

THE  
MOLECULAR  
BASIS  
OF  
ANTIBIOTIC  
ACTION

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SECOND  
EDITION

# The Molecular Basis of Antibiotic Action

SECOND EDITION

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# Preface to the First Edition

In the thirty years which have elapsed since the Second World War there have been many great achievements in medicine and the biological sciences, among which one of the most impressive has been the discovery and development of antibiotics. It is commonplace to remark that antibiotics have revolutionized the treatment of infectious disease, and perhaps equally so to point to their contribution as tools for basic biological research. In both these areas, the remarkable specificity of action of antibiotics has been harnessed to meet a need, for antibiotics have indeed fulfilled the role of 'magic bullets' as originally conceived by Ehrlich. In chemotherapy the magic of the bullets is manifested in selective attack against pathogenic microorganisms. In biological research the magic is no less evident in the use of antibiotics as agents endowed with the capacity to interfere with one or a small number of processes in the complex, integrated reactions of cell metabolism. Small wonder that a knowledge of antibiotic action has become indispensable to the training of medical and biological students.

Most of the antibiotics were discovered before any detailed knowledge was available of the biochemistry underlying their effects. Much of the early work was therefore directed towards uncovering the general sites of action. With the birth and rapid growth of molecular biology it was natural that attempts should be made to elucidate the molecular basis of antibiotic selectivity. Already much has been learned, and it is equally clear that many more important advances lie just around the corner. This book represents an attempt to summarize and take stock of the position to date. There is more to this endeavour than mere curiosity or academic exercise, for it is an axiom of our age that deeper understanding of fundamental biological processes must ultimately be applicable in the service of mankind. In this case a part of the aim must be to improve the efficacy of chemotherapy in medical practice, the philosophy being that a thorough understanding of the nature of such selectivity as is shown by agents known at the present time will help to delineate sites and mechanisms through which selectivity may be achieved, and that, armed with this information, new drugs may be developed to combat disease. In short, the study of the molecular basis of antibiotic action must help to pave the way for a rational approach to

chemotherapy. In this light we have allowed ourselves to indulge in a little reflection and speculation at the beginning and end of the book, including topics such as drug resistance which might not *a priori* be considered relevant to our title. Similarly, we have not slavishly restricted our attention to antibiotics in the strict sense, i.e. substances of natural (microbial) origin, for in several places we felt that the topic could only be satisfactorily treated in context by including discussion of synthetic antimicrobial drugs, and occasionally even substances which are not chemotherapeutic agents at all.

We make no excuses for choosing to write at the present time: we are all too conscious that, if we were to wait a little longer, there would be many more exciting developments to record and the story would be that much more complete. Such will always be the case to some extent, and at the same time the volume of pertinent literature will increase in its relentlessly exponential fashion, requiring a commensurate increase in the number and/or capacity of authors to deal with it. It could fairly be claimed that we are already too late to hope to deal adequately with the relevant material, and to this contention we would be forced to bow. We cannot know everything, and in the course of writing we have become painfully aware of the enormity of the task and our inadequacy to cope with it as we should like. On the other side of the coin, we have been privileged to consult manuscripts and pre-publication material provided by a number of authors, whose interest and help we gratefully acknowledge, and we have occasionally taken the liberty of including unpublished information obtained in our own and other laboratories. In these instances acknowledgment is given in the text. To cope with the potentially enormous number of references worthy of citation we have, in general, adopted the policy of relying on recent reviews to cover the earlier literature and have tried to concentrate on providing references to the most recent and up-to-date original papers. Very often we have reluctantly decided not to give a direct reference to a classic paper when it is treated in reviews. Any errors, omissions, misinterpretations or other infelicities are of course our own responsibility. In attempting to provide a reasonably comprehensive coverage of the field we have, naturally, each written as individuals on those areas in which we 'specialize'. If, as a result, we have failed to achieve uniformity of style and have afforded a ready means of identifying the writers of particular chapters, we shall not complain if we are each held responsible for our own words.

