Recent advances in the chemistry and biology of naturally occurring antibiotics

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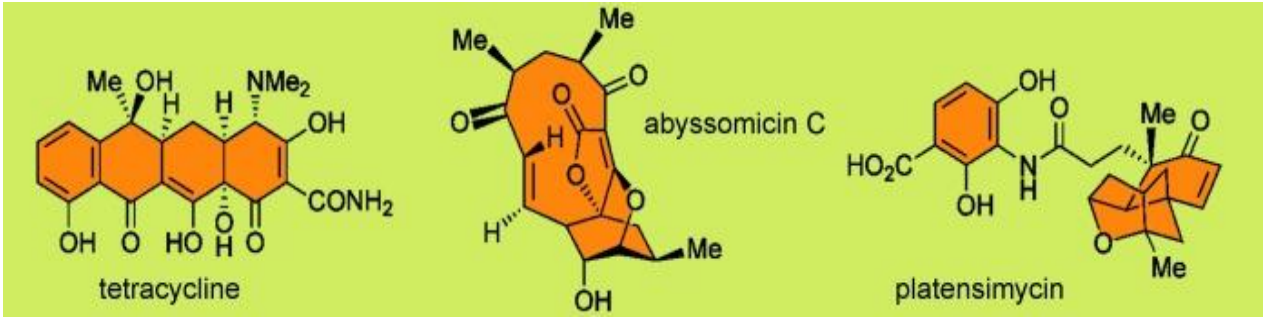
***Abstract*- Ever since the world-shaping discovery of penicillin, nature's molecular diversity has been extensively screened for new medications and lead compounds in drug discovery. Antibiotics markets are huge and the need for new classes of antibiotics is great, but the risks give investors pause. The search for agents intended to combat infectious diseases has been of particular interest and has enjoyed a high degree of success. Indeed, the history of antibiotics is marked with impressive discoveries and drug-development stories, the overwhelming majority of which have their origin in natural products. Chemistry, and in particular chemical synthesis, has played a major role in bringing naturally occurring antibiotics and their derivatives to the clinic, and no doubt these disciplines will continue to be key enabling technologies. In this review article, we highlight a number of recent discoveries and advances in the chemistry, biology, and medicine of naturally occurring antibiotics, with particular emphasis on total synthesis, analogue design, and biological evaluation of molecules with novel mechanisms of action.**

Keywords: **medicines, natural products, synthesis, structure–property relationship, and antibiotics**

Graphical Abstract

This stimulating review article discusses exciting developments in the field of antibiotics as the author highlights research conducted since 2000, highlighting the critical role that total synthesis plays in advancing the field and opening up new avenues for drug design. The structural variety of antibiotics is demonstrated by the three compounds.



Introduction:

One of the most important discoveries of the 20th century was definitely the discovery of penicillin, which led to the development of modern antibiotics. These medications significantly improve the treatment of bacterial illnesses, hence extending life expectancy and improving people's quality of life globally. Millions of lives have been saved by modern antibiotics, and their importance cannot be overstated. In 2005, oral antibiotic sales reached a global total of $25 billion USD.

1.1 Historical Overview

Prontosil (Refer to Figure 1) was the first all-purpose antibiotic used in contemporary medicine. It was first identified by Gerhard Domagk in 1932, developed by Bayer Laboratories, and introduced by the same company in **1935. Prontosil, the first of a broad class of antibacterial agents known as sulfonamides or sulfa medications, is a synthetic diazo dye with a sulfonamide functionality. Sulfonamides still have some limited applications today,**

despite being mainly replaced by later antibiotics. "For the discovery of the antibacterial effects of prontosil," Domagk received the 1939 Nobel Prize in Physiology or Medicine. The quinolones [see ciprofloxacin (2, Figure 1)], are another class of synthetic antibacterial drugs that were first developed in 1962. Remarkably, following research found molecules from natural sources that shared structural similarities with the quinolone antibiotics. It would be nearly forty years before the next synthetic antibiotic was released. This is the oxazolidinone linezolid (3, Figure 1), which the Food and Drug Administration (FDA) of the United States approved in 2000.

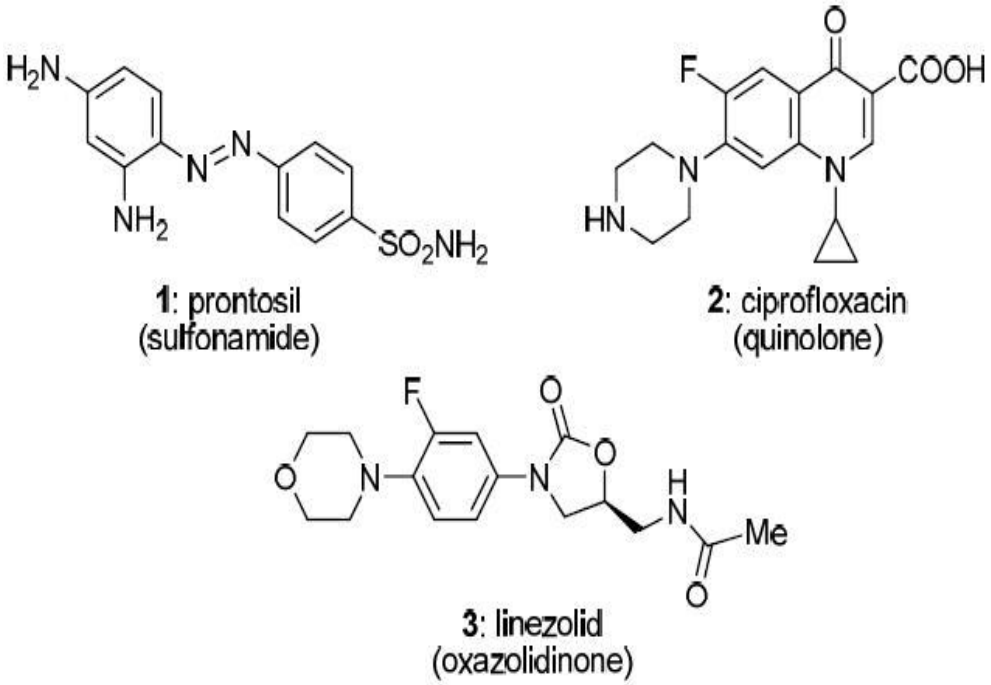


Fig. 1. Molecular structures of selected antibiotics of synthetic origin.

