Secondary Metabolites of the Genus *Amycolatopsis*: Structures, Bioactivities and Biosynthesis

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Review

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Abstract: Actinomycetes are regarded as important sources for the generation of various bioactive secondary metabolites with rich chemical and bioactive diversities. *Amycolatopsis* falls under the rare actinomycete genus with the potential to produce antibiotics. In this review, all literatures were searched in the Web of Science, Google Scholar and PubMed up to March 2021. The keywords used in the search strategy were “*Amycolatopsis*”, “secondary metabolite”, “new or novel compound”, “bioactivity”, “biosynthetic pathway” and “derivatives”. The objective in this review is to summarize the chemical structures and biological activities of secondary metabolites from the genus *Amycolatopsis*. A total of 159 compounds derived from 8 known and 18 unidentified species are summarized in this paper. These secondary metabolites are mainly categorized into polyphenols, linear polyketides, macrolides, macrolactams, thiazolyl peptides, cyclic peptides, glycopeptides, amide and amino derivatives, glycoside derivatives, enediyne derivatives and sesquiterpenes. Meanwhile, they mainly showed unique antimicrobial, anti-cancer, antioxidant, anti-hyperglycemic, and enzyme inhibition activities. In addition, the biosynthetic pathways of several potent bioactive compounds and derivatives are included and the prospect of the chemical substances obtained from *Amycolatopsis* is also discussed to provide ideas for their implementation in the field of therapeutics and drug discovery.

Keywords: Actinomycetes; *Amycolatopsis*; antibiotics; natural products; chemical structures; biological activities; biosynthetic pathways

1. Introduction

Antibiotics produced by microorganisms have made a significant contribution to human health. Among them, Actinomycetes are the most important sources for drug lead compounds. However, researchers have been turned to rare Actinomycetes to develop novel antibiotics with the emergence of multidrug-resistant bacteria [1]. In 1986, Lechevalier et al. defined *Amycolatopsis* as a new genus to accommodate nocardioform Actinomycetes having type IV cell wall composition and lacking mycolic acids [2]. Up to now, by searching in the List of Prokaryotic names with Standing in Nomenclature website (http://www.bacterio.net, accessed on 20 September 2020), this genus covered 94 verified species and 4 subspecies, and forms a unique branch in the evolutionary tree of Pseudonocardiaceae. Among 26 species covered in this review, most of them colonize in a wide variety of soil and a few species survival in terrestrial (insect, lichen, island, plant) and marine (sponge, sediment) environment. The various habitats allow *Amycolatopsis* to produce abundant secondary metabolites.

The genus *Amycolatopsis* is regarded as an important source of diverse valuable bioactive natural products covering many antibiotics [3]. The most notable antibiotics produced by *Amycolatopsis* strains include rifamycin [4] and vancomycin [5]. In the early 1950s, vancomycin had been first extracted from *Amycolatopsis orientalis* that was originally regarded as *Streptomyces orientalis* [6]. Vancomycin was introduced for clinical use in 1958 and...
sparsely used during the first 30 years of its introduction, due to its fewer advantages over semisynthetic antibiotics like penicillin, cephalosporin, lincomycin, and fluoroquinolones. Later, the complex chemical structure of vancomycin was ultimately described in 1983 [7]. The genes of OxyB, OxyA and OxyC, encoding three cytochrome P450 enzymes, have been proven to play an important role in three aromatic cross-links of vancomycin in that order [8]. The discovery of X-domain demonstrated the role of OxyA and OxyB, which introduce bisaryl ether linkages with the help of X-domain; however, the mechanism of final crosslink of the biaryl bond installed by OxyC has not been found yet [9]. In 1959, rifamycin was isolated from Amycolatopsis mediterranei, which was the first group of antimicrobials targeting RNA polymerase. The genes of RifZ and RifQ were crucial regulatory factors of rifamycin biosynthesis. RifZ directly regulated transcription of all operons within the rifamycin biosynthesis gene cluster [10]. RifQ inhibited the export of rifamycin B and inactivating it could increase the yield of rifamycin B without affecting the growth of the A. mediterranei [11]. The understanding of metabolite biosynthesis is helpful to the rational operation of biosynthetic pathways, so as to achieve the goal of producing new natural antibiotics. At present, there are few studies on the biosynthesis of other secondary metabolites of Amycolatopsis [12]. We believe that outstanding bioactive compounds from Amycolatopsis deserve to be further researched on the mechanism of action, biosynthesis and regulatory genes. Some Amycolatopsis species have also been demonstrated to possess great potential in degrading plastics, treating heavy metals, and biotransformation. Herein, we describe a detailed summary about the chemical structures and bioactivities of secondary metabolites from Amycolatopsis reported during 1990–2020 by searching in the Web of Science, Google Scholar and PubMed. In addition, the biosynthetic pathways of several potent bioactive compounds and the derivatives of secondary metabolites via chemical synthesis, semi-synthesis and biosynthesis are also described in this paper.

2. Secondary Metabolites from the Genus Amycolatopsis

Secondary metabolites from Amycolatopsis are classified into polyphenols, linear polyketides, macrolides, macrolactams, thiazolyl peptides, cyclic peptides, glycopeptides, amide and amino derivatives, glycoside derivatives, enediyne derivatives and sesquiterpenes, which are all shown in Table 1.

| Structure Types | Compounds               | Sources           | CAS Registry Numbers | Habitats (T/M b) | Refs. |
|-----------------|-------------------------|-------------------|----------------------|-----------------|------|
| Polyphenols     | Kigamicin A (1)         | Amycolatopsis sp. ML630-mF1 | 680571-49-7          | Soil (T)        | [13] |
|                 | Kigamicin B (2)         | Amycolatopsis sp. ML630-mF1 | 680571-50-0          | Soil (T)        | [13] |
|                 | Kigamicin C (3)         | Amycolatopsis sp. ML630-mF1 | 680571-51-1          | Soil (T)        | [13] |
|                 | Kigamicin D (4)         | Amycolatopsis sp. ML630-mF1 | 680571-52-2          | Soil (T)        | [13] |
|                 | Kigamicin E (5)         | Amycolatopsis sp. ML630-mF1 | 680571-53-3          | Soil (T)        | [13] |
|                 | Amexanthomycin A (6)    | A. mediterranei S699 ΔrifA | /a                   | /c              | [14] |
|                 | Amexanthomycin B (7)    | A. mediterranei S699 ΔrifA | /                    | -               | [14] |
|                 | Amexanthomycin C (8)    | A. mediterranei S699 ΔrifA | /                    | -               | [14] |
|                 | Amexanthomycin D (9)    | A. mediterranei S699 ΔrifA | /                    | -               | [14] |
| Structure Types     | Compounds                          | Sources          | CAS Registry Numbers | Habitats (T/M b) | Refs. |
|---------------------|------------------------------------|------------------|----------------------|------------------|-------|
| Amexanthomycin E (10) | A. mediterranei S699 ΔrifA          |                  |                      |                  | [14]  |
| Amexanthomycin F (11) | A. mediterranei S699 ΔrifA          |                  |                      |                  | [14]  |
| Amexanthomycin G (12) | A. mediterranei S699 ΔrifA          |                  |                      |                  | [14]  |
| Amexanthomycin H (13) | A. mediterranei S699 ΔrifA          |                  |                      |                  | [14]  |
| Amexanthomycin I (14) | A. mediterranei S699 ΔrifA          |                  |                      |                  | [14]  |
| Amexanthomycin J (15) | A. mediterranei S699 ΔrifA          |                  |                      |                  | [14]  |
| Mutactimycin E (16)  | Amycolatopsis sp. 17128             |                  | 1125635-23-5         | Soil (T)         | [15]  |
| Mutactimycin A (17)  | Amycolatopsis sp. 17128             |                  | 131749-16-1          | Soil (T)         | [15]  |
| Mutactimycin D (18)  | Amycolatopsis sp. 17128             |                  | 138689-82-4          | Soil (T)         | [15]  |
| 1-Methoxy-3-methyl-8-hydroxy-anthraquinone (19) | A. thermoflava SFMA-103 | 67116-22-7 | Soil (T) | [16,17] |
| 7-O-Methyl-5-O-α-L-rhamnopyranosylgenestein (20) | Amycolatopsis sp. YIM 130642 | / | Squamarina sp. (T) | [18] |
| 7-O-α-D-Arabinofuranosyl daidzein (21) | Amycolatopsis sp. YIM 130642 | 602329-64-6 | Squamarina sp. (T) | [18] |
| Prunetin (22)        | Amycolatopsis sp. YIM 130642        |                  | 552-59-0             | Squamarina sp. (T)| [18] |
| Kakkatin (23)        | Amycolatopsis sp. YIM 130642        |                  | 57960-04-0           | Squamarina sp. (T)| [18] |
| Isoformononetin (24) | Amycolatopsis sp. YIM 130642        |                  | 486-63-5             | Squamarina sp. (T)| [18] |
| Genistein (25)       | Amycolatopsis sp. YIM 130642        |                  | 446-72-0             | Squamarina sp. (T)| [18] |
| Formononetin (26)    | Amycolatopsis sp. YIM 130642        |                  | 485-72-3             | Squamarina sp. (T)| [18] |
| Sorbicillin (27)     | Amycolatopsis sp. YIM 130687        |                  | 79950-85-9           | P. borleri (T)   | [19]  |
| Pradimicin-IRD (28)  | Amycolatopsis sp. IRD-009           |                  | 2226037-84-7         | Soil (T)         | [20]  |
| (2R,3R)-2-Hydroxy-8-O-methyltetragomycin (29) | Amycolatopsis sp. Hca1 | 1391860-71-1 | O. chinensis (T)    | [21]  |
| (2R,3R)-2-Hydroxy-5-O-methyltetragomycin (30) | Amycolatopsis sp. Hca1 | 1391860-72-2 | O. chinensis (T)    | [21]  |
| Amycomycin A (31)    | Amycolatopsis sp. Hca1             |                  | 1415935-15-7         | O. chinensis (T) | [22]  |
| Amycomycin B (32)    | Amycolatopsis sp. Hca1             |                  | 1415935-16-8         | O. chinensis (T) | [22]  |
| Tetrangomycin (33)   | Amycolatopsis sp. Hca1             |                  | 7351-08-8            | O. chinensis (T) | [21]  |
Table 1. Cont.

