Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-132833--00005-0000
Fecha: 2011-10-14 09:57:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 36

FORMULARIO ÚNICO DE OPOSICIÓN

① OPOSICIÓN A :

- [X] Patente de Invención.
- [ ] Patente de Modelo de Utilidad.
- [ ] Diseño Industrial.
- [ ] Esquema de Trazado para Circuitos Integrados.
- [ ] Marcas de Productos o Servicios.
- [ ] Marca Colectiva.
- [ ] Marca de Certificación.
- [ ] Lema Comercial.

② SOLICITUD PUBLICADA

Número del expediente: 10-132.833
Solicitante: PARATEK PHARMACEUTICALS, INC
Apoderado: LUZ CLEMENCIA SUAREZ DE PAEZ
Título de la nueva creación o denominación del signo: "FORMULACIONES ORALES E INYECTABLES DE COMPUESTOS DE TETRACICLINA"
Gaceta: 630

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: PROCAPS S.A. Dirección: CALLE 80 No. 78b-201 Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA Teléfono: 371 99 00 Fax: 373 0815 E-mail:	IDENTIFICACIÓN C.C. [ ] NIT [X] C.E. [ ] Otro [ ] Cual ____ Número 890.106.527-5
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ Dirección: CARRERA 104 Nº119-95 OF 104 Teléfono: 2131213 Fax: 6121979 E-mail: negocios@optimum-co.com	IDENTIFICACIÓN C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual ____ Número 51.975.664 TP 83823

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ **Comprobante de pago No.** 11-600 908 **Fecha** 14/0/21

⑥ **ANEXOS**

- [X] Comprobante de pago de la tasa.
- [X] Poderes, si fuere el caso.
- [X] Pruebas de los fundamentos de la oposición.
- [ ] Documentos que acrediten el legítimo interés, si fuere el caso.
- [X] Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA:

C.C. 51'975.664 **TP.** 83823

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 100908

Bogotá D.C., Octubre 14 de 2011 - 09:13:17

RECIBIDO DE : PROCAPS S.A. NI 890.106.527

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	145108902	07/10/2011	2.128.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES	12 MARCAS Y LEMAS COMERCIALES	304.000.00	304.000.00
				$304.000.00

SON: **TRESCIENTOS CUATRO MIL PESOS MONEDA CORRIENTE***

Responsable: _____
****

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-132833- -00005-0000
Fecha: 2011-10-14 09:57:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 36

Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Señor Director,

DIRECCIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia	: Expediente N° 10 132833
Asunto	: Oposición a la solicitud de patente de Invención titulada *"FORMULACIONES ORALES E INYECTABLES DE COMPUESTOS DE TETRACICLINA"*
Solicitante	: PARATEK PHARMACEUTICALS, INC.
Opositora	: PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 630 del 21 de julio de 2011

Yo, *ELIANA ISAURA MORENO BOHORQUEZ,* abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **PROCAPS S.A.** conformada bajo las leyes de la Republica de Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada *"FORMULACIONES ORALES E INYECTABLES DE COMPUESTOS DE TETRACICLINA"*, cuyo titular PARATEK PHARMACEUTICALS, INC, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

Carrera 13 N° 119-95. Of. 104 Tel. (571) 2 13 12 13 – 6 20 50 21 – Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular **Tetraciclina**. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 26 de octubre de 2010, reivindicando prioridad bajo la solicitud US20080040398 del 2008-03-28; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial **N° 630 del 21 de julio de 2011**, cuya publicación internacional corresponde a la WO 2009120389 del 2009-10-01.

2.2. La solicitud colombiana 10 132833 objeto de la presente oposición, se refiere a formulaciones orales e inyectables de un compuesto de tetraciclina. En donde, en una modalidad está relacionada con una formulación oral de un compuesto de 9-aminometil tetraciclina, o una sal del mismo, en forma de tableta o capsula. Y adicionalmente menciona que las formulaciones pueden ser utilizadas, por ejemplo, para tratar infecciones.

2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren al uso y no sólo a la composición farmacológica o a un método de fabricación mediante la

cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)"*, los usos no están contemplados como patentables; y, Artículo 20.- *"No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso no seria patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: US 2008070873 publicada el 20 de marzo de 2008.

2.5. Ahora bien, el documento D1 se refiere a métodos para aumentar la biodisponibilidad oral de compuestos de tetraciclina y revela de forma particular en los párrafos 0110 y 0046 (formula II), en el párrafo 0047 donde "R14 = H" y en el párrafo 0099 una formulación oral de 9 - [(2,2-dimetil-propil amino)-metil]-minociclina o una sal del mismo. Adicionalmente dicho documento D1 menciona la posibilidad de administrar el compuesto de la invención teniendo en cuenta opciones conocidas, y necesidad del paciente o tratamiento. Así las cosas, como lo

evidencia dicho documento D1, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica.

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 10 132833 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con ninguno de los tres requisitos necesarios para su protección.

2.7. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.7.1. CARECE DE NOVEDAD: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."*. A la fecha de prioridad, 28 de marzo de 2008 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, un una formulación oral de 9 - [(2,2-dimetil-propil amino)-metil]-minociclina o una sal del mismo, sobre el cual busca protección en el capítulo reivindicatorio.

2.7.2. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."*. A la fecha de prioridad, 28 de marzo de 2008, a partir del documento D1, un experto en la materia sabiendo que las tetraciclinas son conocidos antibióticos, puede llegar de manera evidente a una formulación oral de un compuesto de 9-aminometil tetraciclina, o una sal del mismo, en forma de tableta o capsula, donde dichas formulaciones pueden ser

usadas para tratar infecciones; sobre el cual busca protección en el capítulo reivindicatorio.

2.7.3. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman los usos y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos, no cumplen con el requisito de la aplicación industrial.

2.8. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."*. La solicitud pretendida no cumple con ninguno de los tres requisitos de patentabilidad.

2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada *"FORMULACIONES ORALES E INYECTABLES DE COMPUESTOS DE TETRACICLINA"*, cuyo titular PARATEK PHARMACEUTICALS, INC, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 630 del 21 de julio de 2011.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: US 2008070873 publicada el 20 de marzo de 2008.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

4.1. Numeral 1 del artículo 586 del Código de Comercio.

4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **PROCAPS S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- D1: US 2008070873 publicada el 20 de marzo de 2008.

Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 Nº 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

Carrera 13 Nº 119-95, Of. 104 Tel. (571) 2 13 12 13 - 6 20 50 21 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

PROCAPS

PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA,** mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 **del C.S. de la J.**, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **10 132.833,** titulada "**FORMULACIONES ORALES E INYECTABLES DE COMPUESTOS DE TETRACICLINA",** cuyo titular es **PARATEK PHARMACEUTICALS, INC,** publicada en la gaceta No. 630 del 21 de Julio de 2011.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativamente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 29 días del mes de Septiembre de 2011.

PROCAPS S.A.

C.C. N° 16'251.923
NIT: 890.106.527-5
Representante Legal

APROBADO
29 SET. 2011
PROCAPS S.A.

NOTARIA 3era

NOTARIA TERCERA DEL CIRCULO DE BARRANQUILLA

DILIGENCIA DE RECONOCIMIENTO

Ante el Notario Tercero de Barranquilla se presento:

Walter Tarazona Tatiscaw.

identificado con: CC 16251923 Palmira

Y declaro que el contenido del anterior Documento es cierto y suya la firma que lo refrenda.

Barranquilla: 20 SET. 2011

REPÚBLICA DE COLOMBIA

NOTARIA 3era

José Pertuz Carrillo

NOTARIO ENCARGADO

NOTARIA TERCERA DEL CIRCULO DE BARRANQUILLA

03-12026567 024802 PROCAPS S.A.
Barranquilla, 13 de Sep/bre de 2011 Hr:11:28:52

No.16504469

********** Pag. 1

CAMARA DE COMERCIO
DE BARRANQUILLA

06**********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------
NIT: 890.106.527-5.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----------
limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".----------

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----------
se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".----------

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----------
se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".----------

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----------
se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A. "PROCAPS S.A.".----------

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del

********** C O N T I N U A **********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.----------
NIT: 890.106.527-5.

libro respectivo, la sociedad antes mencionada----------
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A
.----------

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada----------
cambio de razon social, por la denominacion PROCAPS S.A. ----------

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18
710	2009/05/05	Notaria 3 a. de Barranquilla	150,130	2009/06/30
1,054	2009/06/25	Notaria 3 a. de Barranquilla	150,130	2009/06/30

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:
DENOMINACION O RAZON SOCIAL:
PROCAPS S.A.----------
SIGLA: PROCAPS.
DOMICILIO PRINCIPAL: Barranquilla.
NIT No: 890.106.527-5.
MATRICULA MERCANTIL: 24,802.

********** C O N T I N U A **********

03-12026567 024802 PROCAPS S.A.
Barranquilla, 13 de Sep/bre de 2011 Hr:11:28:52

No. 16504470

CAMARA DE COMERCIO DE BARRANQUILLA

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
06**********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------
NIT: 890.106.527-5.

C E R T I F I C A

Direccion para notificaciones judiciales:
CL 80 No 78 B - 201.
De la ciudad de Barranquilla.
Correo electrónico: mlozada@procaps.com.co
Pagina Web:
Telefono: 3719272

C E R T I F I C A

DURACION: Que la sociedad no se halla disuelta y su término de duración se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a) La fabicacion, importacion y comercializacion de alimentos procesados y suplementos dietarios. b)La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, para uso y consumo humano y veterinario. c) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas para uso y consumo humano, animal y vegetal. d) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimen ticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. e) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. f) La compra, venta, exportacion, fabricacion, importacion, distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. g) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos. h) Prestar los servicios de asesorias y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion,

********** C O N T I N U A **********

costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, alimenticios, cosmeticos y farmaceuticos para uso humano, animal o industrial. i) Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, alimenticios, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables, comprar, vender y constituir gravamenes sobre bienes muebles e inmuebles, designar representantes apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de sus obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravamenes reales sobre sus bienes de cualquier naturaleza.----------

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
$**********2,000,000,000	**********2,000,000	**********1,000
Suscrito		
$**********1,298,000,000	**********1,298,000	**********1,000
Pagado		
$**********1,298,000,000	**********1,298,000	**********1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponderá a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva.
La sociedad tendra un Presidente , quien ejercera la representa-

********** C O N T I N U A **********

03-12026567 024802 PROCAPS S.A.
Barranquilla, 13 de Sep/bre de 2011 Hr:11:28:52

No. 16504471

CAMARA DE COMERCIO DE BARRANQUILLA

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
06**********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------
NIT: 890.106.527-5.

cion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la socieda todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguentes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravamenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos

********** C O N T I N U A **********

o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junra Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravamenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente. ----------

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:
PROCAPS S.A.----------
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:
PROCAPS S.A.----------
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*******7,463,982
2. Minski Gontovnik Meyer	CC.*******7,461,324
3. Minski Gontovnik Jose	CC.*******8,671,834

Suplentes

1. Minski Zirberblum Elliot	CC.******72,219,541
2. Minski Deitel Daniel	.****************

********** C O N T I N U A **********

03-12026567 024802 PROCAPS S.A.
Barranquilla, 13 de Sep/bre de 2011 Hr:11:28:52

No. 16504472

CAMARA DE COMERCIO DE BARRANQUILLA

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
06**********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------
NIT: 890.106.527-5.

