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SUPERINTENDENCIA Y COMERCIO

Señor

Radicación : 00047290 00010001

Folios: 10

Fecha (RIB): 2004-10-22 16:35:02

SUPERINTENDENTE DE INDUSTRIA Y COM
DIVISION DE NUEVAS CREACIONES

Trámite : 002 PATENTES D 332 PRESENTAC 329 COMPLEMEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: P1.-JANSSEN PHARMACEUTICA N.V.-Expediente
número 00-047.290.-

1. Me refiero al memorial de sustitución de poder presentado a ese Despacho el 31 de Agosto de 2004.

2. Por medio del presente, atentamente me permito manifestar a ese Despacho, que hubo un cambio de Representante Legal para todos los asuntos de la Propiedad Industrial en Bogotá de **JANSSEN PHARMACEUTICA N.V.**, una sociedad organizada y existente de conformidad con las leyes de Bélgica, domiciliada en Beerse, Bélgica.

3. En consecuencia, atentamente solicito a ese Despacho reconocirme personería, en este asunto, de conformidad con el documento de Representación Legal para todos los asuntos de la Propiedad Industrial en Bogotá de la sociedad **JANSSEN PHARMACEUTICA N.V.**, otorgado a favor de la **SUSCRITA (ALICIA LLOREDA)** y/o al doctor GUSTAVO TAMAYO y/o al doctor IGNACIO SANTAMARIA y/o al doctor ENRIQUE ALVAREZ de acuerdo con la copia debidamente autenticada ante Notario Público que adjunto al presente expediente (Artículos 26 y 39 de la Decisión 486 de la Comunidad Andina de Naciones).

4. Anexo al presente acompaño fotocopia, de

- (a) Documento que acredita a la SUSCRITA y/o al doctor GUSTAVO TAMAYO y/o al doctor IGNACIO SANTAMARIA y/o al doctor ENRIQUE ALVAREZ en los términos del párrafo 1º. del Artículo 543 del Decreto-Ley 410 de 1971, como Representantes Legales en Bogotá para todos los asuntos relacionados con la Propiedad Industrial de la sociedad **JANSSEN PHARMACEUTICA N.V.**, una sociedad organizada y

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existente de conformidad con las leyes de Bélgica, domiciliada
en Beerse, Bélgica;

(b) Certificación Notarial expedida el 24 de Agosto de 2004; y

(c) Traducción Oficial No. 2004-10-04-469 correspondiente a las partes pertinentes del documento anterior, también debidamente legalizada hasta por el Ministerio de Relaciones Exteriores bajo el número 268641 de 4 de Octubre de 2004.

5. Finalmente, llamo la atención de ese Despacho al hecho de que la copia auténtica del documento que me acredita para actuar como Representante Legal de la sociedad peticionaria, reposa en el Expediente número **98-067.209**.

6. Ruego a usted tomar atenta nota de lo anterior y continuar con el trámite correspondiente.

Señor Superintendente,


ALICIA LLOREDA RICAURTE
T.P. 53.215

Los abajo firmados, JANSSEN PHARMACEUTICA N.V., la sociedad organizada y existente de conformidad con las leyes de Bélgica.

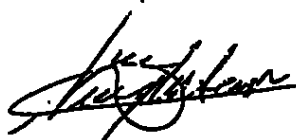
con domicilio en Turnhoutseweg 30
B-2340
Beerse, Bélgica.

nombramos por el presente a ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, domiciliados en Bogotá, Colombia, con oficinas en dicha ciudad, Calle 72 No. 5-83, piso 6o., nuestros representantes legales y verdaderos en Bogotá, con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales, con el fin de dar cumplimiento al parágrafo 1o. del artículo 543 del decreto 410 de 1971.

Los doctores ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, o los apoderados que cualquiera de ellos designe, quedan especialmente facultados para representarnos ante las autoridades colombianas, administrativas, judiciales o de policía, en todos los trámites relativos a la propiedad industrial, a cuyo efecto les facultamos para dar ante dichas autoridades todos los pasos necesarios al objeto indicado; elevar solicitudes, declaraciones, reclamos, recursos y presentar desistimientos; formular descripciones, enmiendas, limitar el alcance de las solicitudes, presentar oposiciones y apelaciones; instaurar cancelaciones, renunciar total o parcialmente a los registros, abonar todos los impuestos y cuotas y efectuar todo otro pago determinado por la ley; recibir todos los documentos y valores, dando el descargo respectivo; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeran conducentes al resguardo de nuestros intereses; y en caso de producirse oposición, pasando los antecedentes a los tribunales, quedan facultados para tomar intervención como demandantes o demandados ante los jueces que sean competentes, pudiendo transar, someter a árbitros, desistir, percibir y apelar, con todas las demás facultades que resulten necesarias, y por el presente declaramos desde ahora válido y bueno cuanto dichos representantes y/o los apoderados que cualquiera de ellos nombre hicieren en nuestro beneficio.

Asimismo, facultamos a los doctores ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, para solicitar en la Oficina de Propiedad Industrial la protocolización de este documento y de cualquier poder que cualquiera de ellos otorgue a nombre nuestro.

Dado y firmado



LUC QUAGHEBEUR
PROXY HOLDER

The undersigned, JANSSEN PHARMACEUTICA N.V., a corporation organized and existing under the laws of Belgium.

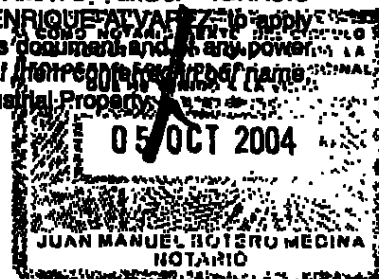
domiciled at Turnhoutseweg 30
B-2340
Beerse, Belgium.

hereby appoint, ALICIA LLOREDA and/or GUSTAVO TAMAYO and/or IGNACIO SANTAMARIA and/or ENRIQUE ALVAREZ, of Bogotá, Colombia, with offices in said town, Calle 72 No. 5-83, Sixth Floor, our true and legal representatives in Bogotá, with power to receive notifications and to appoint judicial or extrajudicial agents, so as to comply with paragraph 1o. of article 543 of decree 410 of 1971.

Doctors ALICIA LLOREDA and/or GUSTAVO TAMAYO and/or IGNACIO SANTAMARIA and/or ENRIQUE ALVAREZ, or the agents by any one of them appointed, are especially empowered to represent us before the administrative, judicial or police authorities of Colombia, in all proceedings pertaining to industrial property, for which purpose we authorize them to take before the said authorities all the necessary steps for the said end; to file petitions, declarations, claims, recourses and withdrawals, to draw up specifications; to file amendments, to limit the scope of applications, file oppositions; file cancellations total or partially waive registrations, to pay all installments and effect all other payments prescribed by law; to receive proper receipts, to comply with all other requirements and, in short, to take all those measures which they may deem fit for the protection of our interests; and in case of opposition, where the proceedings be passed over to the courts, we authorize said agents to act on our behalf, as complainants as well as defendants, before the competent judges, with full powers, to make arrangements, to submit to arbitrators, to desist, to collect, to appeal and, in short, with all such further powers as may be required, and we hereby declare from now on as valid and good all that said representatives and/or the agents by any one of them appointed may do for our benefit.

We also authorize doctors ALICIA LLOREDA and/or GUSTAVO TAMAYO and/or IGNACIO SANTAMARIA and/or ENRIQUE ALVAREZ to apply for protocolization of this document and to have power of attorney by any one of them to be given in name before the Office of Industrial Property.

Given and signed this



NOTARY SHOULD EXECUTE OTHER SIDE

CERTIFICADO NOTARIAL (SOCIEDAD)

Bélgica

(ss

Beerse

Hoy de

de 200 , compareció

, a quien conozco y de quien me consta que firmó el anterior documento, y quien debidamente juramentado declaró y dijo que él es

de

JANSSEN

PHARMACEUTICA N.V., la compañía nombrada en el documento que antecede, una sociedad debidamente organizada y existente conforme a las leyes de Bélgica, domiciliada en la ciudad de Beerse, legalmente constituida para un período de duración que aún no ha terminado, que ejerce su objeto social; conforme a las leyes de Bélgica, que el declarante está autorizado por dicha Compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y en representación de la expresada Compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad.

El suscrito Notario ha visto los Estatutos de Incorporación firmados en

con fecha

y

certifica que de conformidad con la legislación de dicho País, la anterior declaración juramentada es prueba suficiente de que los hechos sobre que ella versa son ciertos o verdaderos, de lo cual da fe.

Notary Public (Notario Público).

NOTARIAL CERTIFICATE (CORPORATION)

Belgium

(ss

Beerse

On this day of

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personally came

to me known, and known to me to be the person who signed the foregoing instrument, who being by me duly sworn did depose and say that he is the

of

JANSSEN

PHARMACEUTICA N.V., the company named within, a Corporation organized and existing under the laws of the Belgium, domiciled at the City of Beerse, legally constituted for a period of tenure not yet expired, which exercises its corporate purposes according to the laws of Belgium, that the deponent is authorized by said Company to confer this power of attorney; that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purposes of the Company.

The undersigned Notary Public has seen the articles of Incorporation of said Corporation executed at

, under date of

, and hereby

certifies that under the laws of said County the foregoing acknowledgment is sufficient proof that the facts therein contained are true, which he attests.

Gezien door ons, Jozef COPPENS, notaris verblijvende te B-2350 Vosselaar, België voor echte verklaring van de handtekening van *Mr. Quaghebeur* Vosselaar, de 24/10/2004

Vu par nous, Jozef COPPENS, notaire, résident à B-2350 Vosselaar, Belgique, pour certification de la signature de *Mr. Quaghebeur* Vosselaar, le 24/10/2004



APOSTILLE

(Conventie van Den Haag van 5 oktober 1961)

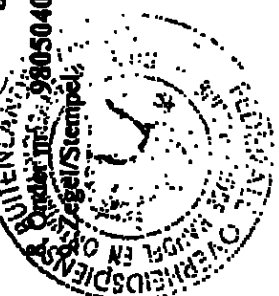
1. Land: België
2. Deze openbare akte is ondertekend door: Coppens, Jozef
3. handelend in de hoedanigheid van: Notaris
4. is voorzien van het zegel/ de stempel van: Notaris Vosselaar

Voor echt verklaard

5. Te Brussel 6. Op: 31/08/2004
7. Door de Federale Overheidsdienst Buitenlandse Zaken, Buitenlandse Handel en Ontwikkelingssamenwerking

Handtekening: 9805040831267560

10. Ondertekening: *G. Melard*



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RECHTBANK VAN KOOPHANDEL
AKTEN VAN ONDERNEMINGEN
NIEUWE KAAI 41 - 2300 TURNHOUT
GETUIGSCHRIFT VAN INSCHRIJVING

KOST:30.00 euro

Rep.nr.2004.00307

ROR.426

De ondergetekende Griffier van de Rechtbank van Koophandel, zitting houdende te Turnhout, bevestigt dat de Naamloze Vennootschap JANSSEN PHARMACEUTICA (JANSSEN PHARMACEUTICA NV), met maatschappelijke zetel te 2341 Beerse, Turnhoutseweg nr 30, ingeschreven is in het handelsregister te Turnhout onder nr 4.203, en gekend bij de Kruispuntbank van Ondernemingen onder nr 0403.834.160, werd opgericht voor het ambt van Notaris Fernand Dierckx te Turnhout op 23 oktober 1934.

De vennootschap kan ook binnen het kader van haar onderzoeks- en ontwikkelingsdivisie de handelsnaam "Johnson & Johnson Pharmaceutical Research & Development" gebruiken.

De vennootschapsnaam en de handelsbenaming kunnen zowel afzonderlijk als samen gebruikt worden.

Het maatschappelijk kapitaal van de vennootschap bedraagt vijftig miljoen tweehonderdduizend (50.200.000) Euro.

De maatschappelijke doelstelling is: alle handelingen die rechtstreeks of onrechtstreeks verband houden met het wetenschappelijk onderzoek, het aankopen, de fabricage, de conditionering of het wederverpakken, de vertegenwoordiging, het licentiegeven of het in licentie nemen, de verkoop, de import en de export, het in huur geven en in het algemeen het afsluiten van alle mogelijke transacties met betrekking tot farmaceutische, fytofarmaceutische, veterinaire, biologische, chemische of aanverwante producten, alsmede medische, veterinaire, hospitaal- en laboratoriumbenodigdheden, van elektronische apparatuur en hun onderdelen, waaronder begrepen computers, bestand voor commerciële, financiële en industriële ondernemingen, van textielwaren, voedingswaren, plasticwaren en verpakkingswaren; het deelnemen, in de ruimste betekenis op alle mogelijke wijze in andere op te richten of reeds opgerichte ondernemingen met gelijkaardig doel, diensvolgens over te gaan tot alle handels of financiële bewerkingen; roerende of onroerende, die rechtstreeks of onrechtstreeks met het maatschappelijk doel verbandhouden, met inbegrip van het stellen van alle daden van beheer en beschikking strekkende tot verkrijging, handhaving, bescherming, overdracht, verkoop, licentienemen en in licentiegeven van alle octroöien individuele en collectieve fabrieks- en handelsmerken en auteursrechten, het vervoer voor rekening van derden. Van het doel is echter uitgesloten, het optreden als verhuurder in financieringshuurovereenkomsten in de zin van het Koninklijk Besluit nummer 55 dd. 11 november negentienhonderd zevenenzestig.

Tot bestuurders van de vennootschap werden benoemd:

Collier Dirk, geboren op 16.02.1956, wonende te Pazantenlaan 20, B-2610 Wilrijk

De Chaffoy de Courcelles Didier, geboren op 19.11.1952, wonende te Karel van Nyeenlaan 4, B-2340 Beerse

Hex René, geboren op 15.03.1951, wonende te Dorpsveldstraat 200, B-3290 Diest

Lauwers Ludo, 27.09.1951, wonende te Mussenburchlei 120, B-2650 Edgem

Papa John A, geboren op 01.11.1950, wonende te 3 Stonehenge Lane, Bridgewater, NJ 08807, USA

Peterson Per, geboren op 11.07.1944, wonende te 380 Mountain Road, Basking Ridge, New Jersey 07920, USA

Poon Christine, geboren op 23.06.1952, wonende te 72 Library Place, Princeton, NJ 08540, USA

Sheffield David, geboren op 24.09.1948, wonende te Sapphire Drive 10, West Windsor, NJ 08550, USA

Shetty Ajit, geboren op 20.05.1946, wonende te Wielewaalstraat 12, B-2350 Vosselaar

Van Reet Gustaaf, geboren op 02.10.1945, wonende te Populierenlaan 14, B-2460 Kasterlee

Van Weenenborge Piet, geboren op 27.10.1938, wonende te Eikelenbergstraat 20, B-1700 Dilbeek

Weisman Harlan, geboren op 17.07.1952, wonende te Rosemont, Pennsylvania 19010, 759 Applegate Lane, USA

Er werd geen vonnis tot faillietverklaring uitgesproken en er werd geen aanvraag ingediend tot het bekomen van een gerechtelijk akkoord.

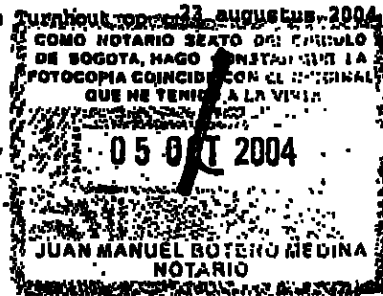
Er is eveneens geen akte tot ontbinding neergelegd, zodat deze vennootschap op vandaag rechtmatig bestaat en de bovenstaande gegevens juist zijn.

Ter oorkonde waarvan het tegenwoordig getuigschrift wordt afgeleverd, te Turnhout op 23 augustus 2004.



de griffier,

J. Meyvis



Wij, G.Somers, Rechter ~~and~~ Voorzitter van de Rechtbank van Koophandel, zitting houdende te Turnhout, verklaren echt en authentiek de handtekening van de Heer J. Meyvis, griffier bij deze Rechtbank, hiervoor gekwalificeerd.



Turnhout, 24 augustus 2004

de wnd. Voorzitter
G.Somers

Gezien in de FEDERALE OVERHEIDSDIENST
JUSTITIE voor legalisatie van de handtekening
van G. Soeters
Brussel, ...

30-08-2004

De gemachtigde ambtenaar,

Y. Van Hauwaert
Y VAN HAUWAERT



APOSTILLE

(Conventie van Den Haag van 5 oktober 1961)

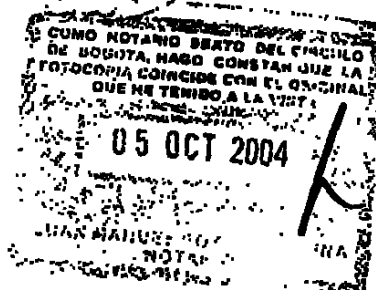
1. Land: België
2. Deze openbare akte is ondertekend door: Van Hauwaert, Yannick
3. handelend in de hoedanigheid van: Ambtenaar
4. is voorzien van het zegel/ de stempel van: FOD Justitie
Bruxelles

Voor echt verklaard

5. Te Brussel 6. Op: 31/08/2004
7. Door de Federale Overheidsdienst Buitenlandse Zaken, Buitenlandse
Handel en Ontwikkelingssamenwerking
8. Onder nr. 9805040831267340
9. Zegel/Stempel

10. Ondertekening

C. Melard
C. Melard



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TRADUCCION OFICIAL No. 2004-10-04-469 de un documento escrito en Inglés/ español, la cual para efectos del presente lleva el sello personal de Martha Lucia Arciniegas M., Traductora e Intérprete Oficial en virtud de la Res 1523 /88 del Ministerio de Justicia.

Legalización de un Poder de Representación Legal conferido a ALICIA LLOREDA y/o GUSTAVO TAMAYO, y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ otorgado por JANSSEN PHARMACEUTICA N.V.

Firmado por:

Luc Quaghebeur

Titular Encargado

Certificación Notarial (Corporación)

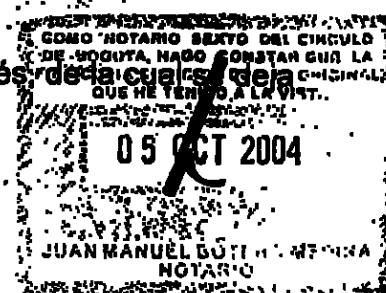
Certificación por la cual se certifica la firma precedente.

(fdo)

Notario Público
Jozef Coppens

Sigue legalización mediante Apostilla

Esta es una traducción fiel y completa de su original en inglés, de la cual se deja copia para futuras referencias



Martha Lucia Arciniegas
MARTHA LUCIA ARCINIEGAS M.
TRADUCTORA E INTERPRETE OFICIAL
RESOLUCION 1523/88 MINJUSTICIA

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Visto para legalización por nosotros, Jozef Coppens, notario con sede en B-
2350 Vosselaar, Bélgica, de la firma de Luc Quaghebeur, Vosselaar el
24/8/2004.

Vosselaar, 24-08-2004.

Sello redondo: Jozef Coppens, Notario de Vosselaar

APOSTILLA

(Convention de La Haye du 5 octobre 1961)

1. País: BELGICA

Esta Acta pública

2. ha sido firmada por Coppens Jozef

3. actuando en calidad de Notario

4. y está prevista del sello de Notaria Vosselaar

Atestada

5. en Bruselas 6. el 31-8-2004

7. por el Servicio Federal Estatal Asuntos Exteriores, Comercio Exterior y Cooperación
al Desarrollo

8. bajo el nr: 9805040831267560

9. sello

10. firma

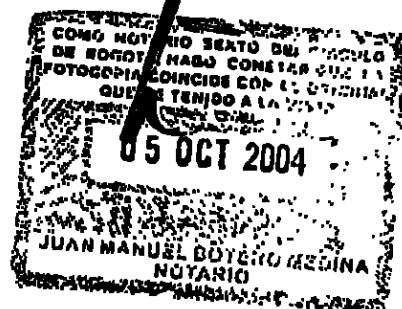
[fue firmado]

C. Melard

Sello redondo: Servicio Federal Estatal Asuntos Exteriores, Comercio Exterior y
Cooperación al Desarrollo

ES TRADUCCIÓN FIEL Y COMPLETA.
Bogotá, 2 octubre 2004

[Firma]
SYLVIA E. VAN UDEN VEEZ
TRADUCTOR E INTERPRETE
OFICIAL
RESOLUCION No. 1116
MINISTERIO DE JUSTICIA 1999



MINISTERIO DE
RELACIONES EXTERIORES

268641

Sylvia
EULA ANGELA APARECE EN EL
DOCUMENTO DESEMPENA
LAS FUNCIONES INDICADAS

05 OCT 2014

JUANITANIEL D

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2004 OCT -4 A 11-16

WCB
JEFE DE LEGALIZACIONES
BOGOTA D.C.

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JUZGADO DE COMERCIO

Acta de empresas

Nieuwe Kaa 41 - 2300 Turnhout

ACTA DE INSCRIPCION

Gastos 30 euros

Nr rep 2004 00307

ROR 426

El suscrito secretario judicial del juzgado de comercio con sede en Turnhout confirma que la sociedad anónima JANSSEN PHARMACEUTICA (JANSSEN PHARMACEUTICA NV) con sede en 2340 Beerse, Turnhoutseweg nr 30, inscrito en el registro mercantil de Turnhout bajo el no 4 203 y conocido en la base de datos empresarial bajo el no 0403 834 160 fue fundada ante el notario Fernand Dierckx en Turnhout el 23 de octubre 1934 La sociedad también puede utilizar el nombre de " Johnson & Johnson Pharmaceutical Research & Development" dentro del marco de su departaemnto de investigación y desarrollo El nombre de la sociedad y la denominación comercial pueden utilizarse o bien sea en forma separada o en forma conjunta El capital social de la sociedad asciende a cincuenta millones doscientos mil euros (50 200 000) El objetivo social es: todas las acciones que tengan relación directa o indirecta con la investigación científica, la compra, la fabricación, el acondicionamiento o el reempaque, la representación, el otorgamiento de licencias o tomar licencia, la venta, la importación y la exportación, arrendar y en general cerrar toda clase de transacción con relación a productos farmacéuticos, fitofarmacéuticos, veterinarios, biológicos, químicos o relacionados al igual que accesorios médicos, veterinarios, hospitalarios y de laboratorio, de equipos electrónicos y sus

9 OCT 2004
SYLVIA E. VAN UDEN PEREZ
TRADUCTORA OFICIAL
RESOLUCION No. 1116
MINISTERIO DE JUSTICIA 1999

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accesorios, incluyendo computadores con destino a empresas comerciales, financieras e industriales, de artículos de textil, alimentos, artículos de plástico y de empaque, la participación en el amplio sentido de la palabra en todas sus formas posibles en otras empresas a fundar o ya fundadas con un fin similar y con todas las implicaciones comerciales y financieras del caso, bienes muebles o inmuebles que tengan una relación directa o indirecta con el fin social incluyendo todas las acciones de gestión hasta la obtención, mantenimiento, protección, entrega, venta, obtención y entrega de licencia de todas las patentes, marcas de fábrica y comerciales individuales y colectivas y derechos de autor, el transporte por cuenta de terceros Sin embargo está excluido del objetivo actuar como arrendador en acuerdos de arriendo financieros en el sentido de la Decisión Real no 55 del 10 de noviembre de mil novecientos sesenta y siete.

Se nombraron como directivos de la sociedad a

Collier Dirk, nacido el 15 02 1956 con domicilio en Fazantenlaan 20, B-2610 Wilrijk

De Chaffoy de Courcelles Didier, nacido el 19 11 1952, con domicilio en Karel van Byenlaan 4, B-2340 Beerse

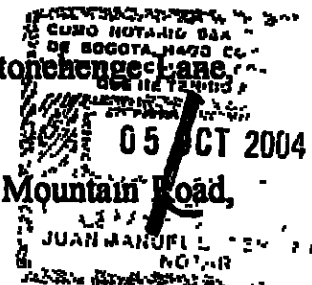
Hex René, nacido el 15 03 1951 con domicilio en Dorpsveldstraat 200, B-3290 Diest

Lauwers Ludo, 27 09 1951 con domicilio en Mussenburglei 120, B-2650 Edegem

Papa John A, nacido el 01 11 1950 con domicilio en 3 Stonehenge Lane, Bridgewater NJ 08807 Estados Unidos

Peterson Per, nacido el 11 07 1944 con domicilio en 380 Mountain Road, Basking Ridge New Jersey 07920, Estados Unidos

Poon Christine, nacida el 23 06.1952, con domicilio Library Place, Princeron NJ 08540, Estados Unidos



SYLVIA E. VAN DEN PEREZ
TRADUCTOR E INTERPRETE
OFICIAL
RESOLUCIÓN No. 1116
MINISTERIO DE JUSTICIA 1998

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Sheffield David, nacido el 24 09.1948, con domicilio en Sapphire Drive 10,
West Windsor NJ 08550, Estados Unidos

Shetty Ajit, nacida el 20 05 1946, con domicilio en Wielewaalstraat 12, B-
2350 Vosselaar

Van Reet Gustaaf, nacido el 02 10 1945 con domicilio en Populierenlaan
14, B-2460 Kasterlee

Van Waeyenberge Piet, nacido el 27 10 1938 con domicilio en
Eikelenbergstraat 20, B-1700 Dilbeek

Weisman Harlan, nacido el 17 07 1952, con domicilio Rosemont,
Pennsylvania 19010, 759 Applegate Lane, Estados Unidos

No se emitió un fallo sobre declaración de quiebra y no se entregó una
solicitud para llegar a un acuerdo judicial. Tampoco se estableció un acta
de disolución de manera que a la fecha esta sociedad existe legalmente y la
información arriba mencionada es correcta

Se procede a expedir el acta en Turnhout el 23 de agosto 2004

El secretario

[fue firmado]

J Meyvis

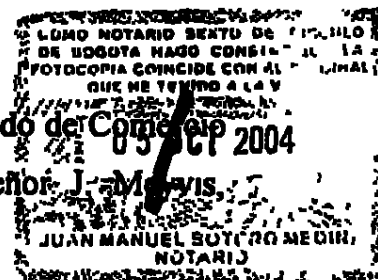
Sello redondo Juzgado de Comercio de Turnhout

Nosotros, G Somers, Juez encargado Presidente del Juzgado de Comercio
con sede en Turnhout declaramos que la firma del señor J. Meyvis,
secretario ante este juzgado es auténtica.

Turnhout, 24 de agosto 2004

[fue firmado]

presidente encargado, G Somers



SYLVIA E VAN LINDEN PEREZ
TRADUCTOR E INTERPRETE
OFICIAL
RESOLUCION No. 1116
MINJUSTICIA 1995

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Sellos

Visto por el servicio Federal estatal de Justicia para legalización de la firma
de G Somers Bruselas, 30-08-2004

El funcionario autorizado, Y van Hauwaert

APOSTILLA

(Convention de La Haye du 5 octobre 1961)

1 País BELGICA

Esta Acta pública

2 ha sido firmada por Van Hauwaert, Yannick

3 actuando en calidad de funcionario público

4 y está prevista del sello de FOD Justicia, Bruselas

Atestada

5 en Bruselas 6 el 31-8-2004

7 por el Servicio Federal Estatal Asuntos Exteriores, Comercio Exterior y Cooperación
al Desarrollo

8 bajo el nr 9805040831267340

9 sello

10 firma

[fue firmado]

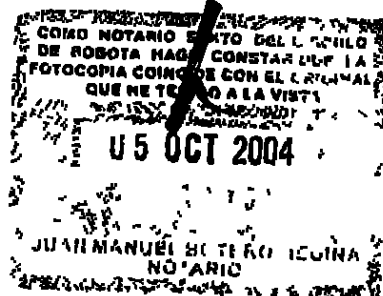
C Melard

Sello redondo Servicio Federal Estatal Asuntos Exteriores, Comercio Exterior y
Cooperación al Desarrollo

ES TRADUCCIÓN FIEL Y COMPLETA

Bogotá, 2 octubre 2004


SYLVIA E. VAN UDEN PÉREZ
TRADUCTORA E INTERPRETE
OFICIAL
RESOLUCION No. 1110
MINISTERIO DE JUSTICIA 1998


COMO NOTARIO EN TO DEL L. CHILO
DE BOGOTA HA CONSTATADO LA
FOTOCOPIA COMO DE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
U 5 OCT 2004
JUAN MANUEL BOTERO MEDINA
NOTARIO

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020

Bogotá, D.C., 28 de febrero de 2006

Apoderado: Alicia Lloreda Ricaurte

Oficio: 3003

ASUNTO

Radicación: 00-47290

Trámite 002

Evento 001

Actuación 430

Folios

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

Documentos estudiados:

- ◆ capítulo descriptivo, folios 05 a 121;
- ◆ capítulo reivindicatorio, folios 293 a 305;
- ◆ 1° examen de forma, folios 270 y 272;
- ◆ respuesta técnica al 1° examen de forma, folios 278 a 284;
- ◆ solicitud de la cual se reivindica prioridad, la traducción de su capítulo reivindicatorio, folios 151 a 270;
- ◆ 2° examen de forma, folio 325;
- ◆ solicitud del examen de patentabilidad 328 y 329.

Objeto de la Invención:

El título de la invención es "DERIVADOS DE BENZIMIDAZOL E IMIDAZOPIRIDINA COMO INHIBIDORES DE LA REPLICACIÓN DE VIRUS SINCITIALES RESPIRATORIOS".

El objeto de la presente solicitud se refiere a compuestos derivados de 3(heterociclo)-3H-imidazo[4,5-b]piridine-2-aminoderivado o amidoderivado; 1-(heterociclo)-1H-benzimidazol-2-aminoderivado ó amidoderivado; 3-(heterociclo)-3H-imidazo[4,5-c]piridine-2-aminoderivado ó amidoderivado; 1-(heterociclo)-1H-imidazo[4,5-c]piridine-2-aminoderivado ó amidoderivado; 1-(heterociclo)-1H-imidazo[4,5-b]piridine-2-carboxamide, con una amplia gama de variación del significado de cada uno los sustituyentes.

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Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comunidad Andina establece que: **"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 del artículo 14 de la Decisión 486, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial, del nuevo con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio. Consultada la fuente de información con que cuenta este despacho se encontró los siguientes documentos:

Item	Documento	Fecha de publicación	Título
D1	EP0099139	25-enero-1984	Novel N-(bicyclic heterocyclyl)-4-piperidinamines.
D2	EP000531	14-noviembre-1977	N-heterocyclyl-4-piperidinamines, methods for their preperation and phermaceutical compositions compresing them.
D3	EP0144101	12-junio-1985	Bicyclic heterocyclyl containing N-(bicyclic heterocyclyl)-4-piperidinamines.
D4	EP0145037	19-junio-1984	Five membered heterocyclic ring containig N-(bicyclic heterocyclyl)-4-piperidinamines.
D5	EP0151824	21-agosto-1985	N-(4-piperidinyl)bicyclic condensed 2-imidazolamine derivatives
D6	EP015826	21-agosto-1985	4-(Bicyclic heterocyclyl)-methyl and -hetero-piperidines
D7	EP0232937	19-agosto-1987	Anti-histaminic cmpositions containing N-heterocyclyl-4-piperidinamines
D8	EP0295742	21-diciembre-1988	Novel N-(4-piperidinil)bicyclic condensed 2-imidazolamine derivatives.
D9	EP0307014	15-marzo-1988	Anti-allergic 2-(heterocyclyl alkyl) Imidazo pyridines and 2-(heterocyclyl alkyl) purines.
D10	EP0297661	04-enero-1989	[(Bicyclic heterocyclyl)methyl and-hetero]substituted haxahydro-1H-azepines and pyrrolidines

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D11	EP0393738	24-octubre-1990	Hydroxyalkylfuranyl derivatives
D12	WO9201687	06-febrero-1992	Novel oxazolyl derivatives
D13	WO9201697	06-febrero-1992	Novel substituted thiazolyl and substituted pyridinyl derivatives

Evaluación de Novedad:

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

En la solicitud en estudio reclama derivados derivados de 3(heterociclo)-3H-imidazo[4,5-b]piridine-2-aminoderivado o amidoderivado; 1-(heterociclo)-1H-benzimidazol-2-aminoderivado ó amidoderivado; 3-(heterociclo)-3H-imidazo[4,5-c]piridine-2-aminoderivado ó amidoderivado; 1-(heterociclo)-1H-imidazo[4,5-c]piridine-2-aminoderivado ó amidoderivado; 1-(heterociclo)-1H-imidazo[4,5-b]piridine-2-carboxamide, con una amplia gama de variación del significado de cada uno los sustituyentes.

-Las anterioridades D1 a D13 enseñan procesos de obtención y compuestos derivados de derivados de 3(heterociclo)-3H-imidazo[4,5-b]piridine-2-aminoderivado o amidoderivado; 1-(heterociclo)-1H-benzimidazol-2-aminoderivado ó amidoderivado; 3-(heterociclo)-3H-imidazo[4,5-c]piridine-2-aminoderivado ó amidoderivado; 1-(heterociclo)-1H-imidazo[4,5-c]piridine-2-aminoderivado ó amidoderivado; 1-(heterociclo)-1H-imidazo[4,5-b]piridine-2-carboxamide, con una amplia gama de variación del significado de cada uno los sustituyentes, al igual que las composiciones farmacéuticas que los comprenden.

Estos antecedentes describen benzimidazoles fusionados con un anillo que tiene las variables -A1-A2-A3-A4- con los mismos significados que la solicitud en estudio al igual que sus análogos bioisostéricos que están sustituidos en la posición 2- con un derivado amino que puede ser 4-piperidina, via una amina y también sustituido en la posición 4 con un heterociclil, eso indica que los compuestos reclamados con la formula Markush (I) eran ampliamente conocidos en el estado de la técnica al momento de presentar la solicitud en estudio.

En conclusión queda plenamente establecido que toda solicitud con falta de novedad, obviamente no tiene nivel inventivo, puesto que dentro de la solicitud se reclaman compuestos del estado de la técnica y por el mero hecho de que luego

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se restrinja arbitrariamente, solamente para que no se intercepten con el estado de la técnica eso no indica que se obtenga el efecto inesperado, respecto al arte previo.

Nº	Reivindicaciones afectadas	Requisito afectado
D1	1 a 15	Novedad & nivel inventivo
D2	1 a 15	Novedad & nivel inventivo
D3	1 a 15	Novedad & nivel inventivo
D4	1 a 15	Novedad & nivel inventivo
D5	1 a 15	Novedad & nivel inventivo
D6	1 a 15	Novedad & nivel inventivo
D7	1 a 15	Novedad & nivel inventivo
D8	1 a 15	Novedad & nivel inventivo
D9	1 a 15	Novedad & nivel inventivo
D10	1 a 15	Novedad & nivel inventivo
D11	1 a 15	Novedad & nivel inventivo
D12	1 a 15	Novedad & nivel inventivo
D13	1 a 15	Novedad & nivel inventivo

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 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. Ya que en el examen anterior rehusó adjuntar los documentos exigidos, completos.

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 fecha
16 MAR. 2006,

CONCEPTO TÉCNICO No	EXAMINADOR TÉCNICO Código No.202012
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Europäisches Patentamt
European Patent Office
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(11) Publication number:

0 099 139
A2

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C07D333/20, C07D403/12,
C07D211/68, C07D405/12,
C07D401/12, C07D409/12,
C07D409/14

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(54) Designated Contracting States:
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(71) Applicant: JANSSEN PHARMACEUTICA N.V.
Turnhoutsebaan 30
B-2340 Beerse(BE)

(72) Inventor: Janssens, Frans Eduard
Tintstraat 79
B-2830 Bonheiden(BE)

(72) Inventor: Terremans, Joseph Leo Ghislainus
Lijsterstraat 11
B-2340 Beerse(BE)

(72) Inventor: Hent, Jozef Francis
Rector de Ransstraat 84
B-2380 Nijlen(BE)

(72) Inventor: van Offenwert, Theophilus Theresia J.M.
Kardinaal Cardijnlaan 83
B-2350 Voerendaal(BE)

(56) Novel N-(biaryl heterocyclyl)-4-piperidinamines.

Novel N-(biaryl heterocyclyl)-4-piperidinamines of the formula

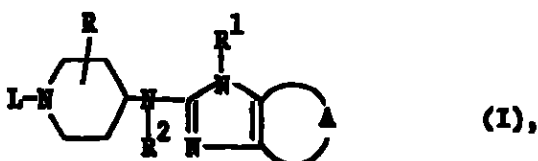


the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, which compounds are useful as anti-allergic agents; pharmaceutical compositions containing such compounds as an active ingredient; methods of preparing said compounds and pharmaceutical compositions; new intermediates, used in the preparation of said compounds, which are themselves useful as anti-allergic agents and pharmaceutical compositions containing the latter as active ingredients.

EP 0 099 139 A2

WHAT IS CLAIMED IS:

- 1 1. A chemical compound having the formula



- 2 a pharmaceutically acceptable acid addition salt or a stereo-
3 chemically isomeric form thereof, wherein:

- 4 A is a bivalent radical having the formula

- 5 $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ (a),
6 $-\text{N}=\text{CH}-\text{CH}=\text{CH}-$ (b),
7 $-\text{CH}=\text{N}-\text{CH}=\text{CH}-$ (c),
8 $-\text{CH}=\text{CH}-\text{N}=\text{CH}-$ (d), or
9 $-\text{CH}=\text{CH}-\text{CH}=\text{N}-$ (e),

- 10 wherein one or two hydrogen atoms in said radicals (a) - (e)
11 may, each independently from each other, be replaced by halo, lower
12 alkyl, lower alkyloxy, trifluoromethyl or hydroxy;

- 13 R is a member selected from the group consisting of hydrogen
14 and lower alkyl;

- 15 R^1 is a member selected from the group consisting of
16 hydrogen, alkyl, cycloalkyl, Ar^1 and lower alkyl substituted with
17 one or two Ar^1 radicals;

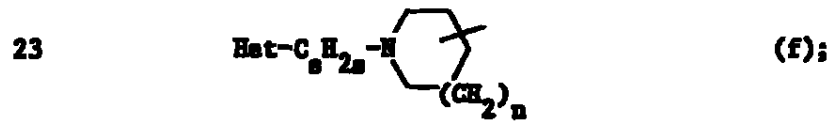
- 18 R^2 is a member selected from the group consisting of
19 hydrogen, lower alkyl, cycloalkyl, (lower alkyl)-CO- and
20 Ar^2 -lower alkyl;

- 21 L is a member selected from the group consisting of

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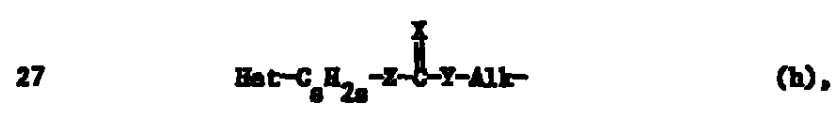
22 a radical of formula



24 a radical of formula



26 a radical of formula



- 28 wherein n is 0 or the integer 1 or 2;
- 29 s is 0 or an integer of from 1 to 6 inclusive;
- 30 Alk is lower alkanediyl;
- 31 Y is O, S, NR³ or a direct bond;
- 32 X is O, S, CH-NO₂ or NR⁴;
- 33 Z is O, S, NR⁵ or a direct bond; and
- 34 Hat is an optionally substituted 6-membered heterocyclic ring
- 35 having at least one nitrogen atom and being optionally condensed
- 36 with an optionally substituted benzene ring, said Hat being
- 37 connected to C_sH_{2s} on a carbon atom;
- 38 said R³ being hydrogen, lower alkyl, (Ar²)lower alkyl,
- 39 2-lower alkyloxy-1,2-dioxoethyl or a radical of formula
- 40 -C(-X)-R⁶, R⁶ being hydrogen, lower alkyl, Ar², Ar²-lower
- 41 alkyl, lower alkyloxy, Ar²-lower alkyloxy, mono- or di(lower
- 42 alkyl)amino, Ar²-lower alkylamino or Ar²-lower alkyl(lower
- 43 alkyl)amino;
- 44 said R⁴ being hydrogen, lower alkyl, cyano, nitro,
- 45 Ar²-sulfonyl, lower alkylsulfonyl, lower alkylcarbonyl or
- 46 Ar²-carbonyl; and
- 47 said R⁵ being hydrogen or lower alkyl;

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48 provided that Het is other than pyridinyl or mono- or di(lower
49 alkyloxy)pyridinyl where L is a radical (g) wherein Y is NR³ or
50 where L is a radical (h) wherein X is O and Z is NR⁵ or a direct
51 bond;

52 wherein Ar¹ is a member selected from the group consisting of
53 phenyl, being optionally substituted with up to three substituents
54 each independently selected from the group consisting of halo,
55 hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower
56 alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower
57 alkyl)amino, carboxyl, lower alkyloxycarbonyl and (lower
58 alkyl)-CO-; thienyl; halothienyl; furanyl; lower alkyl substituted
59 furanyl; pyridinyl; pyrazinyl; thiazolyl and imidazolyl optionally
60 substituted by lower alkyl; and wherein Ar² is a member selected
61 from the group consisting of phenyl being optionally substituted
62 with up to three substituents each independently selected from the
63 group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl,
64 lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino,
65 mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl
66 and (lower alkyl)-CO.

1 2. A chemical compound according to claim 1 wherein Het is
2 a member selected from the group consisting of a pyridinyl radical
3 which is optionally substituted with one or two substituents each
4 independently selected from the group consisting of halo, amino,
5 nitro, cyano, aminocarbonyl, lower alkyl, lower alkyloxy, lower
6 alkylthio, lower alkyloxycarbonyl, hydroxy, lower alkylcarbonyloxy,
7 Ar²-lower alkyl and carboxyl; a pyridinyloxy radical optionally
8 substituted with nitro, a quinolinyl radical which is optionally
9 substituted with a lower alkyl radical; a pyrimidinyl radical which
10 is optionally substituted with one or two substituents each
11 independently selected from the group consisting of halo, amino,
12 hydroxy, lower alkyl, lower alkyloxy, lower alkylthio and
13 (Ar²)-lower alkyl; a quinazolinyl radical which is optionally
14 substituted with a hydroxy radical or a lower alkyl radical; a
15 pyridazinyl radical which is optionally substituted with a lower

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16 alkyl radical or a halo radical; a quinoxaliny radical which is
17 optionally substituted with a lower alkyl radical; a pyrazinyl
18 radical which is optionally substituted with a halo radical, an
19 amino radical or a lower alkyl radical; a phthalazinyl radical
20 which is optionally substituted by a halo radical; and a
21 5,6-dihydro-4H-1,3-thiazin-2-yl radical.

1 3. A chemical compound according to claim 2 wherein L is a
2 radical (g) or (h).

