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Review

The *Streptomyces* Genome and Its Exceptional Capacity for Antibiotics Production

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Abstract: If bacteria are ranked by the number of commercially available antibiotics produced, *Streptomyces* would be number one by an overwhelming margin—producing more approved drugs than all other bacterial genera combined. *Streptomyces* is a group of filamentous, Gram-positive, soil-dwelling bacteria. *Streptomyces* species possess large (7–12 Mb) genomes, significantly larger than those of most other bacteria. Many species also carry large linear plasmids. The hallmark of *Streptomyces* genomics is the presence of numerous secondary metabolite biosynthetic gene clusters (BGCs), one of the most critical reasons for *Streptomyces* species having an exceptional capacity for antibiotics production. Each cluster contains a co-localized set of genes responsible for the biosynthesis, tailoring, regulation, resistance, and transport of a specific secondary metabolite. Major BGC types include polyketide synthase (PKS) clusters, non-ribosomal peptide synthase (NRPS) clusters, hybrid PKS-NRPS clusters, ribosomally synthesized and post-translationally modified peptide clusters, and terpene and siderophore clusters; and the most important classes and prototype examples of antibiotics produced include aminoglycosides (e.g., streptomycin, neomycin, kanamycin, tobramycin), polyketides (e.g., erythromycin, tetracycline, rifampicin), non-ribosomal peptides (e.g., vancomycin, teicoplanin, daptomycin), chloramphenicol, and β-lactam (cephamycins, clavulanic acid, thienamycin, imipenem). Most antibiotic-producing *Streptomyces* species encode self-resistance genes within or near the BGC, ensuring that antibiotic production does not harm the producing organism. Advancement of technologies, such as next-generation sequencing, robust bioinformatics tools, and artificial intelligence-based methods, could reveal the hidden or silent BGCs and enable genome mining, activation of silent pathways and discovery of entirely new antibiotics in *Streptomyces* that traditional methods would miss.

Keywords: *Streptomyces*; genome; antibiotic

1. Introduction

Antibiotics are among the most important therapeutic agents in modern medicine, used to treat and prevent bacterial infections in humans, animals, and to a lesser extent, plants. Since the discovery of penicillin in the early twentieth century, a wide variety of antibiotics have been developed and commercialized [1]. Although antibiotics differ greatly in their chemical structures, mechanism of action, and spectra of activity, they can be broadly

classified according to their sources, which include natural biological sources (e.g., penicillin from *Penicillium chrysogenum*), semi-synthetic modification of natural compounds (e.g., doxycycline, synthetically derived from oxytetracycline, a naturally occurring tetracycline produced by *Streptomyces* species), and fully synthetic chemical processes (e.g., ciprofloxacin, through synthetic organism chemistry, often starting with 2,4-dichloro-5-fluorobenzoyl chloride or similar quinoline derivatives). The natural biological compounds are from either bacterial or fungal sources; and many of the earliest and most important antibiotics are derived from their soil-dwelling species [2]. These microorganisms naturally produce antimicrobial compounds to compete with other microbes in their environment [3–5].

One of the most significant bacterial genera in antibiotic production is *Streptomyces*, a group of filamentous, Gram-positive bacteria ("strepto" = twisted, "myces" = fungus). It was named as such because it grew in branching filaments like fungal hyphae. If bacteria are ranked by the number of commercially available antibiotics, *Streptomyces* would be number one by an overwhelming margin—producing more approved drugs than all other bacterial genera combined (Figure 1) [6]. These natural antibiotics are typically produced commercially through industrial fermentation, in which the bacteria are grown in large bioreactors under controlled conditions to maximize antibiotic yield. Among various reasons, one of the most critical is that *Streptomyces* species have an exceptional capacity for antibiotic production, owing to their large genomes and the high number of secondary metabolite biosynthetic gene clusters (BGCs) they encode [7–10]. In this article, we review the basic genomics of *Streptomyces*, with particular reference to the different types of BGCs for antibiotic production, as well as some prototype examples synthesized by these BGCs. Antibiotics produced by a *Streptomyces* species when it was discovered, but the bacterium was subsequently reclassified into another genus, are also included. For example, rifamycin B and vancomycin were originally discovered from *S. mediterranei* and *S. orientalis*, respectively, which were subsequently reclassified and renamed as *Amycolatopsis rifamycinica* and *Amycolatopsis orientalis*, respectively [11–15].