3. Minski Sharon PA.*990,212,082,805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	
Minski Gontovnik Ruben	CC.*******7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*********802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*******7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*******8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.******70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Tanaka Tatekawa Walter	CC.******16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS

********** C O N T I N U A **********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.----------
NIT: 890.106.527-5.

S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Ppal.	
Vargas Pertuz Ana Isabel	CC.******32,696,645

C E R T I F I C A

Que según Acta No. 158 del 17 de Junio de 2011 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 23 de Junio de 2011 bajo el No. 170,929 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Suplente	
Rodriguez Rey Jose Luis	CC.******72,001,912

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo,----------
y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, ----
3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, -----
3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, ------
obrando como Presidente y Representante Legal de la sociedad C.I. NATURMEGA S.A., que obrando en su condicion de Presidente y -------
Representante Legaql de la sociedad PROCAPS S.A., el presidente ----
debidamente facultado por los Estatutos Sociales y por el Maximo Organo Social, otorga los siguientes poderes: Otorgar poder --------
general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN ----
MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO ------
CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con las facultades que se transcriben a continuacion: a.- Para que -----
representen a la sociedad PROCAPS S.A, ante todo tipo de ----------
autoridades administrativas y jurisdiccionales, en asuntos de ------
naturaleza civil, laboral, comercial, penal, aduanera, cambiaria, tributaria, policiva, administrativa y fiscal. b.- Contestar y -----
presentar demandas, requerimientos, recursos, pedir y aportar ------
pruebas, recibir, notificarse, ejercer la accion de tutela, --------
tramitar incidente de desacato, comparecer en los procesos que -----
cursen contra la sociedad, allanarse en nombre de la sociedad en los asuntos que sean necesarios, transigir, desistir, sustituir, renunciar y reasumir el poder. c.- La facultad expresa de ----------
conciliar, por tanto pueden llegar a acuerdos conciliatorios, ------
transaccionales, judiciales o extrajudiciales o extrajudiciales, cualquiera que sea su cuantia, para lo cual las apoderadas deben aportar la autorizacion simple y escrita del Representante legal de la sociedad. d.- Podran presentar solicitudes de devolucion y/o compensacion de impuestos, ventas y rentas, recibir los pagos por las devoluciones y adelantar todo tramite o proceso administrativo

********** C O N T I N U A **********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------
NIT: 890.106.527-5.

ante la DIAN, de tal forma que en ningun momento quede sin --------- representacion legal de la sociedad. PODERES ESPECIALES: a.- Se ---- confiere poder especial amplio y suficiente a las personas que se determinan seguidamente, que conforman el grupo A y B, para, para que conjuntamente suscriban contratos de suministros de mercancias y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), ------- liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. Grupo A. WALTER NANAKA TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO ---------- CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN ------ VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA ---------- DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO ------- CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial ----- amplio y suficiente al senor WILLIAM ALBERTO BARROS CERRA ---------- CC.No.8.715.941, para que en nombre y representacion de PROCAPS ---- S.A., suscriban declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad, en el giro normal de sus negocios y operaciones sociales, por tanto quedan facultados para firmarlas, como tambien los demas documentos relacionados con ellas, ---------- notificarse, aportar y solicitar las pruebas que sean necesarias. c.-Otorgar poder especial amplio y suficiente al senor MARLON ----- TATIS PAREDES CC.No.72.176.874 y al senor WILLIAM ALBERTO BARROS CERRA CC.No.8.715.941, para que en nombre y representacion de ------ PROCANPS S.A., suscriban las declaraciones, reportes y cualquier documento relacionado con los tramites o registros de Comercio ----- Exterior y o cualquier entidad del Estado que haga sus veces: d) Otorgar poder especial amplio y suficiente a la doctora CARMEN ----- ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y ---------- representacion de PROCAPS S.A.; endosen los titulos valores de la sociedad hasta por la suma de UN MIL MILLONES DE PESOS ---------- (1.000.000.000.00) M.L. CUARTO: EI representante legal de la ------- sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta que la presente reforma fue aprobada por la Asamblea General ------- Extraordinaria de Accionista de PROCAPS S.A., con observancia de las disposiciones legales y estatutarias.----------

C E R T I F I C A

Que por Escritura Pública No. 1,933 del 16 de Sep/bre de 2008, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008 bajo el No. 3,748 del libro respectivo,----------

********** C O N T I N U A **********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.----------
NIT: 890.106.527-5.

Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que comparece en su condicion de Presidente y Representante Legal de la Sociedad PROCAPS S.A., confiere por medio de este instrumento ------ publico Poder especial Amplio y Suficiente a la doctora MILENA ----- ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y ---------- representacion de PROCAPS S.A., suscriba declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad en el giro normal de sus negocios y operaciones sociales, por tanto queda ----- facultada para firmar, como tambien los demas documentos ---------- relacionados con ellas, notificarse, aportar y solicitar las ------- pruebas que sean necesarias.----------

C E R T I F I C A

Que por Documento Privado del 09 de Abril de 2010, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 20 de Abril de 2010 bajo el Nro 4,201 del libro respectivo,----------
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, ---- quien obra en el caracter de Presidente y/o Representante legal de la sociedad PROCAPS S.A., que por medio de este instrumento -------- publico, otorga Poder Especial Amplio y Suficiente a la Doctora ---- MONICA DE HART DE OCHOA, identificada con C.C. No. 32.676.025, para que en nombre y representacion de la sociedad, Endose las Facturas Nacionales e Internacionales hasta por la suma de UN MIL MILLONES DE PESOS ($1.000.000.000.00)M.L. La doctora Monica de Hart de Ochoa, queda facultada para realizar todo acto o tramite necesario para el cabal cumplimiento del presente mandato.----------

C E R T I F I C A

Que por Documento Privado del 10 de Junio de 2010, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 13 de Julio de 2010 bajo el Nro 4,228 del libro respectivo,----------
consta que el señor RUBEN MISNKI GONTOVNIK, cc. No. 7.463.982 en su condicion de Presidente y representante legal de PROCAPS S.A., ----- confiere poder especial, amplio y suficiente al señor RICARDO DORADO HURTADO cc. No. 79.715.772 para que represente a la sociedad, ante el INVIMA, Fondo Nnacional de estupefacientes e ICA, con el fin que gestione, tramite o presente las diferentes solicitudes y ---------- peticiones de la empresa, segun la competencia de estas entidades.
Por lo anterior, el Señor RICARDO DORADO HURTADO, queda facultado para presentar, gestionar, tramitar y firmar las diferentes -------- solicitudes y peticiones de la empresa, segun la competencia de ---- estas entidades, como tambien presentar y firmar todo los ---------- documentos relacionados con estas solicitudes, notificarse de ------ cualquier acto administrativo que expidan, aportar y solicitar las pruebas que sean necesarias, desistir, y en general a realizar todo tramite o acto necesario de tal forma que la sociedad en ningun ---- momento quede sin representacion legal ante estas entidades, en ---- cumplimiento fiel al mandato otorgado.----------

C E R T I F I C A

********** C O N T I N U A **********

03-12026567 024802 PROCAPS S.A.
Barranquilla, 13 de Sep/bre de 2011 Hr:11:28:52

No. 16504474

CAMARA DE COMERCIO DE BARRANQUILLA

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
06**********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------
NIT: 890.106.527-5.

Que por Documento Privado del 03 de Agosto de 2010, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 24 de Agosto de 2010 bajo el Nro 4,258 del libro respectivo,---------- consta que RUBEN MINSKI GONTOVNIK, varón, mayor de edad, de ésta vecindad, identificado con la cédula de ciudadanía No.7.463.982, expedida en Barranquilla, en mi condición de Representante legal y/o Presidente de la sociedad PROCAPS S. A., conforme a las -------- facultades otorgadas por los Estatutos Sociales, todo lo cual ------ demuestro con el certificado de existencia y representación legal expedido por la Cámara de Comercio de Barranquilla, que adjunto a este escrito, me permito manifestarles que confiero poder especial, amplio y suficiente al señor MARIO LÓPEZ LEON, varón, mayor de ----- edad, de esta vecindad, identificado con la cédula de ciudadanía No.72.311.558, expedida en Puerto Colombia (Atlántico), para que en nombre y representación de la sociedad, realice los siguientes ----- actos: 1. Endosar las Facturas Nacionales e Internacionales de esas compañías hasta por la suma de UN MIL MILLONES DE PESOS ---------- ($1.000.000.000.00) Moneda Legal. 2. Suscribir Declaraciones ------- Cambiarias, Aduaneras y Tributarias a las que esta obligada la ----- sociedad en el giro ordinario de sus negocios, quedando facultado para notificarse, aportar y solicitar pruebas relacionados con las declaraciones Cambiarias. El señor MARIO LÓPEZ LEÓN, queda --------- facultado para notificarse, aportar y solicitar pruebas, presentar escritos en caso que resulte necesario en general a realizar todo acto, diligencia o tramite que considere indispensable para el ----- cabal cumplimiento del presente mandato.----------

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 31 de Marzo de 2011.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco días hábiles despues de la correspondiente inscripción, siempre

********** C O N T I N U A **********

que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.

ANEXO 1

US 2008/0070873A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2008/0070873 A1**

Alekshun et al. (43) **Pub. Date: Mar. 20, 2008**

(54) **METHODS OF INCREASING ORAL BIOAVAILABILITY OF TETRACYCLINES**

(75) Inventors: **Michael N. Alekshun**, Marlboro, MA (US); **Adel Bakhtyari**, Andover, MA (US); **Sean Johnston**, Doylestown, PA (US); **Masha Pukshansky**, Brookline, MA (US)

Correspondence Address:
LAHIVE & COCKFIELD, LLP
ONE POST OFFICE SQUARE
BOSTON, MA 02109-2127 (US)

(73) Assignee: **Paratek Pharmaceuticals, Inc.**, Boston, MA

(21) Appl. No.: **11/657,412**

(22) Filed: **Jan. 24, 2007**

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(57) **ABSTRACT**

Methods for increasing the oral bioavailability of tetracycline compounds are described.

METHODS OF INCREASING ORAL BIOAVAILABILITY OF TETRACYCLINES

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application Ser. No. 60/761,819, filed on Jan. 24, 2006; the entire contents of which are hereby incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] The development of the tetracycline antibiotics was the direct result of a systematic screening of soil specimens collected from many parts of the world for evidence of microorganisms capable of producing bacteriocidal and/or bacteriostatic compositions. The first of these novel compounds was introduced in 1948 under the name chlortetracycline. Two years later, oxytetracycline became available. The elucidation of the chemical structure of these compounds confirmed their similarity and furnished the analytical basis for the production of a third member of this group in 1952, tetracycline. A new family of tetracycline compounds, without the ring-attached methyl group present in earlier tetracyclines, was prepared in 1957 and became publicly available in 1967; and minocycline was in use by 1972.

