Kirk-Othmer Encyclopedia of Chemical Technology.

NUCLEOSIDES AND NUCLEOTIDES

The naturally occurring nucleoside and nucleotide antibiotics listed alphabetically in Table 1 exist as either the *C*- or *N*-glycosides (see Nucleic acids). These antibiotics contain a variety of purine and pyrimidine rings, including the diazepin, maleimide, indole, imidazole, pyrrolopyrimidine, pyrazolpyrimidine, pyrazole, oxazine, triazene, hydantoin, and the purine ring having a 6-*N*-phosphoramidate substituent. The structures of the carbohydrate moieties also vary. Some nucleosides have additional carbon atoms attached to the ribosyl moiety and in some cases ribose has been replaced by other sugars such as allulose, olefinic sugars, 2-, 3-, 4-, or 5-amino sugars, 4-fluororibose, 4-aminohexoses, aminouronic acids, disaccharides, or a tricyclic dodecose.

The naturally occurring nucleoside/nucleotide antibiotics, which have been isolated from bacteria, fungi, blue-green algae, and marine sponges, have proven to be useful biochemical probes in eucaryotic, procaryotic, viral, fungal, and plant systems. For example, the tunicamycins [11089-65-9] and mureidomycins are valuable because of their importance in peptidoglycan synthesis, mucopolysaccharide synthesis, and inhibition of the synthesis of the oligosaccharide moiety of the glycoproteins. Antibiotic A201A, which is structurally similar to puromycin, is an inhibitor of protein synthesis. 2′-Deoxycoformycin has found dramatic application in the treatment of hairy cell leukemia (see Chemotherapeutic agents, anticancer) and as a means to increase the therapeutic efficacy of cordycepin, formycin, and arabinofuranosyladenine (ara-A) through inhibition of adenosine deaminase. The 4-aminohexose nucleoside antibiotics and 2′-amino-2′-deoxyguanosine have been useful in elucidating the steps in protein synthesis, whereas psicofuranine and decoyinine have found use as inducers of sporulation in bacteria. Showdomycin is an excellent probe of membrane transport. The arabinosylpyrimidine nucleosides, ara-T and ara-U, have antiviral activities (see Antiviral agents). Several nucleoside analogues have herbicidal activity (see Herbicides). Some excellent reviews on the nucleoside/nucleotide antibiotics are available (1–4) (see also Antiparasitic agents).

1. C-Nucleosides

The naturally occurring *C*-nucleosides containing *C*-glycosyl linkages are shown in Table 1.

1.1. Ezomycins

The ezomycins [58572-97-7] **(1–6)** are naturally occurring pyrimidine nucleosides produced by the *Streptomyces* (1–4). The ezomycins, which are comprised of ezomycin A [60182-24-3], ezomycin B [60182-25-4], and ezomycin C, inhibit the phytopathogenic fungi, *Sclerotinia* and *Botrytis* sp., but not bacteria and yeast. Ezomycins B_1, B_2, C_1, and C_2 are pseudouridine-type *C*-nucleosides, whereas ezomycins A_1 and A_2 are *N*-nucleosides. Ezomycins A_1, B_1, and C_1, but not A_2, B_2, and C_2, contain the L-cystathionine moiety. Ezomycins A_1, A_2, B_1, and B_2 are β-nucleosides; C_1 and C_2 are α-nucleosides.

Table 1. *C*-Nucleoside Antibiotics

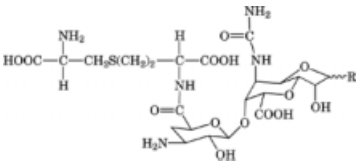
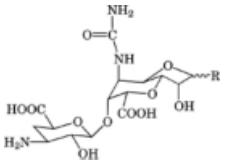
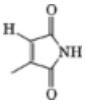
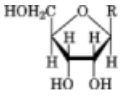
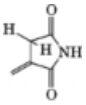
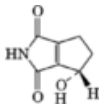
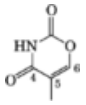
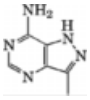
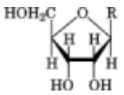
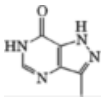
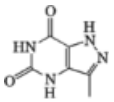
Name	CAS Registry Number	Molecular formula	Structure number	R	Structure
ezomycin A_1 ezomycine B_1 ezomycin C_1	[39422-19-0] [39422-20-3] [58002-06-5]	$C_{26}H_{38}N_8O_{15}S$ $C_{26}H_{39}N_7O_{17}S$ $C_{26}H_{37}N_7O_{16}S$	**(1)(2)(3)**	β-1-cytosine β-5-uracil α-5-uracil	
ezomycin A_2 ezomycin B_2 ezomycin C_2	[54328-22-2] [57973-16-7] [57973-14-5]	$C_{19}H_{26}N_6O_{12}$ $C_{19}H_{25}N_5O_{13}$ $C_{19}H_{25}N_5O_{13}$	**(4)(5)(6)**	β-1-cytosine β-5-uracil α-5-uracil	
showdomycin	[16755-07-0]	$C^9H_{11}NO_6$	**(7)**		
isoshowdomycin	[37760-84-2]	$C_9H_{11}NO_6$	**(8)**		
maleimycin	[50988-16-4]	$C_7H_7NO_3$	**(9)**		
oxazinomycin	[32388-21-9]	$C_9H_{11}NO_7$	**(10)**		
pyrazomycin (pyrazofurin)	[30868-30-5]	$C_9H_{13}N_3O_6$	**(11)**		

Table 1. ***Continued***

Name	CAS Registry Number	Molecular formula	Structure number	R	Structure
formycin formycin B	[6742-12-7] [138877-76-4]	$C_{10}H_{13}N_5O_4$ $C_{10}H_{12}N_4O_5$	**(12)(13)**		
oxoformycin B	[19246-88-9]	$C_{10}H_{12}N_4O_6$	**(14)**		

1.2. Showdomycin

Showdomycin (2-β-D-ribofuranosylmaleimide) **(7)** is a maleimide *C*-nucleoside antibiotic synthesized by *S. showdoensis*; isoshowdomycin **(8)** and maleimycin **(9)** have also been isolated (1–6). Showdomycin is not phosphorylated by nucleoside kinase and is not a substrate for nucleoside phosphorylase. Once **(7)** enters the cell, it blocks the uptake of glucose and other nutrients.

1.3. Oxazinomycin

Oxazinomycin (5-β-D-ribofuranosyl-1,3-oxazine-2,4-dione) **(10)**, also known as minimycin, has been isolated from *S. hygroscopicus* and *S. mediocidicus* (1–4). It inhibits gram-positive and gram-negative bacteria and tumor growth, but not yeast or fungi. The biosynthesis of **(6)** proceeds from [5-^{14}C,3-^{3}H]glutamic acid with carbons 4,5, and 6 of the oxazine ring of **(10)** arising from carbons 5, 4, and 3 of glutamic acid (4). The naturally occurring *C*-nucleoside antibiotics showdomycin **(7)**, formycin **(12)**, oxazinomycin **(10)**, and pyrazomycin **(11)** utilize acetate and glutamate as the carbon source for their aglycons (4, 7–10).

1.4. Pyrazomycin

Pyrazomycin **(11)**, 3-(1-β-D-ribofuranosyl)-4-hydroxypyrazole 5-carboxamide, is isolated from *S. candidus* (1–4, 9, 10). The incorporation of [2-^{13}C]acetate and [1- and U-^{14}C]glutamate into the four contiguous carbons of pyrazomycin has been reported (11, 12). Pyrazomycin 5′-phosphate inhibits orotidylic acid decarboxylase. Pyrazomycin inhibits adenosine phosphorylation and decreases the incorporation of deoxyuridine into DNA of Novikoff hepatoma cells in culture. It also inhibits the growth of tumor cells and the cytopathic effects of vaccinia, herpes simplex, vesicular stomatitis, Newcastle disease, measles, Sindbis, polio, hepatitis A, and coxsackie viruses (13, 14). The inhibitory action of **(11)** on viral multiplication is reversed by uridine.

1.5. Pyrazolopyrimidine Nucleosides

Formycin **(12)**, formycin B **(13)**, and oxoformycin B **(14)** are naturally occurring pyrazolopyrimidine nucleosides isolated from *Nocardia interforma*, *S. lavendulae*, and *S. gunmaences* (1–4, 15). Coformycin, which inhibits adenosine deaminase, is also isolated from *N. interforma*. Glutamate is the precursor for the biosynthesis of

formycin (10). Compound **(12)**, but not **(13)**, is converted to its 5′-mono-, di-, and triphosphates (3). Compound **(12)** inhibits DNA and protein synthesis, but not RNA synthesis (1–4). Formycin 5′-triphosphate (FTP) is incorporated into RNA and codes as an adenosine 5′-triphosphate (ATP) with bacterial, viral, plant, RNA, and DNA polymerases (16). It is also an important probe of nucleoside transport (17–21). The tight binding of formycin 5′-phosphate to adenoside monophosphate (AMP) deaminase has been reported (22). Compound **(12)** has been used to elucidate ribosome-transfer RNA (tRNA) interactions and it has been reported that the stacking of $tRNA^{PheCCF}$, where the tail is phenylalanine–cytosine–cytosine–formycin, is weaker than that of $tRNA^{PheCCA}$ (23, 24). Donor activity for peptide bond formation of formycin-containing tRNA is much lower than that of normal tRNA. Compound **(12)**) is rapidly deaminated by erythrocytic adenosine deaminase; the absence of this deaminase in erythrocytes of adenosine deaminase (ADA)-deficient patients results in the conversion of **(12)** to FTP in quantities three times greater than ATP (25). An analogue of inosine [58-63-9] **(13)**, inhibits tumors and viruses, but does not appear to act via formation of the 5′-phosphates. It has been reported that **(12)** inhibits L5178Y cell growth as a competitive inhibitor of the nicotinamide adenine dinucleotide cation (NAD^+) and showed that **(7)** and **(13)** inhibit poly(ADP-ribose) polymerase (26, 27). The formycin analogue of NAD^+ has been shown to inhibit DNA synthesis (28).

Most recently the structure of pyrrolosine has been shown to be an isomeric *C*-nucleoside analogue of 9-deazainosine, which is 7-(β-D-ribofuranosyl)-4-oxo-3*H*,5*H*-pyrrolo[3-2-*d*]pyrimidine (29). Pyrrolosine inhibits development of starfish embryos.

2. *N*-Nucleosides

The naturally occurring nucleoside analogues discussed in this section contain the *N*-glycosyl linkage and either purine, pyrimidine, imidazole, diazepin, or indole rings. The purine nucleosides inhibit protein synthesis, RNA and DNA synthesis, and methyltransferases; they have antimycoplasmal, antiviral, hypotensive, antifungal, antimycobacterial, and antitumor activities and induce sporulation (1–4). The pyrimidine nucleosides inhibit protein synthesis, virus replication, RNA and DNA synthesis, and cAMP phosphodiesterase. The imidazole nucleosides inhibit nucleic acid synthesis. The diazepin nucleosides inhibit adenosine deaminase (ADA). The indole nucleosides inhibit bacteria, yeast, fungi, and viruses.

