Review Article

NUCLEOSIDE ANTIBIOTICS: STRUCTURE, BIOLOGICAL ACTIVITY, AND BIOSYNTHESIS

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Nucleoside antibiotics are found as diverse groups of secondary metabolites of microbial origin. They include a variety of structural modifications of nucleosides and nucleotides, often leading to intricate molecules. Their biological activities are also wide ranging, including antibacterial, antifungal, antitrypanosomal, antitumor, antiviral, herbicidal, insecticidal, immunostimulating, and often immunosuppressive properties. It is not surprising that nucleoside antibiotics exhibit such diverse biological activities, because nucleosides and nucleotides play pleiotropic roles in most fundamental cellular metabolic pathways such as metabolite carriers, energy donors, secondary messengers, and cofactors for various enzymes. Thus, not only nucleic acid synthesis but also protein synthesis, glycan synthesis, and glycoprotein synthesis are targets of nucleoside antibiotics. The protein kinases, key enzymes for cell proliferation and differentiation, also require nucleotides as phosphate donors. Thus nucleoside antibiotics are potential candidates for the regulation of all aspects of cell growth and differentiation.

The nucleoside antibiotics have been reviewed by SUHADOLNIK in 1970[1] and 1979.[2,3] In 1982, GOODCHILD[4] reviewed their biochemistry and BUCHANAN and WIGHTMAN[5] reviewed the chemistry. However, dozens of new nucleoside antibiotics have been discovered in the last decade and their biological roles have been determined.

In this article, known nucleoside antibiotics at present are listed with their structures. Their chemistry and biology have been briefly reviewed, to avoid overlapping with previous reviews.

One hundred sixty-three nucleoside antibiotics have been classified on the basis of their structures, as follows:

1: Base analogs

2: Simple nucleosides
- (1) Adenosine analogs
- (2) Guanosine analogs
- (3) Pyrrolopyrimidine nucleosides
- (4) Tetrahydroimidazodiazepine nucleosides
- (5) *C*-Nucleosides
- (6) Others

3: Acyl and glycosyl nucleosides
- (1) Sulfamoyl nucleosides

(2) 3′-Aminoacyl-3′-deoxyadenosines
(3) 4′-Aminoacyl-4′-deoxyhexose cytosines
(4) Glycosyl nucleosides
(5) Peptidyl nucleosides
(6) High-carbon sugar nucleosides
(7) Fatty acyl nucleosides

4: Nucleotides

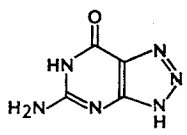
This classification is conventional; some of the antibiotics possess structural features covering more than two groups in the above classification. For example, liposidomycin B (**161**), which is one of the most complex molecules, is an aminohepturonic acid nucleoside glycosylated with a sulfated amino sugar, aminoacylated, and doubly acylated with fatty acids.

Generally, the biological activity of nucleoside antibiotics is closely related to their structural features. For example, simple nucleoside analogs often act as inhibitors of nucleic acid synthesis. However, acyl or glycosyl nucleosides may often inhibit protein or glycan synthesis.

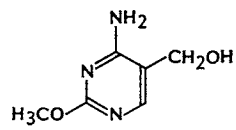
Biosynthetic studies on nucleoside antibiotics is limited. A permeability barrier to unusual nucleosides may make them difficult to study at the cell level. Well-studied examples are the *C*-nucleoside antibiotics and peptidyl nucleosides, polyoxins.

1: Base Analogs

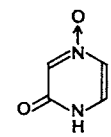
A synthetic purine antagonist, 8-azaguanine (**1**), was found to be a metabolite of *Streptomyces*.[6] It was established that guanine is the carbon-nitrogen precursor for the biosynthesis of **1**.[7]; carbon-8 of guanine is eliminated and replaced by a nitrogen. Mode of action of **1** was reviewed.[8] Bacimethrin (**2**),[9,10] originally isolated from *Bacillus megaterium*, was recently isolated from *Streptomyces albus*.[11] It was revealed that **2** inhibits phosphorylation of 4-amino-5-hydroxymethyl-2-methylpyrimidine during thiamine biosynthesis. A pyrazine derivative, emimycin (**3**), is slightly antibacterial.[12] But it is interesting that a 2-deoxyribofuranosyl derivative showed activity six orders of magnitude higher than **3** and the corresponding riboside, suggesting that the site of action is related to DNA synthesis.[13,14] The antibacterial 4-thiouracil (**4**) was identified as a metabolite of *Streptomyces livani*.[15] Azepinomycin (**5**) inhibits guanine deaminase;[16] it has a ring expanded structure analogous to coformycin (**27**), which blocks adenosine deaminase. Azepinomycin and its β-D-ribofuranoside have been synthesized.[17]



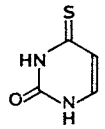
8-Azaguanine (**1**)



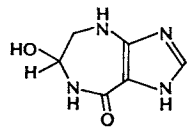
Bacimethrin (**2**)



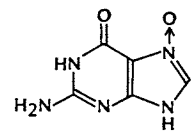
Emimycin (**3**)



4-Thiouracil (**4**)



Azepinomycin (**5**)



Guanine 7-*N*-oxide (**6**)

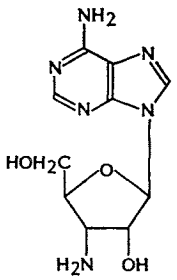
Guanine 7-*N*-oxide (**6**) was shown to be produced by *Streptomyces* sp. by three independent research groups.[18~21] It is interesting that among the oxide isomers, **6** is only one which could not be synthesized in the laboratory. It is effective against L1210 and P388 in mice, and Ehrlich solid carcinoma, by oral administration. Antiviral activity against DNA and RNA viruses of salmonid origin was reported.[22] The effect of **6** was synergistic with neplanocin A (**15**).[23] Its structural similarity to 7-methylguanine, together with some experimental studies suggest that **6** may interfere with messenger RNA maturation.[23] Present evidence indicates that **6** is metabolized into ribofuranoside triphosphate in murine and human cells.[24] The chemical synthesis of **5** was performed from a nitropyrimidone derivative;[25] the riboside, which showed reduced biological activity, was prepared enzymatically.[26,27]

2: Simple Nucleosides

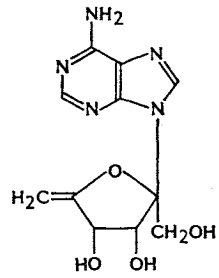
(1) Adenosine Analogs

This is the largest group; classical members are 3′-amino-3′-deoxyadenosine (**7**),[28~30] decoyinine (angustmycin A) (**8**),[31~33] psicofuranine (angustmycin C) (**9**),[31~33] 3′-deoxyadenosine (cordycepin) (**10**),[34,35] and arabinofuranosyladenine (Ara A) (**11**). They are all adenosine analogs with modified sugars. **8** and **9** are inhibitors of XMP aminase. Cordycepin triphosphate has been used extensively to study the mechanism of RNA synthesis. Ara A, first isolated from marine sponge and later from culture filtrates of *Streptomyces antibioticus*,[36,37] is used currently as an antiviral agent. 2′-Amino-2′-deoxyadenosine (**12**) was discovered as a metabolite of *Actinomadura* having antimycoplasma activity.[38]

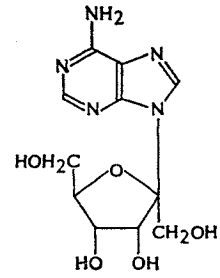
Oxetanocin (**13**) isolated by TAKITA and his collaborators[39] is the first example of a naturally occurring oxetanose derivative from *B. megaterium*. The structure was determined by X-ray analysis.[40]



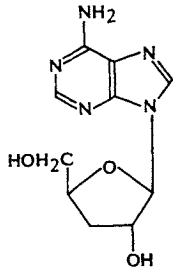
3′-Amino-3′-deoxyadenosine (**7**)



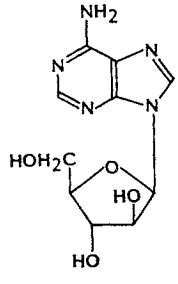
Decoyinine (**8**, angustmycin A)



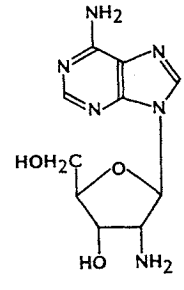
Psicofuranine (**9**, angustmycin C)



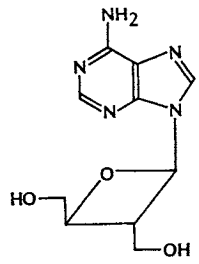
Cordycepin (**10**, 3′-deoxyadenosine)



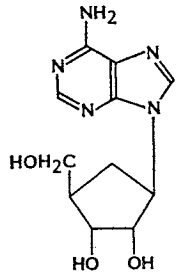
Ara-A (**11**)



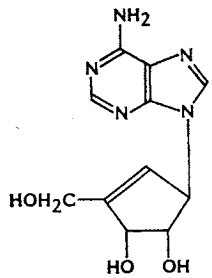
2′-Amino-2′-deoxyadenosine (**12**)



