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Research progress on secondary metabolites of polar microorganisms

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Abstract The extreme environment of the polar regions has driven the evolution of unique metabolic mechanisms in microorganisms, resulting in structurally diverse and highly active secondary metabolites. These metabolites are not only crucial for microbial adaptation to extreme conditions, but also exhibit significant potential for applications in medicine, agriculture (e.g., biocontrol), and industry. This review provides a comprehensive overview of 111 secondary metabolites derived from polar microorganisms reported between 2013 and 2025, with a focus on advances in their classification, biological activities, and biosynthetic gene cluster mining techniques. Additionally, it highlights key strategies for advancing future investigations, providing a valuable reference for continued exploration in this promising field. Notably, polar microbial secondary metabolites also hold promising applications in agriculture, particularly in biocontrol, soil health enhancement, and stress-resistant crop development.

Keywords **polar microorganisms, secondary metabolites, biosynthetic gene clusters, genomics technology, bioactivity**

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1 Introduction

The polar regions (Antarctica and the Arctic) are among the most extreme ecosystems on Earth, marked by harsh conditions such as subzero temperatures, high ultraviolet radiation, oligotrophic nutrient levels, and persistent dryness (Cowan and Tow, 2004). Polar microorganisms, as an integral component of these ecosystems, have developed specialized gene regulatory systems, metabolic and biosynthetic pathways, and adaptive survival strategies through long-term evolutionary processes (Bertrand et al., 2014; Convey and Peck, 2019; Lu et al., 2022; Philippot et al., 2024; Siciliano et al., 2014).

These microorganisms produce structurally diverse and highly bioactive secondary metabolites that distinct from those found in other environments. These compounds play essential role in maintaining biodiversity and ecosystem balance, while also offering significant potential for pharmaceutical innovation and serving as valuable resources in agriculture and industry (Kirkinci et al., 2021; Liu et al., 2013; Tian et al., 2017; Wang et al., 2024a).

In recent years, the integration of multi-omics technologies and bioinformatics has greatly advanced the

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study of secondary metabolites from polar microorganisms (Passarini et al., 2024). Genomic mining and bioinformatic tools have enabled identification of numerous biosynthetic gene clusters (BGCs) within microbial genomes, thereby accelerating the discovery of novel secondary metabolites (Blin et al., 2023). This review summarizes the latest research progress in the field of secondary metabolites derived from polar microorganisms. It first categorizes the types of secondary metabolites, evaluates their bioactivities, and then explores current techniques used to identify and analyze BGCs. Finally, the review outlines strategic approaches for future investigations, aiming to provide a theoretical foundation and methodological guidance for ongoing research in this field.

2 Classification of secondary metabolic products of polar microorganisms

Polar environments present extreme conditions, and microorganisms inhabiting these regions must withstand multiple stresses, including low temperatures, intense ultraviolet radiation, high salinity, repeated freeze–thaw cycles, and nutrient scarcity. To survive, they employ diverse strategies at the morphological, membrane, protein stability, osmotic regulation, and gene regulatory levels. These strategies include altering fatty acid unsaturation and membrane lipid composition, preventing ice crystal damage at protein–matrix interfaces, accumulating compatible solutes (e.g., oligosaccharides, glycerol, betaine, and proline), and synthesizing ice-binding proteins, cold-adapted enzymes, autophagy-related factors, and molecular chaperones (Lauritano et al., 2020; Ramasamy et al., 2023). Such mechanisms constitute fundamental survival strategies and are not always directly associated with secondary metabolite production. In polar microorganisms, secondary metabolites primarily serve ecological functions, including mediating chemical competition, signaling, inhibition of competitors, antioxidation, and defense, rather than acting as direct mechanisms of environmental adaptation (Braga et al., 2016; Dong et al., 2024). In particular, these compounds provide competitive advantages in resource-limited habitats by enabling microorganisms to establish ecological niches and resist pathogenic invasion. At the genomic level, microorganisms harbor numerous BGCs for secondary metabolites, many of which remain cryptic or silent under standard laboratory conditions. However, the activation of these silent BGCs does not represent a natural adaptive response to extreme environments; instead, it reflects experimental strategies used by researchers to discover novel compounds. Recent studies have emphasized approaches such as co-cultivation, chemical elicitors, epigenetic modulation, heterologous expression, and metabolic engineering as effective means of activating silent BGCs (Hur et al., 2023). In recent years, researchers have employed both quantitative and qualitative analyses to isolate and identify structurally diverse secondary metabolites from polar microorganisms, including alkaloids, polyketides, and terpenoids. This study summarizes the source distribution of 29 microbial strains, along with the structures and bioactivities of 111 secondary metabolites (Table 1, Figures 1–3).

2.1 Alkaloids

Alkaloid derived from polar microorganisms typically feature nitrogen-containing heterocyclic scaffolds such as pyrrolidine, isoquinoline, or indole. Substituent groups such as halogens and hydroxyl often enhance their cold tolerance and contribute to functions including freeze protection, allelochemical competition, and anti-predation defense (Cushnie et al., 2014; Shang et al., 2018; Srinivasan and Smolke, 2020).

A study combing non-targeted metabolomics and genomics on Antarctic cyanobacteria identified 246 metabolites, including betaine-like compounds, oligosaccharides, and a variety of unidentified metabolites (Baran et al., 2013). Additionally, several classes of alkaloids such as benzodiazepines, quinolines, diketopiperazines, and polycyclic indole have been isolated from *Penicillium* strains obtained from Antarctic surface soil and Arctic permafrost sediments (Antipova et al., 2018). Four known alkaloids–Cyclopenin (**1**), Dehydrocyclopeptine (**2**), Viridicatin (**3**), and Viridicatol (**4**) were purified from Antarctic marine *Penicillium echinulatum* (Teixeira et al., 2021). Furthermore, 2 novel pyrrolizidine alkaloids, Ochracid A and Ochracid B, were identified from the Antarctic soil fungus *Aspergillus ochraceopetaliformis* (Cong et al., 2023).

2.2 Polyketides

Polyketides are biosynthesized by modular polyketide synthases (PKSs) through successive condensations of acetyl and propionyl building blocks. These compounds encompass macrolides, aromatic polyketides and hybrid polyketides, and often possess complex chiral centers and diverse functional groups. They are characterized by pronounced antibacterial activities and versatile immunomodulatory properties (Caulier et al., 2019; Risdian et al., 2019).

