A BRIEF REVIEW OF NUCLEOSIDE ANTIBIOTICS

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Nucleoside antibiotic-producing organisms, extraction methods, biological activities, UV absorption maxima and chemical structures of the nucleoside antibiotics are briefly reviewed in three summary tables. These tables can be conveniently referred to, when screening new metabolites, to determine chemical structures and to study structure-activity relationships of nucleoside antibiotics. Nucleoside antibiotics are described in order of the aglycone nuclei, namely purine (I-XVIII), pyrrolo(2,3-d)pyrimidine (XIX-XXI), pyrazolo(4,3-d)pyrimidine (XXII-XXIV), pyrimidine (XXV-LVI, LIX, LX), s-triazine (LVII), s-dihydrotriazine (LVIII), imidazole (LXI), pyrazole (LXII), maleimide (LXIII) and 1,3-oxazine (LXIV) in the tables. References of each nucleoside antibiotic are numbered in Table I.

1. Nucleoside Antibiotic-Producing Organisms, Extraction Methods and Biological Activities (Table I)
2. UV Absorption Maxima (Table II)
3. Chemical Structures (Table III)
4. Application of the Summary Tables

4.1 Production of Minimycin by Str. mediocidicus

4.2 A New Nucleoside Antibiotic, Platenocidin

A comprehensive review of nucleoside antibiotics published in 1970 described some 35 nucleosides including 7 biologically inactive substances.[1] More than 29 nucleoside antibiotics have been reported since 1970. Taxonomic studies of producing organisms, extraction methods, antimicrobial spectra and UV spectra of antibiotics are useful for classification or identification of antibiotics, especially in early periods of extraction and purification, to avoid fruitless efforts. The structural diversity in the aglycone base and sugar moieties of nucleoside antibiotics is not independent of the diversity in their biological activities. The diversity of biological activities of nucleoside antibiotics is also related to the diversity in their modes of actions. Thus, classification and identification of nucleoside antibiotics are more complicated than other groups of antibiotics.

1. Nucleoside Antibiotic-Producing Organisms, Extraction Methods and Biological Activities (see Table I)

Most of the nucleoside antibiotics are produced by microbes except for spongosine (XIV), crotonoside (XVII), spongouridine (XXV) and spongothymidine (XXVI). In particular, 55 out of 64 nucleoside antibiotics are produced by Streptomyces and many of the nucleoside antibiotics produced by Streptomyces contain the curious aglycone or sugar moieties.

Most of the nucleoside antibiotics are hydrophilic in nature and generally adsorbed on active carbon or cation or anion exchange resin from the broth filtrate. The antibiotics adsorbed on active carbon can be eluted with aqueous acetone, acidic methanol or alkaline methanol and active components adsorbed on cation or anion exchange resin can be eluted with aqueous ammonium hydroxide or hydrochloric acid. While herbicidin A and B (XII, XIII), puromycin (XVI), toyocamycin (XX), sangivamycin (XXI), amicetin A, B and C (XXXIX-XLI), oxamicetin (XLII) and bamicetin (XLIII) can be extracted with butanol or amyl acetate from broth filtrates at alkaline pH.

Nucleocidin (III), gougerotin (XXIX), blasticidin S (XXX), amicetin A, B and C (XXXIX-XLI), oxamicetin (XLII) and bamicetin (XLIII) have rather wide antimicrobial spectra compared with those of other nucleoside antibiotics. Those antibiotics and puromycin (XVI) are considered to inhibit protein synthesis.[2] Generally, each nucleoside antibiotic has a narrow antimicrobial spectrum and inhibits the growth of a few species of some restricted genera of microbes. Nevertheless, biological activities of nucleoside antibiotics are quite different from one another and abound in changes from antibacterial, antiyeast or antifungal to antitumor, antiviral, acaricidal or immunosuppressive characteristics. Cordycepin (II), angustmycins (IV, V), tubercidin (XIX), toyocamycin (XX) and sangivamycin (XXI) are known as inhibitors of nucleotide synthesis.[2] Though, the -CN group of toyocamycin (XX) is converted to the $-CONH_2$ group in sangivamycin (XXI), the former inhibits the growth of Candida and Mycobacteria and the other is effective against Piricularia but not against Candida and Mycobacteria. The mode of action of polyoxins (XLIV-LIII) is inhibition of cell wall synthesis and the antibiotics inhibit the growth of phytopathogenic fungi.[4]

2. UV Absorption Maxima (see Table II)

Nucleoside antibiotics show notable UV absorption maxima in a wide region of 220-320 nm due to individual aglycone moieties and the UV spectra in neutral, acidic and alkaline solutions are quite characteristic for each antibiotic. Thus, the UV spectra and paper chromatogram followed by bio-autography are quite useful for identification or structural studies of nucleoside antibiotics.

3. Chemical Structures (see Table III)

Nucleoside antibiotics are composed of an aglycone base and a sugar, but some of nucleosides contain an additional sugar or additional amino acids.

