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SUPERINDUSTRIA Y COMERCIO
Radicacion : 02347290 02310231 Folios: 10
Fecha (AMD): 2004-10-22 16:35:02
Tramite : 002 PATENTES D 332 PRESENTAC 329 COMPLEMEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Señor

SUPERINTENDENTE DE INDUSTRIA Y COM

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 reconocerme 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 parágrafo 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; 325

(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.**, una 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 creyeren 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

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 Bogota, 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 of any power of attorney by any one of them conferred in our name, before the Office of Industrial Property.

Given and signed this

COMO NOTARIO DIECISEIS DEL CIRCULO DE BOGOTA D.C. DOY FE QUE HE TENIDO A LA VISTA EL ORIGINAL
05 OCT 2004
JUAN MANUEL BOTERO MEDINA
NOTARIO

NOTARY SHOULD EXECUTE OTHER SIDE

LUC QUAGHEBEUR
PROXY HOLDER

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**, legalmento 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

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Beerse

On this day of , 200 , 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 echtverklaring van de handtekening van Luc Quaghebeur

Vosselaar, de 24/8/2004

Vu par nous, Jozef COPPENS, notaire, résident à B-2350 Vosselaar, Belgique, pour certification de la signature de Luc Quaghebeur

Vosselaar, le 24/8/2004

Jozef COPPENS Notaris te VOSSELAAR

05 OCT 2004

JUAN MANUEL SOTERO MEDINA
NOTARIO

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 Overheidsdiens Buitenlandse Zaken, Buitenlandse Handel en Ontwikkelingssamenwerking
8. Onder nr.: **980504083126756O**
9. Zegel/Stempel
10. Ondertekening: C. Melard

3

RECHTBANK VAN KOOPHANDEL

AKTEN VAN ONDERNEMINGEN
NIEUWE KAAI 41 - 2300 TURNHOUT

GETUIGSCHRIFT VAN INSCHRIJVING

KOST:30.00 euro Rep.nr.2004.00307 ROR.426

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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 2340 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 produkten, alsmede medische, veterinaire, hospitaal- en laboratotariumbenodigdheden, van electronische apparatuur en hun onderdelen, waaronder begrepen computers, bestemd voor commerciële, financiële en industriële ondernemingen, van textielwaren, voedingswaren, plastiekwaren 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 octrooien 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.tien november negentienhonderd zevenenzestig.
Tot bestuurders van de vennootschap werden benoemd :
Collier Dirk, geboren op 16.02.1956, wonende te Fazantenlaan 20, B-2610 Wilrijk
De Chaffoy de Courcelles Didier, geboren op 19.11.1952, wonende te Karel van Nyenlaan 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 Mussenburglei 120, B-2650 Edegem
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, geboen op 02.10.1945, wonende te Populierenlaan 14, B-2460 Kasterlee
Van Waeyenberge 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

RECHTBANK VAN KOOPHANDEL - TURNHOUT - GEN RAAKT MAAKT MACHTIG

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
05 OCT 2004
JUAN MANUEL BOTERO MEDINA
NOTARIO

Wij, G.Somers, Rechter wnd. 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

RECHTBANK VAN KOOPHANDEL - TURNHOUT - GEN RAAKT MAAKT MACHTIG

de wnd. Voorzitter
G.Somers

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Traducción oficial Nr 0465/04 del holandés al español por Sylvia E. van Uden, traductora oficial

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: 980504(831267560
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 PEREZ
TRADUCTOR E INTERPRETE
OFICIAL
RESOLUCION No. 1116
MINJUSTICIA 1995

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL DOCUMENTO QUE HE TENIDO A LA VISTA
05 OCT 2004
JUAN MANUEL GUTIERREZ MEDINA
NOTARIO

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Traducción oficial Nr 0464/04 del holandés al español por Sylvia E. van Uden, traductora oficial

JUZGADO DE COMERCIO

Acta de empresas

Nieuwe Kaai 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 transacciones 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

COMO NOTARIO SEXTO DE BOGOTA, HAGO CONSTAR QUE HE TENIDO A ... 05 OCT 2004 JUAN MANUEL BOTERO MEJIA

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

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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

COMO NOTARIO SEXTO DE BOGOTA, HAGO CONSTAR QUE HE TENIDO A LA VISTA EL PRESENTE DOCUMENTO

05 OCT 2004

JUAN MANUEL [illegible]
NOTARIO

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

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

05 OCT 2004

JUAN MANUEL GUTIERREZ MEDINA
NOTARIO

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375.
2006|03|18

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C., 28 de febrero de 2006

Apoderado: Alicia Lloreda Ricaurte Oficio: 3193

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:

◆capitulo descriptivo, folios 05 a 121;
◆capitulo 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 capitulo reivindicatorio, folios 151 a 270;
◆2° examen de forma, folio 325;
◆solicitud del examen de patentabilidad 328 y 329.

Objeto de la invención:

El titulo 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)-3*H*-imidazo[4,5-*b*]piridine-2-aminoderivado o amidoderivado; 1-(heterociclo)-1*H*-benzimidazol-2-aminoderivado ó amidoderivado; 3-(heterociclo)-3*H*-imidazo[4,5-*c*]piridine-2- aminoderivado ó amidoderivado; 1-(hetrociclo)-1*H*-imidazo[4,5-*c*]piridine-2- aminoderivado ó amidoderivado; 1-(heterociclo)-1*H*-imidazo[4,5-*b*]piridine-2-carboxamide, con una amplia gama de variación del significado de cada uno los sustituyentes.

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	Titulo
D1	EP0099139	25-enero-1984	Novel N-(bicyclyc 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	Bicyclyc heterocyclyl containing N-(bicyclyc heterocyclyl)-4-piperidinamines.
D4	EP0145037	19-junio-1984	Five membered heterocyclic ring containig N-(bicyclyc heterocyclyl)-4-piperidinamines.
D5	EP0151824	21-agosto-1985	N-(4-piperidinyl)bicyclyc 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)bicyclyc 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

D11	EP0393738	24-octubre-1990	Hydroxyalkiylfuranyl 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 de rivados derivdos de 3(heterociclo)-3*H*-imidazo[4,5-*b*]piridine-2-aminoderivado o amidoderivado; 1-(heterociclo)-1*H*-benzimidazol-2-aminoderivado ó amidoderivado; 3-(heterociclo)-3*H*-imidazo[4,5-*c*]piridine-2- aminoderivado ó amidoderivado; 1-(hetrociclo)-1*H*-imidazo[4,5-*c*]piridine-2- aminoderivado ó amidoderivado; 1-(heterociclo)-1*H*-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 derivdos de 3(heterociclo)-3*H*-imidazo[4,5-*b*]piridine-2-aminoderivado o amidoderivado; 1-(heterociclo)-1*H*-benzimidazol-2-aminoderivado ó amidoderivado; 3-(heterociclo)-3*H*-imidazo[4,5-*c*]piridine-2- aminoderivado ó amidoderivado; 1-(hetrociclo)-1*H*-imidazo[4,5-*c*]piridine-2- aminoderivado ó amidoderivado; 1-(heterociclo)-1*H*-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 bioisostericos que están sustituidos en la posición 2- con una derivado amino que puede ser 4-piperidina, via una amina y también sustituido en la posición 4 con un hertéciclil, 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 rehuso 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

347
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D1

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A2

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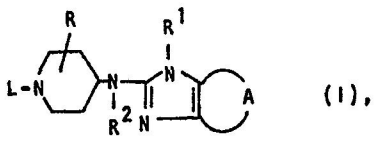
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(54) Novel N-(bicyclic heterocyclyl)-4-piperidinamines.

(57) Novel *N*-(bicyclic heterocyclyl)-4-piperidinamines of the formula



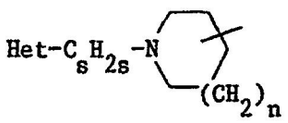
(I),

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.

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a radical of formula

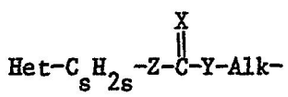


(f);

a radical of formula

$$Het\text{-}C_sH_{2s}\text{-}Y\text{-}Alk\text{-} \qquad (g);$$ and

a radical of formula



(h),

wherein n is 0 or the integer 1 or 2;

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

Alk is lower alkanediyl;

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

X is O, S, $CH\text{-}NO_2$ or NR^4;

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

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

said R^3 being hydrogen, lower alkyl, (Ar^2)lower alkyl, 2-lower alkyloxy-1,2-dioxoethyl or a radical of formula $-C(=X)-R^6$, R^6 being hydrogen, lower alkyl, Ar^2, Ar^2-lower alkyl, lower alkyloxy, Ar^2-lower alkyloxy, mono- or di(lower alkyl)amino, Ar^2-lower alkylamino or Ar^2-lower alkyl(lower alkyl)amino;

said R^4 being hydrogen, lower alkyl, cyano, nitro, Ar^2-sulfonyl, lower alkylsulfonyl, lower alkylcarbonyl or Ar^2-carbonyl; and

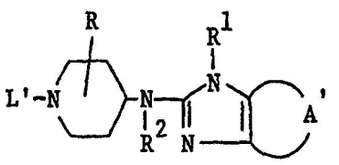
said R^5 being hydrogen or lower alkyl;

provided that Het is other than pyridinyl or mono- or di(lower alkyloxy)pyridinyl where L is a radical (g) wherein Y is NR^3 or where L is a radical (h) wherein X is O and Z is NR^5 or a direct bond;

wherein Ar^1 is a member selected from the group consisting of phenyl, being optionally substituted with up to three substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl and (lower alkyl)-CO-; thienyl; halothienyl; furanyl; lower alkyl substituted furanyl; pyridinyl; pyrazinyl; thiazolyl and imidazolyl optionally substituted by lower alkyl; and wherein Ar^2 is a member selected from the group consisting of phenyl being optionally substituted with up to three substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl and (lower alkyl)-CO.

2. A chemical compound according to claim 1 wherein Het is a member selected from the group consisting of a pyridinyl radical which is optionally substituted with one or two substituents each independently selected from the group consisting of halo, amino, nitro, cyano, aminocarbonyl, lower alkyl, lower alkyloxy, lower alkylthio, lower alkyloxycarbonyl, hydroxy, lower alkylcarbonyloxy, Ar^2-lower alkyl and carboxyl; a pyridinyloxide radical optionally substituted with nitro, a quinolinyl radical which is optionally substituted with a lower alkyl radical; a pyrimidinyl radical which is optionally substituted with one or two substituents each independently selected from the group consisting of halo, amino, hydroxy, lower alkyl, lower alkyloxy, lower alkylthio and (Ar^2)-lower alkyl; a quinazolinyl radical which is optionally substituted with a hydroxy radical or a lower alkyl radical; a pyridazinyl radical which is optionally substituted with a lower

11. A chemical compound having the formula



(XVIII),

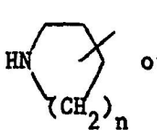
a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein:

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;

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- and Ar^2-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, NR^3 or a direct bond;
Y' is O, S or NR^3;

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

Z' is O, S, or NR^5 ;

said R^3 being hydrogen, lower alkyl, (Ar^2)lower alkyl, 2-lower alkyloxy-1,2-dioxoethyl or a radical of formula $-C(=X)-R^6$, R^6 being hydrogen, lower alkyl, Ar^2, Ar^2-lower alkyl, lower alkyloxy, Ar^2-lower alkyloxy, mono- or di(lower alkyl)amino, Ar^2-lower alkylamino or Ar^2-lower alkyl(lower alkyl)amino;

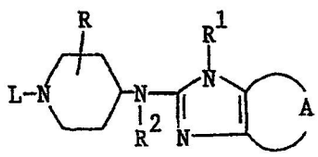
said R^4 being hydrogen, lower alkyl, cyano, nitro, Ar^2-sulfonyl, lower alkylsulfonyl, lower alkylcarbonyl or Ar^2-carbonyl; and

said R^5 being hydrogen or lower alkyl;

wherein Ar^1 is a member selected from the group consisting of phenyl, being optionally substituted with up to three substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl and (lower alkyl)-CO-; thienyl; halothienyl; furanyl; lower alkyl substituted furanyl; pyridinyl; pyrazinyl; thiazolyl and imidazolyl optionally substituted by lower alkyl; and wherein Ar^2 is a member selected from the group consisting of phenyl being optionally substituted with up to three substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl and (lower alkyl)-CO.

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

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



(I),

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

A is a bivalent radical having the formula

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

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

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

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

-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;

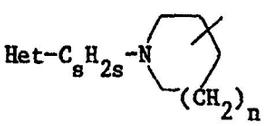
R is a member selected from the group consisting of hydrogen and lower alkyl;

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- and Ar^2-lower alkyl;

L is a member selected from the group consisting of

a radical of formula



(f);

a radical of formula

Het-C_sH_{2s}-Y-Alk- (g); and

a radical of formula

$$Het\text{-}C_sH_{2s}\text{-}Z\text{-}\overset{\overset{X}{\|}}{C}\text{-}Y\text{-}Alk\text{-} \qquad (h),$$

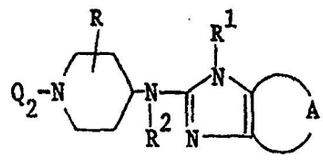
wherein n is 0 or the integer 1 or 2;
s is 0 or an integer of from 1 to 6 inclusive;
Alk is lower alkanediyl;
Y is O, S, NR^3 or a direct bond;
X is O, S, $CH\text{-}NO_2$ or NR^4;
Z is O, S, NR^5 or a direct bond; and
Het is an optionally substituted 6-membered heterocyclic ring having at least one nitrogen atom and being optionally condensed with an optionally substituted benzene ring, said Het being connected to C_sH_{2s} on a carbon atom;

said R^3 being hydrogen, lower alkyl, (Ar^2)lower alkyl, 2-lower alkyloxy-1,2-dioxoethyl or a radical of formula $-C(=X)-R^6$, R^6 being hydrogen, lower alkyl, Ar^2, Ar^2-lower alkyl, lower alkyloxy, Ar^2-lower alkyloxy, mono- or di(lower alkyl)amino, Ar^2-lower alkylamino or Ar^2-lower alkyl(lower alkyl)amino;
said R^4 being hydrogen, lower alkyl, cyano, nitro, Ar^2-sulfonyl, lower alkylsulfonyl, lower alkylcarbonyl or Ar^2-carbonyl; and
said R^5 being hydrogen or lower alkyl;
provided that Het is other than pyridinyl or mono- or di(lower alkyloxy)pyridinyl where L is a radical (g) wherein Y is NR^3 or where L is a radical (h) wherein X is O and Z is NR^5 or a direct bond;

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

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

a) alkylating a piperidine of formula



(III)

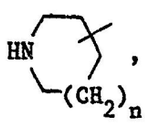
with an intermediate of formula

$$Het\text{-}Q_1 \qquad (II)$$

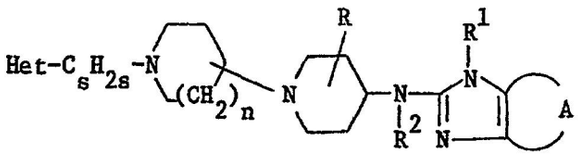
in a reaction-inert solvent

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

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

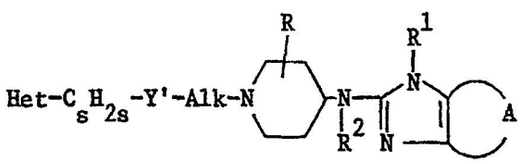


thus preparing a compound of formula



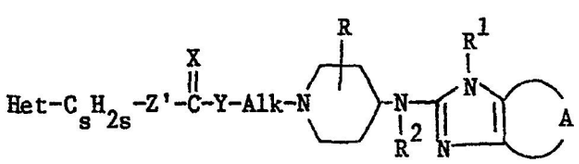
(I-a-1); or

3) Q_1 is a radical of formula $-C_sH_{2s}-W'$ and Q_2 is a radical of formula HY'-Alk-, said Y' having the previously defined meaning of Y provided that Y is other than a direct bond, thus preparing a compound of formula



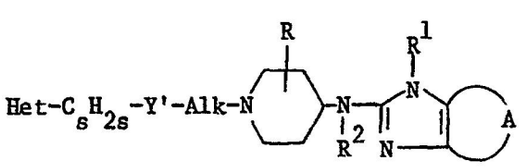
(I-a-2); or

4) Q_1 is a radical of formula $-C_sH_{2s}-W'$ and Q_2 is a radical of formula HZ'-C(X)-Y-Alk-, said Z' having the previously defined meaning of Z provided that Z is other than a direct bond, thus preparing a compound of formula



(I-a-3); or

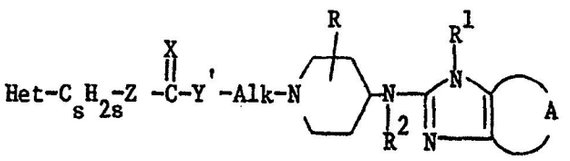
5) Q_1 is a radical of formula $-C_sH_{2s}-Y'H$ and Q_2 is a radical of formula W-Alk-, thus preparing a compound of formula



(I-a-2); or

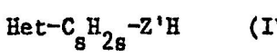
6) Q_1 is a radical of formula $-C_sH_{2s}-Z-C(X)-Y'H$ and

Q_2 is a radical of formula W-Alk, thus preparing a compound of formula



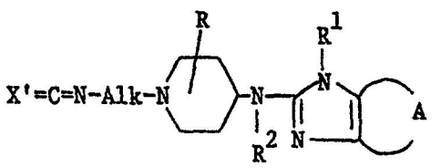
(I-a-4); or

b) reacting an intermediate of formula



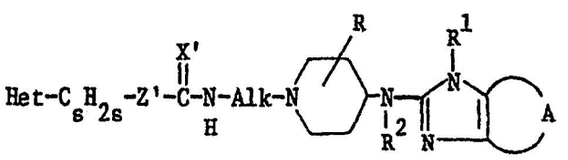
(IV)

with a piperidine of formula



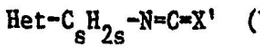
(V)

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



(I-b-1); or

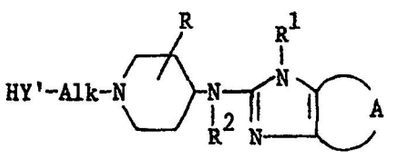
c) reacting an intermediate of formula



(VI)

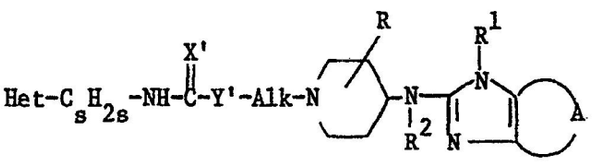
said X' being O or S,

with a piperidine of formula



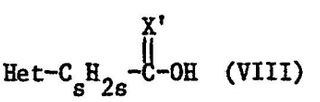
(VII)

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



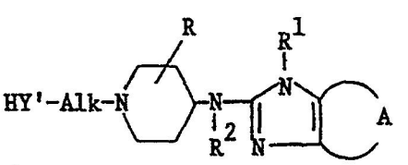
(I-b-2); or

106 d) reacting an intermediate of formula



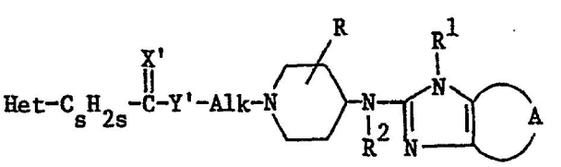
107 (VIII)

108 with a piperidine of formula



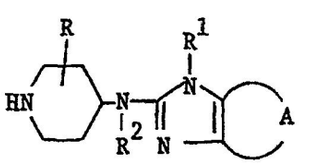
(VII)

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

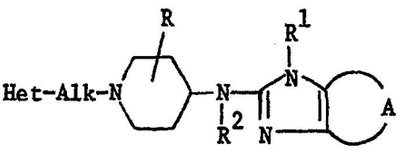


(III-a)

113 with a reagent of formula

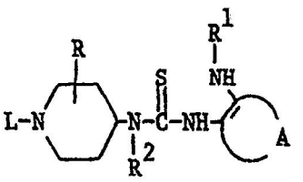
Het-lower alkanediyl-H (IX)

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



(I-d); or

f) cyclodesulfurizing an intermediate of formula



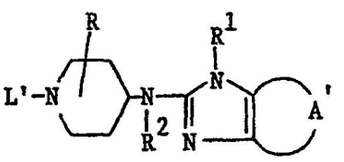
(X)

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

14. A process for preparing a chemical compound selected from the group consisting of 1-[(4-fluorophenyl)methyl]-N-[1-[2-[(2-pyrimidinyl)amino]ethyl]-4-piperidinyl]-1H-benzimidazol-2-amine or a pharmaceutically acceptable acid-addition salt thereof, characterized by reacting N-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-amine or a pharmaceutically acceptable acid-addition salt thereof with 2-chloropyrimidine in a suitable reaction-inert solvent; and, if desired, converting the compounds of formula (I) into the 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.

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



(XVIII),

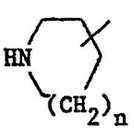
a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein:

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;

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- and Ar^2-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, NR^3 or a direct bond;

Y' is O, S or NR^3;

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

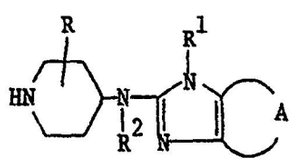
Z' is O, S, or NR^5 ;

said R^3 being hydrogen, lower alkyl, (Ar^2)lower alkyl, 2-lower alkyloxy-1,2-dioxoethyl or a radical of formula -C(=X)-R^6, R^6 being hydrogen, lower alkyl, Ar^2, Ar^2-lower alkyl, lower alkyloxy, Ar^2-lower alkyloxy, mono- or di(lower alkyl)amino, Ar^2-lower alkylamino or Ar^2-lower alkyl(lower alkyl)amino;

said R^4 being hydrogen, lower alkyl, cyano, nitro, Ar^2-sulfonyl, lower alkylsulfonyl, lower alkylcarbonyl or Ar^2-carbonyl; and

said R^5 being hydrogen or lower alkyl;

wherein Ar^1 is a member selected from the group consisting of phenyl, being optionally substituted with up to three substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl and (lower alkyl)-CO-; thienyl; halothienyl; furanyl; lower alkyl substituted furanyl; pyridinyl; pyrazinyl; thiazolyl and imidazolyl optionally substituted by lower alkyl; and wherein Ar^2 is a member selected from the group consisting of phenyl being optionally substituted with up to three substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl and (lower alkyl)-CO characterized by N-alkylating a piperidine of formula



(III-a)

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

converting the compounds of formula (I) into the 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.

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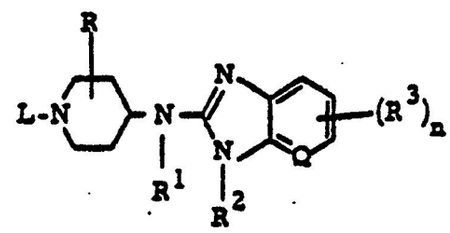
(54) **N-Heterocyclyl-4-piperidinamines, methods for their preparation and pharmaceutical compositions comprising them.**

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

EP 0 005 318 A1

Claims:

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



(I)

and the pharmaceutically acceptable acid addition salts thereof, wherein

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;

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 and 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

L 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, isothiocyanato, lower alkyloxy, 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 of the formula Z-C_mH_{2m}-, wherein

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

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-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; 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

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-$\overset{O}{\overset{\|}{C}}$-$(X)_s$-, wherein

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 aroyl; and

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;

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 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

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 alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 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 alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 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 alkyloxy; and
wherein said aroyl in the definition of said X represents arylcarbonyl
wherein said aryl is as defined hereabove.