2.1. Purine *N*-Nucleosides

The purine *N*-nucleoside antibiotics are given in Tables 2 and 3.

Table 2. Purine *N*-Nucleoside Antibiotics[a]

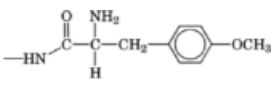
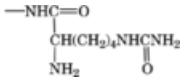
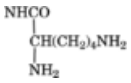
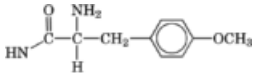
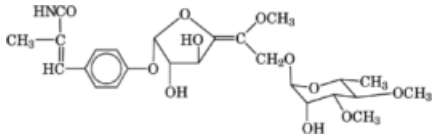
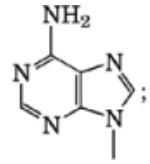
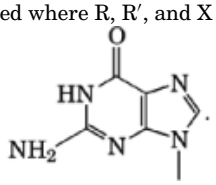
Name	CAS Registry Number	Molecular formula	Structure number	R	R′	X[b]
2′-amino-2′-deoxyadenosine	[10414-81-0]	$C_{10}H_{14}N_6O_3$	(15)	OH	NH_2	A
2′-amino-2′-deoxyguanosine	[60966-26-9]	$C_{10}H_{14}N_6O_4$	(16)	OH	NH_2	G
3′-amino-3′-deoxyadenosine	[2504-55-4]	$C_{10}H_{14}N_6O_3$	(17)	NH_2	OH	A
cordycepin (3′-deoxyadenosine)	[73-03-0]	$C_{10}H_{13}N_5O_3$	(18)	H	OH	A
puromycin	[53-79-2]	$C_{22}H_{29}N_7O_5$	(19)		OH	*N,N*-dimethyl-A

Table 2. *Continued*

Name	CAS Registry Number	Molecular formula	Structure number	R	R′	X[b]
homocitrullylamino adenosine	[59204-62-5]	$C_{17}H_{27}N_9O_5$	(20)		OH	A
lysylaminoadenosine	[31518-64-6]	$C_{16}H_{26}N_8O_4$	(21)		OH	A
chryscandin	[86936-90-5]	$C_{20}H_{23}N_7O_6$	(22)		OH	A
A201A		$C_{37}H_{50}N_6O_{14}$	(23)		OH	*N,N*-dimethyl-A
psicofuranine[c]	[1874-54-0]	$C_{11}H_{15}N_5O_5$	(24)	OH	OH	A
decoyinine[c,d] (angustmycin A)	[2004-04-8]	$C_{11}H_{13}N_5O_4$	(25)	OH	OH	A

[a]Structure as shown unless otherwise indicated where R, R′, and X are as defined.

[b] A = adenine  ; G = guanine  .

[c]A CH_2OH group replaces the H at position 1′.
[d]The CH_2OH and H at position 4′ are replaced by a CH_2 group.

Table 3. Other Purine *N*-Nucleoside Antibiotics, Sugar-1′-X

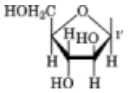
Name	CAS Registry Number	Molecular formula	Structure number	Sugar[a]	X[b]
arabinofuranosyladenine (ara-A, vidarabine)	[5536-17-4]	$C_{10}H_{13}N_5O_4$	**(26)**		A
sinefungin	[58944-73-3]	$C_{15}H_{23}N_7O_5$	(27)	S, R = $CH_2CHNH_2(CH_2)_2CHNH_2COOH$	A
A9145A			(28)	S, R = $CH_2CHNH_2(CH_2)_2CHNH_2CONH_2$	A

Table 3. ***Continued***

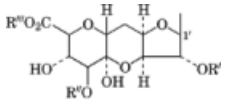
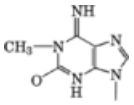
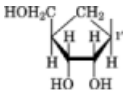
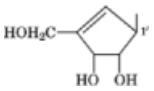
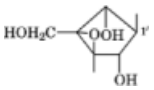
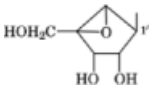
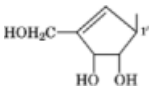
Name	CAS Registry Number	Molecular formula	Structure number	Sugar[a]			X[b]
A9145C	[66753-47-7]	$C_{15}H_{21}N_7O_5$	(29)	S, R = $CHCHNH_2(CH_2)_2CHNH_2COOH$			A
herbicidins	[77699-46-8]						
				R′	R″	R‴	
herbicidin A	[55353-31-6]		(30)	CH_3	$CO(CH_2OH)C{=}CHCH_3$	CH_3	A
herbicidin B	[55353-32-7]		(31)	CH_3	H	CH_3	A
herbidicin E	[72067-15-3]	$C_{23}H_{30}N_5O_{10}$	(32)	CH_3	$COCH(CH_3)_2$	CH_3	A
herbicidin F	[72283-61-5]		(33)	CH_3	$CO(CH_3)C{=}CHCH_3$	CH_3	A
herbicidin G	[72283-62-6]		(34)	H	$CO(CH_3)C{=}CHCH_3$	H	A
doridosine	[73027-05-1]	$C_{11}H_{15}N_5O_5$	(35)	S, R = CH_2OH			
aristeromycin	[19186-33-5]	$C_{11}H_{15}N_5O_3$	**(36)**				A
neplanocin A	[72877-50-0]	$C_{11}H_{13}N_5O_3$	**(37)**				A
neplanocin B	[72877-49-7]	$C_{11}H_{13}N_5O_4$	**(38)**				A
neplanocin C	[72877-48-6]	$C_{11}H_{13}N_5O_4$	**(39)**				A
neplanocin D	[72877-47-5]	$C_{11}H_{12}N_4O_4$	**(40)**				G

Table 3. ***Continued***

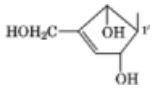
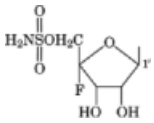
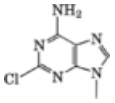
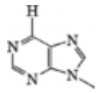
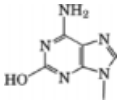
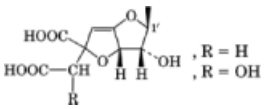
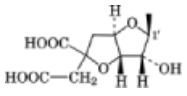
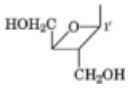
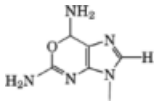
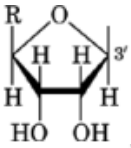
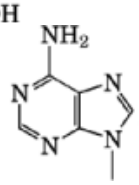
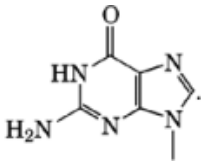
Name	CAS Registry Number	Molecular formula	Structure number	Sugar[a]	X[b]
neplanocin F	[72877-51-1]	$C_{11}H_{13}N_5O_3$	**(41)**		A
nucleocidin	[24751-69-7]	$C_{10}H_{13}FN_6O_6S$	**(42)**		A
ascamycin	[91432-48-3]	$C_{13}H_{18}ClN_7O_7S$	**(43)**		
nebularine	[550-33-4]	$C_{10}H_{12}N_4O_4$	(44)	S, R = CH_2OH	
crotonoside	[3373-53-3]	$C_5H_5N_5O$	(45)	S, R = CH_2OH	
griseolic acid griseolic acid B	[79030-08-3] [98808-01-8]	$C_{14}H_{13}N_5O_8$ $C_{14}H_{13}N_5O_9$	**(46)(47)**		AA
griseolic acid C	[100242-49-7]	$C_{14}H_{15}N_5O_7$	**(48)**		A
oxetanocin A	[103913-16-2]	$C_{10}H_{13}N_5O_3$	**(49)**		A

Table 3. ***Continued***

Name	CAS Registry Number	Molecular formula	Structure number	Sugar[a]	X[b]
oxanosine	[80394-72-5]	$C_{10}H_{12}N_4O_6$	(50)	S, R = CH_2OH	

[a] S =  and R is as indicated.

[b] A = adenine  ; G = guanine  .

2.1.1. 2′-Amino-2′-deoxypurines

2′-Amino-2′-deoxyadenosine (15)is a naturally occurring *N*-nucleoside isolated from *Actinomadura* that shows antimycoplasmal activity (1, 4). Adenosine is the direct precursor for its biosynthesis (30). 2′-Amino-2′-deoxyguanosine (16), isolated from a strain of *Enterobacter cloacae* (1, 4), shows the growth of HeLa S3 cells and Sarcoma 180 *in vivo* and has been tested for antibacterial activity.

2.1.2. 3′-Amino-3′-deoxyadenosine

3′-Amino-3′-deoxyadenosine (17)is elaborated by *Cordyceps militaris*, *Aspergillus nidulans*, and *Helminthosporium* (3, 4). The biosynthesis proceeds directly from adenosine. Compound (17)inhibits RNA polymerase, but not DNA polymerase, and replaces the adenosyl residue at the 3′-terminus of tRNA. Phenylalanyl-(3′-amino-3′-deoxyadenosyl)-tRNA has acceptor but not donor activity (31, 32). Compound (17)also inhibits retroviral RNA-dependent DNA polymerase (33).

2.1.3. Cordycepin (3′-Deoxyadenosine)

Cordycepin (18), also known as 3′-deoxyadeosine, is isolated from *C. militaris* and *A. nidulans* (1–4). The biosynthesis utilizes adenosine. It was originally proposed to be an analogue of adenine having the branched chain sugar, cordycepose. A functional analogue of adenosine, (18)is a most versatile biological probe for studying many reactions in procaryotes, eucaryotes, plants, and viruses. Initial studies indicated that (18)was converted to its 5′-phosphates and inhibits RNA, but not DNA, synthesis. A chain terminator in RNA synthesis, (18)inhibits poly(A) and tRNA methylation of the 5′-terminus of mRNA and blocks the production of RNA viruses. It inhibits 2′-*O*-methylation, forms the 3′-deoxy analogues of *S*-adenosylmethionine (SAM) and *S*-adenosylhomocysteine (SAH), and inhibits initiation of HSV DNA synthesis (34). Both SAM and SAH analogues inhibit nucleic acid methylation. When (18)replaces adenosine at the 3′-end of the $tRNA^{pHe}$, the addition of phenylalanine at the 2′-hydroxyl position results in a charged tRNA that is not a substrate for poly(U)-directed polyphenylalanine synthesis. 3′*d*ATP inhibits RNA and DNA synthesis in permeabilized *E. coli*. 3′*d*ATP has been reported to be a substrate for 2′,5′-oligoadenylate (2-5A) synthetase. The resulting 2′,5′-cordycepin trimer 5′-triphosphate inhibits translation in lysed rabbit reticulocytes better than authentic 2-5A (35). The inhibition

of HIV-1 replication in infected MT-2 cells, and of HIV-1 reverse transcriptase by the cordycepin and phosphorothioate analogues of 2-5A has also been reported (36, 37). Compound (18)damages messenger RNA (mRNA) processing in brain tissue, affects mRNA processing in yeast and *Xenopus* oocytes, increases mRNA stability in HL60 cells, affects mobility of nucleoside transport in cells, disrupts microtubule networks, and has been used to detect mRNAs in nonheat shocked thymic lymphocytes that code for noncordycepin inhibited heat shock proteins (38–47).

