Section III - Chemotherapeutic Agents

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Chapter 11. Antibiotics

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This chapter will be limited to those antibiotics for which antibacterial activity has been demonstrated. Antibiotics which are described exclusively as antitumor, antifungal and antiviral agents as well as subjects related to biosynthesis are excluded. Included is a very limited section on β-lactam antibiotics.

General - The 17th Interscience Conference on Antimicrobial Agents and Chemotherapy, for which abstracts were published,[1] was concerned with its usual wide variety of antibiotic subjects. Zurich hosted the 10th International Congress of Chemotherapy which emphasized clinical topics in the antibiotic field.[2] The pilot volume of a projected new series, called *Topics in Antibiotic Chemistry*, was published.[3]

Aminocyclitols - Large numbers of clinical reports on experiences with aminocyclitol antibiotics continued to appear, including a rather extensive review[4] on various aspects of their use. Clinical effort on new aminocyclitols appeared to center on netilmicin, 1, 1-N-ethylsisomicin, which is active against some of the gentamicin-resistant organisms. In general the preliminary information which was reported last year held up in the current expanded studies. In comparative pharmacological studies[5] of gentamicin, 2, and netilmicin, the latter appeared to produce more predictable blood levels. Another study[6] reported favorable clinical responses for 70% of patients infected with susceptible strains of *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Despite lower nephrotoxicity in experimental animals, some of these patients displayed some renal involvement, as suggested by elevated BUN and serum creatinine and the appearance of granular casts. Several other reports[7,8,9,10] only showed very low incidences of toxicity. A new high-pressure liquid chromatographic assay of netilmicin in plasma[11] gave results which correlated well with microbiological assays.

Synthetic modifications of gentamicin and kanamycin afforded a number of active compounds. Hydroxy-amino-acylates of gentamicin B, 3 and 4, had greatly enhanced antimicrobial activity, but their toxicities were correspondingly higher.[12] Two laboratories reported[13,14] conversions of kanamycin B, 5, to kanamycin C, 6, and 6'-deoxykanamycin C, 7, utilizing nitrous acid deamination at the 6' position of suitably protected intermediates. Only weak activity was shown by 7 against most of the microorganisms tested. A novel derivative, 1-N-[(S)-4-amino-2-hydroxybutyl]

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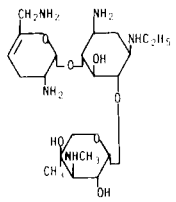

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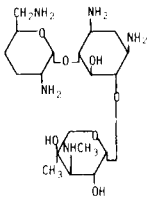

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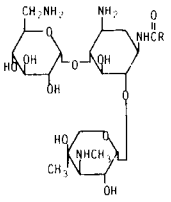
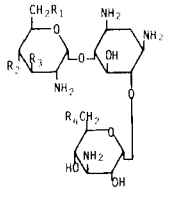
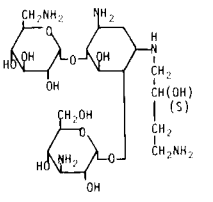


3 R=$CH_2(NH_2)CH_2CH(OH)$-
4 R=$CH_2(NH_2)CH(OH)$-



Compound	R_1	R_2	R_3	R_4
5	NH_2	OH	OH	OH
6	OH	OH	OH	OH
7	H	OH	OH	OH
9	NH_2	H	OH	OH
10	NH_2	OH	H	H



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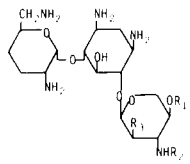
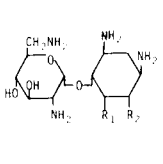
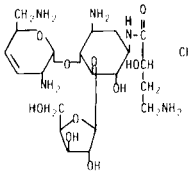


	R_1	R_2	R_3
11	CH_3	H	NH_2
12	H	CH_3	OH



	R_1	R_2
13	H	OH
14	OH	H



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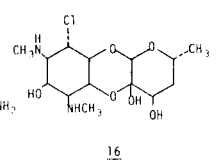