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.

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.

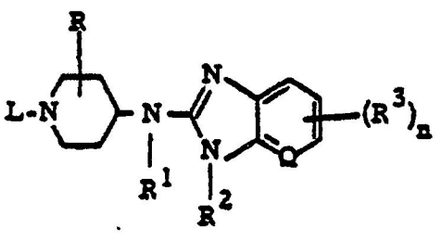
4. A chemical compound selected from the group consisting of {4-[2-{4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinyl}ethyl]phenyl} benzeneacetate and the pharmaceutically acceptable acid addition salts thereof.

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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.

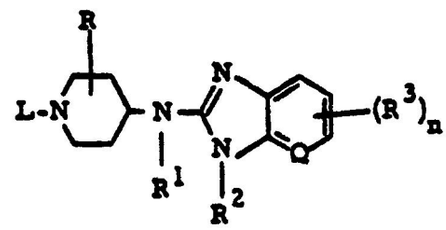
7. An antihistaminic pharmaceutical composition comprising an inert carrier material and as an active ingredient an effective antihistaminic amount of a chemical compound selected from the group consisting of a N-heterocyclyl-4-piperidinamine having the formula



(I)

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

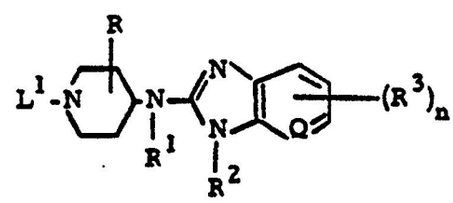
8. A method to prevent the release of histamine in warmblooded animals, which comprises the systemic administration to said animals of an effective anti-histaminic amount of a chemical compound selected from the group consisting of a N-heterocyclyl-4-piperidinamine having the formula



(I)

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 alkyloxycarbonyl and phenylmethoxy-carbonyl;
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;

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 alkylsulfonyllower alkyl, phenyllower alkylsulfonyl, phenylsulfonyllower alkyl, amino, mono- and di-(lower alkyl)amino, lower alkanoyl, a radical of the formula $R^6-C_pH_{2p}-O-$, wherein

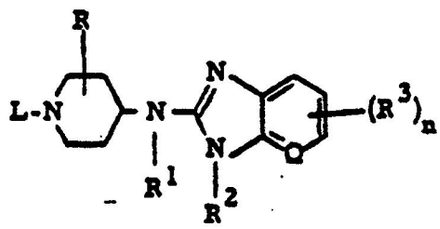
p is an integer of from 1 to 6 inclusive; and

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

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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 alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 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



(I)

and the pharmaceutically acceptable acid addition salts thereof, wherein
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;
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 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 CH and N; and
L 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, isothiocycanato, lower alkyloxy, 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 of the formula Z-C_mH_{2m}-, wherein

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

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-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; 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

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 $W\text{-}\overset{O}{\overset{\|}{C}}\text{-}(X)_s\text{-}$, wherein

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 aroyl; and

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;

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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 alkylsulfonyl-lower alkyl, phenyllower alkylsulfonyl, phenylsulfonyl-lower alkyl, amino, mono- and di-(lower alkyl)amino, lower alkanoyl, a radical of the formula $R^6\text{-}C_pH_{2p}\text{-}O\text{-}$, wherein

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

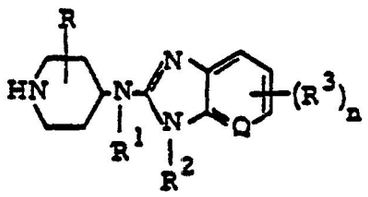
R^6 is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, lower alkenyl; and

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 alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 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 alkyloxy; and wherein said aroyl in the definition of said X represents arylcarbonyl wherein said aryl is as defined hereabove, characterized by

a) introducing onto a starting material of the formula



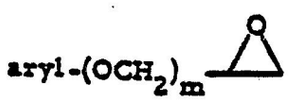
(II)

wherein R, R^1, R^2, R^3, n and Q are as previously defined, the desired L-substituent onto the piperidine nitrogen by the application of art-known methods;

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-methyl-ethenyl 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);

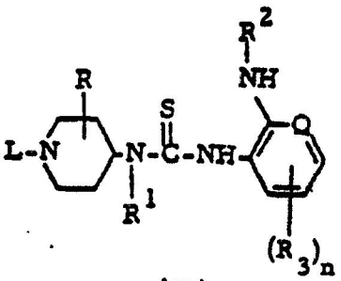
v) when L is, at the point of attachment to the piperidine nitrogen atom, a primary or secondary alkyl group, the compounds (I) may also be prepared by the reductive amination of an aldehyde or ketone corresponding with the alcohol L-OH with a piperidine derivative of formula (II) following art-known 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 susceptable 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 $Z\text{-}C_mH_{2m}\text{-}$, wherein m is an integer of from 2 to 6 inclusive and wherein Z is as previously defined, the compounds of formula (I) can also be prepared by the reaction of (II) with an appropriate alkenyl derivative. $Z\text{-}C_mH_{2m-1}$

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

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

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



(V)

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

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)

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

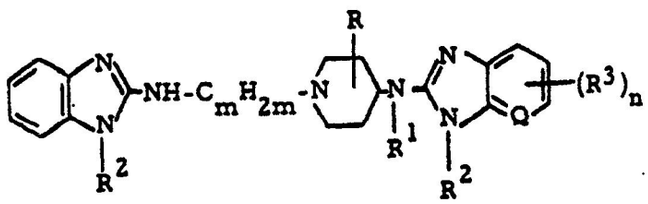
iii) utilizing methanediimines, especially N,N'-methanetetraylbis[cyclo-hexanamine] as cyclodesulfurizing agents in suitable reaction-inert organic solvents; or

c) preparing compounds of formula (I) wherein R^2 is other than hydrogen, said R^2 being represented by R^2_a 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^2_a according to art-known procedures;

i) preferably said compound (I-b) is reacted with an appropriate reactive ester R^2_aY, (VI), wherein R^2_a 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) as described in step a) i); or

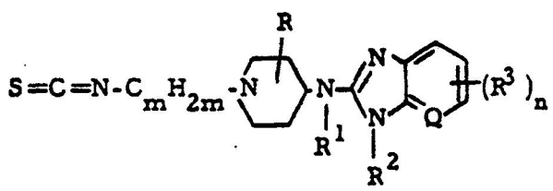
d) preparing compounds of the formula (I) wherein R^1 and R^2 are both different from hydrogen, said R^1 being represented by R^1_a and said R^2 by R^2_a, from the corresponding compounds wherein R^1 is hydrogen by introducing the R^1_a- group in a similar manner as described hereinabove in step c) for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

e) preparing a compound of the formula



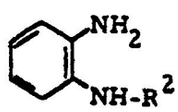
(I-c)

by subjecting an isothiocyanate of the formula



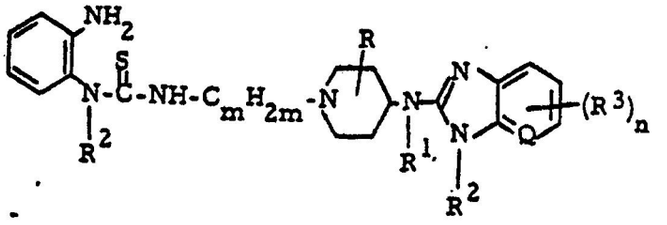
(VII)

to an addition reaction with a benzene diamine of the formula



(VIII)

and subsequently cyclodesulfurizing the intermediately formed thiourea of the formula



(IX)

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

f) preparing compounds of formula (I) wherein L represents a radical $Z\text{-}C_mH_{2m}$-, wherein Z represents a radical of the formula $W\text{-}CO\text{-}(X)_s$-, 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 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

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 said hydroxyl-derivatives from the corresponding lower alkyloxy substituted analogs by hydrolyzing the latter in acidic medium, using for example hydrogen bromide in acetic acid, and, if desired, said hydroxyl-sub-

stituted compounds may in turn be O-alkylated or acylated by reacting the latter with a halide, an alkanoyl halide, an alkyloxycarbonyl halide, or an isocyanate, or said hydroxyl-substituted compounds may 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 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

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

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

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 oxydizing agent; and, if desired, converting the compounds of formula (I) to the therapeutically active non-toxic acid addition salt

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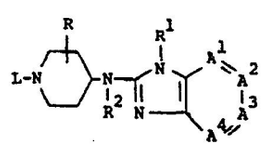
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(54) **Bicyclic heterocyclyl containing N-(bicyclic heterocyclyl)-4-piperidinamines.**

(57) Novel *N*-heterocyclyl-4-piperidinamines of the formula



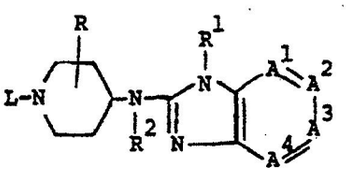
(I),

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.

EP 0 144 101 A2

CLAIMS

1. A chemical compound having the formula



(I),

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

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

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

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

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

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

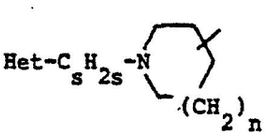
wherein one or two hydrogen atoms in said radicals (a) - (e) may, each independently from each other, be replaced by halo, lower alkyl, lower alkyloxy, trifluoromethyl or hydroxy;

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

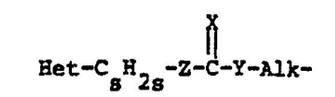


(f);

a radical of formula

Het-C_sH_{2s}-Y-Alk- (g); and

a radical of formula



(h),

wherein n is 0 or the integer 1 or 2;
s is 0 or an integer of from 1 to 6 inclusive;
Alk is lower alkanediyl;
Y is O, S, NR^3 or a direct bond;
X is O, S, $CH-NO_2$ or NR^4;
Z is O, S, NR^5 or a direct bond; and
Het is an optionally substituted five- or six-membered heterocyclic ring containing at least one nitrogen atom and being condensed with an optionally substituted five- or six-membered ring, provided that:

i) when Het is connected to C_sH_{2s} on a carbon atom then said five- or six-membered ring is not condensed with an optionally substituted benzene ring;

ii) when L is a radical either of formula (f), or of formula (g) wherein Y is other than a direct bond, or of formula (h) wherein Z is other than a direct bond, wherein in said radicals (f), (g) or (h) Het is connected to C_sH_{2s} on a nitrogen atom then s is not 0;

iii) when $A^1=A^2-A^3=A^4$ is a radical of formula (a) or (b) and L is a radical of formula (g) wherein s is 0 and Y is a direct bond then Het is other than a 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl or a 2,3-dihydro-3-oxo-benzoxazin-4-yl radical;

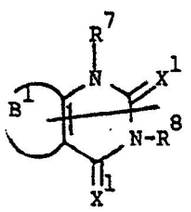
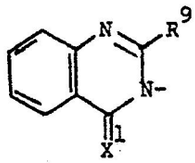
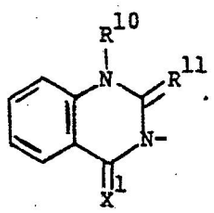
said R^3 being hydrogen, lower alkyl, (Ar^2)lower alkyl, 2-lower alkyloxy-1,2-dioxoethyl or a radical of formula $-C(=X)-R^6$, R^6 being hydrogen, lower alkyl, Ar^2, Ar^2-lower alkyl, lower alkyloxy, Ar^2-lower alkyloxy, mono- or di(lower alkyl)amino, Ar^2-amino, Ar^2-lower alkylamino or Ar^2-lower alkyl(lower alkyl)amino;

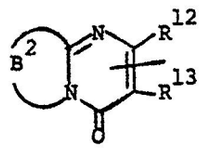
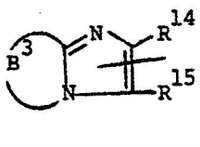
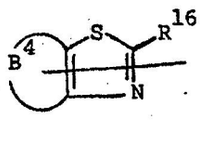
said R^4 being hydrogen, lower alkyl, cyano, nitro, Ar^2-sulfonyl,

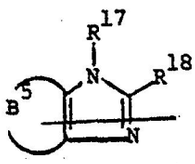
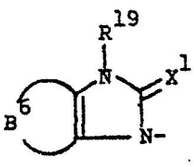
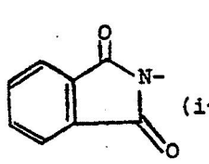
lower alkylsulfonyl, lower alkylcarbonyl or Ar^2-carbonyl; and said R^5 being hydrogen or lower alkyl;

wherein Ar^1 is a member selected from the group consisting of phenyl, being optionally substituted with up to three substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl and lower alkyl-CO-; thienyl; halothienyl; furanyl; lower alkyl substituted furanyl; pyridinyl; pyrazinyl; thiazolyl and imidazolyl optionally substituted by lower alkyl; and wherein Ar^2 is a member selected from the group consisting of phenyl being optionally substituted with up to three substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl and (lower alkyl)-CO.

2. A chemical compound according to claim 1, wherein Het is a member of the group consisting of


(i-1),

(i-2),

(i-3),


(i-4),

(i-5),

(i-6),


(i-7),

(i-8), and

(i-9);

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

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

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

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

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

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

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

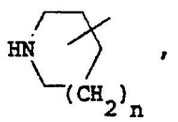
9. A compound as claimed in any one of claims 1 to 4 for use as an anti-allergic medicine.

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

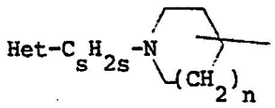
a) alkylating a piperidine of formula Q^2-D (III) with an intermediate of formula Het-Q^1 (II) in a reaction-inert solvent wherein

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

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



thus preparing a compound of formula

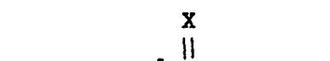


(I-a-1); or

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

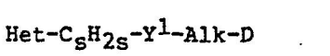
Het-C_sH_{2s}-Y^1-Alk-D (I-a-2); or

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



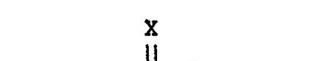
$Het-C_sH_{2s}-Z^1-C(=X)-Y-Alk-D$ (I-a-3); or

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



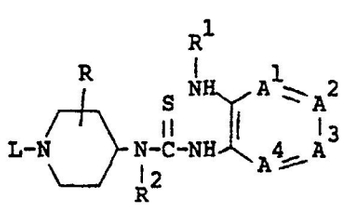
$Het-C_sH_{2s}-Y^1-Alk-D$ (I-a-2); or

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



$Het-C_sH_{2s}-C(=X)-Y^1-Alk-D$ (I-a-4); or

b) cyclodesulfurizing an intermediate of formula



(IV)

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

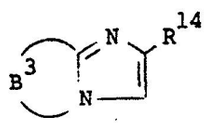
c) reacting an intermediate of formula $Het-C_sH_{2s}-Z^1H$ (V) with a piperidine of formula $X^1=C=N-Alk-D$ (VI) in a suitable reaction-inert solvent, thus preparing a compound of formula $Het-C_sH_{2s}-Z^1-C(X^1)-NH-Alk-D$ (I-b-1); or

d) reacting an intermediate of formula $Het-C_sH_{2s}-N=C=X^1$ (VII), said X^1 being O or S, with a piperidine of formula $HY^1-Alk-D$ (VIII) in a suitable reaction-inert solvent, thus preparing a compound of formula $Het-C_sH_{2s}-NH-C(X^1)-Y^1-Alk-D$ (I-b-2); or

e) reacting an intermediate of formula Het-C_sH_{2s}-$C(X^1)$-OH (IX) with a piperidine of formula HY^1-Alk-D (VIII) in a suitable reaction-inert solvent, if desired, after converting the OH-function in (VIII) in a suitable leaving group, or, if desired, by reacting (IX) with (VIII) together with an appropriate reagent capable of forming amides or esters; thus preparing Het-C_sH_{2s}-$C(X^1)$-Y^1-Alk-D (I-c); or

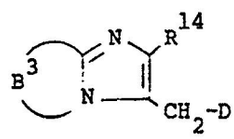
f) reacting a piperidine of formula HD (III-a) with a reagent of formula Het-lower alkenediyl-H (X) in a suitable reaction-inert solvent, thus preparing a compound of formula Het-Alk-D (I-d); or

g) reacting an intermediate of formula HD (III-a) with a reagent of formula



(XI)

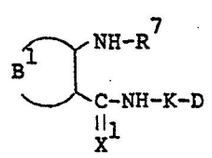
in the presence of formaldehyde or a polymeric form thereof in a suitable solvent, thus preparing a compound of formula



(I-e)

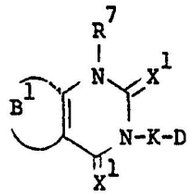
wherein B^3 is -CH=CH-CH=CH-, -CH=N-CH=CH-, $-CH_2$-NH-$(CH_2)_2$-, -S-CH=CH- or -N=CH-CH=CH-; and R^{14} is independently selected from the group consisting of hydrogen, lower alkyl, hydroxy, mercapto, lower alkyloxy, lower alkylthio, halo and (lower alkyloxycarbonyl)-lower alkyl; or

h) reacting an intermediate of formula



(XII)

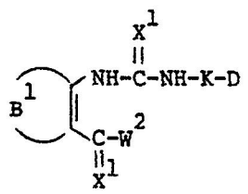
with a $C=X^1$ generating agent in a reaction-inert solvent thus preparing a compound of formula



(I-f-1)

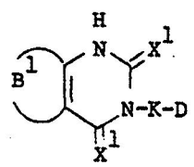
wherein B^1 is -CH=CH-CH=CH-, -S-CH=CH- or -N=CH-NH-; and R^7 is selected from the group consisting of hydrogen, lower alkyl, Ar^2-lower alkyl, hydroxylower alkyl or lower alkyloxycarbonyl; or

i) cyclizing an intermediate of formula



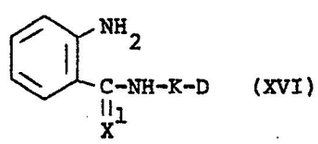
(XIII)

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



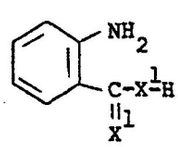
(I-f-1-a); or

j) cyclizing the intermediate of formula



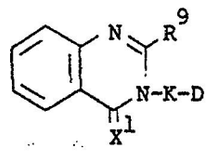
(XVI)

with an acid of formula R^9COOH (XVII) or a functional derivative thereof; or cyclizing an intermediate of formula



(XVIII)

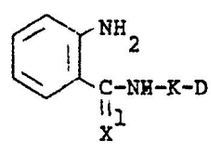
with an atomatic amino acid or -thioacid of the formula $R^9C(O)$-NH-K-D (XIX) in a suitable reaction-inert solvent, thus preparing a compound of formula



(I-f-2)

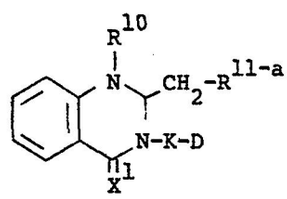
wherein R^9 is selected from the group consisting of hydrogen, lower alkyl, hydroxy, mercapto, lower alkyloxy, lower alkylthio, halo and (lower alkyloxycarbonyl)lower alkyl; or

k) reacting an intermediate of formula



(XVI)

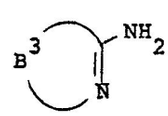
with an acetylene derivative of formula $CH{\equiv}C\text{-}R^{11\text{-}a}$ (XX) in a suitable solvent, thus preparing a compound of formula



(I-f-3)

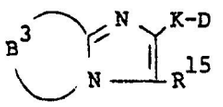
wherein R^{10} is selected from the group consisting of hydrogen, lower alkyl, Ar^2-lower alkyl, hydroxylower alkyl or lower alkyloxycarbonyl; and $R^{11\text{-}a}$ is $(C_{1\text{-}5})$alkyl or (lower alkyloxycarbonyl)$(C_{1\text{-}5})$alkyl; or

l) reacting a reagent of formula



(XXI)

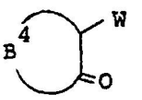
with an intermediate of formula W-CH(R^{15})-C(O)-K-D (XXII) in a suitable reaction-inert solvent thus preparing a compound of formula



(I-f-4)

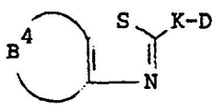
wherein R^{15} is selected from the group consisting of hydrogen, lower alkyl, hydroxy, mercapto, lower alkyloxy, lower alkylthio, halo and (lower alkyloxycarbonyl)lower alkyl; or

m) cyclizing a reagent of formula



(XXIII)

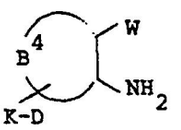
with an intermediate of formula $H_2NC(S)$-K-D (XXIV) in a suitable reaction-inert solvent thus preparing a compound of formula



(I-f-5)

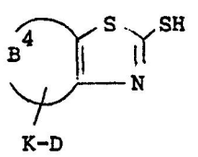
wherein B^4 is $-CH_2-NH-(CH_2)_2-$, -N=CH-CH=CH- or -N=CH-N=CH-; or

n) cyclizing a reagent of formula



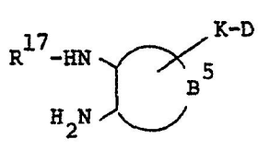
(XXV)

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



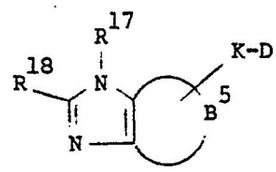
(I-f-6); or

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



(XXVII)

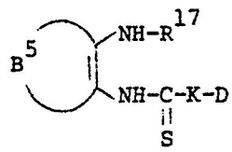
in a suitable reaction-inert solvent thus preparing a compound of formula



(I-f-7)

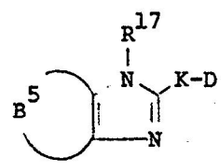
wherein B^5 is -N=CH-CH=CH-, -CH=CH-N=CH- or -CH=N-CH=N-; R^{17} is selected from the group consisting of hydrogen, lower alkyl, Ar^2-lower alkyl, hydroxylower alkyl or lower alkyloxycarbonyl; and R^{18} is selected from the group consisting of hydrogen, lower alkyl, hydroxy, mercapto, lower alkyloxy, lower alkylthio, halo and (lower alkyloxycarbonyl)lower alkyl; or

p) cyclodesulfurizing an intermediate of formula



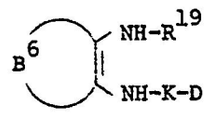
(XXVIII)

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



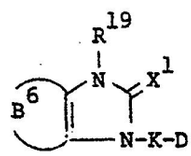
(I-f-8); or

q) reacting an intermediate of formula



(XXIX)

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

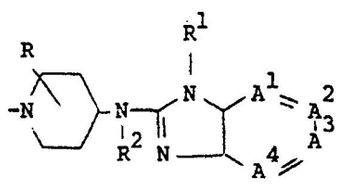


(I-f-9)

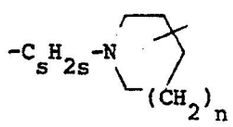
wherein B^6 is -CH=CH-CH=CH- or -CH=N-CH=N-; and R^{19} is selected from the group consisting of hydrogen, lower alkyl, Ar^2-lower alkyl, hydroxylower alkyl or lower alkyloxycarbonyl; or

r) reducing an intermediate of formula Het-C_sH_{2s}-Y-Alk'-C(O)-D (XXX) with a complex metal hydride in a suitable solvent, thus preparing a compound of formula Het-C_sH_{2s}-Y-Alk'-CH_2-D (I-g) wherein Alk' has the previously defined meaning of Alk, provided that one methylene function is missing;

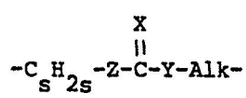
wherein D represents a radical of formula



and K represents a bivalent radical of formula


(i);

-C_sH_{2s}-Y-Alk- (j); or


(k);

optionally converting the compounds of formula (I) into each other following art-known functional 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.