2.1.4. Puromycin

Puromycin (19), elaborated by *S. alboniger* (1–4), inhibits protein synthesis by replacing aminoacyl-tRNA at the A-site of peptidyltransferase (48, 49). Photosensitive analogues of (19)have been used to label the A-site proteins of peptidyltransferase and $tRNA^{Phe}$ (50). Compound (19), and its carbocyclic analogue have been used to study the accumulation of glycoprotein-derived free sialooligosaccharides, accumulation of mRNA, methylase activity, enzyme transport, rat embryo development, the acceptor site of human placental 80S ribosomes, and gene expression in mammalian cells (51–60).

Three other 3′-aminoacyl-3′-deoxyadenosine nucleosides, homocitrullylaminoadenosine (20), lysylaminoadenosine (21), and chryscandin (22), have been reported (61). Unlike (19), chryscandin has strong inhibitory activity against *C. albicans* (61). Antibiotic FR900403, which is structurally similar to (22), has been isolated from the fungus, *Kernia* sp. F-19849; it inhibits *C. albicans* (62).

2.1.5. Antibiotic A201A

Antibiotic A201A (23), produced by *S. capreolus*, is an N^6-dimethyladenine nucleoside structurally similar to puromycin (19). Compound (23)which contains an aromatic acid and monosaccharide residues (1, 4), inhibits the incorporation of amino acids into proteins but has no effect on RNA or DNA synthesis. Compound (23)does not accept polypeptides as does (19), and does appear to block formation of the initiation complex of the 50S subunit. It may block formation of a puromycin-reactive ribosome.

2.1.6. Ketohexose Nucleosides

The ketohexose nucleosides, psicofuranine (24)and decoyinine (25), are isolated from *S. hygroscopicus* (1–4). Psicofuranine, 6-amino-9-(β-D-psicofuranosyl)purine, and decoyinine, 9-β-D-(5,6-psicofuranoseenyl)-6-aminopurine, angustmycin A, inhibit XMP aminase noncompetitively. Unlike many other nucleoside antibiotics, phosphorylation is not necessary for inhibitory action. Compound (25)effectively induces sporulation; (24)inhibits GMP synthesis and subsequently AMP synthesis. Therefore (24)is sufficient to cause sporulation of *B. subtilis*. Guanine and adenine can reverse this inhibition. Compounds (24)and (25)regulate sporulation by induction of the alarmones in bacteria, ie, lowering levels of nucleotides and/or folate, enzyme promoters, and early sporulation genes (63–70).

2.1.7. Arabinosyladenine

Three naturally occurring arabinosyl purine and pyrimidine nucleoside antibiotics (ara-A, ara-T, and ara-U) have been isolated from the sponge, *Cryptotethia crypta* (1–4) 9-β-D-Arabinofuranosyladenine **(26)**, also known as ara-A and Vidarabine, has also been isolated from *S. antibioticus* and *S. herbaceus*. (The adenosine deaminase inhibitor, 2′-deoxycoformycin **(59)**, is also isolated from *S. antibioticus*). The structural elucidation and chemical syntheses of **(26)**, its phosphate triester, and 2-halo and 5′-*O*-acyl derivatives have been reported (1–4, 71–73). An enzymatic synthesis **(26)** via transarabinosylation of ara-U has been reported (74) as has the biosynthesis of **(26)** from [^{14}C, ^{3}H, 2′-^{18}O and 3′-^{18}O]adenosine has been reported (75). Ara-A is a potent antiviral drug that shows great selectivity in its influence on host cell metabolism and virus growth (76–78). Ara-A and its 5′-monophosphate are effective antiviral analogues with known activity against herpes simplex keratitis, herpes simplex encephalitis, neonatal herpes, herpes zoster, and mucocutaneous herpes in humans. Ara-ATP

is a competitive inhibitor of 2′*d*ATP. Compound **(26)** is incorporated into HSV DNA and it is an S-phase specific inhibitor of tumor cell growth (79). Many studies have reported the inhibition of DNA and RNA synthesis in procaryotes, eucaryotes, and viruses by ara-A and ara-ATP (1–4, 80). Eucaryotic and procaryonuclear poly(A) polymerase, poly(ADP-ribose) polymerase, and nuclear poly(A) polymerase are not inhibited by ara-ATP (26, 81, 82). Although ara-ATP does not inhibit the DNA-dependent DNA polymerase from *E. coli*, it does inhibit the DNA-dependent DNA polymerase from mammalian cells. HSV-1 induced DNA polymerase is more sensitive to ara-ATP than is DNA polymerase-α in uninfected rabbit kidney cells (83). In L5178Y cells, **(26)** is deaminated to ara-hypoxanthine which is converted to ara-inosinetic phosphate ara-ITP; ara-ITP does not affect RNA or protein synthesis, but does inhibit DNA polymerase-α in L5178Y cells. In permeabilized mouse leukemic cells, the DNA replicating complex is competitively inhibited by ara-ATP (4). Ara-A inhibits DNA synthesis by blocking formation of new replicons and inhibits DNA repair, nucleoside uptake, and DNA strand elongation (84–87). 2′-Deoxycoformycin **(59)** potentiates the growth inhibition of **(26)** in cultured human cell lines (88). Inhibition of virus replication occurs when **(26)** is converted to ara-ATP (89).

2.1.8. Sinefungins

S. griseolus produces the nucleosides, sinefungin, A9145, A9145A, and A9145C (27–29) (1–4) which are structural analogues of SAM and SAH and inhibit methyltransferase reactions (90). The biosynthesis of (27) was reported to utilize L-arginine and ATP (91). It was demonstrated that adenosine and ornithine are converted to (27) (92) and it has been shown that adenine, ribose, and ornithine are the direct precursors of (27) (93). Regulation of the biosynthesis of (27) has been studied using auxotrophic mutants of *S. incarratus*; mutants with blocks in arginine synthesis were not able to produce (27) (94). Compounds (27–29) have antifungal, antiparasitic, and antiviral activity, and inhibit transformed cells in culture (95–97). They are potent inhibitors of the SAM: *O*-methyltransferases I and III (98, 99). Compound (27) is the most potent inhibitor of protein methylase I activity and is comparable to SAH with respect to its inhibitory effect (100). It inhibits photolabeling of restriction enzyme EcoR-II methyltransferase, protein methylation, EcoR-I adenine DNA methylase, and myelin basic protein (arginine) methyltransferase (101–104). Methyltransferase inhibitors may provide a therapeutic strategy in myasthenia gravis (105).

2.1.9. Herbicidins

Five adenine nucleosides, herbicidins A, B, E, F, and G (30–34), have been isolated from the culture filtrates of *S. sagamonensis* No. 4075 (1, 4) which also produces ara-A and 2′-deoxycoformycin. The herbicidins contain a tricyclic dodecose. They inhibit dicotyledonous plants, germination of plant seeds, growth of blue-green algae, and fungi.

2.1.10. Doridosine

Doridosine, N^1-methylisoguanosine, (35) was isolated from the dorid nudibranchs of *Anisodoris nobilis* and the sponge, *Tedania* (106, 107). The injection of (35) into the saphenous vein of anesthetized rats produces hypotension and bradycardia almost immediately. The observed changes in the electrocardiograms are minor and indicate little interference with conduction of the impulse within the heart (see Cardiovascular agents).

2.1.11. Thraustomycin

Thraustomycin and β-thraustomycin are isolated from *S. exfoliatus* (4). Although their structures have not been totally elucidated, hydrolysis of thraustomycin shows that it contains equimolar quantities of adenine, L-leucine, and a tetrahydroxymonocarboxylic acid. Thraustomycin is a potent inhibitor of the fungus, *M. hiemallis* ($_+$), but does not inhibit bacteria.

2.1.12. Aristeromycin

Aristeromycin **(36)**, the first carbocylic analogue of adenosine, was isolated from the culture filtrates of *S. citricolor* as part of a search for inhibitors of bacterial leaf blight (1–4). A herbicidally active hypoxanthine analogue of **(36)**, coaristeromycin, has also been isolated (108). Several chemical syntheses of **(36)** have appeared (1–4, 109). It inhibits *Xanthomonas oryzae* and *Pyricularia oryzae*, bacterial leaf blight, blast disease of rice plants, and leaf mold of tomato plants, by inhibiting both cell division and elongation. An inhibitor of *S*-adenosylmethionine (SAM) hydrolase, **(36)** also affects *de novo* synthesis of purine nucleotides and RNA. Adenosine and, to a lesser degree, adenine, inosine and 2′-deoxyadenosine reverse inhibition by **(36)**. Aristeromycin diphosphate binds to polynucleotide phosphorylase. The copolymer poly(A, aristeromycin) is formed when aristeromycin 5′-diphosphate is incubated with an excess of ADP. Aristeromycin derivatives of *S*-adenosyl homocysteine (SAH) have been synthesized in an effort to characterize the SAH binding site on mRNA (guanine-7)-methyltranferases that are required for efficient translation and mRNA-ribosome binding. Whereas the aristeromycin derivatives of SAH showed only marginal inhibitory activity, *S*-tubercidinyl-L-homocysteine was a potent inhibitor. The metabolism of analogues of **(36)** and neplanocin A **(37)** have been compared (110). Both nucleosides are converted to the 5′-triphosphates; however, only **(36)** was converted to a guanosine nucleotide derivative. A carbocyclic inosine analogue of **(36)** has potent antileishmanial activity (111). The deazaaristeromycin derivative is an inhibitor of SAH hydrolase and has been widely used in studies related to RNA synthesis in transformed cells and viruses and cell differentiation (112–118). 3-Deazaaristeromycin-resistant clones of human β-lymphoblasts have been reported to display elevated SAM levels (119). The biosynthesis of the cyclopentane ring of **(36)** proceeds by carbon–carbon bond formation between C-2 and C-6 of D-glucose (120).

2.1.13. Neplanocins

Neplanocins A–D and F **(37–41)** are carbocyclic nucleoside antibiotic products of *Ampullariella regularis* (1–4) that are structurally related to **(36)** in that they contain either a cyclopentene or epoxy cyclopentane ring (121, 122). The chemical syntheses of **(37–41)** and the 3-deazaneplanocins have been reported (123–126). Compound **(37)**, which is converted to its 5′-triphosphate, has potent antitumor and antiviral activities (127–129). It strongly inhibits SAM in cells and viruses (128–131) and is converted to the 3′-keto derivative by *S*-adenosylhomocysteine hydrolase (132, 133).