A novel polyketide compound with a diphenyl ketone scaffold, pseudophenone A (**7**), was isolated from the Antarctic fungal strain *Pseudogymnoascus* sp. HSX2#-11 (Shi et al., 2021). Extracts from *Streptomyces coeruleofuscus* SCJ have demonstrated significant anticancer activity, with flavonoid phenols constituents displaying strong antioxidant properties (Rammali et al., 2024). Furthermore, 3 new polyketides, ketidocillinones A–C (**8**–**10**) were isolated from an Antarctica sponge-derived fungus *Penicillium* sp. HDN151272. Among them, ketidocillinones B (**9**) and C (**10**) exhibited broad-spectrum antibacterial activities (Shah

Table 1 Diversity of secondary metabolites of polar microorganisms

Types of compounds	Source	Name	Functional role	References
Alkaloids	*Penicillium echinulatum* (Antarctic Peninsula)	Cyclopenin (**1**)	Light stabilizer	(Teixeira et al., 2021)
		Dehydrocyclopeptine (**2**)	Antioxidant	
		Viridicatin (**3**)	-	
		Viridicatol (**4**)	-	
	Streptomyces nitrosporeus (Arctic)	Nitrosporeusines A (**5**)	Antiviral activity	(Yang et al., 2013)
		Nitrosporeusines B (**6**)	-	
	Penicillium (Antarctic)	Communesin B	Antitumor activity	(Kozlovsky et al., 2020)
		Chaetoglobosin A	Antitumor activity	
	Penicillium funiculosum (Antarctic moss-derived fungus)	Penipyridones A−F (**27**–**32**)	Lipid-lowering activity	(Zhou et al., 2016)
Polyketides	*Pseudogymnoascus* sp. HSX2#-11 (Fields Peninsula, Antarctica)	Pseudophenone A (**7**)	Antibacterial activity	(Shi et al., 2021)
	Aspergillus sydowii MS-19 (Fildes Peninsula, Antarctica)	Versicone A (**33**)	Antifungal activity	(Cong et al., 2020)
		Versicone B (**34**)	-	
	Cadophora luteo-olivacea (King George Island, Antarctica)	Spiciferone A (**35**)	Potential ecological role	(Rusman et al., 2018)
		Spiciferol A (**36**)	-	
		Dihydrospiciferone A (**37**)	-	
		Dihydrospiciferol A (**38**)	-	
		Hexaketides (**39**–**47**)	-	
Terpenoids	*Pseudallescheria boydii* (Cold seep sediment)	Pseuboyenes A–J (**48**–**57**)	Antifungal activity	(Ying et al., 2024)
	Streptomyces sp. SCO736 (Antarctic Marine Sediment)	Antartin (**58**)	Anticancer activity	(Kim et al., 2018)
	Penicillium restrictum (Antarctic)	Andrastin A	Antiviral activity	(Kozlovsky et al., 2020)
		Andrastin C	Antitumor activity	
		Phomenone	Anti-inflammatory activity	
Other compounds	*Aspergillus terreus* (Antarctic)	Terreustoxins A–K (**16**–**26**)	Inhibition of cell proliferation	(Feng et al., 2019)
	Streptomyces sp. CMAA 1653 (King George Island, Antarctica)	Actinomycin V (**59**)	Antitumor activity	(Silva et al., 2020)
	Sporothrix sp. SF-7266 (Antarctic Marine)	Citromycin (**60**)	Anticancer activity	(Choi et al., 2022)

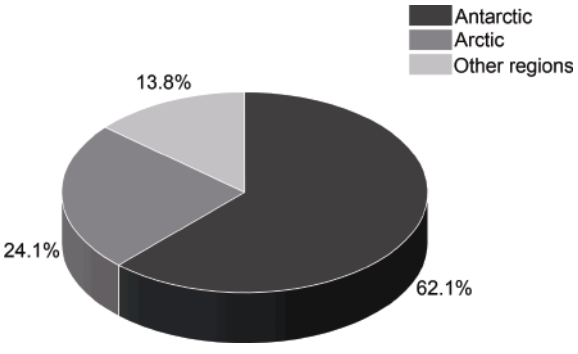


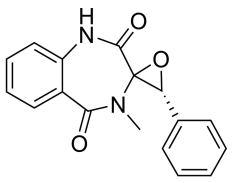
Figure 1 Source distribution of 29 microbial strains.

et al., 2020). In addition, certain polyketide metabolites derived from polar microorganisms have demonstrated notable inhibitory activity against phytopathogenic fungi and bacteria. For example, the ethyl acetate extract of *Streptomyces polyrhachis* strain K6, isolated from Antarctic soil, exhibited strong antifungal effects against *Fusarium oxysporum* f. sp. *cubense*, the causal agent of banana wilt. This result highlights the potential of polyketide-producing polar microbes as environmentally friendly biocontrol agents for agricultural applications (Perez et al., 2024).

2.3 Terpenoids

Terpenoids, derived from the polymerization of isoprene units, encompass a broad range of compounds including monoterpenes, sesquiterpenes, and diterpenes. In polar microorganisms, terpenoids frequently occur as highly oxidized or halogenated structures, shaped by the selective pressures of cold environments. Such structural modifications can enhance their bioactivity, endowing them with potent antioxidant, antiviral, and anti-inflammatory properties (Yamada et al., 2015).

The *Penicillium* strain PR19N-1, isolated from marine sediments in Prydz Bay, Antarctica, produced several chlorinated sesquiterpenoids, along with 3 structurally distinct terpenoids (**11**–**15**) (Wu et al., 2013). Another strain,



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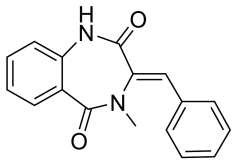

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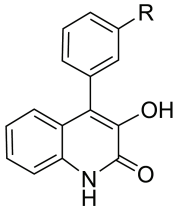
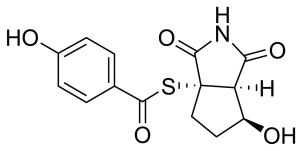


3 R=H
4 R=OH



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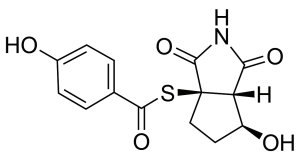

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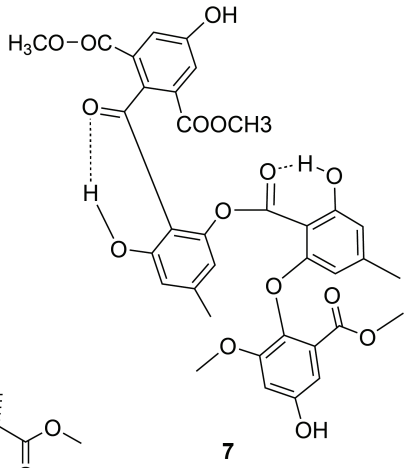

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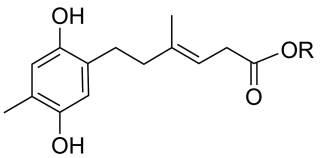
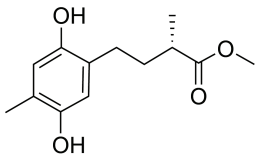


8 R=H
9 R=CH_3



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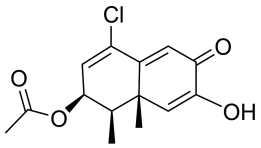

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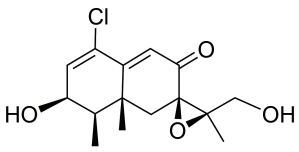

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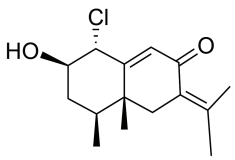

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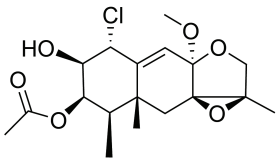