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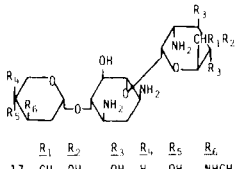
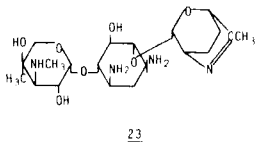


	R_1	R_2	R_3	R_4	R_5	R_6
17	CH_3	OH	OH	H	OH	$NHCH_3$
18	CH_3	OH	OH	OH	H	$NHCH_3$
19	CH_3	NH_2	H	OH	CH_3	NH_2
20	CH_3	$NHCH_3$	H	OH	H	$NHCH_3$
21	CH_3	NH_2	H	OH	H	$NHCH_3$
22	H	NH_2	H	OH	H	$NHCH_3$



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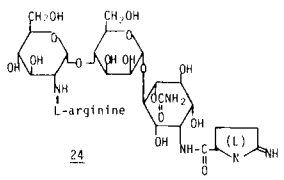

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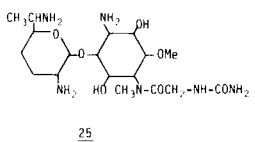

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kanamycin A, 8, was synthesized by a diborane reduction of a trifluoroacetate salt of the corresponding butyryl derivative of kanamycin A.[15] Clinical evaluation is underway for this compound, UK-18892, which demonstrates an order of activity like that of amikacin. Newly synthesized 4'-deoxykanamycin B, 9,[16,17] displayed varied activity against strains of *Staphylococcus aureus*, *S. epidermis*, and *Bacillus brevis* which had been reported to produce aminoglycoside-4'-adenyltransferase. The activity of 6"-deoxytobramycin, 10, was similar to that of tobramycin.[18] Since enzymatic 3-O-phosphorylation inactivates seldomycin factor 5, the 3'-deoxy analog, 11, was prepared in two laboratories.[19,20] Enhanced activity was seen against Gram-negative sensitive strains as well as the target resistant ones. Attachment of gentosamine to 3',4'-dideoxyneamine gave a broad spectrum antibiotic, 12, which was, however, less active than the gentamicin C complex.[21] The 1-*epi*-derivatives of sisomicin, netilmicin and gentamicin C were found to be potent broad spectrum antibiotics which were less toxic than the parent antibiotics.[22] Replacement of the C-6 hydroxyl of neamine with hydrogen as in 14 diminished its antibacterial effect but 5-deoxyneamine, 13, had enhanced activity, especially against kanamycin-resistant strains.[23] While less active than 3',4'-dideoxybutirosin, newly synthesized 3',4'-dideoxy-3'-enobutirosin A, 15,[24] was active against a broad range of sensitive and aminoglycoside-resistant organisms.

A novel approach to aminocyclitol modification sequenced the use of inactivating enzymes with synthetic organic procedures.[25] An enzyme from

Pseudomonas aeruginosa GN573 was used in the presence of ATP and $MgSO_4$ to phosphorylate kanamycin B specifically at the 3' position. Treatment with silylating agents gave the chloride which was subsequently hydrogenated to give kanamycin B.

Since inactivation of spectinomycin occurs by adenylation at the 9-position, the analogs 9-chloro-9-deoxy-4(R)-dihydrospectinomycin, 16, and its 9-epimer, and 9-deoxy-8,9-epimino-4(R)-dihydrospectinomycin were prepared.[26] All three were devoid of antibacterial activity. A spectinomycin resistant *Neisseria gonorrhoeae* was studied[27] with no finding of spectinomycin inactivation. Chromosomal mutation was suggested as causative.