Even though completely synthetic antibacterial medicines are valuable, they make up a very little portion of the antibiotics that are now in use. The majority of antibiotics currently used in clinical practice may be traced back to the identification of a lead ingredient in a natural product. The use of naturally occurring antibiotics in modern medicine dates back to 1928, when Alexander Fleming discovered that Penicillium notatum hindered the growth of bacteria surrounding it. After saving countless troops' lives in World War II, the penicillins [see penicillin G (4, Figure 2)] were made available for civilian use. Penicillins are members of the broad class of β-lactam antibiotics, which also includes carbapenems and cephalosporins. B-lactam antibiotics have consistently been the most extensively prescribed class of antibiotics since their introduction. In 1945, Fleming, Chain, and Florey were awarded the Nobel Prize in Physiology or Medicine “for the discovery of penicillin and its curative effect in various infectious diseases. The Nobel Prize in Physiology or Medicine was given to Fleming, Chain, and Florey in 1945 "for the discovery of penicillin and its curative effect in various infectious diseases." Many novel classes of antibacterial drugs were created from naturally occurring antibiotics in the two decades following World War II and introduced into clinical use. The tetracyclines [see tetracycline (5, Figure 2)], the macrolides [see erythromycin A (7, Figure 2)], the phenylpropanoids [see chloramphenicol (6, Figure 2)], and the glycopeptides [see vancomycin (8, Figure 2)] are some of them. However, the introduction of significant new classes of natural product-based antibacterial agents stagnated after this period of tremendous growth in antibiotic discovery. In 1945, Chain, Fleming, The introduction of the first natural product-based antibiotic from a new structural class in forty-one years occurred with the approval of the lipopeptide daptomycin (9, Figure 2) [8] in 2003.

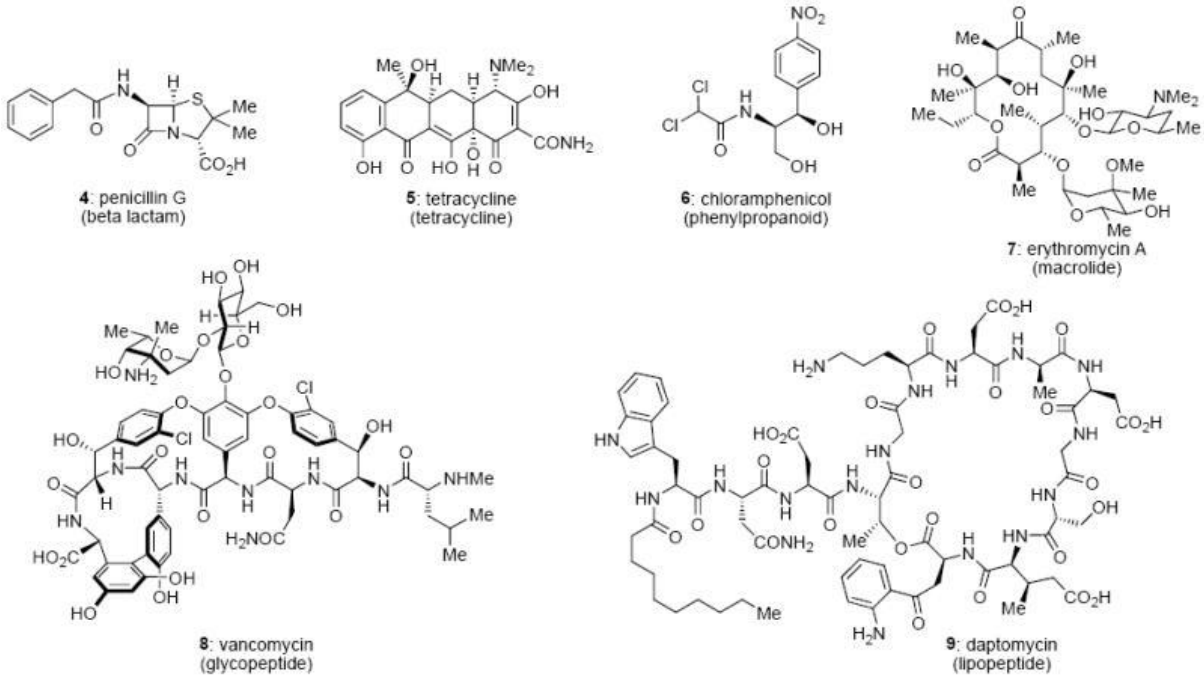


Fig. 2. Molecular structures of selected antibiotics derived from natural products.

A common perception that bacterial illnesses were essentially solved towards the end of the period of rapid development is partially to blame for the protracted break in the introduction of new classes of antibacterial medicines in recent times. But it quickly became evident that this was not the case given the expanding issue of antibiotic resistance among clinically relevant bacteria. The unavoidable emergence of bacterial resistance will necessitate the ongoing search for and development of novel antibacterial drugs, even with cautious antibiotic use. It is true that resistance to last-resort antibiotics like vancomycin has become a clinically serious issue, making the need for new antibiotics more pressing than ever. Most new antibiotics, nevertheless, have been next-generation copies of existing medications, with very few exceptions, and many structural classes are currently in the third or fourth generation of research. This scenario highlights the enormous potential of the current leads, but it also highlights the lack of diversity in the antibacterial agent arsenal employed in contemporary treatment. Due to the current situation, civilization is susceptible to the emergence of superbugs with extreme resistance and the potential for catastrophic outbreaks.

Thankfully, advances in biology and chemistry have made it easier for us to identify new groups of antibiotics that arise naturally. Moreover, figuring out a newly discovered antibiotic's mode of action is now simpler than it has ever been. Even drugs having a specific mechanism of action can be screened for. It's interesting to note that advances in genomics have revealed a number of highly conserved, critical bacterial genes, the majority of which have not yet been used as antibacterial agents. All of these developments are currently making it easier to find new antibacterial agents with cutting-edge modes of action.