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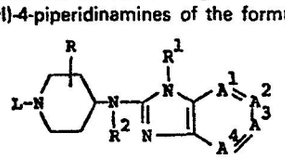
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(54) Five membered heterocyclic ring containing N-(bicyclic heterocyclyl)-4-piperidinamines.

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



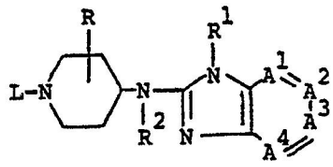
(I),

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.

EP 0 145 037 A2

CLAIMS

1. A chemical compound having the formula



(I),

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

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

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

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

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

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

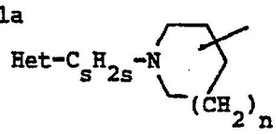
wherein one or two hydrogen atoms in said radicals (a) - (e) may, each independently from each other, be replaced by halo, lower alkyl, lower alkyloxy, trifluoromethyl or hydroxy;

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



(f);

a radical of formula

Het-C_sH_{2s}-Y-Alk- (g); and

a radical of formula

$$Het\text{-}C_sH_{2s}\text{-}Z\text{-}\overset{\overset{X}{\|}}{C}\text{-}Y\text{-}Alk\text{-} \qquad (h),$$

wherein n is 0 or the integer 1 or 2;

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

Alk is lower alkanediyl;

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

X is O, S, $CH\text{-}NO_2$ or NR^4;

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

Het is an optionally substituted 5-membered heterocyclic ring having at least one nitrogen atom and being optionally condensed with an optionally substituted benzene ring, said Het being connected to C_sH_{2s} on a carbon atom;

said R^3 being hydrogen, lower alkyl, (Ar^2)lower alkyl, 2-lower alkyloxy-1,2-dioxoethyl or a radical of formula $-C(=X)-R^6$, R^6 being hydrogen, lower alkyl, Ar^2, Ar^2-lower alkyl, lower alkyloxy, Ar^2-lower alkyloxy, mono- or di(lower alkyl)amino, Ar^2-amino, Ar^2-lower alkylamino or Ar^2-lower alkyl(lower alkyl)amino;

said R^4 being hydrogen, lower alkyl, cyano, nitro, Ar^2-sulfonyl, lower alkylsulfonyl, lower alkylcarbonyl or Ar^2-carbonyl; and

said R^5 being hydrogen or lower alkyl;

provided that:

i) when $A^1=A^2-A^3=A^4$ is a bivalent radical of formula (a) or (b), then Het is other than 1-(lower alkyl)pyrrolyl;

ii) when $A^1=A^2-A^3=A^4$ is a bivalent radical of formula (a) or (b) and L is a radical of formula (g) wherein s is 0 and Y is NR^3, then Het is other than 1H-benzimidazol-2-yl;

wherein Ar^1 is a member selected from the group consisting of phenyl, being optionally substituted with up to three substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl and lower alkyl-CO-; thienyl; halothienyl; furanyl; lower alkyl substituted furanyl; pyridinyl; pyrazinyl; thiazolyl and imidazolyl optionally substituted by lower alkyl; and wherein Ar^2 is a member selected from the group consisting of phenyl being optionally substituted with up to

three substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl and (lower alkyl)CO.

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

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

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

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

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

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

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

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

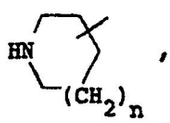
10. A process for preparing a chemical compound as claimed in claim 1, characterized by

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

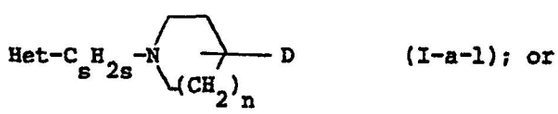
1) Q^2 is hydrogen and Q^1, combined with Het, forms a radical of formula L-W (II-a), said W representing an appropriate reactive

leaving group such as, for example, halo, e.g., chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy or 4-methylphenylsulfonyloxy; or

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



thus preparing a compound of formula



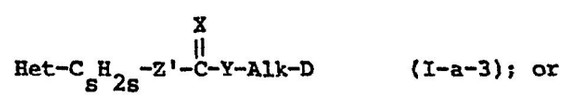
(I-a-1); or

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



(I-a-2); or

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



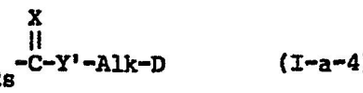
(I-a-3); or

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



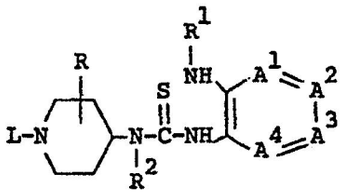
(I-a-2); or

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



(I-a-4); or

b) cyclodesulfurizing an intermediate of formula



(IV)

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

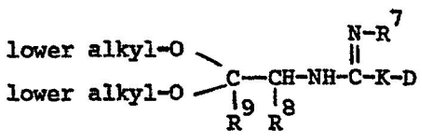
c) reacting an intermediate of formula Het-C_sH_{2s}-Z'H (V) with a piperidine of formula X'=C=N-Alk-D (VI) in a suitable reaction-inert solvent, thus preparing a compound of formula Het-C_sH_{2s}-Z'-C(X')-NH-Alk-D (I-b-1); or

d) reacting an intermediate of formula Het-C_sH_{2s}-N=C=X' (VII), said X' being O or S, with a piperidine of formula HY'-Alk-D (VIII) in a suitable reaction-inert solvent, thus preparing a compound of formula Het-C_sH_{2s}-NH-C(X')-Y'-Alk-D (I-b-2); or

e) reacting an intermediate of formula Het-C_sH_{2s}-C(X')-OH (IX) with a piperidine of formula HY'-Alk-D (VIII) in a suitable reaction-inert solvent, if desired, after converting the OH-function in (VIII) in a suitable leaving group, or, if desired, by reacting (IX) with (VIII) together with an appropriate reagent capable of forming amides or esters; thus preparing Het-C_sH_{2s}-C(X')-Y'-Alk (I-c); or

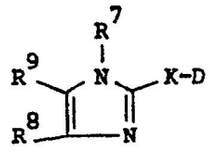
f) reacting a piperidine of formula HD (III-a) with a reagent of formula Het-lower alkenediyl-H (X) in a suitable reaction-inert solvent, thus preparing a compound of formula Het-Alk-D (I-d); or

g) cyclizing an imidamide derivative of formula



(XI)

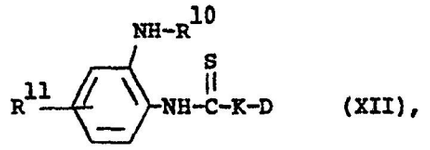
in a reaction-inert solvent and, if desired, in the presence of an appropriate acid, thus preparing a compound of formula



(I-e),

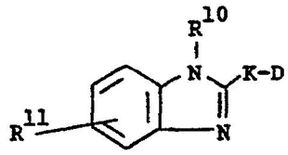
wherein and R^7, R^8 and R^9 are each independently optional substituents of the imidazole ring; or

h) cyclodesulfurizing a thioamide derivative of formula



(XII),

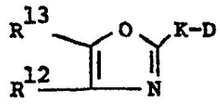
with an appropriate alkyl halide, metal oxide or metal salt in a reaction-inert solvent, thus yielding a compound of formula



(I-f),

wherein R^{10} and R^{11} are each independently optional substituents of the 1H-benzimidazol-2-yl ring; or

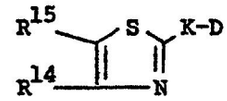
i) condensing a cyanide of formula NC-K-D (XIV) with a reagent of formula R^{12}-C(O)-CH(OH)-R^{13} (XIII), in a reaction-inert solvent and, if desired, in the presence of an appropriate base, thus preparing a compound of formula



(I-g)

wherein R^{12} and R^{13} are each independently optional substituents of the oxazole ring; or

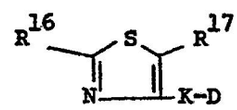
j) condensing a thioamide derivative of formula $H_2N-C(S)-K-D$ (XVI) with a reagent of formula $R^{14}-C(O)-CH(W)-R^{15}$ (XV) in a reaction-inert solvent and, if desired, in the presence of an appropriate base, thus preparing a compound of formula



(I-h)

wherein R^{14} and R^{15} are each independently optional substituents of the thiazole ring; or

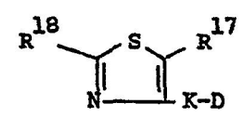
k) condensing a ketone of formula $W-CH(R^{17})-C(O)-K-D$ (XVIII) with a thioamide derivative of formula $R^{16}-C(S)-NH_2$ (XVII) in a reaction-inert solvent and, if desired, in the presence of an appropriate base, thus preparing a compound of formula



(I-i)

wherein R^{16} and R^{17} are each independently optional substituents of the thiazole ring; or

l) condensing a ketone of formula (XVIII) with an isothiocyanate of formula $R^{18}-N=C=S$ (XIX) in the presence of ammonia or an ammonium salt in a reaction-inert solvent and, if desired, in the presence of an appropriate base, thus yielding a compound of formula

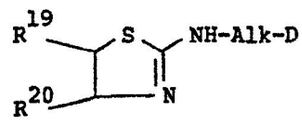


(I-j)

wherein R^{17} and R^{18} are each independently optional substituents of the thiazole ring; or

m) condensing an isothiocyanate of formula S=C=N-Alk-D (VI-a) with a

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

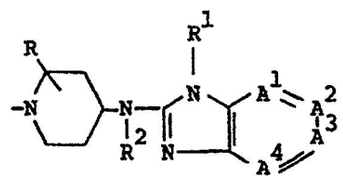


(I-k),

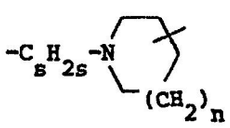
wherein R^{19} and R^{20} are each independently optional substituents of the 4,5-dihydro-thiazole ring; or

n) reducing a compound of formula Het-C_sH_{2s}-Y-Alk'-C(O)-D (XXI) with an appropriate reducing agent in a reaction-inert solvent, thus yielding a compound of formula Het-C_sH_{2s}-Y-Alk'-CH_2-D (I-l), wherein Alk' has the previously defined meaning of Alk, provided that one methylene function is missing;

wherein D represents a radical of formula

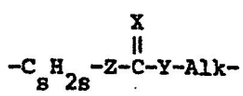


and K represents a bivalent radical of formula



(i);

$-C_sH_{2s}-Y-Alk-$ (j); or



(k); 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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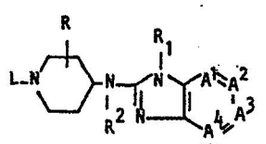
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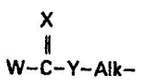
(54) N-(4-piperidinyl) bicyclic condesed 2-imidazolamine derivatives.

(57) Novel N-heterocyclyl-4-piperidinamines of formula

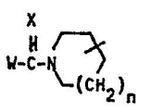


(I),

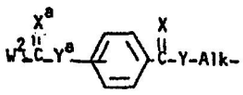
wherein L is a radical of formula



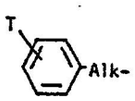
(b-1);



(b-2);



(b-3);



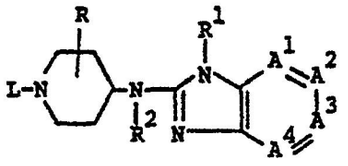
(b-4);

Het-Alk- (b-5); (lower alkenyl)-Y^1-Alk- (b-6); or Ar^1-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.

EP 0 151 824 A2

CLAIMS

1. A chemical compound having the formula



(I),

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

-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),

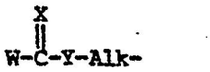
wherein one or two hydrogen atoms in said radicals (a-1) - (a-5) may, each independently from each other, be replaced by halo, lower alkyl, lower alkyloxy, trifluoromethyl or hydroxy;

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

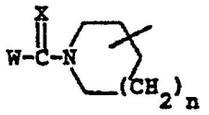
R^1 is a member selected from the group consisting of hydrogen, alkyl, cycloalkyl, Ar^1 and lower alkyl substituted with one or two Ar^1 radicals;

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

L is a radical of formula



(b-1);



(b-2);

Ar^1; and where Z^1 is NR^8, W^1 may also be hydrogen, amino, lower alkylamino, Ar^1-amino or nitro;

said W^2 being a member selected from the group consisting of hydrogen, lower alkyl, Ar^1 and a radical of formula:

$$R^5\text{-}Z^1\text{-} \qquad \text{(c-2-a)},$$

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

said T being a radical of formula:

$$R^6\text{-}Z\text{-}\overset{\overset{X}{\|}}{C}\text{-}Y^2\text{-} \qquad \text{(c-3-a), or}$$

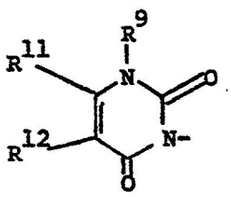
$$R^7\text{-}SO_2\text{-}NR^8\text{-} \qquad \text{(c-3-b)};$$

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

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

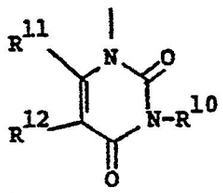
R^8 being hydrogen or lower alkyl;

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



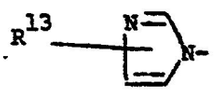
(c-4-a)

or of formula



(c-4-b),

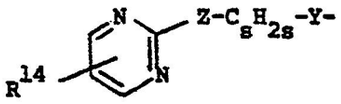
wherein R^9, R^{10}, R^{11} and R^{12} are each independently hydrogen or lower alkyl; or a radical of formula



(c-4-c),

wherein R^{13} is hydrogen, lower alkyl or amino, or

said Het being furan substituted with lower alkyl, said lower alkyl being optionally substituted with hydroxy, mercapto, lower alkyloxy, lower alkylthio, (aminolower alkyl)thio, Ar^1-O- or a radical of formula



(c-4-d-1),

s being an integer of from 1 to 6 inclusive; or where Z or Y is a direct bond, s may also be 0; and R^{14} being hydrogen or lower alkyl;

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

X is O, S, NR^{15} or $CHNO_2$;

Y is O, S, NR^{16} or a direct bond;

Y^1 is O, S or NR^{16};

Y^2 is S or NR^{16};

Z is O, S, NR^8 or a direct bond;

Z^1 is O, S or NR^8;

X^a and Y^a independently having the same meaning of X respectively Y;

said R^{15} being hydrogen, lower alkyl, cyano, nitro, Ar^2-sulfonyl, lower alkylsulfonyl, lower alkylcarbonyl or Ar^2-carbonyl;

said R^{16} being hydrogen, lower alkyl, (Ar^2)lower alkyl, 2-lower alkyloxy-1,2-dioxoethyl; or a radical of formula $-C(=X)-R^{17}$; R^{17} being hydrogen, lower alkyl, Ar^2, Ar^2-lower alkyl, lower alkyloxy, Ar^2-lower alkyloxy, mono- or di(lower alkyl)amino, Ar^2-lower alkylamino or Ar^2-lower alkyl(lower alkyl)amino;

provided that:

i) when $A^1=A^2-A^3=A^4$ is a radical of formula (a-1) or (a-2), and L is a radical of formula (b-1), wherein W is other than hydrogen or other than a radical of formula (c-1-a) or (c-1-b), then X is other than O;

ii) when L is a radical of formula (b-1), wherein W is a radical of formula (c-1-c), wherein Z^1 is NH then W^1 is other than hydrogen or lower alkyl;

iii) when $A^1=A^2-A^3=A^4$ is a radical of formula (a-1) or (a-2), and L is a radical of formula (b-3), wherein X is O, Y is NR^{16}, O or a direct bond, and X^a is O,

a) then Y^a is not O;

b) and W^2 being lower alkyl then Y^a is not a direct bond;

wherein Ar^1 is a member selected from the group consisting of phenyl, being optionally substituted with up to three substituents

each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl and lower alkyl-CO-; thienyl; halothienyl; furanyl; lower alkyl substituted furanyl; pyridinyl; pyrazinyl; thiazolyl and imidazolyl optionally substituted with lower alkyl; and wherein Ar^2 is a member selected from the group consisting of phenyl being optionally substituted with up to three substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, carboxyl, lower alkyloxycarbonyl and (lower alkyl)-CO.

2. A chemical compound according to claim 1, wherein L is a radical of formula (b-1), wherein Y is NH, X is O and W is hydrogen; or L is a radical of formula (b-1) wherein X is S, NH or NCN, Y is NH and W is 1-piperidinyl, 1-pyrrolidinyl, 4-morpholinyl, or a radical of formula (c-1-c), wherein Z^1 is NR^8 and W^1 is amino, nitro or lower alkyl, optionally substituted with one hydroxy, lower alkyloxy, 1-piperidinyl, 1-pyrrolidinyl, 4-morpholinyl or phenyl radical, or with two lower alkyloxy radicals; or L is a radical of formula (b-1), wherein X is S, NH or NCN, Y is NH and W is lower alkyloxy or lower alkylthio; or wherein L is a radical of formula (b-1) wherein W is a radical of formula (c-1-a) or (c-1-b); or

L is a radical of formula (b-2) wherein n is 1, X is O or S and W is a radical of formula (c-1-c), wherein Z^1 is NR^8 and W^1 is lower alkyl; or

L is a radical of formula (b-3), wherein X is O, Y is NH, X^a is O, Y^a is NR^{15} and W^2 is lower alkyl; or

L is a radical of formula (b-4), wherein T is a radical of formula (c-3-a), wherein X is O or S, Z is NR^8 and R^6 is hydrogen or lower alkyl; or wherein T is a radical of formula (c-3-b), wherein R^8 is hydrogen and R^7 is lower alkyl; or

L is a radical of formula (b-5) wherein Het is a radical of formula (c-4-a), wherein R^9, R^{11} and R^{12} are hydrogen; or wherein Het is a radical of formula (c-4-c); or wherein Het is furan substituted with

lower alkyl being substituted with hydroxy or with a radical of formula (c-4-d-1), wherein Y is O or S, Z is NH or a direct bond and R^{14} is hydrogen; or

L is a radical of formula (b-6) wherein Y^1 is O; or

L is a radical of formula (b-7) wherein Ar^1 is phenyl substituted with hydroxy or lower alkyloxy.

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

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

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

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

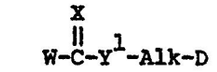
7. A process for preparing a pharmaceutical composition, characterized in that a therapeutically effective amount of a compound as claimed in any of claims 1 and 2 is intimately mixed with a suitable pharmaceutical carrier.

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

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

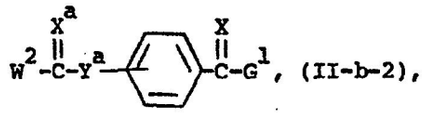
1) Q^2 is hydrogen and Q^1 is an intermediate of formula L-G (II-a), said G representing an appropriate reactive leaving group; or

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



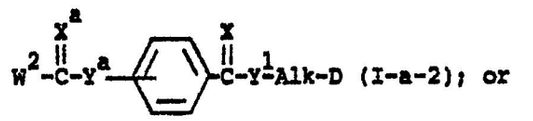
W-C(=X)-Y^1-Alk-D (I-a-1); or

3) Q^1 is an intermediate of formula



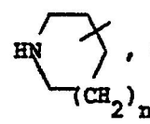
W^2-C(X^a)-Y^a-Ph-C(=X)-G^1, (II-b-2),

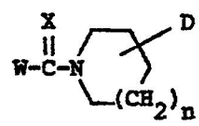
and Q^2 is a radical of formula HY^1-Alk-, thus preparing a compound of formula



(I-a-2); or

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

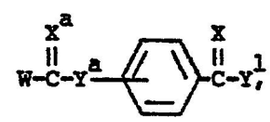
5) Q^1 is an intermediate of formula  (II-b-4) and Q^2 is a radical of formula  , thus preparing a compound of formula



(I-a-4); or

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

7) Q^1 is an intermediate of formula



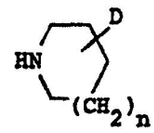
(II-c-2), and Q^2 is a radical of formula G-Alk, thus preparing a compound of formula (I-a-2);

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

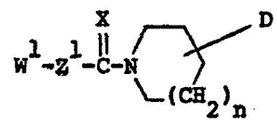
9) Q^1 is an intermediate of formula Het'-H, (II-c-4), wherein said Het' is a radical of formula (c-4-a), (c-4-b) or (c-4-c), and Q^2 is a radical of formula G-Alk, thus preparing a compound of formula Het'-Alk-D (I-a-5); or

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

c) reacting a reagent of formula (II-d) with an intermediate of formula

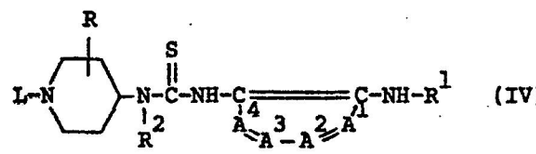


(II-b-2) in the presence of an appropriate >C=X generating agent, in a reaction-inert solvent, thus preparing a compound of formula



(I-a-4-a); or

d) cyclodesulfurizing an intermediate of formula



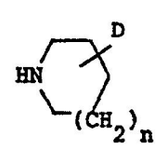
(IV)

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

e) reacting an intermediate of formula W^1-Z^1-H (V) with a piperidine of formula $X^1=C=N$-Alk-D (VI), wherein X^1 is O or S, 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

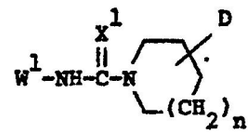
f) reacting an intermediate of formula $W^1-N=C=X^1$ (VII), with a piperidine of formula HY^1-Alk-D (III-b-1) in a reaction-inert solvent, thus preparing a compound of formula $W^1-NH-C(=X^1)-Y^1$-Alk-D (I-b-2); or

g) reacting an intermediate of formula (VII) with a piperidine of formula



(III-b-2), in a reaction-

inert solvent, thus preparing a compound of formula

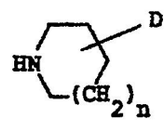


(I-b-3); or

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

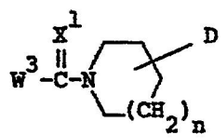
W^3-C(=X^1)-Y^1-Alk-D (I-c-1); or

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



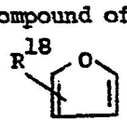
(III-b-2)

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

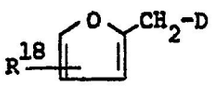


(I-c-2); or

j) reacting a piperidine of formula HD (III-a) with a reagent of formula L^1-lower alkenediyl-H (IX), wherein L^1 is selected so that it forms, combined with -Alk-, a radical of formula (b-1), (b-3), (b-4), (b-5), (b-6) or (b-7), in a suitable reaction-inert solvent, thus preparing a compound of formula L^1-Alk-D (I-d); or

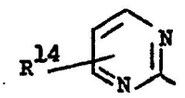
k) reacting a furan of formula  with a piperidine of formula

