

CRC

HANDBOOK OF ANTIBIOTIC COMPOUNDS

Volume XII
Antibiotics from Higher
Forms of Life

János Bérdy
Adorjan Aszalos
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CRC PRESS

CRC Handbook of Antibiotic Compounds

Volume XII Antibiotics from Higher Forms of Life

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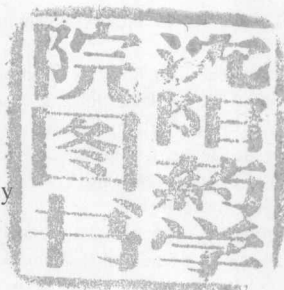
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Y076278



CRC Press, Inc.
Boca Raton, Florida

Library of Congress Cataloging in Publication Data

(Revised for volumes 11 and 12)

Bérdy, János.

CRC Handbook of antibiotic compounds.

Title on spine: Handbook of antibiotic compounds.

Includes bibliographical references and indexes.

Contents: v. 1. Carbohydrate antibiotics. — v. 2.

Macrocyclic lactone (lactam) antibiotics. — [etc.]—

v. 11. Microbial metabolites. 2.v. — v.12. Antibiotics
from higher forms of life.

1. Antibiotics—Handbooks, manuals, etc. 2. Chemistry,

Pharmaceutical—Handbooks, manuals, etc. 3. Antibiotics.

I. Handbook of antibiotic compounds. [DNLM:

QV 350.3 H236]

RS431.A6B47 615'.329 78-31428

ISBN 0-8493-3450-0 (set)

ISBN 0-8493-3465-9 (Volume XII)

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Direct all inquiries to CRC Press, Inc., 2000 Corporate Blvd., N.W., Boca Raton, Florida, 33431.

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International Standard Book Number 0-8493-3450-0 (Complete Set)

International Standard Book Number 0-8493-3465-9 (Volume XII)

Library of Congress Card Number 78-31428

Printed in the United States

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Volume I
Carbohydrate Antibiotics

Volume II
Macrocyclic Lactone (Lactam)
Antibiotics

Volume III
Quinone and Similar Antibiotics

Volume IV Part 1
Amino Acid and Peptide
Antibiotics

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Volume XII
Antibiotics from Higher Forms of Life

HANDBOOK OF ANTIBIOTIC COMPOUNDS, VOLUME XII

INTRODUCTION

During the years that have passed since the publication of the Main Volumes (I through X) of the *CRC Handbook of Antibiotic Compounds*, about 2200 new antibiotics were published in the scientific literature. The Main Volumes covered 6700 antibiotic compounds (according to their sequence numbers), while these volumes cover compounds with sequence numbers 6700 through 8872.

In this cumulative volume about 1000 new compounds isolated from higher forms of life (higher plants, animal organisms), which were published mainly during 1979 to 1981, are collected. In the same period, numerous important additional results appeared in the literature for about 700 already known (old) antibiotics. These new data are included in the first section of this volume, while the novel compounds will be listed in the second section.

Some recently recognized new types of chemical structures and the newly discovered or modified structures of old ones require the completion of the Antibiotic Classification System. Among new entries some 700 compounds have known structures and out of these about 50 have new types of structures.

In most cases the changes in the Antibiotic Numbers are minimal, such as the more precise classification within the antibiotic families or groups, but occasionally several entries have been moved and now appear under a new family or group. For the newly discovered chemical structures, including the plant and animal products also, more than 50 new Antibiotic Code Numbers were constructed to complete the classification system. These changes are summarized in Table 1, which includes the new Antibiotic Numbers of the Plant and Animal products (marked by asterisks).