[0003] Recently, research efforts have focused on developing new tetracycline antibiotic compositions effective under varying therapeutic conditions and routes of administration. New tetracycline analogues have also been investigated which may prove to be equal to or more effective than the originally introduced tetracycline compounds. Examples include U.S. Pat. Nos. 2,980,584; 2,990,331; 3,062,717; 3,165,531; 3,454,697; 3,557,280; 3,674,859; 3,957,980; 4,018,889; 4,024,272; and 4,126,680. These patents are representative of the range of pharmaceutically active tetracycline and tetracycline analogue compositions.

[0004] Historically, soon after their initial development and introduction, the tetracyclines were found to be highly effective pharmacologically against rickettsiae; a number of gram-positive and gram-negative bacteria; and the agents responsible for lymphogranuloma venereum, inclusion conjunctivitis, and psittacosis. Hence, tetracyclines became known as "broad spectrum" antibiotics. With the subsequent establishment of their in vitro antimicrobial activity, effectiveness in experimental infections, and pharmacological properties, the tetracyclines as a class rapidly became widely used for therapeutic purposes. However, this widespread use of tetracyclines for both major and minor illnesses and diseases led directly to the emergence of resistance to these antibiotics even among highly susceptible bacterial species both commensal and pathogenic (e.g., pneumococci and Salmonella). The rise of tetracycline-resistant organisms has resulted in a general decline in use of tetracyclines and tetracycline analogue compositions as antibiotics of choice. Methods and compositions for the oral bioavailability of tetracycline compounds would be of great benefit.

SUMMARY OF THE INVENTION

[0005] In one embodiment, the invention pertains to methods of increasing the oral bioavailability of a tetracycline compound in a subject. The method includes administering to a subject a tetracycline compound in combination with a bioavailability enhancing agent such that the tetracycline compound is released in the intestinal tract.

[0006] In another embodiment, the invention pertains to a pharmaceutical composition comprising a therapeutically effective amount of a tetracycline compound in combination with a bioavailability enhancing agent and a pharmaceutically acceptable carrier for administration of said tetracycline compound to the intestinal tract.

[0007] In a further embodiment, the invention pertains to a kit comprising a tetracycline compound and instructions for administering a therapeutically effective amount of the tetracycline compound in combination with a bioavailability enhancing agent to the intestinal tract of a subject.

DETAILED DESCRIPTION OF THE INVENTION

[0008] In one embodiment, the invention pertains to methods of increasing the oral bioavailability of a tetracycline compound in a subject. The method includes administering to a subject a tetracycline compound in combination with a bioavailability enhancing agent such that the tetracycline compound is released in the intestinal tract.

[0009] The phrase "released in the intestinal tract" refers to the dispersion of the tetracycline in the intestinal tract. The intestinal tract as used herein, includes, for example, the small intestine, the large intestine, the duodenum, the jejunum, the ileum, the colon, and the cecum. Furthermore, the term "the intestinal tract" does not include the mouth, the pharanx, the esophagus, the cardia and the stomach. In one embodiment, the tetracycline compound is released into the small intestine. In another embodiment, the tetracycline compound is released into the duodenum. Methods for releasing the tetracycline compound into the intestinal tract include, for example, the administration of the tetracycline compound in a formulation with an enteric coating, administration by directly injecting the tetracycline compound into the intestinal tract, administration of the tetracycline via a gastric feeding tube and administration of the tetracycline compound by a duodenal feeding tube.

[0010] The term "bioavailability" includes, generally, the degree to which a drug or other substance becomes available to a target tissue after administration. In a further embodiment, the bioavailability of the of the tetracycline compounds may be the bioavailability to a particular target tissue. For example, in an embodiment, the particular target tissue may require traversal of the stomach or the small intestines, therefore the bioavailability data may be obtained from this particular target tissue.

[0011] The term "target tissue" includes any tissue or body fluid of a subject, preferably human. For example, the target tissue may be the brain, blood, nerves, spinal cord, heart, liver, kidneys, stomach, small intestine, duodenum, muscles, lung, pancreas, intestine, bladder, reproductive organs, bones, tendons, or other internal organs or tissues.

[0012] Bioavailibility can be determined according to the following equation:

$$\% F = (AUC)_{po} / (AUC)_{iv} \times (\text{Dose})_{iv} / (\text{Dose})_{po}$$

[0013] In this equation, % F is the fraction of the compound absorbed. AUC is the experimentally determined "area under the curve" and is related to other pharmacodynamic parameters such as clearance (CL), volume of distribution (V_d), and elimination half-life ($t_{1/2}$) (See Hirono, S. et al. Biol Pharm Bull 1994, 17, 306-309).

[0014] The bioavailability of the tetracycline compound may be enhanced by the addition of a bioavailability enhanc-

ing agent. The term "bioavailability enhancing agent" includes agents that, when administered in combination with the tetracycline compound, increase the availability of the tetracycline compound to the target tissue. Suitable bioavailability enhancing agents include, for example, charge masking compounds, solubilizing compounds, reducing compounds, stabilizing compounds, lubricating compounds, enteric coatings, permeability enhancing compounds, or combinations thereof. In one embodiment, the bioavailability enhancing agent is, for example, polysorbate 80 (TWEEN-80), ethylenediaminetetraacetic acid (EDTA), sodium bisulfite, octanol, oil, ethanol, calcium chloride, or silicon dioxide. In a further embodiment, the bioavailability enhancing agent is a lubricating agent in combination with another bioavailability enhancing agent. Examples of combinations include sodium bisulfite with a lubricating compound such as AEROSIL 200.

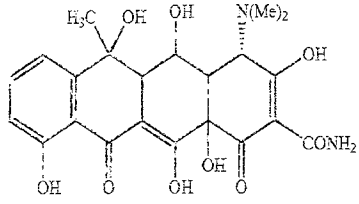
[0015] In one embodiment, the bioavailability of the tetracycline compound when administered in combination with the bioavailability enhancing agent is increased by about 5% or greater, by about 10% or greater, by about 25% or greater, by about 40% or greater or by about 50% or greater as compared to the bioavailability of the compound when not specifically administered to the intestinal tract, i.e., orally administered via mouth without an enteric coating.

[0016] The language "in combination with" a bioavailability enhancing agent includes co-administration of the tetracycline compound and the bioavailability enhancing agent, administration of the tetracycline compound first, followed by the bioavailability enhancing agent and administration of the bioavailability enhancing agent, followed by the tetracycline compound. The bioavailability enhancing agent and the tetracycline compound may be administered at any interval which allows the compounds to perform their intended function, e.g., increase to oral bioavailability of the tetracycline compound. The bioavailability enhancing agent and the tetracycline compound may be administered concurrently in separate or in the same pharmaceutical composition. In other embodiment, the tetracycline compound and the bioavailability enhancing agent may be administered within about 30 minutes, within about one hour, within about two hours, or within another period of time which allows the compounds to perform their intended function.

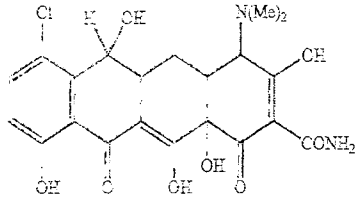
[0017] The term "subject" includes animals (e.g., mammals, e.g., cats, dogs, horses, pigs, cows, sheep, rodents, rabbits, squirrels, bears, primates (e.g., chimpanzees, gorillas, and humans)). It also includes transgenic animal models.

[0018] The term "tetracycline compound" includes substituted or unsubstituted tetracycline compounds or compounds with a similar ring structure to tetracycline. Examples of tetracycline compounds include, chlortetracycline, oxytetracycline, demeclocycline, ethacycline, sancycline, chelocardin, rolitetracycline, lymecycline, apicycline; clomocycline, guamecycline, meglucycline, mepylcycline, penimepicycline, pipacycline, etamocycline, penimocycline, etc. Other derivatives and analogues comprising a similar four ring structure are also included (See Rogalski, "Chemical Modifications of Tetracyclines," the entire contents of which are hereby incorporated herein by reference). Table 1 depicts tetracycline and several known other tetracycline derivatives.

