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Ali Zineddine Boumehira, Hesham Ali El-Enshasy*, Hocine Hacene, Elsayed Ahmed Elsayed, Ramlan Aziz and Enoch Y. Park*

E-mail:
zineddine@ibd.utm.my (AZB)
henshasy@ibd.utm.my (HAE)
h_hacene@yahoo.fr (HH)
eaelsayed@ksu.edu.sa (EAE)
ramlan@ibd.utm.my (RA)
park.enoch@shizuoka.ac.jp (EYP)

Ali Zineddine Boumehira, Hesham Ali El-Enshasy*, Ramlan Aziz
Institute of Bioproduct Development, Universiti Teknologi Malaysia (UTM), Skudai 81310 Johor, Malaysia.
Tel.: +60 75531573.
E-mail: henshasy@ibd.utm.my

Ali Zineddine Boumehira,
Centre de Recherche Scientifique et Technique en Analyses Physico Chimiques, Bou-Ismail, Tipaza, Algeria.

Ali Zineddine Boumehira, Hocine Hacene
University of Sciences and Technology Houari Boumediene, FSB, LBCM, Bab Ezzouar, Algiers, Algeria.

Hesham Ali El-Enshasy
City of Scientific Research and Technology Applications, New Burg Al Arab, Alexandria, Egypt.

Elsayed Ahmed Elsayed
Faculty of Science, King Saud University, Riyadh, Saudi Arabia.

Elsayed Ahmed Elsayed
Natural and Microbial Products Department, National Research Center, Dokki, Cairo, Egypt.

Enoch Y. Park*
Research Institute of Green Science and Technology, Shizouka University, 836 Ohya, Suruga-ku, Shizuoka 422-8529, Japan
Tel.: +81 54 238 4887; fax: +81 54 238 4887.
E-mail: park.enoch@shizuoka.ac.jp

Abstract The emergence of large number of antimicrobial-resistant organisms has given alarming magnitude. Nature is historically the source of drugs, and microorganisms have provided a significant number of antibiotic compounds, which are used every day in the treatment of many infectious diseases. However, the introduction to the pharmaceutical market of new therapeutic molecules has largely decreased during the last two decades. In this review, antibiotics from the genus *Micromonospora* are recognized as potential biofactory for new antibiotic production. The *Micromonospora* has been deeply studied and more than 100 antibiotics isolated from different *Micromonospora* strains. In addition, comprehensive information about the recent development in the field of analytical, biological and bioinformatics screening tools, which recently used in the discovery of new therapeutic compounds, are provided. It is widely believed that reviving old antibiotics produced by *Micromonospora* is possible and the study of this genus is still interesting for novel bioactive molecules discovery.

Keywords: *Micromonospora*, antibiotics, drug discovery, gentamicin, secondary metabolites, natural products.

1. Introduction

The emerging of antimicrobial-resistant organisms became one of the major problem in the treatment of many infectious diseases [1–3]. In December 2014, a report commissioned by the British Prime Minister, David Cameron, under the title "Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations", was published. This report estimates that drug-resistant infections can cause supplement of 10 million deaths annually and an economic loss of over 100 trillion USD in 2050 [4,5]. On the other hand, the introductions of new antibiotics into therapy market have significantly decreased during the last twenty years, because of limitations of drug discovery programs and inappropriate economic-regulatory environment [6–9]. Natural products are an essential source of compounds for drug discovery. In addition to plants, microorganisms provided a large number of therapeutic molecules [10,11]. Recently, a team led by Kim Lewis of Northeastern University in Boston, Massachusetts, have published in *Nature*, the discovery of a new antibiotic called teixobactin, with a new mechanism of action, via a new discovery technology. This was the first new antibiotic of high therapeutic potential since 1987 [8,12].

After the discovery of Gentamicin, the genus *Micromonospora* became an important source in the drug discovery process. Nowadays, more than 740 antibiotics have been isolated from *Micromonospora* strains [13,14]. In this review, we proceed to summarize briefly the most important antibiotics produced by *Micromonospora* species, and we give an update about the different strategies that can be used in the development of new antibiotics from this genus.

2. The Genus *Micromonospora*

The genus *Micromonospora*, a member of the family *Micromonosporaceae,* was initially described by Ørskov in 1923 [15–17]. The species belong to this genus are Gram positive

bacteria, aerobic to microaerophilic, chemo-organotrophic, sensitive to pH below 5.0 and have optimal temperature between 20 and 40°C. Several strains produce carotenoid mycelial pigments, giving the colony which gives different characteristics colors range such as yellow, red, orange, brown, purple or black. From its name, this genus produces singly spore directly attached to substrate mycelium or carried out short sporophore. The cell wall of *Micromonospora* contains *meso*-diaminopimelic acid and/ or 3-OH-diaminopimelic acid. The major phospholipids are phosphatidylethanolamine, phosphatidylinositol, and phosphatidylinositol mannosides [16,17]. The first species of this genera *Micromonospora chalcea* described by Ørskov [15], was isolated by Foulerton in 1905 and classified under the name *Streptothrix chalceae* [18]. This remained the only known strain among the actinomycetes bearing the generic name *Micromonospora* until Jensen in 1930 described a large number of soil micro-organisms which corresponded with Ørskov's description [19]. At the time of writing, the genus consisted of 61 validly named species (http://www.bacterio.net) [20], in addition to the recently described species, like: *M. spongicola* [21], *M. jinlongensis* [22], *M. zeae* [23], *M. maoerensis* [24], *M. endophytica* [25], *M. palomenae* [26], *M. harpali* [26], *M. oryzae* [27], *M. vulcania* [28], *M. fluostatini* [29], *M. nickelidurans* [30], *M. zhanjiangensis* [31].

3. Antibiotic from the genus *Micromonospora*

Actinomycetes are considered as the most important biofactory for therapeutic secondary metabolites production, and most of antibiotic discovery researches are usually focus on the isolation of novel secondary metabolites from actinomycetes. After the discovery of Gentamicin, the genus *Micromonospora* became an important resource of natural molecules. Table 1 shows the most known antibiotics isolated from different strains of the genus *Micromonospora*. It summarizes the chemical class, and producer strain, source of isolation

from Micromonosporin, antibiotic compound isolated and described in 1947 by Waksman *et al.* [32] to the recently discovered compounds such as Neomacquarimicin [33].

The aminoglycosides are one of the widely known classes of antibiotics and include many members widely used in the treatment of infectious diseases caused by Gram-positive and Gram-negative bacteria. The mode of action is mediated through targeting the bacterial ribosome, where they bind to the A-site and interrupt protein synthesis. Aminoglycosides are produced essentially by *Streptomyces* and soil *Micromonospora* strains [34–39].

The most famous antibiotics produced by the genus *Micromonospora* are Gentamicins [40]. The success of this mixture of aminoglycosides is based on the wide spectrum activity against Gram-positive and Gram-negative bacteria. The antibiotic mixture was isolated for the first time from two strains: *M. echinospora* (former *purpurea*) NRRL 2953 and *M. echinospora* NRRL 2985 from soil sample in New York, USA [40–42]. Gentamicins are water soluble antibiotic complex, with main constituents of gentamicin C complex C1, C2, C1a, C2a, and C2b. The chemical structure of this compound is characterized by a central di-aminogenouscyclitol (2-deoxystreptamine (2DOS) 4,6-disubstituted with the auxiliary sugars garosamine and purpurosamine, Fig. 1(A). In addition to gentamicin C complex, many minor components like gentamicins A, B, and X, are used as starting materials for the development of antiprotozoal drugs [43,44]. Gentamicin, was introduced into the pharmaceutical market in 1971 and has been widely used in many medical applications since that time [45]. Currently, Gentamicin is part of the essential drug list of the World Health Organization [46]. In addition, new gentamicin-conjugants exhibit anti-viral effects (anti-HIV) [43,44], and can be also used in genetic therapeutic approaches [47]. In addition, gentamicin was also used successfully in agriculture applications [48].

Antibiotic G-418 (geneticin), is similar structure to gentamicin B1 and produced by *M. rhodorangea*. In addition to its wide spectrum antibiotic activity active against Gram positive

and Gram negative bacteria, it exhibits also some activity against eukaryotic organisms such as Protozoa and Helminths [41,49,50]. The antileishmanial activity of G-418 (against *Leishmania major* and *Leishmania donovani*) is more potent than neomycin and gentamicin [39]. In addition, G-418 is used as an agent for selection in cell culture protocols [51]. Another antibiotic related to gentamicins production is Antibiotics JI-20 (A and B). This antibiotic was first detected during the cultivation of a mutant strain of *M. echinospora* JI-20 (NRRL 2953) [52]. Other antibacterial compound named as Antibiotic 460, was produced by *M. chalcea* subsp. *flavida* NRRL 3222 [53].