Chemical synthesis has been crucial to the discovery and creation of effective antibacterial agents since the dawn of the contemporary antibiotic era. As a result, medicinal chemistry applied to naturally occurring antibiotics has produced anti-infective drugs with enhanced qualities, and semi synthesis frequently provides a straightforward and economical method for producing next-generation compounds on a wide scale. Additionally, because to the shortcomings of the fermentation process, complete synthesis is the favoured approach for producing naturally occurring antibiotics in some situations, such as the production of chloramphenicol. The de novo synthesis of naturally occurring antibiotics and their analogs is essential to comprehending the mechanism of action and Structure Activity Relationships (SARs) of many naturally occurring antibiotics, despite the fact that few clinically used antibiotics are produced by total synthesis. For instance, studies resulting from the entire synthesis of vancomycin (8, Figure 2) have made a substantial contribution to understanding its mode of action as well as to the creation and synthesis of enhanced analogs that successfully combat strains of bacteria resistant to vancomycin.

1.2. Scope of Article

Given the vast amount of research on the chemistry and biology of naturally occurring antibiotics, it is impractical and almost impossible to do a thorough assessment of the field. As a result, the review's purview will be restricted to publications made since 2000, and its highlights will come from naturally occurring antibiotic classes for which complete syntheses have been documented in this period. Certain antibiotics that are covered in this study, such

tetracycline and thiostrepton (12, Figure 3), have been used extensively in both human and veterinary medicine for many years. Others have been used more sparingly up to this point, as pseudomonic acid a (mupirocin, 10, Figure 3). Phase III clinical trials are under underway for ramoplanin A2 (13, Figure 3). Although kinamycin C (11, Figure 3) has not been turned into a therapeutically effective medication, there has been debate over its molecular structure for more than 20 years. As potential therapeutic drugs and candidates for further optimization, the GE thiopeptides, lysobactin (katanosin B, 16, Figure 3), abyssomycin C (14, Figure 3), platensimycin (17, Figure 3), and platencin (18, Figure 3) are all promising new antibiotic families.

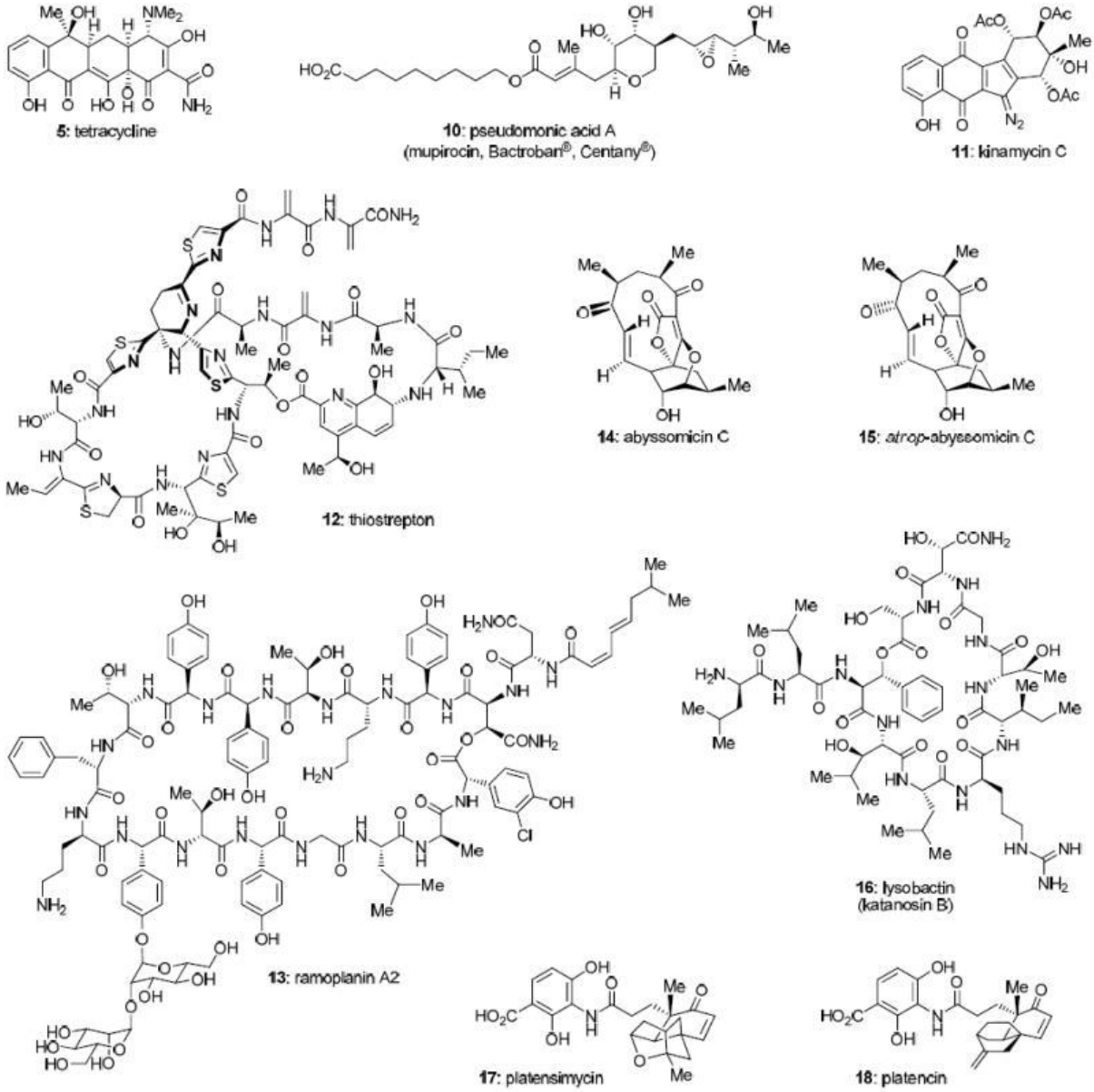


Fig. 3. Representative members of antibiotic classes discussed in this article.