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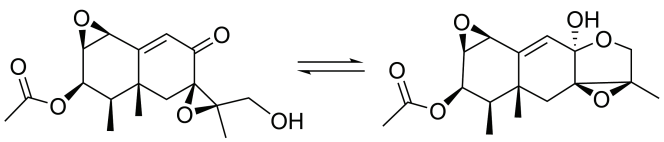

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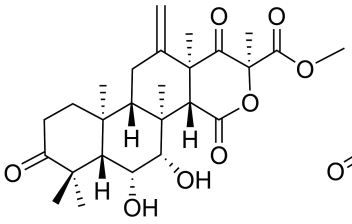

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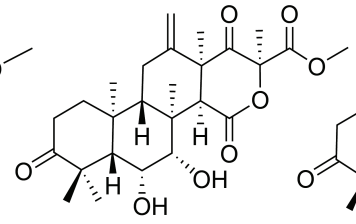

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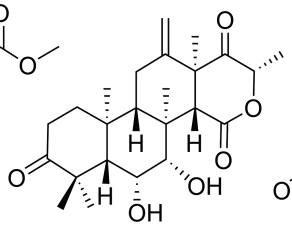

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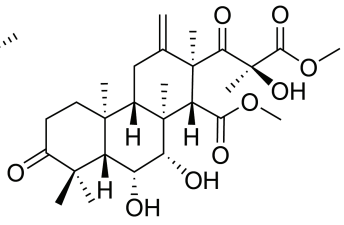

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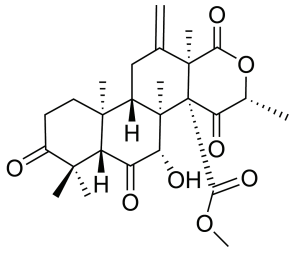

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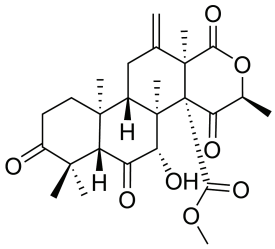

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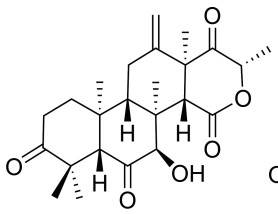

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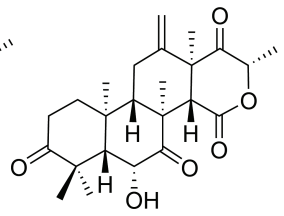

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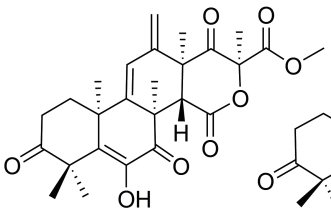

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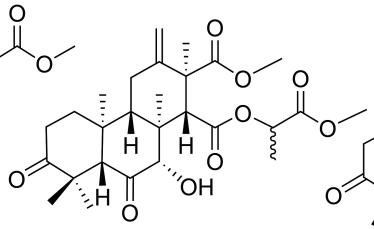

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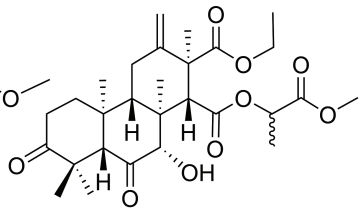

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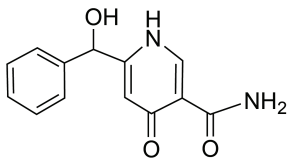

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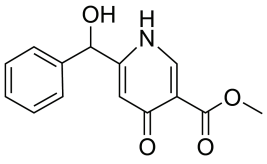

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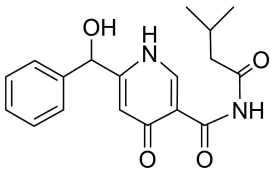

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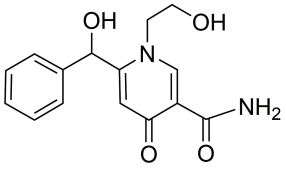

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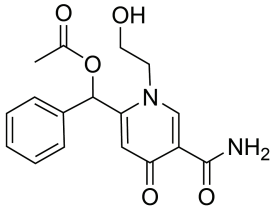

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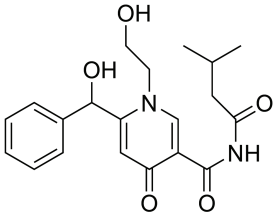

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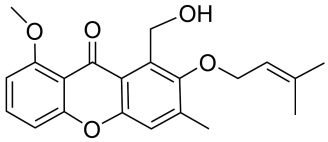

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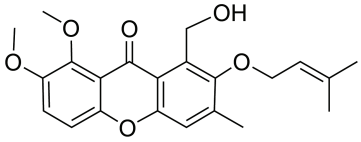

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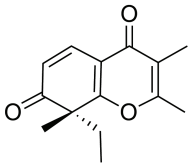

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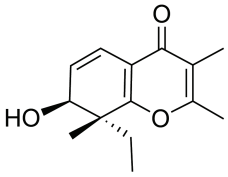

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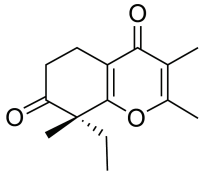

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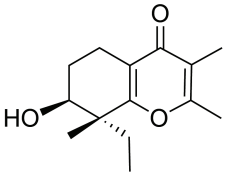

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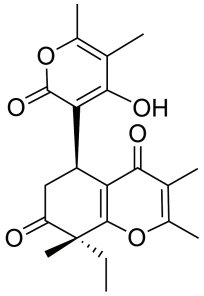

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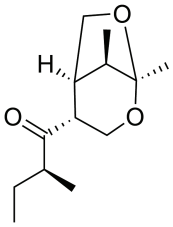

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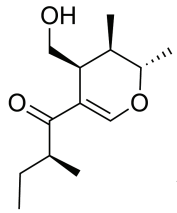

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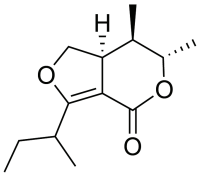

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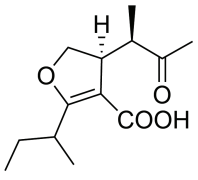

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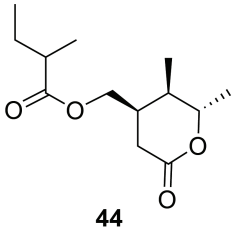

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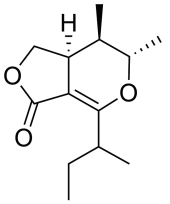

