REVIEW ARTICLE

Extreme environments: microbiology leading to specialized metabolites

A.M. Sayed[1] (iD), M.H.A. Hassan[2], H.A. Alhadrami[3,4], H.M. Hassan[1,2], M. Goodfellow[5] and M.E. Rateb[6] (iD)

1 Pharmacognosy Department, Faculty of Pharmacy, Nahda University, Beni-Suef, Egypt
2 Pharmacognosy Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt
3 Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia
4 Special Infectious Agent Unit, King Fahd Medical Research Centre, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia
5 School of Natural and Environmental Sciences, Newcastle University, Newcastle upon Tyne, UK
6 School of Computing, Engineering & Physical Sciences, University of the West of Scotland, Paisley, UK

Summary

The prevalence of multidrug-resistant microbial pathogens due to the continued misuse and overuse of antibiotics in agriculture and medicine is raising the prospect of a return to the preantibiotic days of medicine at the time of diminishing numbers of drug leads. The good news is that an increased understanding of the nature and extent of microbial diversity in natural habitats coupled with the application of new technologies in microbiology and chemistry is opening up new strategies in the search for new specialized products with therapeutic properties. This review explores the premise that harsh environmental conditions in extreme biomes, notably in deserts, permafrost soils and deep-sea sediments select for micro-organisms, especially actinobacteria, cyanobacteria and fungi, with the potential to synthesize new druggable molecules. There is evidence over the past decade that micro-organisms adapted to life in extreme habitats are a rich source of new specialized metabolites. Extreme habitats by their very nature tend to be fragile hence there is a need to conserve those known to be hot-spots of novel gifted micro-organisms needed to drive drug discovery campaigns and innovative biotechnology. This review also provides an overview of microbial-derived molecules and their biological activities focusing on the period from 2010 until 2018, over this time 186 novel structures were isolated from 129 representatives of microbial taxa recovered from extreme habitats.

Introduction

Micro-organisms remain the most promising source of novel specialized (secondary) metabolites as the chemical diversity of these compounds cannot be matched currently by that of chemical libraries (Krug and Müller 2014) hence the continued interest in the search for new natural products (NP) needed to drive innovative biotechnology (Katz and Baltz 2016). In recent times, the quest for novel bioactive molecules, especially those that can be developed to control multidrug-resistant pathogens and treat chronic conditions such as cancer,

dementia and epilepsy has been focused on the isolation, characterization (taxonomy) and dereplication (assignment of isolates to taxonomically meaningful groups) of previously unknown micro-organisms isolated from the extremobiosphere (Bull 2011; Horikoshi and Bull 2011; Bull and Goodfellow 2019).

The extremobiosphere encompasses a broad range of biomes that include hyperarid deserts, deep-sea sediments and permafrost soils, as well as acid and high-temperature environments. Such extreme habitats are characterized by combinations of environmental variables such as anoxia, aridity, extreme temperatures, low concentrations

of organic matter, high salinity and intense irradiation. The search for new bioactive compounds from the extremobiosphere rests on the premise that harsh abiotic conditions select for novel micro-organisms that express new chemistry (Okoro *et al.* 2009). Micro-organisms which live optimally under extreme conditions are considered to be extremophiles (Macelroy 1974), whereas those that can tolerate such conditions are described as being extremotolerant.

It is well known that actinobacteria from the phylum Actinobacteria (*sensu* Goodfellow 2012) have a unique capacity to synthesize new drug leads (Bérdy 2012; Genilloud 2017). These organisms, notably *Streptomyces*, account for around 70% of known antibiotics, including most of those in clinical use (Newman and Cragg 2016). The recent discovery that filamentous actinobacteria with large genomes contain many NP-biosynthetic gene clusters (NP-BGCs) which express for unknown drug leads partly accounts for the increased focus on these micro-organisms in bioprospecting campaigns (Bull and Goodfellow 2019). Especially gifted actinobacteria that have moderate or large genomes (~5·0–7·9 and >8·0 MB respectively) harbour many NP-BGCs (20–19 and >30 respectively) (Baltz 2017, 2019; Nouioui *et al.* 2019) are at the premium in the search for new chemical leads using state-of-art-technologies, such as genome mining (Harvey *et al.* 2015; Goodfellow *et al.* 2018). Other micro-organisms with large genomes laden with NP-BGCs include cyanobacteria (Vijayakumar and Menakha 2015), ktedonobacteria (Zheng *et al.* 2019), myxobacteria (Hoffmann *et al.* 2018) and fungi (Keller *et al.* 2005). Indeed, members of all of these taxa have been highlighted as potential candidates for drug discovery programmes (Dixit and Suseela 2013; Micallef *et al.* 2015; Baltz 2019; Keller 2019). In light of these developments, it clearly makes good sense to focus bioprospecting campaigns on micro-organisms with moderate to large genomes. Another important development is the realization that in some actinobacterial taxa, such as the genera *Amycolatopsis*, *Frankia* and *Micromonospora*, there is a link between the distribution of NP-BGCs and phylogeny (Adamek *et al.* 2018; Carro *et al* 2018a; Nouioui *et al.* 2019). In addition, information drawn from whole-genome sequences is providing fascinating insights into how micro-organisms adapt to extreme habitats, as witnessed by the ability of members of the actinobacterial family Geodermatophilaceae to withstand extreme environmental conditions that prevail in hyperarid desert habitats (Castro *et al.* 2018a, 2018bb).
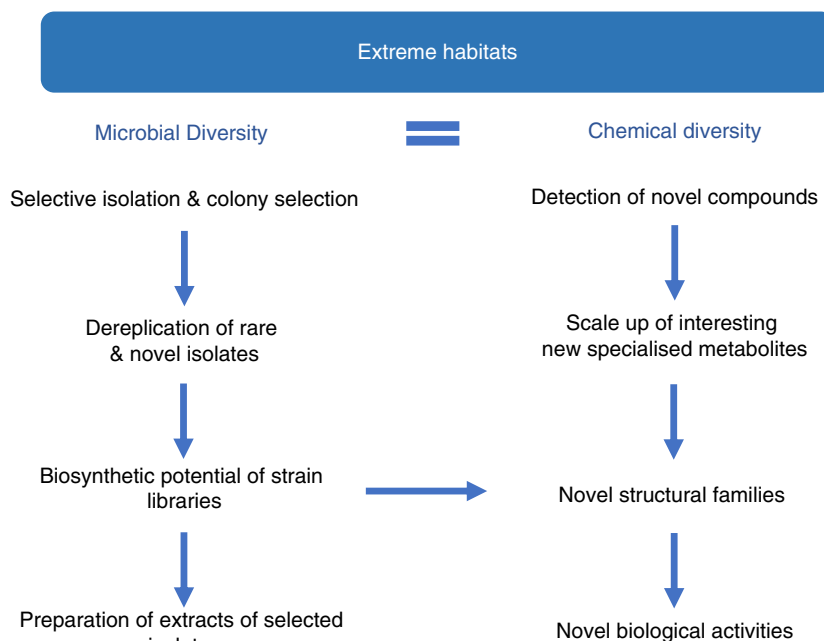
The steps involved in culture-dependent NP discovery pipelines are outlined in Fig. 1. The initial step, the selection of environmental samples is followed by the selective isolation, dereplication and generation of microbial strain libraries. Subsequent steps involve the detection of bioactive compounds from representatives of strain libraries, primary screening of fermentation broths and associated biomass extracts, and chemical dereplication of extracts followed by secondary fermentation using production media. Structural determination of drug leads and biological testing of purified compounds is the final stage in this process. At all of these stages, the application of technological developments and associated bioinformatic procedures in microbiology, molecular biology and chemistry minimizes the costly rediscovery of known compounds which until recently bedevilled bioprospecting campaigns (Baltz 2017).

This review is designed to determine the extent to which micro-organisms, notably actinobacteria, cyanobacteria and fungi isolated from diverse extreme habitats are a rich source of new drug leads of potential value in agriculture, industry and medicine. To this end, we not only discuss the microbiology of specific extreme habitats but also relationships between dereplicated micro-organisms and their ability to synthesize diverse chemical classes of specialized metabolites.

Deserts

Until recently, deserts received little attention from microbiologists even though they account for around 20% of the landmass on the planet (Laity 2009). Desert habitats are challenging for micro-organisms, notably the scarcity of water. Several pilot studies have been carried out to establish the microbial flora of nonpolar deserts (Kurapova *et al.* 2012; Tiwari *et al.* 2015; Ouchari *et al.* 2018) but the most extensive studies of cultivable microbial diversity in desert biomes have been focused on sites in the Atacama Desert in Northern Chile (Bull *et al.* 2016, 2018a; Bull and Goodfellow 2019). The location and abiotic conditions associated with this temperate, nonpolar desert have been the subject of several reviews (Azua-Bustos *et al.* 2012; Cordero *et al.* 2018) and its uniqueness highlighted (Bull *et al.* 2016). Microbial surveys of Atacama Desert soils and regoliths have been focused on the isolation and characterization of micro-organisms, notably actinobacteria, from hyperarid and extreme hyperarid regions where the mean annual rainfall to mean annual evaporation is 0·05 and 0·02% respectively (Houston 2006). These conditions are compounded by other factors such as the presence of inorganic oxidants, very low levels of organic carbon, extreme temperature fluctuations and intense solar radiation; the latter contributes, in a synergistic way, with desiccation to limit the growth and survival of microbial life (Gómez-Silva 2018). Until recently, it was believed that such harsh abiotic conditions made any form of life in the core region of the Atacama Desert virtually impossible (Navarro-González *et al.* 2003). However, it is now known that

```
┌─────────────────────────────────────────────────┐
│                Extreme habitats                   │
└─────────────────────────────────────────────────┘

   Microbial Diversity        ═══        Chemical diversity

Selective isolation & colony selection   Detection of novel compounds

            ↓                                    ↓

    Dereplication of rare              Scale up of interesting
     & novel isolates                new specialised metabolites

            ↓                                    ↓

  Biosynthetic potential of strain  →   Novel structural families
          libraries

            ↓                                    ↓

Preparation of extracts of selected    Novel biological activities
           isolates
```

Figure 1 Culture-dependent bioprospecting strategy (modified from Goodfellow and Fiedler 2010). [Colour figure can be viewed at wileyonlinelibrary.com]

different groups of micro-organisms have adapted to the extreme environmental conditions that prevail in the desert (Schulze-Makuch *et al.* 2018), so much so that a highly unusual rain event in the hyperarid core of the desert led to the decimation of surface microbial communities (Azua-Bustos *et al.* 2018).

Actinobacteria

In recent times innumerable filamentous actinobacteria have been isolated from desert soils and assigned not only to the ubiquitous genus *Streptomyces* but also to rare and poorly studied taxa, such as the genera *Actinomadura, Amycolatopsis, Nocardiopsis, Nonomuraea, Saccharopolyspora* and *Saccharothrix* (Okoro *et al.* 2009; Goodfellow *et al.* 2018). The application of cutting edge taxonomic and screening methods, especially those based on whole-genome sequence data; show that such filamentous actinobacteria are a significant source of novel specialized metabolites (Bull *et al.* 2016; Carro *et al.* 2018a; Carro *et al.* 2018b). In this context, especially gifted isolates from Atacama Desert habitats have been classified as novel species of *Streptomyces*, such as *Streptomyces asenjonii* (Goodfellow *et al.* 2017), *Streptomyces deserti* (Santhanam *et al* 2012a), *Streptomyces atacamaensis* (Santhanam *et al* 2012b), *Streptomyces bullii* (Santhanam *et al.* 2013) and *Streptomyces leeuwenhoekii* (Busarakam *et al.* 2014). Recently, presumptively gifted isolates from a high-altitude Cerro Chajnantor gravel soil in northern Chile have been validly named as *Micromonospora acroterricola* (Carro *et al.* 2019), *Micromonospora arida*

and *Micromonospora inaquosa* (Carro *et al.* 2018a). Similarly, novel dereplicated isolates belonging to less well-known genera have been validly named, as exemplified by *Amycolatopsis vastitatis* (Idris *et al.* 2018), *Lentzea chajnantorensis* (Idris *et al.* 2017a) and *Pseudonocardia nigra* (Trujillo *et al.* 2017). The genomes of some of these isolates have the capacity to synthesize many novel specialized metabolites and contain stress-related genes that provide an insight into how actinobacteria adapt to the extreme environmental conditions found in Atacama Desert habitats (Idris *et al.* 2018; Carro *et al.* 2018b).

A steady flow of filamentous actinobacteria recovered from other nonpolar deserts have been validly named as new species, they include *Amycolatopsis desertii* (Busarakam *et al.* 2016a), *Desertiactinospora gelatinilytica* (Saygin *et al.* 2019), *Nakamurella deserti* (Liu *et al.* 2018a, 2018bb), *Prauserella isguensis* (Saker *et al.* 2015), *Saccharothrix algeriensis* (Zitouni *et al.* 2004), *Saccharothrix tharensis* (Ibeyaima *et al.* 2018) and *Streptosporangium becharense* (Chaouch *et al.* 2016).

Actinobacteria that are amycelial or form rudimentary hyphae have received less attention though they are known to be common in desert soils (Idris *et al.* 2017b; Bull *et al.* 2018b). Members of the family Geodermatophilaceae have received the most attention, notably the genera *Blastococcus, Geodermatophilus* and *Modestobacter*; members of these taxa are known to be resistant to desiccation, ionizing radiation, UV-light and heavy metals (Sghaier *et al.* 2016). Dereplicated Geodermatophilaceae strains from Atacama Desert habitats have been validly named as *Blastococcus atacamensis* (Castro *et al.*

2018a), *Geodermatophilus chilensis* (Castro *et al.* 2018b) and *Modestobacter caceresii* (Busarakam *et al.* 2016b) and shown to have moderately large genomes (3·9–5·9 Mb). Representatives of these taxa not only contain NP-BGCs but also stress-related genes that encode for properties such as carbon starvation, temperature fluxes, osmotic stress and UV-light. Other novel γ-radiation-resistant geodermatophili have been isolated from the Sahara Desert, as exemplified by *Geodermatophilus pulveris* (Hezbri *et al.* 2016). In addition, radiation-resistant actinobacteria belonging to the genera *Agrococcus, Arthrobacter, Cellulomonas, Kocuria, Knoella* and *Nocardioides* have been recovered from the Taklamakam Desert (Yu *et al.* 2015). Amycelial actinobacteria isolated from other deserts include *Arthrobacter deserti* (Hu *et al.* 2016), *Citricoccus alkalitolerans* (Li *et al.* 2005) and *Kocuria aegyptia* (Li *et al.* 2006). A particularly interesting development was the discovery that the sole member of the novel taxon *Desertimonas flava*, which was recovered from the Gurbantünggüt Desert, a desert which occupies a large part of the Dzungarian Basin in northern Xinjiang Province, China, belongs to the newly proposed family Ilumatobacteraceae of the order Acidomicrobiales (Asem *et al.* 2018).

Alkali-halotolerant actinobacteria retrieved from salty hyperarid soils have been shown to be adapted to alkaline, drought and extreme temperatures (Mohammadipanah and Wink 2016). *Streptomyces aburaviensis,* an isolate from saline arid desert soil in Kutch, India grows well at pH 8·5 in the presence of 15% w/v NaCl (Thumar *et al.* 2010). *Mycetocola manganoxydans,* a unique non-sporulating alkaliphilic actinobacterium isolated from the Taklamakan Desert can oxidize manganese ions (Luo *et al.* 2012). In addition, several alkalihalophilic actinobacteria have been isolated from the Qinghai-Tibet Plateau, including members of the genera *Cellulomonas, Saccharothrix* and *Streptosporangium* (Ding *et al.* 2013) whereas *Actinomadura* and *Nocardiopsis* strains have been recovered from alkaline arid soils adjacent to salty lakes in Buryatiya (Lubsanova *et al.* 2014). A novel alkaliphilic *Streptomyces* strain isolated from an alkaline soil in the arid area of Boho, Northern Ireland was found to grow under intense γ-radiation (4 kGy) at pH 10·5, and shown to be a potential source of novel specialized metabolites that inhibit *ESKAPE* pathogens (Terra *et al.* 2018).

Cyanobacteria

These oxygenic photosynthetic prokaryotes, which form a single taxonomic and phylogenetic group, produce a broad range of bioactive compounds including ones that show anti-microbial, anti-protozoal and anti-inflammatory activity (Micallef *et al.* 2015; Vijayakumar and Menakha 2015). Endolithic (rock-inhabiting) cyanobacteria dominated by *Chroococcidiopsis* species were first reported from the Negev Desert (Potts and Friedmann 1981), but are now known to be common in desert biomes given their remarkable ability to cope with extreme aridity and solar radiation (Lacap-Bugler *et al.* 2017). Indeed, cyanobacteria dominate hypolithic (under rock) desert communities and may be major drivers of community assembly and function (Bahl *et al.* 2011). Microbial communities dominated by *Chroococcidiposis* strains inhabit halite deposits in the hyperarid core of the Atacama Desert (Wierzchos *et al.* 2006). It has also been shown that cyanobacteria and associated heterotrophic bacteria reside within pore spaces in nodule-shaped halite crusts (Ríos *et al.* 2010; Roldán *et al.* 2014). These lithic microbial communities have developed adaptive strategies to withstand the extreme environmental conditions that prevail in the Atacama Desert (Gómez-Silva 2018), as is the case with similar communities in the Namib Desert (Stomeo *et al.* 2013). It is evident that green hypoliths in the hyperarid core of the Atacama Desert are dominated by *Chroococcidopsis* and *Nostocales* species and red hypoliths by *Chloroflexi* (Lacap *et al.* 2011), whereas Noctocophycideae and Synechococcophycideae species are present in lower numbers (Vítek *et al.* 2014). Cyanobacteria also produce pigments which may protect them against lethal doses of UV-radiation in hyperarid habitats (Powell *et al.* 2015).

Fungi

Like actinobacteria and cyanobacteria, fungi show a range of adaptive mechanisms which allow them to withstand environmental extremes found in desert ecosystems (Onofri *et al.* 2007; Stevenson *et al.* 2017; Santiago *et al.* 2018), as shown by their ability to synthesize melanin pigments that provide protection against high levels of UV-radiation (Gessler *et al.* 2014). Early isolation studies on soils from the Negev and Sonoran deserts revealed extensive fungal diversity (Taylor-George *et al.* 1983), results now known to square with the view that fungi are the most stress-resistant eukaryotes (Sterflinger *et al.* 2012), a point especially apt with respect to microbial rock fungi (Palmer *et al.* 1987; Gonçalves *et al.* 2016).

