CRC

HANDBOOK OF ANTIBIOTIC COMPOUNDS

Volume II
Macrocyclic Lactone (Lactam) Antibiotics

János Bérdy
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Macrocyclic Lactone (Lactam) Antibiotics

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FOREWORD

The antibiotics today probably represent the most important field of pharmaceutical specialization, providing the largest bulk of manufactured products, the greatest value in monetary terms, and the greatest single source of profit for the pharmaceutical and related industries. For practical purposes the field of antibiotics was born about 40 years ago with the explosive success of penicillin and, though there have been ups and downs in the assessment of promise and in attention to the field, it appears that it always rebounds from any temporary pessimistic interruption. Today the antibiotic field for research and development is once more firmly established and, of course, it continues to be bed-rock solid in medical application and commercial exploitation.

The growth of the field of antibiotics has been reflected not only in the number of scientists involved and in funding for research, development, and production facilities, but also in the discovery and description of new chemical entities which, in spite of inevitable duplication, accelerates with time and with the addition of increasing numbers of new agents each year. It is estimated that in 1977 about 400 new active agents were described and about 600 corrections or expansions of descriptions of previously announced agents were added to the open literature. Such growth imposes an even more difficult and demanding problem on the practicing scientist who requires reduction of the published descriptive data to tabular, recordable, and recallable form, so that meaningful comparisons may be made.

Early in the development of research and development programs in antibiotics and particularly in programs for the discovery of new agents, it became obvious that early recognition of duplication in a new active agent was essential to economic progress. Large antibiotic research groups have been continuously concerned with devising methods of discovering duplications or with the process of "dereplication" as it has come to be known. In the earliest procedures extensive use of biological activity and resistance patterns served to detect similarities, though such detection may also have led to the rejection of some useful antibiotic analogs. Now however, the great convenience of chemical and physical instrumental methods lays the groundwork for more specific identification and "dereplication".

Clearly, early classification of unknown substances may be of great help in eliminating undesirable duplication. However, another obvious benefit of methods based on chemical and physical comparisons lies in direction of the chemist along the paths of more likely concentration or purification of the unknown substance in his beaker. Early comparisons, if they can conveniently be made, can save the chemist endless hours of effort in his pursuit of a new agent which is usually found in complex mixtures in vanishingly small concentrations.

The author of this work has made the classification and characterization of the antibiotics not only his life work, but his avocation as well. By prodigious effort and endless toil, he has assembled a classification system characterizing more than 6000 substances in such form that exact comparisons may be made. In cooperation with the staff of the Chemotherapy Fermentation Laboratory and the Information Systems Group of the Frederick Cancer Research Center, he has committed his record to computer storage and this record is continually brought up-to-date. Thus comparisons can be made for identification purposes either by using the NCI and NIH computer facilities or by using this most convenient publication.

The antibiotic scientist has good reason to thank János Bérdy for this contribution. It will have real and durable impact on the economy of antibiotic research.

Asger F. Langlykke
Frederick Cancer Research Center
September 19, 1978

PREFACE

The principal objective of this Handbook is to provide in a concise form a readily accessible source of information on the field of antibiotics, specifically information about important physical, chemical, and biological characteristics of these compounds. The data included have been selected from the literature and arranged by computer.

Excluded from the Handbook are the synthetic chemotherapeutics, the chemically modified antibiotic derivatives (semisynthetic antibiotics), and the microbial metabolites, about which we have no information regarding their activity.

Due to the many different general characters and methods of investigation, it was justified to separate the material into two groups. The first one contains the most important group of antibiotic compounds produced by the fermentation of microbes, whereas the second group contains the antimicrobial and antitumor agents of other natural sources such as algae, higher plants, and animals. The latter group will appear in Volumes VIII and IX of this series.

For the most part the work is uncriticized; data and structures have been transcribed just as given in the literature, although attempts have been made to select the recent, more rational data to replace the obsolete. Considerable care has been taken to abstract the literature as deeply and as thoroughly as our resources permitted.

The main body of this work is a set of tables and cross indices, giving the physical, chemical, and biological properties of compounds. In order to make the listing of compounds more coherent, a background has been included, emphasizing general characteristics, structural features, occurrence, and practical importance of the antibiotics in a given group. The compounds are arranged according to families or series on the basis of their chemical structures. In the introduction to the chemical types the structural characterization of the compounds is given.

