404

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-074146- -00005-0000
Fecha: 2008-04-07 15:31:10 Dep: 2000 NUEVA CIONI
Tra. 11 PATENTEIYII Eve: NALI
Act. 329 CTOINFORMACION

FORMULARIO ÚNICO DE CORRECCIONES Y MODIFICACIONES

1 SOLICITUD DE :

☐ Corrección de error material ☒ Modificación a una solicitud

2 SOLICITANTE	Nombre: **Nycomed GmbH.** Dirección: Byk-Gulden-Strasse 2, D-78467 Konstanz, Alemania. Nacionalidad o Domicilio: Konstanz, Alemania. Lugar de Constitución: Alemania.	**IDENTIFICACIÓN** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: JIMENA ESCOBAR URIBE Dirección: Cra. 11 No. 86-53 piso 6 Teléfono: 6 162051/61 Fax: 6 161889 E-mail: Jiescobar@clarkemodet.com.co	**IDENTIFICACIÓN** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 39.779.452 T.P.68.228

4 Número del expediente: 06-074.146

5 Descripción de la corrección o modificación solicitada: Que se anote :

Que se anote el **CAMBIO DE NOMBRE** que hace la sociedad **Altana Pharma AG.**, domiciliada en Byk-Gulden-Strasse 2, 78467 Konstanz, Alemania a la sociedad **Nycomed GmbH.**, domiciliada en Byk-Gulden-Strasse 2, D-78467 Konstanz, Alemania.

6 Comprobante de pago No. 08 - 26,821 **Fecha** 3 de abril de 2008

7 Anexos:

☐ Comprobante de pago de la tasa

☐ Poderes, si fuere el caso

☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

8

NOMBRE: JIMENA ESCOBAR URIBE **FIRMA:**

C.C. 39.779.452 de Usaquén T.P. 68228

405
1 de 4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-074146- -00005-0000
Fecha: 2008-04-07 15:31:10 Dep: 2020 NUEVOS SOLICITUDES
Tra: 11 PATENTEIYII Eve: 378 FASE NACIONAL
Act: 329 CTOINFORMACION Folios: 25

RECIBO OFICIAL DE CAJA : 08 - 26,821
FECHA : ABRIL 3 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	NRO. PAGO	FECHA PAGO	VR. PAGO
CLARKE MODET Y CO. COLOMBCONSIGNACION		BANCO DE BOGOTA	062753[illegible]	[illegible]486[illegible]	03/04/2008	[illegible],000.00

***** C O N C E P T O S *****

CANTS.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICACION	12 MARCAS Y LEMAS COMERCIALES	103,000.00
		TOTAL $	103,000.00

SON: CIENTO TRES MIL PESOS

06-074146 x 6

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

2988

2

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$$\frac{1}{2} \times 10,00$$

606138

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Apostille

(Convention de La Haye du 5 octobre 1961)

1. Land: Bundesrepublik Deutschland
   Diese öffentliche Urkunde
2. ist unterschrieben von
   Justizrätin Dr. Stutz
3. in ihrer Eigenschaft als
   Notarin
4. sie ist versehen mit dem Dienststempel
   des Notariats Konstanz

Bestätigt

5. in Konstanz 6. am 05.10.2007
7. durch Vizepräsident des Landgerichts Deppert-Kern
   beim Landgericht Konstanz
8. unter Nr. E 910 a (AR 1361/07)
9. Siegel/Stempel 10. Unterschrift

.....

LANDGERICHT KONSTANZ

LANDGERICHT KONSTANZ

02 ABR 2008

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POWER OF ATTORNEY DOCUMENTO DE PODER

The undersigned
acting on behalf of and representing

Nycomed GmbH.

a company organized under the laws of

domiciled at

hereby appoints **JIMENA ESCOBAR-URIBE and/or IGNACIO ESCOBAR-URIBE and/or JULIANA ESCOBAR-URIBE**

domiciled at Bogota, Colombia
CARRERA 11 No. 86-53 Floor 6

as our true and legal attorneys with the necessary powers: 1. to apply to the administrative, judicial and police authorities of the Republic of Colombia, in any instance or appeal, for obtaining registration of patents, utility models, industrial designs, commercial ensigns, trade and domain names, trademarks, copyrights and neighbouring rights, plant varieties, health licenses as well as their assignments, extensions, renewals, changes of name and domicile; 2. to prepare, apply for, obtain, execute and register contracts, licenses, authorisations and registrations of any kind; 3. to intervene as plaintiffs or defendants, in any instance or appeal, before any judge, court, tribunal, corporation, public officer or authority in any judicial, administrative or police action, such as: actions dealing with commercial ensigns and names; oppositions against trademark registrations; caducity and nullity actions; recovery actions, actions arising from obtainment and working of license agreements; actions dealing with unfair competition; criminal actions; actions claiming indemnity for damages, complaints or remarks on all sort of industrial property matters; the performance of precautionary measures, and in any other similar action, measure or appeal related to industrial property matters, copyrights and neighbouring rights and obtentor of plant varietie's rights.
To this effect, we hereby authorise them to file applications, make descriptions, amendments, protests, declarations, oppositions, cancellations, appeals and claims; to pay taxes, quotas and liens as provided by law; to waive or abandon granted rights or rights in process of being granted, to receive all kind of documents and securities; to issue the respective releases and, in general, to take, before said authorities, pertinent steps to the abovementioned purposes and take all measures they may deem advisable to protect our interests, with all other necessary legal faculties, and we hereby declare as good and valid whatever the attorneys should do to our benefit.
This power comprises the authority to ratify or confirm on our behalf any action, as well as the faculty of receiving, desisting, transacting, compromising, conciliating, substituting and revoking substitutions, taking notifications and appointing judicial or extrajudicial attorneys.

Signed at Constance

on 27th of September 2007

SIGNATURE

ppa. Dr. Bernd Kratzer
Senior Director Intellectual Property

ppa. Alexander Mächler
Senior Legal Counsel

El suscrito
obrando en nombre y representación de

Nycomed GmbH.

una compañía organizada bajo las leyes de

con domicilio en

nombra a **JIMENA ESCOBAR-URIBE y/o IGNACIO ESCOBAR-URIBE y/o JULIANA ESCOBAR-URIBE**

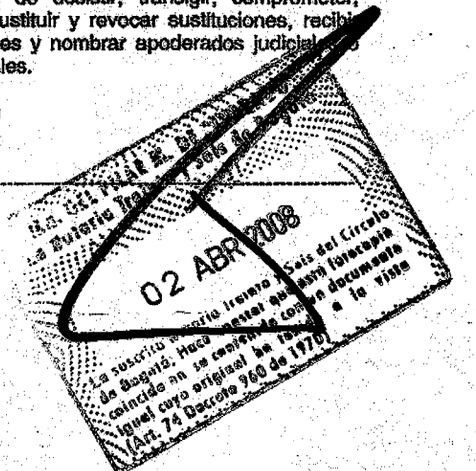
domiciliados en Bogotá, Colombia
CARRERA 11 No. 86-53 *Piso 6*

apoderados verdaderos y legales con poder especial, amplio y suficiente: 1. para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía en cualquier instancia o recurso, la obtención de patentes de invención, modelos de utilidad, diseños industriales, registro de marcas, registro de derechos de autor y derechos conexos, registro de variedades vegetales, depósito de nombres comerciales, nombres de dominio y enseñas, registros sanitarios, así como sus traspasos, prórrogas, renovaciones, cambios de nombre y de domicilio; 2. elaborar, tramitar, solicitar, obtener, realizar, ejecutar y registrar contratos, licencias, autorizaciones y registros de cualesquiera clase; 3. intervenir como demandante o como demandado en cualquier instancia y recurso, y ante cualquier juez, entidad, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía, tales como acciones derivadas del nombre o enseña comerciales; observaciones u oposición al registro de marcas; acciones de caducidad y nulidad; acciones reivindicatorias; acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales y civiles; acciones de indemnización de perjuicios, reclamos u observaciones a cualquier asunto sobre propiedad industrial; el ejercicio de medidas cautelares y cualesquiera otras acciones, medidas o recursos similares relacionados con la propiedad industrial, los derechos de autor y derechos conexos y los derechos de obtentor de variedades vegetales.
A este efecto, los facultamos para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, apelaciones y reclamos, pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de nuestros intereses, con todas las demás facultades necesarias y por este documento desde ahora declaramos válido y bueno todo cuanto los apoderados hicieren en nuestro beneficio.
Este poder comprende la facultad de ratificar o confirmar en nuestro nombre lo actuado, así como la facultad de desistir, transigir, comprometer, conciliar, sustituir y revocar sustituciones, recibir notificaciones y nombrar apoderados judiciales y extrajudiciales.

Firmado en

El

FIRMA



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CERTIFICACIÓN NOTARIAL

El abajo firmante Notario Público certifica que el día de de compareció (cieron) ante mí ,quien (s) me consta que es (son) la (s) persona (s) que firma (n) el instrumento que antecede en su calidad de de la compañía , sociedad existente, debidamente constituida y que ejerce su objeto social de conformidad con las leyes de , domiciliada en .
Certifico, además, que dicha persona está facultada para firmar el documento que antecede en nombre de la citada sociedad, y que los objetivos y finalidades para los que se otorga el mencionado instrumento están comprendidos dentro de los objetivos o actividades de la mencionada sociedad.

Dr. Stutz
Notario
Notario Público

NOTARIAT KONSTANZ

NOTARIAL CERTIFICATION

The undersigned Notary Public certifies that on 27th of Sept. 2007 before me personally appeared Dr. Bernd Kratzer, Alexander Machler , who signed the forgoing instrument as officers with statutory authority of Nycomed GmbH , a corporation existing, duly organized and complying with its corporate purposes in conformity with the laws of Germany , whose home office is located in D-78462 Constance . I further certify that said individual is duly authorized to sign the forgoing instrument in the name of said corporation and that the purposes for which said instrument is granted are within the scope of the objects or activities of said corporation.

Dr. Stutz
Notarin
Notary Public

NOTARIAT KONSTANZ

Esta certificación notarial debe ser llenada en su totalidad y legalizarse por Apostilla
This notarial certification must be filled in completely and be legalized by Apostille

02 ABR 2008

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Notariat III Konstanz
III UR 3569 /2007

This is to certify that before me, Dr. Andrea Stutz, Notary Public in and for Konstanz, Germany, duly admitted and sworn in, there appeared this day

1. Dr. Bernd Kratzer, officer with statutory authority,

2. Alexander Mächler, officer with statutory authority,

personally known to me, the Notary,

address: Byk-Gulden-Str. 2, D-78467 Konstanz,

acting in their capacities of officers with statutory authority respectively of the public limited company named Nycomed GmbH, Konstanz, and as such authorized to represent said company jointly with full legal effect, identified in their said capacities by my examination of the commercial register files of the District-Court of Freiburg- file number: HR B 701257-, and acknowledged their foregoing signatures as their free act and deed.

Witness my hand and seal.

NOTARIAT III KONSTANZ

Dr. Stutz, Notary public
Notariat III Konstanz

D-78462 Konstanz, 27. September 2007

02 ABR 2008

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APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

MINISTERIO DE RELACIONES EXTERIORES

2008 MAR -4 A 9:16

JEFE DE LEGALIZACIONES BOGOTA D.C.

6. País: Republica Federal de Alemania

Este documento publico

7. está firmado por la concejal de justicia Dr. Stutz

8. en su calidad de Notaria

9. está proveido con el sello / timbre del notariado de Konstanz

confirmado

10. en Konstanz 6. el 05.10.2007

10. por el vicepresidente de la audiencia provincial Deppert-Kern en Konstanz

11. bajo el numero E 910 a (AR 1361/07)

12. Sello 10. Firma

Firma ilegible

Sello de la audiencia provincial de Konstanz

734068

NO SE ASUME RESPONSABILIDAD DEL TEXTO

02 APR 2008

Adolf Watzke
Traductor oficial
Res. 2433 Min. Justi

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Traducción oficial de un documento cuyo original está en inglés

Archivo No. 2897/2007

Certificado del Notario

Por medio del presente certifico que las firmas que aparecen en el documento en la otra página fueron reconocidas en mi presencia

1. Dr. Bernd Kratzer, funcionario con autoridad por estatutos.
2. Alexander Mächler, funcionario con autoridad por estatutos.

a quienes conozco personalmente.

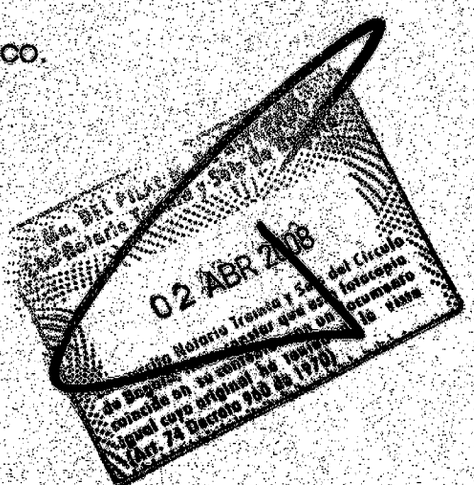
Dirección: Byk-Gulden-Str. 2, D-78467 Konstanz

actuando en su calidad de funcionarios con autoridad por estatutos respectivamente de la compañía limitada pública llamada Nycomed GmbH, Konstanz, y como tales, autorizados para representar a dicha compañía conjuntamente, con efecto legal completo, a quienes identifiqué en dicha calidad por medio de mi examen de los archivos de registro comercial de la Corte de Distrito de Friburgo (archivo No. HR B 701257) y reconocieron sus firmas, puestas anteriormente, como resultado de su libre actuar.

En constancia, pongo mi firma y sello.

(Firmado) Dr. Stutz, Notario Público.

Notaría III de Constanza.



Traductor Oficial
JORGE E. SIERRA REYES
Licencia 276 - 1998 Ministerio

412

D-78462 Konstanz, 27 de septiembre de 2007.

Hay un sello notarial (también un sello seco de seguridad) en alemán de la ciudad de Constanza.

Hay una apostilla de la República Alemana, fechada el 5 de Octubre de 2007 en la ciudad de Constanza [No. E 910 a (AR 1361/07], firmada y sellada.

Certificación:
Certifico que la presente es una traducción fiel del inglés al español del documento adjunto.
Documento: "Notaría - Cert."
Traductor: Jorge Enrique Sierra Reyes, adscrito al Ministerio de Relaciones Exteriores de Colombia.
Licencia No. 376 de 1993, del Ministerio de Justicia (hoy Ministerio del Interior y de Justicia) de la República de Colombia.
Dirección: Cra. 15 No. 99-13 Of. 411
Teléfono: (571) 218-2308, Fax: (571) 623-2925.
E-mail: treseser@yahoo.com
Traducción # 10-670

02 ABR 2008

Traductor Oficial
JORGE E. SIERRA REY
Licencia 376 - 1993 MinJu

606 1348
413
913

Apostille

(Convention de La Haye du 5 octobre 1961)

1. Land: Bundesrepublik Deutschland
   Diese öffentliche Urkunde
2. ist unterschrieben von
   Justizrätin Dr. Stutz
3. in ihrer Eigenschaft als
   Notarin
4. sie ist versehen mit dem Dienststempel
   des Notariats Konstanz

Bestätigt

5. in Konstanz 6. am 14.08.2007
7. durch Vizepräsident des Landgerichts Deppert-Kern
   beim Landgericht Konstanz
8. unter Nr. E 910 a (AR 965/07)
9. Siegel/Stempel 10. Unterschrift

LANDGERICHT KONSTANZ

LANDGERICHT KONSTANZ

02 ABR 2008

10

(Certified translation from the German language)

Commercial Register B of the Local Court (Amtsgericht) in Freiburg i. Br.	Section B Account of the current register entry, data retrieval dated 12.7.2007, 13:06	Company number: **HRB 701257**
- Official copy -	Page 1 of 2	
This copy is not signed and is deemed to be a certified copy.		

1. Number of entries to date:

3

2. a) Company name:

Nycomed GmbH

b) Registered office, place of business, subsidiaries:

Konstanz

c) Object of the company:

The manufacture, research and development, and sale of and trade in chemical, pharmaceutical, cosmetic and dietetic products of all kinds, the construction, acquisition and operation of factories and plant for the manufacture of chemical, pharmaceutical, cosmetic and dietetic products and substances, the acquisition, assignment and exploitation of patent rights and licences, and any other commercial activities in trade and industry in Germany and abroad.

3. Share capital or nominal capital:

EUR 70,000,000.00

4. a) General arrangements relating to representation:

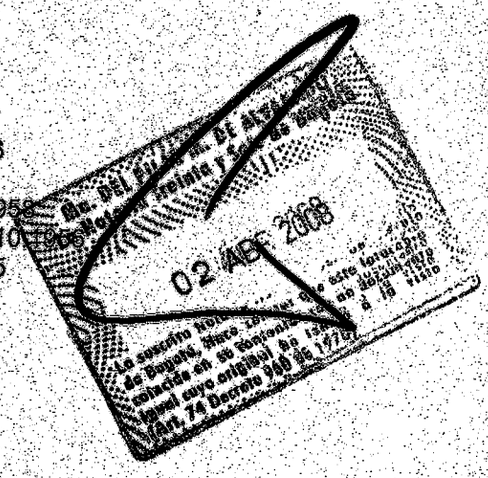
If only one director is appointed, the company shall be represented by him/her alone. If several directors are appointed, the company shall be represented jointly by two directors or by one director and a person with power of attorney ("Prokurist"). Directors can be exempt from the restrictions of Section 181 BGB [German Civil Code].

b) Board of management, managing body, managing directors, personally liable partners, directors, persons holding power of representation and special authorization to represent:

Director: Goll, Alfred H., Allensbach, born 17.10.1956
Director: Dr. Piening, Barthold, Reichenau, born 19.11.1958
Director: Dr. Schwarz, Otto A., Thalwil (Switzerland), born 13.10.1955
Director: Dr. Ullman, Anders, Zurich (Switzerland), born 22.01.1956

5. Power of attorney („Prokura"):

Full power of attorney, jointly with a director or another person holding power of attorney:
Dr. Bösch, Lothar, Allensbach, born 22.07.1950
Frey, Hubertus, Allensbach, born 20.06.1954
Dr. Germann, Paul-Georg, Mölln, born 10.11.1961
Hermann, Walter, Konstanz, born 25.10.1957
Jauch, Joachim, Konstanz, born 02.09.1955
Kanzelmeyer, Wolf-Christian, Allensbach, born 13.04.1956
Kollmann, Stefan, Meerbusch, born 20.11.1956
Kuner, Michael Franz, Freiburg im Breisgau, born 14.12.1958
de Lavenne, Philippe, Kreuzlingen (Switzerland), born 23.10.1956
Leu, Fernando, Bottighofen (Switzerland), born 18.03.1945
Mächler, Alexander, Allensbach, born 24.09.1959
Rademacher, Gilbert, Bergkamen, born 19.10.1956



Schaffer, Michael, Konstanz, *18.09.1965
Schaufler, Ralf, Gaienhofen, *14.11.1964
Dr. Schilling, Ulrich, Konstanz, *11.09.1951
Schneider, Joachim, Konstanz, *29.01.1948
Dr. Wiartalla, Rainer, Gottmadingen, *24.11.1950
Dr. Zech, Karl, Konstanz, *24.02.1944

6. **a) Rechtsform, Beginn, Satzung oder Gesellschaftsvertrag:**

Gesellschaft mit beschränkter Haftung

Gesellschaftsvertrag vom 25.04.2007

b) Sonstige Rechtsverhältnisse:

Die Gesellschaft ist entstanden durch formwechselnde Umwandlung der Aktiengesellschaft
"ALTANA Pharma AG", Konstanz (Amtsgericht Freiburg i.Br. HRB 381925)
gemäß § 190 ff. UmwG.

7. **a) Tag der letzten Eintragung:**

10.07.2007

Freiburg i. Br., 12.07.2007
Der Ausdruck bezeugt den Inhalt des ...ndelsregisters
...pf, Justizsekretärin z. A.
Urkundsbeamter der Geschäftsstelle

AMTSGERICHT

02 ABR 2008

12

(Certified translation from the German language)

416 34

Commercial Register B of the Local Court (Amtsgericht) in Freiburg i. Br.	Section B Account of the current register entry, data retrieval dated 12.7.2007, 13:06	Company number: **HRB 701257**
- Official copy -	Page 1 of 2	
This copy is not signed and is deemed to be a certified copy.		

1. **Number of entries to date:**

   3

2. **a) Company name:**

   Nycomed GmbH

   b) Registered office, place of business, subsidiaries:

   Konstanz

   c) Object of the company:

   The manufacture, research and development, and sale of and trade in chemical, pharmaceutical, cosmetic and dietetic products of all kinds, the construction, acquisition and operation of factories and plant for the manufacture of chemical, pharmaceutical, cosmetic and dietetic products and substances, the acquisition, assignment and exploitation of patent rights and licences, and any other commercial activities in trade and industry in Germany and abroad.

3. **Share capital or nominal capital:**

   EUR 70,000,000.00

4. **a) General arrangements relating to representation:**

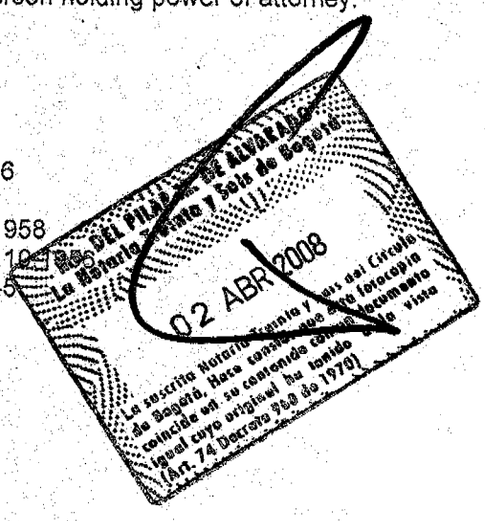
   If only one director is appointed, the company shall be represented by him/her alone. If several directors are appointed, the company shall be represented jointly by two directors or by one director and a person with power of attorney ("Prokurist"). Directors can be exempt from the restrictions of Section 181 BGB [German Civil Code].

   b) Board of management, managing body, managing directors, personally liable partners, directors, persons holding power of representation and special authorization to represent:

   Director: Goll, Alfred H., Allensbach, born 17.10.1956
   Director: Dr. Piening, Barthold, Reichenau, born 19.11.1958
   Director: Dr. Schwarz, Otto A., Thalwil (Switzerland), born 13.10.1955
   Director: Dr. Ullman, Anders, Zurich (Switzerland), born 22.01.1956

5. **Power of attorney („Prokura"):**

   Full power of attorney, jointly with a director or another person holding power of attorney:
   Dr. Bösch, Lothar, Allensbach, born 22.07.1950
   Frey, Hubertus, Allensbach, born 20.06.1954
   Dr. Germann, Paul-Georg, Mölln, born 10.11.1961
   Hermann, Walter, Konstanz, born 25.10.1957
   Jauch, Joachim, Konstanz, born 02.09.1955
   Kanzelmeyer, Wolf-Christian, Allensbach, born 13.04.1956
   Kollmann, Stefan, Meerbusch, born 20.11.1956
   Kuner, Michael Franz, Freiburg im Breisgau, born 14.12.1958
   de Lavenne, Philippe, Kreuzlingen (Switzerland), born 23.10.1956
   Leu, Fernando, Bottighofen (Switzerland), born 18.03.1945
   Mächler, Alexander, Allensbach, born 24.09.1959
   Rademacher, Gilbert, Bergkamen, born 19.10.1956



13

417

(Certified translation from the German language)

Commercial Register B of the Local Court (Amtsgericht) in Freiburg i. Br.	Section B Account of the current register entry, data retrieval dated 12.7.2007, 13:06	Company number: **HRB 701257**
- Official copy -	Page 2 of 2	
This copy is not signed and is deemed to be a certified copy.		

Schaffer, Michael, Konstanz, born 18.09.1965
Schaufler, Ralf, Gaienhofen, born 14.11.1964
Dr. Schilling, Ulrich, Konstanz, born 11.09.1951
Schneider, Joachim, Konstanz, born 29.01.1948
Dr. Wiartalla, Rainer, Gottmadingen, born 24.11.1950
Dr. Zech, Karl, Konstanz, born 24.02.1944

6. **a) Corporate form, commencement, articles of association:**

Private limited company

Articles of Association adopted on 25.04.2007

b) Other legal relations:

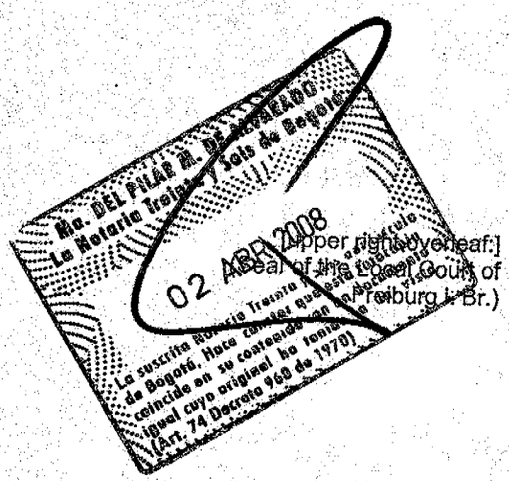
The company resulted from transformation (change of corporate form)
of the public limited company
"ALTANA Pharma AG", Konstanz (Local court of Freiburg i. Br., HRB 381925)
pursuant to Section 190 ff UmwG [German Law Regulating Transformation of Companies].

7. **a) Date of last entry:**

10.07.2007

Freiburg i[m] Br[eisgau], dated 12.07.2007
The copy truly reflects the contents of the
Commercial Register
Kopf, Court Clerk
Registrar

(Seal of the Local Court of Freiburg i. Br.)



[Upper right overleaf:]
Seal of the Local Court of
Freiburg i. Br.)

14

I hereby confirm that this is, to the best of my knowledge and belief, a complete and accurate translation of the original German document/certified copy.

Konstanz, dated: 31.01.07 *

Christel Hunsinger
(Sworn translator)

CHRISTEL HUNSINGER
Öffentlich bestellte und beeidigte Übersetzerin der englischen Sprache für Baden-Württemberg
KONSTANZ



AR
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III UR 2575 / 2007

Certification of Signature

This is to certify that before me, Dr. Andrea Stutz, Notary public in and for Constance/Germany, duly admitted and sworn in, there appeared this day, identified by German passport,

Ms. Christel **H u n s i n g e r**, born 26 September 1954,
address: Byk-Gulden-Str. 2, 78467 Konstanz ,

and acknowledged the foregoing signature as her free act and deed.

Constance, 03 July 2007
NOTARY III

NOTARIAT * KONSTANZ *

Dr. Stutz, notary public

02 ABR 2008

15

419

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

MINISTERIO DE RELACIONES EXTERIORES
2008 MAR -4 A 8:16
JEFE DE LEGALIZACIONES BOGOTA D.C.

6. País: Republica Federal de Alemania

Este documento publico

7. está firmado por la concejal de justicia Dr. Stutz

8. en su calidad de Notaria

9. está proveido con el sello / timbre del notariado de Konstanz

confirmado

NO SE ASUME RESPONSABILIDAD DEL TEXTO
LA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS
7340 66

10. en Konstanz 6. el 14.08.2007

10. por el vicepresidente de la audiencia provincial Deppert-Kern en Konstanz

11. bajo el numero E 910 a (AR 965/07)

12. Sello 10. Firma

Firma ilegible

Sello de la audiencia provincial de Konstanz

Ma. DEL PILAR ... ALVARADO
La Notaria Treinta y Seis de Bogotá
02 ABR 2008
La suscrita Notaria ... hace constar que esta fotocopia se Bogotá, fiel y coincide en su contenido con el documento igual cuyo original he tenido a la vista (Art. 74 Decreto 960 de 1970)

Adolf Watzke
Traductor oficial
Res. 2433 Min. Justicia

16

AZO
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Registro Mercantil de La audiencia provincial Freiburg l. Br.	Sección B reproducción del contenido actual del registro	Numero de la empresa HRB 701257

Impresión oficial Pagina 1 de 2

Esta impresión no es firmada y vale como copia autenticada

1. Numero de registros

   ilegible

2. a) Empresa

   Nycomed GmbH

   b) Domicilio, Filial, Sucursal

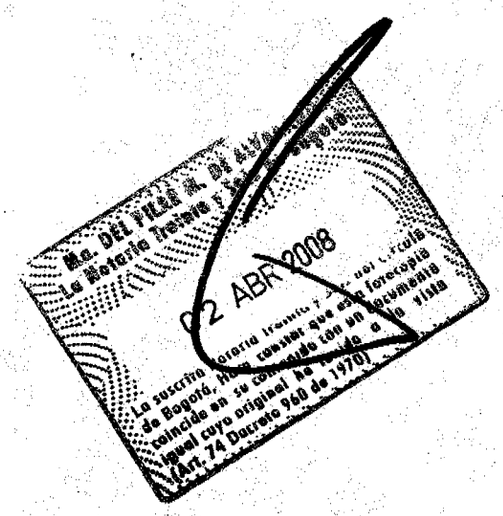
   Konstanz

   c) Objeto de la sociedad

   La producción, investigación y desarrollo, así como la distribución y el andel con productos de todo tipo químicos, farmacéuticos, cosméticos y dietéticas, la creación y puesta en funcionamiento de fabricas y equipos para la producción de productos y sustancias químicas, farmacéuticas, cosméticas y dietéticas, la compra, concesión y aprovechamiento de derechos de protección comercial y licencias, al igual que cualquier tipo de actividad comercial en el sector de la industria, del arte y del comercio en el interior y el extranjero.

