Kirk-Othmer Encyclopedia of Chemical Technology.

ANSAMACROLIDES

The ansamacrolides or ansamycins are a family of antibiotics characterized by an aliphatic ansa-bridge that connects two nonadjacent positions of an the aromatic nucleus (1, 2). Ansamacrolides can be divided into two groups based on the nature of the aromatic nucleus. One group contains a naphthoquinoid nucleus and includes the streptovaricins, the rifamycins, tolypomycin, the halomycins, the naphthomycins, actamycin, the diastovaricins, kanglemycin, awamycin, and ansathiazin. The other group contains a benzoquinoid nucleus and includes geldanamycin, the maytansinoids, the herbimycins, the macbecins, the mycotrienins, the trienomycins, the ansatrienins, and the ansamitocins. Table 1 lists the naturally occurring ansamacrolides and some of their physical properties. Table 2 summarizes the biological activity of these antibiotics.

1. Naphthoquinoids

1.1. Streptovaricins

The streptovaricins are produced by *Streptomyces spectablis* n. sp. (60, 61) and are isolated as a crude complex (62, 63). Substance B 44 P, isolated from *Streptomyces* B 44-P1, was shown to be identical with the streptovaricins (64).

Chemical degradation studies carried out on streptovaricins A and C, which are the primary components of the crude complex, yielded substances shown in Figure 1. Streptovaricin A (**4**), consumes two moles of sodium periodate to yield varicinal A [21913-68-8] (**1**), $C_{13}H_{20}O_7$, which accounts for the aliphatic portion of the molecule, and prestreptovarone [58074-37-6] (**2**), $C_{29}H_{29}NO_9$, which accounts for the aromatic chromophore of the streptovaricins (Fig. 2). Streptovaricin G (**9**) is the only other streptovaricin that yields prestreptovarone upon treatment with sodium periodate. Treatment of streptovaricins A (**4**), B (**5**), C (**6**), E (**8**), and G (**9**) with sodium periodate and osmium tetroxide yields streptovarone [36108-44-8] (**3**), $C_{24}H_{23}NO_9$, which is also produced by the reaction of prestreptovarone with sodium periodate and osmium tetroxide (4, 65). A number of aliphatic products were isolated from the oxidation of streptovaricin C and its derivatives (66).

The relationships among the various streptovaricins were shown by the following reactions: streptovaricin E (**8**) converts to streptovaricin C (**6**) upon treatment with sodium borohydride; streptovaricins A (**4**), G (**9**), and K (**11**) yield the same triacetate derivative upon acetylation; streptovaricins B (**5**), C (**6**), and J (**10**) yield the same tri- and tetraacetate derivatives upon acetylation; streptovaricin G (**9**) converts to streptovaricin F_G (**12**) upon treatment with base (4). The open-chain streptovaricin U (**13**) has also been isolated from the streptovaricin complex (5).

The structures of the streptovaricins were confirmed by x-ray crystallographic studies (67, 68). The absolute configuration of the ansa-bridge is 6(*R*), 7(*R*, 8(*R*, 9(*R*), 10(*S*), 12(*R*), 13(*S*), and 14(*R*) with a helicity of *P* (69). Complete mass spectral (4, 70, 71) and ^{13}C nmr studies have been reported (72).

Table 1. Properties of the Ansamacrolides

Ansamacrolide	CAS Registry Number	Producing organism	Molecular formula	MP, °C	$[\alpha]_D$[a]	Structure no.	Reference
Naphthoquinoid							
streptovaricin A	[23344-16-3]	*Streptomyces spectabilis*	$C_{42}H_{53}NO_{16}$	233–243	+610	(**4**)	3
streptovaricin B	[11031-82-6]	*Streptomyces spectabilis*	$C_{42}H_{53}NO_{15}$	187–189	+576	(**5**)	3
streptovaricin C	[23344-17-4]	*Streptomyces spectabilis*	$C_{40}H_{51}NO_{14}$	189–191	+602	(**6**)	3
streptovaricin D	[32164-26-4]	*Streptomyces spectabilis*	$C_{40}H_{51}NO_{13}$	172–175	+590.3	(**7**)	3
streptovaricin E	[35413-63-9]	*Streptomyces spectabilis*	$C_{40}H_{49}NO_{14}$	198–202	+412.3	(**8**)	3
streptovaricin F_G[b]	[35512-37-9]	*Streptomyces spectabilis*	$C_{39}H_{47}NO_{14}$	222–224	+488[c]	(**12**)	3
streptovaricin G	[11031-85-9]	*Streptomyces spectabilis*	$C_{40}H_{51}NO_{15}$	190–192	473	(**9**)	3
streptovaricin J	[52275-61-3]	*Streptomyces spectabilis*	$C_{42}H_{53}NO_{15}$	177–180	+436	(**10**)	3
streptovaricin K	[23344-16-3]	*Streptomyces spectabilis*	$C_{42}H_{53}NO_{16}$	162–165		(**11**)	4
streptovaricin U	[74200-47-8]	*Streptomyces spectabilis*	$C_{36}H_{49}NO_{10}$	115–140	−110[c]	(**13**)	5
rifamycin B	[13929-35-6]	*Nocardia mediterranei n. sp.* *Streptomyces tolypophorus*	$C_{39}H_{49}NO_{14}$	160–164[d]	−11[c]	(**22**)	(6, 7)
rifamycin O	[14487-05-9]	*Streptomyces mediterranei* No. 4107	$C_{39}H_{47}NO_{14}$	160[d]		(**23**)	(6, 8)
rifamycin A_2					+71.5[e]		
rifamycin S	[13553-79-2]	*Nocardia mediterranei n. sp.*	$C_{37}H_{45}NO_{12}$	146–147	+462	(**24**)	(6, 9)
rifamycin SV	[6998-60-3]	*Nocardia mediterranei mutant ATCC 21271*	$C_{37}H_{47}NO_{12}$	140[d]	−4[c]	(**25**)	(6, 10)
rifamycin Y	[15271-73-5]	*Nocardia mediterranei*	$C_{39}H_{47}NO_{15}$		+325	(**29**)	11
rifamycin L	[26117-02-2]	*Nocardia mediterranei*	$C_{39}H_{49}NO_{14}$	152–153[d]		(**28**)	12
rifamycin W	[53904-81-7]	*Nocardia mediterranei mutant 126*	$C_{35}H_{45}NO_{11}$			(**30**)	(13, 14)
rifamycin R	[59264-04-9]	*Nocardia mediterranei mutant ATCC 31066*	$C_{37}H_{45}NO_{13}$			(**27**)	15
rifamycin P	[59232-87-0]	*Nocardia mediterranei mutant ATCC 13685*	$C_{38}H_{46}N_2O_{11}S$			(**31**)	16
rifamycin Q	[59232-88-1]	*Nocardia mediterranei mutant ATCC 13685*	$C_{39}H_{48}N_2O_{12}S$			(**32**)	16
rifamycin verde	[72428-95-6]	*Nocardia mediterranei mutant ATCC 13685*	$C_{39}H_{46}N_2O_{12}S$			(**33**)	16
rifamycin G	[59996-09-7]	*Nocardia mediterranei*	$C_{36}H_{47}NO_{12}$	250–252		(**26**)	17
tolypomycin Y	[23412-26-2]	*Streptomyces tolypophorus*	$C_{43}H_{54}NO_{14}$	120	+326[f]	(**48**)	7
halomycin A	[56411-51-9]	*Micromonospora halophytica*	$C_{43}H_{58}N_2O_{13}$	192–194		(**54**)	18
halomycin B	[54356-09-1]	*Micromonospora halophytica*	$C_{43}H_{58}N_2O_{12}$	178–182	+100.5	(**55**)	(19, 20)
halomycin C	[64419-06-3]	*Micromonospora halophytica*	$C_{43}H_{58}N_2O_{13}$		+73.1[c]	(**56**)	18
naphthomycin A	[55557-40-9]	*Streptomyces collinu Lindenbein Tü 105*	$C_{40}H_{46}ClNO_9$	ca 200	+153 +432	(**59**)	(21, 22)
naphthomycin B	[86828-40-9]	*Streptomyces galbus Tü 353*	$C_{39}H_{44}ClNO_9$	156–165	+412	(**60**)	23
naphthomycin C	[86825-87-8]	*Streptomyces diastatochromogenes Tü 1892*	$C_{39}H_{45}NO_9$			(**61**)	23
naphthomycin D	[105225-04-5]	*Streptomyces Tü 2357*	$C_{40}H_{47}NO_{10}$		+117.7 +323	(**62**)	22
naphthomycin E	[105225-03-4]	*Streptomyces Tü 2357*	$C_{40}H_{47}NO_9$			(**63**)	22
naphthomycin F	[105225-01-2]	*Streptomyces Tü 2357*	$C_{46}H_{56}N_2O_{12}$		+133.5	(**64**)	22
naphthomycin G	[105225-02-3]	*Streptomyces Tü 2357*	$C_{45}H_{54}N_2O_{12}S$	188	+333.4 +254[c]	(**65**)	22
naphthomycin H[g]	[98525-20-3]	*Streptomyces Y-83, 40369*	$C_{39}H_{44}ClNO_9$	150	+218	(**66**)	(24, 25)

Table 1. ***Continued***

Ansamacrolide	CAS Registry Number	Producing organism	Molecular formula	MP, °C	$[\alpha]_D$[a]	Structure no.	Reference
naphthoquinomycin A	[101190-62-9]	*Streptomyces S-1998*	$C_{40}H_{47}NO_{10}$	173–182	+212	(**67**)	25
naphthoquinomycin B	[101190-61-8]	*Streptomyces S-1998*	$C_{40}H_{47}NO_9S$	171–180	+541	(**68**)	25
actamycin	[76045-67-5]	*Streptomyces E/784*	$C_{39}H_{45}NO_{10}$	190–192		(**69**)	26
diastovaricin I	[102281-52-7]	*Streptomyces diastochromogenes (variabilicolor)*	$C_{39}H_{45}NO_{10}$	237–238	+351[c]	(**70**)	27
diastovaricin II	[102228-99-9]	*Streptomyces diastochromogenes (variabilicolor)*	$C_{44}H_{52}N_2O_{12}S$	160–164	+281[c]	(**71**)	27
kanglemycin A	[114153-91-2]	*Nocardia mediterranei var. kanglensis 1747-64*	$C_{50}H_{63}NO_{19}$	156[d]	+315.4[c]	(**74**)	28
awamycin	[87913-35-7]	*Streptomyces albolongus C 46466*	$C_{38}H_{49}NO_{12}S$	162–165	+949	(**75**)	29
ansathiazin	[105645-37-2]	*Streptomyces albolongus C-46366*	$C_{37}H_{47}NO_{13}S$	170–175	−32	(**76**)	29
Benzoquinoid							
geldanamycin	[30562-34-6]	*Streptomyces hygroscopicus var.geldanus var. nova (UC-5208)*	$C_{29}H_{40}N_2O_9$	252–255	+55	(**77**)	30
herbimycin A	[70563-58-5]	*Streptomyces hygroscopicus AM-3672*	$C_{30}H_{42}N_2O_9$	230	+137	(**82**)	(31, 32)
herbimycin B	[76207-83-5]	*Streptomyces hygroscopicus AM-3672*	$C_{28}H_{38}N_2O_8$	229[d]	+109	(**83**)	33
herbimycin C	[91700-92-7]	*Streptomyces hygroscopicus AM-3672*	$C_{29}H_{40}N_2O_9$	203[d]	+210	(**84**)	34
macbecin I	[73341-72-7]	*Nocardia sp. C-14919 (N-2001)*	$C_{30}H_{42}N_2O_8$	187–188	+351	(**90**)	(35, 36)
macbecin II	[73341-73-78]	*Nocardia sp. C-14919 (N-2001)*	$C_{30}H_{44}N_2O_8$	148[d]	+62	(**91**)	(35, 36)
mycotrienin I	[82189-03-5]	*Streptomyces rishirensis T-23*	$C_{36}H_{48}N_2O_8$	117	+92[c]	(**92**)	(37, 38)
mycotrienin II	[82189-04-6]	*Streptomyces rishirensis T-23*	$C_{36}H_{50}N_2O_8$	151	+288[c]	(**93**)	(37–39)
mycotrienol I	[81904-15-6]	*Streptomyces rishirensis T-23*	$C_{26}H_{33}NO_6$	94–95	+4.3[c]	(**95**)	40
mycotrienol II	[87906-73-0]	*Streptomyces rishirensis T-23C*	$C_{26}H_{35}NO_6$	130–132	+273[c]	(**96**)	40
20-*O*-methylmycotrienin II	[98873-82-6]	*Streptomyces rishirensis T-23*	$C_{37}H_{52}N_2O_8$	128	+373[c]	(**94**)	41
trienomycin A[h]	[97955-33-4]	*Streptomyces rishirensis T-23 Streptomyces sp. No. 83-16*	$C_{36}H_{50}N_2O_7$	135	+174[c]	(**97**)	(41–43)
trienomycin B	[100662-01-09]	*Streptomyces sp. No. 83-16*	$C_{34}H_{48}N_2O_7$	124–126	+170[c]	(**98**)	44
trienomycin C	[100662-01-9]	*Streptomyces sp. No. 83-16*	$C_{34}H_{48}N_2O_7$	119.5–121.5	+186[c]	(**99**)	44
ansatrienin A	[80111-47-3]	*Streptomyces collinus strain Tü 1982*	$C_{36}H_{48}N_2O_8$			(**100**)	45
ansatrienin A_2	[85819-32-4]	*Streptomyces collinus strain Tü 1982*	$C_{34}H_{46}N_2O_8$	115[d]	+115.7[d]	(**101**)	46
ansatrienin A_3	[85819-31-4]	*Streptomyces collinus strain Tü 1982*	$C_{34}H_{46}N_2O_8$	117[d]	+119.4	(**102**)	46
ansatrienin B	[80111-48-4]	*Streptomyces collinus strain Tü 1982*	$C_{34}H_{46}N_2O_8$			(**103**)	45
maytansine	[35486-53-8]	*Maytenus ovatus Loes. Maytenus serrata (Celastraceae)*	$C_{34}H_{46}ClN_3O_{10}$	171–172	−145	(**104**)	(47, 48)
maytanprine	[38997-09-0]	*Maytenus buchananii (Loes.) R. Wilczek Maytenus serrata (Celastraceae)*	$C_{35}H_{48}ClN^3O_{10}$	169–170	−125	(**106**)	(48, 49)
maytanbutine	[38997-10-3]	*Maytenus buchananii (Loes.) R. Wilczek Maytenus serrata (Celastraceae)*	$C_{36}H_{50}ClN_3O_{10}$	170–171	−122	(**107**)	(48, 49)
maytanvaline	[52978-27-5]	*Maytenus buchananii (Loes.) R. Wilczek*	$C_{37}H_{52}ClN_3O_{10}$	175–176.5	−135	(**105**)	(48, 50)

