

Industria y Comercio
SUPERINTENDENCIA

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SUPERINDUSTRIA Y COMERCIO
Radicación: 04007561 00000004 Folios: 46
Fecha (MM): 2005-11-25 11:25:54
Trámite: 011 PCT-PATENT 370 FREE NINCI 400 OPOSICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE OPOSICIÓN

REPÚBLICA DE
NOTARIO
ENCARG
BOGOT

①

OPOSICIÓN A:

- ☒ 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.

SOLICITUD
PUBLICADA

Número del expediente: 04-007561
Solicitante: R.P. SCHERER TECHNOLOGIES, INC.
Apoderado: LUIS FELIPE CASTILLO GIBSON
Título de la nueva creación o denominación del signo: Formulaciones
antihistamínicas para formas de dosificación de capsula blanda
Gaceta: 555

③ OPOSICIÓN PRESENTADA POR:

REPÚBLICA DE C
NOTARIO D
ENCARG
BOGOT

SOLICITANTE	Nombre: <u>PROCAPS S.A.</u>	IDENTIFICACIÓN	
	Dirección: <u>CALLE 80 No. 78b-201</u>	C.C. ☐	NT ☒
	Nacionalidad o Domicilio: <u>COLOMBIA</u>	C.E. ☐	Otro ☐
	Lugar de Constitución: <u>BARRANQUILLA</u>	Cual <u> </u>	
	Teléfono: <u>371 99 00</u> Fax: <u>373 08 18</u>	Número <u>890.106.527-5</u>	
	E-mail: <u> </u>		
REPRESENTANTE O APODERADO	Nombre: <u>REINALDO PINILLA MORENO</u>	IDENTIFICACIÓN	
	Dirección: <u>TRANVERSAL 13 A 119-95 OFICINA 104</u>	C.C. ☒	NT ☐
	Teléfono: <u>613 34 18</u> Fax: <u>24 47 87</u>	C.E. ☐	Otro ☐
	E-mail: <u>negocios@optimum-co.com</u>	Cual <u> </u>	
		Número <u>80425609</u> Tp <u>91563</u>	

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".

NOTARIO D
ENCARG
BOGOT

5 Comprobante de pago No. _____

Fecha _____

6 ANEXOS

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

COLOMBIA
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NOMBRE: REINALDO PINILLA MORENO

FIRMA: 

C.C. 80425609

TP. 91563 CSJ

PRESENTACION PERSONAL

En Bogotá, D.C. a 25 NOV 2005 se present.....

en la Notaría Décima, cuya encargada es MARIA JUDIT PARDO DIAZ

REINALDO PINILLA MORENO

Con cédula No. 80425609

Expedida en USADARA y dijo que

el anterior documento es cierto y que la firma es de su puño y

letra, En constancia se firma 



COLOMBIA
ECIMO
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COLOMBIA
ECIMO
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Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

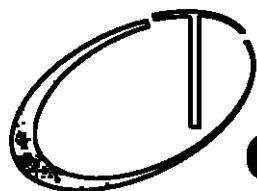
E. S. D.

Referencia : Expediente N° 04-007561
Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMULACIONES ANTIHISTAMINICAS PARA
FORMAS DE DOSIFICACIÓN DE CÁPSULA BLANDA."
Solicitante : R.P. SCHERER TECHNOLOGIES, INC.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 555 del 31 de Agosto de 2005

Yo, **REINALDO PINILLA MORENO**, abogado con tarjeta profesional N° 91563 del consejo superior de la judicatura, en mi condición de apoderado de la sociedad **PROCAPS S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, 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 ANTIHISTAMINICAS PARA FORMAS DE DOSIFICACIÓN DE CÁPSULA BLANDA**", solicitada por **R.P. SCHERER TECHNOLOGIES, INC.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.



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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 debido a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida atentaría directamente a la comercialización que pretende mi representada, en materia de LORATADINA en particular. 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.

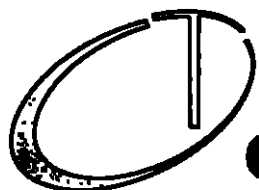
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2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 2 de febrero de 2004, reivindicando prioridad bajo las solicitudes US09909313 del 2001-07-20 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 555 del 31 de agosto de 2005, página 405, N° publicación 418, cuya publicación internacional corresponde a la WO03/007920 del 2003-01-30.

2.2. La solicitud colombiana 04-007561 objeto de la presente oposición, se refiere a una composición farmacéutica para uso en formas de dosis de cápsula blanda, que comprende: a) loratadina y derivados de la misma en una cantidad farmacéuticamente efectiva; y b) Un sistema de solvente que comprende una mezcla de ácidos grasos de cadena media; y, una composición farmacéutica para uso

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en una forma de dosis de cápsula blanda, que consiste esencialmente de: a) Loratadina y derivados de la misma presentes en una cantidad de aproximadamente 6,3% por peso de la composición total; b) mono y diglicéridos de ácidos grasos de cadena media presentes en una cantidad de aproximadamente 87% por peso de la composición total; c) povidona presente en una cantidad de aproximadamente 6,3% por peso de la composición total; y d) Polysorbate TM80 presente en una cantidad de aproximadamente 0.8% por pesos de la composición total.

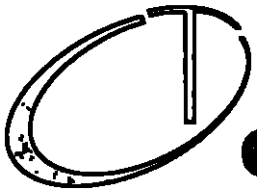
2.3. Ahora bien, el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente:

"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 afectan la novedad y el nivel inventivo de la presente solicitud:

- D1: US4659716, 1987-04-21
- D2: US5595997, 1997-01-21
- D3: US5352704, 1994-04-10

2.4. Ahora bien, el documento D1, en la descripción y particularmente en la columna 7, líneas 57 a 68, se refiere a una dosis oral que comprende un derivado de loratadina tal como descarboetoxiloratadine (DCL) utilizando para el tratamiento de rinitis alérgicos y otros desórdenes sin efectos adversos. Según se describe en dicha patente anterior D1, las preparaciones solidas convertidas en preparaciones liquidas, pueden contener además un derivado de loratadina: saborizantes,

Calle 119 A N° 53-99. Tel. (571) 6 13 34 18 - 6 13 33 74 - Fax. (571) 6 24 47 87
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

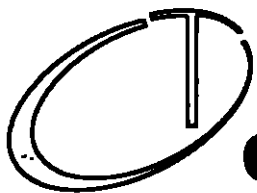


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colorantes, estabilizadores, dulcificantes artificiales y naturales, dispersantes, espesadores y agentes solubilizantes. Según se revela en dicho documento D1, el solvente utilizado para preparar la presentación líquida puede ser agua, agua isotónica, etanol, glicerina, propilenglicol y similares, así como las mezclas de ellos. Igualmente se afirma que el solvente utilizado se escogerá con respecto a la ruta de administración, por ejemplo, para preparaciones líquidas que contienen grandes cantidades de etanol no son convenientes para uso parenteral. Así las cosas, es claro que este documento D1, revela una misma propuesta como solución que incluye un derivado de loratadina y por lo menos un sistema solvente. Por lo tanto, a los ojos de este documento D1, la presente solicitud no es novedosa.

2.5. Por su parte, el documento D2, particularmente en la descripción en conjunto con el capítulo reivindicatorio, revela sistemas de administración de una cantidad efectiva de un derivado de loratadina utilizando para el tratamiento de rinitis alérgicos y otros desórdenes sin efectos adversos. Según se revela en este documento D2, las composiciones farmacéuticas para la administración oral puede presentarse como cápsulas de gelatina blanda, capsulas duras, tabletas o por aspersion, donde cada uno contiene una cantidad determinada del ingrediente activo, como un polvo o gránulos, o como una solución o una suspensión en un líquido acuoso, un líquido no acuoso, una emulsión de aceite en agua o agua en aceite. En el ejemplo 8 de este documento D2, revela un sistema de fabricación de cápsulas de gelatina blanda, que comprende una mezcla del ingrediente activo de loratadina en un aceite digerible tal como aceite de soya, lecitina, aceite de semilla de algodón o aceite de oliva, previamente mezclados y preparados, los cuales después se inyectan en la gelatina para formar cápsulas de gelatina blandas que contienen de 0.1 a 10 miligramos del ingrediente activo. Por lo tanto, el hecho de proteger una cápsula de gelatina blanda que incluye loratadina o un derivado del mismo como ingrediente



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activo, no es novedoso a la luz de este documento D2. Por lo tanto, el documento objeto de oposición no es novedoso con base en el documento D2.

2.6. Ahora bien, el documento D3, revela formas de elaboración de capsulas de gelatina blanda que además de un compuesto activo, puede contener un vehículo convencional tal como aceite vegetal, polietilenglicol o glicerol, o un agente de suspensión aceitoso o un agente humectante tal como un surfactante. En este documento se revelan varias alternativas de solventes específicamente en la columna 5, líneas 10 a 46. Así las cosas, para una persona versada en la materia, al combinar lo incluido en este documento D3, con lo que dicta los documentos D1 y D2, puede llegar a una presentación de cápsula de gelatina blanda que incluye loratadina y derivados de la misma en una cantidad farmacéuticamente efectiva y un sistema de solvente que comprende una mezcla de ácidos grasos.

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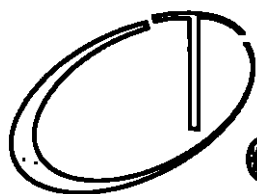
2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 04-007561 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los dos de los tres requisitos necesarios para su protección.

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

2.8.1. **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, 20 de

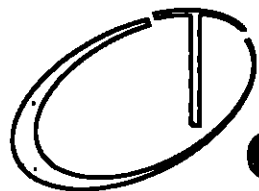
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julio de 2001, ya era conocido, pues como se demostró, era parte del arte anterior con base en los documentos D1 y D2, una cápsula de gelatina blanda que incluye loratadina y derivados de la misma en una cantidad farmacéuticamente efectiva y un sistema de solvente que comprende una mezcla de ácidos grasos sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. 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, 20 de julio de 2001, a partir de los documentos D1, D2, y D3 en combinación, es posible deducir la conformación de una cápsula de gelatina blanda que incluye loratadina y derivados de la misma en una cantidad farmacéuticamente efectiva y un sistema de solvente que comprende una mezcla de ácidos grasos según lo definido en las reivindicaciones de la presente solicitud.

2.9. 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 dos de los tres requisitos de patentabilidad.



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Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

2.10. Por consiguiente, si se concede el registro solicitado se induciría al monopolio de un producto que no cumple con los requisitos primordiales exigidos por la mencionada Decisión 486.

2.11. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Parente de invención denominada **"FORMULACIONES ANTIHISTAMINICAS PARA FORMAS DE DOSIFICACIÓN DE CÁPSULA BLANDA"**, solicitada por **R.P. SCHERER TECHNOLOGIES, INC.**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 555.

3. PRUEBAS

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

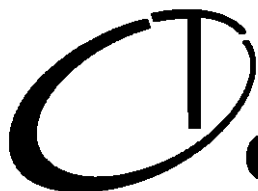
- D1: US4659716, 1987-04-21
- D2: US5595997, 1997-01-21
- D3: US5352704, 1994-04-10

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

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

Calle 119 A N° 51-99, Tel. (571) 6 13 34 13 - 6 13 33 74 - Fax. (571) 6 24 47 87
Email: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia



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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:

- D1: US4659716, 1987-04-21
- D2: US5595997, 1997-01-21
- D3: US5352704, 1994-04-10

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 Transversal 13ª N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,


REINALDO PINILLA MORENO

C.C. 80'425.609 de Bogotá

T.P.A. 91563 del C.S. de la J.

Calle 119 A N° 53-99. Tel. (571) 6 13 34 18 - 6 13 33 74 - Fax. (571) 6 24 47 87
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

PRESENTACION PERSONAL

En Bogotá, D.C. a ...25 NOV 2005... se present...
en la Notaría Décima, cuya encargada es MARIA JUDIT PARDO DIAZ
ASIMLOK PINILLA MANCERO

Con cédula No. 20425609

Expedida en ...USA... y dijo ... que
el anterior documento es cierto y que la firma es de su guño

letra, En constancia so firma





PODER ESPECIAL

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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 **REINALDO PINILLA MORENO**, abogado titulado, identificado como aparece al pie de su firma, con tarjeta profesional No. 91563 expedida por el Consejo Superior de la Judicatura, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 04-007561, de título: **"FORMULACIONES ANTIHISTAMINICAS PARA FORMAS DE DOSIFICACIÓN DE CAPSULA BLANDA"**, publicada en la gaceta No. 555 del 31 Agosto de 2005.

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 administrativa y judicialmente 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 9 días del mes de noviembre de 2005.

PROCAPS S.A.
WALTER TANAKA TATEKAWA
C.C. N° 16.251.923 de Palmira
Representante Legal

Acepto,

REINALDO PINILLA MORENO
C.C. 80'425.609 de Bogotá
T.P.A. 91563 del C.S. de la J.

SEGURO NOTARIA SEGURA NOTARIA SEGURA NOTARIA SEGURA

ADY ISABEL NAMEN SEGURA

NOTARIA SEGURA DEL CANTON DE BARRAHACILLA

DILIGENCIA DE PRESENTACION PERSONAL Y RECONOCIMIENTO

La suscrita Notaria Certifica que ante ella fue
presentado Personalmente por UNICA
TRABAJO 1074446
Identificación con: 16251-923
Expedida en: PALENA
Quiere declarar que su contenido es cierto y que la
firma es verdadera y es suya.

Firma: [Firma]

Firmo: [Firma]

17 NOV. 2005

Huella del Comisionario

CA DE COLOMBIA

OFICIO DE BARRAHACILLA

VENECIA VENECIA VENEZIA VENECIA VENECIA



***** Pag.01
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. -----

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Publica Nro. 1190 del 22 de Julio de 1,976,
torgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 28 de Julio de 1,976 baj
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 Publica Nro. 1307 del 28 de Junio de 1,979,
torgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 23 de Julio de 1,979 baj
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 Publica Nro. 3810 del 31 de Dic/bre de 1,980,
torgada en la Notaria Primera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 30 de Enero de 1,981 bajo
el No. 12,705 del libro respectivo, la sociedad antes mencionada
se transformo en sociedad de responsabilidad limitada bajo al raz n
s cial de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI -
MITADA".-----

C E R T I F I C A

Que por Escritura Publica Nro. 3755 del 10 de Nov/bre de 1,983,
torgada en la Notaria Unica de Soledad, -----
inscrita en esta Camara de Comercio, el 22 de Nov/bre de 1,983 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 Publica Nro. 3615 del 6 de Dic/bre de 1,996,
torgada en la Notaria 2a. de Barranquilla -----
inscrita en esta Camara de Comercio, el 20 de Dic/bre de 1,996 baj

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



***** Pag.02
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

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

PROCAPS S.A. -----

C E R T I F I C A

Direccion para notificaciones judiciales
CL 80 # 78B -201
de la ciudad de BARRANQUILLA

C E R T I F I C A

DURACION: El termino de duracion de la sociedad se fijo hasta el
18 de Agosto del ano 2,073. -----

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-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 y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) 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. e) La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) 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; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, 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, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, de-

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



***** Pag.01
CAMARA DE COMERCIO
DE BARRANQUILLA
06*****
CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Publica Nro. 1190 del 22 de Julio de 1,976,
otorgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 28 de Julio de 1,976 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 Publica Nro. 1307 del 28 de Junio de 1,979,
otorgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 23 de Julio de 1,979 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 Publica Nro. 3810 del 31 de Dic/bre de 1,980,
otorgada en la Notaria Primera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 30 de Enero de 1,981 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 Publica Nro. 3755 del 10 de Nov/bre de 1,983,
otorgada en la Notaria Unica de Soledad, -----
inscrita en esta Camara de Comercio, el 22 de Nov/bre de 1,983 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 Publica Nro. 3615 del 6 de Dic/bre de 1,996,
otorgada en la Notaria 2a. de Barranquilla -----
inscrita en esta Camara de Comercio, el 20 de Dic/bre de 1,996 bajo

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

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PROCAPS S.A. -----

el No. 67,218 del 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 Publica Nro. 3775 del 18 de Dic/bre de 1,996,
otorgada en la Notaria 2a. de Barranquilla -----
inscrita en esta Camara de Comercio, el 23 de Enero de 1,997 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	mm/dd/aaaa	Notaria	No.Ins o Reg	mm/dd/aaaa
39	1/18/1979	Notaria 3a. de Barranquilla	9,452	1/24/1979
992	4/30/1981	Notaria 1a. de Barranquilla	13,112	5/ 6/1981
1,464	8/27/1982	Notaria Unica de Soledad	15,533	9/ 8/1982
2,744	8/18/1983	Notaria Unica de Soledad	17,416	8/26/1983
3,826	7/16/1984	Notaria Unica de Soledad	19,554	7/27/1984
3,835	8/26/1985	Notaria Unica de Soledad	22,230	9/ 4/1985
2,260	9/10/1986	Notaria Unica de Soledad.	24,995	9/15/1986
1,849	7/11/1989	Notaria 2a. de Barranquilla	33,909	7/13/1989
444	2/21/1990	Notaria 2a. de Barranquilla	36,101	3/16/1990
3,090	12/17/1991	Notaria 2a. de Barranquilla	43,993	1/28/1992
269	2/ 1/1993	Notaria 2a. de Barranquilla	48,428	2/16/1993
2,342	7/28/1993	Notaria 2a. de Barranquilla	50,582	8/10/1993
3,652	11/ 9/1993	Notaria 2a. de Barranquilla	51,798	11/22/1993
3,615	12/ 6/1996	Notaria 2a. de Barranquilla	67,218	12/20/1996
89	1/16/1997	Notaria 2a. de Barranquilla	67,704	1/23/1997
2,070	7/17/1997	Notaria 2a. de Barranquilla	70,627	7/31/1997
2,281	8/ 4/1997	Notaria 2a. de Barranquilla	70,813	8/14/1997
765	4/22/1999	Notaria 3a. de Barranquilla	80,628	4/23/1999
459	2/21/2001	Notaria 2a. de Barranquilla	91,502	2/23/2001
2,608	10/ 5/2001	Notaria 2a. de Barranquilla	95,771	11/ 8/2001
1,730	7/29/2004	Notaria 2. de Barranquilla	112,999	8/26/2004
416	3/ 3/2005	Notaria 2. de Barranquilla	116,364	3/10/2005
1,613	7/28/2005	Notaria 2. de Barranquilla	119,322	8/18/2005

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 *****



***** Pag.02
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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
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PROCAPS S.A. -----

C E R T I F I C A

Direccion para notificaciones judiciales
CL 80 # 78B -201
de la ciudad de BARRANQUILLA

C E R T I F I C A

DURACION: El termino de duracion de la sociedad se fijo hasta el
18 de Agosto del ano 2,073. -----

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricaci n de capsulas y otros productos similares a partir de materia-
les tales como gelatinas u otros de distinta naturaleza, que puedan
ser utilizados como envases o recipientes de productos y sustancias
quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y
veterinario; b)-La investigacion, desarrollo y fabricacion de toda
clase de productos y sustancias quimicas, farmaceuticas y cosmeticas
para uso y consumo humano, animal y vegetal; c)-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 l s productos terminados, d) La compra, venta, importacion, ex-
portacion y distribucion de toda clase de elementos instru-
mentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios
para la salud humana y animal. e) La compra, venta, exportacion y dis-
tribucion de dulces, confites, galletas y todo tipo de
golosinas o alimentos para el consumo humano. f) Actuar como re-
presentante o agente de personas naturales y juridicas, nacio-
naci nales y extranjeras en la realizacion de operaciones o tran-
sacciones relacionadas con la industria farmaceutica y en especial
c n cualquiera de las actividades descritas en los literales a),
b), c). d) y e) antes descritos; g) Prestar los servicios de
asesoria y consultoria en las areas administrativas, de mer-
cade , analisis clinico, asistencia tecnica, investigacion, 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, cosmeticos y farmaceuticos para uso humano, animal o in-
dustrial; h)-Adquirir, operar, administrar y explotar, a cualquier
titulo, empresa o establecimientos dedicados a la investigacion, de-