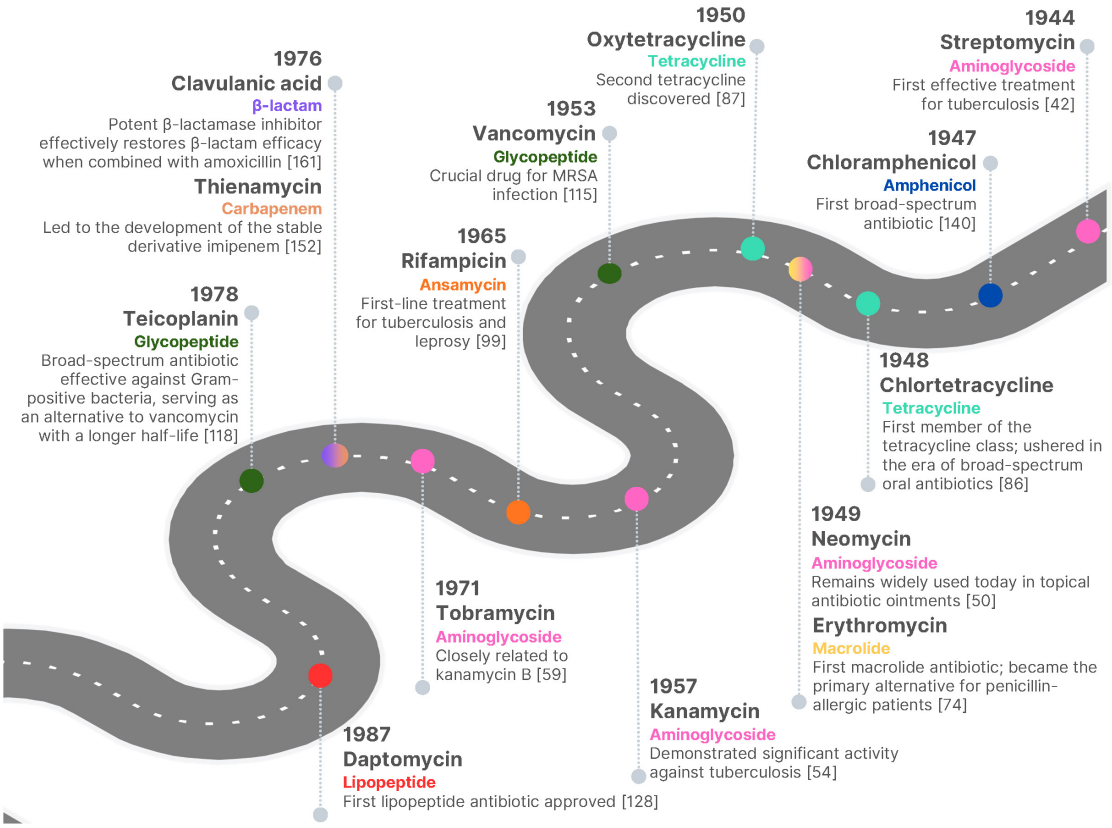

Figure 1. Clinically important antibiotics discovered from *Streptomyces* species during the "golden age" (1940s–1980s).

2. The *Streptomyces* Genome

Streptomyces species possess large bacterial genomes, typically ranging from 7 to 12 megabases, significantly larger than those of many other bacteria (e.g., *Escherichia coli* has a genome size of around 4.6 Mb) [7–9]. The G+C content is high, typically around 70–73%. Although this can impose metabolic costs, it may also facilitate the evolution of complex enzymatic systems such as polyketide synthases (PKSs) and non-ribosomal peptide

synthases (NRPSs), which require large, repetitive gene sequences that benefit from genome stability [16,17]. A distinctive feature of *Streptomyces* genomes is their linear chromosome, which is rare among bacteria [18]. This linear chromosome is capped by terminal inverted repeats and covalently bound terminal proteins that protect chromosome ends. In addition to the main chromosome, many species also carry large linear plasmids, which often encode secondary metabolite BGCs [19,20]. The chromosome itself is functionally compartmentalized into a central core region and variable arms at both ends [21]. The central core region is highly conserved across species and contains essential housekeeping genes, whereas the variable arms are enriched in secondary metabolism genes, mobile elements, and horizontally acquired DNA. This organization allows *Streptomyces* to maintain core cellular functions while rapidly evolving specialized metabolic traits.

The hallmark of *Streptomyces* genomics is the presence of numerous BGCs (Table 1). A single *Streptomyces* genome typically encodes 20–40 BGCs, and in some cases even more [7,22]. Each cluster contains a co-localized set of genes responsible for the biosynthesis, tailoring, regulation, resistance, and transport of a specific secondary metabolite. Major BGC types include PKS clusters, NRPS clusters, hybrid PKS-NRPS clusters, ribosomally synthesized and post-translationally modified peptide clusters, and terpene and siderophore clusters [23]. Interestingly, many of these clusters are silent or poorly expressed under standard laboratory conditions, suggesting that *Streptomyces* has far greater biosynthetic potential than is currently observed [24,25]. Most antibiotic-producing *Streptomyces* species encode self-resistance genes within or near the BGC [26]. These may include drug-modifying enzymes, target-modified variants, essential proteins, or efflux pumps. This tight genetic linkage ensures that antibiotic production does not harm the producing organism; while at the same time, they may also serve as a source of resistance if they are transferred to other bacteria [27]. This co-localization strongly supports the idea that antibiotics evolved primarily as ecological tools rather than as metabolic by-products [28].

