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Señor Director
DIRECCIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.



No. 08-079295- -00005-0000

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Act. 444 RESPUESTAREQUE Folios: 49

Trámite : 011
Evento : 379
Actuación : 444

Referencia
Asunto

Expediente No. 08079295
Solicitud de patente para
DERIVADOS DE N-HETEROARIL CARBOXAMIDAS
TRICICLICAS QUE CONTIENEN UNIDAD DE
BENCIMIDAZOL Y SUS PROCESOS DE PREPARACIÓN

Solicitante
Fecha de solicitud

SANOFI-AVENTIS
30 de julio de 2008

1. Yo, LUZ CLEMENCIA DE PÁEZ, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al oficio No. **15050** notificado por fijación en lista de 28 de agosto de 2012.
2. Mediante oficio No. **15050** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la manera siguiente:

2.1. Título de la solicitud

El examinador objeta el título de la solicitud porque no incluye la frase "que contiene una unidad de bencimidazol".

Al respecto nos permitimos presentar el siguiente título para su consideración:

**DERIVADOS DE N-HETEROARIL CARBOXAMIDAS TRICICLICAS QUE
CONTIENEN UNIDAD DE BENCIMIDAZOL Y SUS PROCESOS DE
PREPARACIÓN**

2.2. Claridad en las reivindicaciones

2.2.1. De acuerdo al Señor Examinador, sugiere restringir la solicitud a una razonable generalización del tipo de compuestos

Al respecto, nos permitimos presentar un nuevo capítulo reivindicatorio que ha sido limitado a las modalidades de la reivindicación 8 original y que se enfoca en los compuestos ejemplificados en las tablas 2 a 4.

2.2.2. El Señor hace algunas otras observaciones relacionadas con el uso de “opcionalmente”, el término “sultama”, el procedimiento de la reivindicación 11.

Nos permitimos presentar un nuevo capítulo reivindicatorio donde las objeciones han sido tenidas en cuenta. Especialmente se indica el reemplazo de algunos términos y la reformulación de la reivindicación 11.

2.3. Unidad de invención

El Señor Examinador indica que no existe unidad de invención en la presente solicitud.

Al respecto, y gracias a las modificaciones y limitaciones hechas al capítulo reivindicatorio, el nuevo conjunto de reivindicaciones posee unidad de invención. Queremos resaltar que las reivindicaciones 1 a 7 y 9 han sido borradas, la reivindicación 8 ha sido reformulada y las restantes reivindicaciones han sido reorganizadas.

Queremos resaltar que el nuevo conjunto de reivindicaciones se centra exclusivamente en la formula Va.

Se entiende entonces superada la objeción.

2.4. Análisis de nivel inventivo

2.4.1. El Señor Examinador refiere que el documento D1 (WO2005028445) afecta el nivel inventivo de la solicitud de la reivindicación 1.

Al respecto, queremos poner de presente que el nuevo capítulo reivindicatorio dista mucho del evaluado por el Señor Examinador. En consecuencia el análisis hecho no corresponde con el nuevo conjunto de reivindicaciones que estamos presentando.

2.4.2. La presente solicitud sí tiene nivel inventivo

En primer lugar, téngase presente que el alcance de las reivindicaciones ha sido restringido a los compuestos ejemplificados

En segundo lugar, téngase presente que el Examen Preliminar Internacional reconoce la altura inventiva de la presente invención visto el documento WO2005/028445

En tercer lugar, téngase en cuenta que los compuestos de formula Va aquí presentados presentan un heteroarilo biciclo unido a un triciclo por medio de un grupo carboxamida. Este tipo de compuestos nunca ha sido descrito en WO 2005/028445 y se encuentran muy lejanos de lo aquí reivindicado. Entonces una persona versada en la materia no podría arribar a lo relacionado en la presente solicitud de acuerdo a lo enseñado por D1. En consecuencia la presente solicitud tiene la altura inventiva para que se conceda el privilegio solicitado.

3. Modificación de la solicitud en trámite

Con el objeto de subsanar las objeciones presentadas por su Despacho y de acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar nuevo capítulo reivindicatorio corregido.

Las modificaciones realizadas fueron las siguientes:

- 3.1. Eliminación las reivindicaciones originales 1 a 7 y 9
- 3.2. Nueva reivindicación 1 que corresponde a la reivindicación original 8.
- 3.3. Se han reorganizado las reivindicaciones restantes.

4. Concesión de solicitudes equivalentes

Si bien entendemos y aceptamos que cada país es autónomo en la concesión o negación de los privilegios de patente, queremos resaltar el hecho que el análisis de los requisitos para el otorgamiento de esos derechos es prácticamente universal. Por lo mismo, también queremos llamar la atención de este Despacho en relación a que esta misma solicitud de patente ha sido concedida en Europa, Australia, Estados Unidos. Nos permitimos entonces presentar el documento EP 1987 010 B1 correspondiente al privilegio concedido en Europa, el documento AU 2007211399 correspondiente al privilegio concedido en Australia y los documentos US 8143248 y US 8288376 correspondientes a los privilegios concedidos en Estados Unidos

- 5. De acuerdo con los argumentos y modificaciones presentados con este escrito, la presente solicitud cumple a cabalidad con los requerimientos exigidos en la Decisión 486 y las objeciones formuladas por el Examinador se ven superadas.

Puesto que se ha dado respuesta a todas las objeciones formuladas por el Examinador, se solicita atentamente proceder al otorgamiento de la solicitud de patente. En este sentido, respetuosamente recordamos al Examinador que la patente no podrá ser negada con base en objeciones diferentes a las expuestas en la acción oficial No. 15050, toda vez que al no haber sido trasladadas a mi representada, dicha decisión violaría tanto el tenor literal del artículo 45 de la Decisión 486 como el derecho constitucional al debido proceso. En este evento, y con base en el inciso 2 del artículo 45, respetuosamente solicitamos al Examinador expedir una nueva acción oficial que permita a mi representada contra argumentar las mismas o modificar la solicitud con el fin de cumplir los requisitos de patentabilidad.

6. ANEXOS

- Nuevo pliego reivindicatorio compuesto por 6 reivindicaciones.
- Formulario para modificaciones.
- Copia del documento EP 1987 010 B1 correspondiente al privilegio concedido en Europa,
- Copia del documento AU 2007211399 correspondiente al privilegio concedido en Australia
- Copia de los documentos US 8143248 y US 8288376 correspondientes a los privilegios concedidos en Estados Unidos


LUZ CLEMENCIA DE PÁEZ
C.C. 35.456.344 de Usaquén
T.P.A. No. 23.555

COLO-14775-0841-070-7
RBL\RBL\ID-230600\WPC14775
No. M-2012-230600\RBL

 Industria y Comercio SUPERINTENDENCIA	Espacio reservado para el adhesivo de radicación
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DIRECCIÓN DE NUEVAS CREACIONES
MODIFICACIONES Y/O CORRECCIONES

1. Identificación del Trámite	
☐ Error material	☒ Modificación a una Solicitud en trámite
☒ Patente de Invención	
☐ Patente de Modelo de Utilidad	
☐ Registro de Diseño Industrial	
☐ Esquema de Trazado de Circuitos Integrados	

2. Datos del solicitante		
Persona Natural	☐	Persona Jurídica ☒
SANOFI-AVENTIS		
Nombre o denominación / Nombre o razón social completa		
Nombre representante legal		
Tipo de empresa	Micro ☐	Pequeña ☐ Mediana ☐ Otra ☐
Documento de identificación:	☐ C.C.	☐ C.E. ☐ NIT ☐ Otro Número _____
Nacionalidad/País de constitución	Dirección y domicilio del titular	Ciudad
Francia	174 Avenue de France,	75013 París
Dirección electrónica	No. Fax	Número telefónico
clientes@cavelier.com	2 11 86 50	3 47 36 11

☐ Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del apoderado:		
Apellidos y Nombre	Documento de identificación	Tarjeta profesional
De Páez Luz Clemencia	C.C. 35.456.344	T.P.A. 23.555
Dirección y domicilio	Ciudad	
Carrera 4ª No. 72 –35	Bogotá	
Dirección electrónica	No. Fax	Número telefónico
cavelier@cavelier.com	2 11 86 50	3 47 36 11
En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo de poder general		

4. Datos del trámite

Corrección:

Expediente No 08.079.295

Aparece

Debe ser

Modificación:**Modificación al capítulo reivindicatorio.**

Presento nuevo capítulo reivindicatorio compuesto por 6 reivindicaciones y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas.

Respetuosamente manifiesto que a pesar de eliminar materia del pliego reivindicatorio originalmente presentado, mi representada no renuncia a la protección que pueda obtener sobre dicha materia y se reserva el derecho de presentar una solicitud divisional que la contenga durante el trámite de la presente solicitud, beneficiándose de la fecha de prioridad inicialmente reivindicada.

**Modificación al capítulo descriptivo.****Modificación al resumen.****Modificación a los dibujos.****Modificación al Título.**

Solicito respetuosamente a su despacho tener en cuenta que el nuevo título de esta solicitud de patente ha quedado como sigue: **"DERIVADOS DE N-HETEROARIL CARBOXAMIDAS TRICICLICAS QUE CONTIENEN UNIDAD DE BENCIMIDAZOL Y SUS PROCESOS DE PREPARACIÓN"**

5. Anexos

Poder, si fuere el caso.



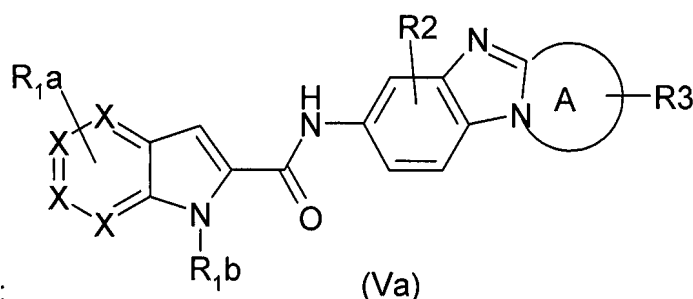
Documento que contiene las modificaciones o correcciones.

6. Firma	
Nombre y apellidos LUZ CLEMENCIA DE PAEZ	Firma 
C.C. 35.456.344 DE Usaquén	Tarjeta Profesional 23.555

RBL\NCA\WPC14775\ID-230669

REIVINDICACIONES

1. Compuesto que responde a la fórmula general (Va) :



en la que:

A junto con el enlace C-N del resto de bencimidazol al que está condensado, representa un heterociclo monocíclico o un heteroarilo monocíclico de 5 a 7 eslabones, que contiene 1 ó 2 heteroátomos elegidos entre O, S o N, incluido el átomo de nitrógeno del resto de bencimidazol;

X representa un átomo de carbono o un átomo de nitrógeno; siendo dichos X iguales o diferentes entre sí, y siendo el número de X = N no superior a 1;

R_{1a} representa uno o varios átomos o grupos, iguales o diferentes, elegidos entre un átomo de hidrógeno, un átomo de halógeno o un grupo alquilo C₁-C₆, fluoroalquilo C₁-C₆, alcoxi C₁-C₆, tioalquilo C₁-C₆, alquil(C₁-C₆)-S(O)₂-, NR₄R₅, nitro ;

R_{1b} representa un átomo de hidrógeno, un grupo alquilo C₁-C₆, heteroariloxi-alquil(C₁-C₆), aril-alquilenoxi(C₁-C₃)-alquilo(C₁-C₆), R₄R₅NC(O)-alquilen(C₁-C₃), arilo, heteroarilo, aril-alquilen(C₁-C₆) o heteroaril-alquilen(C₁-C₆);

estando dichos grupos heteroarilo o arilo de R_{1b} eventualmente sustituidos con uno o varios sustituyentes R₉, iguales o diferentes entre sí;

R₂ representa un átomo de hidrógeno;

R₃ representa un átomo o grupo elegido entre un átomo de hidrógeno, un grupo alquilo C₁-C₆, alcoxi C₁-C₆ o hidroxilo, cuando R₃ está en un átomo de carbono;

o

R₃ representa un átomo o grupo elegido entre un átomo de hidrógeno, un grupo alquilo C₁-C₆, alquil(C₁-C₆)-O-C(O)-, cuando R₃ está en un átomo de nitrógeno;

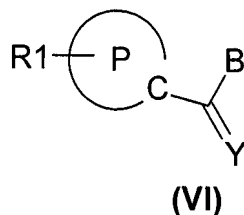
R₄ y R₅, representan, independientemente entre sí, un grupo alquilo C₁-C₆;

o R₄ y R₅ junto con el átomo de nitrógeno que los lleva, forman un grupo pirrolidina o morfolina;

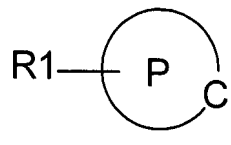
R₉ representa un átomo de halógeno o un grupo alquilo C₁-C₆, alcoxi C₁-C₆, fluoroalquilo C₁-C₆, arilo, heteroarilo, NR₄R₅, ariltio, estando dichos grupos arilo eventualmente sustituidos con uno o varios grupos alquilo C₁-C₆;

en el estado de base o de sal de adición de ácido, así como en el estado de hidrato o de solvato.

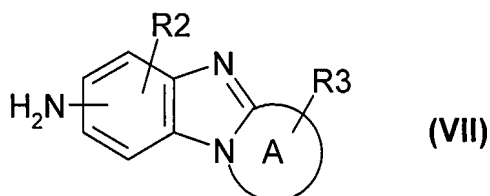
2. Procedimiento de preparación de un compuesto de fórmula (Va) según una reivindicación 1, **CARACTERIZADO PORQUE** se hace reaccionar un compuesto de fórmula general (VI) :



En la que el grupo



Representa un grupo



Donde

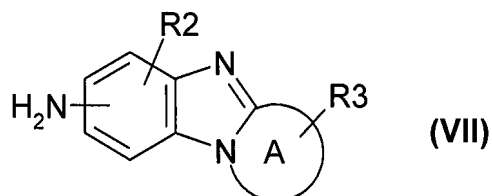
X representa un átomo de carbono o un átomo de nitrógeno; siendo dichos X iguales o diferentes entre sí, y siendo el número de X = N no superior a 1;

R_{1a} representa uno o varios átomos o grupos, iguales o diferentes, elegidos entre un átomo de hidrógeno, un átomo de halógeno o un grupo alquilo C₁-C₆, fluoroalquilo C₁-C₆, alcoxi C₁-C₆, tioalquilo C₁-C₆, alquil(C₁-C₆)-S(O)₂⁻, NR₄R₅, nitro ;

R_{1b} representa un átomo de hidrógeno, un grupo alquilo C₁-C₆, heteroariloxi-alquil(C₁-C₆), aril-alquilenoxi(C₁-C₃)-alquilo(C₁-C₆), R₄R₅NC(O)-alquilen(C₁-C₃), arilo, heteroarilo, aril-alquilen(C₁-C₆) o heteroaril-alquilen(C₁-C₆);

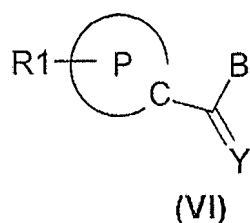
estando dichos grupos heteroarilo o arilo de R_{1b} eventualmente sustituidos con uno o varios sustituyentes R₉, iguales o diferentes entre sí;

Y es un átomo de oxígeno y B representa un grupo alcoxi C₁-C₆, cicloalquiloxi C₃-C₇, cicloalquil(C₃-C₇)-alquilenoxi(C₁-C₃), aril-alquilenoxi(C₁-C₃), se hace reaccionar con un amiduro del compuesto de fórmula general (VII) :

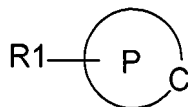


en la que A, R₂ y R₃ son como se definen en la fórmula general (Va) según la reivindicación 1, a reflujo de un disolvente, preparándose el amiduro del compuesto de fórmula general (VII) por acción previa de trimetilaluminio en las aminas de fórmula general (VII).