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

**CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
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PROCAPS S.A. -----

sarroll , fabricaci n comercializacion de productos quimic s, far-
maceuticos, hospitalarios o cosmeticos. En desarrollo de su objet
principal, la sociedad podra tomar interes social como accionista,
socio o fundador de empresas que tengan igual o similar objeto, com-
prar, vender, importar y exportar maquinarias, insumos y repuest s
requeridos para el desarrollo de sus actividades; tomar dinero en
prestamo, financiar y garantizar las operaciones comerciales que ce-
lebre con terceros relativas a su objeto; celebrar y ejecutar todo
tipo de actos y contratos necesarios para desarrollar sus operacio-
nes; girar, aceptar, otorgar y protestar todo tipo de titulos valo-
res e instrumentos negociables; comprar, vender y constituir grava-
menes sobre bienes muebles e inmuebles; designar representantes
apoderados en el pais y en el exterior y, en general, realizar cual-
quier acto o negocio que sea necesario o conveniente para el desa-
rrollo de su objeto social y para la mejor proteccion de sus intere-
ses corporativos o la de sus socios. La sociedad podra garantizar
el cumplimiento de obligaciones adquiridas por terceros o por sus
socios, para lo cual podra inclusive constituir gravámenes reales
s bre sus bienes de cualquier naturaleza.-----

C E R T I F I C A

CAPITAL:	Nro.Acciones	Valor Acci n
AUTORIZADO:		
\$*****2,000,000,000.00	2,000,000.00	1,000.00
SUSCRITO:		
\$*****1,220,000,000.00	1,220,000.00	1,000.00
PAGADO:		
\$*****1,220,000,000.00	1,220,000.00	1,000.00

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corres-
pondera 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 dola-
res 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
s cios, 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-
ci n legal de la sociedad y tendra las siguientes atribu-
ciones entre otras: Ejecutar las decisiones de la Asamblea
General de Accionistas y de la Junta Directiva. Ejercer la Represen-
taci n Legal de la sociedad en todos los actos y contratos que se
requieran para el desarrollo del objeto social, de conformidad c n

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



***** Pag.03
C A M A R A D E C O M E R C I O
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
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PROCAPS S.A. -----

1 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 cuantía 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 día en que se surta la transacción o celebración del acto. Las demás funciones que le correspondan como Representante Legal por disposición de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendrá un suplente, designado por la Junta Directiva, quien reemplazará 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 tendrá un Vicepresidente designado por la Junta Directiva, quien también ejercerá la representación legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendrá las siguientes 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 representación 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 cuantía 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 día en que se surta la aprobación o celebración 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 intereses inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demás funciones que le correspondan como Representante legal por disposición de la ley, de estos estatutos de la Junta Directiva. El Vicepresidente tendrá (1) suplente, designado por la Junta Directiva, quien lo reemplazará conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con idénticas facultades y sin que sea necesario para

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
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PROCAPS S.A. -----

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 partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes 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 segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo,
y por Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos: -----

J U N T A D I R E C T I V A

Principales	Suplentes
1. Minski Gontovnik Ruben	Minski Zilberblum Elliot
2. Minski Gontovnik Meyer	Minski Deitel Daniel
3. Minski Gontovnik Jose	Minski Sharon

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos: -----

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



***** Pag.04
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

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PROCAPS S.A. -----

Cargo	Nombre	Identificaci n
Presidente.	Minski Gontovnik Ruben	C.*****7,463,982=
Suplente del Presidente	Minski Minski Abraham	C.*****802,575=
Vicepresidente	Minski Gontovnik Meyer	C.*****7,461,324=
Suplente del vicepresidente	Minski Gontovnik Jose	C.*****8,671,834=

C E R T I F I C A

Que segun Acta No. 124 del 29 de Marzo de 1,999, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 4 de Agosto de 1,999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificaci n
Revisor Fiscal Ppal.	Vargas Pertuz Ana Isabel	C.****32,696,645=

C E R T I F I C A

Que segun Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificaci n
Suplente del Revisor Fiscal.	Lozada Villareal Milena	C.****32,748,111=

C E R T I F I C A

Que segun Acta No. 11 del 1 de Febrero de 2,001, correspondiente a la Junta Directiva en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 12 de Febrero de 2,001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Gerente General.	Uribe Ochoa Guillermo Luis	C.****70,073,754=

C E R T I F I C A

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

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

PROCAPS S.A. -----

Que segun Acta No. 406 del 2 de Sep/bre de 2,004, correspondiente a la Junta Directiva en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 9 de Sep/bre de 2,004 bajo el No.113,263 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificaci n
Suplente del Gerente.	Tanaka Walter	C.***16,251,923=

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001, otorgada en la Notaria 2a. de Barranquilla, inscrita en esta Camara de Comercio el 8 de Noviembre del 2.001, bajo los Nos. 95.771, 2.056, 2.057, 2.058, 2.059, 2.060, 2.061, 2.062 y 2.064 del libro respectivo, se reforma totalmente el articulo 65, contenido en la escritura publica No. 3.705 de Noviembre 6 de 1.998, de la Notaria Segunda del Circuito de Barranquilla, y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuaci n se indican en razon de su cargo en la sociedad: 1.-Se c n fiere Poder Especial, Amplio y Suficiente a los senores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILLIAM ALBERTO BARROS CERRA, C.C. No. 8.715.941, para que cada uno en forma independiente en nombre y representacion de PROCAPS S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento o solicitudes de informacion de las autoridades tributarias, aduaneras cambiarias, en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial, amplio y suficiente, a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancias y servicios con entidades oficiales, hasta por la suma de US\$800.000.00 (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GUPO A: GUILLERMO LUIS URIBE OCHO C.C. No. 70.073.754, LINO LAZALA SILVA VARGAS C.C. No. 19.260.410, JAIRO MOLINA MEJIA C.C. No. 8.706.380, CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, HENRY CARO DIAZ C.C. No. 19.395.298, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requiera por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la Doctora MARCKLA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, com-

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



***** Pag.05
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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
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PROCAPS S.A. -----

parecer en juicios, pedir la practica de pruebas, recibir notificaciones, interponer recursos y ejercer acciones contencioso administrativas y de tutela, transigir, conciliar, recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato. Para la celebracion de cualquier acuerdo conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantia, los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la sociedad. Los Apoderados podran presentar solicitudes de devolucion y/o compensacion de impuestos y recibir los pagos por devoluciones de impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.-----

C E R T I F I C A

Que segun documento privado de fecha 7 de junio de 2000, inscrito en esta Camara de Comercio el 8 de junio de 2000, bajo el No.1.786 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, ampli y suficiente a KAREN FIGUEROA GARCIA, C.C.No.32.732.070 de Barranquilla, para que en su nombre y representacion de la sociedad suscriba todas declaraciones cambiarias a que este obligada PROCAPS S.A, en el giro normal de sus negocios y operaciones sociales.--

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2.002, inscrito en esta Camara de Comercio el 15 de enero del 2.003 bajo el No.2.290 del libro respectivo, el senor RUBEN MINSKI GONTOVNIK, C.C.No.7.463.982, en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE de PROCAPS S.A., mediante el presente documento otorgo PODER ESPECIAL al Sr. MARLON TATIS PAREDES, C.C.No.72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces. En consecuencia, el Sr. MARLON TATIS PAREDES, podra suscribir en representacion de PROCAPS S.A. declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces.-----

C E R T I F I C A

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

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

PROCAPS S.A. -----

Que segun documento privado del 10 de noviembre del 2004, inscrito en esta Camara de Comercio el 1 de diciembre del 2.004, bajo el No. 2.753 del libro respectivo consta que RUBEN MINSNSKI GONTOVNIK, C.C. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a ANTONIO VARELA DIAZ, C.C.No.72.004.669 de Barranquilla, para que en nombre y representacion de la sociedad firme las declaraciones cambiarias a que este obligada PROCAPS S.A., a suscribir en el giro normal de sus negocios y operaciones sociales. Por lo anterior, el señor ANTONIO VARELA DIAZ, queda facultado para firmar las declaraciones comabiarias y demas documentos relacionados con las declaraciones, notificaciones, aportar y solicitar las pruebas que sean necesarias, desistir en general a realizar todo act necesario de tal forma que pueda cumplir con el mandato dad .-

C E R T I F I C A

Que segun documento privado del 22 de Febrero de 2005, inscrito en esta Camara de Comercio el 28 de Marzo de 2.005, bajo el No. 2.820 del libro respectivo, consta que WALTER TANAKA TATEKAWA C.C. 16.251-923 de Palmira, quien actua como representante legal de la sociedad PROCAPS S.A, otorga Poder Especial, Amplio y Suficiente al señor MARLON TATIS PAREDES C.C. No. 72.176.874, para que en representaci n de PROCAPS S.A., suscriba declaraciones aduaneras, reportes y cualquier tipo de documentos relacionados con los tramites o registros de comercio exterior ante la direccion de impuestos y aduanas naci - nales y/o cualquier entidad que haga sus veces, y para que responda todo tipo de requerimientos y/o solicitudes de informacion de las autoridades aduaneras en los ordenes distrital, departamental y nacional.-----

C E R T I F I C A

Que por Escritura Publica No.1.613 del 28 de Junio del 2.005, otorgada en la Notaria Segunda de Barranquilla, inscrita en esta Camara de Comercio el 18 de agosto del 2.005 bajo el No.2.913 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C.No.7.463.928, en su condicion de Presidente y Representante Legal de la sociedad PROCAPS S.A., confiere poder especial amplio y suficiente a los siguientes senores que conforman el Grupo A y el Grupo B, para que conjuntamente suscriban contratos de suministro de mercancías y servicios con entidades oficiales, hasta por la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS DE AMERICA (US\$800.000), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GRUPO A: MIRIAM RODRIGUEZ DIAZ, C.C.No. 41.473.569. GRUPO B: NELSON SUAREZ CHAVEZ, C.C.No.79.417.971.-----

C E R T I F I C A

Que en esta Camara de Comercio no aparecen inscripciones posteri res de documentos referentes a reforma, disolucion, liquidacion o nombramientos de representantes legales de la expresada sociedad.-----

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



***** Pag.06
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

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

PROCAPS S.A. -----

C E R T I F I C A

Que su ultima Renovacion fue el: 23 de Marzo de 2,005. -----

La informacion sobre embargos de establecimientos se suministra en
Certificados de Matricula, la de contratos sujetos a registro, en
Certificados Especiales.

Maribel Reyes

NO CAUSA IMPUESTO DE TIMBRE

EL SECRETARIO
MARIBEL REYES OVIEDO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radicacion : 04007561 00000004 Folios: 46
Fecha (MM): 2005-11-25 11:25:54
Tramite : 011 PCT-PATENT 378 FASE NNCI 400 OPOSICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 90.446
FECHA : NOVIEMBRE 25 DE 2005

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	36876429	26/10/2005	1,175,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	30005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LENAS COMERCIALES	235,000.00
		TOTAL :	\$ 235,000.00

SON: DOSCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

United States Patent [19]
Villani et al.

[11] **Patent Number:** 4,659,716
[45] **Date of Patent:** Apr. 21, 1987

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D1

[34] **ANTIHISTAMINIC 8-(HALO)-SUBSTITUTED
6,11-DIHYDRO-11-(4-PIPERIDYLIDENE)-5H-
BENZO[3,6]CYCLOHEPTA[1,2-b]PYRIDINES**

[75] **Inventors:** Frank J. Villani, Fairfield; Jesse K.
Wong, Union, both of N.J.

[73] **Assignee:** Schering Corporation, Madison, N.J.

[21] **Appl. No.:** 838,974

[22] **Filed:** Mar. 12, 1986

Related U.S. Application Data

[63] **Continuation-in-part of Ser. No. 580,304, Feb. 15, 1984,
abandoned.**

[51] **Int. Cl.⁴** A61K 31/445; C07D 401/08

[52] **U.S. Cl.** 514/290; 546/93

[58] **Field of Search** 546/93; 514/290

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,326,924 6/1967 Villani 546/93
3,717,647 2/1973 Villani 546/313
4,282,233 8/1981 Villani 546/93 X

FOREIGN PATENT DOCUMENTS

46-20387 6/1971 Japan 546/93

OTHER PUBLICATIONS

PDR, 1984, pp. 515, 529, 557, 558, 566, 593, 594, 611,
631, 633, 648, 664, 667, 668, 709.
Scrip No. 1026, 8/19/85.
Burger's Medicinal Chemistry, 4th Ed, Part III, Wi-
ley-Interscience, NY, 1981, pp. 818-819.
Brandon, M., et al., *Annals of Allergy*, 44, 71-75 (1980).
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Villani, F., et al., *Arzneim.-Forsch.*, 36(11), Nr. 9 1986,
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Goodman and Gilman's, *The Pharmacological Basis of
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1613, 1725, 1726, 1872, 1873, 1879, 1965, 1966, 2276,
2277.

Primary Examiner—Richard A. Schwartz
Attorney, Agent, or Firm—James R. Nelson; Stephen I.
Miller; Richard C. Billups

[57] **ABSTRACT**

Disclosed are 7- and/or 8-(halo or trifluoromethyl)-sub-
stituted-6,11-dihydro-11-(4-piperidylidene)-5H-ben-
zo[3,6]cyclohepta[1,2-b]pyridines and the pharmaceuti-
cally acceptable salts thereof, which possess antihista-
mimic properties with substantially no sedative proper-
ties. Methods for preparing and using the compounds
and salts are described.

16 Claims, No Drawings

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**ANTI-HISTAMINIC 8-(HALO)-SUBSTITUTED
6,11-DIHYDRO-11-(4-PIPERIDYLIDENE)-5H-BEN-
ZO[5,6]CYCLOHEPTA[1,2-B]PYRIDINES**

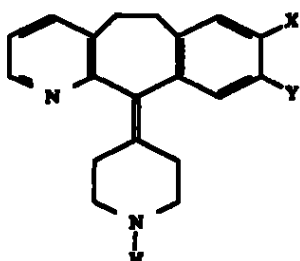
The present application is a continuation-in-part of U.S. application Ser. No. 580,304, filed Feb. 15, 1984, now abandoned, the benefit of which is claimed pursuant to the provisions of 35 U.S.C. 120.

BACKGROUND OF THE INVENTION

U.S. Pat. Nos. 3,326,924, 3,717,647 and 4,282,233 describe certain 11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridines.

SUMMARY OF THE INVENTION

The present invention is directed to compounds having structural formula I:



or pharmaceutically acceptable salts thereof, wherein X and Y independently represent H, halo (i.e., fluoro, chloro, bromo or iodo), or trifluoromethyl with the proviso that at least one of X and Y is halo or trifluoromethyl. Particularly, preferred compounds are those wherein X is F and Y is H and wherein X is Cl and Y is H.

The compounds of the invention have unexpectedly been found to possess advantageous antihistaminic activity and low central nervous system (CNS) activity indicative of non-sedation. The compounds can thus be employed in pharmaceutical compositions in combination with pharmaceutically acceptable carriers and in methods of treating allergic reactions in a mammal.

DESCRIPTION OF THE INVENTION

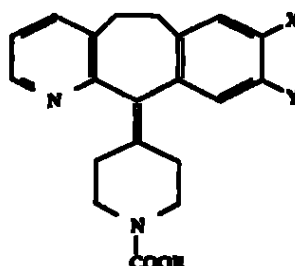
The compounds of the invention can form salts with pharmaceutically acceptable acids such as hydrochloric, methanesulfonic, sulfuric, acetic, maleic, fumaric, phosphoric and the like. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base form may be regenerated by treating the salt forms with a base. For example, dilute aqueous base solutions may be utilized. Dilute aqueous sodium hydroxide, potassium carbonate, ammonia, and sodium bicarbonate solutions are suitable for this purpose. The free base form differs from the respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but the salts are otherwise equivalent to the respective free base form for purposes of the invention.

The compounds of the invention and their corresponding salts can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents

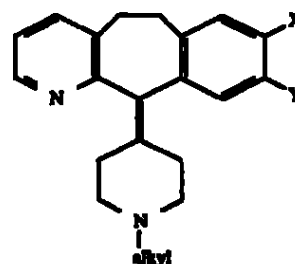
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such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

The compounds of the invention can be prepared by decarbalkoxylation of a compound of the formula II:



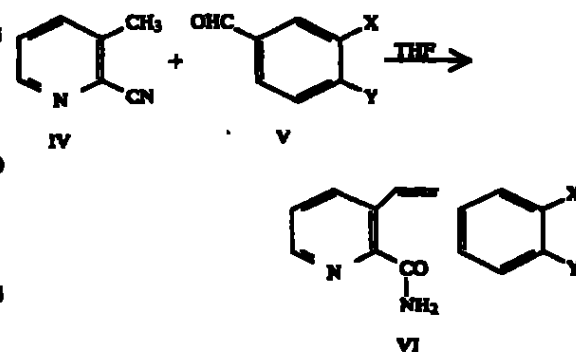
wherein R is an alkyl group (preferably ethyl) and X and Y are as defined above. The compounds of formula II can be prepared by procedures described in U.S. Pat. No. 4,282,233 from the corresponding N-alkyl (preferably N-methyl) compounds of formula III



by employing appropriate starting materials having the desired X and Y substituents.

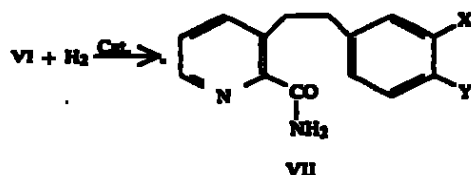
Alternatively, the compounds of the invention can be prepared by dealkylation of compounds of formula III, e.g., by reaction with cyanogen bromide and subsequent hydrolysis of the N-cyano product with, for example, aqueous acid solution to provide the compounds of formula I.

The compounds of formula III can be produced by the procedures described in U.S. Pat. No. 3,326,924 by employing the appropriately X and Y substituted starting materials. For example, 2-cyano-3-picoline of formula IV can be reacted with an appropriate benzaldehyde of formula V in the presence of a strong base such as potassium butoxide to give an ortho-phenethenyl pyridine carboxamide of formula VI

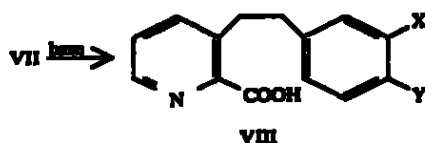


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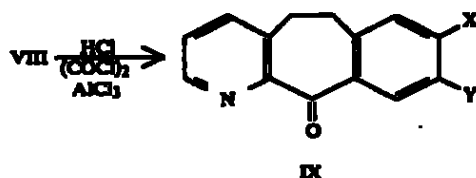
which is then hydrogenated, e.g., by employing a noble metal on carbon catalyst such as palladium or platinum on carbon, to the corresponding ortho-phenethyl pyridine carboxamide of formula VII



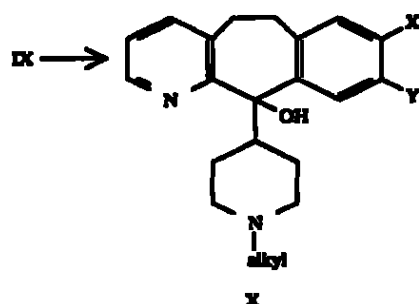
which in turn is hydrolyzed, e.g. with base such KOH, to the ortho-phenethyl pyridine carboxylic acid of formula VIII



The compound of formula VIII can be cyclized, e.g., with oxalyl chloride and aluminum trichloride, to a compound of formula IX

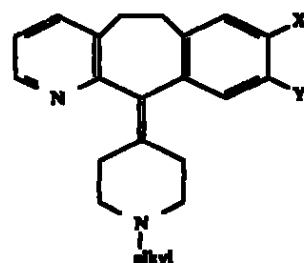


which is reacted with, for example, a Grignard reagent prepared from a 4-halo-N-alkyl-piperidine to produce the compound of formula X



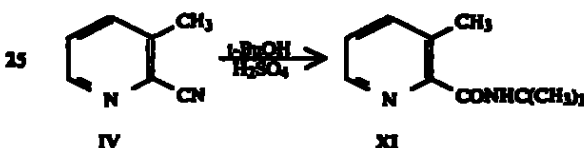
which in turn is dehydrated, e.g., by acid such as polyphosphoric acid or sulfuric acid, to the compound of formula III:

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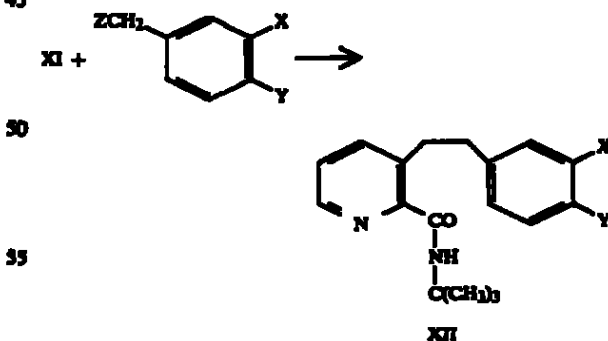
The compound of formula IX may also be reacted with Na in liquid NH_3 and a 4-halo-N-alkyl-piperidine to produce the compound of formula X.