This book is mainly dedicated to providing a reference for chemists, microbiologists, and pharmacologists working in the research of new antibiotics. Moreover, it is felt that the present format of this book could well stand alone in satisfying particular needs in the entire field of antibiotic research, consisting of data of direct interest not only to scientists, but also to research chemists and biologists who are not experts in the subject and require a brief orientation to the material.

The lack of in vivo and detailed pharmacological, toxicological, or clinical data may appear limiting; however, these data are available in detail in numerous reviews and monographs referred to in our work. The Handbook will not provide a complete reference service, but will give all important and the latest references, as well as other information, thereby serving as a reference in breadth. I think this essentially mono-authored Handbook has certain advantages over the multi-authored reference texts in that it avoids unnecessary duplication as well as in the homogeneity of the format and presentation of the data.

The *Handbook of Antibiotic Compounds* owes its existence to the late Professor D. Perlman, University of Wisconsin, who suggested the usefulness of this type of compilation for wide-range publication; if there is any merit in the realization of this work, it is due to him and to Dr. A. F. Langlykke, Frederick Cancer Research Center, who provided assistance in organizing the computerization of the data. The data were put into a computer-searchable format during my half-year stay at NCI-Frederick Cancer Research Center, Frederick, Maryland, and I am greatly indebted to Drs. J. D. Douros and W. Payne for promoting my work.

I have to pay tribute to the late Dr. K. Magyar, Managing Director of the Antibiotic Division, Research Institute for Pharmaceutical Chemistry, Budapest, who initiated the compilation of data on antibiotics on the card file. I want to express my gratitude to Dr. T. Láng, Director of Research Institute for Pharmaceutical Chemistry, Buda-

pest, for encouraging my work. I am grateful to many colleagues in different parts of the world who have been most helpful by sending me reprints of their papers.

The formidable literature search associated with this compilation could not have been undertaken effectively without the kind assistance of the library staff of the Research Institute for Pharmaceutical Chemistry, Budapest. I am deeply indebted to Mrs. Koczka, Mrs. Kemenes (Budapest), and Dr. C. C. Chiu (Frederick) for their cooperation and technical assistance.

János Bérdy
Budapest
March 1978

INTRODUCTION

Antibiotics are chemical substances produced by metabolism of living organisms which have inhibitory activity against microorganisms and some other animal cells, e.g., tumor cells, or viruses. In the last few decades antibiotics have been increasingly exploited by workers in a number of disciplines. Their usefulness in agriculture as plant protecting agents or for the promotion of animal growth, in the food industry as preservatives, and in basic biochemical research as specific inhibitors claims considerable interest. Their use in the newer field of human and veterinary therapy is also very promising.

Most of these substances are produced by three distinct types of microorganisms, namely actinomycetes, fungi, and bacteria. They are the "classical" antibiotics. Some antibiotically active substances were isolated from other natural sources such as lichens, algae, higher plants, or animal organisms. They are also called, in a wider sense, antibiotics.

Antibiotics have antibacterial, antifungal, antiprotozoal, antitumor, or antiviral activities. Consequently, they can primarily be systematized according to their *origin* or *effectiveness*. It is also possible to classify them on the basis of *biosynthesis* or *mode of action*. Most of the monographs either classify the antibiotics according to the above criteria or list the compounds alphabetically. Nevertheless, today the most rational classification is unambiguously based on the *chemical structures* of the active compounds. However, none of the existing classification systems is universal; each has advantages and disadvantages.

The chemical structures of the antibiotics are one of the most diverse among natural products. They cover almost all types of organic molecules. Besides the common types of natural products (sugars, amino acids, polysaccharides, polypeptides, quinones, phenolics, fatty acids, terpenoids, steroids, flavonoids, alkaloids), numerous specific, unusual chemical structures such as macrolides, aminoglycosides, ansa-lactams, β-lactams, cyclopeptides, etc. which are very rare among other natural and synthetic products were recognized among antibiotics. No other area of the natural product field has confronted such novelty, variety, and complexity of structures.