3. Capital social

   70.000.000,00 Euros



Adolf Wätzke
Traductor oficial
Res. 2433 Min. Justicia

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421
4-7

4. a) Reglamentación general de representación

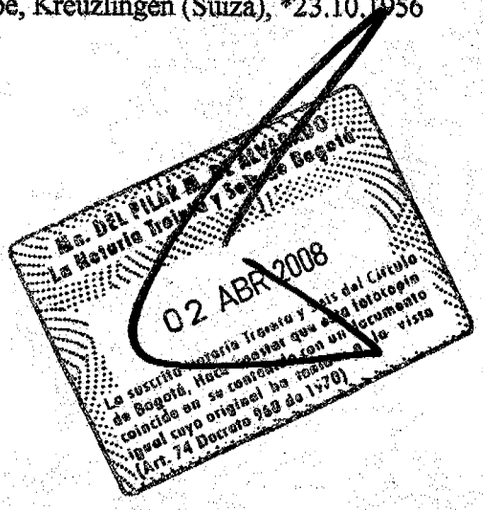
Si solo se ha nombrado un gerente, el representa por si solo. Si hay varios gerentes nombrados, representan dos gerentes en conjunto o un gerente con un apoderado. Los gerentes pueden ser liberados en general de las limitaciones según § 181 del BGB (Código Civil)

b) Junta Directiva, Órganos directivos, Directores, socios personalmente responsables, gerentes, aptos para representar, y con derecho de representación especial:

Gerente: Goll, Alfred, Allensbach, *17.10.1956
Gerente: Dr. Piening, Barthold, Reichenau, *19.11.1958
Gerente: Dr. Schwarz, Otto A., Thalwil (Suiza), *13.10.1955
Gerente: Dr. Ullman, Anders, Zurich (Suiza), *22.01.1956

5. Poder:

Poder General en conjunto con un <gerente o con otro apoderado:
Dr. Bösch, Lothar, Allensbach, *22.07.1950
Frey, Hubertus, Allensbach, *20.06.1954
Dr. Germann, Paul-Georg, Mölln, *10.11.1961
Hermann, Walter, Konstanz, *25.10.1957
Jauch, Joachim, Konstanz, *02.09.1955
Kanzelmeyer, Wolf-Christian, Allensbach, *13.04.1956
Kollmann, Stefan, Meerbusch, *20.11.1956
Kuner, Michael Franz, Freiburg im Breisgau, 14.12.1958
De Lavenne, Phillippe, Kreuzlingen (Suiza), *23.10.1956



Adolf Watzke
Traductor oficial
Res. 2433 Min. Justicia

422
422

Leu, Fernando, Bottighofen (Suiza), *18.03.1945
Mächler, Alexander, Allensbach, *24.09.1959
Rademacher, GIlbert, Bergkamen, * 19.10.1956

Registro Mercantil de	Sección B reproducción	Numero de la empresa
La audiencia provincial	del contenido actual	HRB 701257
Freiburg l. Br.	del registro	

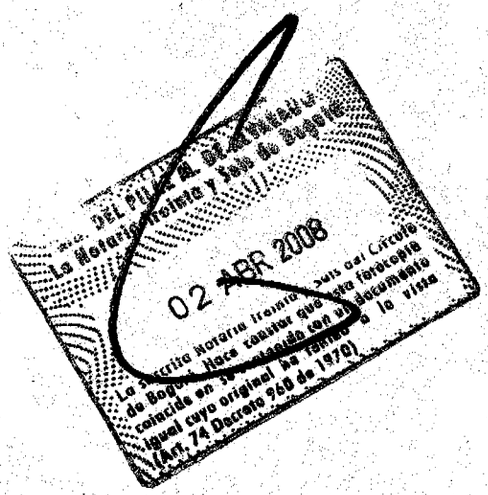
Impresión oficial Pagina 2 de 2

Esta impresión no es firmada y vale como copia autenticada

Schaffer, Michael, Konstanz, *18.09.1965
Schaufler, Ralf, Galenhofen, *14.11.1964
Dr. Schilling, Ulrich, Konstanz, *11.09.1951
Schneider, Joachim, Konstanz, *29.01.1948
Dr. Wiartalla, Rainer, Gottmadingen, *24.11.1950
Dr. Zech, Karl, Konstanz, *24.02.1944

6. a) Forma judicial, Inicio, Estatuto o contrato de sociedad:

Sociedad limitada
Contrato de sociedad del 25.04.2007



Adolf Watzke
Traductor oficial
Res. 2433 Min. Justicia

19

123
123

b) Demás relaciones legales

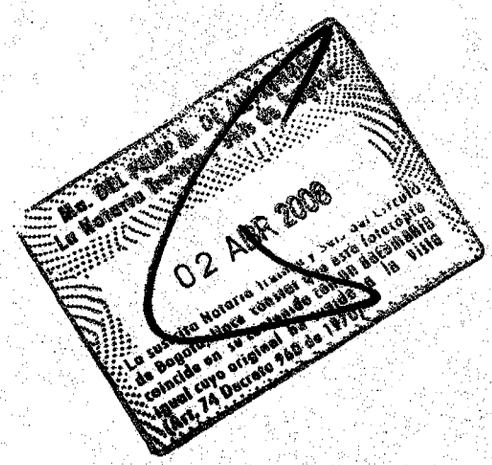
La sociedad se creó por transformación de razón social de la sociedad anónima "ALTANA Pharma AG", Konstanz (Juzgado provincial Freiburg i. Br. HRB 381925) según § 190 ff UmwG.

7. Fecha de ultimo registro

10.07.2007

Freiburg i. Br. 12.07.2007
La impresión certifica el contenido del registro mercantil
Kopf, Secretaria de justicia
Funcionario de documentación de la oficina

Sello de la audiencia provincial de Freiburg i. Br.



Adolf Watzke
Traductor oficial
Res. 2433 Min. Justicia

20

424

Registro Comercial B de la Corte Local (Amtsgericht) en Freiburg i. Br.
Copia Oficial.
Sección B. Cuenta del registro actual, recuperación de datos con fecha 12.7, 2007, 13:06
Pg. 1 de 2.
Número de la compañía: HRB 701257.

Esta copia no esta firmada y se entiende como una copia certificada.

1. Número de asientos ingresados a la fecha: 3

2. a) Nombre de la compañía: Nycomed GmbH

   b) Oficina registrada, lugar de negocios, subsidiarias: Konstanz

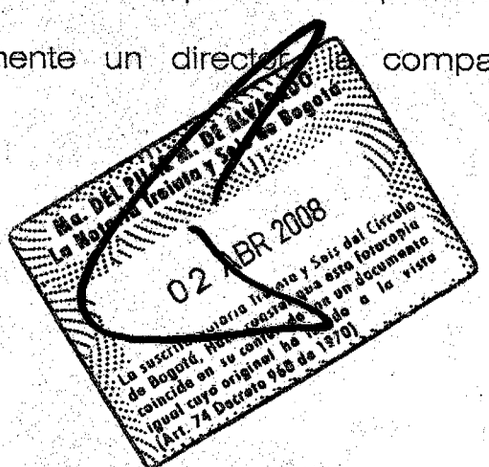
   c) Objeto de la compañía:

   Fabricación, investigación y desarrollo y venta y comercialización de productos químicos, farmacéuticos, cosméticos y dietéticos de todas las clases, construcción, adquisición y manejo de fábricas y planta para la fabricación de productos y sustancias químicos, farmacéuticos, cosméticos y dietéticos, la adquisición, cesión y explotación de derechos de patente y licencias, y cualquier otra actividad comercial en el comercio y la industria en Alemania y en el exterior.

3. Capital accionario o capital nominal: EUR 70,000,000.00

4. a) Disposiciones generales con respecto a la representación:

   Si se nombra solamente un director, la compañía será



Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

representada por él solo. Si se nombran varios directores, la compañía estará representada conjuntamente por dos directores o por un director y una persona con poder de representante ("Prokurist"). Los directores pueden estar exentos de las restricciones de la sección 181 BGB (Código Civil Alemán).

b) Junta de administración, cuerpo administrativo, directores generales, socios responsables personalmente, personas con poder de representación y autorización especial para representar:

Director: Goll, Alfred H., Allensbach, nacido: 17.10.1956.

Director: Dr. Piening, Barthold, Reichenau, nacido: 19.11.1958.

Director: Dr. Schwarz, Otto A., Thalwill (Suiza), nacido: 13.10.1955.

Director: Dr. Ullman, Anders, Zurich (Suiza), nacido: 22.01.1956.

5. Poder ("Prokura")

Poder completo de representante, junto con un director u otra persona que tenga poder de representación:

Dr. Bösh, Lothar, Allensbach, nacido el 22.07.1950
Frey, Hubertus, Allensbach nacido el 20.06.1954
Dr. Germann, Paul-Georg, Mölln, nacido el 10.11.1961
Hermann, Walter, Konstanz, nacido el 25.10.1957.
Jauch, Joachim, Konstanz, nacido el 02.09.1955.
Kanzelmeyer, Wolf-Christian, Allensbach, nacido el 13.04.1956
Kollmann, Stefan, Meerbusch, nacido el 20.11.1956
Kuner, Michael Franz, Freiburg im Breisgau nacido el 14.12.1958.
de Lavenne, Philippe, Kreuzlingen (Suiza) nacido el 23.10.1956.
Leu, Fernando, Bottighofen (Suiza) nacido el 18.03.1945.



426

Mächler, Alexander, Allensbach, nacido el 24.09.1959.
Rademacher, Gilbert, Bergkamen, nacido el 19.10.1956.
Schaffer, Michael, Konstanz, nacido el 18.09.1965.
Schaufler, Ralf, Gaienhofen, nacido el 14.11.1964.
Dr. Schilling, Ulrich, Konstanz, nacido el 11.09.1951.
Schneider, Joachim, Konstanz, nacido el 29.01.1948
Dr. Wiartalia, Rainer, Gottmadingen, nacido el 24.11.1950
Dr. Zech, Karl, Konstanz, nacido el 24.02.1944.

6. a) Forma corporativa, comienzo, estatutos de constitución.

Compañía limitada privada.

Estatutos de constitución adoptados el 25.04.2007.

b) Otras relaciones legales:

La compañía resultó de la trasformación (cambio de forma corporativa) de la compañía limitada pública "ALTANA Pharma AG", Konstanz (Corte local de Freiburg i. Br., HRB 381925), de acuerdo con la sección 190 ff UmwG [ley alemana que reglamenta la transformación de las compañías).

7. a) Fecha del último asiento de datos: 10.07.2007.

Freiburg i[m] Br[eisgau], fechada el 12.07.2007.

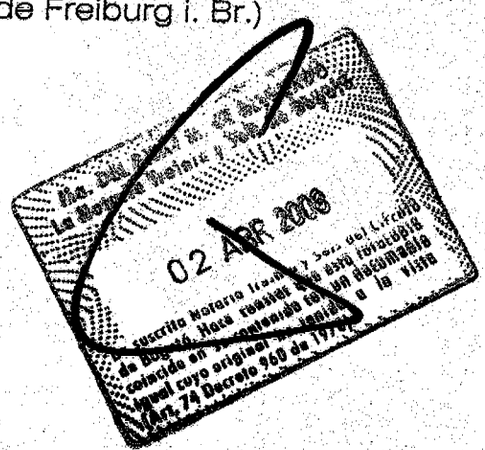
La copia refleja fielmente el contenido del Registro Comercial.

Kopf, Registrador de la Corte. (Sello de la Corte Local de Freiburg i. Br.)

Registrador.

[Reverso de la página, parte superior derecha]:

(Sello de la Corte Local de Freiburg i. Br.)



427
420

Reverso de la hoja:

Sello: "Por medio del presente confirmo que esta es, hasta donde llegan mi conocimiento y convicción, una traducción completa y exacta del documento/copia certificada del original alemán.

Konstanz, 31 de julio de 2007. (Firmado) Traductor Oficial

Sello: "Christel Hunsinger – Konstanz (hay un texto en alemán).

MINISTERIO DE RELACIONES EXTERIORES
JEFE LEGALIZACIONES BOGOTA D.C.
2008 MAR -4 A 9:19

III UR 2575/2007

Certificación de firma.

Se certifica que ante mí, Dr. Andrea Stutz, Notario Público de Constanza (Konstanz), Alemania, debidamente nombrado y juramentado, se presentó este día identificada por su pasaporte alemán la señora Christel Hunsinger, nacida el 26 de septiembre de 1954, residente en Byk-Gulden-Str. 2, 78467 Konstanz, quien reconoció la anterior firma como la puesta por ella de manera libre.

Constanza, 3 de julio de 2007. Notario III (Firmado) Dr. Stutz, Notario Público.

Hay un sello notarial (también un sello seco de seguridad) en alemán de la ciudad de Constanza.

Hay una apostilla de la República Alemana, fechada el 14 de Agosto de 2007 en la ciudad de Constanza [No. E 910 a (AR 965/07], firmada y sellada.

Ra. DE ALVARADO
La Notaría Treinta y Seis de Bogotá
02 ABR 2008
La suscrita Notaria Treinta y Seis del Círculo de Bogotá, Hace constar que la fotocopia coincide con su contenido con el documento igual cuyo original he tenido a la vista (Art. 74 Decreto 960 de 1970)

428
428

Certificación:

Certifico que la presente es una traducción fiel del inglés al español del documento adjunto.

Documento: "Nycomed Gmbh - Reg."

Traductor: Jorge Enrique Sierra Reyes, adscrito al Ministerio de Relaciones Exteriores de Colombia.

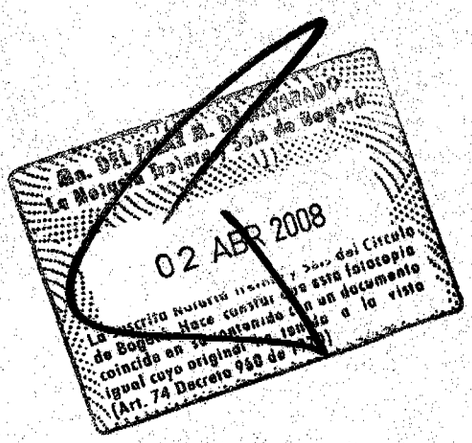
Licencia No. 376 de 1993, del Ministerio de Justicia (hoy Ministerio del Interior y de Justicia) de la República de Colombia.

Dirección: Cra. 15 No. 99-13 Of. 411

Teléfono: (571) 218-2308, Fax: (571) 623-2925.

E-mail: treseser@yahoo.com

Traducción # 10-669



Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-74146

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **570** DE

FECHA **30 DE NOVIEMBRE DE 2006** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **01 DE MARZO DE 2007**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO ___X___

430

430

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

Bogotá, D.C., 22 de enero de 2010

Apoderado: Jimena Escobar Uribe

ASUNTO	Radicación	06-74146
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	887
	Folios	

Patente de Invención ⊗

Vía PCT (fase nacional) ⊗ Cap.I ⊗ Cap. II ☐

No. Sol. Internacional PCT/EP2005/050931

Fecha de Presentación Internal. 02/MAR/2005

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

1. Documentos estudiados

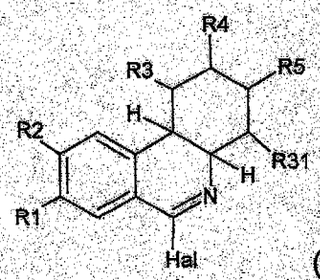
1.1.	Descripción:	Folios: 13 a 258	Como se radicó inicialmente.
1.2.	Reivindicaciones:	Folios 259 a 302	Como se radicó inicialmente.
		Folios 358 a 401	Con modificaciones.
1.3.	Prioridad:	Folio 1: EP 04004973.6, 03/mar/2004	
		EP 04106359.5, 07/dic/2004	

431

2. Objeto de la invención

Título de la solicitud: HIDROXI/6-HETEROARILFENANTRINAS NOVEDOSAS Y SU USO COMO INHIBIDORES DE PDE4.

El objeto de la invención son los derivados 6-heteroharilo-1,2,3,4,4a,10b-hexahidrofenantridinas de fórmula:



(I)

Reivindicaciones 1–22, 25,27-30,: Un compuesto de la fórmula (I).
Reivindicación 23: Un compuesto de la fórmula (I*).
Reivindicación 24: Un compuestos de las fórmulas (Ia*****) y (Ib*****).
Reivindicación 26: composición que comprende los compuestos:

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.): C07D401/04, A61K31/473, A61P11/06.

3. De la solicitud de Patente

3.1. Reivindicaciones *(artículo 30 D 486 de la C.AN)*

-Las reivindicaciones 25,27-30 son incongruentes, porque el encabezado no es consistente con el resto del texto de la reivindicación, se encabeza como compuesto y lo que debe ser la parte técnica que define el compuesto, es una mezcla de uso y método terapéutico, lo cual es inaceptable en las reivindicaciones.

Por lo tanto las reivindicaciones objetadas no cumplen con el requisito de definición, claridad y concisión, no cumplen con lo dispuesto en el al art. 30 de la Decisión 486.y/o art.22 Tratado PCT.

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el estado de la técnica fecha de presentación de la solicitud de la cual se reclama prioridad, 03/mar/2004.

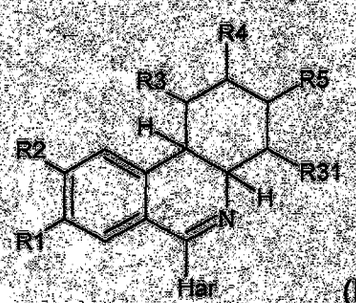
Teniendo en cuenta la fecha indicada se realizó la búsqueda del estado de la técnica, en bases de datos en las que esta oficina tiene acceso libre, en búsqueda de documentos relacionados con la materia que se reclama como nueva e inventiva en presente solicitud, encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D1	WO9735854	Novel phenanthridines substituted in the 6 position	02/oct/1997
D2	WO0042019	6-Aryl phenanthridines with PDE-IV inhibiting avtivity	20/jul/2000
D3	WO0206270	Novel 6-heteroarylphenanthridines	24/ene/2002
D4	US20040038979	Novel 6-heteroarylphenanthridines	26/feb/2004

5. Análisis de patentabilidad (artículo 14 D486 de la C.AN.)

5.1 Novedad (artículo 16 D486 de la C.A.N.)

-La solicitud en estudio reclama los derivados 6-phenyl-1,2,3,4,4a,10b-hexahydrophenanthridine Que caen bajo el alcance de la fórmula Markush (I):



(I)

-Las anterioridades D1 (ver toda la solicitud especialmente las págs. 1-15, 24,25, 39-48, esquema 1/1), D2 (ver la totalidad del documento), D3 (ver la totalidad del documento), D4 (ver la totalidad del documento), estas anterioridades se anticipan a describir los compuestos 6-(heteroaril)-1,2,3,4,4a,10b-hexahydrofenantridina, con los sustituyentes también coincidentes en las posiciones 1,2,3,4,4a,6,8,9,10b, o sea, la

433
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solicitud en estudio reclama como nuevos compuestos del estado de la técnica, por lo tanto no cumple con el requisito exigido en el artículo 16 D486 de la C.A.N.

5. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:
*La solicitud que no ostenta novedad obviamente no posee nivel inventivo.

Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	1-30	Novedad
D2	1-30	Novedad
D3	1-30	Novedad
D4	1-30	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (e)

El anterior requerimiento fue notificado por fijación en lista, de fecha 29 ENE. 2010

CONCEPTO TÉCNICO No. 395	**EXAMINADOR TÉCNICO** Cód. N°202012

PCT WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro
INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 6: C07D 401/04, A61K 31/435, C07D 491/04, 221/12 — A1

(11) Internationale Veröffentlichungsnummer: **WO 97/35854**

(43) Internationales Veröffentlichungsdatum: 2. Oktober 1997 (02.10.97)

(21) Internationales Aktenzeichen: PCT/EP97/01487

(22) Internationales Anmeldedatum: 24. März 1997 (24.03.97)

(30) Prioritätsdaten:
196 13 922.7 — 28. März 1996 (28.03.96) — DE
96105538.2 — 29. März 1996 (29.03.96) — EP

(34) Länder für die die regionale oder internationale Anmeldung eingereicht worden ist: AT usw.
196 13 091.3 — 2. April 1996 (02.04.96) — DE
96105631.5 — 3. April 1996 (03.04.96) — EP

(34) Länder für die die regionale oder internationale Anmeldung eingereicht worden ist: AT usw.

(71) Anmelder *(für alle Bestimmungsstaaten ausser US)*: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH [DE/DE]; Byk-Gulden-Straße 2, D-78467 Konstanz (DE).

(72) Erfinder *(für alle Bestimmungsstaaten ausser CA, US)*: AMSCHLER, Hermine; Höherlowenstraße 19, D-78315 Radolfzell (DE). FLOCKERZI, Dieter; Ackerweg 26, D-78476 Allensbach (DE). ULRICH, Wolf-Rüdiger; Hebelstrasse 2, D-78464 Konstanz (DE). BÄR, Thomas; Hüetistrasse 16, D-78462 Konstanz (DE). MARTIN, Thomas; Seimerbühlstrasse 73, D-78464 Konstanz (DE). SCHÜDT, Christian; Ringstrasse 49, D-78465 Konstanz (DE). HATZELMANN, Armin; Alter Wall 2, D-78467 Konstanz (DE). BEUME, Rolf; Bahnlestrasse 73, D-78465 Konstanz (DE). HABNER, Dietrich; Bertholdsstrasse 5, D-78464 Konstanz (DE). DOSS, Hildegard; Fürstenstr. 3a, D-78464 Konstanz (DE). KLEY, Hans-Peter; Im Weinberg 3b, D-78476 Allensbach (DE).

(72) Erfinder; und
(75) Erfinder/Anmelder *(nur für US)*: GUTTHERER, Beate [DE/DE]; Allensbacher Strasse 6a, D-78476 Allensbach (DE).

(74) Gemeinsamer Vertreter: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; Byk-Gulden-Straße 2, D-78467 Konstanz (DE).

(81) Bestimmungsstaaten: AL, AM, BA, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, VN, VI, eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Veröffentlicht
Mit internationalem Recherchenbericht.

(54) Title: NOVEL PHENANTHRIDINES SUBSTITUTED IN THE 6 POSITION

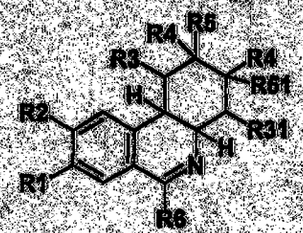
(54) Bezeichnung: NEUE IN 6-POSITION SUBSTITUIERTE PHENANTHRIDINE

(57) Abstract

Compounds of formula (I) in which R1, R2, R3, R31, R4, R5, R51 and R6 have the meanings given in the description, are novel effective bronchial therapeutic agents.

(57) Zusammenfassung

Verbindungen der Formel (I), worin R1, R2, R3, R31, R4, R5, R51 und R6 die in der Beschreibung angegebenen Bedeutungen haben, sind neue wirksame Bronchialtherapeutika.



(I)

1

Neue in 6-Position substituierte Phenanthridine

Anwendungsgebiet der Erfindung

Die Erfindung betrifft neue in 6-Position substituierte Phenanthridine, die in der pharmazeutischen Industrie zur Herstellung von Medikamenten verwendet werden.

Bekannter technischer Hintergrund

In Chem.Ber. 1939, 72, 675-677, J.Chem.Soc., 1956, 4280-4283 und J.Chem.Soc.(C), 1971, 1606 wird die Synthese von 6-Phenylphenanthridinen beschrieben.

Beschreibung der Erfindung

Es wurde nun gefunden, daß die nachfolgend näher beschriebenen neuen in 6-Position substituierten Phenanthridine überraschende und besonders vorteilhafte Eigenschaften besitzen.

Gegenstand der Erfindung sind somit Verbindungen der Formel I (siehe beigefügtes Formelblatt), worin

R1 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

R2 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

oder worin

R1 und R2 gemeinsam eine 1-2C-Alkylendioxygruppe bedeuten,

R3 Wasserstoff oder 1-4C-Alkyl bedeutet,

R31 Wasserstoff oder 1-4C-Alkyl bedeutet,

oder worin

R3 und R31 gemeinsam eine 1-4C-Alkylengruppe bedeuten,

R4 Wasserstoff oder 1-4C-Alkyl bedeutet,

R5 Wasserstoff bedeutet,

R51 Wasserstoff bedeutet,

oder worin

R5 und R51 gemeinsam eine zusätzliche Bindung darstellen,

R6 einen durch R61 substituierten Pyridylrest darstellt oder einen durch R7 und R8 substituierten Phenylrest darstellt, wobei

R31 Wasserstoff, Hydroxy, Halogen, 1-4C-Alkoxy, 1-4C-Alkyl, Carboxyl, Trifluormethyl, 1-4C-Alkoxycarbonyl oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

R7 Hydroxy, Halogen, Cyano, 1-4C-Alkyl, 1-4C-Alkoxy, 1-4C-Alkylcarbonyloxy, Trifluormethyl, Phenyl, Phenyl-1-4C-alkyl, Nitro, Amino, ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy, SO_2-R70 oder N(R71)R72 bedeutet, wobei

R70 1-4C-Alkyl,

R71 Wasserstoff, 1-4C-Alkyl, SO_2-R9 oder SO_2-R10 und

R72 1-4C-Alkyl, 1-4C-Alkylcarbonyl oder SO_2-R10 bedeutet,

R8 Wasserstoff, Hydroxy, Halogen, 1-4C-Alkoxy oder 1-4C-Alkyl bedeutet

und wobei

R9 und R10 unabhängig voneinander 1-4C-Alkyl, Phenyl, Phenyl-1-4C-alkyl oder durch einen oder mehrere gleiche oder verschiedene Substituenten substituiertes Phenyl bedeuten, wobei die Substituenten ausgewählt sind aus der Gruppe Nitro, 1-4C-Alkyl, Halogen, 1-4C-Alkylcarbonylamino, 1-4C-Alkoxy, ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy, Cyano, Phenyl, Naphthyl, Trifluormethyl oder 1-4C-Alkoxycarbonyl,

sowie die Salze dieser Verbindungen.

1-4C-Alkoxy steht für Reste, die neben dem Sauerstoffatom einen geradkettigen oder verzweigten Alkylrest mit 1 bis 4 Kohlenstoffatomen enthalten. Beispielsweise seien genannt der Butoxy-, Iso-Butoxy-, sec.-Butoxy-, tert.-Butoxy-, Propoxy-, Isopropoxy- und bevorzugt der Ethoxy- und Methoxyrest.

3-7C-Cycloalkoxy steht beispielsweise für Cyclopropyloxy, Cyclobutyloxy, Cyclopentyloxy, Cyclohexyloxy und Cycloheptyloxy, wovon Cyclopropyloxy, Cyclobutyloxy und Cyclopentyloxy bevorzugt sind.

3-7C-Cycloalkylmethoxy steht beispielsweise für Cyclopropylmethoxy, Cyclobutylmethoxy, Cyclopentylmethoxy, Cyclohexylmethoxy und Cycloheptylmethoxy, wovon Cyclopropylmethoxy, Cyclobutylmethoxy und Cyclopentylmethoxy bevorzugt sind.

Als ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy seien beispielsweise der 1,2,2-Trifluorethoxy-, der 2,2,3,3,3-Pentafluorpropoxy-, der Perfluorethoxy-, der 1,1,2,2-Tetrafluorethoxy-, der Trifluormethoxy-, insbesondere der 2,2,2-Trifluorethoxy- und bevorzugt der Difluormethoxyrest genannt.

1-4C-Alkyl steht für einen geradkettigen oder verzweigten Alkylrest mit 1 bis 4 Kohlenstoffatomen. Beispielsweise seien genannt der Butyl-, Iso-Butyl-, sec.-Butyl-, tert.-Butyl-, Propyl-, Isopropyl- und bevorzugt der Ethyl- und Methylrest.

1-2C-Alkylendioxy steht beispielsweise für den Methylendioxy-(-O-CH_2-O-) und den Ethylendioxyrest (-O-CH_2-CH_2-O-).

Haben R3 und R31 gemeinsam die Bedeutung 1-4C-Alkylen, so sind die Positionen 1 und 4 in Verbindungen der Formel I durch eine 1-4C-Alkylenbrücke miteinander verknüpft, wobei 1-4C-Alkylen für geradkettige oder verzweigte Alkylenreste mit 1 bis 4 Kohlenstoffatomen steht. Beispielsweise seien die Reste Methylen (-CH_2-), Ethylen (-CH_2-CH_2-), Trimethylen (-CH_2-CH_2-CH_2-), 1,2-Dimethylethylen [-$CH(CH_3)$-$CH(CH_3)$-] und Isopropyliden [-$C(CH_3)_2$-] genannt.

Halogen im Sinne der vorliegenden Erfindung ist Brom, Chlor und Fluor.

1-4C-Alkoxycarbonyl enthält neben der Carbonylgruppe einen der oben genannten 1-4C-Alkoxyreste. Beispielsweise genannt seien der Methoxycarbonyl- und der Ethoxycarbonylrest.

Wenn R5 und R51 gemeinsam eine zusätzliche Bindung bedeuten, dann sind die Kohlenstoffatome in den Positionen 2 und 3 in Verbindungen der Formel I über eine Doppelbindung miteinander verknüpft.

1-4C-Alkylcarbonyloxyreste enthalten neben dem Carbonyloxyrest einen der vorstehend genannten 1-4C-Alkylreste. Beispielsweise sei der Acetyloxyrest (CH_3CO-O-) genannt.

Phenyl-1-4C-alkyl steht für einen der obengenannten 1-4C-Alkylreste, der durch einen Phenylrest substituiert ist. Beispielsweise genannt seien der Benzyl- und der Phenethylrest.

1-4C-Alkylcarbonyl steht für einen Rest, der neben der Carbonylgruppe einen der vorstehend genannten 1-4C-Alkylreste enthält. Beispielsweise genannt sei der Acetylrest.

1-4C-Alkylcarbonylamino steht für einen Aminorest, der durch einen der vorstehend genannten 1-4C-Alkylcarbonylreste substituiert ist. Beispielsweise genannt sei der Acetylaminorest (CH_3CO-NH-).

Als beispielhaft durch R51 substituierte Pyridylreste seien die Reste Pyridyl-4, Pyridyl-3, 2-Chlorpyridyl-4, 2-Hydroxypyridyl-4, 2-Methoxypyridyl-4, 2-Brompyridyl-4, 2-Methylpyridyl-4, 3-Brompyridyl-4, 2-Chlorpyridyl-5, 2-Hydroxypyridyl-5, 2-Methoxypyridyl-5, 2-Methylpyridyl-5, 2-Brompyridyl-5, 3-Brompyridyl-5, 2-Methylpyridyl-3, 2-Chlorpyridyl-3, 4-Methylpyridyl-3, 3-Methoxypyridyl-5, 2-(2,2,2-Trifluorethoxy)pyridyl-3, 3-Methylpyridyl-4, 2-Methoxypyridyl-3, 2-Fluorpyridyl-3, 2-Trifluormethylpyridyl-3, 2-Methoxycarbonylpyridyl-3, 4-Trifluormethylpyridyl-3, 4-Methoxycarbonylpyridyl-3 oder 2-(2,2,2-Trifluorethoxy)pyridyl-5 genannt.

