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As. 82.132 – 94.475

Señora
JEFE DE DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y C[illegible]
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D.

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00021428 00000026 Folios: 3
Fecha (AMD): 2005-07-15 10:32:12
Tramite : 002 PATENTES D 1 REGISTRO/ 444 REPUESTA
Dependencia: 0020 DIVISION DE NUEVAS CREACIONES

REF: Expediente No. 00 021.428 – solicitud de patente de invención a favor de UCB, S.A.

Respuesta a oficio No. 12257 del 03 de marzo de 2005

HECTOR GOMEZ MEJIA, portador de la tarjeta profesional No. 19436 del C.S.J., obrando en calidad de apoderado de la Sociedad UCB, S.A., domiciliada en Bruselas, Bélgica, según lo acredita el documento de poder presentado en esa División, me permito dar respuesta a las observaciones de carácter técnico y jurídico, relacionadas con la patentabilidad, para la concesión de la patente de acuerdo con la Decisión 486 según el concepto técnico No. 304 notificado por fijación en lista de fecha 03 de marzo de 2005, cuyo término fue prorrogado mediante escrito radicado el 02 de junio de 2005.

Las objeciones del señor examinador en relación con la claridad de la solicitud se basan en un análisis equivocado de la misma.

- El señor examinador afirma en primer lugar que en el 1º examen de forma se objeto la unidad inventiva, y el interesado rehusó corregir el capítulo reivindicatorio al respecto, y simplemente se limitó a enviar una copia con los mismos errores originales, sin responder a la objeción de unidad inventiva, durante el tiempo estipulado por la norma para las respuestas al 1º examen de forma.

No estamos de acuerdo con esta afirmación del señor examinador, al respecto es necesario anotar que con nuestro escrito radicado el 11 de julio 2000, en atención al requerimiento formulado en el 1º examen de forma, dimos completa respuesta a las objeciones del señor examinador según las cuales las reivindicaciones 4 y todas sus dependientes no guardan el requisito de unidad de invención. En nuestra respuesta

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EXPEDIENTE No. 00 021.148 Cont.

a esta objeción, manifestamos las primordiales razones por las cuales consideramos que dichas reivindicaciones cumplen con el requisito de unidad de invención, razones que ratificamos y que en general manifestaban lo siguiente:

"respecto a la reivindicación 4, nuestro poderdante puntualiza:
en la reivindicación 1, los compuestos de fórmula I' se define como sigue:
G y G', juntos, conforman HC-N, HC-CH o C=C;
D es –CH= o =N-; y
R^1 y R^2 son, independientemente, hidrógeno o juntos son $-(CH_2)_n-$, siendo n igual a 0, 1, 2 ó 3.

Los compuestos reivindicados en la reivindicación 4 y que tienen la fórmula III corresponden a los compuestos de la reivindicación 1 que tienen la fórmula I donde
G y G', juntos, forman C = C;
D es = N;
R^1 y R^2 juntos son $-(CH_2)_n-$, siendo n igual a 0.

Es claro que la definición de cada sustituyente de los compuestos de la reivindicación 4 está comprendida en la definición de los sustituyentes de la reivindicación 1. Consecuentemente, los compuestos de la reivindicación 4 están incluidos en la descripción de los compuestos de la reivindicación 1; y se cumple con el requisito de la unidad de invención".

De acuerdo con lo anterior, insistimos en que se atendió y se dio apropiada respuesta a la objeción de unidad invención.

- En segundo lugar el señor examinador afirma que "Luego presenta fuera de dicho período estipulado, una divisional que no tiene sentido, ya que contiene nuevamente la misma materia que la originalmente reivindicada, excepto porque a algunos sustituyentes no se le colocan uno o dos significados que originalmente tenía, y que además contiene los mismos defectos formales originales."

Al respecto es necesario anotar que las anteriores declaraciones del señor examinador son clara evidencia de una lectura errónea de los documentos presentados ante su despacho. Es claramente evidente, al leer el capítulo reivindicatorio de la solicitud divisional, contenido en el folio 284, que este comprende solamente una reivindicación. Por dicha razón no tiene sentido aseverar, como lo hace el señor examinador, que el capítulo reivindicatorio de la

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solicitud divisional contiene "[...] los mismos defectos formales originales."

Igualmente el argumento del señor Examinador de que la divisional "[...] contiene nuevamente la misma materia que la originalmente reivindicada [...]" claramente no surge de la lectura de la solicitud divisional. Es perfectamente obvio, de la lectura del capítulo reivindicatorio de la solicitud divisional, que el material reivindicado en la única reivindicación presente no puede de manera alguna ser el mismo que el material presente en las 24 reivindicaciones de la solicitud original.

Resulta entonces "de elemental entendimiento" que para la evaluación y el estudio de la nueva solicitud divisional presentada es necesario realizar una lectura correcta de los documentos presentados y no juzgar a simple vista un material que, evidentemente, no fue leído completamente.

De acuerdo con lo anterior, me permito:

1º. Manifestar que nuestro poderdante ha decidido DESISTIR del trámite de la solicitud de patente original, y

2º. Solicitar se estudie y se continúe el trámite de la solicitud divisional, sobre la base del capítulo reivindicatorio comprendido en el folio 284 de dicha solicitud divisional.

Consecuentemente, sírvase señora jefe proceder de conformidad

Atentamente,

HECTOR GOMEZ MEJIA
T.P. No. 19.436 del C.S.J.
C.C. 22 720 de Bogotá
Carrera 7 No. 16-56 piso 9

Bogotá, 14 de julio de 2005
MEV/CH/yg

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

2020
Bogotá, DC, 19 de agosto de 2005

Apoderado:Hector Goméz Mejia: Oficio: 7731

ASUNTO Radicación: 00-21428
Trámite 002
Evento 001
Actuación 430
Folios

Como resultado del examen de fondo, realizado con fundamento nuevamente en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados:

◆capitulo descriptivo, folios 230 a 286;
◆capitulo reivindicatorio, folios 287 a 299;
◆1° examen de forma, folios a 85 y 86 ;
◆respuesta técnica al 1° examen de forma, folios 224 y 229;
◆Solicitud de una divisional, folios 319 a 526;
◆solicitud de la cual se reivindica prioridad, junto con la traducción requerida, folios 91 a 221;
◆2° examen de forma, folio 315;
◆Solicitud del examen de patentabilidad, folios 317 y 318.
◆Examen de patentabilidad, folios 541 a 543.

Objeto de la invención:

El titulo de la invención es "COMPUESTOS DE PIPERAZINAS 1,4- SUSTITUIDAS, PIPERIDINAS 1,4-SUSTITUIDAS Y 4-ALQUILIDENILPIPERIDINAS 1-SUSTITUIDAS Y PROCEDIMIENTOS PARA EL TRATAMIENTO DE ASMA, ALERGIAS Y TRANSTORNOS INFLAMATORIOS."
El objeto de la presente solicitud se refiere a compuestos de la formula marckus I' que tienenpropiedades farmacologicas como inhibidores de la 5-LO así como propiedades antihistaminicas.

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Claridad de la solicitud:

En el artículo 30 de la Decisión 486 de la Comisión de la Comunidad Andina se establece: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*.

La solicitud divisional no se acepta porque la materia reclamada no aparece en el capitulo reivindicatorio originalmente presentado de la presente solicitud, tampoco dicha materia aparece en el capitulo reivindicatorio de la solicitud de la cual se reivindica prioridad, además cualquier solicitud de patente debe **tener lo siguiente como mínimo respecto a la materia reclamada de acuerdo con la D. 486 C.C.A:**

"Artículo 28.- La descripción deberá divulgar la invención de manera suficientemente clara y completa para su comprensión y para que una persona capacitada en la materia técnica correspondiente pueda ejecutarla. *La descripción de la invención indicará el nombre de la invención e incluirá la siguiente información*:

-el sector tecnológico al que se refiere o al cual se aplica la invención;
-la tecnología anterior conocida por el solicitante que fuese útil para la comprensión y el examen de la invención, y las referencias a los documentos y publicaciones anteriores relativas a dicha tecnología;
-una descripción de la invención en términos que permitan la comprensión del problema técnico y de la solución aportada por la invención, exponiendo las diferencias y eventuales ventajas con respecto a la tecnología anterior;
una reseña sobre los dibujos, cuando los hubiera;
-una descripción de la mejor manera conocida por el solicitante para ejecutar o llevar a la práctica la invención, utilizando ejemplos y referencias a los dibujos, de ser éstos pertinentes; y,
-una indicación de la manera en que la invención satisface la condición de ser susceptible de aplicación industrial, si ello no fuese evidente de la descripción o de la naturaleza de la invención."

Y tal como puede verse en la divisional, se realizó de una manera caprichosa, ya que el capitulo descriptivo de dicha divisional no describe la materia reclamada, sino otra materia totalmente diferente; el arte anterior no hace ni mención a la materia que debía hacer referencia; los ejemplos que debe tener toda solicitud de patente o mejor forma ejecución se refieren a materia diferente a la reclamada; la solución del problema técnico planteado no corresponde con la materia reclamada; por lo tanto dicha divisional no se acepta, ya que no cumple con los requisitos, que debe cumplir cualquier solicitud de patente.

El hecho de que cualquier compuesto aparezca nombrado o enumerado en una

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solicitud, no es una descripción suficiente que cumpla con lo estipulado en el Art-28 de la Decisión 486 C.C.A

Ahora respecto al capitulo reivindicatorio de la solicitud en estudio, folios 287 a 299, posee los siguientes problemas de claridad:

-las definiciones de los significados de M y M', "*un catón farmaceuticamente aceptable o un grupo saliente desde el punto de vista metabólico*" son definiciones funcionales, que no delimitan el alcance de las reivindicaciones, ni poseen un significado químico inequívoco.