One of our major problems was to decide how much background biochemistry to include. We have not always been consistent but, in general, have assumed knowledge of basic biochemical matters and, where possible, referred the reader to recent reviews for detailed treatment.

Finally, we should like to acknowledge our debt to colleagues in many laboratories, to students, visitors and correspondents who have discussed, argued, criticized and so helped the development of our ideas over the years.

We also want to thank Mrs B. Gill for her invaluable help in assembling and preparing the manuscript.

*Cambridge, August 1971*

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E.C.

P.E.R.

M.H.R.

M.J.W.

# Preface to the Second Edition

In the nine years that have elapsed since the first edition was written there have, inevitably, been many advances in our knowledge of the ways in which antibiotics work and a vast increase in the number of papers published on relevant topics. New antibiotics have been isolated and characterized. We have not attempted to produce a comprehensive guide to all the antibiotics that have been described but have concentrated on those which have been studied in sufficient detail to throw light on their action at a molecular level. In general, advances of recent years have not revealed totally new principles of action but have led to a greater depth of understanding of the interplay between antibiotic structure and the properties of the cellular target. Consequently we have retained the same format as that adopted in the first edition but the new developments have meant that, with the exception of Chapter 1 and parts of Chapter 2, the greater part of the book has been rewritten. As before we have included synthetic drugs where consideration of these has aided our understanding of antibiotic action but, generally, not otherwise.

Again we would like to express our gratitude to many colleagues for the advice, criticisms, and discussions they have provided and especially to those who have allowed us to see and quote papers in preparation for publication. We also want to thank Mrs M. Cumpsty for her invaluable assistance in preparing and collecting the manuscript and particularly for rescuing us from a series of crises in the final stages of that preparation.

*Cambridge, May 1980*

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# Contents

<b>1. The concept</b>	<b>1</b>
A. Introduction	1
B. Arsenical Drugs	4
B.1. The development of arsenical drugs	4
B.2. Mode of action	6
C. Sulphonamide drugs	8
C.1. Discovery of sulphanilamide	8
C.2. Relationship to <i>p</i> -aminobenzoic acid	9
C.3. Structure and activity	12
C.4. Mode of action	15
C.5. Nature of selectivity	16
D. Antimetabolites	17
D.1. Early work on antimetabolites	17
D.2. Lethal synthesis	19
References	20
 <b>2. Biochemical targets for drug action</b>	 <b>23</b>
A. Enzymes	24
A.1. Enzyme structure and activity	24
A.2. Action at the active centre; substrate competition	25
A.3. Inhibition at the active centre; cofactor inhibition	32
A.4. Allosteric inhibition and 'false feedback' inhibitors	33
A.5. Exo-inhibitors: inhibitors acting outside the active centre	34
A.6. 'Double blockade'	34
A.7. Transition state inhibitors	35
B. Information transfer	36
B.1. Synthesis of macromolecules	36
B.2. Nucleic acids	37
B.3. Ribosomes	38
B.4. Repression	39



C.	Exclusion and protection mechanisms . . . . .	40
C.1.	Impairment of membranes . . . . .	40
C.2.	Impairment of function or synthesis of cell wall . . . . .	41
D.	Selectivity of action . . . . .	42
D.1.	Bactericidal and bacteriostatic agents . . . . .	42
D.2.	Selective advantage based on the absence of a target from the host . . . . .	43
D.3.	Selection based on homologous targets having different properties . . . . .	44
D.4.	Selective action based on permeability differences . . . . .	45
D.5.	Other grounds for selective action . . . . .	46
	References . . . . .	47