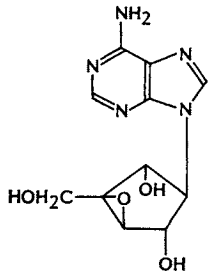
Oxetanocin (**13**)



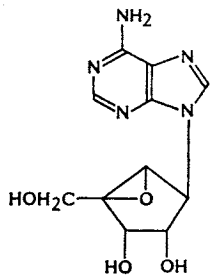
Aristeromycin (**14**)



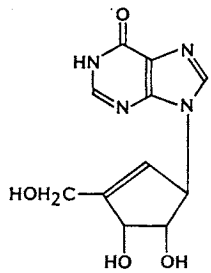
Neplanocin A (**15**)



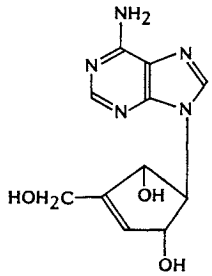
Neplanocin B (**16**)



Neplanocin C (**17**)



Neplanocin D (**18**)

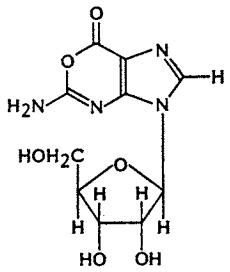


Neplanocin F (**19**)

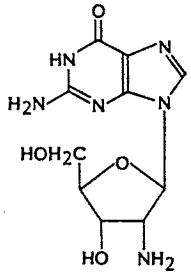
It has strong inhibitory activity against Gram-positive bacteria and antiviral activity against herpes viruses including human immuno-deficiency virus (HIV).[41] **13** has been synthesized from D-ribose. Xanthine, guanine and 2-aminoadenine analogs were also prepared, using chemical or enzymatic processes. (T. TAKITA *et al.*, Riken Symposium, Sept. 1987, Wako). Neplanocins A~D and F (**15**~**19**) are products of a fungus, *Ampullariella regularis*.[42,43] Like aristeromycin (**14**), they are carbocyclic analogs of adenosine, having either an epoxy-cyclopentane or cyclopentene ring. Neplanocin A (**15**) has strong antitumor and antiviral activities. But its antimicrobial activity is limited. Several total syntheses have been achieved.[44~46] **15** is not phosphorylated in cells and the intact molecule strongly inhibits *S*-adenosylmethionine hydrolase in cells, which results in accumulation of *S*-adenosylhomocysteine, thus inhibiting cell and viral methyltransferases involved in messenger RNA maturation steps and other macromolecule synthesis.[47,48]

(2) Guanosine Analogs

Only a small number of compounds are known in this group. Oxanosine (**20**), isolated by UMEZAWA and his collaborators from *Streptomyces capreolus*,[49] is unique both in structure and in biological activity. The structure in which N-1 of guanosine is replaced by oxygen was established by X-ray analysis.[50] An elegant synthesis was achieved from amino- and ester-substituted imidazole nucleoside.[51] The antibiotic showed weak activity against Gram-negative bacteria but suppressed growth of L1210 in mice; intravenous injection of 200 mg/kg to mice showed no toxicity. **20** was found to inhibit *Escherichia coli* GMP synthetase.[52] The mechanism of antitumor activity was studied by UEHARA *et al.*, using rat kidney cells infected with a mutant Rous sarcoma virus, the *src* gene of which is temperature sensitive.[53~55] **20** inhibited cell growth *in vitro*, and nucleic acid synthesis, 10 times more strongly at permissive temperatures (33°C) than at non-permissive temperatures (39°C). With respect to IMP, oxanosine 5′-monophosphate was found to be a potent near-competi-



Oxanosine (**20**)



2′-Amino-2′-deoxyguanosine (**21**)

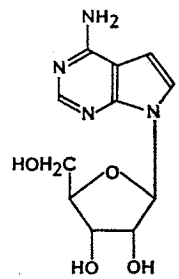
tive inhibitor, of IMP dehydrogenase isolated from cells grown either at 33° ($Ki=1\sim3\times10^{-6}$ M) or at 39° ($Ki=5.2\times10^{-6}$ M). This difference partly explains the preferential cytotoxicity of oxanosine to tumor cells (grow at 33°C).

2′-Amino-2′-deoxyguanosine (**21**) was synthesized in 1967. It was isolated from *Actinomadura* sp. and was shown to possess antimycoplasmal activity.[56]

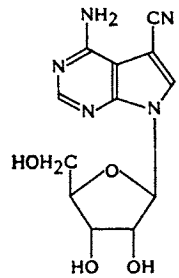
Cadeguomycin (**25**) and kanagawamicin (**26**) can be regarded as guanosine analogs but have been classified as pyrrolopyrimidine nucleosides in this review.

(3) Pyrrolopyrimidine Nucleosides

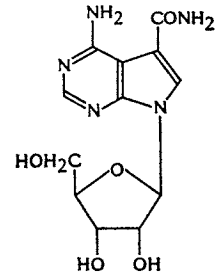
In addition to tubercidin (**22**), toyocamycin (**23**) and sangivamycin (**24**), two new pyrrolopyrimidine nucleosides have been recently reported. Cadeguomycin (**25**) is co-produced with tubercidin by *Streptomyces hygroscopicus*.[57,58] It is interesting that **25** has a 7-deazaguanosine skeleton suggesting that it may be an intermediate in the biosynthesis of tubercidin. SUHADOLNIK in 1971 proved that GTP, not ATP, is a precursor for pyrrolopyrimidine nucleosides biosynthesis. **25** stimulates pyrimidine



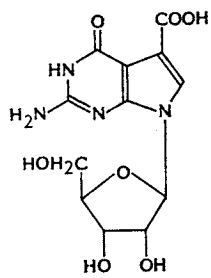
Tubercidin (**22**)



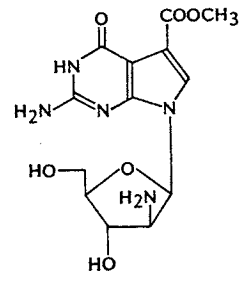
Toyocamycin (**23**)



Sangivamycin (**24**)

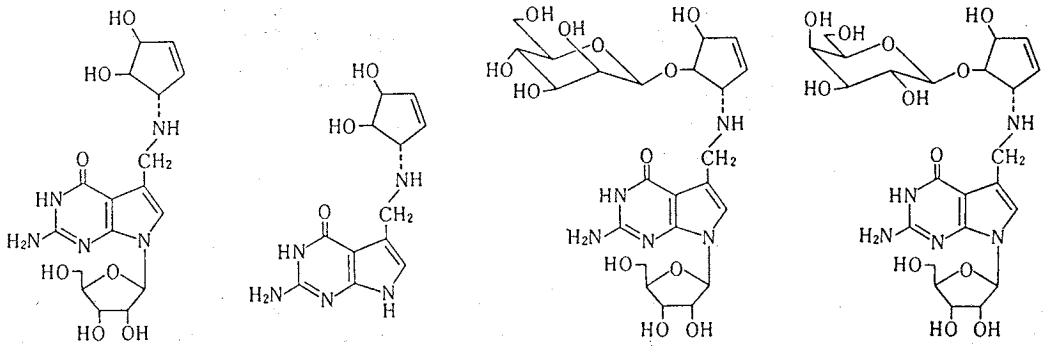


Cadeguomycin (**25**)



Kanagawamicin (**26**)

Fig. 1. Structure of queuosine (A), queuine (B), mannose-containing queuosine (C), and galactose-containing queuosine (D).



A B C D

nucleoside uptake by K562 cells, thus potentiating the cytotoxicity of 1-β-D-arabinofuranosylcytosine.[59~61] It has been proposed that **25** is converted to the monophosphate in cells, which inhibits dCMP deaminase (H. SUZUKI, Riken Symposium, Sept. 1987, Wako). There are indications that **26** inhibits tumor growth and metastasis in association with modification of immune system.[59] Kanagawamicin (AB116) (**26**) is another example of a 7-deazaguanine nucleoside produced by *Actinoplanes kanagawaensis*.[62] In this case, the sugar moiety is also modified, in the form of 2-amino-2-deoxy-arabinofuranose. **26** shows antitumor activity and weak activity against Gram-negative bacteria.

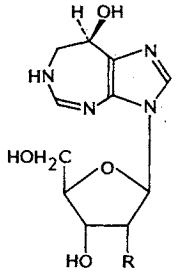
The discovery of Q-base (queuine) in tRNA of prokaryotes and eukaryotes was unexpected; it also, is a 7-deazaguanine derivative substituted at position 7 (Fig. 1). Transfer RNA guanine transglycosylase catalyzes an exchange insertion of Q-base precursors into the first G of tRNA anticodon. The biosynthesis of Q-base is believed to be dependent on intestinal bacteria.

