Appl Microbiol Biotechnol (2013) 97:9291–9321
DOI 10.1007/s00253-013-5229-7

MINI-REVIEW

Culturable rare *Actinomycetes*: diversity, isolation and marine natural product discovery

Ramesh Subramani · William Aalbersberg

Received: 1 July 2013 / Revised: 29 August 2013 / Accepted: 2 September 2013 / Published online: 22 September 2013
© Springer-Verlag Berlin Heidelberg 2013

Abstract Rare *Actinomycetes* from underexplored marine environments are targeted in drug discovery studies due to the *Actinomycetes*' potentially huge resource of structurally diverse natural products with unusual biological activity. Of all marine bacteria, 10 % are *Actinomycetes*, which have proven an outstanding and fascinating resource for new and potent bioactive molecules. Past and present efforts in the isolation of rare *Actinomycetes* from underexplored diverse natural habitats have resulted in the isolation of about 220 rare *Actinomycete* genera of which more than 50 taxa have been reported to be the producers of 2,500 bioactive compounds. That amount represents greater than 25 % of the total *Actinomycetes* metabolites, demonstrating that selective isolation methods are being developed and extensively applied. Due to the high rediscovery rate of known compounds from *Actinomycetes*, a renewed interest in the development of new antimicrobial agents from rare and novel *Actinomycetes* is urgently required to combat the increasing number of multidrug-resistant human pathogens. To facilitate that discovery, this review updates all selective isolation media including pretreatment and enrichment methods for the isolation of marine rare *Actinomycetes*. In addition, this review demonstrates that discovering new compounds with novel scaffolds can be increased by intensive efforts in isolating and screening rare marine genera of *Actinomycetes*. Between 2007 and mid-2013, 80 new rare *Actinomycete* species were reported from marine habitats. They belong to 23 rare families, of which three are novel, and 20 novel genera. Of them, the family *Micromonosporaceae* is dominant as a producer of promising chemical diversity.

R. Subramani (✉) · W. Aalbersberg
Centre for Drug Discovery and Conservation, Institute of Applied Sciences, The University of the South Pacific, Laucala Campus, Suva, Fiji Islands
e-mail: subramani_r@usp.ac.fj

Keywords Rare *Actinomycetes* · Marine habitats · Diversity · Selective isolation · Pretreatment · Microbial natural products

Introduction

Natural products have continued to play a highly significant role in the drug discovery and development process; about 28 % of the new chemical entities and 42 % of the anticancer drugs introduced into the worldwide market between 1981 and 2006 were natural products and their derivatives (Newman and Cragg 2007).

Microbial natural products represent an important route to the discovery of novel chemicals for the development of new therapeutic agents—more than 22,000 biologically active compounds have been obtained from microbes. Among them, 45 % were produced by *Actinobacteria*, especially the excellent producers in the genus *Streptomyces* (Berdy 2005). *Actinobacteria* have made a significant contribution to the health and well-being of people throughout the world (Demain and Sanchez 2009). Even so, the emergence of antibiotic resistance developed in various bacterial pathogens and the increase in numbers of new diseases and pathogens (such as acquired immunodeficiency syndrome, severe acute respiratory syndrome and H1N1 flu virus) has caused a resurgence of interest in finding new biologically active compounds for drug discovery. However, the 'law of diminishing returns' (Fischbach and Walsh 2009) has resulted in fewer new discoveries from the traditional sources (such as plants and soil *Actinomycetes*) of natural products. Thus, it is critical that new groups of microbes from unexplored habitats be pursued as sources of novel antibiotics and other therapeutic agents (Bull et al. 2005).

The oceans are home to high microbial diversity (Stach and Bull 2005; Sogin et al. 2006). These are also being screened intensively throughout the world for their biodiversity

potential (Jensen et al. 2005a, b). Moreover, until now, representatives of a relatively few taxa have been isolated from marine as opposed to terrestrial habitats (Goodfellow 2010). Thus, considering the vastness of the marine environment, the potential rewards of this treasure house represented by the oceans are large (Tiwari and Gupta 2012b).

Novel (new genera in *Actinobacteria*), new (new species of previously reported rare genera) or rare microbes need to be examined in the search for bioactive compounds with diverse biological activity. Rare *Actinomycetes* are usually considered as non-streptomycete *Actinomycete* strains. The isolation frequency of rare *Actinomycetes* is much lower than that of the streptomycete strains isolated by conventional methods (Baltz 2006)—only 11 genera had been isolated by 1970, increasing to 100 genera by 2005 and 220 genera by 2010 (Berdy 2005; Tiwari and Gupta 2012a). This number is quickly increasing due to recently developed taxonomically selective isolation and genetic techniques. Table 1 shows the approximate number of antibiotics produced by *Streptomyces* and rare *Actinomycetes* between 1974 and 2005. By 1974, 125 antibiotics had been isolated from rare *Actinomycetes*, increasing to 2,250 by 2005, and a recent update by Kurtböke (2012) indicates that there were about 2,500 by 2010. Thus, it is clear that isolation of antibiotics and biologically active metabolites has steadily been increasing from rare *Actinomycetes* (Fenical and Jensen 2006; Lam 2006; Subramani and Aalbersberg 2012). Furthermore, contemporary bioprospecting of soil *Actinobacteria* (particularly streptomycetes), the most significant source of new antibiotics in the twentieth century has largely resulted in the rediscovery of already-known compounds (Walsh 2003; Fischbach and Walsh 2009); rare *Actinomycetes* should be targeted for novel drug discovery programmes. Many excellent reviews describing *Actinomycetes* diversity, secondary metabolism, natural product discovery and genetics have appeared over the last 20 years. However, fewer reviews have described rare *Actinomycetes* diversity and their increasing contribution to the production of novel compounds (Lazzarini et al. 2000; Kurtböke 2012; Tiwari and Gupta 2012a, b).

Table 1 Approximate number of antibiotics produced by *Streptomyces* and rare *Actinomycetes*

Genus	1974	1980	1984	1988	2005[a]
Streptomyces	1,934	2,784	3,477	4,876	6,550
Rare *Actinomycetes*	125	361	745	1,276	2,250
Micromonospora	41	129	269	398	740
Nocardia	45	74	107	262	357
Actinomadura	0	16	51	164	345
Actinoplanes	6	40	95	146	248
Streptoverticillium	19	41	64	138	258
Streptosporangium	7	20	26	39	79
Microbispora	4	6	6	10	54
Dactylosporangium	0	4	19	31	58
Saccharopolyspora	0	4	33	44	131
Actinosynnema	0	0	25	14	51
Streptoalloteichus	0	3	14	12	48
Actinomyces	0	14	17	–	–
Pseudonocardia	0	3	8	–	27
Micropolyspora	2	4	7	–	13
Thermomonospora	1	3	4	–	19
Kitasatosporia	0	0	0	11	37
Kibdelosporangium	0	0	0	7	34

Adapted from Goodfellow and Williams (1986), Goodfellow and O'Donnel (1989) and Berdy (2005)

[a] Number stated for each rare *Actinomycete* genera are bioactive metabolites

The goal of this review is to summarize isolation and cultivation methods, and discuss the new and rare *Actinobacteria* findings in studies since 2007 particularly from marine habitats, also to discuss their enormous biotechnological potential in the area of natural products discovery and related applications.

High rate of rediscovery of known compounds

It is important to speculate on the reasons for the high rate of rediscovery of antimicrobial compounds in previous screening programmes. According to Stach (2010), the reasons are likely to include bias in the screening programmes and limitations in analytical technology, but more importantly in the organisms being screened themselves. Many new antibiotics were isolated from *Actinomycetes* (particularly from a single genus *Streptomyces*) between the late 1940s and 1960s—a period which came to be known as the Golden Age of antibiotic discovery—but the rate of new discoveries plummeted thereafter due in large part to the frequent rediscovery of highly abundant existing compounds. Stach (2010) suggested that the distribution of microbial species is probably similar to that of other organisms, i.e. there are small numbers of very rich species and those species may also be those that are readily cultured (as is the case for *Streptomyces*); thus, they represent a small fraction of the available diversity. In addition, many streptomycetes, although isolated from different environments, evidently produce the same known compounds, probably due to the frequent genetic exchange between them (Bredholdt et al. 2007).

However, recent genome sequence information suggests that this *Streptomyces* source of novel compounds is still not yet exhausted. Whole-genome sequencing of several streptomycetes (Bentley et al. 2002; Ikeda et al. 2003; Ohnishi et al. 2008; Song et al. 2010; Medema et al. 2010) revealed that each member can produce on average 20–30 bioactive small molecules, but only a small fraction of these molecules have

ever been detected under various culture conditions. Consequently, over the past decade, researchers have been attempting several methods such as cloning (Peiru et al. 2005) and heterologous expression (Mutka et al. 2006) of biosynthetic gene clusters, interfering with regulatory pathways (Laureti et al. 2011), varying culture conditions (Sánchez et al. 2010), co-culturing two or more organisms together (Kurosawa et al. 2008), the adaptive evolution (Charusanti et al. 2012) and other strategies (Baltz 2011) to stimulate the production of new compounds. Furthermore, the biosynthetic gene pathways used to make the antimicrobial compounds are distributed among the *Actinomycetes* at varying frequencies, such that a single compound may be found in one in ten strains screened. In other words, thousands of compounds should be found in 1 in 10^7 are screened (Baltz 2007; Stach 2010). Previous screening activities appeared to be focused on limited species diversity, and those few species produced a number of common compounds (rediscovered antimicrobials) that would obscure the detection of novel antimicrobials in the lower frequency ranges (Stach 2010). Baltz (2007) defined the challenge as finding the resources necessary to discover new antibiotics at frequencies of <1 in 10^7 within a background noise of 2,000 known antibiotics (Baltz 2007; Stach 2010). Understanding the reasons for rediscovery, coupled with disappointing returns from small molecule libraries, has led to a revival of interest in microbes as sources of new antimicrobial compounds. Proponents of this renaissance have suggested focusing on rare *Actinomycetes*, the assumption being that species novelty will lead to chemical novelty. In this instance, rare *Actinomycetes* are not necessarily those that are scarce in nature, but those that are rarely brought into culture (Stach 2010). Thus, it is reasonable to predict that focusing on environments that have been underexplored, and use of selective isolation methods, will lead to the isolation of novel genera and species of *Actinomycetes* and hence new antimicrobial compounds.

Rare *Actinomycetes*: selective isolation methods

In a report released by the American Academy of Microbiology entitled “The Microbial World: Foundation of the Biosphere”, Young (1997), estimated that less than 1 % of bacterial species are known, and recent evidence indicates that millions of microbial species are undiscovered (Cragg and Newman 2005). Surprisingly, the approach to the search for potentially valuable bacteria has been largely empirical and restricted to sampling a tiny fraction of the microbial community found in natural habitats. Therefore, techniques that enhance the growth of desirable microorganisms in natural samples (enrichment) or eliminate the undesirable streptomycete propagules and other contaminants from the primary isolation plate (pretreatment) must be developed and employed for selectively isolating particularly rare genera of *Actinomycetes* (Tiwari and Gupta 2012a).

Different pretreatment methods and media combinations are effective in the isolation of rare *Actinomycetes* (Tiwari and Gupta 2012a), and many researchers have been attempting to develop methods for isolating desirable rare *Actinomycete* genera from natural habitats (Nonomura 1988; Nonomura and Hayakawa 1988; Hayakawa et al. 1991a, b, c, d; Hayakawa 1990, 1994, 2003; Hayakawa and Nonomura 1993; Seong et al. 2001; Hamaki et al. 2005; Tan et al. 2006; Qiu et al. 2008; Qin et al. 2009; Nakaew et al. 2009; Baskaran et al. 2011; Istianto et al. 2012; Wang et al. 2013a). Their methods include a variety of pretreatments in combination with different enrichment techniques that selectively supplement isolation media with chemicals and selective antimicrobial agents to successfully increase the selectivity of the isolation media for desirable rare *Actinomycetes*.

Humic acid vitamin agar (HVA), first developed by Hayakawa and Nonomura (1987a), is one of the milestones in rare *Actinomycetes* isolation: this medium contains soil humic acid as the sole carbon and nitrogen sources which are suitable for recovery of rare *Actinomycetes* from natural samples. Although humic acid is an extremely heterogeneous cross-linked polymer resistant to biological decomposition and restricts the growth of non-filamentous bacteria colonies (Seong et al. 2001), *Actinomycetes* can utilize it as a nutrient source and also use it to support sporulation. A number of rare genera isolated by researchers described in this review have been discovered through the use of HVA together with different pretreatment and enrichment techniques, to successfully isolate rare *Actinomycetes*. Rare *Actinomycetes* as well as *Streptomyces* grow well on HVA. Although the growth rate of *Actinomycetes* is low, discrimination of typical morphology of colonies is easy on HVA because the black colour of HVA also makes it suitable for determining the morphology of white *Actinomycetes* colonies. The activation of spore germination by humic acid is believed to be one of the causes that increases the number of diverse *Actinomycetes* colonies on HVA (Hayakawa and Nonomura 1987b).

Moist and dry heat treatment

Samples secured from natural habitats cultured without pretreatment surrendered (in order of frequency) bacteria other than *Actinomycetes*, *Streptomyces*, fungi and non-streptomycete *Actinomycetes* (Seong et al. 2001). Consequently, different pretreatment procedures and selective isolation media have been recommended for the selective isolation of novel and rare *Actinomycetes*. The aerial spores of most *Actinomycete* genera resist desiccation and show a slightly higher resistance to wet or dry heat than do the corresponding vegetative hyphae (Seong et al. 2001). Pretreatments of natural habitat samples by drying and heating

stimulated the isolation of rare *Actinomycetes* (Nolan and Cross 1988; Kim et al. 1995). In comparison to the other genera of rare *Actinomycetes*, the rare genera *Streptosporangium* are difficult to isolate by traditional methods as their sporangiospores are able to withstand and resist physical or chemical pretreatments: Hayakawa et al. (1991a) found that dry heat treatment (120 °C for 1 h) of natural samples greatly induces the growth of *Streptosporangium* spp. After surface sterilization, Qin et al. (2009) subjected different medicinal plant samples to continuous drying at 100 °C for 15 min: directly plating on different selective media enabled the isolation of 280 strains belonging to the genera *Pseudonocardia*, *Nocardiopsis*, *Micromonospora* and *Streptosporangium*. Additionally, along with dry heating of samples treated with chemicals such as 0.01 % benzethonium chloride, 0.03 % chlorhexidine gluconate, 0.05 % sodium dodecylsulfate (SDS), 6 % yeast extract and 1.5 % phenol and supplemented with different selective antibiotics such as leucomycin, nalidixic acid on HVA drastically eliminated the unicellular bacteria and other unwanted *Actinomycete* propagules (including *Streptomyces* spp.) from the isolation plates and increased the selectivity for *Streptosporangium* spp., *Microbispora* spp., *Acitinomadura* spp., *Micromonospora* spp., *Nocardia* spp. and *Nonomurea* spp. (Hayakawa et al. 1988, 1991a, b, c, d; Hayakawa 2008; Khamna et al. 2009). Recently, Niyomvong et al. (2012) showed that pretreatment of samples with moist (50 °C for 6 min) and dry (120 °C for 1 h) heating and 1.5 % phenol reduced the number of undesirable bacteria and enhanced the selective isolation of *Actinoplanes*, *Gordonia*, *Microbispora*, *Micromonospora*, *Nocardia* and *Nonomuraea*. The successful isolation of members of the genera *Actinomadura* and *Saccharopolyspora* from caves was reported for the first time using these pretreatments with selective isolation media (Niyomvong et al. 2012).

Phenol treatment

An alternative approach is to make the isolation procedure more selective by adding chemicals such as phenol to the natural samples (Nonomura 1988; Hayakawa et al. 1991c). Phenol is a biocide and toxic to bacteria, fungi and streptomycetes, so treatment with 1.5 % phenol reduces the number of those organisms by removing sensitive species (Hayakawa et al. 1991b, 2004). Khamna et al. (2009) selectively isolated 11 % of non-streptomycetes including the rare genera *Actinomadura*, *Microbispora*, *Micromonospora*, *Nocardia* and *Nonomurea* by pretreating the samples with 1.5 % phenol and then plating on HVA. Although phenol treatment of soil suspension lowered the number of fungi and other bacteria, the *Actinomycetes* were less affected: 65 % of the colonies were rare *Actinomycetes*. The phenol pretreatment of the soil killed bacteria and streptomycetes in the samples, while keeping *Micromonosporae* and *Microbisporae* alive (Hayakawa et al. 1991b; Qiu et al. 2008). In another study, the rare genera *Micromonospora* (49.2 %), *Actinomadura* (13.1 %), *Microbispora* (9.8 %) and *Polymorphospora* (3.3 %) were successfully obtained from soil samples using 1.5 % phenol pretreatment (Istianto et al. 2012).

Selective antimicrobial agents

Several rare *Actinomycetes* are resistant to a wide spectrum of antibiotics. Thus, several antibiotic molecules have been used in selective media to inhibit the competing bacteria including fast-growing *Actinomycetes* (Okami and Hotta 1988). Selective isolation plates containing novobiocin significantly increased the numbers of *Micromonospora*-like colonies (Qiu et al. 2008). Gentamicin is also one of the selective agents used to access *Micromonospora* spp. (Williams and Wellington 1982). Specialized growth media have also been developed to isolate specific *Actinomycete* genera (Seong et al. 2001). Hayakawa and Nonomura (1987a, b) and Cho et al. (1994) chose macromolecules such as casein, chitin, hair hydrolysate and humic acid as carbon and nitrogen sources of rare *Actinomycetes*.

Calcium carbonate treatment

Treatment of natural habitat samples with calcium carbonate increased the populations of rare genera of *Actinomycetes* (Alferova and Terekhova 1988). The mechanism of the calcium carbonate effect is not clear; however, Tsao et al. (1960) described natural samples mixed with powdered calcium carbonate where the pH is altered in favour of the growth of *Actinomycete* propagules and the calcium ions have the ability to stimulate the formation of aerial mycelia by several *Actinomycete* cultures (Natsume et al. 1989). Furthermore, Tsao et al. (1960) demonstrated significant increases in the relative plate counts of the *Actinomycete* populations in soil samples treated with calcium carbonate. In addition, using a combined calcium carbonate rehydration and centrifugation (RC) procedure, Otoguro et al. (2001) successfully isolated diverse *Actinokineospora* spp. and other *Actinomycetes* from soils and plant litter. Recently, Qin et al. (2009) demonstrated that the enrichment stage with calcium carbonate and the RC procedure was also suitable for the isolation of zoosporic and other rare *Actinobacteria*; they were the first to the isolation of *Saccharopolyspora*, *Dietzia*, *Blastococcus*, *Dactylosporangium*, *Promicromonospora*, *Oerskovia*, *Actinocorallia* and *Jiangella* species from endophytic environments. Therefore, the calcium carbonate procedure, in combination with other selective isolation methods, is recommended for the isolation of rare genera of *Actinomycetes* from soil samples (Tiwari and Gupta 2012a).

Microwave irradiation

Many studies have examined the use of microwave energy for sterilization of soil (Wang et al. 2013a), yet there are few reports about the effect of microwave irradiation on the culturability of microorganisms, and especially the culturability of *Actinomycetes* (Bulina et al. 1997; Yang et al. 2008; Xue et al. 2010). Ferriss (1984) reported that microwave irradiation of soil reduced total fungal and total prokaryote counts in soil extracts. Bulina et al. (1997) reported that microwave irradiation significantly increased the number of culturable rare *Actinomycetes* taxa in soil, including *Micromonospora*, *Micropolyspora*, *Norcardia* and *Actinomadura*. Yang et al. (2008) reported that short periods of microwave irradiation increased culturable *Actinomycete* counts and the number of culturable *Actinomycete* isolates in a sandy aeolian soil; they also found that irradiation increased the number of antagonistic *Actinomycete* isolates as a percentage of the total number of cultural *Actinomycete* isolates. Recently, Xue et al. (2010) reported that microwave irradiation of a calcareous soil increased the total counts of culturable *Actinomycetes* such as *Streptomyces* spp. and *Micromonospora* spp. Furthermore, Wang et al. (2013a) isolated biologically active *Streptomyces* spp., *Nocardia* spp., *Streptosporangium* spp. and *Lentzea* spp. using microwave irradiation of soil samples. In addition, some researchers used other physical agents such as electromagnetic radiation (Miguélez et al. 1993; Niyomvong et al. 2012), electric pulses and super high frequency radiation (Bulina et al. 1997), ultrasonic waves (Jiang et al. 2010) and extremely high-frequency radiation (Li et al. 2003) for the selective isolation of *Actinomycetes* in natural samples. All of these methods have significantly increased the total number of rare *Actinomycetes* isolated.

Centrifugation process

Another physical method, centrifugation, eliminates streptomycetes and other non-motile *Actinomycetes* from the liquid phase, thereby facilitating the selective growth of rare—especially motile *Actinomycetes*—on isolation plates subsequent to inoculation (Hayakawa et al. 2000; Qin et al. 2009). The combined enzymatic hydrolysis and differential centrifugation method was particularly useful for isolating endophytic rare *Actinobacteria Pseudonocardia*, *Nocardiopsis* and *Micromonospora* species and species of other genera, including *Amycolatopsis*, *Nocardia*, *Nonomuraea*, *Actinomadura*, *Gordonia*, *Promicromonospora* and *Mycobacterium* (Qin et al. 2009).

Chemoattractants and chlorination methods

Selective isolation of sporulating *Actinomycetes* known to produce motile spores is done by the use of xylose, chloride, γ-collidine, bromide and vanillin (Hayakawa 2008) which act as chemoattractants for accumulating spores of *Actinoplanes*, *Dactylosporangium* and *Catenuloplanes* (Hayakawa 2008). Further, selective isolation of rare genera *Herbidospora*, *Microbispora*, *Microtetraspora* and *Streptosporangium* can be achieved by chloramine treatment (Hong et al. 2009), as chlorination is known to suppress growth of contaminant bacteria and promote the growth of rare *Actinomycetes* when plated on humic acid–vitamin-enriched media (Hong et al. 2009).

Finally, Tiwari and Gupta (2012a) found that selective isolation of rare *Actinomycetes* from natural habitats using combined physical and chemical treatments of natural samples can increase the chance of isolation of rare genera of *Actinomycetes*.

Other methods

Several terms have been used in the literature, including ‘uncultured’, ‘unculturable’ and ‘uncultivable’ to describe bacteria that are not readily cultured in the laboratory. Sampling of diverse environments, such as soil, marine sediment or hot springs shows that only 0.01–1 % of cells visible under the microscope will form colonies on a Petri dish, leaving the remaining majority ‘uncultured’ (D’Onofrio et al. 2010). In recent years, researchers have been attempting various methods such as co-culture (D’Onofrio et al. 2010; Stewart 2012), simulation of the natural environment in vitro (Stewart 2012), colony hybridization, flow cytometry and cell sorting, micromanipulation of single bacterial cells (Vartoukian et al. 2010), design and application of the diffusion chamber, ichip and the microbial trap (Gavrish et al. 2008; Lewis et al. 2010) for isolating unculturable microorganisms. Of all of these methods, co-culture has proven successful and so is widely used method for the cultivation of unculturable, novel or rare microorganisms.

Co-culture method

Recently, D’Onofrio et al. (2010) experimentally described the success of the co-culture methods on the culture of unculturable bacteria. Briefly, pairs of colonies growing within a 2-cm distance of each other were selected from high-density isolation plates (50–200 colonies per plate) and re-streaked in close proximity to each other. Each of the two isolates was streaked on one half of an R2Asea plate and cross-streaked through the centre of the plate; the result was regions of proximal, distal and overlapping inoculation (D’Onofrio et al. 2010). Using this method, they were able to isolate an uncultured marine bacterium *Maribacter polysiphoniae* in the presence of helper strain *Micrococcus luteus* that was isolated from the same environment. Similarly, an uncultured bacterium *Bacillus marisflavi* was obtained from fresh water sediment in the presence of the helper strain

Bacillus megaterium from the same environment (Stewart 2012). Some unculturable colony-forming microorganisms can grow on a Petri dish only in the presence of other species from the same environment (Kaeberlein et al. 2002; Nichols et al. 2008; D'Onofrio et al. 2010). Interspecies symbiosis based on nutrient exchange (syntrophy) is well known in the bacterial world (McInerney et al. 2008). Bacteria are also known to communicate using an interspecies quorum-sensing factor [autoinducer 2 (AI-2)] that induces synthesis of proteins such as toxins or polymer hydrolases that are useful for a community rather than a single cell (Williams et al. 2007a). Uncultured bacteria, however, do not grow on rich synthetic media (such media should largely obviate the need for nutrient supply by other species), and AI-2 has not been found to act as a growth-promoting factor, raising questions about the nature of unknown growth-promoting factors in microbial communities.

