Review

Genus Nocardiopsis: A Prolific Producer of Natural Products

Ting Shi 1,2, Yi-Fei Wang 1, Han Wang 1 and Bo Wang 1,*

1 College of Chemical and Biological Engineering, Shandong University of Science and Technology, Qingdao 266590, China; shiting_jia@126.com (T.S.); kingsley11f115@163.com (Y.-F.W.); h15725209196@163.com (H.W.)
2 State Key Laboratory of Microbial Technology, Institute of Microbial Technology, Shandong University, Qingdao 266200, China
* Correspondence: wb@sdust.edu.cn; Tel.: +86-132-0648-5008

Abstract: Actinomycetes are currently one of the major sources of bioactive secondary metabolites used for medicine development. Accumulating evidence has shown that Nocardiopsis, a key class of actinomycetes, has the ability to produce novel bioactive natural products. This review covers the sources, distribution, bioactivities, biosynthesis, and structural characteristics of compounds isolated from Nocardiopsis in the period between March 2018 and 2021. Our results reveal that 67% of Nocardiopsis-derived natural products are reported for the first time, and 73% of them are isolated from marine Nocardiopsis. The chemical structures of the Nocardiopsis-derived compounds have diverse skeletons, concentrating on the categories of polyketides, peptides, terphenyls, and alkaloids. Almost 50% of the natural products isolated from Nocardiopsis have been discovered to display various bioactivities. These results fully demonstrate the great potential of the genus Nocardiopsis to produce novel bioactive secondary metabolites that may serve as a structural foundation for the development of novel drugs.

Keywords: actinomycetes; Nocardiopsis; natural products; bioactivities; medicinal potentiality

1. Introduction

Actinomycetes belong to Gram-positive bacteria and are one of the biggest bacterial phyla [1,2]. The high G+C DNA content of actinomycetes implied their enormous biosynthetic potential to produce various natural products with diverse structures and important commercial applications [1,2]. Two-thirds of all naturally derived antibiotics have been discovered from actinobacteria [3,4]. Approximately 70% of the pharmaceutically active natural products which are currently used in clinics are isolated from actinobacteria [5–8], including a series of anticancer, antifungal, antibacterial, antihelminthic, and immunosuppressive drugs [3].

Nocardiopsis is an important genus of actinobacterium for its extensive application in agriculture [9], industry [10], and environmental protection [11], especially for its potential ability to produce new natural products [5,12]. By mid-2021, 3% of marine actinomycetes-derived natural products were produced by Nocardiopsis, and Nocardiopsis are the third-largest actinomycetes in terms of producing marine compounds [13]. In addition, Nocardiopsis are a prolific source of bioactive natural products in both marine and terrestrial environments [1] and are widely distributed in multiple ecosystems [12], including deserts [14], deep ocean [15], coastal wetlands [16], and saline–alkali soil [17]. Nocardiopsis species have the ability to survive under different and hostile environmental conditions, mainly benefiting from their excretion of enzymes, multipurpose genetic constitution, and their ability to produce compuponible solutes and surfactants [12,18–20]. Besides these characteristics, the members of this genus have the ability to produce abundant bioactive compounds, which may allow them to prevail in different habitats [12]. Extracts from cultivated Nocardiopsis have exhibited cytotoxic [21,22], antimicrobial [23,24], antifibrotic [25],
and anti-inflammatory [25] activities. Comprehensive analyses of *Nocardiopsis* metabolites by LC-HRES-MS, HRMS, or GC/MS have led to the identification of bioactive and structurally diverse compounds [21,26–28]. The bioactive secondary metabolites isolated from *Nocardiopsis* include antimicrobial agents [29–31], tumor promoters [32], cytotoxic compounds [33,34], kinase and P-glycoprotein inhibitors [35,36], immunoregulators [37], and natural products with other multiple bioactivities [38–40]. The secondary metabolites discovered from *Nocardiopsis* have shown a great diversity of structural frameworks, including polyketides [41–43], alkaloids [44,45], and terpenoids [46,47].

Bennur et al. reviewed the bioactive natural products derived from *Nocardiopsis* prior to 2015 [12], while Ibrahim et al. conducted a literature review regarding all of the secondary metabolites discovered from *Nocardiopsis* from 2016 to February 2018 [5]. In this review, the sources, distribution, bioactivities, biosynthesis, and structural characteristics of the compounds isolated from *Nocardiopsis* between March 2018 and 2021 are comprehensively summarized.

2. Polyketides

Three new angucyclines, nocardiopsistins A–C (1–3), were obtained from the deep-sea sponge-derived *Nocardiopsis* sp. strain HB-J378 (Figure 1) [48]. The antibacterial activities of compounds 1–3 were tested against MRSA (methicillin-resistant *Staphylococcus aureus*) and 1–3 exhibited antibacterial activity with MIC values of 3.12–12.5 µg/mL. Three core genes were identified through bioinformatic analysis of the sketch genome of the strain HB-J378 in a biosynthetic gene cluster encoding a typical aromatic or type II polyketide synthase (PKS) system, including acyl carrier protein (ACP), ketoacyl: ACP synthase α-subunit (KSα) and β-subunit (KSβ). The brief biosynthetic route for 1–3 was proposed according to the discovered oviedomycin pathway [49]. Compounds 1–3 were supposed to be biosynthesized by taking advantage of one molecule of isobutyral-CoA and nine molecules of malonyl-CoA, through complex enzymatic reactions to obtain the key angucycline biosynthetic intermediate UWM6, an analog of 1–3 [50], to acquire 1–3 (see Figure 1) [48].

![Figure 1](image-url) Structural formulas and proposed biosynthesis mechanism for compounds 1–3 [48].

The new strain *Nocardiopsis* sp. CG3 (DSM 106572), collected from the saltpan of Kenadsa (22 km west of Bechar, located in southwest Algeria), was discovered to have the ability to produce new bioactive natural products in a screening program [51]. Chemical investigation of the strain led to the isolation of five new polylene macrolactams, kenalactams.
A–E (4–8) (Figure 2) [51]. The biosynthetic pathway of polyketide kenalactam A (4) was studied by feeding experiments and was found to use L-alanine as the nitrogen-bearing starter unit. Compounds 6–8 exhibited cytotoxic activity against HeLa (cervical cancer cells KB3.1) and PC-3 (human prostate cancer) cell lines, with IC₅₀ values ranging from 2.1 to 6.8 µM [51].

![Structural formulas of compounds 4-8](image)

Figure 2. Structural formulas of compounds 4–8 [51]. (Reprinted with permission from Ref. [51], Copyright 2019, Journal of Natural Products, published by American Chemical Society).

Eight new α-pyrene derivatives, nocahypyrones A–H (9–16), along with one known analog, germicidin G (17) (Figure 3) were isolated from the strains Nocardiopsis sp. HDN154-146 and HDN154-168, which were collected from soil samples derived from the Takla Makan desert area in Xinjiang Province, China. This was the first time it was reported that compounds 13 and 16 showed cytoprotective activity by inducing the expression of phase II detoxifying enzymes [52]. Aldo-keto reductase family1 member C1 (AKR1C1), human NAD(P)H: quinone oxidoreductase 1 (NQO1), superoxide dismutase 2 (SOD2), and heme oxygenase 1(HO-1), belonging to phase II detoxifying enzymes, have been illustrated to possess significant roles in defending mammalian cells against oxidative damage and excessive inflammatory reaction [53,54]. Compounds 13 and 16 displayed cytoprotective activity by inducing the expression level of SOD2 and HO-1 in HaCaT cells [52].

Chemical investigation of the actinobacterium Nocardiopsis sp. HDN 17-237 led to the isolation of one new β,γ-butenoate derivative, phenylbutenote (18), and one new α-pyrene, nocapyrone T (19) (Figure 3). The strain HDN 17-237 was collected from deep-sea water from the Mariana Trench (depth 4448 m, 10°21.100' N, 142°17.574' E, gathered in September 2016). Compounds 18 and 19 were evaluated for antibacterial and antioxidant activities, while neither of them exhibited obvious activity [55].