Table 1. ***Continued***

Ansamacrolide	CAS Registry Number	Producing organism	Molecular formula	MP, °C	$[\alpha]_D$[a]	Structure no.	Reference
maysine	[52978-28-6]	*Maytenus buchananii (Loes.) R. Wilczek*	$C_{28}H_{35}ClN_2O_7$	137–141	−173[f]	(**110**)	(48, 50)
normaysine	[52978-29-7]	*Maytenus buchananii (Loes.) R. Wilczek*	$C_{27}H_{33}ClN_2O_7$	187–188	−217[f]	(**111**)	(48, 50)
maysenine	[52978-30-0]	*Maytenus buchananii (Loes.) R. Wilczek*	$C_{27}H_{33}ClN_2O_6$	184–185	−57[f]	(**112**)	(48, 50)
colubrinol	[50657-35-5]	*Colubrina texensis Gray (Rhamnaceae) Trewia nudiflora L. (Euphorbiaceae)*	$C_{36}H_{50}ClN_2O_{11}$	194–196	−94	(**114**)	(51, 52)
colubrinol acetate	[50499-79-1]	*Colubrina texensis Gray (Rhamnaceae)*	$C_{36}H_{50}ClN_2O_{11}$	179–182	−127	(**115**)	51
maytanacine	[57103-69-2]	*Putterlickia verrucosa Szysyl. (Celastraceae)*	$C_{30}H_{39}ClN_2O_9$	234–237	−119	(**109**)	(48, 53)
maytansinol	[57103-68-1]	*Putterlickia verrucosa Szysyl. (Celastraceae)*	$C_{28}H_{37}ClN_2O_9$	173–174.5	−309	(**113**)	(48, 53)
maytanbutacine	[62414-95-3]	*Maytenus serrata (Celastraceae)*	$C_{34}H_{45}ClN_2O_{11}$	253–255	−90[f]	(**108**)	48
normaytansine	[75983-74-3]	*Maytenus buchananii*	$C_{32}H_{41}ClN_2O_8$	166–167		(**116**)	54
trewiasine	[78987-26-5]	*Trewia nudiflora L (Euphorbiaceae)*	$C_{37}H_{52}ClN_3O_{11}$	182–185	−94	(**117**)	55
dehydrotrewiasine	[78987-27-6]	*Trewia nudiflora L. (Euphorbiaceae)*	$C_{37}H_{50}ClN_3O_{11}$	165–170	−90	(**118**)	55
demethyltrewiasine	[78987-28-7]	*Trewia nudiflora L. (Euphorbiaceae)*	$C_{36}H_{50}ClN_3O_{11}$	129–142	−126	(**119**)	55
trenudine	[82390-94-1]	*Trewia nudiflora L. (Euphorbiaceae)*	$C_{36}H_{48}ClN_3O_{13}$	200–205[d]	−114	(**121**)	(55, 56)
treflorine	[82390-93-0]	*Trewia nudiflora L. (Euphorbiaceae)*	$C_{36}H_{48}ClN_3O_{12}$	205–208[d]	−138	(**120**)	(55, 56)
normaytancyprine	[84123-43-3]	*Putterlickia verucosa Szyszyl. (Celastraceae)*	$C_{37}H_{50}ClN_3O_{10}$	143–145		(**125**)	57
N-methyltrenudone	[82400-19-9]	*Trewia nudiflora L. (Euphorbiaceae)*	$C_{37}H_{48}ClN_3O_{10}$	192–197[d]	−110	(**122**)	56
10-epitrewiasine	[88198-82-7]	*Trewia nudiflora L. (Euphorbiaceae)*	$C_{37}H_{53}ClN_3O_{11}$	159–162	−48	(**123**)	52
nortrewiasine	[88147-94-8]	*Trewia nudiflora L. (Euphorbiaceae)*	$C_{36}H_{50}ClN_3O_{11}$	155–158	−58	(**124**)	52
ansamitocin P-3	[66584-72-3]	*Nocardia sp. C-15003*	$C_{32}H_{43}ClN_2O_9$	190–191	−136	(**127**)	58
ansamitocin P-3′	[66547-09-9]	*Nocardia sp. C-15003*	$C_{32}H_{43}ClN_2O_9$	182–185	−134	(**128**)	58
ansamitocin P-4	[66547-10-2]	*Nocardia sp. C-15003*	$C_{33}H_{45}ClN_2O_9$	177–180	−142	(**129**)	58
ansamitocin PND-0	[77353-66-3]	*Nocardia sp. C-14482 mutant N-1231*	$C_{27}H_{35}ClN_2O_8$	189–191[d]		(**131**)	59
ansamitocin PND-1	[77353-67-4]	*Nocardia sp. C-14482 mutant N-1231*	$C_{29}H_{37}ClN_2O_9$		−55.8[f]	(**132**)	59
ansamitocin PND-2	[77353-68-5]	*Nocardia sp. C-14482 mutant N-1231*	$C_{30}H_{39}ClN_2O_9$		−56.3[f]	(**133**)	59
ansamitocin PND-3	[77353-69-6]	*Nocardia sp. C-14482 mutant N-1231*	$C_{31}H_{41}ClN_2O_9$	226–228[d]	−57.1[f]	(**134**)	59
ansamitocin PND-4	[77353-70-9]	*Nocardia sp. C-14482 mutant N-1231*	$C_{32}H_{43}ClN_2O_9$		−56.6[f]	(**135**)	59
ansamitocin PHM-1	[78619-40-6]	*Nocardia sp. C-14482 mutant N-1231*	$C_{30}H_{39}ClN_2O_{10}$			(**136**)	59
ansamitocin PHM-2	[78619-39-3]	*Nocardia sp. C-14482 mutant N-1231*	$C_{31}H_{41}ClN_2O_{10}$			(**137**)	59
ansamitocin PHM-3	[78619-38-2]	*Nocardia sp. C-14482 mutant N-1231*	$C_{32}H_{43}ClN_2O_{10}$	192–194[d]	−148[f]	(**138**)	59
ansamitocin PHM-4	[78630-36-1]	*Nocardia sp. C-14482 mutant N-1231*	$C_{33}H_{45}ClN_2O_{10}$		−148[f]	(**139**)	59
ansamitocin P-4-βHY	[78619-41-7]	*Nocardia sp. C-14482 mutant N-1231*	$C_{33}H_{45}ClN_2O_{10}$	201–203[d]		(**140**)	59
ansamitocin P-4-γHY	[78709-93-0]	*Nocardia sp. C-14482 mutant N-1231*	$C_{33}H_{45}ClN_2O_{10}$	205–207[d]		(**141**)	59
ansamitocin PND-4-βHY	[78619-43-9]	*Nocardia sp. C-14482 mutant N-1231*	$C_{32}H_{43}ClN_2O_{10}$			(**142**)	59

Table 1. ***Continued***

Ansamacrolide	CAS Registry Number	Producing organism	Molecular formula	MP, °C	$[\alpha]_D$[a]	Structure no.	Reference
ansamitocin deClQ-O	[78630-38-3]	*Nocardia sp. C-14482 mutant N-1231*	$C_{28}H_{38}N_2O_7$			(**145**)	59
ansamitocin QND-O	[78619-44-0]	*Nocardia sp. C-14482 mutant N-1231*	$C_{27}H_{35}ClN_2O_7$			(**144**)	59
ansamitocin deClQND-0	[78630-37-2]	*Nocardia sp. C-14482 mutant N-1231*	$C_{27}H_{36}N_2O_7$			(**143**)	59
ansamitocin PHO-3	[62414-96-4]	*Nocardia sp. C-14482 mutant N-1231*	$C_{32}H_{43}ClN_2O_{10}$	227–229[d]	95.9[f]	(**130**)	59
ansamitocin P-2	[57103-70-5]	*Nordardia sp. C-15003*	$C_{31}H_{41}ClN_2O_9$	188–190[d]	−127	(**126**)	58

[a]Determined in $CHCl_3$ unless otherwise noted.
[b]Originally called streptovaricin F.
[c]Determined in methanol.
[d]Decomposes at this temperature.
[e]Determined in dioxane.
[f]Determined in ethanol.
[g]Same as naphthoquinomycin C.
[h]Same as 23-deoxymycotrienin II.

1.1.1. Chemical Properties and Derivatives

All of the streptovaricins except streptovaricin D (**7**) react with one mole of sodium periodate to yield the corresponding streptovals (4), shown in Table 3. The streptovaricins undergo thermal isomerization to the corresponding atropisostreptovaricins (73). In the natural streptovaricins the ansa-bridge lies above the aromatic nucleus but in the atropisostreptovaricins this bridge lies below the aromatic nucleus. Most spectral properties of the isomers are nearly identical, but the optical rotations, although of approximately equal magnitude, are of opposite sign. If pyridine is used as the solvent, lactonized streptovaricins are obtained similar to streptovaricin F_G (**12**) as well as the atropisostreptovaricins. Treatment of streptovaricin C or D with oxygenated concentrated ammonia–methanol solution yields damavaricin C (**20**) or D (**21**) through loss of the enol acetate and methylenedioxy groups (74) (Table 3). The damavaricins are related to the naturally occurring rifamycin W, and damavaricin D has been isolated from the streptovaricin complex. Besides damavaricins C and D, the basic methanolysis yields the corresponding atropisodamavaricins and lactonized damavaricins. The streptovaricins form acetonides and are hydrogenated to mixtures of di- and tetrahydro derivatives (4). Although few derivatives of the streptovaricins have been prepared, a large number of 19-*O*-substituted damavaricins (75) and lactonized damavaricins (76–78) have been reported. The synthesis of the naphthalene core of streptovaricin D has been accomplished (79) whereas several routes to the ansachain of the streptovaricins have been reported (80–83).