| Structure Types | Compounds | Sources | CAS Registry Numbers | Habitats (T/M)\(^b\) | Refs. |
|-----------------|-----------|---------|----------------------|----------------------|-------|
| Linear polyketides | ECO-0501 (42) | A. orientalis ATCC 43,491 | 848087-04-7 | - | [24] |
| Modified analogs of ECO-0501 (43–47) | | A. orientalis ATCC 43,491 | 848087-07-0, 848087-06-9, 848087-08-1, 848087-09-2, 921224-72-8 | - | [24] |
| Macrolides | Amycolatopsin A (49) | Amycolatopsis sp. MST-108494 | 2209112-96-7 | Soil (T) | [26] |
| | Amycolatopsin B (50) | Amycolatopsis sp. MST-108494 | 2209112-97-8 | Soil (T) | [26] |
| | Amycolatopsin C (51) | Amycolatopsis sp. MST-108494 | 2209112-98-9 | Soil (T) | [26] |
| | 2′-O-Succinyl-apoptolidin A (52) | Amycolatopsis sp. ICBB 8242 | 1778681-11-0 | Borneo (M) | [27] |
| | 3′-O-Succinyl-apoptolidin A (53) | Amycolatopsis sp. ICBB 8242 | 1778681-12-1 | Borneo (M) | [27] |
| | Apoptolidin A (54) | Amycolatopsis sp. ICBB 8242 | 194874-06-1 | Borneo (M) | [27] |
| | Apoptolidin B (55) | Amycolatopsis sp. ICBB 8242 | 861994-72-1 | Borneo (M) | [27] |
| | Apoptolidin C (56) | Amycolatopsis sp. ICBB 8242 | 861994-73-2 | Borneo (M) | [27] |
| | Apoptolidin D (57) | Amycolatopsis sp. ICBB 8242 | 929641-83-8 | Borneo (M) | [27] |
| | Isopapoptolidin A (58) | Amycolatopsis sp. ICBB 8242 | 476647-30-0 | Borneo (M) | [27] |
| Macrolactams | Rifamycinoside A (59) | A. mediterranei S699 | 2329704-84-7 | - | [28] |
| | Rifamycinoside B (60) | A. mediterranei S699 | 2329704-85-8 | - | [28] |
| | 28-Desmethyl-28-hydroxyrifamycin W (61) | A. mediterranei S699 | 2329704-86-9 | - | [28] |
| | 27,28-Epoxy-28-desmethylyrifamycin W (62) | A. mediterranei S699 | 2329704-87-0 | - | [28] |
| | 30-Hydroxyrifamycin W hemiacetal (63) | A. mediterranei S699 | 2329704-88-1 | - | [28] |
| Structure Types                          | Compounds                        | Sources                        | CAS Registry Numbers | Habitats (T/M b) | Refs. |
|----------------------------------------|----------------------------------|--------------------------------|----------------------|-----------------|-------|
| 20-Hydroxyrifamycin S (64)             | A. mediterranei S699             | /                              | -                    | [28]            |
| Rifamycin S (65)                       | A. mediterranei S699             | 13553-79-2                     | -                    | [28]            |
| 16,17-Dehydrorifamycin G (66)          | A. mediterranei S699             | 75922-16-6                     | -                    | [28]            |
| Rifamycin O (67)                       | A. mediterranei S699             | 14487-05-9                     | -                    | [28]            |
| Rifamycin Z (68)                       | A. mediterranei S699             | 79486-49-0                     | -                    | [28]            |
| Rifamycin W (69)                       | A. mediterranei S699             | 53904-81-7                     | -                    | [28]            |
| Rifamorpholine A (70)                  | Amycolatopsis sp. HCa4           | 2101982-41-4                   | L. migratoria (T)    | [29]            |
| Rifamorpholine B (71)                  | Amycolatopsis sp. HCa4           | 2101982-45-8                   | L. migratoria (T)    | [29]            |
| Rifamorpholine C (72)                  | Amycolatopsis sp. HCa4           | 2101982-52-7                   | L. migratoria (T)    | [29]            |
| Rifamorpholine D (73)                  | Amycolatopsis sp. HCa4           | 2101982-58-3                   | L. migratoria (T)    | [29]            |
| Rifamorpholine E (74)                  | Amycolatopsis sp. HCa4           | 2101982-62-9                   | L. migratoria (T)    | [29]            |
| Macrotermycin A (75)                   | Amycolatopsis sp. M39            | 1311284-73-7                   | M. natalensis (T)    | [30]            |
| Macrotermycin B (76)                   | Amycolatopsis sp. M39            | 2095035-09-7                   | M. natalensis (T)    | [30]            |
| Macrotermycin C (77)                   | Amycolatopsis sp. M39            | 2095035-10-0                   | M. natalensis (T)    | [30]            |
| Macrotermycin D (78)                   | Amycolatopsis sp. M39            | 2095035-11-1                   | M. natalensis (T)    | [30]            |
| Ansamycin (79)                         | A. alba DSM 44262                | 2256052-40-9                   | -                    | [31]            |
| Thioamycolamide A (93)                 | Amycolatopsis sp. 26-4           | /                              | Iriomote Island (T)  | [36]            |
| Thioamycolamide B (94)                 | Amycolatopsis sp. 26-4           | /                              | Iriomote Island (T)  | [36]            |
| Thioamycolamide C (95)                 | Amycolatopsis sp. 26-4           | /                              | Iriomote Island (T)  | [36]            |
| Thioamycolamide D (96)                 | Amycolatopsis sp. 26-4           | /                              | Iriomote Island (T)  | [36]            |
| Thioamycolamide E (97)                 | Amycolatopsis sp. 26-4           | /                              | Iriomote Island (T)  | [36]            |
| PRG-A (98)                             | Amycolatopsis sp. ML1-hF4        | 421547-03-7                    | Soil (T)             | [37]            |
| PRG-B (99)                             | Amycolatopsis sp. ML1-hF4        | 2112795-88-5                   | Soil (T)             | [38]            |
| PRG-C (100)                            | Amycolatopsis sp. ML1-hF4        | 2112795-89-6                   | Soil (T)             | [38]            |
| Structure Types | Compounds | Sources | CAS Registry Numbers | Habitats (T/M b) | Refs. |
|----------------|-----------|---------|----------------------|-----------------|-------|
| PRG-D (101)    | Amycolatopsis sp. ML1-hF4 | 2112795-90-9 | Soil (T) | [38] |
| Valgamicin A (102) | Amycolatopsis sp. ML1-hF4 | 2271221-78-2 | Soil (T) | [39] |
| Valgamicin C (103) | Amycolatopsis sp. ML1-hF4 | 2271221-79-3 | Soil (T) | [39] |
| Valgamicin T (104) | Amycolatopsis sp. ML1-hF4 | 2271221-80-6 | Soil (T) | [39] |
| Valgamicin V (105) | Amycolatopsis sp. ML1-hF4 | 2271221-81-7 | Soil (T) | [39] |
| Glycopeptides   | Chloroorienticin A (106) | A. orientalis PA-45052 | 118395-73-6 | - | [40] |
|                 | Chloroorienticin B (107) | A. orientalis PA-45052 | 118373-81-2 | - | [40] |
|                 | Chloroorienticin C (108) | A. orientalis PA-45052 | 118373-82-3 | - | [40] |
|                 | Chloroorienticin D (109) | A. orientalis PA-45052 | 118373-83-4 | - | [40] |
|                 | Chloroorienticin E (110) | A. orientalis PA-45052 | 118373-84-5 | - | [40] |
|                 | Orienticin A (111) | A. orientalis PA-45052 | 111073-20-2 | - | [40] |
|                 | Orienticin D (112) | A. orientalis PA-45052 | 112848-46-1 | - | [40] |
|                 | Vancomycin (113) | A. orientalis PA-45052 | 1404-90-6 | - | [40] |
|                 | Vancomycin aglycone (114) | A. orientalis PA-45052 | 82198-76-3 | - | [40] |
|                 | MM 47,761 (115) | A. orientalis NCBI 12608 | 126985-51-1 | - | [41] |
|                 | MM 49,721 (116) | A. orientalis NCBI 12608 | 126985-52-2 | - | [41] |
|                 | Eremomycin B (117) | A. orientalis subsp. Eremomycini | 1193347-07-7 | - | [42] |
|                 | Eremomycin (118) | A. orientalis subsp. Eremomycini | 110865-90-2 | - | [42] |
| Amide derivatives | Albachelin (119) | A. alba | 2055362-14-4 | - | [43] |
|                 | Albisporachelin (120) | A. albispora WP1 T | / | Sediment (M) | [44] |
|                 | A-102395 (121) | Amycolatopsis sp. SANK 60206 | 1003904-77-5 | Soil (T) | [45] |
|                 | Amyccyclopiazonic acid (122) | A. saalfeldensis | / | Sponge (M) | [23] |
|                 | Amycolactam (123) | A. saalfeldensis | / | Sponge (M) | [23] |
|                 | Carbamothioic S-acid (124) | A. alba DSM 44262△abm9 | / | - | [46] |
|                 | Amycophthalazinone A (125) | Amycolatopsis sp. YIM 130642 | / | Squamaria sp. (T) | [18] |
|                 | 2-Pyruvoylaminobenzamide (126) | Amycolatopsis sp. YIM 130687 | 18326-62-0 | P. borreri (T) | [19] |
|                 | (−)-Chrysogine (127) | Amycolatopsis sp. YIM 130687 | 42599-89-3 | P. borreri (T) | [19] |
|                 | 4-(3-Methylbut-2-enyloxy) benzamide (128) | Amycolatopsis sp. YIM 130687 | 116208-80-1 | P. borreri (T) | [19] |