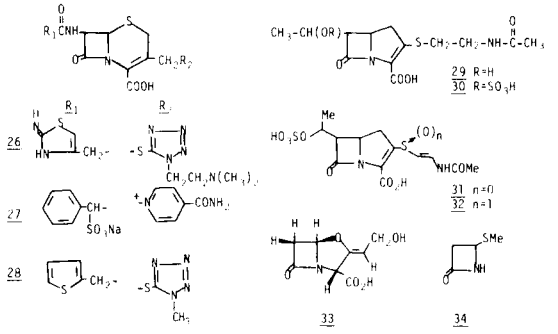
More inactivating enzymes have been found. Strains of *Staphylococcus aureus* elaborated both kanamycin-neomycin[28] and gentamicin[29] phosphotransferases. Another strain of that organism also produced an amikacin-modifying 3'-phosphotransferase while remaining sensitive to the antibiotic.[30] Five strains of *Escherichia coli* have been isolated which inactivate extracellular streptomycin in large quantities.[31] Alkaline phosphotase liberated inorganic phosphate from the inactive compound but the remaining streptomycin-like compound had no activity. Plasmid-induced resistance of a clinically isolated *Pseudomonas aeruginosa* strain to kanamycin, tetracycline, chloramphenicol, and streptomycin was related to decreased cell permeability rather than to inactivating derivatization.[32]

Among the new microbially produced aminocyclitols were seven gentamicin-related substances, 17-23, in the broth of a *Micromonospora* species which produced eighteen additional known antibiotics.[33] Biological details were not reported beyond a mention of broad antibacterial activity. LL-BM123α, 24, a *Nocardia*-produced aminocyclitol, had *myo*-inosamine as the aminocyclitol moiety.[34]

Fortimicin C, 25, elaborated by *Micromonospora olivoasterospora* was active against kanamycin-, gentamicin-, and tobramycin-resistant *E. coli* strains.[35]

Neomycin C has now been synthesized by regioselective glycosidation between suitably protected ribostamycin and neosamine C.[36]

β-Lactams - Clinical evaluation studies were initiated for SCE-963, 26, a new broad spectrum parenteral cephalosporin.[37,38] Another new parenteral cephalosporin for clinical investigation is CGP 7174E (SCE-129), 27, a compound which compared favorably with gentamicin in the treatment of experimental *Pseudomonas aeruginosa* infections.[39,40] FR13301 is a third parenteral cephalosporin receiving



clinical attention. It is most active against Gram-negative organisms[41] as is a fourth clinical candidate, FR10024, 28.[42]

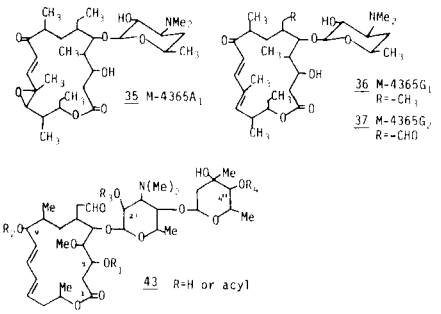
Reports on new microbially-produced β-lactam antibiotics included N-acetyl thienamycin, 29, from *Streptomyces cattleya*,[43] three compounds from *Streptomyces olivaceus* (MM 17880, 30,[44] MM 13902, 31,[45] and MM 4550, 32[45]), and four epithienamycins from *Streptomyces flavogriseus*.[46] The epithienamycins showed antimicrobial activities and β-lactamase susceptibilities which vary widely amongst each other.[47] The thienamycins share a characteristic instability.[48] The first total synthesis of the β-lactamase inhibitor, clavulanic acid, 33, was reported.[49] The starting compound was (±)-4-methylthioazetidin-2-one, 34.

