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# The secondary metabolites of rare actinomycetes: chemistry and bioactivity

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Actinomycetes are outstanding and fascinating sources of potent bioactive compounds, particularly antibiotics. In recent years, rare actinomycetes have had an increasingly important position in the discovery of antibacterial compounds, especially *Micromonospora*, *Actinomadura* and *Amycolatopsis*. Focusing on the period from 2008 to 2018, we herein summarize the structures and bioactivities of secondary metabolites from rare actinomycetes, involving 21 genera.

## 1 Introduction

Actinomycetes can produce novel secondary metabolites, most of which possess significant antibacterial activity. So far, actinomycetes have contributed about two-thirds of available antibiotics, more than 70% of which are produced using *Streptomyces*.<sup>1</sup> In 2013, Chavan *et al.* introduced marine actinomycetes and their biotechnological applications.<sup>2</sup> In recent years, because of the increasing prevalence of bacterial resistance, it is important to discover new antibiotics.<sup>3</sup> However,

with continuous research on *Streptomyces* having been carried out, it has become difficult to find novel compounds with potent antibacterial activity from *Streptomyces*. On the contrary, since many successful antibiotics have been produced using rare actinomycetes, such as rifamycins produced by *Amycolatopsis mediterranei*, erythromycin produced by *Saccharopolyspora erythraea* and teicoplanin produced by *Actinoplanes teichomyceticus*, the significant ability of rare actinomycetes to produce antibiotics has obtained great attention.<sup>4</sup> The proportion of antibiotics produced by rare actinomycetes has increased to being up to 25–30% of known antibiotics in the last two decades.<sup>5</sup> Therefore, rare actinomycetes have become potential resources for the discovery of compounds with significant antibacterial activity.

According to Lechevalie, when using traditional separation methods, the frequency of rare actinomycetes is far below the frequency of *Streptomyces*.<sup>6</sup> Later, Okami corrected the concept

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education at Shanghai Institute of Pharmaceutical Industry, where he acquired a PhD degree in 2002. His major achievements are in the fields of bioactive natural product discovery for therapeutic applications, the chemical biology of natural products, and innovative drug discovery from TCM.



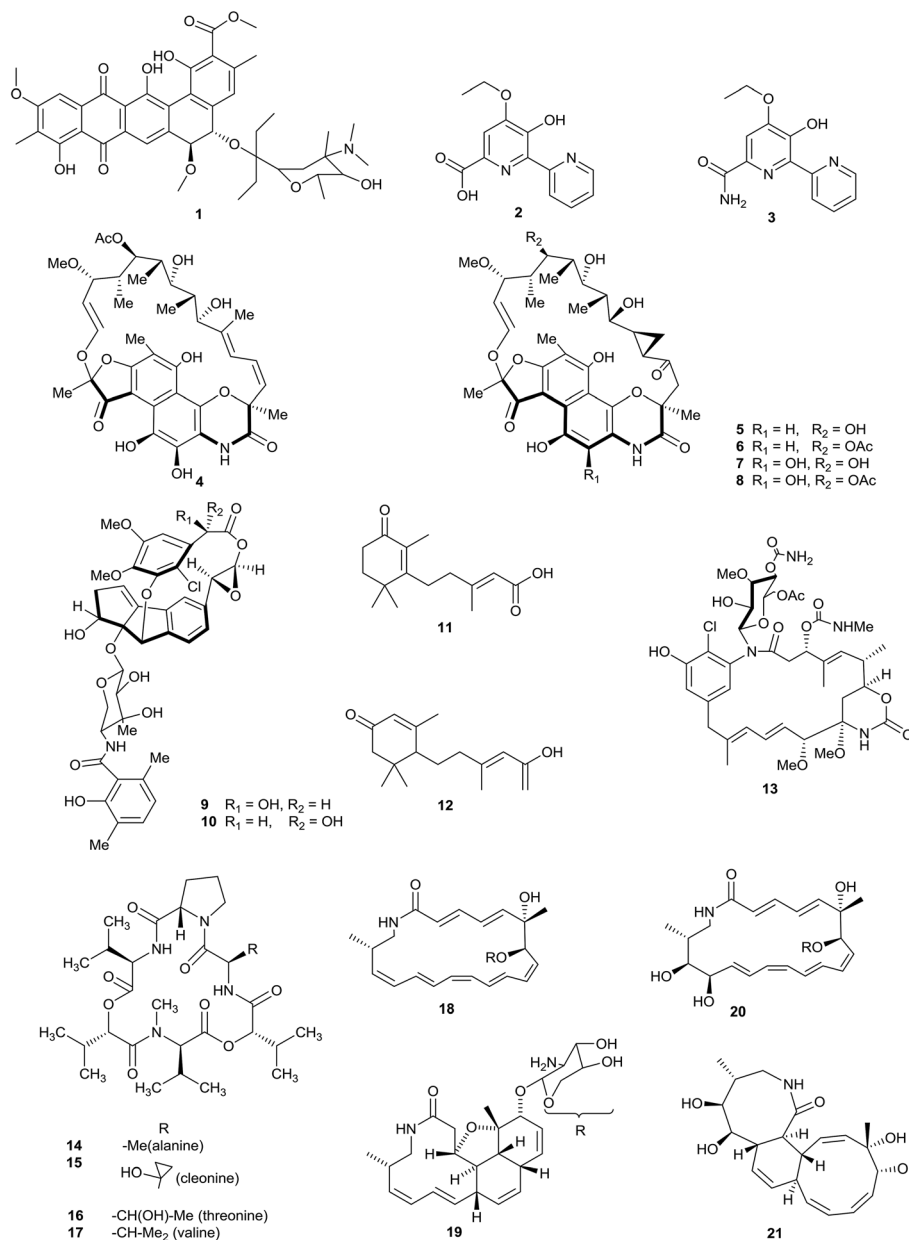


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of rare actinomycetes; he thought that rare actinomycetes had a slow growth rate and small population compared to *Streptomyces*. In addition, unusual growth conditions are necessary, and they result in distinctive physiological properties. Different from *Streptomyces*, it is more difficult to isolate rare actinomycetes from soil or other media. Therefore, research into secondary metabolites of rare actinomycetes has been less frequent than *Streptomyces* research, which has made rare actinomycetes a significant resource for finding new antibiotics. In this review, we mainly summarize the chemical structures and biological activities of the secondary metabolites of rare actinomycetes discovered from 2008 to 2018, involving 21 genera: *Amycolatopsis*, *Actinomadura*, *Nonomuraea*, *Pseudonocardia*, *Micromonospora*, *Saccharothrix*, *Actinosynnema*, *Nocardia*,

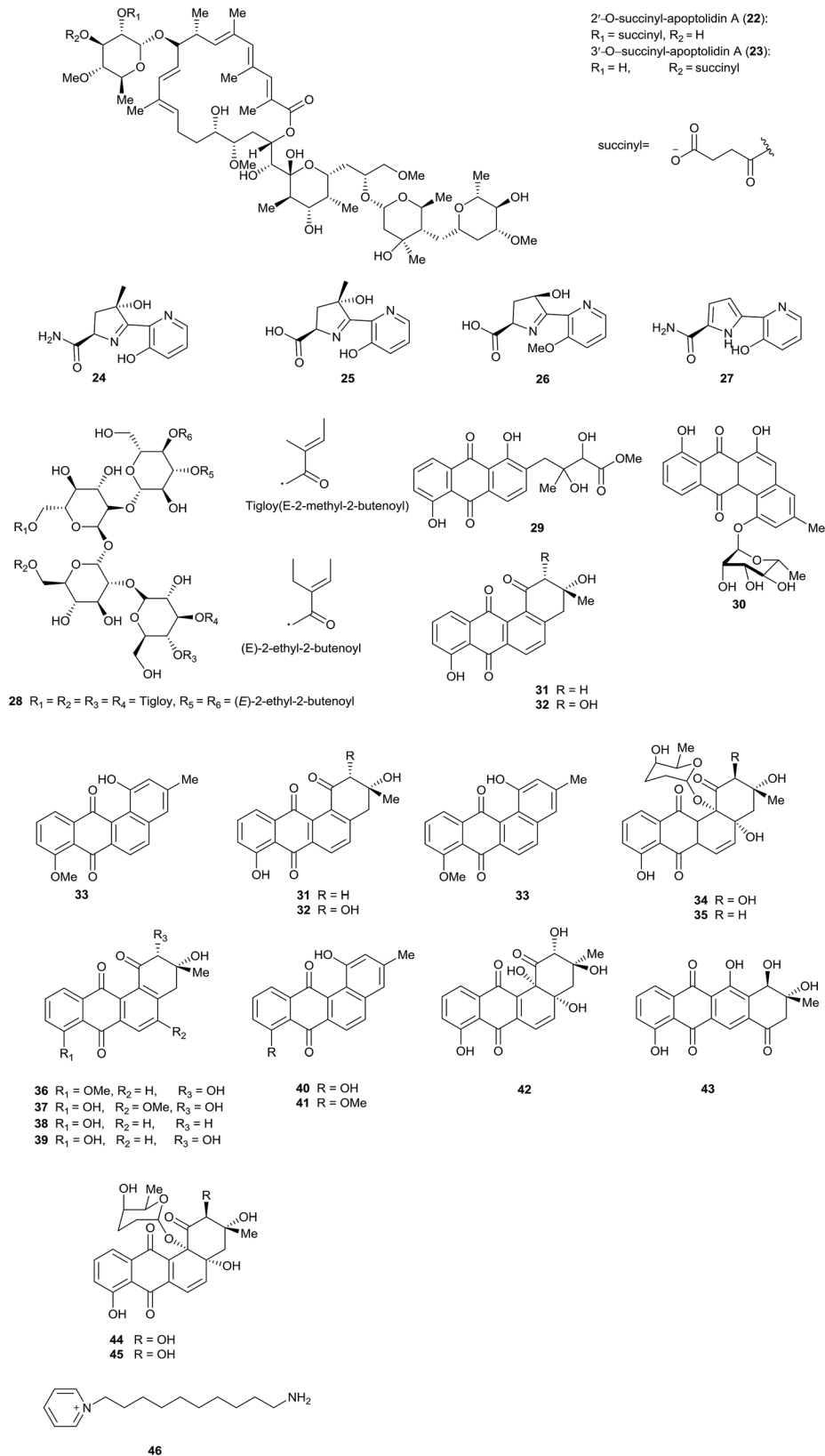
*Actinoplanes*, *Saccharopolyspora*, *Streptosporangium*, *Actinokineospora*, *Microbispora*, *Lechevalieria*, *Planomonospora*, *Microbacterium*, *Kribbella*, *Dietzia timorensis*, *Catenuloplanes*, *Catenulispora* and *Actinoalloteichus*. Soil and insects are the main sources of rare actinomycetes in this review. Beyond these, plants are also important sources.

## 2 Chemistry and biological activity

### 2.1 Secondary metabolites from *Amycolatopsis*

Pradimicin-IRD (1), a new polycyclic antibiotic, was produced by *Amycolatopsis* sp. IRD-009, which was isolated from the soil of an area of Brazilian rainforest undergoing restoration. Pradimicin-IRD showed antimicrobial activity against many



Fig. 1 Secondary metabolites from *Amycolatopsis*.

bacteria, such as *Streptococcus agalactiae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* (all MICs were  $3.1 \mu\text{g mL}^{-1}$ ). Beyond that, the compound also showed strong cytotoxicity

properties against HCT-116 colon carcinoma cells with an  $\text{IC}_{50}$  value of  $0.8 \mu\text{M}$  and against MM 200 melanoma cells with an  $\text{IC}_{50}$  value of  $2.7 \mu\text{M}$  (Fig. 1).<sup>7</sup>



From the rare actinomycete *Amycolatopsis* sp. K16-0194, a new compound named dipyrimicin B (2) was isolated *via* an interaction with Si-ES resin. In addition, another analog, dipyrimicin A (3), was also found without using Si-ES resin. Dipyrimicin A showed strong antimicrobial activity against *Saccharomyces cerevisiae* ATCC 9763, *Kocuria rhizophila* ATCC 9341 and *Escherichia coli* NIHJ at a dose of 30  $\mu\text{g}$ . It also showed significant cytotoxicity against HeLa 3S, A549, THP-1, Jarkat and HL-60 cells with  $\text{IC}_{50} \leq 5 \mu\text{M}$ . However, dipyrimicin B exhibited distinctly poor cytotoxicity and antimicrobial activity. The authors thought the differences in carboxyl and amide groups between the dipyrimicin species is the first factor involved in determining the cytotoxicity and antimicrobial activity.<sup>8</sup>

Xiao *et al.* isolated five unusual macrolactams rifamorpholines A–E (4–8) with an unprecedented 5/6/6/6 ring chromophore structure, representing a new subclass of rifamycin antibiotics. The compounds were produced by *Amycolatopsis* sp. HCa4, isolated from the guts of locusts (*Locusta migratoria*). Rifamorpholines B and D showed significant activities towards methicillin-resistant *Staphylococcus aureus* (MRSA) (MICs = 4.0 and 8.0  $\mu\text{M}$ , respectively).<sup>9</sup> Two novel enediyne-derived natural products, amycolamycin A and B (9–10) with a special 2-(cyclopenta[*a*]-inden-5-yl) oxirane core also were characterized from the same rare actinomycete *Amycolatopsis* sp. HCa4. Amycolamycin A possessed cytotoxic activity ( $\text{IC}_{50} = 7.9 \mu\text{M}$ ) against the M231 cell line. With flow cytometry and Western blot analysis, it was demonstrated that amycolamycin A suppressed the proliferation of M231 cells through inducing apoptosis through the activation of caspase-3.<sup>10</sup> Li *et al.* isolated two new abscisic acid-type sesquiterpenes (11–12) and one new ansamycin (13), together with four known ansamycins from *Amycolatopsis alba* DSM 44262. However, all of these examples showed no evident bacterial inhibition.<sup>11</sup>

Hashizume *et al.* discovered a novel cyclic depsipeptide, valgamycin C (14), containing the extremely rare amino acid cleonine and the related valgamycin compounds A, T and V (15–17) from *Amycolatopsis* sp. ML1-hF4. This is the first report of a cleonine-containing metabolite isolated from a naturally isolated microorganism. Compound 16 showed mild cytotoxicity against human tumor cell lines (MIA Paca 2, HGC-27, NCI-H1650, NB16 and ME-180) with  $\text{IC}_{50}$  values from 6.6 to 21.6  $\mu\text{M}$ .<sup>12</sup>

*Amycolatopsis* sp. M39 was discovered from a *Macrotermes natalensis* colony in a termite worker. The strain produced four new 20-membered glycosylated polyketide macrolactams, named macrotermycin A–D (18–21). Macrotermycin A displayed antimicrobial activity against *Bacillus subtilis* ATCC 6051, *Staphylococcus aureus* ATCC 25923, *Candida albicans* ATCC 24433 and *Saccharomyces cerevisiae* ATCC 9763 ( $\text{IC}_{50} = 1, 1.5, 10$  and 5  $\mu\text{g mL}^{-1}$ , respectively).<sup>13</sup>

*Amycolatopsis* sp. ICBB 8242, isolated from a unique black water ecosystem on the island of Borneo in Indonesia, produced two new apoptolidins, 2'-O-succinyl-apoptolidin A (22) and 3'-O-succinyl-apoptolidin A (23). These compounds can remarkably suppress the proliferation and viability of human H292 ( $\text{IC}_{50}$ s values: 91 and 82 nM, respectively) and HeLa cells ( $\text{IC}_{50} = 240$  and 260 nM, respectively).<sup>14</sup>