Diverse habitats and genera of rare *Actinomycetes*

Soil and plants

Soil is well-studied for *Actinomycetes* populations and most of the rare *Actinomycetes* reported so far have come from different types of soil (Tiwari and Gupta 2012a, b). The isolation of several new and rare genera discussed in this review under the section 'Selective isolation methods' was mostly derived from different soil types. Many rare *Actinomycetes* are now being isolated from plants (Matsumoto et al. 1998; Taechowisan et al. 2003; Janso and Carter 2010), often for the purpose of finding novel microbial resources for use in screening for new bioactive compounds (Inahashi et al. 2011). For example, Qin et al. (2009) reported for the first time the isolation of *Saccharopolyspora*, *Dietzia*, *Blastococcus*, *Dactylosporangium*, *Promicromonospora*, *Oerskovia*, *Actinocorallia* and *Jiangella* species from endophytic environments. A typical endophytic *Actinomycete*, *Frankia*, has nitrogen-fixing activity, a function which plays an important role in ecological systems (Xu et al. 2007).

Extreme environments

Extreme environments have unusual growth conditions such as high and low temperature, salt, alkaline and acidic pH, radioactivity and high pressure. Microorganisms from extreme environments have received great attention owing to their special mechanisms of adapting to the conditions in their extreme environments and also because they can produce unusual compounds (Meklat et al. 2011). Despite the interest however, only a few investigations have been performed with *Actinomycetes* growing under extreme environments: *Actinopolyspora halophila* is an accidentally discovered pioneer (Gochnauer et al. 1975). In recent years, researchers from Yunnan Institute of Microbiology at Yunnan University discovered many novel *Actinomycetes* from salt and alkaline soils in Xinjiang and Qinghai, P. R. China (Jiang and Xu 1996; Jiang et al. 2006). These researchers described a new family *Yaniaceae*, several novel genera including *Streptomonospora*, *Jiangella*, *Myceligenerans*, *Naxibacter*, and a great number of new species of the genera *Actinopolyspora*, *Amycolatopsis*, *Citricoccus*, *Halomonas*, *Isoptericola*, *Jonesia*, *Kocuria*, *Kribbella*, *Liuella*, *Marinococcus*, *Massilia*, *Microbacterium*, *Nesterenkonia*, *Nocardia*, *Nocardiopsis*, *Prauserella*, *Rhodococcus*, *Saccharomonospora*, *Saccharopolyspora*, *Sphingomonas*, *Thermobifida* and *Virgibacillus*. Recently, Meklat et al. (2011) reported a wide spectrum of biologically active halophilic *Actinomycetes* evaluated using a polyphasic approach which showed the presence of a new genus and many new species of the *Actinopolyspora*, *Nocardiopsis*, *Saccharomonospora*, *Streptomonospora* and *Saccharopolyspora* genera. Furthermore, their discovery that from among the rare genera isolated from saline conditions, *Nocardiopsis* strains having high frequency of NRPS genes could be evidence of the high potential of halophilic *Actinomycetes* for producing a large number of biologically active compounds.

Caves

Generally, caves are low in nutrients, temperature and light intensity but they have high humidity (Schabereiter-Gurtner et al. 2002). These factors might encourage competition which could enhance the production of substances such as antibiotics and hydrolytic enzymes that inhibit the growth of other microorganisms (Nakaew et al. 2009). Recently, several new species of *Actinomycetes* have been isolated from caves, including from a gold mine in Korea (Lee et al. 2000a, b, 2001; Lee 2006a, b, c), the Reed Flute Cave in China (Groth et al. 1999), the Grotta Dei Cervi Cave in Italy (Jurado et al. 2005a) and a cave occupied by bats in Spain (Jurado et al. 2005b). Nakaew et al. (2009) reported for the first time the isolation of *Spirillospora* and *Nonomuraea* from a cave soil along with very rare genera such as *Spirillospora*, *Catellatospora*, *Nonomuraea* and *Micromonospora*, and Niyomvong et al. (2012) isolated members of the genera *Actinomadura* and *Saccharopolyspora* from caves along with other rare genera *Actinoplanes*, *Gordonia*, *Microbispora*, *Micromonospora*, *Nocardia*, *Nonomuraea* and the predominant genus *Streptomyces*. These studies confirm that caves may be excellent sources of rare *Actinomycetes* that produce novel compounds.

Insects

The insect world is another unexplored environment for exploring new and novel microorganisms. Fungi culture in the

insect world is practised by ants, termites, beetles and gall midges (Kaltenpoth 2009) and there is evidence that the fungal cultivar produces antibiotics in order to defend itself (Wang et al. 1999; Currie et al. 1999; Little et al. 2006). Ant workers also defend their fungal gardens through a combination of grooming and weeding (Little et al. 2006), producing their own antimicrobials through metapleural gland secretions (Bot et al. 2002) and the application of weedkillers. These weedkillers are natural product antimicrobials produced by symbiotic *Actinomycete* bacteria (Currie et al. 1999; Sen et al. 2009; Haeder et al. 2009; Oh et al. 2009). A long-standing theory suggests that bacteria from the genus *Pseudonocardia* co-evolved with the ants and are transmitted vertically by the gynes (reproductive females) along with the fungal cultivar. However, more recent evidence has emerged that suggests attine ants are also associated with bacteria from the *Actinomycete* genera *Streptomyces* and *Amycolatopsis* and that antibiotic-producing *Actinomycetes* can be horizontally acquired through male dispersal and sampling of *Actinomycetes* from soils (Currie et al. 1999; Mueller et al. 2008). The identities of the antifungal compounds produced by attine ant-associated *Actinomycetes* remain largely unknown. Only two compounds have been identified so far: a previously unknown antifungal named 'Dentigerumycin' that is produced by *Pseudonocardia* species isolated from the lower attines *Apterostigma dentigerum* and 'Candicidin', a well-known antifungal that is produced by *Streptomyces* species isolated from the higher attine ants belonging to the genus *Acromyrmex* (Haeder et al. 2009; Oh et al. 2009). *Pseudonocardia* isolated from *Acromyrmex octospinosus* also inhibit the growth of *Escovopsis* in bioassays, but the antifungal compounds have not been isolated nor identified (Haeder et al. 2009). Recently, Barke et al. (2010) identified a *Pseudonocardia* species in the ant *Acromyrmex octospinosus* that produces an unusual polyene antifungal metabolite. Exploring new bioactive molecules could be increased by switching the search away from explored environments to unexplored ones (Clardy et al. 2009). In this line, the insect world is emerging rapidly as a source to discover *Actinomycetes* for unusual and novel bioactive molecules.

Aquatic environments

Actinomycetes are predominant in river, lake and marine environments, despite some of them being introduced from terrestrial habitats (Cross 1981). High numbers of *Micromonospora*, an indigenous inhabitant of the water and mud from freshwater lakes (Cross 1981), can be isolated from lake sediments as much as 10–50 % of the total microbial population in lake water. Nebish Lake had 3,300 bacteria mL^{-1} of which 15 % was *Micromonospora*, and Crystal Lake 3,600 bacteria mL^{-1} with 16 % *Micromonospora*.

Actinoplanes with sporangium and zoospores will grow at moist conditions and survive as spores in the dry environment (Cross 1981): it colonizes vegetable and animal remains, ranging from pollen and hair to leaves and twigs. Rehydration stimulates the release of zoospores, which swim in the water film of soil or in stream and lake waters until they are able to recolonize a suitable substrate (Cross 1981). Representatives of *Thermoactinomyces*, *Streptomyces* and *Rhodococcus* live in aquatic environments (Cross 1981). Xu and Jiang (1996) studied *Actinomycete* populations of 12 lakes in the middle plateau of Yunnan (China) and found that *Micromonospora* was the dominant genus (39–89 %) in the *Actinomycetes* population in sediments of those lakes. Furthermore, *Streptomyces* was the second most abundant genus. Members of rare genera *Actinoplanes*, *Actinomadura*, *Microbispora*, *Micropolyspora*, *Microtetraspora*, *Mycobacterium*, *Nocardiopsis*, *Nocardia*, *Promicromonospora*, *Rhodococcus*, *Saccharomonospora*, *Saccharopolyspora*, *Streptosporangium*, *Thermoactinomyces*, *Thermomonospora* and *Thermopolyspora* have also been reported from lake sediments (Xu and Jiang 1996).

Other habitats

Rare genera of *Actinomycetes* such as *Microbispora*, *Nocardia*, *Microtetraspora*, *Actinomadura*, *Amycolatopsis* and *Saccharothrix* have been successfully isolated from desert soil (Takahashi et al. 1996), and the novel rare *Actinomycete* genera *Beutenbergia* (Groth et al. 1999) and *Terrabacter* (Lee et al. 2008c) have been reported from small stones collected from caves and agricultural fields, respectively. Recently, rare genera of *Actinomycetes* such as *Streptosporangium*, *Actinomadura*, *Saccharopolyspora*, *Thermoactinomyces* and *Nocardia* were isolated from soils in the nests of solitary wasps and swallow birds (Kumar et al. 2012).

Marine environment: a source of rare *Actinomycetes*

Many natural environments are still either unexplored or underexplored and thus can be considered as potential resources for the isolation of lesser studied microorganisms, including rare *Actinomycetes* (Tiwari and Gupta 2012a). Unexplored marine environments, for example, are now a popular research area due to the potentially huge resources present within them. A recent study (Stach and Bull 2005) of the microbial diversity of deep-sea sediments has shown that this environment might contain more than 1,300 different actinobacterial operational taxonomic units, a great proportion of which are predicted to represent novel species and genera. Furthermore, it is recognized that marine microbes can sense, adapt and respond quickly to diverse environments, and can compete for defense and survival by producing unique secondary metabolites (Knight et al. 2003; Zhang et al. 2005). The hidden wealth of this source needs to be explored further.

The historical paradigm of the deep ocean as a biological 'desert' has shifted to one of a 'rainforest' owing to the isolation of many novel microorganisms and their associated unusual bioactive compounds (Zhang 2005). The marine environment has emerged as an important source of bioactive natural products. There are, for example, several exciting marine-derived molecules on the pharmaceutical market and dozens more progressing through the development pipeline (Mayer et al. 2010). Thus, unexplored and new microbial habitats need to be examined for microbial resources that produce useful bioactive compounds. As with terrestrial soils, marine sediments contain limited amounts of readily available organic matter, with most sources of carbon (such as cellulose and chitin) being present in complex forms. However, culture-independent studies have shown that marine sediment environments contain a wide diversity of *Actinomycetes* and many unique taxa are very different from their terrestrial counterparts (Stach et al. 2003; Gontang et al. 2007). In addition, culture-dependent studies have shown that marine *Actinomycetes* are ubiquitous in marine sediment environments (Maldonado et al. 2005; Jensen et al. 2005a). Many novel bioactive secondary metabolites isolated from marine *Actinomycetes* have been reported (Subramani and Aalbersberg 2012), and they may be a source of novel compounds with pharmaceutical potential (Mayer et al. 2010).

The isolation of a seawater-obligate marine *Actinomycete* species of the genus *Salinispora* was reported in 2005 (Maldonado et al. 2005) and that discovery was followed by the discovery of other genera such as *Demequina*, *Marinispora*, *Solwaraspora*, *Lamerjespora*, *Serinicoccus*, *Salinibacterium*, *Aeromicrobium*, *Williamsia*, *Marinactinospora* and *Sciscionella* that so far appear to be exclusively marine (Subramani and Aalbersberg 2012). Further, these indigenous *Actinomycetes* are robust sources of natural products, such as the genera *Salinispora* [salinosporamide A (NPI-0052), sporolides, saliniquinone A-F, salinosporamide K], *Verrucosispora* (abyssomicins), *Micromonospora* [diazepinomicin (ECO-4601)] (Lam 2006) and *Marinispora* (marinomycins, marinisporolides) (Kwon et al. 2009). The discovery of novel marine actinomycetal taxa is very important for potential new sources of pharmaceuticals.

Rare *Actinomycetes* are widely present in marine habitats (Goodfellow and Williams 1986; Subramani and Aalbersberg 2012). Rare or unusual *Actinomycetes* produce diverse, unique, unprecedented and occasionally complicated compounds with excellent antibacterial potency and usually low toxicity (Berdy 2005). The oceans represent a rich microbial diversity and population (Stach and Bull 2005; Sogin et al. 2006), and intensive research is ongoing for the microbial biodiversity potential in the marine environment (Heidelberg et al. 2010). Moreover, until now, very few marine obligate taxa have been isolated (Goodfellow 2010). Therefore, oceans are expected to harbour prolific sources of new/novel microbial taxa, and Tiwari and Gupta (2012a) argued that to obtain a novel metabolite, a diverse and less exploited reserve of microbes is required. Isolation of rare *Actinomycetes* thus becomes the first and most crucial step towards *Actinomycetes* resource development for drug discovery (Cai et al. 2009).

Marine sediments, seawater, symbiotic and mangroves

Deep-sea sediments cover 63.5 % of the Earth's surface (Emery 1969) and represent the most undersampled marine habitat (Butman and Carlton 1995). As early as 1884, marine bacterial strains were isolated from deep-sea sediments, to depths of 5,100 m (Zobell 1946). Recently, the concept of 'marine microorganism' has been accepted worldwide (Tian et al. 2012), yet the common recognition for 'marine *Actinomycetes*' has undergone a long period of dispute concerning their actual source (Goodfellow and Haynes 1984). Originally, *Actinomycetes* generally were considered to be indigenous to terrestrial habitats because no convincing evidence was available to demonstrate that *Actinomycetes* could adapt to marine habitats (Tian et al. 2012). Nevertheless, the novel genus *Salinispora* (Maldonado et al. 2005) was described and subsequently accepted as the first obligate marine *Actinomycetes* due to its stringent requirement of seawater for growth. Tian et al. (2009b) described another marine actinobacterial genus, *Sciscionella*, which can tolerate high salt concentrations (up to 13 %) for growth. To date, more than 14 novel actinobacterial genera have been discovered from the marine environment (Goodfellow and Fiedler 2010; Kurahashi et al. 2010; Chang et al. 2011; Xiao et al. 2011a). It is becoming increasingly obvious that *Actinomycetes* are an important part of the indigenous microflora in marine ecosystems.

Generally, the pretreatments and enrichment of the samples used for isolation of rare *Actinomycetes* from soil (see earlier) are the same methods followed for treatment of marine samples. Tables 2, 3, 4, 5 and 6 re-emphasize the pretreatment of samples and enrichment culture methods used, particularly for isolation of marine-derived rare *Actinomycetes*. This review summarizes the source, treatment of samples and isolation media for all new rare *Actinomycetes* reported from marine habitats between 2007 and mid-2013, including sediments, seawater, symbiotic and mangrove ecosystems. Wet and dry heat treatments, radiations, cold shock, different chemicals, and antibiotics and 1.5 % phenol-treated marine samples combined with selective isolation media can increase the recovery of new and novel genera of rare *Actinomycetes* in diverse marine samples (Tables 2, 3, 4, 5 and 6). Interestingly, though observed the combination of selective isolation and screening procedures yielded a number of new rare *Actinomycetes* genera in marine samples, also noticed that a number of new rare *Actinomycete* species and even novel

Table 2 Pretreatment or enrichment of marine samples for isolation of rare genera of *Actinomycetes*

Pretreatment/enrichment	Source	Rare genera isolated	Reference
Heat treated by 50 °C for 60 min+addition of nalidixic acid in isolation medium	Marine sediments	*Micromonospora*	Takizawa et al. (1997)
Treated with 41 °C for 10, 30 and 60 days+selective nutrient media	Marine sediments	*Streptomyces*, *Streptoverticillium*, *Catellatospora*, *Nocardia* and *Actinopolyspora*	Kokare et al. (2004)
Different selective methods+different seawater-based media	Marine sediments	*Salinispora* and *Micromonospora*	Jensen et al. (2005a)
Different selective media particularly raffinose–histidine agar	Deep-sea sediments	*Dermacoccus*, *Kocuria*, *Micromonospora*, *Streptomyces*, *Tsukamurella* and *Williamsia*	Pathom-Aree et al. (2006)
(1) UV irradiation of the wet sediment suspension (5 ml) was performed in open Petri dishes for 30 s (2) Super high frequency (SHF) radiation treatment of the suspension (2.5 ml) placed into sterile Eppendorf tubes were carried out in a microwave oven at a frequency of 2,460 MHz and power of 80 W for 45 s (3) Extremely high frequency (EHF) radiation treatment of the suspension (5 ml) was carried out in Petri dishes from the bottom. Emitted radiation had a non-thermal intensity and was amplitude-modulated at a frequency of 1 kHz within wavelength band of 8–11.5 mm using industrial generator (4) Cold-shock by freezing sediment samples at −18 °C+selective nutrient media	Shallow water sediments	*Nocardiopsis*, *Nocardia* and *Pseudonocardia* *Streptosporangium* and *Rhodococcus* *Nocardiopsis*, *Nocardia* and *Streptosporangium*	Bredholdt et al. (2007)
Dry sediment+selective nutrient media	Marine sediments and deep-sea mud samples	Non-*Actinomycetes*, streptomycetes and non-streptomycete *Actinomycetes*	Bredholt et al. (2008)
Treated with 120 °C for 60 min+selective nutrient media	Deep-sea mud samples	Non-streptomycete *Actinomycetes* and non-*Actinomycetes*	
1.5 % Phenol+selective nutrient media	Deep-sea mud samples	Non-streptomycete *Actinomycetes* and non-*Actinomycetes*	
120 °C for 60 min+1.5 % phenol+selective nutrient media	Deep-sea mud samples	Non-streptomycete *Actinomycetes*	
120 °C for 60 min+benzethonium chloride+selective nutrient media	Deep-sea mud samples	Non-streptomycete *Actinomycetes* and non-*Actinomycetes*	
Heat treated by 60 °C for 6 min	Marine sediments	*Streptomyces*, *Nocardia*, *Nonomuraea*, *Rhodococcus*, *Saccharopolyspora* and *Gordonia*	Solano et al. (2009)
Sediments treated with dry heat (120 °C for 60 min); chloramine-T; phenol (1.5 % for 30 min at 30 °C); 0.05 % SDS and 6 % yeast extract (40 °C, 200 rpm for 30 min) and wet heat in sterilized seawater (50 °C for 15 min)+selective isolation media	Mangrove sediments	*Actinomadura*, *Micromonospora*, *Nocardia*, *Nonomuraea*, *Rhodococcus*, *Streptomyces* and *Verrucosispora*	Hong et al. (2009)
Wet heating for 15 min at 70 °C and phenol+hair hydrolysate vitamin agar	Mangrove sediments	*Micromonospora*, *Microbispora*, *Actinoplanes* and *Actinomadura*	Naikpatil and Rathod (2011)
Treated with 55 °C for 15 min in a suspension fluid containing osmoprotectant (quarter strength Ringer's solution)+selective nutrient medium	Mangrove sediments	*Pseudonocardia*	Mangamuri et al. (2012)
Different selective isolation media	Sea grass	*Streptomyces*, *Micromonospora*, *Saccharomonospora*, *Mycobacterium*, *Actinomycetospora*, *Nonomuraea*, *Verrucosispora*, *Nocardiopsis*, *Microbacterium* and *Glycomyces*	Wu et al. (2012)
Different selective isolation media+sponge homogenate	Sponge	*Streptomyces*, *Nocardia*, *Rhodococcus* and *Actinobacterium*	Mehbub and Amin (2012)
Wet heat treated with 55 or 65 °C for 30 min	Marine and estuarine sediments	*Micromonospora*	Terahara et al. (2013)

Table 3 Newly discovered rare *Actinomycetes* from marine sediments during the period 2007–mid-2013

Strain/family	Source	Pretreatment of sample/enrichment culture	Isolated medium	Reference
Nocardioides furvisabuli/ *Nocardioidaceae*	Beach black sand	Sediment sample (1 g) was placed into a sterile tube containing 9 ml sterile seawater. After mixing for 30 min on a tube rotator, aliquots (100 μl) of the serial diluents of the samples were transferred to isolation medium	SC-SW medium (1 % soluble starch, 0.03 % casein, 0.2 % KNO_3, 0.2 % NaCl, 0.002 % $CaCO_3$, 0.005 % $MgSO_4 \cdot 7H_2O$, 0.001 % $FeSO_4 \cdot 7H_2O$ and 1.8 % agar in a 60:40 mixture of natural seawater and distilled water)	Lee (2007c)
Actinotalea fermentans (novel genus)/ *Micrococcineae* (suborder)	Tidal flat sediment	Standard dilution plating method	Marine agar 2216 (MA; Difco)	Yi et al. (2007)
Marmoricola aequoreus/ *Nocardioidaceae*	Sandy sediment under the surface of a beach	Sediment sample (1 g) was placed into a sterile tube containing 9 ml sterile seawater. After mixing for 30 min on a tube rotator, aliquots (100 μl) of the serial diluents of the samples were transferred to isolation medium	SC-SW medium (1 % soluble starch, 0.03 % casein, 0.2 % KNO_3, 0.2 % NaCl, 0.002 % $CaCO_3$, 0.005 % $MgSO_4 \cdot 7H_2O$, 0.001 % $FeSO_4 \cdot 7H_2O$ and 1.8 % agar in a 60:40 mixture of natural seawater and distilled water)	Lee (2007b)
Aestuariimicrobium kwangyangense (novel genus)/ *Propionibacteriaceae*	Oil-contaminated tidal flat sediment	Sediment samples (0.5 mg) were inoculated in 100 ml Bushnell–Haas broth (Difco) that contained 2 % (*w*/*v*) diesel oil were incubated at 30 °C on a horizontal shaker at 150 rpm. The diluted enrichment culture was transferred to isolation medium	R2A agar (Difco)	Jung et al. (2007)
Nocardioides marinisabuli/ *Nocardioidaceae*	Beach sand	Sediment sample (1 g) was placed into a sterile tube containing 9 ml sterile seawater. After mixing for 30 min on a tube rotator, aliquots (100 μl) of the serial diluents of the samples were transferred to agar medium	ISP-4 medium (soluble starch 10.0 g, K_2HPO_4 1.0 g, $MgSO_4 \cdot 7H_2O$ 1.0 g, NaCl 1.0 g, $(NH_4)_2SO_4$ 2.0 g, $CaCO_3$ 2.0 g, $FeSO_4$ 1.0 mg, $MnCl_2$ 1.0 mg, $ZnSO_4$ 1.0 mg, agar 20.0 g supplemented with 60 % (*v*/*v*) natural seawater)	Lee et al. (2007)
Demequina aestuarii (novel genus)/ *Micrococcineae* (suborder)	Tidal flat sediment	Standard dilution plating method	Marine agar 2216 (MA; Difco)	Yi et al. (2007)
Nocardioides dokdonensis/ *Nocardioidaceae*	Beach sediment	Standard dilution plating method	R2A agar (Difco) supplemented with 3.5 % artificial sea salts (Sigma)	Park et al. (2008)
Tessaracoccus flavescens/ *Propionibacteriaceae*	Marine sediment	A wet sediment sample (1 g) was dried aseptically for 24 h and ground lightly with a pestle. The sample was transferred onto an SC-SW agar plate using a sterile stopper by serial stamping eight or nine times in a circular fashion	SC-SW medium (1 % soluble starch, 0.03 % casein, 0.2 % KNO_3, 0.2 % NaCl, 0.002 % $CaCO_3$, 0.005 % $MgSO_4 \cdot 7H_2O$, 0.001 % $FeSO_4 \cdot 7H_2O$ and 1.8 % agar in a 60:40 mixture of natural seawater and distilled water)	Lee and Lee (2008a)
Amycolatopsis marina/ *Pseudonocardiaceae*	Deep-sea sediment	Standard dilution plating method	SM1 agar (yeast nitrogen base (67.0 g; Difco) and casamino acids (100 mg; Difco) were added to a litre of distilled water and the solution sterilized using cellulose filters (0.20 μm) prior to the addition of sterilized K_2HPO_4 (200 ml; 10 %, *w*/*v*); 100 ml of this basal medium was added to 900 ml of sterilized molten agar (1.5 %, *w*/*v*) followed by filter sterilized solutions of D-sorbitol (final concentration 1 %, *w*/*v*), cycloheximide (50 μg ml^{-1}), neomycin sulphate (4 μg ml^{-1}) and nystatin (50 μg ml^{-1})	Bian et al. (2009)
Tessaracoccus profundi/ *Propionibacteriaceae*	940 m depth of deep-sea sediment	The sample (ca. 5 g) was aseptically ground with a sterile pestle in a mortar and transferred to a sterile test tube. One gram of the ground material was aerobically suspended in 10 ml PBS, vortexed for 1 min, and 1 ml of the suspension was transferred to 50 ml of isolation medium	R2A agar (Difco) plates supplemented with NaCl (20 g l^{-1}) and $MgCl_2 \cdot 6H_2O$ (3 g l^{-1}).	Finster et al. (2009)
Marinactinospora thermotolerans (novel genus)/ *Nocardiopsaceae*	Deep-sea black soft mud at 3,865 m depth	Samples were first air-dried aseptically by being placed into a laminar flow hood and then a 2-g air-dried sample was suspended in 18 ml sterile seawater before 0.1 ml was spread on isolation medium	Raffinose-histidine agar (10 g of raffinose, 1 g of L-histidine, 0.5 g of $MgSO_4$, 0.01 g of $FeSO_4$, 20 g of NaCl in liter of seawater)	Tian et al. (2009a)
Paraoerskovia marina (novel genus)/ *Cellulomonadaceae*	Marine sediment	The sediment sample was suspended and serially diluted in sterile artificial seawater	Half-strength marine agar [HSMA; 19 g Bacto marine broth 2216 (Difco), 17 g artificial seawater salts and 15 g agar, dissolved in 1 l distilled water]	Khan et al. (2009)
Sciscionella marina (novel genus)/ *Pseudonocardiaceae*	516 m depth of deep-sea sediment	Standard dilution plating method	Gauze no. 1 medium (20 g soluble starch, 1 g KNO_3, 0.5 g NaCl, 0.5 g $MgSO_4 \cdot 7H_2O$, 0.5 g K_2HPO_4, 10 mg $FeSO_4 \cdot 7H_2O$ prepared with 1 l of seawater)	Tian et al. (2009b)
Promicromonospora flava/ *Promicromonosporaceae*	Marine sediment	Not specified	Fucose-proline medium (5 g fucose, 1 g proline, 1 g $(NH_4)_2SO_4$, 1 g NaCl, 2 g $CaCl_2$, 1 g K_2HPO_4, 1 g $MgSO_4 \cdot 7H_2O$, 20 g agar per litre of Baltic seawater)	Jiang et al. (2009)
Verrucosispora sediminis/ *Micromonosporaceae*	3,602 m depth of deep-sea sediment	Standard dilution plating method	Gauze no. 1 medium (20 g soluble starch, 1 g KNO_3, 0.5 g NaCl, 0.5 g $MgSO_4 \cdot 7H_2O$, 0.5 g K_2HPO_4, 10 mg $FeSO_4 \cdot 7H_2O$ prepared with 1 l of seawater)	Dai et al. (2010)
Isoptericola jiangsuensis/ *Promicromonosporaceae*	Beach sediment	Not specified	Unspecified chitin as a sole carbon source medium	Wu et al. (2010)

