IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE: US Patent No. 6,420,536

ISSUED: July 16, 2002

TO: Bronk, et al.

FOR: 4"-SUBSTITUTED-9-DEOXO-9A-AZA-9A-HOMOERYTHROMYCIN A DERIVATIVES

FROM: US Application No. 09/424,104

OF: May 29, 1998

Commissioner for Patents
Mail Stop Patent Extension
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION
OF THE TERM OF UNITED STATES
PATENT NO. 6,420,536 UNDER 35 U.S.C. §156

Sir:

Your applicant, Pfizer Inc. ("Pfizer"), a corporation of the State of Delaware and having a place of business at 235 East 42nd Street, New York, New York, represents that it is the owner of the entire right, title and interest in and to Letters Patent of the United States No. 6,420,536, granted to Brian S. Bronk, Michael A. Letavic, Takushi Kaneko, Henry Cheng, Bingwei V. Yang and Edward A. Glazer on the 16th day of July 2002, for 4"-SUBSTITUTED-9-DEOXO-9A-AZA-9A-HOMOERYTHROMYCIN A DERIVATIVES, by virtue of an assignment, recorded in the United States Patent and Trademark Office on the 21st day of July, 2000, at Reel 010947, Frame 0171.

Pursuant to the provisions of 37 C.F.R. §1.730, your applicant hereby applies for an extension of the term of 360 days, under 35 U.S.C. §156, based upon the materials set forth herein and in the accompanying papers. In the materials which follow herein, paragraph numbers correspond to the paragraph numbers in 37 C.F.R. §1.740(a).

(1) The approved product is DRAXXIN®, which is comprised of two isomers of the active ingredient, further identified by the following generic name, molecular formula, molecular weight, chemical structures, and chemical names:

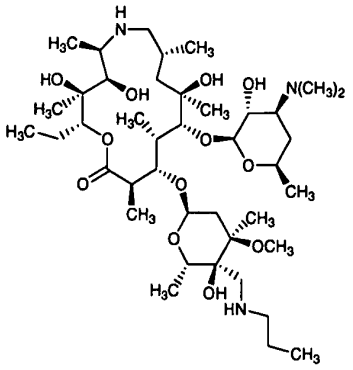
Generic Name. Tulathromycin

Molecular Formula. $C_{41}H_{79}N_3O_{12}$

Molecular Weight. 806.23

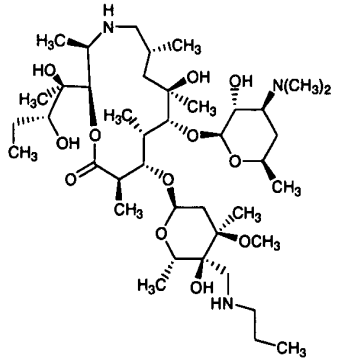
Chemical Structures and Chemical Names.

Isomer 1:



(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyranosyl]oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylohexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one

Isomer 2:



(2R,3R,6R,8R,9R,10S,11S,12R)- 11-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribohexopyranosyl]oxy]-2-[(1R,2R)-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)- β-D-xylo-hexopyranosyl]-oxy]-1-oxa-4-azacyclotridecan-13-one

(2) DRAXXIN® was subject to regulatory review under section 512 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §360(b)).

(3) DRAXXIN® received permission for commercial marketing or use under section 512 of the Food, Drug and Cosmetic Act, 21 U.S.C. §360(b), on May 24, 2005.

(4) The active ingredient in DRAXXIN® is Tulathromycin, described above in (1). Said active ingredient has not been previously approved for commercial

marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act.

(5) This application is being submitted within the sixty day period permitted for its submission pursuant to 37 C.F.R. § 1.270(f). The last day on which this application could be submitted is July 23, 2005.

(6) The patent for which an extension is being sought is identified as follows.

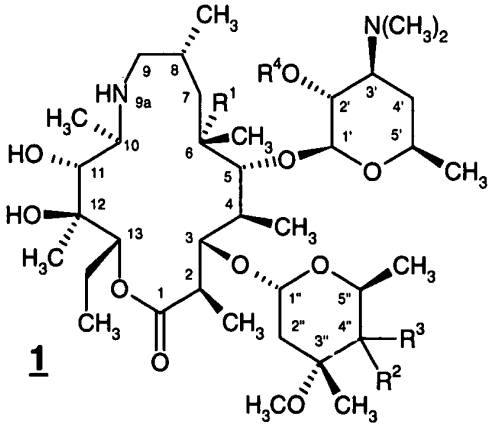
U.S. Patent No.: 6,420,536
TITLE: 4"-SUBSTITUTED-9-DEOXO-9A-AZA-9A-HOMOERYTHROMYCIN A DERIVATIVES
ISSUED: July 16, 2002
EXPIRES: May 29, 2018
INVENTORS: Brian S. Bronk, Michael A. Letavic, Takushi Kaneko, Bingwei V. Yang, Henry Cheng, Edward A. Glazer

(7) A copy of United States Patent No. 6,420,536, the patent for which an extension is being sought, is attached hereto as Exhibit A.

(8) A certificate of correction has issued for United States Patent No. 6,420,536. A copy is attached as Exhibit B. No disclaimers or reexamination certificates have been filed. The first maintenance fee payment is not due until January 16, 2006. Therefore, there is no maintenance fee receipt for United States Patent No. 6,420,536.

(9) United States Patent No. 6,420,536 claims the approved product, in particular Isomer 1 described in the product section (1) above. Claims 1, 2, and 3 claim the approved product per se. The manner in which each applicable patent claim reads on the approved product is as follows.

Claim 1 of U.S. Patent 6,420,536 claims the approved product in a genus of chemical compounds of the general formula



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or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydroxyl, R^2 is hydroxy; R^3 is $CH_2NR^8R^{15}$, or $-(CH_2)NR^8R^{15}$, or $-CH_2SR^8$, R^4 is H, acetyl or benzyloxycarbonyl;

R^5 is $-SR^8$, $-(CH_2)_nC(O)R^8$ wherein n is 0 or 1, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CH_2)_m(C_6$-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^5 groups are optionally substituted by 1 to 3 R^{16} groups;

each R^6 and R^7 is independently H, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-(CH_2)_m(C_6$-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4;

each R^8 is independently H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CH_2)_qCR^{11}R^{12}(CH_2)_rNR^{13}R^{14}$ wherein q and r are each independently an integer ranging from 0 to 3 except q and r are not both 0, $-(CH_2)_m(C_6$-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^8 groups, except H, are optionally substituted by 1 to 3 R^{16} groups;

or where R^8 is as $-CH_2NR^8R^{15}$, R^{15} and R^8 may be taken together to form a 4-10 membered monocyclic or polycyclic saturated ring or a 5-10 membered heteroaryl ring, wherein said saturated and heteroaryl rings optionally include 1 or 2 heteroatoms selected from the group consisting of O, S and $-N(R^8)-$, in addition to the nitrogen to which R^{15} and R^8 are attached, said saturated ring optionally includes 1 or 2 carbon-carbon double or triple bonds, and said saturated and heteroaryl rings are optionally substituted by 1 to 3 R^{16} groups;

each R^9 and R^{10} is independently H or C_1-C_6 alkyl;

each R^{11}, R^{12}, R^{13} and R^{14} is independently selected from the group consisting of H, C_1-C_{10} alkyl, $-(CH_2)_m(C_6$-C_{10} aryl), and $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^{11}, R^{12}, R^{13} and R^{14} groups, except H, are optionally substituted by 1 to 3 R^{16} groups;

or R^{11} and R^{13} are taken together to form $-(CH_2)_p-$ wherein p is an integer ranging from 0 to 3 such that a 4-7 membered saturated ring is formed that optionally includes 1 or 2 carbon-carbon double or triple bonds;

or R^{13} and R^{14} are taken together to form a 4-10 membered monocyclic or polycyclic saturated ring or a 5-10 membered heteroaryl ring, wherein said saturated and heteroaryl rings optionally include 1 or 2 heteroatoms selected from O, S and $-N(R^8)-$, in addition to the nitrogen to which R^{13} and R^{14} are attached, said saturated ring optionally includes 1 or 2 carbon-carbon double or triple bonds, and said saturated and heteroaryl rings are optionally substituted by 1 to 3 R^{16} groups;

R^{15} is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl, wherein the foregoing R^{15} groups are optionally substituted by 1 to 3 substituents independently selected from halo and $-OR^9$;

each R^{16} is independently selected from the group consisting of halo, cyano, nitro, trifluoromethyl, azido, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)OR^{17}$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-(CH_2)_m(C_6$-C_{10} aryl), and $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein said aryl and heteroaryl subsituents are optionally substituted by 1 or 2 substituents independently selected from the group consisting of halo, dyano, nitro, trifluoromethyl, azido, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)OR^{17}$, $-OC(O)OR^{17}$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each R^{17} is independently selected from the group consisting of H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CH_2)_m(C_6$-C_{10} aryl), and $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4;

with the proviso that R^8 is not H where R^3 is $-CH_2SR^8$.

Claim 2 of U.S. Patent 6,420,536

The compound of claim 1 wherein R^3 is --CH_2 NR^{15} R^8 and R^{15} and R^8 are independently selected from H, C_1 -C_{10} alkyl, C_2 -C_{10} alkenyl, and C_2 –C_{10} alkynyl, wherein the foregoing R^{15} and R^8 groups, except H, are optionally substituted by 1 or 2 substituents independently selected from the group consisting of hydroxy, halo and C_1 -C_6 -alkoxy.

Claim 3 of Patent 6,420,536

The compound of claim 2 wherein R^{15} and R^8 are each independently selected from the group consisting of H, methyl, ethyl, allyl, n-butyl, isobutyl, 2-methoxyethyl, cyclopentyl, 3-methoxypropyl, 3-ethoxypropyl, n-propyl, isopropyl, 2-hydroxyethyl, cyclopropyl, 2,2,2-trifluoroethyl, 2-propynyl, sec-butyl, tert-butyl, and n-hexyl.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows, according to Section 1,740 (10) (ii).

A) An exemption under subsection (j) of section 512 of the Federal Food, Drug and Cosmetic Act became effective for Tulathromycin on **9 September 1998** following submission of Investigational New Animal Drug ("INAD") Application No. 10-406 on 2 September 1998, for the evaluation of Tulathromycin in Cattle. This original INAD request was given a second INAD Application No. 10-548, on 10 May 1999, following a request to enlarge the original INAD to include an evaluation of Safety and Efficacy for Swine on 5 May 1999.

B) A New Animal Drug Application ("NADA") under section 512 of the Federal Food, Drug and Cosmetic Act for DRAXXIN® (Tulathromycin) was initially submitted on **18 April 2005**, as NADA No. 141-244.

C) NADA No. 141-244 was approved on **24 May 2005**.

(11) A brief description of the significant activities undertaken by or for the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities is attached hereto as Exhibits C, D, E and F. Exhibit C is a Summary of DRAXXIN® (Tulathromycin) Regulatory Review Activities. Exhibit D is a Brief Description of DRAXXIN® (Tulathromycin) Review Activities for Cattle. Exhibit E is a Brief Description of DRAXXIN® (Tulathromycin) Review Activities for Swine. Exhibit F is a Brief Description of DRAXXIN® (Tulathromycin) NADA Approval and Post-Approval Activities.

(12) Applicant is of the opinion that United States Patent No. 6,420,536 is eligible for an extension, under 35 U.S.C. §156, and the length of extension claimed is 360 days.

The requirements of 35 U.S.C. §156(a) and (c) (4) have been satisfied as follows:

a) U.S. Patent No. 6,420,536 claims a product, DRAXXIN® (Tulathromycin).

b) U.S. Patent No. 6,420,536 is currently set to expire on 29 May 2018 (i.e., the term of the patent has not yet expired).

c) The term of U.S. Patent No. 6,420,536 has never been extended under subsection (e)(1) of 35 U.S.C. §156.

d) This application for extension is being submitted by Pfizer Inc., the owner of record of U.S. Patent No. 6,420,536, by its agent, in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. §156(d).

e) The product DRAXXIN® (Tulathromycin), has been subject to a regulatory review period under section 512 of the Federal Food, Drug and Cosmetic Act before its commercial marketing or use, and the permission for said commercial marketing or use is the first permitted commercial marketing or use of the product under section 512 of the Federal Food, Drug and Cosmetic Act.

f) No patent has to this date been extended, nor has any other extension been applied for, under subsection (e)(1) of 35 U.S.C. §156, for the regulatory review period which forms the basis for this application for extension of the term of U.S. Patent No. 6,420,536.

The length of extension of the term of U.S. Patent No. 6,420,536 of 360 days claimed by applicant was determined according to the provisions of 37 C.F.R. §1.778 as follows:

a) According to 37 C.F.R. §1.778(b), the length of extension is equal to the regulatory review period for the approved product, reduced as appropriate according to paragraphs (d)(1) through (d)(6) of 37 C.F.R. §1.778.

b) According to 37 C.F.R. §1.778(c), the regulatory review period is the sum of:
(A) the number of days in the period beginning on the earlier of the date of a major health or environmental effects test on the drug was initiated or the date on which an exemption under subsection (j) of section 512 of the Federal Food, Drug and Cosmetic Act became effective and ending on the date the NADA was initially submitted under section 512 of the Federal Food, Drug and Cosmetic Act and
(B) the number of days in the period beginning on the date the NADA was approved. The exemption under subsection (j) of section 512 of the Federal Food, Drug and Cosmetic Act became effective on 9 September 1998. The NADA was initially submitted on 18 April 2005; and the NADA was approved on 24 May 2005. Hence the regulatory review period under 37

C.F.R. §1.778(c) is the sum of the period from 9 September 1998 to 18 April 2005 and from 18 April 2005 to 24 May 2005. This is the sum of 2,413 days and 36 days, which is 2,449 days.

c) According to 37 C.F.R. §1.778(d)(1)(i), the number of days in the regulatory review period which were on or before the date on which the patent issued must be subtracted. U.S. Patent No. 6,420,536 issued on 16 July 2002. Subtraction of the period on or before 16 July 2002 leaves a reduced regulatory review period of from 16 July 2002 to 17 April 2005 and from 18 April 2005 to 24 May 2005. This is the sum of 1,007 days and 36 days, which is 1,043 days.

d) 37 C.F.R. §1.778(d)(1)(ii) does not apply.

e) According to 37 C.F.R. §1.778(d)(1)(iii), the regulatory review period must be reduced by one-half of the days remaining in the period defined in 37 C.F.R. §1.778(c)(1). This is one-half of 1,007 days, which is 503 days. After subtraction, and ignoring half days in the subtraction, this now leaves a reduced regulatory review period of 539 days. (37 CFR § 1.778(d)(1)(iii).

f) According to 37 CFR § 1.778(d)(2). When the reduced regulatory review period of 539 days is added to the expiration date of U.S. Patent No. 6,420,536 (29 May 2018), this gives a date of 19 November 2019. (37 CFR § 1.778(d)(2).

g) According to 37 CFR § 1.778(d)(3). When 14 years is added to the date of approval of the application under section 512 of the Federal Food, Drug and Cosmetic Act, May 24, 2005, this gives a date of 24 May 2019. (37 CFR § 1.778(d)(3).

h) According to 37 CFR § 1.778(d)(4). By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) with each other and selecting the earlier date, the earlier date is 24 May 2019.

i) The five year limitation of 35 U.S.C. §156(g)(6)(A) and 37 C.F.R. §1.778(d)(5) applies to this application, because U.S. Patent No. 6,420,536 issued after the date of enactment of the Generic Animal Drug and Patent Term Restoration Act (November 16, 1988). When 5 years is added to the expiration date of U.S. Patent No. 6,420,536 (29 May 2018), this gives a date of 29 May 2023 . This date is later than 24 May 2019, the date obtained according to 37 CFR § 1.778(d)(4). Therefore, under 37 C.F.R. §1.778(d)(5) applicant is entitled to an extension corresponding to the period from 29 May 2018 to 24 May 2019. This is 360 days, which is the length of extension being claimed. Hence, applicant is in compliance with 35 U.S.C. §156 (g)(6)(A) and 37 C.F.R. §1.778(d)(5).

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the 360 day extension being sought to the term of United States Patent No. 6,420,536.

(14) The prescribed fee for receiving and acting on this application for extension is $1,120.00 to be charged to Deposit Account No. 21-0718, as requested in the enclosed transmittal letter.

(15) Please address all inquiries and correspondence relating to this application for patent term extension to:

Thomas A. Wootton
Pfizer Inc.
301 Henrietta Street, MS KZO-32-LAW
Kalamazoo, Michigan 49007

Tel (269) 833-7914
Fax (269) 833-8897

(16) A duplicate of these application papers, certified as such, is enclosed herewith.

(17) A declaration pursuant to 37 C.F.R. §§1.740(a)(17) and 1.740(b) is enclosed herewith.

Respectfully submitted,

Date: 21 Jan 2005

Thomas A. Wootton
Attorney for Applicant(s)
Reg. No. 35,004

Pfizer Inc.
Patent Department
301 Henrietta Street, MS KZO-32-LAW
Kalamazoo, Michigan 49007
(269) 833-7914

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE: US Patent No. 6,420,536

ISSUED: July 16, 2002

TO: Bronk et al.

FOR: 4"-SUBSTITUTED-9-DEOXO-9A-AZA-9A-HOMOERYTHROMYCIN A DERIVATIVES

FROM: US Application No. 09/424,104

OF: May 29, 1998

Commissioner for Patents
Mail Stop Patent Extension
Alexandria, VA 22313-1450

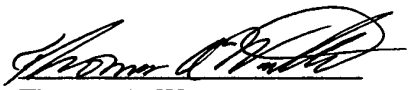
Sir:

TRANSMITTAL LETTER FOR
APPLICATION FOR EXTENSION OF
PATENT TERM UNDER 35 U.S.C. §156

Transmitted herewith is the application of Pfizer Inc., dated July 21, 2005, for extension of the term of United States Patent No. 6,420,536 under 36 U.S.C.§156, together with a duplicate of the papers thereof, certified as such.

Please charge the sum of $1,120.00 to Deposit Account No. 21-0718. Please also charge any additional fees which may be required by the filing of this application for Extension of Patent Term, or credit any overpayment, to Deposit Account No. 21-0718. Two copies of this paper are enclosed.

Date: July 21, 2005



Thomas A. Wootton
Attorney for Applicant(s)
Reg. No. 35,004

Pfizer Inc
Patent Department, MS KZO-32-LAW
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE: US Patent No. 6,420,536

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FOR: 4"-SUBSTITUTED-9-DEOXO-9A-AZA-9A-HOMOERYTHROMYCIN A DERIVATIVES

FROM: US Application No. 09/424,104

OF: May 29, 1998

Commissioner for Patents
Mail Stop Patent Extension
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Declaration Accompanying Application for
Extension of Patent Term Under 35 U.S.C. §156

I, Thomas A. Wootton, declare as follows.

1. I am a patent attorney. I am a member of the Bar of the State of Michigan and I am authorized to practice before the Patent and Trademark Office, Registration No. 35,004.
2. I am employed by Pharmacia & Upjohn Company LLC, a corporation of Delaware, having a place of business at 301 Henrietta St., Kalamazoo, Michigan 49007, which is wholly owned by Pfizer Inc., a corporation of Delaware, having a place of business at 235 East 42nd Street, New York, NY 10017. Pfizer Inc. is the owner of record of United States Patent No. 6,420,536.
3. I have general authority from Pfizer Inc. to act on its behalf in patent matters.
4. I have reviewed and I understand the contents of the application of Pfizer Inc., dated July 21, 2005, which is being submitted herewith for extension of the term of United States Patent No. 6,420,536 under 35 U.S.C. §156 and 37 C.F.R. §1.730.
5. I believe that United States Patent No. 6,420,536 is subject to extension pursuant to 37 C.F.R. §1.710.
6. I believe that the length of extension of term of United States Patent No. 6,420,536 which is being claimed by Pfizer Inc. is justified under 35 U.S.C. §156.
7. I believe that the patent for which extension is being sought meets the conditions for extension of the term of the patent as set forth in 37 C.F.R.§1.720.

I declare further that all statements made herein of my own knowledge are true

and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application being submitted herewith or any extension of patent term granted thereon.

Signed this 21 day of Jan, 2005, at Kalamazoo, Michigan.

Thomas A. Wootton
Attorney for Applicant
Reg. No. 35,004

Pfizer Inc
Patent Department
301 Henrietta Street, MS KZO-32-LAW
Kalamazoo, Michigan 49007
(269) 833-7914

EXHIBIT A

US006420536B1

(12) **United States Patent**
Bronk et al.

(10) **Patent No.: US 6,420,536 B1**
(45) **Date of Patent: Jul. 16, 2002**

(54) **4"-SUBSTITUTED-9-DEOXO-9A-AZA-9A-HOMOERYTHROMYCIN A DERIVATIVES**

(75) Inventors: **Brian Scott Bronk**, Gales Ferry; **Michael Anthony Letavic**, Mystic; **Takushi Kaneko**, Guilford; **Bingwei Vera Yang**; **Edward Alan Glazer**, both of Waterford; **Hengmiao Cheng**, East Lyme, all of CT (US)

(73) Assignee: **Pfizer Inc**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/424,104**

(22) PCT Filed: **May 29, 1998**

(86) PCT No.: **PCT/IB98/00839**

§ 371 (c)(1),
(2), (4) Date: **Nov. 18, 1999**

(87) PCT Pub. No.: **WO98/56802**

PCT Pub. Date: **Dec. 17, 1998**

Related U.S. Application Data

(60) Provisional application No. 60/049,348, filed on Jun. 11, 1997.

(51) **Int. Cl.**[7] **C07H 17/08**
(52) **U.S. Cl.** **536/7.4**
(58) **Field of Search** 536/7.5, 7.2, 18.5, 536/7.4; 579/29

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,512,982 A 4/1985 Hauske et al.
5,441,939 A 8/1995 Yang

FOREIGN PATENT DOCUMENTS

EP 0508699 4/1992
EP 0549040 12/1992

Primary Examiner—Elli Peselev
(74) *Attorney, Agent, or Firm*—Peter C. Richardson; Paul H. Ginsburg; Jeffrey N. Myers

(57) **ABSTRACT**

The invention relates to a method of preparing compounds of the formula

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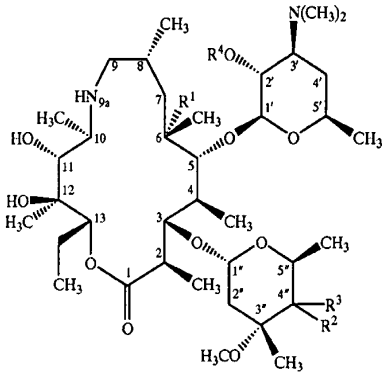

and to pharmaceutically acceptable salts thereof. The compounds of formula 1 are antibacterial agents that may be used to treat various bacterial and protozoa infections. The invention also relates to pharmaceutical compositions containing the compounds of formula 1 and to methods of treating bacterial protozoa infections by administering the compounds of formula 1. The invention also relates to methods of preparing the compounds of formula 1 and to intermediates useful in such preparation.

12 Claims, No Drawings

4"-SUBSTITUTED-9-DEOXO-9A-AZA-9A-HOMOERYTHROMYCIN A DERIVATIVES

CROSS REFERENCE TO RELATED APPLICATIONS

This application is the National Stage of International Application No. PCT/IB98/00839, filed May 29, 1998, which claims the benefit of U.S. Provisional Application No. 60/049,348, filed Jun. 11, 1997.

BACKGROUND OF THE INVENTION

This invention relates to novel C-4" substituted derivatives of 9-deoxo-9a-aza-9a- homoerythromycin A that are useful as antibacterial and antiprotozoa agents in mammals, including man, as well as in fish and birds. This invention also relates to pharmaceutical compositions containing the novel compounds and to methods of treating bacterial infections and protozoa infections in mammals, fish and birds by administering the novel compounds to mammals, fish and birds requiring such treatment.

Macrolide antibiotics are known to be useful in the treatment of a broad sprectrum of bacterial infections and protozoa infections in mammals, fish and birds. Such antibiotics include various derivatives of erythromycin A such as azithromycin which is commercially available and is referred to in U.S. Pat. Nos. 4,474,768 and 4,517,359, both of which are incorporated herein by reference in their entirety. Like azithromycin and other macrolide antibiotics, the novel macrolide compounds of the present invention possess potent activity against various bacterial infections and protozoa infections as described below.

SUMMARY OF THE INVENTION

The present invention relates to compounds of the formula

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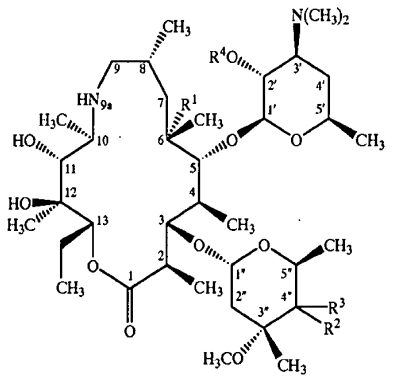


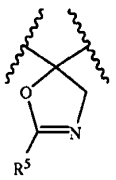
and to pharmaceutically acceptable salts thereof, wherein:

R^1 is H, hydroxy or methoxy;

R^2 is hydroxy;

R^3 is C_1–C_{10} alkyl, C_2–C_{10} alkenyl, C_2–C_{10} alkynyl, cyano, $—CH_2S(O)_nR^8$ wherein n is integer ranging from 0 to 2, $—CH_2OR^8$, $—CH_2N(OR^9)R^8$, $—CH_2NR^8R^{15}$, $—(CH_2)_m(C_6$–C_{10} aryl), or $—(CH_2)_m$(5–10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^3 groups are optionally substituted by 1 to 3 R^{16} groups;

or R^2 and $R^3$are taken together to form an oxazolyl ring as shown below



R^4 is H, $—C(O)R^9$, $—C(O)OR^9$, $—C(O)NR^9R^{10}$ or a hydroxy protecting group;

R^5 is $—SR^8$, $—(CH_2)_nC(O)R^8$ wherein n is 0 or 1, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, C_2–C_{10} alkynyl, $—(CH_2)_m$ (C_6–C_{10} aryl), or $—(CH_2)_m$(5–10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^5 groups are optionally substituted by 1 to 3 R^{16} groups;

each R^6 and R^7 is independently H, hydroxy, C_1–C_6 alkoxy, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, $—(CH_2)_m(C_6$–C_{10} aryl), or $—(CH_2)_m$(5–10 membered heteroaryl), wherein m is an integer ranging from 0 to 4;

each R^8 is independently H, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, C_2–C_{10} alkynyl, $—(CH_2)_qCR^{11}R^2(CH_2)_rNR^{13}R^{14}$ wherein q and r are each independently an integer ranging from 0 to 3 except q and r are not both 0, $—(CH_2)_m(C_6$–C_{10} aryl), or $—(CH_2)_m$(5–10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^8 groups, except H, are optionally substituted by 1 to 3 R^{16} groups;

or where R^8 is as $—CH_2NR^8R^{15}$, R^{15} and R^8 may be taken together to form a 4–10 membered monocyclic or polycyclic saturated ring or a 5–10 membered heteroaryl ring, wherein said saturated and heteroaryl rings optionally include 1 or 2 heteroatoms selected from O, S and $—N(R^8)—$, in addition to the nitrogen to which R^{15} and R^8 are attached, said saturated ring optionally includes 1 or 2 carbon-carbon double or triple bonds, and said saturated and heteroaryl rings are optionally substituted by 1 to 3 R^{16} groups;

each R^9 and R^{10} is independently H or C_1–C_6 alkyl;

each R^{11}, R^{12}, R^{13} and R^{14} is independently selected from H, C_1–C_{10} alkyl, $—(CH_2)_m(C_6$–C_{10} aryl), and $—(CH_2)_m$(5–10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^{11}, R^{12}, R^{13} and R^{14} groups, except H, are optionally substituted by 1 to 3 R^{16} groups;

or R^{11} and R^{13} are taken together to form $—(CH_2)_p—$ wherein p is an integer ranging from 0 to 3 such that a 4–7 membered saturated ring is formed that optionally includes 1 or 2 carbon-carbon double or triple bonds;

or R^{13} and R^{14} are taken together to form a 4–10 membered monocyclic or polycyclic saturated ring or a 5–10 membered heteroaryl ring, wherein said saturated and heteroaryl rings optionally include 1 or 2 heteroatoms selected from O, S and $—N(R^8)—$, in addition to the nitrogen to which R^{13} and R^{14} are attached, said saturated ring optionally includes 1 or 2 carbon-carbon double or triple bonds, and said saturated and heteroaryl rings are optionally substituted by 1 to 3 R^{16} groups;

R^{15} is H, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, or C_2–C_{10} alkynyl, wherein the foregoing R^{15} groups are optionally substituted by 1 to 3 substituents independently selected from halo and $—OR^9$;

each R^{16} is independently selected from halo, cyano, nitro, trifluoromethyl, azido, —C(O)R^{17}, —C(O)OR^{17}, —C(O)OR^{17}, —OC(O)OR^{17}, —NR^6C(O)R^7, —C(O)NR^6R^7, hydroxy, C_1–C_6 alkyl, C_1–C_6 alkoxy, —$(CH_2)_m$(C_6–C_{10} aryl), and —$(CH_2)_m$(5–10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein said aryl and heteroaryl substituents are optionally substituted by 1 or 2 substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, —C(O)R^{17}, —C(O)OR^{17}, —C(O)OR^{17}, —OC(O)OR^{17}, —NR^6C(O)R^7, —C(O)NR^6R^7, —NR^6R^7, hydroxy, C_1–C_6 alkyl, and C_1–C_6 alkoxy;

each R^{17} is independently selected from H, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, C_2–C_{10} alkynyl, —$(CH_2)_m$(C_6–C_{10} aryl), and —$(CH_2)_m$(5–10 membered heteroaryl), wherein m is an integer ranging from 0 to 4;

with the proviso that R^8 is not H where R^3 is —$CH_2S(O)_nR^8$.

Preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is —$CH_2NR^{15}R^8$ or —CH_2SR^8, and R^4 is H.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is —$CH_2NR^8R^{15}$, R^4 is H, R^{15} and R^8 are each selected from H, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, and C_2–C_{10} alkynyl, wherein said R^{15} and R^8 groups, except H, are optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo and C_1–C_6 alkoxy. Specific preferred compounds having the foregoing general structure include those wherein R^{15} is either H or is selected from the following groups from which R^8 is also independently selected: methyl, ethyl, allyl, n-butyl, isobutyl, 2-methoxyethyl, cyclopentyl, 3-methoxypropyl, 3-ethoxypropyl, n-propyl, isopropyl, 2-hydroxyethyl, cyclopropyl, 2,2,2-trifluoroethyl, 2-propynyl, sec-butyl, tert-butyl, and n-hexyl.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is —CH_2NHR^8, R^4 is H, and R^8 is —$(CH_2)_m$(C_6–C_{10} aryl) wherein m is an integer ranging from 0 to 4. Specific preferred compounds having the foregoing general structure include those wherein R^8 is phenyl or benzyl.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is —$CH_2NR^{15}R^8$, R^4 is H, and R^{15} and R^8 are taken together to form a saturated ring. Specific preferred compounds having the foregoing general structure include those wherein R^6 and R^8 are taken together to form a piperidino, trimethyleneimino, or morpholino ring.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is —$CH_2NR^{15}R^8$, R^4 is H, and R^{15} and R^8 are taken together to form a heteroaryl ring optionally substituted by 1 or 2 C_1–C_6 alkyl groups. Specific preferred compounds having the foregoing general structure include those wherein R^{15} and R^8 are taken together to form a pyrrolidino, triazolyl, or imidazolyl ring wherein said heteroaryl groups are optionally substituted by 1 or 2 methyl groups.

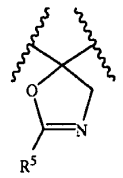
Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is —CH_2SR^8, R^4 is H, and R^8 is selected from C_1–C_{10} alkyl, C_2–C_{10} alkenyl, and C_2–C_{10} alkynyl, wherein said R^8 groups are optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo and C_1–C_6 alkoxy. Specific preferred compounds having the foregoing general structure include those wherein R^8 is methyl, ethyl, or 2-hydroxyethyl.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^4 is H, and R^3 is selected from C_1–C_{10} alkyl, C_2–C_{10} alkenyl, and C_2–C_{10} alkynyl, wherein said R^3 groups are optionally substituted by 1 or 2 substituents independently selected from hydroxy, —C(O)R^{17}, —NR^6R^7, halo, cyano, azido, 5–10 membered heteroaryl, and C_1–C_6 alkoxy. Specific preferred compounds having the foregoing general structure include those wherein R^3 is methyl, allyl, vinyl, ethynyl, 1-methyl-1-propenyl, 3-methoxy-1-propynyl, 3-dimethylamino-1-propynyl, 2-pyridylethynyl, 1-propynyl, 3-hydroxy-1-propynyl, 3-hydroxy-1-propenyl, 3-hydroxypropyl, 3-methoxy-1-propenyl, 3-methoxypropyl, 1-propynyl, n-butyl, ethyl, propyl, 2-hydroxyethyl, formylmethyl, 6cyano-1-pentynyl, 3-dimethylamino-1-propenyl, or 3-dimethylaminopropyl.

Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^4 is H, and R^3 is —$(CH_2)_m$(5–10 membered heteroaryl) wherein m is an integer ranging from 0 to 4. Specific preferred compounds having the foregoing general structure include those wherein R^3 is 2-thienyl, 2-pyridyl, 1-methyl-2-imidazolyl, 2-furyl, or 1-methyl-2-pyrrolyl

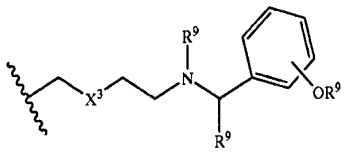
Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^4 is H, and R^3 is —$(CH_2)_m$(C_6C_{10} aryl) wherein m is an integer ranging from 0 to 4. Specific preferred compounds having the foregoing general structure include those wherein R^3 is phenyl.

Specific compounds of formula 1 include those wherein R^2 and R^3 are taken together to form an oxazolyl ring as shown below



wherein R^5 is as defined above.

Specific compounds of formula 1 include those wherein R^3 is selected from the following:



wherein X^3 is O, S or —N(R^{15})—, and wherein the —OR^9 group may be attached at any available carbon on the phenyl group.

The invention also relates to a pharmaceutical composition for the treatment of a bacterial infection or a protozoa infection in a mammal, fish, or bird which comprises a therapeutically effective amount of a compound of formula 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The invention also relates to a method of treating a bacterial infection or a protozoa infection in a mammal, fish, or bird which comprises administering to said mammal, fish or bird a therapeutically effective amount of a compound of formula 1 or a pharmaceutically acceptable salt thereof.

The term "treatment", as used herein, unless otherwise indicated, includes the treatment or prevention of a bacterial infection or protozoa infection as provided in the method of the present invention.

As used herein, unless otherwise indicated, the terms "bacterial infection(s)" and "protozoa infection(s)" include bacterial infections and protozoa infections that occur in mammals, fish and birds as well as disorders related to bacterial infections and protozoa infections that may be treated or prevented by administering antibiotics such as the compounds of the present invention. Such bacterial infections and protozoa infections, and disorders related to such infections, include the following: pneumonia, otitis media, sinusitus, bronchitis, tonsillitis, and mastoiditis related to infection by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus*, or Peptostreptococcus spp.; pharynigitis, rheumatic fever, and glomerulonephritis related to infection by *Streptococcus pyogenes*, Groups C and G streptococci, *Clostridium diptheriae*, or *Actinobacillus haemolyticum*; respiratory tract infections related to infection by *Mycoplasma pneumoniae, Legionella pneumophila, Streptococcus pneumoniae, Haemophilus influenzae*, or *Chlamydia pneumoniae;* uncomplicated skin and soft tissue infections, abscesses and osteomyelitis, and puerperal fever related to infection by *Staphylococcus aureus,* coagulase-positive staphylococci (i.e., *S. epidermidis, S. hemolyticus*, etc.), *Streptococcus pyogenes, Streptococcus agalactiae*, Streptococcal groups C-F (minute-colony streptococci), viridans streptococci, *Corynebacterium minutissimum,* Clostridium spp., or *Bartonella henselae;* uncomplicated acute urinary tract infections related to infection by *Staphylococcus saprophyticus* or Enterococcus spp.; urethritis and cervicitis; and sexually transmitted diseases related to infection by *Chlamydia trachomatis, Haemophilus ducreyi, Treponema pallidum, Ureaplasma urealyticum,* or *Neisseria gonorrheae;* toxin diseases related to infection by *S. aureus* (food poisoning and Toxic shock syndrome), or Groups A, B, and C streptococci; ulcers related to infection by *Helicobacter pylori*; systemic febrile syndromes related to infection by *Borrelia recurrentis;* Lyme disease related to infection by *Borrelia burgdorferi*; conjunctivitis, keratitis, and dacrocystitis related to infection by *Chlamydia trachomatis, Neisseria gonorrhoeae, S. aureus, S. pneumoniae, S. pyogenes, H. influenzae,* or Listeria spp.; disseminated *Mycobacterium avium* complex (MAC) disease related to infection by *Mycobacterium avium,* or *Mycobacterium intracellulare;* gastroenteritis related to infection by *Campylobacter jejuni;* intestinal protozoa related to infection by Cryptosporidium spp.; odontogenic infection related to infection by viridans streptococci; persistent cough related to infection by *Bordetella pertussis;* gas gangrene related to infection by *Clostridium perfringens* or Bacteroides spp.; and atherosclerosis related to infection by *Helicobacter pylori* or *Chlamydia pneumoniae.* Bacterial infections and protozoa infections and disorders related to such infections that may be treated or prevented in animals include the following: bovine respiratory disease related to infection by *P. haem., P. multocida, Mycoplasma bovis,* or Bordetella spp.; cow enteric disease related to infection by *E. coli* or protozoa (i.e., coccidia, cryptosporidia, etc.); dairy cow mastitis related to infection by *Staph. aureus, Strep. uberis, Strep. agalactiae, Strep. dysgalactiae,* Klebsiella spp., Corynebacterium, or Enterococcus spp.; swine respiratory disease related to infection by *A. pleuro., P. multocida,* or Mycoplasma spp.; swine enteric disease related to infection by *E. coli, Lawsonia intracellularis,* Salmonella, or *Serpulina hyodyisinteriae;* cow footrot related to infection by Fusobacterium spp.; cow metritis related to infection by *E. coli*; cow hairy warts related to infection by *Fusobacterium necrophorum* or *Bacteroides nodosus;* cow pink-eye related to infection by *Moraxella bovis; cow premature abortion related to infection by protozoa (i.e. neosporium); urinary tract infection in dogs and cats related to infection by E. coli;* skin and soft tissue infections in dogs and cats related to infection by *Staph. epidermidis, Staph. intermedius,* coagulase neg. *Staph.* or *P. multocida*; and dental or mouth infections in dogs and cats related to infection by Alcaligenes spp., Bacteroides spp., Clostridium spp., Enterobacter spp., Eubacterium, Peptostreptococcus, Porphyromonas, or Prevotella. Other bacterial infections and protozoa infections and disorders related to such infections that may be treated or prevented in accord with the method of the present invention are referred to in J. P. Sanford et al., "The Sanford Guide To Antimicrobial Therapy," 26th Edition, (Antimicrobial Therapy, Inc., 1996).

The present invention also relates to a method of preparing the above compound of formula 1, or a pharmaceutically acceptable salt thereof, wherein R^3 is $—CH_2S(O)_nR^8$, $—CH^2OR^8$ or $—CH_2NR^8R^{15}$, wherein n, R^{15} and R^8 are as defined above with the proviso that R^8 is not H where R^3 is $—CH_2S(O)_nR^8$, which comprises treating a compound of the formula

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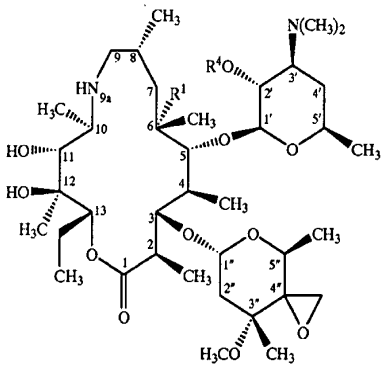

wherein R^1 and R^4 are as defined above, with a compound of the formula HSR^8, HOR^8 or $HNR^{15}R^8$, wherein n, R^{15} and R^8 are as defined above, optionally followed by oxidation of the $—SR^8$ substituent to form $—S(O)R^8$ or $—S(O)_2R^8$.

In a further aspect of the above process of preparing the compound of formula 1, or a pharmaceutically acceptable salt thereof, the above compound of formula 5 is prepared by treating a compound of the formula

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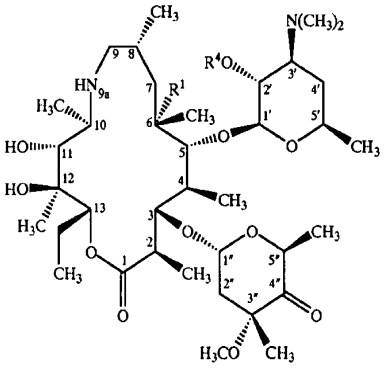


wherein R^1 and R^4 are as defined above, with $(CH_3)_3S(O)_nX^2$, wherein n is 0 or 1 and X^2 is halo, $—BF_4$ or

—PF_6, preferably iodo or —BF_4, in the presence of a base such as as potassium tert-butoxide, sodium tert-butoxide, sodium ethoxide, sodium hydride, 1,1,3,3-tetramethylguanidine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, potassium hexamethyldisilazane (KHMDS), potassium ethoxide, or sodium methoxide, preferably KHMDS or a sodium-containing base such as sodium hydride.

The present invention also relates to the above compounds of formulas 4 and 5 which, as indicated above, are useful in the preparation of the above compounds of formula 1 and pharmaceutically acceptable salts thereof.

The term "hydroxy protecting group", as used herein, unless otherwise indicated, includes acetyl, benzyloxycarbonyl, and various hydroxy protecting groups familiar to those skilled in the art include the groups referred to in T. W. Greene, P. G. M. Wuts, "Protective Groups In Organic Synthesis," (J. Wiley & Sons, 1991).

The term "halo", as used herein, unless otherwise indicated, includes fluoro, chloro, bromo or iodo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, cyclic or branched moieties, or mixtures thereof. It is to be understood that where cyclic moieties are intended, at least three carbons in said alkyl must be present Such cyclic moieties include cyclopropyl, cyclobutyl and cyclopentyl.

The term "alkoxy", as used herein, unless otherwise indicated, includes —O-alkyl groups wherein alkyl is as defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The term "5–10 membered heteroaryl", as used herein, unless otherwise indicated, includes aromatic heterocyclic groups containing one or more heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 5 to 10 atoms in its ring system. Examples of suitable 5–10 membered heteroaryl groups include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, (1,2,3,)- and (1,2,4)-triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, oxazolyl, pyrrolyl and thiazolyl.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of the present invention. The compounds of the present invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of the present invention are those that form non-toxic acid addition salts, i&, salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, add phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. The compounds of the present invention that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above.

Those compounds of the present invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline earth metal salts and, particularly, the calcium, magnesium, sodium and potassium salts of the compounds of the present invention.

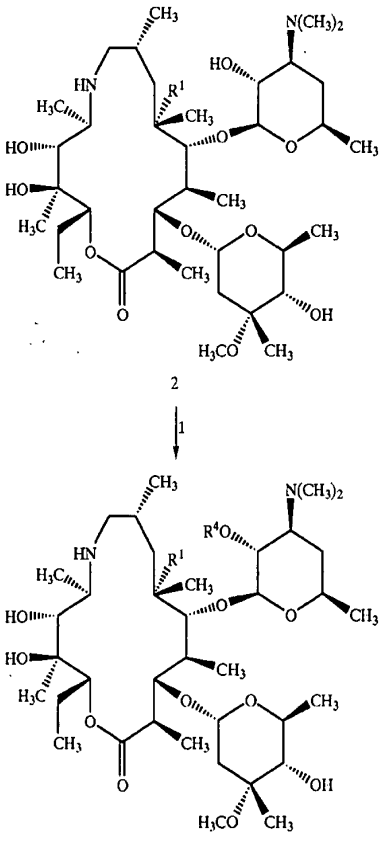
Certain compounds of the present invention may have asymmetric centers and therefore exist in different enantiomeric and diastereomic forms. This invention relates to the use of all optical isomers and stereoisomers of the compounds of the present invention, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them.

The present invention includes the compounds of the present invention, and the pharmaceutically acceptable salts thereof, wherein one or more hydrogen, carbon or other atoms are replaced by isotopes thereof. Such compounds may be useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding assays.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of of the present invention may be prepared according to Schemes 1–3 below and the description that follows.

Scheme 1



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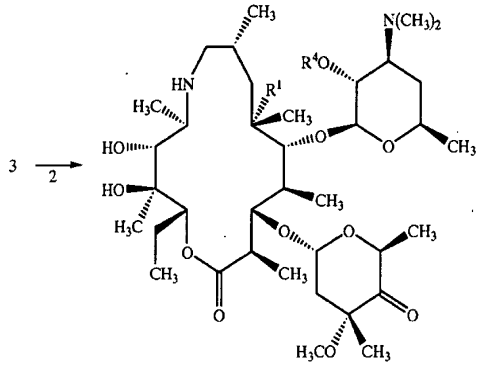

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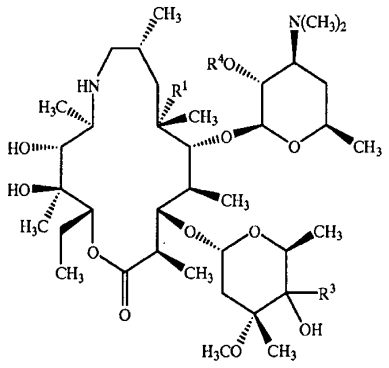

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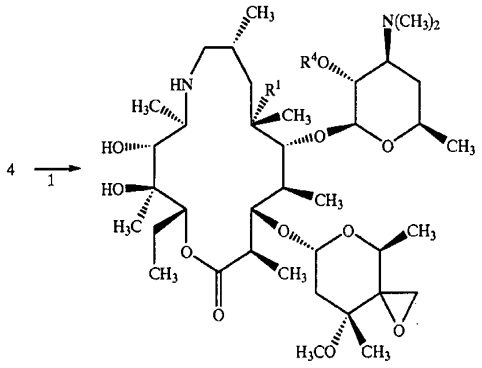
Scheme 2



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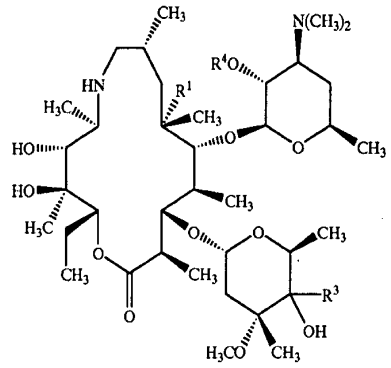

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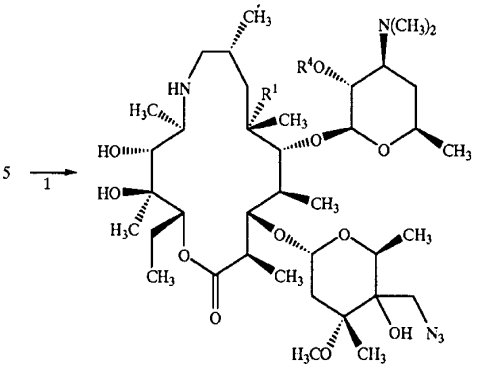
Scheme 3



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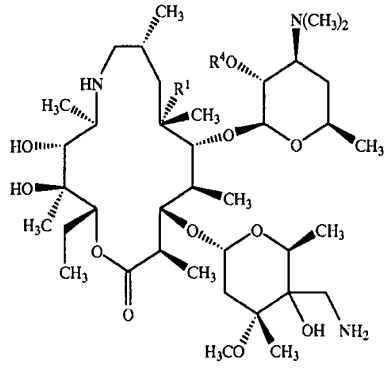

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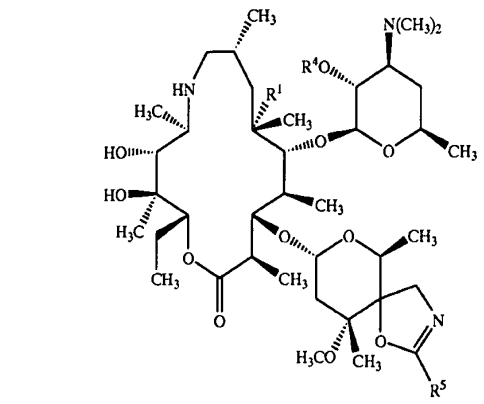

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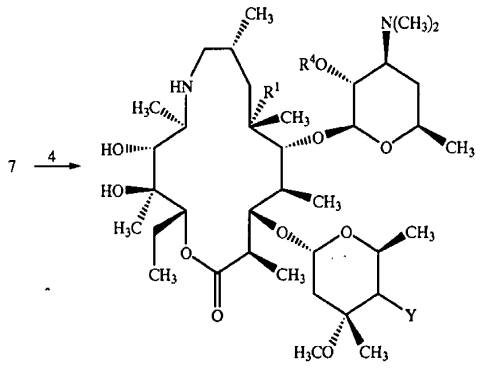

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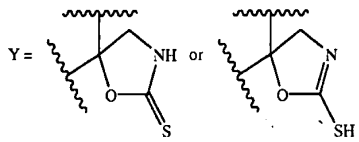

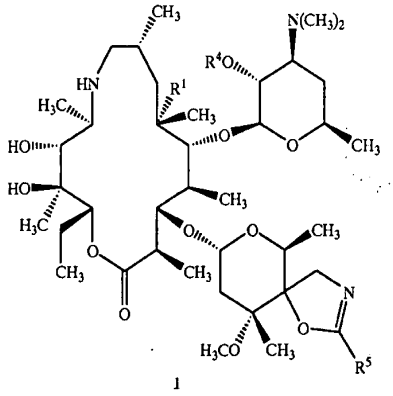

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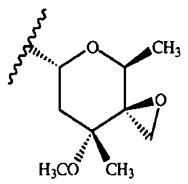
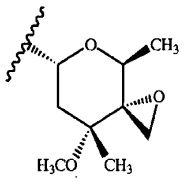
The compounds of the present invention are readily prepared. Referring to the Schemes illustrated above, the starting compound of formula 2 may be prepared according to one or more methods familiar to those skilled in the art including the synthetic methods described in U.S. Pat. Nos. 4,474,768 and 4,517,359, referred to above. In step 1 of Scheme 1, the C-2' hydroxy group may be selectively protected by treating the compound of formula 2 with one equivalent of acetic anhydride in dichloromethane in the absence of external base to provide the compound of formula 3 wherein R^4 is acetyl. The acetyl protecting group may be removed by treating the compound of formula 3 with methanol at 23–65° C. for 10–48 hours. The C-2' hydroxy may also be protected with other hydroxy protecting groups familiar to those skilled in the art, such as the benzyloxycarbonyl (Cbz) group. The C-9a amino group may also require protection before further synthetic modifications are performed. Suitable protecting groups for the amino moiety are Cbz and t-butyloxycarbonyl (Boc) groups. To protect the C-9a amino group, the macrolide may be treated with t-butyl dicarbonate in anhydrous tetrahydrofuran (THF) or benzyloxycarbonyl N-hydroxysuccinimide ester or benzylchloroformate to protect the amino group as its t-butyl or benzyl carbamate. Both the C-9a amino and C-2' hydroxy may be selectively protected with the Cbz group in one step by treating the compound of formula 2 with benzylchloroformate in THF and water. The Boc group may be removed by acid treatment and the Cbz group may be removed by conventional catalytic hydrogenation. In the following description, it is assumed that the C-9a amino moiety and the C-2' hydroxy group are protected and deprotected as would be deemed appropriate by those skilled in the art.

In step 2 of Scheme 1, the C-4" hydroxy group of the compound of formula 3 is oxidized to the corresponding ketone by methods familiar to those skilled in the art, including one or more methods described in the Journal of Antibiotics, 1988, pages 1029–1047. For example, the ketone of formula 4 may be prepared with DMSO and an appropriate activating agent. Typical reaction conditions for the oxidation include: (a) Moffatt oxidation which employs N-ethyl-N'-(N,N-dimethylaminopropyl)carbodiimide and DMSO in the presence of pyridinium trifluoroacetate; or (b) Swem oxidation in which oxalyl chloride and DMSO in CH_2Cl_2 is followed by the addition of triethylamine or alternatively trifluoroacetic anhydride and DMSO in CH_2Cl_2 is followed by the addition of triethylamine. In step 3 of Scheme 1, the compound of formula 4 is treated with R^3MgX^1 or R^3—Li and $Mg(X^1)_2$, wherein X^1 is a halide such as chloro or bromo, in a solvent such as THF, ethylene glycol dimethyl ether (DME), diisopropyl ether, toluene, diethyl ether, or tetramethylenediamine (TMEDA), hexanes, or a mixture of two or more of the foregoing solvents, preferably an ether solvent, at a temperature ranging from about -78° C. to about room temperature (20–25° C.), to provide the compound of formula 1 wherein R^2 is hydroxy and R^1, R^3 and R^4 are as defined above.

Scheme 2 illustrates the preparation of compounds of formula 1 through use of an epoxide intermediate. In step 1 of Scheme 2, the compound of formula 5 may be generated by two methods. In one method (Method A), the compound of formula 4 is treated with $(CH_3)_3S(O)X^2$, wherein X^2 is halo, —BF_4 or —PF_6, preferably iodo, in the presence of a base such as potassium tert-butoxide, sodium tert-butoxide, sodium ethoxide, sodium hydride, 1,1,3,3-tetramethylguanidine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicylo[4.3.0]non-5-ene, potassium ethoxide, or sodium methoxide, preferably a sodium-containing base such as sodium hydride, in a solvent such as THF, an ether solvent, dimethylformamide (DMF), or methyl sulfoxide (DMSO), or a mixture of two or more of the foregoing solvents, at a temperature within the range of about 0° C. to about 60° C., the compound of formula 5 is generated in wich the following configuration of the epoxide moiety may predominate



In a second method (Method B), the compound of formula 4 is treated with $(CH_3)_3SX^2$, wherein X^2 is halo, $—BF_4$ or $—PF_6$, preferably $—BF_4$, in the presence of a base such as as potassium tert-butoxide, sodium ethoxide, sodium tert-butoxide, sodium hydride, 1,1,3,3-tetramethylguanidine, 1,8diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicylo[4.3.0] non-5-ene, potassium ethoxide, potassium hexamethyldisilazide (KHMDS) or sodium methoxide, preferably KHMDS, in a solvent such as THF, an ether solvent, DMF, or DMSO, or a mixture of two or more of the foregoing solvents, at a temperature within the range of about -78° C. to about 60° C., to provide the compound of formula 5 in which the following configuration of the epoxide moiety predominates



In step 2 of Scheme 2, the compound of formula 5 may be converted to a compound of formula 1 wherein R^2 is hydroxy and R^3 is a group that is attached to the C-4" carbon through a methylene group, such as where R^3 is $—CH_2NR^{15}R^8$ or $—CH_2S(O)_nR^8$ wherein n, R^{15} and R^8 are as defined above. To prepare a compound of formula 1 wherein R^3 is $—CH_2NR^{15}R^8$, the compound of formula 5 may be treated with a compound of the formula $HNR^{15}R^8$, wherein R^{15} and R^8 are as defined above, in the absence or presence of a polar solvent such as water, methanol, or THF, or a mixture of the foregoing solvents, at a temperature ranging from about room temperature to about 100° C., preferably about 60° C., optionally in the presence of a halide reagent such as potassium iodide, lithium perchlorate, magnesium perchlorate, lithium tetrafluoroborate, pyridinium hydrochloride, or a tetraalkylammonium halide reagent such as tetrabutylammonium iodide. To prepare a compound of formula 1 wherein R^3 is $—CH_2S(O)_nR^8$ wherein n and R^8 are as defined above, the compound of formula 5 may be treated with a compound of the formula HSR^8 in the presence of K_2CO_3, KI, or sodium methoxide, in an aromatic solvent such as methanol, benzene or toluene at a temperature ranging from about room temperature to about 120° C. As appropriate, the sulfur moiety may be oxidized to —SO— or $—SO_2—$ according to methods familiar to those skilled in the art. To prepare a compound of formula 1 wherein R^3 is $—CH_2SR^8$ and R^8 is $—(CH_2)_qCR^{11}R^{12}(CH_2)_rNR^{13}R^{14}$, wherein the substituents of said R^8 group are as defined above, the compound of formula 5 may be treated with a compound of the formula $HS—(CH_2)_qCR^{11}R^{12}(CH_2)_r—NPhth$, wherein NPhth represents phthalimido, and potassium iodide to provide the compound of formula 1 wherein R^3 is $—CH_2S(CH_2)_qCR^{11}R^{12}(CH_2)_rNH_2$, after removal of the phthalimido moiety, which may be further modified as necessary. Using the same or an analogous method, a compound of formula 1 wherein R^3 is $—CH_2NR^{15}R^8$ and R^8 is $—(CH_2)_qCR^{11}R^{12}(CH_2)_rNR^{13}R^{14}$ may be prepared by treating the compound of formula 5 with either a compound of the formula $HNR^9—(CH_2)_qCR^{11}R^{12}(CH_2)_r—NR^{13}R^{14}$ or a compound of the formula $H_2N—(CH_2)_qCR^{11}R^{12}(CH_2)_r—NH_2$ followed by reductive alkylation of the nitrogen atoms. Using the same or an analogous method, a compound of formula 1 wherein R^3 is $—CH_2OR^8$ and R^8 is as defined above may be prepared by treating a compound of formula 5 with a compound of the formula HOR^8.

Scheme 3 illustrates the preparation of compounds of formula 1 in which R^2 and R^3 are taken together to form an oxazolyl moiety. In step 1 of Scheme 3, the compound of formula 5 is treated with sodium azide in the presence of NH_4Cl in methanol or water, or a mixture of the two solvents, at a temperature ranging from about 0° C. to about 100° C., preferably about 80° C., to provide the compound of formula 6. In step 2 of Scheme 3, the compound of formula 6 may be converted to the corresponding amine of formula 7 via conventional catalytic hydrogenation. Preferably, such hydrogenation is done using Pd (10% on carbon) powder under an H_2 atmosphere (1 atm). The resulting amine of formula 7 may be converted to various compounds of formula 1 wherein R^3 is $—CH_2NR^{15}R^8$ using conventional synthetic methods such as reductive amination.

In step 3 of Scheme 3, the compound of formula 7 may be converted to the compound of formula 1 wherein R^2 and R^3 are taken together as shown by treating the compound of formula 7 with a compound of formula $R^5—CN$, $R^5—C{=}N(OCH_3)$, $R^5—C{=}N(OC_2H_5)$, $R^5—C(O)Cl$, or $R^5—CO_2H$, wherein R^5 is as defined above, except it is not NH_2, in the presence or absence of an acid, such as HCl, or a Lewis acid, such as $ZnCl_2$ or BF_4Et_3O, or a base, such as NaOH or TEA, in a solvent such as THF, a chlorohydrocarbon (such as CH_2Cl_2 or chlorobenzene), at a temperature ranging from about room temperature to reflux. In the alternative, the compound of formula 7 may proceed as indicated in steps 4 and 5 of Scheme 3. In step 4 of Scheme 3, the compound of formula 7 is treated with thiocarbonyldiimidazole in methylene chloride at a temperature ranging from about 0° C. to room temperature to provide the compound of formula 13. In step 5 of Scheme 3, the compound of formula 13 is treated with R^5-X^1, wherein X^1 is a halide such as bromo or iodo, and a base such as sodium methoxide in a solvent such as methanol or acetone, or a mixture of the two solvents, at a temperature ranging from about 0° C. to room temperature.