The structure, biosynthesis and function of queuosine in tRNA has been reviewed by NISHIMURA.[63]

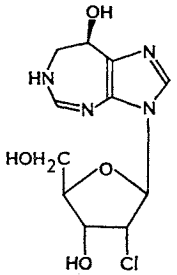
The inhibition of protein kinases including protein kinase C by sangivamycin (**24**) has recently been reported.[64,65] This activity is characteristic of **24**. The carbamoyl group on C-7 is apparently important because **22** and **23** have similar, very weak activity.[65]

(4) Tetrahydroimidazodiazepine Nucleosides

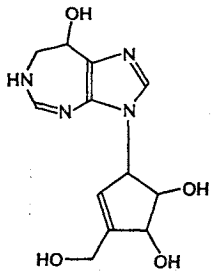
In addition to coformycin (**27**)[66] and deoxycoformycin (pentostatin) (**28**),[67] both potent inhibitors of adenosine deaminase, two new members of this group have recently been discovered by ŌMURA and his collaborators. Adechlorin (**29**) was isolated from culture filtrates of an *Actinomadura* sp.[68] It has a chlorine atom in the 2′-position and a rare example of naturally-occurring halogenosugar. Like the coformycins, it strongly inhibited adenosine deaminase ($Ki=5.3\times10^{-10}$ M) and potentiated the antiviral activity of Ara-A. Adecypenol (**30**) was isolated from *Streptomyces* sp.[69] and it was shown that it has a neplanocin-type cyclopentene derivative as the sugar moiety. Compared with other members of this group, **30** showed weak activity against adenosine deaminase ($Ki=4.7\times10^{-9}$ M). However, because of the structure of the sugar, it is thought that it would not be phosphorylated in cells, thus exhibiting lower toxicity (H. TANAKA, Riken Symposium, Sept. 1987); the configuration of the sugar has not been determined. The biosynthesis of deoxycoformycin was studied and it was shown that **28** is formed by ring expansion of the adenine moiety of adenosine; the C-1 of



Coformycin (**27**) R=OH
Deoxycoformycin (**28**) R=H



Adechlorin (**29**)



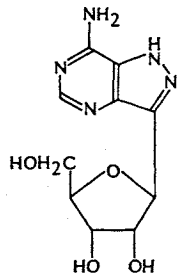
Adecypenol (**30**)

D-ribose is the source of the C-7 carbon of the aglycone.[70]

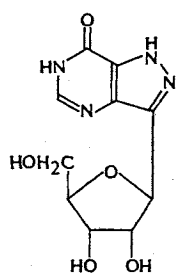
(5) *C*-Nucleosides

Formycins A (**31**) and B (**32**) are pyrazolopyrimidine nucleosides. Pyrazomycin (pyrazofurin) (**33**) is a pyrazole nucleoside. Showdomycin (**34**) has a maleimide ring and minimycin (oxazinomycin) (**35**) has an oxazinedione ring. The chemistry and biology of this group have been extensively reviewed.[1~4] This group of nucleoside has been shown to have a common biosynthetic precursor, glutamate and as shown in Fig. 2, the maleimide ring of showdomycin is formed from carbons-2, 3, 4 and 5 of glutamate.[71~72] However minimycin utilizes carbons-3, 4 and 5,[73,74] and the pyrazole ring of formycin[75,76] and pyrazofurin[77] is formed from carbons-1, 2, 3 and 4. Therefore, a hypothetical common biosynthetic intermediate may be proposed for this group of nucleoside derivatives as shown in Fig. 2.

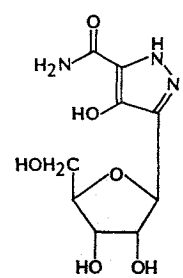
Ezomycins B_1, B_2, C_1, and C_2 (**112**, **113**, **114**, and **115**), have a pseudouridine-type structure[78] with



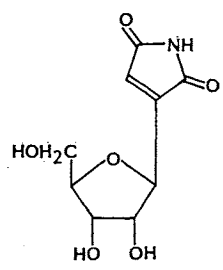
Formycin A (**31**)



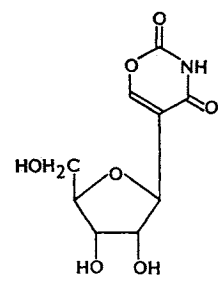
Formycin B (**32**)



Pyrazomycin (**33**, pyrazofurin)

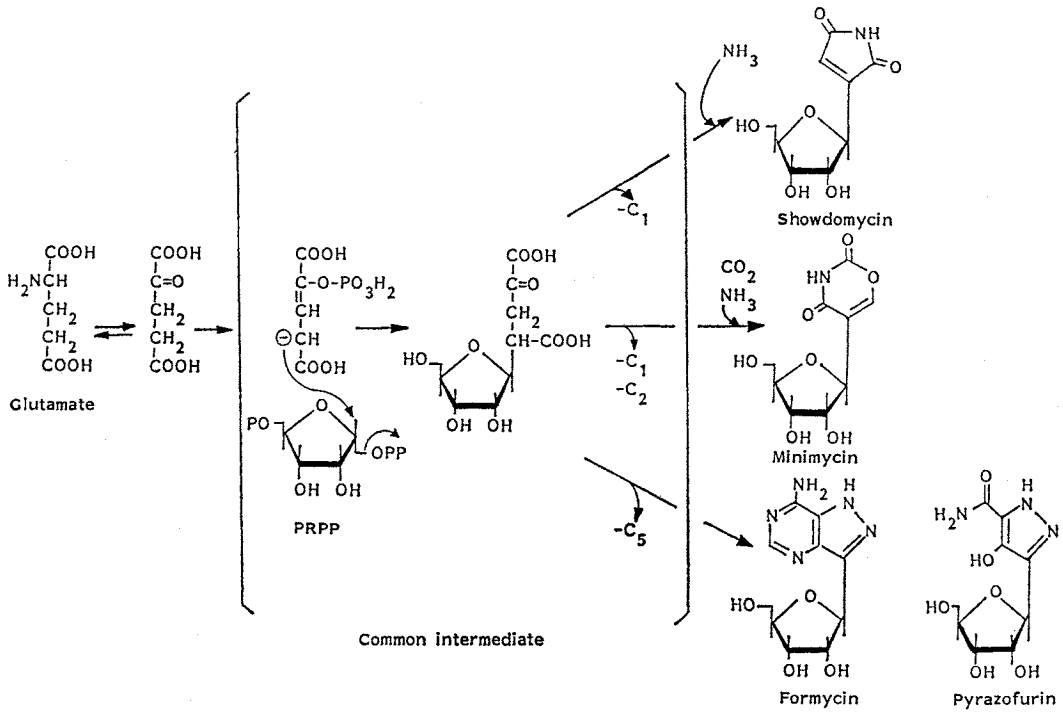


Showdomycin (**34**)



Oxazinomycin (**35**, minimycin)

Fig. 2. Biosynthesis of *C*-nucleosides.

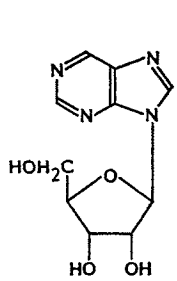


the same carbon skeleton as that of octosyl acids. They will be described later in this review together with the "high-carbon sugar nucleosides".

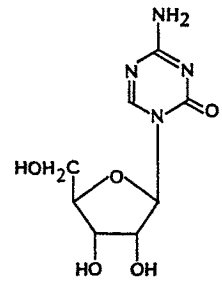
(6) Others

Neburaline (**36**)[78] and 5-azacytidine (**37**)[80,81] are well-known. Bredinin (**38**), an imidazole nucleoside isolated from *Eupenicillium brefeldianum*,[82] has potent cytotoxic effects on mammalian cells in culture and is a promising immunosuppressive agent. Bredinin monophosphate, when formed in cells blocks the conversion of IMP to XMP by inhibiting IMP dehydrogenase.[83,84]

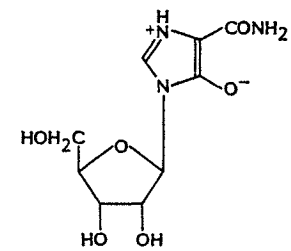
Two indole nucleosides have been described. Neosidomycin (**39**) is produced by *S. hygroscopicus*, and is a weak inhibitor, of Gram-negative bacteria.[85] SF-2140 (**40**) was isolated from culture filtrates of *Actinomadura* sp.[86] and it is a rare example of a compound having an α-nucleosidic linkage. Antibacterial activity of **40** is weak but it showed proliferation-inhibiting activity against



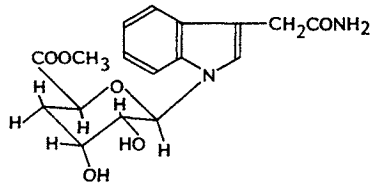
Neburaline (**36**)



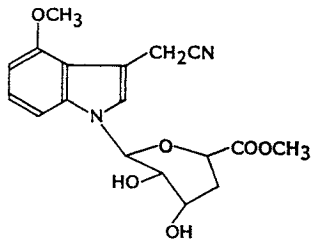
5-Azacytidine (**37**)



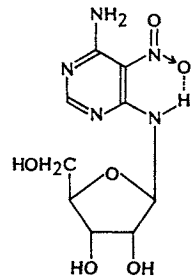
Bredinin (**38**)



Neosidomycin (**39**)



SF-2140 (**40**)



Clitocine (**41**)

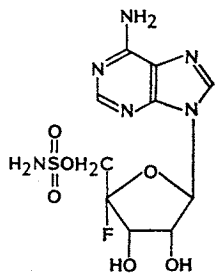
several influenza virus strains. It also prolonged the survival rate of mice infected with influenza virus A_0/PR-8.