1 4. A chemical compound according to claim 3 wherein Het is
2 other than an optionally substituted pyridinyl radical.

1 5. A chemical compound selected from the group consisting of
2 1-[(4-fluorophenyl)methyl]-N-[1-[2-[(2-pyrimidinyl)amino]ethyl]-
3 4-piperidinyl]-1H-benzimidazol-2-amine, the pharmaceutically
4 acceptable acid addition salts and stereochemically isomeric forms
5 thereof.

1 6. An anti-allergic composition comprising an inert carrier
2 material and as an active ingredient an anti-allergically effective
3 amount of a chemical compound as claimed in any one of claims 1 to
4 5.

1 7. An anti-allergic composition according to claim 6 which is
2 in an unit dosage form.

1 8. An anti-allergic composition comprising an inert carrier
2 material and as an active ingredient an anti-allergically effective
3 amount of a chemical compound selected from the group consisting of
4 1-[(4-fluorophenyl)methyl]-N-[1-[2-[(2-pyrimidinyl)amino]ethyl]-
5 4-piperidinyl]-1H-benzimidazol-2-amine, the pharmaceutically
6 acceptable acid addition salts and stereochemically isomeric forms
7 thereof.

1 9. A method of preparing an anti-allergic composition as
2 claimed in any one of claims 6 to 8, characterized by mixing an
3 effective amount of a compound as claimed in any one of claims 1 to
4 5 with an inert carrier.

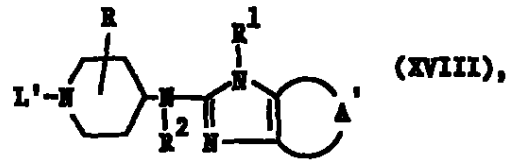
1 10. A compound as claimed in any one of claims 1 to 5 for use
2 as an anti-allergic agent.

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11. A chemical compound having the formula



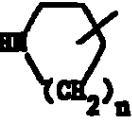
a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein:

- A' is -CH-N-CH-CH- (c)
- CH-CH-N-CH- (d)
- CH-CH-CH-N- (e), said N being attached to the carbon atom in 4-position of the imidazole ring;

R is a member selected from the group consisting of hydrogen and lower alkyl;

R¹ is a member selected from the group consisting of hydrogen, alkyl, cycloalkyl, Ar¹ and lower alkyl substituted with one or two Ar¹ radicals;

R² is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, (lower alkyl)-CO- and Ar²-lower alkyl; and

L' is a radical of formula -Alk'-CH₂, -Alk-Y'H,  or -Alk-Y-C(-X)-Z'H

- wherein n is 0 or the integer 1 or 2;
- Alk is a lower alkanediyl radical having from 1 to 6 carbon atoms;
- Alk' is a lower alkanediyl radical having from 1 to 5 carbon atoms;
- Y is O, S, NR³ or a direct bond;
- Y' is O, S or NR³;

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25 X is O, S, CH-NO₂ or NR⁴; and
26 Z' is O, S, or NR⁵;

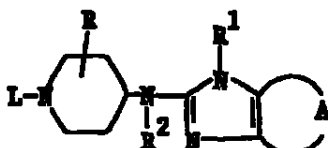
27 said R³ being hydrogen, lower alkyl, (Ar²)lower alkyl,
28 2-lower alkyloxy-1,2-dioxoethyl or a radical of formula
29 -C(-X)-R⁶, R⁶ being hydrogen, lower alkyl, Ar², Ar²-lower
30 alkyl, lower alkyloxy, Ar²-lower alkyloxy, mono- or di(lower
32 alkyl)amino, Ar²-lower alkylamino or Ar²-lower alkyl(lower
33 alkyl)amino;

34 said R⁴ being hydrogen, lower alkyl, cyano, nitro,
35 Ar²-sulfonyl, lower alkylsulfonyl, lower alkylcarbonyl or
36 Ar²-carbonyl; and

37 said R⁵ being hydrogen or lower alkyl;
38 wherein Ar¹ is a member selected from the group consisting of
39 phenyl, being optionally substituted with up to three substituents
40 each independently selected from the group consisting of halo,
41 hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower
42 alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower
43 alkyl)amino, carboxyl, lower alkyloxycarbonyl and (lower
44 alkyl)-CO-; thienyl; halothienyl; furanyl; lower alkyl substituted
45 furanyl; pyridinyl; pyrazinyl; thiazolyl and imidazolyl optionally
46 substituted by lower alkyl; and wherein Ar² is a member selected
47 from the group consisting of phenyl being optionally substituted
48 with up to three substituents each independently selected from the
49 group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl,
50 lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino,
51 mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl
52 and (lower alkyl)-CO.

1 12. An anti-allergic composition comprising an inert
2 carrier material and as an active ingredient an anti-allergically
3 effective amount of a chemical compound as claimed in claim 11.

1 13. A process for preparing a chemical compound having the
2 formula



(I),

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3 a pharmaceutically acceptable acid addition salt or a stereochemically
4 isomeric form thereof, wherein:

5 A is a bivalent radical having the formula

- 6 -CH=CH-CH=CH- (a),
- 7 -N-CH=CH-CH=CH- (b),
- 8 -CH=N-CH=CH- (c),
- 9 -CH=CH-N=CH- (d), or
- 10 -CH=CH-CH=N- (e),

11 wherein one or two hydrogen atoms in said radicals (a) - (e) may,
12 each independently from each other, be replaced by halo, lower alkyl,
13 lower alkyloxy, trifluoromethyl or hydroxy;

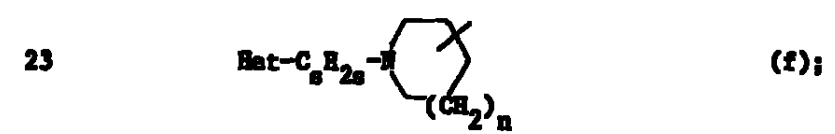
14 R is a member selected from the group consisting of hydrogen and
15 lower alkyl;

16 R¹ is a member selected from the group consisting of hydrogen,
17 alkyl, cycloalkyl, Ar¹ and lower alkyl substituted with one or two
18 Ar¹ radicals;

19 R² is a member selected from the group consisting of hydrogen,
20 lower alkyl, cycloalkyl, (lower alkyl)-CO- and Ar²-lower alkyl;

21 L is a member selected from the group consisting of

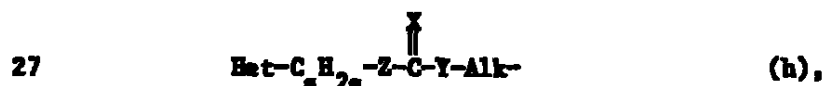
22 a radical of formula



24 a radical of formula



26 a radical of formula



28 wherein n is 0 or the integer 1 or 2;

29 s is 0 or an integer of from 1 to 6 inclusive;

30 Alk is lower alkanediyl;

31 Y is O, S, NR^3 or a direct bond;

32 X is O, S, $\text{CH}-\text{NO}_2$ or NR^4 ;

33 Z is O, S, NR^5 or a direct bond; and

34 Het is an optionally substituted 6-membered heterocyclic ring
35 having at least one nitrogen atom and being optionally condensed
36 with an optionally substituted benzene ring, said Het being
37 connected to C_sH_{2s} on a carbon atom;

38 said R^3 being hydrogen, lower alkyl, (Ar^2) lower alkyl, 2-lower
39 alkyloxy-1,2-dioxoethyl or a radical of formula $-\text{C}(\text{-X})-\text{R}^6$, R^6

40 being hydrogen, lower alkyl, Ar^2 , Ar^2 -lower alkyl, lower
41 alkyloxy, Ar^2 -lower alkyloxy, mono- or di(lower alkyl)amino,

42 Ar^2 -lower alkylamino or Ar^2 -lower alkyl(lower alkyl)amino;

43 said R^4 being hydrogen, lower alkyl, cyano, nitro,

44 Ar^2 -sulfonyl, lower alkylsulfonyl, lower alkylcarbonyl or

45 Ar^2 -carbonyl; and

46 said R^5 being hydrogen or lower alkyl;

47 provided that Het is other than pyridinyl or mono- or di(lower
48 alkyloxy)pyridinyl where L is a radical (g) wherein Y is NR^3 or

49 where L is a radical (h) wherein X is O and Z is NR^5 or a direct
50 bond;

51 wherein Ar^1 is a member selected from the group consisting of
52 phenyl, being optionally substituted with up to three substituents each
53 independently selected from the group consisting of halo, hydroxy, nitro,
54 cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio,
55 mercapto, amino, mono- and di(lower alkyl)amino, carboxyl, lower
56 alkyloxycarbonyl and (lower alkyl)-CO-; thienyl; halothienyl; furanyl;
57 lower alkyl substituted furanyl; pyridinyl; pyrazinyl; thiazolyl and

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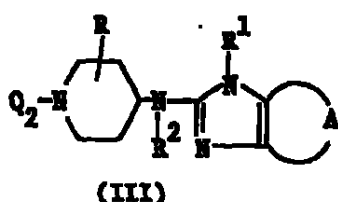
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58 imidazolyl optionally substituted by lower alkyl; and wherein Ar^2 is a
59 member selected from the group consisting of phenyl being optionally
60 substituted with up to three substituents each independently selected
61 from the group consisting of halo, hydroxy, nitro, cyano, trifluoro-
62 methyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino,
63 mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl and
64 (lower alkyl)-CO, characterized by

65 a) alkylating a piperidine of formula



66 with an intermediate of formula

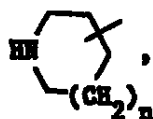


68 in a reaction-inert solvent

69 wherein 1) Q_2 is hydrogen and Q_1 , combined with Het, forms a
70 radical of formula L-W (II-a), said W representing an
71 appropriate reactive leaving group such as, for
72 example, halo, e.g., chloro, bromo or iodo, or a
73 sulfonyloxy group, e.g. methylsulfonyloxy or
74 4-methylphenylsulfonyloxy; or

75 2) Q_1 is a radical of formula $-C_6H_4-W'$, said W' having
76 the previously defined meaning of W provided that, where s
77 in 0, W' may also represent a lower alkyloxy or lower
78 alkylthio group, and Q_2 is a radical of formula

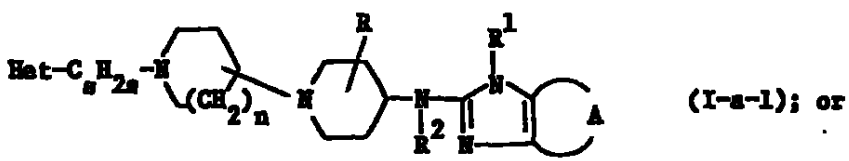
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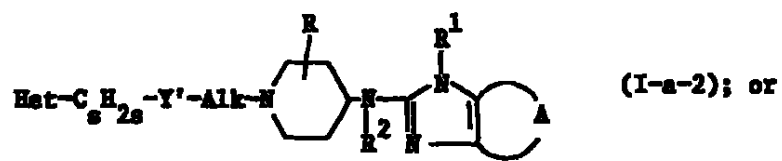
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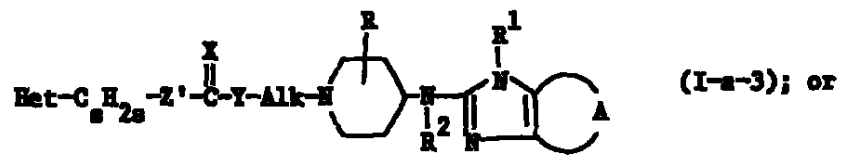
80 thus preparing a compound of formula



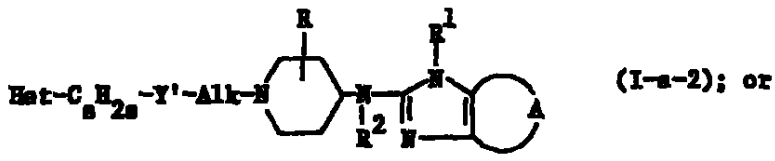
81 3) Q₁ is a radical of formula -C_sH_{2s}-W' and Q₂ is a
82 radical of formula HY'-Alk-, said Y' having the previously
83 defined meaning of Y provided that Y is other than a
84 direct bond, thus preparing a compound of formula



85 4) Q₁ is a radical of formula -C_sH_{2s}-W' and Q₂ is a
86 radical of formula HZ'-C(X)-Y-Alk-, said Z' having the
87 previously defined meaning of Z provided that Z is other
88 than a direct bond, thus preparing a compound of formula



89 5) Q₁ is a radical of formula -C_sH_{2s}-Y'H and Q₂ is a
90 radical of formula W-Alk-, thus preparing a compound of
91 formula



92 6) Q₁ is a radical of formula -C_sH_{2s}-Z-C(X)-Y'H and

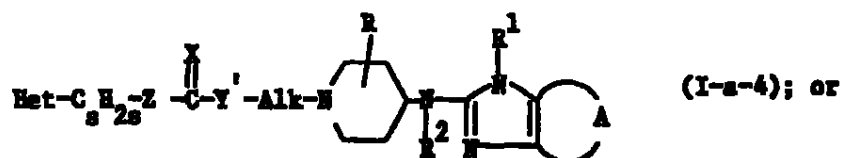
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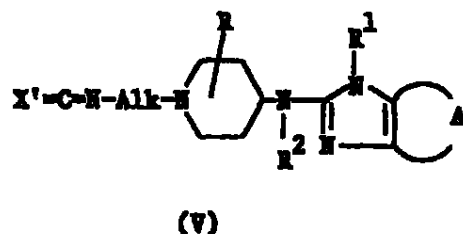
93 Q₂ is a radical of formula W-Alk, thus preparing a
94 compound of formula



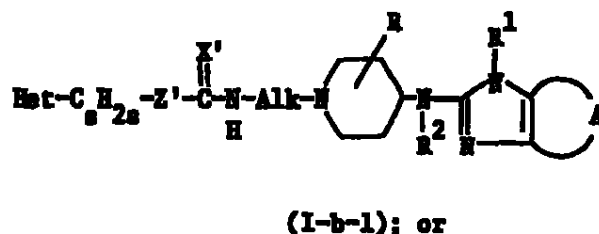
95 b) reacting an intermediate of formula



97 with a piperidine of formula



98 in a suitable reaction-inert solvent, thus preparing a compound of
99 formula

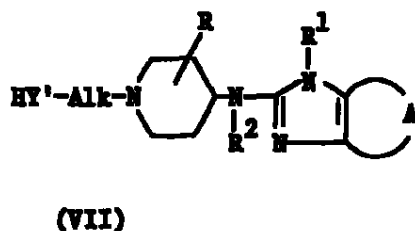


100 c) reacting an intermediate of formula



102 said X' being O or S,

103 with a piperidine of formula



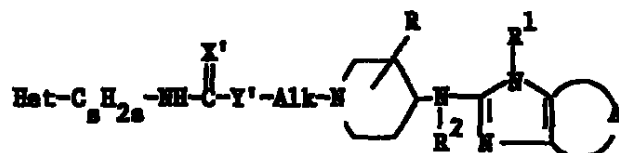
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104 in a suitable reaction-inert solvent, thus preparing a compound of
 105 formula

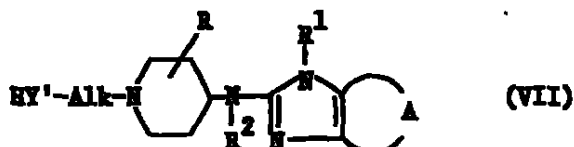


(I-b-2); or

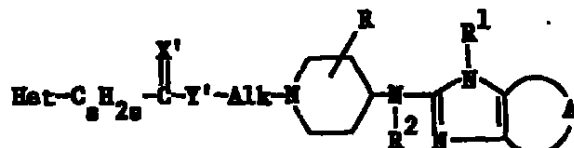
106 d) reacting an intermediate of formula



108 with a piperidine of formula

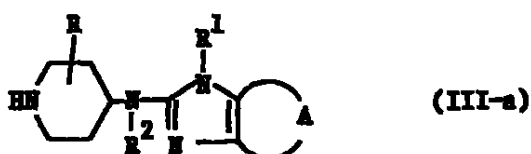


109 in a suitable reaction-inert solvent, if desired, after converting the
 110 OH-function in (VIII) in a suitable leaving group, thus preparing a
 111 compound of formula



(I-c); or

112 e) reacting a piperidine of formula

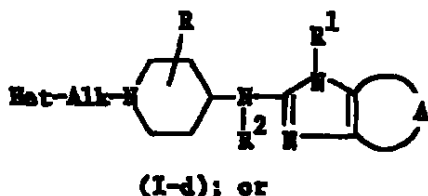


113 with a reagent of formula

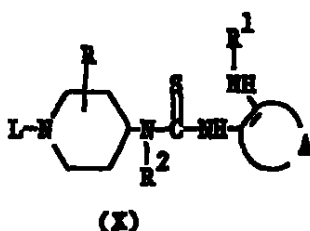
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114 Hat-lower alkanediyl-H (IX)
 115 in a suitable reaction-inert solvent, thus preparing a compound of
 116 formula



117 f) cyclodesulfurizing an intermediate of formula



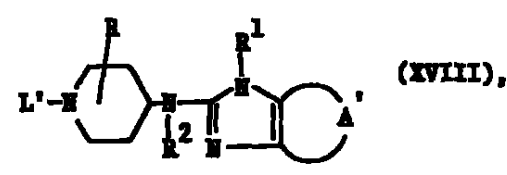
118 with an appropriate alkyl halide, metal oxide or metal salt in a
 119 reaction-inert solvent; and, if desired, converting the compounds of
 120 formula (I) into a therapeutically active non-toxic acid-addition
 121 salt form by treatment with an appropriate acid or, conversely,
 122 converting the acid-addition salt into the free base form with alkali;
 123 and/or preparing stereochemically isomeric forms thereof.

1 14. A process for preparing a chemical compound selected from the
 2 group consisting of 1-[(4-fluorophenyl)methyl]-N-[1-[2-[(2-
 3 pyrimidinyl)amino]ethyl]-4-piperidinyl]-1H-benzimidazol-2-amine or a
 4 pharmaceutically acceptable acid-addition salt thereof, characterized
 5 by reacting N-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-fluorophenyl-
 6 methyl)-1H-benzimidazol-2-amine or a pharmaceutically acceptable
 7 acid-addition salt thereof with 2-chloropyrimidine in a suitable
 8 reaction-inert solvent; and, if desired, converting the compounds of
 9 formula (I) into the therapeutically active non-toxic acid-addition
 10 salt form by treatment with an appropriate acid or, conversely,
 11 converting the acid-addition salt into the free base form with alkali.

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15. A process for preparing a chemical compound having the formula



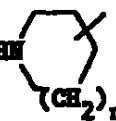
a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein:

- A' is -CH-N-CH-CH- (c)
- CH-CH-N-CH- (d)
- CH-CH-CH-N- (e), said N being attached to the carbon atom in 4-position of the imidazole ring;

R is a member selected from the group consisting of hydrogen and lower alkyl;

R¹ is a member selected from the group consisting of hydrogen, alkyl, cycloalkyl, Ar¹ and lower alkyl substituted with one or two Ar¹ radicals;

R² is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, (lower alkyl)-CO- and Ar²-lower alkyl; and

L' is a radical of formula -Alk'-CN, -Alk-Y'H,  or -Alk-Y-C(=X)-Z'H

wherein n is 0 or the integer 1 or 2;

Alk is a lower alkanediyl radical having from 1 to 6 carbon atoms;

Alk' is a lower alkanediyl radical having from 1 to 5 carbon atoms;

Y is O, S, NR³ or a direct bond;

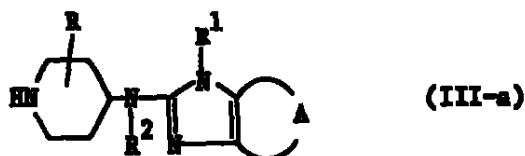
Y' is O, S or NR³;

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25 X is O, S, CH-NO₂ or NR⁴; and
 26 Z' is O, S, or NR⁵;
 27 said R³ being hydrogen, lower alkyl, (Ar²)lower alkyl,
 28 2-lower alkyloxy-1,2-dioxoethyl or a radical of formula
 29 -C(-X)-R⁶, R⁶ being hydrogen, lower alkyl, Ar², Ar²-lower
 30 alkyl, lower alkyloxy, Ar²-lower alkyloxy, mono- or di(lower
 32 alkyl)amino, Ar²-lower alkylamino or Ar²-lower alkyl(lower
 33 alkyl)amino;
 34 said R⁴ being hydrogen, lower alkyl, cyano, nitro,
 35 Ar²-sulfonyl, lower alkylsulfonyl, lower alkylcarbonyl or
 36 Ar²-carbonyl; and
 37 said R⁵ being hydrogen or lower alkyl;
 38 wherein Ar¹ is a member selected from the group consisting of
 39 phenyl, being optionally substituted with up to three substituents
 40 each independently selected from the group consisting of halo,
 41 hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower
 42 alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower
 43 alkyl)amino, carboxyl, lower alkyloxycarbonyl and (lower
 44 alkyl)-CO-; thienyl; halothienyl; furanyl; lower alkyl substituted
 45 furanyl; pyridinyl; pyrazinyl; thiazolyl and imidazolyl optionally
 46 substituted by lower alkyl; and wherein Ar² is a member selected
 47 from the group consisting of phenyl being optionally substituted
 48 with up to three substituents each independently selected from the
 49 group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl,
 50 lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino,
 51 mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl
 52 and (lower alkyl)-CO characterized by N-alkylating a piperidine of
 formula



53 with a reagent having the formula L'-W in a reaction-inert solvent,
 54 said W representing an appropriate reactive leaving group such as,
 55 for example, halo, e.g., chloro, bromo or iodo, or a sulfonyloxy group,
 56 e.g. methylsulfonyloxy or 4-methylphenylsulfonyloxy; and, if desired,

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57 converting the compounds of formula (I) into the therapeutically
58 active non-toxic acid-addition salt form by treatment with an
59 appropriate acid or, conversely, converting the acid-addition salt
60 into the free base form with alkali.

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⑬

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⑳ Applicant: JANSSEN PHARMACEUTICA N.V.,
Turnhoutsebaan 39, Beerse (BE)

㉑ Inventor: Janssens, Frans, Moekelbaan 676/1,
Pelle (BE)
Inventor: Stalbroeck, Raymond, Rode Kruisstraat 12,
Beerse (BE)
Inventor: Terremans, Joseph, Lijsterstraat 11,
Beerse (BE)
Inventor: Loyens, Marcel, Kerkstraat 31, B-2440
Geel (BE)

㉒ Representative: Grundy, Derek George Ritchie et al,
CARPMAELS & RANSFORD 43, Molesbury Square,
London WC1A 2RA (GB)

㉓ N-Heterocycyl-4-piperidinamines, methods for their preparation and pharmaceutical compositions comprising them.

㉔ Novel N-heterocycyl-4-piperidinamines wherein said heterocyclic radical is an optionally substituted 1H-benzimidazol-2-yl or 3H-imidazo[4,5-b]pyridin-8-yl radical, said compounds being useful as antihistaminic agents.

EP 0 005 318 A1

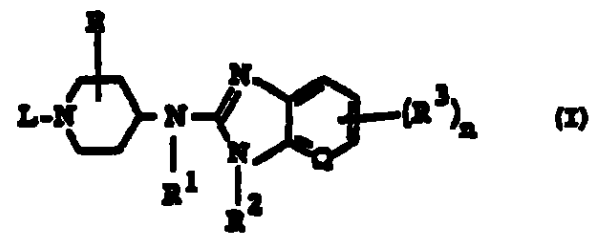
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Claims:

1. A chemical compound selected from the group consisting of a N-heterocyclyl-4-piperidinamine having the formula



- and the pharmaceutically acceptable acid addition salts thereof, wherein
- R is a member selected from the group consisting of hydrogen and lower alkyl;
- R¹ is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl lower alkyl and lower alkanoyl;
- R² is a member selected from the group consisting of hydrogen, alkyl having from 1 to 10 carbon atoms, aryl, cycloalkyl and mono- and diaryl(lower alkyl);
- R³ is a member independently selected from the group consisting of, halo, lower alkyl, lower alkyloxy and trifluoromethyl;
- n is an integer of from 0 to 2 inclusive;
- Q is a member selected from the group consisting of CH and H; and

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1 is a member selected from the group consisting of lower alkyl, which is optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, hydroxy, isothio-
5 cyanato, lower alkyl, aryl, aryloxy, arylthio, arylsulfonyl, amino, lower alkenyl, aryllower alkenyl, cycloalkyl, being optionally substituted with a cyano and/or an aryl group;
1-(aryllower alkyl)-1H-benzimidazol-2-yl; and a radical
10 of the formula $2-C_mH_{2m}-$, wherein
m is an integer of from 1 to 6 inclusive; and

2 is a member selected from the group consisting of 4,5-dihydro-5-oxo-1H-tetrazol-1-yl, being optionally substituted
15 in its 4-position by an aryl radical or a lower alkyl radical;
2,3-dihydro-1,4-benzodioxin-2-yl; 2,3-dihydro-1,4-benzodioxin-6-yl; 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl; 2,3-dihydro-3-oxo-4H-benzoxazin-4-yl; (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)methyl; 4-morpholinyl;
20 1-piperidinyl; 1-pyrrolidinyl; a radical of the formula $T-N(R^4)-$, wherein

R^4 is a member selected from the group consisting of hydrogen, lower alkyl and aryllower alkyl; and
25

T is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, 1H-benzimidazol-2-yl; and

a radical of the formula $W-\overset{\text{O}}{\parallel}{C}-(X)_s-$, wherein

30 s is the integer 0 or 1;

X is a member selected from the group consisting of O and $-N(R^5)-$, said R^5 being a member selected from the group consisting of hydrogen, lower alkyl, aryllower alkyl, lower alkanoyl and areyl; and

5

W is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, amino, arylamino, mono- and di(lower alkyl)amino, mono- and di(aryllower alkyl)amino, 1-piperidinyl, 1-pyrrolidinyl and 4-morpholinyl;

10

wherein aryl as used in the foregoing definitions, is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, (lower alkyl)thienyl, pyridinyl, mono- and di(lower alkyl)pyridinyl, furanyl and 1-(lower alkyl)pyrrolyl; wherein said substituted phenyl is phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfonyl-lower alkyl, phenyllower alkylsulfonyl, phenylsulfonyl-lower alkyl, amino, mono- and di-(lower alkyl)amino, lower alkanoyl, a radical of the formula $R^6-C_pH_{2p}-O-$, wherein

15

20

25

p is an integer of from 1 to 6 inclusive; and

R^6 is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, lower alkyl-oxycarbonyl, phenyllower alkyl-oxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, lower alkyl; and a radical of the formula R^7-O- , wherein

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5 **R⁷ is a member selected from the group consisting of alkanoyl, phenylcarbonyl, phenyllower alkylcarbonyl, lower alkylalkylcarbonyl, phenyllower alkylalkylcarbonyl, aminocarbonyl, phenylaminocarbonyl, mono- and di-**

(lower alkyl)aminocarbonyl, wherein said phenyl in the definition of said R⁷ may be optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, nitro, lower alkyl and lower alkylalkoxy; and
10 **wherein said aroyl in the definition of said x represents arylcarbonyl wherein said aryl is as defined hereinabove.**

15 **2. A chemical compound selected from the group consisting of 1-(4-fluorophenylmethyl)-N-{1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl}-1H-benzimidazol-2-amine and the pharmaceutically acceptable acid addition salts thereof.**

20 **3. A chemical compound selected from the group consisting of 4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl }ethyl]phenol and the pharmaceutically acceptable acid addition salts thereof.**

25 **4. A chemical compound selected from the group consisting of {4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl }ethyl]phenyl} benzeneacetate and the pharmaceutically acceptable acid addition salts thereof.**

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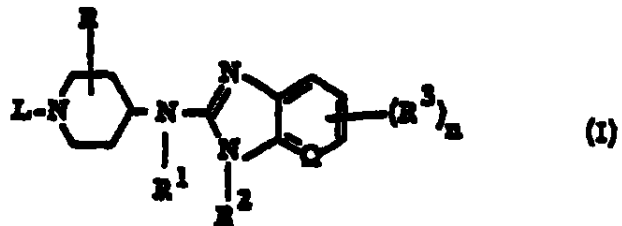
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5. A chemical compound selected from the group consisting of {4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenoxy} acetonitrile and the pharmaceutically acceptable acid addition salts thereof.

6. A chemical compound selected from the group consisting of N-[1-(2-phenylethyl)-4-piperidinyl]-1-(phenylmethyl)-1H-benzimidazol-2-amine and the pharmaceutically acceptable acid addition salts thereof.

7. An antihistaminic pharmaceutical composition comprising an inert carrier material and as an active ingredient an effective antihistaminic amount of a chemical compound selected from the group consisting of a N-heterocyclyl-4-piperidinamine having the formula



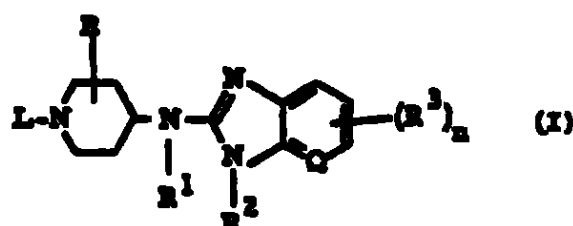
20 as defined in claim 1 and the pharmaceutically acceptable acid addition salts thereof.

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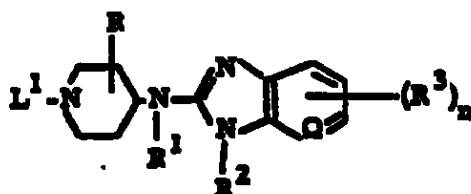
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8. A method to prevent the release of histamine in warmblooded animals, which comprises the systemic administration to said animals of an effective anti-histaminic amount of a chemical compound selected from the group consisting of a N-heterocyclyl-4-piperidineamine having the formula



and the pharmaceutically acceptable acid addition salts thereof, as defined in claim 1.

9. A chemical compound having the formula



wherein:

- L^1 is a member selected from the group consisting of hydrogen, lower alkoxycarbonyl and phenylmethoxycarbonyl;
- R is a member selected from the group consisting of hydrogen and lower alkyl;
- R^1 is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryllower alkyl and lower alkanoyl;

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R^2 is a member selected from the group consisting of hydrogen, alkyl having from 1 to 10 carbon atoms, aryl, cycloalkyl and mono- and diaryl (lower alkyl);
 R^3 is a member independently selected from the group consisting of, halo, lower alkyl, lower alkyloxy, trifluoromethyl;
n is an integer of from 0 to 2 inclusive;
Q is a member selected from the group consisting of CH and N; and wherein aryl as used in the foregoing definitions, is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, (lower alkyl)thienyl, pyridinyl, mono- and di(lower alkyloxy)pyridinyl, furanyl and 1-(lower alkyl)pyrrolyl; wherein said substituted phenyl is phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfonylower alkyl, phenyllower alkylsulfonyl, phenylsulfonylower alkyl, amino, mono- and di-(lower alkyl)amino, lower alkanoyl, a radical of the formula $R^6-C_pH_{2p}-O-$, wherein
p is an integer of from 1 to 6 inclusive; and

R^6 is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, lower alkyl-oxycarbonyl, phenyllower alkyl-oxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, lower alkenyl; and

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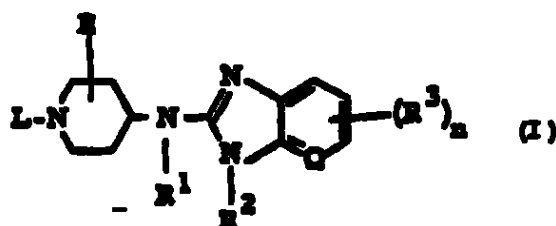
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a radical of the formula R^7-O- , wherein

R^7 is a member selected from the group consisting of alkanoyl, phenylcarbonyl, phenyllower alkylcarbonyl, lower alkylalkoxycarbonyl, phenyllower alkylalkoxycarbonyl, aminocarbonyl, phenylaminocarbonyl, ^{and} mono- and di-(lower alkyl)aminocarbonyl,

wherein said phenyl in the definition of said R^7 may be optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, nitro, lower alkyl and lower alkyloxy.

10. A process for preparing a chemical compound selected from the group consisting of a N-heterocyclyl-4-piperidinamine having the formula



15 and the pharmaceutically acceptable acid addition salts thereof, wherein

R is a member selected from the group consisting of hydrogen and lower alkyl;

20 R^1 is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryllower alkyl and lower alkanoyl;

R^2 is a member selected from the group consisting of hydrogen, alkyl having from 1 to 10 carbon atoms, aryl, cycloalkyl and mono- and diaryl(lower alkyl);

25 R^3 is a member independently selected from the group consisting of, halo, lower alkyl, lower alkyloxy and trifluoromethyl;

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n is an integer of from 0 to 2 inclusive;
Q is a member selected from the group consisting
of CN and N; and
L is a member selected from the group consisting of
5 lower alkyl, which is optionally substituted with
up to 3 substituents each independently selected from
the group consisting of halo, cyano, hydroxy, iso-
thiocyanato, lower alkoxy, aryl, aryloxy, arylthio,
arylsulfonyl, amino, lower alkenyl, aryllower alkenyl,
10 cycloalkyl, being optionally substituted with a cyano
and/or an aryl group; 1-(aryllower alkyl)-1H-benzi-
midazol-2-yl; and a radical of the formula $Z-C_6H_{2m}-$,
wherein
m is an integer of from 1 to 6 inclusive; and
15
Z is a member selected from the group consisting of 4,5-
dihydro-5-oxo-1H-tetrazol-1-yl, being optionally substituted
in its 4-position by an aryl radical or a lower alkyl radical;
2,3-dihydro-1,4-benzodioxin-2-yl; 2,3-dihydro-1,4-benzo-
20 dioxin-6-yl; 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl; 2,3-
dihydro-3-oxo-4H-benzoxazin-4-yl; (10,11-dihydro-5H-di-
benzo[*p,q*]cyclohepta-5-ylidene)methyl; 4-morpholinyl;
1-piperidinyl; 1-pyrrolidinyl; a radical of the formula
T-N(R⁴)-, wherein
25
R⁴ is a member selected from the group consisting
of hydrogen, lower alkyl and aryllower alkyl; and
T is a member selected from the group consisting of
30 lower alkyl, aryl, aryllower alkyl, 1H-benz-
imidazol-2-yl; and

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a radical of the formula $W-\overset{\overset{O}{\parallel}}{C}-(X)_s-$, wherein

s is the integer 0 or 1;

5 X is a member selected from the group consisting of O and $-N(R^5)-$, said R^5 being a member selected from the group consisting of hydrogen, lower alkyl, aryllower alkyl, lower alkanoyl and aroyl; and

10 W is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, amino, arylamino, mono- and di(lower alkyl)amino, mono- and di(aryllower alkyl)amino, 1-piperidinyl, 1-pyrrolidinyl and 4-morpholinyl;

15 wherein aryl as used in the foregoing definitions, is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, (lower alkyl)thienyl, pyridinyl, mono- and di(lower alkyloxy)pyridinyl, furanyl and 1-(lower alkyl)pyrrolyl; wherein said substituted phenyl is
20 phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfonyl-lower alkyl, phenyllower alkylsulfonyl, phenylsulfonyl-lower alkyl, amino, mono- and di-(lower alkyl)amino,
25 lower alkanoyl, a radical of the formula $R^6-C_{pH_2p}-O-$, wherein

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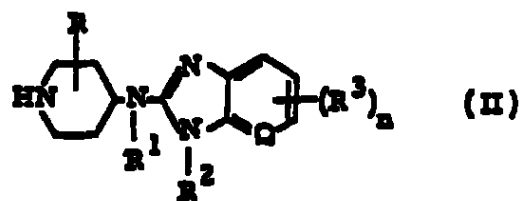
p is an integer of from 1 to 6 inclusive; and

R^6 is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, lower alkyl-oxycarbonyl, phenyllower alkyl-oxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, lower alkenyl; and

a radical of the formula R^7-O- , wherein

R^7 is a member selected from the group consisting of alkanoyl, phenylcarbonyl, phenyllower alkylcarbonyl, lower alkyl-oxycarbonyl, phenyllower alkyl-oxycarbonyl, aminocarbonyl, phenylaminocarbonyl, mono- and di(lower alkyl)aminocarbonyl,

wherein said phenyl in the definition of said R^7 may be optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, nitro, lower alkyl and lower alkyl-oxyl; and wherein said aroyl in the definition of said X represents aroylcarbonyl wherein said aroyl is as defined hereabove, characterized by a) introducing onto a starting material of the formula



wherein R, R¹, R², R³, n and Q are as previously defined, the desired L-substituent onto the piperidine nitrogen by the application of art-known methods,

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i) preferably the introduction of said L into the intermediate (II) may be accomplished by the reaction of (II) with an appropriate reactive ester of the formula L Y, (III), wherein L is as previously defined and Y is a reactive ester residue such as, for example, halo, preferably chloro or bromo, or a sulfonyloxy residue such as, for example, methylsulfonyloxy or 4-methylphenylsulfonyloxy, said condensation reaction preferably being conducted in an inert solvent with the addition of an appropriate base, at elevated temperatures;

ii) when L in formula (I) represents a (2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)lower alkyl radical it is appropriate to use a reactive ester (III) wherein the nitrogen atom in the 3-position of the 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl group is substituted with an appropriate protecting group, preferably a 1-methylethenyl group and removing said protecting group preferably by acid hydrolysis after completion of the condensation reaction;

iii) when L represents a 2-aryl-2-hydroxyethyl or a 3-aryloxy 2-hydroxypropyl radical, the introduction of said substituent into the intermediate (II) may conveniently be carried out by reacting (II) at an elevated temperature with an appropriate oxirane of the formula



(IV)

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wherein m is 0 or 1;

- iv) or compounds of formula (I) wherein L represents a 2-hydroxyethyl radical may be prepared by the reaction of an appropriate piperidine of formula (II) with oxirane, following the same procedure as described for the reaction of (IV) with (II);
- v) when L is, at the point of attachment to the piperidine nitrogen atom, a primary or secondary alkyl group, the compounds (I) may also be prepared by the reductive amination of an aldehyde or ketone corresponding with the alcohol $L-OH$ with a piperidine derivative of formula (II) following art-known procedures, preferably, a mixture of the aldehyde or ketone and (II) in an appropriate organic solvent is hydrogenated in the presence of an appropriate catalyst such as, for example, palladium-on-charcoal; when the piperidine derivative (II) is in the form of an addition salt with a strong acid, e.g., hydrochloric or hydrobromic acid, it is appropriate to add thereto a salt of a strong base with a weak acid, e.g., sodium acetate to bind said strong acid, and when (II) contains groups that are themselves susceptible to catalytic hydrogenation, e.g. when R^2 represents an arylmethyl group, it is appropriate to add to the reaction mixture an appropriate catalyst poison, such as, for example, thiophene;
- vi) when L represents a radical of formula $R-C_mH_{2m}-$, wherein m is an integer of from 2 to 6 inclusive and wherein R is as previously defined, the compounds of formula (I) can also be prepared by the reaction of (II) with an appropriate alkenyl derivative. $R-C_mH_{2m-1}$

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according to art-known methods of carrying out similar addition-reactions, e.g., by stirring and heating the reactants together in an appropriate reaction-inert organic solvent;

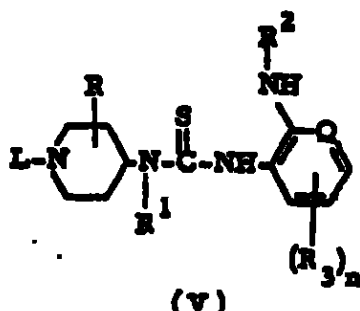
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vii) when L represents a 2-(aroylamino)ethyl radical or a 2-arylethyl radical the compounds (I) can also be obtained by the reaction of (II) with an appropriate 1-aroylaziridine or an appropriate ethenylarene, respectively, said reactions being preferably carried out in an appropriate reaction-inert organic solvent, at elevated temperatures; or

10

b) preparing compounds of formula (I) by the cyclodesulfurization of an appropriate thiourea derivative of the formula

15



i) said cyclodesulfurization reaction being preferably carried out by the reaction of (V) with an appropriate alkyl halide, preferably iodomethane in an appropriate reaction-inert organic solvent;

20

ii) said cyclodesulfurization reaction may be also carried out by the reaction of (V) with an appropriate metal oxide or salt in an appropriate solvent, preferably preparing the compounds of formula (I) by the reaction of (V) with an appropriate Hg(II) or Pb(II)

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oxide or salt, such as, for example, HgO , HgCl_2 ,
 $\text{Hg}(\text{OAc})_2$, PbO or $\text{Pb}(\text{OAc})_2$, or

5 iii) utilizing methanediimines, especially $\text{N,N}'$ -
methanetetraylbis[cyclo-hexanamines] as cyclodesul-
furizing agents in suitable reaction-inert organic
solvents; or

10 c) preparing compounds of formula (I) wherein R^2
is other than hydrogen, said R^2 being represented
by R_a^2 and said compounds by the formula (I-a),
starting from a corresponding compound (I) wherein R^2
is hydrogen, (I-b), by introducing said R_a^2 according
to art-known procedures;

15 i) preferably said compound (I-b) is reacted with
an appropriate reactive ester R_a^2Y , (VI), wherein
 R_a^2 and Y are as defined above, the reaction being
carried out under similar conditions as previously
described herein for the reaction of (II) with (III)
20 as described in step a) i); or

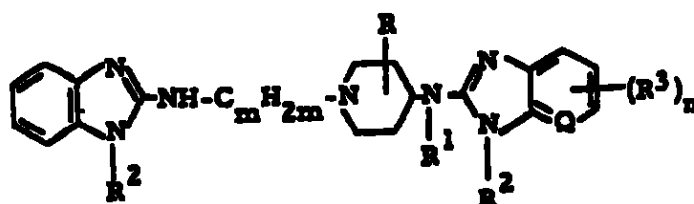
25 d) preparing compounds of the formula (I) wherein R^1
and R^2 are both different from hydrogen, said R^1 being
represented by R_a^1 and said R^2 by R_a^2 , from the
corresponding compounds wherein R^1 is hydrogen by intro-
ducing the R_a^1 - group in a similar manner as described
hereinabove in step c) for the preparation of compound
(I-b) starting from (I-a); or

30 e) preparing a compound of the formula

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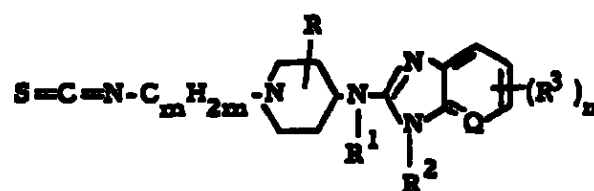
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(I-c)

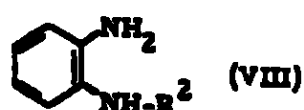
by subjecting an isothiocyanate of the formula



(VII)

5

to an addition reaction with a benzene diamine of the formula

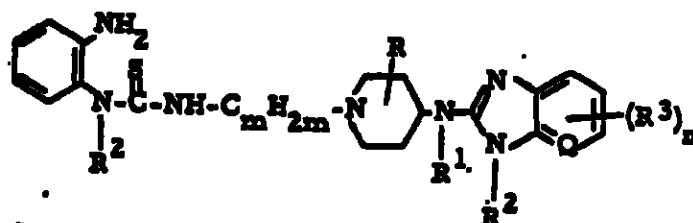


and subsequently cyclodesulfurizing the intermediately formed thiourea of the formula

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(IX)

as described in steps b) i), b) ii), or b) iii) above; or

- 5 f) preparing compounds of formula (I) wherein L represents a radical $\text{Z-C}_m\text{H}_{2m}\text{-}$, wherein Z represents a radical of the formula $\text{W-CO-(X)}_s\text{-}$, wherein s is 1, X is O and W is an optionally substituted amine, a 1-pyrrolidinyl, a 4-morpholinyl or a 1-piperidinyl radical, said compounds being represented by the
- 10 formula (I-d), by the reaction of the corresponding amine, pyrrolidine, morpholine or piperidine with an appropriate N-[1-(halolower alkyl)-4-piperidinyl]-1H-benzimidazol-2-amine in the presence of an appropriate carbonate; or
- 15 g) preparing compounds of formula (I) which contain at least one hydroxyl-group as a substituent, from the corresponding phenylmethoxy substituted compounds by subjecting the latter to a catalytic hydrogenation in the presence of an appropriate catalyst, or deriving
- 20 said hydroxyl-derivatives from the corresponding lower alkyloxy substituted analogs by hydrolysing the latter in acidic medium, using for example hydrogen bromide in acetic acid, and, if desired, said hydroxyl-sub-

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stituted compounds may in turn be O-alkylated or acylated by reacting the latter with a halide, an alkanoyl halide, an alkylloxycarbonyl halide, or an isocyanate, or said hydroxyl-substituted compounds may
5 also be converted into halides by reacting therewith a suitable halogenating agent; or

h) deriving amino-substituted compounds from the corresponding nitro- and cyano-substituted compounds
10 by reducing the latter, e.g., by catalytic hydrogenation in the presence of an appropriate catalyst, and, if desired, said amino-substituted compounds may in turn be N-alkylated or acylated by the reaction thereof with an appropriate alkylating agent or acylating agent; or

15 i) preparing secondary and tertiary amino-substituted compounds of formula (I) by substituting, for example, an appropriate halo-substituted compound with the desired primary or secondary amine; or

20 j) deriving aminocarbonyl-substituted compounds from the corresponding esters by reacting the latter with ammonia or an appropriate primary- or a secondary amine in a suitable solvent; or

25 k) deriving compounds of formula (I) which contain in their structure a sulfonyl group from the corresponding thio compounds by oxidizing the latter with an appropriate oxidizing agent; and, if desired, converting the compounds of formula (I) to the
30 therapeutically active non-toxic acid addition salt

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(71) Applicant JANSSEN PHARMACEUTICA N.V.
Turnhoutsebaan 20
B-2340 Beerse(BE)

(72) Inventor Janssens, Frans Eduard
Tintstraat 78
B-2280 Bonheiden(BE)

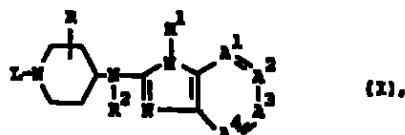
(72) Inventor Torremans, Joseph Leo Ghislanus
Lijsterstraat 11
B-2340 Beerse(BE)

(72) Inventor Hans, Josef Francis
Rector de Ramestraat 54
B-2280 Nijlen(BE)

(72) Inventor van Offenwert, Theophilus Theresia J.M.
Kardinaal Cardijnlaan 63
B-2260 Vosselaar(BE)

(84) Bicyclic heterocyclyl containing N-(bicyclic heterocyclyl)-4-piperidinamines.