Als beispielhafte, durch R7 und R8 substituierte Phenylreste seien die Reste 4-Acetamidophenyl, 3-Acetamidophenyl, 4-Acetoxyphenyl, 3-Aminophenyl, 4-Aminophenyl, 2-Bromphenyl, 4-Bromphenyl, 2-Chlorphenyl, 3-Chlorphenyl, 4-Chlorphenyl, 3-Bromphenyl, 2,3-Dichlorphenyl, 2,4-Dichlorphenyl, 2-Chlor-4-nitrophenyl, 4-Diethylamino-2-methylphenyl, 4-Methoxyphenyl, 3-Methoxyphenyl, 2-Chlor-5-nitrophenyl, 4-Chlor-3-nitrophenyl, 2,6-Dichlorphenyl, 3,5-Dichlorphenyl, 2,5-Dichlorphenyl, 2,6-Di-

bromphenyl, 2-Cyanphenyl, 3-Cyanphenyl, 4-Cyanphenyl, 4-Diethylaminophenyl, 4-Dimethylaminophenyl, 2-Fluorphanyl, 4-Fluorphenyl, 3-Fluorphenyl, 2,4-Difluorphenyl, 2,6-Difluorphenyl, 2-Chlor-6-fluorphanyl, 2-Fluor-5-nitrophenyl, 2-Hydroxyphenyl, 3-Hydroxyphenyl, 3,4-Dichlorphenyl, 4-Hydroxyphanyl, 4-Hydroxy-3-methoxyphenyl, 2-Hydroxy-4-methoxyphenyl, 2,4-Dihydroxyphenyl, 2-Methoxyphenyl, 2,3-Dimethoxyphenyl, 3,4-Dimethoxyphenyl, 2,4-Dimethoxyphenyl, 2-Dimethylaminophenyl, 2-Methylphenyl, 3-Methylphenyl, 4-Methylphenyl, 2-Chlor-6-methylphenyl, 4-Methyl-3-nitrophenyl, 2,4-Dimethylphenyl, 2,6-Dimethylphenyl, 2,3-Dimethylphenyl, 2-Nitrophenyl, 3-Nitrophenyl, 4-Nitrophenyl, 2,4-Dinitrophenyl, 3,4-Dinitrophenyl, 3,5-Dinitrophenyl, 2,6-Dinitrophenyl, 4-Ethoxyphenyl, 2-Trifluormethylphenyl, 4-Trifluormethylphenyl, 3-Trifluormethylphenyl, 4-(p-Nitrophenylsulfonamido)-phenyl, 3-(p-Toluolsulfonamido)phenyl, 4-(p-Toluolsulfonamido)phenyl, 4-(4-Ethylphenylsulfonamido)-phenyl, 4-Bis(p-toluolsulfonyl)aminophenyl, 4-Bis(p-nitrophenylsulfonyl)aminophenyl, 3-(p-Nitrophenylsulfonamido)phenyl, (N-Acetyl-4-p-toluolsulfonamido)phenyl, 4-(Benzylsulfonamido)phenyl, 3-(Benzylsulfonamido)phenyl, 4-(Methylsulfonamido)phenyl, 3-(Methylsulfonamido)phenyl, 4-(N-Methyl-methylsulfonamido)phenyl, 3-(N-Methyl-methylsulfonamido)phenyl, 4-(3,4-Dichlorphenylsulfonamido)phenyl, 3-(3,4-Dichlorphenylsulfonamido)phenyl, 4-(3-Nitrophenylsulfonamido)phenyl, 3-(3-Nitrophenylsulfonamido)phenyl, 4-(4-Bromphenylsulfonamido)phenyl, 3-(4-Bromphenylsulfonamido)phenyl, 4-(3-Bromphenylsulfonamido)phenyl, 3-(3-Bromphenylsulfonamido)phenyl, 4-(3-Fluorphenylsulfonamido)phenyl, 3-(3-Fluorphenylsulfonamido)phenyl, 4-(4-Fluorphenylsulfonamido)phenyl, 3-(4-Fluorphenylsulfonamido)phenyl, 4-(4-Chlorphenylsulfonamido)phenyl, 3-(4-Chlorphenylsulfonamido)phenyl, 4-(3-Chlorphenylsulfonamido)phenyl, 3-(3-Chlorphenylsulfonamido)phenyl, 4-(4-Acetylaminophenylsulfonamido)-phenyl, 3-(4-Acetylaminophenylsulfonamido)phenyl, 4-(4-Methoxyphenylsulfonamido)phenyl, 3-(4-Methoxyphenylsulfonamido)phenyl, 4-(3-Trifluormethylphenylsulfonamido)phenyl, 3-(3-Trifluormethylphenylsulfonamido)phenyl, 4-(4-Trifluormethylphenylsulfonamido)phenyl, 3-(4-Trifluormethylphenylsulfonamido)phenyl, 4-(4-Trifluormethoxyphenylsulfonamido)phenyl, 3-(4-Trifluormethoxyphenylsulfonamido)phenyl, 4-(3-Methylphenylsulfonamido)phenyl, 3-(3-Methylphenylsulfonamido)phenyl, 4-(3,4-Dimethoxyphenylsulfonamido)phenyl, 3-(3,4-Dimethoxyphenylsulfonamido)phenyl, 4-(4-Cyanophenylsulfonamido)phenyl, 3-(4-Cyanophenylsulfonamido)phenyl, 4-(3-Cyanophenylsulfonamido)phenyl, 3-(3-Cyanophenylsulfonamido)phenyl, 4-(3-Chlor-4-methylphenylsulfonamido)phenyl, 3-(3-Chlor-4-methylphenylsulfonamido)phenyl, 4-(4-Biphenylsulfonamido)phenyl, 3-(4-Biphenylsulfonamido)phenyl, 4-(4-Isopropylphenylsulfonamido)phenyl, 3-(4-Isopropylphenylsulfonamido)phenyl, 4-(Naphth-1-ylsulfonamido)phenyl, 3-(Naphth-1-ylsulfonamido)phenyl, 4-(Naphth-2-ylsulfonamido)phenyl, 3-(Naphth-2-ylsulfonamido)phenyl, 4-Benzylphenyl, 4-Biphenyl, 4-Trifluormethoxyphenyl, 3-Trifluormethoxyphenyl, 2-Trifluormethoxyphenyl, 4-Methansulfonylphenyl, 3-Methansulfonylphenyl, 2-Methansulfonylphenyl, 4-(4-Methoxycarbonylphenylsulfonamido)phenyl oder (N-Methyl-4-p-toluolsulfonamido)phenyl genannt.

Hervorzuhebende Verbindungen der Formel I sind solche, worin

R1 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

R2 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

oder worin

R1 und R2 gemeinsam eine 1-2C-Alkylendioxygruppe bedeuten,

R3 Wasserstoff oder 1-4C-Alkyl bedeutet,

R31 Wasserstoff oder 1-4C-Alkyl bedeutet,

oder worin

R3 und R31 gemeinsam eine 1-4C-Alkylengruppe bedeuten,

R4 Wasserstoff oder 1-4C-Alkyl bedeutet,

R5 Wasserstoff bedeutet,

R51 Wasserstoff bedeutet,

oder worin

R5 und R51 gemeinsam eine zusätzliche Bindung darstellen,

R6 einen durch R61 substituierten Pyridylrest darstellt oder einen durch R7 und R8 substituierten Phenylrest darstellt, wobei

R61 Wasserstoff, Hydroxy, Halogen, 1-4C-Alkoxy, 1-4C-Alkyl, Carboxyl, Trifluormethyl, 1-4C-Alkoxycarbonyl oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

R7 Hydroxy, Halogen, Cyano, 1-4C-Alkyl, 1-4C-Alkoxy, 1-4C-Alkylcarbonyloxy, Trifluormethyl, Phenyl, Phenyl-1-4C-alkyl, Nitro, Amino oder N(R71)R72 bedeutet, wobei

R71 Wasserstoff, 1-4C-Alkyl, SO_2-R9 oder SO_2-R10 und

R72 1-4C-Alkyl, 1-4C-Alkylcarbonyl oder SO_2-R10 bedeutet,

R8 Wasserstoff, Hydroxy, Halogen, 1-4C-Alkoxy oder 1-4C-Alkyl bedeutet

und wobei

R9 und R10 unabhängig voneinander 1-4C-Alkyl, Phenyl, Phenyl-1-4C-alkyl oder durch einen oder mehrere gleiche oder verschiedene Substituenten substituiertes Phenyl bedeuten, wobei die Substituenten ausgewählt sind aus der Gruppe Nitro, 1-4C-Alkyl, Halogen, 1-4C-Alkylcarbonylamido, 1-4C-Alkoxy, ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy, Cyano, Phenyl, Naphthyl oder Trifluormethyl,

sowie die Salze dieser Verbindungen.

Eine Ausgestaltung [Ausgestaltung a)] der erfindungsgemäßen Verbindungen sind Verbindungen der Formel I, worin

R1 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

R2 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

oder worin

R1 und R2 gemeinsam eine 1-2C-Alkylendioxygruppe bedeuten,

R3 Wasserstoff oder 1-4C-Alkyl bedeutet,

R51 Wasserstoff oder 1-4C-Alkyl bedeutet,
oder worin
R3 und R31 gemeinsam eine 1-4C-Alkylengruppe bedeuten,
R4 Wasserstoff oder 1-4C-Alkyl bedeutet,
R5 Wasserstoff bedeutet,
R51 Wasserstoff bedeutet,
oder worin
R5 und R51 gemeinsam eine zusätzliche Bindung darstellen,
R6 einen durch R61 substituierten Pyridylrest darstellt, wobei
R61 Wasserstoff, Hydroxy, Halogen, 1-4C-Alkoxy, 1-4C-Alkyl, Carboxyl, Trifluormethyl, 1-4C-Alkoxycarbonyl oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,
sowie die Salze dieser Verbindungen.

Hervorzuhebende Verbindungen der Ausgestaltung a) sind Verbindungen der Formel I, worin
R1 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-2C-Alkoxy bedeutet,
R2 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-2C-Alkoxy bedeutet,
R3 Wasserstoff bedeutet,
R31 Wasserstoff bedeutet,
oder worin
R3 und R31 gemeinsam eine 1-2C-Alkylengruppe bedeuten,
R4 Wasserstoff oder 1-4C-Alkyl bedeutet,
R5 Wasserstoff bedeutet,
R51 Wasserstoff bedeutet,
oder worin
R5 und R51 gemeinsam eine zusätzliche Bindung darstellen,
R6 einen durch R61 substituierten Pyridylrest darstellt, wobei
R61 Wasserstoff, Hydroxy, Halogen oder 1-4C-Alkoxy bedeutet,
sowie die Salze dieser Verbindungen.

Besonders hervorzuhebende Verbindungen der Ausgestaltung a) sind Verbindungen der Formel I, worin
R1 1-4C-Alkoxy, 3-7C-Cycloalkoxy oder ganz oder teilweise durch Fluor substituiertes 1-2C-Alkoxy bedeutet,
R2 1-4C-Alkoxy, 3-7C-Cycloalkoxy oder ganz oder teilweise durch Fluor substituiertes 1-2C-Alkoxy bedeutet,
R3 Wasserstoff bedeutet,
R31 Wasserstoff bedeutet,

oder worin
R3 und R31 gemeinsam eine 1-2C-Alkylengruppe bedeuten,
R4 Wasserstoff oder 1-4C-Alkyl bedeutet,
R5 Wasserstoff bedeutet,
R51 Wasserstoff bedeutet,
oder worin
R5 und R51 gemeinsam eine zusätzliche Bindung darstellen,
R6 einen durch R61 substituierten Pyridylrest darstellt, wobei
R61 Wasserstoff, Hydroxy, Halogen oder 1-4C-Alkoxy bedeutet,
sowie die Salze dieser Verbindungen.

Bevorzugte Verbindungen der Ausgestaltung a) sind Verbindungen der Formel I, worin
R1 1-4C-Alkoxy bedeutet,
R2 1-4C-Alkoxy bedeutet,
R3 Wasserstoff bedeutet,
R31 Wasserstoff bedeutet,
R4 Wasserstoff bedeutet,
R5 Wasserstoff bedeutet,
R51 Wasserstoff bedeutet,
R6 einen durch R61 substituierten Pyridylrest darstellt, wobei
R61 Wasserstoff, Hydroxy oder Halogen bedeutet,
sowie die Salze dieser Verbindungen.

Eine andere Ausgestaltung [Ausgestaltung b)] der erfindungsgemäßen Verbindungen sind solche Verbindungen der Formel I, worin
R1 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,
R2 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,
oder worin
R1 und R2 gemeinsam eine 1-2C-Alkylendioxygruppe bedeuten,
R3 Wasserstoff oder 1-4C-Alkyl bedeutet,
R31 Wasserstoff oder 1-4C-Alkyl bedeutet,
oder worin
R3 und R31 gemeinsam eine 1-4C-Alkylengruppe bedeuten,
R4 Wasserstoff oder 1-4C-Alkyl bedeutet,
R5 Wasserstoff bedeutet,
R51 Wasserstoff bedeutet,
oder worin

Oxalsäure, Weinsäure, Embonsäure, Stearinsäure, Toluolsulfonsäure, Methansulfonsäure oder 3-Hydroxy-2-naphthoesäure, wobei die Säuren bei der Salzherstellung - je nachdem, ob es sich um eine ein- oder mehrbasige Säure handelt und je nachdem, welches Salz gewünscht wird - im äquimolaren oder einem davon abweichenden Mengenverhältnis eingesetzt werden.

Andererseits kommen auch Salze mit Basen in Betracht. Als Beispiele für Salze mit Basen seien Alkali- (Lithium-, Natrium-, Kalium-) oder Calcium-, Aluminium-, Magnesium-, Titan-, Ammonium-, Meglumin- oder Guanidiniumsalze erwähnt, wobei auch hier bei der Salzherstellung die Basen im äquimolaren oder einem davon abweichenden Mengenverhältnis eingesetzt werden.

Pharmakologisch unverträgliche Salze, die beispielsweise bei der Herstellung der erfindungsgemäßen Verbindungen im industriellen Maßstab als Verfahrensprodukte zunächst anfallen können, werden durch dem Fachmann bekannte Verfahren in pharmakologisch verträgliche Salze übergeführt.

Bei den Verbindungen der Formel I handelt es sich um chirale Verbindungen mit Chiralitätszentren in den Positionen 4a und 10b und je nach Bedeutung der Substituenten R2, R31, R4, R5 und R51 weiteren Chiralitätszentren in den Positionen 1,2,3 und 4. Die Erfindung umfaßt daher alle denkbaren reinen Diastereomeren und reinen Enantiomeren als auch deren Gemische in jedem Mischungsverhältnis, einschließlich der Racemate. Bevorzugt sind die Verbindungen der Formel I, in denen die Wasserstoffatome in den Positionen 4a und 10b cis-ständig zueinander sind. Insbesondere bevorzugt sind dabei die reinen cis-Diastereomeren und die reinen cis-Enantiomeren als auch deren Gemische in jedem Mischungsverhältnis und einschließlich der Racemate.

Die Enantiomeren können in an sich bekannter Weise (beispielsweise durch Herstellung und Trennung entsprechender diastereoisomerer Verbindungen) separiert werden. Vorzugsweise erfolgt eine Enantiomerentrennung auf Stufe der Ausgangsverbindungen der Formel III (siehe beigefügtes Formelblatt) beispielsweise über Salzbildung der racemischen Verbindungen der Formel III mit optisch aktiven Carbonsäuren. Alternativ können enantiomerenreine Ausgangsverbindungen der Formel III auch über asymmetrische Synthesen dargestellt werden.

Weiterer Gegenstand der Erfindung ist ein Verfahren zur Herstellung der Verbindungen der Formel I, worin R1, R2, R3, R31, R4, R5, R51 und R6 die oben angegebenen Bedeutungen besitzen, und ihrer Salze. Das Verfahren ist dadurch gekennzeichnet, daß man

a) entsprechende Verbindungen der Formel II (siehe beigefügtes Formelblatt), in denen R1, R2, R3, R31, R4, R5, R51 und R6 die oben angegebenen Bedeutungen besitzen, cyclokondensiert, oder daß man

b) zur Herstellung von Verbindungen der Formel I, worin R1, R2, R3, R31, R4, R5 und R51 die oben angegebenen Bedeutungen besitzen und R6 durch R61 substituiertes Pyridyl darstellt, wobei R61 Hydroxy bedeutet, entsprechende Verbindungen der Formel I, worin R1, R2, R3, R31, R4, R5 und R51 die oben angegebenen Bedeutungen besitzen und R6 durch R61 substituiertes Pyridyl darstellt, wobei R61 Halogen bedeutet, hydrolysiert oder daß man

c) zur Herstellung von Verbindungen der Formel I, worin R1, R2, R3, R31, R4, R5 und R51 die oben genannten Bedeutungen haben und R6 einen durch R7 und R8 substituierten Phenylrest darstellt, wobei R7 Amino bedeutet, entsprechende Verbindungen der Formel I, worin R7 Nitro bedeutet, reduziert, oder daß man

d) zur Herstellung von Verbindungen der Formel I, worin R1, R2, R3, R31, R4, R5 und R51 die oben genannten Bedeutungen haben und R6 einen durch R7 und R8 substituierten Phenylrest darstellt, wobei R7 Hydroxy bedeutet, entsprechende Verbindungen der Formel I, worin R7 1-4C-Alkylcarbonyloxy bedeutet, hydrolysiert, oder daß man

e) Verbindungen der Formel I, worin R1, R2, R3, R31, R4, R5 und R51 die oben genannten Bedeutungen haben und R6 einen durch R7 und R8 substituierten Phenylrest darstellt, wobei R7 Amino bedeutet, mit einem geeignet aktivierten 1-4C-Alkylcarbonylderivat N-acyliert, oder daß man

f) Verbindungen der Formel I, worin R1, R2, R3, R31, R4, R5 und R51 die oben genannten Bedeutungen haben und R6 einen durch R7 und R8 substituierten Phenylrest darstellt, wobei R7 Amino bedeutet, mit einer Sulfonsäureverbindung der Formel X-SO_2-R10, worin R10 die oben genannte Bedeutung besitzt und X eine geeignete Abgangsgruppe darstellt, umsetzt, oder daß man

g) Verbindungen der Formel I, worin R1, R2, R3, R31, R4, R5 und R51 die oben genannten Bedeutungen haben und R6 einen durch R7 und R8 substituierten Phenylrest darstellt, wobei R7 die Gruppe N(H)R72 bedeutet, wobei R72 die Bedeutung 1-4C-Alkylcarbonyl oder SO_2-R10 hat, mit einem geeignet aktivierten 1-4C-Alkylcarbonylderivat N-acyliert, mit einem geeignet aktivierten 1-4C-Alkylderivat N-alkyliert oder mit einer Sulfonsäurevertindung der Formel X-SO_2-R9 oder X-SO_2-R10, worin R9 und R10 die oben genannten Bedeutungen besitzen und X eine geeignete Abgangsgruppe darstellt, umsetzt, und daß man

gewünschtenfalls anschließend nach a), b), c), d), e), f) oder g) erhaltene Verbindungen der Formel I in ihre Salze überführt, oder daß man gewünschtenfalls anschließend nach a), b), c), d), e), f) oder g) erhaltene Salze der Verbindungen der Formel I in die freien Verbindungen überführt.

Die Cyclokondensation nach Verfahrensvariante a) erfolgt auf eine dem Fachmann an sich bekannte Weise gemäß Bischler-Napieralski (z.B. so, wie in J.Chem.Soc., 1956, 4280-4282 beschrieben) in Ge-

Elementaranalyse: Ber.: C 66.50 H 6.05 N 3.23
Gef.: C 66.44 H 6.05 N 3.18

20. (+/-)-cis-3-Ethoxy-8-methoxy-5-(4-p-toluolsulfonamidophenyl)-1,2,3,4,4a,10b-hexahydrophenanthridin

Schmp.: 95°C (Zers.), Ausbeute 51,0 % d.Th.
SF: $C_{30}H_{32}N_2O_4S$; MG: 504.65
Elementaranalyse: Ber.: C 69.02 H 6.59 N 5.55
Gef.: C 69.19 H 6.68 N 5.44

21. (+/-)-cis-3-Ethoxy-8-methoxy-5-(4-nitrophenyl)-1,2,3,4,4a,10b-hexahydrophenanthridin

Schmp.: 122-124°C, Ausbeute 60,5 % d.Th.
SF: $C_{23}H_{24}N_2O_4$; MG: 380.45
Elementaranalyse: Ber.: C 69.46 H 6.36 N 7.36
Gef.: C 69.21 H 6.23 N 7.24

22. (+/-)-cis-3-Ethoxy-8-methoxy-5-(4-methansulfenylphenyl)-1,2,3,4,4a,10b-hexahydrophenanthridin

Schmp.: 186-187°C, Ausbeute 67,2 % d.Th.
SF: $C_{24}H_{27}NO_3S$; MG: 413.54
Elementaranalyse: Ber.: C 66.80 H 6.68 N 3.39
Gef.: C 66.85 H 6.62 N 3.45

23. (+/-)-cis-3-Ethoxy-8-methoxy-5-(4-(3-methoxycarbonylphenylsulfonamido)phenyl)-1,2,3,4,4a,10b-hexahydrophenanthridin-hydrochlorid

Schmp.: Zers. ab 210°C, Ausbeute 55,6 % d.Th.
SF: $C_{31}H_{34}N_2O_6S \times HCl$; MG: 595.12
Elementaranalyse x 0.5 H_2O: Ber.: C 60.63 H 5.77 N 4.72 Cl 5.97 S 5.49
Gef.: C 60.51 H 5.66 N 4.73 Cl 5.89 S 5.63

24. (+/-)-cis-3,8-Diethoxy-5-(pyrid-4-yl)-1,2,3,4,4a,10b-hexahydrophenanthridin-dihydrochlorid

2,2 g (+/-)-cis-N-[2-(3,4-Diethoxyphenyl)cyclohexyl]-isonicotinsäureamid werden in 50 ml Acetonitril und 3,0 ml Phosphoroxychlorid gelöst und 9 h bei 50°C gerührt. Das Reaktionsgemisch wird in 100 ml gesättigte Natriumhydrogencarbonatlösung gegeben und mit Essigsäureethylester extrahiert. Die organische Phase wird mit Natriumhydrogencarbonatlösung und Wasser gewaschen, mit Natriumsulfat getrocknet und eingeengt. Der Rückstand wird über Kieselgel mit einer Mischung aus Toluol/Dioxan/Petrolether/Triethylamin im Verhältnis 6:2:1:0,5 chromatographiert. Die Produktfraktionen werden eingeengt, der Rückstand in 30 ml Ethanol gelöst, mit 7 ml mit Chlorwasserstoff gesättigtem Diethylether versetzt und in 400 ml Diethylether getropft. Der Niederschlag wird abgesaugt, mit Diethylether nachgewaschen und getrocknet. Man erhält 1,6 g (49,4 % d.Th.) der Titelverbindung als Dihydrochlorid mit Schmp.: 223°C (Zers.).

SF: $C_{23}H_{30}N_2O_2 \times 2\,HCl$; MG: 423.39
Elementaranalyse: Ber.: C 57.62 H 6.42 Cl 16.17 N 5.59
Gef.: C 57.09 H 6.40 Cl 17.59 N 5.62

Ausgehend von den nachfolgend beschriebenen Ausgangsverbindungen erhält man entsprechend der Arbeitsweise nach Beispiel 24:

25. (+/-)-cis-3,8-Diethoxy-5-(pyrid-3-yl)-1,2,3,4,4a,10b-hexahydrophenanthridin-hydrochlorid

Schmp.: 233°C, Ausbeute 37,8% d.Th.
SF: $C_{23}H_{30}N_2O_2 \times HCl$; MG: 388.93
Elementaranalyse: Ber.: C 68.39 H 7.69 Cl 9.15 N 7.24
Gef.: C 68.43 H 7.69 Cl 9.29 N 7.30

26. (+/-)-cis-3,8-Diethoxy-5-(2-chlorpyrid-5-yl)-1,2,3,4,4a,10b-hexahydrophenanthridin

Die Titelverbindung erhält man durch Einengen der Produktfraktionen nach Chromatographie analog der Arbeitsweise nach Beispiel 24:

Schmp.: 123-126°C, Ausbeute 75,7 % d.Th.
SF: $C_{23}H_{29}ClN_2O_2$; MG: 384.91
Elementaranalyse: Ber.: C 68.01 H 6.59 Cl 9.13 N 7.21
Gef.: C 68.04 H 6.48 Cl 9.28 N 7.16

27. (+/-)-cis-3,8-Diethoxy-5-(2-hydroxypyrid-5-yl)-1,2,3,4,4a,10b-hexahydrophenanthridin

850 mg (+/-)-cis-3,8-Diethoxy-5-(2-chlorpyrid-5-yl)-1,2,3,4,4a,10b-hexahydrophenanthridin werden in 60 ml Toluol suspendiert, mit 1,0 g Kaliumcarbonat, 2,0 g Kaliumhydroxid und 0,26 mg Tris-[2-(2-methoxyethoxy)ethyl]amin versetzt und über Nacht unter Rückfluß gekocht. Die Suspension wird filtriert, das Lösungsmittel im Vakuum entfernt, der Rückstand in Wasser aufgenommen, mit 0,1 M Salzsäure neutralisiert und mit Essigsäureethylester extrahiert. Die organische Phase wird mit Natri-

Herzinsuffizienz, oder Erkrankungen, die aufgrund der gewebsrelaxierenden Wirkung der PDE-Hemmstoffe behandelt werden können, wie beispielsweise erektile Dysfunktion oder Kolliken der Nieren und der Harnleiter im Zusammenhang mit Nierensteinen.

Ein weiterer Gegenstand der Erfindung ist ein Verfahren zur Behandlung von Säugetieren einschließlich Menschen, die an einer der oben genannten Krankheiten erkrankt sind. Das Verfahren ist dadurch gekennzeichnet, daß man dem erkrankten Säugetier eine therapeutisch wirksame und pharmakologisch verträgliche Menge einer oder mehrerer der erfindungsgemäßen Verbindungen verabreicht.

Weiterer Gegenstand der Erfindung sind die erfindungsgemäßen Verbindungen zur Anwendung bei der Behandlung und/oder Prophylaxe der genannten Krankheiten.

Ebenso betrifft die Erfindung die Verwendung der erfindungsgemäßen Verbindungen zur Herstellung von Arzneimitteln, die zur Behandlung und/oder Prophylaxe der genannten Krankheiten eingesetzt werden.

Weiterhin sind Arzneimittel zur Behandlung und/oder Prophylaxe der genannten Krankheiten, die eine oder mehrere der erfindungsgemäßen Verbindungen enthalten, Gegenstand der Erfindung.

Die Arzneimittel werden nach an sich bekannten, dem Fachmann geläufigen Verfahren hergestellt. Als Arzneimittel werden die erfindungsgemäßen Verbindungen (= Wirkstoffe) entweder als solche, oder vorzugsweise in Kombination mit geeigneten pharmazeutischen Hilfsstoffen z.B. in Form von Tabletten, Dragees, Kapseln, Suppositorien, Pflastern, Emulsionen, Suspensionen, Gelen oder Lösungen eingesetzt, wobei der Wirkstoffgehalt vorteilhafterweise zwischen 0,1 und 95 % beträgt.

Welche Hilfsstoffe für die gewünschten Arzneiformulierungen geeignet sind, ist dem Fachmann aufgrund seines Fachwissens geläufig. Neben Lösemitteln, Gelbildnern, Salbengrundlagen und anderen Wirkstoffträgern können beispielsweise Antioxidantien, Dispergiermittel, Emulgatoren, Konservierungsmittel, Lösungsvermittler oder Permeationspromotoren verwendet werden.

Für die Behandlung von Erkrankungen des Respirationstraktes werden die erfindungsgemäßen Verbindungen bevorzugt auch inhalativ appliziert. Hierzu werden diese entweder direkt als Pulver (vorzugsweise in mikronisierter Form) oder durch Vernebeln von Lösungen oder Suspensionen, die sie enthalten, verabreicht. Bezüglich der Zubereitungen und Darreichungsformen wird beispielsweise auf die Ausführungen im Europäischen Patent 163 965 verwiesen.

Für die Behandlung von Dermatosen erfolgt die Anwendung der erfindungsgemäßen Verbindungen insbesondere in Form solcher Arzneimittel, die für eine topische Applikation geeignet sind. Für die Herstellung der Arzneimittel werden die erfindungsgemäßen Verbindungen (= Wirkstoffe) vorzugs-

weise mit geeigneten pharmazeutischen Hilfsstoffen vermischt und zu geeigneten Arzneiformulierungen weiterverarbeitet. Als geeignete Arzneiformulierungen seien beispielsweise Puder, Emulsionen, Suspensionen, Sprays, Öle, Salben, Fettsalben, Cremes, Pasten, Gele oder Lösungen genannt.

Die erfindungsgemäßen Arzneimittel werden nach an sich bekannten Verfahren hergestellt. Die Dosierung der Wirkstoffe erfolgt in der für PDE-Hemmstoffe üblichen Größenordnung. So enthalten topische Applikationsformen (wie z.B. Salben) für die Behandlung von Dermatosen die Wirkstoffe in einer Konzentration von beispielsweise 0,1-99 %. Die Dosis für die inhalative Applikation beträgt üblicherweise zwischen 0,01 und 1 mg pro Sprühstoß. Die übliche Dosis bei systemischer Therapie p.o. oder i.v. liegt zwischen 0,1 und 200 mg pro Applikation.

1. Hemmung der PDE IV-Aktivität

Methodik

Der Aktivitätstest wurde nach der Methode von Bauer und Schwabe durchgeführt, die auf Mikrotiterplatten adaptiert wurde (Naunyn-Schmiedeberg's Arch. Pharmacol. 1980, 311, 193-198). Hierbei erfolgt im ersten Schritt die PDE-Reaktion. In einem zweiten Schritt wird das entstandene 5'-Nukleotid durch eine 5'-Nukleotidase des Schlangengiftes von Crotalus Atrox zum ungeladenen Nukleosid gespalten. Im dritten Schritt wird das Nukleosid auf Ionenaustauschsäulen vom verbliebenen geladenen Substrat getrennt. Die Säulen werden mit 2 ml 30 mM Ammoniumformiat (pH 6,0) direkt in Minivials eluiert, in die noch 2 ml Szintillatorflüssigkeit zur Zählung gegeben wird.

Die für die erfindungsgemäßen Verbindungen ermittelten Hemmwerte ergeben sich aus der folgenden Tabelle A, in der die Nummern der Verbindungen den Nummern der Beispiele entsprechen.

Tabelle A

Hemmung der PDE IV-Aktivität

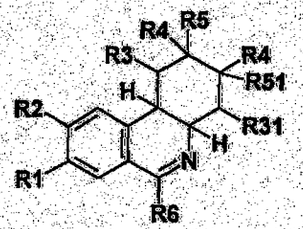
Verbindung	-log IC_{50}
1	7.73
2	6.39
3	7.76
4	6.12
5	7.22
6	6.77
7	6.44
8	6.91
9	6.17
10	6.10
12	5.77
13	8.43
14	8.08
15	7.96
16	7.93
17	8.00
18	8.24

Fortsetzung Tabelle A

Verbindung	-log IC_{50}
19	7.97
20	9.05
21	8.46
22	8.66
23	8.70
24	8.08
25	7.96
26	8.41
27	6.66
29	7.60
30	7.36
31	7.30
32	6.38
33	7.27
34	7.42
35	7.81
36	9.09
37	8.04

Patentansprüche

1. Verbindungen der Formel I,



(I)

worin

R1 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

R2 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

oder worin

R1 und R2 gemeinsam eine 1-2C-Alkylendioxygruppe bedeuten,

R3 Wasserstoff oder 1-4C-Alkyl bedeutet,

R31 Wasserstoff oder 1-4C-Alkyl bedeutet,

oder worin

R3 und R31 gemeinsam eine 1-4C-Alkylengruppe bedeuten,

R4 Wasserstoff oder 1-4C-Alkyl bedeutet,

R5 Wasserstoff bedeutet,

R51 Wasserstoff bedeutet,

oder worin

R5 und R51 gemeinsam eine zusätzliche Bindung darstellen,

R6 einen durch R61 substituierten Pyridylrest darstellt oder einen durch R7 und R8 substituierten Phenylrest darstellt, wobei

R61 Wasserstoff, Hydroxy, Halogen, 1-4C-Alkoxy, 1-4C-Alkyl, Carboxyl, Trifluormethyl, 1-4C-Alkoxycarbonyl oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

R7 Hydroxy, Halogen, Cyano, 1-4C-Alkyl, 1-4C-Alkoxy, 1-4C-Alkylcarbonyloxy, Trifluormethyl, Phenyl, Phenyl-1-4C-alkyl, Nitro, Amino, ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy, SO_2-R70 oder N(R71)R72 bedeutet, wobei

R70 1-4C-Alkyl,

R71 Wasserstoff, 1-4C-Alkyl, SO_2-R9 oder SO_2-R10 und

R72 1-4C-Alkyl, 1-4C-Alkylcarbonyl oder SO_2-R10 bedeutet,

R8 Wasserstoff, Hydroxy, Halogen, 1-4C-Alkoxy oder 1-4C-Alkyl bedeutet

und wobei

R9 und R10 unabhängig voneinander 1-4C-Alkyl, Phenyl, Phenyl-1-4C-alkyl oder durch einen oder mehrere gleiche oder verschiedene Substituenten substituiertes Phenyl bedeuten, wobei die Substituenten ausgewählt sind aus der Gruppe Nitro, 1-4C-Alkyl, Halogen, 1-4C-Alkylcarbonylamino, 1-4C-Alkoxy, ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy, Cyano, Phenyl, Naphthyl, Trifluormethyl oder 1-4C-Alkoxycarbonyl,

sowie die Salze dieser Verbindungen.