In an alternative method 2-cyano-3-methylpyridine can be reacted in a Ritter reaction with a tertiary butyl compound in an acid such as concentrated sulfuric acid or concentrated sulfuric acid in glacial acetic acid to form a compound of formula XI



Suitable tertiary butyl compounds include, but are not limited to, t-butyl alcohol, t-butyl chloride, t-butyl bromide, t-butyl iodide, isobutylene or any other compound which under hydrolytic conditions forms t-butyl carboxamides with cyano compounds. The temperature of the reaction will vary depending on the reactants, but generally the reaction is conducted in the range of from about 90° C. to about 100° C. with t-butyl alcohol. The reaction may be performed with inert solvents but is usually run neat.

The product of the Ritter reaction (formula XI) can be reacted with an appropriate 3 and/or 4-halo or trifluoromethyl-substituted benzyl halide, in the presence of a base to form the compound of formula XII

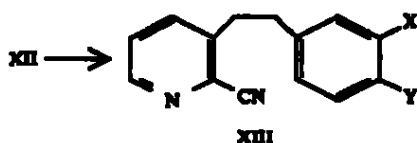


wherein Z is chloro, bromo or iodo. Examples of appropriate benzyl halides include, but are not limited to, 3-chloro-benzyl chloride, 3-fluoro-benzyl bromide, 3,4-dichloro-benzyl chloride, 4-fluoro-benzyl chloride, 3-trifluoromethyl-benzyl chloride, 3-bromobenzyl chloride, etc. Any suitable base can be employed e.g., an alkyl lithium compound such as n-butyl lithium in tetrahydrofuran (THF). Preferably the base has a pK_a of greater than 20 and more preferably greater than 30.

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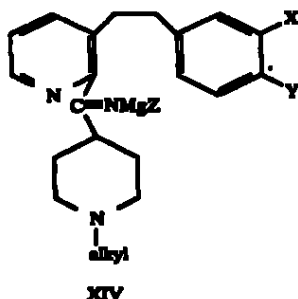
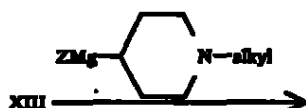
This reaction can be conducted at any suitable temperature, e.g., temperatures of from about -78°C . to about 30°C ., preferably from about -40°C . to about -30°C . The reaction can be performed in any suitable inert solvent such as THF, diethyl ether, etc.

The tertiary-butyl amide of formula XII can be converted to the cyano compound of formula XIII



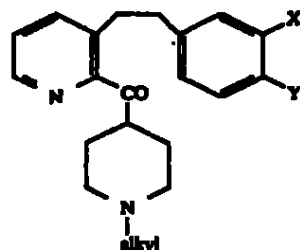
by the use of a suitable dehydrating agent such as POCl_3 , SOCl_2 , P_2O_5 , toluene sulfonyl chloride in pyridine, oxalyl chloride in pyridine, etc. This reaction can be performed in the absence of or with a co-solvent such as xylene. The dehydrating agent such as POCl_3 is employed in equivalent amounts or greater and preferably in amounts of from about 2 to about 15 equivalents. Any suitable temperature and time can be employed for performing the reaction, but generally heat is added to speed up the reaction. Preferably, the reaction is performed at or near reflux.

The cyano compound of formula XIII can then be reacted with a Grignard reagent prepared from the appropriate 1-alkyl-4-halopiperidine. This reaction is generally performed in an inert solvent such as an ether, toluene or tetrahydrofuran. This reaction is performed under the general conditions for a Grignard reaction, e.g., at temperatures of from about 0°C . to about 75°C . The resulting compound of formula XIV



(wherein Z is again chloro, bromo or iodo) is hydrolyzed, e.g., by reaction with aqueous acid such as aqueous HCl to prepare the corresponding ketone of formula XV

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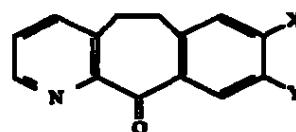
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The compound of formula XV can be ring-closed to form the desired cycloheptene ring system by treating the compound XV with a super acid having a Hammett acidity function of less than about minus 12, e.g., minus 13, minus 14, etc., to produce a compound of formula IX. This measure of acidity is defined in Hammett, Louis P., and Deyup, Alden J., *Journal of the American Chemical Society*, Vol. 54, 1932, p. 2721. Suitable super acids for this purpose include, for example, HF/BF_3 , $\text{CF}_3\text{SO}_3\text{H}$, $\text{CH}_3\text{SO}_3\text{H}/\text{BF}_3$, etc. The reaction can be performed in the absence of or with an inert co-solvent such as CH_2Cl_2 . The temperature and time of the reaction vary with the acid employed. For example, with HF/BF_3 as the super acid system the temperature may be controlled so as to minimize side reactions, such as HF addition to the double bond of the rings. For this purpose, the temperature is generally in the range of from about $+5^{\circ}\text{C}$. to -50°C ., preferably from about -30°C . to -35°C . With $\text{CF}_3\text{SO}_3\text{H}$ as the super acid system, the reaction may be run at elevated temperatures, e.g., from about 25°C . to about 150°C . and at lower temperatures but the reaction then takes longer to complete.

Generally the super acid is employed in excess, preferably in amounts of from about 1.5 to about 30 equivalents. For example, with HF/BF_3 as the super acid system the molar ratio of HF to the compound of formula XV in the reaction mixture is preferably from about 30 to about 1.5, more preferably 2.5 to 1.5. In such system, the molar ratio of BF_3 to the compound of formula XV in the reaction mixture is preferably from about 15 to about 0.75, more preferably from about 1 to about 0.75.

As another alternative, a compound of formula XII above can be cyclized by use of super acid such as $\text{CF}_3\text{SO}_3\text{H}$ or HF/BF_3 to produce a compound of formula IX.



The compounds of formula IX may then be converted to the desired compounds of the invention as described above.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubi-

lizers, lubricants, suspending agents, binders or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active compound. In the tablet the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 5 to about 20 percent of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethyl-cellulose, a low melting wax, cocoa butter and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by adding the active component in water and adding suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit. Alternately, sufficient solid may be provided so that after conversion to liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of the liquid form preparation as with a syringe, teaspoon or other volumetric container. When multiple liquid doses are so prepared, it is preferred to maintain the unused portion of said liquid doses at low temperature (i.e., under refrigeration) in order to retard possible decomposition. The solid form preparations intended to be converted to liquid form may contain, in addition to the active material, flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents and the like. The solvent utilized for preparing the liquid form preparation may be water, isotonic water, ethanol, glycerine, propylene glycol and the like as well as mixtures thereof. Naturally, the solvent utilized will be chosen with regard to the route of administration, for example,

liquid preparations containing large amounts of ethanol are not suitable for parenteral use.

The composition of the invention may also be deliverable transdermally, e.g., with a transdermally acceptable carrier. The transdermal compositions can take the form of creams, lotions and/or emulsions, can be included in an appropriate adhesive for application to the skin or can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably, the transdermally acceptable composition is utilized to prepare a "reservoir type" or "matrix type" patch which is applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of a compound of formula I through the skin. Most preferably, the patch of the invention will be worn for a period of about 24 hours and provide a total daily dosage of about 1 mg to about 40 mg, preferably from about 5 mg to about 10 mg, of a compound of the invention. The patch may then be replaced if necessary with a fresh patch, thereby providing a constant blood level of a compound of formula I to the patient in need thereof.

The utilization of this new transdermal dosage form and its prescribed regimen will provide the advantages described above. Other frequencies of dosage application are anticipated, for example, a once every 3 day frequency or a once every 7 day frequency. Although a once a day dosage regimen may be preferred, it is not intended that the invention be limited to any particular regimen.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, for example, packeted tablets, capsules and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet or tablet itself or it can be the appropriate number of any of these packaged forms.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to 1000 mg according to the particular application. The compositions can, if desired, also contain other therapeutic agents, such as decongestants.

The dosages may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The compounds of the invention possess antihistaminic properties. The antihistaminic properties of these compounds may be demonstrated by use of standard pharmacological testing procedures. For example, the ability of the compounds to reduce histamine-induced paw edema in mice may be measured by use of the following method.

Male CF_1 mice, 25-30 g, are housed under conditions of controlled temperature and humidity with a 12 hour dark/light cycle. Food and water are allowed ad libitum. The mice are randomly assigned to the treatment groups. One hour after treatment with a compound of the invention or vehicle, the mice are lightly anesthetized with ether. The left hind paw of each mouse serves as a control and is injected with 25 μ l of isotonic saline. The right hind paw serves as the experimental

paw and is injected with 25 μ l of isotonic saline containing 13 μ g histamine dihydrochloride. Thirty minutes later the mice are killed by cervical dislocation and both hind paws of each mouse are removed by cutting at the tarsal joint. The weight of each paw is recorded and the difference in weight between the compound-treated and the placebo-treated groups is evaluated using Student's "t" test. The ED₅₀ values (the dose causing 50% inhibition of histamine-induced edema) and 95% confidence limits are determined by the Linear Least Square Dose-Response method [Brownlee, K. A., "Statistical Theory And Methodology In Science and Engineering", 2nd Ed., J. Wiley and Sons, New York, 1965, pp. 346-349]. The compounds of 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[3,6]cyclohepta[1,2-b]pyridine (Compound A) and 8-fluoro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[3,6]cyclohepta[1,2-b]pyridine (Compound B) were tested by this procedure with the results shown in Table 1 below:

TABLE 1

Treatment	Oral Dose mg/kg	No. of Animals	Increased Paw Weight (mg) Mean	% Inhibition	Oral ED ₅₀ (mg/kg)
Placebo	—	7	22.3	—	—
Compound A	0.03	8	19.9	11	0.15
	0.1	7	13.0	42	
	0.3	8	6.1	73	
	1.0	8	2.5	89	
Compound B	—	—	—	—	<3

Compounds A and B were also tested for antihistaminic activity by the procedures set forth in paragraph A below and for CNS activity by the procedures set forth in paragraphs B, C, and D below.

A. Prevention of histamine-induced lethality in guinea pigs. Compounds A and B were evaluated for their ability to protect female albino guinea pigs (250-350 g) against death induced by the intravenous injection of histamine dihydrochloride at 1.1 mg/kg, which is approximately twice the LD₅₀. Doses of the antagonists were administered orally to separate groups of fasted animals 1 hour prior to the challenge with histamine and protection from death recorded for 30 minutes after histamine. ED₅₀ values were determined for each drug by probit analysis.

B. Antagonism of Physostigmine Lethality. The physostigmine-induced lethality test used was a modification of the technique reported by COLLIER et al., *Dr. J. Pharmac.*, 32, 295-310 (1968). Physostigmine salicylate (b 1.0 mg/kg s.c.) produces 100% lethality when administered to mice grouped 10 per plastic cage (11×26×13 cm). Test agents were administered orally 30 minutes prior to physostigmine. The number of survivors were counted 20 minutes after physostigmine administration.

C. Antagonism of Acetic Acid Writhing. The acetic acid writhing test used was essentially that described by HENDERSHOT and FORSAITH, *J. Pharmac. Exp. Ther.*, 125, 237-240 (1959), except that acetic acid rather than phenylquinone was used to elicit writhing. Mice were injected with 0.6% aqueous acetic acid at 10 mg/kg i.p. 15 minutes after oral administration of the test drug. The number of writhes for each animal was counted during a 10 minute period starting 3 minutes after acetic acid treatment. A writhing was defined as a sequence of arching of the back, pelvic rotation and hind limb extension.

D. Antagonism of Electro-Convulsive Shock (ECS). For the ECS test, a modification of the method of

TOMAN et al., *J. Neurophysiol.*, 9, 231-239 (1946), was used. One hour after oral administration of the test drug or vehicle, mice were administered a 13 mA, 60 cycle a.c. electroconvulsant shock (ECS) for 0.2 seconds via corneal electrodes. This shock intensity produces tonic convulsions, defined as extension of the hind limbs, in at least 95% of vehicle-treated mice.

Of the above test procedures for measuring CNS activity of antihistamines, the physostigmine-induced lethality test is believed to be a major index of non-sedating characteristics, since it reflects mainly central anticholinergic potency which is believed to contribute to sedative activity.

The results from the above test procedures are set forth in Table 2 below:

TABLE 2

Antihistamine Activity	CNS Activity			
	A. G. pig.	B. Physostigmine	C. Acetic	D. ECS
Compound	p.o. ED ₅₀ (mg/kg)	lethality ED ₅₀ (mg/kg)	writhing ED ₅₀ (mg/kg)	test ED ₅₀ (mg/kg)
A	0.15	320	147	160
B	.59	320	320	320

The above results demonstrate that the compounds of the invention are a potent antihistamines having low CNS activity indicative of non-sedation. Specifically, Compounds A and B are relatively inactive in all of the CNS test procedures, and in particular, they provide an ED₅₀ in the physostigmine-induced lethality test of greater than 320.

Compound A was also tested to assess its sedative effects in another procedure:

Acute behavioral, neurologic and autonomic effects of Compound A were evaluated in mice by a modification of the method of Irwin S., *Drug Screening And Evaluation Of New Drugs In Animals*, in *Animal And Clinical Pharmacologic Techniques In Drug Evaluation*, Nodine JM and Siegler PE (Eds.), Year Book Medical Publishers Inc., Chicago 1964, pp 36-54]. After oral administration of vehicle or drug, mice (CFI males, 20-24 g) were observed and manipulated to evaluate behavioral, neurologic and autonomic changes. A semi-quantitative scoring scale was used where signs normally present (e.g., spontaneous activity, alertness, pupil size) were assigned a "normal" score of 0 and scores of +1, +2 and +3 indicated slight, moderate and marked increases and scores of -1, -2 and -3 indicated slight, moderate and marked decreases from "normality". When a sign occurred that is not normally present (e.g., convulsions, tremors), its magnitude was graded on a 1-3 scale. Each treatment group consisted of 6 animals and evaluations were conducted 1 hour after dosing. Additional observations for lethality were made for up to 24 hours after dosing. Incidence is de-

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fined as the observation occurring in an animal with a score of 2 or greater according to the scoring method defined above.

Effects of Compound A on behavior, neurologic function and autonomic function in mice	
Measurement	MED, mg/kg po*
Lethality	300
Reactivity	300
Decreased motor activity	300
Decreased muscle tone	300
Tremors/convulsions	300
Ataxia	300
Mydriasis	300
Piloils	300

*Minimal effective dose, defined as the lowest dose that produced a score of 2 or greater according to tests (supra) in at least 3 of 6 animals tested at each dose.

From the above test results, it may be concluded that the compounds of the invention would be essentially non-sedating at a clinically useful antihistaminic dosage. Compound B (i.e., the 8-fluoro compound) is particularly preferred because it has also shown very low toxicity.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptom being treated. A typical recommended dosage regimen is oral administration of from 5 to 100 mg/day, preferably 10 to 20 mg/day, in two to four divided doses to achieve relief of the symptoms.

The following examples are intended to illustrate, but not to limit, the present invention.

EXAMPLE I

A.

N-(1,1-Dimethylethyl)-3-methyl-2-pyridine carboxamide

2-cyano-3-methyl pyridine (400 g) is suspended in t-BuOH (800 mL) and the mixture heated to 70° C. Concentrated sulphuric acid (400 mL) is added dropwise over 45 minutes. The reaction is complete after a further 30 minutes at 75° C. The mixture is then diluted with water (400 mL), charged with toluene (600 mL) and brought to pH 10 with concentrated aqueous ammonia. The temperature is kept at 50°-55° C. during the work up. The toluene phase is separated, the aqueous layer reextracted and the combined toluene phases are washed with water. Removal of the toluene yields an oil, N-(1,1-dimethylethyl)-3-methyl-2-pyridine carboxamide, from which solid product may crystallize. Product yield of 97% is determined by internal standard assay on gas chromatograph.

B.

3-[2-(3-Fluorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide

Tetrahydrofuran (125 mL) and N-(1,1-dimethylethyl)-3-methyl-2-pyridine carboxamide (1 equivalent) are charged and cooled to -40° C. under nitrogen. Two equivalents of n-butyllithium are then added over 40 minutes. When half the n-butyllithium is added the mixture turns purple. Sodium bromide (1.3 g) is added and then 3-fluoro-benzyl bromide (1.05 equivalents) is added dropwise (1:1 solution in tetrahydrofuran) over

40-50 minutes while the temperature is maintained at -40° C. After 30 minutes at -40° C., the mixture is diluted with water (250 mL) and the organic phase separated. This phase is dried over sodium sulphate and the solvent removed yielding an oil from which solid product, 3-[2-(3-fluorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide, may crystallize.

C.

3-[2-(3-Fluorophenyl)ethyl]-2-pyridine-carbonitrile

A solution of 3-[2-(3-fluorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide (36.4 g, 0.121 mole) in 123 mL (202.3 g, 1.32 mole) of phosphorous oxychloride is heated at 110° C. for 3.5 hours and stirred at ambient temperature an additional 15 hours. The reaction is quenched with ice and water and the pH of the solution is brought to 8 by the addition of a saturated aqueous solution of potassium carbonate. The product is extracted into ethyl acetate and the solution is concentrated to a residue. Following purification by silica gel chromatography and trituration with pentane, 16.2 g (0.072 mole) of product is obtained in 60% yield.

D.

(1-Methyl-4-piperidinyl)[3-[2-(3-fluorophenyl)ethyl]-2-pyridinyl]methanone

To a solution of 3-[2-(3-fluorophenyl)ethyl]-2-pyridine carbonitrile (28.0 g, 0.123 mole) in 150 mL of dry THF is added 92 mL (1.48 moles/liter, 0.136 mole) of N-methylpiperidyl magnesium chloride over 10 minutes maintaining the temperature of 45°-50° C. The reaction is maintained at 40° C. to 50° C. for another 10 minutes and at ambient temperature for 45 minutes. The reaction is quenched to below pH 2 and aqueous hydrochloric acid and the resulting solution is stirred at 25° C. for 1 hour. The pH of the solution is adjusted to about 8, the product is extracted with ethylacetate, and the solution is concentrated to a residue. Following purification by silica gel chromatography, 38.3 g of product is obtained as a brown oil.

E.

8-Fluoro-11-(1-methyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

A solution of (1-methyl-4-piperidinyl)[3-[2-(3-fluorophenyl)ethyl]-2-piperidinyl]methanone (15.0 g, 0.046 mole) in 74 mL (125.5 g, 0.837 mole) of trifluoromethanesulfonic acid is stirred at ambient temperature for 18 hours. The reaction is quenched with ice-water and the solution made basic with potassium hydroxide. The product is extracted into ethyl acetate. The ethyl acetate solution is filtered to remove insolubles and the filtrate is concentrated to a residue. Following purification by silica gel chromatography, 5.4 g (0.0175 mole) of product is obtained in 38% yield.

F.

8-Fluoro-11(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

To a stirred solution of 8-fluoro-11-(1-methyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (10.5 g, 34 mmol) and triethylamine (5.2 g, 52 mmol) in dry toluene (120 mL) at 80° C. under an argon atmosphere, was added ethylchloroformate (18.5 g, 170 mmol) via a syringe. The reaction mixture was allowed to stir at this temperature for 30 minutes

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and at room temperature for one hour. The reaction mixture was then filtered and solvent was removed. The residue was triturated with pentane to give 10.1 grams (yield=81%) of the title compound, m.p.=116°-118° C.

