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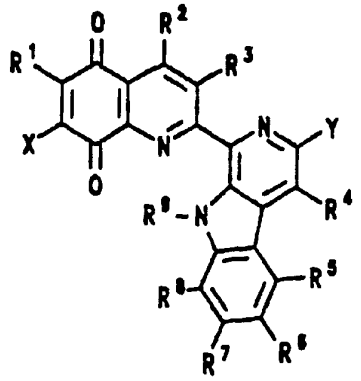
(71)(72) Applicants and Inventors: BEHFOROUZ, Mohammad [IR/US]; 2919 West Beechwood Avenue, Muncie, IN 47304 (US). MERRIMAN, Ronald, L. [US/US]; 5246 Wilton Wood Court, Indianapolis, IN 46254 (US).

(74) Agent: CROOK, Wannell, M.; Willian, Brinks, Hofer, Gilson & Lione, NBC Tower, Suite 3600, 455 North Cityfront Plaza Drive, Chicago, IL 60611-5599 (US).

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(I)

(57) Abstract

The invention provides lavendamycin analogs having formula (I), wherein X, Y and R^1 through R^9 are defined in the specification, and salts of these analogs. The invention also provides a method of making the lavendamycin analogs. The lavendamycin analogs have antitumor and antimicrobial activity.

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LAVENDAMYCIN ANALOGS, THEIR USE AND PREPARATION

This invention was made in part with Government support (NIH grants 1-R15-CA54517 and 1-R15-GM37491). The Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

Lavendamycin **(A)** was isolated from the fermentation broth of *Streptomyces lavendulae* by Doyle and co-workers. See Doyle et al., Tetrahedron Letters, 22, 4595 (1981) and Gould et al., Fortschr. Chem. Org. Naturst., 41, 77 (1982). Lavendamycin has broad spectrum antitumor, antibacterial and antiviral activity. See, e.g., Shibata et al., J. Antibiot., 33, 1231 (1980); Balitz et al., J. Antibiot., 35, 259 (1982); Boger et al., J. Med. Chem., 30, 1918 (1987).

Lavendamycin methyl ester **(B)** is also known. It can be prepared by esterification of lavendamycin. Doyle et al., Tetrahedron Letters, 22, 4595 (1981). The first total synthesis of lavendamycin methyl ester was reported by Kende and Ebetino in 1984. See Kende et al., Tetrahedron Letters, 25, 923 (1984) and Kende et al., Heterocycles, 21, 91 (1984). They accomplished the synthesis of lavendamycin methyl ester through a Bischler-Napieralski condensation of a substituted quinaldic acid with β-methyltryptophan methyl ester followed by cyclization and functionalization of the A ring. Boger and his co-workers have synthesized

lavendamycin methyl ester by a Friedlander condensation of a functionalized aminoaldehyde with a β-carboline followed by other transformations. Boger et al., J. Org. Chem., 50, 5790 (1985). Formal syntheses of lavendamycin methyl ester have been reported in Hibino et al., Heterocycles, 23, 261 (1985) and Rao et al., Tetrahedron, 42, 5065 (1986). For a recent review of lavendamycin syntheses, see Rao, in Recent Progress In Chemical Synthesis Of Antibiotics, 497-531 (Lukacs et al. eds., 1990).

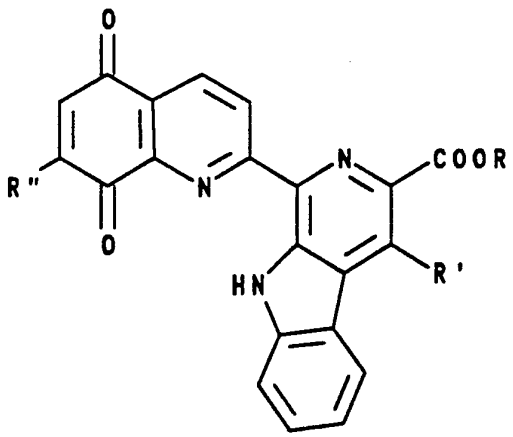
Hibino's group has reported the synthesis of demethyllavendamycin methyl ester **(C)** in Hibino et al., Heterocycles, 20, 1957 (1983). Hibino's group synthesized demethyllavendamycin methyl ester by a Pictet-Spengler type cyclization of 8-benzyloxyquinoline-2-aldehyde with tryptophan methyl ester, followed by aromatization and hydrogenation to give an 8-hydroxyquinoline intermediate. This intermediate was brominated to give the 5,7-dibromo-8-hydroxyquinoline. Oxidation of the 5,7-dibromo-8-hydroxyquinoline yielded the 7-bromoquinolinequinone, and replacement of the bromine with sodium azide, followed by reduction of the azide with sodium hydrosulfite, yielded demethyllavendamycin methyl ester.

This synthetic scheme based on a Pictet-Spengler type cyclization was also used by Hibino's group for the formal synthesis of lavendamycin methyl ester mentioned above. Hibino et al. indicate that lavendamycin ethyl ester can be prepared using this same synthetic scheme. See Hibino et al., Heterocycles, 23, 261 (1985).

The Pictet-Spengler cyclization approach has further been used by Hibino's group to synthesize desaminodesmethyllavendamycin methyl ester **(D)** and

eight other lavendamycin analogs. See Hibino et al., Chem. Pharm. Bull., 34, 1376 (1986). This article reports that the relative mutagenic potency of the lavendamycin analogs was drastically influenced by the nature of the substituent (e.g., methyl and/or bromine) and that lavendamycin analogs having a methyl group at the 3' position were more mutagenic.

The structures of lavendamycin and analogs **B-D** are presented below:



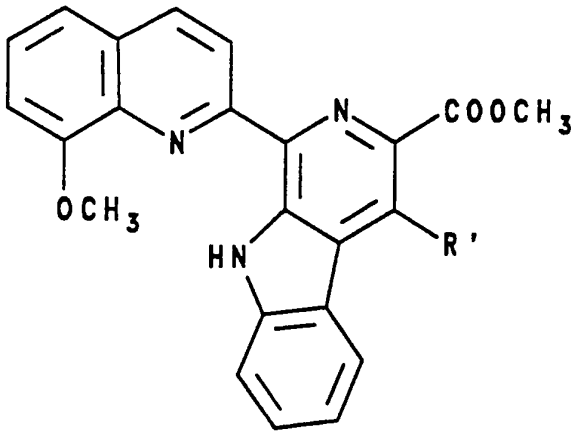
A: R=H, R'=CH_3, R"=NH_2

B: R=CH_3, R'=CH_3, R"=NH_2

C: R=CH_3, R'=H, R"=NH_2

D: R=CH_3, R'=H, R"=H

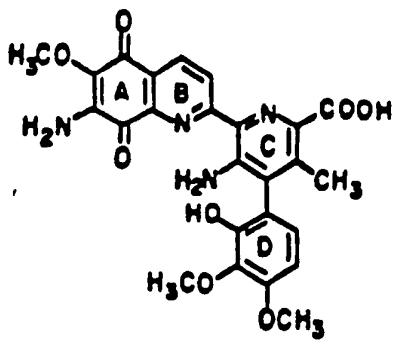
During preliminary work aimed at the total synthesis of lavendamycin, Rao et al. synthesized two additional analogs **(E)** and **(F)** of lavendamycin. See Rao et al., Indian J. Chem., 23B, 496 (1984). The structures of lavendamycin analogs **E-F** are presented below:



E: R′= CH_3

F: R′= H

Lavendamycin is similar structurally to streptonigrin **(G)**. Streptonigrin also has a broad spectrum of antitumor, antibacterial and antiviral activity. Balitz et al., J. Antibiot., 35, 259 (1982); Rao et al., J. Am. Chem. Soc., 85, 2532 (1986); Boger et al., J. Med. Chem., 30, 1918 (1987). With notable exceptions, lavendamycin has been found to be comparable to, although less potent than, streptonigrin in its observed spectrum of activity. Id.; Balitz et al., J. Antibiot., 35, 259 (1982). The structure of streptonigrin is presented below:



(G)

Streptonigrin and several streptonigrin derivatives have been synthesized. See Driscoll et al., Cancer Chemother. Rep. (Part 2), 4, 1 (1974) (four streptonigrin derivatives and 1500 quinones including several quinolinequinone analogs of streptonigrin having various substituents at positions 2, 6 and 7); Rao, Cancer Chemother. Rep. (Part 2), 4, 11 (1974) (streptonigrin derivatives and AB and ABC ring analogs thereof); Kende et al., Tetrahedron Lett., 4775 (1978) (tetracyclic aminoquinone possessing full streptonigrin carbon skeleton but with different substituents on the C and D rings); Basha et al., J. Am. Chem. Soc., 102, 3962 (1980) (streptonigrin); Kende et al., J. Am. Chem. Soc., 103, 1271 (1981) (streptonigrin); Weinreb et al., J. Am. Chem. Soc., 104, 536-44 (1982) (streptonigrin); Panek et al., Diss. Abs. Int'l, 46, 1176B (1985) (streptonigrin); Miyasaka et al., J. Chem. Soc. Perkin Trans., 1, 479 (1986) (streptonigrin 2'-amide derivatives; also mentions a 7-position amide obtained by high-yield microbial synthesis of *Streptomyces griseus*); Tolstikov et al., J. Antibiot., 45, 1020 (1992) (2'-amide, amino-dicarboxylic acid and amino sugar derivatives of streptonigrin); Tolstikov et al., J. Antibiot., 45, 1002 (1992) (2'-decarboxy-2'-amino streptonigrin); Preobrazhenskaya et al., J. Antibiot., 45, 227 (1992) (streptonigrone from streptonigrin, streptonigrin and streptonigrone 8'-alkyl ethers, and other streptonigrin and streptonigrone derivatives); U.S. Patent No. 3,372,090 (ester, 2'-amide, 2'-hydrazide, ether, dihydro, desamino and acetyl (O-acetyl, N-acetyl, tetraacetyl) derivatives of streptonigrin); U.S. Patent No. 3,804,947 (isopropylidene azastreptonigrin, streptonigrin monoxime and esters and other derivatives thereof); and JP 61-280490 (streptonigrin 2'-amides).

The biological activities of several 2'-position streptonigrin derivatives have been studied. The derivatives include 2'-esters, 2'-amides, 2'-hydrazides, and 2-'amino acid derivatives. The effects of the substituents on the biological activity of streptonigrin varied depending on the substituent and the type of activity being studied. See Rivers et al., Cancer Chemotherapy Rep., 46, 17 (1965); Harris et al., Cancer, 18, 49 (1965); Kremer et al., Biochem. Pharmacol., 15, 1111 (1966); Kaung et al., Cancer, 23, 1280 (1969); Inouye et al., J. Antibiot., 38, 1429 (1985); Okada et al., J. Antibiot., 39, 306 (1986); Inouye et al., J. Antibiot., 39, 550 (1986); Okada et al., J. Antibiot., 40, 230 (1987); Take et al., J. Antibiot., 42, 968 (1989); Tolstikov et al., J. Antibiot., 45, 1020 (1992).

The biological properties of streptonigrin, streptonigrin methyl ester and isopropylidene azastreptonigrin have been compared. See Kremer et al., Cancer Chemother. Rep., 51, 19 (1967); Mizuno, Biochem. Pharmacol., 16, 933 (1967); Chaube et al., Cancer Chemother. Rep. (Part 1), 53, 23 (1969) and Chirigos et al., Cancer Chemother. Rep. (Part 1), 57, 305 (1973). Again, the effects of the substituents varied depending on the activity being investigated.

The antibacterial activity of streptonigrin, streptonigrin methyl ester and streptonigrin 8'-alkyl ethers has been studied. See Preobrazhenskaya et al., J. Antibiot., 45, 227 (1992). The 8'-alkyl ethers exhibited slightly greater antibacterial activity than streptonigrin methyl ester, but less than streptonigrin.

A naturally-occurring analog of streptonigrin, 10'-desmethoxystreptonigrin, has been discovered. U.S. Patent No. 5,158,960; Liu et al., J.

Antibiot., 45, 454-57 (1992). In addition to 10'-desmethoxystreptonigrin, U.S. Patent No. 5,158,960 discloses salts, esters and amides of 10'-desmethoxystreptonigrin. Exemplary esters and amides are those prepared by esterifying the 2'-carboxyl or by forming an amide group at the 2'-position. 10'-Desmethoxystreptonigrin was found to have anticancer and antimicrobial, particularly broad spectrum antibacterial, activity. U.S. Patent No. 5,158,960; Liu et al., J. Antibiot., 45, 454-57 (1992). It was also found to be three times more active than streptonigrin in an assay for the inhibition of the farnesylation of *ras* oncogene p21 protein. Id. U.S. Patent No. 5,158,960 teaches that, since 10'-desmethoxystreptonigrin inhibits the farnesylation of *ras* oncogene p21 protein, it may be expected to block the neoplastic effect of *ras* oncogenes in tumor cells.

EP application 185,979 discloses another naturally-occurring streptonigrin analog which has a hydroxyl group in place of the methoxy group at the 6-position of streptonigrin. This compound is reported to exhibit only slightly less antitumor activity than streptonigrin, but to exhibit much lower cytotoxicity. This EP application also discloses derivatives synthesized by making use of the 6-position hydroxyl.

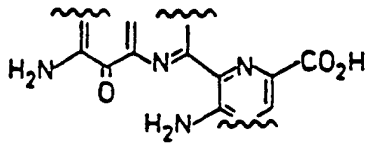
A third naturally-occurring analog of streptonigrin is streptonigrone. Herlt et al., J. Antibiot., 38, 516 (1985). Streptonigrone has also been synthesized from streptonigrin, and streptonigrone 8'-alkyl ethers and other streptonigrone derivatives have been prepared. Preobrazhenskaya et al., J. Antibiot., 45, 227 (1992). Also, 2'-decarboxy-2'-aminostreptonigrin, considered to be an analog of streptonigrone, has been synthesized. Tolstikov

et al., J. Antibiot., 45, 1002 (1992). Streptonigrone and its derivatives have generally been found to be inactive or much less active than streptonigrin. See Herlt et al., J. Antibiot., 38, 516 (1985); Preobrazhenskaya et al., J. Antibiot., 45, 227 (1992); Tolstikov et al., J. Antibiot., 45, 1002 (1992).

Finally, a number of streptonigrin and lavendamycin partial structures have been synthesized and their biological activities studied in an attempt to determine the minimum potent pharmacophore of streptonigrin and lavendamycin. See Driscoll et al., Cancer Chemother. Rep. (Part 2), 4, 1 (1974) (1500 quinones including several quinolinequinone analogs of streptonigrin having various substituents at positions 2, 6 and 7; also four streptonigrin derivatives); Rao, Cancer Chemother. Rep. (Part 2), 4, 11 (1974) (streptonigrin derivatives and AB and ABC ring analogs thereof); Rao, J. Heterocyclic Chem., 12, 725 (1975) (2-phenyl- and 2,2-pyridyl-quinoline-5,8-diones); Rao, J. Heterocyclic Chem., 14, 653 (1977) (ABC ring portion of streptonigrin and derivatives thereof); Lown et al., Can. J. Chem., 54, 2563 (1976) (2-(*o*-nitrophenyl)- and 2-(*o*-aminophenyl)-5,8-quinolinediones); Lown et al., Can. J. Biochem., 54, 446 (1976) (substituted 5,8-quinolinequinones related to streptonigrin); Liao et al., J. Heterocyclic Chem., 13, 1283 (1976) (CD ring portion of streptonigrin); Rao et al., J. Heterocyclic Chem., 16, 1241 (1979) (ABC ring portion of streptonigrin and analogs); Shaikh et al., Diss. Abs. Inter., 44, 1464B (1983) (2,3-disubstituted-1,4-naphthalenediones, 6,7-disubstituted 5,8-quinoline, isoquinoline, quinoxoline, quinazoline, phthalazinediones, and 2-(*o*-nitrophenyl)-6,7-disubstituted-5,8-quinolinediones related to streptonigrin); Boger et al., J. Org. Chem., 50, 5782

(1985) (AB and CDE ring portions of lavendamycin); Panek et al., Diss. Abs. Inter., 46, 1176B (1985) (streptonigrin and lavendamycin carbon framework); Renault et al., J. Am. Chem. Soc., 104, 1715 (1985) (5,8-quinazolinediones); Shaikh et al., J. Med. Chem., 29, 1329 (1986) (a series of aza and diaza bicyclic quinones related to the AB ring system of streptonigrin); Boger et al., Heterocycles, 24, 1067 (1986) (streptonigrin and lavendamycin AB ring systems); Inouye et al., J. Antibiot., 40, 105 (1987) (6-methoxy-5,8-dihydroquinoline-5,8-dione and 6-methoxy-7-methyl-5,8-dihydroquinoline-5,8-dione); Boger et al., J. Med. Chem., 30, 1918 (1987) (various streptonigrin and lavendamycin partial structures are discussed, including the AB, ABC, CD and CDE rings and derivatives thereof); Take et al., J. Antibiot., 40, 679 (1987) (quinoline quinones, 7-isoquinoline quinones, indole quinone); Yasuda et al., J. Antibiot., 24, 1253 (1987) (7-amino-2-(2'-pyridyl) quinoline-5,8-quinone-6'-carboxylic acid); Beach, Diss. Abs. Inter., 49, 3204-B (streptonigrin isoquinoline analogs); Kitahara et al., Chem. Pharm. Bull., 38, 2841 (1990) (8-amino-5,6-quinolinediones); Rao et al., J. Med. Chem., 34, 1871 (1991) (streptonigrin isoquinoline analogs).

Of particular note is Rao, Cancer Chemother. Rep. (Part 2), 4, 11 (1974). This article reports the results of a study of the activity of several streptonigrin derivatives and AB ring analogs which led the author to propose a structure **(H)** for the minimum potent pharmacophore of streptonigrin.



(H)

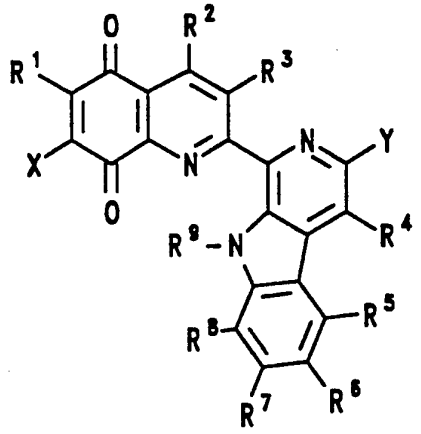
A tricyclic analog of H (corresponding to the ABC rings of streptonigrin) was synthesized and found to be active. Results of interest reported in this article are that replacement of the amine function at position 7 of streptonigrin by OH or OCH_3 led to loss of activity, and streptonigrin derivatives produced by reductive acetylation or methylation of the amine group at position 7 were inactive. Esterification of the carboxyl of streptonigrin with a series of alcohols gave esters which reportedly showed significant activity.

The fully elaborated streptonigrin CD and lavendamycin CDE ring systems, as well as a number of related synthetic structures, have reportedly proved inactive in antimicrobial and cytotoxic assays. Boger et al., J. Med. Chem., 30, 1918 (1987). However, none of the AB and ABC ring analogs of streptonigrin and lavendamycin have been reported to possess cytotoxic, antimicrobial or antitumor activity comparable to streptonigrin. See id.; Driscoll et al., Cancer Chemother. Rep. Part 2, 4, 1 (1974). This suggests a role for the CD rings in the activity of streptonigrin. See Kende et al., Tetrahedron Lett., 48, 4775 (1978).

The following references also describe the synthesis of streptonigrin and lavendamycin partial structures, but do not discuss the activity of the resulting compounds. Liao et al., Angew. Chem. Intern. Edit., 6, 82 (1967) (AB ring portion of streptonigrin); Rao et al., J. Heterocyclic Chem., 12, 731 (1975) (streptonigrin C ring precursors); Liao et al., J. Heterocyclic Chem., 13, 1063 (1976) (the AB ring portion of streptonigrin and the 2-methyl homolog); Hibino et al., J. Org. Chem., 42, 232 (1977) (the AB ring portion of streptonigrin); Wittek et al., J. Org. Chem., 44, 870 (1979) (CD ring portion of streptonigrin); Boger et al., Tetrahedron Lett., 25, 3175 (1984) (the CDE ring portion of lavendamycin); Erickson, Diss. Abs. Inter., 49, 747-B (1988) (4-aminoanthranilic acid, 7-aminoquinaldinic acid, 7-amino-5-hydroxyquinaldinic acid); Molina et al., Tetrahedron Lett., 33, 2891 (1992) (1-substituted-β-carbolines).