1. Tetracycline

The first class of broad spectrum antibiotics to be produced were the tetracyclines, which were first identified in 1945. Tetracyclines work well against both Gram-positive and Gram-negative bacteria as well as bacteria without cell walls. In 1948, chlortetracycline (19, Figure 4) was introduced into the clinic, then in 1953, tetracycline. Only the highlights of the biology, pharmacology, and agricultural applications of tetracyclines will be discussed here, as the rest have been thoroughly studied. The tetracycline family has at least 10 members that have been utilized in human medicine to date. Tetracyclines are also widely utilized in veterinary medicine as feed additives and as a therapy for bacterial infections. Tetracyclines were initially reported to be used as feed additives in 1949, and the FDA first approved this use in 1951. Tetracyclines are also used to prevent and treat illnesses in insects, plants, and fish that are useful for economic purposes. The annual consumption of tetracyclines is expected to be 5000 metric tons. The emergence of several resistant bacterial strains is not surprising, considering how widely tetracyclines have been used over the past 60 years. Undoubtedly, the issue of increasing bacterial resistance has played a role in the decrease in tetracycline

usage in human medicine. Tetracyclines are still the first choice for treating a number of conditions, such as pneumonia, Lyme disease, acne vulgaris, and cholera, due to their wide spectrum activity, high safety profile, and plentiful availability. [16d] Tetracyclines are alternatively employed as therapeutic agents for various purposes, including as the management of specific protozoan illnesses like malaria.

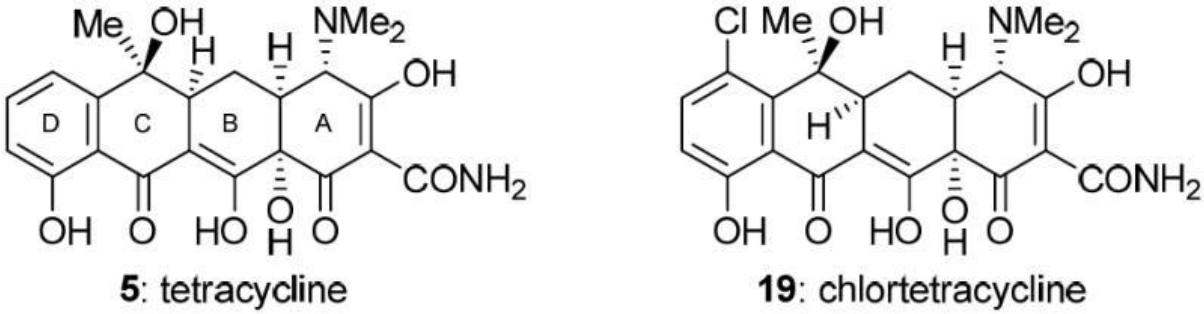
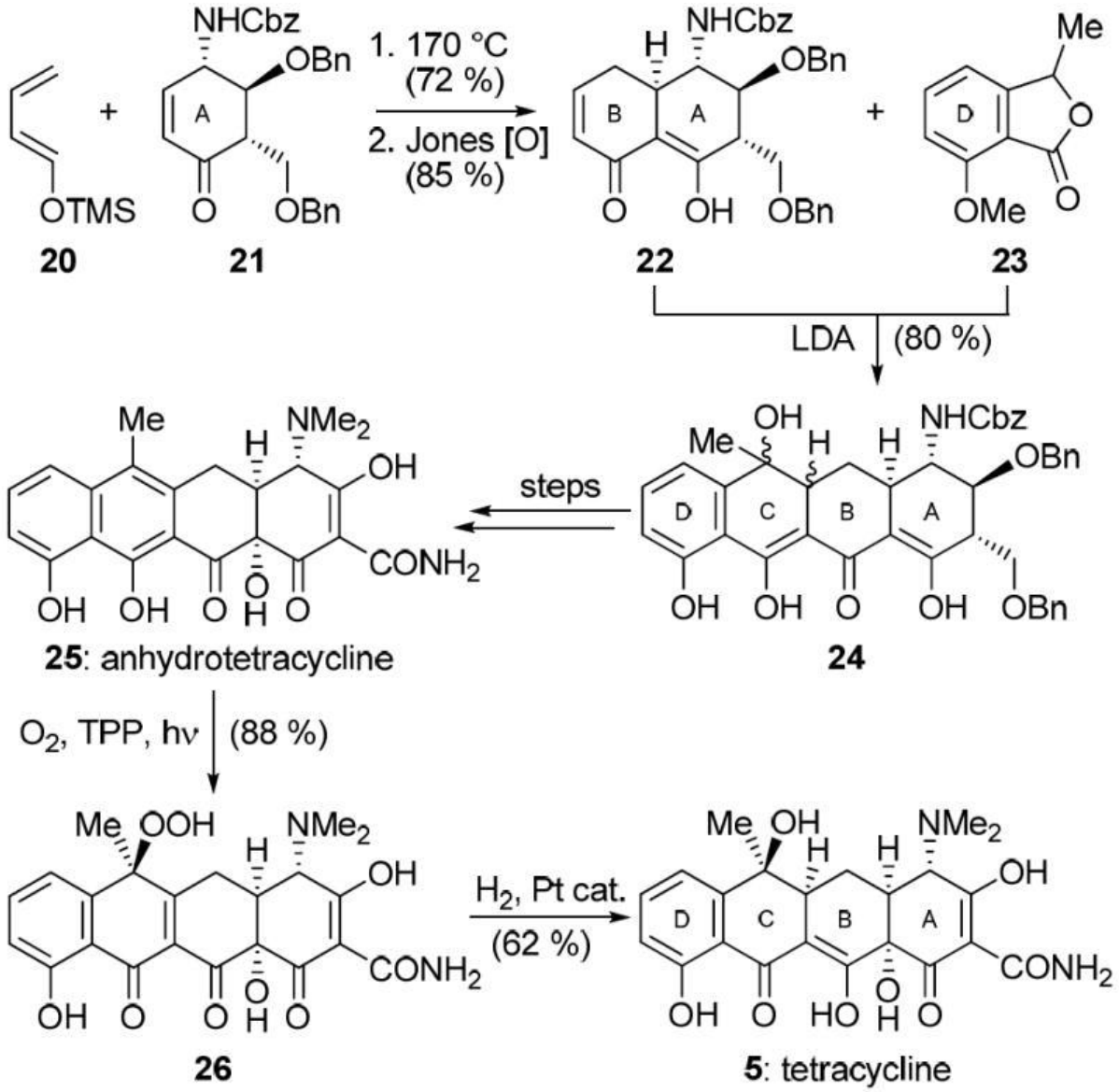


Fig. 4. Molecular structures of tetracycline (5) and chlortetracycline (19).