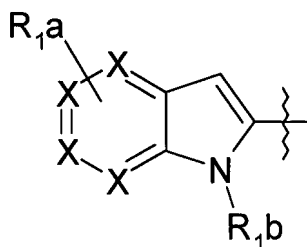
3. Procedimiento de preparación de un compuesto de fórmula (Va) de acuerdo a las reivindicación 1, **CARACTERIZADO PORQUE** se transforma un compuesto de fórmula general (VI) :



en la que el grupo



Representa un grupo



Donde

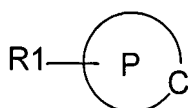
X representa un átomo de carbono o un átomo de nitrógeno; siendo dichos X iguales o diferentes entre sí, y siendo el número de X = N no superior a 1;

R_{1a} representa uno o varios átomos o grupos, iguales o diferentes, elegidos entre un átomo de hidrógeno, un átomo de halógeno o un grupo alquilo C₁-C₆, fluoroalquilo C₁-C₆, alcoxi C₁-C₆, tioalquilo C₁-C₆, alquil(C₁-C₆)-S(O)₂⁻, NR₄R₅, nitro ;

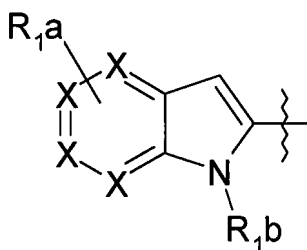
R_{1b} representa un átomo de hidrógeno, un grupo alquilo C₁-C₆, heteroariloxi-alquil(C₁-C₆), aril-alquilenoxi(C₁-C₃)-alquilo(C₁-C₆), R₄R₅NC(O)-alquilen(C₁-C₃), arilo, heteroarilo, aril-alquilen(C₁-C₆) o heteroaril-alquilen(C₁-C₆);

estando dichos grupos heteroarilo o arilo de R_{1b} eventualmente sustituidos con uno o varios sustituyentes R₉, iguales o diferentes entre sí;

Y es un átomo de oxígeno y B es un grupo hidroxilo y es convertido a ácido clorhídrico por la acción de un cloruro de tionilo a reflujo de un solvente y entonces el compuesto de formula (VI) obtenido en el cual el grupo

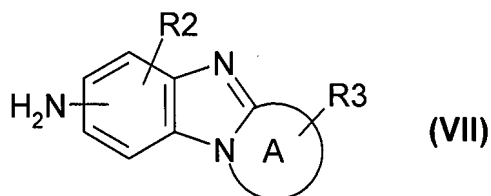


Representa un grupo



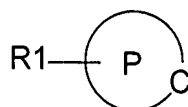
en la que X, R_{1a} y R_{1b} son como se definen en la fórmula general (Va) según la reivindicación 1,

y Y es un átomo de oxígeno y B es un átomo de cloro y reacciona en presencia de una base con el compuesto de formula (VII)

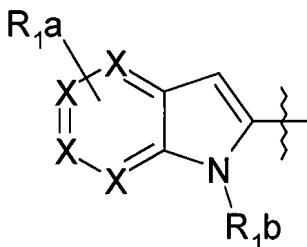


En donde A, R₂ y R₃ son como se define en la formula (Va) de acuerdo con la reivindicación 1

o bien porque se lleva a cabo una reacción de acoplamiento entre un compuesto de fórmula (VI) en donde el grupo



Representa un grupo



Donde

X representa un átomo de carbono o un átomo de nitrógeno; siendo dichos X iguales o diferentes entre sí, y siendo el número de X = N no superior a 1;

R_{1a} representa uno o varios átomos o grupos, iguales o diferentes, elegidos entre un átomo de hidrógeno, un átomo de halógeno o un grupo alquilo C₁-C₆, fluoroalquilo C₁-C₆, alcoxi C₁-C₆, tioalquilo C₁-C₆, alquil(C₁-C₆)-S(O)₂-, NR₄R₅, nitro ;

R_{1b} representa un átomo de hidrógeno, un grupo alquilo C₁-C₆, heteroariloxi-alquil(C₁-C₆), aril-alquilenoxi(C₁-C₃)-alquilo(C₁-C₆), R₄R₅NC(O)-alquilen(C₁-C₃), arilo, heteroarilo, aril-alquilen(C₁-C₆) o heteroaril-alquilen(C₁-C₆);

estando dichos grupos heteroarilo o arilo de R_{1b} eventualmente sustituidos con uno o varios sustituyentes R₉, iguales o diferentes entre sí;

y donde Y es un átomo de oxígeno y B es grupo hidroxilo y el compuesto de formula (VII) en donde A, R₂ y R₃ son como se definen en la fórmula (Va) de acuerdo a la reivindicación 1 en la presencia de un agente de acoplamiento y de una base en un solvente.

4. Un proceso para preparar un compuesto de acuerdo a las reivindicaciones 2 o 3 **CARACTERIZADO PORQUE** el compuesto es escogido de la fórmula general (VIIa), (VIIb), (VIIc), (VIId), (VIIe), (VIIf), (VIIg), (VIIh), (VIIi), (VIIj), (VIIk), (VIII), (VIIIm), (VIIn):



(11) EP 1 987 010 B1

(12) FASCICULE DE BREVET EUROPEEN

(45) Date de publication et mention
de la délivrance du brevet:
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C07D 471/04 (2006.01) A61K 31/437 (2006.01)
A61K 31/4188 (2006.01) A61P 29/00 (2006.01)

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(22) Date de dépôt: 01.02.2007

(87) Numéro de publication Internationale:
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(54) **DÉRIVÉS DE N-HETEROARYL-CARBOXAMIDES TRICYCLIQUES CONTENANT UN MOTIF BENZIMIDAZOLE, LEUR PRÉPARATION ET LEUR APPLICATION EN THÉRAPEUTIQUE**

TRICYCLISCHE N-HETEROARYL-CARBOXAMID-DERIVATE MIT EINER BENZIMIDAZOL-EINHEIT, VERFAHREN ZU IHRER HERSTELLUNG UND IHRE THERAPEUTISCHE VERWENDUNG

TRICYCLIC N-HETEROARYL-CARBOXAMIDE DERIVATIVES CONTAINING A BENZIMIDAZOLE UNIT, METHOD FOR PREPARING SAME AND THEIR THERAPEUTIC USE

(84) Etats contractants désignés:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI
SK TR
Etats d'extension désignés:
AL BA HR MK RS

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F-92160 ANTONY (FR)
- MACHNIK, David
F-92160 Antony (FR)
- RAKOTOARISOA, Nathalie
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(30) Priorité: 03.02.2006 FR 0601007

(74) Mandataire: Gaslonde, Aude et al
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Département Brevets
174, Avenue de France
75013 Paris (FR)

(43) Date de publication de la demande:
05.11.2008 Bulletin 2008/45

(73) Titulaire: Sanofi-Aventis
75013 Paris (FR)

(56) Documents cités:
EP-A- 1 535 922 WO-A-2005/028445
WO-A-2005/105798

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• GILLE, Catherine
F-92160 ANTONY (FR)

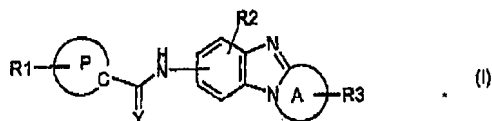
- DATABASE CHEMCATS CHEMICAL
ABSTRACTS SERVICE, COLUMBUS, OHIO, US;
24 janvier 2006 (2006-01-24), XP002399484 extrait
de STN Database accession no. 2006:2135904 &
"Enamine Screening Library" 24 janvier 2006
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Claims

1. Compound corresponding to formula (I)



in which:

A is, with the C-N bond of the benzimidazole unit with which it is fused, a 4- to 7-membered monocyclic heterocycle or monocyclic heteroaryl, containing from one to three heteroatoms selected from O, S and N, including the nitrogen atom of the benzimidazole unit;

P is an 8-, 9-, 10- or 11-membered bicyclic heterocycle or bicyclic heteroaryl, comprising from 1 to 6 heteroatoms selected from N, O and S; P being linked to the -C(Y)- group by a carbon atom;

with the proviso that, when A is a 7-membered saturated heterocycle, P is other than the 2,3-dihydro-1,4-benzodioxane group, the 1-benzopyran-2-one group and the isoindole group;

R₁ is from one to four atoms or groups, which may be identical or different, selected from a hydrogen atom, a halogen atom, and an oxo, thio, C₁-C₈-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, heteroaryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenethio-C₁-C₆-alkyl, heteroaryl-C₁-C₃-alkylenethio-C₁-C₆-alkyl, C₁-C₆-alkoxy, C₃-C₇-cycloalkyloxy, C₃-C₇-cycloalkyl-C₁-C₃-alkylenoxy, C₁-C₆-fluoroalkoxy, cyano, C(O)NR₄R₅, nitro, NR₄R₅, C₁-C₆-thioalkyl, C₃-C₇-cycloalkylthio, C₃-C₇-cycloalkyl-C₁-C₃-alkylenethio, -S(O)-C₁-C₆-alkyl, -S(O)-C₃-C₇-cycloalkyl, -S(O)-C₁-C₃-alkylene-C₃-C₇-cycloalkyl, C₁-C₆-alkyl-S(O)₂, C₁-C₆-fluoroalkyl-S(O)₂, C₃-C₇-cycloalkyl-S(O)₂, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-S(O)₂, SO₂NR₄R₅, SF₅, NR₆C(O)R₇, NR₆SO₂R₈, R₄R₅NC(O)-C₁-C₃-alkylene, aryl, heteroaryl, aryl-C₁-C₅-alkylene, heteroaryl-C₁-C₅-alkylene, aryloxy, arylthio, heteroaryloxy or heteroarylthio group;

said heteroaryl or aryl groups of R₁ being optionally substituted with one or more substituents R₆, which may be identical to or different from one another;

with the proviso that, when R₁ is attached to a nitrogen atom of P, then R₁ is different from a halogen atom, and from an oxo, thio, cyano, nitro, SF₅, NR₄R₅, C₁-C₆-thioalkyl, thioaryl, thioheteroaryl, C₁-C₆-alkoxy, aryloxy, heteroaryloxy, -NR₆COR₇ and NR₆SO₂R₈ group;

Y is an oxygen or sulphur atom;

R₂ is a hydrogen atom, a halogen atom, or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl or C₁-C₆-alkoxy group;

R₃ is from one to three atoms or groups, which may be identical or different, selected from a hydrogen atom, a halogen atom, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, hydroxyl, C₁-C₆-alkoxy, C₃-C₇-cycloalkyloxy or C₃-C₇-cycloalkyl-C₁-C₃-alkylenoxy group, when R₃ is carried by a carbon atom;

or

R₃ is from one to two atoms or groups, which may be identical or different, selected from a hydrogen atom, a halogen atom, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, aryl-C(O)-, C₁-C₆-alkyl-C(O)-, C₃-C₇-cycloalkyl-C(O)-, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-C(O)-, C₁-C₆-fluoroalkyl-C(O)-, aryl-S(O)₂, C₁-C₆-alkyl-S(O)₂, C₁-C₆-fluoroalkyl-S(O)₂, C₃-C₇-cycloalkyl-S(O)₂, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-S(O)₂, C₁-C₆-alkyl-O-C(O)-, aryl-C₁-C₃-alkyl-O-C(O)-, C₃-C₇-cycloalkyl-O-C(O)-, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-O-C(O)-, C₁-C₆-fluoroalkyl-O-C(O)-, aryl-O-C(O)- or heteroaryl-O-C(O)- group, when R₃ is carried by a nitrogen atom;

R₄ and R₅ are, independently of one another, a hydrogen atom or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₅-alkylene or aryl group; or R₄ and R₅ form, together with the nitrogen atom which carries them, an azetidine, pyrrolidine, piperidine, azepine, morpholine, thiomorpholine, piperazine or homopiperazine group, the NR₄R₅ group being optionally substituted with a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₆-alkylene, aryl, heteroaryl, aryl-S(O)₂, C₁-C₆-alkyl-S(O)₂, C₁-C₆-fluoroalkyl-S(O)₂, C₃-C₇-cycloalkyl-S(O)₂, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-S(O)₂, aryl-C(O)-, C₁-C₆-alkyl-C(O)-, C₃-C₇-cycloalkyl-C(O)-, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-C(O)-, C₁-C₆-fluoroalkyl-C(O)-, hydroxyl, C₁-C₆-alkyloxy, C₁-C₆-fluoroalkyl, aryloxy-C₁-C₆-alkylene, aryloxy, heteroaryloxy-C₁-C₆-alkylene or heteroaryloxy group;

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R₆ and R₇ are, independently of one another, a hydrogen atom, or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₆-alkylene or aryl group; or R₆ and R₇ together form a 4- to 7-membered lactam comprising the nitrogen atom and the C(O) group which carry them;

R₈ is a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₆-alkylene or aryl group; or R₈ and R₉ together form a 4- to 7-membered sultam comprising the nitrogen atom and the S(O)₂ group which carry them;

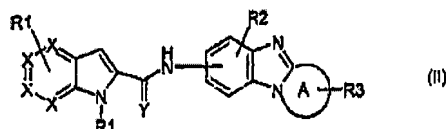
R₉ is a halogen atom, or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkoxy, nitro, cyano, NR₄R₅, R₄R₅N-C₁-C₃-alkylene, aryl, heteroaryl, aryloxy, arylthio, heteroaryloxy or heteroarylthio group, said heteroaryl or aryl groups being optionally substituted with one or more substituents selected from a halogen atom, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkoxy, nitro, cyano, NR₄R₅ or R₄R₅N-C₁-C₃-alkylene group;

the sulphur atom(s) of the heterocycle A may be in oxidized form (S(O) or S(O)₂);

the nitrogen atom(s) may be in oxidized form (N-oxide); in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate;

2-(2-chlorophenyl)-1,3-dioxo-N-(7,8,9,10-tetrahydro-6H-azepino[1,2-a]benzimidazol-3-yl)isolidoline-5-carboxamide being excluded.