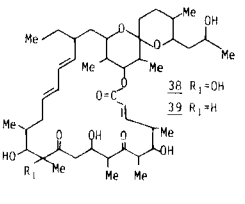
Macrolides - In a symposium on the macrolide antibiotics held at the 173rd Meeting of the American Chemical Society,[50] biological activities were correlated with structure. Rosamicin, a basic macrolide with a 16-membered ring, has shown some clinical promise in the treatment of bacterial prostatitis.[51] SP127, a protein, has been found to enhance the activity of macrolide antibiotics by promoting their ability to penetrate the bacterial cell.[52,53]

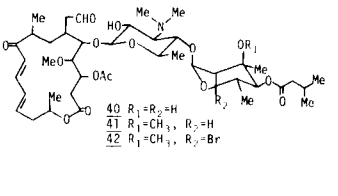
The production by *Micromonospora capillata* of three new macrolides, 35, 36, 37, with 16-membered rings was reported.[54,55] These antibiotics, M-4365A_1,G_1, and G_2 generally inhibited the same organisms that were sensitive to rosamicin and the juvenimicins which were coproduced in the fermentation. The revision of the structures of oligomycins A and C 38, 39, showed them to be closely related to oligomycin B and rutamycin.[56]

A review on the synthesis of macrolide compounds[57] included not only the macrolide antibiotics but ansamycins, macrotetralides, macrodilides, etc. None of the major 14 or 16-membered macrolide antibiotics has yet been synthesized, although a semisynthesis of carbomycin B, 40, from carbonolide B and the two carbohydrate fragments was accomplished.[58] Cladinose analogs of carbomycin B 41, 42, were prepared and found to approximate the *in vitro* antibacterial action of carbomycin B.[59]

A study correlating the structure and activity of the acylated leucomycins, 43, showed that a free 9-hydroxyl group is not essential for ribosomal binding. However, 4"-O-acylation did affect binding which decreased

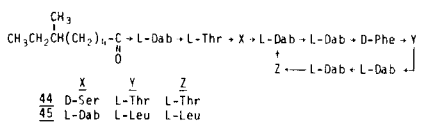


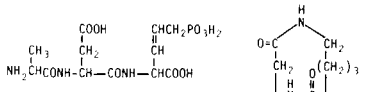




with decreasing acyl size . Incubation with the test microorganism caused hydrolysis of the 2'-O-acyl groups.[60]

Peptides - Several new microbially produced members of the largest class of antibiotics were described. The chemistry, biogenesis, and functions of these peptides were recently reviewed.[61] Polymyxin F from *Bacillus circulans*,[62] and polymyxins S_1, 44, and T_1, 45, from *Bacillus polymyxa*[63,64] were recently isolated and reported to have the usual polymyxin antibacterial spectra, although T_1 is more active against Gram-positive organisms. Tallysomycins[65,66] are bleomycin-like, while nosiheptide[67] and micrococcin P[68] are related to thiostrepton, plauracin is in the virginiamycin sub-group.[69] Structures are unavailable for several other new peptides, NRC-501,[70] compound 41,012,[71] and FCRC-53.[72] Two unique dipeptides were isolated, plumbemycin A, 46,[73] and cairomycin B, 47.[74] The latter had antifungal and antibacterial properties. LL-BM547, viomycin-like, is an antitubercular antibiotic produced by a *Nocardia* species.[75] New or revised structures appeared for a number of the older antibiotics such as the bacillomycins L, 48,[76] the cyclosporins, 49-51,[77,78] and berninamycin, 52.[79] Sulfomycin I was found to contain 2,5-berninamycinic acid.[80] Structures for the peptaibophol[81] sub-group, alamethicin I and II, 53, 54,[81] emericins IV and III, 55, 56,[82] and antiamoebin I, 57,[83] were elucidated. Stenothricin was found to be a complex of peptides varying in the ketoacyl moiety of the general formulas, β-ketoacyl-D-cys(O_3H)-L-Val-DSer-LLys-Sar-DαThr-LSer-LDap-OH.[84]





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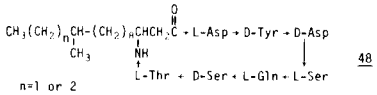