The compounds of the present invention may have asymmetric carbon atoms and therefore exist in different enantiomeric and diastereomeric forms. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. Enantiomers may be separated by converting the enantiomeric mixtures into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. The use of all such isomers, including diastereomer mixtures and pure enantiomers, are considered to be part of the present invention.

The compounds of the present invention that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration

to mammals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid.

Those compounds of the present invention that are acidic in nature are capable of forming base salts with various cations. For compounds that are to be administered to mammals, fish or birds such salts must be pharmaceutically acceptable. Where a pharmaceutically acceptable salt is required, it may be desirable to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter to a pharmaceutically acceptable salt in a process analogous to that described above relating to the conversion of pharmaceutically unacceptable acid addition salts to pharmaceutically acceptable salts. Examples of base salts include the alkali metal or alkaline-earth metal salts and particularly the sodium, amine and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of the present invention. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium, magnesium, various amine cations, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable bases with cations such as sodium, potassium, calcium, magnesium, various amine cations, etc., and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The antibacterial and antiprotozoa activity of the compounds of the present invention against bacterial and protozoa pathogens is demonstrated by the compound's ability to inhibit growth of defined strains of human (Assay I) or animal (Assays II and II) pathogens.

Assay I

Assay I, described below, employs conventional methodology and interpretation criteria and is designed to provide direction for chemical modifications that may lead to compounds that circumvent defined mechanisms of macrolide resistance. In Assay I, a panel of bacterial strains is assembled to include a variety of target pathogenic species, including representatives of macrolide resistance mechanisms that have been characterized. Use of this panel enables the chemical structure/activity relationship to be determined with respect to potency, spectrum of activity, and structural elements or modifications that may be necessary to obviate resistance mechanisms. Bacterial pathogens that comprise the screening panel are shown in the table below. In many cases, both the macrolide-susceptible parent strain and the macrolide-resistant strain derived from it are available to provide a more accurate assessment of the compound's ability to circumvent the resistance mechanism. Strains that contain the gene with the designation of ermA/ermB/ermC are resistant to macrolides, lincosamides, and streptogramin B antibiotics due to modifications (methylation) of 23S rRNA molecules by an Erm methylase, thereby generally prevent the binding of all three structural classes. Two types of macrolide efflux have been described; msrA encodes a component of an efflux system in staphylococci that prevents the entry of macrolides and streptogramins while mefA/E encodes a transmembrane protein that appears to efflux only macrolides. Inactivation of macrolide antibiotics can occur and can be mediated by either a phosphorylation of the 2'-hydroxyl (mph) or by cleavage of the macrocyclic lactone (esterase). The strains may be characterized using conventional polymerase chain reaction (PCR) technology and/or by sequencing the resistance determinant. The use of PCR technology in this application is described in J. Sutcliffe et al., "Detection Of Erythromycin-Resistant Determinants By PCR", Antimicrobial Agents and Chemotherapy, 40(11), 2562–2566 (1996). The assay is performed in microtiter trays and interpreted according to *Performance Standards for Antimicrobial Disk Susceptibility Tests—Sixth Edition: Approved Standard*, published by The National Committee for Clinical Laboratory Standards (NCCLS) guidelines; the minimum inhibitory concentration (MIC) is used to compare strains. Compounds are initially dissolved in dimethylsulfoxide (DMSO) as 40 mg/ml stock solutions.

Strain Designation	Macrolide Resistance Mechanism(s)
Staphylococcus aureus 1116	susceptible parent
Staphylococcus aureus 1117	ermB
Staphylococcus aureus 0052	susceptible parent
Staphylococcus aureus 1120	ermC
Staphylococcus aureus 1032	msrA, mph, esterase
Staphylococcus hemolyticus 1006	msrA, mph
Streptococcus pyogenes 0203	susceptible parent
Streptococcus pyogenes 1079	ermB
Streptococcus pyogenes 1062	susceptible parent
Streptococcus pyogenes 1061	ermB
Streptococcus pyogenes 1064	ermB
Streptococcus agalactiae 1024	susceptible parent
Streptococcus agalactiae 1023	ermB
Streptococcus pneumoniae 1018	susceptible
Streptococcus pneumoniae 1046	ermB
Streptococcus pneumoniae 1095	ermB
Streptococcus pneumoniae 1175	mefE
Streptococcus pneumoniae 0085	susceptible
Haemophilus influenzae 0131	susceptible
Moraxella catarrhalis 0040	susceptible
Moraxella catarrhalis 1055	erythromycin intermediate resistance
Escherichia coli 0266	susceptible

Assay II is utilized to test for activity against *Pasteurella multocida* and Assay III is utilized to test for activity against *Pasteurella haemolytica.*

Assay II

This assay is based on the liquid dilution method in microliter format. A single colony of *P. multocida* (strain 59A067) is inoculated into 5 ml of brain heart infusion (BHI) broth. The test compounds are prepared by solubiliz-

ing 1 mg of the compound in 125 μl of dimethylsulfoxide (DMSO). Dilutions of the test compound are prepared using uninoculated BHI broth. The concentrations of the test compound used range from 200 μg/ml to 0.098 μg/ml by two-fold serial dilutions. The *P. multocida* inoculated BHI is diluted with uninoculated BHI broth to make a 10^4 cell suspension per 200 μl. The BHI cell suspensions are mixed with respective serial dilutions of the test compound, and incubated at 37° C. for 18 hours. The minimum inhibitory concentration (MIC) is equal to the concentration of the compound exhibiting 100% inhibition of growth of *P. multocida* as determined by comparison with an uninoculated control.

Assay III

This assay is based on the agar dilution method using a Steers Replicator. Two to five colonies isolated from an agar plate are inoculated into BHI broth and incubated overnight at 37° C. with shaking (200 rpm). The next morning, 300 μl of the fully grown *P. haemolytica* preculture is inoculated into 3 ml of fresh BHI broth and is incubated at 37° C. with shaking (200 rpm). The appropriate amounts of the test compounds are dissolved in ethanol and a series of two-fold serial dilutions are prepared. Two ml of the respective serial dilution is mixed with 18 ml of molten BHI agar and solidified. When the inoculated *P. haemolytica* culture reaches 0.5 McFarland standard density, about 5 μl of the *P. haemolytica* culture is inoculated onto BHI agar plates containing the various concentrations of the test compound using a Steers Replicator and incubated for 18 hours at 37° C. Initial concentrations of the test compound range from 100–200 μg/ml. The MIC is equal to the concentration of the test compound exhibiting 100% inhibition of growth of *P. haemolytica* as determined by comparison with an uninoculated control.

The in vivo activity of the compounds of formula (I) can be determined by conventional animal protection studies well known to those skilled in the art, usually carried out in mice.

Mice are allotted to cages (10 per cage) upon their arrival, and allowed to acclimate for a minimum of 48 hours before being used. Animals are inoculated with 0.5 ml of a 3×10^3 CFU/ml bacterial suspension (*P. multocida* strain 59A006) intraperitoneally. Each experiment has at least 3 non-medicated control groups including one infected with 0.1× challenge dose and two infected with 1× challenge dose; a 10× challenge data group may also be used. Generally, all mice in a given study can be challenged within 30–90 minutes, especially if a repeating syringe (such as a Cornwall® syringe) is used to administer the challenge. Thirty minutes after challenging has begun, the first compound treatment is given. It may be necessary for a second person to begin compound dosing if all of the animals have not been challenged at the end of 30 minutes. The routes of administration are subcutaneous or oral doses. Subcutaneous doses are administered into the loose skin in the back of the neck whereas oral doses are given by means of a feeding needle. In both cases, a volume of 0.2 ml is used per mouse. Compounds are administered 30 minutes, 4 hours, and 24 hours after challenge. A control compound of known efficacy administered by the same route is included in each test. Animals are observed daily, and the number of survivors in each group is recorded. The *P. multocida* model monitoring continues for 96 hours (four days) post challenge.

The PD_{50} is a calculated dose at which the compound tested protects 50% of a group of mice from mortality due to the bacterial infection which would be lethal in the absence of drug treatment.

The compounds of formula I, and the pharmaceutically acceptable salts thereof (hereinafter "the active compounds"), may be administered through oral, parenteral, topical, or rectal routes in the treatment of bacterial and protozoa infections. In general, these compounds are most desirably administered in dosages ranging from about 0.2 mg per kg body weight per day (mg/kg/day) to about 200 mg/kg/day in single or divided doses (i.e., from 1 to 4 doses per day), although variations will necessarily occur depending upon the species, weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 4 mg/kg/day to about 50 mg/kg/day is most desirably employed. Variations may nevertheless occur depending upon the species of mammal, fish or bird being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compounds may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by the routes previous indicate and such administration may be carried out in single or multiple doses. More particularly, the active compounds may be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compounds are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active compound may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of an active compound in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomnplished by standard pharmaceutical techniques will known to those skilled in the art.

Additionally, it is also possible to administer the active compounds of the present invention topically and this may be done by way of creams, jellies, gels, pastes, patches, ointments and the like, in accordance with standard pharmaceutical practice.

For administration to animals other than humans, such as cattle or domestic animals, the active compounds may be administered in the feed of the animals or orally as a drench composition.

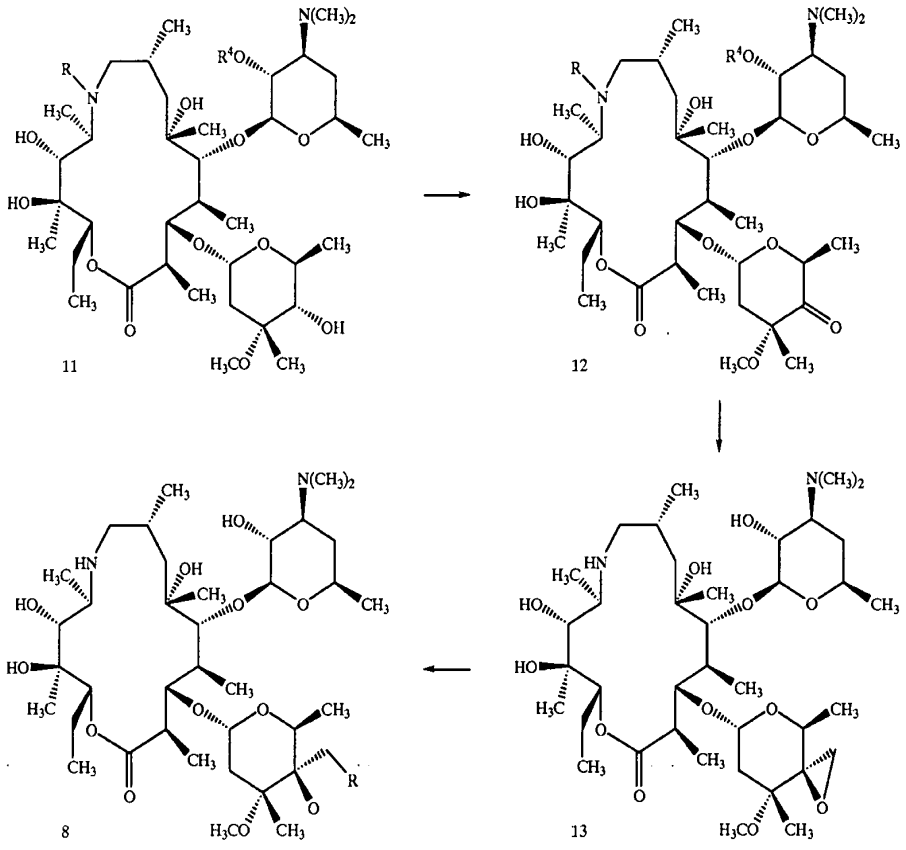
The active compounds may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The active compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide phenyl, polyhydroxyethylaspartamide-phenol, or polyphenyleneoxide-polylysine substituted with palmitoyl-residues. Furthermore, the active compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-inked or amphipathic block copolymers of hydrogels.

The following Examples further illustrate the method and intermediates of the present invention. It is to be understood that the present invention is not limited to the specific details of the Examples provided below.

TABLE 1

The compounds of Examples 1–32 have the general formula 8 below with the R substituents indicated in the table below. The compounds were prepared as described in Preparations 1–7 below. In the table, the yield and mass spectra ("Mass Spec") data apply to the final product.



Example	R Substituent	Preparation	Yield	Mass Spec
1	n-butylamino	1	48%	820
2	2-methoxyethylamino	1	52%	822
3	piperidino	1	61%	832
4	morpholino	1	39%	834
5	t-butylamino	1	23%	821
6	benzylamino	1	34%	854
7	cyclopentylamino	2	23%	832

TABLE 1-continued

The compounds of Examples 1–32 have the general formula 8 below with the R substituents indicated in the table below. The compounds were prepared as described in Preparations 1–7 below. In the table, the yield and mass spectra ("Mass Spec") data apply to the final product.

8	propylamino	2	11%	806
9	anilino	1	21%	841
10	2-methoxypropylamino	1	46%	835
11	azido	3	46%	790
12	hexylamino	1	56%	847
13	3-ethoxypropylamino	1	52%	851
14	diethylamino	2	53%	821
15	N-methylbutylamino	1	76%	835
16	N-methylpropylamino	2	59%	819
17	ethylamino	5	18%	792
18	cyclopropylamino	2	50%	804
19	ethylmethylamino	2	92%	806
20	2,2,2-trifluoroethylamino	2	67%	846
21	allylamino	1	59%	804
22	2-hydroxyethylthio	6	44%	826
23	dimethylamino	1	71%	793
24	imidazol-1-yl	4	42%	815
25	bis(2-hydroxyethyl)amino	7	21%	853
26	pyrrolidino	2	40%	818
27	2-hydroxy-ethylmethylamino	2	23%	822
28	1,2,3-triazol-1-yl	4	69%	817
29	2-propynylamino	2	51%	802
30	2-methylimidazol-1-yl	4	14%	829
31	diallylamino	2	29%	844
32	1,2,4-triazol-1-yl	4	34%	816

Preparation Methods for Table 1

With reference to the Scheme illustrated above, the compound of formula 11 wherein R is H and R^4 is H (25 g (34.01 mmol, 1.0 equiv)) was mixed in a solution with phenol red in 250 mL THF and 125 mL water. To this pink solution was slowly added 29 mL (204.1 mmol, 6.0 equiv) benzylchloroformate and 2N NaOH to keep the solution basic. The reaction was allowed to stir at room temperature overnight. The reaction mixture was concentrated to remove the THF and the aqueous phase was adjusted to the pH of 9.5 and extracted 3x500 mL EtOAc. The combined organic layers were washed with 500 mL brine and then dried over Na_2CO_3. Filtration, concentration of the filtrate, and drying afforded a crude material. Further purification was done by column chromatography (100% CH_2Cl_2 to remove impurities and then 5% MeOH/CH_2Cl_2 to remove product) to yield 32.6 g (96%) of a yellowish solid which was the compound of formula 11 wherein R and R^4 were both Cbz (MS (FAB) m/z 1003). 32.6 g (32.49 mmol, 1.0 equiv) of this product was dissolved in 216.6 mL CH_2Cl_2 and 27.3 mL of DMSO. To this solution, 21.2 g (110.5 mmol, 3.4 equiv) of EDC and 24.1 g (124.8 mmol, 3.8 equiv) PTFA were added. After stirring overnight the reaction was quenched with 150 mL of water and the pH was adjusted to 9.5 with the addition of 2N NaOH. The organic layer was extracted 3x150 mL CH_2Cl_2 and dried over Na_2SO_4. Filtration, concentration of the filtrate, and drying afforded a crude yellow oil. Further purification on a silica gel column (2% MeOH/$CHCl_3$) to give 25.6 g (79%) of a yellowish solid which was the compound of formula 12 wherein both R and R^4 were Cbz.

14 g (13.98 mmol, 1.0 equiv) of the compound of formula 12 prepared as described above was dissolved in 1 L of 2-propanol and to this was added 14 g of 10% Pd/C. The mixture was hydrogenated at 50 psi for three days. 14 g of 10% Pd/C was added to the reaction and allowed to stir for another day. This was repeated again and stirred for another day. The catalyst was removed by filtration through Celite and a minimal wash of 2-propanol to yield 4.8 g (47%) of the compound of formula 12 wherein both R and R^4 were H (MS (APCi) m/z 734).

6.7 g (169.17 mmol, 6.2 equiv) of NaH (60% in oil dispersion) was washed twice with 150 mL hexanes to remove the mineral oil. The solid was diluted in 335 mL of DMSO and 38.4 g (174.62 mmol, 6.4 equiv) of Me_3SOI was added in three portions. The solution was stirred for an hour or until it turned clear. 20 g (27.29 mmol, 1.0 equiv) of the compound of formula 12 wherein both R and R^4 were H was dissolved in 200 mL of THF. The ketone was transferred via cannula to the reaction flask and allowed to stir for 20 minutes. The reaction was quenched with 500 mL saturated $NaHCO_3$, extracted 4x500 mL EtOAc, and dried over Na_2SO_4. Filtration, concentration of the filtrate, and drying gave the crude oil. Further purification on 750 g of silica gel (5% MeOH/$CHCl_3$, 0.3 % NH_4OH) afforded 8.8 g (43%) of a white solid which was the compound of formula 13 (MS (TS) m/z 747).

Preparation 1

250–500 mg of the above compound of formula 13 was dissolved in 1–2 mL of an amine corresponding to the R substituent specified in Table 1. A catalytic amount (20 mg) of pyridinium hydrochloride was added and the solution was heated to 50–85° C. for one to seven days. The reaction was worked up by quenching with 50 mL saturated $NaHCO_3$, extracted with 3x50 mL CH_2Cl_2, and dried over Na_2SO_4. Filtration, concentration of the filtrate, and drying gave a crude oil or solid. Further purification on a silica gel column (2–4% MeOH/$CHCl_3$, 0.2% NH_4OH) afforded the final product.

Preparation 2

250–500 mg of the above compound of formula 13 was dissolved in 1–2 mL of an amine corresponding to the R substituent specified in Table 1 in a sealed tube. A catalytic amount (20 mg) of pyridinium hydrochloride was added and

the solution was heated to 50–75° C. for one to five days. The reaction was worked up by quenching with 50 mL saturated $NaHCO_3$, extracted with 3x50 mL CH_2Cl_2, and dried over Na_2SO_4. Filtration, concentration of the filtrate, and drying gave a crude oil or solid. Further purification on a silica gel column (2–4% MeOH/$CHCl_3$, 0.2% NH_4OH) afforded the final product.

Preparation 3

100 mg of the above compound of formula 13 was dissolved in MeOH/H_2O (8:1). Sodium azide (7 equiv) and ammonium chloride (5.5 equiv) were added and the solution was heated to 60° C. for two days. The reaction was worked up by quenching with 50 mL saturated $NaHCO_3$, extracted with 3x50 mL CH_2Cl_2, and dried over Na_2SO_4. Filtration, concentration of the filtrate, and drying gave a crude oil or solid. Further purification on a silica gel column (2% MeOH/$CHCl_3$, 0.2% NH_4OH) afforded the final product.

Preparation 4

150–250 mg of the above compound of formula 13 was dissolved in 1–2 mL MeOH/H_2O or MeOH. To this was added the heteroaromatic reagent corresponding to the R substituent specified in Table 1 (10–50 equiv) and a catalytic amount (20 mg) of pyridinium hydrochloride. The reaction mixture was heated at 45–50° C. for one to three days. The reaction was then quenched with 100 mL saturated $NaHCO_3$, extracted with 3x25 mL CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated to a solid. The solid was re-dissolved in 100 mL EtOAc and washed with 3x25 mL 2N NaOH to remove the excess reagent. Further purification on a silica gel column (2–5% MeOH/$CHCl_3$, 0.2% NH_4OH) afforded the final product.

Preparation 5

50 mg of the above compound of formula 13 was dissolved in 1 mL of an amine corresponding to the R substituent specified in Table 1. A small scoop of neutral alumina was added and the mixture was stirred at room temperature for seven days. The reaction was worked up by filtering through Celite™ (diatomaceous earth) and concentrated to a crude solid. Further purification on a silica gel column (5% MeOH/$CHCl_3$, 0.2% NH_4OH) afforded the final product

Preparation 6

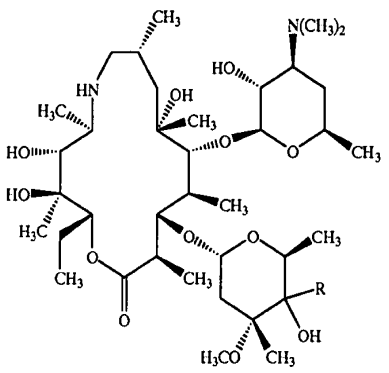
270 mg of the above compound of formula 13 was dissolved in 4 mL benzene. To this was added excess K_2CO_3 and 0.5 mL of thiol. The mixture stirred at room temperature for 16 hours. The reaction was quenched with 100 mL saturated $NaHCO_3$, extracted with 3x25 mL CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated to a solid. Further purification on a silica gel column (2% MeOH/$CHCl_3$, 0.2% NH_4OH) afforded the final product.

Preparation 7

250 mg of the above compound of formula 13 was dissolved in 0.5 mL bis(2-hydroxyethyl)amine and 2 mL 2-propanol in a sealed tube. A catalytic amount (20 mg) of pyridinium hydrochloride was added and the solution was heated to 75° C. for seven days. The reaction was worked up by quenching with 50 mL saturated $NaHCO_3$, extracted with 3x50 mL CH_2Cl_2 and dried over Na_2SO_4. Filtration, concentration of the filtrate, and drying gave a crude oil or solid. Further purification on a silica gel column (2% MeOH/$CHCl_3$, 0.2% NH_4OH) afforded the final product.

Examples 33–68 below describe the preparation of compounds having the general structure of formula 9 below wherein R is as defined in the examples.

9



EXAMPLE 33

To a solution of the compound of formula 4 wherein R^4 is H (0.059 g, 0.08 mmol) in THF (2 mL) at 0° C. was added allylmagnesium bromide in Et_2O (1.0 M, 0.5 mL). After 2 hours at stirring was continued at roam temperature for 12 hours. The reaction was diluted with a saturated aqueous solution of sodium bicarbonate (10 mL) and EtOAc (20 mL). After separation, the aqueous layer was washed with EtOAc (2x15 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (20 mL) and brine (25 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2 :NH_4OH (6:93:1 to 10:89:1) afforded 0.011 g (18% yield) of the compound of formula 9 wherein R is allyl: MS: 776 (TS).

EXAMPLE 34

To a solution of the compound of formula 4 wherein R^4 is H (0.059 g, 0.08 mmol) in DME (3 mL) at 0° C. was added vinylmagnesium bromide in THF (1.0 M, 0.56 mL). After stirring at 0° C. for 1 hour and at room temperature for 1 hour, the reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (10 mL) and EtOAc (10 mL). After separation, the aqueous layer was washed with EtOAc (3x10 mL). The combined organic extracts were washed witty a saturated aqueous solution of sodium bicarbonate (15 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1) afforded 0.016 g (26% yield) of the compound of formula 1 wherein R is vinyl: MS: 762 (FAB).

EXAMPLE 35

To a flask containing $MgCl_2$ (0.095 g, 1 mmol) and DME (1 mL) at 0° C. was added 2-thienyl lithium (1.0 M, 1.0 mL). After 0.5 hour, a solution of the compound of formula 4 wherein R^4 is H (0.073 g, 0.1 mmol) in DME (2 mL) was introduced and stirring was continued at 0° C. for 1 hour, then at room temperature for 0.5 hour. The reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (10 mL) and EtOAc (15 mL). After separation, the aqueous layer was washed with EtOAc (3x10 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (15 mL) and brine

(20 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1) afforded 0.012 g (15% yield) of the compound of formula 9 wherein R is 2-thienyl: MS: 817 (TS).

EXAMPLE 36

To a solution of the compound of formula 4 wherein R^4 is H (0.147 g, 0.2 mmol) in DME (10 mL) at 0° C. was added ethynylmagnesium bromide in THF (0.5 M, 2.8 mL). After stirring at 0° C. for 1 hour and at room temperature for 1 hour, the reaction mixture was diluted with water (20 mL) and EtOAc (35 mL). After separation, the aqueous layer was washed with EtOAc (3×25 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (30 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.068 g (45% yield) of the compound of formula 9 wherein R is ethynyl: MS: 759 (API).

EXAMPLE 37

To a solution of the compound of formula 4 wherein R^4 is H (0.220 g, 0.3 mmol) in DME (15 mL) at 0° C. was added 1-methyl-1-propenylmagnesium bromide in THF (0.5 M, 42 mL). After stirring at room temperature for 3 hours, the reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (20 mL) and EtOAc (30 mL). After separation, the aqueous layer was washed with EtOAc (3×10 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (25 mL) and brine (30 ml), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.068 g (26% yield) of the compound of formula 2 wherein R is 1-1ethyl-1-propenyl: MS: 790 (API).

EXAMPLE 38

To a solution of butylmagnesium bromide in THF (2.0 M, 1.0 ml) at 0° C. was added a solution of methyl propargyl ether (0.154 g, 0.2 mmol) in DME (3 mL). After stirring at 0° C. for 0.5 hour, a solution of the compound of formula 4 wherein R^4 is H (0.147 g, 0.2 mmol) in DME (7 mL) was added. After stirring at 0° C. for 0.5 hour and room temperature for 4 hours, the reaction mixture was diluted with water (20 mL) and EtOAc (25 mL). After separation, the aqueous layer was washed with EtOAc (3×20 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (20 mL) and brine (25 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.081 g (50% yield) of the compound of formula 9 wherein R is 3-methoxy-1-propynyl: MS: 803 (API).

EXAMPLE 39

To a solution of methylmagnesium bromide in Et_2O (3.0 M, 1.8 mL) at 0° C. was added a solution of 1-dimethylamino-2-propyne (0.154 g, 0.2 mmol) in THF (5 mL). After stirring at 0° C. for 6 hours, a solution of the compound of formula 4 wherein R^{13} is H (0.147 g, 0.2 mmol) in DME (10 mL) was added at room temperature. After stirring at room temperature for 3 hours, the reaction mixture was diluted with water (40 mL) and EtOAc (50 mL). After separation, the aqueous layer was washed with EtOAc (3×50 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (40 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 8:91:1) afforded 0.140 g (57% yield) of the compound of formula 9 wherein R is 3-dimethylamino-1-propynyl: MS: 817 (API).

EXAMPLE 40

To a solution of methylmagnesium bromide in Et_2O (3.0 M, 1.8 mL) and DME (1 mL) at 0° C. was added a solution of 2-ethynylpyridine (0.186 g, 1.8 mmol) in DME (2 mL). After stirring at 0° C. for 1 hour and room temperature for 1 hour, a solution of the compound of formula 4 wherein R^4 is H (0.110 g, 0.15 mmol) in DME (7 mL) was added at room temperature. After stirring at room temperature for 3 hours, the reaction mixture was diluted with water (20 mL) and EtOAc (40 mL). After separation, the aqueous layer was washed with EtOAc (3×30 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.066 g (53% yield) of the compound of formula 9 wherein R is 2-pyridylethynyl: MS: 836 (API).

EXAMPLE 41

To a round bottomed flask containing $MgBr_2$ (0.552 g, 3.0 mmol) and propynyl lithium (0.069 g, 1.5 mmol) at 0° C. was added THF (5 mL). After 4 hours, a solution of the compound of formula 4 wherein R^4 is H (0.110 g, 0.15 mmol) in DME, (10 mL) was introduced at room temperature and stirring was continued for 3 hours. The reaction mixture was diluted with water (30 mL) and EtOAc (30 mL). After separation, the aqueous layer was washed with EtOAc (3×40 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 7:92:1) afforded 0.060 g (52% yield) of the compound of formula 9 wherein R is 1-propynyl: MS: 817 (TS).

EXAMPLE 42

To a solution of methylmagnesium bromide in Et_2O (3.0 M, 0.6 mL) mL) at 0° C. was added a solution of propargyl alcohol (0.346 mL, 0.289 g, 2.25 mmol) in THF (5 mL). After stirring at 0° C. for 3 hours, a solution of the compound of formula 4 wherein R^4 is H (0.110 g, 0.15 mmol) in DME (10 mL) was added at room temperature. After stirring at room temperature for 2 hours, the reaction mixture was diluted with water (35 mL) and EtOAc (50 mL). After separation, the aqueous layer was washed with EtOAc (3×40 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 15:84:1) afforded 0.038 g (32% yield) of the compound of formula 9 wherein R is 3-hydroxy-1-propynyl: MS: 790 (API).

EXAMPLE 43

Palladium catalyst (20 mg, 10% Pd/C) was added to a solution of the compound from example 42 in isopropanol (8 mL). The reaction vessel was flushed and filled with hydro-

gen (50 psi) and shaken at room temperature for 24 hours. Filtration of an aliquot of the reaction mixture through Celite™ and concentration under vacuum afforded the compound of formula 9 wherein R is 3-hydroxy-1-propenyl: MS: 791 (API).

EXAMPLE 44

Palladium catalyst (20 mg, 10% Pd/C) was added to the remaining solution from example 43 and the reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 48 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 8:91:1) afforded 0.018 g (57% yield) of the compound of formula 9 wherein R is 3-hydroxypropyl: MS: 793 (API)

EXAMPLE 45

Palladium catalyst (15 mg, 10% Pd/C) was added to a solution of the title compound from example 38 in isopropanol (8 mL). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 24 hours. Filtration of an aliquot of the reaction mixture through Celite™ and concentration under vacuum afforded the compound of formula 9 wherein R is 3-methoxy-1propenyl: MS: 806 (API).