**Table 1.** Cont.
| Structure Types                  | Compounds               | Sources                    | CAS Registry Numbers | Habitats (T/M b) | Refs. |
|----------------------------------|-------------------------|----------------------------|----------------------|-----------------|-------|
| Acetotryptamide (129)            | *Amycolatopsis* sp. YIM 130687 |                            | 1016-47-3            | P. borreri (T)  | [19]  |
| 2-Acetamidophenol (130)          | *Amycolatopsis* sp. YIM 130687 |                            | 614-80-2             | P. borreri (T)  | [19]  |
| Anthranilic acid (131)           | *Amycolatopsis* sp. YIM 130687 |                            | 118-92-3             | P. borreri (T)  | [19]  |
| Phenacetamide (132)              | *Amycolatopsis* sp. YIM 130687 |                            | 103-81-1             | P. borreri (T)  | [19]  |
| 2-Carbamoyl-3-hydroxy-1,4-naphthoquinone (133) | *Amycolatopsis* sp. YIM 130687 |                            | 103646-20-4          | P. borreri (T)  | [19]  |
| Echinosporin (134)               | *Amycolatopsis* sp. PH20520 |                            | 79127-35-8           | Soil (T)        | [47]  |
| 7-Deoxyechinosporin (135)        | *Amycolatopsis* sp. PH20520 |                            | 431945-10-7          | Soil (T)        | [47]  |
| Dipyrimicin A (136)              | *Amycolatopsis* sp. K16-0194 |                            | 1235020-43-5         | -               | [48]  |
| Dipyrimicin B (137)              | *Amycolatopsis* sp. K16-0194 |                            | 1332747-97-3         | -               | [48]  |
| 1-(10-Aminodecyl) pyridinium (138) | *A. alba* var. nov. DVR D4 |                            | 142143-67-9          | Sediment (M)    | [49]  |
| Siderochelin A (139)             | *Amycolatopsis* sp. LZ149 |                            | 77550-87-9           | Cynodon dactylon (T) | [50] |
| Siderochelin B (140)             | *Amycolatopsis* sp. LZ149 |                            | 2252179-56-7         | Cynodon dactylon (T) | [50] |
| Siderochelin C (141)             | *Amycolatopsis* sp. LZ149 |                            | 2252179-55-6         | Cynodon dactylon (T) | [50] |
| Siderochelin D (142)             | *Amycolatopsis* sp. LZ149 |                            | 2249835-41-2         | Cynodon dactylon (T) | [50] |
| Epoxyquinomicin A (143)          | *A. sulphurea* MK299-95F4 |                            | 175448-31-4          | Soil (T)        | [51]  |
| Epoxyquinomicin B (144)          | *A. sulphurea* MK299-95F4 |                            | 175448-32-5          | Soil (T)        | [51]  |
| Epoxyquinomicin C (145)          | *A. sulphurea* MK299-95F4 |                            | 200496-85-1          | Soil (T)        | [51]  |
| Epoxyquinomicin D (146)          | *A. sulphurea* MK299-95F4 |                            | 200496-86-2          | Soil (T)        | [51]  |
| Glycoside derivatives            |                         |                            |                      |                 |       |
| Tigoside (147)                   | *Amycolatopsis* sp. NN0 21702 |                            | 216590-44-2          | -               | [52]  |
| 2,2’-Di-O-β-D-glucopyranosyl-α-D-glucopyranosyl α-D-glucopyranoside (148) | *Amycolatopsis* sp. NN0 21702 |                            | /                    | -               | [52]  |
| Actinotetraose I (149)           | *Amycolatopsis* sp. HC1 |                            | 1427319-31-0         | O. chinensis (T) | [53]  |
| Actinotetraose J (150)           | *Amycolatopsis* sp. HC1 |                            | 1427319-40-1         | O. chinensis (T) | [53]  |
| Actinotetraose K (151)           | *Amycolatopsis* sp. HC1 |                            | 1427319-41-2         | O. chinensis (T) | [53]  |
| Actinotetraose A (152)           | *Amycolatopsis* sp. HC1 |                            | 1421368-85-5         | O. chinensis (T) | [53]  |
| Actinotetraose B (153)           | *Amycolatopsis* sp. HC1 |                            | 1421368-86-6         | O. chinensis (T) | [53]  |
| Actinotetraose C (154)           | *Amycolatopsis* sp. HC1 |                            | 1421368-87-7         | O. chinensis (T) | [53]  |
| Actinotetraose L (155)           | *Amycolatopsis* sp. HC1 |                            | 216590-44-2          | O. chinensis (T) | [54]  |
**Table 1. Cont.**

| Structure Types | Compounds | Sources | CAS Registry Numbers | Habitats (T/M b) | Refs. |
|-----------------|-----------|---------|----------------------|-----------------|-------|
| Enediyne derivatives | Amycolamycin A (156) | *Amycolatopsis* sp. HCa4 | 2243041-65-6 | *L. migratoria* (T) | [55] |
| | Amycolamycin B (157) | *Amycolatopsis* sp. HCa4 | 2243041-66-7 | *L. migratoria* (T) | [55] |
| Sesquiterpenes | (E)-3-methyl-5-(2,6,6-trimethyl-3-oxocyclohex-1-enyl) pent-2-enioic acid (158) | *A. alba* DSM 44262 | 2247139-21-3 | - | [31] |
| | (E)-3-methyl-5-(2,6,6-trimethyl-4-oxocyclohex-2-enyl) pent-2-enioic acid (159) | *A. alba* DSM 44262 | 2256051-20-2 | - | [31] |

* a The CAS registry number was not found; b T: terrestrial environment; M: marine environment; c The habitat was not mentioned.

### 2.1. Polyphenols

Polyphenolic compounds are a large family of natural products and some of them show a series of excellent function in health [56], such as anti-allergenic, anti-inflammatory, anti-microbial, antioxidant, antithrombotic, cardio protective, and vasodilatory effects [57]. The investigation on secondary metabolites of *Amycolatopsis* sp. ML630-mF1 from the soil sample collected in Toba of Japan led to the isolation of five new compounds named kigamicins A–E (1–5). These compounds showed potent effects to resist methicillin-resistant *Staphylococcus aureus* (MRSA) with the IC$_{50}$ values ranging in 0.03–0.22 µM. Besides, they inhibited PANC-1 cell survival under a nutrient-starved condition. Typically, kigamicin D was found to suppress diverse mouse cancer cell line growth, and the IC$_{50}$ value was about 0.95 µM [13]. In the absence of nutrition, kigamicin D exhibited preferential cytotoxicity to cancer cells and could inhibit the PI3K/Akt pathway [58]. A total of 10 novel pentangular polyphenols defined as amexanthomycins A–J (6–15) were obtained from the fermentation products of *Amycolatopsis mediterranei* S699∆rifA (the *A. mediterranei* S699 mutant strain). These compounds were produced through deleting polyketide synthase genes related to rifamycin biosynthesis. In this study, the effects of the above compounds on suppressing topoisomerases IIα (Topo IIα) were examined. The results showed that compounds 6–8 exhibited moderate inhibitory activity against Topo IIα (500 µM), while compounds 9–15 showed no activities [14].

Anthraquinones are the most abundant among the various natural quinone compounds. Earlier, they were mainly used as dyes. But later, their antibacterial, anti-inflammatory, and antiviral effects were discovered. A new anthraacycline, namely, mutactimycin E (16) with two known compounds mutactimycin A (17) and D (18) were isolated from the EtOAc extract of *Amycolatopsis* sp. 17,128 collected from the soil sample near Ruby, Arizona. It had moderate effects to resist some Gram-positive bacteria [15]. Investigation of secondary metabolites from *Amycolatopsis thermoflava* SFMA-103 led to the isolation of the 1-methoxy-3-methyl-8-hydroxy-anthraquinone (19) pigment from the rhizosphere soil of sunflower collected in Medak, Andhra Pradesh, South India. Compound 19 displayed infusive anti-cancer activity in-vitro to resist lymphoblastic leukemia as well as lung cancer cells, with the IC$_{50}$ values of 16.98 and 10.3 µM, respectively. In addition, the DPPH assay showed that this compound had favorable capacity to scavenge free radicals with the EC$_{50}$ value of 18.2 µg/mL [16]. Furthermore, compound 19 suppressed α-glucosidase and α-amylase with IC$_{50}$ values of 10.32 and 0.91 µM, respectively. According to the research on the oral dose for Wistar rats, compound 19 remarkably suppressed the elevated glucose level at a dose of 100 mg/kg. Its toxicity was further assayed by the genotoxic analysis in both Chinese Hamster Ovary cells (in-vitro) and Swiss albino mice (in-vivo). The studies indicated that compound 19 had little effect on mouse survival. It was concluded that compound 19 was used at 100 mg/kg.
to treat hyperglycemia via inhibiting $\alpha$-glucosidase and $\alpha$-amylase enzymes without inducing any genotoxic effect [17]. 7-O-Methyl-5-O-$\alpha$-L-rhamnopyranosylgenestein (20) was a novel isoflavonoid glycoside, while 7-O-$\alpha$-D-arabinofuranosyl daidzein (21) was firstly extracted from natural sources. These two compounds, along with 5 known isoflavonoids, prunetin (22), kakkatin (23), isoformononetin (24), genistein (25), and formononetin (26) were produced by the lichen-associated Amycolatopsis sp. YIM 130642. Compounds 20 and 21 showed modest bacteriostatic activities against one or more pathogenic strains of Candida albicans, Escherichia coli, MRSA, S. aureus, and Salmonella typhi with their minimal inhibition concentrations (MICs) in the range of 32–256 $\mu$g/mL [18]. Sorbicillin (27) was isolated from the lichen-derived actinomycete strain Amycolatopsis sp. YIM 130,687 [19]. Isolation and identification of a new polycyclic antibiotic, pradimicin-IRD (28), was reported from the rare actinobacteria Amycolatopsis sp. IRD-009, which was collected from soil sample of Brazilian rainforest undergoing restoration area. Compound 28 exhibited antimicrobial activity against Streptococcus agalactiae-97, S. aureus-211 and Pseudomonas aeruginosa ATCC 27,859 with MIC values of 3.15 $\mu$g/mL. In addition, the cytotoxicity of compound 28 was determined by MTT assay, which inhibited HCT-116 colon carcinoma, MM 200 melanoma, MCF-7 breast carcinoma and RPE non-tumor retinal pigment epithelial cells with IC$_{50}$ values of 0.8, 2.7, 1.55 and 1.48 $\mu$M, respectively [20]. Compound 28 could induce DNA damage (increased $\gamma$H2AX and p21), cell cycle arrest (reduced Rb phosphorylation) and apoptosis (PARP1 and caspase 3 cleavage). It was capable of impacting on double stranded DNA which might be the novel target for compound 28 [59]. Three new angucyclines, (2R,3R)-2-hydroxy-8-O-methyltetragomycin (29), (2R,3R)-2-hydroxy-5-O-methyltetragomycin (30), amycomycin B (31), and a novel angucycline derivative, amycomycin A (32), with eight known compounds, tetrangomycin (33), pd116779 (34), tetrangulol (35), X-14881E (36), sakyomicin B (37), tetracyclinone (38), sakyomicin A (39), and sakyomicin C (40), were produced by Amycolatopsis sp. Hca1 [21,22], which was collected from the gut of Oxya chinensis. Compounds 33, 34, 39 and 40 possessed cytotoxic activities against the HeLa cells with the IC$_{50}$ values of 0.27, 0.11, 0.56 and 0.39 $\mu$M, respectively, and compound 40 was also cytotoxic against BGC823, HepG2, A375, KB, and Ghost-R5 $\times$ 4 cell lines with the IC$_{50}$ values of 11.03, 17.36, 17.5 and 14.0 $\mu$M, respectively. Amycofuran (41) is a new benzofuran glycoside isolated from Amycolatopsis saalfeldensis collected from a sponge sample [23]. All 41 polyphenols described above are presented in Figure 1.
Figure 1. Structures of polyphenols (1–41) from Amycolatopsis.