2.1.14. Nucleocidin and Ascamycin

Nucleocidin, 4′-fluoro-5′-*O*-sulfamoyladenosine, **(42)** is isolated from the culture filtrates of *S. clavus* (1–4). Among the nucleoside antibiotics **(42)** is unique in that it contains a fluoride group at carbon-4′. Compound **(42)** and its chemically synthesized analogues are inhibitors of bacteria and are extremely toxic to mammals. Compound **(42)** inhibits protein synthesis by blocking peptide elongation. Ascamycin, 5′-*O*-L-alanylsulfamoyl-2-chloroadenosine, **(43)** is similar to **(42)** in that it contains a sulfamoyl group (134, 135). A specific amino-peptidase that hydrolyzes the alanyl group of **(43)** has been purified (136). Two additional 5′-*O*-sulfamoylnucleosides that are isolated from the *Streptomyces* are 5′-*O*-sulfamoyladenosine and 5′-*O*-sulfamoyltubercidin (137).

2.1.15. Nebularine

Nebularine(44) is a naturally occurring purine riboside isolated from *S. yokosukanensis* (1, 3, 4). It is phosphorylated, and inhibits purine biosynthesis and RNA synthesis, but is not incorporated into RNA by *E. coli* RNA polymerase. It has also found application as a transition state analogue for treatment of schistosomiasis and as a substrate for the restriction endonuclease, HindII (138–141).

2.1.16. Crotonoside

Crotonoside, also called isoguanosine, (45) has been isolated from *Croton tiglium* (4). Ip administration of [2-^{14}C]crotonoside to rats results in incorporation into nucleic acids (qv). It inhibits the inducible binding sites, inhibits glutamic acid dehydrogenase, and accumulates cAMP.

2.1.17. Griseolic Acids

The three griseolic acids, A, B, and C **(46–48)**, have been isolated from *S. griseoaurantiacus* (1, 142). They are potent inhibitors of cAMP phosphodiesterase (143, 144). Compound **(46)** stimulates glycogen degradation in mice.

2.1.18. Oxetanocins

Oxetanocin A **(49)**, formerly oxetanocin, is the first naturally occurring oxetanose derivative and is isolated from *Bacillus megaterium* (1, 145). It inhibits gram-positive bacteria, herpes viruses, and human immunodeficiency virus (HIV) (146). The chemical synthesis of **(49)** and several derivatives has been reported (147).

2.1.19. Oxanosine

Oxanosine (50), which is isolated from *S. capreolus* (1, 148), is a potent inhibitor of GMP synthetase and nucleic acid synthesis (149, 150).

2.2. Pyrrolopyrimidine Nucleosides

The pyrrolopyrimidine *N*-nucleoside antibiotics are listed in Table 4. Tubercidin (51), toyocamycin (52), sangivamycin (53), cadeguomycin (54), and kanagawamicin **(55)** are pyrrolopyrimidine nucleoside antibiotics isolated from strains of *Streptomyces* (1–4, 151). In addition, the 5′-α-D-glucopyranosyl derivatives of tubercidin and toyocamycin have been isolated from blue-green algae (152). The structural elucidation, physical and chemical properties, chemical syntheses, and biological activities of these nucleosides and their derivatives have been reported (1–4, 153–172). GTP, but not ATP, is a precursor for the biosynthesis of the pyrrolopyrimidine ring of (51–53) (161). The nitrile group of (52) is enzymatically converted to the carboxamide group in the formation of (53) (162). Tubercidin 5′-triphosphate is not a substrate for either adenosine deaminase or nucleoside phosphorylase. Compound (51) is incorporated into RNA, inhibits the processing of RNA, but does not inhibit the transcription of 45S precursor RNA to 28S and 18S RNA; DNA synthesis is inhibited. The importance of (51) as a methylase inhibitor has been studied in detail (163, 164). *S*-Tubercidinyl homocysteine inhibits methylation (163, 164). It has been used to elucidate the requirements for the catalytic site of RNA polymerase with respect to initiation, elongation, and termination. Rous sarcoma virus and SV40 replication are inhibited by 5-bromotubercidin. Another promising application of (51) is as an anthelmintic agent. It inhibits purine nucleotide synthesis in *Schistosoma mansoni* and xylotubercidin inhibits HSV-2 in mice (165, 166). Toyocamycin (52), a cytotoxic analogue of adenosine, is selectively incorporated into the 45S ribosomal RNA precursor and prevents cleavage into 28S and 18S RNA (1, 4). When Ehrlich ascites cells are incubated with (52) in a medium rich in amino acids, the high transcription rate of rRNA is lowered. Toyocamycin is incorporated into HeLa cell 45S RNA, blocks polyadenylation of heterogenous nuclear RNA (hnRNA), and inhibits Friend, Rous Sarcoma, and vesicular stomatitis virus replication. Sangivamycin (53), which is phosphorylated but not deaminated, is incorporated into RNA and DNA of normal tissue, inhibits *de novo* purine synthesis in L1210 cells in culture, competitively inhibits amino acid activation, charging of tRNA, and can replace ATP in the synthesis of RNA catalyzed by *E. coli* RNA polymerase. The molecular effects of (53) and its thio analogue on RNA and DNA synthesis in L1210 cells and as an inhibitor of rhodopsin kinase have been studied (167, 168). Compound (54) potentiates the cytotoxicity of ara-C and has been used in studies on the T-cell immunostimulatory properties of certain peptides (169–171). Compound **(55)** has antitumor and antibacterial activity (172).

Two other pyrrolopyrimidine nucleoside antibiotics, mycalisines A and B **(56,57)**, have been isolated from the sponge *Mycale* sp. (173). These bioactive marine metabolites inhibit cell division of starfish eggs.

Table 4. Pyrrolopyrimidine, Diazepin, and Other *N*-Nucleoside Antibiotics, Sugar-1′-X

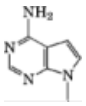
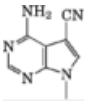
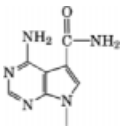
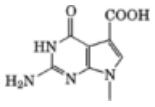
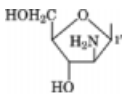
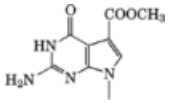
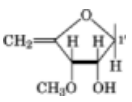
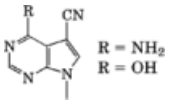
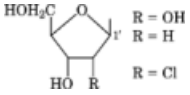
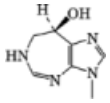
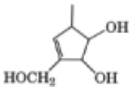
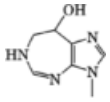
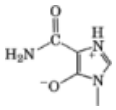
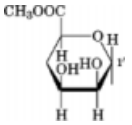
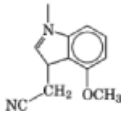
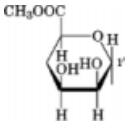
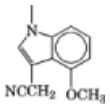
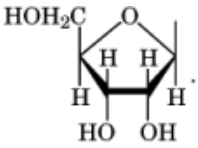
Name	CAS Registry Number	Molecular formula	Structure number	Sugar[a]	X
Pyrrolopyrimidine N-nucleosides					
tubercidin	[69-33-0]	$C_{11}H_{14}N_4O_4$	(51)		
toyocamycin	[606-58-6]	$C_{12}H_{13}N_5O_4$	(52)		
sangivamycin	[18417-89-5]	$C_{12}H_{15}N_5O_5$	(53)		
cadeguomycin	[81645-08-1]	$C_{12}H_{14}N_4O_7$	(54)		
kanagawamicin	[84873-16-5]	$C_{13}H_{17}N_5O_6$	(55)		
mycalisine A mycalisine B	[98890-73-4] [98890-72-3]	$C_{13}H_{13}N_5O_3$ $C_{13}H_{12}N_4O_4$	**(56)(57)**		 R = NH_2 R = OH
Diazepin N-nucleosides					

Table 4. ***Continued***

Name	CAS Registry Number	Molecular formula	Structure number	Sugar[a]	X
coformycin					
2′-deoxycoformycin	[11033-22-0]	$C_{11}H_{16}N_4O_5$			
(co-vidarabine, pentostatin)	[53910-25-1]	$C_{11}H_{16}N_4O_4$	**(58)(59)(60)**		
adechlorin (2′-chloro-2′ deoxycoformycin)	[96328-17-5]	$C_{11}H_{15}ClN_4O_4$			
adecypenol	[104493-13-2]	$C_{12}H_{16}N_4O_4$	**(61)**		
Others					
bredinin	[50924-49-7]	$C_{19}H_{13}N_3O_6$	(62)		
neosidomycin	[72033-44-4]	$C_{17}H_{20}N_2O_6$	**(63)**		
SF-2140	[91284-30-9]	$C_{18}H_{20}N_2O_6$	**(64)**		

[a] S =  .

2.3. Diazepin Nucleosides

Four naturally occurring diazepin nucleosides, coformycin **(58)**, 2′-deoxycoformycin **(59)**, adechlorin or 2′-chloro-2′-deoxycoformycin **(60)**, and adecypenol **(61)**, have been isolated (1–4, 174, 175). The biosynthesis of **(59)** and **(60)** have been reported to proceed from adenosine and C-1 of D-ribose (30, 176, 177). They are strong inhibitors of adenosine deaminase and AMP deaminase (178). Compound (58)protects adenosine and formycin **(12)** from deamination by adenosine deaminase. Advanced hairy cell leukemia has shown rapid response to **(59)** with or without α- or β-interferon treatment (179–187). In addition, **(59)** affects interleukin-2 production,

receptor expression on human T-cells, DNA repair synthesis, immunosuppression, natural killer cell activity, and cytokine production (188–194).

2.4. Bredinin, Neosidomycin, and SF-2140

Bredinin (62), isolated from the culture filtrates of *Eupenicillium brefeldianum* (1, 4), inhibits the multiplication of L5178Y, HeLa S3, RK-13, mouse L-cells, and Chinese hamster cells. GMP can reverse the inhibition by (62), but (62) is not incorporated into the nucleic acids. The inhibition of nucleic acid synthesis and chromosomal damage in the S and G_2 phases that is caused by (62), is reversed by GMP. It blocks the conversion of IMP to XMP and XMP to GMP. In combination with GMP, (62) interferes with intracellular cAMP levels and thereby inhibits cell division.

Neosidomycin **(63)** and SF-2140 **(64)** are indole *N*-glycosides produced by *S. hygroscopicus* and *Actinomadura*, respectively (195, 196). A revised structure for **(63)** has appeared (197). Compound **(64)** contains an α-*N*-glycoside linkage. Both **(63)** and **(64)** show activity against gram-positive bacteria, yeast, fungi, and viruses.