2. Compound of the invention according to Claim 1, characterized in that it corresponds to formula (II):



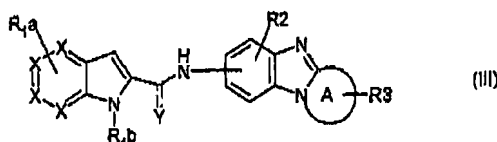
In which:

X is a carbon atom or a nitrogen atom; said X being identical to or different from one another and the number of X = N not being greater than 2;

R₁, R₂, R₃, Y and A being as defined in formula (I) according to Claim 1, it being possible for R₁ to be linked to the 6-element or 5-element unit of the bicycle;

in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

3. Compound of the invention according to Claim 1 or 2, characterized in that it corresponds to formula (III):



In which:

R_{1a} is one or more atoms or groups, which may be identical or different, selected from a hydrogen atom, a halogen atom or a C₁-C₆-alkyl, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxy, C₁-C₆-thioalkyl, C₁-C₆-alkyl-S(O)₂-, NR₄R₅ or nitro group;

R_{1b} is a hydrogen atom, or a C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, R₄R₅NC(O)-C₁-C₃-alkylene, aryl, heteroaryl, aryl-C₁-C₆-alkylene or heteroaryl-C₁-C₆-alkylene group; said heteroaryl or aryl groups of R_{1b}, being optionally substituted with one or more substituents R₉, which may be identical to or different from one another;

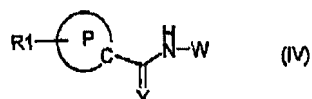
R₃ is a halogen atom or a C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkyl, aryl, heteroaryl, NR₄R₅ or arylthio group, said heteroaryl or aryl groups being optionally substituted with one or more substituents selected from a halogen atom, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkoxy, nitro, cyano or R₄R₅N-C₁-C₃-alkylene group;

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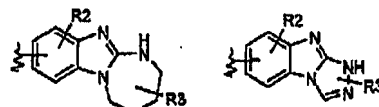
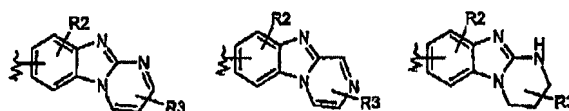
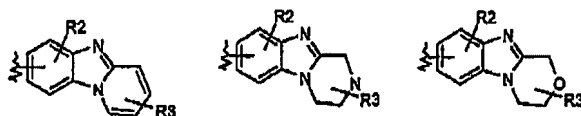
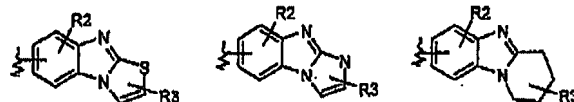
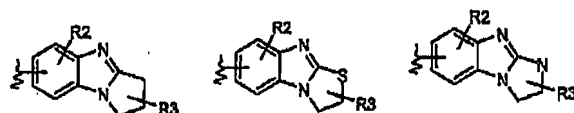
R_2 , R_3 , R_4 , R_5 , A, X and Y being as defined in formula (II) according to Claim 2;

in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

4. Compound of the invention according to any one of Claims 1 to 3, characterized in that it corresponds to formula (IV):



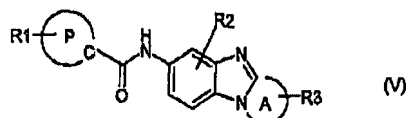
in which W is a tricyclic heterocycle or a tricyclic heteroaryl selected from:



R_1 , R_2 , R_3 , P and Y being as defined in formula (I) according to Claim 1;

in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

5. Compound of the invention according to any one of Claims 1 to 4, characterized in that it corresponds to formula (V)



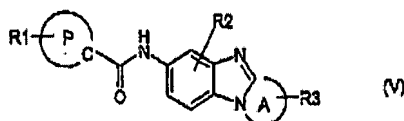
in which:

R_1 , R_2 , R_3 , A and P are as defined in formula (I) according to Claim 1;

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in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

6. Compound of the invention according to any one of Claims 1 to 5, characterized in that it corresponds to formula (V)



In which:

R₂ is a hydrogen atom, or a C₁-C₆-alkyl or C₁-C₆-alkoxy group;

R₃ is from one to three atoms or groups, which may be identical or different, selected from a hydrogen atom, and a C₁-C₆-alkyl, C₁-C₆-alkoxy or hydroxyl group, when R₃ is carried by a carbon atom;

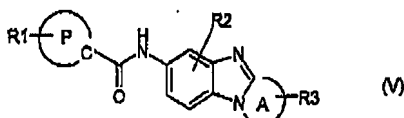
or

R₃ is from one to two atoms or groups, which may be identical or different, selected from a hydrogen atom, and a C₁-C₆-alkyl, C₁-C₆-alkyl-O-C(O)- or aryl-C₁-C₃-alkyl-O-C(O)- group, when R₃ is carried by a nitrogen atom;

R₁, A and P being as defined in formula (I) according to Claim 1;

in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

7. Compound of the invention according to any one of Claims 1 to 6, characterized in that it corresponds to formula (V)



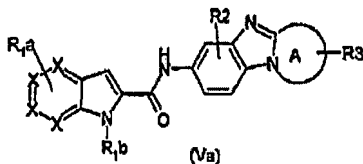
In which:

A is, with the C-N bond of the benzimidazole unit with which it is fused, a 5- to 7-membered monocyclic heterocycle or monocyclic heteroaryl containing from one to three heteroatoms selected from O, S and N, including the nitrogen atom of the benzimidazole unit;

R₁, R₂, R₃ and P being as defined in formula (I) according to Claim 1;

in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

8. Compound of the invention according to any one of Claims 1 to 7, characterized in that it corresponds to formula (Va):



in which

A is, with the C-N bond of the benzimidazole unit with which it is fused, a 5- to 7-membered monocyclic heterocycle or monocyclic heteroaryl containing one or two heteroatoms selected from O, S and N, including the nitrogen atom of the benzimidazole unit;

X is a carbon atom or a nitrogen atom; said X being identical to or different from one another and the number of X = N not being greater than 1;

R_{1a} is one or more atoms or groups, which may be identical or different, selected from a hydrogen atom, a halogen atom or a C₁-C₆-alkyl group, a C₁-C₆-fluoroalkyl group, a C₁-C₆-alkoxy group, a C₁-C₆-thioalkyl group, a C₁-C₆-alkyl-S(O)₂- group, an NR₄R₅ group or a nitro group;

R_{1b} is a hydrogen atom, or a C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, R₄R₅NC

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(O)-C₁-C₃-alkylene, aryl, heteroaryl, aryl-C₁-C₆-alkylene or heteroaryl-C₁-C₆-alkylene group; said heteroaryl or aryl groups of R_{1b} being optionally substituted with one or more substituents R₉, which may be identical to or different from one another;

R₂ is a hydrogen atom;

5 R₃ is an atom or group selected from a hydrogen atom, a C₁-C₆-alkyl group, a C₁-C₆-alkoxy group, or a hydroxyl group, when R₃ is carried by a carbon atom;

or

R₃ is an atom or group selected from a hydrogen atom, a C₁-C₆-alkyl group and a C₁-C₆-alkyl-O-C(O)- group, when R₃ is carried by a nitrogen atom;

10 R₄ and R₅ are, independently of one another, a C₁-C₆-alkyl group;

or R₄ and R₅ form, together with the nitrogen atom which carries them, a pyrrolidine or morpholine group;

R₉ is a halogen atom or a C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkyl, aryl, heteroaryl, NR₄R₅, or arylthio group, said aryl groups being optionally substituted with one or more C₁-C₆-alkyl groups;

in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

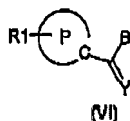
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9. Compound of the invention according to any one of Claims 1 to 8, characterized in that it corresponds to formula (I) in which at the same time R₁ and/or R₂ and/or R₃, and/or A, and/or P and/or Y are as defined in Claims 1 to 8; in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

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10. Process for preparing a compound of formula (I) according to any one of Claims 1 to 9, characterized in that a compound of formula (VI):

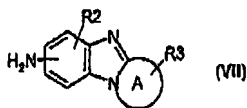
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In which P, R₁ and Y are as defined in formula (I) according to Claim 1 and B is a C₁-C₆-alkoxy, C₃-C₇-cycloalkyloxy, C₃-C₇-cycloalkyl-C₁-C₃-alkylenoxy or aryl-C₁-C₃-alkylenoxy group, with an amide of the compound of formula (VII):

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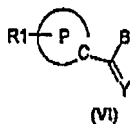


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in which A, R₂ and R₃ are as defined in formula (I) according to Claim 1, at the reflux of a solvent, the amide of the compound of formula (VII) being prepared by the prior action of trimethylaluminium on the amines of formula (VII).

11. Process for preparing a compound of formula (I) according to any one of Claims 1 to 9, characterized in that a compound of formula (VI):

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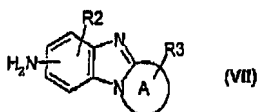


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in which P, R₁ and Y are as defined in formula (I) according to Claim 1 and B is a hydroxyl group, is converted to an acid chloride by the action of thionyl chloride at the reflux of a solvent, and then in that the compound of formula (VI) obtained, in which P, R₁ and Y are as defined in formula (I) according to Claim 1 and B is a chlorine atom, is reacted, in the presence of a base, with the compound of formula (VII):

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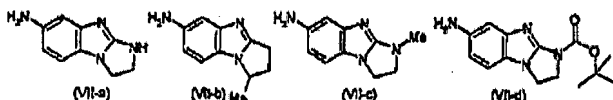
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in which A, R₂ and R₃ are as defined in formula (I) according to Claim 1;
or else in that a coupling reaction is carried out between a compound of formula (VI), in which P, R₁ and Y are as
defined in formula (I) according to Claim 1 and B is a hydroxyl group, and the compound of formula (VII) in which
A, R₂ and R₃ are as defined in formula (I) according to Claim 1, in the presence of a coupling agent and of a base,
in a solvent.

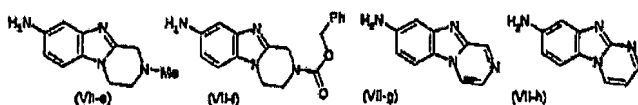
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12. Compound of formula (VIIa), (VIIb), (VIIc), (VIId), (VIIe), (VIIf), (VIIg), (VIIh), (VIIi), (VIIj), (VIIk), (VIIl), (VIIm), (VIIn):

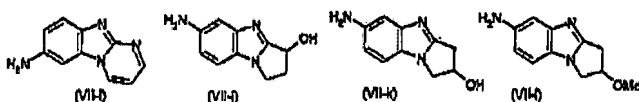
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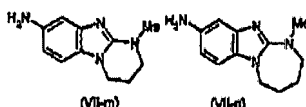
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13. Medicament, characterized in that it comprises at least one compound of formula (I) according to any one of
Claims 1 to 9, or an addition salt of this compound with a pharmaceutically acceptable acid, or else a hydrate or a
solvate of the compound of formula (I).

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14. Pharmaceutical composition, characterized in that it comprises at least one compound of formula (I) according to
any one of Claims 1 to 9, or a pharmaceutically acceptable salt, a hydrate or a solvate of this compound, and also
at least one pharmaceutically acceptable excipient.

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15. Use of a compound of formula (I) according to any one of Claims 1 to 9, for the preparation of a medicament for
use in the prevention or treatment of pathologies in which TPPV1-type receptors are involved.

16. Use of a compound of formula (I) according to any one of Claims 1 to 9, for the preparation of a medicament for
use in preventing or treating pain, inflammation, metabolic disorders, urological disorders, gynaecological disorders,
gastrointestinal disorders, respiratory disorders, psoriasis, pruritis, dermal, ocular or mucosal irritations, herpes,
shingles, multiple sclerosis and depression.

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55 Patentansprüche

1. Verbindung der allgemeinen Formel (I)

(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 2007211399 B2

(54) Title
Tricyclic nu-heteroaryl-carboxamide derivatives containing a benzimidazole unit, method for preparing same and their therapeutic use

(51) International Patent Classification(s)
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A61K 31/4188 (2006.01) C07D 471/04 (2006.01)
A61K 31/437 (2006.01) C07D 487/04 (2006.01)

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(71) Applicant(s)
Sanofi-Aventis

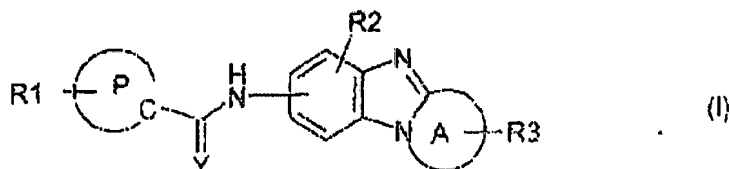
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(56) Related Art
WO 2005/028445
WO 2005/105798
EP 1535922

The claims defining the Invention are as follows:

1. Compound corresponding to formula (I)



in which:

A is, with the C-N bond of the benzimidazole unit with which it is fused, a 4- to 7-membered monocyclic heterocycle or monocyclic heteroaryl, containing from one to three heteroatoms selected from O, S and N, including the nitrogen atom of the benzimidazole unit;

P is an 8-, 9-, 10- or 11-membered bicyclic heterocycle or bicyclic heteroaryl, comprising from 1 to 6 heteroatoms selected from N, O and S; P being linked to the -C(Y)- group by a carbon atom;

with the proviso that, when A is a 7-membered saturated heterocycle, P is other than the 2,3-dihydro-1,4-benzodioxane group, the 1-benzopyran-2-one group and the isoindole group;

R₁ is from one to four atoms or groups, which may be identical or different, selected from a hydrogen atom, a halogen atom, and an oxo, thio, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, heteroaryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenethio-C₁-C₆-alkyl, heteroaryl-C₁-C₃-alkylenethio-C₁-C₆-alkyl, C₁-C₆-alkoxy, C₃-C₇-cycloalkyloxy, C₃-C₇-cycloalkyl-C₁-C₃-alkylenoxy, C₁-C₆-fluoroalkoxy, cyano, C(O)NR₄R₅, nitro, NR₄R₅, C₁-C₆-thioalkyl, C₃-C₇-cycloalkylthio, C₃-C₇-cyclo-

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alkyl-C₁-C₃-alkylenethio, -S(O)-C₁-C₆-alkyl, -S(O)-C₃-C₇-cycloalkyl, -S(O)-C₁-C₃-alkylene-C₃-C₇-cycloalkyl, C₁-C₆-alkyl-S(O)₂-, C₁-C₆-fluoroalkyl-S(O)₂-, C₃-C₇-cycloalkyl-S(O)₂-, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-S(O)₂-, SO₂NR₄R₅, SF₅, NR₆C(O)R₇, NR₆SO₂R₈, R₄R₅NC(O)-C₁-C₃-alkylene, aryl, heteroaryl, aryl-C₁-C₅-alkylene, heteroaryl-C₁-C₅-alkylene, aryloxy, arylthio, heteroaryloxy or hetero-arylthio group;

said heteroaryl or aryl groups of R₁ being optionally substituted with one or more substituents R₉, which may be identical to or different from one another;

with the proviso that, when R₁ is attached to a nitrogen atom of P, then R₁ is different from a halogen atom, and from an oxo, thio, cyano, nitro, SF₅, NR₄R₅, C₁-C₆-thioalkyl, thioaryl, thioheteroaryl, C₁-C₆-alkoxy, aryloxy, heteroaryloxy, -NR₆COR₇ and NR₆SO₂R₈ group;

Y is an oxygen or sulphur atom;

R₂ is a hydrogen atom, a halogen atom, or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl or C₁-C₆-alkoxy group;

R₃ is from one to three atoms or groups, which may be identical or different, selected from a hydrogen atom, a halogen atom, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, hydroxyl, C₁-C₆-alkoxy, C₃-C₇-cycloalkyloxy or C₃-C₇-cycloalkyl-C₁-C₃-alkylenoxy group, when R₃ is carried by a carbon atom;

or

R₃ is from one to two atoms or groups, which may be identical or different, selected from a hydrogen atom, a halogen atom, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, aryl-C(O)-, C₁-C₆-alkyl-C(O)-, C₃-C₇-cycloalkyl-C(O)-, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-C(O)-, C₁-C₆-fluoroalkyl-C(O)-,

