

No. 07-09933- -00004-0000

Fecha: 2008-04-16 16:01:21 Dep: 2020 NULCREACIONE
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Act. 400 OPOSIOBSERVTER Folios: 52

FORMULARIO ÚNICO DE OPOSICIÓN

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OPOSICIÓN A :

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

Numero del expediente: 07-09933

Solicitante: NOVARTIS AG

SOLICITUD
PUBLICADA

Apoderado: CARLOS REINALDO OLARTE GARCIA

Título de la nueva creación o denominación del signo: "METODOS PARA
MEJORAR LA BIODISPONIBILIDAD DE UN INHIBIDOR DE RENINA."

Gaceta: 587

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: <u>GYNOPHARM S.A</u>	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Numero <u>802.006.279-4</u>
	Dirección: <u>CALLE 80 No. 78B -201</u> Nacionalidad o Domicilio: <u>COLOMBIA</u> Lugar de Constitución: <u>BARRANQUILLA</u> Teléfono: <u>(571)3719900</u> Fax: <u>(571)3730818</u> E-mail: _____	
REPRESENTANTE O APODERADO	Nombre: <u>ELIANA ISAURA MORENO BOHORQUEZ</u> Dirección: <u>CARRERA 13 No. 119-95 OF 104</u> Teléfono: <u>(571)2131213</u> Fax: <u>(571)6121979</u> E-mail: <u>negocios@optimum-co.com</u>	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Numero <u>51.975.664</u> TP <u>83823</u>

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor: _____

Justificación: _____

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

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

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: _____

C.C. 51.975.664

TP. 83823

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Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 07009933
Asunto : Oposición a la solicitud de patente de Invención
titulada "MÉTODOS PARA MEJORAR LA
BIODISPONIBILIDAD DE UN INHIBIDOR DE
RENINA"
Solicitante : NOVARTIS AG.
Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 587 del 18 de enero de 2008

Yo, **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio,
identificada como aparece al pie de su firma, con tarjeta profesional No.
83823 del Consejo Superior de la Judicatura, en mi condición de
apoderada de la sociedad **GYNOPHARM S.A.** conformada bajo las leyes
de la República de Colombia y domiciliada en la ciudad de Barranquilla,
Colombia, atentamente manifiesto que estando dentro del término de ley

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y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "MÉTODOS PARA MEJORAR LA BIODISPONIBILIDAD DE UN INHIBIDOR DE RENINA", cuyo titular es NOVARTIS AG, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

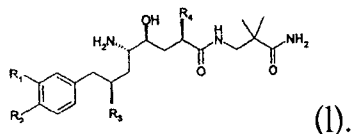
1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular Aliskiren. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

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2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 11 de julio de 2007, reivindicando prioridad bajo la solicitud US20040598700P del 2004-08-03; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 587 del 18 de enero de 2008, cuya publicación internacional corresponde a la WO2006013094 del 09/02/2006.
- 2.2. La solicitud colombiana **07009933** objeto de la presente oposición, se refiere a un método para mejorar la biodisponibilidad de un inhibidor de renina, cuyo método comprende co-administrar a un mamífero que necesite el tratamiento, una combinación de un inhibidor de renina y un inhibidor de proteínas de efusión, donde el inhibidor de renina es un derivado de amida del ácido d-amino-hidroxi-aril-alcanoico, o una sal farmacéuticamente aceptable del mismo; en donde el inhibidor de proteínas de efusión es un inhibidor de MDR1; en donde el derivado de amida del ácido d-amino-hidroxi-aril-alcanoico tiene la fórmula:



en donde R_1 es alcoxi de 1 a 4 átomos de carbono-alcoxi de 1 a 4 átomos de carbono o alcoxi de 1 a 4 átomos de carbono-alquilo de 1 a 4 átomos de carbono; y R_2 es alquilo C_{1-4} o alcoxi C_{1-4} y R_3 y R_4 son independientemente alquilo de 1 a 4 átomos de carbono ramificado; o una sal farmacéuticamente aceptable del mismo.

2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren al uso y a un método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles*

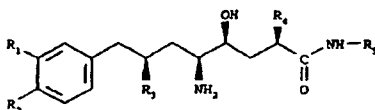
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de aplicación industrial". Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: PREFORMULATION APPROACHES TO IMPROVE THE ORAL BIOAVAILABILITY OF TWO NOVEL PIPERIDINE RENIN INHIBITORS IN DOG. Vol: 52, Nr. 8, Pagina(s): Resumen, publicado en el 2002.
- D2: WO2004002466 publicada el 8 de enero de 2004.

2.5. Ahora bien, el documento D1 revela en el resumen formulaciones experimentales basadas en sistemas acuosos y aceitosos, así como solventes acua-miscibles y dispersiones sólidas investigados para verificar el potencial de aumento de la biodisponibilidad oral (F) de inhibidores de renina piperidina [Ro-X1: (R)-1-metoxi-3-[13, 4R, 5R)-4-[4-[3-(2-metoxi-benziloxi)-propoxi] - fenilo]-5-(4-metoxi-naftalen-2-ylmetoxi)-piperidina-3-yloxi]-propan-2-ol; Ro-X2: (R)-3-[(3S, 4R, 5R)-4-[4-[3-(2-metoxi-benziloxi)-propoxi] - fenilo]-5-(4-metoxi-naftalen-2-ylmetoxi)-piperidina-3-ylmetoxi]-propano-1,2-diol) comparados a su administración como solución ácida acuosa. Esta anterioridad D1 también define que los compuestos fueron caracterizados por una solubilidad baja con un pH 7 (Ro-xi: 3 g/ml, Ro-X2: 24 g/ml) y alto

lipofílico (Ro-X1: LogP = 5.7, Ro-X2: LogP = 3.7). Según dicha anterioridad D1, para vehículos Ro-X1 a base de aceite se encontró una mejor biodisponibilidad oral comparado con la solución acuosa (F = 6 el 1.2 % $\pm$) con un mejor resultado siendo alcanzado con una solución (F = 14.6 el 3.5 % $\pm$). Por el contrario, para Ro-X2 la biodisponibilidad más alta (F = 27.1 el 8.4 % $\pm$) fue alcanzada usando una solución acuosa. También se define en esta anterioridad D1 que con base en una simulación por computador basada en los parámetros fisicoquímicos de los compuestos, sólo predijeron que la fracción del compuesto absorbido en el hombre debería ser casi cuantitativa para Ro-X2 y sólo aproximadamente el 28 % para Ro-X1. Por su parte el documento D2, revela una composición que consiste en un inhibidor de renina no peptídico y un tensoactivo aniónico. Particularmente la anterioridad D2 revela que es posible aumentar sustancialmente la biodisponibilidad de los inhibidores de renina no péptidicos de formula I,



(I)

que son fácilmente solubles en agua si se mezclan con tensioactivos aniónicos y se procesan en formas farmacéuticas de administración oral. Por lo tanto, además que la presente solicitud no puede ser objeto de monopolio toda vez que es contrario a lo que dicta la norma en materia de usos y métodos terapéuticos, tampoco es patentable dado

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que la solución propuesta es derivable de manera obvia y evidente a partir del documento D1 y D2, toda vez que a partir de estas es posible llegar a mejorar la biodipsonibilidad de la renina en combinación con un inhibidor de proteínas de afluencia.

2.6. Por lo tanto, visto dicho documento D2 en combinación con el documento D1, la presente solicitud carece evidentemente de altura inventiva.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 07009933 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

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

2.8.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”* A la fecha de prioridad, 3 de agosto de 2004, a partir del documento D2 en combinación con D1, puede llegar de

manera evidente a una combinación de un inhibidor de renina y un inhibidor de proteínas de afluencia, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación*

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industrial.". La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada "MÉTODOS PARA MEJORAR LA BIODISPONIBILIDAD DE UN INHIBIDOR DE RENINA", cuyo titular es NOVARTIS AG, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 587 del 18 de enero de 2008.

3. PRUEBAS

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

- D1: PREFORMULATION APPROACHES TO IMPROVE THE ORAL BIOAVAILABILITY OF TWO NOVEL PIPERIDINE RENIN INHIBITORS IN DOG. Vol: 52, Nr. 8, Pagina(s): Resumen, publicado en el 2002.
- D2: WO2004002466 publicada el 8 de enero de 2004.

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4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de GYNOPHARM S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

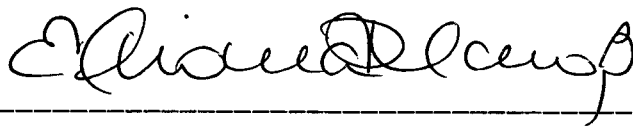
- D1: PREFORMULATION APPROACHES TO IMPROVE THE ORAL BIOAVAILABILITY OF TWO NOVEL PIPERIDINE RENIN INHIBITORS IN DOG. Vol: 52, Nr. 8, Pagina(s): Resumen, publicado en el 2002.
- D2: WO2004002466 publicada el 8 de enero de 2004.

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6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080408

Hora Certificado 11:50:55

Operacion : 02CP20408022

PAGINA No. 1

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

EN JUNIO DE ESTE AÑO SE ELEGIRÁ JUNTA DIRECTIVA DE LA CÁMARA DE COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. PARA INFORMACIÓN DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL O COMUNICARSE AL SIGUIENTE TELÉFONO: 3303911.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del libro respectivo, fue constituida la sociedad-----
anonima denominada GYNOPHARM S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
532	1999/03/25	Notaria 3a. de Barranquilla	80,373	1999/04/13

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

GYNOPHARM S.A.-----

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 16 de Dic/bre de 2047.