Antibiotic chemistry has recently undergone explosive growth due to the advancement of various isolation (HPLC, TLC, CCD, ion-exchange) and structural determination (NMR, mass spectroscopic, and X-ray crystallographic) methods. The use of specialized microseparation methods and various instrumental techniques coupled with electron impact, chemical ionization, and field desorption mass spectrometry led to the rapid identification of numerous complicated molecular structures. Applications of computer-assisted X-ray crystallography, circular dichroism spectroscopy, and molecular magnetic resonance using Fourier-transform techniques, as well as the utilization of CMR for structural and conformational studies, resulted in the rapid determination of the stereostructure of compounds. Nowadays, more than half of the new antibiotics are published with complete structures, and more and more of the structures of "old compounds" (previously isolated) are also being determined.

During the last 10 to 15 years "new" antibiotics have been discovered at an ever-increasing rate. However, the efficiency of this research, namely the discovery of medically useful compounds in this field, has unambiguously declined. This is definitely compensated for by the great success of new semisynthetic antibiotics: cephalosporins, penicillins, aminoglycosides, and rifamycins.

Contrary to the above-mentioned declining tendency, antibiotic research all over the world provides more and more new compounds with diverse chemical structures and biological activities. In this decade at least 200 new antibiotics have been described

every year (this number in 1976 was more than 300) as a result of wide-spread and more sophisticated screening programs involving the use of automated methods.

Selective methods for the isolation and growth of rarely occurring or fastidious microorganisms, the extensive studies of marine organisms and higher plants, and the use of specific fermentation media, together with the application of new techniques, i.e., multipoint applicator, in the strain isolation processes have resulted in an increase in the number and types of microorganisms investigated. Wider variation in fermentation conditions, use of unique substrates, development of various biotransformations, and cometabolism fermentations are also developing possibilities to produce more new antibiotics. The present screening methods include a larger variety of bacterial, fungal, and viral pathogens, hypersensitive mutants, and tumor cell lines, as well as newer techniques for indicating specific chemical types (β-lactams, polyethers, some N-heterocycles) or specific activities (enzyme inhibition, antimetabolite effects). The animal models permit one to follow the in vivo activities of substances in partially purified preparations for an early indication of the compound's utility. Rapid identification of known compounds has also been improved. The various chromatographic and microphysical and chemical methods, using computerized data-base systems for comparisons of properties determined, have significantly enhanced this process.

On the other hand, a lot of well-known fermentation or other natural products (plant products), without known antimicrobial activity, proved to be effective as antibiotic agents or in other tests, i.e., anticancer, anticoccidial, antiviral, insecticide, ionophoretic, feed efficiency improvement, and enzyme inhibition. In addition, some compounds which were discovered on the basis of the above-mentioned specific effects proved to be active as antimicrobial or antitumor agents. As a result, more than 6000 natural products are known today which have antimicrobial, antitumor, or antiviral activity.

As the numer of antibiotics grew almost exponentially, the literature in this area became less and less perspicuous. It soon became evident that it is impossible to keep abreast with traditional documentation methods in the burgeoning literature. It has become an increasingly difficult task to maintain current awareness, especially in the field of nonmedical compounds with no or minimal practical or theoretical importance. In therapy, agriculture, and other fields about 100 antibiotics are used in practice, about which many excellent monographs and compendia exist. The literature on the other well-known antibiotics which exhibit some theoretically or structurally interesting properties is also extensive in various monographs and reviews. The acquisition of retrospective data on the other, less important antibiotics is particularly difficult and is partly alleviated by some literature reviews or monographs which quickly become outdated; they represent only a part of the whole in time and content. Knowledge about these antibiotics is widely scattered in numerous reviews, original papers, patents, congressional reports, and abstracts, from which it is very difficult to acquire retrospective data.

There is no comprehensive and up-to-date compilation which would include all of the antibiotic compounds. The most satisfactory handbook, Umezawa's *Index of Antibiotics,*[1] which may be up-to-date due to its recent continuous supplementation, unfortunately is limited to Actinomycetales antibiotics. The comprehensive compilations of Korzybsky et al.,[2] Shemyakin et al.,[3] and Miller[4] are excellent textbooks but they are outdated. The newest *Encyclopedia of Antibiotics* by Glasby[5] contains only a limited number of compounds and lacks critical aspects.