2.2. Linear Polyketides

Through genomic analysis, the strain *Amycolatopsis orientalis* ATCC 43,491 was found to be the producer of vancomycin, which possessed genetic loci to produce over 10 secondary metabolites apart from vancomycin. It was estimated that a gene cluster containing the type I polyketide synthase mediated the biosynthesis for a new glycosidic polyketide ECO-0501 (42) [24]. Compound 42 exhibited stronger antibacterial activity than van-
comycin against *S. aureus* ATCC TM 6538P in pH 5.0 and 6.0 with the MIC values of 0.125 and 0.25 µg/mL. This compound had potent effect on resisting Gram-positive bacteria MRSA and vancomycin-resistant *Enterococci* (VRE) strains. The mechanistic studies proved that ECO-0501 may impact on either cell wall or membrane biosynthesis [60]. In addition, compound 42 chemical modified analogs, including esterified 43–45, N-acetylated 46, and hydrogenated 47 were reported. Compound 46 showed antibacterial activity against *S. aureus* ATCC TM 6538P with MIC values of 0.25, 0.5 and 2 µg/mL in pH 5, 6 and 7, respectively. The novel antibiotic vancoresmycin (48) was obtained from the culture broth of *Amycolatopsis* sp. ST 101170. It showed a potent effect on resisting the Gram-positive strains of *E. faecium*, *S. aureus*, *S. pneumonia*, *S. epidermidis*, *S. pyogenes*, together with a variety of drug-resistant microorganisms. The IC$_{50}$ values were found to be less than 0.05 µM. By a non-pore forming and concentration-dependent depolarization mechanism, compound 48 selectively targeted the cytoplasmic membrane of gram-positive bacteria [61]. No inhibitory effect against gram-negative bacteria or anti-fungal activity was observed [25]. All 7 linear polyketides described above are presented in Figure 2.

![Figure 2. Structures of linear polyketides (42–48) and macrolides (49–58) from *Amycolatopsis*.](image-url)
2.3. Macrolides

Three novel glycosylated macrolactones, amycolatopsins A–C (49–51), were produced by *Amycolatopsis* sp. MST-108494 obtained from the soil in southern Australia. Both compounds 49 and 51 prevented *M. tuberculosis* (H37Rv, IC$_{50}$ values of 4.4 and 5.7 µM) and *M. bovis* (BCG; IC$_{50}$ values of 0.4 and 2.7 µM) from growing within the liquid culture. In addition, compounds 49 and 50 showed significant toxicity to the human lung cancer (NCIH-460; IC$_{50}$ values of 1.2 and 0.28 µM) and colon carcinoma (SW620; IC$_{50}$ values of 0.08 and 0.14 µM) cell lines. Whereas, compound 51 showed 5- to 100-fold less cytotoxicity with IC$_{50}$ values of 5.9 and 10 µM, respectively [26]. Two new apoptolidins, 2′-O-succinyl-apoptolidin A (52) and 3′-O-succinyl-apoptolidin A (53), with five known compounds, apoptolidins A–D (54–57) and isoapoptolidin A (58), were produced by the Indonesian *Amycolatopsis* sp. ICBB 8242 isolated from the Black Water Ecosystems in Kalimantan. Compound 54 could inhibit the human H292 and HeLa cells with IC$_{50}$ values of 0.02 and 0.04 µM, respectively. Compounds 52 and 53 could suppress the human H292 cell with IC$_{50}$ values of 0.09 and 0.08 µM, respectively [27]. All 10 macrolides described above are presented in Figure 2.

2.4. Macrolactams

Macrolactams have been used in clinical trials since 1940 [62], in which penicillin and cephalosporins are the representative antibiotics. For better exploiting the rifamycin diversity, the *Amycolatopsis mediterranei* S699 strain was cultured on the YMG agar media. Eleven rifamycin congeners, including six new compounds, rifamycinosides A (59) and B (60), 28-desmethyl-28-hydroxyrifamycin W (61), 27,28-epoxy-28-desmethylrifamycin W (62), 30-hydroxyrifamycin W hemiacetal (63) and 20-hydroxyrifamycin S (64), with five known compounds, rifamycins O (67), Z (68) and W (69), were isolated. Compounds 59 and 60 possess the similar skeleton of rifamycin glycosides. The polyketide cores of these two compounds presented the new rifamycin ansa chain cleavage pattern. Compound 64 showed potent inhibitory activity against T3SS, caused G2/M phase arrest, and attracted DNA damage in HCT116 cells [28]. Five unusual macrolactams, rifamorpholines A–E (70–74), were isolated from *Amycolatopsis* sp. HCa4 collected from the gut of Locusta migratoria. Compounds 71 and 73 possessed antimicrobial activity against MRSA, *S. aureus*, *S. pyogenes*, *Bacillus subtilis*, and *Micrococcus luteus* with MIC values in the range of 0.5–8.0 µM [29]. Four new 20-membered glycosylated polyketide macrolactams, macrotermycins A–D (75–78), were produced by *Amycolatopsis* sp. M39 collected from a *Macrotermes natalensis*. Compound 75 exhibited antimicrobial activity against *B. subtilis* ATCC 6051, *S. aureus* ATCC 25923, *Saccharomyces cerevisiae* ATCC 9763 and *C. albicans* ATCC 24,433 with MIC values of 1.0, 1.5, 5.0, 10, respectively. And compound 77 exhibited antimicrobial activity against *B. subtilis* ATCC 6051, *S. aureus* ATCC 25923, *Saccharomyces cerevisiae* ATCC 9763 and *C. albicans* ATCC 24,433 with MIC values of 15, 10, 25 μg/mL, respectively [30]. A novel compound, ansamycin (79), was produced by *Amycolatopsis alba* DSM 44262. However, this compound exhibited no antimicrobial activity for *S. aureus*, *B. subtilis*, *P. aeruginosa* and *C. albicans* [31]. All 21 macrolactams described above are presented in Figure 3.
Figure 3. Structures of macrolactams (59–79) from *Amycolatopsis.*
2.5. Thiazolyl Peptides

After chromatographically fractionating the fermentation broth extract of *Amycolatopsis fastidiosa*, 4 known nocathiacins I-IV (80-83) along with 2 novel thiazolyl peptides, thiazomycin (84) and thiazomycin A (85) were isolated [32-34]. Compounds 84 and 85 showed potent inhibition against Gram-positive bacteria. Continued chemical screening led to the separation of an intermediate product and six new thiazolyl peptide congeners, MJ347-81F4 B (86), thiazomycins B-D (87-89), and E1-E3 (90-92). The new compounds were tested for their antimicrobial activity against gram-positive bacterial strains of *S. aureus*, *E. faecalis*, *S. pneumonia*, and other drug-resistant strains. The results indicated that compounds 87-89 effectively inhibited the growth of the pathogenic bacteria described above, whereas compounds 90-92 showed no obvious antimicrobial activity [35]. Five novel compounds thioamycolamides A-E (93-97) were obtained from the fermentation products of *Amycolatopsis* sp. 26-4 isolated from Iriomote Island near Okinawa, Japan. They were cycliclipopeptides containing sulfur, thioether rings, thiazoline, along with fatty acid moieties. Compounds 93 and 96 showed moderate cytotoxicity with the IC50 values ranging from 6.53 to 21.22 µM. However, compound 97 had an IC50 value greater than 100 µM [36]. All 18 thiazolyl peptides described above are presented in Figure 4.

![Figure 4. Structures of thiazolyl peptides (80–97) and cyclic peptides (98–105) from Amycolatopsis.](image-url)
2.6. Cyclic Peptides

Cyclic peptides always possess antibacterial, antitumor, hypotoxic, immunosuppressive activities and have a merit of favorable binding affinity and selectivity for certain receptors [63]. The limited conformational freedom conferred by cyclization enables cyclic peptides to span large surfaces while retaining the conformational restriction that yields high selectivity and affinity. Such advantages render them the ideal selection for developing therapeutics [64]. While screening antibiotics against MRSA and VRE, the novel cyclic peptide, PRG-A (98), containing the distinct piperazic acid, was obtained from the fermentation broth of *Amycolatopsis* sp. ML1-hF4 isolated from a soil sample collected at Shinagawa, Tokyo, Japan [37]. During the optimization of the production process of PRG-A, three new derivatives, namely, PRG-B (99), C (100), and D (101), were further isolated from the same strain. This study examined the effects of these new PRGs on resisting a variety of Gram-positive and -negative bacteria, like VRE and MRSA. The results showed that compounds 98 and 100 exhibited potent and broad antibacterial activity against gram-positive bacteria with the IC_{50} value of about 0.72 µM. The antibacterial activity of compounds 99 and 101 was lower, with the IC_{50} values ranging from 5.61 to 23.37 µM. However, all compounds failed to show antibacterial activity against gram-negative bacteria [38]. Compound 98 disrupted cell membrane function by disruption of membrane potential [65]. Another four new cyclic depsipeptide compounds, named valgamicins A (102), C (103), T (104) and V (105), were isolated from *Amycolatopsis* sp. ML1-hF4. Compound 105 possessed an excellent cytotoxicity against a series of human tumor cell lines, such as MIA PaCa 2 (Pancreatic cancer), HGC-27 (Gastric cancer), GSS (Gastric cancer), 5637 (Bladder cancer), NCI-H1650 (Lung cancer), GI-1 (Glioma), NB16 (Neuroblastoma), ME-180 (Cervical cancer), and HSC-490 (Tongue cancer), with IC_{50} values from 6.6 to 21.6 µM [39]. All 8 cyclic peptides described above are presented in Figure 4.