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



(I-e); or

1) alkylating a furan derivative of formula $H\text{-}Y^1\text{-}D^1$, (X-a), wherein D^1 represents a radical of formula -(lower alkyl)-  -Alk-D, with an intermediate of formula $E\text{-}Z\text{-}C_sH_{2s}\text{-}G$, (XI-a), wherein E represents a radical of formula



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

$E\text{-}Z\text{-}C_sH_{2s}\text{-}Y^1\text{-}D^1$ (I-e-1);

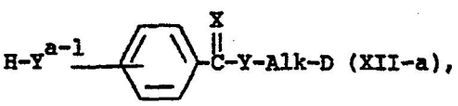
m) alkylating an intermediate of formula $E\text{-}Z\text{-}C_sH_{2s}\text{-}Y^1H$, (XI-b), with a furan derivative of formula $G\text{-}D^1$, (X-b), in a reaction-inert solvent, thus preparing a compound of formula (I-e-1);

n) alkylating a furan derivative of formula $H\text{-}Z^1\text{-}C_sH_{2s}\text{-}Y\text{-}D^1$ (X-c), with an intermediate of formula E-G, (XI-c), in a reaction-inert solvent, thus preparing a compound of formula

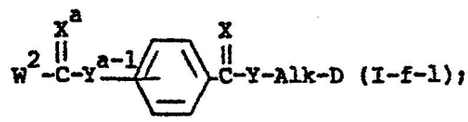
$E\text{-}Z^1\text{-}C_sH_{2s}\text{-}Y\text{-}D^1$, (I-e-2);

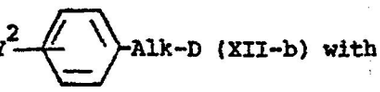
o) alkylating an intermediate of formula $E\text{-}Z^1H$, (XI-d), with a furan derivative of formula $G\text{-}C_sH_{2s}\text{-}Y\text{-}D^1$, (X-d), in a reaction-inert solvent, thus preparing a compound of formula (I-e-2);

p) reacting an intermediate of formula



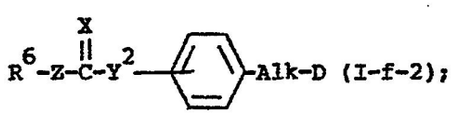
(XII-a), wherein Y^{a-1} has the previously described meaning of Y^a, provided that it is not a direct bond, with a reagent of formula $W^2\text{-}C(=X^a)\text{-}G^1$, (XIII-a), in a reaction-inert solvent, thus preparing a compound of formula

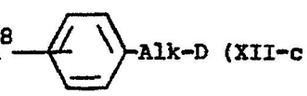


102 q) reacting an intermediate of formula  (XII-b) with

103 a reagent of formula R^6-Z-C(=X)-G^1, in a reaction-inert solvent,

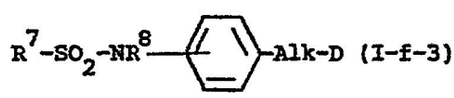
104 thus preparing a compound of formula



105 r) reacting an intermediate of formula  (XII-c)

106 with a reagent of formula R^7-SO_2-G^1, in a reaction-inert

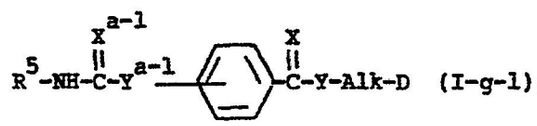
107 solvent, thus preparing a compound of formula



108 s) reacting a reagent of formula R^5-N=C=X^{a-1} (XIV-a), wherein

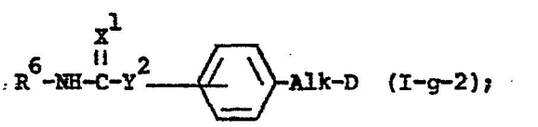
109 X^{a-1} is O or S, with an intermediate of formula (XII-a) in a

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

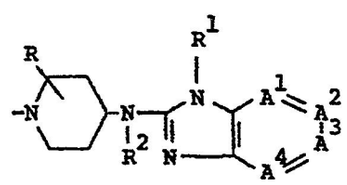


111 t) reacting an intermediate of formula (XII-b) with a reagent of

112 formula R^6-N=C=X^1 (XIV-b), thus preparing a compound of formula



213 wherein D represents a radical of formula

 ; or,

optionally converting the compounds of formula (I) into each other following art-known functional 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.

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D6409

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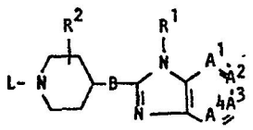
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(54) **4-(Bicyclic heterocyclyl)-methyl and -hetero-piperidines.**

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



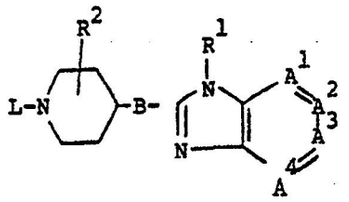
(I),

wherein B is CH_2, O, S, SO or SO_2; 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 0 151 826 A1

CLAIMS

1. A chemical compound having the formula



(I),

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

-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, each independently from each other, be replaced by halo, lower alkyl, lower alkyloxy, trifluoromethyl or hydroxy;

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;

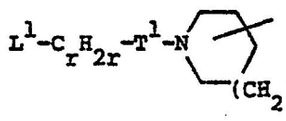
R^2 is a member selected from the group consisting of hydrogen and lower alkyl;

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

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

$L^1-C_rH_{2r}-T-C_sH_{2s}-$ (b-1); and

a radical of formula



(b-2) ;

wherein one or two hydrogen atoms in the bivalent radical $-C_sH_{2s}-$ may, each independently from each other, be replaced by

halo, hydroxy, mercapto, isothiocyanato, isocyanato, lower alkyloxy, lower alkylthio, Ar^1, Ar^1O-, Ar^1S-, Ar^1SO_2-, or NR^3R^5; and

n is 0 or the integer 1 or 2;

r and s are, independently from each other, 0 or an integer of from 1 to 6 inclusive;

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

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

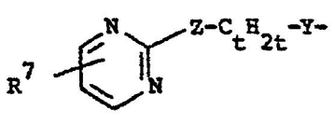
said Y being O, S, NR^3 or a direct bond;
X being O, S, $CH-NO_2$ or NR^4;
Z being O, S, NR^5 or a direct bond; and

said R^3 being hydrogen, lower alkyl, (Ar^2)lower alkyl, 2-lower alkyloxy-1,2-dioxoethyl or a radical of formula $-C(=X)-R^6$, R^6 being hydrogen, lower alkyl, Ar^2, Ar^2-lower alkyl, lower alkyloxy, Ar^2-lower alkyloxy, mono- or di(lower alkyl)amino, Ar^2-amino, Ar^2-lower alkylamino or Ar^2-lower alkyl(lower alkyl)amino;

said R^4 being hydrogen, lower alkyl, cyano, nitro, Ar^2-sulfonyl, lower alkylsulfonyl, lower alkylcarbonyl or Ar^2-carbonyl; and

said R^5 being hydrogen or lower alkyl;

wherein L^1 is a member selected from the group consisting of hydrogen; halo; hydroxy; lower alkyloxy; lower alkylthio; cyano; mercapto; isocyanato; isothiocyanato; Ar^1; Ar^1-carbonyl; Ar^1-sulfonyl; lower alkylsulfonyl; cycloalkyl being optionally substituted with up to two substituents each independently selected from the group consisting of lower alkyl, cyano and Ar^2; [10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene]methyl; Het; and furan substituted with substituted lower alkyl; said substituted lower alkyl being lower alkyl substituted with a member selected from the group consisting of hydroxy, mercapto, lower alkyloxy, lower alkylthio, aminolower alkylthio, Ar^2-oxy and a radical of formula



(c),

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

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

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

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

said Het being an optionally substituted five- or six-membered heterocyclic ring, being optionally condensed with an optionally substituted five- or six-membered carbocyclic or heterocyclic ring;

provided that:

i) when L is a radical of formula (b-1) wherein L^1 is hydrogen and wherein T is $-Z-C(=X)-Y-$ wherein Y is other then a direct bond and Z and X are each independently O or S, then r is not 0; or when L is a radical of formula (b-2) wherein L^1 is hydrogen and wherein T^1 is $-Z-C(=X)-$ wherein Z and X are each independently O or S, then r is not 0;

ii) when L is a radical of formula (b-1) wherein L^1 is halo, hydroxy, lower alkyloxy, mercapto, lower alkylthio, isocyanato, isothiocyanato or Het connected to C_rH_{2r} on a nitrogen atom, and wherein r is 0, then T is a direct bond or a radical $-C(=X)-Y-$; or when L is a radical of formula (b-2) wherein L^1 is halo, hydroxy, lower alkyloxy, mercapto, lower alkylthio, isocyanato, isothiocyanato or Het connected to C_rH_{2r} on a nitrogen atom, and wherein r is 0, then T^1 is a radical $-C(=X)-$;

iii) when L is a radical of formula (b-1) wherein T is Y, said Y being other than a direct bond, or wherein T is $-Z-C(=X)-Y-$, wherein Y

is other than a direct bond, then s is not 0;

wherein Ar^1 is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, lower alkylthienyl, pyridinyl, mono- and di(lower alkyloxy)pyridinyl, pyrrolyl, lower alkylpyrrolyl, furanyl, furanyl substituted with lower alkyl, pyrazinyl, thiazolyl, imidazolyl, lower alkylimidazolyl; said substituted phenyl, being phenyl substituted with up to 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkyloxy, lower alkylthio, mercapto, amino, mono- and di(lower alkyl)amino, lower alkylsulfonyl, lower alkylsulfonyllower alkyl, phenyllower alkylsulfonyl, phenylsulfonyllower alkyl, a radical of formula $R^8-C_pH_{2p}-Y-$, a radical of formula $R^9-Z-C(=X)-Y-$, and a radical of formula $R^{10}SO_2Y-$; wherein p is an integer of from 1 to 6 inclusive and R^8 is a member selected from the group consisting of amino, cyano, phenyl aminocarbonyl, mono- and di(lower alkyl)amino-carbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl, 1-pyrrolidinylcarbonyl, and lower alkenyl; wherein R^9 is member selected from the group consisting of hydrogen, lower alkyl and Ar^2; provided that, when R^9 is hydrogen and Y is other than a direct bond, then Z is not O or S; and wherein R^{10} is lower alkyl or Ar^2;

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

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

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

4. A compound according to claim 3, wherein L is a radical of formula (b-1).

5. A chemical compound according to any of claims 1 to 4 for use as a medicine.

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

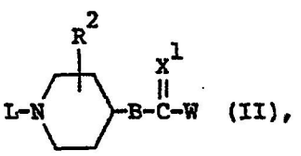
7. A pharmaceutical composition comprising an inert carrier and a pharmaceutically acceptable amount of a compound according to any of claims 1 to 4.

8. A pharmaceutical composition according to claim 7 for use as an anti-allergic medicine.

9. A process for preparing a pharmaceutical composition, characterized in that a therapeutically effective amount of a compound as claimed in any of claims 1 to 4 is intimatately mixed with a suitable pharmaceutical carrier.

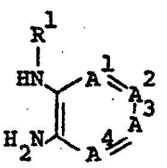
10. A process for preparing a compound according to any of claims 1 to 4 characterized by

I reacting a piperidine of formula



(II),

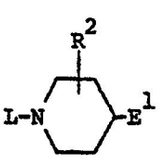
wherein X^1 is O, S or NH and W is a reactive leaving group, with a diamine of formula



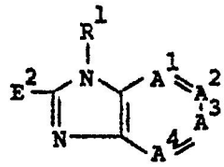
(III)

in a reaction-inert solvent;

II reacting a piperidine of formula



(IV) with an intermediate of

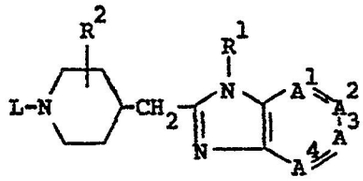


(V), in a reaction-inert solvent, wherein :

a) E^1 is a radical of formula -B-M wherein M is hydrogen or an alkalimetal or earth alkalinemetal and E^2 is a radical of formula -W; or

b) E^1 is a radical of formula -W and E^2 is a radical of formula M-B; or

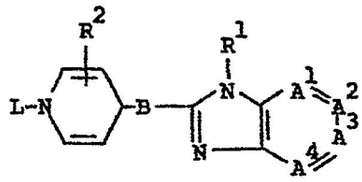
c) E^1 is a radical of formula $-CH_2-W$ and E^2 is a radical of formula -M, thus preparing a compound of formula



(I-a); or

d) E^1 is a radical of formula -M and E^2 is a radical of formula $-CH_2W$, thus preparing a compound of formula (I-a);

III. reducing an intermediate of formula



, (VI)

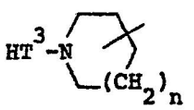
in a reaction-inert solvent; and, if desired, converting the compounds of formula (I) into each other by

a) alkylating a compound of formula Q^2-D (I-c) with a reagent of formula L^1-Q^1 (VII) in a suitable solvent, thus preparing a compound of formula L^2-D (I-b), wherein L^2 has the previously defined meaning of L, provided that it is other than hydrogen, and wherein

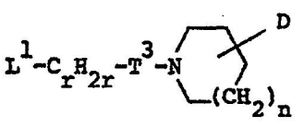
i) Q^1 is -W and Q^2 is hydrogen; or

ii) Q^1 is $-C_rH_{2r}-W^1$ and Q^2 is a radical of formula $HT^2-C_sH_{2s}-$, wherein W^1 is a reactive leaving group and T^2 is O, S, NR^3 or $-Z^1-C(=X)-Y-$, said Z^1 being O, S or NR^5, thus preparing a compound of formula $L^1-C_rH_{2r}-T^2-C_sH_{2s}-D$ (I-b-1-a); or

iii) Q^1 is $-C_rH_{2r}-W^1$ and Q^2 is a radical of formula



, wherein T^3 is a direct bond or $Z^1-(C=X)-$, thus preparing a compound of formula



(I-b-1-b); or

iv) Q^1 is a radical of formula $-C_rH_{2r}-T^4H$ and Q^2 is $W-C_sH_{2s}-$, wherein T^4 is O, S, NR^3 or $-Z-C(=X)-Y^1-$, said Y^1 being O, S or NR^3, thus preparing a compound of formula $L^1-C_rH_{2r}-T^4-C_sH_{2s}-D$ (I-b-2);

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

c) reductively N-alkylating a compound of formula

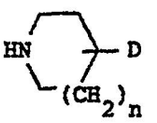
$$HN(R^3)-C_sH_{2s}-D \quad \text{(I-d)}$$

with a carbonyl-compound of formula $L^1-(C_rH_{2r-1})=O$ (IX), said $L^1-(C_rH_{2r-1})=O$ being a compound of formula $L^1-C_rH_{2r}-H$ wherein a $-CH_2-$ radical is oxidated to a carbonyl radical, in a reaction inert solvent, thus preparing a compound of formula $L^1-C_rH_{2r}-N(R^3)-C_sH_{2s}-D$ (I-b-3);

d) reductively N-alkylating an intermediate of formula $L^1-C_rH_{2r}-N(R^3)H$ (X) with a compound of formula $O=(C_sH_{2s-1})-D$ (I-e), said $O=(C_sH_{2s-1})-$ being a radical of formula $H-C_sH_{2s}-$ wherein a $-CH_2-$ radical is oxidated to a carbonyl radical, in a reaction-inert solvent, thus preparing a compound of formula (I-b-3);

e) reacting a reagent of formula $L^1-C_rH_{2r}-Z^1H$ (XI) with a compound of formula $X^2=C=N-C_sH_{2s}-D$ (I-f), wherein X^2 is O or S, in a reaction-inert solvent, thus preparing a compound of formula $L^1-C_rH_{2r}-Z^1-C(=X^2)-NH-C_sH_{2s}-D$ (I-b-4);

f) reacting a reagent of formula $L^1-C_rH_{2r}-N=C=X^2$ (XII) with a compound of formula $HY^1-C_sH_{2s}-D$ (I-c-4), respectively with a compound of formula H-D (I-c-1) or with a compound of formula

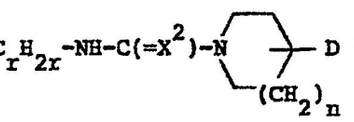


(I-c-5), in a reaction-inert solvent, thus preparing a compound of formula

$L^1-C_rH_{2r}-NH-C(=X^2)-Y^1-C_sH_{2s}-D$, (I-b-5-a),

respectively of formula

$L^1-C_rH_{2r}-NH-C(=X^2)-D$, (I-b-5-b), or of formula



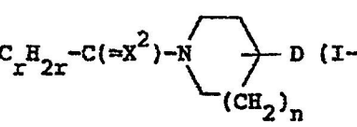
(I-b-5-c);

g) reacting a reagent of formula $L^1-C_rH_{2r}-C(=X^2)-OH$ (XIII) with (I-c-4), respectively with (I-c-1) or (I-c-5), in a reaction-inert solvent, if desired, after converting the OH group in (XIII) in a reactive leaving group or by reacting (XIII) with (I-c-4), respectively (I-c-1) or (I-c-5), in the presence of a reagent capable of forming esters or amides, thus preparing a compound of formula

$L^1-C_rH_{2r}-C(=X^2)-Y^1-C_sH_{2s}-D$, (I-b-6-a),

respectively of formula

$L^1-C_rH_{2r}-C(=X^2)-D$, (I-b-6-b), or of formula



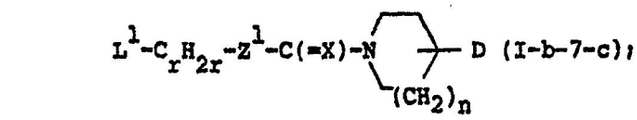
(I-b-6-c);

h) reacting (XI) with (I-c-4), respectively (I-c-1) or (I-c-5) in the presence of a C=X generating agent in a reaction-inert solvent, thus preparing a compound of formula

$L^1-C_rH_{2r}-Z^1-C(=X)-Y^1-C_sH_{2s}-D$, (I-b-7-a),

respectively of formula

$L^1-C_rH_{2r}-Z^1-C(=X)-D$, (I-b-7-b), or of formula



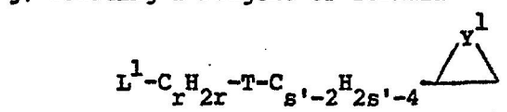
$L^1\text{-}C_rH_{2r}\text{-}Z^1\text{-}C(=X)\text{-}N$ (ring) $\text{-}D$ (I-b-7-c);

$(CH_2)_n$

i) reacting an alkene of formula $L^1\text{-}C_rH_{2r}\text{-}T$-lower alkenediyl-H of formula (XIV) with (I-c-1) in a reaction-inert solvent, thus preparing a compound of formula

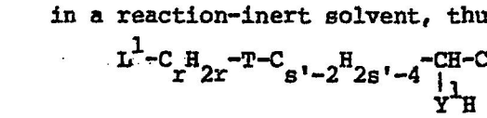
$L^1\text{-}C_rH_{2r}\text{-}T$-lower alkanediyl-D, (I-g);

j) reacting a reagent of formula



$L^1\text{-}C_rH_{2r}\text{-}T\text{-}C_{s'-2}H_{2s'-4}$ (Y^1) , (XV), with (I-c-1),

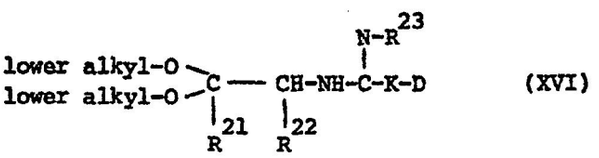
in a reaction-inert solvent, thus preparing a compound of formula



$L^1\text{-}C_rH_{2r}\text{-}T\text{-}C_{s'-2}H_{2s'-4}\text{-}CH(Y^1H)\text{-}CH_2\text{-}D$ (I-h), wherein

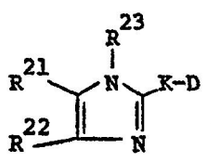
wherein s' is an integer of from 2 to 6 inclusive;

k) cyclizing an imidamide of formula



lower alkyl-O, lower alkyl-O, $C(R^{21})$, $CH(R^{22})$-NH-C($N\text{-}R^{23}$)-K-D (XVI)

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

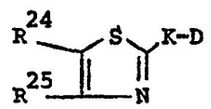


(R^{23}, R^{21}, N, K-D, R^{22}, N) (I-i-1), wherein R^{21}, R^{22}

(I-i-1)

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

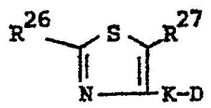
l) condensing a ketone of formula $R^{24}\text{-}CH(W)\text{-}C(=O)\text{-}R^{25}$, (XVII), with a thioamide of formula $H_2N\text{-}C(=S)\text{-}K\text{-}D$, (XVIII), in a reaction-inert solvent, thus preparing a compound of formula



(R^{24}, S, K-D, R^{25}, N) (I-i-2), wherein R^{24} and

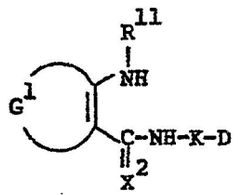
R^{25} are, each independently, optional substituents of the thiazole ring, or where in the compound of formula (I-i-2) said thiazolyl ring is condensed with a five- or six-membered hetero- or carbocyclic ring, R^{24} and R^{25} taken together may form a radical of formula G^3;

m) condensing a thioamide of formula $R^{26}-C(=S)NH_2$, (XIX), with a ketone of formula $W-CHR^{27}-(C=O)-K-D$, (XX), in a reaction-inert solvent, thus preparing a compound of formula

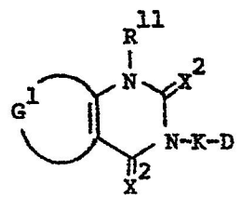


(I-i-3), wherein R^{26} and R^{27} are, each independently, optional substituents of the thiazolyl ring;

n) reacting an amide or thioamide of formula

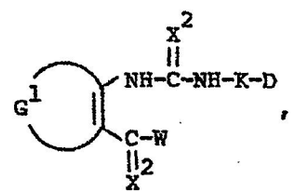


(XXI) with a $>C=X^2$ generating agent, in a reaction-inert solvent, thus preparing a compound of formula



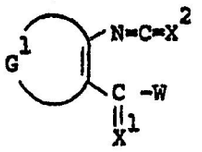
(I-i-4);

o) cyclizing a urea or thiourea of formula



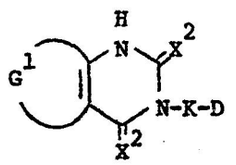
,(XXII),

which in situ may be generated by reacting a reagent



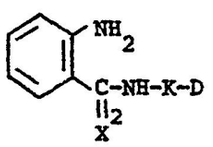
(XXIII), with an amine

H_2N-K-D, (XXIV), in a reaction-inert solvent, thus preparing a compound of formula



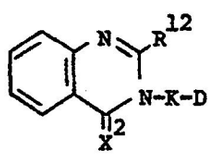
(I-i-4-a);

p) condensing an aniline of formula



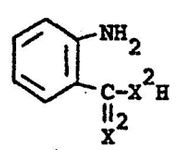
(XXV),

with an acid of formula $R^{12}COOH$ (XXVI), or a reactive derivative thereof, in a reaction-inert solvent, thus preparing a compound of formula



(I-i-5);