C E R T I F I C A

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080408 Hora Certificado 11:50:55

Operacion : 02CP20408022 PAGINA No. 2

OBJETO SOCIAL: a) La fabricacion de capsulas y otro productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario. b) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal. c) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos, medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. e) Actuar como representante o agente de personas naturales y juridicas nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualesquiera de las actividades descritas en los literales a), b), c) y d) antes transcritos. f) Prestar los servicios de asesoria y consultoria en las areas administrativa, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de GYNOPHARM S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial. g) Adquirir, operar, administrar y explotar, a cualquier titulo, empresas o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto; comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o lo de sus socios.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acci?n
Autorizado		
\$*****4,000,000,000	*****4,000,000	*****1,000

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080408

Hora Certificado 11:50:55

Operacion : 02CP20408022

PAGINA No. 4

Principales

1. Llobet Poal Manuel	CC.*****14,670,196
2. Zanatta Reheman Leonardo Andres	CC.*****2,760,271
3. Munoz Marroquin Diego	CC.*****7,688,292
4. Montealegre Gonzalez Andres Leonardo	CC.*****79,950,262

Suplentes

1. Agudelo Pelaez Luis Hernando	CC.*****14,238,997
2. Aroca Almanza Arleth Ayelina	CC.*****36,718,415
3. Penaranda Urbina Adriana Paola	CC.*****53,120,683
4. tovar Vasquez Ruth	CC.*****52,175,756

C E R T I F I C A

Que seg?n Acta No. 18 del 30 de Octubre de 2003 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificaci?n
Gerente General.	
Palacios Aragon Luis Alberto	CE.*****319,788

C E R T I F I C A

Que seg?n Acta No. 49 del 03 de Marzo de 2008 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificaci?n
Suplente del Gerente.	
Mollajoli Centurion Andres Fernando	CE.*****351,283

C E R T I F I C A

Que seg?n Acta No. 2 del 13 de Enero de 1998 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 20 de Enero de 1998 bajo el No. 73,393 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificaci?n
Revisor Fiscal Ppal.	
Barros Cera William Alberto	CC.*****8,715,941
Suplente del Revisor Fiscal.	
Duarte Diaz David	CC.*****73,115,965

C E R T I F I C A

*** CONTINUA ***



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080408

Hora Certificado 11:50:55

Operacion : 02CP20408022

PAGINA No. 5

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo el No. 1.872 del libro respectivo, consta que el señor RUBEN MINSKI GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM S.A., en el giro normal de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 12 de junio del 2.002, bajo el 2.164 del libro respectivo, consta que el señor JORGE CASTELLANOS MARTINEZ, identificado con C.C.No.19.460.089, actuando como representante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Amplio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadanía No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Camara de Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion de GYNOPHARM S.A, suscriba las declaraciones cambiarias a los que esta obligada GYNOPHARM S.A. en el giro ordinario de sus negocios y operaciones sociales.-----

C E R T I F I C A

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

C E R T I F I C A

Que su ultima Renovacion fue el: 23 de Marzo de 2007.

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

*** MATRICULA SIN RENOVAR ***

*** MATRICULA SIN RENOVAR ***

Handwritten signature

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PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **GYNOPHARM S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 07.009.933, titulada "METODOS PARA MEJORAR LA BIODISPONIBILIDAD DE UN INHIBIDOR DE RENINA", cuyo titular es **NOVARTIS AG**, publicada en la gaceta No. 587 del 18 de enero de 2008.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 07 días del mes de Abril de 2008.

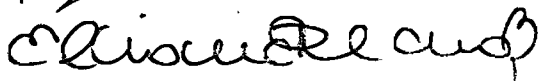
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Cédula de Extranjería: No. 319788.

NIT: 802.006.2704

Representante Legal

Acepto:



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

RECONOCIMIENTO DE DOCUMENTO PRIVADO

Ante mí, **WILMA ZAFRA TURBAY**
Veinticinco de **ABRIL** de **2008**
Identificado con cédula de **10695**
y declara que **DE 319** es suya y que al otorgar el
instrumento del mismo
Bogotá D.C.
FIRMA

10 ABR. 2008

WILMA ZAFRA TURBAY
NOTARIA VENTICINCO

PRESENTACION PERSONAL

El presente escrito fue presentado ante la
NOTARIA VENTICINCO DEL CIRCUITO DE BOGOTÁ D.C.

personalmente por **EDUARDO MORALES**

MORAN BO HONOR

quien exhibió la c.c. **8197 5664**

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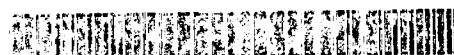
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800175089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-009933- -00004-0000

Fecha: 2008-04-16 16:01:21 Dep: 2020 NULCREACIONE
Tra: 11 PATENTEIYI Eve: 379 FASENACIONALI
Act: 400 OPOSIOBSERVTER Folios: 52RECIBO OFICIAL DE CAJA : 08 - 31,135
FECHA : ABRIL 16 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	VL. PAGO
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	1126680	16/04/2008	1,595,000.00
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	2131329	10/04/2008	795,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LEYAS COMERCIALES	266,000.00
		TOTAL :	\$ 266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

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ANEXO 1

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Courriel : inist@cat.inist.fr**Titre du document / Document title**

Preformulation approaches to improve the oral bioavailability of two novel piperidine renin inhibitors in dog

Auteur(s) / Author(s)BITTNER Beate⁽¹⁾; CHOU Ruby⁽²⁾; SCHLEIMER Michael⁽¹⁾; MORGENROTH Brita⁽¹⁾; ZELL Manfred⁽²⁾; LAVE Thierry⁽¹⁾**Affiliation(s) du ou des auteurs / Author(s) Affiliation(s)**⁽¹⁾ Pharma Division, DMPK Discovery Support, F. Hoffmann-La Roche Ltd., Basel, SUISSE⁽²⁾ Pharma Division, Preclinical Development, F. Hoffmann-La Roche Ltd., Basel, SUISSE**Résumé / Abstract**

Different experimental formulations based on aqueous and oily systems, water miscible solvents, and solid dispersions were investigated for their potential to increase the oral bioavailability (F) of two novel piperidine renin inhibitors [Ro-X1: (R)-1-methoxy-3-[(1S,4R,5R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-5-(4-methoxy-naphthalen-2-ylmethoxy)-piperidin-3-yl]oxy]-propan-2-ol; Ro-X2: (R)-3-[(1S,4R,5R)-4-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-5-(4-methoxy-naphthalen-2-ylmethoxy)-piperidin-3-yl]methoxy]-propane-1,2-diol] in dogs compared to their administration as acidic aqueous solution. The compounds were characterized by a low solubility at pH 7 (Ro-X1: 3 $\mu\text{g/ml}$; Ro-X2: 24 $\mu\text{g/ml}$) and a high lipophilicity (Ro-X1: $\text{LogP} = 5.7$; Ro-X2: $\text{LogP} = 3.7$). For Ro-X1 oil-based vehicles resulted in an improvement in the oral bioavailability compared to the aqueous solution ($F = 6 \pm 1.2\%$) with the best result being achieved with a solution in Capmul ($F = 14.6 \pm 3.5\%$). By contrast, for Ro-X2 the highest bioavailability ($F = 27.1 \pm 8.4\%$) was achieved using an aqueous solution. Computer simulations based on the physicochemical parameters of the compounds only predicted that the fraction of compound absorbed in man should be almost quantitative for Ro-X2 and only about 28% for Ro-X1. These results suggest that other factors such as extensive gut and/or hepatic metabolism as well as exclusion by intestinal transporters such as p-glycoprotein, rather than incomplete solubilization in the gut, are the major reasons for the limited oral bioavailability of both compounds.

Revue / Journal Title

Arzneimittel-Forschung ISSN 0004-4172 CODEN ARZNAD

Source / Source

2002, vol. 52, n°8, pp. 593-599 (30 ref.)

Langue / Language

Anglais

Revue : Divers

Editeur / Publisher

Cantor, Aulendorf, ALLEMAGNE (1951) (Revue)

Mots-clés anglais / English Keywords

Vertebrata; Mammalia; Carnivora; Fissipedia; Enzyme; Hydrolases; Peptidases; Aspartic endopeptidases; Oily solution; Solid dispersion; Aqueous solution; Metabolism; physicochemical property relationship; Pharmaceutical technology; Formulation; Dog; Animal; Oral administration; Distribution; Absorption; Pharmacokinetics; Inhibitor; Renin; Antihypertensive agent; Piperidine derivatives;

Mots-clés français / French Keywords

Vertebrata; Mammalia; Carnivora; Fissipedia; Enzyme; Hydrolases; Peptidases; Aspartic endopeptidases; Solution huileuse; Dispersion solide; Solution aqueuse; Relation propre

21
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Distribution ; Absorption ; Pharmacocinétique ; Inhibiteur ; Renin ; Antihypertenseur ; Pipéridine dérivé

Mots-clés espagnols / Spanish Keywords

Vertebrata ; Mammalia ; Carnivora ; Fissipedia ; Enzima ; Hydrolases ; Peptidasas ; Aspartic endopeptidasas ; Solución oleosa ; Dispersión sólida ; Solución acuosa ; Relación propiedad fisicoquímica metabolismo ; Tecnología farmacéutica ; Formulación ; Perro ; Animal ; Via oral ; Distribución ; Absorción ; Farmacocinética ; Inhibidor ; Renin ; Antihipertensivo ; Piperidina derivado ;

Localisation / Location

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N° notice refdoc (ud4) : 13843221

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
8 January 2004 (08.01.2004)

PCT

(10) International Publication Number
WO 2004/002466 A1

(51) International Patent Classification⁷: **A61K 31/195**,
31/425, 31/415, 38/55

(21) International Application Number:
PCT/EP2003/050266

(22) International Filing Date: 25 June 2003 (25.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1124/02 28 June 2002 (28.06.2002) CH

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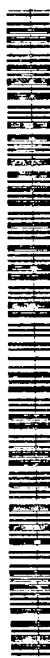
(81) Designated States (*national*): AE, AG, AI, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
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SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GI, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 2004/002466 A1

(54) Title: PHARMACEUTICAL FORMULATION COMPRISING NON-PEPTIDE RENIN INHIBITOR AND SURFACTANT

(57) Abstract: Composition comprising (1) a non-peptide renin inhibitor which is poorly soluble to readily soluble in water and (2) at least one physiologically tolerated anionic surfactant, at least one physiologically tolerated amphoteric surfactant, at least one physiologically tolerated neutral surfactant, or a mixture of at least two of these surfactants, with the quantity of readily soluble renin inhibitor being at least 10% by weight, and the quantity of a poorly soluble renin inhibitor being at least 35% by weight, based on the composition. In oral administration forms, the composition exhibits increased bioavailability.

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ANEXO 2

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PHARMACEUTICAL FORMULATION COMPRISING NON-PEPTIDE RENIN INHIBITOR AND SURFACTANT

The present invention relates to a composition consisting of a non-peptide renin inhibitor and an anionic, amphoteric or neutral surfactant, to oral administration forms comprising this composition, and to a method for improving the bioavailability of non-peptide renin inhibitors.

Non-peptide renin inhibitors are valuable compounds for treating high blood pressure, for example, and other cardiovascular diseases. A variety of these compounds have recently been disclosed. EP-A-0 716 077, WO 01/09083, WO 02/08172 and WO 02/02508 describe ω -phenyloctanecarboxamide derivatives which are very highly soluble in water. *Il Farmaco* 56 (2001), pages 21-27, describes piperidine derivatives. *Bioorganic & Medicinal Chemistry Letters* (1996) Volume 6, pages 1589-1594; *Arzneimittelforschung* (1993), 43(2a), pages 260 to 262; *Am. J. Hypertens.* (1996), 9(6), pages 517-522 and *Xenobiotica* (1996), 26(3), pages 33-345 propose imidazole derivatives. *Circulation* (1995), 91(2), pages 330-338; *Clin. Pharmacol. Ther. (St. Louis)* (1995), 57(3), pages 342-348 and *Tetrahedron* (1999), 55(15), pages 4763-4768 describe thiazole derivatives as renin inhibitors.