2. Verbindungen der Formel I nach Anspruch 1, worin

R1 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

R2 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

oder worin

R1 und R2 gemeinsam eine 1-2C-Alkylendioxygruppe bedeuten,

R3 Wasserstoff oder 1-4C-Alkyl bedeutet,

R31 Wasserstoff oder 1-4C-Alkyl bedeutet,

oder worin

R3 und R31 gemeinsam eine 1-4C-Alkylengruppe bedeuten,

R4 Wasserstoff oder 1-4C-Alkyl bedeutet,

R5 Wasserstoff bedeutet,

R51 Wasserstoff bedeutet,

oder worin

R5 und R51 gemeinsam eine zusätzliche Bindung darstellen,

R6 einen durch R61 substituierten Pyridylrest darstellt, wobei

R61 Wasserstoff, Hydroxy, Halogen, 1-4C-Alkoxy, 1-4C-Alkyl, Carboxyl, Trifluormethyl, 1-4C-Alkoxycarbonyl oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

sowie die Salze dieser Verbindungen.

3. Verbindungen der Formel I nach Anspruch 1, worin

R1 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

R2 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,

oder worin

R1 und R2 gemeinsam eine 1-2C-Alkylendioxygruppe bedeuten,

R3 Wasserstoff oder 1-4C-Alkyl bedeutet,

R31 Wasserstoff oder 1-4C-Alkyl bedeutet,
oder worin
R3 und R31 gemeinsam eine 1-4C-Alkylengruppe bedeuten,
R4 Wasserstoff oder 1-4C-Alkyl bedeutet,
R5 Wasserstoff bedeutet,
R51 Wasserstoff bedeutet,
oder worin
R5 und R51 gemeinsam eine zusätzliche Bindung darstellen,
R6 einen durch R7 und R8 substituierten Phenylrest darstellt, wobei
R7 Hydroxy, Halogen, Cyano, 1-4C-Alkyl, 1-4C-Alkoxy, 1-4C-Alkylcarbonyloxy, Trifluormethyl, Phenyl, Phenyl-1-4C-alkyl, Nitro, Amino oder N(R71)R72 bedeutet, wobei
R71 Wasserstoff, 1-4C-Alkyl, SO_2-R9 oder SO_2-R10 und
R72 1-4C-Alkyl, 1-4C-Alkylcarbonyl oder SO_2-R10 bedeutet,
R8 Wasserstoff, Hydroxy, Halogen, 1-4C-Alkoxy oder 1-4C-Alkyl bedeutet
und wobei
R9 und R10 unabhängig voneinander 1-4C-Alkyl, Phenyl, Phenyl-1-4C-alkyl oder durch einen oder mehrere gleiche oder verschiedene Substituenten substituiertes Phenyl bedeuten, wobei die Substituenten ausgewählt sind aus der Gruppe Nitro, 1-4C-Alkyl, Halogen, 1-4C-Alkylcarbonylamino, 1-4C-Alkoxy, ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy, Cyano, Phenyl, Naphthyl oder Trifluormethyl,
sowie die Salze dieser Verbindungen.

4. Verbindungen der Formel I nach Anspruch 1, worin
R1 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,
R2 Hydroxy, 1-4C-Alkoxy, 3-7C-Cycloalkoxy, 3-7C-Cycloalkylmethoxy oder ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy bedeutet,
oder worin
R1 und R2 gemeinsam eine 1-2C-Alkylendioxygruppe bedeuten,
R3 Wasserstoff oder 1-4C-Alkyl bedeutet,
R31 Wasserstoff oder 1-4C-Alkyl bedeutet,
oder worin
R3 und R31 gemeinsam eine 1-4C-Alkylengruppe bedeuten,
R4 Wasserstoff oder 1-4C-Alkyl bedeutet,
R5 Wasserstoff bedeutet,
R51 Wasserstoff bedeutet,
oder worin
R5 und R51 gemeinsam eine zusätzliche Bindung darstellen,
R6 einen durch R7 und R8 substituierten Phenylrest darstellt, wobei

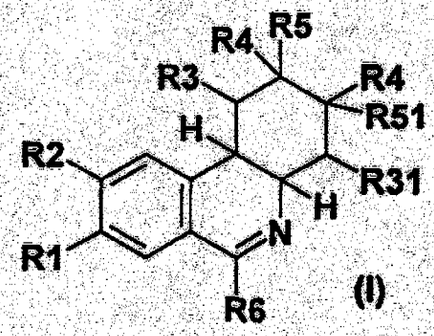
R7 Hydroxy, Halogen, Cyano, 1-4C-Alkyl, 1-4C-Alkoxy, 1-4C-Alkylcarbonyloxy, Trifluormethyl, Phenyl, Phenyl-1-4C-alkyl, Nitro, Amino, ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy, SO_2-R70 oder N(R71)R72 bedeutet, wobei
R70 1-4C-Alkyl,
R71 Wasserstoff, 1-4C-Alkyl, SO_2-R9 oder SO_2-R10 und
R72 1-4C-Alkyl, 1-4C-Alkylcarbonyl oder SO_2-R10 bedeutet,
R8 Wasserstoff, Hydroxy, Halogen, 1-4C-Alkoxy oder 1-4C-Alkyl bedeutet
und wobei
R9 und R10 unabhängig voneinander 1-4C-Alkyl, Phenyl, Phenyl-1-4C-alkyl oder durch einen oder mehrere gleiche oder verschiedene Substituenten substituiertes Phenyl bedeuten, wobei die Substituenten ausgewählt sind aus der Gruppe Nitro, 1-4C-Alkyl, Halogen, 1-4C-Alkylcarbonylamino, 1-4C-Alkoxy, ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy, Cyano, Phenyl, Naphthyl, Trifluormethyl oder 1-4C-Alkoxycarbonyl,
sowie die Salze dieser Verbindungen.

5. Verbindungen der Formel I nach Anspruch 1, worin
R1 1-4C-Alkoxy oder 3-7C-Cycloalkoxy bedeutet,
R2 1-4C-Alkoxy oder 3-7C-Cycloalkoxy bedeutet,
R3 Wasserstoff bedeutet,
R31 Wasserstoff bedeutet,
oder worin
R3 und R31 gemeinsam eine 1-2C-Alkylengruppe bedeuten,
R4 Wasserstoff oder 1-4C-Alkyl bedeutet,
R5 Wasserstoff bedeutet,
R51 Wasserstoff bedeutet,
oder worin
R5 und R51 gemeinsam eine zusätzliche Bindung darstellen,
R6 einen durch R7 und R8 substituierten Phenylrest darstellt, wobei
R7 Hydroxy, Halogen, Cyano, 1-4C-Alkoxy, 1-4C-Alkylcarbonyloxy, Trifluormethyl, Phenyl, Phenyl-1-4C-alkyl, Nitro, Amino, ganz oder teilweise durch Fluor substituiertes 1-4C-Alkoxy, SO_2-R70 oder N(R71)R72 bedeutet, wobei
R70 1-4C-Alkyl,
R71 Wasserstoff, 1-4C-Alkyl oder SO_2-R10 und
R72 1-4C-Alkylcarbonyl oder SO_2-R10 bedeutet,
R8 Wasserstoff, Halogen oder 1-4C-Alkoxy bedeutet
und wobei
R10 durch einen Substituenten substituiertes Phenyl bedeutet, wobei der Substituent ausgewählt ist aus der Gruppe Nitro, 1-4C-Alkyl oder 1-4C-Alkoxycarbonyl,
sowie die Salze dieser Verbindungen.

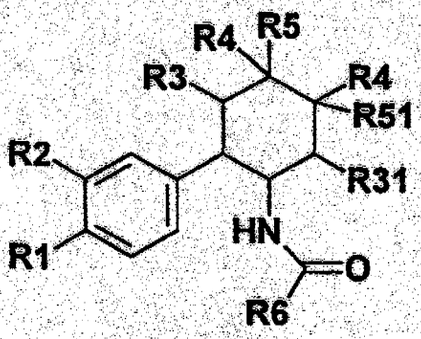
6. Arzneimittel enthaltend mindestens eine Verbindung der Formel I nach Anspruch 1 zusammen mit pharmazeutischen Hilfs- und/oder Trägerstoffen.

7. Verwendung von Verbindungen der Formel I nach Anspruch 1 zur Herstellung von Arzneimitteln für die Behandlung von Atemwegserkrankungen.

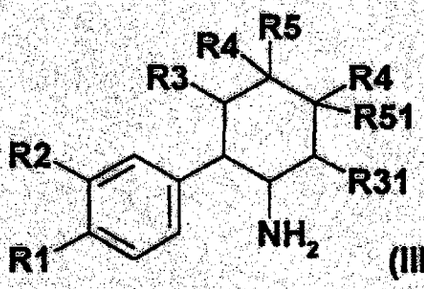
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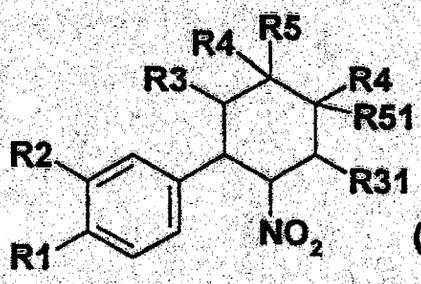
(I)



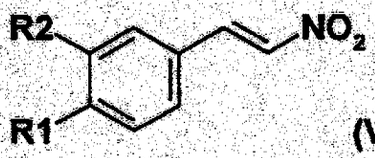
(II)



(III)

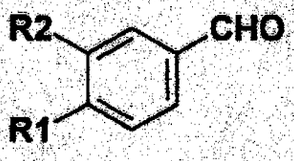


(IV)



(V)

R3-CH=C(R4)-C(R4)=CH-R31 (VI)



(VII)

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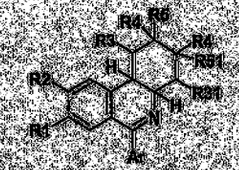
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(I)

(57) Abstract

Compounds of formula (I), in which R1, R2, R3, R31, X4, R5, R51 and Ar have the meanings indicated in the description, are novel, active bronchial therapeutics.

6-ARYLPHENANTHRIDINES WITH PDE-IV INHIBITING ACTIVITY

Field of application of the invention

The invention relates to novel 6-arylphenanthridines, which are used in the pharmaceutical industry for the production of medicaments.

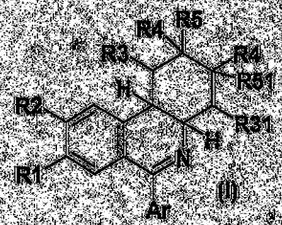
Known technical background

Chem. Ber. 1939, 72, 678-677, J. Chem. Soc., 1965, 4280-4293 and J. Chem. Soc.(C), 1971, 1835 describe the synthesis of 6-phenylphenanthridines. The International Applications WO 97/28131 and WO 97/35864 describe 6-phenyl- and 6-pyridylphenanthridines as PDE4 inhibitors.

Description of the invention

It has now been found that the novel phenanthridines substituted in the 6-position by a bi- or tricyclic aryl radical and described in greater detail below have surprising and particularly advantageous properties.

The invention thus relates to compounds of the formula (I)



(I)

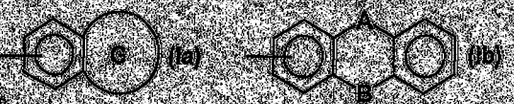
in which

R1 is hydroxy, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R2 is hydroxy, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

or in which

R1 and R2 together are a 1-4C-alkylenedioxy group,
R3 is hydrogen or 1-4C-alkyl,
R31 is hydrogen or 1-4C-alkyl,
or in which
R3 and R31 together are a 1-4C-alkylene group,
R4 is hydrogen or 1-4C-alkyl,
R5 is hydrogen,
R51 is hydrogen,
or in which
R5 and R51 together represent an additional bond,
Ar is an unsubstituted or R6- and/or R7-substituted bi- or tricyclic radical of the formula Ia or Ib,



where
Q is a 5- or 6-membered ring which optionally can contain up to 3 identical or different heteroatoms selected from the group consisting of O and N,
A is a bond, $-CH_2-$, $-CH_2CH_2-$, $-CH_2O-$, $-OCH_2-$, $-C(O)-$, $-O-$, $-N(H)-$, $-N=$, $-CH=$, $-CH=CH-$, $-N=CH-$ or $-CH=N-$,
B is a bond, $-CH_2-$, $-C(O)-$, $-O-$, $-N(H)-$, $-N=$, $-CH=$ or $-S(O)_2-$,
R6 is hydroxyl, halogen, carboxyl, nitro, cyano, amino, aminosulfonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonylamino or completely or predominantly fluorine-substituted 1-4C-alkoxy, and
R7 is hydroxyl, halogen, nitro, 1-4C-alkyl or 1-4C-alkoxy,
and the salts, tautomers and the salts of the N-oxides of these compounds.

1-4C-Alkyl represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and preferably the ethyl and methyl radicals.

1-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy radicals.

3-7C-Cycloalkoxy represents cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy, of which cyclopropyloxy, cyclobutyloxy and cyclopentyloxy are preferred.

3-7C-Cycloalkylmethoxy represents cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy and cycloheptylmethoxy, of which cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy are preferred.

As completely or predominantly fluorine-substituted 1-4C-alkoxy, for example, the 2,2,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and preferably the difluoromethoxy radicals may be mentioned. "Predominantly" in this connection means that more than half of the hydrogen atoms are replaced by fluorine atoms.

1-2C-Alkylenedioxy represents, for example, the methylenedioxy [$-O-CH_2-O-$] and the ethylenedioxy [$-O-CH_2-CH_2-O-$] radicals.

If R3 and R31 together have the meaning 1-4C-alkylene, the positions 1 and 4 in compounds of the formula I are linked to one another by a 1-4C-alkylene bridge. 1-4C-Alkylene represents straight-chain or branched alkylene radicals having 1 to 4 carbon atoms. Examples which may be mentioned are the radicals methylene [$-CH_2-$], ethylene [$-CH_2CH_2-$], trimethylene [$-CH_2-CH_2-CH_2-$], 1,2-dimethylethylene [$-CH(CH_3)-CH(CH_3)-$] and isopropylidene [$-C(CH_3)_2-$].

If R5 and R51 together are an additional bond, then the carbon atoms in positions 2 and 3 in compounds of the formula I are linked to one another via a double bond.

Halogen within the meaning of the invention is bromine, chlorine or fluorine.

In addition to the nitrogen atom, mono- or di-1-4C-alkylamino radicals contain one or two of the abovementioned 1-4C-alkyl radicals. Di-1-4C-alkylamino is preferred and here, in particular, dimethyl-, diethyl- or diisopropylamino.

In addition to the carbonyl group, mono- or di-1-4C-alkylaminocarbonyl radicals contain one of the abovementioned mono- or di-1-4C-alkylamino radicals. Examples which may be mentioned are the N-methyl-, the N,N-dimethyl-, the N-ethyl-, the N-propyl-, the N,N-diethyl- and N-isopropylaminocarbonyl radicals.

1-4C-Alkylcarbonyloxy represents a carbonyloxy group to which one of the abovementioned 1-4C-alkyl radicals is bonded. An example which may be mentioned is the acetoxy radical [$CH_3C(O)-O-$].

1-4C-Alkylcarbonyl represents a radical which, in addition to the carbonyl group, contains one of the abovementioned 1-4C-alkyl radicals. An example which may be mentioned is the acetyl radical.

1-4C-Alkoxycarbonyl represents a carbonyl group to which one of the abovementioned 1-4C-alkoxy radicals is bonded. Examples which may be mentioned are the methoxycarbonyl [CH_3O-C(O)-] and the ethoxycarbonyl [CH_3CH_2O-C(O)-] radicals.

As a 1-4C-Alkylcarbonylamino radical, for example, the propionylamino [$C_2H_5C(O)NH$-] and the acetylamino [$CH_3C(O)NH$-] radicals may be mentioned.

Ar represents an unsubstituted or R6- and/or R7-substituted bi- or tricyclic radical of the formula Ia or Ib.

In the aryl radicals Ar of the formula Ia, G represents a 5- or 6-membered ring which optionally can contain up to three identical or different heteroatoms selected from the group consisting of O and N. The ring G can be monounsaturated (double bonding of the fused phenyl ring), polyunsaturated or aromatic. Exemplary aryl radicals Ar of the formula Ia which may be mentioned are indenyl, indanyl, naphthalenyl, indazolyl, quinolinyl, isoquinolinyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, indolyl, 1H-benzimidazolyl, 1H-benzotriazolyl, benzoxazolyl, benzofuranyl, chromanyl, 2,3-dihydroindolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo[1,4]dioxinyl and benzo[1,3]dioxolyl. The aryl radicals Ar of the formula Ia can be present in unsubstituted form or can be substituted by R6 and/or R7.

In the aryl radicals Ar of the formula Ib, A represents a bond, $-CH_2-$, $-CH_2CH_2-$, $-CH_2O-$, $-OCH_2-$, $-O(CO)-$, $-O-$, $-N(H)-$, $-N=$, $-CH=$, $-CH=CH-$, $-N=CH-$ or $-CH=N-$ and B represents a bond, $-CH_2-$, $-C(O)-$, $-O-$, $-CH=$, $-N(H)-$, $-N=$ or $-S(O)_2-$. The ring containing the atoms or groups of atoms A and B is in this case 4-, 5-, 6- or 7-membered. Exemplary aryl radicals Ar of the formula Ib which may be mentioned are diphenylenyl, fluorenyl, phenanthrenyl, anthracenyl, phenanthridinyl, acridinyl, phenazinyl, xanthenyl, 9-oxo-9H-xanthenyl, 9-oxo-9H-thioxanthenyl-10,10-dioxide, fluoren-9-onyl, anthraquinonyl, 5-oxo-5H-dibenz[b,e]cycloheptenyl, 10,11-dihydro-5H-dibenzo[a,d]cycloheptenyl, 11-oxo-6,11-dihydrodibenz[b,e]oxepinyl, 10,11-dihydro-5H-dibenz[b,f]azepinyl, dibenzofuranyl and carbazolyl. The aryl radicals Ar of the formula Ib can be present in unsubstituted form or can be substituted by R6 and/or R7.

The aryl radicals Ar of the formulae Ia and Ib are condensed ring systems which contain at least one benzene ring. If the aryl radicals Ar of the formulae Ia and Ib only contain one benzene ring, the bonding to the phenanthridine radical takes place via this benzene ring. If the aryl radicals of the formulae Ia and Ib contain a number of benzene rings, the bonding to the phenanthridine radical takes place via one of these benzene rings. Relative to the bonding of the phenanthridine radical, the ring systems fused to the benzene ring can be bonded in the ortho/meta- and in the meta/para-positions.

One embodiment of the compounds of the formula I according to the invention are those in which the bi- or tricyclic radical Ar is selected from the group consisting of naphthalenyl, quinolinyl, 1H-benzimidazolyl, 1H-benzotriazolyl, benzofuranyl, 9-oxo-9H-thioxanthenyl-10,10-dioxide, fluoren-9-onyl or anthraquinonyl.

Exemplary unsubstituted aryl radicals of the formulae Ia and Ib which may be mentioned are the radicals naphth-1-yl, naphth-2-yl, anthracen-2-yl, phenazin-2-yl, fluoren-1-yl, fluoren-2-yl, fluoren-3-yl, fluoren-4-yl, fluoren-9-on-2-yl, fluoren-9-on-3-yl, fluoren-9-on-4-yl, 9-oxo-9H-xanthen-2-yl, 9-oxo-9H-thioxanthen-2-yl-10,10-dioxide, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl, quinolin-8-yl, indan-5-yl, indol-4-yl, indol-5-yl, indol-6-yl, 2,3-dihydroindol-5-yl, 2,3-dihydroindol-6-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzofuran-6-yl, benzofuran-5-yl, benzofuran-6-yl, chroman-5-yl, chroman-7-yl, 1H-benzimidazol-5-yl, 1H-benzotriazol-5-yl, anthraquinon-2-yl, dibenzofuran-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, benzo[1,3]dioxol-5-yl, 5-oxo-5H-dibenzo[a,d]cycloheptan-2-yl, 10,11-dihydro-5H-dibenzo[a,d]cycloheptan-2-yl, 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl and 10,11-dihydro-5H-dibenz[b,f]azepin-2-yl.

Exemplary R6- and/or R7-substituted aryl radicals Ar of the formulae Ia and Ib which may be mentioned are the radicals 7-difluoromethoxy-2-isopropyl-benzofuran-4-yl, 1-bromonaphth-2-yl, 4-fluoronaphth-1-yl, 1-hydroxy-4-bromonaphth-2-yl, 6-nitrooxynaphth-2-yl, 7-carboxynaphth-2-yl, 6-carboxynaphth-1-yl, 4-carboxynaphth-1-yl, 6-methoxycarbonylnaphth-2-yl, 4-nitronaphth-1-yl, 3,7-dihydroxynaphth-2-yl, 6-acetoxynaphth-2-yl, 1,1-dimethylindan-4-yl, 7-nitroindan-1-yl, 2,7-difluoro-9-oxofluoren-4-yl, 7-nitro-9-oxofluoren-2-yl, 7-nitro-9-oxofluoren-4-yl, 7-carboxyl-9-oxofluoren-2-yl, 1,8-dihydroxyanthraquinon-9-yl, 2-methylbenzimidazol-5-yl, 7-hydroxy-9-oxo-9H-xanthen-2-yl, 6-chloro-9-oxoxanthen-2-yl, 6-chloro-9-oxo-9H-xanthen-2-yl, 5-nitroanthraquinon-2-yl, 6-nitroanthraquinon-2-yl, 7-nitroanthraquinon-2-yl and 8-nitroanthraquinon-2-yl.

Possible salts for compounds of the formula I - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable salts of the inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, it being possible to employ the acids in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are also suitable. Examples of salts with bases which may be mentioned are alkali metal (lithium, sodium, potassium) or calcium, aluminium, magnesium, titanium, am-

trantium, meglumine or guanidinium salts, where his or too the bases are employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically tolerable salts which can initially be obtained, for example, as process products in the preparation of the compounds according to the invention on an industrial scale are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

It is known to the person skilled in the art that the compounds according to the invention and their salts, when they are isolated, for example, in crystalline form, can contain various amounts of solvents. The invention therefore also comprises all solvates and in particular all hydrates of the compounds of the formula I, and also all solvates and in particular all hydrates of the salts of the compounds of the formula I.

Compounds of the formula I to be emphasized are those in which

R1 is 1-2C-alkoxy, 3-6C-cycloalkoxy, 3-5C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R2 is 1-2C-alkoxy, 3-6C-cycloalkoxy, 3-5C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is hydrogen or 1-2C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or in which

R5 and R51 together represent an additional bond,

Ar is an unsubstituted or R6- and/or R7-substituted bi- or tricyclic radical selected from the group consisting of indanyl, naphthalenyl, fluorenyl, 9-oxo-9H-thioxanthenyl-10,10-dioxide, phenanthrenyl, anthracenyl, benzofuranyl, indazolyl, quinolyl, isoquinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, indolyl, 1H-benzimidazolyl, 1H-benzotriazolyl, benzoxazolyl, fluoren-9-onyl, anthraquinonyl, dibenzofuranyl, chromanyl, 2,3-dihydroindolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo[1,4]dioxinyl and dibenzo[1,3]dioxolyl,

where

R6 is hydroxyl, halogen, carboxyl, nitro, amino, aminocarbonyl, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkylcarbonyloxy, 1-4C-alkoxycarbonyl or completely or predominantly fluorine-substituted 1-2C-alkoxy, and

R7 is hydroxyl, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

One embodiment of the compounds of the formula I to be emphasized are those in which

R1 is 1-2C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R2 is 1-2C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is hydrogen or 1-2C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or in which

R5 and R51 together represent an additional bond,

Ar is an unsubstituted or R6- and/or R7-substituted bi- or tricyclic radical selected from the group consisting of indanyl, naphthalenyl, fluorenyl, 9-oxo-9H-thioxanthenyl-10,10-dioxide, phenanthrenyl, anthracenyl, benzofuranyl, indazolyl, quinolyl, isoquinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, indolyl, 1H-benzimidazolyl, 1H-benzotriazolyl, benzoxazolyl, fluoren-9-onyl, anthraquinonyl, dibenzofuranyl, chromanyl, 2,3-dihydroindolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo[1,4]dioxinyl and benzo[1,3]dioxolyl,

where

R6 is hydroxyl, halogen, carboxyl, nitro, amino, aminocarbonyl, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkylcarbonyloxy or 1-4C-alkoxycarbonyl, and

R7 is hydroxyl, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of the formula I particularly to be emphasized are those in which

R1 is 1-2C-alkoxy,

R2 is 1-2C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is hydrogen or 1-2C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or in which

R5 and R51 together represent an additional bond,

Ar is an unsubstituted or R6- and/or R7-substituted bi- or tricyclic radical selected from the group consisting of indanyl, naphthalenyl, 9-oxo-9H-thioxanthenyl-10,10-dioxide, fluorenyl, anthracenyl, benzofuranyl, quinolyl, isoquinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, indolyl, 1H-benzimidazolyl, 1H-benzotriazolyl, benzoxazolyl, fluoren-9-onyl, anthraquinonyl, dibenzofuranyl, 2,3-dihydrobenzo[1,4]dioxinyl and benzo[1,3]dioxolyl, where

R6 is hydroxy, halogen, carboxyl, nitro, amino, aminocarbonyl, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkylcarbonyloxy, 1-4C-alkoxycarbonyl or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R7 is 1-4C-alkyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

One embodiment of the compounds of the formula I particularly to be emphasized are those in which

R1 is 1-4C-alkoxy,

R2 is 1-4C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is hydrogen or 1-4C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or in which

R5 and R51 together represent an additional bond,

Ar is an unsubstituted or R6-substituted bi- or tricyclic radical selected from the group consisting of indazolyl, naphthalenyl, 9-oxo-9H-thioxanthenyl-10,10-dioxide, fluorenyl, anthracenyl, benzofuranyl, quinolyl, isoquinolyl, phthalazinyl, cinnolinyl, quinazolinyl, dihydroxy, indolyl, indazolyl, 1H-benzimidazolyl, 1H-benzotriazolyl, benzoxazolyl, fluoren-9-onyl, anthraquinonyl, dibenzofuranyl, 2,3-dihydrobenzo[1,4]dioxinyl and benzo[1,3]dioxolyl, where

R6 is hydroxy, halogen, carboxyl, nitro, amino, aminocarbonyl, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkylcarbonyloxy or 1-4C-alkoxycarbonyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Preferred compounds of the formula I are those in which

R1 is methoxy,

R2 is methoxy,

R3, R31, R4, R5 and R51 are hydrogen,

Ar is a radical selected from the group consisting of 7-difluoromethoxy-2-isopropyl-benzofuran-4-yl, naphthalen-2-yl, quinolin-6-yl, 1H-benzimidazol-6-yl, 2-methyl-benzimidazol-6-yl, 1H-benzotriazol-5-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, benzo[1,3]dioxol-5-yl, 10,10-dioxo-thioxanthen-9-on-3-yl, fluoren-9-on-2-yl and anthraquinon-2-yl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

One embodiment of the preferred compounds of the formula I are those in which

R1 is methoxy,

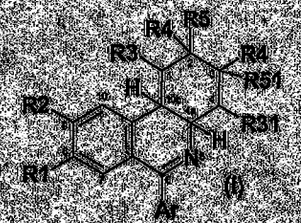
R2 is methoxy,

R3, R31, R4, R5 and R51 are hydrogen,

Ar is a radical selected from the group consisting of naphthalen-2-yl, quinolin-6-yl, 1H-benzimidazol-5-yl, 2-methyl-benzimidazol-5-yl, 1H-benzotriazol-5-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, benzo[1,3]dioxol-5-yl, 10,10-dioxo-thioxanthen-9-on-3-yl, fluoren-9-on-2-yl and anthraquinon-2-yl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

The compounds of the formula I are chiral compounds having chiral centers in positions 4a and 10b and, depending on the meaning of the substituents R3, R31, R4, R5 and R51, further chiral centers in the positions 1, 2, 3 and 4.

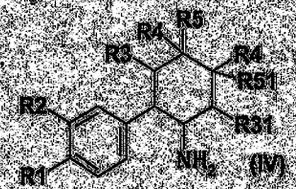


Numbering:

The invention therefore comprises all conceivable pure diastereomers and pure enantiomers and their mixtures in any mixing ratio, including the racemates. The compounds of the formula I are preferred in which the hydrogen atoms in positions 4a and 10b are cis to one another. The pure cis enantiomers are particularly preferred.

In this connection, particularly preferred compounds of the formula I are those in which positions 4a and 10b have the same absolute configuration as the compound (-)-cis-1,2-dimethoxy-4-(3-amino-cyclohexyl)benzene which is a starting compound and having the optical rotation $[\alpha]_D^{20} = -58.6°$ (c = 1, ethanol).

The enantiomers can be separated in a manner known per se (for example by preparation and separation of appropriate diastereomeric compounds). Preferably, an enantiomer separation is carried out at the stage of the starting compounds of the formula IV.

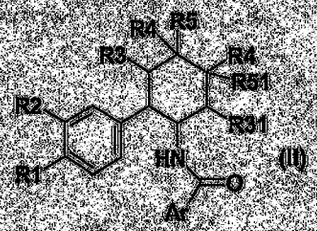


(IV)

for example by means of salt formation of the racemic compounds of the formula IV with optically active carboxylic acids. Examples which may be mentioned in this connection are the enantiomeric forms of mandelic acid, tartaric acid, O,O'-dibenzoyltartaric acid, camphoric acid, quinic acid, glutamic acid, malic acid, camphorsulfonic acid, 3-bromocamphorsulfonic acid, α-methoxyphenylacetic acid, α-methoxy-α-trifluoromethylphenylacetic acid and 2-phenylpropionic acid. Alternatively, enantiomerically pure starting compounds of the formula IV can also be prepared via asymmetric syntheses.