SUMMARY OF THE INVENTION

The invention provides a lavendamycin analog having the following formula (I):



I

wherein,

X is R^{10}-C(=O)-NH- or

R^{10}-C(=S)-NH-,

Y is H, OR^{11}, SR^{11}, $N(R^{11})_2$, $NR^{11}N(R^{11})_2$, a halogen atom, NO_2, CN,

R^{11}-C(=NR^{11})-,

R^{12}-C(=O)-,

R^{12}-C(=S)-, or

an alkyl, aryl, cycloalkyl, alkynyl, alkenyl or heterocyclic residue, each of which may be substituted or unsubstituted,

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8, which may be the same or different, each is independently H, a halogen atom, NO_2, CN, OR^{13}, SR^{13}, $N(R^{13})_2$,

-C(=O)$N(R^{13})_2$,

-C(=S)$N(R^{13})_2$,

-C(=O)R^{13},

-C(=S)R^{13},

$-CR^{13}(=NR^{13})$, or

an alkyl, aryl, cycloalkyl, alkenyl, alkynyl, heteroalkyl, heterocyclic, heteroalkenyl or heteroalkynyl residue, each of which may be substituted or unsubstituted,

R^9 is H,

$R^{12}-C(=O)-$,

$R^{12}-C(=S)-$, or

an alkyl, cycloalkyl, aryl, alkenyl, alkynyl or heterocyclic residue, each of which may be substituted or unsubstituted,

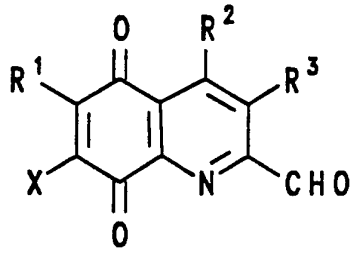
R^{10}, R^{11} and R^{13}, which may be the same or different, each is independently H or an alkyl, cycloalkyl, alkenyl, alkynyl, aryl or heterocyclic residue, each of which may be substituted or unsubstituted,

R^{12} is H, $N(R^{11})_2$, OR^{11}, SR^{11}, $NR^{11}N(R^{11})_2$, $OR^{14}N(R^{11})_2$, or an alkyl, cycloalkyl, aryl, alkenyl, alkynyl or heterocyclic residue, each of which may be substituted or unsubstituted, and

R^{14} is an alkylene residue, and

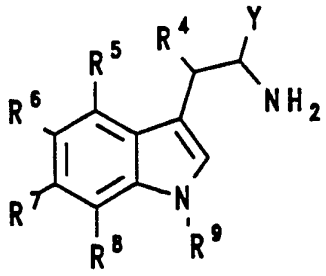
salts of these lavendamycin analogs.

The invention also provides a method of preparing these lavendamycin analogs which comprises reacting an aldehyde having the following formula (K):



K

with a tryptophan analog of the formula (L):



L

wherein X, Y and R^1 through R^9 are as defined above.

The compounds of the invention have antitumor and antimicrobial (antibacterial, antiviral and antiparasitic) activity. In particular, certain of the compounds of the invention have unexpected selective activity against *ras*^{K} tumor cells.

The invention, therefore, provides methods of treating animals having a tumor or suffering from a microbial infection which comprises administering to the animals an effective amount of a lavendamycin analog of the invention or a pharmaceutically-acceptable salt thereof. The invention also provides pharmaceutical compositions comprising a lavendamycin

analog, or a pharmaceutically-acceptable salt thereof, in combination with a pharmaceutically-acceptable carrier.

Finally, the invention provides a method of inhibiting the growth of microbes comprising contacting the microbe with a lavendamycin analog of the invention, or a salt thereof. For instance, the compounds of the invention may be added to liquids to inhibit microbial growth in them. The compounds may also be formulated into disinfectant preparations useful for inhibiting microbial growth on surfaces.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

The lavendamycin analogs of the invention have general formula **I** given above. In the definition of substituents X, Y and R^1 through R^9 of formula **I**, the following terms have the following meanings.

"Alkyl" refers to straight or branched chain alkyl residue containing from 1 to 20 carbon atoms. Alkyl residues include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, isoamyl, *n*-hexyl, 2-methylpentyl, 2,2-dimethylbutyl, *n*-heptyl, 2-methylhexyl, *n*-octyl, etc.

"Aryl" refers to a residue comprising at least one aromatic ring of 5 or 6 carbon atoms. Aryl residues include phenyl, tolyl, biphenyl, naphthyl, etc.

"Cycloalkyl" refers to an aliphatic ring having from 3 to 8 carbon atoms. Cycloalkyl residues include cyclopropyl, cyclopentyl, cyclohexyl, etc.

"Alkenyl" refers to a straight or branched chain alkyl residue which contains from 1 to 20 carbon atoms and at least one carbon-carbon double bond.

Alkenyl residues include vinyl, allyl, 1,1-dimethyl allyl, etc.

"Alkynyl" refers to a straight or branched chain alkyl residue which contains from 1 to 20 carbon atoms and at least one carbon-carbon triple bond. Alkynyl residues include ethynyl, propenyl, etc.

"Alkylene" refers to a straight or branched chain alkylene residue containing from 1 to 20 carbon atoms. Alkylene radicals include methylene, ethylene, propylene, etc.

"Heteroalkyl" refers to an alkyl containing one or more heteroatoms selected from oxygen, sulfur and nitrogen.

"Heterocyclic" refers to a cycloalkyl or aryl containing one or more heteroatoms selected from oxygen, sulfur and nitrogen. Heterocyclic residues include thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isothiazolyl, isoxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, etc.

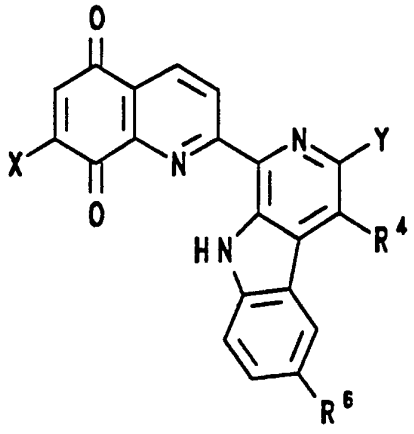
"Heteroalkenyl" refers to an alkenyl containing one or more heteroatoms selected from oxygen, sulfur and nitrogen.

"Heteroalkynyl" refers to an alkynyl containing one or more heteroatoms selected from oxygen, sulfur and nitrogen.

The alkyl, aryl, cycloalkyl, alkenyl, alkynyl, heteroalkyl, heterocyclic, heteroalkenyl and heteroalkynyl residues may be unsubstituted or substituted with one or more substituents. Suitable substituents include R^x, NH_2, R^xNH, $(R^x)_2N$, CN, N_3, NO_2, OH, halogen (Cl, Br, F, I), SH, R^xS, R^xSO_2, R^xSO, R^xO, COOH, $COOR^x$, COR^x, CHO, and $CON(R^x)_2$, wherein R^x is an alkyl, cycloalkyl, aryl, alkenyl, alkynyl or

heterocyclic residue. Preferred substituents are halogen atoms.

Preferred lavendamycin analogs of the invention are those having the formula (J):



J

wherein X, Y, R^4 and R^6 are defined above.

More preferred are lavendamycin analogs of formula J wherein:

X is R^{10}-C(=O)-NH-,

Y is H or R^{12}-C(=O)-,

R^4 is H or an alkyl, and

R^6 is H, a halogen atom or OR^{13},

wherein R^{10}, R^{12} and R^{13} are defined above. R^{10} is preferably an alkyl or substituted alkyl. Y is preferably

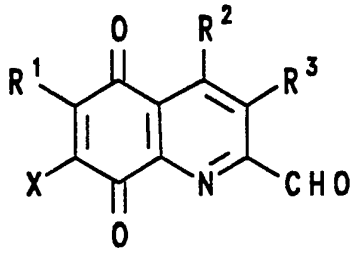
R^{12}-C(=O)-, and when Y is so defined, R^{12} is preferably $N(R^{11})_2$, OR^{11} or $OR^{14}N(R^{11})_2$. When R^{12} is so defined, R^{11} is preferably H or an alkyl or cycloalkyl. When R^{11} is an alkyl, it preferably contains from 2 to 20 carbon atoms, most preferably from 4 to 20 carbon atoms.

Certain lavendamycin analogs of the present invention may contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable acids. The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared by reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthalate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. Other salts of the lavendamicyn analogs containing a basic functional group may be used for non-therapeutic uses.

In other cases, the compounds of the invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable bases. The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention. These salts can be prepared by reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically-acceptable metal cation, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts

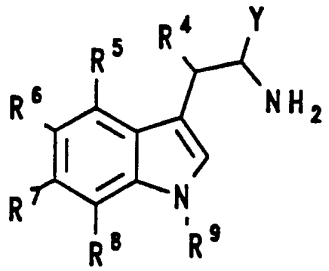
include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. Other salts of the lavendamycin analogs containing an acidic functional group may be used for non-therapeutic uses.

The lavendamycin analogs **I** of the invention may be synthesized by an efficient procedure, the final step of which is a Pictet-Spengler condensation of an aldehyde of the following formula **K**:



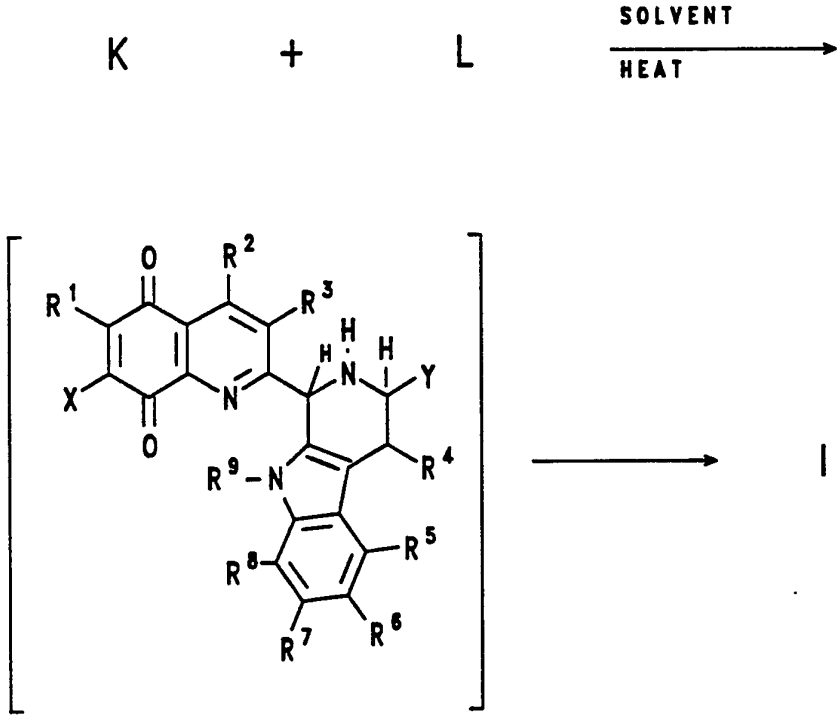
K

with a tryptophan analog of the formula **(L)**:



L

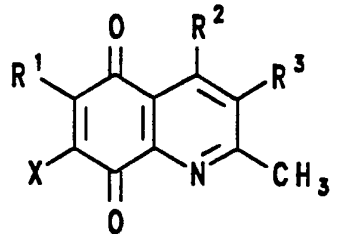
wherein X, Y and R^1 through R^9 are as defined above. See Equation 1 below:



Eq. 1

Typical reactions involve the combination of equimolar amounts of **K** and **L** in a solvent. Suitable solvents include aromatic hydrocarbons such as xylene, toluene, mesitylene, and anisole. The reactants are heated until the reaction is complete. Generally, the temperature will be about 60°C or higher, and the reaction will take about 1 hour or more to reach completion. The lavendamycin analog is obtained in the form of a solid by: (1) cooling the reaction mixture; (2) concentrating the solution and then cooling; or (3) concentration and treatment with other solvents in which the lavendamycin analogs are not soluble. Such solvents include ethyl acetate, pentane, hexane, cyclohexane, petroleum ether, diethyl ether, and acetone.

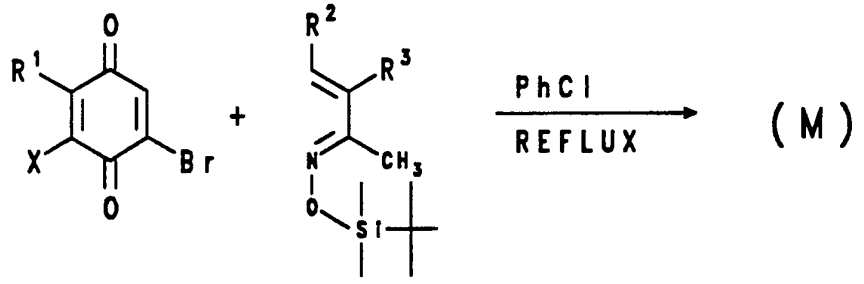
Aldehyde **K** can be prepared by the selenium dioxide oxidation of the corresponding 2-methyl-quinoline-5,8-dione **(M)** in refluxing dioxane-H_2O.



M

The 2-methylquinoline-5,8-diones **M** can be prepared by the Diels-Alder condensation of a 1-silyloxy-azadiene **(N)** with a bromoquinone **(O)** in refluxing chlorobenzene for 24 hours. See Equation 2 below. Bromoquinone **(O)** can be prepared according to

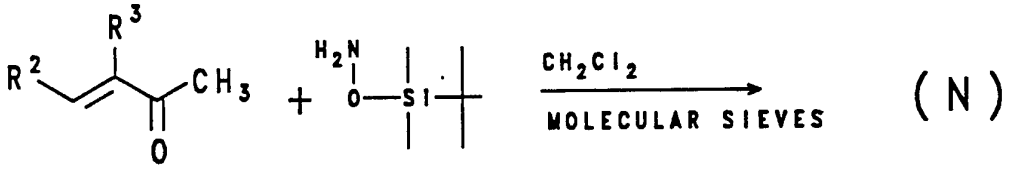
the method described in Kelly et al., J. Org. Chem., 48, 3849 (1983) (see Example 27).



(O) (N)

Eq. 2

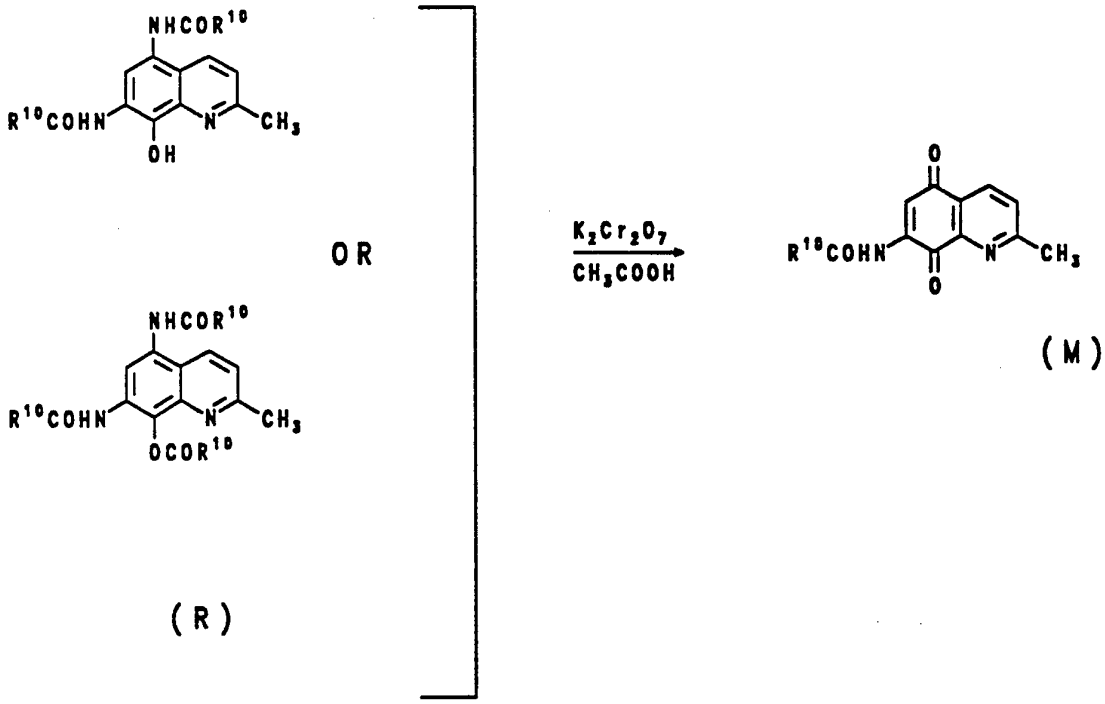
The azadiene **N** can be prepared by the reaction of a silyloxyamine **(P)** with a ketone **(Q)** in dichloromethane at room temperature for 48 hours in the presence of molecular sieves. See Equation 3 below.



(Q) (P)

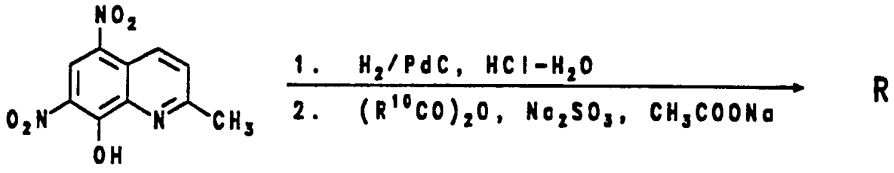
Eq. 3

Some of the 2-methylquinoline-5,8-diones **M** can also be prepared by the oxidation of the corresponding acylamido compounds **(R)** with potassium dichromate in glacial acetic acid. See Equation 4 below.



Eq. 4

The acylamido compounds **R** may be prepared by the reduction of the 5,7-dinitro-8-hydroxy-2-methylquinolines **(S)** by molecular hydrogen in the presence of palladium on carbon followed by treatment with the desired anhydride **(T)**. See Equation 5.



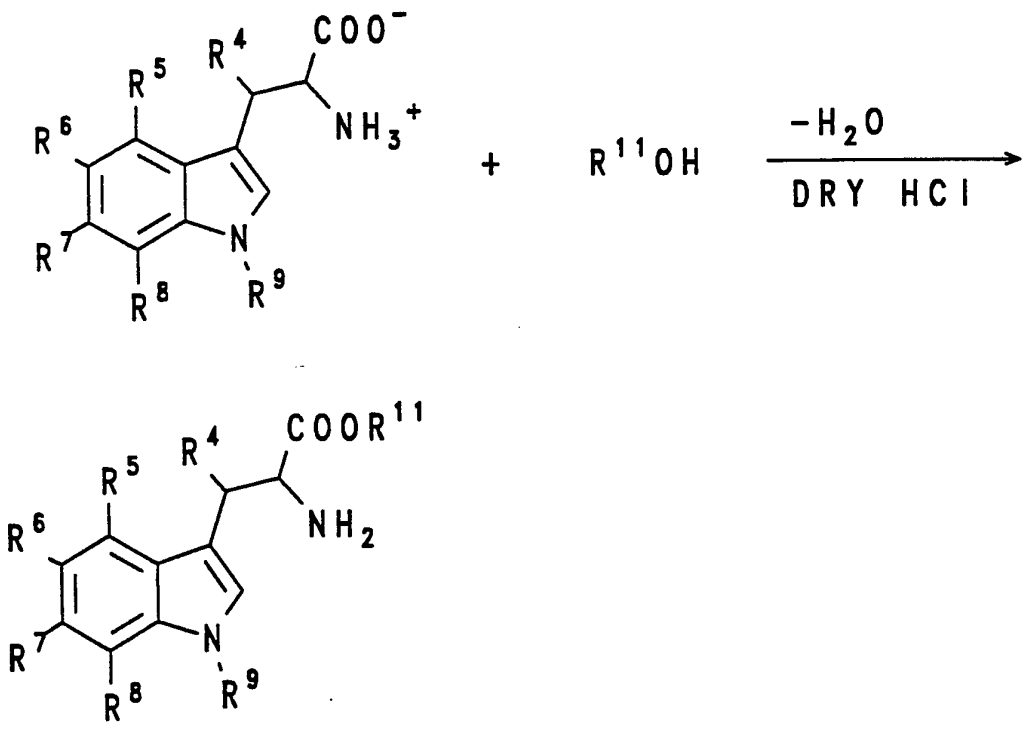
(S)

Eq. 5

Tryptophan and its analogs suitable for use in the method of the invention are available commercially or can be made by methods known in the art. For instance, tryptophan analogs **35**, **38**, **42** and **43** (see Table VI) are commercially available in their salt forms. Also, the following tryptophan analogs useful in the practice of the invention are commercially available from Sigma Chemical Co., St. Louis, MO: N-t-BOC-L-tryptophan *p*-nitrophenyl ester; N-CBZ-L-tryptophan *p*-nitrophenyl ester; DL-tryptophanamide hydrochloride; L-tryptophan benzyl ester hydrochloride; DL-tryptophan butyl ester hydrochloride; DL-tryptophan ethyl ester hydrochloride; L-tryptophan ethyl ester; D-tryptophan methyl ester hydrochloride; L-tryptophan methyl ester; DL-tryptophan octyl ester hydrochloride; 5-methoxy-DL-tryptophan;

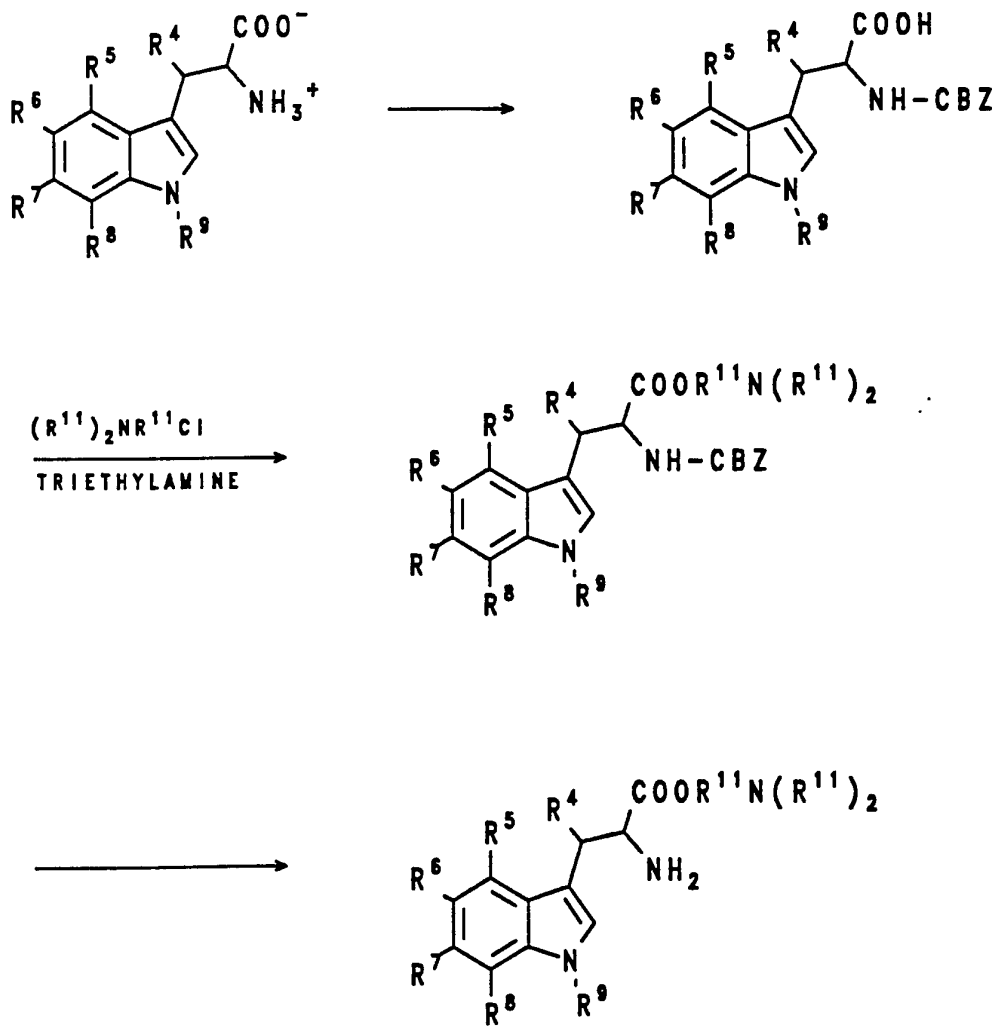
5-fluorotryptamine hydrochloride; 6-fluorotryptamine; DL-4-fluorotryptophan; 5-fluoro-DL-tryptophan; 6-fluoro-DL-tryptophan; 5-hydroxy-D-tryptophan; 5-hydroxy-DL-tryptophan; 5-hydroxy-L-tryptophan; 5-hydroxy-DL-tryptophan ethyl ester hydrochloride. Other tryptophan analogs are available from other sources or can be made by methods known in the art.