Although non-peptide renin inhibitors have been known for a relatively long time and possess outstanding pharmacological properties and a very high degree of activity, they have not thus far been demonstrated to be suitable for broad therapeutic application, for example for treating high blood pressure using oral administration forms. The main reason lies in the low degree of bioavailability following oral administration, as is reported by various authors in *Il Farmaco* 56 (2001), pages 21-27; *Chemistry & Biology* 2000, 7:493-504; *Clin. Pharmacokinet.* (1995), 29(1), pages 6-14 and *Pharmac. Ther.* (1994); Volume 61, pages 325-344. The low degree of oral bioavailability also still continues to restrict therapeutic application. It would therefore be extremely desirable to identify a galenic formulation which exhibits higher bioavailability and which can therefore be used to reduce the high requirement for material (high doses) in order, in this way, to provide suitable forms for oral administration. It is thereby also possible, where appropriate, to obtain an improvement in the case of active compounds which are less well tolerated in order, in this way, to make it possible to achieve a broader therapeutic application for the renin inhibitors.

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The use of surfactants as wetting agents in oral drug forms is described in the literature, for example in H. Sucker, P. Fuchs, P. Speiser, Pharmazeutische Technologie, 2nd edition, Thieme 1989, page 260. It is known from other papers, such as published in Advanced Drug Delivery Reviews (1997), 23, pages 163-183, that it is also possible to use surfactants, inter alia, to improve the permeation and bioavailability of pharmaceutical active compounds; however, this effect does not occur in the case of all active compounds and the extent of the improvement is frequently very slight.

It has now been found, surprisingly, that it is possible to substantially increase the bioavailability of both non-peptide renin inhibitors which are poorly soluble in water and such inhibitors which are particularly readily soluble in water if these inhibitors are mixed with anionic, amphoteric or neutral surfactants and processed into oral administration forms. The effect is particularly surprising in the case of water-soluble renin inhibitors since water-soluble active compounds are not as a rule formulated in combination with surfactants. The effect is also unexpectedly high, because a substantial increase of the bioavailability has been achieved. The increase of bioavailability is so important that therapeutic application is made possible in more well-tolerated doses and/or in more attractive oral dosage forms.

The invention firstly relates to a composition comprising (1) a non-peptide renin inhibitor which is of relatively high molecular weight (MW 500-800) and which is poorly soluble or readily soluble in water and (2) at least one physiologically tolerated anionic surfactant, at least one physiologically tolerated amphoteric surfactant, at least one physiologically tolerated neutral surfactant, or a mixture of at least two of these surfactants, with the quantity of readily soluble renin inhibitor being at least 10% by weight, and the quantity of a poorly soluble renin inhibitor being at least 35% by weight, based on the composition.

Within the context of the invention, readily soluble in water denotes that at least 1 g, preferably at least 30 g, and particularly preferably at least 100 g, of renin inhibitor are dissolved per 100 ml of water. Within the context of the invention, poorly soluble in water denotes that less than 1 g, preferably at most 100 mg, and particularly preferably at most 10 mg, of renin inhibitor are dissolved per 100 ml of water.

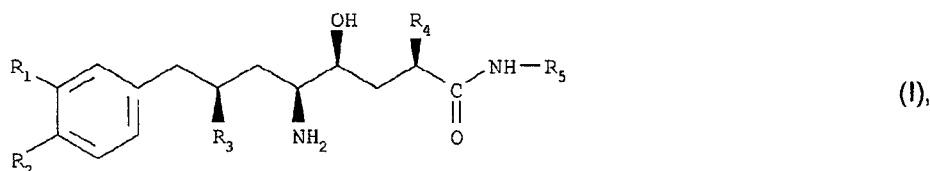
Within the context of the invention, non-peptide means that a renin inhibitor is not only composed of aminocarboxylic acids.

The quantity of readily soluble renin inhibitors can, for example, be from 10 to 90% by weight, preferably from 20 to 90% by weight, particularly preferably from 50 to 90% by weight, and in particular preferably from 60 to 90% by weight, based on the composition.

The quantity of poorly soluble renin inhibitors can, for example, be from 40 to 90% by weight, preferably from 50 to 90% by weight, particularly preferably from 60 to 90% by weight, and in particular preferably from 70 to 90% by weight, based on the composition.

Non-peptide renin inhibitors are known and are described in the literature mentioned at the outset.

ω -Phenyloctanecarboxamide derivatives are described in EP-A-0 716 077, WO 01/09083, WO 02/08172 and WO 02/02508. ω -Phenyloctanecarboxamide derivatives are preferably those of the formula I,



in which

R_1 and R_2 are, independently of each other, H, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, or C_1 - C_6 -alkoxy- C_1 - C_6 -alkyloxy, R_3 is C_1 - C_6 -alkyl, R_4 is C_1 - C_6 -alkyl, and R_5 is C_1 - C_6 -alkyl, C_1 - C_6 -hydroxyalkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, C_1 - C_6 -alkanoyloxy- C_1 - C_6 -alkyl, C_1 - C_6 -aminoalkyl, C_1 - C_6 -alkylamino- C_1 - C_6 -alkyl, C_1 - C_6 -dialkylamino- C_1 - C_6 -alkyl, C_1 - C_6 -alkanoylamido- C_1 - C_6 -alkyl, $HO(O)C$ - C_1 - C_6 -alkyl, C_1 - C_6 -alkyl- O -(O) C - C_1 - C_6 -alkyl, H_2N - $C(O)$ - C_1 - C_6 -alkyl, C_1 - C_6 -alkyl- HN - $C(O)$ - C_1 - C_6 -alkyl or $(C_1$ - C_6 -alkyl) $_2N$ - $C(O)$ - C_1 - C_6 -alkyl.

R_1 and R_2 can, as alkyl, be linear or branched and preferably contain from 1 to 4 C atoms. Examples are methyl, ethyl, n- and i-propyl, n-, i- and t-butyl, pentyl and hexyl.

R_1 and R_2 can, as haloalkyl, be linear or branched and preferably contain from 1 to 4, particularly preferably 1 or 2, C atoms. Examples are fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-chloroethyl and 2,2,2-trifluoroethyl.

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R₁ and R₂ can, as alkoxy, be linear or branched and preferably contain from 1 to 4 C atoms. Examples are methoxy, ethoxy, n- and i-propyloxy, n-, i- and t-butyloxy, pentyloxy and hexyloxy.

R₁ and R₂ can, as alkoxyalkyl, be linear or branched. The alkoxy group preferably contains from 1 to 4, and particularly 1 or 2, C atoms and the alkyl group preferably contains from 1 to 4 C atoms. Examples are methoxymethyl, 1-methoxyeth-2-yl, 1-methoxyprop-3-yl, 1-methoxybut-4-yl, methoxypentyl, methoxyhexyl, ethoxymethyl, 1-ethoxyeth-2-yl, 1-ethoxyprop-3-yl, 1-ethoxybut-4-yl, ethoxypentyl, ethoxyhexyl, propyloxymethyl, butyloxymethyl, 1-propyloxyeth-2-yl and 1-butyloxyeth-2-yl.

R₁ and R₂ can, as C₁-C₆-alkoxy-C₁-C₆-alkyloxy, be linear or branched. The alkoxy group preferably contains from 1 to 4, and particularly 1 or 2, C atoms and the alkyloxy group preferably contains from 1 to 4 C atoms. Examples are methoxymethyloxy, 1-methoxyeth-2-yloxy, 1-methoxyprop-3-yloxy, 1-methoxybut-4-yloxy, methoxypentyloxy, methoxyhexyloxy, ethoxymethyloxy, 1-ethoxyeth-2-yloxy, 1-ethoxyprop-3-yloxy, 1-ethoxybut-4-yloxy, ethoxypentyloxy, ethoxyhexyloxy, propyloxymethyloxy, butyloxymethyloxy, 1-propyloxyeth-2-yloxy and 1-butyloxyeth-2-yloxy.

In a preferred embodiment, R₁ is methoxy- or ethoxy-C₁-C₄-alkyloxy, and R₂ is preferably methoxy or ethoxy. Very particular preference is given to compounds of formula I in which R₁ is 1-methoxyprop-3-yloxy and R₂ is methoxy.

R₃ and R₄ can, as alkyl, be linear or branched and preferably contain from 1 to 4 C atoms. Examples are methyl, ethyl, n- and i-propyl, n-, i- and t-butyl, pentyl and hexyl. In a preferred embodiment, R₃ and R₄ are in each case isopropyl in the compounds of the formula I.

R₅ can, as alkyl, be linear or branched and preferably contain from 1 to 4 C atoms. Examples of alkyl have been mentioned previously. Preference is given to methyl, ethyl, n- and i-propyl, and n-, i- and t-butyl.

R₅ can, as C₁-C₆-hydroxyalkyl, be linear or branched and preferably contain from 2 to 6 C atoms. Some examples are 2-hydroxyeth-1-yl, 2-hydroxyprop-1-yl, 3-hydroxyprop-1-yl, 2-, 3- or 4-hydroxybut-1-yl, hydroxypentyl and hydroxyhexyl.

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R₅ can, as C₁-C₆-alkoxy -C₁-C₆-alkyl, be linear or branched. The alkoxy group preferably contains from 1 to 4 C atoms and the alkyl group preferably contains from 2 to 4 C atoms. Some examples are 2-methoxyeth-1-yl, 2-methoxyprop-1-yl, 3-methoxyprop-1-yl, 2-, 3- or 4-methoxybut-1-yl, 2-ethoxyeth-1-yl, 2-ethoxyprop-1-yl, 3-ethoxyprop-1-yl, and 2-, 3- or 4-ethoxybut-1-yl.

R₅ can, as C₁-C₆-alkanoyloxy-C₁-C₆-alkyl, be linear or branched. The alkanoyl group preferably contains from 1 to 4 C atoms and the alkyl group preferably contains from 2 to 4 C atoms. Some examples are formyloxymethyl, formyloxyethyl, acetyloxyethyl, propionyloxyethyl and butyroyloxyethyl.