Table 1. Examples of antibiotic biosynthetic pathways in *Streptomyces.*

Biosynthetic Pathway	Biosynthetic Mechanism	Example Antibiotic(s)	Producing *Streptomyces* Species (or Former *Streptomyces*)	Antibiotic Class and Mechanism of Action	References
Aminoglycoside	Sugar biosynthesis & linkage: Utilizes specialized glycosyltransferases, aminotransferases, and oxidoreductases to synthesize and link modified amino-sugars (aminocyclitols).	Streptomycin Neomycin Kanamycin Tobramycin	*S. griseus* *S. fradiae* *S. kanamyceticus* *S. tenebrarius*	Aminoglycosides: Broad-spectrum antibiotics that bind to the 30S ribosomal subunit and induce codon misreading.	[29–35]
Type I PKS	Modular assembly line: Giant multi-domain enzymes sequentially add and modify short-chain carboxylic acids (e.g., malonyl-CoA).	Erythromycin Rifampicin	*S. erythreus* * *S. mediterranei* *	Macrolides (Erythromycin): Bind to the 50S ribosomal subunit to inhibit protein synthesis. Ansamycins (Rifampicin): Inhibits bacterial DNA-dependent RNA polymerase.	[13,36–40]
Type II PKS	Iterative complex: A single set of discrete enzymes iteratively builds a highly reactive poly-beta-ketone chain, which is then folded and cyclized into rigid ring systems.	Tetracycline	*S. aureofaciens*	Tetracyclines: Broad-spectrum antibiotics that inhibit bacterial protein synthesis by binding to the 30S ribosomal subunit.	[41–45]
NRPS	Modular assembly line: Similar to Type I PKS, but links amino acids (including non-proteinogenic and D-amino acids) into highly modified peptide chains independently of ribosomes.	Vancomycin Daptomycin	*S. orientalis* * *S. roseosporus*	Glycopeptides (Vancomycin): Inhibit cell wall synthesis by binding to the D-ala-D-ala terminus. Cyclic lipopeptides (Daptomycin): Disrupt Gram-positive bacterial cell membranes.	[46–56]
Chloramphenicol	Shikimate pathway derivative: Synthesized from chorismate via a specialized non-ribosomal branch. Involves unique enzymes like arylamine N-acetyltransferases and halogenases to form its dichloroacetyl and nitro groups.	Chloramphenicol	*S. venezuelae*	Amphenicols: Broad-spectrum antibiotics that inhibit protein synthesis by binding to the peptidyl transferase center of the 50S ribosomal subunit.	[57–62]
β-lactams (NRPS-like)	Peptide condensation & cyclization: Non-ribosomal peptide synthetases (e.g., ACV synthetase) condense amino acids (like L-α-aminoadipic acid, L-cysteine, D-valine), followed by cyclization (e.g., by isopenicillin N synthase) to form the β-lactam ring.	Cephamycins Clavulanic acid Thienamycin	*S. clavuligerus* *S. clavuligerus* *S. cattleya*	β-lactams (Cephamycins, Thienamycin): Bactericidal agents that inhibit cell wall synthesis β-lactamase inhibitors (Clavulanic acid): Prevent bacterial degradation of β-lactams.	[63–72]

PKS: Polyketide synthase; NRPS: Non-ribosomal peptide synthase. * *S. erythreus* has been renamed as *Saccharopolyspora erythraea*; *S. mediterranei* has been renamed as *Amycolatopsis rifamycinica*; *S. orientalis* has been renamed as *Amycolatopsis orientalis*.

Antibiotic production in *Streptomyces* is tightly regulated and usually coupled to the developmental stage and nutrient availability. The key regulator layers include global regulators and cluster-situated regulators. Examples of global regulators include Bld genes, which control morphological differentiation [28]; AdpA, a pleiotropic transcription factor that regulates both developmental and secondary metabolism [73]; and the ppGpp-mediated stringent response, linking nutrient stress to secondary metabolite production [73,74]. As for cluster-situated regulators, most BGCs encode one or more pathway-specific regulators, often belonging to the LuxR, SARP or TetT families [75–77]. These regulators fine-tune the expression of individual clusters in response to environmental or cellular cues. The complexity of this regulatory architecture explains why many antibiotic gene clusters remain cryptic and why genetic or environmental manipulation can unlock new compounds [10,78]. Unlike most bacteria, *Streptomyces* exhibits a filamentous, multicellular lifestyle reminiscent of fungi. Its life cycle includes vegetative hyphal growth, aerial hyphae formation, and sporulation [79]. Antibiotic production is typically initiated during the transition from vegetative growth to aerial development [80,81]. Genomically, this coupling is enforced by shared regulatory circuits controlling both morphogenesis and secondary metabolism. This strategy likely evolved as a competitive response in the soil environments, where antibiotic production coincides with nutrient limitation and sporulation, helping eliminate competitors while spores disperse.

3. Aminoglycosides

Aminoglycosides are a class of polycationic natural products best known for inhibiting bacterial protein synthesis [82]. Aminoglycosides share a few architectural characteristics. First, the most clinically important aminoglycosides contain a central 2-deoxystreptamine ring [83]. This six-membered cyclitol ring carries multiple amino groups. Second, two or more amino-modified sugars are glycosidically linked to the central core. These sugars are also highly hydroxylated and often further modified [29]. Third, the highly polar, polycationic nature enables binding to negatively charged ribosomal RNA in the bacterial 30S subunit [30].

3.1. Streptomycin

Streptomycin was named after the genus *Streptomyces*. It was discovered in 1944 during a systematic screening of soil microorganisms for antibacterial compounds [31]. Although streptomycin was not the first antibiotic discovered from *Streptomyces* (actinomycin and streptothricin were discovered before streptomycin, but were too toxic for clinical use), it was the first to become clinically important [84]. Streptomycin was isolated from *S. griseus* and became the first effective antibiotic against *Mycobacterium tuberculosis*, marking a major breakthrough in tuberculosis treatment and earning its discoverer, Selman Waksman, the Nobel Prize in 1952 [85,86]. Its discovery established *Streptomyces* species as a prolific source of clinically important natural products. The structure of streptomycin is unique among the aminoglycosides, in that it lacks the classic 2-deoxystreptamine core [87].

Biosynthesis of streptomycin is carried out via a complex pathway encoded by the *str* gene cluster [88]. Streptomycin consists of three components: streptidine (a cyclitol), streptose (a sugar), and N-methyl-L-glucosamine (Figure 2A) [88]. Its biosynthesis begins with glucose-6-phosphate which is converted into the cyclitol streptidine through a series of oxidation, amination, and phosphorylation reactions [32]. Glycosyltransferases then attach activated sugar donors to form the disaccharide and ultimately the complete trisaccharide structure [89]. Tailoring enzymes perform methylation and other modifications to yield active streptomycin.