1.1.2. Biological Activity

The streptovaricins are mainly active against gram-positive organisms, and have very good activity against *Mycobacterium tuberculosis*, *M. leprae*, and *Staphylococcus aureus* infections in animals (60, 84). The totally acetylated streptovaricins lose their antibacterial activity. Streptovaricin U has no antibacterial activity. Lactonization greatly reduces any biological activity a streptovaricin possesses. The antibacterial activities of the atropisostreptovaricins are about the same as the natural isomers. Although the damavaricins retain biological activity, they are not as active as the corresponding streptovaricins. However, many of the 19-*O*-substituted damavaricins exhibit greater antibacterial activity than the parent streptovaricins (76). The streptovals are also inactive as antibacterial agents (4).

The streptovaricins inhibit the reverse transcriptase of some RNA oncogenic viruses that may be involved in the process of viral transformation (see Antiviral agents). The atropisostreptovaricins again have similar

Table 2. Biological Activity of the Ansamacrolides

Ansamacrolide	Biological activity
streptovaricins	antibacterial (gram-positive and mycobacteria), antiviral, inhibitors of reverse transcriptase
rifamycins	antibacterial (gram-positive, gram-negative, and mycobacteria), antiviral, inhibitors of reverse transcriptase
tolypomycins	antibacterial (gram-positive)
halomycins	antibacterial (gram-positive)
naphthomycins	antibacterial (gram-positive), vitamin K antagonist
actamycins	inhibitors of fatty acid synthesis
diastovaricins	antileukemic
kanglemycins	antibacterial (gram-positive)
awamycins	antibacterial (gram-positive), antitumor
ansathiazins	antibacterial (gram-positive)
geldanamycins	antiprotozoal, herbicidal, inhibitors of reverse transcriptase
herbimycins	herbicidal, antitumor, antiviral, inhibitors of tyrosine kinase
macbecins	antibacterial (gram-positive), antiprotozoal, antifungal, antitumor
mycotrienins	antifungal
trienomycins	antitumor
ansatrienins	antifungal
maytansinoids	antileukemic, antitumor
ansamitocins	antiprotozoal, antifungal, antitumor

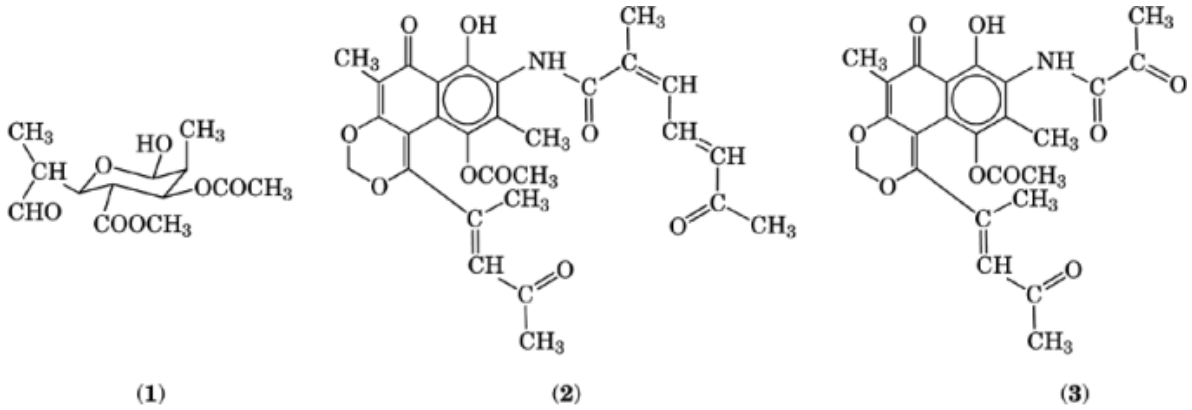


Fig. 1. Products from the chemical degradation of streptovaricins A and C.

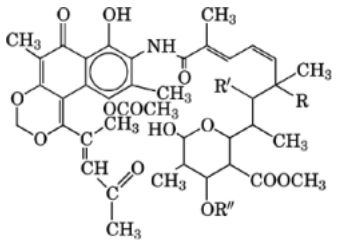
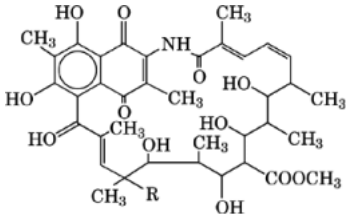
activities to the corresponding natural isomers. The streptovals and streptovarone exhibit greatly improved activity against reverse transcriptase relative to the streptovaricins (85), but their *in vitro* activities were low (86). The damavaricins also inhibit reverse transcriptase (4) as well as tumor cell growth (87).

Clinical studies with streptovaricins have been limited. The most significant toxicity reported in the clinical studies has been gastrointestinal disturbances. However, indications are that the toxicity does not result from the individual streptovaricins but from some impurity in some fermentation lots (85).

1.1.3. Assay Methods

The primary assay for the streptovaricins is the microbiological assay using the agar diffusion method or a turbidimetric procedure (60). The streptovaricins can also be identified by paper (60, 88) or thin-layer chromatography (3).

Table 3. Derivatives of the Streptovaricins

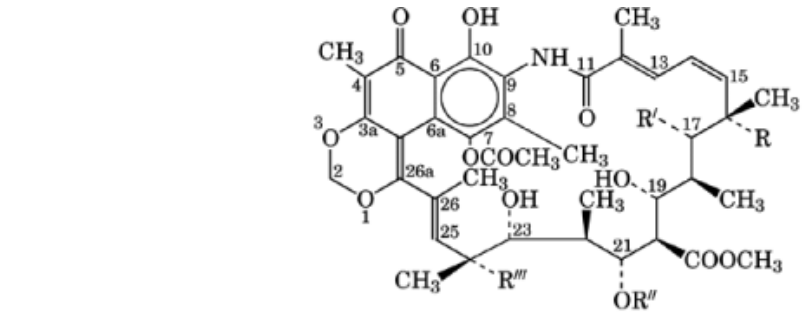
Compound	CAS Registry Number	Molecular formula	Structure number	R	R′	R″
Streptovals						
						
streptoval A	[60760-75-0]	$C_{42}H_{51}NO_{16}$	(**14**)	OH	OH	$COCH_3$
streptoval B	[60735-99-1]	$C_{42}H_{51}NO_{15}$	(**15**)	H	OH	$COCH_3$
streptoval C	[54955-14-5]	$C_{40}H_{49}NO_{14}$	(**16**)	H	OH	H
streptoval E	[60736-00-7]	$C_{40}H_{47}NO_{14}$	(**17**)	H	O	H
streptoval G	[60736-02-9]	$C_{40}H_{49}NO_{15}$	(**18**)	OH	OH	H
streptoval J	[60736-03-0]	$C_{42}H_{51}NO_{15}$	(**19**)	H	$COCH_3$	H
						
Damavaricins						
damavaricin C	[58849-86-8]	$C_{37}H_{47}NO_{13}$	(**20**)	OH		
damavaricin D	[59556-95-5]	$C_{37}H_{47}NO_{12}$	(**21**)	H		

1.2. Rifamycins

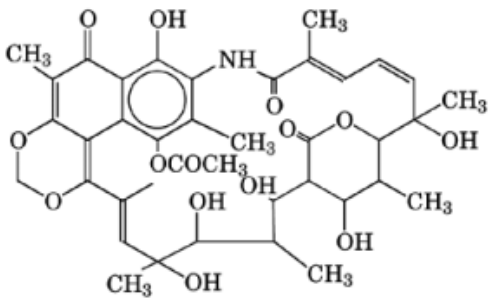
The rifamycins were first isolated from a broth of *Nocardia mediterranei* (the producing organism was originally identified as *Streptomyces mediterranei*). The rifamycins, the structures of which are shown in Figure 3, were originally designated as rifomycins. Only rifamycin B (**22**), which accounts for 10–15% of the crude complex, can be isolated easily as a stable, crystalline compound (6, 89, 90).

Difficulties encountered in the separation and stability of the individual rifamycins led to studies to increase the yield of individual components of the complex. The addition of sodium diethylbarbiturate to the fermentation medium of *N. mediterranei* resulted in the formation of rifamycin B as practically the only substance formed (91, 92).

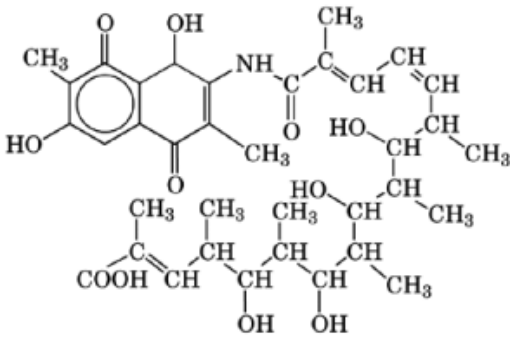
Rifamycin B (**22**) is oxidized by air to the more active rifamycin O (**23**) upon standing in solution. This reaction also occurs when rifamycin B is treated with a variety of oxidizing agents such as hydrogen peroxide. Rifamycin O can be reconverted to rifamycin B by treatment with ascorbic acid. Rifamycin O in turn can be hydrolyzed to the even more active rifamycin S (**24**) by the expulsion of glycolic acid. Rifamycin S can be reduced, using ascorbic acid, to rifamycin SV (**25**) and rifamycin SV can be oxidized to rifamycin S (5, 93, 94).



streptovaricin		R	R′	R″	R‴
A	(**4**)	OH	OH	$COCH_3$	OH
B	(**5**)	H	OH	$COCH_3$	OH
C	(**6**)	H	OH	H	OH
D	(**7**)	H	OH	H	H
E	(**8**)	H	O═	H	OH
G	(**9**)	OH	OH	H	OH
J	(**10**)	H	$OCOCH_3$	H	OH
K	(**11**)	OH	$OCOCH_3$	H	OH



streptovaricin F_G (**12**)



streptovaricin U (**13**)

Fig. 2. Structures of the streptovaricins.

Although rifamycins O and S were originally chemical derivatives of rifamycin B, microorganisms have been found that produce these rifamycins naturally.

Rifamycin G (**26**) is also isolated from the *Nocardia mediterranei* fermentation and appears to be a metabolic product of rifamycin S (17). Rifamycin R (**27**) is produced by a mutant of *N. mediterranei (ATCC 31066)* and appears to be biosynthesized from rifamycin S by the oxidation of the C-2 methyl group (15). Rifamycin L (**28**) is an oxidation product formed by incubating rifamycin S with washed mycelia of *N. mediterranei* (12). Rifamycin Y (**29**) is produced along with rifamycin B when this organism is cultured in the presence of diethylbarbituric acid (11). The amount of rifamycin Y produced was originally high, but through strain improvements, it is now produced in only small amounts (95). Rifamycin W (**30**) is produced by mutant 126 of

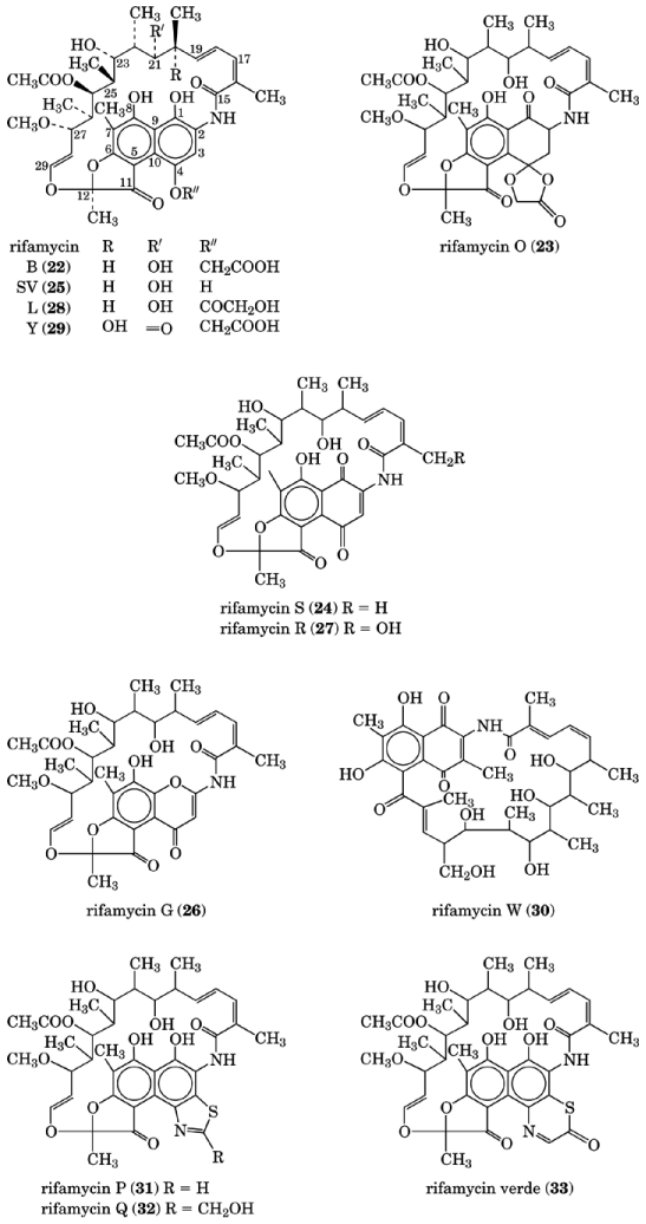


Fig. 3. Structures of the rifamycins.