To date, fungi isolated from desert habitats have featured rarely in bioprospecting campaigns even though fungal taxa, including novel species, are common in desert landscapes. A preliminary survey of Atacama Desert soils by Conley *et al.* (2006), for instance, recorded 13 distinct fungal genera, notably *Alternaria* and *Ulocladium* species; it is now clear that fungal communities in this desert represent an unknown element of global fungal diversity (Santiago *et al.* 2018). Furthermore, a survey

of fungi from Makhtesh Ramon desert soil found 135 novel species dominated by ascomycetes (Grishkan and Nevo 2010). In addition, 77 lichenoid fungal species detected along two altitudinal transects at Alto Patache in the Atacama Desert included four new species, *Amandinea efflorescens, Diploicia canescens, Myriospora smaragdula* and *Rhizocarpon simillimum* (Castillo and Beck 2012), whereas high-altitude rocks in the desert were a source of fungi belonging to the genera *Cladosporium, Neucatenulostroma* and *Penicillium* (Gonçalves *et al.* 2016). Furthermore, two novel halophilic fungi isolated from a cave in the Coastal Range of the Atacama Desert were designated as *Aspergillus atacamensis* and *Aspergillus salisburgensis* (Martinelli *et al.* 2017). Extensive fungal diversity has been recorded in Middle East desert sand (Murgia *et al.* 2018) and three novel fungal species, *Diverispora omaniana, Septoglomus nakheelum* and *Rhizophagus arabicus,* were recorded from a desert in Oman (Symanczik *et al.* 2014).

Desert-associated specialized metabolites

The range of micro-organisms found in deserts are potential sources of new chemical diversity but have been understudied chemically, partly reflecting a view that desert micro-organisms were likely to synthesize bioactive metabolites due to limited numbers of competing microbial species present in extreme biomes (Pettit 2011). However, over the last 20 years, actinobacteria, cyanobacteria and fungi isolated from unusual or extreme desert habitats have been shown to have evolved unique metabolic pathways for the synthesis of novel bioactive specialized metabolites (Peng *et al.* 2011; Jančič *et al.* 2016; Rateb *et al.* 2018). Indeed, by 2008, more than 100 specialized metabolites had been isolated and identified from micro-organisms isolated from such habitats (Wilson and Brimble 2009).

N-containing compounds

Since 2010, most investigated bioactive molecules have been reported from actinobacteria recovered from hyperarid Atacama Desert soils, as shown in Fig. 2. *Streptomyces leeuwenhoekii* strain $C34^T$ produces ansamycin-type macrocyclic polyketides, the chaxamycins A–D (1–4) together with the aminoglycoside antibiotics hygromycin A (5), 5″-dihydrohygromycin A (6), deferrioxamine E (nocardamine, 7) as well as desferrioxamine B (8), the latter were isolated from the same strain using the OSMAC (One Strain Many Compounds) approach (Rateb *et al.* 2011a, 2011bb). Further examples of novel bioactive molecules from Atacama Desert streptomycetes include the aminobenzoquinones, abenquines A, B1, B2, C and D (9–13) which showed inhibitory activity against

bacteria and dermatophytic fungi (Schulz *et al.* 2011). Fermentation of *S. leeuwenhoekii* strain C58 led to the isolation of chaxapeptin (14), a novel ribosomally-synthesized and posttranslationally modified lasso peptide which exhibits significant *in vitro* inhibitory activity against human lung cancer cells (Elsayed *et al.* 2015). Recently, bio-guided fractionation of a culture broth extract of *S. asenjonii* strain 42.f (Goodfellow *et al.* 2017) led to the isolation of new bioactive polyketides of the rare β-diketone family, asenjonamides A–C (15–17) which showed potent antibacterial effects against Gram-positive bacteria., it is particularly interesting that asenjonamide C (17) shows comparable activity to that of tetracycline (Abdelkader *et al.* 2018). In the same study, a series of bioactive acylated 4-aminoheptosyl-β-N-glycosides, spicamycins A–E (18–22), were isolated in a pure form for the first time. These antibiotics were initially found as a nonseparable mixture of seven compounds extracted from *Streptomyces alanosinicus* (Hayakawa *et al.* 1983). There is evidence that this unique class of nucleoside antibiotics may provide a promising lead for the development of new anticancer drugs (Gadgeel *et al.* 2003).

Cyanobacteria are widely distributed in both arid and hyperarid ecosystems, and are the source of many bioactive compounds (Singh *et al.* 2005; Micallef *et al.* 2015). They produce pigments like scytonemin (23) and the mycosporine-like amino acids shinorine (24) and porphyra-334 (25) which may absorb potentially lethal doses of UV-radiation found in hyperarid environments., these compounds are being evaluated as a source of potent sunscreens (Powell *et al.* 2015). Scytonemin (23), which is produced by a *Chroococcidiopsis* strain, has potential as a chemical marker for endolithic cyanobacterial colonies in halite crusts which are common in the hyperarid zone of the Atacama Desert (Vítek *et al.* 2014). This compound is of considerable interest as it causes attenuation of mitogen-induced inflammatory hyperproliferation through inhibition of *polo*-like kinase hence its unique dimeric structure may prove to be a potential scaffold for the development of potent kinase inhibitors (D'Orazio *et al.* 2012). Recently, the mycosporine-like amino acids, shinorine (24) and porphyra-334 (25) were found to exhibit anti-inflammatory effects by interference with NF-κB activation (Becker *et al.* 2016).

Cyanobacteria found in extreme habitats, such as alkaline lakes, hyperarid desert soils, hypersaline environments and polar regions, produce cyanotoxins, diverse specialized metabolites (e.g., alkaloids, amino acids and cyclic peptides) which can be classified into hepatotoxins, neurotoxins and cytotoxins (Metcalf and Codd 2012). Cyanotoxins detected in habitats such as these include the neurotoxins anatoxin-a (26), anatoxin-a(S) (27), β-methylaminopropionic acid (28) and 2,4-diaminobutyric
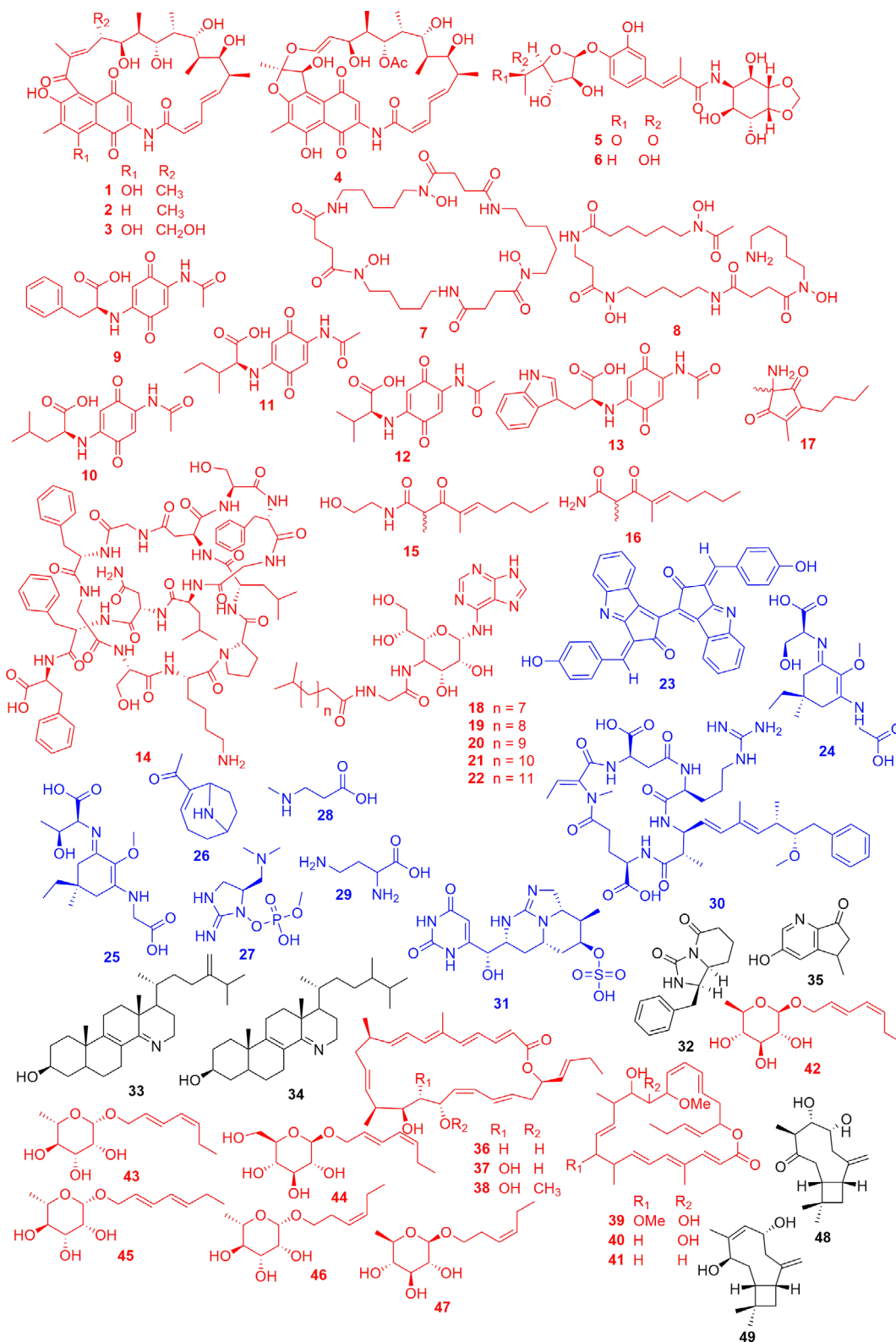
Figure 2 Specialized metabolites derived from actinobacteria (red colour), cyanobacteria (blue colour) and fungi (black colour) recovered from desert habitats (compounds **1**–**49**). [Colour figure can be viewed at wileyonlinelibrary.com]

acid (**29**), as well as the hepatotoxins, nodularin (**30**) and cylindrospermopsin (**31**). Biosynthesis of these toxins is mainly attributed to the cyanobacterial genera *Arthrospira, Oscillatoria* and *Synechococcus* (Cirés *et al.* 2017). Apart from their toxicological properties, cylindrospermopsin (**31**) and anatoxin-a (**26**) show estrogenic activity *in vivo* and *in vitro* assays (Liu *et al.* 2018a, 2018bb).

Recent studies on fungi from desert ecosystems underlines their potential as a prolific source of novel chemical entities which show interesting bioactivities (Santiago *et al.* 2018). Members of the genus *Wallemia,* a taxon which encompasses seven species, were previously considered to be halophilic (Zalar *et al.* 2005). However, *Wallemia sebi*, the sole representative of the genus isolated from the Atacama Desert produces a range of specialized metabolites such as wallimidione (**32**) (Desroches *et al.* 2014), 15-azasterol (**33**) and 24,28-dihydro-15-azasterol (**34**) (Jančič *et al.* 2016). Molecules **33** and **34**, also known as UCA1064-A and UCA1064-B, respectively, exhibit *in vivo* antitumor activity against a mouse mammary tumour model and *in vitro* antiproliferative activity against HeLa S3 cells; they also show antifungal activity against *Saccharomyces cerevisiae* and inhibit Gram-positive bacteria (Jančič *et al.* 2016). Furthermore, the alkaloid cyclopentanopyridine (**35**) isolated from a halophilic strain of *W. sebi* inhibits *Enterobacter aerogenes* (Peng *et al.* 2011).

Macrolides

Streptomyces leeuwenhoekii C34^T from Atacama Desert soil produces chaxalactins A–C (**36–38**), a rare class of 22-membered macrolactone polyketides which show antibacterial activity against Gram-positive bacteria (Rateb *et al.* 2011a, 2011bb). In turn, *S. leeuwenhoekii* strain C38, isolated from the same desert location, synthesizes 22-membered macrolactone antibiotics, the atacamycins A-C (**39–41**) (Nachtigall *et al.* 2011).

Other metabolites

Chemical investigation of *L. chajnantorensis* strain H45 recovered from a high-altitude Atacama Desert soil (Idris *et al.* 2017a) led to the characterization of new diene glycosides, lentzeosides A–F (**42–47**) which show inhibitory activity against HIV integrase (Wichner *et al.* 2017). Furthermore, the Atacama Desert-derived fungus, *W. sebi* produces two unique terpenes, walleminone (**48**) and walleminol (**49**) (Jančič *et al.* 2016).

Permafrost soils

Permafrost is the layer below the earth's crust that has remained at or below 0°C for at least two consecutive years (Jansson and Taş 2014). It is estimated that

approximately 25% of the landmass of the planet is underlayen by permafrost soils. These soils, together with overlying (naturally thawing) layers, provide unique habitats for active, cold-adapted, microbial communities (Bakermans *et al.* 2014; De Maayer *et al.* 2014; Hu *et al.* 2015)., as well as for cells that have remained viable for millions of years (Gilichinsky *et al.* 2008). Indeed, according to the Snow Ball Earth hypothesis, the planet has been completely or almost completely frozen at least once within the last 650 million years suggesting that micro-organisms would have had to adapt to subzero temperatures to survive (Schopf and Klein 1992). Permafrost can be distinguished from other low-temperature biomes, such as sea ice and deep oceans, by its structural heterogeneity given horizontal and vertical differences in soil, ice and organic matter content (Jansson and Taş 2014).

Micro-organisms adapted to temperatures that range from −17 to +10°C are referred to as cryophiles (Feller and Gerday 2003). Water availability and temperature are the most important abiotic factors influencing microbial diversity in cold environments though high viscosity and low thermal energy offer additional challenges (Jansson and Taş 2014). Nucleic acid replication, transcription and translation are inhibited under such conditions, whereas proteins can denaturate causing loss of cell membrane fluidity (Chattopadhyay 2006; D'Amico *et al.* 2006). Micro-organisms adapted to life in such cold environments have developed several strategies for survival, such as initiating dormant states and generating specialized metabolites and proteins (Bakermans *et al.* 2009). Cryophilic micro-organisms can also reduce their metabolism and nutrient uptake by storing energy as polyphosphates, triglycerides, wax esters and glycogen (Bowman 2008) and can adapt their cellular structure by regulating branched and saturated fatty-acid production to maintain cell membrane fluidity at freezing temperatures (Unell *et al.* 2007).

Prokaryotes

Arctic permafrost soils tend to be dominated by *Acidobacteria*, *Actinobacteria*, *Cyanobacteria*, as well as by *Proteobacteria* belonging to the Burkholderiales (β-proteobacteria), Myxococcales (δ-proteobacteria), Rhizobiales (α-proteobacteria) and Xanthomonadales (γ-proteobacteria) (Malard and Pearce 2018). These authors suggested that biogeographic variation may be a feature of Arctic soils as actinobacteria occurred in lower numbers in Greenland and Finland, whereas much higher populations of *Bacteroidetes* were evident in Alaskan, Canadian and Svalbard permafrost., these abundant groups also included *Chloroflexi, Cyanobacteria, Firmicutes, Gemmatimonadetes, Planctomycetes* and *Verrucomicrobia*. In turn,

the dominant taxa found in Chinese permafrost soils were *Actinobacteria*, *Firmicutes* and *Proteobacteria* (Hu *et al.* 2015). The dominant cyanobacterial orders in Arctic soil crusts were found to be the Nostocales, Oscillatoriales and Synechococcales (Steven *et al.* 2013; Pushkareva *et al.* 2015). Indeed, cyanobacteria are mainly responsible for the uptake of CO_2 and N_2 as plants in Arctic ecosystems are unable to fix nitrogen (Malard and Pearce 2018).

Regional populations of cyanobacteria may also be a feature of Antarctic soils (Namsaraev *et al.* 2010). Archaea have also been isolated from permafrost (Jansson and Taş 2014). Archaeal communities in Arctic soils seem to be variable through *Methanobacteria* and *Methanomicrobia* (*Euryarchaeota*) are abundant in Alaskan and Greenland soils (Ganzert *et al.* 2014; Malard and Pearce 2018), whereas isolates related to the genera *Methanolobus* and *Methanomethylovorans* have been recovered from frozen ground in the Zoige wetland of the Qinghai—Tibet plateau (Zhang *et al.* 2008). The methane released by these organisms can be used as a sole carbon source by methanotrophic bacteria, such as α- and γ-proteobacteria (Coolen *et al.* 2011) and members of the Methanococcales (Martineau *et al.* 2014).

Fungi

In general, fungal communities in Arctic permafrost are dominated by Ascomycota, Basidiomycota and Chytridiomycota (Gittel *et al.* 2014; Zhang *et al.* 2016a, 2016bb), through the survival of associated shrubs are dependent on ectomycorrhizal fungi (Deslippe *et al.* 2011; Fujiyoshi *et al.* 2011). In turn, common genera include *Aspergillus*, *Cladosporium*, *Geomyces* and *Penicillium* (Ozerskaya *et al.* 2009). Over 400 taxonomically distinct genera have been recovered from Antarctic soil systems suggesting that fungi may be the most diverse biota in this mileau (Bridge and Spooner 2012); isolates from Cape Royds, Antarctica keyed out to the genera *Cadospora*, *Geomyces* and *Thielava* (Blanchette *et al.* 2010). Indeed, the ascomycete genera *Cadospora* and *Geomyces* may be endemic to Antarctic soils (Arenz and Blanchette 2011). Fungal diversity in Antarctic lichens from King George Island was shown to include the *Arthonimycetes*, *Eurotiomycetes*, *Leoanoromycetes*, *Leotiomycetes* and *Sordariomycetes* (*Ascomycota*) and the *Cystobasidiomycetes* and *Tremellomycetes* of the *Basidiomycota* (Park *et al.* 2015).

Permafrost soil-associated specialized metabolites

N-containing compounds
Their rapid growth rate and ability to metabolize a wide array of substrates have enabled fungi to become the

dominant micro-organisms in polar habitats (Fig. 3). Two new epipolythiodioxopiperazines, the chetracins B and C (**50**, **51**), together with five new diketopiperazines, oidioperazines A–D (**52–55**) and chetracin D (**56**) were isolated from the Antarctic psychrophilic fungus *Oidiodendron truncatum*. Chetracin B (**50**) shows potent anticancer activity at a nanomolar concentration against a panel of human cancer cell lines, whereas chetracin C (**51**) displayed a significant effect at a micromolar concentration suggesting that the sulphide bridge is an essential structural feature for the activity of these compounds (Li *et al.* 2012). Another psychrophilic fungus, *Eutypella* sp. D1, isolated from an Arctic soil on London Island of Fongsfjorden, yielded the new cytochalasins Z_{24}, Z_{25}, Z_{26} (**57–59**). Cytochalasin Z_{24} (**57**) showed moderate cytotoxicity toward human breast cancer MCF-7 cells (Liu *et al.* 2014). Further chemical profiling of the *Eutypella* strain led to the isolation of two new N-containing diterpenes; libertellenone G (**60**) and eutypenoid B (**61**). The former exhibited significant antibacterial activity against Gram-positive and Gram-negative bacteria and the latter potent immunosuppressive activity (Lu *et al.* 2014; Zhang *et al.* 2016a, 2016bb). Lindgomycin (**62**), an unusual polyketide with a novel carbon skeleton, and ascosetin (**63**) were recovered from an Arctic sponge-derived fungal strain and classified in the family *Lindgomycetaceae*. All these metabolites exhibited potent antimicrobial activities against several pathogenic Gram-positive bacteria, including MRSA and the pathogenic yeast *Candida albicans* (Ondeyka *et al.* 2014; Wu *et al.* 2015).