Sisomicin is also belongs to aminoglycosides with chemical structure close to gentamicin C1a and differs by the presence of an unsaturated sugar ring I, Fig. 1(B) [54–57]. The antibacterial activity of sisomicin is higher than other structurally related aminoglycosides like gentamicin, tobramycin, and amikacin [57]. Tansarli *et al.* [58] that sisomicin displayed *in vitro* activity against 41% of *Enterococcus* spp., 97% of *Staphylococcus* spp., and was effective when applied in cream form in the treatment of many diseases. Antibiotic G-52, was produced with sisomicin by *M. zionensis* NRRL 5466, this antibiotic is active against Gram-positive and Gram-negative bacteria [59,60]. Verdamicin is other antibiotic derived from the gray-green colony of *M. grisea* NRRL 3800. This antibiotic demonstrated activity similar to that of gentamicin against members of the family *Enterobacteriaceae* and against *Pseudomonas aeruginosa* [41,61,62]. Sagamicin (XK-62-2), is other important antibiotic produced by soil isolates of *M. sagamiensis* subsp. *nonreducans* ATCC 21803 and *M. sagamiensis* ATCC 21826 [63,64]. In 2002, Marone *et al.*, compared the *in vitro* antibacterial activity of sagamicin, gentamicin, tobramycin and norfloxacin. Sagamicin was one of the most effective compound against *Enterobacteriaceae* with a MIC_{90} of 2 mg/L and presented good antipseudomonal activity similar or higher to that of gentamicin [65]. Fortimicins A, B, C, D, and KE are also aminoglycoside antibiotics produced by *M. olivasterospora* MK-70

(ATCC 21819) [66–70]. Girolami *et al.* (1977), showed that the antibacterial effect of fortimicin A against *Enterobacteriaceae* is comparable to amikacin [71]. Other research reported also the bactericidal effect of Fortimicin A against *Staphylococcus epidermnidis* [72]. Antlermicins A, B and C are antitumor antibiotics produced by soil isolate of *M. chalcea* subsp. *kazitnoensis* T-90 [73,74]. Tetrocarcins A, B, C, E1, E2, F and F-1, were first isolated from *M. chalcea* KY11091 and exhibited antibacterial activity against Gram-positive bacteria [75–77]. The tetrocarcin was effective against different experimental tumor models as mouse sarcoma 180 and mouse leukemia P388 [75,78,79].

Combimicins, A1, A2, B1 and B2 are named after their hybridized structure of kanamycins and gentamicins. These antibiotics were obtained by growing gentamicin producer strain, *Micromonospora* sp. ATCC 31348, or its gentamicin non-producing mutant *Micromonospora* sp. ATCC 31349. Combimicins have strong antibacterial activities against Gram-positive and Gram-negative bacteria [80]. AC6H is antitumor antibiotic, produced by *M. carbonaceae* subsp. *carbonaceae* K55-AC6. The cytotoxicity of AC6H against P388 leukemia and B16 melanoma cells were 6.25 and 25 μg/mL, respectively [81].

Macrolide antibiotics are part of the polyketide group of natural products. The antimicrobial activity of macrolides is mediated through their binding ability to the 50S subunit of the bacterial ribosome which inhibits ribosomal translocation, leading to inhibition of bacterial protein synthesis. Macrolides were also used for the treatment of non-infectious diseases based on their anti-inflammatory and immunomodulatory effects in humans. They can inhibit the production of many pro-inflammatory cytokines such as: IL-1, IL-6, IL-8, and (TNF)-α [82]. Megalomicins A, B, C_1 and C_2, are produced by *M. megalomicea* strains isolated from soil. Megalomicins are characterized by their antiparasitic, antibacterial and antiviral properties [83–87].

Rosamicin (Rosaramicin), isamacrolide antibiotic produced by *M. rosaria* NRRL 3718, in mixture with other minor secondary metabolites [88–91]. The chemical and biological characteristics these compounds are close to erythromycin, Fig. 1(C). Rosamicin have an antibacterial effect against *Staphylococcus aureus, S. epidermidis,* and enterococci [92,93]. Juvenimicins, antibacterial antibiotics were produced by *M. chalcea* subsp. *izumensis* ATCC 21561 which was initially isolated from soil sample [94,95]. Juvenimicin C and 5-O-α-L-rhamnosyltylactone, were obtained from the culture broth of *Micromonospora* sp. The antibiotic Juvenimicin C improved quinone reductase 1 (QR1) enzyme, which is known to have the potential of mediating cancer chemopreventive activity [96].

Mycinamicins were isolated from the culture broth of *M. grisseorubida* A11725 [97]. This speices was able to produce several type of mycinamicins, the strctures of these compounds were published by many authors [97–109].

The antitumor antibiotics Calicheamicins (β 1Br, γ 1Br, α 2I, α 3I, β 1I, γ 1I and δ 1I), were obtained from the culture broth of *M. echinospora* subsp. *calichensis*. Calicheamicin γ 1I, Fig. 1(D) exhibited antitumor activity against P388 leukemia and B16 melanoma in *in vivo* testing. In murine tumor models, it was more effective than Adriamycin, the widely applied antitumor antibiotic in clinical applications [110–112]. Calicheamicins can be used for targeted delivery, through the process of monoclonal antibody conjugation using a hydrazone cleavable linker [113]. This ability was used to conjugate calicheamicin with monoclonal antibodies recognizing CD33 expressed on myeloid progenitors in patients with acute myeloid leukaemia (AML), the result was the active agent of gemtuzumab ozogamicin (Mylotarg©). In May 2000, the U.S. Food and Drug Administration (FDA) approved this antibiotic under the accelerated approval program to treat patients who are 60 years and older in first relapse with CD33+ AML and not considered candidates for chemotherapy [114].

However, in 2010, Pfizer Inc. announced the voluntary withdrawal from the U.S. market after questionable safety and efficacy data in post-approval studies [115–117].

Izumenolide, Fig. 1(E), is a potent inhibitor of β-lactamases, especially when applied in Gram-negative bacteria. This antibiotic produces by *M. chalcea* subsp. *izumensis* SC 11133 [118–121]. Dotriacolide is also β-lactamases inhibitors produced by *M. echinospora* MG299-fF35. Dotriacolide is resembles to izumenolide but differs in the number of the O-sulfate groups and the ring size of the lactone [122]. It was found that dotriacolide enhanced mycinamicin production in *M. griseorubida* [123].

Rustmicin (galbonolide A), is an antifungal antibiotic, with insignificant inhibitory effect on bacterial cell. This antibiotic is produced by *M. chalcea* 980-MC1 [124,125]. Clostomicins (A, B_1, B_2, C and D) are a macrolide antibiotics produce by *M. echinospora* subsp. *armeniaca* KMR-593. Clostomicins exhibited strong antibacterial activities against Gram-positive anaerobic bacteria such as *Clostridium perfringens* and *C. difficile* [126,127]. Quinolidomicins (A_1, A_2 and B_1), were isolated from the fermentation broth of *Micromonospora* sp. JY16 - FERM BP-3940. Quinolidomicin A_1 inhibited the growth of different tumor cells including multidrug-resistant cells. Quinolidomicin B_1 was similarly cytotoxic, while Quinolidomicin A_2 was inactive against tumor cells [128,129].

Pyrrolosporin A is antibiotic compound with antibacterial and antitumor properties. This molecule was obtaiend from soil isolate of *Micromonospora* sp. 2C39217-R109-7 (ATCC 53791) [130–132]. Cymbimicin A and B are cyclophilin-binding structures, they were isolated from the culture broth of *Micromonospora* sp. A92-313709 (DSM 8594). However, cymbimicin A is more biologically active but with six fold lower activity compared to cyclosporin A [133]. IB-96212, has been isolated from the fermentation broth of a marine *Micromonospora* sp. L-25-ES25-008. This macrolide showed a very strong cytotoxic activity against P388 cell lines [134,135]. Arisostatins (A and B) are members of tetrocarcin class of

antibiotics and were isolated from the culture broth of a *Micromonospora* sp. TP-A0316 strain. Arisostatins showed antibiotic activity against Gram-positive bacteria as well as antitumor effects [136,137]. It was found that Arisostatin A induces apoptosis through the activation of caspase-3 and reactive oxygen species generation in AMC-HN-4 cells [138]. Micromonosporin A is a 24-membered polyene lactam macrolide, isolated from the *Micromonospora* sp. TT1-11 [139]. Recently, Levantilide C, 20-membered macrolide, was isolated from the *Micromonospora* sp. FIM07-0019. Levantilide C exhibited moderate antiproliferative activity against several tumor cell lines [140].