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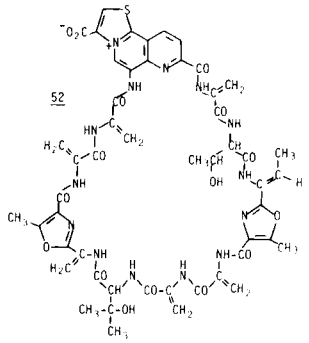

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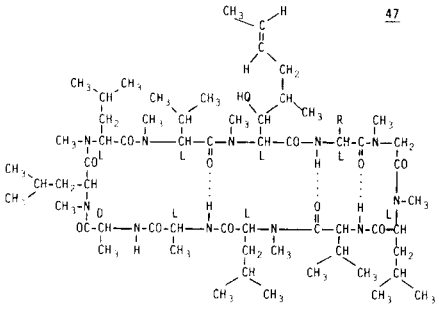


49 R=-CH_3 Cyclosporin B
50 R=$CH(OH)$-CH_3 Cyclosporin C
51 R=$CH(CH_3)_2$ Cyclosporin D

Ac → Aib → L-Pro → Aib → L-Ala → Aib → L-Ala—
(Aib)
→ L-Gln → Aib → L-Val → Aib → Gly → L-Leu → Aib—
→ L-Pro → L-Val → Aib → Aib → L-Glu → L-Gln → L-Phol

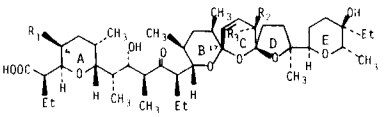
53 (54)

55 (Emerimicin IV): Ac-L-Phe-Aib-Aib-Aib-L-*Val*-Gly-L-Leu-Aib-Aib-L-Hyp-L-Gln-L-Iva-L-Hyp-*Aib*-L-Phol
56 (Emerimicin III): Ac-L-Phe-Aib-Aib-Aib-L-*Val*-Gly-L-Leu-Aib-Aib-L-Hyp-L-Gln-L-Iva-L-Hyp-L-*Ala*-L-Phol
57 (Antiamoebin I): Ac-L-Phe-Aib-Aib-Aib-L-Iva-Gly-L-Leu-Aib-Aib-L-Hyp-L-Gln-L-Iva-L-Hyp-*Aib*-L-*Pro*-L-Phol

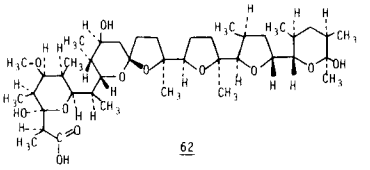
A 19-residue peptide with alamethicin-like activity in liquid bilayer membranes has been synthesized and tested.[85] Virginiamycin S reduction products were prepared, but they were less active than virginiamycin S.[86] EM-49 was converted to a number of active derivatives by acylation and alkylation of the terminal amino groups of the 2,4-diaminobutyric acid residues.[87] Good activity was frequently seen in the Gram-positive areas with decreased antipseudomonal activity. Plasmid-mediated pristinamycin acetyltransferase, produced by a *Staphylococcus* strain, O-acetylated that antibiotic, thereby inactivating it.[88]

When polymyxin B, immobilized on agarose beads, was used to specifically disrupt the outer membrane of Gram-negative bacteria, synergism with bacitracin, rifamycin, or lysozyme was still in effect. Thus polymyxin B plays its role in these combinations at the outer membrane.[89,90]

Polyethers - Mass spectral data[91] required the assignment of the 4-methylsalinomycin structure to narasin, 58. Analyses of the ^{13}C-NMR spectra of salinomycin, 59,[92] and narasin[93] indicated an equatorial orientation for the new methyl group. Another ionophore, A28086B, 60, differs from narasin in the C-ring only, with a keto function replacing the secondary hydroxyl.[91] *Streptomyces albus* (ATCC12838) elaborated deoxy-(O-8) salinomycin, 61, and a second polyether differing from 61 by epimerization at position 17.[94] Mutalomycin, 62, produced by *Streptomyces mutabilis* (NRRL 8088), is active against Gram positive bacteria and *Eimeria tenella*.[95] Carriomycin, 63, another new polyether, contains the sugar residue that is present in septamycin, A130A (lenoremycin) and A-204A according to a crystallographic structure analysis of the thallium salt.[96] The aglycone was similar to lonomycin.