R₅ can, as C₁-C₆-aminoalkyl, be linear or branched and preferably contain from 2 to 4 C atoms. Some examples are 2-aminoethyl, 2- or 3-aminoprop-1-yl and 2-, 3- or 4-aminobut-1-yl.

R₅ can, as C₁-C₆-alkylamino-C₁-C₆-alkyl and C₁-C₆-dialkylamino-C₁-C₆-alkyl, be linear or branched. The alkylamino group preferably contains C₁-C₄-alkyl groups and the alkyl group preferably contains from 2 to 4 C atoms. Some examples are 2-methylaminoeth-1-yl, 2-dimethylaminoeth-1-yl, 2-ethylaminoeth-1-yl, 2-diethylaminoeth-1-yl, 3-methylaminoprop-1-yl, 3-dimethylaminoprop-1-yl, 4-methylaminobut-1-yl and 4-dimethylaminobut-1-yl.

R₅ can, as C₁-C₆-alkanoylamido-C₁-C₆-alkyl, be linear or branched. The alkanoyl group preferably contains from 1 to 4 C atoms and the alkyl group preferably contains from 1 to 4 C atoms. Some examples are 2-formamidoeth-1-yl, 2-acetamidoeth-1-yl, 3-propionylamidoeth-1-yl and 4-butyroylamidoeth-1-yl.

R₅ can, as HO(O)C-C₁-C₆-alkyl, be linear or branched and the alkyl group preferably contains from 2 to 4 C atoms. Some examples are carboxymethyl, carboxyethyl, carboxypropyl and carboxybutyl.

R₅ can, as C₁-C₆-alkyl-O-(O)C-C₁-C₆-alkyl, be linear or branched, and the alkyl groups preferably contain, independently of each other, from 1 to 4 C atoms. Some examples are methoxycarbonylmethyl, 2-methoxycarbonyleth-1-yl, 3-methoxycarbonylprop-1-yl, 4-methoxycarbonylbut-1-yl, ethoxycarbonylmethyl, 2-ethoxycarbonyleth-1-yl, 3-ethoxycarbonylprop-1-yl and 4-ethoxycarbonylbut-1-yl.

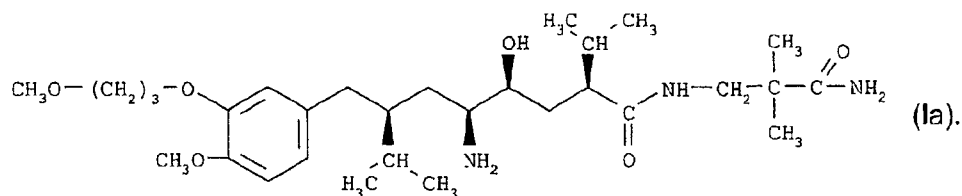
R_5 can, as $H_2N-C(O)-C_1-C_6$ -alkyl, be linear or branched, and the alkyl group preferably contains from 2 to 6 C atoms. Some examples are carbamidomethyl, 2-carbamidoeth-1-yl, 2-carbamido-2,2-dimethyleth-1-yl, 2- or 3-carbamidoprop-1-yl, 2-, 3- or 4-carbamidobut-1-yl, 3-carbamido-2-methylprop-1-yl, 3-carbamido-1,2-dimethylprop-1-yl, 3-carbamido-3-methylprop-1-yl, 3-carbamido-2,2-dimethylprop-1-yl, 2-, 3-, 4- or 5-carbamidopent-1-yl, or 4-carbamido-3,3- or -2,2-dimethylbut-1-yl.

R_5 can, as C_1-C_6 -alkyl- $HN-C(O)-C_1-C_6$ -alkyl or $(C_1-C_6$ -alkyl) $_2N-C(O)-C_1-C_6$ -alkyl, be linear or branched, and the NH -alkyl group preferably contains from 1 to 4 C atoms, and the alkyl group preferably contains from 2 to 6 C atoms. Examples are the previously mentioned carbamidoalkyl groups whose N atom is substituted by one or two methyl, ethyl, propyl or butyl.

A preferred subgroup of compounds of formula I is formed by those in which R_1 is C_1-C_4 -alkoxy or C_1-C_4 -alkoxy- C_1-C_4 -alkyloxy, R_2 is C_1-C_4 -alkoxy, R_3 is C_1-C_4 -alkyl, R_4 is C_1-C_4 -alkyl and R_5 is optionally N-mono- or N-di- C_1-C_4 -alkyl-substituted $H_2NC(O)-C_1-C_6$ -alkyl.

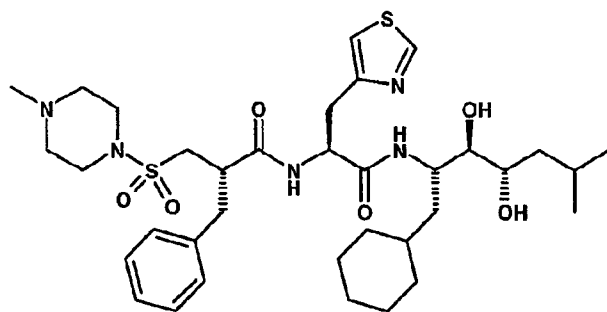
A more preferred subgroup of compounds of the formula I is formed by those in which R_1 is methoxy- C_2-C_4 -alkyloxy, R_2 is methoxy or ethoxy, R_3 is C_2-C_4 -alkyl, R_4 is C_2-C_4 -alkyl and R_5 is $H_2NC(O)-C_1-C_6$ -alkyl.

The ω -phenyloctanecarboxamide derivative which is very particularly preferred is the compound of the formula Ia,



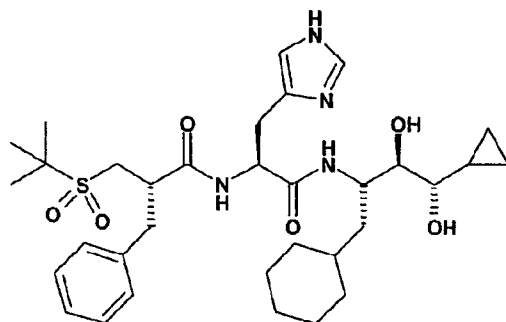
The compound of the formula (A), which is also known as Zankiren, may be mentioned as a representative of thiazole derivatives:

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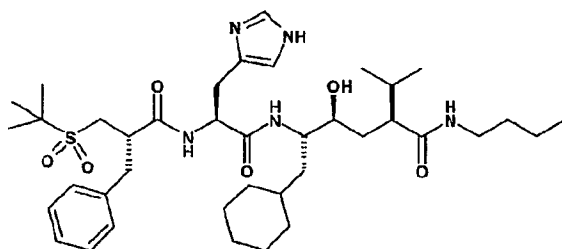
(A).

The compound of the formula (B), which is also known as Remikiren, may be mentioned as a representative of imidazole derivatives:



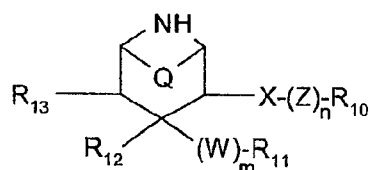
(B).

Another representative of imidazole derivatives is the compound of the formula (C):



(C).

Representatives of a piperidine derivative which may be mentioned are compounds of formula D (see also WO 00/64873, WO 00/64887 and WO 97/09311),



(D),

in which

R_{10} is aryl or heteroaryl or heterocycloalkyl or heterocycloalkenyl, and

R_{11} is phenyl, naphthyl, acenaphthyl, cyclohexyl, pyridyl, pyrimidyl, pyrazinyl, oxopyridinyl, diazinyl, triazolyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, pyrrolyl or furyl which are unsubstituted or substituted by from one to three halogen, hydroxyl, cyano, trifluoromethyl, lower alkyl, halo-lower alkyl, hydroxyl-lower alkyl, lower alkoxy-lower alkyl, cyano-lower alkyl, carboxyl-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-carbonyloxy-lower alkyl, lower alkoxy-carbonyl or lower alkoxy groups or a lower alkylendioxy group, and/or by a radical $L_1-T_1-L_2-T_2-L_3-T_3-L_4-T_4-L_5-U$;

L_1 , L_2 , L_3 , L_4 and L_5 are, independent of each other, a bond, C_1-C_8 -alkylene, C_2-C_8 -alkenylene or C_2-C_8 -alkynylene, or are absent;

T_1 , T_2 , T_3 , T_4 and T_5 are, independent of each other,

(a) a bond or are absent or are one of the groups

(b) $-CH(OH)-$

(c) $-(CHOR_{15})-$

(d) $-(CHNR_{14}R_{15})-$

(e) $-CO-$

(f) $-CR_{16}R_{17}-$

(g) $-O-$ oder $-NR_{15}-$

(h) $-S(O)_{0-2}$

(i) $-SO_2NR_{15}-$

(j) $-NR_{15}SO_2-$

(k) $-CONR_{15}-$

(l) $-NR_{15}CO-$

(m) $-O-CO-$

(n) $-CO-O-$

(o) $-O-CO-O-$

(p) $-O-CO-NR_{15}-$

(q) $-NR_{15}-CO-NR_{15}-$

(r) $-NR_{15}-CO-O-$,

where the bonds issuing from (b), (d), (e) and (g) to (r) lead to a C atom of the adjacent group and this C atom is saturated if the bond issues from a heteroatom and where not more than two groups (b) to (f), three groups (g) to (h) and one group (i) to (r) are present;

R_{12} is hydrogen, hydroxyl, lower alkoxy or lower alkenyloxy;

R_{13} is hydrogen, lower alkyl, lower alkenyl, lower alkoxy, hydroxy-lower alkyl, benzyl, oxo or a group $R_{18}-Z_1-X_{1-}$, where R_{18} is

- (a) H-
- (b) lower alkyl
- (c) lower alkenyl
- (d) hydroxyl-lower alkyl
- (e) polyhydroxyl-lower alkyl
- (f) lower alkyl-O-lower alkyl
- (g) aryl
- (h) heteroaryl or heterocycloalkyl or heterocycloalkenyl
- (i) aralkyl
- (j) heteroaryl- or heterocycloalkyl- or heterocycloalkenyl-lower alkyl
- (k) aryloxy-lower alkyl
- (l) heteroaryloxy- or heterocycloalkyloxy- or heterocycloalkenyloxy-lower alkyl
- (m) $R_{14}R_{15}N-(CH_2)_{1-3}$
- (n) $R_{14}R_{15}N-$
- (o) lower alkyl-S(O)₀₋₂-
- (p) aryl-S(O)₀₋₂-
- (q) heteroaryl-S(O)₀₋₂- or heterocycloalkyl-S(O)₀₋₂- or heterocycloalkenyl-S(O)₀₋₂-
- (r) HO-SO₃- or its salts
- (s) H₂N-C(NH)-NH-
- (t) NC-

and the bonds issuing from (n) to (t) lead to a C atom of the adjacent groups and this C atom is saturated if the bond issues from a heteroatom;