Comprehensive research of the secondary metabolites of an Antarctic marine animal sample-derived actinomycete, N. aegyptia HDN19-252, combined with a molecular networking approach in the Global Natural Products Social (GNPS) platform, obtained the isolation of four new anthraquinone derivatives, saliniquinones G–I (20–22) and heraclemycin E (23) (Figure 3). Compounds 20 and 21 showed potent antibacterial activities against six evaluated bacterial strains—Bacillus subtilis, methicillin-resistant coagulase-negative staphylococci, B. cereus, Proteus sp., Mycobacterium phlei, and Escherichia coli—with MIC values of 3.1–12.5 µM [56].

Three new macrolides, borrelidins C–E, along with one known analog, borrelidin, which showed antibacterial and anticancer activities, were isolated from a saltern-derived halophilic Nocardiopsis sp. in 2017 [43]. These borrelidins were found to have the ability to relieve the amyloid-β induced toxicity in the HT22 cell line in 2021, indicating the potential of borrelidins to be developed as Alzheimer’s disease drugs [57].
3. Alkaloids

The approach of an optimized nitroso-based probe (dienophile probe), promoting the detection of compounds containing conjugated alkenes in crude broth extracts, was employed in the chemical investigation of a marine-derived Nocardiopsis sp. CNY-503 and gained the isolation of one new polyketide alkaloid, named nocarditriene (24), which contained an unprecedented epoxy-2,3,4,5-tetrahydropyridine structure (Figure 4) [58].

The structure of nocarbenzoxazole G (25), isolated from the marine-derived actinomycete N. lucentensis DSM 44048 in 2015 [60], was revised into the nocarbenzoxazole G (26) molecule by total synthesis in 2019. The benzoxazole skeleton was constructed with microwave assistance and continued by carbon–carbon bond formation with relevant aryl bromides [59]. Compound 26 was found to display moderate cytotoxicity against HepG2 and HeLa cell lines with IC50 values of 16 and 14 µM, respectively [60].
Chemical investigation of the strain *N. flavescens* NA01583, which was gained from marine sediment gathered at the coast near Hainan Island in 2016 through the genome mining of an indolocarbazole-type gene cluster, led to the isolation of three new indolocarbazole alkaloids, named loonamycins A–C (27–29) (Figure 5) [61].

![Structural formulas of compounds 27–34](image-url)

**Figure 5.** Structural formulas of compounds 27–34 [22,61–63].

Compound 29 was produced successfully by the allogenetic expression of the complete loo gene cluster in a vicarious host, *Streptomyces lividans* K4–114. The indolocarbazole skeleton of 27–29, belonging to the family of indolocarbazole alkaloids, is structurally similar to that of rebeccamycin and staurosporine with an additional rare modified tryptophan ring. The molecular bases of these modifications were investigated by carefully analyzing loo BGC for further genome mining and combinational biosynthetic research. The loo gene cluster sustains a ∼36 kb continuous DNA sequence, including 25 open reading frames which take charge of biosynthesis, regulation, and resistance (Figure 6A). A possible biosynthetic pathway for loonamycin was detected based on this bioinformatic analysis (Figure 6B). In particular, compound 27 showed potent cytotoxic activities toward eight cancer cell lines, including Sum1315 (breast cancer), SH-SY5Y (neuroblastoma), HCT116 (colorectal cancer), HT29 (colorectal cancer), HCC78 (lung cancer), HeLa (cervical cancer), SW620 (colorectal cancer), and SW872 (liposarcoma), with IC_{50} values of 41–283 nM [61].

The broth culture crude extracts of actinobacterium *Nocardiopsis* sp. SCA30, derived from marine sediments collected from Havelock Island, Andaman, and the Nicobar Islands, India (11.96° N, 93.00° E), displayed cytotoxic activities against a series of cell lines, including HT 29, HCT 15, MDA-MB 468, and MCF 7 at concentrations ranging from 62.5 to 1000 µg/mL. The strain extracts also showed antibacterial activities against MRSA ATCC NR-46171 and NR-46071 with MIC values of 7.81 and 15.62 µg/mL, respectively. Compound 1-acetyl-4-4(hydroxyphenyl)piperazine (30) (Figure 5) was isolated from the crude extracts of *Nocardiopsis* sp. SCA30 through LC-MS analysis and NMR chemical structural identification approved to be an antibacterial and cytotoxic compound [22].
Chemical investigation of actinomycete *N. dassonvillei* SCSIO 40065 derived from the marine sponge *Petrosia* sp., which was collected on the seabed near Yongxing Island in the South China Sea at a depth of 20 m, led to the isolation of two polycyclic thioalkaloids, dassonmycins A (31) and B (32) (Figure 5). The new isolated compounds 31 and 32 contained the skeleton of a 6/6/6/6-fused tetracyclic ring featuring a naphthoquinone [2,3-\(c\)-piperazine-[1,2-\(c\)] thiomorpholine. Both compounds exhibited antibacterial activities against *Micrococcus luteus* SCSIO ML01, *B. subtilis* 1064, MRSA shhsA1, and *S. aureus* ATCC 29213 with MICs of 8–64 µg/mL. Compound 31 was found to display weak inhibited growth of *Vibrio alginolyticus* ATCC 13214 and *Enterococcus faecalis* ATCC 29212, with MIC values of 32 µg/mL. Compounds 31 and 32 exhibited moderate cytotoxicity against four human cancer cell lines—HepG-2, SF-268, MCF-7, and A549—with IC\(50\) values of 12–34 µM [62]. Biosynthetically, 31 and 32 are proposed to be biosynthesized by a non-ribosomal peptide synthetase (NRPS) route combined with a chorismate pathway (Figure 7) [62].

A marine sediment-derived actinobacterium *N. dassonvillei* JS106 showed potent antibiofilm activities against *S. aureus* and *Pseudomonas aeruginosa* [63]. The marine sediment sample was gathered from Lianyungang, China. Secondary metabolites research of the strain JS106 led to the isolation of one new compound, 2-hydroxyacetate-3-hydroxyacetamido-phenoxazine (HHP, 33), and one known analog questionycin A (34) (Figure 5). Both of these two compounds (33 and 34) exhibited antibiofilm activity against *Chromobacterium violaceum* 12472 with IC\(50\) values of 23.59 and 6.82 µg/mL, respectively [63].
Figure 7. Proposed biosynthesis of compounds 31 and 32 [62]. (Reprinted with permission from Ref. [62], Copyright 2021, Organic Letters, published by American Chemical Society).

4. Peptides

The secondary metabolites research of the broth culture of *Nocardiopsis* sp. UR67A, derived from the marine sponge *Callyspongia* sp. collected from the Red Sea in 2018, resulted in the purification of one new cyclic hexapeptide, nocardiotide A (35) (Figure 8) [64]. Compound 35 was synthesized by combining solid-and solution-phase synthesis methods in 2021 [65]. Compound 35 exhibited obvious cytotoxic activities against HeLa, CT26 (murine colon carcinoma), and MM.1S (human multiple myeloma) cell lines with IC$_{50}$ values ranging from 8 to 12 µM [64].

One new diketopiperazine, 1-demethylnocazine A (36) (Figure 8), was separated from the broth culture of the actinomycete *Nocardiopsis* sp. TRM20105, which was derived from a local cotton field in Tarim Basin, through the approach of antifungal activity tracking purification against *Candida albicans*. Compound 36 displayed weak antifungal activity against *C. albicans*, with an MIC value of 3.16 mM [66].

One new cyclic tetrapeptide, androsamide (37), was isolated from the actinobacterium *Nocardiopsis* sp. CNT-189 was gathered from the surf zone sediment of the Bahamas shore (Figure 8) [67]. Androsamide (37) displayed moderate cytotoxicity against Caco2 (human colorectal adenocarcinoma), AGS (human gastric adenocarcinoma), and HCT116 (human colorectal carcinoma) cell lines with the IC$_{50}$ values of 13 µM, 18 µM and 21 µM, respectively. Compound 37 exhibited significant inhibition to the motility of the Caco2 cell line caused by epithelial—mesenchymal transition (EMT) [67]. The expression of cell motility-related genes in Caco2 cells was also examined through Human Cell Motility RT2 Profiler PCR Array. Ras-related C3 botulinum toxin substrate 2 (RAC2) and calpain 1 (CAPN1) have been proved to be the human cell motility-related genes [69–71]. The RT2 Profiler PCR Array results showed that 37 with the significant inhibition of the expression of RAC2 in nontoxic concentration 0.65 µM (1/20 of IC$_{50}$), and decreased the expression of CAPN1 by 1.3 µM (1/10 of IC$_{50}$) in Caco2 cells [67].
Secondary metabolites of *Nocardiopsis* sp. HT88, which was separated from the fresh stems of *Mallotus nudiflorus* L. (plant), was comprehensively studied for its crude extracts displayed significant antibacterial activities. Eight proline (or hydroxyproline, Hyp)-containing cyclic dipeptides: cyclo(L-Pro-L-Leu) (38), cyclo(Pro-Leu) (39), cyclo(*L*-trans-Hyp-L-Leu) (40), cyclo(D-trans-Hyp-D-Leu) (41), cyclo(D-Pro-L-Phe) (42), cyclo(L-Pro-L-Phe) (43), and cyclo(D-cis-Hyp-L-Phe) (44), and cyclo(L-trans-Hyp-L-Phe) (45) (Figure 8) were isolated from the broth culture of HT88 guided by antibacterial bioassay. Unfortunately, none of the purified DKPs (38–45) exhibited antibacterial activity against measured strains at 100 µg/disc [68].