*Via* a bioassay-guided fractionation and isolation process, three new siderochelins, named siderochelin D (25), E (26), and F

(27), along with the known siderochelin A (24), were obtained from *Amycolatopsis* sp. LZ149 isolated from the rhizosphere of *Cynodon dactylon* collected at Baicheng beach in Xiamen.<sup>15</sup> Chemical analysis of the strain *Amycolatopsis* sp. HCa1, which came from the guts of grasshoppers (*Oxya chinensis*), led to the isolation of many chemical constituents. At first, a new tetrasaccharide derivative, actinotetraose L (28), was discovered by Guo *et al.* But the compound was not shown to display potent immunosuppressive activity and cytotoxicity from T-cell viability and MTT assays.<sup>16</sup> One new angucyclinone derivative, amycomycin A (29), and one new angucycline, amycomycin B (30), along with 5 known compounds, tetrangomycin (31), PD116779 (32), X-14881E (33), sakyomicin A (34) and sakyomicin C (35), also were isolated from the rare actinobacterium *Amycolatopsis* sp. HCa1. Compound 35 displayed moderate cytotoxic activity against the human tumor cell lines BGC 823, HepG2, and A375 ( $\text{IC}_{50}$  values: 11.03, 17.36 and 17.5  $\mu\text{M}$ , respectively).<sup>17</sup> The same rare actinobacterium also yielded two new angucyclines, named (2*R*,3*R*)-2-hydroxy-8-O-methyl-tetrangomycin (36) and (2*R*,3*R*)-2-hydroxy-5-O-methyltetrango-mycin (37), together with eight known compounds (38–45). Compounds 38, 39, 43 and 44 displayed significant cytotoxic activities against HeLa cells and the  $\text{IC}_{50}$  values were 0.27, 0.11, 0.56, and 0.39  $\mu\text{M}$ , respectively.<sup>18</sup>

The marine actinomycete *Amycolatopsis alba* var. nov. DVR D4 produced a novel pyridinium compound, 1-(10-aminodecyl) pyridinium (46). The strain was obtained in marine sediment

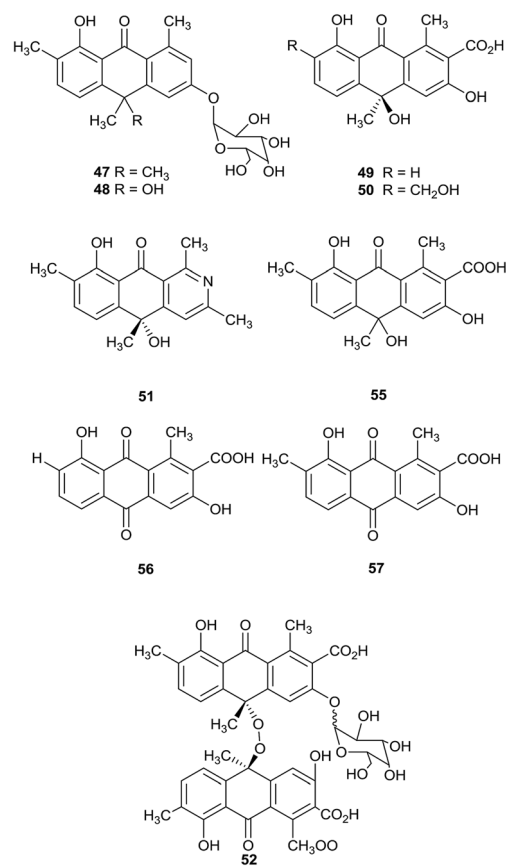


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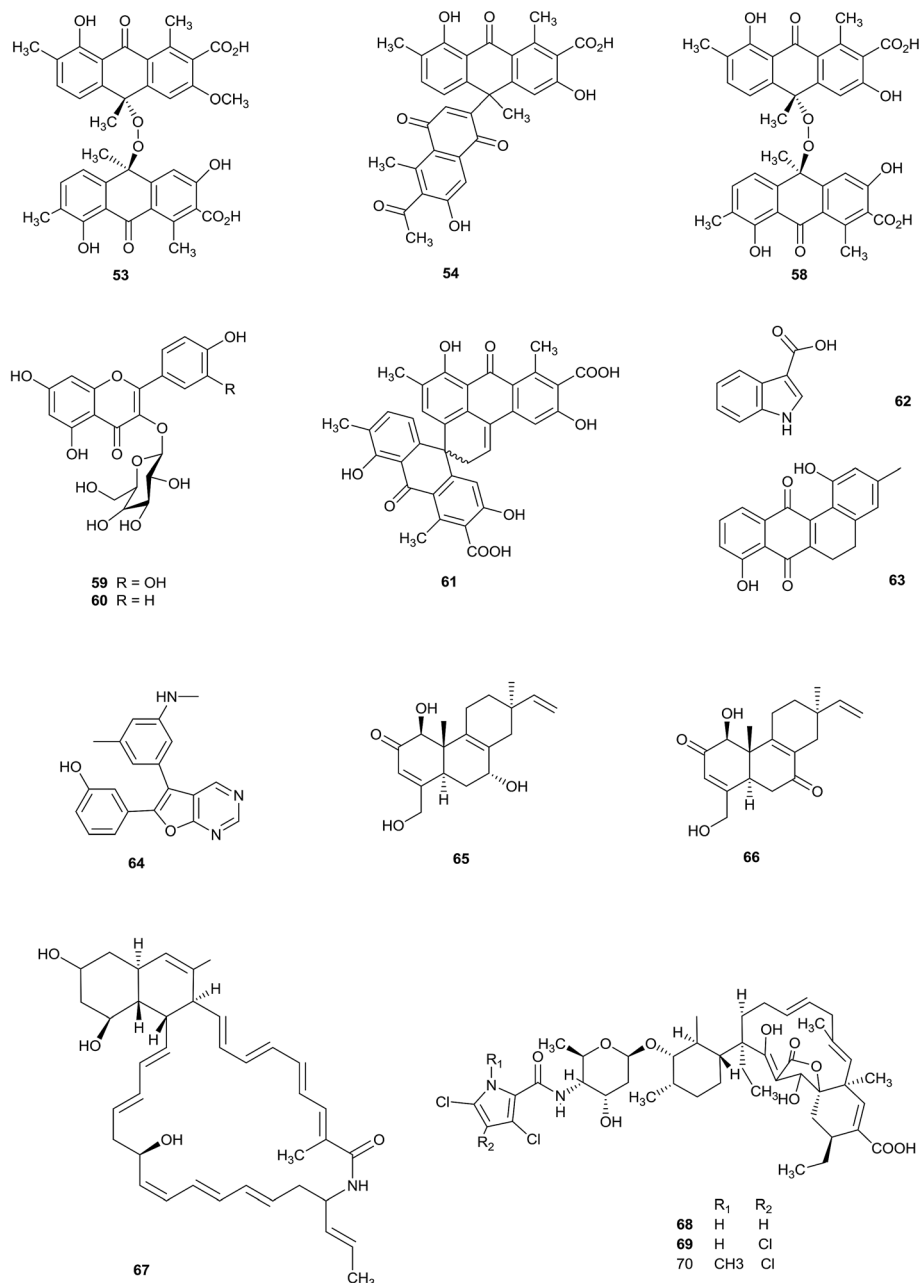


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samples. 1-(10-Aminodecyl)pyridinium showed potent cytotoxicity against HeLa, MCF-7 and U87MG *in vitro* and it also possessed antibacterial activities against Gram-negative and Gram-positive bacteria.<sup>19</sup>

## 2.2 Secondary metabolites from *Actinomadura* (Fig. 2)

The fermentation of *Actinomadura* sp. BCC47066 isolated from soil from Thailand produced eight new anthrone derivatives, (+)-oxanthromicin E (47), F (49), and G (50), (±)-hemi-oxanthromicin D (48), azanthromicin A (51), adxanthromicin A2 (52), 3-methoxy oxanthromicin (53), and (±)-oxanthromicin G (54), along with eight known compounds (55–62).

Adxanthromicin A2 and compounds 58 and 61 possessed anti-*Bacillus cereus* activity (IC<sub>50</sub> values were in the range of 1.56–12.50 µg mL<sup>-1</sup>). In addition, compounds 52 and 58 also showed anti-phytopathogenic activity against *Colletotrichum capsici* and *C. gloeosporioides* (the IC<sub>50</sub> values were all 6.25 µg mL<sup>-1</sup>).<sup>20</sup>

5,6-Dihydro-1,8-dihydroxy-3-methylbenz[*a*]anthracene-7,12-quinone (63), previously reported as an intermediate in the synthesis of tetrangulol, has been isolated from *Actinomadura* sp. DS-MS-114. Deep-sea sediment from Sagami Bay was the habitat of the strain. Compound 63 exhibited antibacterial activity against *S. aureus* NBRC12732T and its inhibition zone was 12.7 mm at 100 µg.<sup>21</sup>





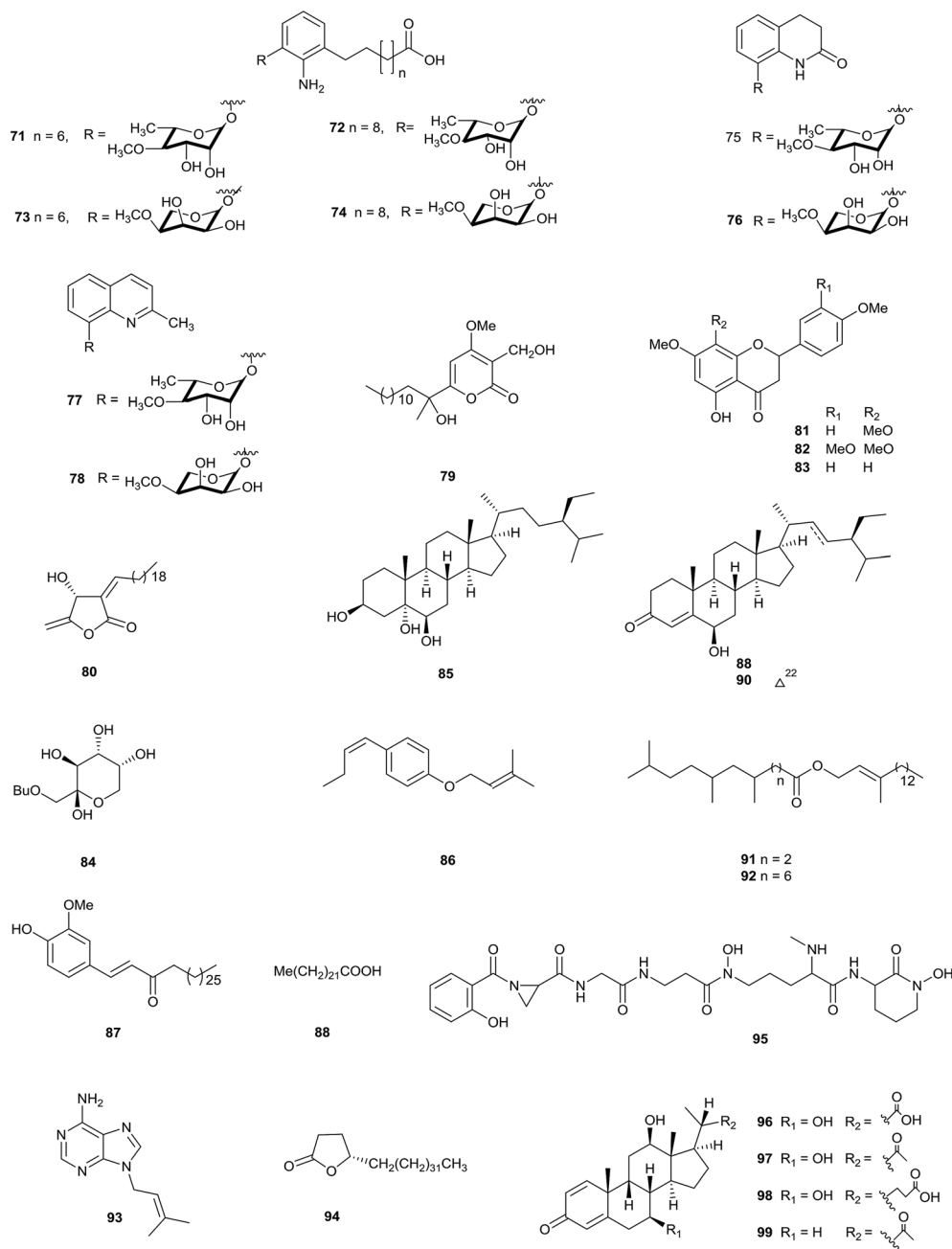


Fig. 2 Secondary metabolites from *Actinomadura*.

Upon the screening of antibacterial endolithic actinobacteria from a granite rock sample, Bhattacharjee *et al.* separated the rare actinomycete *Actinomadura* sp. AL2. A novel antibacterial compound CCP1 (**64**) was characterized from *Actinomadura* sp. AL2 culture. CCP1 showed antimicrobial activity towards *Bacillus subtilis* (MIC = 2.00  $\mu\text{g mL}^{-1}$ ). From *in silico* studies relating to its ability to bind DNA gyrase and 30S RNA molecules, researchers found that the compound demonstrated more favorable docking with DNA gyrase, 30S RNA molecules and OmpF porins.<sup>22</sup>

A new secondary metabolite actinomadurol (**65**), a rare member of the bacterial C-19 norditerpenoid class, and

a known compound JBIR-65 (**66**) were reported from cultures of *Actinomadura* strain KC 191, isolated from a soil sample. Actinomadurol displayed significant antibacterial activity against *Staphylococcus aureus*, *Proteus hauseri* and *Kocuria rhizophila* (MICs = 0.39–0.78  $\mu\text{g mL}^{-1}$ ), but JBIR-65 did not show antimicrobial activity.<sup>23</sup> Sagamilactam (**67**) is a new polyene macrocyclic lactam, which was separated from *Actinomadura* sp. K13-0306 isolated from a soil sample collected in Kanagawa Prefecture, Japan. With strong antitrypanosomal activity, its IC<sub>50</sub> value was 0.25  $\pm$  0.11  $\mu\text{M}$ .<sup>24</sup>

From a soil sample, the rare actinobacterium *Actinomadura* sp. 2EPS was isolated. The strain produced three known



compounds as spirotetronate antibiotics, BE-45722A (**68**), BE-45722B (**69**) and BE-45722C (**70**). The three compounds all possessed potent antibacterial activity against Gram-positive bacteria, *Staphylococcus aureus* ATCC 25923, *Bacillus cereus* ATCC 14579, and *B. subtilis* ATCC 6633 (MICs = 0.08–5.0  $\mu\text{g mL}^{-1}$ ). Moreover, both **68** and **70** also displayed significant inhibitory activities against *Clostridium perfringens* S107 (all MICs = 0.63  $\mu\text{g mL}^{-1}$ ) and *C. difficile* 630 (all MICs = 0.08  $\mu\text{g mL}^{-1}$ ). This is the first report of spirotetronate antibiotics possessing activity against pathogenic *Clostridium* spp.<sup>25</sup>

*Actinomadura* sp. BCC27169 obtained from soil (from Nam Nao National Park, Phetchabun province) was the source of eight new 3-oxyanthranilic acid derivatives (**71–78**). Compounds **73** and **78** had antitubercular activity (MIC = 50  $\mu\text{g mL}^{-1}$ ). Only compound **73** displayed cytotoxicity against KB cells with an  $\text{IC}_{50}$  value of 18.63  $\mu\text{g mL}^{-1}$ .<sup>26</sup>

A previously undescribed  $\gamma$ -pyrone, miaolienone (**79**), and a new butanolide, miaolinolide (**80**), along with 13 known compounds (**81–93**), were obtained from *Actinomadura miaoliensis* BCRC 16873, which was isolated from a soil sample collected in Miaoli County, Taiwan. Compounds **79** and **80** could inhibit the production of TNF- $\alpha$  in U937 cells *in vitro* significantly, and the  $\text{IC}_{50}$  values were 0.59 and 0.76  $\mu\text{M}$ , respectively. Compounds **81–85** showed mild inhibitory activities towards LPS-induced TNF- $\alpha$  production.<sup>27</sup> The same rare actinomycete also yielded one new  $\gamma$ -lactone, actinomialone (**94**), along with seven known compounds, 3,4-methylenedioxy-5-methoxycinnamyl alcohol, myristic acid, casticin, (+)-glaberride I, (+)-syringaresinol, (+)-yangambin, and *trans*-cinnamaldehyde.<sup>28</sup>

From chemical research into the rare actinomycete *Actinomadura* sp. DSMZ 13491, a bioactive metabolite madurastatin C1 (**95**) was obtained.<sup>29</sup> Fermentation of *Actinomadura* sp. SBMs009 from tissue sections of the marine sponge *Suberites japonicas* produced three 3-keto sterols, bendigole D–F (**96–98**), along with the previously described bendigole B (**99**). Bendigole D displayed cytotoxicity against the L929 cell line with an  $\text{IC}_{50}$  value of 30  $\mu\text{M}$  and it displayed significant inhibitory activity towards GR-translocation; at the same time, compound **98** was the most effective inhibitor of NF- $\kappa\text{B}$  nuclear translocation ( $\text{IC}_{50}$  = 71  $\mu\text{M}$ ).<sup>30</sup>

### 2.3 Secondary metabolites from *Nonomuraea*

*Nonomuraea* belongs to the Streptococcus family of actinomycetes, and soil and sediment are its main habitats. From 2009–2012, the number of new species belonging to this genus has increased with the addition of 12 novel species,<sup>31</sup> implying that *Nonomuraea* species could produce more new metabolites with significant biological activity (Fig. 3).