The existence of pyrrolopyrimidine, pyrazolopyrimidine, s-triazine,

s-dihydrotriazine, imidazole, pyrazole, maleimide or 1,3-oxazine nucleus as the aglycone base instead of purine or pyrimidine nucleus is not unusual in nucleoside antibiotics. The unusual C-glycosyl linkage is usual in nucleoside antibiotics containing pyrazolopyrimidine, pyrazole, maleimide or 1,3-oxazine nucleus as the aglycone, while, the N-glycosyl linkage is usual when purine, pyrrolopyrimidine, pyrimidine, s-triazine, s-dihydrotriazine or imidazole nucleus is present as the aglycone except for pseudouridine (LIX) and 1-methylpseudouridine (LX). The C-N bond of the N-glycosyl linkage can be easily hydrolyzed by mild acid to yield the aglycone base and the sugar, while the C-C bond of the C-glycosyl linkage is resistant to acid or alkaline hydrolysis. The aglycone base of formycin A (XXII), 7-aminopyrazolo(4,3-d)-pyrimidine, can be obtained by periodate oxidation of the antibiotic followed by alkaline decomposition and decarboxylation.[5] The C-C bond of the C-glycosyl linkage is not cleaved by mass spectrometry and the C-nucleoside antibiotics like formycin A (XXII), formycin B (XXIII), pseudouridine (LIX), 1-methylpseudouridine (LX) and showdomycin (LXIII) are characterized by a fragmentation pattern containing a base peak at (m/e) B + 30 due to B-ribose $\longrightarrow$ B-CH=$\overset{+}{O}$H, where B is the aglycone moiety.[6-8] While the N-nucleoside antibiotics give a base peak at (m/e) B + 1 or B + 2 by mass spectrometry.

The anomeric protons of the C-nucleosides appear at a higher field in the nmr spectra compared to that of the N-nucleosides. The position of the anomeric proton of formycin A (XXII) or pseudouridine (LIX) is at 5.14 or 4.72 ppm respectively, whereas the position of the anomeric proton of adenosine or uridine is 6.15 or 6.0 ppm respectively.[8-10]

Septacidine (XV) has an extraordinary structure for a nucleoside antibiotic having N^6-glycosyl adenine, L-septose as an uncommon seven-carbon sugar and isopalmitic acid as an unusual acyl moiety.

D-Ribose and 3-deoxy- (II), 4-fluoro- (III), 3-amino-3-deoxy- (VI-IX, XVI) and 2-amino-2-deoxy- (XVIII) derivatives of D-ribose are widely distributed as the sugar moieties in the nucleoside antibiotics. Aristeromycin (XI) contains the carbocyclic analogue of D-ribose. D-Arabinose (X, XXV, XXVI), angustose (IV), D-psicose (V) and the carboxyamino sugar in polyoxins (XLIV-LV) are also present as furanoses in the antibiotics to form the N-glycosyl linkage. L-Septose (XV), the sugar in aspiculamycin or gougerotin (XXVIII, XXIX), the sugar in blasticidin S (XXX), amicetose (XXXIX, XL, XLIII) and 3-hydroxyamicetose (XLII) are involved as pyranoses to form the N-glycosyl linkage. 3-Amino-3-deoxy-D-glucose (XXVII), ezoaminuroic acid (XXXI-XXXVIII), amosamine (XXXIX, XL, XLII) and 4,6-dideoxy-4-methylamino-D-glucose (XLIII) are also pyranoses as the additional sugars of the nucleoside antibiotics to form the O-glycosyl linkage. 3',7'-Anhydro-5'-deoxy-5'-amino-D-threo-D-allo-octafuranuroic acid in ezomycins (XXXI-XXXVI) and the sugar in herbicidins (XII, XIII) are unique sugars in having both furanose and pyranose structures.

The β-N- or β-C-glycosyl structure can be essential for the nucleoside antibiotics to show biological activities with the exception of septacidin (XV).[11] Ezomycin C_2 (XXXVI) having the α-N-glycosyl linkage is an artifact from ezomycin B_2 (XXXIV) having the β-N-glycosyl linkage or D_2 (XXXVIII).[12] Thus, ezomycin C_1 (XXXV) having the α-N-glycosyl linkage may also be an artifact from ezomycin B_1 or D_1 (XXXIII, XXXVII). To the present, no other nucleoside antibiotic has been reported to have the α-N- or α-C-glycosyl linkage or to contain L-sugar similar to septacidin (XV).

4. Application of the Summary Tables (see Table I, II and III)

Though 1-β-D-arabinofuranosylcytosine (Ara-C) has not yet been isolated as a natural product, the structure of Ara-C synthesized is closely related to that of spongoadenosine, spongouridine and spongothymidine (X, XXV, XXVI).[13] Ara-C is effective against neoplasms in mice, rats and human [14] and used

Table I. Producing Organisms, Extraction Methods and Biological Activities of Nucleoside Antibiotics