Table 3 (continued)

Strain/family	Source	Pretreatment of sample/enrichment culture	Isolated medium	Reference
Micromonospora marina/ *Micromonosporaceae*	Sea-shore sediment	Not specified	Starch-casein nitrate agar (10 g starch, 0.3 g sodium caseinate (Difco), 2 g KNO_3 and 15 g agar per litre)	Tanasupawat et al. (2010)
Prauserella marina/ *Pseudonocardiaceae*	3,602 m depth of sea sediment	Not specified	MOPS-proline agar medium (1 g MOPS, 1 g proline, 1 g $(NH_4)_2SO_4$, 1 g NaCl, 1 g $CaCl_2$, 1 g K_2HPO_4, 1 g $MgSO_4 \cdot 7H_2O$ and 20 g agar per litre)	Wang et al. (2010)
Arthrobacter antarcticus/ *Micrococcaceae*	400 m depth of Antarctic marine sediment	The 0.1 g of sample suspended in 1 ml sterile water by vortex mixer and plated on isolation medium	Nutrient agar (10 g peptone, 10 g beef extract, 5 g NaCl and 20 g agar per litre)	Pindi et al. (2010)
Saccharomonospora marina/ *Pseudonocardiaceae*	4 m depth of marine sediment	Not specified	PLA emulsified agar (1 g of polymer was dissolved in 500 ml methylene chloride, followed by emulsification with a homogenizer into 1 l of a basal medium containing 100 mg yeast extract, 10 mg $FeSO_4 \cdot 7H_2O$, 200 mg $MgSO_4 \cdot 7H_2O$, 1,000 mg $(NH_4)_2SO_4$, 20 mg $CaCl_2 \cdot 2H_2O$, 100 mg NaCl, 0.5 mg $Na_2MoO_4 \cdot 2H_2O$, 0.5 mg Na_2WO_4, 0.5 mg $MnSO_4$, 50 mg Plysurf A210G and 18 g agar per litre)	Liu et al. (2010)
Marisediminicola antarctica (novel genus)/ *Microbacteriaceae*	Intertidal sea sediment	Dried sediment (approx. 2 g) was diluted with 10 ml sterile seawater. The diluted sample was vortexed, allowed to settle for 30 min, and 100 µl of the resulting solution was further diluted (1:10) and spread onto isolation medium	Gause mineral agar I (starch soluble 20.0 g, K_2HPO_4 0.5 g, $MgSO_4$ 0.5 g, KNO_3 1.0 g, NaCl 0.5 g, $FeSO_4$ 0.01 g, agar 20.0 g, distilled water 1 l)	Li et al. (2010)
Kocuria sediminis/ *Micrococcaceae*	Marine sediment	Standard dilution plating method	Tryptic soy agar (papaic digest of soybean 5 g, pancreatic digest of casein 15 g, NaCl 5 g and 15 g agar per litre)	Bala et al. (2011)
Spinactinospora alkalitolerans (novel genus)/ *Nocardiopsaceae*	17.5 m depth of marine sediment	Two grams wet sample was suspended in 18 ml sterile seawater and 0.1 ml aliquots of the suspension were spread on isolation media	Sodium propionate-aspartic acid agar (0.1 g aspartic acid, 2.0 g peptone, 4.0 g sodium propionate, 0.05 g $K_2HPO_4 \cdot 3H_2O$, 0.1 g $MgSO_4 \cdot 7H_2O$, 0.01 g $FeSO_4 \cdot 7H_2O$, 20.0 g agar, 1.0 l 2–3 weeks old seawater)	Chang et al. (2011)
Nonomuraea maritima/ *Streptosporangiaceae*	Beach surface sediment	The sediment sample was dried at room temperature, suspended in sterile distilled water, serially diluted, and heated in a water bath at 55 °C for 6 min, and spread-plated on isolation medium	Oatmeal agar [ISP 3 medium; Oatmeal 20.0 g, trace salts solution ($FeSO_4 \cdot 7H_2O$ 0.1 g, $MnCl_2 \cdot 4H_2O$ 0.1 g, $ZnSO_4 \cdot 7H_2O$ 0.1 g, deionized water 100.0 ml) 1.0 ml, agar 18.0 g per litre]	Xi et al. (2011b)
Demequina globuliformis/ *Micrococcineae* (suborder)	Marine sediment	Not specified	HSV medium (metal mix X 250 ml, humic acid mix 100 ml, vitamin mix A 4 ml, vitamin B12 solution 1 ml, cycloheximide 50 mg, griseofluvin 25 mg, nalidixic acid 20 mg, aztreonam 40 mg, agar 20 g and distilled water 650 ml)	Ue et al. (2011a)
Serinicoccus chungangensis/ *Intrasporangiaceae*	Tidal flat sediment	Standard dilution plating method	Glucose yeast extract agar (10 g yeast extract, 10 g glucose and 15 g agar per litre)	Traiwan et al. (2011)
Miniimonas arenae (novel genus)/ *Beutenbergiaceae*	Beach sediment	Not specified	H medium (H mix 100 ml, metal mix X 250 ml, cycloheximide 50 mg, griseofluvin 25 mg, nalidixic acid 20 mg, aztreonam 40 mg, agar 20 g and distilled water 650 ml)	Ue et al. (2011b)
Serinicoccus profundi/ *Intrasporangiaceae*	5,368 m depth of deep-sea sediment	Standard dilution plating method	Oligotrophic medium (seawater, 2.0 % agar)	Xiao et al. (2011b)
Modestobacter marinus/ *Geodermatophilaceae*	2,983 m depth of deep-sea sediment	Not specified	Not mentioned	Xiao et al. (2011c)
Rhodococcus nanhaiensis/ *Nocardiaceae*	84.5 m depth of marine sediment	Standard dilution plating method	A1 medium (10 g starch, 4 g yeast extract, 2 g peptone, 1 l seawater and 12 g agar) and A4 medium (0.25 g yeast extract, 0.5 g K_2HPO_4, 1 l seawater and 12 g agar)	Li et al. (2012b)
Verrucosispora maris/ *Micromonosporaceae*	Deep-sea sediment	Standard dilution plating method	Colloidal chitin agar (chitin 4 g, K_2HPO_4 0.7 g, KH_2PO_4 0.3 g, $MgSO_4 \cdot 5H_2O$ 0.5 g, $FeSO_4 \cdot 7H_2O$ 0.01 g, $ZnSO_4$ 0.001 g, $MnCl_2$ 0.001 g and 20 g of agar per litre)	Goodfellow et al. (2012b)
Nocardia grenadensis/ *Nocardiaceae*	5 m depth of marine sediment	One gram of sample, after a 2-h extraction in 10 ml of 0.1 % (*v*/*v*) Tween 80 containing 5 mg ampicillin, then serially diluted and plated on isolation medium	Soil extract agar (1,000 g of soil with 2 l of 50 mM NaOH and incubated overnight at room temperature. The mixture was incubated and then centrifuged for 60 min at 18,000 rpm. The supernatant was sterilized through a 0.2-µm filter membrane. Soil extract agar containing 500 ml of soil extract and 15 g of agar per litre)	Kämpfer et al. (2012)
Verrucosispora fiedleri/ *Micromonosporaceae*	250 m depth of sea sediment	Not specified	Starch-casein nitrate agar (10 g soluble starch, 3 g vitamin-free casein, 2 g KNO_3, 2 g NaCl, 2 g K_2HPO_4, 0.5 g $MgSO_4$, 0.2 g $CaCO_3$, 0.1 g $FeSO_4 \cdot 7H_2O$ and 18 g agar in 1 l seawater)	Goodfellow et al. (2012a)

Table 3 (continued)

Strain/family	Source	Pretreatment of sample/enrichment culture	Isolated medium	Reference
Demequina flava/ *Micrococcineae* (suborder)	Marine sediment	Approximately 1 g of the sample was diluted 10-, 100- and 1,000-fold with saline before 0.2 ml of each dilution was spread on isolation medium	1/5 NBRC medium 802 (0.2 % polypeptone, 0.04 % yeast extract, 0.02 % $MgSO_4 \cdot 7H_2O$ and 1.5 % agar)	Hamada et al. (2013)
Demequina sediminicola/ *Micrococcineae* (suborder)	Marine sediment	Approximately 1 g of the sample was diluted 10-, 100- and 1,000-fold with saline before 0.2 ml of each dilution was spread on isolation medium	1/5 NBRC medium 802 (0.2 % polypeptone, 0.04 % yeast extract, 0.02 % $MgSO_4 \cdot 7H_2O$ and 1.5 % agar)	Hamada et al. (2013)
Micromonospora sediminicola/ *Micromonosporaceae*	Marine sediment	Not specified	Starch-casein nitrate agar (10 g soluble starch, 1 g sodium caseinate, 2 g KNO_3, 0.5 g KH_2PO_4, 0.5 g $MgSO_4$ and 18 g agar in 1 l seawater)	Supong et al. (2013)
Pseudonocardia antitumoralis/ *Pseudonocardiaceae*	3,258 m depth of deep-sea sediment	Standard dilution plating method	Gauze no. 1 medium (20 g soluble starch, 1 g KNO_3, 0.5 g NaCl, 0.5 g $MgSO_4 \cdot 7H_2O$, 0.5 g K_2HPO_4, 10 mg $FeSO_4 \cdot 7H_2O$ prepared with 1 l of seawater)	Tian et al. (2013)
Microbacterium sediminis/ *Microbacteriaceae*	2,327 m depth of deep-sea sediment	Two grams of sediment was suspended in 18 ml sterile seawater and mixed. Soil particles were allowed to settle down, the liquid phase was diluted 10^5-fold and 100 µl samples were spread onto isolation medium	FJ agar (1 % glucose, 1 % yeast extract, 1.5 % agar, 50 % seawater) with rifampicin (5 mg l^{-1}) and potassium dichromate (50 mg l^{-1})	Yu et al. (2013)

genera of rare *Actinomycetes* were successfully isolated without any pretreatment of the marine samples (Tables 3, 4, 5 and 6). Supportively, Qiu et al. (2008) reported that no matter which pretreatment method was applied, different selective media (particularly HVA, ISP-3 agar and DNB agar) always give better isolation of *Micromonospora*-like colonies than do other media. Furthermore, these authors found that the yield of non-streptomycete colonies increased in all the composite samples. Ongoing research in our group at the University of the South Pacific in Fiji on the isolation of the marine obligate genus *Salinispora* has shown that the direct plating of air-dried sediments on different complex nutrient media allows the successful isolation of *Salinispora* spp. (unpublished data). Therefore, it appears that selective media are playing an important role in the isolation of rare marine *Actinomycetes*. These results clearly reveal that rare or unusual *Actinomycetes* are widely dispersed in marine environments and that they have enormous novel actinobacterial diversity which can be readily obtained using conventional isolation methods.

Marine sediments are rich in actinobacterial diversity. A total of 38 new rare *Actinomycete* species belonging to 15 different *Actinomycete* families have been reported in marine sediments from the period 2007–mid 2013 (Table 3). Among them, nine novel genera such as *Actinotalea*, *Aestuariimicrobium*, *Demequina*, *Marinactinospora*, *Paraoerskovia*, *Sciscionella*, *Marisediminicola*, *Spinactinospora* and *Miniimonas* were reported. The families reported in marine sediments in the period are *Nocardioidaceae* (four new species), *Micrococcineae* (suborder) (five new species), *Propionibacteriaceae* (three new species), *Pseudonocardiaceae* (five new species), *Nocardiopsaceae* (two new species), *Cellulomonadaceae* (one new species), *Promicromonosporaceae* (two new species), *Micromonosporaceae* (five new species), *Micrococcaceae* (two new species), *Microbacteriaceae* (two new species), *Streptosporangiaceae* (one new species), *Intrasporangiaceae* (two new species), *Beutenbergiaceae* (one new species), *Geodermatophilaceae* (one new species) and *Nocardiaceae* (two new species).

The culturability of microorganisms from seawater is considerably lower (0.001–0.10 %) than that from marine sediments (0.25 %) (Amann et al. 1995). Considering the vast volume of seawater in oceans, the extensive microbial diversity for drug discovery efforts should be extended to explore this resource. A total of 11 new rare *Actinomycete* species belonging to six different *Actinomycete* families were reported in seawater from the period 2007 to mid-2013 (Table 4). Among them, four novel genera such as *Marihabitans*, *Ponticoccus*, *Ornithinibacter* and *Oceanitalea* are reported in seawater. The families reported in seawater between 2007 and mid-2013 are *Nocardioidaceae* (four new species), *Intrasporangiaceae* (two new species), *Propionibacteriaceae* (one new species), *Micrococcineae* (suborder) (one new species), *Micrococcaceae* (two new species) and *Bogoriellaceae* (one new species).

Table 4 Newly discovered rare *Actinomycetes* from seawater during the period 2007–mid-2013

Strain/family	Source	Pretreatment of sample/enrichment culture	Isolated medium	Reference
Nocardioides marinus/ *Nocardioidaceae*	Seawater around Dokdo island	Not specified	S medium (10 g Na_2HPO_4, 3 g KH_2PO_4, 1 g K_2SO_4, 30 g NaCl, 0.2 g $MgSO_4 \cdot 7H_2O$, 0.01 g $CaCl_2$, 0.001 g $FeSO_4 \cdot 7H_2O$, 1 g Casamino acids, 1 g yeast extract, 20 g glucose and 20 g Bacto agar, per litre distilled water)	Choi et al. (2007)
Marihabitans asiaticum (novel genus)/ *Intrasporangiaceae*	Seawater collected at the Kesennuma ferry port in Miyagi Prefecture	Not specified	1/10 strength marine agar 2216 (Difco)	Kageyama et al. (2008)
Nocardioides salaries/ *Nocardioidaceae*	Seawater was sampled from the surface of the Korean South Sea	Seawater filtered using a syringe filter (0.2 μm) and dispensed into a 20-ml sterile glass vial. Then the 0.2-μm filtered seawater was supplemented with zooplankton and incubated at a temperature close to the in situ temperature (approx. 10–15 °C). After about 1 year, 50 ml aliquots were taken and spread on a isolation medium	Low-nutrient heterotrophic medium [(0.2 μm pore size filtered and autoclaved seawater amended with 1.0 μM NH_4Cl, 0.1 μM KH2PO4, and vitamin mix at a 10^{-4} dilution of stock or an LNHM supplemented with 1× mixed carbons (1× concentrations of carbon mixtures were composed of 0.001 % (*w*/*v*) D-glucose, D-ribose, succinic acid, pyruvic acid, glycerol, *N*-acetyl D-glucosamine, and 0.002 % (*v*/*v*) ethanol)]	Kim et al. (2008)
Ponticoccus gilvus (novel genus)/ *Propionibacteriaceae*	Seawater sample from seashore of Mara Island	A seawater sample (1 l) was filtered with membrane filter (pore size; 0.45 μm). The filter was placed into a sterile falcon tube containing 10 ml distilled water. After mixing for 10 min, aliquots (100 μl) of suspension were directly transferred onto isolation medium	SC-SW medium (1 % soluble starch, 0.03 % casein, 0.2 % KNO_3, 0.2 % NaCl, 0.002 % $CaCO_3$, 0.005 % $MgSO_4 \cdot 7H_2O$, 0.001 % $FeSO_4 \cdot 7H_2O$ and 1.8 % agar in a 60:40 mixture of natural seawater and distilled water)	Lee and Lee (2008c)
Nocardioides hwasunensis/ *Nocardioidaceae*	Seawater on Hwasun beach	Aliquots (100 μl) of the water sample were transferred directly onto isolation medium	SC-SW medium (1 % soluble starch, 0.03 % casein, 0.2 % KNO_3, 0.2 % NaCl, 0.002 % $CaCO_3$, 0.005 % $MgSO_4 \cdot 7H_2O$, 0.001 % $FeSO_4 \cdot 7H_2O$ and 1.8 % agar in a 60:40 mixture of natural seawater and distilled water)	Lee et al. (2008b)
Brevibacterium marinum/ *Micrococcineae* (suborder)	Seawater collected from Hwasun beach	Aliquots of a seawater sample were directly deposited on isolation medium	Starch-casein agar (starch 10.0 g, KNO_3 2.0 g, NaCl 2.0 g, K_2HPO_4 2.0 g, $MgSO_4 \cdot 7H_2O$ 0.05 g, $CaCO_3$ 0.02 g, $FeSO_4 \cdot 7H_2O$ 0.01 g, casein 0.30 g) supplemented with 60 % natural seawater	Lee (2008b)
Aeromicrobium ponti/ *Nocardioidaceae*	Seawater sample collected from Hwasun beach	Seawater sample was spread directly onto isolation medium	SC-SW medium (1 % soluble starch, 0.03 % casein, 0.2 % KNO_3, 0.2 % NaCl, 0.002 % $CaCO_3$, 0.005 % $MgSO_4 \cdot 7H_2O$, 0.001 % $FeSO_4 \cdot 7H_2O$ and 1.8 % agar in a 60:40 mixture of natural seawater and distilled water)	Lee and Lee (2008b)
Kocuria gwangalliensis/ *Micrococcaceae*	Seawater collected on the Gwangalli coast	Not specified	Nutrient agar medium (Difco)	Seo et al. (2009)
Arthrobacter halodurans/ *Micrococcaceae*	Seawater collected from the South China Sea	Standard dilution-plating technique	Marine agar 2216 (Difco) supplemented with 0–20 % (*w*/*v*) NaCl	Chen et al. (2009a)
Ornithinibacter aureus (novel genus)/ *Intrasporangiaceae*	Seawater collected in the South China Sea	Standard dilution-plating technique	Modified R2A agar (0.5 g yeast extract, 0.5 g bacto peptone, 0.5 g casein acid hydrolysate, 0.5 g glucose, 0.5 g soluble starch, 0.3 g sodium pyruvate, 15 g agar, 750 ml seawater and 250 ml distilled water)	Xiao et al. 2011a
Oceanitalea nanhaiensis (novel genus)/ *Bogoriellaceae*	Seawater sample from the South China Sea	Seawater incubated in a rich organic (RO) medium at 28 °C for 10 days	RO medium (g/l: yeast extract 1.0, Bacto peptone 1.0, sodium acetate 1.0, KCl 0.3, $MgSO_4 \cdot 7H_2O$ 0.5, $CaCl_2 \cdot 2H_2O$, 0.05, NH_4Cl 0.3, K_2HPO_4 0.3, NaCl 20.0 and agar 20 g per litre supplemented with a mixture of vitamins (20 μg of vitamin B_{12}, 200 μg of nicotinic acid, 80 μg of biotin, and 400 μg of thiamine) and 1.0 ml per liter of a trace element solution	Fu et al. 2012

Symbiotic microorganisms—especially *Actinomycetes* (Schneemann et al. 2010; Izumi et al. 2010; Abdelmohsen et al. 2010) from marine invertebrates, plants and animals—are now rapidly emerging for drug discovery programmes (Piel 2009). The symbiotic microbial community is highly novel and diverse, and species composition shows temporal and geographic variation (Webster and Hill 2001). Even so, very little information exists about the taxonomic affiliation of marine symbiotic microorganisms (Friedrich et al. 1999). Most symbionts are as-yet unculturable, although significant advances have been made in the development of cultivation-independent techniques to study such bacteria. Since these methods will likely have a large impact on future chemical studies of symbionts, they will also be discussed because many symbionts remain unidentified (Piel 2009). Interestingly, two novel families such as *Iamiaceae* (Kurahashi et al. 2009) and *Euzebyaceae* (Kurahashi et al. 2010) in *Actinobacteria* were reported from the sea cucumber, *Holothuria edulis* (Table 5). A total of 17 new rare *Actinomycete* species belonging to 11 different *Actinomycete* families have been reported in plants and animals, respectively, between 2007 and mid-2013 (Table 5). Among them, five novel genera *Labedella*, *Phycicola*, *Iamia*, *Euzebya* and *Koreibacter* were reported from marine alga and

Table 5 Newly discovered symbiotic rare *Actinomycetes* from marine samples during the period 2007–mid-2013