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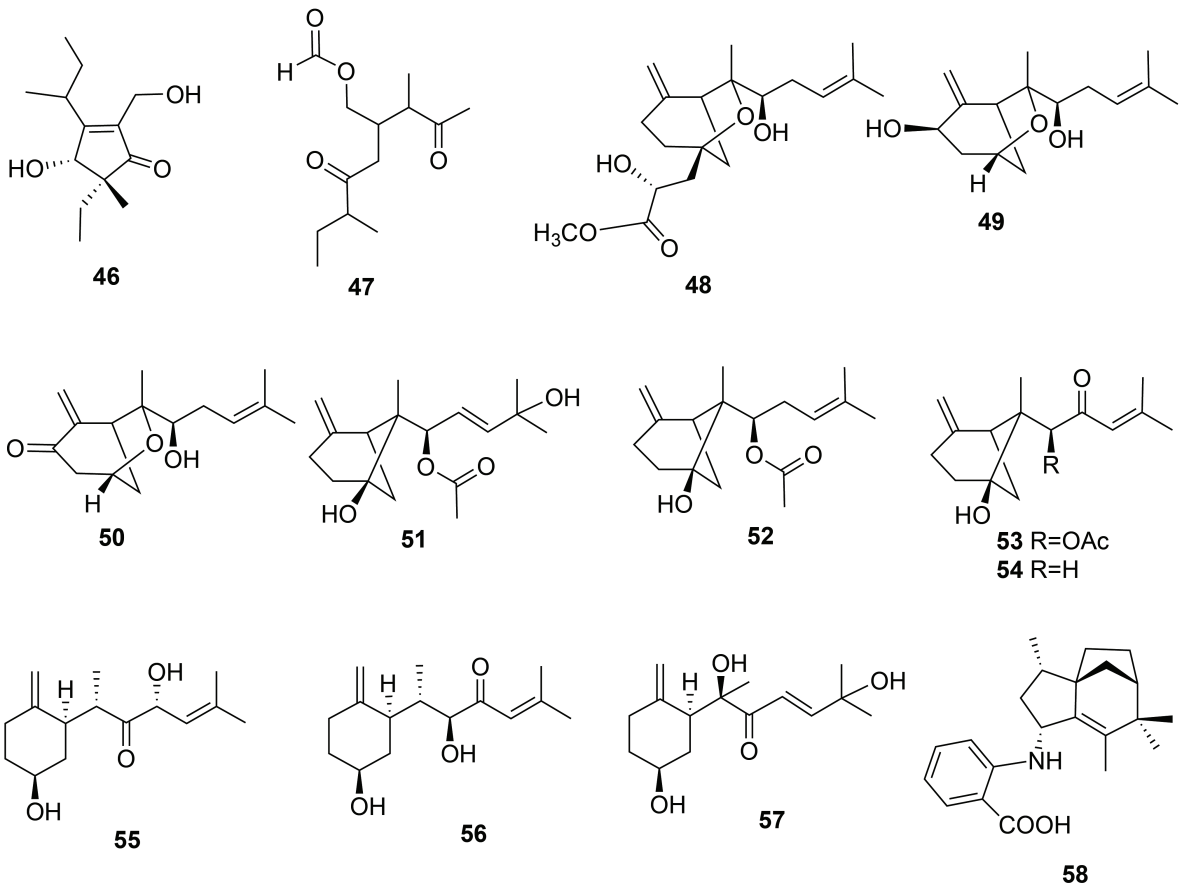


Figure 2 Structure of compound **1**–**58**.

Penicillium restrictum, obtained from Antarctic permafrost, was found to synthesize three notable terpenoid metabolites: andrastins A and C, and phomenone (Kozlovsky et al., 2020). Eleven structurally complex, highly oxidized sesquiterpenoids (**16**–**26**) were identified from Antarctic *Aspergillus terreus* (Feng et al., 2019).

3 Research on the biological activity of secondary metabolites produced by polar microorganisms

Secondary metabolites produced by polar microorganisms exhibit a wide range of potent bioactivities, including antibacterial, anticancer, anti-inflammatory, and antioxidant properties. These compounds act through diverse mechanisms, such as disrupting cell membranes, inhibiting nucleic acid synthesis, or modulating immune signaling pathways, thereby offering significant potential for pharmaceutical and therapeutic development (Baeza et al., 2022; Duan et al., 2025; Lim et al., 2000; Najnin et al., 2016; Ray et al., 1998). Notably, numerous recent studies have demonstrated that secondary metabolites from polar microorganisms exhibit strong inhibitory activity against drug-resistant bacteria, various cancer cell lines, and oxidative stress. Several marine-derived fungi and bacteria isolated from Antarctic and Arctic habitats have demonstrated remarkable antibacterial and anticancer activities, with some metabolites even surpassing commercially available antibiotics and chemotherapeutics in efficacy (Cavalcante et al., 2023; Cavicchioli et al., 2002; Núñez-Pons et al., 2020).

3.1 Antimicrobial activity

Numerous antimicrobial secondary metabolites have been isolated from polar microorganisms in recent years. For example, a phenolic sesquiterpene derivative (**61**) isolated from Arctic fungus *Nectria* sp. B-13 exhibited pronounced cytotoxicity against human cancer cell lines and demonstrated antimicrobial activity against *Escherichia coli*, *Bacillus subtilis*, and *Staphylococcus aureus* (Yu et al., 2019). In another study, 4 Antarctic fungal strains were isolated from soil samples collected near the Pedro Vicente Maldonado Scientific Station in Williamstown, Greenwich Island, Antarctica. Among them, *Penicillium* sp. and *Cryptococcus gilvescens* exhibited potential antibiotic activity against 4 bacterial species: *E. coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, and *S. aureus*

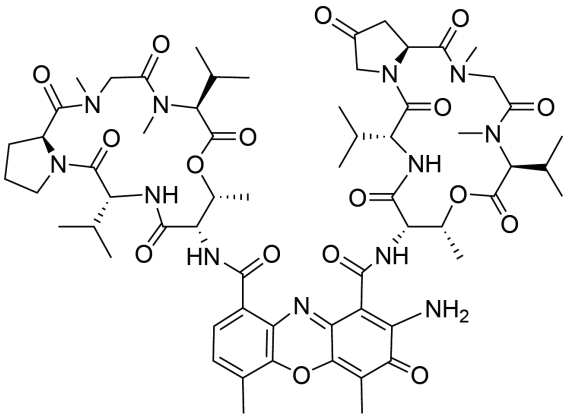
(Ordóñez-Enireb et al., 2022). Furthermore, *Acrostalagmus luteoalbus* CH-6, isolated from Antarctic soil, metabolites such as Luteoalbusin A (**62**) and T988 C (**63**), which displayed significant activity against *Candida albicans* and *Aeromonas salmonicida*. Notably, compound 63 exhibits antimicrobial potency against *A. salmonicida* that was twice as effective as ciprofloxacin, a standard antibiotic control (Shi et al., 2022). Two novel lysine lipids isolated from the Arctic marine bacterium *Lacinutrix* sp. exhibited notable antibacterial and cytotoxic activities. Their bioactivity is primarily attributed to a membrane-disruptive mechanism mediated by their amphipathic structure. These molecules consist of a polar amino acid head group (e.g., ornithine) and a nonpolar iso-branched fatty acid tail, enabling them to integrate into the phospholipid bilayers of target cells. This integration compromises membrane integrity and permeability, ultimately leading to cell lysis or death (Kristoffersen et al., 2021).