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aryl-S(O)₂-, C₁-C₆-alkyl-S(O)₂-, C₁-C₆-fluoroalkyl-S(O)₂-, C₃-C₇-cycloalkyl-S(O)₂-, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-S(O)₂-, C₁-C₆-alkyl-O-C(O)-, aryl-C₁-C₃-alkyl-O-C(O)-, C₃-C₇-cycloalkyl-O-C(O)-, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-O-C(O)-, C₁-C₆-fluoroalkyl-O-C(O)-, aryl-O-C(O)- or heteroaryl-O-C(O)- group, when R₃ is carried by a nitrogen atom;

R₄ and R₅ are, independently of one another, a hydrogen atom or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene or aryl group; or R₄ and R₅ form, together with the nitrogen atom which carries them, an azetidine, pyrrolidine, piperidine, azepine, morpholine, thiomorpholine, piperazine or homopiperazine group, the NR₄R₅ group being optionally substituted with a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene, aryl, heteroaryl, aryl-S(O)₂-, C₁-C₆-alkyl-S(O)₂-, C₁-C₆-fluoroalkyl-S(O)₂-, C₃-C₇-cycloalkyl-S(O)₂-, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-S(O)₂-, aryl-C(O)-, C₁-C₆-alkyl-C(O)-, C₃-C₇-cycloalkyl-C(O)-, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-C(O)-, C₁-C₆-fluoroalkyl-C(O)-, hydroxyl, C₁-C₆-alkyloxy, C₁-C₆-fluoroalkyl, aryloxy-C₁-C₆-alkylene, aryloxy, heteroaryloxy-C₁-C₆-alkylene or heteroaryloxy group;

R₆ and R₇ are, independently of one another, a hydrogen atom, or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene or aryl group; or R₆ and R₇ together form a 4- to 7-membered lactam comprising the nitrogen atom and the C(O) group which carry them;

R₈ is a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene or aryl group; or R₆ and R₈ together form a 4- to 7-membered sultam comprising the nitrogen atom and the S(O)₂ group which

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carry them;

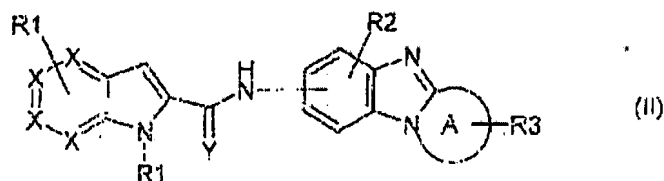
R_9 is a halogen atom, or a C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_3 -alkylene, C_1 - C_6 -fluoroalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -fluoroalkoxy, nitro, cyano, NR_4R_5 , R_4R_5N - C_1 - C_3 -alkylene, aryl, heteroaryl, aryloxy, arylthio, heteroaryloxy or heteroarylthio group, said heteroaryl or aryl groups being optionally substituted with one or more substituents selected from a halogen atom, and a C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_3 -alkylene, C_1 - C_6 -fluoroalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -fluoroalkoxy, nitro, cyano, NR_4R_5 or R_4R_5N - C_1 - C_3 -alkylene group;

the sulphur atom(s) of the heterocycle A may be in oxidized form ($S(O)$ or $S(O)_2$);

the nitrogen atom(s) may be in oxidized form (N-oxide);
in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate;

2-(2-chlorophenyl)-1,3-dioxo-N-(7,8,9,10-tetrahydro-6H-azepino[1,2-a]benzimidazol-3-yl)isoindoline-5-carboxamide being excluded.

2. A compound according to Claim 1, corresponding to formula (II):



in which:

X is a carbon atom or a nitrogen atom; said X being identical to or different from one another and the number of $X = N$ not being greater than 2;

R_1 , R_2 , R_3 , Y and A being as defined in formula (I) according to Claim 1, it being possible for R_1 to be

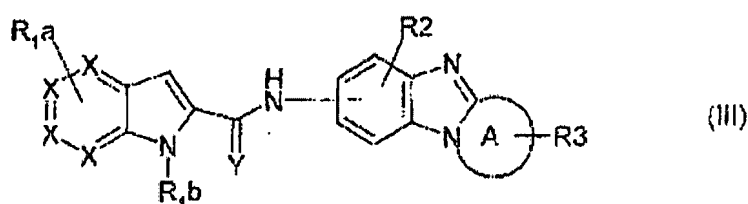
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linked to the 6-element or 5-element unit of the bicycle;

in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

3. A compound according to Claim 1 or 2, corresponding to formula (III):



in which:

R_{1a} is one or more atoms or groups, which may be identical or different, selected from a hydrogen atom, a halogen atom or a C_1 - C_6 -alkyl, C_1 - C_6 -fluoroalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -thioalkyl, C_1 - C_6 -alkyl- $S(O)_2$ -, NR_4R_5 or nitro group;

R_{1b} is a hydrogen atom, or a C_1 - C_6 -alkyl, heteroaryl-oxy- C_1 - C_6 -alkyl, aryl- C_1 - C_3 -alkylenoxy- C_1 - C_6 -alkyl, $R_4R_5NC(O)$ - C_1 - C_3 -alkylene, aryl, heteroaryl, aryl- C_1 - C_6 -alkylene or heteroaryl- C_1 - C_6 -alkylene group;

said heteroaryl or aryl groups of R_{1b} being optionally substituted with one or more substituents R_9 , which may be identical to or different from one another;

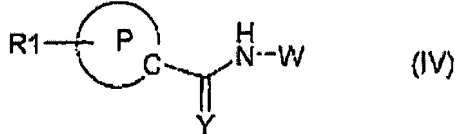
R_9 is a halogen atom or a C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -fluoroalkyl, aryl, heteroaryl, NR_4R_5 or arylthio group, said heteroaryl or aryl groups being optionally substituted with one or more substituents selected from a halogen atom, and a C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_3 -alkylene, C_1 - C_6 -fluoroalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -fluoroalkoxy, nitro, cyano or R_4R_5N - C_1 - C_3 -alkylene group;

R_2 , R_3 , R_4 , R_5 , A , X and Y being as defined in formula (II) according to Claim 2;

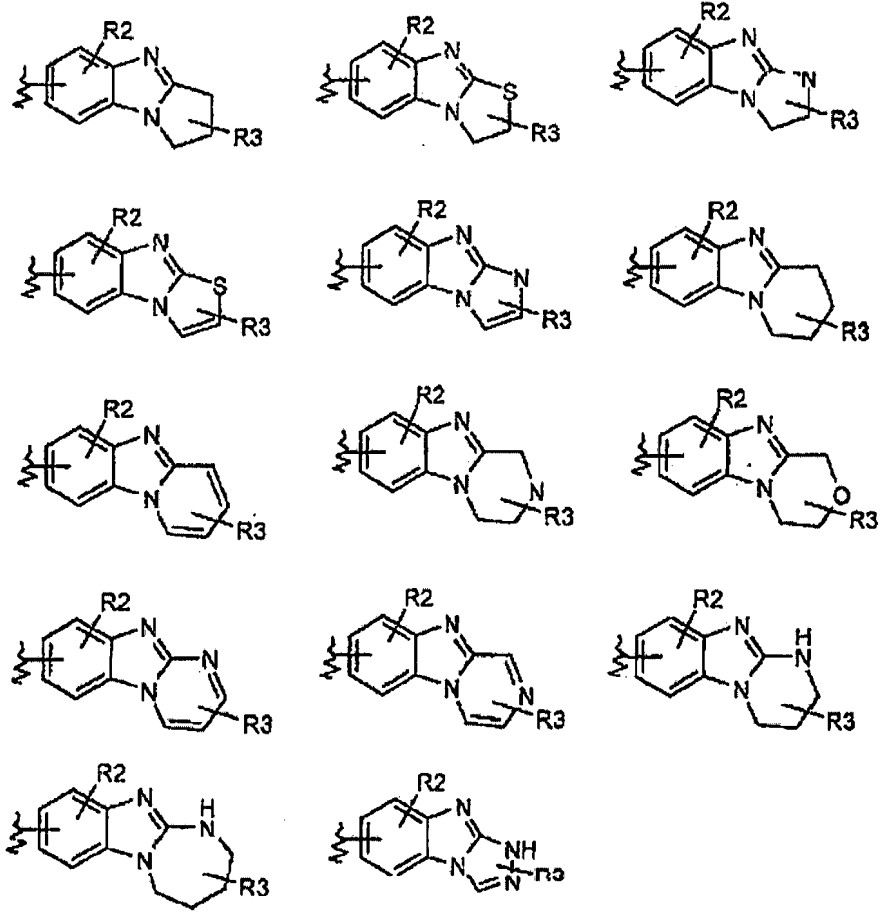
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in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

4. A compound according to any one of Claims 1 to 3, corresponding to formula (IV):



in which W is a tricyclic heterocycle or a tricyclic heteroaryl selected from:

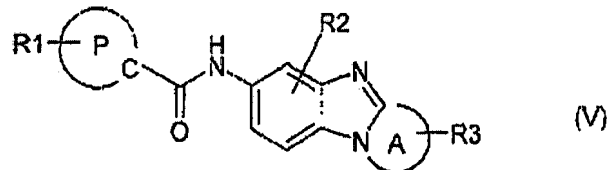


R₁, R₂, R₃, P and Y being as defined in formula (I) according to Claim 1;

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in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

5. A compound according to any one of Claims 1 to 4, corresponding to formula (V)

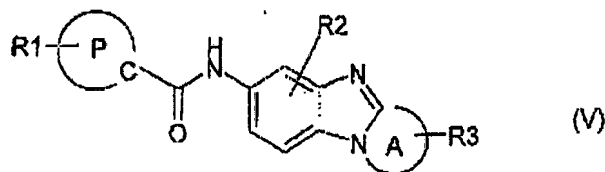


in which:

R₁, R₂, R₃, A and P are as defined in formula (I) according to Claim 1;

in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

6. A compound according to any one of Claims 1 to 5, corresponding to formula (V)



in which:

R₂ is a hydrogen atom, or a C₁-C₆-alkyl or C₁-C₆-alkoxy group;

R₃ is from one to three atoms or groups, which may be identical or different, selected from a hydrogen atom, and a C₁-C₆-alkyl, C₁-C₆-alkoxy or hydroxyl group, when R₃ is carried by a carbon atom;

or

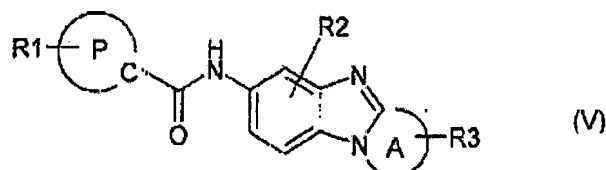
R₃ is from one to two atoms or groups, which may be identical or different, selected from a hydrogen atom, and a C₁-C₆-alkyl, C₁-C₆-alkyl-O-C(O)- or aryl-C₁-C₃-alkyl-O-C(O)- group, when R₃ is carried by a nitrogen atom;

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R₁, A and P being as defined in formula (I) according to Claim 1;

in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

7. A compound according to any one of Claims 1 to 6, corresponding to formula (V)



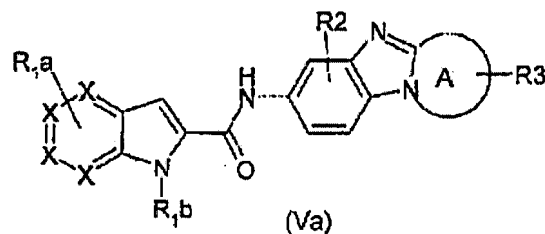
in which:

A is, with the C-N bond of the benzimidazole unit with which it is fused, a 5- to 7-membered monocyclic heterocycle or monocyclic heteroaryl containing from one to three heteroatoms selected from O, S and N, including the nitrogen atom of the benzimidazole unit;

R₁, R₂, R₃ and P being as defined in formula (I) according to Claim 1;

in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

8. A compound according to any one of Claims 1 to 7, corresponding to formula (Va):



in which

A is, with the C-N bond of the benzimidazole unit with which it is fused, a 5- to 7-membered monocyclic heterocycle or monocyclic heteroaryl containing one or two heteroatoms selected from O, S and N, including the

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nitrogen atom of the benzimidazole unit;

X is a carbon atom or a nitrogen atom; said X being identical to or different from one another and the number of X = N not being greater than 1;

R_{1a} is one or more atoms or groups, which may be identical or different, selected from a hydrogen atom, a halogen atom or a C₁-C₆-alkyl group, a C₁-C₆-fluoroalkyl group, a C₁-C₆-alkoxy group, a C₁-C₆-thioalkyl group, a C₁-C₆-alkyl-S(O)₂- group, an NR₄R₅ group or a nitro group;

R_{1b} is a hydrogen atom, or a C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, R₄R₅NC(O)-C₁-C₃-alkylene, aryl, heteroaryl, aryl-C₁-C₆-alkylene or heteroaryl-C₁-C₆-alkylene group; said heteroaryl or aryl groups of R_{1b} being optionally substituted with one or more substituents R₉, which may be identical to or different from one another;

R₂ is a hydrogen atom;

R₃ is an atom or group selected from a hydrogen atom, a C₁-C₆-alkyl group, a C₁-C₆-alkoxy group, or a hydroxyl group, when R₃ is carried by a carbon atom;

or

R₃ is an atom or group selected from a hydrogen atom, a C₁-C₆-alkyl group and a C₁-C₆-alkyl-O-C(O)- group, when R₃ is carried by a nitrogen atom;

R₄ and R₅ are, independently of one another, a C₁-C₆-alkyl group;

or R₄ and R₅ form, together with the nitrogen atom which carries them, a pyrrolidine or morpholine group;

R₉ is a halogen atom or a C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkyl, aryl, heteroaryl, NR₄R₅, or arylthio group, said aryl groups being optionally substituted with one or more C₁-C₆-alkyl groups;

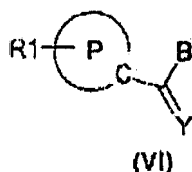
in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

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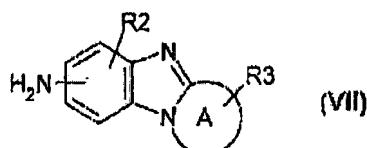
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9. A compound according to any one of Claims 1 to 8, corresponding to formula (I) in which at the same time R_1 and/or R_2 and/or R_3 , and/or A, and/or P and/or Y are as defined in Claims 1 to 8; in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

10. Process for preparing a compound of formula (I) according to any one of Claims 1 to 9, wherein a compound of formula (I):



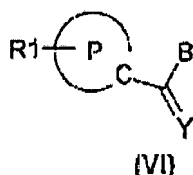
in which P, R_1 and Y are as defined in formula (I) according to Claim 1 and B is a C_1 - C_6 -alkoxy, C_3 - C_7 -cycloalkyloxy, C_3 - C_7 -cycloalkyl- C_1 - C_3 -alkylenoxy or aryl- C_1 - C_3 -alkylenoxy group, is reacted with an amide of the compound of formula (VII):



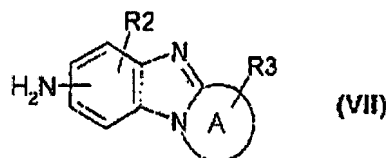
in which A, R_2 and R_3 are as defined in formula (I) according to Claim 1, at the reflux of a solvent, the amide of the compound of formula (VII) being prepared by the prior action of trimethylaluminium on the amines of formula (VII).