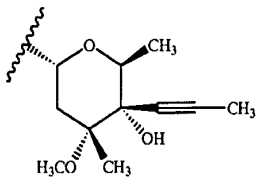
EXAMPLE 46

Palladium catalyst (15 mg, 10% Pd/C) was added to the remaining solution from example 45 and the reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 48 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 7:92:1) afforded 0.017 g (73% yield) of the compound of formula 9 wherein R is 3-methoxy-propyl: MS: 808 (API)

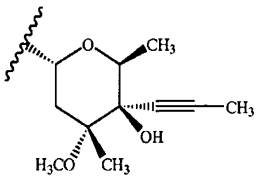
EXAMPLE 47

To a solution of the compound of formula 4 wherein R^4 is benzyloxycarbonyl (0.520 g, 0.6 mmol) in DME (6 mL) and TMEDA (2 mL) at −40° C. was added propynyl lithium (0.414 g, 9.0 mmol). After stirring at −40° C. for 2.5 hours, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (30 mL) and EtOAc (30 mL). After separation, the aqueous layer was washed with EtOAc (3×10 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (25 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (4:95.6:0.4 to 6:93.6:0.4) afforded 0.157 g (29% yield) of the faster eluting diastereomer, along with 0.071 g (13% yield) of the slower eluting diastereomer and 0.070 g (13% yield) of a mixture of the diastereomers.

A solution of the faster eluting diastereomer (0.157 g, 0.17 mmol) in MeOH (5 mL) was allowed to stir at 30° C. for 6 days. Upon concentration under vacuum, silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (4:95.6:04 to 6:93.6:0.4) afforded 0.102 g (78% yield) of the compound of formula 9 wherein R is 1-propynyl according to the following configuration at the C-4" carbon (MS: 774 (API)):



A solution of the slower eluting diastereomer (0.071 g, 0.078 mmol) in MeOH (3 mL) was allowed to stir at 30° C. for 6 days. Upon concentration under vacuum, silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (4:95.6:0.4 to 6:93.6:04) afforded 0.041 g (68% yield) of material identical to that described by the compound of Example 41 which corresponds to the compound of formula 9 wherein R is 1-propynyl according to the following configuration at the C-4" carbon (MS: 774 (API)):

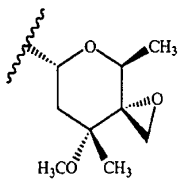


EXAMPLE 48

To a suspension of trimethylsulfonium tetrafluoroborate (1.03 g, 6.3 mmol) in THF (40 mL) at −10° C. was added KHMDS (1.20 g, 6.0 mmol). After stirring below 0° C. for 0.5 hour, the reaction vessel was cooled to −78° C. and a solution of the compound of formula 4 wherein R^{13} is benzyloxycarbonyl (2.60 g, 3 mmol) in DME (10 mL) was added. After 0.5 hour, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (40 mL) and EtOAc (50 mL). After separation, the aqueous layer was washed with EtOAc (3×30 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (2:97.6:0.4 to 4:95.5:0.4) afforded 0.834 g (32% yield) of the compound of formula 5 wherein R^4 is benzyloxycarbonyl (MS: 881 (API)).

EXAMPLE 49

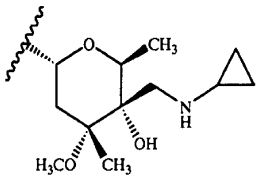
A solution of the compound of Example 48 (0.176 g, 0.2 mmol) in MeOH (5 mL) was allowed to stir at 50° C. for 4 days. Upon concentration, silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (4:95.6:0.4 to 6:93.5:0.4) afforded 0.107 g (72% yield) of the compound of formula 5 wherein R^4 is hydrogen and the epoxide moiety at C-4" has the following configuration (MS: 748 (API)):



EXAMPLE 50

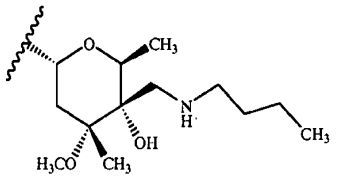
A solution of the compound of Example 48 (0.176 g, 0.2 mmol), potassium iodide (2.32 g, 14 mmol) and cyclopro-

pylamine (2.43 mL, 2.00 g, 35 mmol) in MeOH (30 mL) was allowed to stir at 50° C. for 2 days. Upon concentration, the residue was dissolved in water (50 mL) and EtOAc (100 mL). After separation, the aqueous layer was washed with EtOAc (3x50 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (40 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with $MeOH:CH_2Cl_2:NH_4OH$ (4:95.6:0.4 to 6:93.5:0.4) afforded 0.377 g (69% yield) of the compound of formula 9 wherein R is cyclopropylaminomethyl according to the following configuration at the C-4" carbon (MS: 805 (API)):



EXAMPLE 51

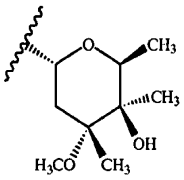
A solution of the compound of Example 48 (0.176 g, 0.2 mmol), tetrabutylammonium iodide (0.739 g, 2.0 mmol) and butylamine (0.395 mL, 0.293 g, 4 mmol) in MeOH (5 mL) was allowed to stir at 50° C. for 2 days. Upon concentration, the residue was dissolved in water (20 mL) and EtOAc (20 mL). After separation, the aqueous layer was washed with EtOAc (3x20 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with $MeOH:CH_2Cl_2:NH_4OH$ (4:95.6:0.4 to 6.93.5:0.4) afforded 0.088 g (54% yield) of the compound of formula 9 wherein R is propylaminomethyl according to the following configuration at the C-4" carbon (MS: 821 (API)):



EXAMPLE 52

To a solution of a compound of formula 4 wherein R^4 is benzyloxycarbonyl and the hydrogen attached to the C-9a nitrogen is replaced by benzyloxycarbonyl (0.500 g, 0.499 mmol) in THF (15 mL) 0° C. was added methylmagnesium bromide in Et_2O (3.0 M, 1.2 mL). After 20 minutes, the reaction was diluted with EtOAc (30 mL) and water (50 mL). After separation, the aqueous layer was washed with EtOAc (3x35 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (100 mL) and brine (120 mL), dried over Na_2SO_4 and concentrated under vacuum to afford 0.500 g (98% yield) of an off-white foam. (MS: 1017, 845 (API)).

Palladium catalyst (0250 g, 10% Pd/C) was added to a solution of the compound described above (0.500 g 0.491 mmol) in isopropanol (50 mL). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 48 hours. Additional palladium catalyst (0.250 g, 10% Pd/C) was added and hydrogenation was continued at 50 psi for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. The resulting oil was dissolved in isopropanol (50 mL), palladium catalyst was added (0.312 g, 10% Pd/C), and hydrogenation was continued at 50 psi for 24 hours. Additional palladium catalyst (0.170 g, 10% Pd/C) was added and hydrogenation was continued at 50 psi for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with $MeOH:CH_2Cl_2:NH_4OH$ (8:91:1 to 10:89:1) afforded 0.120 g (33% yield) of the compound of formula 9 wherein R is methyl according to the following configuration at the C-4" carbon (MS: 749 (API)):



EXAMPLE 53

To a solution of a compound of formula 4 wherein R^4 is benzyloxycarbonyl and the hydrogen attached to the C-9a nitrogen is replaced by benzyloxycarbonyl (0.101 g, 0.101 mmol) in THF (2 mL) at -78° C. was added phenylmagnesium bromide in THF (1.01 M, 1.0 mL). After 15 minutes, stirring was continued 0° C. for 1 hour, then at room temperature for 12 hours. The reaction was diluted with a 10% aqueous solution of sodium bicarbonate (10 mL) and EtOAc (20 mL). After separation, the aqueous layer was washed with EtOAc (3x15 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (20 mL) and brine (25 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with $MeOH:CH_2Cl_2:NH_4OH$ (5:94:1 to 25:74:1) afforded 0.048 g (46% yield) of a white foam (MS 1080 (LSIMS)).

Palladium catalyst (0.024 g, 10% Pd/C) was added to a solution of the compound described above (0.024 g, 0.022 mmol) in methanol (15 mL). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with $MeOH:CH_2Cl_2:NH_4OH$ (5:94.5:1 to 10:89:1) afforded 0.010 g (28% yield) of the compound of formula 9 wherein R is phenyl: MS: 811 (LSIMS).

EXAMPLE 54

To a solution of the starting compound used in Example 53 (0.300 g, 0.30 mmol) in THF (3 mL) at 0° C. was added n-butylmagnesium chloride in THF (2.0 M, 1.5 mL). After 20 minutes the reaction was diluted with water and EtOAc (20 mL). After separation, the aqueous layer was washed with EtOAc (3x50 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (50 mL) and brine (55 mL), dried over Na_2SO_4 and concentrated under vacuum to afford 0.295 g (93% yield) of an off-white foam (MS: 1060 (FAB)).

Palladium catalyst (0.087 g, 10% Pd/C) was added to a solution of the compound described above (0.087 g, 0.082 mmol) in isopropanol (15 mL). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room

temperature for 24 hours. Additional palladium catalyst (0.087 g, 10% Pd/C) was added and hydrogenation was continued at 50 psi for 60 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (5:94.5:0.5 to 10:89:1) afforded 0.010 g (28% yield) of the compound of formula 9 wherein R is n-butyl: MS: 792 (API).

EXAMPLE 55

To a solution of the starting compound used in Example 53 (0.200 g, 0.20 mmol) in THF (2 mL) at 0° C. was added ethylmagnesium bromide in THF (1.0 M, 2.0 mL). After 20 minutes the reaction was diluted with water and EtOAc (20 mL). After separation, the aqueous layer was washed with EtOAc (3x30 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (50 mL) and brine (55 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (5:94.5:0.5 to 20:79:1) afforded 0.079 g (38% yield) of a white foam (MS: 1033 (LSIMS)).

Palladium catalyst (0.035 g, 10% Pd/C) was added to a solution of the compound described above (0.079 g, 0.077 mmol) in ethanol (20 mL). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 24 hours. Additional palladium catalyst (0.036 g, 10% Pd/C) was added and hydrogenation was continued at 50 psi for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum, affording 0.056 g (96% yield) of the compound of formula 9 wherein R is ethyl: MS: 763 (TS).

EXAMPLE 56

To a solution of the starting compound used in Example 53 (0.300 g, 0.30 mmol) in THF (3 mL) at 0° C. was added isopropenylmagnesium chloride in THF (0.5 M, 6.0 mL). After 20 minutes the reaction was diluted with water and EtOAc (20 mL). After separation, the aqueous layer was washed with EtOAc (3x30 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (50 mL) and brine (55 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (3:96.9:0.1 to 20:79.9:0.1) afforded 0.063 g (20% yield) of a white foam (MS: 1045 (LSIMS)).

Palladium catalyst (0.075 g, 10% Pd/C) was added to a solution of the compound described above (0.150 g, 0.165 mmol) in ethanol (30 mL). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 24 hours. Additional palladium catalyst (0.075 g, 10% Pd/C) was added and hydrogenation was continued at 50 psi for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2: NH_4OH (6:93:1 to 10:89:1) afforded 0.024 g (19% yield) of the compound of formula 9 wherein R is isopropenyl: MS: 775 (TS).

EXAMPLE 57

To a solution of the starting compound used in Example 53 (0.750 g, 0.75 mmol) in THF (12 mL) at 0 ° C. was added allylmagnesium chloride in THF (2.0 M, 3.0 mL). After 15 minutes the reaction was diluted with water and EtOAc (40 mL). After separation, the aqueous layer was washed with EtOAc (3x50 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 15:84:1)afforded 0.530 g (68% yield) of an off-white foam (MS: 1044, 910 (API)).

Palladium catalyst (0.175 g, 10% Pd/C) was added to a solution of the compound described above (0.350 g, 0.335 mmol) in isopropanol (100 mL). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 24 hours. Additional palladium catalyst (0.150 g, 10% Pd/C) was added and hydrogenation was continued at 50 psi for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum.

Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.148 g (57% yield) of the compound of formula 9 wherein R is propyl: MS: 778 (API).

EXAMPLE 58

To a solution of the compound used as a starting material in Example 53 (0.750 g, 0.75 mmol) in THF (12 mL) at 0° C. was added allylmagnesium chloride in THF (2.0 M, 3.0 mL). After minutes the reaction was diluted with water and EtOAc (40 mL). After separation, the aqueous layer was washed with EtOAc (3x50 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 15:84:1) afforded 0.530 g (68% yield) of an off-white foam (MS: 1044 (API)).

A solution of the compound described above (0.104 g, 0.100 mmol) and (1S)(+)-10-camphor sulfonic acid (0.046 g, 0200 mmol) in MeOH (4 mL) was cooled to -78° C. and treated with ozone until a deep blue color persisted. The reaction was purged with oxygen, dimethylsulfide (0.13 mL, 1.76 mmol) and pyridine (0.20 mL, 2.42 mmol) were added and stirring was continued for 12 hours. CH_2Cl_2 (30 mL) and 10% aqueous solution of sodium bicarbonate (10 mL) were added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.024 g (23% yield) of an off-white foam (MS: 912 (API)).

To a solution of the compound described above (0.022 g, 0.024 mmol) in MeOH (1 mL) was added sodium borohydride (0.001 g, 0.024 mmol). Additional sodium borohydride (0.004 g, 1.00 mmol) was added over a period of 3 hours. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and 10% sodium bicarbonate solution (20 mL). After separation, the aqueous layer was extracted-with CH_2Cl_2 (3x30 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum to afford 0.022 g (100% yield) of a yellow foam (MS: 914 (API)).

Palladium catalyst (0.012 g, 10% Pd/C) was added to a solution of the compound described above (0.022 g, 0.024 mmol) in isopropanol (10 mL). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 24 hours. Additional palladium catalyst (0.020 g, 10% Pd/C) was added and hydrogenation was continued at 50 psi for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2: NH_4OH

(8:91:1 to 10:89:1) afforded 0.005 mg (23% yield) of the compound of formula 9 wherein R is 2-hydroxyethyl: MS: 779 (API).

EXAMPLE 59

To a solution of the starting compound used in Example 53 (0.750 g, 0.75 mmol) in THF (12 mL) at 0° C. was added allylmagnesium chloride in THF (2.0 M, 3.0 mL). After 15 minutes the reaction was diluted with water and EtOAc (40 mL). After separation, the aqueous layer was washed with EtOAc (3x50 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 15:84:1) afforded 0.530 g (68% yield) of an off-white foam (MS: 1044 (API)).

A solution of the compound described above (0.104 g, 0.100 mmol) and (1S)-(+)-10-camphor sulfonic acid (0.046 g, 0.200 mmol) in MeOH (4 mL) was cooled to −78° C. and treated with ozone until a deep blue color persisted. The reaction was purged with oxygen, dimethylsulfide (0.13 mL, 1.76 mmol) and pyridine (0.20 mL, 2.42 mmol) were added and stirring was continued for 12 hours. CH_2Cl_2 (30 mL) and 10% aqueous solution of sodium bicarbonate (10 mL) were added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.024 g (23% yield) of an off-white foam (MS: 912 (API)).

Palladium catalyst (0.040 g, 10% Pd/C) was added to a solution of the compound described above (0.057 g, 0.063 mmol) in isopropanol (15 mL). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 24 hours. Additional palladium catalyst (0.040 g. 10% Pd/C) was added and hydrogenation was continued at 50 psi for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.010 g (15yield) of the compound of formula 9 wherein R is formylmethyl: MS: 777 (API).

EXAMPLE 60

To a solution of 2-bromopyridine (0.474 g, 3.0 mmol) in THF (5 mL) at −78° C. was added n-butyl lithium (3.0 M, 1.2 mL) at −78° C. After 40 minutes, the solution was transferred via a cannula cooled with a dry ice jacket to a flask containing $MgCl_2$ (0.428 g, 4.5 mmol) and ether (4 mL) at −78° C. After 15 minutes, a solution of a compound of formula 4 wherein R^4 is benzyloxycarbonyl (0.260 g, 0.3 mmol) in THF (3 mL) at −78° C. was introduced and stirring was continued allowing the reaction to warm to room temperature over several hours. After 3.5 hours, the reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (20 mL) and EtOAc (30 mL). After separation, the aqueous layer was washed with EtOAc (3x50 mL).

The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (60 mL), dried over Na_2SO_4 and concentrated under vacuum.

Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93.3:0.7 to 10:89:1) afforded 0.023 g (9.5% yield) of the compound of formula 9 wherein R is 2-pyridyl: MS: 812 (API).

EXAMPLE 61

To a round bottom flask containing n-butyl lithium (3.0 M, 1.62 mL) in diethyl ether (15 mL) at −78° C. was added chilled (−78° C.) 3-bromopyridine (0.790 g, 5 mmol) via a cannula cooled with a dry ice jacket Stirring continued at −78° C. for 35 minutes. A suspension of $MgBr_2$ diethyl ethereate (0.114 g, 0.440 mmol) in diethyl ether (3 mL) at −78° C. was added via a cannula cooled with a dry ice jacket to the 3-pyridyl lithium solution. A solution of a compound of formula 4 wherein R^4 is benzyloxycarbonyl (0.347 g, 0.400 mmol) in diethyl ether (3 mL) at −78° C. was introduced via cannula. Stirring continued at −78° C. for 2 hours and slowly allowed to warm to 0° C. over 3 hours. The reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (20 mL) and EtOAc (30 mL). After separation, the aqueous layer was washed with EtOAc (3x50 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (60 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (4:95.4:0.6 to 20:79:1) afforded 0.075 g (26% yield) of a white foam (MS: 947, 812 (API)).

Palladium catalyst (0.073 g, 10% Pd/C) was added to a solution of the compound described above (0.073 g, 0.077 mmol) in isopropanol (30 mL). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 48 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with. MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 8:91:1) afforded 0.032 g (51% yield) of the compound of formula 9 wherein R is 3pyridyl: MS: 812 (API).

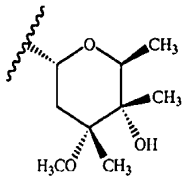
EXAMPLE 62

To a solution of methyl magnesium bromide in diethyl ether (3.0 M, 1.8 mL) at 0° C. was added a solution of 5-hexynenitrile (0.63 mL, 6.00 mmol) in THF (5 mL). After stirring at 0° C. for 6 hours, a solution of the compound of formula 4 wherein R^4 is H (0.220 g, 0.300 mmol) in DME (10 mL) was added and stirring was continued at 0° C. for 0.5 hour, then at room temperature for 4 hours. The reaction mixture was diluted with water (20 mL) and EtOAc (25 mL), the layers were separated and the aqueous layer was washed with EtOAc (3x20 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (20 mL) and brine (25 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.035 g (14% yield) of the compound of formula 9 wherein R is 6-cyano1-pentynyl: MS: 827 (API).

EXAMPLE 63

To a solution of the compound of Example 49, except wherein R^4 is benzyloxycarbonyl, (0.101 g, 0.115) in DME (3 mL) was added $LiAlH_4$ (1.0 M, 2.1 mL) dropwise. After 10 minutes the reaction mixture was treated sequentially with water (0.044 mL), 15% NaOH solution (0.044 mL), and water (0.132 mL), then stirred at rt for 0.5 hour. The mixture was diluted with EtOAc (20 mL) and water (20 mL). After separation the aqueous layer was extracted with EtOAc (3x30 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (60 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with. MeOH:CH_2Cl_2:NH_4OH (3:96.5:0.5 to 3.5:95:0.5)

afforded 0.042 (49% yield) of the compound of formula 9 wherein R is methyl according to the following configuration at the C-4" carbon (MS: 749 (API)):



EXAMPLE 64

To a solution of 1-methylimidazole (0.41 g, 4.99 mmol) in THF (5 ml) at -78° C. was added n-butyl lithium (2.5M,2.02 ml). After 45 minutes at -78° C. the solution was added via cannula to a flask containing $MgCl_2$ (0.71 g, 7.49 mmol) and THF (5 mL) at 0° C. After 1.5 hours at 0° C., a solution of the starting compound used in Example 53 (0.500 g, 0.499 mmol) in DME (2 mL) was introduced and stirring was continued at 0° C. for 1 hour. The reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (100 mL) and EtOAc (100 mL). After separation, the aqueous layer was washed with EtOAc (3x100 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated under vacuum to afford 0.660 g of a yellow foam (MS: 949 (API)).

Palladium catalyst (0.700 g, 10% Pd/C) was added to a solution of the compound described above in isopropanol (60 mL). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 24 hours. Additional palladium catalyst (0.500 g, 10% Pd/C) was added and hydrogenation was continued at 50 psi for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (1:98:1 to 8:91:1) afforded 0.052 g (13% yield) of the compound of formula 9 wherein R is 1-methylimidazol-2-yl: MS: 816 (API).

EXAMPLE 65

To a solution of furan (0.34 g, 4.99 mmol) in THF (5 ml) at -78° C. was added n-butyl lithium (2.5M, 1.98 ml). After 0.5 hour at -78° C. the solution was added to a flask containing $MgCl_2$ (0.71 g, 7.4 mmol) and THF (5 mL) at 0° C. After 1.5 hours at 0° C., a solution of the starting compound used in Example 53 (0.500 g, 0.499 mmol) in DME (2 mL) was introduced and stirring was continued at 0° C. for 1 hour, then at room temperature for 1 hour. The reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (100 mL) and EtOAc (100 mL). After separation, the aqueous layer was washed with EtOAc (3x100 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL), dried over Na_2O_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (1:98:1 to 8:91:1) afforded 0.096 g (24% yield) of a white foam (MS: 935 (API)).

Palladium catalyst (0.100 g, 10% Pd/C) was added to a solution of the compound described above in isopropanol (15 mL). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 72 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (1:98:1 to 8:91:1) afforded 0.053 g (13% yield) of the compound of formula 9 wherein R is 2-furyl: MS: 802 (API).

EXAMPLE 66

To a solution of N-methylpyrrole (0.184 g, 2.31 mmol) in THF (4 ml) at -78° C. was added n-butyl lithium (2.5M, 0.93 ml). The solution was warmed to room temperature over 1 hour and then added via cannula to a flask containing $MgCl_2$ (0.329 g, 3.46 mmol) and Et_2O (4 ml) at room temperature. After 1 hour, a solution of the compound of formula 4 wherein R^4 is benzyloxycarbonyl (0.200 g. 0.231 mmol) in THF (2 mL) was introduced and stirring was continued at room temperature for 45 minutes. The reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (50 mL) and EtOAc (50 mL). After separation, the aqueous layer was washed with EtOAc (3x50 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum to afford 0.293 g of a yellow foam (MS: 949 (API)).

Palladium catalyst (0.324 g, 10% Pd/C) was added to a solution of the compound described above in isopropanol (30 mL). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 24 hours. Additional palladium catalyst (0.300 g, 10% Pd/C) was added and hydrogenation was continued at 50 psi for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 8:91:1) afforded 0.033 g (18% yield) of the compound formula 9 wherein R is 1-methyl-2-pyrrolyl: MS: 814 (API).

EXAMPLE 67

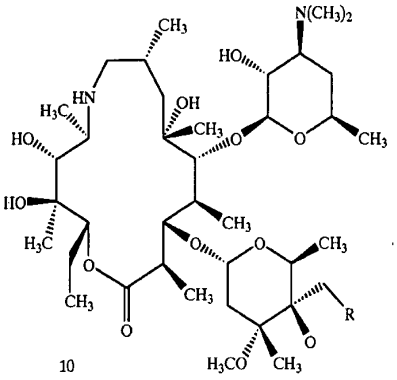
To a solution of unpurified compound prepared as described in Example 39 (0.480 g) in isopropanol (40 mL) was added platinum oxide (0.115 g, 0.505 mmol). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 24 hours. Filtration of an aliquot of the reaction mixture through Celite™ and concentration under vacuum afforded the compound of formula 9 wherein R is 3-dimethylamino-1-propenyl: MS: 819 (API).

EXAMPLE 68

Platinum oxide (0.076 g, 0.335 mmol) was added to the remaining solution from Example 67 and the reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 96 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (4:95:1 to 6:93:1) afforded 0.069 g (15% yield) of the compound of formula 9 wherein R is 3-dimethylpropyl: MS: 821 (API).

TABLE 2

The compounds of Examples 69–81 have the general structure of formula 10 below with the R substituents indicated in the table below. The compounds of Examples 69–82 were prepared following the procedures of Examples 50 and 51, referred to above, with the reaction period specified in the table below. In the table, the yield and mass spectra ("Mass Spec") data apply to the final product.



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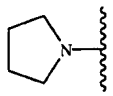
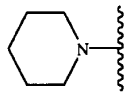
Example	R	Reaction Time (hours)	Yield (%)	Mass Spec
69	1-imidazolyl	72	60	816
70	n-propylamino	48	55	807
71	dimethylamino	24	42	793
72	methylamino	120	55	779
73	ethylamino	120	58	793
74	isopropylamino	48	44	806
75	isobutylamino	48	27	821
76	trimethyleneimino	24	31	804
77	allylamino	24	22	818
78	cyclopropylmethylamino	24	34	820
79	N-ethylmethylamino	48	16	821
80	t-butylamino	96	30	820
81	diethylamino	168	25	818.5
81(a)		48	75	832.6
81(b)		96	95	884.6
82	4-methoxybenzlamino	48	21.7	899.7
83	4-nitrobenzylamino	48	8	888.6
84	4-chlorobenzylamino	48	25.5	890.6
85	3,4-difluorobenzylamino	48	14.5	890.6
85	3-pyridylmethylamino	48	21.0	855.6
86	4-trifluoromethylbenzyl-amino	48	16.5	922.6
87	6-difluorobenzylamino	48	11.0	890.6
88	benzylamino	96	62	854.7
89	4-fluorobenzylamino	48	50.9	872.7
90	3-fluorobenzylamino	48	32.7	872.7
91	2-fluorobenzylamino	48	39.6	872.7
92	2,4-difluorobenzylamino	48	24.6	890.1
93	2,5-difluorobenzylamino	48	28.1	890.1
94	3,5-difluorobenzylamino	48	35.6	890.1
95	1-(4-fluorophenyl)piperazine	48	44.7	927.6
96	2-trifluoromethylbenzyl-amino	48	32.7	922.5
97	4-trifluoromethylbenzyl	48	28.6	938.1
98	3-trifluoromethylbenzyl	48	26.2	922.6
99	2-fluorophenylethylamino	48	33.5	886.2

TABLE 2-continued

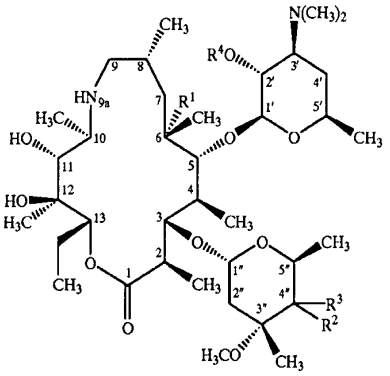
The compounds of Examples 69–81 have the general structure of formula 10 below with the R substituents indicated in the table below. The compounds of Examples 69–82 were prepared following the procedures of Examples 50 and 51, referred to above, with the reaction period specified in the table below. In the table, the yield and mass spectra ("Mass Spec") data apply to the final product.