(87) Novel N-heterocyclyl-4-piperidinamines of the formula



wherein L contains an optionally substituted five- or six-membered ring containing at least one nitrogen atom, and which is condensed with an optionally substituted five- or six-membered ring, the pharmaceutically acceptable acid addition salts and possible stereochemically isomeric forms thereof, which compounds are anti-allergic agents; pharmaceutical compositions containing such compounds as an active ingredient and methods of preparing said compounds and pharmaceutical compositions.

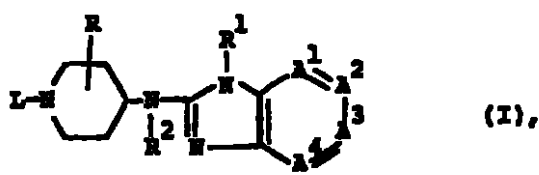
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CLAIMS

1. A chemical compound having the formula



a pharmaceutically acceptable acid addition salt or a possible stereochemically isomeric form thereof, wherein:

$A^1-A^2-A^3-A^4$ is a bivalent radical having the formula

- (a), $-CH=CH-CH=CH-$
- (b), $-N=CH-CH=CH-$
- (c), $-CH=N-CH=CH-$
- (d), or $-CH=CH-N=CH-$
- (e), $-CH=CH-CH=N-$

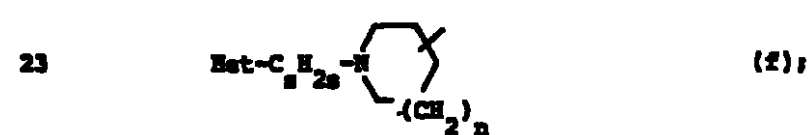
wherein one or two hydrogen atoms in said radicals (a) - (e) may, each independently from each other, be replaced by halo, lower alkyl, lower alkyloxy, trifluoromethyl or hydroxy;

R is a member selected from the group consisting of hydrogen and lower alkyl;

R^1 is a member selected from the group consisting of hydrogen, alkyl, cycloalkyl, Ar^1 and lower alkyl substituted with one or two Ar^1 radicals;

R^2 is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, (lower alkyl)-CO-, lower alkyl-O-(CO)- and Ar^2 -lower alkyl;

L is a member selected from the group consisting of a radical of formula



a radical of formula

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25 $\text{Het-C}_s\text{H}_{2s}\text{-Y-Alk-}$ (g); and

26 a radical of formula

27 $\text{Het-C}_s\text{H}_{2s}\text{-Z-C(=X)-Y-Alk-}$ (h),

28 wherein n is 0 or the integer 1 or 2;

29 s is 0 or an integer of from 1 to 6 inclusive;

30 Alk is lower alkanediyl;

31 Y is O, S, NR^3 or a direct bond;

32 X is O, S, CH-NO_2 or NR^4 ;

33 Z is O, S, NR^5 or a direct bond; and

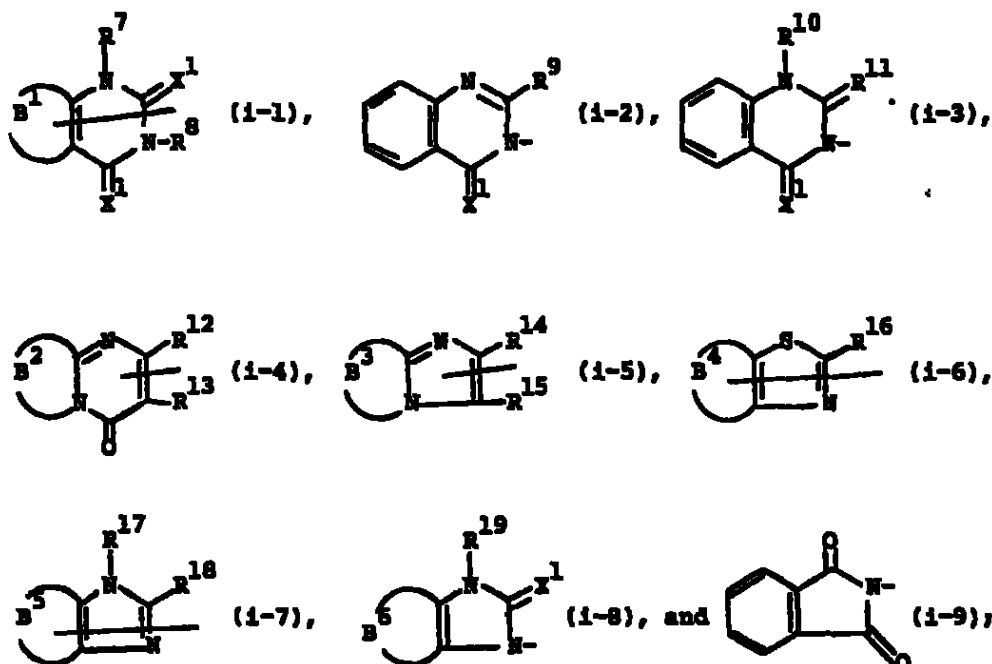
34 Het is an optionally substituted five- or six-membered heterocyclic
35 ring containing at least one nitrogen atom and being condensed with
36 an optionally substituted five- or six-membered ring, provided that:

- 37 i) when Het is connected to C_sH_{2s} on a carbon atom then
38 said five- or six-membered ring is not condensed with an
39 optionally substituted benzene ring;
40 ii) when L is a radical either of formula (f), or of formula
41 (g) wherein Y is other than a direct bond, or of formula
42 (h) wherein Z is other than a direct bond, wherein in said
43 radicals (f), (g) or (h) Het is connected to C_sH_{2s} on
44 a nitrogen atom then s is not 0;
45 iii) when $\text{A}^1\text{-A}^2\text{-A}^3\text{-A}^4$ is a radical of formula (a) or
46 (b) and L is a radical of formula (g) wherein s is 0 and
47 Y is a direct bond then Het is other than a 2,3-dihydro-
48 2-oxo-1H-benzimidazol-1-yl or a 2,3-dihydro-3-oxo-
49 benzoxazin-4-yl radical;

50 said R^3 being hydrogen, lower alkyl, (Ar^2) lower alkyl, 2-lower
51 alkyloxy-1,2-dioxoethyl or a radical of formula -C(=X)-R^6 , R^6
52 being hydrogen, lower alkyl, Ar^2 , Ar^2 -lower alkyl, lower alkyloxy,
53 Ar^2 -lower alkyloxy, mono- or di(lower alkyl)amino, Ar^2 -amino,
54 Ar^2 -lower alkylamino or Ar^2 -lower alkyl(lower alkyl)amino;
55 said R^4 being hydrogen, lower alkyl, cyano, nitro, Ar^2 -sulfonyl,

56 lower alkylsulfonyl, lower alkylcarbonyl or Ar²-carbonyl; and
 57 said R⁵ being hydrogen or lower alkyl;
 58 wherein Ar¹ is a member selected from the group consisting of
 59 phenyl, being optionally substituted with up to three substituents
 60 each independently selected from the group consisting of halo,
 61 hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkoxy,
 62 lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino,
 63 carboxyl, lower alkoxy carbonyl and lower alkyl-CO-; thienyl;
 64 halothienyl; furanyl; lower alkyl substituted furanyl; pyridinyl;
 65 pyrazinyl; thiazolyl and imidazolyl optionally substituted by lower
 66 alkyl; and wherein Ar² is a member selected from the group
 67 consisting of phenyl being optionally substituted with up to three
 68 substituents each independently selected from the group consisting
 69 of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl,
 70 lower alkoxy, lower alkylthio, mercapto, amino, mono- and di(lower
 71 alkyl)amino, carboxyl, lower alkoxy carbonyl and (lower alkyl)-CO.

1 2. A chemical compound according to claim 1, wherein R_{et} is a
 2 member of the group consisting of



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3 wherein each X^1 is independently O or S;
 4 R^7 , R^8 , R^{10} , R^{17} and R^{19} are each independently hydrogen, lower alkyl,
 5 Ar^2 -lower alkyl, hydroxylower alkyl or lower alkyloxycarbonyl;
 6 R^9 , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} and R^{18} are each independently
 7 hydrogen, lower alkyl, hydroxy, mercapto, lower alkyloxy, lower
 8 alkylthio, halo and (lower alkyloxycarbonyl)lower alkyl;
 9 B^1 is $-CH=CH-CH=CH-$, $-S-CH=CH-$ or $-N=CH-NH-$;
 10 B^2 is $-CH=CH-CH=CH-$, $-S-(CH_2)_2$, $-S-(CH_2)_3$ or $-(CH_2)_4$;
 11 B^3 is $-CH=CH-CH=CH-$, $-N=CH-CH=CH-$, $-CH=N-CH=CH-$, $-CH_2-NH-(CH_2)_2-$ or
 12 $-S-CH=CH-$;
 13 B^4 is $-CH_2-NH-(CH_2)_2-$, $-N=CH-CH=CH-$ or $-N=CH-N=CH-$;
 14 B^5 is $-N=CH-CH=CH-$, $-CH=N-CH=CH-$ or $-CH=N-CH=N-$;
 15 B^6 is $-CH=CH-CH=CH-$ or $-CH=N-CH=N-$;
 16 wherein one or two hydrogen atoms in said radicals B^1 , B^2 , B^3 , B^4 ,
 17 B^5 or B^6 or in the benzene part of the radicals of formula (i-2),
 18 (i-3) or (i-9) may be replaced by lower alkyl, lower alkylthio, lower
 19 alkyloxy or halo where said hydrogen atom is bonded on a carbon atom,
 20 or by lower alkyl, lower alkyloxycarbonyl, Ar^2 -lower alkyl, where
 21 said hydrogen is bonded on a nitrogen atom.
 22 It is clear that R^7 , R^8 , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} or R^{18} is absent
 23 where the radical of formula (i-1), respectively (i-4), (i-5), (i-6)
 24 and (i-7) is connected to C_6H_5 on the atom bearing R^7 , R^8 , R^{12} , R^{13} ,
 25 R^{14} , R^{15} , R^{16} , R^{17} or R^{18} .

1 3. A chemical compound according to claim 2 wherein L is a
 2 radical of formula (g) or (h).

1 4. A chemical compound selected from the group consisting of
 2 3-[2-[4-[[3-(2-furanylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]amino]-
 3 1-piperidinyl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one and the
 4 pharmaceutically acceptable acid addition salts thereof.

1 5. A pharmaceutical composition comprising a suitable pharmaceutical
 2 carrier and as an active ingredient a therapeutically effective amount
 3 of a compound as claimed in any one of claims 1 to 4.

1 6. An anti-allergic pharmaceutical composition comprising a
 2 suitable pharmaceutical carrier and as an active ingredient an
 3 effective anti-allergic amount of a compound as claimed in any one of
 4 claims 1 to 4.

1 7. A method of preparing a pharmaceutical composition,
2 characterized in that a therapeutically effective amount of a compound
3 as claimed in any one of claims 1 to 4 is intimately mixed with
4 suitable pharmaceutical carriers.

1 8. A compound as claimed in any one of claims 1 to 4 for use as
2 a medicine.

1 9. A compound as claimed in any one of claims 1 to 4 for use as
2 an anti-allergic medicine.

1 10. A process for preparing a chemical compound as claimed in
2 claim 1, characterized by

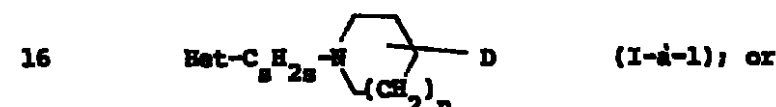
3 a) alkylating a piperidine of formula Q^2-D (III) with an intermediate
4 of formula $Het-Q^1$ (II) in a reaction-inert solvent wherein

5 1) Q^2 is hydrogen and Q^1 , combined with Het , forms a radical of
6 formula $L-W$ (II-a), said W representing an appropriate reactive
7 leaving group such as, for example, halo, e.g., chloro, bromo or
8 iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy or 4-methyl-
9 phenylsulfonyloxy; or

10 2) Q^1 is a radical of formula $-C_sH_{2s}-W^1$, said W^1 having the
11 previously defined meaning of W provided that, where s is 0, W^1 may
12 also represent a lower alkyloxy or lower alkylthio group, and Q^{2a}
13 is a radical of formula



15 thus preparing a compound of formula



17 3) Q^1 is a radical of formula $-C_sH_{2s}-W^1$ and Q^{2a} is a radical
18 of formula HY^1-Alk- , said Y^1 having the previously defined
19 meaning of Y provided that Y is other than a direct bond, thus
20 preparing a compound of formula



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- 22 4) Q^1 is a radical of formula $-C_{s_1}H_{2s_1}-W^1$ and Q^{2a} is a radical
23 of formula $HZ^1-C(X)-Y-Alk-$, said Z^1 having the previously
24 defined meaning of Z provided that Z is other than a direct
25 bond, thus preparing a compound of formula



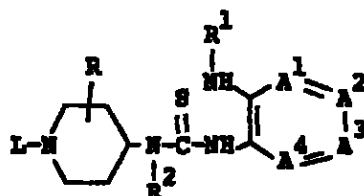
- 27 5) Q^1 is a radical of formula $-C_{s_1}H_{2s_1}-Y^1H$ and Q^2 is a
28 radical of formula $W-Alk-$, thus preparing a compound of formula



- 30 6) Q^1 is a radical of formula $-C_{s_1}H_{2s_1}-Z-C(X)-Y^1H$ and Q^2 is a
31 radical of formula $W-Alk-$, thus preparing a compound of formula



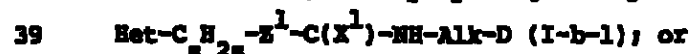
- 33 b) cyclodesulfurizing an intermediate of formula



(IV)

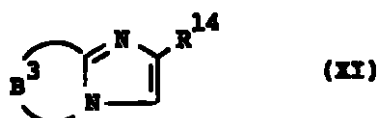
- 34 with an appropriate alkyl halide, metal oxide or metal salt in a
35 reaction-inert solvent; or

- 36 c) reacting an intermediate of formula $Het-C_{s_1}H_{2s_1}-Z^1H$ (V) with a
37 piperidine of formula $X^1-C-N-Alk-D$ (VI) in a suitable reaction-
38 inert solvent, thus preparing a compound of formula

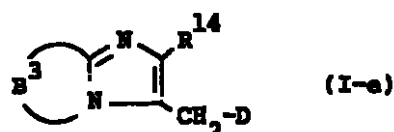


- 40 d) reacting an intermediate of formula $Het-C_{s_1}H_{2s_1}-N-C-X^1$ (VII), said X^1
41 being O or S, with a piperidine of formula $HY^1-Alk-D$ (VIII) in a
42 suitable reaction-inert solvent, thus preparing a compound of formula
43
$$Het-C_{s_1}H_{2s_1}-NH-C(X^1)-Y^1-Alk-D \quad (I-b-2); \text{ or}$$

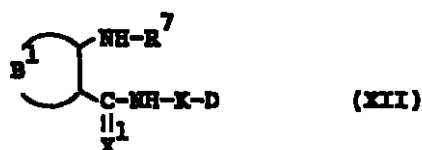
- 44 e) reacting an intermediate of formula $\text{Het-C}_s\text{H}_{2s}\text{-C(X}^1\text{)-OH (IX)}$ with a
 45 piperidine of formula $\text{HY}^1\text{-Alk-D (VIII)}$ in a suitable reaction-inert
 46 solvent, if desired, after converting the OH-function in (VIII) in a
 47 suitable leaving group, or, if desired, by reacting (IX) with (VIII)
 48 together with an appropriate reagent capable of forming amides or
 49 esters; thus preparing $\text{Het-C}_s\text{H}_{2s}\text{-C(X}^1\text{)-Y}^1\text{-Alk-D (I-c)}$; or
 50 f) reacting a piperidine of formula HD (III-a) with a reagent of formula
 51 $\text{Het-lower alkenediyl-H (X)}$ in a suitable reaction-inert solvent, thus
 52 preparing a compound of formula Het-Alk-D (I-d) ; or
 53 g) reacting an intermediate of formula HD (III-a) with a reagent of
 54 formula



- 55 in the presence of formaldehyde or a polymeric form thereof
 56 in a suitable solvent, thus preparing a compound of formula

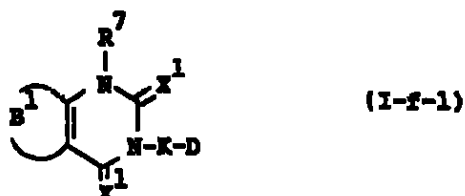


- 57 wherein B^3 is $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{N}-\text{CH}=\text{CH}-$, $-\text{CH}_2\text{-NH-(CH}_2\text{)}_2\text{-}$,
 58 $-\text{S}-\text{CH}=\text{CH}-$ or $-\text{N}=\text{CH}-\text{CH}=\text{CH}-$; and R^{14} is independently selected from the
 59 group consisting of hydrogen, lower alkyl, hydroxy, mercapto, lower
 60 alkyloxy, lower alkylthio, halo and (lower alkyloxycarbonyl)-
 61 lower alkyl; or
 62 h) reacting an intermediate of formula

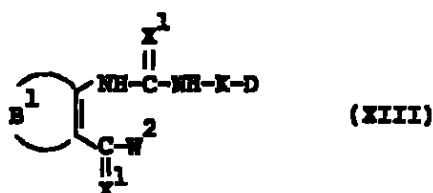


- 63 with a C-X^1 generating agent in a reaction-inert solvent thus
 64 preparing a compound of formula

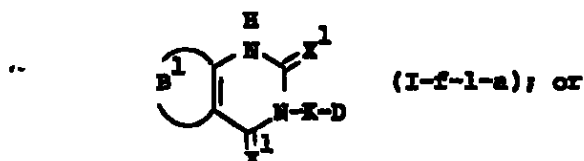
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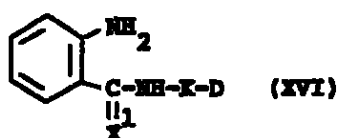
65 wherein B^1 is $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{S}-\text{CH}=\text{CH}-$ or $-\text{N}=\text{CH}-\text{NH}-$; and R^7 is
 66 selected from the group consisting of hydrogen, lower alkyl,
 67 Ar^2 -lower alkyl, hydroxylower alkyl or lower alkyloxycarbonyl; or
 68 i) cyclizing an intermediate of formula



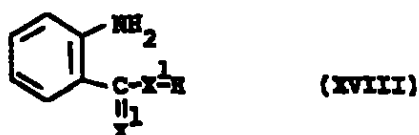
69 wherein W^2 is an appropriate reactive leaving group, in a
 70 reaction-inert solvent and, if desired, in the presence of an
 71 appropriate base, thus preparing a compound of formula



72 j) cyclizing the intermediate of formula

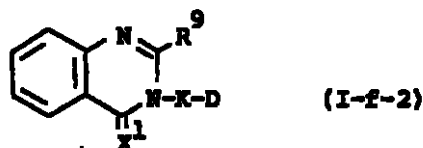


73 with an acid of formula $R^9\text{COOH}$ (XVII) or a functional derivative
 74 thereof; or cyclizing an intermediate of formula

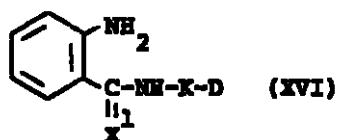


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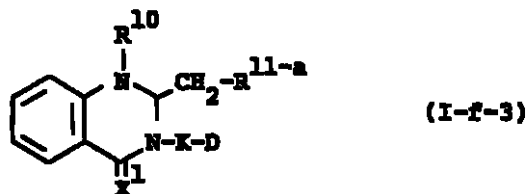
75 with an atomatic amino acid or -thioacid of the formula
76 $R^9C(O)-NH-K-D$ (XIX) in a suitable reaction-inert solvent,
77 thus preparing a compound of formula



78 wherein R^9 is selected from the group consisting of hydrogen,
79 lower alkyl, hydroxy, mercapto, lower alkyloxy, lower alkylthio,
80 halo and (lower alkyloxycarbonyl)lower alkyl; or
81 k) reacting an intermediate of formula



82 with an acetylene derivative of formula $CH\equiv C-R^{11-a}$ (XX) in a
83 suitable solvent, thus preparing a compound of formula

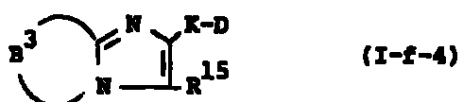


84 wherein R^{10} is selected from the group consisting of hydrogen,
85 lower alkyl, Ar^2 -lower alkyl, hydroxylower alkyl or lower
86 alkyloxycarbonyl; and R^{11-a} is (C_{1-5}) alkyl or (lower alkyloxy-
87 carbonyl) (C_{1-5}) alkyl; or
88 l) reacting a reagent of formula



89 with an intermediate of formula $W-CH(R^{15})-C(O)-X-D$ (XXII) in a
90 suitable reaction-inert solvent thus preparing a compound of formula

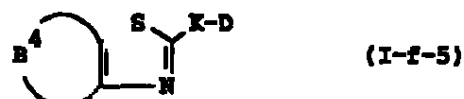
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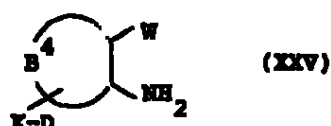
- 91 wherein R^{15} is selected from the group consisting of hydrogen,
 92 lower alkyl, hydroxy, mercapto, lower alkyloxy, lower alkylthio,
 93 halo and (lower alkyloxycarbonyl)lower alkyl; or
 94 m) cyclizing a reagent of formula



- 95 with an intermediate of formula $H_2NC(S)-K-D$ (XXIV) in a suitable
 96 reaction-inert solvent thus preparing a compound of formula



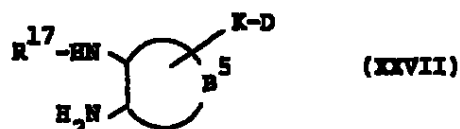
- 97 wherein B^4 is $-CH_2-NH-(CH_2)_2-$, $-N=CH-CH=CH-$ or $-N=CH-N=CH-$; or
 98 n) cyclizing a reagent of formula



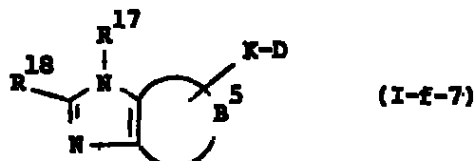
- 99 with CS_2 in a suitable reaction-inert solvent thus preparing a
 100 compound of formula



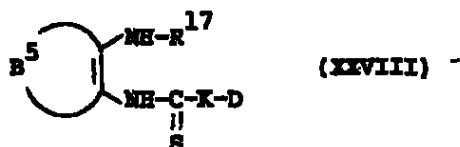
- 101 o) reacting a reagent of formula $R^{18}-C(NH)-N^2$ (XXVI) with an
 102 intermediate of formula



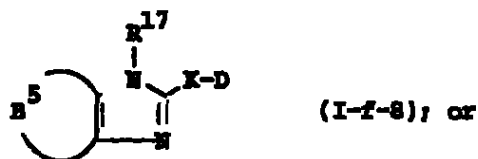
103 in a suitable reaction-inert solvent thus preparing a compound
104 of formula



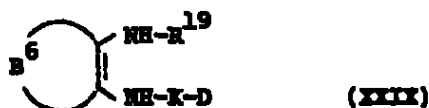
106 wherein B⁵ is -N-CH-CH-CH-, -CH-CH-N-CH- or -CH-N-CH-N-, R¹⁷ is
107 selected from the group consisting of hydrogen, lower alkyl,
108 Ar²-lower alkyl, hydroxylower alkyl or lower alkyloxycarbonyl;
109 and R¹⁸ is selected from the group consisting of hydrogen,
110 lower alkyl, hydroxy, mercapto, lower alkyloxy, lower
111 alkylthio, halo and (lower alkyloxycarbonyl)lower alkyl; or
112 p) cyclodesulfurizing an intermediate of formula



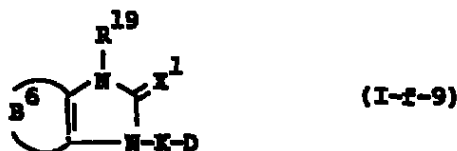
113 with an appropriate alkyl halide, metal oxide or metal salt in a
114 reaction-inert solvent; thus preparing a compound of formula



115 q) reacting an intermediate of formula



116 with a C-X¹ generating agent in a reaction-inert solvent thus
117 preparing a compound of formula

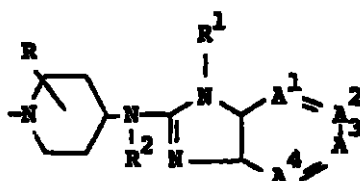


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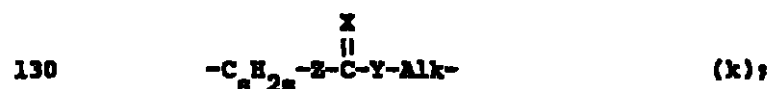
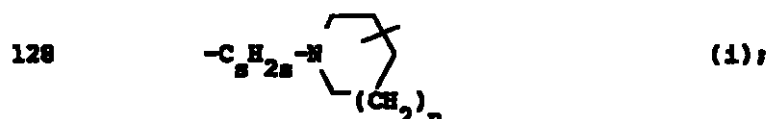
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118 wherein B^6 is $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ or $-\text{CH}=\text{N}-\text{CH}=\text{N}-$; and R^{19} is selected
 119 from the group consisting of hydrogen, lower alkyl, Ar^2 -lower
 120 alkyl, hydroxylower alkyl or lower alkyloxycarbonyl; or
 121 r) reducing an intermediate of formula $\text{Het}-\text{C}_s\text{H}_{2s}-\text{Y}-\text{Alk}'-\text{C}(\text{O})-\text{D}$ (XXX)
 122 with a complex metal hydride in a suitable solvent, thus preparing a
 123 compound of formula $\text{Het}-\text{C}_s\text{H}_{2s}-\text{Y}-\text{Alk}'-\text{CH}_2-\text{D}$ (I-g) wherein Alk' has the
 124 previously defined meaning of Alk , provided that one methylene
 125 function is missing;

126 wherein D represents a radical of formula

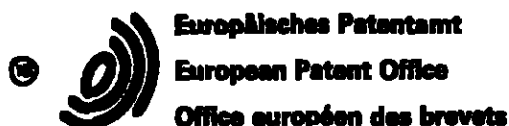


127 and K represents a bivalent radical of formula



131 optionally converting the compounds of formula (I) into each other
 132 following art-known functional grouptransformation procedures; and,
 133 if desired, converting the compounds of formula (I) into a
 134 therapeutically active non-toxic acid-addition salt form by treatment
 135 with an appropriate acid or, conversely, converting the acid-addition
 136 salt into the free base form with alkali; and/or preparing
 137 stereochemically isomeric forms thereof.

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(71) Applicant: JANSSEN PHARMACEUTICA N.V.
Turnhoutsebaan 30
B-2340 Beerse(BE)

(72) Inventor: Janssens, Frans Eduard
Tribstraat 79
B-2380 Bonheiden(BE)

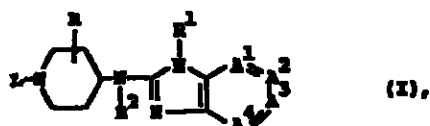
(72) Inventor: Torremans, Joseph Leo Ghislainus
Lijsterstraat 11
B-2340 Beerse(BE)

(72) Inventor: Hans, Josef Francis
Rector de Ransstraat 54
B-2380 Bonheiden(BE)

(72) Inventor: Van Ofterwert, Theophilus Theresia Joannes
Maria
Kortlaan Cardijnlaan 53
B-2380 Vennikel(BE)

(54) Five membered heterocyclic ring containing N-(bicyclic heterocyclyl)-4-piperidinamines.

Novel five membered ring containing N-(bicyclic heterocyclyl)-4-piperidinamines of the formula



the pharmaceutically acceptable acid addition salts and possible stereochemically isomeric forms thereof, which compounds are anti-allergic agents; pharmaceutical compositions containing such compounds as an active ingredient and methods of preparing said compounds and pharmaceutical compositions.

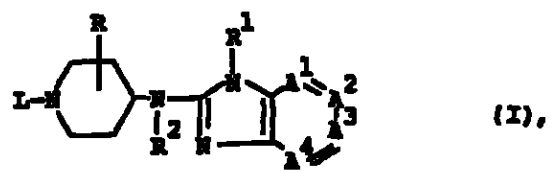
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CLAIMS

1. A chemical compound having the formula



a pharmaceutically acceptable acid addition salt or a possible stereochemically isomeric form thereof, wherein:

$A^1-A^2-A^3-A^4$ is a bivalent radical having the formula

- 5 $-CH=CH-CH=CH-$ (a),
- 6 $-N=CH-CH=CH-$ (b),
- 7 $-CH=N-CH=CH-$ (c),
- 8 $-CH=CH-N=CH-$ (d), or
- 9 $-CH=CH-CH=N-$ (e),

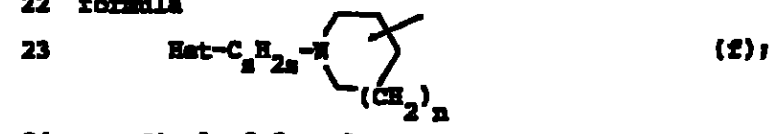
wherein one or two hydrogen atoms in said radicals (a) - (e) may, each independently from each other, be replaced by halo, lower alkyl, lower alkyloxy, trifluoromethyl or hydroxy;

R is a member selected from the group consisting of hydrogen and lower alkyl;

R^1 is a member selected from the group consisting of hydrogen, alkyl, cycloalkyl, Ar^1 and lower alkyl substituted with one or two Ar^1 radicals;

R^2 is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, (lower alkyl)-CO-, (lower alkyl-O)-CO and Ar^2 -lower alkyl;

L is a member selected from the group consisting of a radical of formula



a radical of formula



a radical of formula

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27 $\text{Het}-\text{C}_s\text{H}_{2s}-\overset{\text{X}}{\underset{\text{H}}{\text{C}}}-\text{Y}-\text{Alk}-$ (h),
28 wherein n is 0 or the integer 1 or 2;
29 s is 0 or an integer of from 1 to 6 inclusive;
30 Alk is lower alkanediyl;
31 Y is O, S, NR^3 or a direct bond;
32 X is O, S, $\text{CH}-\text{NO}_2$ or NR^4 ;
33 Z is O, S, NR^5 or a direct bond; and
34 Het is an optionally substituted 5-membered heterocyclic ring having
35 at least one nitrogen atom and being optionally condensed with an
36 optionally substituted benzene ring, said Het being connected to C_sH_{2s}
37 on a carbon atom;
38 said R^3 being hydrogen, lower alkyl, (Ar^2) lower alkyl, 2-lower
39 alkyloxy-1,2-dioxoethyl or a radical of formula $-\text{C}(=\text{X})-\text{R}^6$, R^6 being
40 hydrogen, lower alkyl, Ar^2 , Ar^2 -lower alkyl, lower alkyloxy, Ar^2 -
41 lower alkyloxy, mono- or di(lower alkyl)amino, Ar^2 -amino, Ar^2 -lower
42 alkylamino or Ar^2 -lower alkyl(lower alkyl)amino;
43 said R^4 being hydrogen, lower alkyl, cyano, nitro, Ar^2 -sulfonyl,
44 lower alkylsulfonyl, lower alkylcarbonyl or Ar^2 -carbonyl; and
45 said R^5 being hydrogen or lower alkyl;
46 provided that:
47 i) when $\text{A}^1=\text{A}^2-\text{A}^3=\text{A}^4$ is a bivalent radical of formula (a) or (b),
48 then Het is other than 1-(lower alkyl)pyrrolyl;
49 ii) when $\text{A}^1=\text{A}^2-\text{A}^3=\text{A}^4$ is a bivalent radical of formula (a) or (b)
50 and L is a radical of formula (g) wherein s is 0 and Y is NR^3 ,
51 then Het is other than 1H-benzimidazol-2-yl;
52 wherein Ar^1 is a member selected from the group consisting of phenyl,
53 being optionally substituted with up to three substituents each indepen-
54 dently selected from the group consisting of halo, hydroxy, nitro, cyano,
55 trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto,
56 amino, mono- and di(lower alkyl)amino, carboxyl, lower alkylloxycarbonyl
57 and lower alkyl-CO-; thianyl; halothianyl; furanyl; lower alkyl substi-
58 tuted furanyl; pyridinyl; pyrazinyl; thiazolyl and imidazolyl optionally
59 substituted by lower alkyl; and wherein Ar^2 is a member selected from
60 the group consisting of phenyl being optionally substituted with up to

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61 three substituents each independently selected from the group consisting
62 of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower
63 alkoxy, lower alkylthio, mercapto, amino, mono- and di(lower
64 alkyl)amino, carboxyl, lower alkoxy carbonyl and (lower alkyl)CO.

1 2. A chemical compound according to claim 1 wherein Het is a member
2 selected from the group consisting of thiazolyl, 4,5-dihydrothiazolyl,
3 oxazolyl, imidazolyl, tetrazolyl, 1,3,4-thiadiazolyl, benzimidazolyl,
4 benzothiazolyl, benzoxazolyl, and indolyl whereby each of the said
5 Het-radicals may optionally be substituted with up to two substituents
6 selected from the group consisting of lower alkyl, Ar¹, Ar¹-lower alkyl,
7 amino, (aminoiminomethyl)amino, mono- and di(lower alkyl)amino, Ar¹-amino,
8 nitro and pyrimidinyl.

1 3. A chemical compound according to claim 2 wherein L is a radical
2 of formula (g) or (h).

1 4. A chemical compound according to claim 1 wherein L is a radical
2 of formula (g) or (h), wherein Het is thiazolyl or imidazolyl.

1 5. A pharmaceutical composition comprising a suitable pharmaceutical
2 carrier and as an active ingredient a therapeutically effective amount of
3 a compound as claimed in any one of claims 1 to 5.

1 6. An anti-allergic pharmaceutical composition, comprising a suitable
2 pharmaceutical carrier and as an active ingredient an effective anti-
3 allergic amount of a compound as claimed in any one of claims 1 to 5.

1 7. A method of preparing a pharmaceutical composition as claimed
2 in any one of claims 5 and 6, characterized in that a therapeutically
3 effective amount of a compound as claimed in any one of claims 1 to 5
4 is intimately mixed with suitable pharmaceutical carriers.

1 8. A compound as claimed in any one of claims 1 to 5 for use as a
2 medicine.

1 9. A compound as claimed in any one of claims 1 to 5 for use as an
2 anti-allergic medicine.