Some of the peptides are hydrolyzed fragments of a precursor protein, called ribosomal posttranslational peptides (RiPPs) [72], and others are biosynthesized by non-ribosomal peptide synthetase (NRPS) assembly lines (Figure 9) [73,74].

There is no research on the biosynthesis of compounds 35 and 37. The cyclodipeptides’ (CDP) core structures are biosynthesized through NRPS or tRNA-dependent CDP synthase (CDPS) (Figure 10) pathways [75,76].

Compound 36 is belonging to the family of nocazine and is proposed to be synthesized through a CDPS-dependent pathway (Figure 11) [76]. Compounds 38–45 are modified CDP and are also deduced to be synthesized by the CDPS assembly line.
Figure 9. Biosynthesis of ribosomal and non-ribosomal peptides [73].

Figure 10. Biosynthesis of CDP through CDPS pathway [76].
5. Terphenyls

Chemical investigation of the actinobacterium strain *Nocardiopsis* sp. OUCMDZ-4936, purified from a sample gathered from Dongzhaigang Mangrove Reserve, Hainan Province, China, led to the isolation of three new *p*-terphenyl derivatives, nocarterphenyls A−C (46−48), together with three known analogs (49−51) (Figure 12) [77]. Compound 46 exhibited significant cytotoxicity against the HL60 and HCC1954 cancer cell lines, with IC_{50} values of 0.38 ± 0.01 and 0.10 ± 0.01 μM, respectively. Compounds 49 and 51 showed potent cytotoxic activities against K562 and A549 cancer cell lines with IC_{50} values ranging from 0.10 to 0.77 μM. Compound 51 also exhibited cytotoxicity against MV4-11 and MDA-MB-468 cancer cell lines, with IC_{50} values of 0.77 ± 0.02 and 0.67 ± 0.01 μM, respectively [77].

Five new *p*-terphenyl derivatives—called nocarterphenyls D−H (52−56) (Figure 12)—were gained and identified from the broth culture of the actinobacterium *Nocardiopsis* sp. HDN154086, separated from a marine sediment sample gathered from the South China Sea. It is the first time to find a 2,2′-bithiazole scaffold in natural products. *p*-Terphenylquinones 53 and 54 contain the unusual substitutions of thioether-linked fatty acid methyl ester. Compounds 52 and 53 demonstrated potent activities against seven kinds of bacteria—*E. coli*, *Proteus* sp., *M. phlei*, *V. parahemolyticus*, *B. subtilis*, *B. cereus*, and MRSA—with MIC values of 1.5−12 μM. Notably, compound 53 displayed significant antibacterial activity against MRSA, exceeding the positive control ciprofloxacin [78].
6. Others

Three known compounds, tryptophan (57), kynurenic acid (58), and 4-amino-3-methoxy benzoic acid (59) (Figure 13), were isolated from the actinobacterium Nocardiopsis sp. UR67, which was derived from the marine sponge Callyspongia sp. gained at a depth of 10 m from the Red Sea [64].

One new natural product phenolic acid derivative, 4-amino-6-methylsalicylic acid (60), along with two known compounds, 5-methylresorcinol (61) and linoleic acid (62), were isolated from the Nocardiopsis sp. AS23C strain, which was purified from the marine alga Sargassum arnaudianum derived from the Red Sea at the Hurghada coast, Egypt (Figure 13). The crude extracts of the strain AS23C displayed antibacterial activities against Gram-positive B. subtilis ATCC6051, S. viridochromogenes Tü 57, and S. aureus. Neither of the compounds 60 and 61 displayed cytotoxicity against KB-3-1 (human cervix carcinoma) cell line [79].
A rare actinomycete Nocardiopsis sp. SCA21, deriving from a marine sediment sample gathered from Havelock Island, Andaman, and the Nicobar Islands, India, exhibited the potential ability to produce bioactive secondary metabolites. Chemical investigation of the broth culture of the strain resulted in the purification of two known bioactive compounds—a bromophenol derivative, 4-bromophenol (63), and a phthalate ester, Bis (2-ethylhexyl) phthalate (64) (Figure 13). Compounds 63 and 64 displayed notable enzyme-inhibitory activities against α-glucosidase. However, there was no inhibited activity against α-amylase of compound 64. Both compounds 63 and 64 demonstrated potent free radical scavenging activities against DPPH and ABTS radicals. Additionally, 63 and 64 also revealed broad-spectrum inhibitory activities against MRSA ATCC-46071, MRSA ATCC NR-46171, S. aureus ATCC 12600, B. subtilis ATCC 6633, and Klebsiella pneumonia ATCC 13883 [80].

A novel sterol (65) with an unidentified substitution was isolated from marine actinomycete N. alba MCCB 110. Compound 65 was found to display antibacterial activity against the aquaculture pathogen V. harveyi, and did not exhibit toxicities to the VERO cell line and shrimp hemocytes, up to 1000 ppm [81].

7. Conclusions

From March 2018 to 2021, a total of 63 natural products have been isolated from the genus Nocardiopsis, and 67% of them are first-discovered compounds. These findings sufficiently demonstrate that actinomycetes Nocardiopsis have great potential to produce compounds with novel structures. The structures of the isolated compounds with diverse skeletons are mainly concentrated on the classes of polyketides, peptides, terphenyls, and alkaloids (Table 1 and Figure 14).

Table 1. Compounds isolated from Nocardiopsis during March 2018–2021.

| Types      | Comps. | Sources | Distribution | Bioactivities      | Years | Refs |
|------------|--------|---------|--------------|--------------------|-------|------|
| Polyketides| 1–3    | Sponge Thonella sp. derived Nocardiopsis sp. HB-J378 (GenBank No. MH79065) | Xinjiang, China | Antibacterial activity | 2018 | [48] |
| 4, 5       | Saltpan-derived Nocardiopsis sp. CG3 (GenBank No. MG972881) | Kenadsa, Algeria | Cytotoxicity | 2019 | [51] |
| 6–8        | Saltpan-derived Nocardiopsis sp. CG3 (GenBank No. MG972881) | Kenadsa, Algeria | Cytotoxicity | 2019 | [51] |
| 9–12, 14, 15, 17 | Desert soil-derived Nocardiopsis spp. HDN154-146 (Genbank no. KY794927) and HDN154-168 (Genbank No. MF952649) | Xinjiang, China | Antibacterial activity | 2019 | [52] |
| 13, 16     | Desert soil-derived Nocardiopsis spp. HDN154-146 (Genbank no. KY794927) and HDN154-168 (Genbank No. MF952649) | Xinjiang, China | Cytoprotective activity | 2019 | [52] |
| 18, 19     | Deep-sea water-derived N. dassonvillei subsp. albrirubida HDN 17-237 (Genbank No. MN416280) | Mariana Trench | Antibacterial activity | 2020 | [55] |
| 20, 21     | Marine animal-derived N. aegyptia HDN19-252 (GenBank No. MN822699) | Antarctic | Antibacterial activity | 2021 | [56] |
| 22, 23     | Marine animal derived strain N. aegyptia HDN19-252 (GenBank No. MN822699) | Antarctic | Antibacterial activity | 2021 | [56] |
Table 1. Cont.