Strain/family	Source	Pretreatment of sample/enrichment culture	Isolated medium	Reference
Aeromicrobium tamlense/ *Nocardioidaceae*	Dried seaweed	A dried seaweed sample (1 g) was placed into a sterile tube containing 9 ml sterile distilled water. After mixing for 30 min using a tube rotator, aliquots (100 µl) of serial dilutions of the sample were transferred onto isolation medium	SC-SW medium (1 % soluble starch, 0.03 % casein, 0.2 % KNO_3, 0.2 % NaCl, 0.002 % $CaCO_3$, 0.005 % $MgSO_4 \cdot 7H_2O$, 0.001 % $FeSO_4 \cdot 7H_2O$ and 1.8 % agar in a 60:40 mixture of natural seawater and distilled water)	Lee and Kim 2007
Labedella gwakjiensis (novel genus)/ *Microbacteriaceae*	Dried seaweed	A piece of dried seaweed was transferred directly onto a isolation medium	WAT-SW agar (0.05 % $MgSO_4 \cdot 7H_2O$, 0.05 % $CaCl_2 \cdot 2H_2O$ and 1.5 % agar in 60 % natural seawater and 40 % distilled water)	Lee 2007a
Tsukamurella spongiae/ *Tsukamurellaceae*	Deep-water (220 m depth) marine hexactinellid sponge	A small section of the sponge was gently rinsed in sterile natural seawater, cut into smaller pieces and then homogenized at low speed (5,000 rpm) with an ethanol-sterilized high-speed homogenizer. The sponge suspension was then heat-treated (70 °C for 15 min) and plated onto isolation medium	Maltose–seawater agar (2.0 g maltose, 1.0 ml trace metal solution (2.86 g H_3BO_3, 1.81 g $MnCl_2 \cdot 4H_2O$, 1.36 g FeEDTA, 0.08 g $CuSO_4 \cdot 5H_2O$, 0.049 g $Co(NO_3)_2 \cdot 6H_2O$, 0.39 g $NaMoO_4 \cdot 2H_2O$, 0.22 g $ZnSO_4 \cdot 7H_2O$, 1 l distilled H_2O), 1.0 ml PO_4 solution (5.0 g $NaH_2PO_4 \cdot H_2O$, 1 l distilled H_2O), 1 l filtered seawater, 18 g agar)	Olson et al. 2007
Agrococcus jejuensis/ *Microbacteriaceae*	Dried seaweed	A piece of dried seaweed was transferred directly onto a isolation medium	SC-SW medium (1 % soluble starch, 0.03 % casein, 0.2 % KNO_3, 0.2 % NaCl, 0.002 % $CaCO_3$, 0.005 % $MgSO_4 \cdot 7H_2O$, 0.001 % $FeSO_4 \cdot 7H_2O$ and 1.8 % agar in a 60:40 mixture of natural seawater and distilled water)	Lee 2008a
Phycicola gilvus (novel genus)/ *Microbacteriaceae*	Living seaweed	A seaweed sample (1 g) was placed into a sterile plastic tube containing 9 ml sterile distilled water. After mixing for 30 min using a tube rotator, aliquots (100 µl) of serial dilutions of the sample were transferred onto isolation medium	SC-SW medium (1 % soluble starch, 0.03 % casein, 0.2 % KNO_3, 0.2 % NaCl, 0.002 % $CaCO_3$, 0.005 % $MgSO_4 \cdot 7H_2O$, 0.001 % $FeSO_4 \cdot 7H_2O$ and 1.8 % agar in a 60:40 mixture of natural seawater and distilled water)	Lee et al. (2008a)
Saccharopolyspora cebuensis/ *Pseudonocardiaceae*	Philippine sponge *Haliclona* sp.	Sponge tissues were rinsed 3× in sterile seawater, minced with a razor blade and homogenized. The homogenates of sponge tissues were serially diluted with sterile seawater and 3×100 µl was plated on isolation media	M1 medium (10 g starch, 4 g yeast extract, 2 g peptone and 18 g of agar per litre of artificial seawater)	Pimentel-Elardo et al. (2008)
Nocardiopsis litoralis/ *Nocardiopsaceae*	Sea anemone	Homogenates of a sea anemone by plating 1:10 serial dilutions of the sample on isolation medium	Marine agar 2216 (Difco) supplemented with 10 % (*w*/*v*) NaCl	Chen et al. (2009b)
Iamia majanohamensis (novel genus)/ *Iamiaceae* (novel family)	Abdominal epidermis of a sea cucumber, *Holothuria edulis*	The collected marine animal was washed several times with sterile seawater. Excised gastrointestinal tracts and attached internal organs were homogenized and diluted serially to a ratio of 1:10 in sterile sea water. Aliquots (0.1 ml each) of the dilution were spread onto a isolation medium	SN medium (750 ppm $NaNO_3$, 15.9 ppm K_2HPO_4, 5.6 ppm di-sodium EDTA dihydrate, 10.4 ppm Na_2CO_3, 1.0 ppm vitamin B_{12} and 1.0 ppm cyano trace metal solution [(l l distilled water)$^{-1}$: 6.25 g citric acid.H_2O, 6.0 g ferric ammonium citrate, 1.4 g $MnCl_2 \cdot 4H_2O$, 0.39 g $Na_2MoO_4 \cdot 2H_2O$, 0.025 g $Co(NO_3)_2 \cdot 6H_2O$ and 0.222 g $ZnSO_4 \cdot 7H_2O$] in filtered 75 % seawater)	Kurahashi et al. (2009)
Arthrobacter psychrochitiniphilus/ *Micrococcaceae*	Fresh guano of Antarctic Adelie penguins	The samples were diluted at a ratio of approximately 1:5 (*w*/*v*) in distilled water and 100 µl aliquots of the suspension were spread on a isolation medium	M9 agar (12.8 g $Na_2HPO_4 \cdot 7H_2O$, 3 g KH_2PO_4, 0.5 g NaCl, 1 g NH_4Cl and 1.5 g agar containing 1 % (*w*/*v*) colloidal chitin per litre of distilled water)	Wang et al. (2009)
Euzebya tangerine (novel genus)/ *Euzebyaceae* (novel family)	Abdominal epidermis of a sea cucumber, *Holothuria edulis*	The collected marine animal was washed several times with sterile sea water. Excised gastrointestinal tracts and attached internal organs were homogenized and diluted serially to a ratio of 1:10 in sterile sea water. Aliquots (0.1 ml each) of the dilution were spread onto a isolation medium	SN medium (750 ppm $NaNO_3$, 15.9 ppm K_2HPO_4, 5.6 ppm disodium EDTA dihydrate, 10.4 ppm Na_2CO_3, 1.0 ppm vitamin B_{12} and 1.0 ppm cyano trace metal solution [(l l distilled water)$^{-1}$: 6.25 g citric acid·H_2O, 6.0 g ferric ammonium citrate, 1.4 g $MnCl_2 \cdot 4H_2O$, 0.39 g $Na_2MoO_4 \cdot 2H_2O$, 0.025 g $Co(NO_3)_2 \cdot 6H_2O$ and 0.222 g $ZnSO_4 \cdot 7H_2O$] in filtered 75 % seawater)	Kurahashi et al. (2010)
Aeromicrobium halocynthiae/ *Nocardioidaceae*	Siphon tissue of a marine ascidian, *Halocynthia roretzi*	As soon as the ascidian was collected, it was washed with sterile seawater. The incurrent and excurrent siphon tissues were ground and diluted with autoclaved seawater (ratio of ground tissue to seawater 1:10). The diluted suspension (100 µl) was spread on isolation medium	A1+C agar (10 g starch, 4 g peptone, 2 g yeast extract, 1 g calcium carbonate and 18 g agar in 1 l filtered seawater)	Kim et al. (2010)
Koreibacter algae (novel genus)/ *Micrococcineae* (suborder)	Unknown seaweed	A piece of dried seaweed was transferred directly onto a isolation medium	SC-SW medium (1 % soluble starch, 0.03 % casein, 0.2 % KNO_3, 0.2 % NaCl, 0.002 % $CaCO_3$, 0.005 % $MgSO_4 \cdot 7H_2O$, 0.001 % $FeSO_4 \cdot 7H_2O$ and 1.8 % agar in a 60:40 mixture of natural seawater and distilled water)	Lee and Lee (2010)
Demequina oxidasica/ *Micrococcineae* (suborder)	*Zostera marina* Linnaeus	Not specified	1/10 Marine agar 2216 (Difco)	Ue et al. (2011a)
Demequina aurantiaca/ *Micrococcineae* (suborder)	Sea alga	Not specified	HSV medium (metal mix X 250 ml, humic acid mix 100 ml, vitamin mix A 4 ml, vitamin B_{12} solution 1 ml, cycloheximide 50 mg, griseofluvin 25 mg, nalidixic acid 20 mg, aztreonam 40 mg, agar 20 g and distilled water 650 ml)	Ue et al. (2011a)
Agarivorans gilvus/ *Alteromonadaceae*	Surface of seaweed	The seaweed samples were washed several times with sterile seawater and subsequently put into a centrifuge tube with	Marine agar 2216 (BD)	Du et al. (2011)

Table 5 (continued)

Strain/family	Source	Pretreatment of sample/enrichment culture	Isolated medium	Reference
		sterile seawater and shaken vigorously. Aliquots (0.1 ml each) of the dilution were spread onto isolation medium		
Micromonospora yangpuensis/ *Micromonosporaceae*	Cup-shaped marine sponge	The sample was homogenized and diluted in series with sterile artificial seawater and then spread onto isolation medium	SMP agar (0.5 g mannitol, 0.1 g peptone, 1,000 ml artificial seawater, 15 g agar)	Zhang et al. (2012)
Nocardiopsis coralliicola/ *Nocardiopsaceae*	Gorgonian coral, *Menella praelonga*	The coral sample was washed with 75 % (*v*/*v*) ethanol and sterilized distilled water, processed in a sterile commercial blender, and 0.2 ml volumes were plated on isolation medium	Trehalose-proline medium (trehalose 1 g, proline 0.5 g, $MgCl_2 \cdot 6H_2O$ 0.2 g, KNO_3 0.5 g, agar 12 g, 1 l distilled water)	Li et al. (2012a)

animals. The families reported in marine plants and animals during 2007–mid-2013 are *Nocardioidaceae* (two new species), *Microbacteriaceae* (three new species), *Micrococcineae* (suborder) (three new species), *Micrococcaceae* (one new species), *Tsukamurellaceae* (one new species), *Pseudonocardiaceae* (one new species), *Nocardiopsaceae* (two new species), *Iamiaceae* (one new species), *Euzebyaceae* (one new species), *Alteromonadaceae* (one new species) and *Micromonosporaceae* (one new species).

Mangroves are a unique woody plant community of intertidal coasts in tropical and subtropical zones, located at the transition area between the land and the sea (Holguin et al. 2001; Kathiresan and Bingham 2001). They play a very important role as refuge, feeding and breeding areas for many organisms and sustain an extensive food web based on detritus. The mangrove ecosystem is distinguished from other ecosystems by periodic tidal flooding and variable environmental factors such as salinity, tidal gradients and nutrient availability which are believed to be effective selectors for metabolic pathway adaptations that could generate unusual metabolites (Long et al. 2005). This belief has led to increasing exploitation of the mangrove microorganism resources (Alongi 1988; Long et al. 2005; Holguin et al. 2006). A total of 14 new rare *Actinomycete* species belonging to seven different families have been reported in mangrove sediments from the period 2007–mid-2013 (Table 6). Among them, two novel genera, *Ilumatobacter* and *Lysinimicrobium*, were reported from mangrove sediments. The families reported in mangrove sediments between 2007 and mid-2013 are *Micromonosporaceae* (seven new species), *Acidimicrobiaceae* (one new species), *Micrococcineae* (suborder) (one new species), *Promicromonosporaceae* (one new species), *Streptosporangiaceae* (two new species), *Thermomonosporaceae* (one new species) and *Demequinaceae* (one new species). Interestingly, Hamada et al. (2012) reported a novel family *Demequinaceae* from mangrove sediments. Mangrove sediments are an abundant source of *Actinomycetes* population having versatile producers of various enzymes and antimicrobial molecules (Subramani and Narayanasamy 2009).

To conclude, a total of 80 new rare *Actinomycete* species belonging to 23 different rare *Actinomycete* genera, of which 20 novel genera and 3 novel families, have been reported from marine environments, particularly between 2007 and mid-2013 (Tables 3, 4, 5 and 6; Fig. 1). Furthermore, the family *Micromonosporaceae* is dominant in marine habitats; genera *Nocardioidaceae*, *Micrococcineae* (suborder) and *Pseudonocardiaceae* are almost as abundant (Fig. 1). The marine environment, representing more than two thirds of the Earth's surface, is thus a prolific resource for the isolation of less exploited, rare and novel *Actinomycetes*.

Importance of microbial natural products in novel drug leads

Many of the bacterial pathogens associated with epidemics of human disease have evolved into multidrug-resistant (MDR) forms subsequent to antibiotic use (Davies and Davies 2010). Tuberculosis (TB) is a leading cause of death in the world today and is exacerbated by the prevalence of multi-(MDRTB), extensively (XDR-TB), and totally (TDR-TB) drug-resistant strains. Cancer is the next leading cause of death worldwide. Although more than 30,000 diseases have been clinically described, less than one third of them can be treated symptomatically and fewer can be cured (Schultz and Tsaklakidis 1997). Therefore, the current shortfall in drugs against multidrug-resistant pathogens and other deadly diseases demands urgent attention to develop new antibiotics (Wright and Sutherland 2007). Concern over the paucity of new antibiotics has raised questions regarding the next source of new chemical entities (NCEs) to meet the challenge of continually emerging resistance (Walsh 2003; Macherla et al. 2007). Between 1981 and 2002, the vast majority of NCEs approved for use as antibiotics were natural product derived (Newman et al. 2003), indicating that nature (in particular microorganisms) offers highly relevant scaffolds for developing therapies in the infectious disease arena. While many of the NCEs approved for use at the end of the past century resulted from semi-synthetic modifications to

Table 6 Newly discovered rare *Actinomycetes* from mangrove environment during the period 2007–mid-2013

Strain/family	Source	Pretreatment of sample/enrichment culture	Isolated medium	Reference
Micromonospora rifamycinica/ *Micromonosporaceae*	Mangrove sediment from the South China Sea	Standard dilution-plating technique	Gauze no. 1 medium (20 g soluble starch, 1 g KNO_3, 0.5 g NaCl, 0.5 g $MgSO_4 \cdot 7H_2O$, 0.5 g K_2HPO_4, 10 mg $FeSO_4 \cdot 7H_2O$ prepared with 1 l of seawater)	Huang et al. (2008)
Micromonospora pattaloongensis/ *Micromonosporaceae*	Mangrove sediment from Pattaloong province	Not specified	Starch-casein nitrate agar (starch 10.0 g, KNO_3 1.0 g, NaCl 2.0 g, K_2HPO_4 2.0 g, $MgSO_4 \cdot 7H_2O$ 0.05 g, $CaCO_3$ 0.02 g, $FeSO_4 \cdot 7H_2O$ 0.01 g, casein 0.30 g per litre)	Thawai et al. (2008)
Verrucosispora lutea/ *Micromonosporaceae*	Mangrove sediment collected from the Shenzhen Futian Mangrove	Not specified	Gauze no. 1 medium (20 g soluble starch, 1 g KNO_3, 0.5 g NaCl, 0.5 g $MgSO_4 \cdot 7H_2O$, 0.5 g K_2HPO_4, 10 mg $FeSO_4 \cdot 7H_2O$ prepared with 1 l of seawater)	Liao et al. (2009)
Ilumatobacter fluminis (novel genus)/ *Acidimicrobiaceae*	Sediment sample collected at the Kuiragawa river	The sample (0.5 cm^3) was homogenized with a glass rod in 5 ml of sterile seawater. The homogenate (50 μl) was used to isolate a bacterium on medium	R medium (NaCl 25 g, $MgSO_4 \cdot 7H_2O$ 9 g, $CaCl_2 \cdot 2H_2O$ 0.14 g, KCl 0.7 g, $Na_2HPO_4 \cdot 12H_2O$ 0.25 g, Na_2-EDTA 30 mg, H_3BO_3 34 mg, $FeSO_4 \cdot 7H_2O$ 10 mg, $FeCl_3 \cdot 6H_2O$ 1.452 mg, $MnCl_2 \cdot 4H_2O$ 4.32 mg, $ZnCl_2$ 0.312 mg, $CoCl_2 \cdot 6H_2O$ 0.12 mg, NaBr 6.4 mg, $Na_2MoO \cdot 2H_2O$ 0.63 mg, $SrCl_2 \cdot 6H_2O$ 3.04 mg, RbCl 0.1415 mg, LiCl 0.61 mg, KI 0.00655 mg, V_2O_5 0.001785 mg, cycloheximide 50 mg, griseofluvin 25 mg, nalidixic acid 20 mg, aztreonam 40 mg, RPMI1640 500 mg, eagle medium 500 mg, L-glutamine 15 mg, $NaHCO_3$ 100 mg, agar 20 g and distilled water 1 l)	Matsumoto et al. (2009)
Demequina salsinemoris/ *Micrococcineae* (suborder)	Mangrove sediment of Amami Island	Standard dilution-plating technique	GPM agar (1 % glucose, 0.5 % peptone, 0.5 % meat extract, 0.3 % NaCl, 1.2 % agar) containing benlate (20 mg l^{-1}; DuPont) with ascorbic acid (440 mg l^{-1}) or rutin (120 mg l^{-1})	Matsumoto et al. (2010)
Isoptericola chiayiensis/ *Promicromonosporaceae*	Mangrove sediment collected in Chiayi County	Not specified	Humic acid vitamin agar (humic acid 1.0 g, KCl 1.7 g, Na_2HPO_4 0.5 g, $MgSO_4 \cdot 7H_2O$ 0.5 g, $CaCO_3$ 0.02 g, $FeSO_4 \cdot 7H_2O$, 0.01 g, B vitamins (0.5 mg each of thiamin, riboflavin, niacin, pyridoxin, calcium d-pantothenate, inositol, *p*-aminobenzoic acid and 0.25 mg biotin), cycloheximide 50 mg; nalidixic acid 20 mg, agar 15.0 g per litre of distilled water)	Tseng et al. (2011)
Micromonospora rhizosphaerae/ *Micromonosporaceae*	Rhizosphere sediment of mangrove, *Excocaria agallocha*	One gram of sediment was heated in a hot air oven at 120 °C for 60 min, treated with a solution of 1.0 % chloramine-T for 20 min and diluted to 10^{-2}, then 100 μl of the resultant solution was inoculated on isolation medium	Humic acid vitamin agar (humic acid 1.0 g, KCl 1.7 g, Na_2HPO_4 0.5 g, $MgSO_4 \cdot 7H_2O$ 0.5 g, $CaCO_3$ 0.02 g, $FeSO_4 \cdot 7H_2O$, 0.01 g, B vitamins (0.5 mg each of thiamin, riboflavin, niacin, pyridoxin, calcium d-pantothenate, inositol, *p*-aminobenzoic acid and 0.25 mg biotin), cycloheximide 50 mg; nalidixic acid 20 mg, agar 15.0 g per litre of distilled water)	Wang et al. (2011a)
Nonomuraea wenchangensis/ *Streptosporangiaceae*	Rhizosphere sediment of mangrove, *Bruguiera sexangula*	The soil sample was heat treated at 100 °C for 1 h after being air-dried at room temperature for 7 days, and treated with a solution of chloramine-T (1 %, *w*/*v*). The pretreated soil sample was diluted 1:10 (*v*/*v*) with sterile 1/4 Ringer's solution (K_2HPO_4 0.38 %, KH_2PO_4 0.12 %, $MgSO_4 \cdot 7H_2O$ 0.51 %, NaCl 0.25 %, $Fe_2(SO_4)_3 \cdot 7H_2O$ 0.005 %, $MnSO_4$ 0.005 %) and serial diluted. One hundred microlitres of the 10^{-1} to 10^{-3} suspensions were spread on isolation medium	Humic acid-vitamin medium (humic acid 1.0 g, KCl 1.7 g, Na_2HPO_4 0.5 g, $MgSO_4 \cdot 7H_2O$ 0.5 g, $CaCO_3$ 0.02 g, $FeSO_4 \cdot 7H_2O$, 0.01 g, B vitamins (0.5 mg each of thiamin, riboflavin, niacin, pyridoxin, calcium d-pantothenate, inositol, *p*-aminobenzoic acid and 0.25 mg biotin), nalidixic acid 20 mg, tunicamycin 20 mg, agar 15.0 g per litre of distilled water)	Wang et al. (2011b)
Verrucosispora qiuiae/ *Micromonosporaceae*	Mangrove swamp sediment in Sanya	The sediment sample was dried at room temperature, suspended in sterile distilled water and diluted in series; the suspensions		Xi et al. (2011a)

Table 6 (continued)

Strain/family	Source	Pretreatment of sample/enrichment culture	Isolated medium	Reference
		were then heated in an oven at 100 °C for 60 min. The heat-treated suspensions were plated on isolation medium	Oatmeal agar [ISP 3 medium; oatmeal 20.0 g, trace salts solution ($FeSO_4 \cdot 7H_2O$ 0.1 g, $MnCl_2 \cdot 4H_2O$ 0.1 g, $ZnSO_4 \cdot 7H_2O$ 0.1 g, deionized water 100.0 ml) 1.0 ml, agar 18.0 g per litre]	
Asanoa hainanensis/ *Micromonosporaceae*	Rhizosphere sediment of mangrove fern *Acrostichum speciosum*	One gram sample of sediment was heated in a hot air oven at 100 °C for 60 min and diluted $\times 10^{-2}$ with quarter-strength Ringer's solution before sonicating for 10 min in order to disperse the soil. Then, 100 µl volumes of the suspensions were inoculated on to isolation medium	Glucose asparagine medium (glucose 1 %, asparagine 0.1 %, K_2HPO_4 0.1 %, $FeSO_4 \cdot 7H_2O$ 0.0001 %, $MnCl_2 \cdot 4H_2O$ 0.0001 %, $ZnSO_4 \cdot 7H_2O$ 0.001 %, agar 1.5 %)	Xu et al. (2011)
Microbispora hainanensis/ *Streptosporangiaceae*	Rhizosphere sediment of mangrove, *Excoecaria agallocha*	Not specified	Humic acid vitamin agar (humic acid 1.0 g, KCl 1.7 g, Na_2HPO_4 0.5 g, $MgSO_4 \cdot 7H_2O$ 0.5 g, $CaCO_3$ 0.02 g, $FeSO_4 \cdot 7H_2O$, 0.01 g, B vitamins (0.5 mg each of thiamin, riboflavin, niacin, pyridoxin, calcium d-pantothenate, inositol, *p*-aminobenzoic acid and 0.25 mg biotin), cycloheximide 50 mg; nalidixic acid 20 mg, agar 15.0 g per litre of distilled water)	Xu et al. (2012)
Actinomadura sediminis/ *Thermomonosporaceae*	Mangrove sediment collected from Dugong Creek	Sediment (1 g) was added to 9 ml sterile distilled water and mixed by vortexing. A 10-fold dilution of this suspension was prepared in sterilized distilled water and 0.1 ml was spread on isolation medium	Kuster's agar (glycerol 10 g, casein 0.3 g, KNO_3 2 g, NaCl 20 g, K_2HPO_4 2 g, $MgSO_4 \cdot 7H_2O$ 0.05 g, $CaCO_3$ 0.02 g, $FeSO_4 \cdot 7H_2O$ 0.01 g, agar 15 g and distilled water 1,000 ml)	He et al. (2012)
Lysinimicrobium mangrovi (novel genus)/ *Demequinaceae* (novel family)	Rhizosphere sediment of mangrove, *Bruguiera gymnorhiza*	Approximately 1 g of the sample was diluted 10-, 100- and 1,000-fold with saline before 0.2 ml of each dilution was spread on isolation medium	NBRC medium 802 (0.2 % polypeptone, 0.04 % yeast extract, 0.02 % $MgSO_4 \cdot 7H_2O$ and 1.5 % agar) supplemented with 5.0 % NaCl.	Hamada et al. (2012)
Micromonospora maritima/ *Micromonosporaceae*	Mangrove sediment from Samut Sakhon Province	Not specified	Starch-casein nitrate agar (10 g starch, 0.3 g sodium caseinate (Difco), 2 g KNO_3 and 15 g agar per litre)	Songsumanus et al. (2013)

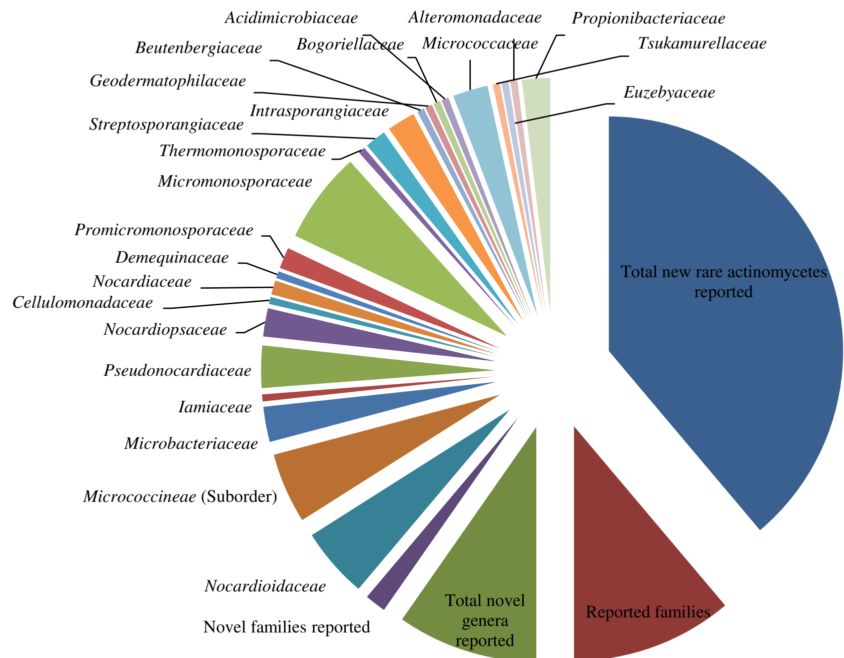

Fig. 1 Total number of new/novel families, genera and rare *Actinomycete* strains reported from marine habitats between 2007 and mid-2013

compounds discovered during the 'Golden Age' of antibiotics, some recent discoveries indicate that alternative technologies are providing access to new antibiotic scaffolds (Clardy et al. 2006). One approach—which maintains credence in the historic success of microbial-derived NCEs—is to culture new microorganisms from unique natural environments as a source of novel chemistry. A genus previously unexploited from unexplored habitats in the natural product screening collection warrants particular attention, as suggested by Donadio et al. (2002). Recent reports on the isolation and characterization of novel *Actinomycetes* from poorly researched habitats illustrate the potential of this approach (Bredholt et al. 2008; Eccleston et al. 2008; Okoro et al. 2009). Therefore, screening such organisms and the prospect of discovering new natural products increases which can later be developed as a resource for biotechnology. Despite the vastness of the Earth's oceans and their inherent biodiversity, the marine environment remains a largely untapped source of new microorganisms, and evidence has emerged that focused exploration of the marine environment will yield unprecedented, chemically prolific species (Fenical and Jensen 2006).