3.2. Neomycin

Neomycin was discovered in 1949 from *S. fradiae*, part of Selman Waksman's broader program on systematic screening of soil actinomycetes, which also yielded streptomycin [33]. Neomycin belongs to the 2-deoxystreptamine aminoglycoside family. Its biosynthesis is catalyzed by enzymes encoded in the *neo* gene cluster [90]. It begins with glucose-6-phosphate undergoing cyclization, amination, and dehydrogenation to produce 2-deoxystreptamine [91]. Glycosyltransferases attach amino sugar moieties derived from UDP-activated sugars. These include neosamine and ribose-like sugars. Additionally, amination, acetylation, and epimerization refine the final structure [92].

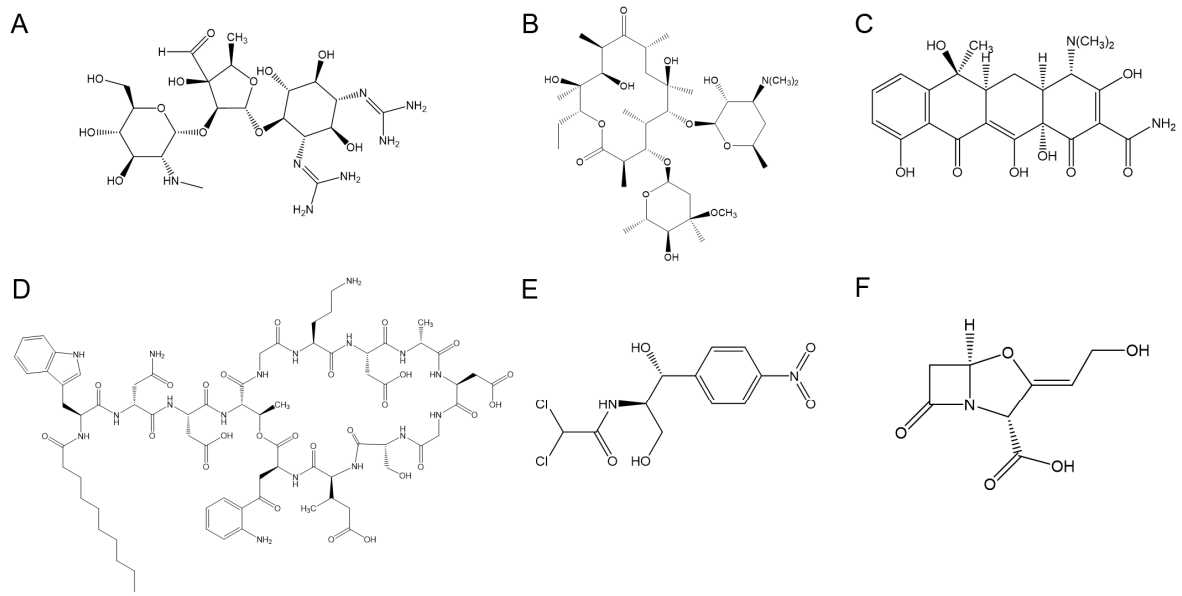

Figure 2. Highly diverse chemical structures of representative antibiotics produced by *Streptomyces* species. (**A**) Streptomycin, an aminoglycoside unique for lacking the 2-deoxystreptamine core found in neomycin and kanamycin. (**B**) Erythromycin A, a Type I polyketide characterized by a 14-membered macrolactone ring with attached sugars. (**C**) Tetracycline, a Type II polyketide defined by its four linearly fused rings. (**D**) Daptomycin, a cyclic lipopeptide synthesized by NRPS, features a 10-amino acid ring and a lipid tail that inserts into bacterial membranes. (**E**) Chloramphenicol, a simple phenylpropanoid containing a nitrobenzene group and a dichloroacetyl tail. (**F**) Clavulanic acid, a β-lactamase inhibitor containing the characteristic four-membered β-lactam ring.

3.3. Kanamycin

Kanamycin was discovered in 1957 in Japan from *S. kanamyceticus* [34]. It demonstrated strong activity against *M. tuberculosis* and became an important second-line treatment for tuberculosis [93]. Kanamycin exists as several closely related compounds: kanamycin A (clinically dominant), kanamycin B, and kanamycin C [94]. Like neomycin, kanamycin belongs to the 2-deoxystreptamine family and shares early biosynthetic steps. After forming the 2-deoxystreptamine, a glycosyltransferase attaches an N-acetylglucosamine-derived sugar to the 2-deoxystreptamine nucleus [95]. A second amino sugar is added, forming the trisaccharide scaffold characteristic of kanamycin. Oxidation, transamination, and deacetylation produce kanamycin A, B, or C [96].

3.4. Tobramycin

Tobramycin was discovered in the 1960s from *S. tenebrarius*. It is structurally closely related to kanamycin B [35]. Tobramycin biosynthesis shares extensive homology with the kanamycin pathway [97]. After forming the 2-deoxystreptamine, sequential attachment of amino sugars forms a kanamycin-like intermediate. A key distinguishing step is the removal of a hydroxyl group at the 3′ position of one sugar moiety. The modification is catalyzed by specific dehydratase or reductase enzymes encoded in the *tob* gene cluster [98]. Transaminases and other modifying enzymes yield the final tobramycin structure [99].