3.2 Antitumor activity

Certain polar microbial secondary metabolites have demonstrated potent cytotoxic and antitumor activity. For instance, *Streptomyces coelicolor* MLA-21, isolated from Arctic sediment, produces methyl p-hydroxybenzoate (**64**) and 3-(4-propylphenoxy)-propanoic acid (**65**), both of which exhibit strong cytotoxic effects against human hepatocellular carcinoma cell line HepG-2, human breast cancer cell line MCF-7, and human lung cancer cell line A549 (Xing et al., 2013). Similarly, compounds chrysonin (**66**) and xanthocillin X (**67**) isolated from Antarctic-derived *Penicillium chrysogenum* CCTCC M 2020019, displayed significant cytotoxic activity. While chrysonin (**66**) exhibits α-glucosidase inhibition, xanthocillin X (**67**) demonstrated broad-spectrum activity against Gram-negative pathogens, such as *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, and also notable anticancer effects (Khan et al., 2020). *Nocardiopsis dassonvillei* SCSIO 502F, isolated from Arctic deep-sea sediments, yielded 2 new phenazine alkaloids and 1 new phenoxazine alkaloid, along with several known compounds such as N-(2-hydroxyphenyl)-2-phenazinamine (**68**), endophenazine (**69**), and 2-aminophenoxazin-3-one (**70**). Biological activity evaluations revealed that phenazine derivatives compounds 68 and 69 exhibited notable antitumor effects against osteosarcoma cells, whereas phenoxazine derivatives compounds **70**–**72** demonstrated significant antiallergic activities (Song et al., 2023). In another study, *Streptomyces albidoflavus* (ANT_B131), isolated from near King George Island, was shown to produce several bioactive non-ribosomal peptides, surugamides A–D (**73**–**77**), which exhibited strong antimicrobial and antiproliferative activity against multiple human tumor cell lines (De França et al., 2023). Another example is that actinobacteria isolated from the rhizosphere of Antarctic plants exhibited significant antiproliferative potential, likely mediated by diverse secondary metabolites. Mass spectrometric analysis revealed that *Streptomyces* sp. CMAA 1653 produced actinomycin-type compounds, which belong to the chromopeptide lactone family. These compounds can intercalate into double-stranded DNA and inhibit RNA polymerase activity, thereby blocking transcription and inducing apoptosis in tumor cells. Additionally, the identification of cinerubin B, a member of the anthracycline class structurally related to clinically used anticancer agents such as daunorubicin and doxorubicin, suggests another mode of action involving inhibition of topoisomerase II, generation of reactive oxygen species (ROS), and interference with DNA replication (Silva et al. 2020).

3.3 Antiviral activity

Secondary metabolites from polar microorganisms also show promising antiviral activity. For example, *Phoma muscivora* CPCC 401424, isolated from Arctic moss samples, produces compounds such as Phomarcticone C (**78**), Phomalichenone D (**79**), and (+)-LL-D253c (**80**), which exhibit strong inhibitory antiviral activity against H1N1 influenza virus. Remarkably, compounds 79 and 80 exhibited antiviral effects 7–10 times greater than the control drug ribavirin (Tang et al., 2023). In a separate study, two novel alkaloids, nitrosporeusine A (**81**) and nitrosporeusine B (**82**), isolated from Arctic *Streptomyces nitrosporeus* CQT14-24, showed effective antiviral activity in Madin-Darby canine kidney cells infected with HIN1 (Yang et al., 2013). Moreover, the Antarctic soil-derived strain *Aspergillus ochraceopetaliformis* SCSIO 05702 produced 5 novel α-pyrone sesquiterpene compounds, ochraceopones A–E (**83**–**87**), among which ochraceopone A (**83**) exhibited significant antiviral activity against both H1N1 and H3N2 influenza viruses. Mechanistic studies suggest that these compounds inhibit viral entry by disrupting envelope fusion or blocking interactions between the viral envelope and host cell membranes. Additionally, the presence of multiple hydroxyl groups and epoxide moieties in their structures may facilitate interactions with viral glycoproteins or host cell receptors. The amphipathic nature of these meroterpenoids suggests a membrane-targeting mechanism, which aligns with their observed broad-spectrum antiviral activity (Wang et al., 2016). Four new compounds, Spirochrains A–D (**88**–**91**), were isolated from the Antarctic fungus *Aspergillus ochraceopetaliformis* SCSIO 05702. All 4 exhibited inhibitory activity against respiratory syncytial virus (RSV), with Spirochrain B (**89**) showing the strongest effect. Mechanistic studies revealed that Spirochrain B acts at the early stage of viral infection by blocking RSV adsorption and binding to the RSV G protein, thereby interfering with viral entry into host cells (Cong et al., 2025). Collectively, these findings highlight the therapeutic potential of cold-adapted fungal metabolites and support the continued development of marine-derived natural products as antiviral agents.



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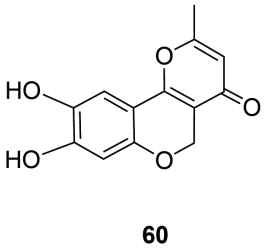

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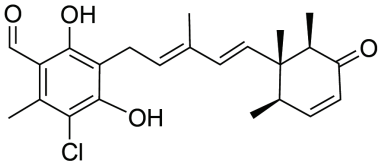

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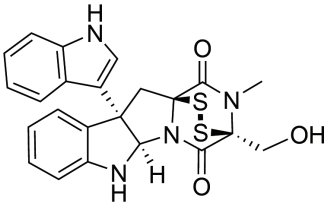

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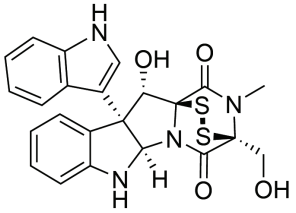

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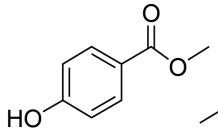

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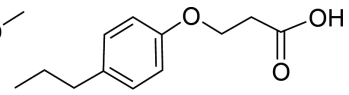

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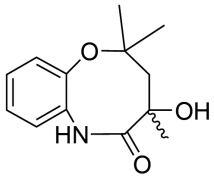

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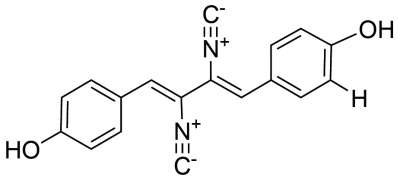

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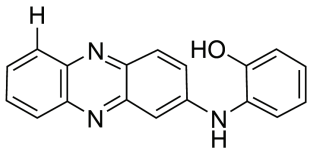

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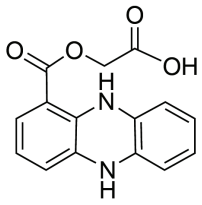

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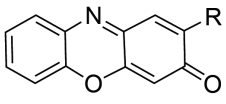

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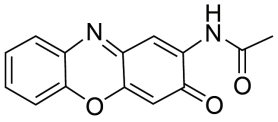

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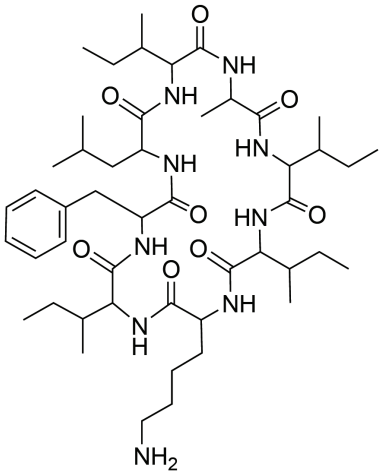