100	3-fluorophenylethylamino	48	28.7	886.1
101	4-pyridylmethylamino	48	46	855.2
102	methyl, 3-pyridylmethylamino	72	28.8	869.6
103	4-hydroxy-3-methoxybenzyl-amino	48	12.0	900.1
104	piperonylamino	48	14.0	898.1
105	3-methoxybenzylamino	48	33.0	884.1
106	2-methoxybenzylamino	48	24.0	884.5
107	2-pyridylmethylamino	48	28.9	855.1

What is claimed is:

1. A compound of the formula

1



or a pharmaceutically acceptable salt thereof, wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $—CH_2NR^8R^{15}$ or $—CH_2SR^8$;

R^4 is H, acetyl or benzyloxycarbonyl;

R^5 is $—SR^8$, $—(CH_2)_nC(O)R^8$ wherein n is 0 or 1, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, C_2–C_{10} alkynyl, $—(CH_2)_m(C_6$–C_{10} aryl), or $—(CH_2)_m$(5–10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^5 groups are optionally substituted by 1 to 3 R^{16} groups;

each R^6 and R^7 is independently H, hydroxy, C_1–C_6 alkoxy, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, $—(CH_2)_m(C_6$–C_{10} aryl), or $—(CH_2)_m$(5–10 membered heteroaryl), wherein m is an integer ranging from 0 to 4;

each R^8 is independently H, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, C_2–C_{10} alkynyl, $—(CH_2)_qCR^{11}R^{12}(CH_2)_rNR^{13}R^{14}$ wherein q and r are each independently an integer ranging from 0 to 3 except q and r are not both 0, $—(CH_2)_m(C_6$–C_{10} aryl), or $—(CH_2)_m$(5–10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^8 groups, except H, are optionally substituted by 1 to 3 R^{16} groups;

or where R^8 is as $—CH_2NR^8R^{15}$, R^{15} and R^8 may be taken together to form a 4–10 membered monocyclic or polycyclic saturated ring or a 5–10 membered heteroaryl ring, wherein said saturated and heteroaryl rings optionally include 1 or 2 heteroatoms selected from the group consisting of O, S and $—N(R^8)—$, in

addition to the nitrogen to which R^{15} and R^8 are attached, said saturated ring optionally includes 1 or 2 carbon-carbon double or triple bonds, and said saturated and heteroaryl rings are optionally substituted by 1 to 3 R^{16} groups;

each R^9 and R^{10} is independently H or C_1–C_6 alkyl;

each R^{11}, R^{12}, R^{13} and R^{14} is independently selected from the group consisting of H, C_1–C_{10} alkyl, —$(CH_2)_m$(C_6–C_{10} aryl), and —$(CH_2)_m$(5–10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^{11}, R^{12}, R^{13} and R^{14} groups, except H, are optionally substituted by 1 to 3 R^{16} groups;

or R^{11} and R^{13} are taken together to form —$(CH_2)_p$— wherein p is an integer ranging from 0 to 3 such that a 4–7 membered saturated ring is formed that optionally includes 1 or 2 carbon-carbon double or triple bonds;

or R^{13} and R^{14} are taken together to form a 4–10 membered monocyclic or polycyclic saturated ring or a 5–10 membered heteroaryl ring, wherein said saturated and heteroaryl rings optionally include 1 or 2 heteroatoms selected from the group consisting of O, S and —N(R^8)—, in addition to the nitrogen to which R^{13} and R^{14} are attached, said saturated ring optionally includes 1 or 2 carbon-carbon double or triple bonds, and said saturated and heteroaryl rings are optionally substituted by 1 to 3 R^{16} groups;

R_{15} is H, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, or C_2–C_{10} alkynyl, wherein the foregoing R^{15} groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of halo and —OR^9;

each R^{16} is independently selected from the group consisting of halo, cyano, nitro, trifluoromethyl, azido, —$C(O)R^{17}$, —$C(O)OR^{17}$, —$OC(O)OR^{17}$, —$NR^6C(O)R^7$, —$C(O)NR^6R^7$, —NR^6R^7, hydroxy, C_1–C_6 alkyl, C_1–C_6 alkoxy, —$(CH_2)_m$(C_6–C_{10} aryl), and —$(CH_2)_m$(5–10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein said aryl and heteroaryl substituents are optionally substituted by 1 or 2 substituents independently selected from the group consisting of halo, dyano, nitro, trifluoromethyl, azido, —$C(O)R^{17}$, —$C(O)OR^{17}$, —$OC(O)OR^{17}$, —$NR^6C(O)R^7$, —$C(O)NR^6R^7$, —NR^6R^7, hydroxy, C_1–C_6 alkyl, and C_1–C_6 alkoxy;

each R^{17} is independently selected from the group consisting of H, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, C_2–C_{10} alkynyl, —$(CH_2)_m$(C_6–C_{10} aryl), and —$(CH_2)_m$(5–10 membered heteroaryl), wherein m is an integer ranging from 0 to 4;

with the proviso that R^8 is not H where R^3 is —CH_2SR^8.

2. The compound of claim **1** wherein R^3 is —$CH_2NR^{15}R^8$ and R^{15} and R^8 are independently selected from H, C_1–C_{10} alkyl, C_2–C_{10} alkenyl, and C_2–C_{10} alkynyl, wherein the foregoing R^{15} and R^8 groups, except H, are optionally substituted by 1 or 2 substituents independently selected from the group consisting of hydroxy, halo and C_1–C_6-alkoxy.

3. The compound of claim **2** wherein R^{15} and R^8 are each independently selected from the group consisting of H, methyl, ethyl, allyl, n-butyl, isobutyl, 2-methoxyethyl, cyclopentyl, 3-methoxypropyl, 3-ethoxypropyl, n-propyl, isopropyl, 2-hydroxyethyl, cyclopropyl, 2,2,2-trifluoroethyl, 2-propynyl, sec-butyl, tert-butyl, and n-hexyl.

4. The compound of claim **1** wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is —CH_2NHR^8 and R^8 is —$(CH_2)_m$(C_6–C_{10} aryl) wherein m is an integer ranging from 0 to 4.

5. The compound of claim **4** wherein R^8 is phenyl or benzyl.

6. The compound of claim **1** wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is —$CH_2NR^{15}R^8$ and R^{15} and R^8 are taken together to form a 4–10 membered saturated ring.

7. The compound of claim **6** wherein R^{15} and R^8 are taken together to form a piperidino, trimethyleneimino, or morpholino ring.

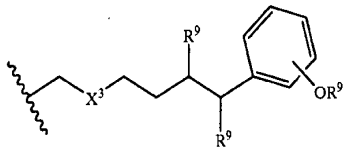
8. The compound of claim **1** wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is —$CH_2NR^{15}R^8$ and R^{15} and R^8 are taken together to form a 5–10 membered heteroaryl ring optionally substitute by 1 or 2 C_1–C_6 alkyl groups.

9. The compound of claim **8** wherein R^{15} and R^8 are taken together to form a pyrrolidino, triazolyl, or imidazolyl ring wherein said heteroaryl groups are optionally substituted by 1 or 2 methyl groups.

10. The compound of claim **1** wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is —CH_2SR^8, and R^8 is selected from the group consisting of C_1–C_{10} alkyl, C_2–C_{10} alkenyl and C_2–C_{10} alkynyl, wherein said R^8 groups are optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo and C_1–C_6 alkoxy.

11. The compound of claim **10** wherein R^8 is methyl, ethyl, or 2-hydroxyethyl.

12. The compound of claim **1** wherein R^4 is H, acetyl or benzyloxycarbonyl, wherein R^3 is selected from the following:



wherein X^3 is O, S or —$N(R^{15})$—, R^9 and R^{15} are as defined in claim **1**, and the —OR^9 group may be attached at any available carbon on the phenyl group.

* * * * *

EXHIBIT B

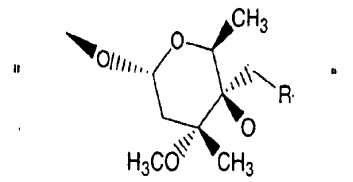
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

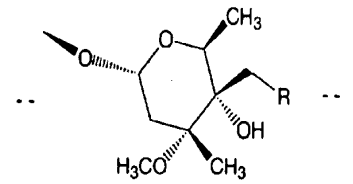
PATENT NO. : 6,420,536 B1
DATED : July 16, 2002
INVENTOR(S) : Brian Scott Bronk et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 37,
Lines 15-25, Table 2, Formula 10, that portion of the formula heading



should read



Signed and Sealed this

Twentieth Day of July, 2004

JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

EXHIBIT C

EXHIBIT C

Summary of DRAXXIN® (Tulathromycin) Regulatory Review Activities

INAD 10-406

Established	September 9, 1998
Last Submission	June 6, 2005
Last Review Under the INAD	April 6, 2005

ADMINISTRATIVE NADA 141-244

Submitted	April 18, 2005
Approved	May 24, 2005

Separate Submissions Under the INAD 10-406

MANUFACTURING METHODS, FACILITIES AND CONTROLS

First Submission	September 30, 2002
Last Submission	July 15, 2004
Final Review Complete	December 30, 2004

Details of submissions

9/30/2002 – Pfizer requested directed review of the drug substance and drug product CMC Technical Section for DRAXXIN.

6/19/2003 – CVM incompletes CMC technical section.

9/4/2003 – Response to an incomplete letter amending the Chemistry, Manufacturing and Control Technical Section.

10/9/2003 – Pfizer Amendment to incomplete response submitted 4 Sep 2003.

2/26/2004 – Pfizer Response to CVM questions regarding CMC submission of 9/4/03.

3/16/2004 – CVM provides comments on incomplete CMC Technical Section.

7/15/2004 – Pfizer submission of an amendment to the CMC technical section alerting CVM of the change in GMP status for the Sandwich UK manufacturing facility.

12/30/2004 – CVM completes Chemistry, Manufacturing and Controls Technical Section.

LABEL TECHNICAL SECTION

First Submission	November 22, 2004
Last Submission	April 4, 2005
Final Review Complete	April 8, 2005

Details of submissions

11/22/2004 – Pfizer submission of the Product Labeling Technical Section.

3/01, 3/02, 3/08/2005 – CVM Informal Technical Section E-mail comments

3/14/2005 – Pfizer submission of DRAXXIN Cattle Label, Approval Amendment

4/4/2005 - Pfizer submission of revised labeling, slaughter withdrawal time revised from 23 to 18 days.

4/8/2005 – CVM completes Technical Section.

HUMAN FOOD SAFETY

This section has 7 parts as follows: Analytical Methods, Comparative Metabolism, Microbial Food Safety, Human Intestinal Flora Correspondence, General Toxicology, Genetic Toxicology, and Residue Chemistry.

First Submission	December 3, 2001
Last Submission	March 14, 2005
Final Review Complete	April 6, 2005

ANALYTICAL METHODS

First Submission	December 19, 2001
Last Submission	August 17, 2004
Final Review Complete	April 6, 2005

Details of submissions

12/19/2001 – Pfizer requests directed review of the total and marker residue depletion studies.

7/8/2002 – CVM reviewed the total and marker residue depletion studies and made several comments including a request for an electronic copy along w/ hard copy updates.

10/28/2003 – Pfizer responds to incomplete Residue Chemistry, Metabolic Profile and Regulatory Method.

2/16/2004 – Pfizer submits response to a CVM request for additional storage stability data to support our Method submission of 28 October 2003 and additional chromatograms to support tabular data.

8/17/2004 – Pfizer submits Regulatory Method and request for HFS Technical Section Complete entitled Multi-Laboratory Sponsor-Monitored Method Trial for the Determinative Procedures for Tulathromycin Marker Residue in Bovine Liver and in Porcine Kidney.

1/31/2005 – CVM accepts determinative and confirmatory procedures however, there remains outstanding residue chemistry questions.

4/05/2005 - CVM completes Human Food Safety Technical Section, Freedom of Information Summary is included.

4/06/2005 - CMV completes All Other Information Technical Section.

COMPARATIVE METABOLISM

First Submission	January 14, 2002
Last Submission	February 23, 2004
Final Review Complete	April 6, 2005

Details of submissions

Cattle/Swine

1/14/2002 – Pfizer requests directed review of study 1576N-60-00-211 describing the metabolism of tulamycin, and the summary report CM-01-01 which relates metabolism across all species studied.

4/24/2002 – Pfizer requests directed review the Technical Section providing results for a battery of genetic toxicology tests.

5/1/2002 – CVM comments on the comparative metabolism study in rats and dogs, and the comparative metabolism study report of rats, dogs, cattle and swine.

8/12/2003 – Pfizer submits response to queries on Comparative Metabolism Studies.

12/02/2003 - CVM accepts portions of PAH response to queries but still has additional questions.

12/9/2003 - CVM responds to swine comparative metabolism studies.

2/23/2004 – Pfizer submits response to CVM regarding questions from H-0116 and request for final concurrence that the toxicology species, dogs and rats are systematically exposed to the major residues present in edible tissue of cattle and swine.

10/22/2004 - Component Complete – cattle (pending isomer ratio question)

10/25/2004 - Component Complete – swine (pending isomer ratio question)

4/05/2005 - CVM completes Human Food Safety Technical Section, Freedom of Information Summary is included.

4/06/2005 - CMV completes All Other Information Technical Section.

MICROBIAL FOOD SAFETY

First Submission	December 3, 2001
Last Submission	September 16, 2004
Final Review Complete	April 6, 2005

Details of submissions

Cattle/Swine

12/3/2001 – Pfizer requests directed review of the in vitro studies pertaining to bacterial resistance related to tulamycin by recommendation of Dr. Weld to minimize the impact of any future review delays while CDER's review remains open.

4/5/2002 – Pfizer amends 03 December 2001 Antimicrobial Resistance Studies including answers to CVM's three queries of 12 March 2002 TelCon.

4/30/2002 – Pfizer submits additional information for (2) of CVM's queries re the Antimicrobial Resistance Studies Submission (gel photographs for 8 isolates and results of the 'micro' and 'macro' methods.

1/2/2003 – CVM reviewed the additional information submitted as requested and finds that Pfizer has satisfied the requirements for microbial food safety and states that this letter serves as a complete letter.

7/8/2004 – CVM decides a review by VMAC committee is needed. Meeting set for 13 October 2004.

9/16/2004 – Document entitled, Tulathromycin solution for Parenteral Injection for Treatment of Bovine and Swine Respiratory Diseases – Microbiological Effects on Bacteria of Human Health Concern - A Qualitative Risk Estimation, submitted for review by the Veterinary Medicine Advisory Committee (VMAC) as part of the microbial food safety assessment.

1/14/2005 - CVM's responds to VMAC presentation. The requirements for microbial food safety with respect to antimicrobial resistance have been met.

4/5/2005 – CVM completes Human Food Safety Technical Section. Freedom of Information Summary is included.

4/6/2005 – CVM completes All Other Information Technical Section.

HUMAN INTESTINAL FLORA CORRESPONDENCE

First Submission	July 15, 2002
Last Submission	July 15, 2002
Final Review Complete	April 6, 2005

Details of submissions

Cattle/Swine

7/15/2002 – Pfizer requests review of the enclosed technical section providing an assessment of the effects of tulathromycin residues on human intestinal flora.

3/28/2003 – CVM comments on the 15 July 2002 residues on human intestinal flora submission.

4/5/2005 – CVM completes Human Food Safety Technical Section, Freedom of Information Summary is included.

4/6/2005 – CVM completes All Other Information Technical Section.

GENERAL TOXICOLOGY

First Submission	6/12/2002
Last Submission	8/31/2004
Final Review Complete	4/6/2005

Details of submissions

6/12/2002 – Pfizer requests directed review of the Toxicology Technical Section including the ADI and SC.

8/27/2002 – Pfizer requests review of the dosing solution data, an amendment to the 12 June 2002 Toxicology Technical Section.

2/12/2003 – CVM reviewed the Toxicology Technical section and makes comments noting that the FOI will not be reviewed until the listed issues are addressed.

7/18/2003 – Pfizer submission of response to CVM 12 Feb 03 letter, including a revised FOI, additional comments of interpretation of the study data.

9/11/2003 – Pfizer requests concurrence on calculated safe concentrations, tolerance values, and the safe withdrawal period for the edible tissues.

9/18/2003 – Pfizer requests approval for swine tolerance, SC and withdrawal

10/31/2003 – For review, Pfizer submits Sponsor-Monitored Method Trial Protocol for determinative procedures for marker residue in bovine liver & swine kidney.

3/15/2004 – CVM supplies comments regarding submission: outstanding formulation questions, muscle tolerance, isomer ratio and ADI and current consumption values.

3/23/2004 – CVM comments on submission 1) outstanding formulation questions; 2) Using 5 ug/kg/day as the assigned ADI; 3) confirming use of same isomer ratio to establish 5.5 ppm; 4) Assignment of muscle tolerance, advise Reside Chemistry Team; 5) confirmation of same isomer ratio to assign 23-day withdrawal.

8/31/2004 – Pfizer submits isomer ratio clarification (plus requested regulatory method information)

1/31/2005 – CVM accepts determinative and confirmatory procedures, however, there remains outstanding residue chemistry questions.

4/5/2005 – Cattle HFS Technical Section Complete

4/6/2005 – Swine HFS Technical Section Complete

GENETIC TOXICOLOGY

First Submission	4/24/2002
Last Submission	11/4/2003
Final Review Complete	4/6/2005

Details of submissions

4/24/2002 – Pfizer requests directed review the Technical Section providing results for a battery of genetic toxicology tests.

1/10/2003 – CVM has reviewed the 24 April 2002 submission and has made several comments on the study reports, Genetic Toxicology reports and the FOI.

11/4/2003 - Pfizer submits response to incomplete letter as well as a revised FOI.

4/30/2004 – CVM comments on the submission re the incomplete, noting that the comments made by Pfizer to be adequate and acceptable.

4/5/2005 – CVM completes Human Food Safety Technical Section, Freedom of Information Summary is included.

4/6/2005 – CMV completes All Other Information Technical Section.

RESIDUE CHEMISTRY

First Submission	December 19, 2001
Last Submission	September 3, 2004
Final Review Complete	April 6, 2005

Details of submissions

Cattle

12/19/2001 – Pfizer requests directed review of the total and marker residue depletion studies.

7/8/2002 – CVM reviewed the total and marker residue depletion studies and made several comments including a request for an electronic copy along with hard copy updates.

10/28/2003 – Pfizer responds to incomplete Residue Chemistry, Metabolic Profile and Regulatory Method.

8/9/2004 – CVM comments on the submission response to the incomplete letter. There are still some outstanding formulation questions remaining; CVM requests that Pfizer re-submit residue studies and their interpretations; there is uncertainty re the presence or absence of the M1 metabolite; CVM requests submission of Pfizer investigation of the fragmentation pattern; CVM finds great error associated with the swine kidney analyses.

8/31/2004 – Pfizer response to the Incomplete letter (P0123) re Target Tissue, Marker Residue and Regulatory Method.

4/5/2005 – CVM completes Human Food Safety Technical Section, Freedom of Information Summary is included.

Swine

1/9/2002 – Pfizer submission of Target Tissue and Marker Residue Component.

7/9/2002 – CVM reviewed Total and Marker Residue depletion studies and includes comments, noting that in the future all Method validation data be submitted in electronic format.

10/30/2003 – Pfizer response to incomplete letter for residue chemistry, metabolic profile and regulatory methods.

4/6/2004 – Swine HFS Technical Section Complete

8/9/2004 – CVM comments on the submission response to the incomplete letter. There are still some outstanding formulation questions remaining; CVM requests that Pfizer re-submit residue studies and their interpretations; there is uncertainty re the presence or absence of the M1 metabolite; CVM requests submission of Pfizer investigation of the fragmentation pattern; CVM finds great error associated with the swine kidney analyses.

9/3/2004 – Pfizer Response to incomplete CVM letter for Target Tissue, Marker Residue and Regulatory Methods.

4/6/2005 – CVM complete Human Food Safety Technical Section, comments provide.

EFFICACY

First Submission	December 22, 2000
Last Submission	October 31, 2002
Final Review Complete	September 8, 2003

Details of submissions

Cattle

12/22/2000 – Pfizer requests review of the clinical efficacy studies intended to be pivotal to support label indications.

1/28/2002 – CVM is unable to complete the review of the clinical studies, thereby the effectiveness technical section remains incomplete.

2/15/2002 – Request review of microbiological data and review of the proposed label text and draft FOI Summary. To complete the Efficacy Technical Section, we enclosed a PK study and a clinical summary.

8/29/2002 – Pfizer submitted additional Pharmacology information requested by CVM to support Efficacy and Labeling.

4/23/2003 – CVM acknowledges receipt for and has reviewed the submissions containing microbiology susceptibility data and PK studies and considers the effectiveness technical section to be complete.

Swine

10/31/2002 – Pfizer requests review of the Effectiveness Technical Section Phased Review including the proposed Label text and draft FOI Summary.

9/8/2003 – CVM approves Effectiveness Technical Section, FOI included.

TARGET ANIMAL SAFETY

First Submission	September 13, 2001
Last Submission	November 21, 2001
Final Review Complete	June 6, 2002

Details of submissions

Cattle

9/13/2001 – Pfizer requests review of the target animal safety technical section. This data is intended to be pivotal safety data for the treatment of BRD and for treatment of animals at high risk of BRD.

5/31/2002 – Based on the information provided, CVM considers the target animal safety technical section to be complete, and has made changes to the label and FOI summary.

Swine

11/21/2001 – Pfizer submits memo of Telcon requesting status of the Cattle Efficacy Studies. Also mentioned was "Tulamycin" being the final name for the drug.

6/6/2002 – CVM reviewed TAS data and found the technical section to be complete for recommending NADA approval. CVM made changes to the FOI and included a copy of the revised FOI summary.

EXHIBIT D

Exhibit D: Brief Description of DRAXXIN (tulathromycin) Review Activities for Cattle

INAD - 10-406 | Tulathromycin | Tulathromycin **6/28/2005**

Date	Source	Type	Doc Id	Volume	Tab	Description
02-SEP-1998	PFE	Original Submission		1	994	Request for the establishment of an INAD file to evaluate the safety and efficacy of an injectable azalide antibiotic for the treatment of Bovine Respiratory Disease (BRD).
09-SEP-1998	CVM	Original Submission	**none**	1	995	(Re:994) CVM acknowledges receipt of the submission for the establishment of an INAD for the investigational use of injectable azalide antibiotic for the treatment of BRD. The submission has been assigned INAD number 10-406 and has been forwarded to the proper reviewer for consideration.
18-SEP-1998	PFE	HFS-Residue Method, HFS-Toxicology		1	996	Request confirmation of meeting scheduled for 30Sep1998 at 1:30pm to discuss critical issues associated with proposed studies to fulfill the toxicology and residue chemistry technical sections for the NADA application for a livestock injectable azalide. Proposed meeting agenda attached.
12-NOV-1998	PFE	HFS-Residue Method, HFS-Toxicology		1	997	(Re:996) Meeting minutes of meeting held 30Sep1998 re the Toxicology and Residue Technical Sections. As agreed at the meeting, enclosed are the minutes, a complete copy of the overheads presented, and a copy of the genetic toxicology testing recommendations for veterinary food animal products provided by CVM.
20-NOV-1998	CVM	Original Submission	**A0000**	1	998	(Re:994) CVM notes that Pfizer did not request either a slaughter authorization for treated animals or a categorical exclusion from the requirement to prepare an environmental assessment for the INAD.
30-NOV-1998	PFE	HFS-Toxicology		1	999	Submission for review a genetic toxicity protocol entitled, "L5178Y TK Mouse Lymphoma Forward Mutation Assay."
12-JAN-1999	CVM	HFS-Residue Method, HFS-Toxicology	**Y0002**	1	1000	CVM Memorandum of Meeting for 30 September 1998 re Toxicology and Chemistry Residue Issues.
20-JAN-1999	CVM	HFS-Toxicology	**E0003**	1	1001	CVM finds the protocol submitted for the mouse lymphoma assay (MLA) is acceptable to the Center and comments.
12-FEB-1999	PFE	HFS-Residue Method, HFS-Toxicology		1	1002	Submission of (4) genetic toxicity protocols for review.
24-FEB-1999	PFE	Development Plans, HFS-Microbial Safety		1	1003	Request confirmation of meeting scheduled for 10 March 1999 to discuss critical issues assoc w/ pivotal efficacy and TAS development programs for cattle and swine.
26-FEB-1999	PFE	Development Plans, HFS-Microbial Safety		1	1004	(Re:1003) Memo of TelCon re meeting confirmation. It was decided swine would be discussed at a later date, CVM suggested we come w/ some proposed wording for label claims, and we discussed dual withdrawal times.
05-APR-1999	PFE	Chemistry Manufacture Control		1	1005	Memo of telcon re requesting approval for a formulation without a preservative. Dr Leinbach (CVM) was not in favor of a teleconference, but would review a proposal if submitted.

INAD - 10-406 | Tulathromycin | Tulathromycin **6/28/2005**

Date	Source	Type	Doc Id	Volume	Tab	Description
26-APR-1999	PFE	HFS-Residue Method		1	1006	Submit for review a total residue study protocol entitled, Radiotracer total residue study in edible tissues of cattle treated subcutaneously w/ CP-472,295.
06-MAY-1999	PFE	HFS-Microbial Safety		1	1007	(Re:1003) Submission of Sponsor's Meeting Minutes of 15 April 1999 re critical issues of Efficacy and TAS.
07-MAY-1999	PFE	Chemistry Manufacture Control, Effectiveness		1	1008	Request review of protocol 13005 entitled Acute tolerance of CP-472,295 (e) 10% Injectable solution in ruminant cattle.
10-MAY-1999	CVM	HFS-Residue Method, HFS-Toxicology	**E0004**	1	1009	(Re:1002) The submitted protocols are acceptable to the Center at this time except for the bacterial reverse mutation assay protocols which require modifications as specified in letter.
11-MAY-1999	PFE	Target Animal Safety		1	1010	Submission of protocol 13004 entitled Margin of Safety of CP-472,295 (e) 10% injectable solution in ruminant cattle.
25-MAY-1999	PFE	Animal Disposition		1-2	1011	Request authorization for the use of products from cattle treated with CP-472,295(e)during clinical trials for human consumption and rendering.
04-JUN-1999	PFE	Chemistry Manufacture Control		2	1012	Request review of a proposed formulation of CP-472,295 as a partially aqueous sterile injectable solution containing approx 50% w/v propylene glycol.
23-JUN-1999	PFE	Effectiveness		2	1013	Request review of protocol 13002 entitled Efficacy of CP-472,295(e) against spontaneous bovine respiratory disease."
09-JUL-1999	PFE	Effectiveness, HFS-Microbial Safety		2	1014	Request review of protocol 13009 entitled Efficacy of CP-472,295(e) injectable solution for treatment of cattle that are at high risk of developing BRD.
16-JUL-1999	PFE	Chemistry Manufacture Control		3	1015	(Re:1005) Memo of telcon requesting permission to fax additional PET results for the Phenol-Free Formulation protocol.
26-JUL-1999	PFE	Effectiveness		3	1016	Letter to confirm teleconference scheduled on 04 August 1999 re efficacy testing against bovine coccidiosis.
04-AUG-1999	CVM	HFS-Residue Method	**E0006**	3	1017	(Re:1006) CVM completed review of a total residue study protocol and has listed comments.
04-AUG-1999	PFE	Effectiveness		3	1018	Memo of TelCon arranged by CVM re the Coccidiosis Efficacy Study Design and discussing dosage and fecal scores.
09-AUG-1999	PFE	Effectiveness, Target Animal Safety		3	1019	Memo of TelCon re status of Clinical protocols pending review by CVM.
11-AUG-1999	PFE	Chemistry Manufacture Control		3	1020	Memo of TelCon re status of Phenol-Free Formulation Protocol to be reviewed by CVM. CVM left message stating Pfizer should know outcome as previously discussed and ltr would come at the end of following week.

INAD - 10-406 | Tulathromycin | Tulathromycin **6/28/2005**

Date	Source	Type	Doc Id	Volume	Tab	Description
12-AUG-1999	PFE	Effectiveness, Target Animal Safety		3	1021	Memo of TelCon re Tolerance and Margin of Safety Protocols. CVM requested another sampling be performed between dosing days 0 and 7. In re to MOS Protocol, CVM felt that what Pfizer proposed was not adequately justified by data.
13-AUG-1999	PFE	Chemistry Manufacture Control, Effectiveness, Target Animal Safety		3	1022	(Re:1021) Memo of TelCon - Dr Flynn called re the Tolerance Protocol Review and agreed he would fax his four comments re this.
17-AUG-1999	PFE	Chemistry Manufacture Control, Effectiveness		3	1023	(Re:1022, 1021, 1008) Ammended Protocol 13005 for review with revisions that were communicated from CVM.
18-AUG-1999	CVM	Chemistry Manufacture Control	**E0011**	3	1024	(Re:1012) CVM concurs that the formulation is self preserved and the completed evaluation should be included in the CMC section when submitted.
20-AUG-1999	PFE	Target Animal Safety		3	1025	Memo of Telcon regarding drug accumulation data and the margin of safety protocol.
23-AUG-1999	PFE	Target Animal Safety		3	1026	Submit for review protocol 13001 entitled Injection site toleration of CP-472,295(e) in ruminant cattle.
27-AUG-1999	PFE	Target Animal Safety		3	1027	(Re:1010) Submission of amended MOS protocol 13004 with the revisions communicated from CVM.
03-SEP-1999	CVM	HFS-Microbial Safety	**Y0008**	3	1028	(Re:1007, 1003) CVM found the sponsor's minutes were consistent with their record of meeting. CVM states they enclosed their minutes but "MGH" did not find them when letter received 9/10/99.
03-SEP-1999	CVM	Chemistry Manufacture Control, Effectiveness	**E0007, E0015**	3	1029	(Re:1023, 1022, 1021, 1008) CVM has reviewed the Acute tolerance protocol and finds it acceptable.
13-SEP-1999	CVM	Target Animal Safety	**E0009, E0017**	3	1030	(Re:1027, 1010) CVM reviewed the protocol and finds the revised version acceptable.
13-SEP-1999	PFE	Effectiveness		3	1031	Memo of telecon re the review status of the BRD treatment efficacy protocol.
15-SEP-1999	CVM	Effectiveness	**None**	3	1032	(Re:1031, 1013) CVM comments on the BRD Efficacy Protocol needing revision.
17-SEP-1999	PFE	Effectiveness		3	1033	(Re:1032, 1031, 1013) Faxed copy of Amended Treatment of BRD Protocol for review including revisions outlined in CVM fax of 15 September 1999.
17-SEP-1999	PFE	Effectiveness		3	1034	(Re:1032, 1031, 1013) Submission of amended Treatment of BRD protocol 13002 with revisions communicated from CVM.
20-SEP-1999	CVM	Effectiveness, HFS-Microbial Safety	**None**	3	1035	(Re:1014) CVM faxed comments on the "high risk" BRD protocol.
21-SEP-1999	PFE	Notification of Claim Investigational Exemption		3	1036	Supplemental drug shipement to Dr K.Lechtenberg, Oakland NE, for Pivotal clinical efficacy study 1133C-60-99-307.
23-SEP-1999	PFE	Notification of Claim Investigational Exemption		3	1037	Initial drug shipment to Dr D.Bechtol, Canyon TX, for Pivotal clinical efficacy study 1133C-60-99-305.