	Antibiotic	Producing Organism	Extraction Method	Biological Activity (primarily active against)
1	Nebularine [15-17] (9-β-D-Ribofuranosylpurine)	Agaricus nebularis Str. yokosukanensis	adsorbed on carbon, eluted with 70 % aqu. Me_2CO at pH 2	Mycobacteria, Sarcoma 180
2	Cordycepin [18, 19] (3'-Deoxyadenosine)	Cordyceps militaris Aspergillus pidulan	adsorbed on carbon, eluted with Me_2CO	Bacillus, Ehrlich ascites tumor
3	Nucleocidin [20-23]	Str. calvus	adsorbed on Darco G 60-celite 545 at pH 7, eluted with 95 % aqu. Me_2CO or acidic EtOH	Gram +, −, Mycobacteria, Endoamoeba, Trypanosoma
4	Angustmycin A [24-27] (Decoynine)	Str. hygroscopicus	adsorbed on carbon at pH 7.6, eluted with 80 % aqu. Me_2CO at pH 2	Mycobacteria
5	Angustmycin C (Psicofuranine)			"
6	3'-Amino-3'-deoxy-adenosine [28-30]	Helminthosporium Cordyceps militaris Aspergillus nidulans	adsorbed on Dowex-50-H^+, eluted with NH_4Cl	Cryptococcus, Candida, Ehrlich ascites tumor
7	3'-Acetoamido-3'-deoxyadenosine [31, 32]	Helminthosporium	adsorbed on Dowex-50-NH_4^+, eluted with 0.5 N NH_4OH	none
8	Homocitrullyamino-adenosine [33, 34]	Cordyceps militaris	extracted from mycelia with MeOH	Inhibition of protein synthesis of cell-free extracts of E. coli or rat liver
9	Lysylaminoadenosine [35]	Cordyceps militaris	adsorbed on Dowex-50-NH_4^+, eluted with 3 N NH_4OH	
10	Spongoadenosine [36-38] (Ara-A, 9-β-D-Arabino-furanosyladenine)	Str. antibioticus	adsorbed on carbon, eluted with 50 % aqu. Me_2CO	DNA virus
11	Aristeromycin [39-41]	Str. citricolor	adsorbed on carbon at pH 8, eluted with 80 % aqu. Me_2CO	*Xanthomonas, Piricularia*
12	Herbicidin A [42-44]	Str. saganonensis	adsorbed on Duolite S-30, eluted with 50 % aqu. Me_2CO	Trichophyton, Candida, Pellicularia
13	Herbicidin B			"
14	Spongosine [45]	Cryptotechia crypta	extracted from mycelia with Me_2CO	none
15	Septacidin [46, 47]	Str. fimbriatus	extracted from mycelia with aqu. BuOH	Trichophyton, Fusarium, Adenocarcinoma
16	Puromycin [48, 49]	Str. alboniger	extracted with n-BuOH at pH 9-9.5	Gram +, Tripanosoma, Virus, HeLa cell
17	Crotonoside [50, 51]	Croton tiglium	extracted of ground seeds with MeOH	none
18	2'-Amino-2'-deoxy-guanosine [52, 53]	Aerobacter	adsorbed on IRC-50, eluted with 0.5 N NH_4OH	E. coli KY 8323, HeLa cell, Sarcoma 180

19	Tubercidin [54, 55]	Str. tubercidicus	adsorbrd on carbon, eluted with acidic aqu. Me_2CO	Mycobacteria, Candida, Tumor
20	Toyocamycin [56-58]	Str. toyocaensis	adsorbed on Ionex-C-H^+, eluted with 80 % aqu. Me_2CO	Mycobacteria, Candida, HeLa cell
21	Sangivamycin [59-61]	Str. purpureofuscus	adsorbed on carbon, eluted with acidic MeOH	Leukemia L1210, HeLa cell, Piricularia
22	Formycin A [62-66]	Nocardia interforma	adsorbed on carbon at pH 7, eluted with 50 % aqu. MeOH or 50 % aqu. Me_2CO	Mycobacteria, Xanthomonas, Leukemia L1210, HeLa cell
23	Formycin B (Laurusin)	Nocardia interforma Str. lavendulae		Xanthomonas
24	Oxoformycin B [66, 67]			none
25	Spongouridine [68] (Ara-U, 1-β-D-Arabino-furanosyluracil)	Cryptotethia crypta	Dried sponges are extracted with Me_2CO	none
26	Spongothymidine [69, 70] (Ara-T, 1-β-D-Arabino-furanosylthymine)			
27	Hikijimycin [71, 72]	Streptomyces	adsorbed on IRC-50, eluted with 0.5 N NH_4OH	Pseudomonas, Alternaria
28	Aspiculamycin [73-75]	Str. toyocaensis	adsorbed on IRC-50-H^+, eluted with 1 N NH_4OH	anthelmintic, acaricidal
29	Gougerotin [76, 77]	Str. gougerotii	adsorbed on IRC-50-Na, eluted with 0.5 N HCl	Gram +, -, Mycobacteria
30	Blasticidin S [78-82]	Str. griseochromogenes Str. moro-okaensis	adsorbed on IRC-50-Na, eluted with 0.5 N HCl	Gram +, -, Piricularia
31	Ezomycin A_1 [12, 83-86]	Str. kitazawaensis	adsorbed on Dowex 1 X 1, eluted with 0.5 N HCl	Sclerotinia, Botrytis
32	Ezomycin A_2			none
33	Ezomycin B_1			Sclerotinia, Botrytis
34	Ezomycin B_2			none
35	Ezomycin C_1			"
36	Ezomycin C_2			"
37	Ezomycin D_1			"
38	Ezomycin D_2			"
39	Amicetin A [87-93]	Str. vinaceus-drappus Str. fasciculatus Str. sacromyceticus	adsorbed on IRC-50-H^+ or IR 100, eluted with acidic 80 % aqu. Me_2CO	Gram +, Mycobacteria
40	Amicetin B (Plicacetin)	Str. vinaceus-drappus Str. plicatus	extracted with BuOH or AcOEt at pH 7-8.5	"
41	Amicetin C	Str. vinaceus-drappus	extracted with AcOAm at pH 7-8.5	"
42	Oxamicetin [94-96]	Arthrobacter oxamicetus	extracted with BuOH at pH 8.2-8.4	Gram +, -, Mycobacteria