For instance, tryptophan esters can be prepared by reacting tryptophan or an appropriately functionalized tryptophan with an alcohol to give the desired ester. See Equation 6 below.



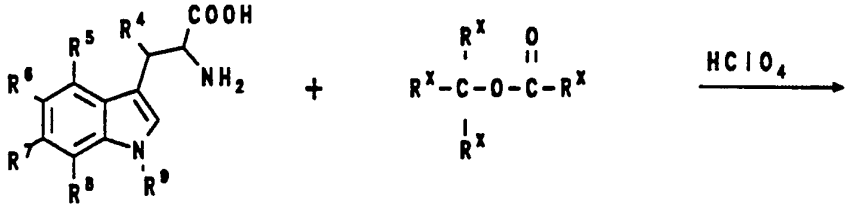
Eq. 6

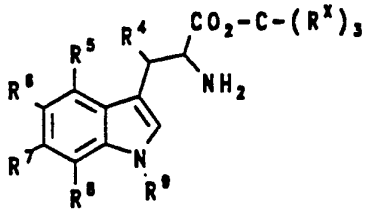
Alkylaminoalkyl esters can be prepared by protecting the amine on the tryptophan (or functionalized tryptophan analog) and then reacting the protected tryptophan with the appropriate alkylaminoalkyl halide as described in Matao Kanaoka et al., J. Phar. Soc. of Japan, 95, 231 (1975). See Equation 7 below.



Eq. 7

Tryptophan esters of tertiary alcohols can be prepared by the method of Rosowsky et al., J. Med. Chem., 24, 1450 (1981) as shown in Equation 8:

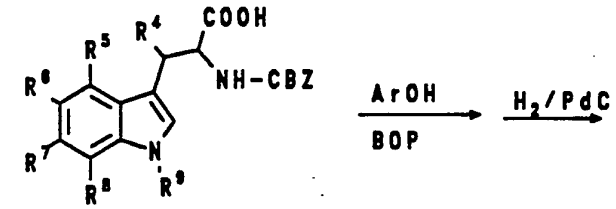


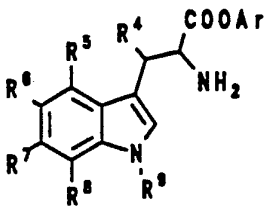


Eq. 8

wherein R^X is an alkyl, and each R^X may be the same or different.

Tryptophan aryl esters can be prepared by the methods of Castro et al. Synthesis, 413 (1977) and Rosowsky et al. J. Med. Chem., 24, 1450 (1981) as shown in Equation 9:

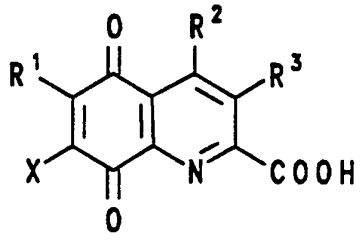




Eq. 9

Finally, tryptophan esters and amides can be prepared by the neutralization of the commercially available salts with, e.g., ammonium hydroxide, followed by extraction.

In addition to the method of preparing the lavendamycin analogs of the invention just described, the lavendamycin analogs can also be prepared by means of a Bischer-Napieralski condensation of an appropriately functionalized quinoline-2-carboxylic acid **(U)** with an appropriately functionalized tryptophan **L**. This method is similar to the method described in Kende et al., Tetrahedron Letters, 25, 923 (1984).



(U)

The lavendamycin analogs of the invention are useful as antitumor, antibacterial, antiviral and antiparasitic agents. For instances, they can be used to treat bacterial infections caused by both gram-positive and gram-negative bacteria, for example, bacteria of the genus Staphylococcus (such as *Staphylococcus aureus*), Streptococcus (such as *Streptococcus agalactine* and *Streptococcus faecalis*), Micrococcus (such as *Micrococcus luteus*), Bacillus (such as *Bacillus subtilis*), Listerella (such as *Listerella monocytogenes*), Escherichia (such as

Escherichia coli), Klebsiella (such as *Klebsiella pneumoniae*), Proteus (such as *Proteus mirabilis* and *Proteus vulgaris*), Salmonella (such as *Salmonella typhosa*), Shigella (such as *Shigella sonnei*), Enterobacter (such as *Enterobacter aerogenes*), Serratia (such as *Serratia marcescens*), Pseudomonas (such as *Pseudomonas aeruginosa*), Acinetobacter such as *Acinetobacter anitratus*), Nocardia (such as *Nocardia autotrophica*), and Mycobacterium (such as *Mycobacterium fortuitum*).

The lavendamycin analogs of the invention also have antiviral activity. For instance, they can be used to treat viral infections caused by the Retroviridae (e.g., HIV-1, HIV-2, HTLV-I and HTLV-II), Herpesviridae (e.g., herpes simplex, varicella zoster, Epstein-Barr virus, and herpes genitalia), Hepadnaviridae (e.g., hepatitis B), Picornaviridae (e.g., hepatitis A virus and poliomyelitis virus), hepatitis non A non B virus, Orthomyxoviridae (e.g., influenza virus), Poxviridae (e.g., variola virus and vaccinia virus), Flaviviridae (e.g., yellow fever virus), Rubiviridae (e.g., rubella virus), Paramyxoviridae (e.g., measles, parainfluenza, mumps and canine distemper viruses), Rhabdoviridae (e.g., rabies virus), Papovaviridae, and Adenoviridae.

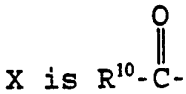
The lavendamycin analogs can also be used to treat parasitic infections. Such infections include those caused by Amoeba, Giardia, Babesia, Balantidium, Eimeriorina, Entamoeba, Histomonas, Naegleria, Nosema, Plasmodium, Toxoplasma, and Trypanosoma.

The lavendamycin analogs also have antitumor activity. They may be used to treat a variety of tumors, including ovarian, colon, breast, cervical, esophageal, glioblastoma, neuroblastoma, stomach, kidney, skin, lung, pancreatic, seminoma, melanoma,

bladder, thyroid, myeloid and lymphoid tumors. They have been found to be especially effective against solid tumors and malignant tumors.

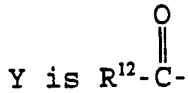
In particular, certain of the lavendamycin analogs of the invention have unexpectedly been found to be selectively active against *ras*^{K} tumor cells. By "selectively active," it is meant that these lavendamycin analogs are more cytotoxic towards the *ras*^{K} tumor cells than towards normal cells. Example 47 describes a method of determining which lavendamycin analogs are selectively active against *ras*^{K} tumor cells. Other methods are known in the art.

The lavendamycin analogs of the invention which have been found to be selectively active against *ras*^{K} tumor cells are those compounds of formula J wherein:



X is R^{10}-C-NH-,

R^{10} is an alkyl,



Y is R^{12}-C-,

R^{12} is OR^{11} or $OR^{14}N(R^{11})_2$,

R^{11} is an alkyl,

R^4 is H or an alkyl, and

R^6 is H.

Three of these compounds have been found to exhibit unprecedented highly selective activity against *ras*^{K} tumor cells. They are compounds of formula J wherein:

X is R^{10}-C(=O)-NH-,

R^{10} is CH_3,

Y is R^{12}-C(=O)-,

R^{12} is OR^{11},

R^{11} is methyl, isoamyl, or *n*-octyl,

R^4 is CH_3 when R^{11} is methyl, and R^4 is H when R^{11} is isoamyl or *n*-octyl, and

R^6 is H.

The *ras*^{K} oncogene has been associated with the causation of a large number of human solid tumors, including 90% of pancreatic cancers, 60% of colon cancers and 30% of breast cancers. Prior to the present invention there were no effective drugs available to treat patients with solid tumors whose malignant phenotype was maintained by the *ras*^{K} oncogene.

Treatment of bacterial, viral and parasitic infections according to the invention includes both mitigation, as well as elimination, of the infection. Treatment of tumors includes maintaining or reducing the size of, or eliminating, the tumor.

To treat an animal suffering from a microbial (bacterial, viral or parasitic) infection or having a tumor, an effective amount of a lavendamycin analog of the invention, or a pharmaceutically-acceptable salt thereof, is administered to the animal. Animals treatable according to the invention include mammals such as dogs, cats, other domestic animals, and humans.

To treat an animal suffering from a microbial infection or cancer, an effective amount of a lavendamycin analog, or a pharmaceutically-acceptable

salt thereof, is administered to the animal. Effective dosage forms, modes of administration and dosage amounts, may be determined empirically, and making such determinations is within the skill of the art. It is understood by those skilled in the art that the dosage amount will vary with the activity of the particular lavendamycin analog employed, the severity of the microbial infection or tumor, the route of administration, the rate of excretion of the lavendamycin analog, the duration of the treatment, the identity of any other drugs being administered to the animal, the age, size and species of the animal, and like factors well known in the medical and veterinary arts. In general, a suitable daily dose of a compound of the present invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Exemplary daily dosages are those within the range of from about 1 mg/kg/day to about 3g/kg/day, preferably from 10mg/kg/day to 500mg/kg/day. However, the total daily dosage will be determined by an attending physician or veterinarian within the scope of sound medical judgment. If desired, the effective daily dose of a lavendamycin analog, or a pharmaceutically-acceptable salt thereof, may be administered as two, three, four, five, six or more sub-doses, administered separately at appropriate intervals throughout the day.

The compounds of the present invention may be administered to an animal patient for therapy by any suitable route of administration, including orally, nasally, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually. The preferred routes of administration are orally and parenterally.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition). The pharmaceutical compositions of the invention comprise one or more of the compounds of the invention as an active ingredient in admixture with one or more pharmaceutically-acceptable carriers and, optionally, with one or more other compounds, drugs or other materials. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

Pharmaceutical formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. Regardless of the route of administration selected, the compounds of the present invention, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

The amount of active ingredient (a lavendamycin analog or a pharmaceutically-acceptable salt thereof which will be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration and all of the other factors described above. The amount of active ingredient which will be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which is the lowest dose effective to produce a therapeutic effect.

Methods of preparing pharmaceutical formulations or compositions include the step of bringing into association a compound of the present

invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient (a lavendamycin analog of the invention, or a pharmaceutically-acceptable salt thereof,) is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate;

(5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in

varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in microencapsulated form.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically-acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient (a lavendamycin analog of the invention, or a pharmaceutically-acceptable salt thereof,), the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for

example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or salicylate and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound. Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the invention to the body. Such dosage forms can be made by dissolving, dispersing or otherwise incorporating a compound of the invention in a proper medium, such as an elastomeric matrix material. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate-controlling membrane or dispersing the compound in a polymer matrix or gel.

Pharmaceutical compositions of this invention suitable for parenteral administrations comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable

mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as wetting agents, emulsifying agents and dispersing agents. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like in the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly-(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

The injectable materials can be sterilized for example, by filtration through a bacterial-retaining filter.

The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a lyophilized condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the type described above.

The pharmaceutical compositions of the present invention may also be used in the form of veterinary formulations, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, boluses, powders, granules or pellets for admixture with feed stuffs, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or suspension or, when appropriate, by intramammary injection where a suspension or solution is introduced into the udder of the animal via its teat; (3) topical application, for example, as a cream, ointment or spray applied to the skin; or (4) intravaginally, for example, as a pessary, cream or foam.

The lavendamycin analogs of the invention may also be employed as antimicrobial (antibacterial, antiviral, antiparasitic) agents useful in inhibiting the growth of microbes. "Inhibition of growth" as used herein includes killing of the microbes. For instance, the compounds of the invention may be used to inhibit the growth of microbes present on a surface or in a medium outside a living host. The invention,

therefore, provides a method for inhibiting the growth of a bacterium, virus or parasite comprising the step of contacting the microbe with a lavendamycin analog of the invention, or a salt thereof, in an amount effective for the inhibition. Thus, the compounds of the invention may be employed, for example, as disinfectants for surface treatments or as preservatives for a variety of solid and liquid media susceptible to microbial growth. Effective amounts of a lavendamycin analog for such uses may be determined empirically by methods known to the skilled artisan.

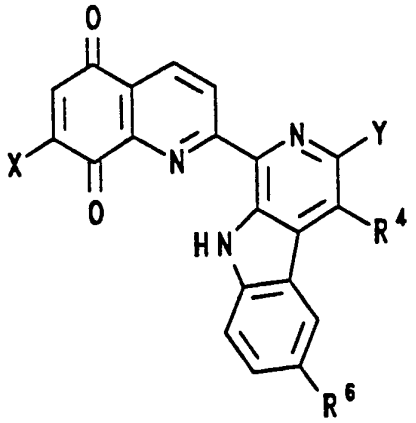
EXAMPLES

EXAMPLES 1-46: SYNTHESIS OF LAVENDAMYCIN ANALOGS

Examples 1-46 describe the synthesis of 22 lavendamycin analogs. The following general procedures were utilized in Examples 1-46. Melting points (uncorrected) were determined on a Thomas Hoover capillary apparatus and are in degrees Celsius. Infrared (IR) spectra were obtained with a Nicolet 5ZDX spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were obtained with a Varian Gemini-200 spectrophotometer in $CDCl_3$ or DMSO-d_6 with tetramethylsilane (TMS) as internal standard. Mass spectra (MS) were obtained with a Hewlett-Packard 5980A instrument fitted with a vacummetrics solid probe or with a Kratos MS 50. Elemental analyses were performed by Midwest Microlabs, Ltd.

EXAMPLES 1-22: SYNTHESIS OF 7-N-ACYLLAVENDAMYCINS

The 22 lavendamycin analogs which were prepared have formula **J**:



wherein:

X is R^{10}-C(=O)-NH-,

R^{10} is an alkyl or substituted alkyl,

Y is H or R^{12}-C(=O)-,

R^4 is H or an alkyl,

R^6 is H, a halogen atom or OR^{13},

R^{12} is $N(R^{11})_2$, OR^{11} or OR^{14} $N(R^{11})_2$,

R^{11} is H, an alkyl or a cycloalkyl,

R^{13} is an alkyl, and

R^{14} is an alkylene.

Table I contains a list of the lavendamycin analogs and specifies the substituents for each analog.

The lavendamycin analogs were prepared by reacting an appropriately functionalized aldehyde **K** with an appropriately functionalized tryptophan analog **L** as described above (see Equation 1 above). The reaction conditions and yields for the 22 lavendamycin analogs are listed in Table I, and the procedures used to make 11 of the analogs are described in detail

below. Table II gives the ^1H NMR, MS and high resolution MS (HRMS) values for the 22 analogs.

7-N-Acetyllavendamycin Methyl Ester (Compound 1, Table I): A stirred mixture of aldehyde **23** (prepared as described in Example 23) (12.02 mg, 0.05 mmol) and tryptophan ester **39** (prepared as described in Behforouz et al., J. Heterocycl. Chem., 25, 1627 (1988); see Example 39 below) (11.6 mg, 0.05 mmol) and dry xylene (16 mL) under argon was slowly heated (3 hours) to boiling and then refluxed for 19 hours. The solution was concentrated to 5 mL and then cooled. The pure orange crystals of the 7-N-acetyllavendamycin methyl ester were filtered. A yield of 17.8 mg, 78.4%, was obtained. The melting point (mp) was > 300°C. IR (KBr) 3473 (br), 3310, 3121, 1728, 1708, 1680, 1645, 1588, 1504, 1398, 1335, 1307, 1229, 1124, 738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (s,3,$COCH_3$), 3.19 (s,3,$ArCH_3$), 4.07 (s,3,CO_2CH_3), 7.39 (t,1,J=8 Hz.,H-11'), 7.65 (t,1,J=8 Hz.,H-10'), 7.74 (d,1,J=8 Hz., H-9'), 8.00 (s,1,H-6), 8.35 (d,1,J=8 Hz., H-12'), 8.41 (br s,1,CONH), 8.5 (d,1,J=7 Hz.,H-3), 9.1 (d,1,J=7.5 Hz.,H-4); 11.85 (br s,1,NH); MS m/e (relative intensity) 454 (M^+,68), 396 (14), 394 (25), 352 (17), 106 (36), 91 (100), 77 (14), 54 (14); HRMS, m/e for $C_{25}H_{18}N_4O_5$ calculated 454.1277, found 454.1277.

7-N-ACETYLDEMETHYLLAVENDAMYCIN (Compound 2, Table I): L-tryptophan (20.4 mg, 0.1 mmol) and anisole were stirred and heated in a 60-70°C oil bath. Then, a mixture of 7-N-acetamido-2-formylquinoline-5,8-dione **(23)** (prepared as described in Example 23) (24.4 mg, 0.1 mmol) and 20 ml anisole was added dropwise over a one-hour period. The mixture was heated in the oil bath at 120°C for 23.5 hr. and rotoevaporated to

dryness. The residue was chromatographed on a silicon gel column (4g silica gel, column 13 cm X 10 cm), and eluted with CH_2Cl_2 (50ml), methanol: CH_2Cl_2 (2.5:100, 100 ml) to give orange crystals (0.6 mg., yield 1.4%).

7-N-CHLOROACETYLLAVENDAMYCIN METHYL ESTER (Compound 7, Table I): In a 40 ml. round-bottomed flask equipped with a reflux condenser, argon-filled balloon and a magnetic bar, 7-chloroacetamido-2-formylquinoline-5,8-dione **(24)** (prepared as described in Example 24) (0.0278 g., 0.10 mmol), β-methyltryptophan methyl ester **(39)** (prepared as described in Behforouz et al., J. Heterocycl. Chem., 25, 1627 (1988); see Example 39 below) (0.0232 g., 0.10 mmol), and 40 ml. of dried, distilled xylene were slowly heated to 135°C over a three-hour period. The mixture was heated at this temperature for an additional 16 hours. A light brown precipitate began to form at the maximum temperature. The completion of the reaction was monitored by TLC. The mixture was filtered hot to remove the precipitated impurities, and the filtrate was allowed to cool, resulting in the formation of an orange-red solid. This solid was filtered, collected, and dried under vacuum. The yield of the product was 0.0226 g. (46%): mp > 300°C; ^{1}H NMR (DMSO-d_6) δ 3.08 (3H, s, $ArCH_3$), 3.97 (3H, s, $COCH_3$), 4.64 (2H, s, C-7NHCO$\underline{CH_2}$Cl), 7.42 (1H, dd, J = 8.4 Hz., J = 8.4 Hz., C-11'H), 7.69 (1H, dd, J = 8.4 Hz., J = 8.4 Hz., C-10'H), 7.71 (1H, d, J = 8.4 Hz., C-9'H), 7.75 (1H, s, C-6H), 8.40 (1H, d, J = 8.4 Hz., C-12'H), 8.50 (1H, d, J = 8.4 Hz., C-3H), 8.64 (1H, d, J = 8.4 Hz., C-4H), 10.58 (1H, br s, C-7NH), 11.94 (1H, br s, NH); IR (KBr) ν_{max} 3342, 3106, 3010, 2950, 1679, 1652, 1589, 1507, 1492, 1339, 1307, 742 cm^{-1}; electron impact MS (EIMS), m/e (relative intensity) 488/490 (M^+,

2.25/1, 16), 454 (96), 412 (base), 394 (36), 380 (20), 352 (88), 335 (29); HRMS, m/e for $C_{25}H_{17}ClN_4O_5$ calculated 488.088748, found 488.087100.