There are more than 22,000 known microbial secondary metabolites, 70 % of which are produced by *Actinomycetes*, 20 % from fungi, 7 % from *Bacillus* spp. and 1–2 % by other bacteria. Among the *Actinomycetes*, the streptomycetes group is economically important because out of the approximately more than 10,000 known antibiotics, 50–55 % are produced by that genus (Berdy 2005; Subramani and Aalbersberg 2012). *Actinomycetes* are the most economically and biotechnologically useful prokaryotes and hold a prominent position due to their diversity and proven ability to produce novel bioactive compounds (Subramani and Aalbersberg 2012; Blunt et al. 2013). To date, nearly 400 new compounds with cytotoxicity and antimicrobial activity have been isolated from marine *Actinomycetes* (Proksch and Muller 2006; Fenical and Jensen 2006; Blunt et al. 2009, 2010, 2011). The ecological role of *Actinomycetes* in the marine ecosystem is largely neglected and various assumptions meant there was little incentive to isolate marine strains for search and discovery of new drugs. The search for and discovery of rare and new *Actinomycetes* is of significant interest to drug discovery due to a growing need for the development of new and potent therapeutic agents (Subramani and Aalbersberg 2012).

Rare *Actinomycetes* as a source of new antibiotics

Recently, non-streptomycete *Actinomycetes* (rare *Actinomycetes*) have increased significantly up to ~25–30 % share of all known antibiotics (Tishkov 2001; Berdy 2005). Given this, the probability of finding a new compound of economic significance using conventional methodologies of microbial isolation and assay is remote. Efforts to find organisms producing novel antibiotics require either high-throughput screening or specific sampling methods or selections that enrich the unexamined subsets of *Actinomycetes* (Tiwari and Gupta 2012b). Tiwari and Gupta (2012b) recently reviewed bioactive compounds reported from different genera of rare *Actinomycetes* obtained from various natural habitats. They conclude that many of the successful antimicrobial agents currently available in the market are produced by rare *Actinomycetes*, like rifamycins by *Amycolatopsis mediterranei*,

erythromycin by *Saccharopolyspora erythraea*, teicoplanin by *Actinoplanes teichomyceticus*, vancomycin by *Amycolatopsis orientalis*, gentamicin from *Micromonopsora purpurea* and a chronological sequence of antibiotic compounds discovered as products of *Micromonospora* spp., *Actinoplanes* spp. and *Streptosporangium* spp. (Cooper et al. 1990; Lancini and Lorenzetti 1993; Lazzarini et al. 2000; Pfefferle et al. 2000). Among the available rare *Actinomycetes* genera, *Amycolatopsis*, *Saccharopolyspora*, *Actinoplanes* and *Micromonopsora* have been exploited as a prolific source of novel secondary metabolites (Geok et al. 2007; Murakami et al. 2007; Renu et al. 2008; Zhuge et al. 2008; Igarashi et al. 2008; Berdnikova et al. 2009; Beth et al. 2009; Liras and Demain 2009; Zhang et al. 2009; Dharmendra et al. 2010; Dasari et al. 2012); however, lesser exploited rare genera such as *Actinomadura*, *Nocardiopsis*, *Dactylosporangium*, *Kibdelosporangium*, *Microbispora*, *Kitasatospora*, *Planomonospora*, *Planobispora*, *Salinispora*, *Marinispora*, *Serinicoccus* and *Verrucosispora* are now drawing attention. These impacts emphasize the need to continue research in this area and the investments in rare *Actinomycetes* can be considered as being completely warranted.

Novel/new metabolites from marine rare *Actinomycetes*

This review also tried to update the information on rare *Actinomycetes* obtained from marine habitats and the antibiotic compounds identified from other groups of marine rare *Actinomycetes* during 2007–mid-2013. Table 7 shows some examples of new bioactive metabolites isolated from marine rare *Actinomycetes* from 2007 to mid-2013. This is by no means an exhaustive search of all novel secondary metabolites produced by marine rare *Actinomycetes* genera during this 6-year period; nevertheless, this list is impressive and illustrates the many different diverse structures with biological activities reported. Among them, a few compounds such as groups of abyssomicins, proximicins, thiocoralines and gifhornenolones produced by *Verrucosispora* spp. and lipoxazolidinones, lynamicins and marinisporolides produced by *Marinispora* spp. (Figs. 2, 3 and 4) are of particular interest due to their rarity, potency and diverse bioactivity. The recently isolated rare and first marine obligate genus *Salinispora* produced an array of novel metabolites which have previously been discussed (Subramani and Aalbersberg 2012).

Now, emphasizing another interesting rare *Actinomycete* genus *Verrucosispora* is quite limited presumably due to its limited distribution in the marine environment. Recently, *Verrucosispora* spp. produced an array of new and novel abyssomicins (Fig. 2), a new class of unique polycyclic natural products with potent antibacterial, antitubercular, antitumor and anti-Bacille Calmette Guerin activity (Keller et al. 2007a, b; Wang et al. 2013b). Abyssomicins are of great significance since these molecules are the first to inhibit biosynthesis of *para*-aminobenzoic acid biosynthetic pathway, a pathway essential for many microorganisms but absent in humans (Riedlinger et al. 2004; Keller et al. 2007b). Ongoing interest in the synthesis, biosynthesis and pharmacology of the abyssomicins has fuelled further exploration of this interesting class of compounds and perhaps may lead to related derivatives with better biological profiles (Wang et al. 2013b). The recent first complete genome sequence of *Verrucosispora* sp. increased the expectancy from this group of strains in novel biodiscovery efforts (Roh et al. 2011).

Proximicins (Fig. 3), novel aminofuran antibiotics also produced by *Verrucosispora* spp., bear the hitherto unknown γ-amino acid 4-aminofuran-2-carboxylic acid moeity, which adds a new element of structural diversity to the previously described heterocyclic antibiotics (Fiedler et al. 2008; Schneider et al. 2008). The biological activity of proximicins did not show appreciable antibacterial activity against drug-resistant human pathogens. However, they displayed potent antitumor activity against a range of human tumor cell lines.

Gifhornenolones A and B (Fig. 2) are new terpenoids isolated from the marine ascidian-associated *Verrucosispora gifhornensis*. The biological activity of gifhornenolone A showed potent inhibitory activity to the androgen receptor (Shirai et al. 2010).

Thiochondrillines (Fig. 3), analogs of thiocoraline, are potent cytotoxic thiodepsipeptides isolated from the sponge-associated *Verrucosispora* sp. (Wyche et al. 2011). The marine environment, which harbours over 20 million microbes (Qui 2010), has provided several microbial-derived compounds, such as salinosporamide A (Feling et al. 2003), TZT-1027 (Kobayashi et al. 1997) and ILX-651 (Mita et al. 2006) that are currently in clinical trials (Mayer et al. 2010). Among the list of microbial-derived marine natural products with therapeutic relevance is thiocoraline, a potential candidate for clinical trials (Faircloth et al. 1997). Thiocoraline and its analogs have potent cytotoxic properties against a wide range of human cancer cell lines (Romero et al. 1997; Erba et al. 1999; Negri et al. 2007; Wyche et al. 2011).

Lipoxazolidinones A–C (Fig. 4) are novel 2-alkylidene-5-alkyl-4-oxazolidinones isolated from novel and rare genus *Marinispora* (Macherla et al. 2007). The biological activity of lipoxazolidinones exhibited broad spectrum antimicrobial activity similar to that of the commercial antibiotic linezolid (Zyvox), a 2-oxazolidinone (Macherla et al. 2007). Hydrolysis of the amide bond of the 4-oxazolidinone ring of lipoxazolidinone A resulted in loss of antibacterial activity. The 2-alkylidene-4-oxazolidinone represents a new antibiotic pharmacophore and is unprecedented in nature.

Lynamicins A–E (Fig. 4) are chlorinated bisindole pyrroles isolated from the rare *Actinomycete Marinispora* sp. (McArthur et al. 2008). The antimicrobial spectrum of lynamicins was evaluated against a panel of 11 pathogens,

Table 7 Novel/new bioactive compounds produced by marine rare *Actinomycetes* between 2007 and mid-2013

Compound	Marine source	Biological activity	Reference
3-((6-Methylpyrazin-2-yl)methyl)-1H-indole	*Serinicoccus profundi*	Weak antibacterial	Yang et al. (2013)
Juvenimicin C	*Micromonospora* sp.	Chemopreventive activity	Carlson et al. (2013)
Kocurin	*Kocuria* sp.	Antibacterial	Palomo et al. (2013)
Nocazines D and E	*Nocardiopsis alba*	Weak cytotoxicity	Zhang et al. (2013)
Abyssomicins J–L	*Verrucosispora* sp.	Antitubercülr	Wang et al. (2013b)
Pyridinium	*Amycolatopsis alba*	Antibacterial, anticancer	Dasari et al. (2012)
Anthracyclinones 1–4	*Micromonospora* sp.	Anticancer	Sousa et al. (2012)
atrop-abyssomicin C and proximicin A	*Verrucosispora maris*	Antibacterial, antitubercülr, antitumor	Roh et al. (2011)
Levantilides A and B	*Micromonospora* sp.	Antiproliferative activity	Gärtner et al. (2011)
Bipyridines 1–5 and Caerulomycins F–K	*Actinoalloteichus cyanogriseus*	Cytotoxic	Fu et al. (2011)
Bendigoles D–F	*Actinomadura* sp.	Cytotoxic, inhibitor of NF-κB nuclear translocation	Simmons et al. (2011)
Thiocoralines 1–5	*Verrucosispora* sp.	Anticancer	Wyche et al. (2011)
Salinosporamide K	*Salinispora pacifica*	Proteasome inhibitor	Eustaquio et al. (2011)
Pseudonocardians A–C	*Pseudonocardia* sp.	Antibacterial, anticancer	Li et al. (2011)
Thiopeptide TP-1161	*Nocardiopsis* sp.	Antibacterial	Engelhardt et al. (2010)
Fijiolides A and B	*Nocardiopsis* sp.	Inhibitor of TNF-α induced NFκB activation	Nam et al. (2010)
Nocardiopsins A and B	*Nocardiopsis* sp.	Immunosuppressive agents	Raju et al. (2010)
Arenimycin	*Salinispora arenicola*	Antibacterial, anticancer	Asolkar et al. (2010)
Gifhornenolones A and B	*Verrucosispora gifhornensis*	Inhibitor to androgen receptor	Shirai et al. (2010)
Saliniquinones A–F	*Salinispora arenicola*	Potent cytostatic	Murphy et al. (2010)
Dermacozines (A–G)	*Dermacoccus abyssi*	Highest radical scavenger activity, moderate cytotoxic	Abdel-Mageed et al. (2010)
Phthalates	*Nocardia levis*	Antibacterial, antifungal	Kavitha et al. (2009)
Lodopyridone	*Saccharomonospora* sp.	Anticancer	Maloney et al. (2009)
Marinisporolides A and B	*Marinispora* sp.	Weak antifungal	Kwon et al. (2009)
Rifamycin S	*Micromonospora rifamycinica*	Antibacterial	Huang et al. (2009)
FW03-1149	*Micromonospora* sp.	Antifungal	Yi-lei et al. (2009)
Ayamycin	*Nocardia* sp.	Antibacterial, antifungal	El-Gendy et al. (2008)
Proximicins A–C	*Verrucosispora* sp.	Cytostatic, weak antibacterial, antitumor	Fiedler et al. (2008); Schneider et al. (2008)
Pacificanones A and B	*Salinispora pacifica*	Antibacterial	Oh et al. (2008)
Salinipyrones A and B	*Salinispora pacifica*	Mild cytotoxicity	
Lynamicins A–E	*Marinispora* sp.	Antibacterial	McArthur et al. (2008)
Lucentamycins A–D	*Nocardiopsis lucentensis*	Cytotoxic	Cho et al. (2007)
Lipoxazolidinones A–C	*Marinispora* sp.	Antimicrobial	Macherla et al. (2007)
Abyssomicins G, H and atrop-Abyssomicin C	*Verrucosispora* sp.	Antibacterial	Keller et al. (2007a)
Kitastatin 1	*Kitasatospora* sp.	Anticancer, antibacterial, antifungal	Pettit et al. (2007)
Salinosporamide A	*Salinispora tropica*	Anticancer, antimalarial	Jensen et al. (2007); Prudhomme et al. (2008)
Sporolide A	*Salinispora tropica*	Unknown	Jensen et al. (2007)
Saliniketal	*Salinispora arenicola*	Cancer chemoprevention	
Cyanosporaside A	*Salinispora pacifica*	Unknown	
Salinispyrone	*Salinispora pacifica*	Unknown	
Arenicolides A–C	*Salinispora arenicola*	Mild cytotoxicity	Williams et al. (2007b)

which demonstrated that these substances possess broad spectrum activity against both Gram-positive and Gram-negative pathogens. Significantly, lynamicins were active against drug-resistant pathogens such as methicillin-resistant *Staphylococcus*

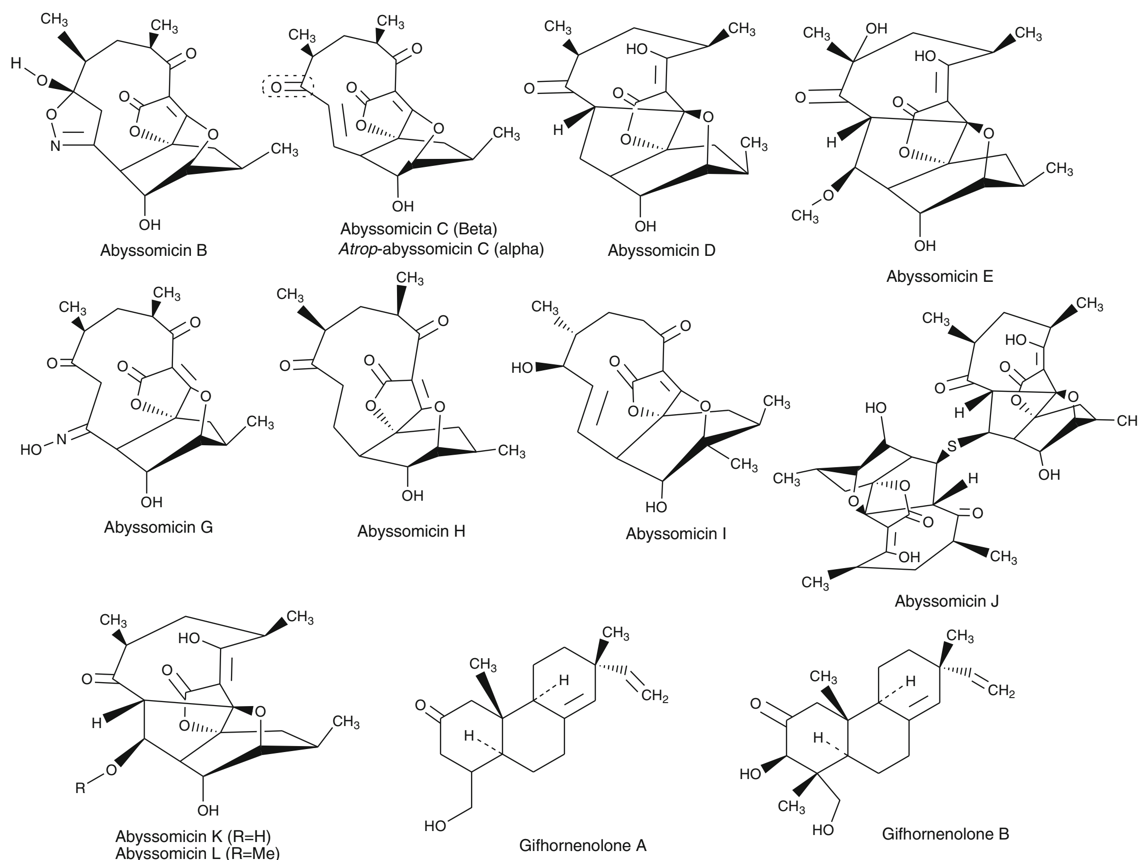

Fig. 2 Array of new abyssomicins and gifhornenolones produced by rare *Verrucosispora* spp.

aureus and vancomycin-resistant *Enterococcus faecium* (McArthur et al. 2008).

In addition, marinisporolides A and B (Fig. 4) are polyene-polyol macrolides also isolated from *Marinispora* sp. (Kwon et al. 2009). The marinisporolides are 34-membered macrolides composed of a conjugated pentaene and several pairs of 1,3-dihydroxyl functionalities and show interesting photoreactivity and chiroptical properties. Marinisporolide A contains a bicyclic spiro-bis-tetrahydropyran ketal functionality, while marinisporolide B is the corresponding hemiketal.

These highlighted structures, chemical diversity, biological properties and discovery of these new compounds (Table 7; Figs. 2, 3 and 4) continue to indicate that rare and new/novel *Actinomycetes* of the genera will be a significant resource for structurally/biologically interesting molecules.

Conclusions

Over the past three decades, the marine environment has continuously been providing a number of new/novel *Actinomycetes* and bioactive compounds, but the potential of this area still remains virtually unexplored. Until recently, microbiologists were greatly limited in their study of natural microbial ecosystems due to an inability to cultivate most naturally occurring microorganisms (Cragg and Newman 2005). The marine environment is huge and harbours an enormous hidden microbial diversity. As-yet undiscovered and unusual or rare microorganisms may contain possible cures for diseases demanding new antibiotics to combat the multidrug-resistant human pathogens and emerging deadly diseases. Application of selective isolation and enriched methods can lead to the discovery of new/novel and rare bioactive *Actinobacteria* from marine ecological niches having the potential to biosynthesize novel bioactive compounds. As summarized in this review, a combination of different pretreatment techniques along with suitable selective isolation media, enrichment culture supplemented with specific antibiotics, enabled the isolation of rare and novel *Actinomycetes* and the production of unusual bioactive metabolites.

Furthermore as reviewed above, the marine environment contains a myriad of new and rare *Actinobacteria* providing novel structural diversity waiting to be discovered and used in the biotechnological and pharmaceutical industries. Even so, the study on marine rare *Actinobacteria* is just beginning. Researchers are in the early stages of a renaissance in natural product discovery from marine *Actinobacteria*. It is now known that new *Actinomycete* taxa occur in the ocean and that some display specific adaptations for their life in the marine environment (Mincer et al. 2002; Jensen et al. 2005a,

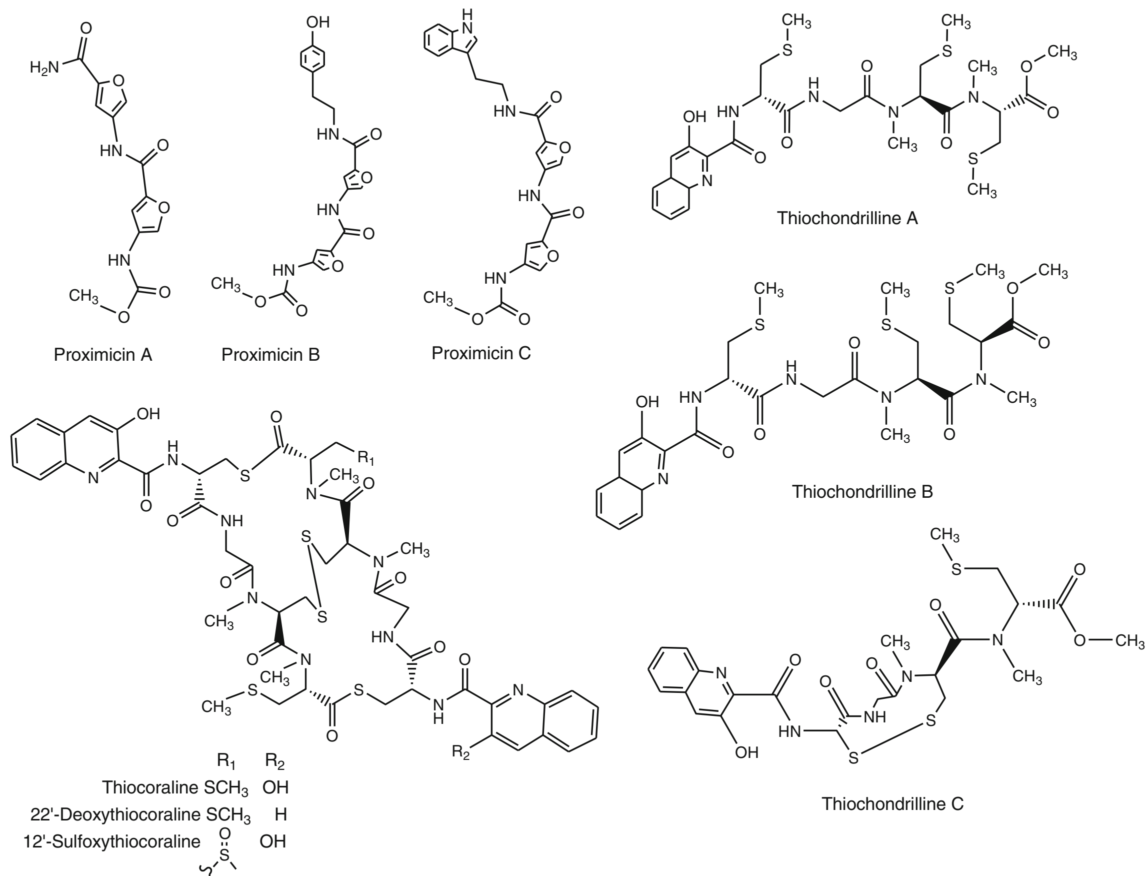

Fig. 3 Array of new proximicins and thiocoralines produced by rare *Verrucosispora* spp.

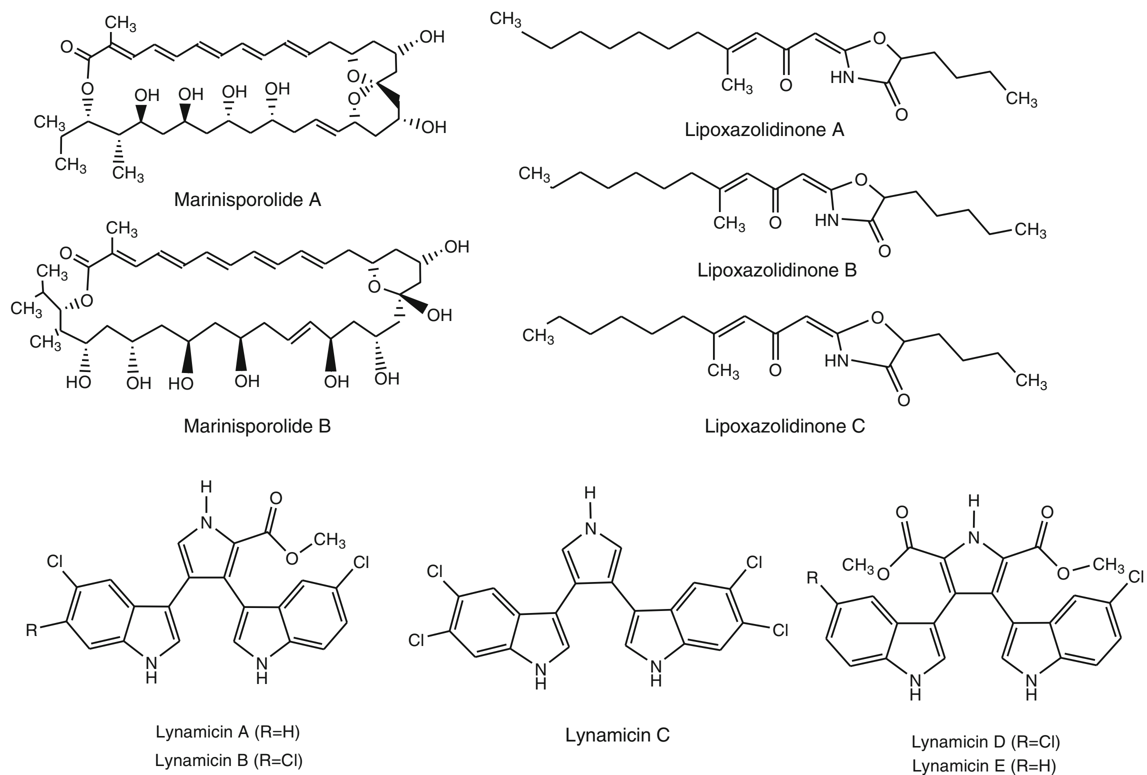

Fig. 4 Some new/novel secondary metabolites produced by rare *Marinispora* spp.