43	Bamicetin [97, 98]	Str. plicatus	extracted with BuOH at pH 7.1-8.6	Gram +, Mycobacteria
44	Polyoxin A [99-103]	Str. cacaoi	adsorbed on carbon at pH 2, eluted with 60 % aqu. Me_2CO	Alternaria, Cochliobolus, Piricularia
45	Polyoxin B			"
54	Polyoxin C			none
49	Polyoxin G			Alternaria, Cochliobolus, Piricularia
55	Polyoxin I			none
50	Polyoxin H			Alternaria, Cochliobolus, Piricularia
51	Polyoxin J			"
46	Polyoxin D			"
47	Polyoxin E			"
48	Polyoxin F			"
52	Polyoxin K			"
53	Polyoxin L			"
56	Nikkomycin [104]	Str. tendae	adsorbed on Dowex 50W X 4-Na, eluted with 0.01 N NH_4OH	Phytophathogenic fungi
57	5-Azacytidine [105, 106]	Streptoverticillium ladakanus	adsorbed on Darco G-60, eluted with 50 % aqu. Me_2CO	Gram -, Leukemia L1210, Ehrlich ascites tumor
58	U-44590 [8]	Str. platensis		
59	Psudouridine [8, 107]	Str. hygroscopicus Str. platensis Agrobacterium tumefaciens	adsorbed on IRA-400, eluted with 0.4 N HCl	none
60	1-Methylpseudouridine [8)]	Str. platensis	adsorbed on CAL-carbon, eluted with 75 % aqu. Me_2CO	Gram +, -, Herpes virus
61	Bredinin [108]	Eupenicillium brefeldianum	adsorbed on IRA 411-OH^-, eluted with 2 % aqu. AcOH	Candida, Vaccinia virus, Immunosuppressive
62	Pyrazomycin [109]	Str. candidus	adsorbed on carbon, eluted with 50 % aqu. Me_2CO	Rhino, Measkes, Herpes, Simplex and Vaccinia virus
63	Showdomycin [10, 110, 111]	Str. showdoensis	adsorbed on carbon at pH 5, eluted with 80 % aqu. Me_2CO	Gram +, -, Ehrlich ascites tumor
64	Minimycin [112-114] (Oxazinomycin)	Str. hygroscopicus Str. tanesashinensis	adsorbed on carbon at pH 2, eluted with 50 % aqu. Me_2CO	Gram +, -, Ehrlich ascites tumor, Sarcoma 180

Str.=Streptomyces, Gram + =Gram positive bacteria, Gram - =Gram negative bacteria

Table II. Ultraviolet Absorption Maxima of Nucleoside Antibiotics

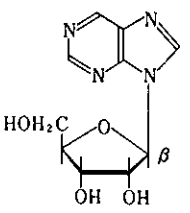
	Antibiotic	$\lambda_{max}^{neutral}$ (nm)	λ_{max}^{acid} (nm)	$\lambda_{max}^{alkaline}$ (nm)
1	Nebularine (9-β-D-Ribofuranosylpurine)		262 (E, 232)	263 (E, 361)
2	Cordycepin (3'-Deoxyadenosine)		260 (e, 14400)	260 (e, 14600)
3	Nucleocidin	256 (e, 15500)	255-257 (E, 392)	259 (E, 406)
4	Angustmycin A (Decoynine)	260 (E, 570)	260 (e, 17100)	260 (e, 17100)
5	Angustmycin C (Psicofuranine)		259 (E, 508)	261 (E, 527)
6	3'-Amino-3'-deoxyadenosine	260 (e, 17300)		
7	3'-Acetoamido-3'-deoxyadenosine	260 (e, 15600)		
8	Homocitrullylaminoadenosine			
9	Lysylaminoadenosine			
10	Spongoadenosine (Ara-A, 9-β-D-Arabino-furanosyladenine)	259 (e, 13400)	257.5 (e, 12700)	259 (e, 14000)
11	Aristeromycin	262 (E, 555)	262 (E, 555)	262 (E, 555)
12	Herbicidin A	258 (e, 11500 in MeOH)		
13	Herbicidin B	258 (e, 9200 in MeOH)		
14	Spongosine	267 (e, 12500)	249 (e, 8350), 274 (e, 11900)	268 (e, 12700)
15	Septacidin	264 (E, 253 in MeOH)		272 (E, 275)
16	Puromycin		267.5 (E, 195)	275 (E, 203)
17	Crotonoside	230 (e, 6000), 270 (e, 10500)	235 (e, 9000), 285 (e, 9000)	240 (e, 4000), 275 (e, 7500)
18	2'-Amino-2'-deoxyguanosine	252 (e, 14100), 275 (sh, e, 9500)	255 (e, 12500), 278 (sh, e, 8500)	258 (e, 12000), 267 (e, 12100)
19	Tubercidin		227 (e, 25200), 270 (e, 12200)	270 (e, 12100)