The preparation of the compounds of the formula I in which R1, R2, R3, R31, R4, R5, R51 and Ar have the meanings indicated above and their salts can be carried out, for example, by the process described below in greater detail.

The process comprises cyclocondensing compounds of the formula II



(II)

in which R1, R2, R3, R31, R4, R5, R51 and Ar have the meanings indicated above, and, optionally, then converting the compounds of the formula I obtained into their salts, or, optionally, then converting salts of the compounds of the formula I obtained into the free compounds.

Compounds of the formula I obtained can be converted, optionally, into further compounds of the formula I by derivatization.

For example, from compounds of the formula I in which

a) R5 represents an ester group, it is possible by means of acidic and alkaline hydrolysis to obtain the corresponding acids, or it is possible by reaction with suitably substituted amines to prepare the corresponding amides;

b) R5 represents a 1-4C-alkylcarbonyloxy group, it is possible by means of acidic or alkaline hydrolysis to obtain the corresponding hydroxyl compounds;

c) R5 and/or R7 represent a nitro group, it is possible by means of selective catalytic hydrogenation to obtain the corresponding amino compounds, which for their part can be further derivatized again.

The methods mentioned under a), b) and c) are expediently carried out analogously to the methods known to the person skilled in the art.

In addition, the compounds of the formula I can be converted, optionally, into their N-oxides, for example with the aid of hydrogen peroxide in methanol or with the aid of m-chloroperoxybenzoic acid in dichloromethane. The person skilled in the art is familiar on the basis of his/her expert knowledge with the reaction conditions which are specifically necessary for carrying out the N-oxidation.

The cyclocondensation is carried out in a manner known per se to the person skilled in the art, according to Bischler-Napieralski (e.g. as described in J. Chem. Soc., 1955, 4250-4262) in the presence of a suitable condensing agent, such as, for example, polyphosphoric acid, phosphorus pentachloride, phosphorus pentoxide or preferably phosphorus oxychloride, in a suitable inert solvent, e.g. in a chlorinated hydrocarbon such as chloroform, or in a cyclic hydrocarbon such as toluene or xylene, or another inert solvent such as acetonitrile, or without further solvent using an excess of condensing agent, preferably at elevated temperature, in particular at the boiling temperature of the solvent or condensing agent used.

Compounds of the formula II in which R1, R2, R3, R31, R4, R5, R51 and Ar have the meanings indicated above are accessible from the corresponding compounds of the formula IV, in which R1, R2, R3, R31, R4, R5 and R51 have the meanings indicated above, by reaction with compounds of the formula III,

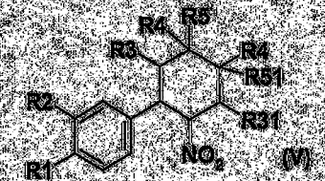


(III)

in which Ar has the meanings indicated above and X represents a suitable leaving group, preferably a chlorine atom. For example, this acylation or benzoylation is carried out as described in the following examples or as in J. Chem. Soc (C), 1971, 1899-1903.

Compounds of the formula III and compounds of the formula IV are either known or can be prepared in a known manner.

The compounds of the formula IV can be prepared, for example, from compounds of the formula V,



(V)

in which R1, R2, R3, R31, R4, R5 and R51 have the abovementioned meanings, by reduction of the nitro group.

The reduction is carried out in a manner known to the person skilled in the art, for example as described in J. Org. Chem. 1962, 27, 4026 or as described in the following examples.

The reduction can be carried out, for example, by catalytic hydrogenation, e.g. in the presence of Raney nickel, in a lower alcohol such as methanol or ethanol at room temperature and under normal or elevated pressure. Optionally, a catalytic amount of an acid, such as, for example, hydrochloric acid, can be added to the solvent. Preferably, however, the reduction is carried out using metals such as zinc or iron with organic acids such as acetic acid or mineral acids such as hydrochloric acid.

The compounds of the formula IV in which R1, R2, R3, R31 and R4 have the meanings indicated above and R5 and R51 together represent an additional bond can be prepared from the corresponding compounds of the formula V by selective reduction of the nitro group in a manner known to the person skilled in the art, for example in the presence of Raney nickel in a lower alcohol as solvent using hydrazine hydrate as a hydrogen donor.

The compounds of the formula V, in which R1, R2, R3, R31 and R4 have the meanings indicated above and R5 and R51 are hydrogen, are either known or can be prepared from corresponding compounds of the formula V in which R5 and R51 together are an additional bond. The reaction can be carried out in a manner known to the person skilled in the art, preferably by hydrogenation in the presence of a cata-

lyst, such as, for example, palladium on active carbon, e.g. as described in J. Chem. Soc. (C), 1971, 1899-1903.

The compounds of the formula V, in which R5 and R51 together are an additional bond, are either known or can be obtained by the reaction of compounds of the formula (VI)



(VI)

in which R1 and R2 have the meanings mentioned above, with compounds of the formula VII

R3-CH=C(R4)-C(R4)=CH-R31 (VII)

in which R3, R31 and R4 have the meanings mentioned above.

Compounds of the formula V, in which R5 and R51 together represent an additional bond and R3 and R31 together are a 1-4C-alkylene group, can, for example, be obtained by reaction of cyclic compounds of the formula VII, in which R4 has the abovementioned meanings and R3 and R31 together are a 1-4C-alkylene group (for example cyclohexa-1,3-dien, 2,3-dimethylcyclohexa-1,3-dien, cycloepta-1,3-dien, 2,3-dimethylcycloheptа-1,3-dien or cycloocta-1,3-dien) with compounds of the formula VI, in which R1 and R2 have the above-mentioned meanings.

The cycloaddition is in this case carried out in a manner known to the person skilled in the art according to Diels-Alder, e.g. as described in J. Amer. Chem. Soc. 1987, 79, 6558 or in J. Org. Chem. 1992, 57, 951 or as described in the following examples.

Compounds of the formula V obtained in the cycloaddition, in which the phenyl ring and the nitro group are trans to one another, can be converted in a manner known to the person skilled in the art into the corresponding cis compounds, e.g. as described in J. Amer. Chem. Soc. 1957, 79, 6558 or as described in the following examples.

The compounds of the formulae VI and VII are either known or can be prepared in a known manner. The compounds of the formula VII can be prepared, for example, in a manner known to the person skilled in the art from corresponding compounds of the formula VIII as described in J. Chem. Soc. 1951, 2524 or in J. Org. Chem. 1944, 9, 170 or as described in the following examples.

The compounds of the formula VIII



(VIII)

in which R1 and R2 have the meanings indicated above, are either known or can be prepared in a manner known to the person skilled in the art, as described, for example, in Ber. Disch. Chem. Ges. 1925, 58, 233.

It is moreover known to the person skilled in the art that if there are a number of reactive centers on a starting or intermediate compound it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description of the use of a large number of known protective groups is found, for example, in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

The isolation and purification of the substances according to the invention is carried out in a manner known per se, by distilling off the solvent in vacuo and recrystallizing the resulting residue from a suitable solvent or subjecting it to one of the customary purification methods, such as, for example, column chromatography on suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (e.g. a ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, an ether, such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight alcohol, such as ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by alkalization or by acidification into the free compounds, which in turn can be converted into salts. In this way, pharmacologically intolerable salts can be converted into pharmacologically tolerable salts.

The following examples serve to illustrate the invention further without restricting it. Likewise, further compounds of the formula I, whose preparation is not explicitly described, can be prepared in an analogous manner or in a manner familiar per se to the person skilled in the art using customary process techniques.

In the examples, mp stands for melting point, h for hours, RT for room temperature, Bf for empirical formula, MW for molecular weight, calc. for calculated, fnd. for found. The compounds mentioned in the examples and/or their salts are a preferred subject of the invention.

Examples

Final products

1. (cis)-9-Benzo[1,3]dioxol-5-yl-3,4-dimethoxy-1,2,3,4,4a,10b-hexahydrophenanthridine

5.0 g of (cis)-N-[2-(3,4-dimethoxyphenyl)cyclohexyl]-3,4-methylenedioxybenzamide (compound A6) are dissolved in 150 ml of acetonitrile and 20 ml of phosphoryl chloride are the solution is stirred at 80°C for 2 h. The reaction mixture is concentrated under reduced pressure and the residue is treated with sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic phase is dried using sodium sulfate and concentrated. After chromatography on silica gel using petroleum ether/dioxane/triethylamine in the ratio 7.8/1.8/1, 2.35 g of the title compound are obtained.

EP: $C_{21}H_{21}NO_4$; MW: 355.43

Elemental analysis: calc.: C 72.61 H 6.24 N 3.93
found: C 71.82 H 6.29 N 3.69

Optical Rotation: $[\alpha]_D^{20}$ = -49.3° (c=0.2, ethanol)

Starting from the starting compounds described below, the following are obtained by the procedure according to Example 1:

2. (+)-cis-3,4-Dimethoxy-6-quinolin-6-yl-1,2,3,4,4a,10b-hexahydrophenanthridine

EP: $C_{23}H_{24}N_2O_2$; MW: 372.47

Elemental analysis x 0.5 H_2O: calc.: C 76.87 H 6.81 N 7.36
found: C 76.69 H 6.69 N 7.17

Optical Rotation: $[\alpha]_D^{20}$ = +62.6° (c=0.2, ethanol)

3. (+)-cis-3,4-Dimethoxy-6-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

EP: $C_{24}H_{25}NO_4$; MW: 375.43

Elemental analysis x 0.5 H_2O: calc.: C 71.11 H 6.76 N 3.61
found: C 71.28 H 6.81 N 3.49

Optical Rotation: $[\alpha]_D^{20}$ = +78.3° (c=0.2, ethanol)

4. (+)-cis-6-(1H-Benzotriazol-5-yl)-3,4-dimethoxy-1,2,3,4,4a,10b-hexahydrophenanthridine

EP: $C_{23}H_{24}N_4O_2$; MW: 388.44; 47; mp. 213-214°C

Elemental analysis x 0.4 H_2O: calc.: C 69.24 H 6.26 N 18.18
found: C 69.50 H 6.16 N 18.01

Optical Rotation: $[\alpha]_D^{20}$ = +108.4° (c=0.2, ethanol)

5. (+)-cis-3,4-Dimethoxy-6-naphthalen-2-yl-1,2,3,4,4a,10b-hexahydrophenanthridine

EP: $C_{26}H_{25}NO_2$; MW: 371.48

Elemental analysis x 0.15 H_2O: calc.: C 80.16 H 6.82 N 3.74
found: C 80.21 H 6.98 N 3.68

Optical Rotation: $[\alpha]_D^{20}$ = +130.3° (c=0.2, ethanol)

6. (+)-cis-3,4-Dimethoxy-6-(10,10-dioxothioxanthen-3-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

EP: $C_{28}H_{25}NO_4S$; MW: 487.62

Elemental analysis: calc.: C 68.98 H 5.17 N 2.87
found: C 68.17 H 5.20 N 2.94

Optical Rotation: $[\alpha]_D^{20}$ = +288° (c=0.2, DMF)

7. (+)-cis-3,4-Dimethoxy-6-(quinolin-3-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine hydrochloride

EP: $C_{23}H_{24}N_2O_2 \times HCl$; MW: 408.98

^{1}H-NMR (400 MHz, DMSO-d_6): 1.26-1.59 ppm (m, 2H), 2.21-2.4 ppm (m, 1H), 3.1-3.21 ppm (m, 1H), 3.56 ppm (s, 3H), 3.66 ppm (s, 3H), 4.01-4.3 ppm (m, 5H), 6.88 ppm (s, 1H), 7.3 ppm (s, 1H), 7.46-7.88 ppm (m, 1H), 7.65-7.81 ppm (m, 2H), 7.96-8.13 ppm (m, 4H)

Optical Rotation: $[\alpha]_D^{20}$ = +120° (c=0.2, ethanol)

8. (+)-cis-3,4-Dimethoxy-6-(naphthalen-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

EP: $C_{26}H_{25}NO_2$; MW: 491.59; mp. 213-214°C

Elemental analysis: calc. C 67.44 H 6.59 N 3.10
found C 67.39 H 6.63 N 3.09

Optical Rotation: $[\alpha]_D^{20}$ = -319.7° (c=0.2, DMF)

9. (-)-cis-5-[(3,4-Benzimidazol-5-yl)-6,8-dimethoxy-1,2,3,4-tetrahydronaphtalen]anhydrine

EF: $C_{22}H_{24}N_2O_4$, MW: 381.45
Rf: 0.20 (silica gel, neutral, PE:EA:TEA:MeOH = 5:5:1:1)

Optical Rotation: $[\alpha]_D^{20}$ = -60° (c=0.2, ethanol)

10. (3-cis-6,8-Dimethoxy-5-(2-methyl-3H-benzimidazol-5-yl)-1,2,3,4-tetrahydronaphtalen]anhydrine

EF: $C_{23}H_{26}N_2O_4$, MW: 394.47
Rf: 0.62 (silica gel, neutral, PE:EA:TEA:MeOH = 2:8:0:0)

Optical Rotation: $[\alpha]_D^{20}$ = -64° (c=0.2, ethanol)

11. (3-cis-5-[(2-Diisopropylaminoethoxy-2-isopropylbenzofuran-5-yl]-6,8-dimethoxy-1,2,3,4-tetrahydronaphtalen]anhydrine

EF: $C_{37}H_{48}N_2O_5$, MW: 600.80
Rf: 0.68 (silica gel, neutral, PE : EE : TEA = 4 : 6 : 1)

Optical Rotation: $[\alpha]_D^{20}$ = -97.7° (c=0.2, ethanol)

Starting compounds

A1. (3-cis)-5-[2-(3,4-Dimethoxyphenylacetoxy)-6,8-methylenedioxynaphtalene

4.0 g of (±)-cis-1,2-dimethoxy-4,(2-amino)ethoxyphenylnaphtalene (compound B2) are dissolved in 100 ml of methylene chloride and 5.0 ml of triethylamine. A solution of 3.8 g of 3,4-methylenedioxybenzoyl chloride in 50ml of methylene chloride is added dropwise at RT and the mixture is extracted with 100 ml each of water, 2N hydrochloric acid, solid sodium hydrogencarbonate solution and water again after stirring overnight. The organic phase is dried using sodium sulfate and concentrated. 6.2 g of the title compound are obtained.

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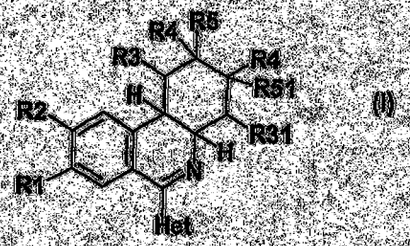
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(54) Title: NOVEL 6-HETEROARYLPHENANTHRIDINES



(I)

(57) Abstract: Compounds of the formula I, in which Het is an unsubstituted or R5- and/or R7-substituted pyridyl, thienyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolinyl, pyrazinyl or pyridazinyl radical, or an unsubstituted or R5- and/or R7-substituted fused bi- or tricyclic ring system comprising at least one aromatic ring and up to 4 heteroatoms selected from the group consisting of Oxygen, Sulphur or Nitrogen, which is bonded to the phenanthridinyl radical via one of the rings comprising one or more heteroatoms, inventive PDE4 inhibitors.

WO 02/06270 A1

Novel 6-heteroarylphenanthridines

Field of application of the invention

The invention relates to novel 6-heteroarylphenanthridines, which are used in the pharmaceutical industry for the production of medicaments.

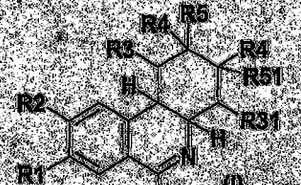
Known technical background

Chem.Ber. 1939, 72, 675-677, J. Chem. Soc., 1958, 4230-4233 and J. Chem. Soc.(C), 1971, 1635 describe the synthesis of 6-phenylphenanthridines. The International Applications WO 97/23151, WO 97/36884, WO 99/06113 and WO 99/06113 describe 6-phenyl- and 6-pyridylphenanthridines as PDE4 inhibitors.

Description of the invention

It has now been found that the novel phenanthridines substituted in position 6 by a 5- or 6-cyclic heteroaryl radical and described in greater detail below have surprising and particularly advantageous properties.

The invention thus relates to compounds of the formula I,



(I)

in which

R1 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R2 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

or in which

R1 and R2 together are a 1-2C-alkylenedioxy group,

R3 is hydrogen or 1-4C-alkyl,
R3' is hydrogen or 1-4C-alkyl,
or in which
R3 and R3' together are a 1-4C-alkylene group,
R6 is hydrogen or 1-4C-alkyl,
R8 is hydrogen,
R8' is hydrogen,
or in which
R5 and R5' together represent an additional bond,
Het is an unsubstituted or R6- and/or R7-substituted pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrazinyl or pyridazinyl radical, or an unsubstituted or R6- and/or R7-substituted fused bi- or tricyclic ring system comprising at least one aromatic ring and up to 4 heteroatoms - selected from the group consisting of O (oxygen), S (sulphur) or N (nitrogen) - which is bonded to the phenanthridinyl radical via one of the rings comprising one or more heteroatoms, where
R6 is hydroxyl, halogen, nitro, cyano, sulfino, sulfinocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminosulfonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonylamino, phenyl or completely or predominantly fluorine-substituted 1-4C-alkoxy, and
R7 is hydroxyl, halogen, nitro, 1-4C-alkyl or 1-4C-alkoxy,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

1-4C-Alkyl represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and preferably the ethyl and methyl radicals.

1-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy radicals.

3-7C-Cycloalkoxy represents cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy, of which cyclopropyloxy, cyclobutyloxy and cyclopentyloxy are preferred.

3-7C-Cycloalkylmethoxy represents cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy and cycloheptylmethoxy, of which cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy are preferred.

As completely or predominantly fluorine-substituted 1-4C-alkoxy, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,1,2,2-tetrafluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and preferably the difluoromethoxy radicals may be mentioned. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy radical are replaced by fluorine atoms.

1-2C-Alkylenedioxy represents, for example, the methylenedioxy [-O-CH$_2$-O-] and the ethylenedioxy [-O-CH$_2$-CH$_2$-O-] radicals.

If R3 and R3' together have the meaning 1-4C-alkylene, the positions 1 and 4 in compounds of the formula I are linked to one another by a 1-4C-alkylene bridge. 1-4C-Alkylene representing straight-chain or branched alkylene radicals having 1 to 4 carbon atoms. Examples which may be mentioned are the radicals methylene [-CH$_2$-], ethylene [-CH$_2$-CH$_2$-], trimethylene [-CH$_2$-CH$_2$-CH$_2$-], 1,2-dimethylethylene [-CH(CH$_3$)-CH(CH$_3$)-] and isopropylidene [-C(CH$_3$)$_2$-].

If R5 and R5' together are an additional bond, then the carbon atoms in positions 2 and 3 in compounds of the formula I are linked to one another via a double bond.

Halogen within the meaning of the invention is bromine, chlorine or fluorine.

In addition to the nitrogen atom, mono- or di-1-4C-alkylamino radicals contain one or two of the above-mentioned 1-4C-alkyl radicals. Di-1-4C-alkylamino is preferred and here, in particular, dimethyl-, diethyl- or diisopropylamino.

In addition to the carbonyl group, mono- or di-1-4C-alkylaminocarbonyl radicals contain one of the above-mentioned mono- or di-1-4C-alkylamino radicals. Examples which may be mentioned are the N-methyl-, the N,N-dimethyl-, the N-ethyl-, the N-propyl-, the N,N-diethyl- and N-isopropylaminocarbonyl radicals.

1-4C-Alkylcarbonyloxy represents a carbonyloxy group to which one of the above-mentioned 1-4C-alkyl radicals is bonded. An example which may be mentioned is the acetoxy radical [CH$_3$C(O)-O-].

1-4-Alkylcarbonyl represents a radical which, in addition to the carbonyl group, contains one of the 1-4C-alkyl radicals mentioned above. An example which may be mentioned is the acetyl radical.

1-4C-Alkoxycarbonyl represents a carbonyl group to which one of the above-mentioned 1-4C-alkoxy radicals is bonded. Examples which may be mentioned are the methoxycarbonyl [CH$_3$O-C(O)-] and the ethoxycarbonyl [CH$_3$CH$_2$O-C(O)-] radicals.

As a 1-4C-alkylcarbonylamino radical, for example, the propionylamino radical [$C_2H_5C(O)NH$-] and the acetylamino radical [$CH_3C(O)NH$-] may be mentioned.

Het represents an unsubstituted or R8- and/or R7- substituted pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl or pyridazinyl radical, or an unsubstituted or R8- and/or R7-substituted fused bi- or tricyclic ring system comprising at least one aromatic ring and up to 4 heteroatoms - selected from the group consisting of O (oxygen), S (sulphur) or N (nitrogen) - which is bonded to the phenanthridinyl radical via one of the rings comprising one or more heteroatoms.

Exemplary unsubstituted heterocyclyl radicals Het which may be mentioned are benzofuran-2-yl, benzofuran-3-yl, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzofuran-3-yl, benzothiophen-2-yl, benzothiophen-3-yl, 2,3-dihydrobenzothiophen-2-yl, 2,3-dihydrobenzothiophen-3-yl, chroman-2-yl, chroman-3-yl, chroman-4-yl, isochroman-1-yl, 1,4-benzodioxan-2-yl, 1,3-benzodioxol-2-yl, quinolin-2-yl, quinolin-4-yl, quinolin-3-yl, isoquinolin-3-yl, isoquinolin-1-yl, isoquinolin-4-yl, 1,2,3,4-tetrahydroacridin-9-yl, acridin-9-yl, indolizin-2-yl, indolizin-3-yl, indolizin-5-yl, indolizin-6-yl, indolizin-7-yl, indolizin-8-yl, phenanthridin-6-yl, cinnolin-3-yl, cinnolin-4-yl, quinazolin-4-yl, quinoxalin-2-yl, phthalazin-1-yl, 1,7-naphthyridin-3-yl, 1,8-naphthyridin-3-yl, 1,8-naphthyridin-4-yl, 1,5-naphthyridin-3-yl, 1,5-naphthyridin-2-yl, 1,5-naphthyridin-3-yl, 1,5-naphthyridin-4-yl, 1,6-naphthyridin-5-yl, 1,6-naphthyridin-7-yl, 1,6-naphthyridin-8-yl, indol-3-yl, indol-2-yl, indazol-3-yl, benzimidazol-2-yl, 2,3-dihydro-1H-indol-2-yl, 2,3-dihydro-1H-indol-3-yl, 2,3-dihydro-1H-isoindol-1-yl, 2,3-dihydro-1H-isoindol-3-yl, 1,2,3,4-tetrahydroquinolin-2-yl, 1,2,3,4-tetrahydroquinolin-3-yl, 1,2,3,4-tetrahydroquinolin-4-yl, 1,2,3,4-tetrahydroisoquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-4-yl, β-carbolin-1-yl, β-carbolin-2-yl, β-carbolin-3-yl, β-carbolin-4-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, 1H-pyrrol-2-yl, 1H-pyrrol-3-yl, pyrazol-3-yl, pyrazol-4-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, [1,2,3]thiadiazol-4-yl, [1,2,3]thiadiazol-5-yl, pyridin-4-yl, pyrimidin-6-yl, pyrimidin-2-yl, pyridazin-4-yl, pyridazin-3-yl and pyrazin-2-yl.

Exemplary R8- and/or R7-substituted heterocyclyl radicals Het which may be mentioned are 1-methyl-1H-pyrrol-2-yl, 5-methyl-3-phenylisoxazol-4-yl, 5-methylthiophen-2-yl, 6-fluoro-1H-indol-2-yl, 5-methoxy-1H-indol-2-yl, 3-methylfuran-2-yl, 3,5-dimethylisoxazol-4-yl, 4-phenyl-[1,2,3]thiadiazol-5-yl, 4-methyl-[1,2,3]thiadiazol-5-yl, 1,3-dimethyl-1H-pyrazol-5-yl, 3-methylbenzofuran-2-yl, 5-methoxybenzofuran-2-yl, 7-methoxybenzofuran-2-yl, 7-ethoxybenzofuran-2-yl, 5-chlorobenzofuran-2-yl, 5-nitrobenzofuran-2-yl, 4-chloro-6-nitroquinolin-2-yl, 2-chloroquinolin-4-yl, 6-methoxyquinolin-4-yl, 2-hydroxyquinolin-4-yl, 6-nitroquinolin-4-yl, 2-cyclopropylquinolin-4-yl, 2-cyclohexyl-6-methylquinolin-4-yl, 1-chloroisoquinolin-4-yl, 4-hydroxyquinolin-2-yl, 2,6-dihydroxyquinolin-2-yl, 5-nitroquinolin-2-yl,

4-methoxyquinolin-2-yl, 4-hydroxy-7-chloroquinolin-2-yl, 6-hydroxyquinolin-2-yl, 6,7-dimethoxyisoquinolin-3-yl, 6-hydroxypyrido[1,2-a]indol-10-yl, 1-methylindol-2-yl, 1-methyl-1H-benzo[d]imidazol-2-yl, 1-methylindol-2-yl, 1-methyl-1H-indazol-3-yl, 1-acetyl-1H-indazol-3-yl, 5-methyl-indol-2-yl, 7-nitroindol-2-yl, 7-methylindol-2-yl, 4,6-dimethoxyindol-2-yl, 5,6-dimethoxyindol-2-yl, 5-methoxyindol-2-yl, 6-hydroxyindol-2-yl, 5-methoxypyrimidin-2-yl, 6-hydroxypyrimidin-4-yl, 2-chloro-6-methylpyrimidin-4-yl, 2,6-bis(dimethylamino)pyrimidin-4-yl, 2,6-dimethoxypyrimidin-4-yl, 6-methylpyrazin-2-yl, 2-methylpyrazin-5-yl, 6-hydroxypyrazin-2-yl, 2-methylaminopyrazin-6-yl, 2-methoxypyrazin-3-yl and 5-chloropyrazin-2-yl.

Possible salts for compounds of the formula I - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable salts of the inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, trifluoroacetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, it being possible to employ the acids in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are also suitable. Examples of salts with bases which may be mentioned are alkali metal (lithium, sodium, potassium) or calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, where here too the bases are employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts which can initially be obtained, for example, as process products in the preparation of the compounds according to the invention on an industrial scale are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

It is known to the person skilled in the art that the compounds according to the invention and their salts, when they are isolated, for example, in crystalline form, can contain various amounts of solvents. The invention therefore also comprises all solvates and in particular all hydrates of the compounds of the formula I, and also all solvates and in particular all hydrates of the salts of the compounds of the formula I.

Compounds of the formula I to be emphasized are those in which

R1 is 1-2C-alkoxy, 3-6C-cycloalkoxy, 3-6C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R2 is 1-2C-alkoxy, 3-6C-cycloalkoxy, 3-6C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R21 is hydrogen,

R4 is hydrogen or 1-2C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or in which

R5 and R51 together represent an additional bond,

Het is an unsubstituted or R6- and/or R7-substituted radical selected from the group consisting of benzofuran-2-yl, benzofuran-3-yl, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzofuran-3-yl, benzothiophen-2-yl, benzothiophen-3-yl, 2,3-dihydrobenzothiophen-2-yl, 2,3-dihydrobenzothiophen-3-yl, chroman-2-yl, chroman-3-yl, chroman-4-yl, isochroman-1-yl, 1,4-benzodioxan-2-yl, 1,3-benzodioxol-2-yl, quinolin-2-yl, quinolin-4-yl, quinolin-3-yl, isoquinolin-3-yl, isoquinolin-1-yl, isoquinolin-4-yl, 1,2,3,4-tetrahydroacridin-9-yl, acridin-9-yl, indolizin-2-yl, indolizin-3-yl, indolizin-5-yl, indolizin-6-yl, indolizin-7-yl, indolizin-8-yl, phenanthridin-6-yl, cinnolin-3-yl, cinnolin-4-yl, quinazolin-4-yl, quinoxalin-2-yl, phthalazin-1-yl, 1,7-naphthyridin-8-yl, 1,8-naphthyridin-3-yl, 1,8-naphthyridin-4-yl, 1,6-naphthyridin-8-yl, 1,6-naphthyridin-2-yl, 1,6-naphthyridin-3-yl, 1,6-naphthyridin-4-yl, 1,6-naphthyridin-6-yl, 1,6-naphthyridin-7-yl, 1,6-naphthyridin-9-yl, indol-3-yl, indol-2-yl, indazol-3-yl, benzimidazol-2-yl, 2,3-dihydro-1H-indol-2-yl, 2,3-dihydro-1H-indol-3-yl, 2,3-dihydro-1H-isoindol-1-yl, 2,3-dihydro-1H-isoindol-2-yl, 1,2,3,4-tetrahydroquinolin-2-yl, 1,2,3,4-tetrahydroquinolin-3-yl, 1,2,3,4-tetrahydroquinolin-4-yl, 1,2,3,4-tetrahydroisoquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-4-yl, β-carbolin-1-yl, β-carbolin-3-yl, β-carbolin-4-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, 1H-pyrrol-2-yl, 1H-pyrrol-3-yl, pyrazol-3-yl, pyrazol-4-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, [1,2,3]triazol-4-yl, [1,2,3]triazol-5-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyridazin-2-yl, pyridazin-4-yl, pyrazin-2-yl and pyrazin-3-yl, where

R6 is hydroxyl, halogen, nitro, amino, aminocarbonyl, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkylsulfanyloxy, 1-4C-alkoxycarbonyl or completely or predominantly fluorine-substituted 1-2C-alkoxy, and

R7 is hydroxyl, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of the formula I to be particularly emphasized are those in which

R1 is 1-4C-alkoxy,

R2 is 1-2C-alkoxy,

R3, R21, R4, R5 and R51 are hydrogen,

Het is an unsubstituted or R6- and/or R7-substituted radical selected from the group consisting of benzofuran-2-yl, benzothiophen-2-yl, quinolin-2-yl, quinolin-4-yl, isoquinolin-1-yl, indol-2-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, 1H-pyrrol-2-yl, pyrazol-3-yl, thiazol-2-yl, thiazol-5-yl, isoxazol-4-yl, isoxazol-5-yl, [1,2,3]triazol-5-yl and pyrazin-2-yl, where

R6 is halogen, 1-4C-alkyl, 1-4C-alkoxy or phenyl, and

R7 is 1-4C-alkyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Preferred compounds of the formula I are those in which

R1 is methoxy,

R2 is methoxy,

R3, R21, R4, R5 and R51 are hydrogen, and

Het is quinolin-4-yl, quinolin-2-yl, 3-methyl-furan-2-yl, 5-methyl-benzofuran-2-yl, 7-methoxy-benzofuran-2-yl, 5-methoxy-benzofuran-2-yl, thiophen-2-yl, 5-methyl-thiophen-2-yl, thiophen-3-yl, 1H-indol-2-yl, 5-fluoro-1H-indol-2-yl, 6-methoxy-1H-indol-2-yl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

One embodiment (embodiment A) of the compounds of formula I are those compounds in which

R1 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R2 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

or in which

R1 and R2 together are a 1-2C-alkylenedioxy group,

R3 is hydrogen or 1-4C-alkyl,

R51 is hydrogen or 1-4C-alkyl,

or in which

R3 and R21 together are a 1-4C-alkylene group,

R4 is hydrogen or 1-4C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or in which

R5 and R51 together represent an additional bond,

Het is an unsubstituted or R6- and/or R7-substituted pyrimidinyl, pyrazinyl or pyridazinyl radical, or an unsubstituted or R6- and/or R7-substituted fused 6/6- or 6/5-cyclic ring system comprising at least one aromatic ring and up to 4 heteroatoms - selected from the group consisting of O (oxygen) or N (nitrogen) - which is bonded to the phenanthridinyl radical via one of the rings containing one or more heteroatoms, where

R6 is hydroxyl, halogen, nitro, azano, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, 1-4C-alkoxycarbonyloxy or completely or predominantly fluorine-substituted 1-4C-alkoxy, and

R7 is hydroxyl, halogen, nitro, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of the formula I of embodiment A to be emphasized are those in which

R1 is 1-2C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R2 is 1-2C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is hydrogen or 1-2C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or in which

R5 and R51 together represent an additional bond,

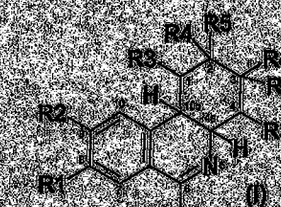
Het is an unsubstituted or R6- and/or R7-substituted radical selected from the group consisting of benzofuran-2-yl, benzofuran-3-yl, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzofuran-3-yl, chromen-2-yl, chromen-3-yl, chromen-4-yl, isochromen-1-yl, 1,4-benzodioxen-2-yl, 1,3-benzodioxol-2-yl, quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-6-yl, isoquinolin-3-yl, isoquinolin-1-yl, isoquinolin-4-yl, 1,2,3,4-tetrahydroacridin-9-yl, acridin-9-yl, indolizin-2-yl, indolizin-3-yl, indolizin-6-yl, indolizin-8-yl, indolizin-7-yl, indolizin-5-yl, phenanthridin-6-yl, phenolin-2-yl, cinnolin-4-yl, quinazolin-4-yl, quinoxalin-6-yl, phthalazin-4-yl, 1,7-naphthyridin-3-yl, 1,8-naphthyridin-3-yl, 1,8-naphthyridin-4-yl, 1,8-naphthyridin-5-yl, 1,6-naphthyridin-2-yl, 1,6-naphthyridin-3-yl, 1,6-naphthyridin-4-yl, 1,6-naphthyridin-5-yl, 1,6-naphthyridin-7-yl, 1,5-naphthyridin-3-yl, 1,5-naphthyridin-4-yl, 1,5-naphthyridin-2-yl, 1,5-naphthyridin-7-yl, 1,5-naphthyridin-6-yl, indol-3-yl, indol-2-yl, indazol-3-yl, benzimidazol-2-yl, 2,3-dihydro-1H-indol-2-yl, 2,3-dihydro-1H-indol-3-yl, 2,3-dihydro-1H-isoindol-1-yl, 2,3-dihydro-1H-isoindol-3-yl, 1,2,3,4-tetrahydroquinolin-2-yl, 1,2,3,4-tetrahydroquinolin-3-yl, 1,2,3,4-tetrahydroquinolin-4-yl, 1,2,3,4-tetrahydroisoquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-4-yl, β-carbolin-1-yl, β-carbolin-3-yl, β-carbolin-4-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-2-yl, pyridazin-4-yl, pyridazin-3-yl and pyrazin-2-yl, where

R6 is hydroxyl, halogen, nitro, amino, aminocarbonyl, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkylcarbonyloxy, 1-4C-alkoxycarbonyl or completely or predominantly fluorine-substituted 1-2C-alkoxy, and

R7 is hydroxyl, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

The compounds of the formula I are chiral compounds having chiral centers in positions 4a and 10b and, depending on the meaning of the substituents R3, R31, R4, R5 and R51, further chiral centers in the positions 1, 2, 3 and 4.