7-N-CHLOROACETYLDEMETHYLLAVENDAMYCIN ISOAMYL ESTER (Compound 9, Table I): In a 100 ml. three-necked, round-bottomed flask equipped with a reflux condenser, flowing argon and a magnetic bar, 7-chloro-acetamido-2-formylquinoline-5,8-dione **(24)** (prepared as described in Example 24) (0.0500 g., 0.18 mmol), L-tryptophan isoamyl ester **(37)** (prepared as described in Example 37) (0.0490 g., 0.18 mmol), and 75 ml. of dried and distilled xylene were slowly heated to 76°C over a five-hour period. Upon the first detection of the formation of a light-colored precipitate, the mixture was filtered hot. The filtrate was concentrated under reduced pressure to about 10 ml. The filtrate was stored in a refrigerator overnight during which a considerable amount of a dark orange-brown solid formed. This was filtered and washed with cold ethyl acetate giving 25.5 mg. of the crude product (a yield of 27%). The filtrate was further concentrated which, upon cooling, yielded an additional 15 mg. of the product (16% yield, total yield 43%): mp. 280-284°C; ^{1}H NMR ($CDCl_3$) δ 1.05 (6H, d, J = 6.3 Hz., $(CH_3)_2$), 1.76 - 1.95 (3H, m, $COOCH_2CH_2CH$), 4.29 (2H, s, C-7NHCOCH_2Cl), 4.52 (2H, t, J = 6.8 Hz., $COOCH_2$), 7.39 (1H, dd, J = 8.0 Hz., J = 8.0 Hz., C-11'H), 7.66 (1H, dd, J = 8.0 Hz., J = 8.0 Hz., C-10'H), 7.78 (1H, d, J = 8.0 Hz., C-9'H), 7.95 (1H, s, C-6H), 8.23 (1H, d, J = 8.0 Hz., C-12'H), 8.54 (1H, d, J = 8.3 Hz., C-3H), 8.93 (1H, s, C-3'H), 9.18 (1H, d, J = 8.3 Hz., C-4H), 9.56 (1H, br s, C-7NH), 11.76 (1H, br s, NH); IR (KBr) ν_{max} 3336, 2957, 2929, 2908, 2871, 1713, 1680, 1651, 1588, 1520, 1337, 1308, 1265, 1219, 1119, 738 cm^{-1}

^{1}; EIMS, m/e (relative intensity) 530/532 (M^+, 2.4/1, 45), 496 (58), 480 (6), 454 (39), 416 (83), 382 (95), 366 (15), 340 (base); HRMS, m/e for $C_{28}H_{23}ClN_4O_5$ calculated 530.135698, found 530.135781.

7-N-CHLOROACETYLDEMETHYLLAVENDAMYCIN OCTYL ESTER (Compound 10, Table I): In a 50 ml. three-necked round-bottomed flask equipped with a reflux condenser, flowing argon and a magnetic bar, 7-chloroacetamido-2-formylquinoline-5,8-dione **(24)** (prepared as described in Example 24) (0.0279 g., 0.10 mmol), L-tryptophan octyl ester **(38)** (prepared as described in Example 38) (0.0316 g., 0.10 mmol), and 32 ml. of dried and distilled xylene were slowly heated to 100°C over a six-hour period. This temperature was maintained for an additional 2.5 hours. During the last three hours, a brown precipitate formed. TLC of the mixture indicated the major spot to be the desired product. The mixture was filtered hot to remove the precipitated impurities, and the filtrate was rotoevaporated to dryness affording 0.0301 g. of a dark-red solid which ^{1}H NMR indicated was crude product (yield of 53%). The crude product was further purified by recrystallization with ethyl acetate: mp 215 - 217°C; ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, J = 6.8 Hz., $(CH_2)_7\underline{CH_3}$)), 1.23 - 1.70 (10'H, $(\underline{CH_2})_5CH_3$)), 1.84 - 1.95 (2H, m, $COOCH_2\underline{CH_2}$), 4.29 (2H, s, C-7NHCO$\underline{CH_2}$Cl), 4.48 (2H, t, J = 6.8 Hz., $COOCH_2$), 7.39 (1H, dd, J = 7.6 Hz., J = 7.6 Hz., C-11'H), 7.66 (1H, dd, J = 7.6 Hz., J = 7.6 Hz., C-10'H), 7.79 (1H, d, J = 7.6 Hz., C-9'H), 7.97 (1H, s, C-6H), 8.24 (1H, d, J = 7.6 Hz., C-12'H), 8.56 (1H, d, J = 8.4 Hz., C-3H), 8.95 (1H, s, C-3'H), 9.21 (1H, d, J = 8.4 Hz., C-4H), 9.58 (1H, br s, C-7NH), 11.79 (1H, br s, NH); IR (KBr) ν_{max} 3331, 2955, 2926, 2854, 1708, 1680, 1652, 1588, 1519, 1337, 1307, 1264, 1219, 738

cm^{-1}; EIMS, m/e (relative intensity) 573 (M^+, 1), 538 (10), 496 (35), 382 (53), 366 (30), 340 (base); HRMS, m/e for $C_{35}H_{40}ClN_4O_7S_2$ calculated 727.202696, found 727.200500.

7-N-BUTYRYLLAVENDAMYCIN METHYL ESTER (Compound 11, Table I): In a 25 ml. round-bottomed flask equipped with a reflux condenser, argon-filled balloon, and a magnetic bar, 7-butyramido-2-formylquinoline-5,8-dione **(26)** (prepared as described in Example 26) (0.0272 g., 0.10 mmol), β-methyltryptophan methyl ester **(39)** (prepared as described in Example 39) (0.0232 g., 0.10 mmol), and 30 ml. of dried and distilled xylene were slowly heated to 130°C over a three-hour period. This temperature was maintained for an additional 16 hours, during which a slight amount of a light brown precipitate formed. The completion of the reaction was monitored by TLC. The mixture was filtered hot to remove the precipitate. The filtrate was then concentrated under reduced pressure to the point of crystallization and then allowed to cool. The orange-red solid was filtered and then dried under vacuum. The weight of the solid was 0.0210 g. (a yield of 44%): mp. 270-273°C; ^1H NMR ($CDCl_3$) δ 1.06 (3H, t, J = 7.6 Hz., C-7NHCOCH$_2$CH$_2$CH$_3$), 1.75 - 1.90 (2H, m, C-7NHCOCH$_2$CH$_2$CH$_3$), 2.52 (2H, t, J = 7.6 Hz., C-7NHCOCH$_2$CH$_2$CH$_3$), 3.16 (3H, s, Ar-CH$_3$), 4.07 (3H, s, COCH$_3$), 7.36 (1H, dd, J = 8.0 Hz., J = 8.0 Hz., C-11'H), 7.63 (1H, dd, J = 8.0 Hz., J = 8.0 Hz., C-10'), 7.70 (1H, d, J = 8.0 Hz., C-9'H), 7.92 (1H, s, C-6H), 8.31 (1H, d, J = 8.0 Hz., C-12'H), 8.34 (1H, br s, C-7NH), 8.41 (1H, d, J = 8.3 Hz., C-3H), 9.01 (1H, d, J = 8.3 Hz., C-4H), 11.76 (1H, br s, NH); IR (KBr) ν_{max} 3316, 3199, 2959, 2933, 2874, 1724, 1710, 1679, 1646, 1586, 1501, 1335, 1307, 1227 cm^{-1}; EIMS, m/e

(relative intensity) 482 (M^+, base), 466 (11), 450 (13), 422 (32), 380 (9), 352 (35), HRMS, m/e for $C_{27}H_{22}N_4O_5$ calculated 482.159020, found 482.160385.

7-N-BUTYRYLDEMETHYLLAVENDAMYCIN ISOAMYL ESTER (Compound 13, Table I): In a 50 ml. three-necked, round-bottomed flask equipped with a reflux condenser, flowing argon, and a magnetic bar, 7-butyramido-2-formylquinoline-5,8-dione **(26)** (prepared as described in Example 26) (0.0279 g., 0.10 mmol), L-tryptophan isoamyl ester **(37)** (prepared as described in Example 37) (0.0274 g., 0.10 mmol), and 30 ml. of dried and distilled xylene were slowly heated to reflux over a four-hour period. This temperature was maintained for an additional 17 hours. A small amount of an orange-brown solid was formed. The completion of the reaction was monitored by TLC. The mixture was filtered hot to remove the precipitate which was not the product. The filtrate was concentrated under reduced pressure to approximately 2 ml. Upon cooling, this solution yielded a bright orange precipitate which weighed 0.0166 g. (32% yield). The mother liquor was evaporated to dryness to yield an additional amount of crude product that weighed 0.0198 g. (38% yield), giving a total yield of 70%: mp. 234-235° C; ^{1}H NMR ($CDCl_3$) δ 1.04 (6H, d, J = 6.8 Hz., $(CH_3)_2$), 1.06 (3H, t, J = 7.4 Hz., C-7NHCOCH$_2$CH$_2$CH$_3$), 1.75 - 1.95 (5H, m, C-7NHCOCH$_2$CH$_2$, COOCH$_2$CH$_2$CH), 2.53 (2H, t, J = 7.4 Hz., C-7NHCOCH$_2$), 4.52 (2H, t, J = 6.8 Hz., COOCH$_2$), 7.39 (1H, dd, J = 7.8 Hz., J = 7.8 Hz., C-11'H), 7.66 (1H, dd, J = 7.8 Hz., J = 7.8 Hz., C-10'H), 7.74 (1H, d, J = 7.8 Hz., C-9'H), 7.99 (1H, s, C-6H), 8.24 (1H, d, J = 7.8 Hz., C-12'H), 8.41 (1H, br s, C-7NH), 8.55 (1H, d, J = 8.4 Hz., C-3'H), 8.94 (1H, s, C-3'H), 9.18 (1H, d, J = 8.4 Hz., C-4H), 11.80 (1H, br s, NH); IR (KBr) ν_{max}

3369, 3346, 3313, 2960, 2935, 2873, 1728, 1715, 1700, 1681, 1646, 1587, 1494, 1335, 1307, 1261, 1221, 1119, 739 cm^{-1}; EIMS, m/e (relative intensity) 524 (69), 454 (6), 410 (base), 394 (5), 340 (22); HRMS, m/e for $C_{30}H_{28}N_4O_5$ calculated 524.205970, found 524.207494.

7-N-BUTYRYLDEMETHYLLAVENDAMYCIN OCTYL ESTER (Compound 14, Table I): In a 50 ml. three-necked, round-bottomed flask equipped with a reflux condenser, flowing argon, and a magnetic bar, 7-N-butyramido-2-formylquinoline-5,8-dione **(26)** (prepared as described in Example 26) (0.0230 g., 0.085 mmol), L-tryptophan octyl ester **(38)** (prepared as described in Example 38) (0.0270 g., 0.085 mmol), and 30 ml. of dried and distilled xylene were slowly heated to 85°C over a five hour period. This temperature was maintained for an additional 16 hours. During this period a small amount of a dark precipitate appeared. The completion of the reaction was monitored by TLC. The mixture was filtered hot to remove the precipitated impurities, and the filtrate was rotoevaporated to dryness affording 0.0386 g. of a dark-red solid which ^1H NMR indicated was crude product (yield of 80%). The crude product was further purified by recrystallization from ethyl acetate: mp. 166 - 171° C; ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, J = 6.8 Hz., $(CH_2)_7\underline{CH_3}$), 1.06 (3H, t, J = 7.3 Hz., C-7NHCOCH$_2$CH$_2\underline{CH_3}$), 1.20 - 1.60 (10'h, $(\underline{CH_2})_5CH_3$), 1.65 - 1.95 (4H, m C-7NHCOCH$_2\underline{CH_2}$, COOCH$_2\underline{CH_2}$), 2.53 (2H, t, J = 7.3 Hz., C-7NHCO$\underline{CH_2}$), 4.47 (2H, t, J = 6.8 Hz., COO$\underline{CH_2}$), 7.36 (1H, dd, J = 8.0 Hz., J = 8.0 Hz., C-11'H), 7.63 (1H, dd, J = 8.0 Hz., J = 8.0 Hz., C-10'H), 7.65 (1H, d, J = 8.0 Hz., C-9'H), 7.93 (1H, s, C-6H), 8.19 (1H, d, J = 8.0 Hz., C-12'H), 8.35 (1H, br s, C-7NH), 8.44 (1H, d, J = 8.4 Hz., C-3H), 8.87 (1H, s, C-3'H), 9.08 (1H, d, J = 8.4 Hz., C-4H), 11.67 (1H, br s, NH); IR

(KBr) ν_{max} 3317, 2957, 2926, 2855, 1728, 1704, 1679, 1646, 1587, 1504, 1333, 1307, 1260, 1222, 1118, 739 cm^{-1}; EIMS, m/e (relative intensity) 566 (M^+, 14), 550 (45), 534 (15), 496 (6), 410 (12), 394 (base), 378 (22), 340 (17); HRMS, m/e for $C_{33}H_{34}N_4O_5$ calculated 566.252921, found 566.251991.

7-N-ACETYLDEMETHYLLAVENDAMYCIN CARBOXAMIDE (Compound 16, Table I): 7-N-Acetamido-2-formylquinoline-5,8-dione **(23)** (prepared as described in Example 23) (42.3 mg 0.15 mmol), L-tryptophan amide **(43)** (prepared as described in Example 43) (30.44 mg, 0.015 mmol) and anisole (60 ml) were heated slowly in an oil bath from room temperature to 160°C over a 2.5-hr. period, and then held 160°C for 14 hr. The reaction mixture was cooled in the refrigerator for 3 hr. Then it was filtered to give a lemon yellow solid. The solid was washed with hexane and dried to give 39.6 mg., a yield of 62%.

7-N-ACETYLDEMETHYLLAVENDAMYCIN METHYL ESTER (Compound 17, Table I): 7-N-Acetamido-2-formylquinoline-5,8-dione **(23)** (prepared as described in Example 23) (44.8 mg, 0.2 mmol), L-tryptophan methyl ester **(35)** (prepared as described in Example 35) (43.6 mg, 0.2 mmol), dry xylene (90 ml) were mixed. The mixture was stirred and slowly heated in an oil bath from room temperature to 140°C over a 3-hr period and from 140°C to 154°C over a 20-hr period. The reaction mixture was allowed to cool to room temperature to give 53 mg (yield of 60%) of a yellow solid.

7-N-ACETYLLAVENDAMYCIN ISOAMYL ESTER (Compound 18, Table I): 7-Acetamido-2-formylquinoline-5,8-dione **(23)** (prepared as described in Example 23)

(44.8 mg, 0.2 mmol), β-methyltryptophan isoamyl ester **(36)** (prepared as described in Example 36) (57.6 mg, 0.2 mmol) and 64 ml of dry xylene were stirred and heated slowly in an oil bath from room temperature to 140°C over a 3-hour period and was then kept at 140°C for 1 hour. The hot reaction mixture was filtered to give an orange solid. The filtrate afforded more product upon cooling. The total weight obtained of the product was 60.2 mg, a 59% yield.

7-N-ACETYLLAVENDAMYCIN N,N-DIMETHYLAMINOETHYL ESTER (Compound 19, Table I): 7-Acetamido-2-formylquinoline-5,8-dione **(23)** (prepared as described in Example 23) (317 mg, 0.13 mmol) was dissolved in 16 ml of dry anisole and heated to 80°C. β-methyltryptophan N,N-dimethylaminoethyl ester **(41)** (prepared as described in Example 41) (37.5 mg, 0.13 mmol) was added with stirring, and the stirred mixture was heated at 100°C for 5.5 hr. The reaction mixture was allowed to cool to room temperature and the solid was filtered. The filtrate was distilled under vacuum to dryness. Ethyl acetate (3 ml) was added, and the mixture was stirred. Upon filtration 24.5 mg (a yield of 36%) of an orange solid was obtained.

7-N-ACETYLDEMETHYLLAVENDAMYCIN ISOAMYL ESTER (Compound 20, Table I): 7-Acetamido-2-formylquinoline-5,8-dione **(23)** (prepared as described in Example 23) (244 mg, 0.1 mmol), L-tryptophan isoamyl ester **(37)** (prepared as described in Example 37) (239 mg, 1 mmol) and xylene (64 ml) were mixed. The mixture was stirred and slowly heated in an oil bath from room temperature to 110°C over a one-hour period, and then from 110°C to 140°C over a 3-hr period. The hot reaction mixture was filtered to remove the brown

impurity. The filtrate was evaporated under vacuum. The residue was treated with ethylacetate/hexane to give an orange solid (213 mg, 42% yield).

7-N-ACETYLDEMETHYLLAVENDAMYCIN n-OCTYL ESTER (Compound 21, Table I): 7-Acetamido-2-formylquinoline-5,8-dione **(23)** (prepared as described in Examples 23-26) (44.8 mg, 0.2 mmol), L-tryptophan N-octyl ester **(38)** (prepared as described in Example 38) (63.2 mg, 0.2 mmol) and 64 ml of dry xylene were stirred and slowly heated in an oil bath from room temperature to 150°C over a 3-hr period and then maintained at 150°C for 2h. The hot mixture was filtered, and the brown solid was collected. More brown solid was obtained from the filtrate upon treatment with ethylacetate and hexane (total yield 51 mg, 48%).

7-N-ACETYLDEMETHYLLAVENDAMYCIN N,N-DIMETHYLAMINOETHYL ESTER (Compound 22, Table I): 7-Acetamido-2-formylquinoline-5,8-dione **(23)** (prepared as described in Example 23) (12.2 mg, 0.05 mmol), L-tryptophan N,N-dimethylaminoethyl ester **(40)** (prepared as described in Example 40) (14 mg, 0.05 mmol) and 18 ml of anisole were heated at 100°C for 27 h. The mixture was allowed to cool to room temperature and was filtered to remove impurities. The filtrate was evaporated under reduced pressure, and the resulting residue was dissolved in 6 ml of $CHCl_3$ and purified by thick layer chromatography on alumina. A pure orange solid (5 mg, 20% yield) was obtained.

Table I

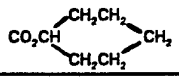
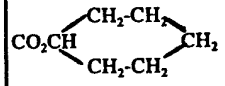
Compd.	R^{10}	Y	R^4	R^6	Solvent	Hours (°C)	Yield (%)
1	CH_3	CO_2CH_3	CH_3	H	Xylene	19 (reflux)	78.4
2	CH_3	CO_2H	H	H	Anisole	23.5 (120°)	1.4
3	CH_3		H	H	Xylene	3 (25°-reflux) 1 (reflux)	59
4	CH_3	$CO_2(CH_2)_3CH_3$	H	OCH_3	Anisole	6 (70-90°)	66
5	CH_3	$CO_2(CH_2)_3CH_3$	H	F	Anisole	5 (120°)	49
6	CH_3	H	H	H	Anisole	3 (25-160°) 16 (160°)	54
7	$ClCH_2$	CO_2CH_3	CH_3	H	Xylene	16 (135°)	46
8	$ClCH_2$	$CO_2(CH_2)_3CH_3$	H	H	Xylene	3 (<76°) 5.75 (76°)	20
9	$ClCH_2$	$CO_2(CH_2)_2CH(CH_3)_2$	H	H	Xylene	5 (≤76°)	43 (crude)
10	$ClCH_2$	$CO_2(CH_2)_7CH_3$	H	H	Xylene	6 (<100°) 2.5 (100°)	53 (crude)
11	$CH_3(CH_2)_2$	CO_2CH_3	CH_3	H	Xylene	16 (130°)	44
12	$CH_3(CH_2)_2$	$CO_2(CH_2)_3CH_3$	H	H	Xylene	55 (130°)	30
13	$CH_3(CH_2)_2$	$CO_2(CH_2)_2CH(CH_3)_2$	H	H	Xylene	4 (25°-reflux) 17 (reflux)	70 (crude)
14	$CH_3(CH_2)_7$	$CO_2(CH_2)_7CH_3$	H	H	Xylene	5 (<85°) 16 (85°)	80 (crude)
15	$(CH_3)_2CH$	$CO_2(CH_2)_3CH_3$	H	H	Xylene	8 (125°)	65.2
16	CH_3	$CONH_2$	H	H	Anisole	2.5 (<160°) 14 (160°)	62
17	CH_3	CO_2CH_3	H	H	Xylene	3 (<140°) 20 (154°)	60
18	CH_3	$CO_2CH_2CH_2CH(CH_3)_2$	CH_3	H	Xylene	3 (<140°) 1 (140°)	59
19	CH_3	$CO_2(CH_2)_2N(CH_3)_2$	CH_3	H	Anisole	5.5 (100°) 1 (<140°)	36
20	CH_3	$CO_2CH_2CH_2CH(CH_3)_2$	H	H	Xylene	1 (140°) 3 (<150°)	42
21	CH_3	$CO_2(CH_2)_7CH_3$	H	H	Xylene	3 (<180°) 2 (150°)	48
22	CH_3	$CO_2CH_2CH_2N(CH_3)_2$	H	H	Anisole	27 (100°)	20