The new benzoxazine glycosides, arcticoside (**64**) and C-1027 chromophore-V (**65**) derived from an Arctic marine *Streptomyces* strain showed inhibitory activity against *Candida albicans* isocitrate lyase and breast and colorectal carcinoma cells. Additionally, C-1027 chromophore-III (**66**) and fijiolides A and B (**67**, **68**) were isolated from the same strain (Moon *et al.* 2014). An Arctic freshwater-derived bacterium, *Pseudomonas fluorescens* BD5 produced unusual cyclic lipopeptide biosurfactants, namely pseudofactin I and II (**69**, **70**), the structure of which is unique as a palmitic acid is connected to a terminal peptide moiety of eighth amino acids. Interestingly, the stability and emulsification activity of these metabolites were greater than those of the conventional synthetic surfactants Triton X-100 and Tween 20 suggesting that they may be of potential value in bioremediation and biomedicine (Janek *et al.* 2010).

Polyketides
Two highly oxygenated polyketides, penilactones A and B (**71**, **72**), isolated from an Antarctic deep-sea-derived fungus, *Penicillium crustosum*, inhibited the nuclear factor-

κB (NF-κB) (Wu *et al.* 2012). Furthermore, a psychrophilic fungal strain isolated from an Antarctic marine sponge and assigned to the genus *Pseudogymnoascus* produced four new nitroasterric acid derivatives, pseudogymnoascins A–C (**73–75**) and 3-nitroasterric acid (**76**); these polyketides are the first nitro-derivatives of the known fungal metabolite asterric acid. In general, most reported asterric acid derivatives have been found to show antibacterial and antifungal activity but the present nitro-derivatives were inactive possibly due to the presence of the nitro group (Figueroa *et al.* 2015). Bio-guided fractionation of the culture broth of the Antarctic soil-derived *Aspergillus ochraceopetaliformis* strain led to the isolation of five new highly oxygenated polyketides, ochraceopones A–E (**77–81**), along with a new double bond isomer of asteltoxin (**82**), isoasteltoxin (**83**), as well as asteltoxin B (**84**). Among these metabolites, ochraceopones A (**77**) and isoasteltoxin (**83**) showed promising antiviral activity against the influenza viruses H1N1 and H3N2 (Wang *et al.* 2016).

Terpenes

A psychrophilic fungal *Eutypella* strain isolated from an Arctic soil on London Island was the source of four new diterpenes; scoparasin B (**85**), libertellenone H (**86**) and eutypenoids A and C (**87, 88**) (Liu *et al.* 2014). In turn, the meroterpenoids chrodrimanins I and J (**89, 90**) and five known structurally related chrodrimanins were purified from the culture broth of the Antarctic moss-derived fungus *Penicillium funiculosum*, the novel chrodrimanins showed week inhibitory activity against influenza A virus H1N1 (Zhou *et al.* 2015).

Lipids

Screening for new anti-*Burkholderia cepacia* complex compounds from bacteria isolated from the Ross Sea (Antarctica) led to the isolation of three new rhamnolipids (**91–93**) from *Pseudomonas* strain BNT1 (Tedesco *et al.* 2016).

Deep-sea sediments

Taxonomically diverse micro-organisms able to synthesize bioactive metabolites are common in marine habitats (Goodfellow and Fiedler 2010; Wang *et al.* 2016). In contrast, partly for logistics reasons, less attention has been given to the microflora of deep-sea sediments, notably those in polar regions and oceanic trenches. However, it is now becoming apparent that bacteria and fungi adapted to extreme conditions in these habitats, notably low temperatures (−1 to 4°C), dearth of nutrients and high hydrostatic pressure, provide interesting targets for bioprospecting campaigns (Zhang *et al.* 2014a, 2014bb; Dickinson *et al.* 2016; Gonçalves *et al.* 2017).

Bacteria

Arctic marine sediments contain diverse actinobacterial communities including representatives of putatively novel species (Zhang *et al.* 2014a, 2014bb) whereas samples taken along a transcend between the Atlantic Peninsula and South America were dominated in terms of genetic diversity by ɣ-proteobacteria and euryarchaeota (López-García *et al.* 2001). Furthermore, subsea floor core samples from the Nakau and Okinawa Troughs showed a range of halotolerant actinobacteria related to well-known antibiotic producing genera, such as *Nocardia*, *Pseudonocardia* and *Streptomyces* (Ulanova and Goo 2015). These results are in good agreement with those of earlier studies on actinobacteria isolated from deep-sea sediments, including ones recovered from the Challenge Deep of the Mariana Trench (Pathom-aree *et al.* 2006). Neither cyanobacteria nor archaea are common in polar marine deep sediments (Dickinson *et al.* 2016).
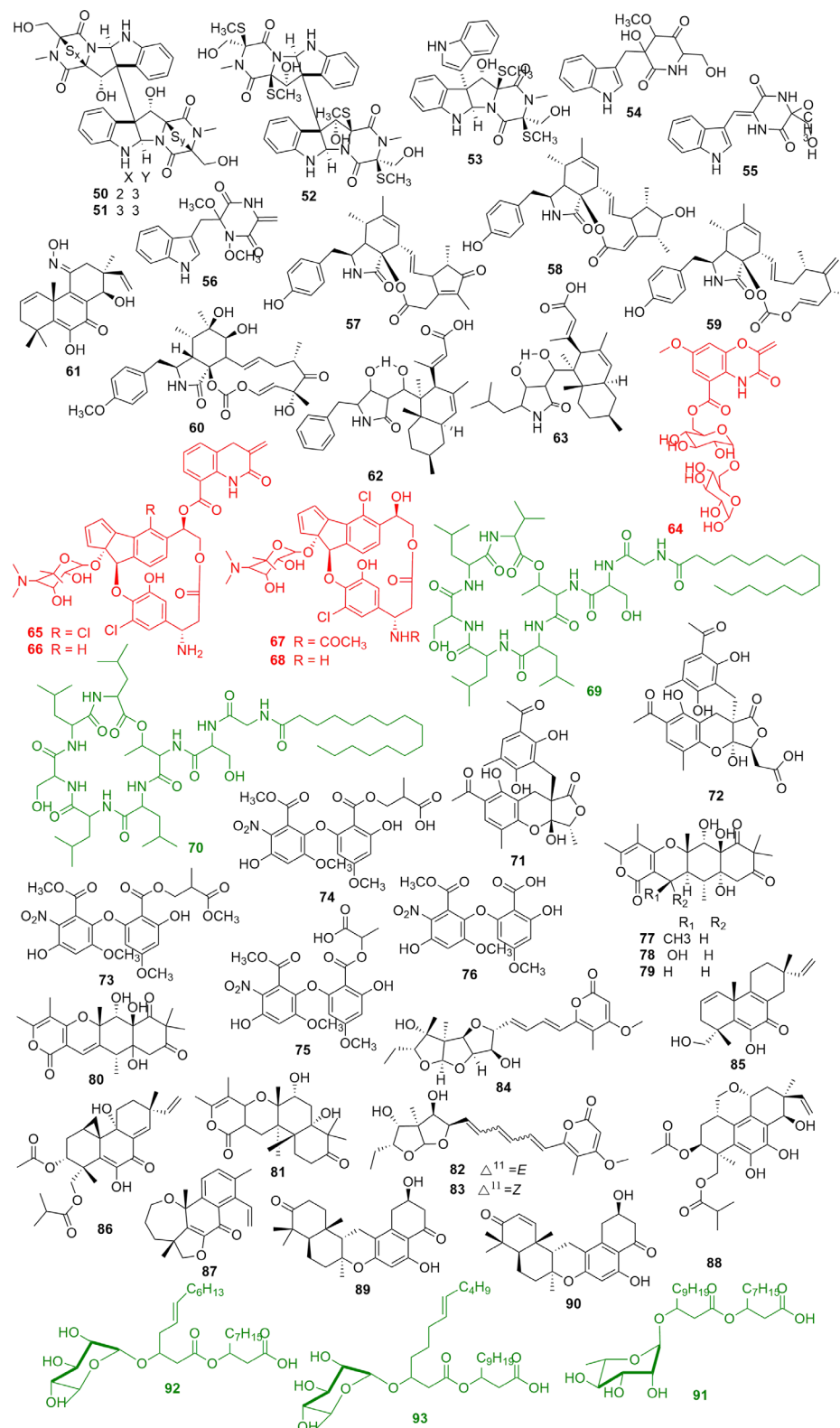
Fungi

Taxonomically diverse marine fungi are a feature of cold deep-sea sediments. Seawater sediments taken from across the northern Antarctic penisula, for instance, contained diverse fungal assemblages despite the harsh environmental conditions (Gonçalves *et al.* 2017), as is the case with deep-sea sediments from the East Indian Ocean (Zhang *et al.* 2014a, 2014bb). Dominant cold-adapted yeasts from the deep Polar Sea include *Candida*, *Cryptococcus*, *Pichia* and *Rodotorula* spp. (Nagano *et al.* 2013). In addition, filamentous yeasts and fungi belonging to the *Ascomycota* have been isolated from deep-sea sediments from the Central Indian Basin (Singh *et al.* 2010, 2012). Many *Graphium* sp. that displayed barotolerance at 100-bar pressure were recovered from Northern Antarctic Peninsula (Gonçalves *et al.* 2017).
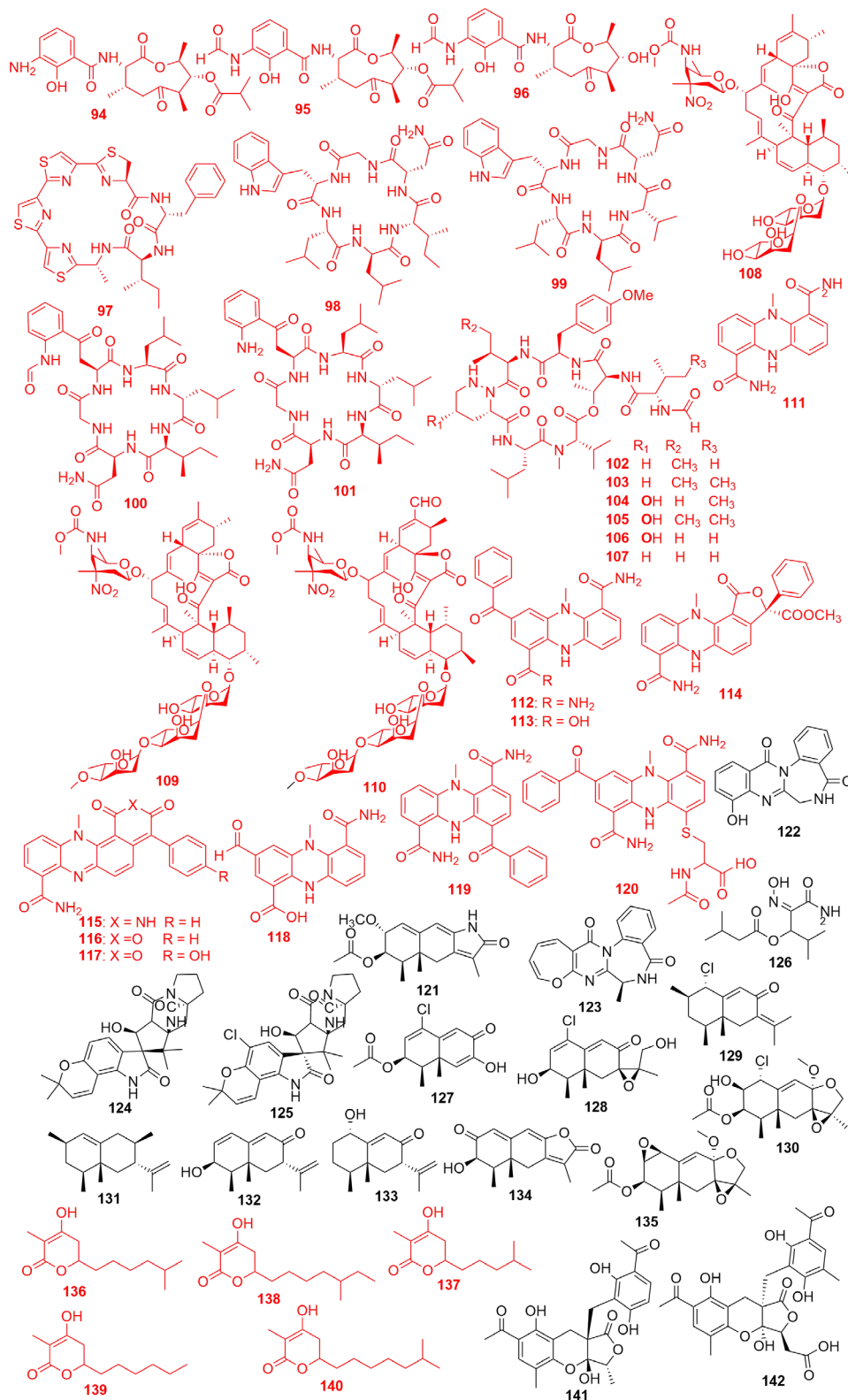
Deep-sea sediment-associated specialized metabolites

N-containing compounds

Regulatory genes such as *whiB*-like (*wblA*$_{50}$) play significant roles in actinobacterial specialized metabolism. Inactivation of *wblA*$_{50}$ and *vioB* from a cold deep-sea-derived *Streptomyces somaliensis* strain led to spectacular changes in the production of specialized metabolites (Fig. 4), notably in the synthesis of the new antimycin-type depsipeptide, somalimycin (**94**) and two analogues, USF-19A and urauchimycin D (**95, 96**) (Li *et al.* 2017). Chemical investigation of *Marinactinospora thermotolerans*, *Streptomyces scopuliridis* and *Streptomyces drozdowiczii* strains recovered from deep-sea samples collected off South China (3865 m) led to the isolation of the cyclic peptides,

Figure 3 Specialized metabolites derived from actinobacteria (red colour), bacteria (green colour) and fungi (black colour) isolated from permafrost soils (compounds **50–93**). [Colour figure can be viewed at wileyonlinelibrary.com]

Figure 4 Specialized metabolites derived from actinobacteria (red colour) and fungi (black colour) isolated from deep-sea sediments (compounds **94**–**142**). [Colour figure can be viewed at wileyonlinelibrary.com]

marthiapeptide A (**97**), desotamide (**98**), desotamide B-D (**99–101**) and marfomycins A–F (**102–107**) all of which showed antimicrobial activity against pathogenic Gram-positive bacteria (Zhou *et al.* 2012, 2014; Song *et al.* 2014). Additionally, three spirotetronate polyketides, lobophorin E (**108**), F (**109**) and H (**110**) extracted from two *Streptomyces* strains isolated from the same location at a depth of 2134 m, were shown to have antibacterial activity against a panel of Gram-positive bacteria (Niu *et al.* 2011; Pan *et al.* 2013). Furthermore, a novel piezo-tolerant actinobacterium, *Dermacoccus abyssi*, isolated from Mariana Trench sediment produced novel phenazine metabolites, dermacozines A-J (**111–120**); dermacozines F (**116**) and G (**117**) showed interesting antiproliferative activity towards the leukaemia cell line K562 with IC_{50} values of 9 and 7 mmol l^{-1} (Abdel-Mageed *et al.* 2010; Wagner *et al.* 2014). Chemical investigation of the Antarctic deep-sea fungus *Penicillium* sp. PR19N-1 led to the isolation of a new rare lactam-type metabolite, eremophilane (**121**) (Lin *et al.* 2014). Fermentation of another deep-sea fungus, *Aspergillus westerdijkiae* DFFSCS013, led to the isolation of two new benzodiazepine alkaloids circumdatins K and L (**122**, **123**), and two new indole alkaloids, 10-epi-sclerotiamide and 5-chlorosclerotiamide (**124**, **125**) together with the novel amide, aspergilliamide B (**126**) (Peng *et al.* 2013).

Terpenes
A novel chloro-trinoreremophilane sesquiterpene (**127**) and three new chlorinated eremophilane sesquiterpenes (**128–130**) were also obtained from the Antarctic deep-sea fungus *Penicillium* sp. PR19N-1, these compounds showed moderate cytotoxic activity against the cancer cell lines HL-60 and A549 (Wu *et al.* 2013). Further chemical investigation on this strain led to the isolation of five new cytotoxic eremophilane-type sesquiterpenes (**131–135**) (Lin *et al.* 2014).

Polyketides
Five new α-pyrone derivatives, violapyrone A–C, J and H (**136–140**), which showed anti-MRSA activity were isolated from a *Streptomyces somaliensis* strain isolated from a deep-sea sediment (Huang *et al.* 2016). Extensive chemical profiling of the Antarctic deep-sea fungus *Penicillium crustosum* PRB-2 resulted in the identification of penilactones A and B (**141**, **142**), two novel polyketides with unusual highly oxygenated structures, along with known phenolic metabolites (Wu *et al.* 2012).

Highly acidic habitats

In general, extreme acidophiles can be defined as micro-organisms that grow optimally at pH values below 3 (Johnson and Quatrini 2016). These micro-organisms are common in acid lakes, acid sulphate soils and acid mine wastes (Druschel *et al.* 2004; Mirete *et al.* 2017). Most studies have been focused on the structure and function of microbial communities in acid mine drainage (AMD) systems given their simplicity from a biological and geochemical perspective (Denef *et al.* 2010). Primary environmental variables that shape AMD habitats are dissolved metal concentrations, total organic carbon, dissolved oxygen, pH and temperature (Méndez-García *et al.* 2015). These factors, notably pH, help to drive microbial diversity patterns in acid mine wastes (Kuang *et al.* 2013). Acidophilic algae, archaea, bacteria and fungi have developed ways of thriving or tolerating conditions in acidic biomes (Baker-Austin and Dopson 2007; Denef *et al.* 2010), as exemplified by roles played by cell membranes in archaea and bacteria (Konings *et al.* 2002; Falteisek and Čepička 2012).