4. Polyketides

Bacterial polyketides are a large and structurally diverse class of secondary metabolites derived from simple carboxylic acid building blocks, most commonly acetyl-CoA and malonyl-CoA [36]. Structurally, they are characterized by repeating carbon-carbon units formed through decarboxylative Claisen condensations [100]. This mode of assembly is conceptually similar to fatty acid biosynthesis, but polyketide synthesis allows far greater chemical variation [101,102]. As a result, polyketides can be linear, cyclic, aromatic, or highly oxygenated and decorated with sugars, methyl groups, or other functional moieties.

The biosynthesis of bacterial polyketides is catalyzed by PKSs, which are large, multi-enzyme systems. Three types of PKSs are recognized in bacteria: Type I, II, and III. Type I PKSs are large, modular, multifunctional proteins. Each module is responsible for one cycle of chain elongation and contains a defined set of catalytic domains [103]. The minimal domains include ketosynthase (which catalyzes carbon-carbon bond formation), acyltransferase (which selects and loads the extender unit), and acyl carrier protein (which tethers the growing

chain). Optional tailoring domains such as ketoreductase, dehydratase, and enoyl reductase modify the β-keto group after each condensation [36]. Type II PKSs consist of discrete, monofunctional enzymes that act iteratively rather than in a modular fashion. They typically produce aromatic polyketides [41]. A minimal Type II PKS includes a ketosynthase-α, a ketosynthase-β, and an acyl carrier protein, which together generate a poly-β-keto chain that later cyclizes and aromatizes [42,43]. Type III PKSs are simpler, homodimeric enzymes that do not use acyl carrier protein [104]. They directly use CoA-linked substrates and perform iterative condensations. Type III PKSs are not as common as Type I and II PKSs in bacteria. Once the polyketide backbone is assembled, chain release typically occurs via thioesterase-mediated hydrolysis or cyclization [105]. Extensive post-PKS tailoring follows, including oxygenation, reduction, glycosylation, methylation, and halogenation. These steps are crucial for biological activity and often determine the final pharmacological properties of the compound [106].

4.1. Erythromycin

Erythromycin was discovered in 1949 during the post-World War II golden age of antibiotic research, closely tied to systematic soil-screening programs aimed at identifying novel antimicrobial compounds produced by *Streptomyces* species [107]. A soil sample collected from the Philippines yielded a microorganism that produced a potent antibacterial compound distinct from penicillin and streptomycin, the dominant antibiotics of the era. The producing organism was initially named *S. erythreus*, reflecting the reddish pigmentation of its colonies [37]. At a time when penicillin resistance was becoming an increasing concern, erythromycin quickly gained attention because of its effectiveness against penicillin-resistant *Staphylococcus aureus* [108]. Moreover, it was also less allergenic than penicillin, making it a valuable alternative for patients with penicillin hypersensitivity [109]. Structurally, erythromycin is defined by a 14-membered macrolactone ring decorated with two deoxy sugars: desosamine and cladinose (Figure 2B) [110]. These features are critical for its antibacterial activity, which arises from binding to the bacterial 50S ribosomal subunit and inhibiting protein synthesis [38].

The biosynthesis of erythromycin is one of the best-studied examples of bacterial polyketide biosynthesis and provides key insights into modular enzyme systems. The core macrolactone, 6-deoxyerythronolide B, is assembled by a Type I modular PKS known as 6-deoxyerythronolide B synthase (DEBS), which consists of three large multifunctional proteins (DEBS1, DEBS2 and DEBS3), which together contain six sequential modules [111]. Each module catalyzes one round of chain elongation using methylmalonyl-CoA as the extender unit, starting from a propionyl-CoA primer [112]. The collinearity between PKS modules and the structure of 6-deoxyerythronolide B was a key piece of evidence supporting the modular paradigm of Type I PKSs [113]. Within each module, the ketosynthase, acyltransferase, and acyl carrier protein domains form the core catalytic machinery. After six cycles of elongation and processing, the thioesterase domain catalyzes macrolactonization, releasing the 14-membered ring. After forming 6-deoxyerythronolide B, the molecule undergoes extensive post-PKS tailoring. Hydroxylation at C-6 by a cytochrome P450 enzyme produces erythronolide B [114]. glycosyltransferases then attach the sugars desosamine and cladinose, which are themselves synthesized through dedicated deoxysugar biosynthetic pathways [115]. Additional methylation and modifications yield the final active antibiotic, erythromycin A. This natural antibiotic can be further chemically converted into additional semi-synthetic macrolides, such as clarithromycin and azithromycin, which have longer half-lives, different antibacterial spectra, etc. [116].

4.2. Tetracycline

Similar to erythromycin, tetracycline was discovered during a systematic screening program for new antibiotics. In 1948, chlortetracycline was first discovered from *S. aureofaciens* and was marketed as aureomycin [44]. Shortly thereafter, oxytetracycline was discovered in 1950 from *S. rimosus* [117], and tetracycline itself was identified in 1953 (Figure 2C) [118]. Its improved stability and broad antimicrobial spectrum make it particularly attractive for clinical use. The development of fermentation-based large-scale production methods allowed tetracyclines to become widely accessible. Overtime, semi-synthetic derivatives such as doxycycline and minocycline were developed to improve pharmacokinetic properties and overcome emerging resistance [118].

Tetracycline biosynthesis in *Streptomyces* species occurs via a type II PKS system that catalyzes the formation of the tetracycline carbon backbone [119]. The polyketide chain then undergoes controlled cyclization to form the characteristic four-ring structure of tetracycline. Following cyclization, the nascent tetracycline scaffold is extensively modified by tailoring enzymes, such as oxygenases, methyltransferases, aminotransferases, and hydroxylases [45]. These enzymes introduce functional groups critical for antibiotic activity. For example, aminotransferase-mediated introduction of the dimethylamino group at the C4 position is essential for binding to bacterial ribosomes [45]. The BGC also encodes self-resistance mechanisms such as efflux pumps and ribosomal protection protein, enabling the producing organism to avoid autotoxicity [120–122].