20	Toyocamycin	230 (E, 400), 277 (E, 548)	235 (E, 760), 273 (E, 563)	233 (E, 398), 280 (E, 571)
21	Sangivamycin	229 (e, 8200 in EtOH), 278 (e, 15100 in EtOH)	228 (e, 9500), 273 (e, 12800)	227 (e, 14100), 277 (e, 14400)
22	Formycin A	295 (E, 380)	234 (E, 280), 295 (E, 340)	235 (E, 500), 305 (E, 260)
23	Formycin B (Laurusin)	280 (E, 294)	221 (E, 543), 276 (E, 300)	230 (E, 643), 292 (E, 338)
24	Oxoformycin B	288 (e, 395)	288 (E, 220)	304 (E, 168)
25	Spongouridine (Ara-U, 1-β-D-Arabinofuranosyl-uracil)	265 (e, 9300)	265 (e, 9300)	236 (e, 8250), 268 (e, 8600)
26	Spongothymidine (Ara-T, 1-β-D-Arabinofuranosyl-thymine)	270 (e, 9200)	270 (e, 6800)	270 (e, 7600)
27	Hikijimycin	266 (e, 5600)	274 (e, 8000)	268 (e, 5500)
28	Aspiculamycin	236 (e, 8250), 268 (e, 8600)	276 (e, 11300)	236 (e, 8250), 268 (e, 8600)
29	Gougerotin	228 (e, 8900), 269 (e, 9400)	276 (e, 13300)	228 (e, 8900), 269 (e, 9600)
30	Blasticidin S		275 (e, 14300)	266-270 (e, 9450)
31	Ezomycin A_1		278 (e, 10500)	271 (e, 7900)
32	Ezomycin A_2		278 (e, 11100)	229 (e, 6100), 271 (e, 7100)
33	Ezomycin B_1		262 (e, 7000)	286 (e, 6100)
34	Ezomycin B_2		261.5 (e, 6300)	286 (e, 4900)
35	Ezomycin C_1		263 (e, 6400)	287 (e, 4900)
36	Ezomycin C_2		263.5 (e, 6200)	287 (e, 4800)
37	Ezomycin D_1		263.5 (e, 6900)	287 (e, 5200)
38	Ezomycin D_2		264 (e, 6700)	287 (e, 4900)
39	Amicetin A	305 (E, 465)	316 (E, 433)	322 (E, 470)
40	Amicetin B (Plicacetin)	249 (a, 26.6), 321 (a, 53.5)	257 (a, 36.8), 311.5 (a, 29.2)	329 (a, 63.9)
41	Amicetin C	257 (E, 288), 304 (E, 250)	255 (E, 183), 313 (E, 332)	274 (E, 174), 318 (E, 217)

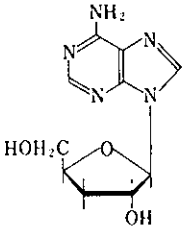
42	Oxamicetin	305 (e, 31700)	316 (e, 26600)	322 (e, 21900)
43	Bamicetin	302 (a, 45.5)	314 (a, 43.7)	322 (a, 52.5)
44	Polyoxin A		262 (E, 142)	264 (E, 103)
45	Polyoxin B		262 (E, 172)	264 (E, 130)
54	Polyoxin C		262 (E, 297)	264 (E, 231)
49	Polyoxin G		262 (E, 170)	264 (E, 134)
55	Polyoxin I		262.5 (E, 165)	264 (E, 123)
50	Polyoxin H		262 (E, 127)	266 (E, 103)
51	Polyoxin J		264 (log e, 3.91)	267 (log e, 3.81)
46	Polyoxin D		218 (E, 217), 276 (E, 127)	271 (E, 137)
47	Polyoxin E		218 (E, 200)	271 (E, 128)
48	Polyoxin F		218 (E, 200), 276 (E, 200)	271 (E, 118)
52	Polyoxin K		259 (log e, 3.95)	267 (log e, 3.86)
53	Polyoxin L		259 (log e, 3.96)	262 (log e, 3.85)
56	Nikkomycin		225 (sh, a, 0.88), 290 (a, 1.5)	242 (a, 1.58), 305 (a, 1.0)
57	5-Azacytidine	241 (e, 8767)	249 (e, 3077)	223 (e, 24200)
58	U-44590			
59	Pseudouridine	262 (e, 8470)	262 (e, 8390)	286 (e, 8400)
60	1-Methylpseudouridine	209 (e, 7546), 270 (e, 9081)	209 (e, 10342), 270 (e, 8923)	267 (e, 6192)
61	Brdinin	245 (E, 250), 279 (E, 580)	245 (E, 260), 281 (E, 495)	277 (E, 660)
62	Pyrazomycin	263 (e, 6200)		307 (e, 8100)
63	Showdomycin	220-221 (E, 442)		
64	Minimycin (Oxazinomycin)		230 (E, 188)	

E=E $^{1\ \%}_{1\ cm}$, e=Molecular extinction, a=Absorption, sh=Shoulder

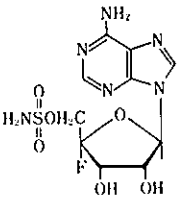
Table III. Chemical Structures of Nucleoside Antibiotics