Everninomicins (A–E), are complex oligosaccharide antibiotics, produced by *M. carbonacea* NRRL 2972 and *M. carbonacea* subsp. *aurantiaca* NRRL 2997 [141,142]. The Everninomicin (SCH27899), Fig. 1(F) is produced by *M. carbonacea* var. *africana* ATCC 39149 [143]. Based on *in vitro* study, everninomicins B and D are active against all Gram-positive bacteria, *Neisseria*, and *Bacteroides* [144]. A multinational study of a total of 33 laboratories demonstrated that evernimicin possesses high antimicrobial activity against Gram-positive organisms, which was higher than that of vancomycin [145]. However, the clinical development of evernimicin (Ziracin) was discontinued in Phase III clinical trials, one of the reason, it could not be formulated reproducibly to be used as an intravenous drug [146,147]. Trehazolin, is a pseudodisaccharide, Fig. 1(G) and was first isolated from the culture broth of *Micromonospora* sp. SANK 62390. The antibiotic properties of this compound is mediated through trehalase glycosidase inhibition activity [148]. Trehalamine, was obtained by acid hydrolysis of trehazolin. Even though, it is poor inhibitor of trehalase but it inhibits more potently rat intestinal sucrase (IC_{50} 6.8 x 10^{-5} M) than trehazolin [149].

Halomicins A, B, C and D belong to the group of ansamycin antibiotics, are produced by *M. halophytica* subsp. *halophytica* NRRL 2998 and *M. halophytica* subsp. *nigra* NRRL 3097. These antibiotics are highly active against Gram-positive bacteria. The structure of Halomicin

A is shown in Fig. 1 (H) [41,150,151]. *Micromonospora* produced also oxazoles such as LL-E19085 alpha and Citreamicins (α, β, γ, ζ and η). These compounds were isolated from the fermentation broth of *M. citrea* NRRL 18351 [152,153].

Some species of the genus *Micromonospora* produce thiopeptide antibiotics, like, Sch 40832, which produced by *M. carbonecea* var. *africana* ATCC 39149. It has potent *in vitro* activity against Gram-positive bacteria [154–156]. The dipeptide, N-(2,6-diamino-6-hydroxymethylpimelyl)-L-alanine, was isolated from the culture broth of *M. chalcea* PA-3534. It exhibits antibacterial activity against *E. coli*, and the activity is synergistically enhanced when applied with cell wall synthesis-inhibitors [157]. The amino acid L-2-(1-methylcyclopropyl)glycine, produce by *M. miyakonensis* PA-4046, has also antibacterial activity [158,159]. The inhibitor of angiotensin I converting enzyme (ACE), K-13, is a cyclic dipeptide, isolated from the culture broth of, *M. halophytica* subsp. *exilisia* K-13 [160,161]. The antifungal compound Sch 37137 was isolated from the cultured broth of *Micromonospora* sp. SCC 1792 [162]. The antitumor antibiotic Korkormicins, are cyclic depsipeptides complex, produced by *Micromonospora* sp. C39500. The major component of the complex, korkormicin A, showed high *in vivo* antitumor activity against P388 leukemia and M109 lung carcinoma. Thus, it considered as potential antitumor agent for cancers with wild type p53 [163-166]. Rakicidin A is a cytotoxic agent and isolated from culture broth of a *Micromonospora* sp. R385-2 [167–169] and characterized by cyclic depsipeptide structure [167,170,171]. Thiocoraline, Fig. 1(I) is a thiodepsipeptide and produced by both of *Micromonospora* sp. ACM2-092 and *Micromonospora* sp. ML1. It showed potent cytotoxic activity against P-388, A-549 and MEL-28 cell lines, and exhibits a strong antibacterial activity against Gram-positive bacteria [172–175]. The antitumor activity of this antibiotic is mediated via DNA polymerase alpha inhibition and characterized by high cytotoxic potency against cancer cells [176,177]. Recently, it was reported that thiocoraline exhibits cytotoxic

activity in BON and H727 cells, activates the Notch pathway in carcinoids and reduces tumor progression [178,179]. Maklamicin was obtained from the culture broth of the endophytic strain *Micromonospora* sp. GMKU326. It demonstrates antibacterial activity against Gram-positive bacteria [180].

M-92, is a Naphthoquinones antibiotic complex, produced by *M. verruculosa* MCRL 0404. The six major components of the complex antibiotic have a similar type of antimicrobial spectrum. Between these components, VA-2 exhibited the most effective antimicrobial and antitumor activities [181–183]. Another Naphthoquinone, Crisamicin A, Fig. 1(J), is produced by *M. purpureochromogenes* subsp. *halotolerans* RV-79-9-101. It showed *in vitro* activity against Gram-positive bacteria, B16 murine melanoma cells, and herpes simplex, vaccinia, and vesicular stomatitis viruses [184,185]. 9-Hydroxycrisamicin A, was extracted from the broth of *Micromonospora* sp. SA246. This compound exhibited antibacterial and cytotoxic activity [186]. Yoon *et al.* (2004), found that 9-hydroxycrisamicin-A, showed potential for activating hepatitis B virus (HBV) replication [187]. K-259-2, an Anthraquinone, is inhibitor of Ca^{2+} and calmodulin-dependent cyclic nucleotide phosphodiesterase, it was obtained from the fermentation broth of *M. olivasterospora* K-259 [188]. Dynemicin A, was isolated from the culture broth of *M. chersina* ATCC 53710 and exhibited antibacterial and cytotoxic activity [189-191]. Deoxy-dynemicin A, was produced together with dynemicin A in culture of *M. globosa* FERM P-10651 [192]. Lupinacidins A, B and C, are produced by *M. lupini* Lupac 08, isolated from root nodules of *Lupinus angustifolius* collected in the mid-west Spain [193,194]. Lupinacidin C displayed a potent anti-invasive activity against murine colon 26-L5 carcinoma cells [194].

Streptonigrin and 7-(1-methyl-2 oxopropyl) streptonigrin are two other bioactive compounds produced by *Micromonospora* sp. IM 2670. Streptonigrin can induce apoptosis through a p53-dependent pathway in human neuroblastoma cells [195]. The quinocycline

antibiotic Kosinostatin, was isolated from the culture broth of *Micromonospora* sp. TP-A0468. It showed antibacterial and cytotoxic activity [196,197]. Spartanamicins A and B, are two antifungal anthracycline antibiotics produced by *Micromonospora* sp. ATCC 53803, isolated from a potted soil containing asparagus (*Asparagus officinalis* L.) plants [198]. Cororubicin, Fig. 1(K), generated superoxide radicals in KB human epidermoid cancer cells and N18-RE-105 neuronal hybridoma cells, and showed cytotoxicity. This antibiotic is produced by *Micromonospora* sp. JY16 isolated from soil [199]. Micromonomycin is antibacterial anthracycline compound, showed potent inhibitory activity against *S. aureus, Streptococcus pneumoniae*, and supersensitive *E. coli*, and also displayed weak antifungal activity against *S. cerevisiae* and *C. albicans* [200]. In 2012, Sousa *et al*., isolated *Micromonospora* strains associated with the tunicate *Eudistoma vannamei* and can produce four new anthracyclinones, two of them were cytotoxic against human colon adenocarcinoma cell line HCT-8 [201].

Hazimicins, a class of broad spectrum antibiotics, were isolated from the culture broth of *M. echinospora* var. *challisensis* SCC 1411 [202]. The nucleoside antibiotics, Dapiramicin A and B, have been isolated from the fermentation broth of *Micromonospora* sp. SF-1917. Dapiramicin A was highly effective in the control of sheath blight, a destructive disease of rice plants caused by *Rhizoctonia solani*, in a pot test [203,204]. Neihumicin was isolated from the fermentation broth of *M. neihuensis* Wu NH3-1 and shows *in vitro* cytotoxicity against KB tissue culture cells as well as antifungal activity against *S. cerevisiae* ATCC 9763 [205-207]. Sibanomicin, is a pyrrolo-[1,4]-benzodiazepine antitumor antibiotic produced by a culture of *Micromonospora* sp. SF2364 [208]. Macquarimicins (A, B and C), were produced by the two strains *M. chalcea* AB 965S-73 and *M. chalcea* AB 969J-62. Macquarimicin B has inhibitory activity against the leukemia cell line P-388 [209,210]. A naturally occurring dibenzodiazepine, BU-4664L, was produced in fermentation broth of *Micromonospora* sp.

ATCC 55378. The compound possesses anti-inflammatory and anti-tumor activities [211]. The initial structure assigned for BU-4664L was revised by Igarashi *et al.* [212]. In 2010, Miyanaga *et al.* demonstrated that BU-4664L suppresses invasion and angiogenesis *in vitro*. It inhibited the gelatinase activities of MMP-2 and MMP-9 with an IC_{50} value of 0.46 μg/mL and 0.60 μg/mL, respectively [213].