By reversibly binding to the prokaryotic 30S ribosomal subunit and preventing the ribosome from interacting with aminoacyl-tRNA, tetracyclines prevent the development of bacteria by impeding the synthesis of proteins. [16d] Tetracyclines, on the other hand, have a poor interaction with the eukaryotic 80S ribosomal subunit. Tetracyclines do, however, block the formation of mitochondrial proteins, which explains part of their antiparasitic action. It's interesting to note that some parasites that are vulnerable to tetracyclines lack mitochondria; it's unknown how tetracyclines work against these types of protozoa. Tetracycline resistance is typically given by the acquisition of one or more resistance genes rather than being the result of a mutation in the bacterial 30S ribosomal subunit. [16d] Over thirty of these genes have been identified; they either encode an efflux pump or a ribosome-protecting protein.

Tetracycline (5) has six contiguous stereocenters and a crowded array of functions within its tetracyclic framework (ABCD; see Figure 4). The semisynthetic glycylglycines [16b, 22] are a new development that highlights the ongoing significance of researching semisynthetic analogs. Semisynthetic tetracyclines have been the subject of substantial research. De novo synthesis would, however, eventually open up a wider range of analogs. .. It should come as no surprise that many synthetic organic chemists are interested in tetracyclines due to their broad spectrum antibacterial action and tremendous chemical complexity inside a seemingly basic carbon framework. In the quest for the complete synthesis of tetracyclines, R. B. Woodward, H. Muxfeldt, and G. Stork's laboratory produced groundbreaking research. H. H. Wasserman and associates' semisynthesis of tetracycline is also noteworthy. Though extensively researched, the mechanism of tetracycline biosynthesis [16a] offers little help to synthetic chemists.

Tatsuta et al. reported the first complete synthesis of tetracycline in 2000.The Diels-Alder cycloaddition used in their synthesis to create the AB ring system and the Michael reaction Dieckmann condensation cascade used to add the C and D rings are depicted in Scheme 1. Diels-Alder cycloadduct was therefore produced by heating diene 20 and D-glucosamine-derived enone 21 to 170 °C. This cycloadduct was then exposed to Jones oxidation conditions, resulting in the AB ring system 22. Then, in a Michael reaction–Dieckmann condensation cascade, the newly generated enone moiety interacted with the lithium anion of lactone 23 to produce tetracyclic compound 24, which contained the complete tetracycline carbon structure as a negligible mixture of diastereomers. After a sequence of functional group modifications produced anhydrotetracycline, it was photooxidized in the presence of molecular oxygen and tetraphenylporphine (TPP) as a sensitizer to produce hydroperoxide 26 using the technique outlined in the semisynthesis of tetracycline (5) revealed by Wasserman and colleagues. The entire synthesis of tetracycline was accomplished by platinum black-promoted hydrogenolysis of the crude hydroperoxide and simultaneous reduction of the tetrasubstituted olefin (5).



Scheme 1. Highlights of the first total synthesis of tetracycline (5)

The described total syntheses of tetracycline may facilitate the development of another generation of tetracycline-based therapeutics. Indeed, the Myers total synthesis was part of a program directed towards the development of new tetracycline-based antibiotics. [30] While de novo synthesis of tetracycline analogs may not match the low cost of fermentation, it allows access to analogs that are not obtainable by semisynthesis. Notable analogs designed, synthesized, and evaluated by the Myers laboratory include 6-deoxytetracycline (41, Figure 5) and pentacyclic derivative 42 (Figure 5). Antibacterial testing of these analogs (Table 1) revealed promising properties, including activity against pathogens that are resistant to tetracycline (such as Staphylococcus aureus ATCC 700699). No doubt, further research may uncover even more effective compounds within the tetracycline class, giving hope for the emergence of a new generation of antibiotics.

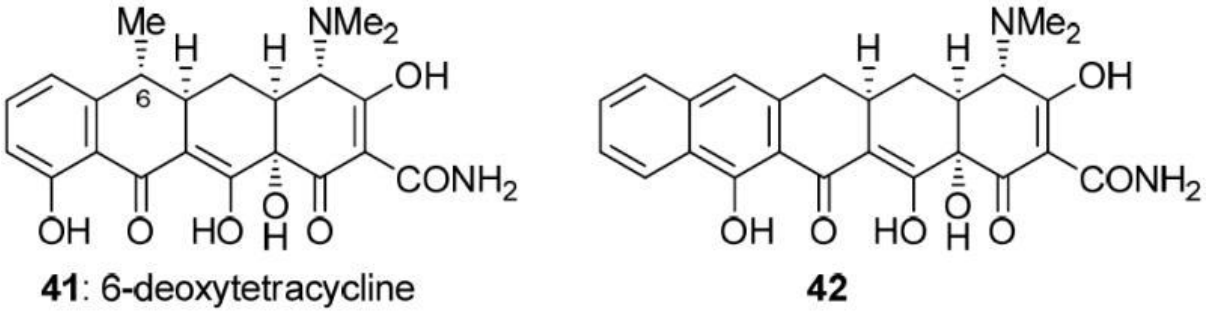


Fig 5. Selected synthetic tetracycline analogs

Table 1: Antibiotic properties of selected tetracycline analogs against Gram-positive bacteria

Bacterial strain	tetracycline (5) MIC (μg mL^{-1})	41 MIC (μg mL^{-1})	42MIC (μg mL^{-1})
Staphylococcus aureus ATCC 29213	1	1	1
Staphylococcus epidermidis ACH-0016	1	0.5	0.5
Staphylococcus haemolyticus ACH-0013	8	2	1
Enterococcus faecalis ATCC 700802	1	0.5	1
Staphylococcus aureus ATCC 700699	> 64	2	1

1. Kinamycin C

The class of antibacterial medicines known as the kinamycins [see kinamycin C] was initially identified in 1970 by Omura and associates. The kinamycins are highly effective against bacteria that are Gram-positive, and kinamycin C is also somewhat cytotoxic. Kinamycin C was initially given the cyanamide-containing structure 168 based on X-ray crystallographic study and chemical correlation (Figure). Over a lengthy and well researched journey, the structure of the kinamycins was studied for many years. The result of these investigations was a modification of the structures that were initially attributed to the diazobenzofluorene compounds (as in compound 11), as published independently in 1994 by the Gould and Dmitrienko groups.