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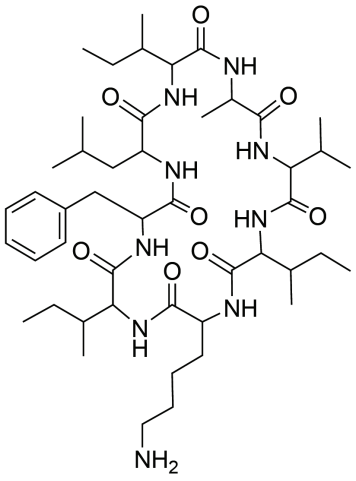

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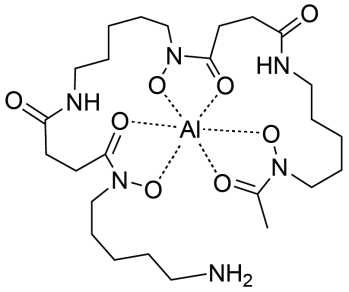

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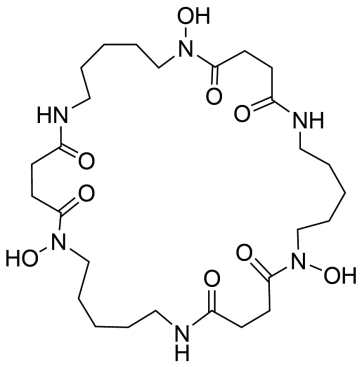

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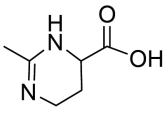

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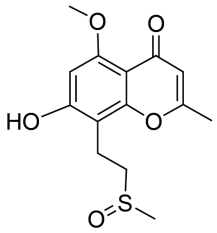

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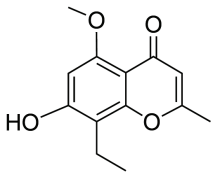

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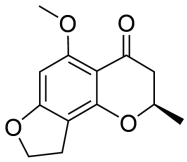

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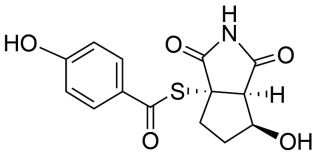

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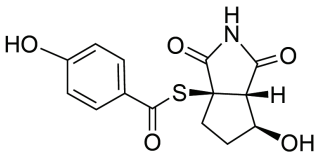

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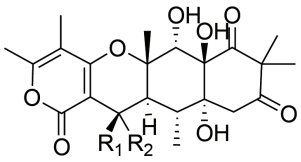

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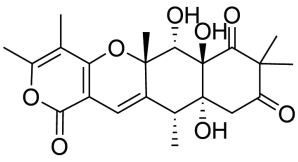
84 R_1=OH R_2=H
85 R_1=H R_2=H



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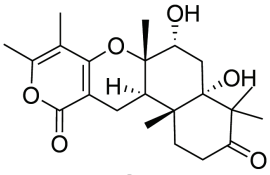

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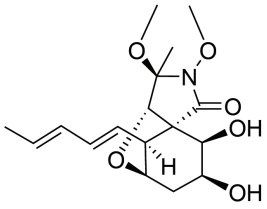

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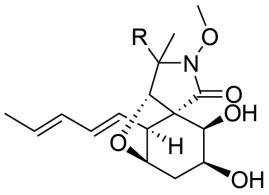

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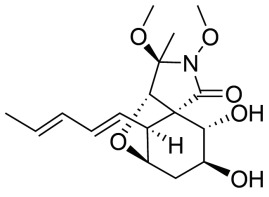

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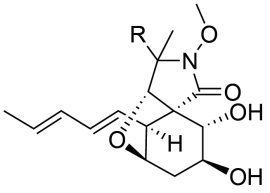

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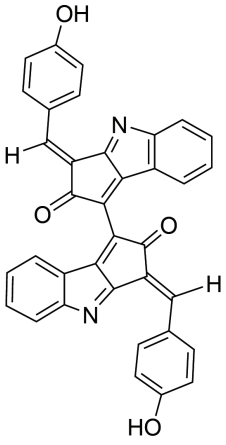

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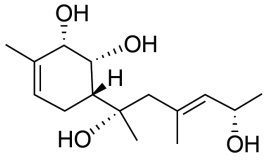

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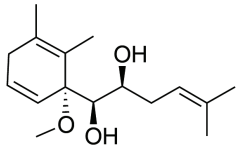

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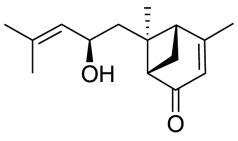

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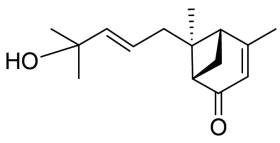

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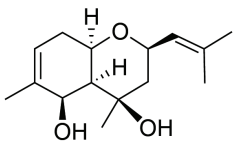

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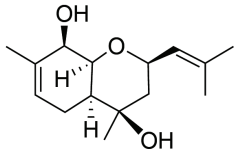

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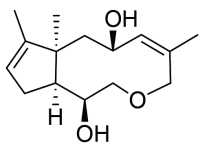