2.7. Glycopeptides

Glycopeptide antibiotics are used as a key weapon in against bacteria, especially multidrug-resistant Gram-positive pathogens. The ground-breaking work about glycopeptide antibiotics resistance mechanisms in Gram-positive pathogens were published in the 1990s [66]. Chloroorienticins were similar to vancomycin-type antibiotics. Five new chloroorienticins A–E (106–110), oricentins A (111) and D (112), vancomycin (113) and its aglycone (114) were isolated from the fermentation broth of *Amycolatopsis orientalis* PA-45052. Some of them showed higher antibacterial activity than vancomycin. Compounds 106–110 showed significant antibacterial activity against *S. aureus* JC-1 and MRSA with MIC values in the range of 0.2–0.78 µg/mL. Vancomycin (113) was comparatively against these two bacteria with MIC values of 0.78 and 1.58 µg/mL, respectively [40]. MM 47,761 (115) and MM 49,721 (116) were obtained from *Amycolatopsis orientalis* NCBI 12,608 and displayed a favorable antimicrobial effect on Gram-positive strains. Compounds 115 and 116 could inhibit B. subtilis ATCC6633, Corynebacterium xerosis NCTC9755, M. luteus NCTC8340, S. aureus Oxford, S. aureus Russell, S. aureus V573 MRa, S. saprophyticus FL1, S. epidermidis 60137, S. epidermidis 54815, Streptococcus pyogenes CN10, S. agalactiae Hester, S. sanguis ATCC 10556, S. faecalis I with the MIC values from 0.5 to 8 µg/mL [41]. A new bioactive antibiotic, eremomycin B (117), along with one known antibiotic, eremomycin (118), were isolated from the culture broth of *Amycolatopsis orientalis* subsp. *Eremomycini* [42]. All 13 glycopeptides described above are presented in Figure 5.
2.8. Amide Derivatives

Albachelin (119), a novel siderophore, was obtained from the *Amycolatopsis alba* culture with iron depletion. Then, ESI–MS/MS together with NMR spectroscopy was performed to characterize the gallium (III) complex [43]. Albisporachelin (120), a new siderophore, was obtained from the *Amycolatopsis albispora* WP1<sup>T</sup> culture broth with iron depletion using sediments obtained at −2945 m from the Indian Ocean [44]. In the course of bacterial translocase I inhibitor screening, a new compound, A-102395 (121) was isolated from *Amycolatopsis* sp. SANK 60206. A-102395 (isolated from a soil sample collected in Hokkaido, Japan) showed strong inhibition on the bacterial translocase I with the IC<sub>50</sub> value of 0.01 µM. This compound showed no antibacterial effect on the analyzed strains [45]. The indole alkaloids are associated with cyclopiazonic acids, which were previously only detected in fungi. In addition, amycocyclopiazonic acid (122), along with amycolactam (123), was obtained from *Amycolatopsis saalfeldensis*. Combined with spectroscopic data, the structures of compounds 122 and 123 were identified to be new indole alkaloids related to cyclopiazonic acids. Amycolactam was significantly cytotoxic to gastric cancer SNU638 and colon cancer HCT116 cells, and the IC<sub>50</sub> values were 0.8 and 2.0 µM, respectively [23]. The novel derivative of carbamothioic S-acid (124) was obtained from *Amycolatopsis alba* DSM 44262<sup>Δabm9</sup> fermentation extract exposed to 25 mM N-acetyl-D-glucosamine [46]. Amycophthalazinone A (125), the first example of natural occurring new...
phthalazinone derivative, was discovered from the fermentation products of the lichen-associated *Amycolatopsis* sp. YIM 130,642 [18]. Compound 125 had potent antibacterial effect on *S. typhi*, *C. albicans*, and *S. aureus*, with IC\textsubscript{50} values of 6.92, 13.84, and 6.92 \(\mu\text{M}\), respectively. 2-Pyruvoylaminobenzamide (126), (−)-chrysogine (127), 4-(3-methylbut-2-enyloxy) benzamide (128), acetotryptamide (129), 2-acetamidophenol (130), anthranilic acid (131), phenacetamide (132) and 2-carbamoyl-3-hydroxy-1,4-naphthoquinone (133) were isolated from the cultural of *Amycolatopsis* sp. YIM 130687. Compounds 128 and 133 were firstly discovered from microorganisms [19].

Two novel echinosporin derivatives, echinosporin (134) and 7-deoxyechinosporin (135), were obtained from the culture broth of *Amycolatopsis* sp. YIM PH20520 from the *Panax notoginseng* rhizosphere soil samples collected from Wenshang, Yunnan Province of China. Compound 134 had potent effect on resisting four *P. notoginseng* root-rot pathogens, including *Fusarium solani*, *Fusarium oxysporum*, *Phoma herbarum* and *Alternaria panax*, and the MIC values were 64, 64, 64 and 64 \(\mu\text{g/mL}\), respectively. Compound 135 had moderate effect on resisting *F. solani*, *F. oxysporum*, *P. herbarum* and *A. panax*, with the MIC values of 128, 128, 128 and 64 \(\mu\text{g/mL}\), respectively [47]. Two novel compounds, dipyrimicins A (136) and B (137), were produced by *Amycolatopsis* sp. K16-0194. Compound 136 exhibited excellent antimicrobial activity against *S. cerevisiae* ATCC 9763, *Kocuria rhizophila* ATCC 9341, *B. subtilis* ATCC 6633, *E. coli* NIHJ, *Xanthomonas campestris* pv. oryzae KB 88 with the inhibition zone from 16 to 21 mm in a dose of 30 \(\mu\text{g}\) and from 11 to 27 mm in a dose of 100 \(\mu\text{g}\). Compound 136 also displayed strong cytotoxic activity against Hela 3S, HT29, A549, H1299, Panc1, TPH-1, *Jarkat* and *HL-60* with the IC\textsubscript{50} values of 5.1 ± 0.5, 6.2 ± 0.3, 4.3 ± 0.2, 9.2 ± 0.5, 9.4 ± 3.5, 9.4 ± 3.5, 4.4 ± 0.5 and 3.9 ± 0.7 \(\mu\text{M}\), respectively. Compound 137 only had a moderate inhibition on H1299 cell line with an IC\textsubscript{50} value of 6.8 ± 3.3 \(\mu\text{M}\) [48]. A new pyridinium, 1-(10-aminodecyl) pyridinium (138), was produced by *Amycolatopsis alba* var. nov. DVR D4, which was collected from marine sediment of Visakhapatnam coast. With a dose of 1000 \(\mu\text{g/mL}\), compound 138 had a great effect on HeLa, MCF-7 (breast cancer), U87MG (brain cancer) cells with percentage viability (%) and percentage inhibition (%) of 39.54, 60.36, 58.15 and 60.46, 39.64, 41.85, respectively [49]. Three novel siderochelins D–F (140–142), with the known siderochelin A (139) were obtained from *Amycolatopsis* sp. LZ149, derived from the rhizosphere of *Cynodon dactyIon* in the Baicheng beach of Xiamen, Fujian, China. Compound 139 exhibited antimicrobial activity against *Bacillus pumilus* CMCC55051, *B. subtilis* CMCC63501, *E. coli* CMCC4103 and *S. aureus* CMCC2600 with the diameter of inhibition zone from 10 to 15 mm [50]. Epoxyquinomicins A–D (143–146), four new compounds were isolated from the culture broth of *A. sulphurea* MK299-95F4 from the soil sample collected at Sendai City, Miyagi Prefecture, Japan. Compounds 143 and 144 exhibited antimicrobial activity against *M. luteus* IFO3333 and *M. luteus* PCI1001 with MIC values from 3.12 to 6.25 \(\mu\text{g/mL}\) [51]. Compounds 143–146 (1–4 mg/kg) possessed an inhibition ability of type II collagen-induced arthritis [67]. All 28 amide and amino derivatives described above are presented in Figure 6.
2.9. Glycoside Derivatives

HPLC-diode array screening was used to isolate tigloside (147) and 2,2′-di-O-β-D-glucopyranosyl-α-D-glucopyranosyl α-D-glucopyranoside (148) from the Amycolatopsis sp. NN0 21,702 mycelium. Chromatographic approaches were used to purify these new com-
pounds, while NMR spectroscopy together with chemical degradation assays was adopted to confirm their structures \[52\]. Three new tetrasaccharide derivatives, actinotetraoses I–K (149–151), with three known compounds, actinotetraoses A–C (152–154), were isolated from *Amycolatopsis* sp. HCa1, which was collected from the gut of grasshopper \[53\]. Another novel tetrasaccharide derivative, actinotetraose L (155), was also obtained from the *Amycolatopsis* sp. HCa1 \[54\]. However, these compounds showed no significant bioactivity. The 9 glycoside derivatives described above are presented in Figure 7.

![Figure 7](image)

**Figure 7.** Structures of glycoside derivatives (147–155), enediyne derivatives (156–157) and sesquiterpenes (158–159) from *Amycolatopsis*.

2.10. **Enediyne Derivatives**

Amycolamycins A (156) and B (157), two new enediyne derivatives, were isolated from *Amycolatopsis* sp. HCa4, which was collected from locust. Compound 156 could inhibit M231 cell lines by inducing apoptosis through activation of caspase-3 with the IC$_{50}$ value of 7.9 µM \[55\]. The two enediyne derivatives described above are presented in Figure 7.