In 1960 a compilation of the important chemical, physical, and microbiological data of antibiotics was attempted, initiated by the card index file system at the Research Institute for Pharmaceutical Chemistry, Budapest, Hungary.[6,7] This project was primarily an aid for the early identification of new antibiotics isolated at this Institute by

means of comparing the characteristics of isolated unknown compounds with the data of known antibiotics. The scope and content as well as the expectations of the original card file system were changed during the years that passed, but the general principles of compilation remained unchanged. On the basis of this system a comprehensive chemical classification of antibiotics was proposed recently.[8,9]

The satisfactory and effective arrangement of the huge mass of data for wide-ranging application was evidently inconceivable without data processing using computers. The data which have been compiled continuously during the last 15 years at the Research Institute for Pharmaceutical Chemistry were put into computer-searchable form by cooperative efforts at the NCI-Frederick Cancer Research Center, Frederick, Maryland in 1975/76 to assist in the identification of newly isolated antibiotics.[10]

The interest so often expressed by various persons and establishments in this card file and in the computerized data base system led to the reorganization of the data compiled into the format presented here. A certain degree of editing was necessary to correct the chemical classification and clarify the structural correlations. The completion of the data bank with some introductory and explanatory material, structural formulae of compounds, and references was also required. This work has been undertaken and has hopefully removed the ambiguities and duplications, and it will increase the usefulness of this Handbook. To meet the requirements of computer programming, a few compromises were necessary, which we hope will affect neither the accessibility nor the usefulness of the data in any significant way.

This Handbook is not intended to be only a simple data bank. Although no interpretation of data has been included, some critical treatment has been made regarding the selection of certain data from the original literature, and the summarized discussion of general characteristics and structural features has been accomplished. The prime aim during the editing of this work was to unite the advances of textbooks and the comprehensive data books; therefore, a rapid visual retrieval of important information regarding a class of compounds has been emphasized before the mass of various data. Prior to the tabulation of individual compounds, which are arranged according to their chemical types, a short characterization of these compounds, including common physical, chemical, microbiological, and pharmacological properties, will be given. These introductions touch on the problems of biosynthesis, mechanism of action, and clinical or other applications. A short historical survey is sometimes also included.

The listing of data is followed by a set of cross indices designed to permit entry into the main body of the book for any of the several points of view. We sincerely hope this format will meet the needs of the scientific community.

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THE AUTHOR

János Bérdy, Ph.D., is a Senior Research Fellow of the Institute of Drug Research (formerly the Research Institute for Pharmaceutical Chemistry), Budapest.

Dr. Bérdy graduated in 1958 from Eötvös Loránd University, Budapest, and received his Ph.D. degree (summa cum laude) in organic chemistry in 1961 from Kossuth Lajos University, Debrecen. He was qualified as a Pharmaceutical Chemistry Engineer in 1969 at the Technical University, Budapest. He is a member of the Hungarian Chemical Society and many other scientific associations.

Dr. Bérdy's research interests include the isolation of new antibiotics, the development of industrial production, and classification and identification problems of antibiotics, as well as the theoretical problems of antibiotics research.

CONTRIBUTORS

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Dr. Aszalos graduated from Technical University of Budapest, Hungary with B.S. and M.S. degrees in chemical engineering and biochemistry. He received his Ph.D. in bioorganic chemistry from Technical University of Vienna, Austria in 1961. Subsequently, he was Post-Doctoral Fellow at Rutgers University.

Dr. Aszalos is a member of the American Chemical Society, Interscience Foundation, and New York Academy of Sciences. In the latter society, he served as Vice Chairman of the Biophysics Section in 1973 to 1975. Dr. Aszalos received, among other awards, the Austrian Industrial Research Award and the Army Post-Doctoral Research Award.

Dr. Aszalos has presented over 30 lectures at National and International meetings and published over 60 research papers and several review articles and chapters. His current major interest is antibiotics and enzymes in chemotherapy.

Melvin S. Bostian is Manager of the Information Systems Department at the Frederick Cancer Research Center, Frederick, Maryland. In his former position as Senior Programmer/Analyst he directed the conversion of the antibiotic compound data base to machine-readable form and designed the data base system used for the conversion.

Mr. Bostian has a degree in mathematics and specializes in the analysis of biomedical data generated by laboratory instruments.

Karen L. McNitt is a Senior Programmer at the Frederick Cancer Research Center, Frederick, Maryland. In this capacity she was responsible for the programming and implementation of the data base system used to collect the information on the antibiotic compounds. She also directed the data entry and validation of the compound information.