2.5. Pyrimidine–Nucleoside Antibiotics

2.5.1. Fatty Acyl Nucleosides

The nucleoside antibiotics with fatty acyl groups containing adenine, uracil, and dihydrouracil aglycons, the tunicamycins [11089-65-9] (**65–74**), streptovirudins (**75–84**), corynetoxins (**85–97**), are given in Table 5. The structure of liposidomycin 1, septacidins [62362-59-8] 1, spicamycin [62362-59-8] 1, and FR900848 are given in Figure 1. The chemistry of the tunicamycins has been extensively reviewed (198). The structural elucidation of (**75–78**) has been described (199). The isolation and structural elucidation of liposidomycins A, B, and C, septacidins, corynetoxins, and spicamycins have been described (200–205). Compounds (**85–97**), produced by *Corynebacterium rathayi*, infect rye grass which is toxic to grazing animals (205). A recently discovered fatty acyl nucleoside antibiotic with antifungal activity, antibiotic FR900848 [120500-69-8] 1, contains one isolated and four serial cyclopropane rings (206).

Table 5. Pyrimidine Fatty Acyl N-Nucleoside

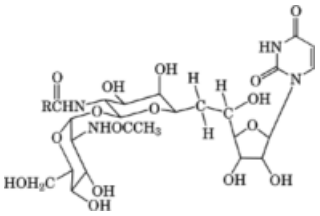
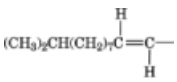
Name	CAS Registry Number	Molecular formula	Structure number	R
				
Tunicamycins [11089-65-9]				
I(A_0)	[73942-10-6]	$C_{36}H_{58}N_4O_{16}$	**(65)**	

Table 5. ***Continued***

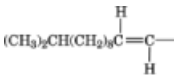
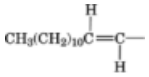
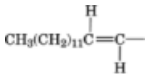
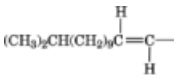
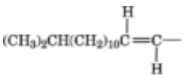
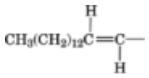
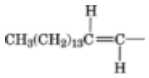
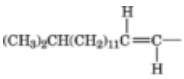
Name	CAS Registry Number	Molecular formula	Structure number	R
II(C)	[66081-37-6]	$C_{37}H_{60}N_4O_{16}$	**(66)**	
III(A_2)	[76544-45-1]	$C_{37}H_{60}N_4O_{16}$	**(67)**	
IV(B_2)	[73942-09-3]	$C_{38}H_{62}N_4O_{16}$	**(68)**	
V(A)	[66054-36-2]	$C_{38}H_{62}N_4O_{16}$	**(69)**	
VI	[88263-43-8]	$C_{38}H_{62}N_4O_{16}$	(70)	$(CH_3)_2CH(CH_2)_{11}$—
VII(B)	[66081-36-5]	$C_{39}H_{64}N_4O_{16}$	**(71)**	
VIII(C_2)	[73942-07-1]	$C_{39}H_{64}N_4O_{16}$	**(72)**	
IX(D_1)	[73942-08-2]	$C_{40}H_{66}N_4O_{16}$	**(73)**	
X(D)	[66081-38-7]	$C_{40}H_{66}N_4O_{16}$	**(74)**	
Streptovirudins (A_1–D_1)[a]				
A_1	[51330-28-0]	$C_{35}H_{58}N_4O_{16}$	(75)	$(CH_3)_2CH(CH_2)_6CH{=}CH$—

Table 5. ***Continued***

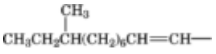
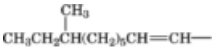
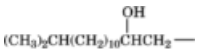
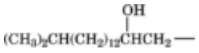
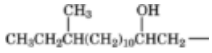
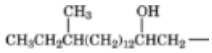
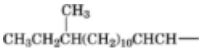
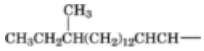
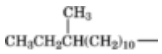
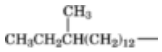
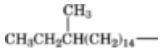
Name	CAS Registry Number	Molecular formula	Structure number	R
B_1	[51330-30-4]	$C_{36}H_{60}N_4O_{16}$	**(76)**	
B_{1a}	[81093-26-7]	$C_{36}H_{60}N_4O_{16}$	(77)	$(CH_3)_2CH(CH_2)_7CH{=}CH—$
C_1	[51330-32-6]	$C_{37}H_{62}N_4O_{16}$	(78)	$(CH_3)_2CH(CH_2)_8CH{=}CH—$
D_1	[51330-34-8]	$C_{38}H_{64}N_4O_{16}$	**(79)**	
Streptovirudins (A_2–D_2)[b]				
A_2	[51330-29-1]	$C_{35}H_{56}N_4O_{16}$	(80)	$(CH_3)_2CH(CH_2)_6CH{=}CH—$
B_2	[51330-31-5]	$C_{36}H_{58}N_4O_{16}$	**(81)**	
B_{2a}	[73942-10-6]	$C_{36}H_{58}N_4O_{16}$	(82)	$(CH_3)_2CH(CH_2)_7CH{=}CH—$
C_2	[51330-33-7]	$C_{37}H_{60}N_4O_{16}$	(83)	$(CH_3)_2CH(CH_2)_9CH{=}CH—$
D_2	[51330-35-9]	$C_{38}H_{62}N_4O_{16}$	**(84)**	
Corynetoxins[c]				
H16*i*	[82138-73-6]	$C_{39}H_{66}N_4O_{17}$	**(85)**	
H18*i*	[82138-74-7]	$C_{41}H_{70}N_4O_{17}$	**(86)**	
H17*a*	[82151-55-1]	$C_{40}H_{68}N_4O_{17}$	**(87)**	
H19*a*	[82151-56-2]	$C_{42}H_{72}N_4O_{17}$	**(88)**	
U16*i*	[66081-36-5]	$C_{39}H_{64}N_4O_{16}$	(89)	$(CH_3)_2CH(CH_2)_{10}CHCH—$
U18*i*	[82138-75-8]	$C_{41}H_{68}N_4O_{16}$	(90)	$(CH_3)_2CH(CH_2)_{12}CHCH—$
U17*a*	[82151-57-3]	$C_{40}H_{66}N_4O_{16}$	**(91)**	

Table 5. ***Continued***

Name	CAS Registry Number	Molecular formula	Structure number	R
U19*a*	[82138-76-9]	$C_{42}H_{70}N_4O_{16}$	**(92)**	
S16*i*	[82138-77-0]	$C_{39}H_{66}N_4O_{16}$	(93)	$(CH_3)_2CH(CH_2)_{12}$—
S18*i*	[82138-78-1]	$C_{41}H_{70}N_4O_{16}$	(94)	$(CH_3)_2CH(CH_2)_{14}$—
S15*a*	[82138-79-2]	$C_{38}H_{64}N_4O_{16}$	**(95)**	
S17*a*	[82138-80-5]	$C_{40}H_{68}N_4O_{16}$	**(96)**	
S19*a*	[82138-87-6]	$C_{42}H_{72}N_4O_{16}$	**(97)**	

[a]Dihydrouracil incorporated, ie, uracil C═C bond is saturated.
[b]Uracil as shown in structure.
[c]The H stands for β-hydroxy, S for saturated, and U for α–β unsaturated; i = iso; a = anteiso.

The tunicamycins, streptovirudins, corynetoxins, and liposidomycins inhibit the formation of glycoproteins and peptidoglycans. Oligosaccharide synthesis for glycoproteins requires a polyisoprenoid carrier followed by transfer to the nascent polypeptide (207–209). The tunicamycins and streptovirudins are lipophilic nucleoside analogues of UDP-*N*-acetylglucosamine and inhibit the first transferase reaction in the lipid-linked saccharide pathway, ie, the formation of dolichyl pyrophosphoryl-*N*-acetylglucosamine, by inhibiting dolichyl-P:*N*-acetylglucosamine-1-*P* transferase. Compounds (**65–74**) are also biological probes for cell wall polymer synthesis in bacteria, fungi, immunoglobulin synthesis, and glycoprotein biosynthesis in insects and plants. By blocking synthesis of the phosphomannosyl residues on lysosomal enzymes with tunicamycin, the secretion of the lysosomal enzymes is inhibited as is the synthesis of rhodopsin and the conversion of procollagen to collagen (210–212). The effect of the tunicamycins and streptovirudins on adherence of group B streptococci to influenza virus-infected kidney cells has been investigated (213). In hen oviduct microsomes, tunicamycin abolished *N*-glycosylation, but had no effect on *O*-glycosylation (214). Tunicamycin inhibits peptidoglycan and 1,3-poly(glycerol phosphate) teichoic acid in *B. licheniformis*, the formation of undecaprenylacetyl-glucosaminyl-lipid and the formation of the peptidoglycan and teichuronic acid, *N*-acetylglucosamine-lipid formation in plants, glycosylation of human interferon, glycosaminoglycan synthesis in cultured embryonic chick fibroblasts, and polysaccharide chain formation of corneal keratan sulfate (215–218). Tunicamycin has also been used to investigate virus assembly. The reduction of glycosamine incorporation caused by tunicamycin is accompanied by a decrease in infectious virus particle production (219). In a model system for *N*-glycosylation of the intracellular transport of rabies virus, tunicamycin blocks surface expression and accumulation of G protein (220), the first step in the lipid cycle of *E. coli* and *S. cerevisiae* (221) and IgE binding protein (222). Tunicamycin inhibits the incorporation of *O*-linked sugars on the CD45 phosphotyrosine phosphatase (223), glycosylation of tumor necrosis factor (224), causes accumulation of dolicholphosphoryl-mannose, an essential anchor to CHO cell mutants (225), and inhibits lipoprotein lipase complex mannose *N*-linked oligosaccharides

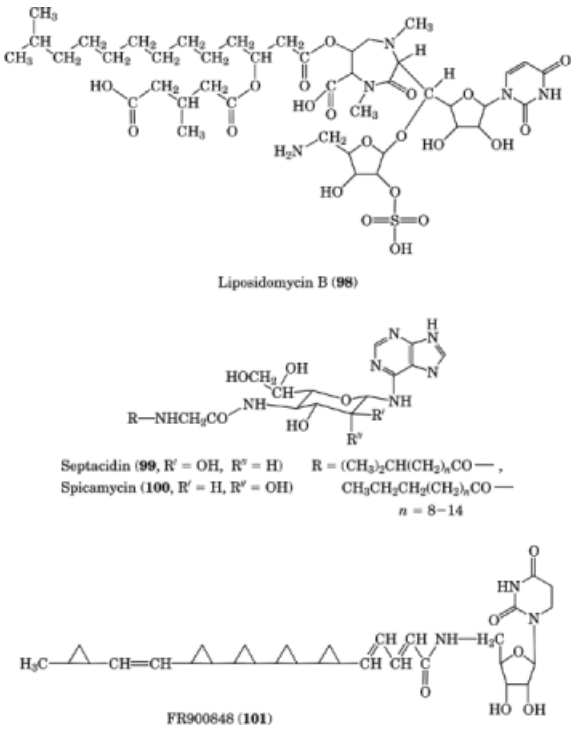


Fig. 1. Structures of fatty acyl *N*-nucleosides.