Two new metabolites, nonomuric acid (**100**) and 3-hydroxy deoxydaunorubicinol aglycone (**101**), together with two known compounds,  $\epsilon$ -rhodomycinone (**102**) and 7-deoxy-13-dihydrocarminomycinone (**103**), were separated from *Nonomuraea rhodomycinica* NR4-ASC07 from soil from the Sirindhorn peat swamp forest. Compounds **100** and **102** displayed antimalarial activity, and their  $\text{IC}_{50}$  values were 8.00 and 8.88  $\mu\text{g}$

$\text{mL}^{-1}$ , respectively. Meanwhile, compound **103** displayed inhibitory activity against *Mycobacterium tuberculosis* and *Bacillus cereus* with MIC values of 50.0 and 12.50  $\mu\text{g mL}^{-1}$ , respectively.<sup>32</sup>

Madurahydroxylactone (**104**), as a new inhibitor of *Staphylococcus aureus* FtsZ, and its derivatives **105–108** have been obtained from *Nonomuraea* sp. AN100570 from soil collected near Gongju city, Korea. Madurahydroxylactone showed potent antimultidrug-resistant bacterial activities against *S. aureus* FtsZ ( $\text{IC}_{50}$  value of 53.4  $\mu\text{M}$ ), *S. aureus* and MRSA (all MIC values: 1  $\mu\text{g mL}^{-1}$ ). In cell division phenotype assays, compound **104** could induce cell elongation, suggesting that madurahydroxylactone exerted potent antibacterial activity against FtsZ.<sup>33</sup>

An investigation into secondary metabolites from the culturing of *Nonomuraea* species from the soil of a hypogeal ecosystem afforded a new S-bridged pyronaphthoquinone dimer, hypo-geamicin A (**109**), along with its monomeric precursors hypo-geamicin B–D (**110–112**). Compound **109** had significant cytotoxic activity against the colon cancer derived cell line TCT-1 with  $\text{IC}_{50}$  = 6.4–12.8  $\mu\text{M}$ , but it did not show antibacterial activity. On the contrary, its monomeric precursors did not showed observable

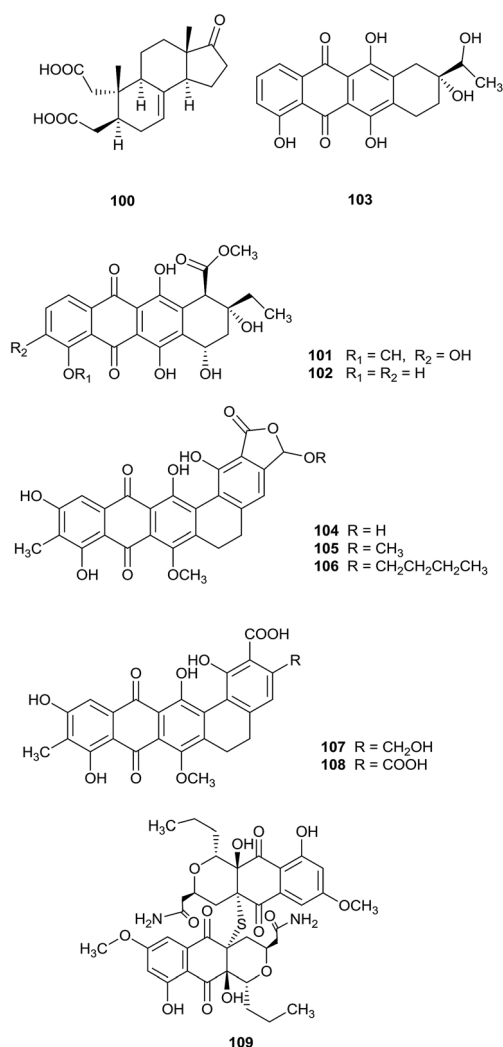


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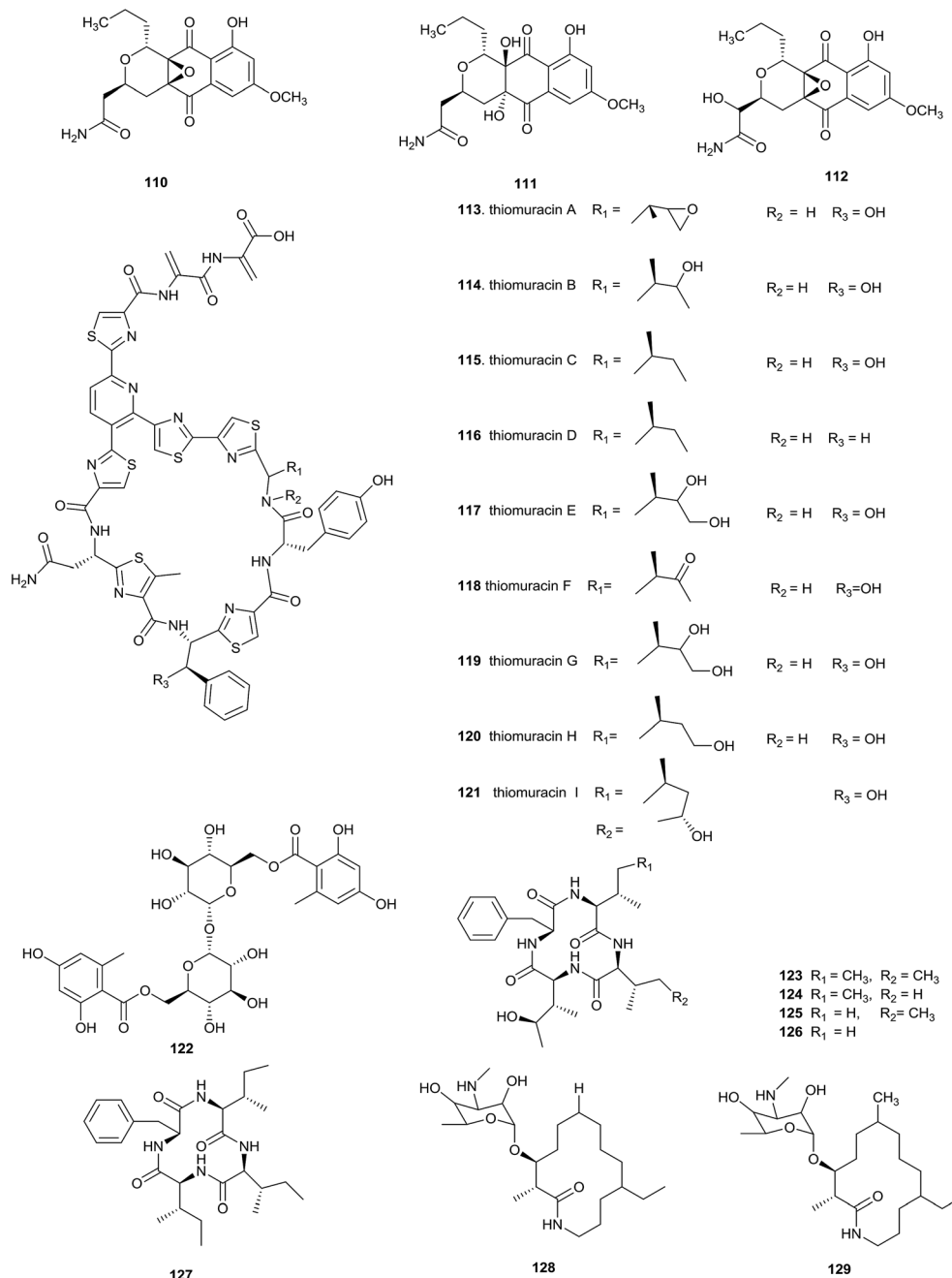


Fig. 3 Secondary metabolites from *Nonomuraea*.

cytotoxicities but possessed antimicrobial activities towards *B. subtilis* ( $MIC = 7\text{--}28 \mu\text{g mL}^{-1}$ ).<sup>34</sup>

A novel family of thiopeptides, thiomuracin A–H (**113–121**), which are decorated with thiazoles and defined by a central six-membered heterocyclic ring system, has been obtained from *Nonomuraea* strain Bp3714-39. The complicated biosynthetic pathway to this class of antibiotics was revealed through mining the genomes of thiopeptide-producing strains.<sup>35</sup>

A new trehalose-derived metabolite, brartemicin (**122**), was found from *Nonomuraea* strain TP-A0870. The strain was

separated from a dried leaf of *Artemisia vulgaris* L. The compound possessed inhibitory activity towards the invasion of murine colon carcinoma 26-L5 cells ( $IC_{50} = 0.39 \mu\text{M}$ ) in a concentration-dependent manner and showed no cytotoxic effects.<sup>36</sup>

Five new cyclic tetrapeptides, **123–127**, were separated by Terui *et al.* from *Nonomuraea* sp. TA-0426 from a soil sample collected in Henan province, China. Compounds **124–127** exhibited potent inhibitory activity towards GlyT1. A preliminary structure–activity relationship (SAR) study demonstrated that a cyclic tetrapeptide structure is necessary for inhibitory activity towards GlyT.<sup>37</sup>





Two new macrolactams, 6-desmethyl-*N*-methylfluvirucin A1 (**128**) and *N*-methylfluvirucin A1 (**129**), have been obtained from *Nonomuraea turkmeniaca* MA7364, which was isolated from a soil sample collected in Mexico. 6-Desmethyl-*N*-methylfluvirucin A1 showed activity against *Haemonchus contortus* larvae *in vitro* with an EC<sub>90</sub> value of  $15 \pm 5 \mu\text{g mL}^{-1}$ .<sup>38</sup>

## 2.4 Secondary metabolites from *Pseudonocardia*

The deep sea is a potential source of new antibiotics, because it is an extreme environment with high pressure, low temperature, darkness, high salinity, and low oxygen concentrations.<sup>39</sup> Two new macrolide antibiotics, branimycin B (**130**) and C (**131**), were reported from a culture of *Pseudonocardia carboxydivorans* M-227, which was isolated from a water column at a depth of 3000 m in the Cantabrian Sea. These compounds showed antibacterial activities against Gram-positive bacteria, including *Corynebacterium urealyticum* (MIC values of 8 and  $16 \mu\text{g mL}^{-1}$ , respectively), *Clostridium perfringens* (MIC values of 32 and  $16 \mu\text{g mL}^{-1}$ , respectively), and *Micrococcus luteus* (MIC values of 1 and  $16 \mu\text{g mL}^{-1}$ , respectively), and against the Gram-negative bacterium *Neisseria meningitidis* (MIC values of 32 and  $64 \mu\text{g mL}^{-1}$ , respectively). In addition, branimycin B exhibited mild antibacterial activity against other Gram-negative bacteria, such as *Bacteroides fragilis* (MIC =  $32 \mu\text{g mL}^{-1}$ ), *Haemophilus influenza* ATCC 492471 (MIC =  $32 \mu\text{g mL}^{-1}$ ), and *Escherichia coli* (MIC =  $64 \mu\text{g mL}^{-1}$ ). At the same time, branimycin C displayed antimicrobial activity toward the Gram-positive *Enterococcus faecalis* 10544 (MIC =  $64 \mu\text{g mL}^{-1}$ ) and methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (for *Staphylococcus aureus* ATCC 25923, MIC =  $64 \mu\text{g mL}^{-1}$ ; for *Staphylococcus aureus* ATCC 6538P, MIC =  $32 \mu\text{g mL}^{-1}$ ) (Fig. 4).<sup>40</sup>

Seven new  $\gamma$ -butyrolactones, pseudonocardide A–G (**132**–**138**), were isolated from *Pseudonocardia* sp. YIM M13669. The strain was isolated from a marine sediment sample from the South China Sea (2448 m depth). From paper disc diffusion assays, none of the compounds showed antimicrobial activity against *M. smegmatis* MC2155 at  $30 \mu\text{g}$  per disc.<sup>41</sup>

*Pseudonocardia* sp. HS7, isolated from the cloacal aperture of sea cucumber (*Holothuria moebii*), produced an unknown macrolide curvularin-7-*O*- $\alpha$ -D-glucopyranoside (**141**) with a rare  $\alpha$ -D-glucopyranose substituent, and four other curvularin macrolides (**139**–**140**, **142**–**143**). Compound **142** showed potential cytotoxicity toward six tested cancer cell lines (C6, U87-MG, SHG-44, U251, HCT-15 and SW620), and the IC<sub>50</sub> values were from 0.59 to  $3.39 \mu\text{M}$ .<sup>42</sup>

From a chemical study of *Pseudonocardia* sp. EC080529-01, which was isolated from the fungus-growing ant *Apterostigma dentigerum*, pseudonocardone A–C (**144**–**146**) were yielded as new members of the angucycline class of antibiotics, together with the known antibiotics 6-deoxy-8-*O*-methylrabelomycin (**147**) and X-14881 E (**148**). Compounds **147** and **148** had antibacterial activity against *Bacillus subtilis* 3610 (MIC values of 25 and  $3.13 \mu\text{g mL}^{-1}$ , respectively) and liver-stage *Plasmodium berghei* (IC<sub>50</sub> = 18.5 and  $3.0 \mu\text{M}$ , respectively).<sup>43</sup>

Three new diazaanthraquinone derivatives, pseudonocardian A–C (**149**–**151**), along with the previously synthesized compound deoxynyboquinone (**152**), were discovered from *Pseudonocardia* sp.