Evaluación de la Unidad de Invención:

Esta solicitud de patente comprende solamente una invención o un grupo de invenciones relacionadas entre sí, de manera que se integra un único concepto inventivo conforme al artículo 25 de la Decisión 486 de la Comisión de la Comunidad Andina. Para el presente caso es una invención reclamada con diferentes categorías de reivindicaciones:

-1° invención 1-(diaril-metilino ó metil)piperazino, y sus derivados;
-2° invención 1-(diaril-metilino ó metil)piperidin y sus derivados ;
-3°invención derivados 6,11-dihidro-5H-benzo[5,6]ciclohepta[1,2-b]piridina y sus derivados de loratadina.
-4°invención derivados 4-(10,11-dihidro-5H-dibenzo[a,d]anulen-5-ileden)piperidin también con piperidin.

Y para cada grupo de invenciones se debe hacer una búsqueda independiente, por ejemplo de los compuestos de la reivindicación 3 no se puede llegar a los compuestos de la reivindicación 4 o viceversa, eso indica claramente que no comparten las características técnicas especiales, o sea, cada una de las estructuras que se aportan como nuevas al estado de la técnica son diferente.

Excepciones de Patentabilidad:

El artículo 20 de la Decisión 486 de la Comisión de la Comunidad Andina establece en su inciso d) que no serán patentables: "*los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales*".

Las reivindicaciones 22 a 24, reclaman un método para tratamiento del cuerpo humano o animal, por lo tanto están inmersas bajo el alcance del artículo 20 de la Decisión 486 C.C.A

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Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión establece: "*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. Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40.*"

Item	Documento	Fecha de publicación	Titulo
D1	US 4282233	4-ago-1981	Antihistaminic 11-(4-piperidylidene)-5H-benzo-[5,6]-cyclohepta-[1,2-B]-pyridines
D2	US 4525358	25-jun-1985	2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids and their amides.
D3	US 5066658	19-nov-1991	Substituted hydroxyureas
D4	US 5438062	1-ago-1995	Benzo(5,6)cycloheptapyridines, compositions and methods of use.

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: "*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.*"

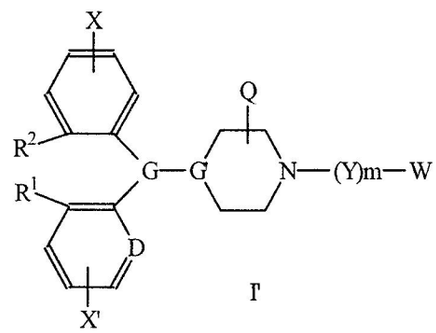
En cumplimiento con este artículo, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la Novedad:

El art.16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: "*Una invención se considerará nueva cuando no está comprendida en el estado de*

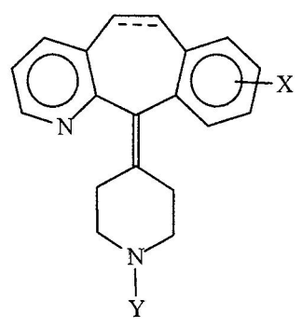
la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida".

La solicitud en estudio reclama derivados compuestos de formula Marckush I':



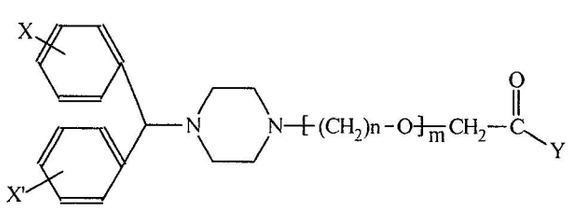
I'

La anterioridad D1 enseña compuestos 11-(4-piperidiledeno)-5H-benzo-[5,6]-ciclohepta-[1,2-B]-piridinas de formula:



-De esta anterioridad la solicitud en estudio reclama todos los compuestos que están descritos por ejemplo en la columna 1, de los renglones 25 a 60. Por lo tanto los compuestos son reclamados en la solicitud en estudio la formula amplia y especulativa que no posee ninguna parte fija no son nuevos, y la anterioridad es especifica respecto a la solicitud en estudio.

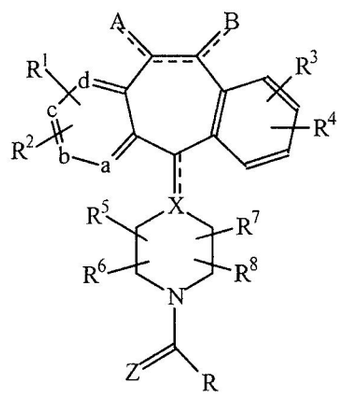
-La anterioridad D2 que se refiere a compuestos ácido 2-[4-difenilmetil)-1-piperazinil]-acético y sus amidas de formula:



-Especialmente si observamos los compuestos descritos en la columna 1, renglones 15 a 37, y las reivindicaciones de esta anterioridad, vemos que todos estos compuestos caen dentro del alcance de la materia reclamada en la solicitud.

-La anterioridad D3 describe compuestos derivados de hidroxiureas y en su ejemplo 75 detalla el 4-(difenilmetil)-N-metilpiperidina-1-carboxamida, que es un compuesto especifico que demuestra que los compuestos de la solicitud no son nuevos.

-La anterioridad D4 describe compuestos derivados benzo[5,6]ciclohepta piridina de fórmula:



Compuestos de esta formula caen dentro del alcance de lo reclamado por la solicitud en estudio con, especialmente columnas 1, 2, 9, 10, tabla IA, IB y reivindicaciones, se puede entonces decir que los compuestos de la solicitud son del estado de la técnica.

Y tal como se puede ver la solicitud en estudio realmente no tiene unidad inventiva, tal como se indico arriba.

No	Documento:	Reivindicaciones afectadas:	Requisito afectado
D1	US 428233	1,2, 4 a 20	Novedad
D2	US 4525358	1 a 3, 5 a 20	Novedad
D3	US 5066658	1 a 3, 5 a 20	Novedad
D4	US 5438062	1, 2, 4 a 20	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de

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sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la circular única No. 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de 01 SET. 2005
fecha_____

CONCEPTO TÉCNICO N °	EXAMINADOR TÉCNICO Código 202012

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United States Patent [19]

Vilani

[11] **4,282,233**

[45] **Aug. 4, 1981**

[54] **ANTIHISTAMINIC 11-(4-PIPERIDYLIDENE)-5H-BENZO-[5,6]-CYCLOHEPTA-[1,2-B]-PYRIDINES**

[75] Inventor: **Frank J. Vilani**, West Caldwell, N.J.

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

[21] Appl. No.: **160,795**

[22] Filed: **Jun. 19, 1980**

[51] **Int. Cl.**[3] **A61K 31/445**; C07D 401/04

[52] **U.S. Cl.** **424/267**; 546/93

[58] **Field of Search** 546/93; 424/267

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,326,924	6/1967	Villani	546/93
3,357,986	12/1967	Villani	546/93
3,366,635	1/1968	Villani	546/93
3,419,565	12/1968	Villani	546/93

OTHER PUBLICATIONS

Villani, F., et al., *J. Med. Chem.*, 15 (7), 750–754 (1972).

Primary Examiner—Richard A. Schwartz
Attorney, Agent, or Firm—Paul H. Ginsburg

[57] **ABSTRACT**

11-(4-Piperidylidene)-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridines and their 5,6-dihydro derivatives are disclosed. The compounds are useful as antihistamines with little or no sedative effects.

13 Claims, No Drawings

D1

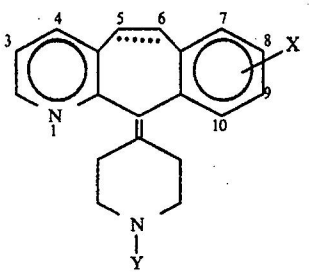
ANTIHISTAMINIC 11-(4-PIPERIDYLIDENE)-5H-BENZO-[5,6]-CYCLOHEPTA-[1,2-B]-PYRIDINES

The present invention relates to novel 11-(4-piperidylidene)-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridines.

U.S. Pat. No. 3,326,924 discloses 6,11--dihydro-11-(N-methyl-4-piperidylidene)-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine and 11-(N-methyl-4-piperidylidene-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine, useful as antihistamines.

The compounds of the present invention are likewise useful as antihistamines, but are preferred to the compounds of the aforementioned patent because the present compounds have little or no sedative effects, thus being preferred for use with patients that must operate machinery or automobiles or perform other mental or physical tasks requiring a high level of concentration.

The compounds of the present invention are compounds of the formula



(I)

wherein the dotted line represents an optional double bond and wherein the numbering system used herein is illustrated. In this formula, X is hydrogen or halo and Y is substituted carboxylate or substituted sulfonyl for example Y is —COOR or SO_2R, with the proviso that when Y is —COOR, R is C_1 to C_{12} alkyl, substituted $C_1$to C_{12} alkyl, phenyl, substituted phenyl, C_7 to C_{12} phenyl alkyl, C_7 to C_{12} phenyl alkyl wherein the phenyl moiety is substituted or R is -2,-3, or -4 piperidyl or N-substituted piperidyl wherein the substituents on said substituted C_1 to C_{12} alkyl are selected from amino or substituted amino and the substituents on said substituted amino are selected from C_1 to C_6 alkyl, the substituents on said substituted phenyl and on said substituted phenyl moiety of the C_7 to C_{12} phenyl alkyl are selected from C_1 to C_6 alkyl and halo, and the substituent on said N-substituted piperidyl is C_1 to C_4 alkyl; and with the proviso that when Y is SO_2R, R is C_1 to C_{12} alkyl, phenyl, substituted phenyl, C_7 to C_{12} phenyl alkyl, C_7 to C_{12} phenyl alkyl wherein the phenyl moiety is substituted, wherein the substituents on said substituted phenyl and said substituted phenyl moiety of the C_7 to C_{12} phenyl alkyl are selected from C_1 to C_6 alkyl and halo.