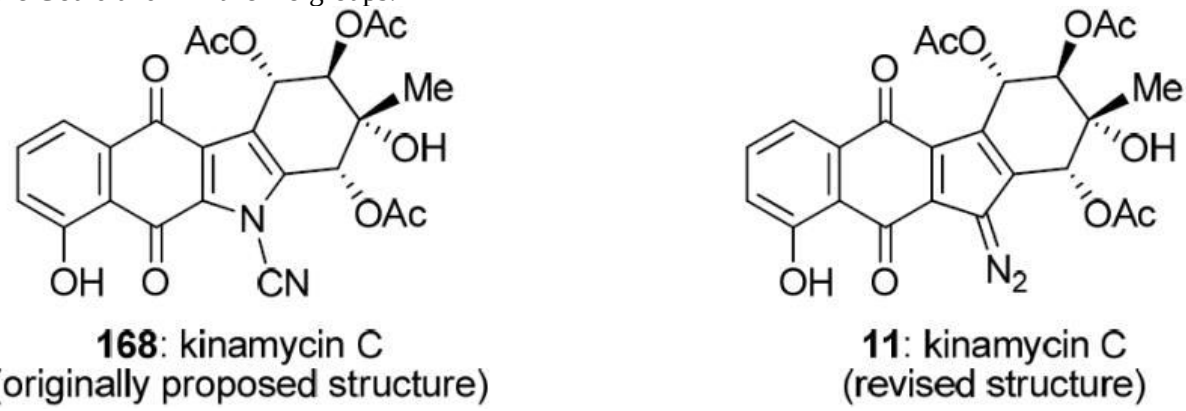


Fig. Originally proposed (168) and revised (11) structures of kinamycin C.

Not surprisingly, the interesting biological profile and the novel and disputed structures of the kinamycins attracted the attention of several synthetic chemists. The first total synthesis of kinamycin C was completed by Lei and Porco in 2006. The Porco total synthesis features a Stille cross coupling reaction and a Friedel–Crafts acylation to assemble the kinamycin skeleton. Cross coupling partner 172 was prepared from phenol 169 as shown in Scheme 23. Thus, phenol 169 was oxidized to a partially protected quinone, and manipulation of the protecting groups provided compound 170. A one-carbon unit was installed onto 170 under Baylis–Hillman conditions to give, after an enantioselective epoxidation, epoxide 171. Sharpless asymmetric epoxidation conditions provided the epoxide in 85 % yield and 70 % ee. The low performance of this process prompted further studies that ultimately led to a tartrate-promoted asymmetric nucleophilic epoxidation, which gave the desired epoxide in 94 % yield and 90 % ee. Epoxide 171 was then converted through a standard sequence of manipulations to vinyl bromide 172. Stille cross coupling of vinyl bromide 172 with aryl stannane 173 yielded coupled products 174, which was transformed into carboxylic acid 175 by standard chemistry. This set the stage for a critical intramolecular Friedel–Crafts acylation, which proceeded smoothly upon exposure of 175 to trifluoroacetic anhydride to furnish tetracyclic intermediate 176. MOM deprotection and oxidation of the so-revealed dihydroquinone yielded quinone 177. To complete the synthesis of kinamycin C (11), the diazo group was introduced by condensation of 177 with protected hydrazine 178 to afford the corresponding hydrazone, which was oxidized by the action of PhIF2 to install the diazo moiety. Synthetic kinamycin C (11) exhibited indentical physical data to those of the natural substance, lying to rest any lingering doubts of the true structure of the kinamycins.