Prokaryotes

Individual acidic habitats tend to be dominated by one or a few species (Mueller *et al.* 2010), as illustrated by the dominance of *Acidithiobacillus thioxydans* on the ceilings of acidic caves (Ziegler *et al.* 2013); this extreme acidic chemolithotroph, which is a member of the order Acidothiobacilliales (Williams and Kelly 2013), is a feature of acid mine wastes across the world (Hedrich and Johnson 2013). Furthermore, acidic, warm ferruginous mine wastes are dominated by *Ferroplasma* and *Leptospirillum* spp. (Denef *et al.* 2010) and their cold counterparts by *Acidithiobacillus thiooxidans* (Liljeqvist *et al.* 2015). In turn, *Leptospirillum* species are common members of acidophilic communities that catalyse the oxidation of ferrous ion (Goltsman *et al.* 2013). However, the primary bacterial lineages found in acid mine wastes are *Acidobacteria*, *Actinobacteria*, *Aquificae*, *Firmacutes*, *Nitrospora*, *Proteobacteria* and *Candidatus* division TH7 (Chen *et al.* 2016). Predominant sulphate-reducing bacteria detected in AMD systems include *Desulfurella*, *Desulfomonile*, *Syntrophobacter* and *Thermodesulfolobium* spp. (Sánchez-Andrea *et al.* 2012). Taxonomically diverse archaea present in acid mine wastes include *Acidianus*, *Metallophaera*, *Sulfolobus* and *Sulfurisporae* spp. (phylum Crenarchaeota) and the genus *Ferroplasma* of the phylum Euryarchaeota (Chen *et al.* 2015, 2016). Extremely acidophilic archaea are classified within the Euryarchaeota (such as a *Picrophilus* sp. which is considered the most acidophilic of all known life-forms) and Crenarchaeota phyla have been regarded as thermoacidophiles (Aguilera *et al.* 2016).

Eukaryotes

Relatively little is known about algae and fungi in acidic habitats even though they are an integral part of

microbial communities (Falteisek and Čepička 2012). However, *Penicillum* spp. isolated from an abandoned open-pit containing acid-metal waste in Montana, USA were found to produce interesting, novel bioactive compounds (Zhang *et al.* 2018), whereas algae from acid mine waste have been identified as *Chlorella protothecoids* var. *acidicola* and *Euglena mutabolis* (Johnson 2012).

Acidic habitats-associated specialized metabolites

Polyketides

In 2012, azaphilone-type polyketides, berkazaphilones A and B (**143**, **144**) together with berkazaphilones C (**145**), berkedienoic acid (**146**), berkedienolactone (**147**), vermistatin (**148**), dihydrovermistatin (**149**), penisimplicissin (**150**) and methylparaconic acid (**151**) were isolated from an extremophilic fungus recovered from the acid mine waste lake in Montana and identified as *Penicillium rubrum* (Fig. 5). Berkazaphilones B and C (**144**, **145**) and penisimplicissin (**151**) exhibited selective inhibitory activity against leukemia cancer cell lines through inhibition of caspase-1 (Stierle *et al.* 2012a). An extremophilic fungus assigned to the genus *Pleurostomophora* isolated from the same acid mine lake produced three new azaphilones, berkchaetoazaphilones A–C (**152**–**154**) and the red pigment berkchaetorubramine (**155**), berkchaetoazaphilone B (**153**) showed *in vitro* anti-inflammatory activity by inhibiting of the production of IL-1β, TNFα and IL-6 inflammatory mediators, and exhibited potent cytotoxic effects against human retinoblastoma, leukaemia and melanoma cell lines (Stierle *et al.* 2015).

Terpenes

The *P. rubrum* strain mentioned above also produced interesting meroterpenoids, namely berkeleyones A–C (**156**–**158**), berkeleydione (**159**) and berkeleytrione (**160**), as well as preaustinoid A and A₁ (**161**, **162**)., these metabolites inhibited the *in vitro* production of interleukin 1-β (Stierle *et al.* 2011). Moreover, two new drimane sesquiterpene lactones, berkedrimanes A and B (**163**, **164**) and a new tricarboxylic acid (**165**) were isolated from another extremophilic fungal strain isolated from the Montana acid mine lake and identified as *Penicillium solitum*, berkedrimanes A and B (**163**, **164**) showed *in vitro* anti-inflammatory activity as they inhibited the enzymes caspase-1 and 3 (Stierle *et al.* 2012b).

Saline and hypersaline habitats

Saline habitats can be considered as ones where salt concentrations correspond to the level found in seawater (3·5% w/v of total dissolved salts, Díaz-Cárdenas *et al.* 2017), whereas high salt environments have

concentrations of salts >100 g l^{-1}. (Enache *et al.* 2017) as found in Antarctic biomes and hypersaline lakes. Halophilic micro-organisms thrive under harsh environmental conditions that prevail in such habitats as they have evolved molecular and cellular mechanisms to cope with factors such as osmotic pressure and low water activity (Oren 1999; Gunde-Cimerman and Zalar 2014; Waditee-Sirisattha *et al.* 2016), whereas their halotolerant counterparts generally grow in the absence of salt but can tolerate high salt concentrations. Halophilic micro-organisms, in particular, are being seen as a source of novel bioactive compounds (Waditee-Sirisattha *et al.* 2016; Díaz-Cárdenas *et al.* 2017).

Prokaryotes

Phylogenetically diverse halophilic and highly halotolerant archaea are common in hypersaline systems and include members of the class *Halobacteria* (Andrei *et al.* 2012). Extreme halophilic archaea have been isolated from hypersaline lakes in the Transylvanian Basin close to the salt minos of Turda (Baricz *et al.* 2014, 2015). Novel archaea isolated from commercial salt include *Halarchaeum acidophilum* (Minegishi *et al.* 2010) and *Natronoarchaeum mannanilyticum* (Shimane *et al.* 2010). Common bacteria recovered from hypersaline habitats have been assigned to the phyla *Actinobacteria* (*Streptomyces*), *Bacteriodetes* (*Flavobacteria*), *Cyanobacteria*, *Firmacutes* (*Bacilli* and *Clostridia*) and *Proteobacteria* (α and γ-proteobacteria) (Enache *et al.* 2017). Archaea and bacteria are also common in ancient halite (Jaakkola *et al.* 2016).

Eukaryotes

Extremely halotolerant and halophylic fungi have been isolated from biomes in solar salterns across the world, as exemplified by melanized members of the genera *Aspergillus*, *Cladosporium* and *Penicillium* spp., and *Emericella* and *Eurotium* spp., nonmelanized yeasts and *Wallemia* spp. (Gunde-Cimerman and Zalar 2014). Unclassified eukaryotes have been detected in a hypersaline sulphate lake (Pontefract *et al.* 2017).

Saline and hypersaline habitats-associated specialized metabolites

N-containing compounds

Chemical investigation of *Streptomyces* strains derived from a saltern in Shinui Island (Republic of Korea) led to the isolation of a new chlorinated manumycin, salternamide A (**166**) and a new indolosesquiterpene, xiamycin D (**167**) (Fig. 5). Salternamide A (**166**) showed potent cytotoxicity against human colon and gastric cancer cell lines, whereas xiamycin D (**167**) exhibited potent antiviral
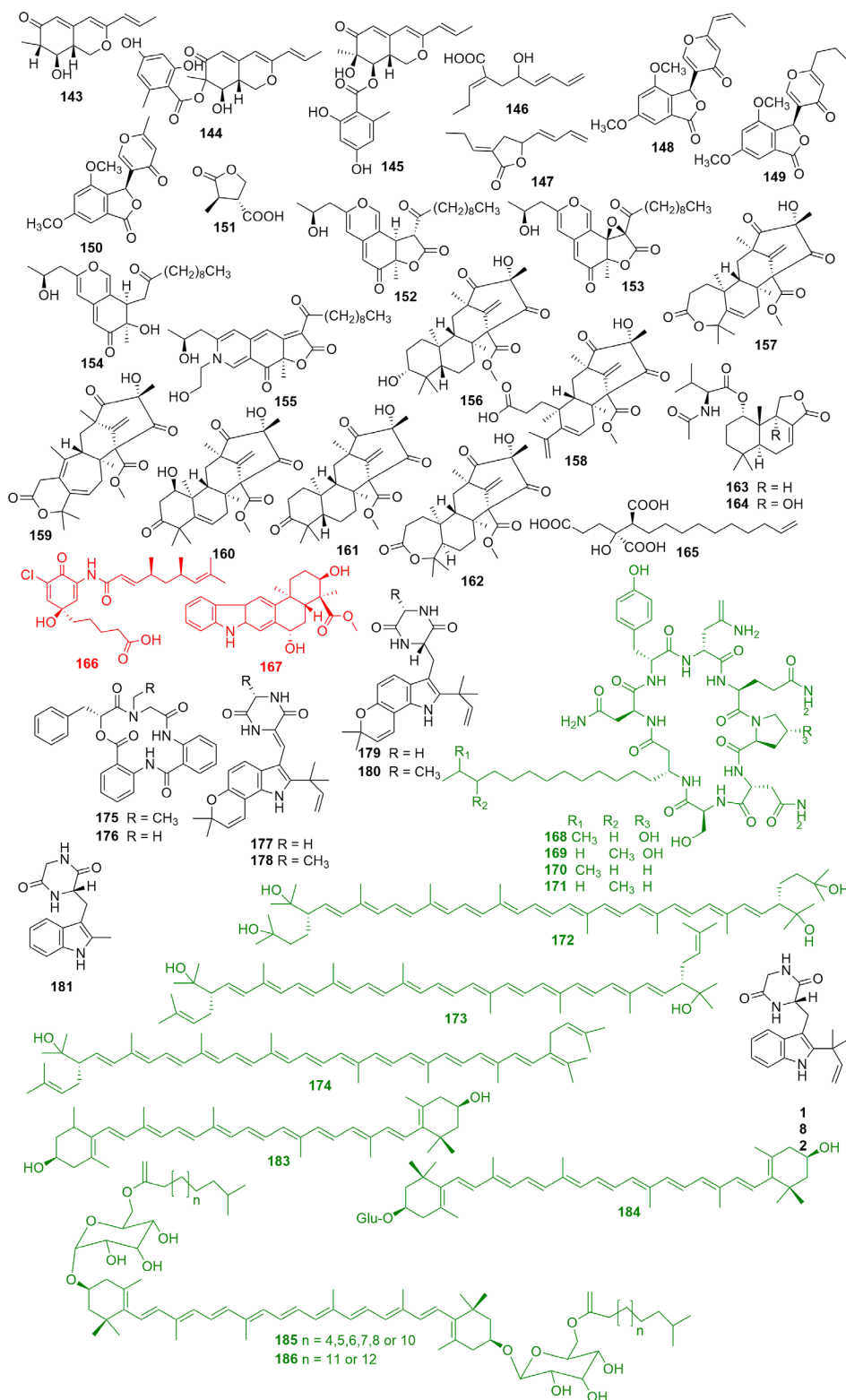
Figure 5 Specialized metabolites derived from actinobacteria (red colour), bactrria (green colour) and fungi (black colour), isolated from acidic, hypersaline and high-temperature habitats (compounds **143**–**186**). [Colour figure can be viewed at wileyonlinelibrary.com]

activity against the porcine epidemic diarrhoea virus (Kim *et al.* 2015). Chemical profiling of bioactive specialized metabolites from a *Bacillus* strain isolated from a saltern in Incheon, Korea led to the isolation of three new lipopeptides, iturin F_1 (**168**), iturin F_2 (**169**) and iturin A_9 (**170**), together with iturin A_8 (**171**). All of these compounds showed potent activity against pathogenic fungi and moderate antiproliferative activity against HeLa and *src*ts-NRK cell lines. Moreover, an *in vitro* enzymatic assay of iturin A_8 (**171**) demonstrated significant inhibitory activity towards indoleamine 2,3-dioxygenase (Son *et al.* 2016).

Carotenoids

A *Halobacterium salinarium* strain was found to produce a group of potent antioxidant carotenoids, namely bacterioruberin (**172**), bisanhydrobacterioruberin (**173**) and trisanhydrobacterioruberin (**174**) (Mandelli *et al.* 2012).

High-temperature environments

Thermophilic and hyperthermophilic micro-organisms are common in hot-springs and deep-sea hydrothermal vents, but are also found in artificial habitats such as compost (Rastogi *et al.* 2010; Urbieta *et al.* 2015). The optimal growth temperature for thermophiles is around 55°C and that for hyperthermophiles is above 80°C though other extreme variables, such as low pH and high salt concentrations may affect their distribution. Hyperthermophilic micro-organisms contain polyamines, these long chain functional polymers contribute to their survival at high temperatures (Hidese *et al.* 2018). Heat loving micro-organisms continue to attract the interest of biotechnologists, notably as a source of liquid biofuels and thermostable enzymes (de Miguel Bouzas *et al.* 2006; Rastogi *et al.* 2010; Goh *et al.* 2013; Urbieta *et al.* 2015;

Zeldes *et al.* 2015). Urbieta and her colleagues have spelt out the advantages of using thermophilic micro-organisms in biotechnological processes.

Prokaryotes

Archaea and bacteria are common in high-temperature environments, notably hot-springs. Common thermophilic bacteria include members of the genera *Anoxybacillus*, *Geobacillus*, *Miobacillus* and *Thermus* whereas their hyperthermophilic counterparts belong to the genera *Aquificae* and *Thermatoga* of the families Aquificaceae and Thermatogaceae respectively (Urbieta *et al.* 2015). The majority of hyperthermophiles are archaea, as exemplified by the genera *Desulfurococcus*, *Pyrodiotum*, *Pyrococcus*, *Pyrolobus*, *Sulfolobus*, *Thermophylum* and *Thermoproteus* of the *Crenarchaeota* (de Miguel Bouzas *et al.* 2006; Zeldes *et al.* 2015). Actinobacteria have been detected in hot springs, including representatives of the genera *Couchiplanes*, *Glycomyces* and *Mycobacterium* (Valverrde *et al.* 2012) and *Actinospica*, *Amycolatopsis* and *Rhodococcus* strains (Kusuma & Goodfellow, pers. com.).

Fungi

Thermophilic fungi received little attention though strains keyed out as *Aspergillus clavatus* (Jiang *et al.* 2013) and *Talaromyces thermophilus* (Chu *et al.* 2010; Guo *et al.* 2011) have been reported.

High-temperature environments-associated specialized metabolites

N-containing compounds

Clavatustides A and B (**175**, **176**, Fig. 5), two unusual cyclodepsipeptides containing an anthranilic acid dimer
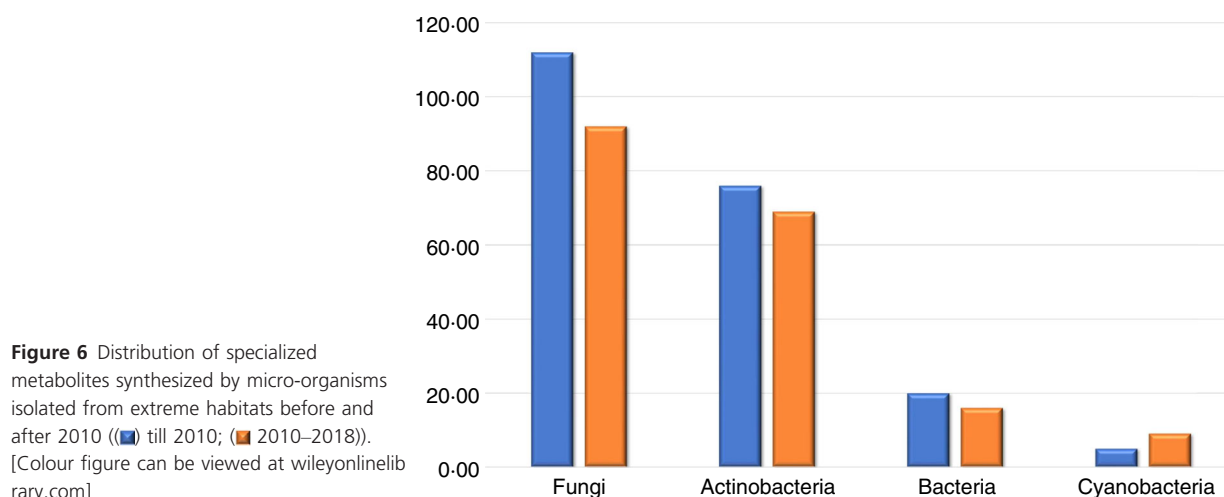
Figure 6 Distribution of specialized metabolites synthesized by micro-organisms isolated from extreme habitats before and after 2010 (■ till 2010; ■ 2010–2018)). [Colour figure can be viewed at wileyonlinelibrary.com]

and phenyllactic acid residues were isolated from an *A. clavatus* strain associated with the thermophilic crab, *Xenograpsus testudinatus* which lives around the sulphur-rich hydrothermal vents in Taiwan, these compounds inhibit the proliferation of hepatocellular carcinoma cell lines (HepG2) by arresting their growth at G1 phase (Jiang *et al.* 2013). Chemical investigation of the thermophilic fungus *T. thermophilus* afforded two new prenylated alkaloids talathermophilins A and B (**177**, **178**) which showed nematicidal toxicity against the parasitic worm *Panagrellus redivevus* (Chu *et al.* 2010). Subsequently, four talathermophilins (**179**–**182**) were isolated from the same fungus (Guo *et al.* 2011).

Carotenoids

The thermophilic bacillus, *Thermus filiformis* was found to produce a group of potent antioxidant carotenoids, the all-trans-zeaxanthin (**183**), zeaxanthin monoglucoside (**184**), thermozeaxanthins (**185**) and thermobiszeaxanthins (**186**) (Mandelli *et al.* 2012).

