	Extract/Fraction	Mol. Wt.	Mol. Formula	Location	Ref.
Craterodoratin F (33)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	284	C ₁₅ H ₂₄ O ₅	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Dihydroprehelminthosporol (34)	<i>Bipolaris</i> sp. No. 36/Johnson grass leaf	EtOAc extract	238	C ₁₅ H ₂₆ O ₂	Wake County, North Carolina, USA	[36,37]
Helminthosporal acid (35)	<i>Bipolaris</i> sp. No. 36/Johnson grass leaf	EtOAc extract	250	C ₁₅ H ₂₂ O ₃	Wake County, North Carolina, USA	[36]
Helminthosporol (36)	<i>Bipolaris</i> sp. No. 36/Johnson grass leaf	EtOAc extract	236	C ₁₅ H ₂₄ O ₂	Wake County, North Carolina, USA	[36]
Helminthosporic acid (37)	<i>Bipolaris</i> sp. No. 36/Johnson grass leaf	EtOAc extract	252	C ₁₅ H ₂₄ O ₃	Wake County, North Carolina, USA	[36]
Tricyclic Bergamotane Sesquiterpenoids						
Prehelminthosporol (38)	<i>Bipolaris</i> sp. No. 36/Johnson grass leaf	EtOAc extract	236	C ₁₅ H ₂₄ O ₂	Wake County, North Carolina, USA	[36,37]
Prehelminthosporolactone (39)	<i>Bipolaris</i> sp. No. 36/Johnson grass leaf	EtOAc extract	234	C ₁₅ H ₂₂ O ₂	Wake County, North Carolina, USA	[37]
Victoxinine (40)	<i>Helminthosporium victoriae</i> (Totiviridae)	Diethyl ether extract	263	C ₁₇ H ₂₉ NO	USA	[36,38,39]
	<i>Helminthosporium sativum</i> (Totiviridae)	Diethyl ether fraction/CHCl ₃ extract	-	-	Canada	[40]
Victoxinine- α -glycerophosphate (41)	<i>H. sativum</i> (Totiviridae)	<i>n</i> -BuOH extract	417	C ₂₀ H ₃₆ NO ₆ P	USA	[41]
Craterodoratin S (42)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	277	C ₁₇ H ₂₇ NO ₂	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Isosativenediol (43)	<i>Bipolaris</i> sp. No. 36/Johnson grass leaf	EtOAc extract	236	C ₁₅ H ₂₄ O ₂	Wake County, North Carolina, USA	[36]
Pinthunamide (44)	<i>Ampulliferina</i> sp. No. 27 (Ampullicephala)/ <i>Pinus thunbergii</i> (dead tree, Pinaceae)	Acetone extract	277	C ₁₅ H ₁₉ NO ₄	Japan	[42]
	<i>Paraconiothyrium brasiliense</i> Verkley (M3-3341) (Leptosphaeriaceae)/ <i>Acer truncatum</i> Bunge (branches, Sapindaceae)	Acetone extract	-	-	Dongling Mountain, Beijing, China	[43]
Brasilamide A (45)	<i>Paraconiothyrium brasiliense</i> Verkley (M3-3341) (Leptosphaeriaceae)/ <i>Acer truncatum</i> Bunge (branches, Sapindaceae)	Acetone extract	293	C ₁₅ H ₁₉ NO ₅	Dongling Mountain, Beijing, China	[43,44]

Table 1. Cont.

Compound Name	Fungal Source/Host	Extract/Fraction	Mol. Wt.	Mol. Formula	Location	Ref.
Brasilamide B (46)	<i>Paraconiothyrium brasiliense</i> Verkley (M3–3341) (Leptosphaeriaceae)/ <i>Acer truncatum</i> Bunge (branches, Sapindaceae)	Acetone extract	265	C ₁₅ H ₂₃ NO ₃	Dongling Mountain, Beijing, China	[43]
Brasilamide C (47)	<i>Paraconiothyrium brasiliense</i> Verkley (M3–3341) (Leptosphaeriaceae)/ <i>Acer truncatum</i> Bunge (branches, Sapindaceae)	Acetone extract	279	C ₁₅ H ₂₁ NO ₄	Dongling Mountain, Beijing, China	[43,44]
Brasilamide D (48)	<i>Paraconiothyrium brasiliense</i> Verkley (M3–3341) (Leptosphaeriaceae)/ <i>Acer truncatum</i> Bunge (branches, Sapindaceae)	Acetone extract	321	C ₁₇ H ₂₃ NO ₅	Dongling Mountain, Beijing, China	[43]
Brasilamide K (49)	<i>Paraconiothyrium brasiliense</i> Verkley (M3–3341) (Leptosphaeriaceae)/ <i>Acer truncatum</i> Bunge (branches, Sapindaceae)	EtOAc extract	279	C ₁₅ H ₂₁ NO ₄	Dongling Mountain, Beijing, China	[44]
Brasilamide L (50)	<i>Paraconiothyrium brasiliense</i> Verkley (M3–3341) (Leptosphaeriaceae)/ <i>Acer truncatum</i> Bunge (branches, Sapindaceae)	EtOAc extract	265	C ₁₅ H ₂₃ NO ₃	Dongling Mountain, Beijing, China	[44]
Brasilamide M (51)	<i>Paraconiothyrium brasiliense</i> Verkley (M3–3341) (Leptosphaeriaceae)/ <i>Acer truncatum</i> Bunge (branches, Sapindaceae)	EtOAc extract	293	C ₁₅ H ₁₉ NO ₅	Dongling Mountain, Beijing, China,	[44]
Brasilamide N (52)	<i>Paraconiothyrium brasiliense</i> Verkley (M3–3341) (Leptosphaeriaceae)/ <i>Acer truncatum</i> Bunge (branches, Sapindaceae)	EtOAc extract	279	C ₁₅ H ₂₁ NO ₄	Dongling Mountain, Beijing, China	[44]
Craterodoratin I (53)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	250	C ₁₅ H ₂₂ O ₃	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Craterodoratin J (54)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	282	C ₁₅ H ₂₂ O ₅	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Craterodoratin K (55)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	282	C ₁₅ H ₂₂ O ₅	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Craterodoratin L (56)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	278	C ₁₅ H ₁₈ O ₅	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]

Table 1. Cont.

Compound Name	Fungal Source/Host	Extract/Fraction	Mol. Wt.	Mol. Formula	Location	Ref.
Sporuloic acid A (57)	<i>Paraconiothyrium sporulosum</i> YK-03 Verkley (Leptosphaeriaceae)/Sea mud	EtOAc extract	282	C ₁₅ H ₂₂ O ₅	Intertidal zone of Bohai Bay river in Liaoning, China	[31]
Sporuloic acid B (58)	<i>Paraconiothyrium sporulosum</i> YK-03 Verkley (Leptosphaeriaceae)/Sea mud	EtOAc extract	280	C ₁₅ H ₂₀ O ₅	Intertidal zone of Bohai Bay river in Liaoning, China	[31]
Sporulamide A (59)	<i>Paraconiothyrium sporulosum</i> YK-03 Verkley (Leptosphaeriaceae)/Sea mud	EtOAc extract	265	C ₁₅ H ₂₃ NO ₃	Intertidal zone of Bohai Bay river in Liaoning, China	[31]
Sporulamide B (60)	<i>Paraconiothyrium sporulosum</i> YK-03 Verkley (Leptosphaeriaceae)/Sea mud	EtOAc extract	249	C ₁₅ H ₂₃ NO ₂	Intertidal zone of Bohai Bay river in Liaoning, China	[31]
Massarinolin B (61)	<i>Massarina tunicata</i> (Lophios-tomataceae)/Submerged twig	EtOAc extract	266	C ₁₅ H ₂₂ O ₄	Lemonweir River in Adams County, Wisconsin, USA	[23]
	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	-	-	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Massarinolin B methyl ester (62)	<i>Paraconiothyrium sporulosum</i> YK-03 Verkley (Leptosphaeriaceae)/Sea mud	EtOAc extract	280	C ₁₆ H ₂₄ O ₄	Intertidal zone of Bohai Bay river in Liaoning, China	[31]
Craterodoratin R (63)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	282	C ₁₅ H ₂₂ O ₅	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Craterodoratin G (64)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	278	C ₁₆ H ₂₂ O ₄	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Craterodoratin H (65)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	278	C ₁₆ H ₂₂ O ₄	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Brasilterpene A (66)	<i>Paraconiothyrium brasiliense</i> HDN15-135 (Leptosphaeriaceae)/Deep-sea sediment	EtOAc extract	294	C ₁₆ H ₂₂ O ₅	Indian Ocean, China	[45]
Brasilterpene B (67)	<i>Paraconiothyrium brasiliense</i> HDN15-135 (Leptosphaeriaceae)/Deep-sea sediment	EtOAc extract	294	C ₁₆ H ₂₂ O ₅	Indian Ocean, China	[45]
Brasilterpene C (68)	<i>Paraconiothyrium brasiliense</i> HDN15-135 (Leptosphaeriaceae)/Deep-sea sediment	EtOAc extract	278	C ₁₆ H ₂₂ O ₄	Indian Ocean, China	[45]

Table 1. Cont.

Compound Name	Fungal Source/Host	Extract/Fraction	Mol. Wt.	Mol. Formula	Location	Ref.
Brasilterpene D (69)	<i>Paraconiothyrium brasiliense</i> HDN15-135 (Leptosphaeriaceae)/Deep-sea sediment	EtOAc extract	278	C ₁₆ H ₂₂ O ₄	Indian Ocean, China	[45]
Brasilterpene E (70)	<i>Paraconiothyrium brasiliense</i> HDN15-135 (Leptosphaeriaceae)/Deep-sea sediment	EtOAc extract	278	C ₁₆ H ₂₂ O ₄	Indian Ocean, China	[45]
Craterodoratin B (71)	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	266	C ₁₅ H ₂₂ O ₄	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Tetracyclic Bergamotane Sesquiterpenoids						
Expansolide A (72)	<i>Penicillium expansum</i> (Trichocomaceae)/Fruit	EtOAc extract	306	C ₁₇ H ₂₂ O ₅	France	[25]
Expansolide C (73)	<i>Aspergillus fumigatus</i> Fresenius (Trichocomaceae)/Leaf litter	EtOAc extract	-	-	Waipoua Forest, New Zealand	[26]
Expansolide C (73)	<i>Penicillium expansum</i> ACCC37275/ Agricultural Culture	Acetone extract	264	C ₁₅ H ₂₀ O ₄	China	[46]
Decipienolide A (74)	<i>Podospora decipiens</i> Niessl (JS 270) (Podosporaceae)/Sheep dung	EtOAc extract	378	C ₂₁ H ₃₀ O ₆	South Australia	[24]
Decipienolide B (75)	<i>Podospora decipiens</i> Niessl (JS 270) (Podosporaceae)/Sheep dung	EtOAc extract	378	C ₂₁ H ₃₀ O ₆	South Australia	[24]
Donacinolide B (76)	<i>Montagnula donacina</i> (Montagnulaceae)/ <i>Craterellus odoratus</i> (fruiting bodies, Cantharellaceae)	EtOAc extract	246	C ₁₅ H ₁₈ O ₃	Southern part of the Gaoligong Mountains in Yunnan, China	[32]
Massarinolin A (77)	<i>Massarina tunicata</i> (Lophios-tomataceae)/Submerged twig	EtOAc extract	262	C ₁₅ H ₁₈ O ₄	LemonweirRiver in Adams County, Wisconsin, USA	[23]
	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	-	-	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Sporuloketal A (78)	<i>Paraconiothyrium sporulosum</i> YK-03 Verkley (Leptosphaeriaceae)/Sea mud	EtOAc extract	262	C ₁₅ H ₁₈ O ₄	Intertidal zone of Bohai Bay river in Liaoning, China	[31]
Sporuloketal B (79)	<i>Paraconiothyrium sporulosum</i> YK-03 Verkley (Leptosphaeriaceae)/Sea mud	EtOAc extract	262	C ₁₅ H ₁₈ O ₄	Intertidal zone of Bohai Bay river in Liaoning, China	[31]
Expansolide B (80)	<i>Penicillium expansum</i> (Trichocomaceae)	EtOAc extract	306	C ₁₇ H ₂₂ O ₅	France	[25]
	<i>Aspergillus fumigatus</i> Fresenius (Trichocomaceae)/Leaf litter	EtOAc extract	-	-	Waipoua Forest, New Zealand	[26]

Table 1. Cont.