N. mediterranei (13, 14). The sulfur containing rifamycins P (**31**), Q (**32**), and verde (**33**) are produced by the mutant *Nocardia mediterranei* ATCC 31685 (16).

The structures of the rifamycins were arrived at by chemical degradation studies (1, 4, 96, 97) and confirmed by x-ray crystallography (98–100). The absolute configuration of the ansa-bridge is 6(*S*), 7(*S*), 8(*R*), 9(*R*), 10(*R*), 11(*S*), 12(*R*), and 13(*S*) (101). Studies of ^{13}C nmr (4, 13, 14, 102–104) and ir (104) have been reported and mass spectra of the rifamycins have been obtained (105–107).

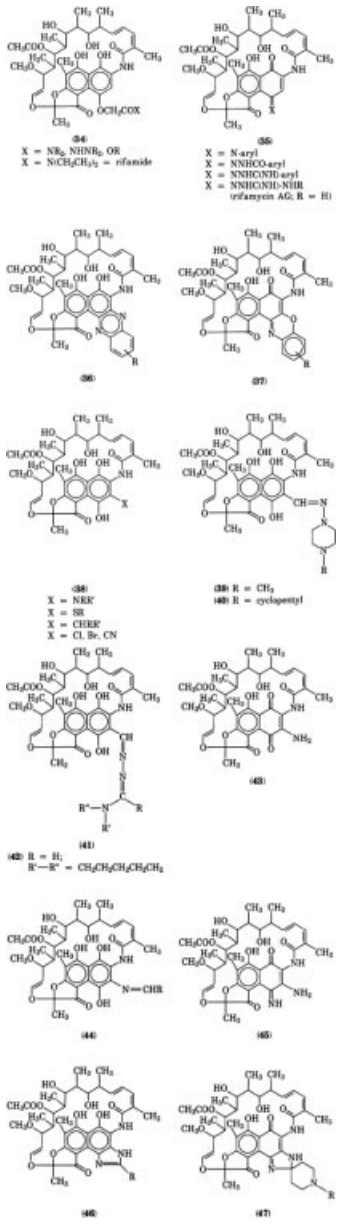


Fig. 4. Structures of rifamycin derivatives

1.2.1. Chemical Properties and Derivatives

There have been thousands of rifamycin derivatives prepared in an attempt to obtain a broader spectrum antibiotic having good oral absorption. Some of these are shown in Figure 4. Rifamycins B, O, and S have served as starting materials for the preparation of numerous classes of derivatives. Several of the semisynthetic derivatives are more active, have a broader spectrum of biological activity, and are therapeutically more effective than the parent antibiotics.

Treatment of rifamycin B (**22**) with amines, hydrazines, and alcohols yields the corresponding amides, hyrazides, and esters (**34**), respectively (4, 6, 108–110). The most active of this class is the *N,N*-diethyl derivative known as rifamide [2750-76-7], $C_{43}H_{58}N_2O_{13}$ (111). Rifamide is active against gram-positive bacteria and has very low toxicity (112–114). Good activity is exhibited against *M. tuberculosis*.

Rifamycin O (**23**) reacts with a variety of aromatic amines, hydrazines, amidrazones, and aminoguanidines to yield quinonimine derivatives (**35**). All of the derivatives show good activity against gram-positive bacteria. The condensation product with aminoguanidine, known as rifamycin AG, is a broad-spectrum antibiotic possessing good activity against gram-positive and gram-negative bacteria and *M. tuberculosis* (6, 109, 115).

Reaction of rifamycin S (**24**) with a variety of *o*-phenylenediamines and *o*-aminophenols produces a series of phenazines (**36**) and phenoxazines (**37**), respectively. Rifazine [10238-70-7] (**37**, R = H), $C_{43}H_{49}N_3O_{11}$, is the simplest of the phenazines (116–119).

Rifamycin S also undergoes conjugate addition reactions to the quinone ring by a variety of nucleophiles including ammonia, primary and secondary amines, mercaptans, carbanions, and enamines giving the C-3 substituted derivatives (**38**) of rifamycin SV (117, 120, 121). Many of the derivatives show excellent antibacterial properties (109, 118, 122, 123). The 3-cyclic amino derivatives of rifamycin SV also inhibit the polymerase of RNA tumor viruses (123, 124).

Treatment of rifamycin S with formaldehyde and secondary amines yields the 3-aminomethyl derivatives (**38**, X = CH_2NR_2) which are not of therapeutic interest (125). However, upon oxidation in acidic medium, the aminomethyl derivatives yield 3-formylrifamycin SV, also known as rifaldehyde [13292-22-3] (**38**, X = CHO), $C_{38}H_{47}NO_{13}$. Treatment of rifaldehyde with amines, hydrazines, hydroxylamines, and hydrazides yields a number of derivatives of the 3-formyl group having excellent biological activity (109, 126–128). The most therapeutically useful derivative is the *N*-amino-*N*′-methylpiperazine hydrazone of rifaldehyde known as rifampin in the United States and rifampicin elsewhere.

Rifampicin [13292-46-1] (**39**), $C_{43}H_{58}N_4O_{12}$, is active against a variety of gram-positive and gram-negative bacteria; however, resistance develops rapidly if it is used alone (129–131). Rifampicin finds its greatest use in the treatment of tuberculosis (130, 132–134). Because resistance develops rapidly, rifampicin is normally given in combination with other antituberculosis drugs, eg, isoniazid [54-85-3], $C_6H_7N_3O$ (130, 132, 135). Rifampicin has been used to treat nontuberculosis infections (136–138), with especially good activity against *Staphylococcus aureus* and *Staphylococcus epidermidis* (139).

Rifampicin has also shown antiviral activity but at levels 500–1000 times greater than required for antibacterial activity (130, 140–142). Rifampicin shows promise in the treatment of leprosy (130, 143). A large number of rifampicinlike derivatives are potent inhibitors of reverse transcriptase (123, 144–148).

Rifapentine (DL473) [61379-65-5] (**40**), $C_{47}H_{64}N_4O_{12}$, a piperazinyl hydrazone of 3-formyl rifamycin SV, is similar to rifampicin. Rifapentine has activity similar to rifampicin, but its half-life is much longer (149, 150).

A number of oxime derivatives of rifaldehyde have been prepared. Many of these derivatives exhibit good activity against rifampicin-resistant organisms (151, 152).

Another class of active derivatives prepared from rifaldehyde, are the 3-aminomethylazinomethyl rifamycins (**41**). This class of compounds is prepared by treating rifaldehyde with hydrazine to yield hydrazones of the 3-aldehyde of rifamycin SV (**38**, X = CH═NNH_2), which is further treated with a suitable chloroformiminium chloride or the dimethyl acetals of tertiary amides to yield (**41**) (155, 154, 155). The piperidine analogue known as FCE 22250 (**42**) was chosen for further studies because of low toxicity coupled with high activity and a long half-life.

Three new classes of rifamycin derivatives were prepared from the common intermediate 3-aminorifamycin S [51756-80-0] (**43**), $C_{37}H_{46}N_2O_{12}$. Reduction of (**43**) in the presence of an aldehyde yields derivatives of the general formula (**44**). Reaction of (**43**) and ammonia in THF solution yields (**45**) [62041-01-4] which in turn can be converted to imidazo-rifamycins (**46**) or to spiro-piperidyl-rifamycins (**47**) by treatment with

aldehydes under reducing conditions or with ketones, respectively. All three classes of derivatives have *in vitro* antibacterial activities comparable to those of rifampicin (156). The spiro-piperidyl-rifamycin rifabutin (LM 427) [72559-06-9] (**47,** R = $CH_2CH(CH_3)CH_3$), $C_{46}H_{62}N_4O_{11}$, showed good *in vitro* and *in vivo* activity against *Mycobacterium tuberculosis* (157) as well as displaying a broad spectrum of biological activity (158). It was also shown to be active against *M. aviumintracellulare* (159), which is frequently encountered in patients having acquired immune deficiency syndrome (AIDS). Rifabutin, used to treat AIDS patients having *Mycobacterium* infections, was shown to inhibit replication of human immunodeficiency virus type 1 (HIV-1) (160).

Modifications to the ansa-bridge of the rifamycins decreases the activity against gram-positive bacteria. Hydrogenation of the ansa-bridge double bonds increases the activity towards gram-negative bacteria as does removal of the C-11 acetate group (109).

Synthesis of the aromatic portion of rifamycin S has been accomplished (161) as has the ansa-bridge portion (162–164). Joining of these fragments resulted in rifamycin S total synthesis (165, 166).

1.2.2. Biological Activity

The rifamycins are biologically active against gram-positive microorganisms and mycobacteria, particularly *M. tuberculosis* (6, 167–170). At higher concentrations, the rifamycins are also active against gram-negative bacteria. The rifamycins show antiviral activity (140, 141) and inhibit reverse transcriptase (171–173).

Rifamycin B is not biologically active but is spontaneously converted in aqueous solution to the active rifamycins O, S, and SV. Rifamycin SV was chosen for further studies because of its good *in vivo* activity, low toxicity, and solubility properties. Rifamycin SV is effective against a variety of infections as well as being active against tuberculosis and leprosy (168). Rifamycin P is the most active of the naturally occurring rifamycins (174).

1.2.3. Manufacture and Processing

Although fermentation procedures have not been reported, assumptions concerning fermentation media and optimal conditions have been made (95, 174). The transformation of the biologically inactive rifamycin B to the biologically active rifamycin S is usually accomplished chemically. Several rifamycin B oxidases have been isolated that can enzymatically transform rifamycin B to rifamycin O, which is hydrolyzed in the fermentation medium to rifamycin S. The enzymes from *Monocillium spp. ATC 20621* and *Humicola spp. ATCC 20620* are intracellular (175, 176) whereas the enzyme from *Curvularia lunata var. aeri* is extracellular (177). The use of a fluidized bed reactor containing immobilized whole cells of *Humicola* for the transformation of rifamycin B to rifamycin S has been described (178). Rifamycin SV producing strains have been isolated, but it is not known if these strains are used commercially.

1.2.4. Assay Methods

A large number of assays exist for the determination of the various rifamycins. Rifamycin SV and rifampicin can be determined by a microbiological assay using *Sarcina lutea ATTC 9341* as the test organism (130, 168), and rifampicin can be determined using *S. aureus* 560 (179). Rifamycins B, S, and SV can be separated by electrophoresis on agar gel and determined microbiologically using *B. subtilis* or *S. lutea* (180). Spectrophotometric assays exist for the rifamycins (130, 168, 181, 182) and for rifampicin (183–185). Rifamycins B, O, S, and SV can be determined via polarography (186) or by amperometric titration (187). Rifamycins B, O, S, and SV can be separated by thin-layer chromatography on silica gel or by paper chromatography (188). Fluorimetric assays exist for rifamycin B (189) and rifampicin (179). High performance liquid chromatographic (hplc) procedures exist for rifamycins B, O, S, and SV (190), for rifampicin in formulations (191, 192), in body fluids (193–197), in mixtures of antibiotics (198, 199), and for rifapentine in plasma (200).