Clitocine (**41**) is 6-amino-5-nitro-4-imino[ribofuranosyl]pyrimidine, which was isolated from a mushroom *Clitocybe inversa* and showed insecticidal activity against *Pectinophora gossypiella.*[87]

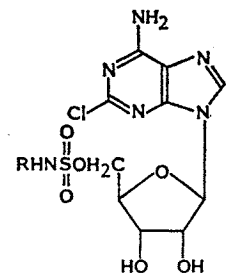
3: Acyl and Glycosyl Nucleosides

(1) Sulfamoyl Nucleosides

Nucleocidin (**42**) is one of the oldest known nucleoside antibiotics and had a long history before the correct structure was obtained.[88] It contains a unique sulfamoyl group and fluorosugar; it is believed that the sulfamoyl group mimics a phosphate group. Recently ascamycin (**43**) was isolated from *Streptomyces.*[89] The structure is 5′-*O*-L-alanylsulfamoyl-2-chloroadenosine and the dealanyl analog (AT-265) (**44**)[90] is produced by the same strain. Although **44** has a broad antibacterial spectrum, **45** showed a selective activity against *Xanthomonas* sp. It has been suggested that **44** can permeate cell membrane but **43** cannot. Subsequently, *Xanthomonas citri* was found to have a specific aminopeptidase on its cell envelope which hydrolyzes the alanyl group of **43** to give **44.**[91] The aminopeptidase has been purified and characterized as Xc-aminopeptidase, which is specific to L-prolyl and L-alanyl peptides.[92] **43** and several aminoacyl analogs have been synthesized,[93,94] whose antimicrobial activities correlated well with their susceptibility to Xc-aminopeptidase. 5′-*O*-Sulfamoyladenosine (**45**), isolated from *Streptomyces* sp., is inhibitory to bacteria and cytotoxic to P388 cells.[95] More recently 5′-*O*-sulfamoyltubercidin (**46**), which has herbicidal activity has been isolated from *Streptomyces mirabilis.*[96]

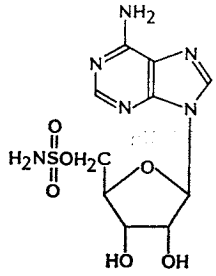


Nucleocidin (**42**)

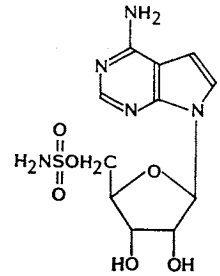


Ascamycin (**43**) R=$H_2NCH(CH_3)CO$– (L)

Dealanylascamycin (**44**, AT-265) R=H



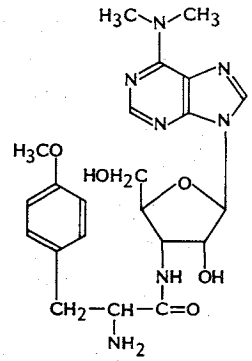
5′-*O*-Sulfamoyladenosine (**45**)



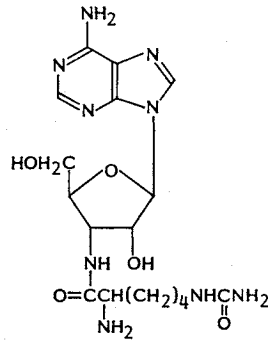
5′-*O*-Sulfamoyltubercidin (**46**)

(2) 3′-Aminoacyl-3′-deoxyadenosines

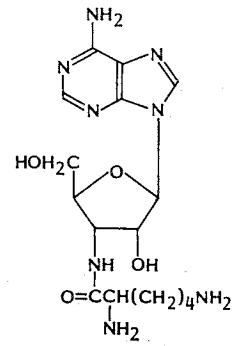
3′-Aminoacylamino-3′-deoxyadenosines (**47**, **48**, and **49**), among which puromycin (**47**) is the best known representative, are known to inhibit protein synthesis. Recently, chryscandin (**50**) has been isolated from *Chrysosporium pannorum*,[97] and the structure deduced from spectroscopic data and confirmed by total synthesis.[98,99] The structure differs from puromycin in having: (1) COOH in place of 5′-CH_2OH and (2) NH_2 in place of 6-$N(CH_3)_2$. In spite of such small structural differences the biological activities of **47** and **50** are quite different. Although puromycin shows broad antibacterial



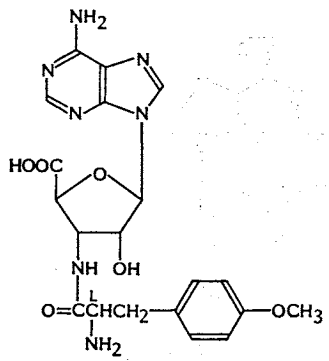
Puromycin (**47**)



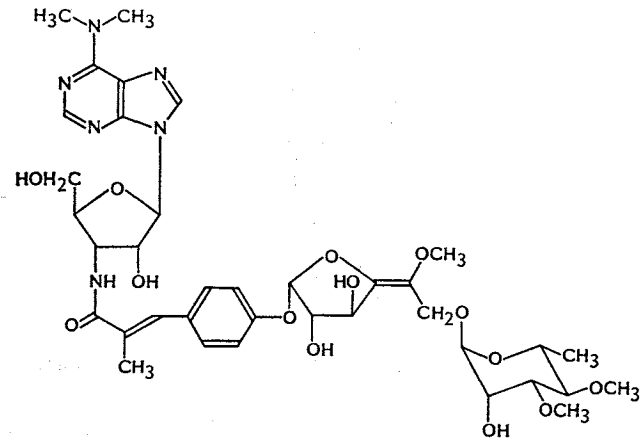
Homocitrullylaminoadenosine (**48**)



Lysylaminoadenosine (**49**)



Chryscandin (**50**)



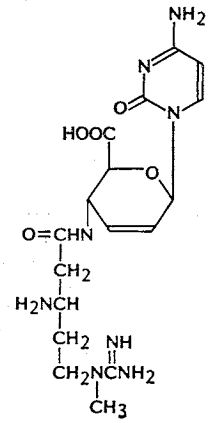
A201A (**51**)

activity but no activity to *Candida albicans*, chryscandin showed selective and strong inhibitory activity against *C. albicans*. Such inhibition was accompanied by swelling of the *Candida* cells. In contrast to the high toxicity of puromycin to animals, a 1-g/kg intraperitoneal injection of chryscandin showed no toxicity to mice. The morphological change induced in **50**-treated *Candida* cells suggests the site of action may be associated with cell wall biosynthesis. However, as yet, no detailed studies has been reported. A number of aminoacyl analogs of **50** were synthesized.[100] Among them, the *S*-benzylcyteinyl derivative was most active against *C. albicans*. The *in vitro* activity was quite comparable to that of 5-fluorocytosine.

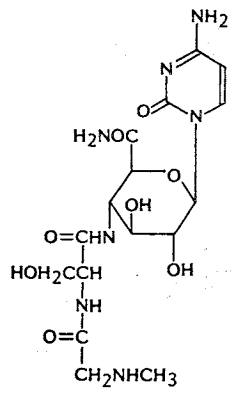
A201A (**51**) is an acyl derivative of puromycin nucleoside.[101] The structure can be regarded as a hybrid of puromycin and the glycoside antibiotic, hygromycin A. It is produced by *S. capreolus* and is active against Gram-positive bacteria.

(3) 4′-Aminoacyl-4′-deoxyhexose Cytosines

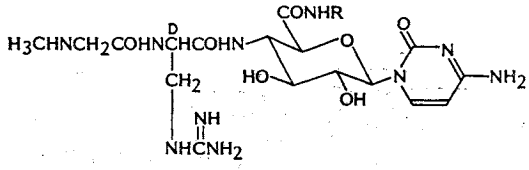
An agriculturally-useful fungicide, blasticidin S (**52**),[102] which inhibit peptidyltransferase in protein synthesis, is a representative of this group. Gougerotin (**53**)[103] and the bagougeramines A and B (**54** and **55**) belong to this group.[104,105] Structurally they are 4-aminoacyl-4-deoxyhexopyranose uronic acid cytosines. More recently arginomycin (**56**) was found to be produced by *Streptomyces arginensis*,[106] weakly active against Gram-positive bacteria and fungi. In spite of its close structural similarity to blasticidin S, it showed much lower toxicity to mice (LD_{50} 1,300 mg/kg, ip).