11. Process for preparing a compound of formula (I) according to any one of Claims 1 to 9, wherein a compound of formula (VI):

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in which P, R₁ and Y are as defined in formula (I) according to Claim 1 and B is a hydroxyl group, is converted to an acid chloride by the action of thionyl chloride at the reflux of a solvent, and then in that the compound of formula (VI) obtained, in which P, R₁ and Y are as defined in formula (I) according to Claim 1 and B is a chlorine atom, is reacted, in the presence of a base, with the compound of formula (VII):



in which A, R₂ and R₃ are as defined in formula (I) according to Claim 1;

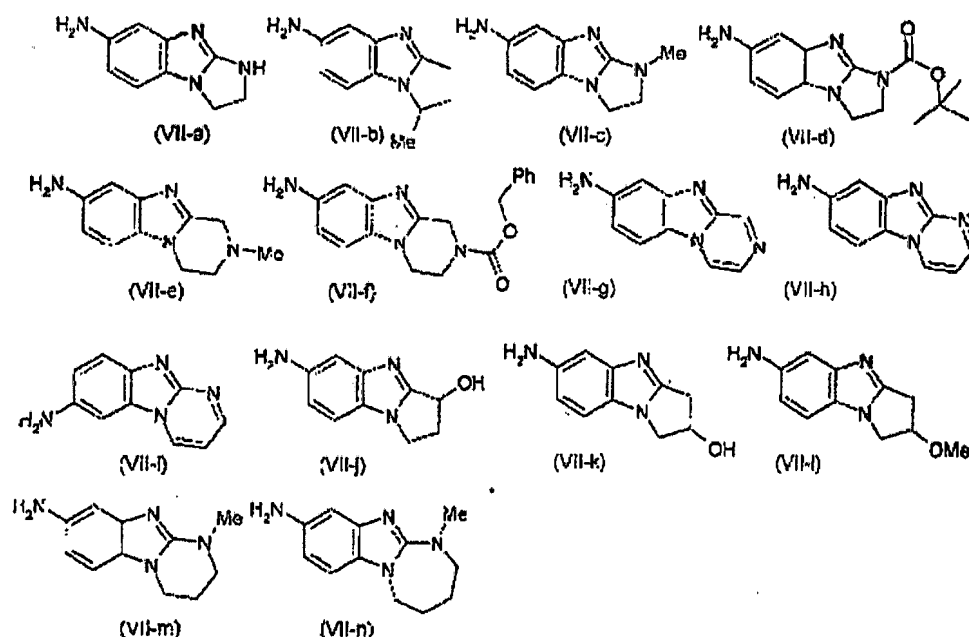
or else in that a coupling reaction is carried out between a compound of formula (VI), in which P, R₁ and Y are as defined in formula (I) according to Claim 1 and B is a hydroxyl group, and the compound of formula (VII) in which A, R₂ and R₃ are as defined in formula (I) according to Claim 1, in the presence of a coupling agent and of a base, in a solvent.

12. Compound of formula (VIIa), (VIIb), (VIIc), (VIId), (VIIe), (VIIf), (VIIg), (VIIh), (VIIi), (VIIj), (VIIk), (VIIl), (VIIm), (VIIn):

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13. Medicament, comprising at least one compound of formula (I) according to any one of Claims 1 to 9, or an addition salt of this compound with a pharmaceutically acceptable acid, or else a hydrate or a solvate of the compound of formula (I).

14. Pharmaceutical composition, comprising at least one compound of formula (I) according to any one of Claims 1 to 9, or a pharmaceutically acceptable salt, a hydrate or a solvate of this compound, and also at least one pharmaceutically acceptable excipient.

15. Use of a compound of formula (I) according to any one of Claims 1 to 9, for the preparation of a medicament for use in the prevention or treatment of pathologies in which TRPV1-type receptors are involved.

16. Use of a compound of formula (I) according to any one of Claims 1 to 9, for the preparation of a medicament for use in preventing or treating pain, inflammation, metabolic disorders, urological

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disorders, gynaecological disorders, gastrointestinal disorders, respiratory disorders, psoriasis, pruritis, dermal, ocular or mucosal irritations, herpes, shingles, multiple sclerosis and depression.

17. A method of treating or preventing pathologies in which TRPV1-type receptors are involved comprising administering to a subject an effective amount of a compound of formula (I) according to any one of claims 1 to 9, or a pharmaceutically acceptable salt, a hydrate or a solvate thereof.

18. A method of treating or preventing pain, inflammation, metabolic disorders, urological disorders, gynaecological disorders, gastrointestinal disorders, respiratory disorders, psoriasis, pruritis, dermal, ocular or mucosal irritations, herpes, shingles, multiple sclerosis or depression comprising administering to a subject an effective amount of a compound of formula (I) according to any one of claims 1 to 9, or a pharmaceutically acceptable salt, a hydrate or a solvate thereof.

19. A compound as claimed in any one of claims 1 to 9 or 12; a process as claimed in claim 10 or claim 11; a medicament as claimed in claim 13; a pharmaceutical composition as claimed in claim 14; a use as claimed in claim 15 or claim 16; or a method as claimed in claim 17 or claim 18; substantially as herein described with reference to any example thereof.



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(12) **United States Patent**
Dubois et al.

(10) **Patent No.:** US 8,288,376 B2
(45) **Date of Patent:** *Oct. 16, 2012

(54) **TRICYCLIC
N-HETEROARYL-CARBOXAMIDE
DERIVATIVES CONTAINING A
BENZIMIDAZOLE UNIT, METHOD FOR
PREPARING SAME AND THEIR
THERAPEUTIC USE**

(75) **Inventors:** Laurent Dubois, Antony (FR); Yannick Evanno, Antony (FR); Luc Even, Antony (FR); Catherine Gille, Antony (FR); Andre Malanda, Antony (FR); David Machnik, Antony (FR); Nathalie Rakotoarisoa, Antony (FR)

(73) **Assignee:** Sanofi, Paris (FR)

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
This patent is subject to a terminal disclaimer.

(21) **Appl. No.:** 13/357,015

(22) **Filed:** Jan. 24, 2012

(65) **Prior Publication Data**
US 2012/0122852 A1 May 17, 2012

Related U.S. Application Data
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(30) **Foreign Application Priority Data**
Feb. 3, 2006 (FR) 06 01007

(51) **Int. Cl.**
A61K 31/535 (2006.01)
(52) **U.S. Cl.** 514/230.2; 514/292; 514/338;
514/300; 514/267; 546/273.1; 546/113; 546/85;
548/302.4; 544/101; 544/250
(58) **Field of Classification Search** 514/230.2,
514/292, 338, 300, 267; 546/273.1, 113,
546/85; 548/302.4; 544/101, 250
See application file for complete search history.

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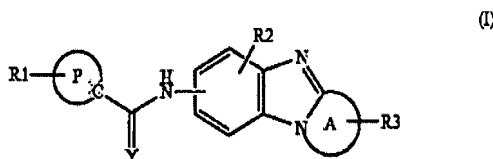
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(57) ABSTRACT

The invention concerns tricyclic N-heteroaryl-carboxamide derivatives containing a benzimidazole unit of general formula (I):



Wherein A, P, Y, R₁, R₂, and R₃ are as defined herein. The invention also concerns a method of preparing the compounds and their therapeutic use.

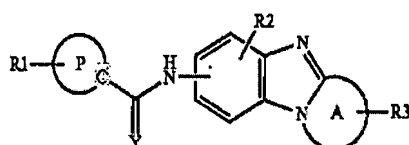
17 Claims, No Drawings

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effective dose of at least one compound according to the invention, or a pharmaceutically acceptable salt, a hydrate or a solvate thereof.

What is claimed is:

1. A method of modulating the activity of TRPV1 receptors comprising administering to a patient a modulatory amount of a compound of formula (I):



or pharmaceutically acceptable salt thereof in which:

A is, with the C—N bond of the benzimidazole unit with which it is fused, a 4- to 7-membered monocyclic heterocycle or monocyclic heteroaryl, containing from one to three heteroatoms selected from O, S and N, including the nitrogen atom of the benzimidazole unit;

P is an 8-, 9-, 10- or 11-membered bicyclic heterocycle or bicyclic heteroaryl, containing from 1 to 6 heteroatoms selected from N, O and S; P being linked to the -C(Y)- group by a carbon atom;

with the proviso that, when A is a 7-membered saturated heterocycle, P is other than 2,3-dihydro-1,4-benzodioxane, the 1-benzopyran-2-one or isoindole;

R1 is substituted on P one to four times and each R1 may be identical or different, R1 being selected from hydrogen, halogen, oxo, thio, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, heteroaryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenethio C₁-C₆-alkyl, heteroaryl-C₁-C₃-alkylenethio-C₁-C₆-alkyl, C₁-C₆-alkoxy, C₃-C₇-cycloalkyloxy, C₃-C₇-cycloalkyl-C₁-C₃-alkylenoxy, C₁-C₆-fluoroalkoxy, cyano, C(O)NR₄R₅, nitro, NR₄R₅, C₁-C₆-thioalkyl, C₃-C₇-cycloalkylthio, C₃-C₇-cycloalkyl-C₁-C₃-alkylenethio, -S(O)-C₁-C₆-alkyl, -S(O)-C₃-C₇-cycloalkyl, -S(O)-C₁-C₃-alkylene-C₃-C₇-cycloalkyl, C₁-C₆-alkyl-S(O)₂-, C₁-C₆-fluoroalkyl-S(O)₂-, C₃-C₇-cycloalkyl-S(O)₂-, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-S(O)₂-, SO₂NR₄R₅, SF₅, NR₄R₅, NR₄R₅NC(O)-C₁-C₃-alkylene, aryl, heteroaryl, aryl-C₁-C₃-alkylene, heteroaryl-C₁-C₃-alkylene, aryloxy, arylthio, heteroaryloxy and heteroarylthio;

said heteroaryl or aryl of R1 being optionally substituted with one or more substituents R₆, which may be identical to or different from one another;

with the proviso that, when R1 is attached to a nitrogen atom of P, then R1 is not halogen, oxo, thio, cyano, nitro, SF₅, NR₄R₅, C₁-C₆-thioalkyl, thioaryl, thioheteroaryl, C₁-C₆-alkoxy, aryloxy, heteroaryloxy, -NR₄COR₇, or NR₄SO₂R₈;

Y is an oxygen or sulphur atom;

R2 is hydrogen, halogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl or C₁-C₆-alkoxy;

R3 is substituted on a carbon atom of A, each R3 may be substituted 1 to 3 times on a carbon atom of A, each R3 substituted on a carbon atom of A may be identical or

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different, said R3 substituted on a carbon atom of A being selected from hydrogen, halogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, hydroxyl, C₁-C₆-alkoxy, C₃-C₇-cycloalkyloxy and C₃-C₇-cycloalkyl-C₁-C₃-alkylenoxy;

or

R3 is substituted on a nitrogen atom of A, each R3 may be substituted once or twice on a nitrogen atom of A and may be identical or different, said R3 substituted on a nitrogen atom of A being selected from hydrogen, halogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, aryl-C(O)-, C₁-C₆-alkyl-C(O)-, C₃-C₇-cycloalkyl-C(O)-, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-C(O)-, C₁-C₆-fluoroalkyl-C(O)-, aryl-S(O)₂-, C₁-C₆-alkyl-S(O)₂-, C₁-C₆-fluoroalkyl-S(O)₂-, C₃-C₇-cycloalkyl-S(O)₂-, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-S(O)₂-, C₁-C₆-alkyl-O-C(O)-, aryl-C₁-C₃-alkyl-O-C(O)-, C₃-C₇-cycloalkyl-O-C(O)-, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-O-C(O)-, C₁-C₆-fluoroalkyl-O-C(O)-, aryl-O-C(O)- and heteroaryl-O-C(O)-;

R₄ and R₅ are, independently of one another, hydrogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene or aryl;

or R₄ and R₅ form, together with the nitrogen atom which carries them, azetidine, pyrrolidine, piperidine, azepine, morpholine, thiomorpholine, piperazine or homopiperazine group, the NR₄R₅ group being optionally substituted with C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene, aryl, heteroaryl, aryl-S(O)₂-, C₁-C₆-alkyl-S(O)₂-, C₁-C₆-fluoroalkyl-S(O)₂-, C₃-C₇-cycloalkyl-S(O)₂-, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-S(O)₂-, aryl-C(O)-, C₁-C₆-alkyl-C(O)-, C₃-C₇-cycloalkyl-C(O)-, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-C(O)-, C₁-C₆-fluoroalkyl-C(O)-, hydroxyl, C₁-C₆-alkyloxy, C₁-C₆-fluoroalkyl, aryloxy-C₁-C₆-alkylene, aryloxy, heteroaryloxy-C₁-C₆-alkylene or heteroaryloxy;

R₆ and R₇ are, independently of one another, a hydrogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene or aryl;

or R₆ and R₇ together form a 4- to 7-membered lactam comprising the nitrogen atom and the C(O) group which carry them;

R₈ is C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene or aryl;

or R₆ and R₈ together form a 4- to 7-membered sultam comprising the nitrogen atom and the S(O)₂ group which carry them;

R₉ is halogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkoxy, nitro, cyano, NR₄R₅, R₄R₅N-C₁-C₃-alkylene, aryl, heteroaryl, aryloxy, arylthio, heteroaryloxy or heteroarylthio, said heteroaryl or aryl being optionally substituted with one or more substituents selected from halogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkoxy, nitro, cyano, NR₄R₅ and R₄R₅N-C₁-C₃-alkylene;

the sulphur atom(s) of the heterocycle A may be in oxidized form (S(O) or S(O)₂);

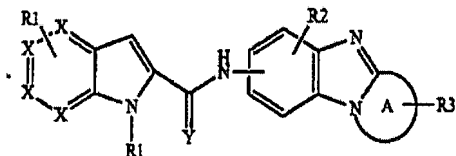
the nitrogen atom(s) may be in oxidized form (N-oxide);

and with the proviso that 2-(2-chlorophenyl)-1,3-dioxo-N-(7,8,9,10-tetrahydro-6H-azepino[1,2-a]benzimidazol-3-yl)isoindoline-5-carboxamide is excluded.

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3. The method according to claim 1, wherein the compound is of formula (II):

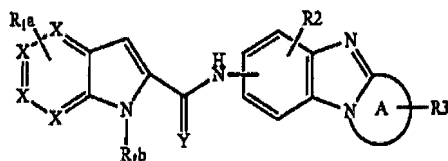


(II) 5

or a pharmaceutically acceptable salt thereof
in which:

X is a carbon atom or a nitrogen atom; said X being identical to or different from one another and the number of X=N not being greater than 2.

4. The method according to claim 3, wherein the compound is of formula (III):



(III)

or a pharmaceutically acceptable salt thereof
in which:

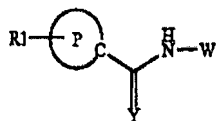
R_{1a} is bonded to the ring containing X atoms one or more times, each R_{1a} may be identical or different, each R_{1a} is selected from hydrogen, a halogen, a C₁-C₆-alkyl, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxy, C₁-C₆-thioalkyl, C₁-C₆-alkyl-S(O)₂-, NR₄R₅ and nitro;

R_{1b} is hydrogen, C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, R₄R₅NC(O)-C₁-C₃-alkylene, aryl, heteroaryl, aryl-C₁-C₆-alkylene or heteroaryl-C₁-C₆-alkylene;

said heteroaryl or aryl of R_{1b} being optionally substituted with one or more substituents R₉, which may be identical to or different from one another;

R₉ is halogen, C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkyl, aryl, heteroaryl, NR₄R₅ or arylthio, said heteroaryl or aryl being optionally substituted with one or more substituents selected from halogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkoxy, nitro, cyano and R₄R₅N-C₁-C₃-alkylene.