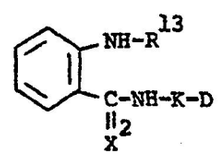
q) condensing an aniline of formula



(XXVII), with an amide

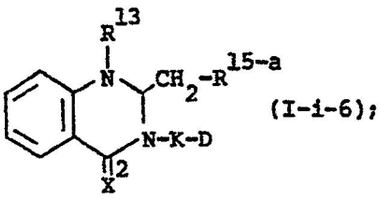
of formula R^{12}-C(=O)-NH-K-D (XXVIII) in a reaction-inert solvent, thus preparing a compound of formula (I-i-5);

r) condensing an aniline of formula



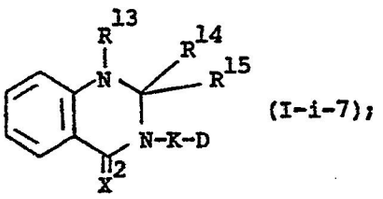
(XXIX),

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



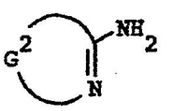
(I-i-6);

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



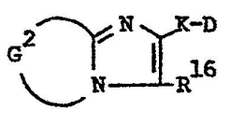
(I-i-7);

t) condensing a reagent of formula



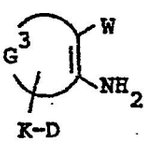
,(XXXII),

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



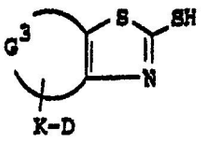
(I-i-8);

u) condensing an amine of formula



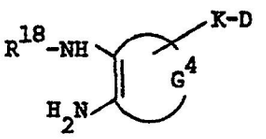
,(XXXIV),

with CS_2, in a reaction-inert solvent, thus preparing a compound of formula



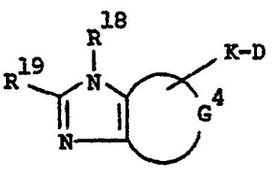
(I-i-9);

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



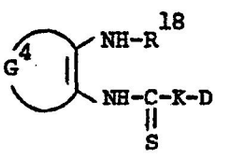
(XXXVI),

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



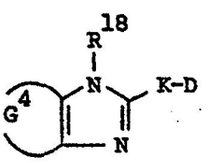
(I-i-10);

w) cyclodesulfurizing a thioamide of formula



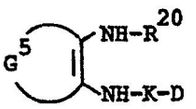
(XXXVII),

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



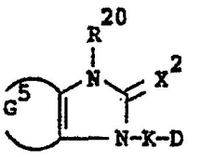
(I-i-11);

x) condensing an amine of formula



(XXXVIII),

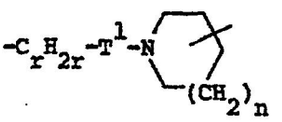
with a $>C=X^2$ generating agent, in a reaction-inert solvent, thus preparing a compound of formula



(I-i-12);

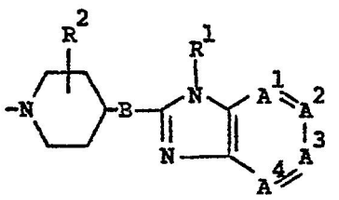
wherein K is a bivalent radical of formula

$-C_rH_{2r}-T-C_sH_{2s}-$ (d-1); or



(d-2);

wherein D represents a radical of formula



, and

R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{20} are, each independently optional substituents of the previously described bicyclic radicals and G^1, G^2, G^3, G^4 and G^5 are, each independently, optionally substituted bivalent radicals, selected so that they form, combined with the five- or six-membered heterocycle to which they are attached, a bicyclic Het-system; or optionally converting the compounds 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.

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A2

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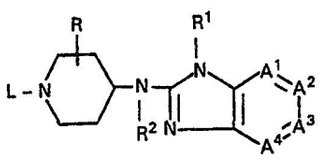
(84) Designated Contracting States: **AT BE CH DE ES FR GB GR IT LI LU NL SE**

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(54) Anti-histaminic compositions containing N-heterocyclyl-4-piperidinamines.

(57) Anti-histaminic compositions containing as active ingredient a N-heterocyclyl-4-piperidinamine of formula



(I),

wherein,

L is hydrogen, C_{1-6}alkyloxycarbonyl or phenylmethoxycarbonyl;

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

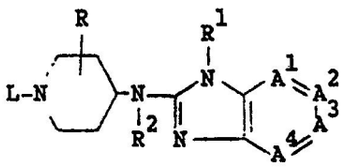
$-CH = CH - CH = CH -$ (a),
$-N = CH - CH = CH -$ (b),
$-CH = N - CH = CH -$ (c),
$-CH = CH - N = CH -$ (d), or
$-CH = CH - CH = N -$ (e),

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



(I),

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

L is hydrogen, C_{1-6} alkyloxycarbonyl or phenylmethoxycarbonyl;

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

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

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

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

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

-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, C_{1-6} alkyl, C_{1-6} alkyloxy, trifluoromethyl or hydroxy;

R is a member selected from the group consisting of hydrogen and C_{1-6} alkyl;

R^1 is a member selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{3-6} cycloalkyl, Ar^1 and C_{1-6} alkyl substituted with one or two Ar^1 radicals;

R^2 is a member selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, (C_{1-6}alkyl)-CO-, (C_{1-6}alkyloxy)-CO and Ar^2-C_{1-6} alkyl;

wherein Ar^1 is a member selected from the group consisting of phenyl, being optionally substituted with up to three 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} alkyl-CO-; thienyl; halothienyl; furanyl; C_{1-6} alkyl substituted furanyl; pyridinyl;

pyrazinyl; thiazolyl and imidazolyl optionally substituted with C_{1-6} alkyl; and wherein Ar^2 is a member selected from the group consisting of phenyl being optionally substituted with up to three 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} alkyl)-CO.

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

3. A composition according to any of claims 1 or 2 wherein $A^1=A^2-A^3=A^4$ is a bivalent radical of formula (a) or (b) and R^1 is C_{1-6} alkyl substituted with Ar^1.

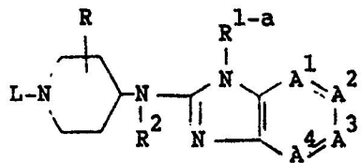
4. A composition according to claim 3 wherein R is hydrogen, R^2 is hydrogen or C_{1-6} alkyl and Ar^1 is phenyl being optionally substituted with up to two substituents independently selected from the group consisting of halo, hydroxy, and C_{1-6} alkyl; pyridyl; imidazolyl; thienyl; halothienyl; furanyl;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

5. A composition according to claim 4 wherein R^1 is furanylmethyl or (C_{1-6} alkyl)furanylmethyl.

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

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

8. A chemical compound having the formula



(I-c),

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

L is hydrogen, C_{1-6}alkyloxycarbonyl or phenylmethoxycarbonyl;

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

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

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

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

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

-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, C_{1-6} alkyl, C_{1-6} alkyloxy, trifluoromethyl or hydroxy;

R is a member selected from the group consisting of hydrogen and C_{1-6} alkyl;

R^{1-a} is C_{1-6}alkyl substituted with C_{1-6}alkyl-substituted furanyl and wherein said C_{1-6}alkyl-substituted furanyl is other than 5-methyl-2-furanyl;

R^2 is a member selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, (C_{1-6} alkyl)-CO-, (C_{1-6} alkyloxy)-CO and Ar^2-C_{1-6} alkyl;

wherein Ar^2 is a member selected from the group consisting of phenyl being optionally substituted with up to three 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} alkyl)-CO.

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

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

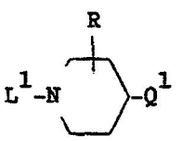
11. A chemical compound of formula (I) as defined in any of claims 1 to 7 for use as a medicine.

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

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

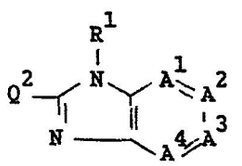
14. A compound as claimed in any one of claims 8 to 10 for use as an anti-allergic medicine.

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



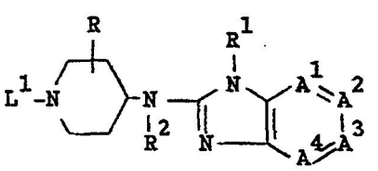
(II)

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



(III)

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



(I-a)

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

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

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(11) Publication number: **0 295 742**
A1

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: **88201172.9**

(22) Date of filing: **08.06.88**

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(43) Date of publication of application: **21.12.88 Bulletin 88/51**

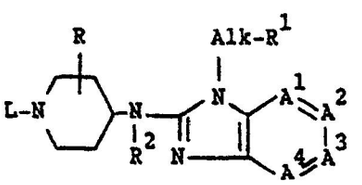
(84) Designated Contracting States: **AT BE CH DE ES FR GB GR IT LI LU NL SE**

(71) Applicant: **JANSSEN PHARMACEUTICA N.V.**
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B-2340 Beerse(BE)
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Oosteinde 12
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(54) **Novel N-(4-piperidinyl) bicyclic condensed 2-imidazolamine derivatives.**

(57) Novel N-(4-piperidinyl) bicyclic condensed 2-imidazolamine derivatives of formula



(I),

wherein: $A^1=A^2-A^3=A^4$ 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 C_{1-6}alkyl; R^1 is furanyl substituted with C_{1-6}alkyl, pyrazinyl, thiazolyl, or imidazolyl optionally substituted with C_{1-6}alkyl; L is C_{3-6}alkenyl optionally substituted with Ar^3, or L is a radical of formula -Alk-R^3, -Alk-O-R^4, -Alk-N-(R^5)-R^6, -Alk-Z-C(=O)-R^7 or -CH_2-CH(OH)-CH_2-O-R^9; 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.

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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 (Opaspray K-1-2109®) 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. Aftercooling 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..

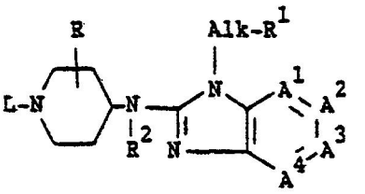
The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg A.I. per ml. The solution was sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

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



(I),

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

$A^1 = A^2\text{-}A^3 = A^4$ 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;

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

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

-Alk-R^3 (b-1),
-Alk-O-R^4 (b-2),
-Alk-N-(R^5)-R^6 (b-3),
-Alk-Z-C(=O)-R^7 (b-4), or
-CH_2-CH(OH)-CH_2-O-R^8 (b-5);

R^3 is hydrogen, Ar^1-thio, Ar^3-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-benzo dioxin-6-yl, 4-morpholinyl, 1-piperidinyl or 1-pyrrolidinyl, or when R^1 is furanyl substituted with C_{1-6}alkyl and $A^1 = A^2$-

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

R^4 is C_{1-6}alkyl or Ar^1;

R^5 is C_{1-6}alkyl optionally substituted with Ar^2;

R^6 is Ar^2 or C_{1-6}alkyl optionally substituted with Ar^2 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 C_{1-6}alkyl, Ar^2-C_{1-6}alkyl, Ar^2, amino, Ar^2-amino, mono- and di(C_{1-6}alkyl)amino, mono- and di(Ar^2-C_{1-6}alkyl)amino, 1-piperidinyl, 1-pyrrolidinyl, 4-morpholinyl, C_{3-6}cycloalkyloxy, C_{1-6}alkyloxy or Ar^1-C_{1-6}alkyloxy;

Z is O, NR^8 or a direct bond; said R^8 being hydrogen or C_{1-6}alkyl optionally substituted with Ar^1;

R^9 is Ar^3;

each Alk independently being C_{1-6}alkanediyl;

Ar^1 is phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, C_{1-6}alkyl 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, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}althylthio, mercapto, C_{1-6}alkylsulfonyl, C_{1-6}alkysulfonylC_{1-6}alkyl, phenyl-C_{1-6}alkylsulfonyl, phenylsulfonylC_{1-6}alkyl, amino, mono- and di(C_{1-6}alkyl)amino, carboxy, C_{1-6}alkyloxycarbonyl and C_{1-6}alkylcarbonyl;

Ar^2 has the same meanings of Ar^1, and may also be pyridinyl, mono- and di(C_{1-6}alkyloxy)pyridinyl or furanyl substituted with C_{1-6}alkyl; and

Ar^3 has the same meanings of Ar^2, and may also be pyrazinyl, 1-(C_{1-6}alkyl)pyrrolyl, thiazolyl or imidazolyl optionally substituted with C_{1-6}alkyl;

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, R^1 is furanyl substituted with C_{1-6}alkyl and R^2 is hydrogen or C_{1-4}alkyl.

3. A chemical compound according to claim 2 wherein L is C_{3-6}alkenyl optionally substituted with phenyl or substituted phenyl, or wherein L is a radical of formula (b-1), (b-2) or (b-5) wherein R^4 is C_{1-6}alkyl, phenyl or substituted pheny, R^7 is phenyl, substituted phenyl or C_{1-6}alkyl optionally substituted with phenyl or substituted phenyl, R^8 is hydrogen C_{1-6}alkyl, and R^9 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 R^3 is hydrogen, phenylsulfonyl, 4,5-dihydro-5-oxo-1H-tetrazol-1-yl being optionally substituted in its 4-position with C_{1-4}alkyl, 2,3-dihydro-1,4-benzodioxin-2-yl, 4-morpholinyl, 1-piperidinyl or 1-pyrrolidinyl, or when R^1 is furanyl substituted with C_{1-6}alkyl and $A^1=A^2-A^3=A^4$ is a bivalent radical of formula (a-1) or (a-2), R^3 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-piperidinyl)-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-W^1 (III), wherein W^1 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 L'=O (IV), said L'=O being an intermediate of formula L'H_2 wherein two geminal hydrogen atoms are replaced by =O, in a reaction-inert solvent thus preparing a compound of formula L'H-D (I-a), wherein L' is a geminal bivalent radical comprising R^3-C_{1-6}alkylidene, R^4-O-C_{1-6}alkylidene, R^6R^5-N-C_{1-6}alkylidene and R^7-C(=O)-Z-C_{1-6}alkylidene;

c) O-alkylating an intermediate of formula HO-Alk-D (V) with a reagent of formula R^{4-a}-W^1 (VI) wherein R^{4-a} is Ar^1, 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 W¹-Alk-D (VII) with a reagent of formula R^{4-a}-O-H (VIII) wherein R^{4-a} is Ar^1, in a reaction-inert solvent, thus preparing a compound of formula (I-b);

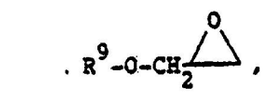
e) reacting an isocyanate of formula R^{7-a}-N=C=O (X) wherein R^{7-a}-NH- is amino, Ar^2-amino, C_{1-6}alkylamino or Ar^2-C_{1-6}alkylamino, with an intermediate of formula H-Z'-Alk-D (IX) wherein Z' is NR^8 or O, in a reaction-inert solvent, thus preparing a compound of formula R^{7-a}-NH-C(=O)-Z'-Alk-D (I-c-1);

f) reacting a reagent of formula R^{7-b}-H (XII) wherein R^{7-b} has the previously defined meaning of R^7 provided that it is other than Ar^2 or C_{1-6}alkyl optionally substituted with Ar^2, with an isocyanate of formula O=C=N-Alk-D (XI) in a reaction-inert solvent, thus preparing a compound of formula R^{7-b}-C(=O)-NH-Alk-D (I-c-2);

g) reacting a reagent of formula R^{7-c}-C(=O)-OH (XIII), wherein R^{7-c} is Ar^2 or C_{1-6}alkyl optionally substituted with Ar^2, 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^{7-c}-C(=O)-Z'-Alk-D (I-c-3);

h) reacting an alkenylene of formula L^2-C_{2-6}alkenediyl-H (XIV), wherein L^2 being Ar^1-thio, Ar^3-sulfonyl, Ar^2, C_{1-6}alkylcarbonyl, Ar^2-C_{1-6}alkylcarbonyl, Ar^2-carbonyl, C_{1-6}alkyloxycarbonyl, Ar^1-C_{1-6}alkyloxycarbonyl or C_{3-6}cycloalkyloxycarbonyl, with a piperidine of formula H-D (II), in a reaction-inert solvent, thus preparing a compound of formula L^2-C_{2-6}alkanediyl-D (I-d);

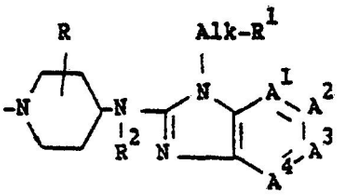
i) reacting a reagent of formula



with a piperidine of formula H-D (II), in a reaction-inert solvent, thus preparing a compound of formula R^9-O-CH_2-CH(OH)-CH_2-D (I-e);

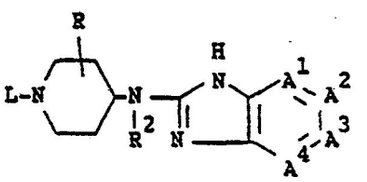
j) reducing an intermediate of formula C_{1-6}alkyl-O-C(=O)-D (XVI) with a reductant in a reaction-inert solvent, thus preparing a compound of formula CH_3-D (I-f);

wherein D represents a radical of formula



wherein A^1=A^2-A^3=A^4, R, R^1 and R^2 have the previously described meanings; or

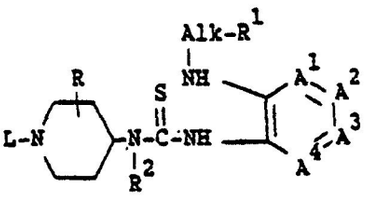
k) N-alkylating an intermediate of formula



(XVII)

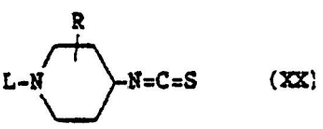
with a reagent of formula W-Alk-R^1 (XVIII) in a reaction-inert solvent, or

l) cyclodesulfurizing an intermediate of formula



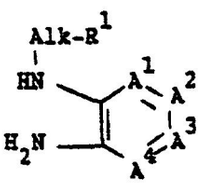
(XIX)

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



(XX)

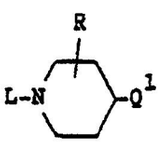
with a diamine of formula



(XXI),

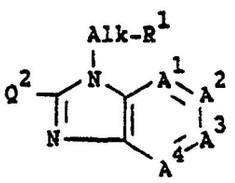
with an alkylhalide, metal oxide or metal salt in a reaction-inert solvent; or

m) reacting a piperidine of formula



(XXII)

with a benzimidazole derivative of formula



(XXIII)

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

Q^1 is $-NHR^2$ and Q^2 is W, or

Q^1 is W^1 and Q^2 is $-NHR^2$, or

Q^1 is $=O$ and Q^2 is $-NHR^2$; 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.

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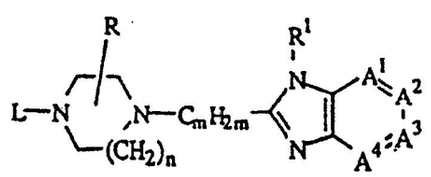
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(54) **Anti-allergic 2-(heterocyclyl alkyl) imidazo pyridines and 2-(heterocyclyl alkyl) purines.**

(57) Antiallergic 2-(heterocyclylalkyl)imidazopyridines of formula



(I),

wherein
$-A^1=A^2-A^3=A^4-$ is $-N=CH-CH=CH-$, $-CH=N-CH=CH-$, $-CH=CH-N=CH-$, $-CH=CH-CH=N-$, $-N=CH-N=CH-$ or $-CH=N-CH=N-$;
R^1 is hydrogen, C_{1-10}alkyl, C_{3-6}cycloalkyl, Ar^1, C_{1-6}alkyl or a radical of formula -Alk-G-R^2;
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 -Alk-R^4, -Alk-Y-R^5, Alk-Z^1-C(X)-Z^2-R^6 or $-CH_2$-CHOH-CH_2-O-R^7;
the pharmaceutically acceptable acid addition salts and possible stereochemically isomeric forms thereof, novel compounds of formula (I); pharmaceutical compositions containing such compounds as an active

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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

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 (Sterotex ®). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each comprising 0.01 g of the active ingredient.

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 (Opaspray K-1-2109 ®) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example 37 : INJECTABLE SOLUTION

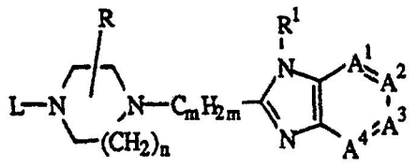
1.8 g Methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50° C there were added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I. The solution was cooled to room temperature and supplemented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

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 (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 0.03 g of the active ingredient.

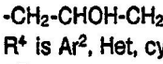
Claims

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



(I),

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
$-N=CH-CH=CH-$ (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
$-CH=N-CH=N-$ (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_{1-10}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
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;
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}alkyoxycarbonyl, 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 .
$-Alk-R^4$ (b-1)
$-Alk-Y-R^5$ (b-2)



(b-3), or
$-CH_2-CHOH-CH_2-O-R^7$ (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;
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;
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 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 same meaning of the previously defined X and A is hydrogen, Ar^2 or C_{1-6}alkyl being optionally substituted with Ar^2, Cbeing 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 4 substituents, said £p¶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^9 O or S, then Z^2 is other than O or S;

Ar^1 is phenyl, being optionally substituted with 1, 2 or 3 substituents each independently selected from 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; thienyl; halothienyl; furanyl; C_{1-6}alkyl substituted furanyl; pyridinyl; pyrimidinyl; pyrazinyl; thiazolyl or imidazolyl optionally substituted with C_{1-6}alkyl; and

Ar^2 is phenyl being optionally substituted with 1, 2 or 3 substituents each independently selected from 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 of formula (I) as defined in claim 1, provided that when L is C_{1-2}alkyl, R^1 is other than hydrogen, 2-methylphenyl, benzyl, 4-chlorobenzyl or 4-methoxybenzyl.

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 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 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 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; 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^9, 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_{1-6}alkyl substituted with Ar^1 or wherein R^1 is a radical -Alk-O-R^2, said R^2 being hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}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_{1-6}alkyl or a radical of formula (b-1), (b-2) or (b-3).

6. A chemical compound according to claim 5, wherein R^4 is Ar^2 or Het; R^5 and R^6 independently are C_{1-4}alkyl, Ar^2 or Het; R^8 is hydrogen or C_{1-4}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.

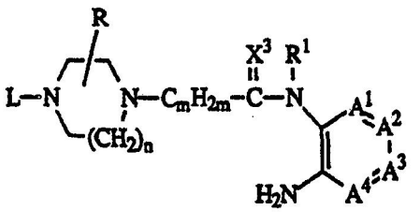
8. An anti-allergic pharmaceutical composition comprising a suitable pharmaceutical carrier and as active ingredient an effective anti-allergic amount of a compound as claimed in any one of claims 2 to 6.

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.

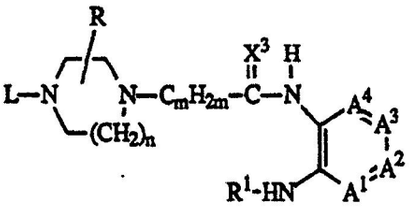
10. A compound as claimed in any of claims 2 to 6 for use as a medicine.