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23-SEP-1999	PFE	Notification of Claim Investigational Exemption		3	1038	Initial drug shipment to Dr E.Johnson, Parma ID for Pivotal clinical efficacy study 1133C-60-99-306.
23-SEP-1999	PFE	Notification of Claim Investigational Exemption		3	1039	Initial drug shipment to Dr T.TerHune, Tulare CA, for Pivotal clinical efficacy study 1133C-60-99-308.
24-SEP-1999	PFE	Effectiveness		3	1040	Request review of master protocol 13010 entitled Efficacy of CP-472,295(e) against artificially-induced infections of coccidia in cattle.
04-OCT-1999	CVM	Effectiveness	**E0012, E0018**	3	1041	(Re:1013) CVM faxed review of Efficacy protocol against spontaneous bovine respiratory disease and finds protocol to be acceptable.
04-OCT-1999	CVM	Effectiveness	**E0012, E0018**	3	1042	(Re:1013) CVM reviewed the Efficacy protocol against spontaneous bovine respiratory disease and finds it acceptable.
21-OCT-1999	PFE	Effectiveness		3	1043	(Re:1035, 1014) Amended Treatment of Cattle at high risk of BRD protocol submitted for review.
21-OCT-1999	PFE	Notification of Claim Investigational Exemption		3	1044	Initial drug shipment to Dr T.TerHune, Tulare CA, for Pivotal clinical efficacy study 1133C-60-99-312.
21-OCT-1999	PFE	Notification of Claim Investigational Exemption		3	1045	Initial drug shipment to Dr K.Lechtenberg, Oakland NE, for Pivotal clinical efficacy study 1133C-60-99-311.
21-OCT-1999	PFE	Notification of Claim Investigational Exemption		3	1046	Initial drug shipment to Dr D.Bechtol, Canyon TX, for Pivotal clinical efficacy study 1133C-60-99-309.
21-OCT-1999	PFE	Notification of Claim Investigational Exemption		3	1047	Initial drug shipment to Dr E.Johnson, Parma ID, for Pivotal clinical efficacy study 1133C-60-99-310.
26-OCT-1999	PFE	Notification of Claim Investigational Exemption		3	1048	(Re:1046) Supplemental drug shipment to Dr D.Bechtol, Canyon TX, for Pivotal Clinical Efficacy study 1133C-60-99-309.
26-OCT-1999	PFE	Notification of Claim Investigational Exemption		3	1049	(Re:1047) Supplemental drug shipment to Dr E.Johnson, Parma ID, for Pivotal Clinical Efficacy study 1133C-60-99-310.
26-OCT-1999	PFE	Notification of Claim Investigational Exemption		3	1050	(Re:1045) Supplemental drug shipment to Dr K.Lechtenberg, Oakland NE, for Pivotal Clinical Efficacy study 1133C-60-99-311.
29-OCT-1999	PFE	Notification of Claim Investigational Exemption		3	1051	Initial drug shipment to Dr T.TerHune, Tulare CA, for Pivotal Clinical Efficacy study 1142N-60-99-304.
29-OCT-1999	PFE	Notification of Claim Investigational Exemption		3	1052	Intial drug shipment to Dr T.TerHune, Tulare CA, for Pivotal Clinical Efficacy study 1432N-60-99-303.
05-NOV-1999	CVM	Animal Disposition	**O0010**	4	1053	(Re:1011) CVM finds that a categorical exclusion is appropriate for this INAD. CVM also concurs with Pfizer request for a 40-day withdrawal period for edible tissues but does not concur w/ 10 day withdrawal time for liver.
19-NOV-1999	CVM	Effectiveness	**E0013, E0024**	4	1054	(Re:1043, 1035, 1014) Faxed CVM review of protocol to treat cattle with high risk of developing BRD and finds the revised protocol acceptable.
19-NOV-1999	CVM	Effectiveness	**E0013, E0024**	4	1055	(Re:1043, 1035, 1014) CVM review of protocol to treat cattle with high risk of developing BRD and finds the revised protocol acceptable.

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30-NOV-1999	PFE	HFS-Residue Method		4	1056	Submission for review Protocol 13330 entitled marker residue depletion study in edible tissues of cattle treated subcutaneously w/ CP-472,295 (e).
16-DEC-1999	CVM	Effectiveness	**E0023**	4	1057	(Re:1040) Faxed CVM review finds Coccidiosis Efficacy Protocol not acceptable, listscomments, and states a discussion with CVM is necessary prior to submission of the revised protocol.
16-DEC-1999	CVM	Effectiveness	**E0023**	4	1058	(Re:1040) CVM review finds Coccidiosis Efficacy Protocol not acceptable, lists comments, and states a discussion with CVM is necessary prior to submission of the revised protocol.
21-DEC-1999	PFE	Effectiveness		4	1059	(Re:1055, 1043, 1035, 1014) Faxed rough draft of Pfizer's responses to CVM's review comments on the Coccidiosis Efficacy Protocol.
05-JAN-2000	PFE	Chemistry Manufacture Control		4	1060	Request review of the stability program proposal for drug substance CP-472,295 and drug product (50, 100, 250, 500 mL vials of 10% sterile injectable solution).
06-JAN-2000	PFE	Effectiveness		4	1061	(Re:1059, 1058, 1055, 1043, 1040, 1035, 1014) Request review of the revised master protocol 13010 entitled Efficacy of CP-472,295(e) injectable solution against artificially-induced infections of coccidia in cattle.
21-JAN-2000	CVM	Effectiveness	**E0036**	4	1062	(Re:1061, 1059, 1058, 1055, 1043, 1040, 1035, 1014) CVM reviewed the Efficacy protocol 13010 against artificially-induced infections and finds it acceptable as submitted.
27-JAN-2000	CVM	HFS-Residue Method	**E0034**	4	1063	(Re:1056) CVM reviewed the Marker Residue Depletion study protocol and comments.
16-FEB-2000	PFE	Notification of Claim Investigational Exemption		4	1064	Initial drug shipment to Dr T.TerHune, Tulare CA, for Pivotal non-clinical tas study 1433N-60-99-332.
18-FEB-2000	CVM	Target Animal Safety	**E0016**	4	1065	(Re:1026) CVM has reviewed the Injection Site Toleration protocol and finds it is generally acceptable as submitted including general comments.
21-FEB-2000	PFE	Notification of Claim Investigational Exemption		4	1066	Initial drug shipment to Dr G.Davis, Delaware OH, for Pivotal clinical efficacy, induced infection study 1230C-60-00-346.
21-FEB-2000	PFE	Notification of Claim Investigational Exemption		4	1067	Initial drug shipment to Dr B.Stromberg, St Paul MN, for Pivotal clinical efficacy, induced infection study 1230C-60-99-338.
23-FEB-2000	CVM	Chemistry Manufacture Control	**E0035**	4	1068	(Re:1060) CVM comments on the stability protocols submitted.
25-APR-2000	PFE	HFS-Toxicology		4	1069	Request review of the protocol entitled CHO/HGPRT Forward Mutation Assay.
02-MAY-2000	PFE	Animal Disposition		4	1070	Notice of Final Animal Disposition, Study 1133C-60-99-305, Dr D.Bechtol, Canyon TX, 40 head returned to herd.
02-MAY-2000	PFE	Animal Disposition		4	1071	Notice of Final Animal Disposition, study 1133C-60-99-306, Dr E.Johnson, Parma ID, 80 head returned to herd.

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02-MAY-2000	PFE	Animal Disposition		4	1072	Notice of Final Animal Disposition, study 1133C-60-99-307, Dr K.Lechtenberg, Oakland NE, 77 head returned to herd, 2 necropsied and buried, 1 euthanized/died and buried.
02-MAY-2000	PFE	Animal Disposition		4	1073	Notice of Final Animal Disposition, study 1133C-60-99-308, Dr T.TerHune, Tulare CA, 79 head returned to herd, 1 died and buried.
02-MAY-2000	PFE	Animal Disposition		4	1074	Notice of Final Animal Disposition, study 1133C-60-99-309, Dr D.Bechtol, Canyon TX, 102 head returned to herd, 2 died and buried.
02-MAY-2000	PFE	Animal Disposition		4	1075	Notice of Final Animal Disposition, study 1133C-60-99-310, Dr E.Johnson, Parma ID, 103 head returned to herd, 2 necropsied and buried.
02-MAY-2000	PFE	Animal Disposition		4	1076	Notice of Final Animal Disposition, study 1133C-60-99-311, Dr K.Lechtenberg, Oakland NE, 104 head returned to herd.
02-MAY-2000	PFE	Animal Disposition		4	1077	Notice of Final Animal Disposition, study 1133C-60-99-312, Dr T.TerHune, Tulare CA, 98 head returned to herd, 2 died and buried.
15-MAY-2000	PFE	Chemistry Manufacture Control		4	1078	Memo of TelCon w/ Dr Leinbach, CVM, re CVM's rejection of the bracketing and abbreviation strategy for the 500ml vial. Dr Leinbach explained this and also added that the testing should be complete, abbreviated testing was not acceptable.
15-MAY-2000	PFE	HFS-Toxicology		4	1079	Request review of protocol 00-1507-29, a six month oral dog study to qualify CP-472,295(e) for use of a safety factor of 100 in calculating the ADI.
08-JUN-2000	CVM	HFS-Toxicology	**E0049**	4	1080	(Re:1079) CVM reviewed the 6-month oral toxicity study in dogs and comments on the protocol.
10-AUG-2000	PFE	HFS-Microbial Safety		4	1081	Request confirmation for meeting scheduled for 23 August 2000 to discuss requirements for antimicrobials for food animals and that our proposals meet the requirements.
10-OCT-2000	CVM	HFS-Toxicology	**E0040**	4	1082	(Re:1069) CVM has reviewed the CHO/HGPrt protocol and comments that the submission would be acceptable if the protocol is modified to include (listed) requirements. Also it recommends the MLA study be conducted.
07-NOV-2000	PFE	Environmental Assessment		4	1083	Request for categorical exclusion from the requirements for preparation of an environmental assessment or an environmental impact statement.
22-DEC-2000	PFE	Effectiveness		4-16	1084	Request review of the clinical efficacy studies intended to be pivotal to support label indications.
08-JAN-2001	PFE	Development Plans, HFS-Microbial Safety		16	1085	Request confirmation , in accordance w/ CVM guiidelines, that CP-472,295(e) be considered a Category II drug w/ low potential for human exposure. Request review of the pre-approval development plan for assessing microbiological safety.
13-JUN-2001	CVM	Chemistry Manufacture Control, HFS-Toxicology	**None**	16	1086	Inspection report of an ongoing Pfizer study 00-1507-29, an oral toxicity study in beagle dogs, finds the dosing solution was a mixture not outlined in the submitted protocol

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28-JUN-2001	PFE	Chemistry Manufacture Control, HFS-Toxicology		16	1087	(Re:1086) Pfizer acknowledges receipt of the inspection report from CVM and in response, plans to submit data generated to support approval of this product under the phased review submission policy.
16-JUL-2001	PFE	Development Plans, HFS-Microbial Safety		16	1088	(Re:1085) Memo of Telcon requesting review status. CVM would be meeting 18Jul2001 to discuss the proposal and make a decision, and that a response could come in the next few weeks.
16-JUL-2001	PFE	Effectiveness		16	1089	Memo of telcon re submission of raw data of studies as an amendment to the BRD Efficacy Technical Section.
18-JUL-2001	PFE	HFS-Microbial Safety		16	1090	Memo of telcon, CVM had called for clarification of "triamilide", also explained the process for categorization review and would forward our request on to CDER and expect a response in a few weeks.
18-JUL-2001	CVM	Environmental Assessment	**G0051**	16	1091	(Re:1083) CVM agrees that a categorical exclusion is appropriate for the NADA and neither an environmental assessment nor an environmental impact statement is required.
30-JUL-2001	PFE	Chemistry Manufacture Control		16	1092	Request confirmation of a meeting scheduled for 10 September 2001 to solicit CVM's input to the CMC Technical Section of the NADA.
02-AUG-2001	PFE	Development Plans, Effectiveness		16	1093	Request confirmation of a meeting scheduled for 30 August 2001 to solicit CVM's input to our proposed Phase IIIb development plan. Agenda attached.
03-AUG-2001	PFE	Effectiveness		16-21	1094	(Re:1089) Raw data submitted as Amendment to Clinical Efficacy Confirmation Studies including the Data Capture Forms and CD to facilitate the review.
20-AUG-2001	PFE	Development Plans, Effectiveness		22	1095	(Re:1093) Additional information in the form of draft slides for the upcoming meeting, 30 August 2001, re development plans for phase IIIb.
05-SEP-2001	PFE	Notification of Claim Investigational Exemption		22	1096	Initial drug shipment to Dr D.Bechtol, Canyon TX, for Non-pivotal comparitive field efficacy study 2132T-60-01-051.
07-SEP-2001	PFE	Notification of Claim Investigational Exemption		22	1097	Initial drug shipment to Dr E.Johnson, Parma ID, for Non-pivotal comparitive field efficacy study 2132T-60-01-063.
13-SEP-2001	PFE	Target Animal Safety		22-28	1098	Request review of the target animal safety technical section. This data is intended to be pivotal safety data for the treatment of BRD and for treatment of animals at high risk of BRD.
18-SEP-2001	PFE	Notification of Claim Investigational Exemption		28	1099	Initial drug shipment to Dr O.Schunicht, Okotoks Alberta Canada, for Non-pivotal comparitive field efficacy study 2132T-60-01-050.
15-OCT-2001	PFE	Notification of Claim Investigational Exemption		28	1100	Initial drug shipment to Dr M.Wray, Longmont CO, for Non-pivotal field efficacy study 2132T-60-01-067.
24-OCT-2001	PFE	Notification of Claim Investigational Exemption		28	1101	Initial drug shipment to Dr M.Wray, Longmont CO, for Non-pivotal field efficacy study 2132T-60-01-069.
07-NOV-2001	CVM	Development Plans	**Z0059**	28	1102	(Re:1093) CVM meeting minutes of 30 August 2001 meeting held to discuss Pfizer's pre-approval post-marketing studies.

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15-NOV-2001	PFE	Environmental Assessment		28	1103	Memo of Telcon inquiring status of 08 January 2001 submission requesting categorization of tulamycin. CVM suggested to file studies and data w/o waiting for CDER's review.
21-NOV-2001	PFE	Effectiveness		28	1104	Memo of Telcon requesting status of the Cattle Efficacy Studies. Also mentioned was "Tulamycin" being the final name for the drug.
03-DEC-2001	PFE	HFS-Microbial Safety		29	1105	Request directed review of the in vitro studies pertaining to bacterial resistance related to tulamycin by recommendation of Dr Weld to minimize the impact of any future review delays while CDER's review remains open.
19-DEC-2001	PFE	HFS-Residue Method		29-36	1106	Request directed review of the total and marker residue depletion studies.
07-JAN-2002	PFE	HFS-Microbial Safety		37	1107	Request confirmation that the memo of telecon reflects the understanding of 03 January 2002 conversation re Category II/Low Exposure drug submission.
14-JAN-2002	PFE	HFS-Metabolism		37	1108	Request directed review of study 1576N-60-00-211 describing the metabolism of tulamycin, and the summary report CM-01-01 which relates metabolism across all species studied.
23-JAN-2002	CVM	HFS-Microbial Safety	**Y0069**	37	1109	(Re:1107) CVM reviewed the minutes submitted to 03 January 2002 teleconference and has made some additional comments and included their official minutes of record.
28-JAN-2002	CVM	Effectiveness	**P0052, T0058**	37	1110	(Re:1084) CVM is unable to complete the review of the clinical studies, thereby the effectiveness technical section remains incomplete.
13-FEB-2002	PFE	Chemistry Manufacture Control		37	1111	Concise summaries of issues that we hope to discuss w/ CVM in (2) meetings re Qualification of Impurities, Drug Product Manufacturing Site change, and CMC filing Strategy.
15-FEB-2002	PFE	Effectiveness		37-42	1112	(Re:1110, 1084) Request review of microbiological data and review of the proposed label text and draft FOI Summary. To complete the Eff Tech Sect, we enclose a PK study and a clinical summary.
27-FEB-2002	PFE	Chemistry Manufacture Control, HFS-Toxicology		42	1113	Fax-detailed information on the impurities (structures, structure assessment, source, and concentration) for the upcoming meeting.
28-FEB-2002	PFE	HFS-Residue Method		42	1114	Meeting request for 28 March 2002, re a common understanding of Guidance #52, assessment of the effects and present data. Collaboratively define a strategy to facilitate review of the technical section.
05-MAR-2002	PFE	HFS-Residue Method		42	1115	Meeting request for 28 March 2002, re a common understanding of Guidance #52, assessment of the effects and present data. Collaboratively define a strategy to facilitate review of the technical section.

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05-MAR-2002	PFE	HFS-Toxicology		42	1116	Memo of voicemail message received from Dr Leinbach re the details to the upcoming request for meeting. Her message stated that CVM would discuss the material and inform us if a face to face mtg or telcon was warranted.
12-MAR-2002	PFE	HFS-Microbial Safety		42	1117	(Re:1105) Dr Weld (CVM) called requesting additional information re Antimicrobial Resistance Data Submission of 03 December 2001.
28-MAR-2002	PFE	HFS-Toxicology		42	1118	Memo of telcon re a request to meet briefly w/ Dr Leinbach. Her response was that she would contact Pfizer after an internal meeting was held w/ no need for any meeting prior to that.
05-APR-2002	PFE	HFS-Microbial Safety		42	1119	(Re:1105) Amendment to 03 December 2001 Antimicrobial Resistance Studies including answers to CVM's three queries of 12 March 2002 TelCon.
24-APR-2002	PFE	HFS-Toxicology		42-43	1120	Request directed review the the Technical Section providing results for a battery of genetic toxicology tests.
30-APR-2002	PFE	HFS-Microbial Safety		43	1121	(Re:1105) Additional information for (2) of CVM's queries re the Antimicrobial Resistance Studies Submission (gel photographs for 8 isolates and results of the 'micro' and 'macro' methods.
01-MAY-2002	CVM	HFS-Metabolism	**H0070**	43	1122	(Re:1108) CVM Comments on the comparative metabolism study in rats and dogs, and the comparative metabolism study report of rats, dogs, cattle and swine.
15-MAY-2002	PFE	Effectiveness, Target Animal Safety		43	1123	Memo of May 7, 9, 15 Telcons re the status of phased filing for cattle & Swine TAS and Efficacy. TAS was finished and had moved to next level; Pfizer should file a single submission including mycoplasmal & bacterial MIC data; South Dakota FDA 483.
30-MAY-2002	PFE	Notification of Claim Investigational Exemption		43	1124	Initial drug shipment to Dr K.Lechtenberg, Oakland NE, for Non-pivotal comparitive field efficacy study 1133P-60-02-373.
31-MAY-2002	CVM	Target Animal Safety	**P0064**	43	1125	(Re:1098) Based on the information provided, CVM considers the target animal safety technical section to be complete, and has made changes to the label and FOI summary (enclosed).
11-JUN-2002	PFE	Effectiveness, Target Animal Safety		43	1126	(Re:1123) Re 07 May 2002 TelCon and Dr Punderson's request for further details, this memo of telcon lists the repots to be sent so that review could be done by 20 August 2002.
12-JUN-2002	PFE	HFS-Toxicology		43-57	1127	Request directed review of the Toxicology Technical Section including the ADI and SC.
20-JUN-2002	PFE	Effectiveness		58	1128	(Re:1112, 1110, 1084) Additional details re "related data" study abstracts previously submitted and updated debarment statement.
08-JUL-2002	CVM	HFS-Residue Method	**P0068**	58	1129	(Re:1106) CVM reviewed the total & marker residue depletion studies and made several comments including a request for an electronic copy along w/ hard copy updates.

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12-JUL-2002	PFE	HFS-Microbial Safety		58	1130	Mtg Minutes for 28 March 2002 re the application of CVM Guidance #52. Based on the discussions, Pfizer has prepared a microbiological safety assessment document, reports of study data, and compilation of published literature, which we anticipate fil
15-JUL-2002	PFE	HFS-Microbial Safety		58-60	1131	Request review of the enclosed technical section providing an assessment of the effects of tulathromycin residues on human intestinal flora.
24-JUL-2002	PFE	Effectiveness		60	1132	Request review of master protocol 13016 entitled Efficacy of CP-472,295(e), injectable, for the treatment of infectious bovine keratoconjuctivitis.
30-JUL-2002	PFE	Notification of Claim Investigational Exemption		60	1133	Initial drug shipment to Dr T.Terhune, Tulare CA, for Non-pivotal exploratory efficacy study 1133E-60-01-365.
31-JUL-2002	PFE	Chemistry Manufacture Control		60	1134	Request review of Pfizer's approach to impurity qualification in drug substance and drug product and secure CVM's position on the application to the compound.
31-JUL-2002	PFE	HFS-Toxicology		60	1135	(Re:1127) CVM called to request additional info re the stability and concentration of the dosing solutions in the general toxicology filing of 12 June 2002.
14-AUG-2002	PFE	Effectiveness		60	1136	CVM called requesting additional information re Efficacy Tech Section submission.
15-AUG-2002	CVM	HFS-Residue Method	**Y0082**	60	1137	(Re:1115) CVM's minutes of 28 March 2002 meeting discussing the pathway approach proposed in Guidance #52.
27-AUG-2002	PFE	HFS-Toxicology		60	1138	(Re:1135, 1127) Request review of the dosing solution data, an amendment to the 12 June 2002 Toxicology Technical Section.
29-AUG-2002	PFE	Effectiveness		60	1139	(Re:1136) Additional Pharmacology information requested by CVM to support Efficacy and Labeling.
30-AUG-2002	PFE	HFS-Microbial Safety		60	1140	Request review of data provided as a response to CVM letter re 10-548. Original submission also referenced 10-406 but we have not received confirmation of the microbial food safety component.
30-SEP-2002	PFE	Chemistry Manufacture Control		60-64	1141	Request directed review of the drug substance and drug product CMC technical section for DRAXXIN.
21-OCT-2002	PFE	Notification of Claim Investigational Exemption		65	1142	Initial drug shipment to Dr K.Rogers, Greeley CO, for Non-pivotal comparative efficacy study 1133R-60-02-376.
22-OCT-2002	PFE	Animal Disposition		65	1143	Notice of Final Disposition, 249 returned to herd, 1 animal buried at a landfill, Dr M.Wray, Wellington CO, study 2132T-60-01-069.
22-OCT-2002	PFE	Animal Disposition		65	1144	Notice of Final Disposition, 100 returned to herd, Dr M.Wray, Wellington CO, study 2132T-60-01-067.
25-OCT-2002	PFE	HFS-Microbial Safety		65	1145	Request for Teleconference, 30 October 2002, re CVM's review of Antimicrobial Resistance data and request clarification of how additional data might change study results/conclusions.

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06-NOV-2002	PFE	Notification of Claim Investigational Exemption		65	1146	Initial drug shipment to Dr K.Lechtenberg, Oakland NE, for Non-pivotal Exploratory Artificial Infection study 1131E-60-02-380.
02-DEC-2002	PFE	HFS-Microbial Safety		65	1147	(Re:1145, 1140) Request review of the requested data. Pending your determination, we request confirmation that the microbial food safety component be considered complete.
02-JAN-2003	CVM	HFS-Microbial Safety	**H0097**	65	1148	(Re:1147, 1145, 1140) CVM reviewed the additional info submitted as requested and finds that Pfizer has satisfied the requiremnts for microbial food safety and this ltr serves as a complete letter.
10-JAN-2003	CVM	HFS-Toxicology, Freedom of Information Summary	**P0076**	65	1149	(Re:1120) CVM has reviewed the 24 April 2002 submission and has made several comments on the study reports, Genetic Toxicology reports and the FOI.
14-JAN-2003	PFE	Notification of Claim Investigational Exemption		65	1150	Initial drug shipment to Dr L.George, Davis CA, for Non-pivotal Exploratory study 1131E-60-02-385.
31-JAN-2003	PFE	Notification of Claim Investigational Exemption		65	1151	Initial drug shipment to Dr K.Rogers, Greeley CO, for Non-pivotal Comparative Efficacy study 1133R-60-02-376.
05-FEB-2003	PFE	Chemistry Manufacture Control		65	1152	Request review of sponsor's minutes of meeting of 29January2003 regarding the plans to transfer the manufacture of VMP at Lee's Summit MO to an alternate PGM facility.
12-FEB-2003	CVM	Effectiveness	**E0084**	65	1153	(Re:1132) CVM find the draft protocol for treatment of IBK to be not acceptable and lists issues requiring revision.
12-FEB-2003	CVM	HFS-Toxicology	**P0079, T0087, H0086**	65	1154	(Re:1127) CVM reviewed the Toxicology Technical section and makes comments noting that the FOI will not be reviewed until the listed issues are addressed.
28-FEB-2003	PFE	Chemistry Manufacture Control		65	1155	Request directed review of the drug substance and drug product stability data update. This update reports data through 24 months & 18 months for programs 1 & 2.
11-MAR-2003	PFE	HFS-Microbial Safety		65	1156	Email to CVM re details of how the ADI values were calculated.
12-MAR-2003	CVM	Chemistry Manufacture Control	**Z-0099**	65	1157	(Re:1152) CVM's minutes to 29January 2003 meeting to discuss the move of Lee's Summit MO manufacturing site to alternative facilities.
14-MAR-2003	PFE	Notification of Claim Investigational Exemption		65	1158	Initial drug shipment to Dr K.Lechtenberg, Oakland NE, for Non-pivotal Comparative efficacy study 1133R-60-03-389.
14-MAR-2003	PFE	Notification of Claim Investigational Exemption		65	1159	Initial drug shipment to Dr K.Lechtenberg, Oakland NE, for Non-pivotal Comparative efficacy study 1133R-60-03-390.
21-MAR-2003	PFE	Effectiveness		65	1160	Request of Teleconference for 16-21 April 2003 re the IBK protocol and to assure a common understanding of CVM's comments and discuss major changes to study design.
24-MAR-2003	PFE	HFS-Toxicology		65	1161	Request for Teleconference for 03 April 2003 re CVM's review of Toxicology Technical Section and come to an understanding to their comments and discuss critical issues prior to reactivation.

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Date	Source	Type	Doc Id	Volume	Tab	Description
28-MAR-2003	CVM	HFS-Microbial Safety	**P0083**	65	1162	(Re:1131) CVM comments on the 15 July 2002 residues on human intestinal flora submission.
03-APR-2003	PFE	Notification of Claim Investigational Exemption		65	1163	Initial drug shipment to Dr D.Bechtol, Canyon TX, for Non-pivotal comparative efficacy study 1133R-60-03-388.
15-APR-2003	CVM	Chemistry Manufacture Control	**Z0091**	65	1164	CVM meeting minutes of 16 October 2002 re the use of matrix standards, use of weighting factors, and the inclusion of a surrogate used in the calculations.
23-APR-2003	CVM	Effectiveness	**P0071, T0080, T0088**	65	1165	(Re:1139, 1136, 1128, 1112, 1110, 1084) CVM acknowledges receipt for and has reviewed the submissions containing microbiology susceptibility data and PK studies and considers the effectiveness technical section to be complete.
29-MAY-2003	PFE	Effectiveness, Protocol		65	1166	Request review of Field efficacy for treatment of footrot master protocol.
19-JUN-2003	CVM	Chemistry Manufacture Control, Incomplete	**P0090**	66	1167	CVM incompletes CMC technical section.
18-JUL-2003	PFE	HFS-Toxicology, Freedom of Information Summary		66	1168	Submission of response to CVM 12Feb03 letter, including a revised FOI, additional comments of interpretation of the study data.
29-JUL-2003	PFE	Protocol		66	1169	Submission of revised master protocol 1133C-ML-02-016.
12-AUG-2003	PFE	HFS-Residue Method		66	1170	Response to Queries on Comparative Metabolism Studies.
04-SEP-2003	PFE	Chemistry Manufacture Control		66-67	1171	Response to an incomplete letter amending the Chemistry, Manufacturing and Control Technical Section.
05-SEP-2003	PFE	Chemistry Manufacture Control, HFS-Residue Method		67	1172	Request for a meeting 8 October 2003, to discuss method trial process.
11-SEP-2003	PFE	HFS-Residue Method, HFS-Toxicology		67	1173	Pfizer requests concurrence on calculated safe concentrations, tolerance values, and the safe withdrawal period for the edible tissues.
25-SEP-2003	PFE	Effectiveness		67-68	1174	Routine Data Sweep Pertinent to Safety and Efficacy.
30-SEP-2003	PFE	Chemistry Manufacture Control		68	1175	MOC of teleconference: impurities qualifications.
09-OCT-2003	PFE	Chemistry Manufacture Control		68	1176	Amendment to incomplete response submitted 4Sep2003.
10-OCT-2003	PFE	Chemistry Manufacture Control, HFS-Residue Method		68	1177	(Re:1172) Follow-up information for method trial teleconference held 8 October 2003.
20-OCT-2003	PFE	Development Plans, Chemistry Manufacture Control, HFS-Residue Method		68	1178	(Re:1172) Confirmation of meeting 11/5/03 to discuss residue methods trials.
28-OCT-2003	PFE	HFS-Residue Method, Incomplete		69-70	1179	Pfizer responds to incomplete Residue Chemistry, Metabolic Profile and Regulatory Method.
31-OCT-2003	PFE	HFS-Residue Method		70	1180	For review, Pfizer submits Sponsor-Monitored Method Trial Protocol for determinative procedures for marker residue in bovine liver & swine kidney.