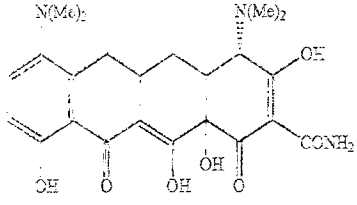
TABLE 1



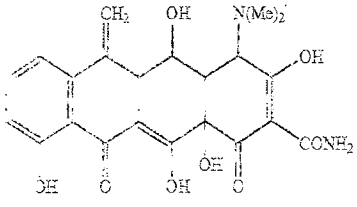
Oxytetracycline



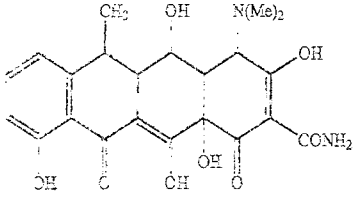
Demeclocycline



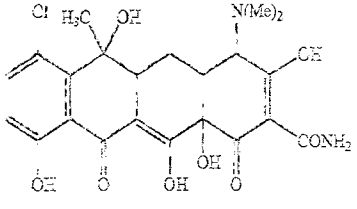
Minocycline



Methacycline

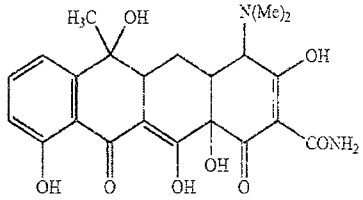


Doxycycline

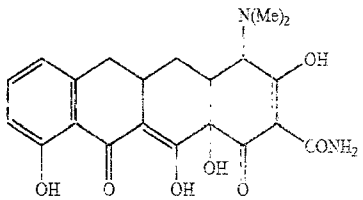


Chlortetracycline

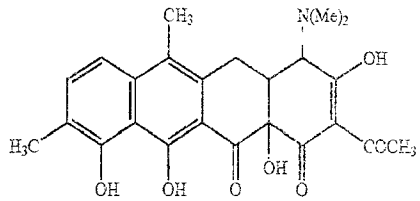
TABLE 1-continued



Tetracycline



Sancycline

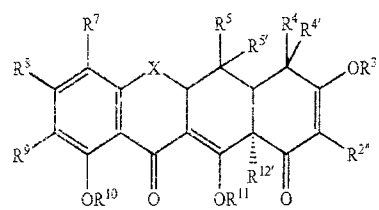


Chelocardin

[0019] Other tetracycline compounds which may be modified using the methods of the invention include, but are not limited to, 6-demethyl-6-deoxy-4-dedimethylaminotetracycline; tetracyclino-pyrazole; 7-chloro-4-dedimethylaminotetracycline; 4-hydroxy-4-dedimethylaminotetracycline; 12α-deoxy-4-dedimethylaminotetracycline; 5-hydroxy-6α-deoxy-4-dedimethylaminotetracycline; 4-dedimethylamino-12α-deoxyanhydrotetracycline; 7-dimethylamino-6-demethyl-6-deoxy-4-dedimethylaminotetracycline; tetracyclinonitrile; 4-oxo-4-dedimethylaminotetracycline 4,6-hemiketal; 4-oxo-11a C1-4-dedimethylaminotetracycline-4,6-hemiketal; 5a,6-anhydro-4-hydrazon-4-dedimethylamino tetracycline; 4-hydroxyimino-4-dedimethylamino tetracyclines; 4-hydroxyimino-4-dedimethylamino 5a,6-anhydrotetracyclines, 4-amino-4-dedimethylamino-5a,6 anhydrotetracycline; 4-methylamino-4-dedimethylamino tetracycline; 4-hydrazono-11a-chloro-6-deoxy-6-demethyl-6-methylene-4-dedimethylamino tetracycline; tetracycline quaternary ammonium compounds; anhydrotetracycline betaines; 4-hydroxy-6-methyl pretetramides; 4-keto tetracyclines; 5-keto tetracyclines; 5a,11a dehydro tetracyclines; 11a C1-6, 12 hemiketal tetracyclines; 11a C1-6-methylene tetracyclines; 6,13 diol tetracyclines; 6-benzylthiomethylene tetracyclines; 7,11a-dichloro-6-fluoro-methyl-6-deoxy tetracyclines; 6-fluoro (α)-6-demethyl-6-deoxy tetracyclines; 6-fluoro (β)-6-demethyl-6-deoxy tetracyclines;6-αacetoxy-6-demethyl tetracyclines; 6-β acetoxy-6-demethyl tetracyclines; 7,13-epithiotetracyclines; oxytetracyclines; pyrazolotetracyclines; 11a halogens of tetracyclines; 12a formyl and other esters of tetracyclines; 5,12a esters of tetracyclines; 10,12a-diesters of tetracyclines; isotetracycline; 12-a-deoxyanhydro tetracyclines; 6-demethyl-12a-deoxy-7-chloroanhydrotetracyclines; B-nortetracyclines; 7-methoxy-6-demethyl-6-deoxytetracyclines; 6-demethyl-6-deoxy-5a-epitetracyclines; 8-hydroxy-6-demethyl-6-deoxy tetracyclines; monardene; chromocycline; 5a methyl-6-demethyl-6-deoxy tetracyclines; 6-oxa tetracyclines, and 6 thia tetracyclines.

[0020] The term "substituted tetracycline compound" includes tetracycline compounds with one or more additional substituents, e.g., at the 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 11a, 12, 12a or 13 position or at any other position which allows the substituted tetracycline compound of the invention to perform its intended function.

[0021] In a one embodiment, the tetracycline compound of the invention is of formula I:



(I)

wherein

[0022] R^1 is hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, amido, alkylamino, amino, arylamino, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, alkoxy, alkoxycarbonyl, alkylcarbonyloxy, alkyloxycarbonyloxy, arylcarbonyloxy, aryloxy, thiol, alkylthio, arylthio, alkenyl, heterocyclic, hydroxy, or halogen, optionally linked to R^2 to form a ring;

[0023] $R^{2''}$ is cyano or C(=O)—NR^2R^2;

[0024] R^2 is hydrogen, alkyl, halogen, alkenyl, alkynyl, aryl, hydroxyl, thiol, cyano, nitro, acyl, formyl, alkoxy, amino, alkylamino, heterocyclic, or absent, optionally linked to R^1 to form a ring;

[0025] $R^{2'}$, R^{4a}, and R^{4b} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

[0026] R^{10}, R^{11}, and R^{12} are each independently hydrogen, alkyl, aryl, benzyl, arylalkyl, or a pro-drug moiety;

[0027] $R^{12''}$ is O—R^{12}, hydrogen, or substituted amino;

[0028] R^4 and $R^{4'}$ are each independently $NR^{4a}R^{4b}$, alkyl, acyl, alkenyl, alkynyl, hydroxyl, halogen, hydrogen, or taken together =N—OR^{4a};

[0029] R^5 and $R^{5'}$ are each independently hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

[0030] R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

[0031] R^7 is hydrogen, dialkylamino, hydroxyl, halogen, thiol, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, arylalkenyl, arylalkynyl, acyl, aminoalkyl, heterocy-

clic, boronic ester, alkylcarbonyl, thionitroso, or $-(CH_2)_{0-3}(NR^{7c})_{0-1}C(=W')WR^{7g}$;

[0032] R^8 is hydrogen, hydroxyl, halogen, thiol, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, amino, arylalkenyl, arylalkynyl, acyl, aminoalkyl, heterocyclic, thionitroso, or $-(CH_2)_{0-3}(NR^{8c})_{0-1}C(=E')ER^{8g}$;

[0033] R^9 is hydrogen, hydroxyl, halogen, thiol, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, arylalkenyl, arylalkynyl, acyl, aminoalkyl, heterocyclic, thionitroso, or $-(CH_2)_{0-3}(NR^{9c})_{0-1}C(=Z')ZR^{9g}$;

[0034] R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, R^{8a}, R^{8b}, R^{8c}, R^{8d}, R^{8e}, R^{8f}, R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e}, and R^{9f} are each independently hydrogen, acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

[0035] R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, aryl, alkylsulfinyl alkylsulfonyl, alkylamino, or an arylalkyl;

[0036] E is $CR^{8d}R^{8e}$, S, NR^{8b} or O;

[0037] E' is O, NR^{8f} or S;

[0038] Q is a double bond when R^3 is absent, Q is a single bond when R^3 is hydrogen, alkyl, halogen, hydroxyl, thiol, alkenyl, alkynyl, aryl, acyl, formyl, alkoxy, amino, alkylamino, cyano, nitro, or heterocyclic;

[0039] W is $CR^{7d}R^{7e}$, S, NR^{7b} or O;

[0040] W' is O, NR^{7f}, or S;

[0041] X is CHC(R^{13}Y'Y), C=CR^{13}Y, CR^5R^6, S, NR^6, or O;

[0042] Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

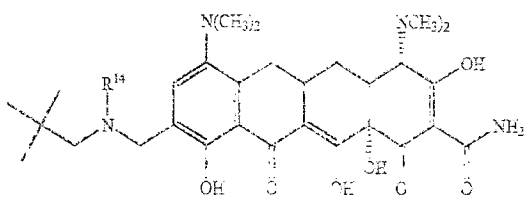
[0043] Z is $CR^{9a}R^{9e}$, S, NR^{9b} or O;

[0044] Z' is O, S, or NR^{9f}; and pharmaceutically acceptable salts, esters and enantiomers thereof.

[0045] In another embodiment, R^2 is $C(=O)NH_2$; R^3, R^{10}, R^{11}, and R^{12} are each hydrogen or a prodrug moiety; R^4 is $NR^{4a}R^{4b}$; R^{4a} and R^{4c} are each methyl; R^{4b} is hydrogen; R^8 is hydrogen; X is CR^6R^6; R^5 is hydrogen; and R^7 and $R^{7'}$ are hydrogen.

[0046] In a further embodiment, the tetracycline compound of the invention is of formula II.

(II)



wherein

[0047] R^{14} is hydrogen or prodrug moiety, and pharmaceutically acceptable salts thereof.

[0048] In one embodiment, R^{14} is hydrogen.

[0049] In a further embodiment, R^{14} is of the formula

$-(C=O)-E^1-G^1$

wherein

[0050] E^1 is oxygen, nitrogen, or a covalent bond;

[0051] G^1 is alkyl; heterocyclicalkyl; aryl; alkylcarbonyloxyalkyl; arylcarbonyloxyalkyl; alkyloxycarbonyloxyalkyl; arylalkylcarbonyloxyalkyl; alkyloxyalkylcarbonyloxyalkyl; or alkoxyalkoxycarbonyloxyalkyl.

[0052] In one embodiment, E^1 is a covalent bond and G^1 is alkyl.

[0053] In another embodiment, E^1 is nitrogen and G^1 is aryl, such as substituted or unsubstituted phenyl.

[0054] In one embodiment, E^1 is oxygen and G^1 is alkylcarbonyloxyalkyl. In yet another embodiment, G^1 is of the formula $-(CH_2)_m-O-(C=O)-R^{15}$, wherein m is 1-5 and R^{15} is alkyl. In a further embodiment, m is 1 or 2. In yet another embodiment, R^{15} is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, $-(CH_2)_{10}-CH_3$, or $-(CH_2)_{11}CH_3$. In a further embodiment, R^{15} is cycloalkyl.

[0055] In one embodiment, E^1 is oxygen and G^1 is $-(CH_2)_2-O-C(=O)-CH_3$. In another embodiment, E^1 is oxygen and G^1 is $-CH_2-O-(C=O)-C(CH_3)_3$.

[0056] In one embodiment, E^1 is oxygen and G^1 is alkyl. Suitable alkyl groups include, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, $-(CH_2)_{10}-CH_3$, or $-(CH_2)_{11}CH_3$.

[0057] In one embodiment, E^1 is oxygen and G^1 is arylcarbonyloxyalkyl. In one particular embodiment, G^1 is of the formula: $-(CH_2)_f-O-(C=O)-R^{17}$, wherein f is 1-5 and R^{17} is aryl. In a further embodiment, f is 1 and R^{17} is substituted or unsubstituted phenyl. Suitable substituted phenyl groups include, for example, phenyl substituted with one or more substituents selected from the group consisting of halogen, alkoxy, or alkyl.

[0058] In yet another embodiment, E^1 is oxygen and G^1 is alkyloxycarbonyloxyalkyl. In one particular embodiment, G^1 is of the formula $-(CH_2)-O-(C=O)-O-R^{18}$, wherein R^{18} is alkyl. Suitable alkyl groups, include, for example, methyl, ethyl, propyl, butyl or pentyl.

[0059] In a further embodiment, E^1 is oxygen and G^1 is arylalkylcarbonyloxyalkyl. In one particular embodiment, G^1 is of the formula $-(CH_2)-O-(C=O)-(CH_2)_h-R^{19}$, wherein h is 1-5, and R^{19} is aryl. In another embodiment, h is 1 or 2 and R^{19} is phenyl.

[0060] In a further embodiment, E^1 is oxygen and G^1 is alkyloxyalkylcarbonyloxyalkyl. In one particular embodiment, G_1 is of the formula $-(CH_2)-O-(C=O)-(CH_2)_i-O-R^{20}$, wherein i is 1-5, and R^{20} is alkyl. In a further embodiment, i is 1, 2, or 3. In yet another embodiment, R^{20} is methyl.

[0061] In one embodiment, E^1 is oxygen and G^1 is alkoxyalkoxyalkylcarbonyloxyalkyl. In one particular embodiment, G_1 is of the formula $-(CH_2)-O-(C=O)-(CH_2)_j-O-(CH_2)_k-O-R^{21}$, wherein j and k are each 1-5 and R^{21} is alkyl. In one embodiment, j is 1 and k is 2. In a further embodiment, R^{21} is methyl.

enyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Cycloalkyls can be further substituted, e.g., with the substituents described above. An "alkylaryl" or an "arylalkyl" moiety is an alkyl substituted with an aryl (e.g., phenylmethyl(benzyl)). The term "alkyl" also includes the side chains of natural and unnatural amino acids

[0067] The term "aryl" includes groups, including 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, phenyl, pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isooxazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like. Furthermore, the term "aryl" includes multicyclic aryl groups, e.g., tricyclic, bicyclic, e.g., naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl, quinoline, isoquinoline, napthridine, indole, benzofuran, purine, benzofuran, deazapurine, or indolizine. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles", "heterocycles," "heteroaryls" or "heteroaromatics". The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminocarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (e.g., tetralin).

[0068] The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond.