Conclusions

The microbiological and chemical data drawn from the recent literature on bioprospecting in selected extreme biomes provide strong backing for the premise that the harsh environmental conditions which prevail in the extreme biomes select for micro-organisms that express
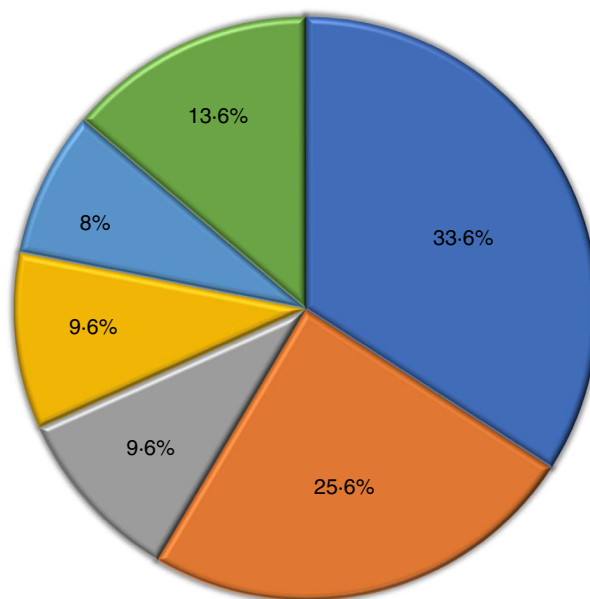
Figure 7 Bioactivities of specialized metabolites produced by micro-organisms recovered from diverse extremophile habitats ((▪ anti-bacterial); (▪ anticancer); (▪ anti-fungal); (▪ anti-inflamatory); (▪ anti-viral); (▪ other activities)). [Colour figure can be viewed at wileyonlinelibrary.com]

new chemistry thereby opening up opportunities for therapeutic drug process development. Indeed, by the end of 2009, approximately 221 specialized metabolites were
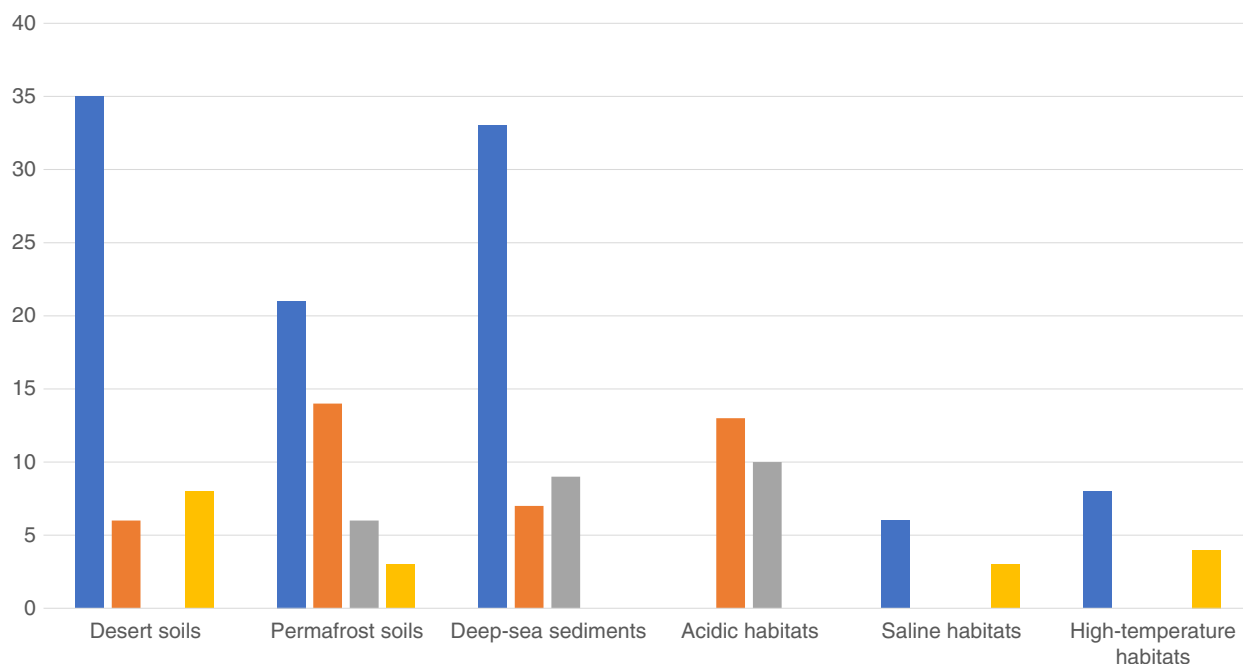
Figure 8 Classes of specialized metabolites produced by micro-organisms isolated from extremophile habitats ((▪ N-containing) (▪ polyketides) (▪ terpenes) (▪ other)). [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1 Examples of actinobacteria isolated from selected extreme biomes and assigned to established genera and associated novel or validly named species*

Hyper/extreme hyperarid, Atacama Desert soils	Deep-Sea sediments	Saline/hypersaline habitats	Hot springs
Genera	Genera	Genera	Genera
Actinomadura	*Dermacoccus*	*Micromonospora*	*Actinospica*
Amycolatopsis	*Micromonospora*	*Nocardia*	*Amycolatopsis*
Arthrobacter	*Rhodococcus*	*Pseudonocardia*	*Couchiplanes*
Blastococcus	*Streptomyces*	*Streptomyces*	*Glycomyces*
Geodermatophilus	*Tsukamurella*		*Mycobacterium*
Kribbella[b]	*Williamsia*		
Lentzea			
Modestobacter			
Microlunatus			
Micromonospora[b]			
Mycobacterium			
Nocardia[b]			
Nocardioides[b]			
Nonomuraea[b]			
Pseudonocardia[b]			
Saccharopolyspora[b]			
Saccharothrix[b]			
Streptomyces[b]			
Terrabacter			
Species	Species		
Amycolatopsis desertii	*Dermacoccus abysii*[c]		
Amycolatopsis vastitatis	*Dermacoccus barathri*		
Blastococcus atacamensis	*Dermacoccus profundi*		
Geodermatophilus chilensis	*Williamsia marianensis*		
Lentzea chajnantorensis[c]			
Micromonospora acroterricola			
Micromonospora arida			
Micromonospora inaquosa			
Pseudonocardia nigra			
Modestobacter caceresii			
Streptomyces asenjonii[c]			
Streptomyces atacamensis			
Streptomyces bullii[c]			
Streptomyces desertii			
Streptomyces leeuwenhoekii[c]			

*Uncharacterized members of the phylum *Actinobacteria* (*sensu* Goodfellow 2012) have been isolated from highly acidic habitats and permaforest soils.

[a]Filamentious actinobacteria.

[b]Novel specialized metabolites produced by members of these species.

identified from diverse extremophilic micro-organisms inhabiting different extreme habitats. However, over a subsequent 8-year period, taxonomically diverse extremophilic and extremotolerant micro-organisms were the source of nearly 200 new specialized metabolites (Fig. 6), the most frequently isolated classes of specialized metabolites were N-containing compounds and polyketides, many of which were produced by filamentous actinobacteria and fungi (Fig. 6). It is also encouraging that these micro-organisms synthesized a broad range of bioactive compounds with a skew towards the production of antibacterial and anticancer agents (Fig. 7). In turn,

micro-organisms isolated from permafrost soils synthesized a broader range of chemical compounds than those from the other extreme habitats (Fig. 8). In contrast, strains isolated from all of the extreme biomes, apart from the highly acidic habitats, were the source of many N-containing metabolites such as alkaloids and peptides. However, relatively little activity was shown by micro-organisms isolated from saline and hypersaline habitats or from high-temperature environments. In this context, it would be interesting to establish the extent of microbial diversity within and between diverse extreme biomes using culture-dependant procedures to determine the

Table 2 Examples of fungi isolated from selected extreme biomes and assigned to established genera and associated novel or validly named species[a]

Atacama Desert soils	Permaforest soils	Deep-sea sediments	Saline/hypersaline habitats
Genera	Genera	Genera	Genera
Alternaria	*Aspergillus*	*Aspergillus*	*Aspergillus*
Amandinea	*Cladospora*	*Cryptococcus*	*Cladosporium*
Aspergillus	*Cladosporium*	*Pichia*	*Emericella*
Buellia	*Geomyces*	*Graphium*	*Eurotium*
Caloplaca	*Oidiodendron*	*Penicillium*	*Hortea*
Cladosporium	*Penicillium*	*Rhodotorula*	*Penicillium*
Diploicia	*Thielavia*		*Trimmatostroma*
Fusarium			*Wallenia*
Myriospora			
Neucatenulostroma			
Penicillium			
Rhizocarpon			
Ulocladium			
Species[b]	Species[b]	Species[b]	Species[b]
Amandinea efflorescens	*Aspergillus ocraceo*	*Aspergillus westerdijkiae*	*Hortea werneckii*
Aspergillus atacamensis	*Diploicia etaliformis*	*Penicillium crustosum*	*T. salinum*
Aspergillus salisburgensis	*Oidiodendron truneatum*		
Diploicia canescens	*Penicillium crustosum*		
Myriospora smaragula	*Penicillium fumiculosum*		
Rhizocarpon simillunum			

[a]Little is known about fungi in highly acidic and hot springs habitats.
[b]Novel specialized metabolites produced by members of these species.

distribution of gifted microbial taxa *sensu* Baltz (2017, 2019).

The results of this survey provide further evidence of the value of the taxonomic approach to the discovery of new drugs, as outlined in Fig. 1. It is evident from Tables 1 and 2 that novel species of filamentous actinobacteria and fungi, particularly those isolated from Atacama Desert habitats, are a very good source of new bioactive compounds thereby underpinning the view that these micro-organisms should feature strongly in bioprospecting campaigns (Bull and Goodfellow 2019). Substantial improvements in the taxonomic approach to drug discovery can be expected given developments in the classification and identification of eukaryotes and prokaryotes driven by advances in whole-genome sequencing procedures and associated improvements in bioinformatics as exemplified by Nouiou *et al.* (2019), increased understanding of the extent of microbial diversity in natural habitats (Bull *et al.* 2018b) coupled with developments designed to provide chemical dereplication (Bull and Goodfellow 2019).

It can also be anticipated that improvements in search and discovering pipelines will be promoted in no small measure by focusing heavily on novel culturable micro-organisms with large genomes, as advocated by Baltz (2017, 2019). In this context, future bioprospecting campaigns should not only be focused on micro-organisms

like actinobacteria and fungi that are known to have a prosperity to synthesize antibiotics of therapeutic value (Bérdy 2012; Newman and Cragg 2016; Zhang *et al.* 2018), but also on representatives of under-explored micro-organisms with genomes rich in NP-BGCs, such as cyanobacteria, frankiae, ktedonobacteria and myxobacteria, representatives of all of these taxa are known to be attractive candidates for drug discovery programmes (Dixit and Suseela 2013; Micallef *et al.* 2015; Baltz 2019; Nouioui *et al.* 2019).

It can be concluded that there are strong grounds for believing that microbial NPs will continue to be a source of new therapeutic agents, an optimism we share with others (Genilloud 2017; Baltz 2017, 2019; Bull and Goodfellow 2019). In particular, there are good reasons for believing that extremophilic and extremotolerant micro-organisms will have pride of place in the provision of a new generation of clinically significant drugs thereby preventing a return to preantibiotic days of medicine. However, the success of future bioprospecting campaigns will depend upon access to extreme biomes, notably ones like the Atacama Desert, that are known to be reservoirs of gifted micro-organisms, especially Actinobacteria and Cyanobacteria (Bull *et al.* 2016; Goodfellow *et al.* 2018; Bull and Goodfellow 2019). However, extreme habitats by their very nature are fragile and hence vulnerable to human activities such as mining and to climate

breakdown, as shown by the decimation of microbial communities in hyperarid core areas in the Atacama Desert due to unprecedented rain (Azua-Bustos *et al.* 2018) and the melting of permafrost soils (Mackelprang *et al.* 2011; Hultman *et al.* 2015). Although concerns along these lines are revisited from time to time (Cockell and Jones 2009; Bull and Goodfellow 2019), there is a crying need for microbiologists and associated institutions to ensure that policy makers promote microbial conservation, especially in habitats known to be the source of gifted micro-organisms.

Conflict of Interest

The authors have no conflict of interest.

References

Abdelkader, M.S., Philippon, T., Asenjo, J.A., Bull, A.T., Goodfellow, M., Ebel, R., Jaspars, M. and Rateb, M.E. (2018) Asenjonamides A-C, antibacterial metabolites isolated from *Streptomyces asenjonii* strain KNN 42.f from an extreme hyper-arid Atacama Desert soil. *J Antibiot* **71**, 425–431.

Abdel-Mageed, W.M., Milne, B.F., Wagner, M., Schumacher, M., Sandor, P., Pathom-aree, W., Goodfellow, M., Bull, A.T. *et al.* (2010) Dermacozines, a new phenazine family from deep-sea dermacocci isolated from a Mariana Trench sediment. *Org Biomol Chem* **8**, 2352–2362.

Adamek, M., Alanjary, M., Sales-Ortells, H., Goodfellow, M., Bull, A.T., Winkler, A., Wibberg, D., Kalinowski, J. *et al.* (2018) Comparative genomics reveals phylogenetic distribution patterns of secondary metabolites in *Amycolatopsis* species. *BMC Genom* **19**, 426. https://doi.org/10.1186/s12864-018-4809-4.

Aguilera, A., Olsson, S. and Puente-Sánchez, F. (2016) Physiological and phylogenetic diversity of acidophilic eukaryotes. In *Acidophiles: Life in Extremely Acidic Environments* ed. Quatrini, R. and Barrie Johnson, D. pp 107–118. UK: Caister Academic Press

Andrei, A.Ş., Banciu, H.L. and Oren, A. (2012) Living with salt: metabolic and phylogenetic diversity of archaea inhabiting saline ecosystems. *FEMS Microbiol Lett* **330**, 1–9.

Arenz, B.E. and Blanchette, R.A. (2011) Distribution and abundance of soil fungi in Antarctica at sites on the Peninsula, Ross Sea Region and McMurdo Dry Valleys. *Soil Biol Biochem* **43**, 308–315.

Asem, M.D., Shi, L., Jiao, J.Y., Wang, D., Han, M.X., Dong, L., Liu, F., Salam, N. *et al.* (2018) *Desertimonas flava* gen. nov., sp. nov. isolated from a desert soil, and proposal of Ilumatobacteraceae fam. nov. *Int J Syst Evol Microbiol* **68**, 3593–3599.

Azua-Bustos, A., Urrejola, C. and Vicuña, R. (2012) Life at the dry edge: microorganisms of the Atacama Desert. *FEBS Lett* **586**, 2939–2945.

Azua-Bustos, A., Fairén, A.G., González-Silva, C., Ascaso, C., Carrizo, D., Fernández-Martínez, M.Á., Fernández-Sampedro, M., García-Descalzo, L. *et al.* (2018) Unprecedented rains decimate surface microbial communities in the hyperarid core of the Atacama Desert. *Sci Rep* **8**, 16706.

Bahl, J., Lau, M.C., Smith, G.J., Vijaykrishna, D., Cary, S.C., Lacap, D.C., Lee, C.K., Papke, R.T. *et al.* (2011) Ancient origins determine global biogeography of hot and cold desert cyanobacteria. *Nat Comm* **2**, 163. https://doi.org/10.1038/ncomms1167.

Baker-Austin, C. and Dopson, M. (2007) Life in acid: pH homeostasis in acidophiles. *Trends Microbiol* **15**, 165–171.

Bakermans, C., Bergholz, P.W., Ayala-del-Río, H. and Tiedje, J. (2009) Genomic insights into cold adaptation of permafrost bacteria. In *Permafrost soils* ed. Margesin, R. pp. 159–168. Berlin, Heidelberg: Springer.

Bakermans, C., Skidmore, M.L., Douglas, S. and McKay, C.P. (2014) Molecular characterization of bacteria from permafrost of the Taylor Valley, Antarctica. *FEMS Microbiol Ecol* **89**, 331–346.

Baltz, R.H. (2017) Gifted microbes for genome mining and natural product discovery. *J Ind Microbiol Biotechnol* **44**, 573–588.

Baltz, R.H. (2019) Natural product drug discovery in the genomic era: conjectures, misconceptions and opportunities. *J Ind Microbiol Biotechnol* **46**, 281–299.

Baricz, A., Coman, C., Andrei, A.Ş., Muntean, V., Keresztes, Z.G., Păuşan, M., Alexe, M. and Banciu, H.L. (2014) Spatial and temporal distribution of archaeal diversity in meromictic, hypersaline Ocnei Lake (Transylvanian Basin, Romania). *Extremophiles* **18**, 399–413.

Baricz, A., Cristea, A., Muntean, V., Teodosiu, G., Andrei, A.-Ş., Molnár, I, Alexe, M., Rakosy-Tican, E. *et al.* (2015) Culturable diversity of aerobic halophilic archaea (Fam. Halobacteriaceae) from hypersaline, meromictic Transylvanian lakes. *Extremophiles* **19**, 525–537.

Becker, K., Hartmann, A., Ganzera, M., Fuchs, D. and Gostner, J. (2016) Immunomodulatory effects of the mycosporine-like amino acids shinorine and porphyra-334. *Mar Drugs* **14**, 119. https://doi.org/10.3390/md14060119.

Bérdy, J. (2012) Thoughts and facts about antibiotics: where we are now and where we are heading. *J Antibiot* **65**, 385–395.

Blanchette, R.A., Held, B.W., Arenz, B.E., Jurgens, J.A., Baltes, N.J., Duncan, S.M. and Farrell, R.L. (2010) An Antarctic hot spot for fungi at Shackleton's historic hut on Cape Royds. *Microb Ecol* **60**, 29–38.

Bowman, J.P. (2008) Genomic analysis of psychrophilic prokaryotes. In *Psychrophiles: From Biodiversity to Biotechnology* ed. Margesin, R., Schinner, F., Marx, J.-C. and Gerday, C. pp. 265–284. Berlin, Heidelberg: Springer.

Bridge, P.D. and Spooner, B.M. (2012) Non-lichenized Antarctic fungi: transient visitors or members of a cryptic ecosystem? *Fungal Ecol* 5, 381–394.

Bull, A.T. (2011) Actinobacteria of the extremobiosphere. In *Extremophiles Handbook* ed. Horikoshi, K. pp. 1204–1240. Tokyo: Springer.

Bull, A.T. and Goodfellow, M. (2019) Rare, and inspirational microbial matter in the extremobiosphere: 16 thousand meters of geopprospecting campaigns. *Microbiology* (In press). https://doi.org/10.1099/mic.0.000822

Bull, A.T., Asenjo, J.A., Goodfellow, M. and Gomez-Silva, B. (2016) The Atacama Desert: technical resources and the growing importance of novel microbial diversity. *Ann Rev Microbiol* 70, 215–234.

Bull, A.T., Andrews, B.A., Dorador, C. and Goodfellow, M. (2018a) Microbiology of the Atacama Desert. *Antonie Van Leeuwenhoek* 111, 1269–1491.

Bull, A.T., Idris, H., Sanderson, R., Asenjo, J., Andrews, B. and Goodfellow, M. (2018b) High altitude, hyper-arid soils of the Central-Andes harbor mega-diverse communities of actinobacteria. *Extremophiles* 22, 47–57.

Busarakam, K., Bull, A.T., Girard, G., Labeda, D.P., van Wezel, G.P. and Goodfellow, M. (2014) *Streptomyces leeuwenhoekii* sp. nov., the producer of chaxalactins and chaxamycins, forms a distinct branch in *Streptomyces* gene trees. *Antonie Van Leeuwenhoek* 105, 849–861.

Busarakam, K., Brown, R., Bull, A.T., Tan, G.Y.A., Zucchi, T.D., da Silva, L.J., de Souza, W.R. and Goodfellow, M. (2016a) Classification of thermophilic actinobacteria isolated from arid desert soils, including the description of *Amycolatopsis deserti* sp. nov. *Antonie Van Leeuwenhoek* 109, 319–334.

Busarakam, K., Bull, A.T., Trujillo, M.E., Riesco, R., Sangal, V., van Wezel, G.P. and Goodfellow, M. (2016b) *Modestobacter caceresii* sp. nov., novel actinobacteria with an insight into their adaptive mechanisms for survival in extreme hyper-arid Atacama Desert soils. *Syst Appl Microbiol* 39, 243–251.

Carro, L., Nouioui, I., Sangal, V., Meier-Kolthoff, J.P., Trujillo, M.E., Montero-Calasanz, M.C., Sahin, N., Smith, D.L. *et al.* (2018a) Genome-based classification of micromonosporae with a focus on their biotechnological and ecological potential. *Sci Rep* 8, 525.

Carro, L., Razmilic, V., Nouioui, I., Richardson, L., Pan, C., Golinska, P., Asenjo, J.A., Bull, A.T. *et al.* (2018b) Hunting for cultivable *Micromonospora* strains in soils of the Atacama Desert. *Antonie Van Leeuwenhoek* 111, 1–13.