YM-47515, is an isonitrile antibiotic, produced by *M. echinospora* subsp. *echinospora* Y-03559J and showed antimicrobial activity against Gram-positive bacteria [214]. The antibiotic glutarimide streptimidone, Ao58A, showed a high antifungal activity against some plant pathogenic fungi and inhibit the growth of *Phytophthora capsici, Didymella bryoniae, Magnaporthe grisea,* and *Botrytis cinerea* in the range of 3-10 $\mu g/mL^{-1}$ of MICs [215]. Bravomicins, are obtained by fermentation of a strain of *M. polytrota*, isolated from soil sample. Six bioactive compounds, designated bravomicins (A–F), are obtained and found to have antibacetrial activity against methicillin resistant *S. aureus* (MRSA) and multiply resistant *E. faecium* (MREF) [216]. The initial structure proposed by the US 5,994,543 patent, was revised by Banskota *et al.* (2009), and they also suggested a strong similarity between the structures of TLN-05220, echinosporamicin and bravomicin A [217]. Staurosporine, 4'-N-methyl-5'-hydroxystaurosporine and 5'-hydroxystaurosporine, were produced by the marine strain, *Micromonospora* sp. L-31-CLCO-002, isolated from Sponge *Clathrina coriacea*. They showed cytotoxic activity [218]. SB-219383, the potent and selective inhibitor of bacterial tyrosyl-tRNA synthetase, was isolated from *Micromonospora* sp. NCIMB 40684 [219,220]. Lomaiviticins A and B, are produced by *M. lomaivitiensis* LL-37I366, isolated from ascidian *Polysyncraton lithostrotum*. Lomaiviticin A and B were demonstrated to be potent DNA damaging agents by the biochemical induction assay (BIA). Lomaiviticins C−E, were isolated recently by Woo *et al.* (2012). It was found that the dimeric diazofluorene of (−)-lomaiviticin exhibit antiproliferative activity [221,222]. The lomaiviticin A was also tested

against different cancer cell lines and showed cytotoxicity with IC_{50} values ranging between 0.01 and 98 ng/mL. Lomaiviticins A and B showed also antibacterial activity against Gram-positive bacteria [223].

R176502, is an antiproliferative bafilolide metabolite, extracted from liquid cultures of *Micromonospora* sp. JS1035 [224]. Sch725418, is a Diketopiperazine, isolated from *Micromonospora* sp. It exhibits inhibitory activity against a supersensitive strain of *S. cerevisiae* [225]. Echinosporamicin, an antibiotic produced by *M. echinospora* subsp. *echinospora* LL-P175, contain aromatic polycyclic system and a piperazinone moiety. It exhibited potent activity against methicillin-resistant Staphylococci and vancomycin-resistant Enterococci strains [226]. Diazepinomicin is a dibenzodiazepine alkaloid compound originally isolated from a marine *Micromonospora* sp. DPJ12 [227]. It was also produced by *Micromonospora* sp. RV115 strain isolated from the sponge *Aplysina aerophoba* [228]. Preclinical data demonstrated that diozepinomicin is a targeted anticancer drug with dual activity: selective binding to the peripheral benzodiazepine receptor (PBR), which induces tumor apoptosis, and inhibition of the Ras/MAP kinase signaling pathway [229]. It showed also antioxidant activity for diazepinomicinin human kidney (HK-2) and human promyelocytic (HL-60) cell lines. In addition, it exhibits antiparasitic activity against trypomastigote forms of *Trypanosoma brucei* with IC_{50} of 13.5 mM [230]. Retymicin, Galtamycin B, Saquayamycin Z and Ribofuranosyllumichrome, were produced by *Micromonospora* sp. Tü 6368. Retymicin, galtamycin B and saquayamycin Z show cytostatic activity against several human tumor cell lines [231,232].

In addition to these compounds, many other antibiotics previously produced by other actinomycetes were also produced by *Micromonospora*. Neomycin B, which was isolated originally from *Streptomyces fradiae* in 1949, was also found in the culture broth of *Micromonospora* sp. 69-683 [233]. The comparison of aminoglycoside acetyltransferase-

encoding gene (aac), and aminoglycoside phosphoryltransferase gene (aph) of *Streptomyces fradiae* and *Mcromonospora chalcea* indicates considerable divergence [234,235]. Others antibiotics produced by other genera were also reported by genus *Micromonospora*. These include Primycin [41,236], Rifamycins [41,237,238], Erythromycin B [41,239]. Actinomycins [240,241], Bottromycins [41], and Telomycin [242–244].

4. Different strategies for the development of new antibiotics from the genus *Micromonospora*.

Understanding how the researchers identified antibiotics produced by *Micromonospora* strains in the past, and updating knowledge for the new analytical, biological and bioinformatics tools, can help to improve the strategy for the discovery of new chemical of antibiotic properties, which can reduce the cost and the time during biomolecule discovery. Fig. 2 summarizes the complete biomolecule discovery platform of potential antimicrobial activity from the genus *Micromonospora.*

The isolation source is important for the isolation of new strains, which can produce new compounds. In the past, only cultured *Micromonospora* strains were used as source of antibiotics, but the developments of culture-independent methods increased the potential of novel molecule discovery. Using metabolomics-based tools can help for the early screening to identify new molecule. Utilization of genetic engineering, metabolomic pathways engineering, bioprocess development, and biotransformation techniques are widely applied not only to increase yields of production of secondary metabolites but also to lead to the synthesis of new more effective compounds. In addition, synthetic chemistry and structure modification methods are also important as component of the drug discovery platform in order to obtain a bioeffective final product approved by the regulatory authorities.

4.1. Natural habitat of *Micromonospora* and the research of new resources

In general, soil is the main source for the isolation of *Micromonospora* producing antibiotics strains (Table 1). Also, they have been found to be constituents of endophytic actinobacterial populations recovered from plant tissues; they are a normal occupant of actinorhizal nodules [245]. In aquatic ecosystems (freshwater and marine environments), they were isolated from water samples, sediments, and aquatic organisms such as ascidians, sponges, soft coral and molluscs [246]. From the geographical point of view, from the data presented in Table 1, the highest numbers of *Micromonospora* producing antibiotics strains were isolated from Japan and United States. The 6 new species of *Micromonospora* discovered in 2014, was isolated from China, and one of them was isolated from Chinese black ant (*Polyrhachis vicina* Roger) [22–24,247–249]. Biogeographic studies of the distribution of bacterial strains producing secondary metabolites, are helpful for the selection of sampling coordinates [250]. For example, in the recent study of Charlop-Powers and his group was focused on the comparative biosynthetic gene richness and diversity of 96 soil microbiomes from different soil samples in USA. They used 454-pyroseqencing of non-ribosomal peptide adenylation (AD) and polyketide ketosynthase (KS) domain and concluded that the arid soils show the richest observed biosynthetic diversity, whereas brackish sediments and pine forest soils show the least [251].

4.2. Culture depending approach

The cultivation approach is still important in the screening for the discovery of new natural products. Different methods of sample pretreatment and medium formulation were used in the isolation and screening of *Micromonospora* species. Most of these methods use the resistance characteristic of *Micromonospora* spores as target [14,17,252,253]. For example, it was found that sample pretreatment at 65°C for 30 min is effective for the isolation of

Micromonospora colonies from the estuarine sediments [254]. Bacteriophages were also applied in the screening of rare actinomycetes that can produce bioactive compounds [255]. The innovation of new isolation methods, can be useful for the cultivation of new *Micromonospora* strains, these include novel media formulation, new pretreatment protocols, and *in situ* cultivation strategy [256]. The best example is that of the isolation of the teixobactin producer strain *Eleftheria terrae* using new technique called isolation Chip Technique (iChip) [12].

4.3. Culture-independent approach

In the past, only cultured microorganisms were the source of natural product drug discovery, but the developments of culture-independent methods have allowed additional insights into the drug discovery research. Metagenomics is a reliable approach for the study of the micororganisms diversity, the measure of the potential reservoir of natural compounds and antibiotic resistance genes in the cultured and uncultured microbial population in the environment. In the same manner, meta-transcriptomics and meta-proteomics can also be used. The development of the next-generation deep sequencing, bio-informatics tools and available databases, represent a strong support to this line of research [257–262].

4.4. Metabolomics-based approaches for secondary metabolite discovery

Determination of the microbial metabolome is an important way for natural product discovery, and it is supported with the recent development of tools and methods that can detect and quantify metabolites [263–267]. The emerging of mass spectrometry techniques allowed the direct analysis of microbial colonies [268]. The matrix-assisted laser desorption/ionization mass spectrometry (MALDI-TOF MS) is used for the fast identification of bacterial and fungal microorganisms [269]. The MALDI-TOF MS was used before in

characterization of some *Micromonospora* species [270]. The recent research has used this method for the rapid *in situ* detection of actinomycins in surface extracts of *Streptomyces* cells picked from agar plates [271]. Others promising methods of imaging mass spectrometry and real-time mass spectrometry will be also good tools for the identification of natural product from bacteria in the future [268], For example, Hsu *et al.* (2013), used ambient Electrospray Ionization Flow-Probe, to study in Real-Time metabolomics on living microorganisms [268,272]. On the other hand, the use mass spectrometry methods for microorganisms isolated from extreme environments may encountered some problems, like the database of MALDI TOF MS which need extension for reliable identification of bacteria from extreme environments [273]. For the best use of these methods for the identification and the early screening of *Micromonospora* strains, a comprehensive database of bioactive compounds should be available for comparison.