TABLE II

Cmpd.	R^{10}	Y	R^4	R^6	^1H, NMR	MS	HRMS
1	CH_3	CO_2CH_3	CH_3	H	2.38 (s, 3H), 3.22 (s, 3H), 4.10 (s, 3H), 7.42 (dd, J=7.6Hz, 1H), 7.68 (dd, J=7.6Hz, 1H), 7.77 (d, J=8.2Hz, 1H), 8.00 (s, 1H), 8.38 (d, J=8.2Hz, 1H), 8.44 (s, 1H), 8.53 (d, J=8.2Hz, 1H), 9.13 (d, J=8.2Hz, 1H), 11.88 (br s, 1H)	454 (M^+, 68), 396 (14), 394 (25), 352 (17), 106 (36), 91 (100), 77(14), 54 (14)	$C_{25}H_{18}N_4O_5$ Calc. 454.1277 Found 454.1277
2	CH_3	CO_2H	H	H	2.37 (s, 3H), 7.65 (dd, 1H), 7.70 (dd, 1H), 8.0 (s, 1H), 8.13 (d, 1H), 8.21 (d, 1H), 8.45 (br s, 1H), 8.57 (d, 1H), 8.62 (s,1H), 9.11 (d,1H), 11.65 (br s, 1H)		
3	CH_3		H	H	1.66-2.17 (m, 10H), 2.37 (s, 3H), 5.20 (m, 1H), 7.41 (dd, 1H), 7.68 (dd, 1H), 7.75 (d, 1H), 7.98 (s, 1H), 8.27 (d, 1H), 8.42 (br s, 1H), 8.56 (d, 1H), 8.95 (s, 1H), 9.22 (d, 1H), 11.8 (br s, 1H).	508 (M^+, 35), 426 (12), 382 (base), 366 (15), 340 (25), 312(5), 283 (4), 256 (6), 154 (4), 130 (4)	$C_{29}H_{24}N_4O_5$ Calc. 508.174670 Found 508.173290
4	CH_3	$CO_2(CH_2)_3CH_3$	H	OCH_3	1.04 (t,3H), 1.6-1.85 (m,4H), 2.38 (s,3H), 4.0 (s,3H), 4.35 (t, 2H), 7.33 (d,1H), 7.66 (d,1H), 7.67 (s,1H), 7.99 (s,1H), 8.42 (br s, 1H), 8.57 (d,1H), 8.93 (s,1H), 9.22(d,1H), 11.7 (br s,1H)	512/513 (M^+, base), 412(30) 397(6), 355(8)	$C_{28}H_{24}N_4O_6$ Calc. 512.169585 Found 512.168362
5	CH_3	$CO_2(CH_2)_3CH_3$	H	F	1.07 (s,3H), 1.89-1.25(m, 4H), 2.37 (s,3H), 4.51 (t, 2H), 7.19 (s,1H), 7.92 (d, 1H), 7.94 (d, 1H), 8.02 (s, 1H), 8.45 (br s, 1H), 8.62 (d, 1H), 8.93 (s,1H), 9.25 (d, 1H), 11.88 (br s, 1H)		
6	CH_3	H	H	H	2.37 (s,3H), 7.35 (dd,1H), 7.68 (dd, 1H), 7.71 (d, 1H), 7.99 (s,1H), 8.13(d,1H), 8.21 (d, 1H), 8.45 (br s, 1H), 8.61 (d, 1H), 8.56 (d, 1H), 9.10 (d, 1H), 11.64 (br s, 1H)	382/383(M^+ base), 340 (58), 313 (24), 284 (12), 244(19), 140 (10)	$C_{22}H_{12}N_4O_3$ Calc. 340.096026 Found 340.095347
7	$ClCH_2$	CO_2CH_3	CH_3	H	(DMSO) 3.08 (s,3H), 3.97 (s,3H), 4.64(s,2H), 7.42 (dd, J=8.4Hz, 8.4Hz, 1H), 7.69 (dd, J=8.4, 8.4Hz, 1H), 7.71 (d, J=8.4Hz, 1H), 7.75 (s, 1H), 8.40 (d, J=8.4Hz, 1H), 8.50 (d, J=8.4Hz, 1H), 8.64 (d, J=8.4Hz, 1H), 10.58 (br s, 1H), 11.94 (br s, 1H)	488/490 (M^+ 2.25/1, 16), 454 (96), 412 (base), 394 (36), 380 (20), 352 (88), 335 (29)	$C_{25}H_{17}ClN_4O_5$ Calc 488.088748 Found 488.087100

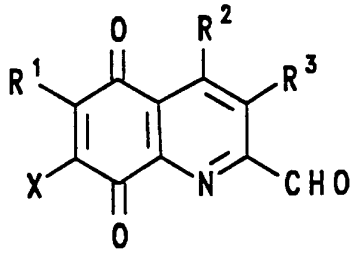
Cmpd.	R^{10}	Y	R^4	R^6	^1H, NMR	MS	HRMS
8	$ClCH_2$	$CO_2(CH_2)_3CH_3$	H	H	1.06 (t,3H), 1.85-1.95 (m, 4H), 4.25 (s,2H), 4.50 (t,2H), 7.35-7.45 (m, 1H), 7.65-7.73 (t,1H), 7.80-7.84 (t,1H), 8.01 (s,1H), 8.25-8.79 (d, 1H), 8.58-8.62 (d, J=8.34Hz, 1H), 8.98 (s, 1H), 9.23-9.27 (d, J=8.38 Hz, 1H), 9.62 (br s,1H), 11.8 (br s,1H)	482 (M^+-Cl+1, 41.2), 466 (base), 440 (46.6), 424 (32.4), 382 (30.2), 364 (15.3), 352 (23.0), 350 (7.9), 340 (300), 326 (25.9), 325 (15.0), 281 (41.7), 207 (94.1), 182 (14.3), 181 (14.2), 168 (59.9), 129 (14.9), 117 (47.5), 115 (21.3)	
9	$ClCH_2$	$CO_2(CH_2)_2CH(CH_3)_2$	H	H	1.05 (d, J=6.3Hz, 6H), 1.76-1.95 (m, 3H), 4.29 (s, 2H), 4.52 (t, J=6.8Hz, 2H), 7.39 (dd, J=8.0, 8.0 Hz, 1H), 7.66 (dd, J=8.0, 8.0Hz, 1H), 7.78 (d, J=8.0 Hz, 1H), 7.95 (s,1H), 8.23 (d, J=8.0 Hz,1H), 8.54 (d, J=8.3Hz, 1H), 8.93 (s, 1H), 9.18 (d, J=8.3Hz, 1H), 9.56 (br s, 1H), 11.76 (br s, 1H).	530/532 (M^+ 2.4/1, 45) 496(58), 480(6), 454 (39), 416 (83), 382 (95), 366 (15), 340 (base).	$C_{28}H_{23}ClN_4O_5$ Calc 530.135698 Found 530.135781
10	$ClCH_2$	$CO(CH_2)_7CH_3$	H	H	0.88 (t, J=6.8 Hz, 3H), 1.23-1.70 (m,10H), 1.84-1.95 (m, 2H), 4.29 (s,2H), 4.48 (t, J=6.8Hz, 2H), 7.39 (dd, J=7.6, 7.6 Hz,1H), 7.66 (dd, J=7.6Hz, 7.6Hz, 1H), 7.79 (d, J=7.6Hz, 1H), 7.97 (s, 1H), 8.24 (d, J=7.6Hz, 1H), 8.56 (d, J=8.4Hz, 1H), 8.95 (s, 1H), 9.21 (d, J=8.4Hz, 1H), 9.58 (br s, 1H), 11.79 (br s, 1H)	573(M^+, 1), 538 (10), 496 (35), 382 (53), 366 (30), 340 (base)	$M+C_4H_{10}O_2S_2$ $C_{35}H_{40}ClN_4O_5S_2$ Calc 727.202696 Found 727.200500
11	$CH_3(CH_2)_2$	CO_2CH_3	CH_3	H	1.06 (t,J=7.6Hz, 3H), 1.75-1.90 (m, 2H), 2.52 (t, J= 7.6Hz, 2H), 3.16 (s, 3H), 4.07 (s, 3H), 7.36 (dd, J=8.0, 8.0Hz, 1H), 7.63 (dd, J=8.0, 8.0Hz, 1H), 7.70 (d, J=8.0Hz, 1H), 7.92 (s, 1H), 8.31 (d, J=8.0Hz, 1H), 8.34, (br s, 1H)	482 (M^+, base) 466 (11), 450 (13) 422 (32), 380 (9), 352 (35)	$C_{27}H_{22}N_4O_5$ Calc 482.159020 Found 482.160385
12	$CH_3(CH_2)_2$	$CO_2(CH_2)_3CH_3$	H	H	1.10 (t, 6H), 1.6 (m, 2H), 1.85-2.00 (m, 4H), 2.55 (t, 2H), 4.50 (t,2H), 7.38 (t, 1H), 7.65-7.70 (m, 2H), 7.97 (s, 1H), 8.20-8.24 (d, 1H), 8.39 (br s, 1H), 8.50-8.54 (d,J=8.3Hz, 1H), 8.92 (s, 1H), 9.13-9.23 (d, J=8.2 Hz, 1H), 11.75 (br s, 1H)	510 (M^+, 69), 494 (21.4), 446 (11.8), 417 (11.5), 410 (base), 394 (35.9), 379 (10.3), 340 (38.4) 339 (16.7), 217 (130)	$C_{29}H_{26}N_4O_5$ Calc 510.090320 Found 510.091661
13	$CH_3(CH_2)_2$	$CO_2(CH_2)_2CH(CH_3)_2$	H	H	1.04 (d, J=6.8Hz, 6H), 1.06 (t, J=7.4Hz, 3H), 1.75-1.95 (m, 5H), 2.53 (t, J=7.4Hz, 2H), 4.52 (t, J=6.8Hz, 2H), 7.39 (dd, J=7.8, 7.8Hz, 1H), 7.66 (dd, J=7.8, 7.8Hz, 1H), 7.74 (d, J=7.8Hz, 1H), 7.99 (s,1H), 8.24 (d, J=7.8Hz, 1H), 8.41 (br s, 1H), 8.55 (d, J=8.4Hz, 1H), 8.94 (s,1H), 9.18 (d, J=8.4Hz, 1H), 11.80 (br s, 1H)	524 (69), 454 (6), 410 (base), 394 (5), 340 (22)	$C_{30}H_{28}N_4O_5$ Calc 524.205970 Found 524.207494

Cmpd.	R^{10}	Y	R^4	R^6	^1H, NMR	MS	HRMS
14	$CH_3(CH_2)_2$	$CO_2(CH_2)_7CH_3$	H	H	0.86 (t, J=6.8Hz, 3H), 1.06 (t, J=7.3Hz, 3H), 1.20-1.60 (m, 10H), 1.65-1.95 (m, 4H), 2.53 (t, J=7.3Hz, 2H), 4.47 (t, J=6.8Hz, 2H), 7.36 (dd, J=8.0, 8.0Hz, 1H), 7.63 (dd, J=8.0, 8.0Hz, 1H), 7.65 (d, J=8.0Hz, 1H), 7.93 (s,1H), 8.19(d, J=8.0Hz, 1H), 8.35 (br s, 1H), 8.44 (d, J=8.4Hz, 1H), 8.87 (s,1H), 9.08 (d, J=8.4Hz, 1H), 11.67 (br s, 1H)	566 (M^+, 14), 550 (45), 534 (15), 496 (6), 410 (12), 394 (base), 378 (22), 340 (17)	$C_{33}H_{34}N_4O_5$ Calc. 566.252921 Found 566.251991
15	$(CH_3)_2CH$	$CO_2(CH_2)_3CH_3$	H	H	1.04 (t, J=7.3Hz, 7.32Hz, 3H), 1.33 (d, J=6.68Hz, 6H), 2.73 (m, J=6.76Hz, 6.88Hz, 1H), 4.49 (t, J=6.88, 6.58Hz, 2H), 7.39 (d, J=7.3Hz, 1H), 7.41 (dd, J=7.3Hz, 1H), 7.73 (dd, J=7.3Hz, 1H), 7.99 (s, 1H), 8.24 (d, J=8Hz, 1H), 8.49 (s, 1H), 8.55 (d, J=8.4Hz, 1H), 8.94 (s, 1H), 9.18 (d, J=8.4Hz, 1H), 11.8 (br s, 1H)	510/512 (M^+, base), 494 (37.1), 492 (22.4), 469 (5.8), 440 (6), 410 (18.1), 394 (35.4), 337 (9.7)	$C_{29}H_{26}N_4O_5$ Calc. 510.190320 Found 510.188750
16	CH_3	$CONH_2$	H	H	2.23 (s,3H), 7.39 (t, 1H), 7.70 (t, 1H), 7.79 (d,1H), 8.46 (br s, 1H), 8.57 (d, 1H), 9.05 (s, 1H), 9.06 (d,1H), 9.61 (s,1H), 9.77 (br s, 2H), 10.15 (d,1H), 12.39 (br s, 1H)	425 (M^+, base), 409 (50), 382 (23), 366 (31), 340 (25)	$C_{23}H_{15}N_5O_4$ Calc. 425.112404 Found 425.111507
17	CH_3	CO_2CH_3	H	H	2.38 (s, 3H), 4.12 (s, 3H), 7.40 (dd, 1H), 7.76 (dd, 1H), 7.76 (d, 1H), 8.03 (s, 1H), 8.27 (d, 1H), 8.48 (br s, 1H), 8.62 (d, 1H), 9.03 (s, 1H), 9.26 (d, 1H), 11.82 (br s, 1H)	443 (M^+3, base), 441 (23), 440 (81), 439 (14), 438 (39)	$C_{24}H_{16}O_5N_4$ Calc. 440.112070 Found 440.111984
18	CH_3	$CO_2CH_2CH_2CH(CH_3)_2$	CH_3	H	1.06 (d, 6H), 1.8-1.9 (m, 3H), 2.37 (s, 3H), 3.19 (s, 3H), 4.53 (t, 2H), 7.40 (dd, 1H), 7.60 (dd, 1H), 7.70 (d, 1H), 7.97 (s, 1H), 8.36 (d, 1H), 8.39 (br s, 1H), 8.50 (d, 1H), 9.10 (d, 1H), 11.80 (br s, 1H)	510 (M^+68), 396 (90), 354 (21), 281(16)	$C_{29}H_{26}O_5N_4$ Calc. 510.190320 Found 510.187804
19	CH_3	$CO_2CH_2CH_2N(CH_3)_2$	CH_3	H	2.37 (s,3H), 2.43 (s,6H), 2.8 (t, 2H), 3.2 (s,3H), 4.6 (t, 2H), 7.40 (dd, 1H), 7.69 (dd, 1H), 7.74 (d, 1H), 7.97 (s, 1H), 8.3 (d, 1H), 8.4 (br s, 1H), 8.5 (d, 1H) 9.10 (d, 1H), 11.80 (br s, 1H)	514 (M+3$^+$ 20), 425 (17), 397 (21), 387 (16), 355 (30), 207 (17), 155 (51), 147 (48), 119 (base)	
20	CH_3	$CO_2CH_2CH_2CH(CH_3)_2$	H	H	1.06 (d, 6H), 1.8-1.9 (m, 3H), 2.38 (s, 3H), 4.54 (t, 2H), 7.41 (dd, 1H), 7.69 (dd, 1H), 7.71 (d, 1H), 8.01 (s,1H), 8.27 (d, 1H), 8.45 (br s, 1H), 8.58 (d, 1H), 8.97 (s,1H), 9.22 (d, 1H), 11.80 (br s, 1H)	496(M^+55), 382 (100), 340 (17)	$C_{28}H_{24}O_5N_4$ Calc. 496.174610 Found 496.175570
21	CH_3	$CO_2(CH_2)_7CH_3$	H	H	0.89 (t, 3H), 1.33 (m, 10H), 1.95 (m, 2H), 2.37 (s,3H), 4.5 (t, 2H), 7.43 (dd, 1H), 7.70 (dd, 1H), 7.73 (d, 1H), 8.0 (s, 1H), 8.26 (d, 1H), 8.44 (br s, 1H), 8.6 (d, 1H), 8.97 (s, 1H), 9.2 (d, 1H), 11.8 (br s, 1H)	538 (M^+, 55), 382 (100), 366 (5), 340 (16)	$C_{31}H_{30}N_4O_5$ Calc. 538.221620 Found 538.222007

Cmpd.	R^{10}	Y	R^4	R^6	^1H, NMR	MS	HRMS
22	CH_3	$CO_2CH_2CH_2N(CH_3)_2$	H	H	2.38 (s,3H), 2.47 (s, 6H), 2.93 (t, 2H), 4.63 (t, 2H), 7.44 (dd, 1H), 7.69 (dd, 1H), 7.70 (d, 1H), 7.98 (s, 1H), 8.24 (d, 1H), 8.42 (br s, 1H), 8.5 (d, 1H), 8.96 (s, 1H), 9.17 (d, 1H), 11.79 (br s, 1H)	391 (12), 279 (10), 167 (25), 150 (17), 149 (base), 113 (26)	

EXAMPLES 23-26: PREPARATION OF QUINOLINEDIONE ALDEHYDES

The starting materials for preparing the lavendamycin analogs of Examples 1-22 include the 7-N-acyl-2-formylquinoline-5,8-diones of formula K:



wherein

$X = R^{10}\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH\text{-}$,

R^{10} is an alkyl or substituted alkyl,

R^1 = H,

R^2 = H, and

R^3 = H.

These aldehydes were prepared by the selenium dioxide oxidation of the corresponding 7-N-acyl-2-methylquinoline-5,8-diones in refluxing dioxane-H_2O as described above. Table III lists four such aldehydes prepared by this method and the reaction times, yields, ^1H NMR, MS and elemental analysis for these aldehydes. The procedures used to synthesize three of these aldehydes are described in detail below.

7-ACETAMIDO-2-FORMYLQUINOLINE-5,8-DIONE (Compound 23, Table III): A mixture of 7-acetamido-2-methylquinoline-5,8-dione **(27)** (prepared as described in Example 27) (230 mg, 1 mmol), selenium dioxide (139 mg, 1.25 mmol) in dry dioxane (3.5 mL) and water (0.13 mL) was stirred and refluxed under argon for 9 hours. A fresh grade of 99.9+% of SeO_2 (Aldrich) was used. Dioxane was purified and distilled according to the procedure described in Perrin et al., Purification Of Laboratory Chemicals (Pergammon Press 1980). Dioxane (7 mL) was added, allowed to reflux for 10 min., and then filtered hot. The residue on the filter paper was added to the reaction flask containing 20 mL of dichloromethane, refluxed for 5 min and filtered. This process was repeated four more times. The filtrates were combined and evaporated to give 222 mg (yield of 91%) of a yellow solid which was 7-acetamido-2-methyl-quinoline-5,8-dione **(23)**. An analytical sample obtained by sublimation (150-180°C/0.5 mm): mp 225°C dec.; IR (KBr) 3346, 3085, 1721, 1687, 1652, 1609, 1504, 1328, 1216, 1124, 1068, 885 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s,3,$COCH_3$), 8.05 (s,1,H-6), 8.31 (d,1,J=8Hz,H-3), 8.43 (br s,1,NH), 8.62 (d,1,J=8Hz,H-4), 10.29 (s,1,CHO); MS m/e (relative intensity) 244 (M^+, 81), 216 (19), 202 (51), 175 (37), 174 (21), 97 (19), 85 (20), 71 (30), 68 (18), 57 (34), 43 (100). Elemental analysis calculated for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N, 11.47; Found: C, 58.99; H, 3.38; N, 10.91.

7-CHLOROACETAMIDO-2-FORMYLQUINOLINE-5,8-DIONE (Compound 24, Table III): In a 25 ml. round-bottomed flask equipped with a magnetic bar, water-cooled reflux condenser, and argon-filled balloon, 7-chloroacetamido-2-methylquinoline-5,8-dione **(28)** (prepared as described in Example 28) (0.529 g., 2 mmol), selenium dioxide

(0.255 g., 2.3 mmol), 12 ml of dried, distilled 1,4-dioxane, and 0.25 ml. of water were stirred and slowly heated to reflux over a two-hour period. The reaction was monitored by TLC and allowed to go to completion (29.5 hours). The selenium was allowed to settle, and the supernatant solution was pipetted off and filtered. 1,4-Dioxane (10 ml.) was added to the residue, stirred and refluxed for five minutes. The entire mixture was filtered and the selenium was washed with dichloromethane (10 ml.). All filtrates were combined and stored at 4°C overnight. Solid precipitate from the chilled mixture was filtered yielding 0.0985 g. of crude product (yield of 18%). This was purified by recrystallization from ethyl acetate/dichloromethane. The original remaining filtrate was diluted with 50 ml of dichloromethane and washed with 3% sodium bicarbonate solution (2 x 50 ml.). The aqueous layer was then extracted with dichloromethane (2 x 20 ml.) The organic layers were dried with magnesium sulfate and rotoevaporated to give a dark orange solid. The product was dried under vacuum overnight and 0.2941 g. of product was obtained (yield of 52%, total 70%). This product could be further purified by flash chromatography and recrystallization from ethyl acetate/dichloromethane: mp 190-192°C; ^{1}H NMR ($CDCl_3$) δ 4.26 (2H, s, C-7NHCO$\underline{CH_2}$Cl), 8.04 (1H, s, C-6H), 8.33 (1H, d, J = 8.1 Hz, C-3H), 8.62 (1H, d, J = 8.1 Hz, C-4H), 9.54 (1H, br. s, C-7NH), 10.28 (1H, s, C-2CHO); IR (KBr) ν_{max} 3310, 3089, 2950, 2852, 1731, 1720, 1678, 1644, 1521, 1118 cm^{-1}; EIMS, m/e (relative intensity) 278/280 (M^+, 2.7/1, 95), 243 (33), 229 (33), 215 (55), 202 (base), 175 (61), 146 (17); HRMS, m/e for $C_{14}H_9ClN_2O_3$ calculated 278.009435, found 278.008764; analysis for $C_{14}H_9ClN_2O_3$ calculated C, 51.72; H, 2.53; Cl, 12.72; N, 10.05; Found C, 51.81; H, 2.9; Cl, 12.79; N, 9.86.