99

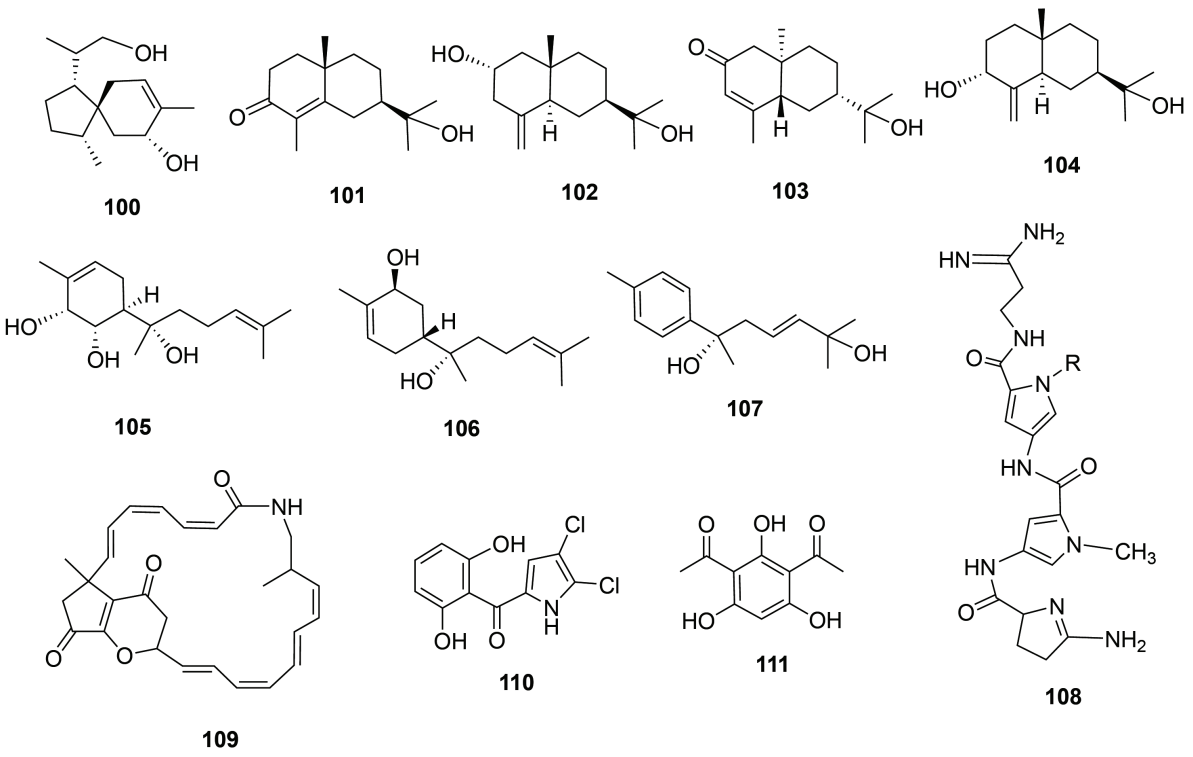

Figure 3 Structure of compound **59**–**111**.

3.4 Other activities

Beyond antimicrobial, antitumor, and antiviral effects, several secondary metabolites from polar microorganisms possess antioxidant and anti-inflammatory properties. For example, scytonemin (**92**), extracted from the Antarctic cyanobacterium *Nostoc commune*, exhibits strong photoprotective and antioxidant capabilities, making it a potential candidate for natural UV-protective skincare formulations (Ručová et al., 2023). In another study, the Arctic-derived *Eutypella* sp. D-1 genetically modified to activate dormant biosynthetic pathways, leading to the production of multiple novel compounds (**93**–**107**) with significant anti-inflammatory effects in the RAW264.7 cell line. The acorane-type compound 100 effectively suppressed nitric oxide production and modulated MAPK and NLRP3/caspase-1 signaling pathways. Additionally, the acorane-type compound 99 alleviated neuroinflammation in a transgenic zebrafish model induced by $CuSO_4$ exposure (Ning et al., 2024).

In addition, Antarctic bacterial endophytes such as *Ewingella* and *Pseudomonas* contribute to plant growth under cold stress by producing secondary metabolites including indole-3-acetic acid, proteases, ammonia, and siderophores. These compounds, along with genes involved in phytohormone biosynthesis, ROS detoxification, and cold shock protein production, enhance crop cold tolerance (Licciardello et al., 2025). These findings underscore the important role of polar microbial secondary metabolites in promoting plant resilience to environmental stresses.

The Antarctic strain *Pseudomonas* sp. ANT_H12B produces mixed-type siderophores at concentrations up to 1.065 mmol·L^{-1}, increasing soil iron bioavailability by approximately 40%. *Bacillus* sp. ANT_WA51 secretes catechol-type siderophores and lipopeptide biosurfactants that enhance soil nutrient mobility (Styczynski et al., 2022). Additionally, *Streptomyces* species isolated from Deception Island possess nitrogen fixation-related genes (e.g., *nifS*), and their secondary metabolites facilitate nitrogen transformation processes (Passarini et al. 2024). These examples highlight the potential of Antarctic microbial secondary metabolites to enhance soil fertility, nutrient cycling, and crop productivity, underscoring their promising applications in sustainable agriculture under cold and nutrient-limited conditions. Such capabilities demonstrate the value of exploiting extremophile-derived metabolites for improving agricultural resilience in challenging environments.

4 BGC mining approaches in polar microorganisms

In the investigation of secondary metabolites from polar microorganisms, numerous compounds produced in extreme environments have been validated for their unique bioactivities and promising application potential (Fu et al., 2024; Kachiprath et al., 2025; Su et al., 2019). BGCs in polar microorganisms are tightly regulated, and many

remain silent under laboratory conditions, limiting the discovery of novel metabolites (Begani et al., 2018; Liu et al., 2021; Touchette et al., 2022). Consequently, identifying and activating silent BGCs has become a critical step in natural product discovery from polar microorganisms.

Recent advances in genomics and bioinformatics have enabled researchers to adopt diverse strategies for functional characterization of BGCs and to improve the discovery rate of novel bioactive compounds (Wolfender et al., 2015).

4.1 Genome mining and bioinformatic tools

Advances in genome sequencing have enabled systematic mining of microbial genomes using bioinformatics platforms such as antiSMASH, which remains the most widely adopted tool for BGC prediction and functional annotation (Tamang et al., 2024).

In one study, antiSMASH analysis of *Bacillus halotolerans* AQ11M9 revealed 10 active genes potentially responsible for antifungal activity against *Candida auris*, including NRPS and PKS enzymes. Several of the corresponding bioactive compounds were subsequently isolated and characterized using liquid chromatography-mass spectrometry (LC/MS) (Borgio et al., 2024).

In another example, a novel *Streptomyces* strain (21So2-11) was isolated from Antarctic soil. Genome mining using antiSMASH identified 28 putative BGCs, including those encoding iron carriers, peptides, terpenoids, NRPS, and PKS, in addition to numerous genes involved in environmental adaptation and ecological functions (Du et al., 2024). These findings highlight the utility of antiSMASH in uncovering the biosynthetic potential of polar microorganisms.

Metagenomics provides direct access to the genetic repertoire of uncultured or yet-to-be-cultured polar microorganisms, allowing exploration of their biosynthetic capacity at the community level (Ejaz et al., 2024; Martínez-Rosales et al., 2012).

In one pioneering study, metagenomic analysis was applied to examine the distribution of BGCs in Arctic microorganisms. A total of 149 ketosynthase (KS) domain operational taxonomic unit (OTU) sequences were identified, approximately 36% of which represented previously uncharacterized gene clusters. Additionally, 179 BGCs were reconstructed from 74 assembled bacterial metagenomes, highlighting the significant biosynthetic potential of the Arctic Ocean planktonic microbiome for novel natural product (Rego et al., 2021).

In another study, over 1,400 BGCs were identified from surface soil samples collected from the Antarctic Mars Oasis. Among them, 55 of these BGCs exhibiting extremely low similarity to known BGCs, suggesting the existence of entirely novel biosynthetic pathways and secondary metabolites. These studies underscore the power of metagenomics as a tool for discovery of novel bioactive compounds from extreme environments (Waschulin et al., 2022).

4.2 Molecular strategies for pathway activation

The CRISPR/Cas9 system is a prokaryotic adaptive immune mechanism that enables bacteria and archaea to recognize and cleave invading bacteriophage DNA with high specificity (Lee et al., 2024). In recent years, CRISPR/Cas9-based genome editing technologies have been extensively developed and applied in various fields, including gene disruption, gene knock-in/knock-out, transcriptional regulation, and activation of silent BGCs (Palma et al., 2024).

In one study, CRISPR/Cas9-mediated gene knockout was employed to inactivate 3 BGCs (*athv10*, *athv15*, and *athv19*) in *Streptomyces venezuelae*, which were identified as responsible for anthelvencin (108) biosynthesis. The absence of anthelvencin production in the knockout mutant strains confirmed the essential role of these clusters in the biosynthetic pathway (Lee et al., 2021).