58 R_1=CH_3; R_2=OH; R_3=H
59 R_1=R_3=H; R_2=OH
60 R_1=CH_3; R_2, R_3=O
61 R_1=R_2=R_3=H



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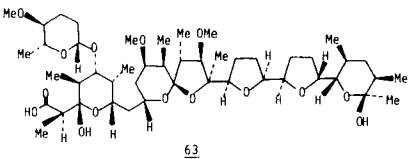

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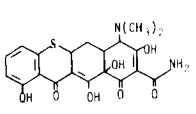

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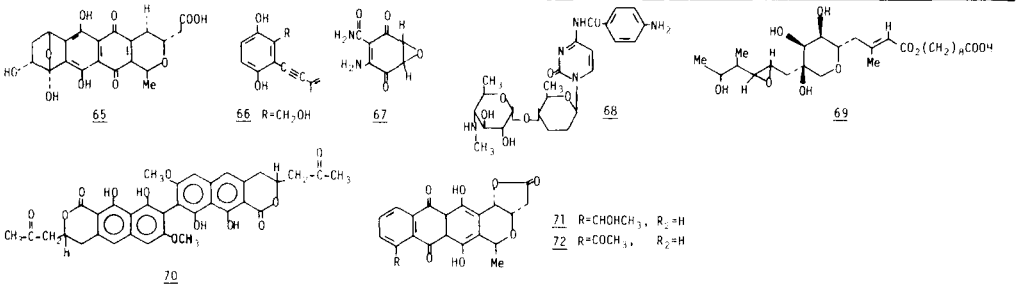
Tetracyclines - EMD33,330, 64, was one of a number of 6-thiatetracyclines of synthetic origin.[97] Its minimum inhibitory concentrations for a broad range of organisms were lower than those of doxycycline and tetracycline, except for *Pseudomonas aeruginosa* where it was less active. Tetracycline-resistant strains were sensitive. High and prolonged serum concentrations were seen in mice and dogs, with peaks 2-3 times those of doxycycline.

Miscellaneous Antibiotics - The search for new antibiotics again afforded a number of new activities which are summarized in Table 1.