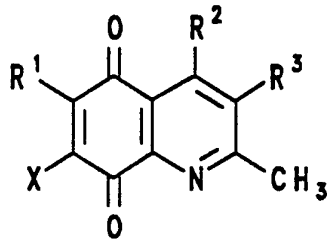
7-BUTYRAMIDO-2-FORMYLQUINOLINE-5,8-DIONE (Compound 26, Table III): In a 25 ml. round-bottomed flask equipped with a magnetic bar, water-cooled reflux condenser, and an argon filled balloon, 7-butyramido-2-methylquinoline-5,8-dione **(30)** (prepared as described in Example 30) (0.516 g., 2 mmol), selenium dioxide (0.255 g., 2.3 mmol), 12 ml. of dried, distilled 1,4-dioxane, and 0.25 ml. of water were stirred and slowly heated to reflux over a two-hour period. The reaction was monitored by TLC and found to be complete after 33.5 hours. The selenium metal was allowed to settle, and the supernatant solution was pipetted off and filtered. 1,4-Dioxane (10 ml.) was added to the residue, stirred and refluxed for five minutes. The entire mixture was filtered and the selenium was washed with dichloromethane (10 ml.). All filtrates were combined and stored at 4°C overnight. This solution was diluted with 50 ml of dichloromethane and washed with a 3% sodium bicarbonate solution (2 x 50 ml.). The organic layer was dried with magnesium sulfate and rotoevaporated to give a pale yellow product. The solid was dried under vacuum overnight and weighed 0.356 g. (yield of 65%). The product was recrystallized from ethyl acetate: mp. 208-210° C; ^{1}H NMR ($CDCl_3$) δ 1.02 (3H, t, J = 7.4 Hz, C-7NHCOCH$_2$CH$_2$CH$_3$), 1.70 - 1.89 (2H, m, 7NHCOCH$_2$CH$_2$CH$_3$), 2.52 (2H, t, J = 7.4 Hz, 7NHCOCH$_2$CH$_2$CH$_3$), 8.06 (1H, s, C-6H), 8.31 (1H, d, J = 8.0 Hz, C-3H), 8.39 (1H, br. s, C-7NH), 8.61 (1H, d, J = 8.0 Hz, C-4H), 10.28 (1H, s, C-2CHO); IR (KBr) ν_{max} 3299, 3081, 2966, 2935, 2876, 1723, 1694, 1638, 1606, 1505 cm^{-1}; EIMS, m/e (relative intensity) 272 (54), 202 (36), 175 (9); HRMS, m/e for $C_{14}H_{12}N_2O_4$ calculated 272.079707, found 272.078696; analysis for $C_{14}H_{12}N_2O_4$ calculated C, 61.76; H, 4.44; N, 10.29; found C, 61.31; H, 4.36; N, 9.94.

TABLE III

Cmpd.	R^{10}	Hr.	%Yield	mp(°C)	^1H, NMR ($CDCl_3$)	MS	Elemental Analysis or HRMS
23	CH_3	9	91	225 (dec)	2.33 (s, 3H), 8.05 (s, 1H), 8.31 (d, 1H), 8.43 (br s, 1H), 8.62 (d, 1H), 10.29 (s, 1H)	244 (M^+, 81), 216 (19), 202 (51), 175 (37), 174 (21), 97 (19), 85 (20), 71 (30), 68 (18), 57 (34), 43 (base)	Calc.: C, 59.02; H, 3.30; N, 11.47; Found: C, 58.99; H, 3.38; N, 10.91
24	$ClCH_2$	29.5	70(crude)	190-192	4.26 (s, 2H), 8.04 (s, 1H), 8.33 (d, J=8.1 Hz, 1H), 8.62 (d, J=8.1 Hz, 1H), 9.54 (br s, 1H), 10.28 (s, 1H)	278/280 (M^+, 2.7/1.95), 243 (33), 229 (33), 215 (55), 202 (base), 175 (61), 146 (17).	$C_{14}H_9ClN_2O_3$ Calc. 278.009435 Found 278.008764
25	$(CH_3)_2CH$	20	65	183-184	1.29 (d, J=7Hz, 6H), 2.67-2.72 (m, J=6.92, 6.88, 6.96 Hz, 1H), 8.06 (s, 1H), 8.3 (d, J=8Hz, 1H), 8.4 (s, 1H), 8.6 (d, J=8Hz, 1H), 10.29 (s, 1H)	272 (M^+, Base), 229 (4.5), 217 (4.1), 203 (26.4), 175 (4.7)	
26	$CH_3(CH_2)_2$	33.5	65(crude)	208-210	1.02 (t, J=7.4Hz, 3H), 1.70-1.89 (m, 2H), 2.52 (t, J=7.4Hz, 2H), 8.06 (s, 1H), 8.31 (d, J=8.0Hz, 1H), 8.39 (br s, 1H), 8.61 (d, J=8.0Hz, 1H), 10.28 (s, 1H)	272 (M^+, 54), 202 (36), 175 (9)	$C_{14}H_{12}N_2O_4$ Calc. 272.079707 Found 272.078696 Calc. C:61.76, H:4.44, N:10.29 Found C:61.31, H:4.36, N:9.94

Examples 27-30: Preparation of 7-Acetamido-2-Methylquinoline-5,8-diones

The 7-N-acyl-2-methylquinoline-5,8-diones used as starting materials in Examples 23-26 are compounds of formula **M**:



wherein

$X = R^{10}\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH\text{-}$,

R^{10} is an alkyl or substituted alkyl,

R^1 = H,

R^2 = H, and

R^3 = H.

They were prepared by one of two methods: (1) The oxidation of the corresponding acylamido compounds with potassium dichromate in glacial acetic acid as illustrated in Equation 4 above; or (2) The Diels-Alder condensation of a 1-silyloxy-azadiane with a 2-acetamido-6-bromobenzoquinone as illustrated in Equation 2 above. Table IV lists four 7-N-acyl-2-methylquinoline-5,8-diones, their % yields, melting points, elemental analyses, ^{1}H NMR and MS. The following are the detailed procedures used for the preparation of these quinolinediones.

7-ACETAMIDO-2-METHYLQUINOLINE-5,8-DIONE (Compound 27, Table IV):

This compound was prepared by the oxidation of the corresponding acylamido with potassium dichromate in glacial acetic acid. Into a 1000 ml Erlenmeyer flask, 240 ml of glacial acetic acid, and 5,7-diacetamido-2-methyl-8-acetoxyquinoline **(31)** (prepared as described in Example 31) (6.3 g, 2.0 mmol) were added. To the resulting suspension, a solution of potassium dichromate (17.64 g) in 200 ml of water was added. This black solution was magnetically stirred at room temperature for 20-24 hours. The solution was then poured into 900 ml of water and extracted with dichloromethane (5 x 200 ml). The organic extracts were washed with a solution of 5% sodium carbonate in a saturated salt solution (3 x 300 ml). The organic layer was dried overnight with anhydrous magnesium sulfate. The magnesium sulfate was filtered off, and the solvent was evaporated to leave an orange/yellow solid. The solid 7-acetamino-2-methylquinoline-5,8-dione **(27)** was dried overnight under vacuum. 2.6g of product was obtained for a yield of 56%.

7-ACETAMIDO-2-METHYLQUINOLINE-5,8-DIONE (27):

7-Acetamido-2-methylquinoline-5,8-dione **(27)** was also prepared by Diels-Alder condensation of a 1-silyloxy-azadiene with 2-acetamido-6-bromobenzoquinone. The azadiene was prepared by the reaction of methyl vinyl ketone with t-butyldimethylsilyloxyamine in the presence of molecular sieves as illustrated in Equation 2 above. In a dry 50 mL round-bottomed flask containing 5.7g of dry molecular sieve 4A°, 1.4g (0.02 mol) of freshly distilled methyl vinyl ketone in 10 mL dry dichloromethane was placed. Then a solution of the O(*tert*-butyldimethylsilyl)hydroxylamine (Aldrich) in

5 mL of dry dichloromethane was added. The mixture was stirred at room temperature under argon for 48 h and then filtered off. Evaporation of the solution under reduced pressure and fractional distillation of the residue afforded 2.04 g (51% yield, bp 67-71°C/8 mm) of azadiene. Nuclear magnetic resonance spectroscopy showed the product to be an E/Z mixture (7:3) which was used as such in the next reaction. An analytical sample of the major isomer was obtained by silica gel column chromatography using petroleum ether and then petroleum ether plus ethylacetate (200:1) as solvents. IR (liquid film) 2959, 2931, 2860, 1630, 1581, 1462, 1363, 1251, 1061, 983, 948, 871, 836, 808, 787, 674 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.15 (s,6,$Si(CH_3)_2$), 0.91 (s,9,$C(CH_3)_3$), 1.95 (s,3,C-$2CH_3$), 5.35-5.57 (m,2,=CH_2), 6.38-6.52 (m,1,=CH); MS, m/e (relative intensity) 199 (M^+, 0.3), 142 (100), 75 (68), 68 (97), 42 (20); Elemental analysis calculated for $C_{10}H_{21}NOSi$: C, 60.24; H, 10.62; N, 7.03; found: C, 60.22; H, 10.56; N, 7.10.

Then, 7-acetamido-2-methylquinoline-5,8-dione **(27)** was prepared. A solution of bromoquinone (317 mg, 1.3 mmol), 1-(*tert*-butyldimethylsilyloxy)-2-methyl-1-aza-1,3-butadiene (130 mg, 0.65 mmol) in 28 mL dry chlorobenzene was refluxed under argon for 22h. Chlorobenzene (10 mL) was added and refluxed for another 2h. The reaction mixture was allowed to cool and then put onto a silica gel column (2 x 9.5 cm). The column was eluted with ethylacetate/ petroleum ether (2:1), EtoAc and then EtOH. The solvent was removed, benzene was added, heated and filtered. Evaporation of the filtrate gave 99 mg of yellow solid **(27)** (a yield of 66%). An analytical sample recrystallized from chloroform gave mp 217°C (dec.); IR (KBr) 3339, 1750, 1714, 1679, 1651, 1609, 1588, 1510, 1370, 1314, 1222, 1131, 744, 519 cm^{-1}; ^1H NMR ($CDCl_3$) δ

2.30 (s,3,$COCH_3$), 2.75 (s,3,$ArCH_3$), 7.55 (d,1,J=8Hz,H-3), 7.909 (s,1,H-6), 8.29 (d,1,J=8Hz,H-4), 8.38 (br s,1,NH); MS m/e (relative intensity) 230 (M^+, 69), 188 (81), 161 (100), 132 (20), 93 (15), 43 (31). Analysis calculated for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17; Found: C, 62.52; H, 4.28; N, 11.93.

7-CHLOROACETAMIDO-2-METHYLQUINOLINE-5,8-DIONE (Compound 28, Table IV): This compound was prepared by the oxidation of the corresponding acylamido with potassium dichromate in glacial acetic acid. In a 500 ml. round-bottom flask equipped with a magnetic bar, 5,7-bis(chloroacetamido)-8-hydroxy-2-methylquinoline **(32)** (prepared as described in Example 32) (3.42 g., 0.01 mol) was suspended in 122 ml. of glacial acetic acid. A solution of potassium dichromate (8.8 g., 0.03 mol) in 115 ml. of water was added and the resulting dark solution was stirred at room temperature overnight. The solution was extracted with dichloromethane (12 x 50 ml.). The organic extracts were washed with 3% sodium bicarbonate solution (200 ml.), dried with magnesium sulfate, and rotoevaporated to yield a bright yellow solid. After vacuum drying, the nearly pure product weighed 1.56 g. (yield of 59%). The product was recrystallized from ethyl acetate: mp 196-200°C (dec.); ^1H NMR ($CDCl_3$) δ 2.76 (3H, s, C-2CH_3), 4.23 (2H, s, C-7NHCO$\underline{CH_2}$Cl), 7.56 (1H, d, J = 8.1 Hz, C-3H), 7.89 (1H, s, C-6H), 8.30 (1H, d, J = 8.1 Hz, C-4H), 9.48 (1H, br. s, C-7NH); IR (KBr) ν_{max} 3299, 3078, 2948, 1712, 1683, 1641, 1614, 1588, 1515, 1398, 1384, 1323, 1130 cm^{-1}; EIMS, m/e (relative intensity) 264/266 (M^+, 2.9/1, 67) 229 (62), 215 (74), 201 (43), 188 (86), 161 (base), 132 (21); HRMS, m/e for $C_{14}H_9ClN_2O_3$, calculated 264.030170, found 264.029824; analysis for $C_{14}H_9ClN_2O_3$

calculated: C, 54.46; H, 3.43; Cl, 13.40; N, 10.58; found: C, 54.19; H, 3.37; Cl, 13.29; N, 10.36.

7-BUTYRAMIDO-2-METHYLQUINOLINE-5,8-DIONE (Compound 30, Table IV): This compound was prepared by the oxidation of the corresponding acylamido with potassium dichromate in glacial acetic acid. In a 500 ml. round-bottomed flask equipped with a magnetic bar, 5,7-dibutyramido-8-butyroxy-2-methylquinoline **(34)** (prepared as described in Examples 31-34) (3.29 g., 8.25 mmol) was suspended in 122 ml of glacial acetic acid. A solution of potassium dichromate (8.8 g., 0.03 mol) in 115 ml. of water was added and stirred. The stirred suspension began to dissolve but, after two hours, more solid continued to precipitate. Dichloromethane (70 ml.) was added to promote solution. The resulting two-phase solution mixture was stirred at room temperature overnight. The two-phase solution mixture was extracted with dichloromethane (12 x 50 ml.). The organic extracts were washed with a 3 % sodium bicarbonate solution (200 ml.), dried with magnesium sulfate, and rotoevaporated to yield an orange-yellow solid. After vacuum drying, the solid weighed 1.65 g. (a yield of 77%). The product was recrystallized from ethyl acetate: mp. 188-189°C; ^{1}H NMR ($CDCl_3$) δ 1.00 (3H, t, J = 7.4 Hz, C-7NHCOCH$_2$CH$_2$CH$_3$), 1.69 - 1.82 (2H, m, C-7NHCOCH$_2$CH$_2$CH$_3$), 2.48 (2H, t, J = 7.4 Hz, C-7NHCOCH$_2$CH$_2$CH$_3$), 2.74 (3H, s, C-2CH$_3$), 7.53 (1H, d, J = 8.0 Hz, C-3H), 7.90 (1H, s, C-6H), 8.28 (1H, d, J = 8.0 Hz, C-4H), 8.36 (1H, br. s, C-7NH); IR (KBr) ν_{max} 3338, 3275, 2964, 2935, 2875, 1711, 1682, 1654, 1644, 1615, 1588, 1502, 1323, 1310, 1133 cm^{-1}; EIMS, m/e (relative intensity) 258 (81), 215 (7), 188 (base), 161 (66); HRMS, m/e for $C_{14}H_{14}N_2O_3$ calculated 258.100442, found 258.100227; analysis for $C_{14}H_{14}N_2O_3$

calculated C, 65.11; H, 5.46; N, 10.85; found C, 65.22; H, 5.51; N 10.01.

TABLE IV

Cmpd.	R^{10}	%Yield	mp(°C)	^1H, NMR ($CDCl_3$)	MS	Elemental Analysis or HRMS
27	CH_3	66	217	2.30 (s, 3H), 2.75 (s, 3H), 7.55 (d, 1H), 7.90 (s, 1H), 8.29 (d, 1H), 8.38 (br s, 1H)	230 (M^+, 69), 188 (81), 161 (100), 132 (20), 93 (15), 43 (31)	Calc. C, 62.61; H, 4.38; N, 12.17 Found C, 62.52; H, 4.28; N, 11.93
28	$ClCH_2$	59	196-200 (dec)	2.76 (s, 3H), 4.23 (s, 2H), 7.56 (d, J=8.1Hz, 1H), 7.89 (s, 1H), 8.30 (d, J=8.1Hz, 1H), 9.48 (br s, 1H).	264/266 (M^+2.9/1, 67), 229 (62), 215 (74), 201 (43), 188 (86), 161 (base), 132 (21)	$C_{14}H_9ClN_2O_3$ Calc: 264.030170 Found: 264.029824 Calc.: C, 54.46; H,3.43; N,10.58; Cl, 13.40 Found: C,54.19, H,3.37, N,10.36; Cl,13.29
29	$(CH_3)_2CH$	73	189-190 (dec)	1.26 (d, J=6.76Hz, 6H), 2.7 (m, J=6.76Hz, 1H), 2.75 (s, 3H), 7.54 (d, J=8Hz, 1H), 7.9 (s, 1H), 8.29 (d, J=8Hz, 1H), 8.42 (br s, 1H)	258 (M^+, base), 215 (25.9), 189 (41.5), 161 (266), 108 (41.1)	
30	$CH_3(CH_2)_2$	77	188-189	1.00 (t, J=7.4Hz, 3H), 1.69-1.82 (m, 2H), 2.48 (t, J=7.4Hz, 2H), 2.74 (s, 3H), 7.53 (d, J=8.0Hz, 1H), 7.90 (s, 1H), 8.28 (d, J=8.0Hz, 1H), 8.36 (br s, 1H)	258 (M^+, 81), 215 (7), 188 (base), 161 (66)	$C_{14}H_{14}N_2O_3$ Calc 258.100442 Found 258.100227 Calc. C,65.11; H,5.46; N,10.85 Found: C,65.22; H,5.51; N,10.91

Examples 31-34: PREPARATION OF 5,7-DIACYLAMIDO-8-ACETOXY-2-METHYLQUINOLINES

These compounds, which were used as starting materials for the preparation of the 7-N-acyl-2-methyl-quinoline-5,8-diones of Examples 27-30, were prepared by the reduction of 5,7-dinitro-8-hydroxy-2-methylquinoline by molecular hydrogen in the presence of palladium on charcoal (Pd/C) followed by treatment with the desired anhydrides as illustrated in Equation 5 above. Table V lists four 2-methylquinolines prepared by this method, their % yields, melting points, elemental analysis, ^{1}H NMR and MS. The following procedures were used to prepare these compounds. Also, the preparation of 5,7-dinitro-8-hydroxy-2-methylquinoline is described; this compound was prepared according to a literature method.

PREPARATION OF 5,7-DIACETAMIDO-2-METHYL-8-ACETOXYQUINOLINE (Compound 31, Table V): Into a 500 ml hydrogenation bottle, 5,7-dinitro-8-hydroxy-2-methyl-quinoline **(47)** (preparation described below) (6.03 g, 24.2 mmol), water (100 ml), and concentrated HCl (13 ml) were added. To this suspension, 5% Pd/C (2.00 g) was added as a catalyst. This mixture was hydrogenated at 40 psi overnight or until no more hydrogen is absorbed. This reaction takes approximately four hours.

The resultant solution was then carefully vacuum filtered to remove the Pd/C. Note: Do not rinse the Pd/C that is on the filter paper with water. This will dilute the solution which is concentration-sensitive. The filtrate should take up, at most, 130 ml.

The filtrate was transferred to a 500 ml beaker. To the filtrate, sodium sulfite (2.85 g),

sodium acetate (3.58 g), and acetic anhydride (2.5 ml) were added with stirring using a magnetic stirrer. Generally, no precipitate formed. After 30 minutes, the same amounts of the above three compounds were added again. The addition of acetic anhydride (7.5 ml) caused an orange/white precipitate to form. Note: If no precipitate forms, remove the solvent under reduced pressure and heat until a small amount of solution is obtained. Add the three compounds (sodium sulfite, sodium acetate, and acetic anhydride) in small quantities (approximately one-quarter of that required in the procedure), and then wait 15 minutes. Next add 5 ml acetic anhydride and stir the mixture vigorously. Add small amounts of sodium sulfite and sodium acetate while vigorously stirring for 10 minutes. Stop the stirring and allow the mixture to stand, the precipitate should then form. This problem can be avoided, however, by following the prescribed procedure exactly as written. The mixture was then vacuum filtered, and the precipitate was washed three times with water (3 x 100 ml). This process washed the orange color out of the precipitate, and left a white solid on the filter paper. The filtrate was evaporated down to one-quarter of its volume. Any precipitate that formed was filtered and washed, as above. The filtrate was treated with sodium acetate and acetic anhydride again until no more precipitate was formed (Note: The addition of the acetic anhydride is what generally causes more precipitate to form). All washed precipitates were combined and allowed to dry overnight under the hood or on a vacuum pump. The yield was 80% (6.05g of product, mp 255°C).

5,7-BIS(CHLOROACETAMIDO)-8-HYDROXY-2-METHYLQUINOLINE (Compound 32, Table V): In a 500 ml heavy-walled hydrogenation bottle, 8-hydroxy-2-methyl-5,7-dinitroquinoline **(47)** (5.25 g., 0.021 mol) and 5% Pd/C (1.75 g.) were suspended in 90 ml. of water and 9 ml. of concentrated HCl. This mixture was shaken under 30 psi of hydrogen for 20 hours. The catalyst was filtered off, and the dark red solution containing the dihydrochloride salt of 5,7-diamino-8-hydroxy-2-methylquinoline was placed in a 250 ml. rounded-bottomed flask equipped with a magnetic bar. To this stirred solution was added in sequence as quickly as possible, sodium sulfite (12 g.), sodium acetate (16 g.), and chloroacetic anhydride (65 g.). Heat was evolved, and the formation of a light colored, thin precipitate occurred. After 15 minutes of stirring the precipitate dissolved. An additional amount of chloroacetic anhydride (5 g.) was added and the reaction mixture stirred for one hour. The solution was concentrated under reduced pressure until a precipitate appeared. This mixture was poured into a 400 ml beaker containing 100 ml. of ice-water and stirred for 5 minutes. The mixture was vacuum filtered and the product was washed with cold ethanol, dried under vacuum and collected (2.14g.). The filtrate, upon standing overnight, yielded an additional amount of product (1.47 g.). Total weight of the product was 3.61 g. (a yield of 50%). The product was recrystallized from ethanol and water: mp 194-196°C (dec.); ^{1}H NMR (DMSO-d_6) δ 2.71 (3H, s, C-2CH_3), 4.37 (2H, s, $COCH_2Cl$), 4.44 (2H, s, $COCH_2Cl$), 7.43 (1H, d, J = 8.8 Hz, C-3H), 8.15 (1H, d, J = 8.8 Hz, C-4H), 8.16 (1H, s, C-6H), 9.89 (1H, br s, NH), 10.18 (1H, br s, NH); IR (KBr) ν_{max} 3392, 3361, 3262, 3005, 2950, 1680, 1660, 1646, 1557, 1523, 1508, 1456, 1416 cm^{-1}; EIMS, m/e

(relative intensity) 341/343 (M^+, 1.5/1, 52), 305 (60), 292 (base), 264 (28), 250 (7), 228 (60), 214 (10), 200 (12), 188 (70), 173 (11), 160 (17); HRMS, m/e for $C_{14}H_{13}Cl_2N_3O_3$ calculated 341.033397, found 341.033888; analysis for $C_{12}H_{13}Cl_2N_3O_3$, calculated C, 49.14; H, 3.83; Cl, 20.72; N, 12.28; found, C, 49.24; H, 3.89; Cl, 20.43; N, 12.16.