4.3. Rifampicin

Rifampicin is a semi-synthetic antibiotic renowned for its potent activity against *M. tuberculosis* [123]. Similar [101,102] to erythromycin and tetracycline, it was discovered in the late 1940s–1950s, during a period of intensive global screening for novel antibiotics from soil microorganisms [124]. In 1957, researchers isolated a new actinomycete from a soil sample collected in France [125]. The organism was named as *S. mediterranei*, which was subsequently reclassified and renamed as *Amycolatopsis rifamycinica* [13]. This microbe produced a group of structurally related compounds collectively termed rifampicins, among which rifamycin B showed promising antibacterial activity. Subsequent studies revealed that rifamycin B itself had limited oral bioavailability, prompting efforts to generate more clinically useful derivatives [126]. Through chemical modification, rifampicin was developed in the early 1960s by introducing a piperazine ring and other structural changes that enhanced stability, oral absorption, and antimicrobial potency [127]. Rifampicin was officially introduced into clinical practice in the late 1960s and rapidly became a cornerstone of tuberculosis therapy [128]. It has a unique mechanism of action, selective inhibition of bacterial DNA-dependent RNA polymerase, and is highly effective against slow-growing mycobacteria [39]. This has enabled the treatment duration of tuberculosis to be markedly reduced through various combination treatments using isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin. Rifampicin is also an important drug for the treatment of other mycobacterial infections, such as leprosy, caused by *M. leprae* (combination of rifampicin, dapsone, and clofazimine) [129] and *M. avium* complex infection (combination of clarithromycin/azithromycin, ethambutol, and rifampicin) [130].

The biosynthesis of rifampicin begins with the formation of the rifamycin core by a Type I modular PKS system encoded by the *rif* gene cluster in *A. rifamycinica* [40]. This gene cluster spans over 90 kb and contains genes responsible for polyketide assembly, tailoring reactions, regulation, and export [40]. The process is initiated by the unusual starter unit 3-amino-5-hydroxybenzoic acid (AHBA), which distinguishes rifamycins from many other polyketides [131]. AHBA is synthesized via a dedicated pathway involving intermediates from the shikimate and amino acid biosynthetic routes [132]. Once formed, AHBA is loaded onto the PKS machinery. The PKS chain is then elongated through successive condensations of acetate and propionate units, catalyzed by a series of PKS modules [133]. Each module introduces specific chemical modifications, such as ketoreduction, dehydration, and enoyl reduction, resulting in the formation of a linear polyketide intermediate. This intermediate undergoes macrocyclization to form the characteristic ansa macrolactam ring, a defining structural feature of rifamycins [134]. Following polyketide assembly. Extensive post-PKS tailoring reactions occur. These include oxidation, hydroxylation, methylation, and glycosylation steps, mediated by enzymes encoded with the *rif* cluster [135]. The primary natural product formed is rifamycin B, which can then be chemically converted into rifampicin through semi-synthetic processes.

5. Non-Ribosomal Peptides

Bacterial NRPs are a large class of biologically active secondary metabolites synthesized independently of the ribosome. Unlike ribosomal peptides, which are translated directly from mRNA, NRPs are assembled by massive, multi-enzyme complexes called NRPSs [46]. NRPs often have complex structures that include unusual amino acids, D-amino acids, fatty acids, and extensive modifications [47]. This structural diversity gives rise to a wide range of biological activities [48]. NRPS enzymes operate in a modular assembly-line fashion. Each module is responsible for incorporating one specific building block into the growing peptide chain [46]. A typical module contains an adenylation domain that selects and activates a specific amino acid, a thiolation domain that temporarily holds the activated amino acid via a phosphopantetheine arm, and a condensation domain that forms the peptide bond [49]. Additional domains may epimerize L-amino acids to D-forms, methylate residues, cyclize structures, oxidize, or reduce functional groups [50]. The final peptide is usually released by a thioesterase domain, often resulting in cyclization. Since NRPS systems are not constrained by the genetic code or ribosomal machinery, they can incorporate many unusual building blocks and generate structurally complex molecules [51].

5.1. Vancomycin and Teicoplanin

Vancomycin was discovered in 1953 from a soil sample collected in Borneo [136]. The producing bacterium was *S. orientalis*, subsequently renamed as *A. orientalis* [52]. It was introduced clinically in 1958. Although attention was only mild in the beginning with the availability of β-lactams, interest resurged in the 1980s due to the emergence of methicillin-resistant *Staphylococcus aureus* [137]. Teicoplanin was discovered in the late 1970s, from *Actinoplanes teichomyceticus*, isolated from a soil sample in Italy [138]. It belongs to the same class as vancomycin—the glycopeptide antibiotics—but differs structurally by having a lipophilic side chain and existing as a mixture of closely related compounds (teicoplanin A2 complex) [139]. It was introduced clinically in the

1980s [140]. Both vancomycin and teicoplanin act by binding to the D-Ala-D-Ala terminus of peptidoglycan precursors, preventing cell wall synthesis in Gram-positive bacteria [53]. Although they both have a similar spectrum of activity, teicoplanin has a longer half-life and lower nephrotoxicity than vancomycin [141].