Others platforms such as Nuclear Magnetic Resonance (NMR), Gas Chromatography-Mass Spectrometry (GC/MS), and Liquid Chromatography-Mass Spectrometry (LC/MS) are also useful in metabolomics study. Nowadays, LC/MS is the most widely used method in metabolomic analysis, due to its ability to separate and detect a wide range of molecules with high sensitivity [265,274]. Hou *et al.* [275] found a principal component analysis (PCA) using LC/MS is effective in the screening of marine bacterial strains of high metabolic activities and the detection of new products in drug discovery programs. Micromonolactam, produced by *Micromonospora* sp. CMS I1-30 and *Micromonospora* sp. CMS I2-32, was discovered during routine chemical screening (LC-DAD-ESIMS) of chemical fraction library of marine actinobacteria [276]. Recently, the secondary metabolites Neomacquarimicin, produced by *Micromonospora* sp. NPS2077, was identified during screening program for secondary metabolite with a polycyclic ring system from a bacterial species using LC-MS/UV-based chemical analysis [277]. In addition, the metabolomics methods are adapted to

be used in the high-throughput discovery metabolomics platforms. Thus, it is now possible to do mass spectrometric analysis of several hundred metabolites, with dense coverage of primary metabolism, in complex biological extracts and at throughputs of >1000 samples per day and the process can also be directed to specific target like enzyme activity [278,279]. The recent Advances in Infrared and Raman spectroscopy are also helpful in the rapid and low cost differentiation, identification and metabolome characterization of microbial strains [280,281]. Zhao *et al.* [282] studied FT-IR spectra of *Micromonospora* strains isolated from coastal sediments and found that this method can be applied to indicate in which environmental isolates have been cultured previously.

4.5. Screening of biological activities

It is essential before starting of any screening program of microorganisms for therapeutic metabolites production to select biological target. The classical screening methods were focused at first on antimicrobial activity (i.e. antibacterial, antifungal, anti-parasitic and antiviral). After the emergence and widespread of cancer and other new diseases, the current screening also include anticancer, cytotoxic, antioxidant and anti-inflammatory activities [246,283]. Nowadays, screening could include more specific target, for example: the antitumor antibiotics calicheamicins were discovered in a fermentation products screening program by the use of the biochemical induction assay (BIA), which utilized a genetically engineered strain of *E. coli* to detect DNA damaging agents [111]. MS-444, is naphtho[2,3-c] furan derivatives, Fig. 1(L), also exhibited myosin light-chain kinase inhibition activity (MLCK), without any antimicrobial effect [284,285]. This compound interfere with HuR RNA binding, HuR trafficking, cytokine expression and T-cell activation and showed good pharmacokinetics and low toxicity in mice [286]. Antascomicins, were obtained from a wide range screening program of more than 12,000 strains for selective isolation of macrophilin-

binding metabolites. The most active strain was identified and given the name *Micromonospora* sp. A92-306401 and deposited in the German collection of microbes and cell culture under accession No. (DSMZ 8429). Antascomicins are structurally related to FK506, bind strongly to FKBP12 (also known as FKBPA1), but do not show immunosuppressive activity [287]. In addition, the presence of large therapeutic target databases is also helpful for the development of new biological assay [288]. Currently, with the development of High Throughput Screening (HTS) process, it is possible for concurrent screening of multiple biological activities of a large number of compounds [289].

4.6. Genomic and metabolomic pathways engineering

Determination of gene cluster required for the biosynthesis of certain metabolite can help to understand the possible biosynthetic pathways and thus used for the optimization of secondary metabolites production by metabolic engineering tools. The Gentamicin gene cluster was sequenced [43], it is a total of 32 ORFs have been assigned to the gentamicins gene cluster, 19–25 could encode biosynthetic enzyme functions, like gntK, a gene required for the methylation of purpurosamine C-6′ in gentamicin biosynthesis [42,44]. The assigning functions to individual gene in gentamicin gene cluster, facilitated the study of diverse antibiotic biosynthesis pathways. Several biosynthetic pathways for gentamicin C complex production were proposed [43,44,290]. In 2014, Guo *et al.*, gave information about late stage biosynthesis of gentamicins from the pseudo-disaccharideparomamine to the branch point at gentamicin X2, which was known substrate for C-methylation at C-6' to form G418 catalyzed by the radical SAM-dependent enzyme GenK, might instead undergo oxidation at C-6' to form an aldehyde, catalyzed by the flavin-linked dehydrogenase GenQ [290]. Recently, Huang *et al*. [291] identified four key enzymes that lead from the first-formed pseudotrisaccharide to gentamicin X2. These data can help for the optimization of secondary

metabolites production. For example, to obtain a gentamicin C1a-overproducing strain, gacD gene was inactivated in *M. echinospora.* The inactivation of gacD blocks the metabolic pathways from X2 to G418 and leads to the accumulation of gentamicin C1a [292]. Through the use of combined traditional and recombinant genetic techniques it was possible to obtain strain with improved G418 production by 19 fold with minimal by product formation [293].

The function of cytochrome P450 enzyme-encoding genes *rosC* and *rosD* in the biosynthesis of rosamicin by *M. rosaria* was reported [294]. The production of rosamicin derivatives in *M. rosaria* was enhanced by the introduction of D-mycinose biosynthetic gene with PhiC31-derived integration vector pSET152 [295]. Recent research showed also that the introduction of d-mycinose biosynthesis genes in mycinamicin II biosynthesis gene cluster of *M. guriseorubida* A11725 into the *rosC* and *rosD* disrupted mutants of *M. rosaria* IFO13697 enhanced the production process. The resulting engineered strains, *M. rosaria* TPMA0054 and TPMA0069, produced mycinosyl rosamicin derivatives, IZIV and IZV, respectively. IZIV was identified as a novel mycinosyl rosamicin derivative, 23-O-mycinosyl-20-deoxo-20-dihydrorosamicin [296]. By using genome scanning data of the hazimicin producer, *M. echinospora* ssp. *challisensis* NRRL 12255, it was possible to isolate TLN-05220, TLN-05223, which have cytotoxic activities against various human tumor cell lines [217].

Others gene cluster and biosynthetic pathways of *Micromonospora* antibiotics have been reported, like the biosynthetic gene cluster of thiocoraline [297–299], evernimicin biosynthetic gene cluster from *M.* carbonacea var. *africana* ATCC39149 [143], mycinamycin gene cluster and biosyntheic pathway [300–303], and diazepinomicin biosynthetic pathway [304–306]. More recently, methionine gamma-lyase gene was identified in the calicheamicin biosynthesis gene cluster of *M. echinospora* [307].

4.7. Bioprocess development and Biotransformation

The aim of the bioprocess development is to increase yields of secondary metabolites production. Bioprocess is influenced by several factors, from the culture medium design (nutrients composition and concentrations), to cultivation parameters (temperature, pH, agitation, aeration, etc…) [308–310]. Therefore, it is important to optimize all these parameters for maximal production yield using different approaches and also to transfer the process from small laboratory scale to pilot and large scale bioreactor level.

For example, gentamicin is manufactured through a complex process using *Micromonospora* strains. In general, the gentamicin is produced in submerged fermentation. The production medium optimization is an empirical process, as medium must be economic with high yield of production. Also it is important to use ingredients which help the down-stream process [311]. Different Carbon sources were used in gentamicin production such as starch, sucrose, and soybean oil [312–316]. Nitrogen sources are important for cell growth and antibiotic production. Soybean meal, yeast extract, peptone and corn steep liquor have been reported as suitable substrates for gentamicin production [312,313,317,318]. Di-potassium phosphate (K_2HPO_4) was usually the source of phosphate, and it is essential for the growth and antibiotic production [311]. It is apparent that cobalt is a requisite for the gentamicin synthesis. Charney *et al*. [312] found that medium must contain at least 0.01 μg/ml of cobalt (as $CoCl_2.6H_2O$), which is equivalent to 2.5×10^{-9} gram of cobalt per milliliter. In 2006, Himabindu *et al.* [315] used Response Surface Methodology (RSM) for the medium optimization to increase production of gentamicin by *M. echinospora* ATCC 15838. They found that a medium with Starch (9 g/L), Soyabean meal (3 g/L), K_2HPO_4 (0.9 g/L) and $CoCl_2$ (0.001g/L), can give 880 (mg/L) of gentamicin. However, the problem of using complex medium components is seasonal variations and consistency of the chemical composition, which affect the yiled of the production process [311,319]. The pH of the culture medium can affect growth and gentamicin production in submerged cultures. Charney

et al. [312], found that the optimal pH for production lies between 6.9 and 7.0. Other research conducted by Abou-zeid and Eissa [313] showed that the most suitable initial pH for antibiotic production was between 7 and 7.5. The dissolved oxygen (DO) is other critical limiting factor for both growth and gentamicin production. It was reported that gentamicin production reachs its maximal production when keeping the DO level at 40% saturation [311,320]. In addition, physiological status and size of the inoculum can also play critical role in gentamincin production process [311,321].