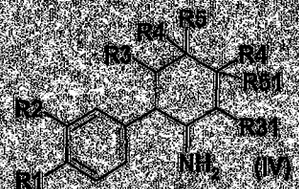


Numbering:

The invention therefore comprises all conceivable pure diastereomers and pure enantiomers and their mixtures in any mixing ratio, including the racemates. The compounds of the formula I are preferred in which the hydrogen atoms in positions 4a and 10b are cis to one another. The pure cis enantiomers are particularly preferred.

In this connection, particularly preferred compounds of the formula I are those in which positions 4a and 10b have the same absolute configuration as the compound (4-cis-1,2-dimethoxy-4-(2-aminocyclohexyl)benzene conceivable as a starting compound and having the optical rotation $[\alpha]_D^{20} = -66.6°$ (c = 1, ethanol).

The enantiomers can be separated in a manner known per se (for example by preparation and separation of appropriate diastereomeric compounds). Preferably, an enantiomer separation is carried out at the stage of the starting compounds of the formula IV.

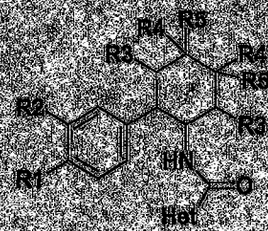


(IV)

for example by means of salt formation of the racemic compounds of the formula IV with optically active carboxylic acids. Examples which may be mentioned in this connection are the enantiomeric forms of mandelic acid, tartaric acid, O,O'-dibenzoyltartaric acid, camphoric acid, quinic acid, glutamic acid, malic acid, camphorsulfonic acid, 3-bromocamphorsulfonic acid, α-methoxyphenylacetic acid, α-methoxy-α-trifluoromethylphenylacetic acid and 2-phenylpropionic acid. Alternatively, enantiomerically pure starting compounds of the formula IV can also be prepared via asymmetric synthesis.

The preparation of the compounds of the formula I in which R1, R2, R3, R31, R4, R5, R51 and Het have the meanings indicated above and their salts can be carried out, for example, by the process described below in greater detail.

The process comprises cyclocondensing compounds of the formula II



(II)

in which R1, R2, R3, R31, R4, R5, R51 and Het have the meanings indicated above, and if desired then converting the compounds of the formula I obtained into their salts, or by, if desired, then converting salts of the compounds of the formula I obtained into the free compounds.

Compounds of the formula I obtained can, if desired, be converted into further compounds of the formula I by derivatization.

For example, starting from compounds of the formula I in which

a) R3 is an ester group, the corresponding acidic can be prepared by reaction with suitable alkylating agents;

b) R5 is a 1-4C-alkylcarbonyloxy group, the corresponding hydroxy compounds can be obtained by acidic or alkaline hydrolysis;

c) R5 and/or R51 is a nitro group, the corresponding amino compounds, which for their part can be further derivatized, are obtained by selective catalytic hydrogenation of the corresponding nitro compounds.

The methods mentioned under a), b) and c) are expediently carried out analogously to the methods known to the person skilled in the art.

In addition, the compounds of the formula I can be converted, if desired, into their N-oxides, for example with the aid of hydrogen peroxide in methanol or the alkali metal salt of 3-chloroperoxybenzoic acid in dichloromethane. The person skilled in the art is familiar on the basis of his/her expert knowledge with reaction conditions which are specifically necessary for carrying out the N-oxidation.

The cyclocondensation is carried out in a manner known per se to the person skilled in the art according to Bischler-Napieralski (e.g. as described in J. Chem. Soc. (1959, 4290-4292) in the presence of a suitable condensing agent, such as polyphosphoric acid, phosphorus pentachloride, phosphorus pentoxide or preferably phosphorus oxychloride, in a suitable inert solvent, eg. in a chlorinated hydrocarbon such as chloroform, or in a cyclic hydrocarbon such as toluene or xylene, or another inert solvent such as acetonitrile, or without further solvent using an excess of condensing agent, preferably at elevated temperature, in particular at the boiling temperature of the solvent or condensing agent used.

Compounds of the formula II in which R1, R2, R3, R31, R4, R5, R51 and Het have the meanings indicated above are accessible by reaction of the compounds of the formula IV in which R1, R2, R3, R31, R4, R5 and R51 have the meanings indicated above with compounds of the formula III



(III)

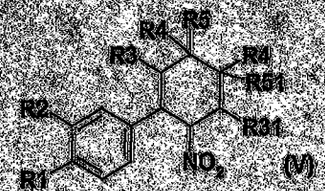
in which Hal has the meanings indicated above and X is a suitable leaving group, preferably a chlorine atom. For example, the cyclization or benzoylation is carried out as described in the following examples or as in J. Chem. Soc. (C), 1971, 1806-1808.

Alternatively to the process described above, compounds of the formula II in which R1, R2, R3, R31, R4, R5, R51 and Hal have the meanings indicated above can also be prepared from the corresponding compounds of the formula IV in which R1, R2, R3, R31, R4, R5 and R51 have the meanings indicated above and compounds of the formula III in which Hal has the meanings indicated above and X is hydroxyl, by reaction with amide bond-linking reagents known to the person skilled in the art. Examples of amide bond linking reagents known to the person skilled in the art which may be mentioned are, for example, the carbodiimides (e.g. dicyclohexylcarbodiimide), azodicarboxylic acid derivatives (e.g. diethyl azodicarboxylate), uronium salts (e.g. O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate) and N,N'-carbonyldiimidazole.

This alternative preparation process is particularly suitable for the preparation of compounds of the formula II in which Hal is substituted by amino or hydroxyl substituents or in which Hal represents a condensed bi- or tricyclic ring system comprising at least one aromatic ring and one NH group.

Compounds of the formula III and compounds of the formula IV are either known or can be prepared in a known manner.

The compounds of the formula IV can be prepared, for example, from compounds of the formula V,



(V)

in which R1, R2, R3, R31, R4, R5 and R51 have the abovementioned meanings, by reduction of the nitro group.

The reduction is carried out in a manner known to the person skilled in the art, for example as described in J. Org. Chem. 1962, 27, 4426 or as described in the following examples.

The reduction can be carried out, for example, by catalytic hydrogenation, e.g. in the presence of Raney nickel, in a lower alcohol such as methanol or ethanol at room temperature and under normal or

elevated pressure. If desired, a catalytic amount of an acid, such as, for example, hydrochloric acid, can be added to the solvent. Preferably, however, the reduction is carried out using metal such as zinc or iron with organic acids such as acetic acid or mineral acids such as hydrochloric acid.

The compounds of the formula IV in which R1, R2, R3, R31 and R4 have the meanings indicated above and R5 and R51 together represent an additional bond can be prepared from the corresponding compounds of the formula V by selective reduction of the nitro group in a manner known to the person skilled in the art, for example in the presence of Raney nickel in a lower alcohol as solvent using hydrazine hydrate as a hydrogen donor.

The compounds of the formula V, in which R1, R2, R3, R31 and R4 have the meanings indicated above and R5 and R51 are hydrogen, are either known or can be prepared from corresponding compounds of the formula V in which R5 and R51 together are an additional bond. The reaction can be carried out in a manner known to the person skilled in the art, preferably by hydrogenation in the presence of a catalyst, such as, for example, palladium on active carbon, e.g. as described in J. Chem. Soc. (C), 1971, 1806-1808.

The compounds of the formula V, in which R5 and R51 together are an additional bond, are either known or can be obtained by the reaction of compounds of the formula VI,



(VI)

in which R1 and R2 have the meanings mentioned above, with compounds of the formula VII,

R3-CH=C(R4)-C(R4)=CH-R31 (VII)

in which R3, R31 and R4 have the meanings mentioned above.

Compounds of the formula V in which R5 and R51 are together an additional bond and R3 and R31 are together a 1-4C-alkylene group can be obtained, for example, by reaction of cyclic compounds of the formula VII, in which R4 has the meanings indicated above and R3 and R31 together are a 1-4C-alkylene group (e.g. cyclohexa-1,3-diene, 2,3-dimethylcyclohexa-1,3-diene, cyclohepta-1,3-diene, 2,3-dimethylcyclohepta-1,3-diene or cycloocta-1,3-diene), with compounds of the formula VI in which R1 and R2 have the abovementioned meanings.

The cycloaddition is in this case carried out in a manner known to the person skilled in the art according to Diels-Alder, e.g. as described in J. Amer. Chem. Soc. 1957, 79, 6553 or in J. Org. Chem. 1962, 27, 691 or as described in the following examples.

Compounds of the formula V obtained in the cycloaddition, in which the phenyl ring and the nitro group are trans to one another, can be converted in a manner known to the person skilled in the art into the corresponding cis compounds, e.g. as described in J. Amer. Chem. Soc. 1957, 79, 6553 or as described in the following examples.

The compounds of the formulae VI and VII are either known or can be prepared in a known manner. The compounds of the formula VI can be prepared, for example, in a manner known to the person skilled in the art from corresponding compounds of the formula VIII as described, for example, in J. Chem Soc. 1951, 2624 or in J. Org. Chem. 1944, 9, 170 or as described in the following examples.

The compounds of the formula VIII



(VIII)

in which R1 and R2 have the meanings indicated above, are either known or can be prepared in a manner known to the person skilled in the art, as described, for example, in Ber. Dtsch. Chem. Ges. 1926, 59, 203.

It is known to the person skilled in the art that, in the case of a number of reactive centers on a starting or intermediate compound, it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description of the use of a large number of proven protective groups is found, for example, in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

The isolation and purification of the substances according to the invention is carried out in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallising the resulting residue from a suitable solvent or subjecting it to one of the customary purification methods, such as, for example, column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (e.g. a ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, an ether, such as diethyl ether, tetrahydrofuran or

dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol, such as ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a nonsolvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by alkalization or by acidification into the free compounds, which in turn can be converted into salts. In this way, pharmacologically intolerable salts can be converted into pharmacologically tolerable salts.

The following examples serve to illustrate the invention further without restricting it. Likewise, further compounds of the formula I, whose preparation is not explicitly described, can be prepared in an analogous manner or in a manner familiar per se to the person skilled in the art using customary process techniques.

In the examples, mp. stands for melting point, h for hour(s), RT for room temperature, EF for empirical formula, MW for molecular weight, calc. for calculated and fnd. for found. The compounds mentioned in the examples and their salts are a preferred subject of the invention.

MS-method: EI-MS: Electron impact ionisation MS.

HPLC-Method:

Column: Superspher 60 RP-select B (Merck) 75 x 4 mm
Column temperature: 40°C
Solvent System: A: Water (+ 0.6% Trifluoroacetic acid)
B: Acetonitrile (+ 0.6% Trifluoroacetic acid)

Course of gradient:

Time [min]	% A	% B
0.0	80	20
1.0	80	20
7.0	25	75
10.0	25	75
12.0	80	20
14.0	80	20

Flow: 1 ml/min
Detection: UV (254 nm)

Examples

Final products

1. (-)-cis-8,9-Dimethoxy-6-quinolin-4-yl-1,2,3,4,4a,10b-hexahydrophenanthridine

A solution of 4.0 g of (-)-cis-N-[2-(3,4-dimetoxyphenyl)cyclohexyl]quinoline-4-carboximide (compound A100) in 30 ml of acetonitrile is added dropwise at RT in the course of 30 min to 10 g of phosphorus pentachloride in 20 ml of acetonitrile. After stirring at RT for 3 h, the mixture is diluted with ethyl acetate and hydrolyzed by addition of water. The organic phase is extracted with 1 N sodium hydroxide solution and water, dried using sodium sulfate and then concentrated under reduced pressure. The residue is chromatographed on silica gel using petroleum ether/ethyl acetate/triethylamine in the ratio 6/4/1.

MS: calc.: $C_{25}H_{24}N_2O_2$ (372.46); found: [M+1] 373.3

Specific rotation: $[\alpha]_D^{20} = -67.8°$ (c = 0.2; DMF)

2. cis-8,9-Dimethoxy-6-(1-methyl-1H-pyrrol-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

To a solution of 44.83 mg furan-3-carboxylic acid in 2800 µl dichloromethane 94 mg (-)-cis-1,2-dimethoxy-4-(2-aminocyclohexyl)benzene (compound B2) and 92 mg N-dimethylaminopropyl-N'-ethyl-carbodiimide are added and the resulting mixture is stirred for 16 h at RT. The reaction mixture is put on a cartridge loaded with 0 g silica and 3 g aluminium oxide neutral and eluted with ethyl acetate. The filtrate is evaporated to dryness and dissolved again in 1600 µl acetonitrile. To this solution 100 mg phosphorus pentachloride are added and the resulting mixture is stirred for 16 h at RT, after which 800 µl of a sodium hydroxide solution (40%) are added. After stirring for further 2 h at RT, the reaction mixture is evaporated to dryness and the title compound is purified by flash chromatography.

MS: calc. $C_{24}H_{23}NO_3$ (374.44); found: [M+1] 326.4

The following examples are prepared analogously to compound 2:

3. cis-8,9-Dimethoxy-6-(5-methyl-3-phenyl-isoxazol-4-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc. $C_{30}H_{30}N_2O_3$ (402.48); found: [M+1]: 403.3

4. cis-8,9-Dimethoxy-6-(furan-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc. $C_{18}H_{19}NO_3$ (311.35); found: [M+1]: 312.3 HPLC [min]: 6.36

5. cis-8,9-Dimethoxy-6-(1H-pyrrol-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc. $C_{18}H_{20}N_2O_2$ (310.40); found: [M+1]: 311.3

6. cis-8,9-Dimethoxy-6-(furan-3-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc. $C_{18}H_{19}NO_3$ (311.36); found: [M+1]: 312.3 HPLC [min]: 6.44

7. cis-8,9-Dimethoxy-6-(thiophen-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc. $C_{18}H_{19}NO_2S$ (327.45); found: [M+1]: 328.3 HPLC [min]: 6.79

8. cis-8,9-Dimethoxy-6-(5-methyl-thiophen-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc. $C_{19}H_{21}NO_2S$ (341.46); found: [M+1]: 342.3

9. cis-8,9-Dimethoxy-6-(thiophen-3-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc. $C_{18}H_{19}NO_2S$ (327.46); found: [M+1]: 328.3 HPLC [min]: 6.79

10. cis-8,9-Dimethoxy-6-(1H-indol-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine trifluoroacetate

MS: calc. $C_{22}H_{22}F_3N_2O_4$ (380.43); found: [M+1]: 381.3

11. cis-8,9-Dimethoxy-6-(6-fluoro-1H-indol-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine trifluoroacetate

MS: calc. $C_{22}H_{21}F_4N_2O_4$ (378.43); found: [M+1]: 379.2

12. cis-8,9-Dimethoxy-6-(6-methoxy-1H-indol-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine trifluoroacetate

MS: calc. $C_{23}H_{25}F_3N_2O_5$ (360.40); found: [M+1]: 391.4

13. cis-8,9-Dimethoxy-6-(benzofuran-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc: $C_{24}H_{23}NO_3$ (373.44); found: [M+1]: 382.3

14. cis-8,9-Dimethoxy-6-(pyrazin-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc: $C_{20}H_{21}N_3O_2$ (335.40); found: [M+1]: 324.3

15. cis-8,9-Dimethoxy-6-(quinolin-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc: $C_{25}H_{24}N_2O_2$ (372.47); found: [M+1]: 373.2 HPLC [min]: 6.22

16. cis-8,9-Dimethoxy-6-(3-methyl-furan-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc: $C_{20}H_{23}NO_3$ (325.41); found: [M+1]: 326.3

17. cis-8,9-Dimethoxy-6-(benzo[b]thiophen-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc: $C_{24}H_{23}NO_2S$ (373.51); found: [M+1]: 376.3

18. cis-8,9-Dimethoxy-6-(3,5-dimethyl-isoxazol-4-yl)-1,2,3,4,4a,10b-hexahydro-phenanthridine

MS: calc: $C_{21}H_{26}N_2O_3$ (340.45); found: [M+1]: 341.3

19. cis-8,9-Dimethoxy-6-(4-phenyl-[1,2,3]thiadiazol-5-yl)-1,2,3,4,4a,10b-hexahydro-phenanthridine

MS: calc: $C_{24}H_{24}N_4O_2S$ (408.52); found: [M+1]: 409.4

20. cis-8,9-Dimethoxy-6-(3-methyl-benzofuran-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc: $C_{25}H_{25}NO_3$ (375.47); found: [M+1]: 376.3 HPLC [min]: 6.68

21. cis-8,9-Dimethoxy-6-(7-methoxy-benzofuran-2-yl)-1,2,3,4,4a,10b-hexahydro-phenanthridine

MS: calc: $C_{25}H_{25}NO_4$ (391.47); found: [M+1]: 392.3 HPLC [min]: 6.75

22. cis-8,9-Dimethoxy-6-(5-methyl-pyrazin-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc: $C_{21}H_{23}N_3O_2$ (349.43); found: [M+1]: 350.3

23. cis-8,9-Dimethoxy-6-(6-methoxy-benzofuran-2-yl)-1,2,3,4,4a,10b-hexahydro-phenanthridine

MS: calc: $C_{25}H_{25}NO_4$ (391.47); found: [M+1]: 392.3 HPLC [min]: 6.75

24. cis-8,9-Dimethoxy-6-(1,3-dimethyl-1H-pyrazol-4-yl)-1,2,3,4,4a,10b-hexahydro-phenanthridine

MS: calc: $C_{21}H_{26}N_3O_2$ (339.44); found: [M+1]: 340.4

25. cis-8,9-Dimethoxy-6-(4-methyl-1,2,3]thiadiazol-5-yl)-1,2,3,4,4a,10b-hexahydro-phenanthridine

MS: calc: $C_{19}H_{21}N_3O_2S$ (343.45); found: [M+1]: 344.1

26. cis-8,9-Dimethoxy-6-(isoxazol-5-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc: $C_{18}H_{20}N_2O_3$ (312.37); found: [M+1]: 313.3

27. cis-8,9-Dimethoxy-6-(isoquinolin-1-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

MS: calc: $C_{25}H_{24}N_2O_2$ (372.47); found: [M+1]: 373.4 HPLC [min]: 6.92

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(54) NOVEL 6-HETEROARYLPHENANTHRIDINES

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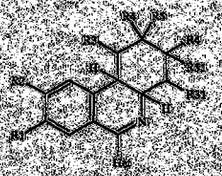
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(57) ABSTRACT

Compounds of the formula I, in which the is an unsubstituted or R6- and/or R7-substituted pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl or pyridazinyl radical, or an unsubstituted or R6- and/or R7-substituted fused 5- or 6-cyclic ring system comprising at least one aromatic ring and up to 4 heteroatoms—selected from the group consisting of O (oxygen), S (sulphur) or N (nitrogen)—which is bonded to the phenanthridinyl radical via one of the rings comprising one or more heteroatoms, exhibit PDE4 inhibitors.



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NOVEL 6-HETEROARYLPHENANTHRIDINES

FIELD OF APPLICATION OF THE INVENTION

[0001] The invention relates to novel 6-heteroarylphenanthridines, which are used in the pharmaceutical industry for the production of medicaments.

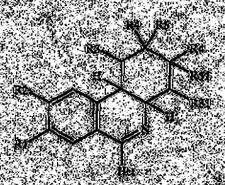
KNOWN TECHNICAL BACKGROUND

[0002] Chem Ber 1959; 92, 675-677, J. Chem. Soc., 1956; 4280-4285 and J. Chem. Soc (C), 1971, 1803 describe the synthesis of 6-phenylphenanthridines. The International Applications WO 97/23451, WO 97/35854, WO 97/05101 and WO 99/06319 describe 6-phenyl- and 6-pyridylphenanthridines as PDE4 inhibitors.

DESCRIPTION OF THE INVENTION

[0003] It has now been found that the novel phenanthridines, substituted in position 6 by a 5- or 6-cyclic heteroaryl radical, and described in greater detail below have surprising and particularly advantageous properties.

[0004] The invention thus relates to compounds of the formula I,



(I)

[0005] in which

[0006] R1 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

[0007] R2 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

[0008] or in which

[0009] R1 and R2 together are a 1-2C-alkylenedioxy group,

[0010] R3 is hydrogen or 1-4C-alkyl,

[0011] R31 is hydrogen or 1-4C-alkyl,

[0012] or in which

[0013] R3 and R31 together are a 1-4C-alkylene group,

[0014] R4 is hydrogen or 1-4C-alkyl,

[0015] R5 is hydrogen,

[0016] R51 is hydrogen,

[0017] or in which

[0018] R5 and R51 together represent an additional bond,

[0019] the is unsubstituted or R6- and/or R7-substituted pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl or pyridazinyl radical, or an unsubstituted or R6- and/or R7-substituted fused 5- or 6-cyclic ring system comprising at least one aromatic ring and up to 4 heteroatoms—selected from the group consisting of O (oxygen), S (sulphur) or N (nitrogen)—which is bonded to the phenanthridinyl radical via one of the rings comprising one or more heteroatoms, where

[0020] R6 is hydroxyl, halogen, nitro, cyano, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, mono- or di-1-4C-alkylaminosulphonyl, 1-4C-alkylsulphonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkylcarbonyloxy, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonylamino, phenyl or completely or predominantly fluorine-substituted 1-4C-alkoxy, and

[0021] R7 is hydroxyl, halogen, nitro, 1-4C-alkyl or 1-4C-alkoxy,

[0022] and the salts, the N-oxides and the salts of the N-oxides of these compounds.

[0023] 1-4C-Alkyl represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and preferably the ethyl and methyl radicals.

[0024] 1-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy radicals.

[0025] 3-7C-Cycloalkoxy represents cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy, of which cyclopropyloxy, cyclohexyloxy and cyclopentyloxy are preferred.

[0026] 3-7C-Cycloalkylmethoxy represents cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy and cycloheptylmethoxy, of which cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy are preferred.

[0027] As completely or predominantly fluorine-substituted 1-4C-alkoxy, for example, the 2,2,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,1,2,2-tetrafluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and preferably the difluoromethoxy radicals may be mentioned. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy radical are replaced by fluorine atoms.

[0028] 1-2C-Alkylenedioxy represents, for example, the methylenedioxy [—O—CH_2—O—] and the ethylenedioxy [—O—CH_2—CH_2—O—] radicals.

[0029] If R3 and R31 together have the meaning 1-4C-alkylene, the positions 1 and 4 in compounds of the formula I are linked to one another by a 1-4C-alkylene bridge,

1-4C-alkylene representing straight-chained or branched alkylene radicals having 1 to 4 carbon atoms. Examples which may be mentioned are the radicals methylene [—CH2—], ethylene [—CH2—CH2—], dimethylene [—CH(CH3)—CH2— or —CH2—CH(CH3)—], 1,2-dimethylethylene [—CH(CH3)—CH(CH3)—] and isopropylidene [—C(CH3)2—].

[0030] If R8 and R9 together form an additional bond, then the carbon atoms in positions 2 and 3 in compounds of the formula I are linked to one another via a double bond.

[0031] Halogen within the meaning of the invention is bromine, chlorine or fluorine.

[0032] In addition to the nitrogen atom, mono- or di-1-4C-alkylamine radicals contain one to two of the above-mentioned 1-4C-alkyl radicals. Di-1-4C-alkylamine is preferred and here, for example, dimethyl-, diethyl- or diisopropylamine.

[0033] In addition to the carbonyl group, mono- or di-1-4C-alkylaminocarbonyl radicals contain one of the above-mentioned mono- and/or di-1-4C-alkylamino radicals. Examples which may be mentioned are the N-methyl-, the N,N-dimethyl-, the N-ethyl-, the N-propyl-, the N,N-diethyl- and N-isopropylaminocarbonyl radicals.

[0034] 1-4C-alkylcarbonyl represents a carbonyl-bonded group to which one of the above-mentioned 1-4C-alkyl radicals is bonded. An example which may be mentioned is the acetoxy radical [CH3C(O)—O—].

[0035] 1-4C-alkoxycarbonyl represents a carbonyl group to which one of the above-mentioned 1-4C-alkoxy radicals is bonded. Examples which may be mentioned are the methoxycarbonyl [CH3O—C(O)—] and the ethoxycarbonyl [CH3CH2O—C(O)—] radicals.

[0036] As a 1-4C-alkylaminocarbonylamino radical, for example, the methylaminocarbonylamino radical [CH3NHC(O)NH—] and the acetylamino radical [CH3C(O)NH—] may be mentioned.

[0038] Het represents an unsubstituted or R6- and/or R7-substituted pyrrolyl, furanyl, pyridinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinonyl, pyrrazinyl or pyridazinyl radical, or an unsubstituted or R6- and/or R7-substituted fused bi- or tricyclic ring system comprising at least one aromatic ring and up to 4 heteroatoms—selected from the group consisting of O (oxygen), S (sulphur) or N (nitrogen)—which is bonded to the phenanthridinyl radical via one of the rings comprising one or more heteroatoms.

[0039] Exemplary unsubstituted heteroaryl radicals like which may be mentioned are benzofuran-2-yl, benzofuran-3-yl, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzofuran-3-yl, benzothiophen-2-yl, benzothiophen-3-yl, 2,3-dihydrobenzothiophen-2-yl, 2,3-dihydrobenzothiophen-3-yl, chroman-2-yl, chroman-3-yl, isochroman-1-yl, 1,4-benzodioxan-2-yl, 1,3-benzodioxol-2-yl, quinolin-2-yl, quinolin-4-yl, quinolin-3-yl, isoquinolin-1-yl, isoquinolin-4-yl, 1,2,3,4-tetrahydroacridin-9-yl, acridin-9-yl, indolizin-2-yl, indolizin-3-yl, indolizin-5-yl, indolizin-8-yl, indolizin-7-yl, indolizin-6-yl, indolizin-5-yl, phenanthridin-6-yl, cinnolin-3-yl, cinnolin-4-yl, quinazolin-2-yl, quinoxalin-2-yl, phthalazin-1-yl, 1,7-naphthyridin-3-yl, 1,6-naphthyridin-3-yl, 1,5-naphthyridin-3-yl, 1,6-naphthyridin-4-yl, 1,6-naphthyridin-5-yl, 1,5-naphthyridin-4-yl, 1,5-naphthyridin-2-yl, 1,8-naphthyridin-3-yl, 1,8-naphthyridin-4-yl, 1,5-naphthyridin-3-yl, 1,5-naphthyridin-8-yl, indol-2-yl, indol-3-yl, indazol-3-yl, benzimidazol-2-yl, 2,3-dihydro-1H-indol-2-yl, 2,3-dihydro-1H-indol-3-yl, 2,3-dihydro-1H-isoindol-1-yl, 2,3-dihydro-1H-isoindol-3-yl, 1,2,3,4-tetrahydroquinolin-2-yl, 1,2,3,4-tetrahydroquinolin-3-yl, 1,2,3,4-tetrahydroquinolin-4-yl, 1,2,3,4-tetrahydroisoquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-4-yl, β-carbolin-1-yl, β-carbolin-3-yl, β-carbolin-4-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, 1H-pyrrol-2-yl, 1H-pyrrol-3-yl, pyrazol-3-yl, pyrazol-4-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, [1,2,3]thiadiazol-4-yl, [1,2,3]thiadiazol-5-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-5-yl and pyrazin-2-yl.