Ms. McNitt has a degree in computer science and specializes in the analysis of scientific data.

TABLE OF CONTENTS

Indices

SELECTION OF COMPOUNDS INCLUDED

The guiding principles in selection of material to include in the Handbook are as follows:

1. The compounds listed in this book are derived from the whole living world, including all types of prokaryotes and eukaryotes, namely microorganisms, lichens, fungi, mosses, algae, higher plants, protozoa, molluscs, sponges, worms, insects, and vertebrates.
2. An essential requirement is the in vitro, or perhaps only in vivo, antimicrobial (at least at a concentration of 500 $\mu g/m\ell$) activity or some antitumor, cytotoxic, antiprotozoal, or antiviral (antiphage) effect, regardless that this activity is observable in a specific medium or circumstance only.
3. Every chemical entity, e.g., stereoisomer, forms a separate entry. Components of antibiotic complexes, when they are separated and when some of their properties are determined, are listed individually.
4. The unresolved antibiotic complexes (components are detected by chromatography only) form a single entry. These complexes in many instances differ only by proportions of the same components (e.g., streptothricin or heptaene antibiotic complexes) and are designated by their own name.
5. Crude antibiotic extracts, characterized by some properties such as UV spectra, stability, or others, possessing interesting activity, especially those originating from uncommon sources, also form separate entries.
6. Derivatives of antibiotics made by chemical methods are not listed, unless they are produced by biosynthetic or enzymatic methods also. The products of directed and conversion-type fermentations or mutational biosynthetic processes employing precursor-like compounds incorporated into the active products are included.
7. Alkaloids, stress metabolites, insecticides, anthelminthics with some antimicrobial or antitumor activity, and mycotoxins without significant antimicrobial effect but with high (cyto)toxicity are included. Phytotoxins, enzyme inhibitors, plant growth regulators, animal growth promoters, and other physiologically active metabolites without any antimicrobial, antitumor, antiviral, or cytotoxic activities are excluded from this Handbook.

Consequently this work includes all antibiotically active natural products (antibacterial, antifungal, antiprotozoal, antitumor, antiviral, and occasionally anthelminthic or insecticide agents) discovered, having one or more of the characteristic properties described, although many compounds have not been isolated in pure state and their structures are unknown. After all, the number of entries is not exactly identical with the number of presently existing antibiotic compounds. It is very likely that numerous identities are undetermined and numerous components are unresolved yet.

This Handbook series contains more than 6000 entries, of which about 4500 represent the antibiotics prepared by the fermentation of microorganisms. Approximately 3000 antibiotics are derived from different *Actinomycetales* species, of which about 88 to 90% originate from *Streptomyces* species. It must be noted that in this decade about 20% of *Actinomycetales* antibiotics were derived from non-*Streptomyces* species. Almost 1000 antibiotics come from different fungi, and 500 to 600 come from various bacterial strains (including *Pseudomonales*).

The total number of antibiotics with known chemical structure is about 2500 (nearly 2000 are microbial antibiotics), and about 400 compounds are synthetized. Additionally, there are about 1500 antibiotics about which we have satisfactory knowledge re-

garding their chemical structure (degradation products, skeleton, principal moieties, etc.). Numerous compounds might be classified on the basis of physical, chemical, and microbiological similarities (e.g., cross-resistance) to the known type compounds. After all, about 85% of the antibiotics have more or less known chemical structural features.

HOW TO USE THIS HANDBOOK

Although this Handbook details vastly different types of compounds, an effort has been made to present the material according to a general format. All compounds (antibiotic entries) have a specific *compound number*, which serves as a title to a group of entries and as a unique numerical identifier. This number consists of two parts. The first element is, in fact, identical to our previously reported[9] *antibiotic code number* (without the separation by commas), which is characteristic of the chemical type of the compound. The second element of the compound number, separated by a hyphen, is a simple *sequence number* assigned individually to any compound according to its addition to the data base. The complete compound number provides access to that compound through the indices for any compound for which no name is listed.

Most of the compounds in this Handbook have been arranged according to our previously reported, continuously revised and completed chemical classification system.[9] This system follows the formal chemical classification but not in the strictest sense. Since this is merely a superficial classification, taking into account some biogenetic and other points of view, it is obvious that the same compound may belong to more than one class. To avoid these duplications, we selected nine basic chemical moieties (principal constituents) most characteristic of the compound, and the primary classification was done accordingly.