SCSIO 01299. The habitat of this strain was a sediment sample from a depth of 3258 m from the South China Sea. Interestingly, most of the diazaanthraquinone species showed strong antitumor or antibacterial activities, which highlighted their potential for drug development. From bioassays, pseudonocardian A–C displayed significant cytotoxicities towards the three tumor cell lines SF-268, MCF-7 and NCI-H460 (IC<sub>50</sub> values between 0.01 and  $0.21 \mu\text{M}$ ), and they also displayed antibacterial activities towards *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Bacillus thuringiensis* SCSIO BT01 (MIC =  $1\text{--}4 \mu\text{g mL}^{-1}$ ).<sup>44</sup>

## 2.5 Secondary metabolites from *Micromonospora*

A novel benzo[*b*]fluorene compound, nenestatin A (**153**), was isolated from *Micromonospora echinospora* SCSIO 04089, obtained

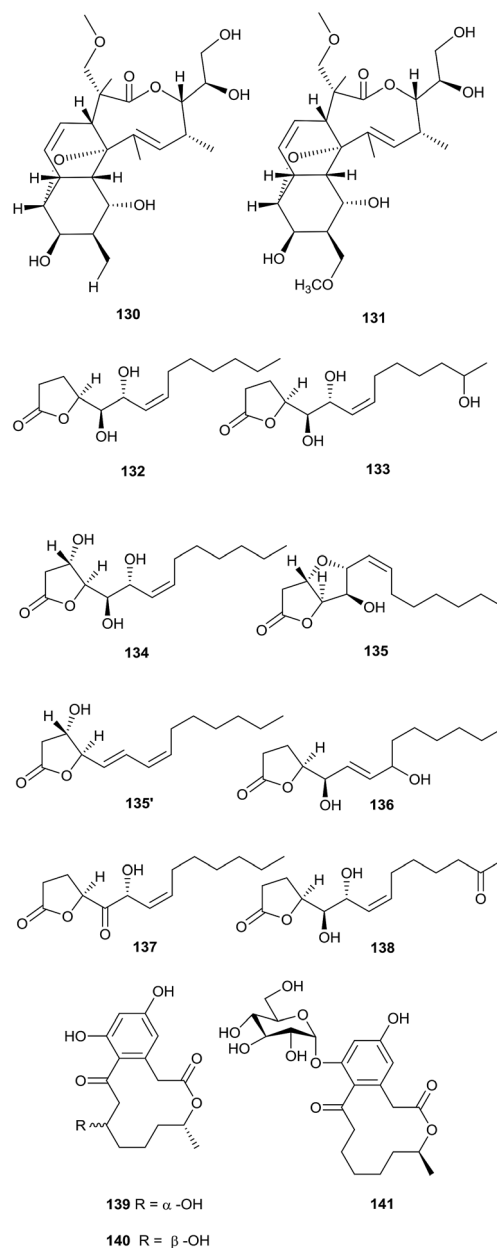


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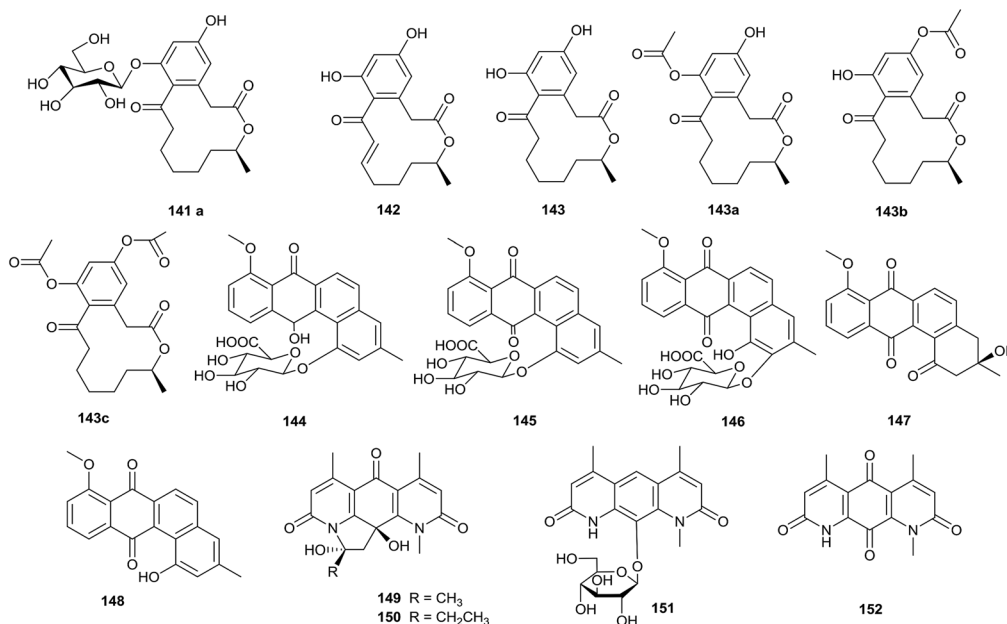


Fig. 4 Secondary metabolites from *Pseudonocardia*.

from the deep sea. Interestingly, the biosynthetic intermediate homo-dehydrabelomycin E (**154**) was also afforded *via* gene disruption experiments *in vivo*, which verified the biosynthetic gene cluster of nenestatin A (Fig. 5).<sup>45</sup>

FW05328-1 (**155**) is a new 26-membered polyene macrolactam, which was discovered from *Micromonospora* sp. FIM05328. The strain was separated from a soil sample collected from the East China Sea. A known compound, aurodox (**156**), was also

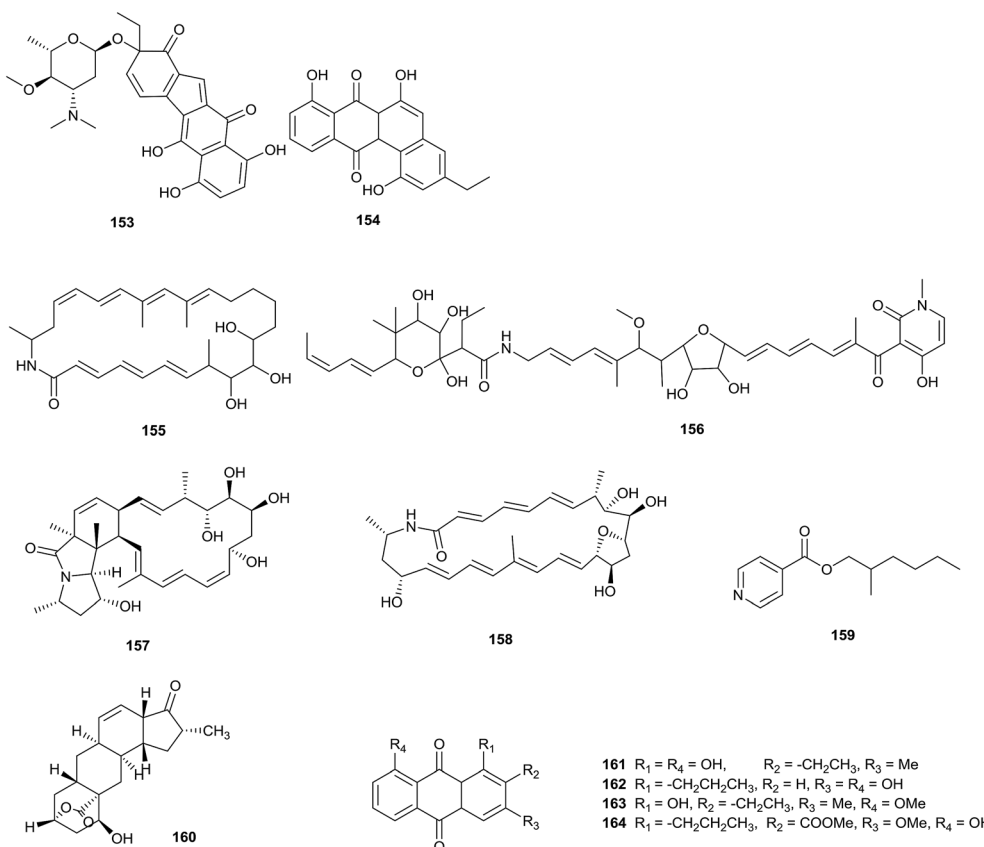


Fig. 5 Secondary metabolites from *Micromonospora*.



identified during the same experiment. Compounds **155** and **156** displayed fantastic antiproliferative activities towards KYSE30, KYSE180 and EC109 human tumor cell lines.<sup>46</sup>

Two novel macrolactams, dracolactam A (**157**) and B (**158**), were obtained from a combined-culture of *Micromonospora* species and *Tsukamurella pulmonis* TP-B0596, which is a mycolic-acid containing bacterium (MACB). The combined-culture was proposed by Bode in a one-strain-many-compounds (OSMAC) strategy, which is aimed at increasing the number of secondary metabolites from a single microbial source.<sup>47</sup> In this work, the cryptic oxidase genes of *Micromonospora* species were activated by MACB, which maybe induced downstream polyene macrolactam cyclization.<sup>48</sup>

An oily bioactive compound, 2-methylheptylisonicotinate (**159**), was obtained from *Micromonospora auratinigra* HK-10, isolated from a soil sample from an Indo-Burma biodiversity hotspot in Northeast India. 2-Methylheptylisonicotinate showed antimicrobial activity against *Staphylococcus aureus*,

*Bacillus subtilis*, *Proteus vulgaris*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Mycobacterium abscessus* (MIC values of 70, 40, 80, 60, 60, and 50  $\mu\text{g mL}^{-1}$ , respectively).<sup>49</sup>

The rare actinomycete *Micromonospora* sp. NPS2077, separated from an unidentified marine sponge (from Uranouchi Bay, Kochi, Japan), was the source of a novel  $\beta$ -hydroxyl- $\delta$ -lactone compound, neomacquarimicin (**160**). The compound did not show significant inhibitory activity against human acidic sphingomyelinase and rat neutral sphingomyelinase at 0.07–700  $\mu\text{M}$ . Meanwhile, it showed no potential activity against *Bacillus subtilis* ATCC 43223 and *Escherichia coli* ATCC 10536 at concentrations ranging from 50 to 0.50  $\mu\text{M}$ .<sup>50</sup>

Two new anthraquinone derivatives, 2-ethyl-1,8-dihydroxy-3-methyl-anthraquinone (**161**) and 3,8-dihydroxy-1-propylantraquinone (**162**), along with two known anthraquinone derivatives (**163–164**), were produced from *Micromonospora rhodorangae* isolated from marine soil.<sup>51</sup>

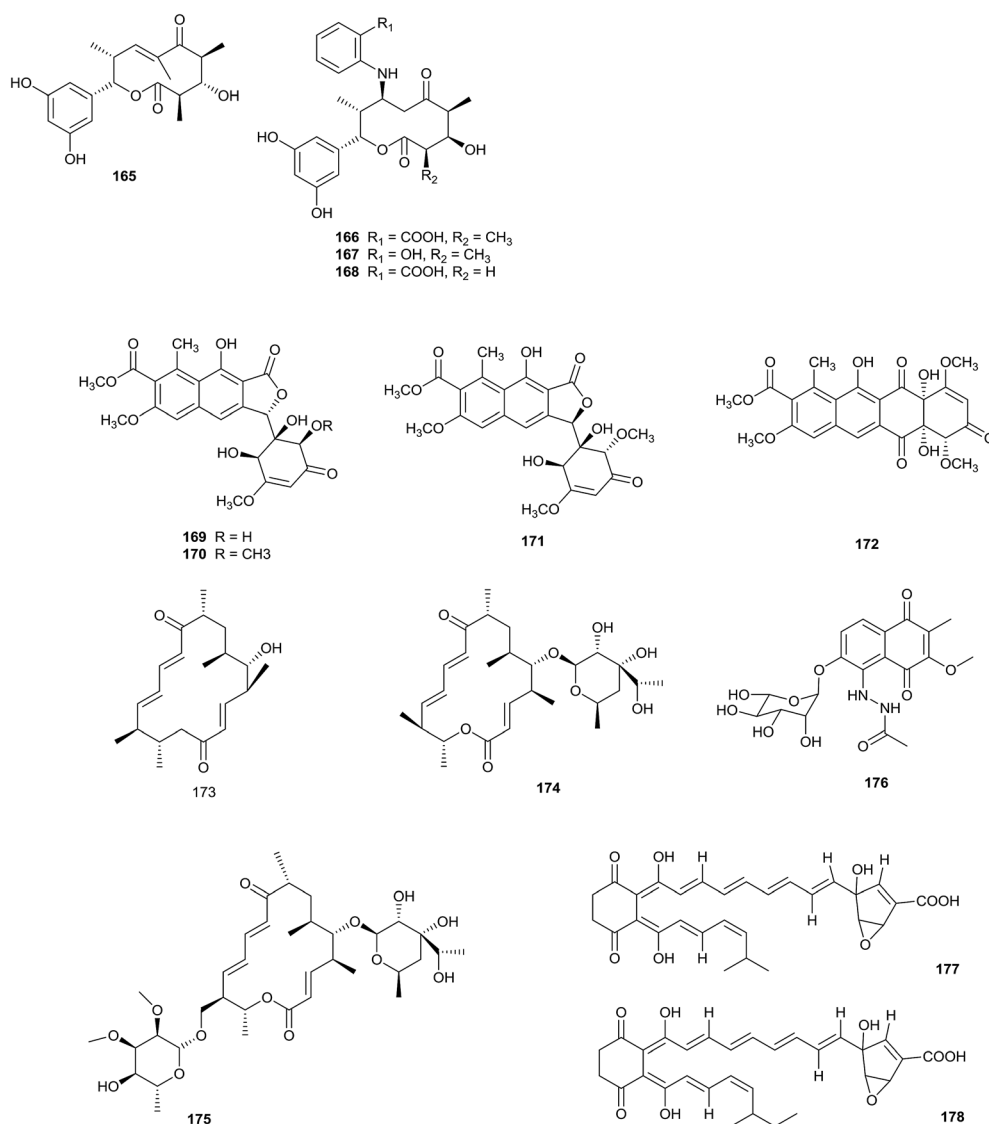


Fig. 6 Secondary metabolites from *Saccharothrix*.