[0069] For example, the term "alkenyl" includes straight-chain alkenyl groups (e.g., ethylenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, etc.), branched-chain alkenyl groups, cycloalkenyl(alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. The term alkenyl further includes alkenyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer carbon atoms in its backbone (e.g., C_2-C_6 for straight chain, C_3-C_6 for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_2-C_6 includes alkenyl groups containing 2 to 6 carbon atoms.

[0070] Moreover, the term alkenyl includes both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0071] The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond.

[0072] For example, the term "alkynyl" includes straight-chain alkynyl groups (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, etc.), branched-chain alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. The term alkynyl further includes alkynyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (e.g., C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term C_2-C_6 includes alkynyl groups containing 2 to 6 carbon atoms.

[0073] Moreover, the term alkynyl includes both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0074] Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as

defined above, but having from one to five carbon atoms in its backbone structure. "Lower alkenyl" and "lower alkynyl" have chain lengths of, for example, 2-5 carbon atoms

[0075] The term "acyl" includes compounds and moieties which contain the acyl radical (CH_3CO—) or a carbonyl group. It includes substituted acyl moieties. The term "substituted acyl" includes acyl groups where one or more of the hydrogen atoms are replaced by for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0076] The term "acylamino" includes moieties wherein an acyl moiety is bonded to an amino group. For example, the term includes alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

[0077] The term "aroyl" includes compounds and moieties with an aryl or heteroaromatic moiety bound to a carbonyl group. Examples of aroyl groups include phenylcarboxy, naphthyl carboxy, etc.

[0078] The terms "alkoxyalkyl", "alkylaminoalkyl" and "thioalkoxyalkyl" include alkyl groups, as described above, which further include oxygen, nitrogen or sulfur atoms replacing one or more carbons of the hydrocarbon backbone, e.g., oxygen, nitrogen or sulfur atoms.

[0079] The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropyloxy, propoxy, butoxy, and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, etc.

[0080] The term "amine" or "amino" includes compounds where a nitrogen atom is covalently bonded to at least one carbon or heteroatom. The term includes "alkyl amino" which comprises groups and compounds wherein the nitrogen is bound to at least one additional alkyl group. The term "dialkyl amino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups. The term "arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. The term "alkylarylamino," "alkylaminoaryl" or "arylaminoalkyl" refers to an amino group which is bound to at least one alkyl group and at least one aryl group. The term "alkaminoalkyl" refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom which is also bound to an alkyl group.

[0081] The term "amide," "amido" or "aminocarbonyl" includes compounds or moieties which contain a nitrogen atom which is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes "alkaminocarbonyl" or "alkylaminocarbonyl" groups which include alkyl, alkenyl, aryl or alkynyl groups bound to an amino group bound to a carbonyl group. It includes arylaminocarbonyl and arylcarbonylamino groups which include aryl or heteroaryl moieties bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. The terms "alkylaminocarbonyl," "alkenylaminocarbonyl," "alkynylaminocarbonyl," "arylaminocarbonyl," "alkylcarbonylamino," "alkenylcarbonylamino," "alkynylcarbonylamino," and "arylcarbonylamino" are included in term "amide." Amides also include urea groups (aminocarbonylamino) and carbamates (oxycarbonylamino).

[0082] The term "carbonyl" or "carboxy" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom. The carbonyl can be further substituted with any moiety which allows the compounds of the invention to perform its intended function. For example, carbonyl moieties may be substituted with alkyls, alkenyls, alkynyls, aryls, alkoxy, aminos, etc. Examples of moieties which contain a carbonyl include aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc.

[0083] The term "thiocarbonyl" or "thiocarboxy" includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom.

[0084] The term "ether" includes compounds or moieties which contain an oxygen bonded to two different carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl" which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom which is covalently bonded to another alkyl group.

[0085] The term "ester" includes compounds and moieties which contain a carbon or a heteroatom bound to an oxygen atom which is bonded to the carbon of a carbonyl group. The term "ester" includes alkoxycarboxy groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, etc. The alkyl, alkenyl, or alkynyl groups are as defined above.

[0086] The term "thioether" includes compounds and moieties which contain a sulfur atom bonded to two different carbon or hetero atoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term "alkthioalkyls" include compounds with an alkyl, alkenyl, or alkynyl group bonded to a sulfur atom which is bonded to an alkyl group. Similarly, the term "alkthioalkenyls" and alkthioalkynyls" refer to compounds or moieties wherein an alkyl, alkenyl, or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group.

[0087] The term "hydroxy" or "hydroxyl" includes groups with an —OH or —O⁻.

[0088] The term "halogen" includes fluorine, bromine, chlorine, iodine, etc. The term "perhalogenated" generally refers to a moiety wherein all hydrogens are replaced by halogen atoms.

[0089] The terms "polycycyl!" or "polycyclic radical" refer to two or more cyclic rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, alkylaminoacarbonyl, arylalkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkyl carbonyl, alkenylcarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amido, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkyl alkylaryl, or an aromatic or heteroaromatic moiety.

[0090] The term "heteroatom" includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

[0091] The term "prodrug moiety" includes moieties which can be metabolized in vivo to a hydroxyl group and moieties which may advantageously remain esterified in vivo. Preferably, the prodrugs moieties are metabolized in vivo by esterases or by other mechanisms to hydroxyl groups or other advantageous groups. Examples of prodrugs and their uses are well known in the art (See, e.g., Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19). The prodrugs can be prepared in situ during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form or hydroxyl with a suitable esterifying agent. Hydroxyl groups can be converted into esters via treatment with a carboxylic acid. Examples of prodrug moieties include substituted and unsubstituted, branch or unbranched lower alkyl ester moieties, (e.g., propionoic acid esters), lower alkenyl esters, di-lower alkyl-amino lower-alkyl esters (e.g., dimethylaminoethyl ester), acylamino lower alkyl esters (e.g., acetyloxymethyl ester), acyloxy lower alkyl esters (e.g., pivaloyloxymethyl ester), aryl esters (phenyl ester), aryl-lower alkyl esters (e.g., benzyl ester), substituted (e.g., with methyl, halo, or methoxy substituents) aryl and aryl-lower alkyl esters, amides, lower-alkyl amides, di-lower alkyl amides, and hydroxy amides. Preferred prodrug moieties are propionoic acid esters and acyl esters.

[0092] It will be noted that the structure of some of the tetracycline compounds of this invention includes asymmetric carbon atoms. It is to be understood accordingly that the isomers arising from such asymmetry (e.g., all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis. Furthermore, the structures and other compounds and moieties discussed in this application also include all tautomers thereof.

[0093] In a further embodiment, the invention pertains to a kit comprising a tetracycline compound and instructions for administering a therapeutically effective amount of the tetracycline compound in combination with a bioavailability enhancing agent to the intestinal tract of a subject.

[0094] In another embodiment, the invention pertains to pharmaceutical composition comprising a therapeutically effective amount of a tetracycline compound in combination with a bioavailability enhancing agent and a pharmaceutically acceptable carrier for administration of said tetracycline compound to the intestinal tract. The bioavailability enhancing agent and the tetracycline compound may be administered concurrently in separate or in the same pharmaceutical composition.

[0095] The language "effective amount" of the tetracycline compound is that amount necessary or sufficient to treat a subject. The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular tetracycline compound. For example, the choice of the tetracycline compound can affect what constitutes an "effective amount". One of ordinary skill in the art would be able to study the aforementioned factors and make the determination regarding the effective amount of the tetracycline compound without undue experimentation.

[0096] The language "pharmaceutically acceptable carrier" includes substances capable of being coadministered with the tetracycline compound(s), and which allow both to perform their intended function. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously react with the active compounds of the invention.

[0097] The tetracycline compounds of the 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 the tetracycline compounds of the invention that are basic in nature are those that form non-toxic acid addition salts, i.e., salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid 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 palmoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. Although such salts must be pharmaceutically

acceptable for administration to a subject, e.g., a mammal, it is often desirable in practice to initially isolate a tetracycline compound of the 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 preparation of other tetracycline compounds of the invention not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

[0098] The tetracycline compounds of the invention that are acidic in nature are capable of forming a wide variety of base salts. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those tetracycline compounds of the invention that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmaceutically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines. The pharmaceutically acceptable base addition salts of tetracycline compounds of the invention that are acidic in nature may be formed with pharmaceutically acceptable cations by conventional methods. Thus, these salts may be readily prepared by treating the tetracycline compound of the invention with an aqueous solution of the desired pharmaceutically acceptable cation and evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, a lower alkyl alcohol solution of the tetracycline compound of the invention may be mixed with an alkoxide of the desired metal and the solution subsequently evaporated to dryness.

[0099] The tetracycline compounds of the invention and pharmaceutically acceptable salts thereof can be administered orally. In general, these compounds are most desirably administered in effective dosages, depending upon the weight and condition of the subject being treated and the particular route of administration chosen. Variations may occur depending upon the species of the subject 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.

[0100] The tetracycline compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the routes previously mentioned, and the administration may be carried out in single or multiple doses. For example, the novel therapeutic agents of this invention can be administered advantageously 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, aqueous suspensions, injectable solutions 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 therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

[0101] 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. The compositions of the invention may be formulated such that the tetracycline compositions are released over a period of time after administration.

[0102] For enteral application, particularly suitable are tablets, dragees or capsules having talc and/or carbohydrate carrier binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch. Sustained release compositions can be formulated including those wherein the active component is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc.

[0103] Enteric coatings (which generally do not substantially dissolve in solutions with a pH lower than about 5.5) may delay release of the tetracycline compound until delivery to the intestinal tract. Examples of enteric coatings include, but are not limited to, coatings made from methacrylic acid copolymers, cellulose acetate (and its succinate and phthalate versions), styrol maleic acid copolymers, polymethacrylic acid/acrylic acid copolymer, hydroxypropyl methyl cellulose phthalate, polyvinyl acetate phthalate, hydroxyethyl ethyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, cellulose acetate tetrahydrophtalate, acrylic resin, timellitate, and shellac, and combinations thereof.

[0104] In addition to treatment of human subjects, the therapeutic methods of the invention also will have significant veterinary applications, e.g. for treatment of livestock such as cattle, sheep, goats, cows, swine and the like; poultry such as chickens, ducks, geese, turkeys and the like; horses; and pets such as dogs and cats.

[0105] It will be appreciated that the actual preferred amounts of active compounds used in a given therapy will vary according to the specific compound being used, the particular compositions formulated, the mode of application, the particular site of administration, etc. Optimal administration rates for a given protocol of administration can be readily ascertained by those skilled in the art using conventional dosage determination tests conducted with regard to the foregoing guidelines.

[0106] In general, compounds of the invention for treatment can be administered to a subject in dosages used in

prior tetracycline therapies. See, for example, the *Physicians' Desk Reference*. For example, a suitable effective dose of one or more compounds of the invention will be in the range of from 0.01 to 100 milligrams per kilogram of body weight of recipient per day, preferably in the range of from 0.1 to 50 milligrams per kilogram body weight of recipient per day, more preferably in the range of 1 to 20 milligrams per kilogram body weight of recipient per day. The desired dose is suitably administered once daily, or several sub-doses, e.g. 2 to 5 sub-doses, are administered at appropriate intervals through the day, or other appropriate schedule.