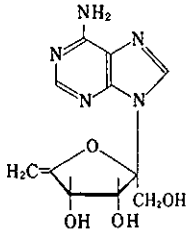
(I) Nebularine



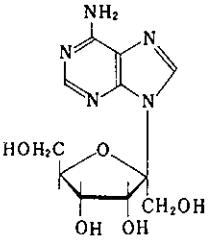
(II) Cordycepin



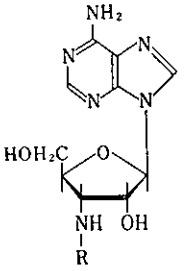
(III) Nucleocidin



(IV) Angustmycin A



(V) Angustmycin C



(VI) 3'-Amino-3'-deoxy-adenosine

R=-H

(VII) 3'-Acetoamido-3'-deoxy-adenosine

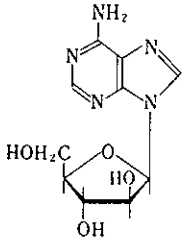
R=-$COCH_3$

(VIII) Homocitrullylamino-adenosine

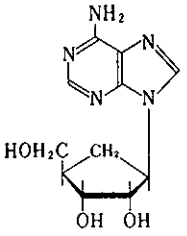
R=-$COCHCH_2CH_2CH_2CH_2$
NH_2 $NHCONH_2$

(IX) Lysylaminoadenosine

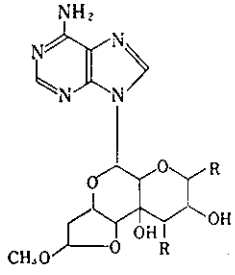
R=-$COCHCH_2CH_2CH_2CH_2NH_2$
NH_2



(X) Spongoadenosine



(XI) Aristeromycin



(XII) Herbicidin A

R= H_3C CH_2OH
H $C=C$
$COO-$

or

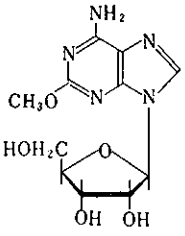
R=-$COOCH_3$, R'= H_3C CH_2OH
H $C=C$
$COO-$