| Types       | Comps. | Sources                     | Distribution       | Bioactivities                              | Years | Refs    |
|-------------|--------|-----------------------------|--------------------|--------------------------------------------|-------|---------|
| Alkaloids   | 24     | Marine-derived Nocardiopsis sp. CNY-503 |                    |                                            | 2018  | [58]    |
|             |        | Marine sediment-derived N. flavescens NA01583 (GenBank No. MT371575) |                    |                                            | 2020  | [61]    |
|             | 27     | Marine sediment-derived N. flavescens NA01583 (GenBank No. MT371575) |                    | Cytotoxicity                               | 2020  | [61]    |
|             | 28, 29 | Marine sediment-derived Nocardiopsis sp. SCA30 (GenBank No. MT573349) | Hainan China      | Antibacterial and anticancer activities    | 2021  | [22]    |
|             | 30     | Sponge Petrosia sp.-derived N. dassonvilleti SCSIO 40065 (GenBank No. MW492395) | Havelock Island   | Antibacterial and cytotoxic activities     | 2021  | [62]    |
|             | 31, 32 | Marine sediment-derived N. dassonvilleti JS106 (GenBank No. MN416229) | South China Sea   |                                            | 2021  | [63]    |
|             | 33, 34 | Marine sediment-derived Nocardiopsis sp. HDN154086 (GenBank No. MK129184) | South China Sea   | Antibacterial activity                     | 2021  | [78]    |
|             | 35     | Sponge Callyspongia sp.-derived Nocardiopsis sp. UR67 | Red Sea            | Cytotoxicity                               | 2018  | [64]    |
|             | 36     | Cotton field-derived Nocardiopsis sp. TRM20105 | Tarim Basin       | Antifungal activity                        | 2019  | [66]    |
|             | 37     | Shore sediment-derived Nocardiopsis sp. CNT-189 (GenBank No. KY111725.1) | Bahamas            | Cytotoxicity and colorectal cancer motility inhibitor | 2020  | [67]    |
|             | 38—45  | Stems of Mallotus nudiflorus L-derived Nocardiopsis sp. HT88 (Genbank No. MH817156) |                    |                                            | 2020  | [68]    |
| Terphenyls  | 46, 49—51 | Mangrove-derived Nocardiopsis sp. OUCMDZ-4936 (Genbank No. MK129184) | Hainan China      | Cytotoxicity                               | 2019  | [77]    |
|             | 47, 48 | Mangrove-derived Nocardiopsis sp. OUCMDZ-4936 (Genbank No. MK129184) | Hainan China      |                                            | 2019  | [77]    |
|             | 52, 53 | Marine sediment-derived Nocardiopsis sp. HDN154086 (GenBank No. MK129184) | South China Sea   | Antibacterial activity                     | 2021  | [78]    |
|             | 54—56  | Marine sediment-derived Nocardiopsis sp. HDN154086 (GenBank No. MK129184) | South China Sea   |                                            | 2021  | [78]    |
| Others      | 57—59  | Sponge Callyspongia sp.-derived Nocardiopsis sp. UR67 | Red Sea            |                                            | 2018  | [64]    |
|             | 60—62  | Alga Sargassum arnaudianum-derived Nocardiopsis sp. AS23C (GenBank No. MH144210) | Red Sea            |                                            | 2019  | [79]    |
|             | 63, 64 | Marine sediment-derived Nocardiopsis sp. SCA21 (GenBank No. MH105056) | Havelock Island   | Enzyme inhibitory, antibacterial, and free radical scavenging activities | 2019  | [80]    |
|             | 65     | Marine-derived N. alba MCCB110 (GenBank No. EU008081) |                    | Antibacterial activity                     | 2021  | [81]    |
The sources of the genus *Nocardiopsis* are distributed throughout diverse ecological systems, including desert, marine, mangrove, and salt pan areas (Figure 15). More than two out of three natural products were isolated from marine-derived *Nocardiopsis*, demonstrating that the ocean is a vast treasure house with abundant microbial sources to produce various novel natural products. From March 2018 to 2021, the percentage of the marine-derived compounds increased by 10%, compared with the period 2015–February 2018 [5], which further demonstrates that more and more attention has been concentrated on the development of the marine resources. Among the marine-derived natural products, the sources of *Nocardiopsis* strains are mainly collected from marine sediment and sponges (Figure 15).

The genus *Nocardiopsis* has the potential ability to produce a great diversity of bioactive secondary metabolites, including antibacterial, cytotoxic, cytoprotective, enzyme inhibitory, free radical scavenging, antiquorum sensing, colorectal cancer motility inhibitory, and antifungal compounds (Figure 16). Almost 50% of the *Nocardiopsis*-derived natural products have been discovered to exhibit various bioactivities. The activities of the bioactive compounds are mainly focused on the categories of antibacterial and cytotoxic activities (Figure 16), which serves as a reminder that there is huge potential for new antibiotics and anticancer compounds to be developed from *Nocardiopsis*. 

![Figure 14. Structural types of compounds isolated from Nocardiopsis from March 2018 to 2021.](image1)

![Figure 15. Sources of natural products from Nocardiopsis from March 2018 to 2021.](image2)
Figure 16. Bioactivities of natural products from Nocardiopsis discovered from March 2018 to 2021.

There were 13 antibacterial natural products isolated from Nocardiopsis in the period March 2018 to 2021 (Table 2). Among them, compounds 2, 30, and 53 exhibit strong antibacterial activity against MRSA, and compounds 20 and 21 display significant antibacterial activity against MRCNS (Table 2). These five compounds might be developed into new antibiotics to respond to the challenge of increasing antibacterial resistance. Compound 52 shows significant antibacterial activities against a series of strains, which has the potential to be exploited into novel antibiotics with a broad spectrum of antibacterial activity (Table 2). Compound 65 with antibacterial activity displays no toxic against VERO cell line and shrimp hemocytes up to 1000 ppm, could be developed as an environmentally friendly antibiotic (Table 2). All of the isolated antibacterial secondary metabolites provide the structural basis for novel antibiotic research.

There were 13 cytotoxic natural products isolated from Nocardiopsis in the period March 2018 to 2021 (Table 3). Compound 27 shows extremely significant and broad-spectrum cytotoxicity against a series of cell lines with the IC₅₀ values at the nM level, and compounds 46 and 49–51 display potent and broad-spectrum cytotoxicity (Table 3). All four compounds have the potential to be developed as new anticancer drugs. Compounds 8, 31, 32, 35, and 37 with moderate cytotoxicity provide structural inspiration for the research and development of new anticancer drugs (Table 3).

Table 2. Antibacterial activities of compounds isolated from Nocardiopsis from March 2018 to 2021.

| Strains   | Comps. | Values (MIC) | Pros                                      | Cons                                      |
|-----------|--------|--------------|-------------------------------------------|-------------------------------------------|
| MRSA      | 1, 3   | 12.5 µg/mL   | Specific inhibition of MRSA               | Moderate activity [48]                    |
|           | 2      | 3.12 µg/mL   | Strong activity; Specific inhibition of MRSA | [48]                                      |
| MRCNS     |        | 6.2/6.2      | Broad-spectrum antibacterial activity; Strong activity against MRCNS compared with positive control | Moderate activity against B. subtilis and Proteus sp. compared with positive control [56] |
| B. subtilis|        | 6.2/6.2      |                                           |                                           |
| Proteus sp.|        | 12.5/6.2     |                                           |                                           |
| B. cereus | 20/21 (µM) | 6.2/6.2      |                                           |                                           |
| E. coli   |        | 6.2/6.2      |                                           |                                           |
| M. Phlei  |        | 6.2/3.1      |                                           |                                           |
| MRSA ATCC NR-46071 | 30 (µg/mL) | 15.6         | Strong activity                            | [22]                                      |
| MRSA ATCC NR-46171 |        | 7.8          |                                           |                                           |
**Table 2.** Cont.