Compound Name	Fungal Source/Host	Extract/Fraction	Mol. Wt.	Mol. Formula	Location	Ref.
Expansolide D (81)	<i>Penicillium expansum</i> ACCC37275, (Trichocomaceae)/Agricultural Culture	Acetone extract	264	C ₁₅ H ₂₀ O ₄	China	[46]
Donacinolide A (82)	<i>Montagnula donacina</i> (Montagnulaceae)/ <i>Craterellus odoratus</i> (fruiting bodies, Cantharellaceae)	EtOAc extract	246	C ₁₅ H ₁₈ O ₃	Southern part of the Gaoligong Mountains in Yunnan, China	[32]
Purpurolide B (83)	<i>Penicillium purpurogenum</i> IMM003 (Trichocomaceae)/ <i>Edgeworthia Chrysantha</i> (leaves, Thymelaeaceae)	EtOAc extract	336	C ₁₇ H ₂₀ O ₇	Hangzhou Bay, Hangzhou, Zhejiang, China	[47]
Purpurolide C (84)	<i>Penicillium purpurogenum</i> IMM003 (Trichocomaceae)/ <i>Edgeworthia Chrysantha</i> (leaves, Thymelaeaceae)	EtOAc extract	308	C ₁₆ H ₂₀ O ₆	Hangzhou Bay, Hangzhou, Zhejiang, China	[47]
Purpurolide D (85)	<i>Penicillium purpurogenum</i> IMM003 (Trichocomaceae)/ <i>Edgeworthia Chrysantha</i> (leaves, Thymelaeaceae)	EtOAc extract	294	C ₁₅ H ₁₈ O ₆	Hangzhou Bay, Hangzhou, Zhejiang, China	[48]
Purpurolide E (86)	<i>Penicillium purpurogenum</i> IMM003 (Trichocomaceae)/ <i>Edgeworthia Chrysantha</i> (leaves, Thymelaeaceae)	EtOAc extract	278	C ₁₅ H ₁₈ O ₅	Hangzhou Bay, Hangzhou, Zhejiang, China	[48]
Purpurolide F (87)	<i>Penicillium purpurogenum</i> IMM003 (Trichocomaceae)/ <i>Edgeworthia Chrysantha</i> (leaves, Thymelaeaceae)	EtOAc extract	464	C ₂₅ H ₃₆ O ₈	Hangzhou Bay, Hangzhou, Zhejiang, China	[48]
Donacinoic acid A (88)	<i>Montagnula donacina</i> (Montagnulaceae)/ <i>Craterellus odoratus</i> (fruiting bodies, Cantharellaceae)	EtOAc extract	264	C ₁₅ H ₂₀ O ₄	Southern part of the Gaoligong Mountains in Yunnan, China	[32]
	<i>Craterellus odoratus</i> (Cantharellaceae)	EtOAc extract	-	-	Southern part of the Gaoligong-Mountains, Yunnan, China	[30]
Sporulaminal A (89)	<i>Paraconiothyrium sporulosum</i> YK-03 (Leptosphaeriaceae)/Sea mud	EtOAc extract	247	C ₁₅ H ₂₁ NO ₂	Intertidal zone of Bohai river in Liaonign, China	[49]
Sporulaminal B (90)	<i>Paraconiothyrium sporulosum</i> YK-03 (Leptosphaeriaceae)/Sea mud	EtOAc extract	247	C ₁₅ H ₂₁ NO ₂	Intertidal zone of Bohai river in Liaonign, China	[49]
Ampullicin (91)	<i>Ampulliferina</i> -like sp. No. 27 (Ampullicephala)/ <i>Pinus thunbergii</i> (dead tree, Pinaceae)	Acetone extract	259	C ₁₅ H ₁₇ NO ₃	Japan	[50,51]
Isoampullicin (92)	<i>Ampulliferina</i> -like sp. No. 27 (Ampullicephala)/ <i>Pinus thunbergii</i> (dead tree, Pinaceae)	Acetone extract	259	C ₁₅ H ₁₇ NO ₃	Japan	[50]

Table 1. Cont.

Compound Name	Fungal Source/Host	Extract/Fraction	Mol. Wt.	Mol. Formula	Location	Ref.
Dihydroampullicin (93)	<i>Ampulliferina</i> -like sp. No. 27 (Ampullicephala)/ <i>Pinus thunbergii</i> (dead tree, Pinaceae)	Acetone extract	261	C ₁₅ H ₁₉ NO ₃	Japan	[51]
Eutypellacytosporin A (94)	<i>Eutypella</i> sp. D-1 (Diatrypaceae)/Soil sample	CH ₂ Cl ₂ fraction of EtOAc extract	714	C ₄₀ H ₅₈ O ₁₁	London Island of Kongsfjorden of the Ny-Ålesund District, Arctic, Norway	[52]
Eutypellacytosporin B (95)	<i>Eutypella</i> sp. D-1 (Diatrypaceae)/Soil sample	CH ₂ Cl ₂ fraction of EtOAc extract	714	C ₄₀ H ₅₈ O ₁₁	London Island of Kongsfjorden of the Ny-Ålesund District, Arctic, Norway	[52]
Eutypellacytosporin C (96)	<i>Eutypella</i> sp. D-1 (Diatrypaceae)/Soil sample	CH ₂ Cl ₂ fraction of EtOAc extract	714	C ₄₀ H ₅₈ O ₁₁	London Island of Kongsfjorden of the Ny-Ålesund District, Arctic, Norway	[52]
Eutypellacytosporin D (97)	<i>Eutypella</i> sp. D-1 (Diatrypaceae)/Soil sample	CH ₂ Cl ₂ fraction of EtOAc extract	714	C ₄₀ H ₅₈ O ₁₁	London Island of Kongsfjorden of the Ny-Ålesund District, Arctic, Norway	[52]

Surveying their bioactivities may open a new research area for the synthesis of new agents from these metabolites by synthetic and medicinal chemists. The literature search for the reported data was performed using diverse databases and publishers, including Web of Science, Google Scholar, PubMed, Scopus, SciFinder, Wiley, SpringerLink, and ACS Publications, using specific keywords (bergamotane, marine, fungi, biosynthesis, and biological activities).

2. Structural Assignment and Stereochemistry Determination

A total of 97 metabolites have been separated from various fungal source extracts using different chromatographic techniques and characterized by NMR, MS, and IR spectral analyses as well as chemical derivatization. The relative configuration of these metabolites was established using NOESY or ROESY spectral analyses. Various studies reported the assigning of their absolute stereochemistry using total synthesis [53,54], Mosher's method [26], X-ray diffraction, chemical conversion [34,43,55], and ECD analyses [31]. The reported metabolites have been categorized into bi-, tri-, and tetracyclic derivatives.

3. Biological Activities of Bergamotane Sesquiterpenoids

Various reported studies revealed the assessment of bergamotane sesquiterpenoids for diverse bioactivities, including plant growth regulation, phototoxic, antimicrobial, anti-HIV, cytotoxic, pancreatic lipase inhibition, antidiabetic, anti-inflammatory, and immunosuppressive, which were summarized in this work (Table 2). Additionally, the reported structure–activity relation was included.

Table 2. Biological activities of fungal naturally occurring in bergamotane sesquiterpenoids.

Compound Name	Biological Activity	Assay, Organism, or Cell Line	Biological Results		Ref.
			Compound	Positive Control	
<i>E</i> - β - <i>trans</i> -5,8,11-trihydroxybergamot-9-ene (4)	Cytotoxicity	MTT/U937	84.9 (IC ₅₀)	Doxorubicin 0.021 μ M (IC ₅₀)	[29]
Craterodoratin M (7)	Immunosuppressive	BALB/c mice T and B lymphocyte/LPS	15.43 μ M (IC ₅₀)	Cyclosporin A 0.47 μ M (IC ₅₀)	[30]
Craterodoratin N (8)	Immunosuppressive	BALB/c mice T and B lymphocyte/LPS	13.26 μ M (IC ₅₀)	Cyclosporin A 0.47 μ M (IC ₅₀)	[30]
Craterodoratin O (9)	Immunosuppressive	BALB/c mice T and B lymphocyte/LPS	17.12 μ M (IC ₅₀)	Cyclosporin A 0.47 μ M (IC ₅₀)	[30]
Craterodoratin Q (11)	Immunosuppressive	BALB/c mice T and B lymphocyte/Concanavalin A	31.50 μ M (IC ₅₀)	Cyclosporin A 0.04 μ M (IC ₅₀)	[30]
Xylariterpenoid A (16)	Anti-inflammatory	Spectrophotometrically/LPS	17.5 μ M (IC ₅₀)	Quercetin 17.0 μ M (IC ₅₀) NG-monomethyl-L-arginine 9.7 μ M (IC ₅₀)	[35]
Xylariterpenoid B (17)	Anti-inflammatory	Spectrophotometrically/LPS	21.0 μ M (IC ₅₀)	Quercetin 17.0 μ M (IC ₅₀) NG-monomethyl-L-arginine 9.7 μ M (IC ₅₀)	[35]
Eutypeterpene B (18)	Anti-inflammatory	Spectrophotometrically/LPS	13.4 μ M (IC ₅₀)	Quercetin 17.0 μ M (IC ₅₀) NG-monomethyl-L-arginine 9.7 μ M (IC ₅₀)	[35]
Eutypeterpene C (19)	Anti-inflammatory	Spectrophotometrically/LPS	16.8 μ M (IC ₅₀)	Quercetin 17.0 μ M (IC ₅₀) NG-monomethyl-L-arginine 9.7 μ M (IC ₅₀)	[35]
Eutypeterpene D (20)	Anti-inflammatory	Spectrophotometrically/LPS	21.4 μ M (IC ₅₀)	Quercetin 17.0 μ M (IC ₅₀) NG-monomethyl-L-arginine 9.7 μ M (IC ₅₀)	[35]
Eutypeterpene E (21)	Anti-inflammatory	Spectrophotometrically/LPS	18.7 μ M (IC ₅₀)	Quercetin 17.0 μ M (IC ₅₀) NG-monomethyl-L-arginine 9.7 μ M (IC ₅₀)	[35]
Eutypeterpene F (22)	Anti-inflammatory	Spectrophotometrically/LPS	24.3 μ M (IC ₅₀)	Quercetin 17.0 μ M (IC ₅₀) NG-monomethyl-L-arginine 9.7 μ M (IC ₅₀)	[35]
(10S)-Xylariterpenoid A (23)	Anti-inflammatory	Spectrophotometrically/LPS	86.0 μ M (IC ₅₀)	Aminoguanidine 23.0 μ M (IC ₅₀)	[34]
(10R)-Xylariterpenoid B (24)	Anti-inflammatory	Spectrophotometrically/LPS	230.0 μ M (IC ₅₀)	Aminoguanidine 23.0 μ M (IC ₅₀)	[34]
Xylariterpenoid E (25)	Anti-inflammatory	Spectrophotometrically/LPS	120.0 μ M (IC ₅₀)	Aminoguanidine 23.0 μ M (IC ₅₀)	[34]
Xylariterpenoid F (26)	Anti-inflammatory	Spectrophotometrically/LPS	85.0 μ M (IC ₅₀)	Aminoguanidine 23.0 μ M (IC ₅₀)	[34]

Table 2. Cont.

Compound Name	Biological Activity	Assay, Organism, or Cell Line	Biological Results		Ref.
			Compound	Positive Control	
Xylariterpenoid G (27)	Anti-inflammatory	Spectrophotometrically/LPS	85.0 μ M (IC ₅₀)	Aminoguanidine 23.0 μ M (IC ₅₀)	[34]
Eutypeterpene A (28)	Anti-inflammatory	Spectrophotometrically/LPS	21.0 μ M (IC ₅₀)	Quercetin 17.0 μ M (IC ₅₀) NG-monomethyl-L-arginine 9.7 μ M (IC ₅₀)	[35]
Craterodoratin C (30)	Immunosuppressive	BALB/c mice T and B lymphocyte/LPS	12.62 μ M (IC ₅₀)	Cyclosporin A 0.47 μ M (IC ₅₀)	[30]
Craterodoratin S (42)	Immunosuppressive	BALB/c mice T and B lymphocyte/LPS	22.68 μ M (IC ₅₀)	Cyclosporin A 0.47 μ M (IC ₅₀)	[30]
Craterodoratin J (54)	Immunosuppressive	BALB/c mice T and B lymphocyte/LPS	19.40 μ M (IC ₅₀)	Cyclosporin A 0.47 μ M (IC ₅₀)	[30]
Craterodoratin L (56)	Immunosuppressive	BALB/c mice T and B lymphocyte/LPS	13.71 μ M (IC ₅₀)	Cyclosporin A 0.47 μ M (IC ₅₀)	[30]
Massarinolin B (61)	Immunosuppressive	BALB/c mice T and B lymphocyte/Concanavalin A	0.98 μ M (IC ₅₀)	Cyclosporin A 0.04 μ M (IC ₅₀)	[30]
Brasilterpene A (66)	Hypoglycemic	Spectrophotometrically/Diabetic zebrafish model	449.3 pmol/larva (IC ₅₀)	Rosiglitazone 395.6 pmol/larva (IC ₅₀)	[45]
Brasilterpene C (68)	Hypoglycemic	Spectrophotometrically/Diabetic zebrafish model	420.4 pmol/larva (IC ₅₀)	Rosiglitazone 395.6 pmol/larva (IC ₅₀)	[45]
Expansolide C (73)	α -Glucosidase inhibition	Spectrophotometrically/ α -glucosidase enzyme	0.50 mM (IC ₅₀)	Acarbose 1.90 mM (IC ₅₀)	[46]
Expansolide D (81)	α -Glucosidase inhibition	Spectrophotometrically/ α -glucosidase enzyme	0.50 mM (IC ₅₀)	acarbose 1.90 mM (IC ₅₀)	[46]
Purpurolide B (83)	Pancreatic lipase inhibition	Spectrophotometrically/pancreatic lipase enzyme	5.45 μ M (IC ₅₀)	Kaempferol 1.50 μ M (IC ₅₀)	[47]
Purpurolide C (84)	Pancreatic lipase inhibition	Spectrophotometrically/pancreatic lipase enzyme	6.63 μ M (IC ₅₀)	Kaempferol 1.50 μ M (IC ₅₀)	[47]
Purpurolide D (85)	Pancreatic lipase inhibition	Spectrophotometrically/pancreatic lipase enzyme	1.22 μ M (IC ₅₀)	Kaempferol 1.50 μ M (IC ₅₀)	[48]
Purpurolide E (86)	Pancreatic lipase inhibition	Spectrophotometrically/pancreatic lipase enzyme	6.50 μ M (IC ₅₀)	Kaempferol 1.50 μ M (IC ₅₀)	[48]
Purpurolide F (87)	Pancreatic lipase inhibition	Spectrophotometrically/pancreatic lipase enzyme	7.88 μ M (IC ₅₀)	Kaempferol 1.50 μ M (IC ₅₀)	[48]
Donacinoic acid A (88)	Immunosuppressive	BALB/c mice T and B lymphocyte/LPS	13.23 μ M (IC ₅₀)	Cyclosporin A 0.47 μ M (IC ₅₀)	[30]
Eutypellacytosporin A (94)	Cytotoxicity	CCK-8/DU145	17.1 μ M (IC ₅₀)	Cisplatin 2.9 μ M (IC ₅₀)	[52]
		CCK-8/SW1990	7.3 μ M (IC ₅₀)	Cisplatin 1.2 μ M (IC ₅₀)	[52]
		CCK-8/Huh7	8.4 μ M (IC ₅₀)	Cisplatin 2.2 μ M (IC ₅₀)	[52]
		CCK-8/PANC-1	9.7 μ M (IC ₅₀)	Cisplatin 4.5 μ M (IC ₅₀)	[52]

Table 2. Cont.