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Date	Source	Type	Doc Id	Volume	Tab	Description
31-OCT-2003	CVM	General, HFS-Residue Method, HFS-Toxicology, Freedom of Information Summary, Protocol	**P0114**	70	1181	(Re:1168) CVM accepts ADI of 15 mcg/kg/day. The letter also provides suggestions for the HFS FOI and requests that a revised (including language regarding antimicrobial resistance) be submitted. Letter sent 31Oct, routed to Gorton back to Rockville and then to Kalamazoo, received 2Dec.
04-NOV-2003	PFE	HFS-Toxicology, Freedom of Information Summary, Approval		70-71	1182	(Re:1149, 1120) Pfizer submits response to incomplete letter as well as a revised FOI.
10-NOV-2003	CVM	Effectiveness, Protocol	**E0108**	71	1183	(Re:1166) CVM recommends revisions and resubmitting protocol after addressing issues.
19-NOV-2003	CVM	Development Plans, HFS-Residue Method	**Z0122**	71	1184	(Re:1178, 1172) MOC for 5 Nov meeting, no conclusions or agreements were reached, however, CVM stated that they would provide additional information to Pfizer before 27 Nov.
20-NOV-2003	CVM	HFS-Residue Method	**Z0117**	71	1185	(Re:1177, 1172) MOC of meeting held as well as a follow-up meeting 8 October 2003, seeking approval of the revised assay.
21-NOV-2003	CVM	Effectiveness, Protocol	**E0115**	71	1186	(Re:1169) CVM response with follow-up comments, they encourage a final protocol to achieve acceptance.
25-NOV-2003	CVM	General, HFS-Toxicology, Freedom of Information Summary	**P0014**	71	1187	(Re:1181, 1168) CVM acknowledges return of 31Oct03 memo and change in address for Pfizer Animal Health.
02-DEC-2003	CVM	HFS-Metabolism, HFS-Residue Method	**H0116**	71	1188	(Re:1170) CVM accepts portions of PAH response to queries but still have additional questions.
11-DEC-2003	PFE	Animal Disposition		71	1189	Notice of Final Disposition, 115 retained and 5 buried, Logan Valley Feeders, Oakland NE, 1133R-60-03-390.
11-DEC-2003	PFE	Animal Disposition		71	1190	Notice of Final Disposition, 97 sold after 70 day withdrawal and 2 were buried, Veterinary Research, K.Rogers, Greeley CO, 1133R-60-02-376.
11-DEC-2003	PFE	Animal Disposition		71	1191	Notice of Final Disposition, 119 retained and 1 buried, Logan Valley Feeders, Oakland NE, 1133R-60-03-389.
16-DEC-2003	PFE	HFS-Residue Method		71	1192	Request for a meeting to discuss tissue residue assay methods proposed date 5Feb04.
17-DEC-2003	PFE	Animal Disposition		71	1193	Notice of Final Disposition of 20 returned to herd following a 40 day withdrawal plus a 30 day observation period, Midwest Vet Services, Oakland NE, 1131E-60-01-380.
23-DEC-2003	PFE	HFS-Metabolism		71	1194	Follow-up from teleconference 17Dec03, Pfizer submits questions for CVM clarification on comments they made of our comparative metabolism submission. CVM response included.
30-DEC-2003	CVM	Animal Disposition	**E:Mail**	71	1195	(Re:1190) Discrepancy between numbers of animals listed in Disposition, Pfizer clarified discrepancy and amendment is not required.

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Date	Source	Type	Doc Id	Volume	Tab	Description
31-DEC-2003	CVM	HFS-Residue Method, HFS-Toxicology, Freedom of Information Summary, Protocol	**E0124**	71	1196	(Re:1181, 1168) CVM provides additional recommendations to Method Trial Protocol.
07-JAN-2004	PFE	Protocol		71	1197	(Re:1196, 1181, 1168) CVM agrees Pfizer should not address the muscle tolerance in our current method trial, Pfizer committed that we will address post approval. It was also suggested if the assay for muscle was very similar to the target tissue methods that CVM will likely request reduced methods testing, to be discussed at that time.
15-JAN-2004	PFE	HFS-Residue Method, Protocol		71	1198	(Re:1196, 1181, 1168) Pfizer will incorporate CVM suggestions into protocol and/or trial as appropriate. Pfizer commits to the establishment of the muscle tolerance for both cattle and swine muscle and the associated regulatory method following the approval of the NADAs. The NADA will contain published tolerances for the target tissue and a regulatory method for same. Also we grant CVM permission to transfer the assay method and materials to FSIS prior to NADA approval.
26-JAN-2004	PFE	HFS-Residue Method, HFS-Toxicology, Freedom of Information Summary		71	1199	(Re:1181, 1168) Submission of corrected section of FOI for final review.
03-FEB-2004	PFE	Animal Disposition		71	1200	NFAD of 3 animals died (81, 123 & 129 days after treatment) and were rendered, the remaining 247 went to slaughter 6-7 months after treatment. Agri Research, Canyon TX, 1131R-60-03-388.
06-FEB-2004	PFE	HFS-Residue Method		71	1201	(Re:1192) CVM telephone with "thumbs up" to move to method demonstration.
10-FEB-2004	PFE	HFS-Residue Method		71	1202	(Re:1201, 1192) Regarding details setting up Method Demonstration, schedules and participants.
16-FEB-2004	PFE	HFS-Residue Method		71	1203	Sponsor Meeting Minutes for 5 February 2004 meeting, re details of the analytical method for detection of residues in bovine liver and porcine kidney for the "desk review" component of the method trail process.
16-FEB-2004	PFE	HFS-Residue Method		71-72	1204	(Re:1203, 1179) Response to a CVM request for additional storage stability data to support our Method submission of 28 October 2003 and additional chromatograms to support tabular data.
23-FEB-2004	PFE	HFS-Metabolism, HFS-Residue Method		72	1205	(Re:1188, 1170) Response to CVM questions from H-0116 and request for final concurrence that the toxicology species, dogs and rats are systematically exposed to the major residues present in edible tissue of cattle and swine.
26-FEB-2004	PFE	Chemistry Manufacture Control, Incomplete, Amendment		72	1206	(Re:1171) Response to CVM questions regarding CMC submission of 9/4/03.
09-MAR-2004	PFE	Chemistry Manufacture Control		72	1207	Meeting request for site transfer Re: closing of Lee's Summit Plant.
16-MAR-2004	CVM	Chemistry Manufacture Control, Incomplete	**P0118**	72	1208	(Re:1206, 1171) CVM provides comments on incomplete CMC Technical Section.

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Date	Source	Type	Doc Id	Volume	Tab	Description
22-MAR-2004	PFE	Effectiveness, Protocol		72	1209	Submission of revised master protocol 1133C-ML-03-017, Foot Rot.
23-MAR-2004	CVM	HFS-Residue Method	**Z0132**	73	1210	(Re:1192) MOC of 5 Feb 2004 meeting to discuss analytical method issues.
23-MAR-2004	CVM	HFS-Residue Method, HFS-Toxicology	**P0119**	73	1211	(Re:1173) CVM comments on submission 1) outstanding formulation questions; 2) Using 5 ug/kg/day as the assigned ADI; 3) confirming use of same isomer ratio to establish 5.5 ppm; 4) Assignment of muscle tolerance, advise Reside Chemistry Team; 5) confirmation of same isomer ratio to assign 23-day withdrawal.
31-MAR-2004	CVM	HFS-Residue Method	**EMail**	73	1212	(Re:1210, 1192) Agreements and response to outstanding issues from 5Feb04 meeting, method trial.
31-MAR-2004	PFE	Protocol		73	1213	(Re:1186, 1169) Pfizer requests a meeting to discuss CVM comments on IBK Master Protocol letter dated 21Nov03.
05-APR-2004	PFE	HFS-Microbial Safety, HFS-Residue Method		73	1214	Pfizer request review and conclusion on need for a VMAC . (Antibiotic Resistance)
05-APR-2004	PFE	HFS-Residue Method		73	1214a	Multiple unofficial correspondence re Tulathromycin method trial, blinded samples, and Phase II results for protocol 13411.
13-APR-2004	PFE	Chemistry Manufacture Control		73	1215	(Re:1207) Amendment in Meeting Request, supporting materials requested by CVM.
13-APR-2004	PFE	Effectiveness, Protocol		73	1216	Meeting request for update of submissions to date along with an approximate time-line for completion of outstanding activities and submissions required for approvals.
14-APR-2004	PFE	Protocol		74	1217	(Re:1213, 1186, 1169) Meeting cancelled. CVM phone to indicate they agreed with proposed scoring system, revised final IBK protocol was requested.
27-APR-2004	PFE	Protocol		74	1218	(Re:1217, 1213, 1186, 1169) Submission of revised IBK protocol.
30-APR-2004	CVM	HFS-Toxicology, Freedom of Information Summary, Approval	**P0125**	74	1219	(Re:1182, 1149, 1120) CVM comments on the submission re the incomplete, noting that the comments made by Pfizer to be adequate and acceptable.
14-MAY-2004	PFE	Effectiveness, Protocol		74	1220	(Re:1216) eMail as a summary of the key take-home messages from the 12 May 04 conference with CVM to discuss Draxxin BRD/SRD submissions and timelines to NADA approval.
17-MAY-2004	PFE	Notification of Claim Investigational Exemption		74	1221	Initial Drug Shipment to Dr L.Smith, Lodi WI, for Pivotal Phase IIIa Efficacy study # 1133C-60-04-435. NCIE states quantity of 100ml. This error should have read 20 - 50 mL vials of 1mg/mL, a total of 1000 mL.
17-MAY-2004	PFE	Notification of Claim Investigational Exemption		74	1222	Initial Drug Shipment to Dr T.TerHune, Tulare CA, for Pivotal Phase IIIa Efficacy study # 1133C-60-04-435. NCIE states quantity of 100ml. This error should have read 20 - 50 mL vials of 1mg/mL, a total of 1000 mL.
21-MAY-2004	PFE	Chemistry Manufacture Control, Incomplete, Protocol		74	1223	Request review of the sterile process validation package protocol.

Date	Source	Type	Doc Id	Volume	Tab	Description
26-MAY-2004	PFE	Protocol		74	1223a	Multiple unofficial correspondence re IBK Protocol including a 26 May 2004 Fax, 07 June 2004 email, 10 June 2004 email, 15 June 2004 email, and 16 June 2004 email.
28-MAY-2004	PFE	Notification of Claim Investigational Exemption		74	1224	(Re:1222, 1221) eMail re the two drug shipments for IBK Field Studies. There was an error on both forms. Rather than 100 mL, it should have read 1000 mL (20 x 50 mL vials = 1000mL).
24-JUN-2004	CVM	Protocol	**Z0145**	74	1225	(Re:1216) CVM minutes to the 12 May 2004 meeting. Meeting was held to provide a project update and discuss future plans (expansion claims) for the product.
29-JUN-2004	CVM	General, Chemistry Manufacture Control	**Z0141**	74	1226	(Re:1207) CVM sends official MOC record of the meeting to discuss manufacturing requirements for the transfer of A-180 to the Amboise, France manufacturing facility.
08-JUL-2004	CVM	HFS-Microbial Safety, HFS-Residue Method	**G0144**	74	1227	(Re:1214) CVM decided that the microbial food safety of tulathromycin is subject to a review by the VMAC committee. A tentative date for this meeting has been set for 13 October 2004.
08-JUL-2004	PFE	Effectiveness, Approval, Protocol		74	1228	(Re:1186, 1169) Revised master protocol 13016 entitled Efficacy of tulathromycin injectable solution for the treatment of infectious bovine keratoconjunctivitis associated with Moraxella bovis.
09-JUL-2004	PFE	Effectiveness, Approval, Protocol		74	1229	(Re:1209) Revised Protocol 13017 entitled Clinical efficacy of tulathromycin injectable solution against naturally occuring bovine interdigital phlegmon associated with Fusobacterium necrophorum and Bacteroides melaninogenicus.
14-JUL-2004	CVM	Chemistry Manufacture Control, Incomplete, Protocol	**E0150**	74	1230	(Re:1223) CVM incompletes the protocol entitled Sterilization Process Validation Package - Pre-Registration Validation Protocol Proposal.
15-JUL-2004	PFE	Chemistry Manufacture Control, Amendment		74	1231	(Re:1206, 1171) Submission of an amendment to the CMC technical section alerting CVM of the change in GMP status for the Sandwich UK manufacturing facility.
19-JUL-2004	CVM	Effectiveness, Approval, Protocol	**E0142**	74	1232	(Re:1229, 1209) CVM finds the revised Clinical Efficacy protocol (13017) acceptable.
20-JUL-2004	CVM	HFS-Residue Method, Freedom of Information Summary	**P0135**	74	1233	(Re:1199, 1181, 1168) CVM comments on the submission which provided the revised Freedom of Information Summary for Toxicology and Microbial Food Safety.
09-AUG-2004	CVM	HFS-Residue Method, Incomplete	**P0123**	74	1234	(Re:1179) CVM comments on the submission response to the incomplete letter. There are still some outstanding formulation questions remaining; CVM requests that Pfizer re-submit residue studies and their interpretations; there is uncertainty re the presence or absence of the M1 metabolite; CVM requests submission of Pfizer investigation of the fragmentation pattern; CVM finds great error associated with the swine kidney analyses.

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Date	Source	Type	Doc Id	Volume	Tab	Description
13-AUG-2004	PFE	Effectiveness, Incomplete, Protocol		74	1235	Submission of the pivotal protocol 13441 entitled Efficacy of tulathromycin injectable solution for treatment of experimentally induced Mycoplasma bovis infection in cattle. Following is the plan to obtain the efficacy data necessary to add M.bovis to the tulathromycin BRD indication to be filed in a supplemental NADA application following approval.
17-AUG-2004	PFE	HFS-Residue Method		75-82	1236	Regulatory Method Submission and request for HFS Technical Section Complete entitled Multi-Laboratory Sponsor-Monitored Method Trial for the Determinative Procedures for Tulathromycin Marker Residue in Bovine Liver and in Porcine Kidney.
31-AUG-2004	PFE	HFS-Residue Method, Incomplete, Amendment		82	1237	(Re:1234, 1179) Response to the Incomplete letter (P0123) re Target Tissue, Marker Residue and Regulatory Method.
08-SEP-2004	PFE	General, HFS-Microbial Safety		82	1238	Meeting Request for an In-Person Conference for 13 October 2004 to discuss the VMAC.
16-SEP-2004	PFE	General, HFS-Microbial Safety, Approval		83	1239	Document entitled, Tulathromycin solution for Parenteral Injection for Treatment of Bovine and Swine Respiratory Diseases - Microbialogical Effects on Bacteria of Human Health Concern - A Qualitative Risk Estimation, submitted for review by the Veterinary Medicine Advisory Committee (VMAC) as part of the microbial food safety assessment.
28-SEP-2004	PFE	HFS-Residue Method, Amendment		83	1240	(Re:1237, 1234, 1179) Minor Amendment to our response to CVM's incomplete letter re the target tissue, marker residue and suitability of the revised regulatory method. This amendment corrects the header in New Table 2 on page 3 which inadvertently did not get CP-472,295(e) equivalents changed to CP-60,300 (marker residue).
25-OCT-2004	CVM	HFS-Metabolism, HFS-Residue Method	**P0139**	83	1241	(Re:1205, 1188, 1170) CVM comments on Pfizer's response to CVM's previous concerns re the toxicology species, dogs and rats, and that they were exposed to the major residues present in edile tissues of the target species. CVM also comments on the FOI Summary.
27-OCT-2004	PFE	General, Chemistry Manufacture Control		83	1242	(Re:1226, 1207) eMail re a call from CVM which discussed the SPVP protocols for the Amboise site transfers. Protocols for INADs and NADAs are handled completely different with separate review cycles since Draxxin is not yet approved. Also discussed was the F(bio) approach.
02-NOV-2004	CVM	Effectiveness, Approval, Protocol	**E0151**	83	1243	(Re:1228, 1186, 1169) CVM approves the revised protocol entitled Efficacy of Tulathromycin for the Treatement of Infectious Bovine Keratoconjuntivitis associated with Moraxella bovis.
22-NOV-2004	PFE	Label, Approval, Amendment		83	1244	Submission of the Product Labeling Technical Section.
01-DEC-2004	CVM	Effectiveness, Incomplete, Protocol	**F0154**	83	1245	(Re:1235) CVM finds the Efficacy of Tulathromycin Injectable Solution for Treatment of Experimentally-Induced Mycoplasma bovis Infection in Cattle submission unacceptable and lists several issues which need to be addressed and a revised protocol be submitted.

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Date	Source	Type	Doc Id	Volume	Tab	Description
06-DEC-2004	PFE	All Other Information, Approval		83-84	1246	Submission to provide the All Other Information (AOI) Technical Section for tulathromycin INADs.
21-DEC-2004	PFE	Protocol		84	1247	Request for a meeting to discuss M.bovis (cattle) and M. hyo (swine) protocol reviews.
30-DEC-2004	CVM	Chemistry Manufacture Control, Amendment	**P-0153**	84	1248	(Re:1231, 1206, 1171) CVM completes Chemistry, Manufacturing and Controls Technical Section.
10-JAN-2005	CVM	General, HFS-Microbial Safety, Approval	**None**	84	1249	(Re:1239) Summary and transcript of VMAC meeting held 13 October 2004.
13-JAN-2005	PFE	HFS-Residue Method, Approval, Amendment		84	1250	(Re:1240, 1237, 1234, 1179) Minor amendment to correct typographical error and request a Technical Secton Complete.
14-JAN-2005	CVM	General, HFS-Microbial Safety, Approval	**G0158**	84	1251	(Re:1249, 1239) CVM's respone to VMAC presetnation, the requirements for microbial food safety with respect to antimirobial resistance have been met.
26-JAN-2005	PFE	Incomplete, Protocol		84	1252	(Re:1245, 1235) Submission of revised protocol 1131C-60-04-441, Efficacy of tulathromycin injectable solution for treatment of experimentally-induced Mycoplasma bovis infection in cattle.
31-JAN-2005	CVM	HFS-Residue Method	**P-0155**	84	1253	(Re:1236) CVM accepts determinative and confirmatory procedures however, there remains outstanding residue chemistry questions.
01-FEB-2005	PFE	Notification of Claim Investigational Exemption		84	1254	Drug shipped to Dr. Kelly Lectenberg, Oakland, NE; 1131C-60-04-441.
14-FEB-2005	PFE	HFS-Residue Method		85	1254a	(Re:1237, 1234, 1179) E:Mail response to Valerie Reeves regarding chromatograms, attachments not include, were send in submission 15Feb2005.
15-FEB-2005	PFE	HFS-Residue Method, Amendment		85	1255	Submission of a minor amendment to a Response to Incomplete Letter to the HFS TS - Target Tissue, Marker Residue and Regulatory Method including chromatograms and a CD containing these files. This submission will not reset the review time clock.
14-MAR-2005	PFE	Label, Approval, Amendment		85	1256	(Re:1244) Draxxin - Cattle - Amend Label
15-MAR-2005	CVM	Protocol	**Z-0162**	85	1257	(Re:1247) MOC of 19Jan2005 meeting to discuss proposed revision t effectiveness protocols.
18-MAR-2005	CVM	Protocol	**E-0164**	85	1258	(Re:1252, 1245, 1235) CVM concurrs with the design, execution and analyses proposed in the study protocol submitted for examine effectiveness, 1131C-60-04-441.
23-MAR-2005	PFE	Notification of Claim Investigational Exemption		85	1259	Drug shipped to Dr. Terry, Terhune, Tulare, CA; 1131C-60-05-471.
04-APR-2005	PFE	Label, Approval, Amendment		85	1260	(Re:1256, 1244) Submission of revised labeling, slaughter withdrawal time revised from 23 to 18 days.
05-APR-2005	CVM	General, HFS-Residue Method, Approval	**P-0156**	86	1261	(Re:1250, 1240, 1237, 1234, 1179) CVM completes Human Food Safety Technical Section, Freedom of Information Summary is included.
06-APR-2005	CVM	All Other Information, Approval	**M-0161**	86	1262	(Re:1246) CMV completes All Other Information Technical Section

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Date	Source	Type	Doc Id	Volume	Tab	Description
08-APR-2005	CVM	Label, Approval, Amendment	**M-0160**	86	1263	(Re:1260, 1256, 1244) CVM completes Labeling Technical Section.
18-APR-2005	CVM	Freedom of Information Summary	**Q-0166**	86	1264	CVM generates the Freedom of Informaion Summary.
26-APR-2005	PFE	General, Approval		86	1265	(Re:1261, 1250, 1240, 1237, 1234, 1179) Submission to comply to CVM requested to add a caution to the Confirmatory Method Procedure assay, E:Mail request from agency included, 7 April 2005.

EXHIBIT E

Exhibit E: Brief Description of DRAXXIN (tulathromycin) Review Activities for Swine

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Date	Source	Type	Doc Id	Volume	Tab	Description
05-MAY-1999	PFE	Original Submission, Effectiveness, Target Animal Safety, Environmental Assessment Exclusion		1	1	Submission of original INAD request to evaluate Safety and Efficacy for use in Swine.
10-MAY-1999	CVM	Original Submission, Effectiveness, Target Animal Safety	**None**	1	2	(Re:1) CVM assigns INAD Number 10-548.
07-JUL-1999	PFE	Target Animal Safety		1	3	Margin of Safety Study Protocol 1422N-ML-99-007 with reference to 11 May 1999 submission to 10-406 re alternative study design that does not strictly match CVM guidelines.
03-SEP-1999	CVM	Original Submission, Effectiveness, Target Animal Safety, Environmental Assessment Exclusion	**A0000**	1	4	(Re:1) CVM reviewed INAD file request and previously assigned 10-548. Then noted that Pfizer did not request an EA be excluded.
14-SEP-1999	PFE	Original Submission, Effectiveness, Target Animal Safety, Environmental Assessment Exclusion		1	5	(Re:4, 1) Submission of Categorical Exclusion of an Environmental Assessment.
17-SEP-1999	CVM	Target Animal Safety	**E0001**	1	6	(Re:3) CVM Faxed response for discussion re 07 July 1999 Protocol of drug tolerance and MOS study is not acceptable and requires recommended (included)revisions.
03-NOV-1999	PFE	Target Animal Safety		1	7	(Re:6, 3) TelCon to discuss Pfizer proposed protocol revisions re need for urinalysis and a list of tissues for histologic examination.
04-NOV-1999	PFE	Target Animal Safety		1	8	(Re:7, 6, 3) Amended Protocol 1422N-ML-99-007 intending to conduct tolerance test separate from MOS and with revisions that were outlined in 17 September 1999 fax and subsequent telcons.
08-NOV-1999	PFE	Notification of Claim Investigational Exemption		1	9	Initial drug shipment to Dr D.Fagerberg, Ft Collins, CO for Pivotal safety, non-clinical study 1422N-60-99-173.
17-NOV-1999	PFE	Target Animal Safety		1	10	(Re:8, 7, 6, 3) E-Mail re the consideration of amending the Margin of Safety protocol about when to collect blood samples. CVM responded with an OK but to submit a hard copy.
29-NOV-1999	PFE	Target Animal Safety		1	11	(Re:10, 8, 7, 6, 3) Amendment to 04 November 1999 Margin of Safety Protocol re blood samples.
30-NOV-1999	PFE	Target Animal Safety		1	12	(Re:8, 7, 6, 3) Submission of Tolerance Protocol 1422N-ML-99-008 incorporating agreements during review and revision of MOS protocol in Swine.
09-DEC-1999	PFE	HFS-Residue Method		1	13	Submission of Protocol 1525N-60-99-175 a Radiotracer Total Residue Study designed to conform to CVM guidelines.

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10-DEC-1999	PFE	HFS-Residue Method		1	14	Submission of protocol 1521N-60-99-176, a Marker Residue Depletion Study and is designed to conform to CVM guidelines.
20-DEC-1999	PFE	Effectiveness, Target Animal Safety, Label		1	15	Submission of Efficacy protocol 1123C-ML-99-011 and randomization plan for allocating animals to treatments/pens.
04-JAN-2000	CVM	Target Animal Safety	**E0004, E0005**	1	16	(Re:11, 10, 8, 7, 6, 3) CVM finds the 29 November 1999 Revised Toxicity Protocol to be acceptable and encourages a final protocol to be submitted and recommends a statistical analysis.
27-JAN-2000	CVM	HFS-Residue Method	**E0007**	1	17	(Re:14) CVM review of Marker Residue Study Protocol with listed recommendations.
27-JAN-2000	CVM	HFS-Residue Method	**E0008**	1	18	(Re:13) CVM review of Residue Depletion Study Protocol with listed recommendations.
03-FEB-2000	PFE	HFS-Residue Method		1	19	(Re:18, 17, 14, 13) TelCon to CVM giving more explanation to CVM's comments re Marker and Residue Protocol reviews.
15-MAR-2000	PFE	Effectiveness, Target Animal Safety, Label		1	20	(Re:15) Memo of TelCon to CVM re Review status of SRD efficacy protocol and proposed statistical analysis of hematology and serum chemistry in MOS study.
22-MAR-2000	CVM	Environmental Assessment Exclusion	**G0002**	1	21	(Re:5, 4, 1) CVM reviewed and agrees with the categorical exclusion requested.
27-MAR-2000	PFE	Target Animal Safety		1	22	Submission of Injection Site Tolerance Protocol 1422N-ML-99-006.
30-MAR-2000	CVM	Target Animal Safety	**E0006**	1	23	(Re:12, 8, 7, 6, 3) CVM accepts Tolerance Protocol as submitted.
10-JUL-2000	PFE	Notification of Claim Investigational Exemption		1	24	Initial Drug Shipment to Dr K.Lechtenberg, Oakland, NE, for Pivotal field efficacy study 1123C-60-00-179.
13-JUL-2000	PFE	Notification of Claim Investigational Exemption		1	25	(Re:24) Supplemental Drug Shipment
14-JUL-2000	PFE	Notification of Claim Investigational Exemption		1	26	Initial drug shipment to Dr T.TerHune, Tulare, CA, for Pivotal target animal safety study 1423N-60-00-181.
14-JUL-2000	PFE	Notification of Claim Investigational Exemption		1	27	Initial drug shipment to D.Ronning, Ft Collins, CO, for Pivotal target animal safety study 1422-60-00-182.
17-JUL-2000	PFE	Effectiveness, Target Animal Safety, Label		1	28	(Re:20, 15) Submission for review a Revised Efficacy protocol 1123C-ML-99-011 to be substituted for the 20 December 1999 Protocol which the Division has not yet reviewed.
10-AUG-2000	PFE	HFS-Metabolism, Target Animal Safety		2	29	Meeting Request to present a proposed approach and solicit CVM input on pre-approval studies to assure human safety of antimicrobial effects.
16-AUG-2000	PFE	Effectiveness, Label		2	30	(Re:28, 20, 15) Memo - TelCon from CVM requesting and agreed that an FNR would be appropriate for 17 July 2000 Efficacy protocol and whether trials would be conducted referencing a Feb call re statistical methods.
25-AUG-2000	PFE	Notification of Claim Investigational Exemption		2	31	Initial drug shipment to Dr K.Lechtenberg, Oakland, NE, for Pivotal field efficacy study 1123C-60-00-184.

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30-AUG-2000	PFE	Notification of Claim Investigational Exemption		2	32	Initial drug shipment to Dr L.Kesl, Ames, IA, for Pivotal field efficacy study 1123C-60-00-183.
25-SEP-2000	CVM	Target Animal Safety	**E0010**	2	33	(Re:22) CVM reviewed Injection Site Tolerance Protocol 1422N-ML-99-006 and finds it is not acceptable as written and lists required revisions.
06-OCT-2000	PFE	Effectiveness, Target Animal Safety		2	34	(Re:28, 20, 15) Response to CVM request for Clarification of the proposed multi-study statistical analysis. We anticipate the master protocol to be replicated at least (3) times to obtain adequate enrollment to detect the efficacy.
07-NOV-2000	PFE	Environmental Assessment Exclusion		2	35	Submission requests use of CP-472,295(e) be categorically excluded from the requirements for preparation of an EA or an environmental impact statement in the NADA.
15-NOV-2000	PFE	Notification of Claim Investigational Exemption		2	36	Initial drug shipment to Dr J.Kula, French Village, MO, for Pivotal clinical efficacy study 1123C-60-00-187.
08-JAN-2001	PFE	Development Plans, General, HFS-Microbial Safety		2	37	Request for a Review of the Pre-Approval Development Plan for assessing microbiological safety.
16-JAN-2001	PFE	Notification of Claim Investigational Exemption		2	38	Initial drug shipment to Dr T.TerHune, Tulare, CA, for Pivotal clinical efficacy, natural infection study 1123C-60-00-190.
08-FEB-2001	CVM	Effectiveness	**E0014**	2	39	(Re:28, 20, 15) CVM reviewed Efficacy Protocol 1123C-ML-99-011 and as writen, is not accptable listing issues that require revision.
16-FEB-2001	PFE	Effectiveness		2	40	Teleconference request for 20 February 2001 re revisions to Proposed Protocol for enrollment/responder.
21-MAR-2001	PFE	Effectiveness, Label		2	41	Meeting Request for 04 April 2001 to discuss studies required to support the efficacy technical section of the NADA.
22-MAR-2001	PFE	Notification of Claim Investigational Exemption		2	42	Initial drug shipment to Dr K.Lechtenberg, Oakland, NE, for Pivotal Clinical efficacy, natural infection study 1123C-60-01-193.
22-MAR-2001	PFE	Label		2	43	Submission of Efficacy protocol 1121E-ML-01-015 to generate pivotal data in support of a label indication.
23-MAR-2001	PFE	Effectiveness, Label		2	44	Submission of Efficacy protocol 1123C-02-01-192 to generate pivotal data in support of a label indication for treatment of pneumonia by bacterial/mycoplasmal pathogens in pigs.
27-MAR-2001	PFE	Notification of Claim Investigational Exemption		2	45	Initial drug shipment to Dr J.Brennan, Burford Ontario, Canada, for Clinical efficacy, natural infection study 1123C-60-01-192.
30-MAR-2001	PFE	Effectiveness, Label		2	46	(Re:41) Submission of slides with a change in date, 15 May 2001, for the new meeting to reach agreement on the package as pivotal support of NADA approval.
12-APR-2001	PFE	Effectiveness, Label		2	47	(Re:44) Submission of amendment to protocol 1123C-02-01-192, "Efficacy in treatment of natural outbreaks...associated with bacterial & mycoplasmal pathogens."
30-APR-2001	PFE	Notification of Claim Investigational Exemption		2	48	Corrected Drug Shipment to Dr K.Lechtenberg, Oakland, NE, for Pivotal clinical efficacy, natural infection study 1123C-60-01-193.