In general, gentamicin is usually produced as intracellular product. Different physical and chemical approaches were used to extract the antibiotic from the cells. Among them, ultrasonic treatment was the most efficient method in this process [317,322]. However, for large scale production, gentamycins are usually recovered by adsorption, solvent extraction, and crystallization [311]. One of the first reports of gentamicin purification was the work of Luedemann and Weinstein in 1963, in which they used cationic and anionic exchange adsorption column and methanol extraction in the purification process of gentamicin [323]. As gentamicin is a complex consisting of several minor and three major components, the proportions of these components can vary depending on the fermentation process, and some of the impurities can be also toxic [311,324]. Therefore, pharmaceutical industries are usually earger to develop more powerful methods of separation. In 2012, Grote *et al.* [324] described a method for synthesis of a single conjugate of gentamicin. They found that the reaction of the gentamicin complex with excess benzyl chloroformate provided a mixture of the amine protected components which can be separable by preparative HPLC using UV detection, which give opportunity to get a single gentamicin conjugate.

Gentamicin is administered intravenously, and the bactericidal activity is “concentration-dependent”. Therefore, the dose used should be carefully adjusted. Also, gentamicin is not metabolized and eliminated by the kidneys and overdoses can increase the risks of renal

toxicity and ototoxicity [325,326]. Routinely, in the pharmaceutical industry, and because of the chemical nature of the gentamicin complex, only the relative percentage of its major constituents are measured by liquid chromatography combined with pulsed electrochemical detection (LC–PED). Microbiological assays, immunoassays, and ELISA methods also can be used in gentamicin analysis [327]. Li *et al.* [328], reported a LC–PED method, with a reversed-phase C18 column and a mobile phase consisting of trifluoroacetic acid (TFA), pentafluoropropionic acid (PFPA), sodium hydroxide and acetonitrile, which showed better separation and more sensitive detection of the gentamicin components than the method using a polymer column. In the same time, Vucicevic-Prcetic *et al.* [327], developed a new analytical method for the determination of gentamicin based on Liquid Chromatography with tandem Mass Spectrometry (LC/MS/MS), which provides complete base line separation of components C_1, C_{1a}, C_2, C_{2a} and C_{2b} according to the European and British Pharmacopoeias.

Biotransformation approach is also an efficient tool for the modification of existing antibiotic molecule to create new therapeutic agents. The addition of analogues of 2-deoxystreptamine to mutant of *M. inyoensis* NRRL 3292, the sisomicin-producing organism, resulted in the formation of new antibiotics called Mutamicins [329]. Mutamicin 1, produced by the addition of streptamine to the fermentation broth, and Mutamicin 2 is produced by the addition of 2, 5-dideoxystreptamine [329]. Other research showed also that employing a recombinant *Streptomyces venezuelae* strain as a microbial catalyst, a reduced macrolide, 10, 11-dihydrorosamicin, was created from rosamicin macrolide. The new rosamicin analog showed 2-4-fold higher antibacterial activity against two strains of methicillin-resistant *S. aureus* compared to its parent rosamicin [330]. In the presence of serum, rustmicin rapidly epimerizes at the C-2 position and is converted to a γ-lactone, a product that is devoid of activity. In order to synthesize derivatives of Rustmicin with improved chemical stability and

antifungal activity profiles, Shafiee *et al*. [331,332], used *Streptomyces halstedii*, in order to synthesize more stable compounds by the way of microbial hydroxylation.

4.8. Synthetic chemistry and structure modification

In many cases, it is difficult to use antibiotics with their original structure directly as therapeutic agents. This based on the development of antibiotic resistance strains, cytoxicity of the molecule, and improper pharmacokinetic and pharmacodynamics of the compound. For example, Gentamicin C1a can be used as a starting material for etimicin production, which is an antibiotic against drug-resistant bacteria and exhibit antimicrobial activity against both Gram-positive and Gram-negative bacteria [333,334]. Isepamicin is a semi-synthetic derivative of gentamicin B, which possesses a high level of stability to aminoglycoside inactivating enzymes and low levels of toxicity to the kidney and inner ear. In addition, isepamicinis active against Gram-negative bacteria with resistance to amikacin and other aminoglycosides [335–337]. Netilmicin is a semisynthetic 1-N-ethyl derivative of sisomicin has similar activity as for gentamicin but less toxic [338]. Plazomicin, was synthetically derived from sisomicin by appending a hydroxy-aminobutyric acid substituent at position 1 and a hydroxyethyl substituent at position 6′. It is characterized by a dose-depending activity against both Gram-positive and Gram-negative pathogens [339–341]. In addition, derivative 6'-hydroxysisomicin, exhibits promising activity against a broad range of protozoan parasites [342]. Thiochoraline can be chemically synthesis [343,344], and different product were derivative from thiocoraline, like antitumor antibiotics NMe-azathiocoraline and Oxathiocoraline [345–347]. Already MS-444 and Rakicidin A have been also successfully chemically synthesized [171,348].

5. Future perspectives

The genus *Micromonospora* had been the source of many drugs, some of them, like gentamicin, are considered as essential to the global health medical system [46]. Although, there were some disappointments, despite the large number of papers and patents published, few number of bioactive molecules from this group of microorganisms reached the pharmaceutical market. In many cases, the drug development process was terminated at clinical trial level such as in case of evernimicin and rosaramicin [147]. However, new legislations and investments in biotechnology, can help the antibiotic development. In the last decade 11 new antibiotics were approved, and four in 2014 alone [9,349]. The biopharmaceutical industry need to be adapted to the global antibacterial drugs market, which is to reach an estimated value of $45.09 billion in 2019 [350], and the current prescription data for aminoglycosides as antimicrobial represent over a $500 million in U.S market. That is why, some biopharmaceutical companies start to acquire the intellectual property rights covering next-generation antibiotic derivatives, which retain the biologic activity, and appear less cytotoxic [350,351]. Also, reviving old antibiotics could be a good approach [352]. With the recent advances in screening program management, and the availability of more sophisticated analytical, biological and bioinformatics tools, the study of the genus *Micromonospora* is still important in the race of the discovery of new therapeutic agents. The investigation of new isolation sources and the use of innovative methods are good alternatives for the discovery of novel antibiotics from the genus *Micromonospora*.

Declarations of interest

The authors report no declarations of interest.

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Table 1.

Antibiotics molecules produced by the genus *Micromonospora*

Legend for Figures

Fig. 1. Chemical structure of some antibiotics produced by different *Micromonospora* strains. The molecular structures were downloaded from ChemSpider [356].

Fig. 2. Different approaches used in the development of new antibiotics from the genus *Micromonospora*.

Table 1. Antibiotics molecules produced by the genus *Micromonospora*

Antibiotic	Class	Strain	Source	Year	Biological Activity	Ref.
Micromonosporin	Chromoprotein	*Micromonospora* sp.	Soil	1947	Antibacterial activity	[29]
Actinomycins	Polypeptide	*Micromonospora* sp. 608	-	1951	Anticancer activity	[236]
Gentamicins	Aminoglycosides	*M. echinospora* NRRL 2953 *M. echinospora* NRRL 2985	Soil, New York, USA Soil, New York, USA	1963	Antibacterial activity	[37]
Everninomicins	Oligosaccharides	*M. carbonacea* NRRL 2972 *M. carbonacea* subsp. *aurantiaca* NRRL 2997 *M. carbonacea* var. *africana* ATCC39149	Soil, New York, USA Soil, New York, USA Soil, Kenya	1964	Antibacterial activity	[38, 137]
Halomicins	Ansamysins	*M. halophytica* subsp. *halophytica* NRRL 2998 *M. halophytica* subsp. *nigra* NRRL 3097	Salt pool, Syracuse, New York, USA	1967	Antibacterial activity	[146]
Antibiotic 460	Aminoglycosides	*M. chalcea* subsp. *flavida* NRRL 3222	Soil, New York, USA	1969	Antibacterial activity	[50]
Megalomicins	Macrolides	*M. megalomicea* subsp. *megalomicea* NRRL 3274 *M. megalomicea* subsp. *nigra* NRRL 3275	Soil	1969	Antibacterial activity Antiparasitic activity Antiviral activity	[79, 81]
Primycin	Macrolides	*M. galeriensis*	-	1969	Antibacterial activity Antifungal activity	[38, 232]
Sisomicin	Aminoglycosides	*M. inyoensis* NRRL 3292	Soil, California, USA	1970	Antibacterial activity	[51]
Rosamicin	Macrolides	*M. rosaria* NRRL 3718	Soil, Texas, USA	1972	Antibacterial activity	[84]
Neomycin B	Aminoglycosides	*M. chalcea* 69-683	-	1973	Antibacterial activity	[229]
Verdamicin	Aminoglycosides	*M. grisea* NRRL 3800	Soil, Kansas, USA.	1974	Antibacterial activity	[59]
Mutamicins	Aminoglycosides	*M. inyoensis* NRRL 3292	Soil, California, USA	1974	Antibacterial activity	[325]
Sagamicin	Aminoglycosides	*M. sagamiensis* subsp. *nonreducans* ATCC 21803 *M. sagamiensis* ATCC 21826	Soil, Illinois, USA Soil, Kanagawa, Japan	1974	Antibacterial activity	[60, 61]
Antibiotic G-418	Aminoglycosides	*M. echinospora* NRRL 5326	Soil	1974	Antibacterial activity Antiparasitic activity Selective agent for mammalian cell studies	[46, 47]
Bottromycin	Macrocyclic peptide	*M. chalcea* FERM-P 1823	-	1974	Antibacterial activity	[38]
Antibiotics JI-20	Aminoglycosides	*M. echinospora* NRRL 5467	Soil, New York, USA	1975	Antibacterial activity	[38, 49]