[0040] Exemplary R6- and/or R7-substituted heteroaryl radicals like which may be mentioned are 1-methyl-1H-pyrrol-2-yl, 5-methyl-3-phenylisoxazol-4-yl, 3-methylthiophen-2-yl, 5-fluoro-1H-indol-2-yl, 5-methoxy-1H-indol-2-yl, 3-methyl-furan-2-yl, 3,5-dimethylisoxazol-4-yl, 4-phenyl-[1,2,3]thiadiazol-5-yl, 4-methyl-[1,2,3]triadiazol-5-yl, 1,3-dimethyl-1H-pyrazol-5-yl, 3-methyl-benzofuran-2-yl, 5-methoxybenzofuran-2-yl, 7-methoxybenzofuran-2-yl, 7-ethoxybenzofuran-2-yl, 5-chlorobenzofuran-2-yl, 5-nitrobenzofuran-2-yl, 4-chloro-6-nitroquinolin-2-yl, 2-chloroquinolin-4-yl, 6-methoxyquinolin-4-yl, 2-hydroxyquinolin-4-yl, 6-nitroquinolin-4-yl, 2-cyclopropylquinolin-4-yl, 3-cyclohexyl-6-methylquinolin-4-yl, 7-chloroquinolin-4-yl, 4-hydroxyquinolin-2-yl, 2,8-dihydroxyquinolin-4-yl, 5-nitroquinolin-2-yl, 6-methoxyquinolin-8-yl, 4-hydroxy-2-chloroquinolin-7-yl, 6-hydroxyquinolin-2-yl, 6,7-dimethoxyisoquinolin-3-yl, 3-hydroxypyridin-2-yl, indol-2-yl, 1-methylindol-2-yl, 1-methoxy-1H-benzotriazol-5-yl, 1-methylindol-3-yl, 1-methyl-1H-indazol-3-yl, 1-acetyl-1H-indazol-3-yl, 5-nitroindol-2-yl, 7-nitroindol-2-yl, 7-methylindol-2-yl, 6,6-dimethoxyindol-2-yl, 5,6-dimethoxyindol-2-yl, 5-methoxyindol-2-yl, 5-hydroxyindol-2-yl, 5-methoxypyrimidin-2-yl, 6-hydroxypyrimidin-4-yl, 2-chloro-6-methylpyrimidin-4-yl, 2,6-bis(dimethylamino)pyrimidin-4-yl, 2,6-dimethoxypyrimidin-4-yl, 5-methylpyridin-2-yl, 2-methylpyrazin-5-yl, 2-hydroxypyrazin-2-yl, 2-methylaminopyrazin-6-yl, 2-methoxypyrazin-5-yl and 5-chlorpyrazin-2-yl.

[0041] Possible salts for compounds of the formula I—depending on substitution—are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable salts of the inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, trifluoroacetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, it being possible to employ the acids in salt preparation—depending on whether a mono- or polybasic acid is concerned and depending on which acid is desired—in an equimolar quantitative ratio or one differing therefrom.

[0042] On the other hand, salts with bases are also suitable. Examples of salts with bases which may be mentioned are alkali metal (lithium, sodium, potassium) or alkaline, aluminium, magnesium, thorium, ammonium, meglumine or guanidinium salts, where here too the bases are employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

[0043] Pharmacologically intolerable salts which are initially obtained, for example, as process products in the preparation of the compounds according to the invention on an industrial scale are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

[0044] It is known to the person skilled in the art that the compounds according to the invention and their salts, when they are isolated, for example, in crystalline form, may contain various amounts of solvents. The invention therefore also comprises all solvates and in particular all hydrates of the compounds of the formula I, and also all solvates and in particular all hydrates of the salts of the compounds of the formula I.

[0045] Compounds of the formula I to be emphasized are those in which

[0046] R1 is 1-2C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

[0047] R2 is 1-2C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

[0048] R3 is hydrogen,

[0049] R31 is hydrogen,

[0050] R4 is hydrogen or 1-2C-alkyl,

[0051] R5 is hydrogen,

[0052] R51 is hydrogen,

[0053] or in which

[0054] R5 and R51 together represent an additional bond,

[0055] Het is an unsubstituted or R6- and/or R7-substituted radical selected from the group consisting of benzofuran-2-yl, benzofuran-3-yl, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzofuran-3-yl, benzothiophen-2-yl, benzothiophen-3-yl, 2,3-dihydrobenzothiophen-2-yl, 2,3-dihydrobenzothiophen-3-yl, chroman-2-yl, chroman-3-yl, isochroman-1-yl, 1,4-benzodioxan-2-yl, 1,3-benzodioxol-2-yl, quinolin-2-yl, quinolin-4-yl, quinolin-3-yl, isoquinolin-1-yl, isoquinolin-4-yl, 1,2,3,4-tetrahydroacridin-9-yl, acridin-9-yl, indolizin-2-yl, indolizin-3-yl, indolizin-5-yl, indolizin-8-yl, indolizin-7-yl, indolizin-6-yl, indolizin-5-yl, phenanthridin-6-yl, cinnolin-3-yl, cinnolin-4-yl, quinazolin-2-yl, quinoxalin-2-yl, phthalazin-1-yl, 1,7-naphthyridin-3-yl, 1,6-naphthyridin-3-yl, 1,5-naphthyridin-3-yl, 1,6-naphthyridin-4-yl, 1,6-naphthyridin-5-yl, 1,5-naphthyridin-4-yl, 1,5-naphthyridin-2-yl, 1,8-naphthyridin-3-yl, 1,8-naphthyridin-4-yl, 1,5-naphthyridin-3-yl, 1,5-naphthyridin-8-yl, indol-2-yl, indol-3-yl, indazol-3-yl, benzimidazol-2-yl, 2,3-dihydro-1H-indol-2-yl, 2,3-dihydro-1H-indol-3-yl, 2,3-dihydro-1H-isoindol-1-yl, 2,3-dihydro-1H-isoindol-3-yl, 1,2,3,4-tetrahydroquinolin-2-yl, 1,2,3,4-tetrahydroquinolin-3-yl, 1,2,3,4-tetrahydroquinolin-4-yl, 1,2,3,4-tetrahydroisoquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-4-yl, β-carbolin-1-yl, β-carbolin-3-yl, β-carbolin-4-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, 1H-pyrrol-2-yl, 1H-pyrrol-3-yl, pyrazol-3-yl, pyrazol-4-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, [1,2,3]thiadiazol-4-yl, [1,2,3]thiadiazol-5-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-5-yl and pyrazin-2-yl, where

[0056] R6 is hydroxyl, halogen, nitro, amino, azido, isocarboxyl, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkylcarbonyloxy, 1-4C-alkoxycarbonyl or completely or predominantly fluorine-substituted 1-2C-alkoxy, and

[0057] R7 is hydroxyl, halogen, 1-4C-alkyl or 1-4C-alkoxy,

[0058] and the salts, the N-oxides and the salts of the N-oxides of these compounds.

[0059] Compounds of the formula I to be particularly emphasized are those in which

[0060] R1 is 1-2C-alkoxy,

[0061] R2 is 1-2C-alkoxy,

[0062] R3, R31, R4, R5 and R51 are hydrogen,

[0063] Het is an unsubstituted or R6- and/or R7-substituted radical selected from the group consisting of benzofuran-2-yl, benzothiophen-2-yl, quinolin-2-yl, quinolin-4-yl, isoquinolin-1-yl, indol-2-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, 1H-pyrrol-2-yl, pyrazol-3-yl, thiazol-2-yl, thiazol-4-yl, isoxazol-3-yl, [1,2,3]thiadiazol-4-yl and pyrazin-2-yl, where

[0064] R6 is halogen, 1-4C-alkyl, 1-4C-alkoxy or phenyl, and

[0065] R7 is 1-4C-alkyl,

[0066] and the salts, the N-oxides and the salts of the N-oxides of these compounds.

[0067] Preferred compounds of the formula I are those in which

[0068] R1 is methoxy,

[0069] R2 is methoxy,

[0070] R3, R31, R4, R5 and R51 are hydrogen, and

[0071] Het is quinolin-4-yl, quinolin-2-yl, 3-methyl-furan-2-yl, 3-methyl-benzofuran-2-yl, 7-methoxy-benzofuran-2-yl, 5-methoxy-benzofuran-2-yl,

7-ethoxy-benzofuran-2-yl, 5-chloro-benzofuran-2-yl, 5-nitro-benzofuran-2-yl, 4-chloro-6-nitro-quinolin-2-yl, 6-methoxy-quinolin-4-yl, 6-nitro-quinolin-4-yl, 2-cyclopropyl-quinolin-4-yl, 3-cyclohexyl-6-methyl-quinolin-4-yl, 7-chloro-quinolin-4-yl, 4-hydroxy-quinolin-2-yl, 2,8-dihydroxy-quinolin-4-yl, 5-nitro-quinolin-2-yl, 6-methoxy-quinolin-8-yl, 4-hydroxy-2-chloro-quinolin-7-yl, 6-hydroxy-quinolin-2-yl, 6,7-dimethoxy-isoquinolin-3-yl, 3-hydroxy-pyridin-2-yl, indol-2-yl, 1-methyl-indol-2-yl, 1-methoxy-1H-benzotriazol-5-yl, 1-methyl-indol-3-yl, 1-methyl-1H-indazol-3-yl, 1-acetyl-1H-indazol-3-yl, 5-nitro-indol-2-yl, 7-nitro-indol-2-yl, 7-methyl-indol-2-yl, 6,6-dimethoxy-indol-2-yl, 5,6-dimethoxy-indol-2-yl, 5-methoxy-indol-2-yl, 5-hydroxy-indol-2-yl, 5-methoxy-pyrimidin-2-yl, 6-hydroxy-pyrimidin-4-yl, 2-chloro-6-methyl-pyrimidin-4-yl, 2,6-bis(dimethylamino)-pyrimidin-4-yl, 2,6-dimethoxy-pyrimidin-4-yl, 5-methyl-pyridin-2-yl, 2-methyl-pyrazin-5-yl, 2-hydroxy-pyrazin-2-yl, 2-methylamino-pyrazin-6-yl, 2-methoxy-pyrazin-5-yl and 5-chlor-pyrazin-2-yl,

[0072] and the salts, the N-oxides and the salts of the N-oxides of these compounds.

[0073] Very preferred compounds of the formula I are those in which

[0074] R1 is methoxy,

[0075] R2 is methoxy,

[0076] R3, R31, R4, R5 and R51 are hydrogen, and

[0077] Het is quinolin-4-yl, quinolin-2-yl, 3-methyl-furan-2-yl, 3-methyl-benzofuran-2-yl, 7-methoxy-benzofuran-2-yl, 5-methoxy-benzofuran-2-yl,

7-ethoxy-benzofuran-2-yl, 5-chloro-benzofuran-2-yl, 5-nitro-benzofuran-2-yl, 4-chloro-6-nitro-quinolin-2-yl, 6-methoxy-quinolin-4-yl, 6-nitro-quinolin-4-yl, 2-cyclopropyl-quinolin-4-yl, 3-cyclohexyl-6-methyl-quinolin-4-yl, 7-chloro-quinolin-4-yl, 4-hydroxy-quinolin-2-yl, 2,8-dihydroxy-quinolin-4-yl, 5-nitro-quinolin-2-yl, 6-methoxy-quinolin-8-yl, 4-hydroxy-2-chloro-quinolin-7-yl, 6-hydroxy-quinolin-2-yl, 6,7-dimethoxy-isoquinolin-3-yl, 3-hydroxy-pyridin-2-yl, indol-2-yl, 1-methyl-indol-2-yl, 1-methoxy-1H-benzotriazol-5-yl, 1-methyl-indol-3-yl, 1-methyl-1H-indazol-3-yl, 1-acetyl-1H-indazol-3-yl, 5-nitro-indol-2-yl, 7-nitro-indol-2-yl, 7-methyl-indol-2-yl, 6,6-dimethoxy-indol-2-yl, 5,6-dimethoxy-indol-2-yl, 5-methoxy-indol-2-yl, 5-hydroxy-indol-2-yl, 5-methoxy-pyrimidin-2-yl, 6-hydroxy-pyrimidin-4-yl, 2-chloro-6-methyl-pyrimidin-4-yl, 2,6-bis(dimethylamino)-pyrimidin-4-yl, 2,6-dimethoxy-pyrimidin-4-yl, 5-methyl-pyridin-2-yl, 2-methyl-pyrazin-5-yl, 2-hydroxy-pyrazin-2-yl, 2-methylamino-pyrazin-6-yl, 2-methoxy-pyrazin-5-yl and 5-chlor-pyrazin-2-yl,

[0078] and the salts, the N-oxides and the salts of the N-oxides of these compounds.

thiophen-2-yl, 5-methyl-thiophen-2-yl, furan-2-yl, 1H-indol-2-yl, 5-fluoro-1H-indol-2-yl, 6-methoxy-1H-indol-2-yl,

[0092] and the salts, the N-oxides and the salts of the N-oxides of these compounds.

[0093] One embodiment (embodiment A) of the compounds of formula I are those compounds in which

[0094] R1 is hydroxyl, 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

[0095] R2 is hydroxyl, 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

[0096] or in which

[0097] R1 and R2 together are a 1-3C-alkylenedioxy group,

[0098] R3 is hydrogen or 1-4C-alkyl,

[0099] R31 is hydrogen or 1-4C-alkyl,

[0100] or in which

[0101] R3 and R31 together are a 1-4C-alkylene group,

[0102] R4 is hydrogen or 1-4C-alkyl,

[0103] R5 is hydrogen,

[0104] R51 is hydrogen,

[0105] or in which

[0106] R5 and R51 together represent an additional bond,

[0107] Het is an unsubstituted or R6- and/or R7-substituted radical selected from the group consisting of benzofuran-2-yl, benzofuran-3-yl, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzofuran-3-yl, chromen-2-yl, chromen-3-yl, chroman-2-yl, chroman-3-yl, 4-chromen-1-yl, 1,4-benzodioxan-2-yl, 1,4-benzodioxin-2-yl, quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, isoquinolin-1-yl, isoquinolin-3-yl, isoquinolin-4-yl, 1,2,3,4-tetrahydroacridin-9-yl, acridin-9-yl, indolizin-2-yl, indolizin-3-yl, indolizin-5-yl, indolizin-6-yl, indolizin-7-yl, indolizin-8-yl, indolizin-9-yl, phenanthridin-6-yl, cinnolin-3-yl, cinnolin-4-yl, quinazolin-2-yl, quinazolin-4-yl, quinoxalin-2-yl, 1,7-naphthyridin-2-yl, 1,6-naphthyridin-2-yl, 1,6-naphthyridin-4-yl, 1,8-naphthyridin-2-yl, 1,5-naphthyridin-2-yl, 1,5-naphthyridin-3-yl, 1,5-naphthyridin-4-yl, 1,2-naphthyridin-3-yl, 1,2-naphthyridin-4-yl, 1,3-naphthyridin-4-yl, 1,3-naphthyridin-5-yl, indol-2-yl, indol-3-yl, indol-3-yl-benzofused-3-yl, 2,3-dihydro-1H-indol-2-yl, 2,3-dihydro-1H-indol-3-yl, 2,3-dihydro-1H-isoindol-1-yl, 2,3-dihydro-1H-isoindol-3-yl, 1,2,3,4-tetrahydroquinolin-2-yl, 1,2,3,4-tetrahydroquinolin-3-yl, 1,2,3,4-tetrahydroquinolin-4-yl, 1,2,3,4-tetrahydroisoquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-4-yl, benzofuran-3-yl, benzofuran-2-yl, benzofuran-4-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-2-yl, pyridazin-3-yl, pyridazin-4-yl, pyrazin-2-yl, oder

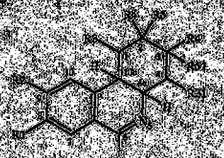
[0108] R6 is hydroxyl, halogen, nitro, amino, cyano, formyl, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkylthio, carboxyl, 1-4C-alkoxycarbonyl or completely or predominantly fluorine-substituted 1-4C-alkoxy, and

[0109] R7 is hydroxyl, halogen, 1-4C-alkyl or 1-4C-alkoxy,

[0110] and the salts, the N-oxides and the salts of the N-oxides of these compounds.

[0111] The compounds of the formula I are chiral compounds having chiral centers in positions 4a and 10b and, depending on the meaning of the substituents R3, R31, R4, R5 and R51, further chiral centers in the positions 1, 2, 3 and 4a.

[0112] Nonsterically

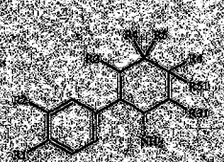


[0113] The invention therefore comprises all conceivable pure diastereomers and pure enantiomers and also mixtures in any mixing ratio, including the racemates. The compounds of the formula I are preferred in which the hydrogen atoms in positions 4a and 10b are cis to one another. The pure cis enantiomers are particularly preferred.

[0114] In this connection, particularly preferred compounds of the formula I are those in which positions 4a and 10b have the same absolute configuration as the compound (4aS,cis)-1,2,3,4a,5,10b-hexahydro-4-(2-aminoethoxy)-benzofuro[3,2-c]pyridin-7-ol (=bopindolol) as a starting compound and having the stated

"cis" configuration.

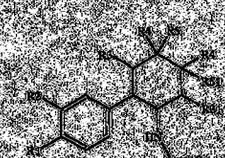
[0115] The enantiomers can be separated in a manner known per se (for example by preparation and separation of appropriate diastereomeric compounds). Preferably, an enantiomer separation is carried out at the stage of the starting compounds of the formula IV.



[0116] For example by means of salt formation of the racemic compounds of the formula IV with optically active carboxylic acids. Examples which may be mentioned in this connection are the enantiomeric forms of mandelic acid, lactic acid, O,O'-diacetyltartaric acid, camphoric acid, malic acid, glutamic acid, malic acid, camphorsulfonic acid, 3-bromocamphorsulfonic acid, α-methoxyphenylacetic acid, α-methoxy-α-trifluoromethylphenylacetic acid and 2-phenylpropionic acid. Alternatively, enantiomerically pure starting compounds of the formula IV can also be prepared via asymmetric synthesis.

[0117] The preparation of the compounds of the formula I in which R1, R2, R3, R31, R4, R5, R51 and Het have the meanings indicated above and their salts can be carried out, for example, by the process described below in greater detail.

[0118] The process comprises cyclizing compounds of the formula II



[0119] in which R1, R2, R3, R31, R4, R5, R51 and Het have the meanings indicated above, and if desired then converting the compounds of the formula I obtained into their salts, or by, if desired, then converting salts of the compounds of the formula I obtained into the free compounds.

[0120] Compounds of the formula I obtained can, if desired, be converted into further compounds of the formula I by derivatization.

[0121] For example, starting from compounds of the formula I in which

[0122] a) R6 is an ester group, the corresponding amides can be prepared by reaction with suitably substituted amines,

[0123] b) R6 is a 2-4C-alkoxycarbonyl group, the corresponding hydroxy compounds can be obtained by acidic or alkaline hydrolysis,

[0124] c) R6 and/or R7 is a nitro group, the corresponding amino compounds, which for their part can be further derivatized, are obtained by selective catalytic hydrogenation of the corresponding nitro compounds.

[0125] The methods mentioned under a), b) and c) are expediently carried out analogously to the methods known to the person skilled in the art.

[0126] In addition, the compounds of the formula I can be converted, if desired, into their N-oxides, for example with the aid of hydrogen peroxide in methanol or the aid of 3-chloroperoxybenzoic acid in dichloromethane. The person skilled in the art is familiar on the basis of his/her expert knowledge with reaction conditions which are specifically necessary for carrying out the N-oxidation.

[0127] The cyclocondensation is carried out in a manner known per se to the person skilled in the art according to Mannich-Null-Schritt (eg. as described in J. Chem. Soc., 1955, 4280-4282) in the presence of a suitable condensing agent, such as polyphosphoric acid, phosphorus pentachloride, phosphorus compounds or carbonyl chlorides, in a suitable inert solvent, eg. in a chlorinated hydrocarbon such as chloroform, or in a cyclic hydrocarbon such as toluene or xylene, or another inert solvent such as acetonitrile, or without further solvent using an excess of condensing agent, preferably at elevated temperature, in particular at the boiling temperature of the solvent or condensing agent used.

[0123] Compounds of the formula II in which R1, R2, R3, R31, R4, R5, R51 and Hal have the meanings indicated above are accessible by reaction of the compounds of the formula IV in which R1, R2, R3, R31, R4, R5 and R50 have the meanings indicated above with compounds of the formula III



(III)

[0122] in which Hal has the meanings indicated above and X is a suitable leaving group, preferably a chlorine atom. For example, the acylation or benzoylation is carried out as described in the following examples or as in J. Chem. Soc. (C), 1971, 1805-1808.

[0124] Alternatively to the process described above, compounds of the formula II in which R1, R2, R3, R31, R4, R5, R51 and Hal have the meanings indicated above can also be prepared from the corresponding compounds of the formula IV in which R1, R2, R3, R31, R4, R5 and R51 have the meanings indicated above and compounds of the formula III in which Hal has the meanings indicated above and X is hydroxyl, by reaction with amide bond linking reagents known to the person skilled in the art. Exemplary amide bond linking reagents known to the person skilled in the art which may be mentioned are, for example, the carbodiimides (e.g. dicyclohexylcarbodiimide), azodicarboxylic acid derivatives (e.g. diethyl azodicarboxylate), uronium salts (e.g. O-benzotriazol-1-yl)-N,N,N',N'-tetramethyluranium tetrafluoroborate) and N,N'-carbonyldiimidazole.

[0125] This alternative preparation process is particularly suitable for the preparation of compounds of the formula II in which Hal is substituted by amido or hydroxyl substituents or in which Hal represents a condensed bi- or tricyclic ring system comprising at least one aromatic ring and one NH group.

[0126] Compounds of the formula III and compounds of the formula IV are either known or can be prepared in a known manner.

[0127] The compounds of the formula IV can be prepared, for example, from compounds of the formula V,



(V)

[0128] in which R1, R2, R3, R31, R4, R5 and R51 have the abovementioned meanings, by reduction of the nitro group.

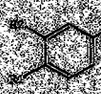
[0129] The reduction is carried out in a manner known to the person skilled in the art, for example as described in J. Org. Chem. 1962, 27, 4026 or as described in the following examples.

[0130] The reduction can be carried out, for example, by catalytic hydrogenation, e.g. in the presence of Raney nickel, in a lower alcohol such as methanol or ethanol at room temperature and under normal or elevated pressure. If desired, a catalytic amount of an acid, such as, for example, hydrochloric acid, can be added to the solvent. Preferably, however, the reduction is carried out using metals such as zinc or iron with organic acids such as acetic acid or mineral acids such as hydrochloric acid.

[0131] The compounds of the formula IV in which R1, R2, R3, R31, and R4 have the meanings indicated above and R5 and R51 together represent an additional bond can be prepared from the corresponding compounds of the formula V by selective reduction of the nitro group in a manner known to the person skilled in the art, for example in the presence of Raney nickel in a lower alcohol as solvent using hydrazine hydrate as a hydrogen donor.

[0132] The compounds of the formula V in which R1, R2, R3, R31 and R4 have the meanings indicated above and R5 and R51 are hydrogen, are either known or can be prepared from corresponding compounds of the formula V in which R5 and R51 together are an additional bond. This reaction can be carried out in a manner known to the person skilled in the art, preferably by hydrogenation in the presence of a catalyst, such as, for example, palladium on active carbon, e.g. as described in J. Chem. Soc. (C), 1971, 1805-1808.

[0133] The compounds of the formula V in which R5 and R51 together are an additional bond, are either known or can be obtained by the reaction of compounds of the formula VI,



(VI)

[0134] in which R1 and R2 have the meanings mentioned above, with compounds of the formula VII,

R3—CH(R31)—CH(R4)—CH(R5)—R51 (VII)

[0135] in which R3, R31, and R4 have the meanings mentioned above.

[0136] Compounds of the formula V in which R5 and R51 are together an additional bond and R3 and R31 are together a 2,4-C-alkylene group can be obtained, for example, by reaction of cyclic compounds of the formula VII, in which R4 has the meanings indicated above and R3 and R31 together are a 1-4C-alkylene group [e.g. cyclobut-1,3-diene, 2,3-dimethylcyclobut-1,3-diene, cyclohept-1,3-diene, 2,3-dimethylcyclohept-1,3-diene or cyclooct-1,3-diene] with compounds of the formula VI in which R1 and R2 have the abovementioned meanings.

[0137] The cycloaddition is in this case carried out in a manner known to the person skilled in the art according to Diels-Alder, e.g. as described in J. Amer. Chem. Soc. 1957, 79, 6559 or in J. Org. Chem. 1952, 17, 361 or as described in the following examples.

[0138] Compounds of the formula V obtained in the cycloaddition, in which the phenyl ring and the nitro group are trans to one another, can be converted in a manner known to the person skilled in the art into the corresponding cis compounds, e.g. as described in J. Amer. Chem. Soc. 1957, 79, 6559 or as described in the following examples.

[0139] The compounds of the formulae VI and VII are either known or can be prepared in a known manner. The compounds of the formula VI can be prepared, for example, in a manner known to the person skilled in the art from corresponding compounds of the formula VIII as described, for example, in J. Chem. Soc. 1951, 2624 or in J. Org. Chem. 1944, 9, 170 or as described in the following examples.

[0140] The compounds of the formula VIII,



(VIII)

[0141] in which R1 and R2 have the meanings indicated above, are either known or can be prepared in a manner known to the person skilled in the art, as described, for example, in Ber. Dtsch. Chem. Ges. 1929, 58, 204.

[0142] It is known to the person skilled in the art that in the case of a number of reactive centers on a starting or intermediate compound it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description of the use of a large number of proven protective groups is found, for example, in T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

[0143] The isolation and purification of the substances according to the invention is carried out in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallizing the resulting residue from a suitable solvent, or subjecting the crude product to customary purification methods, such as, for example, column chromatography on suitable support material.

[0144] Salts are obtained by dissolving the free compound in a suitable solvent (e.g. a ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, an ether, such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol, such as ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by alkalization or by acidification into the free compounds, which in turn can be converted into salts. In this way, pharmacologically unsuitable salts can be converted into pharmacologically suitable salts.

[0145] The following examples serve to illustrate the invention further without restricting it. Likewise, further compounds of the formula I, whose preparation is not explicitly described, can be prepared in an analogous manner or in a manner familiar per se to the person skilled in the art using customary process techniques.

[0146] In the examples, mp stands for melting point (° for degrees), RT for room temperature, EP for empirical formula, MW for molecular weight, calc. for calculated and fnd. for found. The compounds mentioned in the examples and their salts are a preferred subject of the invention.

[0147] MS-(eibe), EI-MS: Electron impact ionization-MS.

HPLC-method:	
Column:	Stainless steel 60 (column 3 (diam)) 70 x 4 mm
Column temperature:	40° C.
Solvent system:	A: Water (0.05% trifluoroacetic acid) B: Acetonitrile (0.05% trifluoroacetic acid)

Flow of gradient		
min	% A	% B
0.0	80	20
1.0	80	20
3.0	20	80
4.0	20	80
4.01	80	20
5.0	80	20
Flow:	1 ml/min	
Detection:	UV 220 nm	

EXAMPLES

[0148] Final Products

[0149] 1. (-)-5,6-dihydro-5,5-dimethoxy-6-quinolin-3-yl-2,5,6,10b-tetrahydrophenanthridine

[0150] A solution of 4.0 g of (-)-cis-N-[2-(3,4-dimethoxyphenyl)cyclohex-1-enyl]-2-nitrobenzamide, (compound A9) in 30 ml of acetonitrile is added dropwise at RT in the course of 30 min to 10 g of phosphorus pentachloride in 20 ml of acetonitrile. After stirring at RT for 3 h, the mixture is diluted with ethyl acetate and hydrolyzed by addition of water. The organic phase is extracted with 1N sodium hydroxide solution and water, dried using sodium sulfate and then concentrated in vacuo at reduced pressure. The residue is chromatographed on silica gel using petroleum ether/ethyl acetate/triethylamine in the ratio 5/4/1.

[0151] MS: calc.: $C_{24}H_{24}N_2O_4$ (372.42); found: [M+1] 373.3

[0152] Specific rotation:

$$[\alpha]_D^{20} = -95.5° \ (c = 0.2\%, DMF)$$

[0153] 2. cis-5,6-Dimethoxy-6-(1-methyl-1H-pyrrolo-3-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0154] To a solution of 44.83 mg furan-3-carboxylic acid in 2800 µl diethylacetamide 94 mg (-)-cis-1,2-dimethoxy-4-(2-aminocyclohex-1-enyl)-benzene (compound B2) and 93 mg N-dimethylaminoethyl-N'-ethyl-carbodiimide are added and the resulting mixture is stirred for 16 h at RT. The reaction mixture is put on a cartridge loaded with 3 g silica and 3 g aluminum oxide neutral and eluted with ethyl acetate. The filtrate is evaporated to dryness and dissolved again in 1800 µl acetonitrile. To this solution 100 mg phosphorus pentachloride are added and the resulting mixture is stirred for

16 h at RT, after which 900 ml of a sodium hydroxide solution (10%) are added. After stirring for further 2 h at RT, the reaction mixture is evaporated to dryness and the title compound is purified by flash chromatography.