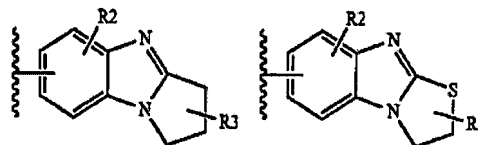
5. The method according to claim 1, wherein the compound is of formula (IV):



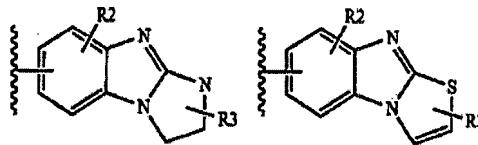
(IV)

or a pharmaceutically acceptable salt thereof
in which W is a tricyclic heterocycle or a tricyclic heteroaryl selected from:

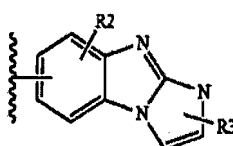
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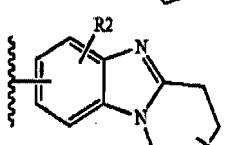
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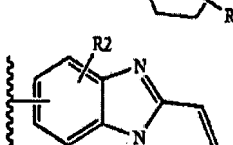
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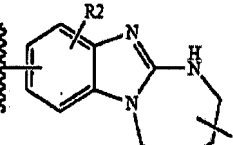
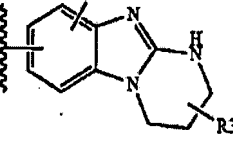
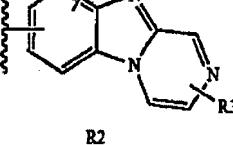
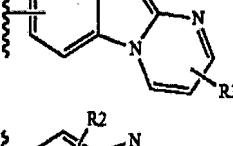
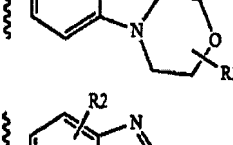
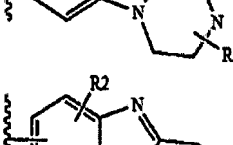
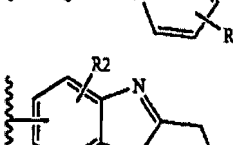
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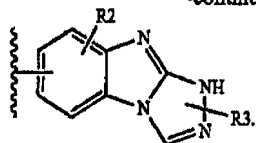
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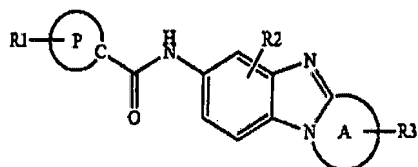
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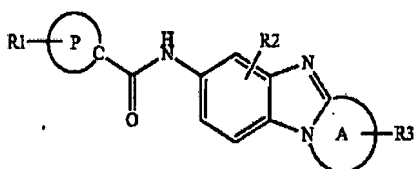


6. The method according to claim 1, wherein the compound is of formula (V):



or a pharmaceutically acceptable salt thereof.

7. (by Amended) The method according to claim 1, wherein the compound is of formula (V):



or a pharmaceutically acceptable salt thereof
in which:

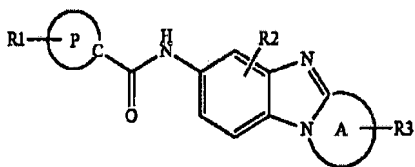
R² is hydrogen, C₁-C₆-alkyl or C₁-C₆-alkoxy;

R3 is substituted on a carbon atom of A one to three times, each R3 substituted on a carbon atom of A may be identical or different, and is selected from hydrogen, C₁-C₆-alkyl, C₁-C₆-alkoxy and hydroxyl;

or

R3 is substituted on a nitrogen atom of A, one to two times, each R3 substituted on a nitrogen atom of A may be identical or different, and is selected from hydrogen, C₁-C₆-alkyl, C₁-C₆-alkyl-O-C(O)- and aryl-C₁-C₃-alkyl-O-C(O)-.

8. The method according to claim 1, wherein the compound is of formula (V):

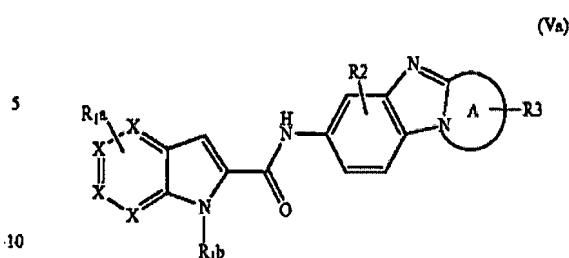


or a pharmaceutically acceptable salt thereof
in which:

A is, with the C—N bond of the benzimidazole unit with which it is fused, a 5- to 7-membered monocyclic heterocycle or monocyclic heteroaryl containing from one to three heteroatoms selected from O, S and N, including the nitrogen atom of the benzimidazole unit.

9. The method according to claim 1, wherein the compound is of formula (Va):

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or a pharmaceutically acceptable salt thereof

in which

A is, with the C—N bond of the benzimidazole unit with which it is fused, a 5- to 7-membered monocyclic heterocycle or monocyclic heteroaryl containing one or two heteroatoms selected from O, S and N, including the nitrogen atom of the benzimidazole unit;

X is a carbon atom or a nitrogen atom; said X being identical to or different from one another and the number of X=N not being greater than 1;

R_{1a} is one or more atoms or groups, which may be identical or different, selected from a hydrogen, halogen, C_1 - C_6 -alkyl, a C_1 - C_6 -fluoroalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -thioalkyl, C_1 - C_6 -alkyl-S(O)₂—, NR_4R_5 , and nitro;

R₁₆ is hydrogen, C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, R₄R₅NC(O)-C₁-C₃-alkylene, aryl, heteroaryl, aryl-C₁-C₆-alkylene or heteroaryl-C₁-C₆-alkylene;

said heteroaryl or aryl of R_{1b} being optionally substituted with one or more substituents R_9 , which may be identical to or different from one another;

R2 is hydrogen;

R3 is substituted on a carbon atom of X, and selected from hydrogen, C₁-C₆-alkyl, C₁-C₆-alkoxy, and hydroxyl;

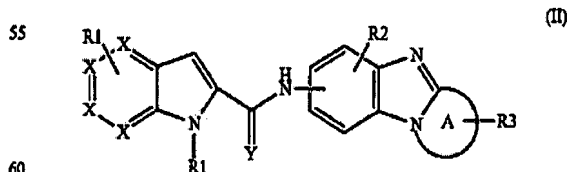
or R3 is substituted on a nitrogen atom of X, and is selected from hydrogen, C₁-C₆-alkyl and C₁-C₆-alkyl-O-C(O)-;

R_4 and R_5 are, independently of one another, C₁-C₆-alkyl;

or R₄ and R₅ form, together with the nitrogen atom which carries them, a pyrrolidine or morpholine; and

R₉ is halogen, C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkyl, aryl, heteroaryl, NR₄R₅, or arylthio, said aryl being optionally substituted with one or more C₁-C₆-alkyl.

10. The method according to claim 2, wherein the compound is of formula (II):



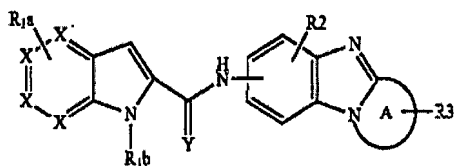
or a pharmaceutically acceptable salt thereof

in which:

X is a carbon atom or a nitrogen atom; said X being identical to or different from one another and the number of X=N not being greater than 2.

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11. The method according to claim 10, wherein the compound is of formula (III):



(III) 5

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or a pharmaceutically acceptable salt thereof in which:

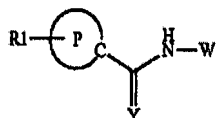
R_{1a} is bonded to the ring containing X atoms one or more times, each R_{1a} may be identical or different, each R_{1a} is selected from hydrogen, halogen, C_1 - C_6 -alkyl, C_1 - C_6 -fluoroalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -thioalkyl, C_1 - C_6 -alkyl-S(O)₂—, NR_4R_5 , and nitro;

R_{1b} is hydrogen, C_1 - C_6 -alkyl, heteroaryloxy- C_1 - C_6 -alkyl, aryl- C_1 - C_3 -alkylenoxy- C_1 - C_6 -alkyl, $R_4R_5NC(O)$ - C_1 - C_3 -alkylene, aryl, heteroaryl, aryl- C_1 - C_6 -alkylene or heteroaryl- C_1 - C_6 -alkylene;

said heteroaryl or aryl of R_{1b} being optionally substituted with one or more substituents R_6 , which may be identical to or different from one another;

R_6 is halogen, C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -fluoroalkyl, aryl, heteroaryl, NR_4R_5 or arylthio group, said heteroaryl or aryl being optionally substituted with one or more substituents selected from halogen, C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_3 -alkylene, C_1 - C_6 -fluoroalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -fluoroalkoxy, nitro, cyano and R_4R_5N - C_1 - C_3 -alkylene.

12. The method according to claim 2, wherein the compound is of formula (IV):

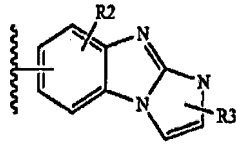
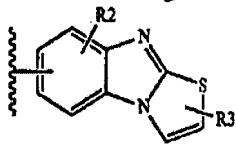
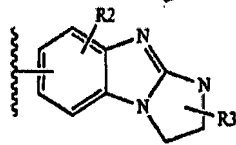
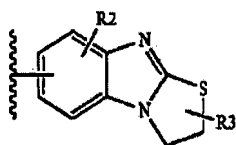
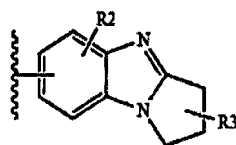


(IV) 40

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or a pharmaceutically acceptable salt thereof

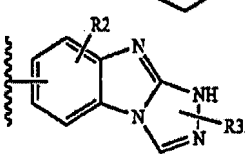
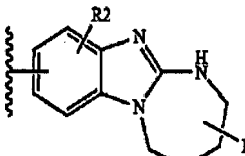
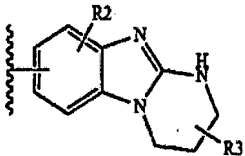
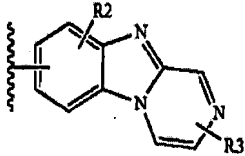
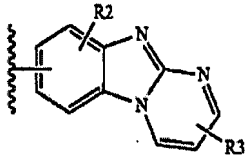
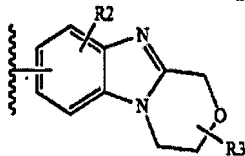
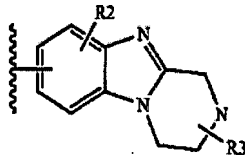
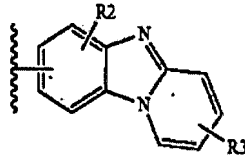
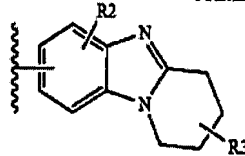
in which W is a tricyclic heterocycle or a tricyclic heteroaryl selected from:



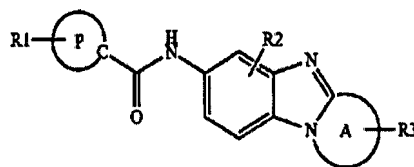
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-continued



13. The method according to claim 2, wherein the compound is of formula (V):



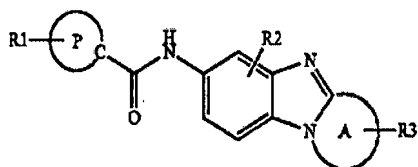
(V)

or a pharmaceutically acceptable salt thereof.

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14. The method according to claim 2, wherein the compound is of formula (V):



or a pharmaceutically acceptable salt thereof in which:

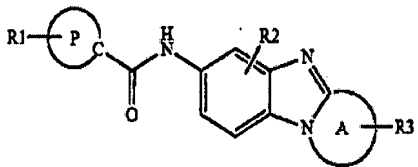
R2 is hydrogen, C₁-C₆-alkyl or C₁-C₆-alkoxy;

R3 is substituted on a carbon atom of A one to three times, each R3 substituted on a carbon atom of A may be identical or different, and is selected from hydrogen, C₁-C₆-alkyl, C₁-C₆-alkoxy and hydroxyl;

or

R3 is substituted on a nitrogen atom of A, one to two times, each R3 substituted on a nitrogen atom of A may be identical or different, and is selected from hydrogen, C₁-C₆-alkyl, C₁-C₆-alkyl-O-C(O)- and aryl-C₁-C₃-alkyl-O-C(O)-.

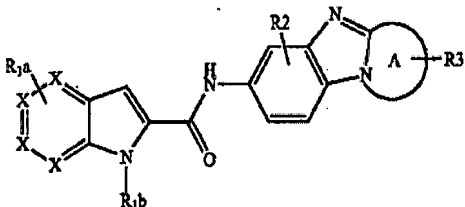
15. The method according to claim 2, wherein the compound is of formula (V):



or a pharmaceutically acceptable salt thereof in which:

A is, with the C—N bond of the benzimidazole unit with which it is fused, a 5- to 7-membered monocyclic heterocycle or monocyclic heteroaryl containing from one to three heteroatoms selected from O, S and N, including the nitrogen atom of the benzimidazole unit.

16. The method according to claim 2, wherein the compound is of formula (Va):



or a pharmaceutically acceptable salt thereof in which

A is, with the C—N bond of the benzimidazole unit with which it is fused, a 5- to 7-membered monocyclic heterocycle or monocyclic heteroaryl containing one or two heteroatoms selected from O, S and N, including the nitrogen atom of the benzimidazole unit;

X is a carbon atom or a nitrogen atom; said X being identical to or different from one another and the number of X=N not being greater than 1;

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R_{1a} is one or more atoms or groups, which may be identical or different, selected from a hydrogen, halogen, C₁-C₆-alkyl, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxy, C₁-C₆-thioalkyl, C₁-C₆-alkyl-S(O)₂—, NR₄R₅ and nitro;

R_{1b} is hydrogen, C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, R₄R₅NC(O)—C₁-C₃-alkylene, aryl, heteroaryl, aryl-C₁-C₆-alkylene or heteroaryl-C₁-C₆-alkylene;

said heteroaryl or aryl groups of R_{1b} being optionally substituted with one or more substituents R₉, which may be identical to or different from one another;

R2 is a hydrogen atom;

R3 is substituted on a carbon atom of X, and selected from hydrogen, C₁-C₆-alkyl, C₁-C₆-alkoxy, and hydroxyl;

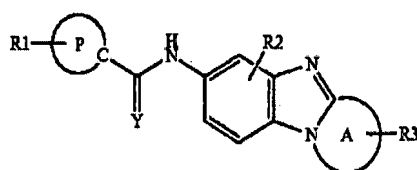
or

R3 is substituted on a nitrogen atom of X, and is selected from hydrogen, C₁-C₆-alkyl and C₁-C₆-alkyl-O-C(O)—;

R₄ and R₅ are, independently of one another, C₁-C₆-alkyl; or R₄ and R₅ form, together with the nitrogen atom which carries them, pyrrolidine or morpholine; and

R₉ is halogen, C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkyl, aryl, heteroaryl, NR₄R₅, or arylthio, said aryl being optionally substituted with one or more C₁-C₆-alkyl groups.