[0107] It will also be understood that normal, conventionally known precautions will be taken regarding the administration of tetracyclines generally to ensure their efficacy under normal use circumstances. Especially when employed for therapeutic treatment of humans and animals in vivo, the practitioner should take all sensible precautions to avoid conventionally known contradictions and toxic effects. Thus, the conventionally recognized adverse reactions of gastrointestinal distress and inflammations, the renal toxicity, hypersensitivity reactions, changes in blood, and impairment of absorption through aluminum, calcium, and magnesium ions should be duly considered in the conventional manner.

EXEMPLIFICATION OF THE INVENTION

Example 1

Bioavailability of 9-[(2,2, Dimethyl-propyl amino)-methyl]-Minocycline Following Intravenous Administration in Rats

[0108] The bioavailability of 9-[(2,2, dimethyl-propyl amino)-methyl]-minocycline following intravenous administration in rats was studied. The freebase ("FB") and the HCl salt ("HCl salt") of 9-[(2,2, dimethyl-propyl amino)-methyl]-minocycline were used. All formulations were prepared fresh on the day of the experiment. Samples for pharmacokinetic analysis were collected from a cannula within the carotid artery of the rats. Intravenous doses of (1 mg/kg) were administered to rats through cannulas in either the jugular or portal veins. The results of this studied are summarized in Table 2.

TABLE 2

PK parameters following intravenous administration of 9-[(2,2, dimethyl-propyl amino)-methyl[-minocycline in rats.

Formulation	Route of admin.	Fed state	AUC (ug*hr/mL)
FB	Jugular vein	Fasted	0.57 (0.50; 0.63)
HCl salt	Jugular vein	Fed	0.46 ± 0.04
HCl salt	Jugular vein	Fasted	0.59 (0.45; 0.73)
HCl salt	Portal vein	Fasted	0.59 (0.52; 0.66)

[0109] It was found that there were no siginificant differences in pharmacokinetic parameters after IV administration of the freebase (FB) or the HCl salt in fasted animals. However, tendency for higher clearance (~22%) was observed in a fed group. The total exposure (e.g., the area under the curve (AUC)) and clearance after administration of the HCL salt into the portal vein was equal to its exposure and clearance after administration into the jugular vein in fasted animals. It was determined that there were no significant effects of first pass hepatic elimination on pharmacokinetics of PTK after IV dosing.

Example 2

Bioavailability of 9-[(2,2, Dimethyl-propyl amino)-methyl]-Minocycline Following Oral Administration in Rats

[0110] Solutions of 9-[(2,2, dimethyl-propyl amino)-methyl]-minocycline freebase (5 mg/kg [2 ml/kg]) were administered by oral gavage. The solutions were composed of 9-[(2,2, dimethyl-propyl amino)-methyl]-minocycline alone or in combination with bioavailability enhancing agents to assess their effect on oral bioavailability.

TABLE 3

Pharmacokinetic parameters of 9-[(2,2, dimethyl-propyl amino)-methyl[-minocycline following dosing via oral gavage.

Formulation	AUC (hr*ug/mL)	% F [a]
FB, Polysorbate 80 (TWEEN-80) 10%	0.47	16.6 (17.8; 15.3)
FB, Octanol	0.26	9.3 (3.1; 15.4)
FB, Octanol:oil (1:9)	0.15 ± 0.10	5.3 ± 3.5
FB, Ethanol:oil (1:9)	0.20 ± 0.17	7.1 ± 6.2
FB	0.33 ± 0.12	11.7 ± 4.1
FB, PTK-FB, NaBisulfite	0.33 ± 0.12	11.7 ± 4.3
FB, $CaCl_2$	0.24 ± 0.06	8.5 ± 2.0

[0111] The oral bioavailability (% F) for the various solutions is shown in Table 3. The % F was calculated using the IV data presented in Example 1 and the equation: % F=Oral AUC/IV AUC.

Example 3

Site of Absorption Effects of 9-[(2,2, Dimethyl-propyl amino)-methyl]-Minocycline in Rats

[0112] In order to measure the effect of delivering 9-[(2,2, dimethyl-propyl amino)-methyl]-minocycline directly into the duodenum, rats bearing duodenal cannulas were administered 9-[(2,2, dimethyl-propyl amino)-methyl]-minocycline freebase alone or in combination with bioavailability enhancing agents to assess their effects on bioavailability.

TABLE 4

PK parameters of 9-[(2,2, dimethyl-propyl amino)-methyl]-minocycline following intra-duodenal administration.

Formulation	AUC (ug*hr/mL)	% F
FB	0.44 ± 0.15	15.4 ± 5.2
FB, 10% Polysorbate 80 (TWEEN 80)	0.79 (0.76; 0.82)	28 (27; 29)
FB, 20% Polysorbate 80 (TWEEN 80)	1.21 ± 0.18	42.7 ± 6.5
FB, NaBis, Lubricant	1.12 (1.18; 1.06)	39.6 (41.6; 37.3)
FB, 0.5 mM EDTA	0.89 ± 0.30	31.4 ± 10.7
FB, 0.5 mM EDTA, 10% Polysorbate 80 (TWEEN 80)	1.47 (1.79; 1.16)	52.1 (63.3; 40.9)

[0113] This study shows that there is a significant increase in AUC, when the freebase is administered directly to the rats' duodenum. It was also found that polysorbate 80 (TWEEN-80) had a positive effect on bioavailability (% F). Based on AUC, 10% and 20% polysorbate 80 (TWEEN-80) resulted in a 2-fold and 3-fold greater exposure, respectively. The increase in bioavailability was linearly related to the concentration of polysorbate 80 (TWEEN-80). It was also noted that 0.5 M of EDTA had a significant (2-fold) impact on bioavailability of the compound. The addition of both 0.5 M of EDTA and 10% polysorbate 80 (TWEEN-80) had a synergistic effect. Individually, each additive increased bioavailability by ~2-fold whereas both agents together had a greater than 3-fold effect. In addition, sodium bisulfite (an antioxidant) and colloidal silicon dioxide (AEROSIL) (a lubricant) also lead to a 2-fold increase in bioavailability.

Example 4

Effects of Permeability Enhancers on the Bioavailability of 9-[(2,2, Dimethyl-propyl amino)-methyl]-Minocycline

[0114] As a control, a solution of 9-[(2,2, dimethyl-propyl amino)-methyl]-minocycline freebase ("freebase") was prepared using sterile water and the final pH was adjusted to ~5. To prepare the sodium caprate (sodium decanoate, a compound that increases paracellular permeability) containing solution, the freebase was first dissolved in sterile water and sodium caprate was then added to a final concentration of 13 mM. The resulting solution was administered to rats via oral gavage without pH adjustment. The solution of freebase containing 1.5% chitosan was then prepared by first dissolving the freebase in sterile water and then adjusting the pH of this solution (pH ~8.1) to a final pH ~5 using 1N HCl. Chitosan was then added to a final concentration of 1.5% and the resulting solution was administered to rats via oral gavage as a slurry.

TABLE 5

Effects of permeability enhancers on the bioavailability of 9-[(2,2, dimethyl-propyl amino)-methyl]-minocycline administered by oral gavage.

Formulation	AUC (μg*hr/mL)	% F
FB (pH 8.1)	0.33 ± 0.12	11.7 ± 4.1
FB (pH 5)	0.42 ± 0.11	14.7 ± 3.8
FB, sodium caprate	0.44 (0.37; 0.51)	15.5 (13.1; 17.9)
FB, chitosan	0.47 ± 0.25	16.5 ± 8.9

[0115] It was found that the permeability enhancers sodium caprate and chitosan did not show a statistically significant effect on bioavailability.

EQUIVALENTS

[0116] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of the present invention and are covered by the following claims. The contents of all references, patents, and patent applications cited throughout this application are hereby incorporated by reference. The appropriate components, processes, and methods of those patents, applications and other documents may be selected for the present invention and embodiments thereof.

1. A method for increasing oral bioavailability of a tetracycline compound in a subject, comprising administering said tetracycline compound to a subject in combination with a bioavailability enhancing agent such that the tetracycline compound is released in the intestinal tract.

2. The method of claim 1, wherein the bioavailability is increased by about 5% or greater.

3. The method of claim 1, wherein the bioavailability is increased by about 10% or greater.

4. The method of claim 1, wherein the bioavailability is increased by about 25% or greater.

5. The method of claim 1, wherein the bioavailability is increased by about 40% or greater.

6. The method of claim 1, wherein the bioavailability is increased by about 50% or greater.

7. The method of claim 1, wherein the bioavailability enhancing agent is a charge masking compound, a solubilizing compound, a reducing compound, a stabilizing compound, a lubricating compound, a permeability enhancing compound, or a combination thereof.

8. The method of claim 7 wherein the bioavailability enhancing agent is polysorbate 80 (TWEEN-80), ethylenediaminetetraacetic acid (EDTA), sodium bisulfite, octanol, oil ethanol, calcium chloride, or silicon dioxide.

9. The method of claim 7, wherein the bioavailability enhancing agent comprises a combination of a lubricating compound with another agent.

10. The method of claim 9, wherein the bioavailability enhancing agent is a combination of a lubricating compound with sodium bisulfite.

11. The method of claim 10, wherein said lubricating compound is AEROSIL 200.

12. The method of claim 1, wherein the tetracycline compound is administered to the small intestine.

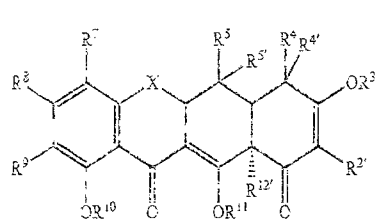
13. The method of claim 1, wherein the tetracycline compound is administered to the duodenum.

14. The method of claim 1, wherein the tetracycline compound is administered by a gastric feeding tube.

15. The method of claim 1, wherein the tetracycline compound is administered by a duodenal feeding tube.

16. The method of claim 1, wherein the tetracycline compound is formulated with an enteric coating.

17. The method of claim 1, wherein said tetracycline compound is of formula I:



(I)

wherein

R^1 is hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, amido, alkylamino, amino, arylamino, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, alkoxy, alkoxycar-

bonyl, alkylcarbonyloxy, alkyloxycarbonyloxy, arylcarbonyloxy, aryloxy, thiol, alkylthio, arylthio, aikenyl, heterocyclic, hydroxy, or halogen, optionally linked to R^2 to form a ring;

$R^{2''}$ is cyano or C(=O)—$NR^2R^{2'}$;

R^2 is hydrogen, alkyl, halogen, alkenyl, alkynyl, aryl, hydroxyl, thiol, cyano, nitro, acyl, formyl, alkoxy, amino, alkylamino, heterocyclic, or absent, optionally linked to R^1 to form a ring;

$R^{2'}$, R^{4a}, and R^{4b} are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R^{10}, R^{11}, and R^{12} are each independently hydrogen, alkyl, aryl, benzyl, arylalkyl, or a pro-drug moiety;

$R^{12''}$ is O—R^{12}, hydrogen, or substituted amino;

R^4 and $R^{4'}$ are each independently $NR^{4a}R^{4b}$, alkyl, acyl, alkenyl, alkynyl, hydroxyl, halogen, hydrogen, or taken together =N—OR^{4a};

R^5 and $R^{5'}$ are each independently hydroxy., hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^7 is hydrogen, dialkylamino, hydroxyl, halogen, thiol, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, arylalkenyl, arylalkynyl, acyl, aminoalkyl, heterocyclic, boronic ester, alkylcarbonyl, thionitroso, or —$(CH_2)_{0-3}(NR^{7c})_{0-1}C(=W')WR^{7a}$;