## 2.6 Secondary metabolites from *Saccharothrix*

The highly reactive precursor molecule presaccharothriolide X (165) was separated from *Saccharothrix* sp. A1506. Through Michael addition, saccharothriolide B (166) exhibited unique masking/activating properties towards 2-aminophenol. From a SAR study involving human fibrosarcoma HT1080 cells and fission yeast cells, presaccharothriolide X was proposed to be the real source of the cytotoxicity of compound 166 (Fig. 6).<sup>52</sup>

An investigation into secondary metabolites from a culture of the rare actinomycete *Saccharothrix* sp. A1506 (from a soil sample) yielded three new 10-membered macrolides, saccharothriolide D–F (166–168). Compounds 167 and 168 displayed cytotoxicity towards human fibrosarcoma HT1080 cells with  $IC_{50}$  values of 29.2 and 66.4  $\mu M$ , respectively.<sup>53</sup>

Saccharothrixone A–C, as new aromatic polyketide seco-tetracenomycins (169–171), and a new tetracenomycin analogue, saccharothrixone D (172), have been discovered from *Saccharothrix* sp. 10–10. The strain was separated from a marine sediment sample. Importantly, this is the first seco-tetracenomycin where the quinone ring B is cleaved and re-formed into a furanone ring. Saccharothrixone D exhibits cytotoxic activity towards the HepG2 cancer cell line ( $IC_{50} = 7.5 \mu M$ ).<sup>54</sup>

A chemical investigation into the crude extract of *Saccharothrix xinjiangensis* NRRL B-24321 led to the isolation of two new 16-membered macrolactone-type polyketides, tianchimycin A (173) and B (174), along with a known compound, swalpmycin B (175). From antibacterial screening, compound 174 displayed wonderful selective inhibition towards *Enterococcus faecalis* ATCC 29212 (MIC value of  $6.25 \mu g mL^{-1}$ ), while tianchimycin A and B displayed weaker antimicrobial activities than swalpmycin B.<sup>55</sup>

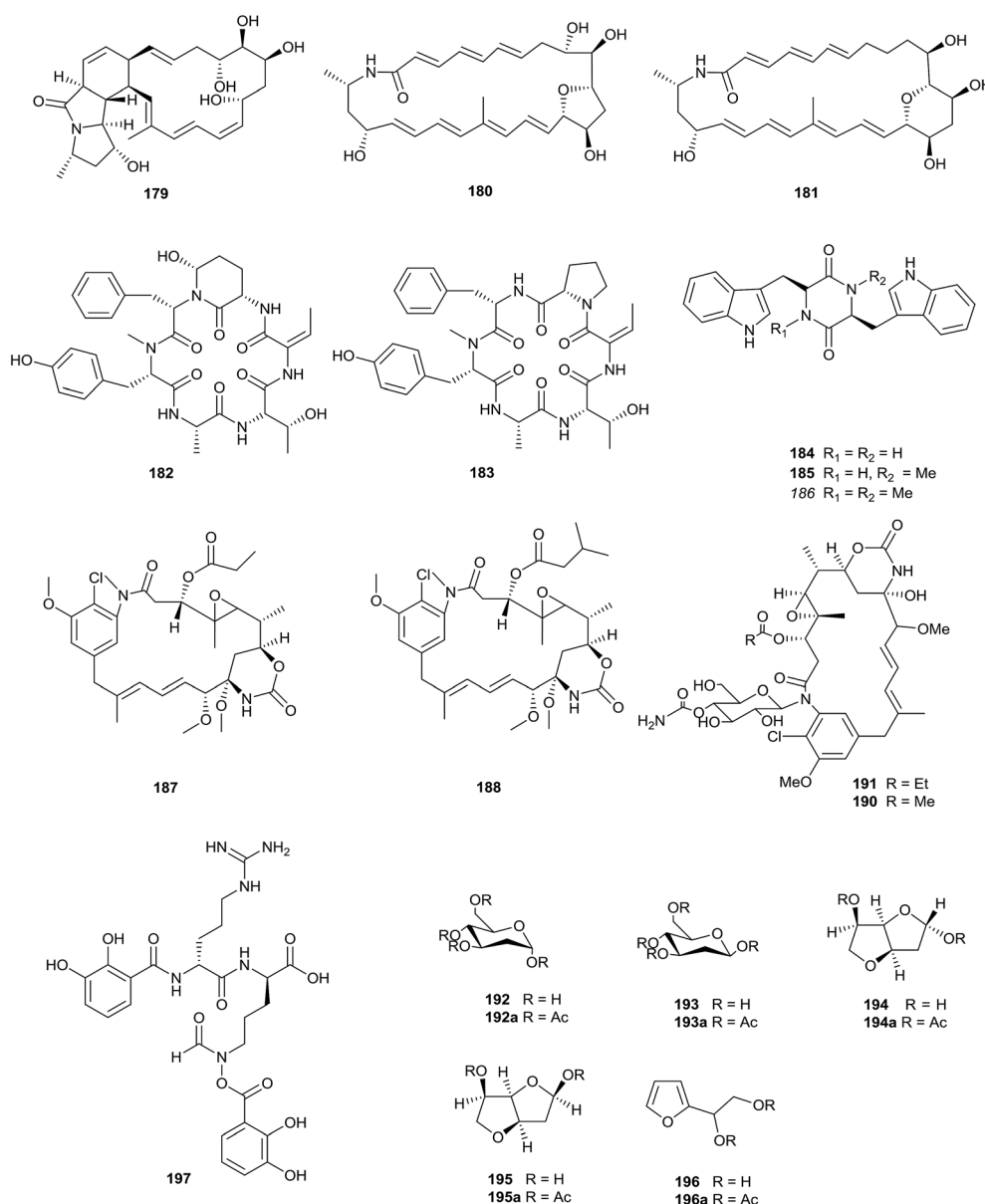


Fig. 7 Secondary metabolites from *Actinosynnema*.



Nakae *et al.* reported a new naphthoquinone derivative saccharthridine A (**176**) with an acetylhydrazino moiety, obtained from *Saccharothrix* sp. MI559-46F5 isolated from a soil sample collected from Higashikagawa, Kagawa Prefecture, Japan. As a prostaglandin release inhibitor, the compound showed inhibitory activity towards prostaglandin E2 release in human synovial sarcoma SW982 cells, without affecting cell growth.<sup>56</sup>

The new compounds A4 (**177**) and A5 (**178**) were reported from a culture of *Saccharothrix* SA198. The strain was discovered from a Saharan soil sample from Algeria. A4 and A5 showed significant inhibition towards the fungi *M. ramannianus* (MIC = 5–1  $\mu\text{g mL}^{-1}$ ), *A. carbonarius* (MIC values from 10 to 2  $\mu\text{g mL}^{-1}$ ) and *P. expansum* (all MIC values were 2  $\mu\text{g mL}^{-1}$ ).<sup>57</sup>

## 2.7 Secondary metabolites from *Actinosynnema*

Three novel polycyclic macrolactams, mirilactam C–E (**179–181**), were obtained from a combined culture of *Actinosynnema mirum* NBRC 14064 and the mycolic acid-containing bacterium, *Tsukamurella pulmonis* TP-B0596, which can activate cryptic natural product biosynthesis in co-cultures with actinobacteria. In 2017, Hoshino *et al.* also found two novel macrolactams, dracolactam A (**156**) and B (**157**), under co-culture conditions. None of the compounds displayed antimicrobial activity (towards *Candida albicans*, *Bacillus cereus*, and methicillin-sensitive *Staphylococcus aureus*) or cytotoxicity towards HeLa, MCF-7 and A549 at concentrations of up to 100  $\mu\text{M}$  (Fig. 7).<sup>58</sup>

The chemical analysis of *Actinosynnema pretiosum* ATCC31565 led to the isolation of two novel cyclic hexapeptides, actinosynneptide A (**182**) and B (**183**), along with three tryptophan-containing diketopiperazines (**184–186**). Importantly, actinosynneptide A was the first cyclic peptide to be reported that contained 3-amino-6-hydroxy-2-piperidone. Actinosynneptide A and B displayed mild cytotoxicities towards HeLa (IC<sub>50</sub> = 34.4 and 13.0  $\mu\text{M}$ ), PC3 (IC<sub>50</sub> = 31.0 and 19.8  $\mu\text{M}$ ) and HCT116 (IC<sub>50</sub> = 50 and 32.0  $\mu\text{M}$ ).<sup>59</sup> Two new ansamitocin analogs, maytansinol-9-methyl ether-3-propionate (**187**) and maytansinol-9-methyl ether-3'-methoxybutyrate (**188**), were isolated from *Actinosynnema pretiosum* FIM06-0063. However their bioactivities are unknown.<sup>60</sup>

*Actinosynnema pretiosum* ssp. *auranticum* ATCC 31565 could produce two new ansamitocins, *N*-(6-*O*-carbamoyl-*b*-D-glucopyranosyl)-*N*-demethylansamitocin P2 (**189**) and *N*-(4-*O*-carbamoyl-*b*-D-glucopyranosyl)-*N*-demethylansamitocin P1 (**190**), together with the known *N*-(*O*-carbamoylglucopyranosyl)ansamitocin (**191**).<sup>61</sup> The same rare actinomycete also yielded five special hexose derivatives, 2-deoxy- $\alpha$ -D-arabino-hexopyranose (**192**), 2-deoxy- $\beta$ -D-arabino-hexopyranose (**193**), 3,6-anhydro-2-deoxy- $\alpha$ -D-arabino-hexofuranose (**194**), 3,6-anhydro-2-deoxy- $\beta$ -D-arabino-hexofuranose (**195**), and 2-(D-glycerol-1,2-dihydroxyethyl)furan (**196**).<sup>62</sup>

Isolation of the rare actinomycete *Actinosynnema mirum* yielded a siderophore, named mirubactin (**197**), containing an *O*-acyl hydroxamic acid ester, which is a rare type of chemical functionality in secondary metabolites. Meanwhile, mirubactin is the first siderophore isolated from the genus *Actinosynnema*,

and a complete bioinformatic overview of the *mrB*-gene cluster has been demonstrated.<sup>63</sup>

## 2.8 Secondary metabolites from *Nocardia*

Eight different types of compound (**198–205**) have been discovered from *Nocardia* sp. YIM 64630, of which compound **198**, 5'-*O*-acetyl-2'-deoxyuridine, was a new natural nucleotide, seen for the first time. The rare actinomycete was isolated from healthy root tissue of *Tripterygium wilfordii*, which was collected in Kunming, in Yunnan province, China (Fig. 8).<sup>64</sup>

Chemical research into *Nocardia* sp. ML96-86F2, which was separated from a soil sample collected in Tokyo, led to the isolation of a new antitumor compound, intervenolin (**206**). Intervenolin displayed excellent antitumor activity through modulating the interactions between stromal cells and tumor cells, which can inhibit the progression of tumors. Towards HCT-15 cells and CCD-18Co stromal cells, the compound showed significant inhibitory activities at 25  $\text{mg kg}^{-1}$  in female nude mice. In addition, intervenolin displayed potent antimicrobial activities against *H. pylori*, *H. pylori* JCM12093 and *H. pylori* JCM12095 strains, with MIC values ranging from 0.016 to 0.008  $\mu\text{g mL}^{-1}$ .<sup>65</sup>

Nocardithiocin (**207**), a novel thiopeptide antibiotic with thiazole, and natural and unnatural amino acid moieties, was isolated from pathogenic *Nocardia pseudobrasilensis* IFM 0757 collected from a patient at the Health Center, University of Texas. It is difficult to isolate pathogenic actinomycetes, which makes pathogenic actinomycetes a relatively unknown resource for the discovery of novel bioactive compounds. Compound **207** displayed significant antimicrobial activities towards rifampicin-resistant and -sensitive *Mycobacterium tuberculosis* strains, most of which were inhibited at concentrations of 0.025–1.56  $\mu\text{g mL}^{-1}$ .<sup>66</sup>

Chemical research into the rare actinomycete *Nocardia alba* sp. nov, which was separated from a soil sample collected from

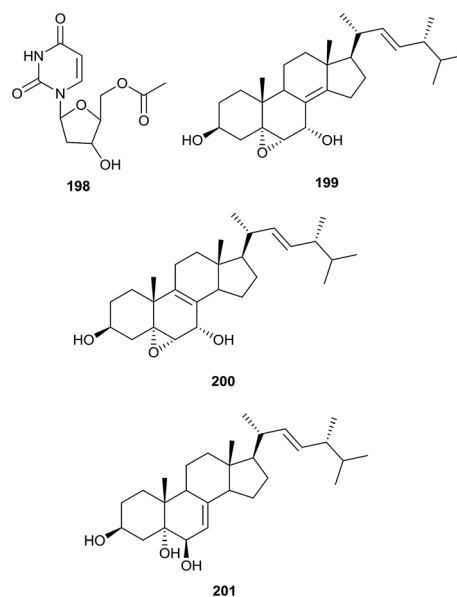


Fig. 8 (contd.)





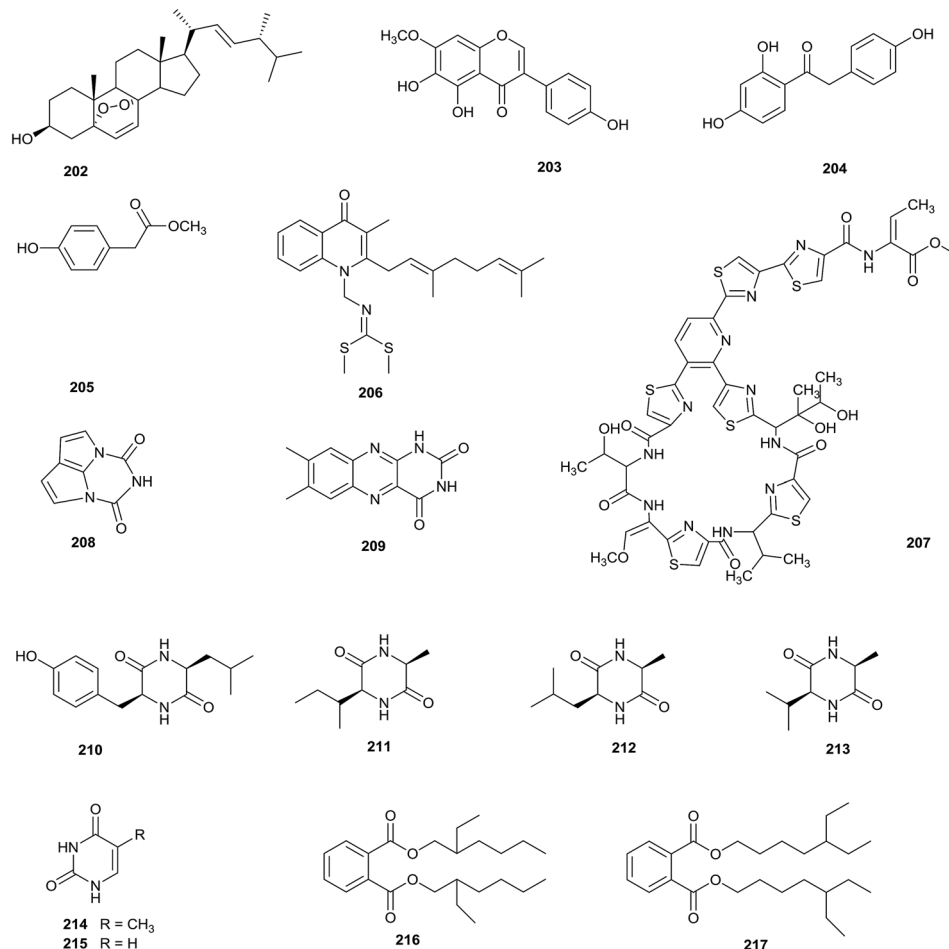


Fig. 8 Secondary metabolites from *Nocardia*.