1 10. A process for preparing a chemical compound as claimed in claim 1,
2 characterized by

3 a) alkylating a piperidine of formula Q²-D (III) with an intermediate
4 of formula Het-Q¹ (II) in a reaction-inert solvent wherein

5 1) Q² is hydrogen and Q¹, combined with Het, forms a radical of
6 formula I-W (II-a), said W representing an appropriate reactive

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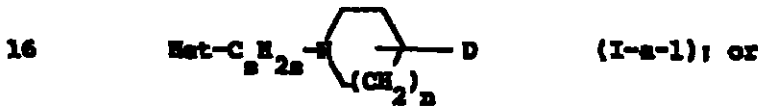
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7 leaving group such as, for example, halo, e.g., chloro, bromo or
8 iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy or 4-methyl-
9 phenylsulfonyloxy; or
10 2) Q^1 is a radical of formula $-C_sH_{2s}-W'$, said W' having the
11 previously defined meaning of W provided that, where s is 0, W' may
12 also represent a lower alkyloxy or lower alkylthio group, and Q^2
13 is a radical of formula



15 thus preparing a compound of formula



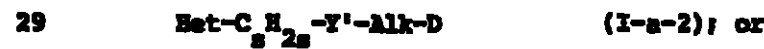
17 3) Q^1 is a radical of formula $-C_sH_{2s}-W'$ and Q^2 is a radical
18 of formula $HY'-Alk-$, said Y' having the previously defined
19 meaning of Y provided that Y is other than a direct bond, thus
20 preparing a compound of formula



22 4) Q^1 is a radical of formula $-C_sH_{2s}-W'$ and Q^2 is a radical
23 of formula $HZ'-C(X)-Y-Alk-$, said Z' having the previously
24 defined meaning of Z provided that Z is other than a direct
25 bond, thus preparing a compound of formula



27 5) Q^1 is a radical of formula $-C_sH_{2s}-Y'H$ and Q^2 is a
28 radical of formula $W-Alk-$, thus preparing a compound of formula



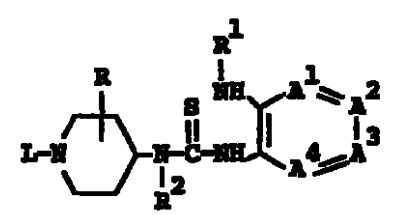
30 6) Q^1 is a radical of formula $-C_sH_{2s}-Z-C(X)-Y'H$ and Q^2 is a
31 radical of formula $W-Alk$, thus preparing a compound of formula

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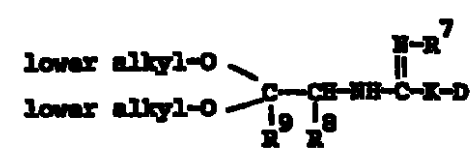


33 b) cyclodesulfurizing an intermediate of formula



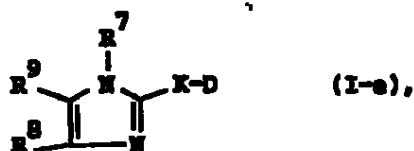
(IV)

- 34 with an appropriate alkyl halide, metal oxide or metal salt in a
 35 reaction-inert solvent; or
 36 c) reacting an intermediate of formula $\text{Het-C}_8\text{H}_{28}-\text{Z}'\text{H}$ (V) with a
 37 piperidine of formula $\text{X}'-\text{C}-\text{H}-\text{Alk-D}$ (VI) in a suitable reaction-
 38 inert solvent, thus preparing a compound of formula
 39 $\text{Het-C}_8\text{H}_{28}-\text{Z}'-\text{C}(\text{X}')-\text{NH}-\text{Alk-D}$ (I-b-1); or
 40 d) reacting an intermediate of formula $\text{Het-C}_8\text{H}_{28}-\text{S}-\text{C}-\text{X}'$ (VII), said X'
 41 being O or S, with a piperidine of formula $\text{HY}'-\text{Alk-D}$ (VIII) in a
 42 suitable reaction-inert solvent, thus preparing a compound of formula
 43 $\text{Het-C}_8\text{H}_{28}-\text{NH}-\text{C}(\text{X}')-\text{Y}'-\text{Alk-D}$ (I-b-2); or
 44 e) reacting an intermediate of formula $\text{Het-C}_8\text{H}_{28}-\text{C}(\text{X}')-\text{OH}$ (IX) with a
 45 piperidine of formula $\text{HY}'-\text{Alk-D}$ (VIII) in a suitable reaction-inert
 46 solvent, if desired, after converting the OH-function in (VIII) in a
 47 suitable leaving group, or, if desired, by reacting (IX) with (VIII)
 48 together with an appropriate reagent capable of forming amides or
 49 esters; thus preparing $\text{Het-C}_8\text{H}_{28}-\text{C}(\text{X}')-\text{Y}'-\text{Alk}$ (I-c); or
 50 f) reacting a piperidine of formula HD (III-a) with a reagent of formula
 51 $\text{Het-lower alkenediyl-H}$ (X) in a suitable reaction-inert solvent, thus
 52 preparing a compound of formula Het-Alk-D (I-d); or
 53 g) cyclizing an imidamide derivative of formula

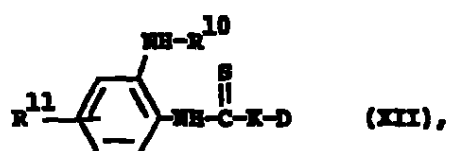


(XI)

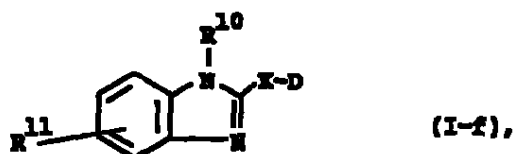
in a reaction-inert solvent and, if desired, in the presence of an appropriate acid, thus preparing a compound of formula:



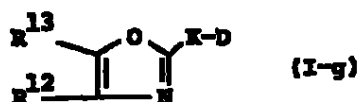
56 wherein R^7 , R^8 and R^9 are each independently optional
57 substituents of the imidazole ring; or
58 b) cyclodesulfurizing a thioamide derivative of formula



59 with an appropriate alkyl halide, metal oxide or metal salt in a
60 reaction-inert solvent, thus yielding a compound of formula



61 wherein R^{10} and R^{11} are each independently optional substituents
62 of the 1H-benzimidazol-2-yl ring; or
63 1) condensing a cyanide of formula NC-R-D (XIV) with a reagent of
64 formula $R^{12}-C(O)-CH(OH)-R^{13}$ (XIII), in a reaction-inert solvent
65 and, if desired, in the presence of an appropriate base, thus
66 preparing a compound of formula



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- 67 wherein R^{12} and R^{13} are each independently optional substituents
68 of the oxazole ring; or
69 j) condensing a thioamide derivative of formula $H_2N-C(S)-K-D$ (XVI)
70 with a reagent of formula $R^{14}-C(O)-CH(W)-R^{15}$ (XV) in a reaction-
71 inert solvent and, if desired, in the presence of an appropriate
72 base, thus preparing a compound of formula



- 73 wherein R^{14} and R^{15} are each independently optional substituents
74 of the thiazole ring; or
75 k) condensing a ketone of formula $W-CH(R^{17})-C(O)-K-D$ (XVIII) with a
76 thioamide derivative of formula $R^{16}-C(S)-NH_2$ (XVII) in a
77 reaction-inert solvent and, if desired, in the presence of an
78 appropriate base, thus preparing a compound of formula



- 79 wherein R^{16} and R^{17} are each independently optional substituents
80 of the thiazole ring; or
81 l) condensing a ketone of formula (XVIII) with an isothiocyanate of
82 formula $R^{18}-N=C=S$ (XIX) in the presence of ammonia or an ammonium
83 salt in a reaction-inert solvent and, if desired, in the presence
84 of an appropriate base, thus yielding a compound of formula



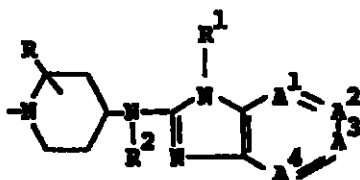
- 85 wherein R^{17} and R^{18} are each independently optional substituents
86 of the thiazole ring; or
87 m) condensing an isothiocyanate of formula $S=C=N-Alk-D$ (VI-a) with a

-75-

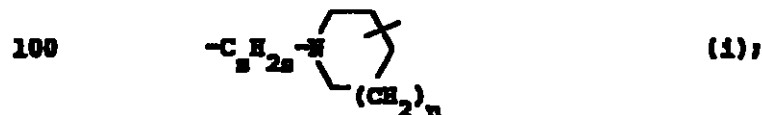
88 reagent of formula $W-CH(R^{19})-CH(R^{20})-NH_2$, in a reaction-inert solvent
89 and, if desired, in the presence of an appropriate base, thus yielding
90 a compound of formula



91 wherein R¹⁹ and R²⁰ are each independently optional substituents
92 of the 4,5-dihydro-thiazole ring; or
93 n) reducing a compound of formula Het-C₅H_{2s}-Y-Alk'-C(O)-D (XXI)
94 with an appropriate reducing agent in a reaction-inert solvent,
95 thus
96 yielding a compound of formula Het-C₅H_{2s}-Y-Alk'-CH₂-D (I-1),
97 wherein Alk' has the previously defined meaning of Alk, provided
98 that one methylene function is missing;
99 wherein D represents a radical of formula



99 and K represents a bivalent radical of formula



103 converting the compounds of formula (I) into a therapeutically active
104 non-toxic acid-addition salt form by treatment with an appropriate
105 acid or, conversely, converting the acid-addition salt into the free
106 base form with alkali; and/or preparing stereochemically isomeric
107 forms thereof.

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⑫

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⑱ Applicant: JANSSEN PHARMACEUTICA N.V.
Turnhoutsebaan 30
B-2240 Beerse(BE)

⑲ Inventor: Janssens, Frans Eduard
Thiestraat 78
B-2230 Boshuizen(BE)

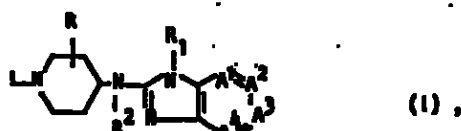
⑳ Inventor: Torrensens, Joseph Leo Ghislainus
Lijsterstraat 11
B-2240 Beerse(BE)

㉑ Inventor: Haze, Josef Francis
Rector de Ramestraat 54
B-2230 Nijlen(BE)

㉒ Inventor: Van Offeswert, Theophilus Theresia Joannes
Kardinaal Cardijnlaan 63
B-2230 Voerendaal(BE)

㉓ N-(4-piperidinyl) bicyclic condensed 2-imidazoline derivatives.

㉔ Novel N-heterocyclyl-4-piperidinamines of formula

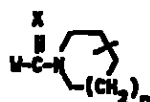


wherein L is a radical of formula



Hot-Alk- (b-5); (lower alkanyl)-Y¹-Alk- (b-6); or Ar¹-Alk- (b-7); the pharmaceutically acceptable acid addition salts and possible stereochemically isomeric forms thereof, which compounds are anti-allergic agents, pharmaceutical compositions containing such compounds as an active ingredient and processes for preparing the said compounds and compositions.

(b-1) :



(b-2) :



(b-3) :



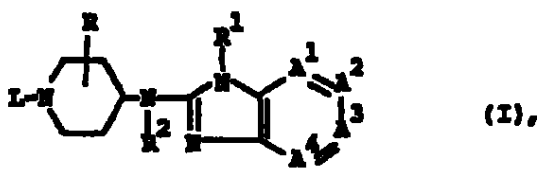
(b-4) :

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CLAIMS

1. A chemical compound having the formula



2 a pharmaceutically acceptable acid addition salt or a possible
3 stereochemically isomeric form thereof, wherein:

4 $A^1-A^2-A^3-A^4$ is a bivalent radical having the formula

- 5 $-CH-CH-CH-CH-$ (a-1),
- 6 $-N-CH-CH-CH-$ (a-2),
- 7 $-CH-N-CH-CH-$ (a-3),
- 8 $-CH-CH-N-CH-$ (a-4), or
- 9 $-CH-CH-CH-N-$ (a-5),

10 wherein one or two hydrogen atoms in said radicals (a-1) - (a-5) may,
11 each independently from each other, be replaced by halo, lower alkyl,
12 lower alkyloxy, trifluoromethyl or hydroxy;

13 R is a member selected from the group consisting of hydrogen and
14 lower alkyl;

15 R^1 is a member selected from the group consisting of
16 hydrogen, alkyl, cycloalkyl, Ar^1 and lower alkyl substituted with
17 one or two Ar^1 radicals;

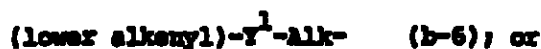
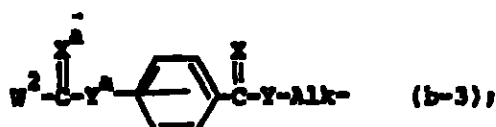
18 R^2 is a member selected from the group consisting of hydrogen,
19 lower alkyl, cycloalkyl, (lower alkyl)-CO-, (lower alkyloxy)-CO- and
20 Ar^2 -lower alkyl; and

21 L is a radical of formula



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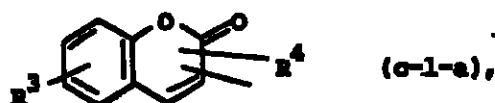
22 1) where $\text{A}^1 - \text{A}^2 - \text{A}^3 - \text{A}^4$ is a radical of formula (a-3), (a-4) or
23 (a-5), or

24 ii) where $\text{A}^1 - \text{A}^2 - \text{A}^3 - \text{A}^4$ is a radical of formula (a-1) or (a-2),
25 and R^1 is Ar^3 or lower alkyl substituted with one or two
26 Ar^3 radicals, said Ar^3 being pyrazinyl, thiasolyl or
27 imidazolyl, optionally substituted with lower alkyl;

28 L may also be a radical of formula:



29 said W being a member selected from the group consisting of
30 hydrogen, lower alkyl, Ar^1 , Ar^1 -lower alkyl, 1-piperidinyl,
31 1-pyrrolidinyl, 4-morpholinyl, a radical of formula



32 a radical of formula



33 a radical of formula



34 wherein R^3 and R^4 are each independently hydrogen or lower alkyl;
35 and W^1 is cycloalkyl or lower alkyl, optionally substituted with up
36 to two substituents selected from the group consisting of hydroxy,
37 lower alkyloxy, 1-piperidinyl, 1-pyrrolidinyl, 4-morpholinyl and

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- 38 Ar^1 , and where Z^1 is NR^8 , W^1 may also be hydrogen, amino,
39 lower alkylamino, Ar^1 -amino or nitro;
40 said W^2 being a member selected from the group consisting of
41 hydrogen, lower alkyl, Ar^1 and a radical of formula:



- 42 wherein R^5 is hydrogen, lower alkyl or Ar^1 ;

- 43 said T being a radical of formula:

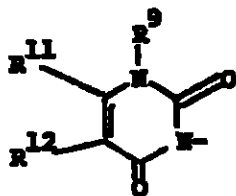


- 44 R^6 being hydrogen, lower alkyl or Ar^1 ;

- 45 R^7 being lower alkyl or Ar^1 ; and

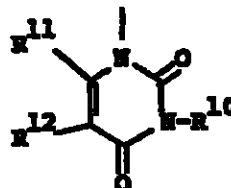
- 46 R^8 being hydrogen or lower alkyl;

- 47 said Het being a radical of formula (c-1-a), (c-1-b), or a radical
48 of formula



(c-4-a)

or of formula



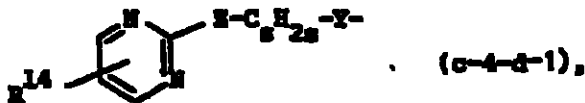
(c-4-b),

- 49 wherein R^9 , R^{10} , R^{11} and R^{12} are each independently hydrogen
50 or lower alkyl; or a radical of formula



(c-4-c),

- 51 wherein R^{13} is hydrogen, lower alkyl or amino, or
52 said Het being furan substituted with lower alkyl, said lower alkyl
53 being optionally substituted with hydroxy, mercapto, lower alkyloxy, lower
54 alkylthio, (aminolower alkyl)thio, Ar^1 -O- or a radical of formula



(c-4-d-1),

55 s being an integer of from 1 to 6 inclusive; or where Z or Y is a
56 direct bond, s may also be 0; and R^{14} being hydrogen or lower alkyl;
57 wherein: n is 0 or the integer 1 or 2;
58 X is O, S, NR^{15} or $CHNO_2$;
59 Y is O, S, NR^{16} or a direct bond;
60 Y^1 is O, S or NR^{16} ;
61 Y^2 is S or NR^{16} ;
62 Z is O, S, NR^8 or a direct bond;
63 Z^1 is O, S or NR^8 ;
64 X^a and Y^a independently having the same meaning of X
65 respectively Y;
66 said R^{15} being hydrogen, lower alkyl, cyano, nitro,
67 Ar^2 -sulfonyl, lower alkylsulfonyl, lower alkylcarbonyl
68 or Ar^2 -carbonyl;
69 said R^{16} being hydrogen, lower alkyl, (Ar^2) lower
70 alkyl, 2-lower alkyloxy-1,2-dioxoethyl; or a radical of
71 formula $-C(=X)-R^{17}$, R^{17} being hydrogen, lower alkyl,
72 Ar^2 , Ar^2 -lower alkyl, lower alkyloxy, Ar^2 -lower
73 alkyloxy, mono- or di(lower alkyl)amino, Ar^2 -lower
74 alkylamino or Ar^2 -lower alkyl(lower alkyl)amino;
75 provided that:
76 i) when $A^1-A^2-A^3-A^4$ is a radical of formula (a-1) or (a-2), and L
77 is a radical of formula (b-1), wherein W is other than hydrogen
78 or other than a radical of formula (c-1-a) or (c-1-b), then X
79 is other than O;
80 ii) when L is a radical of formula (b-1), wherein W is a radical
81 of formula (c-1-c), wherein Z^1 is NH then W^1 is other than
82 hydrogen or lower alkyl;
83 iii) when $A^1-A^2-A^3-A^4$ is a radical of formula (a-1) or (a-2), and L
84 is a radical of formula (b-3), wherein X is O, Y is NR^{16} , O
85 or a direct bond, and X^a is O,
86 a) then Y^a is not O;
87 b) and W^2 being lower alkyl then Y^a is not a direct bond;
88 wherein Ar^1 is a member selected from the group consisting of
89 phenyl, being optionally substituted with up to three substituents

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90 each independently selected from the group consisting of halo, hydroxy,
91 nitro, cyano, trifluoromethyl, lower alkyl, lower alkoxy, lower
92 alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl,
93 lower alkoxy-carbonyl and lower alkyl-CO-, thienyl, halothienyl,
94 furanyl, lower alkyl substituted furanyl, pyridinyl, pyrazinyl,
95 thiazolyl and imidazolyl optionally substituted with lower alkyl; and
96 wherein R^2 is a member selected from the group consisting of phenyl
97 being optionally substituted with up to three substituents each
98 independently selected from the group consisting of halo, hydroxy,
99 nitro, cyano, trifluoromethyl, lower alkyl, lower alkoxy, lower
100 alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl,
101 lower alkoxy-carbonyl and (lower alkyl)-CO.

1 2. A chemical compound according to claim 1, wherein L is a radical
2 of formula (b-1), wherein Y is NH, X is O and W is hydrogen; or L is a
3 radical of formula (b-1) wherein X is S, NH or NCH, Y is NH and W is
4 1-piperidinyl, 1-pyrrolidinyl, 4-morpholinyl, or a radical of formula
5 (c-1-c), wherein R^1 is NR^8 and W^1 is amino, nitro or lower
6 alkyl, optionally substituted with one hydroxy, lower alkoxy,
7 1-piperidinyl, 1-pyrrolidinyl, 4-morpholinyl or phenyl radical, or
8 with two lower alkoxy radicals; or L is a radical of formula (b-1),
9 wherein X is S, NH or NCH, Y is NH and W is lower alkoxy or lower
10 alkylthio; or wherein L is a radical of formula (b-1) wherein W is a
11 radical of formula (c-1-a) or (c-1-b); or
12 L is a radical of formula (b-2) wherein n is 1, X is O or S and W is a
13 radical of formula (c-1-c), wherein R^1 is NR^8 and W^1 is lower
14 alkyl; or
15 L is a radical of formula (b-3), wherein X is O, Y is NH, X^A is O,
16 Y^A is NR^{15} and W^2 is lower alkyl; or
17 L is a radical of formula (b-4), wherein T is a radical of formula
18 (c-3-a), wherein X is O or S, Z is NR^8 and R^6 is hydrogen or lower
19 alkyl; or wherein T is a radical of formula (c-3-b), wherein R^8 is
20 hydrogen and R^7 is lower alkyl; or
21 L is a radical of formula (b-5) wherein Het is a radical of formula
22 (c-4-a), wherein R^9 , R^{11} and R^{12} are hydrogen; or wherein Het is
23 a radical of formula (c-4-c); or wherein Het is furan substituted with

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24 lower alkyl being substituted with hydroxy or with a radical of
 25 formula (c-4-d-1), wherein Y is O or S, Z is NH or a direct bond and
 26 R^{14} is hydrogen; or
 27 L is a radical of formula (b-6) wherein Y^1 is O; or
 28 L is a radical of formula (b-7) wherein Ar^1 is phenyl substituted
 29 with hydroxy or lower alkyloxy.

1 3. A chemical compound according to any of claims 1 and 2 for use as
 2 a medicine.

1 4. A chemical compound according to any of claims 1 and 2 for use as
 2 an anti-allergic medicine.

1 5. A pharmaceutical composition comprising an inert carrier and a
 2 pharmaceutically acceptable amount of a compound according to any of
 3 claims 1 and 2.

1 6. A pharmaceutical composition according to claim 5 for use as an
 2 anti-allergic medicine.

1 7. A process for preparing a pharmaceutical composition,
 2 characterized in that a therapeutically effective amount of a compound
 3 as claimed in any of claims 1 and 2 is intimately mixed with a suitable
 4 pharmaceutical carrier.

1 8. A process for preparing a compound according to any of claims 1
 2 and 2 characterized by

3 a) alkylating a piperidine of formula Q^2 -D (III) with an intermediate
 4 of formula Q^1 (II) in a reaction-inert solvent wherein

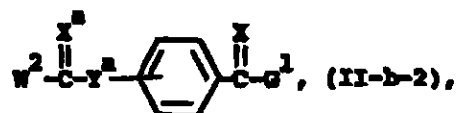
5 1) Q^2 is hydrogen and Q^1 is an intermediate of formula I-G

6 (II-a), said G representing an appropriate reactive leaving
 7 group; or

8 2) Q^1 is an intermediate of formula $W-C(=X)-G^1$, (II-b-1), said
 9 G^1 representing an appropriate reactive leaving group, and
 10 Q^2 is a radical of formula HY^1 -Alk-, thus preparing a
 11 compound of formula



12 3) Q^1 is an intermediate of formula



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13 and Q^2 is a radical of formula RY^1-Alk- , thus preparing a
14 compound of formula

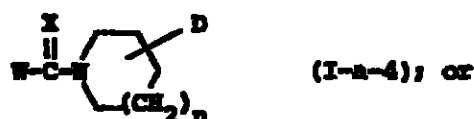


15 4) Q^1 is an intermediate of formula (lower alkenyl)-G, (II-b-3),
16 and Q^2 is a radical RY^1-Alk- , thus preparing a compound of
17 formula (lower alkenyl)- $Y^1-Alk-D$ (I-a-3); or

18 5) Q^1 is an intermediate of formula $W-\overset{\overset{X}{\parallel}}{C}-G^1$ (II-b-4) and Q^2 is
19 a radical of formula

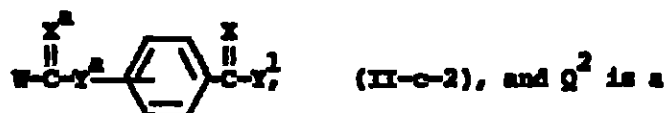


21 formula



22 6) Q^1 is an intermediate of formula $W-C(=X)-Y^1-H$ (II-c-1) and
23 Q^2 is a radical of formula $G-Alk$, thus preparing a compound of
24 formula (I-a-1);

25 7) Q^1 is an intermediate of formula



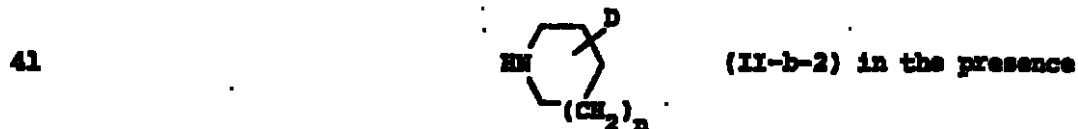
26 radical of formula $G-Alk$, thus preparing a compound of formula
27 (I-a-2);

28 8) Q^1 is an intermediate of formula (lower alkenyl)- Y^1-H ,
29 (II-c-3), and Q^2 is a radical of formula $G-Alk-$, thus
30 preparing a compound of formula (I-a-3);

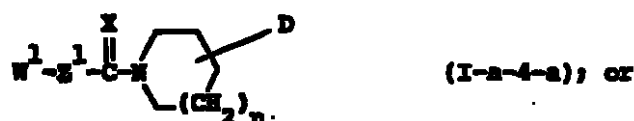
31 9) Q^1 is an intermediate of formula Het^1-H , (II-c-4), wherein
32 said Het^1 is a radical of formula (c-4-a), (c-4-b) or (c-4-c),
33 and Q^2 is a radical of formula $G-Alk$, thus preparing a
34 compound of formula $Het^1-Alk-D$ (I-a-5); or

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- 35 b) reacting a reagent of formula W^1-Z^1-H (II-d) with an
 36 intermediate of formula $HY^1-Alk-D$ (III-b-1) in the presence of an
 37 appropriate C-X generating agent, in a reaction-inert solvent,
 38 thus preparing a compound of formula $W^1-Z^1-C(=X)-Y^1-Alk-D$,
 39 (I-a-1-a); or
 40 c) reacting a reagent of formula (II-d) with an intermediate of formula



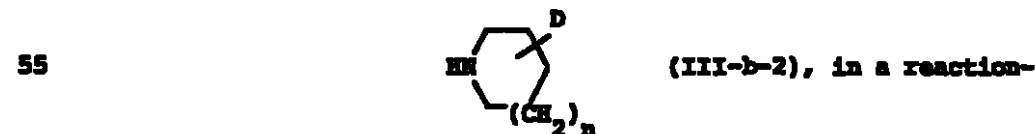
- 42 of an appropriate C-X generating agent, in a reaction-inert
 43 solvent, thus preparing a compound of formula



- 44 d) cyclodesulfurizing an intermediate of formula



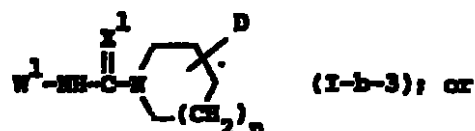
- 45 with an appropriate alkyl halide, metal oxide or metal salt in a
 46 reaction-inert solvent; or
 47 e) reacting an intermediate of formula W^1-Z^1-H (V) with a
 48 piperidine of formula $X^1-C-N-Alk-D$ (VI), wherein X^1 is O or S,
 49 in a reaction-inert solvent, thus preparing a compound of formula
 $W^1-Z^1-C(=X^1)-NH-Alk-D$ (I-b-1); or
 50 f) reacting an intermediate of formula $W^1-H-C-X^1$ (VII), with a
 51 piperidine of formula $HY^1-Alk-D$ (III-b-1) in a reaction-inert
 52 solvent, thus preparing a compound of formula
 $W^1-NH-C(=X^1)-Y^1-Alk-D$ (I-b-2); or
 53 g) reacting an intermediate of formula (VII) with a piperidine of
 54 formula



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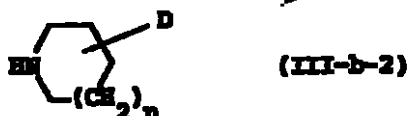
56 inert solvent, thus preparing a compound of formula



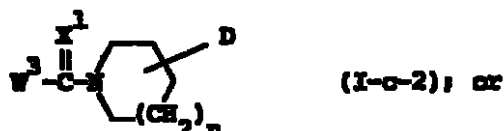
57 h) reacting an intermediate of formula $W^3-C(=X^1)-OH$ (VIII), said
 58 W^3 having the previously described meaning of W , provided that
 59 W^3 is other than a radical of formula (c-1-c), with a piperidine
 60 of formula $HY^1-Alk-D$ (III-b-1) in a reaction-inert solvent, if
 61 desired, after converting the OH-function in (VIII) in a suitable
 62 leaving group, or, if desired, by reacting (III-b-1) with (VIII)
 63 together with an appropriate reagent capable of forming amides or
 64 esters, thus preparing a compound of formula

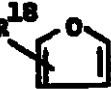


65 i) reacting an intermediate of formula $W^3-C(=X^1)-OH$ (VIII), said
 66 W^3 having the previously defined meaning, with a piperidine of
 67 formula



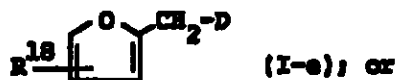
68 in a reaction-inert solvent, if desired, after converting the
 69 OH-function in (VIII) in a suitable leaving group, or, if desired,
 70 by reacting (III-b-2) with (VIII) together with an appropriate
 71 reagent capable of forming amides or esters, thus preparing a
 72 compound of formula



73 j) reacting a piperidine of formula HD (III-a) with a reagent of
 74 formula L^1 -lower alkenediyl-H (IX), wherein L^1 is selected so
 75 that it forms, combined with -Alk-, a radical of formula (b-1),
 76 (b-3), (b-4), (b-5), (b-6) or (b-7), in a suitable reaction-inert
 77 solvent, thus preparing a compound of formula $L^1-Alk-D$ (I-d); or
 78 k) reacting a furan of formula R^{18}  with a piperidine of formula

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79 (III-a) in the presence of formaldehyde or a polymeric form
80 thereof, in a reaction-inert solvent, thus preparing a compound of



81 1) alkylating a furan derivative of formula $\text{R-Y}^1\text{-D}^1$, (X-a),
82 wherein D^1 represents a radical of formula
83 $\text{---(lower alkyl)---O---Alk-D}$, with an intermediate of formula



84 $\text{R-Z-C}_6\text{H}_4\text{-G}$, (XI-a), wherein Z represents a radical of formula



85 in reaction-inert solvent, thus preparing a compound of formula

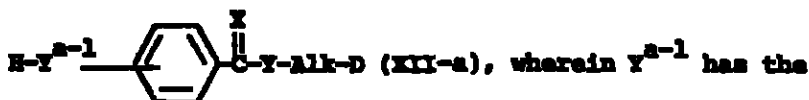


86 m) alkylating an intermediate of formula $\text{R-Z-C}_6\text{H}_4\text{-Y}^1\text{H}$, (XI-b),
87 with a furan derivative of formula G-D^1 , (X-b), in a
88 reaction-inert solvent, thus preparing a compound of formula
89 (I-e-1);

90 n) alkylating a furan derivative of formula $\text{R-Z}^1\text{-C}_6\text{H}_4\text{-Y-D}^1$
91 (X-c), with an intermediate of formula R-G , (XI-c), in a
92 reaction-inert solvent, thus preparing a compound of formula

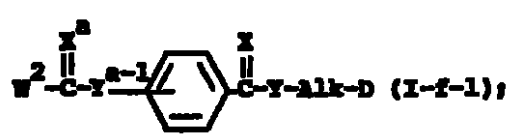


93 o) alkylating an intermediate of formula $\text{R-Z}^1\text{H}$, (XI-d), with a furan
94 derivative of formula $\text{G-C}_6\text{H}_4\text{-Y-D}^1$, (X-d), in a reaction-
95 inert solvent, thus preparing a compound of formula (I-e-2);
96 p) reacting an intermediate of formula



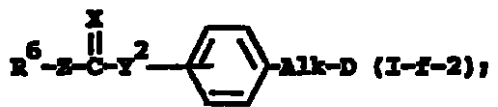
98 previously described meaning of Y^a , provided that it is not a
99 direct bond, with a reagent of formula $\text{W}^2\text{-C(=X)-G}^1$,
100 (XIII-a), in a reaction-inert solvent, thus preparing a compound of
101 formula

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102 q) reacting an intermediate of formula $\text{HY}^2-\text{C}_6\text{H}_4-\text{Alk-D}$ (XII-b) with

103 a reagent of formula $\text{R}^6-\text{Z}-\text{C}(=\text{X})-\text{G}^1$, in a reaction-inert solvent,
104 thus preparing a compound of formula

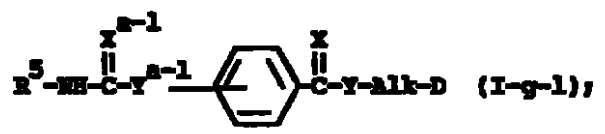


105 r) reacting an intermediate of formula $\text{HNR}^8-\text{C}_6\text{H}_4-\text{Alk-D}$ (XII-c)

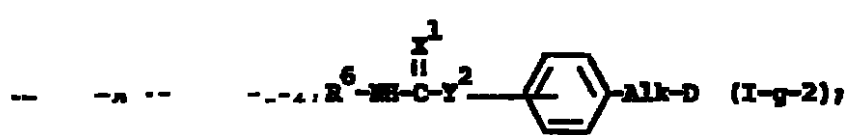
106 with a reagent of formula $\text{R}^7-\text{SO}_2-\text{G}^1$, in a reaction-inert
107 solvent, thus preparing a compound of formula



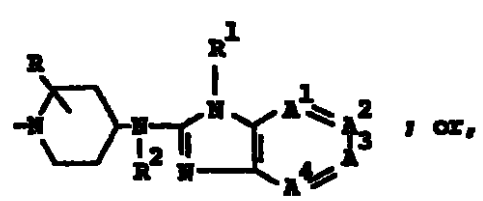
108 s) reacting a reagent of formula $\text{R}^5-\text{N}-\text{C}-\text{X}^{A-1}$ (XIV-a), wherein
109 X^{A-1} is O or S, with an intermediate of formula (XII-a) in a
110 reaction-inert solvent, thus preparing a compound of formula



111 t) reacting an intermediate of formula (XII-b) with a reagent of
112 formula $\text{R}^6-\text{N}-\text{C}-\text{X}^1$ (XIV-b), thus preparing a compound of formula



213 wherein D represents a radical of formula



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114 optionally converting the compounds of formula (I) into each other
115 following art-known functional group transformation procedures; and, if
116 desired, converting the compounds of formula (I) into a therapeuti-
117 cally active non-toxic acid-addition salt form by treatment with an
118 appropriate acid or, conversely, converting the acid-addition salt
119 into the free base form with alkali; and/or preparing stereochemically
120 isomeric forms thereof.

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(71) Applicant: JANSSEN PHARMACEUTICA N.V.
Turnhoutsebaan 30
B-2340 Beerse(BE)

(72) Inventor: Janssens, Frans Edmond
Tilstraat 79
B-2330 Boecheloo(BE)

(72) Inventor: Kennik, Ludo Edmond Josephine
Guido Gevaertstraat 58
B-2380 Turnhout(BE)

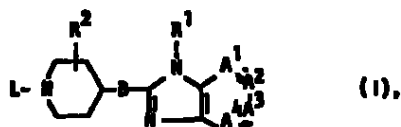
(72) Inventor: Haes, Josef Francis
Guido Gevaertstraat 50
B-2380 Nijlen(BE)

(72) Inventor: Torremans, Joseph Leo G.
Lijsterstraat 11
B-2340 Beerse(BE)

(72) Inventor: Dine, Gaston Stanislas M.
Oostende 12
B-2380 Ruvels(BE)

(54) 4-(bicyclic heterocyclyl)methyl and -hetero-piperidines.

(57) Novel 4-(bicyclic heterocyclyl)methyl and -hetero-piperidines of formula

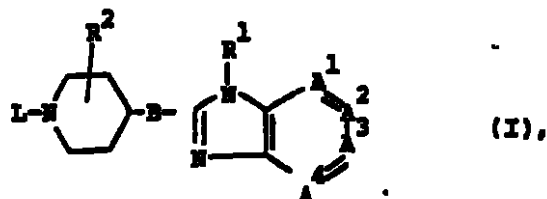


wherein B is CH₂, O, S, SO or SO₂, the pharmaceutically acceptable acid addition salts and the possible stereochemically isomeric forms thereof, which compounds are anti-allergic agents, pharmaceutical compositions containing such compounds as an active ingredient and processes for preparing the said compounds and compositions

EP U 101 826 A1

CLAIMS

1 1. A chemical compound having the formula



2 a pharmaceutically acceptable acid addition salt or a possible
3 stereochemically isomeric form thereof, wherein:

4 $A^1-A^2-A^3-A^4$ is a bivalent radical having the formula

5 $-CH=CH-CH=CH-$ (a-1),

6 $-N=CH-CH=CH-$ (a-2),

7 $-CH=N-CH=CH-$ (a-3),

8 $-CH=CH-N=CH-$ (a-4), or

9 $-CH=CH-CH=N-$ (a-5),

10 wherein one or two hydrogen atoms in said radicals (a-1) - (a-5) may,
11 each independently from each other, be replaced by halo, lower alkyl,
12 lower alkyloxy, trifluoromethyl or hydroxy;

13 R^1 is a member selected from the group consisting of hydrogen,
14 alkyl, cycloalkyl, Ar^1 and lower alkyl substituted with one or two
15 Ar^1 radicals;

16 R^2 is a member selected from the group consisting of hydrogen and
17 lower alkyl;

18 B is CH_2 , O, S, SO or SO_2 ;

19 L is a member selected from the group consisting of a radical of
20 formula

21 $L^1-C_{F_{2x}}H_{2x}-T-C_{S_{2y}}H_{2y}-$ (b-1); and

22 a radical of formula



24 wherein one or two hydrogen atoms in the bivalent radical

25 $-C_{S_{2y}}H_{2y}-$ may, each independently from each other, be replaced by

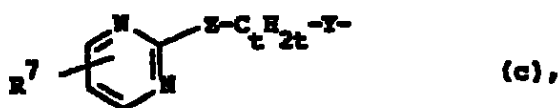
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26 halo, hydroxy, mercapto, isothiocyanato, isocyanato, lower alkyloxy,
27 lower alkylthio, Ar^1 , $\text{Ar}^1\text{O}-$, $\text{Ar}^1\text{S}-$, Ar^1SO_2- , or NR^3R^5 ; and
28 n is 0 or the integer 1 or 2;
29 r and s are, independently from each other, 0 or an integer of from
30 1 to 6 inclusive;

31 T is $-\text{Y}-$ or $-\text{Z}-\overset{\text{X}}{\underset{\text{||}}{\text{C}}}-\text{Y}-$;

32 T^1 is $-\text{Z}-\overset{\text{X}}{\underset{\text{||}}{\text{C}}}-$ or a direct bond;

33 said Y being O, S, NR^3 or a direct bond;
34 X being O, S, CH-NO_2 or NR^4 ;
35 Z being O, S, NR^5 or a direct bond; and
36 said R^3 being hydrogen, lower alkyl, (Ar^2) lower alkyl, 2-lower
37 alkyloxy-1,2-dioxoethyl or a radical of formula $-\text{C}(=\text{X})-\text{R}^6$, R^6
38 being hydrogen, lower alkyl, Ar^2 , Ar^2 -lower alkyl, lower alkyloxy,
39 Ar^2 -lower alkyloxy, mono- or di(lower alkyl)amino, Ar^2 -amino,
40 Ar^2 -lower alkylamino or Ar^2 -lower alkyl(lower alkyl)amino;
41 said R^4 being hydrogen, lower alkyl, cyano, nitro, Ar^2 -sulfonyl,
42 lower alkylsulfonyl, lower alkylcarbonyl or Ar^2 -carbonyl; and
43 said R^5 being hydrogen or lower alkyl;
44 wherein L^1 is a member selected from the group consisting of hydro-
45 gen; halo; hydroxy; lower alkyloxy; lower alkylthio; cyano; mercapto;
46 isocyanato; isothiocyanato; Ar^1 ; Ar^1 -carbonyl; Ar^1 -sulfonyl;
47 lower alkylsulfonyl; cycloalkyl being optionally substituted with up to
48 two substituents each independently selected from the group consisting
49 of lower alkyl, cyano and Ar^2 ; [10,11-dihydro-5H-dibenzo[a,d]cyclo-
50 hepten-5-ylidene]methyl; Het; and furan substituted with substituted
51 lower alkyl; said substituted lower alkyl being lower alkyl substituted
52 with a member selected from the group consisting of hydroxy, mercapto,
53 lower alkyloxy, lower alkylthio, aminolower alkylthio, Ar^2 -oxy and a
54 radical of formula



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55 wherein: t is 0 or an integer of from 1 to 6 inclusive; and
56 R^7 is hydrogen or lower alkyl;
57 provided that: when in said radical of formula (c) t is
58 0, then Z or Y is a direct bond; and

59 where r is 0, L^1 may also be lower alkenyl, Ar^1 -lower alkenyl or
60 lower alkyl substituted with two lower alkoxy radicals; and

61 where r is 0 and T is NR^3 , or T is $-N(R^5)-C(=X)-Y$ or T^1 is $-N(R^5)-C(=X)-$,
62 L^1 may also be amino, lower alkylamino or Ar^1 -amino; and

63 where r is 0, and T is $-N(R^5)-C(=X)-Y$ or T^1 is $-N(R^5)-C(=X)-$,
64 L^1 may also be nitro;

65 said Het being an optionally substituted five- or six-membered hetero-
66 cyclic ring, being optionally condensed with an optionally substituted
67 five- or six-membered carbocyclic or heterocyclic ring;

68 provided that:

- 69 i) when L is a radical of formula (b-1) wherein L^1 is hydrogen and
70 wherein T is $-Z-C(=X)-Y-$ wherein Y is other than a direct bond
71 and Z and X are each independently O or S, then r is not 0; or
72 when L is a radical of formula (b-2) wherein L^1 is hydrogen and
73 wherein T^1 is $-Z-C(=X)-$ wherein Z and X are each independently
74 O or S, then r is not 0;
75 ii) when L is a radical of formula (b-1) wherein L^1 is halo,
76 hydroxy, lower alkoxy, mercapto, lower alkylthio, isocyanato,
77 isothiocyanato or Het connected to $C_{x-2r}H_{2r}$ on a nitrogen atom,
78 and wherein r is 0, then T is a direct bond or a radical
79 $-C(=X)-Y-$; or when L is a radical of formula (b-2) wherein L^1
80 is halo, hydroxy, lower alkoxy, mercapto, lower alkylthio,
81 isocyanato, isothiocyanato or Het connected to $C_{x-2r}H_{2r}$ on a
82 nitrogen atom, and wherein r is 0, then T^1 is a radical $-C(=X)-$;
83 iii) when L is a radical of formula (b-1) wherein T is Y , said Y being
84 other than a direct bond, or wherein T is $-Z-C(=X)-Y-$, wherein Y

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85 is other than a direct bond, then x is not 0;

86 wherein Ar^1 is a member selected from the group consisting of
87 phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, lower
88 alkylthienyl, pyridinyl, mono- and di(lower alkyl)pyridinyl,
89 pyrrolyl, lower alkylpyrrolyl, furanyl, furanyl substituted with lower
90 alkyl, pyrazinyl, thiazolyl, imidazolyl, lower alkylimidazolyl;
91 said substituted phenyl, being phenyl substituted with up to 3
92 substituents each independently selected from the group consisting of
93 halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower
94 alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower
95 alkyl)amino, lower alkylsulfonyl, lower alkylsulfonyl lower alkyl,
96 phenyl lower alkylsulfonyl, phenylsulfonyl lower alkyl, a radical of
97 formula $R^8-C \begin{smallmatrix} H \\ P \end{smallmatrix} \begin{smallmatrix} H \\ 2p \end{smallmatrix} -Y-$, a radical of formula $R^9-Z-C(=X)-Y-$, and a
98 radical of formula $R^{10}SO_2Y-$; wherein p is an integer of from 1 to
99 6 inclusive and R^8 is a member selected from the group consisting of
100 amino, cyano, phenyl aminocarbonyl, mono- and di(lower alkyl)amino-
101 carbonyl, lower alkylloxycarbonyl, phenyl lower alkylloxycarbonyl,
102 4-morpholinylcarbonyl, 1-piperidinylcarbonyl, 1-pyrrolidinylcarbonyl,
103 and lower alkenyl; wherein R^9 is member selected from the group
104 consisting of hydrogen, lower alkyl and Ar^2 ; provided that, when
105 R^9 is hydrogen and Y is other than a direct bond, then Z is not 0 or
106 S; and wherein R^{10} is lower alkyl or Ar^2 ;

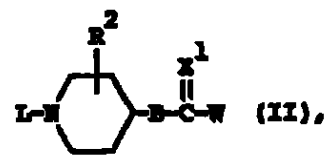
107 wherein Ar^2 is a member selected from the group consisting of
108 phenyl, substituted phenyl, thienyl and furanyl, said substituted
109 phenyl being phenyl optionally substituted with up to three
110 substituents each independently selected from the group consisting of
111 halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower
112 alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower
113 alkyl)amino, carbonyl, lower alkylloxycarbonyl and (lower alkyl)-CO.

1 2. A compound according to claim 1, wherein x is 0 and L^1 is
2 hydrogen, hydroxy, lower alkyl, lower alkylthio, mercapto, Het,
3 Ar^1 , cyanato, isothiocyanato, or isocyanato.

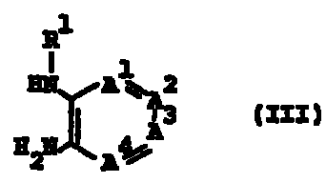
1 3. A compound according to claim 2, wherein R^1 is lower alkyl
2 substituted with one Ar^1 radical.