| Strains           | Comps. | Values (MIC) | Pros                                      | Cons                     |
|-------------------|--------|--------------|-------------------------------------------|--------------------------|
| B. subtilis 1064  |        | 8/16         | Broad-spectrum antibacterial activity     | Weak activity [62]       |
| M. Luteus SCSIO ML01 |        | 16/32        |                                           |                          |
| S. aureus ATCC 29213 | 31/32 (µg/mL) | 64/64 |                                            |                          |
| MRSA shhsA1        | 32/32  |              |                                           |                          |
| E. faecalis ATCC 29212 |        | 32/-         |                                           |                          |
| V. alginolyticus 13214 |        | 32/64        |                                           |                          |
| Proteus sp.        |        | 3.1/12       | 52 showed strong and broad-spectrum activity, and 53 displayed strong activity of MRSA |                          |
| B. cereus          |        | 1.5/-        | 52 showed strong and broad-spectrum activity, and 53 displayed strong activity of MRSA |                          |
| M. phlei           |        | 6.2/-        |                                           |                          |
| B. subtilis        |        | 3.1/12       |                                           |                          |
| MRSA               |        | -/-6.2       |                                           |                          |
| V. parahemolyticus |        | 6.2/-        |                                           |                          |
| E. coli            |        | 3.1/-        |                                           |                          |
| K. pneumoniae ATCC 13883 |        | 125/250      |                                           |                          |
| Listeria cytogen ATCC 13932 |        | 62.5/-       | Broad-spectrum antibacterial activity     | Weak activity [80]       |
| S. aureus ATCC 12600 |        | 62.5/125     |                                           |                          |
| B. subtilis ATCC 6633 |        | 7.81/7.81    |                                           |                          |
| MRSA ATCC NR-46171 |        | 15.62/7.81   |                                           |                          |
| MRSA ATCC NR-46071 |        | 125/15.62    |                                           |                          |
| V. harveyi MCCB 111 |        | 20 mm (zone of inhibition) | Not toxic against VERO cell line and shrimp hemocytes up to 1000 ppm |                          |

**Table 3.** Cytotoxicity and other activities of compounds isolated from Nocardiopsis from March 2018 to 2021.

| Bioactivities   | Cells/Stains/Enzyme | Comps. | Values | Pros                                      | Cons                     |
|-----------------|---------------------|--------|--------|-------------------------------------------|--------------------------|
| Cytotoxicity (IC$_{50}$) | Hela cells KB3.1 | 6/7/8 (µM) | 6.8/5.4/2.4 | Compound 8 with broad-spectrum cytotoxicity | Moderate activity [51] |
|                 | PC-3                |        | 6.3/5.0/2.1 |                                           |                          |
|                 | A549                |        | -/-6.5   |                                           |                          |
|                 | SKOV-3              |        | -/-10.0/5.5 |                                           |                          |
|                 | SH-SY5Y             | 283.6  |          |                                           |                          |
|                 | Sum1315             | 121.3  |          |                                           |                          |
|                 | HT29                | 81.3   |          |                                           |                          |
|                 | SW620               | 90.5   |          |                                           |                          |
|                 | HCT116              | 31.4   |          |                                           |                          |
|                 | HeLa                | 100.1  |          |                                           |                          |
|                 | SW872               | 92.3   |          | Extremely potent and broad-spectrum cytotoxicity |                          |
|                 | HCC78               | 41.5   |          |                                           |                          |
| Bioactivities | Cells/Stains/Enzyme | Compounds | Values | Pros | Cons |
|---------------|--------------------|-----------|--------|------|------|
| Cytotoxicity (IC$_{50}$) | | | | | |
| | SF-268 | 30/32 (µM) | 17.0/11.9 | Broad-spectrum cytotoxicity | IC$_{50}$ untested [22] |
| | MCF-7 | 25.7/20.7 | Broad-spectrum cytotoxicity | Moderate activity |
| | HepG2 | 31.2/12.0 | | |
| | A549 | 34.4/13.5 | | |
| | MM. 1S | 8 | Broad-spectrum cytotoxicity | Moderate activity |
| | HeLa | 11 | | |
| | CT26 | 12 | | |
| | AGS | 13 | | |
| | Caco2 | 18 | Broad-spectrum cytotoxicity | Moderate activity |
| | HCT116 | 21 | | |
| | L-02 | 17 | | |
| | A549 | 5.1 | | |
| | K562 | 0.77 | | |
| | MCF-7 | 6.0 | | |
| | P6C | 9.4 | | |
| | N87 | -/1.0/- | Strong and broad-spectrum cytotoxicity | [77] |
| | A673 | -/0.76/8.9 | | |
| | MV4-11 | 4.0/0.16/0.77 | | |
| | K562 | 9.0/4.8/8.9 | | |
| | A549 | 7.8/0.48/9.7 | | |
| | BT474 | 6.0/3.6/- | | |
| | H1229 | -/0.72/- | | |
| | HUCCCT1 | -/0.20/- | | |
| | B16F10 | -/0.76/- | | |
| | MDA-MB-468 | 2.8/1.1/0.67 | | |
| | H1975 | -/3.1/4.4 | | |
| | HL60 | 0.38/0.17/5.0 | | |
| | A431 | 4.6/-/- | | |
| | U251 | -/4.7/- | | |
| | HCC1954 | 0.10/0.48/2.0 | | |
| | MCF-7 | 18/-/17 | | |
| | MKN-45 | -/0.49/12 | | |
| | DU-145 | -/0.52/1.0 | | |
| | SPC-A1 | -/2.0/9.8 | | |
| | HCT116 | -/1.9/- | | |
| | 143B | 5.5/5.0/7.7 | | |
| | H2228 | 1.7/0.94/5.0 | | |
| | MDA-MB-231 | -/2.0/2.0 | | |
Eight secondary metabolites isolated from *Nocardiopsis* have various bioactivities, including cytoprotective, antiquorum sensing, colorectal cancer motility and enzyme inhibitory, and free radical scavenging activities (Table 3).

Although the *Nocardiopsis*-derived natural products exhibit excellent diverse bioactivities, further research on their bioactive mechanisms is deficient. Only three compounds, 13, 16, and 37, have been studied for their active mechanisms between March 2018 and 2021. To the best of our knowledge, all the activity tests were evaluated in vitro, and bioactive evaluations in vivo are also lacking between March 2018 and 2021. In terms of the current situation, it is still a long way from the drugs being approved for clinical use.

In this review, we summarized the secondary metabolites isolated from *Nocardiopsis* in the period between March 2018 and 2021. The literature survey comprehensively indicates that actinomycetes *Nocardiopsis* have great potential as producers to generate abundant and diverse novel bioactive secondary metabolites. Some potent antibacterial and cytotoxic compounds isolated from *Nocardiopsis* have the potential to be developed into new drugs. Additionally, all the natural products isolated from *Nocardiopsis* provide a structural foundation for drug design.

### Author Contributions
T.S. collected the literature regarding natural products isolated from *Nocardiopsis*, and wrote the paper; Y.-F.W. and H.W. revised the manuscript; B.W. organized and guided the writing of the manuscript. All authors have read and agreed to the published version of the manuscript.

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### Conflicts of Interest
The authors declare no conflict of interest.

### References
1. Jose, P.A.; Maharshi, A.; Jha, B. Actinobacteria in natural products research: Progress and prospects. *Microbiol. Res.* 2021, 246, 126708. [CrossRef] [PubMed]
2. Barka, E.A.; Vatsa, P.; Sanchez, L.; Cioeau-Vallant, N.; Jacquard, C.; Clement, C.; Meier-Kolthoff, J.P.; Klenk, H.-P.; Ouhdouch, Y.; van Wezel, G.P. Taxonomy, physiology, and natural products of actinobacteria. *Microbiol. Mol. Biol. Rev.* 2016, 80, 1–43. [CrossRef]
3. Demain, A.L.; Sanchez, S. Microbial drug discovery: 80 years of progress. *J. Antibi.* 2009, 62, 5–16. [CrossRef]
4. Mahajan, G.B.; Balachandran, L. Antibacterial agents from actinomycetes—A review. *Front. Biosci. Elite Ed.* 2012, E4, 240–253. [CrossRef]
5. Ibrahim, A.H.; Desoukey, S.Y.; Fouad, M.A.; Abdelmohsen, U.R.; Kamel, M.S.; Gulder, T.A.M. Natural product potential of the genus *Nocardiopsis*. *Mar. Drugs* 2018, 16, 147. [CrossRef] [PubMed]
6. Li, J.W.H.; Vederas, J.C. Drug discovery and natural products: End of an era or an endless frontier? *Science* **2009**, *325*, 161–165. [CrossRef] [PubMed]

7. Manivasagan, P.; Kang, K.-H.; Sivakumar, K.; Li-Chan, E.C.Y.; Oh, H.-M.; Kim, S.-K. Marine actinobacteria: An important source of bioactive natural products. *Environ. Toxicol. Pharmacol.* **2014**, *38*, 172–188. [CrossRef] [PubMed]