János Bérdy
Budapest
March, 1982

Table 1
NEW ANTIBIOTIC TYPES

AN	CT	Representative
12224	Aminoglycoside	S-11-A, SU-2
12225	Aminoglycoside, Combimicin t.	Combimicins, I-SK-A1
1235	Aminoglycoside l.	X-14847
21224	Macrolide	Mycinamycin II
21234	Macrolide	Mycinamycin IV
2324	Macrolactone	Izumenolide
2333	Dilactone, Elaiophillin t.	Azalomycin B
23513	Macrolactone, Tetrocarcin t.	Antlermicin, Kijanmycin
23514*	Macrolactone	Latrunculins
2355	Macrolactone, Nargenicin t.	Nargenicins, Nodusmicin
3124	Anthracyclinone l.	Tetracenomycins
3138	Anthraquinone l.	Viocrystin
32227	Naphtoquinone derivatives	Guanacin
32228		
3315	Benzoquinone derivatives	Sarubicin, U-58431
3325	Saframycin t.	Saframycins, Chloracarcin
3326	Dnactin t.	Dnactins
34133	Semiquinone	Cercosporin
3414*	Semiquinone	Obtusaquinone
41125	Amino Acid	Forphenicine
41216	Beta lactam, Monobactam t.	Monobactams, Sulfazecin
4214	Oligopeptide l., Indole derivatives	CC-1065, Rachelmycin
4227	Peptide, Leucinamycin t.	P-168, Trichopolins
4426	Peptolide	A-21978
4445	Peptolide	Lipopeptins
4537	Cell-Wall Component	CP, 60-F, CW-5
51134	Tetramic acid derivatives, Oligopeptide l.	Capsimycin, Ikarugamycin
51223	Pyridone derivatives	G-1549, BN-227
5141	Azepine derivatives	Ophiocordin
5224*	N-Heterocyclic derivatives	Azaskatole, Spinaceamine
5235	Indole glycoside	Sydomyacin
5236		Oxanosine
5311*	Alkaloid (Terpene alkaloids)	Norcassidine, aconitine
5312*	Alkaloid (Colchicine t.)	Demecolcine, colchicine
5313*	Alkaloid (Aliphatic alkaloids)	Sphaerophysine
5321*	Alkaloid (Pyrrole, imidazole derivative)	Chacsine
5322*	Alkaloid (Pyridine, piperidine derivative)	Anabasin, Visanin
5331*	Alkaloid (Harmane t.)	Gramine, Chanthin-6-one
5332*	Alkaloid (Ellipticine t.)	Olivacine, guatambuine
5333*	Alkaloid (Ibogaïne alkaloids)	Coronaridin, apparicine
5334*	Alkaloid (Vinca alkaloids)	Vinchristine, gabunine
5335*	Alkaloid (Other indole alkaloids)	Caracurine
5341*	Alkaloid (Bisbenzylisoquinoline t.)	Tetradrine, curine
5342*	Alkaloid (Benzphenanthridine t.)	Nitidine, sanguinarine
5343*	Alkaloid (Protoberberin t.)	Berberin, coralyne
5344*	Alkaloid (Glaucine t.)	Liriodenine, annonaine
5345*	Alkaloid (Other isoquinoline alkaloids)	Emetine, protopine
5346*	Alkaloid (Quinoline t.)	Quinine, Casimiroin
534*	Alkaloid	Vasicin, febrifugin
5351*	Alkaloid (Pyrrolizidine t.)	Indicine, senecionine
5352*	Alkaloid (Quinolizidine t.)	Tylophorine, lycorine
5353*	Alkaloid (Cephalotaxine t.)	Harringtonine
5354*	Alkaloid (Camptothecin t.)	Camptothecins

Table 1 (continued)
NEW ANTIBIOTIC TYPES

AN	CT	Representative
5355*	Alkaloid	Sparteine, matrine
5361*	Alkaloid (O-heterocyclic alkaloids)	Acronycin, pteleatin
5362*	Alkaloid (S-heterocyclic alkaloids)	Gerrardin, cassipourine
5371*	Alkaloid	
5431	Thiazol deriv.	Myxothiazol
5432*		Cycloalliin
6213*		Pederin
6234		Diplosporin
6316*	Flavan t.	7-Hydroxyflavan
6346*	Chromane	2,2-Dimethylchromane
6351*		Demethoxyageratochomen
6352*		Lathodoratin
6417*		Malyngolide
65111	Polyether, Monensin t.	Monensins, Laidlomycin
65112	Polyether	CP-47433
6523	Polyether	M-139603
72143*	Sesterterpene	Desacetylscalaradial
7216*	Carotenoides	Retinal, Retinoids
73114*	Limonoid	Aphanostatin
73135*	Physalin t.	Physalin-B
7324*	Limonoid	Hispidins
8313*	Tropolone derivative	Hainanolide
8412	Aromatic ether	
8413*	Aromatic ether	
84221	Glycosidic antibiotic, Chartreusin t.	Chartreusin, G-261-B
84222	Glycosidic antibiotic, Chartreusin l.	Gilvocarcins, Toromycin
8424	Glycosidic antibiotic, Trioxacarcin t.	Trioxacarcins
8425*		Amygdalin

Deleted Antibiotic Type

4413 ^a	Peptide l., Taitomycin t.	Taitomycin, RP-9671
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^a Compounds moved to type: 43211

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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.

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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.