In a preferred embodiment of the present invention, Y is —COOR and R is C_1 to C_6 alkyl or substituted alkyl, phenyl, substituted phenyl, C_7 to C_{12} aralkyl or substituted aralkyl or -2, -3 or -4 piperidyl or N-substituted piperidyl. When R is substituted alkyl, R is substituted with amino or with substituted amino. The substituents on said substituted amino are C_1 to C_6 alkyl. The substituents on the aforementioned substituted phenyl and on the phenyl moiety of the substituted aralkyl are preferably C_1 to C_6 alkyl or halo.

In a second preferred embodiment of the present invention, Y is SO_2R and R is C_1 to C_6 alkyl, phenyl, substituted phenyl, C_7 to C_{12} aralkyl or substituted aralkyl, wherein the substituents on said substituted phenyl and on the phenyl moiety of the substituted aralkyl are C_1 to C_6 alkyl or halo.

The aforementioned alkyl groups may be linear, branched or cyclic or may contain both cyclic and linear or cyclic and branched moieties. Halo may be fluoro, chloro, bromo or iodo.

The present invention also relates to a pharmaceutical composition comprising an effective amount of a compound of the formula I as defined above, together with a pharmaceutically acceptable carrier and to a method of effecting an anti-allergic response in an animal comprising administering to the animal an effective amount of a compound of the formula I as defined above.

Generally, compounds of the present invention are prepared by replacing a methyl or another replacable substituent, for example carbophenoxy on the nitrogen of the piperidylidene ring of an appropriate compound of the formula I with the desired substituent.

For example, compounds of the formula I wherein Y is —COOR are prepared by reacting a compound of the formula I wherein Y is methyl (Compound IA) or an appropriate derivative of Compound IA with an appropriate chloroformate, for example, an alkylchloroformate or phenyl chloroformate in order to replace the N-methyl group on the piperidylidene group of Compound IA.

Compounds of the formula I wherein Y is —COOR may also be prepared by reacting a compound of the formula I wherein Y is —COOR and R is phenyl with the sodium salt of an appropriate alcohol.

Compounds of the formula I wherein Y is —COOR and R is tert-butyl may be prepared by reacting a compound of the formula I wherein Y is hydrogen with a di-tertiarybutyl carbonate in an inert solvent, for example, tetrahydrofuran.

Compounds of the formula I wherein Y is $-SO_2R$ are prepared by reacting a compound of the formula I wherein Y is hydrogen with a compound of the formula Cl—SO_2R, wherein R has the same value as R in the desired product, in the presence of an excess of anhydrous potassium carbonate in an inert solvent, for example dry toluene.

The following non-limiting Examples further illustrate the preparation of the compounds of the present invention:

EXAMPLE 1

A.

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

To a solution of 10.9 g (0.1 mole) of ethylchloroformate in 300 ml. of anhydrous benzene is added dropwise, with stirring at room temperature, a solution of 14.5 g (0.05 M) of 11-(N-methyl-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine (Compound IA) in 200 ml of benzene. The solution is stirred and is heated under reflux overnight (16–20 hrs.). The mixture is cooled and is poured into ice water and the organic layer is separated, washed with water, dried, and then concentrated to dryness. The residue is triturated with petroleum ether and a white solid having

a melting point of 106°–107° C. is recrystallized from isopropyl ether after decolorization with decolorizing carbon.

B.

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

Using the procedure of Example IA, react 16.2 g of the 8-chloro derivative of Compound IA and 10.9 g (0.1 mole) of ethylchloroformate to prepare the title compound, having a melting point of 128°–130° C. The 7,9 and 10-chloro analogues are similarly prepared.

C.

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

Using the procedure of Example IA, react 14.5 g of Compound IA and 9.4 g of methylchloroformate to prepare the title compound, having a melting point of 116°–118° C.

EXAMPLE 2

11-(N-Carbophenoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine (Compound IB)

To a solution of 29.1 g (0.1 mole) of Compound IA in 150 ml. of anhydrous carbon tetrachloride is added 17 g of phenylchloroformate in an equal volume of anhydrous carbontetrachloride. Heat under reflux for 15 minutes with stirring and pour into water. Separate and wash the organic layer with water and remove solvent. Extract the residue with ether, filter off the insoluble material and remove the ether. The residue is recrystallized from isopropyl ether to yield the title compound having a melting point of 127°–130° C.

Similarly prepare the 7,8,9, or 10-chloro derivatives of the title compound using this procedure:

EXAMPLE 3

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

Dissolve 0.5 g sodium metal in 50 ml isopropanol and add 7.9 g of Compound IB from Example 2. Heat with stirring for 5 hours on the steam bath at 90°–95° and allow to cool overnight.

Add ice water to precipitate the product and extract 3 times with ether and once with chloroform. Wash with water, distill off solvents, triturate with hexane and recrystallize from isopropylether. The melting point is 147°–148° C.

Using this procedure and replacing the isopropanol with n-butanol, cyclopentanol, allylalcohol, cyclopropylmethanol, benzylalcohol, p-chlorobenzylalcohol, phenethylalcohol, dimethylaminoethylalcohol or N-methyl-4-hydroxy piperidine prepare the corresponding carbamoyl derivatives. Similarly, using the chloro derivatives of Compound IB and the sodium salts of the aforementioned alcohols, prepare the chloro derivatives of the aforementioned carbamoyl derivatives.

EXAMPLE 4

11-(N-Carbo-t-butoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine.

Dissolve 13.8 g of 11-(4-piperidylidene)-6,11 dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine (Compound IC) prepared according to Villani et. al., J. Med. Chem. 15, 750 (1972) in 250 ml of dry tetrahydrofuran. With stirring, add in one portion 12 g of di-t-butyl carbonate and stir at room temperature overnight. The mixture is poured into water, is extracted with ether, is washed with water and the solvent removed. Recrystallize the residue from isopropyl ether. The melting point is 144°–145° C.

EXAMPLE 5

11-(N-Methanesulfonyl-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine.

To 10 g of Compound IC in 200 ml of dry toluene add 13 g of anhydrous potassium carbonate. After several minutes of stirring at room temperature, add dropwise a solution of 6 g of methanesulfonyl chloride in 20 ml of toluene. Continue stirring for 16 to 20 hours and then filter. Recrystallize the solid material from ethanol. The melting point is 223°–224° C.

Using this procedure and adjusting the weight of the requisite sulfonyl chloride so that 0.04 moles of said alkanesulfonyl chloride are used, the ethanesulfonyl, n-propylsulfonyl, n-butylsulfonyl, cyclopropylsulfonyl, heptylsulfonyl, dodecylsulfonyl, phenylsulfonyl, p-methylphenyl-sulfonyl, p-fluorophenylsulfonyl, p-chlorophenylsulfonyl, benzylsulfonyl, p-chlorobenzylsulfonyl, p-tertbutylphenylsulfonyl and cyclopentylsulfonyl compounds of formula I wherein Y is SO_2R are obtained.

Similarly, prepare the tricyclic ring substituted chloro derivatives.

Substituting the appropriate starting material having a double bond between the 5 and 6 positions of the ring system, and using the procedures set forth in Examples 1 to 5 above for the corresponding 6,11-dihydro compounds, the corresponding 6,11-dehydro compounds are prepared. Also, by substituting the appropriate bromo or other halo analogue, as desired, of the chloro compounds of the Formula I used as starting materials, the desired halo compounds of the formula I are prepared.

The compounds of the present invention are useful as non-sedating antihistamines. These compounds act as anti-allergic agents in the treatment of such conditions as perennial and seasonal allergic rhinitis and chronic urticaria.

The compounds of the present invention are administered in pharmaceutical formulations comprising the compound in admixture with a pharmaceutical carrier suitable for enteral or parenteral administration. The formulations may be in solid form, as for example tablets and capsules, or in liquid form as for example syrups, elixirs, emulsions, and injectables. In the formulation of pharmaceutical dosage forms there generally is utilized excipients as for example, water, gelatin, lactose, starches, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, and petroleum jelly. Preferred formulations are more fully illustrated in Example 6.

Although the required dosage will be determined by such factors as the patient's age, sex, weight and the severity of the allergic reaction to be treated, the preferred human dosage range is likely to be 4 to 50 mg of the effective compound 1 to 3 times per day. The preferred dosage ranges for other animals can readily be determined by using standard testing methods.

The following Examples are illustrative of the aforementioned pharmaceutical compositions:

United States Patent [19]

Baltes et al.

[11] Patent Number: 4,525,358

[45] Date of Patent: Jun. 25, 1985

[54] 2-[4-(DIPHENYLMETHYL)-1-PIPERAZINYL]-ACETIC ACIDS AND THEIR AMIDES

[75] Inventors: Eugène Baltes, Rhode-St.Genese; Jean de Lannoy; Ludovic Rodriguez, both of Brussels, all of Belgium

[73] Assignee: UCB Pharmaceuticals, Inc., Dover, Del.

[21] Appl. No.: 496,489

[22] Filed: May 17, 1983

Related U.S. Application Data

[63] Continuation of Ser. No. 345,918, Feb. 4, 1982, abandoned.

[30] Foreign Application Priority Data

Feb. 6, 1981 [GB] United Kingdom 8103768
Apr. 8, 1981 [GB] United Kingdom 8110990

[51] Int. Cl.[3] A61K 31/50; C07D 295/14
[52] U.S. Cl. 514/255; 544/396
[58] Field of Search 544/396; 424/250

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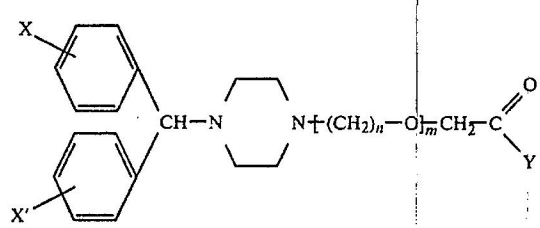
Pong et al., *J. Pharm. Sci.,* 1974, 63 (10), 1527–1532.