(226). Monoclonal antibodies to HSV glycoproteins did not react with cell extracts of tunicamycin treated cells (227). The inhibition of *N*-glycosylation processing and transport surface expression also has been reported (227–231).

2.6. Peptidyl *N*-Nucleoside Antibiotics

2.6.1. Polyoxins and Neopolyoxins

The polyoxins [11113-80-7] (**102–113**), and neopolyoxins 2, shown in Figure 2, are peptidylpyrimidine nucleoside antibiotics that have achieved use as agricultural fungicides (1–4, 232) (see Fungicides, agricultural). Polyoxins A–M, which have the pyrimidine chromophore, have been isolated from *S. cacaoi var asoensis* and *S. piomogenus*. Polyoxin N [37362-29-1] 2, $C_{16}H_{23}N_5O_{12}$, neopolyoxin A [75044-69-8] [72864-26-7] 2, $C_{20}H_{25}N_5O_{10}$, and neopolyoxin B [75005-71-9] 2, $C_{20}H_{25}N_5O_{11}$, have the imidazole chromophore and neopolyoxin C [75044-71-9] 2, $C_{20}H_{25}N_5O_{10}$, contains uracil and a 3-hydroxypyridine rings (1–4). The thymine chromophore of the polyoxins is formed by a pathway independent of thymidylate synthetase (233). The aminouronic acid moiety is not directly synthesized from glucose, but rather via phosphoenolpyruvate and the 5′-aldehyde of uridine to give the intermediate octofuranose uronic acid nucleoside (1). Oxidative elimination of the two terminal carbons (carbon 7′ and 8′) followed by the addition of the amino group on carbon-5′ results in the formation of the polyoxin nucleoside. Azetidine carboxylic acid (polyoximic acid) is formed from the carbon–nitrogen skeleton of isoleucine and carbamoylpolyoxamic acid, is formed from glutamate. Compounds (**102–116**) inhibit sheath-blight disease of rice crops, ie, the pathogenic fungus *Pellicularia philamentosa f. sasakii*. The polyoxins, which are structurally similar to UDP-*N*-acetylglucosamine, inhibit chitin synthetase (1). Polyoxin D (**104**) is a competitive inhibitor of UDP-*N*-acetylglucosamine. Polyoxin-resistant mutants of *A. kikuchiana* have a

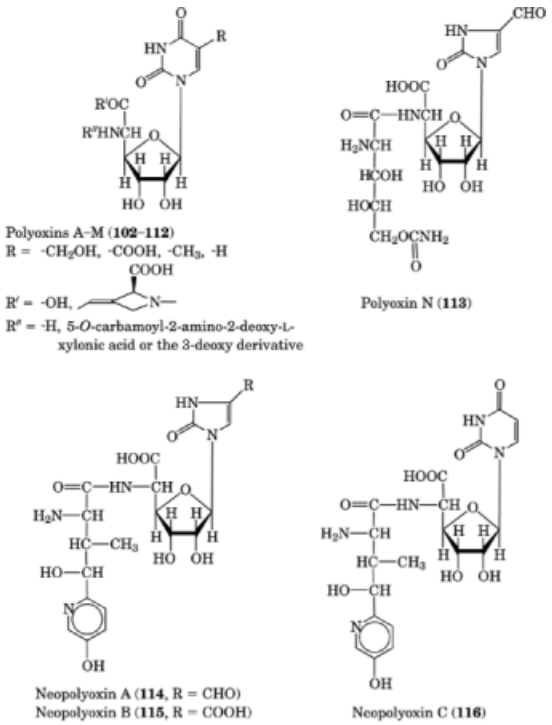


Fig. 2. Structures of the polyoxins. Polyoxin A [19396-03-3] [11016-31-2], $C_{23}H_{32}N_6O_{14}$; polyoxin B [19396-06-6] [11016-32-3] [24695-50-9], $C_{17}H_{25}N_5O_{13}$; polyoxin C [21027-33-8] [11043-74-6], $C_{11}H_{15}N_3O_8$; polyoxin D [22976-86-9] [33401-46-6] [11043-75-7] [29762-31-0], $C_{17}H_{23}N_5O_{14}$; polyoxin E [22976-87-0] [11043-76-8], $C_{17}H_{23}N_5O_{13}$; polyoxin F [23116-76-9] [11043-77-9], $C_{23}H_{30}N_6O_{15}$; polyoxin G [22976-88-1] [11043-78-0], $C_{17}H_{25}N_5O_{12}$; polyoxin H [24695-54-3] [11043-79-1], $C_{23}H_{32}N_6O_{13}$; polyoxin I [22886-33-5] [11043-80-4], $C_{17}H_{22}N_4O_9$; polyoxin J [22976-89-2] [25546-71-8], $C_{17}H_{25}N_5O_{12}$; polyoxin K [22886-46-0], $C_{22}H_{30}N_6O_{13}$; polyoxin L [22976-90-5] [100566-82-3] [25546-73-0] [59519-82-3], $C_{16}H_{23}N_5O_{12}$; and polyoxin M [34718-88-2], $C_{16}H_{23}N_5O_{11}$.

decreased uptake of the polyoxins. To overcome the resistance of these mutants, three approaches have been used: transnucleosidation, biosynthesis of a polyoxin with the 5-fluorouracil moiety, and decarboxylation of the 5-carboxyuracil polyoxins.

2.7. Mureidomycins and Pacidamycins

The mureidomycins and pacidamycins are listed in Table 6. The four peptidylnucleosides, mureidomycins A–D (**117–120**), are produced by *S. flavidovirens* (234). They contain two moles of *m*-tyrosine, one mole of 2-amino-3-*N*-methylaminobutyric acid, and one mole of methionine (235). The mureidomycins inhibit *Pseudomonas aeruginosa* (236). Treatment of *P. aeruginosa* with mureidomycin C results in cell lysis. The mureidomycins show low toxicity to mice and protect them from infection with *P. aeruginosa*. Mureidomycin A inhibits peptidoglycan synthesis and lipid-intermediate formation from UDP-*N*-acetylmuramyl (MurNAc)-pentapeptide and UDP-*N*-acetylglucosamine (237). Mureidomycin A inhibits translocase, thereby blocking formation of undecaprenyl-pyrophosphoryl-MurNAc-pentapeptide.

The seven pacidamycins (121–127), which are isolated from the culture filtrates of *S. coeruleorubidus*, are structurally similar to the mureidomycins. These seven peptidyl nucleoside antibiotics differ in the terminal

Table 6. The Mureidomycins[a] and the Pacidamycins[b]

Name	CAS Registry Number	Molecular formula	Structure number	R′	R″
Mureidomycins					
mureidomycin A	[114797-04-5]	$C_{38}H_{48}N_8O_{12}S$	(117)	H	*m*-hydroxyphenyl
mureidomycin B[c]	[114797-05-6]	$C_{38}H_{50}N_8O_{12}S$	(118)	H	*m*-hydroxyphenyl
mureidomycin C	[114797-06-7]	$C_{40}H_{51}N_9O_{13}S$	(119)	glycyl	*m*-hydroxyphenyl
mureidomycin D[c]	[114797-07-8]	$C_{40}H_{53}N_9O_{13}S$	(120)	glycyl	*m*-hydroxyphenyl
Pacidamycins					
pacidamycin 1	[121264-05-9]		(121)	alanyl	indol-3-yl
pacidamycin 2	[121264-06-0]	$C_{39}H_{49}N_9O_{12}$	(122)	alanyl	phenyl
pacidamycin 3	[121280-49-7]	$C_{39}H_{49}N_9O_{13}$	(123)	alanyl	*m*-hydroxyphenyl
pacidamycin 4			(124)	H	indol-3-yl
pacidamycin 5	[121255-43-0]	$C_{36}H_{44}N_8O_{11}$	(125)	H	phenyl
pacidamycin 6			(126)	glycyl	indol-3-yl
pacidamycin 7		$C_{38}H_{47}N_9O_{12}$	(127)	glycyl	phenyl

[a] R is $(CH_2)_2SCH_3$.
[b] R is CH_3.
[c] Positions 5, 6 of the uracil moiety are saturated to give dihydrouracil.

amino acid residues (238). The biosynthesis of these nucleoside antibiotics is markedly affected by the amino acids added to the culture medium (239).

2.8. 4-Aminohexose Nucleosides

The 4-aminohexose nucleosides **(128–140)** are listed in Table 7 (1–4,240–242). A biosynthetic relationship between the 4-aminohexose peptidyl nucleoside antibiotics and the pentopyranines has been proposed (1). The 4-aminohexose pyrimidine nucleoside antibiotics block peptidyl transferase activity and inhibit transfer of amino acids from aminoacyl-tRNA to polypeptides. Hikizimycin, gougerotin, amicetin, and blasticidin S bind to the peptidyl transferase center at overlapping sites (243).

2.9. Nikkomycins

The nikkomycins (**141–159**), isolated from *S. tendae*, are nucleoside-peptide antibiotics (1,4,244,245) as shown in Table 8. Nikkomycins X and Z are structurally identical to neopolyoxins A and C, respectively. Compound **(141)** is a competitive inhibitor of chitin synthetase. Two new nikkomycins, nikkomycin pseudo-Z and pseudo-J **(158, 159)**, contain a *C*-glycosidic bond between C-5 of uracil and C-1′ of 5-amino-5-deoxy-D-*allo*furanuronic acid (245). Other peptidyl nucleosides, the albomycins [1414-39-7] **(160–162)**, amipurimycin **(163)**, and miharamycins A and B **(164, 165)**, are shown in Table 9 (246–248). These nucleosides are either iron chelators or inhibitors of plant pathogens (244, 246–248).