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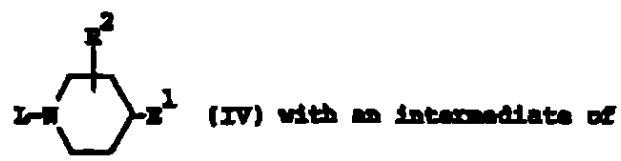
- 1 4. A compound according to claim 3, wherein L is a radical of
2 formula (b-1).
- 1 5. A chemical compound according to any of claims 1 to 4 for use
2 as a medicine.
- 1 6. A chemical compound according to any of claims 1 to 4 for use
2 as an anti-allergic medicine.
- 1 7. A pharmaceutical composition comprising an inert carrier and a
2 pharmaceutically acceptable amount of a compound according to any of
3 claims 1 to 4.
- 1 8. A pharmaceutical composition according to claim 7 for use as an
2 anti-allergic medicine.
- 1 9. A process for preparing a pharmaceutical composition,
2 characterized in that a therapeutically effective amount of a
3 compound as claimed in any of claims 1 to 4 is intimately mixed
4 with a suitable pharmaceutical carrier.
- 1 10. A process for preparing a compound according to any of claims
2 1 to 4 characterized by
3 I reacting a piperidine of formula



4 wherein X^1 is O, S or NH and W is a reactive leaving group, with
5 a diamine of formula

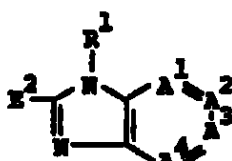


- 6 in a reaction-inert solvent;
- 7 II reacting a piperidine of formula



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9



(V), in a reaction-inert

10

solvent, wherein :

11

a) E¹ is a radical of formula -B-M wherein M is hydrogen or an alkali metal or earth alkaline metal and E² is a radical of formula -W; or

12

13

14

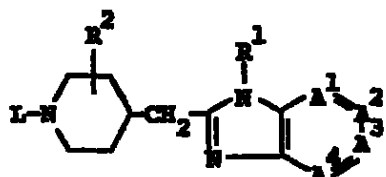
b) E¹ is a radical of formula -W and E² is a radical of formula M-B; or

15

16

c) E¹ is a radical of formula -CH₂-W and E² is a radical of formula -M, thus preparing a compound of formula

17



(I-a); or

18

19

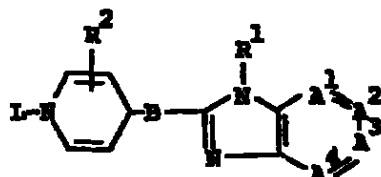
d) E¹ is a radical of formula -M and E² is a radical of

20

formula -CH₂W, thus preparing a compound of formula (I-a);

21

III. reducing an intermediate of formula



, (VI)

22

in a reaction-inert solvent; and, if desired, converting the

23

compounds of formula (I) into each other by

24

a) alkylating a compound of formula Q²-D (I-c) with a reagent of formula L¹-Q¹ (VII) in a suitable solvent, thus preparing a compound of formula L²-D (I-b), wherein L² has the

25

26

27

previously defined meaning of L, provided that it is other than hydrogen, and wherein

28

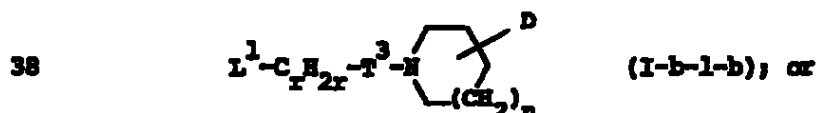
29

1) Q¹ is -W and Q² is hydrogen; or

- 30 ii) Q^1 is $-C_{xH_{2x}}-W^1$ and Q^2 is a radical of formula
 31 $HT^2-C_{sH_{2s}}-$, wherein W^1 is a reactive leaving group
 32 and T^2 is O, S, NR^3 or $-Z^1-C(=X)-Y-$, said Z^1 being
 33 O, S or NR^5 , thus preparing a compound of formula
 34 $L^1-C_{xH_{2x}}-T^2-C_{sH_{2s}}-D$ (I-b-1-a); or
 35 iii) Q^1 is $-C_{xH_{2x}}-W^1$ and Q^2 is a radical of formula



37 or $Z^1-(C=X)-$, thus preparing a compound of formula



- 39 iv) Q^1 is a radical of formula $-C_{xH_{2x}}-T^4H$ and Q^2 is
 40 $H-C_{sH_{2s}}-$, wherein T^4 is O, S, NR^3 or $-S-C(=X)-Y^1-$,
 41 said Y^1 being O, S or NR^3 , thus preparing a compound of
 42 formula $L^1-C_{xH_{2x}}-T^4-C_{sH_{2s}}-D$ (I-b-2);

43 b) reductively N-alkylating a compound of formula H-D, (I-c-1),
 44 with a carbonyl-compound of formula $L^{2-a}-C=O$ (VIII), said
 45 $L^{2-a}-C=O$ being a compound of formula L^2-H wherein a $-CH_2-$
 46 radical is oxidized to a carbonyl radical, in a reaction-inert
 47 solvent, thus preparing a compound of formula L^2-D (I-b);

48 c) reductively N-alkylating a compound of formula



50 with a carbonyl-compound of formula $L^1-(C_{xH_{2x-1}})=O$ (IX),

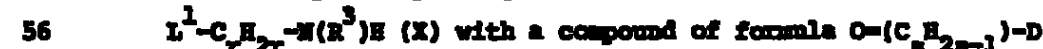
51 said $L^1-(C_{xH_{2x-1}})=O$ being a compound of formula



53 carbonyl radical, in a reaction inert solvent, thus preparing a

54 compound of formula $L^1-C_{xH_{2x}}-N(R^3)-C_{sH_{2s}}-D$ (I-b-3);

55 d) reductively N-alkylating an intermediate of formula



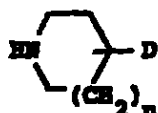
57 (I-e), said $O-(C_{sH_{2s-1}})-$ being a radical of formula $H-C_{sH_{2s}}-$

58 wherein a $-CH_2-$ radical is oxidized to a carbonyl radical, in a

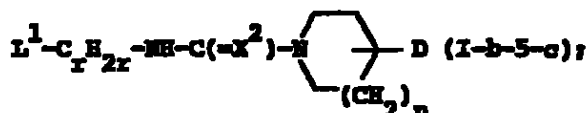
59 reaction-inert solvent, thus preparing a compound of formula (I-b-3);

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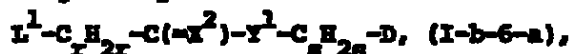
- 60 e) reacting a reagent of formula $L^1-C_xH_{2x}-Z^1H$ (XI) with a
 61 compound of formula $X^2-C-N-C_yH_{2y}-D$ (I-f), wherein X^2 is
 62 O or S, in a reaction-inert solvent, thus preparing a compound
 63 of formula $L^1-C_xH_{2x}-Z^1-C(=X^2)-NH-C_yH_{2y}-D$ (I-b-4);
 64 f) reacting a reagent of formula $L^1-C_xH_{2x}-N-C-X^2$ (XII) with
 65 a compound of formula $NY^1-C_yH_{2y}-D$ (I-c-4), respectively
 66 with a compound of formula $H-D$ (I-o-1) or with a compound of
 67 formula



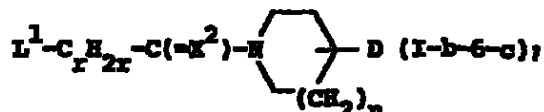
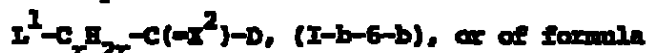
- 68 in a reaction-inert solvent, thus
 69 preparing a compound of formula
 70 $L^1-C_xH_{2x}-NH-C(=X^2)-Y^1-C_yH_{2y}-D$, (I-b-5-a),
 71 respectively of formula
 72 $L^1-C_xH_{2x}-NH-C(=X^2)-D$, (I-b-5-b), or of formula
 73



- 74
 75 g) reacting a reagent of formula $L^1-C_xH_{2x}-C(=X^2)-OH$ (XIII)
 76 with (I-c-4), respectively with (I-o-1) or (I-o-5), in a
 77 reaction-inert solvent, if desired, after converting the OH
 78 group in (XIII) in a reactive leaving group or by reacting
 79 (XIII) with (I-c-4), respectively (I-o-1) or (I-o-5), in the
 80 presence of a reagent capable of forming esters or amides, thus
 81 preparing a compound of formula

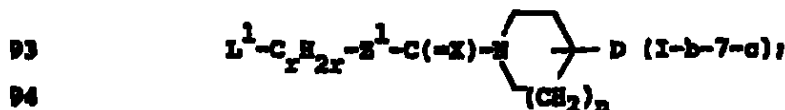


- 82
 83 respectively of formula

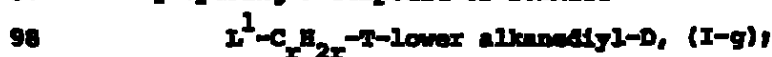


- 84
 85
 86 h) reacting (XI) with (I-o-4), respectively (I-c-1) or (I-o-5) in
 87 the presence of a C-X generating agent in a reaction-inert
 88 solvent, thus preparing a compound of formula
 89 $L^1-C_xH_{2x}-Z^1-C(=X)-Y^1-C_yH_{2y}-D$, (I-b-7-a),
 90 respectively of formula
 91 $L^1-C_xH_{2x}-Z^1-C(=X)-D$, (I-b-7-b), or of formula
 92

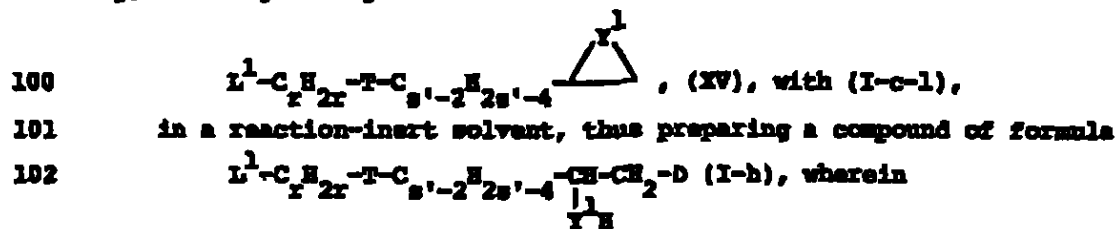
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95 i) reacting an alkane of formula $L^1-C_{x_1}H_{2x_1}-T$ -lower alkanediyl-H
96 of formula (XIV) with (I-c-1) in a reaction-inert solvent, thus
97 preparing a compound of formula

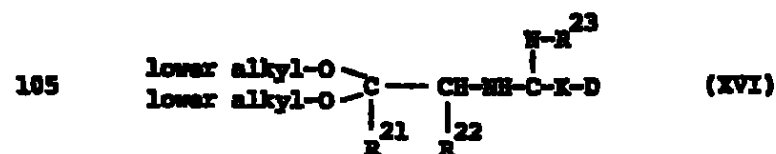


99 j) reacting a reagent of formula

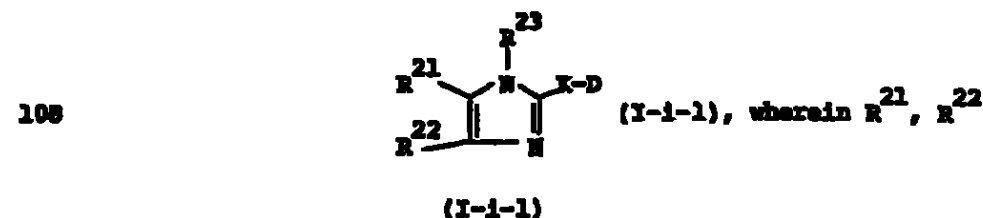


103 wherein s' is an integer of from 2 to 6 inclusive;

104 k) cyclizing an imidamide of formula

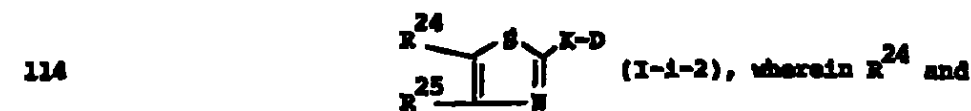


106 in a reaction-inert solvent in the presence of an acid, thus
107 preparing a compound of formula

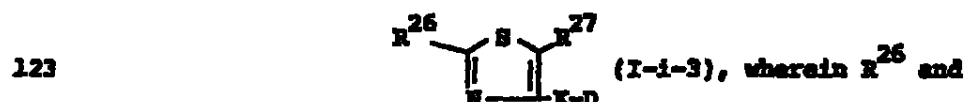


109 and R^{23} are, each independently, optional substituents of the
110 imidazole ring;

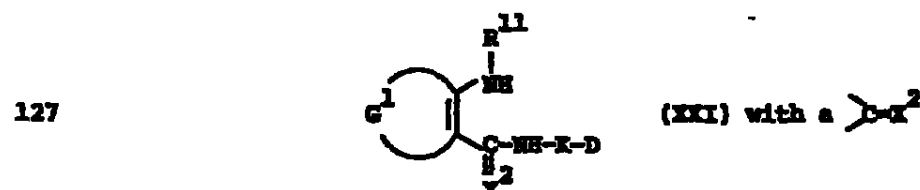
111 l) condensing a ketone of formula $R^{24}-CH(W)-C(=O)-R^{25}$, (XVII),
112 with a thioamide of formula $H_2N-C(=S)-K-D$, (XVIII), in a
113 reaction-inert solvent, thus preparing a compound of formula



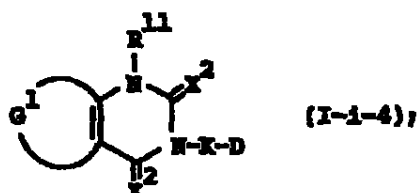
- 115 R^{25} are, each independently, optional substituents of the
 116 thiazole ring, or where in the compound of formula (I-i-2) said
 117 thiazolyl ring is condensed with a five- or six-membered hetero-
 118 or carbocyclic ring, R^{24} and R^{25} taken together may form a
 119 radical of formula G^3 ,
 120 m) condensing a thioamide of formula $R^{26}-C(=S)NH_2$, (XIX), with
 121 a ketone of formula $W-CR^{27}-(C=O)-K-D$, (XX), in a reaction-
 122 inert solvent, thus preparing a compound of formula



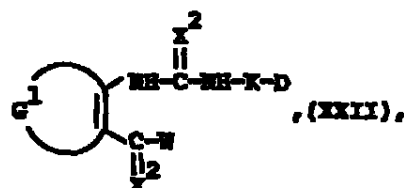
- 124 R^{27} are, each independently, optional substituents of the
 125 thiazolyl ring;
 126 n) reacting an amide or thioamide of formula



- 128 generating agent, in a reaction-inert solvent, thus preparing a
 129 compound of formula



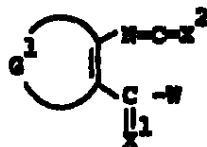
- 130 o) cyclizing a urea or thiourea of formula



- 131 which in situ may be generated by reacting a reagent

425
420

132



(XXIII), with an amine

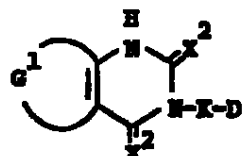
133

H₂N-K-D, (XXIV), in a reaction-inert solvent, thus preparing a

134

compound of formula

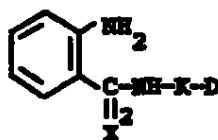
135



(I-1-4-a);

136

p) condensing an aniline of formula



(XXV),

137

with an acid of formula R¹²COOH (XXVI), or a reactive

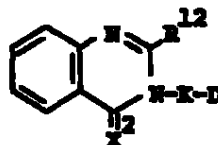
138

derivative thereof, in a reaction-inert solvent, thus preparing

139

a compound of formula

140

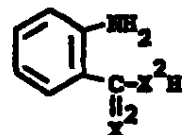


(I-1-5);

141

q) condensing an aniline of formula

142



(XXVII), with an amide

143

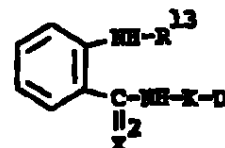
of formula R¹²-C(=O)-NH-K-D (XXVIII) in a reaction-inert

144

solvent, thus preparing a compound of formula (I-1-5);

145

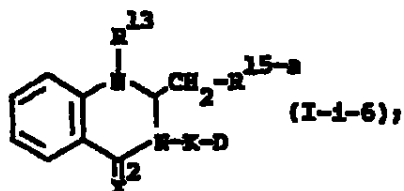
r) condensing an aniline of formula



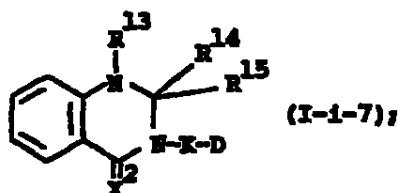
(XXIX),

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421

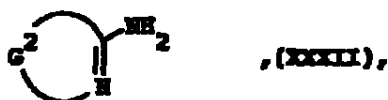
146 with an acetylene of formula $\text{CH}_3\text{C}-\text{R}^{14}$ (XXX), in a reaction-
147 inert solvent, thus preparing a compound of formula



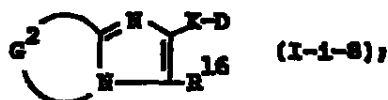
148 s) condensing (XXIX) with a ketone of formula $\text{R}^{14}-\text{C}(=\text{O})-\text{R}^{15}$
149 (XXXI), in a reaction-inert solvent, thus preparing a compound
150 of formula



151 t) condensing a reagent of formula



152 with a ketone of formula $\text{W}-\text{CH}(\text{R}^{16})-\text{C}(=\text{O})-\text{X}-\text{D}$ (XXXIII), in a
153 reaction-inert solvent, thus preparing a compound of formula

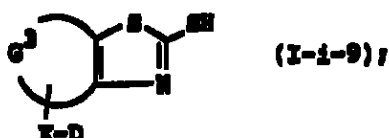


154 u) condensing an amine of formula

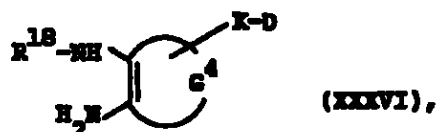


155 with CH_2 , in a reaction-inert solvent, thus preparing a
156 compound of formula

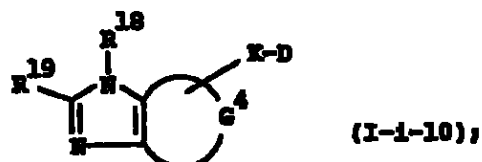
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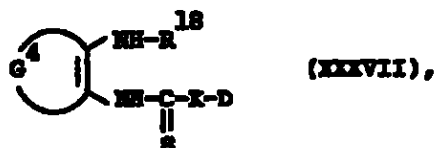
- 157 v) reacting a reagent of formula $R^{19}-C(=NH)-W$ (XXXV) with an
158 amine of formula



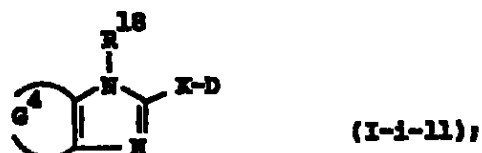
- 159 in a reaction-inert solvent, thus preparing a compound of formula



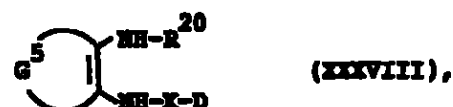
- 160 w) cyclodesulfurizing a thioamide of formula



- 161 with an appropriate alkyl halide, metal oxide or metal salt in a
162 reaction-inert solvent, thus preparing a compound of formula

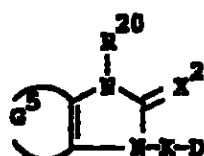


- 163 x) condensing an amine of formula



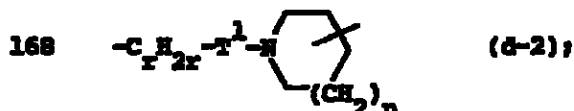
- 164 with a $>C=X^2$ generating agent, in a reaction-inert solvent,
165 thus preparing a compound of formula

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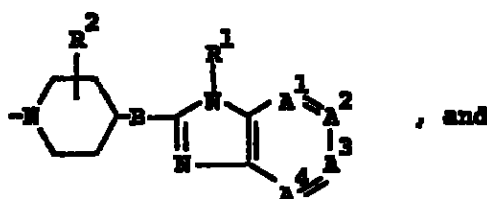


(I-1-12);

166 wherein X is a bivalent radical of formula



169 wherein D represents a radical of formula



, and

170 $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9$ and R^{20} are, each
 171 independently optional substituents of the previously described
 172 bicyclic radicals and G^1, G^2, G^3, G^4 and G^5 are, each independently,
 173 optionally substituted bivalent radicals, selected so that they form,
 174 combined with the five- or six-membered heterocycle to which they are
 175 attached, a bicyclic Het-system; or optionally converting the
 176 compounds of formula (I) into each other following art-known
 177 grouptransformation procedures, and, if desired, converting the
 178 compounds of formula (I) into a therapeutically active non-toxic
 179 acid-addition salt form by treatment with an appropriate acid or,
 180 conversely, converting the acid-addition salt into the free base form
 181 with alkali; and/or preparing stereochemically isomeric forms thereof.



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A 61 K 31/415, A 61 K 31/425,
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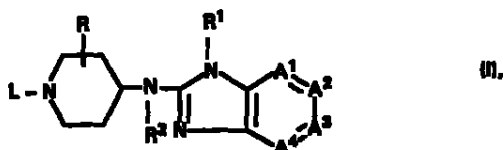
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23 Applicant JANSEN PHARMACEUTICA N.V.,
Turnhoutseweg 30, B-2340 Beerse (BE)

24 Inventor Janssens, Frans H., Tinstreet 70,
B-2830 Bonheiden (BE)
Inventor Hana, Jozef F., Rector de Ruysstraat 54,
B-2280 Nijlen (BE)
Inventor Tommeens, Joseph L.G., Lijsterstraat 11,
B-2340 Beerse (BE)
Inventor Heykants, Jozef J.P., Karel Druytsaan 8,
B-2280 Voerendaal (BE)

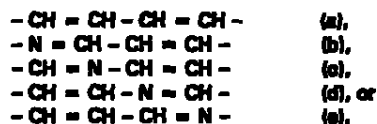
25 Anti-histaminic compositions containing N-heterocyclyl-4-piperidineamines.

Anti-histaminic compositions containing as active in-
gredient a N-heterocyclyl-4-piperidineamine of formula



wherein,
L is hydrogen, C₁₋₆alkyloxy-carbonyl or phenylmethoxy-
carbonyl;

A¹ = A² - A³ = A⁴ is a bivalent radical having the
formula



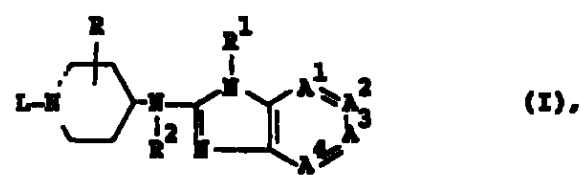
a pharmaceutically acceptable acid addition salt and possible
stereochemically isomeric form thereof; methods of preparing
said compounds and pharmaceutical compositions, novel
compounds of formula (I)

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CLAIMS

- 1 1. A pharmaceutical composition comprising a suitable
- 2 pharmaceutical carrier and as active ingredient a therapeutically
- 3 effective amount of a chemical compound having the formula



- 4 a pharmaceutically acceptable acid addition salt or a possible
- 5 stereochemically isomeric form thereof, wherein:
- 6 L is hydrogen, C₁₋₆ alkyloxycarbonyl or phenylmethoxycarbonyl;
- 7 A¹-A²-A³-A⁴ is a bivalent radical having the formula
- 8 -CH=CH-CH=CH- (a),
- 9 -N=CH-CH=CH- (b),
- 10 -CH=N-CH=CH- (c),
- 11 -CH=CH-N=CH- (d), or
- 12 -CH=CH-CH=N- (e),
- 13 wherein one or two hydrogen atoms in said radicals (a) - (e) may, each
- 14 independently from each other, be replaced by halo, C₁₋₆ alkyl,
- 15 C₁₋₆ alkyloxy, trifluoromethyl or hydroxy;
- 16 R is a member selected from the group consisting of hydrogen and
- 17 C₁₋₆ alkyl;
- 18 R¹ is a member selected from the group consisting of hydrogen,
- 19 C₁₋₁₀ alkyl, C₃₋₆ cycloalkyl, Ar¹ and C₁₋₆ alkyl substituted
- 20 with one or two Ar¹ radicals;
- 21 R² is a member selected from the group consisting of hydrogen,
- 22 C₁₋₆ alkyl, C₃₋₆ cycloalkyl, (C₁₋₆alkyl)-CO-, (C₁₋₆alkyloxy)-CO
- 23 and Ar²-C₁₋₆ alkyl;
- 24 wherein Ar¹ is a member selected from the group consisting of
- 25 phenyl, being optionally substituted with up to three substituents
- 26 each independently selected from the group consisting of halo,
- 27 hydroxy, nitro, cyano, trifluoromethyl, C₁₋₆ alkyl, C₁₋₆ alkyloxy,
- 28 C₁₋₆ alkylthio, mercapto, amino, mono- and di(C₁₋₆ alkyl)amino,
- 29 carboxyl, C₁₋₆ alkyloxycarbonyl and C₁₋₆ alkyl-CO-; thienyl;
- 30 halothienyl; furanyl; C₁₋₆ alkyl substituted furanyl; pyridinyl;

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31 pyrazinyl; thiazolyl and imidazolyl optionally substituted with C₁₋₆
32 alkyl; and wherein Ar² is a member selected from the group
33 consisting of phenyl being optionally substituted with up to three
34 substituents each independently selected from the group consisting of
35 halo, hydroxy, nitro, cyano, trifluoromethyl, C₁₋₆ alkyl, C₁₋₆
36 alkoxy, C₁₋₆ alkylthio, mercapto, amino, mono- and di(C₁₋₆
37 alkyl)amino, carboxyl, C₁₋₆ alkoxy carbonyl and (C₁₋₆ alkyl)-CO.

1 2. An anti-allergic pharmaceutical composition comprising a
2 suitable pharmaceutical carrier and as active ingredient an
3 effective anti-allergic amount of a compound of formula (I) as
4 defined in claim 1.

1 3. A composition according to any of claims 1 or 2 wherein
2 A¹=A²-A³=A⁴ is a bivalent radical of formula (a) or (b) and R¹ is
3 C₁₋₆ alkyl substituted with Ar¹.

1 4. A composition according to claim 3 wherein R is hydrogen,
2 R² is hydrogen or C₁₋₆ alkyl and Ar¹ is phenyl being optionally
3 substituted with up to two substituents independently selected from
4 the group consisting of halo, hydroxy, and C₁₋₆ alkyl; pyridyl;
5 imidazolyl; thienyl; halothienyl; furanyl; C₁₋₆ alkyl substituted
6 furanyl; thiazolyl and pyrazinyl.

1 5. A composition according to claim 4 wherein R¹ is furanylmethyl
2 or (C₁₋₆ alkyl)furanylmethyl.

1 6. A composition according to claim 5 wherein the compound is
2 3-[(5-methyl-2-furanyl)methyl]-N-(4-piperidinyl)-3H-imidazo[4,5-b]-
3 pyridin-2-amine.

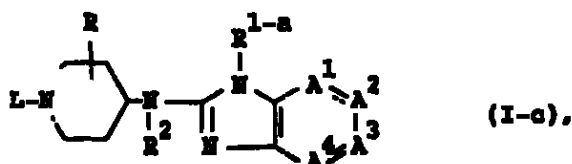
1 7. A method of preparing a pharmaceutical composition as claimed
2 in any of claims 1 to 7, characterized in that a therapeutically
3 effective amount of a compound of formula (I) as defined in any of said
4 claims 1 to 7 is intimately mixed with suitable pharmaceutical carriers.

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1 8. A chemical compound having the formula



2 a pharmaceutically acceptable acid addition salt or a possible
3 stereochemically isomeric form thereof, wherein:

4 L is hydrogen, C₁₋₆alkyloxycarbonyl or phenylmethoxycarbonyl;

5 A¹-A²-A³-A⁴ is a bivalent radical having the formula

6 -CH=CH-CH=CH- (a),

7 -N=CH-CH=CH- (b),

8 -CH=N-CH=CH- (c),

9 -CH=CH-N=CH- (d), or

10 -CH=CH-CH=N- (e),

11 wherein one or two hydrogen atoms in said radicals (a) - (e) may,
12 each independently from each other, be replaced by halo, C₁₋₆
13 alkyl, C₁₋₆ alkyloxy, trifluoromethyl or hydroxy;

14 R is a member selected from the group consisting of hydrogen and
15 C₁₋₆ alkyl;

16 R^{1-a} is C₁₋₆alkyl substituted with C₁₋₆alkyl-substituted
17 furanyl and wherein said C₁₋₆alkyl-substituted furanyl is other
18 than 5-methyl-2-furanyl;

19 R² is a member selected from the group consisting of hydrogen,
20 C₁₋₆ alkyl, C₃₋₆ cycloalkyl, (C₁₋₆ alkyl)-CO-, (C₁₋₆ alkyloxy)-CO
21 and Ar²-C₁₋₆ alkyl;

22 wherein Ar² is a member selected from the group consisting of
23 phenyl being optionally substituted with up to three substituents
24 each independently selected from the group consisting of halo,
25 hydroxy, nitro, cyano, trifluoromethyl, C₁₋₆ alkyl, C₁₋₆
26 alkyloxy, C₁₋₆ alkylthio, mercapto, amino, mono- and di(C₁₋₆
27 alkyl)amino, carboxyl, C₁₋₆ alkyloxycarbonyl and (C₁₋₆ alkyl)-CO.

1 9. A compound according to claim 8 wherein R^{1-a} is C₁₋₆alkyl
2 substituted with 3- or 4-(C₁₋₆alkyl)-2-furanyl or with 2-(C₁₋₆alkyl)-
3 3-furanyl.

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1 10. A compound according to claim 9 wherein R^{1-a} is methyl
2 substituted with 3-(C_{1-6} alkyl)-2-furanyl, R^2 is hydrogen, R is
3 hydrogen and $A^1=A^2-A^3=A^4$ is $CH=CH-CH=CH$ or $N=CH-CH=CH$.

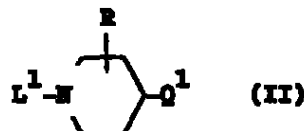
1 11. A chemical compound of formula (I) as defined in any of
2 claims 1 to 7 for use as a medicine.

1 12. A chemical compound of formula (I) as defined in any of
2 claims 1 to 7 for use as an anti-allergic medicine.

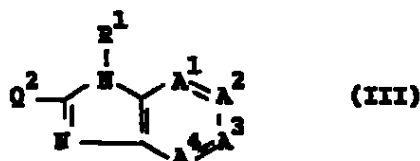
1 13. A compound as claimed in any one of claims 8 to 10 for use as
2 a medicine.

1 14. A compound as claimed in any one of claims 8 to 10 for use as
2 an anti-allergic medicine.

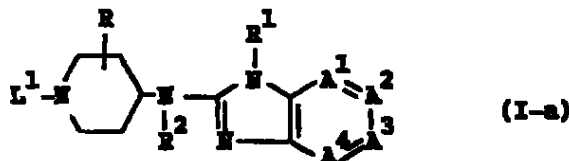
1 15. A process for preparing a chemical compound of formula (I) as
2 defined in claim 1, characterized by
3 reacting a piperidine of formula



4 wherein L^1 is as L provided that it is not hydrogen, with a
5 benzimidazole of formula



6 in a reaction-inert solvent and, if desired, subsequently decar-
7 boxylating the group L^1 in the thus obtained compound of formula



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8 wherein in (II) and (III) either
9 Q^1 is $-NHR^2$ and Q^2 is $-W$, or
10 Q^1 is $-W$ and Q^2 is $-NHR^2$, or
11 Q^1 is $=O$ and Q^2 is $-NHR^2$,
12 said W being a reactive leaving group;
13 and, if further desired, converting the compounds of formula (I)
14 into a salt form by treatment with an appropriate acid; or
15 conversely, converting the salt into the free base with alkali;
16 and/or preparing stereochemically isomeric forms thereof.

1 16. A process according to claim 15 wherein R^1 is R^{1-a} as
2 defined in claim 8.

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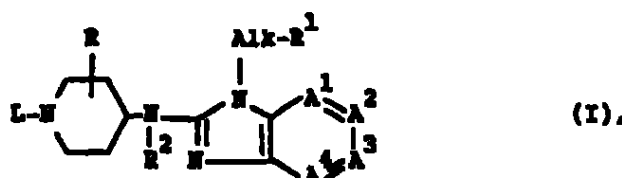
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(27) Applicant: JANSSEN PHARMACEUTICA N.V.
Turnhoutseweg 30
B-2340 Beerse(BE)

(28) Inventor Janssens, Frans Eduard
Tijnsstraat 79
B-2630 Bonheiden(BE)
Inventor Torramans, Joseph Leo Ghislarius
Lijsterstraat 11
B-2340 Beerse(BE)
Inventor Diels, Gaston Stanislas Marcelle
Oostelinde 12
B-2380 Ravels(BE)

(29) Novel N-(4-piperidiny) bicyclic condensed 2-imidazolamine derivatives.

(30) Novel N-(4-piperidiny) bicyclic condensed 2-imidazolamine derivatives of formula



wherein: A¹=A²=A³=A⁴ is -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH or -CH=CH-CH=N-; R is hydrogen or C₁-alkyl, R¹ is furyl substituted with C₁-alkyl, pyrazinyl, thiazolyl, or imidazolyl optionally substituted with C₁-alkyl, L is C₆-alkenyl optionally substituted with Ar³, or L is a radical of formula -Alk-R², -Alk-O-R⁴, -Alk-N(R³)-R⁵, -Alk-Z-C(=O)-R⁷ or -CH₂-CH(OH)-CH₂-O-R⁸, the pharmaceutically acceptable acid addition salts and possible stereochemically isomeric forms thereof, which compounds are anti-histaminic agents, pharmaceutical compositions containing such compounds as an active ingredient and methods of preparing said compounds and pharmaceutical compositions.

EP 0 295 742 A1

dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension (Opspray K-1-21089) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example 21. INJECTABLE SOLUTION

1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50° C there were added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I.

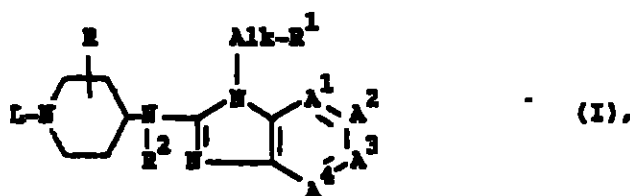
The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg A.I. per ml. The solution was sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

Example 22. SUPPOSITORIES

3 g A.I. was dissolved in a solution of 3 g 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 g Surfactant (SPAN®) and triglycerides (Witepsol 555 ®) q.s. ad 300 g were molten together. The latter mixture was mixed well and the former solution. The thus obtained mixture was poured into moulds at a temperature of 37-38° C to form 100 suppositories each containing 30 mg of the active ingredient.

Claims

1. A chemical compound having the formula



a pharmaceutically acceptable acid-addition salt or a stereochemically isomeric form thereof, wherein

$A^1 = A^2 = A^3 = A^4$ is a bivalent radical having the formula

- CH=CH-CH=CH- (a-1),
- N=CH-CH=CH- (a-2),
- CH=N-CH=CH- (a-3),
- CH=CH-N=CH- (a-4), or
- CH=CH-CH=N- (a-5);

wherein one or two hydrogen atoms in said radicals (a-1)-(a-5) may, independently from each other, be replaced by halo, C_{1-6} alkyl, C_{1-6} alkyloxy, trifluoromethyl or hydroxy;

R is hydrogen or C_{1-6} alkyl;

R¹ is furanyl substituted with C_{1-6} alkyl, pyrazinyl, thiazolyl, or imidazolyl optionally substituted with C_{1-6} alkyl,

R² is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, Ar^3 - C_{1-6} alkyl or $(C_{1-6}$ alkyl)-CO,

L is C_{2-6} alkenyl optionally substituted with Ar^3 , or L is a radical of formula

- Alk-R³ (b-1),
- Alk-O-R⁴ (b-2),
- Alk-N(R⁵)-R⁶ (b-3),
- Alk-Z-C(=O)-R⁷ (b-4), or
- CH₂-CH(OH)-CH₂-O-R⁸ (b-5);

R³ is hydrogen, Ar^1 -thio, Ar^2 -sulfonyl, 4,5-dihydro-5-oxo-1H-tetrazol-1-yl being optionally substituted in its 4-position with Ar^3 or C_{1-6} alkyl, 2,3-dihydro-1,4-benzodioxin-2-yl, 2,3-dihydro-1,4-benzodioxan-6-yl, 4-morpholinyl, 1-piperidinyl or 1-pyrrolidinyl, or when R¹ is furanyl substituted with C_{1-6} alkyl and $A^1 = A^2 =$

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$A^3=A^4$ is a bivalent radical of formula (a-1) or (a-2), R^3 may also be Ar 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl or 1-(C₁₋₆alkyl)pyrrolyl,

R^4 is C₁₋₆alkyl or Ar¹,

R^5 is C₁₋₆alkyl optionally substituted with Ar²;

R^6 is Ar² or C₁₋₆alkyl optionally substituted with Ar² or when $A^1=A^2-A^3=A^4$ is a radical of formula (a-1) or (a-2), R^6 may also be 1H-benzimidazol-2-yl,

R^7 is C₁₋₆alkyl, Ar²-C₁₋₆alkyl, Ar² amino, Ar²-amino, mono- and di(C₁₋₆alkyl)amino, mono- and di(Ar²-C₁₋₆alkyl)amino, 1-piperidiny, 1-pyrrolidiny, 4-morpholinyl, C₃₋₆cycloalkyloxy, C₁₋₆alkyloxy or Ar¹-C₁₋₆alkyloxy,

Z is O, NR⁸ or a direct bond, said R⁸ being hydrogen or C₁₋₆alkyl optionally substituted with Ar¹

R^9 is Ar¹,

each Alk independently being C₁₋₆alkenedyl,

Ar¹ is phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, C₁₋₆alkyl substituted thienyl or furanyl, wherein said substituted phenyl is phenyl substituted with 1, 2 or 3 substituents, each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, mercapto, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfonyl(C₁₋₆alkyl), phenyl-C₁₋₆alkylsulfonyl, phenylsulfonyl(C₁₋₆alkyl), amino, mono- and di(C₁₋₆alkyl)amino, carboxy, C₁₋₆alkyloxycarbonyl and C₁₋₆alkylcarbonyl,

Ar² has the same meanings of Ar¹, and may also be pyridinyl, mono- and di(C₁₋₆alkyloxy)pyridinyl or furanyl substituted with C₁₋₆alkyl, and

Ar³ has the same meanings of Ar², and may also be pyrazinyl, 1-(C₁₋₆alkyl)pyrrolyl, thiazolyl or imidazolyl optionally substituted with C₁₋₆alkyl;

provided that $A^1=A^2-A^3=A^4$ is a radical of formula (a-1) or (a-2) when L is a radical of formula (b-4).

2. A chemical compound according to claim 1 wherein R is hydrogen, R¹ is furanyl substituted with C₁₋₆alkyl and R² is hydrogen or C₁₋₆alkyl

3. A chemical compound according to claim 2 wherein L is C₃₋₆alkenyl optionally substituted with phenyl or substituted phenyl, or wherein L is a radical of formula (b-1), (b-2) or (b-5) wherein R⁴ is C₁₋₆alkyl, phenyl or substituted phenyl, R⁷ is phenyl, substituted phenyl or C₁₋₆alkyl optionally substituted with phenyl or substituted phenyl, R⁸ is hydrogen, C₁₋₆alkyl, and R⁹ is phenyl, substituted phenyl or naphthalenyl

4. A chemical compound according to claim 3 wherein L is a radical of formula (b-1) or (b-2) wherein R⁵ is hydrogen, phenylsulfonyl, 4,5-dihydro-5-oxo-1H-tetrazol-1-yl being optionally substituted in its 4-position with C₁₋₆alkyl, 2,3-dihydro-1,4-benzodioxin-2-yl, 4-morpholinyl, 1-piperidiny, 1-pyrrolidiny, or when R¹ is furanyl substituted with C₁₋₆alkyl and $A^1=A^2-A^3=A^4$ is a bivalent radical of formula (a-1) or (a-2), R³ may also be 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl, thienyl, furanyl, phenyl or substituted phenyl.

5. A chemical compound according to claim 1 wherein the compound is 3-[(5-methyl-2-furanyl)methyl]-N-(1-methyl-4-piperidiny)-3H-imidazo[4,5-b]pyridin-2-amine

6. A pharmaceutical composition comprising a suitable pharmaceutical carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5.

7. An anti-histaminic pharmaceutical composition comprising a suitable pharmaceutical carrier and as active ingredient an effective anti-histaminic amount of a compound as claimed in any one of claims 1 to 5.