Fouda et al., *J. Pharm. Sci.,* 1979, 68 (11), 1456–1458.

Primary Examiner—Donald G. Daus
Assistant Examiner—G. Hendricks
Attorney, Agent, or Firm—Wenderoth, Lind & Ponack

[57] ABSTRACT

New 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids, their amides and their salts, processes for the preparation thereof and therapeutic compositions. These compounds have the formula



wherein Y=—OH or —NH_2; X and X′=H, halogen, alkoxy or trifluoromethyl; m=1 or 2 and n=1 or 2.

The amides of the 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids are prepared either by reacting a 1-(diphenylmethyl)-piperazine with an omegahaloacetamide, or by reacting an alkali metal salt of an omega-[4-(diphenylmethyl)-1-piperazinyl]-alkanol with a 2-haloacetamide, or yet by reacting ammonia with a halide or alkyl ester of a 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acid, whereas the 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids are prepared by hydrolyzing the corresponding amide or lower alkyl ester.

These compounds have in particular an antiallergic, spasmolytic and antihistaminic activity.

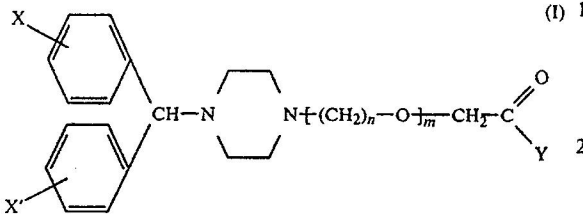
31 Claims, No Drawings

2-[4-(DIPHENYLMETHYL)-1-PIPERAZINYL]-ACETIC ACIDS AND THEIR AMIDES

This application is a continuation of application Ser. No. 345,918, filed Feb. 4, 1982 (now abandoned).

The present invention relates to new 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acids and the amides and non-toxic, pharmaceutically acceptable salts thereof, as well as to processes for the preparation thereof and to pharmaceutical compositions containing them.

The new compounds according to the present invention have the general formula:



(I)

wherein

Y is a hydroxyl group or an $-NH_2$ group,

X and X' represents independently a hydrogen atom, a halogen atom, a straight or branched chain lower alkoxy radical or a trifluoromethyl radical,

m is 1 or 2, and

n is 1 or 2, preferably 2,

as well as the non-toxic, pharmaceutically acceptable salts thereof.

The term "lower alkoxy" as used herein means residues of both straight and branched chain aliphatic alcohols having from 1 to 4 carbon atoms, such as methoxy, ethoxy, propoxy and the like. The halogen atom is preferably a chlorine or fluorine atom.

The expression "non-toxic, pharmaceutically acceptable salts" are used herein means not only the addition salts of the acids and amides of formula I with pharmaceutically acceptable acids, such as acetic, citric, succinic, ascorbic, hydrochloric, hydrobromic, sulfuric and phosphoric acid, but also the pharmaceutically acceptable salts of the acids of formula I such as the metal salts (for example sodium or potassium salts), the ammonium salts, the amine salts and the aminoacid salts.

These pharmaceutically acceptable salts may be prepared from compounds of formula I by per se known methods.

The preferred compounds according to the present invention are:

2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl-]ethoxy]-acetic acid and its dihydrochloride;

potassium 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetate;

2-[2-[4-(diphenylmethyl)-1-piperazinyl]ethoxy]-acetic acid and its dihydrochloride;

2-[2-[4-[(4-fluorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid and its hydrate.

The compounds of formula I possess interesting pharmacological properties. In particular, they are useful as antiallergic, antihistaminic, bronchodilatory and antispasmodic agents.

Furthermore, they are characterized by the fact that their secondary effects of stimulating or depressing the central nervous system, which are frequently observed in the case of conventional antihistaminic agents, are minimal. In addition, they display interesting anaesthetic and antiinflammatory properties and also display an activity in cases of cerebral and cardiovascular insufficiency.

In an article by H. B. WRIGHT and D. L. MARTIN (J. med. Chem. 11, (1968), 390–391) the activity of 2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-acetamide (formula I: $Y=NH_2$; X=p—Cl; X'=H; but m=O) as a hypocholesteremic agent is studied but the results obtained were not very encouraging.

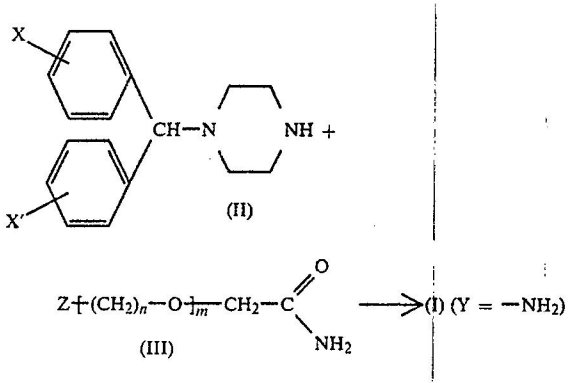
Furthermore, according to Belgian Patent Specification No. 763,609, 2-[4-(diphenylmethyl)-1-piperazinyl]-acetamide (formula I: $Y=NH_2$; X=X'=H; but m=O) possesses a diuretic activity. It also describes similar acetamides in which the nitrogen atom of the amide group is substituted and wich possess various other pharmacological properties.

The pharmacological tests which we have carried out demonstrate that the antiallergic, antispasmodic and antihistaminic activities of these acetamides, as well as of the corresponding acids, are of little interest (see B. Pharmacology).

A. PROCESSES OF PREPARATION

I. The amides of formula I ($Y=-NH_2$) may be prepared by several methods, namely:

I.1. reacting a 1-(diphenylmethyl)-piperazine of formula II with an omegahaloacetamide of formula III according to the following equation:

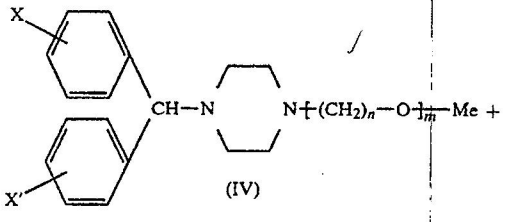


(II) (III) (I) (Y = $-NH_2$)

in which X, X', m and n have the same meanings as above and Z is a halogen atom.

This reaction is generally carried out by heating the reaction mixture to 80° to 150° C. for several hours in an inert solvent, which is preferably an aliphatic alcohol, an aliphatic ketone, for example methyl ethyl ketone, or an aromatic hydrocarbon, such as toluene or xylene, in the presence of an acid acceptor, such as a tertiary organic base, for example triethylamine, or an inorganic base, for example sodium carbonate.

I.2. reacting an alkali metal salt of an omega-[4-(diphenylmethyl)-1-piperazinyl]-alkanol of formula IV with a 2-haloacetamide of formula V according to the following equation:



(IV)

search Conference on Medicinal Chemistry, Aug. 3-7, 1959, at Colby Junior College, New London).

Progressive doses of the test compounds are administered intraperitoneally to groups of three male mice (body weight 18 to 22 g) and the general behaviour of the animals is observed according to known criteria.

The following reference compounds are used:

hydroxyzine=2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethoxy]-ethanol.

oxazepm=7-chloro-1,3-dihydro-3-hydroxy-5-phenyl:2H-1,4-benzodiazepin-2-one.

The following Table III gives the doses (in mg/kg) which induce the first manifestations of tranquilization in the animals:

TABLE III

Test Compound	Tranquilizing dose in mg/kg
A	>255
B	38.7
C	115
D	>460
E	136
F	94
G	34
H	46.2
J	138
K	106
L	141
M	505
N	372
Hydroxyzine	27
Oxazepam	2.6

It can be seen from this Table that the compounds according to the invention have little sedative effect in comparison with the reference compounds.

Furthermore, in this test, the toxicity of the compounds according to the present invention proves to be very low.

In the following Table IV, the lethal doses in mg/kg (two animals out of three) are given for compounds of the invention when administered intraperitoneally in mice:

TABLE IV

Test compound	Lethal dose ($\frac{2}{3}$) in mg/kg
A	255
B	232
C	386
D	460
E	456
F	282
G	339
H	277
I	116
J	138
K	708
L	942
M	505
N	372

If Tables III and IV (tranquilizing dose and lethal dose) are compared, it can be seen that for certain compounds the sedative effect only appears at a dose which is near the lethal dose.

4. DL 50 Lethal dose.

The low toxicity of the compounds according to the present invention has been confirmed by the measure of the DL 50 toxicity when administered per os. Thus, for compound J, in Wistar rats DL 50 is 703 mg/kg for the male rat and 865 mg/kg for the female rat.

In mice, the DL 50 for the same compound is respectively 600 mg/kg (male mouse) and 752 mg/kg (female mouse).

POSOLOGY AND ADMINISTRATION.

The pharmaceutical compositions containing the compounds of the present invention may be administered orally, parenterally or rectally. They may also be administered by nasal instillation (aerosols) or in the form of unguents or creams. The pharmaceutical compositions which can be used for oral administration may be solid or liquid, for example, in the form of uncoated or coated tablets, pills, dragees, gelatine capsules, solutions, syrups and the like. The compositions which can be used for parenteral administration may be any of those pharmaceutical compositions known for this mode of administration, for example, aqueous or oily solutions, suspensions or emulsions. For administration by the rectal route, the compositions containing the compounds of the present invention are generally used in the form of suppositories.

The pharmaceutical forms, such as injectable solutions, injectable suspensions, tablets, drops, suppositories and the like, are prepared by conventional pharmaceutical methods. The compounds of the present invention are mixed with a solid or liquid, non-toxic and pharmaceutically acceptable carrier and possibly also mixed with a dispersing agent, a distintegration agent, a stablilizing agent and the like. If appropriate, it is also possible to add preservations, sweeteners, coloring agents and the like.

The percentage of active compound in the pharmaceutical compositions may be varied within wide limits, according to the patient and the mode of administration and, in particular, the frequency of administration.