### 3. Inhibitors of bacterial and fungal cell wall synthesis 49

A.	Introduction . . . . .	49
A.1.	Composition of bacterial cell walls . . . . .	49
A.2.	Structure of cell wall polymers . . . . .	51
A.3.	Synthesis of peptidoglycan . . . . .	56
B.	Inhibition of biosynthetic enzymes . . . . .	63
B.1.	Fosfomycin (Phosphonomycin, <i>cis</i> -1,2-epoxypropylphosphonic acid) . . . . .	63
B.2.	D-cycloserine and <i>O</i> -carbamyl-D-serine . . . . .	65
B.2.a.	Biochemical investigations . . . . .	65
B.2.b.	Structure/activity relationships . . . . .	66
B.2.c.	Molecular basis of action . . . . .	67
B.2.d.	Resistance to D-cycloserine . . . . .	73
B.3.	Alafosfalin (Alaphosphin, L-alanyl-L-1-aminoethylphosphonic acid) . . . . .	74
B.4.	Tunicamycin . . . . .	76
B.5.	(i) Diumycin, moenomycin, prasinomycin, macarbomycin, 11837 RP; (ii) Janiemycin, enduracidin . . . . .	78
B.6.	$\beta$ -Lactam antibiotics—penicillins and cephalosporins . . . . .	79
B.6.a.	Early biochemical investigations . . . . .	79
B.6.b.	Penicillin-sensitive enzymes and penicillin-binding proteins . . . . .	83
B.6.b.i.	Penicillin-sensitive enzymes: transpeptidases, D,D-carboxypeptidases, L,D-carboxypeptidases/transpeptidases and endopeptidases . . . . .	83
B.6.b.ii.	The binding of penicillin . . . . .	86

B.6.b.iii.	Purification and activities of penicillin-binding proteins . . . . .	87
B.6.b.iv.	Function of penicillin-binding proteins . . . . .	92
B.6.b.v.	Identification of lethal target . . . . .	100
B.6.c.	Interaction of $\beta$ -lactam antibiotics and peptide substrates with penicillin-sensitive enzymes . . . . .	103
B.6.c.i.	Kinetic studies . . . . .	103
B.6.c.ii.	Chemical nature of the penicillin and substrate-binding sites and possible relationship of D,D-carboxypeptidases/transpeptidases to $\beta$ -lactamases . . . . .	106
B.6.c.iii.	Breakdown of $\beta$ -lactam-enzyme complexes . . . . .	111
B.6.c.iv.	Molecular basis of interaction of $\beta$ -lactams with proteins . . . . .	112
B.6.d.	Structure/activity relationships . . . . .	116
B.6.d.i.	Penicillins . . . . .	116
B.6.d.ii.	Cephalosporins . . . . .	122
B.6.d.iii.	Non-classical $\beta$ -lactams . . . . .	129
B.6.e.	Resistance . . . . .	130
B.6.e.i.	Modification of target . . . . .	130
B.6.e.ii.	The role of $\beta$ -lactamases . . . . .	131
B.6.e.iii.	Penetrability of the outer membrane of Gram-negative bacteria . . . . .	133
B.6.f.	How are bacteria killed by $\beta$ -lactam antibiotics? . . . . .	134
C.	Antibiotics which combine with carrier molecules . . . . .	137
C.1.	Bacitracin . . . . .	137
D.	Antibiotics which combine with substrates . . . . .	144
D.1.	Vancomycin, Ristocetin A and B, Ristomycin A and B, Actinoidin A and B, Avoparcin A and B, and Antibiotic A 35512B . . . . .	144
D.1.a.	Introduction . . . . .	144
D.1.b.	Effects on living cells . . . . .	144
D.1.c.	Effects on cell-free systems . . . . .	145
D.1.d.	Binding to bacteria, cell walls, and wall peptides . . . . .	147
D.1.e.	Interaction of vancomycin and ristocetin with cell walls <i>in vivo</i> . . . . .	153
D.1.f.	Structure of vancomycin and other antibiotics of the group . . . . .	155