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



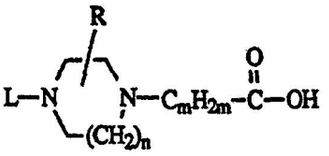
(II-a) , or



(II-b)

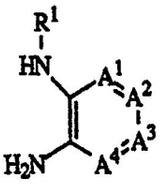
wherein X^3 is O, S or NH, in a reaction-inert solvent, if desired, in the presence of a dehydrating agent;

b) reacting an acid of formula



(III)

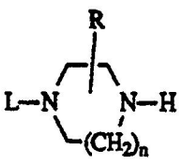
or a functional derivative thereof, with an aromatic diamine of formula



(III)

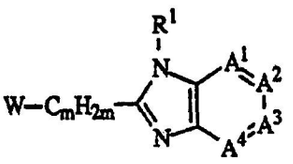
in a reaction-inert solvent;

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



(V)

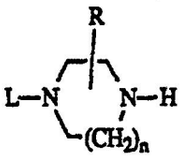
with an imidazopyridine or imidazopyrimidine of formula



(VI)

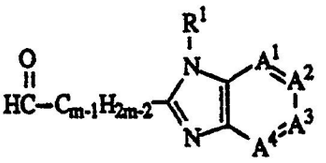
wherein W is a reactive leaving group, in a reaction-inert solvent; if desired, in the presence of a base;

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



(V)

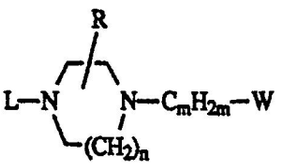
with an imidazopyridine or imidazopyrimidine of formula



(VII)

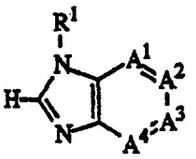
in a reductive medium;

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



(VIII)

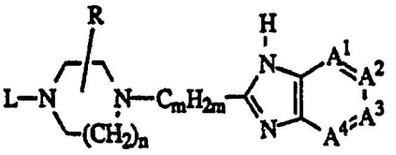
with an imidazopyridine or imidazopyrimidine of formula



(IX)

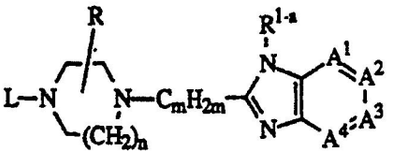
or the metal substitution form thereof, in a reaction-inert medium;

f) N-alkylating a compound of formula



(I-b)

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



(I-a)

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

g) N-alkylating a compound of formula H-D (I-d) with a reagent of formula L^1-W (XI) in a reaction-inert solvent, thus preparing a compound of formula L^1-D (I-c), wherein L^1 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 $L^2=O$ (XII), said $L^2=O$ being an intermediate of formula L^2H_2 wherein two geminal hydrogen atoms are replaced by =O, in a reductive medium thus preparing a compound of formula L^2H-D (I-c-1); wherein L^2 is a geminal bivalent radical comprising C_{3-6}cycloalkylidene, C_{1-12}alkylidene, R^4-C_{1-6}alkylidene, R^5-Y-C_{1-6}alkylidene and R^6-Z^2-C(=X)-Z^1-C_{1-6}alkylidene;

i) alkylating a compound of formula H-Y-Alk-D (I-c-3) with an intermediate of formula R^{5-a}-W^1 (XIII), wherein R^{5-a} is Ar^2 or Het, in a reaction-inert solvent, thus preparing a compound of formula R^{5-a}-Y-Alk-D (I-c-2);

j) alkylating an intermediate of formula R^{5-a}-Y-H (XIV) wherein R^{5-a} is Ar^2 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 R^5-Z^{2-a}-H (XV), wherein Z^{2-a} has the previously defined meaning of Z^2 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 R^5-Z^{2-a}-C(=X)-NH-Alk-D (I-c-5);

l) reacting an isocyanate or isothiocyanate of formula R^6-N=C=X (XVI) with a compound of formula H-Z^{1-a}-Alk-D (I-c-8), wherein Z^{1-a} has the previously defined meaning of Z^2 provided that it is other than a direct bond, in a reaction-inert solvent, thus preparing a compound of formula R^6-NH-C(=X)-Z^{1-a}-Alk-D (I-c-7);

m) reacting a reagent of formula R^6-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 R^6-C(=X)-Z^{1-a}-Alk-D (I-c-9);

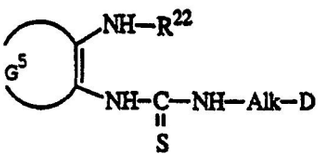
n) reacting an alkenylene of formula L^3-C_{2-6}alkenediyl-H (XVIII), wherein L^3 being Ar^2, Het, Ar^2-sulfonyl or a radical of formula R^6-Z^2-C(=X)-, with a compound of formula (I-d), in a reaction-inert solvent, thus preparing a compound of formula L^3-C_{2-6}alkenediyl-D (I-c-10);

o) reacting a reagent of formula R^{25}



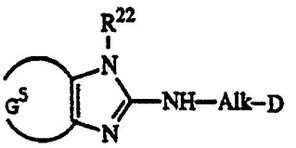
wherein R^{25} is hydrogen or a radical R^7-O-CH_2-, with a compound of formula (I-d), in a reaction-inert solvent, thus preparing a compound of formula R^{25}-CH(OH)-CH_2-D (I-c-11);

p) cyclodesulfurizing a compound of formula



(I-c-13)

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



(I-c-12)

wherein G^5 and R^{22} are as previously defined; or

q) cyclizing a guanidine derivative of formula

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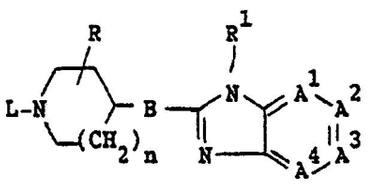
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(54) [(Bicyclic heterocyclyl)methyl and -hetero] substituted hexahydro-1H-azepines and pyrrolidines.

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



(I),

wherein

$-A^1=A^2-A^3=A^4-$ 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 $-CH=N-CH=N-$,

R^1 is hydrogen, C_{1-10}alkyl, C_{3-6}cycloalkyl, Ar^1 or C_{1-6}alkyl substituted with one or two Ar^1 radicals;

B is NR^2, CH_2, O, S, SO or SO_2;

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

n is 0 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 -Alk-R^3, -Alk-Y-R^4, -Alk-Z^1-C(X)-Z^2-R^5, or $-CH_2-CHOH-CH_2-O-R^6$;

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

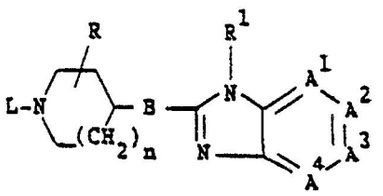
EP 0 297 661 A1

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



(I),

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),

$-CH=CH-CH=N-$ (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, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl or hydroxy;

R^1 is hydrogen, C_{1-10}alkyl, C_{3-6}cycloalkyl, Ar^1 or C_{1-6}alkyl substituted with one or two Ar^1 radicals;

B is NR^2, CH_2, O, S, SO or SO_2; said R^2 being hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl and Ar^2-C_{1-6}alkyl;

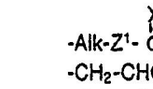
R is hydrogen or C_{1-6}alkyl;

n is 0 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

$-Alk-R^3$ (b-1)

$-Alk-Y-R^4$ (b-2)



(b-3), or

$-CH_2-CHOH-CH_2-O-R^6$ (b-4); wherein

R^3 is Ar^2, Het, cyano, isocyanato, isothiocyanato, Ar^2-sulfonyl or halo;

R^4 is hydrogen, Ar^2, Het or C_{1-6}alkyl optionally substituted with halo, Ar^2 or Het;

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

R^6 is Ar^2 or naphthalenyl;

Y is O, S, NR^7;

said R^7 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^8 or a direct bond;

said R^8 being hydrogen or C_{1-6}alkyl;

X is O, S or NR^9;

said R^9 is hydrogen, C_{1-6}alkyl or cyano;

each Alk independently being C_{1-6}alkanediyl;

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^8, 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; halothienyl; 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

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^8, 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^3, 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.

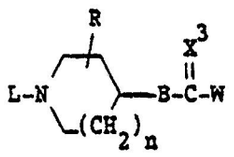
7. An anti-allergic pharmaceutical composition comprising a suitable pharmaceutical carrier and as active ingredient an effective anti-allergic amount of a compound as claimed in any one of claims 1 to 5.

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.

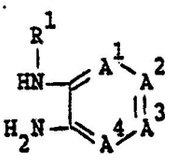
10. A compound as claimed in any one of claims 1 to 5 for use as an anti-allergic medicine.

11. A process for preparing a chemical compound as claimed in any one of claims 1 to 5, characterized by
a) reacting a pyrrolidine or hexahydro-1H-azepine of formula



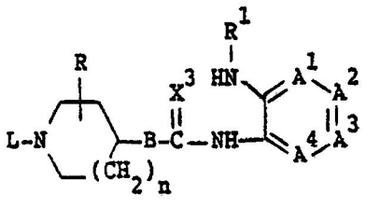
(II)

wherein X^3 is O, S or NH and W is a reactive leaving group, with an aromatic diamine of formula



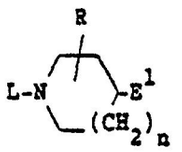
(III),

in a reaction-inert medium, said reaction proceeding in some instances via an intermediate of formula



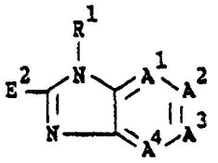
(II-a)

which may in situ, or if desired, after isolating and further purifying it, be cyclized to yield the desired compounds of formula (I);
b) reacting a pyrrolidine or hexahydro-1H-azepine of formula



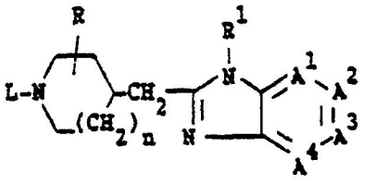
(IV)

with an intermediate of formula



(V),

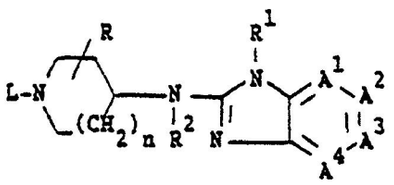
in a reaction-inert solvent if desired in the presence of a reductant, wherein:
i) E^1 is a radical of formula -B-M wherein M is hydrogen or an alkali metal or earth alkaline metal and E^2 is a radical of formula -W; or
(ii) E^1 is a radical of formula $-W^1$ and E^2 is a radical of formula M-B-; or
iii) E^1 is a radical of formula $-CH_2W^1$ and E^2 is a radical of formula -M, thus preparing a compound of formula



(I-a); or

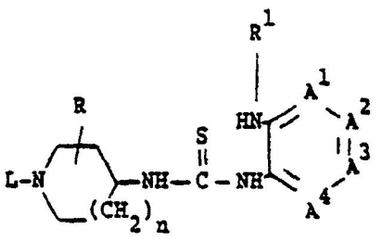
iv) E^1 is a radical of formula -M and E^2 is a radical of formula $-CH_2-W^1$, thus preparing a compound of formula (I-a); or

v) E^1 is a radical of formula =O and E^2 is a radical of formula R^2-NH-, thus preparing a compound of formula



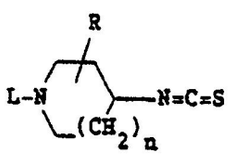
(I-b); or

c) cyclodesulfurizing an intermediate of formula



(VII),

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

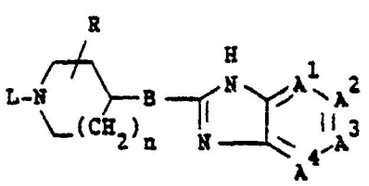


(VI)

with a diamine of formula (III),

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

d) N-alkylating an intermediate of formula



(VIII)

with a reagent of formula

W^1-R^1 (IX)

wherein W^1 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 L^1-W^1 (X) in a reaction-inert

solvent, thus preparing a compound of formula L^1-D (I-c), wherein L^1 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 $L^2=O$ (XI), said $L^2=O$ being an intermediate of formula L^2H_2 wherein two geminal hydrogen atoms are replaced by $=O$, in a reaction inert medium thus preparing a compound of formula L^2H-D (I-c-1), wherein L^2 is 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 and R^5-Z^2-C(=X)-Z^1-C_{1-6}alkylidene;

g) alkylating a compound of formula H-Y-Alk-D (I-c-3) with an intermediate of formula R^{4-a}-W^1 (XII), wherein R^{4-a} is a Ar^2 or Het, in a reaction-inert solvent, thus preparing a compound of formula R^{4-a}-Y-Alk-D (I-c-2);

h) alkylating an intermediate of formula R^{4-a}-Y-H (XIII) wherein R^{4-a} is Ar^2 or Het with a compound of formula W^1-Alk-D (I-c-4), in a reaction-inert solvent, thus preparing a compound of formula (I-c-2);

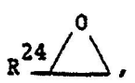
i) reacting a reagent of formula R^5-Z^{2-a}-H (XIV), werein Z^{2-a} has the previously defined meaning of Z^2 provided that it is other than a direct bond, with a compound of formula X=C=N-Alk-D (I-c-6), in a reaction-inert solvent, thus preparing a compound of formula R^5-Z^{2-a}-C(=X)-NH-Alk-D (I-c-5);

j) reacting an isocyanate or isothiocyanate of formula R^5-N=C=X (XV) with a compound of formula H-Z^{1-a}-Alk-D (I-c-8), wherein Z^{1-a} has the previously defined meaning of Z^1 provided that it is other than a direct bond, in a reaction-inert solvent, thus preparing a compound of formula R^5-NH-C(=X)-Z^{1-a}-Alk-D (I-c-7);

k) reacting a reagent of formula R^5-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 R^5-C(=X)-Z^{1-a}-Alk-D (I-c-9);

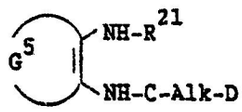
l) reacting an alkenylene of formula L^3-C_{2-6}alkenediyl-H (XVII), wherein L^3 being Ar^2, Het, Ar^2-sulfonyl or a radical of formula R^5-Z^2-C(=X)-, with a compound of formula (I-d), in a reaction-inert solvent, thus preparing a compound of formula L^3-C_{2-6}alkanediyl-D (I-c-10);

m) reacting a reagent of formula



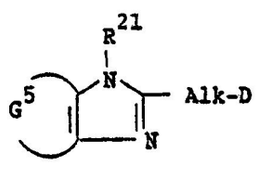
wherein R^{24} is hydrogen or a radical R^6-O-CH_2-, with a compound of formula (I-d), in a reaction-inert solvent, thus preparing a compound of formula R^{24}-CH(OH)-CH_2-D (I-c-11); or

n) cyclodesulfurizing a compound of formula



(I-c-13)

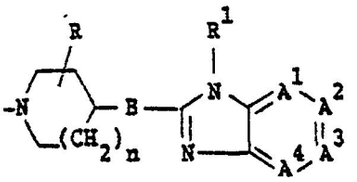
with an alkylhalide, metal oxide or metal salt in a reaction-inert solvent, thus preparing a compound of formula



(I-c-12),

wherein G^5 and R^{21} are as previously defined;

wherein D represents a radical of formula



;

wherein -A^1=A^2-A^3=A^4-, B, G, R, R^1 and n have the previously described meanings; or optionally converting the compounds 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.

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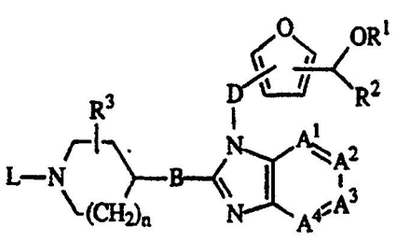
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(54) **Hydroxyalkylfuranyl derivatives.**

(57) Hydroxylalkylfuranyl derivatives of formula



(I),

wherein
$-A^1=A^2-A^3=A^4-$ 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 C_{1-4}alkanediyl ;
R^1 is hydrogen, C_{1-6}alkyl, arylC_{1-6}alkyl or C_{1-6}alkylcarbonyl ;
R^2 and R^3 are hydrogen or C_{1-6}alkyl ;
n is 0, 1 or 2 ;
B is NR^4, O, S, SO_2 or CH_2;
R^4 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl or arylC_{1-6}alkyl ;
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, arylC_{1-6}alkyloxycarbonyl, C_{1-6}alkylsulfonyl, arylsulfonyl, or a radical of formula -Alk-R^5, -Alk-Y-R^6, -Alk-Z^1-C(=X)-Z^2-R^7, or $-CH_2$-CHOH-CH_2-O-R^8,
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.

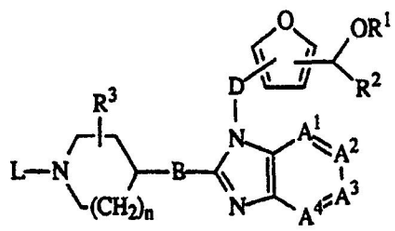
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Example 32 : INJECTABLE SOLUTION

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

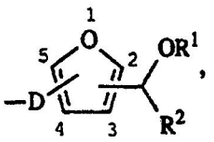


(I),

a pharmaceutically acceptable acid addition salt thereof 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),
$-CH=CH-CH=N-$ (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, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl or hydroxy ;
D is C_{1-4}alkanediyl ;
R^1 is hydrogen, C_{1-6}alkyl, arylC_{1-6}alkyl or C_{1-6}alkylcarbonyl ;
R^2 is hydrogen or C_{1-6}alkyl ;
R^3 is hydrogen or C_{1-6}alkyl ;
n is 0, 1 or 2 ;
B is NR^4, O, S, SO, SO_2 or CH_2;
R^4 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl or arylC_{1-6}alkyl ;
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, arylC_{1-6}alkyloxycarbonyl, C_{1-6}alkylsulfonyl, arylsulfonyl, or a radical of formula
-Alk-R^5 (b-1),
-Alk-Y-R^6 (b-2),
-Alk-Z^1-C(=X)-Z^2-R^7 (b-3), or
$-CH_2-CHOH-CH_2-O-R^8$ (b-4), wherein
R^5 is halo, cyano, isocyanato, isothiocyanato, aryl, Het or arylsulfonyl ;
R^6 is hydrogen, aryl, Het or C_{1-6}alkyl optionally substituted with halo, aryl or Het;
R^7 is hydrogen, aryl, Het or C_{1-6}alkyl optionally substituted with halo, aryl or Het;
R^8 is aryl or naphthalenyl;
Y is O, S, NR^9; said R^9 being hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl ;
Z^1 and Z^2 each independently are O, S, NR^{10} or a direct bond;
said R^{10} being hydrogen or C_{1-6}alkyl;
X is O, S or NR^{11}; said R^{11} being hydrogen, C_{1-6}alkyl or cyano;
each Alk independently is C_{1-6}alkanediyl;
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

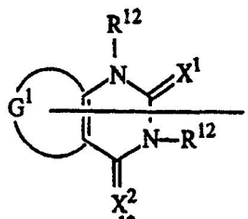
latter ring does not con-tain more than 2 oxygen and/or sulfur atoms and that the total number of heteroatoms in the bicyclic ring system is less than 6 ; and when Het is a monocyclic ring system it may optionally be substituted with up to 4 substituents, when Het is a bicyclic ring system it may optionally 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 -Z^1-C(=X)-Z^2-E ; wherein X, Y, Z^1 and Z^2 are as previously defined hereinabove ; and E is hydrogen, aryl or C_{1-6}alkyl being optionally substituted with aryl, C_{1-6}alkyloxy, aryloxy, hydroxy or C_{1-6}alkyloxycarbonyl;
each aryl is phenyl optionally substituted with 1, 2 or 3 substituents each indepen-dently selected from 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}alkyloxy-carbonyl and C_{1-6}alkylcarbonyl ; and
provided that when R^5 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 C_{1-6}alkyl 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 -$(CH_2)_2$-, -$(CH_2)_3$-, -CH=CH-, -CH=N-, -N=CH-, or -N=CH-CH_2-, wherein one or where possible two hydrogen atoms of said bivalent radicals each independently from one another may be replaced by C_{1-6}alkyl.

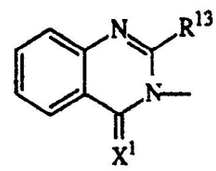
2. A compound according to claim 1 wherein R^1 is hydrogen or arylC_{1-6}alkyl ; R^3 is hydrogen ; B is NH or CH_2 ; n is 1 or 2 ; L is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, or a radical of formula (b-1), (b-2), (b-3) or (b-4) ; or the moiety

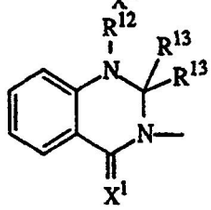


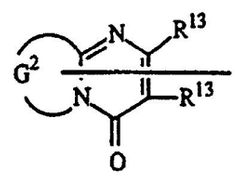
is (2-CHR^{2}OR^1-furan-5-yl)C_{1-4}alkyl or (3-CHR^{2}OR^1-furan-5-yl)-C_{1-4}alkyl, wherein aryl is as defined in claim 1.