Compound Name	Biological Activity	Assay, Organism, or Cell Line	Biological Results		Ref.
			Compound	Positive Control	
Eutypellacytosporin B (95)	Cytotoxicity	CCK-8/DU145	11.0 μM (IC_{50})	Cisplatin 2.9 μM (IC_{50})	[52]
		CCK-8/SW1990	4.9 μM (IC_{50})	Cisplatin 1.2 μM (IC_{50})	[52]
		CCK-8/Huh7	4.9 μM (IC_{50})	Cisplatin 2.2 μM (IC_{50})	[52]
		CCK-8/PANC-1	7.9 μM (IC_{50})	Cisplatin 4.5 μM (IC_{50})	[52]
Eutypellacytosporin C (96)	Cytotoxicity	CCK-8/DU145	13.5 μM (IC_{50})	Cisplatin 2.9 μM (IC_{50})	[52]
		CCK-8/SW1990	9.6 μM (IC_{50})	Cisplatin 1.2 μM (IC_{50})	[52]
		CCK-8/Huh7	11.2 μM (IC_{50})	Cisplatin 2.2 μM (IC_{50})	[52]
		CCK-8/PANC-1	10.2 μM (IC_{50})	Cisplatin 4.5 μM (IC_{50})	[52]
Eutypellacytosporin D (97)	Cytotoxicity	CCK-8/DU145	13.4 μM (IC_{50})	Cisplatin 2.9 μM (IC_{50})	[52]
		CCK-8/SW1990	8.2 μM (IC_{50})	Cisplatin 1.2 μM (IC_{50})	[52]
		CCK-8/Huh7	9.6 μM (IC_{50})	Cisplatin 2.2 μM (IC_{50})	[52]
		CCK-8/PANC-1	7.5 μM (IC_{50})	Cisplatin 4.5 μM (IC_{50})	[52]

3.1. Anti-Inflammatory Activity

NO (nitric oxide) is a substantial pro-inflammatory mediator, and its excessive production is accompanied with various inflammatory illnesses; therefore, it possesses a remarkable role for regulating immune responses and inflammation [56]. NO production inhibitors may represent the potential capacity for treating various inflammatory disorders. Thus, further research for fungal metabolites must be conducted to discover novel anti-inflammation agents.

The epigenetic chemical manipulation of *Eutypella* sp. derived from deep-sea hydrothermal sulfide deposit by co-treatment with SBHA (histone deacetylase inhibitor, suberohydroxamic acid) and 5-Aza (DNA methyltransferase inhibitor, 5-azacytidine) was shown to activate a biosynthetic sesquiterpene-linked gene cluster [35]. From elicitor-treated cultures EtOAc extract, eutypeterpenes A–F (18–22 and 28) along with xylariterpenoids A (16) and B (17) were purified using SiO_2 /RP-18/HPLC that were identified by spectral analyses, as well as by using chemical conversion, X-ray diffraction, ECD, and calculated NMR for configuration assignments.

Eutypeterpene A (28) is the first bergamotene sesquiterpene incorporating a dioxolanone moiety. These metabolites were assessed for their NO production inhibitory capacity induced by LPS (lipopolysaccharide) in RAW 264.7 macrophages [35]. The results indicated that compound 18 and 19 (IC_{50} 13.4 and 16.8 μM , respectively) displayed more effectiveness than quercetin (IC_{50} of 17.0 μM), whereas other metabolites had noticeable potentials (IC_{50} values ranged from 18.7 to 24.3 μM) with weak cytotoxic capacities (IC_{50} > 100 μM). A structure–activity study revealed that the analog with a triol unit (18) at the side chain was more effective than compound 16, 17, and 19 with a diol unit, which were more potent than compound 20, 21, and 28 with one hydroxy group. Furthermore, the α,β -unsaturated ketone unit (as in compound 21 and 22) and the OH-linked carbon configuration also affected the activities (16 versus 17) [35] (Figure 1).

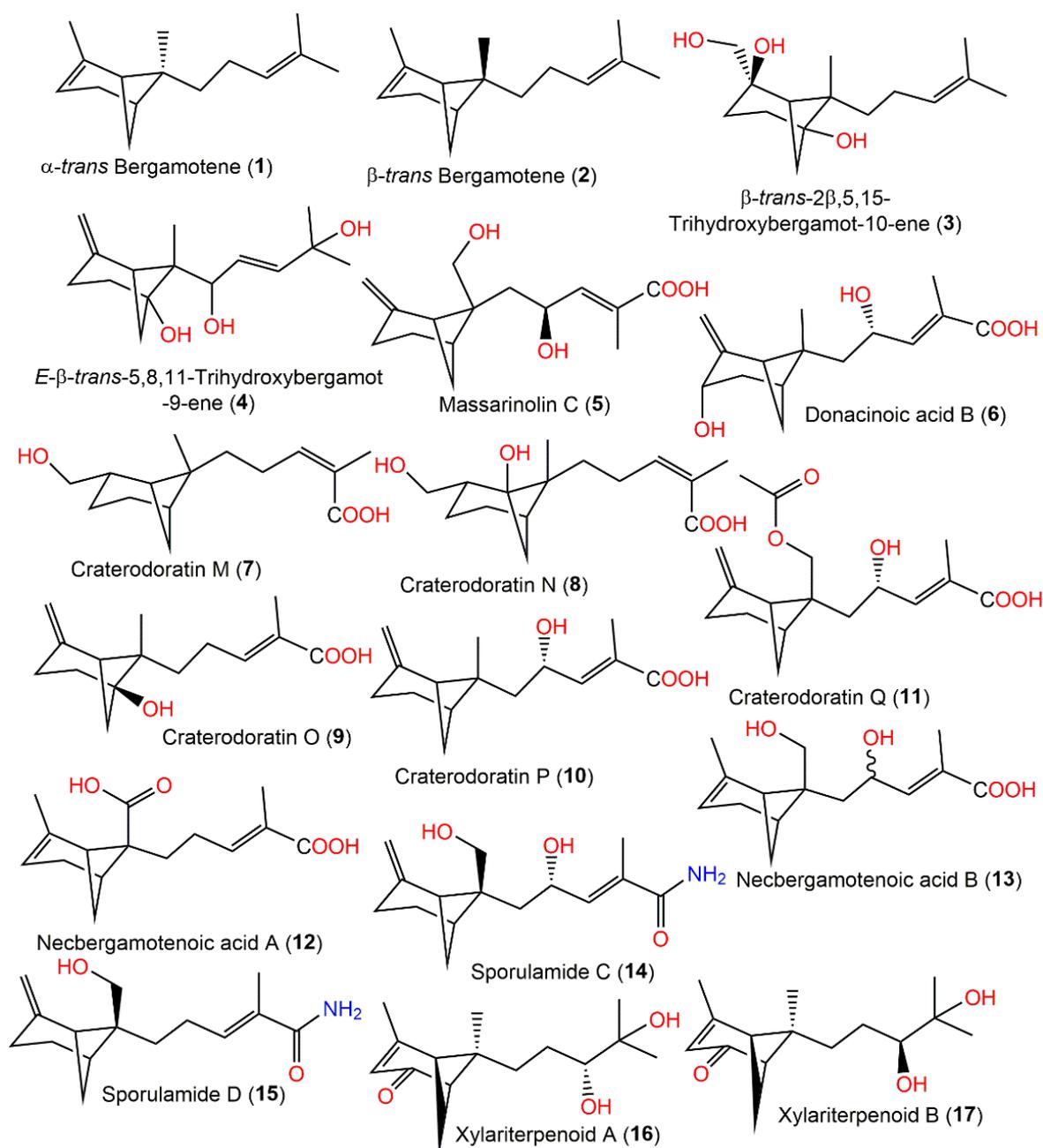
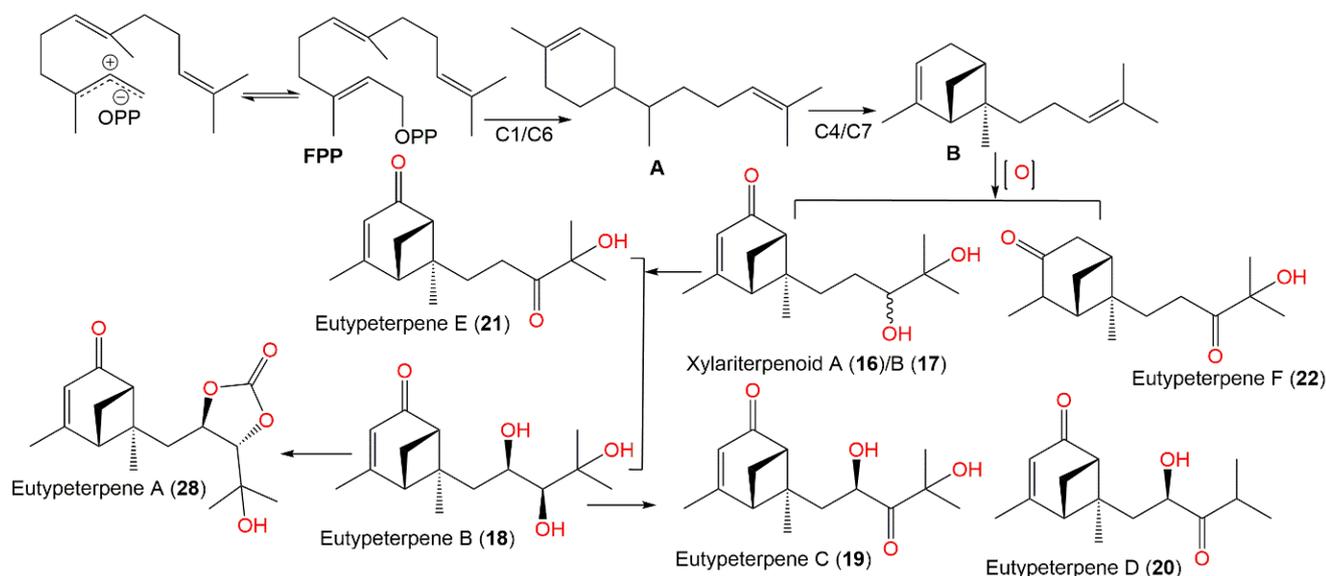


Figure 1. Structures of bicyclic bergamotane sesquiterpenoids (1–17).

Biogenetically, compounds **18–22** are derived from FPP that performs a 1,6-cyclization to produce bisabolane (**A**). The 4,7-cyclization of **A** generates bergamotane (**B**), which further generates **18–22** via diverse oxidation and reduction processes. Additionally, compound **28** is formed from **18** by carbonate incorporation [35] (Scheme 1).

The deep-sea-isolated *Graphostroma* sp. MCCC3A00421 associated with the Atlantic Ocean hydrothermal sulfide deposits biosynthesized new bergamotane sesquiterpenoids: (10*S*)-xylariterpenoid A (**23**), (10*R*)-xylariterpenoid B (**24**), xylariterpenoid E (**25**), xylariterpenoid F (**26**), and xylariterpenoid G (**27**), which were purified using SiO₂/OSD/Sephadex LH-20/RP-18 CC and preparative TLC. They were characterized by extensive spectral data, and their absolute configuration was established by ECD, Cu-K α -single-crystal X-ray diffraction, and modified Mosher's method analyses. Compound **25** is trinor-bergamotane. Compounds **23**, **26**, and **27** revealed moderate inhibition potentials (IC₅₀s of 86, 85, and

85 μM , respectively) of NO production in LPS-stimulated RAW264.7 macrophages compared with aminoguanidine (IC_{50} of 23 μM). It was noted that bergamotane moiety's 10S configuration obviously boosted the activity as in compound **23** (10S, IC_{50} of 85 μM) versus compound **24** (10R, of IC_{50} 230 μM) (Figure 2) [34].



Scheme 1. Biosynthetic pathway of eutypeterpenes A–F (compounds **18–22** and **28**) [35].

3.2. Phytotoxic Activity

Prehelminthosporol (**38**) and dihydroprehelminthosporol (**34**) along with compounds **35–37**, **39**, **40**, and **43** were separated by SiO_2 , flash CC, and preparative TLC from the EtOAc extract of the *Bipolaris* species, which is a *Sorghum halepense* (Johnson grass) pathogen (Figure 3). These metabolites were assessed for their phytotoxic potential towards *Sorghum bicolor* (Sorghum) and *Sorghum halepense* (Johnson grass) in leaf spot assays [36,37]. Compounds **34**, **38**, and **39** produced similar lesions to those caused by the fungus in the field. The lesions appeared as a reddish-brown area (0.3–0.5 cm diameter) surrounded by a black circle with an outer chlorotic zone. Compounds **34** and **38** (concentration of 25 $\mu\text{g}/5 \mu\text{L}$) had comparable toxic effectiveness, while compound **38** maintained its effect at a lower concentration of 2.5 $\mu\text{g}/5 \mu\text{L}$; meanwhile, the other compounds were non-toxic [36,37]. Victoxinine was also toxic to cereals in the order of oats > rye and barley > wheat > sorghum in a root inhibition assay [37]. The phytotoxic influence of compounds **34** and **38–40** versus sorghum, corn, bent-grass, sickle-pod, and morning glory was also assessed in leaf spot assays. Moreover, victoxinine caused a water-soaked translucent appearance with defined irregular necrotic edges. It is worth mentioning that 3-deoxyanthocyanidins are sorghum stress response metabolites (phytoalexins), which were accountable for the red wound response. Compounds **34**, **38**, and **39** were elicitors of a very strong reddening compared with the wounding-produced reddening, but compound **40** did not elicit a sorghum phytoalexin response. In bent grass and corn, compounds **34** and **38–40** produced a light-brown area limited by a chlorotic region, whereas in sickle pod and morning glory, they showed necrotic lesions that extended at high concentrations beyond the under-drop area. It is noteworthy that compound **38** was the most toxic compound versus all tested plants except for the morning glory [37].