(XIII) Herbicidin B

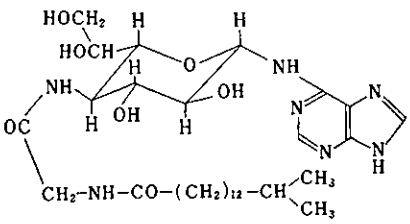
R=-OH, R'=-$COOCH_3$

or

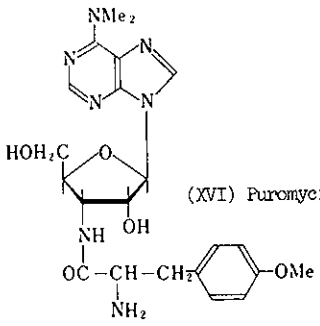
R=-$COOCH_3$, R'=-OH



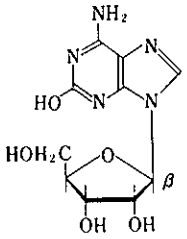
(XIV) Spongosine



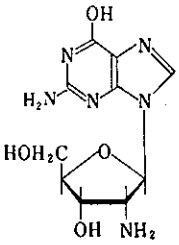
(XV) Septacidin



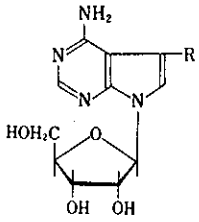
(XVI) Puromycin



(XVII) Crotonoside



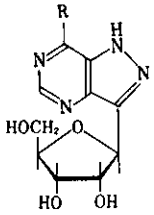
(XVIII) 2'-Amino-2'-deoxy-guanosine



(XIX) Tubercidin, R=-H

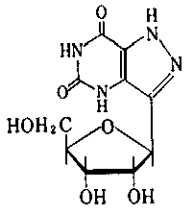
(XX) Toyocamycin, R=-CN

(XXI) Sangivamycin, R=-$CONH_2$

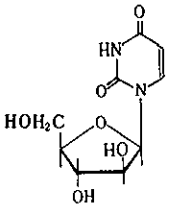


(XXII) Formycin A, R=-NH_2

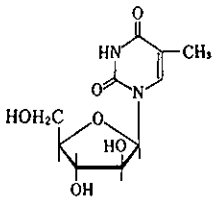
(XXIII) Formycin B, R=-OH



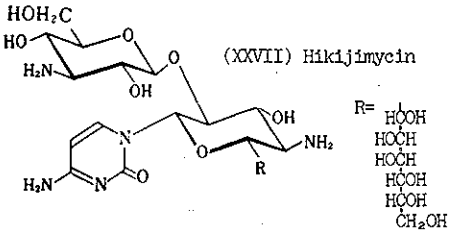
(XXIV) Oxoformycin B



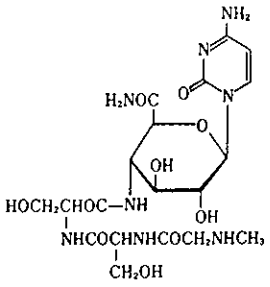
(XXV) Spongouridine



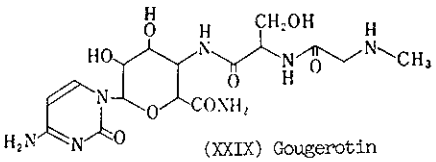
(XXVI) Spongothymidine



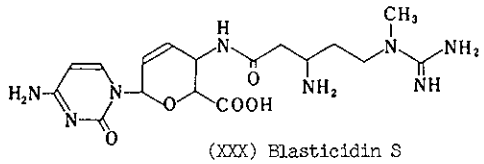
(XXVII) Hikijimycin



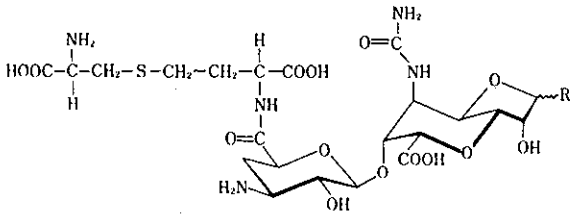
(XXVIII) Aspiculamycin



(XXIX) Gougerotin



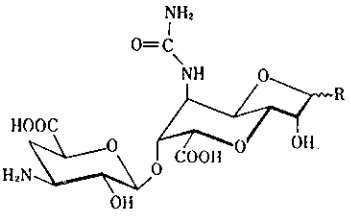
(XXX) Blasticidin S



(XXXI) Ezomycin A_1, R=β-1-Cytosine

(XXXIII) Ezomycin B_1, R=β-5-Uracil

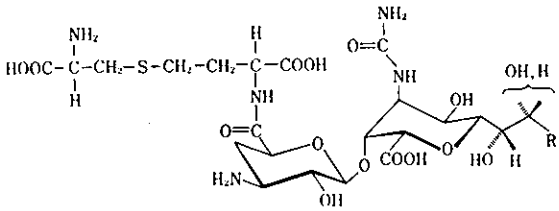
(XXXV) Ezomycin C_1, R=α-5-Uracil



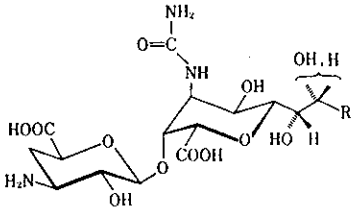
(XXXII) Ezomycin A_2, R=β-1-Cytosine

(XXXIV) Ezomycin B_2, R=β-5-Uracil

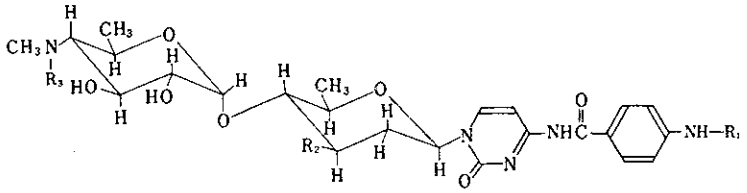
(XXXVI) Ezomycin C_2, R=α-5-Uracil



(XXXVII) Ezomycin D_1, R=5-Uracil



(XXXVIII) Ezomycin D_2, R=5-Uracil



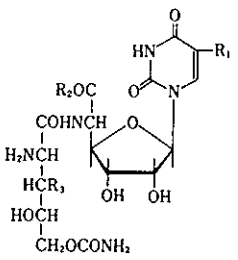
(XXXIX) Amicetin A; R_1=–CO–C(CH₃)(NH₂)–CH₂OH, R_2=–H, R_3=–CH_3

(XL) Plicacetin; R_1=–H, R_2=–H, R_3=–CH_3

(XLI) Amicetin C; ?

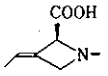
(XLII) Oxamicetin; R_1=–CO–C(CH₃)(NH₂)–CH₂OH, R_2=–OH, R_3=–CH_3

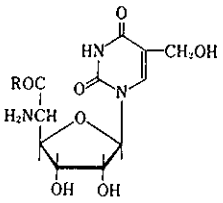
(XLIII) Bamicetin; R_1=–CO–C(CH₃)(NH₂)–CH₂OH, R_2=–H, R_3=–H



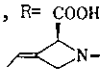
Polyoxin	R_1	R_2	R_3
(XLIV)	A	$-CH_2OH$	POAM	$-OH$
(XLV)	B	$-CH_2OH$	$-OH$	$-OH$
(XLVI)	D	$-COOH$	$-OH$	$-OH$
(XLVII)	E	$-COOH$	$-OH$	$-H$
(XLVIII)	F	$-COOH$	POAM	$-OH$
(XLIX)	G	$-CH_2OH$	$-OH$	$-H$
(L)	H	$-CH_3$	POAM	$-OH$
(LI)	J	$-CH_3$	$-OH$	$-OH$
(LII)	K	$-H$	POAM	$-OH$
(LIII)	L	$-H$	$-OH$	$-OH$

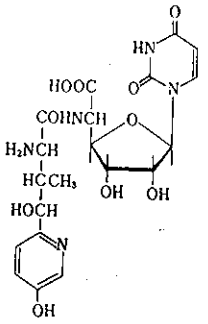
POAM: Polyoximic acid moiety





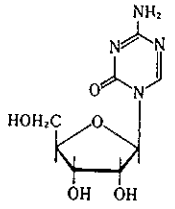
(LIV) Polyoxin C, R=-OH

(LV) Polyoxin I, R= 

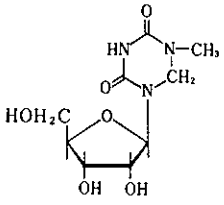


(LVI) Nikkomycin

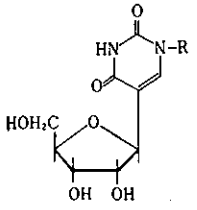
(Configuration of the sugar moiety is not yet determined.)