Carro, L., Golinska, P., Nouioui, I., Bull, A.T., Igual, J.M., Klenk, H.-P. and Goodfellow, M. (2019). *Micromonospora acroterricola* sp. nov; a novel actinobacterium isolated from a high altitude Atacama Desert soil. *Int J Syst Evol Microbiol* 9, 4678. https://doi.org/10.1038/s41598-019-38789-z

Castillo, R.V. and Beck, A. (2012) Photobiont selectivity and specificity in *Caloplaca* species in a fog-induced community in the Atacama Desert, northern Chile. *Fungal Biol* 116, 665–676.

Castro, J.F., Nouioui, I., Sangal, V., Choi, S., Yang, S.-J., Kim, B.-Y., Trujillo, M.E., Riesco, R. *et al.* (2018a) *Blastococcus atacamensis* sp. nov., a novel strain adapted to life in the Yungay core region of the Atacama Desert. *Int J Syst Evol Microbiol* 68, 2712–2721.

Castro, J.F., Nouioui, I., Sangal, V., Trujillo, M.E., Montero-Calasanz, M.C., Rahmani, T., Bull, A.T., Asenjo, J.A. *et al.* (2018b) *Geodermatophilus chilensis* sp. nov., from soil of the Yungay core-region of the Atacama Desert, Chile. *Syst Appl Microbiol* 41, 427–436.

Chaouch, F.C., Bouras, N., Mokrane, S., Zitouni, A., Schumann, P., Spröer, C., Sabaou, N. and Klenk, H.-P. (2016) *Streptosporangium becharense* sp. nov., an actinobacterium isolated from desert soil. *Int J Syst Evol Microbiol* 66, 2484–2490.

Chattopadhyay, M.K. (2006) Mechanism of bacterial adaptation to low temperature. *J. Biosci* 31, 157–165.

Chen, L.X., Hu, M., Huang, L.N., Hua, Z.S., Kuang, J.-L., Li, S.-J. and Shu, W.-S. (2015) Comparative metagenomic and metatranscriptomic analyses of microbial communities in acid mine drainage. *ISME J* 9, 1579–1589.

Chen, L.X., Huang, L.N., Mendez-Garcia, C., Kuang, J.L., Hua, Z.-S., Liu, J. and Shu, W.-S. (2016) Microbial communities, processes and functions in acid mine drainage ecosystems. *Curr Opin Biotechnol* 38, 150–158.

Chu, Y.S., Niu, X.M., Wang, Y.L., Guo, J.P., Pan, W.Z., Huang, X.W. and Zhang, K.Q. (2010) Isolation of putative biosynthetic intermediates of prenylated indole alkaloids from a thermophilic fungus *Talaromyces thermophilus*. *Org Lett* 12, 4356–4359.

Cirés, S., Casero, M.C. and Quesada, A. (2017) Toxicity at the edge of life: a review on cyanobacterial toxins from extreme environments. *Mar Drugs* 15, 233. https://doi.org/10.3390/md15070233.

Cockell, C.S. and Jones, H.L. (2009) Advancing the case for microbial conservation. *Oryx* 43, 520–526.

Conley, C.A., Ishkhanova, G., Mckay, C.P. and Cullings, K. (2006) A preliminary survey of non-lichenized fungi cultured from the hyperarid Atacama Desert of Chile. *Astrobiol* 6, 521–526.

Coolen, M.J., van de Giessen, J., Zhu, E.Y. and Wuchter, C. (2011) Bioavailability of soil organic matter and microbial community dynamics upon permafrost thaw. *Environ Microbiol* 13, 2299–2314.

Cordero, R.R., Damiani, A., Jorquera, J., Sepúlveda, E., Caballero, M., Fernandez, S., Feron, S., Llanillo, P.J. *et al.* (2018) Ultraviolet radiation in the Atacama Desert. *Antonie Van Leeuwenhoek* 111, 1301–1313.

D'Orazio, N., Gammone, M.A., Gemello, E., De Girolamo, M., Cusenza, S. and Riccioni, G. *et al.* (2012) Marine bioactives: Pharmacological properties and potential applications against inflammatory diseases. *Mar Drugs* 10, 812–833.

D'Amico, S., Collins, T., Marx, J.C., Feller, G. and Gerday, C. (2006) Psychrophilic microorganisms: challenges for life. *EMBO Rep* **7**, 385–389.

De Maayer, P., Anderson, D., Cary, C. and Cowan, D.A. (2014) Some like it cold: Understanding the survival strategies of psychrophiles. *EMBO Rep* **15**, 508–517.

Denef, V.J., Mueller, R.S. and Banfield, J.F. (2010) AMD biofilms: using model communities to study microbial evolution and ecological complexity in nature. *ISME J* **4**, 599–610.

Deslippe, J.R., Hartmann, M., Mohn, W.W. and Simard, S.W. (2011) Long-term experimental manipulation of climate alters the ectomycorrhizal community of *Betula nana* in Arctic tundra. *Glob Change Biol* **17**, 1625–1636.

Desroches, T.C., McMullin, D.R. and Miller, J.D. (2014) Extrolites of *Wallemia sebi*, a very common fungus in the built environment. *Indoor Air* **24**, 533–42.

Díaz-Cárdenas, C., Cantillo, A., Rojas, L.Y., Sandoval, T., Fiorentino, S., Robles, J., Ramos, F.A., Zambrano, M.M. *et al.* (2017) Microbial diversity of saline environments: searching for cytotoxic activities. *AMB Express* **7**, 223. https://doi.org/10.1186/s13568-017-0527-6.

Dickinson, I., Goodall-Copestake, W., Thorne, M., Schlitt, T., Ávila-Jiménez, M. and Pearce, D. (2016) Extremophiles in an Antarctic marine ecosystem. *Microorganisms* **4**, 8. https://doi.org/10.3390/microorganisms4010008.

Ding, D., Chen, G., Wang, B., Wang, Q., Liu, D., Peng, M. and Shi, P. (2013) Culturable actinomycetes from desert ecosystem in northeast of Qinghai-Tibet Plateau. *Annals Microbiol* **63**, 259–266.

Dixit, R.B. and Suseela, M.R. (2013) Cyanobacteria: potential candidates for drug discovery. *Antonie Van Leeuwenhoek* **103**, 947–961.

Druschel, G.K., Baker, B.J., Gihring, T.M. and Banfield, J.F. (2004) Acid mine drainage biogeochemistry at Iron Mountain, California. *Geochem Trans* **5**, 13. https://doi.org/10.1186/1467-4866-5-13.

Elsayed, S.S., Trusch, F., Deng, H., Raab, A., Prokes, I., Busarakam, K., Asenjo, J.A., Andrews, B.A. *et al.* (2015) Chaxapeptin, a lasso peptide from extremotolerant *Streptomyces leeuwenhoekii* strain C58 from the hyperarid Atacama Desert. *J Org Chem* **80**, 10252–10260.

Enache, M., Teodosiu, G., Itoh, T., Kamekura, M. and Stan-Lotter, H. (2017) Halophilic microorganisms from man-made and natural hypersaline environments: physiology, ecology, and biotechnological potential. In *Adaption of Microbial Life to Environmental Extremes* ed. Stan-Lotter, H. and Fendrihan, S. pp. 201–226. Cham: Springer.

Falteisek, L. and Čepička, I. (2012) Microbiology of diverse acidic and non-acidic microhabitats within a sulfidic ore mine. *Extremophiles* **16**, 911–922.

Feller, G. and Gerday, C. (2003) Psychrophilic enzymes: hot topics in cold adaptation. *Nat Rev Microbiol* **1**, 200–208.

Figueroa, L., Jiménez, C., Rodríguez, J., Areche, C., Chávez, R., Henríquez, M., de laCruz, M. and Díaz, C. *et al.* (2015) 3-Nitroasterric acid derivatives from an Antarctic sponge-derived *Pseudogymnoascus* sp. fungus. *J Nat Prod* **78**, 919–923.

Fujiyoshi, M., Yoshitake, S., Watanabe, K., Murota, K., Tsuchiya, Y., Uchida, M. and Nakatsubo, T. (2011) Successional changes in ectomycorrhizal fungi associated with the polar willow *Salix polaris* in a deglaciated area in the High Arctic, Svalbard. *Polar Biol* **34**, 667–673.

Gadgeel, S.M., Boinpally, R.R., Heilbrun, L.K., Wozniak, A., Jain, V., Redman, B., Zalupski, M., Wiegand, R. *et al.* (2003) A phase I clinical trial of spicamycin derivative KRN5500 (NSC 650426) using a phase I accelerated titration "2B" design. *Invest New Drugs* **21**, 63–74.

Ganzert, L., Bajerski, F. and Wagner, D. (2014) Bacterial community composition and diversity of five different permafrost-affected soils of Northeast Greenland. *FEMS Microbiol Ecol* **89**, 426–441.

Genilloud, O. (2017) Actinomycetes: still a source of novel antibiotics. *Nat Prod Rep* **34**, 1203–1232.

Gessler, N.N., Egorova, A.S. and Belozerskaya, T.A. (2014) Melanin pigments of fungi under extreme environmental conditions. *Appl Biochem Microbiol* **50**, 105–113.

Gilichinsky, D., Vishnivetskaya, T., Petrova, M., Spirina, E., Mamykin, V. and Rivlina, K. (2008) Bacteria in permafrost. In *Psychrophiles: From Biodiversity to Biotechnology* ed. Margesin, R., Schinner, F., Marx, J.C. and Gerday, C. pp 83–102. Berlin, Heidelberg: Springer.

Gittel, A., Bárta, J., Kohoutová, I., Mikutta, R., Owens, S., Gilbert, J., Schnecker, J., Wild, B. *et al.* (2014) Distinct microbial communities associated with buried soils in the Siberian tundra. *ISME J* **8**, 841–853.

Goh, K.M., Kahar, U.M., Chai, Y.Y., Chong, C.S., Chai, K.P., Ranjani, V., Illias, R.M. and Chan, K.-G. (2013) Recent discoveries and applications of *Anoxybacillus*. *Appl Microbiol Biotechnol* **97**, 1475–1488.

Goltsman, D.S.A., Dasari, M., Thomas, B.C., Shah, M.B., VerBerkmoes, N.C., Hettich, R.L. and Banfield, J.F. (2013) A new group in the *Leptospirillum* clade: cultivation-independent community genomics, proteomics and transcriptomics of the new species *Leptospirillum* group IV UBA BS. *Appl Environ Microbiol* **79**, 5384–5393.

Gómez-Silva, B. (2018) Lithobiontic life:"Atacama rocks are well and alive". *Antonie Van Leeuwenhoek* **111**, 1333–1343.

Gonçalves, V.N., Cantrell, C.L., Wedge, D.E., Ferreira, M.C., Soares, M.A., Jacob, M.R., Oliveira, F.S., Galante, D. *et al.* (2016) Fungi associated with rocks of the Atacama Desert: taxonomy, distribution, diversity, ecology and bioprospection for bioactive compounds. *Environ Microbiol* **18**, 232–245.

Gonçalves, V.N., Vitoreli, G.A., de Menezes, G.C., Mendes, C.R., Secchi, E.R., Rosa, C.A. and Rosa, L.H. (2017) Taxonomy, phylogeny and ecology of cultivable fungi present in seawater gradients across the Northern Antarctica Peninsula. *Extremophiles* **21**, 1005–1015.

Goodfellow, M. (2012) Phylum XXVI. *Actinobacteria* phyl. nov. In *Bergey's Manual of Systematic Bacteriology. The Actinobacteria, Part A, vol 5, 2nd Edition* pp. 33–34. New York: Springer.

Goodfellow, M. and Fiedler, H.P. (2010) A guide to successful bioprospecting: informed by actinobacterial systematics. *Antonie Van Leeuwenhoek* **98**, 119–142.

Goodfellow, M., Busarakam, K., Idris, H., Labeda, D.P., Nouioui, I., Brown, R., Kim, B.-Y., del Carmen Montero-Calasanz, M. *et al.* (2017) *Streptomyces asenjonii* sp. nov., isolated from hyper-arid Atacama Desert soils and emended description of *Streptomyces viridosporus* Pridham et al. 1958. *Antonie Van Leeuwenhoek* **110**, 1133–1148.

Goodfellow, M., Nouioui, I., Sanderson, R., Xie, F. and Bull, A.T. (2018) Rare taxa and dark microbial matter: novel bioactive actinobacteria abound in Atacama Desert soils. *Antonie Van Leeuwenhoek* **111**, 1315–1332.

Grishkan, I. and Nevo, E. (2010) Spatiotemporal distribution of soil microfungi in the Makhtesh Ramon area, central Negev desert, Israel. *Fungal Ecol* **3**, 326–337.

Gunde-Cimerman, N. and Zalar, P. (2014) Extremely halotolerant and halophilic fungi inhabit brine in solar salterns around the globe. *Food Technol Biotechnol* **52**, 170–179.

Guo, J.P., Tan, J.L., Wang, Y.L., Wu, H.Y., Zhang, C.-P., Niu, X.-M., Pan, W.-Z., Huang, X.-W. *et al.* (2011) Isolation of talathermophilins from the thermophilic fungus *Talaromyces thermophilus* YM3-4. *J Nat Prod* **74**, 2278–2281.

Harvey, A.L., Edrada-Ebel, R. and Quinn, R.J. (2015) The re-emergence of natural products for drug discovery in the genomics era. *Nat Rev drug Disc* **14**, 11–129.

Hayakawa, Y., Nakagawa, M., Kawai, H., Tanabe, K., Nakayama, H., Shimazu, A., Seto, H. and Otake, N. (1983) Studies on the differentiation inducers of myeloid leukemic cells. *J Antibiot* **36**, 934–937.

Hedrich, S. and Johnson, D.B. (2013) *Acidithiobacillus ferridurans* sp. nov., an acidophilic iron-, sulfur-and hydrogen-metabolizing chemolithotrophic gammaproteobacterium. *Int J Syst Evol Microbiol* **63**, 4018–4025.

Hezbri, K., Ghodhbane-Gtari, F., delCarmen Montero-Calasanz, M., Nouioui, I., Rohde, M., Spröer, C., Schumann, P., Klenk, H.-P. *et al.* (2016) *Geodermatophilus pulveris* sp. nov., a gamma-radiation-resistant actinobacterium isolated from the Sahara desert. *Int J Syst Evol Microbiol* **66**, 3828–3834.

Hidese, R., Fukuda, W., Niitsu, M. and Fujiwara, S. (2018) Identification of branched-chain polyamines in hyperthermophiles. In *Polyamines* ed. Alcázar, R. and Tiburcio, A.F. pp. 81–94. New York, NY: Humana Press.

Hoffmann, T., Krug, D., Bozkurt, N., Duddela, S., Jansen, R., Garcia, R., Gerth, K., Steinmetz, H. *et al.* (2018) Correlating chemical diversity with taxonomic distance for discovery of natural products in myxobacteria. *Nat Comm* **9**, 803. https://doi.org/10.1038/s41467-018-03184-1.

Horikoshi, K. and Bull, A.T. (2011) Prologue: Definition, categories, distribution, origin and evolution, pioneering studies, and emerging fields of extremophiles. In *Extremophiles Handbook* ed. Horikoshi, K. pp. 3–15. Tokyo: Springer.

Houston, J. (2006) Evaporation in the Atacama Desert: an empirical study of spatio-temporal variations and their causes. *J Hydrol* **330**, 402–412.

Hu, W., Zhang, Q., Tian, T., Cheng, G., An, L. and Feng, H. (2015) The microbial diversity, distribution, and ecology of permafrost in China: a review. *Extremophiles* **19**, 693–705.

Hu, Q.W., Chu, X., Xiao, M., Li, C.T., Yan, Z.F., Hozzein, W.N., Kim, C.J., Zhi, X.Y. *et al.* (2016) *Arthrobacter deserti* sp. nov., isolated from a desert soil sample. *Int J Syst Evol Microbiol* **66**, 2035–2040.

Huang, H., Hou, L., Li, H., Qiu, Y., Ju, J. and Li, W. (2016) Activation of a plasmid-situated type III PKS gene cluster by deletion of a *wbl* gene in deepsea-derived *Streptomyces somaliensis* SCSIO ZH66. *Microb Cell Fact* **15**, 116. https://doi.org/10.1186/s12934-016-0515-6.

Hultman, J., Waldrop, M.P., Mackelprang, R. and David, M.M. (2015) Multi-omics of permafrost, active layer and thermokarst bog soil microbiomes. *Nature* **521**, 208–212.

Ibeyaima, A., Singh, A.K., Lal, R., Gupta, S., Goodfellow, M. and Sarethy, I.P. (2018) *Saccharothrix tharensis* sp. nov., an actinobacterium isolated from the Thar Desert, India. *Antonie Van Leeuwenhoek* **111**, 2141–2147.

Idris, H., Nouioui, I., Asenjo, J.A., Bull, A.T. and Goodfellow, M. (2017a) *Lentzea chajnantorensis* sp. nov., an actinobacterium from a very high altitude Cerro Chajnantor gravel soil in northern Chile. *Antonie Van Leeuwenhoek* **110**, 795–802.

Idris, H., Goodfellow, M., Sanderson, R., Asenjo, J.A. and Bull, A.T. (2017b) Actinobacterial rare biospheres and dark matter revealed in habitats of the Chilean Atacama Desert. *Sci Rep* **7**, 8373. https://doi.org/10.1038/s41598-017-08937-4.

Idris, H., Nouioui, I., Pathom-Aree, W., Castro, J.F., Bull, A.T., Andrews, B.A., Asenjo, J.A. and Goodfellow, M. (2018) *Amycolatopsis vastitatis* sp. nov., an isolate from a high altitude subsurface soil on Cerro Chajnantor, northern Chile. *Antonie Van Leeuwenhoek* **111**, 1523–1533.

Jaakkola, S.T., Ravantti, J.J., Oksanen, H.M. and Bamford, D.H. (2016) Buried alive: microbes from ancient halite. *Trends Microbiol* **24**, 148–160.

Jančič, S., Frisvad, J.C., Kocev, D., Gostinčar, C., Džeroski, S. and Gunde-Cimerman, N. (2016) Production of secondary metabolites in extreme environments: food-and airborne *Wallemia* spp. produce toxic metabolites at hypersaline conditions. *PLoS ONE* **11**, e0169116. https://doi.org/10.1371/journal.pone.0169116.

Janek, T., Łukaszewicz, M., Rezanka, T. and Krasowska, A. (2010) Isolation and characterization of two new lipopeptide biosurfactants produced by *Pseudomonas fluorescens* BD5 isolated from water from the Arctic

Archipelago of Svalbard. *Bioresour Technol* **101**, 6118–6123.

Jansson, J.K. and Taş, N. (2014) The microbial ecology of permafrost. *Nat Rev Microbiol* **12**, 414–425.