17. A method for modulating TRPV1 receptor activity comprising exposing the TRPV1 receptor to a modulatory amount of a compound of the formula (I):



or pharmaceutically acceptable salt thereof in which:

A is, with the C—N bond of the benzimidazole unit with which it is fused, a 4- to 7-membered monocyclic heterocycle or monocyclic heteroaryl, containing from one to three heteroatoms selected from O, S and N, including the nitrogen atom of the benzimidazole unit;

P is an 8-, 9-, 10- or 11-membered bicyclic heterocycle or bicyclic heteroaryl, containing from 1 to 6 heteroatoms selected from N, O and S; P being linked to the —C(Y)— group by a carbon atom;

with the proviso that, when A is a 7-membered saturated heterocycle, P is other than 2,3-dihydro-1,4-benzodioxane, 1-benzopyran-2-one or isoindole;

R1 is substituted on P one to four times and each R1 may be identical or different, R1 being selected from hydrogen, halogen, oxo, thio, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, heteroaryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenethio-C₁-C₆-alkyl, heteroaryl-C₁-C₃-alkylenethio-C₁-C₆-alkyl, C₁-C₆-alkoxy, C₃-C₇-cycloalkyloxy, C₃-C₇-cycloalkyl-C₁-C₃-alkylenoxy, C₁-C₆-fluoroalkoxy, cyano, C(O)NR₄R₅, nitro, NR₄R₅, C₁-C₆-thioalkyl, C₃-C₇-cycloalkylthio, C₃-C₇-cycloalkyl-C₁-C₃-alkylenethio, —S(O)—C₁-C₆-alkyl, —S(O)—C₃-C₇-cycloalkyl, —S(O)—C₁-C₃-alkylene-C₃-C₇-cycloalkyl, C₁-C₆-alkyl-S(O)₂—, C₁-C₆-fluoroalkyl-S(O)₂—, C₃-C₇-cycloalkyl-S(O)₂—, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-S

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(O)₂—, SO₂NR₄R₅, SF₅, NR₆C(O)R₇, NR₆SO₂R₈, R₄R₅NC(O)—C₁-C₃-alkylene, aryl, heteroaryl, aryl-C₁-C₃-alkylene, heteroaryl-C₁-C₃-alkylene, aryloxy, arylthio, heteroaryloxy or heteroarylthio;

said heteroaryl and aryl of R1 being optionally substituted with one or more substituents R₉, which may be identical to or different from one another;

with the proviso that, when R1 is attached to a nitrogen atom of P, then R1 is not halogen, oxo, thio, cyano, nitro, SF₅, NR₄R₅, C₁-C₆-thioalkyl, thioaryl, thioheteroaryl, C₁-C₆-alkoxy, aryloxy, heteroaryloxy, -NR₆COR₇ or NR₆SO₂R₈;

Y is an oxygen or sulphur atom;

R2 is hydrogen, halogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl or C₁-C₆-alkoxy;

R3 is substituted on a carbon atom of A, each R3 may be substituted 1 to 3 times on a carbon atom of A, each R3 substituted on a carbon atom of A may be identical or different, said R3 substituted on a carbon atom of A being selected from hydrogen, halogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, hydroxyl, C₁-C₆-alkoxy, C₃-C₇-cycloalkyloxy and C₃-C₇-cycloalkyl-C₁-C₃-alkylenoxy;

or

R3 is substituted on a nitrogen atom of A, each R3 may be substituted once or twice on a nitrogen atom of A and may be identical or different, said R3 substituted on a nitrogen atom of A being selected from hydrogen, halogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, aryl-C(O)—, C₁-C₆-alkyl-C(O)—, C₃-C₇-cycloalkyl-C(O)—, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-C(O)—, C₁-C₆-fluoroalkyl-C(O)—, aryl-S(O)₂—, C₁-C₆-alkyl-S(O)₂—, C₁-C₆-fluoroalkyl-S(O)₂—, C₃-C₇-cycloalkyl-S(O)₂—, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-S(O)₂—, C₁-C₆-alkyl-O-C(O)—, aryl-C₁-C₃-alkyl-O-C(O)—, C₃-C₇-cycloalkyl-O-C(O)—, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-O-C(O)—, C₁-C₆-fluoroalkyl-O-C(O)—, aryl-O-C(O)— and heteroaryl-O-C(O)—;

R₄ and R₅ are, independently of one another, hydrogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene or aryl;

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or R₄ and R₅ form, together with the nitrogen atom which carries them, azetidine, pyrrolidine, piperidine, azepine, morpholine, thiomorpholine, piperazine or homopiperazine group, the NR₄R₅ group being optionally substituted with C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene, aryl, heteroaryl, aryl-S(O)₂—, C₁-C₆-alkyl-S(O)₂—, C₁-C₆-fluoroalkyl-S(O)₂—, C₃-C₇-cycloalkyl-S(O)₂—, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-S(O)₂—, aryl-C(O)—, C₁-C₆-alkyl-C(O)—, C₃-C₇-cycloalkyl-C(O)—, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-C(O)—, C₁-C₆-fluoroalkyl-C(O)—, hydroxyl, C₁-C₆-alkyloxy, C₁-C₆-fluoroalkyl, aryloxy-C₁-C₆-alkylene, aryloxy, heteroaryloxy-C₁-C₆-alkylene or heteroaryloxy;

R₆ and R₇ are, independently of one another, a hydrogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene or aryl;

or R₆ and R₇ together form a 4- to 7-membered lactam comprising the nitrogen atom and the C(O) group which carry them;

R₈ is a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene or aryl;

or R₆ and R₈ together form a 4- to 7-membered sultam comprising the nitrogen atom and the S(O)₂ group which carry them;

R₉ is halogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkoxy, nitro, cyano, NR₄R₅, R₄R₅N—C₁-C₃-alkylene, aryl, heteroaryl, aryloxy, arylthio, heteroaryloxy or heteroarylthio, said heteroaryl or aryl being optionally substituted with one or more substituents selected from halogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkoxy, nitro, cyano, NR₄R₅ and R₄R₅N—C₁-C₃-alkylene;

the sulphur atom(s) of the heterocycle A may be in oxidized form (S(O) or S(O)₂);

the nitrogen atom(s) may be in oxidized form (N-oxide);

and with the proviso that 2-(2-chlorophenyl)-1,3-dioxo-N-(7,8,9,10-tetrahydro-6H-azepino[1,2-a]benzimidazol-3-yl)isindoline-5-carboxamide is excluded.

* * * * *



(12) **United States Patent**
Dubois et al.

(10) **Patent No.:** **US 8,143,248 B2**
(45) **Date of Patent:** **Mar. 27, 2012**

- (54) **TRICYCLIC
N-HETEROARYL-CARBOXAMIDE
DERIVATIVES CONTAINING A
BENZIMIDAZOLE UNIT, METHOD FOR
PREPARING SAME AND THEIR
THERAPEUTIC USE**
- (75) **Inventors:** Laurent Dubois, Antony (FR); Yannick
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Antony (FR); Catherine Gilie, Antony
(FR); Andre Malanda, Antony (FR);
David Machnik, Antony (FR); Nathalie
Rakotoarisoa, Antony (FR)
- (73) **Assignee:** Sanofi-Aventis, Paris (FR)
- (*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 734 days.
- (21) **Appl. No.:** 12/184,437
- (22) **Filed:** Aug. 1, 2008
- (65) **Prior Publication Data**
US 2009/0042873 A1 Feb. 12, 2009
- Related U.S. Application Data**
- (63) **Continuation of application No.**
PCT/FR2007/000183, filed on Feb. 1, 2007.
- (30) **Foreign Application Priority Data**
Feb. 3, 2006 (FR) 06 01007
- (51) **Int. Cl.**
A61K 31/535 (2006.01)
- (52) **U.S. Cl.** 514/230.2; 514/292; 514/338;
514/300; 514/267; 546/273.1; 546/113; 546/85;
548/302.4; 544/101; 544/250
- (58) **Field of Classification Search** 514/230,
514/292, 338, 300, 267; 546/273.1, 113,
546/85; 548/302.4; 544/101, 250
See application file for complete search history.

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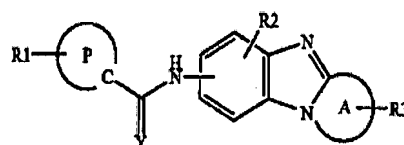
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Primary Examiner — Yong Chu
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(74) **Attorney, Agent, or Firm** — Scully, Scott, Murphy &
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(57) **ABSTRACT**

The invention concerns tricyclic N-heteroarylcarboxamide
derivatives containing a benzimidazole unit of general for-
mula (I):

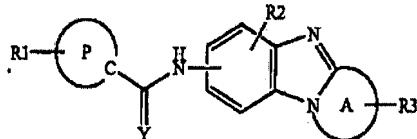


Wherein A, P, Y, R₁, R₂ and R₃ are as defined herein. The
invention also concerns a method of preparing the com-
pounds and their therapeutic use.

19 Claims, No Drawings

What is claimed is:

1. A compound of the formula (I):



in which:

A is, with the C—N bond of the benzimidazole unit with which it is fused, a 4- to 7-membered monocyclic heterocycle or monocyclic heteroaryl, containing from one to three heteroatoms selected from O, S and N, including the nitrogen atom of the benzimidazole unit;

P is an 8-, 9-, 10- or 11-membered bicyclic heterocycle or bicyclic heteroaryl, containing from 1 to 6 heteroatoms selected from N, O and S; P being linked to the —C(Y)— group by a carbon atom;

with the proviso that, when A is a 7-membered saturated heterocycle, P is other than the 2,3-dihydro-1,4-benzodioxane group, the 1-benzopyran-2-one group and the isoindole group;

R1 is substituted on P one to four times and each R1 may be identical or different, R1 selected from a hydrogen atom, a halogen atom, and an oxo, thio, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, heteroaryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenethio-C₁-C₆-alkyl, heteroaryl-C₁-C₃-alkylenethio-C₁-C₆-alkyl, C₁-C₆-alkoxy, C₃-C₇-cycloalkyloxy, C₃-C₇-cycloalkyl-C₁-C₃-alkylenoxy, C₁-C₆-fluoroalkoxy, cyano, C(O)NR₄R₅, nitro, NR₄R₅, C₁-C₆-thioalkyl, C₃-C₇-cycloalkylthio, C₃-C₇-cycloalkyl-C₁-C₃-alkylenethio, —S(O)—C₁-C₆-alkyl, —S(O)—C₃-C₇-cycloalkyl, —S(O)—C₁-C₃-alkylene-C₃-C₇-cycloalkyl, C₁-C₆-alkyl-S(O)₂, C₁-C₆-fluoroalkyl-S(O)₂, C₃-C₇-cycloalkyl-S(O)₂, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-S(O)₂, SO₂NR₄R₅, SF₅, NR₆C(O)R₇, NR₆SO₂R₈, R₄R₅NC(O)—C₁-C₃-alkylene, aryl, heteroaryl, aryl-C₁-C₃-alkylene, heteroaryl-C₁-C₃-alkylene, aryloxy, arylthio, heteroaryloxy or heteroarylthio group;

said heteroaryl or aryl groups of R1 being optionally substituted with one or more substituents R₉, which may be identical to or different from one another;

with the proviso that, when R1 is attached to a nitrogen atom of P, then R1 is not a halogen atom, an oxo, thio, cyano, nitro, SF₅, NR₄R₅, C₁-C₆-thioalkyl, thiocarbonyl, thioheteroaryl, C₁-C₆-alkoxy, aryloxy, heteroaryloxy, —NR₄COR₇ or NR₆SO₂R₈ group;

Y is an oxygen or sulphur atom;

R2 is a hydrogen atom, a halogen atom, or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl or C₁-C₆-alkoxy group;

R3 is substituted on a carbon atom of A, each R3 may be substituted 1 to 3 times on a carbon atom of A, each R3 substituted on a carbon atom of A may be identical or different, said R3 substituted on a carbon atom of A selected from hydrogen, halogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, hydroxyl, C₁-C₆-alkoxy, C₃-C₇-cycloalkyloxy and C₃-C₇-cycloalkyl-C₁-C₃-alkylenoxy group;

or

R3 is substituted on a nitrogen atom of A, each R3 may be substituted once or twice on a nitrogen atom of A and may be identical or different, said R3 substituted on a nitrogen atom of A selected from hydrogen, halogen, C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, aryl-C(O)—, C₁-C₆-alkyl-C(O)—, C₃-C₇-cycloalkyl-C(O)—, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-C(O)—, C₁-C₆-fluoroalkyl-C(O)—, aryl-S(O)₂—, C₁-C₆-alkyl-S(O)₂—, C₁-C₆-fluoroalkyl-S(O)₂—, C₃-C₇-cycloalkyl-S(O)₂—, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-S(O)₂—, C₁-C₆-alkyl-O—C(O)—, aryl-C₁-C₃-alkyl-O—C(O)—, C₃-C₇-cycloalkyl-O—C(O)—, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-O—C(O)—, C₁-C₆-fluoroalkyl-O—C(O)—, aryl-O—C(O)— or heteroaryl-O—C(O)— group;

R₄ and R₅ are, independently of one another, a hydrogen atom or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene or aryl group;

or R₄ and R₅ form, together with the nitrogen atom which carries them, an azetidine, pyrrolidine, piperidine, azepine, morpholine, thiomorpholine, piperazine or homopiperazine group, the NR₄R₅ group being optionally substituted with a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene, aryl, heteroaryl, aryl-S(O)₂—, C₁-C₆-alkyl-S(O)₂—, C₁-C₆-fluoroalkyl-S(O)₂—, C₃-C₇-cycloalkyl-S(O)₂—, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-S(O)₂—, aryl-C(O)—, C₁-C₆-alkyl-C(O)—, C₃-C₇-cycloalkyl-C(O)—, C₃-C₇-cycloalkyl-C₁-C₃-alkylene-C(O)—, C₁-C₆-fluoroalkyl-C(O)—, hydroxyl, C₁-C₆-alkyloxy, C₁-C₆-fluoroalkyl, aryloxy-C₁-C₆-alkylene, aryloxy, heteroaryloxy-C₁-C₆-alkylene or heteroaryloxy group;

R₆ and R₇ are, independently of one another, a hydrogen atom, or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene or aryl group;

or R₆ and R₇ together form a 4- to 7-membered lactam comprising the nitrogen atom and the C(O) group which carry them;

R₈ is a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, aryl-C₁-C₃-alkylene or aryl group;

or R₆ and R₈ together form a 4- to 7-membered sultam comprising the nitrogen atom and the S(O)₂ group which carry them;

R₉ is a halogen atom, or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkoxy, nitro, cyano, NR₄R₅, R₄R₅N—C₁-C₃-alkylene, aryl, heteroaryl, aryloxy, arylthio, heteroaryloxy or heteroarylthio group, said heteroaryl or aryl groups being optionally substituted with one or more substituents selected from a halogen atom, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkoxy, nitro, cyano, NR₄R₅ or R₄R₅N—C₁-C₃-alkylene group;

the sulphur atom(s) of the heterocycle A may be in oxidized form (S(O) or S(O)₂);

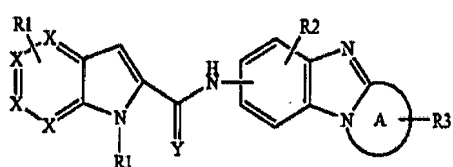
the nitrogen atom(s) may be in oxidized form (N-oxide); or an addition salt thereof; and with the proviso that 2-(2-chlorophenyl)-1,3-dioxo-N-(7,8,9,10-tetrahydro-6H-azepino[1,2-a]benzimidazol-3-yl)isoindoline-5-carboxamide is excluded.