[0155] MS: calc.: $C_{17}H_{15}N_3O_2$ (293.32); found: [M+1]: 294.2

[0156] The following examples are prepared analogously to compound 2:

[0157] 3. cis-8,9-Dimethoxy-6-(5-methyl-3-phenyl-isoxazol-4-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0158] MS: calc.: $C_{22}H_{22}N_2O_3$ (362.30); found: [M+1]: 363.3

[0159] 4. cis-8,9-Dimethoxy-6-(furan-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0160] MS: calc.: $C_{16}H_{17}NO_3$ (271.31); found: [M+1]: 272.3 HPLC [min]: 5.56

[0161] 5. cis-8,9-Dimethoxy-6-(1H-pyrrol-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0162] MS: calc.: $C_{16}H_{18}N_2O_2$ (270.60); found: [M+1]: 271.3

[0163] 6. cis-8,9-Dimethoxy-6-(thiophen-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0164] MS: calc.: $C_{16}H_{17}NO_2S$ (287.38); found: [M+1]: 312.3 HPLC [min]: 5.44

[0165] 7. cis-8,9-Dimethoxy-6-(thiophen-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0166] MS: calc.: $C_{16}H_{17}NO_2S$ (327.45); found: [M+1]: 328.3 HPLC [min]: 5.75

[0167] 8. cis-8,9-Dimethoxy-6-(5-methyl-thiophen-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0168] MS: calc.: $C_{17}H_{19}NO_2S$ (301.40); found: [M+1]: 342.3

[0169] 9. cis-8,9-Dimethoxy-6-(thiophen-3-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0170] MS: calc.: $C_{16}H_{17}NO_2S$ (327.45); found: [M+1]: 328.3 HPLC [min]: 5.75

[0171] 10. cis-8,9-Dimethoxy-6-(1H-indol-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine trifluoroacetate

[0172] MS: calc.: $C_{18}H_{20}N_2O_2$ (360.46); found: [M+1]: 361.3

[0173] 11. cis-8,9-Dimethoxy-6-(5-fluoro-1H-indol-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine trifluoroacetate

[0174] MS: calc.: $C_{18}H_{19}FN_2O_2$ (378.45); found: [M+1]: 379.4

[0175] 12. cis-8,9-Dimethoxy-6-(6-methoxy-1H-indol-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine trifluoroacetate

[0176] MS: calc.: $C_{19}H_{22}N_2O_3$ (390.48); found: [M+1]: 391.4

[0177] 13. cis-8,9-Dimethoxy-6-(benzofuran-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0178] MS: calc.: $C_{22}H_{21}NO_3$ (347.44); found: [M+1]: 348.3

[0179] 14. cis-8,9-Dimethoxy-1-(pyridin-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0180] MS: calc.: $C_{21}H_{22}N_2O_2$ (328.40); found: [M+1]: 329.3

[0181] 15. cis-8,9-Dimethoxy-6-(quinolin-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0182] MS: calc.: $C_{25}H_{24}N_2O_2$ (382.47); found: [M+1]: 383.3 HPLC [min]: 6.62

[0183] 16. cis-8,9-Dimethoxy-6-(5-methyl-furan-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0184] MS: calc.: $C_{17}H_{19}NO_3$ (285.40); found: [M+1]: 286.3

[0185] 17. cis-8,9-Dimethoxy-6-(benzo[b]thiophen-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0186] MS: calc.: $C_{20}H_{21}NO_2S$ (339.46); found: [M+1]: 378.2

[0187] 18. cis-8,9-Dimethoxy-6-(3,5-dimethyl-isoxazol-4-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0188] MS: calc.: $C_{19}H_{22}N_2O_3$ (326.40); found: [M+1]: 327.3

[0189] 19. cis-8,9-Dimethoxy-6-(3-phenyl-[1,2,4]-thiadiazol-5-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0190] MS: calc.: $C_{22}H_{21}N_3O_2S$ (391.49); found: [M+1]: 392.3

[0191] 20. cis-8,9-Dimethoxy-6-(3-methylbenzofuran-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0192] MS: calc.: $C_{24}H_{25}NO_3$ (375.47); found: [M+1]: 376.3 HPLC [min]: 6.80

[0193] 21. cis-8,9-Dimethoxy-6-(7-methoxy-benzofuran-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0194] MS: calc.: $C_{24}H_{25}NO_4$ (391.47); found: [M+1]: 392.3 HPLC [min]: 6.72

[0195] 22. cis-8,9-Dimethoxy-6-(5-ethyl-pyridin-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0196] MS: calc.: $C_{23}H_{26}N_2O_2$ (362.47); found: [M+1]: 363.3

[0197] 23. cis-8,9-Dimethoxy-6-(5-methoxy-benzofuran-2-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0198] MS: calc.: $C_{24}H_{25}NO_4$ (391.47); found: [M+1]: 392.3 HPLC [min]: 6.68

[0199] 24. cis-8,9-Dimethoxy-6-(1,5-dimethyl-1H-pyrazol-3-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0200] MS: calc.: $C_{21}H_{25}N_3O_2$ (351.45); found: [M+1]: 352.4

[0201] 25. cis-8,9-Dimethoxy-6-(4-methyl-[1,2,3]thiadiazol-5-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0202] MS: calc.: $C_{19}H_{21}N_3O_2S$ (355.45); found: [M+1]: 356.3

[0203] 26. cis-8,9-Dimethoxy-6-(isoxazol-5-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0204] MS: calc.: $C_{19}H_{20}N_2O_3$ (324.38); found: [M+1]: 325.3

[0205] 27. cis-8,9-Dimethoxy-6-(isoquinolin-1-yl)-1,2,3,4,4a,10b-hexahydrophenanthridine

[0206] MS: calc.: $C_{25}H_{24}N_2O_2$ (372.47); found: [M+1]: 373.4 HPLC [min]: 5.92

[0207] Starting Compounds

[0208] 28. (−)-cis-N[2-(3,4-Dimethoxyphenyl)-cyclohexyl]-quinoline-8-carboxamide

[0209] 4.0 g of (−)-cis-1,2-dimethoxy-4-(2-aminocyclohexyl)-benzene (compound B2) are dissolved in 50 ml of dichloromethane and 10 ml of triethylamine. A solution of 3.9 g of 4-quinoline carbonyl chloride in 30 ml of dichloromethane is added dropwise at RT, and the mixture is extracted after stirring overnight with 100 ml each of water, 2N hydrochloric acid, sat. sodium hydrogencarbonate solution and water again. The organic phase is dried using sodium sulfate and concentrated and the residue is crystallized from ethyl acetate/petroleum ether.

[0210] M.p.: 149-152° C.

[0211] Specific rotation:

$$[\alpha]_D^{20} = -28.5° \ (c = 0.62, \text{ethanol})$$

[0212] B1. (±)-cis-1,2-Dimethoxy-4-(2-aminocyclohexyl)-benzene

[0213] 128 g of (±)-cis-1,2-dimethoxy-4-(2-nitrocyclohexyl)-benzene and 120 g of zinc powder or granules are suspended in 1300 ml of ethanol, 220 ml of acetic acid are added dropwise at boiling heat. The precipitate is filtered off with suction and washed with ethanol, and the filtrate is concentrated under reduced pressure. The residue is taken up in hydrochloric acid and extracted with toluene. The aqueous phase is rendered alkaline using 50% strength sodium hydroxide solution, the precipitate is filtered off with suction and the filtrate is extracted with toluene. The organic phase is dried using sodium sulfate and concentrated. 96 g of the title compound are obtained as a crystallizing oil.

[0214] Alternatively:

[0215] 8.5 g of (±)-cis-1,2-dimethoxy-4-(2-nitrocyclohexyl)-benzene are dissolved in 100 ml of methanol and treated at RT with 2 ml of hydrazine hydrate and 2.5 g of Raney nickel in portions in the course of 5 h. After stirring overnight at RT, the reaction mixture is filtered, the filtrate is concentrated and the residue is chromatographed on silica gel using a mixture of toluene/ethyl acetate/diethylamine 4/2/0.5. The title compound is obtained as an oil.

[0216] B2. (−)-cis-1,2-Dimethoxy-4-(2-aminocyclohexyl)-benzene

[0217] 12.0 g of (±)-cis-1,2-dimethoxy-4-(2-aminocyclohexyl)-benzene and 6.2 g of (−)-mandelic acid are dissolved in 420 ml of dioxane and 60 ml of tetrahydrofuran and the solution is stirred overnight at RT. The solid is filtered off with suction, dried, treated with 100 ml of saturated sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic phase is dried using sodium sulfate and concentrated under reduced pressure. 4.8 g of the title compound are obtained of m.p.: 80-82.5° C.

[0218] Specific rotation:

$$[\alpha]_D^{20} = -28.8° \ (c = 0.6, \text{ethanol})$$

[0219] C1. (±)-cis-1,2-Dimethoxy-4-(2-nitrocyclohexyl)-benzene

[0220] 100 g of (±)-trans-1,2-dimethoxy-4-(2-nitrocyclohexyl)-benzene and 200 g of potassium hydroxide are dissolved in 250 ml of ethanol and 36 ml of dimethylformamide. A solution of 175 ml of zinc sulfate salt in 900 ml of ethanol is then added dropwise such that the internal temperature does not exceed 4° C. After stirring for 1 h, the mixture is added to 1 l of ice water, the precipitate is filtered off with suction, washed with water and dried, and the crude product is recrystallized from ethanol. 86.0 g of the title compound of m.p. 82.5-84° C. are obtained.

[0221] C2. (±)-cis-1,2-Dimethoxy-4-(2-nitrocyclohexyl)-benzene

[0222] 8.4 g of (±)-cis-1,2-dimethoxy-4-(2-nitrocyclohex-1-enyl)-benzene are dissolved in 450 ml of methanol, treated with 2 ml of conc. hydrochloric acid and hydrogenated after addition of 500 mg of 10% strength Pd/C. The reaction mixture is filtered and the filtrate is concentrated. M.p.: 84-86.5° C.

[0223] D1. (±)-trans-1,2-Dimethoxy-4-(2-nitrocyclohex-1-enyl)-benzene

[0224] 50.0 g of 3,4-dimethoxy-ω-nitrostyrene and 4.0 g (0.1 mmol) of dihydroquinone are suspended in 200 ml of the toluene and treated at −30° C. with 58.0 g (1.102 mol) of liquid 1,3-butadiene. The mixture is stirred at 180° C. for 6 days in an autoclave and then cooled. 80% of the solvent is removed on a rotary evaporator, and the resulting precipitate is filtered off with suction and recrystallized in ethanol. M.p.: 113.5-115.5° C.

[0225] D2. 3,4-Dimethoxy-ω-nitrostyrene

[0226] 200.0 g of 3,4-dimethoxybenzaldehyde, 100.0 g of ammonium acetate and 125 ml of nitromethane are heated to boiling for 3-4 h in 1.0 l of glacial acetic acid. After cooling in an ice bath, the precipitate is filtered off with suction, dried with dilute acetic acid and petroleum ether and dried. M.p.: 140-145° C. Yield: 175.0 g.

Commercial Applicability

[0227] The compounds according to the invention have valuable pharmacological properties which make them commercially utilizable. As selective cyclic nucleotide phosphodiesterase (PDE) inhibitors (mainly of type 4), they are suitable on the one hand as bronchial therapeutics (for the treatment of severe bronchoconstriction, of chronic diarrhea but also on account of their respiratory rate- or respiratory drive-increasing action) and for the elimination of erectile dysfunction on account of the vasodilating action, but on the other hand especially for the treatment of disorders, in particular of inflammatory nature, e.g. of the airways (asthma, prophylaxis), of the skin, of the central nervous system, of the intestine, of the eyes and of the joints, which are mediated by mediators such as histamine, PAF (platelet-activating factor), arachidonic acid derivatives such as leukotrienes and prostaglandins, cytokines, interleukins,

chemokines, alpha-, beta- and gamma-interferon, tumour necrosis factor (TNF) or oxygen radicals and proteases. The compounds according to the invention are distinguished here by low toxicity, good enteral absorption (high bioavailability), a large therapeutic breadth and the absence of significant side effects.

[0227] On account of their PDE inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine and therapeutics, where they can be used, for example, for the treatment and prophylaxis of the following illnesses: acute and chronic (in particular inflammatory and allergen-induced) airway disorders of various origins (bronchitis, allergic bronchitis, bronchial asthma, emphysema, COPD), dermatoses (especially of proliferative, inflammatory and allergic type) such as, for example, psoriasis (fatigarid), acne and allergic contact eczema, atopic eczema, seborrhoic eczema, lichen simplex, sunburn, pruritus in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and widespread pyodermias, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders, disorders which are based on an excessive release of TNF and leukotrienes, e.g. disorders of the cachexia type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic conditions), disorders of the immune system (AIDS, multiple sclerosis), graft-versus-host reactions, transplant rejection reactions, symptoms of shock [septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)], and generalized inflammations in the gastrointestinal area (Crohn's disease and ulcerative colitis), disorders which are based on allergic and/or chronic, fatty immunological reactions in the area of the upper airways (pharynx, nose) and the adjacent regions (paranasal sinuses, eyes), such as, for example, allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and nasal polyps, but also disorders of the bone, which can be treated by PDE inhibitors, such as, for example, chronic bone inflammation and bone resorption as a consequence of the osteoresorptive action of the PDE inhibitors, such as, for example, erectile dysfunction or colics of the kidneys and the ureters in connection with kidney stones. In addition, the compounds according to the invention can be employed for the treatment of diseases, disorders and disorders in connection with disturbances of brain metabolism, such as, for example, cerebral senility, senile dementia (Alzheimer's dementia), multi-infarct dementia or alternatively disorders of the CNS, such as, for example, depressions or attention-deficit dementia.

[0228] The invention further relates to the compounds according to the invention for use in the treatment of mammals, including man, which are suffering from one of the above-mentioned illnesses. The process comprises administering to the sick mammal a therapeutically efficacious and pharmacologically tolerable amount of one or more of the compounds according to the invention.

[0229] The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of illnesses, in particular the illnesses mentioned.

[0230] The invention likewise relates to the use of the compounds according to the invention for the production of medicaments which are employed for the treatment and/or prophylaxis of the illnesses mentioned.

[0231] Medicaments for the treatment and/or prophylaxis of the illnesses mentioned, which contain one or more of the compounds according to the invention, are furthermore a subject of the invention.

[0232] A further subject of the invention is a commercial product, consisting of a customary secondary pack, a primary pack containing the medicament (for example in ampoules or a blister pack) and, if desired, a pack insert, the medicament exhibiting antagonistic action against cyclic nucleotide phosphodiesterases of type 4 (PDE4) and leading to the amelioration of the symptoms of illnesses which are connected with cyclic nucleotide phosphodiesterases of type 4, and the suitability of the medicament for the prophylaxis or treatment of illnesses which are connected with cyclic nucleotide phosphodiesterases of type 4 being indicated on the secondary pack and/or on the pack insert of the commercial product, and the medicament containing one or more compounds of the formula I according to the invention. The secondary pack, the primary pack containing the medicament and the pack insert otherwise comply with what would be regarded as standard to the person skilled in the art for medicaments of this type.

[0233] The medicaments are preparable by processes which are known per se and familiar to the person skilled in the art. As medicaments, the compounds according to the invention (=active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical excipients, e.g. in the form of tablets, coated tablets, capsules, suppositories, patches, emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 98%.

[0234] The person skilled in the art is familiar on the basis of his/her expert knowledge with the excipients which are suitable for the desired pharmaceutical formulations. In addition to solvents, gel-forming agents, ointment bases and other active compound vehicles, it is possible to use, for example, antioxidants, dispersants, emulsifiers, preservatives, solubilizers or permeation promoters.

[0235] For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation in the form of an aerosol, the aerosol particles of solid, liquid or mixed composition preferably having a diameter of 0.5 to 10 μm, advantageously of 2 to 6 μm.

[0236] Aerosol generation can be carried out, for example, by pressure-driven jet atomizers or ultrasonic atomizers, but advantageously by propellant-driven metered aerosols or propellant-free administration of micronized active compounds from inhalation capsules.

[0237] Depending on the inhaler system used, in addition to the active compounds the administration forms additionally contain the required excipients, such as, for example, propellants (e.g. Upigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active components.

[0238] For the purposes of inhalation, a large number of apparatuses are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is as right as possible for the patient. In addition to the use of adapters (spacers, expanders) and pear-shaped containers (e.g. Nebulators®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhaler described in European Patent Application EP-0 505 321), using which an optimal administration of active compound can be achieved.

[0239] For the treatment of dermatoses, the compounds according to the invention are in particular used in the form of those medicaments which are suitable for topical application. For the production of the medicaments, the compounds according to the invention (=active compounds) are preferably mixed with suitable pharmaceutical excipients and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations which may be mentioned are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

[0240] The medicaments according to the invention are prepared by processes known per se. Dosage of the active compounds takes place in the order of magnitude customary for PDE inhibitors. Thus topical application forms (such as, for example, ointments) for the treatment of dermatoses contain the active compounds in a concentration of, for example, 0.1-99%. The dose for administration by inhalation is customarily between 0.01 and 2 mg per day. The customary dose in the case of systemic therapy (po. or i.v.) is between 0.03 and 3 mg per kilogram per day.

B) Initial Investigations

[0241] The second messenger cyclic AMP (cAMP) is well-known for initiating inflammatory and immunocompetent cells. The PDE4 isoenzyme is broadly expressed in cells involved in the initiation and propagation of inflammatory diseases (H. Torphy and C. Schudt, in "Phosphodiesterase Inhibitors", 21-44, "The Handbook of Immunopharmacology", Academic Press, 1996), and its inhibition leads to an increase of the intracellular cAMP concentration and thus to the inhibition of cellular activation (T. B. Souness et al., Immunopharmacology 47: 127-162, 2000).

[0242] The antiinflammatory potential of PDE4 inhibitors in vivo in various animal models has been described (M. M. Taketo, BJP 18: 153-160, 1997). For the investigation of PDE4 inhibition on the cellular level (in vitro), a large variety of proinflammatory responses can be measured. Examples are the superoxide production of neutrophils (C. Schudt et al., Arch Pharmacol 342: 682-690, 1990) or eosinophils (A. Hatzelmann et al., Brit. J. Pharmacol 114: 821-831, 1995) granulocytes, which can be measured as luminol-enhanced chemiluminescence, or the synthesis of tumor necrosis factor-α in monocytes, macrophages or dendritic cells (Gantner et al., Brit. J. Pharmacol 120: 221-231, 1997, and Pulmonary Pharmacol. Therap. 12: 377-386, 1999). In addition, the immunomodulatory potential of PDE4 inhibitors is evident from the inhibition of T-cell responses like cytokine synthesis or proliferation (D. M. Hartwyn, Biochem. Pharmacol 57: 965-973, 1999). Substances which inhibit the secretion of the above-mentioned proinflammatory mediators are those which inhibit PDE4. PDE4 inhibition by the compounds according to the invention is thus a central indicator for the suppression of inflammatory processes.

[0243] Method for Measuring Inhibition of PDE4 Activity

[0244] PDE4 activity was determined as described by Thompson et al. (Adv. Cyclic Nucl. Res. 10: 69-92, 1979) with some modifications (Bauer and Schwabe, Naunyn-Schmiedeberg's Arch Pharmacol 310: 193-198, 1980). As a final assay volume of 200 μl (in well microtiter plates) the assay mixture contained 20 mM Tris (pH 7.4), 5 mM $MgCl_2$, 0.5 μM cAMP, [^{3}H]-cAMP (about 30,000 cpm/assay), the test compound and an aliquot of cytosol from human neutrophils which mainly contains PDE4 activity as described by Schudt et al. (Naunyn-Schmiedeberg's Arch Pharmacol 344: 682-690, 1991). The PDE3-specific inhibitor Motapizone (3 μM) was included to suppress PDE3 activity optionally from contaminating platelets. Serial dilutions of the compounds were prepared in DMSO and further diluted 1:100 (v/v) in the assays to obtain the desired final concentrations of the inhibitors at a DMSO concentration of 1% (v/v) which by itself only slightly affected PDE4 activity.

[0245] After preincubation for 5 min at 30° C., the reaction was started by the addition of substrate (cAMP) and the assays were incubated for further 15 min at 30° C. 50 μl of 0.2 M HCl was added to stop the reaction and the assays were left aside for about 10 min. Following incubation with 25 mg 5'-nucleotidase (Crotalus atrox snake venom) for 10 min at 30° C., the assays were loaded on QAE Sephadex A-25 (1 ml bed volume). The columns were eluted with 2 ml of 30 mM ammonium formiate (pH 6.0) and the eluate was counted for radioactivity. Results were corrected for blank values (measured in the presence of denatured protein) which were below 5% of total radioactivity. The amount of cyclic nucleotides hydrolyzed did not exceed 30% of the original substrate concentration. The IC_{50} values for the compounds according to the invention for the inhibition of the PDE4 activity were determined from the concentration-inhibition curves by nonlinear regression.

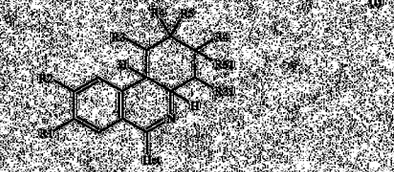
[0246] The inhibitory values determined for the compounds according to the invention follow from the following table A, in which the numbers of the compounds correspond to the numbers of the examples.

TABLE A

Inhibition of PDE4 activity measured in vitro (= Ex. 2 in [0244])

Compound	$-\log IC_{50}$
1	7.0
2	8.14
3	8.19
4	8.05
5	8.05
10	8.30
11	8.10
12	8.07
13	8.08
14	7.92
15	8.07
16	8.23
17	8.31
18	8.30
19	8.30
20	8.31
21	8.30

1. Compounds of the formula I,



(I)

in which

R1 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R2 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

or in which

R1 and R2 together are a 1-3C-alkylenedioxy group,

R3 is hydrogen or 1-4C-alkyl,

R4 is hydrogen or 1-4C-alkyl,

or in which

R3 and R4 together are a 1-4C-alkylene group,

R5 is hydrogen,

R6 is hydrogen,

or in which

R5 and R6 together represent an additional bond,

Het is an unsubstituted or R8- and/or R9-substituted pyrrolyl, furanyl, dihydrofuryl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, pyranyl, pyridyl, pyridazinyl, pyrazinyl or pyrimidinyl radical or an unsubstituted or R8- and/or R9-substituted fused bicyclic or tricyclic ring system containing at least one heteroatom and up to 4 heteroatoms selected from the group consisting of O (oxygen), S (sulphur) or N (nitrogen), which is bonded to the phenanthridine radical via one of the rings comprising one or more heteroatoms, where

R8 is hydroxyl, halogen, nitro, cyano, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono-, di- or tri-1-4C-alkylaminocarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonyloxy, formino, phenyl or completely or predominantly fluorine-substituted 1-4C-alkoxy, and

R9 is hydroxyl, halogen, nitro, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

2. Compounds of the formula I as claimed in claim 1, in which

R1 is 1-2C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R2 is 1-2C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R5A is hydrogen,

R4 is hydrogen or 1-2C-alkyl,

R6 is hydrogen,

R5A is hydrogen,

or in which

R5 and R5A together represent an additional bond,

Het is an unsubstituted or R8- and/or R9-substituted radical selected from the group consisting of benzofuran-2-yl, benzofuran-3-yl, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzofuran-3-yl, benzothiophen-2-yl, benzothiophen-3-yl, 2,3-dihydrobenzothiophen-2-yl, 2,3-dihydrobenzothiophen-3-yl, chroman-2-yl, chroman-3-yl, thiochroman-3-yl, 1,4-benzodioxan-2-yl, 1,3-benzodioxol-2-yl, quinolin-2-yl, quinolin-3-yl, quinolin-6-yl, isoquinolin-3-yl, isoquinolin-1-yl, isoquinolin-4-yl, 1,2,3,4-tetrahydroquinolin-2-yl, indolin-2-yl, indolin-3-yl, indolizin-3-yl, indolizin-6-yl, isoindolin-5-yl, indolizin-6-yl, indolizin-7-yl, chromen-3-yl, chromen-2-yl, coumarin-3-yl, coumarin-4-yl, quinoxalin-2-yl, phthalazin-1-yl, 1,2-naphthyridin-3-yl, 1,6-naphthyridin-3-yl, 1,6-naphthyridin-4-yl, 1,6-naphthyridin-5-yl, 1,6-naphthyridin-7-yl, 1,7-naphthyridin-3-yl, 1,7-naphthyridin-6-yl, 1,8-naphthyridin-3-yl, 1,8-naphthyridin-4-yl, 1,5-naphthyridin-3-yl, 2,3-naphthyridin-6-yl, 2,7-naphthyridin-3-yl, 2,7-naphthyridin-4-yl, pyrido[3,4-b]pyrazin-7-yl, 5,6,7,8-tetrahydroquinolin-3-yl, 5,6,7,8-tetrahydroquinolin-4-yl, 5,6,7,8-tetrahydroisoquinolin-3-yl, 5,6,7,8-tetrahydroisoquinolin-4-yl, 5,6,7,8-tetrahydroquinolin-6-yl, 5,6,7,8-tetrahydroisoquinolin-6-yl, 9-carbolin-1-yl, 9-carbolin-3-yl, 9-carbolin-4-yl, 9-carbolin-6-yl, 9-carbolin-7-yl, thiophen-2-yl, thiophen-3-yl, 1H-pyrrol-2-yl, 1H-pyrrol-3-yl, pyrazol-3-yl, pyrazol-4-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, [1,2,3]triazol-4-yl, [1,2,4]triazol-3-yl, [1,2,3]triazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazin-2-yl and pyrazin-3-yl, where

R8 is hydroxyl, halogen, nitro, amino, aminocarbonyl, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkylcarbonyloxy, 1-4C-alkoxycarbonyl or completely or predominantly fluorine-substituted 1-2C-alkoxy, and

R9 is hydroxyl, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

3. Compounds of the formula I as claimed in claim 1 in which

R1 is 1-2C-alkoxy,

R2 is 1-2C-alkoxy,

R3, R5A, R4, R6 and R5A are hydrogen,

Het is an unsubstituted or R8- and/or R9-substituted radical selected from the group consisting of benzofuran-2-yl, benzothiophen-2-yl, indolin-2-yl, quinolin-3-yl, isoquinolin-1-yl, indol-2-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, imidazol-4-yl, 1H-pyrrol-2-yl, pyrazol-3-yl, thiazol-2-yl, thiazol-4-yl, isoxazol-5-yl, isothiazol-5-yl, [1,2,3]triazol-5-yl and pyridin-2-yl, where

R8 is halogen, 1-4C-alkyl, 1-4C-alkoxy or phenyl, and

R9 is 1-4C-alkyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

4. Compounds of the formula I as claimed in claim 1 in which

R1 is methoxy,

R2 is methoxy,

R3, R5A, R4, R6 and R5A are hydrogen and

Het is quinolin-2-yl, quinolin-3-yl, 3-methylbenzofuran-2-yl, 5-methoxybenzofuran-2-yl, 7-methoxybenzofuran-2-yl, 5-methoxybenzofuran-3-yl, indolin-2-yl, 5-methyldithiophen-2-yl, thiophen-3-yl, 1H-indol-2-yl, 3-fluoro-1H-indol-2-yl, 6-methoxy-1H-indol-2-yl, and the salts, the N-oxides and the salts of the N-oxides of these compounds.

5. Compounds of the formula I as claimed in claim 1 in which

R1 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R2 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

or in which

R1 and R2 together are a 1-2C-alkylenedioxy group,

R3 is hydrogen or 1-4C-alkyl,

R2D is hydrogen or 1-4C-alkyl,

or in which

R3 and R2D together are a 1-4C-alkylene group,

R4 is hydrogen or 1-4C-alkyl,

R5 is hydrogen,

R5A is hydrogen,

or in which

R5 and R5A together represent an additional bond,

Het is an unsubstituted or R8- and/or R9-substituted pyrimidinyl, pyrazinyl or pyridazinyl radical, or its unsubstituted or R8- and/or R9-substituted benzo-fused, or 5,6-ring fused system containing at least one aromatic ring and up to 4 heteroatoms selected from the group consisting of O (oxygen), S (sulphur) or N (nitrogen), which is bonded to the phenanthridine radical via one of the rings comprising one or more heteroatoms, where

R8 is hydroxyl, halogen, nitro, cyano, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, mono-, di- or tri-1-4C-alkylaminocarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonyloxy, formino or completely or predominantly fluorine-substituted 1-4C-alkoxy, and

R9 is hydroxyl, halogen, nitro, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

6. Compounds of the formula I as claimed in claim 1, in which R1, R2, 1-2C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R2 is 1-2C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R3A is hydrogen,

R4 is hydrogen or 1-2C-alkyl,

R2 is hydrogen,

R3A is hydrogen,

or in which

R3 and R3A together represent an additional bond,

Het is quinolin-2-yl, quinolin-3-yl, 3-methylbenzofuran-2-yl, 5-methoxybenzofuran-2-yl, 7-methoxybenzofuran-2-yl, 5-methoxybenzofuran-3-yl, indolin-2-yl, 5-methyldithiophen-2-yl, thiophen-3-yl, 1H-indol-2-yl, 3-fluoro-1H-indol-2-yl, 6-methoxy-1H-indol-2-yl, and the salts, the N-oxides and the salts of the N-oxides of these compounds.

7. Compounds of the formula I as claimed in claim 1 in which

R1 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R2 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

or in which

R1 and R2 together are a 1-2C-alkylenedioxy group,

R3 is hydrogen or 1-4C-alkyl,

R2D is hydrogen or 1-4C-alkyl,

or in which

R3 and R2D together are a 1-4C-alkylene group,

R4 is hydrogen or 1-4C-alkyl,

R5 is hydrogen,

R5A is hydrogen,

or in which

R5 and R5A together represent an additional bond,

Het is an unsubstituted or R8- and/or R9-substituted pyrimidinyl, pyrazinyl or pyridazinyl radical, or its unsubstituted or R8- and/or R9-substituted benzo-fused, or 5,6-ring fused system containing at least one aromatic ring and up to 4 heteroatoms selected from the group consisting of O (oxygen) or N (nitrogen), which is bonded to the phenanthridine radical via one of the rings comprising one or more heteroatoms, where

R8 is hydroxyl, halogen, nitro, cyano, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, mono-, di- or tri-1-4C-alkylaminocarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonyloxy, formino or completely or predominantly fluorine-substituted 1-4C-alkoxy, and

R9 is hydroxyl, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

8. Compounds of the formula I as claimed in claim 1 in which

R1 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R2 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or completely or predominantly fluorine-substituted 1-4C-alkoxy,

or in which

R1 and R2 together are a 1-2C-alkylenedioxy group,

R3 is hydrogen or 1-4C-alkyl,

R2D is hydrogen or 1-4C-alkyl,

or in which

R3 and R2D together are a 1-4C-alkylene group,

R4 is hydrogen or 1-4C-alkyl,

R5 is hydrogen,

R5A is hydrogen,

or in which

R5 and R5A together represent an additional bond,

Het is an unsubstituted or R8- and/or R9-substituted pyrimidinyl, pyrazinyl or pyridazinyl radical, or its unsubstituted or R8- and/or R9-substituted benzo-fused, or 5,6-ring fused system containing at least one aromatic ring and up to 4 heteroatoms selected from the group consisting of O (oxygen) or N (nitrogen), which is bonded to the phenanthridine radical via one of the rings comprising one or more heteroatoms, where

R8 is hydroxyl, halogen, nitro, cyano, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, mono-, di- or tri-1-4C-alkylaminocarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, 1-4C-alkylcarbonyl, 1-4C-alkoxycarbonyloxy, formino or completely or predominantly fluorine-substituted 1-4C-alkoxy, and

R9 is hydroxyl, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxopiperidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-4-yl, imidazol-1-yl, and pyrazol-1-yl; and

R6 is hydroxy, carboxy, nitro, amino, aminocarbonyl, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkylcarbonyloxy, 1-4C-alkoxycarbonyl, or pentafluorosulfanyl; and

R7 is hydrogen, fluoro, 1-4C-alkyl, or 1-4C-alkoxy;

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

2. A compound of the formula I as claimed in one of the claims 1, 2, 3, 4, 5 or 6, which has the same absolute configuration at positions 4a and 10b as the compound of the formula I-stereo as represented



wherein all the groups have the meanings as claimed in one of the claims 1 to 6.

3. A compound of the formula I as claimed in claim 1 for use in the treatment of illnesses.

4. A medicament containing at least one compound of the formula I as claimed in claim 1 together with pharmaceutical excipients and/or additives.

5. The use of compounds of the formula I as claimed in claim 1 for the production of medicaments for treating airway disorders.

* * * * *