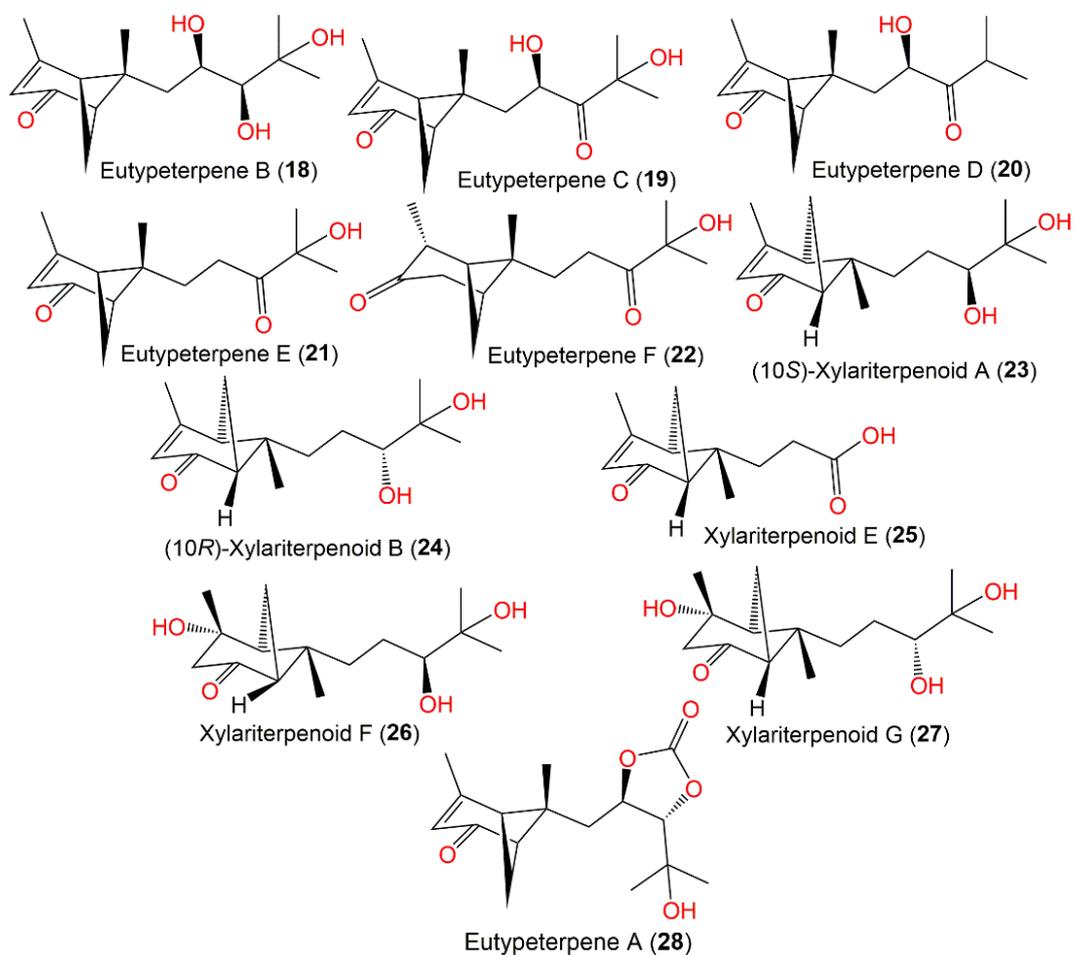


Figure 2. Structures of bicyclic bergamotane sesquiterpenoids (compounds 18–28).

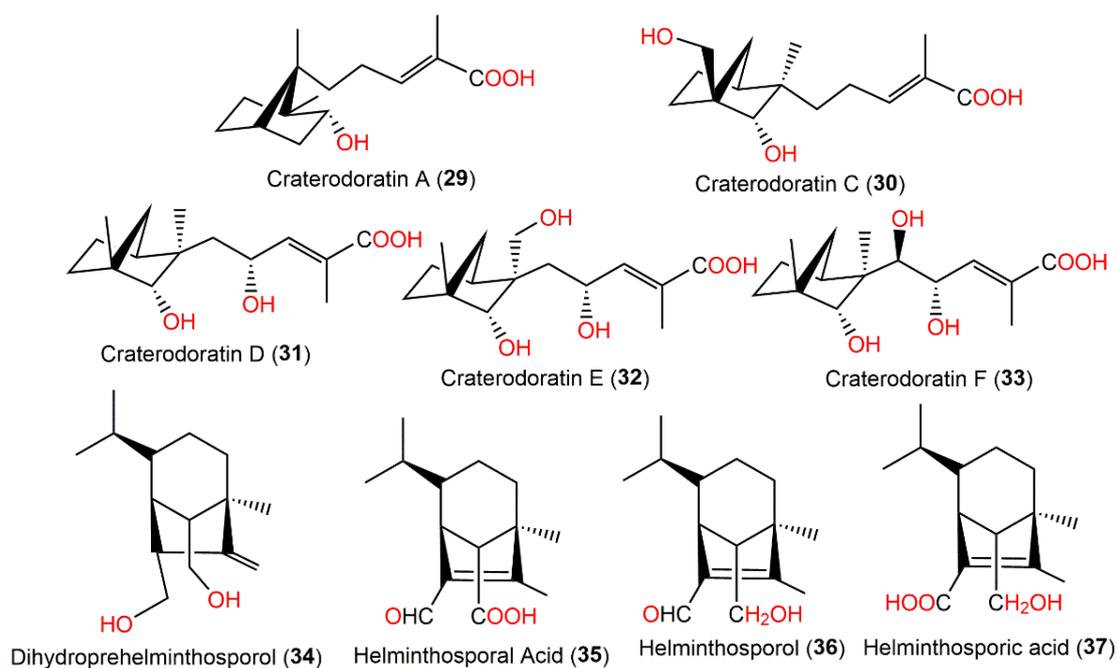


Figure 3. Structures of the bicyclic bergamotane sesquiterpenoids (compounds 29–37).

Helminthosporium victoriae, the causative agent of oats Victoria blight disease yielded phytotoxins, victoxinine (**40**) and victoxinine α -glycerophosphate (**41**), which were separated from its diethyl ether extract using Sephadex LH-20 and SiO₂ CC and detected on the TLC plate by giving a blue color with 5% vanillin:H₂SO₄ [41] (Figure 4). The existence of α -glycerophosphate moiety was established by coupling between the phosphorous and carbon. Compound **40** completely prohibited the root growth of toxin-susceptible and toxin-resistant oats (concentration of 2.5×10^{-4} M); it was ≈ 7500 times more toxic for susceptible plants on a weight basis, while its toxicity for resistant plants was nearly similar, suggesting a role of the victoxinine moiety on the toxicity [38,39,41]. On the other side, compound **41** (concentration of 100 μ g/mL) demonstrated little or no growth inhibition effectiveness on either susceptible or resistant oats [41].

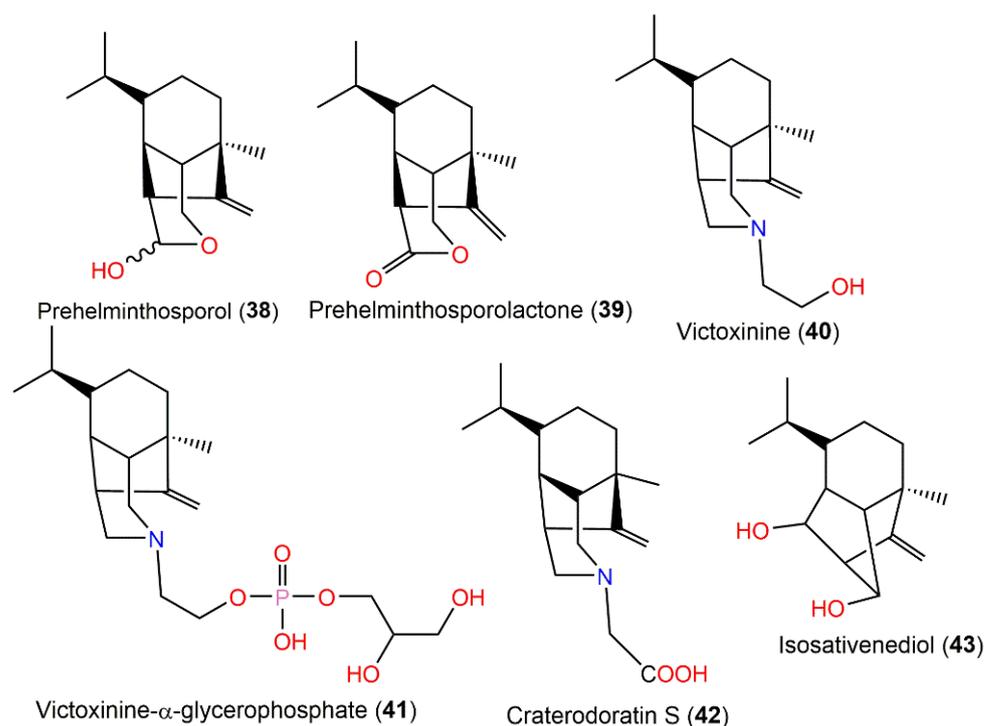


Figure 4. Structures of tricyclic bergamotane sesquiterpenoids (compounds 38–43).

3.3. Anti-HIV Activity

From *Paraconiothyrium brasiliense*, new tricyclic sesquiterpenoids, brasilamides A–D (**45–48**) and the formerly reported pinthunamide (**44**), were separated from the culture's EtOAc extract utilizing SiO₂/Sephadex LH-20 CC and HPLC. Their structures were established using NMR and X-ray analyses (Figure 5). Compounds **45** and **46** are rare metabolites having a 4-oxatricyclo[3.3.1.0^{2,7}]nonane moiety with a tetrahydro-2*H*-pyrone or a tetrahydro-2*H*-pyran linked with bicyclo[3.1.1]heptane ring at C-5 and C-2, whereas compounds **47** and **48** are analogs of **44**, possessing an unprecedented 9-oxatricyclo[4.3.0.0^{4,7}]nonane core.

The differences of the above-mentioned compounds from **44** were the existence of a tetrahydrofuran moiety connected to the bicyclo[3.1.1]heptane unit instead of γ -lactone ring, as well as different C-10 substituents. Compounds **45–48** demonstrated inhibitory effectiveness (EC₅₀s of 108.8, 57.4, and 48.3 μ M, respectively) versus HIV-1 replication in C8166 cells compared with indinavir sulfate (EC₅₀ of 8.2 nM) [43]. Biogenetically, they were derived from the mevalonate/*trans-cis*-farnesol/bisabolene/bergamotane pathway (Scheme 2).

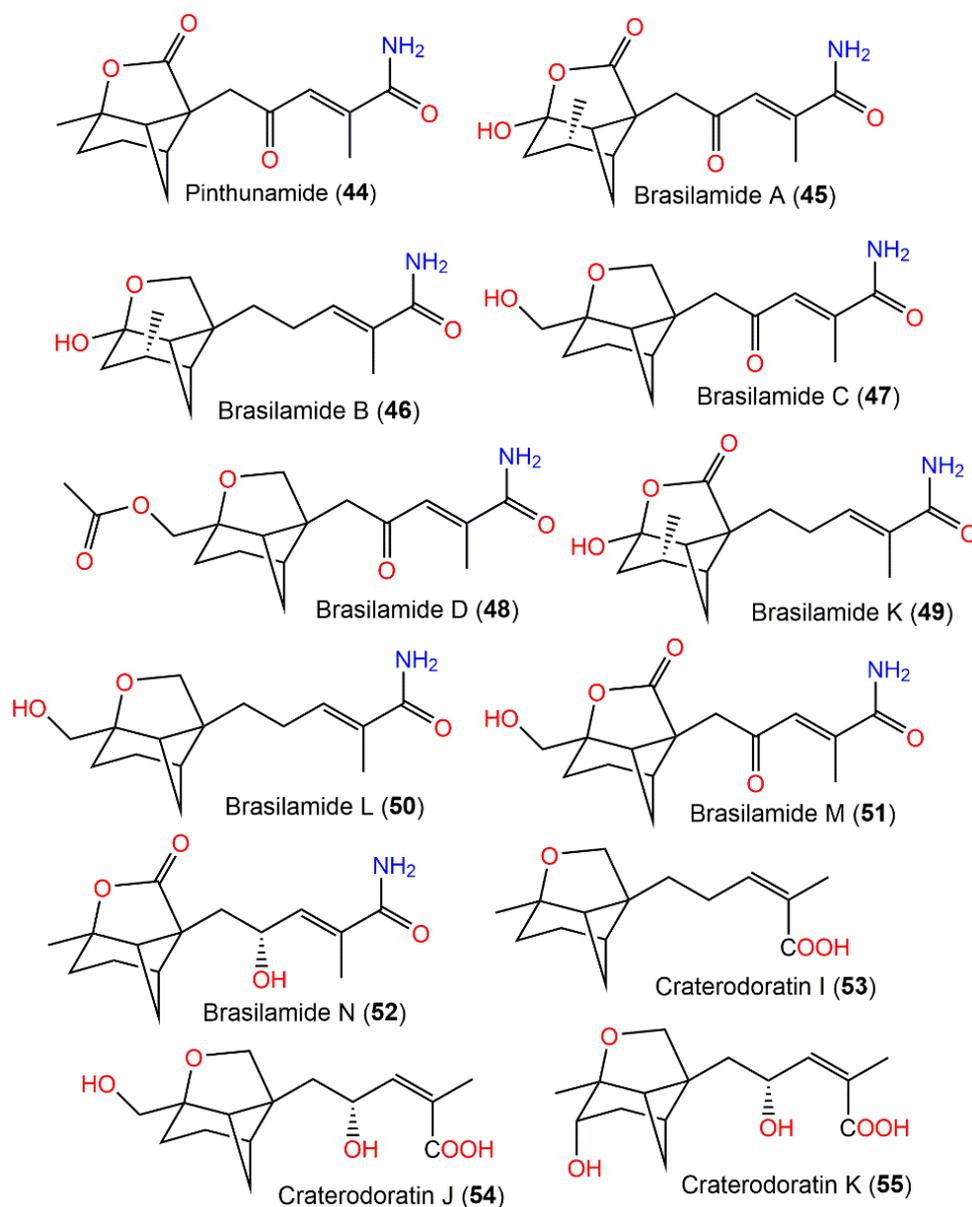


Figure 5. Structures of tricyclic bergamotane sesquiterpenoids (44–55).