8. Manivasagan, P.; Venkatesan, J.; Sivakumar, K.; Kim, S.-K. Pharmacologically active secondary metabolites of marine actinobacteria. *Microbiol. Res.* **2014**, *169*, 262–278. [CrossRef]

9. AbdElGawad, H.; Zinta, G.; Abuelsoud, W.; Hassan, Y.M.; Alkhaliﬁah, D.H.M.; Hozeen, W.N.; Zrieq, R.; Beemster, G.T.; Schoenaers, S. An actinomycete strain of *Nocardiopsis lucentensis* reduces arsenic toxicity in barley and maize. *J. Hazard. Mater.* **2021**, *417*, 126055. [CrossRef] [PubMed]

10. Adenan, N.H.; Lim, Y.Y.; Ting, A.S.Y. *Nocardiopsis* sp. for the removal of triphenylmethane dyes: Decolorization and optimization studies. *Water Air Soil Pollut.* **2021**, *232*, 414. [CrossRef]

11. Patel, G.B.; Rakholiya, P.; Shindhal, T.; Varjani, S.; Tabhani, N.; Shah, K.R. Lipolytic *Nocardiopsis* for reduction of pollution load in textile industry effluent and SWISS model for structural study of lipase. *Bioreasour. Technol.* **2021**, *341*, 125673. [CrossRef] [PubMed]

12. Bennur, T.; Ravi Kumar, A.; Zinjarde, S.S.; Javdekar, V. *Nocardiopsis* species: A potential source of bioactive compounds. *J. Appl. Microbiol.* **2016**, *120*, 1–16. [CrossRef] [PubMed]

13. Chen, J.; Xu, L.; Zhou, Y.; Han, B. Natural products from actinomycetes associated with marine organisms. *Mar. Drugs* **2021**, *19*, 629. [CrossRef] [PubMed]

14. Kumar, S.; Solanki, D.S.; Parthar, K.; Tak, A.; Gehlot, P.; Pathak, R.; Singh, S.K. Actinomycetes isolates of arid zone of Indian Thar desert and efﬁcacy of their bioactive compounds against human pathogenic bacteria. *Biol. Futur.* **2021**, *72*, 431–440. [CrossRef]

15. Pinto-Almeida, A.; Bauermeister, A.; Luppino, L.; Grilo, I.R.; Oliveira, J.; Sousa, J.R.; Petras, D.; Rodrigues, C.F.; Prieto-Davo, A.; Tasdemir, D.; et al. The diversity, metabolomics proﬁling, and the pharmacological potential of actinomycetes isolated from the Estremadura Spur Pockmarks (Portugal). *Mar. Drugs* **2022**, *20*, 21. [CrossRef]

16. Chen, L.; Wang, Z.; Du, S.; Wang, G. Antimicrobial activity and functional genes of actinomycetes from coastal wetland. *Curr. Microbiol.* **2021**, *78*, 3058–3067. [CrossRef]

17. Tatar, D. Isolation, phylogenetic analysis and antimicrobial activity of halophilic actinomycetes from different saline environments located near Corum province. *Biologia* **2021**, *76*, 773–780. [CrossRef]

18. Li, H.-W.; Zhi, X.-Y.; Yao, J.-C.; Zhou, Y.; Tang, S.-K.; Klenk, H.-P.; Zhao, J.; Li, W.-J. Comparative genomic analysis of the genus *Nocardiopsis* provides new insights into its genetic mechanisms of environmental adaptability. *PLoS ONE* **2013**, *8*, e61528.

19. Bennur, T.; Kumar, A.R.; Zinjarde, S.; Javdekar, V. *Nocardiopsis* species as potential sources of diverse and novel extracellular enzymes. *Appl. Microbiol. Biotechnol.* **2014**, *98*, 9173–9185. [CrossRef] [PubMed]

20. Bennur, T.; Kumar, A.R.; Zinjarde, S.; Javdekar, V. *Nocardiopsis* species: Incidence, ecological roles and adaptations. *Microbiol. Res.* **2015**, *174*, 33–47. [CrossRef] [PubMed]

21. Shady, N.H.; Tawﬁke, A.F.; Yahia, R.; Fouad, M.A.; Brachmann, A.O.; Piel, J.; Abdelmohsen, U.R.; Kamel, M.S. Cytotoxic activity of actinomycetes *Nocardia* sp. and *Nocardiopsis* sp. associated with marine sponge *Amphimedon* sp. *Nat. Prod. Res.* **2021**, *1–6*. [CrossRef] [PubMed]

22. Siddharth, S.; Aswathanaranay, J.B.; Kuruburu, M.G.; Madhunapantula, S.R.V.; Vittal, R.R. Diketopiperazine derivative from marine actinomycetes *Nocardiopsis* sp. SCA30 with antimicrobial activity against MRSA. *Arch. Microbiol.* **2021**, *203*, 6173–6181. [CrossRef] [PubMed]

23. Trivedi, N.; Thumar, J. Chemical proﬁling of antimicrobial metabolites from halophilic actinomycete *Nocardiopsis* sp. Al-H10-1 (KF384482) isolated from Alang, Gulf of Khammad, India. *bioRxiv* 2021. [CrossRef]

24. Goel, N.; Fatima, S.W.; Kumar, S.; Sinha, R.; Khare, S.K. Antimicrobial resistance in bioﬁlms: Exploring marine actinobacteria as a potential source of antibiotics and bioﬁlm inhibitors. *Biotechnol. Rep.* **2021**, *30*, e00613. [CrossRef] [PubMed]

25. Choi, G.; Kim, G.J.; Choi, H.; Choi, I.-W.; Lee, D.-S. Anti-inﬂammatory and anti-ﬁbrotic activities of *Nocardiopsis* sp. 13G027 in lipopolysaccharides-induced RAW 264.7 macrophages and transforming growth factor-beta-1-stimulated nasal polyp-derived ﬁbroblasts. *Microbiol. Biotechnol. Lett.* **2021**, *49*, 543–551. [CrossRef]

26. Sarmiento-Vizcaíno, A.; Martin, J.; Reyes, F.; García, L.A.; Blanco, G. Bioactive natural products in actinobacteria isolated in rainwater from storm clouds transported by western winds in Spain. *Front. Microbiol.* **2021**, *12*, 773095. [CrossRef]

27. Gameleldin, N.M.; Bakeer, W.; El-Gendy, A.O.; Sayed, A.M.; Shamikh, Y.I.; Hassan, H.M.; Horn, H.; Abdelmohsen, U.R.; Hozeen, W.N. Exploration of chemical diversity and antityrosinase activity of some Red Sea-derived actinomycetes using the OSMAC approach supported by LC-MS-based metabo- lomics and molecular modelling. *Antibiotics* **2020**, *9*, 629. [CrossRef]

28. Widad, J.; Damayanti, E.; Alhakim, M.R.; Yuwono, T.; Mustofa, M. Two strains of airborne *Nocardiopsis alba* producing different volatile organic compounds (VOCs) as biofungicide for *Ganoderma boninense*. *FEBS Microbiol. Lett.* **2021**, *368*, fnb138. [CrossRef]

29. Wang, Z.; Fu, P.; Liu, P.; Wang, P.; Hou, J.; Li, W.; Zhu, W. New pyran-2-ones from alkalophilic actinomycete, *Nocardiopsis alkaliphila* sp. nov. *YIM-80379*. *Chem. Biodivers.* **2013**, *10*, 281–287. [CrossRef]

30. Lu, C.; Li, Y.; Wang, H.; Wang, B.; Shen, Y. A new phenoxazine derivative isolated from marine sediment actinomycetes, *Nocardiopsis* sp. 236. *Drug Discov. Ther.* **2013**, *7*, 101–104. [CrossRef]

31. Tian, S.; Yang, Y.; Liu, K.; Xiong, Z.; Xu, L.; Zhao, L. Antimicrobial metabolites from a novel halophilic actinomycete *Nocardiopsis terrae* YIM 90022. *Nat. Prod. Res.* **2014**, *28*, 344–346. [CrossRef] [PubMed]
32. Yamashita, T.; Imoto, M.; Isshiki, K.; Sawaw, T.; Naganawawa, H.; Kurasawa, S.; Zhu, B.; Umezawa, K. Isolation of a new indole alkaloid, pendoxyacin, from Nocardiosis. J. Nat. Prod. 1988, 51, 1184–1187. [CrossRef]