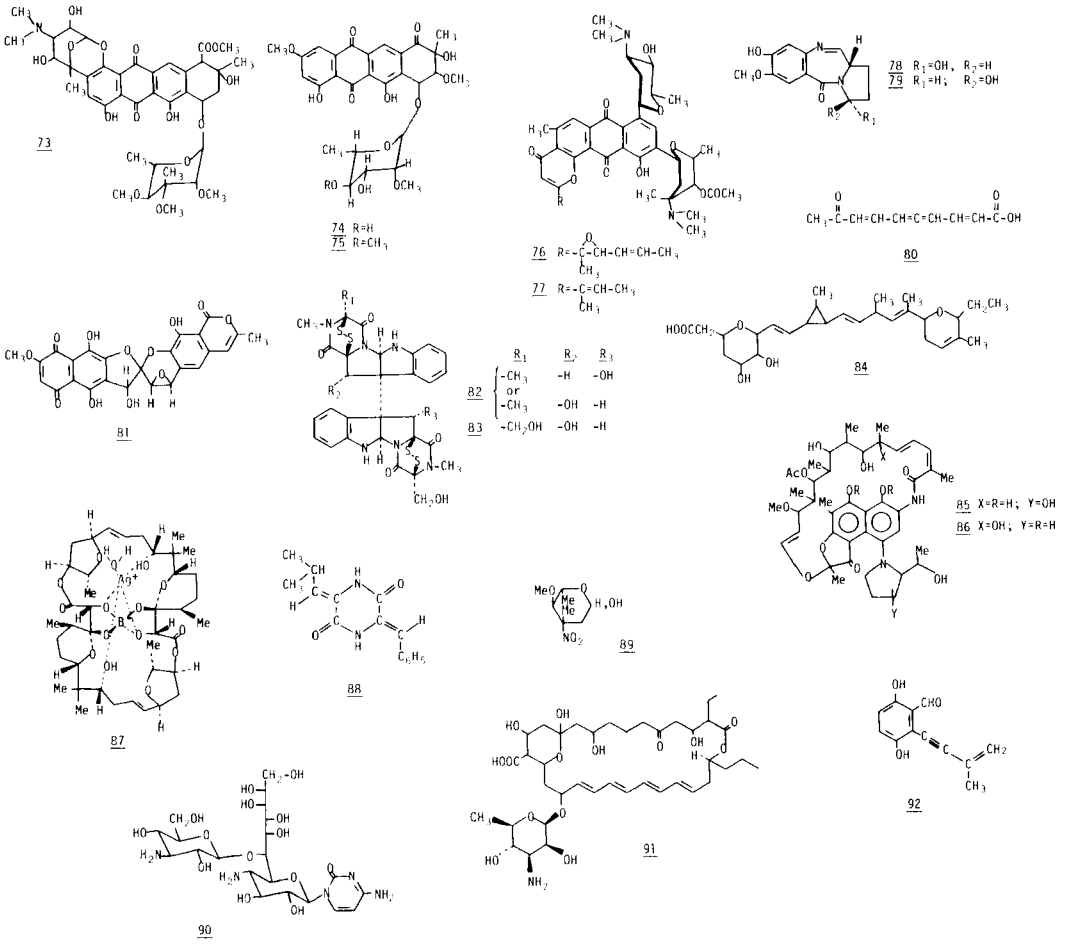
TABLE 1: NEW ANTIBIOTIC ENTITIES

Antibiotic	Producing Organism	Activity	Structure or Structure/Type	Reference
A-35512	*Streptomyces candidus*	G+	Glycopeptide/Vancomycin	98
Baumycins	*Streptomyces coeruleorubidus*	G+, AT	Anthracycline	99
Chloquinomycin	*Streptomyces californicus* var. *rivalis*	G+	—	100
CP-41043 CP-41494	*Pseudonocardia fastidiosa*	G+, G-	Thiostrepton	101
CP-42752 CP-43038 CP-43139	*Micromonospora saitamica*	G+, G-	—	102
Demethylblasticidin S	*Streptomyces griseochromogenes*	G+, AF	Nucleoside	103
3-*epi*-Deoxynegamycin	*Streptomyces goshikiensis*	G+, G-	Hydrazide/Amino Acid	104
Dihydrograna ticin	*Streptomyces thermoviolaceus*	G+	65	105
Dihydromocimycin	*Streptomyces mocetsimus*	G+, G-, AP	Mocimycin	106
Frustulosinol	*Stereum frustulosum*	G+, *Vibrio sp.*	66	107
G-7063-2	*Streptomyces sp.*	G+, G-, AF	67	108
Glycinothricin	*Streptomyces griseus*	G+, G-	Streptothricin	109
Hydroxynybomycin	*Streptomyces sp.* D-57	G+, G-	Nybomycin	110
K-52B	*Streptovertiicillium roseovertiicillatum* subsp. *albosporum*	G+, G-	—	111
Leucyl-3-*epi*-deoxynegamycin	*Streptomyces goshikiensis*	G+, G-	Amino Acid/Hydrazide	104
MA-144 Complex	*Streptomyces galilaeus*	G+, AF, AT	Anthracycline	112
Marcellomycin	*Actinosporangium sp.* C-36145	G+, G-, AT	Anthracycline	113,114
Musettamycin	*Actinosporangium sp.* C-36145	G+, G-, AT	Anthracycline	113,114
Nocamycin	*Nocardiopsis syringae*	G+, AT	—	115
Norplicacetin	*Streptomyces plicatus*	G+, *Mycobacteria*	68	116
OS-1804	*Streptomyces michiganensis*	G+, G-, AF	—	117
OS-4742	*Streptomyces rutensis* subsp. *vineus*	G+, AT	Anthracycline	118
Pseudomonic Acid B	*Pseudomonas fluorescens*	G+	69	119
Rhodirubins A, B	*Streptomyces sp.*	G+, *Mycobacteria*, AT	Anthracycline	120
Saframycins	*Streptomyces lavendulae*	G+, G-	—	121
SC30532	*Spicaria divaricata*	G+, G-, AP, AF	70	122
Secalonic Acid F	*Aspergillus aculeatus*	G+	Secalonic Acids	123
Striatins	*Cyathus striatus*	G+, G-, AF	—	124
T-41348	*Streptomyces sp.*	G+, G-	Phenazine	125
Trichorin A	*Trichoderma sp.* strain K472	G-	*epi*Polythiadiketopiperazine	126
Zg		G+	71	105
Zgg (Bisanhydrograna ticin)	*Streptomyces thermoviolaceus*	G+	72	105
792	*Streptomyces bottropensis*	G+, G-, AF, AT	—	127