8. A method of preparing a pharmaceutical composition, characterized in that a therapeutically effective amount of a compound as defined in any of claims 1 to 5 is intimately mixed with suitable pharmaceutical carriers

9. A compound as claimed in any one of claims 1 to 5 for use as a medicine.

10. A compound as claimed in any one of claims 1 to 5 for use as an anti-histaminic medicine.

11. A process for preparing a chemical compound as claimed in any one of claims 1 to 5, characterized by

a) N-alkylating a piperidine of formula H-D (II) with a reagent of formula L-W¹ (III), wherein W¹ represents a reactive leaving group, in a reaction-inert solvent;

b) reductively N-alkylating a piperidine of formula H-D (II) with a ketone or aldehyde of formula L¹=O (IV), said L¹=O being an intermediate of formula L¹H₂ wherein two geminal hydrogen atoms are replaced by =O, in a reaction-inert solvent thus preparing a compound of formula L¹H-D (I-a), wherein L¹ is a geminal bivalent radical comprising R³-C₁₋₆alkylidene, R⁴-O-C₁₋₆alkylidene, R⁵R⁶-N-C₁₋₆alkylidene and R⁷-C(=O)-Z-C₁₋₆alkylidene;

c) O-alkylating an intermediate of formula HO-Alk-D (V) with a reagent of formula R^{4-a}-W¹ (VI) wherein R^{4-a} is Ar¹, in a reaction-inert solvent, thus preparing a compound of formula R^{4-a}-O-Alk-D (I-b);

d) O-alkylating an intermediate of formula W'-Alk-D (VII) with a reagent of formula R^{4a}-O-H (VIII) wherein R^{4a} is Ar¹, in a reaction-inert solvent, thus preparing a compound of formula (I-b);

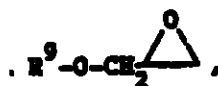
e) reacting an isocyanate of formula R^{7a}-N=C=O (IX) wherein R^{7a}-NH- is amino, Ar²-amino, C₁₋₆-alkylamino or Ar²-C₁₋₆-alkylamino, with an intermediate of formula H-Z'-Alk-D (IX) wherein Z' is NR⁶ or O, in a reaction-inert solvent, thus preparing a compound of formula R^{7a}-NH-C(=O)-Z'-Alk-D (I-c-1);

f) reacting a reagent of formula R^{7b}-H (XII) wherein R^{7b} has the previously defined meaning of R⁷ provided that it is other than Ar² or C₁₋₆-alkyl optionally substituted with Ar², with an isocyanate of formula O=C=N-Alk-D (XI) in a reaction-inert solvent, thus preparing a compound of formula R^{7b}-C(=O)-NH-Alk-D (I-c-2);

g) reacting a reagent of formula R^{7c}-C(=O)-OH (XIII), wherein R^{7c} is Ar² or C₁₋₆-alkyl optionally substituted with Ar², with (IX), in a reaction-inert solvent, if desired, after converting the OH group in (XIII) in a reactive leaving group or by reacting (XIII) with (IX) in the presence of a reagent capable of forming esters or amides, thus preparing a compound of formula R^{7c}-C(=O)-Z'-Alk-D (I-c-3);

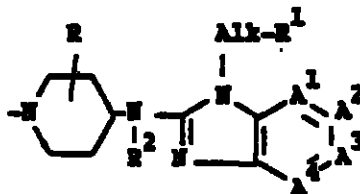
h) reacting an alkylene of formula L²-C₂₋₆-alkenediy-H (XIV), wherein L² being Ar¹-thio, Ar²-sulfonyl, Ar², C₁₋₆-alkylcarbonyl, Ar²-C₁₋₆-alkylcarbonyl, Ar²-carbonyl, C₁₋₆-alkyloxycarbonyl, Ar²-C₁₋₆-alkyloxycarbonyl or C₂₋₆-cycloalkyloxycarbonyl, with a piperidine of formula H-D (II), in a reaction-inert solvent, thus preparing a compound of formula L²-C₂₋₆-alkenediy-D (I-d);

i) reacting a reagent of formula



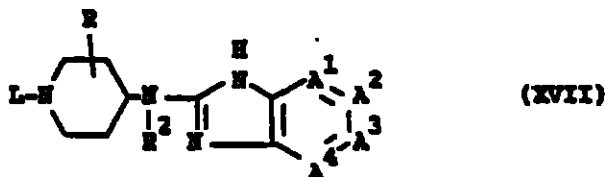
with a piperidine of formula H-D (II), in a reaction-inert solvent, thus preparing a compound of formula R⁹-O-CH₂-CH(OH)-CH₂-D (I-e);

j) reducing an intermediate of formula C₁₋₆-alkyl-O-C(=O)-D (XVI) with a reductant in a reaction-inert solvent, thus preparing a compound of formula CH₂-D (I-f); wherein D represents a radical of formula



wherein A¹ = A² = A³ = A⁴, R, R¹ and R² have the previously described meanings; or

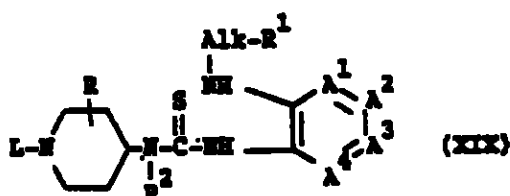
k) N-alkylating an intermediate of formula



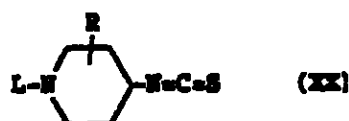
with a reagent of formula W-Alk-R¹ (XVIII) in a reaction-inert solvent, or

l) cyclodesulfurizing an intermediate of formula

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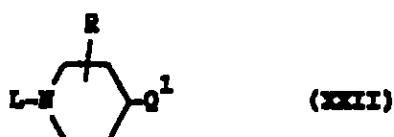
10 which may in situ be prepared by condensing an isothiocyanate of formula



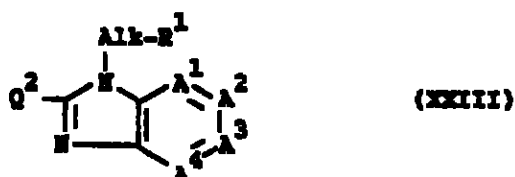
20 with a diamine of formula



30 with an alkylhalide, metal oxide or metal salt in a reaction-inert solvent; or
m) reacting a piperidine of formula



40 with a benzimidazole derivative of formula



50 in a reaction-inert solvent wherein in (XXII) and (XXIII) either

Q¹ is -NHR² and Q² is W, or

Q¹ is W¹ and Q² is -NHR², or

Q¹ is =O and Q² is -NHR²; or

optionally converting the compound of formula (I) into each other following art-known grouptransformation procedures, and, if desired, converting the compounds of formula (I) into a therapeutically active non-toxic acid-addition salt form by treatment with an appropriate acid or, conversely, converting the acid-addition salt into the free base form with alkali; and/or preparing stereochemically isomeric forms thereof.

Example 35: CAPSULES

20 g Of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 0.02 g of the A.I.

Example 36: FILM-COATED TABLETS

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Preparation of tablet core

A mixture of 100 g of the A.I., 570 g lactose and 200 g starch was mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone (Kollidon-K 90 ®) in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 g microcrystalline cellulose (Avicel ®) and 15 g hydrogenated vegetable oil (Stearotax ®). The whole was mixed well and compressed into tablets, giving 10,000 tablets, each comprising 0.01 g of the active ingredient.

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Coating

To a solution of 10 g methyl cellulose (Methocel 60 HG ®) in 75 ml of denaturated ethanol there was added a solution of 5 g of ethyl cellulose (Ethocel 22 cps ®) in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propane triol. 10 g Of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated color suspension (Opspray K-1-2108 ®) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

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Example 37 : INJECTABLE SOLUTION

1.8 g Methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50° C there were added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 0.004 g A.I. per ml. The solution was sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

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Example 38 : SUPPOSITORIES

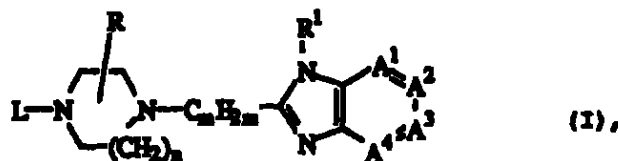
3 g A.I. was dissolved in a solution of 3 g 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 G surfactant (SPAN ®) and triglycerides (Witapal 555 ®) q.s. ad 300 g were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37-38° C to form 100 suppositories each containing 0.03 g of the active ingredient.

Claims

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1. The use for the manufacture of a medicament for treating allergic diseases of a compound having the formula

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a pharmaceutically acceptable acid addition salt or a stereochemically isomeric forms thereof, wherein
 $-A^1=A^2=A^3=A^4-$ is a bivalent radical having the formula

- 70 $-N=CH-CH=CH-$ (a-1),
 $-CH=N-CH=CH-$ (a-2),
 $-CH=CH-N=CH-$ (a-3),
 $-CH=CH-CH=N-$ (a-4),
 $-N=CH-N=CH-$ (a-5), or
15 $-CH=N-CH=N-$ (a-6),

wherein one or two hydrogen atoms in said radicals (a-1) - (a-6) may, each independently from each other, be replaced by halo, C_{1-6} alkyl, C_{1-6} alkyloxy, trifluoromethyl or hydroxy;

R^1 is hydrogen, C_{1-12} alkyl, C_{3-6} cycloalkyl, Ar^1 , C_{1-6} alkyl substituted with one or two Ar^1 radicals, or a radical of formula $-Alk-G-R^2$; wherein

- 20 R^2 is hydrogen; C_{2-6} alkenyl optionally substituted with Ar^2 ; C_{3-6} alkynyl; Ar^1 or C_{1-6} alkyl optionally substituted with Ar^1 , hydroxy, C_{1-6} alkyloxy, carboxyl, C_{1-6} alkyloxycarbonyl, Ar^2 -oxycarbonyl or Ar^2 - C_{1-6} alkyloxycarbonyl; and

G is O, S or NR^3 ; said R^3 being hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyloxycarbonyl or Ar^2 - C_{1-6} alkyl;

- 25 R is hydrogen or C_{1-6} alkyl;

m is 1 to 4;

n is 1 or 2;

- L is hydrogen, C_{1-6} alkylcarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkyloxycarbonyl, Ar^2 - C_{1-6} alkyloxycarbonyl, Ar^2 -carbonyl, Ar^2 -sulfonyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl optionally substituted with Ar^2 , C_{1-12} alkyl, a radical of formula

- 30 $-Alk-R^4$ (b-1)
 $-Alk-Y-R^5$ (b-2)

$-Alk-Z^1-C^X-Z^2-R^6$ (b-3), or

- 35 $-CH_2-CHOH-CH_2-O-R^7$ (b-4); wherein

R^4 is Ar^2 , Het, cyano, isocyanato, isothiocyanato, Ar^2 -sulfonyl or halo;

R^5 is hydrogen, Ar^2 , Het or C_{1-6} alkyl optionally substituted with halo, Ar^2 or Het;

R^6 is hydrogen, Ar^2 , Het or C_{1-6} alkyl optionally substituted with halo, Het or Ar^2 ;

R^7 is Ar^2 or naphthalenyl;

- 40 Y is O, S, NR^8 ; said R^8 being hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl or Ar^1 -carbonyl;

Z^1 and Z^2 each independently are O, S, NR^9 or a direct bond;

said R^9 being hydrogen or C_{1-6} alkyl;

X is O, S or NR^{10} ; said R^{10} being hydrogen, C_{1-6} alkyl or cyano; and each Alk independently being C_{1-6} alkanediyl;

- 45 Het is a five- or six-membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms, said heteroatoms being selected from the group consisting of oxygen, sulfur and nitrogen, provided that no more than two oxygens or sulfurs are present, said five or six-membered ring being optionally condensed with a five- or six-membered carbocyclic or heterocyclic ring also containing 1, 2, 3 or 4 heteroatoms, the latter heteroatoms being selected from the group consisting of oxygen, sulfur and nitrogen, provided that no more than 2
50 oxygens or sulfurs are present, and when said Het is a bicyclic ring system it may optionally be substituted with up to 8 substituents, and when said Het is a monocyclic ring system it may optionally be substituted with up to 4 substituents, said substituents of Het being selected from the group consisting of a bivalent radical of formula $=X$; halo; isocyanato; isothiocyanato; nitro; cyano; trifluoromethyl; a radical of formula $-A$; a radical of formula $-Y-A$; or a radical of formula $-Z^1-C(=X)-Z^2-A$; wherein said $=X$ independently has the
55 same meaning of the previously defined X and A is hydrogen, Ar^2 or C_{1-6} alkyl being optionally substituted with Ar^2 , C being selected from the group consisting of oxygen, sulfur and nitrogen, provided that no more than 2 oxygens or sulfurs are present, and when said Het is a bicyclic ring system it may optionally be substituted with up to 8 substituents, and when said Het is a monocyclic ring system it may optionally be

substituted with up to 4 substituents, said Et^1 -alkyloxy, Ar^2 -O, hydroxy, or C_1 -alkyloxycarbonyl; and Y, Z^1 and Z^2 independently have the same meaning of the previously defined Y, Z^1 and Z^2 ; provided that (i) when in the radical $-\text{Y}-\text{A}$, A is hydrogen, then Y is other than a direct bond, or (ii) when in the radical $-\text{Z}^1-\text{C}(=\text{X})-\text{Z}^2-\text{A}$, A is hydrogen and Z^1 is NR^3 , O or S, then Z^2 is other than O or S;

5 Ar^1 is phenyl, being optionally substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C_1 -alkyl, C_1 -alkyloxy, C_1 -alkylthio, mercapto, amino, mono- and di(C_1 -alkyl)amino, carboxyl, C_1 -alkyloxycarbonyl and C_1 -alkylcarbonyl; thienyl; halothienyl; furanyl; C_1 -alkyl substituted furanyl; pyridinyl; pyrimidinyl; pyrazinyl; thiazolyl or imidazolyl optionally substituted with C_1 -alkyl; and

10 Ar^2 is phenyl being optionally substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C_1 -alkyl, C_1 -alkyloxy, C_1 -alkylthio, mercapto, amino, mono- and di(C_1 -alkyl)amino, carboxyl, C_1 -alkyloxycarbonyl and C_1 -alkylcarbonyl.

2. A chemical compound of formula (I) as defined in claim 1, provided that when L is C_1 -alkyl, R^1 is other than hydrogen, 2-methylphenyl, benzyl, 4-chlorobenzyl or 4-methoxybenzyl.

15 3. A chemical compound according to claim 2 wherein Het is (i) an optionally substituted five- or six-membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, provided that no more than two oxygens or sulfurs are present; or Het is (ii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, being fused with an optionally substituted
20 five- or six-membered ring through two ring carbon atoms or one ring carbon and one ring nitrogen atom, containing in the remainder of the fused ring only carbon atoms; or Het is (iii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, being fused with an optionally substituted five- or six-membered heterocyclic ring through two ring carbon atoms or one ring carbon and one ring nitrogen atom, containing in the
25 remainder of the fused ring 1 or 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen; wherein Het may optionally be substituted with up to 4 substituents when Het is a monocyclic ring system, and wherein Het may optionally be substituted with up to 8 substituents when Het is a bicyclic ring system, said substituents of Het being selected from the group consisting of a bivalent radical of formula $=\text{X}$; halo; isocyanato; isothiocyanato; nitro; cyano; trifluoromethyl; a radical of formula $-\text{A}$; a radical of
30 formula $-\text{Y}-\text{A}$; or a radical of formula $-\text{Z}^1-\text{C}(=\text{X})-\text{Z}^2-\text{A}$; wherein said $=\text{X}$ independently has the same meaning of the previously defined X and A is hydrogen, Ar^2 or C_1 -alkyl being optionally substituted with Ar^2 , C_1 -alkyloxy, Ar^2 -O, hydroxy, or C_1 -alkyloxycarbonyl; and Y, Z^1 and Z^2 independently have the same meaning of the previously defined Y, Z^1 and Z^2 ; provided that (i) when in the radical $-\text{Y}-\text{A}$, A is hydrogen, then Y is other than a direct bond, or (ii) when in the radical $-\text{Z}^1-\text{C}(=\text{X})-\text{Z}^2-\text{A}$, A is hydrogen and Z^1 is NR^3 ,
35 O or S, then Z^2 is other than O or S.

4. A chemical compound according to claim 3 wherein R^1 is C_1 -alkyl substituted with Ar^1 or wherein R^1 is a radical $-\text{Alk}-\text{O}-\text{R}^2$, said R^2 being hydrogen, C_1 -alkyl, C_2 -alkenyl, C_3 -alkynyl or Ar^1 .

5. A chemical compound according to claim 4, wherein R is hydrogen, m is 1, n is 1, and L is hydrogen, C_1 -alkyl or a radical of formula (b-1), (b-2) or (b-3).

40 6. A chemical compound according to claim 5, wherein R^4 is Ar^2 or Het; R^5 and R^6 independently are C_1 -alkyl, Ar^2 or Het; R^7 is hydrogen or C_1 -alkyl; X is O or S; and Z^1 and Z^2 are each independently NH or a direct bond.

7. A pharmaceutical composition comprising a suitable pharmaceutical carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 2 to 6.

45 8. An anti-allergic pharmaceutical composition comprising a suitable pharmaceutical carrier and as active ingredient an effective anti-allergic amount of a compound as claimed in any one of claims 2 to 6.

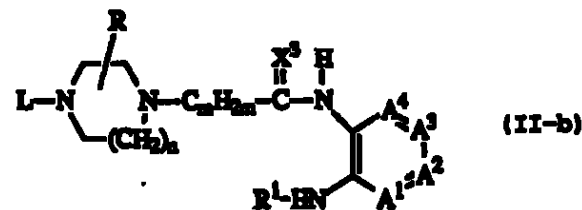
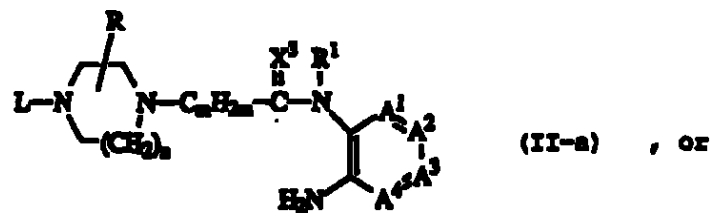
9. A method of preparing a pharmaceutical composition, characterized in that a therapeutically effective amount of a compound as defined in any of claims 2 to 6 is intimately mixed with suitable pharmaceutical carriers.

50 10. A compound as claimed in any of claims 2 to 6 for use as a medicine.

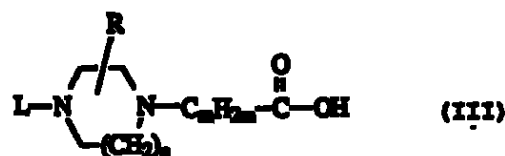
11. A compound as claimed in any of claims 2 to 6 for use as an anti-allergic medicine.

12. A process for preparing a chemical compound as claimed in any of claims 2 to 6, characterized by
a) cyclizing an intermediate of formula

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wherein X^{S} is O, S or NH, in a reaction-inert solvent, if desired, in the presence of a dehydrating agent;
b) reacting an acid of formula

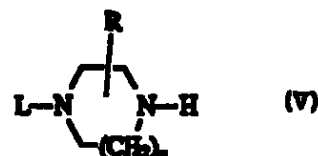


or a functional derivative thereof, with an aromatic diamine of formula

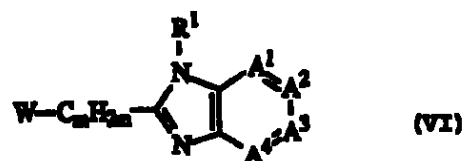


in a reaction-inert solvent;

c) N-alkylating a piperazine or hexahydro-1H-1,4-diazepine of formula

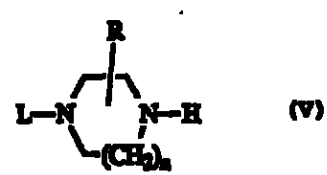


with an imidazopyridine or imidazopyrimidine of formula

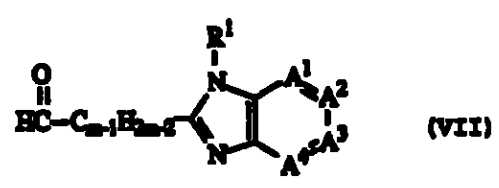


wherein W is a reactive leaving group, in a reaction-inert solvent; if desired, in the presence of a base;
d) reductively N-alkylating a piperazine or hexahydro-1H-1,4-diazepine of formula

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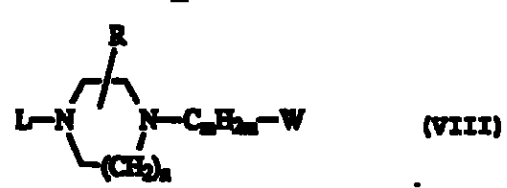


with an imidazopyridine or imidazopyrimidine of formula

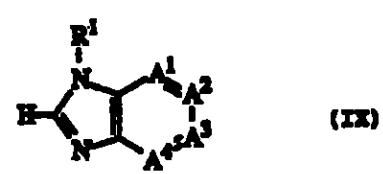


in a reductive medium;

e) reacting a piperazine or hexahydro-1H-1,4-diazepine of formula

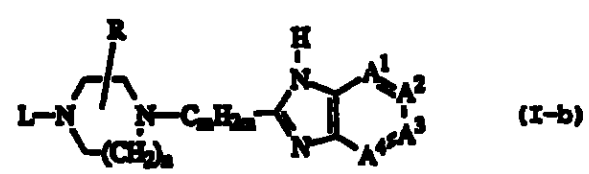


with an imidazopyridine or imidazopyrimidine of formula

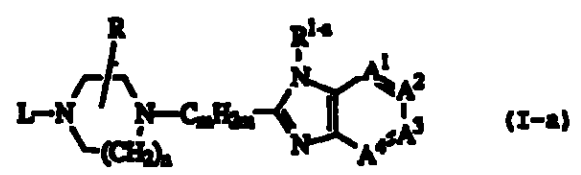


or the metal substitution form thereof, in a reaction-inert medium;

f) N-alkylating a compound of formula



with a reagent of formula W-R^{1-a} (X), wherein W is a reactive leaving group, in a reaction-inert solvent, thus preparing a compound of formula



wherein R^{1-a} has the same meaning of R^1 provided that it is other than hydrogen; or

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g) N-alkylating a compound of formula H-D (I-d) with a reagent of formula L¹-W (XI) in a reaction-inert solvent, thus preparing a compound of formula L¹-D (I-c), wherein L¹ has the previously defined meaning of L, provided that it is other than hydrogen;

h) reductively N-alkylating a compound of formula H-D (I-d) with a ketone or aldehyde of formula L²=O (XII), said L²=O being an intermediate of formula L²H₂, wherein two geminal hydrogen atoms are replaced by =O, in a reductive medium thus preparing a compound of formula L²H-D (I-c-1); wherein L² is a geminal bivalent radical comprising C₂₋₆cycloalkylidene, C₁₋₁₂alkylidene, R⁴-C₁₋₆alkylidene, R⁵-Y-C₁₋₆alkylidene and R⁵-Z²-C(=X)-Z¹-C₁₋₆alkylidene;

i) alkylating a compound of formula H-Y-Alk-D (I-c-3) with an intermediate of formula R⁵-W¹ (XIII), wherein R⁵ is Ar² or Het, in a reaction-inert solvent, thus preparing a compound of formula R⁵-Y-Alk-D (I-c-2);

j) alkylating an intermediate of formula R⁵-Y-H (XIV) wherein R⁵ is Ar² or Het with a compound of formula W-Alk-D (I-c-4), in a reaction-inert solvent, thus preparing a compound of formula (I-c-2);

k) reacting a reagent of formula R⁵-Z²-H (XV), wherein Z² has the previously defined meaning of Z² provided that it is other than a direct bond, with a compound of formula X=C=N-Alk-D (I-c-8), in a reaction-inert solvent, thus preparing a compound of formula R⁵-Z²-C(=X)-NH-Alk-D (I-c-5);

l) reacting an isocyanate or isothiocyanate of formula R⁵-N=C=X (XVI) with a compound of formula H-Z¹-Alk-D (I-c-6), wherein Z¹ has the previously defined meaning of Z² provided that it is other than a direct bond, in a reaction-inert solvent, thus preparing a compound of formula R⁵-NH-C(=X)-Z¹-Alk-D (I-c-7);

m) reacting a reagent of formula R⁵-C(=X)-OH (XVII) with (I-c-8), in a reaction-inert solvent, if desired, after converting the OH group in (XVII) in a reactive leaving group or by reacting (XVII) with (I-c-8) in the presence of a reagent capable of forming esters or amides, thus preparing a compound of formula R⁵-C(=X)-Z¹-Alk-D (I-c-8);

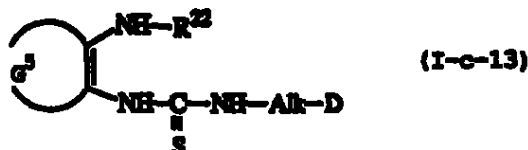
n) reacting an alkanylene of formula L³-C₂₋₆alkanedithyl-H (XVIII), wherein L³ being Ar², Het, Ar⁴-sulfonyl or a radical of formula R⁵-Z²-C(=X)-, with a compound of formula (I-d), in a reaction-inert solvent, thus preparing a compound of formula L³-C₂₋₆alkanedithyl-D (I-c-10);

o) reacting a reagent of formula R⁵

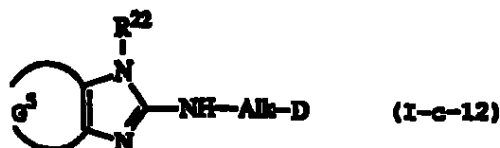


wherein R⁵ is hydrogen or a radical R⁷-O-CH₂-, with a compound of formula (I-d), in a reaction-inert solvent, thus preparing a compound of formula R⁵-CH(OH)-CH₂-D (I-c-11);

p) cyclodesulfurizing a compound of formula

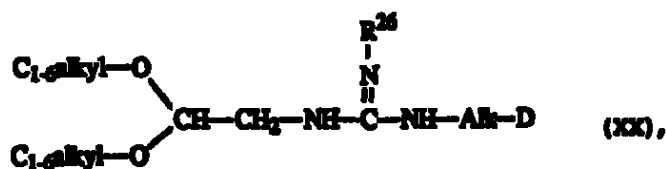


with an alkylhalide, metal oxide or metal salt in a reaction-inert solvent, thus preparing a compound of formula

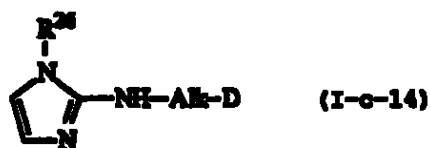


wherein G³ and R²² are as previously defined; or

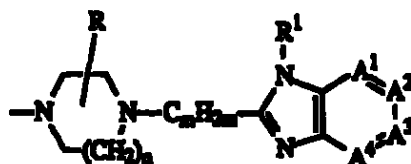
q) cyclizing a guanidine derivative of formula



in a reaction inert-solvent, thus preparing a compound of formula



wherein R^{26} is hydrogen, C_{1-6} alkyl or $\text{Ar}2\text{-C}_{1-6}$ alkyl;
wherein D represents a radical of formula



wherein $\text{A}^1=\text{A}^2=\text{A}^3=\text{A}^4$, R, R^1 , n and m have the previously described meanings; or optionally converting the compounds of formula (I) into each other following art-known groups transformation procedures, and, if desired, converting the compounds of formula (I) into a therapeutically active non-addition salt form by treatment with an appropriate acid or, conversely, converting the acid-addition salt into the free base form with alkali; and/or preparing stereochemically isomeric forms thereof.

EUROPEAN PATENT APPLICATION

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Date of filing: 23.06.88

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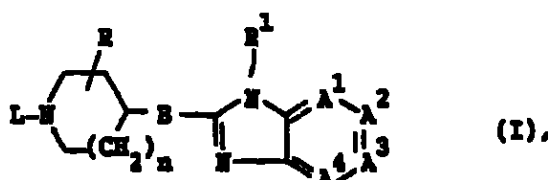
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Applicant: JANSSEN PHARMACEUTICA N.V.
 Turnhoutseweg 30
 B-2340 Beerse(BE)

Inventor: Janssens, Frans Eduard
 Tinststraat 79
 B-2630 Bonheiden(BE)
 Inventor: Diele, Gaston Stanislas Marcella
 Oostende 12
 B-2380 Ravels(BE)
 Inventor: Pille, Gaert Marcel Ester
 Mortaelstraat 42
 B-2620 Edgem(BE)

[(Bicyclic heterocyclyl)methyl and -hetero] substituted hexahydro-1H-azepines and pyrrolidines.

Novel [(Bicyclic heterocyclyl)methyl and -hetero] substituted hexahydro-1H-azepines and pyrrolidines of formula



wherein

-A¹ = A² = A³ = A⁴ is -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH-, or -CH=N-CH=N-,

R¹ is hydrogen, C₁₋₁₂alkyl, C₂₋₆cycloalkyl, Ar¹ or C₁₋₆alkyl substituted with one or two Ar¹ radicals;

B is NR², CH₂, O, S, SO or SO₂;

R is hydrogen or C₁₋₆alkyl;

n is 0 or 2;

L is hydrogen, C₁₋₆alkylcarbonyl, C₁₋₆alkylsulfonyl, C₁₋₆alkyloxycarbonyl, Ar²-C₁₋₆alkyloxycarbonyl, Ar²-carbonyl, Ar²-sulfonyl, C₂₋₆cycloalkyl, C₂₋₆alkenyl optionally substituted with Ar², C₁₋₁₂alkyl, a radical of formula -Alk-R³, -Alk-Y-R⁴, -Alk-Z¹-COO-Z²-R⁵, or -CH₂-CHOH-CH₂-O-R⁶;

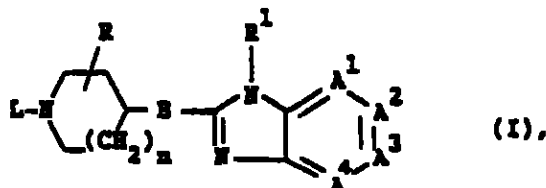
the pharmaceutically acceptable acid addition salts and possible stereochemically isomeric forms thereof,

Example 52 : SUPPOSITORIES

3 g A.I. was dissolved in a solution of 3 g 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 g Surfactant (SPAN®) and triglycerides (Witepsol 555 ®) q.s. ad 300 g were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37-38 °C to form 100 suppositories each containing 30 mg of the active ingredient.

Claims

1. A chemical compound having the formula



a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein

-A¹ = A² = A³ = A⁴ - is a bivalent radical having the formula

-CH=CH-CH=CH- (a-1),

-N=CH-CH=CH- (a-2),

-CH=N-CH=CH- (a-3),

-CH=CH-N=CH- (a-4),

-CH=CH-CH=N- (a-5),

-N=CH-N=CH- (a-6), or

-CH=N-CH=N- (a-7),

wherein one or two hydrogen atoms in said radicals (a-1) - (a-7) may, each independently from each other, be replaced by halo, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl or hydroxy;

R¹ is hydrogen, C₁₋₁₀alkyl, C₂₋₆cycloalkyl, Ar¹ or C₁₋₆alkyl substituted with one or two Ar¹ radicals;

B is NR², CH₂, O, S, SO or SO₂; said R² being hydrogen, C₁₋₆alkyl, C₂₋₆cycloalkyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl and Ar²-C₁₋₆alkyl;

R is hydrogen or C₁₋₆alkyl;

n is 0 or 2;

L is hydrogen, C₁₋₆alkylcarbonyl, C₁₋₆alkylsulfonyl, C₁₋₆alkyloxycarbonyl, Ar²-C₁₋₆alkyloxycarbonyl, Ar²-carbonyl, Ar²-sulfonyl, C₂₋₆cycloalkyl, C₂₋₆alkenyl optionally substituted with Ar², C₁₋₁₂alkyl, a radical of formula

-Alk-R³ (b-1)

-Alk-Y-R⁴ (b-2)

-Alk-Z¹-C(=X)-Z²-R⁵ (b-3), or

-CH₂-CHOH-CH₂-O-R⁶ (b-4); wherein

R³ is Ar², Het, cyano, isocyanato, isothiocyanato, Ar²-sulfonyl or halo;

R⁴ is hydrogen, Ar², Het or C₁₋₆alkyl optionally substituted with halo, Ar² or Het;

R⁵ is hydrogen, Ar², Het or C₁₋₆alkyl optionally substituted with halo, Ar² or Het;

R⁶ is Ar² or naphthalenyl;

Y is O, S, NR⁷;

said R⁷ being hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl or Ar¹-carbonyl;

Z¹ and Z² each independently are O, S, NR⁸ or a direct bond;

said R⁸ being hydrogen or C₁₋₆alkyl;

X is O, S or NR⁹;

said R⁹ is hydrogen, C₁₋₆alkyl or cyano;

each Alk independently being C₁₋₆alkanediyl;

Het is a five- or six-membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms, said heteroatoms being selected from the group consisting of oxygen, sulfur and nitrogen, provided that no more than two oxygens or sulfurs are present, said five or six-membered ring being optionally condensed with a five- or

six-membered carbocyclic or heterocyclic ring also containing 1, 2, 3 or 4 heteroatoms, the latter heteroatoms being selected from the group consisting of oxygen, sulfur and nitrogen, provided that no more than 2 oxygens or sulfurs are present, and when said Het is a bicyclic ring system it may optionally be substituted with up to 6 substituents, and when said Het is a monocyclic ring system it may optionally be substituted with up to 3 substituents, said substituents of Het being selected from the group consisting of a bivalent radical of formula $=X$; halo; isocyanato; isothiocyanato; nitro; cyano; trifluoromethyl; a radical of formula $-A$; a radical of formula $-Y-A$; or a radical of formula $-Z^1-C(=X)-Z^2-A$; wherein said $=X$ independently has the same meaning of the previously defined X and A is hydrogen, Ar^2 or C_{1-6} alkyl being optionally substituted with Ar^2 , C_{1-6} alkyloxy, Ar^2-O , hydroxy, or C_{1-6} alkyloxycarbonyl; and Y , Z^1 and Z^2 independently have the same meaning of the previously defined Y , Z^1 and Z^2 ; provided that (i) when in the radical $-Y-A$, A is hydrogen, then Y is other than a direct bond, or (ii) when in the radical $-Z^1-C(=X)-Z^2-A$, A is hydrogen and Z^1 is NR^3 , O or S , then Z^2 is other than O or S ;

Ar^1 is a member selected from the group consisting of phenyl, being optionally substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, mercapto, amino, mono- and di(C_{1-6} alkyl)amino, carboxy, C_{1-6} alkyloxycarbonyl and C_{1-6} alkylcarbonyl; thienyl; halothieryl; furanyl; C_{1-6} alkyl substituted furanyl; pyridinyl; pyrimidinyl; pyrazinyl; thiazolyl and imidazolyl optionally substituted with C_{1-6} alkyl; and

Ar is a member selected from the group consisting of phenyl being optionally substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, mercapto, amino, mono- and di(C_{1-6} alkyl)amino, carboxyl, C_{1-6} alkyloxycarbonyl and C_{1-6} alkylcarbonyl.

2. A chemical compound according to claim 1 wherein $n = 2$.
3. A chemical compound according to claim 1 wherein $n = 0$.
4. A chemical compound according to claim 1 wherein
 - 25 Het is (i) an optionally substituted five- or six-membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, provided that no more than two oxygens or sulfurs are present; or
 - Het is (ii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, being ortho-condensed with an optionally substituted five- or six-membered ring through two ring carbon atoms or one ring carbon and one ring nitrogen atom, containing in the remainder two ring carbon atoms or one ring carbon and one ring nitrogen atoms, containing in the remainder of the condensed ring 1 or 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen; wherein Het may optionally be substituted with up to 2 substituents when Het is a monocyclic ring system, and wherein Het may optionally be substituted with up to 5 substituents when Het is a bicyclic ring system, said substituents of Het being selected from the group consisting of a bivalent radical of formula $=X$; halo; isocyanato; isothiocyanato; nitro; cyano; trifluoromethyl; an radical of formula $-A$; a radical of formula $-Y-A$; or a radical of formula $-Z^1-C(=X)-Z^2-A$; wherein said $=X$ independently has the same meaning of the previously defined X and Z is hydrogen, Ar^2 or C_{1-6} alkyl being optionally substituted with Ar^2 , C_{1-6} alkyloxy, Ar^2-O , hydroxy, or C_{1-6} alkyloxycarbonyl; and Y , Z^1 and Z^2 independently have the same meaning of the previously defined Y , Z^1 and Z^2 ; provided that (i) when in the radical $-Y-A$, A is hydrogen, then Y is other than a direct bond, or (ii) when in the radical $-Z^1-C(=X)-Z^2-A$, A is hydrogen and Z^1 is NR^3 , O or S , then Z^2 is other than O or S .
3. A chemical compound according to claim 2 wherein R is hydrogen, R^1 is C_{1-6} alkyl substituted with one Ar^1 and B is NH or CH_2 .
4. A chemical compound according to claim 3 wherein L is hydrogen, C_{1-6} alkyl or a radical of formula (b-1), (b-2) or (b-3) and B is NH .
5. A chemical compound according to claim 4 wherein R^2 , R^4 and R^5 are each Ar^2 or Het, R^7 is hydrogen or C_{1-6} alkyl, X is O , and Z^1 and Z^2 are each independently NH or a direct bond.
6. A pharmaceutical composition comprising a suitable pharmaceutical carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5.
7. An anti-allergic pharmaceutical composition comprising a suitable pharmaceutical carrier and as active ingredient an effective anti-allergic amount of a compound as claimed in any one of claims 1 to 5.
8. A method of preparing a pharmaceutical composition, characterized in that a therapeutically effective amount of a compound as defined in any of claims 1 to 5 is intimately mixed with suitable pharmaceutical carriers.
9. A compound as claimed in any one of claims 1 to 5 for use as a medicine.
10. A compound as claimed in any one of claims 1 to 5 for use as an anti-allergic medicine.

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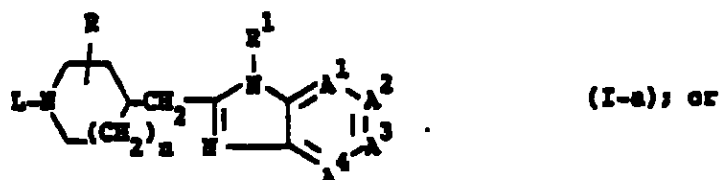


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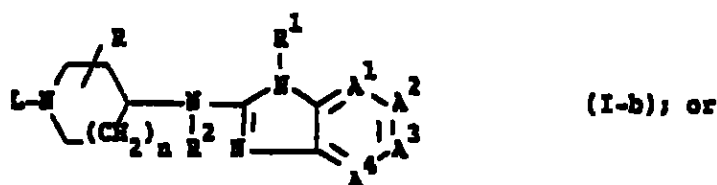
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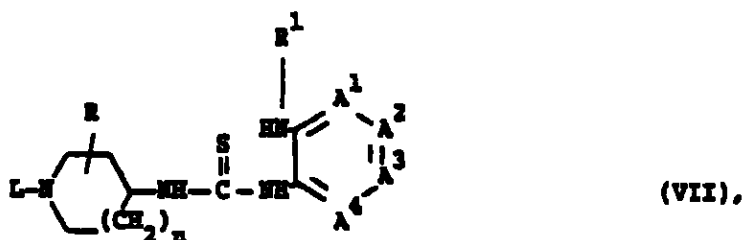


10 iv) E¹ is a radical of formula -M and E² is a radical of formula -CH₂-W¹, thus preparing a compound of formula (I-a); or

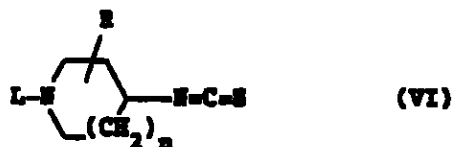
v) E¹ is a radical of formula -O and E² is a radical of formula R²-NH-, thus preparing a compound of formula



20 c) cyclodesulfurizing an intermediate of formula



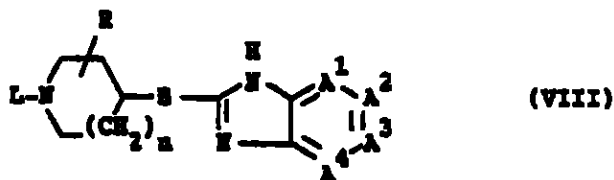
30 which may in situ be prepared by condensing an isothiocyanate of formula



40 with a diamine of formula (III),

with an alkylhalide, metal oxide or metal salt in a reaction-inert solvent;

45 d) N-alkylating an intermediate of formula



55 with a reagent of formula



wherein W¹ is a reactive leaving group, in a reaction-inert medium; or

e) N-alkylating a compound of formula H-D (I-d) with a reagent of formula L¹-W¹ (X) in a reaction-inert

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- solvent, thus preparing a compound of formula L¹-D (I-c), wherein L¹ has the previously defined meaning of L, provided that it is other than hydrogen;
- f) reductively N-alkylating a compound of formula H-D (I-d) with a ketone or aldehyde of formula L²=O (XI), said L²=O being an intermediate of formula L²H₂ wherein two geminal hydrogen atoms are replaced by =O, in a reaction inert medium thus preparing a compound of formula L²H-D (I-c-1), wherein L² is a geminal bivalent radical comprising C₂- ϵ cycloalkylidene, C₁₋₁₂alkylidene, R³-C₁- ϵ alkylidene, R⁴-Y-C₁- ϵ alkylidene and R⁵-Z²-C(=X)-Z¹-C₁- ϵ alkylidene;
- g) alkylating a compound of formula H-Y-Alk-D (I-c-3) with an intermediate of formula R^{4a}-W¹ (XII), wherein R^{4a} is a Ar² or Het, in a reaction-inert solvent, thus preparing a compound of formula R^{4a}-Y-Alk-D (I-c-2);
- h) alkylating an intermediate of formula R^{4a}-Y-H (XIII) wherein R^{4a} is Ar² or Het with a compound of formula W¹-Alk-D (I-c-4), in a reaction-inert solvent, thus preparing a compound of formula (I-c-2);
- i) reacting a reagent of formula R⁵-Z^{2a}-H (XIV), wherein Z^{2a} has the previously defined meaning of Z² provided that it is other than a direct bond, with a compound of formula X=C=N-Alk-D (I-c-6), in a reaction-inert solvent, thus preparing a compound of formula R⁵-Z^{2a}-C(=X)-NH-Alk-D (I-c-5);
- j) reacting an isocyanate or isothiocyanate of formula R⁵-N=C=X (XV) with a compound of formula H-Z^{1a}-Alk-D (I-c-8), wherein Z^{1a} has the previously defined meaning of Z¹ provided that it is other than a direct bond, in a reaction-inert solvent, thus preparing a compound of formula R⁵-NH-C(=X)-Z^{1a}-Alk-D (I-c-7);
- k) reacting a reagent of formula R⁵-C(=X)-OH (XVI) with (I-c-8), in a reaction-inert solvent, if desired, after converting the OH group in (XVI) in a reactive leaving group or by reacting (XVI) with (I-c-8) in the presence of a reagent capable of forming esters or amides, thus preparing a compound of formula R⁵-C(=X)-Z^{1a}-Alk-D (I-c-9);
- l) reacting an alkenylene of formula L³-C₂- ϵ alkenediyl-H (XVII), wherein L³ being Ar², Het, Ar²-sulfonyl or a radical of formula R⁵-Z²-C(=X)-, with a compound of formula (I-d), in a reaction-inert solvent, thus preparing a compound of formula L³-C₂- ϵ alkenediyl-D (I-c-10);
- m) reacting a reagent of formula



- wherein R²⁴ is hydrogen or a radical R⁵-O-CH₂-, with a compound of formula (I-d), in a reaction-inert solvent, thus preparing a compound of formula R²⁴-CH(OH)-CH₂-D (I-c-11); or
- n) cyclodesulfurizing a compound of formula



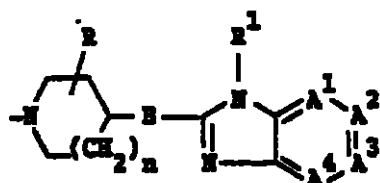
- with an alkylhalide, metal oxide or metal salt in a reaction-inert solvent, thus preparing a compound of formula



- wherein G⁵ and R²¹ are as previously defined;
- wherein D represents a radical of formula

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wherein $-A^1=A^2-A^3=A^4-$, B, G, F, R^1 and n have the previously described meanings; or optionally converting the compounds of formula (I) into each other following art-known group transformation procedures, and, if desired, converting the compounds of formula (I) into a therapeutically active non-toxic acid-addition salt form by treatment with an appropriate acid or, conversely, converting the acid-addition salt into the free base form with alkali; and/or preparing stereochemically isomeric forms thereof.