3.4. Immunosuppressive Activity

Immunosuppressants are drugs that prohibit body immunity and are principally utilized in organ transplantation to overcome rejection and in auto-immune illnesses [57]. Currently, many immunosuppressive agents act by prohibiting T-cell proliferation; however, there is no new, safe, and efficient immune-suppressive agent that prohibits B-cell proliferation [58].

Dai et al. separated eighteen bergamotane sesquiterpenoids from the EtOAc extract of *Craterellus ordoratus*: craterodoratins A–R (7–11, 29–33, 53, 55, 56, 63–65, and 71) and a new victoxinine derivative, craterodoratin S (42), along with the previously isolated 5, 61, 77, and 88 by SiO₂/RP-18/Sephadex LH-20/preparative HPLC (Figure 6) [30].

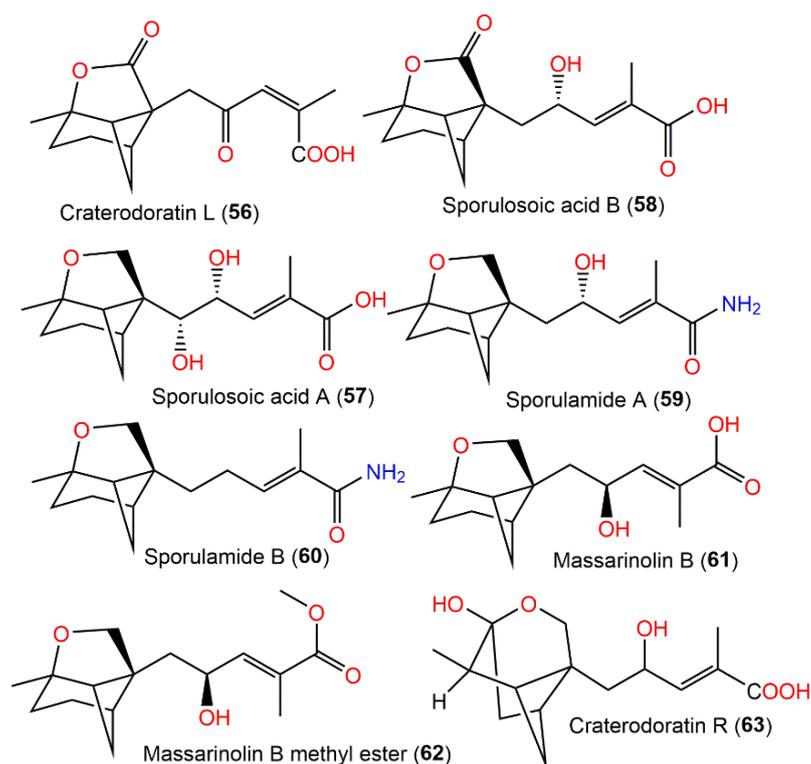


Figure 6. Structures of tricyclic bergamotane sesquiterpenoids (56–63).

Their structures with absolute configurations were established by spectral, X-ray diffraction, and ECD analyses and NMR calculations. Compounds **29** and **71** possess a rare skeleton, where the C-14methyl in **71** showed a further 1,2-migration. On the other hand, compounds **7–11**, **53**, **55**, **56**, and **63–65** belong to β -pinene derivatives that produced **30–33** through an alkyl migration (Figure 7). Compounds **7–10**, **30**, **42**, **55**, **61**, and **88** demonstrated potent inhibitory potential versus LPS-caused B lymphocyte cell proliferation (IC_{50} s ranged from 0.67 to 22.68 μ M) in BALB/c mice compared with cyclosporin A (IC_{50} of 0.47 μ M), where compound **61** (IC_{50} 0.67 μ M) had the most potent effectiveness. Moreover, compounds **11** and **61** possessed inhibition (IC_{50} s of 31.50 and 0.98 μ M, respectively) on T lymphocyte cells proliferation induced by ConA (concanavalin A) compared with cyclosporin A (IC_{50} 0.04 μ M). Structurally, it was noted that the α,β -unsaturated-carboxylic acid unit could be the key functional group for the immunosuppressive potential of these metabolites. Furthermore, compounds **61** and **7–10** with a β -pinene main core had a wider range of bioactivities [30].

3.5. Antimicrobial Activity

From *Podospora decipiens*, two new tetracyclic sesquiterpenoids, decipienolides A (**74**) and B (**75**), were separated from the EtOAc extract by SiO_2 CC and HPLC analyses. They were obtained as a mixture of inseparable epimers, having a 3-hydroxy-2,2-dimethylbutyric acid sidechain as elucidated by an NMR analysis (Figure 8). The **74/75** mixture had an antibacterial influence versus *B. subtilis* (inhibition zone diameter of 9–10 mm, concentration of 200 μ g/disk). Neither of them demonstrated capacity versus *Ascobolus furfuraceus* NRRL6460, *Sordaria fimicola* NRRL6459, and *C. albicans* ATCC90029 [24]. Donacinolides A (**82**) and B (**76**) (concentration of 50 μ g/mL) revealed weak inhibition versus *Salmonella enterica* subsp. *enterica* (inhibition rates of 24.3, 23.9, and 26.2%) in the microdilution assay [32]. Furthermore, there were no observed antibacterial activity for purpurolides B (**83**) and C (**84**) (concentration of 50 μ M) versus *E. coli* ATCC25922, *M. smegmatis* mc2155 ATCC70084, *S. aureus* ATCC25923, and *S. epidermidis* ATCC12228 [47].

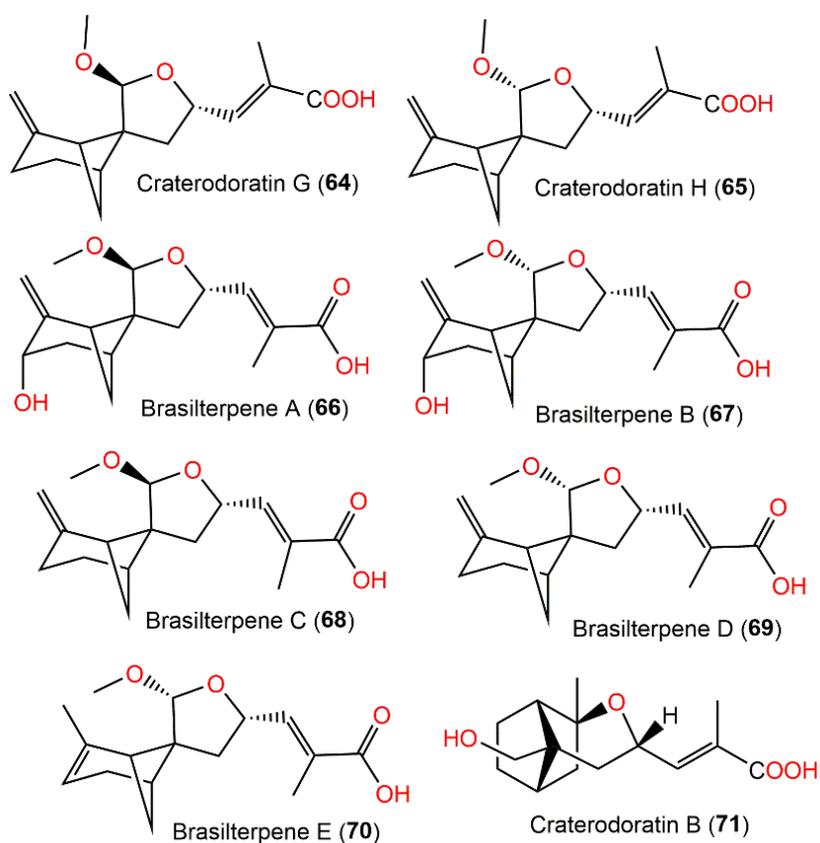


Figure 7. Structures of tricyclic bergamotane sesquiterpenoids (64–71).

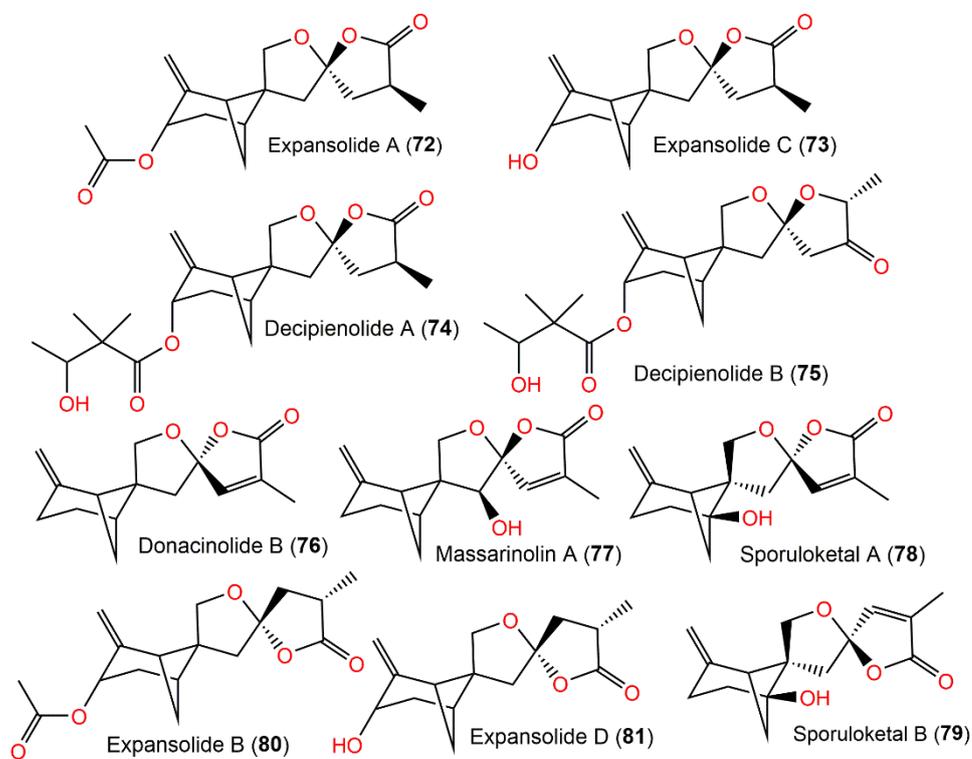


Figure 8. Structures of tetracyclic bergamotane sesquiterpenoids (72–79).

3.6. Pancreatic Lipase Inhibition

Purpurolides B (83) and C (84) are new 6/4/5/5-tetracyclic sesquiterpenoids that were separated from *Penicillium purpurogenum* IMM003 cultures by SiO₂/RP-18/preparative HPLC analysis. The structures and configurations of compounds 83 and 84 were established using spectral and X-ray analyses as well as ECD and GIAO NMR data calculations (Figure 9).