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

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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 $\mu\text{g}/\text{ml}$) 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, anthelmintics 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 anthelmintic 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 synthesized. 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 reported⁹ *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	Poly lactones	Nonactin, tetranactin
235	Condensed macrolactones	Chlorothricin, cytochalasin
24	Macrolactam antibiotics	
241	Ansamycin group	Rifamycin, tolypomycin
242	Ansa-lactams (maytanosides)	Ansamitocin, maytansin
243	Lactone-lactams	Viridenomycin
3	Quinone and similar antibiotics	
31	Tetracyclic compounds and anthraquinones	
311	Tetracyclines	Tetracycline, chlorotetracycline
312	Anthracyclines	Adriamycin, rhodomycin
313	Anthraquinone derivatives	Ayamycin, hedamycin
32	Naphtoquinones	
321	Simple naphtoquinones	Javanicin, juglomycin
322	Condensed naphtoquinones	Granaticin, rubromycin
33	Benzoquinones	
331	Simple benzoquinones	Spinulosin, oosporein
332	Condensed benzoquinones	Mitomycin, streptonigrin
34	Quinone-like compounds	
341	Semiquinones	Resistomycin, maytenin
342	Other quinone-like compounds	Epoixon, aeroplysin

Table 1 (continued)
CLASSIFICATION OF ANTIBIOTIC COMPOUNDS

AN	Family, subfamily, group	Important representatives
4	Amino acid, peptide antibiotics	
41	Amino acid derivatives	
411	Simple amino acids	Cycloserine, alanosin
412	Amino acid derivatives	Penicillin, aureothricin
413	Diketopiperazine derivatives	Glitoxin, chaetocin
42	Homopeptides	
421	Oligopeptides	Netropsin, negamycin
422	Linear homopeptides	Gramicidin, alamethicin
423	Cyclic homopeptides	Tyrocidin, bacitracin, viomycin
43	Heteromer peptides	
431	Cyclic lipopeptides	Polymyxin, amphomycin, iturin
432	Thiapeptides	Thiostrepton, althiamycin
433	Chelate-forming peptides	Bleomycin, sideromycins
44	Peptolides	
441	Chromopeptolides	Actinomycin, quinomycin
442	Lipopeptolides	Enduracidin, surfactin
443	Heteropeptolides	Etamycin, ostreogrycin B
444	Simple peptolides	Telomycin, grisellimycin
445	Depsipeptides	Valinomycin, ostreogrycin A
45	Macromolecular peptides	
451	Polypeptides	Nisin, licheniformin
452	Proteins	Neocarzinostatin, pacibilin
453	Proteids (chromo-, gluco-, nucleo-)	Asparaginase, bacteriocins
5	Nitrogen (or S) containing heterocyclic antibiotics	
51	Single heterocycles	
511	Five-membered ring	Pyrrolnitrin, azomycin
512	Six-membered ring	Mocimycin, abikoviromycin
513	Pyrimidine glycosides	Amicetin, polyoxin, blasticidins
52	Condensed heterocycles	
521	Aromatic fused compounds	Albofungin, pyocyanine
522	Fused heterocycles	Anthramycin, fervenulin
523	Purine glycosides	Puromycin, tubercidin
53	Alkaloids	
54	S-containing heterocycles	
6	Oxygen-containing heterocyclic antibiotics	
61	Furan derivatives	
611	Simple furans	Botriodiplodin
612	Condensed furans	Usnic acid, aflatoxins
613	Benzofurans	Furasterin
62	Pyran derivatives	
621	Simple pyrans	Aucubin, plumericin
622	α -Pyrones	Phomalactone, asperline
623	γ -Pyrones	Distacin, kojic acid
63	Benzopyran derivatives	
631	Flavonoids	Chloroflavonin, eupafolin
632	Isoflavonoids	Pisatin, pterocarpan
633	Neoflavones	Dalbergione
634	Other benzopyran derivatives	Radicinin, morellin
64	Small lactones	
641	Simple lactones	Acetomycin, penicillic acid
642	Condensed lactones (coumarins)	Actinobolin, mycophenolic acid