Assignment to antibiotic families is performed according to the following principal constituents

1. Sugar
2. Macrocyclic lactone ring (more than eight members)
3. Quinone (or quinone-like) skeleton
4. Amino acid
5. Nitrogen-containing heterocyclic system
6. Oxygen-containing heterocyclic system
7. Alicyclic skeleton
8. Aromatic skeleton
9. Aliphatic chain

The construction of some more or less arbitrary class of compounds seems to be justified. The formation of a family for the macrocyclic lactones and the separation of the quinones and quinone-like compounds from the aromatic (mainly phenolics) compounds was unavoidable. Beyond their frequent occurrence and great importance, their complete new biological properties, different from those of normal aliphatic and aromatic antibiotics, justifies listing them as a separate family of antibiotics. Moreover, the limitation of the carbohydrate (sugar) family of compounds to the mostly sugar-containing structures, excluding most of the glycosides (macrolide-, anthracycline-, peptide-, purine-pyrimidine-, and aromatic-glycosides), which are classified on the basis of their diversified aglycones, surely contributes to the logical classification. In the course of detailed systemization, some further arbitrary decisions became necessary. The grouping of streptothricines among the carbohydrates was permitted because of their properties and activities similar to other water-soluble basic antibiotics. The tetracyclines are grouped together with anthracycline quinones in the family of quinone compounds. Again, all glutarimides were grouped together as alicyclic compounds, rather than grouping them as heterocyclic, aromatic (actiphenol), or aliphatic (streptimidone) compounds. Alkaloids having antimicrobial or antitumor activity (except steroid alkaloids) were grouped as N-heterocyclic compounds. The terpenes were distributed according to their structures into the alicyclic, aromatic, or aliphatic families. The skeleton of this system includes only the families, subfamilies, and groups shown in Table 1.

Table 1

CLASSIFICATION OF ANTIBIOTIC COMPOUNDS

AN	Family, subfamily, group	Important representatives
1	Carbohydrate antibiotics	
11	Pure saccharides	
111	Mono and oligosaccharides	Streptozotocin, nojirimycin
112	Polysaccharides	Glucans, soedomycin
12	Aminoglycoside antibiotics	
121	Streptamine derivatives	Streptomycins, bluensomycin
122	2-Deoxystreptamine derivatives	Neomycin, gentamicin, etc.
123	Inositol-inoseamine derivatives	Kasugamycin, validamycin
124	Other aminocyclitols	Fortimicin
125	Aminohexitols	Sorbistin
13	Other glycosides	
131	Streptothricin group	Streptolin, racemomycin
132	Glycopeptides, C-glycosides	Vancomycin, chromomycin
14	Sugar derivatives	
141	Sugar esters, amides	Everninomicin, lincomycin
142	Sugar lipids	Moenomycin, labilomycin
2	Macrocyclic lactone (lactam) antibiotics	
21	Macrolide antibiotics	
211	Small (12-, 14-membered) macrolide	Erythromycin, picromycin
212	16-membered macrolides	Leucomycin, tylosin
213	Other macrolides	Borrelidin, lankacidin
22	Polyene antibiotics	
221	Trienes	Mycotrienine, proticin
222	Tetraenes	Nystatin, rimocidin
223	Pentaenes	Eurocidin, filipin
224	Hexaenes	Candihexin, mediocidin
225	Heptaenes	Candicidin, amphotericin B
226	Octaenes	Ochramycin
227	Oxo-polyenes	Flavofungin, dermostatin
228	Mixed polyenes	Tetrahexin
23	Macrocyclic lactone antibiotics	
231	Macrolide-like antibiotics	Oligomycin, primycin
232	Simple lactones	Albocyclin, A-26771 B
233	Dilactones	Antimycin, boromycin
234	Polylactones	Nonactin, tetranactin
235	Condensed macrolactones	Chlorothricin, cytochalasin
24	Macrolactam antibiotics	
241	Ansamycin group	Rifamycin, tolypomycin
242	Ansa-lactams (maytanosides)	Ansamitocin, maytansin
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332	Condensed benzoquinones	Mitomycin, streptonigrin
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342	Other quinone-like compounds	Epoxidon, aeroplysinin