G.

8-Fluoro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]cyclohepta[1,2-b]pyridine

8-Fluoro-11-(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (3.6 g, 9.8 mmol.) was refluxed with KOH (4.5 g) in 50 mL of ethanol/water (1:1) for 66 hours under an argon atmosphere. The reaction mixture was poured into a brine solution and extracted twice with ethyl acetate. The extracts were combined and then dried over Na₂SO₄ and filtered. Solvent was removed to give 2.76 grams (yield=95%) of the title compound, m.p.=133.5°-134.5° C.

EXAMPLE II

A.

3-[2-(3-Fluorophenyl)ethenyl]-picolinamide

A solution of 2-cyano-3-picoline (142 g, 1.2 mole) and 3-fluorobenzaldehyde (164 g, 1.32 mole) in 750 mL of dry tetrahydrofuran (THF) is prepared. This solution is added dropwise to a solution of 162.0 grams of potassium *t*-butoxide (1.44 mole) dissolved in 750 mL of dry THF at -15° C. to -20° C.

The addition requires $\frac{1}{2}$ hour, and the temperature is maintained below -15° C. The mixture is stirred at -15° to -20° C. for 1 hour, then at 0° to 5° C. for 2 hours.

Saturated NH₄Cl solution (400 mL) is added to the mixture followed by 250 mL of H₂O. The mixture is stirred for $\frac{1}{2}$ hour, and the aqueous layer is separated and extracted with 300 mL of CH₂Cl₂, which is combined with the THF layer. The organic solution is washed with 400 mL of saturated NH₄Cl solution, dried over Na₂SO₄, treated with charcoal and filtered through diatomaceous earth.

The solvent is removed on a rotary evaporator, and the oily residue is dissolved in 350 mL of boiling toluene. The mixture is filtered hot to remove impurities and cooled overnight at 0° to 5° C. The off-white solid that precipitates is filtered, washed twice with 100 mL of cold toluene, and dried at 60° C. for 6 hours, yielding 122.1 grams (42.1%) of the title compound, m.p.=133°-135° C.

B.

3-[2-(3-Fluorophenyl)ethenyl]-picolinamide

A solution is prepared by dissolving 121 grams of 3-[2-(3-fluorophenyl)ethenyl]-picolinamide (0.5 mole) in 300 mL of acetic acid. To the solution is added 8.0 grams of 5% Pd/C and the mixture is placed on a Parr hydrogenator overnight. A theoretical amount of H₂ is absorbed, and mixture is filtered through diatomaceous earth and poured into 4 liters of H₂O. The off-white suspension is stirred for 2 hours and cooled at 0° to 5° C. for 20 hours.

The solid product 3-[2-(3-fluorophenyl)ethenyl]-picolinamide is filtered and washed three times with 100 mL of H₂O and dried at 60° C. for 20 hours, yielding 108 grams (yield=88.6%) of the title compound, m.p.=102°-104° C.

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C.

3-[2-(3-Fluorophenyl)ethenyl]-picolinic acid

A suspension of 73.2 grams of 3-[2-(3-fluorophenyl)ethenyl]-picolinamide (0.3 mole) in 500 mL of ethanol and 125 grams of 45% KOH (1.0 mole) is prepared. H₂O (200 mL) is added, and the mixture is refluxed for 20 hours. TLC shows complete conversion to the acid.

The alcohol is removed by distillation until the vapor temperature reaches 100° C. The suspension is cooled to room temperature, 100 mL of H₂O is added and the solution is brought to a pH of 4-4.5 with 12N HCl (110 mL). The suspension is stirred for 1 hour and cooled overnight. The solid is filtered, washed three times with 100 mL of H₂O and dried at 65° C. for 24 hours, yielding 69.6 grams (yield=94.8%) of the title compound, m.p.=118°-122° C.

D.

8-Fluoro-6,11-dihydro-5H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-one

A solution of 61.3 grams of 3-[2-(3-fluorophenyl)ethenyl]-picolinic acid (0.25 mole) in 900 mL of tetrachloroethane is prepared. Anhydrous HCl gas is passed through the solution at room temperature for $\frac{1}{2}$ hour. Oxalylchloride (48.3 grams, 0.38 mole) is carefully added, and stirred for 24-26 hours at room temperature (slight heating at 35°-40° C. for 4 hours is needed to obtain a dark solution). The solution is cooled to 0°-5° C., and 67 grams of AlCl₃ (0.5 mole) are slowly added over $\frac{1}{2}$ hour. The mixture is stirred at 0° to 5° C. for 18 hours. An additional 17 grams of AlCl₃ (0.125 mole) is added, and mixture is stirred for 2 hours.

Then 500 mL of 3.7% HCl is added, and the mixture is stirred for $\frac{1}{2}$ hour and filtered through diatomaceous earth. The top aqueous layer is separated, and the organic layer is washed twice with 500 mL of 3.7N HCl. The combined aqueous layer is washed twice with 500 mL of ether.

Benzene (1 liter) is added. The mixture is cooled to 5°-10° C. and brought to pH>9 with slow addition of 390 grams of 50% NaOH. The mixture is stirred for $\frac{1}{2}$ hour and filtered through diatomaceous earth. The aqueous layer is separated and washed twice with 300 mL of benzene, which are combined with the first benzene layer.

The combined organic layers are washed with 250 mL of 5% NaHCO₃ and 250 mL of saturated NaCl solution. The organic layer is dried over Na₂SO₄, and solvent is removed leaving 49.6 grams of a yellow solid. The solid is dissolved in 100 mL of butyl acetate (hot) and cooled for 24-48 hours at 0° to 5° C. The solid is filtered, washed twice with 30 mL of cold ethyl acetate, and dried at 60° C. for 20 hours, yielding 38.8 grams (yield=68.5%) of the title compound, m.p.=116°-119° C.

E.

1-Methyl-4-[8-fluoro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]piperidin-11-OL

A suspension is prepared by mixing 22.7 grams of 11-oxo-8-fluoro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (0.1 mole) with 500 mL of liquid NH₃, and 5.1 grams of Na (0.22 mole) are added. The resulting blue mixture is stirred for $\frac{1}{2}$ hour. A solution containing 15.9 grams of 4-chloro-N-methyl-piperidine (0.12 mole)

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in 400 mL of dry THF is slowly added over $\frac{1}{2}$ hour and stirred for 2 hours at -25°C .

NH_4Cl (17.5 grams, 0.33 mole) is added, and the mixture is stirred for $\frac{1}{2}$ hour until the mixture warms to 0°C . Saturated NH_4Cl solution (200 mL) is added, followed by 50 mL of H_2O , and mixture is stirred for $\frac{1}{2}$ hour.

The aqueous layer is separated and extracted with 200 mL of CH_2Cl_2 , which is combined with the THF layer. The combined organic layer is washed with 250 mL of saturated NH_4Cl solution, and dried over Na_2SO_4 . The solvent is removed, leaving 34.7 grams of an oil, which crystallizes upon cooling.

The solid material is dissolved in 65 mL of hot *n*-butyl acetate and cooled overnight. The solid obtained is filtered, washed twice with 15 mL of cold ethyl acetate, and then dried at 75°C for 6 hours, yielding 15.8 grams of the title compound, m.p. = $123.5^{\circ}\text{--}125^{\circ}\text{C}$.

The solvent is removed from the filtrate, leaving 11.0 grams of a yellow solid, which is dissolved in 20 mL boiling ethyl acetate, filtered hot, and cooled at $0^{\circ}\text{--}5^{\circ}\text{C}$ for 4 hours. The solid obtained is filtered, washed twice with 5 mL of ethyl acetate, and dried at 60°C for 5 hours, yielding 4.3 grams (total yield = 61.7%).

F.

8-Fluoro-11-(1-methyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

A solution of 13.1 grams of 1-methyl-4-[8-fluoro-6,11-dihydro-11-hydroxy-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]piperidine (0.04 mole) in 40 mL of 93% H_2SO_4 is prepared. The solution is stirred overnight at room temperature. CH_2Cl_2 (200 mL) is added, and with external cooling, the mixture is neutralized to $\text{pH} > 9$ using 50% NaOH , while maintaining the temperature below 30°C . The aqueous layer is separated and re-extracted twice with 150 mL of CH_2Cl_2 , which is combined with the first layer. The combined organic layer is washed with 150 mL of saturated NaHCO_3 solution and 150 mL of saturated NaCl solution, dried over Na_2SO_4 , treated with charcoal and filtered through diatomaceous earth. The solvent is removed on a rotary evaporator leaving 12.9 grams of a yellow oil, which solidified upon standing.

The oil is dissolved in 70 mL of hot diisopropyl ether (6 parts) and poured into a hot solution of 9.5 grams of maleic acid (0.082 mole) dissolved in 60 mL of diisopropyl ether. The solution is cooled to $0^{\circ}\text{--}5^{\circ}\text{C}$ with stirring and a yellow oil forms. The mixture is cooled overnight at $0^{\circ}\text{--}5^{\circ}\text{C}$ with a yellow solid forming. The solid is filtered, washed twice with 20 mL of cold diisopropyl ether, and dried at 60°C for 4 hours, yielding 18.2 grams.

This solid is dissolved in 2 parts boiling diisopropyl ether and filtered hot. The filtrate is cooled at $0^{\circ}\text{--}5^{\circ}\text{C}$ with stirring for 1 hour with a heavy white precipitate forming. The suspension is cooled at $0^{\circ}\text{--}5^{\circ}\text{C}$ for 6 hours. The solid formed is filtered, washed three times with 15 mL of cold diisopropyl ether and dried at $75^{\circ}\text{--}80^{\circ}\text{C}$ for 48 hours, yielding 15.6 grams (yield = 72.2%) of the title compound, m.p. = $151^{\circ}\text{--}152^{\circ}\text{C}$.

The product of step F above can then be employed in the process described in Example 1.F. and 1.G. to provide 8-fluoro-11-(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

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and 8-fluoro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, respectively.

EXAMPLE III

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine acetic acid salt

To 12 grams of sodium hydroxide in 30 mL ethyl alcohol (70%) add 6 grams of 8-chloro-6,11-dihydro-11-(1-ethoxy-carbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (prepared as described in U.S. Pat. No. 4,282,233) and reflux with stirring for 24 hours. After about the first 6-8 hours an additional 30 mL of 70% ethyl alcohol may be added.

Remove about 50% of the solvent by distillation in vacuo. Add a small amount of ice water and acidify with glacial acetic acid.

Extract with chloroform (6-8 $\times$), since the product precipitates from the acetic acid solution as a thick emulsion which cannot be filtered.

Concentrate the chloroform extracts to a small volume and precipitate the product with hexane. Crude m.p. $197^{\circ}\text{--}200^{\circ}\text{C}$.

Recrystallize from benzene-hexane to obtain the product, m.p. $199^{\circ}\text{--}200^{\circ}\text{C}$. Yield 4.0-4.5 grams.

EXAMPLE IV

B.

3-[2-(3-Chlorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide

31.5 g of N-(1,1-dimethylethyl)-3-methyl-2-pyridine carboxamide (e.g., as prepared in step A of Example I above) is dissolved in 600 mL of dry tetrahydrofuran and the resulting solution is cooled to -40°C . Two equivalents of *n*-butyllithium in hexane are added while the temperature is maintained at -40°C . The solution turned deep purple-red. 1.6 g of sodium bromide is added and the mixture is stirred. A solution of 26.5 g (0.174 mole) *m*-chlorobenzylchloride in 125 mL of tetrahydrofuran is added while the temperature is maintained at -40°C . The reaction mixture is stirred until the reaction is complete as determined by thin layer chromatography. Water is added to the reaction until the color is dissipated. The reaction mixture is extracted with ethyl acetate, washed with water, and concentrated to a residue. A yield of 92% for the product is shown by chromatography.

C.

3-[2-(3-Chlorophenyl)ethyl]-2-pyridine-carbonitrile

A solution of 3-[2-(3-chlorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide (175 g, 0.554 mole), in 525 mL (863 g, 5.63 mole) of phosphorous oxychloride is heated at reflux for 3 hours. Completion of the reaction is determined by thin layer chromatography. Excess phosphorous oxychloride is removed by distillation at reduced pressure and the residue is quenched into a mixture of water and isopropanol. The pH is brought to 5-7 by addition of 50% aqueous sodium hydroxide solution while maintaining the temperature below 30°C . The crystalline slurry of crude product is filtered and washed with water. Crude product is purified by slurrying the wet cake in hot isopropanol followed by cooling at $0^{\circ}\text{--}5^{\circ}\text{C}$. The product is filtered, washed with hexane and dried at below 50°C . Yield: 118 g (HPLC purity 95.7%), m.p. $72^{\circ}\text{--}73^{\circ}\text{C}$, 89.4% of theory.

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D.

(1-Methyl-4-piperidinyl)[3-[2-(3-chlorophenyl)ethyl]-2-pyridinyl]methanone hydrochloride

To a solution of product of Step C above (118 g, 0.487 mole) in 1.2 L of dry tetrahydrofuran is added 395 mL (2.48 mole/liter, 0.585 mole, 1.2 eq.) of N-methyl-piperidyl magnesium chloride over about 15 minutes maintaining the temperature at 45° C.-50° C. by cooling with water as necessary. The reaction is maintained at 40° C. to 50° C. for about another 30 minutes. Completion of the reaction is determined by thin-layer chromatography. The reaction is quenched to pH below 2 with 2N hydrochloric acid and the resulting solution is stirred at about 25° C. for 1 hour. The bulk of the tetrahydrofuran is removed by distillation and the resulting solution is adjusted to pH 3.5 by the addition of aqueous sodium hydroxide. After cooling to 0° to 5° C., the crystalline hydrochloride salt product is filtered off, washed with ice cold water and dried to constant weight at 60° C. Yield: 168.2 g (HPLC purity 94%), m.p. 183°-185° C., 89% of theory.

E.

8-Chloro-6,11-dihydro-11-(1-methyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

To a solution of a product of Step D above (59 g, 0.15 mole) in 120 mL (120 g, 6.0 mole) of hydrofluoric acid at -35° C. is added boron trifluoride (44.3 g, 0.66 mole) over 1 hour. Completeness of the reaction is determined by thin-layer chromatography. The reaction is quenched using ice, water and potassium hydroxide to a final pH of 10. The product is extracted into toluene and the toluene solution is washed with water and brine. The toluene solution is concentrated to a residue, which is dissolved in hot hexane. Insolubles are removed by filtration and the filtrate is concentrated to an off-white powder. Yield: 45.7 g (HPLC purity: 96%), 92% of theory.

Alternative Step E**8-Chloro-6,11-dihydro-11-(1-methyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine**

A solution of 177 g (0.49 mole) of a product of Step D above in 480 mL (814.1 g, 5.31 mole) of trifluoromethanesulfonic acid at 90°-95° C. for 18 hours under nitrogen. Completeness of the reaction is determined by thin-layer chromatography. The cooled reaction is quenched with ice-water and the pH is adjusted to 6 with barium carbonate. The product is extracted into methylene chloride, which is concentrated under reduced pressure to about 1 liter and washed with water. The product is extracted into 1N hydrochloric acid, which is treated with 30 g of Darco, and filtered through celite. The pH of the filtrate is adjusted to 10 with 50% aqueous sodium hydroxide and the product is extracted into methylene chloride, which is removed under reduced pressure. The residue is dissolved in hot hexane, which is filtered to remove insolubles. The filtrate is concentrated to a residual beige powder. Yield: 126 g (HPLC purity 80%), 65% of theory.

EXAMPLE V**8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine**

The acetic acid salt prepared as in Example II is dissolved in a minimum amount of water and the solu-

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tion is made basic with a dilute aqueous solution of potassium carbonate. A pink colored oil separates.

Extract the organic material with chloroform, wash with water and remove the solvent. Triturate the residue with hexane. Recrystallize from a large volume of hexane after charcoal decolorization to obtain the product, m.p. 151°-152° C.

EXAMPLE VI**8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine**

A.

8-chloro-6,11-dihydro-11-(1-cyano-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

Dissolve 16.2 grams (0.05 mole) of 8-chloro-6,11-dihydro-11-(1-methyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (prepared by the methods described in U.S. Pat. No. 3,326,924) in 300 mL of dry benzene. To this solution, add slowly under nitrogen a solution of cyanogen bromide (6.4 g) dissolved in 75 mL of benzene. Allow this mixture to stir at room temperature overnight (approximately 20 hours).

Filter the solution, and concentrate the filtrate in vacuo to a small volume and precipitate the product by the addition of petroleum ether or hexane until precipitation is complete. Filter and recrystallize from ethanol/water to yield the product 15 grams (89%), m.p. 140°-142° C.

Anal. Calcd. for $C_{20}H_{18}N_2Cl$: C, 71.53; H, 5.40; N, 12.51. Found, C, 71.73; H, 5.43; N, 12.27.

B.

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

A solution of 14 grams of the N-cyano compound from part A in 60 mL of concentrated hydrochloric acid, 600 mL of glacial acetic acid and 400 mL of water is refluxed with stirring for 20 hours. The solvents are removed in vacuo and the residue dissolved in water and neutralized with ammonium hydroxide. The material is extracted several times with chloroform, the chloroform extracts washed with water and concentrated to dryness, and the residue triturated with petroleum ether or hexane to yield 11.5 grams (93%) m.p. 149°-151° C. After recrystallization from hexane, the product melts at 150°-151° C.

Anal. Calcd. for $C_{19}H_{19}N_2Cl$: C, 73.42; H, 6.16; N, 9.01. Found: C, 73.19; H, 6.14; N, 8.91.

EXAMPLE VII

A.

N-(1,1-dimethylethyl)-3-[2-(4-fluorophenyl)ethyl]-2-pyridine carboxamide

To a cooled (-40° C.) solution of N-(1,1-dimethylethyl)-3-methyl-2-pyridinecarboxamide (38.4 g, 0.2 mole) in dry THF (250 mL) is added n-butyl lithium (185 mL, 0.44 mole). Then sodium bromide (1.9 g, 18 mmol) is added and is allowed to stir for 15 minutes. 4-Fluorobenzoylchloride (31.8 g, 0.22 mole) was added and the reaction is allowed to stir for 2½ hours while warming up to -5° C. The reaction is then quenched with water and the product is extracted twice with ethyl acetate followed by washing twice with brine. The organic phase is dried over Na_2SO_4 , filtered and

solvent is removed to give desired compound (60.0 g) in 99% yield, m.p. 59°-61° C.

By a similar procedure, the corresponding 3-fluorophenyl, 3,4-dichlorophenyl, 3-bromophenyl, 4-chlorophenyl and 3,4-dibromophenyl analogs can be prepared by employing the appropriate substituted benzyl chloride.

B.

3-[2-(4-Fluorophenyl)ethyl]-2-pyridine-carbonitrile

The product of previous Step A (60.0 g, 0.2 mole) in POCl_3 (200 mL) is heated at 110° C. under an argon atmosphere for 3½ hours. The reaction mixture is poured onto ice and basified with 50% NaOH solution. It is then extracted three times with ethyl acetate, washed with water and brine, and dried over Na_2SO_4 . Solvent is removed and the residue is passed through a coarse SiO_2 (60-200 mesh) column to give the desired product as a white solid (40 g) in 88% yield, m.p. 48°-49° C.

C.

9-Fluoro-5,6-dihydro-(1H)-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one

The product of Step B hereof (31.5 g, 139 mmol) is cyclized in polyphosphoric acid (1.24 kg) at 200° C. for 5½ hours. The hot reaction is poured into ice and then basified with 50% NaOH solution. The product is extracted three times with CHCl_3 and then washed with brine. The organic phase is dried (Na_2SO_4), filtered, and solvent is removed to give the desired product (20.4 g) in 64% yield, m.p. 78°-81° C. after recrystallization from diisopropyl ether.

D.