2.11. **Sesquiterpenes**

Two novel abscisic acid-type sesquiterpenes, (E)-3-methyl-5-(2,6,6-trimethyl-3-oxocyclohex-1-enyl)pent-2-enoic acid (158) and (E)-3-methyl-5-(2,6,6-trimethyl-4-oxocyclohex-2-enyl)pent-
2-enoic acid (159), were produced by *Amycolatopsis alba* DSM 44,262 [31]. However, these two compounds exhibited no antimicrobial activity against *S. aureus*, *B. subtilis*, *P. aeruginosa* and *C. albicans*. The two sesquiterpenes described above are presented in Figure 7.

3. Biofunction of *Amycolatopsis* Species

The *Amycolatopsis* species have potential for biological degradation, bioconversion and biosorption, which might solve the problem of environmental pollution in the future [68].

3.1. Biological Degradation

ZJ0273 was a widely used broad-spectrum herbicide and left in soil in large numbers. Cai et al. found that ZJ0273 could be utilized by *Amycolatopsis* sp. M3-1 as the sole carbon and energy source with higher degrading activity. At 30 °C and pH 7.0, the efficiency of ZJ0273 degradation by *Amycolatopsis* sp. M3-1 was 59.3% and 68.5% in 25 and 60 days, respectively [69]. Naproxen was a drug utilized by humans; however, it was detected in surface waters and sanitary effluents in 71 countries, causing toxic effects on biota and further destroying the ecological environment [70]. At the concentration of 50 mg/L, naproxen could be used as the sole carbon and energy source of *Amycolatopsis* sp. Poz 14 and completely degraded in 18 days, while it will affect the growth of *Amycolatopsis* when its concentration was more than 50 mg/L [71]. It takes a long time for plastics to degrade in nature and the resulting environmental pollution problems are becoming more and more serious. Some *Amycolatopsis* strains possessed a polylactic acid (PLA) degradation capability including *Amycolatopsis* sp. HT-32, *Amycolatopsis* sp. 3118, *Amycolatopsis* sp. KT-s-9, *A. mediterranei* ATCC 27649, *Amycolatopsis* sp. 41, *Amycolatopsis* sp. K104-1, *A. orientalis* sp. orientalis, *Amycolatopsis thailandensis* CMU-PLA07T and *Amycolatopsis* sp. SCM_MK2-4 [72]. Tan et al. proved that *A. mediteranei* was capable to hydrolyze the aliphatic plastics poly(ε-caprolactone) and poly(1,4-butylene succinate) via a extracellular lipase [73]. In addition, *Amycolatopsis* sp. ATCC 39,116 could depolymerize high molecular weight lignin species and catabolize a significant portion of the low molecular weight aromatics and may become a mature route for biological lignin valorization in the future [74].

3.2. Bioconversion

The strains of *Amycolatopsis* sp. HR167 and *Amycolatopsis* sp. ATCC39116 were able to convert ferulic acid (cell wall component of higher plants) into vanillin (important flavor compound) with concentrations of 11.5 and 13.9 g/L, respectively. The vanillin production of vdh (encoded vanillin dehydrogenase) mutant of *Amycolatopsis* sp. ATCC39116 was increased 2.3 times due to the enzyme catalyzed the catabolism of vanillin [75]. Wuxistatin, a novel HMG–CoA reductase inhibitor, was transformed from lovastatin by hydroxylase (cytochrome P450) and isomerases of *Amycolatopsis* sp. CGMCC 1149, showing a four-fold activity, more than lovastatin [76,77].

3.3. Biosorption

Albarracin et al. discovered that *A. tucumanensis* DSM 45,259 (initially named as *Amycolatopsis* sp. AB0) possessed copper specific biosorption ability (25 mg/g) [78,79]. In the presence of Cu(II), *A. tucumanensis* DSM 45,259 enhanced the ability of reducing Cr(VI) [80]. The bioemulsifiers produced by *A. tucumanensis* DSM 45,259 was able to mediate two times Cr(VI) recovery compared to deionized water from soil and maybe utilized to recover Cr(VI) in the future [81]. Baz et al. collected *Amycolatopsis* sp. GT6, *Amycolatopsis* sp. GT15 and *Amycolatopsis* sp. GT39 from abandoned mining areas, which could tolerate high concentrations of metals (Cu, 0.1; Zn, 0.1; Cr, 0.15; Pb, 0.25 mg/mL) [82].

4. Bioactivities of Secondary Metabolites from *Amycolatopsis*

The bioactivities of secondary metabolites from *Amycolatopsis* strains have been also presented in Table 2, including antimicrobial, cytotoxic, antioxidant, topo IIα inhibition, anti-hyperglycemic, enzyme inhibition and DNA damage.
Table 2. The antimicrobial, cytotoxic and other bioactivities of secondary metabolites from *Amycolatopsis*.

| Activity Types | Compounds | Bioactivities (MIC, µg/mL or IC₅₀, µM) | Refs. |
|---------------|-----------|--------------------------------------|-------|
| **Antimicrobial activities** | Kigamicins A–E (1–5) | MRSA (0.03–0.22 µM) | [13] |
| Mutactimycin E (16) | | MRSA, *S. pneumoniae, E. faecium* (1–16 µg/mL) | [15] |
| 7-O-Methyl-3-O-α-L-rhamnopyranosyleugenol (20) and 7-O-α-D-arabinofuranosyl daidzein (21) | | *C. albicans, E. coli, MRSA, S. aureus, and S. typhi* (32–256 µg/mL) | [18] |
| Pradimicin-IRD (28) | | *S. agalactiae, S. aureus and P. aeruginosa* (3.15 µg/mL) | [20] |
| ECO-0501 (42) | | MRSA (0.125–0.25 µg/mL) | [24] |
| Vancoresmycin (48) | | MRSA, *E. faecium, E. faecalis* (0.05 µM) | [25] |
| Amycolatopsins A, C (49, 51) | | *M. bovis* (0.4 and 2.7 µM) | [26] |
| Rifamorpholine B (71) | | MRSA, *S. aureus, S. pyogenes, B. subtilis, M. luteus* (0.5–4.0 µM) | [29] |
| Rifamorpholine D (73) | | MRSA, *S. aureus, S. pyogenes, B. subtilis, M. luteus* (1.0–8.0 µM) | [29] |
| Macrotermycin A (75) | | *B. subtilis, S. aureus, C. cerevisiae, C. albicans* (1.0–10 µg/mL) | [29] |
| Macrotermycin C (77) | | *B. subtilis, S. aureus, C. cerevisiae, C. albicans* (10–25 µg/mL) | [29] |
| Thiazomycin (84) and thiazomycins A–D (85, 87–89) | | *S. aureus, E. faecalis, S. pneumonia* and their drug-resistant type (0.002–0.06 µg/mL) | [31–34] |
| PRG-A, C (98, 100) | | MRSA, *E. faecalis, M. luteus, B. subtilis* (0.72 µM) | [37,38] |
| PRG-B, D (99, 101) | | MRSA, *E. faecalis, M. luteus, B. subtilis* (5.62–23.37 µM) | [38] |
| Chloroorienticins A–E (106–110) | | *S. aureus* JC-1 and MRSA (0.2–0.78 µg/mL) | [40] |
| Vancomycin (113) | | *S. aureus* JC-1 (0.78 µg/mL) and MRSA (1.58 µg/mL) | [40] |
| MM 47,761 (115) and MM 49,721 (116) | | *B. subtilis* ATCC6633, *C. xerosis* NCTC9755, *M. luteus* NCTC3840, *S. aureus*, *S. saprophyticus* FL1, *S. epidermidis* 60137, *S. pyogenes* CN10, *S. agalactiae* Hester, *S. sanguis* ATCC 10556, *S. faecalis* I (0.5–8 µg/mL) | [41] |
| Amycophthalazinone A (125) | | *S. aureus, S. typhi, C. albicans* (6.92–13.84 µM) | [18] |
| Echinosporin (134) | | *F. oxysporum, F. solani, A. panax, and P. herbarum* (32–128 µg/mL) | [47] |
| 7-deoxyechinosporin (135) | | *F. oxysporum, F. solani, A. panax, and P. herbarum* (32–128 µg/mL) | [47] |
| Dipyrimicin A (136) | | *S. cerevisiae, Kocuria rhizophila, B. subtilis, Escherichia coli NIH, Xanthomonas campestris pv. oryzae* KB 88 (16–21 mm) | [48] |
| Siderochelin A (139) | | *Bacillus pumilus, B. subtilis, E. coli and S. aureus* (10–15 mm) | [50] |
| Epoxyquinomicins A (143) and B (144) | | *M. luteus* IFO3333, *M. luteus* PCH1001 (3.12–6.25 µg/mL) | [51] |
| **Cytotoxic activity** | Kigamicin D (4) | Mouse tumor cell lines LB32T, L-1210, EL-4, F388D1, B16BL6, FS3, Colon26 (0.95 µM) | [13] |
| 1-methoxy-3-methyl-8-hydroxy-anthraquinone (19) | | Lung cancer (10.3 µM) | [17] |
Table 2. Cont.