Structures were published for a number of antibiotics which have been known for some time including nogalamycin, 73[128] steffimycin and steffimycin B, 74, 75,[129] pluramycin A, and neopluramycin, 76, 77,[130] all of which show both antibacterial and antitumor activity. Elucidations of the structures of neothramycins A and B, 78, 79,[131] LA-1 80,[132] griseorhodin A 81,[133] melinacidins II, III 82, 83,[134] and ambruticin, 84, (formerly acid S)[135] were also disclosed. Halomicins A and C, 85, 86,[136] are ansamycins and the silver salt of aplasmomycin, 87, was shown by crystallography to be a macrocyclic dilactone with boron in the center.[137] The configurational assignments of albonoursin, 88, were made by synthesizing the four possible isomers.[138] Revisions of structures for everninomicin[139] at the C-3 of evernitrose, 89, anthelmycin (hikizimycin), 90,[140] rimocidin, 91,[141] and frustulosin, 92,[107] were published.

Total syntheses for miscellaneous antibiotic substances were reported for the first time. These included oxazinomycin,[142] elaiomycin,[143] dl-cerulenin,[144,145,146] (±)-methylenomycin A,[147] minosaminomycin,[148] lydimycin (α-dehydrobiotin),[149] dl-porfiromycin,[150] mitomycins A and C,[151] vermiculine[152] and mimosamycin.[153]



Various studies forecasted potential benefits for the use of antibiotics in combination. Benzylpenicillin displayed remarkable activity against a number of *Bacteroides fragilis* strains when combined with clavulanic acid.[154] Clinical trials for a mixture of rifamycin and trimethoprim were recommended on the basis of *in vitro* studies showing that the mixture decreased the incidence of resistance.[155] Another report stated that novobiocin effectively eliminated plasmids from several bacterial species.[156] Polymyxin B and rifamycin was an effective combination for 8 out of 12 patients with resistant nosocomial *Serratia marcescens* infections.[157] Novobiocin demonstrated a "probenicid effect" with β-lactam antibiotics in the treatment of experimental *Salmonella schottmuelleri* infections in mice.[158] Combinations of fosfomycin with chloramphenicol or ampicillin were effective in the treatment of *Salmonella typhi* infections in humans.[159] Fosfomycin, alone, was also shown to be particularly effective in the treatment of humans infected with Gram-negative bacilli and Gram-positive cocci.[160]

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