9-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinyl)-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-OL

A solution of the product of previous Step C above (10.0 g, 44 mmol) in THF (100 mL) is added slowly to a cooled (-40° C.) solution of the Grignard reagent prepared from N-methyl-4-chloro-piperidine (57.9 mL, 88 mmol) in THF (70 mL). This is allowed to stir for about 1 hour while warming up to 0° C. The reaction is then quenched with NH_4Cl solution and then extracted twice with ethyl acetate. The organic phase is washed with brine, dried over Na_2SO_4 , filtered and solvent removed. The residue is flash chromatographed and eluted with 5% methanol in CHCl_3 to give the desired compound (10.1 g) in 70% yield as white granular crystals, m.p. 126°-127° C. after recrystallization from diisopropyl ether.

E.

9-Fluoro-11-[1-methyl-4-piperidylene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

To an ice-bath-cooled acid (146 mL) of H_2SO_4 and $\text{CF}_3\text{SO}_3\text{H}$ (1:1) is added the product of previous Step D (7.3 g, 22.3 mmol). The reaction mixture is allowed to stir for ½ hour at ice bath temperature and then at room temperature for 1½ hour. The reaction mixture is poured onto ice and then basified with 50% NaOH solution. The product is extracted three times with ethyl acetate and washed with brine. The organic phase is desired (Na_2SO_4), filtered and solvent is removed to give a crude oil which is charcoaled and recrystallized from

ethyl acetate and isopropyl ether to give the desired product (5.6 g) in 82% yield, m.p. 134.5°-135.5° C.

F.

9-fluoro-11-[1-ethoxycarbonyl-4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

To a stirred solution of the product of previous Step E (5.0 g, 16.2 mmol) and triethylamine (2.6 g, 26 mmol) in dry toluene (60 mL) at 80° C. under an argon atmosphere, is added ethylchloroformate (9.8 g, 90 mmol) via a syringe. The reaction is allowed to stir at this temperature for 30 minutes and at room temperature for an hour. The reaction is filtered and solvent is removed. The residue is passed through coarse SiO_2 (60-200 mesh), eluted with CHCl_3 to give the desired product (4.5 g) in 76% yield as a white solid, m.p. 112°-114° C. after trituration with pentane.

G.

9-Fluoro-11-[4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

The product of previous Step F (3.83 g, 10.4 mmol) is refluxed with KOH (4.6 g) in 50 mL of ethanol/ H_2O (1:1) for 4 hours under an argon atmosphere. The reaction mixture is poured into a brine solution and extracted twice with ethyl acetate. It is then dried over Na_2SO_4 and filtered. Solvent is removed to give the named compound (2.86 g) in 90% yield, m.p. 138°-140° C.

EXAMPLE VIII

A.

3-[2-(3,4-Dichlorophenyl)ethyl]-2-pyridinecarbonitrile

A solution of 3-[2-(3,4-dichlorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide (37.8 g, 0.107 mole) in 120 mL (197.4 g, 1.29 mole) of phosphorous oxychloride is heated at 110° C. for 4.5 hours. Completion of the reaction is determined by thin-layer chromatography. The reaction is quenched with ice and H_2O and the pH of the solution is brought to 8 by the addition of a saturated solution of potassium carbonate. The product is extracted into ethylacetate. The solution is concentrated to a solid residue which upon recrystallization from diethyl ether/ethyl acetate provides the desired product, (27.1 g, 0.098 mole), in 91.6% yield.

B.

(1-Methyl-4-piperidinyl)-[3-[2-(3,4-dichlorophenyl)ethyl]-2-piperidinyl]methanone

To a solution of the product of previous Step A (21.2 g, 0.0765 mole) in 140 mL of dry tetrahydrofuran at reflux is added 50 mL (1.48 mole/liter, 0.074 mole) of N-methylpiperidyl magnesium chloride over about 10 minutes. The reaction is maintained at reflux for an additional 10 minutes. The reaction is quenched to pH below 2 with aqueous hydrochloric acid and the resulting solution is stirred at 25° C. for 1 hour. The pH of the solution is adjusted to about 8, the product is extracted with ethyl acetate and the solution is concentrated to a residue. Following purification by silica gel chromatography and crystallization from diisopropyl ether, the desired product (19.86 g, 0.0526 mole) is obtained in 69% yield.

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C.

8,9-Dichloro-6,11-dihydro-11-(1-methyl-4-piperidylidene-5H-benzo[5,6]cyclohepta[1,3-b]pyridine

A solution of the product of previous Step B (9.8 g, 0.0259 mole) in 100 mL (169.6 g, 1.13 mole) of trifluoromethanesulfonic acid is heated at 85° C. for 48 hours. The reaction is quenched with ice-water and the solution made basic with potassium hydroxide. The product is extracted into ethyl acetate and the solution is concentrated to a residue. Following purification by reverse phase HPLC and crystallization from acetone/pentane, the desired product (2.38 g, 0.0066 mole) is obtained in 25.5% yield.

D.

8,9-Dichloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

Ethyl chloroformate (1.9 mL, 2.16 g, 0.020 mole) in 10 mL of toluene is slowly added at 80° C. to a solution of the product of previous Step C (1.44 g, 0.004 mole) and triethylamine (1.5 mL, 1.09 g, 0.011 mole) in 50 mL of toluene. Following complete addition, the temperature is maintained at 80° C. for 2.5 hours. Insolubles in the reaction mixture are removed by filtration, and the filtrate is concentrated to a residue. Following silica gel chromatography and crystallization from pentane, the desired product (1.2 g, 0.0029 mole) is obtained in 72.5% yield.

E.

8,9-Dichloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

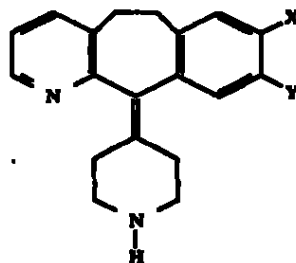
A solution of the product of previous Step D (0.925 g, 0.0022 mole) and potassium hydroxide (1.5 g, 0.039 mole) in 7.5 mL of water and 8.5 mL of ethanol is heated at reflux for 27 hours. The reaction mixture is diluted with water and the product is extracted into ethyl acetate. The solution is concentrated to a residue and the named compound (0.685 g, 0.0020 mole) is obtained from crystallization with toluene. Yield 91%.

By employing the appropriately substituted benzyl chloride in Example I. B. above in place of 3-fluorobenzyl chloride, the following compounds of formula I or their pharmaceutically acceptable salts may also be prepared:

Compound No.		
X		
Y		
1	H	Cl
2	H	Br
3	H	I
4	H	CF ₃
5	Br	H

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-continued



Compound No.	X	Y
6	I	H
7	CF ₃	H
8	F	H
9	Br	Br
10	Cl	F
11	Cl	Br
12	F	Cl
13	Br	Cl
14	F	Br
15	Br	F

The following formulations exemplify some of the dosage forms of the compositions of this invention. In each, the term "active compound" designates a compound of the invention, e.g., Compound A or Compound B, or a pharmaceutically acceptable salt or solvate thereof.

PHARMACEUTICAL DOSAGE FORM EXAMPLES

EXAMPLE A

Tablets			
No.	Ingredient	mg/tablet	mg/tablet
1.	Active Compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	1	7
Total		300	700

Method of Manufacture

Mix item nos. 1 and 2 in a suitable mixer for 10-15 minutes. Granulate the mixture with item no. 3. Mill the damp granules through a coarse screen (e.g., 1/2") if needed. Dry the damp granules. Screen the dried granules if needed and mix with item no. 4 and mix for 10-15 minutes. Add item no. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

EXAMPLE B

Capsules			
No.	Ingredient	mg/capsule	mg/capsule
1.	Active Compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	4	7
Total		250	700

35
65

Method of Manufacture

Mix item nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add item no. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

EXAMPLE C

Parenteral		
Ingredient	mg/vial	mg/vial
Active Compound Sterile Powder	100	500

Add sterile water for injection or bacteriostatic water for injection, for reconstitution.

EXAMPLE D

Injectable	
Ingredient	mg/vial
Active Compound	100
Methyl para-hydroxybenzoate	1.8
Propyl para-hydroxybenzoate	0.2
Sodium Bisulfite	3.2
Disodium Edetate	0.1
Sodium Sulfate	2.6
Water for Injection q.s. ad	1.0 mL

Method of Manufacture

1. Dissolve the para-hydroxybenzoates in a portion (85% of the final volume) of the water for injection at 65°-70° C.
2. Cool to 25°-35° C. Charge and dissolve the sodium bisulfite, disodium edetate and sodium sulfate.
3. Charge and dissolve active compound.
4. Bring the solution to final volume by adding water for injection.
5. Filter the solution through a 0.22 membrane and fill into appropriate containers.
6. Finally, sterilize the units by autoclaving.

The following examples illustrate formulations including a compound of formula I for transdermal application. Compound A refers to 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, but again other compounds of formula I such as compound B above may be employed in its place.

EXAMPLE E

Ointment	
Compound A	200
White Petrolatum	800

EXAMPLE F

Ointment	
Compound A	200
Propylene glycol	200
White Petrolatum	600

EXAMPLE G

Cream	
Compound A	200
Mineral Oil	48
White Petrolatum	120
Octosteryl Alcohol	57.6
Polyethylene glycol 1000 monosteryl ether	16.0
Propylene glycol	80
Water	476.4

EXAMPLE H

Gel	
Compound A	200
Fluoroc F-127	250
Ethanol	200
Water	350

EXAMPLE I

Cream	
Compound A	100.00
Mineral Oil	54.0
White Petrolatum	115.0
Octosteryl Alcohol	65.0
Octyl 20	20.0
Propylene Glycol	100.0
Water q.s. ad	1.0 g

The formulations of Examples B-I above can be packaged to produce a "reservoir type" transdermal patch with or without a rate-limiting patch membrane. The size of the patch and or the rate limiting membrane can be chosen to deliver the transdermal flux rates desired. Such a transdermal patch can consist of a polypropylene or polyester impervious backing member heat sealed to a polypropylene porous/permeable membrane to form a reservoir therebetween. The patch can include a pharmaceutically acceptable adhesive (such as a acrylate adhesive) on the membrane layer to adhere the patch to the skin of the host, e.g., a mammal such as a human. A release liner such as a polyester release liner can also be provided, to cover the adhesive layer prior to application of the patch to the skin as is conventional in the art. This patch assembly can be packaged in an aluminum foil or other suitable pouch again as is conventional in the art.

Alternatively, a compound of formula I or a salt thereof can be formulated into a "matrix-type" transdermal patch as in Examples J and K below. Drug Delivery Systems Characteristics and Biomedical Application, R. L. Juliano, ed., Oxford University Press, N.Y. (1980); and Controlled Drug Delivery Vol. I Basic Concepts, Stephen D. Bruck (1983) described the theory and application of methods useful for transdermal delivery systems. The relevant teachings of these texts are herein incorporated by reference. The drug-matrix could be formed utilizing various polymers, e.g. silicone, polyvinyl alcohol, polyvinyl chloride-vinyl acetate copolymer. The "drug matrix" may then be packaged into an appropriate transdermal patch.

EXAMPLE J

Patch	mg/g
Compound A	200
silicone polymer	800

EXAMPLE K

Patch	mg/g
Compound A	300
Polyvinyl chloride	700
vinyl acetate co-polymer	

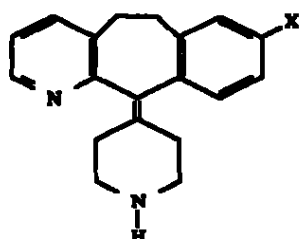
The invention also contemplates a package which contains a specific number of transdermal patches that may be utilized to complete a specified course of treatment. For example a package containing 7, 24 hour patches would be utilized to complete a one week course of therapy.

The relevant teachings of all published references cited herein as incorporated by reference.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

We claim:

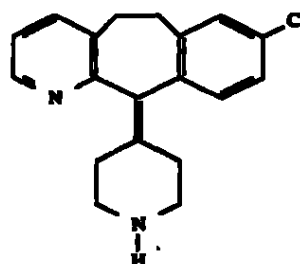
1. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein X represents Cl or F.

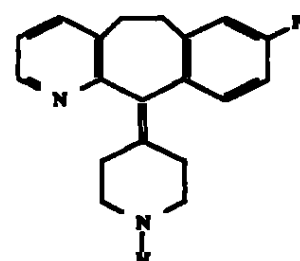
2. A compound defined in claim 1 in the form of the acetic acid salt.

3. A compound having the structural formula



or a pharmaceutically acceptable salt thereof.

4. A compound having the structural formula



or a pharmaceutically acceptable salt thereof.

5. An antihistaminic pharmaceutical composition which comprises an antihistaminic effective amount of a compound as defined in claim 1 in combination with a pharmaceutically acceptable carrier.

6. An antihistaminic pharmaceutical composition which comprises an antihistaminic effective amount of the compound defined in claim 2 in combination with a pharmaceutically acceptable carrier.

7. An antihistaminic pharmaceutical composition which comprises an antihistaminic effective amount of the compound defined in claim 3 in combination with a pharmaceutically acceptable carrier.

8. An antihistaminic pharmaceutical composition which comprises an antihistaminic effective amount of the compound defined in claim 4 in combination with a pharmaceutically acceptable carrier.

9. A composition as defined in claim 7 in unit dosage form.

10. A composition as defined in claim 8 in unit dosage form.

11. A transdermally acceptable pharmaceutical composition comprising an anti-allergic effective amount of a compound as defined in claim 1 and a pharmaceutically acceptable transdermal carrier.

12. A transdermally acceptable pharmaceutical composition comprising a anti-allergic effective amount of a compound as defined in claim 3 and a pharmaceutically acceptable transdermal carrier.

13. A transdermally acceptable pharmaceutical composition comprising an anti-allergic effective amount of a compound as defined in claim 4 and a pharmaceutically acceptable transdermal carrier.

14. A method for treating allergic reactions in a mammal which comprises administering to said mammal an anti-allergic effective amount of a compound as defined in claim 1.

15. A method of treating allergic reactions in a mammal which comprises administering to said mammal an anti-allergic effective amount of a compound as defined in claim 3.

16. A method for treating allergic reactions in a mammal which comprises administering to said mammal an anti-allergic effective amount of a compound as defined in claim 4.

* * * * *



US005595997A

United States Patent [19]

[11] Patent Number: 5,595,997

Aberg et al.

[45] Date of Patent: Jan. 21, 1997

[54] METHODS AND COMPOSITIONS FOR
TREATING ALLERGIC RHINITIS AND
OTHER DISORDERS USING
DESCARBOETHOXYLORATADINE

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[21] Appl. No.: 366,651

[22] Filed: Dec. 30, 1994

[51] Int. Cl.⁴ A61K 31/44

[52] U.S. Cl. 514/290; 514/291; 514/292

[58] Field of Search 514/290, 291,
514/292

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Primary Examiner—Theodore J. Crites
Attorney, Agent, or Firm—Pennis & Edmonds

[57] ABSTRACT

Methods are disclosed utilizing DCL, a metabolic derivative of loratadine, for the treatment of allergic rhinitis, and other disorders, while avoiding the concomitant liability of adverse side-effects associated with other non-sedating antihistamines.

7 Claims, No Drawings

67-22
D2

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METHODS AND COMPOSITIONS FOR TREATING ALLERGIC RHINITIS AND OTHER DISORDERS USING DESCARBOETHOXYLORATADINE

1. BACKGROUND OF THE INVENTION

The methods of the present invention comprise administering a therapeutically effective amount of a metabolic derivative of loratadine. Chemically, this derivative is 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine and known as descarboethoxyloratadine (DCL). This compound is specifically described in Quercia, et al. *Hosp. Formul.*, 28: 137-53 (1993) and U.S. Pat. No. 4,659,716.

Loratadine is an antagonist of the H-1 histamine receptor protein. The histamine receptors H-1 and H-2 are two well-identified forms. The H-1 receptors are those that mediate the response antagonized by conventional antihistamines. H-1 receptors are present, for example, in the ileum, the skin, and the bronchial smooth muscle of man and other mammals.

Loratadine binds preferentially to peripheral rather than to central H-1 receptors. Quercia et al., *Hosp. Formul.* 28: 137-53 (1993). Loratadine has been shown to be a more potent inhibitor of serotonin-induced bronchospasm in guinea pigs than terfenadine. Id. at 137-38. Its anti-allergic activity in animal models was shown to be comparable to that of terfenadine and astemizole. Id. at 138. However, using standard animal model testing, on a milligram by milligram basis, loratadine was shown to be four times more potent than terfenadine in the inhibition of allergic bronchospasm. Id. Moreover, loratadine's antihistaminic activity was demonstrated in humans by evaluation of the drug's ability to suppress wheal formation. Id. Clinical trials of efficacy indicated that loratadine is an effective H-1 antagonist. See Clissold et al., *Drugs* 37:42-57 (1989).

Through H-2 receptor-mediated responses, histamine stimulates gastric acid secretion in mammals and the chronotropic effect in isolated mammalian atria. Loratadine has no effect on histamine-induced gastric acid secretion, nor does it alter the chronotropic effect of histamine on atria. Thus, loratadine has no apparent effect on the H-2 histamine receptor.

Loratadine is well absorbed but is extensively metabolized. Hilbert, et al., *J. Clin. Pharmacol.* 27: 694-98 (1987). The main metabolite, DCL, which has been identified, is reported to be pharmacologically active. Clissold, *Drugs* 37:42-57 (1989). It is also reported as having antihistaminic activity in U.S. Pat. No. 4,659,716. This patent recommends an oral dosage range of 5 to 100 mg/day and preferably 10 to 20 mg/day.

Loratadine's efficacy in treating seasonal allergic rhinitis is comparable to that of terfenadine. Quercia et al., *Hosp. Formul.* 28: 137, 141 (1993). Loratadine also has a more rapid onset of action than astemizole. Id.

Clissold et al., *Drugs* 37: 42, 50-54 (1989) describes studies showing loratadine as effective for use in seasonal and perennial rhinitis, colds (with pseudoephedrine), and chronic urticaria. It has also been suggested that loratadine would be useful for the treatment of allergic asthma. Temple et al. *Prostaglandins* 35:549-554 (1988).

Loratadine may also be useful for the treatment of motion sickness and vertigo. Some antihistamines have been found to be effective for the prophylaxis and treatment of motion

sickness. See Wood, *Drugs*, 17:471-79 (1979). Some antihistamines have also proven useful for treating vestibular disturbances, such as Meniere's disease, and in other types of vertigo. See Cohen et al., *Archives of Neurology*, 27: 129-35 (1972).

In addition, loratadine may be useful in the treatment of diabetic retinopathy and other small vessel disorders associated with diabetes mellitus. In tests on rats with streptozocin-induced diabetes, treatment by antihistamines prevented the activation of retinal histamine receptors which have been implicated in the development of diabetic retinopathy. The use of antihistamines to treat retinopathy and small vessel disorders associated with diabetes mellitus is disclosed in U.S. Pat. No. 5,019,591.

It has also been suggested that loratadine, in combination with non-steroidal antiinflammatory agents or other non-narcotic analgesics, would be useful for the treatment of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, headache, fever, and general malaise associated therewith. Such compositions used in the methods of treating the above-described symptoms may optionally include one or more other active components including a decongestant (such as pseudoephedrine), a cough suppressant/antitussive (such as dextromethorphan) or an expectorant (such as guaifenesin).

Many antihistamines cause adverse side-effects. These adverse side-effects include, but are not limited to, sedation, gastrointestinal distress, dry mouth, constipation or diarrhea. Loratadine has been found to cause relatively less sedation as compared with other antihistamines. Moreover, the incidence of fatigue, headache, and nausea was similar to those observed for terfenadine. See Quercia et al., *Hosp. Formul.* 28: 137,142 (1993).

Furthermore, compounds within the class of non-sedating antihistamines, including loratadine, astemizole, and terfenadine, have been known to cause other severe adverse electrophysiologic side-effects. These adverse side-effects are associated with a prolonged QT interval and include but are not limited to ventricular fibrillation and cardiac arrhythmias, such as ventricular tachyarrhythmias or torsades de pointes. Knowles, *Canadian Journal Hosp. Pharm.*, 45: 33,37 (1992); Craft, *British Medical Journal*, 292: 660 (1986); Simons et al., *Lancet*, 2: 624 (1988); and Unknown, *Side Effects of Drugs Annual*, 12: 142 and 14: 135.