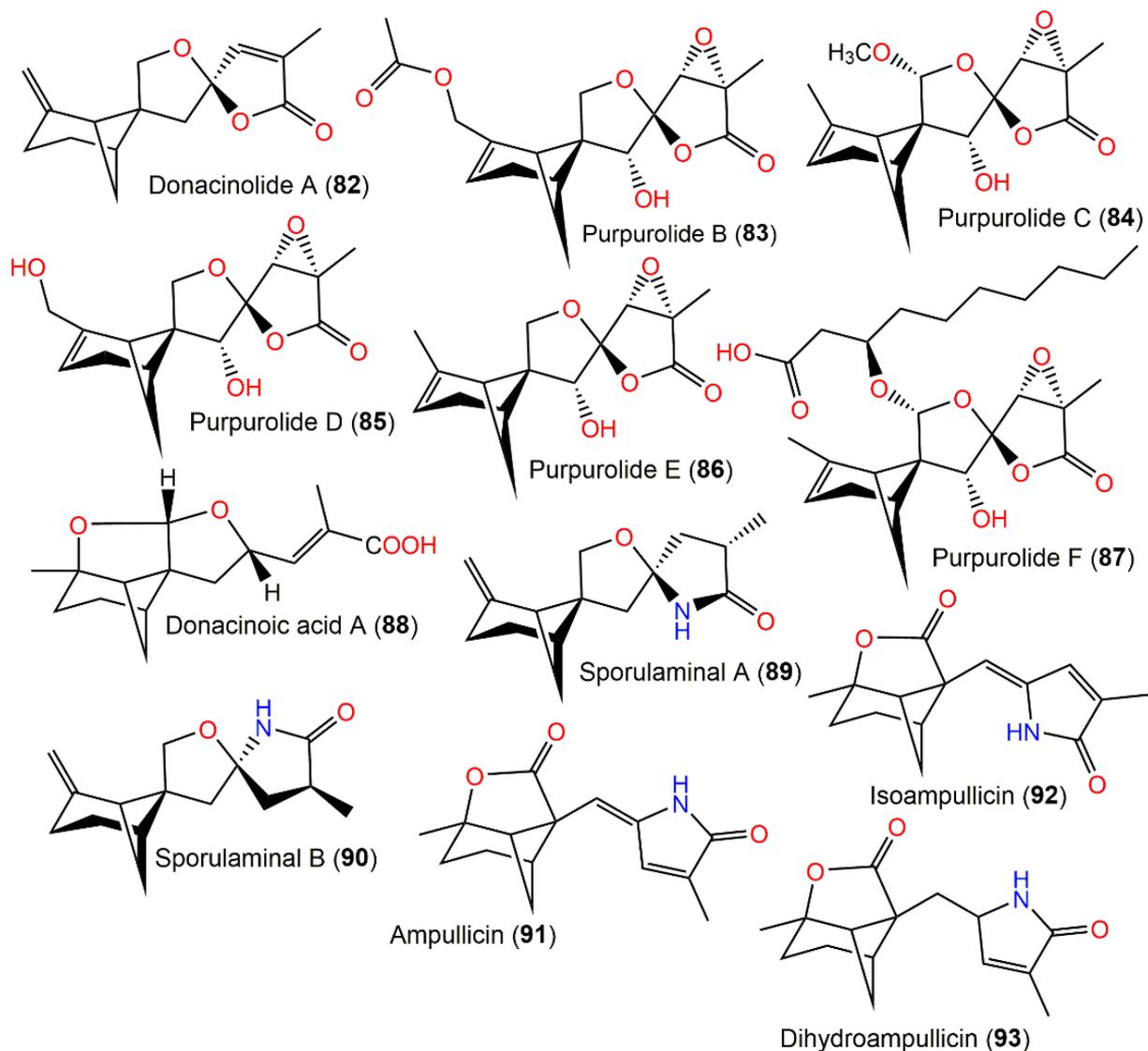
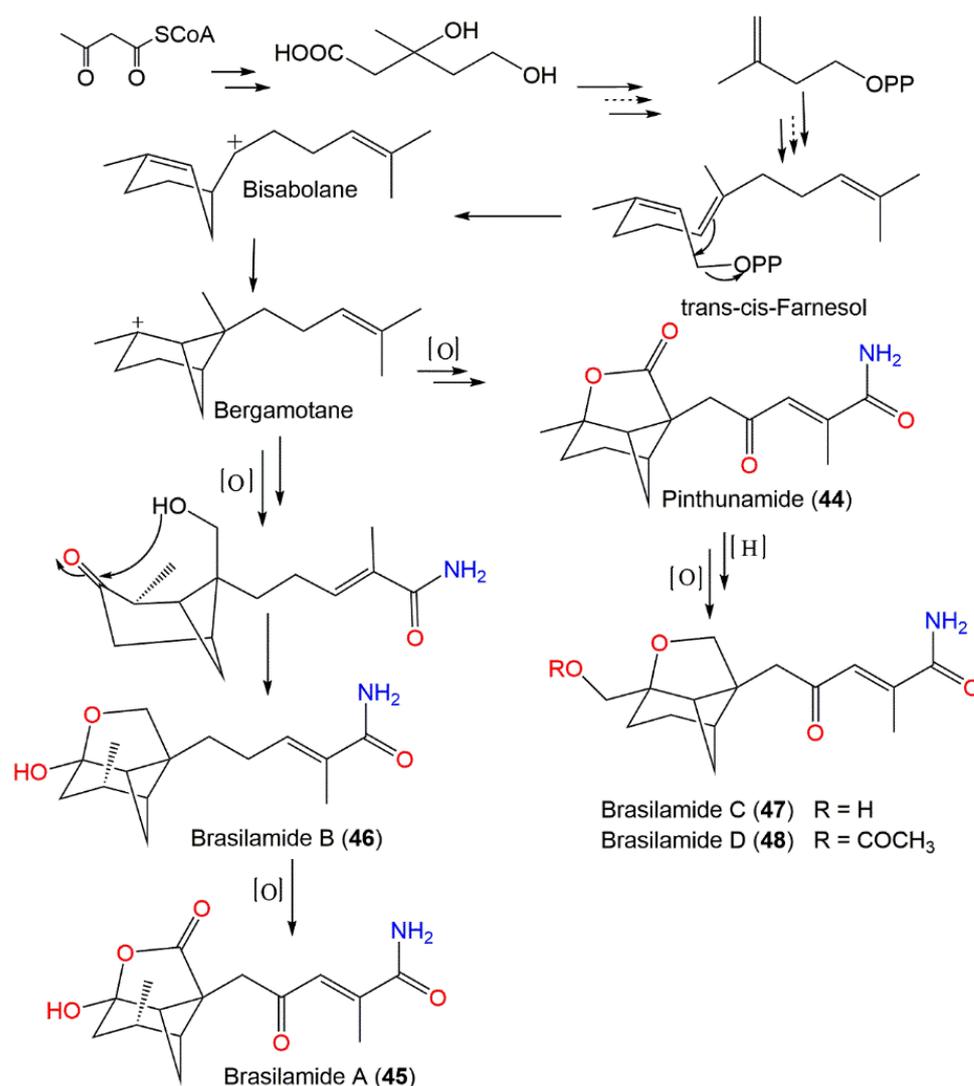


Figure 9. Structures of tetracyclic bergamotane sesquiterpenoids (80–93).

Compounds 83 and 84 demonstrated potent pancreatic lipase inhibition (IC_{50} s of 5.45 and 6.63 μ M, respectively), compared with kaempferol (IC_{50} of 1.50 μ M) [47]. These compounds were possibly biosynthesized via numerous the cyclization and enzyme-catalyzed oxidation of FPP (farnesyl pyrophosphate), leading to four- and six-membered rings and the formation of two five-membered heterocyclic rings (Scheme 3) [47].



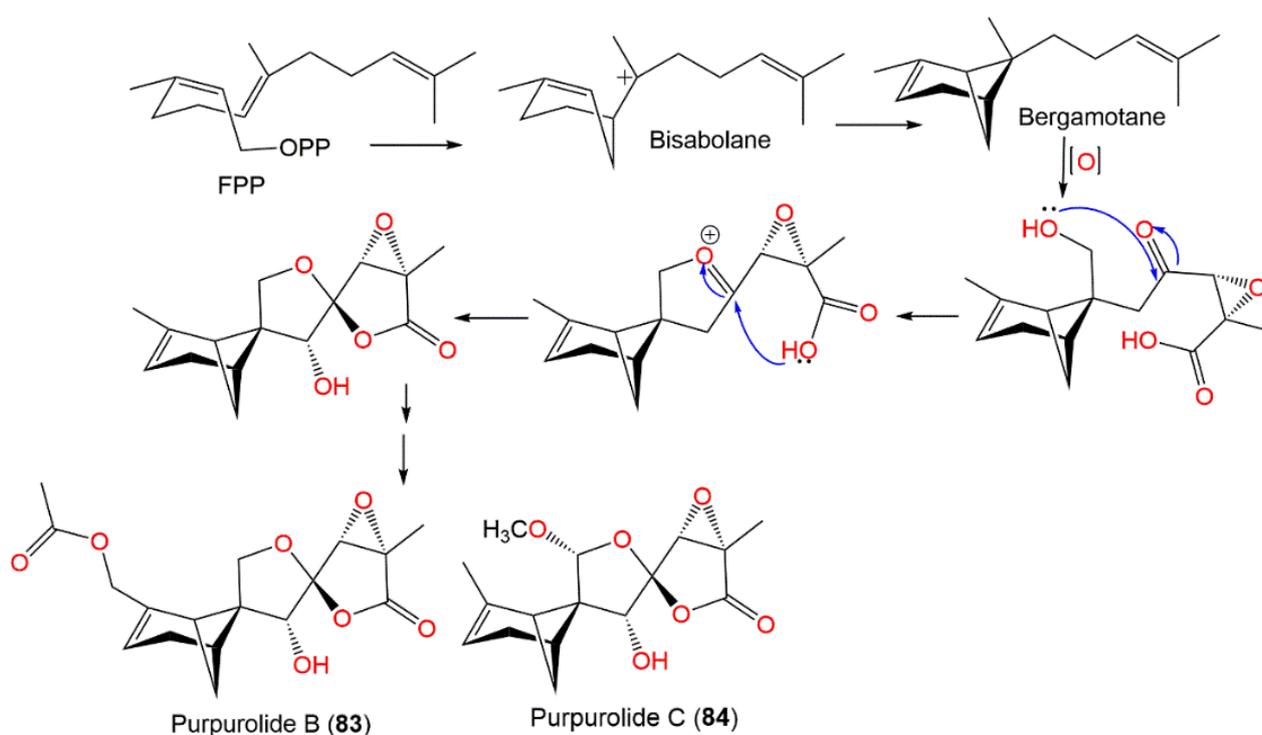
Scheme 2. Biosynthetic pathways of brasilamides A–D (45–48) [43].

Xia et al. separated from *Penicillium purpurogenum* IMM003 purpuroolides D–F (85–87), which are new polyoxygenated 6/4/5/5-tetracyclic bergamotanes, using SiO₂/Sephadex-LH-20/RP-18 CC and preparative HPLC processing [48]. Their elucidation was accomplished using spectral ¹³C NMR calculations coupled with DP⁴⁺ probability and ECD analyses. Compound 87 had potent pancreatic lipase inhibition potential (IC₅₀ of 1.22 μM) compared with kaempferol (IC₅₀ of 1.50 μM) and orlistat (IC₅₀ of 0.75 μM), whereas compounds 85 and 86 (IC₅₀s of 6.50 and 7.88 μM, respectively) were five or six-fold less powerful than 87, revealing that the C-14 hydroxylated decanoic acid moiety increased the potency [48]. Therefore, polyoxygenated bergamotanes could be viable candidates as pancreatic lipase inhibitors for further clinical development [48].

3.7. Antidiabetic Activity

From the deep sea-derived *Paraconiothyrium brasiliense* HDN15-135 EtOAc extract, new bergamotane sesquiterpenoids, brasilterpenes A–E (66–70), featuring an uncommon 6/4/5-tricyclic ring system, were separated by SiO₂/RP-18/Sephadex LH-20/HPLC and assigned by diverse NMR analyses and X-ray diffraction, ECD, and DFT-NMR (density functional theory calculations of nuclear magnetic resonance) data [45]. Their hypoglycemic potential was estimated utilizing β-cell-ablated zebrafish larvae. Compounds 66 and 68 (concentration of 10 μM) remarkably lessened the glucose level down to 449.3 and

420.4 pmol/larva respectively, compared with the β -cell-ablated group (Teton+) (glucose level of 502.8 pmol/larva) and rosiglitazone (glucose level 395.6 pmol/larva) with no toxic influence on zebrafish larvae up to 200 μ M. It was found that compounds **66** and **68** notably minimized free blood glucose in vivo in hyperglycemic zebrafish by suppressing gluconeogenesis and improving insulin sensitivity, which revealed that compound **68** had promising antidiabetic potential [45]. The structure–activity study revealed that the activity may be linked to the C-14 *S*-configuration of compounds **66** and **68**, which represent the main structural difference from **67** and **69**. The existence of C-3-OH may weaken the influence in **68** versus **66**; however, the Δ^2 endocyclic double bond may enhance the potential in **70** versus **69** [45]. Therefore, compound **68** may provide a scaffold for hypoglycemic drug development. Compounds **66–70** are also biosynthesized by the FPP pathway (Scheme 4). The cyclization of FPP via NPP (nerolidyl diphosphate) followed by a bisabolane intermediate yields the bergamotane skeleton. These compounds are created by further oxidation, 9-OH-nucleophilic attack, and methylation processes. Because of the nucleophilic attack direction flexibility during the furan ring formation, compounds **66–69** appeared as C14-epimers in pairs [45] (Scheme 4).



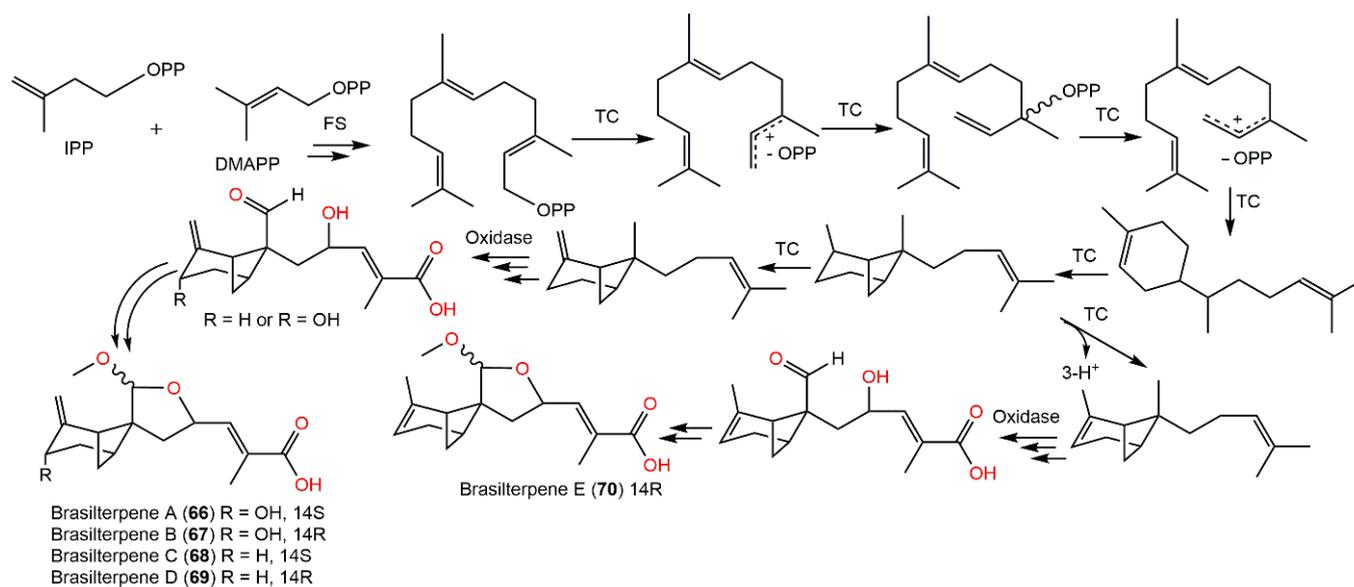
Scheme 3. Biosynthetic pathway of purpurolides B and C (**83** and **84**) [47].