Z_1 is

- (a) a bond, is absent or is one of the groups
- (b) lower alkylene
- (c) lower alkenylene
- (d) -O-, -NR₁₉- or -S(O)₀₋₂
- (e) -CO-
- (f) -CO-O-

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(g) $-O-CO-O-$ (h) $-O-CO-NR_{19}-$ (i) $-NR_{19}-CO-O-$ (j) $-O-CO-NR_{19}-$ (k) $-NR_{19}-CO-$ (l) $-NR_{19}-CO-NR_{19}-$ (m) $-CH(OR_{20})-$

and the bonds issuing from (d) and (f) to (m) lead to a C atom of the adjacent group and this C atom is saturated if the bond issues from a heteroatom;

X_1 is

(a) a bond, is absent or is one of the groups

(b) $-O-$

(c) $-NR_{19}-$

(d) $-S(O)_{0-2}-$

(e) $-(CH_2)_{1-3}-$;

or R_{12} and R_{13} are together a bond;

R_{14} and R_{15} are hydrogen, lower alkyl, lower alkenyl, aryl-lower alkyl or acyl, or, together with the N atom to which they are bonded, are a five-membered or six-membered heterocyclic ring which can contain an additional N, O or S atom, with the additional N atom optionally being substituted by lower alkyl;

R_{16} and R_{17} , together with the C atom to which they are bonded, are a three-membered to seven-membered ring which can contain one or two O or S atoms or $-O-$ or $-SO_2-$ groups;

R_{19} is hydrogen or lower alkyl;

R_{20} is hydrogen, lower alkyl, acyl or aralkyl;

R_{21} is carboxyalkyl, alkoxycarbonylalkyl, alkyl or hydrogen;

U is hydrogen, lower alkyl, cycloalkyl, cyano, optionally substituted cycloalkyl, aryl, heteroaryl or heterocycloalkyl or heterocycloalkenyl;

Q is ethylene or is absent,

X is a bond, oxygen, sulfur or groups $-CH-R_{19}-$, $-CHOR_{20}$, $-O-CO-$, $-CO-$ or $-C=NOR_{21}$; where the bond issuing from an oxygen atom or sulfur atom leads to a saturated C atom of the group Z or to R_{10} ;

W is oxygen or sulfur;

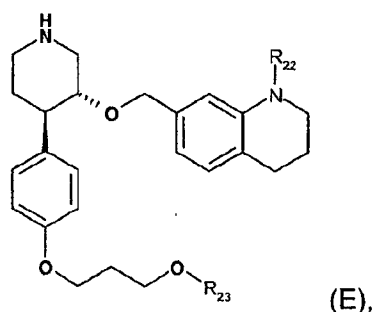
Z is lower alkylene, lower alkenylene, hydroxyl-lower alkylidene, $-O-$, $-S-$, $-O-Alk-$, $-S-Alk-$, $-Alk-O-$ or $-Alk-S-$, where Alk is lower alkylene; and where

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- a) if Z is -O- or -S-, X is -CH-R₁₉- and either R₁₁ contains a substituent L₁-T₁-L₂-T₂-L₃-T₃-L₄-T₄-L₅-T₅-U or R₁₃ is a substituent which is defined as above and which is different from hydrogen;
- b) if Z is -O-Alk- or -S-Alk-, X is -CH-R₁₉-; and
- c) if X is a bond, Z is lower alkylene, lower alkenylene, -Alk-O- or -Alk-S-;
- n is 1 or, if X is -O-CO-, is 0 or 1;
- m is 0 or 1;
- and pharmaceutically utilizable salts thereof.

The term "lower" denotes a content of from 1 to 6, and preferably from 1 to 4, C atoms.

A preferred subgroup of the compounds of the formula D is formed by those of the formula E



in which

R₂₂ is

- (a) -(CH₂)_k-NR₂₄R₂₅ and k is 2, 3 or 4;
- (b) -(CH₂)_k-OR₂₄ and k is 2, 3 or 4;
- (c) -(CH₂)_m-OR₂₆ and m is 1 or 2; or
- (d) -(CH₂)_l-R₂₇ and l is 1, 2 or 3;

R₂₃ is cycloalkyl-lower alkyl, 1,1,1-trifluoroethyl, phenyl or benzyl, or phenyl or benzyl which is substituted by one to three halogen, cyano, C₁-C₃-alkoxy or nitro;

R₂₄ is hydrogen or C₁-C₃-alkyl;

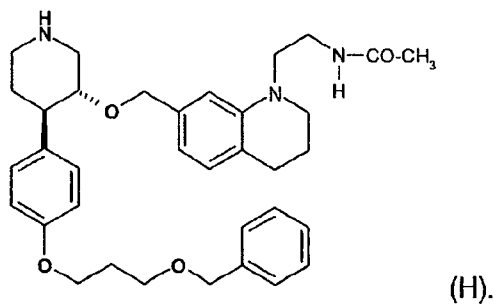
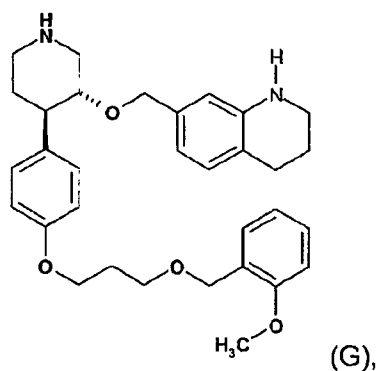
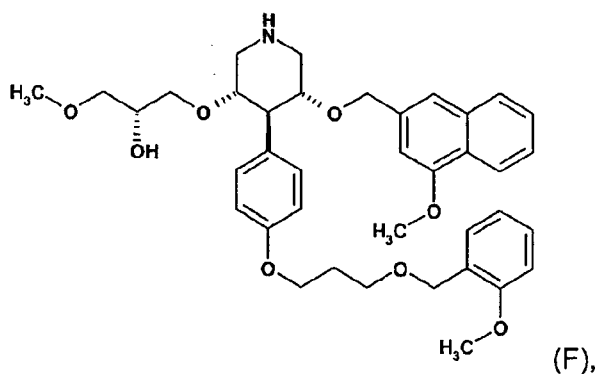
R₂₅ is hydrogen, C₁-C₃-alkyl, C₁-C₃-alkylsulfonyl, aminosulfonyl, C₁-C₃-alkylaminosulfonyl, C₁-C₃-alkylaminocarbonyl, C₁-C₃-alkylcarbonyl, trifluoromethylcarbonyl, trifluoromethylsulfonyl or aminocarbonyl;

R₂₆ is C₁-C₃-alkoxycarbonyl, aminocarbonyl, C₁-C₃-alkylaminocarbonyl, di-C₁-C₃-alkylamino-carbonyl or cyano;

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R₂₇ is imidazolyl or triazolyl, with the proviso that l is 2 or 3 when imidazolyl or triazolyl is bonded by way of a C-N bond;
and pharmaceutically utilizable salts thereof.

Some specific examples are piperidine derivatives of the formulae F, G and H:



The compounds of the formulae A to H, I and Ia can also be present as salts, for example of monocarboxylic or dicarboxylic acids. Particular preference is given to hemifumarates and succinates. (The hemifumarate of the formula Ia is termed SPP100B below. The succinate of the formula F is termed SPP500A below).

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The renin inhibitors are relatively large molecules. The compounds of formulae A to H are poorly soluble in water; by contrast, ω -phenyloctanecarboxamide derivatives, particularly of the formula Ia, are very readily soluble in water. All these properties suggest low oral bioavailability.

Physiologically tolerated anionic and neutral surfactants are known as auxiliary substances in oral formulations of pharmaceutical active compounds and are listed, for example, in the American Code of Federal Regulations Title 21 (Food and Drugs), revised 1 April 2001.

Anionic surfactants are widely known. They are mainly organic acids and their physiologically tolerated salts, such as alkali metal salts (Na or K) or alkaline earth metal salts (Mg or Ca) which contain a hydrophobic substituent. Examples of suitable acids are carboxylic acids, sulfonic acids, sulfinic acids, phosphonic acids, phosphonous acids, sulfuric acid monoesters, monoesters of sulfurous acid, phosphoric acid monoesters or diesters and monoesters or diesters of phosphorous acid, and also sulfated unsaturated carboxylic acid esters. Preferred acids are sulfated unsaturated carboxylic acid esters, sulfonic acids, phosphonic acids, sulfuric acid monoesters and phosphoric acid monoesters or diesters. Particular preference is given to sulfuric acid monoesters, dialkyl sulfosuccinates and phosphoric acid monoesters or diesters.

The acids preferably contain saturated or unsaturated hydrocarbon radicals having at least 6, preferably at least 8, C atoms and up to 30, preferably up to 20, C atoms. The hydrocarbon radicals can be interrupted by O, S, CO, -C(O)-O- and/or -C(O)-NH-, and/or be unsubstituted or substituted by -OH, -O-C₁-C₂₀-alkyl, -NH-C(O)-C₁-C₂₀-alkyl and/or -O-C(O)-C₁-C₂₀-alkyl. The hydrocarbon radicals can be selected from the group linear and branched alkyl, C₁-C₂₀-alkyl-substituted C₅-C₁₂-cycloalkyl and preferably C₅-C₈-cycloalkyl, C₁-C₂₀-alkyl-substituted C₆-C₁₀-aryl and C₅-C₁₂-cycloalkyl-substituted or C₈-C₃₀-polycycloalkyl-substituted C₁-C₂₀-alkyl. Polycycloalkyl preferably means condensed ring systems as can be found in the naturally occurring steroid and bile acids.

The anionic surfactant can correspond to the formulae II and IIa,



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in which R is a saturated or unsaturated hydrocarbon radical having from 6 to 30 C atoms which is optionally interrupted by -O-, -S-, -CO-, -C(O)-O- and/or -C(O)-NH-, and/or is unsubstituted or substituted by -OH, -O-C₁-C₂₀-alkyl, -NH-C(O)-C₁-C₂₀-alkyl and/or -O-C(O)-C₁-C₂₀-alkyl, R₆ is C₂-C₄-alkylene and X is -SO₃H, -COOH or -OSO₃H, and also their sodium, potassium, magnesium and calcium salts. Examples of surfactants of the formula II are C₆-C₂₀-monoalkyl sulfates such as octyl sulfate, decyl sulfate, dodecyl sulfate, tetradecyl sulfate, hexadecyl sulfate and octadecyl sulfate, and also salts of fatty acids (Na oleate or Na caprate). Examples of surfactants of the formula IIa are 1-acylaminoethane-2-sulfonic acids, such as 1-octanoylaminoethane-2-sulfonic acid, 1-decanoylaminoethane-2-sulfonic acid, 1-dodecanoylaminoethane-2-sulfonic acid, 1-tetradecanoylaminoethane-2-sulfonic acid, 1-hexadecanoylaminoethane-2-sulfonic acid, and 1-octadecanoylaminoethane-2-sulfonic acid, and taurocholic acid and taurodeoxycholic acid. Bile acids and their salts, such as cholic acid, deoxycholic acid and sodium glycocholates, are also suitable.