| Activity Types                  | Compounds                | Bioactivities (MIC, µg/mL or IC₅₀, µM) | Refs. |
|---------------------------------|--------------------------|---------------------------------------|-------|
| Pradimicin-IRD (28)             | HCT-116 (0.8 µM), MM 200 (2.7 µM), MCF-7 (1.55 µM), RPE (1.48 µM) | [20]  |
| Tetrangomycin (33)              | Hela cells (0.27 µM)     | [21]                                  |
| Pd116779 (34)                   | Hela cells (0.11 µM)     | [21]                                  |
| Sakymicin A (39)                | Hela cells (0.56 µM)     | [21]                                  |
| Sakymicin C (40)                | Hela cells (0.39 µM)     | [21]                                  |
| Amycolatopsins A, B (49, 50)    | SW620 (0.08 and 0.14 µM), NCIH-460 (1.2 and 0.28 µM) | [26]  |
| 3′-O-succinyl-apoptolidin A (52)| H292 cells (0.09 µM)     | [27]                                  |
| 2′-O-succinyl-apoptolidin A (53)| H292 cells (0.08 µM)     | [27]                                  |
| Apoptolidin A (54)              | H292 cells (0.02 µM), Hela cells (0.04 µM) | [27]  |
| Thioamycolamides A, D (93, 96)  | HT1080 (11.94 and 21.22 µM), Hela S3 (6.53 and 9.34 µM) | [27]  |
| Valgamicin V (105)              | MIA Paca 2, HGC-27, GSS, 5637, NCI-H1650, NB16, ME-180, HSC-490 (6.6–21.6 µM) | [39]  |
| Amycolactam (123)               | SNU638 (0.8 µM), HCT116 (2.0 µM) | [23]  |
| Dipyrimicin A (136)             | Hela 3S, HT29, A549, H1299, Panc1, THP-1, Jarkat, HL-60 (3.9–9.4 µM) | [48]  |
| Dipyrimicin B (137)             | H1299 cell (6.8 ± 3.3 µM) | [48]                                  |
| Amycolamycin A (156)            | M231 (7.9 µM)            | [55]                                  |
| Other activities                |                          |                                       |
| Amexanthomycins A–C (6–8)       | Inhibiting human DNA Topo II x | [14]                                 |
| 1-methoxy-3-methyl-8-hydroxy-anthraquinone (19) | Antioxidant | [17] |
| Rifamycinoside A and B (59–60), 28-Desmethyl-28-hydroxyrifamycin W (61), 30-Hydroxyrifamycin W hemiacetal (63), Rifamycin O (67) | Inhibiting human DNA Topo I (50 and 100 µM) | [28] |
| Rifamycinoside A and B (59–60), 28-Desmethyl-28-hydroxyrifamycin W (61), 30-Hydroxyrifamycin W hemiacetal (63), Rifamycin S, O and Z (65, 67 and 68) | Inhibiting human DNA Topo II x (50 µM) | [28] |
| 20-hydroxyrifamycin S (64)      | Inducing G2/M phase arrest, Causing DNA damage in HCT116 | [28] |
| A-102395 (121)                  | Inhibiting bacterial translocase I (0.01 µM) | [45] |
| Epoxyquinomicins C (145) and D (146) | Inhibiting type II collagen-induced arthritis | [51] |

Among the total of 159 secondary metabolites, 41 compounds exhibited potent antimicrobial activities, a majority of which showed inhibition on Gram-positive bacteria growth. Most of them were also found to be active against various multi-drug resistant strains. Kigamicins (1–5), mutactimycin E (16), pradimicin-IRD (28), ECO-0501 (42), vancoresmycin (48), amycolatopsins A (49) and C (51), rifamorpholines B (71) and D (73), macrotermycins A (75) and C (77), thiazomycin (84), thiazomycins A–D (85, 87–89), PRG-A–D (98–101), chloroorienticins A–E (106–110), vancomycin (113), MM 47,761 (115), MM 49,721 (116) and amycophthalazinone A (125) showed significant inhibitory effects against gram-positive bacteria and their drug-resistant types with MIC and IC₅₀ values less than 1 µg/mL and 25 µM, respectively. While epoxyquinomicins A (143) and B
displayed moderate activities with MIC values in the range of 3.12–6.25 μg/mL. 7-O-Methyl-5-O-α-L-rhamnopyranosylgenestein (20), 7-O-α-D-arabino-furanosyl daidzein (21), echinonoprin (134) and 7-deoxyechinonoprin (135) showed modest antibacterial activities with MIC values in the range of 32–256 μg/mL.

Of these reported substances, a total of 18 compounds had strong cytotoxicities to different cancer cell lines. For instance, kigamicin D (4) suppressed mouse cancer cell growth, and the IC50 value was approximately 0.95 μM. 1-Methoxy-3-methyl-8-hydroxy-anthraquinone (19) displayed intensive anti-cancer effect on lymphoblastic leukemia together with lung cancer cells, and the IC50 values were 16.98 and 10.3 μM, respectively. Pradimicin-IRD (28) showed excellent cytotoxicity to HCT-116, MM 200, MCF-7 and RPE with the IC50 values of 0.8, 2.7, 1.55 and 1.48 μM, respectively. Tetrangomycin (33), pd116779 (34), sakyomicins A (39) and C (40) could inhibit the Hela cells with the IC50 values of 0.27, 0.11,0.56 and 0.39 μM, respectively. Amycolatopsins A (49) and B (50) had potent effects on resisting human colon cancer (SW620; IC50 values, 0.08 and 0.14 μM) as well as lung cancer (NCIH-460; IC50 values, 1.2, and 0.28 μM) cell lines. 3′-O-Succinyl-apoptolidin A (52), 2′-O-succinyl-apoptolidin A (53) and apoptolidins A (54) could inhibit the H292 cells with the IC50 values of 91, 82 and 22 μM, respectively. Thioamycolamides A (93) and D (96) showed moderate cytotoxicity to fibrosarcoma HT1080 and cervix adenocarcinoma HeLa with the IC50 values ranging from 6.53 to 21.22 μM. Valgamicins V (105) could inhibit the cancer cells, such as MIA Paca 2, HGC-27, GSS, 5637, NCI-H1650, NB16, ME-180, HSC-490 (IC50 values, 6.6-21.6 μM). Amycolactam (123) had marked effect on resisting gastric cancer SNU638 cells as well as colon cancer HCT116 cells. The IC50 values were recorded to be 0.8 and 2.0 μM, respectively. Dipyrimicin A (136) exhibited moderate cytotoxicity to a series of cancer cells (Hela 3S, HT29, A549, H1299, Panc1, THP-1, Jarkat, HL-60) with the IC50 from 3.9 to 9.4 μM. However, dipyrimicin B (137) only suppressed the H1299 with the IC50 value of 6.8 ± 3.3 μM. Amycolamycin A (156) showed moderate cytotoxicity to M321 with the IC50 value of 7.9 μM.

A total of 15 compounds showed other bioactivities. Amexanthomycins A–J (6–15) possessed a xanthen-containing pentangular polyphenol core. Compounds 9–15 had no inhibitory effect on DNA topoisomerase IIα (Topo IIα), while compounds 6–8 exhibited moderate inhibitory activity against Topo IIα at 500 μM. These results showed that the different numbers and types of deoxysugars in compounds 6–15 will affect the inhibitory activity of topoisomerase. Compound 19 was used at 100 mg/kg to treat hyperglycemia without inducing any genotoxic effect and also inhibiting α-amylase and α-glucosidase with the IC50 values of 0.91 and 10.32 μM, respectively. Experiments in mice have proven the safety and efficacy of compound 19. Compounds 59–61, 63 and 67 exhibited strong activity for inhibiting Topo I at 50 and 100 μM. Moreover, compounds 59–61, 63, 65, 67 and 68 showed the activity of inhibiting Topo IIα at 50 μM. Compound 64 had strong effect on inhibiting T3SS, resulted in cell cycle arrest at G2/M phase, and led to DNA damage within the HCT116 cells. A-102395 (121) was identified as the strong bacterial translocase I inhibitor, and its IC50 value was 0.011 μM. At the dose of 1–4 mg/kg, epoxyquinomicins C (145) and D (146) could inhibit type II collagen-induced arthritis.

5. Synthesis of Secondary Metabolites from Amycolatopsis and Their Derivatives
5.1. Biosynthetic Pathways of Secondary Metabolites from Amycolatopsis

Research on biosynthetic pathways is essential for the further study on secondary metabolites. For example, finding the regulatory gene could increase or decrease the production of metabolites and also uncover how the concerted efforts of various enzymes to form the compound [83]. In this review, we list the hypothetical biosynthetic pathways for several potent bioactive compounds. Few studies have been conducted and need to arouse the attention of researchers.

The mutant strain A. mediterranei S699ΔrifA, which was deleted for the biosynthesis gene of rifamycins, displayed the ability for producing ten new pentangular polyphenols, amexanthomycins A–J (6–15) [14]. As described in the literature, the production of as-
associated genes included polyketide synthase (PKS), glycosyltransferase, methyltransferase, monooxygenase, dehydrogenase, oxidoreductase, cytochrome P450 and epimerase (Figure 8A). The biosynthetic pathway of amexanthomycins were proposed by Li et al. [14] and exhibited in the Figure 8B. An acetyl-CoA starter unit and 11 malonyl-CoA extender units could produce prediction intermediate, the pentacyclic xanthone core, by min-PKS synthase, cyclase, and oxidoreductase. Then, the predicted oxidase catalyzed the oxidative rearrangement reaction of intermediate. Finally, this aglycone was glycosylated by the glycosyl transferases, completing the biosynthesis of compounds 6–15 (Figure 8B) [14].

Figure 8. (A) The gene clusters of amexanthomycins A–J. (B) The biosynthetic pathway of amexanthomycins A–J [14].

The genome of A. orientalis ATCC 43,491 included a type I PKS which encoded by ORF 18-23 and synthesized the polyketide chain [24]. The monooxygenase and acyl-CoA ligase were encoded by ORF 7 and 25 which catalyzed arginine to 4-guanidino butyryl-CoA. D-glucose was catalyzed by oxidoreductase (ORF 13) and turned into D-glucuronic acid. Glycine and succinyl-CoA were transformed into 5-aminolevulinate by acyltransferase (ORF 16), and then turned into 5-aminolevulinate-CoA by acyl-CoA ligase (ORF 17). 5-aminolevulinate-CoA was transformed into aminohydroxycyclopentenone...
through cyclization reaction by the coenzyme A ester. Three ORFs (14, 15 and 24) provided glycosyltransferase, amide synthetase and acyltransferase to add 4-guanidino butyryl-CoA, D-glucuronic acid and aminohydroxycyclopentenone onto the polyketide chain which formed compound 47 (Figure 9) [24].