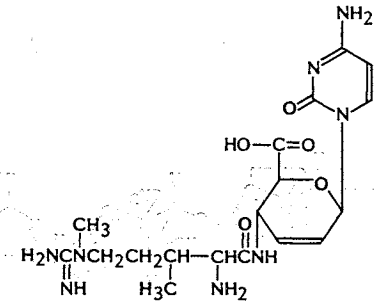
Blasticidin S (**52**)



Gougerotin (**53**)



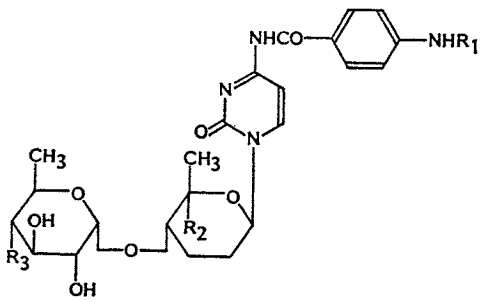
Bagougeramine A (**54**) R=H
Bagougeramine B (**55**) R=$(CH_2)_3NH(CH_2)_4NH_2$



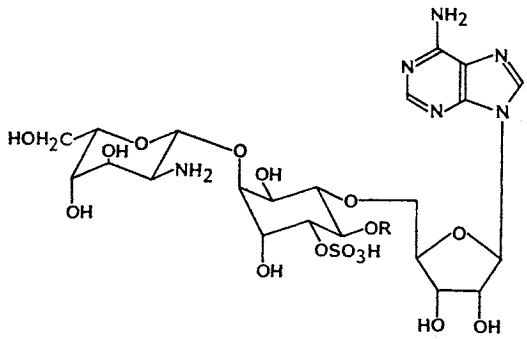
Arginomycin (**56**)

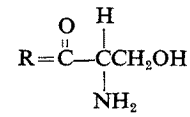
(4) Glycosyl Nucleosides

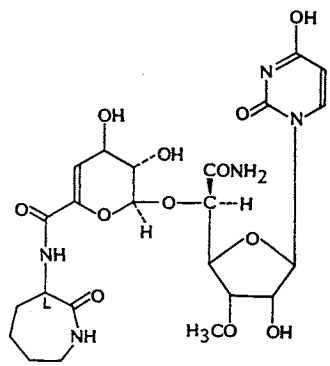
This group of antibiotics contains more than two sugars often having amino groups. Classical members are the cytosine nucleosides, amicetin (**57**),[107~109] bamicetin (**58**),[109] and plicacetin (**59**).[109] Oxamicetin (**60**) was isolated from *Arthrobacter oxamicetus* sp. nov.[110,111] and like blasticidin S, **57** is an inhibitor of protein synthesis. Adenomycin (**61**)[112] is an adenosine derivative glycosylated with an unique sulfated sugar and capuramycin (**62**) is a uracil nucleoside having an unsaturated uronic acid.[113,114] Both antibiotics showed only weak antibacterial activities. Dapiramicins (**63**, **64**, and **65**), isolated from *Micromonospora* sp., have a 7-deazaguanine of the toyocamycin type.[115,116] Disaccharide is linked to the amino group on the 2-position. Dapiramicin A (**63**) was effective



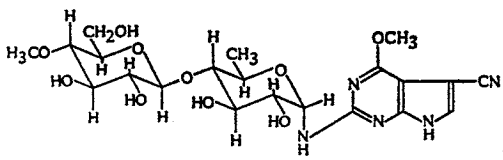
Amicetin (**57**)	R_1=α-Methylseryl	R_2=H	R_3=$N(CH_3)_2$
Bamicetin (**58**)	R_1=α-Methylseryl	R_2=H	R_3=$NHCH_3$
Plicacetin (**59**)	R_1=H	R_2=H	R_3=$N(CH_3)_2$
Oxamicetin (**60**)	R_1=α-Methylseryl	R_2=OH	R_3=$N(CH_3)_2$



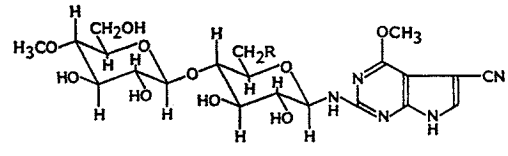
Adenomycin (**61**) R= 



Capuramycin (**62**)



Dapiramicin A (**63**)

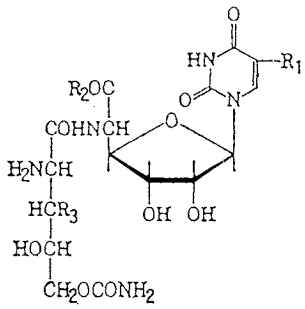


Epidapiramicin A (**64**) R=H
Dapiramicin B (**65**) R=OH

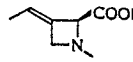
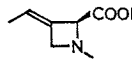
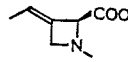
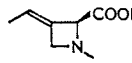
against sheath blight of rice plants caused by *Rhizoctonia solani* in pot test. Epidapiramicin A (**64**) and dapiramicin B (**65**) were less effective. Apparently the α-glycosidic configuration is important for antifungal activity.

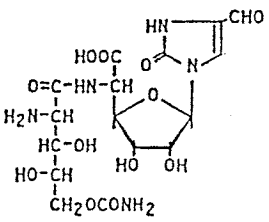
(5) Peptidyl Nucleosides

This group includes nucleosides, the sugar terminal of which constitutes an L-amino acid structure, to which more than one amino acid is peptide-linked. The agricultural fungicides, the polyoxins (**66**~**76**) discovered in this laboratory,[117,118] are representatives of this group. Polyoxins were the first nucleoside antibiotics found to inhibit fungal cell wall chitin biosynthesis. Their structures mimic UDP-*N*-acetylglucosamine, a substrate for chitin synthetase. Lack of activity against *Candida* sp. is believed to be due to a permeability barrier. In an effect to utilize the property of *Candida* dipeptide transport, several peptide analogs have been prepared, which were found to have weak anti-*Candida* activity.[119,120] The biosynthesis of polyoxins has been extensively investigated (Fig. 3). The nucleoside skeleton is synthesized by condensation of uridine (probably through 5'-aldehyde) and phosphoenolpyruvate.[121] Subsequently, two carbons are lost to give the allose uronic acid nucleoside. The isolation of the octosyl acids[104~106] supported this pathway. Carbon-3 of L-serine is then introduced into the 5-position of uracil to form a methyl, hydroxymethyl or carboxyl group by a different

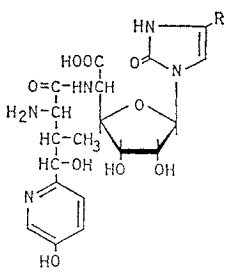


Polyoxins

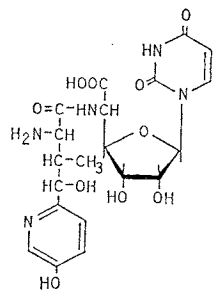
Polyoxin	R_1	R_2	R_3
A (**66**)	CH_2OH		OH
B (**67**)	CH_2OH	OH	OH
D (**68**)	COOH	OH	OH
E (**69**)	COOH	OH	H
F (**70**)	COOH		OH
G (**71**)	CH_2OH	OH	H
H (**72**)	CH_3		OH
J (**73**)	CH_3	OH	OH
K (**74**)	H		OH
L (**75**)	H	OH	OH
M (**76**)	H	OH	H



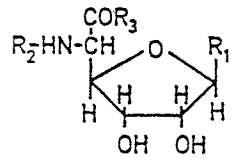
Polyoxin N (**77**)



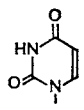
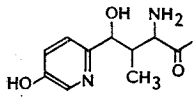
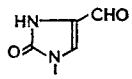
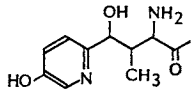
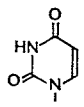
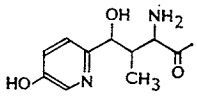
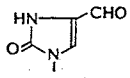
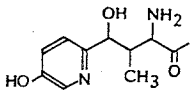
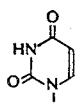
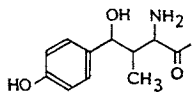
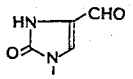
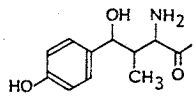
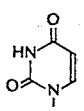
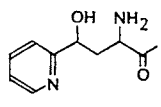
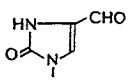
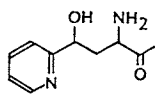
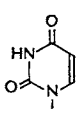
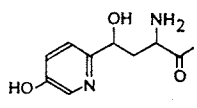
Neopolyoxin A (**78**) R=CHO
Neopolyoxin B (**79**) R=COOH

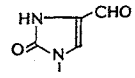
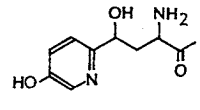
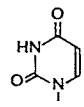
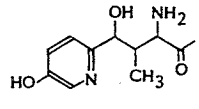
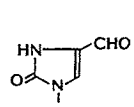
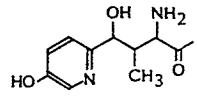
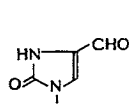
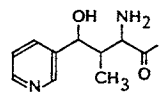
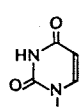
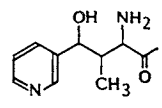
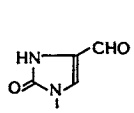
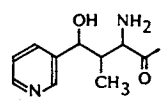
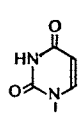
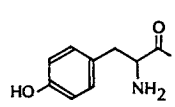
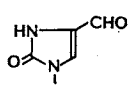
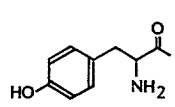