Other suitable anionic surfactants are semiesters composed of polycarboxylic acids, such as malonic acid, succinic acid, glutaric acid, adipic acid, maleic acid and fumaric acid, and C₆-C₂₀-alkanols or C₆-C₂₀-alkenols, and their salts, for example sodium stearylsuccinate.

Particularly preferred anionic surfactants are alkali (alkaline earth) metal salts of saturated fatty acids such as sodium caprate or sodium laurate and unsaturated fatty acids, such as sodium oleate as well as alkyl sulfates, such as sodium lauryl sulfate and sodium cetyl sulfate. Other examples of particularly preferred compounds are sulfated castor oil and sodium dioctylsulfosuccinate.

Amphoteric surfactants are also suitable; among these, preference is given to natural or modified lecithins and phospholipids. The lecithins can be natural, partially hydrogenated or hydrogenated lecithins or sphingolipids. Natural lecithins are mixtures of different phospholipids. Examples of phospholipids are phosphatidylcholine, phosphatidyl ethanolamine, lysophosphatidyl choline, phosphatidyl glycerol, phosphatidic acid and phosphatidyl serine and their partially hydrogenated or completely hydrogenated derivatives. Examples of phospholipids containing defined fatty acids are 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dioleoyl-sn-glycero-3-phosphocholine, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, 1,2-dimyristoyl-sn-glycero-3-phospho-rac-glycerol, 1,2-dipalmitoyl-sn-

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glycero-3-phospho-rac-glycerol and 1,2-distearoyl-sn-glycero-3-phospho-rac-glycerol. Preference is given to using lecithin and phosphatidyl choline

Examples of other known amphoteric surfactants are N-mono- or -dialkylated aminocarboxylic acids (betaines), with it being possible for the alkyl group to contain from 6 to 30, preferably from 8 to 20, C atoms. Examples are cocamidopropylbetaine and laurylbetaine (Amphoteen® 24). Other amphoteric surfactants are known from the class of the aminocarboxylic acids and their salts, and also as derivatives of imidazolines.

Natural lecithin is a preferred amphoteric surfactant.

Neutral surfactants are also known. These can, for example, be fatty alcohols and cholesterol, which are frequently used in combination with alkyl sulfates or polyethylene glycol monoalkyl esters.

Other known surfactants are monoesters or diesters composed of glycerol and C₈-C₃₀-carboxylic acids, in particular fatty acids, for example glycerol mono- or -distearate, glycerol mono- or -dioleate and glycerol mono- or -dipalmitate. Another group are ethoxylated partial fatty acid esters composed of polyols, such as ethylene glycol, propylene glycol, glycerol or pentaerythritol, and optionally hydrogenated polyoxy castor oils which can be obtained commercially as Chremophors®. Chremophor® EL and Chremophor® RH40 are preferred surfactant types.

Suitable neutral surfactants are also partial fatty acid esters of sorbitan which can be obtained commercially as SPAN® or ARLACEL®, and also partial fatty acid esters of sucrose.

Other suitable surfactants are fatty acid esters of polyols, such as ethylene glycol or pentaerythritol or polyethylene glycols, such as polyoxyethylene stearate, which esters can be obtained commercially in various types, for example as Myrj®.

Known neutral surfactants are also fatty alcohol ethers of polyoxyethylene, for example lauryl-, myristyl-, cetyl- and oleylpolyoxyethylene ethers. These can be obtained commercially in various types, for example as Brij®.

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Sorbitan-based ethoxylated partial fatty acid esters are also known to be surfactants, with these surfactants being termed polysorbates and being offered for sale commercially in various types, for example as TWEEN®

Finally, polyethylene polypropylene glycols should also be mentioned. These surfactants are block copolymers containing blocks composed of polyoxyethylene and polyoxypropylene, with these block copolymers being termed poloxamers and being available commercially as Pluronic®. The blocks can be of varying chain length and the substances can be liquid to solid. Polyoxyethylene blocks can, for example, contain from 5 to 120, preferably from 10 to 100, oxyethylene units and polyoxypropylene blocks can contain from 10 to 80, and preferably from 10 to 50, oxypropylene units. The chain lengths of the blocks and the molecular weight of the substance can be used to achieve desired properties in a selective manner. Poloxamers 124, 188 and 407 are preferred examples.

Preferred neutral surfactants are block copolymers composed of polyoxyethylene and polyoxypropylene, partial fatty acid esters of sorbitan, ethoxylated partial fatty acid esters of sorbitan, fatty alcohol ethers and fatty acid esters of polyoxyethylenes and hydrogenated, polyethoxylated castor oils.

Suitable surfactants are described, for example, in pharmacopoeias such as USP25/NF20 or can be identified from the literature, in this present case for example, from Martindale, thirty-second edition 1999, pages 1324-1329 and 1468-1469.

The composition according to the invention can be produced in a simple manner by mixing the components. The composition can be liquid to oily, semisolid or solid. The consistency of the composition depends essentially on the choice of surfactant or combination of surfactants and the quantitative composition. Known methods for mixing the components are dry mixing of pulverulent components, melting methods, and solution methods, involving dissolving the components and subsequently removing the solvents.

Solvents are expediently selected such that they can be removed virtually completely. Suitable solvents are water and organic solvents, particularly polar organic solvents, which can also be used as mixtures of at least two solvents. Examples of pharmaceutically customary solvents are halohydrocarbon (methylene chloride); ketones (acetone); alcohols

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(methanol, ethanol, n- or i-propanol, or n- or i-propanediol); nitriles (acetonitrile); and tertiary amines (N-methylpyrrolidine).

Because of its increased bioavailability, the composition according to the invention is outstandingly suitable for producing forms for oral administration. Because of the increased bioavailability, it is possible to provide doses which are physiologically harmless as far as the active compound and surfactant are concerned.

The invention also relates to an oral dosage form which comprises a composition according to the invention.

Examples of oral dosage forms are tablets or sugar-coated tablets, capsules composed of hard or soft gelatin or starch, and potable preparations.

Depending on the intended therapy, i.e. single or repeated consecutive and chronologically delayed administration, the oral administration form can comprise a renin inhibitor in quantities of from 10 to 600 mg, preferably of from 30 to 300 mg, and in particular of from 50 to 200 mg.

The skilled person is familiar with the production of tablets, sugar-coated tablets, capsules and potable preparations and the auxiliary substances which are required for this purpose.

Potable preparations principally comprise water. In addition, they can comprise physiologically tolerated solvents, for example alkanols such as ethanol. Customary thickeners can be used in order to stabilize suspensions.

Capsules can be filled directly with the composition according to the invention. However, the composition of the material which is used to fill the capsules can also comprise customary pharmaceutical auxiliary substances such as fillers, binders, disintegrants, lubricants and flavourings.

It is possible to use customary auxiliary substances, such as binders, fillers, lubricants and flavourings, for formulating tablets and sugar-coated tablets. These auxiliary substances are known and are therefore not described in detail.

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All the solid administration forms can be provided with a coating of any given functionality. Pharmaceutically customary auxiliary substances, such as semisynthetic or fully synthetic film-forming agents, and suitable additives, such as plasticizers and dye pigments, have also to be provided for this purpose.

The invention also relates to a method for increasing the bioavailability of non-peptide renin inhibitors which is characterized in that the said renin inhibitor is mixed with at least one physiologically tolerated anionic surfactant or at least one physiologically tolerated neutral or amphoteric surfactant or with a mixture consisting of at least two of these surfactants.

The composition according to the invention makes it possible to produce oral forms for administering renin inhibitors which, because of an increased bioavailability, can be used for higher dosages and are practical for a patient.

The following examples explain the invention in more detail.

A) Producing compositions

Example A1: Producing a powder mixture

75 g of SPP100B and 75 g of sodium lauryl sulfate are weighed into a mixing box and mixed for 10 minutes in a Turbula mixer. The resulting mixture is brushed through a sieve having a mesh aperture of 0.5 mm. The sieve mixture is then once again agitated for 10 minutes in the Turbula mixer.

The desired quantities of these powders are apportioned and aliquoted, for example, into bottles. Prior to administration, the preparation is dissolved in water or another suitable physiologically well-tolerated liquid.

Example A2: Producing a powder mixture

75 g of SPP500A and 75 g of sodium laurate are weighed into a mixing box and mixed for 10 minutes in a Turbula mixer. The resulting mixture is brushed through a sieve having a mesh aperture of 0.5 mm. The sieved mixture is finally agitated once again in the Turbula mixer for 10 minutes.

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The desired quantities of these powders are apportioned and aliquoted, for example, into bottles. Prior to administration, the preparation is suspended or dissolved in water or another suitable physiologically well-tolerated liquid.

Example A3: Melting method

100 g of Poloxamer 188 are weighed into a glass flask and melted at 70°C in a waterbath. 25 g of SPP500A are added to the melt. This mixture is cooled while being stirred continuously and then suitably comminuted. Portions depending on the dose are packaged into suitable receptacles or processed into oral administration forms.

Example A4: Solution method

75 g of SPP100B are kneaded with 7.5 g of sorbitan monooleate and 15 g of Polysorbat 80, dissolved in 15 ml of 99% ethanol. The resulting mass is dried at 50°C in vacuo until a constant weight is reached. Portions depending on the dose are packaged into suitable receptacles or processed to produce oral administration forms.

B) Producing oral administration forms

Example B1: Producing hard gelatin capsules

One capsule contains:

SPP100B	83 mg
Microcrystalline cellulose	95 mg
Crospovidone (a polyvinylpyrrolidone)	26 mg
Colloidal silicon dioxide	2 mg
Sodium lauryl sulfate	30 mg
Magnesium stearate	4 mg

The active compound, the filler, the disintegrant, the flow regulating agent and the surfactant are mixed in one operational step. The mixture is sieved and mixed once again in the dry. Finally, magnesium stearate is added as lubricant and admixed for 3 minutes. In conclusion, the mass, corresponding to 240 mg, is aliquoted into size 0 capsules.