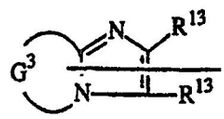
3. A compound according to claim 2 wherein R^1 is hydrogen; R^2 is hydrogen; n is 1 or 2; L is methyl or a radical of formula (b-1), (b-2) or (b-3); R^5 is aryl or Het; R^6 is C_{1-6}alkyl or Het; R^7 is aryl, Het or C_{1-6}alkyl; Y is O or NH; Z^1 and Z^2 each independently are NR^{10} or a direct bond, R^{10} being hydrogen or C_{1-6}alkyl; X is O; each Alk is C_{2-4}alkanediyl; Het is selected from pyridinyl, optionally substituted with one or two substituents each independently selected from halo, amino, mono- and di(C_{1-6}alkyl)amino, arylC_{1-6}alkylamino, nitro, cyano, aminocarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxycarbonyl, hydroxy, C_{1-6}alkylcarbonyloxy, arylC_{1-6}alkyl and carboxyl; pyridinyloxide, optionally substituted with nitro; pyrimidinyl, optionally substituted with one or two substituents each independently selected from halo, amino, C_{1-6}alkylamino, arylC_{1-6}alkylamino, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio and arylC_{1-6}alkyl; pyridazinyl, optionally substituted with C_{1-6}alkyl or halo; pyrazinyl, optionally substituted with halo, amino or C_{1-6}alkyl; thienyl, optionally substituted with halo or C_{1-6}alkyl; furanyl, optionally substituted with halo or C_{1-6}alkyl; pyrrolyl, optionally substituted with C_{1-6}alkyl; thiazolyl, optionally substituted with C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, aryl or arylC_{1-6}alkyl; imidazolyl, optionally substituted with one or two substituents each independently selected from C_{1-6}alkyl, arylC_{1-6}alkyl and nitro; tetrazolyl, optionally substituted with C_{1-6}alkyl; 1,3,4-thiadiazolyl, optionally substituted with C_{1-6}alkyl; 5,6-dihydro-4H-1,3-thiazin-2-yl, optionally substituted with C_{1-6}alkyl; 4,5-dihydrothiazolyl, optionally substituted with C_{1-6}alkyl; oxazolyl, optionally substituted with C_{1-6}alkyl; 4,5-dihydro-5-oxo-1H-tetrazolyl, optionally substituted with C_{1-6}alkyl; 1,4-dihydro-2,4-dioxo-3(2H)-pyrimidinyl, optionally substituted with C_{1-6}alkyl; 4,5-dihydro-4-oxopyrimidinyl, optionally substituted with up to 3 substituents selected from C_{1-6}alkyl, amino, C_{1-6}alkylaminocarbonylamino, arylaminocarbonylamino, arylC_{1-6}alkylamino and C_{1-6}alkylamino; 2,3-dihydro-3-oxopyridazinyl; 2-oxo-3-oxazolidinyl; pyrrolidinyl; piperidinyl; morfolinyl; thiomorfolinyl; dioxanyl, optionally substituted with C_{1-6}alkyl; indolyl, optionally substituted with hydroxy or C_{1-6}alkyl; quinolinyl, optionally substituted with hydroxy or C_{1-6}alkyl; quinazolinyl, optionally substituted with hydroxy or C_{1-6}alkyl; quinoxalinyl, optionally substituted with C_{1-6}alkyl; phthalazinyl, optionally substituted with halo; 1,3-dioxo-1H-isoindol-2(3H)-yl; 2,3-dihydro-3-oxo-4H-benzoxazinyl and 2,3-dihydro-1,4-benzodioxinyl, both being optionally substituted with C_{1-6}alkyl or halo; 2-oxo-2H-1-benzopyranyl and 4-oxo-4H-1-benzopyranyl, both being optionally substituted with C_{1-6}alkyl, and
a bicyclic heterocyclic radical of formula

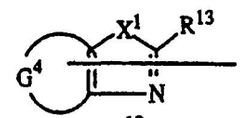

(c-1),

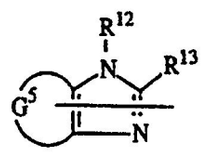

(c-2),

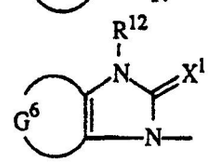

(c-3),


(c-4),


(c-5),

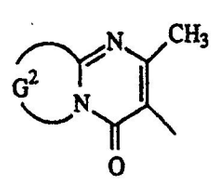

(c-6),


(c-7),


(c-8),

wherein X^1 and X^2 each independently are O or S ;
each R^{12} independently is hydrogen, C_{1-6}alkyl, arylC_{1-6}alkyl, C_{1-6}alkyloxy-C_{1-6}alkyl, hydroxyC_{1-6}alkyl or C_{1-6}alkyloxycarbonyl ;
each R^{13} independently is hydrogen, C_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, halo or C_{1-6}alkyloxycarbonylC_{1-6}alkyl ;
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 R^{12} and R^{13}, may represent the bond linking Het to respectively Alk, Y or Z^2 in the radicals of formula (b-1), (b-2) and (b-3) ;
G^1 is -CH=CH-CH=CH- or -S-CH=CH- ;
G^2 is -CH=CH-CH=CH-, $-(CH_2)_4$-, -S-$(CH_2)_2$-, -S-$(CH_2)_3$-, -S-CH=CH-, -CH=CH-O-, -CH=C(CH_3)-O-, -NH-$(CH_2)_2$-, -NH-$(CH_2)_3$-, -NH-CH=CH-, -NH-N=CH-CH_2-, -NH-CH=N- or -NH-N=CH- ;
G^3 is -CH=CH-CH=CH-, -CH_2-NH-$(CH_2)_2$-, -S-CH=CH-, -S-$(CH_2)_3$-, -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- ;
G^4 is -CH=CH-CH=CH-, -CH_2-NH-$(CH_2)_2$-, -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-;
G^5 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- ;
G^6 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- ;
wherein one or two hydrogen atoms in said radicals G^1, G^2, G^3, G^4, G^5 or G^6 or in the benzene part of the radicals of formula (c-2) or (c-3) may be replaced by C_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkyloxy or halo when connected to a carbon atom ; or by C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl or arylC_{1-6}alkyl when connected to a nitrogen atom, wherein each aryl is as defined in claim 1.

4. A compound according to claim 3 wherein R^5 is phenyl optionally substituted with C_{1-6}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


(c-4-a),

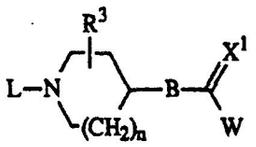
wherein G^2 is -CH=CH-CH=CH-, -S-$(CH_2)_3$-, -S-$(CH_2)_2$-, -S-CH=CH- or -CH=C(CH_3)-O-; or
R^6 is C_{1-6}alkyl; pyridinyl optionally substituted with nitro; pyrimidinyl; pyrazinyl; pyridazinyl optionally substituted with halo; or 2,3-dihydro-3-oxopyridazinyl; or the radical (b-3) is (arylcarbonyl)C_{1-6}alkyl, C_{1-6}alkylaminocarbonylC_{1-6}alkyl or a radical Het^1-C(=O)-NH-C_{1-6}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.

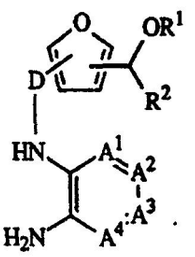
7. A compound as claimed in any of claims 1 to 4 for use as a medicine.

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



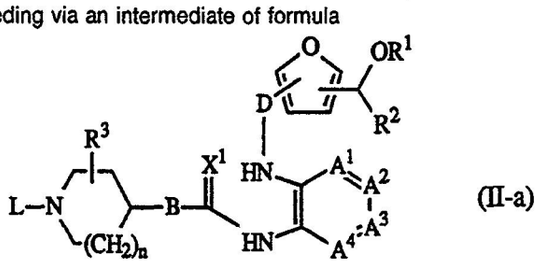
(II)

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



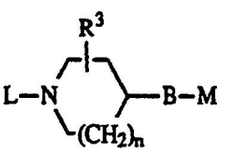
(III)

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



(II-a)

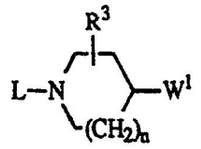
which may in situ, or if desired, after isolating and purifying it, be cyclized to yield a compound of formula (I);
b) reacting an intermediate of formula



(IV)

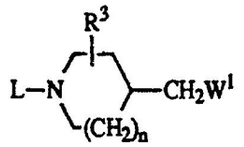
wherein M is hydrogen when B is other than CH_2 or M represents an alkali or earth alkaline metal when B represents CH_2 and R^3, L, B and n are as defined in claim 1, with an intermediate of formula W-Q (V) wherein W is a reactive leaving group, in a reaction-inert solvent;

c) reacting an intermediate of formula



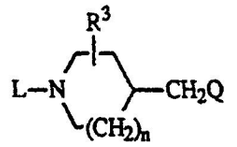
(VI)

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 M-B-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



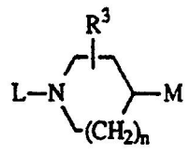
(VIII)

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 M-Q (IX) wherein M is an alkali or earth alkaline metal, in a reaction-inert solvent, thus yielding a compound of formula



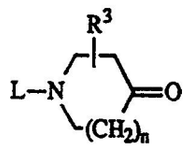
(I-a);

e) reacting an intermediate of formula



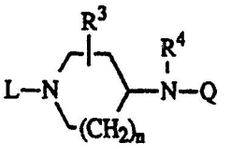
(X)

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 W^1-CH_2-Q (XI) wherein W^1 is a reactive leaving group, in a reaction-inert solvent, thus yielding a compound of formula (I-a);
f) reductively N-alkylating an intermediate of formula



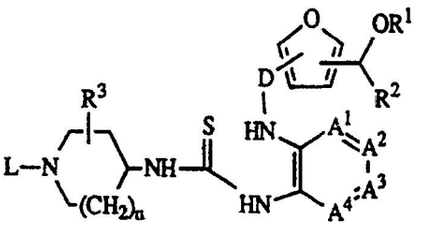
(XII)

wherein L, R^3 and n are as defined in claim 1, with an intermediate of formula R^4-NH-Q (VII-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 (VII-a) to form an enamine which may be isolated and purified, and subsequently reducing said enamine, thus yielding a compound of formula



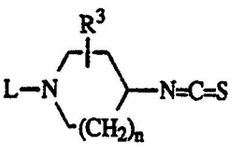
(I-b);

g) cyclodesulfurizing a thiourea of formula



(II-a-1)

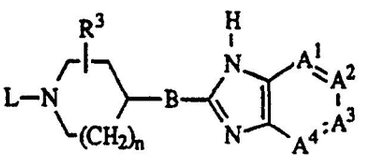
wherein -A^1 = A^2-A^3 = A^4-, R^1, R^2, R^3, D, L and n are as defined in claim 1, which may be formed in situ by condensing an isothiocyanate of formula



(XIII)

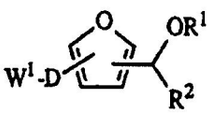
with a diamine of formula (III), with an alkylhalide, metal oxide or metal salt in a reaction-inert solvent;

h) N-alkylating an intermediate of formula



(XV)

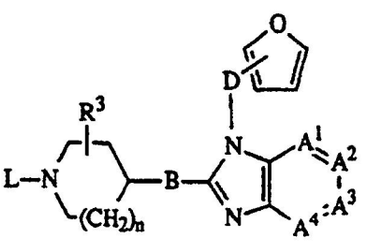
wherein -A^1 = A^2-A^3 = A^4-, B, L, R^3 and n are as defined in claim 1, with an alkylating reagent of formula



(XIV)

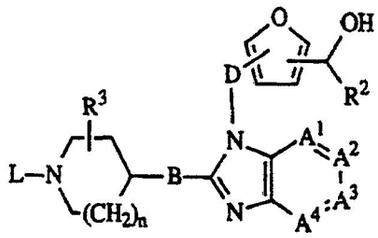
wherein W^1 is a reactive leaving group and R^1, R^2 and D are as defined in claim 1, in a reaction-inert solvent;

i) condensing a furan-derivative of formula



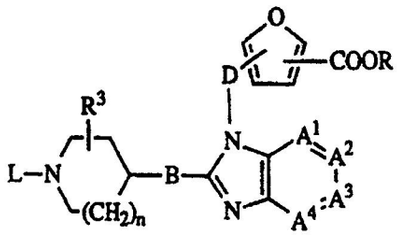
(XVI)

wherein -A¹=A²-A³=A⁴-, D, B, L, R³ and n are as defined in claim 1, with an aldehyde of formula R²-CHO (XVII) wherein R² is as defined in claim 1, in a reaction-inert solvent thus yielding a compound of formula



(I-c);

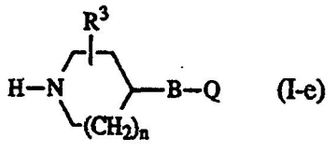
j) reacting a carboxylic acid derivative of formula



(XVIII)

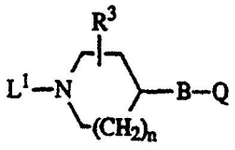
wherein R is hydrogen, alkyl or aryl and -A¹=A²-A³=A⁴-, D, B, L, R³ and n are as defined in claim 1, with a reducing agent in a reaction-inert solvent; or reacting (XVIII) with a C_{1-6}alkyllithium and reducing the thus obtained intermediate ketone with a reducing agent in a reaction-inert solvent, thus yielding a compound of formula (I-c);

k) N-alkylating a compound of formula



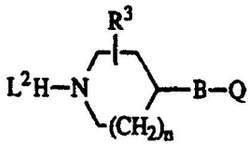
(I-e)

wherein B, R³ and n are as defined in claim 1, with an alkylating reagent of formula L¹-W¹ (XIX) wherein W¹ is a reactive leaving group and L¹ is L as defined in claim 1 but other than hydrogen, in a reaction-inert solvent, thus yielding a compound of formula



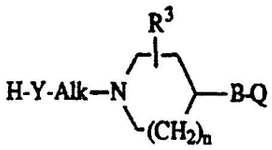
(I-d);

l) reductively N-alkylating a compound of formula (I-e) with a ketone or aldehyde of formula L²=O (XX) wherein L² is a geminal bivalent radical comprising C_{3-6}cycloalkylidene, C_{1-12}alkylidene, R^5-C_{1-6}alkylidene, in a reaction-inert solvent, thus yielding a compound of formula



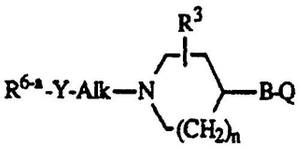
(I-d-1);

m) alkylating a compound of formula



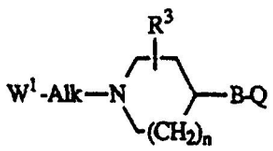
(I-d-3)

wherein B, R^3, Alk, Y and n are as defined in claim 1, with a reagent of formula R^{6-a}-W^1 (XXI) wherein W^1 is a reactive leaving group and R^{6-a} 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



(I-d-2);

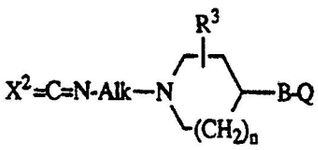
n) alkylating a reagent of formula R^{6-a}-Y-H (XXII) wherein R^{6-a} is aryl or Het, Y and said aryl and Het being as defined in claim 1, with a compound of formula



(I-d-4)

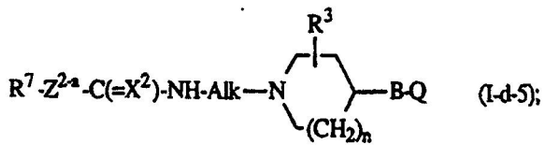
wherein B, Alk, R^3 and n are as defined in claim 1 and W^1 is a reactive leaving group, in a reaction-inert solvent, thus yielding a compound of formula (I-d-2);

o) reacting a compound of formula



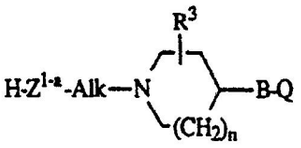
(I-d-6)

wherein X^2 is O or S and B, Alk, R^3 and n are as defined in claim 1, with a reagent of formula R^7-Z^{2-a}-H (XXIII) wherein Z^{2-a} is O, S or NR^{10}, R^7 and R^{10} being as defined in claim 1, in a reaction-inert solvent, thus yielding a compound of formula



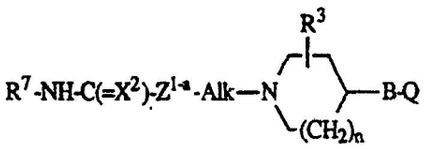
(I-d-5);

p) reacting a compound of formula



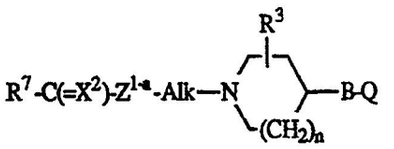
(I-d-8)

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 (X^2 = O) or isothiocyanate (X^2 = S) of formula R^7-N=C=X^2 (XXIV) wherein R^7 is as defined in claim 1, in a reaction-inert solvent, thus yielding a compound of formula



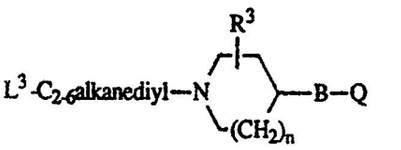
(I-d-7);

q) reacting a compound of formula (I-d-8) with a reagent of formula R^7-C(=X^2)-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 of amides, or by reacting (I-d-8) 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



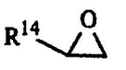
(I-d-9);

r) adding a compound of formula (I-e) to an alkene of formula L^3-C_{2-6}alkenediyl-H (XXVI) wherein L^3 is aryl, Het, arylsulfonyl or a radical of formula R^7-Z^2-C(=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



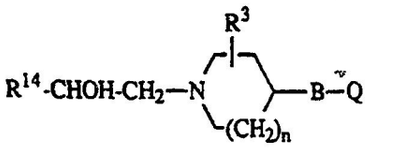
(I-d-10);

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



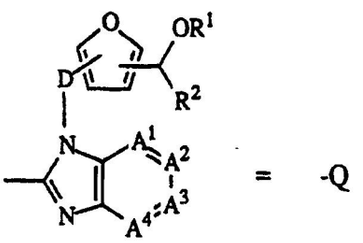
(XXVII)

wherein R^{14} is hydrogen, C_{1-4}alkyl or a radical of formula R^8-O-CH_2-, R^8 being as defined in claim 1, in a reaction-inert solvent, thus preparing a compound of formula



(I-d-11);

wherein Q represents a radical of formula



= -Q

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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C07D 473/34, 471/04

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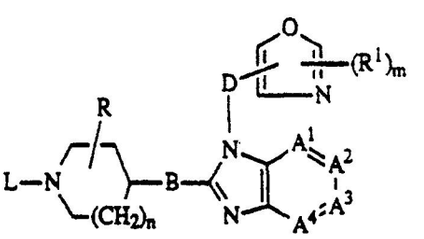
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Published
With international search report.

(54) Title: NOVEL OXAZOLYL DERIVATIVES



(I)

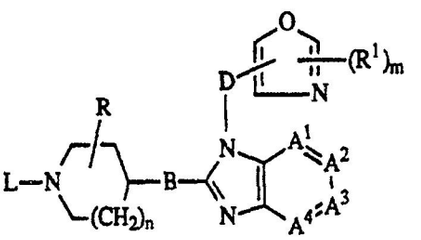
(57) Abstract

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_{1-6}alkyl or hydroxy-C_{1-6}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_{3-6}alkenyl optionally substituted with aryl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; arylcarbonyl; arylC_{1-6} 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.

+ See back of page

Claims

1. A compound having the formula :



(I),

a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, 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);

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;

R represents hydrogen or C_{1-4}alkyl;

R^1 represents hydrogen, C_{1-6}alkyl or hydroxyC_{1-6}alkyl;

m is 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 is 0, 1 or 2 ;

L represents 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; arylC_{1-6}alkyloxy-carbonyl; 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); wherein

R^3 represents cyano, aryl or Het;

R^4 represents hydrogen, aryl, Het or C_{1-6}alkyl optionally substituted with aryl or Het;

R^5 represents hydrogen, aryl, Het or C_{1-6}alkyl optionally substituted with aryl or Het;

R^6 represents aryl or naphthalenyl;

Y represents O, S, NR^7; said R^7 being hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

Z^1 and Z^2 each independently represent O, S, NR^8 or a direct bond; said R^8 being hydrogen or C_{1-6}alkyl;

X represents O, S or NR^9; said R^9 being hydrogen, C_{1-6}alkyl or cyano;

each Alk independently is C_{1-6}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(C_{1-6}alkyl)amino, arylC_{1-6}alkylamino, nitro, cyano, aminocarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, hydroxy, mercapto, hydroxyC_{1-6}alkyl, C_{1-6}alkyl-

carbonyloxy, aryl, arylC_{1-6}alkyl, carboxyl, C_{1-6}alkylaminocarbonylamino, arylaminocarbonylamino, oxo or thio;

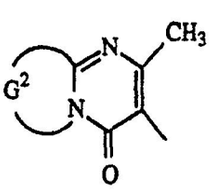
each aryl is phenyl optionally substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, mercapto, amino, mono- and di(C_{1-6}alkyl)amino, carboxyl, C_{1-6}alkyloxycarbonyl and C_{1-6}alkylcarbonyl.

2. A compound according to claim 1 wherein R represents hydrogen; m is 1; and R^1 represents hydrogen or C_{1-6}alkyl.

3. A compound according to claim 1 wherein $-A^1=A^2-A^3=A^4-$ represents a bivalent radical having the formula -CH=CH-CH=CH- (a-1) or -N=CH-CH=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 :

-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

each Alk independently represents C_{1-4}alkanediyl; R^3 represents phenyl, hydroxyphenyl, C_{1-4}alkyloxyphenyl, 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-2,6-dioxo-1H-purin-7-yl, 2,3-dihydro-2-oxo-1-benzimidazolyl or a radical of formula

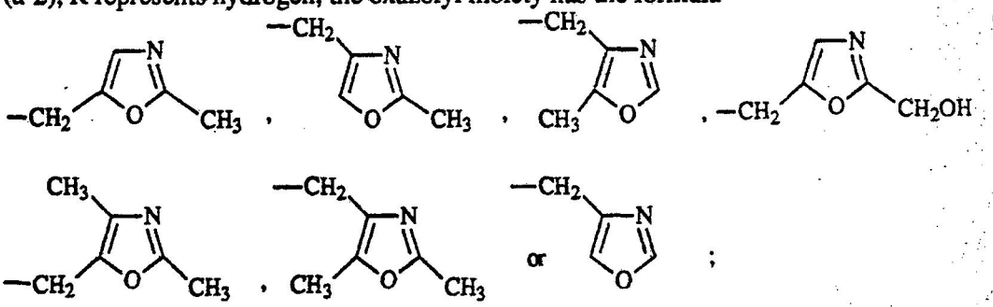


(c-4-a),

wherein G^2 represents -CH=CH-CH=CH-, $-(CH_2)_4-$, $-S-(CH_2)_2-$, $-S-(CH_2)_3-$, -S-CH=CH-, $-N(CH_2)_3$, $-N=C(CH_3)-CH_2-$, $-N(CH_3)-N=C(CH_3)-$; $-N(CH_3)-CH=CH-$ or $CH=C(CH_3)-O-$; Y represents NH, O or S; R^4 represents

hydrogen, C_{1-4}alkyl, 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; Z^1 and Z^2 each independently represent O, NH or a direct bond; X represents O or S; R^5 represents hydrogen, C_{1-4}alkyl, aminophenyl, C_{1-4}alkylphenyl, pyridinyl, aminopyridinyl, aminopyrazinyl, 1-methylpyrrolyl, furanyl or 1-methylindolyl; and R^6 represents phenyl.

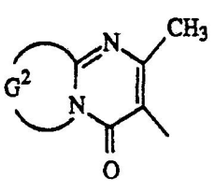
4. A compound according to claim 3 wherein $-A^1=A^2-A^3=A^4-$ represents a bivalent radical having the formula -CH=CH-CH=CH- (a-1) or -N=CH-CH=CH- (a-2), R represents hydrogen; the oxazolyl moiety has the formula



B represents NH, S or CH_2; n is 1; L represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, propenyl, 3-phenylpropenyl or a radical of formula

-Alk-R^3	(b-1);
-Alk-Y-R^4	(b-2);
-Alk-NH-C(=O)-R^{5-a}	(b-3-a); or
-Alk-C(=O)-Z^2-R^{5-b}	(b-3-b); wherein

each Alk independently represents C_{1-3}alkanediyl; R^3 represents phenyl, 4-methoxyphenyl, 4-hydroxyphenyl, pyridinyl, thienyl, 4,5-dihydro-4-ethyl-5-oxo-1H-tetrazolyl, 2-oxo-2H-1-benzopyranyl, 2-(amino- or methylamino)-3,4-dihydro-3,6-dimethyl-4-oxo-5-pyrimidinyl, 6-purinyl, or a radical of formula



(c-4-a),

wherein G^2 represents -CH=CH-CH=CH-, $-(CH_2)_4-$, $-S-(CH_2)_2-$, $-S-(CH_2)_3-$, -S-CH=CH- or $-N(CH_3)-N=C(CH_3)-CH_2-$; Y represents NH or O; R^4 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; Z^2 represents O; and R^{5-b} represents hydrogen.

5. A compound according to claim 1 wherein the compound is 1-[(2-methyl-5-oxazolyl)methyl]-N-(1-methyl-4-piperidinyl)-1H-benzimidazol-2-amine, a solvate or a pharmaceutically acceptable addition salt thereof.

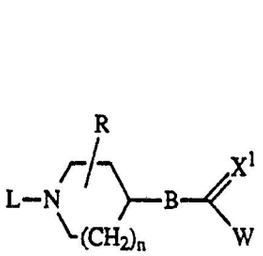
6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient an effective antiallergic amount of a compound as claimed in any of claims 1 to 5.

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.