Table 7. 4-Aminohexose Nucleosides

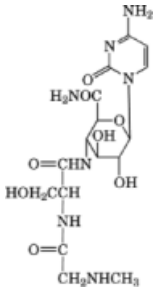
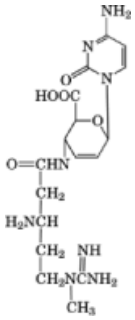
Name	CAS Registry Number	Molecular formula	Structure number	Structure
gougerotin	[2096-42-6]	$C_{16}H_{25}N_7O_8$	**(128)**	
blasticidin S	[2079-00-7]	$C_{17}H_{26}N_8O_5$	**(129)**	

Table 8. The Nikkomycins

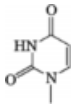
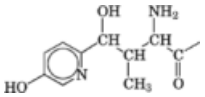
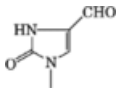
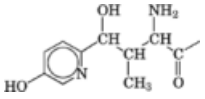
Nikkomycin	CAS Registry Number	Molecular formula	Structure number	R	R′	R″
Z	[59456-70-1]	$C_{20}H_{25}N_5O_{10}$	**(141)**			OH
Z	[75044-70-1]	$C_{20}H_{25}N_5O_{10}$				
X	[72864-26-7]	$C_{20}H_{25}N_5O_{10}$	**(142)**			OH

Table 8. ***Continued***

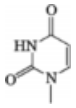
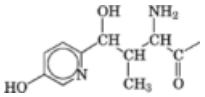
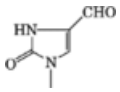
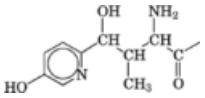
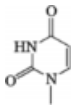
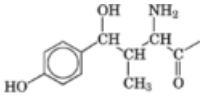
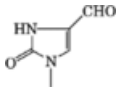
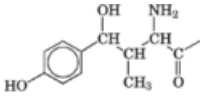
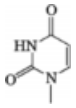
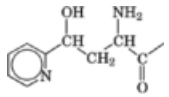
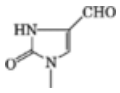
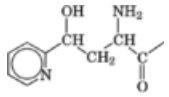
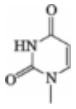
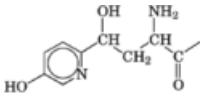
Nikkomycin	CAS Registry Number	Molecular formula	Structure number	R	R′	R″
J	[77368-59-3]	$C_{25}H_{32}N_6O_{13}$	**(143)**			Glu
I	[77368-60-6]	$C_{25}H_{32}N_6O_{13}$	**(144)**			Glu
B_z			**(145)**			OH
B_x	[75410-71-8]	$C_{21}H_{26}N_4O_{10}$	**(146)**			OH
K_z	[95259-45-3]	$C_{19}H_{23}N_5O_9$	**(147)**			OH
K_x	[95259-46-4]	$C_{19}H_{23}N_5O_9$	**(148)**			OH
O_z	[95259-47-5]	$C_{19}H_{23}N_5O_{10}$	**(149)**			OH

Table 8. ***Continued***

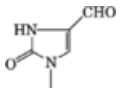
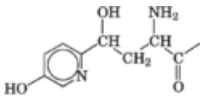
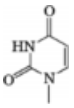
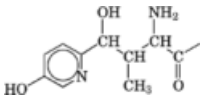
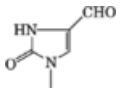
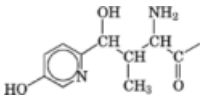
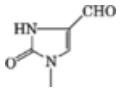
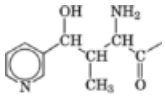
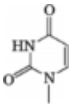
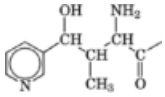
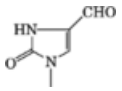
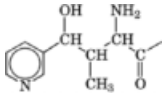
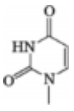
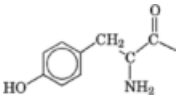
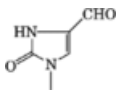
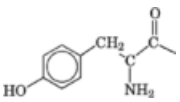
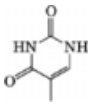
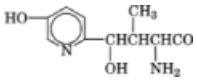
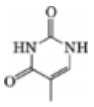
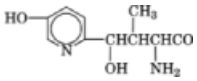
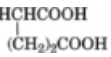
Nikkomycin	CAS Registry Number	Molecular formula	Structure number	R	R′	R″
O_x	[95259-49-7]	$C_{19}H_{23}N_5O_{10}$	**(150)**			OH
Q_z	[95259-50-0]	$C_{24}H_{32}N_6O_{12}$	**(151)**			Homo-Ser
Q_x	[95259-48-6]	$C_{24}H_{32}N_6O_{12}$	**(152)**			Homo-Ser
P_x		$C_{20}H_{25}N_5O_9$	**(153)**			OH
R_z		$C_{25}H_{32}N_6O_{12}$	**(154)**			Glu
R_x		$C_{25}H_{32}N_6O_{12}$	**(155)**			Glu
W_z		$C_{19}H_{21}N_4O_9$	**(156)**			OH
W_x		$C_{19}H_{21}N_4O_9$	**(157)**			OH

Table 8. ***Continued***

Nikkomycin	CAS Registry Number	Molecular formula	Structure number	R	R′	R″
pseudo-Z	[120796-21-6]	$C_{20}H_{25}N_5O_{10}$	**(158)**			OH
pseudo-J	[120796-22-7]	$C_{25}H_{32}N_6O_{13}$	**(159)**			

2.10. Glycosyl Nucleosides

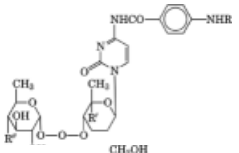
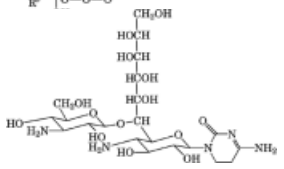
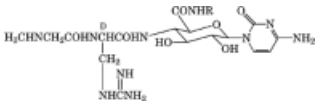
There are five glycosyl antibiotics with either the adenine, uracil, or 7-deazaguanine aglycon given in Table 10. The glycosylated moieties are either *N*-linked disaccharides, unsaturated uronic acid, or a sulfated sugar. The antibacterial and antifungal activities of these compounds have been described (249–253).

2.11. Octosyl Acids

Three octosyl uronic acid nucleosides, produced by *S. cacaoi sub sp. asoensis* are shown in Figure 3. The biosynthesis of (**172**) and (**173**) has been reported (1). The replacement of the pyrimidine chromophore of (**171**) with adenine results in a nucleoside analogue that is a competitive inhibitor of cAMP.

2.12. Arabinosylpyrimidine Nucleosides

1-β-D-Arabinofuranosylthymine [605-23-2] (ara-T) (**174**), $C_{10}H_{14}N_2O_6$, and 1-β-D-arabinofuranosyluracil [3083-77-0] (ara-U) (**175**), $C_9H_{12}N_2O_6$, also known as spongouridine, were first isolated from the sponge *C. crypta* (1–4). The structures of these compounds are shown in Figure 4. Compound (**174**) moderately inhibits *E. coli* and is not toxic to mammalian cells. It inhibits the replication of HSV-1 and varicella zoster virus and is converted to the 5′-triphosphate which inhibits HSV-induced deoxypyrimidine kinase. The chemical synthesis of 4 from thymidine has been reported (254). Ara-TTP competitively inhibits DNA polymerase-α and -β isolated from L5178Y cells with respect to dTTP; thymidine and uridine reverse the inhibition by 4. RNA polymerases are not inhibited by ara-TTP. It is phosphorylated to its 5′-triphosphate in noninfected and HSV-infected cells. Ara-U 4 can satisfy the uracil requirement of an auxotroph of *E. coli* and can be phosphorylated to its 5′-phosphate. Although 4 has little or no antiviral activity, the 5-alkyl derivatives of (**175**) show antiherpesviral activity and inhibition of cell growth in human lung embryonic fibroblasts (255). The 5-halogenated derivatives of ara-UTP inhibit DNA polymerase-α, -β, and -γ and reverse transcriptase.

Name	CAS Registry Number	Molecular formula	Structure number	R	R′	R″	Structure
amicetin	[17650-86-1]	$C_{29}H_{42}N_6O_9$	**(130)**	α-	HH	$N(CH_3)_2$	
bamicetin	[43043-14-7]	$C_{28}H_{40}N_6O_9$	**(131)**	methylserylα-	OH	$NHCH_3$	
oxamicetin	[52665-75-5]	$C_{29}H_{42}N_6O_{10}$	**(132)**	methylserylα-	H	$N(CH_3)_2$	
plicacetin	[43043-15-8]	$C_{25}H_{35}N_5O_7$	**(133)**	methylserylH	H	$N(CH_3)_2$	
norplicacetin	[64040-47-7]	$C_{24}H_{33}N_5O_7$	**(134)**	H		$NHCH_3$	
hikizimycin (anthelmycin)	[12706-94-4]	$C_{21}H_{37}N_5O_{14}$	**(135)**				
bagougeramine A	[104840-35-9]	$C_{17}H_{28}N_{10}O_7$	**(136)**	R = H			
bagougeramine B	[104840-34-8]	$C_{24}H_{44}N_{12}O_7$	**(137)**	$R = (CH_2)_3NH(CH_2)_4NH_2$			

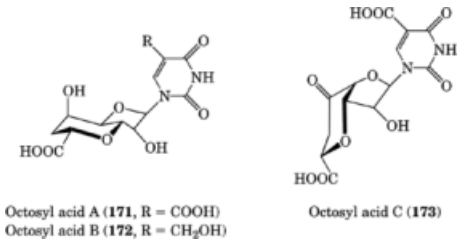
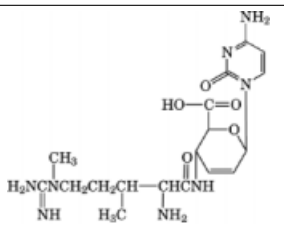
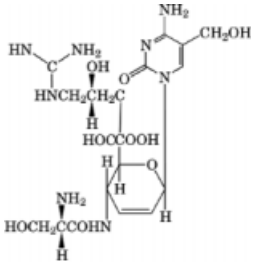
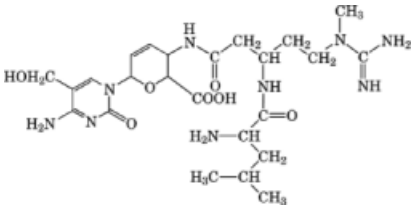


Fig. 3. Octosyl acids.

2.13. 5-Azacytidine

5-Azacytidine [320-67-2] (**176**), $C_8H_{12}N_4O_5$, 4-amino-1-β-D-ribofuranosyl-*S*-triazine-2-(1*H*-one), was chemically synthesized in 1964 and subsequently isolated from culture filtrates of S. *ladakanus* (1–4). Compound (**176**) and 2′-deoxy-5-azacytidine, which are cytotoxic analogues of cytidine, are potent anticancer agents that inhibit DNA methylation (256). Compound (**176**) is incorporated into RNA and tRNA and subsequently inhibits protein synthesis. It inhibits the maturation of 28S and 18S RNA, but not 13S RNA. Polysome degradation increases in the presence of (**176**) with an accumulation of monosomes and an inhibition of protein synthesis. The incorporation of 2′-deoxy-5-azacytidine 5′-monophosphate into DNA causes chromosome breakage. 5-Azacytidine induces 2-5A synthetase in human lymphoid cells (257). This hypomethylating nucleoside is a useful probe to analyze specific gene products in the earliest stages of chemical carcinogenesis (258, 259). It can retransform cells by a mechanism other than DNA methylation (260). In addition, (*176*) induces cytidine deaminase in HL-60 cells, is incorporated into RNA and DNA, inhibits HIV-1 replication, upregulates Epstein-Barr virus nuclear antigen-2, suppresses ADP-ribosylation, and causes chromosomal aberrations (261–268). Compound (**176**) has been used in the treatment of thalassemia (269). The biochemistry of (**176**) has been reviewed (270).