5,7-DIBUTYRAMIDO-8-BUTYROXY-2-METHYLQUINOLINE (Compound 34, Table V): In a 500 ml heavy-walled hydrogenation bottle, 8-hydroxy-2-methyl-5,7-dinitroquinoline **(47)** (5.0 g., 0.02 mol) and 5% Pd/C (1.5 g.) were suspended in 100 ml. of water and 12 ml. of concentrated HCl. This mixture was shaken under 30 psi of hydrogen for 15 hours. The catalyst was filtered off, and the dark red solution containing the dihydrochloride salt of 5,7-diamino-8-hydroxy-2-methylquinoline was placed in a 250 ml. round-bottomed flask equipped with a magnetic bar. To this stirred solution, was added in sequence as quickly as possible, sodium sulfite (12 g.), sodium acetate (16 g.), and butyric anhydride (65 ml.). The thick whitish precipitate which continued to form over a 3-hour period was filtered and washed with water. After vacuum drying, the product weighed 7.4 g (a yield of 93%). Since recrystallization with methanol-water resulted in the hydrolysis of the butyrate, analyses were performed on the crude product: mp. 195-205°C (dec.); ^{1}H NMR (DMSO-d_6) δ 0.92 (3H, t, J = 8.0 Hz, $NHCOCH_2CH_2\underline{CH_3}$), 0.96 (3H, t, J = 8.0 Hz, $NHCOCH_2CH_2\underline{CH_3}$), 1.08 (3H, t, J = 8.0 Hz, $OCOCH_2CH_2\underline{CH_3}$), 1.52 - 1.72 (4H, m, 2 $NHCOCH_2\underline{CH_2}CH_3$), 1.73-1.89 (2H, m, $OCOCH_2\underline{CH_2}CH_3$), 2.30-2.40 (4H, m, $2NHCO\underline{CH_2}CH_2CH_3$), 2.58 (3H, s, C-$2CH_3$), 2.70 (2H, t, J = 8.0 Hz, $OCO\underline{CH_2}CH_2CH_3$), 7.37 (1H, d, J = 8.8 Hz, C-3H), 8.21 (1H, d, J = 8.8 Hz, C-4H), 8.24

(1H, s, C-6H), 9.65 (1H, br s, C-5NH), 9.94 (1H, br s, C-7NH); IR (KBr) ν_{max} 3343, 3258, 2964, 2935, 2874, 1738, 1693, 1656, 1630, 1541, 1505 cm^{-1}.

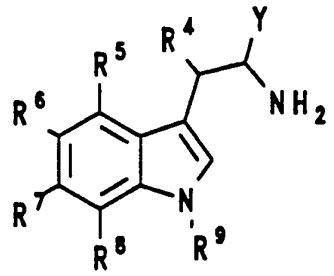
8-HYDROXY-2-METHYL-5,7-DINITROQUINOLINE (Compound 47): Compound **47** was prepared according to the method described in Boger et al., J. Org. Chem., 50, 5782 (1985). In a 500 ml. Erlenmeyer flask, equipped with a magnetic bar was placed 300 ml. of a 70% (v/v) solution of concentrated nitric acid - sulfuric acid. The solution was stirred and cooled in an ice bath. To this stirred, chilled solution, 8-hydroxy-2-methylquinoline (30.0 g., 0.188 mol) was added in small portions over a ten minute period. Upon addition of the 8-hydroxy-2-methylquinoline, a brownish gas was evolved. The mixture was continually stirred in the ice bath for two hours. The mixture was then poured into a 2 L. beaker containing 1200 ml. ice water (1:2, ice:water) and stirred vigorously with a glass rod. The bright yellow precipitate was vacuum filtered, washed with ethanol (300 ml.), and then washed with ethyl ether (2 x 300 ml.). The resulting 8-hydroxy-2-methyl-5,7-dinitroquinoline was left to air dry overnight and then further dried under vacuum for 24 hours. The yellow solid weighed 28.1 g. (a yield of 60%): mp. 295-300°C; ^1H NMR (DMSO-d_6) δ 2.93 (3H, s, C-2CH_3), 8.13 (1H, d, J = 9.1 Hz, C-3H), 9.20 (1H, s, C-6H), 9.65 (1H, d, J = 9.1 Hz, C-4H); IR (KBr) ν_{max} 3067, 1593, 1527, 1336, 1320, 1299, 1259 cm^{-1}.

Table V

Compd	R^{18}	% Yield	mp°(C)	^1H NMR (DMSO)	MS	Elemental Analysis or HRMS
31	CH_3	80	284 (dec)	2.14 (s, 3H), 2.15 (s, 3H), 2.41 (s, 3H), 2.60 (s, 3H), 7.37 (d, 1H), 8.24 (d, 1H), 8.31 (s, 1H), 9.75 (s, 1H), 10.02 (s, 1H)		Calc. C-60.94, H-5.43, N-13.33 Found C-61.15, H-5.39, N-13.27
32	$ClCH_2$	50	194-196 (dec)	2.71 (s, 3H), 4.37 (s, 2H), 4.44 (s, 2H), 7.43 (d, J=8.8 Hz, 1H), 8.15 (d J=8.8 Hz, 1H), 8.16 (s, 1H), 9.89 (br s, 1H), 10.18 (br s, 1H)	341/343 (M^+ 1.5/1, 52), 305 (60), 292 (base), 264 (28), 250(7), 228 (60), 214 (10), 200 (12), 188 (70), 173 (11), 160 (17)	$C_{14}H_{13}Cl_2N_3O_2$ Calc 341.033397 Found 341.033888
33	$(CH_3)_2CH$	75 (crude)	245-247 (dec)	1.12 (d, J=6.8Hz, 6H), 1.19 (d, J=6.8Hz, 6H), 1.38 (d, J=7Hz, 6H), 2.6 (s, 3H), 2.84-2.72 (m, 2H), 3.04-3.01 (m, 1H), 7.4 (d, J=8.8Hz, 1H), 8.13 (s, 1H) 8.23 (d, J=8.8Hz, 1H), 9.62 (br s, 1H), 9.92 (br s, 1H)	399 (M^+, 0.2), 329 (base), 286 (67.9), 259 (39.4), 241 (12.9), 188 (75.2)	
34	$CH_3(CH_2)_2$	93 (crude)	200-208 (dec)	0.73 (t, J=7.0Hz, 3H), 0.76 (t, J=7.0Hz, 3H), 1.33-1.55 (m, 4H), 2.1-2.3 (m, 4H), 2.3 (s, 3H), 7.17 (d, J=8.8Hz, 1H), 7.82 (s, 1H), 7.90 (d, J=8.8Hz, 1H), 9.28 (br s, 1H), 9.52 (br s, 1H)	329 (95), 286 (20), 259 (98), 241 (17), 216 (6), 188 (base), 161 (13)	$C_{16}H_{22}N_3O_2$ Calc. 329.173942 Found 329.173043

Examples 35-46: Preparation of Tryptophan Analogs

The tryptophan analogs used for the synthesis of lavendamycin analogs **1-22** are listed in Table VI. They have formula **L**:



wherein R^5, R^7, R^8 and R^9 are H, and R^4, R^6 and Y are as given in Table VI below. Tryptophan esters **36**, **37**, and **44-46** (see Table VI) were synthesized as illustrated in Equation 6 above. Tryptophan esters **40-41** (see Table VI) were synthesized as illustrated in Equation 7 above. The procedures used for the synthesis of all of the tryptophan analogs are described below.

Tryptophan Esters 36, 37 and 44-46 (Table VI): Tryptophan (or β-methyltryptophan) (3g, 0.015 mol) and dry HCl-saturated isoamyl alcohol (or other alcohols) (180 ml) were stirred and refluxed for 24 hr. The reaction mixture was rotoevaporated to give a white crystal salt. After it was washed with ether, the salt was neutralized with 14% NH_4OH in 25 ml ethyl acetate. Then, it was washed with water and dried with anhydrous magnesium sulfate. Finally, it was roto-evaporated to give 33.21g colorless oil (or crystal) (yield 80-90%).

Tryptophan Esters 40 and 41 (Table VI):

(1) Carbobenzoxy-tryptophan (or Carbobenzoxy-β-Methyltryptophan): A mixture of tryptophan (4.1g, 0.02 mol) (or β-methyltryptophan), NaOH (2N, 10 ml), water (20 ml), benzylchloroformate (3.4g., 0.02 mol, in 2.2 ml of toluene) was stirred in an ice bath. Another 5 ml of NaOH (4N) was added dropwise over 20 minutes and stirred for an additional 10 minutes. The mixture was acidified to Congo Red with hydrochloric acid, filtered, washed with cold water and dried to give 5.86 g. product (yield 87%). N-CBZ-β-methyltryptophan was produced in a yield of 93%.

(2) N-CBZ-Tryptophan (or N-CBZ-β-Methyltryptophan) N,N-Dimethylethylamino Ethyl Ester: N-CBZ-tryptophan (3.384 g., 0.01 mol) (or N-CBZ-β-methyltryptophan), N,N-dimethylaminoethylchloride (2.1 N benzene solution, 6 ml), ethyl acetate (20 ml) was stirred and heated. Triethylamine (1.4 ml) was added dropwise, and the mixture was then refluxed 5 hr. and filtered. The filtrate was washed with saturated NaCl in water, 5% $NaHCO_3$ and saturated NaCl in water, dried with anhydrous $MgSO_4$, rotaryevaporated to give 1.76 g. of a spongy gel (a yield of 43%). N-CBZ-β-methyltryptophan-N,N-dimethylethylaminoethyl ester was produced in a yield of 81%.

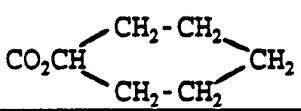
(3) Tryptophan (or β-Methyltryptophan) N,N-Dimethylethylamino Ethyl Ester: A mixture of ammonium formate (125 mg) and N-CBZ-tryptophan-N,N-dimethyl-ethylaminoethyl ester (205 mg, 0.5 mmol) (or N-CBZ-β-methyltryptophan-N,N-dimethylethylaminoethyl ester), DMF (5 ml), 10% Pd/C (100 mg) was stirred under argon at room temperature for 30 minutes and then filtered.

The filtrate was rotaryevaporated to an oil. Chloroform (10 ml) was added to the oil and filtered again. The filtrate was rotaryevaporated to dryness and dissolved in ethyl acetate (25 ml), washed with 3 x 5 ml saturated NaCl solution, dried over anhydrous $MgSO_4$, evaporated in a vacuum to give 101 mg of the oily product (a yield of 74%). β-methyltryptophan N,N-dimethylethylamino ethyl ester was produced in a yield of 68%.

Tryptophan Analogs 35, 38, 42 and 43 (Table VI): These compounds are commercially available as the hydrochloride salts. They were converted to the free amines by neutralization with 14% ammonium hydroxide, followed by extraction with ethyl acetate.

Tryptophan Ester 39 (Table VI): This compound was made as described in Behforouz et al., J. Heterocycl. Chem., 25, 1627 (1988).

TABLE VI

Compound	R^4	R^6	Y
35	H	H	CO_2CH_3
36	CH_3	H	$CO_2CH_2CH_2CH(CH_3)_2$
37	H	H	$CO_2CH_2CH_2CH(CH_3)_2$
38	H	H	$CO_2(CH_2)_7CH_3$
39	CH_3	H	CO_2CH_3
40	H	H	$CO_2CH_2CH_2N(CH_3)_2$
41	CH_3	H	$CO_2CH_2CH_2N(CH_3)_2$
42	H	H	$CO_2(CH_2)_3CH_3$
43	H	H	CO_2NH_2
44	H	H	
45	H	OCH_3	$CO_2(CH_2)_3CH_3$
46	H	F	$CO_2(CH_2)_3CH_3$

Example 47: In Vitro Cytotoxicity

The in vitro cytotoxicity of some of the lavendamycin analogs was determined according to the methods described below against a panel of five cell types. A few quinoline diones were also tested for cytotoxicity.

A. Cell Lines and Culture Conditions. Stock cultures of normal rat kidney epithelial (NRKE) cells [De Larco et al., J. Cell Physiol., 94, 335 (1978)] and Lewis lung carcinoma cells [Suguira et al., Cancer (Phila.), 5, 382 (1952)] were obtained from the American Type Culture Collection (ATCC, Rockville, MD). Both cell lines were grown in antibiotic-free culture medium [Dulbecco's high glucose MEM supplemented with 10% fetal bovine serum]. The cell number of the Lewis lung and NRKE cell lines was expanded by 5 passages, and the cell lines were stored in liquid nitrogen, all according to standard procedures [Freshney, Culture of Animal Cells: A Manual of Basic Technique, pages 6, 216-225 (2nd ed. 1987)]. These cryopreserved cells were used for the assays described below. All cell lines were grown using standard cell culture methods. [Freshney, Culture Of Animal Cells: A Manual Of Basic Technique, page 127 (2nd ed. 1987)] All cell culture manipulations were done under gold fluorescent light to prevent damage by photooxidation.

B. Selection of Transformed Cells and Oncogene Transfections. NRKE cells transformed by the ras^K, ras^N, and ras^H oncogenes were used in the panel. Only transformants with a minimal deviation phenotype as compared to NRKE cells were used. Transformants with this phenotype have a low oncogene copy number and in vitro growth characteristics the same as

nontransformed NRKE cells. These criteria were chosen so that compounds were evaluated for antitumor activity, rather than anti-growth activity based on the rate of cell division.

The ras oncogene-transformed NRKE cells were prepared as follows. The plasmids pUCEJ6.6 (no. 41028), containing a transforming human ras^H gene, pNRsac (no. 41031) containing a transforming human ras^N gene, pKSma (no. 41048), containing a v-ras^K gene, and the RSVneo gene were obtained from the ATCC. NRKE cells were cotransfected with an oncogene plus the RSVneo gene using standard calcium phosphate coprecipitation and neomycin resistance selection methods. [Davis et al., Basic Methods In Molecular Biology, 285 (1985)]. Approximately 14 days after transfection and selection with G-418 antibiotic (Sigma Chemical Co., St. Louis, MO), colonies were isolated by the ring cloning procedure. [Freshney, Culture Of Animal Cells: A Manual Of Basic Technique (2nd ed. 1987)]. The clones were stored in liquid nitrogen after expansion of their cell number by 4 passages in culture medium with G-418. Approximately 50 clones were evaluated by several criteria for their use in the in vitro cytotoxicity and in vivo antitumor tests described below. The criteria used to select clones were the following: (1) the clone had to have the same growth rate as the parental NRKE cells, (2) the growth rate of the clone must be stable with repeated passage (e.g., up to 100 subcultures), and (3) they must be tumorigenic in immunologically deficient mice. Criteria 1 and 2 are key to assuring the differential cytotoxicity assay selects for compounds that have antitumor activity rather than a general anti-growth activity. Oncogene copy number was determined using standard Southern blotting procedures [Current

Protocols in Molecular Biology, Chapter 2, Frederick M. Ausuhel et al. eds., 1987 - 1992]. Cell growth characteristics were evaluated using standard methods (Freshney, Culture of Animal Cells: A Manual of Basic Technique, pages 227-244 (2nd ed., 1987)].

The clones K/1-NRKE, transformed by v-ras^K gene, H/1.2-NRKE, transformed by the human ras^H gene, and N/4.2-NRKE transformed by the human ras^N gene, were selected for in vitro cytotoxicity and in vivo antitumor testing. These clones have 3 to 4 oncogene copies that are stably integrated. The in vitro doubling time of these cells is 24 hours, which is the same as NRKE cells.

C. In Vitro Cytotoxicity Assay. Compounds were screened for antitumor activity with an oncogene-based differential cytotoxicity assay. With this assay the cytotoxic action of compounds against oncogene-transformed cells relative to their action against the nontransformed parent epithelial cells was determined. For the evaluation of compounds, the Lewis lung carcinoma was used as a murine reference tumor. This tumor is commonly used in screens for new oncolytics. The differential cytotoxicity assay can identify compounds that interact directly with oncogene proteins, but more importantly it can also find compounds that interfere with the biochemical pathways activated or driven by oncogenes. The inhibitory action in both cases may be specific for a transformed cell.

Briefly, the procedure used for the differential cytotoxicity assay is as follows. Cell suspensions were prepared by trypsin dissociation using standard methods [Freshney, Culture Of Animal Cells: A Manual Of Basic Technique, page 132], and 50 cells were

seeded into each well of 12-well culture dishes. Groups of triplicate wells were divided into media control, drug vehicle-control and drug treatment groups. One day after seeding, media was replaced with media containing vehicle or drugs, and the cultures were incubated for an additional 5 days.

After exposure to the vehicles or drugs, the cultures were washed, fixed and stained with a modification of Mallory's stain. [Richardson et al., Stain Technol., 35, 313 (1960)]. Colony number and colony area were determined with an Artek model 982 image analyzer (Artek System Corp., Farmington, N.Y.). The cytocidal action of compounds was determined from the colony number as originally described by Puck and Marcus, J. Exp. Med., 103, 653 (1956). Colony areas were normalized for colony number and were used to determine if a compound had a cytostatic action. The concentration giving 50% cell kill (LC_{50}) was determined, and a differential index of cytotoxicity was determined by dividing the LC_{50} value for the normal epithelial cells by the LC_{50} value for the tumor cells. The differential index value was used to determine the amount of selective toxicity a compound had for the tumor cells. All data analysis was performed using SAS software [SAS Users Guide: Statistics (Version 5 edition, SAS Institute Inc., Cary, N.C. 1985)] on a VAX 8300 computer. The results are shown in Tables VII, VIII and IX.

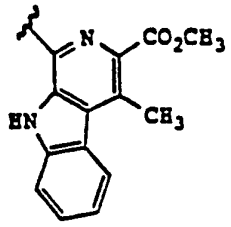
TABLE VII

Compound	LC_{50} (μM)			
	NRKE	K/1	H/1.2	3LL
27; R^{15}=NHAc R^1, R^3=H, R^{16}=CH_3	2.4	5.9	4.4	2.0
23; R^{15}=NHAc R^1, R^3=H, R^{16}=CHO	1.3	2.6	2.5	1.2
48; R^{15}=NHAc R^1, R^3=H, R^{16}=COOH	>33	>33	31	26
49; R^{15}=NHAc R^1=H, R^3=CH_3, R^{16}=H	1.3	1.8	1.1	1
50; R^{15}=NH_2 R^1=H, R^3=CH_3, R^{16}=H	0.8	1.3	0.6	0.8
51; R^{15}=NH_2 R^1, R^3=H, R^{16}=CHO	2.4	4.3	2.2	2.3
52; R^{15}=H, R^1=NHAc, R^3=H, R^{16}=CH_3	21.5	>33	20	>33
53; R^{15}=OCH_3, R^1, R^3=H, R^{16}=CH_3	6.9	11.8	4.2	7.4
54; R^{15}=$O(CH_2)_4OH$, R^1, R^3=H, R^{16}=CH_3	10.5	13.5	10.5	3.8
1; R^{15}=NHAc, R^1, R^3=H, R^{16}=BC	0.9	0.1	0.7	>33
55; R^{15}=NH_2, R^1, R^3=H, R^{16}=BC	0.1	0.2	0.1	0.5

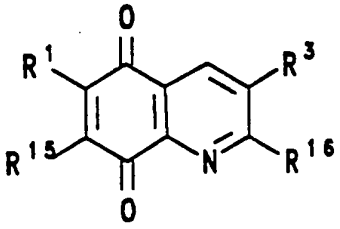
NRKE = Normal Rat Kidney Epithelial Cells.
K/1 = $\underline{ras}^K$ Transformed NRKE Cells.
H/1.2 = $\underline{ras}^H$ Transformed NRKE Cells.
3LL = Lewis Lung Carcinoma Cells.

Ac = $CH_3C(=O)-$

BC = β-carboline moiety having the formula:



In Table VII, the compounds tested have the following formula:



Compounds **1**, **23** and **27** were prepared as described in Examples 1, 23 and 27. Compounds **49** and **52** were prepared according to Equation 2. Compound **48** was obtained by the oxidation of **23**. Treatment of **27** with methanol in the presence of acid gave **53**, and treatment of **27** with tetrahydrofuran in the presence of acid gave **54**. Compounds **50**, **51** and **55** were obtained by the acid hydrolysis of **49**, **23** and **1** respectively.