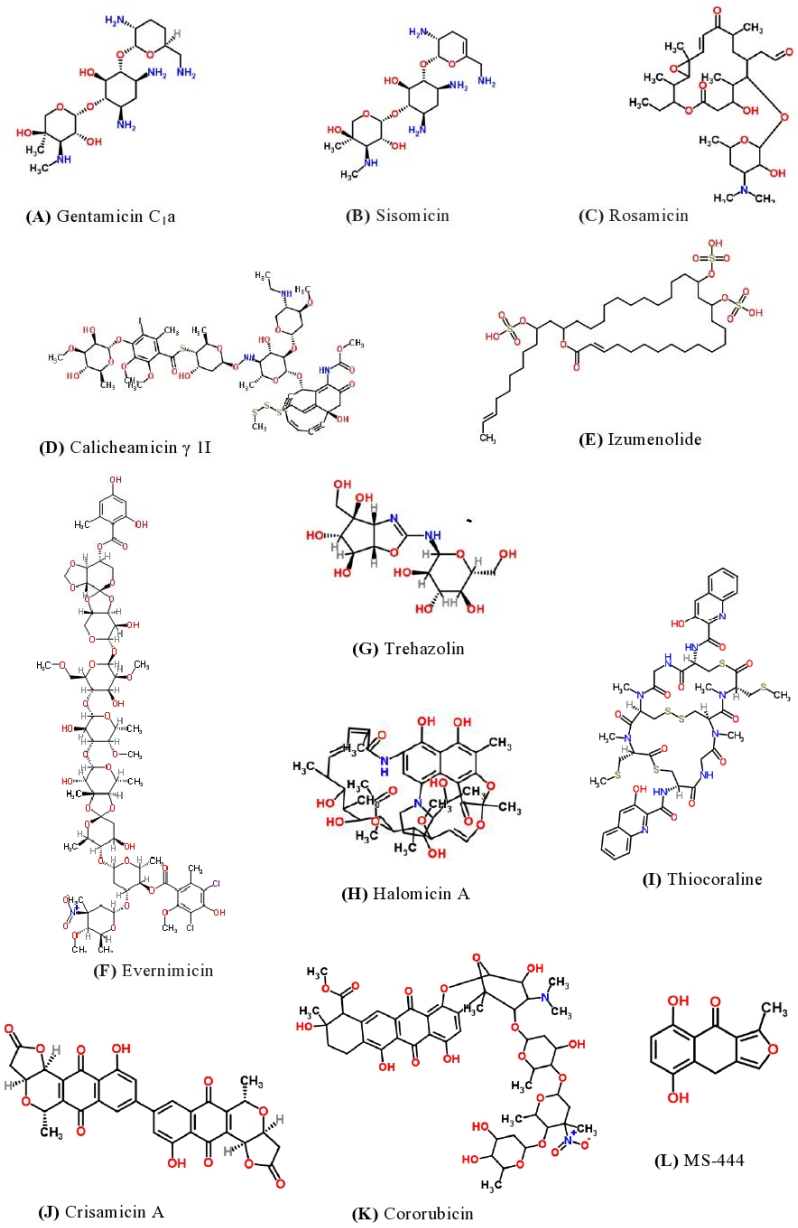
Rifamycins	Ansamysins	*M. lacustris* ATCC 21975	Mud, Connecticut, USA	1975	Antibacterial activity	[233]
Antibiotic G-52	Aminoglycosides	*M. zionensis* NRRL 5466	Soil, Utah, USA	1975	Antibacterial activity	[56]
Fortimicins	Aminoglycosides	*M. olivasterospora* ATCC 21819	Soil. Hiroshima, Japan	1976	Antibacterial activity	[63]
Juvenimicins	Macrolides	*M. chalcea* subsp. *izumensis* ATCC 21561	Soil, Osaka, Japan	1976	Antibacterial activity	[90]
Erythromycin B	Macrolides	*Micromonospora* sp. 1225	-	1976	Antibacterial activity	[38]
Mycinamicins	Macrolides	*M. grisseorubida* A11725	Soil, Toyama, Japan	1980	Antibacterial activity	[93]
Antlermicins	Aminoglycosides	*M. chalcea* subsp. *kazitnoensis* T-90	Soil, Akita, Japan	1980	Antibacterial activity Anticancer activity	[70, 71]
Tetrocarcins	Aminoglycosides	*M. chalcea* KY11091	Soil, Miyagi, Japan	1980	Antibacterial activity Anticancer activity	[349]
Izumenolide	Lactones	*M. chalcea* subsp. *izumensis* SC 11133	Soil, South Africa	1980	Antibacterial activity	[114]
N-(2,6-Diamino-6-hydroxymethylpimelyl)-L-alanine	Dipeptide	*M. chalcea* PA-3534	Soil, Ariake Bay, Fukuoka. Japan	1981	Antibacterial activity	[153]
L-2-(1-Methylcyclopropyl) glycine	Amino acid	*M. miyakonensis* PA-4046	Soil, Okinawa, Japan	1981	Antibacterial activity	[154, 155]
Combimicins	Aminoglycoside	*Micromonospora* sp. ATCC 31348 *Micromonospora* sp. ATCC 31349	Soil, Japan	1981	Antibacterial activity	[76]
Dotriacolide	Lactones	*M. echinospora* MG299-fF35	Soil, Hokkaido, Japan	1981	Antibacterial activity	[118]
M-92	Naphthoquinones	*M. verruculosa* M-92	Soil, Nago City, Okinawa, Japan	1982	Antibacterial activity Anticancer activity	[177]
Hazimicins	Nitriles	*M. echinospora* var. *challisensis* SCC 1411	Soil, Challis, Idaho. USA	1983	Antibacterial activity Anti- yeast avtivity	[198]
Dapiramicin	Ribonucleosides	*Micromonospora* sp. SF-1917	Soil, Japan	1983	Antifungal activity	[199]
Rustmicin	Macrolides	*M. chalcea* 980-MC1	Soil, Japan	1985	Antifungal activity	[120]
Clostomicins	Macrolide	*M. echinospora* subsp. *armeniaca* KMR-593	Soil, Niigata, Japan	1986	Antibacterial activity	[122]
Crisamicin A	Naphthoquinones	*M. purpureochromogenes* subsp. *halotolerans* RV-79-9-101	Mud sample, Philippines	1986	Antibacterial activity Anticancer activity	[180]
K-13	Cyclic Peptides	*M. halophytica* subsp. *exilisia* K-13	Soil	1987	Inhibitor of angiotensin I converting enzyme (ACE)	[156]
K-259-2	Anthraquinone	*M. olivasterospora* K-259	Soil, Nagaizumi-cho, Sunto-gun, Shizuoka, Japan	1987	Inhibitor of Ca2+ and calmodulin-dependent	[184]