Neopolyoxin C (**80**)

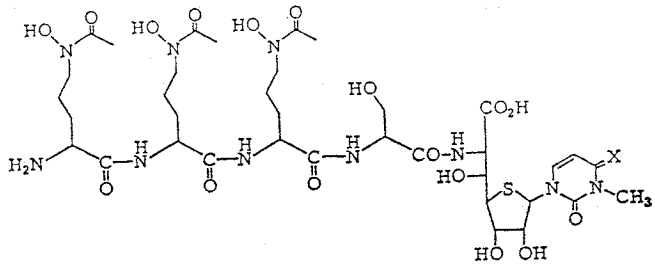


Nikkomycins

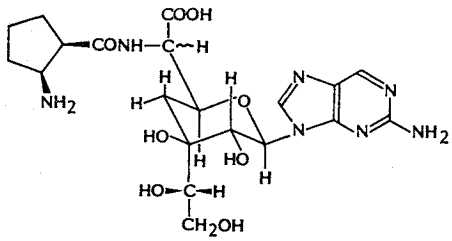
Nikkomycin	R_1	R_2	R_3
Z (81)			OH
$X_Z^{\prime}$ (82)			OH
J (83)			Glu
I (84)			Glu
B_Z (85)			OH
B_X (86)			OH
$K_Z^{\prime}$ (87)			OH
K_X (88)			OH
O_Z (89)			OH

Nikkomycin	R_1	R_2	R_3
O_X (90)			OH
Q_Z (91)			Homo-Ser
$Q_X^{\prime}$ (92)			Homo-Ser
P_X (93)			OH
R_{Z_a} (94)			Glu
R_X (95)			Glu
W_Z (96)			OH
W_X (97)			OH

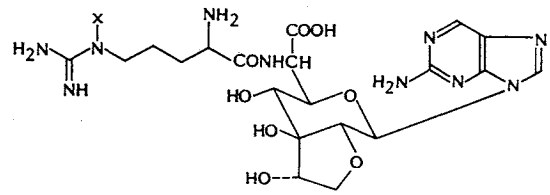
pathway from thymidylate synthetase. L-Glutamic acid and L-isoleucine were shown to be precursors of the two highly modified side chain amino acids (carbamoylpolyoxamic acid and polyoximic acid). Aberrant 5-fluoropolyoxins were biosynthesized by feeding 5-fluorouracil.[122] It is interesting to note that C-1 unit incorporation into the 5-position was completely inhibited in this case, suggesting that the mechanism is similar to the inhibition of thymidylate synthetase by FUDR phosphate. The chemistry, biosynthesis and biological properties of polyoxins have been reviewed.[118]



Albomycin δ_2 (**98**) X=$NCONH_2$
Albomycin ε (**99**) X=NH
Albomycin δ_1 (**100**) X=O

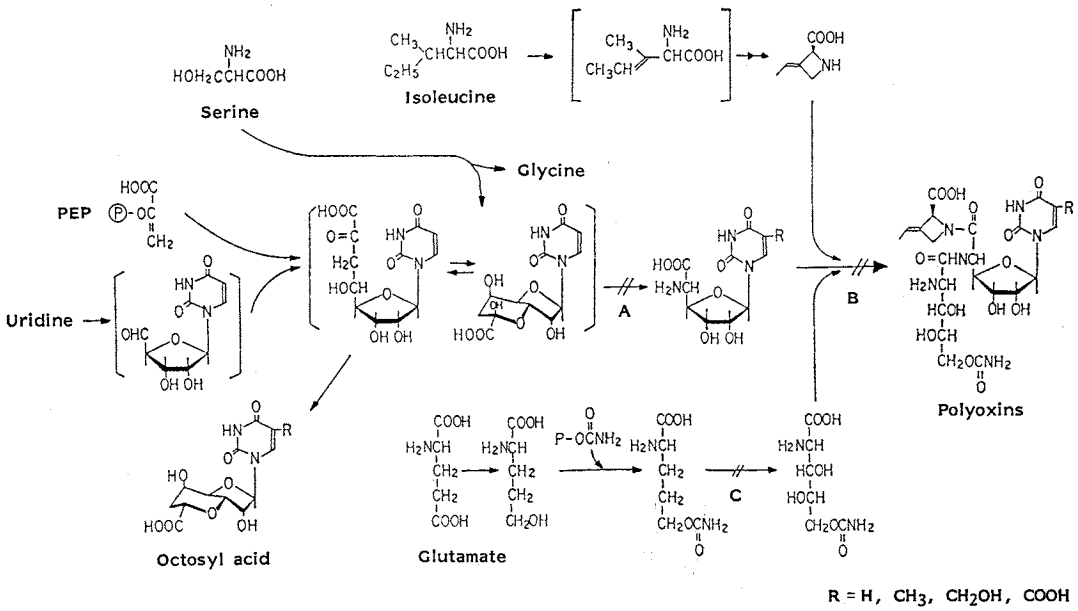


Amipurimycin (**101**)



Miharamycin A (**102**) X=OH
Miharamycin B (**103**) X=H

Fig. 3. Biosynthesis of the polyoxins.
Letters A, B, and C indicate blocked mutants obtained.



More recently, neopolyoxins A, B, and C (**78**, **79**, and **80**) were isolated from a newly isolated strain of *Streptomyces cacaoi* subsp. *asoensis*.[123,124] Neopolyoxin A (**78**) has 4-formyl-2-oxoimidazole instead of uracil and a side chain amino acid having 3-hydroxypyridine. **78** showed higher activity than the polyoxins both *in vitro* and *in vivo*. It is also inhibitory to *C. albicans*. Although the uracil

nucleoside obtained from **79** was converted chemically to the corresponding 4-carboxy-2-oxoimidazoline nucleoside, ^{14}C-labeled uracil was not incorporated into **78** by *S. cacaoi* (K. ISONO; unpublished data). Polyoxin N (**77**) produced by *Streptomyces piomogenes*, has a hybrid polyoxin-neopolyoxin structure.

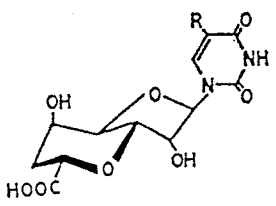
ZÄHNER and his collaborators have described the nikkomycins (**81**~**97**), a group nucleosides isolated from culture filtrates of *Streptomyces tandae*. Among them, nikkomycins Z (**81**) and X (**82**) are believed to be identical to neopolyoxins C and A, respectively. Acaricidal and insecticidal activities have been reported for these compounds. Some base analogs were also prepared by mutasynthesis, utilizing a uracil auxotroph of *S. tendae*. The characteristics of the nikkomycins were recently reviewed by FIEDLER.[125]

Albomycins are highly inhibitory to Gram-positive and Gram-negative bacteria and were well known long before their structure elucidation.[126] BENZ *et al.* have reisolated albomycins δ_2, ε, and δ_1 (**98**, **99**, and **100**) from *Streptomyces* sp. and determined their structures, which have a unique nucleoside-sugar skeleton, 6-amino-6-deoxy-4-thio-L-glycero-L-ido-heptofuranose uronic acid with a tetrapeptide side chain.[127,128] The nucleoside configuration was established by X-ray analysis of the sulfoxide derivative.[129] The tri-N^{δ}-acetyl-N^{δ}-hydroxyornithine moiety of these compounds acts as a siderophore, chelating with ferric ion.

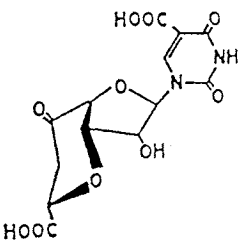
Amipurimycin (**101**)[130~132] and miharamycins (**102** and **103**)[133] have branched pyranose sugars and 2-aminopurine. They are both produced by *Streptomyces* and are inhibitory to *Pyricularia oryzae*, a pathogen of rice blast disease. Their mechanisms of action have not been studied.