Yunnan province, yielded a novel compound nocarsin A (208), along with seven known compounds: lumichrome (209), cyclo(L-Leu-L-Tyr) (210), cyclo(L-Ala-L-Ile) (211), cyclo(L-Ala-L-Leu) (212), cyclo(L-Val-L-Ala) (213), 5-methyluracil (214) and uracil (215).<sup>67</sup>

The fermentation of *Nocardia levis* MK-VL\_113 obtained from laterite soils from the Guntur region produced two new phthalate esters, bis-(2-ethyl-hexyl)phthalate (216) and bis-(5-ethylheptyl)phthalate (217). Compounds 216 and 217 showed antimicrobial activities against the tested bacteria (*Staph. aureus*, *Bacillus cereus*, *Bacillus megaterium*, *Bacillus subtilis*, *Corynebacterium diphtheriae*, *Escherichia coli*, *Proteus vulgaris*, and *Pseudomonas aeruginosa*) with MIC values ranging from 30 to 175  $\mu\text{g mL}^{-1}$  and 50 to 225  $\mu\text{g mL}^{-1}$ , respectively. Meanwhile, the compounds were found to display inhibitory effects towards *Aspergillus flavus*, *Aspergillus niger*, *Alternaria alternata*, *Curvularia maculans*, *Curvularia lunata*, *Fusarium oxysporum* and *Penicillium citrinum*, with MIC values varying from 50 to 300  $\mu\text{g mL}^{-1}$  and 75 to 400  $\mu\text{g mL}^{-1}$ , respectively. Overall, bis-(2-ethylhexyl)phthalate displayed more significant antimicrobial activities than bis-(5-ethylheptyl)phthalate. In addition, this is the first report of bis-(5-ethylheptyl)phthalate and bis-(2-ethylhexyl)phthalate from the genus *Nocardia*.<sup>68</sup>

## 2.9 Secondary metabolites from *Actinoplanes*

A novel prenylated indole derivative, 3-hydroxy-6-dimethylallylindolin-2-one (218), and its biosynthetic precursors, 6-dimethylallyltryptophan (DMAT, 219) and 6-DMAI (220), were isolated from *Actinoplanes missouriensis* NBRC 102363. The complete genome of *A. missouriensis* was searched to discover the biosynthesis genes of these compounds, and the authors found that the gene cluster was composed of an *iptA* homolog (*AMIS\_22580*, named *iptA-Am*) and a putative tryptophanase gene (*AMIS\_22590*, named *tnaA-Am*) (Fig. 9).<sup>69</sup>

From a bioactivity-guided approach, an antifungal metabolite, 5-hydroxyl-5-methyl-2-hexenoic acid (221), was found from *Actinoplanes* sp. HBDN08 obtained from a soil sample collected in Harbin, China. Compound 221 displayed significant antifungal activities *in vitro* towards *Botrytis cinerea*, *Cladosporium cucumerinum* and *Corynespora cassicola* (IC<sub>50</sub> values of 32.45, 27.17, and 30.66  $\text{mg L}^{-1}$ , respectively), and could effectively control *in vivo* diseases caused by *B. cinerea*, *C. cucumerinum* and *C. cassicola*, with inhibitory rates of 71.42%, 78.63% and 65.13%, respectively, at 350  $\text{mg L}^{-1}$ . In summary, 5-hydroxyl-5-methyl-2-hexenoic acid could be a potential candidate for new antifungal drugs.<sup>70</sup> The strain also produced a new chlorinated



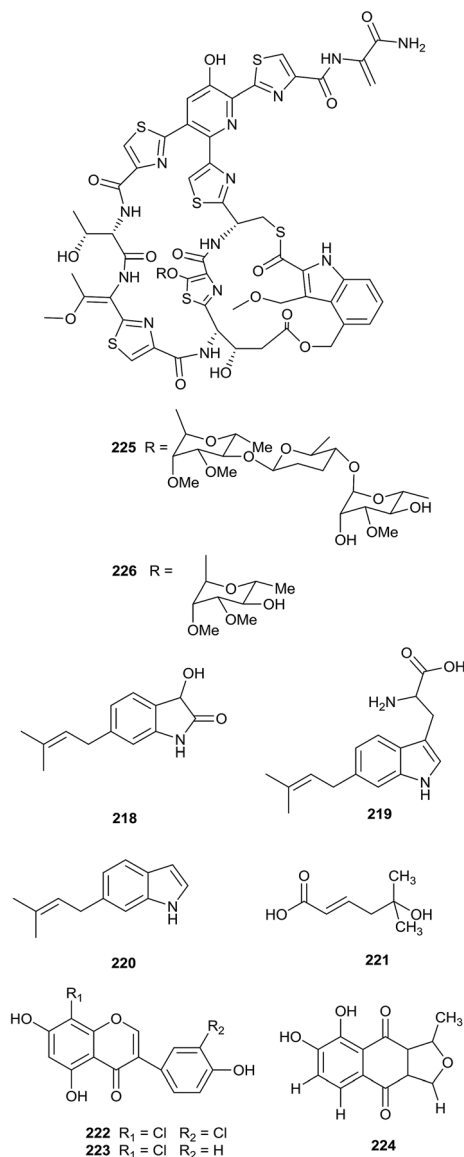


Fig. 9 Secondary metabolites from *Actinoplanes*.

isoflavone, 3',8-dichlorogenistein (222), along with 8-chlorogenistein (223). 3',8-Dichlorogenistein and 8-chlorogenistein displayed significant antioxidant activities ( $IC_{50} = 5.2$  and  $7.5 \mu M$ , respectively), which were stronger than the positive control genistein ( $IC_{50}$  value:  $13.6 \mu M$ ).<sup>71</sup>

A new isofuranonaphthoquinone, 7,8-dihydroxy-1-methylnaphtho[2,3-*c*]furan-4,9-dione (224), was obtained from *Actinoplanes* sp. ISO06811. The strain was found in a soil sample collected in the state of Colorado using *in situ* diffusion technology. The compound showed no antimicrobial activities against *Bacillus subtilis* 1A1 or *Escherichia coli* K12, but it is able to complex with  $Fe(III)$  at circumneutral pH values.<sup>72</sup>

From bioassay-guided isolation, philipimycin (225), a new thiazolyl peptide glycoside, and an acid-catalyzed degradation product (226) were identified from *Actinoplanes philippinensis* MA7347. All compounds possessed excellent antimicrobial activities against Gram-positive bacteria, including MRSA (MIC =  $0.015$ – $1 \mu g mL^{-1}$ ). Importantly, philipimycin displayed

excellent antimicrobial activity in an *in vivo* mouse model of *S. aureus* infection ( $ED_{50} = 8.4 mg kg^{-1}$ ).<sup>73</sup>

## 2.10 Secondary metabolites from *Saccharopolyspora*

An investigation into *Saccharopolyspora cebuensis* MCCC 1A09850, which was isolated from deep-sea sediment from the Atlantic Ocean, afforded one new cyclic tetrapeptide, saccharopolytide A (227), and two known polyketides (228, 229), along with six miscellaneous compounds (230–235). Compound 230 displayed a weak anti-allergic effect ( $IC_{50} = 55.75 \mu g mL^{-1}$ ). In addition, compound 228 could weakly inhibit the proliferation of HeLa and H1299 tumor cell lines (Fig. 10).<sup>74</sup>

4''-O-glucosyl tenvermectin A (236) and 4''-O-glucosyl tenvermectin B (237), two new 16-membered macrocyclic lactone antibiotics, have been obtained from *Saccharopolyspora erythraea* ATCC 11635 via the microbial conversion of tenvermectin A and B. Compounds 236 and 237 showed weak nematocidal activities ( $LC_{50} = 6.7984 mg L^{-1}$  and  $5.7980 mg L^{-1}$ , respectively), which were stronger than those of the precursors tenvermectin A and B. At the same time, the compounds showed inhibitory abilities towards *T. cinnabarinus* adult mites with  $LC_{50}$  values of  $0.0156$  and  $0.0113 mg L^{-1}$ , respectively.<sup>75</sup>

Research into *Saccharopolyspora* sp. BCC 21906 obtained from soil collected in the Evergreen forest, Thailand, yielded three new angucyclinones (238–240), saccharosporone A, B and C, and the known compounds (+)-ochromycinone, (+)-rubiginone B2, tetragulol methyl ether and fujianmycin A. Saccharosporone A and B showed antimicrobial activities towards *Plasmodium falciparum* K1. The  $IC_{50}$  values were  $4.1$  and  $3.9 \mu M$ , respectively. In addition, compounds 238 and 239 possessed cytotoxicities towards KB ( $IC_{50}$  values of  $9.1$  and  $4.9 \mu M$ ), MCF-7 ( $IC_{50} = 3.4$  and  $3.6 \mu M$ ), NCI-H187 ( $IC_{50} = 7.7$ – $4.5 \mu M$ ) and nonmalignant Vero cells ( $IC_{50} = 9.1$ – $12.3 \mu M$ ).<sup>76</sup>

A new compound, JBIR-66 (241), was discovered by Takagi *et al.* from *Saccharopolyspora* sp. SS081219JE-28, which was isolated from an unidentified tunicate collected from the sea shore of Tateyama city, Japan.<sup>77</sup> PM070747 (242) is a new benz[*a*]anthraquinone, which was obtained from *Saccharopolyspora taberi* PEM-06-F23-019B collected from a marine sponge near the coast of Tanzania. The compound showed cytotoxicity activities against MDA-MB-231 cells, HT-29 cells and A-549 cells ( $GI_{50}$  values of  $0.71$ ,  $1.42$  and  $3.28 \mu M$ , respectively; TGI values of  $1.06$ ,  $1.97$  and  $4.64 \mu M$ , respectively; and  $LC_{50}$  values of  $1.72$ ,  $>2.73$  and  $6.82 \mu M$ , respectively).<sup>78</sup>

An investigation into the metabolites from a 400 L culture of *Saccharopolyspora pogona* (NRRL30141) afforded 31 new macrolides (243–273). Most of the metabolites were different from the 'classical' spinosyn series because of the presence of a but-1-enyl group at C-21 instead of an ethyl group. In addition to this, there were lots of other new functional groups, such as rare forosamine sugar replacements, hydroxylations and new 14-membered macrolide ring derivatives.<sup>79</sup>

## 2.11 Secondary metabolites from *Streptosporangium*

To research the secondary metabolites of *Streptosporangium* sp. CGMCC 4.7309, which was isolated from sediment from the



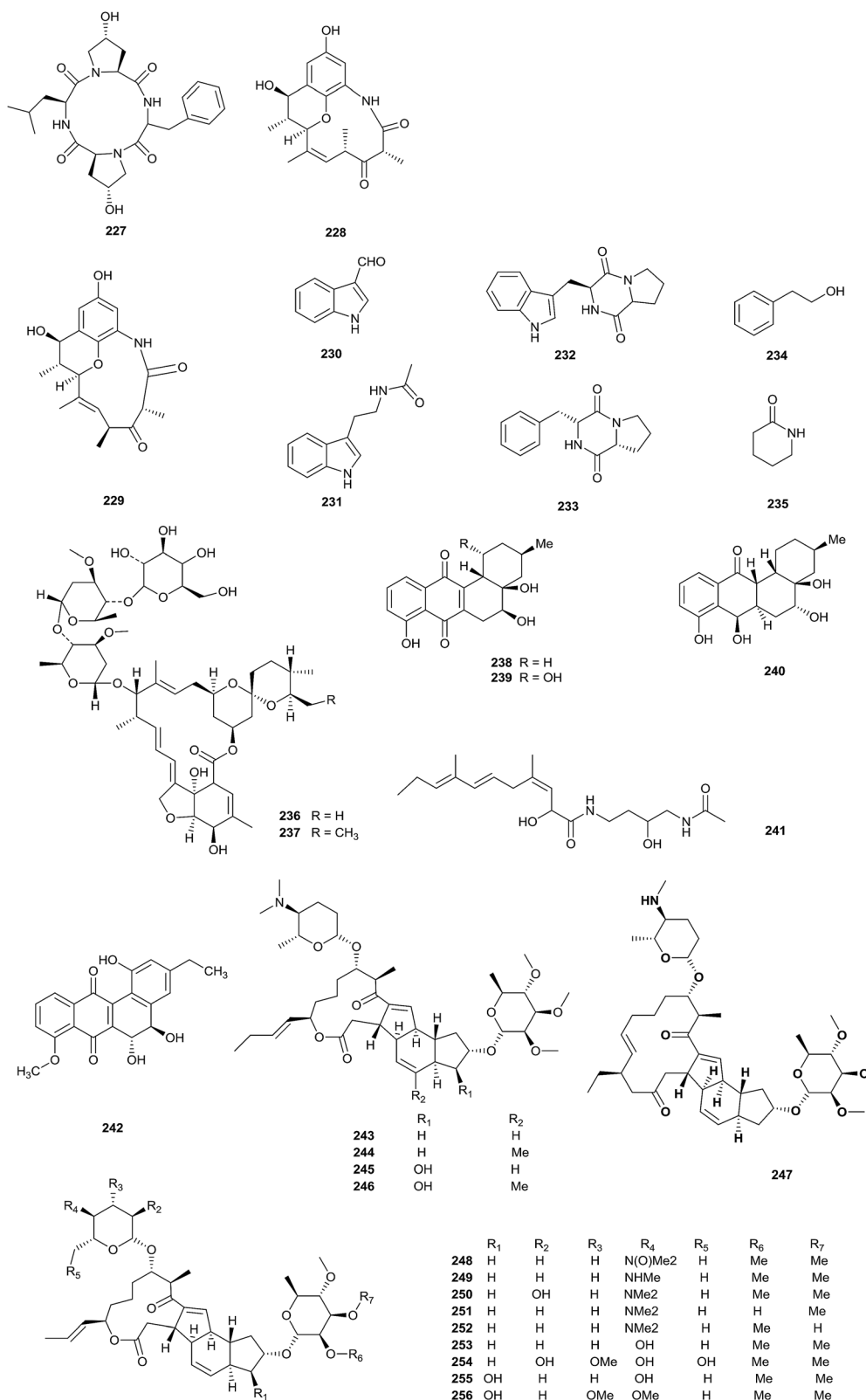


Fig. 10 (contd.)

Huanghai Sea, genome mining was applied. Draft genome sequencing showed that there were more than 20 silent biosynthetic clusters, including a type-II polyketide synthase-

containing cluster. Genome mining could allow for the choosing of suitable detection methods and avoid isolating known secondary metabolites through predicting the skeletons



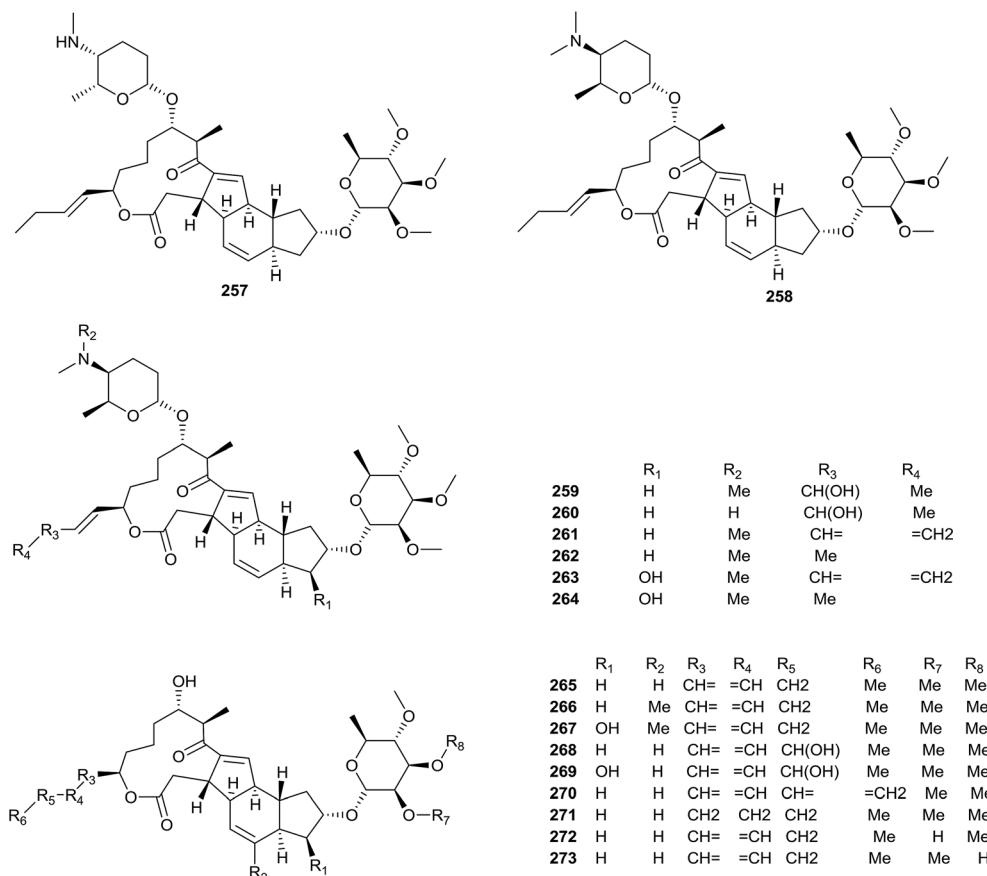


Fig. 10 Secondary metabolites from *Saccharopolyspora*.