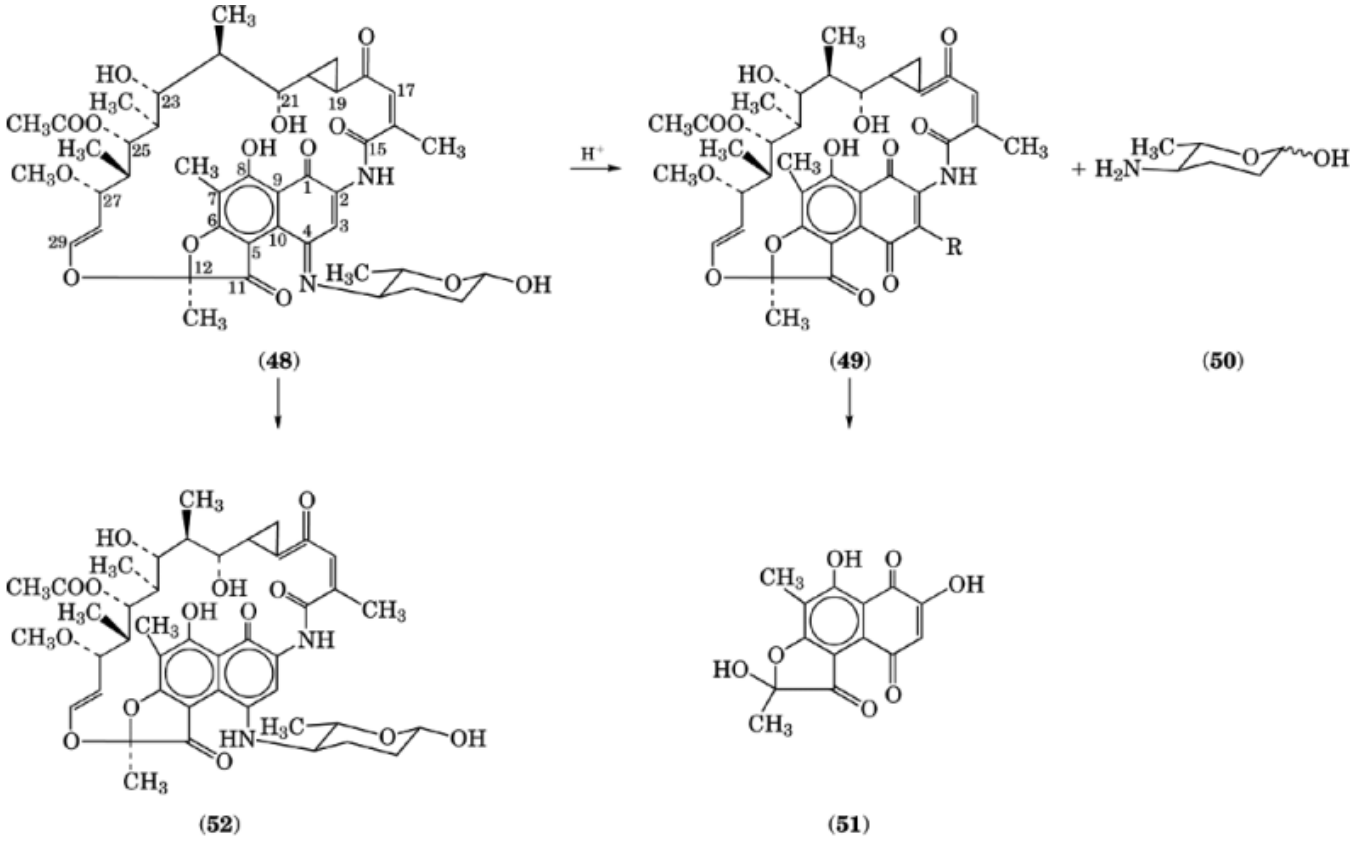


Fig. 5. Structures of the tolypomycins and degradation products.

The *British Pharmacopoeia* specifies a biological assay for the sodium salt of rifamycin SV [14897-39-3]. It also specifies a spectrophotometric assay for rifampicin (201). The *United States Pharmacopeia* requires an hplc assay for rifampin (202).

1.3. Tolypomycins

The addition of small amounts of iron salts to the fermentation medium increases the production of tolypomycin Y (**48**) (7, 203, 204), the structure of which was arrived at by chemical degradation (205, 206) and confirmed by x-ray crystallographic analysis (207) (Fig. 5). Mild acid hydrolysis of tolypomycin Y yields tolypomycinone [22356-23-6] (**49**, R = H), $C_{37}H_{43}NO_{13}$, and tolyposamine [34174-76-0], $C_{16}H_{13}NO_2$, (**50**). Further hydrolysis of tolypomycinone using acid yields tolyponone [24317-12-2] (**51**), $C_{14}H_{10}O_7$, which is also formed upon mild acid hydrolysis of rifamycin S. Reduction of tolypomycin Y produces tolypomycin R [33889-22-4] (**52**), $C_{43}H_{56}N_2O_{14}$ (208).

Tolypomycin Y (**48**) shows strong antibacterial activity against gram-positive bacteria and *Neisseria gonorrheae*. When administered by subcutaneous, intraperitoneal, and intravenous routes, tolypomycin Y is effective in mice infected with *Staphylococcus aureus*, *Streptococcus pyrogenes*, and *Diplococcus pneumoniae.* Cross-resistance is observed with rifampicin but not with other antibiotics. Resistance to tolypomycin Y develops rapidly. The bioactivity of tolypomycin R (**52**) is similar to that of tolypomycin Y (**48**) (208).

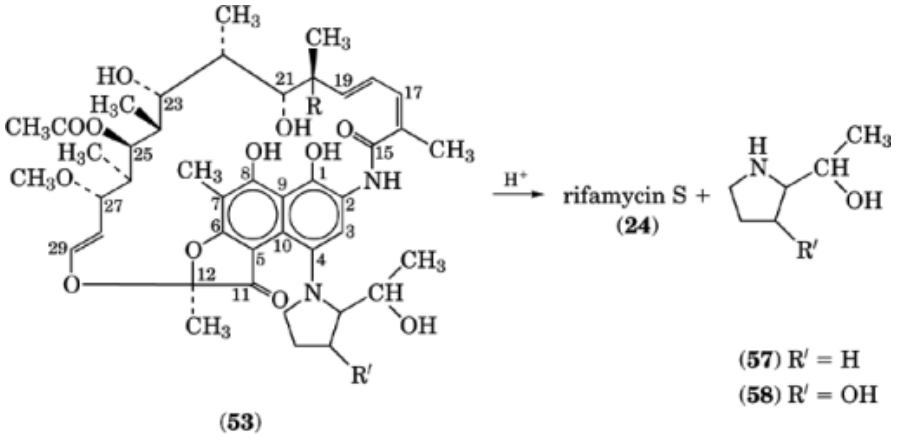


Fig. 6. Structures of the halomycins (**53**) and degradation products where for halomycin A (**54**) $_{R=}$ H, $_{R'=}$ OH; for halomycin B (**55**) $_{R=R'=}$ H; and for halomycin C (**56**) $_{R=}$ OH, $_{R'=}$ H.

Tolypomycinone reacts with primary amines to form 3-*N*-substituted derivatives (209). The most interesting representative of this class of derivatives is 3-[β-(*N*-morpholyl)ethylamino]tolypomycinone (M/045) [63793-73-7] (**49,** R = $NHCH_2CH_2N(CH_2CH_2)_2O$), $C_{43}H_{55}N_3O_{14}$, which has greater activity against gram-positive bacteria than tolypomycin Y, whereas its activity towards gram-negative bacteria is similar to that of rifampicin. Because of greater stability in acidic solution, M/045 has a greater therapeutic effect than tolypomycin Y in mice (210).

A differential bioassay was developed to distinguish tolypomycin Y from rifamycin B (211).

1.4. Halomycins

The halomycins are a group of four antibiotics produced by *Micromonospora halophytica* and separated by partition chromatography on Chromosorb W coated with formamide (19). Further purification was accomplished using preparative tlc (212).

Treatment of halomycin B (**55**) using nitrous acid yields rifamycin S (**24**) and the pyrrolidine (**57**) as shown in Figure 6. The halomycin B structure was confirmed by heating rifamycin O (**23**) and (**57**) in tetrahydrofuran to yield halomycin B (20) which can also be converted to rifamycin S by electrochemical oxidation (213). Upon treatment with nitrous acid, halomycin A (**54**) yields rifamycin S along with the pyrrolidine (**58**). The structure for halomycin C (**56**) was determined to be 20-hydroxy halomycin B based on mass spectral data (212).

The halomycins are active against gram-positive bacteria. The halomycin complex exhibited high activity against bacterial strains resistant to penicillin G. Halomycin C appears to be the most active component of the complex (19). X-ray crystallographic studies indicated that the pyrrolidine ring alters the conformation of the ansa-chain relative to rifamycin SV by changing the spatial arrangements of the C-21 and C-23 hydroxyl groups, which are important for biological activity against DNA-dependent RNA polymerase (214).

1.5. Naphthomycins, Naphthoquinomycins, Actamycin, and Diastovaricins

The naphthomycins, shown in Figure 7, are a group of closely related antibiotics differing in the substituent at C-2 and C-30, and in the geometry about the C-4 and C-6 double bonds. The naphthoquinomycins, diastovaricins, and actamycin are all closely related to the naphthomycins. Naphthomycin A (**59**) is isolated from a fermentation beer of *Streptomyces collinus (Tü 105)* (21). The structure originally proposed, based solely

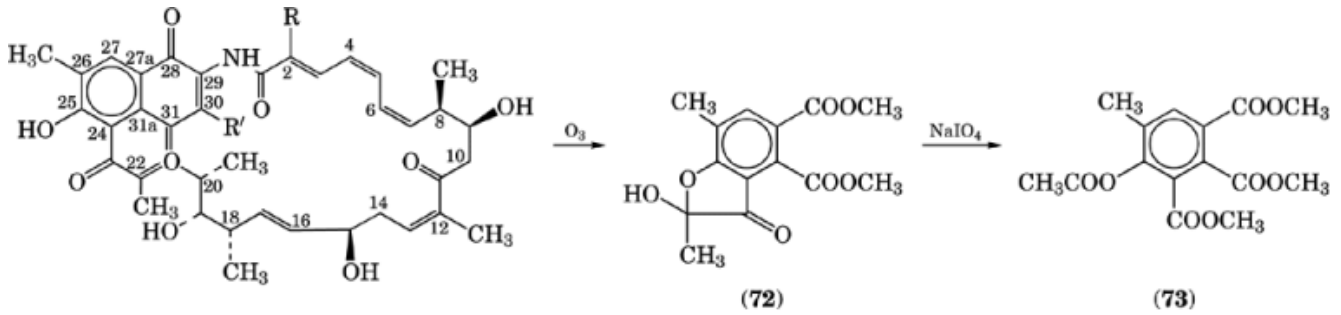


Fig. 7. Structures of the naphthomycins, naphthoquinomycins actamycins, and diastovaricins.

on nmr data, placed the phenolic group at C-27 rather than at C-25 as shown (215). However, spectral data for streptovaricin precursors and the reported value for the chemical shift of the phenolic proton, led to the proposal that the phenolic group was at C-25 (216). This was confirmed by degradation studies (217). Ozonolysis of (**59**) followed by treatment with diazomethane resulted in the isolation of (**72**) [72033-45-5], which, by reaction with sodium periodate, yielded (**73**) [72033-46-6] after treatment with diazomethane. The isolation of (**72**) and (**73**) confirmed the placement of the phenolic group at C-25. X-ray crystallographic studies confirmed the geometries assigned to the double bonds based on nmr studies and established the configuration as 8(*S*), 9(*S*), 15(*S*), 18(*S*), 19(*S*), and 20(*S*) (218). Naphthomycin A is active against gram-positive bacteria, but this activity is reversed by the addition of cysteine. It is also a vitamin K antagonist. Several sulfur-containing derivatives of naphthomycin A have been prepared (219) where the chlorine atom is replaced by an SR group. The biological activity of the C-3 *S*-substituted derivatives is similar to that of naphthomycin A.