Jiang, W., Ye, P., Chen, C.T., Wang, K., Liu, P., He, S., Wu, X., Gan, L. et al. (2013) Two novel hepatocellular carcinoma cycle inhibitory cyclodepsipeptides from a hydrothermal vent crab-associated fungus *Aspergillus clavatus* C2WU. *Mar Drugs* **11**, 4761–4772.

Johnson, D.B. (2012) Acidophilic algae isolated from mine-impacted environments and their roles in sustaining heterotrophic acidophiles. *Front Microbiol* **3**, 325. https://doi.org/10.3389/fmicb.2012.00325.

Johnson, D.B. and Quatrini, R. (2016) Acidophile microbiology in space and time. In *Acidophiles: Life in Extremely Acidic Environments* ed. Quatrini, R. and Barrie Johnson, D. pp. 3–16. Norfolk: Caister Academic Press.

Katz, L. and Baltz, R.H. (2016) Natural product discovery: past, present, and future. *J Ind Microbiol Biotechnol* **43**, 155–176.

Keller, N.P. (2019) Fungal secondary metabolism: regulation, function and drug discovery. *Nat Rev Microbiol* **17**, 167–180.

Keller, N.P., Turner, G. and Bennett, J.W. (2005) Fungal secondary metabolism-from biochemistry to genomics. *Nat Rev Microbiol* **3**, 637–647.

Kim, S.H., Shin, Y., Lee, S.H., Oh, W.K., Oh, K.B., Lee, S.K., Shin, J. and Oh, D.C. (2015) The secondary metabolites from halophilic actinomycetes from a solar saltern in Korea. *Planta Med* **81**, PQ17. https://doi.org/10.1055/s-0035-1556351.

Konings, W.N., Albers, S.V., Koning, S. and Driessen, A.J. (2002) The cell membrane plays a crucial role in survival of bacteria and archaea in extreme environments. *Antonie Van Leeuwenhoek* **81**, 61–72.

Krug, D. and Müller, R. (2014) Secondary metabolomics: the impact of mass spectrometry-based approaches on the discovery and characterization of microbial natural products. *Nat Prod Rep* **31**, 768–783.

Kuang, J.L., Huang, L.N., Chen, L.X., Hua, Z.S., Li, S.-J., Hu, M., Li, J.-T. and Shu, W.-S. (2013) Contemporary environmental variation determines microbial diversity patterns in acid mine drainage. *ISME J* **7**, 1038–1050.

Kurapova, I., Zenova, G.M., Sudnitsyn, I.I., Kizilova, A.K., Manucharova, N.A., Norovsuren, Z.H. and Zvyagintsev, D.G. (2012) Thermotolerant and thermophilic actinomycetes from soils of Mongolia Desert Steppe Zone. *Microbiology* **81**, 98–108.

Lacap, D.C., Warren-Rhodes, K.A., McKay, C.P. and Pointing, S.B. (2011) Cyanobacteria and chloroflexi-dominated hypolithic colonization of quartz at the hyper-arid core of the Atacama Desert, Chile. *Extremophiles* **15**, 31–38.

Lacap-Bugler, D.C., Lee, K.K., Archer, S., Gillman, L.N., Lau, M.C.Y., Leuzinger, S., Lee, C.K., Maki, T. et al. (2017) Global diversity of desert hypolithic cyanobacteria. *Front Microbiol* **8**, 867. https://doi.org/10.3389/fmicb.2017.00867.

Laity, J.J. (2009) *Deserts and Desert Environments*. Chichester: John Wiley & Sons.

Li, W.J., Chen, H.H., Zhang, Y.Q., Kim, C.J., Park, D.J., Lee, J.C., Xu, L.H. and Jiang, C.L. (2005) *Citricoccus alkalitolerans* sp. nov., a novel actinobacterium isolated from a desert soil in Egypt. *Int J Syst Evol Microbiol* **55**, 87–90.

Li, W.J., Zhang, Y.Q., Schumann, P., Chen, H.H., Hozzein, W.N., Tian, X.P., Xu, L.H. and Jiang, C.L. (2006) *Kocuria aegyptia* sp. nov., a novel actinobacterium isolated from a saline, alkaline desert soil in Egypt. *Int J Syst Evol Microbiol* **56**, 733–737.

Li, L., Li, D., Luan, Y., Gu, Q. and Zhu, T. (2012) Cytotoxic metabolites from the antarctic psychrophilic fungus *Oidiodendron truncatum*. *J Nat Prod* **75**, 920–927.

Li, H., Huang, H., Hou, L., Ju, J. and Li, W. (2017) Discovery of antimycin-type depsipeptides from a wbl gene mutant strain of deepsea-derived *Streptomyces somaliensis* SCSIO ZH66 and their effects on pro-inflammatory cytokine production. *Front MIicrobiol* **8**, 678. https://doi.org/10.3389/fmicb.2017.00678.

Liljeqvist, M., Ossandon, F.J., González, C., Rajan, S., Stell, A., Valdes, J., Holmes, D.S. and Dopson, M. (2015) Metagenomic analysis reveals adaptations to a cold-adapted lifestyle in a low-temperature acid mine drainage stream. *FEMS Microbiol Ecol* **91**, https://doi.org/10.1093/femsec/fiv011.

Lin, A., Wu, G., Gu, Q., Zhu, T. and Li, D. (2014) New eremophilane-type sesquiterpenes from an Antarctic deepsea derived fungus *Penicillium* sp. PR19N-1. *Arch Pharm Res* **37**, 839–844.

Liu, J.T., Hu, B., Gao, Y., Zhang, J.P., Jiao, B.H., Lu, X.L. and Liu, X.Y. (2014) Bioactive tyrosine-derived cytochalasins from fungus *Eutypella* sp. D-1. *Chem Biodivers* **11**, 800–806.

Liu, J., Hernández, S.E., Swift, S. and Singhal, N. (2018a) Estrogenic activity of cylindrospermopsin and anatoxin-a and their oxidative products by FeIII-B*/H$_2$O$_2$. *Water Res* **132**, 309–319.

Liu, S.W., Li, F.N., Qi, X., Xie, Y.Y. and Sun, C.H. (2018b) *Nakamurella deserti* sp. nov., isolated from rhizosphere soil of Reaumuria in the Taklamakan desert. *Int J Systc Evol Microbiol* **69**, 214–219.

López-García, P., López-López, A., Moreira, D. and Rodríguez-Valera, F. (2001) Diversity of free-living prokaryotes from a deep-sea site at the Antarctic Polar Front. *FEMS Microbiol Ecol* **36**, 193–202.

Lu, X.L., Liu, J.T., Liu, X.Y., Gao, Y., Zhang, J., Jiao, B.-H. and Zheng, H. (2014) Pimarane diterpenes from the Arctic fungus *Eutypella* sp. D-1. *J Antibiot* **67**, 171–174.

Lubsanova, D.A., Zenova, G.M., Kozhevin, P.A., Manucharova, N.A. and Shvarov, A.P. (2014) Filamentous actinobacteria of the salinesoils of arid territories. *Moscow Univ Soil Sci Bull* **69**, 88–92.

Luo, X., Wang, J., Zeng, X.C., Wang, Y., Zhou, L., Nie, Y., Dai, J. and Fang, C. (2012) *Mycetocola manganoxydans* sp.

nov., an actinobacterium isolated from the Taklamakan desert. *Int J Syst Evol Microbiol* **62**, 2967–2970.

Macelroy, R.D. (1974) Some comments on the evolution of extremophiles. *Biosystem* **6**, 74–75.

Mackelprang, R., Waldrop, M.P., DeAngelis, K.M., David, M.M., Chavarria, K.L., Blazewicz, S.J., Rubin, E.M. and Jansson, J.K. (2011) Metagenomic analysis of a permafrost microbial community reveals a rapid response to thaw. *Nature* **480**, 368–371.

Malard, L.A. and Pearce, D.A. (2018) Microbial diversity and biogeography in Arctic soils. *Environ Microbiol Rep* **10**, 611–625.

Mandelli, F., Miranda, V.S., Rodrigues, E. and Mercadante, A.Z. (2012) Identification of carotenoids with high antioxidant capacity produced by extremophile microorganisms. *World J Microbiol Biotechnol* **28**, 1781–1790.

Martineau, C., Pan, Y., Bodrossy, L., Yergeau, E., Whyte, L.G. and Greer, C.W. (2014) Atmospheric methane oxidizers are present and active in Canadian high Arctic soils. *FEMS Microbiol Ecol* **89**, 257–269.

Martinelli, L., Zalar, P., Gunde-Cimerman, N., Azua-Bustos, A., Sterflinger, K. and Piñar, G. (2017) *Aspergillus atacamensis* and *A. salisburgensis*: two new halophilic species from hypersaline/arid habitats with a phialosimplex-like morphology. *Extremophiles* **21**, 755–773.

Méndez-García, C., Peláez, A.I., Mesa, V., Sánchez, J., Golyshina, O.V. and Ferrer, M. (2015) Microbial diversity and metabolic networks in acid mine drainage habitats. *Front Microbiol* **6**, 475. https://doi.org/10.3389/fmicb.2015.00475.

Metcalf, J.S. and Codd, G.A. (2012) Cyanotoxins. In *Ecology of Cyanobacteria II* pp. 651–675. Berlin, Germany: Springer.

Micallef, M.L., D'Agostino, P.M., Sharma, D., Viswanathan, R. and Moffitt, M.C. (2015) Genome mining for natural product biosynthetic gene clusters in the Subsection V cyanobacteria. *BMC Genom* **16**, 669. https://doi.org/10.1186/s12864-015-1855-z.

de Miguel Bouzas, T., Barros-Velázquez, J. and Gonzalez Villa, T. (2006) Industrial applications of hyperthermophilic enzymes: a review. *Protein Pept Lett* **13**, 645–651.

Minegishi, H., Echigo, A., Nagaoka, S., Kamekura, M. and Usami, R. (2010) *Halarchaeum acidiphilum* gen. nov., sp. nov., a moderately acidophilic haloarchaeon isolated from commercial solar salt. *Int J Syst Evol Microbiol* **60**, 2513–2516.

Mirete, S., Morgante, V. and González-Pastor, J.E. (2017) Acidophiles: diversity and mechanisms of adaptation to acidic environments. In *Adaption of Microbial Life to Environmental Extremes* ed. Stan-Lotter, H. and Fendrihan, S. pp. 227–251. Cham: Springer.

Mohammadipanah, F. and Wink, J. (2016) Actinobacteria from arid and desert habitats: diversity and biological activity. *Front Microbiol* **6**, 1541. https://doi.org/10.3389/fmicb.2015.01541.

Moon, K., Ahn, C.H., Shin, Y., Won, T., Ko, K., Lee, S., Oh, K.-B., Shin, J. *et al.* (2014) New benzoxazine secondary metabolites from an Arctic actinomycete. *Mar Drugs* **12**, 2526–2538.

Mueller, R.S., Denef, V.J., Kalnejais, L.H., Suttle, K.B., Thomas, B.C., Wilmes, P., Smith, R.L., Nordstrom, D.K. *et al.* (2010) Ecological distribution and population physiology defined by proteomics in a natural microbial community. *Mol Syst Biol* **6**, 374. https://doi.org/10.1038/msb.2010.30.

Murgia, M., Fiamma, M., Barac, A., Deligios, M., Mazzarello, V., Paglietti, B., Cappuccinelli, P., Al-Qahtani, A. *et al.* (2018) Biodiversity of fungi in hot desert sands. *Microbiol Open* **8**, e00595, https://doi.org/10.1002/mbo3.595.

Nachtigall, J., Kulik, A., Helaly, S., Bull, A.T., Goodfellow, M., Asenjo, J.A., Maier, A., Wiese, J. *et al.* (2011) Atacamycins A-C, 22-membered antitumor macrolactones produced by *Streptomyces* sp. C38. *J Antibiot* **64**, 775–780.

Nagano, Y., Nagahama, T. and Abe, F. (2013) Cold-adapted yeasts in deep-sea environments. In *Cold-adapted Yeasts* ed. Buzzini, P. and Margesin, R. pp. 149–171. Berlin: Springer.

Namsaraev, Z., Mano, M.J., Fernandez, R. and Wilmotte, A. (2010) Biogeography of terrestrial cyanobacteria from Antarctic ice-free areas. *Annals Glaciol* **51**, 171–177.

Navarro-González, R., Rainey, F.A., Molina, P., Bagaley, D.R., Hollen, B.J., de laRosa, J., Small, A.M., Quinn, R.C. *et al.* (2003) Mars-like soils in the Atacama Desert, Chile, and the dry limit of microbial life. *Science* **302**, 1018–1021.

Newman, D.J. and Cragg, G.M. (2016) Natural products as sources of new drugs from 1981 to 2014. *J Nat Prod* **79**, 629–661.

Niu, S., Li, S., Chen, Y., Tian, X., Zhang, H., Zhang, G., Zhang, W., Yang, X. *et al.* (2011) Lobophorins E and F, new spirotetronate antibiotics from a South China Sea-derived *Streptomyces* sp. SCSIO 01127. *J Antibiot* **64**, 711–716.

Nouioui, I., Cortez-albabay, C., Carro, L., Castro, J.J., Gtari, M., Ghodhbane-Gtari, F., Peter Klenk, H., Tisa, L.S. *et al.* (2019) Genomic insights into plant-growth promoting potential of the genus Frankia. *Front Microbiol* **10**, 1457. https://doi.org/10.3389/fmicb.2019.01457.

Okoro, C.K., Brown, R., Jones, A.L., Andrews, B.A., Asenjo, J.A., Goodfellow, M. and Bull, A.T. (2009) Diversity of culturable actinomycetes in hyper-arid soils of the Atacama Desert, Chile. *Antonie Van Leeuwenhoek* **95**, 121–133.

Ondeyka, J.G., Smith, S.K., Zink, D.L., Vicente, F., Basilio, A., Bills, G.F., Polishook, J.D., Garlisi, C. *et al.* (2014) Isolation, structure elucidation and antibacterial activity of a new tetramic acid, ascosetin. *J Antibiot* **67**, 527–531.

Onofri, S., Selbmann, L., De Hoog, G.S., Grube, M., Barreca, D., Ruisi, S. and Zucconi, L. (2007) Evolution and adaptation of fungi at boundaries of life. *Adv Space Res* **40**, 1657–1664.

Oren, A. (1999) Bioenergetic aspects of halophilism. *Microbiol Mol Biol Rev* **63**, 334–348.

Ouchari, L., Boukeskasse, A., Bouizgarne, B. and Ouhdouch, Y. (2018) Antimicrobial potential of actinomycetes isolated from unexplored hot Merzouga desert and their taxonomic diversity. *Biol Open* **bio-035410**, https://doi.org/10.1242/bio.035410.

Ozerskaya, S., Kochkina, G., Ivanushkina, N. and Gilichinsky, D.A. (2009) Fungi in permafrost. In *Permafrost Soils* pp. 85–95. Berlin, Heidelberg: Springer.

Palmer, F.E., Emery, D.R., Stemmler, J. and Staley, J.T. (1987) Survival and growth of microcolonial rock fungi as affected by temperature and humidity. *New Phytol* **107**, 155–162.

Pan, H.Q., Zhang, S.Y., Wang, N., Li, Z.L., Hua, H.-M., Hu, J.-C. and Wang, S.-J. (2013) New spirotetronate antibiotics, lobophorins H and I, from a South China Sea-derived *Streptomyces* sp. 12A35. *Mar Drugs* **11**, 3891–3901.

Park, C.H., Kim, K.M., Elvebakk, A., Kim, O.S., Jeong, G. and Hong, S.G. (2015) Algal and fungal diversity in Antarctic lichens. *J Eukaryot Microbiol* **62**, 196–205.

Pathom-aree, W., Stach, J.E., Ward, A.C., Horikoshi, K., Bull, A.T. and Goodfellow, M. (2006) Diversity of actinomycetes isolated from Challenger Deep sediment (10,898 m) from the Mariana Trench. *Extremophiles* **10**, 181–189.

Peng, X.P., Wang, Y., Liu, P.P., Hong, K., Chen, H., Yin, X. and Zhu, W.-M. (2011) Aromatic compounds from the halotolerant fungal strain of *Wallemia sebi* PXP-89 in a hypersaline medium. *Arch Pharm Res* **34**, 907–912.

Peng, J., Zhang, X.Y., Tu, Z.C., Xu, X.Y. and Qi, S.H. (2013) Alkaloids from the deep-sea-derived fungus *Aspergillus westerdijkiae* DFFSCS013. *J Nat Prod* **76**, 983–987.

Pettit, R.K. (2011) Culturability and secondary metabolite diversity of extreme microbes: expanding contribution of deep sea and deep-sea vent microbes to natural product discovery. *Mar Biotechnol* **13**, 1–11.

Pontefract, A., Zhu, T.F., Walker, V.K., Hepburn, H., Lui, C., Zuber, M.T., Ruvkun, G. and Carr, C.E. (2017) Microbial diversity in a hypersaline sulfate lake: a terrestrial analog of ancient Mars. *Front Microbiol* **8**, 1819. https://doi.org/10.3389/fmicb.2017.01819.

Potts, M. and Friedmann, E.I. (1981) Effects of water stress on cryptoendolithic cyanobacteria from hot desert rocks. *Arch Microbiol* **130**, 267–271.

Powell, J.T., Chatziefthimiou, A.D., Banack, S.A., Cox, P.A. and Metcalf, J.S. (2015) Desert crust microorganisms, their environment, and human health. *J Arid Environ* **112**, 127–133.

Pushkareva, E., Pessi, I.S., Wilmotte, A. and Elster, J. (2015) Cyanobacterial community composition in Arctic soil crusts at different stages of development. *FEMS Microbiol Ecol* **91**, fiv143. https://doi.org/10.1093/femsec/fiv143.

Rastogi, G., Bhalla, A., Adhikari, A., Bischoff, K.M., Hughes, S.R., Christopher, L.P. and Sani, R.K. (2010) Characterization of thermostable cellulases produced by *Bacillus* and *Geobacillus* strains. *Bioresour Technol* **101**, 8798–8806.

Rateb, M.E., Houssen, W.E., Arnold, M., Abdelrahman, M.H., Deng, H., Harrison, W.T., Okoro, C.K., Asenjo, J.A. *et al.* (2011a) Chaxamycins A-D, bioactive ansamycins from a hyper-arid desert *Streptomyces* sp. *J Nat Prod* **74**, 1491–1499.

Rateb, M.E., Houssen, W.E., Harrison, W.T., Deng, H., Okoro, C.K., Asenjo, J.A., Andrews, B.A., Bull, A.T. *et al.* (2011b) Diverse metabolic profiles of a *Streptomyces* strain isolated from a hyper-arid environment. *J Nat Prod* **74**, 1965–1971.

Rateb, M.E., Ebel, R. and Jaspars, M. (2018) Natural product diversity of actinobacteria in the Atacama Desert. *Antonie Van Leeuwenhoek* **111**, 1467–1477.