Name	CAS Registry Number	Molecular formula	Structure number	Structure
arginomycin	[106133-33-9]	$C_{18}H_{28}N_8O_5$	**(138)**	
mildiomycin	[67527-71-3]	$C_{19}H_{30}N_8O_9$	**(139)**	
SCH 36605 (rodaplutin)	[113667-06-4]	$C_{24}H_{39}N_9O_7$	**(140)**	

2.14. 5,6-Dihydro-5-azathymidine

5,6-Dihydro-5-azathymidine [57350-36-4] (**177**), $C_9H_{15}N_3O_5$, contains the *s*-triazine ring and is isolated from the culture filtrates of *S. platensis var. clarensis* (4). The inhibition of viral replication by (**177**) can be reversed by either thymidine, deoxyuridine, or deoxycytidine. Compound (**177**) protects mice following intracerebral inoculation with HSV-1 and appears to inhibit the phosphorylation of thymidine rather than its incorporation into DNA. Resistance to (**177**) by *E. coli* appears to result from a change in thymidine phosphorylase.

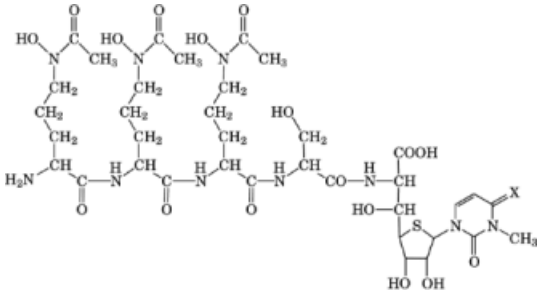
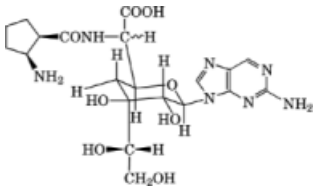
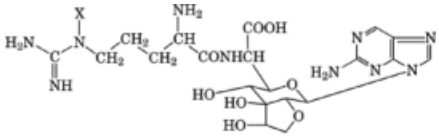
2.15. Clitocine

Clitocine [105798-74-1] (**178**), $C_9H_{13}N_5O_6$, isolated from the mushroom, *Clitocybe inversa*, is 5-nitro-4-(β-D-ribofuranosylamino)pyrimidine-6-amine (271). The crystal structure indicates that the nitro group is hydrogen bonded to the 4-amino hydrogen atom as shown in Figure 4 (272). The base is in the *anti* conformation and the sugar moiety is disordered. Chemical syntheses of (**178**) have been described (273, 274). Clitocine shows strong insecticidal activity against *Pectinophora gossypiella* (271) and is a substrate and inhibitor of adenosine kinase (274).

2.16. Uridine Analogues

5-Formyloxymethyluridine (**179**), $C_{11}H_{14}N_2O_8$, produced by *Serratia plymuthica* (274), inhibits bacterial growth. 3-Methylpseudouridine (**180**), $C_{10}H_{14}N_2O_6$, has been isolated and identified from the culture filtrates

Table 9. Other Peptidyl Nucleosides

Name	CAS Registry Number	Molecular formula	Structure number	X	Structure
albomycin δ_2	[82113-67-5]	$C_{37}H_{60}N_{12}O_{18}S$	**(160)**	$NCONH_2NHO$	
albomycin ϵ	[82113-68-6]	$C_{36}H_{59}N_{11}O_{17}S$	**(161)**		
albomycin δ_1	[82113-69-7]	$C_{36}H_{58}N_{10}O_{18}S$	**(162)**		
amipurimycin	[61991-08-0]	$C_{20}H_{29}N_7O_8$	**(163)**		
miharamycin A	[12626-16-3]	$C_{20}H_{30}N_{10}O_9$	**(164)(165)**	OHH	
miharamycin B	[12626-15-2]	$C_{20}H_{30}N_{10}O_8$			

of *Nocardia lactamdurans* (275). 1-Methylpseudouridine was previously isolated from *S. platensis* (276). 4-Thiouridine (**181**), $C_9H_{12}N_2O_5S$, has been isolated from an actinomycete resembling *S. hygroscopicus* (277).

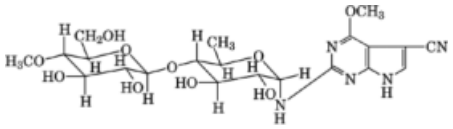
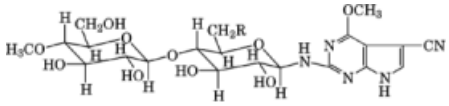
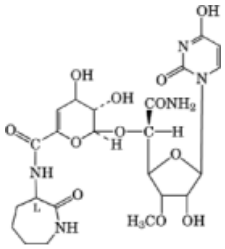
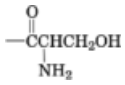
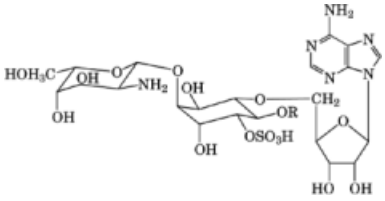
2.17. Hydantocidin

Hydantocidin (**182**), $C_7H_{10}N_2O_6$, is elaborated by *S. hygroscopicus* (278). It is unique in that the anomeric carbon of the ribosyl moiety forms the spiro bond of hydantoin (279). The ribofuranose moiety which has been reported to be in a C_2-*endo* conformation (279) has been synthesized (280, 281). Hydantocidin is a herbicidal nucleoside with activity against monocotyledenous and dicotyledenous plants.

3. *N*-Nucleotides

The *N*-nucleotide antibiotics are given in Table 11. Agrocin 84 **(183)** is an adenine 6-*N*-phosphoramidate nucleotide analogue that contains adenine, phosphate, and ?D-glucose in a 1:2:1 ratio (1, 4). It is produced by *Agrobacterium radiobacter* strain K-84. Crown gall tumors are induced in a number of dicotyledonous plants following inoculation at wound sites with virulent *A. tumefaciens*. Crown gall tumors are caused by the

Table 10. Glycosyl Nucleosides

Name	CAS Registry Number	Molecular formula	Structure number	R	Structure
dapiramicin A	[67298-15-1]	$C_{21}H_{29}N_5O_{10}$	**(166)**		
epidapiramicin A dapiramicin B	[90044-19-2] [90044-18-1]	$C_{21}H_{29}N_5O_{10}$ $C_{21}H_{29}N_5O_{11}$	**(167)(168)**	HOH	
capuramycin	[102770-00-3]	$C_{23}H_{31}N_5O_{12}$	**(169)**		
adenomycin	[76174-56-6]	$C_{25}H_{39}N_7O_{18}S$	**(170)**		

incorporation of part of a virulent plasmid carried by *A. tumefaciens*. Proof that a large plasmid was essential is that the virulent strain C-58 can be converted to a stable avirulent strain. Crown gall formation by *A. tumefaciens* represents the first case where there is a transfer of genetic information from *A. tumefaciens* into the genome of the plant. This type of interaction has been termed "genetic colonization."

Thuringiensin **(184)**, produced by *B. thuringiensis* (1, 4) is a β-exotoxin that exerts its toxic action on insects and mammals through the inhibition of RNA polymerases.

The structure of the nucleotide antibiotic, phosmidosine **(185)**, isolated from the culture filtrates of *Streptomyces* sp. RK-16 has been elucidated (282). Phosmidosine inhibits pore formation of *Botrytis cinerea* and *Aspergillus niger*.

Fosfadecin **(186)** and fosfocytocin **(187)** are adenine and cytosine nucleotide antibiotics isolated from the culture filtrates of *Pseudomonas viridiflava* PK-5 and *P. fluorescens* PK-52, respectively (283). Hydrolysis

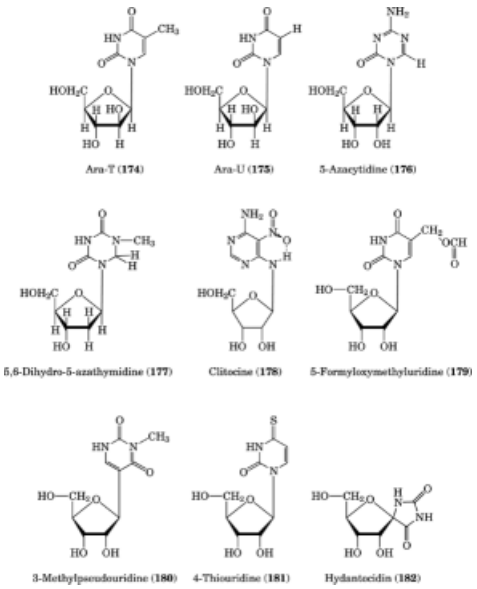
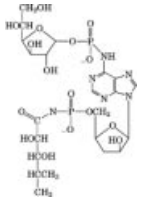
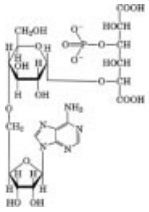
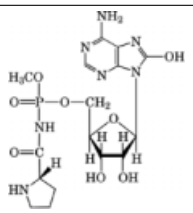
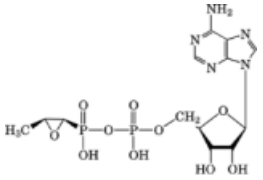
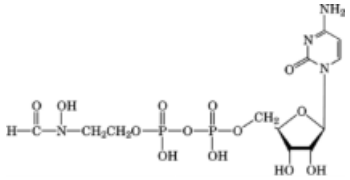


Fig. 4. Structures of pyrimidine nucleosides.

Table 11. *N*-Nucleoside Antibiotics

Name	CAS Registry Number	Molecular formula	Structure number	Structure
agrocin 84	[59111-78-3]	$C_{21}H_{34}N_6O_{16}P_2$	**(183)**	
thuringiensin	[23526-02-5]	$C_{22}H_{30}N_5O_{19}P$	**(184)**	

produces fosfoxacinwhich is also isolated from the culture filtrates. Compounds **(186)** and **(187)** inhibit gram-positive and gram-negative bacteria.

Name	CAS Registry Number	Molecular formula	Structure number	Structure
phosmidosine		$C_{16}H_{24}N_7O_8P$	**(185)**	
fosfadecin	[120909-50-4]	$C_{13}H_{19}N_5O_{10}P_2$	**(186)**	
fosfocytocin	[126986-25-2]	$C_{12}H_{20}N_4O_{13}P_2$	**(187)**	

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