					cyclic nucleotide phosphodiesterase	
Sch 37137	Dipeptides	*Micromonospora* sp. SCC 1792	Soil, South Africa	1988	Antifungal activity	[158]
Neihumicin	Pyrazines	*M. neihuenis* NH3-1 Wu	Soil, Nei-Hu, near Taipei, Taiwan	1988	Cytotoxic activity Antifungal activity	[201]
Sibanomicin	Pyrrole-Benzodiazepines	*Micromonospora* sp. SF2364		1988	Anticancer activity	[204]
LL-E19085 alpha	Oxazoles	*M. citrea* NRRL 18351	Soil, Tanzania	1989	Antibacterial activity	[148]
Calicheamicins	Enediynes	*M. echinospora* sp. *calichensis*. NRRL 15839 *M. echinospora* sp. *calichensis* NRRL 15975 *M. echinospora* sp. *calichensis* NRRL 18149	Soil, Texas, USA	1989	Antibacterial activity Anticancer activity	[106, 107]
Citreamicins	Oxazoles	*M. citrea* NRRL 18351	Soil, Tanzania	1990	Antibacterial activity	[149]
Dynemicin A	Anthraquinone	*M. chersina* ATCC 53710	Soil, India	1989	Antibacterial activity Anticancer activity	[185]
Deoxydynemicin A	Anthraquinone	*M. globosa* FERM P-10651	Soil, Japan	1990	Antibacterial activity	[188]
Trehazolin	Pseudodisaccharide	*Micromonospora* sp. SANK 62390	Soil, Tochigi, Japan	1991	Trehalase glycosidase inhibitor	[144]
Spartanamicins	Anthracycline	*Micromonospora* sp. ATCC 53803	Soil	1992	Antifungal activity	[194]
Trehalamine	Oxazoles	*Micromonospora* sp. SANK 62390	Soil, Nikko, Tochigi, Japan	1993	Inhibit rat intestinal sucrase	[145]
Quinolidomicins	Macrolides	*Micromonospora* sp. JY16 - FERM BP-3940	Soil, Gunma, Japan	1993	Antitumoral activity	[124]
AC6H	Aminoglycoside	*M. carbonaceae* subsp. *carbonaceae* K55-AC6	Soil, Hyogo, Japan	1993	Antitumor activity	[77]
MS-444	Naphthols	*Micromonospora* sp. KY7123	Soil, Okinawa, Japan	1993	Vasodilator/ Bronchodilator Antitumoral activity Anti-HIV	[280, 350, 351]
Cororubicin	Anthracycline	*Micromonospora* sp. JY16	Soil, Gunma, Japan	1994	Cytotoxic activity	[195]
Macquarimicins	Oxabicyclo[6.2.2] Systems	*M. chalcea* AB 965S-73 *M. chalcea* AB 969J-62	Soil, Sydney, Australia Soil, Virginia, USA	1995	Antitumoral activity	[205]

Korkormicins	Peptidic compounds	*Micromonospora* sp. C39500	Soil	1995	Antitumoral activity	[159]
Rakicidin A	Cyclic depsipeptide	*Micromonospora* sp. R385-2	Soil, Andhra Pradesh, India	1995	Cytotoxic : Hypoxia-Selective Cytotoxin	[163]
Antascomicins	Macrocyclic lactones	*Micromonospora* sp. DSM 8429	Soil, China	1996	Antagonize the immunosuppressive activity of FK506 and rapamycin (FKBP12 binding molecules)	[283]
BU-4664L	Dibenzazepines	*Micromonospora* sp. ATCC 55378	Soil, Colombo, Sri Lanka	1996	Anti-inflammatory anti-tumor cell activities	[207]
Pyrrolosporin A	Macrolides	*Micromonospora* sp. ATCC 53791	Soil, Puerto Viejo, Peru	1996	Antibacterial activity	[126]
9-Hydroxycrisamicin-A	Naphthoquinone	*Micromonospora* sp. SA246	Soil, Taejon, Korea	1997	Antitumor antibiotic Cytotoxic antibiotic, Activate hepatitis B virus (HBV) replication	[182, 183]
Thiocoraline	Thiodepsipeptide	*Micromonospora* sp. ACM2-092 *Micromonospora* sp. ML1	Soft coral and mollusc, Mozambique	1997	Antibacterial activity Anticancer activity	[169]
YM-47515	Isonitrile compound	*M. echinospora* subsp. *echinospora* Y-03559J	Soil, Saitama, Japan	1997	Antibacterial activity	[210]
Cymbimicin A and B	Lactone	*Micromonospora* sp. DSM 8594	Soil, Bromo, Indonesia	1997	Cyclophilin-binding structures immuno-suppressive	[129]
Sch 40832	Thiostrepton	*M. carbonacea* var. *africana* ATCC 39149	Soil, Kenya	1998	Antibacterial activity	[150]
Streptimidone Ao58A	Glutarimide	*M. coerulea* Ao58	Sea-mud soil, Young-Jong island, Korea	1999	Antifungal activity	[211]
Bravomicins	Bravomicins	*M. polytrota*	Soil	1999	Antibacterial activity	[212]
IB-96212	Macrolide	*Micromonospora* sp. CECT 3333	Homogenates of a sponge, Indian Ocean. Coast of Mozambique	2000	Cytotoxic activity	[130]
Arisostatins	Tetrocarcin	Micromonospora sp. TP-A0316	Seawater sample, Toyama Bay, Japan	2000	Antibacterial activity Antitumor activity	[133]
4'-N-Methyl-5'hydroxystaurosporine 5'-hydroxystaurosporine	Indolocarbazole alkaloids	*Micromonospora* sp.L-31-CLCO-002	Sponge *Clathrina Coriacea*, Canary Islands archipielago	2000	Cytotoxic activity	[214]

SB-219383	Furan	*Micromonospora* sp. NCIMB 40684	Soil, South Africa	2000	Antibacterial activity	[215]
Lomaiviticins	Dimeric diazobenzofluorene glycosides	*M. lomaivitiensis* LL-37I366	Ascidian *Polysyncratonlithostrotum*	2001	Antitumor antibiotics	[217]
Streptonigrin 7-(1-methyl-2 oxopropyl)streptonigrin	Quinone	*Micromonospora* sp. IM 2670	Soil, Botanic Garden, Singapore	2002	Cytotoxic activity	[191]
Kosinostatin	Quinocycline	*Micromonospora* sp. TP-A0468	Seawater sample, Toyama. Japan.	2002	Antibacterial activity Cytotoxic	[192]
R176502	Bafilolide metabolite	*Micromonospora* sp. JS1035	River bottom sediment, Cameroon	2003	Antiproliferative	[220]
Micromonomycin	Anthracycline	*Micromonospora* sp.	-	2004	Antibacterial activity Antifungal activity	[196]
Micromonosporin A	Macrolide	*Micromonospora* sp.	Acidic peat swamp forest, Thailand	2004		[135]
Sch 725418	Diketopiperazine	*Micromonospora* sp.	-	2004	Antifungal activity	[221]
Echinosporamicin	Aromatic polycyclic system and a piperazinone moiety	*M. echinospora* subsp. *echinospora* LL-P175	Soil, tidepool near Ventura, California, USA	2004	Antibacterial activity	[222]
Diazepinomicin	Natural dibenzodiazepine	*Micromonospora* sp. DPJ12 *Micromonospora* sp. RV115	Ascidian *Didemnum proliferum*, Japan Sponge *Aplysina aerophoba*, Croatia	2004	Anticancer activity Anti-inflammatory Antiparasitic activity	[223, 224]
Retymicin	Xanthone	*Micromonospora* sp. Tü 6368	Soil, Romania	2005	Cytostatic effects	[227]
Galtamycin B	Galtamycin	*Micromonospora* sp. Tü 6368	Soil, Romania	2005	Cytostatic effects	[227]
Saquayamycin Z	Saquayamycin	*Micromonospora* sp. Tü 6368	Soil, Romania	2005	Cytostatic effects	[227]
Lupinacidins	Anthraquinones	*M. lupine* Lupac 08	Root nodules of *Lupinus angustifolius*, Spain	2007	anti-invasive activity against murine colon 26-L5 carcinoma cells	[189]
TLN-05220, TLN-05223	Echinosporamicin-type antibiotics	M. echinospora subsp. challisensis NRRL 12255	USA	2009	Antibacterial activity Anticancer activity	[213]
Maklamicin	Spirotetronate-class polyketide	*Micromonospora* sp. GMKU326	Root of a leguminous plant, Thailand	2011	-	[176]

Anthracyclinones	Anthracyclinones	*Micromonospora* sp.	Tunicate *Eudistoma vannamei*	2012	-	[197]
Juvenimicin C, 5-O-Alpha-L-rhamnosyltylactone	Macrolides	*Micromonospora* sp.	Marine sample	2013	-	[92]
Telomycin	Macrocyclic peptide lactone	*M. schwarzwaldensis*	Soil, the Black Forest, Germany	2013	Antibacterial activity	[240]
Levantilide C	Macrolide	*Micromonospora* sp. FIM07-0019	Hallow coastal waters, island of Chiloe, Chile	2013	Anticancer activity	[136]
MBJ-0003	Hydroxamate metabolite	*Micromonospora* sp. 29867	Shellfish, Shizuoka, Japan	2014	Cytotoxic activity	[352]
Neomacquarimicin	Carbocylic polyketide	*Micromonospora* sp. NPS2077	Marine sponge, Japan.	2014	-	[273]



(A) Gentamicin C_1a

(B) Sisomicin

(C) Rosamicin

(D) Calicheamicin γ 1I

(E) Izumenolide

(F) Evernimicin

(G) Trehazolin

(H) Halomicin A

(I) Thiocoraline

(J) Crisamicin A

(K) Cororubicin

(L) MS-444

Fig. 2, Boumheira