D.1.g. Molecular basis of action: the interaction of aglycones with peptides ending in acyl-D-alanine . . . . .	158
E. Antibiotics affecting fungal cell wall biosynthesis . . . . .	161
E.1. Structure and biosynthesis of fungal cell walls . . . . .	161
E.2. Inhibition of chitin synthesis by Polyoxin D . . . . .	162
E.3. Inhibition of mannan biosynthesis by tunicamycin . . . . .	165
References . . . . .	165
 <b>4. Antibiotics affecting the function of the cytoplasmic membrane</b>	<b>175</b>
A. The membrane . . . . .	175
A.1. Composition . . . . .	175
A.2. The cytoplasmic membrane: molecular structure . . . . .	177
A.3. The outer membrane of Gram-negative organisms . . . . .	180
A.4. Artificial membranes . . . . .	181
B. Transport across membranes . . . . .	182
C. Drugs producing leakage of small molecules from sensitive cells; early work . . . . .	183
D. Drugs causing major disorganization of the cytoplasmic membrane . . . . .	185
D.1. Surface-active agents . . . . .	185
D.2. Tyrocidins . . . . .	187
D.3. Phenols . . . . .	188
D.4. Polymyxins and octapeptins . . . . .	189
D.4.a. Structure and activity . . . . .	189
D.4.b. Site of action . . . . .	190
D.4.c. Mode of action . . . . .	193
D.5. Molecular basis of action . . . . .	195
E. Antibiotics believed to act by the production of aqueous pores in membranes . . . . .	195
E.1. Gramicidins . . . . .	195
E.1.a. Structure and activity . . . . .	195
E.1.b. Mode of action . . . . .	196
E.1.c. Molecular basis . . . . .	198
E.2. Polyenes . . . . .	201
E.2.a. Structure and activity . . . . .	201
E.2.b. Action on micro-organisms . . . . .	204
E.2.c. Sterol requirement . . . . .	206
E.2.d. Selectivity . . . . .	207
E.2.e. <i>In vitro</i> studies . . . . .	207
E.2.f. Structure of the pore . . . . .	209

E.2.g.	Do polyene-sterol pores explain the action of amphotericin?	214
E.2.h.	Filipin	218
E.3.	Alamethicin, suzukacillin	219
E.3.a.	Structure and activity	219
E.3.b.	Mode of action	220
E.4.	Monazomycin	225
E.5.	Comparison of channels	225
F.	Drugs producing specific changes in cation permeability (ionophores)	226
F.1.	Dinitrophenol	226
F.2.	Salicylanilides and other disinfectants	227
F.3.	Valinomycin, enniatins, macrotetralides	229
F.3.a.	Structure and activity	229
F.3.b.	Molecular basis of ionophore activity	234
F.4.	Ionophores binding mono- and di-valent cations	241
G.	Antibiotics which inhibit membrane-bound enzymes involved in energy transfer	242
G.1.	Direct inhibition of adenosinetriphosphatase (ATPase)	242
G.2.	Indirect inhibition of ATPase	245
H.	Inhibition of the synthesis of membrane lipids	245
H.1.	Cerulenin	245
H.2.	Miconazole	246
I.	Sideromycins	248
	References	249

## 5. Inhibitors of nucleic acid synthesis 258

A.	Introduction	258
B.	Agents which interfere with nucleotide metabolism	260
B.1.	Inhibitors of nucleotide synthesis	261
B.2.	Inhibitors of nucleotide interconversion	264
B.3.	Inhibitors of nucleotide utilization	269
B.4.	Agents which become incorporated into polynucleotides	270
C.	Agents which impair the template function of DNA	273
C.1.	The classical intercalating drugs: acridines and ethidium	274
C.1.a.	Binding to DNA	275
C.1.b.	The intercalation model	280
C.1.c.	Interaction with circular DNA	293
C.1.d.	Selective action on plasmids, kinetoplasts, and mitochondria	298
C.1.e.	Frameshift mutagenesis	300