Quercia et al., *Hosp. Formul.* 28: 137, 142 (1993) noted that serious cardiovascular adverse side-effects, including torsades de pointes and other ventricular arrhythmias, were reported in "healthy" patients who received terfenadine concurrently with either ketoconazole or erythromycin. Quercia et al., also states that arrhythmias have also been reported with the concomitant administration of astemizole and erythromycin or erythromycin plus ketoconazole. Thus, he cautions against using loratadine concurrently with ketoconazole, itraconazole, and macrolides, such as erythromycin.

Additionally, it is also known that ketoconazole and/or erythromycin interfere with cytochrome P450, and thereby inhibit the metabolism of non-sedative antihistamines such as terfenadine and astemizole. Because of the interference with the metabolism of loratadine, there exists a greater potential for adverse interaction between loratadine or other non-sedating antihistamines and drugs known to inhibit cytochrome P450, such as but not limited to ketoconazole, itraconazole, and erythromycin.

In Brandes et al., *Cancer Res.* (52) 3796-3800 (1992), Brandes showed that the propensity of drugs to promote

tumor growth in vivo correlated with potency to inhibit concanavalin A stimulation of lymphocyte mitogenesis. In Brandes et al., *J. Nat'l Cancer Inst.*, 86:(10) 771-775 (1994), Brandes assessed loratadine in an in vitro assay to predict enhancement of in vivo tumor growth. He found that loratadine and astemizole were associated with growth of both melanoma and fibrosarcoma tumors. The dose for loratadine in this study was 10 mg/day.

None of the above references teach or enable the methods of the present invention comprising administering DCL to a human while avoiding adverse side-effects associated with the administration of other non-sedating antihistamines; nor do the references alone or in combination suggest these methods. Thus, it would be particularly desirable to find methods of treatment with the advantages of known non-sedating antihistamines which would not have the aforementioned disadvantages.

2. SUMMARY OF THE INVENTION

It has now been discovered that DCL is an effective, non-sedating antihistamine which is useful in treating allergic rhinitis in a human, while avoiding adverse side-effects normally associated with the administration of other compounds within the class of non-sedating antihistamines such as loratadine, astemizole, and terfenadine. Such adverse side-effects include, but are not limited to, cardiac arrhythmias, cardiac conduction disturbances, fatigue, headache, gastrointestinal distress, appetite stimulation, weight gain, dry mouth, and constipation or diarrhea.

Furthermore, DCL is useful for treating allergic rhinitis while avoiding tumor promotion associated with loratadine and other non-sedating antihistamines. Thus, this invention also relates to novel methods of treating allergic rhinitis in a human having a higher than normal propensity for or incidence of cancer.

Furthermore, it has now also been discovered that DCL, is useful in treating allergic asthma in a human, while avoiding the adverse side-effects associated with the administration of other non-sedating antihistamines. As stated above, examples of such side-effects are appetite stimulation, weight gain, tumor promotion, cardiac arrhythmias, and cardiac conduction disturbances. Thus, this invention also relates to novel methods of treating allergic asthma in a human having a higher than normal propensity for or incidence of cancer.

In addition, DCL is useful in treating such disorders in a human as retinopathy and small vessel disorders associated with diabetes mellitus while avoiding the adverse side-effects associated with administration of other non-sedating antihistamines and while avoiding tumor promotion associated with the administration of loratadine and other non-sedating antihistamines. Thus, this invention also relates to novel methods of treating retinopathy and small vessel disorders associated with diabetes mellitus, in a human having a higher than normal propensity for or incidence of cancer.

It has also been discovered that DCL, in combination with non-steroidal antiinflammatory agents or other non-narcotic analgesics, is useful for the treatment of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, headache, fever, and general malaise associated therewith in a human, while avoiding the adverse side-effects associated with the administration of other non-sedating antihistamines. The use of such pharmaceutical compositions, containing DCL, and non-narcotic analgesics or non-steroidal

antiinflammatory agents such as aspirin, acetaminophen or ibuprofen, may optionally include one or more other active components including a decongestant (such as pseudoephedrine), a cough suppressant/antitussive (such as dextromethorphan) or an expectorant (such as guaifenesin).

The present invention also involves the use of the above-described compositions to treat the above-described conditions while avoiding tumor promotion associated with loratadine and other non-sedating antihistamines. Thus, the present invention also relates to the use of these compositions to treat such conditions in a human having a higher than normal propensity for or incidence of cancer.

The present invention also relates to a method of avoiding interaction between DCL and a drug that inhibits cytochrome P450 including but not limited to ketoconazole, itraconazole, erythromycin, and others known by those skilled in the art, while treating allergic rhinitis, allergic asthma, diabetic retinopathy and other small vessel disorders due to diabetes.

This invention is also directed to a method of avoiding interaction between DCL and a drug that inhibits cytochrome P450 including but not limited to ketoconazole, itraconazole, erythromycin, and others known to those skilled in the art, while treating cough, cold, cold-like and/or flu symptoms and the discomfort, headache, pain, fever and general malaise associated therewith, in a human, which comprises administering a composition to said human, said composition comprising DCL and a non-steroidal antiinflammatory agent or non-narcotic analgesic. The aforementioned compositions may optionally contain one or more other active components including a decongestant, cough suppressant/antitussive, or expectorant.

It has also been discovered that DCL is useful in treating other allergic disorders related to its activity as an antihistamine, including but not limited to, urticaria and symptomatic dermatographism, in a human, while avoiding the adverse side-effects associated with the administration of other non-sedating antihistamines and/or while avoiding tumor promotion associated with the administration of loratadine and other non-sedating antihistamines. Thus, this invention also relates to novel methods of treating allergic disorders, including but not limited to, urticaria and symptomatic dermatographism in a human having a higher than normal propensity for or incidence of cancer. The present invention also relates to methods of avoiding interaction between loratadine or other non-sedating antihistamines and a drug that inhibits cytochrome P450 including but not limited to ketoconazole, itraconazole, and erythromycin, and others known by those skilled in the art, while treating allergic disorders, including but not limited to, urticaria and symptomatic dermatographism wherein said human is administered DCL.

3. DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a method of treating allergic rhinitis in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, which comprises administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

The present invention further encompasses a method of treating allergic asthma in a human while avoiding the concomitant liability of adverse side-effects associated with

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the administration of non-sedating antihistamines, which comprises administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

Also included in the present invention is a method of treating retinopathy or other small vessel diseases associated with diabetes mellitus in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, which comprises administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

The present invention further encompasses a method of treating cough, cold, cold-like, and/or flu symptoms and the discomfort, headache, pain, fever, and general malaise associated therewith, in a human, while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, which comprises administering to said human a composition, said composition comprising (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof and (ii) a therapeutically effective amount of at least one non-steroidal antiinflammatory agent or non-narcotic analgesic such as acetylsalicylic acid, acetaminophen, ibuprofen, ketoprofen, and naproxen, or a pharmaceutically acceptable salt thereof.

Additionally, the present invention encompasses a method of treating cough, cold, cold-like, and/or flu symptoms and the discomfort, headache, pain, fever, and general malaise associated therewith, in a human, while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, which comprises administering to said human a composition, said composition comprising (i) a therapeutically effective amount of DCL or pharmaceutically acceptable salt thereof, and (ii) a therapeutically effective amount of a decongestant such as pseudoephedrine or a pharmaceutically acceptable salt thereof.

It has been found that DCL is five to seven times less active in tumor promotion than loratadine. Thus, the present invention further encompasses a method of treating allergic rhinitis in a human while avoiding the concomitant liability of tumor promotion associated with the administration of loratadine and other non-sedating antihistamines, which comprises administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

A further aspect of the present invention includes a method of treating allergic asthma in a human while avoiding the concomitant liability of tumor promotion associated with the administration of loratadine and other non-sedating antihistamines, which comprises administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

The present invention further encompasses a method of treating retinopathy or other small vessel diseases associated with diabetes mellitus in a human while avoiding the concomitant liability of tumor promotion associated with the administration of loratadine and other non-sedating antihistamines, which comprises administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

Because DCL is much less active than loratadine at promoting tumors, a further aspect of this invention is a method of treating allergic rhinitis in a human wherein said human has a higher than normal propensity for or incidence

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of cancer, which comprises administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

The present invention further encompasses a method of treating allergic asthma in a human wherein said human has a higher than normal propensity for or incidence of cancer, which comprises administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

Also included in the present invention is a method for treating retinopathy or other small vessel diseases associated with diabetes mellitus in a human wherein said human has a higher than normal propensity for or incidence of cancer, which comprises administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

Furthermore, the present invention also includes a method of treating cough, cold, cold-like, and/or flu symptoms and the discomfort, headache, pain, fever and general malaise associated therewith, in a human, wherein said human has a higher than normal propensity for or incidence of cancer, which comprises administering to said human a composition, said composition comprising (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically effective amount of a non-steroidal antiinflammatory agent or non-narcotic analgesic such as acetylsalicylic acid, acetaminophen, ibuprofen, ketoprofen, and naproxen, or a pharmaceutically acceptable salt thereof.

Moreover, the present invention further encompasses a method of treating cough, cold, cold-like and/or flu symptoms and the discomfort, headache, pain, fever and general malaise associated therewith, in a human, wherein said human has a higher than normal propensity for or incidence of cancer, which comprises administering to said human a composition, said composition comprising (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically effective amount of a decongestant such as pseudoephedrine or a pharmaceutically acceptable salt thereof.

It has also been found that when DCL is concurrently administered with a drug that inhibits cytochrome P450 including but not limited to ketoconazole, itraconazole, erythromycin and others known by those skilled in the art, the interaction between said DCL and said drug is decreased in comparison to the concurrent administration of loratadine or other non-sedating antihistamines with said drug.

Therefore, this invention also encompasses a method of avoiding interaction between DCL and a drug that inhibits cytochrome P450 including but not limited to ketoconazole, itraconazole, erythromycin and others known by those skilled in the art, while treating allergic rhinitis in a human, wherein said human is administered DCL or a pharmaceutically acceptable salt thereof.

Moreover, this invention also encompasses a method of avoiding interaction between loratadine or other non-sedating antihistamines and a drug that inhibits cytochrome P450 including but not limited to ketoconazole, itraconazole, erythromycin and others known by those skilled in the art, while treating allergic asthma in a human, wherein said human is administered DCL or a pharmaceutically acceptable salt thereof.

This invention also encompasses a method of avoiding interaction between DCL and a drug that inhibits cytochrome P450 including but not limited to ketoconazole, itraconazole, erythromycin and others known by those

skilled in the art, while treating retinopathy or other small vessel diseases associated with diabetes mellitus in a human, wherein said human is administered DCL or a pharmaceutically acceptable salt thereof.

Also encompassed by the present invention is a method of avoiding interaction between DCL and a drug that inhibits cytochrome P450 including but not limited to ketoconazole, itraconazole, erythromycin and others known by those skilled in the art, while treating cough, cold, cold-like, and/or flu symptoms and the discomfort, headache, pain, fever and general malaise associated therewith, in a human, which comprises administering to said human a composition, said composition comprising (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically effective amount of a non-steroidal antiinflammatory agent or non-narcotic analgesic, such as acetylsalicylic acid, acetaminophen, ibuprofen, ketoprofen, and naproxen, or a pharmaceutically acceptable salt thereof.

A further aspect of the invention is a method of avoiding interaction between DCL and a drug that inhibits cytochrome P450 including but not limited to ketoconazole, itraconazole, erythromycin and others known by those skilled in the art, while treating cough, cold, cold-like, and/or flu symptoms and the discomfort, headache, pain, fever and general malaise associated therewith, in a human, which comprises administering to said human a composition, said composition comprising (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically effective amount of a decongestant such as pseudoephedrine or a pharmaceutically acceptable salt thereof.

A further aspect of this invention includes a method of treating urticaria in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, comprising administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

Furthermore, the present invention includes a method of treating symptomatic dermatographism in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, comprising administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

It has also now been found that DCL is at least about twenty times more potent at the histamine receptor when compared to loratadine. Thus, the dosage range by the modes of administration described herein and for use in the methods of the present invention, are about 0.1 to less than about 10 mg per day. This is significantly lower than what has been recommended for other non-sedating antihistamines, including loratadine which has a recommended oral dose of 5 to 100 mg per day. However, due to the significantly less side-effects, DCL can be given in doses higher than those suggested for loratadine thereby offering an improved therapeutic range than loratadine.

Loratadine and other non-sedating antihistamines have antihistaminic activity and provide therapy and a reduction of symptoms for a variety of conditions and disorders related to allergic rhinitis and other allergic disorders, diabetes mellitus and other conditions; however, such drugs, while offering the expectation of efficacy, causes adverse side-effects. Utilizing DCL results in clearer dose-related definitions of efficacy, diminished adverse side-effects, and accordingly, an improved therapeutic index. It is, therefore,

more desirable to use DCL than to use loratadine itself or other non-sedating antihistamines.

The term "adverse effects" includes, but is not limited to cardiac arrhythmias, cardiac conduction disturbances, appetite stimulation, weight gain, sedation, gastrointestinal distress, headache, dry mouth, constipation, and diarrhea. The term "cardiac arrhythmias" includes, but is not limited to ventricular tachyarrhythmias, torsades de pointes, and ventricular fibrillation.

The phrase "therapeutically effective amount" means that amount of DCL which provides a therapeutic benefit in the treatment or management of allergic rhinitis and other allergic disorders such as urticaria, symptomatic dermatographism, allergic asthma, retinopathy or other small vessel disorders associated with diabetes mellitus, and the symptoms associated with allergic rhinitis such as cough, cold, cold-like, and/or flu symptoms including, but not limited to, sneezing, rhinorrhea, lacrimation, and dermal irritation.

The term "allergic asthma" is defined as a disorder characterized by increased responsiveness of the trachea and bronchi to various stimuli which results in symptoms which include wheezing, cough, and dyspnea.

The term "diabetic retinopathy" or "retinopathy associated with diabetes mellitus" is that disorder caused by increased permeability of the capillaries in the eye which leads to hemorrhages and edema in the eye and can lead to blindness. The term "small vessel disorders associated with diabetes mellitus" includes, but is not limited to, diabetic retinopathy and peripheral vascular disease.

The magnitude of a prophylactic or therapeutic dose of DCL in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose range, for the conditions described herein, is from about 0.1 mg to less than about 10 mg administered in single or divided doses orally, topically, transdermally, or locally by inhalation. For example, a preferred oral daily dose range should be from about 0.1 mg to about 5 mg. A more preferred oral dose is about 0.2 mg to about 1 mg.

It is further recommended that children, patients aged over 65 years, and those with impaired renal or hepatic function initially receive low doses, and that they then be titrated based on individual response(s) or blood level(s). It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

The term "therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof" is encompassed by the above-described dosage amounts. In addition, the terms "said composition comprising (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically effective amount of at least one non-steroidal antiinflammatory agent or non-narcotic or a pharmaceutically acceptable salt thereof"; and "said composition comprising (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically effective amount of a decongestant such as pseudoephedrine or a pharmaceutically acceptable salt thereof" are also encompassed by the above-described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage of DCL.

according to the methods of the present invention. For example, oral, rectal, parenteral, transdermal, subcutaneous, intramuscular, and like forms of administration may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, and the like.

The pharmaceutical compositions used in the methods of the present invention comprise DCL, the metabolic derivative of loratadine, as active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

The term "pharmaceutically acceptable salt" refers to a salt prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids or bases or organic acids or bases. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, sulfuric, and phosphoric. Appropriate organic acids may be selected, for example, from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pantoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic, stearic, sulfanilic, algeric, and galacturonic. Examples of such inorganic bases include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc. Appropriate organic bases may be selected, for example, from *N,N*-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (*N*-methylglucamine), lysine and procaine.

The compositions for use in the methods of the present invention include compositions such as suspensions, solutions and elixirs; aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like, in the case of oral solid preparations (such as powders, capsules, and tablets), with the oral solid preparations being preferred over the oral liquid preparations. The most preferred oral solid preparations are tablets.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compound for use in the methods of the present invention may also be administered by controlled release means and/or delivery devices such as those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, the disclosures of which are hereby incorporated by reference.

Pharmaceutical compositions for use in the methods of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, or aerosol sprays, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 0.1 mg to less than about 10 mg of the active ingredient, and each cachet or capsule contains from about 0.1 mg to about less than 10 mg of the active ingredient, i.e., DCL.

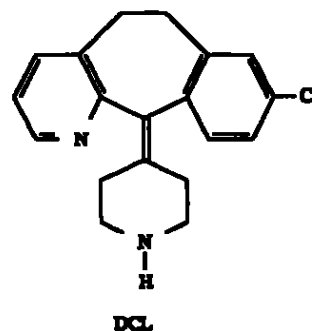
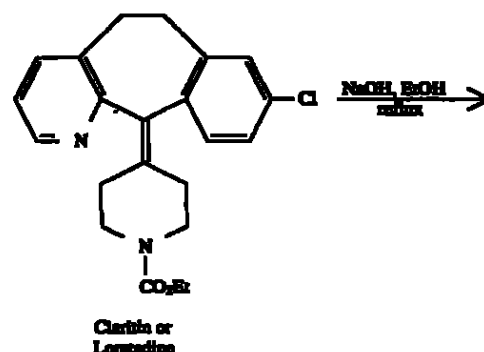
The invention is further defined by reference to the following examples describing in detail the preparation of the compound and the compositions used in the methods of the present invention, as well as their utility. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced which are within the scope of this invention.

4. EXAMPLES

4.1 Example 1

Preparation of loratadine and its metabolites

Loratadine can be synthesized by methods disclosed in U.S. Pat. No. 4,282,233. The metabolites are prepared similarly, by reaction steps conventional in the art, as described in U.S. Pat. No. 4,639,716 which is incorporated here by reference in its entirety. One common method of preparing DCL is to reflux loratadine in the presence of sodium hydroxide and ethanol as depicted below.



Extraction of Commercially Available Claritin Tablets (600x 10 mg):

Tablets of loratadine, were diluted with water and chloroform. The mixture was stirred, then filtered through celite, rinsed with chloroform until the filtrate contained no lor-

tadine. The separated aqueous layer was extracted with chloroform twice. The combined organic layer was washed with water, brine and dried over sodium sulfate. The solvent was evaporated to give pure loratadine as a white solid.

Saponification of loratadine:

Loratadine (4.0 g) was added to a solution of sodium hydroxide (5.9 g) in 280 mL of absolute ethanol and the mixture was stirred at reflux for four days. The mixture was cooled and concentrated to remove ethanol. The residue was diluted with water and aqueous layer was extracted with methylene chloride five times. The combined organic layer was washed with water, brine and dried over sodium sulfate. The solvent was evaporated to give 2.82 g (87%) of pure loratadine derivative (or metabolite) as a pale-tan solid.

4.2 Example 2

Antihistaminic Activity.

The antihistaminic activity of loratadine and DCL were compared in isolated strips of guinea pig ileum contracted with histamine. This preparation is generally accepted by those skilled in the art as predicative of its efficacy as a peripheral histamine H-1 receptor.

Methods:

Experiments were performed on pieces of ileum taken from male guinea pigs (Hartley strain, 419-560 grams; Elm Hill Breeding Laboratories, Chelmsford, Mass.). The tissues were suspended in tissue chambers containing 40 ml of Tyrode's solution aerated with 95% oxygen and 5% carbon dioxide at 35° C. The Tyrode's solution contained (in mM) 137 NaCl, 2.7 KCl, 2.2 CaCl₂, 0.025 MgCl₂, 0.4 NaHPO₄, 11.9 NaHCO₃ and 5.5 glucose. Contractions in response to histamine were recorded with isotonic transducers (Model 357, Harvard Apparatus Company, South Natick, Mass.) using an ink-writing polygraph (Model 7, Grass Instrument Company, Quincy, Mass.). A tension of one gram was maintained on all tissues at all times.

two successive exposures to histamine produced contractions of approximately the same magnitude, loratadine or DCL, at final concentrations that varied three- or ten-fold, was added to all but one of the tissue chambers, the untreated tissue serving as a control for the treated tissues. After each exposure of drug-treated tissues to histamine, the fluid in the tissue chamber was replaced with fluid free of histamine but containing the same drug at the same concentration. The histamine challenges were made at 5, 20, 35, 50, 65, 80, 95, 110 and 125 minutes of exposure to the drug or at comparable times in the control tissues.