Ying et al. isolated two new derivatives, expansolides C (**73**) and D (**81**), in addition to **72** and **80** from the plant pathogen *Penicillium expansum* ACCC37275 [46]. In an α -glucosidase inhibition assay; the **73/81** epimeric mixture (ratio 2:1) possessed a more powerful effectiveness (IC_{50} of 0.50 mM) compared with acarbose (IC_{50} 1.90 mM), while the **72/80** epimeric mixture possessed no apparent potential. It was assumed that the acetyl group in compounds **72** and **80** impeded their binding with the α -glucosidase, resulting in loss of activity [46].

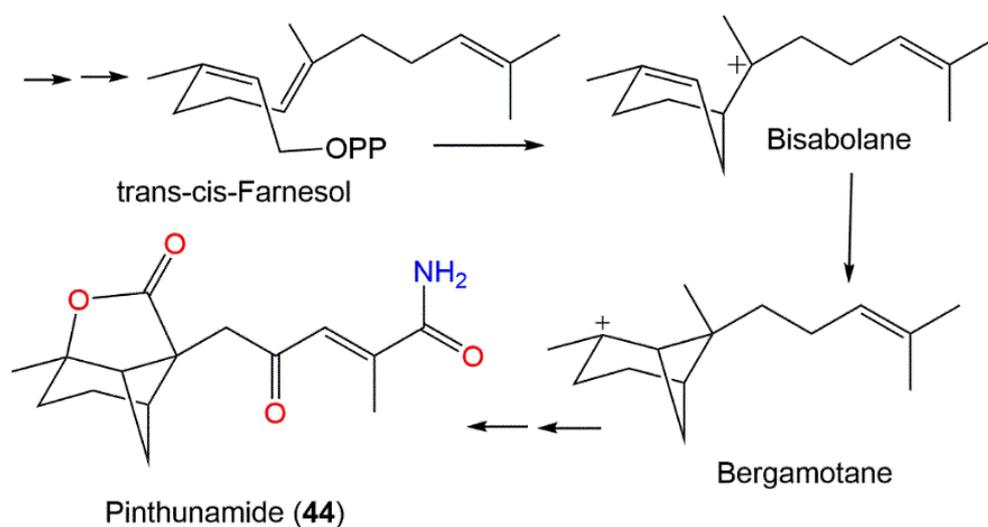
3.8. Plant Growth Regulation

Kimura et al. purified the tricyclic amide sesquiterpenoid pinthunamide (**44**) from the acetone extract of *Ampulliferina* sp. at pH 2.0 utilizing SiO₂ and sephadex LH20 CC processing as well as crystallization from EtOAc extract, which gave positive NH₂OH-HCl-FeCl₃ and KMnO₄ reactions [42]. The compound was assigned by X-ray diffraction and NMR methods. Its plant growth regulation effectiveness was evaluated using a lettuce

seedling assay, where it (dose 300 mg/L) produced a 150% root growth acceleration over the control seedlings (100%) while scarcely influencing the hypocotyl elongation at the tested concentrations [42]. Its structure combined a unique configuration of six-, five-, and four-membered rings that was proposed to be biosynthesized via the mevalonate/*trans-cis*-farnesol/bisabolene/bergamotane pathway (Scheme 5) [42].



Scheme 4. Biosynthetic pathway of brasilterpenes A-E (66–70) [45]. IPP: isopentenyl diphosphate; FS: farnesyl synthase; NPP: nerolidyl diphosphate; TC: terpenyl cyclase; DMAPP: dimethylallyl diphosphate; FPP: farnesyl diphosphate.



Scheme 5. Biosynthesis pathway of pinthunamide (44) [42].

Furthermore, in 1990, Kimura et al. purified another two new plant growth regulators, ampullicin (91) and isoampullicin (92) from *Ampulliferina* sp. No. 27 associated with *Pinus thunbergii* dead tree by SiO₂ CC utilizing benzene:acetone as an eluent [50] (Figure 10). They were stereoisomers that had γ -lactam rings. Additionally, they (doses of 300 and 30 mg/L) were shown to promote lettuce seedling root growth by 200% over the control lettuce seedlings (100%) [50]. In 1993, the same group separated a minor metabolite, dihydroampullicin (93), characterized by the absence of the C8-C9 double bond. The compound promoted a 160% growth rate in lettuce seedling roots (dose of 300 mg/L) compared with the control; however, it had no influence on the hypocotyl growth, indicating that the C8-C9-double bond (C8-C9) was substantial in lettuce seedlings' root growth [51]. Bermejo et al. reported the synthesis of (+)-91 and 92 from (R)-(-)-carvone with a 4.5% overall yield using a stereo-selective 18-step sequence application [59]. The EtOAc extract of *Aspergillus fumigatus* Fresenius separated from leaf litter yielded expansolides A (72) and B (80). They had 2S/4S/6S/7R/9R/11S and 2S/4R/6S/7R/9R/11S, respectively, based on modified Mosher's method. The compounds noticeably prohibited etiolated wheat coleoptiles growth by 100% and 59% at 10⁻³ M and 10⁻⁴ M solution compared with LOGRAN (commercial herbicide) (%inhibition of 80 and 42%) at the same concentrations [26].

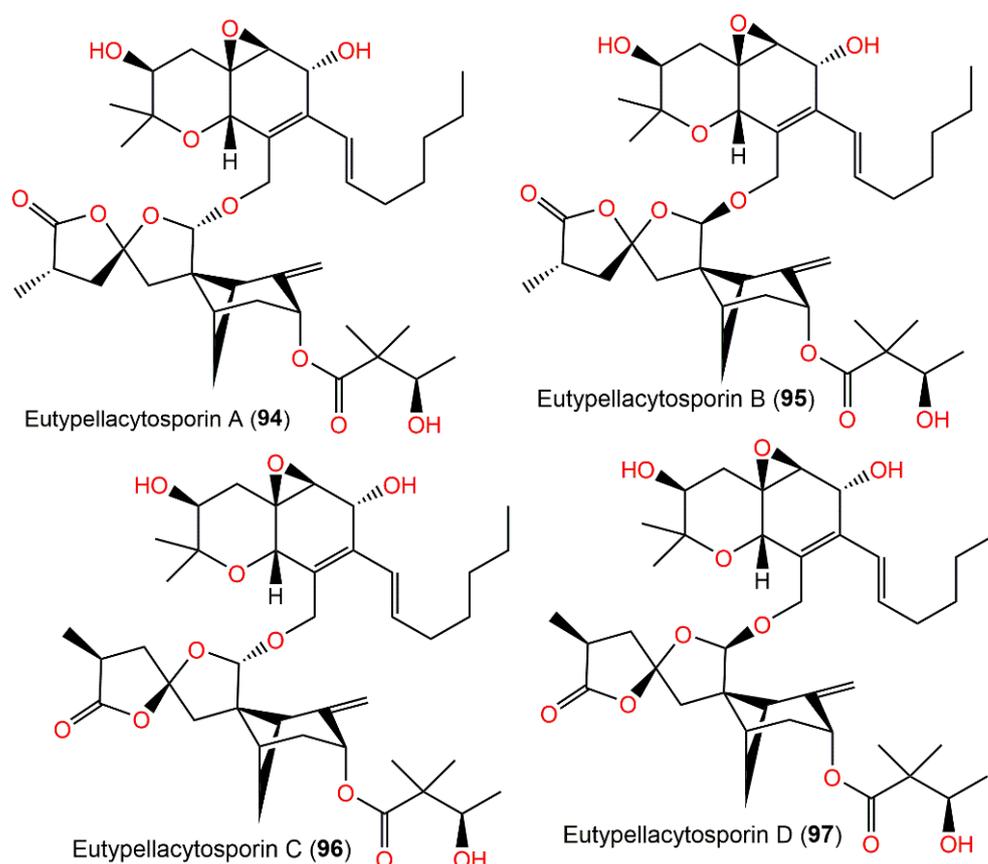


Figure 10. Structures of tetracyclic bergamotane sesquiterpenoids (94–97).

3.9. Cytotoxic Activity

Compounds 3 and 4, which were new β -bergamotane sesquiterpenoids, were separated by SiO₂/RP-18/HPLC from the marine-associated *Aspergillus fumigatus*-YK-7 EtOAc extract. Their antiproliferative effects on the U937 and PC-3 cell lines were measured in vitro in an MTT assay. Compound 4 revealed a weak growth inhibition capacity (IC₅₀ of 84.9 μ M) versus the U937 cell line, while 3 had no activity (IC₅₀ > 100 μ M) compared with doxorubicin hydrochloride (IC₅₀ of 0.021 μ M). On the other sides, both had no effect versus PC-3 cells [29]. Wu et al. reported the separation of two new derivatives, xylariterpenoids

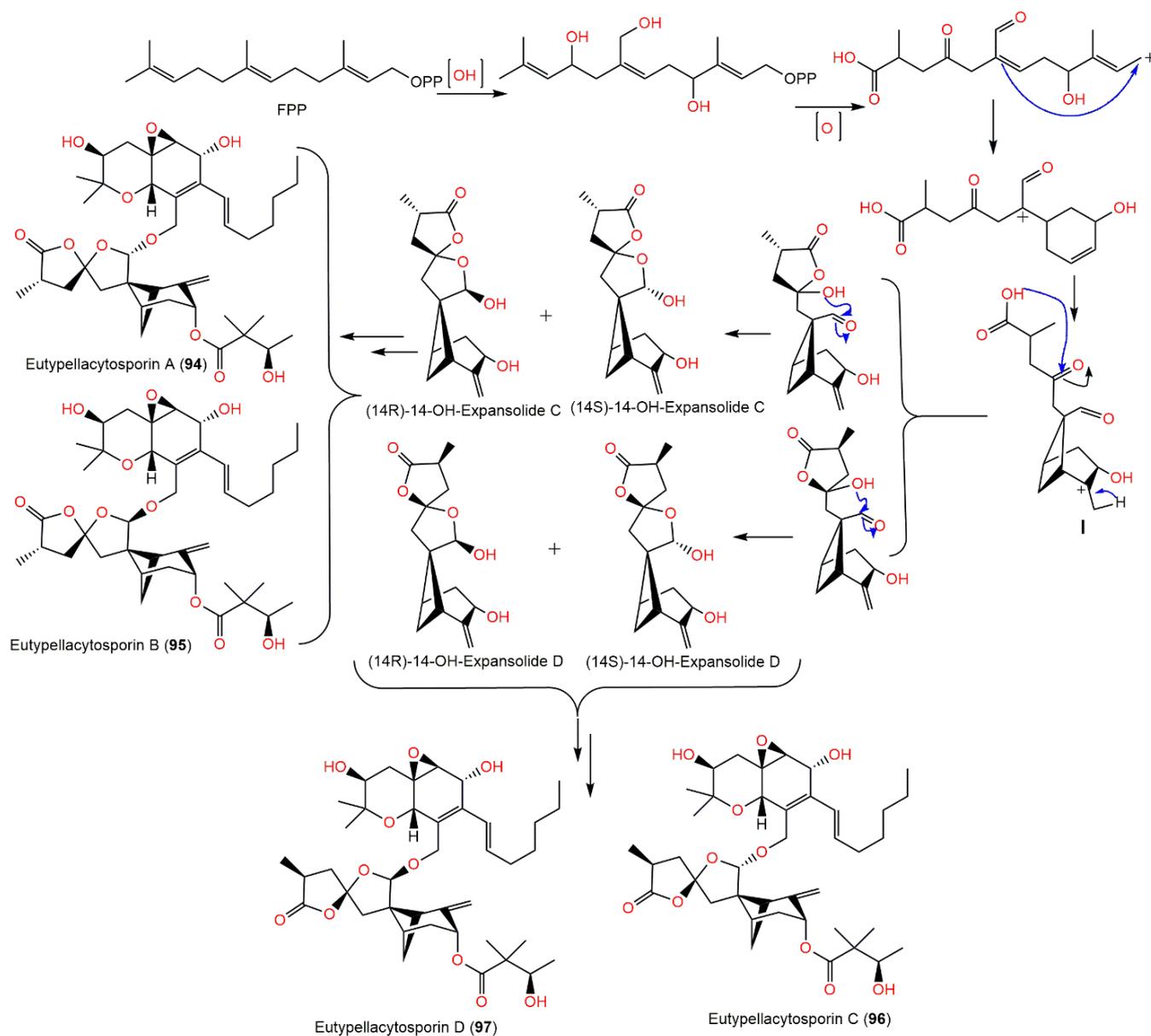
A and B (**16** and **17**), from the EtOAc extract of *Xylariaceae* fungus by Sephadex LH-20/ODS CC and reversed-phase HPLC processing [33]. Their structures and stereo-configuration were proved utilizing NMR and CD methods. They are C-10 epimers having 2S/6S/7S/10R and 2S/6S/7S/10S configurations, respectively. Unfortunately, they ($IC_{50} > 40 \mu M$) exhibited no cytotoxic potential versus HL-60, MCF-7, SMMC-7721, A-549, and SW480 in an MTT assay [33].