(6) High-carbon Sugar Nucleosides

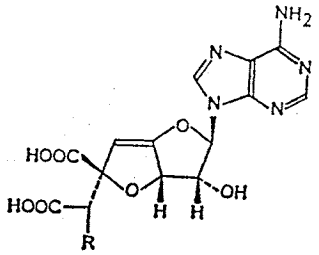
This group of antibiotics is presumed to be formed by the condensation of various nucleosides with sugars, amino acids, or organic acids. The octosyl acids (**104**, **105**, and **106**)[134] co-produced with polyoxins by *S. cacaoi* subsp. *asoensis*, are the sole case, in which the biosynthetic pathway has been elucidated. Octosyl acid A (**104**) is formed by an aldol-type condensation of uridine (5′-aldehyde) and phosphoenolpyruvate.[135] The 5-carboxyuracil of **104** is then replaced with adenine by chemical transglycosylation, and the product showed weak inhibitory activity against cAMP phosphodiesterases from mammalian cells.[136,137] The bicyclic carbon skeleton of **104** is similar to that of cAMP. Later, more potent inhibitors, the griseolic acids A, B, and C (**107**, **108**, and **109**) have been isolated from *Streptomyces griseoaurantiacus* by the Sankyo group.[138~140] Inhibition of the phosphodiesterase was competitive (Ki=0.26 μM). It was reported that **107** increases the cAMP level of rat plasma and liver by several fold. **107** also stimulated liver glycogen metabolism, which resulted in an increase of blood glucose level of mice. It also induced differentiation of murine neuro-



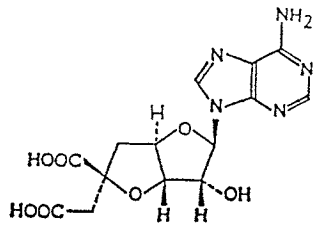
Octosyl acid A (**104**) R=COOH
Octosyl acid B (**105**) R=CH_2CH



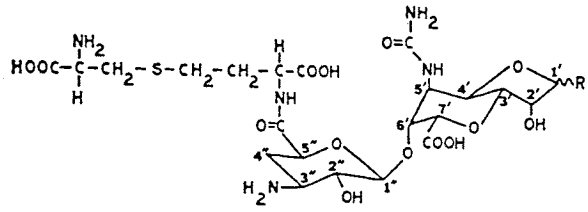
Octosyl acid C (**106**)



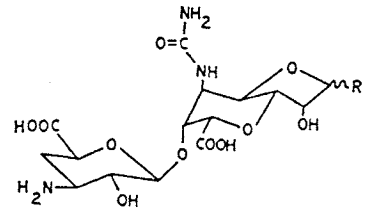
Griseolic acid A (**107**) R=H
Griseolic acid B (**108**) R=OH



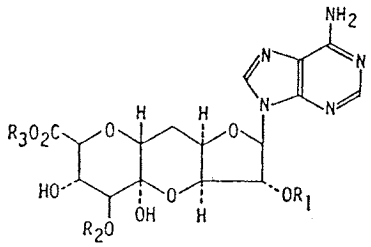
Griseolic acid C (**109**)



Ezomycin A_1 (**110**) R=β-1-Cytosine
Ezomycin B_1 (**112**) R=β-5-Uracil
Ezomycin C_1 (**114**) R=α-5-Uracil

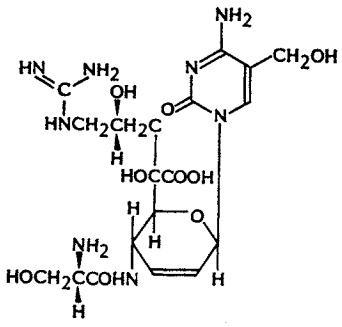


Ezomycin A_2 (**111**) R=β-1-Cytosine
Ezomycin B_2 (**113**) R=β-5-Uracil
Ezomycin C_2 (**115**) R=α-5-Uracil

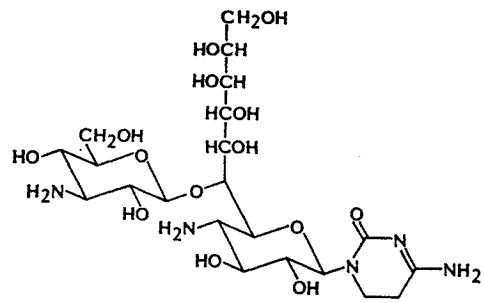


Herbicidins

Herbicidin	R_1	R_2	R_3
A (**116**)	CH_3	$CO(CH_2OH)C\overset{E}{=}CHCH_3$	CH_3
B (**117**)	CH_3	H	CH_3
E (**118**)	CH_3	$COCH(CH_3)_2$	CH_3
F (**119**)	CH_3	$CO(CH_3)C\overset{E}{=}CHCH_3$	CH_3
G (**120**)	H	$CO(CH_3)C\overset{E}{=}CHCH_3$	H



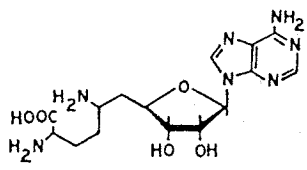
Mildiomycin (**121**)



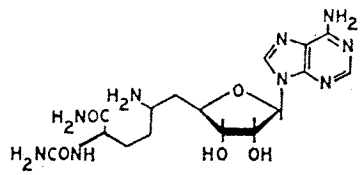
Anthelmycin (**122**, hikizimycin)

blastoma (Neuro 2a) (H. NAKAGAWA, Riken Symposium, Sept. 1987, Wako). Oxaloacetate or a biochemical equivalent may be involved in the biosynthesis of the griseolic acids.

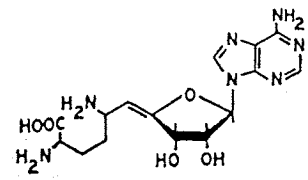
Ezomycins (**110**~**115**) have the same carbon skeleton as the octosyl acids.[78,141] Ezomycins A_1 (**110**) and A_2 (**111**) are cytosine nucleosides. In contrast, ezomycins B_1 (**112**), B_2 (**113**), C_1 (**114**), and C_2 (**115**) are of the pseudouridine-type. The presence of an α-nucleoside may be the result of iso-



Sinefungin (**123**, A9145)

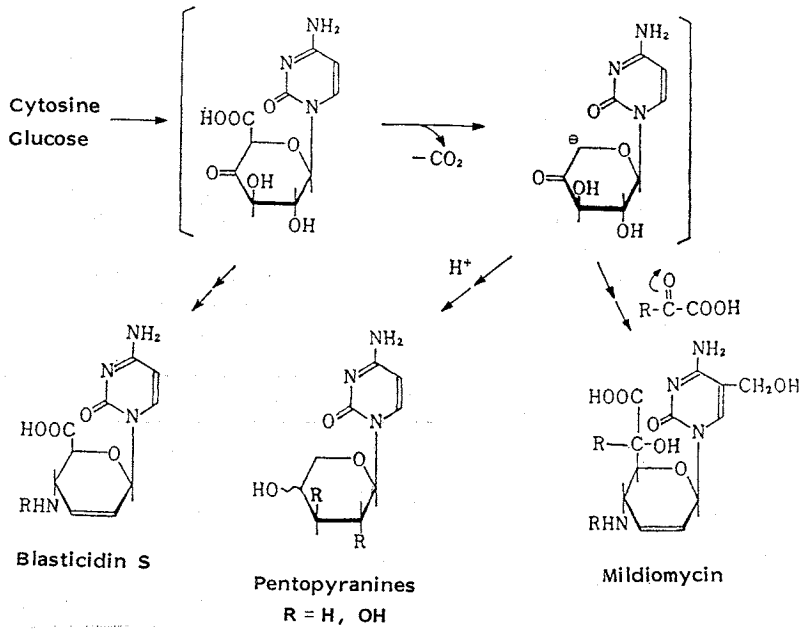


A9145A (**124**)



A9145C (**125**)

Fig. 4. Hypothetical biosynthetic relationship among blasticidin S, pentopyranines, and mildiomycin.



merization similar to pseudouridine;[142] thus, **114** and **115** are probably artifacts of isolation. The ezomycins show selective toxicity to a plant pathogenic fungus, *Botrytis cinerea*. However, no studies of mechanism of action have been reported. Herbicidins A, B, E, F, and G (**116**~**120**) contain a tricyclic dodecose.[143~147] They show selective herbicidal activity and limited antimicrobial activity and are markedly low-toxic to mice.

Mildiomycin (**121**) with a unique decose carbon skeleton[148~150] was isolated from *Streptoverticillium rimofaciens*,[151~152] and showed selective inhibitory activities against several phytopathogenic fungi. It has been successfully applied in the prevention of plant anthracnose. The mode of action of mildiomycin was studied in a cell-free system from *E. coli* and inhibition of protein synthesis at an early stage was suggested. Some cytosine analogs of mildiomycin were obtained by feeding 5-substituted cytosines to the producing organism.[153] An interesting question concerns its biosynthesis since the carboxyl carbon may originate from sugar or amino acid. The latter may be more likely, because the 4′-urose nucleoside is considered to be a key intermediate in the biosynthesis of mildiomycin, blasticidin S, and the pentopyranines (Fig. 4). GABRIEL has proposed that 4-urose nucleotide is a biosynthetic precursor for 4-epimerization, 6-deoxygenation, decarboxylation of hexose uronic acids, and rearrangement of carbon skeleton.[154]

Hikizimycin (anthelmycin) (**122**), 4-amino-4-deoxyundecose nucleoside is a disaccharide nucleoside isolated for the first time in 1964.[155~157] It has broad antimicrobial activity and strong anthelmintic activity has been reported. The mode of action appears to be inhibition of transpeptidation in protein synthesis.