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Publication number:

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A1

EUROPEAN PATENT APPLICATION

Application number: 90200720.2

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C07D 405/14, A61K 31/445,
A61K 31/34

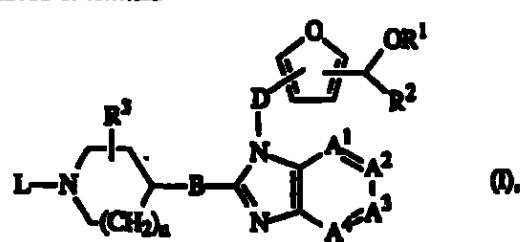
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Applicant: JANSSEN PHARMACEUTICA N.V.
Turnhoutseweg 30
B-2340 Beerse(BE)

Inventor: Janssens, Frans Eduard
Tintstraat 79
B-2830 Bonheiden(BE)
Inventor: Diels, Gaston Stanislas Marcella
Oostende 12
B-2380 Ravele(BE)
Inventor: Leenaerts, Joseph Elisabeth
Maxburgdreef 1
B-2321 Hoogstraten(BE)

Hydroxyalkylfuranyl derivatives.

Hydroxyalkylfuranyl derivatives of formula



wherein
-A¹=A²-A³=A⁴- is -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH- or -CH=N-CH=N- ;
D is C₁-₄alkenediyl ;
R¹ is hydrogen, C₁-₆alkyl, aryl(C₁-₆alkyl) or C₁-₆alkylcarbonyl ;
R² and R³ are hydrogen or C₁-₆alkyl ;
n is 0, 1 or 2 ;
B is NR⁴, O, S, SO₂ or CH₂ ;
R⁴ is hydrogen, C₁-₆alkyl, C₃-₆cycloalkyl or aryl(C₁-₆alkyl) ;
L is hydrogen, C₁-₁₂alkyl, C₃-₆cycloalkyl, C₂-₆alkenyl optionally substituted with aryl, C₁-₆alkylcarbonyl, C₁-₆alkyloxycarbonyl, arylcarbonyl, aryl(C₁-₆alkyloxycarbonyl), C₁-₆alkylsulfonyl, arylsulfonyl, or a radical of formula -Alk-R⁵, -Alk-Y-R⁵, -Alk-Z¹-C(=X)-Z²-R⁷, or -CH₂-CHOH-CH₂-O-R⁵,
the acid addition salts and stereochemically isomeric forms thereof, said compounds having antiallergic activity. Pharmaceutical compositions containing such compounds as an active ingredient; methods of preparing said compounds and pharmaceutical compositions.

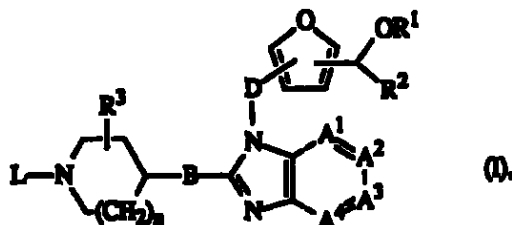
EP 0 393 738 A1

Example 32 : INJECTABLE SOLUTION

60 Parts of A.I. and 12 parts of benzylalcohol were mixed well and sesame oil was added q.s. ad 1 l, giving a solution comprising 60 mg/ml of A.I. The solution was sterilized and filled in sterile containers.

Claims

1. A compound having the formula



a pharmaceutically acceptable acid addition salt thereof or a stereochemically isomeric form thereof, wherein

-A¹ = A²-A³ = A⁴- is a bivalent radical having the formula

-CH=CH-CH=CH- (a-1),

-N=CH-CH=CH- (a-2),

-CH=N-CH=CH- (a-3),

-CH=CH-N=CH- (a-4),

-CH=CH-CH=N- (a-5),

-N=CH-N=CH- (a-6) or

-CH=N-CH=N- (a-7),

wherein one or two hydrogen atoms in said radicals (a-1) to (a-7) each independently from one another may be replaced by halo, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl or hydroxy;

D is C₁₋₆alkanediyl;

R¹ is hydrogen, C₁₋₆alkyl, arylC₁₋₆alkyl or C₁₋₆alkylcarbonyl;

R² is hydrogen or C₁₋₆alkyl;

R³ is hydrogen or C₁₋₆alkyl;

n is 0, 1 or 2;

B is NR⁴, O, S, SO, SO₂ or CH₂;

R⁴ is hydrogen, C₁₋₆alkyl, C₂₋₆cycloalkyl or arylC₁₋₆alkyl;

L is hydrogen, C₁₋₁₂alkyl, C₂₋₆cycloalkyl, C₂₋₆alkenyl optionally substituted with aryl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, arylcarbonyl, arylC₁₋₆alkyloxycarbonyl, C₁₋₆alkylsulfonyl, arylsulfonyl, or a radical of formula

-Alk-R⁵ (b-1),

-Alk-Y-R⁶ (b-2),

-Alk-Z¹-C(=X)-Z²-R⁷ (b-3), or

-CH₂-CHOH-CH₂-O-R⁸ (b-4), wherein

R⁵ is halo, cyano, isocyanato, isothiocyanato, aryl, Het or arylsulfonyl;

R⁶ is hydrogen, aryl, Het or C₁₋₆alkyl optionally substituted with halo, aryl or Het;

R⁷ is hydrogen, aryl, Het or C₁₋₆alkyl optionally substituted with halo, aryl or Het;

R⁸ is aryl or naphthalenyl;

Y is O, S, NR⁹; said R⁹ being hydrogen, C₁₋₆alkyl or C₁₋₆alkylcarbonyl;

Z¹ and Z² each independently are O, S, NR¹⁰ or a direct bond;

said R¹⁰ being hydrogen or C₁₋₆alkyl;

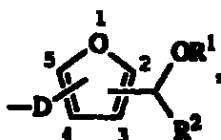
X is O, S or NR¹¹; said R¹¹ being hydrogen, C₁₋₆alkyl or cyano;

each Alk independently is C₁₋₆alkanediyl;

each Het is a five- or six-membered heterocyclic ring containing 1, 2, 3 or 4 hetero-atoms selected from oxygen, sulfur and nitrogen, provided that no more than 2 oxygen and/or sulfur atoms are present, said five or six-membered ring being optionally condensed with a five- or six-membered carbocyclic or heterocyclic ring also containing 1, 2, 3 or 4 hetero-atoms selected from oxygen, sulfur and nitrogen, provided that the

letter ring does not contain more than 2 oxygen and/or sulfur atoms and that the total number of heteroatoms in the bicyclic ring system is less than 8; and when Het is a monocyclic ring system it may optionally be substituted with up to 4 substituents, when Het is a bicyclic ring system it may optionally be substituted with up to 6 substituents, said substituents being selected from a bivalent radical of formula X; halo; isocyanato; isothiocyanato; nitro; cyano; trifluoro-methyl; a radical of formula -E; a radical of formula -Y-E; or a radical of formula -Z¹-C(=X)-Z²-E; wherein X, Y, Z¹ and Z² are as previously defined hereinabove; and E is hydrogen, aryl or C₁₋₆alkyl being optionally substituted with aryl, C₁₋₆alkyloxy, aryloxy, hydroxy or C₁₋₆alkyloxycarbonyl; each aryl is phenyl optionally substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C₁₋₆alkyl C₁₋₆alkyloxy, C₁₋₆alkylthio, mercapto, amino, mono- and di(C₁₋₆alkyl)amino, carboxyl, C₁₋₆alkyloxycarbonyl and C₁₋₆alkylcarbonyl; and provided that when R² is Het, said Het is other than a 2-amino-3,4-dihydro-4-oxo-5-pyrimidinyl group, wherein the hydrogen on the 6-position may be replaced by a C₁₋₆alkyl radical and wherein the nitrogen atom in the 3-position and the nitrogen atom of the amino group optionally are substituted, or are linked by a bivalent radical of formula -(CH₂)_n-, -(CH₂)_n-, -CH=CH-, -CH=N-, -N=CH-, or -N=CH-CH₂-, wherein one or where possible two hydrogen atoms of said bivalent radicals each independently from one another may be replaced by C₁₋₆alkyl.

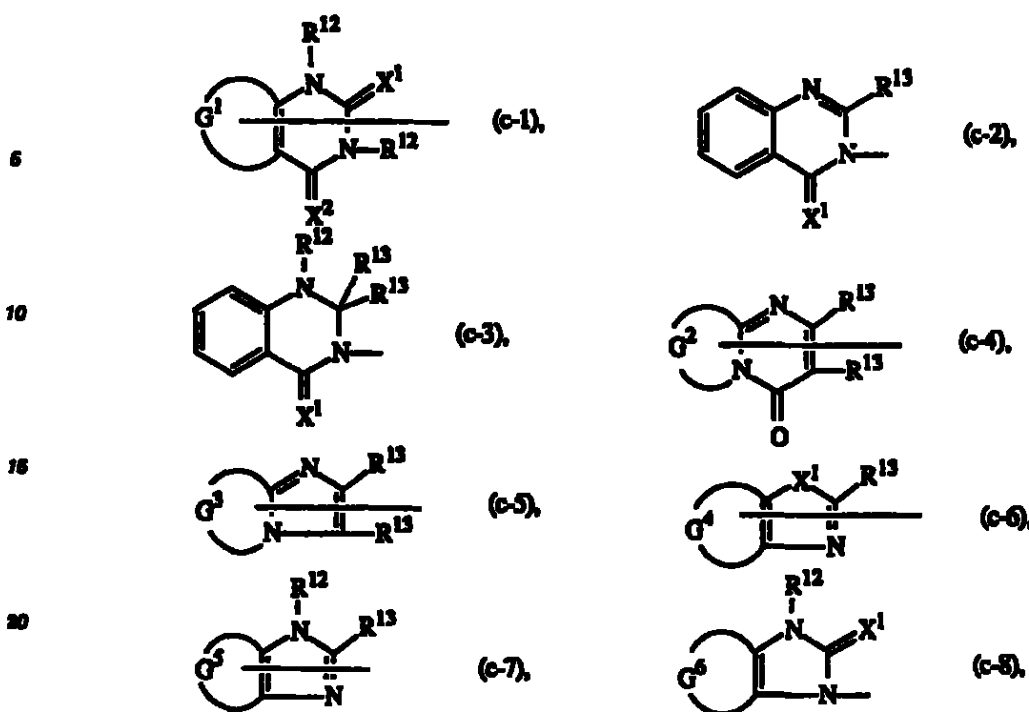
2. A compound according to claim 1 wherein R¹ is hydrogen or arylC₁₋₆alkyl; R² is hydrogen; B is NH or CH₂; n is 1 or 2; L is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, or a radical of formula (b-1), (b-2), (b-3) or (b-4); or the moiety



is (2-CH(R²)OR¹-furan-5-yl)C₁₋₆alkyl or (3-CH(R²)OR¹-furan-5-yl)-C₁₋₆alkyl, wherein aryl is as defined in claim 1.

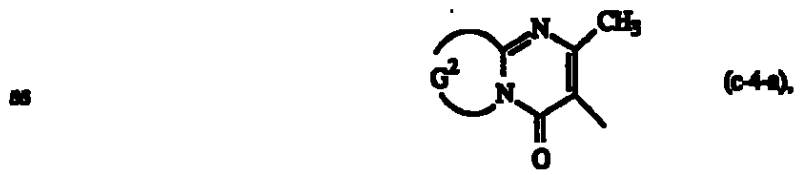
3. A compound according to claim 2 wherein R¹ is hydrogen; R² is hydrogen; n is 1 or 2; L is methyl or a radical of formula (b-1), (b-2) or (b-3); R³ is aryl or Het; R⁴ is C₁₋₆alkyl or Het; R⁵ is aryl, Het or C₁₋₆alkyl; Y is O or NH; Z¹ and Z² each independently are NR¹⁰ or a direct bond, R¹⁰ being hydrogen or C₁₋₆alkyl; X is O; each Alk is C₂₋₆alkanediyl; Het is selected from pyridinyl, optionally substituted with one or two substituents each independently selected from halo, amino, mono- and di(C₁₋₆alkyl)amino, arylC₁₋₆alkylamino, nitro, cyano, aminocarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxycarbonyl, hydroxy, C₁₋₆alkylcarbonyloxy, arylC₁₋₆alkyl and carboxyl; pyridinyloxy, optionally substituted with nitro; pyrimidinyl, optionally substituted with one or two substituents each independently selected from halo, amino, C₁₋₆alkylamino, arylC₁₋₆alkylamino, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio and arylC₁₋₆alkyl; pyridazinyl, optionally substituted with C₁₋₆alkyl or halo; pyrazinyl, optionally substituted with halo, amino or C₁₋₆alkyl; thienyl, optionally substituted with halo or C₁₋₆alkyl; furanyl, optionally substituted with halo or C₁₋₆alkyl; pyrrolyl, optionally substituted with C₁₋₆alkyl; thiazolyl, optionally substituted with C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, aryl or arylC₁₋₆alkyl; imidazolyl, optionally substituted with one or two substituents each independently selected from C₁₋₆alkyl, arylC₁₋₆alkyl and nitro; tetrazolyl, optionally substituted with C₁₋₆alkyl; 1,3,4-thiadiazolyl, optionally substituted with C₁₋₆alkyl; 5,6-dihydro-4H-1,3-thiazin-2-yl, optionally substituted with C₁₋₆alkyl; 4,5-dihydrothiazolyl, optionally substituted with C₁₋₆alkyl; oxazolyl, optionally substituted with C₁₋₆alkyl; 4,5-dihydro-5-oxo-1H-tetrazolyl, optionally substituted with C₁₋₆alkyl; 1,4-dihydro-2,4-dioxo-3(2H)-pyrimidinyl, optionally substituted with C₁₋₆alkyl; 4,5-dihydro-4-oxopyrimidinyl, optionally substituted with up to 3 substituents selected from C₁₋₆alkyl, amino, C₁₋₆alkylaminocarbonylamino, arylaminocarbonylamino, arylC₁₋₆alkylamino and C₁₋₆alkylamino; 2,3-dihydro-3-oxopyridazinyl; 2-oxo-3-oxazolidinyl; pyrrolidinyl; piperidinyl; morpholinyl; thiomorpholinyl; dioxanyl, optionally substituted with C₁₋₆alkyl; indolyl, optionally substituted with hydroxy or C₁₋₆alkyl; quinolinyl, optionally substituted with hydroxy or C₁₋₆alkyl; quinazolinyl, optionally substituted with hydroxy or C₁₋₆alkyl; quinoxalinyl, optionally substituted with C₁₋₆alkyl; phthalazinyl, optionally substituted with halo; 1,3-dioxo-1H-indol-2(3H)-yl; 2,3-dihydro-3-oxo-4H-benzoxazinyl and 2,3-dihydro-1,4-benzodioxinyl, both being optionally substituted with C₁₋₆alkyl or halo; 2-oxo-2H-1-benzopyranylyl and 4-oxo-4H-1-benzopyranylyl, both being optionally substituted with C₁₋₆alkyl, and a bicyclic heterocyclic radical of formula

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25 wherein X¹ and X² each independently are O or S ;
 each R¹² independently is hydrogen, C₁-alkyl, arylC₁-alkyl, C₁-alkyloxy-C₁-alkyl, hydroxyC₁-alkyl or C₁-alkyloxycarbonyl ;
 each R¹³ independently is hydrogen, C₁-alkyl, hydroxy, mercapto, C₁-alkyloxy, C₁-alkylthio, halo or C₁-alkyloxycarbonylC₁-alkyl ;
 30 and the long dash in the radicals (c-1), (c-4), (c-5), (c-6) and (c-7) signifies that any hydrogen atom of said radicals, including R¹² and R¹³, may represent the bond linking Het to respectively Alk, Y or Z² in the radicals of formula (b-1), (b-2) and (b-3) ;
 G¹ is -CH=CH-CH=CH- or -S-CH=CH- ;
 35 G² is -CH=CH-CH=CH-, -(CH₂)₄-, -S-(CH₂)₂-, -S-(CH₂)₃-, -S-CH=CH-, -CH=CH-O-, -CH=C(CH₃)-O-, -NH-(CH₂)₂-, -NH-(CH₂)₃-, -NH-CH=CH-, -NH-N=CH-CH₂-, -NH-CH=N- or -NH-N=CH- ;
 G³ is -CH=CH-CH=CH-, -CH₂-NH-(CH₂)₂-, -S-CH=CH-, -S-(CH₂)₂-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH- or -CH=N-CH=N- ;
 40 G⁴ is -CH=CH-CH=CH-, -CH₂-NH-(CH₂)₂-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH- or -CH=N-CH=N- ;
 G⁵ is -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH- or -CH=N-CH=N- ;
 45 wherein one or two hydrogen atoms in said radicals G¹, G², G³, G⁴, G⁵ or G⁶ or in the benzene part of the radicals of formula (c-2) or (c-3) may be replaced by C₁-alkyl, C₁-alkylthio, C₁-alkyloxy or halo when connected to a carbon atom ; or by C₁-alkyl, C₁-alkyloxycarbonyl or arylC₁-alkyl when connected to a nitrogen atom, wherein each aryl is as defined in claim 1.

4. A compound according to claim 3 wherein R⁵ is phenyl optionally substituted with C₁-alkyloxy; pyridinyl; 4,5-dihydro-5-oxo-1H-tetrazolyl; 2-oxo-3-oxazolidinyl; 2,3-dihydro-2-oxo-1H-benzimidazolyl; or a bicyclic radical of formula



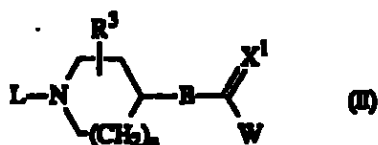
wherein G^2 is $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{S}-(\text{CH}_2)_3-$, $-\text{S}-(\text{CH}_2)_2-$, $-\text{S}-\text{CH}=\text{CH}-$ or $-\text{CH}=\text{C}(\text{CH}_3)-\text{O}-$; or R^6 is $\text{C}_1-\epsilon$ alkyl; pyridinyl optionally substituted with nitro; pyrimidinyl; pyrazinyl; pyridazinyl optionally substituted with halo; or 2,3-dihydro-3-oxopyridazinyl; or the radical (b-3) is (arylcabonyl) $\text{C}_1-\epsilon$ alkyl, $\text{C}_1-\epsilon$ alkylaminocarbonyl $\text{C}_1-\epsilon$ alkyl or a radical $\text{Het}^1-\text{C}(=\text{O})-\text{NH}-\text{C}_1-\epsilon$ alkyl wherein Het^1 is 1-methyl-1H-pyrrolyl, furanyl, thienyl or aminopyrazinyl; wherein aryl is as defined in claim 1.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any of claims 1 to 4.

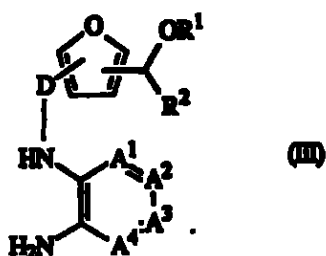
6. A method of preparing a pharmaceutical composition as claimed in claim 5, characterized in that a therapeutically effective amount of a compound as claimed in any of claims 1 to 4 is intimately mixed with a pharmaceutical carrier.

7. A compound as claimed in any of claims 1 to 4 for use as a medicine.

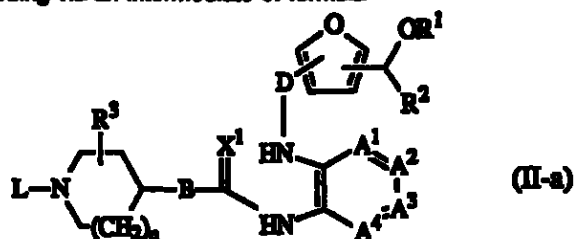
8. A process for preparing a compound as claimed in any of claims 1 to 4, characterized by a) reacting an intermediate of formula



wherein X^1 is O, S or NH, W is a reactive leaving group and R^3 , L, B and n are as defined in claim 1, with a substituted diamine of formula

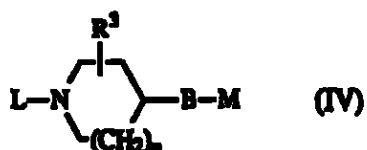


wherein R^1 , R^2 , D and $-\text{A}^1=\text{A}^2=\text{A}^3=\text{A}^4-$ are as defined in claim 1, in a reaction-inert solvent, said reaction in some instances proceeding via an intermediate of formula



which may in situ, or if desired, after isolating and purifying it, be cyclized to yield a compound of formula (I);

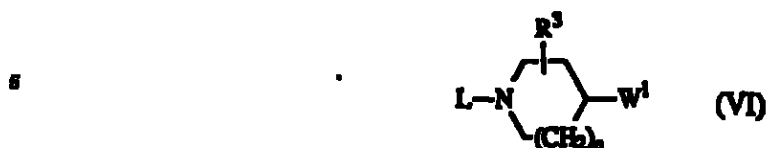
b) reacting an intermediate of formula



wherein M is hydrogen when B is other than CH_2 or M represents an alkali or earth alkaline metal when B represents CH_2 and R^3 , L, B and n are as defined in claim 1, with an intermediate of formula W-Q (V) wherein W is a reactive leaving group, in a reaction-inert solvent;

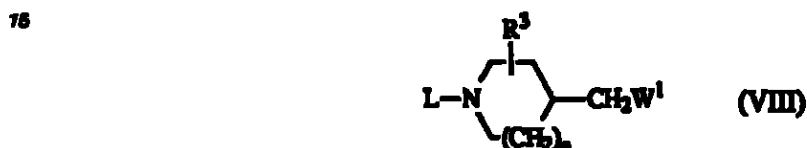
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c) reacting an intermediate of formula

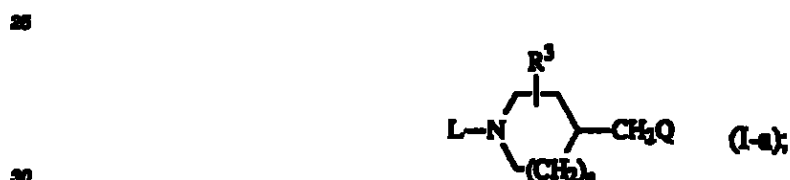


10 wherein W^1 represents a reactive leaving group and L, R^3 and n are as defined in claim 1, with an intermediate of formula $\text{M}-\text{B}-\text{Q}$ (VII) wherein M is hydrogen when B is other than CH_2 or M represents an alkali or earth alkaline metal when B represents CH_2 , in a reaction-inert solvent;

d) reacting an intermediate of formula



wherein W^1 is a reactive leaving group and L, R^3 and n are as defined in claim 1, with an intermediate of formula $\text{M}-\text{Q}$ (IX) wherein M is an alkali or earth alkaline metal, in a reaction-inert solvent, thus yielding a compound of formula

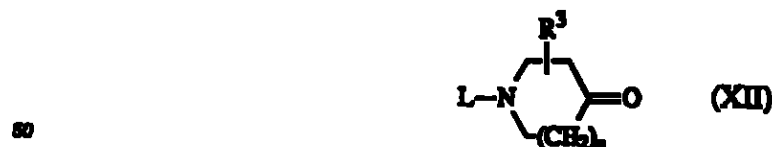


e) reacting an intermediate of formula

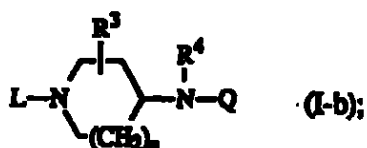


wherein M is an alkali or earth alkaline metal and L, R^3 and n are as defined in claim 1, with an intermediate of formula $\text{W}^1-\text{CH}_2-\text{Q}$ (XI) wherein W^1 is a reactive leaving group, in a reaction-inert solvent, thus yielding a compound of formula (I-a);

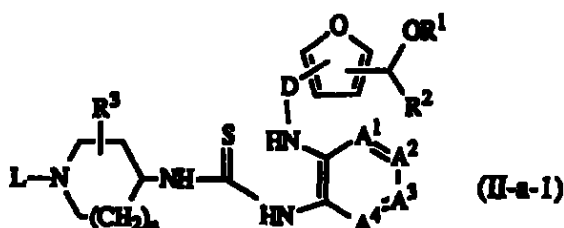
45 f) reductively N-alkylating an intermediate of formula



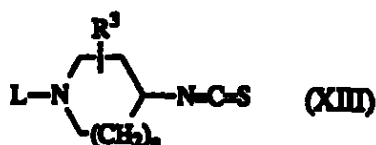
55 wherein L, R^3 and n are as defined in claim 1, with an intermediate of formula $\text{R}^4-\text{NH}-\text{Q}$ (VI-a) wherein R^4 is as defined in claim 1, in a reaction-inert solvent with a reductant, said reductive N-alkylation reaction in some instances being conducted by reacting intermediates (XII) and (VI-a) to form an enamine which may be isolated and purified, and subsequently reducing said enamine, thus yielding a compound of formula



g) cyclodesulfurizing a thiourea of formula

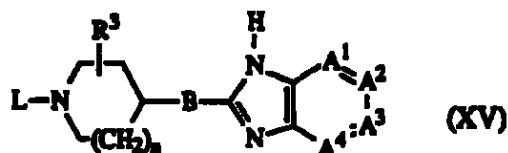


wherein $-A^1=A^2=A^3=A^4-$, R^1 , R^2 , R^3 , D , L and n are as defined in claim 1, which may be formed in situ by condensing an isothiocyanate of formula

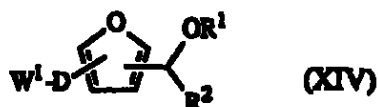


with a diamine of formula (II), with an alkylhalide, metal oxide or metal salt in a reaction-inert solvent;

h) N-alkylating an intermediate of formula

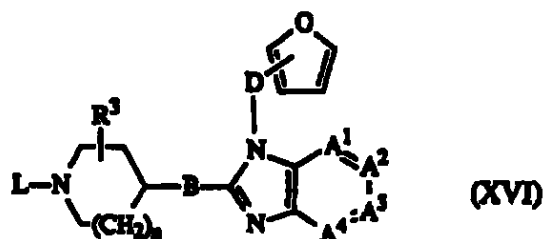


wherein $-A^1 = A^2 - A^3 = A^4-$, B, L, R² and n are as defined in claim 1, with an alkylating reagent of formula

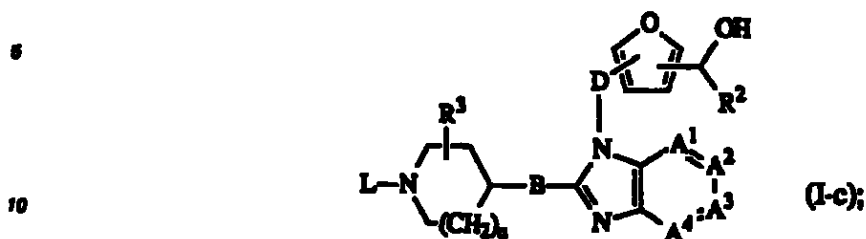


wherein W' is a reactive leaving group and R¹, R² and D are as defined in claim 1, in a reaction-inert solvent;

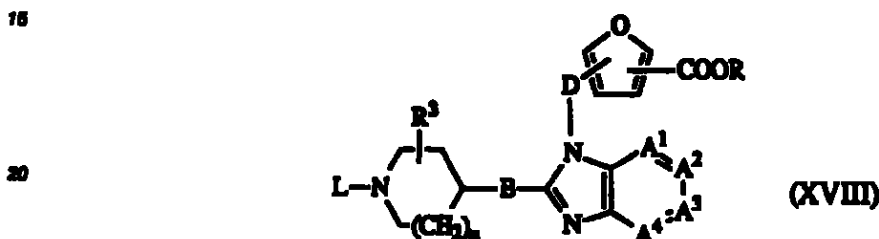
i) condensing a turan-derivative of formula



wherein $-A^1 \approx A^2 \approx A^3 \approx A^4$, D, B, L, R^3 and n are as defined in claim 1, with an aldehyde of formula R^2-CHO (XVII) wherein R^2 is as defined in claim 1, in a reaction-inert solvent thus yielding a compound of formula



j) reacting a carboxylic acid derivative of formula

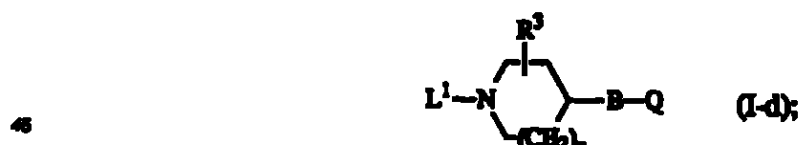


25 wherein R is hydrogen, alkyl or aryl and $-A^1 \approx A^2 \approx A^3 \approx A^4$, D, B, L, R^3 and n are as defined in claim 1, with a reducing agent in a reaction-inert solvent; or reacting (XVIII) with a C_1 - C_4 alkyllithium and reducing the thus obtained intermediate ketone with a reducing agent in a reaction-inert solvent, thus yielding a compound of formula (I-c);

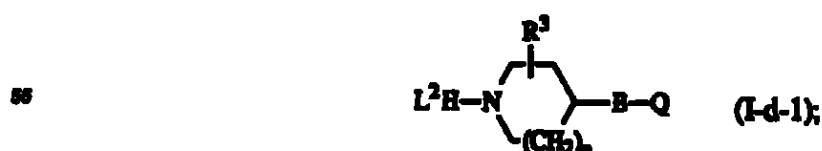
k) N-alkylating a compound of formula



40 wherein B, R^3 and n are as defined in claim 1, with an alkylating reagent of formula L^1-W^1 (XX) wherein W^1 is a reactive leaving group and L^1 is L as defined in claim 1 but other than hydrogen, in a reaction-inert solvent, thus yielding a compound of formula



50 l) reductively N-alkylating a compound of formula (I-e) with a ketone or aldehyde of formula $L^2=O$ (XX) wherein L^2 is a geminal bivalent radical comprising C_3 - C_6 cycloalkylidene, C_1 - C_{12} alkylidene, R^5 - C_1 - C_6 alkylidene, in a reaction-inert solvent, thus yielding a compound of formula



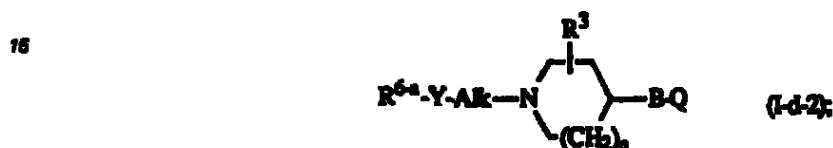
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m) alkylating a compound of formula



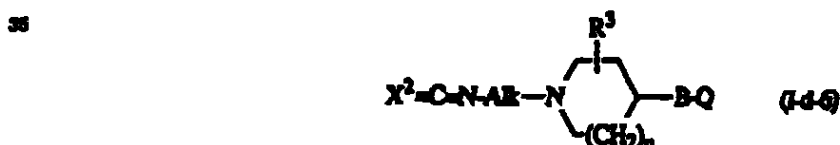
10 wherein B, R³, Alk, Y and n are as defined in claim 1, with a reagent of formula R^{6a}-W¹ (ODI) wherein W¹ is a reactive leaving group and R^{6a} is aryl or Het, said aryl and Het being as defined in claim 1, in a reaction-inert solvent, thus yielding a compound of formula



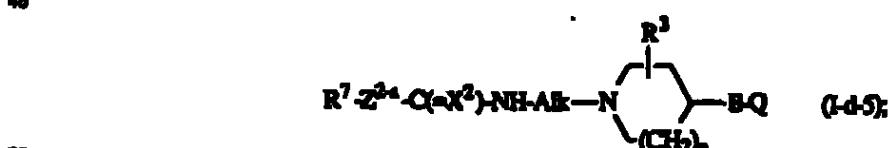
20 n) alkylating a reagent of formula R^{6a}-Y-H (ODI) wherein R^{6a} is aryl or Het, Y and said aryl and Het being as defined in claim 1, with a compound of formula



30 wherein B, Alk, R³ and n are as defined in claim 1 and W¹ is a reactive leaving group, in a reaction-inert solvent, thus yielding a compound of formula (I-d-2);
o) reacting a compound of formula



40 wherein X² is O or S and B, Alk, R³ and n are as defined in claim 1, with a reagent of formula R⁷-Z^{2a}-H (ODI) wherein Z^{2a} is O, S or NR¹⁰, R⁷ and R¹⁰ being as defined in claim 1, in a reaction-inert solvent, thus yielding a compound of formula

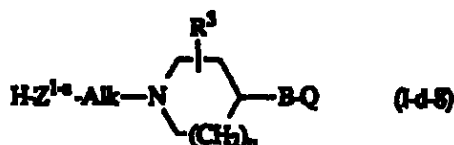


p) reacting a compound of formula

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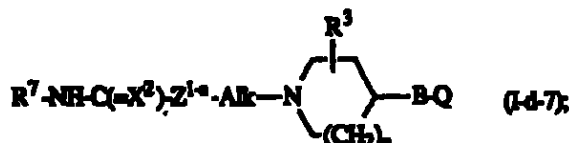
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wherein Z^{1-a} is O, S or NR^{10} ; B, Alk, R^3 , R^{10} and n being as defined in claim 1, with an isocyanate ($\text{X}^2 = \text{O}$) or isothiocyanate ($\text{X}^2 = \text{S}$) of formula $\text{R}^7-\text{N}=\text{C}=\text{X}^2$ (XXIV) wherein R^7 is as defined in claim 1, in a reaction-inert solvent, thus yielding a compound of formula

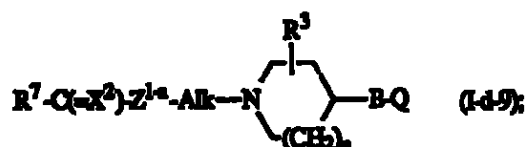
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q) reacting a compound of formula (I-d-5) with a reagent of formula $\text{R}^7-\text{C}(=\text{X}^2)-\text{OH}$ (XXV) wherein X^2 is O or S, and R^7 is as defined in claim 1, in a reaction-inert solvent in the presence of a reagent capable of forming esters or amides, or by reacting (I-d-5) with a reactive functional derivative of (XXV), after converting the hydroxy group in (XXV) into a reactive leaving group, in a reaction-inert solvent, thus preparing a compound of formula

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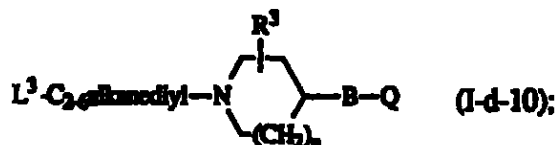


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r) adding a compound of formula (I-e) to an alkene of formula $\text{L}^3-\text{C}_2=\text{alkenediyl}-\text{H}$ (XXVI) wherein L^3 is aryl, Het, arylsulfonyl or a radical of formula $\text{R}^7-\text{Z}^2-\text{C}(=\text{X})$, said aryl, Het, R^7 , Z^2 and X being as defined in claim 1, in a reaction-inert solvent, thus preparing a compound of formula

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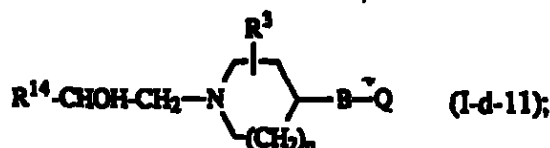
s) reacting a compound of formula (I-e) with an epoxide of formula

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wherein R^{14} is hydrogen, C_1 -alkyl or a radical of formula $\text{R}^8-\text{O}-\text{CH}_2$, R^8 being as defined in claim 1, in a reaction-inert solvent, thus preparing a compound of formula

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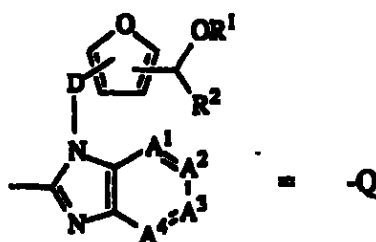
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wherein Q represents a radical of formula

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wherein $-A^1 = A^2 - A^3 = A^4-$, R^1 , R^2 and D are as defined in claim 1, or optionally converting the compounds of formula (I) into each other following art-known functional group transformation reactions, and, if desired, converting a compound of formula (I) into a therapeutically active acid addition salt form by treatment with an appropriate acid, or conversely, converting an acid addition salt form into a free base form with alkali; and/or preparing stereochemically isomeric forms thereof.

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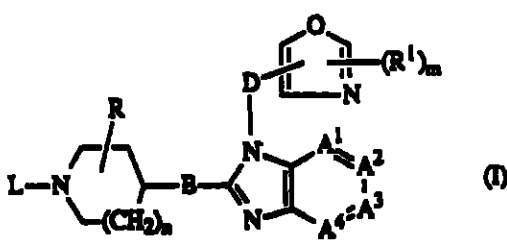
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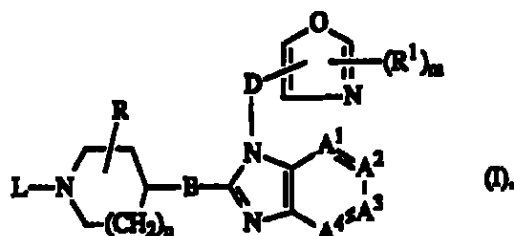
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 413/14, 513/04, 519/00 C07D 487/04, 417/14 A61K 31/415, C07D 498/04 C07D 473/34, 471/04	A1	(11) International Publication Number: WO 92/01687 (43) International Publication Date: 6 February 1992 (06.02.92)
(21) International Application Number: PCT/EP91/01291 (22) International Filing Date: 9 July 1991 (09.07.91) (30) Priority data: 554,326 19 July 1990 (19.07.90) US (71) Applicant: JANSSEN PHARMACEUTICA N.V. (BE/BE); Turnhoutseweg 30, B-2340 Beerse (BE). (72) Inventors: JANSSENS, Frans, Eduard ; Tinststraat 79, B-2820 Bonheiden (BE). SOMMEN, François, Maria ; Langenberg 49, B-2323 Wortel (BE). DIERCKX, Ann, Christina, Joannes ; Mgr. Miertstraat 49/2, B-2460 Kasterlee (BE). COOYMANS, Ludwig, Paul ; Grote Beekstraat 22/1, B-2340 Beerse (BE).		(81) Designated States: AT (European patent), AU, BR, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), NL (European patent), NO, PL, RO, SE (European patent), SN (OAPI + patent), SU, TD (OAPI patent), TG (OAPI patent). Published With international search report.
(54) Title: NOVEL OXAZOLYL DERIVATIVES  (I)		
(57) Abstract Oxazolyl derivatives of formula (I), wherein -A ¹ =A ² -A ³ =A ⁴ - represents a bivalent radical having the formula -CH=CH-CH=CH- (a-1), -N=CH-CH=CH- (a-2), -CH=N-CH=CH- (a-3), -CH=CH-N=CH- (a-4), -CH=CH-CH=N- (a-5), -N=CH-N=CH- (a-6) or -CH=N-CH=N- (a-7); R represents hydrogen or C ₁₋₄ alkyl; R ¹ represents hydrogen, C ₁₋₄ alkyl or hydroxy-C ₁₋₄ alkyl; m represents 1 or 2; D represents C ₁₋₄ alkanediyl; B represents NR ² , CH ₂ , O, S, SO or SO ₂ wherein R ² is hydrogen or C ₁₋₄ alkyl; n represents 0, 1 or 2; L represents hydrogen; C ₁₋₁₂ alkyl; C ₃₋₆ cycloalkyl; C ₂₋₆ alkenyl optionally substituted with aryl; C ₁₋₄ alkylcarbonyl; C ₁₋₄ alkyloxycarbonyl; arylcarbonyl; aryl(C ₁₋₄ alkyloxycarbonyl); or a radical of formula -Alk-R ³ (b-1); -Alk-Y-R ⁴ (b-2); -Alk-Z ¹ -C(=X)-Z ² -R ⁵ (b-3); or -CH ₂ -CHOH-CH ₂ -O-R ⁶ (b-4), the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof have antiallergic properties. Compositions containing the same and methods of treating warm-blooded animals suffering from allergic diseases.		

Claims

1. A compound having the formula :



a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein

10 -A¹-A²-A³-A⁴- represents a bivalent radical having the formula

-CH=CH-CH=CH- (a-1),

-N=CH-CH=CH- (a-2),

-CH=N-CH=CH- (a-3),

15 -CH=CH-N=CH- (a-4),

-CH=CH-CH=N- (a-5),

-N=CH-N=CH- (a-6) or

-CH=N-CH=N- (a-7);

20 wherein one or two hydrogen atoms in said radicals (a-1) to (a-7) may each independently be replaced by halo, C₁-₆alkyl, C₁-₆alkyloxy, hydroxy or trifluoromethyl;

R represents hydrogen or C₁-₄alkyl;

25 R¹ represents hydrogen, C₁-₆alkyl or hydroxyC₁-₆alkyl;

m is 1 or 2;

D represents C₁-₄alkanediyl;

B represents NR², CH₂, O, S, SO or SO₂ wherein R² is hydrogen or C₁-₄alkyl;

n is 0, 1 or 2;

30 L represents hydrogen; C₁-₁₂alkyl; C₃-₆cycloalkyl; C₃-₆alkenyl optionally substituted with aryl; C₁-₆alkylcarbonyl; C₁-₆alkyloxycarbonyl; arylcarbonyl; arylC₁-₆alkyloxy-carbonyl; or a radical of formula :

- Alk-R³ (b-1);
 -Alk-Y-R⁴ (b-2);
 -Alk-Z¹-C(=X)-Z²-R⁵ (b-3); or
 -CH₂-CHOH-CH₂-O-R⁶ (b-4); wherein

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R³ represents cyano, aryl or Het;

R⁴ represents hydrogen, aryl, Het or C₁-alkyl optionally substituted with aryl or Het;

10

R⁵ represents hydrogen, aryl, Het or C₁-alkyl optionally substituted with aryl or Het;

R⁶ represents aryl or naphthalenyl;

Y represents O, S, NR⁷; said R⁷ being hydrogen, C₁-alkyl or C₁-alkylcarbonyl;

Z¹ and Z² each independently represent O, S, NR⁸ or a direct bond, said R⁸ being hydrogen or C₁-alkyl.