From *Paraconiothynium brasiliense* Verkley, new bergamotane sesquiterpenoids brasilamides K-N (**49–52**), featuring 4-oxatricyclo-(3.3.1.0^{2,7})-nonane (as in **49**) and 9-oxatricyclo-(4.3.0.0^{4,7})-nonane (as in **50–52**) skeletons in addition to the formerly reported brasilamides A and C (**45** and **46**), were purified from the fungus scale-up fermentation cultures using SiO₂/Sephadex LH-20/HPLC processing. They were elucidated via NMR analyses and compound **52**'s configuration was assured using modified Mosher's method. Compound **49** is a **45**-hydrogenated analog that has a tetrahydro-2H-pyrone unit linked at C-2 and C-5 to the bicyclo(3.1.1)heptane framework, forming a 4-oxatricyclo-(3.3.1.0^{2,7})-nonane skeleton, whereas compounds **50–52** displayed unusual 9-oxatricyclo-(4.3.0.0^{4,7})-nonane skeletons. Compounds **50** and **51** are hydrogenated and oxygenated derivatives of **46**, respectively, while **52** differed from **46** by having a C-8-carbonyl, C-1-methyl, and C-12 hydroxyl group instead of methylene, oxy-methylene, and ketone carbonyl, respectively. These metabolites (concentration of 50 μM) possessed no potential versus A549, A375, MCF-7, CNE1-LMP1, EC109, MGC, PANC-1, and Hep3B-2 in the MTS assay [44].

Montagnula donacina (edible mushroom) biosynthesized rare tetracyclic bergamotane sesquiterpenoids, donacinolides A (**82**) and B (**76**) and donacinoic acids A (**88**) and B (**6**), which were separated using SiO₂ CC/Sephadex LH-20 CC/HPLC processing and were characterized using spectroscopic data, X-ray diffraction analysis, and computational methods. Compounds **76** and **82** are C9 epimers with a spiroketal moiety having 1S/5S/6S/9R and 1S/5S/6S/9S configurations, respectively, whereas **88** and **6** exhibited α,β -unsaturated carboxylic acid moiety and had 1R/2R/5S/6S/9S/14S and 1R/3S/5R/6R/9S configurations, respectively. These metabolites lacked a marked cytotoxic potential ($IC_{50} > 40 \mu M$) versus HL-60, SW480, A549, SMMC-7721, and MCF-7 [32].

In addition, purpurolides B (**83**) and C (**84**) had no cytotoxicity versus M14, HCT-116, U87, A2780, BGC-823, Bel-7402, and A549 [47], whereas compounds **85–87** (concentration of 50 μM) were inactive versus HCT-116, BGC-823, and Bel-7402 cell lines [48].

The chemical investigation of Arctic fungus *Eutypella* sp. D-1's EtOAc extract yielded new derivatives, eutypellacytosporins A–D (**94–97**), which were established by spectroscopic analysis and modified Mosher's method. Structurally, these metabolites are related to decipienolides and cytosporins. They exhibited (IC_{50} s ranging from 4.9 to 17.1 μM) weak-to-moderate cytotoxic influence versus DU145, SW1990, Huh7, and PANC-1 in the CCK-8 assay, whereas Huh7 and SW1990 cell lines had more sensitivity to **94–97** (IC_{50} s ranging from 4.9 to 8.4 μM). On the other hand, compounds **95** and **97** possessed noticeable potential versus PANC-1 (IC_{50} s of 7.9 and 7.5 μM , respectively) compared with cisplatin (IC_{50} 4.5 μM). The results revealed that the decipienolide moiety was substantial for activity; however, the C-33 configuration did not affect the activity [52]. It was proposed that compounds **94–97** are created from gentisaldehyde precursor with subsequent isoprenyl unit addition, double bond epoxidation, keto group hydrogenation, and an aliphatic chain addition (Scheme 6). The other precursor, the 14-OH of decipienolide A **74** or B **75**, is produced from hydroxylation, allylic oxidation, and cyclization of farnesyl diphosphate to give **I** with a bicycle[3.1.1]heptane. Additionally, (14S)-14-OH-expansolide C, (14R)-14-OH-expansolide C, (14S)-14-OH-expansolide D, and (14R)-14-OH-expansolide D are formed via two steps of reface- and si-face attacks of the OH groups on the ketone and aldehyde groups, respectively. After these steps, compounds **94–97** were produced from the two groups of 14-OH-expansolides C and D through condensation reactions with (S)-3-hydroxy-2,2-dimethylbutanoic acid and cytosporin D, respectively [52].



Scheme 6. Biosynthetic pathway of eutypellacytosporins A–D (94–97) [52].

4. Conclusions

Fungal metabolites are an unparalleled pool for pharmaceutical lead discovery. Sesquiterpenoids involving the bergamotane skeleton have been separated from various sources, including fungi. In the current work, 97 bergamotane sesquiterpenoids were reported from various fungal species derived from different sources, including endophytic (24 compounds), mushroom (21 compounds), sea mud (14 compounds), sea sediment (13 compounds), deep-sea deposit (8 compounds), and sponges (3 compounds) (Figure 11).

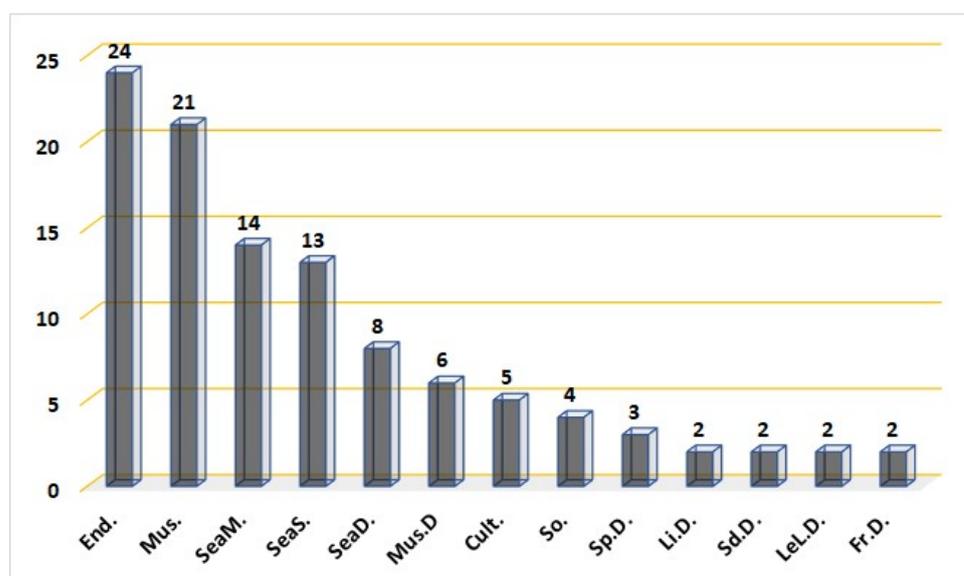


Figure 11. Number of bergamotane sesquiterpenoids reported from fungi derived from various sources. End.: endophytic; Mus.: mushroom; SeaM.: sea mud-derived; SeaS.: sea sediment-derived; SeaD.: sea deposit-derived; Mus.D.: mushroom-derived; Cult.: cultured; So.: soil-derived; Sp.D.: sponge-derived; Li.D.: lichen-derived; Sd.D.: sheep dung-derived; LeL.D.: leaf litter-derived; Fr.D.: fruit-derived.

The majority of compounds have been reported from *Paraconiothyrium* (25 compounds), *Craterellus* (23 compounds), and *Eutypella* (12 compounds) species (Figure 12). Interestingly, many of these metabolites normally occurred as inseparable mixtures. These metabolites were assessed for diverse bio-activities. It is obvious that cytotoxic evaluation accounts for the largest proportion of biological assessments, where they had weak or no effectiveness on the tested cell lines. On the other hand, there are limited reports on their phytotoxic, plant growth regulation, antimicrobial, anti-HIV, cytotoxic, anti-inflammatory, pancreatic lipase inhibition, immunosuppressive, and antidiabetic activities. Therefore, this suggested more potential for trying other types of pharmacological effectiveness. Victoxinine (40) and prehelminthosporolactone (39) displayed potential phytotoxic capacities; therefore, they could be utilized as bioherbicides or as lead metabolites for synthesizing more efficacious phytotoxic compounds against various weeds. Pinthunamide (44), ampullicin (91), isoampullicin (92), and dihydroampullicin (93) were found to selectively promote the root growth. However, the phytotoxic and plant growth promotion potential should be transferred from laboratory experiments into field settings for assessing the environmental influences on these activities. Purpurolide F (87) had potent pancreatic lipase inhibition potential that could be a viable candidate as a pancreatic lipase inhibitor for further clinical development. Massarinolin B (61) had prominent immunosuppressive potential, suggesting further in vivo and mechanistic investigations for the development of this metabolite as an immunosuppressant. In silico studies for the reported metabolites that have not been tested or have had no noticeable effectiveness in the estimated activities could be a possible area of future research. Moreover, synthesis and structural modifications of these metabolites may produce more potential and useful tags of these metabolites through click chemistry, which is a new approach for synthesizing drug-like molecules that can boost the drug discovery process.

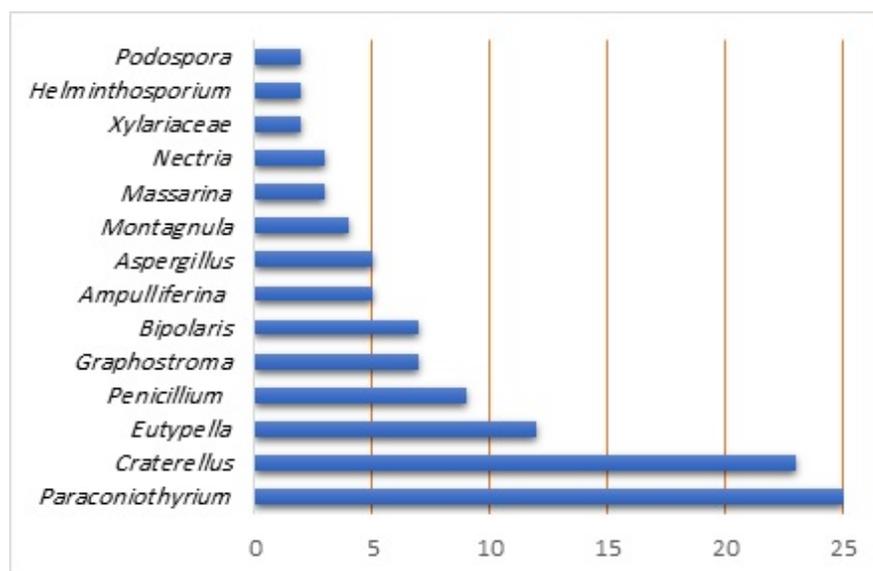


Figure 12. Bergamotane sesquiterpenoids from various fungal species.

Biogenetically, these metabolites are generated from acyclic farnesyl-diphosphate, which undertakes various condensation and rearrangement reactions. This work could be a beneficial reference for researchers studying this class of fungal metabolites. Several strategies, including co-culture, molecular and epigenetic manipulations, OSMAC (one strain many compounds), heterologous gene expression, and inter-species cross-talk approaches could be successively employed to access undescribed natural metabolites from silent biosynthetic pathways. It was found that the selective epigenetic target manipulation utilizing small molecule inhibitors toward DNA methyltransferase and histone deacetylase activities resulted in the enhancement of biosynthetic pathway expression for new secondary metabolite production. Highlighting the biosynthesis of these metabolites in this review could draw the attention of molecular biologists and genetics-interested researchers for isolating genes accountable for the biosynthesis of these interesting metabolites; this could allow for the discovery of the detailed mechanisms of their formation by various enzymes, which could allow for the preparation these metabolites and their analogs by engineering their biosynthetic pathways.

Author Contributions: Conceptualization, S.R.M.I. and G.A.M.; resources, M.T.K., K.A.M. and A.M.O.; discussion of the contents, A.M.O., G.A.M. and S.R.M.I.; writing—original draft, M.T.K., K.A.M., A.M.O., G.A.M. and S.R.M.I.; writing—review and editing, G.A.M. and S.R.M.I. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

5-Aza	5-azacytidine
A2780	Human ovarian cancer cell line
4-MUO	4-methylumbelliferyl oleate
A549	Lung adenocarcinoma epithelial cell line
Bel-7402	Human hepatoma cell line
BGC-823	Human stomach cancer cell line
BuOH	<i>n</i> -Butanol
C8166	Human T-cell leukaemia
CC	Column chromatography
CC ₅₀	The 50% cytotoxic concentration
CCK-8	Cell Counting Kit-8
CHCl ₃	Chloroform
CH ₂ Cl ₂	Dichloromethane
CNE1-LMP1	Stable oncoprotein LMP1 integrated nasopharyngeal carcinoma cell line
DU145	Human prostate carcinoma cell line
EC109	Human esophageal cancer cell line
ED ₅₀	Half-maximal effective concentration
H ₂ SO ₄	Sulfuric acid
Hep3B-2	Human hepatoma carcinoma cell line
HCT-116	Human colon cancer cell line
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
Huh7	Human hepatoma adenocarcinoma cell line
IR	Infrared
HL-60	Human myeloid leukemia cell line
LPS	Lipopolysaccharide
M14	Human melanoma cell line
MCF-7	Human breast cancer cell line
MGC	Human gastric cancer cell line
MTS	(3-(4,5-Dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium inner salt)
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NMR	Nuclear magnetic resonance
NO	Nitric oxide
RP-18	Reversed phase-18
SBHA	Histone deacetylase inhibitor, suberohydroxamic acid
SiO ₂	Silica gel
SMMC-7721	Hepatocellular carcinoma cell line
SW480	Colon cancer cell line
SW1990	Human pancreatic adenocarcinoma cell line
PANC-1	Human pancreatic carcinoma cell line
PC-3	Human prostate cancer cell line
TLC	Thin-layer chromatography
U937	Human leukemic monocyte lymphoma cell line

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