The sinefungin (A9145) (**123**), A9145A (**124**), and A9145C (**125**) have been isolated from *Streptomyces griseolus* as antifungal antibiotics.[158~161] Like polyoxins, they are structures of a sugar and an amino acid. Adenosine and ornithine were incorporated efficiently into **123**.[162] It appears that **123** is an inhibitor of *S*-adenosylhomocysteinase (similar to neplanocin A and aristeromycin), thus inhibiting transmethylases. It was also shown that **123** and **125** inhibit Newcastle disease virus and are competitive inhibitors of the mRNA (guanine-7)-methyltransferase and (nucleoside-2′)-methyltransferase of vaccinia virus.[163] Inhibition of 1-aminocyclopropane-1-carboxylic acid synthetase from tomatoes was also reported.[164]

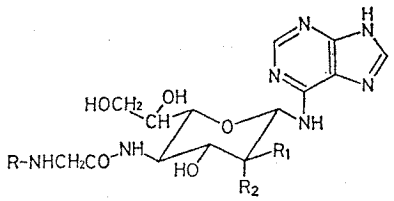
(7) Fatty Acyl Nucleosides

Spicamycin (**127**)[165] is a 2′-epimer of septacidin (**126**)[166,167] and contains a complex of a number of normal and *iso* fatty acyl groups on the amino group of the glycyl moiety. It is toxic to murine leukemia cell M1 and induces phagocytic activity; it is also inhibitory to *Candida* and *Saccharomyces*.

The tunicamycins (**128~137**)[168] were first isolated from the fermentation broth of *Streptomyces lysosuperificus* nov. sp. as antiviral principles by G. TAMURA and his collaborators. The structure is composed of uracil, fatty acid and two glycosidically linked sugars, *N*-acetylglucosamine and undecadialdose. The structure mimics the reaction intermediate in transglycosylation of *N*-acetylglucosamine from uridine diphosphate to lipid phosphate. Tunicamycins inhibit the formation of lipid intermediates in various glycoconjugate syntheses such as glycoproteins of vertebrates, plants, yeasts, and viruses, peptidoglycan synthesis of bacteria, teichoic acid and teichuronic acid syntheses of bacteria, and glycosaminoglycan syntheses of vertebrates. This diverse activity makes them extremely useful biological probes. The chemistry and biology of tunicamycins were extensively reviewed by TAMURA.[169]

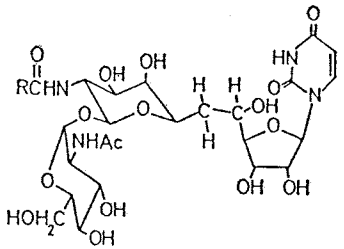
Streptovirudins (**138~147**) are structurally related to tunicamycin;[170] some (**143~147**) have dihydrouracil in place of uracil. Corynetoxins (**148~160**) are produced by *Corynebacterium rathayi*, whose infestation in galled seedheads of ryegrass is a toxic to grazing animals in Australia. The toxins were isolated and found to be new members of the tunicamycin group of antibiotics.[171]

Liposidomycins A, B, and C are a family of fatty acyl nucleoside antibiotics recently isolated in our laboratory from *Streptomyces griseosporeus*, and which strongly inhibit bacterial peptidoglycan synthesis (ID_{50} 0.03 μg/ml).[172] Structure **161** was recently proposed for liposidomycin B from chem-



Septacidin (**126**) R_1=OH R_2=H
Spicamycin (**127**) R_1=H R_2=OH

R=$(CH_3)_2CH(CH_2)_nCO$–,
$CH_3CH_2CH_2(CH_2)_nCO$–
n=8~14



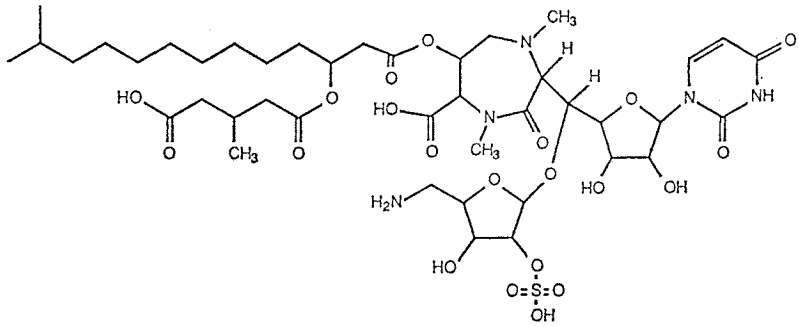
Tunicamycins	R
I (128)	$(CH_3)_2CH(CH_2)_7C{=}C(H)-$
II (C) (129)	$(CH_3)_2CH(CH_2)_8C{=}C(H)-$
III (130)	$CH_3(CH_2)_{10}C{=}C(H)-$
IV (131)	$CH_3(CH_2)_{11}C{=}C(H)-$
V (A) (132)	$(CH_3)_2CH(CH_2)_9C{=}C(H)-$
VI (133)	$(CH_3)_2CH(CH)_{11}-$
VII (B) (134)	$(CH_3)_2CH(CH)_{10}C{=}C(H)-$
VIII (135)	$CH_3(CH)_{12}C{=}C(H)-$
IX (136)	$CH_3(CH)_{13}C{=}C(H)-$
X (D) (137)	$(CH_3)_2CH(CH_2)_{11}C{=}C(H)-$

Streptovirudins	R
A_1 (138)	$(CH_3)_2CH(CH_2)_6CH{=}CH-$
B_1 (139)	$CH_3CH_2(CH_3)CH(CH_2)_6CH{=}CH-$
B_{1a} (140)	$(CH_3)_2CH(CH_2)_7CH{=}CH-$
C_1 (141)	$(CH_3)_2CH(CH_2)_8CH{=}CH-$
D_1 (142)	$CH_3CH_2(CH_3)CH(CH_2)_8CH{=}CH-$

	Base
A_2 (143)	Dihydrouracil
B_2 (144)	Dihydrouracil
B_{2a} (145)	Dihydrouracil
C_2 (146)	Dihydrouracil
D_2 (147)	Dihydrouracil

Corynetoxins	R
	β-Hydroxy
148	*i*-C_{16}
149	*i*-C_{18}
150	*a*-C_{17}
151	*a*-C_{19}
	α,β-Unsaturated
152	*i*-C_{16}
153	*i*-C_{18}
154	*a*-C_{17}
155	*a*-C_{19}
	Saturated
156	*i*-C_{16}
157	*i*-C_{18}
158	*a*-C_{15}
159	*a*-C_{17}
160	*a*-C_{19}

i: *iso*, *a*: *anteiso*.

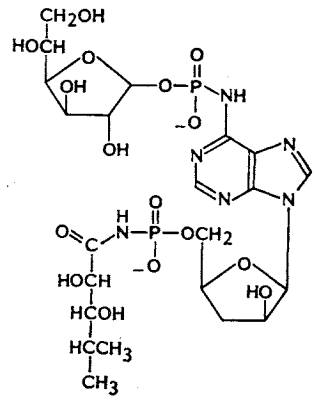


Liposidomycin B (**161**)

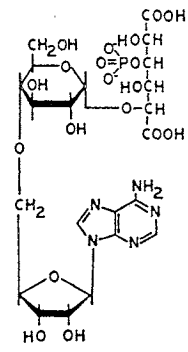
ical and NMR and mass spectroscopic evidence; this resembles the reaction intermediate between UDP-*N*-acetylmuramylpentapeptide and undecaprenyl phosphate in the lipid cycle of peptidoglycan synthesis.[173] Indeed, it was recently found that liposidomycin C inhibits the formation of undecaprenyl diphospho-*N*-acetylmuramylpentapeptide from the corresponding UDP-sugar peptide and lipid phosphate by a particulate enzyme prepared from *E. coli* Y-10 (K. KIMURA *et al.*; to be published). It is of interest to note, that the activity of liposidomycin is selective to peptidoglycan synthesis, which is in sharp contrast with that of tunicamycin, which inhibits glycoconjugate syntheses of various origins. In spite of its high *in vitro* activity, liposidomycin showed only limited inhibitory activity against Gram-positive, Gram-negative bacteria, and mycobacteria. The liposidomycins show low toxicity to mice.

4: Nucleotides

Agrocin 84 (**162**) is a rare example of an adenine nucleotide of bacteriocin-like activity, which is elaborated by the non-pathogenic strain, *Agrobacterium radiobacter* strain 4, used for biological control of crown gall.[174] This compound is a general inhibitor of pathogenic *Agrobacterium* of the same or related species, including oncogenic strain of *Agrobacterium tumefaciens*. TATE *et al.*[175] determined the structure of **162** by sequential degradation and showed that a 5′-phosphoryl linkage from the "fraudulent" nucleoside core, 9-(3′-deoxy-β-D-*threo*-pentofuranosyl)adenine to the amide group of D-*threo*-2,3-dideoxy-4-methylpentanamide is required for antibiotic activity, but that bacteriocin-like specificity is conferred by a D-glycofuranosyloxyphosphoryl substituent at N^6 of adenine. The mode



Agrocin 84 (**162**)



Thuringiensin (**163**)

of action of agrocin was suggested to be inhibition of DNA synthesis because it inhibits thymidine uptake by agrocin-sensitive *A. tumefaciens*.[176]

Another example of an adenine nucleotide analog is thuringiensin (**163**), produced by *Bacillus thuringiensis* (for review, see ref 2). It is a so-called β-exotoxin and highly toxic to insects and mammals, it inhibiting both prokaryotic and eukaryotic RNA polymerases. B. T. (*B. thuringiensis*) is used for the microbial control of insects and mites in many countries, but in this case the active ingredient is the protein endotoxin produced in bacterial cells.

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