of compounds.<sup>80</sup> By this method, three pentangular polyphenols, hexaricin A (274), B (275), and C (276), were found from *Streptosporangium* sp. CGMCC 4.7309 (Fig. 11).<sup>81</sup>

Two new compounds, amethysione (277) and amethysamide (278), along with six known related derivatives, were isolated from *Streptosporangium amethystogenes* BCC 27081, which was isolated from soil under a banana tree collected from an evergreen forest. Amethysione displayed weak cytotoxicities towards KB and NCI-H187 (IC<sub>50</sub> = 16.94 µg mL<sup>-1</sup> and 36.99 µg mL<sup>-1</sup>, respectively).<sup>82</sup>

A new angucyclinone, compound R2 (279), was discovered from *Streptosporangium* sp. Sg3 through chemical analysis. Compound R2 displayed excellent antimicrobial activity towards *Micrococcus luteus* ATCC 9314 and *Bacillus subtilis* ATCC 6633 with MIC values of 0.5 and 1 µg mL<sup>-1</sup>, respectively, and mild activity towards *Staphylococcus aureus* CIP 7625 with an MIC value of 10 µg mL<sup>-1</sup>. Meanwhile, the compound also exhibited weak activities against *Listeria monocytogenes* CIP 82110 and *Mycobacterium smegmatis* ATCC 607 with MIC values of 40 and 50 µg mL<sup>-1</sup>, respectively.<sup>83</sup>

## 2.12 Secondary metabolites from *Actinokineospora*

Heidari *et al.* found two alkaloid compounds, *N*-acetyltyramine (280) and *N*-acetyltryptamine (281), which came from *Actinokineospora* sp. UTMCC 968. The strain was collected from a soil sample (Isfahan province, Iran). Compounds 280 and 281 exhibited excellent antiradical activities, as shown by

antiradical activity bioassays. The IC<sub>50</sub> values showing the DPPH radical scavenging capabilities of *N*-acetyltyramine and *N*-acetyltryptamine were 64.7 ± 0.5 and 131.3 ± 1.8 µg mL<sup>-1</sup>, respectively (Fig. 12).<sup>84</sup>

Actinokineosin (282), a new antibacterial peptide, was reported from a culture broth of *Actinokineospora spheciospongiae* using genome mining, which is a helpful tool to enable the discovery of more secondary metabolites. Actinokineosin displayed antibacterial activity towards *M. luteus* with a diameter of 8 mm at a concentration of 50 µg per disk.<sup>85</sup>

Chemical research into *Actinokineospora bangkokensis* strain 44EHW led to the isolation of thailandin A (283) and B (284), two new polyene macrolactone antibiotics. Compounds 283 and 284 possessed broad-spectrum antifungal activity against *Colletotrichum gloeosporioides* DoA d0762, *Colletotrichum gloeosporioides* DoA c1060 and *Colletotrichum capsici* DoA c1511, which could lead to anthracnose disease. Additionally, the pathogenic yeasts *Candida albicans* MT 2013/1, *Candida parasilopsis* DKMU 434 and *Cryptococcus neoformans* MT 2013/2 also were inhibited by the compounds (MIC values = 16–32 µg mL<sup>-1</sup>).<sup>86</sup>

Applying an OSMAC strategy, trying different fermentation approaches, led to the isolation of two new antioxidant actinosporin analogues, actinosporin C (285) and D (286). Differently from a general culture, a culture of



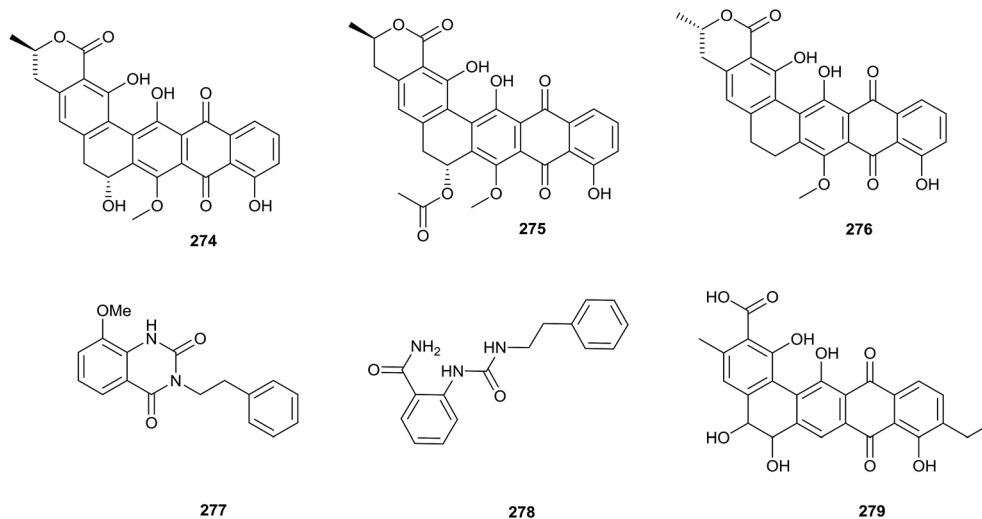


Fig. 11 Secondary metabolites from *Streptosporangium*.

*Actinokineospora* sp. strain EG49 included calcium alginate. The marine sponge *Spheciospongia vagabunda* was the habitat of this strain. At a concentration of 1.25  $\mu\text{M}$ , both compounds displayed excellent antioxidant and protective activities towards genomic damage in the HL-60 cell line induced by hydrogen peroxide.<sup>87</sup>

### 2.13 Secondary metabolites from *Microbispora*

A new natural diketopiperazine, *trans-cyclo*-(D-tryptophanyl-L-tyrosyl) (287), was obtained from *Microbispora aerata* strain imbas-11A isolated from penguin excrement collected on Livingston Island in the Antarctic. Compound 287 displayed weak anti-proliferative and cytotoxic effects towards L-929 mouse fibroblast cells, K-562 human leukemia cells (all  $\text{GI}_{50}$  values = 50.0  $\mu\text{g mL}^{-1}$ ) and HeLa human cervix carcinoma ( $\text{CC}_{50}$  = 47.0  $\mu\text{g mL}^{-1}$ ). However, *trans-cyclo*-(D-tryptophanyl-L-tyrosyl) did not show obvious antibacterial activity at a dose of 50 mg per disc (Fig. 13).<sup>88</sup>

Linfuranone A (288) is a new furanone-containing polyketide, which was discovered in a fermentation culture of *Microbispora* sp. GMKU 363 isolated from the root of a Thai medicinal plant (*Clinacanthus siamensis* Bremek.). However, the compound did not show significant activity in antimicrobial and cytotoxic research.<sup>89</sup>

Seven new 20-membered ring macrodiolide antibiotics (289–295), bispolide A1, A2, A3, B1, B2a, B2b and B3, were isolated from *Microbispora* sp. A34030 collected from a soil sample from a forest station. All compounds showed antimicrobial activities against Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus* (MRSA) at concentrations ranging from 1 to 4  $\mu\text{g mL}^{-1}$ .<sup>90</sup>

### 2.14 Secondary metabolites from *Lechevalieria*

Two new thiazolyl pyridine compounds, pyrizomicin A (296) and B (297), have been obtained from *Lechevalieria aerocolonigenes* K10-0216, which was separated from mangroves (Iriomote Island).

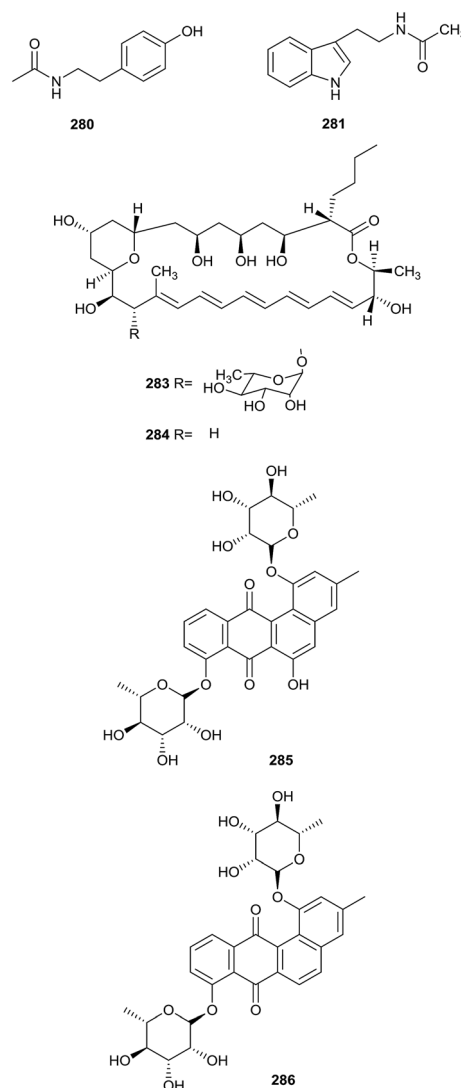
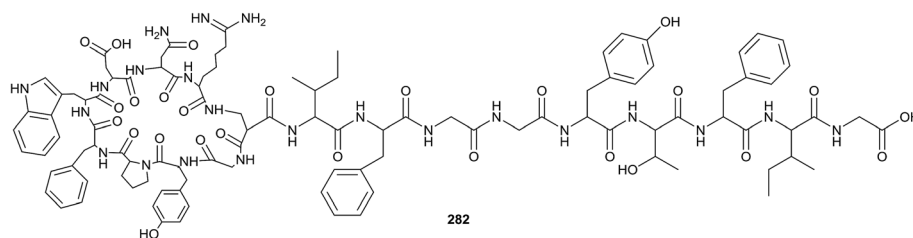


Fig. 12 (contd.)





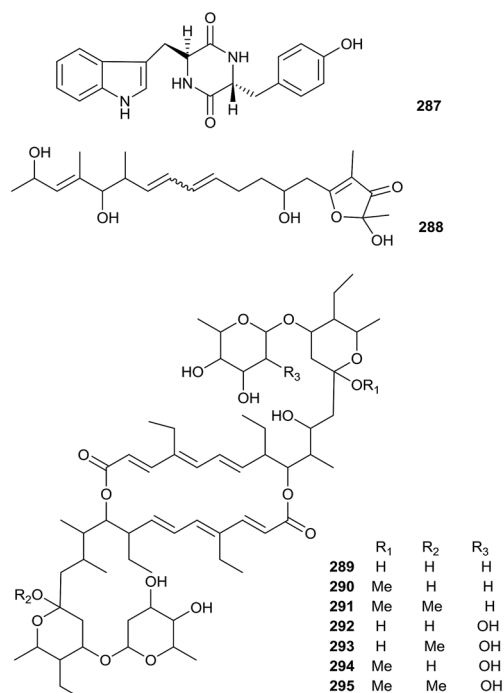
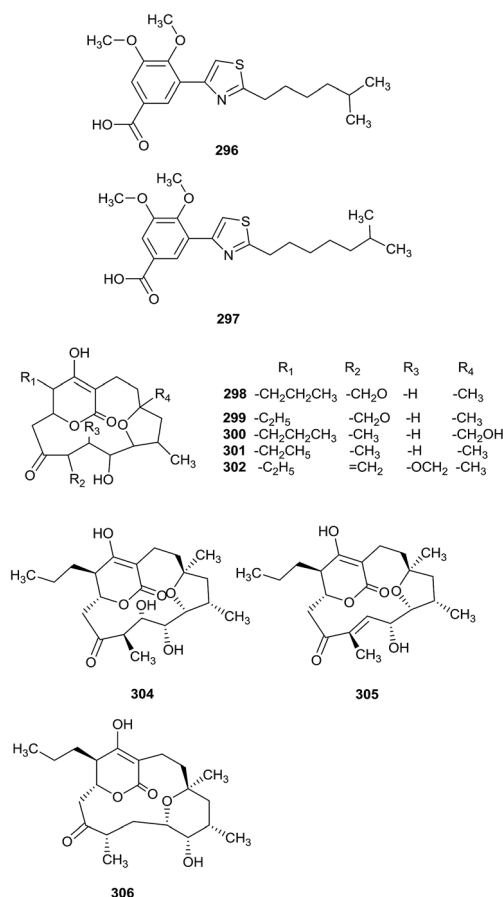
Fig. 12 Secondary metabolites from *Actinokineospora*.

Pyrizomicin A and B displayed antimicrobial activities towards *Bacillus subtilis* ATCC 6633, *Kocuria rhizophila* ATCC 9341, *Escherichia coli* NIHJ, *Xanthomonas campestris* pv. *oryzae* KB 88, and *Candida albicans* ATCC 64548, with a diameter of 6 mm at 10  $\mu\text{g}$  using a paper disk method. In addition, compound **296** also showed inhibition against *Staphylococcus aureus* ATCC 6538P, *K. rhizophila* ATCC 9341, *X. campestris* pv. *oryzae* KB 88 and *E. coli* NIHJ (MICs = 32, 32, 32 and 64  $\mu\text{g mL}^{-1}$ , respectively).<sup>91</sup> The same rare actinomycetes also produced six rare cyclopentadecane skeletons, mangromicin D, E, F, G, H and I (**298–303**), with a tetrahydrofuran unit and 5,6-dihydro-4-hydroxy-2-pyrone moiety. From bioassay results, all compounds displayed radical scavenging activities inhibiting DPPH free radicals and NO generation from LPS-stimulated RAW264.7 cells.<sup>92</sup> Mangromicin A (**304**) and B (**305**), two new cyclopentadecane antibiotics with a tetrahydrofuran unit and 5,6-dihydro-4-hydroxy-2-pyrone moiety, were also discovered from the same strain. The secondary metabolites had excellent inhibitory activities towards *Trypanosoma brucei brucei* GUT ( $\text{IC}_{50} = 2.4 \mu\text{g mL}^{-1}$ ). Additionally, they showed more potent cytotoxicities against MRC-5 cells than control drugs (suramin and

eflornithine). However, mangromicin B was weaker than mangromicin A in terms of antitrypanosomal and cytotoxic activities.<sup>93</sup> Finally, the same research group obtained a new analog, mangromicin C (**306**), which possessed a tetrahydropyran ring, from the same rare actinomycete *Lechevalieria aerocolonigenes* K10-0216. Mangromicin C displayed more significant scavenging activity against DPPH free radicals with an  $\text{IC}_{50}$  value of 3.8  $\mu\text{M}$  (Fig. 14).<sup>94</sup>

## 2.15 Secondary metabolites from *Actinoalloteichus*

Chemical research into *Actinoalloteichus nanshanensis* NEAU 119, isolated from the rhizosphere of a fig tree, afforded three new cyclopentenone derivatives (**307–309**). Towards A549, K562 and ACHN cell lines, compound **307** displayed cytotoxic properties ( $\text{IC}_{50} = 14.67, 11.87, \text{ and } 23.36 \mu\text{g mL}^{-1}$ , respectively). However

Fig. 13 Secondary metabolites from *Microbispora*.Fig. 14 Secondary metabolites from *Lechevalieria*.

other compounds did not display inhibition towards the tested cell lines at  $100 \mu\text{g mL}^{-1}$  (Fig. 15).<sup>95</sup>