33. Lin, Z.; Torres, J.P.; Ammon, M.A.; Marett, L.; Teichert, R.W.; Reilly, C.A.; Kwan, J.C.; Hughen, R.W.; Flores, M.; Tianero, M.D.; et al. A bacterial source for mollusk pyrone polyketides. Chem. Biol. 2013, 20, 73–81. [CrossRef] [PubMed]

34. Gao, X.; Lu, Y.; Xing, Y.; Ma, Y.; Lu, J.; Bao, W.; Wang, Y.; Xi, T. A novel anticancer and antifungus phenazine derivative from a marine actinomycete BM-17. Microbiol. Res. 2012, 167, 616–622. [CrossRef]

35. Kase, H.; Iwashashi, K.; Matsuda, Y. K-252a, a potent inhibitor of protein kinase C from microbial origin. J. Antibiot. 1986, 39, 1059–1065. [CrossRef]

36. Raju, R.; Piggott, A.M.; Huang, X.-C.; Capon, R.J. Nocardioazines: A novel bridged diketopiperazine scaffold from a marine-derived bacterium inhibits P-glycoprotein. Org. Lett. 2011, 13, 2770–2773. [CrossRef]

37. Kim, M.C.; Kwon, O.-W.; Park, J.-S.; Kim, S.Y.; Kwon, H.C. Nocapyrones H–J, 3,6-disubstituted α-pyrones from the marine actinomycete Nocardiosis sp. KMF-3001. J. Chem. Sci. 2013, 61, 511–515. [CrossRef]

38. Wu, Z.; Xie, L.; Xia, G.; Zhang, J.; Nie, Y.; Hu, J.; Wang, S.; Zhang, R. A new tetrodotoxin-producing actinomycete, Nocardiosis dassonvelli, isolated from the ovaries of puffer fish Fugu rubripes. Toxicon 2005, 45, 851–859. [CrossRef]

39. Peltola, J.S.P.; Andersson, M.A.; Kämpfer, P.; Auling, G.; Kroppenstedt, R.M.; Busse, H.-J.; Salkinoja-Salonen, M.S.; Rainey, F.A. Isolation of toxicogenic Nocardiosis strains from indoor environments and description of two new Nocardiosis species, N. exhalans sp. nov. and N. umidisola nov. sp. Appl. Environ. Microbiol. 2001, 67, 4293–4304. [CrossRef]

40. Kim, Y.; Ogura, H.; Akasaka, K.; Oikawa, T.; Matsuura, N.; Imada, C.; Yasuda, H.; Igarashi, Y. Nocapyrones: α- and γ-pyrones from a marine-derived Nocardiosis DSM 44012. Drugs 2014, 12, 4110–4125. [CrossRef]

41. Sun, M.-W.; Guo, Z.-X.; Lu, C.-H. Two new polyketides from Nocardiosis lucentensis DSM 44084. Nat. Prod. Res. 2016, 30, 1036–1041. [CrossRef] [PubMed]

42. Zhang, H.; Saurav, K.; Yu, Z.; Mandi, A.; Kurtan, T.; Li, J.; Tian, X.; Zhang, Q.; Zhang, W.; Zhang, C. α-Pyrones with diverse hydroxy substitutions from three marine-derived Nocardiosis strains. J. Nat. Prod. 2016, 79, 1610–1618. [CrossRef] [PubMed]

43. Kim, J.; Shin, D.; Kim, S.-H.; Park, W.; Shin, Y.; Kim, W.K.; Lee, S.K.; Oh, K.-B.; Shin, J.; Oh, D.-C. Borrelidins C–E: New antibacterial macrolides from a saltern-derived halophilic Nocardiosis sp. Mar. Drugs 2017, 15, 166. [CrossRef] [PubMed]

44. Zhang, X.; He, H.; Ma, R.; Ji, Z.; Wei, Q.; Dai, H.; Zhang, L.; Song, F. Madurastatin B3, a rare aziridine derivative from actinomycete Nocardiosis sp. LS150010 with potent anti-tuberculosis activity. J. Ind. Microbiol. Biotechnol. 2017, 44, 589–594. [CrossRef]

45. Eliwa, E.M.; Abdel-Razek, A.S.; Fresse, M.; Wibberg, D.; Halawa, A.H.; El-Agrody, A.M.; Bedair, A.H.; Kalinowski, M.; Sewald, N.; Shaaban, M. New bioactive compounds from the marine-derived actinomycete Nocardiosis lucentensis sp. ASMR2. Z. Naturforsch. B J. Chem. Sci. 2017, 72, 351–360. [CrossRef]

46. Sun, M.-W.; Zhang, X.-M.; Bi, H.-L.; Li, W.-J.; Lu, C.-H. Two new sesquiterpenoids produced by halophilic Nocardiosis chromatogenes YIM 90109. Nat. Prod. Res. 2017, 31, 77–83. [CrossRef] [PubMed]

47. Hamed, A.; Abdel-Razek, A.S.; Fresse, M.; Stammler, H.G.; El-Haddad, A.F.; Ibrahim, T.M.A.; Sewald, N.; Shaaban, M. Terretonin N: A new meroterpenoid from marine-derived Nocardiosis sp. J. Ind. Microbiol. Biotechnol. 2018, 82, 1081–1088. [CrossRef] [PubMed]

48. Xu, D.; Nepal, K.K.; Harmody, D.; McCarthy, P.J.; Wright, A.E.; Wang, G.; Chen, J.; Zhu, H. Nocardiosistins A–C: New angucyclines with anti-MRSA activity isolated from a marine sponge-derived Nocardiosis sp. HB-J378. Synth. Syst. Biotechnol. 2018, 3, 246–251. [CrossRef]

49. Loumbro, F.; Brana, A.F.; Salas, J.A.; Mendez, C. Genetic organization of the biosynthetic gene cluster for the antitumor angucycline oviewidocin in Streptomyces antibioticus ATCC 11891. ChemBioChem 2004, 5, 1181–1187. [CrossRef] [PubMed]

50. Kharel, M.K.; Pahari, P.; Shepherd, M.D.; Tibrewal, N.; Nybo, S.E.; Shaaban, K.A.; Rohr, J. Angucyclines: Biosynthesis, mode-of-action, new natural products, and synthesis. Nat. Prod. Rep. 2012, 29, 264–325. [CrossRef] [PubMed]

51. Messaoudi, O.; Sudarman, E.; Bendahou, M.; Jansen, R.; stadler, M.; Wink, J. Kenalactams A–E, polyene macrolides isolated from Nocardiosis CG3. J. Nat. Prod. 2019, 82, 1081–1088. [CrossRef]

52. Zhao, T.; Chang, Y.; Zhu, T.; Li, J.; Gu, Q.; Li, D.; Che, Q.; Zhang, G. α-Pyrones derivatives with cyto-protective activity from two Takla Makan desert soil derived actinomycete Nocardiosis strains recovered in seawater based medium. Nat. Prod. Res. 2019, 33, 2498–2506. [CrossRef] [PubMed]

53. Bolling, B.W.; Parkin, K.L. Limited contribution of isoflavones to hepatocellular phase II enzyme-inducing activity of soybean (Glycine max) extracts. Food Chem. 2009, 113, 1069–1075. [CrossRef]

54. Park, J.S.; Jung, J.S.; Jeong, Y.H.; Hyun, J.W.; Le, T.K.V.; Kim, D.H.; Choi, E.C.; Kim, H.S. Antioxidant mechanism of isoflavone metabolites in hydrogen peroxide-stimulated rat primary astrocytes: Critical role of hemoxigenase-1 and NQ01 expression. J. Neurochem. 2011, 119, 909–919. [CrossRef]

55. Wang, J.-X.; Sun, C.-X.; Shah, M.; Zhang, G.-J.; Gu, Q.-Q.; Zhu, T.-J.; Che, Q.; Li, D.-H. New metabolites from a Mariana Trench-derived actinomycete Nocardiosis sp. HDN 17-237. J. Asian Nat. Prod. Res. 2020, 22, 1031–1036. [CrossRef] [PubMed]

56. Zhou, L.; Chen, X.; Sun, C.; Chang, Y.; Huang, X.; Zhu, T.; Zhang, G.; Che, Q.; Li, D. Saliniquinones A–G–I and heraclemycin E, from the marine animal-derived Nocardiosis egyptia HDN19-252. Mar. Drugs 2021, 19, 575. [CrossRef] [PubMed]