R^8 is hydrogen, hydroxyl, halogen, thiol, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, amino, arylalkenyl, arylalkynyl, acyl, aminoalkyl, heterocyclic, thionitroso, or —$(CH_2)_{0-3}(NR^{8c})_{0-1}C(=E')ER^{8a}$;

R^9 is hydrogen, hydroxyl, halogen, thiol, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, arylalkenyl, arylalkynyl, acyl, aminoalkyl, heterocyclic, thionitroso, or —$(CH_2)_{0-3}(NR^{9c})_{0-1}C(=Z')ZR^{9a}$;

R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, R^{8a}, R^{8b}, R^{8c}, R^{8d}, R^{8e}, R^{8f}, R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e}, and R^{9f} are each independently hydrogen, acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, aryl, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

E is $CR^{8d}R^{8e}$, S, NR^{8b} or O;

E' is O, NR^{8f}, or S;

Q is a double bond when R^2 is absent, Q is a single bond when R^2 is hydrogen, alkyl, halogen, hydroxyl, thiol, alkenyl, alkynyl, aryl, acyl, formyl, alkoxy, amino, alkylamino, cyano, nitro, or heterocyclic;

W is $CR^{7d}R^{7e}$, S, NR^{7b} or O;

W' is O, NR^{7f}, or S;

X is CHC(R^{13}Y'Y), C=CR^{13}Y, $CR^{6'}R^6$, S, NR^6, or O;

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

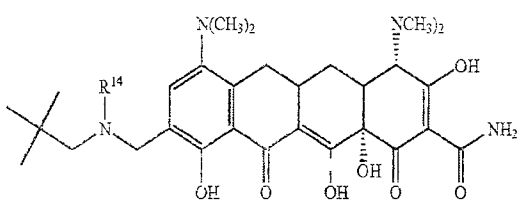
Z is $CR^{9d}R^{9e}$, S, NR^{9b} or O;

Z' is O, S, or NR^{9f}, and pharmaceutically acceptable salts, esters and enantiomers thereof.

18. The method of claim 17, wherein $R^{2''}$ is $C(=O)NH_2$; R^3, R^{10}, R^{11}, and R^{12} are each hydrogen or a prodrug moiety; R^4 is $NR^{4a}R^{4b}$; R^{4a} and R^{4b} are each methyl; R^5 is hydrogen; R^8 is hydrogen; X is $CR^6R^{6'}$; R^6 is hydrogen; and $R^{5'}$ and R^6 are hydrogen.

19. The method of claim 17, wherein said tetracycline compound is of the formula II:

(II)



wherein

R^{14} is hydrogen or prodrug moiety, and pharmaceutically acceptable salts thereof.

20. The method of claim 19, wherein R^{14} is hydrogen.

21. The method of claim 19, wherein R^{14} is of the formula

—(C=O)-E^1-G^1

wherein

E^1 is oxygen, nitrogen, or a covalent bond;

G^1 is alkyl; heterocyclicalkyl; aryl; alkylcarbonyloxyalkyl; arylcarbonyloxyalkyl; alkyloxycarbonyloxyalkyl; arylalkylcarbonyloxyalkyl; alkyloxyalkylcarbonyloxyalkyl; or alkoxyalkoxycarbonyloxyalkyl.

22. The method of claim 21, wherein E^1 is oxygen.

23. The method of claim 21, wherein G^1 is alkylcarbonyloxyalkyl.

24. The method of claim 21, wherein G^1 is of the formula —$(CH_2)_m$—O—(C=O)—R^{15}, wherein m is 1-5 and R^{16} is alkyl.

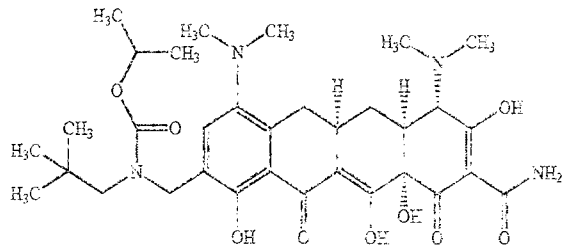
25. The method of claim 24, wherein m is 1.

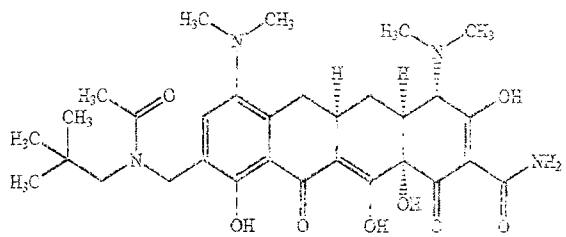
26. The method of claim 24, wherein R^{15} is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, —$(CH_2)_{10}$—CH_3, or —$(CH_2)_{11}CH_3$.

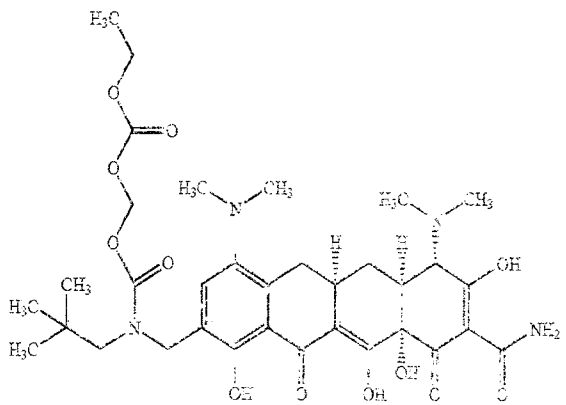
27. The method of claim 21, wherein E^1 is oxygen and G^1 is —$(CH_2)_2$—O—C(=O)—CH_3.

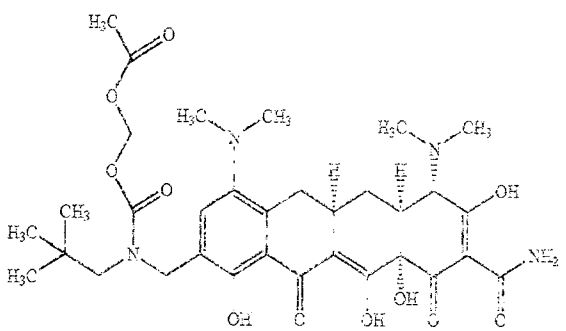
28. The method of claim 21, wherein E^1 is oxygen and G^1 is —CH_2—O—(C=O)—$C(CH_3)_3$.

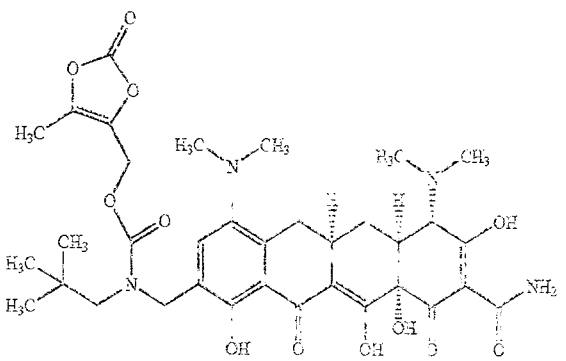
29. The method of claim 17, wherein the tetracycline compound is:











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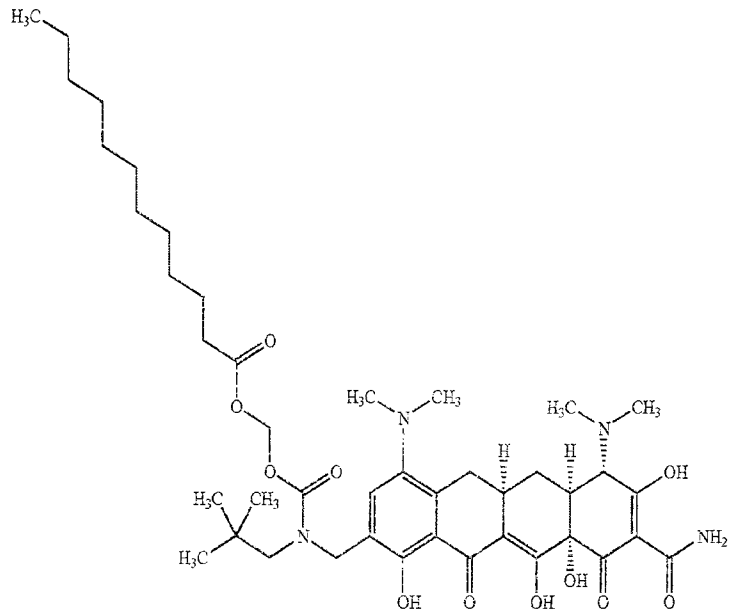

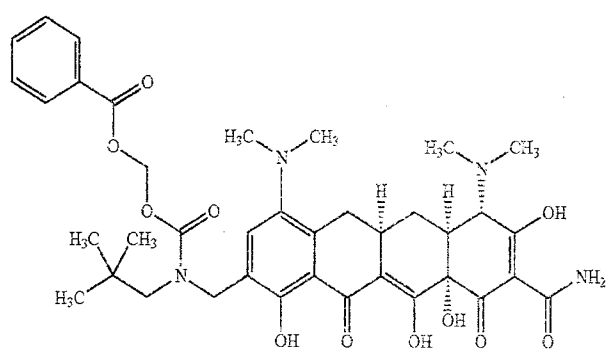

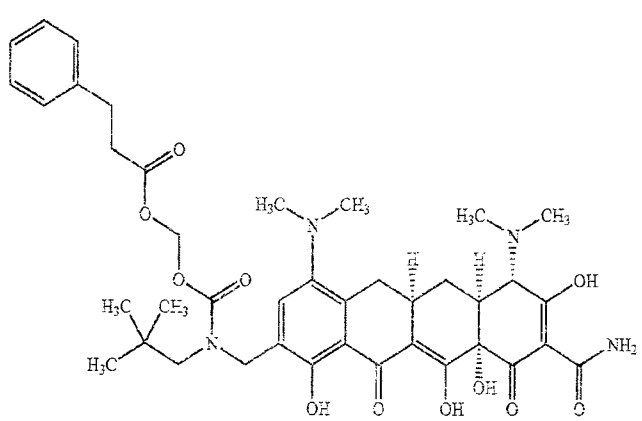

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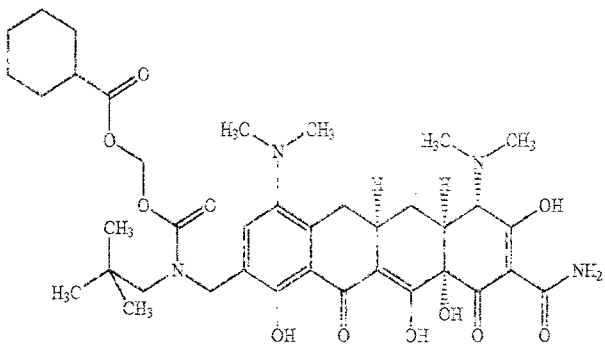