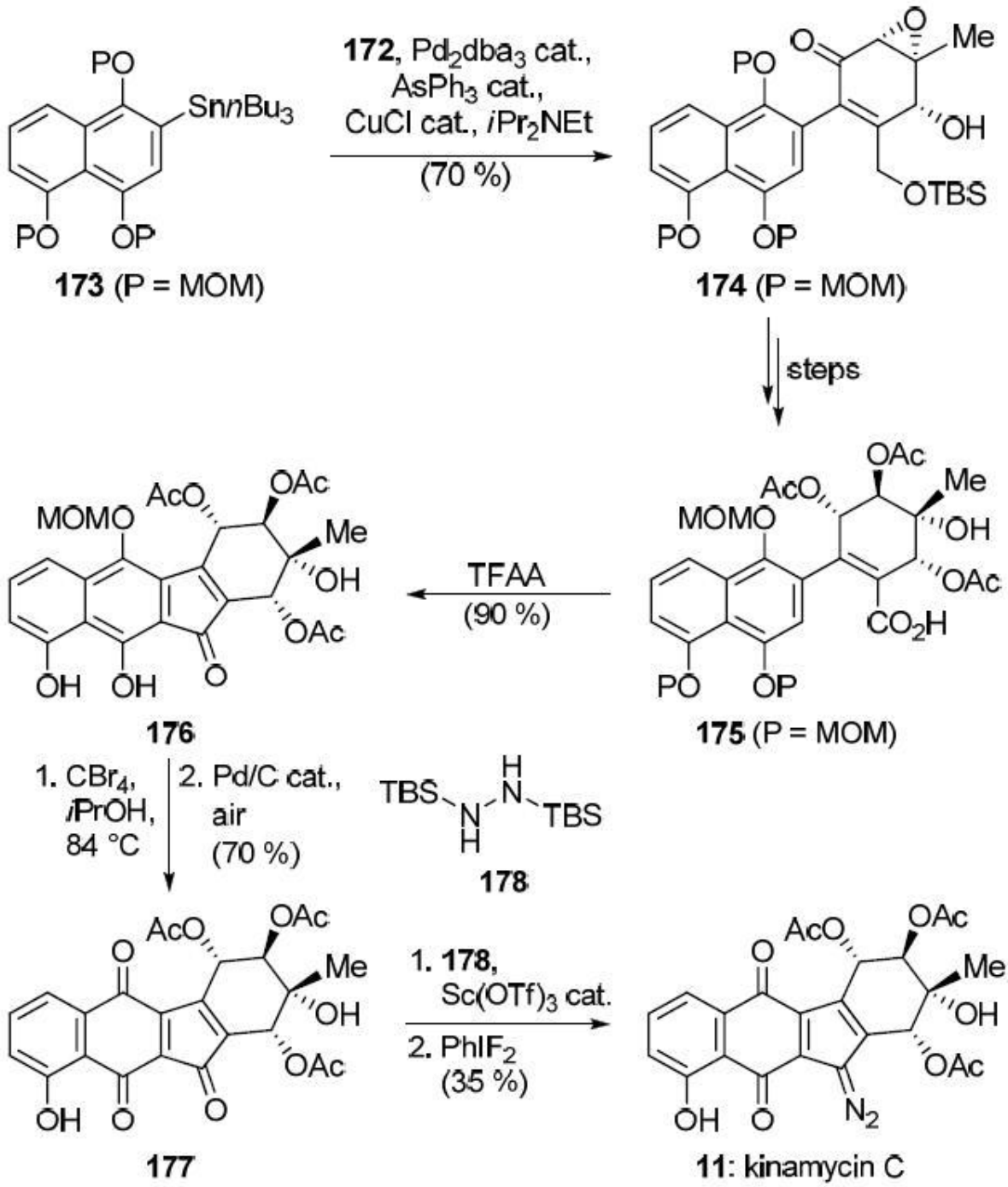


Fig. Highlights of the completion of the total synthesis of kinamycin C (11)

In 2007, Kumamoto, Ishikawa, and coworkers reported a synthesis of methyl kinamycin C. an intramolecular Friedel–Crafts acylation of carboxylic acid 179 provided a cyclic ketone, which was oxidized to enone 180 by the action of IBX. Diels–Alder cycloaddition of enone 180 with diene 181 furnished, after silyl deprotection, tetracyclic intermediate 182. This intermediate was then oxidized by KF and air in DMSO to give tertiary alcohol 183. This compound was elaborated in a sequence of standard manipulations to afford advanced intermediate 184. Exposure of 184 to Burgess Reagent then promoted dehydration of the unprotected tertiary alcohol, after which the acetonide moiety was cleaved and the resulting secondary alcohol was acetylated to give dienone 185. Hydrazone formation and CAN-promoted oxidation to the required diazo moiety with concomitant oxidation of the protected dihydroquinone yielded methyl kinamycin C (186).

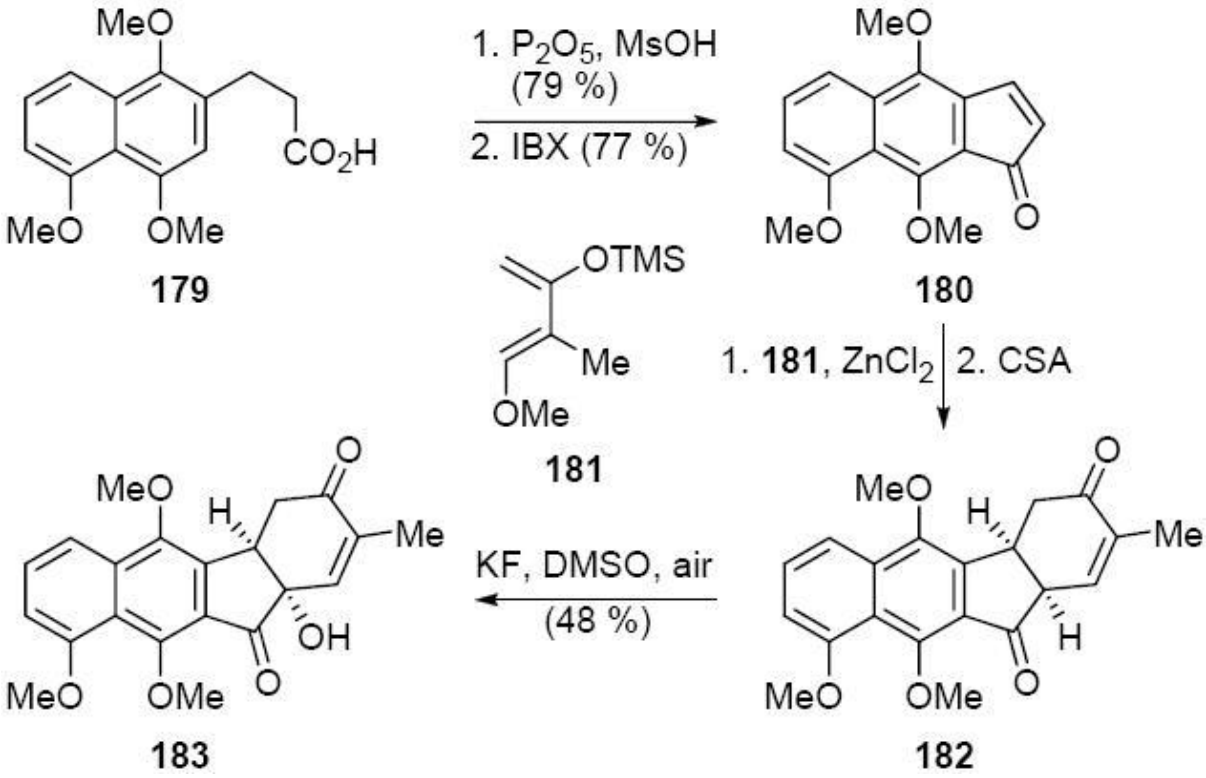


Fig. Synthesis of the kinamycin tetracyclic framework

2. Lysobactin

A depsipeptide antibiotic called lysobactin (katanosin B, 16, Fig.) was independently reported in 1988 by Shoji and colleagues at Shionogi and O'Sullivan and colleagues at Squibb. It exhibits great potency against Gram-positive bacteria (e.g., Streptococcus pneumoniae, MIC 0.06 μg mL−1; in contrast, vancomycin has a MIC of 0.5 μg mL−1) and may also effectively combat strains resistant to several other antibiotics, including vancomycin. For instance, lysobactin has MICs ranging from 0.4 to 0.8 μg mL−1, making it up to 50 times more effective against VRE than vancomycin. Lysobactin suppresses peptidoglycan manufacturing in a manner similar to that of vancomycin, albeit its precise mechanism of action is still unknown. Von Nussbaum and colleagues at Bayer presented an exquisite complete synthesis of lysobactin in 2007. The synthesis was based on insights obtained from the compound's crystal structure. The Van Nieuwenhze group announced a second complete synthesis that provides this antibiotic with a comparable level of efficiency shortly after. A review of lysobactin's biology and chemistry was published relatively recently.