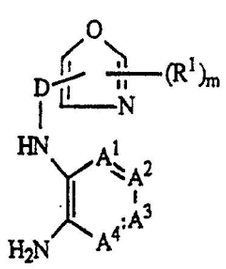
9. A process of preparing a compound as defined in any of claims 1 to 5, characterized by

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),



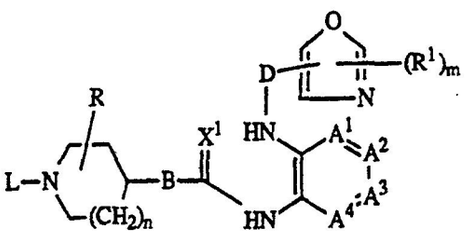
(II)

+



(III)

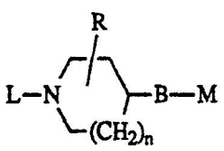
in a reaction-inert solvent thus yielding a compound of formula (I), or optionally yielding a compound of formula (II-a)



(II-a)

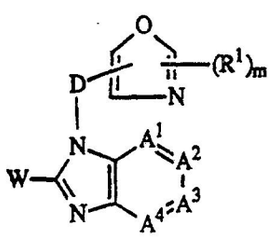
which can be cyclized to a compound of formula (I) by treatment with an alkyl halide, a metal oxide or a metal salt in a reaction-inert solvent;

b) reacting an intermediate of formula (IV)



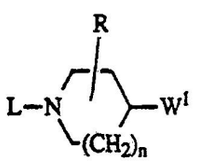
(IV)

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, with an intermediate of formula



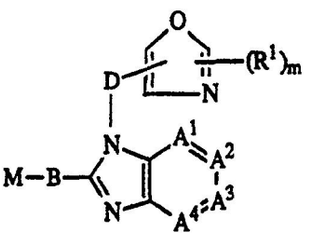
wherein W represents a reactive leaving group, in a reaction-inert solvent, optionally in the presence of a base;

c) reacting an intermediate of formula (VI)



(VI)

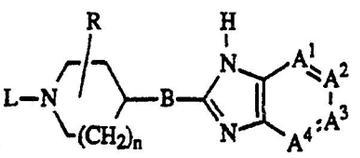
wherein W^1 represents a reactive leaving group with an intermediate of formula (VII)



(VII)

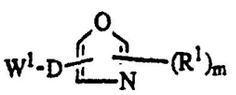
wherein M and B have the meaning as defined under formula (IV), in a reaction-inert solvent, optionally in the presence of a base;

d) N-alkylating an intermediate of formula (XV)



(XV)

with an alkylating reagent of formula (XIV)

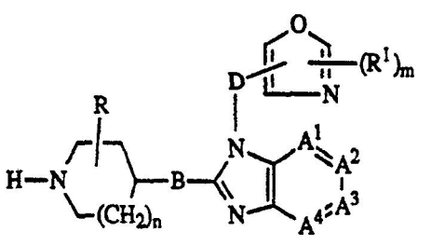


(XIV)

wherein W^1 represents a reactive leaving group, in a reaction-inert solvent in the presence of a base;

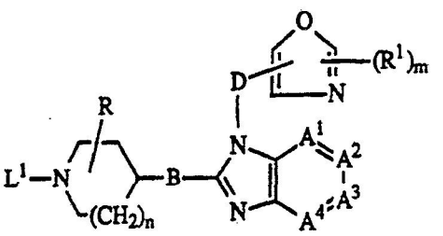
e) converting a compound of formula (I) wherein L represents benzyl into a compound of formula (I) wherein L represents C_{1-6}alkyloxycarbonyl by treatment with C_{1-6}alkylchloroformate;

f) hydrolyzing a compound of formula (I) wherein L represents C_{1-6}alkyloxycarbonyl in an aqueous acidic or basic medium, thus yielding a compound of formula (I-e)



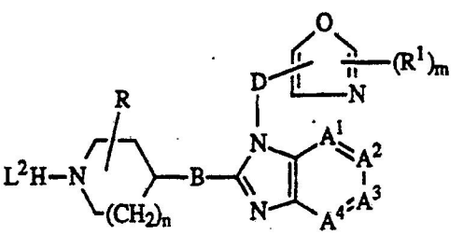
(I-e) ;

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)



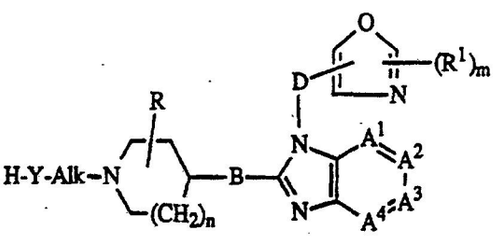
(I-d) ;

h) reductively N-alkylating a compound of formula (I-e) with a reagent of formula L^2=O (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)



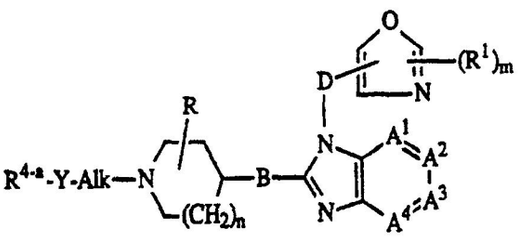
(I-d-1) ;

i) alkylating a compound of formula (I-d-3)



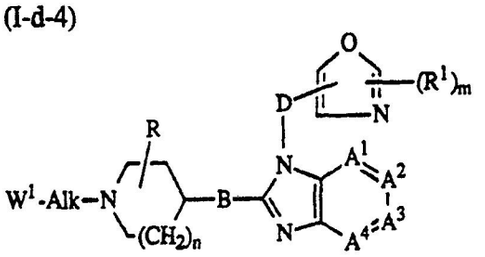
(I-d-3)

with a reagent of formula R^{4-a}-W^1 (XVIII) wherein R^{4-a} is aryl of Het, in a reaction-inert solvent, optionally in the presence of a base thus yielding a compound of formula (I-d-2)



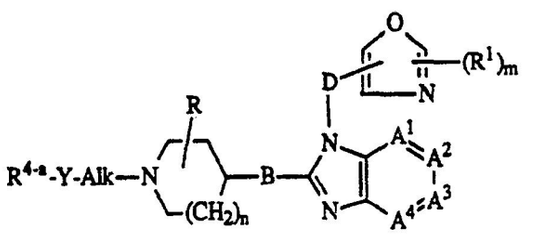
(I-d-2) ;

j) alkylating an intermediate of formula R^{4-a}-Y-H (XIX) with a compound of formula (I-d-4)



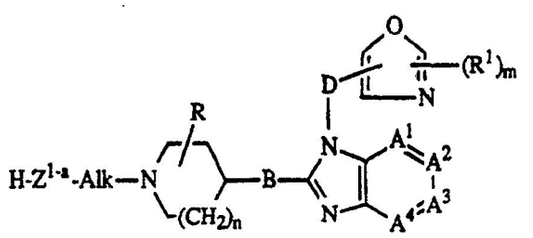
(I-d-4) ;

in a reaction-inert solvent, optionally in the presence of a base, thus yielding a compound of formula (I-d-2)



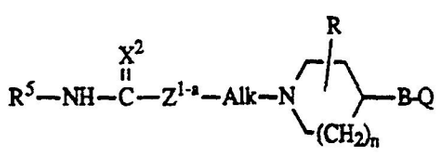
(I-d-2) ;

k) reacting a compound of formula (I-d-7)



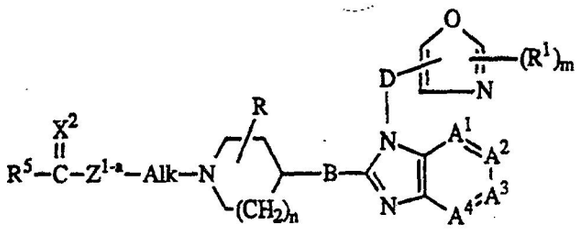
(I-d-7)

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)



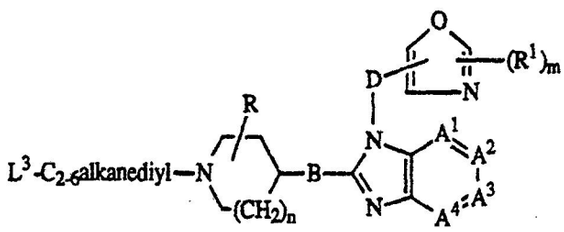
(I-d-6) ;

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)



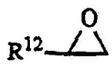
(I-d-8) ;

m) reacting a compound of formula (I-e) with an alkene of formula L^3-C_{2-6}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)



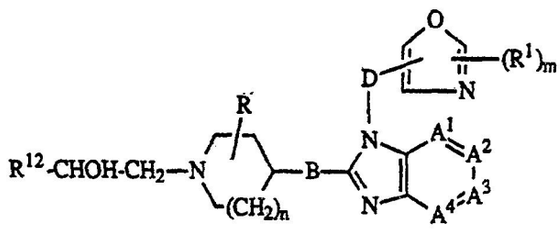
(I-d-9) ;

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



(XXV)

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)



(I-d-10) ;

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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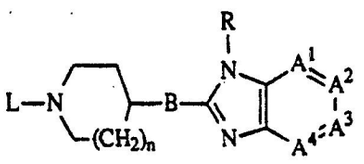
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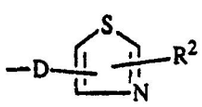
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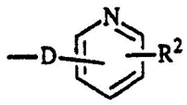
(54) Title: NOVEL SUBSTITUTED THIAZOLYL AND SUBSTITUTED PYRIDINYL DERIVATIVES



(I)



(b-1)



(b-2)

(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}alkanediyl; 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 -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.

+ See back of page

-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); wherein

R^3 is cyano, aryl or Het;
R^4 is hydrogen, aryl, Het or C_{1-6}alkyl optionally substituted with aryl or Het;
R^5 is hydrogen, aryl, Het or C_{1-6}alkyl optionally substituted with aryl or Het;
R^6 is aryl or naphthalenyl;
Y is O, S, NR^7; said R^7 being hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl ;
Z^1 and Z^2 each independently are O, S, NR^8 or a direct bond; said R^8 being hydrogen or C_{1-6}alkyl;
X is O, S or NR^9; said R^9 being hydrogen, C_{1-6}alkyl or cyano;
each Alk independently is C_{1-6}alkanediyl;

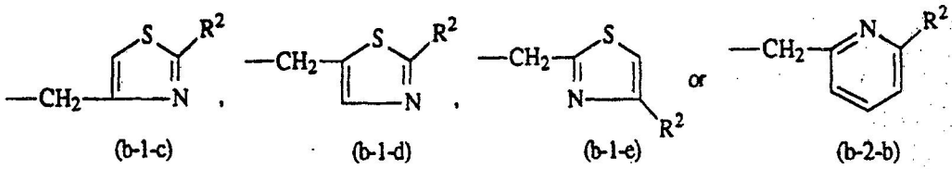
each Het is :

(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;
(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(C_{1-6}alkyl)amino, arylC_{1-6}alkylamino, nitro, cyano, aminocarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, hydroxy, mercapto, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyloxy, aryl, arylC_{1-6}alkyl, carboxyl, C_{1-6}alkylaminocarbonylamino, arylaminocarbonylamino, oxo or thio; and

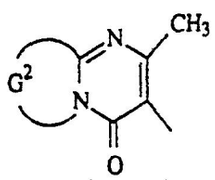
each aryl is phenyl optionally substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, mercapto, amino, mono- and di(C_{1-6}alkyl)amino, carboxyl, C_{1-6}alkyloxycarbonyl and C_{1-6}alkylcarbonyl.

2. A compound according to claim 1 wherein -A^1=A^2-A^3=A^4- represents a bivalent radical of formula -CH=CH-CH=CH- (a-1) or -N=CH-CH=CH- (a-2); B represents NH, CH_2 or O; R represents a radical of formula



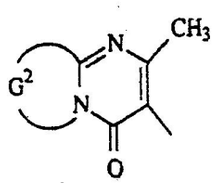
(b-1-c) (b-1-d) (b-1-e) (b-2-b)

R^2 represents C_{1-4}alkyl; n is 1; L represents hydrogen, C_{1-4}alkyl, C_{1-4}alkyloxycarbonyl or a radical of formula -Alk-R^3 (c-1), -Alk-Y-R^4 (c-2) or -Alk-Z^1-C(=X)-Z^2-R^5 (c-3); Alk represents C_{1-4}alkanediyl; R^3 represents phenyl, C_{1-4}alkyloxyphenyl or a radical of formula



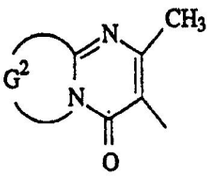
wherein G^2 represents -CH=CH-CH=CH-, -S-$(CH_2)_3$-, -S-$(CH_2)_2$- or -S-CH=CH-; Y represents O or NH; R^4 represents hydrogen, C_{1-4}alkyl or pyrimidinyl; R^5 represents C_{1-4}alkyl; Z^1 represents NH; Z^2 represents O; and X represents O.

3. A compound according to claim 1 wherein B represents NH or CH_2; R^2 represents methyl; L represents C_{1-4}alkyl or a radical of formula -Alk-R^3 (c-1), -Alk-Y-R^4 (c-2) or -Alk-Z^1-C(=X)-Z^2-R^5 (c-3); Alk represents C_{2-4}alkanediyl; R^3 represents 4-methoxyphenyl or a radical of formula



wherein G^2 represents -CH=CH-CH=CH-, -S-$(CH_2)_3$-, -S-$(CH_2)_2$-, -S-CH=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 formula -Alk-R^3 (c-1), Alk represents 1,2-ethanediyl and R^3 represents 4-methoxyphenyl or a radical of formula



wherein G^2 represents CH=CH-CH=CH-, -S-$(CH_2)_3$-, -S-$(CH_2)_2$- or -S-CH=CH-.

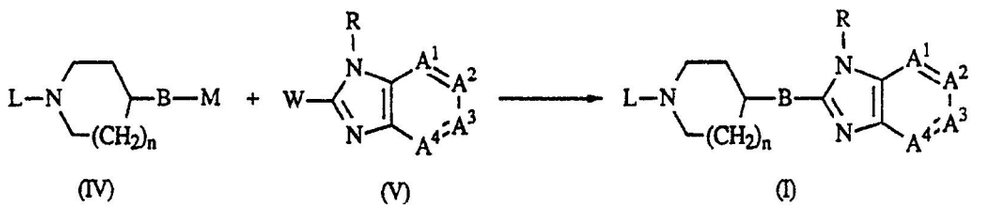
5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient an effective antiallergic amount of a compound as claimed in claim 1.

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.

8. A process of preparing a compound as claimed in claim 1, characterized by

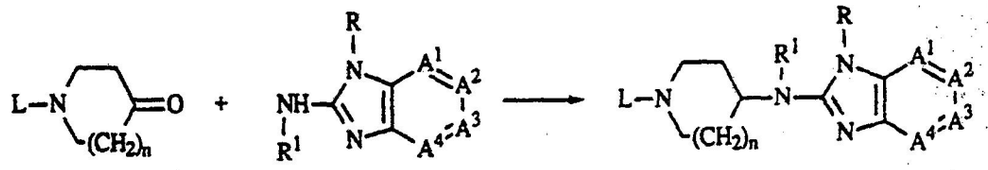
a) reacting a piperidine of formula (IV) wherein M represents hydrogen when B is other than hydrogen, or wherein M represents an alkali or earth alkaline metal when B represents CH_2, with a reagent of formula (V) wherein W represents a reactive leaving group,



(IV) (V) (I)

in a reaction-inert solvent, optionally in the presence of a base;

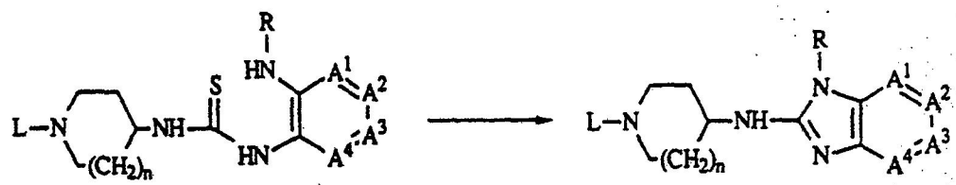
b) reductively N-alkylating a 4-piperidinone derivative of formula (XII) with an amine of formula (VII-a),



(XII) (VII-a) (I-b)

in the presence of an appropriate reductant in a reaction-inert solvent, thus yielding a compound of formula (I-b);

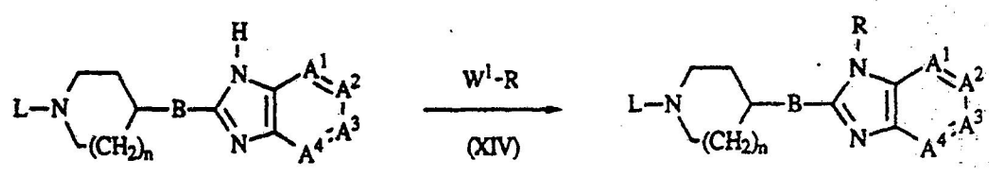
c) cyclodesulfurizing a thiourea of formula (II-a-1),



(II-a-1) (I-b-1)

by reaction with a metal oxide or salt in a reaction-inert solvent, optionally in the presence of a small amount of sulfur;

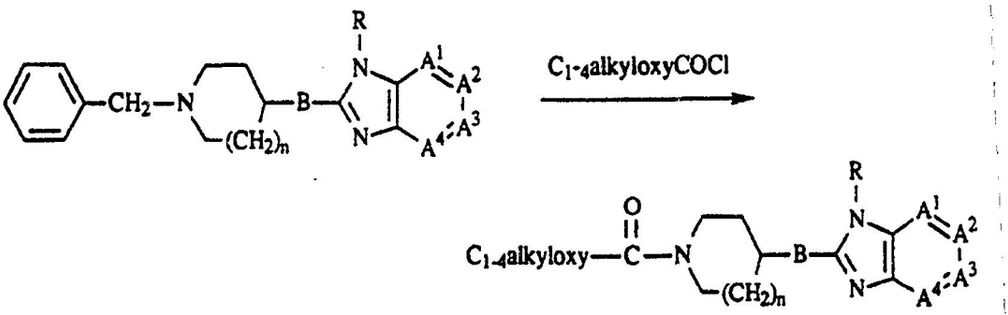
d) N-alkylating an intermediate of formula (XV) with an alkylating reagent of formula (XIV) wherein W represents a reactive leaving group,



(XV) (XIV) (I)

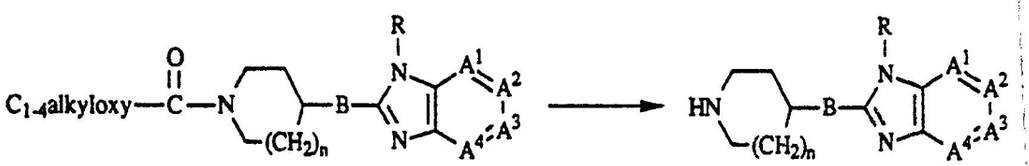
in a reaction-inert solvent in the presence of a base and at an elevated temperature;

e) converting a compound of formula (I) wherein L represents benzyl into a compound wherein L represents C_{1-4}alkyloxycarbonyl,



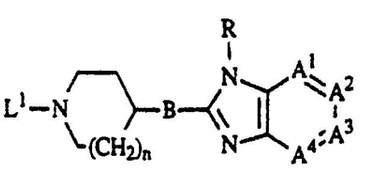
by reaction with a C_{1-4}alkylchloroformate in the presence of a base in a reaction-inert solvent;

f) hydrolyzing a compound of formula (I) wherein L represents C_{1-4}alkyloxy-carbonyl in an aqueous acidic or basic medium to a compound of formula (I-e),



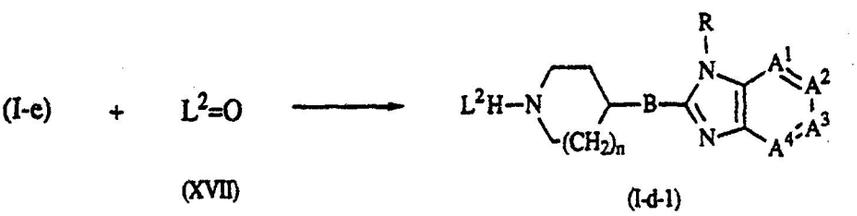
(I-e)

g) N-alkylating a compound of formula (I-e) with an alkylating reagent of formula L^1-W^1 (XVI) in a reaction-inert solvent in the presence of a base, thus preparing a compound of formula



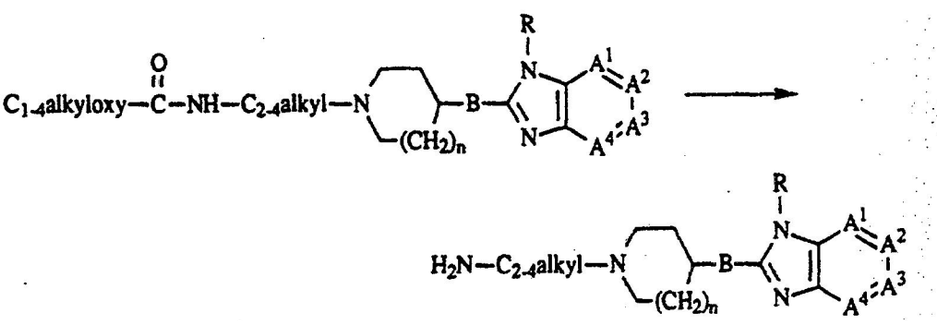
(I-d)

h) reductively N-alkylating a compound of formula (I) with an aldehyde or ketone of formula L^2=O (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,

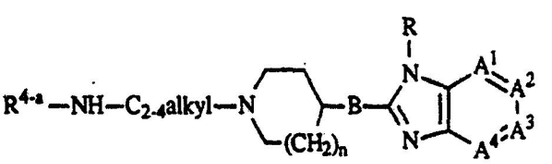


in a reaction-inert sovent in the presence of a reductant;

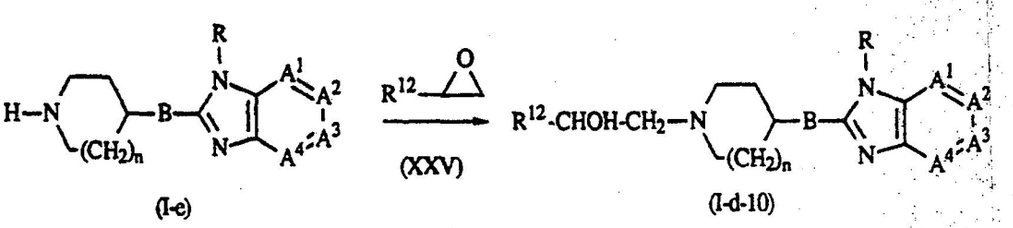
i) hydrolyzing a compound of formula (I) wherein L represents C_{1-4}alkyloxy-carbonylaminoC_{2-4}alkyl in a basic aqueous medium thus yielding a compound wherein L represents an aminoC_{2-4}alkyl radical,



j) alkylating the thus obtained compound wherein L represents aminoC_{2-4}alkyl with a reagent of formula $R^{4-a}W^1$ wherein R^{4-a} represents aryl or Het and W^1 represents a reactive leaving group thus yielding a compound of formula



k) reacting a compound of formula (I-e) with an epoxide of formula (XXV) wherein R^{12} represents hydrogen, C_{1-4}alkyl or R^6-O-CH_2-,



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.