(LVII) 5-Azacytidine

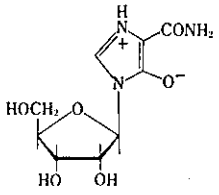


(LVIII) U-44590

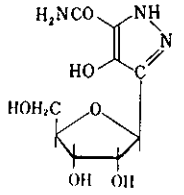


(LIX) Pseudouridine, R=-H

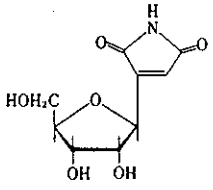
(LX) 1-Mehtylpseudouridine R=-CH_3



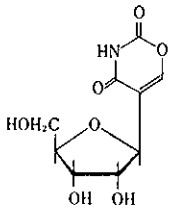
(LXI) Bredinin



(LXII) Pyrazomycin



(LXIII) Showdomycin



(LXIV) Minimycin

clinically in cancer chemotherapeutics. The nucleoside antibiotics are interesting to study for structure-activity relationships, because of their diversity in chemical structures as well as in biological activities.

Application of the summary tables is described as follows.

4.1 Production of Minimycin by Str. mediocidicus [115]

Culture broth of Str. H 86-NSY-6 identified as Str. mediocidicus was shown to produce an antibiotic inhibiting E. coli K-12 ML 1629 which was known to be resistant to aminocyclitol antibiotics. The antibiotic was adsorbed on active carbon from the broth filtrate at pH 2. The antibiotic adsorbed on carbon was eluted with 80 % aqueous acetone at pH 7 and the acetone was removed in vacuo. The active component was further adsorbed on Amberlite IRA-400 (OH^--type) and eluted with H_2O at pH 2. The active eluate was lyophilized after neutralization with dil. NH_4OH to recover the crude antibiotic. The crude antibiotic was purified by column chromatography on Avicel (microcrystalline cellulose) developed with n-BuOH:acetone:H_2O=4:1:1 after gel filtration on Sephadex G-15 eluted with H_2O and following gel filtration on Sephadex LH 20 eluted with MeOH. The pure antibiotic was recovered by recrystallization from n-BuOH as white plates, decomp. p., 161.5-165.0°.

UV; λ_{max}^{MeOH}=232 nm ($E_{1\,cm}^{1\,\%}$=184).

The antibiotic inhibits the growth of restricted species of Gram positive and negative bacteria by the agar dilution method. The antibiotic shows an inhibition zone by the cylinder agar plate method against E. coli K-12 ML 1629, while the antibiotic is inactive against the same bacteria by the agar dilution method.

Extraction method, biological activity and UV spectrum of the antibiotic are identical with that of minimycin (LXIV). The antibiotic was confirmed to be minimycin by comparing the bioautograms and IR spectra of the antibiotic and minimycin. Str. hygroscopicus and Str. tanesashinensis are known to

produce minimycin (see Table I). Thus, this is the first report on the production of minimycin by Str. mediocidicus.

4.2 A New Nucleoside Antibiotic, Platenocidin [116]

Culture broth of Str. H 273-NSY-2, identified as Str. platensis [117] was shown to produce an antibiotic effective only against Candida but not against other yeasts, fungi or bacteria. The antibiotic can be neither extracted with n-BuOH nor adsorbed on active carbon from the broth filtrate. The antibiotic can be adsorbed on Amberlite IR 120 (H^+-form) and eluted with 1 N NH_4OH followed by lyophilization to yield the crude antibiotic. A small amount of the crude antibiotic was purified by paper chromatography followed by elution and lyophilization. The purified antibiotic showed a UV spectra quite similar to that of polyoxin A, B, C and G (XLIV, XLV, LIV, XLIX). Nevertheless, polyoxins are inactive against Candida. While Str. platensis is known to produce the nucleoside antibiotics, namely U-44590 (LVIII), pseudouridine (LIX) and 1-methylpseudouridine (LX) (see Table I), physicochemical and biological properties of the antibiotic produced by Str. H 273-NSY-2 are differentiated from those antibiotics. Thus, the antibiotic produced by Str. H 273-NSY-2 can be considered to be a new nucleoside antibiotic and is named platenocidin, relating it to the antibiotic-producing microbe.

Platenocidin is amphoteric in nature and purified by DEAE-Sephadex A-25 column chromatography eluted with 0.1 M of pyridine-acetate buffer (pH 4.8), gel filtration on Sephadex G-10 column eluted with 0.05 M of the same buffer, SP-Sephadex column chromatography eluted with 0.02 M of the same buffer and finally DEAE-Sephadex A-25 column chromatograohy eluted with 0.05 M of the same buffer. The pure antibiotic was obtained as white amorphous powder, decomp. p., 117-120°. Elementary microanalysis gave C, 43.03; H, 4.73; N, 15.62 % and no halogen or sulfur was observed.

UV; λ_{max} ($E^{1\%}_{1\,cm}$), 255 nm (216) in H_2O, 260 nm (257) in 0.1 N HCl and 257 nm (230) in 0.1 N NaOH. The UV spectra of platenocidin are quite similar to those of polyoxin A (XLIV) except for higher extinction, but the papergram of platenocidin dose not accord with that of polyoxins. Though the structure has not yet been fully elucidated, nikkomycin (LVI) can be considered to be closely related to polyoxins. Nevertheless, the UV maxima of nikkomycin can be differentiated from that of platenocidin.

The existence of 5-hydroxymethyluracil in platenocidin is suggested from the UV spectra and 5-hydroxymethyluracil is obtained by mild acid hydrolysis of platenocidin. Thus, platenocidin can be considered to be a new nucleoside antibiotic having 5-hydroxymethyluracil as the aglycone and the N-glycosyl linkage. The structure of platenocidin is now under investigation and progress in its elucidation will be reported in the future.

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