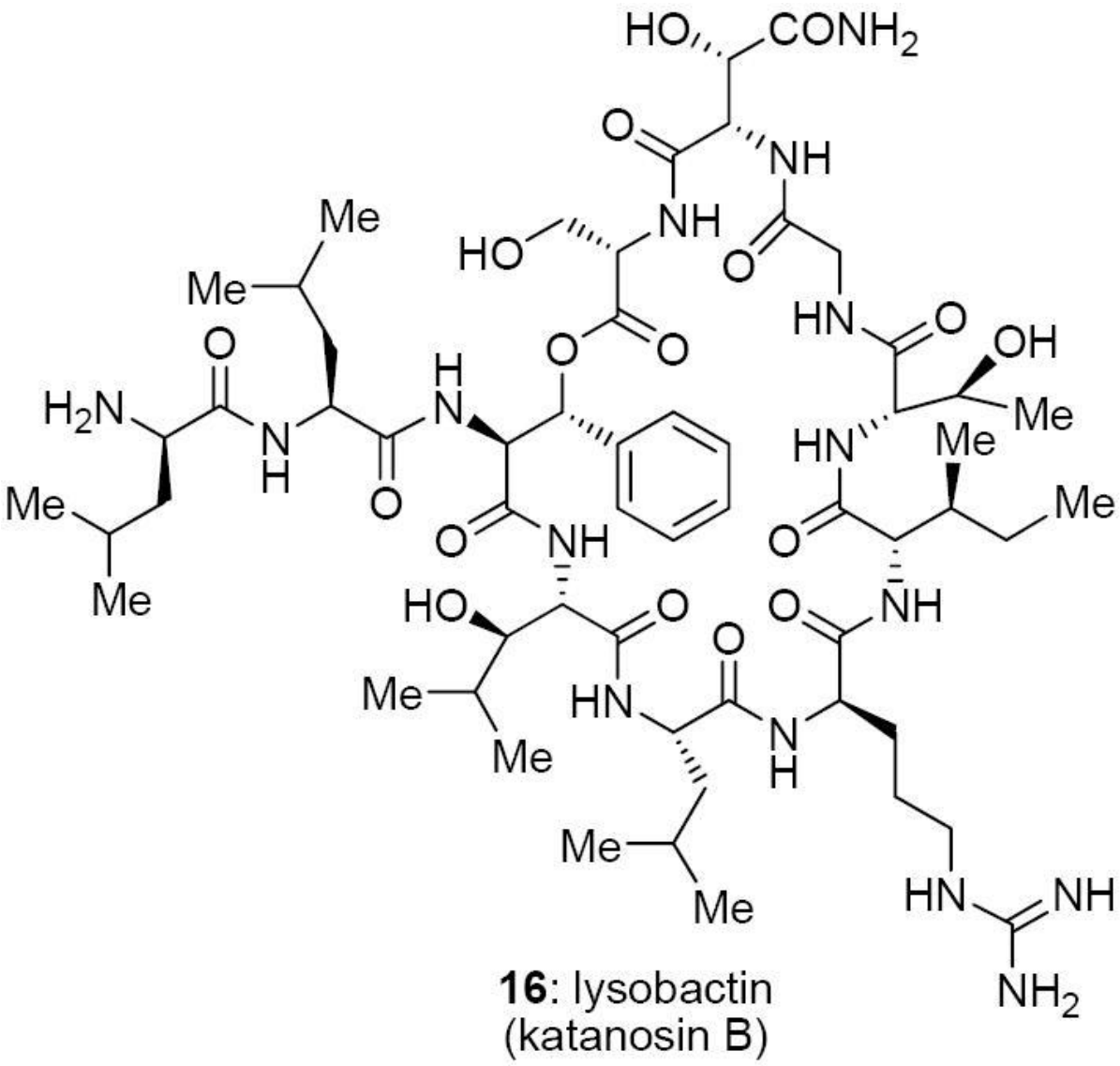


Fig. Molecular structure of lysobactin (16).

3. Summary and Outlook :

This review began with a brief overview of the history of antibiotics before highlighting current developments in the field's chemistry, biology, and medicine. The emergence and survival of drug-resistant bacterial strains, along with the knowledge that a catastrophic outbreak of lethal illnesses caused by these bacteria is not implausible, appears to have spurred an apparent rise in these investigations. Natural products have been at the forefront of antibiotic research since the outset. This discipline is obviously back in demand, and further ground-breaking discoveries should be anticipated. This is due in large part to recent developments in biology as well as effective screening and isolation techniques. This analysis shows how quickly synthetic chemists will follow suit when a new, promising lead is found from nature. And because of the amazing and never-ending capacity of chemical synthesis, these compounds and their analogs are now available for additional laboratory research. Indeed, the discovery of novel compounds from nature combined with their clever use in the lab will undoubtedly result in the antibiotics of the future working together. These novel medications are unquestionably necessary if we are to fend against the relentless incursions of our dreaded adversaries, the superbugs.

Acknowledgments:

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Abbreviations:

Ac acetyl
Acc acetyl-CoA carboxylase
ACP acyl carrier protein
AIBN 2, 2'-azobis (2-methylpropionitrile)
Ala alanine
Alloc allyloxycarbonyl
Asn asparagine
ATP adenosine triphosphate
C cysteine
CoA coenzyme A
Cys cysteine
DHP 3, 4-dihydro-2*H*-pyran
His histidine
TFA trifluoroacetic acid
TRNA transfer RNA
PABA *para*-amino benzoic acid
NADP nicotinamide adenine dinucleotide phosphate
SAR Structure Activity Relationship
RNA ribonucleic acid
DNA deoxyribonucleic acid

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