C.2.	Other intercalating agents . . . . .	306
C.2.a.	Anthracycline antibiotics . . . . .	306
C.2.b.	Ellipticine, miracil D, chloroquine, and tilorone . . . . .	311
C.3.	Actinomycin . . . . .	314
C.3.a.	Nature of the binding site . . . . .	316
C.3.b.	Molecular models . . . . .	319
C.3.c.	Inhibition of RNA polymerase . . . . .	331
C.4.	Echinomycin, triostin, and related antibiotics . . . . .	333
C.5.	Diacridines and other <i>bis</i> -intercalating drugs . . . . .	337
C.6.	Non-covalent interaction with DNA . . . . .	341
C.6.a.	Chromomycin, mithramycin, and olivomycin . . . . .	341
C.6.b.	Netropsin and distamycin . . . . .	345
C.6.c.	Aromatic diamidines . . . . .	349
C.6.d.	Steroidal diamines . . . . .	350
C.6.e.	Hedamycin and rubiflavin . . . . .	351
C.6.f.	Luteoskyrin and kanchanomycin . . . . .	352
C.7.	Covalent and strand-breaking interactions with DNA . . . . .	353
C.7.a.	Cross-linking agents: Mitomycin C . . . . .	353
C.7.b.	Other cross-linking agents and carcinogens . . . . .	360
C.7.c.	Anthramycin, sibiromycin, and tomaymycin . . . . .	362
C.7.d.	Strand-breaking antibiotics: streptonigrin, bleomycin, and phleomycin . . . . .	364
D.	Agents which inhibit enzymic processes in nucleic acid synthesis . . . . .	370
D.1.	Inhibitors of RNA polymerase . . . . .	370
D.1.a.	Rifamycins and streptovaricins . . . . .	370
D.1.b.	Streptolydigin . . . . .	375
D.1.c.	$\alpha$ -Amanitin . . . . .	376
D.2.	Inhibitors of DNA replication . . . . .	377
D.2.a.	Nalidixic acid . . . . .	377
D.2.b.	Novobiocin and coumermycin . . . . .	381
D.2.c.	Arylhydrazinopyrimidines . . . . .	382
D.2.d.	Aphidicolin . . . . .	384
D.2.e.	Phenethyl alcohol . . . . .	384
References	. . . . .	386

## 6. Antibiotic inhibitors of ribosome function 402

A.	Introduction . . . . .	402
A.1.	The structure of ribosomes . . . . .	402
A.2.	Reconstitution of ribosomes . . . . .	406

A.3.	The mechanism of protein synthesis . . . . .	407
A.3.a.	Polypeptide chain elongation . . . . .	408
A.3.b.	Polypeptide chain initiation . . . . .	408
A.3.c.	Polypeptide chain termination . . . . .	409
B.	The mode of action of puromycin . . . . .	410
B.1.	Relationship of the puromycin reaction to protein synthesis . . . . .	412
C.	Ribosomal specificity of antibiotic action . . . . .	412
C.1.	Subunit localization of antibiotic action . . . . .	414
C.1.a.	Studies with radiolabelled antibiotics . . . . .	414
C.1.b.	Competition with radiolabelled antibiotics of known specificity . . . . .	414
C.1.c.	Formation of hybrid ribosomes . . . . .	415
C.1.d.	Cross-resistance with antibiotics of known specificity . . . . .	415
C.1.e.	Supplementation of inhibited systems . . . . .	415
C.1.f.	Inhibition of biochemical processes known to involve a particular subunit . . . . .	416
C.1.g.	Examination of components of antibiotic-resistant ribosomes . . . . .	416
C.2.	Direct examination of antibiotic binding sites in ribosomes . . . . .	417
C.2.a.	Use of antibiotic affinity analogues . . . . .	417
C.2.b.	Use of the splitting-reconstitution technique . . . . .	418
C.2.c.	Reconstitution with components from resistant ribosomes . . . . .	418
D.	Inhibitors of the smaller ribosomal subunit . . . . .	418
D.1.	Streptomycin . . . . .	419
D.1.a.	Streptomycin exerts a variety of effects <i>in vivo</i> . . . . .	419
D.1.b.	Streptomycin exerts a range of effects in cell-free systems . . . . .	420
D.1.c.	Localization of the site of action of streptomycin . . . . .	421
D.1.d.	Binding of dihydrostreptomycin to ribosomes . . . . .	422
D.1.e.	The ribosomal binding site for streptomycin . . . . .	422
D.1.f.	Misreading of the genetic message caused by aminoglycosides <i>in vitro</i> . . . . .	423
D.1.g.	Misreading of the genetic message <i>in vivo</i> . . . . .	425
D.1.h.	There are three streptomycin-phenotypes . . . . .	427
D.1.i.	Effects of streptomycin upon protein synthesis . . . . .	428
D.1.j.	Effects of streptomycin upon partial reactions of protein synthesis . . . . .	429
D.1.k.	Properties of reconstituted ribosomes lacking protein S12 . . . . .	430