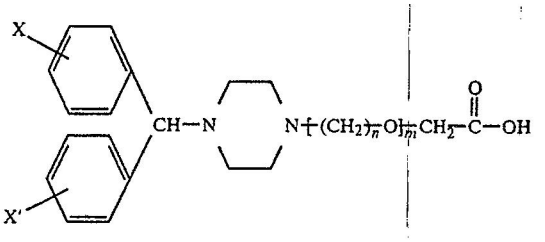
With regard to the posology, it may be varied within a wide range of dosage units, for example from 0.5 to 250 mg of active compound.

As an Example of a composition containing a compound of the present invention, the following formulation of a gelatine capsule for administration per os is given:

compound J	100 mg
lactose	67 mg
magnesium stearate	1 mg
silicon dioxide (Aerosil)	2 mg

We claim:

1. A compound of the formula



wherein

X and X' represents independently a hydrogen atom, a halogen atom, a straight or branched chain lower alkoxy radical or a trifluoromethyl radical,

m is 1 or 2, and

n is 1 or 2

or a non-toxic pharmaceutically acceptable salt thereof.

2. A compound or non-toxic pharmaceutically acceptable salt thereof according to claim 1 wherein n is 2.

3. A compound according to claim 1, said compound being 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid or a non-toxic pharmaceutically acceptable salt thereof.

4. A compound as claimed in claim 1, namely potassium 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetate.

5. A compound as claimed in claim 1, namely 2-[2-[4-(diphenylmethyl)-1-piperazinyl]ethoxy]-acetic acid or its dihydrochloride.

6. A compound as claimed in claim 1, namely 2-[2-[4-[(4-fluorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid or its hydrate.

7. The compound 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid.

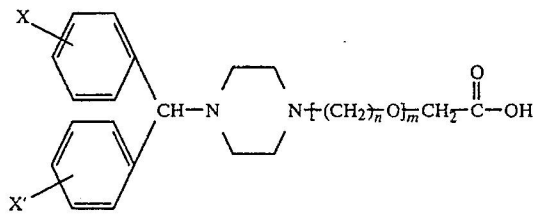
8. The substantially pure crystalline compound according to claim 7 having a melting point of 110°–115° C.

9. A non-toxic pharmaceutically acceptable salt of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid.

10. The dihydrochloride of 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid.

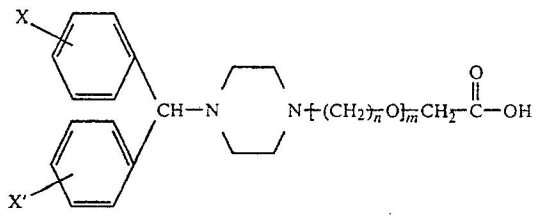
11. The substantially pure dihydrochloride of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid having a melting point of about 225° C.

12. A pharmaceutical composition which comprises a pharmaceutically effective amount of a compound of the formula



wherein
X and X′ represent independently a hydrogen atom, a halogen atom, a straight or branched chain lower alkoxy radical or a trifluoromethyl radical,
m is 1 or 2, and
n is 1 or 2
or a non-toxic pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier thereof.

13. An antihistaminic composition according to claim 12, said composition containing an antihistaminically effective amount of a compound of the formula



wherein
X and X′ represent independently a hydrogen atom, a halogen atom, a straight or branched chain lower alkoxy radical or a trifluoromethyl radical,
m is 1 or 2, and
n is 1 or 2
or a non-toxic pharmaceutically acceptable salt thereof.

14. An antihistaminic composition according to claim 13, said composition containing an antihistaminically effective amount of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid or a non-toxic pharmaceutically acceptable salt thereof.

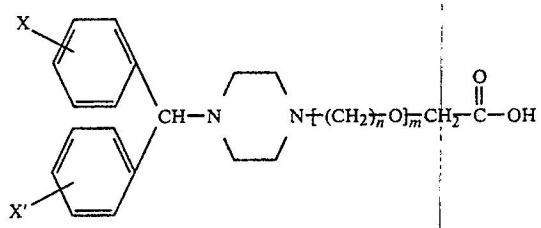
15. A composition according to claim 13 containing an antihistaminically effective amount of a non-toxic pharmaceutically acceptable salt of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid.

16. A composition according to claim 15 containing an antihistaminically effective amount of the dihydrochloride of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid.

17. A composition according to claim 16 in dosage unit form containing from 0.5 to 250 mg of the said dihydrochloride.

18. A composition according to claim 17 in orally administrable dosage unit form.

19. An antiallergic composition comprising an antiallergically effective amount of a compound of the formula



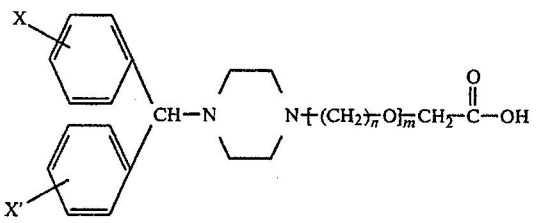
wherein
X and X′ represent independently a hydrogen atom, a halogen atom, a straight or branched chain lower alkoxy radical or a trifluoromethyl radical,
m is 1 or 2, and
n is 1 or 2
or a non-toxic pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier therefor.

20. A composition according to claim 19, said composition containing an antiallergically effective amount of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid or a non-toxic pharmaceutically acceptable salt thereof.

21. A composition according to claim 20 containing a non-toxic pharmaceutically acceptable salt of 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid.

22. A composition according to claim 21 containing the dihydrochloride of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid.

23. A method for achieving an antiallergic, antihistaminic, bronchodilator or antispasmodic effect in a patient in need thereof which comprises administering to said patient an effective amount of a compound of the formula



wherein
X and X′ represent independently a hydrogen atom, a halogen atom, a straight or branched chain lower alkoxy radical or a trifluoromethyl radical,
m is 1 or 2, and
n is 1 or 2
or a non-toxic pharmaceutically acceptable salt thereof.

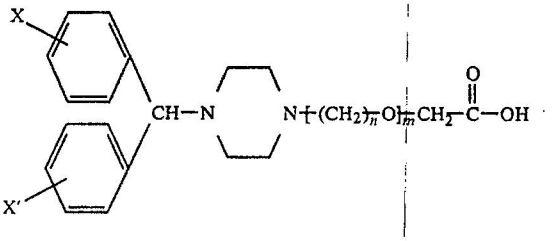
24. A method for achieving an antihistaminic effect in a patient in need thereof which comprises administering to said patient an antihistaminically effective amount of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl-]ethoxy]-acetic acid or a non-toxic pharmaceutically acceptable salt thereof.

25. A method according to claim **24** wherein a non-toxic pharmaceutically acceptable salt of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid is employed.

26. A method according to claim **25** wherein the dihydrochloride of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinly]ethoxy]-acetic acid is employed.

27. A method according to claim **26** wherein the administration is by the oral route.

28. A method for the treatment of allergic symptoms in a patient in need thereof which comprises administering to said patient an antiallergically effective amount of



wherein
X and X′ represent independently a hydrogen atom, a halogen atom, a straight or branched chain lower alkoxy radical or a trifluoromethyl radical,
m is 1 or 2, and
n is 1 or 2
or a non-toxic pharmaceutically acceptable salt thereof.

29. A method according to claim **28** wherein 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid or a non-toxic pharmaceutically acceptable salt thereof is employed.

30. A method according to claim **29** wherein a non-toxic pharmaceutically acceptable salt of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetic acid is employed.

31. A method according to claim **30** wherein the dihydrochloride of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethoxy]-acetic acid is employed.

* * * * *

United States Patent [19]

Demers et al.

[11] **Patent Number: 5,066,658**

[45] **Date of Patent: Nov. 19, 1991**

[54] **SUBSTITUTED HYDROXYUREAS**

[75] Inventors: **James P. Demers**, New York, N.Y.; **Richard B. Sulsky**, Somerville, N.J.

[73] Assignee: **Ortho Pharmaceutical Corporation**, Raritan, N.J.

[21] Appl. No.: **477,000**

[22] Filed: **Feb. 7, 1990**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 269,808, Nov. 10, 1988, abandoned, which is a continuation-in-part of Ser. No. 21,815, Mar. 4, 1987, abandoned.

[51] **Int. Cl.**[5] **A61K 31/505**; A61K 31/415; C07D 239/02; C07D 235/30

[52] **U.S. Cl.** **514/269**; 514/274; 514/392; 514/863; 544/318; 544/298; 548/307

[58] **Field of Search** 544/318, 298; 548/307; 514/269, 274, 392, 863

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,618,692 10/1986 Scheffler et al. 544/57

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Chou et al., CA87-83966q (1977).
Sulsky et al., Chem. Abst. 112-216835e (1990).

Primary Examiner—Cecilia Shen
Attorney, Agent, or Firm—Benjamin F. Lambert

[57] **ABSTRACT**

The present invention relates to substituted hydroxyureas. These compounds inhibit the enzyme 5-lipoxygenase. In addition, certain of the compounds also inhibit the enzyme-cyclooxygenase. The compounds are useful for treating asthma, allergies, arthritis, posoriasis, ischemia, dermatitis, inflammation and/or broncho-constriction and/or inflammatory diseases of the eye.

10 Claims, No Drawings

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EXAMPLE 75

4-(Diphenylmethyl)-N-hydroxy-N-methylpiperidine-1-carboxamide

By the method of Example 51, 4-(diphenylmethyl)-piperidine was converted to the named compound, and recrystallized from hexane-ethyl acetate to provide a white solid, mp 143°–144° C.

EXAMPLE 76

N-Hydroxy-N-methyl-N'-[2-(3-phenoxyphenyl)ethyl-]urea

By the method of Example 40, 3-(3-phenoxyphenyl)-propionic acid was converted to the title compound. Recrystallization from 1,2-dichloroethane/hexane provided a white solid, mp 84.5°–86° C.