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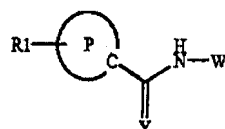
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2. The compound according to claim 1, which is of formula (II):



(II) 5

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(IV)

in which W is a tricyclic heterocycle or a tricyclic heteroaryl selected from:

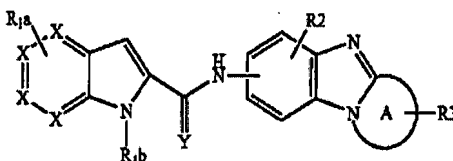
in which:

X is a carbon atom or a nitrogen atom; said X being identical to or different from one another and the number of X=N not being greater than 2;

R2, R3, Y and A being as defined in formula (I) according to claim 1;

and each R1 maybe the same or different and is defined as in Formula I according to claim 1; or an addition salt thereof.

3. The compound according to claim 2, which is of formula (III):



(III)

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in which:

R_{1a} is bonded to the ring containing X atoms one or more times, each R_{1a} may be identical or different, each R_{1a} is selected from hydrogen, a halogen a C₁-C₆-alkyl, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxy, C₁-C₆-thioalkyl, C₁-C₆-alkyl-S(O)₂—, NR₄R₅ and nitro group;

R_{1b} is a hydrogen atom, or a C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, aryl-C₁-C₃-alkylenoxy-C₁-C₆-alkyl, R₄R₅NC(O)—C₁-C₃-alkylene, aryl, heteroaryl, aryl-C₁-C₆-alkylene or heteroaryl-C₁-C₆-alkylene group;

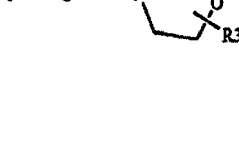
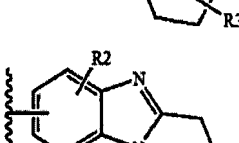
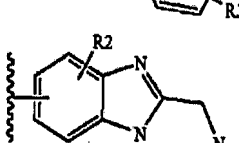
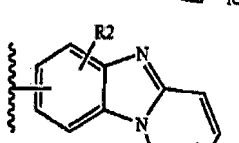
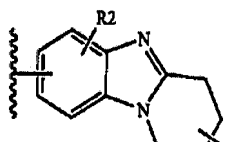
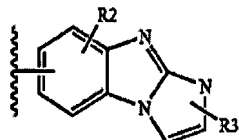
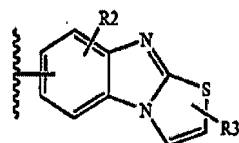
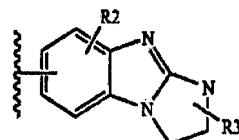
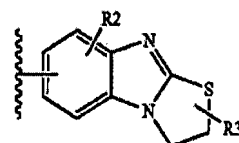
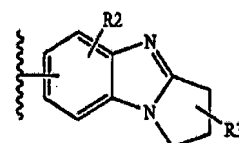
said heteroaryl or aryl groups of R_{1b} being optionally substituted with one or more substituents R₉, which may be identical to or different from one another;

R₉ is a halogen atom or a C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkyl, aryl, heteroaryl, NR₄R₅ or arylthio group, said heteroaryl or aryl groups being optionally substituted with one or more substituents selected from a halogen atom, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxy, C₁-C₆-fluoroalkoxy, nitro, cyano or R₄R₅N—C₁-C₃-alkylene group;

R2, R3, R₄, R₅, A, X and Y are as defined in formula (II) according to claim 2;

or an addition salt thereof.

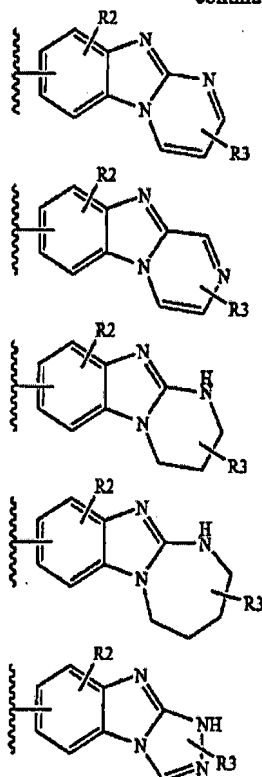
4. The compound according to claim 1, which is of formula (IV):



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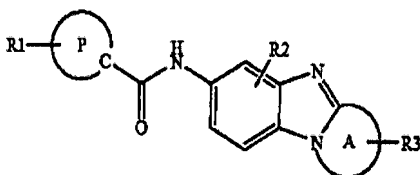
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and wherein:

R1, R2, R3, P and Y being as defined in formula (I) according to claim 1;
or an addition salt thereof.

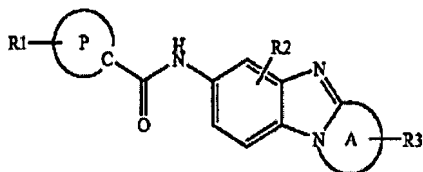
5. The compound according to claim 1, which is of formula (V):



in which:

R1, R2, R3, A and P are as defined in formula (I) according to claim 1;
or an addition salt thereof.

6. The compound according to claim 1, which is of formula (V):



in which:

R2 is a hydrogen atom, or a C₁-C₆-alkyl or C₁-C₆-alkoxy group;

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R3 is substituted on a carbon atom of A one to three times, each R3 substituted on a carbon atom of A may be identical or different, and is selected from hydrogen, C₁-C₆-alkyl, C₁-C₆-alkoxy and hydroxyl group;

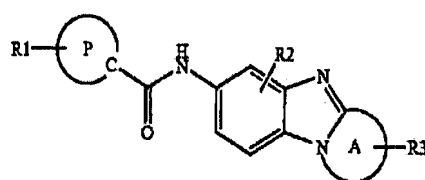
or

R3 is substituted on a nitrogen atom of A, one to two times, each R3 substituted on a nitrogen atom of A may be identical or different, and is selected from hydrogen, C₁-C₆-alkyl, C₁-C₆-alkyl-O-C(O)- and aryl-C₁-C₃-alkyl-O-C(O)- group; and wherein

R1, A and P are as defined in formula (I) according to claim 1;

or an addition salt thereof.

7. The compound according to claim 1, which is of formula (V):



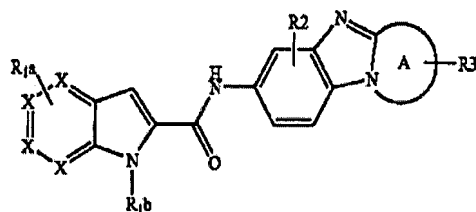
in which:

A is, with the C—N bond of the benzimidazole unit with which it is fused, a 5- to 7-membered monocyclic heterocycle or monocyclic heteroaryl containing one to three heteroatoms selected from O, S and N, including the nitrogen atom of the benzimidazole unit; and wherein

R1, R2, R3, and P are as defined in formula (I) according to claim 1;

or an addition salt thereof.

8. The compound according to claim 1, which is of formula (Va):



in which

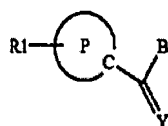
A is, with the C—N bond of the benzimidazole unit with which it is fused, a 5- to 7-membered monocyclic heterocycle or monocyclic heteroaryl containing one or two heteroatoms selected from O, S and N, including the nitrogen atom of the benzimidazole unit;

X is a carbon atom or a nitrogen atom; said X being identical to or different from one another and the number of X=N not being greater than 1;

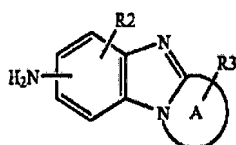
R_{1a} is one or more atoms or groups, which may be identical or different, selected from a hydrogen atom, a halogen atom or a C₁-C₆-alkyl group, a C₁-C₆-fluoroalkyl group, a C₁-C₆-alkoxy group, a C₁-C₆-thioalkyl group, a C₁-C₆-alkyl-S(O)₂- group, an NR₄R₅ group or a nitro group;

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R_{1b} is a hydrogen atom, or a C_1-C_6 -alkyl, heteroaryloxy- C_1-C_6 -alkyl, aryl- C_1-C_3 -alkylenoxy- C_1-C_5 -alkyl, $R_4R_5NC(O)-C_1-C_3$ -alkylene, aryl, heteroaryl, aryl- C_1-C_6 -alkylene or heteroaryl- C_1-C_6 -alkylene group; said heteroaryl or aryl groups of R_{1b} being optionally substituted with one or more substituents R_6 , which may be identical to or different from one another;
 R_2 is a hydrogen atom;
 R_3 is substituted on a carbon atom of X, and selected from hydrogen, C_1-C_6 -alkyl, 6 C_1-C_6 -alkoxy, and hydroxyl;
 or
 R_3 is substituted on a nitrogen atom of X, and is selected from hydrogen, a C_1-C_6 -alkyl group and a C_1-C_6 -alkyl- $O-C(O)-$ group;
 R_4 and R_5 are, independently of one another, a C_1-C_6 -alkyl group;
 or R_4 and R_5 form, together with the nitrogen atom which carries them, a pyrrolidine or morpholine group; and
 R_6 is a halogen atom or a C_1-C_6 -alkyl, C_1-C_6 -alkoxy, C_1-C_6 -fluoroalkyl, aryl, heteroaryl, NR_4R_5 , or arylthio group, said aryl groups being optionally substituted with one or more C_1-C_6 -alkyl groups;
 or an addition salt thereof.
 9. A process for preparing a compound of formula (I) according to claim 1 comprising:
 reacting a compound of formula (VI):

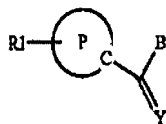


in which P, R1 and Y are as defined in formula (I) according to claim 1 and B is a C_1-C_6 -alkoxy, C_3-C_7 -cycloalkyloxy, C_3-C_7 -cycloalkyl- C_1-C_3 -alkylenoxy or aryl- C_1-C_3 -alkylenoxy group, with the resulting amide formed from the reaction of trimethyl-aluminum on the amine of formula VII:



in which A, R2 and R3 are as defined in formula (I) according to claim 1.

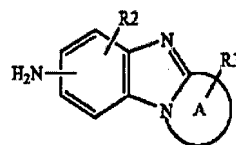
10. A process for preparing a compound of formula (I) according to claim 1 comprising:
 converting a compound of formula (VI):



in which P, R1 and Y are as defined in formula (I) according to claim 1 and B is a hydroxyl group, to an acid chloride by the action of thionyl chloride at the reflux of a solvent, and

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reacting the compound of formula (VI) obtained therefrom, in which P, R1 and Y are as defined in formula (I) according to claim 1 and B is a chlorine atom, in the presence of a base, with the compound of formula (VII):

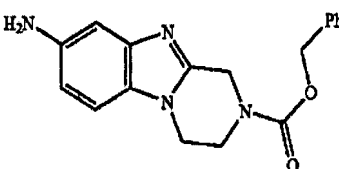
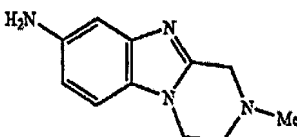
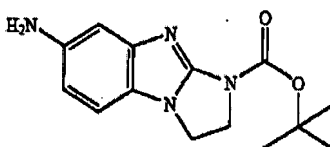
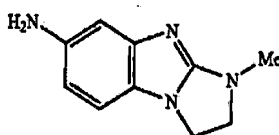
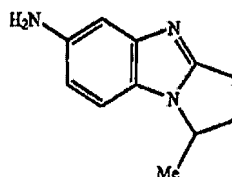
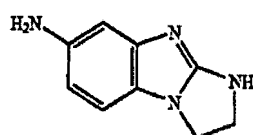


in which A, R2 and R3 are as defined in formula (I) according to claim 1;

or

subjecting to a coupling reaction a compound of formula (VI), in which P, R1 and Y are as defined in formula (I) according to claim 1 and B is a hydroxyl group, and a compound of formula (VII) in which A, R2 and R3 are as defined in formula (I) according to claim 1, in the presence of a coupling agent and a base in a solvent.

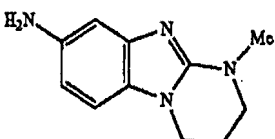
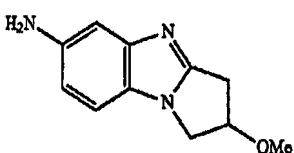
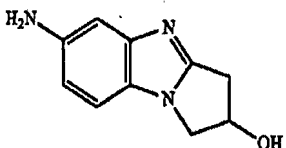
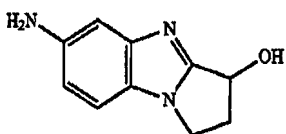
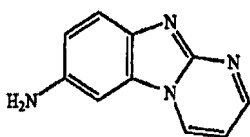
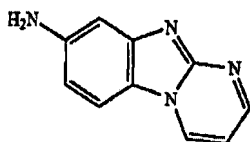
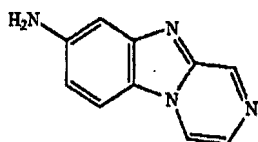
11. A compound of formula (VIIa), (VIIb), (VIIc), (VIId), (VIIe), (VII-f), (VIIg), (VIIh), (VIIi), (VIIj), (VIIk), (VIIl), (VIIm) or (VII-n):



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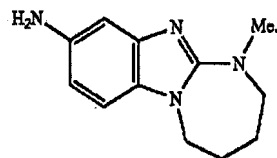


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(VII-g)

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(VII-n)

(VII-h)

10 12. A pharmaceutical composition comprising at least one compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof in combination with at least one pharmaceutically acceptable excipient.

(VII-i)

15 13. A pharmaceutical composition comprising at least one compound of formula (I) according to claim 2 or a pharmaceutically acceptable salt thereof in combination with at least one pharmaceutically acceptable excipient.

(VII-j)

20 14. A pharmaceutical composition comprising at least one compound of formula (I) according to claim 3 or a pharmaceutically acceptable salt thereof in combination with at least one pharmaceutically acceptable excipient.

(VII-k)

25 15. A pharmaceutical composition comprising at least one compound of formula (I) according to claim 4 or a pharmaceutically acceptable salt thereof in combination with at least one pharmaceutically acceptable excipient.

(VII-l)

30 16. A pharmaceutical composition comprising at least one compound of formula (I) according to claim 5 or a pharmaceutically acceptable salt thereof in combination with at least one pharmaceutically acceptable excipient.

(VII-m)

35 17. A pharmaceutical composition comprising at least one compound of formula (I) according to claim 6 or a pharmaceutically acceptable salt thereof in combination with at least one pharmaceutically acceptable excipient.

40 18. A pharmaceutical composition comprising at least one compound of formula (I) according to claim 7 or a pharmaceutically acceptable salt thereof in combination with at least one pharmaceutically acceptable excipient.

19. A pharmaceutical composition comprising at least one compound of formula (I) according to claim 8 or a pharmaceutically acceptable salt thereof in combination with at least one pharmaceutically acceptable excipient.

* * * * *