Subsequent analyses of the results from each experiment involved (i) normalization of the data from each tissue for differences in inherent contractility by expressing all contractions as a percent of the last predrug contraction, (ii) normalization of the data for possible time-related changes in contractility by expressing the contractions recorded during drug-exposure as a percent of the corresponding value for the untreated tissue, and finally (iii) calculation of the drug-related percent reduction of each contraction.

The resultant sets of data for drug concentration and corresponding percent reduction in histamine-response were then used to estimate for each experiment the concentration of drug that would have produced a 50 percent reduction in the histamine response, the IC₅₀. This was done by fitting straight lines to the data using the method of least squares and calculating the IC₅₀ from the equation of the line. The mean ± standard error of the values for the experiments on each drug were calculated, and differences between the drugs was examined using the Kruskal Wallis 1-way analysis of variance by ranks.

A summary of the results are shown in the following two tables. The percentages of reduction of histamine-induced contractions of the isolated guinea pig ileum produced by exposure for 125 minutes to various concentrations of each drug are set forth below:

TABLE 1

		Reduction of Histamine-Induced Guinea Pig Ileum Contractions (Percent)					
Drug	Expt	Concentration of drug (mol/l)					
	No.	3 × 10 ⁻⁸	1 × 10 ⁻⁷	3 × 10 ⁻⁷	1 × 10 ⁻⁶	3 × 10 ⁻⁶	1 × 10 ⁻⁵
Loratadine	1	—	19.05	—	13.33	—	88.57
	2	—	—	—	28.32	54.42	98.66
	3	—	—	—	39.64	44.68	93.38
	4	—	—	—	55.86	43.83	86.46
DCL	1	11.93	73.12	—	—	—	—
	2	38.91	38.81	56.71	—	—	—
	3	40.00	62.89	76.21	—	—	—
	4	35.43	44.13	76.43	—	—	—

In each experiment three or four pieces of ileum were removed from a single animal, suspended in individual tissue chambers and allowed to equilibrate with the bathing solution for one hour before the administration of any drugs. In four initial experiments in which tissues were exposed to histamine at concentrations of 1×10⁻⁷, 1×10⁻⁶ and 1×10⁻⁵ mol/l, histamine at 1×10⁻⁶ mol/l produced strong contractions on the linear portion of the log-concentration-effect curve and this concentration of histamine was chosen for use in all further experiments.

For determining the antihistaminic effects of loratadine and DCL, tissues were exposed briefly (about 15 seconds) to 1×10⁻⁶ mol/l of histamine at intervals of 15 minutes. After

TABLE 2

Reduction of Histamine-Induced Guinea Pig Ileum Contractions (IC ₅₀)		
Drug	Expt	IC ₅₀ (M)
Loratadine	1	1.90 × 10 ⁻⁶
	2	2.21 × 10 ⁻⁶
	3	2.10 × 10 ⁻⁶
	4	1.22 × 10 ⁻⁶
	Mean	1.86 × 10 ⁻⁶
	S.E.	0.22
DCL	1	6.36 × 10 ⁻⁶

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TABLE 2-continued

Reduction of Histamine-Induced Guinea Pig Intest Contractions (IC ₅₀)		
Drug	Expt	IC ₅₀ (M)
	2	19.2 × 10 ⁻¹⁰
	3	5.26 × 10 ⁻¹⁰
	4	8.66 × 10 ⁻¹⁰
	Mean	9.75 × 10 ⁻¹⁰
	S.E.	3.20

Note: There is a statistically significant drug-related difference in IC₅₀ values (P = 0.0209).

These results indicate that DCL is approximately 20 fold more potent at the histamine receptor than loratadine.

4.3 Example 3

Receptor binding studies

Receptor binding studies on the binding affinities of loratadine and DCL at histamine H-1 receptors were performed.

The methods described by Dini et al., which is hereby incorporated by reference herein (Agents and Actions, 33:181-184, 1991), were used for these binding studies. Guinea pig cerebella membranes were incubated with 0.5 nM 3H-pyrimidine for 10 min at 25° C. Following incubation, the assays were rapidly filtered under vacuum through GF/B glass fiber filters (Whatman) and washed several times with ice-cold buffer using a Brandel Cell Harvester. Bound radioactivity was determined with a liquid scintillation counter (LS 6000, Beckman) using a liquid scintillation cocktail (Formula 989, DuPont NEN).

IC₅₀ values were determined for compounds tested and pyrimidine at the H-1 histamine receptor:

TABLE 3

Inhibition of Pyrimidine Binding at H-1 Receptor		
Compound	H-1 receptor	
	IC ₅₀ (nM)	(nM)
Loratadine	721	(1.55)
DCL	51.1	(1.12)
Pyrimidine	1.4	(0.98)

As shown above, DCL was found to have a 14 fold greater affinity than loratadine for histamine H-1 receptors. These results are consistent with the findings demonstrating a higher potency of DCL over loratadine for inhibition of histamine-induced contractions of guinea pig ileum.

These studies confirm that DCL has a higher potency for histamine receptors than loratadine.

4.4 Example 4

Tumor Promoting Activity

Inhibition of lymphocyte mitogenesis was used to screen the potencies of loratadine and DCL as tumor promoting agents.

Mitogenesis studies:

Fresh spleen cells (5×10⁵) obtained from 5-week old BALB/c mice (Charles River, ST. Constant, PQ) were suspended in RPMI 1640 medium containing 2% fetal calf serum (Grand Island Biological Co., Grand Island, N.Y.) seeded into replicate microwell plates (Nunc) to which concanavalin (Con) A (2 µg/ml; Sigma Chemical Co., St. Louis, Mo.) was added and incubated (37° C., 95% air, 5%

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CO₂) in the absence or presence of increasing concentrations of the test agents dissolved in saline or other vehicles. Forty-three hours after the addition of Con A, 0.25 nmol ³H-thymidine (6.7 Ci/nmol; ICN Radiopharmaceuticals, Montreal, PQ) was added to each well. After an additional 5-hour incubation, the cells were washed from the wells onto filter papers employing an automated cell sorter. The filters were placed into vials containing 5 ml scintillation fluid (ReadySafe; Beckman), and radioactivity incorporated into DNA at 48 hours was determined (n=8). IC₅₀ values for inhibition of mitogenesis were determined over wide range of concentrations (0.1 to 10 µM).

TABLE 4

Inhibition of Concanavalin A Induced Stimulation of Lymphocytes (IC ₅₀)	
Loratadine	1.0 µM
DCL	5.6 µM

These results indicate that DCL is 5-7 fold less active than loratadine at promoting tumor growth.

4.5 Example 5

Cardiovascular Effects

The effects of DCL on cardiac potassium currents were studied.

Methods:

Single ventricular myocytes of the guinea-pig and the rabbit were dissociated by enzymatic dispersion (see Carmeliet, *J. Pharmacol. Exper. Ther.*, 1992, 262, 809-817 which is incorporated herein by reference in its entirety). The single suction patch electrode, with a resistance of 2 to 5 M Ω was used for voltage clamp (Axoclamp 200 A). P-clamp software (Axon Instruments) was used to generate voltage-clamp protocols and to record and analyze data. The standard solution contained in mM: NaCl 137.6, KCl 5.4, CaCl₂ 1.8, MgCl₂ 0.5, HEPES 11.6 and glucose 5, and NaOH was added to pH 7.4. The intracellular solution contained KCl 120, MgCl₂ 6, CaCl₂ 0.154, Na₂ATP 5, EGTA 5, and HEPES 10, with KOH added until pH 7.2. Effect on the delayed rectifying K⁺ current, (I_{kr}) in rabbit ventricular myocytes:

The voltage clamp protocol consisted of clamps from a holding potential of -50 mV to +10 mV for a duration of 4 sec. The change in tail current was measured as a function of the drug concentration. This concentration was changed between 10⁻⁷ and 10⁻⁹M in five steps. Exposure to each concentration lasted 15 min. At the end, washout was attempted during 30 min.

Effect on the inward rectifier current in guinea-pig myocytes:

The inward rectifier was measured by applying ramp voltage clamps starting from -50 mV and hyperpolarizing the membrane to -120 mV at a speed of 10 mV/sec. The starting concentration was the 50% efficiency concentration, determined in the preceding experiments. Higher concentrations were applied if this initial concentration was without effect.

Effect on I_K, in guinea-pig ventricular myocytes:

Tail currents were measured following depolarizing clamps of 2 sec duration to potentials between -30 mV and +60 mV; holding potential -50 mV.

The results from these studies indicate that DCL is less active than terfenadine in inhibiting the cardiac delayed rectifier and thus has no potential for cardiac side-effects.

Thus, the methods of the present invention are less toxic than methods which use other non-sedating antihistamines.

4.6 Example 6

Inhibition of cytochrome P450.

This study is conducted to determine the extent that loratadine and DCL inhibit human cytochrome P4503A4 (CYP3A4). CYP3A4 is involved in many drug-drug interactions and quantitation of inhibition of CYP3A4 by loratadine or DCL indicates the potential of such drug-drug interactions. Inhibition is measured using the model substrate testosterone and cDNA-derived CYP3A4 in microsomes prepared from a human lymphoblastoid cell line designated h3A4v3.

Study Design:

The inhibition study consists of the determination of the 50% inhibitory concentration (IC_{50}) for the test substance. A single testosterone concentration (120 μ M, approximately twice the apparent K_m) and ten test substance concentrations, separated by approximately $\frac{1}{2}$ log, are tested in duplicate. Testosterone metabolism is assayed by the production of the 6(β)-hydroxytestosterone metabolite. This metabolite is readily quantitated via HPLC separation with absorbance detection.

Storage/Preparation of the test substances and addition to the incubations:

The test substances will be stored at room temperature. The test substances will be dissolved in ethanol for addition to the incubations. The solvent concentration will be constant for all concentrations of the test substance.

IC_{50} Determination:

Final test substance concentrations will be 100, 30, 10, 3, 1, 0.3, 0.1, 0.03, 0.01, 0.003 and 0 μ M. Each test concentration will be tested in duplicate incubations in accordance with the method below:

Method:

A 0.5 ml reaction mixture containing 0.7 mg/ml protein, 1.3 mM NADP⁺, 3.3 mM glucose-6-phosphate, 0.4 U/ml glucose-6-phosphate dehydrogenase, 3.3 mM magnesium chloride and 120 μ M testosterone in 100 mM potassium phosphate (pH 7.4) will be incubated at 37° C. for 30 min. A known quantity of 11(β)-hydroxytestosterone will be added as an internal standard to correct for recovery during extraction. The reaction mixture will be extracted with 1 ml methylene chloride. The extract will be dried over anhydrous magnesium sulfate and evaporated under vacuum. The sample will be dissolved in methanol and injected into a 4.6x250 mm 5u C18 HPLC column and separated at 50° C. with a mobile phase methanol/water at a flow rate of 1 ml per min. The retention times are approximately 6 min for the 6(β)-hydroxy, 8 min for 11(β)-hydroxy and 12 min for testosterone. The product and internal standard are detected by their absorbance at 254 nm and quantitated by correcting for the extraction efficiency using the absorbance of the 11(β)-hydroxy peak and comparing to the absorbance of a standard curve for 6(β)-hydroxytestosterone.

Data reporting:

For each test substance, the concentration of 6(β)-hydroxytestosterone metabolite in each replicate incubation is determined and the percentage inhibition relative to solvent control is calculated. The IC_{50} is calculated by linear interpolation.

Useful pharmaceutical dosage forms for administration of the compounds used in the methods of the present invention can be illustrated as follows:

4.7. Example 7

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 0.1 to 10 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

4.8. Example 8

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, lecithin, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 0.1 to 10 milligrams of the active ingredient. The capsules are washed and dried.

4.9 Example 9

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 0.1 to 10 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Various modifications of the invention in addition to those shown and described herein will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

The foregoing disclosure includes all the information deemed essential to enable those skilled in the art to practice the claimed invention. Because the cited patents or publications may provide further useful information these cited materials are hereby incorporated by reference in their entirety.

What is claimed is:

1. A method of treating allergic rhinitis in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, comprising administering to said human a therapeutically effective amount of decarboethoxyloratadine or a pharmaceutically acceptable salt thereof.
2. The method of claim 1 wherein said adverse side-effect is cardiac arrhythmia or tumor promotion.
3. The method of claim 1 wherein said human has a higher than normal propensity for or incidence of cancer.
4. The method of claim 1, wherein interaction between DCL and a drug that inhibits cytochrome P450 is avoided.
5. The method of claim 1 wherein the amount of DCL administered is from about 0.1 mg to less than about 10 mg per day.
6. The method of claim 5 wherein the amount of DCL administered is from about 0.1 mg to about 5 mg per day.
7. The method of claim 1 wherein the amount of said DCL or a pharmaceutically acceptable salt thereof is administered together with a pharmaceutically acceptable carrier.

* * * * *

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United States Patent [19]
Okuyama et al.

[11] Patent Number: 5,352,704
[45] Date of Patent: Oct. 4, 1994

US005352704A

[54] GUANIDINO BENZENE DERIVATIVES

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[21] Appl. No.: 963,528

[22] Filed: Oct. 20, 1992

Related U.S. Application Data

[63] Continuation of Ser. No. 630,985, Dec. 24, 1990, abandoned.

[30] Foreign Application Priority Data

Dec. 22, 1989 [JP] Japan 1-334188

[51] Int. Cl.³ A61K 31/165; C07C 233/64

[52] U.S. Cl. 514/619; 564/168

[58] Field of Search 564/168, 230, 237, 238,
564/164; 514/619, 620, 634, 631

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Flayer

[57] ABSTRACT

A guanidinobenzene derivative represented by the formula (I):



wherein R¹ represents a substituent selected from the group consisting of a phenyl group substituted by an amidino group and a naphthyl group substituted by an amidino group, and salt thereof; a process for the production thereof; and an antiviral pharmaceutical composition comprising the compound.

2 Claims, No Drawings

GUANIDINO BENZENE DERIVATIVES

This application is a continuation of U.S. application Ser. No. 07/630,985 filed Dec. 24, 1990, now abandoned.

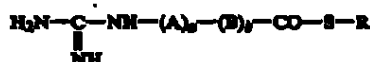
BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to novel guanidinobenzene derivatives, a process for the production thereof, and an antiviral agent comprising a guanidinobenzene derivative. These derivatives are useful for the treatment for various viral-related diseases.

2. Description of the Related Art

Japanese Unexamined Patent Application (KOKAI) No. 49-24917 discloses thiol esters of guanidino organic acid having an antiviral activity represented by the general formula:



wherein A represents a linear or branched alkylene group having 1 to 10 carbon atoms; B represents p-phenylene group or a cycloalkylene group; a represents 0 or 1; b represents 0 or 1; a+b totals 1 or 2; R represents a linear or branched alkyl group having 1 to 10 carbon atoms, a carboethoxyalkyl group having 1 to 10 carbon atoms, a cycloalkyl group, an aromatic group or a phenylalkyl group, wherein the cycloalkyl group and the aromatic group can be substituted with a lower alkyl group, a carboethoxy group, a carboethoxy-lower alkyl group, a carboxyalkyl group, a halogen atom, an alkoxy group, an aryamide group, an alkylsulfonyl group, a carboxy group, a thiocarboxy group, a mercapto-carboxy group, a nitro group or a carbamoyl group. These types of compounds, however, exhibit an antiviral activity that is too weak for practical use.

In addition, as different types of antiviral agents, various kinds of nucleic acid derivatives are known; for example, amantadine, etc., are known as anti-influenza virus agents. The nucleic acid derivative type antiviral agents, however, cause side-effects such as liver function disorder, mutagenity and subacute toxicity, and the amantadine causes side effects such as teratogenicity, and further, the higher the frequency of use, the lower becomes efficacy (Virology, Raven Press, pp 323-348, 1985).

Therefore, new antiviral agents not having the above-mentioned drawback are urgently required.

SUMMARY OF THE INVENTION

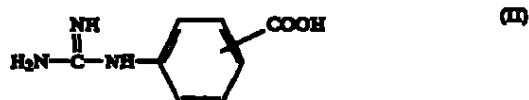
Accordingly, the present invention provides new guanidinobenzene derivatives having a potent antiviral activity and less side effects, represented by the formula (I):



wherein R¹ represents a substituent selected from the group consisting of a phenyl group substituted by an

amidino group and a naphthyl group substituted by an amidino group.

Moreover, the present invention provides a process for the production of the guanidinobenzene derivatives, comprising the step of reacting a guanidinobenzoic acid represented by the formula (II):



or an acid addition salt thereof with an amine compound represented by the formula (III):



wherein R¹ represents a substituent selected from the group consisting of a phenyl group substituted by an amidino group and a naphthyl group substituted by an amidino group, or an acid addition salt thereof, in an inert solvent.

Moreover, the present invention provides an antiviral pharmaceutical composition comprising one of the above-mentioned guanidinobenzene derivatives and a pharmaceutically acceptable carrier.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

As the present guanidinobenzene derivatives, the following compounds are exemplified:

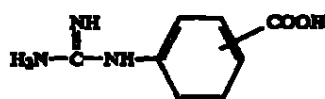
- (1) 4-Guanidinobenzoic acid 4-amidinobenzamide,
- (2) 4-Guanidinobenzoic acid 3-amidinobenzamide,
- (3) 4-Guanidinobenzoic acid 2-amidinobenzamide,
- (4) 3-Guanidinobenzoic acid 4-amidinobenzamide,
- (5) 3-Guanidinobenzoic acid 3-amidinobenzamide,
- (6) 3-Guanidinobenzoic acid 2-amidinobenzamide,
- (7) 2-Guanidinobenzoic acid 4-amidinobenzamide,
- (8) 2-Guanidinobenzoic acid 3-amidinobenzamide,
- (9) 2-Guanidinobenzoic acid 2-amidinobenzamide,
- (10) 4-Guanidinobenzoic acid 2-amidino-1-naphthylamide,
- (11) 4-Guanidinobenzoic acid 3-amidino-1-naphthylamide,
- (12) 4-Guanidinobenzoic acid 4-amidino-1-naphthylamide,
- (13) 4-Guanidinobenzoic acid 5-amidino-1-naphthylamide,
- (14) 4-Guanidinobenzoic acid 6-amidino-1-naphthylamide,
- (15) 4-Guanidinobenzoic acid 7-amidino-1-naphthylamide,
- (16) 4-Guanidinobenzoic acid 8-amidino-1-naphthylamide,
- (17) 3-Guanidinobenzoic acid 2-amidino-1-naphthylamide,
- (18) 3-Guanidinobenzoic acid 3-amidino-1-naphthylamide,
- (19) 3-Guanidinobenzoic acid 4-amidino-1-naphthylamide,
- (20) 3-Guanidinobenzoic acid 5-amidino-1-naphthylamide,
- (21) 3-Guanidinobenzoic acid 6-amidino-1-naphthylamide,
- (22) 3-Guanidinobenzoic acid 7-amidino-1-naphthylamide,

- (23) 3-Guanidinobenzoic acid 8-amidino-1-naphthylamide,
 (24) 2-Guanidinobenzoic acid 2-amidino-1-naphthylamide,
 (25) 2-Guanidinobenzoic acid 3-amidino-1-naphthylamide,
 (26) 2-Guanidinobenzoic acid 4-amidino-1-naphthylamide,
 (27) 2-Guanidinobenzoic acid 5-amidino-1-naphthylamide,
 (28) 2-Guanidinobenzoic acid 6-amidino-1-naphthylamide,
 (29) 2-Guanidinobenzoic acid 7-amidino-1-naphthylamide,
 (30) 2-Guanidinobenzoic acid 8-amidino-1-naphthylamide,
 (31) 4-Guanidinobenzoic acid 1-amidino-2-naphthylamide,
 (32) 4-Guanidinobenzoic acid 3-amidino-2-naphthylamide,
 (33) 4-Guanidinobenzoic acid 4-amidino-2-naphthylamide,
 (34) 4-Guanidinobenzoic acid 5-amidino-2-naphthylamide,
 (35) 4-Guanidinobenzoic acid 6-amidino-2-naphthylamide,
 (36) 4-Guanidinobenzoic acid 7-amidino-2-naphthylamide,
 (37) 4-Guanidinobenzoic acid 8-amidino-2-naphthylamide,
 (38) 3-Guanidinobenzoic acid 1-amidino-2-naphthylamide,
 (39) 3-Guanidinobenzoic acid 3-amidino-2-naphthylamide,
 (40) 3-Guanidinobenzoic acid 4-amidino-2-naphthylamide,
 (41) 3-Guanidinobenzoic acid 5-amidino-2-naphthylamide,
 (42) 3-Guanidinobenzoic acid 6-amidino-2-naphthylamide,
 (43) 3-Guanidinobenzoic acid 7-amidino-2-naphthylamide,
 (44) 3-Guanidinobenzoic acid 8-amidino-2-naphthylamide,
 (45) 2-Guanidinobenzoic acid 1-amidino-2-naphthylamide,
 (46) 2-Guanidinobenzoic acid 3-amidino-2-naphthylamide,
 (47) 2-Guanidinobenzoic acid 4-amidino-2-naphthylamide,
 (48) 2-Guanidinobenzoic acid 5-amidino-2-naphthylamide,
 (49) 2-Guanidinobenzoic acid 6-amidino-2-naphthylamide,
 (50) 2-Guanidinobenzoic acid 7-amidino-2-naphthylamide, and
 (51) 2-Guanidinobenzoic acid 8-amidino-2-naphthylamide.