EXAMPLE 77

Inhibition of 5-lipoxygenase

The inhibition of 5-lipoxygenase was tested in a cell-free homogenate by the procedure of B. Jakschik et al., *Biochem. Biophys. Res. Comm.* 95, 103 (1980). Basically, rat basophilic leukemia cells (RBL-1 cells) were maintained in culture in a suitable medium, and were collected by centrifugation prior to assay. The cell-free homogenate was prepared by sonication of the cells followed by centrifugation at 40,000 xg. The $CaCl_2$ dependent production of lipoxygenase products from ^{14}C-arachidonic acid in the 40,000 xg supernatant was monitored in the presence of buffer (or other vehicle) or drug. Products were isolated by acidification and extraction, followed by thin layer chromatography. Radioactive areas corresponding to the authentic lipoxygenase products were quantitated by liquid scintillation counting. Data was reported as the IC_{50}, the concentration causing 50% inhibition of the generation of lipoxygenase products. The results are shown it Table I as the percent inhibition at 3 μM or the amount of compound necessary to cause 50% inhibition.

EXAMPLE 78

Pulmonary Mechanics Assay

The bronchodilating activity of the compounds was tested in a pulmonary mechanics assay. Basically, male Hartley guinea pigs (about 400–500 g) were anesthetized with urethane (2 g/kg, i.p.) and placed in a whole body Plethysmograph. Cannulations of a jugular vein and carotid artery were performed for compound administration and monitoring blood pressure, respectively. The trachea was cannulated for respiration at a constate volume via a miniature starling pump. A Validyne differential pressure transducer (±20 cm H_2O) sensed transpleural pressure via a 15 gauge needle inserted into the pleural cavity and a sidearm from the tracheal cannula. Tidal volume was sensed by another Validyne differential pressure transducer (±2 cm H_2O) from pressure changes inside the plethysmograph. An on-line Buxco pulmonary mechanics computer calculated air flow, dynamic lung compliance and lung resistance. The values were recorded on a print-out.

The guinea pigs were pretreated with succinyl choline (1.2 mg/kg, i.v.) to arrest spontaneous respiration. A control challenge of arachidonic acid (0.5–1.0 mg/kg, i.v.) was administered, and the animals were then dosed with the test compound by various routes. At least 10 minutes were allowed to expire between arachidonic acid challenges. A second challenge was given and compared to the control response. This comparison was indicative of cyclooxygenase inhibition. Indomethacin (10 mg/kg, i.v.) was administered immediately after the second challenge. A third challenge of a higher dose of arachidonic acid (5–10 mg/kg, i.v.) was given. This response was induced by SRS-A and compared to the responses elicited by a separate control group of animals. Activity was indicative of lipoxygenase inhibition. Propranolol (0.005 mg/kg. i.v.) may be given prior to the third challenge to enhance the response to SRS-A.

Bronchoconstriction induced by arachidonic acid with or without indomethacin was expressed as maximum percent change in dynamic lung compliance (Cdyn) and maximum percent increase in lung resistance (R_L). Each guinea pig served as its own control for cyclooxygenase evaluation. The results are shown in Table I and are expressed as the percent inhibition of control.

EXAMPLE 79

Arachidonic Acid-Induced Ear Edema Assay

The topical anti-inflammatory activity of a compound was determined by its ability to inhibit an experimentally-induced inflammation in the mouse ear. Basically, four milligrams of arachidonic acid in acetone were applied to the dorsal surface of one ear with a microliter pipette. The mice were sacrificed at various times after application of arachidonic acid (one-half to six hours). A section of each ear was removed with a 7 mm round punch and weighed on an electronic or analytical balance. The difference in weight between treated and untreated ears was determined. Compounds to be evaluated for anti-inflammatory activity can be incorporated directly into the irritant mixture or at various times prior to or after application of arachidonic acid.

The degree of anti-inflammatory activity is shown in Table I, and is expressed in terms of the percent inhibition of ear weight increase.

TABLE I

BIOLOGICAL ACTIVITY OF HYDROXYUREAS

	Inhibition of 5-Lipoxygenase		Inhibition of Arachidonate-Induced Ear Edema		Inhibition of Arachidonate-Indusced Bronchospasm (IV Dosing)		(ID Dosing)	
Ex. No.	% Inh. @ 3 μM	IC_{50} (μM)	% Inh. (μg topically)	ED_{50} (μg)	% Inh. w/wo Indomethacin	Dose, mg/kg	% Inh. w/wo Indomethacin	Dose, mg/kg
1	100		52 (400)		38/54	15		
2		0.09	82 (400)	29	44/32	15		
3	100		51 (400)					
4	100		65 (400)		<20/−39	15		
5	100		49 (400)		37/<20	15		
6	100		30 (400)		<20/−45	15		
7	77	1.8		49	41/61	15		
8	93		95 (200)					

US005438062A

United States Patent [19]

Piwinski et al.

[11] Patent Number: 5,438,062

[45] Date of Patent: * Aug. 1, 1995

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562

[54] **BENZO(5,6)CYCLOHEPTAPYRIDINES, COMPOSITIONS AND METHODS OF USE**

[75] Inventors: **John J. Piwinski**, Parsippany; **Ashit K. Ganguly**, Upper Montclair; **Michael J. Green**, Skillman; **Frank J. Villani**, Fairfield; **Jesse Wong**, Union, all of N.J.

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

[*] Notice: The portion of the term of this patent subsequent to Feb. 18, 2009 has been disclaimed.

[21] Appl. No.: **950,986**

[22] Filed: **Sep. 23, 1992**

Related U.S. Application Data

[60] Continuation of Ser. No. 816,777, Jan. 2, 1992, abandoned, which is a division of Ser. No. 345,604, May 1, 1989, Pat. No. 5,089,496, which is a continuation-in-part of Ser. No. 181,860, Apr. 15, 1988, abandoned, which is a continuation-in-part of Ser. No. 925,342, Oct. 31, 1986, Pat. No. 4,826,853.

[30] **Foreign Application Priority Data**

Oct. 29, 1987 [EP] European Pat. Off. 87115890

[51] **Int. Cl.**[6] **C07D 221/06**; C07D 401/14; A61K 31/44; A61K 31/495

[52] **U.S. Cl.** **514/290**; 514/255; 544/361; 546/286; 546/323; 546/93

[58] **Field of Search** 546/93, 79; 514/290; 544/361, 255

[56] **References Cited**

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4,355,036	10/1982	Villani	546/80 X
4,356,184	10/1982	Deason et al.	514/324
4,609,664	9/1986	Hasspacher	514/324
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Villani et al. "Derivatives of 10, 11-Dihydro-5-H-dibenzo [a,d] cycloheptene . . . " J. Med. Chem. vol. 15, No. 7, pp. 750–754 (1972).

Villani et al., "N-substituted 11-(4-piperidylidene)-5,6 dihydro-11H-benzo(5,6)cyclohepta(1,2-b)pyridines", Arzneimittel-Forschung/Drug Research, vol. 36 (II), No. 9, 1311–1314 (1986).

Maurer et al., *J. Chromatogr.*, 382, (1986), 147–165.

Maurer et al., *J. Chromatogr.*, 430, (1988), 31–41.

Maurer et al., *J. Clin. Chem. Clin. Biochem.*, 25, No. 9 620, 1987 with translation.

Primary Examiner—Alan L. Rotman

Attorney, Agent, or Firm—Henry C. Jeanette; James R. Nelson

[57] **ABSTRACT**

Derivatives of benzo[5,6]cyclohepta pyridine, and pharmaceutically acceptable salts and solvates thereof are disclosed, which possess anti-allergic and anti-inflammatory activity. Methods for preparing and using the compounds are also described.

8 Claims, No Drawings

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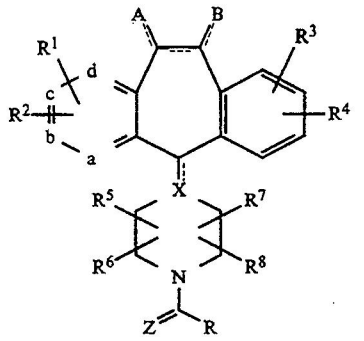
BENZO(5,6)CYCLOHEPTAPYRIDINES, COMPOSITIONS AND METHODS OF USE

The present application is a continuation of U.S. application Ser. No. 07/816,777 now abandoned, filed Jan. 2, 1992, which is a division of U.S. application Ser. No. 345,604, filed May 1, 1989 (now U.S. Pat. No. 5,089,496), which is a continuation-in-part of U.S. application Ser. No. 181,860, filed Apr. 15, 1988, now abandoned which in turn is a continuation-in-part of U.S. application Ser. No. 925,342, filed Oct. 31, 1986 (now U.S. Pat. No. 4,826,853); and the benefits of these application is claimed under 35 U.S.C. 120.

The present invention relates to benzo[5,6]cyclohepta pyridines and to pharmaceutical compositions and methods of using such compounds.

U.S. Pat. Nos. 3,326,924, 3,717,647 and 4,282,233, European published Application No. 0042544 and Villani et al., *Journal of Medicinal Chemistry*, Vol. 15, No. 7, pp 750–754 (1972) and *Arzn. Forch* 36 1311–1314 (1986) describe certain 11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta [1,2-b]pyridines as antihistamines. U.S. Pat. No. 4,355,036 describes certain N-substituted piperidylidene compounds.