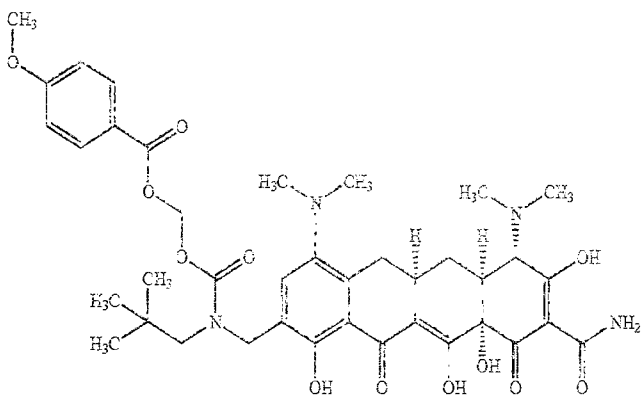

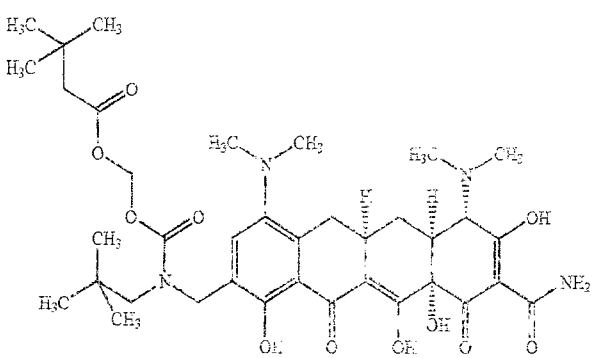

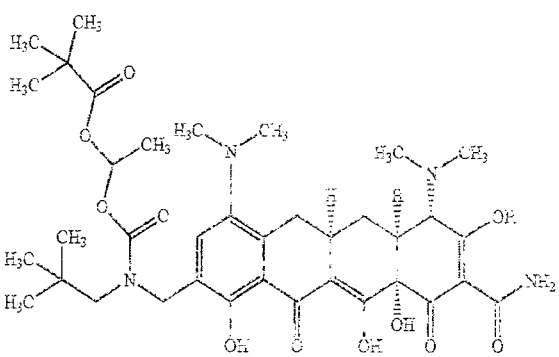

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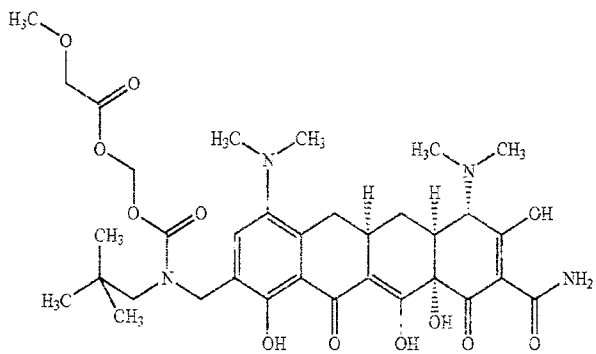

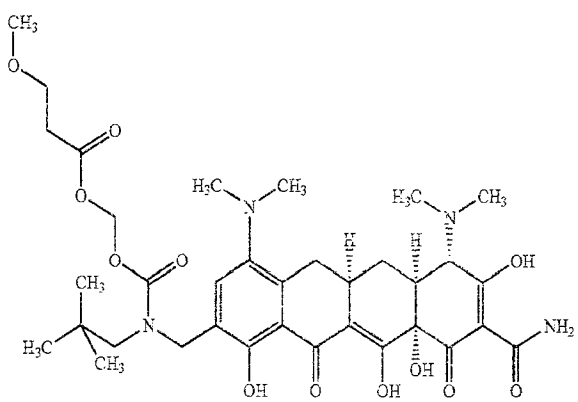

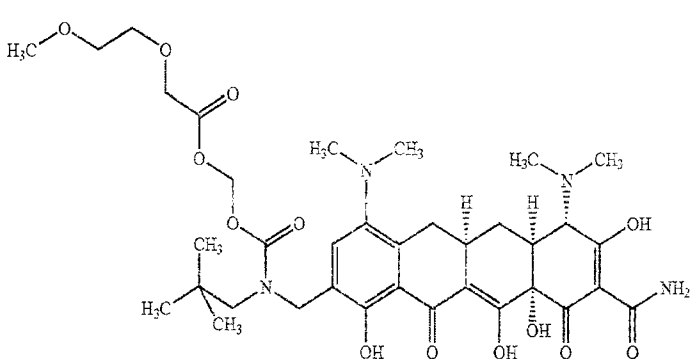

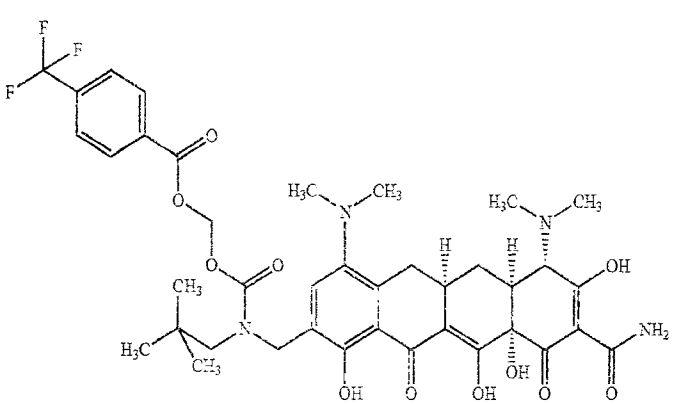

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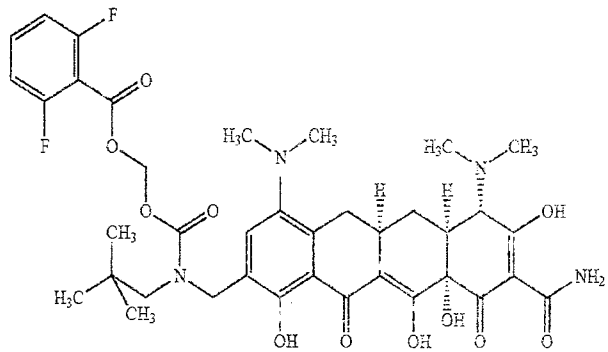

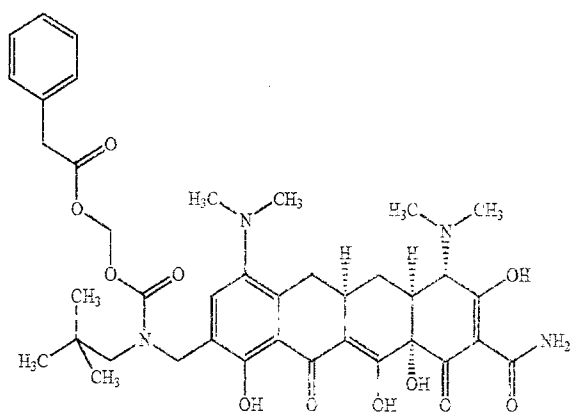

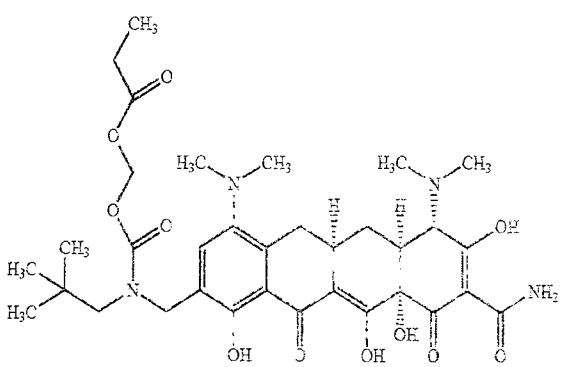

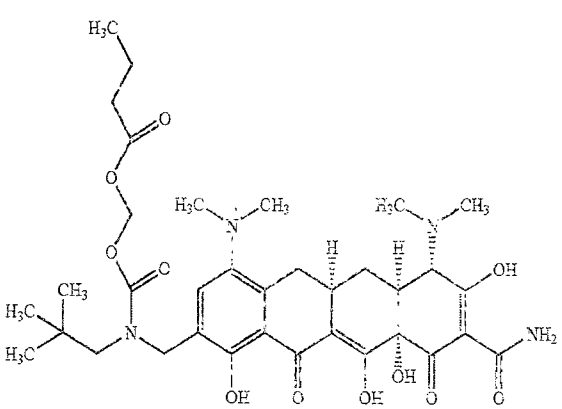

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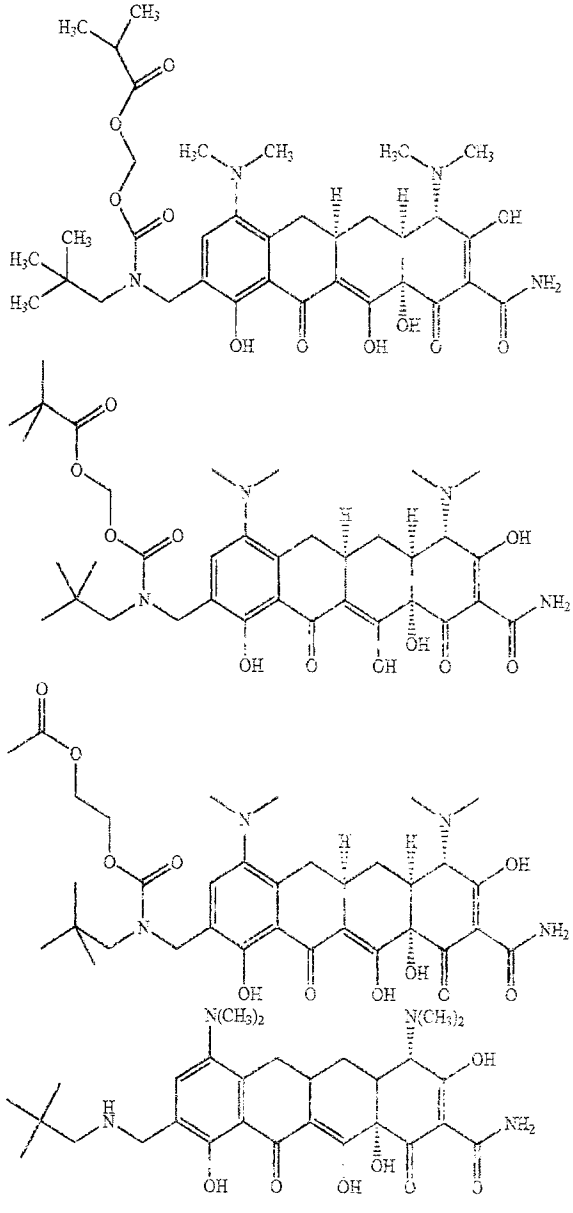

and pharmaceutically acceptable salts thereof.

30. A pharmaceutical composition comprising a therapeutically effective amount of a tetracycline compound in combination with a bioavailability enhancing agent and a pharmaceutically acceptable carrier for administration of said tetracycline compound to the intestinal tract.

31. The pharmaceutical composition of claim 30, wherein said tetracycline compound and said bioavailability enhancing agent are formulated for separate administration.

32. The pharmaceutical composition of claim 30, wherein said tetracycline compound and said bioavailability enhancing agent are formulated for concurrent administration.

33. A kit comprising a tetracycline compound and instructions for administering a therapeutically effective amount of the tetracycline compound in combination with a bioavailability enhancing agent to the intestinal tract of a subject.

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