Acid addition salts of the present invention are preferably pharmaceutically acceptable acid addition salts and, for example, include salts of an inorganic acid such as hydrochloric acid, sulfuric acid, carbonic acid or phosphoric acid, or salts of an organic acid such as acetic acid, lactic acid, citric acid, methanesulfonic acid, p-toluenesulfonic acid, succinic acid, fumaric acid or maleic acid.

Compounds of the present invention represented by the formula (I) can be prepared, for example, by react-

ing a guanidinobenzoic acid represented by the formula (II):



(II)

or an acid addition salt thereof with an amino compound represented by the formula (III):



wherein R^1 represents a substituent selected from the group consisting of a phenyl group substituted by an amidino group and a naphthyl group substituted by an amidino group, or an acid addition salt thereof.

The above-mentioned reaction is preferably carried out in an inert solvent, for example, an aprotic polar solvent such as pyridine, methylene chloride, N,N-dimethylformamide or dimethylsulfoxide, or a mixture thereof, at -20°C . to a room temperature, preferably at -10°C . to 0°C ., in the presence of a condensation agent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, for 5 to 24 hours.

In this process the acid addition salts of the compounds (II) and (III) used as starting materials are, for example, those of hydrochloric acid, sulfuric acid or phosphoric acid, preferably the salt of hydrochloric acid.

To isolate and purify the present compound from a reaction mixture obtained as described above, for example, the solvent is evaporated from the reaction mixture, to give a residue, which is then suspended in an alcohol such as methanol, ethanol or isopropanol, and a saturated sodium bicarbonate aqueous solution is added thereto to afford a carbonate of the present compound.

The thus-obtained carbonate of the present compound can be converted to another salt by adding a mixture of water and an alcohol such as methanol or ethanol to the carbonate, followed by the addition of an appropriate acid. If a further purification is desired, the above-mentioned procedure can be repeated.

The compounds represented by the formula (II) and (III) and acid addition salts thereof, used as starting materials for the production of the present compounds are commercially available, or can be easily produced according to a procedure described in *J. Am. Chem. Soc.*, Vol. 65, 239-242, 1943, or *Pharmazie*, Vol. 34, 227-228, 1979.

The present compounds are useful for the treatment of viral infection diseases caused by, for example, an envelope virus such as a retrovirus, for example, influenza virus, parainfluenza virus, herpesvirus, or human immunodeficiency virus (HIV).

An antiviral pharmaceutical composition of the present invention comprising a compound of the formula (I) can be administered through various routes, and the effective dose of the compound varies depending on the administration route used, as well as the age, sex, body weight and other conditions of a patient. For example, for an oral administration, the effective dose is 1 to 500 mg per administration, which is administered 1 to 3 times a day; for a rectal administration, 1 to 100 mg per administration, 1 to 3 times a day; for inhalation to the bronchia, 0.1 to 500 mg per one inhalation, 2 to 3 times a day; for an intravenous administration, 0.1 to 10 mg per

administration, 1 to 2 times a day; for an intranasal administration, 0.1 to 500 mg per administration, 2 to 4 times a day; for eye dropping, 0.1 to 50 mg per administration, 3 to 4 times a day; and as an ointment, 1 to 500 mg per administration, 1 to 3 times a day.

The present pharmaceutical composition can be formulated in any way corresponding to the administration route thereof as described above, and this includes external and parenteral formulations.

For an oral administration, the present pharmaceutical composition is preferably formulated in a unit dose form, such as tablets, troches, powders, dragee, particles or capsules. For the formulation of these compositions, a binder such as gum arabic, gelatin, sorbitol, tragacanth gum, polyvinyl pyrrolidone, polyvinyl alcohol, hydroxypropyl methyl cellulose, methyl cellulose, crystalline cellulose or sodium carboxymethyl cellulose; a filler such as lactose, sucrose, mannitol, potato starch, calcium phosphate, sorbitol or crystalline cellulose; a lubricant such as magnesium stearate, talc, polyethylene glycol or silica; and/or a disintegration agent such as potato starch, lower-substituted hydroxypropyl cellulose, calcium carboxymethyl cellulose or sodium carboxymethyl starch, alone or in combination, are used. Soft capsule may contain a conventional vehicle such as plant oil, polyethylene glycol or glycerol, or an oily suspending agent given hereinafter, a solution, or a wetting agent such as surfactant.

A liquid formulation is, for example, an aqueous or oily suspension, solution, syrup or elixir. Alternatively, a lyophilized product may be reconstructed to form a liquid formulation immediately prior to use. For the liquid formulation, a suspension agent such as methyl cellulose, sodium carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, tragacanth gum, gelatin or sodium alginate; an emulsifier such as lecithin, sorbitan, fatty acid ester, gum arabic or tragacanth gum; a wetting agent such as polyoxyethylene sorbitan fatty acid ester, polyoxyethylene fatty acid ester, hydrogenated ricinus oil, sesame oil, soybean oil, propylene glycol, polyethylene glycol or ethyl alcohol; a preservative such as methyl p-hydroxybenzoate, propyl p-hydroxybenzoate or sorbic acid, and an additive such as simple syrup, sucrose, sorbitol or mannitol, may be used alone or in combination.

As a base for a rectal administration formulation, an oily base such as cocoa butter, white pool or triglyceride, or a water soluble base such as glycerol, glycerogelatin or macrogol is used.

An additive for an injection formulation includes a dissolving aid such as polyoxyethylene, hardened ricinus oil or sodium benzoate, an osmotic pressure-adjusting agent such as glucose, sodium chloride or glycerol; a stabilizer such as sodium sulfite, anhydrous sodium sulfite, sodium metabisulfite or glycerol may be used alone or in combination.

For an inhalation to a respiratory organ such as the bronchia or nose, an aerosol, inhalation solution, liquid, powders, capsules or ointment can be used. The aerosol may be an oily aerosol comprising a non-ionic surfactant such as alcel or Span 80, an ampholytic surface active agent such as lecithin, or a dispersant such as oleyl alcohol, and a propellant such as butane or Freon (TM); or an aqueous aerosol comprising an osmotic pressure-adjusting agent such as physiological saline, phosphate buffer or acetate buffer, and purified water or injectable distilled water. For the liquid formulation,

for example, polyethylene glycol, sorbitol, polysorbate or physiological saline may be used as a carrier. For powders, for example, crystalline cellulose, α -cellulose, cross-linked sodium carboxymethyl cellulose, hydroxypropyl cellulose, carboxymethyl starch or amylose may be used as a carrier. In addition, these powders may be filled in a capsule. For an ointment, for example, polyethylene glycol, hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or the like may be used as a carrier. Moreover, the active ingredient may be placed on the mucosa by inhalation or a nasal application, to deliver the ingredient in a sustained manner. For this purpose, the formulation may contain, for example, a cellulose ether such as methyl cellulose, ethyl cellulose, propyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose or hydroxypropyl cellulose, or a synthetic polymer such as polyacrylate or carboxyvinyl polymer, as the base material.

These pharmaceutical compositions can be prepared according to a conventional procedure.

The present pharmaceutical composition may contain one of the present compounds in an amount of about 0.1 to 100%, preferably 0.5 to 90%, by weight of the composition.

Next, the antiviral activity of the present compound is demonstrated by the following pharmacological tests. In the tests the following compounds:

Compound A: 4-guanidinobenzoic acid 4-amidinobenzamide.2 methanesulfonate; and

Compound B: 4-guanidinobenzoic acid 6-amidino-2-naphthylamide.2 methanesulfonate, were used.

Pharmacological test 1. Inhibitory action on plaque formation by human influenza virus

The inhibitory activity of the present compounds A and B on plaque formation by human influenza virus A/WSN was measured according to a method described in Virology Vol. 29, 84-91, 1966.

Namely, 1×10^6 MDCK cells (dog kidney cells) were inoculated in 6 cm plastic dish containing D-MEM medium, and cultured in a CO_2 incubator for 24 hours, and after discarding the medium, 0.1 ml of a diluted virus solution containing about 50 plaque forming units of human influenza virus A/WSN was added to the cultured cells. After shaking, the dish was allowed to stand at room temperature for 30 minutes, a solubilized agar containing a desired amount of a test compound was overlaid. After 3 days culture, the agar layer was removed, and cells were stained with a staining solution to count the number of plaques. Next, a plaque formation inhibition ratio was calculated according to the following equation. The result is shown in Table 1.

$$\text{Inhibition ratio (\%)} = (1 - T/C) \times 100$$

wherein

T: mean number of plaques in the presence of a test compound;

C: mean number of plaques of control.

Note, in the above test, the D-MEM medium, the solution for diluting the virus, the upper layer agar, and the staining solution were prepared as follows:

[D-MEM medium]

First, 9.5 g of powder of Dulbecco's Modified EAGLE MEDIUM "Nissui" was dissolved in 1 l of distilled water (the resulting solution is designated 1stDMEM hereinafter), and the solution was autoclaved. L-glutamine (0.584 g), filtered aqueous solution of kanamycin (0.1 g), and 20 ml of a 7.5% sodium bicar-

bonate, and 110 ml of heat-inactivated fetal bovine serum were added thereon.

[Solution for dilution of virus]

First, 10 g of calcium chloride, 10 g of magnesium chloride, and 5.8 ml of 30% bovine serum albumin were dissolved in 1 l of a phosphate buffered saline, and the solution was filtered before use.

[Upper layer agar]	
A: Distilled water	16 ml
2*DMEM + bovine serum albumin	50 ml
1% DEAE dextran	1 ml
7.5% sodium bicarbonate aqueous solution	2 ml
B: 2.0% agar (Noble)	30 ml
Filtrated A solution was added to autoclaved solidified agar.	
[2*DMEM + bovine serum albumin]	
4*Dulbecco	250 ml
1M HEPES	10 ml
10% bovine serum albumin	20 ml
7.5% sodium bicarbonate aqueous solution	16 ml
6%-glutamine aqueous solution	10 ml
10% kanamycin aqueous solution	1 ml
Distilled water	193 ml

The solutions were mixed and filtered before use.

[Staining solution]

After dissolving 100 mg of crystal violet in 20 ml of ethanol, 80 ml of water was added thereto.

TABLE 1

Test sample	Concentration (μg/ml)	Inhibition ratio(%) of plaque formation
Compound A	12.5	2.9
	25	31.0
	50	80.8
Compound B	10	31.4
	20	67.6
	50	82.4

Pharmacological test 2

The growth inhibitory activity of compound B on influenza virus in the lung of hamsters was tested according to J. Mills, *The Journal of Infectious Diseases*, Vol. 123, 145-157, 1971.

Namely, anesthetized mole hamster was intranasally infected with 0.1 ml of a virus solution containing 3.8×10^3 PFU of influenza virus A/Udron/72 (H3N2) grown in a growing chicken egg. At 6, 11 and 24 hours after the infection, 50 μl of test solution containing the compound B in 3.3% hydroxypropyl cellulose solution was intranasally administered. After 28 hours from the infection the hamster was sacrificed by the anesthesia, and the lung was removed. The lung was thoroughly homogenized in a mortar with sea sand, and the homogenate was centrifuged. An amount of virus contained in the resulting supernatant was measured as plaque forming ability in dog kidney cells. The results are shown in Table 2.

TABLE 2

Test compound	Concentration (mg/ml)	Number of animals	PFU/lung	% Inhibition
Control	—	3	$4.8 \pm 2.2 \times 10^3$	—

TABLE 2-continued

Test compound	Concentration (mg/ml)	Number of animals	PFU/lung	% Inhibition
Compound B	10.0	5	$5.0 \pm 10.0 \times 10^3$	99.0*

*P < 0.01, t-Test

As shown in Table 2, compound of the present invention strongly inhibited the growth of influenza virus in lungs of the hamster.

Therefore, since the present compounds efficiently inhibit the growth of envelope viruses such as human influenza virus, they are useful for the treatment of diseases due to viral infections.

EXAMPLES

The present invention will now be further illustrated by, but is by no means limited to, the following examples.

Example 1.

4-Guanidinobenzoic acid 4-amidinobenzamide.2 methanesulfonate

First, 100 mg of 4-guanidinobenzoic acid hydrochloride and 145 mg of 4-amidinobenzamide.2 hydrochloride were suspended in 2 ml of absolute pyridin, and after adding 133 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride thereto, the mixture was stirred at room temperature for 19 hours. The solvent was distilled off under reduced pressure at 30° C., and after drying under reduced pressure, the resulting residue was suspended in ethanol. Then, a saturated sodium bicarbonate aqueous solution was added to the suspension, and the resulting precipitate was filtered. The precipitate was washed with water and acetone, and suspended in methanol, and methanesulfonic acid was added thereto to dissolve the precipitate. Then, the solution was triturated with ethyl ether to afford the methanesulfonate, which was then filtered and dried in vacuo to give 59.2 mg of the title compound as an off-white powder.

Melting point: 264° C.-265° C. (2 methanesulfonate)

High resolution FAB-MS (for $(C_{13}H_{16}N_6O+H)^+$)

Calculated: 297.1464

Found: 297.1443

IR (cm⁻¹, KBr): 3340, 3172, 1683, 1608, 1575, 1509, 1338, 1197, 1044

¹H-NMR (δ, DMSO-d₆): 2.35 (s, 6H), 7.40 (d, J=8.9 Hz, 2H), 7.67 (s, 4H), 7.85 (d, J=8.9 Hz, 2H), 8.03 (d, J=8.9 Hz, 2H), 8.07 (d, J=8.9 Hz, 2H), 8.88 (s, 2H), 9.22 (s, 2H), 9.99 (s, 1H), 10.65 (s, 1H).

Example 2.

4-Guanidinobenzoic acid 6-amidino-2-naphthylamide.2 methanesulfonate

First, 100 mg of 6-amino-2-naphthosmidine.2 hydrochloride and 86.6 mg of 4-guanidinobenzoic acid hydrochloride were condensed to afford an amide hydrochloride according to the same procedure described in Example 1, and the amide hydrochloride was converted to the corresponding carbonate according to the same procedure described in Example 1, for purification. Then methanesulfonic acid was added to a suspension of the carbonate to obtain 17.10 mg of the title compound as a pale yellow amorphous solid.

High resolution FAB-MS (for $(C_{19}H_{18}N_6O+H)^+$)

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Calculated: 347.1620
Found: 347.1621

¹H-NMR (8, DMSO-d₆): 2.32 (s, 6H), 7.40 (d, J=8.9 Hz, 2H), 7.62 (brs, 4H), 7.79 (dd, J=8.9, 1.9 Hz, 1H), 7.98 (dd, J=8.9, 1.7 Hz, 1H), 8.09 (dd, J=8.9, 1.6 Hz, 4H), 8.42 (d, J=1.9 Hz, 1H), 8.63 (d, J=1.7 Hz, 1H), 8.97 (brs, 2H), 9.37 (brs, 2H), 9.93 (brs, 1H), 10.63 (brs, 1H).

Example 3

First, 10 g of 4-guanidinobenzoic acid 4-amidinobenzamide.2 methanesulfonate, 300 g of polyethylene glycol 400 and 0.5 g of polysorbate 80 were stirred while heated, to form a homogeneous solution and a nasal liquid formulation, which could be intranasally administered in a unit dose of 0.1 ml.

Example 4

First, 200 mg of 4-guanidinobenzoic acid 6-amidino-2-naphthylamide.2 methanesulfonate and 100 mg of hydroxypropyl cellulose were thoroughly triturated in a mortar to form a homogeneous powder, which was filled in capsules to prepare intranasal capsules.

Example 5

First, 50 mg of 4-guanidinobenzoic acid 4-amidinobenzamide.2 methanesulfonate and 50 mg of hydroxypropyl cellulose were dissolved in 5 ml of injectible distilled water, and the solution then lyophilized

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to form a homogeneous solid composition, which was then filled in capsules to obtain intranasal capsules.

Example 6

First, 1.0 g of 4-guanidinobenzoic acid 6-amidino-2-naphthylamide.2 methanesulfonate 2.5 g of hydroxypropyl cellulose and 20 g of carbopale were homogeneously mixed, and 0.5 g of magnesium stearate was added to the mixture. The mixture was compressed to form 10 plane tablets, and one tablet was applied to the mucosa in mouth.

We claim:

1. A guanidinobenzene derivative represented by the formula (I):



wherein R¹ represents a substituent selected from the group consisting of a phenyl group substituted by an amidino group and a naphthyl group substituted by an amidino group or a pharmaceutically acceptable acid addition salt thereof.

2. An antiviral pharmaceutical composition comprising a compound represented by the formula (I) according to claim 1, and a pharmaceutically acceptable carrier.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Radicacion : 84687561 88388465 Folios: 16
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Dependencia: 2020 DIVISION DE MARCAS COMERCIALES

RECIBO OFICIAL DE CAJA : 05 - 90,897
FECHA : NOVIEMBRE 28 DE 2005

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	42211324	28/11/2005	903,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LEYAS COMERCIALES	235,000.00
		TOTAL :	\$ 235,000.00

SON: DOSCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

14

83

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO

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Dependencia: 2020 DIVISION DE NUEVAS OPERACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	42211324	28/11/2005	903,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-00	PRORROGA DE TERMINOS	
31		PRORROGA DE TERMINOS	66,000.00
TOTAL :			\$ 66,000.

SON: SESENTA Y SEIS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

84 15

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 90,896
FECHA : NOVIEMBRE 28 DE 2005

SUP-INDUSTRIA Y COM-10
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Dependencia: 2000 DIVISION DE MARCAS COMERCIALES

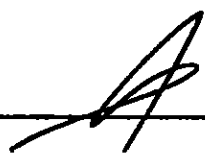
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	42211324	28/11/2005	903,000.00

***** CONCEPTO *****

CANT. CONTABILISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	235,000.00
	TOTAL :	\$ 235,000.00

SON: DOSCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

85 16

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RECIBO OFICIAL DE CAJA : 05 - 90.900
FECHA : NOVIEMBRE 28 DE 2005

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Tramite : 011 PCT-PATENT 378 FASE NUL3 400 OMASION
Dependencia: 8229 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	42211324	28/11/2005	903,000.

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-00	PRORROGA DE TERMINOS	
		31 PRORROGA DE TERMINOS	66,000.00
		TOTAL :	\$ 66,000.00

SON: SESENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____