Ansamacrolide	Substituent		Double-bond geometry					
	R	R′	C-2	C-4	C-6	C-12	C-16	C-21
naphthomycin A (**59**)	CH_3	Cl	Z	Z	E	E	E	E
naphthomycin B (**60**)	H	Cl	Z	E	Z	E	E	E
naphthomycin C (**61**)	H	H	Z	E	Z	E	E	E
naphthomycin D (**62**)	CH_3	OH	Z	Z	E	E	E	E
naphthomycin E (**63**)	CH_3	H	Z	Z	E	E	E	E
naphthomycin F (**64**)	CH_3	$SCH_2CH(NHCOCH_3)COOCH_3$	Z	Z	E	E	E	E
naphthomycin G (**65**)	CH_3	$SCH_2CH(NHCOCH_3)COOH$	Z	Z	E	E	E	E
naphthomycin H (**66**)	H	Cl	Z	Z	E	E	E	E
naphthoquinomycin A (**67**)	H	OCH_3	Z	Z	E	E	E	E
naphthoquinomycin B (**68**)	H	SCH_3	Z	Z	E	E	E	E
actamycin (**69**)	H	OH	Z	Z	E	E	E	E
diastovaricin I (**70**)	H	OH	Z	E	Z	E	E	E
diastovaricin II (**71**)	H	$SCH_2CH(NHCOCH_3)COOH$	Z	E	Z	E	E	E

Naphthomycin B (**60**) is produced by *Streptomyces galbus (Tü 353)* whereas naphthomycin C (**61**) is produced by *Streptomyces diastatochromogenes (Tü 1892)* (220). The structures for (**60**) and (**61**) were arrived at on the basis of nmr data in comparison with those of (**59**). The antibacterial activity of naphthomycin B is similar to that of naphthomycin A. Naphthomycin C is nearly inactive against bacteria and fungi. Naphthomycins D (**62**), E (**63**), F (**64**), and G (**65**) are isolated from a fermentation beer of *Streptomyces aurantiogriseus (Tü 2357)* (221). Structures were determined by nmr and degradation studies using ozone. Naphthomycin F exhibits some activity against gram-positive bacteria and fungi while naphthomycins D, E, and G are biologically inactive.

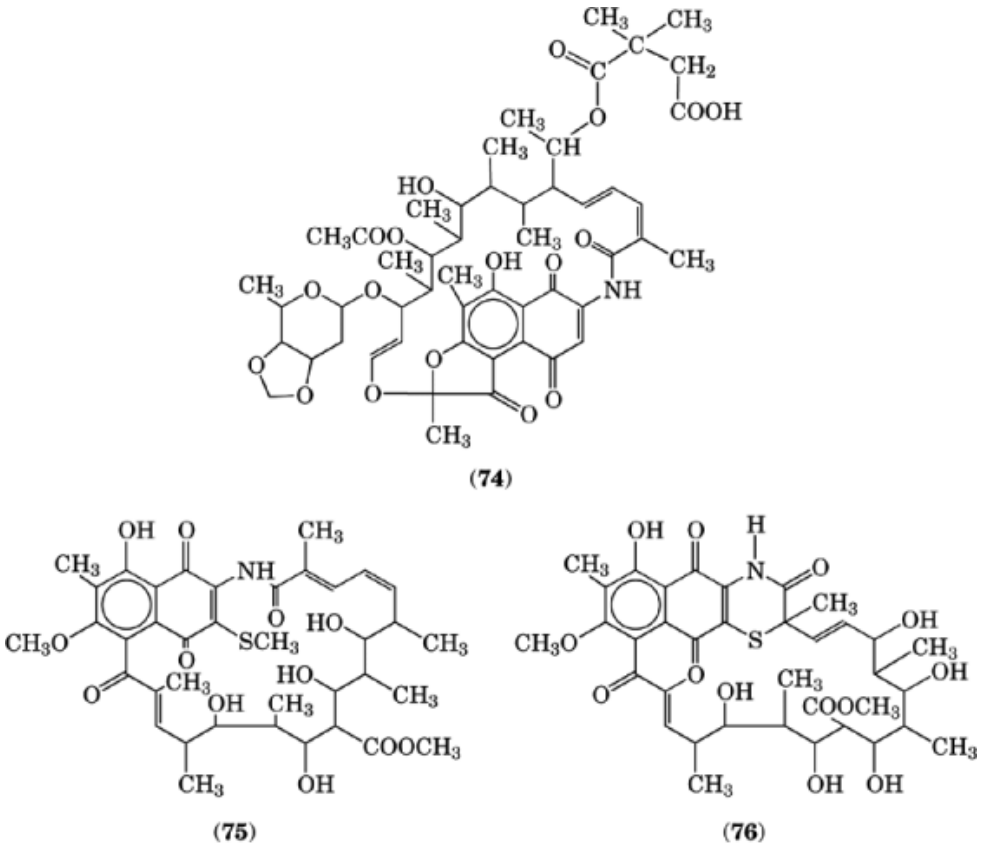


Fig. 8. Structures of kanglemycin (**74**), awamycin (**75**), and ansathiazin (**76**).

Naphthomycin H (**66**) is isolated from *Streptomyces* Y-83,40369 and was shown to be a geometrical isomer of naphthomycin B (222). The biological activity of naphthomycin H is similar to that of naphthomycins A and B.

Naphthoquinomycins A (**67**) and B (**68**) are isolated from *Streptomyces S-1998* (223) and the structures for (**67**) and (**68**) assigned on the basis of spectral data. Naphthoquinomycins A and B inhibit fatty acid synthesis in *E. coli.* Actamycin (**69**) is obtained from *Streptomyces sp. E/784*, and its structure arrived at on the basis of spectral data and degradation studies (224, 225).

Diastovaricins I (**70**) and II (**71**) are produced by *Streptomyces diastochromogenes.* Diastovaricins I and II are active against Friend mouse leukemia cells. Spectral data were used to determine the structures (226).

1.6. Kanglemycin

Kanglemycin (**74**) (Fig. 8) is isolated from the fermentation broth filtrate of *Nocardia mediterranei* var *kanglensis* (1747-64) and its structure determined by x-ray crystallographic studies. The antibiotic is active against gram-positive bacteria (28).

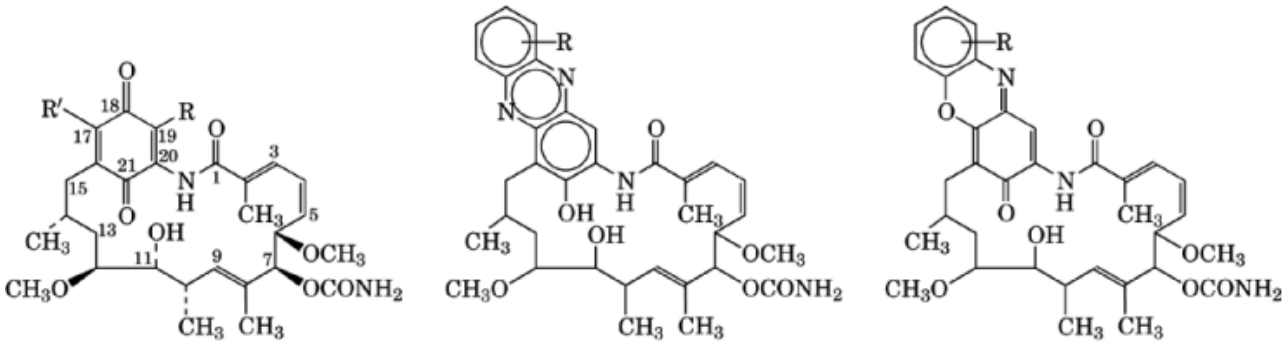


Fig. 9. Structures of geldanamycin (**77**) and derivatives.

1.7. Awamycin and Ansathiazin

Awaymycin (**75**) and ansathiazin (**76**) (Fig. 8) are produced by *Streptomyces albolongus* C-46366 (29); awamycin is also produced by *Streptomyces sp. No. 80-217* (227). A mutant of *S. albolongus* (CM-11) formed by uv-mutagenesis produced 10 times more antibiotic than the parent strain. The structures for awamycin and ansathiazin were assigned on the basis of spectral data. Both antibiotics are active against gram-positive bacteria and awamycin is reported to have antitumor activity.

2. Benzoquinoids

2.1. Geldanamycin

Geldanamycin (**77**) (Fig. 9) is isolated from the filtered beer of *Streptomyces hygroscopicus var. geldanus var. nova* (30). This organism also produces nigericin, nocardamine, and a libanamycinlike activity depending on the composition of the fermentation medium (228). The structure of geldanamycin was assigned in great part on the basis of nmr studies (4, 229). Unlike the naphthoquinoid ansamacrolides, geldanamycin has little antibacterial activity, being primarily active against protozoa and fungi, especially *Tetrahymena pyriformis* and *Crithidia fasciculata* (see Antiparasitic agents) (30). Geldanamycin also has herbicidal activity (see Herbicides) (230, 231).

Geldanamycin undergoes reaction with *o*-phenylenediamines and *o*-aminophenols to give compounds similar to rifazine (**36**, R = H). The corresponding geldanazines (**78**) and geldanoxazines (**79**) are active *in vitro* against reverse transcriptase but have no significant *in vivo* activity (232, 233). Oxime and hydrazone derivatives of geldanaldehyde (**80**) similar to rifampicin (**39**) have been prepared and found to inhibit reverse transcriptase (234). Geldanamycin derivatives in which the 17-methoxy group has been replaced by a 17-alkylamino group (**81**) were found to have antitumor activity (235).

2.2. Herbimycins

Herbimycins A (**82**), B (**83**), and C (**84**), shown in Figure 10 along with some derivatives, are isolated from the fermentation broth of *Streptomyces hygroscopicus AM-3672* (31). The structure of herbimycin A was assigned

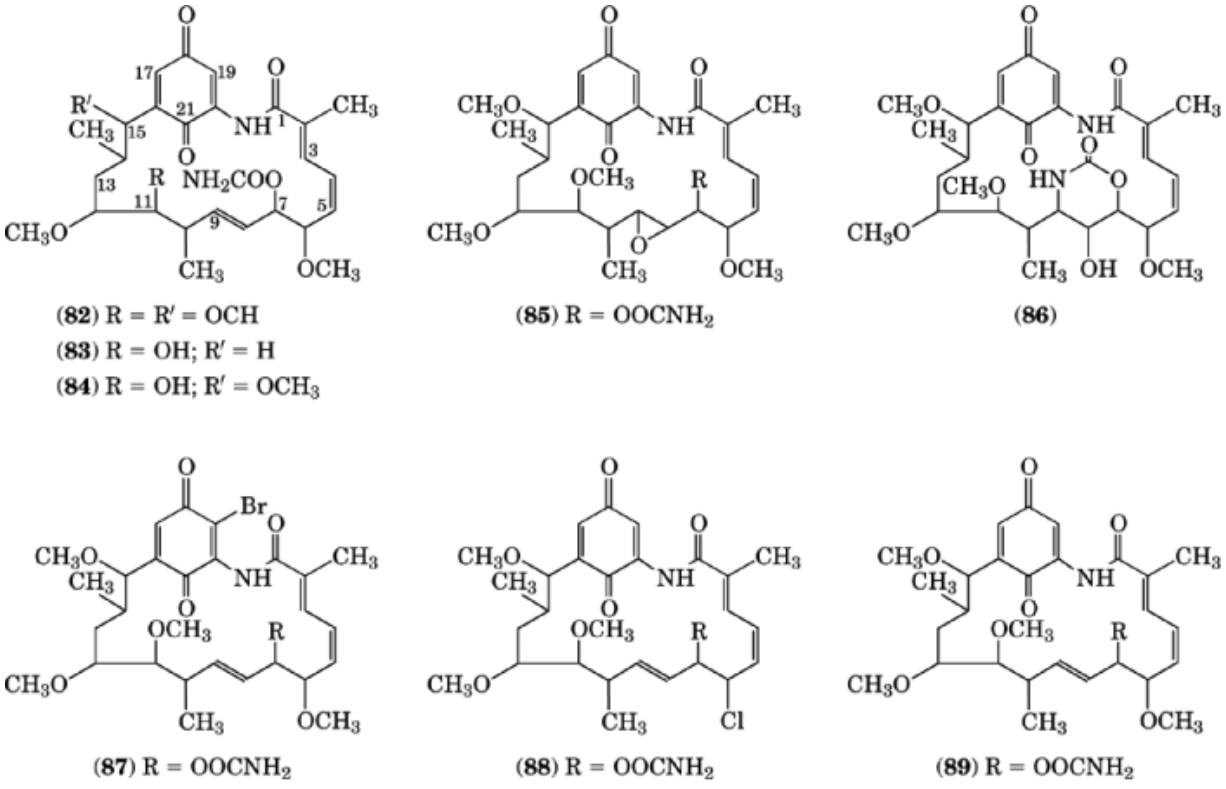


Fig. 10. Structures of the herbimycins and derivatives.

on the basis of spectral data (32) and confirmed by x-ray crystallographic studies (236). The structures for herbimycins B and C were derived by comparing spectral data to those for herbimycin A (34, 35). The herbimycins possess strong herbicidal activity and exhibit some antitumor and antiviral activity.