15

X represents O, S or NR⁹; said R⁹ being hydrogen, C₁-alkyl or cyano; each Alk independently is C₁-alkanediyl;

each Het represents :

(i) an optionally substituted five- or six-membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms selected from oxygen, sulfur and nitrogen, provided that no more than 2 oxygen and/or sulfur atoms are present;

(ii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen, being fused with an optionally substituted five- or six-membered ring through 2 carbon atoms or 1 carbon and 1 nitrogen atom, containing in the remainder of the fused ring only carbon atoms; or

(iii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen, being fused with an optionally substituted five- or six-membered heterocyclic ring through 2 carbon atoms or 1 carbon and 1 nitrogen atom, containing in the remainder of the fused ring 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen;

wherein Het being a monocyclic ring system may be optionally substituted with up to 4 substituents; and wherein Het being a bicyclic ring system may be optionally substituted with up to 6 substituents, said substituents being selected from halo, amino, mono- and di(C₁-alkyl)amino, arylC₁-alkylamino, nitro, cyano, aminocarbonyl, C₁-alkyl, C₁-alkyloxy, C₁-alkylthio, C₁-alkyloxycarbonyl, C₁-alkyloxyC₁-alkyl, C₁-alkyloxycarbonylC₁-alkyl, hydroxy, mercapto, hydroxyC₁-alkyl, C₁-alkyl-

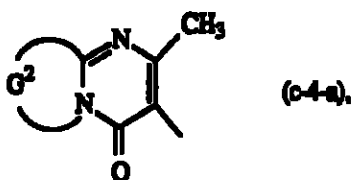
each aryl is phenyl optionally substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C₁-alkyl, C₁-alkyloxy, C₁-alkylthio, mercapto, amino, mono- and di(C₁-alkyl)amino, carboxyl, C₁-alkyloxycarbonyl and C₁-alkylcarbonyl.

3. A compound according to claim 1 wherein $-A^1=A^2-A^3=A^4-$ represents a bivalent radical having the formula $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ (a-1) or $-\text{N}=\text{CH}-\text{CH}=\text{CH}-$ (a-2), wherein one hydrogen atom in said radical (a-1) may be replaced by halo, C_{1-6} alkyloxy or hydroxy; R represents hydrogen or methyl; R^1 represents hydrogen, methyl or hydroxymethyl; m is 1 or 2; D represents CH_2 ; B represents NH , NCH_3 , CH_2 , O, S or SO; n is 0, 1 or 2; L represents hydrogen; C_{1-4} alkyl; cyclohexyl, propenyl, 3-phenylpropenyl; C_{1-4} alkyloxycarbonyl; or a radical of formula :

20

-Alk-R ³	(b-1);
-Alk-Y-R ⁴	(b-2);
-Alk-Z ¹ -C(=X)-Z ² -R ⁵	(b-3); or
-CH ₂ -CHOH-CH ₂ -O-R ⁶	(b-4); wherein

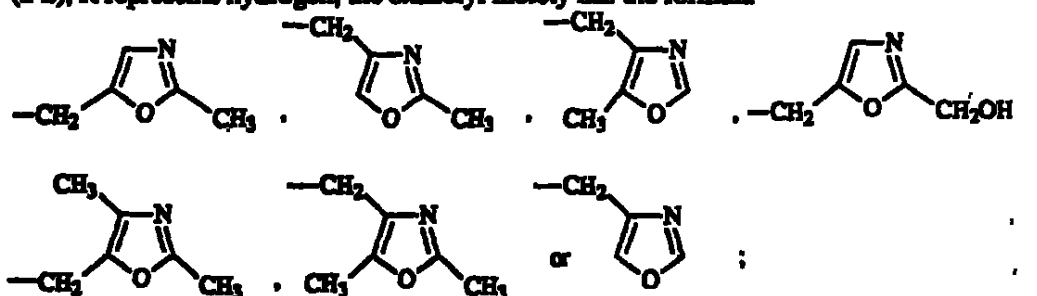
25 each Alk independently represents C₁₋₄alkanedyl; R³ represents phenyl, hydroxyphenyl, C₁₋₄alkyloxyphenyl, 3,4,5-trimethoxyphenyl, pyridinyl, thienyl, 2-methyl-5-oxazolyl, 4,5-dihydro-4-ethyl-5-oxo-1H-tetrazolyl, 2,3-dihydro-6-methyl-3-oxopyridazinyl, 2-oxo-3-oxazolidinyl, 2-(amino or methylamino)-3,4-dihydro-3,6-dimethyl-4-oxo-5-pyrimidinyl, 2-oxo-2H-1-benzopyranyl, 3,7-dihydro-1,3-dimethyl-
30 2,6-dioxo-1H-purin-7-yl, 2,3-dihydro-2-oxo-1-benzimidazolyl or a radical of formula



wherein G^2 represents $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-(\text{CH}_2)_4-$, $-\text{S}-(\text{CH}_2)_2-$, $-\text{S}-(\text{CH}_2)_3-$,
 35 $-\text{S}-\text{CH}=\text{CH}-$, $-\text{N}(\text{CH}_2)_3$, $-\text{N}=\text{C}(\text{CH}_3)-\text{CH}_2-$, $-\text{N}(\text{CH}_3)-\text{N}=\text{C}(\text{CH}_3)-$,
 $-\text{N}(\text{CH}_3)-\text{CH}=\text{CH}-$ or $\text{CH}=\text{C}(\text{CH}_3)-\text{O}-$; Y represents NH, O or S; R^4 represents

- hydrogen, C₁₋₄alkyl, halophenyl, pyridinyl, halopyridinyl, pyrimidinyl, 1,4-dihydro-2,4-dioxo-3(2H)-pyrimidinyl, 1,4-dihydro-4-oxopyrimidinyl, pyridazinyl, halopyridazinyl, 1-methylimidazolyl, thiazolyl, 2-amino-1,3,4-thiadiazolyl, 6-purinyl or imidazo[4,5-c]pyridinyl; Z¹ and Z² each independently represent O, NH or a direct bond; X represents O or S; R⁵ represents hydrogen, C₁₋₄alkyl, aminophenyl, C₁₋₄alkylphenyl, pyridinyl, aminopyridinyl, aminopyrazinyl, 1-methylpyrrolyl, furanyl or 1-methylindolyl; and R⁶ represents phenyl.

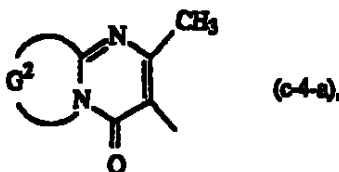
4. A compound according to claim 3 wherein -A¹=A²-A³=A⁴- represents a bivalent radical having the formula -CH=CH-CH=CH- (a-1) or -N=CH-CH=CH-



- B represents NH, S or CH₂; n is 1; L represents hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, propenyl, 3-phenylpropenyl or a radical of formula

- Alk-R³ (b-1);
 -Alk-Y-R⁴ (b-2);
 -Alk-NH-C(=O)-R^{5-a} (b-3-a); or
 -Alk-C(=O)-Z²-R^{5-b} (b-3-b); wherein

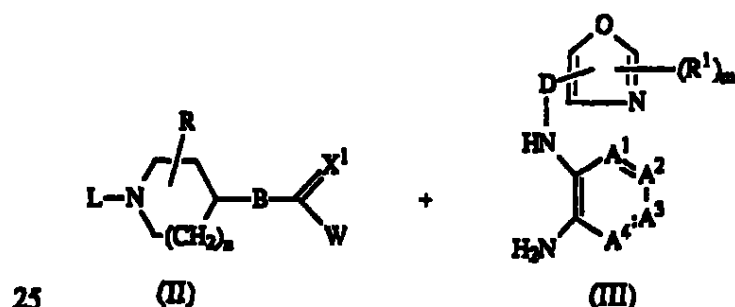
- each Alk independently represents C₁₋₃alkenediyl; R³ represents phenyl, 4-methoxyphenyl, 4-hydroxyphenyl, pyridinyl, thienyl, 4,5-dihydro-4-ethyl-5-oxo-1H-tetrazolyl, 2-oxo-2H-1-benzopyran-2-yl, 2-(amino- or methylamino)-3,4-dihydro-3,6-dimethyl-4-oxo-5-pyrimidinyl, 6-purinyl, or a radical of formula



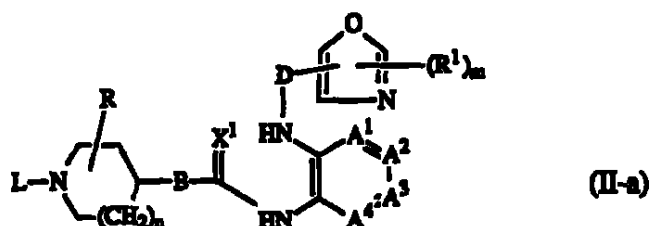
- wherein G² represents -CH=CH-CH=CH-, -(CH₂)₄-, -S-(CH₂)₂-, -S-(CH₂)₃-, -S-CH=CH- or -N(CH₃)-N=C(CH₃)-CH₂-; Y represents NH or O; R⁴ represents

pyrimidinyl, 5-amino-1,3,4-thiadiazolyl, pyridazinyl, imidazo[4,5-c]pyridinyl or 1,4-dihydro-4-oxo-2-pyrimidinyl; R^{5-a} represents aminopyrazinyl or furanyl; Z² represents O; and R^{5-b} represents hydrogen.

- 5 5. A compound according to claim 1 wherein the compound is 1-[(2-methyl-5-oxazolyl)methyl]-N-(1-methyl-4-piperidiny)-1H-benzimidazol-2-amine, a solvate or a pharmaceutically acceptable addition salt thereof.
- 10 6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient an effective antiallergic amount of a compound as claimed in any of claims 1 to 5
- 15 7. A process of preparing a composition as claimed in claim 6, characterized by intimately mixing a therapeutically effective amount of a compound as defined in any of claims 1 to 5 with a pharmaceutical carrier.
8. A compound as claimed in any of claims 1 to 5 for use as a medicine
- 20 9. A process of preparing a compound as defined in any of claims 1 to 5, characterized by
- a) reacting an intermediate of formula (II) wherein W^1 represents a reactive leaving group and X^1 denotes O, S or NH, with a substituted diamine of formula (III),



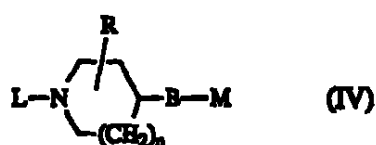
in a reaction-inert solvent thus yielding a compound of formula (I), or optionally yielding a compound of formula (II-a)



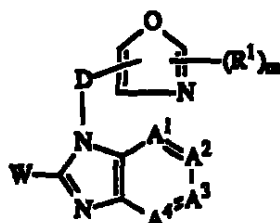
which can be cyclized to a compound of formula (I) by treatment with an alkyl halide, a metal oxide or a metal salt in a reaction-inert solvent;

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b) reacting an intermediate of formula (IV)

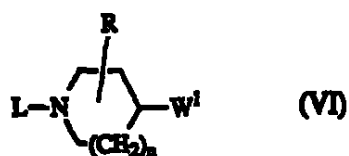


10 wherein M is hydrogen when B is other than CH₂ or M represents an alkali or earth alkaline metal when B represents CH₂, with an intermediate of formula



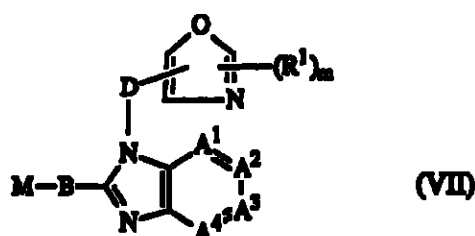
15 wherein W represents a reactive leaving group, in a reaction-inert solvent, optionally in the presence of a base;

c) reacting an intermediate of formula (VI)



wherein W^1 represents a reactive leaving group with an intermediate of formula (VII)

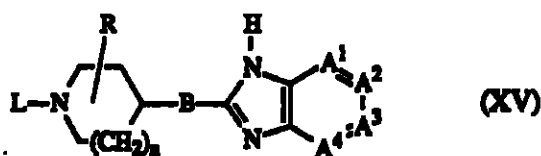
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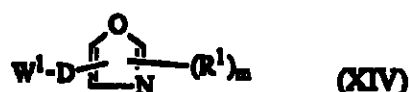
wherein M and B have the meaning as defined under formula (IV), in a reaction-inert solvent, optionally in the presence of a base;

5

d) N-alkylating an intermediate of formula (XV)



10 with an alkylating reagent of formula (XIV)



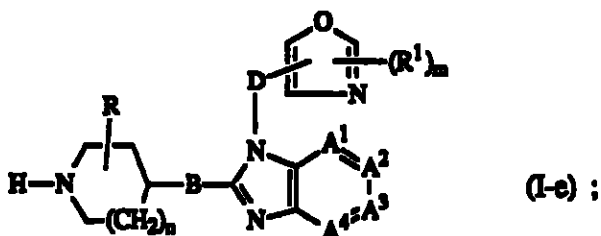
wherein W¹ represents a reactive leaving group, in a reaction-inert solvent in the presence of a base;

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e) converting a compound of formula (I) wherein L represents benzyl into a compound of formula (I) wherein L represents C₁-galkyloxycarbonyl by treatment with C₁-galkylchloroformate;

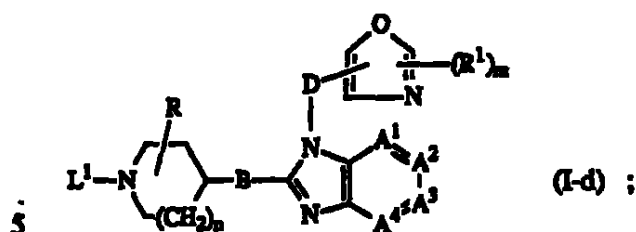
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f) hydrolyzing a compound of formula (I) wherein L represents C₁-galkyloxycarbonyl in an aqueous acidic or basic medium, thus yielding a compound of formula (I-e)

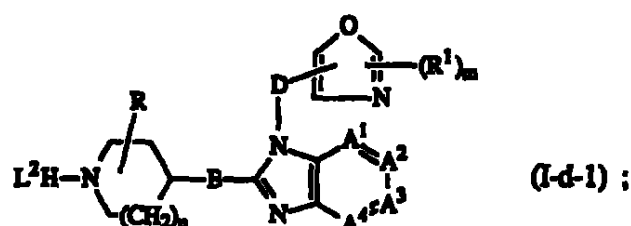


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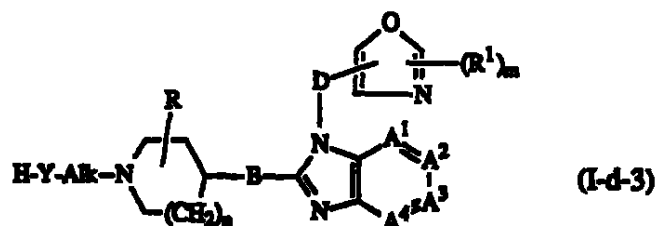
g) N-alkylating a compound of formula (I-e) with an alkylating reagent of formula L^1-W^1 (XVI) wherein L^1 is defined as L but other than hydrogen, in a reaction-inert solvent in the presence of a base, thus yielding a compound of formula (I-d)



h) reductively N-alkylating a compound of formula (I-e) with a reagent of formula L^2-H (XVII) wherein L^2 represents a geminal bivalent radical comprising C_{3-6} cycloalkylidene, C_{1-12} alkylidene, R^3-C_{1-6} alkylidene, R^4-Y-C_{1-6} alkylidene or $R^5-Z^2-C(=X)-Z^1-C_{1-6}$ alkylidene, in a reaction-inert solvent in the presence of hydrogen and a hydrogenation catalyst, thus yielding a compound of formula (I-d-1)



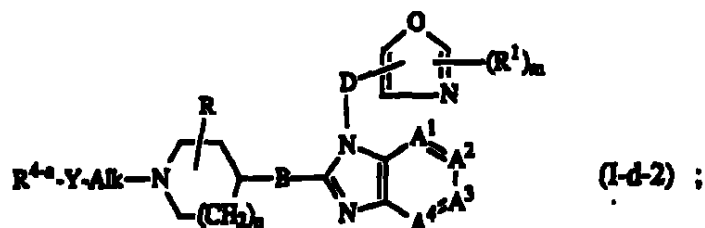
15 i) alkylating a compound of formula (I-d-3)



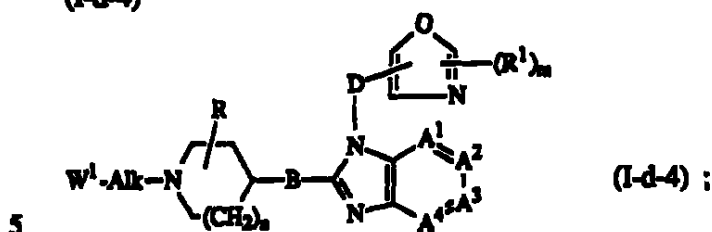
20 with a reagent of formula $R^{4-a}-W^1$ (XVIII) wherein R^{4-a} is aryl or Het, in a reaction-inert solvent, optionally in the presence of a base thus yielding a compound of formula (I-d-2)

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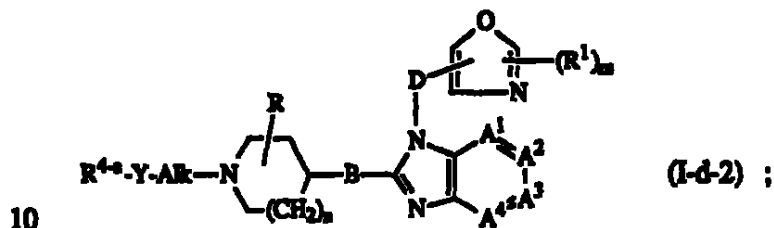
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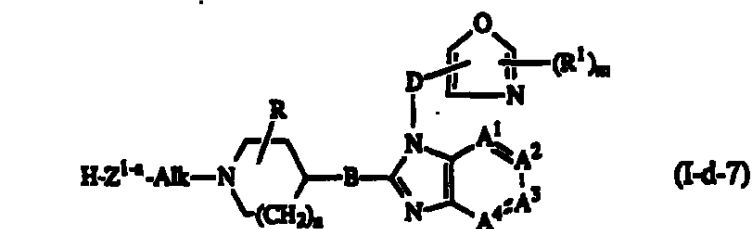
j) alkylating an intermediate of formula $R^{4-a}-Y-H$ (XIX) with a compound of formula (I-d-4)



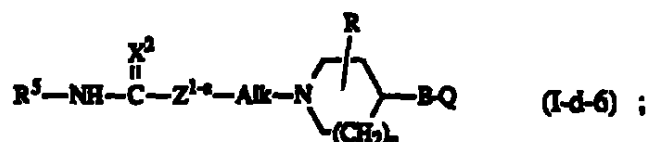
in a reaction-inert solvent, optionally in the presence of a base, thus yielding a compound of formula (I-d-2)



k) reacting a compound of formula (I-d-7)

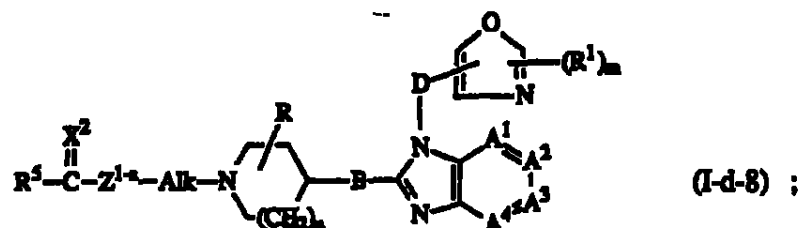


with a reagent of formula $R^5-N-C-Z^2$ (XXII) wherein Z^2 represents O or S, in a reaction-inert solvent, thus yielding a compound of formula (I-d-6)



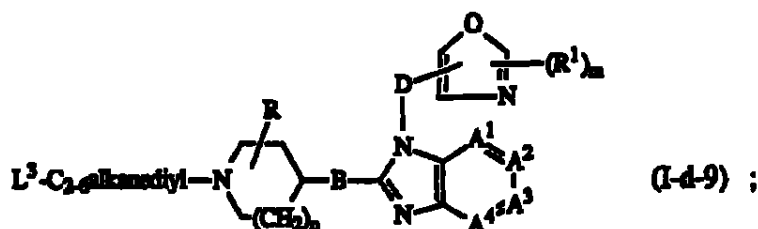
l) reacting a compound of formula (I-d-7) with a reagent of formula $R^5-C(=X)-OH$ (XXIII) or a reactive derivative thereof in a reaction-inert solvent, thus yielding a compound of formula (I-d-8)

5



m) reacting a compound of formula (I-e) with an alkene of formula $L^3-C_2\text{-alkenediyl-H}$ (XXIV) wherein L^3 represents aryl, Het or a radical of formula $R^5-Z^2-C(=X)-$ in a reaction-inert solvent, thus yielding a compound of formula (I-d-9)

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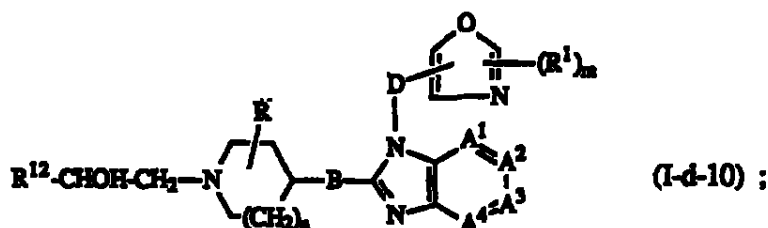
n) reacting a compound of formula (I-e) with an epoxide of formula (XXV)

15



wherein R^{12} represents hydrogen, C_{1-4} alkyl, or a radical of formula R^6-O-CH_2- , in a reaction-inert solvent, thus yielding a compound of formula (I-d-10)

20



and, if desired, converting the compounds of formula (I) into each other following art-known functional group transformation reactions, and further, if desired, converting the compounds of formula (I) into a therapeutically active non-toxic addition salt form by treatment with an acid or a base; or conversely, converting the salt into the free base or acid with alkali, respectively acid, and/or preparing stereochemically isomeric forms thereof.

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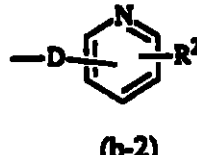
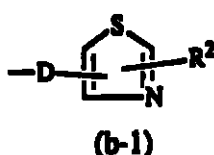
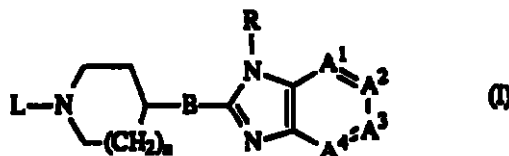
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(51) International Patent Classification ⁵ : C07D 513/04, 401/14, 401/04 C07D 519/00, 473/40 A61K 31/505, 31/425 C07D 417/14, 471/04, 473/00 C07D 473/30, A61K 31/52	A1	(11) International Publication Number: WO 92/01697 (43) International Publication Date: 6 February 1992 (06.02.92)
(21) International Application Number: PCT/EP91/01292 (22) International Filing Date: 9 July 1991 (09.07.91) (30) Priority data: 554,325 19 July 1990 (19.07.90) US (71) Applicant: JANSSEN PHARMACEUTICA NV [BE/BE], Turnhoutseweg 30, B-2340 Beerse (BE). (72) Inventors: JANSSENS, Frans, Eduard, Tinstraat 79, B-2820 Bonheiden (BE). SOMMEN, François, Maria, Langenberg 49, B-2323 Wortel (BE). DIÉLS, Gaston, Stanislas, Marcella, Oostelinde 12, B-2380 Ravels (BE).	(81) Designated States: AT (European patent), AU, BR, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, PL, RO, SD, SE (European patent), SN + (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent). Published With international search report.	

(54) Title: NOVEL SUBSTITUTED THIAZOLYL AND SUBSTITUTED PYRIDINYL DERIVATIVES

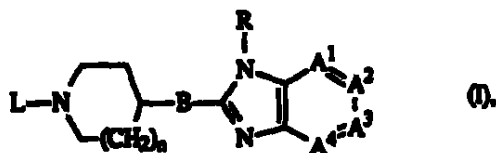


(57) Abstract

Substituted thiazolyl and substituted pyridinyl derivatives of formula (I), the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein $-A^1-A^2-A^3-A^4-$ is a bivalent radical having the formula $-CH=CH-CH=CH-$ (a-1), $-N=CH-CH=CH-$ (a-2), $-CH=N-CH=CH-$ (a-3), $-CH=CH-N=CH-$ (a-4), $-CH=CH-CH=N-$ (a-5), $-N=CH-N=CH-$ (a-6) or $-CH=N-CH=N-$ (a-7), B represents NR^1 , CH_2 , O, S, SO or SO_2 wherein R^1 is hydrogen or C_{1-4} alkyl; R is a radical of formula (b-1) or (b-2), wherein D is C_{1-4} alkanedryl, R^2 is C_{1-4} alkyl, n is 0, 1 or 2, L is hydrogen, C_{1-12} alkyl, C_{3-6} cycloalkyl, C_{3-6} alkenyl optionally substituted with aryl; C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl, arylcarbonyl; aryl C_{1-4} alkyloxycarbonyl; or a radical of formula $-Alk-R^3$ (c-1), $-Alk-Y-R^4$ (c-2), $-Alk-Z^1-C(=X)-Z^2-R^5$ (c-3), or $-CH_2-CHOH-CH_2-O-R^6$ (c-4), have antiallergic properties. Compositions containing the same and methods of treating warm-blooded animals suffering from allergic diseases

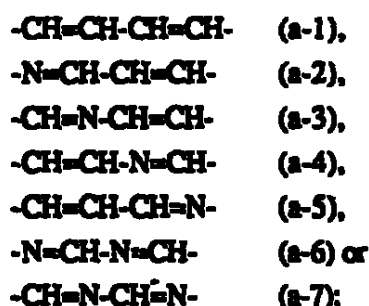
Claims

1. A compound having the formula :



a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein

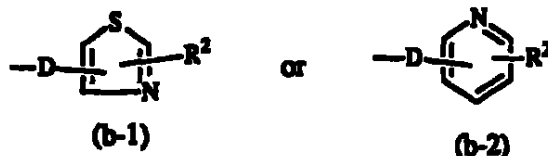
10 $-A^1=A^2-A^3=A^4-$ is a bivalent radical having the formula



20 wherein one or two hydrogen atoms in said radicals (a-1) to (a-7) may each independently be replaced by halo, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy or trifluoromethyl;

B represents NR^1 , CH_2 , O, S, SO or SO_2 wherein R^1 is hydrogen or C_{1-4} alkyl,

25 R is a radical of formula;



wherein D is C_{1-4} alkanediyl;

30 R^2 is C_{1-6} alkyl;

n is 0, 1 or 2;

L is hydrogen; C_{1-12} alkyl; C_{3-6} cycloalkyl; C_{3-6} alkenyl optionally substituted with aryl; C_{1-6} alkylcarbonyl; C_{1-6} alkyloxycarbonyl; arylcarbonyl; aryl C_{1-6} alkyloxycarbonyl; or a radical of formula

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- Alk-R³ (c-1);
 -Alk-Y-R⁴ (c-2);
 -Alk-Z¹-C(=X)-Z²-R⁵ (c-3); or
 -CH₂-CHOH-CH₂-O-R⁶ (c-4); wherein

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R³ is cyano, aryl or Het;

R⁴ is hydrogen, aryl, Het or C₁-alkyl optionally substituted with aryl or Het;

R⁵ is hydrogen, aryl, Het or C₁-alkyl optionally substituted with aryl or Het;

R⁶ is aryl or naphthalenyl;

10 Y is O, S, NR⁷; said R⁷ being hydrogen, C₁-alkyl or C₁-alkylcarbonyl;

Z¹ and Z² each independently are O, S, NR⁸ or a direct bond; said R⁸ being
 hydrogen or C₁-alkyl;

X is O, S or NR⁹; said R⁹ being hydrogen, C₁-alkyl or cyano;
 each Alk independently is C₁-alkanediyl;

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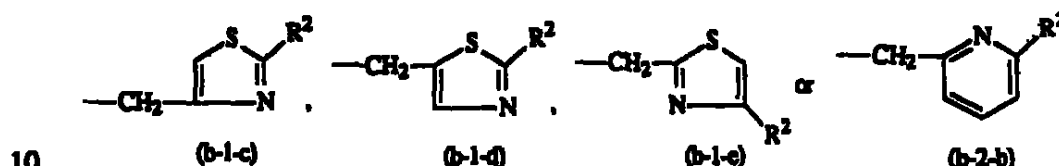
each Het is :

- (i) an optionally substituted five- or six-membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms selected from oxygen, sulfur and nitrogen, provided that no more than 2 oxygen and/or sulfur atoms are present;
- 20 (ii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen, being fused with an optionally substituted five- or six-membered ring through 2 carbon atoms or 1 carbon and 1 nitrogen atom, containing in the remainder of the fused ring only carbon atoms; or
- 25 (iii) an optionally substituted five- or six-membered heterocyclic ring containing 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen, being fused with an optionally substituted five- or six-membered heterocyclic ring through 2 carbon atoms or 1 carbon and 1 nitrogen atom, containing in the remainder of the fused ring 1 or 2 heteroatoms selected from oxygen, sulfur and nitrogen;
- 30 wherein Het being a monocyclic ring system may be optionally substituted with up to 4 substituents; and wherein Het being a bicyclic ring system may be optionally substituted with up to 6 substituents, said substituents being selected from halo, amino, mono- and di(C₁-alkyl)amino, arylC₁-alkylamino, nitro, cyano, aminocarbonyl, C₁-alkyl, C₁-alkyloxy, C₁-alkylthio, C₁-alkyloxycarbonyl, C₁-alkyloxyC₁-alkyl, C₁-alkyloxycarbonylC₁-alkyl, hydroxy, mercapto, hydroxyC₁-alkyl, C₁-alkylcarbonyloxy, aryl, arylC₁-alkyl, carboxyl, C₁-alkylaminocarbonylamino, arylaminocarbonylamino, oxo or thio; and
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each aryl is phenyl optionally substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C₁-alkyl, C₁-alkyloxy, C₁-alkylthio, mercapto, amino, mono- and di(C₁-alkyl)amino, carboxyl, C₁-alkyloxycarbonyl and C₁-alkylcarbonyl

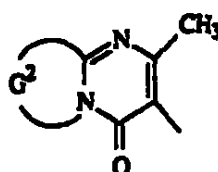
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2. A compound according to claim 1 wherein -A¹=A²-A³=A⁴- represents a bivalent radical of formula -CH=CH-CH=CH- (a-1) or -N=CH-CH=CH- (a-2); B represents NH, CH₂ or O; R represents a radical of formula



R² represents C₁-alkyl; n is 1, L represents hydrogen, C₁-alkyl, C₁-alkyloxycarbonyl or a radical of formula -Alk-R³ (c-1), -Alk-Y-R⁴ (c-2) or -Alk-Z¹-C(=X)-Z²-R⁵ (c-3); Alk represents C₁-alkanediyl, R³ represents phenyl, C₁-alkyloxyphenyl or a radical of formula

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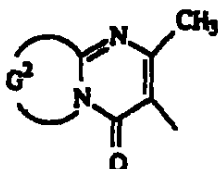


wherein G² represents -CH=CH-CH=CH-, -S-(CH₂)₃-, -S-(CH₂)₂- or -S-CH=CH-, Y represents O or NH; R⁴ represents hydrogen, C₁-alkyl or pyrimidinyl, R⁵ represents C₁-alkyl, Z¹ represents NH; Z² represents O; and X represents O.

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3. A compound according to claim 1 wherein B represents NH or CH₂; R² represents methyl; L represents C₁-alkyl or a radical of formula -Alk-R³ (c-1), -Alk-Y-R⁴ (c-2) or -Alk-Z¹-C(=X)-Z²-R⁵ (c-3); Alk represents C₂-alkanediyl; R³ represents 4-methoxyphenyl or a radical of formula

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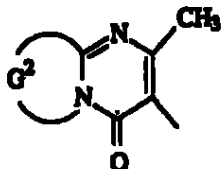


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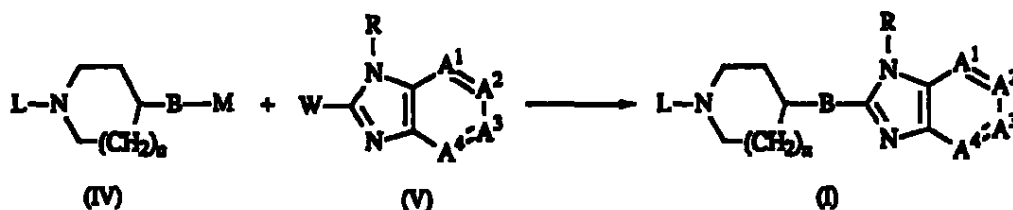
wherein G^2 represents $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{S}-(\text{CH}_2)_3-$, $-\text{S}-(\text{CH}_2)_2-$, $-\text{S}-\text{CH}=\text{CH}-$;
Y represents O or NH; R^4 represents C_{1-4} alkyl or 2-pyrimidinyl.

4. A compound according to claim 1 wherein L represents methyl or a radical of
5 formula $-\text{Alk}-\text{R}^3$ (c-1), Alk represents 1,2-ethanediyl and R^3 represents 4-methoxy-phenyl or a radical of formula



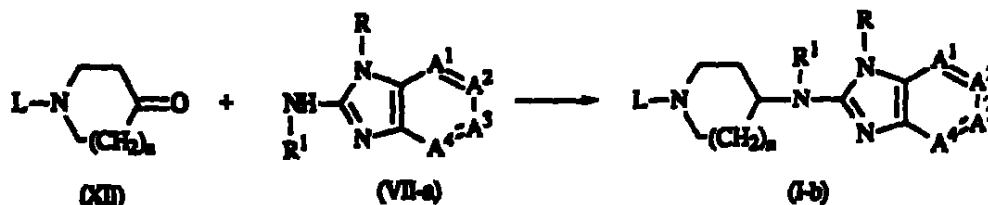
- 10 wherein G^2 represents $\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{S}-(\text{CH}_2)_3-$, $-\text{S}-(\text{CH}_2)_2-$ or $-\text{S}-\text{CH}=\text{CH}-$.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and
as active ingredient an effective antiallergic amount of a compound as claimed in claim 1.
- 15 6. A process for preparing a pharmaceutical composition as claimed in claim 5,
characterized in that a therapeutically effective amount of a compound as claimed in any
of claims 1 to 4 is intimately mixed with a pharmaceutically acceptable carrier.
7. A compound as claimed in any of claims 1 to 4 for use as a medicine.
- 20 8. A process of preparing a compound as claimed in claim 1, characterized by
- a) reacting a piperidine of formula (IV) wherein M represents hydrogen when B is
other than hydrogen, or wherein M represents an alkali or earth alkaline metal when B
25 represents CH_2 , with a reagent of formula (V) wherein W represents a reactive leaving
group,



- 30 in a reaction-inert solvent, optionally in the presence of a base;

b) reductively N-alkylating a 4-piperidinone derivative of formula (XII) with an amine of formula (VII-a),

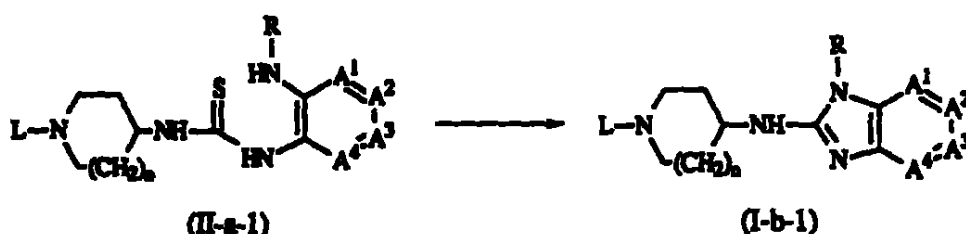


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in the presence of an appropriate reductant in a reaction-inert solvent, thus yielding a compound of formula (I-b);

c) cyclodesulfurizing a thiourea of formula (II-a-1),

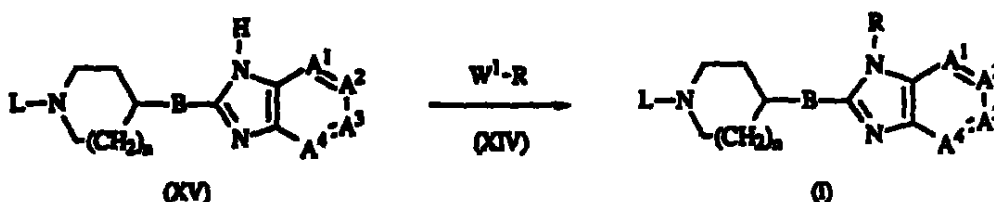
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by reaction with a metal oxide or salt in a reaction-inert solvent, optionally in the presence of a small amount of sulfur;

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d) N-alkylating an intermediate of formula (XV) with an alkylating reagent of formula (XIV) wherein W represents a reactive leaving group,



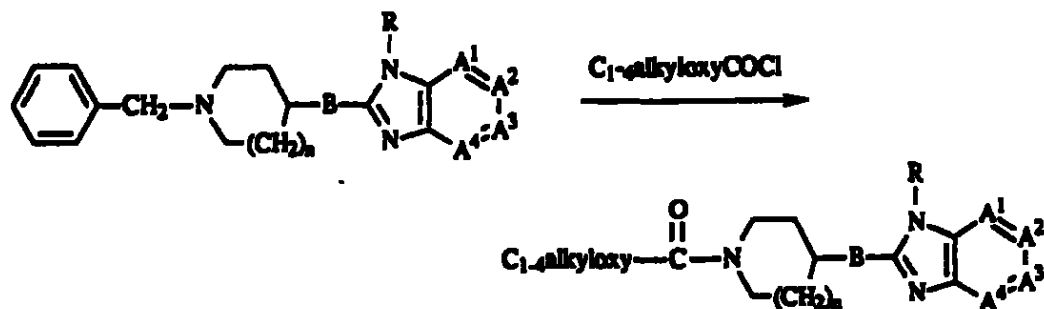
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in a reaction-inert solvent in the presence of a base and at an elevated temperature;

e) converting a compound of formula (I) wherein L represents benzyl into a compound wherein L represents C₁₋₄alkyloxycarbonyl,

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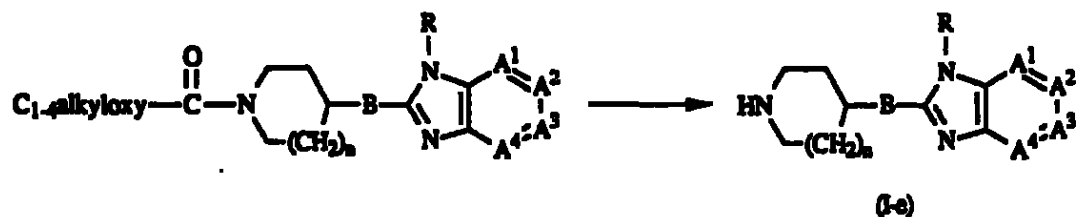
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by reaction with a $\text{C}_1\text{-}_4$ alkylchloroformate in the presence of a base in a reaction-inert solvent;

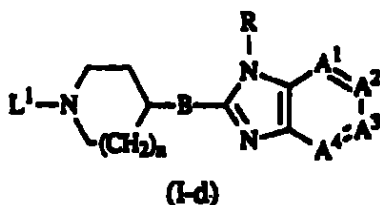
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f) hydrolyzing a compound of formula (I) wherein L represents $\text{C}_1\text{-}_4$ alkyloxy-carbonyl in an aqueous acidic or basic medium to a compound of formula (I-e),



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g) N-alkylating a compound of formula (I-e) with an alkylating reagent of formula $\text{L}^1\text{-W}^1$ (XVI) in a reaction-inert solvent in the presence of a base, thus preparing a compound of formula



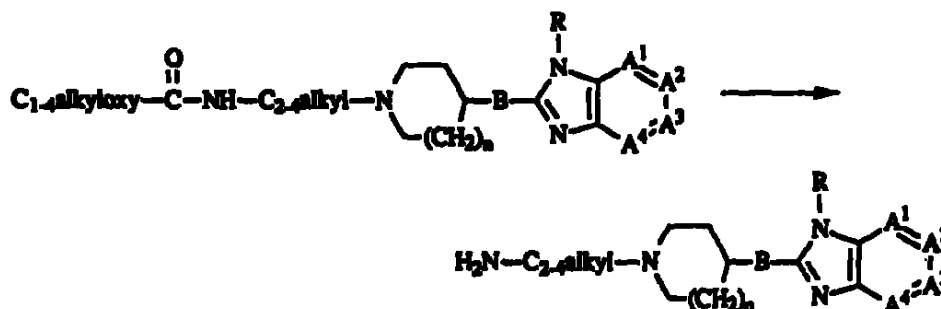
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h) reductively N-alkylating a compound of formula (I) with an aldehyde or ketone of formula $\text{L}^2\text{-O}$ (XVII) wherein L^2 represents a geminal bivalent radical comprising $\text{C}_3\text{-}_6$ cycloalkylidene, $\text{C}_1\text{-}_12$ alkylidene, $\text{R}^3\text{-C}_1\text{-}_6$ alkylidene, $\text{R}^4\text{-Y-C}_1\text{-}_6$ alkylidene or $\text{R}^5\text{-Z}^2\text{-C(=X)-Z}^1\text{-C}_1\text{-}_6$ alkylidene,

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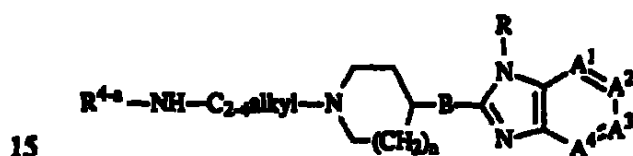


- 5 I) hydrolyzing a compound of formula (I) wherein L represents C₁₋₄alkyloxy-carbonylaminoC₂₋₄alkyl in a basic aqueous medium thus yielding a compound wherein L represents an aminoC₂₋₄alkyl radical.

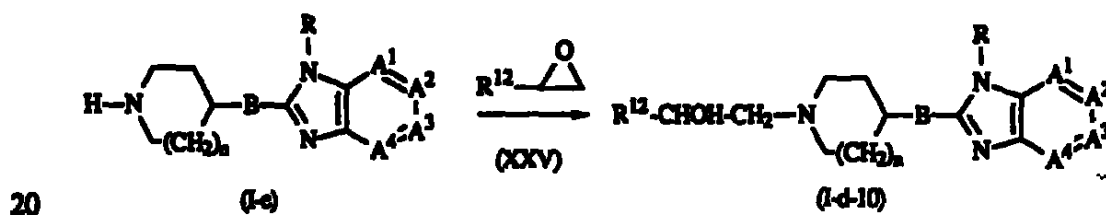


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- j) alkylating the thus obtained compound wherein L represents aminoC₂₋₄alkyl with a reagent of formula R^{4-a}-W¹ wherein R^{4-a} represents aryl or Het and W¹ represents a reactive leaving group thus yielding a compound of formula



- k) reacting a compound of formula (I-c) with an epoxide of formula (XXV) wherein R^{12} represents hydrogen, C_{1-4} alkyl or R^6-O-CH_2- ,



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in a reaction-inert solvent; and, if desired, converting the compounds of formula (I) into a salt form by treatment with a pharmaceutically acceptable acid or conversely, converting the salt form into the free base by treatment with alkali; and/or preparing stereochemically isomeric forms thereof.

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