Additionally, CRISPR interference (CRISPRi) was used to repress the *JadR2* gene, a key repressor of polyketide biosynthetic gene cluster in *Streptomyces*, resulting in the activation of the jadomycin B biosynthetic pathway. These findings demonstrate the potential of CRISPR-based systems in activating silent BGCs and promoting the discovery of novel microbial natural products (Ameruoso et al., 2022). Although most CRISPR-based applications to date have been conducted in model actinomycete species, the conceptual advances and molecular toolkits established in these systems provide valuable technical references for future studies on BGC activation in extremophilic microorganisms.

5 Emerging strategies for activating and utilizing polar microbial secondary metabolites

The exploration of secondary metabolites from polar microorganisms is often hindered by the limited cultivability of native strains and the silent expression of BGCs under laboratory conditions. To overcome these challenges, a wide range of activation strategies has been developed in microbial research, such as heterologous expression, co-culture, flux balance analysis (FBA), promoter engineering, chemical and epigenetic modulation, environmental stress stimulation, and synthetic biology (Genre et al., 2020; Liao et al., 2024; Meunier et al., 2020; Rodríguez-Marconi et al., 2015). While many of these strategies were originally established in model or industrial microorganisms, they provide valuable methodological references and conceptual frameworks that can be adapted to unlock the biosynthetic potential of polar taxa. In this section, 3 representative approaches—heterologous expression, co-culture induction, and FBA—are discussed in detail,

with emphasis on their relevance and potential application to polar microorganisms.

5.1 Heterologous expression

Heterologous expression involves transferring BGCs from native polar strains into genetically tractable model organisms, such as *E. coli*, *Streptomyces coelicolor*, and *Saccharomyces cerevisiae* (Huo et al., 2019). This approach enables the production and functional analysis of secondary metabolites that are otherwise silent or poorly expressed in their native hosts (İncir and Kaplan, 2024; Jiang et al., 2024; Karbalaei et al., 2020; Sugrue et al., 2024; Zhang et al., 2019). For instance, cold-adapted enzymes or PKS pathways derived from Antarctic bacteria have been successfully expressed in mesophilic hosts, allowing for the discovery of novel bioactive compounds under optimized fermentation conditions. A glutathione peroxidase gene (*PsGPx*) from *Pseudoalteromonas* sp. ANT506 was heterologously expressed in *E. coli*, where it retained 45% of its maximum activity at 0 ℃ (Wang et al., 2017). Similarly, expression of the cryptic *wdl* cluster from *Streptomyces* sp. DSS69 led to the identification of a novel compound, weddellamycin (**109**), with antibacterial and antiviral activity (Chen et al., 2024). Heterologous systems also provide better control over regulatory elements, making it easier to manipulate expression levels and optimize yields.

5.2 Co-culture induction

Co-culture strategies simulate microbial interactions in polar environments and can effectively activate silent BGCs. Interspecies signaling, competition, and stress often induce secondary metabolite production that remains undetected in monocultures (Berleman et al., 2006; Cavicchioli 2006; Santamaría et al., 2023; Wong et al., 2019). Studying microbial interactions not only provides insights into how metabolic products respond to environmental stresses but also offers valuable references for understanding the synthetic pathways, regulatory mechanisms, and ecological functions of secondary metabolites in polar microbial interactions (Reed et al., 2013; Tendulkar et al., 2021). For example, co-culturing *Streptomyces coelicolor* with *Myxococcus xanthus* DK1622 activated BGCs related to actinorhodin and siderophore biosynthesis via iron competition, rather than direct contact (Lee et al., 2020). In another study, *Pseudomonas capeferrum* F8 modulated the expression of pyoluteorin (**110**) and DAPG (**111**) in *P. protegens* DTU9.1, enhancing its antibacterial activity (Hansen et al., 2022). These cases highlight co-culture as a powerful tool to unlock cryptic BGCs and expand chemical diversity, offering insights into metabolite regulation under ecological stress.

5.3 Flux balance analysis

While still in its early application to polar microbes, FBA offers a computational framework for simulating metabolic networks and predicting the biosynthetic potential of secondary metabolics (Orth et al., 2010; Sen, 2024). When genome-scale metabolic models (GEMs) are available, FBA enables the identification of key regulatory nodes and optimization of flux toward target compound production. For example, the iRL766 model of *Ashbya gossypii* accurately predicted riboflavin yields under defined conditions, revealing critical roles of β-oxidation and glyoxylate cycle (Ledesma-Amaro et al., 2014). Similarly, the genome-scale metabolic (Salb-GEM) model of *Streptomyces albus* J1074 predicted metabolic targets for enhancing the production of both native (paulomycin, antimycin, and candicidin) and heterologous (thiocoraline and naringenin) compounds, with key nodes located in the shikimate pathway and fatty acid biosynthesis pathway (Kittikunapong et al., 2021). Although the application of FBA in polar species remains limited by the availability of high-quality genome annotations, these examples highlight its potential in rational strain engineering and host selection for secondary metabolite optimization.

Integrating these strategies with genomic mining, metagenomics, and synthetic biology platforms will accelerate the discovery and functional characterization of novel secondary metabolites from polar microorganisms, contributing to their application in pharmaceutical and biotechnological industries.

6 Conclusions and future direction

Polar microorganisms, shaped by long-term adaptation to extreme environments, possess unique genetic and metabolic characteristics that enable them to synthesize structurally diverse and biological active secondary metabolites. These compounds not only contribute to microbial survival in cold ecosystems but also hold significant potential for applications in pharmaceuticals, agriculture, and biotechnology. In recent years, research into the classification, bioactivities, and BGCs of polar microbial secondary metabolites has advanced substantially, progressively enriching our understanding of their diversity and functional potential.

Despite these advancements, the field still faces several challenges. Current studies remain unsystematic, and limitations persist in constructing comprehensive databases for polar microbial BGCs, optimizing bioinformatic algorithms, and developing efficient screening and predictive models (Andersen et al., 2013; Khater et al., 2016). Moreover, the silent expression of many gene clusters under laboratory conditions continues to hinder the discovery and utilization of novel compounds. Looking ahead, the integration of multi-omics technologies, machine learning, synthetic biology, and computational modeling is expected to greatly enhance the discovery and development of polar microbial secondary metabolites.

Advances in genome mining, CRISPR-based activation, metagenomics, and heterologous expression will accelerate the identification of silent BGCs and facilitate the production of bioactive metabolites. Furthermore, interdisciplinary approaches that combine bioinformatics, artificial intelligence, and environmental microbiology will bring new momentum to the field (Chemat et al., 2019; Faruk et al., 2014; Mullowney et al., 2023; Wang et al., 2024b; Zhou and Tang, 2020).

Continued exploration of the metabolic mechanisms and biotechnological applications of polar microbial secondary metabolites will not only deepen our understanding of microbial ecology in cold environments but also provide critical theoretical and practical support for various applied fields. These include ecological conservation, agricultural innovation through the development of microbial biopesticides, plant growth promoters, and cold-adapted biofertilizers. In addition, such research will contribute to biological resource development, sustainable bioprospecting, and innovative drug development.

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