Several derivatives of herbimycin A have been prepared that possess greater antitumor activity than the parent. Treatment of herbimycin A with *m*-chloroperbenzoic acid yields 8,9-epoxyherbimycin A [94513-90-3] (**85**), $C_{30}H_{42}N_2O_{10}$, which upon treatment with boron trifluoride etherate is converted to herbimycin A-7,9-cyclic carbamate [94513-91-4] $C_3H_{42}N_2O_{10}$ (**86**). Treatment of (**82**), (**85**), or (**86**) with substituted amines yields the corresponding 17- or 19-amino derivatives. Most of the 19-amino derivatives examined, along with (**85**) and (**86**), have increased antitumor activity relative to herbimycin A (237). Other derivatives possessing antitumor activity include: 19-bromoherbimycin A [103224-24-4] (**87**). $C_{30}H_{41}BrN_2O_9$, which is formed by treating herbimycin A with pyridinium hydrobromide perbromide; 6-chloro-6-demethoxyherbimycin A [103224-10-8] (**88**), $C_{29}H_{39}ClN_2O_8$, which is formed by treating herbimycin A with boron trichloride; and, 2,3,4,5-tetrahydroherbimycin A [103224-30-2] (**89**), $C_{30}H_{46}N_2O_9$, formed by catalytic hydrogenation of herbimycin A (238).

2.3. Macbecins

Macbecin I (**90**) and II (**91**) (Fig. 11) are isolated from the fermentation broth of *Nocardia sp. C-14919* (35, 239). The structures were assigned on the basis of ^1H nmr studies on the intact antibiotics as well as on several degradation products. The assigned structures were confirmed by x-ray crystallographic studies (36).

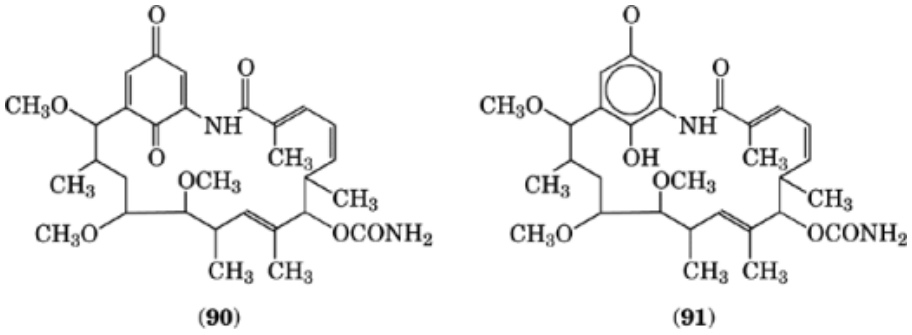


Fig. 11. Structures of macbecin I (**90**) and macbecin II (**91**).

The macbecins are active against gram-positive bacteria, fungi, and protozoa and exhibit *in vitro* antitumor activity against murine leukemia P 388 and melanoma B 16 (35) (see Chemotherapeutics, anticancer).

2.4. Mycotrienins, Mycotrienols, Trienomycins, and Ansatrienins

The mycotrienins are produced by *Streptomyces rishiriensis T-23* (38). The structures for mycotrienins I (**92**) and II (**93**) are shown in Figure 12. They were assigned primarily on the basis of nmr spectral analysis (37, 240). Mycotrienins I and II are interconvertible via a redox reaction and acid hydrolysis of either compound yields D-alanine. Minor amounts of 20-*O*-methylmycotrienin II (**94**) and 23-de-oxymycotrienin II [97955-33-4], $C_{36}H_{50}N_2O_7$, which is identical to trienomycin A (**97**), are also isolated from the *Streptomyces rishiriensis T-23* fermentation broth (41). The structures are also shown in Figure 12.

Streptomyces rishiriensis T-23 also produces mycotrienols I (**95**) and II (**96**), the structures of which were based on spectral analysis. Treatment of mycotrienin II (**93**) with lithium aluminum hydride yields a mixture of mycotrienols I and II (40). The mycotrienols are also interconvertible via a redox reaction. The mycotrienins possess no antibacterial activity but are active against fungi and yeasts (qv), and exhibit weak antitumor activity. The mycotrienols are an order of magnitude less active than the mycotrienins, suggesting that the cyclohexanecarbonylalanine group is important for biological activity.

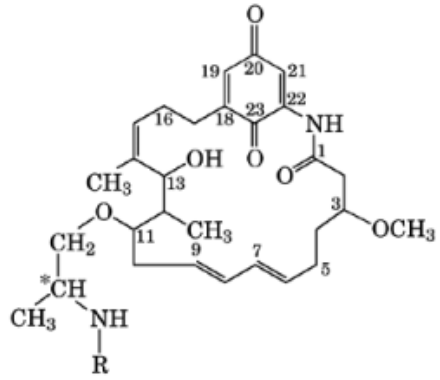
The trienomycins are isolated from *Streptomyces sp. 83-16* (43, 44). The assigned structures (Fig. 12) were based on spectral data. Acid hydrolysis of trienomycin A yielded D-alanine (42, 44). The trienomycins have no antimicrobial activity but have good antitumor activity. Trienomycin A is the most active, exhibiting good *in vivo* antitumor activity against sarcoma 180 and P 388 leukemia in mice (241).

The ansatrienins are produced by *Streptomyces collinus Tü 1982*. The structures (Fig. 12) were assigned on the basis of spectral data of the intact antibiotics as well as several derivatives. Acid hydrolysis of the ansatrienins yields L-alanine. The structures of ansatrienins A and B are the same as those for mycotrienins I and II, respectively, except for the configuration of the alanine moiety. The ansatrienins are active against fungi (45, 46).

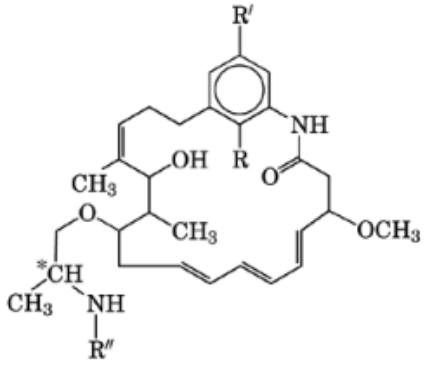
2.5. Maytansinoids and Maytansides (Ansamitocins)

2.5.1. Isolation and Structure Proof

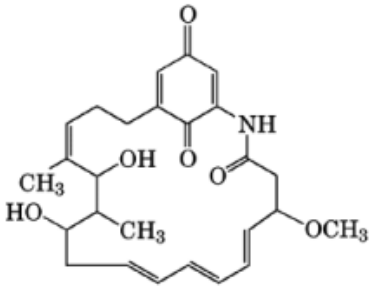
The maytansinoids were the first ansamacrolides to be found in plants. The term "maytansinoids" refers to those ansamacrolides related to maytansine (**104**), shown in Figure 13, whereas the term "maytansides" refers to maytansinoids lacking the ester side chain at C-3 as well as the corresponding elimination products (50). Maytansine (**104**) was first isolated from the alcoholic extract of *Maytenus ovatus Loes*. (47). Several other



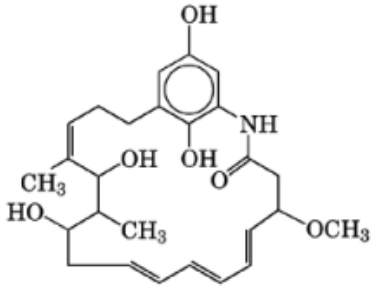
	R	*
mycotrienin I (**92**)	$CO(CH_2)_6$	D
ansatrienin A (**100**)	$CO(CH_2)_6$	L
ansatrienin A_2 (**101**)	$COCH(CH_3)CH_2CH_3$	L
ansatrienin A_3 (**102**)	$COCH_2CH(CH_3)_2$	L



	R	R′	R″	*
mycotrienin II (**93**)	OH	OH	$CO(CH_2)_6$	D
20-*O*-methylmycotrienin II (**94**)	OH	OCH_3	$CO(CH_2)_6$	D
trienomycin A (**97**)	H	OH	$CO(CH_2)_6$	D
trienomycin B (**98**)	H	OH	$COCH_2CH(CH_3)_2$	D
trienomycin C (**99**)	H	OH	$COCH(CH_3)CH_2CH_3$	D
ansatreinin B (**103**)	OH	OH	$CO(CH_2)_6$	L



mycotroenol I (**95**)

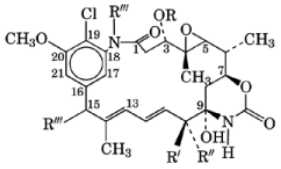


mycotrienol II (**96**)

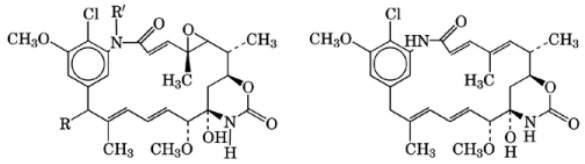
Fig. 12. Structures of the mycotrienins, mycotrienols, trienomycins, and ansatrienins where * represents configuration of the asymmetric center.

maytansinoids and maytansides have been isolated from this species (Table 1). The structure of maytansine was established by x-ray crystallographic analysis (47, 242), and the structures of the other maytansinoids and maytansides were arrived at by comparative nmr studies using maytansine (48–52). The absolute configuration of maytansine is 3(*S*), 4(*S*), 5(*S*), 6(*R*), 7(*S*), 10(*R*), and 2′(*S*). Maytanvaline (**105**) is converted to maysine (**110**) and *N*-isovaleryl-*N*-methyl-L-alanine by basic methanolysis. Basic methanolysis of maytansine (**104**) also yields maysine alone with *N*-acetyl-*N*-methyl-L-alanine. Normaysine (**111**) is converted to maysenine (**112**) by treatment with chromous chloride in acetic acid. Maytanbutine (**107**) and maytanacine (**109**) are converted to maytansinol (**113**) upon reduction with lithium aluminum hydride. Maytansinol can be converted to maytanacine by treatment with acetic anhydride–pyridine.

Colubrinol (**114**) and colubrinol acetate (**115**) are isolated from *Colubrina texensis Gray (Rhamnaceae)* along with maytanbutine (51). Colubrinol is also isolated from *Trewia nudiflora (Euphorbiaceae)* (52). The

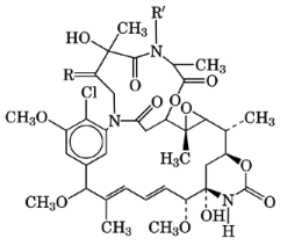


	R	R′	R″	R‴	R″″
maytansine (**104**)	$COCHCH_3NCH_3COCH_3$	H	OCH_3	H	CH_3
maytanvaline (**105**)	$COCHCH_3NCH_3COCH_2CH(CH_3)_2$	H	OCH_3	H	CH_3
maytanprine (**106**)	$COCHCH_3NCH_3COCH_2CH_3$	H	OCH_3	H	CH_3
maytanbutine (**107**)	$COCHCH_3NCH_3COCH(CH_3)_2$	H	OCH_3	H	CH_3
maytanbutacine (**108**)	$COCH(CH_3)_2$	H	OCH_3	$OCOCH_3$	CH_3
maytanacine (**109**)	$COCH_3$	H	OCH_3	H	CH_3
maytansinol (**113**)	H	H	OCH_3	H	CH_3
colubrinol (**114**)	$COCHCH_3NCH_2COCH(CH_3)_2$	H	OCH_3	OH	CH_3
colubrinol acetate (**115**)	$COCHCH_3NCH_3COCH(CH_3)_2$	H	OCH_3	$OCOCH_3$	CH_3
normaytansine (**116**)	$COCHCH_3NCH_3COCH_3$	H	OCH_3	H	H
trewiasine (**117**)	$COCHCH_3NCH_3COCH(CH_3)_2$	H	OCH_3	OCH_3	CH_3
dehydrotrewiasine (**118**)	$COCHCH_3NCH_3COCCH_3{=}CH_2$	H	OCH_3	OCH_3	CH_3
demethyltrewiasine (**119**)	$COCHCH_3NHCOCH(CH_3)_2$	H	OCH_3	OCH_3	CH_3
10-epitrewiasine (**123**)	$COCHCH_3NCH_3COCH(CH_3)_2$	OCH_3	H	OCH_3	CH_3
nortrewiasine (**124**)	$COCHCN_3NCH_3COCH(CH_3)_2$	H	OCH_3	OCH_3	CH_3
normaytancyprine (**125**)	$COCHCH_3NCH_3C$)-dimethyl-cyclopropyl	H	OCH_3	H	H



	R	R′
maysine (**110**)	H	CH_3
normaysine (**111**)	H	H

maysenine (**112**)



	R	R′
treflorine (**120**)	H, H	H
trenudine (**121**)	H, OH	H
N-methyltrenudone (**122**)	O	CH_3

Fig. 13. Structures of the maytansinoids from plant sources.

structures for colubrinol and colubrinol acetate (Fig. 13) were established by high resolution ms and the comparison of their nmr spectra with that of the known maytanbutine.