The invention in its chemical compound aspect is a compound having the structural formula I:



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or NR^9 where R^9 is O^-, $-CH_3$ or $-(CH_2)_nCO_2H$ where n is 1 to 3, and the remaining a, b, c and d groups are CH, which remaining a, b, c and d groups optionally may be substituted with R^1 or R^2;

R^1 and R^2 may be the same or different and each independently represents halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$ $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, alkynyl, alkenyl or alkyl, which alkyl or alkenyl group may be substituted with halo, $-OR^{11}$ or $-CO_2$;

R^3 and R^4 may be the same or different and each independently represents H, any of the substituents of R^1 and $R^2R^3R^4$, or and together may represent a saturated or unsaturated C_5–C_7 ring fused to the benzene ring;

R^5, R^6, R^7 and R^8 each independently represent H, $-CF_3$, $-COR^{10}$, $-CO_2R^{10}$, alkyl or aryl, which alkyl or aryl may be substituted with $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$, $-NO_2$, COR^{10}, $OCOR^{10}$, OCO_2R^{11}, CO_2R^{10}, OPO_3R^{10} or one of R^5, R^6, R^7, and R^8 may be taken in combination with R as defined below to represent $-(CH_2)_r-$ where r is 1 to 4 which may be substituted with lower alkyl, lower alkoxy, $-CF_3$ or aryl or R^5 may be combined with R^6 to represent =O or =S, and R^7 may be combined with R^8 to represent =O or =S;

R^{10} represents H, alkyl or aryl;

R^{11} represents alkyl or aryl;

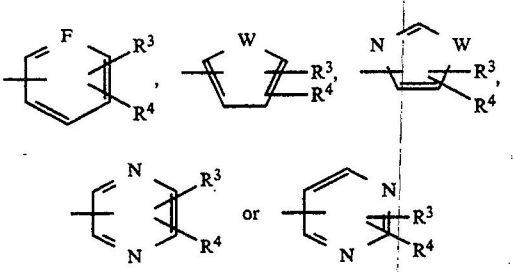
X represents N or C;

when X represents C, an optional double bond to carbon atom 11 may be present;

the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent H, $-R^{10}$, $-OR^{10}$ or $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{10})_2$, H and halo, dihalo, alkyl and H, $(alkyl)_2$, —H and $-OC(O)R^{10}$, H and $-OR^{10}$, =O, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ where p is 2, 3 or 4 and R^{10} is as previously defined;

Z represents O, S, $=NR^{13}$ or H_2 with R^{13} representing R^{10} or —CN such that

(a) when Z is O or NR^{13}, R may be taken in combination with R^5, R^6, R^7 or R^8 as defined above, or R represents H, aryl, alkyl, $-SR^{11}$, $-N(R^{10})_2$, cycloalkyl, alkenyl, alkynyl or —D wherein —D represents heterocycloalkyl,



wherein R^3 and R^4 are as previously defined and W is O, S or NR^{10} wherein R^{10} is as defined above,

said cycloalkyl, alkyl, alkenyl and alkynyl being optionally substituted with from 1–3 groups selected from halo, $-CON(R^{10})_2$, aryl, $-CO_2R^{10}$, $-OR^{12}$, $-SR^{12}$, $-N(R^{10})_2$, $-N(R^{10})CO_2R^{10}$, $-COR^{12}$, $-NO_2$ or D, wherein —D and R^{10} are as defined above and R^{12} represents R^{10}, $-(CH_2)_mOR^{10}$ or $-(CH_2)_qCO_2R^{10}$ wherein R^{10} is as previously defined, m is 1 to 4 and q is 0 to 4,

said alkenyl and alkynyl R groups not containing —OH, —SH or $-N(R^{10})_2$ on a carbon containing a double or triple bond respectively;

(b) when Z represents S, R represents in addition to those R groups above, aryloxy or alkoxy; and

(c) when Z represents H_2, R represents $-COOR^{10}$, $-E-COOR^{10}$ or $-E-OR^{12}$ where E is alkanediyl which may be substituted with aryl $-OR^{10}$, $-SR^{10}$, $-N(R^{10})_2$ or —D where D, R^{10} and R^{12} are as previously defined.

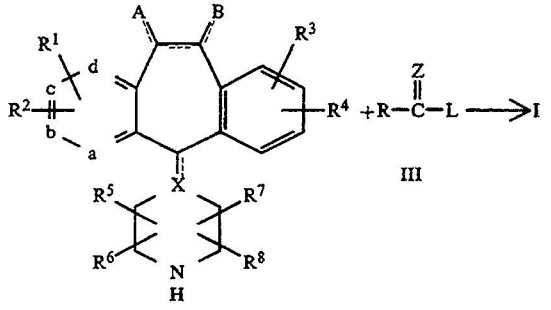
In a preferred embodiment of the invention, Z represents O or S, and R represents alkyl, cycloalkyl, alkenyl, aryl or alkyl substituted with $-OR^{12}$, $-SR^{12}$, $-N(R^{10})_2$ or $-COR^{12}$. More preferably, when Z represents O or S, R represents alkyl having from 1 to 3 carbon atoms, or alkyl of from 1 to 3 carbon atoms substituted with $-OR^{12}$, $-SR^{12}$, $-N(R^{10})_2$, or COR^{12}. Preferably one or both of R^3 and R^4 is halo, e.g. chloro or fluoro. The most preferred value of R^3 and/or R^4 is a halogen located at carbon atom 8 and/or 9, as shown in the following numbered ring structure:

aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The quaternary ammonium salts are prepared by conventional methods, e.g., by reaction of a tertiary amino group in a compound of formula I with a quaternizing compound such as an alkyl iodide, etc. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

All such acid, base and quaternary salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

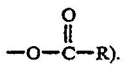
The following processes may be employed to produce compounds of general structural formula I.

A. A compound of general formula II may be reacted with compound III in the presence of base to produce compounds of general structural formula I.



II III

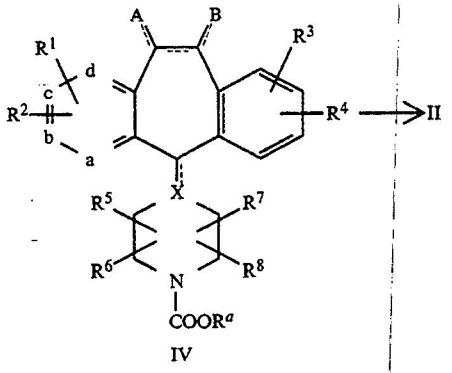
Representative examples of appropriate bases are pyridine and triethylamine. L designates a suitable leaving group. For example, if Z is 0 or S, a compound of compound III may be an acyl halide (e.g., L=halo) or acyl anhydride, (e.g., L is



Alternatively, if the leaving group is hydroxy, a coupling reagent may be employed to form Compound I. Examples of coupling agents include N,N'-dicyclohexylcarbodiimide (DCC) and N,N'-carbonyldiimidazole (CDI). The leaving group may also be alkoxy, in which case the compounds of formula I may be produced by refluxing a compound of formula II with an excess of a compound of formula III.

If compound III is a compound R—CH_2—L, L can be any easily displaced group, such as halo, p-toluene sulfonyloxy, methyl sulfonyloxy, trifluoromethylsulfonyloxy and the like.

Compounds of general formula II may be prepared by cleaving the group $COOR^a$ from the corresponding carbamates IV, for example, via acid hydrolysis (e.g., HCl) or base hydrolysis (e.g., KOH):

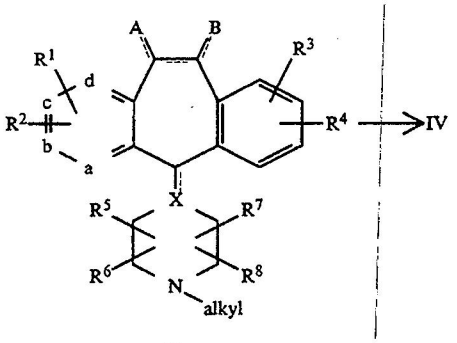


IV

wherein R^a is a group which does not prevent the cleavage reaction, e.g., R^a is an optionally substituted alkyl such as ethyl.

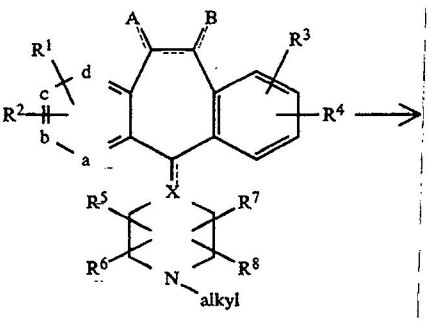
Alternatively, depending upon the nature of R^a, as determined by one skilled in the art, Compound IV may be treated with an organometallic reagent (e.g., CH_3Li), a reductive reagent (e.g., Zn in acid), etc., to form compounds of formula II.

Compound IV may be prepared from the N-alkyl compound shown as formula V below, in the manner disclosed in U.S. Pat. Nos. 4,282,233 and 4,335,036.



V

It also will be apparent to one skilled in the art that there are other methods for converting Compound V to Compound II. For example, treatment of Compound V with BrCN via yon Braun reaction conditions would provide nitrile IVa. Subsequent hydrolysis of the nitrile under either aqueous basic or acidic conditions would produce Compound II. This method is preferable when there is substitution on the piperidine or piperazine ring.