Ríos, A.D.L., Valea, S., Ascaso, C., Davila, A.F., Kastovsky, J., McKay, C.P., Gómez-Silva, B. and Wierzchos, J. (2010) Comparative analysis of the microbial communities inhabiting halite evaporites of the Atacama Desert. *Int Microbiol* **13**, 79–89.

Roldán, M., Ascaso, C. and Wierzchos, J. (2014) Fluorescent fingerprints of endolithic phototrophic cyanobacteria living within halite rocks in the Atacama Desert. *Appl Environ Microbiol* **80**, 2998–3006.

Saker, R., Bouras, N., Meklat, A., Zitouni, A., Schumann, P., Spröer, C., Sabaou, N. and Klenk, H.P. (2015) *Prauserella isguensis* sp. nov., a halophilic actinomycete isolated from desert soil. *Int J Syst Evol Microbiol* **65**, 1598–1603.

Sánchez-Andrea, I., Knittel, K., Amann, R., Amils, R. and Sanz, J.L. (2012) Quantification of Tinto River sediment microbial communities: the importance of sulfate-reducing bacteria and their role in attenuating acid mine drainage. *Appl Environ Microbiol* **78**, 4638–4645.

Santhanam, R., Okoro, C.K., Rong, X., Huang, Y., Bull, A.T., Andrews, B.A., Asenjo, J.A., Weon, H.-Y. *et al.* (2012a) *Streptomyces deserti* sp. nov., isolated from hyper-arid Atacama Desert soil. *Antonie Van Leeuwenhoek* **101**, 575–581.

Santhanam, R., Okoro, C.K., Rong, X., Huang, Y., Bull, A.T., Weon, H.-Y., Andrews, B.A., Asenjo, J.A. *et al.* (2012b) *Streptomyces atacamensis* sp. nov., isolated from an extreme hyper-arid soil of the Atacama Desert, Chile. *Int J Syst Evol Microbiol* **62**, 2680–2684.

Santhanam, R., Rong, X., Huang, Y., Andrews, B.A., Asenjo, J.A. and Goodfellow, M. (2013) *Streptomyces bullii* sp. nov., isolated from a hyper-arid Atacama Desert soil. *Antonie Van Leeuwenhoek* **103**, 367–373.

Santiago, I.F., Gonçalves, V.N., Gómez-Silva, B., Galetovic, A. and Rosa, L.H. (2018) Fungal diversity in the Atacama Desert. *Antonie Van Leeuwenhoek* **111**, 1345–1360.

Saygin, H., Ay, H., Guven, K., Cetin, D. and Sahin, N. (2019) *Desertiactinospora gelatinilytica* gen. nov., sp. nov., a new member of the family *Streptosporangiaceae* isolated from the Karakum Desert. *Antonie Van Leeuwenhoek* **112**, 409–423.

Schopf, J.W. and Klein, C. (eds.) (1992) *The Proterozoic Biosphere: A Multidisciplinary Study*. Camridge, UK: Cambridge University Press.

Schulz, D., Beese, P., Ohlendorf, B., Erhard, A., Zinecker, H., Dorador, C. and Imhoff, J.F. (2011) Abenquines A-D: aminoquinone derivatives produced by *Streptomyces* sp. strain DB634. *J Antibiot* **64**, 763–768.

Schulze-Makuch, D., Wagner, D., Kounaves, S.P., Mangelsdorf, K., Devine, K.G., de Vera, J.-P., Schmitt-Kopplin, P., Grossart, H.-P. *et al.* (2018) Transitory microbial habitat in the hyperarid Atacama Desert. *Procd Natl Acad Sci* **115**, 2670–2675.

Sghaier, H., Hezbri, K., Ghodhbane-Gtari, F., Pujic, P., Sen, A., Daffonchio, D., Boudabous, A., Tisa, L.S. *et al.* (2016) Stone-dwelling actinobacteria *Blastococcus saxobsidens*, *Modestobacter marinus* and *Geodermatophilus obscurus* proteogenomes. *ISME J* **10**, 21–29.

Shimane, Y., Hatada, Y., Minegishi, H., Mizuki, T., Echigo, A., Miyazaki, M., Ohta, Y., Usami, R. *et al.* (2010) *Natronoarchaeum mannanilyticum* gen. nov., sp. nov., an aerobic, extremely halophilic member of the Archaea isolated from commercial salt made in Niigata, Japan. *Int J Syst Evol Microbiol* **60**, 2529–2534.

Singh, S., Kate, B.N. and Banerjee, U.C. (2005) Bioactive compounds from cyanobacteria and microalgae: an overview. *Crit Rev Biotechnol* **25**, 73–95.

Singh, P., Raghukumar, C., Verma, P. and Shouche, Y. (2010) Phylogenetic diversity of culturable fungi from the deep-sea sediments of the Central Indian Basin and their growth characteristics. *Fungal Diver* **40**, 89–102.

Singh, P., Raghukumar, C., Meena, R.M., Verma, P. and Shouche, Y. (2012) Fungal diversity in deep-sea sediments revealed by culture-dependent and culture-independent approaches. *Fungal Ecol* **5**, 543–553.

Son, S., Ko, S.K., Jang, M., Kim, J., Kim, G., Lee, J., Jeon, E. Futamura, Y. *et al.* (2016) New cyclic lipopeptides of the iturin class produced by saltern-derived *Bacillus* sp. KCB14S006. *Mar Drugs* **14**, 72, doi:https://doi.org/10.3390/md14040072

Song, Y., Li, Q., Liu, X., Chen, Y., Zhang, Y., Sun, A., Zhang, W., Zhang, J. *et al.* (2014) Cyclic hexapeptides from the deep South China sea-derived *Streptomyces scopuliridis* SCSIO ZJ46 active against pathogenic gram-positive bacteria. *J Nat Prod* **77**, 1937–1941.

Sterflinger, K., Tesei, D. and Zakharova, K. (2012) Fungi in hot and cold deserts with particular reference to microcolonial fungi. *Fungal Ecol* **5**, 453–462.

Steven, B., Lionard, M., Kuske, C.R. and Vincent, W.F. (2013) High bacterial diversity of biological soil crusts in water tracks over permafrost in the high arctic polar desert. *PLoS ONE* **8**, e71489. https://doi.org/10.1371/journal.pone.0071489.

Stevenson, A., Hamill, P.G., O'kane, C.J., Kminek, G., Rummel, J.D., Voytek, M.A., Dijksterhuis, J. and Hallsworth, J.E. (2017) *Aspergillus penicillioides* differentiation and cell division at 0.585 water activity. *Environ Microbiol* **19**, 687–697.

Stierle, D.B., Stierle, A.A., Patacini, B., McIntyre, K., Girtsman, T. and Bolstad, E. (2011) Berkeleyones and related meroterpenes from a deep water acid mine waste fungus that inhibit the production of interleukin 1-β from induced inflammasomes. *J Nat Prod* **74**, 2273–2277.

Stierle, A.A., Stierle, D.B. and Girtsman, T. (2012a) Caspase-1 inhibitors from an extremophilic fungus that target specific leukemia cell lines. *J Nat Prod* **75**, 344–350.

Stierle, D.B., Stierle, A.A., Girtsman, T., McIntyre, K. and Nichols, J. (2012b) Caspase-1 and-3 inhibiting drimane sesquiterpenoids from the extremophilic fungus *Penicillium solitum*. *J Nat Prod* **75**, 262–266.

Stierle, A.A., Stierle, D.B., Girtsman, T., Mou, T.C., Antczak, C. and Djaballah, H. (2015) Azaphilones from an acid mine extremophile strain of a *Pleurostomophora* sp. *J Nat Prod* **78**, 2917–2923.

Stomeo, F., Valverde, A., Pointing, S.B., McKay, C.P., Warren-Rhodes, K.A., Tuffin, M.I., Seely, M. and Cowan, D.A. (2013) Hypolithic and soil microbial community assembly along an aridity gradient in the Namib Desert. *Extremophiles* **17**, 329–337.

Symanczik, S., Błaszkowski, J., Chwat, G., Boller, T., Wiemken, A., Al-Yahyaei, N. and N Al-Yahya'ei, M. (2014) Three new species of arbuscular mycorrhizal fungi discovered at one location in a desert of Oman: *Diversispora omaniana*, *Septoglomus nakheelum* and *Rhizophagus arabicus*. *Mycology* **106**, 243–259.

Taylor-George, S., Palmer, F., Staley, J.T., Borns, D.J., Curtiss, B. and Adams, J.B. (1983) Fungi and bacteria involved in desert varnish formation. *Microb Ecol* **9**, 227–245.

Tedesco, P., Maida, I., Palma Esposito, F., Tortorella, E., Subko, K., Ezeofor, C.C., Zhang, Y., Tabudravu, J. *et al.* (2016) Antimicrobial activity of monoramnholipids produced by bacterial strains isolated from the Ross Sea (Antarctica). *Mar Drugs* **14**, 83. https://doi.org/10.3390/md14050083.

Terra, L., Dyson, P.J., Hitchings, M.D., Thomas, L., Abdelhameed, A., Banat, I.M., Gazze, S.A., Vujaklija, D. *et al.* (2018) A novel alkaliphilic *Streptomyces* inhibits ESKAPE pathogens. *Front Microbiol* **9**, https://doi.org/10.3389/fmicb.2018.02458.

Thumar, J.T., Dhulia, K. and Singh, S.P. (2010) Isolation and partial purification of an antimicrobial agent from halotolerant alkaliphilic *Streptomyces aburaviensis* strain Kut-8. *World J Microbiol Biotechnol* **26**, 2081–2087.

Tiwari, K., Upadhyay, D.J., Mösker, E., Süssmuth, R. and Gupta, R.K. (2015) Culturable bioactive actinomycetes from the Great Indian Thar Desert. *Annals Microbiol* **65**, 1901–1914.

Trujillo, M.E., Idris, H., Riesco, R., Nouioui, I., Igual, J.M., Bull, A.T. and Goodfellow, M. (2017) *Pseudonocardia nigra* sp. nov., isolated from Atacama Desert rock. *Int J Syst Evol Microbiol* **67**, 2980–2985.

Ulanova, D. and Goo, K.S. (2015) Diversity of actinomycetes isolated from subseafloor sediments after prolonged low-temperature storage. *Folia Microbiol* **60**, 211–216.

Unell, M., Kabelitz, N., Jansson, J.K. and Heipieper, H.J. (2007) Adaptation of the psychrotroph *Arthrobacter chlorophenolicus* A6 to growth temperature and the presence of phenols by changes in the anteiso/iso ratio of branched fatty acids. *FEMS Microbiol Lett* **266**, 138–143.

Urbieta, M.S., Donati, E.R., Chan, K.G., Shahar, S., Sin, L.L. and Goh, K.M. (2015) Thermophiles in the genomic era: biodiversity, science, and applications. *Biotechnol Adv* **33**, 633–647.

Valverrde, A., Tuffin, M. and Cowan, D.A. (2012) Biogeography of bacterial communities in hot springs: a focus on the actinobacteria. *Extremophiles* **16**, 669–679.

Vijayakumar, S. and Menakha, M. (2015) Pharmaceutical applications of cyanobacteria - a review. *J Acute Med* **5**, 15–23.

Vítek, P., Jehlička, J., Ascaso, C., Mašek, V., Gómez-Silva, B., Olivares, H. and Wierzchos, J. (2014) Distribution of scytonemin in endolithic microbial communities from halite crusts in the hyperarid zone of the Atacama Desert, Chile. *FEMS Microbiol Ecol* **90**, 351–366.

Waditee-Sirisattha, R., Kageyama, H. and Takabe, T. (2016) Halophilic microorganism resources and their applications in industrial and environmental biotechnology. *AIMS Microbiol* **2**, 42–54.

Wagner, M., Abdel-Mageed, W.M., Ebel, R., Bull, A.T., Goodfellow, M., Fiedler, H.P. and Jaspars, M. (2014) Dermacozines H-J isolated from a deep-sea strain of *Dermacoccus abyssi* from Mariana Trench sediments. *J Nat Prod* **77**, 416–420.

Wang, J., Wei, X., Qin, X., Tian, X., Liao, L., Li, K., Zhou, X., Yang, X. *et al.* (2016) Antiviral merosesquiterpenoids produced by the Antarctic fungus *Aspergillus ochraceopetaliformis* SCSIO 05702. *J Nat Prod* **79**, 59–65.

Wichner, D., Idris, H., Houssen, W.E., McEwan, A.R., Bull, A.T., Asenjo, J.A., Goodfellow, M., Jaspars, M. *et al.* (2017) Isolation and anti-HIV-1 integrase activity of lentzeosides A-F from extremotolerant *Lentzea* sp. H45, a strain isolated from a high-altitude Atacama Desert soil. *J Antibiot* **70**, 448.

Wierzchos, J., Ascaso, C. and McKay, C.P. (2006) Endolithic cyanobacteria in halite rocks from the hyperarid core of the Atacama Desert. *Astrobiology* **6**, 415–422.

Williams, K.P. and Kelly, D.P. (2013) Proposal for a new class within the phylum Proteobacteria, *Acidithiobacillia classis* nov., with the type order *Acidithiobacillales*, and emended description of the class *Gammaproteobacteria*. *Int J Syst Evol Microbiol* **63**, 2901–2906.

Wilson, Z.E. and Brimble, M.A. (2009) Molecules derived from the extremes of life. *Nat Prod Rep* **26**, 44–71.

Wu, G., Ma, H., Zhu, T., Li, J., Gu, Q. and Li, D. (2012) Penilactones A and B, two novel polyketides from

Antarctic deep-sea derived fungus *Penicillium crustosum* PRB-2. *Tetrahedron* **68**, 9745–9749.

Wu, G., Lin, A., Gu, Q., Zhu, T. and Li, D. (2013) Four new chloro-eremophilane sesquiterpenes from an Antarctic deep-sea derived fungus *Penicillium* sp. Pr19n-1. *Mar Drugs* **11**, 1399–1408.

Wu, B., Wiese, J., Labes, A., Kramer, A., Schmaljohann, R. and Imhoff, J. (2015) Lindgomycin, an unusual antibiotic polyketide from a marine fungus of the *Lindgomycetaceae*. *Mar Drugs* **13**, 4617–4632.

Yu, L.Z.H., Luo, X.S., Liu, M. and Huang, Q. (2015) Diversity of ionizing radiation-resistant bacteria obtained from the Taklimakan Desert. *J Basic Microbiol* **55**, 135–140.

Zalar, P., de Hoog, G.S., Schroers, H.J., Frank, J.M. and Gunde-Cimerman, N. (2005) Taxonomy and phylogeny of the xerophilic genus *Wallemia* (Wallemiomycetes and Wallemiales, cl. et ord. nov.). *Antonie Van Leeuwenhoek* **87**, 311–328.

Zeldes, B.M., Keller, M.W., Loder, A.J., Straub, C.T., Adams, M.W.W. and Kelly, R.M. (2015) Extremely thermophilic microorganisms as metabolic engineering platforms for production of fuels and industrial chemicals. *Front Microbiol* **6**, 1209. https://doi.org/10.3389/fmicb.2015.01209.

Zhang, G., Jiang, N., Liu, X. and Dong, X. (2008) Methanogenesis from methanol at low temperatures by a novel psychrophilic methanogen, "*Methanolobus psychrophilus*" sp. nov., Pprevalent in Zoige Wetland of the Tibetan Plateau. *Appl Environ Microbiol* **47**, 6114–6120.

Zhang, G., Cao, T., Ying, J., Yang, Y. and Ma, L. (2014a) Diversity and novelty of actinobacteria in Arctic marine sediments. *Antonie Van Leeuwenhoek* **105**, 743–754.

Zhang, X.-Y., Tang, G.-L., Xu, X.-Y., Nong, X.-H. and Qi, S.-H. (2014b) Insights into deep-sea sediment fungal communities from the East Indian Ocean using targeted environmental sequencing combined with traditional cultivation. *PLoS ONE* **9**, e109118. https://doi.org/10.1371/journal.pone.0109118.

Zhang, L.Q., Chen, X.C., Chen, Z.Q., Wang, G.M., Zhu, S.-G., Yang, Y.-F., Chen, K.-X., Liu, X.-Y. *et al.* (2016a) Eutypenoids A-C: Novel pimarane diterpenoids from the Arctic fungus *Eutypella* sp. D-1. *Mar Drugs* **14**, 44. https://doi.org/10.3390/md14030044.

Zhang, T., Wang, N.F., Liu, H.Y., Zhang, Y.Q. and Yu, L.Y. (2016b) Soil pH is a key determinant of soil fungal community composition in the Ny-Ålesund region, Svalbard (high Arctic). *Front Microbiol* **7**, 227. https://doi.org/10.3389/fmicb.2016.00227.

Zhang, X., Li, S.J., Li, J.J., Liang, Z.Z. and Zhao, C.Q. (2018) Novel natural products from extremophilic fungi. *Mar Drugs* **16**, 194. https://doi.org/10.3390/md16060194.

Zheng, Y., Saitou, A., Wang, C.M., Toyoda, A., Minakuchi, Y., Sekiguchi, Y., Ueda, K., Takano, H. *et al.* (2019) Genome features and secondary metabolites biosynthetic potential

of the class *Ktedonobacteria*. *Front Microbiol* **10**, 893. https://doi.org/10.3389/fmicb.2019.00893.

Zhou, X., Huang, H., Chen, Y., Tan, J., Song, Y., Zou, J., Tian, X., Hua, Y. *et al.* (2012) Marthiapeptide A, an anti-infective and cytotoxic polythiazole cyclopeptide from a 60 L scale fermentation of the deep sea-derived *Marinactinospora thermotolerans* SCSIO 00652. *J Nat Prod* **75**, 2251–2255.

Zhou, X., Huang, H., Li, J., Song, Y., Jiang, R., Liu, J., Zhang, S., Hua, Y. *et al.* (2014) New anti-infective cycloheptadepsipeptide congeners and absolute stereochemistry from the deep sea-derived *Streptomyces drozdowiczii* SCSIO 10141. *Tetrahedron* **70**, 7795–7801.

Zhou, H., Li, L., Wang, W., Che, Q., Li, D., Gu, Q. and Zhu, T. (2015) Chrodrimanins I and J from the Antarctic moss-derived fungus *Penicillium funiculosum* GWT2-24. *J Nat Prod* **78**, 1442–1445.

Ziegler, S., Dolch, K., Geiger, K., Krause, S., Asskamp, M., Eusterhues, K., Kriews, M., Wilhelms-Dick, D. *et al.* (2013) Oxygen-dependent niche formation of a pyrite-dependent acidophilic consortium built by archaea and bacteria. *ISME J* **7**, 1725–1737.

Zitouni, A., Lamari, L., Boudjella, H., Badji, B., Sabaou, N., Gaouar, A., Mathieu, F., Lebrihi, A. *et al.* (2004) *Saccharothrix algeriensis* sp. nov., isolated from Saharan soil. *Int J Syst Evol Microbiol* **54**, 1377–1381.