Normaytansine (**116**) is isolated from *Maytenus buchananii* (54) and the maytansinoids trewiasine (**117**), dehydrotrewiasine (**118**), and demethyltrewiasine (**119**) are isolated from the ethanolic extract of the seed from *Trewia nudiflora L. (Euphorbiaceae)* (55). Also isolated from *Trewia nudiflora* are the maytansinoids treflorine (**120**), trenudine (**121**), and *N*-methyltrenudone (**122**), all of which contain an additional macrocyclic ring

linking C-3 to the aromatic amide nitrogen (56). Several minor constituents were also isolated from the extract of *Trewia nudiflora* and include 10-epitrewiasine (**123**), nortrewiasine (**124**), and colubrinol (52). As with the other maytansinoids, these structures were elucidated by nmr and mass spectral studies. Normaytancyprine (**125**) is isolated along with maytansine from *Putterlickia verrucosa Szyszyl. (Celastracea)* (57).

Another large group of maytansinoids are produced by the microorganism *Nocardia sp. C-25003 (N-1)* and are designated ansamitocins (243). The structures of the ansamitocins, shown in Figure 14, were determined by spectral analysis. By comparison of reported physical data, it was concluded that ansamitocins P-0 (**113**), P-1 (**109**), and P-2 (**126**) were identical to maytansinol, maytanacine, and maytansinol propionate, respectively. Reductive cleavage of each ansamitocin yielded maytansinol. Alkaline hydrolysis of ansamitocins P-3 (**127**), P-3 (**128**), and P-4 (**129**) yielded isobutyric, butyric, and isovaleric acids, respectively.

A mutant of *Nocardia sp. C-14482 (N-1001)* was prepared by treatment with ethidium bromide to produce the strain N-1231 which subsequently produced ansamitocins P-3 and P-4 in high yield. This mutant also produces sixteen minor ansamitocins isolated following the scheme used for the parent strain. The structures of the newer ansamitocins were determined on the basis of spectroscopic evidence and were designated PHO-3 (**130**), PND-0 (**131**), PND-1 (**132**), PND-2 (**133**), PND-3 (**134**), PND-4 (**135**), PHM-1 (**136**), PHM-2 (**137**), PHM-3 (**138**), PHM-4 (**139**), P4-βHY (**140**), P4-γHY (**141**), PND-4βHY (**142**), deClQND-0 (**143**), QND-0 (**144**), and deClQ-0 (**145**) (59, 244) (Fig. 14). There is speculation that microorganisms such as *Nocardia* may be involved in the production of maytansinoids in plants (243). Ansamitocin P-3 has been isolated from two thudiaceous mosses, *Claopodium crispifolium* (Hook.) Ren. and Card. and *Anomodon attenuatus (Hedw.) Hueb.* (245).

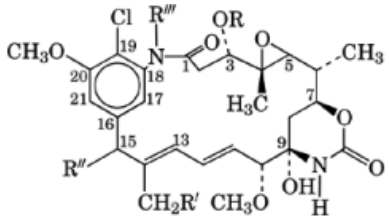
Factors affecting the accumulation of ansamitocins P-2, P-3, and P-4 in *Nocardia sp. C-15003* have been studied (246): the addition of isoleucine, propionate, propionaldehyde, or *n*-propyl alcohol to the fermentation medium resulted in the increased production of P-2; the addition of valine, isobutyrate, isobutyraldehyde, or isobutyl alcohol increased the production of P-3, reaching more than 90% of the total ansamitocins produced; and the addition of leucine, isovalerate, isovaleraldehyde, or isoamyl alcohol increased the production of P-4.

Large-scale isolation of maytansine (**104**), maytanprine (**106**), and maytanbutine (**107**) from the seeds of *Maytenus rothian* (Walp) Lobreau-Callen from India is possible using preparative lc. As much as 75 g of crude extract can be chromatographed to yield maytansinoids in gram quantities. *Maytenus rothian* is the best known source of maytansinoids (247). A preparative separation using hplc has also been developed for the ansamitocins, capable of handling 5 g of material per run. A quantitative hplc assay has also been developed to determine the amount of ansamitocins in the fermentation of beer (248).

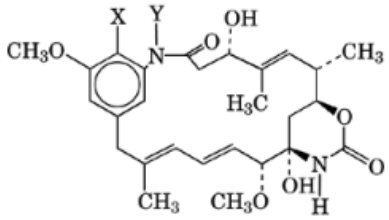
Compilations of the physical properties of the maytansinoids are found in two reviews (249, 250).

2.5.2. Chemical Properties and Derivatives

Procedures for the total synthesis of several of the maytansinoids have been thoroughly reviewed (249, 250). A variety of bacteria, actinomycetes, yeasts, and fungi were screened for their ability to modify the ansamitocins. Four general types of transformations were performed by many of the strains examined, most of which were actinomycetes. *Bacillus megaterium IFO 12108*, *Streptomyces flavotricini IFO 12770*, and *Streptomyces platensis IFO 12901* converted ansamitocins P-4, P-3, P-2, P-1, and P-0 to the corresponding 20-*O*-demethyl derivatives (designated PMD-4, PMD-3, PMD-2, PMD-1, and PMD-0, respectively). PMD-3 was found to have better antitumor activity against P 388 and L 1210 than P-3. Maytansine was also 20-*O*-demethylated by the two *Streptomyces* strains. *Streptomyces coelicolor IFO 3807* and *Streptomyces galbus IFO 13399* deacylated P-4, P-3, P-2, and P-1 to yield maytansinol (P-0). Maytansine was not deacylated by either organism. *Streptomyces castaneus IFO 13670* converts P-4, P-3, P-2, and P-1 to the corresponding 15-hydroxylated derivatives (designated PHO-4, PHO-3, PHO-2, and PHO-1, respectively). Upon further study, it was discovered that ansamitocin P-3 was converted into two 15-hydroxyl derivatives designated PHO-3 and epi-PHO-3. The configuration at C-15 was established as (*R*) for PHO-3 and (*S*) for epi-PHO-3 by x-ray analysis. *Streptomyces minutiscleroticus*



	R	R′	R″	R‴
ansamitocin P-0 (maytansinol) (**113**)	H	H	H	CH_3
ansamitocin P-1 (maytanacine) (**109**)	$COCH_3$	H	H	CH_3
ansamitocin P-2 (**126**)	$COCH_2CH_3$	H	H	CH_3
ansamitocin P-3 (**127**)	$COCH(CH_3)_2$	H	H	CH_3
ansamitocin P-3 (**128**)	$COCH_2CH_2CH_3$	H	H	CH_3
ansamitocin P-4 (**129**)	$COCH_2CH(CH_3)_2$	H	H	CH_3
ansamitocin PHO-3 (**130**)	$COCH(CH_3)_2$	H	OH	CH_3
ansamitocin PND-0 (**131**)	H	H	H	H
ansamitocin PND-1 (**132**)	$COCH_3$	H	H	H
ansamitocin PND-2 (**133**)	$COCH_2CH_3$	H	H	H
ansamitocin PND-3 (**134**)	$COCH(CH_3)_2$	H	H	H
ansamitocin PND-4 (**135**)	$COCH_2CH(CH_3)_2$	H	H	H
ansamitocin PHM-1 (**136**)	$COCH_3$	OH	H	CH_3
ansamitocin PHM-2 (**137**)	$COCH_2CH_3$	OH	H	CH_3
ansamitocin PHM-3 (**138**)	$COCH(CH_3)_2$	OH	H	CH_3
ansamitocin PHM-4 (**139**)	$COCH_2CH(CH_3)_2$	OH	H	CH_3
ansamitocin P4-βHY (**140**)	$COCH_2C(OH)(CH_3)_2$	H	H	CH_3
ansamitocin P4-γHY (**141**)	$COCH_2CH(CH_2OH)CH_3$	H	H	CH_3
ansamitocin PND-4βHY (**142**)	$COCH_2C(OH)(CH_3)_2$	H	H	H



	X	Y
ansamitocin deClQND-0 (**143**)	H	H
ansamitocin QND-0 (**144**)	Cl	H
ansamitocin de ClQ-0 (**145**)	H	CH_3

Fig. 14. Structures of the ansamitocins (maytansinoids from microorganisms).

IFO 13361 converted P-4, P-3, P-2, P-1, and P-0 to the corresponding *N*-demethylated derivatives designated PND-4 (**135**), PND-3 (**134**) PND-2 (**133**), PND-1 (**132**), and PND-0 (**131**), respectively (251–253).

Several semisynthetic maytansinoids have been prepared by acylating the C-3 hydroxyl group of maytansinol. Some of these derivatives have antiprotozoal and antitumor activity similar to maytansine (**104**) and ansamitocin P-3 (**127**) (52, 254). 3-Epimaytansinoids have been synthesized and were not biologically active (255).

2.5.3. Biological Activity

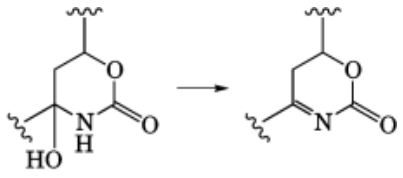
The maytansinoids possess antitumor activity, particularly against P 388 lymphocytic leukemia, B 16 melanocarcinoma, and Lewis lung carcinoma. A number of semisynthetic esters of maytansinol have been prepared and exhibit good antileukemic activity (52, 255). The maytansides lack antitumor activity, indicating that the ester at C-3 is a requirement for activity (50, 52). The carbinolamide also appears to be necessary for antitumor activity. The maytansinoids do not inhibit bacterial RNA polymerase as do the other ansamacrolides. Besides having antitumor activity, the ansamitocins have antiprotozoal and antifungal activity (243). Maytansine has undergone Phase I and II clinical studies and does not appear to be effective (249, 250, 256).

3. Mode of Action and Biosynthesis

The mode of action of the naphthoquinoid ansamacrolides was established through studies using the rifamycins and streptovaricins (84, 141, 257, 258). The ansamacrolides inhibit bacterial growth by inhibiting RNA synthesis. This is accomplished by forming a tight complex with DNA-dependent RNA polymerase. This complex is between the ansamacrolide and the β-unit of RNA polymerase. The formation of the complex inhibits the initation step of RNA synthesis (259, 260). The ansamacrolides form no such complex with mammalian RNA polymerase and thus have low mammalian toxicity.

The antiviral activity of the ansamacrolides does not result from inhibition of RNA polymerase but rather from the inhibition of the assembly of the virus particles (141, 258).

The antitumor activity of geldanamycin and its derivatives appears to result from inhibition of DNA synthesis whereas RNA synthesis is not affected (261). The antitumor activity of the maytansinoids also appears to result from the inhibition of DNA synthesis. The mechanism of action of maytansine (**104**) has been hypothesized to be the acid catalyzed loss of water from the C-9 hydroxyl group of the carbinolamide to form a reactive acyl imine intermediate, which reacts rapidly with nucleophiles on the bases of DNA (262).



carbinolamide acyl imine

The ansa-chain of the ansamycins streptovaricins (4), rifamycins (263), geldanamycin (4), and herbimycin (32) has been shown to be polyketide in origin, being made up of propionate and acetate units with the *O*-methyl groups coming from methionine. The remaining aromatic C_7N portion of the ansamacrolides is derived from 3-amino-5-hydroxybenzoic acid (264–266) which is formed via shikimate precursors. Based on the precursors of the rifamycins and streptovaricins isolated from mutant bacteria strains, a detailed scheme for the biosynthesis of most of the ansamacrolides has been proposed (95, 263).

4. Commercially Available Ansamacrolides

Rifampicin, the only commercially available ansamacrolide, is manufactured by Merrell Dow under the tradename Rifadin, and by CIBA under the trade name Rimactane. Rifampicin is also supplied in combination with isoniazid or pyrazinamide [98-96-4]. The rifampicin–isoniazid combination is known as Rifamate (Merrell

Dow), Rifinah (Merrell Dow), and Rimactazid (CIBA); the rifampicin–pyrazinamide as Rifater (Merrell Dow). Several other rifamycin derivatives including rifabutin and rifapentine are undergoing clinical studies.

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