In Table VIII and IX, the compounds tested have the following formula:

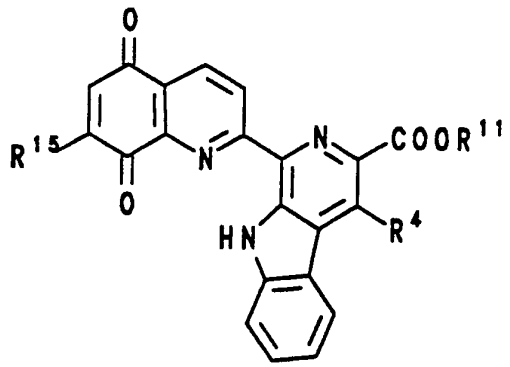


TABLE VIII

Compound	Substituent			LC50 (μM)				
	R^{15}	R^{11}	R^4	NRKE	H/1.2	K/1	N/4.2	3LL
1	NHAc	CH_3	CH_3	0.90	0.70	0.10	N.T.	>33.00
17	NHAc	CH_3	H	0.50	0.51	0.11	0.52	0.84
18	NHAc	$CH_2CH_2CH(CH_3)_2$	CH_3	4.61	4.30	5.00	3.89	7.40
19	NHAc	$CH_2CH_2N(CH_3)_2$	CH_3	0.09	0.09	0.06	0.09	0.48
20	NHAc	$CH_2CH_2CH(CH_3)_2$	H	1.62	1.42	0.09	1.50	1.69
21	NHAc	$(CH_2)_7CH_3$	H	>33.00	7.60	0.25	9.00	>33.00
22	NHAc	$CH_2CH_2N(CH_3)_2$	H	0.37	0.24	0.14	0.29	0.50
55	NH_2	CH_3	CH_3	0.1	0.1	0.2	N.T.	0.5

TABLE IX

Compound	Substituent			Differential Index			
	R^{15}	R^{11}	R^{4}	H/1.2	K/1	N/4.2	3LL
1	NHAc	CH_3	CH_3	1.29	9.00	—	>0.03
17	NHAc	CH_3	H	0.98	4.55	0.96	0.59
18	NHAc	$CH_2CH_2CH(CH_3)_2$	CH_3	1.07	0.92	1.19	0.62
19	NHAc	$CH_2CH_2N(CH_3)_2$	CH_3	1.00	1.50	1.00	0.19
20	NHAc	$CH_2CH_2CH(CH_3)_2$	H	0.62	18.00	1.08	0.96
21	NHAc	$(CH_2)_7CH_3$	H	>4.3	>132.00	>3.66	~1.00
22	NHAc	$CH_2CH_2N(CH_3)_2$	H	1.54	2.64	1.28	0.74
55	NH_2	CH_3	CH_3	1.0	0.50	—	0.20

N.T. = Not tested

N/4.2 = *ras*^{K} transformed NRK cells

See Table VII for NRK, K/1, H/1.2, 3 LL and Ac.

As shown in Table VIII, the lavendamycin analogs **1** and **17-22** were all toxic to one or more of the tumor cells tested. The lavendamycin analogs also generally showed selective cytotoxicity against the *ras*^{K} oncogene bearing cells (see Tables VIII and IX). In particular, lavendamycin analogs **1**, **20**, and **21** showed unprecedented highly selective toxicity (9-, 18-, and 132-fold, respectively) against *ras*^{K} oncogene bearing tumor cells as compared to the normal, non-transformed cells. By comparison, the prior art compound lavendamycin methyl ester **55** has a selective toxicity of 0.5 (Table IX).

Example 48: In Vivo Activity Against Tumors

The antitumor activity of N-acetyl-lavendamycin methyl ester (**1**), N-acetyldemethyl-lavendamycin isoamyl and *n*-octyl esters (**20** and **21**) and cyclophosphamide (CY) (reference) were evaluated

against K/1-NRKE tumor (*ras*^{K}-transformed NRKE cells) grown as a xenograft in nude mice.

1. The Mice

Female CD1 nu/nu nude and female C57B1/6 mice were obtained from Charles Rivers, Inc. Animals were housed in plastic shoebox type cages covered with a microisolator top. All animal feed, water, bedding and cages were sterilized. The animals were provided water (pH 3.0) and Purina mouse diet ad libitum. All animal manipulations were done with sterile procedures in a 100% exhaust, vertical laminar flow, HEPA filtered hood. To maintain consistent tumor growth, only mice between 4 and 6 weeks of age were used.

2. Tumor Implantation And Measurement

Transformed cells obtained by oncogene transfection of NRKE cells as described in Example 47 above were grown as xenograft tumors in the female CD1 nu/nu mice. Transformed cells grown in vitro through passage 7 were used to establish the xenografts. The Lewis lung carcinoma was grown as a syngeneic tumor in C57B1/6 mice as described previously in Merriman et al., Cancer Research, 49, 4509-4516 (1989). Tumors were initiated by the subcutaneous implantation of 1 x 10^6 cells approximately 1 cm from the first mammary gland. After implantation, the mice were randomized and divided into treatment groups of 10 mice per group. Starting one day after tumor implantation, the mice were dosed IP with drug daily for 8 days as described in the next section. On day 10, tumor mass was determined as described by Tomayko and Reynolds, Cancer Chemother. Pharmacol., 24, 148-154 (1989) with the following ellipsoid volume equation:

Mg tumor = 1/2 (length x width x height)

Percent inhibition of tumor growth was calculated from the ratio of the tumor mass for the drug treated animals relative to the mass for the vehicle treated animals. All animals were weighed at the beginning and end of treatment to determine if inhibition of tumor growth was due to weight loss.

Adenocarcinomas are produced in female CD1 nu/nu nude mice approximately 3 days after the subcutaneous implantation of 1 x 10^6 cells. These tumors grow with a doubling time of 24 hours. In contrast, no tumors are produced in nude mice up to one year after the subcutaneous implantation of 10^8 parent NRKE cells.

3. Drug Treatment

CY was dissolved in isotonic saline, **20** and **21** were dissolved in corn oil, and **1** was dissolved in 10 percent emulphor 620 in Dulbecco's phosphate buffered saline. It should be noted that **1** was poorly soluble in this vehicle. Starting 1 day after tumor implantation, drugs were administered interperitoneally (IP) at the doses given in Table X. CY and compounds **20** and **21** were given once daily for 8 days. Compound **1** was administered in three doses per day at lower dose levels, and the animals were treated for 7 days. On day 10, tumor masses, percent inhibition of tumor growth, and weight changes were determined.

4. Results

The results, presented in Table X, show that the three lavendamycin analogs **1**, **20** and **21** gave excellent tumor growth inhibition in vivo. Other investigators have found that a dose of 100mg/kg/day of

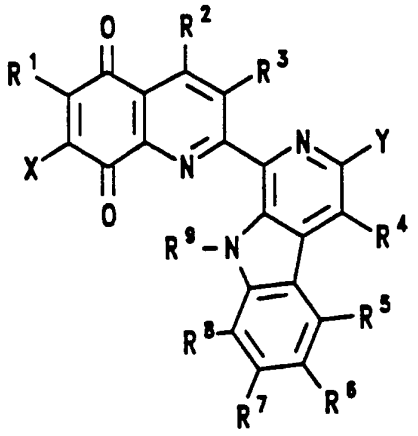
lavendamycin and related compounds is lethal, but compounds **1**, **20** and **21** showed little or no toxicity even at doses up to 300 mg/kg/day. The weight loss induced by compound **20** may be due to the presence of the isoamyl group, and replacement of this group by groups having an even number of carbons may reduce the slight toxicity. Since compounds **1** and **21** showed no toxicity, use of higher dose levels may increase the inhibition of tumor growth with little or no toxicity.

Table X

Compound	Dose (Mg/Kg/Day)	Number Dead / Number Treated	Percent Wt. Change (g)	Percent Inhibition Of Tumor Growth
20	150 300	0/7 0/7	-11.5 ± 0.05 -15.7 ± 0.08	88 ± 5 89 ± 12
21	150 300	0/7 0/7	+2.0 ± 0.12 -1.0 ± 0.05	34 ± 16 78 ± 13
CY	60	0/7	-3.0 ± 0.09	97 ± 2
1	10 30 100	0/7 0/7 0/7	+8.4 ± 0.68 +9 ± 0.54 +2.5 ± 1.70	10 ± 14 26 ± 18 69 ± 5

WE CLAIM:

1. A compound having the following formula:



wherein,

X is R^{10}-C(=O)-NH- or

R^{10}-C(=S)-NH-,

Y is H, OR^{11}, SR^{11}, $N(R^{11})_2$, $NR^{11}N(R^{11})_2$, a halogen atom, NO_2, CN,

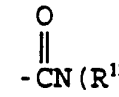
R^{11}-C(=NR^{11})-,

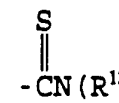
R^{12}-C(=O)-,

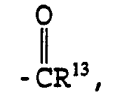
R^{12}-C(=S)-, or

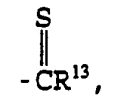
an alkyl, aryl, cycloalkyl, alkynyl, alkenyl or heterocyclic residue, each of which may be substituted or unsubstituted,

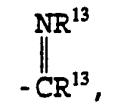
R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8, which may be the same or different, each is independently H, a halogen atom, NO_2, CN, OR^{13}, SR^{13}, $N(R^{13})_2$,





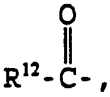


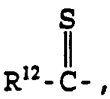




an alkyl, aryl, cycloaklyl, alkenyl, alkynyl, or heteroalkyl, heterocyclic, heteroalkenyl or heteroalkynyl residue, each of which may be substituted or unsubstituted,

R^9 is H,





an alkyl, cycloalkyl, aryl, alkenyl, alkynyl or heterocyclic residue, each of which may be substituted or unsubstituted,

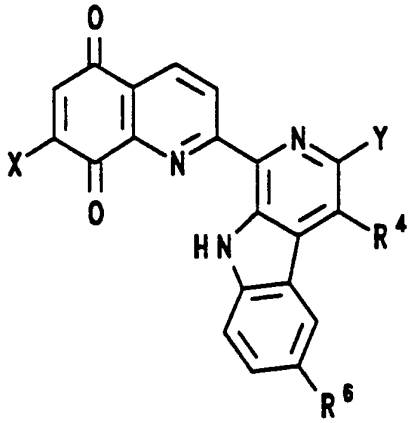
R^{10}, R^{11} and R^{13}, which may be the same or different, each is independently H or an alkyl, cycloalkyl, alkenyl, alkynyl, aryl or heterocyclic residue, each of which may be substituted or unsubstituted,

R^{12} is H, $N(R^{11})_2$, OR^{11}, SR^{11}, $NR^{11}N(R^{11})_2$, $OR^{14}N(R^{11})_2$, or an alkyl, cycloalkyl, aryl, alkenyl, alkynyl or heterocyclic residue, each of which may be substituted or unsubstituted, and

R^{14} is an alkylene residue, and

the salts thereof.

2. The compound of Claim 1 having the formula:



wherein X, Y, R^4 and R^6 are as defined in Claim 1.

3. The compound of Claim 2 wherein,

X is R^{10}-C(=O)-NH-,

Y is H or R^{12}-C(=O)-,

R^4 is H or an alkyl residue, and

R^6 is H, a halogen atom or OR^{13},

wherein R^{10}, R^{12} and R^{13} are as defined in Claim 1.

4. The compound of Claim 3 wherein, R^{10} is an alkyl or substituted alkyl.

5. The compound of Claim 3 wherein Y is H or R^{12}-C(=O)-, R^{12} is $N(R^{11})_2$, OR^{11} or $OR^{14}N(R^{11})_2$, and R^{11} is H or an alkyl or cycloalkyl residue.

6. The compound of Claim 4 wherein Y is H or R^{12}-C(=O)-, R^{12} is $N(R^{11})_2$, OR^{11} or $OR^{14}N(R^{11})_2$, and R^{11} is H or an alkyl or cycloalkyl residue.

7. The compound of Claim 6 wherein R^{10} is an alkyl, Y is R^{12}-C(=O)-, R^{12} is OR^{11} or $OR^{14}N(R^{11})_2$, and R^{11} is an alkyl.

8. The compound of Claim 7 wherein R^{10} is methyl, R^{12} is OR^{11}, R^{11} is methyl, R^4 is methyl, and R^6 is H.

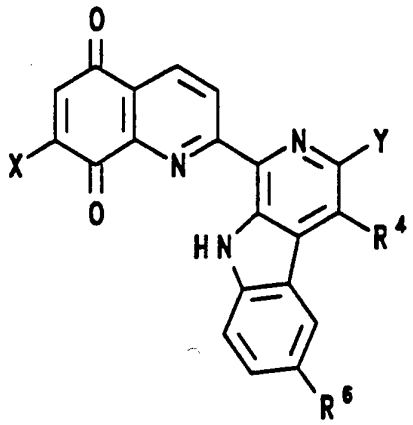
9. The compound of Claim 7 wherein R^{10} is methyl, R^{12} is OR^{11}, R^{11} is isoamyl, R^4 is H, and R^6 is H.

10. The compound of Claim 7 wherein R^{10} is methyl, R^{12} is OR^{11}, R^{11} is *n*-octyl, R^4 is H, and R^6 is H.

11. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and the compound

of Claim 1 or a pharmaceutically-acceptable salt thereof.

12. The composition of Claim 11 wherein the compound has the formula:



wherein X, Y, R^4 and R^6 are as defined in Claim 1.

13. The composition of Claim 12 wherein,

X is R^{10}-C(=O)-NH-,

Y is H or R^{12}-C(=O)-,

R^4 is H or an alkyl residue, and

R^6 is H, a halogen atom or OR^{13},

wherein R^{10}, R^{12} and R^{13} are defined in Claim 1.

14. The composition of Claim 13 wherein, R^{10} is an alkyl or substituted alkyl.

15. The composition of Claim 13 wherein Y is H or R^{12}-C(=O)-, R^{12} is $N(R^{11})_2$, OR^{11} or $OR^{14}N(R^{11})_2$, and R^{11} is H or an alkyl or cycloalkyl residue.

16. The composition of Claim 14 wherein Y is H or R^{12}-C(=O)-, R^{12} is $N(R^{11})_2$, OR^{11} or $OR^{14}N(R^{11})_2$, and R^{11} is H or an alkyl or cycloalkyl residue.

17. The composition of Claim 16 wherein R^{10} is an alkyl, Y is R^{12}-C(=O)-O, R^{12} is OR^{11} or $OR^{14}N(R^{11})_2$, and R^{11} is an alkyl.

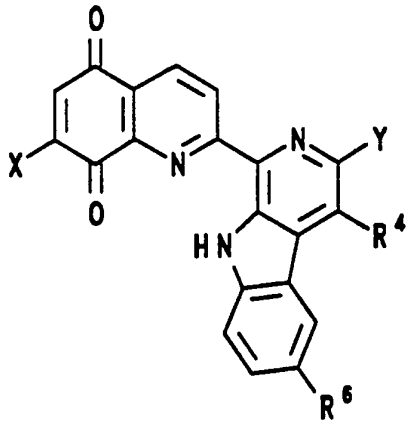
18. The composition of Claim 17 wherein R^{10} is methyl, R^{12} is OR^{11}, R^{11} is methyl, R^4 is methyl, and R^6 is H.

19. The composition of Claim 17 wherein R^{10} is methyl, R^{12} is OR^{11}, R^{11} is isoamyl, R^4 is H, and R^6 is H.

20. The composition of Claim 17 wherein R^{10} is methyl, R^{12} is OR^{11}, R^{11} is *n*-octyl, R^4 is H, and R^6 is H.

21. A method of treating an animal having a tumor comprising administering to the animal an effective amount of the compound of Claim 1 or a pharmaceutically-acceptable salt thereof.

22. The method of Claim 21 wherein the compound has the formula:



wherein X, Y, R^4 and R^6 are as defined in Claim 1.

23. The method of Claim 22 wherein,

X is R^{10}-C(=O)-NH-,

Y is H or R^{12}-C(=O)-,

R^4 is H or an alkyl residue, and

R^6 is H, a halogen atom or OR^{13},

wherein R^{10}, R^{12} and R^{13} are as defined in Claim 1.

24. The method of Claim 23 wherein, R^{10} is an alkyl or substituted alkyl.

25. The method of Claim 23 wherein Y is H or R^{12}-C(=O)-, R^{12} is $N(R^{11})_2$, OR^{11} or $OR^{14}N(R^{11})_2$, and R^{11} is H or an alkyl or cycloalkyl residue.

26. The method of Claim 24 wherein Y is H or R^{12}-C(=O)-, R^{12} is $N(R^{11})_2$, OR^{11} or $OR^{14}N(R^{11})_2$, and R^{11} is H or an alkyl or cycloalkyl residue.

27. The method of Claim 26 wherein R^{10} is an alkyl, Y is R^{12}-C(=O)-O, R^{12} is OR^{11} or $OR^{14}N(R^{11})_2$, and R^{11} is an alkyl.

28. The method of Claim 27 wherein R^{10} is methyl, R^{12} is OR^{11}, R^{11} is methyl, R^4 is methyl, and R^6 is H.

29. The method of Claim 27 wherein R^{10} is methyl, R^{12} is OR^{11}, R^{11} is isoamyl, R^4 is H, and R^6 is H.

30. The method of Claim 27 wherein R^{10} is methyl, R^{12} is OR^{11}, R^{11} is *n*-octyl, R^4 is H, and R^6 is H.

31. The method of Claim 21 wherein the tumor comprises cells containing a *ras* oncogene.

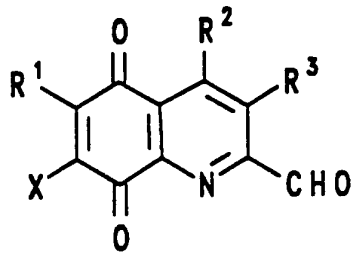
32. The method of Claim 27 wherein the tumor comprises cells containing a ras^K oncogene.

33. A method of treating a bacterial, viral or parasitic infection comprising administering to an animal suffering from such an infection an effective amount of the compound of Claim 1 or a pharmaceutically-acceptable salt thereof.

34. A method of inhibiting the growth of a bacterium, virus or parasite comprising contacting the

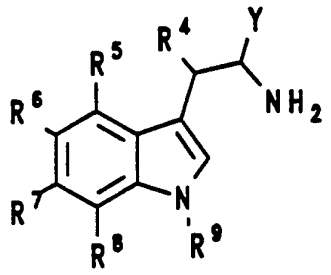
bacterium, virus or parasite with the compound of Claim 1 or a salt thereof.

35. A method of preparing a lavendamycin analog comprising reacting an aldehyde having the following formula:



K

with a tryptophan analog having the following formula:



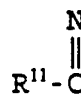
L

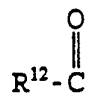
wherein,

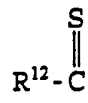
X is R^{10}-C(=O)-NH- or

R^{10}-C(=S)-NH-,

Y is H, OR^{11}, SR^{11}, $N(R^{11})_2$, $NR^{11}N(R^{11})_2$, a halogen atom, NO_2, CN,

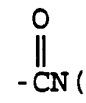


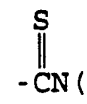


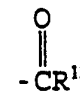


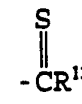
an alkyl, aryl, cycloalkyl, alkynyl, alkenyl or heterocyclic residue, each of which may be substituted or unsubstituted,

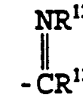
R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8, which may be the same or different, each is independently H, a halogen atom, NO_2, CN, OR^{13}, SR^{13}, $N(R^{13})_2$,





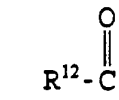


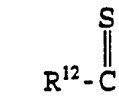




an alkyl, aryl, cycloaklyl, alkenyl, alkynyl, or heteroalkyl, heterocyclic, heteroalkenyl or heteroalkynyl residue, each of which may be substituted or unsubstituted,

R^9 is H,





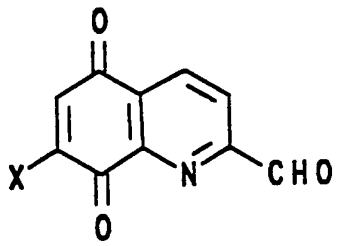
an alkyl, cycloalkyl, aryl, alkenyl, alkynyl or heterocyclic residue, each of which may be substituted or unsubstituted,

R^{10}, R^{11} and R^{13}, which may be the same or different, each is independently H or an alkyl, cycloalkyl, alkenyl, alkynyl, aryl or heterocyclic residue, each of which may be substituted or unsubstituted,

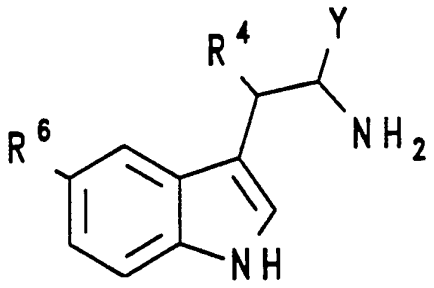
R^{12} is H, $N(R^{11})_2$, OR^{11}, SR^{11}, $NR^{11}N(R^{11})_2$, $OR^{14}N(R^{11})_2$, or an alkyl, cycloalkyl, aryl, alkenyl, alkynyl or heterocyclic residue, each of which may be substituted or unsubstituted, and

R^{14} is an alkylene residue.

36. The method of Claim 35 wherein the aldehyde has the following formula:



and the tryptophan analog has the following formula:



wherein X, Y, R^4 and R^6 are as defined in Claim 35.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/06150

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07D 471/04; A61K 31/44
US CL :546/87; 514/292
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/85; 87; 514/292

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	The Journal of Organic Chemistry, Vol. 58, No. 25, issued December 1993, Behforouz et al., "A Highly Concise Synthesis of Lavendamycin Methyl Ester," pages 7089-91.	1-36
A -- X	The Journal of Organic Chemistry, Vol. 50, No. 26, issued December 1985, Boger et al., "TOTAL SYNTHESIS OF LAVENDAMYCIN METHYL ESTER," pages 5790-5795, entire document.	35, 36 --------- 35, 36
A ------ X	Tetrahedron Letters, Vol. 25, No. 9, issued March 1984, Kende et al., "The Regiospecific Total Synthesis of Lavendamycin Methyl Ester," pages 423-926, entire document.	35, 36 --------- 35, 36

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 27 SEPTEMBER 1994	Date of mailing of the international search report 11 OCT 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ALAN ROTMAN ach Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/06150

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A -- X	The Journal of Medicinal Chemistry, Vol. 30, No. 10, issued October 1987, Boger et al., "STREPTONIGRIN AND LAVENDAMYCIN PARTIAL STRUCTURES, PROBES FOR THE MINIMUM, POTENT PHARMACOPORE OF STREPTONIGRIN LAVENDAMYCIN AND SYNTHETIC QUINOLINE - 5, 8-DIONES", pages 1918-1928, entire document.	35, 36 --------- 35, 36

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/06150

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

STN FILES
1. CHEM. ABSTRACTS
2 . CAS REACT
3 . TOXLIT
4 . BEILSTEIN