2007). These taxa include the chemically prolific genera *Salinispora* and *Marinispora* which produce exciting new and novel structural classes of secondary metabolites. In this line, another rare *Actinomycete* genus, *Verrucosispora*, is also proving to be a productive source of new metabolites such as the abyssomicins. In addition, the rare *Actinomycetes* obtained from marine sediments are metabolically active and produce interesting bioactive molecules (Dai et al. 2010; Goodfellow et al. 2012a, b; Tian et al. 2013). These results provide clear evidence that targeting rare and new/novel marine *Actinomycete* genera and species will lead to the discovery of new chemotypes with significant biological activity and the potential to become leads for drug discovery.

Acknowledgments This work was supported by the US National Institutes of Health's International Cooperative Biodiversity Groups program (grant NIH ICBG U01-TW007401). The authors thank Dr. Brad Carte and Dr. Patricia Kailola for critically reading the manuscript, their helpful comments and encouraging remarks.

References

Abdel-Mageed WM, Milne BF, Wagner M, Schumacher M, Sandor P, Pathom-aree W, Goodfellow M, Bull AT, Horikoshi K, Ebel R, Diederich M, Fiedler HP, Jaspars M (2010) Dermacozines, a new phenazine family from deep-sea *Dermacocci* isolated from a Mariana Trench sediment. Org Biomol Chem 8:2352–2362

Abdelmohsen UR, Pimentel-Elardo SM, Hanora A, Radwan M, Abou-El-Ela SH, Ahmed S, Hentschel U (2010) Isolation, phylogenetic analysis and anti-infective activity screening of marine sponge-associated *Actinomycetes*. Mar Drugs 8:399–412

Alferova IV, Terekhova LP (1988) Use of the method of enriching of soil samples with calcium carbonate for isolation of *Actinomyces*. Antibiot Khimioter 33:888–890

Alongi DM (1988) Bacterial productivity and microbial biomass in tropical mangrove sediments. Microb Ecol 15:59–79

Amann RI, Ludwig W, Schleifer KH (1995) Phylogenetic identification and in situ detection of individual microbial cells without cultivation. Microbiol Rev 59:143–169

Asolkar RN, Kirkland TN, Jensen PR, Fenical W (2010) Arenimycin, an antibiotic effective against rifampin- and methicillin-resistant *Staphylococcus aureus* from the marine *Actinomycete Salinispora arenicola*. J Antibiot (Tokyo) 63:37–39

Bala M, Kaur C, Kaur I, Khan F, Mayilraj S (2011) *Kocuria sediminis* sp. nov., isolated from a marine sediment sample. Antonie Van Leeuwenhoek 101:469–478

Baltz RH (2006) Marcel Faber Roundtable: is our antibiotic pipeline unproductive because of starvation, constipation or lack of inspiration? J Ind Microbiol Biotechnol 33:507–513

Baltz RH (2007) A call to arms. Nat Rev Drug Discov 6:8–12

Baltz RH (2011) Strain improvement in *Actinomycetes* in the postgenomic era. J Ind Microbiol Biotechnol 38:657–666

Barke J, Seipke RF, Grüschow S, Heavens D, Drou N, Bibb MJ, Goss RJM, Yu DW, Hutchings MI (2010) A mixed community of *Actinomycetes* produce multiple antibiotics for the fungus farming ant *Acromyrmex octospinosus*. BMC Biol 8:109–118

Baskaran R, Vijayakumar R, Mohan PM (2011) Enrichment method for the isolation of bioactive *Actinomycetes* from mangrove sediments of Andaman Islands, India. Malaysian J Microbiol 7:26–32

Bentley SD, Chater KF, Cerdeño-Tárraga AM, Challis GL, Thomson NR, James KD, Harris DE, Quail MA, Kieser H, Harper D, Bateman A, Brown S, Chandra G, Chen CW, Collins M, Cronin A, Fraser A, Goble A, Hidalgo J, Hornsby T, Howarth S, Huang CH, Kieser T, Larke L, Murphy L, Oliver K, O'Neil S, Rabbinowitsch E, Rajandream MA, Rutherford K, Rutter S, Seeger K, Saunders D, Sharp S, Squares R, Squares S, Taylor K, Warren T, Wietzorrek A, Woodward J, Barrell BG, Parkhill J, Hopwood DA (2002) Complete genome sequence of the model *Actinomycete Streptomyces coelicolor* A3(2). Nature 417:141–147

Berdnikova TF, Shashkov AS, Katrukha GS, Lapchinskaia OA, Iurkevich NV, Grachev AA, Nifantev NE (2009) The structure of antibiotic Eremomycin B. Bioorg Khim 35:550–556

Berdy J (2005) Bioactive microbial metabolites. J Antibiot (Tokyo) 58:1–26

Beth J, Andre W, Michelle H, Mike L, Jens C, Neal C (2009) *Actinomycetes* scale-up for the production of the antibacterial, Nocathiacin. Biotechnol Prog 25:176–188

Bian J, Li Y, Wang J, Song FH, Liu M, Dai HQ, Ren B, Gao H, Hu X, Liu ZH, Li WJ, Zhang LX (2009) *Amycolatopsis marina* sp. nov., an *Actinomycete* isolated from an ocean sediment. Int J Syst Evol Microbiol 59:477–481

Blunt JW, Copp BR, Hu WP, Munro MH, Northcote PT, Prinsep MR (2009) Marine natural products. Nat Prod Rep 26:170–244

Blunt JW, Copp BR, Munro MH, Northcote PT, Prinsep MR (2010) Marine natural products. Nat Prod Rep 27:165–237

Blunt JW, Copp BR, Munro MH, Northcote PT, Prinsep MR (2011) Marine natural products. Nat Prod Rep 28:196–268

Blunt JW, Copp BR, Keyzers RA, Munro MHG, Prinsep MR (2013) Marine natural products. Nat Prod Rep 30:237–323

Bot ANM, Ortius-Lechner D, Finster K, Maile R, Boomsma JJ (2002) Variable sensitivity of fungi and bacteria to compounds produced by the metapleural glands of leaf-cutting ants. Insect Soc 49:363–370

Bredholdt H, Galatenko OA, Engelhardt K, Fjaervik E, Terekhova LP, Zotchev SB (2007) Rare *Actinomycete* bacteria from the shallow water sediments of the Trondheim fjord, Norway: isolation, diversity and biological activity. Environ Microbiol 9:2756–2764

Bredholt H, Fjaervik E, Johnsen G, Zotchev SB (2008) *Actinomycetes* from sediments in the Trondheim Fjord, Norway: diversity and biological activity. Mar Drugs 6:12–24

Bulina TI, Alferova IV, Terekhova LP (1997) A novel approach to isolation of *Actinomycetes* involving irradiation of soil samples with microwaves. Microbiology 66:231–234

Bull AT, Stach JE, Ward AC, Goodfellow M (2005) Marine *Actinobacteria*: perspectives, challenges, future directions. Antonie Van Leeuwenhoek 87:65–79

Butman CA, Carlton JT (1995) Marine biological diversity—some important issues, opportunities and critical research needs. Rev Geophys 33:1201–1209

Cai Y, Xue Q, Chen Z, Zhang R (2009) Classification and salt-tolerance of *Actinomycetes* in the Qinghai lake water and lakeside saline soil. J Sustainable Dev 2:107–110

Carlson S, Marler L, Nam SJ, Santarsiero BD, Pezzuto JM, Murphy BT (2013) Potential chemopreventive activity of a new macrolide antibiotic from a marine-derived *Micromonospora* sp. Mar Drugs 11: 1152–1161

Chang XB, Liu WZ, Zhang XH (2011) *Spinactinospora alkalitolerans* gen. nov. sp. nov., an *Actinomycete* isolated from marine sediment. Int J Syst Evol Microbiol 61:2805–2810

Charusanti P, Fong NL, Nagarajan H, Pereira AR, Li HJ, Abate EA, Su Y, Gerwick WH, Palsson BO (2012) Exploiting adaptive laboratory evolution of *Streptomyces clavuligerus* for antibiotic discovery and overproduction. PLoS One 7:e33727

Chen YG, Tang SK, Zhang YQ, Li ZY, Yi LB, Wang YX, Li WJ, Cui XL (2009a) *Arthrobacter halodurans* sp. nov., a new halotolerant bacterium isolated from sea water. Antonie Van Leeuwenhoek 96:63–70

Chen YG, Wang YX, Zhang YQ, Tang SK, Liu ZX, Xiao HD, Xu LH, Cui XL, Li WJ (2009b) *Nocardiopsis litoralis* sp. nov., a halophilic marine *Actinomycete* isolated from a sea anemone. Int J Syst Evol Microbiol 59:2708–2713

Cho SH, Hwang CW, Chung HK, Yang CS (1994) A new medium for the selective isolation of soil *Actinomycetes*. K J Appl Microbiol Biotechnol 22:561–563

Cho JY, Williams PG, Kwon HC, Jensen PR, Fenical W (2007) Lucentamycins A-D, cytotoxic peptides from the marine-derived *Actinomycete Nocardiopsis lucentensis*. J Nat Prod 70:1321–1328

Choi DH, Kim HM, Noh JH, Cho BC (2007) *Nocardioides marinus* sp. nov. Int J Syst Evol Microbiol 57:775–779

Clardy J, Fischbach MA, Walsh CT (2006) New antibiotics from bacterial natural products. Nat Biotechnol 24:1541–1550

Clardy J, Fischbach MA, Currie CR (2009) The natural history of antibiotics. Curr Biol 19:R437–R441

Cooper R, Das P, Federbush C, Mierzwa R, Patel M, Pramanik B, Truumees I (1990) Characterization of peptidyl-nucleoside antifungal antibiotics from fermentation broth. J Ind Microbiol 5:1–8

Cragg GM, Newman DJ (2005) Biodiversity: a continuing source of novel drug leads. Pure Appl Chem 77:7–24

Cross T (1981) Aquatic *Actinomycetes*: a critical survey of the occurrence, growth and role of *Actinomycetes* in aquatic habitats. J Appl Bacteriol 50:379–423

Currie CR, Scott JA, Summerbell RC, Malloch D (1999) Fungus-growing ants use antibiotic-producing bacteria to control garden parasites. Nature 398:701–705

D'Onofrio A, Crawford JM, Stewart EJ, Witt K, Gavrish E, Epstein S, Clardy J, Lewis K (2010) Siderophores from neighboring organisms promote the growth of uncultured bacteria. Chem Biol 17:254–264

Dai HQ, Wang J, Xin YH, Pei G, Tang SK, Ren B, Ward A, Ruan JS, Li WJ, Zhang LX (2010) *Verrucosispora sediminis* sp. nov., a cyclodipeptide-producing *Actinomycete* from deep-sea sediment. Int J Syst Evol Microbiol 60:1807–1812

Dasari VR, Muthyala MK, Nikku MY, Donthireddy SR (2012) Novel pyridinium compound from marine *Actinomycete*, *Amycolatopsis alba* var. nov. DVR D4 showing antimicrobial and cytotoxic activities in vitro. Microbiol Res 167:346–351

Davies J, Davies D (2010) Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev 74:417–433

Demain AL, Sanchez S (2009) Microbial drug discovery: 80 years of progress. J Antibiot 62:5–16

Dharmendra SD, Jesus MF, Gary TMH (2010) Influence of cultivation conditions on the production of a thermostable extracellular lipase from *Amycolatopsis mediterranei* DSM 43304. J Ind Microbiol Biotechnol 37:1–17

Donadio S, Monciardini P, Alduina R, Mazza P, Chiocchini C, Cavaletti L, Sosio M, Puglia AM (2002) Microbial technologies for the discovery of novel bioactive metabolites. J Biotechnol 99:187–198

Du ZJ, Lv GQ, Rooney AP, Miao TT, Xu QQ, Chen GJ (2011) *Agarivorans gilvus* sp. nov. isolated from seaweed. Int J Syst Evol Microbiol 61:493–496

Eccleston GP, Brooks PR, Kurtböke DI (2008) The occurrence of bioactive *Micromonosporae* in aquatic habitats of the Sunshine Coast in Australia. Mar Drugs 6:243–261

El-Gendy MM, Hawas UW, Jaspars M (2008) Novel bioactive metabolites from a marine derived bacterium *Nocardia* sp. ALAA 2000. J Antibiot (Tokyo) 61:379–386

Emery KO (1969) The continental shelves. Sci Am 221:106–122

Engelhardt K, Degnes KF, Kemmler M, Bredholt H, Fjaervik E, Klinkenberg G, Sletta H, Ellingsen TE, Zotchev SB (2010) Production of a new thiopeptide antibiotic, TP-1161, by a marine *Nocardiopsis* species. Appl Environ Microbiol 76:4969–4976

Erba E, Bergamaschi D, Ronzoni S, Faretta M, Taverna S, Bonfanti M, Catapano CV, Faircloth G, Jimeno J, D'Incalci M (1999) Mode of action of thiocoraline, a natural marine compound with anti-tumour activity. Br J Cancer 80:971–980

Eustaquio AS, Nam SJ, Penn K, Lechner A, Wilson MC, Fenical W, Jensen PR, Moore BS (2011) The discovery of salinosporamide K from the marine bacterium *Salinispora pacifica* by genome mining gives insight into pathway evolution. ChemBioChem 12:61–64

Faircloth G, Jimeno J, D'Incalci M (1997) Biological activity of thiocoraline, a novel marine depsipeptide. Eur J Cancer 33:S175

Feling RH, Buchanan GO, Mincer TJ, Kauffman CA, Jensen PR, Fenical W (2003) Salinosporamide A: a highly cytotoxic proteasome inhibitor from a novel microbial source, a marine bacterium of the new genus *Salinospora*. Angew Chem Int Ed Engl 42:355–357

Fenical W, Jensen PR (2006) Developing a new resource for drug discovery: marine *Actinomycete* bacteria. Nat Chem Biol 2:666–673

Ferriss RS (1984) Effects of microwave oven treatment on microorganisms in soil. Phytopathology 74:121–126

Fiedler HP, Bruntner C, Riedlinger J, Bull AT, Knutsen G, Goodfellow M, Jones AL, Maldonado L, Pathom-aree W, Beil W, Schneider K, Keller S, Sussmuth RD (2008) Proximicin A, B and C, novel aminofuran antibiotic and anticancer compounds isolated from marine strains of the *Actinomycete Verrucosispora*. J Antibiot 61:158–163

Finster KW, Cockell CS, Voytek MA, Gronstal AL, Kjeldsen KU (2009) Description of *Tessaracoccus profundi* sp. nov., a deep-subsurface *Actinobacterium* isolated from a Chesapeake impact crater drill core (940 m depth). Antonie Van Leeuwenhoek 96:515–526

Fischbach MA, Walsh CT (2009) Antibiotics for emerging pathogens. Science 325:1089–1093

Friedrich AB, Merkert H, Fendert T, Hacker J, Proksch P, Hentschel U (1999) Microbial diversity in the marine sponge *Aplysina cavernicola* (formerly *Verongia cavernicola*) analyzed by fluorescence in situ hybridization (FISH). Mar Biol 134:461–470

Fu P, Wang S, Hong K, Li X, Liu P, Wang Y, Zhu W (2011) Cytotoxic bipyridines from the marine-derived *Actinomycete Actinoalloteichus cyanogriseus* WH1-2216-6. J Nat Prod 74:1751–1756

Fu Y, Li Q, Liu K, Xu Y, Wang Y, Jiao N (2012) *Oceanitalea nanhaiensis* gen. nov., sp. nov., an *Actinobacterium* isolated from seawater. Int J Syst Evol Microbiol 62:2490–2494

Gärtner A, Ohlendorf B, Schulz D, Zinecker H, Wiese J, Imhoff JF (2011) Levantilides A and B, 20-membered macrolides from a *Micromonospora* strain isolated from the mediterranean deep sea sediment. Mar Drugs 9:98–108

Gavrish E, Bollmann A, Epstein S, Lewis K (2008) A trap for in situ cultivation of filamentous *Actinobacteria*. J Microbiol Methods 72: 257–262

Geok YAT, Stuart R, Ernest L, Roselyn B, Wonyong K, Michael G (2007) *Amycolatopsis regifaucium* sp. nov., a novel *Actinomycete* that produces Kigamicin. Int J Syst Bacteriol 57:2562–2567

Gochnauer MB, Leppard GG, Komaratat P, Kates M, Novitsky T, Kushner DJ (1975) Isolation and characterization of *Actinopolyspora halophila*, gen. et sp. nov., an extremely halophilic *Actinomycete*. Can J Microbiol 21:1500–1511

Gontang EA, Fenical W, Jensen PR (2007) Phylogenetic diversity of Gram-positive bacteria cultured from marine sediments. Appl Environ Microbiol 73:3272–3282

Goodfellow M (2010) Selective isolation of *Actinobacteria*. In: Baltz RH, Davies J, Demain AL (eds) Manual of industrial microbiology and biotechnology. Section 1: isolation and screening of secondary metabolites and enzymes. Bull AT, Davies JE (section eds). ASM, Washington, 3:13-27

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

Goodfellow M, Haynes JA (1984) *Actinomycetes* in marine sediments. In: Ortiz-Ortiz L (ed) Biological, biochemical and biomedical aspects of *Actinomycetes*. Academic, New York, pp 453–472

Goodfellow M, O'Donnel AG (1989) Search and discovery of industrially significant *Actinomycetes*. In: Baumberg S, Hunter IS, Rhodes PM (eds) Microbial products. New approaches, society for general microbiology symposium No. 44. Cambridge University Press, Cambridge, pp 343–383

Goodfellow M, Williams E (1986) New strategies for the selective isolation of industrially important bacteria. Biotechnol Genet Eng Rev 4:213–262

Goodfellow M, Brown R, Ahmed L, Pathom-Aree W, Bull AT, Jones AL, Stach JE, Zucchi TD, Zhang L, Wang J (2012a) *Verrucosispora fiedleri* sp. nov., an *Actinomycete* isolated from a fjord sediment which synthesizes proximicins. Antonie Van Leeuwenhoek 103: 493–502

Goodfellow M, Stach JE, Brown R, Bonda AN, Jones AL, Mexson J, Fiedler HP, Zucchi TD, Bull AT (2012b) *Verrucosispora maris* sp. nov., a novel deep-sea *Actinomycete* isolated from a marine sediment which produces abyssomicins. Antonie Van Leeuwenhoek 101:185–193

Groth I, Schumann P, Schuetze B, Augsten K, Kramer I, Stackebrandt E (1999) *Beutenbergia cavernae* gen. nov., sp. nov., an L-lysine-containing *Actinomycete* isolated from a cave. Int J Syst Bacteriol 49:1733–1740

Haeder S, Wirth R, Herz H, Spiteller D (2009) Candicidin-producing *Streptomyces* support leaf-cutting ants to protect their fungus garden against the pathogenic fungus *Escovopsis*. Proc Natl Acad Sci U S A 106:4742–4746

Hamada M, Tamura T, Yamamura H, Suzuki K, Hayakawa M (2012) *Lysinimicrobium mangrovi* gen. nov., sp. nov., an *Actinobacterium* isolated from the rhizosphere of a mangrove. Int J Syst Evol Microbiol 62:1731–1735

Hamada M, Tamura T, Yamamura H, Suzuki K, Hayakawa M (2013) *Demequina flava* sp. nov. and *Demequina sediminicola* sp. nov., isolated from sea sediment. Int J Syst Evol Microbiol 63:249–253

Hamaki T, Suzuki M, Fudou R, Jojima Y, Kajiura T, Tabuchi A, Sen K, Shibai H (2005) Isolation of novel bacteria and *Actinomycetes* using soil-extract agar medium. J Biosci Bioeng 99:485–492

Hayakawa M (1990) Studies on selective isolation methods and distribution of soil *Actinomycetes*. Actinomycetol 4:103–112

Hayakawa M (1994) Selective isolation methods for rare *Actinomycetes* (in Japanese). In: Hotta K, Horinouchi S (eds) Bioscience and *Actinomycetes*. Igakusyuppan Center, Tokyo, pp 219–229

Hayakawa M (2003) Selective isolation of rare *Actinomycetes* genera using pretreatment techniques. In: Kurtböke I (ed) Selective isolation of rare *Actinomycetes*. Queensland Complete Printing Service, Nambour, pp 55–81

Hayakawa M (2008) Studies on the isolation and distribution of rare *Actinomycetes* in soil. Actinomycetol 22:12–19

Hayakawa M, Nonomura H (1987a) Humic acid-vitamin agar, a new medium for the selective isolation of soil *Actinomycetes*. J Ferment Technol 65:501–509

Hayakawa M, Nonomura H (1987b) Efficacy of artificial humic acid as a selective nutrient in HV agar used for the isolation of soil *Actinomycetes*. J Ferment Technol 65:609–616

Hayakawa M, Nonomura H (1993) In: Beppu T, Seino A, Hotta K (eds) Selective isolation methods for soil *Actinomycetes* (in Japanese). Japan Scientific Societies, Tokyo

Hayakawa M, Ishizawa K, Nonomura H (1988) Distribution of rare *Actinomycetes* in Japanese soils. J Ferment Technol 66:367–373

Hayakawa M, Kajiura T, Nonomura H (1991a) New methods for the highly selective isolation of *Streptosporangium* and *Dactylosporangium* from soil. J Ferment Bioeng 72:327–333

Hayakawa M, Sadakata T, Kajiura T, Nonomura H (1991b) New methods for the highly selective isolation of *Micromonospora* and *Microbispora* from soil. J Ferment Bioeng 72:320–326

Hayakawa M, Tamura T, Iino H, Nonomura H (1991c) Pollen-baiting and drying method for highly selective isolation of *Actinoplanes* spp. from soil. J Ferment Bioeng 72:433–438

Hayakawa M, Tamura T, Nonomura H (1991d) Selective isolation of *Actinoplanes* and *Dactylosporangium* from soil by using γ-collidine as the chemoattractant. J Ferment Bioeng 72: 426–432

Hayakawa M, Otoguro M, Takeuchi T, Yamazaki T, Iimura Y (2000) Application of a method incorporating differential centrifugation for selective isolation of motile *Actinomycetes* in soil and plant litter. Antonie Van Leeuwenhoek 78:171–185

Hayakawa M, Yoshida Y, Iimura Y (2004) Selection of bioactive soil *Actinomycetes* belonging to the *Streptomyces violaceusniger* phenotypic cluster. J Gen Appl Microbiol 96:973–981

He J, Xu Y, Sahu MK, Tian XP, Nie GX, Xie Q, Zhang S, Sivakumar K, Li WJ (2012) *Actinomadura sediminis* sp. nov., a marine *Actinomycete* isolated from mangrove sediment. Int J Syst Evol Microbiol 62:1110–1116

Heidelberg KB, Gilbert JA, Joint I (2010) Marine genomics: at the interface of marine microbial ecology and biodiscovery. Microb Biotechnol 3:531–543

Holguin G, Vazquez P, Bashan Y (2001) The role of sediment microorganisms in the productivity, conservation, and rehabilitation of mangrove ecosystems: an overview. Biol Fertil Soils 33:265–278

Holguin G, Gonzalez-Zamorano P, de-Bashan LE, Mendoza R, Amador E, Bashan Y (2006) Mangrove health in an arid environment encroached by urban development—a case study. Sci Total Environ 363:260–274

Hong K, Gao AH, Xie QY, Gao H, Zhuang L, Lin HP, Yu HP, Li J, Yao XS, Goodfellow M, Ruan JS (2009) *Actinomycetes* for marine drug discovery isolated from mangrove soils and plants in China. Mar Drugs 7:24–44

Huang H, Lv J, Hu Y, Fang Z, Zhang K, Bao S (2008) *Micromonospora rifamycinica* sp. nov., a novel *Actinomycete* from mangrove sediment. Int J Syst Evol Microbiol 58:17–20

Huang H, Wu X, Yi S, Zhou Z, Zhu J, Fang Z, Yue J, Bao S (2009) Rifamycin S and its geometric isomer produced by a newly found *Actinomycete*, *Micromonospora rifamycinica*. Antonie Van Leeuwenhoek 95:143–148

Igarashi M, Sawa R, Kinoshita N, Hashizume H, Nakagawa N, Homma Y, Nishimura Y, Akamatsu Y (2008) Pargamicin A, a novel cyclic peptide antibiotic from *Amycolatopsis* sp. J Antibiot 61:387–393