Table 1 (continued)
CLASSIFICATION OF ANTIBIOTIC COMPOUNDS

AN	Family, subfamily, group	Important representatives
65	Polyether antibiotics	
651	Saturated polyethers	Monensin, nigericin
652	Unsaturated polyethers	Narasin, salinomycin
653	Aromatic polyethers	Lasalocid
654	Polyether-like antibiotics	A-23187
7	Alicyclic antibiotics	
71	Cycloalkane derivatives	
711	Cyclopentane derivatives	Sarcomycin, pentanenomycin
712	Cyclohexane derivatives	Fumagillin, ketomycin
713	Glutarimide antibiotics	Cycloheximide, streptimidone
72	Small terpenes	
721	Simple mono, sesqui, and diterpenes	Coriolin, cyathin, siccanin
722	Terpene lactones	Vernolepin, enmein, quassin
73	Oligoterpenes	
731	Steroids	Fusidic acid, viridin
732	Triterpenes	Saponins, cardenolides, etc.
733	Terpenoides (Scirpene derivatives)	Trichotecin, verrucarins
8	Aromatic antibiotics	
81	Benzene derivatives	
811	Monocyclic derivatives	Flavipin, versicolin
812	Alkyl-benzene derivatives	Chloramphenicol, ascochlorin
813	Polycyclic benzene derivatives	Xanthocyllin, alternariol
82	Condensed aromatic compounds	
821	Spiro compounds (Grisans)	Griseofulvin, geodin
822	Naphtalene derivatives	Gossypol, carzinophyllin
823	Anthracene-phenantrene derivatives	Thermorubin, orchinol
83	Nonbenzoid aromatic compounds	
831	Tropolones	Puberulic acid
832	Azulene	Lactaroviolin
84	Other aromatic derivatives	
841	Aromatic ethers	Zinninol, bifuhalol
842	Glycosidic antibiotics	Novobiocin, hygromycin A
843	Aromatic esters	Nidulin, phlorizin
9	Aliphatic antibiotics	
91	Alkane derivatives	
911	Saturated alkane derivatives	Elaiomycin, lipoxamycin
912	Polyines	Marasin, mycomycin
92	Carboxylic acid derivatives	
921	Small carboxylic acid derivatives	Enteromycin, cellocidin
922	Fatty acid derivatives	Eulicin, myriocin
93	Sulfur- and phosphor-containing aliphatic compounds	
931	S-containing compounds	Allicin, fluopsin
932	P-containing compounds	Phosphonomycin

The most characteristic feature of this classification system is the utilization of the previously mentioned *antibiotic code number* (AN). This number carries information about the structure or structural type of the compound. The first member of this five-digit number indicates the nine large antibiotic families to which the compound belongs. The second, third, fourth, and occasionally the fifth digits indicate the subfamilies, groups, types, and subtypes, respectively, e.g., 12222 represents the gentamicin

subtype among the 4,5-disubstituted (1222) deoxystreptamine (122) derivatives of aminoglycoside antibiotics (12) in the family of carbohydrate antibiotics (1). The less well-known agents receive only the first few figures, indicating the large group to where the compound can surely be ranged. Thus, 12000 indicates an aminoglycoside antibiotic with unknown type. The zero means lack of information; thus the compounds listed throughout the tables without the antibiotic code number (00000) are those for which structural information has not been established as yet. They represent about 600 (10% of all) compounds which are listed in separate volume(s) divided into sections according to type of producing organisms, namely, the compounds produced by Actinomycetales, fungi, and bacteria as well as plants and animals have been arranged alphabetically according to their producing genus and species.

Another identifier, *chemical type*, is a short description of the structural type (aminoglycoside, ansamycin, purine glycoside, etc.) and/or the specification of a peculiar type (neomycin type, oligomycin type, cycloheximide type, etc.) of compound. While the compound always bears one antibiotic code number, sometimes two designations are attached to it. One is characteristic of the larger group, while the other refers to the specific type, e.g., aminoglycoside, neomycin type. Occasionally a compound may bear the antibiotic code number without any chemical type designation. This usually belongs to the newer groups or types of compounds with only a few representatives.

In some cases compounds have been included in the most probable group, even though insufficient data are available to verify the final grouping, hoping that these entries will promote further work in a class of these compounds. Close chemical and microbiological properties will certainly suggest to investigators to do further work on these compounds.

SELECTION OF DATA INCLUDED

The data included in this book were determined by the content of our original card index file system. The selection of data for maintenance in the file system and in the computerized data bank was decided on the basis of their usefulness in screening work searching for new antibiotics. Consequently, the properties which are characteristic for the crude substances or active extracts, isolated in the early phase of research, were emphasized. This is one reason why some properties such as melting points or NMR spectral data are excluded.

The following data, when available, are included for each antibiotic compound:

1. Name, alternate names, and trade name	Name
2. Identical with	Identical
3. Producing organism(s)	PO
4. Chemical type, chemical nature	CT
5. Molecular formula	Formula
6. Elemental analysis	EA
7. Molecular/equivalent weight	MW/EW
8. Color, appearance: Physical characteristics	PC
9. Optical rotation	OR
10. Ultraviolet spectra, solvent(s)	UV
11. Solubility	
Good	SOL-Good
Fair	SOL-Fair
Poor	SOL-Poor
12. Qualitative chemical reactions	Qual