![Diagram of biosynthetic pathway](attachment:image.png)

**Figure 9.** The biosynthetic pathway of ECO-0501 (47) [24].

The genome of *Amycolatopsis* sp. HCa4 was analyzed by antiSMASH and 2ndfind, the cluster 19 was highly similar to the biosynthetic gene cluster of rifamycin [29]. A 3-amino-5-hydroxybenzoic acid starter unit and two malonyl CoA and eight methyl malonyl CoA extender units could produce intermediate 1 on a type I polyketide synthase. The release of the polyketide chain and the formation of intramolecular amide were catalyzed by the amide synthase encoded by Rmp F and then generated proansamycin X (intermediate 2). Proansamycin X was then catalyzed by a serious of enzymes encoded by Rmp T, U, 11, 5, etc., and turned into the key intermediate 3, dimethyl-desacetyl-rifamycin S. All the above synthetic processes were the same as the synthesis of rifamycin, but Xiao et al. did not find the rifamycin analogs in this strain and they suspected that maybe an unidentified enzyme catalyzed the keto–enol tautomerization of intermediate 3 to form intermediate 4. The intermediate 4 was formed to the intermediate 5 through a crucial 1,6-cyclization, which was further converted into compound 70 and compounds 71–74 followed by two branch pathways. The formation of compound 70 was catalyzed by 25-O-acetyltransferase
(Rmp 20) and C-27-O-methyltransferase (Rmp 14), as well as epimerization of C-21. However, the formation of compounds 71–74 was not speculated (Figure 10) [29].

Figure 10. The biosynthetic pathway of rifamorpholines A–E [29].

A-102395 (121) was a capuramycin-type nucleoside antibiotics possessed high specific chemical features, which were isolated from Amycolatopsis sp. SANK 60206. By synthase encoded by Cpr38, chorismate was catalyzed to form 4-amino-4-deoxychorismate (ADC), which subsequently catalyzed elimination of pyruvate by aminotransferase (Cpr12) to form para-aminobenzoic acid (PABA). Catalyzed by actinomycin synthetase (Cpr37), PABA became activated acyl-adenylate and combined with the free-standing carrier protein (Cpr36) to yield the thioester-linked PABA. Under the synergic catalyzation of ketosyn-
thase (Cpr34) and chain length factor (Cpr35), the thioester-linked PABA as a recipient was decarboxylatively condensed with malonyl-S-acyl carrier protein (ACP) to form \( \beta \)-ketothioester. That \( \beta \)-ketothioester was reduced by 3-oxoacyl-ACP reductase Cpr33 and then hydroxylated by luciferase-like monooxygenase Cpr32 to form 3-(4-aminophenyl)-2,3-dihydroxypropanoic acid. The next step was polyamide biosynthesis, in which 3-(4-aminophenyl)-2,3-dihydroxypropanoic acid was catalyzed by a serious of enzymes including a hydrophilic amino acid (Cpr54), two carrier proteins (Cpr48 and 55), a condensation domain protein (Cpr47), and three transglutaminase-like proteins (Cpr49, 50 and 57) to form an A-102395 core. The coupling of the arylamine-containing polyamide to the A-102395 core was catalyzed by carboxyl methyltransferase (Cpr27) and MitI transacylase (Cpr51) [84]. However, the mechanism of Cpr51 has not been proven and needs further research (Figure 11).

**Figure 11.** The biosynthetic pathway of A-102395 [84].

The strain *Amycolatopsis* sp. HCa4 possessed *acm* gene of amycolamycins A and B, which spanned a \( \sim \)76 kb contiguous DNA region. The Acm A2, A3, A4 and A5 provided NDP-glucose dehydrogenase, glucuronic acid decarboxylase, C-methyltransferase and aminotransferase. These enzymes catalyzed the NDP-glucose to NDP activated aminosugar. The 6-methylsalicylic acid synthase, CoA ligase and C-methyltransferase were encoded by Acm B, B2 and B1, which catalyzed three successive steps starting from acetyl-CoA and malonyl-CoA to 3,6- dimethylsalicylyl CoA. The genes of Acm P1, P2, P3, P5, P6 and P4 encoded the glycosyltransferase, NRPS A-PCP didomain protein, hydroxylase, monooxygenase, O-methyltransferase and halogenase. These enzymes catalyzed six successive steps converting p-hydroxyphenylpyruvate to 2-chloro-3-hydroxy-4,5-dimethoxymandelate moiety. Acetyl-CoA and malonyl-CoA were catalyzed to form enediyne core by a series of enzymes, which were encoded by E, E2-E11, D2, L, M and N. The next step needed B3.
(acetyltransferase) to connect NDP activated aminosugar to 3,6-dimethylsalicylyl CoA. The NDP activated aminosugar and 2-chloro-3-hydroxy-4,5-dimethoxymandelate moiety were then connected to the enediyne core, which needs the Acm A6 (acetyltransferase) and Acm P10 (type II condensation enzyme), respectively. The connection product was transformed into compounds 156 and 157 by bergman cyclization (Figure 12) [55].

Figure 12. The biosynthetic pathway of amycolamycins A and B [55].
5.2. Chemical Synthesis, Semi-Synthesis and Biosynthesis of the Derivatives

5.2.1. Chemical Synthesis of DHM2EQ

DHM2EQ was a derivative of epoxyquinomicin C and possessed greater strong inhibitory activity on type II collagen-induced arthritis than epoxyquinomicin C. The derivative was synthesized from 2,5-dimethoxyaniline in 5 steps via chemical synthesis. In pyridine, 2,5-dimethoxyaniline (a) and acetylsalicyloyl chloride were coupled to give salicylamide (b). In methanol, compound (b) was oxidized into quinone monoketal (c) by iodobenzene diacetate. Under deprotection of the phenolic acetyl group, epoxidation of (c) in aqueous THF with alkaline hydrogen peroxide gave epoxide (d). Compound (d) was reduced by NaBH₄ yield (e) and the deprotection of compound (e) with p-TsOH gave DHM2EQ (Figure 13) [85].

![Chemical synthesis pathway of DHM2EQ](image)

5.2.2. Semi-Synthesis of 24-Desmethylrifampicin

24-Desmethylrifampicin (d) was a semi-synthetic derivative of rifamycin B and 24-desmethylrifamycin B (a) was semi-synthetic precursor of (d). Nigam et al. replaced the acyltransferase domain of module 6 of rifamycin polyketide synthase (rifAT6) with that of module 2 of rapamycin polyketide synthase (rapAT2) to gain a mutant *A. mediterranei* S699 DCO#34, which could produce 24-desmethylrifamycin B (a). 24-Desmethylrifamycin S (b) was the oxidation product of compound (a) using CuCl₂ as catalyst. Compound (b) was then treated with paraformaldehyde and 1,3,5-trimethyl-hexahydro-1,3,5-triazine in acetic acid to gain 3-methyl-1,3-oxazino(5,6-c)-24-desmethylrifamycin (c), which was subsequently treated with 1-amino-4-methylpiperazine to give 24-desmethylrifampicin (d) [86]. Nirjara et al. uncovered that the damage of RifP, RifQ, transport cascade was an essential reason of the low yield of only 20 mg/L of compound (a). They thought the production of compound (a) could be increased by blocking RifQ to restore the function of RifP in the future (Figure 14) [87].
5.2.3. Biosynthesis of CDCHD

Chelocardin (CHD) isolated from *A. sulphurea* was a structurally atypical tetracycline [2]. CHD possessed excellent anti-microbial activity with little toxicity. 2-Carboxamido-2-deacetyl-chelocardin (CDCHD) was a derivative of CDH by introducing oxyD (amido-transferase) and oxyP (thiolase) genes from *Streptomyces rimosus* otc gene cluster into *A. sulphurea*. The production of CDCHD was very low when only introduced OxyD into *A. sulphurea* because OxyP could suppress priming of CDH by removing the competing acetyl units [88]. Then, the CDH gene cluster took over the rest of reaction [89]. These two genes worked together to change the main product from CHD to CDCHD (Figure 15).

6. Conclusions

This review summarizes the various chemical structures and biological activities of 159 compounds isolated from *Amycolatopsis* species inhabiting soil, insects, lichen, islands, the marine and plants between 1990–2020. A total of 45 compounds possessed bioactiv-
ities, of which 32 compounds have glycosides and 31 compounds have cyclic skeletons. Thus, the novel compounds with glycosides and cyclic skeletons should be considered by researchers. For example, compound 51, the homolog of 49 and 50, lacked glycoside and showed 5- to 100-fold less cytotoxicity [26]. The multitudinous secondary metabolites of the genus *Amycolatopsis* represent great research value and deserve further investigation. On the other hand, the genus of *Amycolatopsis* could metabolize a variety of carbon sources and grow in a wide temperature range, which provides the possibility for them to become important biotechnological tools. It has been proven that this genus has great potential in degrading plastics, treating heavy metals, and biotransformation [68]. More researches are needed to transform these potentials into applications to solve practical problems to benefit mankind.

The study of biosynthetic pathway is a crucial process for excavating bioactive natural products. However, people are more willing to study the biosynthesis and mechanism of action of vancomycin, rifamycin and their derivatives. There are relatively fewer studies on the biosynthesis of other bioactive compounds and more attention is needed to be paid to researchers. In the course of the biosynthetic pathway study, a series of tools, for example, antiSMASH [90] or PRISM [91], have been fully exploited, which could derive a prediction of natural products, including the enzymes, regulatory genes and biosynthetic genes et al. through the genome sequencing results. We could also use these tools to reveal sufficiently more silent biosynthetic gene clusters and uncover more and more new interesting bioactive natural products. The biosynthetic potency of *Amycolatopsis* species is evidenced to be massive and this genus possesses many silent biosynthetic gene clusters waiting to be found [92]. Recently, Pan et al. obtained two new compounds, amycloapeptins A and B by combined-cultivating two strains of *Amycolatopsis* sp. 26-4 and *Tsukamurella pulmonis* TP-B0596 for the first time, while they could not be discovered in a monoculture of *Amycolatopsis* sp. 26-4 [93], which provided a new path for the cultivation of *Amycolatopsis*.

In conclusion, the research on the genus *Amycolatopsis* needs to be further considered in-depth. Most of all, the mechanism of action and biosynthetic regulatory genes of potent active compounds deserve to be deeply explored since they could determine the utility value of these compounds. Derivatives sometimes tend to have stronger activity so that more study might be focused on the structural modification of secondary metabolites for providing more analogues to be screened for antibiotics. In addition, compounds with excellent bioactivity that have been discovered should be solved for mass production due to their promising medicinal application. The potential ecological effects of *Amycolatopsis* species should be also taken seriously. The environmental pollution problem might be solved in some ways by thoroughly excavating the biofunction of the strains. In the future, we firmly believe that the genus *Amycolatopsis* will show its expansive utilization and serve for pharmaceutical area and environmental protection.

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