D.1.l.	Properties of ribosomes exposed to streptomycin <i>in vivo</i> and <i>in vitro</i> . . . . .	430
D.1.m.	Dominance of sensitivity over resistance in heterozygotes . . . . .	431
D.1.n.	How does streptomycin kill cells? . . . . .	432
D.2.	Aminoglycosides: Neomycin, kanamycin, gentamicin, and hygromycin B . . . . .	433
D.3.	Spectinomycin . . . . .	438
D.4.	Kasugamycin . . . . .	439
D.5.	Aurintricarboxylic acid . . . . .	442
D.6.	Pactamycin . . . . .	443
D.6.a.	Binding of pactamycin to ribosomes . . . . .	444
D.6.b.	Effects of pactamycin in eukaryotic systems . . . . .	444
D.6.c.	Effects of pactamycin in bacterial systems . . . . .	446
D.7.	Edeine . . . . .	446
D.8.	Tetracyclines . . . . .	448
D.8.a.	Resistance to tetracyclines . . . . .	448
D.8.b.	Binding of tetracyclines to ribosomes . . . . .	448
D.8.c.	The mode of action of tetracyclines . . . . .	450
D.8.d.	Effects of tetracyclines on polyribosome metabolism . . . . .	451
D.8.e.	Functions of the ribosomal A site . . . . .	452
D.8.f.	Structure and function in tetracycline: $\beta$ -chelocardin . . . . .	452
D.9.	Emetine and tubulosine . . . . .	453
D.10.	Cryptopleurine, tylophorine, and tylocrebrine . . . . .	454
E.	Inhibitors of the larger ribosomal subunit . . . . .	456
E.1.	Puromycin . . . . .	456
E.2.	Chloramphenicol . . . . .	460
E.2.a.	Structural modifications and analogies . . . . .	460
E.2.b.	Mode of action of chloramphenicol . . . . .	462
E.2.c.	Binding of chloramphenicol to ribosomes . . . . .	464
E.2.d.	The ribosomal binding site(s) for chloramphenicol . . . . .	465
E.2.e.	Resistance to chloramphenicol . . . . .	467
E.2.f.	Concluding remarks on chloramphenicol . . . . .	467
E.3.	Macrolides . . . . .	468
E.3.a.	Binding of macrolides to ribosomes . . . . .	469
E.3.b.	Effects of macrolides <i>in vitro</i> . . . . .	472
E.3.c.	Effects of macrolides upon polyribosomes . . . . .	473
E.3.d.	An anomalous effect of chalcomycin . . . . .	474
E.4.	Erythromycin . . . . .	474
E.4.a.	Binding of erythromycin to ribosomes . . . . .	475