Ikeda H, Ishikawa J, Hanamoto A, Shinose M, Kikuchi H, Shiba T, Sakaki Y, Hattori M, Omura S (2003) Complete genome sequence and comparative analysis of the industrial microorganism *Streptomyces avermitilis*. Nat Biotechnol 21:526–531

Inahashi Y, Matsumoto A, Omura S, Takahashi Y (2011) *Streptosporangium oxazolinicum* sp. nov., a novel endophytic *Actinomycete* producing new antitrypanosomal antibiotics, spoxazomicins. J Antibiot 64:297–302

Istianto Y, Koesoemowidodo RSA, Saputra H, Watanabe Y, Pranamuda H, Marwoto B (2012) Application of phenol pretreatment for the isolation of rare *Actinomycetes* from Indonesian soil. Microbiology (Indonesia) 6:42–47

Izumi H, Gauthier MEA, Degnan BM, Ng YK, Hewavitharana AK, Shaw PN, Fuerst JA (2010) Diversity of *Mycobacterium* species from marine sponges and their sensitivity to antagonism by sponge-derived rifamycin synthesizing *Actinobacterium* in the genus *Salinispora*. FEMS Microbiol Lett 313:33–40

Janso JE, Carter GT (2010) Biosynthetic potential of phylogenetically unique endophytic *Actinomycetes* from tropical plants. Appl Environ Microbiol 76:4377–4386

Jensen PR, Gontang E, Mafnas C, Mincer TJ, Fenical W (2005a) Culturable marine *Actinomycetes* diversity from tropical Pacific Ocean sediments. Environ Microbiol 7:1039–1048

Jensen PR, Mincer TJ, Williams PG, Fenical W (2005b) Marine *Actinomycete* diversity and natural product discovery. Antonie Van Leeuwenhoek 87:43–48

Jensen PR, Williams PG, Oh DC, Zeigler L, Fenical W (2007) Species-specific secondary metabolite production in marine *Actinomycetes* of the genus *Salinispora*. Appl Environ Microbiol 73:1146–1152

Jiang CL, Xu LH (1996) Diversity of soil *Actinomycetes* in Yunnan, China. Appl Environ Microbiol 62:244–248

Jiang Y, Li WJ, Xu P, Tang SK, Xu LH (2006) Study on *Actinomycete* diversity under salt and alkaline environments. Wei Sheng Wu Xue Bao 46:191–195

Jiang Y, Wiese J, Cao YR, Xu LH, Imhoff JF, Jiang CL (2009) *Promicromonospora flava* sp. nov., isolated from sediment of the Baltic Sea. Int J Syst Evol Microbiol 59:1599–1602

Jiang Y, Cao Y, Zhao L, Wang Q, Jin R, He W, Xue Q (2010) Ultrasonic treatment of soil samples for *Actinomycete* isolation. Wei Sheng Wu Xue Bao 50:1094–1097

Jung SY, Kim HS, Song JJ, Lee SG, Oh TK, Yoon JH (2007) *Aestuariimicrobium kwangyangense* gen. nov., sp. nov., an LL-diaminopimelic acid-containing bacterium isolated from tidal flat sediment. Int J Syst Evol Microbiol 57:2114–2118

Jurado V, Groth I, Gonzalez JM, Laiz L, Saiz-Jimenez C (2005a) *Agromyces salentinus* sp. nov. and *Agromyces neolithicus* sp. nov. Int J Syst Evol Microbiol 55:153–157

Jurado V, Groth I, Gonzalez JM, Laiz L, Saiz-Jimenez C (2005b) *Agromyces subbeticus* sp. nov., isolated from a cave in southern Spain. Int J Syst Evol Microbiol 55:1897–1901

Kaeberlein T, Lewis K, Epstein SS (2002) Isolating "uncultivable" microorganisms in pure culture in a simulated natural environment. Science 296:1127–1129

Kageyama A, Haga T, Kasai H, Shizuri Y, Omura S, Takahashi Y (2008) *Marihabitans asiaticum* gen. nov., sp. nov., a meso-diaminopimelic acid-containing member of the family *Intrasporangiaceae*. Int J Syst Evol Microbiol 58:2429–2432

Kaltenpoth M (2009) *Actinobacteria* as mutualists: general healthcare for insects? Trends Microbiol 17:529–535

Kämpfer P, Lodders N, Grün-Wollny I, Martin K, Busse HJ (2012) *Nocardia grenadensis* sp. nov., isolated from sand of the Caribbean Sea. Int J Syst Evol Microbiol 62:693–697

Kathiresan K, Bingham BL (2001) Biology of mangroves and mangrove ecosystems. Adv Mar Biol 40:81–251

Kavitha A, Prabhakar P, Vijayalakshmi M, Venkateswarlu Y (2009) Production of bioactive metabolites by *Nocardia levis* MK-VL_113. Lett Appl Microbiol 49:484–490

Keller S, Nicholson G, Drahl C, Sorensen E, Fiedler HP, Süssmuth RD (2007a) Abyssomicins G and H and atrop-abyssomicin C from the marine *Verrucosispora* strain AB-18-032. J Antibiot (Tokyo) 60: 391–394

Keller S, Schadt HS, Ortel I, Süssmuth RD (2007b) Action of atrop-abyssomicin C as an inhibitor of 4-amino-4-deoxychorismate synthase PabB. Angew Chem Int Ed Engl 46:8284–8286

Khamna S, Yokota A, Lumyong S (2009) *Actinomycetes* isolated from medicinal plant rhizosphere soils: diversity and screening of antifungal compounds, indole-3-acetic acid and siderophore production. World J Microbiol Biotechnol 25:649–655

Khan ST, Harayama S, Tamura T, Ando K, Takagi M, Kazuo SY (2009) *Paraoerskovia marina* gen. nov., sp. nov., an *Actinobacterium* isolated from marine sediment. Int J Syst Evol Microbiol 59: 2094–2098

Kim CJ, Lee KH, Shimazu A, Kwon OS, Park DJ (1995) Isolation of rare *Actinomycetes* in various types of soil. Korean J Appl Microbiol Biotechnol 23:36–42

Kim HM, Choi DH, Hwang CY, Cho BC (2008) *Nocardioides salarius* sp. nov., isolated from seawater enriched with zooplankton. Int J Syst Evol Microbiol 58:2056–2064

Kim SH, Yang HO, Sohn YC, Kwon HC (2010) *Aeromicrobium halocynthiae* sp. nov., a taurocholic acid-producing bacterium isolated from the marine ascidian *Halocynthia roretzi*. Int J Syst Evol Microbiol 60:2793–2798

Knight V, Sanglier JJ, DiTullio D, Braccili S, Bonner P, Waters J, Hughes D, Zhang L (2003) Diversifying microbial natural products for drug discovery. Appl Microbiol Biotechnol 62:446–458

Kobayashi M, Natsume T, Tamaoki S, Watanabe J, Asano H, Mikami T, Miyasaka K, Miyazaki K, Gondo M, Sakakibara K, Tsukagoshi S (1997) Antitumor activity of TZT-1027, a novel dolastatin 10 derivative. Jpn J Cancer Res 88:316–327

Kokare CR, Mahadik KR, Kadam SS (2004) Isolation of bioactive marine *Actinomycetes* from sediments isolated from Goa and Maharashtra coastlines (west coast of India). Indian J Mar Sci 33:248–256

Kumar V, Bharti A, Gupta VK, Gusain O, Bisht GS (2012) *Actinomycetes* from solitary wasp mud nest and swallow bird mud nest: isolation and screening for their antibacterial activity. World J Microbiol Biotechnol 28:871–880

Kurahashi M, Fukunaga Y, Sakiyama Y, Harayama S, Yokota A (2009) *Iamia majanohamensis* gen. nov., sp. nov., an *Actinobacterium* isolated from sea cucumber *Holothuria edulis*, and proposal of *Iamiaceae* fam. nov. Int J Syst Evol Microbiol 59:869–873

Kurahashi M, Fukunaga Y, Sakiyama Y, Harayama S, Yokota A (2010) *Euzebya tangerina* gen. nov., sp. nov., a deeply branching marine *Actinobacterium* isolated from the sea cucumber *Holothuria edulis*, and proposal of *Euzebyaceae* fam. nov., *Euzebyales* ord. nov. and *Nitriliruptoridae* subclassis nov. Int J Syst Evol Microbiol 60:2314–2319

Kurosawa K, Ghiviriga I, Sambandan TG, Lessard PA, Barbara JE, Rha C, Sinskey AJ (2008) Rhodostreptomycins, antibiotics biosynthesized following horizontal gene transfer from *Streptomyces padanus* to *Rhodococcus fascians*. J Am Chem Soc 130:1126–1127

Kurtböke Dİ (2012) Biodiscovery from rare *Actinomycetes*: an eco-taxonomical perspective. Appl Microbiol Biotechnol 93:1843–1852

Kwon HC, Kauffman CA, Jensen PR, Fenical W (2009) Marinisporolides, polyene-polyol macrolides from a marine *Actinomycetes* of the new genus *Marinispora*. J Org Chem 74:675–684

Lam KS (2006) Discovery of novel metabolites from marine *Actinomycetes*. Curr Opin Microbiol 9:245–251

Lancini G, Lorenzetti R (1993) Biotechnology of antibiotics and other bioactive microbial metabolites. Plenum, New York, pp 49–57

Laureti L, Song L, Huang S, Corre C, Leblond P, Challis GL, Aigle B (2011) Identification of a bioactive 51-membered macrolide complex by activation of a silent polyketide synthase in *Streptomyces ambofaciens*. Proc Natl Acad Sci U S A 108:6258–6263

Lazzarini A, Cavaletti L, Toppo G, Marinelli F (2000) Rare genera of *Actinomycetes* as potential producers of new antibiotics. Antonie Van Leeuwenhoek 78:399–405

Lee SD (2006a) *Actinocorallia cavernae* sp. nov., isolated from a natural cave in Jeju, Korea. Int J Syst Evol Microbiol 56:1085–1088

Lee SD (2006b) *Amycolatopsis jejuensis* sp. nov. and *Amycolatopsis halotolerans* sp. nov., novel *Actinomycetes* isolated from a natural cave. Int J Syst Evol Microbiol 56:549–553

Lee SD (2006c) *Nocardia jejuensis* sp. nov., a novel *Actinomycetes* isolated from a natural cave on Jeju Island, Republic of Korea. Int J Syst Evol Microbiol 56:559–562

Lee SD (2007a) *Labedella gwakjiensis* gen. nov., sp. nov., a novel *Actinomycete* of the family *Microbacteriaceae*. Int J Syst Evol Microbiol 57:2498–2502

Lee SD (2007b) *Marmoricola aequoreus* sp. nov., a novel *Actinobacterium* isolated from marine sediment. Int J Syst Evol Microbiol 57:1391–1395

Lee SD (2007c) *Nocardioides furvisabuli* sp. nov., isolated from black sand. Int J Syst Evol Microbiol 57:35–39

Lee SD (2008a) *Agrococcus jejuensis* sp. nov., isolated from dried seaweed. Int J Syst Evol Microbiol 58:2297–2300

Lee SD (2008b) *Brevibacterium marinum* sp. nov., isolated from seawater. Int J Syst Evol Microbiol 58:500–504

Lee SD, Kim SJ (2007) *Aeromicrobium tamlense* sp. nov., isolated from dried seaweed. Int J Syst Evol Microbiol 57:337–341

Lee DW, Lee SD (2008a) *Tessaracoccus flavescens* sp. nov., isolated from marine sediment. Int J Syst Evol Microbiol 58:785–789

Lee DW, Lee SD (2008b) *Aeromicrobium ponti* sp. nov., isolated from seawater. Int J Syst Evol Microbiol 58:987–991

Lee DW, Lee SD (2008c) *Ponticoccus gilvus* gen. nov., sp. nov., a novel member of the family *Propionibacteriaceae* from seawater. J Microbiol 46:508–512

Lee DW, Lee SD (2010) *Koreibacter algae* gen. nov., sp. nov., isolated from seaweed. Int J Syst Evol Microbiol 60:1510–1515

Lee SD, Kang SO, Hah YC (2000a) *Catellatospora koreensis* sp. nov., a novel *Actinomycete* isolated from goldmine cave. Int J Syst Evol Microbiol 50:1103–1111

Lee SD, Kim ES, Roe JH, Kim J, Kang SO, Hah C (2000b) *Saccharothrix violacea* sp. nov., isolated from a gold mine cave, and *Saccharothrix albidocapillata* comb. nov. Int J Syst Evol Microbiol 50:1315–1323

Lee SD, Kim ES, Min KL, Lee WY, Kang SO, Hah YC (2001) *Pseudonocardia kongjuensis* sp. nov., isolated from a gold mine cave. Int J Syst Evol Microbiol 51:1505–1510

Lee DW, Hyun CG, Lee SD (2007) *Nocardioides marinisabuli* sp. nov., a novel *Actinobacterium* isolated from beach sand. Int J Syst Evol Microbiol 57:2960–2963

Lee DW, Lee JM, Seo JP, Schumann P, Kim SJ, Lee SD (2008a) *Phycicola gilvus* gen. nov., sp. nov., an *Actinobacterium* isolated from living seaweed. Int J Syst Evol Microbiol 58:1318–1323

Lee JE, Seo JP, Lee DW, Ko YH, Lee SD (2008b) *Terrabacter lapilli* sp. nov., an *Actinomycete* isolated from stone. Int J Syst Evol Microbiol 58:1084–1088

Lee SD, Lee DW, Kim JS (2008c) *Nocardioides hwasunensis* sp. nov. Int J Syst Evol Microbiol 58:278–281

Lewis K, Epstein S, D'Onofrio A, Ling LL (2010) Uncultured microorganisms as a source of secondary metabolites. J Antibiot (Tokyo) 63:468–476

Li IV, Terekhova LP, Alferova IV, Galatenko OA, Gapochka MG (2003) The application of succession analysis in combination with extremely high-frequency irradiation to the selective isolation of *Actinomycetes* from soil. Mikrobiologiia 72:131–135

Li HR, Yu Y, Luo W, Zeng YX (2010) *Marisediminicola antarctica* gen. nov., sp. nov., an *Actinobacterium* isolated from the Antarctic. Int J Syst Evol Microbiol 60:2535–2539

Li S, Tian X, Niu S, Zhang W, Chen Y, Zhang H, Yang X, Zhang W, Li W, Zhang S, Ju J, Zhang C (2011) Pseudonocardians A-C, new diazaanthraquinone derivatives from a deap-sea *Actinomycete Pseudonocardia* sp. SCSIO 01299. Mar Drugs 9:1428–1439

Li J, Yang J, Zhu WY, He J, Tian XP, Xie Q, Zhang S, Li WJ (2012a) *Nocardiopsis coralliicola* sp. nov., isolated from the gorgonian coral, *Menella praelonga*. Int J Syst Evol Microbiol 62:1653–1658

Li J, Zhao GZ, Long LJ, Wang FZ, Tian XP, Zhang S, Li WJ (2012b) *Rhodococcus nanhaiensis* sp. nov., an *Actinobacterium* isolated from marine sediment. Int J Syst Evol Microbiol 62:2517–2521

Liao ZL, Tang SK, Guo L, Zhang YQ, Tian XP, Jiang CL, Xu LH, Li WJ (2009) *Verrucosispora lutea* sp. nov., isolated from a mangrove sediment sample. Int J Syst Evol Microbiol 59:2269–2273

Liras P, Demain AL (2009) Enzymology of beta-lactam compounds with cephem structure produced by *Actinomycete*. Methods Enzymol 458:401–429

Little AEF, Murakami T, Mueller UG, Currie CR (2006) Defending against parasites: fungus-growing ants combine specialized behaviours and microbial symbionts to protect their fungus gardens. Biol Lett 2:12–16

Liu Z, Li Y, Zheng LQ, Huang YJ, Li WJ (2010) *Saccharomonospora marina* sp. nov., isolated from an ocean sediment of the East China Sea. Int J Syst Evol Microbiol 60:1854–1857

Long H, Xiang W, Zhuang T, Lin P (2005) Microorganism resource of mangrove ecosystems. Chinese J Ecol 24:696–702

Macherla VR, Liu J, Sunga M, White DJ, Grodberg J, Teisan S, Lam KS, Potts BC (2007) Lipoxazolidinones A, B, and C: antibacterial 4-oxazolidinones from a marine *Actinomycete* isolated from a Guam marine sediment. J Nat Prod 70:1454–1457

Maldonado LA, Fenical W, Jensen PR, Kauffman CA, Mincer TJ, Ward AC, Bull AT, Goodfellow M (2005) *Salinispora arenicola* gen. nov., sp. nov. and *Salinispora tropica* sp. nov., obligate marine *Actinomycetes* belonging to the family *Micromonosporaceae*. Int J Syst Evol Microbiol 55:1759–1766

Maloney KN, MacMillan JB, Kauffman CA, Jensen PR, DiPasquale AG, Rheingold AL, Fenical W (2009) Lodopyridone, a structurally unprecedented alkaloid from a marine *Actinomycete*. Org Lett 11: 5422–5424

Mangamuri UK, Muvva V, Poda S, Kamma S (2012) Isolation, identification and molecular characterization of rare *Actinomycetes* from mangrove ecosystem of Nizampatnam. Malaysian J Microbiol 8:83–91

Matsumoto A, Takahashi Y, Mochizuki M, Seino A, Iwai Y, Omura S (1998) Characterization of *Actinomycetes* isolated from fallen leaves. Actinomycetologica 12:46–48

Matsumoto A, Kasai H, Matsuo Y, Omura S, Shizuri Y, Takahashi Y (2009) *Ilumatobacter fluminis* gen. nov., sp. nov., a novel *Actinobacterium* isolated from the sediment of an estuary. J Gen Appl Microbiol 55:201–205

Matsumoto A, Nakai K, Morisaki K, Omura S, Takahashi Y (2010) *Demequina salsinemoris* sp. nov., isolated on agar media supplemented with ascorbic acid or rutin. Int J Syst Evol Microbiol 60:1206–1209

Mayer AM, Glaser KB, Cuevas C, Jacobs RS, Kem W, Little RD, McIntosh JM, Newman DJ, Potts BC, Shuster DE (2010) The odyssey of marine pharmaceuticals: a current pipeline perspective. Trends Pharmacol Sci 31:255–265

McArthur KA, Mitchell SS, Tsueng G, Rheingold A, White DJ, Grodberg J, Lam KS, Potts BC (2008) Lynamicins A-E, chlorinated bisindole pyrrole antibiotics from a novel marine *Actinomycete*. J Nat Prod 71: 1732–1737

McInerney MJ, Struchtemeyer CG, Sieber J, Mouttaki H, Stams AJ, Schink B, Rohlin L, Gunsalus RP (2008) Physiology, ecology, phylogeny, and genomics of microorganisms capable of syntrophic metabolism. Ann NY Acad Sci 1125:58–72

Medema MH, Trefzer A, Kovalchuk A, van den Berg M, Müller U, Heijne W, Wu L, Alam MT, Ronning CM, Nierman WC, Bovenberg RA, Breitling R, Takano E (2010) The sequence of a 1.8-mb bacterial linear plasmid reveals a rich evolutionary reservoir of secondary metabolic pathways. Genome Biol Evol 2:212–224

Mehbub MF, Amin AKMR (2012) Isolation and identification of *Actinobacteria* from two south Australian marine sponges *Aplysilla rosea* and *Aplysina* sp. Bangladesh Res Publ J 7:345–354

Meklat A, Sabaou N, Zitouni A, Mathieu F, Lebrihi A (2011) Isolation, taxonomy, and antagonistic properties of halophilic *Actinomycetes* in Saharan soils of Algeria. Appl Environ Microbiol 77:6710–6714

Miguélez EM, Martín C, Hardisson C, Manzanal MB (1993) Synchronous germination of *Streptomyces antibioticus* spores: tool for the analysis of hyphal growth in liquid cultures. FEMS Microbiol Lett 109:123–129

Mincer TJ, Jensen PR, Kauffman CA, Fenical W (2002) Widespread and persistent populations of a major new marine *Actinomycete* taxon in ocean sediments. Appl Environ Microbiol 68:5005–5011

Mita AC, Hammond LA, Bonate PL, Weiss G, McCreery H, Syed S, Garrison M, Chu QS, DeBono JS, Jones CB, Weitman S, Rowinsky EK (2006) Phase I and pharmacokinetic study of tasidotin hydrochloride (ILX651), a third-generation dolastatin-15 analogue, administered weekly for 3 weeks every 28 days in patients with advanced solid tumors. Clin Cancer Res 12:5207–5215

Mueller UG, Dash D, Rabeling C, Rodrigues A (2008) Coevolution between attine ants and *Actinomycete* bacteria: a reevaluation. Evolution 62:2894–2912

Murakami R, Fujita Y, Kizuka M, Kagawa T, Muramatsu Y, Miyakoshi S, Takatsu T, Inukai M (2007) A-102395, a new inhibitor of bacterial