Caerulomycin F–J, five new bipyridine alkaloids (**310–314**), a new phenylpyridine alkaloid, caerulomycin K (**315**), and five known analogues (**316–320**), caerulomycin A, caerulomycin C, caerulomycinamide, caerulomycinonitrile, and (*Z*)-4-methoxy-2,20-bipyridine-6-carbaldehyde oxime, have been obtained from *Actinoballoteichus cyanogriseus* WH1-2216-6. The strain came from marine sediment from the seashore in Weihai, China. Compounds **310–319** displayed inhibitory activities towards HL-60, K562, KB, and A549 cell lines ( $\text{IC}_{50}$  values range from 0.26 to  $15.7 \mu\text{M}$ ). In addition, caerulomycin A and C exhibited antimicrobial activities towards *Escherichia coli*, *Aerobacter aerogenes*, *Pseudomonas aeruginosa*, and *Candida albicans* (MIC values range from 9.7 to  $38.6 \mu\text{M}$ ).<sup>96</sup> Further chemical studies of *Actinoballoteichus cyanogriseus* WH1-2216-6 yielded four new glycosidic bipyridine derivatives, cyanogriside A–D (**321–324**), containing a rare cyclic glycoside, which was formed from the vicinal hydroxyl groups of an aglycone with both the anomeric center and adjacent carbonyl of a keto sugar. Cyanogriside A displayed potent inhibition against K562, KB, and MCF-7 cells ( $\text{IC}_{50} = 1.2, 4.7,$

and  $9.8 \mu\text{M}$ , respectively). At the same time, the  $\text{IC}_{50}$  values of cyanogriside C against K562 and KB cells were 0.73 and  $4.7 \mu\text{M}$ , respectively. Additionally, cyanogriside B could reverse the multiple drug resistances of K562/A02, MCF-7/Adr and KB/VCR cells at  $10 \mu\text{M}$ .<sup>97</sup> Cyanogriside E–H (**325–328**), as new acyclic bipyridine glycosides, also have been discovered from *Actinoballoteichus cyanogriseus* WH1-2216-6 via the inactivation of the *O*-methyltransferase gene *crmM*. Cyanogriside E and H showed moderate cytotoxicities towards K562 ( $\text{IC}_{50}$  values = 6.0 and  $0.8 \mu\text{M}$ ). In addition, cyanogriside F and G could inhibit HCT116 and HL-60 cells with  $\text{IC}_{50}$  values of 0.8/3.6, and 3.1/2.0  $\mu\text{M}$ , respectively.<sup>98</sup>

## 2.16 Secondary metabolites from other genera

Sphaericin (**329**), a new lasso peptide, was obtained from *Planomonospora sphaerica*. At a concentration of  $50 \mu\text{g}$  per disk, sphaericin exhibited potential antimicrobial activity against *Micrococcus luteus* (Fig. 16).<sup>99</sup>

Nicrophorusamide A and B (**330–331**), two new chlorinated cyclic hexapeptides, were isolated from the gut of the carrion beetle *Nicrophorus concolor*. Compound **330** possessed antimicrobial

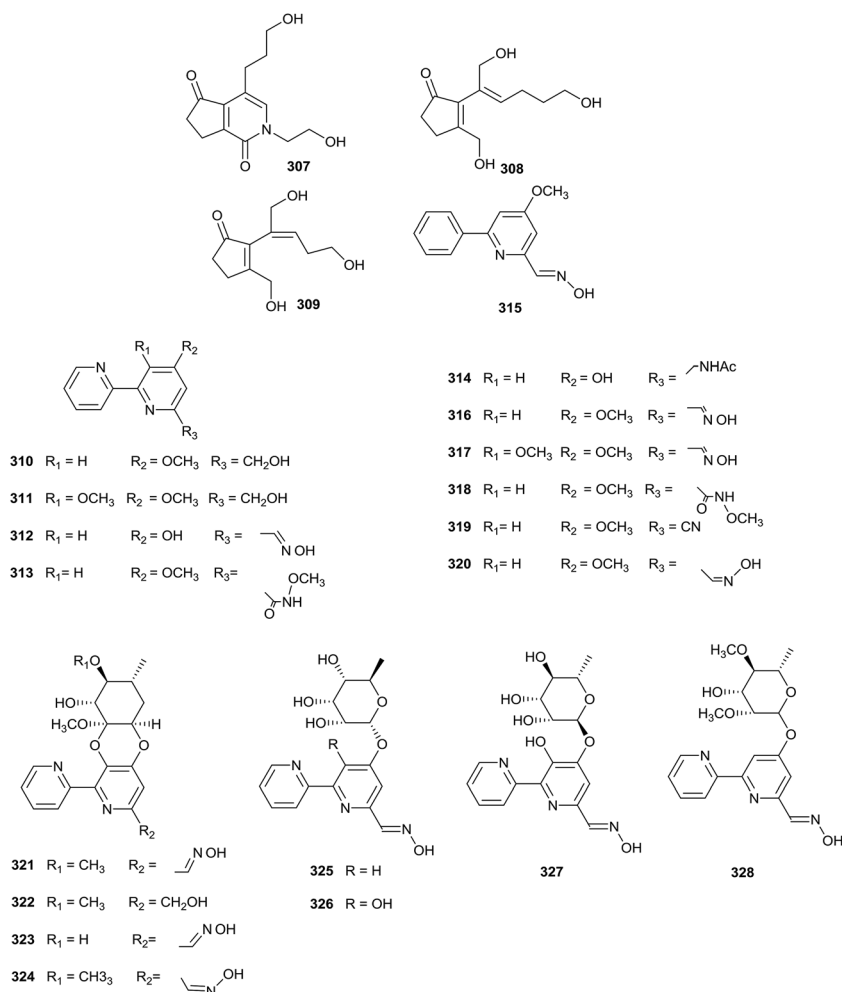


Fig. 15 Secondary metabolites from *Actinoballoteichus*.

activities towards *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 19433, *Enterococcus faecium* ATCC 19434, and *Salmonella enterica* ATCC 14028 (MIC values = 8–16  $\mu\text{g mL}^{-1}$ ).<sup>100</sup>

An investigation of the fermentation broth of *Kribbella* sp. MI481-42F6, which was isolated from a soil sample collected in Japan, yielded kribelloside A–D (332–335), four new alkyl

glyceryl ethers. Kribelloside A–D showed inhibitory activities towards Cet1p (RNA 5'-triphosphatase) from *Saccharomyces cerevisiae* *in vitro* ( $\text{IC}_{50}$  = 5–8  $\mu\text{M}$ ). Beyond that, all compounds possessed antifungal activities towards *S. cerevisiae* (MIC values = 3.12–100  $\mu\text{g mL}^{-1}$ ).<sup>101</sup>

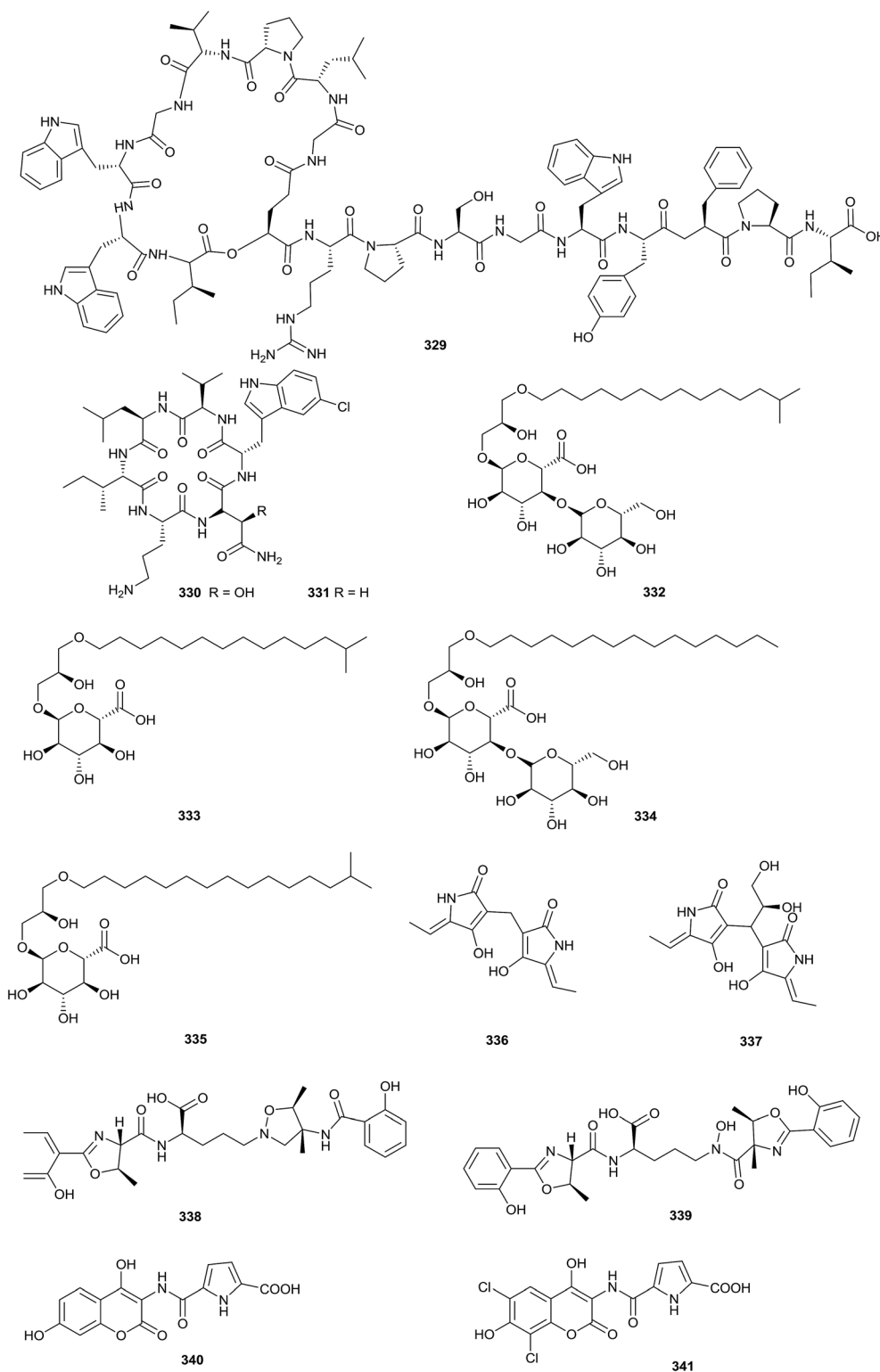


Fig. 16 Secondary metabolites from other genera.



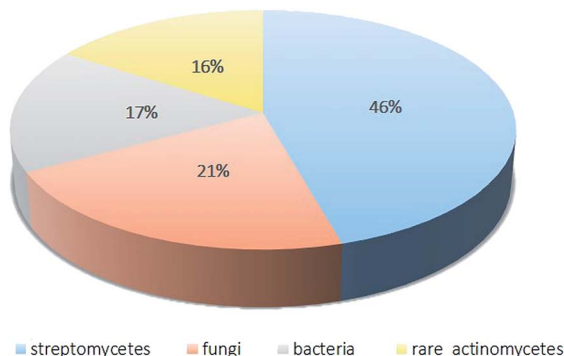


Fig. 17 The distribution of the sources of antibiotics from microorganisms.<sup>4</sup>

Two novel tetramic acid dimers (336–337), dietziamide A and B, were obtained from *Dietzia timorensis* MZ-3 from a soil sample. Dietziamide A and B exhibited mild DPPH radical scavenging activities, with  $IC_{50}$  values of 34 and 37  $\mu$ M, respectively.<sup>102</sup>

Catenulobactin A (338) and B (339) are two new heterocyclic peptide isomers obtained from *Catenuloplanes* sp. RD067331. It's remarkable that a co-culture of *Catenuloplanes* sp. RD067331 and the mycolic acid-containing bacterium *T. pulmonis* TP-B0596 could increase the output of compounds. Catenulobactin B could form a 1 : 1 Fe(III) complex, which displayed characteristic <sup>56</sup>Fe- and <sup>54</sup>Fe-containing positive ion species. In addition, it could inhibit P388 murine leukemia cells ( $IC_{50}$  = 22.4  $\mu$ M). However, catenulobactin A showed no cytotoxicity, even at 100  $\mu$ M.<sup>103</sup>

Using genome mining, a new aminocoumarin gene cluster was identified from *Catenulisporea acidiphila* DSM 44928. Then, two new aminocoumarins, cacibiocin A and B (340–341), were discovered from the strain. Interestingly, heterologous expression with *Streptomyces coelicolor* M1152 could increase the production of cacibiocin from 4.9 mg L<sup>-1</sup> to 60 mg L<sup>-1</sup>.<sup>104</sup>

### 3 Conclusions

As this review mentions, among the 341 compounds reported, most metabolites belong to the classes of cyclic peptides and quinones. Over the period from 2008 to 2018, the rare actinomycetes with the most potential were *Amycolatopsis*, *Actinomadura*, *Nonomuraea* and *Micromonospora*. The most preferable habitat for rare actinomycetes is soil. In addition, marine habitats, plants and insects are important habitats for unknown rare actinomycetes (Fig. 17).

In recent years, rare actinomycetes have produced numerous secondary metabolites with diverse structures and significant bioactivities, such as cytotoxicity and antimicrobial activity. Because of their excellent bioactivities, those secondary metabolites show great commercial prospects. According to Lazzarini,<sup>4</sup> there have been more than 8000 antimicrobial products, of which 45.6% came from streptomycetes and 16% came from rare streptomycetes.

More importantly, the proportion of rare actinomycetes has been increasing.<sup>4</sup> According to our review, 2'-O-succinyl-apoptolidin A (22), 3'-O-succinyl-apoptolidin A (23), miao-lienone (79) and brartemicin (122) showed significant anti-tumor activities. More importantly, using brartemicin as a lead compound, Jiang *et al.* synthesized 19 brartemicin analogs and studied their structure–activity relationships as anti-invasive agents. One analog was as potent as brartemicin against the invasion of murine colon 26-L5 carcinoma cells *in vitro*.<sup>105</sup> As potent antibacterial agents, actinomadurol (65) (for *Staphylococcus aureus*, *Proteus hauseri* and *Kocuria rhizophila*; MIC values = 0.39–0.78  $\mu$ g mL<sup>-1</sup>)<sup>23</sup> and nocardithiocin (207) (towards rifampicin-resistant and -sensitive *Mycobacterium tuberculosis* strains, most of which were inhibited at concentrations of 0.025–1.56  $\mu$ g mL<sup>-1</sup>)<sup>66</sup> have shown excellent antimicrobial activities. As for potent antifungal agents, the new compounds A4 (177) and A5 (178) have displayed significant inhibition towards the fungi *M. ramannianus*, *A. carbonarius* and *P. expansum*. Based on their excellent bioactivities and diverse structures, secondary metabolites of rare actinomycetes can draw more attention from the scientific community.

Great progress has been made in the research of secondary metabolites from rare actinomycetes recently. Although many new species and rare actinomycetes have been identified, it is estimated that only 0.1–1% of actinomycete species have been isolated and researched. Therefore, actinomycetes are still a rich resource waiting to be investigated. On one hand, unexplored habitats have become a wonderful option as sources for the isolation of new genera that may produce novel secondary metabolites. On the other hand, lots of novel technologies should be tried to discover more novel compounds with excellent bioactivities. The OSMAC (one-strain-many-compounds) strategy combined with gene scanning will increase the chances of discovering novel compounds. Gene scanning technology could be used to find new biosynthetic gene clusters of microbial secondary metabolites. At the same time, the structures and some physical properties of the compounds can be predicted from the analysis of gene clusters, which is conducive to separation and identification.<sup>106</sup> Because of advances in microbiological and biotechnological technology, we do believe that the ability of rare actinomycetes to produce novel secondary metabolites will be better exploited. As a result, more and more antibiotics will be produced using rare actinomycetes.

### Conflicts of interest

There are no conflicts to declare.

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