Vancomycin and teicoplanin are nonribosomal glycopeptide antibiotics, synthesized by NRPSs. A defining feature of glycopeptides is their rigid, crosslinked three-dimensional structure. After assembly of the linear peptide by the corresponding NRPS, a series of cytochrome P450 monooxygenases catalyze oxidative phenolic coupling reactions [142]. These reactions form aryl-ether and biaryl crosslinks between aromatic side chains, generating the characteristic cup-shaped scaffold essential for D-Ala-D-Ala binding [143]. Further tailoring steps catalyzed by specific enzymes differentiate vancomycin from teicoplanin. In vancomycin, the sugar moiety vancosamine is added by glycosyltransferase and chlorine atoms are introduced by halogenases [144]; and for teicoplanin, an additional lipid side chain is attached, increasing membrane anchoring and prolonging half-life [145]. These tailoring enzymes are encoded within the BGCs, which also often include genes for self-resistance (e.g., altered cell wall precursors such as D-Ala-D-Lac) [54].

5.2. Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic discovered during a natural products screening program in the late 1980s [55]. It was isolated from the soil actinomycete *S. roseosporus* [55]. However, early clinical development in the 1990s was halted due to concerns about skeletal muscle toxicity [146]. Interest in the compound was revived later after optimization of the dosing regimen, significantly reducing toxicity. Currently, daptomycin is particularly important for the treatment of methicillin-resistant *S. aureus* and vancomycin-resistant enterococci infections [147,148]. Structurally, daptomycin is a cyclic lipopeptide composed of a 13-amino-acid peptide core with a decanoyl fatty acid tail attached to the N-terminus (Figure 2D) [149]. The peptide contains several nonproteinogenic amino acids, including D-amino acids and unusual residues such as L-kynurenine and 3-methylglutamic acid [150]. A distinctive feature is its macrolactone ring, formed through an ester bond between the threonine residue and the terminal kynurenine residue [151]. This cyclic structure is essential for its biological activity. The lipid tail is also critical, enabling calcium-dependent insertion into bacterial membranes, which ultimately leads to membrane depolarization and rapid cell death [56].

The biosynthesis of daptomycin occurs via a NRPS pathway encoded by the *dpt* cluster in the *S. roseosporus* genome [152]. The daptomycin NRPS machinery consists of three large synthetase proteins (DptA, DptBC and DptD), which together contain 13 modules corresponding to the 13 amino acids of the peptide core [152]. Each module typically includes an adenylation domain, which selects and activates and specific amino acid as an aminoacyl-AMP; a thiolation domain, also known as a peptidyl carrier protein, which tethers the activated amino acid via a phosphopantetheine arm; and a condensation domain, which catalyzes peptide bond formation [153] Some modules also contain epimerization domains that convert L-amino acids to their D-forms, accounting for the presence of D-residues in daptomycin [152]. The lipid tail is incorporated at the initiation stage by a specialized acyltransferase that attaches a fatty acid to the first amino acid before peptide elongation proceeds. After assembly of the linear lipopeptide chain, a thioesterase domain at the terminus of the NRPS catalyzes cyclization and release of the mature molecule, forming the characteristic macrolactone ring [154]. Additional tailoring enzymes encoded within the gene cluster are responsible for generating unusual amino acid precursors, such as kynurenine from tryptophan [155].

6. Chloramphenicol

Chloramphenicol was discovered in 1947 during a screening program for antimicrobial compounds from soil actinomycetes [156]. It was isolated from *S. venezuelae* [57]. Structurally, it is distinct from many other natural product antibiotics. It is a small molecule containing a nitrobenzene ring, a dichloroacetamide moiety, and a propanediol side chain with two stereoecenters [157]. Unlike peptide-based antibiotics or complex polyketides, chloramphenicol has a relatively simple architecture (Figure 2E), which makes it the first antibiotic to be produced on a large scale by total chemical synthesis rather than solely by fermentation [158].

The biosynthesis of chloramphenicol in *S. venezuelae* is encoded by the *cml* gene cluster [58]. Chloramphenicol is derived primarily from chorismate, an intermediate of the shikimate pathway, which is responsible for aromatic amino acid biosynthesis [58]. Chorismate is converted into p-aminophenylalanine, a key precursor that provides the aromatic ring structure [59]. Once formed, the amino group on the aromatic ring of p-aminophenylalanine is oxidized to a nitro group through a multistep enzymatic process [60]. Concurrently, enzymes construct the dichloroacetyl side chain, which is derived from central metabolic intermediates and subsequently chlorinated. Halogenation is catalyzed by specific halogenases encoded within the gene cluster,

introducing two chlorine atoms that are essential for biological activity [61]. The final assembly step links the dichloroacetyl moiety to the propanediol side chain and aromatic core via amide bond formation. Stereospecific enzymes ensure the correct configuration of the two chiral centers in the propanediol unit, critical for ribosomal binding [62]. The completed molecule is exported from the producing organism. And resistance genes within the cluster encode chloramphenicol acetyltransferases that inactivate the antibiotic intracellularly, protecting the host bacterium [58].

7. β-Lactams

β-lactam antibiotics share a core four-membered cyclic amide ring known as the β-lactam ring [159]. This ring consists of three carbon atoms and one nitrogen atom. The β-lactam ring is essential for antibacterial activity, as it binds to penicillin-binding proteins and inhibits bacterial cell wall synthesis [63]. Although β-lactams as a group consist of the largest number of commercially available antibiotics, only a few of them are directly or indirectly originated from *Streptomyces* species, the most notable ones being cefoxitin, imipenem and clavulanic acid [64,65,160].