Translocase I, produced by *Amycolatopsis* sp. SANK 60206. J Antibiot 60:690–695
Murphy BT, Narender T, Kauffman CA, Woolery M, Jensen PR, Fenical W (2010) Saliniquinones A-F, new members of the highly cytotoxic anthraquinone-c-pyrones from the marine *Actinomycete Salinispora arenicola*. Aust J Chem 63:929–934
Mutka SC, Carney JR, Liu Y, Kennedy J (2006) Heterologous production of epothilone C and D in *Escherichia coli*. Biochemistry 45:1321–1330
Naikpatil SV, Rathod JL (2011) Selective isolation and antimicrobial activity of rare *Actinomycetes* from mangrove sediment of Karwar. J Ecobiotechnol 3:48–53
Nakaew N, Pathom-aree W, Lumyong S (2009) Generic diversity of rare *Actinomycetes* from Thai cave soils and their possible use as new bioactive compounds. Actinomycetologica 23:21–26
Nam SJ, Gaudencio SP, Kauffman CA, Jensen PR, Kondratyuk TP, Marler LE, Pezzuto JM, Fenical W (2010) Fijiolides A and B, inhibitors of TNF-alpha-induced NFkappaB activation, from a marine-derived sediment bacterium of the genus *Nocardiopsis*. J Nat Prod 73:1080–1086
Natsume M, Yasui K, Marumo S (1989) Calcium ion regulates aerial mycelium formation in *Actinomycetes*. J Antibiot 42:440–447
Negri A, Marco E, García-Hernández V, Domingo A, Llamas-Saiz AL, Porto-Sandá S, Riguera R, Laine W, David-Cordonnier MH, Bailly C, García-Fernández LF, Vaquero JJ, Gago F (2007) Antitumor activity, X-ray crystal structure, and DNA binding properties of thiocoraline A, a natural bisintercalating thiodepsipeptide. J Med Chem 50:3322–3333
Newman DJ, Cragg GM (2007) Natural products as sources of new drugs over the last 25 years. J Nat Prod 70:461–477
Newman DJ, Cragg GM, Snader KM (2003) Natural products as sources of new drugs over the period 1981–2002. J Nat Prod 66:1022–1037
Nichols D, Lewis K, Orjala J, Mo S, Ortenberg R, O'Connor P, Zhao C, Vouros P, Kaeberlein T, Epstein SS (2008) Short peptide induces an "uncultivable" microorganism to grow in vitro. Appl Environ Microbiol 74:4889–4897
Niyomvong N, Pathom-aree W, Thamchaipenet A, Duangmal K (2012) *Actinomycetes* from tropical limestone Caves. Chiang Mai J Sci 39: 373–388
Nolan RD, Cross T (1988) Isolation and screening of *Actinomycetes*. In: Goodfellow M, Williams ST, Mordarski M (eds) *Actinomycetes* in biotechnology. Academic, London, pp 2–8
Nonomura H (1988) Isolation, taxonomy and ecology of soil *Actinomycetes*. Actinomycetologia 3:45–54
Nonomura H, Hayakawa M (1988) New methods for the selective isolation of soil *Actinomycetes*. In: Okami Y, Beppu T, Ogawara H (eds) Biology of *Actinomycetes*. Japan Scientific Societies, Tokyo, pp 288–293
Oh DC, Gontang EA, Kauffman CA, Jensen PR, Fenical W (2008) Salinipyrones and pacificanones, mixed-precursor polyketides from the marine *Actinomycete Salinispora pacifica*. J Nat Prod 71:570–575
Oh DC, Poulsen M, Currie CR, Clardy J (2009) Dentigerumycin: a bacterial mediator of an ant–fungus symbiosis. Nat Chem Biol 5: 391–393
Ohnishi Y, Ishikawa J, Hara H, Suzuki H, Ikenoya M, Ikeda H, Yamashita A, Hattori M, Horinouchi S (2008) Genome sequence of the streptomycin-producing microorganism *Streptomyces griseus* IFO 13350. J Bacteriol 190:4050–4060
Okami B, Hotta AK (1988) Search and discovery of new antibiotics. In: Goodfellow M, Williams ST, Mordarski M (eds) *Actinomycetes* in biotechnology. Pergamon, Oxford, pp 33–67
Okoro CK, Brown R, Jones AL, Andrews BA, Asenjo JA, Goodfellow M, Bull AT (2009) Diversity of culturable *Actinomycetes* in hyper-arid soils of the Atacama Desert, Chile. Antonie Van Leeuwenhoek 95:121–133
Olson JB, Harmody DK, Bej AK, McCarthy PJ (2007) *Tsukamurella spongiae* sp. nov., a novel *Actinomycete* isolated from a deep-water marine sponge. Int J Syst Evol Microbiol 57:1478–1481
Otoguro M, Hayakawa M, Yamazaki T, Iimura Y (2001) An integrated method for the enrichment and selective isolation of *Actiniokineospora* spp. in soil and plant litter. J Appl Microbiol 91:118–130
Palomo S, González I, de la Cruz M, Martín J, Tormo JR, Anderson M, Hill RT, Vicente F, Reyes F, Genilloud O (2013) Sponge-derived *Kocuria* and *Micrococcus* spp. as sources of the new thiazolyl peptide antibiotic kocurin. Mar Drugs 11:1071–7086
Park SC, Baik KS, Kim MS, Chun J, Seong CN (2008) *Nocardioides dokdonensis* sp. nov., an *Actinomycete* isolated from sand sediment. Int J Syst Evol Microbiol 58:2619–2623
Pathom-Aree W, Stach JE, Ward AC, Horikoshi K, Bull AT, Goodfellow M (2006) Diversity of *Actinomycetes* isolated from Challenger Deep sediment (10,898 m) from the Mariana Trench. Extremophiles 10:181–189
Peiru S, Menzella HG, Rodriguez E, Carney J, Gramajo H (2005) Production of the potent antibacterial polyketide erythromycin C in *Escherichia coli*. Appl Environ Microbiol 71:2539–2547
Pettit GR, Tan R, Pettit RK, Smith TH, Feng S, Doubek DL, Richert L, Hamblin J, Weber C, Chapuis JC (2007) Antineoplastic agents 560. Isolation and structure of kitastatin 1 from an Alaskan *Kitasatospora* sp. J Nat Prod 70:1069–1072
Pfefferle C, Theobald U, Gürtler H, Fiedler HP (2000) Improved secondary metabolite production in the genus *Streptosporangium* by optimization of the fermentation conditions. J Biotechnol 80:135–142
Piel J (2009) Metabolites from symbiotic bacteria. Nat Prod Rep 26:338–362
Pimentel-Elardo SM, Tiro LP, Grozdanov L, Hentschel U (2008) *Saccharopolyspora cebuensis* sp. nov., a novel *Actinomycete* isolated from a Philippine sponge (Porifera). Int J Syst Evol Microbiol 58:628–632
Pindi PK, Manorama R, Begum Z, Shivaji S (2010) *Arthrobacter antarcticus* sp. nov., isolated from an Antarctic marine sediment. Int J Syst Evol Microbiol 60:2263–2266
Proksch P, Muller WEG (2006) Frontiers in marine biotechnology. Routledge, Norfolk, pp 225–288
Prudhomme J, McDaniel E, Ponts N, Bertani S, Fenical W, Jensen P, Roch KL (2008) Marine *Actinomycetes*: a new source of compounds against the human malaria parasite. PLoS One 3:e2335
Qin S, Li J, Chen HH, Zhao GZ, Zhu WY, Jiang CL, Xu LH, Li WJ (2009) Isolation, diversity, and antimicrobial activity of rare *Actinobacteria* from medicinal plants of tropical rain forests in Xishuangbanna, China. Appl Environ Microbiol 75:6176–6186
Qiu D, Ruan J, Huang Y (2008) Selective isolation and rapid identification of members of the genus *Micromonospora*. Appl Environ Microbiol 74:5593–5597
Qui J (2010) Nature News. doi:10.1038/news.2010.190. http://www.nature.com/news/2010/100418/full/news.2010.190.html. Accessed 18 April 2010
Raju R, Piggott AM, Conte M, Tnimov Z, Alexandrov K, Capon RJ (2010) Nocardiopsins: new FKBP12-binding macrolide polyketides from an Australian marine-derived *Actinomycete*, *Nocardiopsis* sp. Chemistry 16:3194–3200
Renu S, Monisha K, Rup L (2008) Bioactive compounds from marine *Actinomycetes*. Indian J Microbiol 48:410–431
Riedlinger J, Reicke A, Zähner H, Krismer B, Bull AT, Maldonado LA, Ward AC, Goodfellow M, Bister B, Bischoff D, Süssmuth RD, Fiedler HP (2004) Abyssomicins, inhibitors of the para-aminobenzoic acid pathway produced by the marine *Verrucosispora* strain AB-18-032. J Antibiot (Tokyo) 57:271–279
Roh H, Uguru GC, Ko HJ, Kim S, Kim BY, Goodfellow M, Bull AT, Kim KH, Bibb MJ, Choi IG, Stach JEM (2011) Genome sequence of the abyssomicin- and proximicin producing marine *Actinomycete Verrucosispora maris* AB-18-032. J Bacteriol 193:3391–3392

Romero F, Espliego F, Pérez Baz J, García De Quesada T, Grávalos D, de la Calle F, Fernández-Puentes JL (1997) Thiocoraline, a new depsipeptide with antitumor activity produced by a marine *Micromonospora*. I. Taxonomy, fermentation, isolation, and biological activities. J Antibiot (Tokyo) 50:734–737

Sánchez S, Chávez A, Forero A, García-Huante Y, Romero A, Sánchez M, Rocha D, Sánchez B, Avalos M, Guzmán-Trampe S, Rodríguez-Sanoja R, Langley E, Ruiz B (2010) Carbon source regulation of antibiotic production. J Antibiot (Tokyo) 63:442–459

Schabereiter-Gurtner C, Saiz-Jimenez C, Pinar G, Lubitz W, Rolleke S (2002) Altamira Cave Paleolithic paintings harbour partly unknown bacterial communities. FEMS Microbiol Lett 211:7–11

Schneemann I, Nagel K, Kajahn I, Labes A, Wiese J, Imhoff JF (2010) Comprehensive investigation of marine *Actinobacteria* associated with the sponge *Halichondria panicea*. Appl Environ Microbiol 76: 3702–3714

Schneider K, Keller S, Wolter FE, Roglin L, Beil W, Seitz O, Nicholson G, Bruntner C, Riedlinger J, Fiedler HP, Sussmuth RD (2008) Proximicins A, B and C antitumor furan analogues of netropsin from the marine *Actinomycetes Verrucosispora* induced up regulation of p53 and the cyclin kinase inhibitor p21. Angew Chem Int Ed 47:3258–3261

Schultz M, Tsaklakidis C (1997) Nach Chem Tech Lab 45:159–165

Sen R, Ishak HD, Estrada D, Dowd SE, Hong E, Mueller UG (2009) Generalized antifungal activity and 454-screening of *Pseudonocardia* and *Amycolatopsis* bacteria in nests of fungus-growing ants. Proc Natl Acad Sci U S A 106:17805–17810

Seo YB, Kim DE, Kim GD, Kim HW, Nam SW, Kim YT, Lee JH (2009) *Kocuria gwangalliensis* sp. nov., an *Actinobacterium* isolated from seawater. Int J Syst Evol Microbiol 59:2769–2772

Seong CN, Choi JH, Baik KS (2001) An improved selective isolation of rare *Actinomycetes* from forest soil. J Microbiol 39:17–23

Shirai M, Okuda M, Motohashi K, Inoto M, Furihata K, Matsuo Y, Shizuri Y, Seto H (2010) Terpenoids produced by *Actinomycetes*: isolation, structural elucidation and biosynthesis of new diterpenes: gifhornenolones A and B from *Verrucosispora gifhornensis* YM28-088. J Antibiot 63:245–250

Simmons L, Kaufmann K, Garcia R, Schwär G, Huch V, Müller R (2011) Bendigoles D-F, bioactive sterols from the marine sponge-derived *Actinomadura* sp. SBMs009. Bioorg Med Chem 19:6570–6575

Sogin ML, Morrison HG, Huber JA, Mark WD, Huse SM, Neal PR, Arrieta JM, Herndl GJ (2006) Microbial diversity in the deep sea and the underexplored “rare biosphere”. Proc Natl Acad Sci U S A 103:12115–12120

Solano G, Rojas-Jiménez K, Jaspars M, Tamayo-Castillo G (2009) Study of the diversity of culturable *Actinomycetes* in the North Pacific and Caribbean coasts of Costa Rica. Antonie Van Leeuwenhoek 96:71–78

Song JY, Jeong H, Yu DS, Fischbach MA, Park HS, Kim JJ, Seo JS, Jensen SE, Oh TK, Lee KJ, Kim JF (2010) Draft genome sequence of *Streptomyces clavuligerus* NRRL 3585, a producer of diverse secondary metabolites. J Bacteriol 192:6317–6318

Songsumanus A, Tanasupawat S, Igarashi Y, Kudo T (2013) *Micromonospora maritima* sp. nov., isolated from mangrove soil. Int J Syst Evol Microbiol 63:554–559

Sousa TS, Jimenez PC, Ferreira EG, Silveira ER, Braz-Filho R, Pessoa OD, Costa-Lotufo LV (2012) Anthracyclinones from *Micromonospora* sp. J Nat Prod 75:489–493

Stach J (2010) Antimicrobials: treasures from the oceans. Microbiol Today 105:1–3

Stach JE, Bull AT (2005) Estimating and comparing the diversity of marine *Actinobacteria*. Antonie Van Leeuwenhoek 87:3–9

Stach JEM, Maldonado LA, Ward AC, Goodfellow M, Bull AT (2003) New primers for the class *Actinobacteria*: application to marine and terrestrial environments. Environ Microbiol 5:828–841

Stewart EJ (2012) Growing unculturable bacteria. J Bacteriol 194:4151–4160

Subramani R, Aalbersberg W (2012) Marine *Actinomycetes*: an ongoing source of novel bioactive metabolites. Microbiol Res 167:571–580

Subramani R, Narayanasamy M (2009) Screening of marine *Actinomycetes* isolated from the Bay of Bengal, India for antimicrobial activity and industrial enzymes. World J Microbiol Biotechnol 25:2103–2111

Supong K, Suriyachadkun C, Tanasupawat S, Suwanborirux K, Pittayakhajonwut P, Kudo T, Thawai C (2013) *Micromonospora sediminicola* sp. nov., isolated from marine sediment. Int J Syst Evol Microbiol 63:570–575

Taechowisan T, Peberdy JF, Lumyong S (2003) Isolation of endophytic *Actinomycetes* from selected plants and their antifungal activity. World J Microbiol Biotechnol 19:381–385

Takahashi Y, Matsumoto A, Seino A, Iwai Y, Omura S (1996) Rare *Actinomycetes* isolated from desert soils. Actinomycetologica 10: 91–97

Takizawa M, Colwell RR, Hill RT (1997) Isolation and diversity of *Actinomycetes* in the Chesapeake Bay. Appl Environ Microbiol 59:997–1002

Tan GY, Ward AC, Goodfellow M (2006) Exploration of *Amycolatopsis* diversity in soil using genus-specific primers and novel selective media. Syst Appl Microbiol 29:557–569

Tanasupawat S, Jongrungruangchok S, Kudo T (2010) *Micromonospora marina* sp. nov., isolated from sea sand. Int J Syst Evol Microbiol 60:648–652

Terahara T, Kobayashi T, Imada C (2013) An effective method based on wet-heat treatment for the selective isolation of *Micromonospora* from estuarine sediments. World J Microbiol Biotechnol 29:1677–1684

Thawai C, Tanasupawat S, Kudo T (2008) *Micromonospora pattaloongensis* sp. nov., isolated from a Thai mangrove forest. Int J Syst Evol Microbiol 58:1516–1521

Tian XP, Tang SK, Dong JD, Zhang YQ, Xu LH, Zhang S, Li WJ (2009a) *Marinactinospora thermotolerans* gen. nov., sp. nov., a marine *Actinomycete* isolated from a sediment in the northern South China Sea. Int J Syst Evol Microbiol 59:948–952

Tian XP, Zhi XY, Qiu YQ, Zhang YQ, Tang SK, Xu LH, Zhang S, Li WJ (2009b) *Sciscionella marina* gen. nov., sp. nov., a marine *Actinomycete* isolated from a sediment in the northern South China Sea. Int J Syst Evol Microbiol 59:222–228

Tian XP, Xu Y, Zhang J, Li J, Chen Z, Kim CJ, Li WJ, Zhang CS, Zhang S (2012) *Streptomyces oceani* sp. nov., a new obligate marine *Actinomycete* isolated from a deep-sea sample of seep authigenic carbonate nodule in South China Sea. Antonie Van Leeuwenhoek 102:335–343

Tian XP, Long LJ, Li SM, Zhang J, Xu Y, He J, Li J, Wang FZ, Li WJ, Zhang CS, Zhang S (2013) *Pseudonocardia antitumoralis* sp. nov., a deoxynyboquinone-producing *Actinomycete* isolated from a deep-sea sediment. Int J Syst Evol Microbiol 63:893–899

Tishkov S (2001) Bioactive products from *Actinomycetes*—antibiotics, enzyme inhibitors, immunomodulators. In: Moncheva P, Tishkov S, Chipeva V (eds) Innovative aspects in biotechnology of prokaryotes. National bank for industrial microorganisms and cell cultures, Sofia, pp 111–138

Tiwari K, Gupta RK (2012a) Diversity and isolation of rare *Actinomycetes*: an overview. Crit Rev Microbiol 39:256–294

Tiwari K, Gupta RK (2012b) Rare *Actinomycetes*: a potential storehouse for novel antibiotics. Crit Rev Biotechnol 32:108–132

Traiwan J, Park MK, Kim W (2011) *Serinicoccus chungangensis* sp. nov., isolated from tidal flat sediment, and emended description of the genus *Serinicoccus*. Int J Syst Evol Microbiol 61:1299–1303

Tsao PH, Leben C, Keitt GW (1960) An enrichment method for isolating *Actinomycetes* that produce diffusible antifungal antibiotics. Phytopathology 50:88–89

Tseng M, Liao HC, Chiang WP, Yuan GF (2011) *Isoptericola chiayiensis* sp. nov., isolated from mangrove soil. Int J Syst Evol Microbiol 61: 1667–1670

Ue H, Matsuo Y, Kasai H, Yokota A (2011a) *Demequina globuliformis* sp. nov., *Demequina oxidasica* sp. nov. and *Demequina aurantiaca* sp. nov., *Actinobacteria* isolated from marine environments, and proposal of *Demequinaceae* fam. nov. Int J Syst Evol Microbiol 61:1322–1329

Ue H, Matsuo Y, Kasai H, Yokota A (2011b) *Miniimonas arenae* gen. nov., sp. nov., an *Actinobacterium* isolated from sea sand. Int J Syst Evol Microbiol 61:123–127

Vartoukian SR, Palmer RM, Wade WG (2010) Strategies for culture of 'unculturable' bacteria. FEMS Microbiol Lett 309:1–7

Walsh C (2003) Where will new antibiotics come from? Nat Rev Microbiol 1:65–70

Wang Y, Mueller UG, Clardy J (1999) Antifungal diketopiperazines from symbiotic fungus of fungus growing ant *Cyphomyrmex minutus*. J Chem Ecol 25:935–941

Wang F, Gai Y, Chen M, Xiao X (2009) *Arthrobacter psychrochitiniphilus* sp. nov., a psychrotrophic bacterium isolated from Antarctica. Int J Syst Evol Microbiol 59:2759–2762

Wang J, Li Y, Bian J, Tang SK, Ren B, Chen M, Li WJ, Zhang LX (2010) *Prauserella marina* sp. nov., isolated from ocean sediment of the South China Sea. Int J Syst Evol Microbiol 60:985–989

Wang C, Xu XX, Qu Z, Wang HL, Lin HP, Xie QY, Ruan JS, Hong K (2011a) *Micromonospora rhizosphaerae* sp. nov., isolated from mangrove rhizosphere soil. Int J Syst Evol Microbiol 61:320–324

Wang F, Xu XX, Qu Z, Wang C, Lin HP, Xie QY, Ruan JS, Sun M, Hong K (2011b) *Nonomuraea wenchangensis* sp. nov., isolated from mangrove rhizosphere soil. Int J Syst Evol Microbiol 61:1304–1308

Wang DS, Xue QH, Zhu WJ, Zhao J, Duan JL, Shen GH (2013a) Microwave irradiation is a useful tool for improving isolation of *Actinomycetes* from soil. Microbiology 82:102–110

Wang Q, Song F, Xiao X, Huang P, Li L, Monte A, Abdel-Mageed WM, Wang J, Guo H, He W, Xie F, Dai H, Liu M, Chen C, Xu H, Liu M, Piggott AM, Liu X, Capon RJ, Zhang L (2013b) Abyssomicins from the South China Sea deep-sea sediment *Verrucosispora* sp.: natural thioether Michael addition adducts as antitubercular prodrugs. Angew Chem Int Ed Engl 52:1231–1234

Webster NS, Hill RT (2001) The culturable microbial community of the Great Barrier Reef sponge *Rhopaloeides odorabile* is dominated by an α-*Proteobacterium*. Mar Biol 138:843–851

Williams ST, Wellington EMH (1982) Principles and problems of selective isolation of microbes. In: Bullock JD, Nisbet LJ, Winstanley DJ (eds) Bioactive microbial products I: search and discovery. Academic, London, pp 9–26

Williams P, Winzer K, Chan WC, Camara M (2007a) Look who's talking: communication and quorum sensing in the bacterial world. Philos Trans R Soc Lond B Biol Sci 362:1119–1134

Williams PG, Miller ED, Asolkar RN, Jensen PR, Fenical W (2007b) Arenicolides A-C, 26- membered ring macrolides from the marine *Actinomycete Salinispora arenicola*. J Org Chem 72:5025–5034

Wright GD, Sutherland AD (2007) New strategies for combating multidrug-resistant bacteria. Trends Mol Med 13:260–267

Wu Y, Li WJ, Tian W, Zhang LP, Xu L, Shen QR, Shen B (2010) *Isoptericola jiangsuensis* sp. nov., a chitin-degrading bacterium. Int J Syst Evol Microbiol 60:904–908

Wu H, Chen W, Wang G, Dai S, Zhou D, Zhao H, Guo Y, Ouyang YC, Li X (2012) Culture-dependent diversity of *Actinobacteria* associated with seagrass (*Thalassia hemprichii*). African J Microbiol Res 6:87–94

Wyche TP, Hou Y, Braun D, Cohen HC, Xiong MP, Bugni TS (2011) First natural analogs of the cytotoxic thiodepsipeptide thiocoraline A from a marine *Verrucosispora* sp. J Org Chem 76:6542–6547

Xi L, Zhang L, Ruan J, Huang Y (2011a) Description of *Verrucosispora qiuiae* sp. nov., isolated from mangrove swamp sediment, and emended description of the genus *Verrucosispora*. Int J Syst Evol Microbiol 62:1564–1569

Xi L, Zhang L, Ruan J, Huang Y (2011b) *Nonomuraea maritima* sp. nov., isolated from coastal sediment. Int J Syst Evol Microbiol 61:2740–2744

Xiao C, Huang H, Ye J, Wu X, Zhu J, Zhan B, Bao S (2011a) *Ornithinibacter aureus* gen. nov., sp. nov., a novel member of the family *Intrasporangiaceae*. Int J Syst Evol Microbiol 61:659–664

Xiao J, Luo Y, Xie S, Xu J (2011b) *Serinicoccus profundi* sp. nov., an *Actinomycete* isolated from deep-sea sediment, and emended description of the genus *Serinicoccus*. Int J Syst Evol Microbiol 61:16–19

Xiao J, Luo Y, Xu J, Xie S, Xu J (2011c) *Modestobacter marinus* sp. nov., a psychrotolerant *Actinobacterium* from deep-sea sediment, and emended description of the genus *Modestobacter*. Int J Syst Evol Microbiol 61:1710–1714

Xu LH, Jiang CL (1996) A study on diversity of aquatic *Actinomycetes* in lakes of the middle plateau, Yunnan, China. Appl Environ Microbiol 62:249–253

Xu LH, Li WJ, Liu ZH, Jiang CL (2007) *Actinomycete* taxonomy. Acedemic, Beijing, pp 202–208

Xu XX, Qu Z, Wang H, Lin HP, Wang C, Xie QY, Ruan JS, Hong K (2011) *Asanoa hainanensis* sp. nov., isolated from rhizosphere soil of *Acrostichum speciosum* in a mangrove, and emended description of the genus *Asanoa*. Int J Syst Evol Microbiol 61:2384–2388

Xu XX, Wang HL, Lin HP, Wang C, Qu Z, Xie QY, Ruan JS, Hong K (2012) *Microbispora hainanensis* sp. nov., isolated from rhizosphere soil of *Excoecaria agallocha* in a mangrove. Int J Syst Evol Microbiol 62:2430–2434

Xue Q, Dua CM, Wang LN, Lin YB (2010) The influence of microwave irradiation to the isolation effect of soil *Actinomycetes*. Chinese J Microbiol 3:19–24

Yang B, Xue QH, Chen ZQ, Zhou YQ, Zhang XL, Xu YJ, Guo ZY (2008) Effects of microwave irradiation on isolation of soil *Actinomycetes*. Ying Yong Sheng Tai Xue Bao 5:1091–1098

Yang XW, Zhang GY, Ying JX, Yang B, Zhou XF, Steinmetz A, Liu YH, Wang N (2013) Isolation, characterization, and bioactivity evaluation of 3-((6-methylpyrazin-2-yl)methyl)-1H-indole, a new alkaloid from a deep-sea-derived *Actinomycete Serinicoccus profundi* sp. nov. Mar Drugs 11:33–39

Yi H, Schumann P, Chun J (2007) *Demequina aestuarii* gen. nov., sp. nov., a novel *Actinomycete* of the suborder *Micrococcineae*, and reclassification of *Cellulomonas fermentans* Bagnara et al. 1985 as *Actinotalea fermentans* gen. nov., comb. nov. Int J Syst Evol Microbiol 57:151–156

Yi-lei N, Ru L, Yang X, Hong J (2009) Isolation, purification and structure determination of antifungal antibiotic FW03-1149 produced by marine *Micromonospora* sp. FIM03-1149. Chinese J Mar Drugs 01

Young P (1997) Major microbial diversity initiative recommended. ASM News 63:417–421

Yu L, Lai Q, Yi Z, Zhang L, Huang Y, Gu L, Tang X (2013) *Microbacterium sediminis* sp. nov., a psychrotolerant, thermotolerant, halotolerant and alkalitolerant *Actinomycete* isolated from deep-sea sediment. Int J Syst Evol Microbiol 63:25–30

Zhang L (2005) Integrated approaches for discovering novel drugs from microbial natural products. In: Zhang L, Demain AL (eds) Natural products. Drug discovery and therapeutic medicine. Humana, Totowa, pp 33–35

Zhang L, An R, Wang J, Sun N, Zhang S, Hu J, Kuai J (2005) Exploring novel bioactive compounds from marine microbes. Curr Opin Microbiol 8:276–281

Zhang C, Herath K, Jayasuriya H, Ondeyka JG, Zink DL, Occi J, Birdsall G, Venugopal J, Ushio M, Burgess B, Masurekar P, Barrett JF, Singh

SB (2009) Thiazomycins, thiazolyl peptide antibiotics from *Amycolatopsis fastidiosa*. J Nat Prod 72:841–847

Zhang L, Xi L, Ruan J, Huang Y (2012) *Micromonospora yangpuensis* sp. nov., isolated from a sponge. Int J Syst Evol Microbiol 62:272–278

Zhang Q, Li S, Chen Y, Tian X, Zhang H, Zhang G, Zhu Y, Zhang S, Zhang W, Zhang C (2013) New diketopiperazine derivatives from a deep-sea-derived *Nocardiopsis alba* SCSIO 03039. J Antibiot (Tokyo) 66:31–36

Zhuge B, Fang HY, Yu H, Rao ZM, Shen W, Song J, Zhuge J (2008) Bioconversion of Lovastatin to a novel statin, Wuxistatin by *Amycolatopsis* sp. Appl Microbiol Biotechnol 79:209–216

Zobell CE (1946) Marine microbiology. Chronica Botanica Co, Waltham