57. Shin, J.; Yang, S.-H.; Du, Y.E.; Park, K.; Kim, D.; Shin, D.; Kim, J.; Kim, S.-H.; Kim, Y.K.; Shin, J. Borrelidin from saltern-derived halophilic Nocardiosis lucentensis sp. dissociates amyloid-β and tau fibrils. J. Alzheimer’s Dis. Rep. 2021, 5, 7–13. [CrossRef]
58. Castro-Falcon, G.; Millan-Aguinaga, N.; Roullier, C.; Jensen, P.R.; Hughes, C.C. Nitrosopyridine probe to detect polyketide natural products with conjugated alkenes: Discovery of novodaryamide and nocarditriene. ACS Chem. Biol. 2018, 13, 3097–3106. [CrossRef]

59. Kim, T.; Lee, S.-A.; Noh, T.; Choi, P.; Choi, S.-J.; Song, B.G.; Kim, Y.; Park, Y.-T.; Huh, G.; Kim, Y.-J.; et al. Synthesis, structure revision, and cytotoxicity of nocardbenzoxazole G. J. Nat. Prod. 2019, 82, 1325–1330. [CrossRef] [PubMed]

60. Sun, M.; Zhang, X.; Hao, H.; Li, W.; Lu, C. Nocardbenzoxazoles A–G, benzoxazoles produced by halophilic Nocardiopsis lucentensis DSM 44048. J. Nat. Prod. 2015, 78, 2123–2127. [CrossRef]

61. Yang, C.L.; Zhang, B.; Xue, W.W.; Li, W.; Xu, Z.F.; Shi, J.; Shen, Y.; Jiao, R.H.; Tan, R.X.; Ge, H.M. Discovery, biosynthesis, and heterologous production of loonamycin, a potent anticancer indolocarbazole alkaloid. Org. Lett. 2020, 22, 4665–4669. [CrossRef] [PubMed]

62. Zhang, X.; Chen, S.; Zhang, L.; Zhang, Q.; Zhang, W.; Chen, Y.; Zhang, H.; Zhang, H.; Zhang, C. Dassonnmycins A and B, polycyclic thioalkaloids from a marine sponge-derived Nocardiopsis dassonvillei SCSIO 40065. Org. Lett. 2021, 23, 2858–2862. [CrossRef]

63. Miao, L.; Qian, S.; Qi, S.; Jiang, W.; Dong, K. Culture medium optimization and active compounds investigation of an anti-quorum sensing marine actinobacterium Nocardiopsis dassonvillei JS106. Microbiology 2021, 90, 112–123. [CrossRef]

64. Ibrahim, A.H.; Attia, E.Z.; Desoukey, S.Y.; Fouad, M.A.; Abdelmohsen, U.R.; Hajjar, D.; Anany, M.A.; Wajant, H.; Kamel, M.S.; Gulder, T.A.M. New cytotoxic cyclic peptide from the marine sponge-associated Nocardiopsis sp. UR67. Mar. Drugs 2018, 16, 290. [CrossRef]

65. Muhajir, M.I.; Hardianto, A.; Al-Anshori, J.; Sumiarsa, D.; Mayanti, T.; Hidayat, A.T.; Supratman, U.; Maharani, R. Total synthesis of nocardiotide A by using a combination of solid-and solution-phase methods. ChemistrySelect 2021, 6, 12941–12946. [CrossRef]

66. Chen, H.; Wan, C.; Zhang, L. A new diketopiperazine isolated from a Nocardiosis strain TRM20105 guided by bioassay against Candida albicans. Nat. Prod. Res. 2019, 33, 3421–3425. [CrossRef] [PubMed]

67. Lee, J.; Gamage, C.D.B.; Kim, G.J.; Hillman, P.F.; Lee, C.; Lee, E.Y.; Choi, H.; Kim, H.; Nam, S.-J.; Fenical, W. Androsamide, a cyclic tetrapeptide from a marine Nocardiosis sp. suppresses motility of colorectal cancer cells. J. Nat. Prod. 2020, 83, 3166–3172. [CrossRef] [PubMed]

68. Xiang, W.-X.; Liu, Q.; Li, X.-M.; Lu, C.-H.; Shen, Y.-M. Four pairs of proline-containing cyclic dipeptides from Nocardiosis sp. HT88, an endophytic bacterium of Mallotus nudiflorus. L. Nat. Prod. Res. 2020, 34, 2219–2224. [CrossRef]

69. Storr, S.J.; Carragher, N.O.; Frame, M.C.; Parr, T.; Martin, S.G. The calpain system and cancer. Nat. Rev. Cancer 2011, 11, 364–374. [CrossRef]

70. Joshi, S.; Singh, A.R.; Zulcic, M.; Bao, L.; Messer, K.; Ideker, T.; Dutkowski, J.; Durden, D.L. Rac2 controls tumor growth, metastasis and M1-M2 macrophage differentiation in vivo. PLoS ONE 2014, 9, e95893. [CrossRef] [PubMed]

71. Wertheimer, E.; Gutierrez-Uzquiza, A.; Rosemblit, C.; Lopez-Haber, C.; Sosa, M.S.; Kazanian, M.G. Rac signaling in breast cancer: A tale of GEFs and GAPs. Cell. Signal. 2012, 24, 353–362. [CrossRef] [PubMed]

72. Arnison, P.G.; Bibb, M.J.; Bierbaum, G.; Bowers, A.A.; Bugni, T.S.; Bulaj, G.; Camarero, J.A.; Campopiano, D.J.; Challis, G.L.; Clardy, J. Ribosomally synthesized and post-translationally modified peptide natural products: Overview and recommendations for a universal nomenclature. Nat. Prod. Rep. 2013, 30, 108–160. [CrossRef] [PubMed]

73. Walsh, C.T.; O’Brien, R.V.; Khosla, C. Nonproteinogenic amino acid building blocks for nonribosomal peptide and hybrid polyketide scaffolds. Angew. Chem. Int. Ed. 2013, 52, 7098–7124. [CrossRef] [PubMed]

74. Walsh, C.T.; Tang, Y. Natural Product Biosynthesis; The Royal Society of Chemistry: London, UK, 2017.

75. Mishra, A.K.; Choi, J.; Choi, S.-J.; Baek, K.-H. Cyclodipeptides: An overview of their biosynthesis and biological activity. Molecules 2017, 22, 1796. [CrossRef] [PubMed]

76. Giessen, T.W.; Marahiel, M.A. The tRNA-dependent biosynthesis of modified cyclic dipeptides. Int. J. Mol. Sci. 2014, 15, 14610–14631. [CrossRef] [PubMed]

77. Wang, D.; Wang, Y.; Ouyang, Y.; Fu, P.; Zhu, W. Cytotoxic p-terphenyls from a marine-derived Nocardiosis species. J. Nat. Prod. 2019, 82, 3504–3508. [CrossRef] [PubMed]

78. Chang, Y.; Che, Q.; Xing, L.; Ma, C.; Han, Y.; Zhu, T.; Pfeifer, B.A.; Peng, J.; Zhang, G.; Li, D. Antibacterial p-terphenyl with a rare 2,2′-bithiazole substructure and related compounds isolated from the marine-derived actinomycete Nocardiosis sp. HDN154086. J. Nat. Prod. 2021, 84, 1226–1231. [CrossRef]

79. Ekiwa, E.M.; Abdal-Razeq, A.S.; Frese, M.; Halawa, A.H.; El-Agody, A.M.; Bedair, A.H.; Sewald, N.; Shaaban, M. New naturally occurring phenolic derivatives from marine Nocardiosis sp. AS23C: Structural elucidation and in silico computational studies. Vietnam J. Chem. 2019, 57, 164–174. [CrossRef]

80. Siddharth, S.; Rai, V.R. Isolation and characterization of bioactive compounds with antibacterial, antioxidant and enzyme inhibitory activities from marine-derived rare actinobacteria, Nocardiosis sp. SCA21. Microb. Pathog. 2019, 137, 103775. [CrossRef]

81. Sunish, K.S.; Sreedharan, P.; Daniel, S.; Biji, M.; Rosamma, P.; Sukumaran, V.; Mohandas, A.; Singh, I.S.B. A novel substituted derivative of sterol from marine actinomycetes Nocardiosis alba MCCB 110 antagonistic to the aquaculture pathogen Vibrio harveyi. Microb. Pathog. 2021, 157, 104967. [CrossRef]