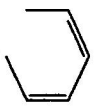
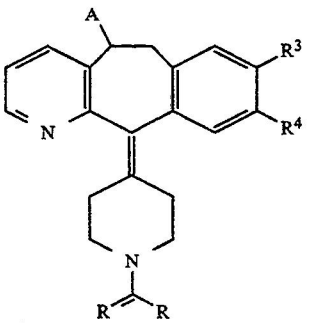


V

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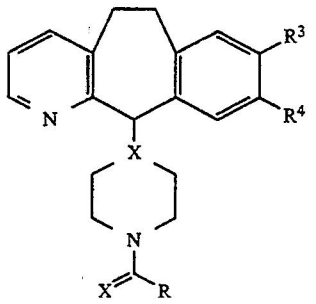
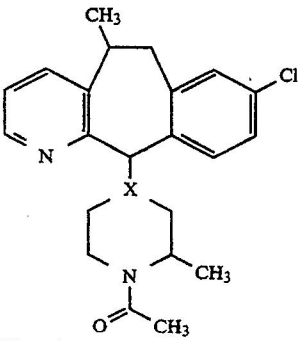
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TABLE IA-continued

Compound	Antihistaminic Activity: Guinea pig oral dose (mg/kg) Dose	% Survival	CNS Activity: Physostigmine lethality ED_{50} (mg/kg)	Acetic writhing ED_{50} (mg/kg)	ECS test ED_{50} (mg/kg)	PAF Antagonism (in vitro): Dose (micromoles)	% PAF Antagonism
$R^3 = Cl\ R^4 = H$	1 PO	60					
$Z = O\ R = Ph$	5 PO	100	*	*	*	10	9
$R^3 = Cl\ R^4 = H$	1 PO	0					
$R = -CH_2OCH_3$	5 PO	80	>320	>320	>320	6	50
$R^3 = Cl\ R^4 = H$	1 PO	80					
$Z = O$							
$R = -CH_2CH_2CH_3$	5 PO	100	>320	>320	>320	*	*
$R^3 = Cl\ R^4 = H$	1 PO	40					
$Z = O$							
$R = -SCH_2CH_3$	5 PO	80	>320	>320	>320	10	0
$R^3 = Cl\ R^4 = H$	1 PO	100					
$Z = O$							
$R = CH_2CH_2$	5 PO	80	>320	>320	>320	3	60
$R^3 = Cl\ R^4 = H$	1 PO	40					
$Z = O$							
$R = -CH_2OCH_3$	5 PO	100	<320	<320	<320	10	9
$R^3 = F\ R^4 = H$	1 PO	100					
$Z = O$							
$R = -CH_3\ Z = O$	5 PO	20	*	*	*	0.7	50
$R^3 = F\ R^4 = H$							
$R = -CH_3\ Z = O$	5 PO	0[1]	*	*	*	0.9	50
$R^3 = H\ R^4 = F$							
$R^3 = Br,\ R^4 = H,$						1.2	50
$R = CH_3\ Z = O$							
$R^3, R^4 =$ 						5	35
$R = CH_3$							
$Z = O$							
$R^3 = Cl,\ R^4 = H$						25	63
$R = CH{=}CH_2\ Z = O$							
$R^3 = Cl,\ R^4 = H$						50	29
$R = NHCH_3$							
$Z = O$							
							
$R^3 = Cl,\ R^4 = H$						5	50
$R = CH_3\ Z = O$							
$A = OH$							
$R^3 = Cl,\ R^4 = H$						1.0	50
$R = CH_3\ Z = O$							
$A = CH_3$							
$R^3 = Cl,\ R^4 = H$						1.2	50
$R = CH_3\ Z = O$							
$A = Keto$							
$R^3 = H,\ R^4 = H$	ED_{50} =		6.1	8.9	>80	>100	50
$A = H$	0.009						
$CZR = CH_3$**							
$R = OC_2H_5$**	ED_{50} =		>320	>320	>320	175	50
$R^3 = Cl,\ R_4 = H$	0.19						
$Z = O$							

*Not Tested
**Standard Known Antihistamine
[1]Expected to have some activity at a higher dose

TABLE IB

Compound	PAF Antagonism (in vitro) Dose (micromoles)	% PAF Antagonism
 $R^3 = H, R^4 = H$ $R = CH_3$ $Z = O$ $X = CH$	5	50
$R^3 = Cl, X = N$ $R = CH_3$ $Z = O$ $R^4 = H$	.5	43
$R^3 = Cl, X = N$ $R = H$ $Z = O$ $R^4 = H$	5	50
$R^3 = Cl, X = N$ $R = CH_2OCH_3$ $Z = O$ $R^4 = H$	5	50
	5	63

*Not tested

**Standard known antihistamine.

TABLE IC

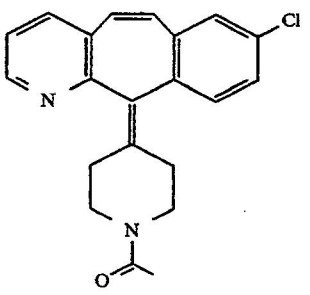
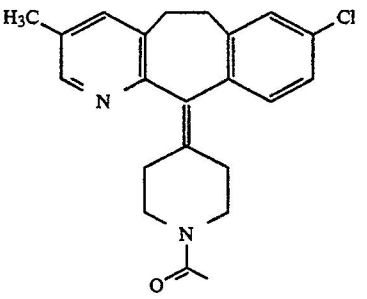
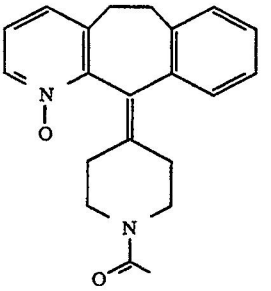
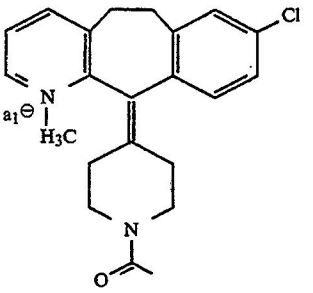
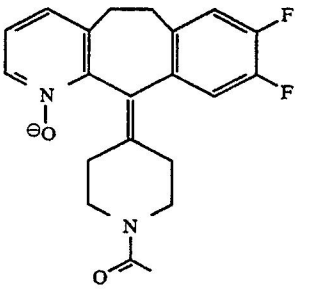
Compound	PAF Antagonism (in vitro) Dose (micromoles)	% PAF Antagonism
	.5	50

TABLE IC-continued

Compound	PAF Antagonism (in vitro) Dose (micromoles)	% PAF Antagonism
	.12	44
	1.5	50
	5	58
	2.5	53

As seen from the data of Tables IA, IB and IC and from the PAF induced bronchospasm inhibition test results, the compounds of structural formula I exhibit PAF antagonist and antihistaminic properties to varying degrees, i.e., certain compounds have strong PAF antagonistic activity, but have weaker antihistaminic activity. Other compounds are strong antihistamines but weaker PAF antagonists. Several of the compounds are both strong PAF antagonists and potent antihistamines. Consequently, it is within the scope of this invention to use each of these compounds when clinically appropriate. For example, if a strong PAF antagonist is required, but weaker antihistaminic activity is necessary, such a compound could be chosen by the clinician.

Alternatively, if both potent PAF antagonism and antihistaminic activity are required, a different compound of the invention would be utilized by the clinician.

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. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. 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 form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

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.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

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, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 100 mg, according to the particular application. The appropriate dosage can be determined by comparing the activity of the compound with the activity of a known antihtstaminic compound such as 8-chloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, which compound is disclosed in U.S. Pat. No. 4,282,233.

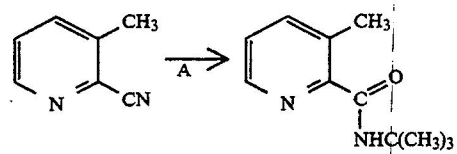
The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be requlated according to the judgement 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 10 mg to 1500 mg/day preferably 10 to 750 mg/day, in two to four divided doses to achieve relief of the symptoms. The compounds are non-toxic when administered within this dosage range.

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

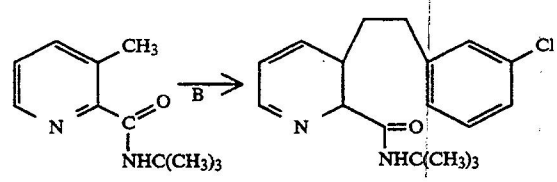
PREPARATIVE EXAMPLE I

A. N-(1,3-DIMETHYLETHYL)-3-METHYL-2-PYRIDINE CARBOXAMIDE



Suspend 2-cyano-3-methyl pyridine (400 g) in t-butanol (800 mL) and heat to 70° C. Add concentrated sulphuric acid (400 mL) dropwise over 45 minutes. Maintain the temperature at 75° C., until the reaction is complete, and for an additional 30 minutes. Dilute the mixture with water (400 mL), charge with toluene (600 mL) and bring to pH 10 with concentrated aqueous ammonia. Maintain the temperature at 50°-55° C. during the work up. Separate the toluene phase, and reextract the aqueous layer. Combine toluene phases and wash with water. Remove the toluene to yield the title compound N-(1,1-dimethylethyl-(3-methyl-2-pyridine carboxamide, as an oil, from which solid product is crystallized. (Yield 97%, as determined by an internal standard assay with gas chromatography).

B. 3-[2-(3-CHLOROPHENYL)ETHYL]-N-(1,1-DIMETHYLETHYL)-2-PYRIDINE CARBOXAMIDE



Dissolve the title compound of Preparative Example 1A, N-(1,1-dimethylethyl)-3-methyl-2-pyridine carboxamide (31.5 g.) in tetrahydrofuran (600 mL) and cool the resulting solution to −40° C. Add n-butyllithium (2 eg.) in hexane while maintaining the temperature at −40° C. The solution turns deep purple-red. Add sodium bromide (1.6 g) and stir the mixture. Add solution of m-chlorobenzylchloride (26.5 g., 0.174 mole) in tetrahydrofuran (125 mL) while maintaining the temperature at −40° C. Stir the reaction mixture until the reaction is complete as determined by thin layer chromatography. Add water to the reaction until the color is dissipated. Extract the reaction mixture with ethyl acetate, wash with water, and concentrate to a residue which is the title compound. (Yield 92% as shown by chromatography).

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: **0-21428** EDICTO No. **2382**

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió **Resolución** No. **1491** de **30-ENE-2006**. Que el contenido de la parte resolutiva es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "COMPUESTOS Y PROCEDIMIENTOS PARA EL TRATAMIENTO DE ASMA, ALERGIA Y TRANSTORNOS INFLAMATORIOS".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Héctor Gómez Mejía, o a quien haga sus veces, en su calidad de apoderado de UCB, S.A., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 30 ENE. 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JAIRO RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc **10-FEB-2006** Este edicto se desfija hoy **23-FEB-2006** a las cinco (5:00 p.m.)
Secretaría General Ad-Hoc
EDICTO No. **2382**