E.4.b.	Effects of erythromycin on protein synthesis . .	475
E.4.c.	Resistance to erythromycin and other macro- lides . . . . .	477
E.5.	Lincomycin . . . . .	478
E.5.a.	Binding of lincomycin to ribosomes . . . . .	478
E.5.b.	Mode of action of lincomycin . . . . .	479
E.6.	Streptogramins . . . . .	480
E.6.a.	Binding of streptogramins to ribosomes . . . . .	483
E.6.b.	Mode of action of streptogramins . . . . .	484
E.6.c.	Resistance to streptogramins . . . . .	485
E.7.	Sparsomycin . . . . .	485
E.8.	Althiomycin . . . . .	488
E.9.	Fusidic acid . . . . .	489
E.10.	Thiostrepton and related antibiotics . . . . .	492
E.10.a.	Inhibition of polypeptide chain elongation . . . . .	494
E.10.b.	Inhibition of polypeptide chain initiation . . . . .	496
E.10.c.	Inhibition of polypeptide chain termination . . . . .	496
E.10.d.	Summary of the action of thiostrepton . . . . .	496
E.10.e.	The ribosomal binding site for thiostrepton . . . . .	497
E.10.f.	Resistance to thiostrepton . . . . .	498
E.10.g.	Concluding remarks on thiostrepton . . . . .	499
E.11.	Viomycin and capreomycin . . . . .	500
E.12.	Cycloheximide and related glutarimide antibiotics . . . . .	502
E.12.a.	Effects of cycloheximide on protein synthesis . . . . .	503
E.12.b.	Effects of cycloheximide on nucleic acid synthesis . . . . .	506
E.13.	Anisomycin . . . . .	507
E.14.	Trichothecenes . . . . .	508
E.15.	Alkaloids active on the 60S ribosomal subunit . . . . .	511
E.15.a.	Narciclasine and the <i>Amaryllidaceae</i> alkaloids . . . . .	511
E.15.b.	Harringtonine and the <i>Cephalotaxus</i> alkaloids . . . . .	512
E.15.c.	Bruceantin . . . . .	514
E.15.d.	Pederine . . . . .	514
F.	Miscellaneous inhibitors of protein synthesis . . . . .	515
F.1.	Amicetin, gougerotin, blasticidin S., actinobolin, and anthelmycin . . . . .	515
F.2.	Bottromycin . . . . .	516
F.3.	Tenuazonic acid . . . . .	517
F.4.	Negamycin . . . . .	518
F.5.	Kirromycin . . . . .	518
F.6.	Pulvomycin . . . . .	519
G.	Catalytic inhibitors of protein synthesis . . . . .	520
G.1.	Diphtheria toxin and PA toxin . . . . .	520



G.2. Abrin and ricin . . . . .	522
G.3. Modeccin . . . . .	524
G.4. Croton and curcin . . . . .	525
G.5. Pokeweed anti-viral peptide . . . . .	526
G.6. Alpha sarcin . . . . .	526
G.7. Colicin E3 and cloacin DF13 . . . . .	527
Acknowledgements . . . . .	529
References . . . . .	529

## **7. Bacterial resistance to antibiotics 548**

A. Introduction . . . . .	548
B. Biochemical basis of resistance . . . . .	550
B.1. Modification of the target . . . . .	550
B.2. Reduction in the physiological importance of the target . . . . .	553
B.3. Duplication of the target . . . . .	554
B.4. Prevention of access . . . . .	554
B.5. Resistance to inactivation . . . . .	556
B.5.a. Antibiotic-destroying enzymes . . . . .	556
B.5.b. Enzymes inactivating by substitution . . . . .	557
C. Genetic basis of resistance . . . . .	561
C.1. Gene modification . . . . .	562
C.1.a. Modification of the gene specifying the target . . . . .	562
C.1.b. Modification of genes other than those specifying the target . . . . .	565
C.2. Resistance based on additional genetic material . . . . .	566
C.3. Genetic location of resistance genes . . . . .	566
C.3.a. Plasmid versus chromosomal location . . . . .	566
C.3.b. Replicon interactions . . . . .	568
C.3.c. The advantage of a plasmid location for a resistance gene . . . . .	574
C.3.d. Transmissibility of plasmids . . . . .	575
C.3.e. Structure of R-plasmids . . . . .	577
D. Evolution of antibiotic resistance . . . . .	582
D.1. Evolution of resistance determinants . . . . .	582
D.1.a. $\beta$ -Lactamases . . . . .	583
D.1.b. Chloramphenicol acetyl transferases . . . . .	583
D.1.c. Other proteins as possible evolutionary precursors for resistance enzymes . . . . .	585
D.2. Evolution of plasmids . . . . .	586
E. The overall picture . . . . .	587
References . . . . .	590