7.1. Cephamycins and Cefoxitin

Cephamycins were discovered in the early 1970s during efforts to identify naturally occurring β-lactam antibiotics with improved resistance to β-lactamases [160]. Cephamycins possess an unusual 7-α-methoxy group on the β-lactam nucleus, which confers enhanced stability against many β-lactamases compared to earlier cephalosporins [161]. Cefoxitin is a semi-synthetic derivative of cephamycin C, a compound isolated from *S. lactamdurans* [162,163].

Biosynthesis of cephamycin C begins with formation of the tripeptide precursor L-α-aminoadipate, L-cysteine and L-valine, assembled by a NRPS [66]. This linear tripeptide cyclizes to form isopenicillin N via isopenicillin N synthase. Unlike penicillin biosynthesis in fungi, the pathway in *Streptomyces* proceeds through ring expansion to form the cephem nucleus, and a defining step in cephamycin production is the introduction of the 7-α-methoxy group, catalyzed by specific oxygenase and methyltransferase encoded in the cephamycin gene cluster [67–69]. Cefoxitin is then produced by chemical modification of cephamycin C, particularly alteration of the 3-position side chain to improve antibacterial activity and stability [163].

7.2. Clavulanic Acid

Clavulanic acid was discovered in 1976 during a screening program for new β-lactam antibiotics [164]. It was isolated from *S. clavuligerus*, a soil-dwelling actinomycete [65]. Although clavulanic acid contains a β-lactam ring, it showed only weak intrinsic antibacterial activity. However, it was found to be a potent β-lactamase inhibitor [165]. It binds to β-lactamases and protects co-administered antibiotics [65]. Its clinical importance was established through combination with amoxicillin, marketed as Augmentin [166,167].

Unlike penicillins and cephalosporins, which are derived from amino acid precursors via peptide assembly, clavulanic acid biosynthesis originates from primary metabolic intermediates. The gene cluster encodes enzymes for precursor supply, β-lactam formation, tailoring reactions, regulation, and self-resistance [168–170]. The pathway begins with the condensation of glyceraldehyde-3-phosphate and L-arginine-derived units [171]. Then, an oxidative cyclization step forms the characteristic β-lactam ring, but notably without the fused thiazolidine or dihydrothiazine rings seen in penicillins and cephalosporins [172]. Lastly, several oxygenase-mediated steps modify the intermediate clavaminic acid to generate the final bicyclic clavulanic acid (Figure 2F) [169,173].

7.3. Thienamycin and Imipenem

Thienamycin, a naturally occurring carbapenem antibiotic, was discovered in the late 1970s from *S. cattleya* [64]. It has an exceptionally broad antibacterial spectrum and strong resistance to most β-lactamases [174]; however, thienamycin was chemically unstable in aqueous solution, limiting direct clinical use [175]. Imipenem was created as a more stable N-formimidoyl derivative of thienamycin through chemical modification [174]. It became the first clinically useful carbapenem antibiotic and was introduced in the 1980s [176]. Since it is hydrolyzed in the kidney by dehydropeptidase I, it is co-administered with cilastatin, an enzyme inhibitor that prevents renal degradation and prolongs its activity [177,178].

Biosynthesis of thienamycin is catalyzed by enzymes encoded in the *thn* cluster [179]. It begins with the assembly of a simple precursor derived from malonyl-CoA and amino acid building blocks [70]. β-lactam ring formation is catalyzed by carbapenem synthase [71]. Unlike penicillins, carbapenems lack sulfur in the fused ring

and instead contain a carbon-based unsaturated five-membered ring [179]. Then, oxygenases and other tailoring enzymes introduce double bonds and stereochemical features essential for activity, and the characteristic cysteaminyl side chain is formed [72].

8. Concluding Remarks and Future Perspectives

Among all bacterial genera, *Streptomyces* has been the most prolific in producing clinically useful antibiotics. So far, most of the antibiotics from *Streptomyces* have been discovered through screening soil samples. From the 1940s to 1970s, researchers collected soil from diverse environments, isolated *Streptomyces* strains, cultured them, and screened their metabolites for activity against pathogenic bacteria [180–182]. In the last few decades, antibiotic resistance has exploded, and the discovery of new antibiotics has become a high priority [183–186]. With advances in technology, it is expected that newer approaches will be used to discover natural antibiotics from *Streptomyces*. For example, whole-genome sequencing through the expanding next-generation sequencing platforms and downstream bioinformatics analysis will be able to predict BCGs that encode secondary metabolites, such as novel polyketides, NRPs, and other antibiotic classes. Metagenomic sequencing of environmental DNA samples will also lead to the discovery of BGCs from *Streptomyces* that cannot be cultured. Artificial intelligence can help analyze large genomic datasets to identify and classify BCGs more accurately than rule-based bioinformatics alone [187]. It can also predict which gene clusters are most likely to produce bioactive compounds. This allows us to prioritize the most promising clusters rather than experimentally testing hundreds at random. As a whole, these advanced techniques and rigorous in silico analysis could lead to revealing the hidden BGCs in *Streptomyces*, enabling genome mining, activation of silent pathways, and discovery of entirely new antibiotics that traditional methods would miss [188–190].

Author Contributions

Conceived and designed the study: P.C.Y.W. Literature search: E.W.T.T., S.K.P.L. and P.C.Y.W. Writing—original draft: E.W.T.T., S.K.P.L. and P.C.Y.W. Writing—review and editing: E.W.T.T., S.K.P.L. and P.C.Y.W. 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.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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