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Date	Source	Type	Doc Id	Volume	Tab	Description
21-MAY-2001	PFE	Notification of Claim Investigational Exemption		2	49	Initial drug shipment to Dr L.Kesl, Ames, IA, for Pivotal Clinical Field Efficacy study 1123C-60-01-195.
21-MAY-2001	PFE	Notification of Claim Investigational Exemption		2	50	Initial drug shipment to Dr G.Davis, Delaware, OH, for Pivotal Clinical Field Efficacy study 1123C-60-01-196.
29-MAY-2001	PFE	Notification of Claim Investigational Exemption		2	51	Initial drug shipment to Dr J.Brennan, Burford, Ontario Canada, for Pivotal Clinical-Natural Field Infection study 1123C-02-01-197.
31-MAY-2001	PFE	Notification of Claim Investigational Exemption		2	52	Initial drug shipment to Dr K.Lechtenberg, Oakland NE, for Pivotal Clinical efficacy, experimentally-induced infection study 1121C-60-00-180.
01-JUN-2001	CVM	Effectiveness, Label	**E0025, T0028**	2	53	(Re:47, 44) CVM reviewed Submission and the amended protocol and finds the protocol is not acceptable as written and lists several issues requiring revision.
01-JUN-2001	CVM	Environmental Assessment Exclusion	**G0019**	2	54	(Re:35) CVM completed their review for a categorical exclusion and agrees that it is appropriate for the NADA.
11-JUN-2001	CVM	Effectiveness	**Z0024**	2	55	(Re:41) CVM Minutes of 15 May 2001 Meeting to discuss studies required to support the efficacy technical section of the NADA.
27-JUN-2001	PFE	Notification of Claim Investigational Exemption		2	56	(Re:49) Supplemental drug shipment to Dr L.Kesl, Ames, IA for Pivotal Clinical Field Efficacy study 1123C-60-01-195.
27-JUN-2001	PFE	Notification of Claim Investigational Exemption		2	57	(Re:50) Supplemental drug shipment to Dr G.Davis, Delaware, OH, for Pivotal Clinical Field Efficacy study 1123C-60-01-196.
16-JUL-2001	PFE	Development Plans, General, HFS-Microbial Safety		2	58	(Re:37) TelCon to CVM to check on review status of 08 January 2001 submission of the proposed categorization and study plan.
18-JUL-2001	PFE	Development Plans, HFS-Microbial Safety		2	59	(Re:37) Dr.Gilbert/CVM called re 08 January 2001 submission and asked for clarification of the term triamilide.
10-OCT-2001	PFE	Notification of Claim Investigational Exemption		2	60	Initial drug shipment to Dr J.Brennan, Burford, Ontario Canada, for Pivotal Clincal Efficacy, natural infection study 1123C-02-01-197.
15-NOV-2001	PFE	Development Plans, General, HFS-Microbial Safety		2	61	(Re:58, 37) TelCon to CVM requesting status update on 08 January 2001 submission requesting categorization and that Pfizer was waiting to file studies and data. CVM recommended filing without waiting for submission approval.
16-NOV-2001	PFE	Notification of Claim Investigational Exemption		2	62	Initial drug shipment to Dr. K.Lechtenberg, Oakland NE, for Pivotal clinical efficacy, natural infection study 1123C-60-01-198.
21-NOV-2001	PFE	Target Animal Safety, Freedom of Information Summary, Label		3-8	63	Submission of the Target Animal Safety Technical Section.
23-NOV-2001	CVM	Label	**E0026**	9	64	(Re:43) CVM reviewed protocol 1121E-ML-01-015 and comments that they are not prepared to review protocol submissions for effectiveness and need a better understanding of the extent and characterization of the disease.

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03-DEC-2001	PFE	Development Plans, HFS-Microbial Safety		9	65	(Re:37) Pfizer requests directed review of in vitro studies by recommendation of Dr.Weld because categorization request was still under review. Complete hard copy found in 10-406.
21-DEC-2001	PFE	Notification of Claim Investigational Exemption		9	66	Initial drug shipment to K.Fogarty-Fairbanks, Brookings, SD, for Clinical efficacy, natural infection study 1123C-60-01-203.
07-JAN-2002	PFE	HFS-Microbial Safety		9	67	(Re:65, 37) Request confirmation that the Memo of TelCon reflects understanding of 03 January 2002 conversation and that the request for categorization be addressed in relation to 03 December 2001 submission.
09-JAN-2002	PFE	HFS-Residue Method		9-13	68	Request for Directed review of Total and Marker Residue Depletion studies.
14-JAN-2002	PFE	HFS-Metabolism, HFS-Toxicology		14	69	Request directed review of 1576N-60-00-211 describing the metabolism in dogs & rats including a summary report relating metabolism across all species studied.
23-JAN-2002	CVM	HFS-Microbial Safety	**Y-0043**	10	70	(Re:67, 65, 37) CVM reviewed submission of Pfizer's TelCon minutes and has listed comments and included the official TelCon minutes of record.
27-FEB-2002	PFE	Chemistry Manufacture Control, Target Animal Safety		14	71	Faxed submission of detailed information for an upcoming meeting on the impurities (structures, structure assessment, source, and concentration) of test materials used in safety studies.
05-MAR-2002	PFE	Chemistry Manufacture Control, Target Animal Safety		14	72	(Re:71) TelCon from CVM re faxed details of the impurities had been received and distributed and they would need to hold an internal meeting to discuss the issue before getting back to us.
12-MAR-2002	PFE	HFS-Microbial Safety		14	72a	(Re:65, 37) CVM called seeking additional information re 03 December 2001 submission.
28-MAR-2002	PFE	All Other Information		14	72b	TelCon to CVM requesting to meet briefly w/ Dr Leinbach. She declined informing Pfizer that she would contact them for the next step.
05-APR-2002	PFE	HFS-Microbial Safety		14	73	(Re:65, 37) Amendment to 03 December 2001 Antimicrobial Resistance Studies including answers to TelCon of 12 March 2002 where CVM gave us three queries.
24-APR-2002	CVM	HFS-Metabolism, HFS-Toxicology	**H-0045**	14	74	(Re:69) CVM reviewed the comparative Metabolism Study submission and comments on several areas requesting more experimental details be provided.
30-APR-2002	PFE	HFS-Microbial Safety		14	75	(Re:65, 37) Submission of answers to queries raised in a 09 April 2002 TelCon arising from the 03December 2001 submission re Antimicrobial Resistance Studies.
07-MAY-2002	PFE	Effectiveness, Target Animal Safety		14	76	TelCons (07, 09, 15 May 2002) re swine efficacy and preparing to submit results of field studies in September or October. Also discussed was the S.Dakota inspection.

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Date	Source	Type	Doc Id	Volume	Tab	Description
06-JUN-2002	CVM	Target Animal Safety, Freedom of Information Summary, Label	**P0040**	14	77	(Re:63) CVM reviewed TAS data and has found the technical section to be complete for recommending NADA approval. CVM made changes to the FOI and includes a copy of the revised FOI summary.
12-JUN-2002	PFE	HFS-Toxicology		14	77a	Request directed review of the Toxicology Technical Section.
19-JUN-2002	CVM	Development Plans, HFS-Microbial Safety	**P-0041**	14	78	(Re:75, 73, 65, 37) CVM reviewed submissions and finds Pfizer needs to sequence the PCR product from E.coli and CVM needs additional susceptibility information.
09-JUL-2002	CVM	HFS-Residue Method	**P0044**	14	79	(Re:68) CVM reviewed Total and Marker Residue depletion studies and includes comments, noting that in the future all Method validation data be submitted in Electronic format.
12-JUL-2002	PFE	HFS-Microbial Safety, HFS-Residue Method, User Safety		14	80	Sponsor's meeting minutes for 28 March 2002 Microbiological Safety Assessment and a request for CVM's minutes.
15-JUL-2002	PFE	HFS-Microbial Safety, HFS-Residue Method, User Safety		14	81	(Re:80) Requested review of the Technical Section of Microbiological Safety. Complete hard copy included in 10-406.
31-JUL-2002	PFE	Chemistry Manufacture Control, Target Animal Safety		14	82	(Re:71) Requesting CVM's review of "Qualification of Impurities in Drug Substance and Product" along with supporting data that describes the approach that presents Pfizer's interpretation of guidance documents and request clarification of CVM's position ther
01-AUG-2002	PFE	HFS-Toxicology		14	83	(Re:77a) CVM called to request additional information re the stability and concentration of the dosing solutions.
15-AUG-2002	CVM	HFS-Microbial Safety	**Y-0051**	14	84	(Re:80) CVM's meeting minutes from 28 March 2002 re safety of residues present in edible tissues.
27-AUG-2002	PFE	HFS-Toxicology		14	85	(Re:77a) Submission of an Amendment to 21 June 2002 Toxicology Technical Section-Dosing Solution Data for review.
30-AUG-2002	PFE	HFS-Microbial Safety		15	86	(Re:78, 75, 73, 65, 37) Requested review of data in response to CVM letter of 19 June 2002 re Antibactierial Resistance.
30-SEP-2002	PFE	Chemistry Manufacture Control		15	86a	Requesting directed review of the Chemistry, Manufacturing and Controls Technical Section. Complete hard copy found in 10-406.
10-OCT-2002	PFE	Animal Disposition		15	87	Notice of Final Disposition for landfill. Dr K.Lectenberg, Oakland, NE Study 1123C-60-00-179.
10-OCT-2002	PFE	Animal Disposition		15	88	Notice of Final disposition, Incineration of 12 animals, Dr L.Kesl, Ames, IA, 1123C-60-00-183.
10-OCT-2002	PFE	Animal Disposition		15	89	Notice of Final disposition, Landfill of 40 animals, Dr K.Lechtenberg, Oakland, NE, 1123C-60-00-184.
10-OCT-2002	PFE	Animal Disposition		15	90	Notice of Final disposition, Return to herd w/o treatment, Dr J.Kula, French Village, MO, 1123C-60-00-187.
10-OCT-2002	PFE	Animal Disposition		15	91	Notice of Final disposition, Landfill or Incineration, HMS Vet Development, Tulare, CA, 1123C-60-00-190.
10-OCT-2002	PFE	Animal Disposition		15	92	Notice of Final Disposition for Shur-Gain Agresearch, Burford Ontario, for Incineration of 30 animals

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Date	Source	Type	Doc Id	Volume	Tab	Description
10-OCT-2002	PFE	Animal Disposition		15	93	Notice of Final disposition, Landfill of 24 animals, Dr K.Lechtenberg, Oakland NE, 1121C-60-00-180.
10-OCT-2002	PFE	Animal Disposition		15	94	Notice of Final Disposition by Landfill or Incineration for 48 animals, Midwest Vet Services, Oakland NE, 1123C-60-01-193.
10-OCT-2002	PFE	Animal Disposition		15	95	Notice of Final Disposition by returning to herd w/o treatment, Shur-Gain Agresearch, 1123C-02-01-197.
10-OCT-2002	PFE	Animal Disposition		15	96	Notice of Final Disposition by Landfill for 48 animals, Dr G.Davis, Delaware OH, 1123C-60-01-196.
10-OCT-2002	PFE	Animal Disposition		15	97	Notice of Final Disposition of 48 animals by Landfill, Dr K.Lechtenberg, Oakland NE, 1123C-60-01-198.
10-OCT-2002	PFE	Animal Disposition		15	98	Notice of Final Disposition of 48 animals by Landfill, Dr K.Fogarty-Fairbanks, Brooklings SD, 1123C-60-01-203.
10-OCT-2002	PFE	Animal Disposition		15	99	Notice of Final Disposition for Dr L.Kesl, Ames, IA, for incineration of 12 animals.
31-OCT-2002	PFE	Effectiveness		15-31	100	Request review of the Effectiveness Technical Section Phased Review including the proposed Label text and draft FOI Summary.
02-DEC-2002	PFE	Development Plans, HFS-Microbial Safety		31	101	(Re:86, 78, 75, 73, 65, 37) Response to CVM's queries regarding Macrolide Resistance Gene Survey of field isolates using PCR.
02-JAN-2003	CVM	HFS-Microbial Safety	**H-0071**	31	102	(Re:101, 86, 78, 75, 73, 65, 37) CVM finds the information Pfizer has provided to adequately address concerns re bacterial cross resistance betweeen the product and ketolides. This ltr serves as the microbial food safety component complete letter.
10-JAN-2003	CVM	HFS-Toxicology, Freedom of Information Summary	**P0076**	31	102a	CVM Response to 24 April 2002 toxicology submission to 10-406 referencing 10-548 in letter.
05-FEB-2003	PFE	Chemistry Manufacture Control		31	102b	Request review of memo of conference held 29 January 2003 to discuss plans for transferring manufacture from Lee's Summit to other PGM facilities.
12-FEB-2003	CVM	HFS-Metabolism, HFS-Toxicology	**T-0054, H -0053**	31	103	(Re:74, 69) CVM reviewed and comments on the Toxicology Technical Section.
28-FEB-2003	PFE	Chemistry Manufacture Control		31	104	(Re:86a) Request review of the stability data update. Complete hard copy found in 10-406.
11-MAR-2003	PFE	Chemistry Manufacture Control		31	104a	Email referencing calculations presented in the microbiological ADI submission offering a more detailed presentation of the ADI values listed in Table 5.
12-MAR-2003	CVM	Chemistry Manufacture Control	**Z0072**	31	105	CVM minutes from 29 January 2003 meeting to discuss the transfer of the manufacturing of Dectomax/Tulathromycin from Lee's Summit to alternate manufacturing sites.
24-MAR-2003	PFE	HFS-Toxicology		31	105a	(Re:103, 74, 69) Request for Teleconference re CVM's Review of Toxicology Technical Section.

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28-MAR-2003	CVM	HFS-Microbial Safety, HFS-Residue Method, User Safety	**P0052**	31	106	(Re:81, 80) CVM reviewed Residue submission and finds need for revision re Effects and Exposure (susceptibility, residues) and Microbiological ADI.
25-JUN-2003	PFE	Effectiveness		31	107	MOC telephone conversation inquiring of progress of Efficacy technical section, current estimate letter should issue early August.
14-JUL-2003	CVM	Effectiveness	**E:Mail**	31	108	(Re:107) E:Mail from CVM seeking clarification of formulas and lot numbers as well as an informal introduction for change in regulatory responsibilities.
30-JUL-2003	PFE	General		31	109	Notification of change in sponsor contact .
12-AUG-2003	PFE	HFS-Metabolism, HFS-Residue Method		31	110	Response to Queries on Comparative Metabolism Studies.
04-SEP-2003	PFE	Chemistry Manufacture Control		31	111	Amendment to CMC Technical Section, full copy sent to INAD 10-406 not formally sent to INAD 10-548.
05-SEP-2003	PFE	Development Plans, Chemistry Manufacture Control		31	112	Request for a meeting 8 October 2003, to discuss method trial process.
08-SEP-2003	CVM	Effectiveness, Freedom of Information Summary, Approval	**P-0070, T -0075**	31	113	CVM approves Effectiveness Technical Section, FOI included.
18-SEP-2003	PFE	HFS-Toxicology		31	114	Request for Concurrence of Safe Concentrations and Tolerance Values and Establishment of Edible Tissue Withdrawal Period.
30-SEP-2003	PFE	Chemistry Manufacture Control		31	115	MOC of teleconference: impurities qualifications. Request a technical section complete letter upon approval of 04Sept2003 submission and amendment.
09-OCT-2003	PFE	Development Plans, Chemistry Manufacture Control		31	116	(Re:112) Amendment to incomplete response submitted 4 September 2003.
10-OCT-2003	CVM	HFS-Residue Method	**None**	31	117	Follow-up information for method trial teleconference held 8 October 2003.
20-OCT-2003	PFE	HFS-Residue Method		31	118	Meeting request to discuss mutually acceptable approach to completing residue methods trials.
30-OCT-2003	PFE	HFS-Residue Method		31-32	119	Response to incomplete letter for residue chemistry, metabolic profile and regulatory methods.
31-OCT-2003	PFE	HFS-Residue Method, HFS-Toxicology, Protocol		32	120	Submission of a protocol without data for sponsor monitored method trial cover letter only see INAD 10-406 Tab 5011 for complete document.
04-NOV-2003	PFE	HFS-Residue Method, HFS-Toxicology		32	121	(Re:120) Response to incomplete letter for genetic toxicity studies and FOI summary, complete submission in INAD 10-406
19-NOV-2003	CVM	HFS-Residue Method	**Z0080**	32	122	(Re:118) MOC for 5 Nov meeting, no conclusions or agreements were reached, however, CVM stated that they would provide additional information to Pfizer before 27 Nov.

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20-NOV-2003	CVM	HFS-Residue Method	**031008**	32	123	(Re:117) Follow-up information for method trial teleconference held 8 October 2003.
09-DEC-2003	CVM	HFS-Metabolism, HFS-Residue Method	**H0076**	32	124	(Re:110) CVM response to comparative metabolism studies.
23-DEC-2003	PFE	HFS-Metabolism		32	125	Follow-up from teleconference 17Dec03, Pfizer submits questions for clarification on comments CVM provided to our comparative metabolism submission. CVM response included.
31-DEC-2003	CVM	HFS-Residue Method, Protocol		32	126	(Re:120) CVM provides additional recommendations to Method Trial Protocol.
07-JAN-2004	PFE	HFS-Residue Method, Protocol		32	127	(Re:126, 120) CVM agrees Pfizer should not address the muscle tolerance in our current method trial, Pfizer committed that we will address post approval. It was also suggested if the assay for muscle was very similar to the target tissue methods that CVM will likely request reduced methods testing, to be discussed at that time.
15-JAN-2004	PFE	HFS-Residue Method		32	128	(Re:127, 126, 120) Pfizer will incorporate CVM suggestions into protocol and/or trial as appropriate. Pfizer commits to the establishment of the muscle tolerance for both cattle and swine muscle and the associated regulatory method following the approval of the NADAs. The NADA will contain published tolerances for the target tissue and a regulatory method for same. Also we grant CVM permission to transfer the assay method and materials to FSIS prior to NADA approval.
20-JAN-2004	PFE	HFS-Residue Method		32	129	(Re:119) Request for a meeting (5Feb04) for in depth discussion of tissue residue assay regulatory method.
26-JAN-2004	PFE	HFS-Residue Method, Freedom of Information Summary		32	130	Submission of corrected Toxicology and Residuesections of FOI for final review. Hard Copy found in 10-406.
06-FEB-2004	PFE	HFS-Residue Method		33	131	(Re:128, 127, 126, 120) CVM telephone with "thumbs up" to move to method demonstration.
10-FEB-2004	PFE	HFS-Residue Method		33	132	(Re:131, 128, 127, 126, 120) Regarding details setting up Method Demonstration, schedules and participants.
16-FEB-2004	PFE	HFS-Residue Method		33	133	Submission of Sponsor Meeting Minutes for 5 February 2004 meeting, purpose was to discuss details of the analytical method for detection of residues in bovine liver and porcine kidney for the "desk review" component of the method trail process.
16-FEB-2004	PFE	HFS-Residue Method		33	134	(Re:132, 131, 128, 127, 126, 120) Response to a CVM request for additional storage stability data to support our Method submission of 28 October 2003 and additional chromatograms to support tabular data. See INAD 10-406 for complete submission.

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23-FEB-2004	PFE	HFS-Residue Method		33	135	(Re:124, 110) Response to CVM questions from H-0076 and request for final concurrence that the toxicology species, dogs and rats are systematically exposed to the major residues present in edible tissue of cattle and swine.
26-FEB-2004	PFE	Chemistry Manufacture Control, Approval, Incomplete		33	136	(Re:115) Response to CVM questions regarding CMC submission of 9/4/03.
09-MAR-2004	PFE	Chemistry Manufacture Control		33	137	Meeting request for site transfer Re: closing of Lee's Summit Plant.
15-MAR-2004	CVM	HFS-Toxicology	**P-0078**	33	137a	(Re:114) CVM supplies comments regarding submission: outstanding formulation questions, muscle tolerance, isomer ratio and ADI and current consumption values.
16-MAR-2004	CVM	Chemistry Manufacture Control, Incomplete	**P0077**	33	138	(Re:136, 115) CVM provides comments on incomplete CMC Technical Section.
23-MAR-2004	CVM	HFS-Residue Method	**Z0085**	33	139	MOC from conference held 5Feb2004 to discuss analytical method issues.
31-MAR-2004	CVM	HFS-Residue Method		33	140	(Re:139) Agreements and response to outstanding issues from 5Feb04 meeting, method trial.
31-MAR-2004	PFE	Protocol		33	141	Pfizer requests a meeting to discuss CVM comments on IBK Master Protocol letter dated 21Nov03.
05-APR-2004	PFE	General, HFS-Microbial Safety		33	142	Pfizer request review and conclusion on need for a VMAC . (Antibiotic Resistance)
13-APR-2004	PFE	Chemistry Manufacture Control		33	143	(Re:137) Amendment in Meeting Request, supporting materials requested by CVM.
13-APR-2004	PFE	Protocol		33	144	Meeting request for update of submissions to date along with an approximate time-line for completion of outstanding activities and submissions required for approvals.
21-MAY-2004	PFE	Chemistry Manufacture Control		33	145	Submission to request review of Protocol for Sterile Process Validation Package (SPVP).
15-JUN-2004	PFE	Notification of Claim Investigational Exemption		33	146	Drug Shipment to Dr. Nathan Winkelman, Mossis, MN, 1121E-60-04-213.
24-JUN-2004	CVM	Protocol	**Z-0093**	33	147	(Re:144) MOC of 12 May 2004 meeting to discuss project update and future plans (expansion claims) for the product.
08-JUL-2004	CVM	General, HFS-Microbial Safety	**G0092**	33	148	(Re:142) CVM decides this needs to be review by the VMAC committee. Meeting has been set for 13 October 2004.
14-JUL-2004	CVM	Chemistry Manufacture Control	**E0094**	33	149	(Re:145) CVM imcompletes "Sterilization Process Validation Package - Pre-Registration Validation Protocol Proposal".
15-JUL-2004	PFE	Chemistry Manufacture Control		33	150	Change in GMP Status for Manufacturing Facility; 36 Month Stability; Minor Commitments and Clarification. See NADA 10-406 for complete doucment.

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Date	Source	Type	Doc Id	Volume	Tab	Description
20-JUL-2004	CVM	HFS-Residue Method, Freedom of Information Summary	**P0087**	33	151	(Re:130) CVM provides FOI Summary Review: Microbial Food Safety, Toxicity Studies, Microbiological Safety and Safe Concentration of Residues.
09-AUG-2004	CVM	HFS-Residue Method	**P0123**	33	152	(Re:119) CVM provides comments regarding concurrence on the proposed target tissue, the proposed marker residue and the suitability of the revised regulatory method.
17-AUG-2004	PFE	HFS-Residue Method		33	153	Regulatory Method Technical Section submission. See INAD 10-406 for complete submission.
03-SEP-2004	PFE	HFS-Residue Method, Approval		33	154	(Re:152, 119) Response to incomplete CVM letter for Target Tissue, Marker Residue and Regulatory Methods.
08-SEP-2004	PFE	HFS-Residue Method, Protocol		33	155	Submission of Protocol 1121C-60-03-209, "Efficacy of tulathromycin injectable solution for the treatment of experimentally-induced Mycoplasma hyopneumoniae Pneumonia in Swine".
16-SEP-2004	PFE	General, HFS-Microbial Safety, Approval		33	156	(Re:148, 142) Submission of a document "Tulathromycin Solution for Parenteral Injection For Treatment Of Bovine and Swine Respiratory Diseases-Microbiological Effects on Bacteria of Human Health Concern-A Qualitative Risk Estimation". See INAD 10-406 for complet
28-SEP-2004	PFE	HFS-Residue Method, Approval, Amendment, Protocol		34	157	(Re:155) Amendment to response to incompletion of Target Tissue, Marker Residue and Regulatory Methods.
22-OCT-2004	CVM	HFS-Residue Method	**P0090**	34	158	(Re:135, 124, 110) CVM provides comment regarding residues; formulation, comparative metabolism stud and FOI.
17-NOV-2004	CVM	Protocol	**E-0100**	34	159	(Re:155) CVM does not accept protocol 1121C-60-03-209.
22-NOV-2004	PFE	Label, Approval, Amendment		34	160	Submission of Product Labeling Technical Section.
06-DEC-2004	PFE	All Other Information, Approval		34	161	Submission of AOI Technical Section. See INAD 10-406 for complete document.
21-DEC-2004	PFE	Protocol		34	162	Meeting request to discuss bovis and swine protocol reviews.
30-DEC-2004	CVM	Chemistry Manufacture Control, Approval	**P-0097**	34	163	(Re:136, 115) CVM completes Chemistry, Manufacturing and Controls Technical Section.
04-JAN-2005	PFE	Notification of Claim Investigational Exemption		34	164	Notification of cancellation of study due to lack of availability of appropriate study candidates.
05-JAN-2005	PFE	Notification of Claim Investigational Exemption		34	165	Notification of cancellation of study due to lack of availability of appropriate study candidates.
06-JAN-2005	PFE	Notification of Claim Investigational Exemption		34	166	Drug wasn't shipped, determined that the available experimental durg was too close to expiry.
10-JAN-2005	CVM	General, HFS-Microbial Safety	**None**	34	167	(Re:156, 148, 142) Summary and transcript of VMAC meeting held 13 October 2004.
13-JAN-2005	PFE	HFS-Residue Method, Approval, Amendment		34	168	(Re:157, 155) Minor amendment to correct typographical error and request a Technical Section Complete.

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Date	Source	Type	Doc Id	Volume	Tab	Description
13-JAN-2005	CVM	General, HFS-Microbial Safety, Approval	**G0101**	34	169	(Re:156, 148, 142) CVM's response to VMAC presentation, the requirements for microbial food safety with respect to antimicrobial resistance have been met.
31-JAN-2005	CVM	HFS-Residue Method	**P-0098**	34	170	(Re:153) CVM accepts determinative and confirmatory procedures however, there remains outstanding residue chemistry questions.
14-FEB-2005	PFE	Protocol		34	171	E:Mail response to Valerie Reeves regarding chromatograms, attachments not include, were send in submission 15Feb2005. See 31Aug2004 INAD 10-406 for original submission.
15-FEB-2005	PFE	HFS-Residue Method, Approval		34	172	(Re:170, 153) Cover letter only for Minor Amendment to a response to an incomplete letter for Target Tissue, Marker Residue and Regulatory Method. See INAD 10-406 for complete submission, this submission will not re-set the clock.
15-FEB-2005	PFE	Effectiveness, Approval, Protocol		34	173	Submission of a revised Effectiveness Protocol 1121C-60-03-209 incorporating CVM's suggestions dated 17 November 2004.
14-MAR-2005	PFE	Label, Amendment		34	174	(Re:160) Draxxin - Swine - Amend Label
15-MAR-2005	CVM	Protocol	**Z-0105**	34	175	(Re:162) MOC of 19Jan2005 meeting to discuss proposed revisions to effectiveness protocols.
04-APR-2005	PFE	Label, Approval, Amendment		34	176	(Re:174, 160) Submission to revise labeling, slaughter withdrawal time revised from 23 to 18 days, cover letter only, see INAD 10-406 for complete submission.
06-APR-2005	CVM	Effectiveness, Approval, Protocol	**E-0112**	34	177	(Re:173) CVM concur with study protocol 1121C-60-03-209 for Efficacy of tulathromycin injectable solution for the treatment of experimentally-induced Mycoplasma hyopneumoniae pneumonia in swine.
06-APR-2005	CVM	All Other Information, Approval	**M-0104**	34	178	(Re:161) CVM completes All Other Information Technical Section.
06-APR-2005	CVM	HFS-Residue Method, Approval, Amendment	**P-0099**	35	179	(Re:172, 170, 168, 157, 155, 154, 153, 152, 119) CVM completes Human Food Safety Technical Section, comments provided.
08-APR-2005	CVM	Label, Approval	**M-0105**	35	180	(Re:176, 174, 160) CVM completes Labeling Technical Section.
18-APR-2005	CVM	Freedom of Information Summary	**Q-0110**	35	181	CVM approves and generates Freedom Of Information Summary.
26-APR-2005	PFE	HFS-Residue Method, Approval		35	182	(Re:179, 172, 170, 168, 157, 155, 154, 153, 152, 119) Submission to comply with a CVM request to add a caution to the Confirmatory Method Procedure assay, E:Mail request from the agency included dated 7 April 2005.

EXHIBIT F

Exhibit F: Brief Description of Draxxin (tulathromycin) NADA Approval and Post-Approval Activities

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Date	Source	Type	Doc Id	Volume	Tab	Description
18-APR-2005	PFE	Original Submission, Approval		1	1	Administrative NADA filing for cattle and swine.
22-APR-2005	CVM	Original Submission	**None**	1	2	(Re:1) CVM Assigns NADA Number 141-244
24-MAY-2005	CVM	Original Submission, Label, Approval	**A-0000**	1	3	(Re:1) CVM approves Draxxin Injectable in beef and non-lactating dairy cattle for treatment of bovine respiratory disease (BRD) and in swine for the treatment swine respiratory disease (SRD) and issues FOI.
27-MAY-2005	PFE	Label, Approval		1	4	(Re:3, 1) Submission to submit Final Product Labeling.
06-JUN-2005	PFE	Drug Experience Report		1	5	Update Drug Product Listing to add Draxxin Injectable Solution.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE: US Patent No. 6,420,536

ISSUED: July 16, 2002

TO: Bronk, et al.

FOR: 4"-SUBSTITUTED-9-DEOXO-9A-AZA-9A-HOMOERYTHROMYCIN A DERIVATIVES

FROM: US Application No. 09/424,104

OF: May 29, 1998

Commissioner of Patents
Mail Stop Patent Extension
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

CERTIFICATION

I hereby certify that attached hereto is a duplicate copy of the application papers of Pfizer Inc., dated July 21, 2005, for extension of the term of United States Patent No. 6,420,536 under 35 U.S.C. §156.

Date: 21 July 2005

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