Example B2: Producing soft gelatin capsules

One capsule contains:

SPP100B	75 mg
Hydrogenated vegetable oil	50 mg
Medium-chain triglycerides (MCT)	250 mg

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Lecithin	150 mg
Glycerol stearate	50 mg
Yellow wax	30 mg
Oleic acid	10 mg
Ascorbyl palmitate	5 mg

All the auxiliary substances are weighed into a glass vessel. The mass is heated and stirred until a clear solution is obtained. The melt is then homogenized for 10 minutes. SPP100B is added and the mass is brought to a suitable temperature for aliquoting, while being subjected to further stirring and homogenization, and encapsulated in soft gelatin.

C) Application examples:

Example C1: Determining the bioavailability

The bioavailability of a powder mixture composed of surfactant and active compound is compared with that of SPP100B on its own in an absorption study carried out in rats. The rat model is chosen since, in this model, the absorption of the active compound is low and small quantities of active compound can be investigated.

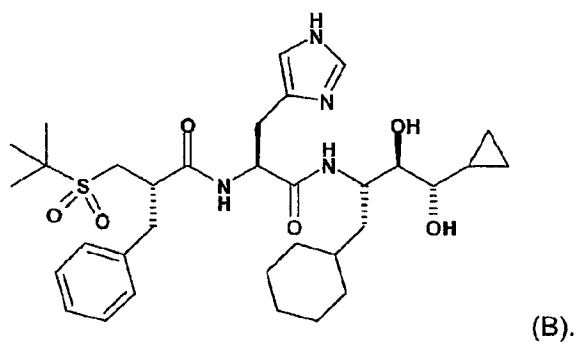
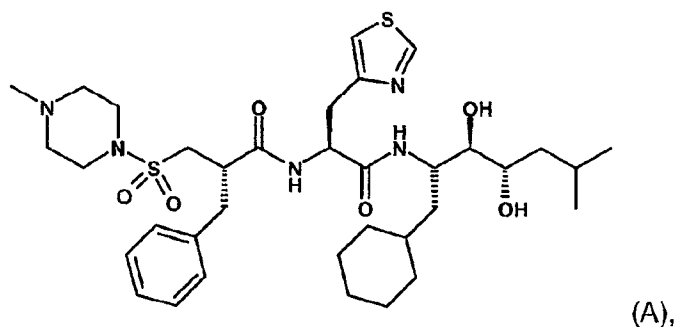
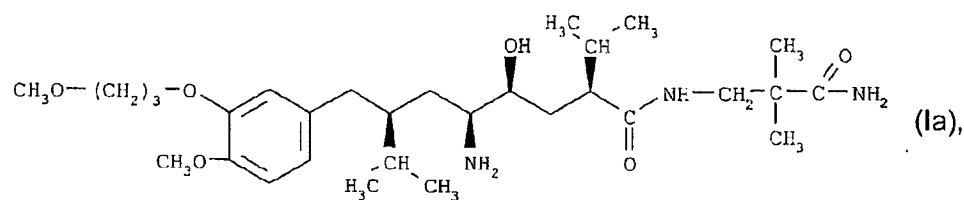
The active compound, or a mixture of 2 parts of SPP100B and 1 part of sodium lauryl sulfate, is in each case administered to 10 rats. The plasma levels are measured over a period of 24 hours after administering the dose. In this model, it is found that adding this surfactant to the renin inhibitor significantly increases oral bioavailability.

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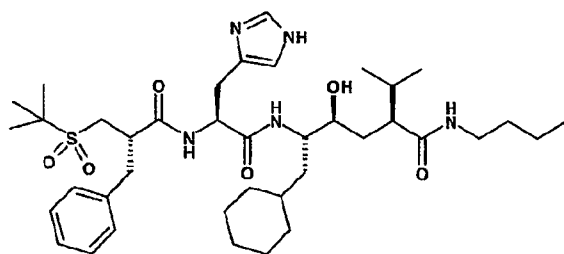
Patent claims:

1. Composition comprising (1) a non-peptide renin inhibitor which is poorly soluble to readily soluble in water and (2) at least one physiologically tolerated anionic surfactant, at least one physiologically tolerated amphoteric surfactant, at least one physiologically tolerated neutral surfactant, or a mixture of at least two of these surfactants, with the quantity of a readily soluble renin inhibitor being at least 10% by weight, and the quantity of a poorly soluble renin inhibitor being at least 35% by weight, based on the composition.
2. Composition according to claim 1, characterized in that the renin inhibitor comprises compounds of the formula Ia or its physiologically tolerated salts or of the formulae A, B, C, F, G or H:

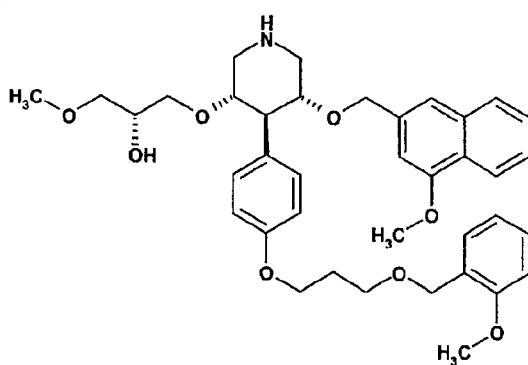


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m

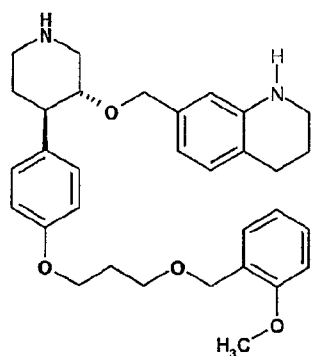
- 22 -



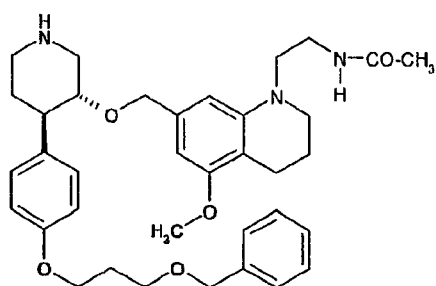
(C).



(F),



(G),



(H).

3. Composition according to claim 1 characterized in that the quantity of water-soluble renin inhibitors is from 10 to 90% by weight, based on the composition.

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4. Composition according to claim 3, characterized in that the quantity of water-soluble renin inhibitors is from 50 to 90% by weight, based on the composition.
5. Composition according to claim 1, characterized in that the quantity of poorly soluble renin inhibitors is from 40 to 90% by weight, based on the composition.
6. Composition according to claim 5, characterized in that the quantity of poorly soluble renin inhibitors is from 60 to 90% by weight, based on the composition.
7. Composition according to claim 1, characterized in that the anionic surfactants are organic acids, and their physiologically tolerated salts of alkali metals or alkaline earth metals, which contain a hydrophobic substituent.
8. Composition according to claim 7, characterized in that it is sodium lauryl sulfate, sodium cetyl sulfate, sulfated castor oil or sodium dioctyl sulfosuccinate.
9. Composition according to claim 1, characterized in that the amphoteric surfactants are natural or modified lecithins, phospholipids and betains.
10. Composition according to claim 9, characterized in that the amphoteric surfactants are natural lecithins.
11. Composition according to claim 1, characterized in that the neutral surfactants are selected from the group monoesters or diesters composed of glycerol and C₈-C₃₀-carboxylic acids, ethoxylated partial C₈-C₃₀-carboxylic acid esters of polyols, optionally hydrogenated polyoxyl castor oils, partial C₈-C₃₀-carboxylic acid esters of sorbitan, C₈-C₃₀-carboxylic acid esters of polyols, C₈-C₃₀-alkyl ethers of polyoxyethylene, ethoxylated C₈-C₃₀-carboxylic acid esters of sorbitan and polyethyleneoxy/polypropyleneoxy block copolymers.
12. Oral administration form comprising a composition according to claim 1.
13. Oral administration form according to claim 12, characterized in that it comprises tablets, sugar-coated tablets, capsules or a potable preparation.

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14. Oral administration form according to claim 12, characterized in that the renin inhibitor is present in a quantity of from 10 to 600 mg, based on the administration form.

15. Method for increasing the bioavailability of non-peptide renin inhibitors, characterized in that the said renin inhibitor is mixed with at least one physiologically tolerated anionic surfactant, with at least one physiologically tolerated amphoteric surfactant or at least one physiologically tolerated neutral surfactant, or with a mixture of at least two of these surfactants.

INTEF TIONAL SEARCH REPORT

International application No
PCT/EP 03/50266

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/195 A61K31/425 A61K31/415 A61K38/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 523 289 A (ALVAREZ FRANCISCO J ET AL) 4 June 1996 (1996-06-04) claims 1,3 examples 1A,-1D column 24; table 1	1-15
Y	EP 0 031 603 A (AMERICAN CYANAMID CO) 8 July 1981 (1981-07-08) page 3, line 9 -page 5, line 2	1-15
Y	US 6 346 537 B1 (HATA TAKEHISA ET AL) 12 February 2002 (2002-02-12) column 1, line 4-8 column 2, line 4-7 column 8, line 52 -column 10, line 16	1-15
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

11 November 2003

Date of mailing of the international search report

28/11/2003

Name and mailing address of the ISA

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Authorized officer

Peris Antoli, B

INTEF TIONAL SEARCH REPORT

International Application No

PCT/EP 03/50266

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2001/007663 A1 (VON CORSWANT CHRISTIAN) 12 July 2001 (2001-07-12)	1-15
A	column 1, paragraphs 5,9	
Y	LECLUYSE EDWARD L ET AL: "In vitro models for selection of development candidates. Permeability studies to define mechanisms of absorption enhancement" ADV DRUG DELIVERY REV;ADVANCED DRUG DELIVERY REVIEWS JAN 15 1997 ELSEVIER SCIENCE B.V., AMSTERDAM, NETHERLANDS, vol. 23, no. 1-3, 15 January 1997 (1997-01-15), pages 163-183, XP001155996 cited in the application page 166, column 2, paragraph 1 -page 167, column 1, paragraph 3 page 176, column 1	1-15
A	KIM D-C ET AL: "EVALUATION OF THE BILE ACID TRANSPORTER IN ENHANCING INTESTINAL PERMEABILITY TO RENIN-INHIBITORY PEPTIDES" JOURNAL OF DRUG TARGETING, HARWOOD ACADEMIC PUBLISHERS GMBH, DE, vol. 1, no. 4, 1993, pages 347-359, XP000564343 ISSN: 1061-186X abstract	1-15

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-15

Present claims 1-15 relate to compositions comprising (1) compounds defined by reference to a desirable characteristic or property, namely renin-inhibitors which are further defined as being non-peptide and being poorly to readily soluble in water; and (2) surfactants, which as such relate to an extremely large number of possible compounds.

Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of renin-inhibitors and surfactants. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, with due regard to the idea underlying the subject matter of the claims, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to renin-inhibitors as specified in claim 2, to surfactants in general and to those specific surfactants used in the examples of the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/50266

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-15
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP 03/50266

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5523289	A	04-06-1996	AU 2596592 A	21-05-1993
			PT 100976 A	28-02-1994
			WO 9307886 A1	29-04-1993
			AT 123282 T	15-06-1995
			AU 646859 B2	10-03-1994
			AU 7607791 A	14-11-1991
			CA 2041825 A1	12-11-1991
			DE 69110086 D1	06-07-1995
			DE 69110086 T2	14-12-1995
			DK 456185 T3	30-10-1995
			EP 0456185 A2	13-11-1991
			ES 2075261 T3	01-10-1995
			GR 3017168 T3	30-11-1995
			IE 911404 A1	20-11-1991
			IL 97994 A	16-10-1996
			JP 1980629 C	17-10-1995
			JP 4279572 A	05-10-1992
			JP 7000607 B	11-01-1995
			JP 5271194 A	19-10-1993
			MX 9202877 A1	30-06-1992
			PT 97631 A , B	31-03-1992
			US 5275950 A	04-01-1994
			US 5344990 A	06-09-1994
			US 5178877 A	12-01-1993
			US 5310740 A	10-05-1994
			US 5284849 A	08-02-1994
EP 0031603	A	08-07-1981	AU 6501980 A	09-07-1981
			EP 0031603 A1	08-07-1981
			JP 56100718 A	12-08-1981
US 6346537	B1	12-02-2002	AU 726451 B2	09-11-2000
			AU 5136998 A	29-06-1998
			BR 9713866 A	14-03-2000
			CN 1245424 A	23-02-2000
			EP 0943327 A1	22-09-1999
			HU 0000587 A2	28-09-2000
			WO 9824418 A1	11-06-1998
			KR 2000057242 A	15-09-2000
			RU 2197226 C2	27-01-2003
			TW 426516 B	21-03-2001
			ZA 9710927 A	15-06-1998
US 2001007663	A1	12-07-2001	AT 228822 T	15-12-2002
			AU 702366 B2	18-02-1999
			AU 7003796 A	01-04-1997
			BR 9610089 A	05-01-1999
			CA 2230730 A1	20-03-1997
			CN 1201386 A	09-12-1998
			CZ 9800643 A3	12-08-1998
			DE 69625213 D1	16-01-2003
			DE 69625213 T2	28-08-2003
			DK 850046 T3	03-03-2003
			EE 9800070 A	15-10-1998
			EP 0850046 A2	01-07-1998
			ES 2186802 T3	16-05-2003
			HU 9901215 A2	30-08-1999
			JP 11512424 T	26-10-1999

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/50266

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2001007663	A1	NO 981021 A	09-03-1998
		NZ 318530 A	29-09-1999
		PL 325825 A1	03-08-1998
		PT 850046 T	31-03-2003
		RU 2164134 C2	20-03-2001
		WO 9709964 A1	20-03-1997
		SK 28398 A3	04-11-1998
		TR 9800437 T1	21-05-1998

Copia: 181

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-009933- -00004-0000

Fecha: 2008-04-16 13:01:21 Dep. 2020 NUECREACION
Tra. 11 PATENTE IYI Eve: 379 FASE NACIONAL II
Act 400 OPOS.OBSERVTER Folios: 52

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 07009933
Asunto : Oposición a la solicitud de patente de Invención
titulada "MÉTODOS PARA MEJORAR LA
BIODISPONIBILIDAD DE UN INHIBIDOR DE
RENINA"
Solicitante : NOVARTIS AG.
Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 587 del 18 de enero de 2008

Yo, *ELIANA ISAURA MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad *GYNOPHARM S.A.* conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley

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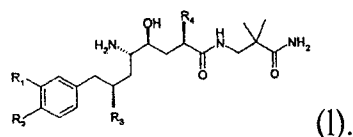
y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "MÉTODOS PARA MEJORAR LA BIODISPONIBILIDAD DE UN INHIBIDOR DE RENINA", cuyo titular es NOVARTIS AG, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular Aliskiren. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 11 de julio de 2007, reivindicando prioridad bajo la solicitud US20040598700P del 2004-08-03; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 587 del 18 de enero de 2008, cuya publicación internacional corresponde a la WO2006013094 del 09/02/2006.
- 2.2. La solicitud colombiana **07009933** objeto de la presente oposición, se refiere a un método para mejorar la biodisponibilidad de un inhibidor de renina, cuyo método comprende co-administrar a un mamífero que necesite el tratamiento, una combinación de un inhibidor de renina y un inhibidor de proteínas de efusión, donde el inhibidor de renina es un derivado de amida del ácido d-amino-hidroxi-aril-alcanoico, o una sal farmacéuticamente aceptable del mismo; en donde el inhibidor de proteínas de efusión es un inhibidor de MDR1; en donde el derivado de amida del ácido d-amino-hidroxi-aril-alcanoico tiene la fórmula:



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en donde R_1 es alcoxi de 1 a 4 átomos de carbono-alcoxi de 1 a 4 átomos de carbono o alcoxi de 1 a 4 átomos de carbono-alquilo de 1 a 4 átomos de carbono; y R_2 es alquilo C_{1-4} o alcoxi C_{1-4} y R_3 y R_4 son independientemente alquilo de 1 a 4 átomos de carbono ramificado; o una sal farmacéuticamente aceptable del mismo.

2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren al uso y a un método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles*

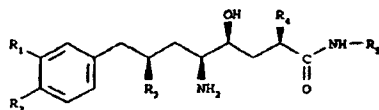
de aplicación industrial". Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: PREFORMULATION APPROACHES TO IMPROVE THE ORAL BIOAVAILABILITY OF TWO NOVEL PIPERIDINE RENIN INHIBITORS IN DOG. Vol: 52, Nr. 8, Pagina(s): Resumen, publicado en el 2002.
- D2: WO2004002466 publicada el 8 de enero de 2004.

2.5. Ahora bien, el documento D1 revela en el resumen formulaciones experimentales basadas en sistemas acuosos y aceitosos, así como solventes acua-miscibles y dispersiones sólidas investigados para verificar el potencial de aumento de la biodisponibilidad oral (F) de inhibidores de renina piperidina [Ro-X1: (R)-1-metoxi-3-[13, 4R, 5R)-4-[4-[3-(2-metoxi-benziloxi)-propoxi] - fenilo]-5-(4-metoxi-naftalen-2-ylmetoxi)-piperidina-3-yloxi]-propan-2-ol; Ro-X2: (R)-3-[(3S, 4R, 5R)-4-[4-[3-(2-metoxi-benziloxi)-propoxi] - fenilo]-5-(4-metoxi-naftalen-2-ylmetoxi)-piperidina-3-ylmetoxi]-propano-1,2-diol) comparados a su administración como solución ácida acuosa. Esta anterioridad D1 también define que los compuestos fueron caracterizados por una solubilidad baja con un pH 7 (Ro-xi: 3 g/ml, Ro-X2: 24 g/ml) y alto

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lipofílico (Ro-X1: LogP = 5.7, Ro-X2: LogP = 3.7). Según dicha anterioridad D1, para vehículos Ro-X1 a base de aceite se encontró una mejor biodisponibilidad oral comparado con la solución acuosa (F = 6 el 1.2 % $\pm$) con un mejor resultado siendo alcanzado con una solución (F = 14.6 el 3.5 % $\pm$). Por el contrario, para Ro-X2 la biodisponibilidad más alta (F = 27.1 el 8.4 % $\pm$) fue alcanzada usando una solución acuosa. También se define en esta anterioridad D1 que con base en una simulación por computador basada en los parámetros fisicoquímicos de los compuestos, sólo predijeron que la fracción del compuesto absorbido en el hombre debería ser casi cuantitativa para Ro-X2 y sólo aproximadamente el 28 % para Ro-X1. Por su parte el documento D2, revela una composición que consiste en un inhibidor de renina no peptídico y un tensoactivo aniónico. Particularmente la anterioridad D2 revela que es posible aumentar sustancialmente la biodisponibilidad de los inhibidores de renina no péptidos de formula I,



(I)

que son fácilmente solubles en agua si se mezclan con tensioactivos aniónicos y se procesan en formas farmacéuticas de administración oral. Por lo tanto, además que la presente solicitud no puede ser objeto de monopolio toda vez que es contrario a lo que dicta la norma en materia de usos y métodos terapéuticos, tampoco es patentable dado

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que la solución propuesta es derivable de manera obvia y evidente a partir del documento D1 y D2, toda vez que a partir de estas es posible llegar a mejorar la biodisponibilidad de la renina en combinación con un inhibidor de proteínas de afluencia.

2.6. Por lo tanto, visto dicho documento D2 en combinación con el documento D1, la presente solicitud carece evidentemente de altura inventiva.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 07009933 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

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

2.8.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”*. A la fecha de prioridad, 3 de agosto de 2004, a partir del documento D2 en combinación con D1, puede llegar de

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manera evidente a una combinación de un inhibidor de renina y un inhibidor de proteínas de afluencia, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486

de la CAN consagra en su artículo 14 lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*.

La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación*

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industrial.". La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"MÉTODOS PARA MEJORAR LA BIODISPONIBILIDAD DE UN INHIBIDOR DE RENINA"**, cuyo titular es **NOVARTIS AG**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 587 del 18 de enero de 2008.

3. PRUEBAS

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

- D1: PREFORMULATION APPROACHES TO IMPROVE THE ORAL BIOAVAILABILITY OF TWO NOVEL PIPERIDINE RENIN INHIBITORS IN DOG. Vol: 52, Nr. 8, Pagina(s): Resumen, publicado en el 2002.
- D2: WO2004002466 publicada el 8 de enero de 2004.

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4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

- 1. Poder para actuar en el presente.
- 2. Documento que acredita al representante legal de GYNOPHARM S.A.
- 3. Recibo de caja del respectivo pago de tasa.
- 4. Copias de los documentos:

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- D1: PREFORMULATION APPROACHES TO IMPROVE THE ORAL BIOAVAILABILITY OF TWO NOVEL PIPERIDINE RENIN INHIBITORS IN DOG. Vol: 52, Nr. 8, Pagina(s): Resumen, publicado en el 2002.
- D2: WO2004002466 publicada el 8 de enero de 2004.

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6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.